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[Continued on next page]

(54) Title: SYNTHESIS OF OLIGOMERIC NEOLIGNANS AND THEIR USE

(57) Abstract: Compounds having the structure formule (I) and their uses are described herein.

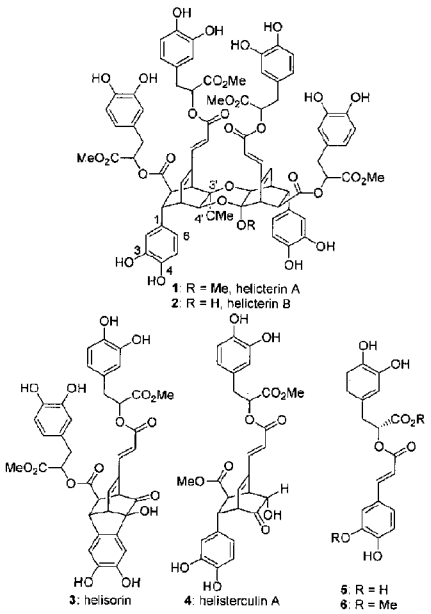
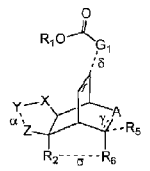


Figure 1.



(I)

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SYNTHESIS OF OLIGOMERIC NEOLIGNANS AND THEIR USE

This application claims the benefit of U.S. Provisional Application No. 61/203,737, filed December 23, 2008, the entire content of which is hereby incorporated by reference herein.

Throughout this application, certain publications are referenced in brackets. Full citations for these publications may be found immediately preceding the claims. The disclosures of these publications in their entireties are hereby incorporated by reference into this application in order to describe more fully the state of the art to which this invention relates.

Background of the Invention

Helicterins A and B (**1** and **2**), helisorin (**3**), and helisterculin A (**4**) are structurally unique natural products with the ability to combat the avian myeloblastosis virus (see Figure 1). From a biogenetic perspective, their architectures are considered to be products of seemingly straightforward Diels-Alder, radical-based, or acid-induced dimerizations of common, simpler precursors. Yet, the pursuit of such blueprints in the laboratory has failed thus far in enabling their successful synthesis.

In late 1999 and early 2000, Tezuka and co-workers reported the isolation and structural characterization of helicterins A and B, helisorin, and helisterculin A (**1-4**),

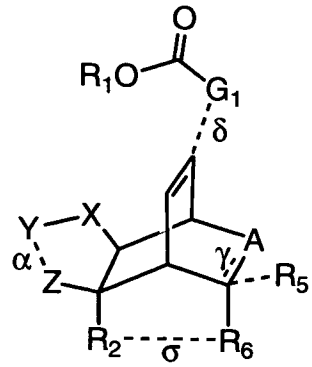
four members of a family of structurally distinct neolignans from the Indonesian plant *Helicteres isora* that possess mild inhibitory activity against the avian myeloblastosis virus [1]. Similar to many plant-derived polyphenols, their architectural complexity likely derives from the oligomerization of a simpler building block, in this case either rosmarinic acid (**5**) [2] or its doubly methylated form, oresbiusin B (**6**) [3], if one assumes that all of the unassigned stereogenic centers in these isolates possess the same absolute chirality. Indeed, as shown in Figure 2, a possible biosynthesis of these adducts could begin via oxidation of the conjugated aromatic ring within **5** (cf. Figure 1) to its corresponding *o*-quinone (**10**), followed by a Diels-Alder reaction with the olefinic domain of unoxidized **5** (shown here as **9**) to provide key intermediate **8**. This molecule, in turn, could give rise to helisorin (**3**) via a Friedel-Crafts reaction of the pendant aromatic ring onto the proximal ketone, while changes in its oxidation state could provide pathways to helisterculin A (**4**) and intermediate **7**, the likely precursor needed to forge the acetal-based core of helicterin A and B (**1** and **2**). Alternatively, critical intermediate **8** could also be envisioned to arise via a radical-based union of appropriate carbon-centered radicals (**12a** and **12b**) followed by a C-C bond-forming event.

Yet, despite the elegance and apparent simplicity of these general sequences, ones proposed by the original isolation chemists [1] and mirrored by many [4] in assessing putative biosynthetic pathways to related polyphenol natural products, the challenge for synthetic chemistry is accomplishing them in the absence of the enzymes that

Nature likely deploys to achieve the requisite chemoselectivity [5]. For instance, the proposed conversion of **8** into **7** requires the selective delivery of hydride from the more hindered face of the [2.2.2]-bicycle onto the less accessible of its two ketones, and *ortho*-quinones of the type postulated for the opening Diels-Alder reaction typically decompose prior to intermolecular cycloaddition [6]. How, then, to achieve a laboratory synthesis of these molecules? Herein, the first synthetic solution to this problem, an answer revealing that many of the general tenets of the proposed biosynthetic scheme can be reduced to practice, but only by utilizing a building block that is structurally distinct from Nature's presumed starting material in combination with carefully conceived reaction conditions that achieve appropriate control on sensitive frameworks, is described. It is demonstrated herein that a non-natural building block, highly complex retro Diels-Alder/Diels-Alder reaction cascades, an unconventional protecting group to achieve the proper balance of chemical reactivity on sensitive scaffolds, and several carefully developed reaction conditions that effectively balance competing reaction pathways are the keys to accomplishing the first total synthesis of three of these natural products, and also their analogs.

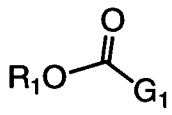
Summary of the Invention

This invention provides a compound having the structure

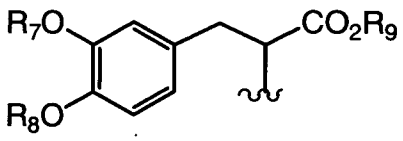


wherein

α, γ, δ and σ are each, independently, present or absent;

wherein when δ is absent,  is absent;

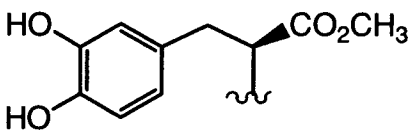
G_1 is C_{1-10} alkylene, C_{2-10} alkenylene, or C_{2-10} alkynylene;

R_1 is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or ,

wherein R_7 and R_8 are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; or $-SO_2R_{10}$,

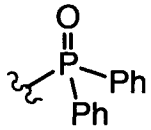
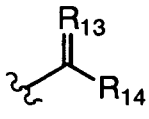
wherein R_{10} is C_{1-10} alkyl, or unsubstituted or substituted aryl;

R_9 is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

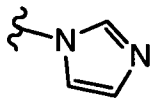
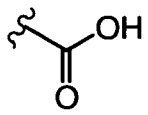
when R_7 and R_8 are H and R_9 is CH_3, then R_1 is ; and

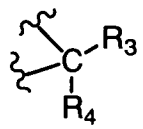
when γ is present; R_5 is absent and A is C-R_4,

wherein R_4 is H, halogen, or OR_{11},

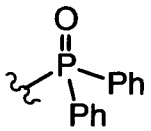
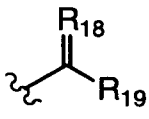
wherein R_{11} is H, C_{1-10} alkyl, $-CH_2SH$, $-BHCH_2CH_3$, -CH=SH, , $-SO_2R_{12}$, , or $-Si(R_{15})_3$;

wherein R_{12} and each occurrence of R_{15} is C_{1-10} alkyl; or unsubstituted or substituted aryl; and

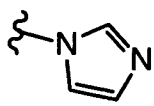
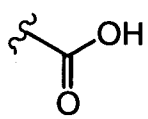
R_{13} is S or O; and R_{14} is $-SCH_3$, , or ; and

when γ is absent; R_5 is present and A is a direct bond or ;

wherein R_3 and R_4 are each, independently, H, halogen, or OR_{16};

wherein R_{16} is H, C_{1-10} alkyl, $-CH_2SH$, $-BHCH_2CH_3$, -CH=SH, , $-SO_2R_{17}$, , or $-Si(R_{20})_3$;

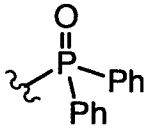
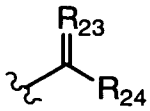
wherein R_{17} and each occurrence of R_{20} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

R_{18} is S or O; and R_{19} is $-SCH_3$, , or ; or

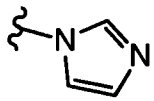
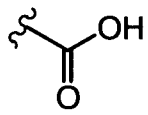
R_3 and R_4 taken together form =O; and

wherein R_5 is H, halogen, or OR_{21},

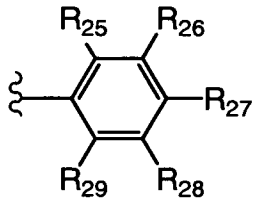
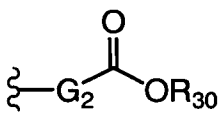
wherein R_{21} is H, C_{1-10} alkyl, $-CH_2SH$, $-BHCH_2CH_3$, $-CH{=}SH$,


, $-SO_2R_{22}$,

, or $-Si(R_{25})_3$,

wherein R_{22} and each occurrence of R_{25} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

R_{23} is S or O; and R_{24} is $-SCH_3$,

, or

; and

when σ is absent;

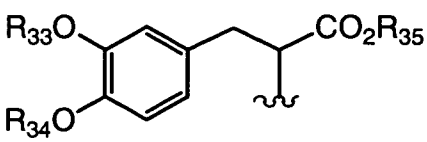
R_2 is H,

, or

;

wherein R_{25}, R_{26}, R_{27}, R_{28}, and R_{29} are each, independently, H, halogen, $-NO_2$, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; $-OR_{31}$, $-SR_{31}$, $-OSO_2R_{31}$, or $-NR_{31}R_{32}$,

wherein R_{31} and R_{32} are each, independently, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or unsubstituted or substituted aryl;

wherein G_2 is C_{1-10} alkylene, C_{2-10} alkenylene, or C_{2-10} alkynylene; and

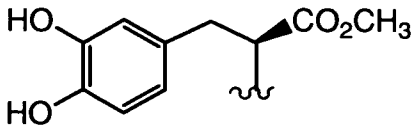
R_{30} is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or



wherein R_{33} and R_{34} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; or $-SO_2R_{36}$,

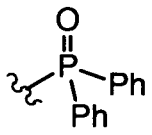
wherein R_{36} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

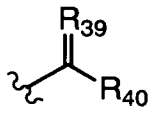
wherein R_{35} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

when R_{33} and R_{34} are H and R_{35} is CH_3, then R_{30} is 

; and

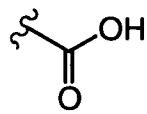
R_6 is H, halogen, or OR_{37};

wherein R_{37} is H, C_{1-10} alkyl, $-CH_2SH$, $-BHCH_2CH_3$, $-CH{=}SH$, 

, $-SO_2R_{38}$, 

, or $-Si(R_{41})_3$;

wherein R_{38} and each occurrence of R_{41} is C_{1-10} alkyl; or unsubstituted or substituted aryl;

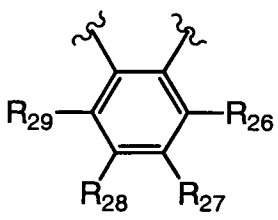
R_{39} is S or O; and R_{40} is $-SCH_3$; -NH-aryl, heteroaryl, heterocyclyl; or 

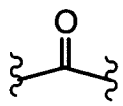
; or

R_5 when present and R_6 taken together form =O; or

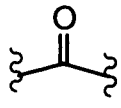
R_4 joined to R_6 form a 5-membered heterocyclic ring; and

when σ is present;

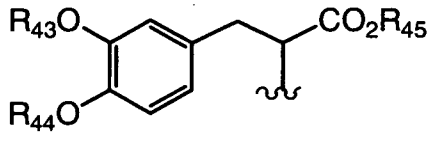
R_2 is 

; and R_6 is a direct bond or 

; and

wherein X is a direct bond, , or $C(OMe)_2$;

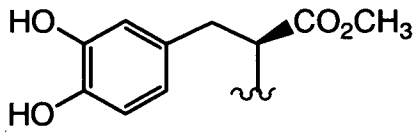
Y is H or OR_{42}; or when α is present, Y is ;

wherein R_{42} is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or ,

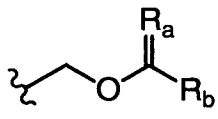
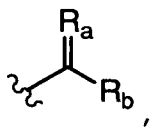
wherein R_{43} and R_{44} are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; or $-SO_2R_{46}$,

wherein R_{46} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

R_{45} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and when R_{43} and R_{44} are H and R_{45} is CH_3,

then R_{42} is ; or

wherein each occurrence of alkyl, alkylene, alkenyl, alkenylene, alkynyl, or alkynylene is branched or unbranched, unsubstituted or substituted;

Z is H, CN,  or ,

wherein R_a is S or O; R_b is $-O-(C_1-C_{10})$alkyl, $-O-(C_2-C_{10})$alkenyl, heterocyclyl, or heteroaryl; or

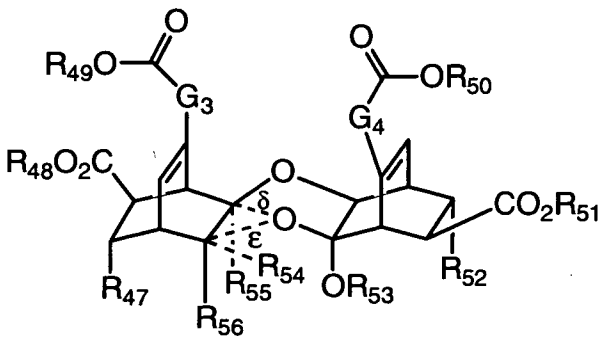
when α is present, Z is -CH=CH-;

and

when α is present, R_1 is other than methyl;

or a salt thereof.

This invention provides a compound having the structure



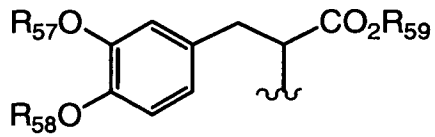
wherein ε and δ are present or absent;

wherein R_{54} and R_{55} are present or absent; and

when ε is present; δ and R_{54} are absent, and R_{55} is present; and

when δ is present; ε and R_{55} are absent, and R_{54} is present;

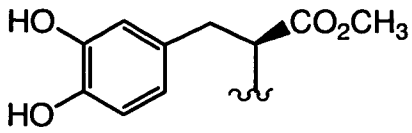
wherein G_3 and G_4 are each, independently, is C_{1-10} alkylene, C_{2-10} alkenylene, or C_{2-10} alkynylene;

R_{48}, R_{49}, R_{50}, and R_{51} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; or 

,

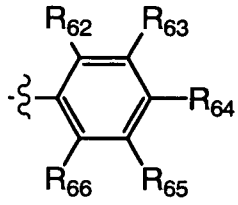
wherein R_{57} and R_{58} are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, unsubstituted or substituted aryl(C_{1-10})alkyl, or $-SO_2R_{60}$,

wherein R_{60} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

wherein R_{59} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and when R_{57} and R_{58} are H and R_{59} is CH_3, then R_{48}, R_{49}, R_{50}, or R_{51} is  ; and

wherein R_{53} is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, unsubstituted or substituted aryl(C_{1-10})alkyl, or $-SO_2R_{61}$,

wherein R_{61} is C_{1-10} alkyl, or unsubstituted or substituted aryl;

R_{47} and R_{52} are each H, CN, or  ,

wherein R_{62}, R_{63}, R_{64}, R_{65}, and R_{66} are each, independently, H, halogen, $-NO_2$, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; $-OR_{67}$, $-SR_{67}$, $-OSO_2R_{67}$, or $-NR_{67}R_{68}$,

wherein R_{67} and R_{68} are each, independently, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or unsubstituted or substituted aryl; and

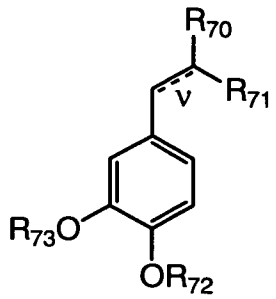
wherein R_{54} when present, R_{55} when present, and R_{56} are each, independently, H or OR_{69},

wherein R_{69} is H or C_{1-10} alkyl; or

wherein each occurrence of alkyl, alkylene, alkenyl, alkenylene, alkynyl, alkynylene is branched or unbranched, unsubstituted or substituted;

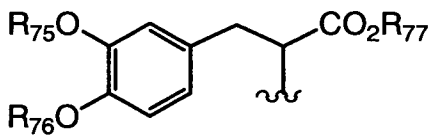
or a salt thereof.

This inventions further provides a compound having the structure



wherein ν is present or absent;

wherein R_{70} and R_{71} are each, independently, H, OH, $-CO_2R_{74}$,

wherein R_{74} is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or ,

wherein R_{75} and R_{76} are independently H; C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; or $-SO_2R_{78}$,

wherein R_{78} is C_{1-10} alkyl; or unsubstituted or substituted aryl; and

wherein R_{77} is H; C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and at least one of R_{75} and R_{76} is other than H;

wherein R_{72} and R_{73} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; $-SO_2R_{79}$, or $-Si(R_{80})_3$,

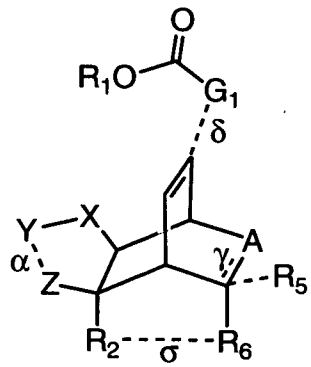
wherein R_{79} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

wherein each occurrence of R_{80} is, independently, C_{1-10} alkyl, or unsubstituted or substituted aryl; and when R_{74} is H or CH_3, R_{73} is other than H or Me; and

wherein each occurrence of alkyl, alkylene, alkenyl, alkenylene, alkynyl, or alkynylene is branched or unbranched, unsubstituted or substituted;

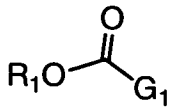
or a salt thereof.

This invention provides a process for preparing a compound having the structure

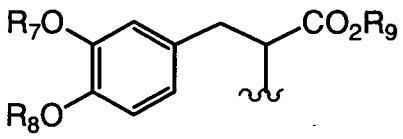


wherein

α, γ, δ and σ are each, independently, present or absent;

wherein when δ is absent,  is absent;

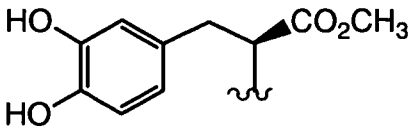
G_1 is C_{1-10} alkylene, C_{2-10} alkenylene, or C_{2-10} alkynylene;

R_1 is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or ,

wherein R_7 and R_8 are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; or $-SO_2R_{10}$,

wherein R_{10} is C_{1-10} alkyl, or unsubstituted or substituted aryl;

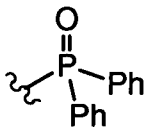
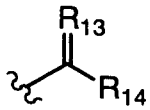
R_9 is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and when R_7 and R_8 are H and R_9 is CH_3, then R_1 is



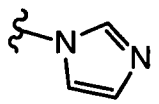
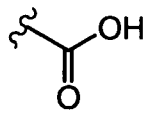
; and

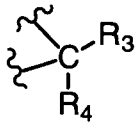
when γ is present; R_5 is absent and A is $C=R_4$,

wherein R_4 is H, halogen, or OR_{11},

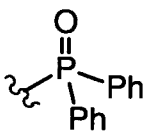
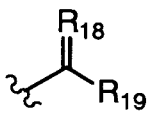
wherein R_{11} is H, C_{1-10} alkyl, $-CH_2SH$, $-BHCH_2CH_3$, $-CH=SH$, , $-SO_2R_{12}$, , or $-Si(R_{15})_3$;

wherein R_{12} and each occurrence of R_{15} is C_{1-10} alkyl; or unsubstituted or substituted aryl; and

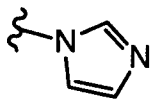
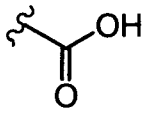
R_{13} is S or O; and R_{14} is $-SCH_3$, , or ; and

when γ is absent; R_5 is present and A is a direct bond or ;

wherein R_3 and R_4 are each, independently, H, halogen, or OR_{16};

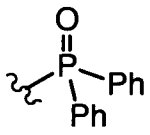
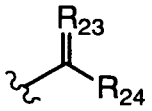
wherein R_{16} is H, C_{1-10} alkyl, $-CH_2SH$, $-BHCH_2CH_3$, $-CH=SH$, , $-SO_2R_{17}$, , or $-Si(R_{20})_3$;

wherein R_{17} and each occurrence of R_{20} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

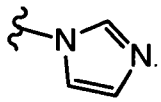
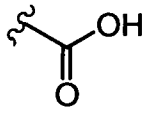
R_{18} is S or O; and R_{19} is $-SCH_3$, , or ; or

R_3 and R_4 taken together form =O; and

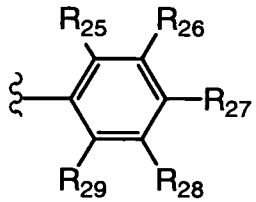
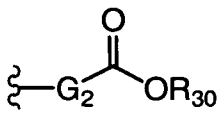
wherein R_5 is H, halogen, or OR_{21},

wherein R_{21} is H, C_{1-10} alkyl, $-CH_2SH$, $-BHCH_2CH_3$, $-CH{=}SH$, , $-SO_2R_{22}$, , or $-Si(R_{25})_3$,

wherein R_{22} and each occurrence of R_{25} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

R_{23} is S or O; and R_{24} is $-SCH_3$, , or ; and

when σ is absent;

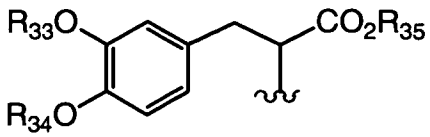
R_2 is H, , or ;

wherein R_{25}, R_{26}, R_{27}, R_{28}, and R_{29} are each, independently, H, halogen, $-NO_2$, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; $-OR_{31}$, $-SR_{31}$, $-OSO_2R_{31}$, or $-NR_{31}R_{32}$,

wherein R_{31} and R_{32} are each, independently, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or unsubstituted or substituted aryl;

wherein G_2 is C_{1-10} alkylene, C_{2-10} alkenylene, or C_{2-10} alkynylene; and

R_{30} is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or



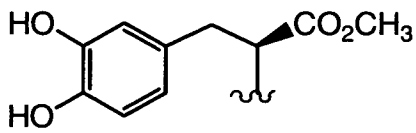
,

wherein R_{33} and R_{34} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; or $-SO_2R_{36}$,

wherein R_{36} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

wherein R_{35} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

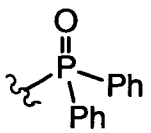
when R_{33} and R_{34} are H and R_{35} is CH_3, then R_{30} is



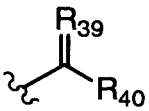
; and

R_6 is H, halogen, or OR_{37};

wherein R_{37} is H, C_{1-10} alkyl, $-CH_2SH$, $-BHCH_2CH_3$, $-CH{=}SH$,



, $-SO_2R_{38}$,

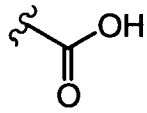


, or $-Si(R_{41})_3$;

wherein R_{38} and each occurrence of R_{41} is C_{1-10} alkyl; or unsubstituted or substituted aryl;

R_{39} is S or O; and R_{40} is $-SCH_3$; -NH-aryl,

heteroaryl, heterocyclyl; or

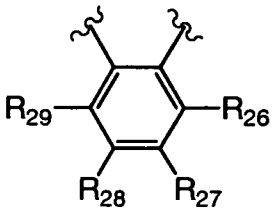


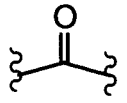
; or

R_5 when present and R_6 taken together form =O; or

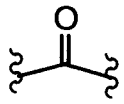
R_4 joined to R_6 form a 5-membered heterocyclic ring; and

when σ is present;

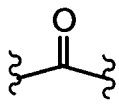
R_2 is 

; and R_6 is a direct bond or 

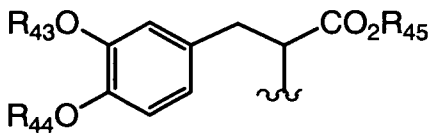
;
and

wherein X is a direct bond, 

, or $C(OMe)_2$;

Y is H or OR_{42}; or when α is present, Y is 

;

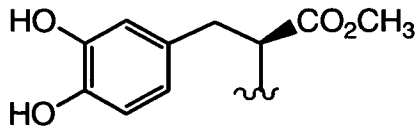
wherein R_{42} is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or 

,

wherein R_{43} and R_{44} are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; or $-SO_2R_{46}$,

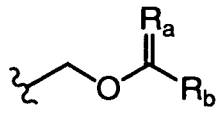
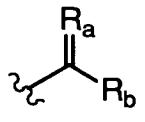
wherein R_{46} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

R_{45} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and when R_{43} and R_{44} are H and R_{45} is CH_3,

then R_{42} is 

; or

wherein each occurrence of alkyl, alkylene, alkenyl, alkenylene, alkynyl, or alkynylene is branched or unbranched, unsubstituted or substituted;

Z is H, CN,  or ,

wherein R_a is S or O; R_b is -O-(C_1-C_{10})alkyl, -O-(C_2-C_{10})alkenyl, heterocyclyl, or heteroaryl; or

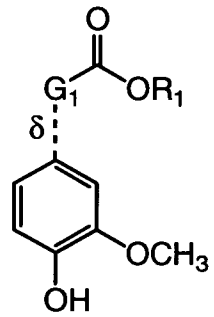
when α is present, Z is -CH=CH-;

and

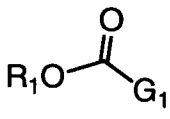
when α is present, R_1 is other than methyl;

comprising:

a) contacting a compound having the structure

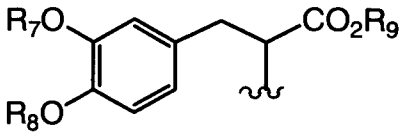
,

wherein

when δ is absent,  is absent;

G_1 is C_{1-10} alkylene, C_{2-10} alkenylene, or C_{2-10} alkynylene;

R_1 is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or

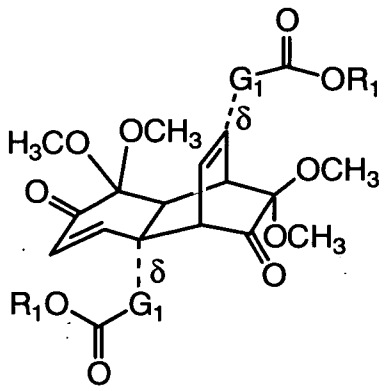
,

wherein R_7 and R_8 are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; or $-SO_2R_{10}$,

wherein R_{10} is C_{1-10} alkyl, or unsubstituted or substituted aryl;

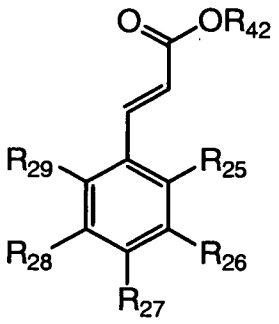
R_9 is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl;

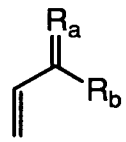
with a first suitable oxidizing agent in the presence of methanol so as to form the compound having the structure

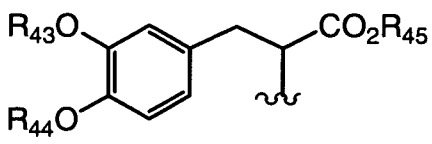


;

b) contacting the product of step a) with a compound having the structure



, NC-CH=CH_2, or 

wherein R_{42} is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or 

,

wherein R_{43} and R_{44} are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; or $-SO_2R_{46}$,

wherein R_{46} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

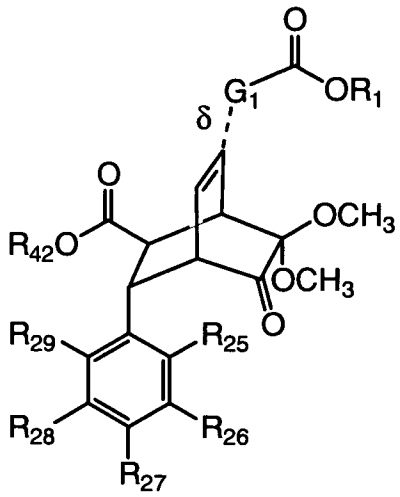
R_{45} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl;

R_{25}, R_{26}, R_{27}, R_{28}, and R_{29} are each, independently, H, halogen, $-NO_2$, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; $-OR_{31}$, $-SR_{31}$, $-OSO_2R_{31}$, or $-NR_{31}R_{32}$,

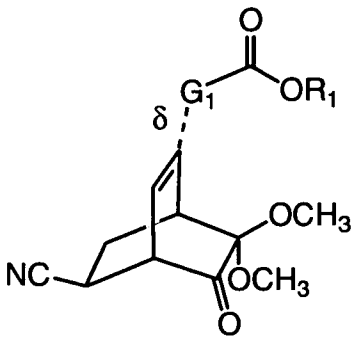
wherein R_{31} and R_{32} are each, independently, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or unsubstituted or substituted aryl; and

wherein R_a is S or O; R_b is $-O-(C_1-C_{10})$alkyl, $-O-(C_2-C_{10})$alkenyl, heterocyclyl, or heteroaryl;

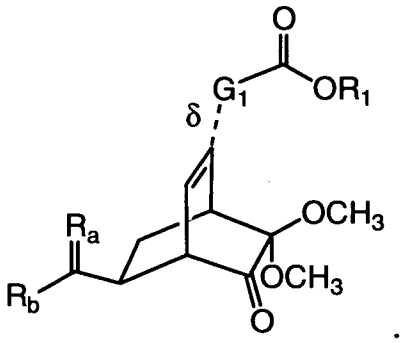
in the presence of a first suitable energy source so as to form the compound having the structure



,

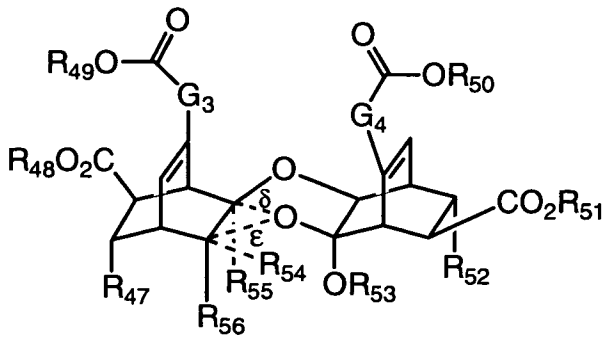


, or



.

This invention further provides a process for preparing a compound having the structure



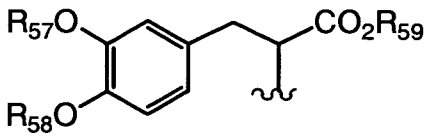
wherein ε and δ are present or absent;

wherein R_{54} and R_{55} are present or absent; and

when ε is present; δ and R_{54} are absent, and R_{55} is present; and

when δ is present; ε and R_{55} are absent, and R_{54} is present;

wherein G_3 and G_4 are each, independently, is C_{1-10} alkylene, C_{2-10} alkenylene, or C_{2-10} alkynylene;

R_{48}, R_{49}, R_{50}, and R_{51} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; or ,

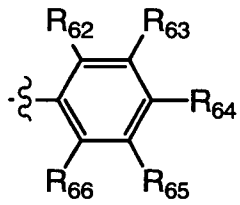
wherein R_{57} and R_{58} are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, unsubstituted or substituted aryl(C_{1-10})alkyl, or $-SO_2R_{60}$,

wherein R_{60} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

wherein R_{59} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

wherein R_{53} is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, unsubstituted or substituted aryl(C_{1-10})alkyl, or $-SO_2R_{61}$,

wherein R_{61} is C_{1-10} alkyl, or unsubstituted or substituted aryl;

R_{47} and R_{52} are each H, CN, or ,

wherein R_{62}, R_{63}, R_{64}, R_{65}, and R_{66} are each, independently, H, halogen, $-NO_2$, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; $-OR_{67}$, $-SR_{67}$, $-OSO_2R_{67}$, or $-NR_{67}R_{68}$,

wherein R_{67} and R_{68} are each, independently, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or unsubstituted or substituted aryl; and

wherein R_{54} when present, R_{55} when present, and R_{56} are each, independently, H or OR_{69},

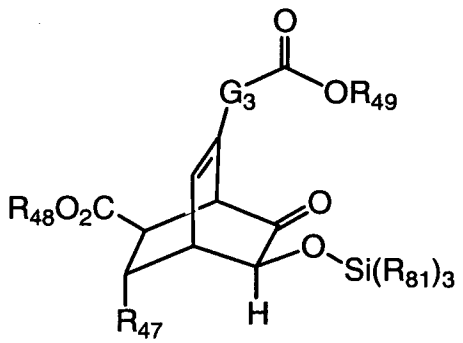
wherein R_{69} is H or C_{1-10} alkyl; or

wherein each occurrence of alkyl, alkylene, alkenyl, alkenylene, alkynyl, alkynylene is branched or unbranched, unsubstituted or substituted;

or a salt thereof;

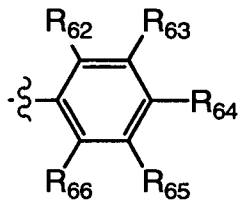
comprising:

a) contacting a compound having the structure



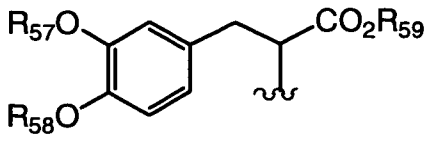
,

wherein G_3 is C_{1-10} alkylene, C_{2-10} alkenylene, or C_{2-10} alkynylene;

R_{47} is H, CN, or ,

wherein R_{62}, R_{63}, R_{64}, R_{65}, and R_{66} are each, independently, H, halogen, $-NO_2$, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; $-OR_{67}$, $-SR_{67}$, $-OSO_2R_{67}$, or $-NR_{67}R_{68}$,

wherein R_{67} and R_{68} are each, independently, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or unsubstituted or substituted aryl;

R_{48} and R_{49} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; or ,

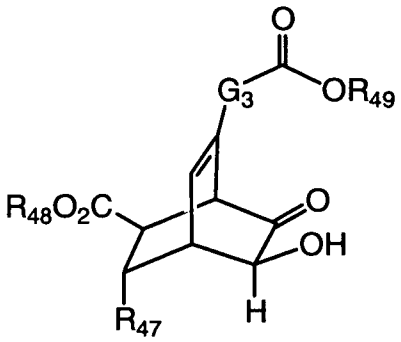
wherein R_{57} and R_{58} are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, unsubstituted or substituted aryl(C_{1-10})alkyl, or $-SO_2R_{60}$,

wherein R_{60} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

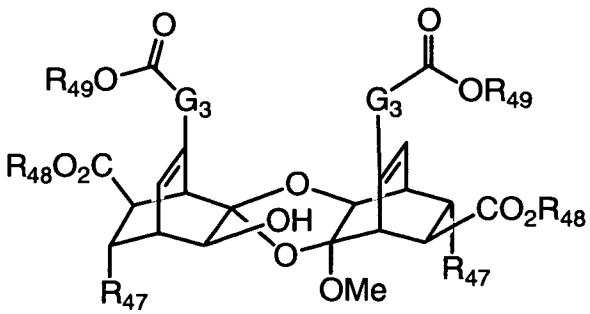
wherein R_{59} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

wherein each occurrence of R_{81} is, independently, C_{1-10} alkyl, or unsubstituted or substituted aryl;

with tetra-n-butylammonium fluoride so as to form a compound having the structure

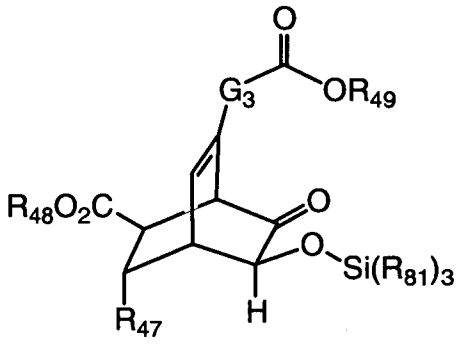
;

b) contacting the product of step a) with sodium hydride so as to form a compound having the structure

;

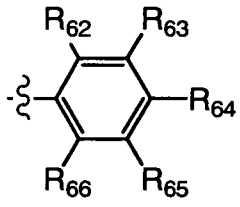
or

a') contacting a compound having the structure



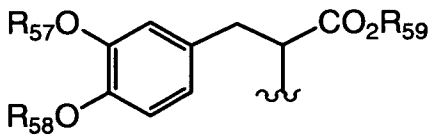
,

wherein G_3 is C_{1-10} alkylene, C_{2-10} alkenylene, or C_{2-10} alkynylene;

R_{47} is H, CN, or ,

wherein R_{62}, R_{63}, R_{64}, R_{65}, and R_{66} are each, independently, H, halogen, $-NO_2$, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; $-OR_{67}$, $-SR_{67}$, $-OSO_2R_{67}$, or $-NR_{67}R_{68}$,

wherein R_{67} and R_{68} are each, independently, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or unsubstituted or substituted aryl;

R_{48} and R_{49} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; or ,

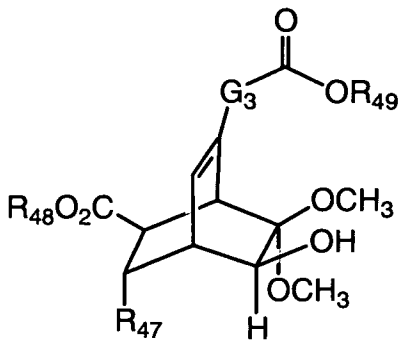
wherein R_{57} and R_{58} are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, unsubstituted or substituted aryl(C_{1-10})alkyl, or $-SO_2R_{60}$,

wherein R_{60} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

wherein R_{59} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

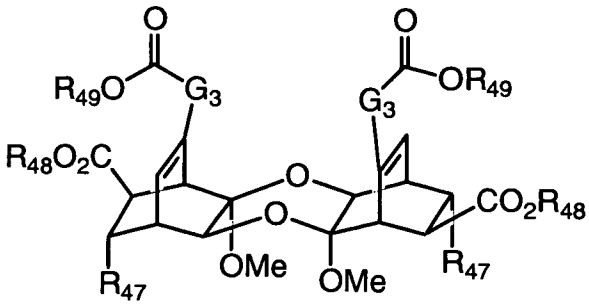
wherein each occurrence of R_{81} is, independently, C_{1-10} alkyl, or unsubstituted or substituted aryl;

with a first suitable Bronsted acid in the presence of methanol so as to form a compound having the structure



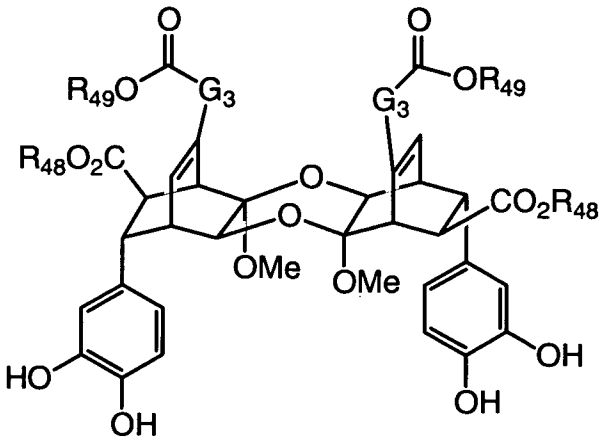
;

b') contacting the product of a') with a first suitable Lewis acid so as to form a compound having the structure

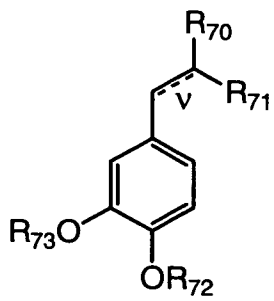


;

c') contacting the product of step b') with a second suitable Lewis acid so as to form a compound having the structure

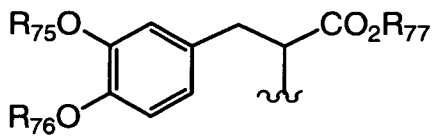


This invention provides a process for preparing a compound having the structure



wherein ν is present or absent;

wherein R_{70} and R_{71} are each, independently, H, OH, $-CO_2R_{74}$,

wherein R_{74} is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or ,

wherein R_{75} and R_{76} are independently H; C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; or $-SO_2R_{78}$,

wherein R_{78} is C_{1-10} alkyl; or unsubstituted or substituted aryl; and

wherein R_{77} is H; C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl;

wherein R_{72} and R_{73} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; $-SO_2R_{79}$, or $-Si(R_{80})_3$,

wherein R_{79} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

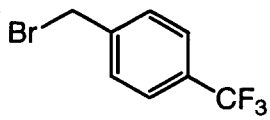
wherein each occurrence of R_{80} is, independently, C_{1-10} alkyl, or unsubstituted or substituted aryl; and

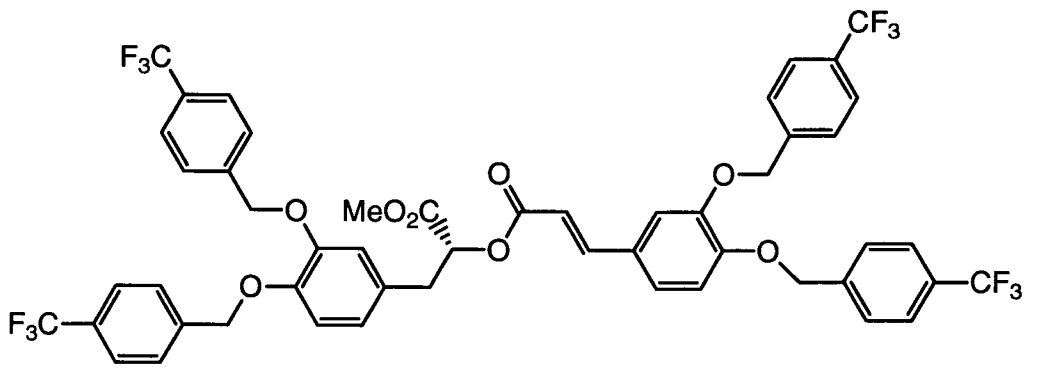
wherein each occurrence of alkyl, alkylene, alkenyl, alkenylene, alkynyl, or alkynylene is branched or unbranched, unsubstituted or substituted;

or a salt thereof;

comprising:

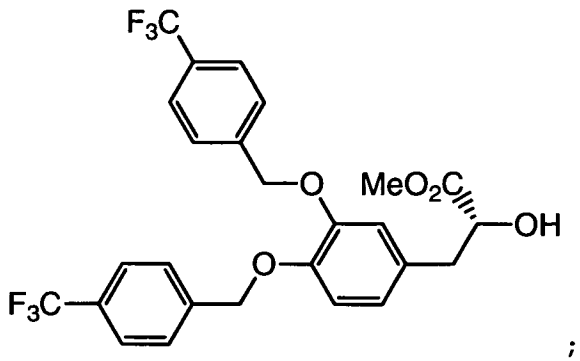
a) contacting rosmarinic acid with $TMSCHN_2$;

b) contacting the product of step a) with a compound having the structure  in the presence of a first suitable base so as to form a compound having the structure



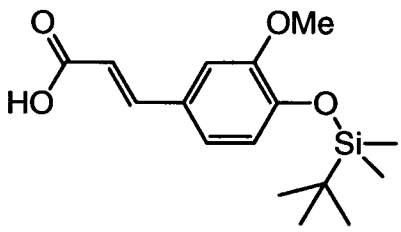
62. The process of claim 61 further comprising:

c) contacting the product of step b) with a second suitable base so as to form a compound having the structure



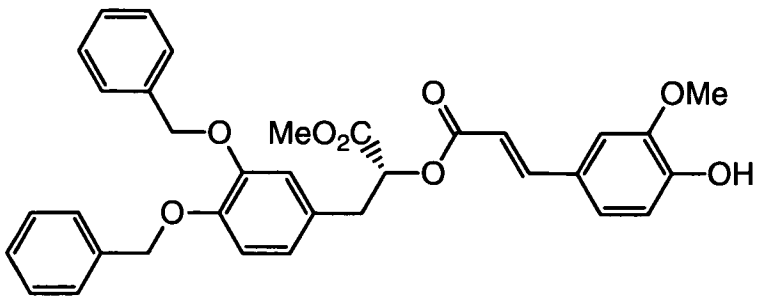
;

d) contacting the product of step c) with a compound having the structure



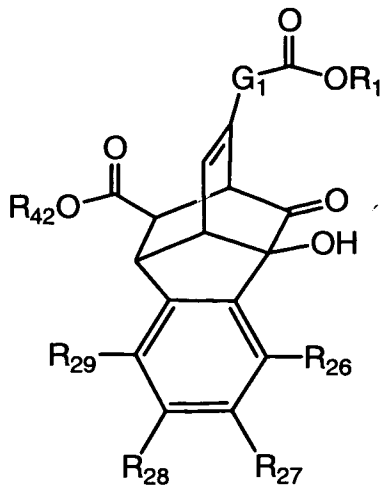
in the presence of *N*-ethyl-*N'*-(3-dimethylaminopropyl)carbodiimide and a third suitable base;

e) contacting the product of step d) with tetra-n-butylammonium fluoride so as to form a compound having the structure



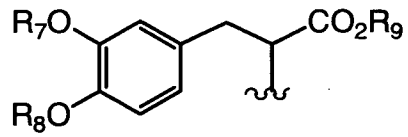
.

This invention further provides a process for preparing a compound having the structure



wherein G_1 is C_{1-10} alkylene, C_{2-10} alkenylene, or C_{2-10} alkynylene;

R_1 is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or



,

wherein R_7 and R_8 are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; or $-SO_2R_{10}$,

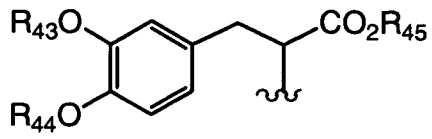
wherein R_{10} is C_{1-10} alkyl, or unsubstituted or substituted aryl;

R_9 is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl;

R_{26}, R_{27}, R_{28}, and R_{29} are each, independently, H, halogen, $-NO_2$, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; $-OR_{31}$, $-SR_{31}$, $-OSO_2R_{31}$, or $-NR_{31}R_{32}$,

wherein R_{31} and R_{32} are each, independently, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or unsubstituted or substituted aryl; and

R_{42} is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or



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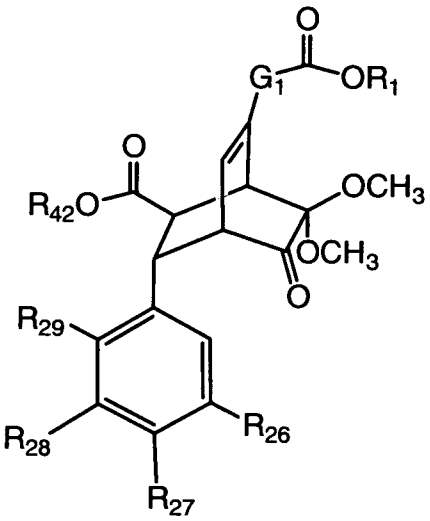
wherein R_{43} and R_{44} are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; or $-SO_2R_{46}$,

wherein R_{46} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

R_{45} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl;

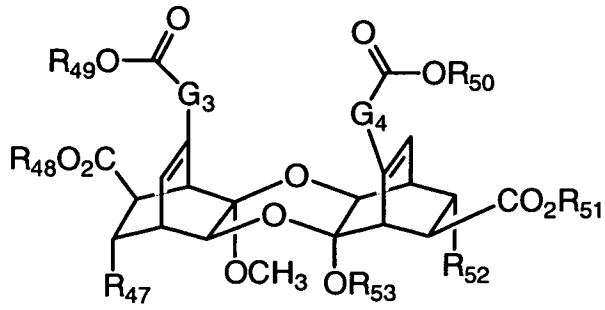
comprising:

a) exposing a compound having the structure

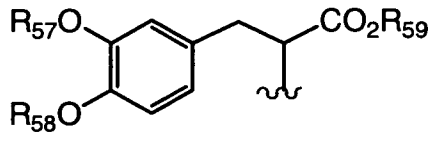


to a suitable Lewis acid so as to form the compound.

This invention yet further provides a process for preparing a compound having the structure



wherein G_3 and G_4 are each, independently, is C_{1-10} alkylene, C_{2-10} alkenylene, or C_{2-10} alkynylene;

R_{48}, R_{49}, R_{50}, and R_{51} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; or ,

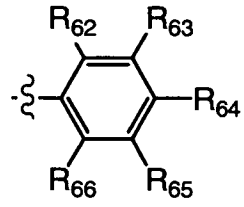
wherein R_{57} and R_{58} are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, unsubstituted or substituted aryl(C_{1-10})alkyl, or $-SO_2R_{60}$,

wherein R_{60} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

wherein R_{59} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

wherein R_{53} is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, unsubstituted or substituted aryl(C_{1-10})alkyl, or $-SO_2R_{61}$,

wherein R_{61} is C_{1-10} alkyl, or unsubstituted or substituted aryl;

R_{47} and R_{52} are each H, CN, or ,

wherein R_{62}, R_{63}, R_{64}, R_{65}, and R_{66} are each, independently, H, halogen, $-NO_2$, C_{1-10} alkyl, C_{2-10}

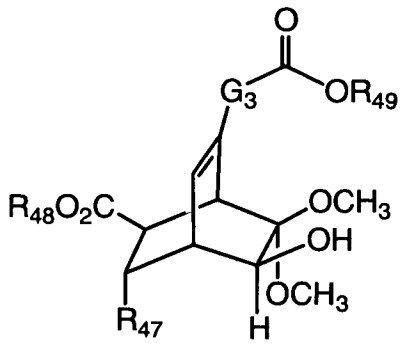
alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; $-OR_{67}$, $-SR_{67}$, $-OSO_2R_{67}$, or $-NR_{67}R_{68}$, wherein R_{67} and R_{68} are each, independently, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or unsubstituted or substituted aryl; or

wherein each occurrence of alkyl, alkylene, alkenyl, alkenylene, alkynyl, alkynylene is branched or unbranched, unsubstituted or substituted;

or a salt thereof;

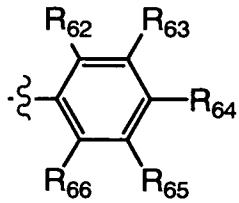
comprising:

a) contacting a compound having the structure



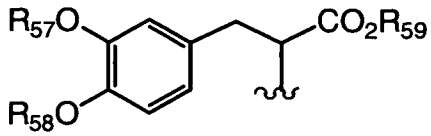
,

wherein G_3 is C_{1-10} alkylene, C_{2-10} alkenylene, or C_{2-10} alkynylene;

R_{47} is H, CN, or ,

wherein R_{62}, R_{63}, R_{64}, R_{65}, and R_{66} are each, independently, H, halogen, $-NO_2$, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; $-OR_{67}$, $-SR_{67}$, $-OSO_2R_{67}$, or $-NR_{67}R_{68}$,

wherein R_{67} and R_{68} are each, independently, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or unsubstituted or substituted aryl;

R_{48} and R_{49} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; or ,

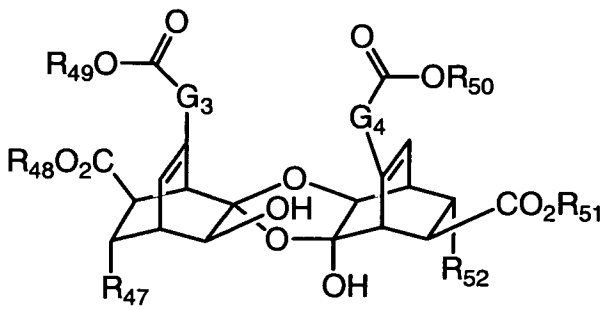
wherein R_{57} and R_{58} are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, unsubstituted or substituted aryl(C_{1-10})alkyl, or $-SO_2R_{60}$,

wherein R_{60} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

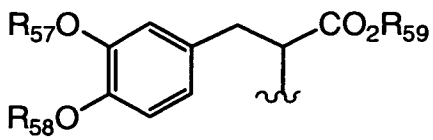
wherein R_{59} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl;

with a suitable Lewis acid so as to form the compound.

This invention provides a process for preparing a compound having the structure



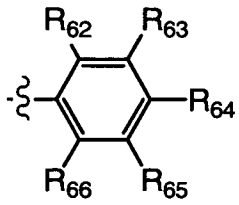
wherein G_3 and G_4 are each, independently, is C_{1-10} alkylene, C_{2-10} alkenylene, or C_{2-10} alkynylene;

R_{48}, R_{49}, R_{50}, and R_{51} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; or ,

wherein R_{57} and R_{58} are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, unsubstituted or substituted aryl(C_{1-10})alkyl, or $-SO_2R_{60}$,

wherein R_{60} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

wherein R_{59} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

R_{47} and R_{52} are each H, CN, or 

,

wherein R_{62}, R_{63}, R_{64}, R_{65}, and R_{66} are each, independently, H, halogen, $-NO_2$, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; $-OR_{67}$, $-SR_{67}$, $-OSO_2R_{67}$, or $-NR_{67}R_{68}$,

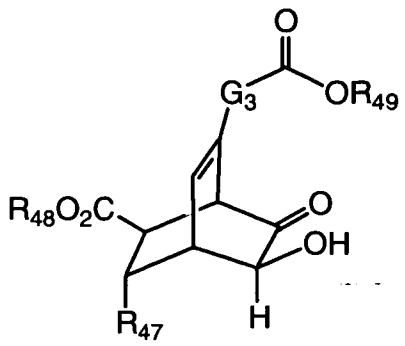
wherein R_{67} and R_{68} are each, independently, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or unsubstituted or substituted aryl; or

wherein each occurrence of alkyl, alkylene, alkenyl, alkenylene, alkynyl, alkynylene is branched or unbranched, unsubstituted or substituted;

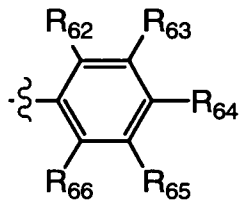
or a salt thereof;

comprising:

a) contacting a compound having the structure



wherein G_3 is C_{1-10} alkylene, C_{2-10} alkenylene, or C_{2-10} alkynylene;

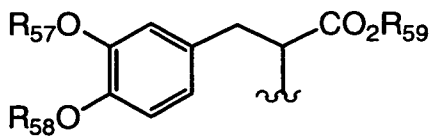


R_{47} is H, CN, or ,

wherein R_{62}, R_{63}, R_{64}, R_{65}, and R_{66} are each, independently, H, halogen, $-NO_2$, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; $-OR_{67}$, $-SR_{67}$, $-OSO_2R_{67}$, or $-NR_{67}R_{68}$,

wherein R_{67} and R_{68} are each, independently, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or unsubstituted or substituted aryl;

R_{48} and R_{49} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; or



,

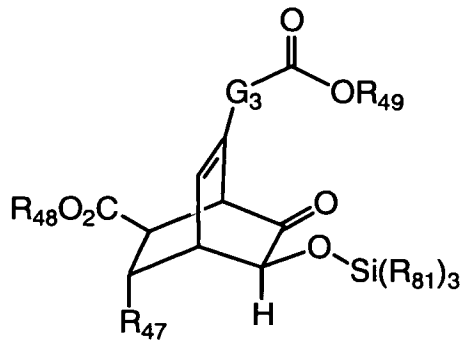
wherein R_{57} and R_{58} are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, unsubstituted or substituted aryl(C_{1-10})alkyl, or $-SO_2R_{60}$,

wherein R_{60} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

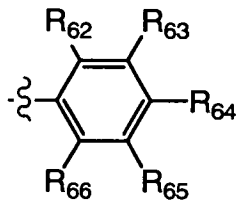
wherein R_{59} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl;

with a suitable base so as to form the compound.

This invention further provides a process for preparing a compound having the structure

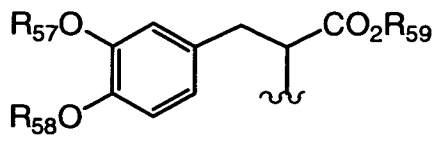


wherein G_3 is C_{1-10} alkylene, C_{2-10} alkenylene, or C_{2-10} alkynylene;

R_{47} is H, CN, or ,

wherein R_{62}, R_{63}, R_{64}, R_{65}, and R_{66} are each, independently, H, halogen, $-NO_2$, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; $-OR_{67}$, $-SR_{67}$, $-OSO_2R_{67}$, or $-NR_{67}R_{68}$,

wherein R_{67} and R_{68} are each, independently, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or unsubstituted or substituted aryl;

R_{48} and R_{49} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; or ,

wherein R_{57} and R_{58} are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, unsubstituted or substituted aryl(C_{1-10})alkyl, or $-SO_2R_{60}$,

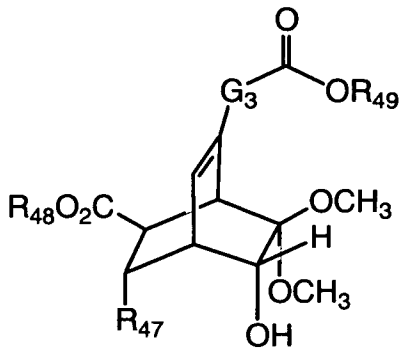
wherein R_{60} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

wherein R_{59} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

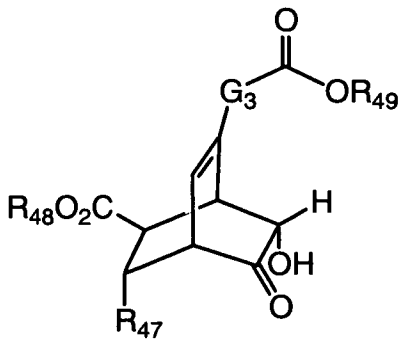
wherein each occurrence of R_{81} is, independently, C_{1-10} alkyl, or unsubstituted or substituted aryl;

comprising:

a) contacting a compound having the structure



with a suitable Bronsted acid so as to form a compound having the structure



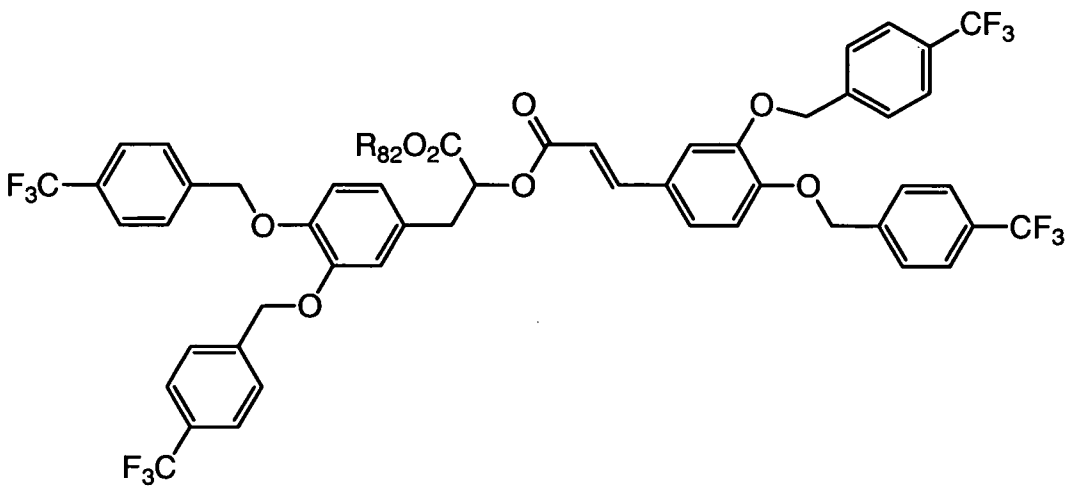
;

b) contacting the product of step a) with a suitable hydride reducing agent;

c) contacting the product of step b) with a suitable silylating agent;

d) contacting the product of step c) with a suitable oxidizing agent so as to form the compound.

This invention provides a process for preparing a compound having the structure



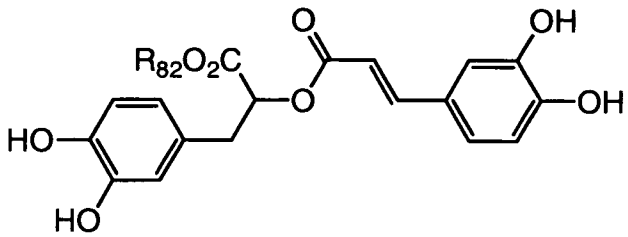
wherein R_{82} is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl;

wherein each occurrence of alkyl, alkylene, alkenyl, alkenylene, alkynyl, or alkynylene is branched or unbranched, unsubstituted or substituted;

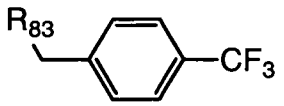
or a salt thereof;

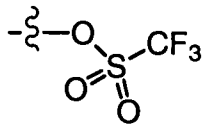
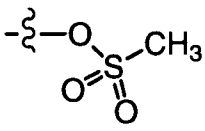
comprising:

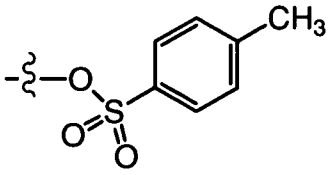
a) contacting a compound having the structure



with a compound having the structure



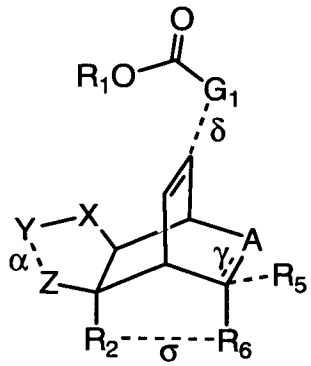
wherein R_{83} is halogen, -OH,  ,  ,



or ;

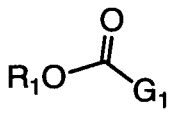
in the presence of a suitable base so as to form the compound.

This invention provides a composition, free of plant extract, comprising a compound having the structure



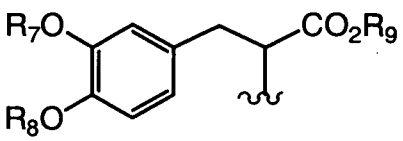
wherein

α, γ, δ and σ are each, independently, present or absent;

wherein when δ is absent,  is absent;

G_1 is C_{1-10} alkylene, C_{2-10} alkenylene, or C_{2-10} alkynylene;

R_1 is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or



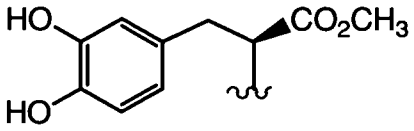
,

wherein R_7 and R_8 are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; or $-SO_2R_{10}$,

wherein R_{10} is C_{1-10} alkyl, or unsubstituted or substituted aryl;

R_9 is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

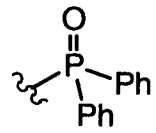
when R_7 and R_8 are H and R_9 is CH_3, then R_1 is

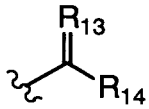


; and

when γ is present; R_5 is absent and A is C-R_4,

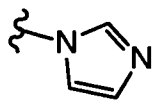
wherein R_4 is H, halogen, or OR_{11},

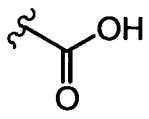
wherein R_{11} is H, C_{1-10} alkyl, $-CH_2SH$, $-BHCH_2CH_3$, $-CH{=}SH$, 

, $-SO_2R_{12}$, 

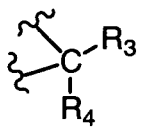
, or $-Si(R_{15})_3$;

wherein R_{12} and each occurrence of R_{15} is C_{1-10} alkyl; or unsubstituted or substituted aryl; and

R_{13} is S or O; and R_{14} is $-SCH_3$, 

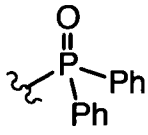
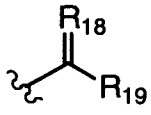
, or 

; and

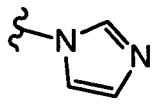
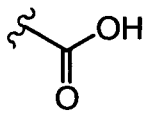
when γ is absent; R_5 is present and A is a direct bond or 

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wherein R_3 and R_4 are each, independently, H, halogen, or OR_{16};

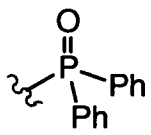
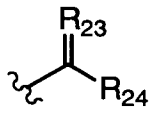
wherein R_{16} is H, C_{1-10} alkyl, $-CH_2SH$, $-BHCH_2CH_3$, $-CH{=}SH$, , $-SO_2R_{17}$, , or $-Si(R_{20})_3$;

wherein R_{17} and each occurrence of R_{20} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

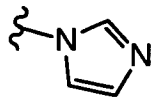
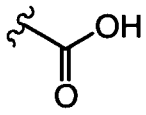
R_{18} is S or O; and R_{19} is $-SCH_3$, , or ; or

R_3 and R_4 taken together form =O; and

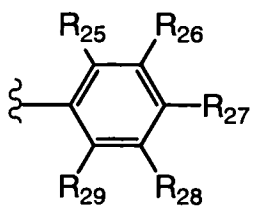
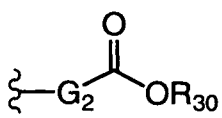
wherein R_5 is H, halogen, or OR_{21},

wherein R_{21} is H, C_{1-10} alkyl, $-CH_2SH$, $-BHCH_2CH_3$, $-CH{=}SH$, , $-SO_2R_{22}$, , or $-Si(R_{25})_3$,

wherein R_{22} and each occurrence of R_{25} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

R_{23} is S or O; and R_{24} is $-SCH_3$, , or ; and

when σ is absent;

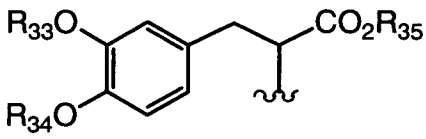
R_2 is H, , or ;

wherein R_{25}, R_{26}, R_{27}, R_{28}, and R_{29} are each, independently, H, halogen, $-NO_2$, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; $-OR_{31}$, $-SR_{31}$, $-OSO_2R_{31}$, or $-NR_{31}R_{32}$,

wherein R_{31} and R_{32} are each, independently, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or unsubstituted or substituted aryl;

wherein G_2 is C_{1-10} alkylene, C_{2-10} alkenylene, or C_{2-10} alkynylene; and

R_{30} is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or



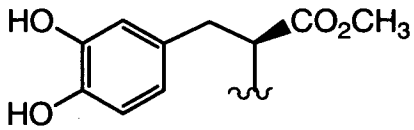
,

wherein R_{33} and R_{34} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; or $-SO_2R_{36}$,

wherein R_{36} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

wherein R_{35} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

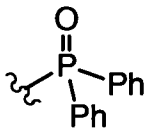
when R_{33} and R_{34} are H and R_{35} is CH_3, then R_{30} is



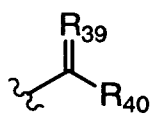
; and

R_6 is H, halogen, or OR_{37};

wherein R_{37} is H, C_{1-10} alkyl, $-CH_2SH$, $-BHCH_2CH_3$, $-CH=SH$,



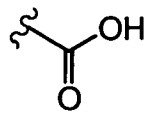
, $-SO_2R_{38}$,



, or $-Si(R_{41})_3$;

wherein R_{38} and each occurrence of R_{41} is C_{1-10} alkyl; or unsubstituted or substituted aryl;

R_{39} is S or O; and R_{40} is $-SCH_3$; -NH-aryl,

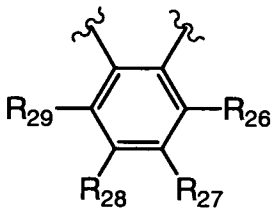


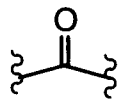
heteroaryl, heterocyclyl; or ; or

R_5 when present and R_6 taken together form =O; or

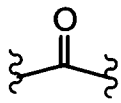
R_4 joined to R_6 form a 5-membered heterocyclic ring; and

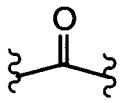
when σ is present;

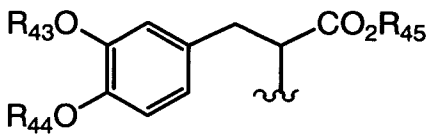


R_2 is ; and R_6 is a direct bond or ;

and

wherein X is a direct bond, , or $C(OMe)_2$;

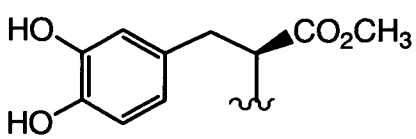
Y is H or OR_{42}; or when α is present, Y is ;

wherein R_{42} is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or ,

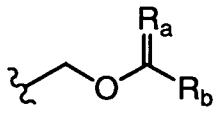
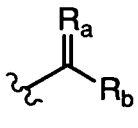
wherein R_{43} and R_{44} are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; or $-SO_2R_{46}$,

wherein R_{46} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

R_{45} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and when R_{43} and R_{44} are H and R_{45} is CH_3,

then R_{42} is  ; or

wherein each occurrence of alkyl, alkylene, alkenyl, alkenylene, alkynyl, or alkynylene is branched or unbranched, unsubstituted or substituted;

Z is H, CN,  or ,

wherein R_a is S or O; R_b is -O-(C_1-C_{10})alkyl, -O-(C_2-C_{10})alkenyl, heterocyclyl, or heteroaryl; or

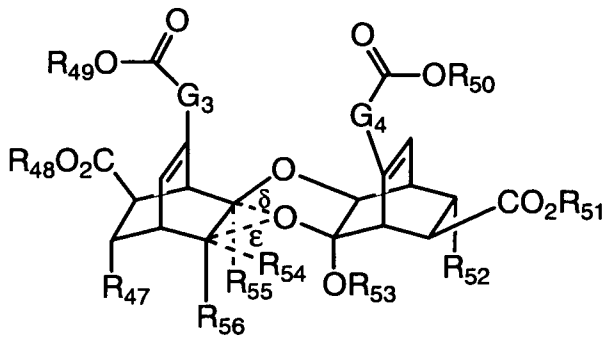
when α is present, Z is -CH=CH-;

and

when α is present, R_1 is other than methyl;

or a salt thereof.

This invention provides a composition, free of plant extract, comprising a compound having the structure



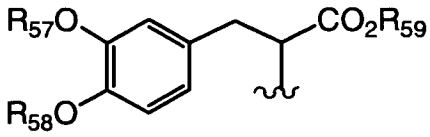
wherein ε and δ are present or absent;

wherein R_{54} and R_{55} are present or absent; and

when ε is present; δ and R_{54} are absent, and R_{55} is present; and

when δ is present; ε and R_{55} are absent, and R_{54} is present;

wherein G_3 and G_4 are each, independently, is C_{1-10} alkylene, C_{2-10} alkenylene, or C_{2-10} alkynylene;

R_{48}, R_{49}, R_{50}, and R_{51} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; or 

,

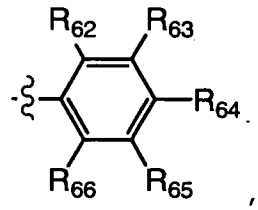
wherein R_{57} and R_{58} are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, unsubstituted or substituted aryl(C_{1-10})alkyl, or $-SO_2R_{60}$,

wherein R_{60} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

wherein R_{59} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

wherein R_{53} is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, unsubstituted or substituted aryl(C_{1-10})alkyl, or $-SO_2R_{61}$,

wherein R_{61} is C_{1-10} alkyl, or unsubstituted or substituted aryl;

R_{47} and R_{52} are each H, CN, or 

,

wherein R_{62}, R_{63}, R_{64}, R_{65}, and R_{66} are each, independently, H, halogen, $-NO_2$, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; $-OR_{67}$, $-SR_{67}$, $-OSO_2R_{67}$, or $-NR_{67}R_{68}$,

wherein R_{67} and R_{68} are each, independently, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or unsubstituted or substituted aryl; and

wherein R_{54} when present, R_{55} when present, and R_{56} are each, independently, H or OR_{69},

wherein R_{69} is H or C_{1-10} alkyl; or

wherein each occurrence of alkyl, alkylene, alkenyl, alkenylene, alkynyl, alkynylene is branched or unbranched, unsubstituted or substituted;

or a salt thereof.

This invention provides a method of treating a cell expressing a mutant human huntingtin gene, wherein the expression of the mutant huntingtin gene results in a huntingtin protein having a polyglutamine N-terminal, comprising contacting the cell with any of the compositions described herein so as to treat the cell.

This invention provides a method of treating a cell expressing a mutant human huntingtin gene, wherein the expression of the mutant huntingtin gene results in a huntingtin protein having a polyglutamine N-terminal, comprising contacting the cell with any of the compounds described herein so as to treat the cell.

This invention provides a method of reducing cell death in a population of cells expressing a mutant human huntingtin gene, wherein the expression of the mutant huntingtin gene results in a huntingtin protein having a polyglutamine N-terminal, comprising contacting the population of cells with any of the compositions described herein so as to reduce cell death in the population of cells.

This invention provides a method of reducing cell death in a population of cells expressing a mutant human huntingtin gene, wherein the expression of the mutant huntingtin gene results in a huntingtin protein having a polyglutamine N-terminal, comprising contacting the population of cells with any of the compounds described herein so as to reduce cell death in the population of cells.

Brief Description of the Figures

Figure 1. Structures of helicterin A and B (**1** and **2**) and related natural products (**3-6**).

Figure 2. Proposed biogenetic routes to helicterin A and B (**1** and **2**). "R" denotes a general functional group.

Figure 3. Preliminary efforts to achieve their core synthesis.
Reagents and conditions: (a) $PhI(OAc)_2$ (1.05 equiv), $MeOH:CH_2Cl_2$ (6:1), 25 °C, 14 h, 87%; (b) $PhI(OAc)_2$ (1.1 equiv), $MeOH:CH_2Cl_2$ (5:1), 25 °C, 14 h, 97%; (c) acrylonitrile (100 equiv), toluene, 80 °C, 48 h, 43%; (d) AgOAc (1.1 equiv), toluene, 60 °C, 20 h, 20%.

Figure 4. Proposed use of a unique dimeric form of rosmarinic acid to overcome laboratory issues of chemoselectivity as observed with Nature's starting material.

Figure 5. Model studies to create the helisorin core.
Reagents and conditions: (a) 13 (6.7 equiv), mesitylene, 220 °C, 83% b.r.s.m.; (b) BBr_3 (1.0 M in CH_2Cl_2, 6.0 equiv), -78 °C, 1 h, 86%; (c) $BF_3 \cdot OEt_2$ (6.0 equiv), CH_2Cl_2, 0->25 °C, 16 h, 82%; (d) $BF_3 \cdot OEt_2$ (20 equiv), CH_2Cl_2, 25 °C, 16 h, 80%; (e) $BF_3 \cdot OEt_2$ (6.0 equiv), CH_2Cl_2, 0->25 °C, 16 h, 53%.

Figure 6. Synthesis of building blocks **27**, **28**, and **32** from rosmarinic acid (**5**).
Reagents and conditions: (a) $TMSCHN_2$ (0.95 equiv), THF:MeOH (10:1), -78 °C, 1 h; (b) p-CF_3-BnBr (6.0 equiv), K_2CO_3 (6.0 equiv), KI (catalytic), 60 °C, 8 h, 84% overall; (c) NaOMe

(1.0 equiv), MeOH:CH_2Cl_2 (1:1), 25 °C, 2 h, 92% 28, 90% 29; (d) 31 (2.0 equiv), EDC•HCl (2.0 equiv), 4-DMAP (1.0 equiv), CH_2Cl_2, 25 °C, 3 h; (e) TBAF (2.0 equiv), AcOH, THF, 0 °C, 10 min, 94% overall; (f) TBSCl (2.5 equiv), i-Pr_2NEt (3.0 equiv), CH_2Cl_2, 25 °C, 14 h, then K_2CO_3 (excess), H_2O, THF, 25 °C, 2 h, 99%.

Figure 7. Total synthesis of helisorin (**3**).
Reagents and conditions: (a) $PhI(OAc)_2$ (1.05 equiv), MeOH:CH_2Cl_2 (5:1), 25 °C, 14 h, 99%; (b) 27 (6.7 equiv), mesitylene, 220 °C, 30 min, 71% b.r.s.m.; (c) $BF_3•OEt_2$ (30 equiv), H_2O (5.0 equiv), C_6H_6, 0->25 °C, 16 h, 82% b.r.s.m.; (d) BBr_3 (1.0 M in CH_2Cl_2, 20 equiv), CH_2Cl_2, -78 °C, 30 min, 77%.

Figure 8. Synthesis of model dimerization percursors **40** and 42 from Diels-Alder product **21**.
Reagents and conditions: (a) $NaBH_4$ (excess), MeOH:CH_2Cl_2, 0 °C, 1 h, 99%; (b) 0.2 M HCl, H_2O, toluene, 0 °C, 20 h, 86%; (c) 0.5 M HCl, H_2O, THF, 25 °C, 14 h, 84%; (d) $Me_4NBH(OAc)3$ (5.0 equiv), MeCN:AcOH (10:1), 25 °C, 5 h, 75%; (e) TBSOTf (1.0 equiv), Et_3N (5.0 equiv), CH_2Cl_2, -78->25 °C, 1 h; (f) Dess-Martin periodinane (1.5 equiv), $NaHCO_3$ (10 equiv), CH_2Cl_2, 25 °C, 1 h, 94% over 2 steps; (g) TBAF (1.0 M in THF, 2.0 equiv), AcOH (2.0 equiv), THF, 25 °C, 2 h, 76% b.r.s.m.; (h) 0.4 M HCl, MeOH:$CH(OMe)_3$ (4:1), 25 °C, 14 h, 93%.

Figure 9. Model studies directed towards the synthesis of the helicterin core via attempted dimerizations of **40** and **42**.

Reagents and conditions: (a) HCl (g), 100 °C, 45 min, 99%; (b) 160 °C, 4 h, 32% b.r.s.m.;(c) KHMDS (0.5 M in toluene, 1.3 equiv), Tf_2NPh (2.6 equiv), THF, -78 °C, 10 min, 74%; (d) $BF_3 \cdot OEt_2$ (4.0 equiv), CH_2Cl_2, 0 °C, 30 min, 79%. (e) NaH (10 equiv), THF, 25 °C, 20 min, 99%.

Figure 10. Total synthesis of helicterin B (**2**).
Reagents and conditions: (a) $NaBH_4$ (1.5 equiv), MeOH:THF (4:1), -30 °C, 1 h; (b) 0.5 M HCl, MeCN:H_2O (100:1), 25 °C, 14 h, 56% overall; (c) $Me_4NBH(OAc)_3$ (5.0 equiv), MeCN:AcOH (80:1), 25 °C, 28 h; (d) TBSOTf (1.05 equiv), Et_3N (5.0 equiv), CH_2Cl_2, -78 °C, 1 h; (e) Dess-Martin periodinane (1.5 equiv), $NaHCO_3$ (excess), CH_2Cl_2, 25 °C, 1 h; (f) 0.4 M HCl MeOH:$CH(OMe)_3$ (4:1), 25 °C, 14 h, 43% overall; (g) $BF_3 \cdot OEt_2$ (8.0 equiv), CH_2Cl_2, 0 °C, 30 min, 67%; (h) BBr_3 (1.0 M in CH_2Cl_2, 20 equiv), CH_2Cl_2, -78 °C, 45 min, 76%.

Figure 11. Total synthesis of helisterculin A (**4**).
Reagents and conditions: (a) 28 (6.7 equiv), mesitylene, 220 °C, 30 min, 44% (78% b.r.s.m.); (b) $NaBH_4$ (1.5 equiv), MeOH:THF (4:1), 0 °C, 1 h, 79%; (c) 0.2 M HCl, MeCN:H_2O (15:1), 25 °C, 2 h, 74%; (d) BBr_3 (1.0 M in CH_2Cl_2, 8.0 equiv), CH_2Cl_2, -78 °C, 30 min, 92%.

Figure 12. Functionalization of the C(4') alcohol.
Reagents and conditions: (a) thiocarbonyl diimidazole (6.0 equiv), 4-DMAP (1.5 equiv), CH_2Cl_2, 40 °C, 48 h, 91%; (b) Et_3B (1.0 M in hexanes, 5.0 equiv), n-Bu_3SnH (5.0 equiv), O_2 (excess), CH_2Cl_2, 0 °C, 2 h, 72%; (c) NaH (5.0 equiv), THF:CS_2:MeI (4:1:1), 40 °C, 15 h, 94%; (d) AIBN (4.0 equiv), n-Bu_3SnH (6.0 equiv), PhSeSePh (4.0 equiv), toluene, 80 °C, 15 min., 84%; (e) 0.7 M HCl, THF, 25 °C, 3 h, 66%; (f) AIBN

(1.2 equiv), n-Bu_3SnH (3.0 equiv), PhSeSePh (2.0 equiv), toluene, 80 °C, 3 h, 72% b.r.s.m.; (g) Et_3B (6.0 equiv), O2 (excess), CH_2Cl_2, 25 °C, 48 h, 75% b.r.s.m.

Figure 13. Further functionalization of the C(4') alcohol and other products.
Reagents and conditions: (a) $Cl(PO)Ph_2$ (5.0 equiv), Et_3N (5.0 equiv), DCE:THF (1:1), 60 °C, 48 h, 89%; (b) MsCl (20 equiv), Et_3N (15 equiv), THF, 25 °C, 6 h, 20 %; (c) oxalyl chloride (2.0 equiv), Et_3N (2.0 equiv), 4-DMAP (catalytic), CH_2Cl_2, 2 h, then 5% HCl, H_2O, 1 h, 25 °C, 98%; (d) Tf_2O (4.0 equiv), pyridine, 0->35 °C, 2 h, 22% 61 and 46% 62 b.r.s.m.; (e) DIBAOi-Pr (0.93 M in toluene, 1.1 equiv), toluene, 60 °C, 48 h, 46% b.r.s.m.

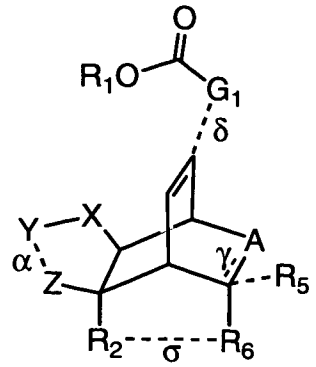
Figure 14. Compound **51** suppressed cell death in PC12 cells that were transfected with the human huntingtin gene containing mutant polyglutamine repeats, flanked by EGFP. Protein expression was induced by tebufenozide and ecdysone analogs. Compound **51** had no effect on uninduced cells.

Figures 15-20. Results of compounds **64-80** screened against PC12 cells that were transfected with the human huntingtin gene containing mutant polyglutamine repeats.

Figure 21. Biomek setup for triplicate addition of compound and cell media to assay plates

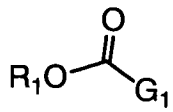
Detailed Description of the Invention

This invention provides a compound having the structure



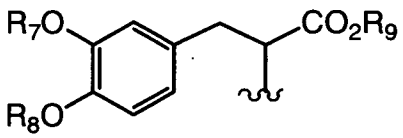
wherein

α, γ, δ and σ are each, independently, present or absent;

wherein when δ is absent,  is absent;

G_1 is C_{1-10} alkylene, C_{2-10} alkenylene, or C_{2-10} alkynylene;

R_1 is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or



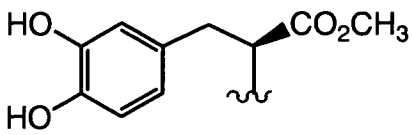
,

wherein R_7 and R_8 are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; or $-SO_2R_{10}$,

wherein R_{10} is C_{1-10} alkyl, or unsubstituted or substituted aryl;

R_9 is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

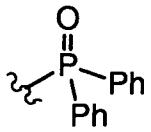
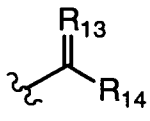
when R_7 and R_8 are H and R_9 is CH_3, then R_1 is



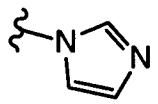
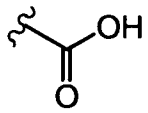
; and

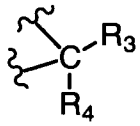
when γ is present; R_5 is absent and A is C-R_4,

wherein R_4 is H, halogen, or OR_{11},

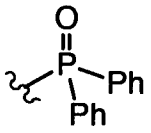
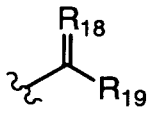
wherein R_{11} is H, C_{1-10} alkyl, $-CH_2SH$, $-BHCH_2CH_3$, -CH=SH, , $-SO_2R_{12}$, , or $-Si(R_{15})_3$;

wherein R_{12} and each occurrence of R_{15} is C_{1-10} alkyl; or unsubstituted or substituted aryl; and

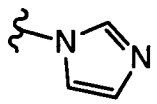
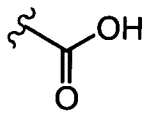
R_{13} is S or O; and R_{14} is $-SCH_3$, , or ; and

when γ is absent; R_5 is present and A is a direct bond or ;

wherein R_3 and R_4 are each, independently, H, halogen, or OR_{16};

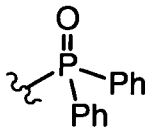
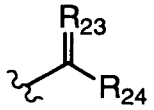
wherein R_{16} is H, C_{1-10} alkyl, $-CH_2SH$, $-BHCH_2CH_3$, -CH=SH, , $-SO_2R_{17}$, , or $-Si(R_{20})_3$;

wherein R_{17} and each occurrence of R_{20} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

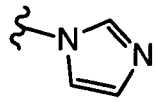
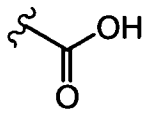
R_{18} is S or O; and R_{19} is $-SCH_3$, , or ; or

R_3 and R_4 taken together form =O; and

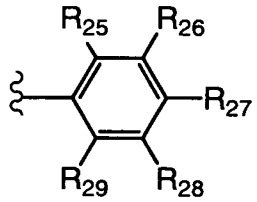
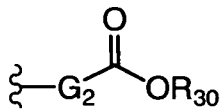
wherein R_5 is H, halogen, or OR_{21},

wherein R_{21} is H, C_{1-10} alkyl, $-CH_2SH$, $-BHCH_2CH_3$, $-CH=SH$, , $-SO_2R_{22}$, , or $-Si(R_{25})_3$,

wherein R_{22} and each occurrence of R_{25} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

R_{23} is S or O; and R_{24} is $-SCH_3$, , or ; and

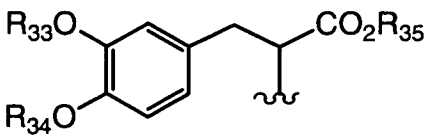
when σ is absent;

R_2 is H, , or ;

wherein R_{25}, R_{26}, R_{27}, R_{28}, and R_{29} are each, independently, H, halogen, $-NO_2$, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; $-OR_{31}$, $-SR_{31}$, $-OSO_2R_{31}$, or $-NR_{31}R_{32}$,

wherein R_{31} and R_{32} are each, independently, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or unsubstituted or substituted aryl;

wherein G_2 is C_{1-10} alkylene, C_{2-10} alkenylene, or C_{2-10} alkynylene; and

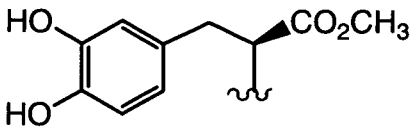
R_{30} is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or ,

wherein R_{33} and R_{34} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; or $-SO_2R_{36}$,

wherein R_{36} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

wherein R_{35} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

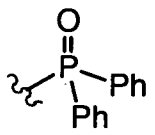
when R_{33} and R_{34} are H and R_{35} is CH_3, then R_{30} is

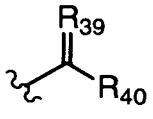


; and

R_6 is H, halogen, or OR_{37};

wherein R_{37} is H, C_{1-10} alkyl, $-CH_2SH$, $-BHCH_2CH_3$, $-CH=SH$,

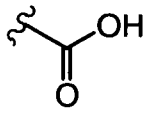


, $-SO_2R_{38}$, 

, or $-Si(R_{41})_3$;

wherein R_{38} and each occurrence of R_{41} is C_{1-10} alkyl; or unsubstituted or substituted aryl;

R_{39} is S or O; and R_{40} is $-SCH_3$; -NH-aryl,

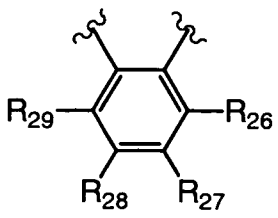
heteroaryl, heterocyclyl; or 

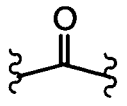
; or

R_5 when present and R_6 taken together form =O; or

R_4 joined to R_6 form a 5-membered heterocyclic ring; and

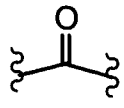
when σ is present;

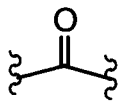
R_2 is 

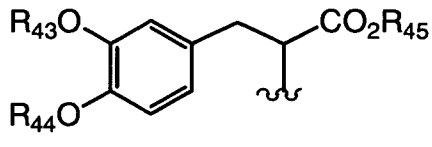
; and R_6 is a direct bond or 

;

and

wherein X is a direct bond, , or $C(OMe)_2$;

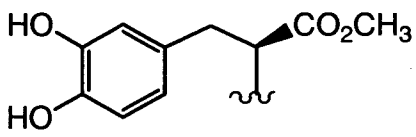
Y is H or OR_{42}; or when α is present, Y is ;

wherein R_{42} is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or ,

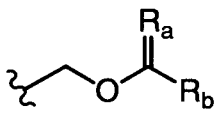
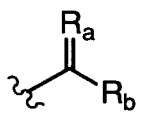
wherein R_{43} and R_{44} are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; or $-SO_2R_{46}$,

wherein R_{46} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

R_{45} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and when R_{43} and R_{44} are H and R_{45} is CH_3,

then R_{42} is ; or

wherein each occurrence of alkyl, alkylene, alkenyl, alkenylene, alkynyl, or alkynylene is branched or unbranched, unsubstituted or substituted;

Z is H, CN,  or ,

wherein R_a is S or O; R_b is $-O-(C_1-C_{10})$alkyl, $-O-(C_2-C_{10})$alkenyl, heterocyclyl, or heteroaryl; or

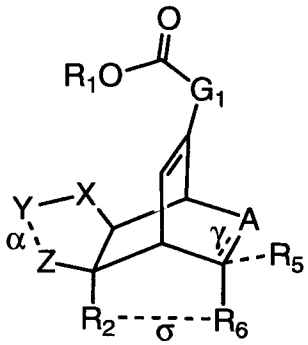
when α is present, Z is -CH=CH-;

and

when α is present, R_1 is other than methyl;

or a salt thereof.

In an embodiment, the compound has the structure

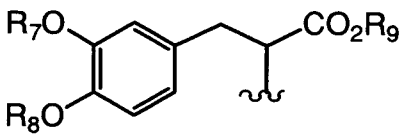


wherein

α, γ, and σ are each, independently, present or absent;

G_1 is C_{1-10} alkylene, C_{2-10} alkenylene, or C_{2-10} alkynylene;

R_1 is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or



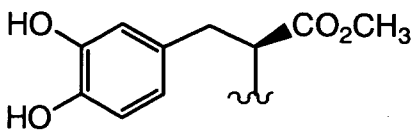
,

wherein R_7 and R_8 are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; or $-SO_2R_{10}$,

wherein R_{10} is C_{1-10} alkyl, or unsubstituted or substituted aryl;

R_9 is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

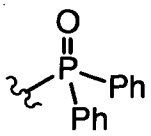
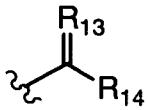
when R_7 and R_8 are H and R_9 is CH_3, then R_1 is



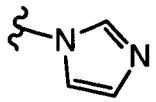
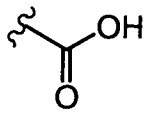
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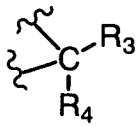
when γ is present; R_5 is absent and A is C-R_4,

wherein R_4 is H, halogen, or OR_{11},

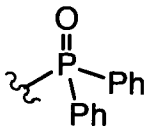
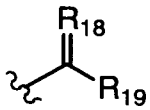
wherein R_{11} is H, C_{1-10} alkyl, $-CH_2SH$, $-BHCH_2CH_3$, $-CH{=}SH$, , $-SO_2R_{12}$, , or $-Si(R_{15})_3$;

wherein R_{12} and each occurrence of R_{15} is C_{1-10} alkyl; or unsubstituted or substituted aryl; and

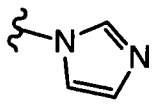
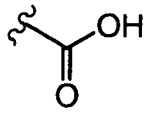
R_{13} is S or O; and R_{14} is $-SCH_3$, , or ; and

when γ is absent; R_5 is present and A is a direct bond or ;

wherein R_3 and R_4 are each, independently, H, halogen, or OR_{16};

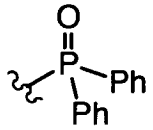
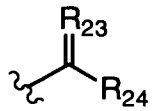
wherein R_{16} is H, C_{1-10} alkyl, $-CH_2SH$, $-BHCH_2CH_3$, $-CH{=}SH$, , $-SO_2R_{17}$, , or $-Si(R_{20})_3$;

wherein R_{17} and each occurrence of R_{20} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

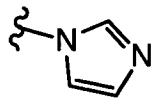
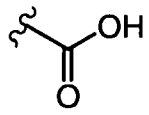
R_{18} is S or O; and R_{19} is $-SCH_3$, , or ; or

R_3 and R_4 taken together form =O; and

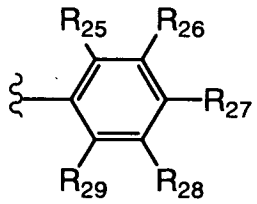
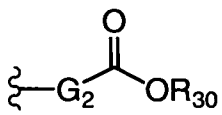
wherein R_5 is H, halogen, or OR_{21},

wherein R_{21} is H, C_{1-10} alkyl, $-CH_2SH$, $-BHCH_2CH_3$, $-CH=SH$, , $-SO_2R_{22}$, , or $-Si(R_{25})_3$,

wherein R_{22} and each occurrence of R_{25} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

R_{23} is S or O; and R_{24} is $-SCH_3$, , or ; and

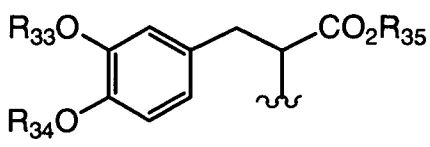
when σ is absent;

R_2 is H, , or ;

wherein R_{25}, R_{26}, R_{27}, R_{28}, and R_{29} are each, independently, H, halogen, $-NO_2$, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; $-OR_{31}$, $-SR_{31}$, $-OSO_2R_{31}$, or $-NR_{31}R_{32}$,

wherein R_{31} and R_{32} are each, independently, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or unsubstituted or substituted aryl;

wherein G_2 is C_{1-10} alkylene, C_{2-10} alkenylene, or C_{2-10} alkynylene; and

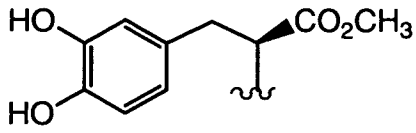
R_{30} is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or ,

wherein R_{33} and R_{34} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; or $-SO_2R_{36}$,

wherein R_{36} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

wherein R_{35} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

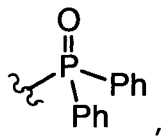
when R_{33} and R_{34} are H and R_{35} is CH_3, then R_{30} is



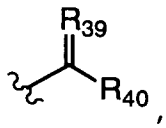
; and

R_6 is H, halogen, or OR_{37};

wherein R_{37} is H, C_{1-10} alkyl, $-CH_2SH$, $-BHCH_2CH_3$, $-CH{=}SH$,



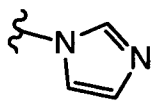
, $-SO_2R_{38}$,



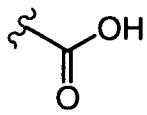
, or $-Si(R_{41})_3$;

wherein R_{38} and each occurrence of R_{41} is C_{1-10} alkyl; or unsubstituted or substituted aryl;

R_{39} is S or O; and R_{40} is $-SCH_3$;



; or

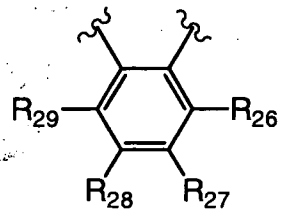
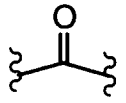


; or

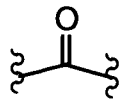
R_5 when present and R_6 taken together form =O; or

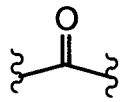
R_4 joined to R_6 form a 5-membered heterocyclic ring; and

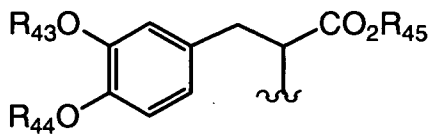
when σ is present;

R_2 is  ; and R_6 is a direct bond or ;

and

wherein X is a direct bond, , or $C(OMe)_2$;

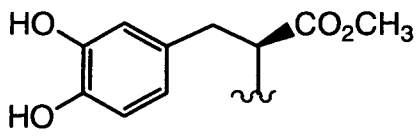
Y is H or OR_{42}; or when α is present, Y is ;

wherein R_{42} is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or ,

wherein R_{43} and R_{44} are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; or $-SO_2R_{46}$,

wherein R_{46} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

R_{45} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and when R_{43} and R_{44} are H and R_{45} is CH_3,

then R_{42} is  ; or

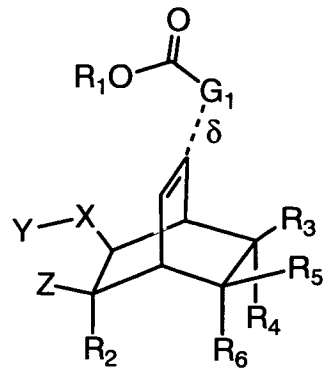
wherein each occurrence of alkyl, alkylene, alkenyl, alkenylene, alkynyl, or alkynylene is branched or unbranched, unsubstituted or substituted;

Z is H or CN; or when α is present, Z is -CH=CH-; and

when α is present, R_1 is other than methyl;

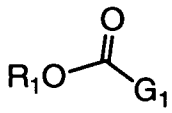
or a salt thereof.

In an embodiment, the compound has the structure

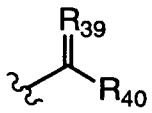


wherein

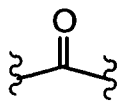
δ is present or absent;

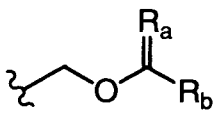
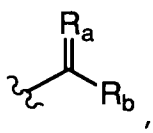
wherein when δ is absent,  is absent;

R_6 is OR_{37};

wherein R_{37} is ;

wherein R_{39} is S or O; and R_{40} is -NH-aryl, heteroaryl, heterocyclyl; or

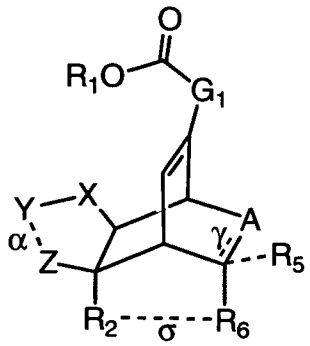
X is a direct bond or ;

Z is H, CN,  or ,

wherein R_a is S or O; R_b is -O-(C_1-C_{10})alkyl, -O-(C_2-C_{10})alkenyl, heterocyclyl, or heteroaryl; or

or a salt thereof.

In an embodiment, the compound has the structure

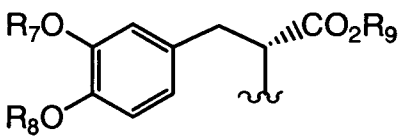


wherein

α, γ, and σ are each, independently, present or absent;

G_1 is C_{1-10} alkylene, C_{2-10} alkenylene, or C_{2-10} alkynylene;

R_1 is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or



wherein R_7 and R_8 are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; or $-SO_2R_{10}$,

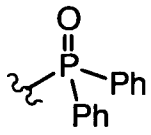
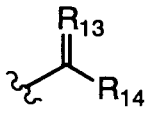
wherein R_{10} is C_{1-10} alkyl, or unsubstituted or substituted aryl;

R_9 is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

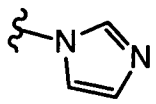
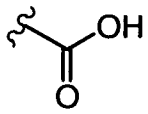
at least one of R_7 and R_8 is other than H; and

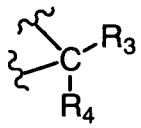
when γ is present; R_5 is absent and A is C-R_4,

wherein R_4 is H, halogen, or OR_{11},

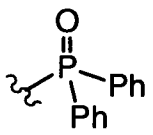
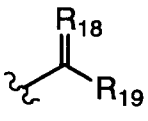
wherein R_{11} is H, C_{1-10} alkyl, $-CH_2SH$, $-BHCH_2CH_3$, $-CH{=}SH$, , $-SO_2R_{12}$, , or $-Si(R_{15})_3$;

wherein R_{12} and each occurrence of R_{15} is C_{1-10} alkyl; or unsubstituted or substituted aryl; and

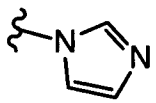
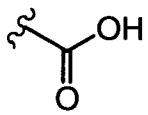
R_{13} is S or O; and R_{14} is $-SCH_3$, , or ; and

when γ is absent; R_5 is present and A is a direct bond or ;

wherein R_3 and R_4 are each, independently, H, halogen, or OR_{16};

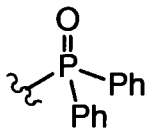
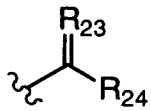
wherein R_{16} is H, C_{1-10} alkyl, $-CH_2SH$, $-BHCH_2CH_3$, $-CH{=}SH$, , $-SO_2R_{17}$, , or $-Si(R_{20})_3$;

wherein R_{17} and each occurrence of R_{20} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

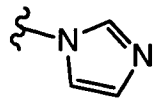
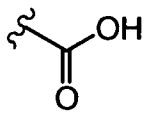
R_{18} is S or O; and R_{19} is $-SCH_3$, , or ; or

R_3 and R_4 taken together form =O; and

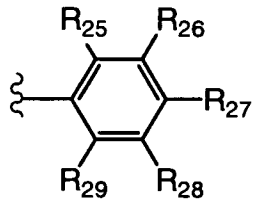
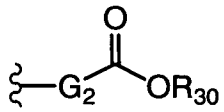
wherein R_5 is H, halogen, or OR_{21},

wherein R_{21} is H, C_{1-10} alkyl, $-CH_2SH$, $-BHCH_2CH_3$, $-CH{=}SH$, , $-SO_2R_{22}$, , or $-Si(R_{25})_3$,

wherein R_{22} and each occurrence of R_{25} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

R_{23} is S or O; and R_{24} is $-SCH_3$, , or ; and

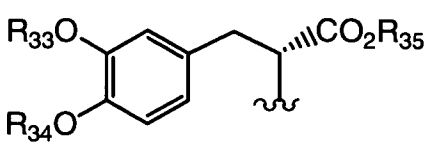
when σ is absent;

R_2 is H, , or ;

wherein R_{25}, R_{26}, R_{27}, R_{28}, and R_{29} are each, independently, H, halogen, $-NO_2$, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; $-OR_{31}$, $-SR_{31}$, $-OSO_2R_{31}$, or $-NR_{31}R_{32}$,

wherein R_{31} and R_{32} are each, independently, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or unsubstituted or substituted aryl;

wherein G_2 is C_{1-10} alkylene, C_{2-10} alkenylene, or C_{2-10} alkynylene; and

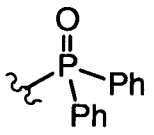
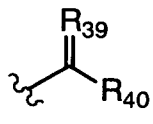
R_{30} is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or 

wherein R_{33} and R_{34} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; or $-SO_2R_{36}$,

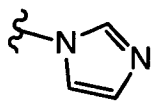
wherein R_{36} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and at least one of R_{33} and R_{34} is other than H; and

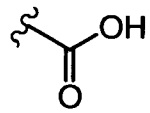
wherein R_{35} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

R_6 is H, halogen, or OR_{37};

wherein R_{37} is H, C_{1-10} alkyl, $-CH_2SH$, $-BHCH_2CH_3$, $-CH=SH$, , $-SO_2R_{38}$, , or $-Si(R_{41})_3$;

wherein R_{38} and each occurrence of R_{41} is C_{1-10} alkyl; or unsubstituted or substituted aryl;

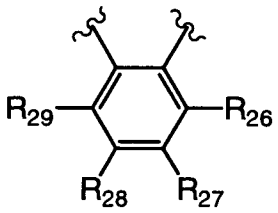
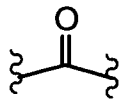
R_{39} is S or O; and R_{40} is $-SCH_3$; ; or

; or

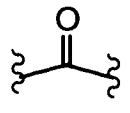
R_5 when present and R_6 taken together form =O; or

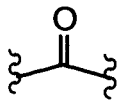
R_4 joined to R_6 form a 5-membered heterocyclic ring; and

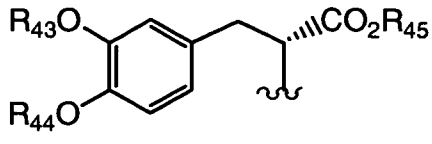
when σ is present;

R_2 is ; and R_6 is a direct bond or ;

and

wherein X is a direct bond, , or $C(OMe)_2$;

Y is H or OR_{42}; or when α is present, Y is ;

wherein R_{42} is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or ,

wherein R_{43} and R_{44} are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; or $-SO_2R_{46}$,

wherein R_{46} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

R_{45} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and at least one of R_{43} and R_{44} is other than H; or

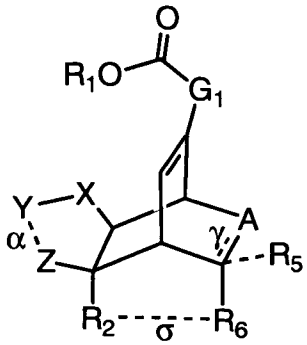
wherein each occurrence of alkyl, alkylene, alkenyl, alkenylene, alkynyl, or alkynylene is branched or unbranched, unsubstituted or substituted;

Z is H or CN; or when α is present, Z is -CH=CH-; and

when α is present, R_1 is other than methyl;

or a salt thereof.

In an embodiment, the compound has the structure

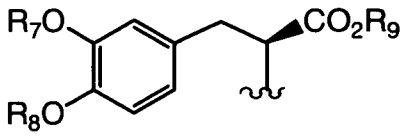


wherein

α, γ, and σ are each, independently, present or absent;

G_1 is C_{1-10} alkylene, C_{2-10} alkenylene, or C_{2-10} alkynylene;

R_1 is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or



,

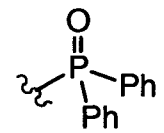
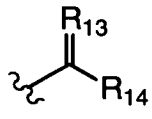
wherein R_7 and R_8 are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; or $-SO_2R_{10}$,

wherein R_{10} is C_{1-10} alkyl, or unsubstituted or substituted aryl;

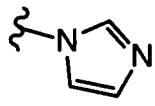
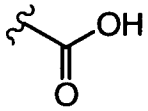
R_9 is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

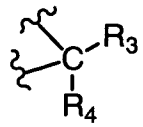
when γ is present; R_5 is absent and A is C-R_4,

wherein R_4 is H, halogen, or OR_{11},

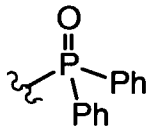
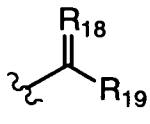
wherein R_{11} is H, C_{1-10} alkyl, $-CH_2SH$, $-BHCH_2CH_3$, $-CH{=}SH$, , $-SO_2R_{12}$, , or $-Si(R_{15})_3$;

wherein R_{12} and each occurrence of R_{15} is C_{1-10} alkyl; or unsubstituted or substituted aryl; and

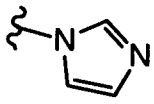
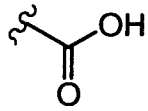
R_{13} is S or O; and R_{14} is $-SCH_3$, , or ; and

when γ is absent; R_5 is present and A is a direct bond or ;

wherein R_3 and R_4 are each, independently, H, halogen, or OR_{16};

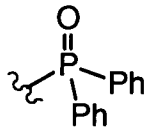
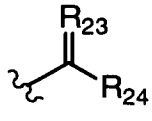
wherein R_{16} is H, C_{1-10} alkyl, $-CH_2SH$, $-BHCH_2CH_3$, $-CH{=}SH$, , $-SO_2R_{17}$, , or $-Si(R_{20})_3$;

wherein R_{17} and each occurrence of R_{20} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

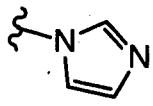
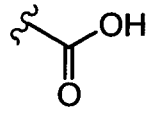
R_{18} is S or O; and R_{19} is $-SCH_3$, , or ; or

R_3 and R_4 taken together form =O; and

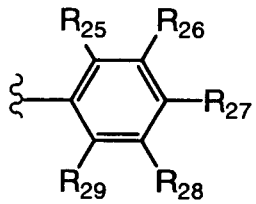
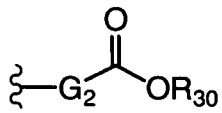
wherein R_5 is H, halogen, or OR_{21},

wherein R_{21} is H, C_{1-10} alkyl, $-CH_2SH$, $-BHCH_2CH_3$, $-CH{=}SH$, , $-SO_2R_{22}$, , or $-Si(R_{25})_3$,

wherein R_{22} and each occurrence of R_{25} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

R_{23} is S or O; and R_{24} is $-SCH_3$, , or ; and

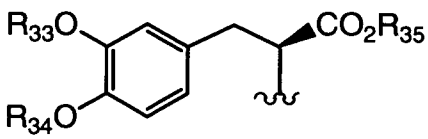
when σ is absent;

R_2 is H, , or ;

wherein R_{25}, R_{26}, R_{27}, R_{28}, and R_{29} are each, independently, H, halogen, $-NO_2$, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; $-OR_{31}$, $-SR_{31}$, $-OSO_2R_{31}$, or $-NR_{31}R_{32}$,

wherein R_{31} and R_{32} are each, independently, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or unsubstituted or substituted aryl;

wherein G_2 is C_{1-10} alkylene, C_{2-10} alkenylene, or C_{2-10} alkynylene; and

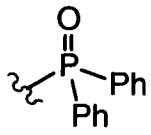
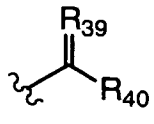
R_{30} is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or ,

wherein R_{33} and R_{34} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; or $-SO_2R_{36}$,

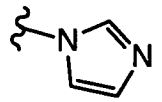
wherein R_{36} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

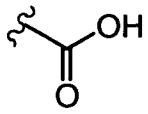
wherein R_{35} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

R_6 is H, halogen, or OR_{37};

wherein R_{37} is H, C_{1-10} alkyl, $-CH_2SH$, $-BHCH_2CH_3$, $-CH=SH$, , $-SO_2R_{38}$, , or $-Si(R_{41})_3$;

wherein R_{38} and each occurrence of R_{41} is C_{1-10} alkyl; or unsubstituted or substituted aryl;

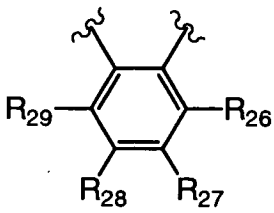
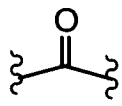
R_{39} is S or O; and R_{40} is $-SCH_3$; ; or

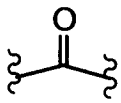
; or

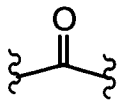
R_5 when present and R_6 taken together form =O; or

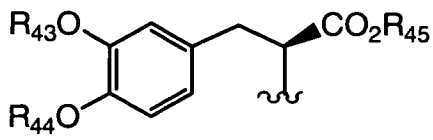
R_4 joined to R_6 form a 5-membered heterocyclic ring; and

when σ is present;

R_2 is ; and R_6 is a direct bond or ; and

wherein X is a direct bond, , or $C(OMe)_2$;

Y is H or OR_{42}; or when α is present, Y is ;

wherein R_{42} is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or 

wherein R_{43} and R_{44} are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; or $-SO_2R_{46}$,

wherein R_{46} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

R_{45} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; or

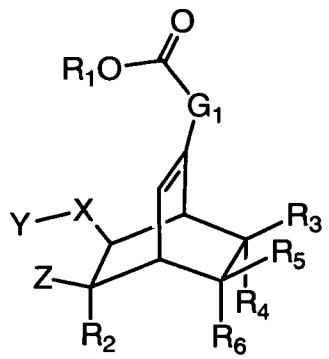
wherein each occurrence of alkyl, alkylene, alkenyl, alkenylene, alkynyl, or alkynylene is branched or unbranched, unsubstituted or substituted;

Z is H or CN; or when α is present, Z is -CH=CH-; and

when α is present, R_1 is other than methyl;

or a salt thereof.

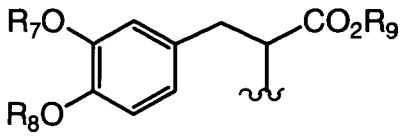
In any of the above embodiments, the compound has the structure



wherein

G_1 is C_{1-10} alkylene, C_{2-10} alkenylene, or C_{2-10} alkynylene;

R_1 is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or



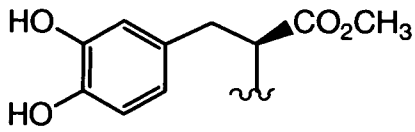
,

wherein R_7 and R_8 are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; or $-SO_2R_{10}$,

wherein R_{10} is C_{1-10} alkyl, or unsubstituted or substituted aryl;

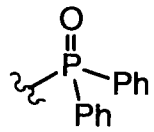
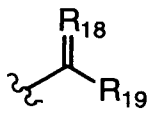
R_9 is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

when R_7 and R_8 are H and R_9 is CH_3, then R_1 is

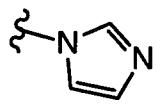


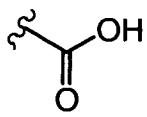
; and

wherein R_3 and R_4 are each, independently, H, halogen, or OR_{16};

wherein R_{16} is H, C_{1-10} alkyl, $-CH_2SH$, $-BHCH_2CH_3$, $-CH{=}SH$, , $-SO_2R_{17}$, , or $-Si(R_{20})_3$;

wherein R_{17} and each occurrence of R_{20} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

R_{18} is S or O; and R_{19} is $-SCH_3$, , or

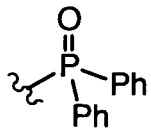
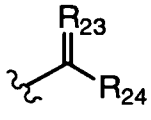


; or

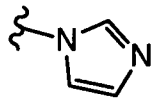
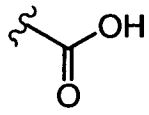
R_3 and R_4 taken together form =O; and

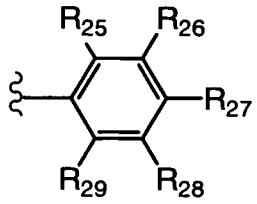
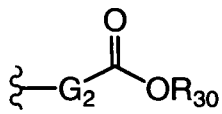
wherein R_5 is H, halogen, or OR_{21},

wherein R_{21} is H, C_{1-10} alkyl, $-CH_2SH$, $-BHCH_2CH_3$, $-CH=SH$,


, $-SO_2R_{22}$,

, or $-Si(R_{25})_3$,

wherein R_{22} and each occurrence of R_{25} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

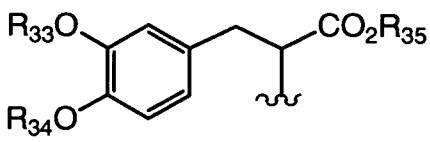
R_{23} is S or O; and R_{24} is $-SCH_3$,

, or

; and

R_2 is H,

, or

;

wherein R_{25}, R_{26}, R_{27}, R_{28}, and R_{29} are each, independently, H, halogen, $-NO_2$, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; $-OR_{31}$, $-SR_{31}$, $-OSO_2R_{31}$, or $-NR_{31}R_{32}$,

wherein R_{31} and R_{32} are each, independently, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or unsubstituted or substituted aryl;

wherein G_2 is C_{1-10} alkylene, C_{2-10} alkenylene, or C_{2-10} alkynylene; and

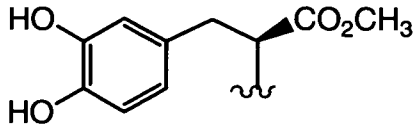
R_{30} is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or

,

wherein R_{33} and R_{34} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; or $-SO_2R_{36}$,

wherein R_{36} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

wherein R_{35} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

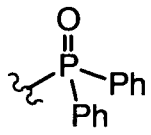
when R_{33} and R_{34} are H and R_{35} is CH_3, then R_{30} is



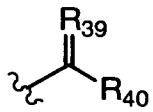
; and

R_6 is H, halogen, or OR_{37};

wherein R_{37} is H, C_{1-10} alkyl, $-CH_2SH$, $-BHCH_2CH_3$, $-CH=SH$,



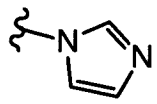
, $-SO_2R_{38}$,



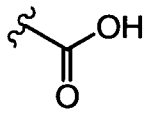
, or $-Si(R_{41})_3$;

wherein R_{38} and each occurrence of R_{41} is C_{1-10} alkyl; or unsubstituted or substituted aryl;

R_{39} is S or O; and R_{40} is $-SCH_3$;



; or

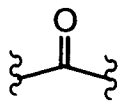


; or

R_5 when present and R_6 taken together form =O; or

R_4 joined to R_6 form a 5-membered heterocyclic ring; and

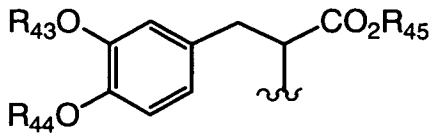
wherein X is a direct bond or



; and

Y is H or OR_{42},

wherein R_{42} is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or

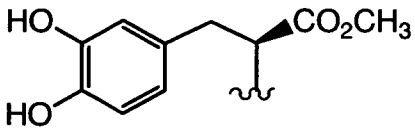


,

wherein R_{43} and R_{44} are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; or $-SO_2R_{46}$,

wherein R_{46} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

R_{45} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and when R_{43} and R_{44} are H and R_{45} is CH_3,

then R_{42} is 

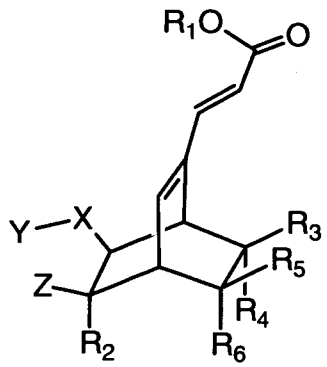
; or

wherein each occurrence of alkyl, alkylene, alkenyl, alkenylene, alkynyl, or alkynylene is branched or unbranched, unsubstituted or substituted;

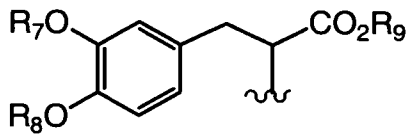
Z is H or CN;

or a salt thereof.

In any of the above embodiments, the compound has the structure



wherein

R_1 is H, CH_3, or 

,

wherein R_7 and R_8 are p-trifluoromethylbenzyl; and

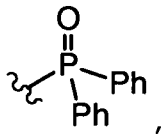
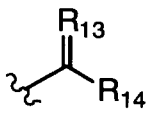
R_9 is CH_3; and

wherein R_3 is H, OCH_3, Br, $-OSO_2CF_3$, or -OiPr;

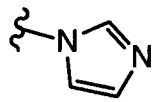
R_4 is H, OH, or OCH_3;

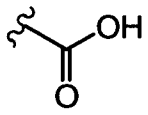
R_5 is H, OH, $-OSO_2CF_3$, or $-OSi(CH_3)_2$(t-butyl); and

R_6 is H or OR_{11},

wherein R_{11} is H, $-CH_2SH$, $-BHCH_2CH_3$, $-CH=SH$, , $-SO_2R_{12}$, or ,

wherein R_{12} is CH_3 or CF_3;

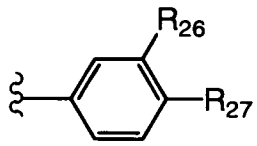
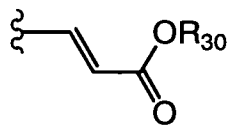
R_{13} is S or O; and R_{14} is $-SCH_3$; ; or

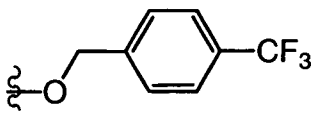
; or

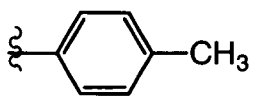
R_5 and R_6 together form =O; or

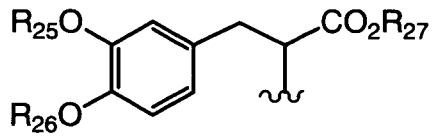
R_3 and R_4 together form =O; or

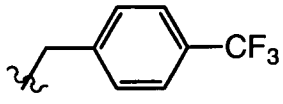
R_4 joined to R_6 form a 5-membered heterocyclic ring; and

wherein R_2 is H, , or ,

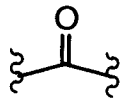
wherein R_{26} and R_{27} are each, independently, $-OCH_3$, , or $-OSO_2R_{24}$,

wherein R_{24} is ;

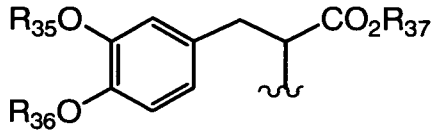
wherein R_{30} is CH_3 or ,

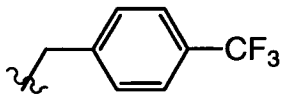
wherein R_{25} and R_{26} are each ;

wherein R_{27} is CH_3; and

wherein X is a direct bond, , or $C(OMe)_2$;

Y is H or OR_{34},

wherein R_{34} is CH_3 or ,

wherein R_{35} and R_{36} are each ; and

R_{37} is CH_3; and

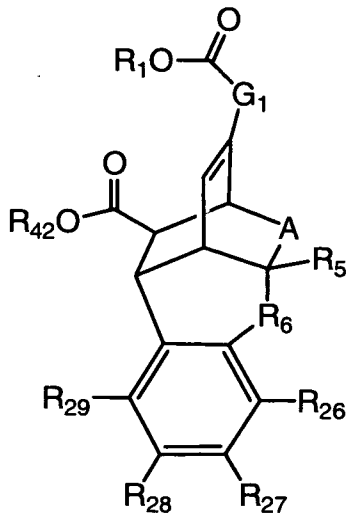
Z is H or CN;

or a salt thereof.

In any of the above embodiments, the compound is selected from the group consisting of Compound 17, 21, 24, 26, 33, 34, 36, 36, 37, 39, 40, 42, 44, 45, 47, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63.

In any of the above embodiments, the compound is selected from the group consisting of Compound 51.

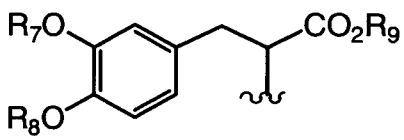
In any of the above embodiments, the compound has the structure



wherein

G_1 is C_{1-10} alkylene, C_{2-10} alkenylene, or C_{2-10} alkynylene;

R_1 is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or



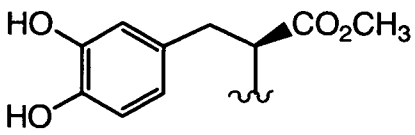
,

wherein R_7 and R_8 are independently H; C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, unsubstituted or substituted aryl(C_{1-10})alkyl, or $-SO_2R_{10}$,

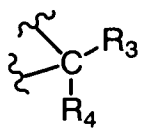
wherein R_{10} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

R_9 is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

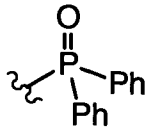
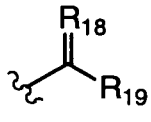
when R_7 and R_8 are H and R_9 is CH_3, then R_1 is



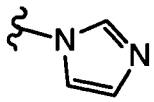
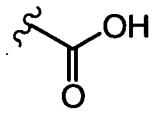
;

A is a direct bond or  ;

wherein R_3 and R_4 are each, independently, H, halogen, or OR_{16};

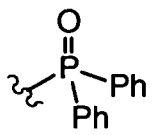
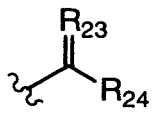
wherein R_{16} is H, C_{1-10} alkyl, $-CH_2SH$, $-BHCH_2CH_3$, $-CH{=}SH$, , $-SO_2R_{17}$, , or $-Si(R_{20})_3$;

wherein R_{17} and each occurrence of R_{20} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

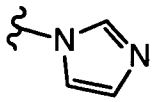
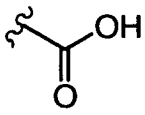
R_{18} is S or O; and R_{19} is $-SCH_3$, , or ; or

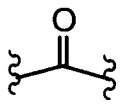
R_3 and R_4 taken together form =O; and

wherein R_5 is H, halogen, or OR_{21},

wherein R_{21} is H, C_{1-10} alkyl, $-CH_2SH$, $-BHCH_2CH_3$, $-CH{=}SH$, , $-SO_2R_{22}$, , or $-Si(R_{25})_3$,

wherein R_{22} and each occurrence of R_{25} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

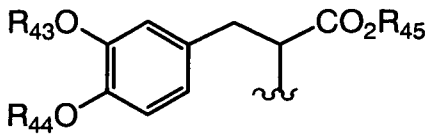
R_{23} is S or O; and R_{24} is $-SCH_3$, , or ; and

wherein R_6 is a direct bond or ; and

wherein R_{26}, R_{27}, R_{28}, and R_{29} are each, independently, H, halogen, $-NO_2$, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; $-OR_{31}$, $-SR_{31}$, $-OSO_2R_{31}$, or $-NR_{31}R_{32}$,

wherein R_{31} and R_{32} are each, independently, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or unsubstituted or substituted aryl;

wherein R_{42} is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or

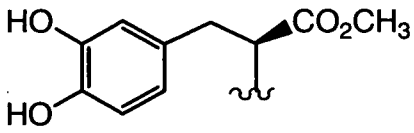


,

wherein R_{43} and R_{44} are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; or $-SO_2R_{46}$,

wherein R_{46} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

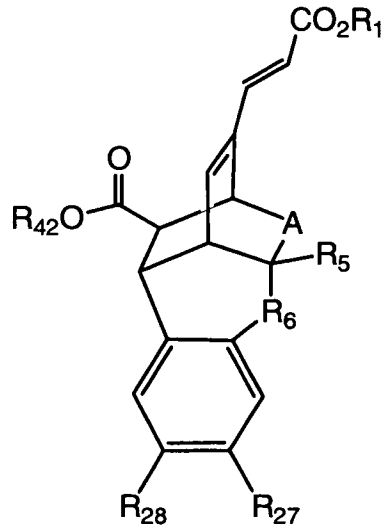
R_{45} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and when R_{43} and R_{44} are H and R_{45} is CH_3,

then R_{42} is  ; or

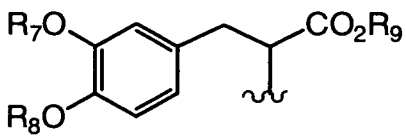
wherein each occurrence of alkyl, alkylene, alkenyl, alkenylene, alkynyl, or alkynylene is branched or unbranched, unsubstituted or substituted;

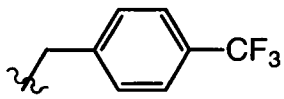
or a salt thereof.

In any of the above embodiments, the compound has the structure

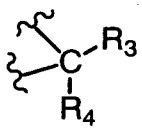


wherein

R_1 is CH_3 or 

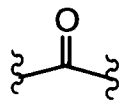
wherein R_7 and R_8 are  ; and

R_9 is CH_3;

A is a direct bond or  ;

wherein R_3 and R_4 taken together form =O;

R_5 is H or OH;

R_6 is a direct bond or  ;

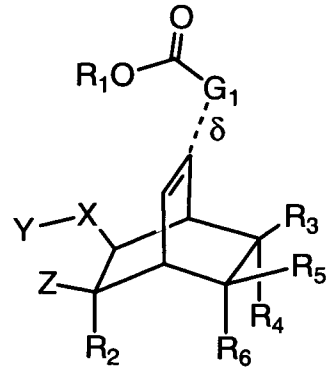
R_{27} and R_{28} are each $-OCH_3$; and

wherein R_{42} is CH_3; or

a salt thereof.

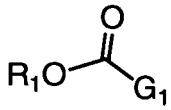
In an embodiment, the compound is selected from the group consisting of: Compound 23 and 25.

In an embodiment, the compound has the structure

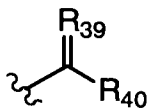


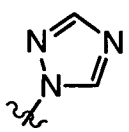
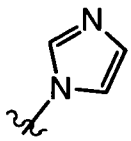
wherein

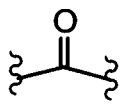
δ is present or absent;

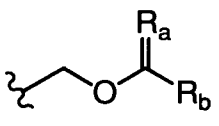
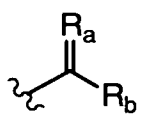
wherein when δ is absent,  is absent;

R_6 is OR_{37};

wherein R_{37} is ;

wherein R_{39} is S; and R_{40} is  or ;

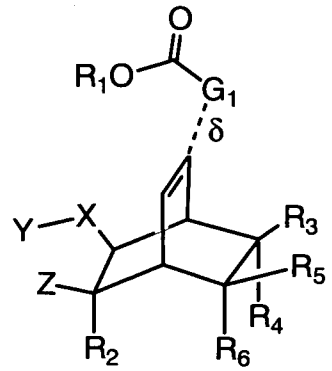
X is a direct bond or ;

Z is H, CN,  or ,

wherein R_a is S or O; R_b is -O-(C_1-C_{10})alkyl, -O-(C_2-C_{10})alkenyl, heterocyclyl, or heteroaryl; or

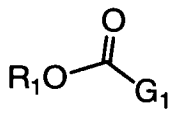
or a salt thereof.

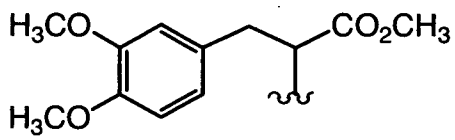
In an embodiment, the compound has the structure

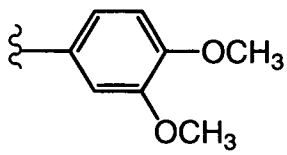


wherein

δ is present or absent;

wherein when δ is absent,  is absent;

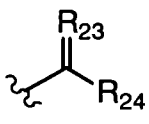
R_1 is H, methyl or ;

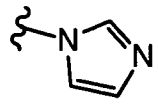


R_2 is H or ;

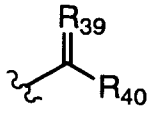
R_3 and R_4 are each $-OCH_3$;

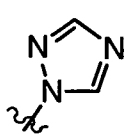
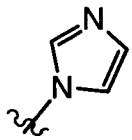
R_5 is H or OR_{21},

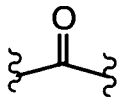
wherein R_{21} is ,

wherein R_{23} is S; and R_{24} is ; and

R_6 is OR_{37};

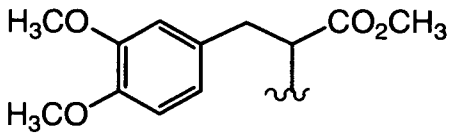
wherein R_{37} is ;

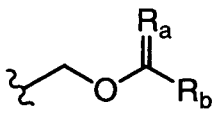
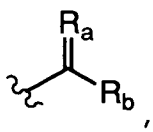
wherein R_{39} is S; and R_{40} is  or ;

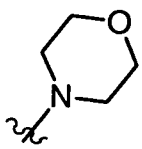
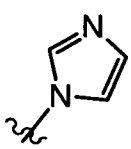
X is a direct bond or ;

Y is H or OR_{42};

wherein R_{42} is methyl, $-CH_2CH=CH_2$ or

;

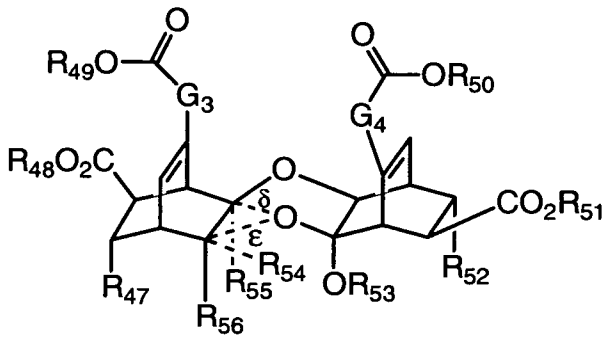
Z is H, CN,  or ,

wherein R_a is S or O; R_b is $-OCH_3$, $-OCH(CH_3)_2$, $OCH_2CH=CH_2$, $-OCH_2CH_2CH_2CH_3$, , or ;

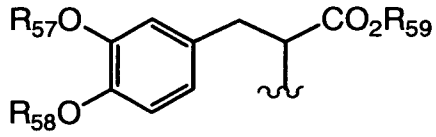
or a salt thereof.

In an embodiment, the compound is selected from the group consisting of Compound 64, 65, 66, 67, 68, 73, 74, 75, 76, 77, 78, 79, 80, and a pharmaceutically acceptable salt thereof.

This invention provides a compound having the structure



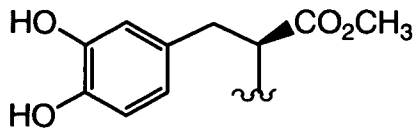
wherein ε and δ are present or absent;
wherein R_{54} and R_{55} are present or absent; and
when ε is present; δ and R_{54} are absent, and R_{55} is present; and
when δ is present; ε and R_{55} are absent, and R_{54} is present;

wherein G_3 and G_4 are each, independently, is C_{1-10} alkylene, C_{2-10} alkenylene, or C_{2-10} alkynylene;
R_{48}, R_{49}, R_{50}, and R_{51} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; or ,

wherein R_{57} and R_{58} are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, unsubstituted or substituted aryl(C_{1-10})alkyl, or $-SO_2R_{60}$,

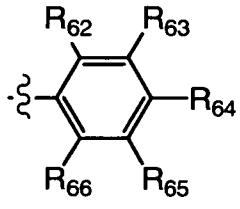
wherein R_{60} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

wherein R_{59} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and when R_{57} and R_{58} are H and R_{59} is CH_3, then

R_{48}, R_{49}, R_{50}, or R_{51} is  ; and

wherein R_{53} is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, unsubstituted or substituted aryl(C_{1-10})alkyl, or $-SO_2R_{61}$,

wherein R_{61} is C_{1-10} alkyl, or unsubstituted or substituted aryl;

R_{47} and R_{52} are each H, CN, or  ,

wherein R_{62}, R_{63}, R_{64}, R_{65}, and R_{66} are each, independently, H, halogen, $-NO_2$, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; $-OR_{67}$, $-SR_{67}$, $-OSO_2R_{67}$, or $-NR_{67}R_{68}$,

wherein R_{67} and R_{68} are each, independently, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or unsubstituted or substituted aryl; and

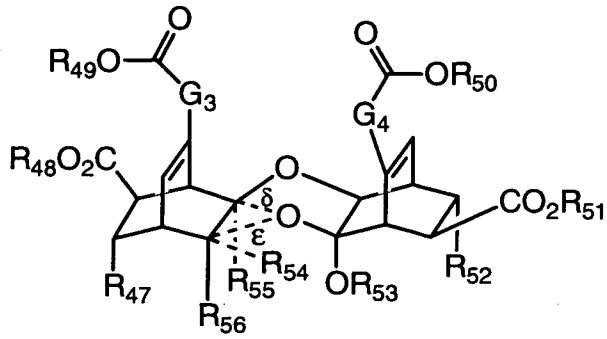
wherein R_{54} when present, R_{55} when present, and R_{56} are each, independently, H or OR_{69},

wherein R_{69} is H or C_{1-10} alkyl; or

wherein each occurrence of alkyl, alkylene, alkenyl, alkenylene, alkynyl, alkynylene is branched or unbranched, unsubstituted or substituted;

or a salt thereof.

In an embodiment, the compound has the structure



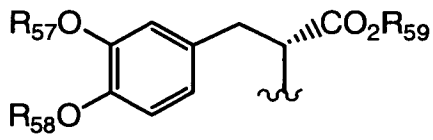
wherein ε and δ are present or absent;

wherein R_{54} and R_{55} are present or absent; and

when ε is present; δ and R_{54} are absent, and R_{55} is present; and

when δ is present; ε and R_{55} are absent, and R_{54} is present;

wherein G_3 and G_4 are each, independently, is C_{1-10} alkylene, C_{2-10} alkenylene, or C_{2-10} alkynylene;

R_{48}, R_{49}, R_{50}, and R_{51} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; or ,

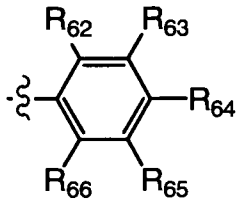
wherein R_{57} and R_{58} are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, unsubstituted or substituted aryl(C_{1-10})alkyl, or $-SO_2R_{60}$,

wherein R_{60} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

wherein R_{59} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and at least one of R_{57} and R_{58} is other than H; and

wherein R_{53} is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, unsubstituted or substituted aryl(C_{1-10})alkyl, or $-SO_2R_{61}$,

wherein R_{61} is C_{1-10} alkyl, or unsubstituted or substituted aryl;



R_{47} and R_{52} are each H, CN, or ,

wherein R_{62}, R_{63}, R_{64}, R_{65}, and R_{66} are each, independently, H, halogen, $-NO_2$, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; $-OR_{67}$, $-SR_{67}$, $-OSO_2R_{67}$, or $-NR_{67}R_{68}$,

wherein R_{67} and R_{68} are each, independently, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or unsubstituted or substituted aryl; and

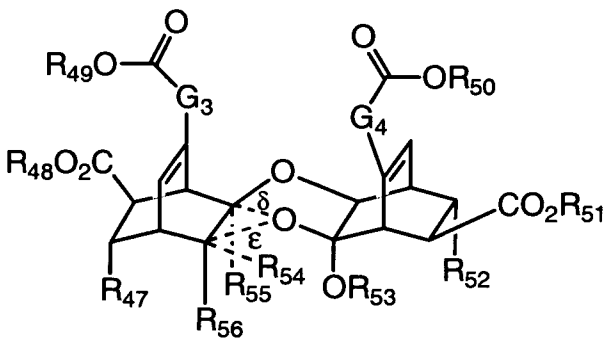
wherein R_{54} when present, R_{55} when present, and R_{56} are each, independently, H or OR_{69},

wherein R_{69} is H or C_{1-10} alkyl; or

wherein each occurrence of alkyl, alkylene, alkenyl, alkenylene, alkynyl, alkynylene is branched or unbranched, unsubstituted or substituted;

or a salt thereof.

In an embodiment, the compound has the structure



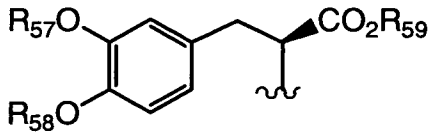
wherein ε and δ are present or absent;

wherein R_{54} and R_{55} are present or absent; and

when ε is present; δ and R_{54} are absent, and R_{55} is present; and

when δ is present; ε and R_{55} are absent, and R_{54} is present;

wherein G_3 and G_4 are each, independently, is C_{1-10} alkylene, C_{2-10} alkenylene, or C_{2-10} alkynylene;

R_{48}, R_{49}, R_{50}, and R_{51} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; or ,

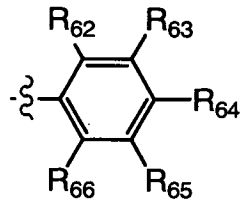
wherein R_{57} and R_{58} are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, unsubstituted or substituted aryl(C_{1-10})alkyl, or $-SO_2R_{60}$,

wherein R_{60} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

wherein R_{59} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

wherein R_{53} is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, unsubstituted or substituted aryl(C_{1-10})alkyl, or $-SO_2R_{61}$,

wherein R_{61} is C_{1-10} alkyl, or unsubstituted or substituted aryl;

R_{47} and R_{52} are each H, CN, or ,

wherein R_{62}, R_{63}, R_{64}, R_{65}, and R_{66} are each, independently, H, halogen, $-NO_2$, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; $-OR_{67}$, $-SR_{67}$, $-OSO_2R_{67}$, or $-NR_{67}R_{68}$,

wherein R_{67} and R_{68} are each, independently, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or unsubstituted or substituted aryl; and

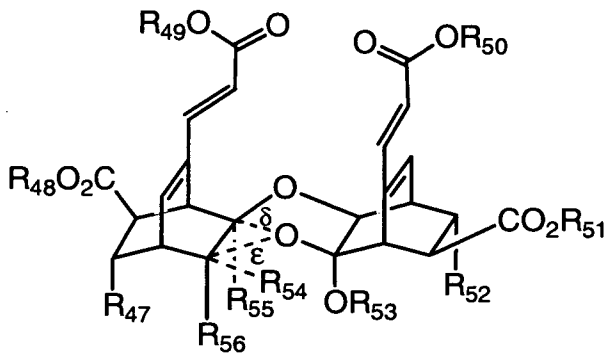
wherein R_{54} when present, R_{55} when present, and R_{56} are each, independently, H or OR_{69},

wherein R_{69} is H or C_{1-10} alkyl; or

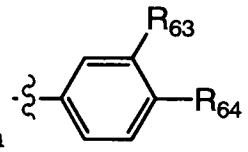
wherein each occurrence of alkyl, alkylene, alkenyl, alkenylene, alkynyl, alkynylene is branched or unbranched, unsubstituted or substituted;

or a salt thereof.

In any of the above embodiments, the compound has the structure



wherein ε and δ are present or absent;
wherein R_{54} and R_{55} are present or absent; and
when ε is present; δ and R_{54} are absent, and R_{55} is present; and
when δ is present; ε and R_{55} are absent, and R_{54} is present;
R_{48}, R_{49}, R_{50}, and R_{51} are each CH_3;
R_{53} is H or CH_3;

R_{47} and R_{52} are each 

,

wherein R_{63} and R_{64} are each $-OCH_3$; and

wherein R_{54} when present, R_{55} when present, and R_{56} are each, independently, H or OR_{69},

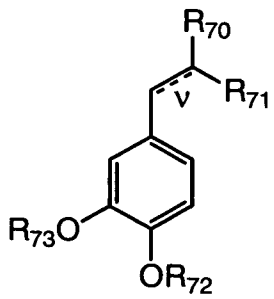
wherein R_{69} is H or CH_3;

wherein each occurrence of alkyl, alkylene, alkenyl, alkenylene, alkynyl, alkynylene is branched or unbranched, unsubstituted or substituted;

or a salt thereof.

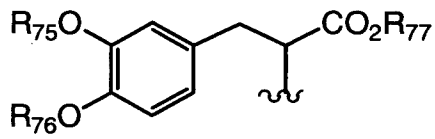
In an embodiment, the compound is selected from the group consisting of: Compound 43 and 48.

This invention provides a compound having the structure



wherein ν is present or absent;

wherein R_{70} and R_{71} are each, independently, H, OH, $-CO_2R_{74}$,

wherein R_{74} is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or 

,

wherein R_{75} and R_{76} are independently H; C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; or $-SO_2R_{78}$,

wherein R_{78} is C_{1-10} alkyl; or unsubstituted or substituted aryl; and

wherein R_{77} is H; C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and at least one of R_{75} and R_{76} is other than H;

wherein R_{72} and R_{73} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; $-SO_2R_{79}$, or $-Si(R_{80})_3$,

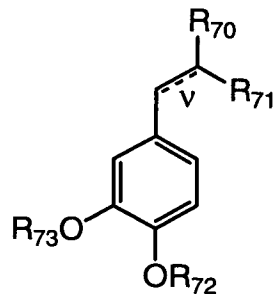
wherein R_{79} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

wherein each occurrence of R_{80} is, independently, C_{1-10} alkyl, or unsubstituted or substituted aryl; and when R_{74} is H or CH_3, R_{73} is other than H or Me; and

wherein each occurrence of alkyl, alkylene, alkenyl, alkenylene, alkynyl, or alkynylene is branched or unbranched, unsubstituted or substituted;

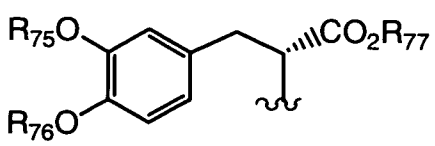
or a salt thereof.

In an embodiment, the compound has the structure



wherein ν is present or absent;

wherein R_{70} and R_{71} are each, independently, H, OH, $-CO_2R_{74}$,

wherein R_{74} is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or 

,

wherein R_{75} and R_{76} are independently H; C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; or $-SO_2R_{78}$,

wherein R_{78} is C_{1-10} alkyl; or unsubstituted or substituted aryl; and

wherein R_{77} is H; C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and at least one of R_{75} and R_{76} is other than H;

wherein R_{72} and R_{73} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; $-SO_2R_{79}$, or $-Si(R_{80})_3$,

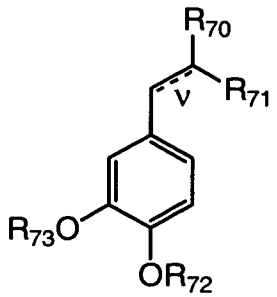
wherein R_{79} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

wherein each occurrence of R_{80} is, independently, C_{1-10} alkyl, or unsubstituted or substituted aryl; and when R_{74} is H or CH_3, R_{73} is other than H or Me; and

wherein each occurrence of alkyl, alkylene, alkenyl, alkenylene, alkynyl, or alkynylene is branched or unbranched, unsubstituted or substituted;

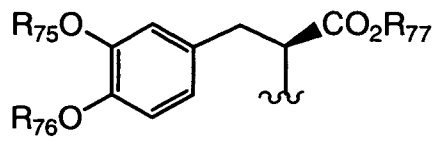
or a salt thereof.

In an embodiment, the compound has the structure



wherein ν is present or absent;

wherein R_{70} and R_{71} are each, independently, H, OH, $-CO_2R_{74}$,

wherein R_{74} is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or ,

wherein R_{75} and R_{76} are independently H; C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; or $-SO_2R_{78}$,

wherein R_{78} is C_{1-10} alkyl; or unsubstituted or substituted aryl; and

wherein R_{77} is H; C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and at least one of R_{75} and R_{76} is other than H;

wherein R_{72} and R_{73} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; $-SO_2R_{79}$, or $-Si(R_{80})_3$,

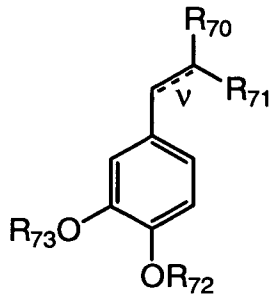
wherein R_{79} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

wherein each occurrence of R_{80} is, independently, C_{1-10} alkyl, or unsubstituted or substituted aryl; and when R_{74} is H or CH_3, R_{73} is other than H or Me; and

wherein each occurrence of alkyl, alkylene, alkenyl, alkenylene, alkynyl, or alkynylene is branched or unbranched, unsubstituted or substituted;

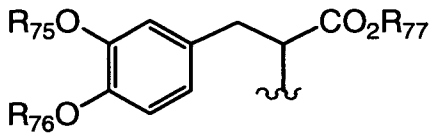
or a salt thereof.

In any of the above embodiments, the compound has the structure

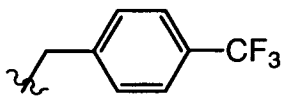


wherein ν is present or absent;

wherein R_{70} and R_{71} are each, independently, H, OH, $-CO_2R_{74}$,



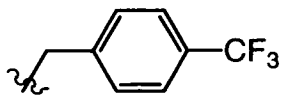
wherein R_{74} is H, CH_3, or ,



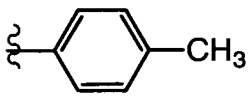
wherein R_{75} and R_{76} are each ; and

wherein R_{77} is CH_3;

wherein R_{72} and R_{73} are each, independently, H, CH_3,



, $-SO_2R_{79}$, or $-Si(R_{80})_3$,

wherein R_{79} is  ; and

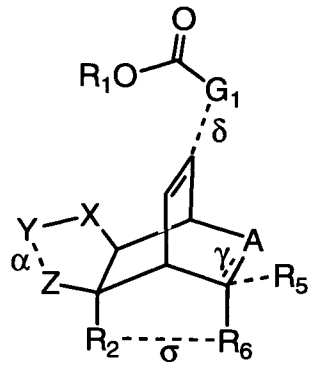
wherein each occurrence of R_{80} is, independently, CH_3 or t-butyl; and

wherein each occurrence of alkyl, alkylene, alkenyl, alkenylene, alkynyl, or alkynylene is branched or unbranched, unsubstituted or substituted;

or a salt thereof.

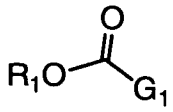
In an embodiment, the compound is selected from the group consisting of: Compound 14, 27, 28, 29, 31, and 32.

This invention provides a process for preparing a compound having the structure

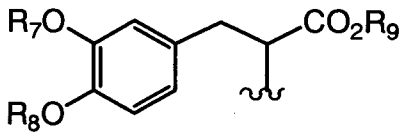


wherein

α, γ, δ and σ are each, independently, present or absent;

wherein when δ is absent,  is absent;

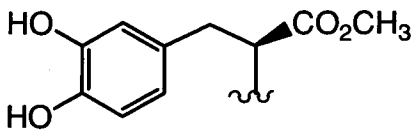
G_1 is C_{1-10} alkylene, C_{2-10} alkenylene, or C_{2-10} alkynylene;

R_1 is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or ,

wherein R_7 and R_8 are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; or $-SO_2R_{10}$,

wherein R_{10} is C_{1-10} alkyl, or unsubstituted or substituted aryl;

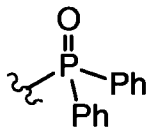
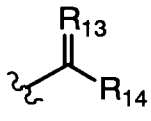
R_9 is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and when R_7 and R_8 are H and R_9 is CH_3, then R_1 is



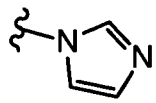
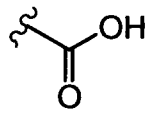
; and

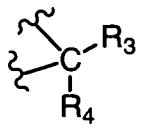
when γ is present; R_5 is absent and A is C-R_4,

wherein R_4 is H, halogen, or OR_{11},

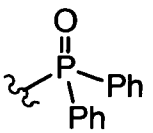
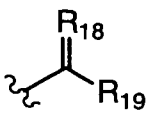
wherein R_{11} is H, C_{1-10} alkyl, $-CH_2SH$, $-BHCH_2CH_3$, $-CH{=}SH$, , $-SO_2R_{12}$, , or $-Si(R_{15})_3$;

wherein R_{12} and each occurrence of R_{15} is C_{1-10} alkyl; or unsubstituted or substituted aryl; and

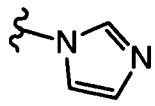
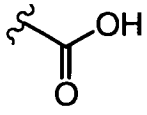
R_{13} is S or O; and R_{14} is $-SCH_3$, , or ; and

when γ is absent; R_5 is present and A is a direct bond or ;

wherein R_3 and R_4 are each, independently, H, halogen, or OR_{16};

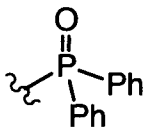
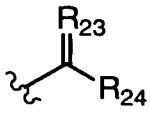
wherein R_{16} is H, C_{1-10} alkyl, $-CH_2SH$, $-BHCH_2CH_3$, $-CH{=}SH$, , $-SO_2R_{17}$, , or $-Si(R_{20})_3$;

wherein R_{17} and each occurrence of R_{20} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

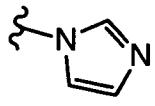
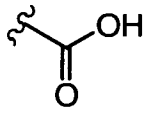
R_{18} is S or O; and R_{19} is $-SCH_3$, , or ; or

R_3 and R_4 taken together form =O; and

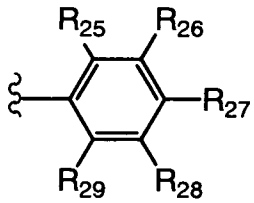
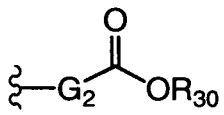
wherein R_5 is H, halogen, or OR_{21},

wherein R_{21} is H, C_{1-10} alkyl, $-CH_2SH$, $-BHCH_2CH_3$, $-CH{=}SH$, , $-SO_2R_{22}$, , or $-Si(R_{25})_3$,

wherein R_{22} and each occurrence of R_{25} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

R_{23} is S or O; and R_{24} is $-SCH_3$, , or ; and

when σ is absent;

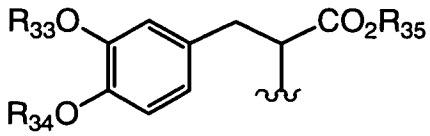
R_2 is H, , or ;

wherein R_{25}, R_{26}, R_{27}, R_{28}, and R_{29} are each, independently, H, halogen, $-NO_2$, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; $-OR_{31}$, $-SR_{31}$, $-OSO_2R_{31}$, or $-NR_{31}R_{32}$,

wherein R_{31} and R_{32} are each, independently, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or unsubstituted or substituted aryl;

wherein G_2 is C_{1-10} alkylene, C_{2-10} alkenylene, or C_{2-10} alkynylene; and

R_{30} is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or



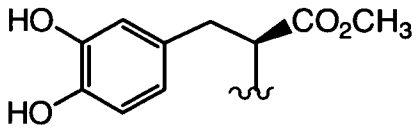
,

wherein R_{33} and R_{34} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; or $-SO_2R_{36}$,

wherein R_{36} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

wherein R_{35} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

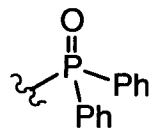
when R_{33} and R_{34} are H and R_{35} is CH_3, then R_{30} is



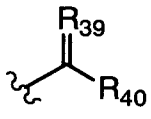
; and

R_6 is H, halogen, or OR_{37};

wherein R_{37} is H, C_{1-10} alkyl, $-CH_2SH$, $-BHCH_2CH_3$, $-CH=SH$,



, $-SO_2R_{38}$,

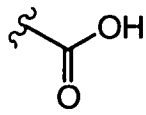


, or $-Si(R_{41})_3$;

wherein R_{38} and each occurrence of R_{41} is C_{1-10} alkyl; or unsubstituted or substituted aryl;

R_{39} is S or O; and R_{40} is $-SCH_3$; -NH-aryl,

heteroaryl, heterocyclyl; or

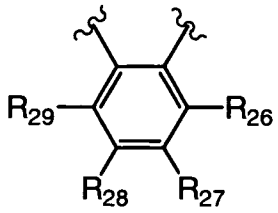
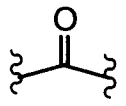


; or

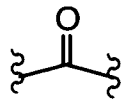
R_5 when present and R_6 taken together form =O; or

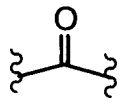
R_4 joined to R_6 form a 5-membered heterocyclic ring; and

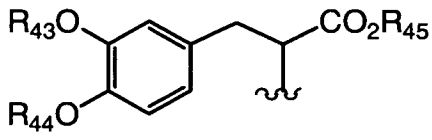
when σ is present;

R_2 is  ; and R_6 is a direct bond or ;

and

wherein X is a direct bond, , or $C(OMe)_2$;

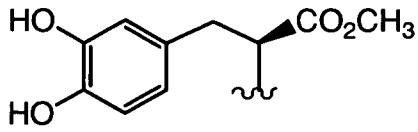
Y is H or OR_{42}; or when α is present, Y is ;

wherein R_{42} is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or ,

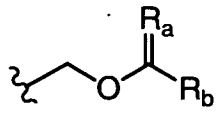
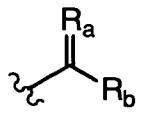
wherein R_{43} and R_{44} are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; or $-SO_2R_{46}$,

wherein R_{46} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

R_{45} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and when R_{43} and R_{44} are H and R_{45} is CH_3,

then R_{42} is  ; or

wherein each occurrence of alkyl, alkylene, alkenyl, alkenylene, alkynyl, or alkynylene is branched or unbranched, unsubstituted or substituted;

Z is H, CN,  or ,

wherein R_a is S or O; R_b is -O-(C_1-C_{10})alkyl, -O-(C_2-C_{10})alkenyl, heterocyclyl, or heteroaryl; or

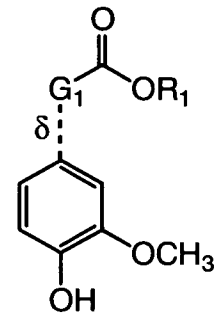
when α is present, Z is -CH=CH-;

and

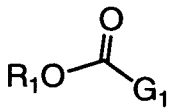
when α is present, R_1 is other than methyl;

comprising:

a) contacting a compound having the structure

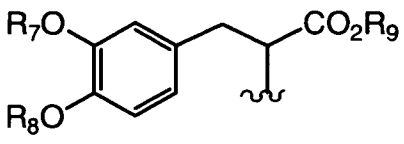
,

wherein

when δ is absent,  is absent;

G_1 is C_{1-10} alkylene, C_{2-10} alkenylene, or C_{2-10} alkynylene;

R_1 is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or

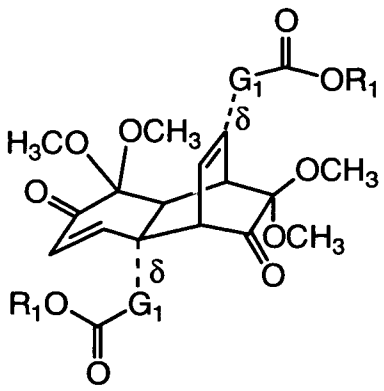
,

wherein R_7 and R_8 are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; or $-SO_2R_{10}$,

wherein R_{10} is C_{1-10} alkyl, or unsubstituted or substituted aryl;

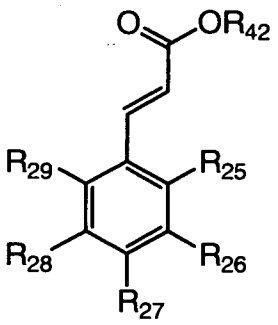
R_9 is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl;

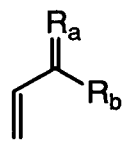
with a first suitable oxidizing agent in the presence of methanol so as to form the compound having the structure

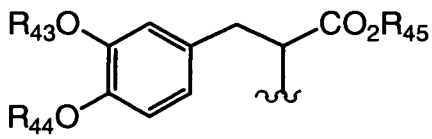


;

b) contacting the product of step a) with a compound having the structure



, NC-CH=CH_2, or 

wherein R_{42} is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or 

,

wherein R_{43} and R_{44} are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; or $-SO_2R_{46}$,

wherein R_{46} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

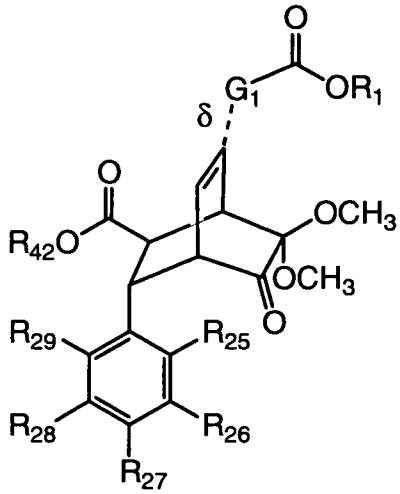
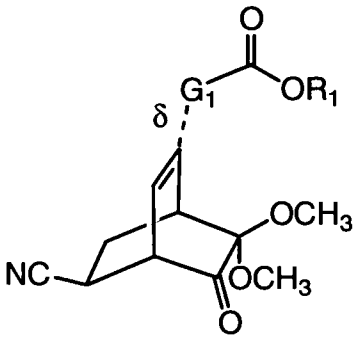
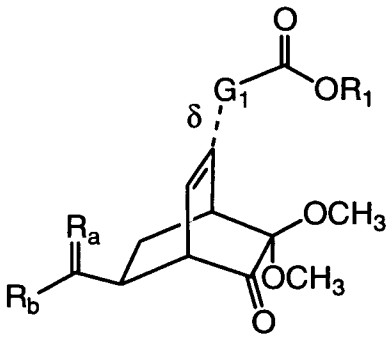
R_{45} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl;

R_{25}, R_{26}, R_{27}, R_{28}, and R_{29} are each, independently, H, halogen, $-NO_2$, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; $-OR_{31}$, $-SR_{31}$, $-OSO_2R_{31}$, or $-NR_{31}R_{32}$,

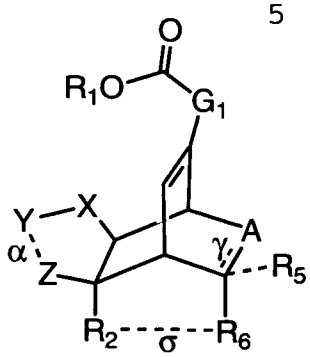
wherein R_{31} and R_{32} are each, independently, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or unsubstituted or substituted aryl; and

wherein R_a is S or O; R_b is -O-(C_1-C_{10})alkyl, -O-(C_2-C_{10})alkenyl, heterocyclyl, or heteroaryl;

in the presence of a first suitable energy source so as to form the compound having the structure



or


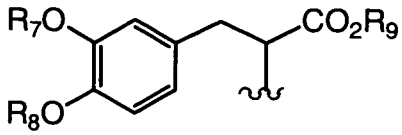
In an embodiment, the compound has the structure



wherein

α, γ, and σ are each, independently, present or absent;

G_1 is C_{1-10} alkylene, C_{2-10} alkenylene, or C_{2-10} alkynylene;

R_1 is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or 

,

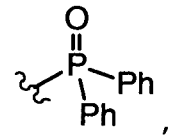
wherein R_7 and R_8 are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; or $-SO_2R_{10}$,

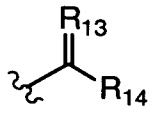
wherein R_{10} is C_{1-10} alkyl, or unsubstituted or substituted aryl;

R_9 is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

when γ is present; R_5 is absent and A is C-R_4,

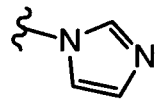
wherein R_4 is H, halogen, or OR_{11},

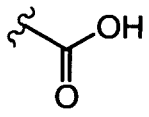
wherein R_{11} is H, C_{1-10} alkyl, $-CH_2SH$, $-BHCH_2CH_3$, $-CH{=}SH$, 

, $-SO_2R_{12}$, 

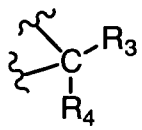
, or $-Si(R_{15})_3$;

wherein R_{12} and each occurrence of R_{15} is C_{1-10} alkyl; or unsubstituted or substituted aryl; and

R_{13} is S or O; and R_{14} is $-SCH_3$, 

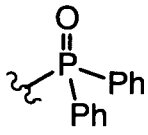
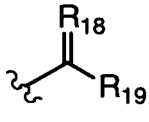
, or 

; and

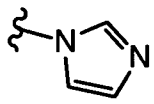
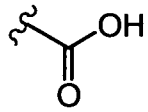
when γ is absent; R_5 is present and A is a direct bond or 

;

wherein R_3 and R_4 are each, independently, H, halogen, or OR_{16};

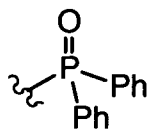
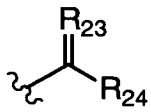
wherein R_{16} is H, C_{1-10} alkyl, $-CH_2SH$, $-BHCH_2CH_3$, $-CH{=}SH$, , $-SO_2R_{17}$, , or $-Si(R_{20})_3$;

wherein R_{17} and each occurrence of R_{20} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

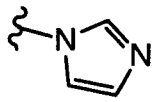
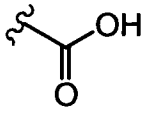
R_{18} is S or O; and R_{19} is $-SCH_3$, , or ; or

R_3 and R_4 taken together form =O; and

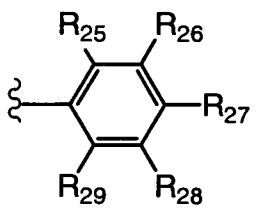
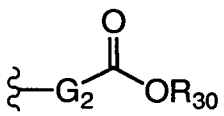
wherein R_5 is H, halogen, or OR_{21},

wherein R_{21} is H, C_{1-10} alkyl, $-CH_2SH$, $-BHCH_2CH_3$, $-CH{=}SH$, , $-SO_2R_{22}$, , or $-Si(R_{25})_3$,

wherein R_{22} and each occurrence of R_{25} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

R_{23} is S or O; and R_{24} is $-SCH_3$, , or ; and

when σ is absent;

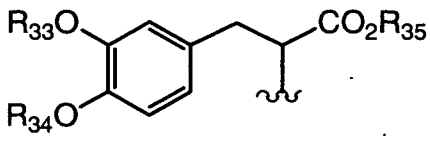
R_2 is H, , or ;

wherein R_{25}, R_{26}, R_{27}, R_{28}, and R_{29} are each, independently, H, halogen, $-NO_2$, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; $-OR_{31}$, $-SR_{31}$, $-OSO_2R_{31}$, or $-NR_{31}R_{32}$,

wherein R_{31} and R_{32} are each, independently, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or unsubstituted or substituted aryl;

wherein G_2 is C_{1-10} alkylene, C_{2-10} alkenylene, or C_{2-10} alkynylene; and

R_{30} is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or



,

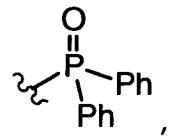
wherein R_{33} and R_{34} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; or $-SO_2R_{36}$,

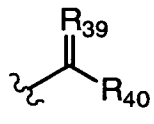
wherein R_{36} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

wherein R_{35} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

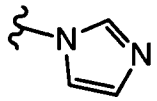
R_6 is H, halogen, or OR_{37};

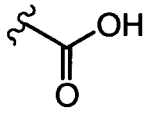
wherein R_{37} is H, C_{1-10} alkyl, $-CH_2SH$, $-BHCH_2CH_3$, $-CH{=}SH$,



, $-SO_2R_{38}$, , or $-Si(R_{41})_3$;

wherein R_{38} and each occurrence of R_{41} is C_{1-10} alkyl; or unsubstituted or substituted aryl;

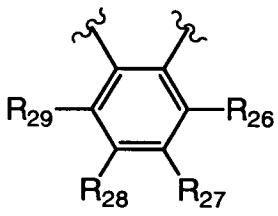
R_{39} is S or O; and R_{40} is $-SCH_3$;  ; or

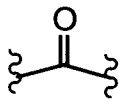
 ; or

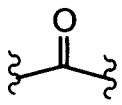
R_5 when present and R_6 taken together form =O; or

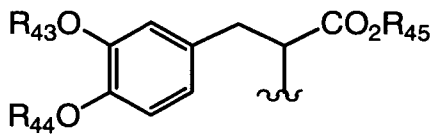
R_4 joined to R_6 form a 5-membered heterocyclic ring; and

when σ is present;

R_2 is  ; and R_6 is a direct bond or  ; and

wherein X is a direct bond,  , or $C(OMe)_2$;

Y is H or OR_{42}; or when α is present, Y is  ;

wherein R_{42} is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or  ,

wherein R_{43} and R_{44} are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; or $-SO_2R_{46}$,

wherein R_{46} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

R_{45} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; or

wherein each occurrence of alkyl, alkylene, alkenyl, alkenylene, alkynyl, or alkynylene is branched or unbranched, unsubstituted or substituted;

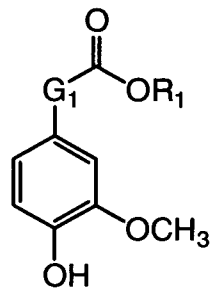
Z is H or CN; or when α is present, Z is -CH=CH-; and

when α is present, R_1 is other than methyl;

or a salt thereof;

comprising:

a) contacting a compound having the structure

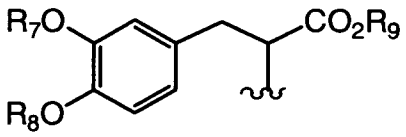


,

wherein

G_1 is C_{1-10} alkylene, C_{2-10} alkenylene, or C_{2-10} alkynylene;

R_1 is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or



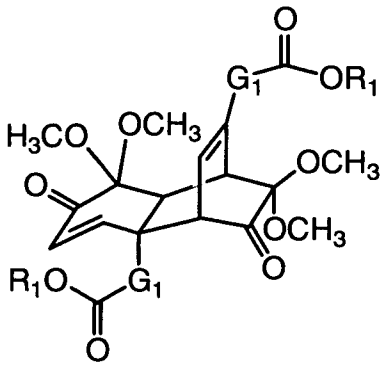
,

wherein R_7 and R_8 are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; or $-SO_2R_{10}$,

wherein R_{10} is C_{1-10} alkyl, or unsubstituted or substituted aryl;

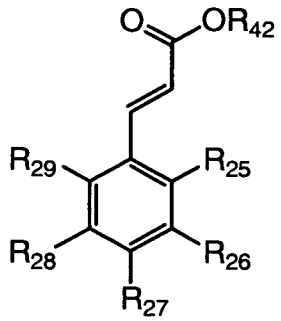
R_9 is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl;

with a first suitable oxidizing agent in the presence of methanol so as to form the compound having the structure

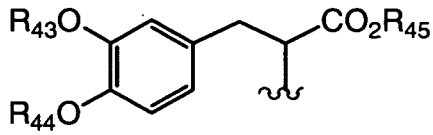


;

b) contacting the product of step a) with a compound having the structure



wherein R_{42} is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or



,

wherein R_{43} and R_{44} are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; or $-SO_2R_{46}$,

wherein R_{46} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

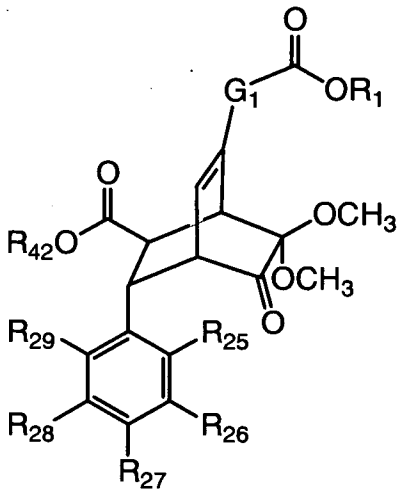
R_{45} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl;

R_{25}, R_{26}, R_{27}, R_{28}, and R_{29} are each, independently, H, halogen, $-NO_2$, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl;

unsubstituted or substituted aryl(C_{1-10})alkyl; $-OR_{31}$, $-SR_{31}$, $-OSO_2R_{31}$, or $-NR_{31}R_{32}$,

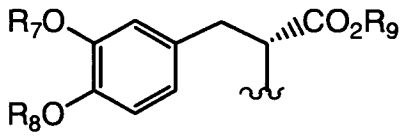
wherein R_{31} and R_{32} are each, independently, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or unsubstituted or substituted aryl;

in the presence of a first suitable energy source so as to form the compound having the structure



In an embodiment of the process,

R_1 is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or



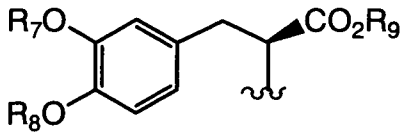
wherein R_7 and R_8 are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, unsubstituted or substituted aryl(C_{1-10})alkyl, or $-SO_2R_{10}$,

wherein R_{10} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

R_9 is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl.

In an embodiment of the process,

R_1 is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or



,

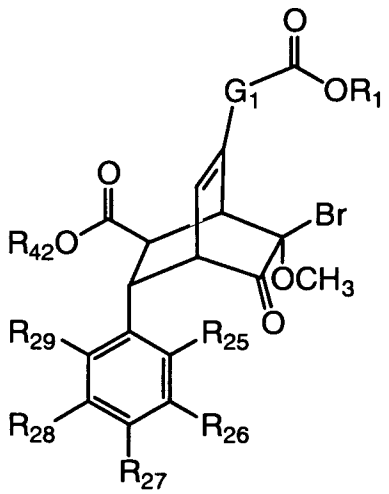
wherein R_7 and R_8 are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, unsubstituted or substituted aryl(C_{1-10})alkyl, or $-SO_2R_{10}$,

wherein R_{10} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

R_9 is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl.

In any of the above embodiments, the process further comprises:

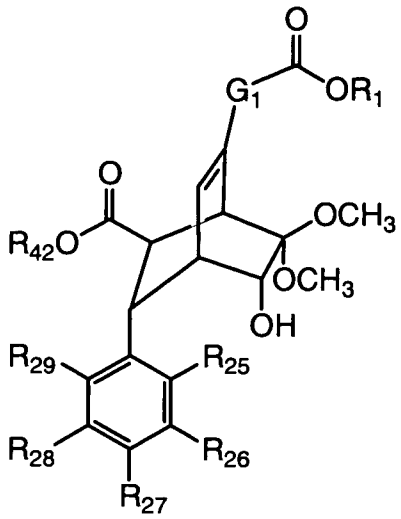
c) contacting the product of step b) with BBr_3 so to form a compound having the structure



.

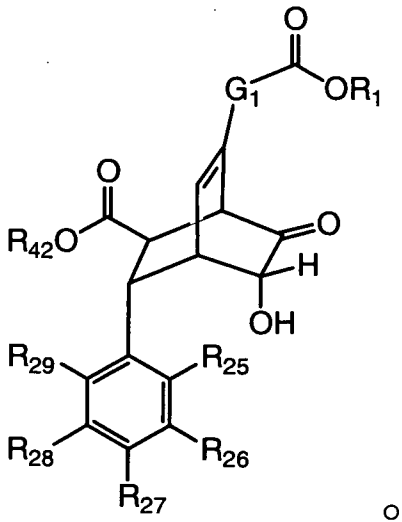
In any of the above embodiments, the process further comprises:

c) contacting the product of step b) with a first suitable hydride reducing agent so as to form a compound having the structure

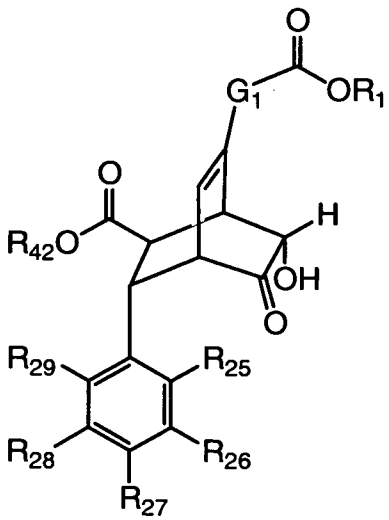


In any of the above embodiments, the process further comprises:

d) exposing the product of step c) to a first suitable Bronsted acid so as to form a compound having the structure

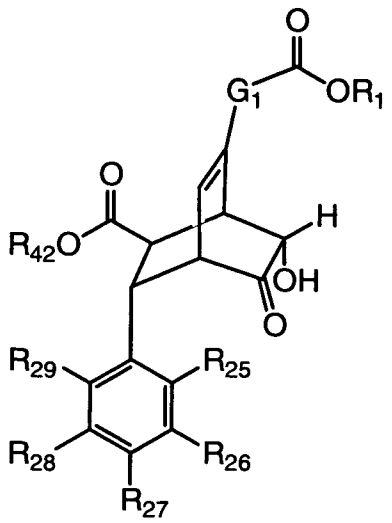


or



In any of the above embodiments, the process further comprises:

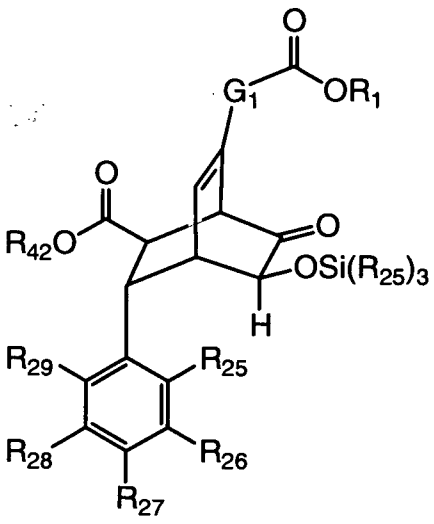
e) contacting the product of step d) having the structure



with a second suitable hydride reducing agent;

f) contacting the product of step e) with a suitable silylating agent;

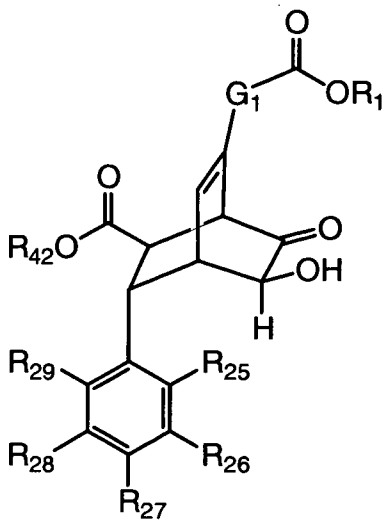
g) contacting the product of step f) with a second suitable oxidizing agent so as to form a compound having the structure



, wherein each occurrence of R_{25} is C_{1-10} alkyl; or unsubstituted or substituted aryl.

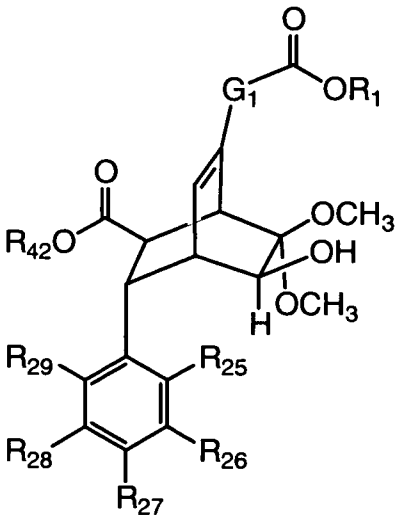
In any of the above embodiments, the process further comprises:

h) exposing the product of step g) to tetra-n-butylammonium fluoride so as to form a compound having the structure



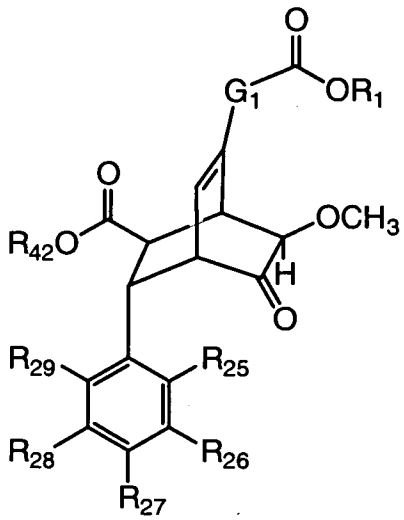
In any of the above embodiments, the process further comprises:

h) exposing the product of step g) to a second suitable Bronsted acid in the presence of methanol so as to form a compound having the structure



In any of the above embodiments, the process further comprises:

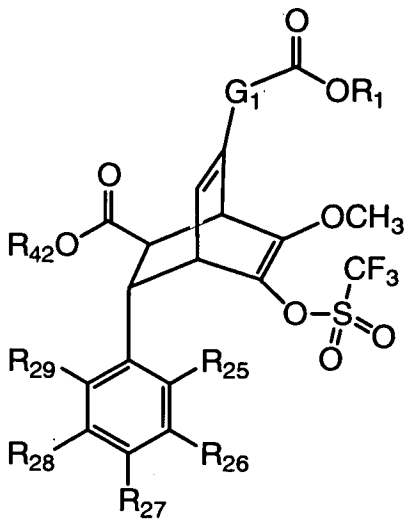
i) exposing the product of step h) to a second suitable energy source so as to form a compound having the structure



In any of the above embodiments, the process further comprises:

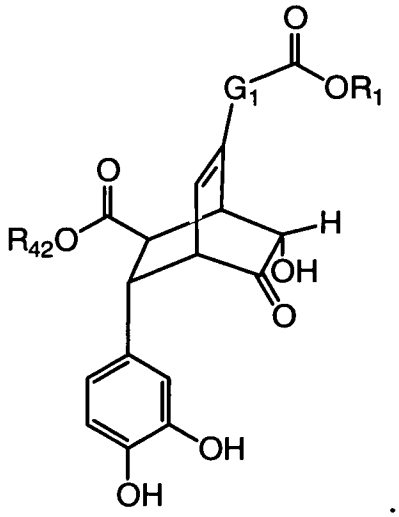
i) exposing the product of step h) to a third suitable Bronsted acid;

j) contacting the product of step i) with Tf_2NPh in the presence of a base so as to form a compound having the structure

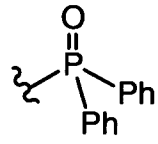
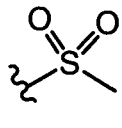
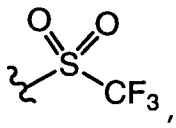
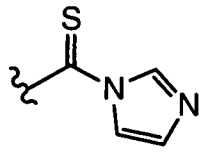
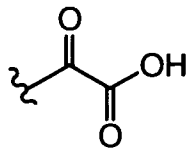
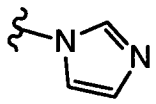
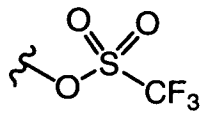


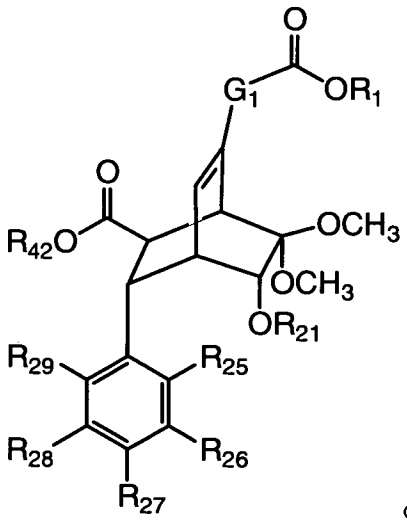
In any of the above embodiments, the process further comprises:

e) exposing the product of step d) to a first suitable Lewis acid so as to from a compound having the structure

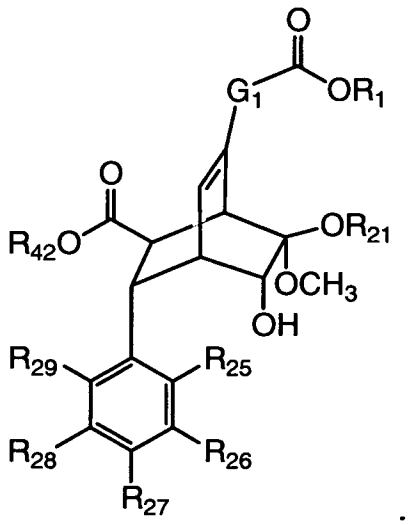


In an embodiment, the process further comprises:

d) exposing the product of step c) to a compound having the structure R_{21}-L, wherein R_{16} is , , , , or ; and L is Cl, , or ; in the presence of a base so as to form a compound having the structure



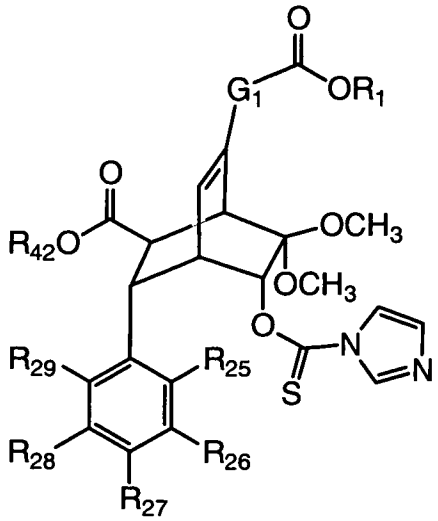
or



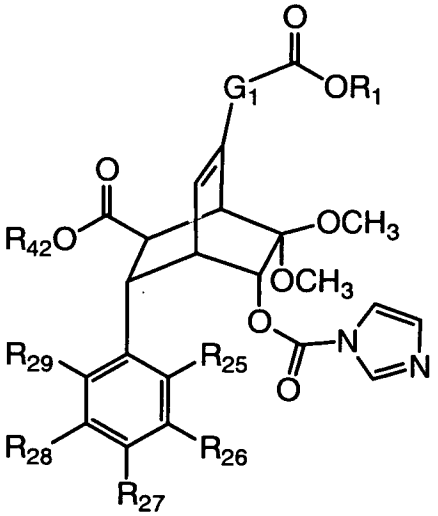
.

In any of the above embodiments, the process further comprises:

e) contacting the product of step d) having the structure

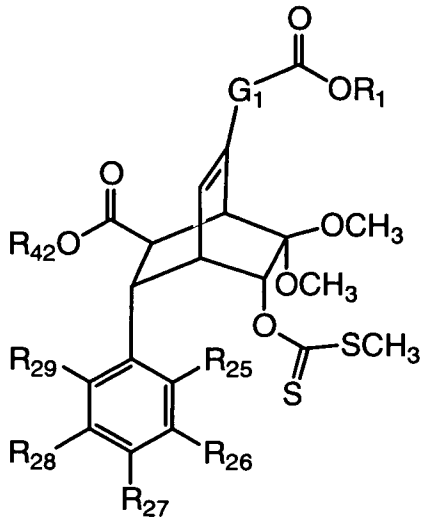


with Et_3B and nBu_3SnH in the presence of O_2 so as to form a compound having the structure



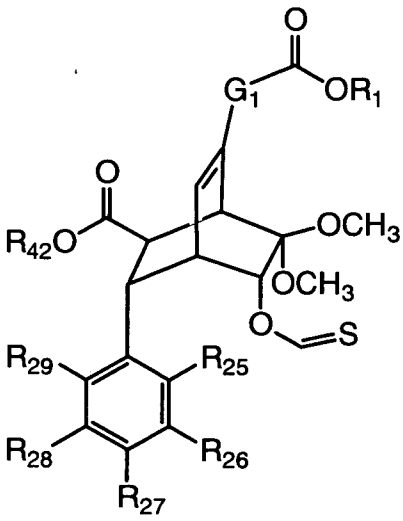
In any of the above embodiments, the process further comprises:

d) exposing the product of step c) to a base and carbon disulfide followed by methyl iodide so as to form a compound having the structure

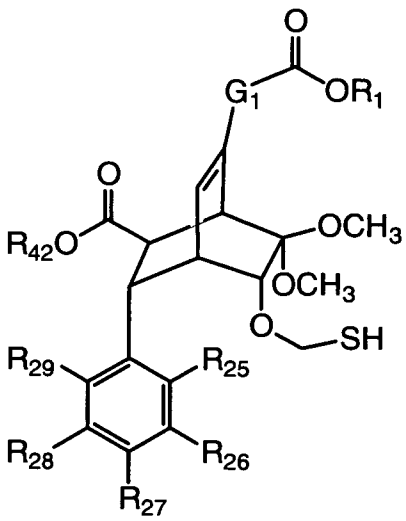


In any of the above embodiments, the process further comprises:

e) exposing the product of step d) to PhSeSePh in the presence of AIBN and nBu_3SnH so as to form a compound having the structure

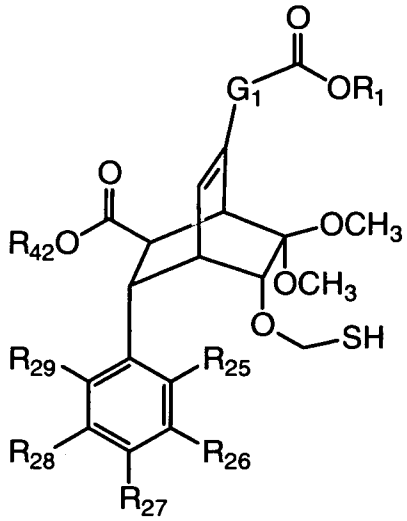


or

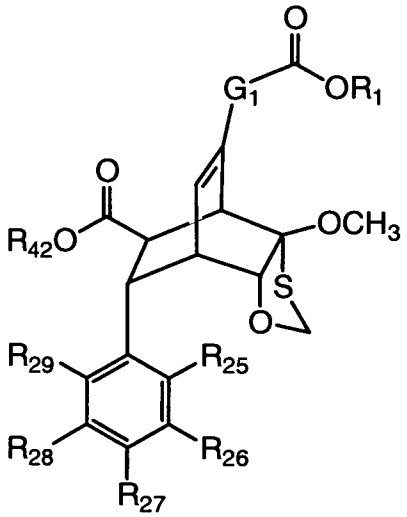


In any of the above embodiments, the process further comprises:

f) exposing the product of step e) having the structure

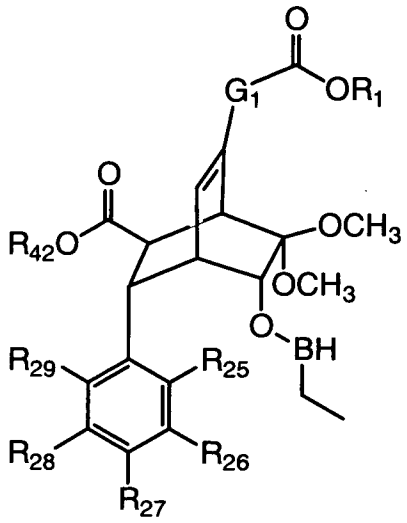


to HCl so as to form a compound having the structure



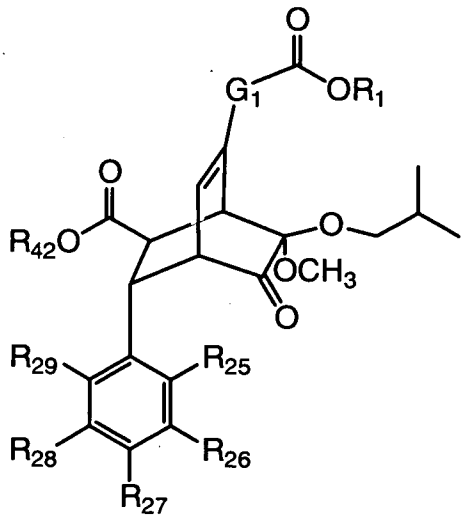
In any of the above embodiments, the process further comprises:

e) contacting the product of step d) with Et_3B in the presence of O_2 so as to form a compound having the structure



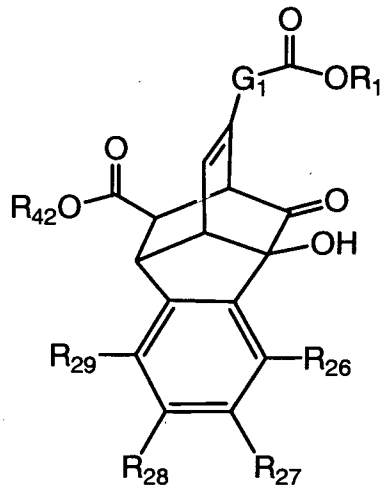
In an embodiment, the process further comprises:

c) contacting the product of step b) with i-$Bu_2Al(OiPr)$ so as to form a compound having the structure



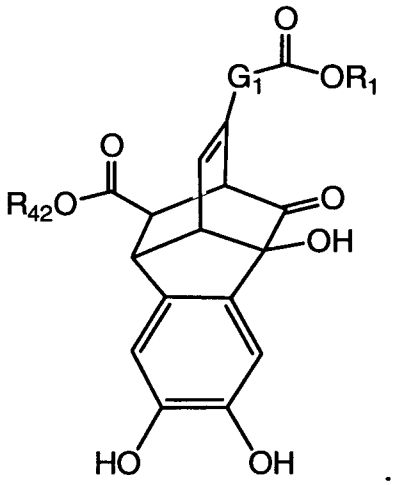
In an embodiment, the process further comprises:

c) exposing the product of step b) to a first suitable Lewis acid so as to form a compound having the structure



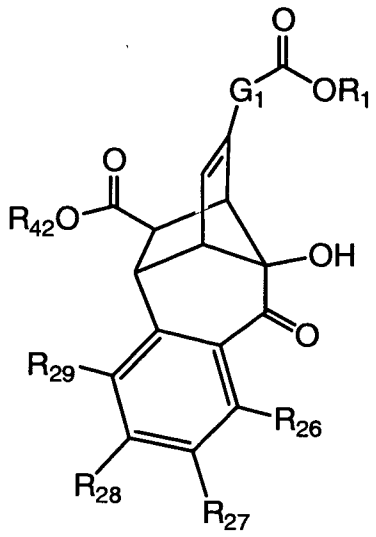
In an embodiment, the process further comprises:

d) contacting the product of step c) with a second suitable Lewis acid so as to form a compound having the structure



In an embodiment, the process further comprises:

d) contacting the product of step c) with a second suitable Lewis acid so as to form a compound having the structure

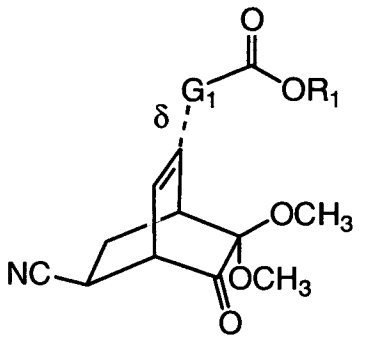


In any of the above embodiments of the process, the compound prepared is selected from a group consisting of:

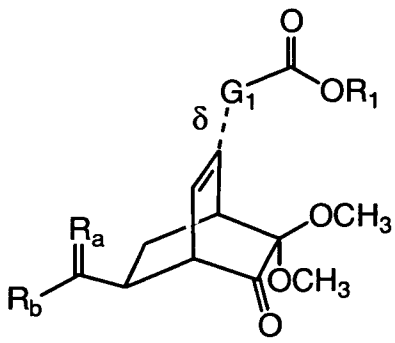
Compound 3, 4, 21, 23, 24, 25, 26, 33, 34, 35, 36, 37, 39, 40, 42, 44, 45, 47, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, and 63.

In an embodiment, the process further comprises:

c) contacting the product of step b) having the structure



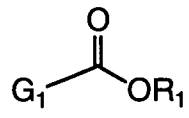
or



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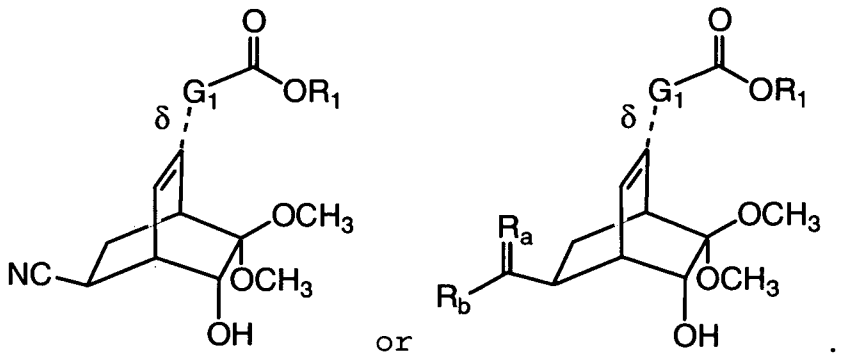
wherein

δ is present or absent;

wherein when δ is present,  is present;

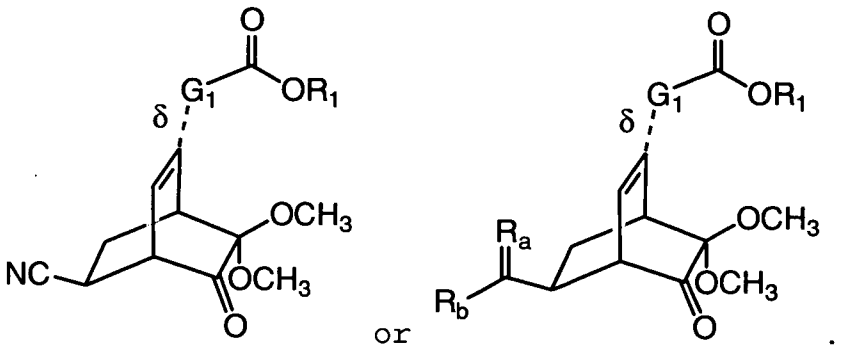
R_a is S or O; R_b is -O-(C_1-C_{10})alkyl, -O-(C_2-C_{10})alkenyl, heterocyclyl, or heteroaryl;

with a first suitable hydride reducing agent so as to form a compound having the structure



In an embodiment, the process further comprises:

d) exposing the product of step c) to a first suitable Bronsted acid so as to form a compound having the structure

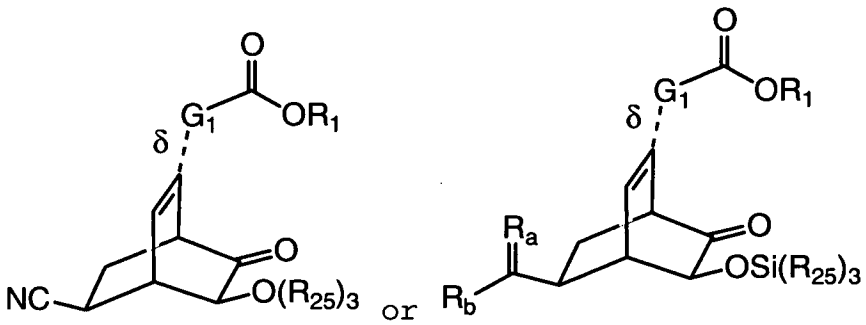


In an embodiment, the process further comprises:

e) contacting the product of step d) with a second suitable hydride reducing agent;

f) contacting the product of step e) with a suitable silylating agent;

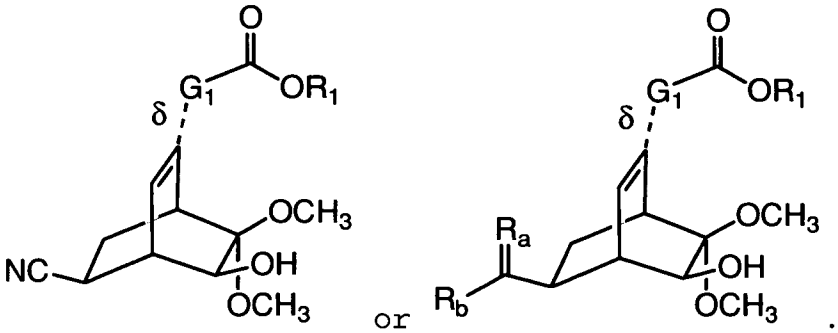
g) contacting the product of step f) with a second suitable oxidizing agent so as to form a compound having the structure



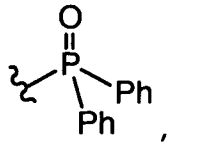
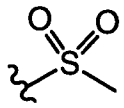
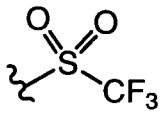
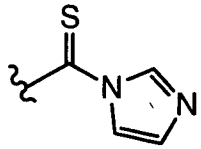
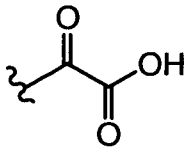
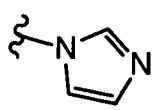
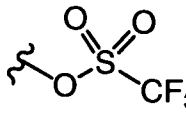
wherein each occurrence of R_{25} is C_{1-10} alkyl; or unsubstituted or substituted aryl.

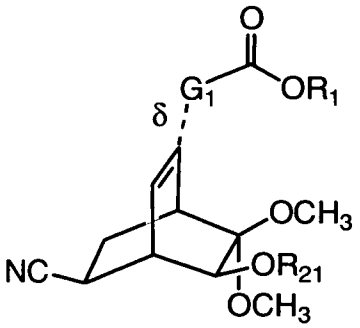
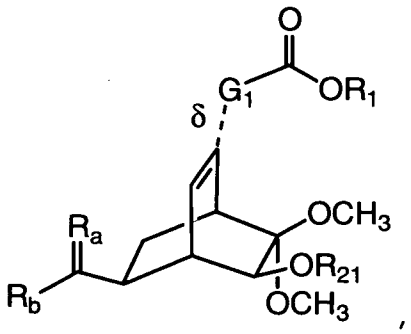
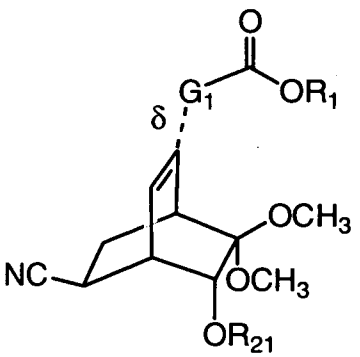
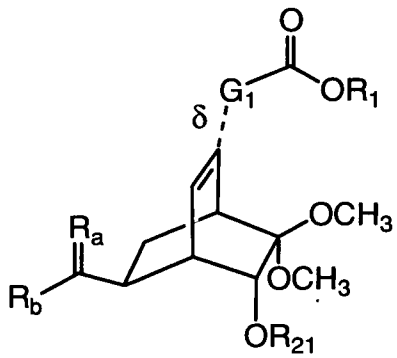
In an embodiment, the process further comprises:

h) exposing the product of step g) to a second suitable Bronsted acid in the presence of methanol so as to form a compound having the structure

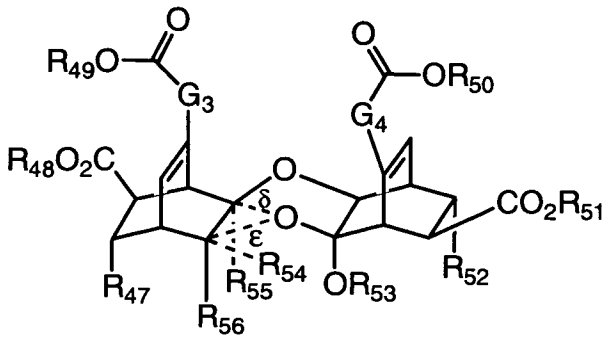


In an embodiment, the process further comprises:

exposing the final product to a compound having the structure R_{21}-L, wherein R_{16} is  ,  ,  ,  , or  ; and L is Cl,  , or  ; in the presence of a base so as to form a compound having the structure

 ,  ,  , or  .

This invention provides a process for preparing a compound having the structure



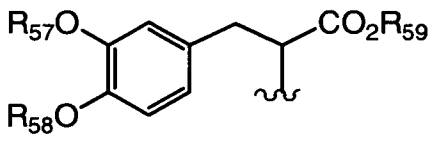
wherein ε and δ are present or absent;

wherein R_{54} and R_{55} are present or absent; and

when ε is present; δ and R_{54} are absent, and R_{55} is present; and

when δ is present; ε and R_{55} are absent, and R_{54} is present;

wherein G_3 and G_4 are each, independently, is C_{1-10} alkylene, C_{2-10} alkenylene, or C_{2-10} alkynylene;

R_{48}, R_{49}, R_{50}, and R_{51} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; or ,

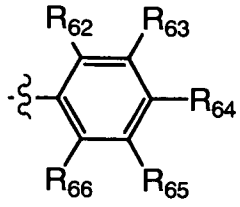
wherein R_{57} and R_{58} are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, unsubstituted or substituted aryl(C_{1-10})alkyl, or $-SO_2R_{60}$,

wherein R_{60} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

wherein R_{59} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

wherein R_{53} is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, unsubstituted or substituted aryl(C_{1-10})alkyl, or $-SO_2R_{61}$,

wherein R_{61} is C_{1-10} alkyl, or unsubstituted or substituted aryl;



R_{47} and R_{52} are each H, CN, or ,

wherein R_{62}, R_{63}, R_{64}, R_{65}, and R_{66} are each, independently, H, halogen, $-NO_2$, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; $-OR_{67}$, $-SR_{67}$, $-OSO_2R_{67}$, or $-NR_{67}R_{68}$,

wherein R_{67} and R_{68} are each, independently, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or unsubstituted or substituted aryl; and

wherein R_{54} when present, R_{55} when present, and R_{56} are each, independently, H or OR_{69},

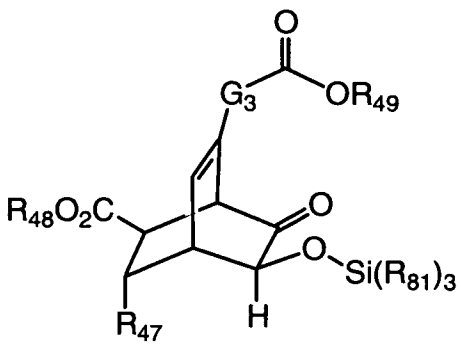
wherein R_{69} is H or C_{1-10} alkyl; or

wherein each occurrence of alkyl, alkylene, alkenyl, alkenylene, alkynyl, alkynylene is branched or unbranched, unsubstituted or substituted;

or a salt thereof;

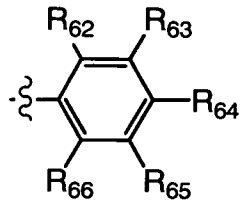
comprising:

a) contacting a compound having the structure



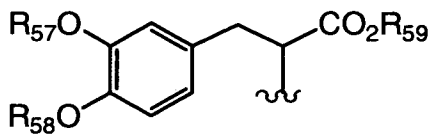
,

wherein G_3 is C_{1-10} alkylene, C_{2-10} alkenylene, or C_{2-10} alkynylene;

R_{47} is H, CN, or ,

wherein R_{62}, R_{63}, R_{64}, R_{65}, and R_{66} are each, independently, H, halogen, $-NO_2$, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; $-OR_{67}$, $-SR_{67}$, $-OSO_2R_{67}$, or $-NR_{67}R_{68}$,

wherein R_{67} and R_{68} are each, independently, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or unsubstituted or substituted aryl;

R_{48} and R_{49} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; or ,

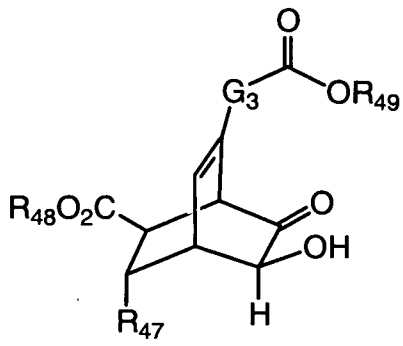
wherein R_{57} and R_{58} are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, unsubstituted or substituted aryl(C_{1-10})alkyl, or $-SO_2R_{60}$,

wherein R_{60} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

wherein R_{59} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

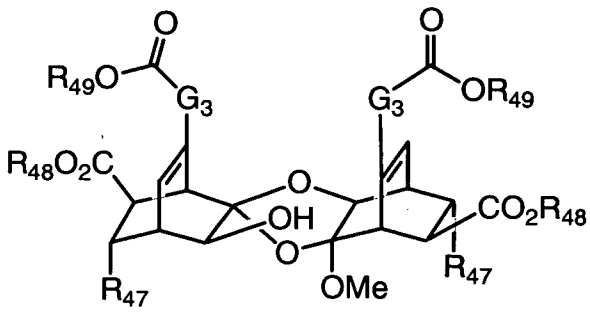
wherein each occurrence of R_{81} is, independently, C_{1-10} alkyl, or unsubstituted or substituted aryl;

with tetra-n-butylammonium fluoride so as to form a compound having the structure



;

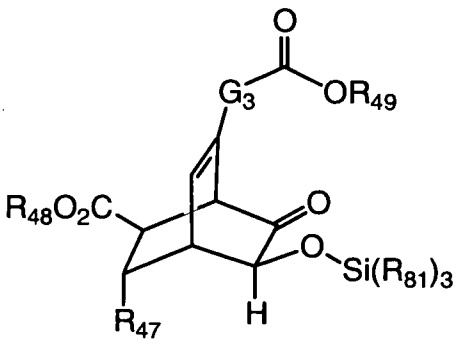
b) contacting the product of step a) with sodium hydride so as to form a compound having the structure



;

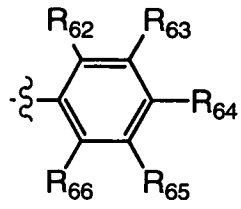
or

a') contacting a compound having the structure



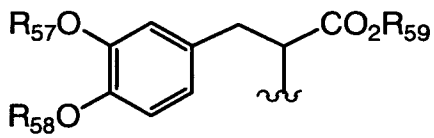
,

wherein G_3 is C_{1-10} alkylene, C_{2-10} alkenylene, or C_{2-10} alkynylene;

R_{47} is H, CN, or ,

wherein R_{62}, R_{63}, R_{64}, R_{65}, and R_{66} are each, independently, H, halogen, $-NO_2$, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; $-OR_{67}$, $-SR_{67}$, $-OSO_2R_{67}$, or $-NR_{67}R_{68}$,

wherein R_{67} and R_{68} are each, independently, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or unsubstituted or substituted aryl;

R_{48} and R_{49} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; or ,

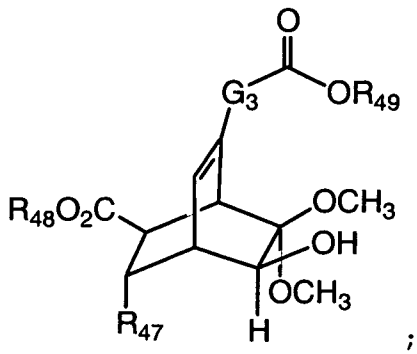
wherein R_{57} and R_{58} are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, unsubstituted or substituted aryl(C_{1-10})alkyl, or $-SO_2R_{60}$,

wherein R_{60} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

wherein R_{59} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

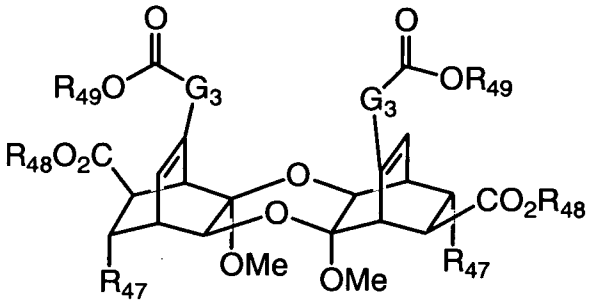
wherein each occurrence of R_{81} is, independently, C_{1-10} alkyl, or unsubstituted or substituted aryl;

with a first suitable Bronsted acid in the presence of methanol so as to form a compound having the structure



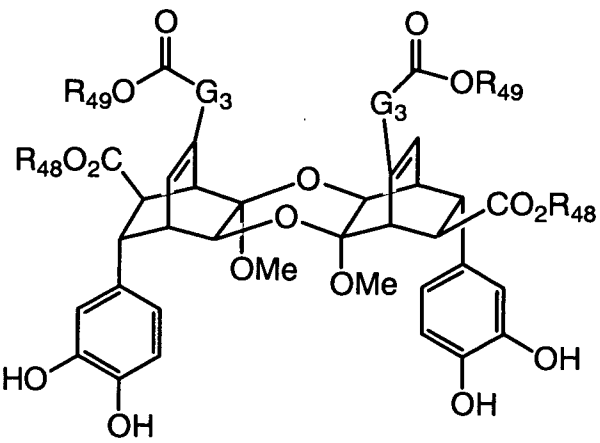
;

b') contacting the product of a') with a first suitable Lewis acid so as to form a compound having the structure



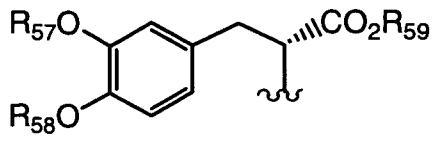
;

c') contacting the product of step b') with a second suitable Lewis acid so as to form a compound having the structure



.

In an embodiment of the process,

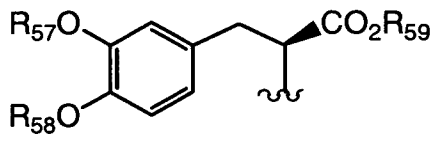
R_{48} and R_{49} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; or ,

wherein R_{57} and R_{58} are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, unsubstituted or substituted aryl(C_{1-10})alkyl, or $-SO_2R_{60}$,

wherein R_{60} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

wherein R_{59} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl.

In an embodiment of the process,

R_{48} and R_{49} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; or ,

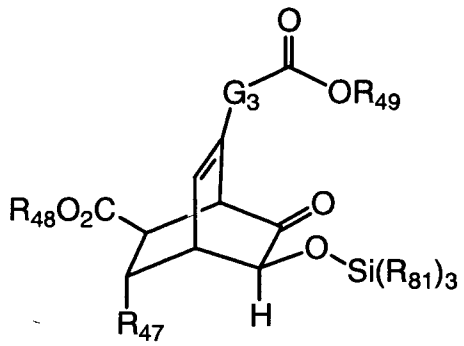
wherein R_{57} and R_{58} are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, unsubstituted or substituted aryl(C_{1-10})alkyl, or $-SO_2R_{60}$,

wherein R_{60} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

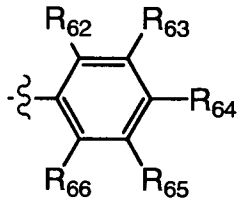
wherein R_{59} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl.

In an embodiment, the process further comprises:

a) contacting a compound having the structure

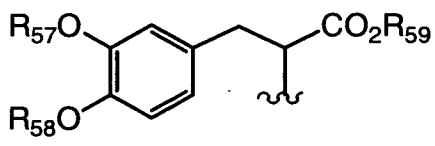


wherein G_3 is C_{1-10} alkylene, C_{2-10} alkenylene, or C_{2-10} alkynylene;

R_{47} is H, CN, or ,

wherein R_{62}, R_{63}, R_{64}, R_{65}, and R_{66} are each, independently, H, halogen, $-NO_2$, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; $-OR_{67}$, $-SR_{67}$, $-OSO_2R_{67}$, or $-NR_{67}R_{68}$,

wherein R_{67} and R_{68} are each, independently, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or unsubstituted or substituted aryl;

R_{48} and R_{49} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; or ,

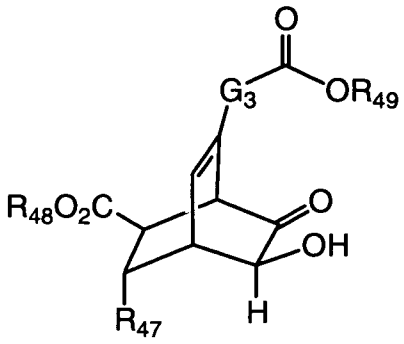
wherein R_{57} and R_{58} are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, unsubstituted or substituted aryl(C_{1-10})alkyl, or $-SO_2R_{60}$,

wherein R_{60} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

wherein R_{59} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

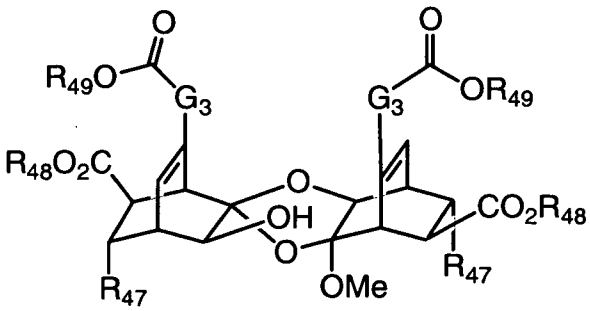
wherein each occurrence of R_{81} is, independently, C_{1-10} alkyl, or unsubstituted or substituted aryl;

with tetra-n-butylammonium fluoride so as to form a compound having the structure



;

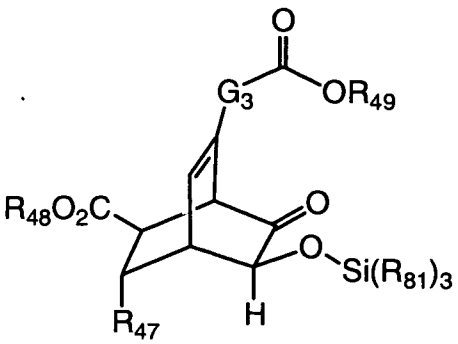
b) contacting the product of step a) with sodium hydride so as to form a compound having the structure



.

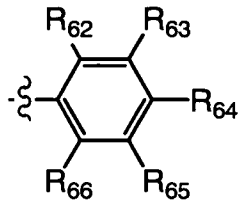
In an embodiment, the process further comprises:

a') contacting a compound having the structure



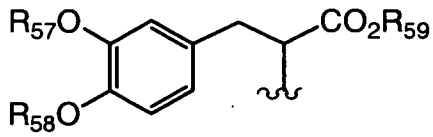
,

wherein G_3 is C_{1-10} alkylene, C_{2-10} alkenylene, or C_{2-10} alkynylene;

R_{47} is H, CN, or ,

wherein R_{62}, R_{63}, R_{64}, R_{65}, and R_{66} are each, independently, H, halogen, $-NO_2$, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; $-OR_{67}$, $-SR_{67}$, $-OSO_2R_{67}$, or $-NR_{67}R_{68}$,

wherein R_{67} and R_{68} are each, independently, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or unsubstituted or substituted aryl;

R_{48} and R_{49} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; or ,

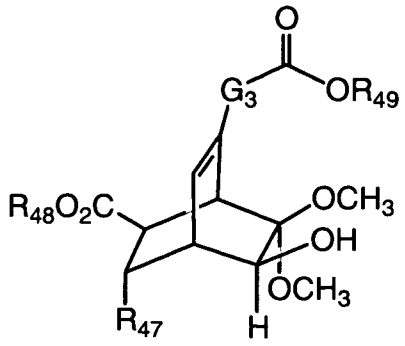
wherein R_{57} and R_{58} are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, unsubstituted or substituted aryl(C_{1-10})alkyl, or $-SO_2R_{60}$,

wherein R_{60} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

wherein R_{59} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

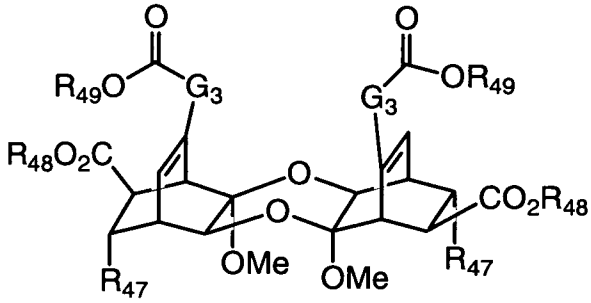
wherein each occurrence of R_{81} is, independently, C_{1-10} alkyl, or unsubstituted or substituted aryl;

with a first suitable Bronsted acid in the presence of methanol so as to form a compound having the structure



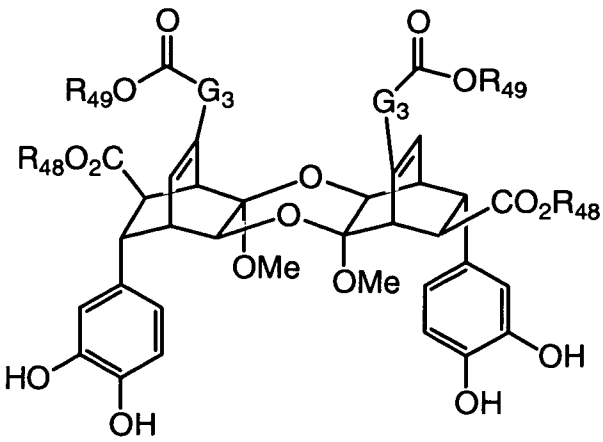
;

b') contacting the product of a') with a first suitable Lewis acid so as to form a compound having the structure



;

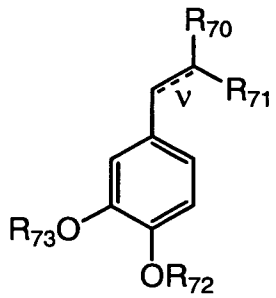
c') contacting the product of step b') with a second suitable Lewis acid so as to form a compound having the structure



.

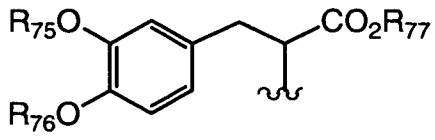
In an embodiment of the process, the compound prepared is selected from the group consisting of: Compound 2, 43, and 48.

This invention provides a process for preparing a compound having the structure



wherein ν is present or absent;

wherein R_{70} and R_{71} are each, independently, H, OH, $-CO_2R_{74}$,

wherein R_{74} is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or ,

wherein R_{75} and R_{76} are independently H; C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; or $-SO_2R_{78}$,

wherein R_{78} is C_{1-10} alkyl; or unsubstituted or substituted aryl; and

wherein R_{77} is H; C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl;

wherein R_{72} and R_{73} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; $-SO_2R_{79}$, or $-Si(R_{80})_3$,

wherein R_{79} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

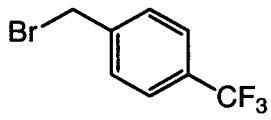
wherein each occurrence of R_{80} is, independently, C_{1-10} alkyl, or unsubstituted or substituted aryl; and

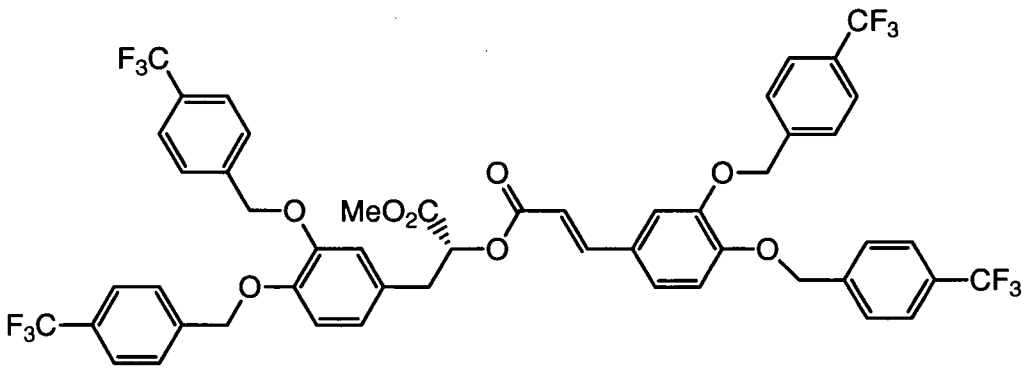
wherein each occurrence of alkyl, alkylene, alkenyl, alkenylene, alkynyl, or alkynylene is branched or unbranched, unsubstituted or substituted;

or a salt thereof;

comprising:

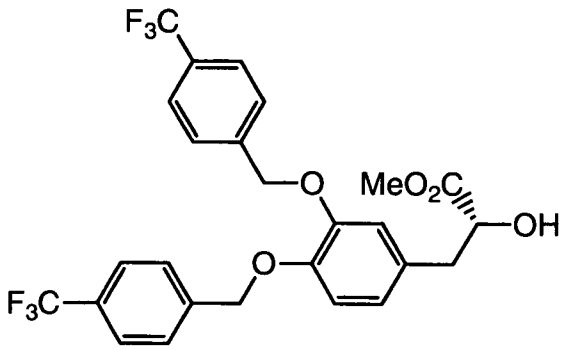
a) contacting rosmarinic acid with $TMSCHN_2$;

b) contacting the product of step a) with a compound having the structure  in the presence of a first suitable base so as to form a compound having the structure



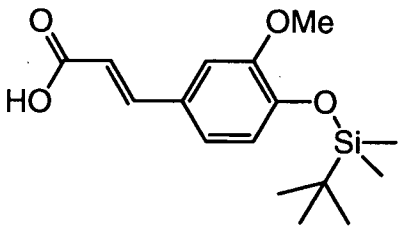
In an embodiment, the process further comprises:

c) contacting the product of step b) with a second suitable base so as to form a compound having the structure



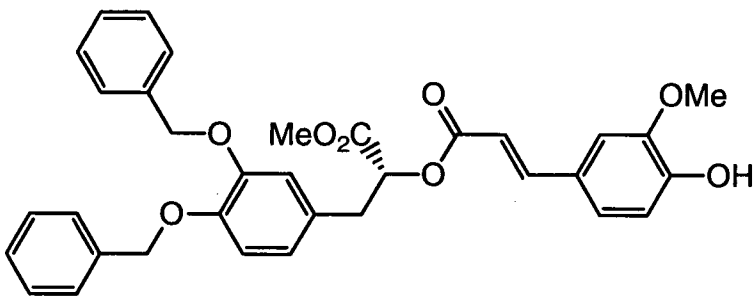
;

d) contacting the product of step c) with a compound having the structure

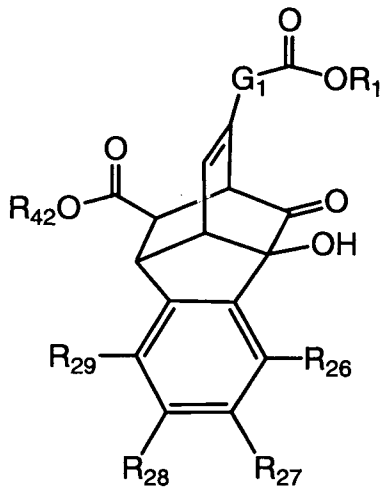


in the presence of *N*-ethyl-*N'*-(3-dimethylaminopropyl)carbodiimide and a third suitable base;

e) contacting the product of step d) with tetra-n-butylammonium fluoride so as to form a compound having the structure

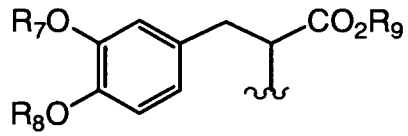


This invention provides a process for preparing a compound having the structure



wherein G_1 is C_{1-10} alkylene, C_{2-10} alkenylene, or C_{2-10} alkynylene;

R_1 is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or



,

wherein R_7 and R_8 are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; or $-SO_2R_{10}$,

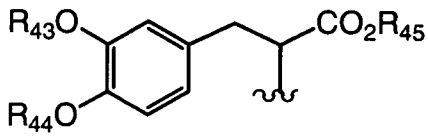
wherein R_{10} is C_{1-10} alkyl, or unsubstituted or substituted aryl;

R_9 is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl;

R_{26}, R_{27}, R_{28}, and R_{29} are each, independently, H, halogen, $-NO_2$, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; $-OR_{31}$, $-SR_{31}$, $-OSO_2R_{31}$, or $-NR_{31}R_{32}$,

wherein R_{31} and R_{32} are each, independently, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or unsubstituted or substituted aryl; and

R_{42} is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or



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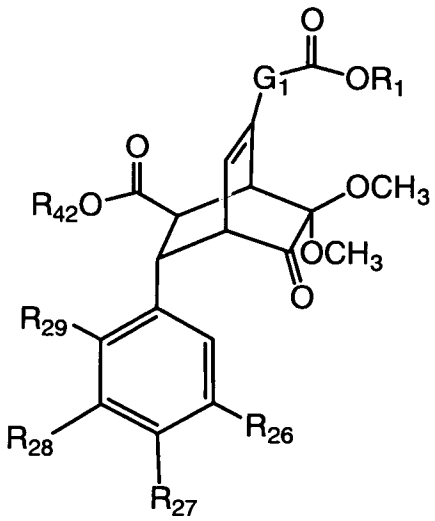
wherein R_{43} and R_{44} are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; or $-SO_2R_{46}$,

wherein R_{46} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

R_{45} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl;

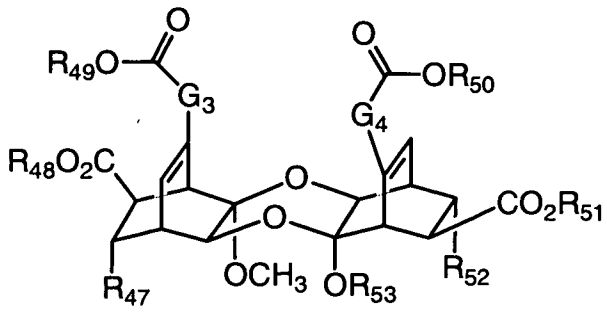
comprising:

a) exposing a compound having the structure

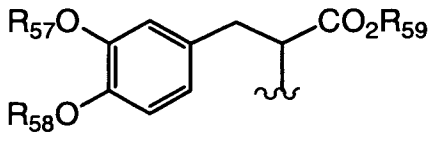


to a suitable Lewis acid so as to form the compound.

This invention further provides a process for preparing a compound having the structure



wherein G_3 and G_4 are each, independently, is C_{1-10} alkylene, C_{2-10} alkenylene, or C_{2-10} alkynylene;

R_{48}, R_{49}, R_{50}, and R_{51} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; or ,

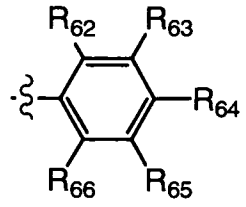
wherein R_{57} and R_{58} are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, unsubstituted or substituted aryl(C_{1-10})alkyl, or $-SO_2R_{60}$,

wherein R_{60} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

wherein R_{59} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

wherein R_{53} is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, unsubstituted or substituted aryl(C_{1-10})alkyl, or $-SO_2R_{61}$,

wherein R_{61} is C_{1-10} alkyl, or unsubstituted or substituted aryl;

R_{47} and R_{52} are each H, CN, or ,

wherein R_{62}, R_{63}, R_{64}, R_{65}, and R_{66} are each, independently, H, halogen, $-NO_2$, C_{1-10} alkyl, C_{2-10}

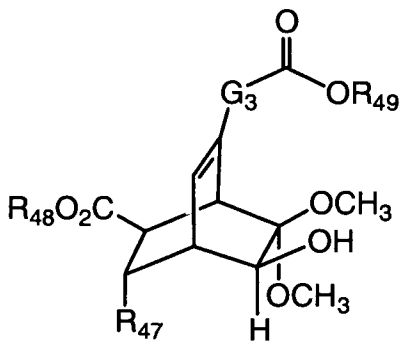
alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; $-OR_{67}$, $-SR_{67}$, $-OSO_2R_{67}$, or $-NR_{67}R_{68}$, wherein R_{67} and R_{68} are each, independently, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or unsubstituted or substituted aryl; or

wherein each occurrence of alkyl, alkylene, alkenyl, alkenylene, alkynyl, alkynylene is branched or unbranched, unsubstituted or substituted;

or a salt thereof;

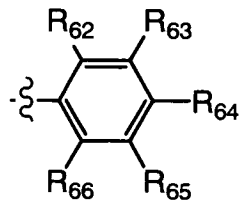
comprising:

a) contacting a compound having the structure



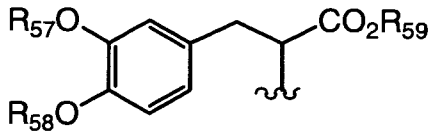
,

wherein G_3 is C_{1-10} alkylene, C_{2-10} alkenylene, or C_{2-10} alkynylene;

R_{47} is H, CN, or ,

wherein R_{62}, R_{63}, R_{64}, R_{65}, and R_{66} are each, independently, H, halogen, $-NO_2$, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; $-OR_{67}$, $-SR_{67}$, $-OSO_2R_{67}$, or $-NR_{67}R_{68}$,

wherein R_{67} and R_{68} are each, independently, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or unsubstituted or substituted aryl;

R_{48} and R_{49} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; or ,

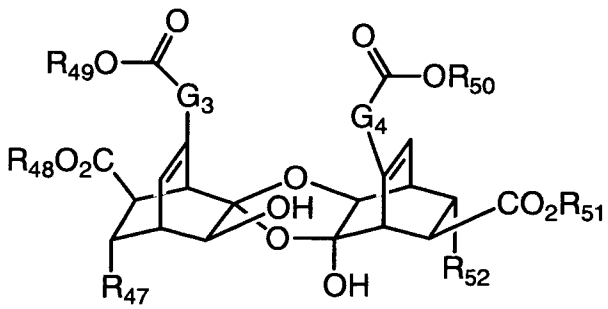
wherein R_{57} and R_{58} are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, unsubstituted or substituted aryl(C_{1-10})alkyl, or $-SO_2R_{60}$,

wherein R_{60} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

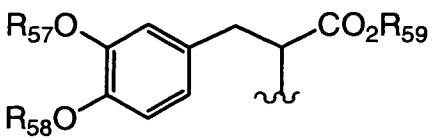
wherein R_{59} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl;

with a suitable Lewis acid so as to form the compound.

This invention provides a process for preparing a compound having the structure



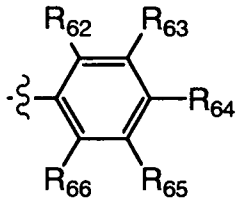
wherein G_3 and G_4 are each, independently, is C_{1-10} alkylene, C_{2-10} alkenylene, or C_{2-10} alkynylene;

R_{48}, R_{49}, R_{50}, and R_{51} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; or ,

wherein R_{57} and R_{58} are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, unsubstituted or substituted aryl(C_{1-10})alkyl, or $-SO_2R_{60}$,

wherein R_{60} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

wherein R_{59} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

R_{47} and R_{52} are each H, CN, or 

,

wherein R_{62}, R_{63}, R_{64}, R_{65}, and R_{66} are each, independently, H, halogen, $-NO_2$, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; $-OR_{67}$, $-SR_{67}$, $-OSO_2R_{67}$, or $-NR_{67}R_{68}$,

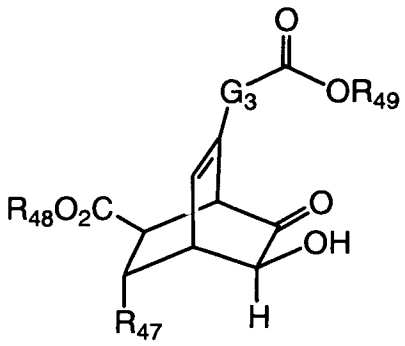
wherein R_{67} and R_{68} are each, independently, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or unsubstituted or substituted aryl; or

wherein each occurrence of alkyl, alkylene, alkenyl, alkenylene, alkynyl, alkynylene is branched or unbranched, unsubstituted or substituted;

or a salt thereof;

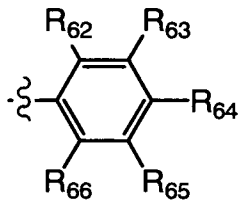
comprising:

a) contacting a compound having the structure



,

wherein G_3 is C_{1-10} alkylene, C_{2-10} alkenylene, or C_{2-10} alkynylene;

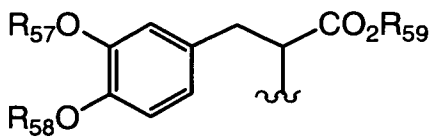


R_{47} is H, CN, or ,

wherein R_{62}, R_{63}, R_{64}, R_{65}, and R_{66} are each, independently, H, halogen, $-NO_2$, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; $-OR_{67}$, $-SR_{67}$, $-OSO_2R_{67}$, or $-NR_{67}R_{68}$,

wherein R_{67} and R_{68} are each, independently, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or unsubstituted or substituted aryl;

R_{48} and R_{49} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; or



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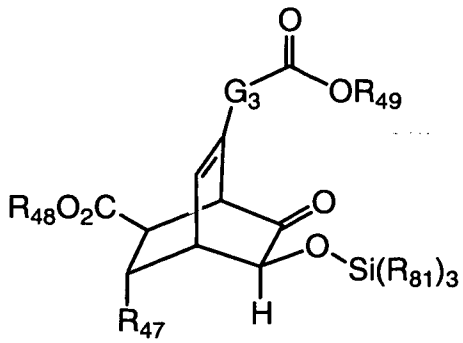
wherein R_{57} and R_{58} are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, unsubstituted or substituted aryl(C_{1-10})alkyl, or $-SO_2R_{60}$,

wherein R_{60} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

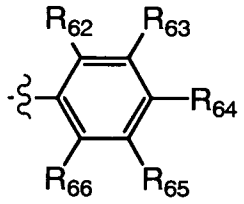
wherein R_{59} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl;

with a suitable base so as to form the compound.

This invention provides a process for preparing a compound having the structure

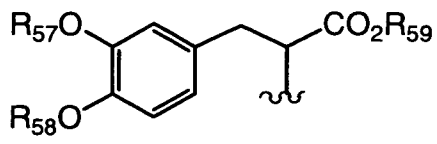


wherein G_3 is C_{1-10} alkylene, C_{2-10} alkenylene, or C_{2-10} alkynylene;

R_{47} is H, CN, or ,

wherein R_{62}, R_{63}, R_{64}, R_{65}, and R_{66} are each, independently, H, halogen, $-NO_2$, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; $-OR_{67}$, $-SR_{67}$, $-OSO_2R_{67}$, or $-NR_{67}R_{68}$,

wherein R_{67} and R_{68} are each, independently, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or unsubstituted or substituted aryl;

R_{48} and R_{49} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; or ,

wherein R_{57} and R_{58} are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, unsubstituted or substituted aryl(C_{1-10})alkyl, or $-SO_2R_{60}$,

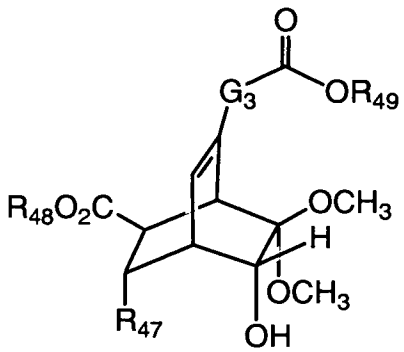
wherein R_{60} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

wherein R_{59} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

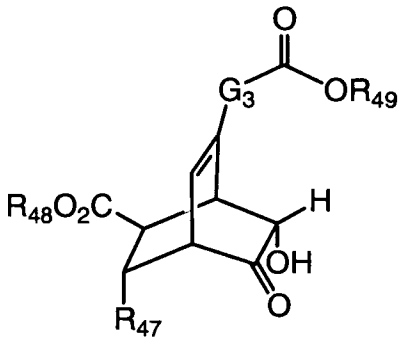
wherein each occurrence of R_{81} is, independently, C_{1-10} alkyl, or unsubstituted or substituted aryl;

comprising:

a) contacting a compound having the structure



with a suitable Bronsted acid so as to form a compound having the structure



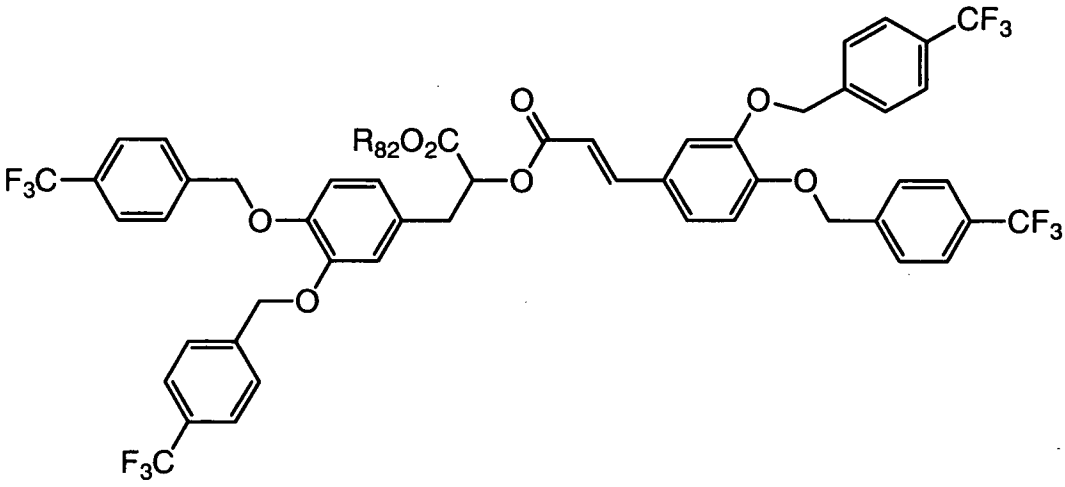
;

b) contacting the product of step a) with a suitable hydride reducing agent;

c) contacting the product of step b) with a suitable silylating agent;

d) contacting the product of step c) with a suitable oxidizing agent so as to form the compound.

This invention provides a process for preparing a compound having the structure



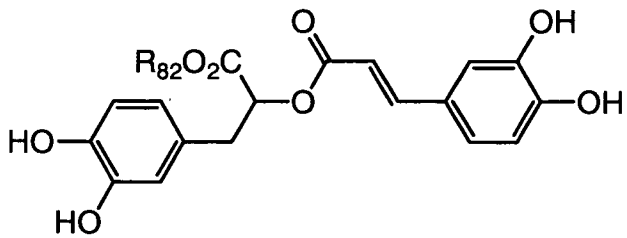
wherein R_{82} is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl;

wherein each occurrence of alkyl, alkylene, alkenyl, alkenylene, alkynyl, or alkynylene is branched or unbranched, unsubstituted or substituted;

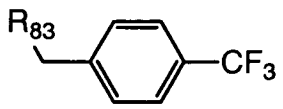
or a salt thereof;

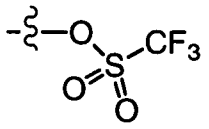
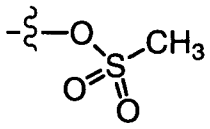
comprising:

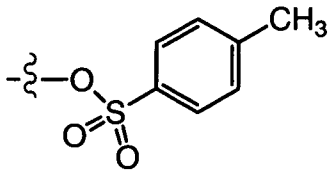
a) contacting a compound having the structure



with a compound having the structure



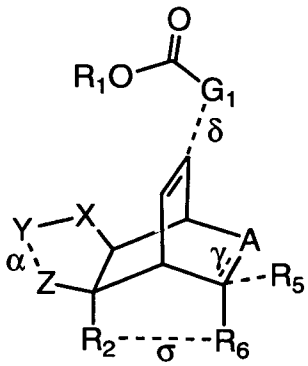
wherein R_{83} is halogen, -OH,  ,  ,



or ;

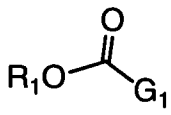
in the presence of a suitable base so as to form the compound.

This invention provides a composition, free of plant extract, comprising a compound having the structure



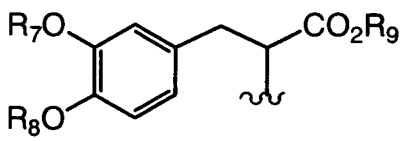
wherein

α, γ, δ and σ are each, independently, present or absent;

wherein when δ is absent,  is absent;

G_1 is C_{1-10} alkylene, C_{2-10} alkenylene, or C_{2-10} alkynylene;

R_1 is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or



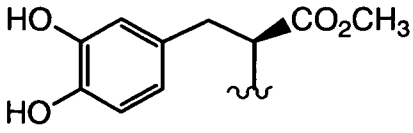
,

wherein R_7 and R_8 are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; or $-SO_2R_{10}$,

wherein R_{10} is C_{1-10} alkyl, or unsubstituted or substituted aryl;

R_9 is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

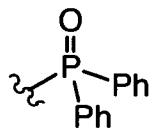
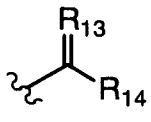
when R_7 and R_8 are H and R_9 is CH_3, then R_1 is



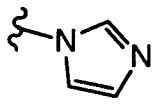
; and

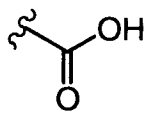
when γ is present; R_5 is absent and A is C-R_4,

wherein R_4 is H, halogen, or OR_{11},

wherein R_{11} is H, C_{1-10} alkyl, $-CH_2SH$, $-BHCH_2CH_3$, $-CH{=}SH$, , $-SO_2R_{12}$, , or $-Si(R_{15})_3$;

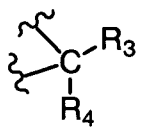
wherein R_{12} and each occurrence of R_{15} is C_{1-10} alkyl; or unsubstituted or substituted aryl; and

R_{13} is S or O; and R_{14} is $-SCH_3$, , or



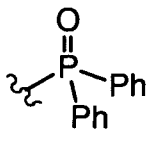
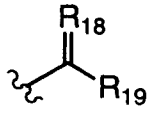
; and

when γ is absent; R_5 is present and A is a direct bond or

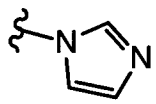
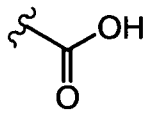


;

wherein R_3 and R_4 are each, independently, H, halogen, or OR_{16};

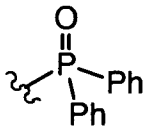
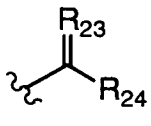
wherein R_{16} is H, C_{1-10} alkyl, $-CH_2SH$, $-BHCH_2CH_3$, $-CH{=}SH$, , $-SO_2R_{17}$, , or $-Si(R_{20})_3$;

wherein R_{17} and each occurrence of R_{20} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

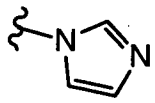
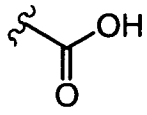
R_{18} is S or O; and R_{19} is $-SCH_3$, , or ; or

R_3 and R_4 taken together form =O; and

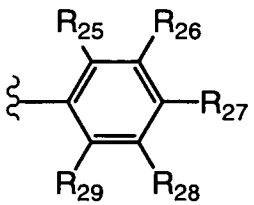
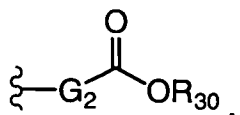
wherein R_5 is H, halogen, or OR_{21},

wherein R_{21} is H, C_{1-10} alkyl, $-CH_2SH$, $-BHCH_2CH_3$, $-CH{=}SH$, , $-SO_2R_{22}$, , or $-Si(R_{25})_3$,

wherein R_{22} and each occurrence of R_{25} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

R_{23} is S or O; and R_{24} is $-SCH_3$, , or ; and

when σ is absent;

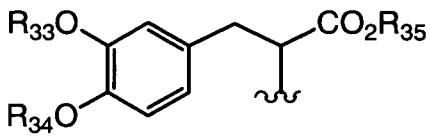
R_2 is H, , or ;

wherein R_{25}, R_{26}, R_{27}, R_{28}, and R_{29} are each, independently, H, halogen, $-NO_2$, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; $-OR_{31}$, $-SR_{31}$, $-OSO_2R_{31}$, or $-NR_{31}R_{32}$,

wherein R_{31} and R_{32} are each, independently, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or unsubstituted or substituted aryl;

wherein G_2 is C_{1-10} alkylene, C_{2-10} alkenylene, or C_{2-10} alkynylene; and

R_{30} is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or



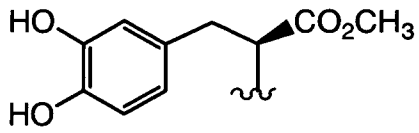
,

wherein R_{33} and R_{34} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; or $-SO_2R_{36}$,

wherein R_{36} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

wherein R_{35} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

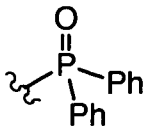
when R_{33} and R_{34} are H and R_{35} is CH_3, then R_{30} is



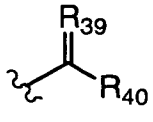
; and

R_6 is H, halogen, or OR_{37};

wherein R_{37} is H, C_{1-10} alkyl, $-CH_2SH$, $-BHCH_2CH_3$, $-CH{=}SH$,



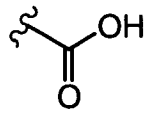
, $-SO_2R_{38}$,



, or $-Si(R_{41})_3$;

wherein R_{38} and each occurrence of R_{41} is C_{1-10} alkyl; or unsubstituted or substituted aryl;

R_{39} is S or O; and R_{40} is $-SCH_3$; -NH-aryl,

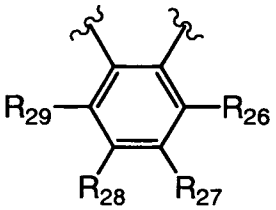


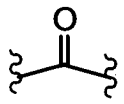
heteroaryl, heterocyclyl; or ; or

R_5 when present and R_6 taken together form =O; or

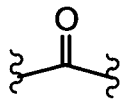
R_4 joined to R_6 form a 5-membered heterocyclic ring; and

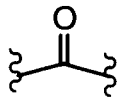
when σ is present;

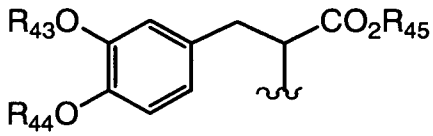


R_2 is ; and R_6 is a direct bond or ;

and

wherein X is a direct bond, , or $C(OMe)_2$;

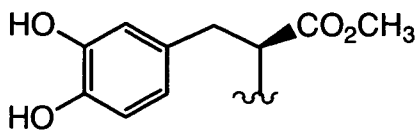
Y is H or OR_{42}; or when α is present, Y is ;

wherein R_{42} is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or ,

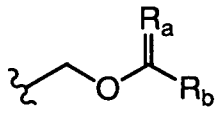
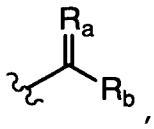
wherein R_{43} and R_{44} are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; or $-SO_2R_{46}$,

wherein R_{46} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

R_{45} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and when R_{43} and R_{44} are H and R_{45} is CH_3,

then R_{42} is  ; or

wherein each occurrence of alkyl, alkylene, alkenyl, alkenylene, alkynyl, or alkynylene is branched or unbranched, unsubstituted or substituted;

Z is H, CN,  or ,

wherein R_a is S or O; R_b is -O-(C_1-C_{10})alkyl, -O-(C_2-C_{10})alkenyl, heterocyclyl, or heteroaryl; or

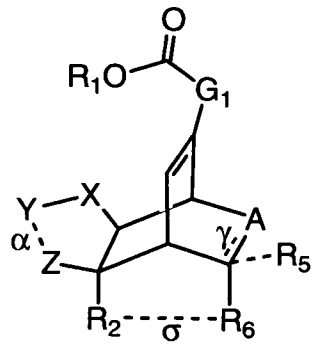
when α is present, Z is -CH=CH-;

and

when α is present, R_1 is other than methyl;

or a salt thereof.

In an embodiment, the composition comprises a compound having the structure

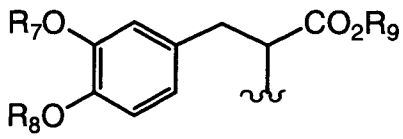


wherein

α, γ, and σ are each, independently, present or absent;

G_1 is C_{1-10} alkylene, C_{2-10} alkenylene, or C_{2-10} alkynylene;

R_1 is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or



,

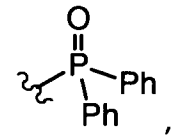
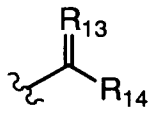
wherein R_7 and R_8 are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; or $-SO_2R_{10}$,

wherein R_{10} is C_{1-10} alkyl, or unsubstituted or substituted aryl;

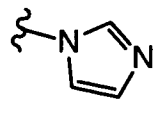
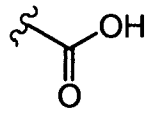
R_9 is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

when γ is present; R_5 is absent and A is C-R_4,

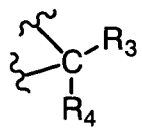
wherein R_4 is H, halogen, or OR_{11},

wherein R_{11} is H, C_{1-10} alkyl, $-CH_2SH$, $-BHCH_2CH_3$, -CH=SH, , $-SO_2R_{12}$, , or $-Si(R_{15})_3$;

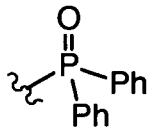
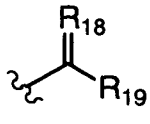
wherein R_{12} and each occurrence of R_{15} is C_{1-10} alkyl; or unsubstituted or substituted aryl; and

R_{13} is S or O; and R_{14} is $-SCH_3$, , or ; and

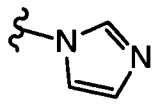
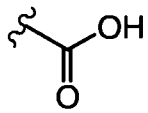
when γ is absent; R_5 is present and A is a direct bond or

;

wherein R_3 and R_4 are each, independently, H, halogen, or OR_{16};

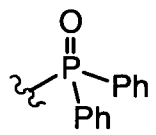
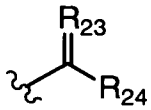
wherein R_{16} is H, C_{1-10} alkyl, $-CH_2SH$, $-BHCH_2CH_3$, $-CH{=}SH$, , $-SO_2R_{17}$, , or $-Si(R_{20})_3$;

wherein R_{17} and each occurrence of R_{20} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

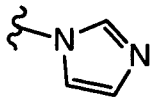
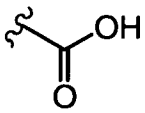
R_{18} is S or O; and R_{19} is $-SCH_3$, , or ; or

R_3 and R_4 taken together form =O; and

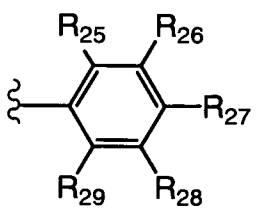
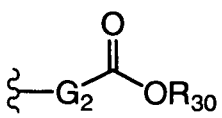
wherein R_5 is H, halogen, or OR_{21},

wherein R_{21} is H, C_{1-10} alkyl, $-CH_2SH$, $-BHCH_2CH_3$, $-CH{=}SH$, , $-SO_2R_{22}$, , or $-Si(R_{25})_3$,

wherein R_{22} and each occurrence of R_{25} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

R_{23} is S or O; and R_{24} is $-SCH_3$, , or ; and

when σ is absent;

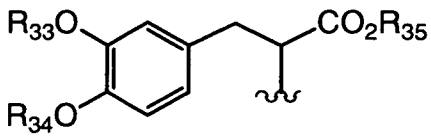
R_2 is H, , or ;

wherein R_{25}, R_{26}, R_{27}, R_{28}, and R_{29} are each, independently, H, halogen, $-NO_2$, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; $-OR_{31}$, $-SR_{31}$, $-OSO_2R_{31}$, or $-NR_{31}R_{32}$,

wherein R_{31} and R_{32} are each, independently, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or unsubstituted or substituted aryl;

wherein G_2 is C_{1-10} alkylene, C_{2-10} alkenylene, or C_{2-10} alkynylene; and

R_{30} is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or



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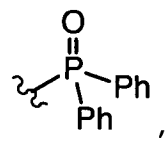
wherein R_{33} and R_{34} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; or $-SO_2R_{36}$,

wherein R_{36} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

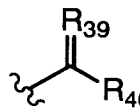
wherein R_{35} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

R_6 is H, halogen, or OR_{37};

wherein R_{37} is H, C_{1-10} alkyl, $-CH_2SH$, $-BHCH_2CH_3$, $-CH{=}SH$,

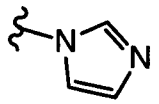


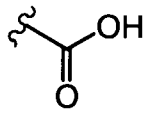
, $-SO_2R_{38}$,



, or $-Si(R_{41})_3$;

wherein R_{38} and each occurrence of R_{41} is C_{1-10} alkyl; or unsubstituted or substituted aryl;

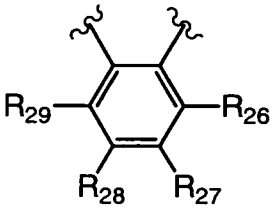
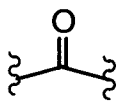
R_{39} is S or O; and R_{40} is $-SCH_3$;  ; or

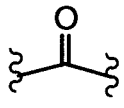
 ; or

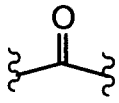
R_5 when present and R_6 taken together form =O; or

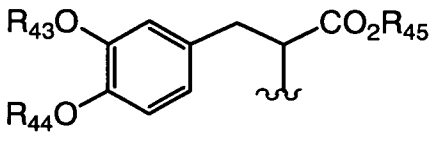
R_4 joined to R_6 form a 5-membered heterocyclic ring; and

when σ is present;

R_2 is  ; and R_6 is a direct bond or  ; and

wherein X is a direct bond,  , or $C(OMe)_2$;

Y is H or OR_{42}; or when α is present, Y is  ;

wherein R_{42} is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or  ,

wherein R_{43} and R_{44} are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; or $-SO_2R_{46}$,

wherein R_{46} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

R_{45} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; or

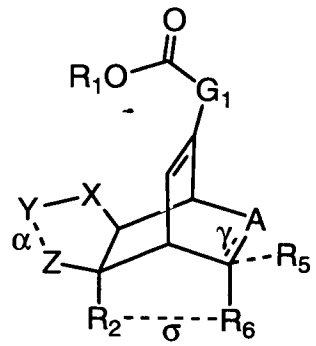
wherein each occurrence of alkyl, alkylene, alkenyl, alkenylene, alkynyl, or alkynylene is branched or unbranched, unsubstituted or substituted;

Z is H or CN; or when α is present, Z is -CH=CH-; and

when α is present, R_1 is other than methyl;

or a salt thereof.

In an embodiment, the composition comprises the compound has the structure

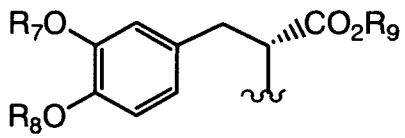


wherein

α, γ, and σ are each, independently, present or absent;

G_1 is C_{1-10} alkylene, C_{2-10} alkenylene, or C_{2-10} alkynylene;

R_1 is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or



,

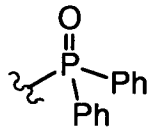
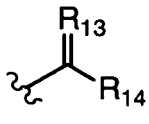
wherein R_7 and R_8 are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; or $-SO_2R_{10}$,

wherein R_{10} is C_{1-10} alkyl, or unsubstituted or substituted aryl;

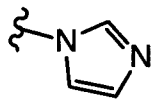
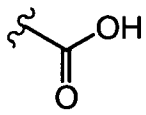
R_9 is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

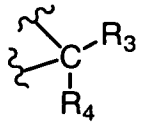
when γ is present; R_5 is absent and A is C-R_4,

wherein R_4 is H, halogen, or OR_{11},

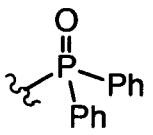
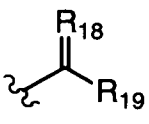
wherein R_{11} is H, C_{1-10} alkyl, $-CH_2SH$, $-BHCH_2CH_3$, -CH=SH, , $-SO_2R_{12}$, , or $-Si(R_{15})_3$;

wherein R_{12} and each occurrence of R_{15} is C_{1-10} alkyl; or unsubstituted or substituted aryl; and

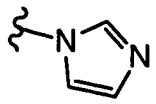
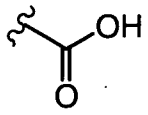
R_{13} is S or O; and R_{14} is $-SCH_3$, , or ; and

when γ is absent; R_5 is present and A is a direct bond or ;

wherein R_3 and R_4 are each, independently, H, halogen, or OR_{16};

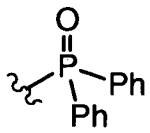
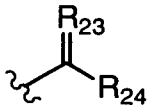
wherein R_{16} is H, C_{1-10} alkyl, $-CH_2SH$, $-BHCH_2CH_3$, -CH=SH, , $-SO_2R_{17}$, , or $-Si(R_{20})_3$;

wherein R_{17} and each occurrence of R_{20} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

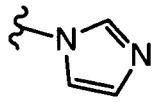
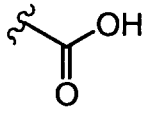
R_{18} is S or O; and R_{19} is $-SCH_3$, , or ; or

R_3 and R_4 taken together form =O; and

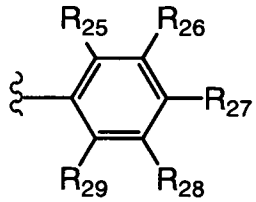
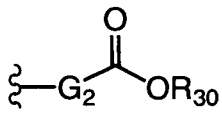
wherein R_5 is H, halogen, or OR_{21},

wherein R_{21} is H, C_{1-10} alkyl, $-CH_2SH$, $-BHCH_2CH_3$, $-CH{=}SH$, , $-SO_2R_{22}$, , or $-Si(R_{25})_3$,

wherein R_{22} and each occurrence of R_{25} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

R_{23} is S or O; and R_{24} is $-SCH_3$, , or ; and

when σ is absent;

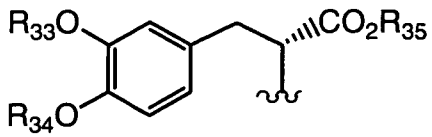
R_2 is H, , or ;

wherein R_{25}, R_{26}, R_{27}, R_{28}, and R_{29} are each, independently, H, halogen, $-NO_2$, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; $-OR_{31}$, $-SR_{31}$, $-OSO_2R_{31}$, or $-NR_{31}R_{32}$,

wherein R_{31} and R_{32} are each, independently, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or unsubstituted or substituted aryl;

wherein G_2 is C_{1-10} alkylene, C_{2-10} alkenylene, or C_{2-10} alkynylene; and

R_{30} is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or



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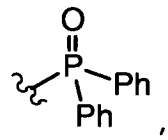
wherein R_{33} and R_{34} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; or $-SO_2R_{36}$,

wherein R_{36} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

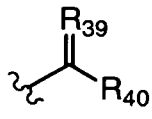
wherein R_{35} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

R_6 is H, halogen, or OR_{37};

wherein R_{37} is H, C_{1-10} alkyl, $-CH_2SH$, $-BHCH_2CH_3$, $-CH=SH$,



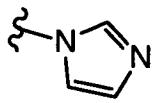
, $-SO_2R_{38}$,



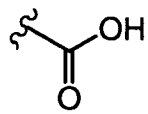
, or $-Si(R_{41})_3$;

wherein R_{38} and each occurrence of R_{41} is C_{1-10} alkyl; or unsubstituted or substituted aryl;

R_{39} is S or O; and R_{40} is $-SCH_3$;



; or

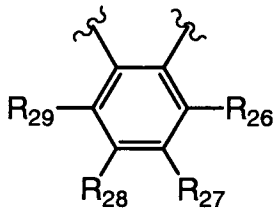
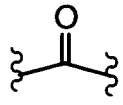


; or

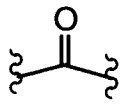
R_5 when present and R_6 taken together form =O; or

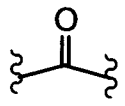
R_4 joined to R_6 form a 5-membered heterocyclic ring; and

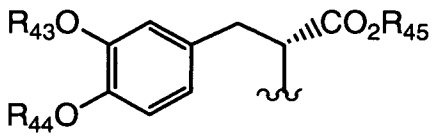
when σ is present;

R_2 is  ; and R_6 is a direct bond or ;

and

wherein X is a direct bond, , or $C(OMe)_2$;

Y is H or OR_{42}; or when α is present, Y is ;

wherein R_{42} is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or ,

wherein R_{43} and R_{44} are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; or $-SO_2R_{46}$,

wherein R_{46} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

R_{45} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; or

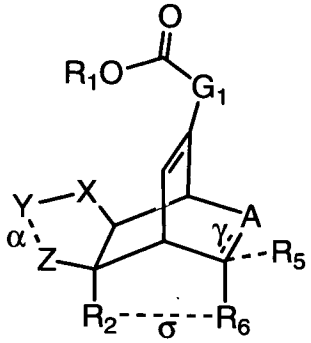
wherein each occurrence of alkyl, alkylene, alkenyl, alkenylene, alkynyl, or alkynylene is branched or unbranched, unsubstituted or substituted;

Z is H or CN; or when α is present, Z is -CH=CH-; and

when α is present, R_1 is other than methyl;

or a salt thereof.

In an embodiment, the composition comprises the compound has the structure

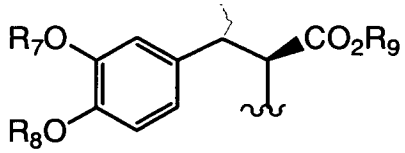


wherein

α, γ, and σ are each, independently, present or absent;

G_1 is C_{1-10} alkylene, C_{2-10} alkenylene, or C_{2-10} alkynylene;

R_1 is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or



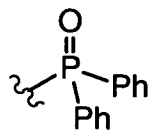
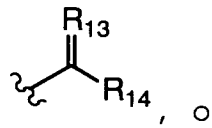
wherein R_7 and R_8 are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; or $-SO_2R_{10}$,

wherein R_{10} is C_{1-10} alkyl, or unsubstituted or substituted aryl;

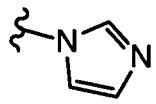
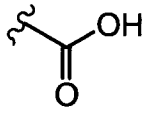
R_9 is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

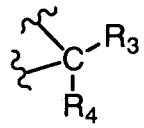
when γ is present; R_5 is absent and A is C-R_4,

wherein R_4 is H, halogen, or OR_{11},

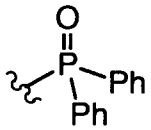
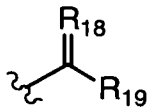
wherein R_{11} is H, C_{1-10} alkyl, $-CH_2SH$, $-BHCH_2CH_3$, $-CH{=}SH$, , $-SO_2R_{12}$, , or $-Si(R_{15})_3$;

wherein R_{12} and each occurrence of R_{15} is C_{1-10} alkyl; or unsubstituted or substituted aryl; and

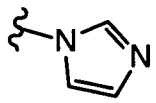
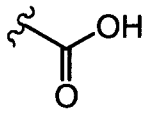
R_{13} is S or O; and R_{14} is $-SCH_3$, , or  ; and

when γ is absent; R_5 is present and A is a direct bond or  ;

wherein R_3 and R_4 are each, independently, H, halogen, or OR_{16};

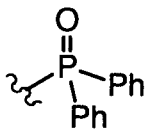
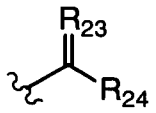
wherein R_{16} is H, C_{1-10} alkyl, $-CH_2SH$, $-BHCH_2CH_3$, $-CH{=}SH$, , $-SO_2R_{17}$, , or $-Si(R_{20})_3$;

wherein R_{17} and each occurrence of R_{20} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

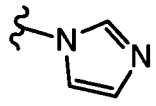
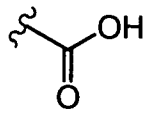
R_{18} is S or O; and R_{19} is $-SCH_3$, , or  ; or

R_3 and R_4 taken together form =O; and

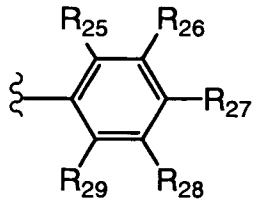
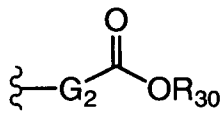
wherein R_5 is H, halogen, or OR_{21},

wherein R_{21} is H, C_{1-10} alkyl, $-CH_2SH$, $-BHCH_2CH_3$, $-CH{=}SH$, , $-SO_2R_{22}$, , or $-Si(R_{25})_3$,

wherein R_{22} and each occurrence of R_{25} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

R_{23} is S or O; and R_{24} is $-SCH_3$, , or ; and

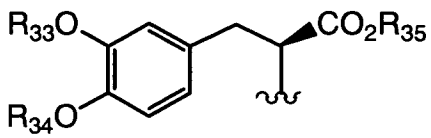
when σ is absent;

R_2 is H, , or ;

wherein R_{25}, R_{26}, R_{27}, R_{28}, and R_{29} are each, independently, H, halogen, $-NO_2$, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; $-OR_{31}$, $-SR_{31}$, $-OSO_2R_{31}$, or $-NR_{31}R_{32}$,

wherein R_{31} and R_{32} are each, independently, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or unsubstituted or substituted aryl;

wherein G_2 is C_{1-10} alkylene, C_{2-10} alkenylene, or C_{2-10} alkynylene; and

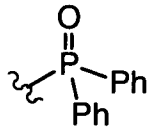
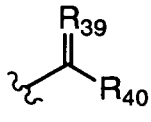
R_{30} is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or ,

wherein R_{33} and R_{34} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; or $-SO_2R_{36}$,

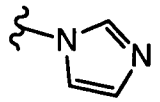
wherein R_{36} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

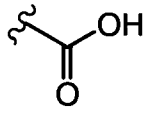
wherein R_{35} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

R_6 is H, halogen, or OR_{37};

wherein R_{37} is H, C_{1-10} alkyl, $-CH_2SH$, $-BHCH_2CH_3$, $-CH=SH$, , $-SO_2R_{38}$, , or $-Si(R_{41})_3$;

wherein R_{38} and each occurrence of R_{41} is C_{1-10} alkyl; or unsubstituted or substituted aryl;

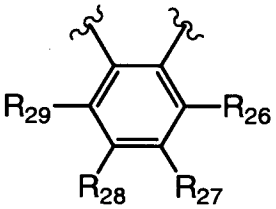
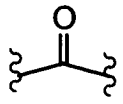
R_{39} is S or O; and R_{40} is $-SCH_3$; ; or

; or

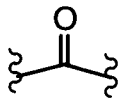
R_5 when present and R_6 taken together form =O; or

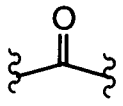
R_4 joined to R_6 form a 5-membered heterocyclic ring; and

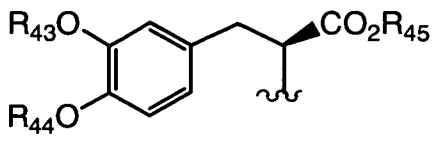
when σ is present;

R_2 is ; and R_6 is a direct bond or ;

and

wherein X is a direct bond, , or $C(OMe)_2$;

Y is H or OR_{42}; or when α is present, Y is ;

wherein R_{42} is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or ,

wherein R_{43} and R_{44} are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; or $-SO_2R_{46}$,

wherein R_{46} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

R_{45} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; or

wherein each occurrence of alkyl, alkylene, alkenyl, alkenylene, alkynyl, or alkynylene is branched or unbranched, unsubstituted or substituted;

Z is H or CN; or when α is present, Z is -CH=CH-; and

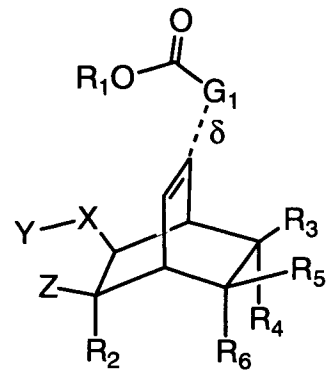
when α is present, R_1 is other than methyl;

or a salt thereof.

In an embodiment, the composition comprises the compound selected from the group consisting of: Compound 3, 4, 21, 23, 24, 25, 26, 33, 34, 35, 36, 37, 39, 40, 42, 44, 45, 47, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, and 63.

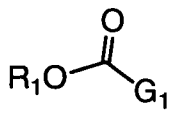
In an embodiment, the composition comprises compound 51.

In an embodiment, the composition comprises a compound having the structure

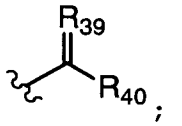


wherein

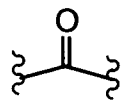
δ is present or absent;

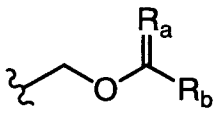
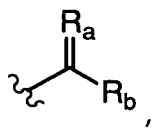
wherein when δ is absent,  is absent;

R_6 is OR_{37};

wherein R_{37} is ;

wherein R_{39} is S or O; and R_{40} is -NH-aryl, heteroaryl, heterocyclyl; or

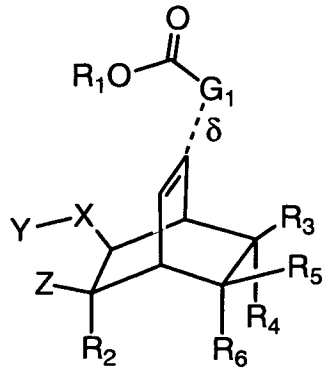
X is a direct bond or ;

Z is H, CN,  or ,

wherein R_a is S or O; R_b is -O-(C_1-C_{10})alkyl, -O-(C_2-C_{10})alkenyl, heterocyclyl, or heteroaryl; or

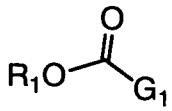
or a salt thereof.

In an embodiment, the composition comprises a compound having the structure

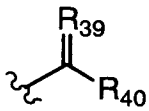


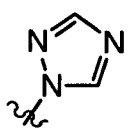
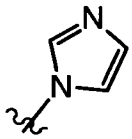
wherein

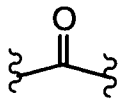
δ is present or absent;

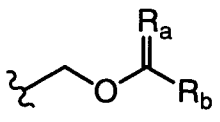
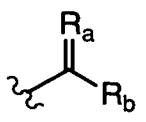
wherein when δ is absent,  is absent;

R_6 is OR_{37};

wherein R_{37} is ;

wherein R_{39} is S; and R_{40} is  or ;

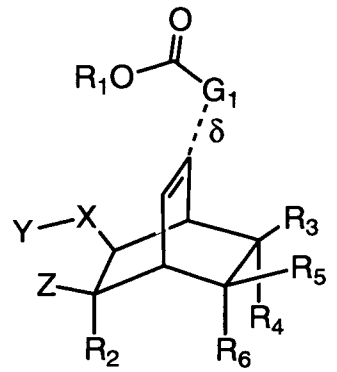
X is a direct bond or ;

Z is H, CN,  or ,

wherein R_a is S or O; R_b is -O-(C_1-C_{10})alkyl, -O-(C_2-C_{10})alkenyl, heterocyclyl, or heteroaryl; or

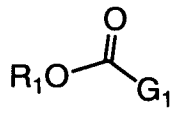
or a salt thereof.

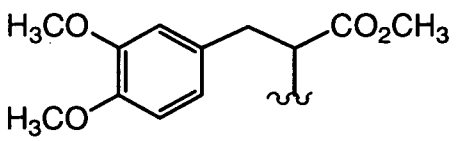
In an embodiment, the composition comprises a compound having the structure

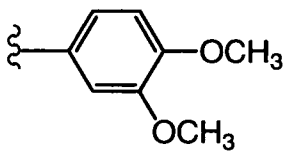


wherein

δ is present or absent;

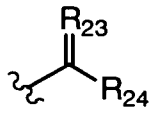
wherein when δ is absent,  is absent;

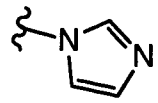
R_1 is H, methyl or ;

R_2 is H or ;

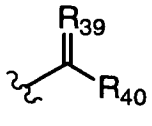
R_3 and R_4 are each $-OCH_3$;

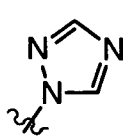
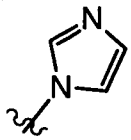
R_5 is H or OR_{21},

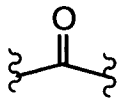
wherein R_{21} is ,

wherein R_{23} is S; and R_{24} is ; and

R_6 is OR_{37};

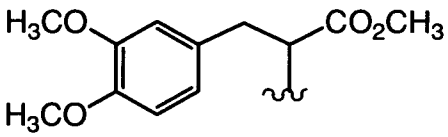
wherein R_{37} is ;

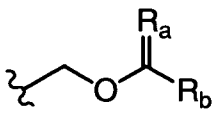
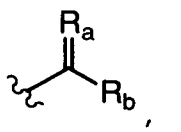
wherein R_{39} is S; and R_{40} is  or ;

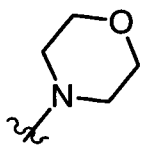
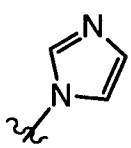
X is a direct bond or ;

Y is H or OR_{42};

wherein R_{42} is methyl, $-CH_2CH=CH_2$ or

;

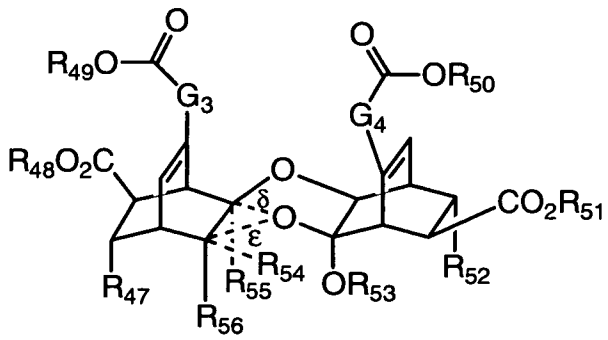
Z is H, CN,  or ,

wherein R_a is S or O; R_b is $-OCH_3$, $-OCH(CH_3)_2$, $-OCH_2CH=CH_2$, $-OCH_2CH_2CH_2CH_3$, , or ;

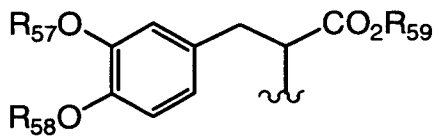
or a salt thereof.

In an embodiment, the composition comprises a compound selected from the group consisting of Compound 64, 65, 66, 67, 68, 73, 74, 75, 76, 77, 78, 79, 80, and a pharmaceutically acceptable salt thereof.

This invention provides a composition, free of plant extract, comprising a compound having the structure



wherein ε and δ are present or absent;
wherein R_{54} and R_{55} are present or absent; and
when ε is present; δ and R_{54} are absent, and R_{55} is present; and
when δ is present; ε and R_{55} are absent, and R_{54} is present;

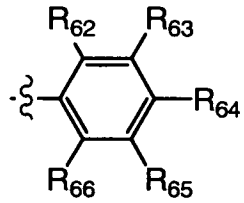
wherein G_3 and G_4 are each, independently, is C_{1-10} alkylene, C_{2-10} alkenylene, or C_{2-10} alkynylene;
R_{48}, R_{49}, R_{50}, and R_{51} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; or ,
wherein R_{57} and R_{58} are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, unsubstituted or substituted aryl(C_{1-10})alkyl, or $-SO_2R_{60}$,

wherein R_{60} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

wherein R_{59} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

wherein R_{53} is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, unsubstituted or substituted aryl(C_{1-10})alkyl, or $-SO_2R_{61}$,

wherein R_{61} is C_{1-10} alkyl, or unsubstituted or substituted aryl;



R_{47} and R_{52} are each H, CN, or ,

wherein R_{62}, R_{63}, R_{64}, R_{65}, and R_{66} are each, independently, H, halogen, $-NO_2$, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; $-OR_{67}$, $-SR_{67}$, $-OSO_2R_{67}$, or $-NR_{67}R_{68}$,

wherein R_{67} and R_{68} are each, independently, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or unsubstituted or substituted aryl; and

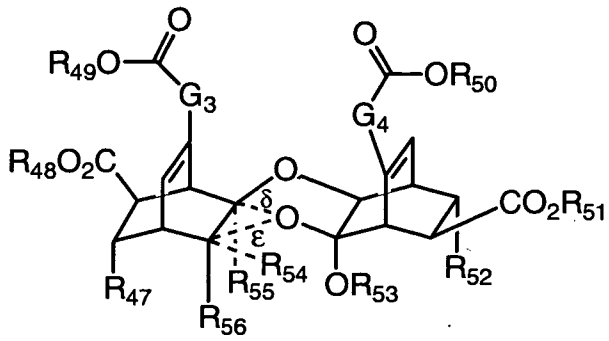
wherein R_{54} when present, R_{55} when present, and R_{56} are each, independently, H or OR_{69},

wherein R_{69} is H or C_{1-10} alkyl; or

wherein each occurrence of alkyl, alkylene, alkenyl, alkenylene, alkynyl, alkynylene is branched or unbranched, unsubstituted or substituted;

or a salt thereof.

In an embodiment of the composition, the compound has the structure



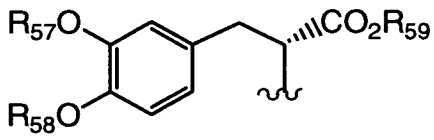
wherein ε and δ are present or absent;

wherein R_{54} and R_{55} are present or absent; and

when ε is present; δ and R_{54} are absent, and R_{55} is present; and

when δ is present; ε and R_{55} are absent, and R_{54} is present;

wherein G_3 and G_4 are each, independently, is C_{1-10} alkylene, C_{2-10} alkenylene, or C_{2-10} alkynylene;

R_{48}, R_{49}, R_{50}, and R_{51} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; or ,

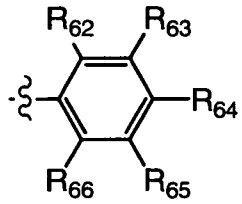
wherein R_{57} and R_{58} are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, unsubstituted or substituted aryl(C_{1-10})alkyl, or $-SO_2R_{60}$,

wherein R_{60} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

wherein R_{59} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

wherein R_{53} is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, unsubstituted or substituted aryl(C_{1-10})alkyl, or $-SO_2R_{61}$,

wherein R_{61} is C_{1-10} alkyl, or unsubstituted or substituted aryl;



R_{47} and R_{52} are each H, CN, or ,

wherein R_{62}, R_{63}, R_{64}, R_{65}, and R_{66} are each, independently, H, halogen, $-NO_2$, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; $-OR_{67}$, $-SR_{67}$, $-OSO_2R_{67}$, or $-NR_{67}R_{68}$,

wherein R_{67} and R_{68} are each, independently, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or unsubstituted or substituted aryl; and

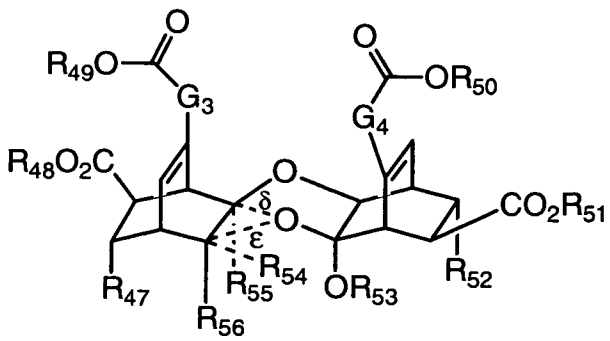
wherein R_{54} when present, R_{55} when present, and R_{56} are each, independently, H or OR_{69},

wherein R_{69} is H or C_{1-10} alkyl; or

wherein each occurrence of alkyl, alkylene, alkenyl, alkenylene, alkynyl, alkynylene is branched or unbranched, unsubstituted or substituted;

or a salt thereof.

In an embodiment of the composition, the compound has the structure



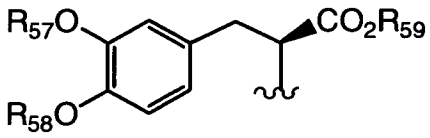
wherein ε and δ are present or absent;

wherein R_{54} and R_{55} are present or absent; and

when ε is present; δ and R_{54} are absent, and R_{55} is present; and

when δ is present; ε and R_{55} are absent, and R_{54} is present;

wherein G_3 and G_4 are each, independently, is C_{1-10} alkylene, C_{2-10} alkenylene, or C_{2-10} alkynylene;

R_{48}, R_{49}, R_{50}, and R_{51} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; or 

,

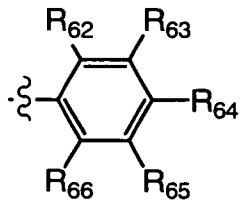
wherein R_{57} and R_{58} are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, unsubstituted or substituted aryl(C_{1-10})alkyl, or $-SO_2R_{60}$,

wherein R_{60} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

wherein R_{59} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

wherein R_{53} is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, unsubstituted or substituted aryl(C_{1-10})alkyl, or $-SO_2R_{61}$,

wherein R_{61} is C_{1-10} alkyl, or unsubstituted or substituted aryl;

R_{47} and R_{52} are each H, CN, or 

,

wherein R_{62}, R_{63}, R_{64}, R_{65}, and R_{66} are each, independently, H, halogen, $-NO_2$, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; $-OR_{67}$, $-SR_{67}$, $-OSO_2R_{67}$, or $-NR_{67}R_{68}$,

wherein R_{67} and R_{68} are each, independently, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or unsubstituted or substituted aryl; and

wherein R_{54} when present, R_{55} when present, and R_{56} are each, independently, H or OR_{69},

wherein R_{69} is H or C_{1-10} alkyl; or

wherein each occurrence of alkyl, alkylene, alkenyl, alkenylene, alkynyl, alkynylene is branched or unbranched, unsubstituted or substituted;

or a salt thereof.

In an embodiment of the composition, the compound is selected from the group consisting of: Compound 2, 43, and 48.

In an embodiment, the composition further comprises a pharmaceutically acceptable carrier.

This invention provides a method of treating a cell expressing a mutant human huntingtin gene, wherein the expression of the mutant huntingtin gene results in a huntingtin protein having a polyglutamine N-terminal, comprising contacting the cell with any of the compositions described herein so as to treat the cell.

This invention provides a method of treating a cell expressing a mutant human huntingtin gene, wherein the expression of the mutant huntingtin gene results in a huntingtin protein having a polyglutamine N-terminal,

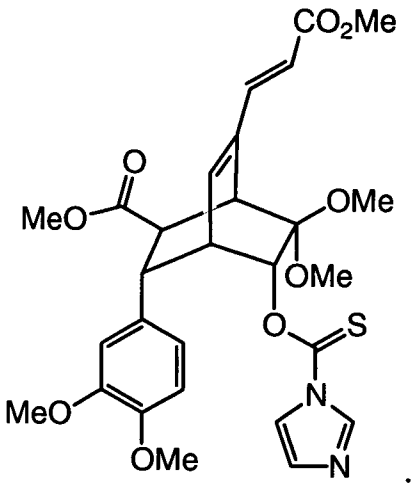
comprising contacting the cell with any of the compounds described herein so as to treat the cell.

This invention provides a method of reducing cell death in a population of cells expressing a mutant human huntingtin gene, wherein the expression of the mutant huntingtin gene results in a huntingtin protein having a polyglutamine N-terminal, comprising contacting the population of cells with any of the compositions described herein so as to reduce cell death in the population of cells.

This invention provides a method of reducing cell death in a population of cells expressing a mutant human huntingtin gene, wherein the expression of the mutant huntingtin gene results in a huntingtin protein having a polyglutamine N-terminal, comprising contacting the population of cells with any of the compounds described herein so as to reduce cell death in the population of cells.

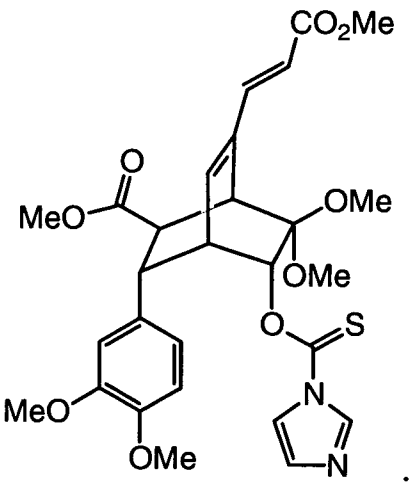
In an embodiment, the cell is a mammalian nerve cell.

In an embodiment of the method, the composition comprises a compound having the structure



In any of the above embodiments, the population of cells is a population of mammalian nerve cells.

In any of the above embodiments of the method, the compound has the structure



"Free of plant extract" with regard to a composition as used here means that the composition is absent any amount of neolignan containing-plant material or neolignan-based oligomer containing-plant material. Thus only synthetically produced compounds and compositions are free of plant extract. Any compound or compositions isolated from a plant

would always contain at least some trace amount of plant material.

The compounds of the present invention include all hydrates, solvates, and complexes of the compounds used by this invention. If a chiral center or another form of an isomeric center is present in a compound of the present invention, all forms of such isomer or isomers, including enantiomers and diastereomers, are intended to be covered herein. Compounds containing a chiral center may be used as a racemic mixture, an enantiomerically enriched mixture, or the racemic mixture may be separated using well-known techniques and an individual enantiomer may be used alone. The compounds described in the present invention are in racemic form or as individual enantiomers. The enantiomers can be separated using known techniques, such as those described in Pure and Applied Chemistry 69, 1469-1474, (1997) IUPAC. In cases in which compounds have unsaturated carbon-carbon double bonds, both the cis (Z) and trans (E) isomers are within the scope of this invention. In cases wherein compounds may exist in tautomeric forms, such as keto-enol tautomers, each tautomeric form is contemplated as being included within this invention whether existing in equilibrium or predominantly in one form.

It will be noted that the structure of the compounds of this invention includes an asymmetric carbon atom and thus the compounds occur as racemates, racemic mixtures, and isolated single enantiomers. All such isomeric forms of these compounds are expressly included in this invention. Each stereogenic carbon may be of the R or S configuration. It is to be understood accordingly that the isomers arising

from such asymmetry (e.g., all enantiomers and diastereomers) are included within the scope of this invention, unless indicated otherwise. Such isomers can be obtained in substantially pure form by classical separation techniques and by stereochemically controlled synthesis, such as those described in "Enantiomers, Racemates and Resolutions" by J. Jacques, A. Collet and S. Wilen, Pub. John Wiley & Sons, NY, 1981. For example, the resolution may be carried out by preparative chromatography on a chiral column.

The subject invention is also intended to include all isotopes of atoms occurring on the compounds disclosed herein. Isotopes include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include tritium and deuterium. Isotopes of carbon include C-13 and C-14.

It will be noted that any notation of a carbon in structures throughout this application, when used without further notation, are intended to represent all isotopes of carbon, such as ^{12}C, ^{13}C, or ^{14}C. Furthermore, any compounds containing ^{13}C or ^{14}C may specifically have the structure of any of the compounds disclosed herein.

It will also be noted that any notation of a hydrogen in structures throughout this application, when used without further notation, are intended to represent all isotopes of hydrogen, such as ^{1}H, ^{2}H, or ^{3}H. Furthermore, any compounds containing ^{2}H or ^{3}H may specifically have the structure of any of the compounds disclosed herein.

Isotopically-labeled compounds can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the Examples disclosed herein using an appropriate isotopically-labeled reagents in place of the non-labeled reagents employed.

As used herein, "alkyl" includes both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms and may be unsubstituted or substituted. Thus, C_1-C_n as in "C_1-C_n alkyl" is defined to include groups having 1, 2, ..., n-1 or n carbons in a linear or branched arrangement. For example, C_1-C_6, as in "C_1-C_6 alkyl" is defined to include groups having 1, 2, 3, 4, 5, or 6 carbons in a linear or branched arrangement, and specifically includes methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, pentyl, hexyl, and octyl.

As used herein, "alkenyl" refers to a non-aromatic hydrocarbon radical, straight or branched, containing at least 1 carbon to carbon double bond, and up to the maximum possible number of non-aromatic carbon-carbon double bonds may be present, and may be unsubstituted or substituted. For example, "C_2-C_6 alkenyl" means an alkenyl radical having 2, 3, 4, 5, or 6 carbon atoms, and up to 1, 2, 3, 4, or 5 carbon-carbon double bonds respectively. Alkenyl groups include ethenyl, propenyl, butenyl and cyclohexenyl.

The term "alkynyl" refers to a hydrocarbon radical straight or branched, containing at least 1 carbon to carbon triple

bond, and up to the maximum possible number of non-aromatic carbon-carbon triple bonds may be present, and may be unsubstituted or substituted. Thus, "C_2-C_6 alkynyl" means an alkynyl radical having 2 or 3 carbon atoms and 1 carbon-carbon triple bond, or having 4 or 5 carbon atoms and up to 2 carbon-carbon triple bonds, or having 6 carbon atoms and up to 3 carbon-carbon triple bonds. Alkynyl groups include ethynyl, propynyl and butynyl.

"Alkylene", "alkenylene" and "alkynylene" shall mean, respectively, a divalent alkane, alkene and alkyne radical, respectively. It is understood that an alkylene, alkenylene, and alkynylene may be straight or branched. An alkylene, alkenylene, and alkynylene may be unsubstituted or substituted.

As used herein, "aryl" is intended to mean any stable monocyclic, bicyclic or polycyclic carbon ring of up to 10 atoms in each ring, wherein at least one ring is aromatic, and may be unsubstituted or substituted. Examples of such aryl elements include phenyl, p-toluenyl (4-methylphenyl), naphthyl, tetrahydro-naphthyl, indanyl, biphenyl, phenanthryl, anthryl or acenaphthyl. In cases where the aryl substituent is bicyclic and one ring is non-aromatic, it is understood that attachment is via the aromatic ring.

The term "arylalkyl" refers to alkyl groups as described above wherein one or more bonds to hydrogen contained therein are replaced by a bond to an aryl group as described above. It is understood that an "arylalkyl" group is connected to a core molecule through a bond from the alkyl group and that the aryl group acts as a substituent

on the alkyl group. Examples of arylalkyl moieties include, but are not limited to, benzyl (phenylmethyl), p-trifluoromethylbenzyl (4-trifluoromethylphenylmethyl), 1-phenylethyl, 2-phenylethyl, 3-phenylpropyl, 2-phenylpropyl and the like.

The term "heteroaryl", as used herein, represents a stable monocyclic, bicyclic or polycyclic ring of up to 10 atoms in each ring, wherein at least one ring is aromatic and contains from 1 to 4 heteroatoms selected from the group consisting of O, N and S. Bicyclic aromatic heteroaryl groups include phenyl, pyridine, pyrimidine or pyridizine rings that are (a) fused to a 6-membered aromatic (unsaturated) heterocyclic ring having one nitrogen atom; (b) fused to a 5- or 6-membered aromatic (unsaturated) heterocyclic ring having two nitrogen atoms; (c) fused to a 5-membered aromatic (unsaturated) heterocyclic ring having one nitrogen atom together with either one oxygen or one sulfur atom; or (d) fused to a 5-membered aromatic (unsaturated) heterocyclic ring having one heteroatom selected from O, N or S. Heteroaryl groups within the scope of this definition include but are not limited to: benzoimidazolyl, benzofuranyl, benzofurazanyl, benzopyrazolyl, benzotriazolyl, benzothiophenyl, benzoxazolyl, carbazolyl, carbolinyl, cinnolinyl, furanyl, indolinyl, indolyl, indolazinyl, indazolyl, isobenzofuranyl, isoindolyl, isoquinolyl, isothiazolyl, isoxazolyl, naphthpyridinyl, oxadiazolyl, oxazolyl, oxazoline, isoxazoline, oxetanyl, pyranyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridopyridinyl, pyridazinyl, pyridyl, pyrimidyl, pyrrolyl, quinazolinyl, quinolyl, quinoxalinyl, tetrazolyl, tetrazolopyridyl, thiadiazolyl,

thiazolyl, thienyl, triazolyl, azetidinyl, aziridinyl, 1,4-dioxanyl, hexahydroazepinyl, dihydrobenzoimidazolyl, dihydrobenzofuranyl, dihydrobenzothiophenyl, dihydrobenzoxazolyl, dihydrofuranyl, dihydroimidazolyl, dihydroindolyl, dihydroisooxazolyl, dihydroisothiazolyl, dihydrooxadiazolyl, dihydrooxazolyl, dihydropyrazinyl, dihydropyrazolyl, dihydropyridinyl, dihydropyrimidinyl, dihydropyrrolyl, dihydroquinolinyl, dihydrotetrazolyl, dihydrothiadiazolyl, dihydrothiazolyl, dihydrothienyl, dihydrotriazolyl, dihydroazetidinyl, methylenedioxybenzoyl, tetrahydrofuranyl, tetrahydrothienyl, acridinyl, carbazolyl, cinnolinyl, quinoxalinyl, pyrrazolyl, indolyl, benzotriazolyl, benzothiazolyl, benzoxazolyl, isoxazolyl, isothiazolyl, furanyl, thienyl, benzothienyl, benzofuranyl, quinolinyl, isoquinolinyl, oxazolyl, isoxazolyl, indolyl, pyrazinyl, pyridazinyl, pyridinyl, pyrimidinyl, pyrrolyl, tetra-hydroquinoline. In cases where the heteroaryl substituent is bicyclic and one ring is non-aromatic or contains no heteroatoms, it is understood that attachment is via the aromatic ring or via the heteroatom containing ring, respectively. If the heteroaryl contains nitrogen atoms, it is understood that the corresponding N-oxides thereof are also encompassed by this definition.

The term "heterocycle" or "heterocyclyl" refers to a mono- or poly-cyclic ring system which can be saturated or contains one or more degrees of unsaturation and contains one or more heteroatoms. Preferred heteroatoms include N, O, and/or S, including N-oxides, sulfur oxides, and dioxides. Preferably the ring is three to ten-membered and is either saturated or has one or more degrees of unsaturation. The heterocycle may be unsubstituted or

substituted, with multiple degrees of substitution being allowed. Such rings may be optionally fused to one or more of another "heterocyclic" ring(s), heteroaryl ring(s), aryl ring(s), or cycloalkyl ring(s). Examples of heterocycles include, but are not limited to, tetrahydrofuran, pyran, 1,4-dioxane, 1,3-dioxane, piperidine, piperazine, pyrrolidine, morpholine, thiomorpholine, tetrahydrothiopyran, tetrahydrothiophene, 1,3-oxathiolane, and the like.

The alkyl, alkenyl, alkynyl, aryl, heteroaryl and heterocyclyl substituents may be substituted or unsubstituted, unless specifically defined otherwise.

In the compounds of the present invention, alkyl, alkenyl, alkynyl, aryl, heterocyclyl and heteroaryl groups can be further substituted by replacing one or more hydrogen atoms be alternative non-hydrogen groups. These include, but are not limited to, halo, hydroxy, mercapto, amino, carboxy, cyano and carbamoyl.

The term "substituted" refers to a functional group as described above in which one or more bonds to a hydrogen atom contained therein are replaced by a bond to non-hydrogen or non-carbon atoms, provided that normal valencies are maintained and that the substitution results in a stable compound. Substituted groups also include groups in which one or more bonds to a carbon(s) or hydrogen(s) atom are replaced by one or more bonds, including double or triple bonds, to a heteroatom. Examples of substituent groups include the functional groups described above, and, in particular, halogens (i.e., F, Cl,

Br, and I); alkyl groups, such as methyl, ethyl, n-propyl, isopropryl, n-butyl, tert-butyl, and trifluoromethyl; hydroxyl; alkoxy groups, such as methoxy, ethoxy, n-propoxy, and isopropoxy; aryloxy groups, such as phenoxy; arylalkyloxy, such as benzyloxy (phenylmethoxy) and p-trifluoromethylbenzyloxy (4-trifluoromethylphenylmethoxy); heteroaryloxy groups; sulfonyl groups, such as trifluoromethanesulfonyl, methanesulfonyl, and p-toluenesulfonyl; nitro, nitrosyl; mercapto; sulfanyl groups, such as methylsulfanyl, ethylsulfanyl and propylsulfanyl; cyano; amino groups, such as amino, methylamino, dimethylamino, ethylamino, and diethylamino; and carboxyl. Where multiple substituent moieties are disclosed or claimed, the substituted compound can be independently substituted by one or more of the disclosed or claimed substituent moieties, singly or plurally. By independently substituted, it is meant that the (two or more) substituents can be the same or different.

It is understood that substituents and substitution patterns on the compounds of the instant invention can be selected by one of ordinary skill in the art to provide compounds that are chemically stable and that can be readily synthesized by techniques known in the art, as well as those methods set forth below, from readily available starting materials. If a substituent is itself substituted with more than one group, it is understood that these multiple groups may be on the same carbon or on different carbons, so long as a stable structure results.

The term "energy source" refers to a source that provides energy suitable for activating a chemical reaction and

enabling such a reaction to occur. Examples of energy sources include, but are not limited to, electromagnetic radiation, such as microwave radiation, ultraviolet radiation, infrared radiation, or visible light; thermal sources, such as heat; and sonic sources, such as ultrasound.

The term "acid" refers to acids under both the Bronsted-Lowry and the Lewis definitions of acids. Under the Bronsted-Lowry definition, acids are defined as proton (H^+) donors. Examples of Bronsted-Lowry acids include, but are not limited to, inorganic acids such as hydrofluoric, hydrochloric, hydrobromic, hydroiodic, perchloric, hypochlorous, sulfuric, sulfurous, sulfamic, phosphoric, phosphorous, nitric, nitrous, and the like; and organic acids such as formic, acetic, trifluoroacetic, p-toluenesulfonic, camphorsulfonic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, methanesulfonic, ethane disulfonic, oxalic, isethionic, and the like. Under the Lewis definition, an acid is an electron acceptor capable of accepting electron density by virtue of possessing unoccupied orbitals. Examples of Lewis acids include, but are not limited to, metal salts such as $AlCl_3$, $FeCl_3$, $FeCl_3 \cdot SiO_2$, $CrCl_2$, $HgCl_2$, CuCl, $TiCl_4$, $Yb(OTf_3)$, InOTf, $TiCl_2(OiPr)_2$, and $Ti(OiPr)_4$; organometallic species such as trimethylaluminum and dimethylaluminum chloride; and boron species such as BH_3, $B(Et)_3$, BF_3, BF_3-OEt_2, BBr_3, $B(OMe)_3$, and $B(OiPr)_3$.

Examples of bases include, but are not limited to, alkali metal hydroxides, such as lithium hydroxide, sodium hydroxide, potassium hydroxide, and cesium hydroxide; alkali metal alkoxides, such as sodium methoxide, sodium ethoxide, sodium isopropoxide, sodium tert-butoxide, potassium tert-butoxide, lithium methoxide; alkali metal hydrides, such as lithium hydride, sodium hydride, and potassium hydride; alkali metal bicarbonates and carbonates, such as sodium bicarbonate, sodium carbonate, lithium bicarbonate, lithium carbonate, potassium carbonate, potassium bicarbonate, cesium carbonate, and cesium bicarbonate; organolithium bases, such as methyllithium, n-butyllithium, s-butyllithium, tert-butyllithium, isobutyllithium, phenyllithium, ethyllithium, n-hexyllithium, and isopropyllithium; amide bases, such as lithium amide, sodium amide, potassium amide, lithium hexamethyldisilazide, sodium hexamethyldisilazide, potassium hexamethyldisilazide, lithium diisopropylamide, lithium diethylamide, lithium dicyclohexylamide, and lithium 2,2,6,6-tetramethylpiperidide; and amine bases, such as pyridine, 4-(dimethylamino)pyridine, trimethylamine, diethylamine, triethylamine, diisopropylethylamine, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), 1,4-diazabicyclo[2.2.2]octane (DABCO), and the like.

The term "silylating agent" refers to a reagent that, when reacted with a nucleophile, generates a silyl derivative of the nucleophile. For example, reaction of a free hydroxyl with a silylating agent generates a silyl ether. Examples of silylating agents include, but are not limited to, trimethylsilyl chloride, trimethylsilyl triflate

(trifluoromethanesulfonate), triethylsilyl triflate, triisopropylsilyl chloride, triisopropylsilyl triflate, dimethylisopropylsilyl chloride, dimethylthexylsilyl chloride, dimethylthexylsilyl triflate, t-butyldimethylsilyl chloride, t-butyldimethylsilyl triflate, t-butyldiphenylsilyl chloride, and the like.

The term "hydride reducing agent" refers to a reducing agent capable of providing hydride. Examples of hydride reducing agents include, but are not limited to, aluminium hydrides, such as $(i\text{-}Bu)_2AlH$, $(i\text{-}Bu)_3Al$, $LiAlH_4$, $LiAlH(OMe)_3$, $LiAlH(Ot\text{-}Bu)_3$, and $NaAlH_2(OCH_2CH_2OCH_3)_2$; boron hydrides such as 9-BBN, $NaBH_4$, $NaBH_4$-$CeCl_3$, $LiBH_4$, $LiEt_3BH$, $Li(s\text{-}Bu)_3BH$, $K(s\text{-}Bu)_3BH$, $Na(s\text{-}Bu)_3BH$, KPh_3BH, $(Ph_3P)_2CuBH_4$, $Zn(BH_4)_2$, $Ca(BH_4)_2$, $Li(n\text{-}Bu)BH_3$, $NaBH(OMe)_3$, $NaBH(OAc)_3$, $NaBH_3CN$, Et_4NBH_4, $Me_4NBH(OAc)_3$, $(n\text{-}Bu)_4NBH_3CN$, and $(n\text{-}Bu)_4NBH(OAc)_3$; and (3) silicon hydrides such as Et_3SiH, $PhMe_2SiH$, Ph_2SiH_2, and $PhSiH_3$-$Mo(CO)_6$.

The term "oxidizing agent" refers to a reagent that, when reacted with a molecule, increases the oxidation state of the molecule. For example, exposure of a primary alcohol to an oxidizing agent produces the corresponding aldehyde or carboxylic acid. Similarly, for example, reaction of an oxidizing agent with a secondary alcohol produces the corresponding ketone. Examples of oxidizing agents include, but are not limited to, hypervalent iodine reagents, such as 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one (Dess-Martin Periodinane), iodosobenzene diacetate, iodosobenzene bis(trifluoroacetate), iodosylbenzene, 2-iodoxybenzoic acid (IBX), and iodobenzene dichloride; chromium(VI) reagents, such as chromium trioxide,

pyridinium chlorochromate (PCC), pyridinium dichromate (PDC), potassium dichromate, and sodium dichromate; and heavy metal complexes, such as lead tetraacetate, tetrapropylammonium perruthenate, cerium(IV) ammonium nitrate, and the like.

As used herein, abbreviations are defined as follows:

Ac = acetyl

4-DMAP = 4-(dimethylamino)pyridine

DMF = *N*,*N*-dimethylformamide

EDC = *N*-ethyl-*N'*-(3-dimethylaminopropyl)carbodiimide

TBAF = tetra-*n*-butylammonium fluoride

TBS = *tert*-butyldimethylsilyl

TMS = trimethylsilyl

Tf = trifluoromethanesulfonyl

KHMDS = potassium bis(trimethylsilyl)amide or potassium hexamethyldisilazide

AIBN = 1,1'-azobisisobutyronitrile

9-BBN = 9-borabicyclo[3.3.1]nonane

DIBA = diisobutylaluminum

THF = tetrahydrofuran

MeOH = methanol

DCE = 1,2-dichloroethane

Ph = phenyl

Me = methyl

Et = ethyl

iPr = isopropyl

n-Bu = n-butyl

i-Bu = isobutyl

s-Bu = *sec*-butyl

t-Bu = *tert*-butyl

Ms = methanesulfonyl

Ts = p-toluenesulfonyl
SET = single electron transfer

In choosing the compounds of the present invention, one of ordinary skill in the art will recognize that the various substituents, i.e. R_1, R_2, etc. are to be chosen in conformity with well-known principles of chemical structure connectivity.

The various R groups attached to the aromatic rings of the compounds disclosed herein may be added to the rings by standard procedures, for example those set forth in Advanced Organic Chemistry: Part B: Reaction and Synthesis, Francis Carey and Richard Sundberg, (Springer) 5th ed. Edition. (2007), the content of which is hereby incoporated by reference.

The compounds of the instant invention may be in a salt form. As used herein, a "salt" is salt of the instant compounds which has been modified by making acid or base salts of the compounds. In the case of compounds used for treatment of cancer, the salt is pharmaceutically acceptable. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as phenols. The salts can be made using an organic or inorganic acid. Such acid salts are chlorides, bromides, sulfates, nitrates, phosphates, sulfonates, formates, tartrates, maleates, malates, citrates, benzoates, salicylates, ascorbates, and the like. Phenolate salts are the alkaline earth metal salts, sodium, potassium or lithium. The term "pharmaceutically acceptable

salt" in this respect, refers to the relatively non-toxic, inorganic and organic acid or base addition salts of compounds of the present invention. These salts can be prepared *in situ* during the final isolation and purification of the compounds of the invention, or by separately reacting a purified compound of the invention in its free base or free acid form with a suitable organic or inorganic acid or base, and isolating the salt thus formed. Representative salts include the hydrobromide, hydrochloride, sulfate, bisulfate, phosphate, nitrate, acetate, valerate, oleate, palmitate, stearate, laurate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, napthylate, mesylate, glucoheptonate, lactobionate, and laurylsulphonate salts and the like. (See, *e.g.*, Berge *et al.* (1977) "Pharmaceutical Salts", *J. Pharm. Sci.* 66:1-19).

The compositions of this invention may be administered in various forms, including those detailed herein. The treatment with the compound may be a component of a combination therapy or an adjunct therapy, i.e. the subject or patient in need of the drug is treated or given another drug for the disease in conjunction with one or more of the instant compounds. This combination therapy can be sequential therapy where the patient is treated first with one drug and then the other or the two drugs are given simultaneously. These can be administered independently by the same route or by two or more different routes of administration depending on the dosage forms employed.

As used herein, a "pharmaceutically acceptable carrier" is a pharmaceutically acceptable solvent, suspending agent or

vehicle, for delivering the instant compounds to the animal or human. The carrier may be liquid or solid and is selected with the planned manner of administration in mind. Liposomes are also a pharmaceutically acceptable carrier.

The dosage of the compounds administered in treatment will vary depending upon factors such as the pharmacodynamic characteristics of a specific chemotherapeutic agent and its mode and route of administration; the age, sex, metabolic rate, absorptive efficiency, health and weight of the recipient; the nature and extent of the symptoms; the kind of concurrent treatment being administered; the frequency of treatment with; and the desired therapeutic effect.

A dosage unit of the compounds may comprise a single compound or mixtures thereof with anti-cancer compounds, or tumor growth inhibiting compounds, or with other compounds also used to treat neurite damage. The compounds can be administered in oral dosage forms as tablets, capsules, pills, powders, granules, elixirs, tinctures, suspensions, syrups, and emulsions. The compounds may also be administered in intravenous (bolus or infusion), intraperitoneal, subcutaneous, or intramuscular form, or introduced directly, e.g. by injection or other methods, into the cancer, all using dosage forms well known to those of ordinary skill in the pharmaceutical arts.

The compounds can be administered in admixture with suitable pharmaceutical diluents, extenders, excipients, or carriers (collectively referred to herein as a pharmaceutically acceptable carrier) suitably selected with

respect to the intended form of administration and as consistent with conventional pharmaceutical practices. The unit will be in a form suitable for oral, rectal, topical, intravenous or direct injection or parenteral administration. The compounds can be administered alone but are generally mixed with a pharmaceutically acceptable carrier. This carrier can be a solid or liquid, and the type of carrier is generally chosen based on the type of administration being used. In one embodiment the carrier can be a monoclonal antibody. The active agent can be co-administered in the form of a tablet or capsule, liposome, as an agglomerated powder or in a liquid form. Examples of suitable solid carriers include lactose, sucrose, gelatin and agar. Capsule or tablets can be easily formulated and can be made easy to swallow or chew; other solid forms include granules, and bulk powders. Tablets may contain suitable binders, lubricants, diluents, disintegrating agents, coloring agents, flavoring agents, flow-inducing agents, and melting agents. Examples of suitable liquid dosage forms include solutions or suspensions in water, pharmaceutically acceptable fats and oils, alcohols or other organic solvents, including esters, emulsions, syrups or elixirs, suspensions, solutions and/or suspensions reconstituted from non-effervescent granules and effervescent preparations reconstituted from effervescent granules. Such liquid dosage forms may contain, for example, suitable solvents, preservatives, emulsifying agents, suspending agents, diluents, sweeteners, thickeners, and melting agents. Oral dosage forms optionally contain flavorants and coloring agents. Parenteral and intravenous forms may also include minerals

and other materials to make them compatible with the type of injection or delivery system chosen.

Specific examples of pharmaceutical acceptable carriers and excipients that may be used to formulate oral dosage forms of the present invention are described in U. S. Pat. No. 3,903,297 to Robert, issued Sept. 2, 1975. Techniques and compositions for making dosage forms useful in the present invention are described-in the following references: 7 Modern Pharmaceutics, Chapters 9 and 10 (Banker & Rhodes, Editors, 1979); Pharmaceutical Dosage Forms: Tablets (Lieberman et al., 1981); Ansel, Introduction to Pharmaceutical Dosage Forms 2nd Edition (1976); Remington's Pharmaceutical Sciences, 17th ed. (Mack Publishing Company, Easton, Pa., 1985); Advances in Pharmaceutical Sciences (David Ganderton, Trevor Jones, Eds., 1992); Advances in Pharmaceutical Sciences Vol 7. (David Ganderton, Trevor Jones, James McGinity, Eds., 1995); Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms (Drugs and the Pharmaceutical Sciences, Series 36 (James McGinity, Ed., 1989); Pharmaceutical Particulate Carriers: Therapeutic Applications: Drugs and the Pharmaceutical Sciences, Vol 61 (Alain Rolland, Ed., 1993); Drug Delivery to the Gastrointestinal Tract (Ellis Horwood Books in the Biological Sciences. Series in Pharmaceutical Technology; J. G. Hardy, S. S. Davis, Clive G. Wilson, Eds.); Modem Pharmaceutics Drugs and the Pharmaceutical Sciences, Vol 40 (Gilbert S. Banker, Christopher T. Rhodes, Eds.). All of the aforementioned publications are incorporated by reference herein.

Tablets may contain suitable binders, lubricants, disintegrating agents, coloring agents, flavoring agents, flow-inducing agents, and melting agents. For instance, for oral administration in the dosage unit form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic, pharmaceutically acceptable, inert carrier such as lactose, gelatin, agar, starch, sucrose, glucose, methyl cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol, sorbitol and the like. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth, or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes, and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride, and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum, and the like.

The compounds can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamallar vesicles, and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine, or phosphatidylcholines. The compounds may be administered as components of tissue-targeted emulsions.

The compounds may also be coupled to soluble polymers as targetable drug carriers or as a prodrug. Such polymers include polyvinylpyrrolidone, pyran copolymer, polyhydroxylpropylmethacrylamide-phenol,

polyhydroxyethylasparta-midephenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, the compounds may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacylates, and crosslinked or amphipathic block copolymers of hydrogels.

The active ingredient can be administered orally in solid dosage forms, such as capsules, tablets, and powders, or in liquid dosage forms, such as elixirs, syrups, and suspensions. It can also be administered parentally, in sterile liquid dosage forms.

Gelatin capsules may contain the active ingredient compounds and powdered carriers, such as lactose, starch, cellulose derivatives, magnesium stearate, stearic acid, and the like. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as immediate release products or as sustained release products to provide for continuous release of medication over a period of hours. Compressed tablets can be sugar coated or film coated to mask any unpleasant taste and protect the tablet from the atmosphere, or enteric coated for selective disintegration in the gastrointestinal tract.

For oral administration in liquid dosage form, the oral drug components are combined with any oral, non-toxic,

pharmaceutically acceptable inert carrier such as ethanol, glycerol, water, and the like. Examples of suitable liquid dosage forms include solutions or suspensions in water, pharmaceutically acceptable fats and oils, alcohols or other organic solvents, including esters, emulsions, syrups or elixirs, suspensions, solutions and/or suspensions reconstituted from non-effervescent granules and effervescent preparations reconstituted from effervescent granules. Such liquid dosage forms may contain, for example, suitable solvents, preservatives, emulsifying agents, suspending agents, diluents, sweeteners, thickeners, and melting agents.

Liquid dosage forms for oral administration can contain coloring and flavoring to increase patient acceptance. In general, water, a suitable oil, saline, aqueous dextrose (glucose), and related sugar solutions and glycols such as propylene glycol or polyethylene glycols are suitable carriers for parenteral solutions. Solutions for parenteral administration preferably contain a water soluble salt of the active ingredient, suitable stabilizing agents, and if necessary, buffer substances. Antioxidizing agents such as sodium bisulfite, sodium sulfite, or ascorbic acid, either alone or combined, are suitable stabilizing agents. Also used are citric acid and its salts and sodium EDTA. In addition, parenteral solutions can contain preservatives, such as benzalkonium chloride, methyl- or propyl-paraben, and chlorobutanol. Suitable pharmaceutical carriers are described in Remington's Pharmaceutical Sciences, Mack Publishing Company, a standard reference text in this field.

The compounds of the instant invention may also be administered in intranasal form via use of suitable intranasal vehicles, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in that art. To be administered in the form of a transdermal delivery system, the dosage administration will generally be continuous rather than intermittent throughout the dosage regimen.

Parenteral and intravenous forms may also include minerals and other materials to make them compatible with the type of injection or delivery system chosen.

The compounds and compositions of the invention can be coated onto stents for temporary or permanent implantation into the cardiovascular system of a subject.

The compounds and compositions of the invention are useful in reducing cell death in cells expressing a mutant human huntingtin gene, wherein the expression of the mutant huntingtin gene results in a huntingtin protein having a polyglutamine N-terminal.

This invention will be better understood by reference to the Experimental Details which follow, but those skilled in the art will readily appreciate that the specific experiments detailed are only illustrative of the invention as described more fully in the claims which follow thereafter.

Experimental Details

General Procedures. All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Dry tetrahydrofuran (THF), acetonitrile (MeCN), toluene, benzene, diethyl ether (Et_2O) and methylene chloride (CH_2Cl_2) were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns. Yields refer to chromatographically and spectroscopically (^1H and ^{13}C NMR) homogeneous materials, unless otherwise stated. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent and an ethanolic solution of phosphomolybdic acid and cerium sulfate, and heat as developing agents. SiliCycle silica gel (60, academic grade, particle size 0.040-0.063 mm) was used for flash column chromatography. Preparative thin-layer chromatography (PTLC) separations were carried out on 0.50 mm E. Merck silica gel plates (60F-254). NMR spectra were recorded on Bruker DRX-300, DRX-400 and DMX-500 instruments and calibrated using residual undeuterated solvent as an internal reference. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, br = broad, app = apparent. IR spectra were recorded on a Perkin-Elmer 1000 series FT-IR spectrometer. Melting points were taken on a Mettler Toledo Type FP62 instrument, and are uncorrected. Microwave experiments were performed in a CEM Corporation MARS 1200W reactor. High-resolution mass spectra (HRMS) were recorded in the

Columbia University Mass Spectral Core facility on a JOEL HX110 mass spectrometer using FAB (fast atom bombardment), MALDI (matrix-assisted laser desorption/ionization) and APCI (atmospheric pressure chemical ionization) techniques.

Diels-Alder dimer (15). $PhI(OAc)_2$ (8.58 g, 26.6 mmol, 1.05 equiv) was added to a solution of *trans*-3-methoxy-4-hydroxycinnamic acid methyl ester (**14**, 5.28 g, 25.4 mmol, 1.0 equiv) in MeOH:CH_2Cl_2 (6:1, 35 mL) at 25 °C, and the resultant light yellow solution was stirred at 25 °C for 14 h. Upon completion, the reaction contents were concentrated directly and the resultant crude yellow oil was purified by flash column chromatography (silica gel, hexanes:EtOAc, 3:2) to give Diels-Alder adduct **15** (5.26 g, 87% yield) as a yellow amorphous solid. **15**: R_f = 0.22 (silica gel, hexanes:EtOAc, 1:1); IR (film) λ_{max} 2950, 1710, 1650, 1635, 1436, 1313, 1196, 1174, 1132, 1050, 733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, *J* = 16.0 Hz, 1 H), 6.97 (d, *J* = 16.0 Hz, 1 H), 6.19 (dd, *J* = 7.2, 2.0 Hz, 1 H), 6.17 (d, *J* = 10.0 Hz, 1 H), 6.06 (d, *J* = 15.6 Hz, 1 H), 6.01 (d, *J* = 10.0 Hz, 1 H), 6.00 (d, *J* = 16.4 Hz, 1 H), 3.76 (s, 3 H), 3.74 (s, 3 H), 3.44 (s, 3 H), 3.43 (s, 3 H), 3.40 (app t, *J* = 1.6 Hz, 1 H), 3.35 (s, 1 H), 3.30 (d, *J* = 6.4 Hz, 1 H), 3.22 (s, 3 H), 3.05 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.9, 191.2, 166.7, 166.1, 147.7, 146.1, 141.0, 140.2, 132.4, 128.2, 121.7, 119.8, 97.6, 94.1, 58.2, 51.7, 51.6, 50.6, 50.5, 50.2, 50.0, 48.7, 43.3, 40.6; HRMS (FAB) calcd for $C_{24}H_{28}O_{10}^+$ [M^+] 476.1682, found 476.1613.

3-Methoxy-4-Hydroxydihydrocinnamic Acid Methyl Ester (16). Concentrated HCl (2 drops) was added to a solution of 3-

methoxy-4-hydroxydihydrocinnamic acid (0.225 g, 1.15 mmol, 1.0 equiv) in anhydrous MeOH (10 mL) at 25 °C, and the resultant solution was stirred at 25 °C for 20 h. Upon completion, the reaction contents were concentrated directly and the resultant crude yellow oil was purified by flash column chromatography (silica gel, hexanes:EtOAc, 3:2) to afford **16** (0.231 g, 96% yield) as a colorless oil. **16**: R_f = 0.63 (silica gel, hexanes:EtOAc, 1:1); IR (film) ν_{max} 3445, 2951, 1731, 1606, 1515, 1434, 1364, 1290, 1234, 1202, 1152, 1121, 1033, 818, 791, 732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.83 (d, J = 8.0 Hz, 1 H), 6.70 (s, 1 H), 6.69 (d, J = 9.6 Hz, 1 H), 5.51 (s, 1 H), 3.87 (s, 3 H), 3.67 (s, 3 H), 2.88 (t, J = 7.8 Hz, 2 H), 2.60 (t, J = 7.8 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.4, 146.4, 144.0, 132.4, 120.8, 114.3, 110.9, 55.8, 51.6, 36.1, 30.7; HRMS (FAB) calcd for $C_{11}H_{14}O_4^+$ [M^+] 210.0892, found 210.0905.

Diels-Alder adduct 17. $PhI(OAc)_2$ (0.384 g, 1.19 mmol, 1.1 equiv) was added to a solution of **16** (0.228 g, 1.08 mmol, 1.0 equiv) in MeOH:CH_2Cl_2 (5:1, 12 mL) at 25 °C, and the resultant yellow solution was stirred at 25 °C for 1 h. Upon completion, the reaction contents were concentrated directly and the resultant crude yellow oil was purified by flash column chromatography (silica gel, hexanes:EtOAc, 7:3) to afford the desired orthoquinone monoketal intermediate (0.253 g, 97% yield) as a bright yellow oil. [Note: this product was stored as a 0.2 M solution in toluene at 4 °C to prevent its dimerization]. Acrylonitrile (7.60 mL, 116 mmol, 100 equiv) was then added to a solution of this newly formed orthoquinone monoketal (0.2 M in toluene, 5.8 mL, 1.16 mmol, 1.0 equiv) and the reaction

mixture was stirred in a sealed tube at 80 °C for 2 days. Upon completion, the reaction contents were concentrated directly and the resultant crude yellow oil was purified by flash column chromatography (silica gel, hexanes:EtOAc, 7:3) to afford **17** (0.148 g, 43% yield) as a colorless oil. **17**: R_f = 0.41 (silica gel, hexanes:EtOAc, 1:1); IR (film) ν_{max} 3004, 2969, 2921, 2139, 1740, 1713, 1445, 1422, 1365, 1222, 1091, 1069, 894 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.90 (d, *J* = 6.4 Hz, 1 H), 3.70 (s, 3 H), 3.35 (dd, *J* = 6.4, 2.0 Hz, 1 H), 3.32 (s, 3 H), 3.28 (s, 3 H), 3.13 (ddd, *J* = 10.0, 5.6, 2.0 Hz, 1 H), 3.04 (dd, *J* = 4.8, 2.8 Hz, 1 H), 2.62-2.53 (m, 4 H), 3.13 (ddd, *J* = 13.2, 10.0, 3.0 Hz, 1 H), 1.65 (ddd, *J* = 13.2, 5.2, 3.2 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.8, 172.9, 149.7, 120.7, 117.3, 93.4, 51.9, 50.9, 49.8, 49.2, 42.5, 31.5, 30.0, 26.2, 25.3; HRMS (FAB) calcd for $C_{15}H_{20}O_5N^+$ [M + H^+] 294.1341, found 294.1356.

Dihydrofuran 18. AgOAc (0.452 g, 2.71 mmol, 1.1 equiv) was added to a solution of *trans*-3-methoxy-4-hydroxydihydrocinnamic acid methyl ester (**14**, 0.513 g, 2.46 mmol) in toluene (8 mL) at 25 °C. The reaction mixture was then warmed to 60 °C and stirred for 20 h. Upon completion, the reaction contents were filtered through Celite, concentrated, and purified by flash column chromatography (silica gel, hexanes:EtOAc, 7:3) to afford dihydrobenzofuran **18** (0.105 g, 20% yield) as a white amorphous solid. **18**: R_f = 0.36 (silica gel, hexanes:EtOAc, 7:3); IR (film) ν_{max} 3444, 2952, 1736, 1705, 1634, 1601, 1518, 1496, 1435, 1171, 1145, 1033, 980, 846 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 16.0 Hz, 1 H), 7.26 (s, 1 H), 7.18 (s, 1 H), 6.91-6.86 (m, 3 H), 6.31 (d, *J* = 16.0

Hz, 1 H), 6.10 (d, J = 8.4 Hz, 1 H), 5.79 (br s, 1 H), 4.34 (d, J = 8.4 Hz, 1 H), 3.90 (s, 3 H), 3.85 (s, 3 H), 3.82 (s, 3 H), 3.79 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6, 167.5, 149.8, 146.7, 146.0, 144.6, 144.6, 131.2, 128.4, 125.6, 119.2, 117.8, 115.3, 114.5, 112.0, 108.7, 87.3, 56.0, 55.8, 55.3, 52.7, 51.5; HRMS (FAB) calcd for $C_{22}H_{22}O_8^+$ [M^+] 414.1315, found 414.1331.

Mixed Diels-Alder Adduct 21. A solution of **15** (1.21 g, 2.54 mmol, 1.0 equiv) and dienophile **13** (3.78 g, 17.0 mmol, 6.7 equiv) in mesitylene (3.0 mL) was carefully degassed 3 times using the freeze-pump-thaw method, and then sealed under argon in a tube equipped with a magnetic stir bar. The reaction solution was stirred at 220 °C (oil bath) for 30 min. After cooling to 25 °C, the reaction contents were purified directly by flash column chromatography (silica gel, hexanses:EtOAc, 4:1→1:1) to afford recovered **13** (3.20 g) alongside a light yellow solid which was recrystallized from Et_2O to provide Diels-Alder adduct **21** (1.00 g, 43% yield, 83% yield based on recovered starting material) as a crystalline white solid. **21**: R_f = 0.36 (silica gel, hexanes:EtOAc, 3:2); m.p. 143.0-143.5 °C; IR (film) ν_{max} 2951, 1735, 1719, 1632, 1519, 1436, 1311, 1287, 1269, 1239, 1195, 1172, 1146, 1062, 1027 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, J = 15.6 Hz, 1 H), 6.82-6.77 (m, 3 H), 6.62 (dd, J = 6.8, 2.4 Hz, 1 H), 6.11 (d, J = 15.6 Hz, 1 H), 3.92 (app t, J = 0.2 Hz, 1 H), 3.85 (s, 3 H), 3.84 (s, 3 H), 3.78 (s, 3 H), 3.67 (s, 3 H), 3.58 (dd, J = 6.8, 2.8 Hz, 1 H), 3.48 (s, 3 H), 3.44 (dd, J = 6.8, 2.0 Hz, 1 H), 3.34 (s, 3 H), 3.30 (dd, J = 6.8, 2.4 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.9, 173.3, 167.2, 149.0, 148.1, 141.7, 140.0, 134.3,

133.1, 119.7, 118.2, 111.2, 111.08, 93.8, 56.3, 55.8, 52.4, 51.8, 51.0, 49.9, 47.0, 44.5, 42.4; HRMS (FAB) calcd for $C_{24}H_{28}O_9^+$ [M^+] 460.1733, found 460.1759.

Helisorin Core 23. $BF_3 \cdot OEt_2$ (0.016 mL, 0.130 mmol, 6.0 equiv) was added to a solution of Diels-Alder adduct **21** (0.010 g, 0.022 mmol, 1.0 equiv) in CH_2Cl_2 (0.5 mL) at 0 °C, and the reaction was slowly warmed to 25 °C and stirred from an additional 16 h. Upon completion, the reaction was quenched with saturated aqueous $NaHCO_3$ (10 mL) and extracted with EtOAc (2 × 10 mL). The combined organic layers were then washed with saturated aqueous $NaHCO_3$ (10 mL), brine (10 mL), dried ($MgSO_4$) and concentrated. The resultant thick orange oil was purified by flash column chromatography (silica gel, hexanes:EtOAc, 1:1) to afford compound **23** (7.5 mg, 82% yield) as a colorless solid. **23**: R_f = 0.24 (silica gel, hexanes:EtOAc, 3:7); IR (film) ν_{max} 3462, 2952, 1725, 1631, 1499, 1437, 1306, 1221, 1167, 1116, 1003 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, J = 15.6 Hz, 1 H), 6.82 (app s, 2 H), 6.74 (d, J = 5.2 Hz, 1 H), 6.05 (d, J = 15.6 Hz, 1 H), 4.14 (d, J = 3.6 Hz, 1 H), 3.88 (s, 3 H), 3.88 (s, 3 H), 3.88-3.85 (m, 2 H), 3.77 (s, 3 H), 3.62 (s, 3 H), 3.25 (s, 1 H), 3.09 (d, J = 3.6 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.6, 170.6, 167.0, 150.5, 149.5, 139.9, 138.7, 136.7, 136.4, 132.9, 118.5, 106.6, 105.8, 81.2, 56.1, 56.1, 55.9, 52.2, 51.8, 51.6, 51.4, 42.4; HRMS (FAB) calcd for $C_{22}H_{23}O_8^+$ [$M+H^+$] 415.1393, found 415.1401.

Diketone 24. Solid $NaHCO_3$ (0.040 g, 0.480 mmol, 10 equiv) and Dess-Martin periodinane (0.041 g, 0.096 mmol, 2.0 equiv) were added sequentially in single portions to a

solution of hydroxyketone **37** (0.040 g, 0.048 mmol, 1.0 equiv) in CH_2Cl_2 (1 mL) at 25 °C. The resultant suspension was stirred at 25 °C for 1 h. Upon completion, saturated aqueous Na_2SO_3 (2 mL) was added and the resultant biphasic mixture was stirred vigorously for 1 h to quench any remaining oxidizing agents. The reaction contents were then poured into water (10 mL), and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL), dried ($MgSO_4$), and concentrated to afford crude diketone **24** (0.037 g, 93% yield) as a thick yellow oil, which was used immediately without further purification. **24**: R_f = 0.15 (silica gel, hexanes:EtOAc, 3:2); IR (film) ν_{max} 2925, 1733, 1717, 1630, 1518, 1437, 1312, 1264, 1196, 1172, 1146, 1025, 809 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38 (d, *J* = 16.0 Hz, 1 H), 6.78 (app d, *J* = 8.5 Hz, 2 H), 6.58–6.57 (m, 2 H), 6.16 (d, *J* = 15.5 Hz, 1 H), 4.27 (t, *J* = 2.0 Hz, 1 H), 3.87–3.83 (m, 7 H), 3.84 (s, 3 H), 3.83 (s, 3 H), 3.80 (s, 3 H), 3.80–3.78 (m, 1 H), 3.72 (s, 3 H), 3.43 (dd, *J* = 6.0, 2.0 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.8, 187.8, 171.4, 166.5, 149.4, 148.6, 139.5, 137.7, 135.2, 131.8, 120.5, 119.2, 111.6, 110.8, 56.5, 55.9, 55.8, 52.9, 52.0, 50.7, 46.8, 45.3; LRMS (FAB) calcd for $C_{22}H_{22}O_8^+$ [M^+] 414.13, found 414.14.

Rearragement Product 25. $BF_3 \cdot OEt_2$ (0.054 mL, 0.434 mmol, 20 equiv) was added to a solution of Diels-Alder adduct **21** (0.010 g, 0.022 mmol, 1.0 equiv) in CH_2Cl_2 (0.5 mL) at 25 °C, and the reaction was stirred at 25 °C for 12 h. Upon completion, the reaction contents were quenched with saturated aqueous $NaHCO_3$ (10 mL) and extracted with EtOAc (2 × 10 mL). The combined organic layers were then washed with

saturated aqueous $NaHCO_3$ (10 mL), brine (10 mL), dried ($MgSO_4$) and concentrated. The resultant thick orange oil was purified by flash column chromatography (silica gel, hexanes:EtOAc, 1:1) to afford a thick yellow oil which was recrystallized from Et_2O to afford **25** (7.5 mg, 88% yield from **21**) as a white crystalline solid. Compound **25** was also obtained from helisorin core **23** under identical reaction conditions (80% yield) and from diketone **24** using 6.0 equiv of $BF_3 \bullet OEt_2$ (53% yield). **25**: R_f = 0.26 (silica gel, hexanes:EtOAc, 3:7); m.p. = 105.8-106.4 °C; IR (film) ν_{max} 3463, 2924, 1734, 1717, 1596, 1308, 1264, 1209, 1114 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.50 (s, 1 H), 7.43 (d, J = 16.0 Hz, 1 H), 6.82 (d, J = 3.0 Hz, 1 H), 6.62 (d, J = 3.0 Hz, 1 H), 5.95 (d, J = 16.0 Hz, 1 H), 3.97 (s, 3 H), 3.93 (s, 3 H), 3.90 (s, 1 H), 3.76 (s, 3 H), 3.52 (s, 3 H), 3.52 (s, 3 H), 3.40 (s, 1 H), 3.35 (d, J = 4.5 Hz, 1 H), 3.29 (d, J = 2.0 Hz, 1 H), 2.90 (dd, J = 4.5, 1.5 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.1, 171.5, 167.2, 154.9, 148.6, 145.3, 143.7, 138.6, 138.3, 122.6, 119.3, 109.7, 108.4, 95.9, 61.7, 56.3, 56.2, 54.2, 51.6, 50.1, 42.9; HRMS (FAB) calcd for $C_{22}H_{23}O_8^+$ [M+H$^+$] 415.1393, found 415.1401.

Bromoketal 26. BBr_3 (1.0 M in CH_2Cl_2, 0.365 mL, 0.365 mmol, 6.0 equiv) was added to a solution of Diels-Alder adduct **21** (0.028 g, 0.061 mmol, 1.0 equiv) in CH_2Cl_2 (1 mL) at -78 °C, and the reaction was stirred at -78 °C for 1 h. Upon completion, the reaction contents were poured into saturated aqueous $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were then washed with brine (10 mL), dried ($MgSO_4$), and concentrated. The resultant crude material was purified by flash column

chromatography (silica gel, hexanes:EtOAc, 2:1) to afford bromoketal **26** (0.027 g, 86% yield) as a thick colorless oil. **26**: R_f = 0.47 (silica gel, hexanes:EtOAc, 1:1); IR (film) ν_{max} 2951, 1735, 1718, 1635, 1519, 1437, 1313, 1247, 1196, 1173, 1148, 1027, 669 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, J = 16.0 Hz, 1 H), 6.79-6.73 (m, 3 H), 6.70 (dd, J = 6.8, 1.6 Hz, 1 H), 6.15 (d, J = 16.0 Hz, 1 H), 4.40 (t, J = 0.2 Hz, 1 H), 3.85 (s, 3 H), 3.84 (s, 3 H), 3.80 (s, 3 H), 3.68 (s, 3 H), 3.68 (s, 3 H), 3.68-3.67 (m, 1 H), 3.52 (dd, J = 6.6, 2.2 Hz, 1 H), 3.46 (dd, J = 6.8, 2.4 Hz, 1 H); LRMS (APCI) calcd for $C_{23}H_{25}BrO_8^+$ [M^+] 508.1, found 508.2.

Dienophile 27. TMS-diazomethane (2.0 M in Et_2O, 7.9 mL, 15.8 mmol, 0.95 equiv) was added in small portions over 1 h to a solution of rosmarinic acid (**5**, 6.00 g, 16.7 mmol, 1.0 equiv) in THF:MeOH (10:1, 110 mL) at -78 °C. Upon completion, the reaction contents were allowed to warm to 25 °C over 1 h, concentrated directly, and filtered through a short plug of silica gel (CH_2Cl_2:MeOH, 19:1). The resultant thick brown oil was dried thoroughly under high vacuum to provide the desired ester intermediate that was carried forward without any additional purification. Next, *p*-trifluoromethylbenzyl bromide (7.40 mL, 48.0 mmol, 6.0 equiv), K_2CO_3 (6.60 g, 48.0 mmol, 6.0 equiv), and KI (catalytic) were added sequentially and in single portions to a solution of half of the crude ester just prepared (8.0 mmol, 1.0 equiv) in DMF (30 mL) at 25 °C. The resultant reaction mixture was then stirred at 60 °C for 8 h, and at 25 °C for 16 h. Upon completion, the reaction contents were carefully quenched by the addition of 1 M aqueous HCl (until gas evolution ceased), poured into water (50 mL), and

extracted with EtOAc (2 × 100 mL). The combined organic layers were then washed with 1 M aqueous HCl (50 mL), saturated aqueous $NaHCO_3$ (50 mL) and brine (50 mL), dried ($MgSO_4$), and concentrated. The resultant crude material was purified by flash column chromatography (silica gel, hexanes:EtOAc:CH_2Cl_2, 17:1:2→5:4:1) to afford dienophile **27** (6.00 g, 84% yield over 2 steps) as a white amorphous solid. **27**: R_f = 0.45 (silica gel, hexanes:EtOAc:CH_2Cl_2, 3:1:1); IR (film) ν_{max} 1751, 1715, 1625, 1598, 1511, 1324, 1265, 1160, 1120, 1065, 1016, 824, 736 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.66–7.49 (m, 17 H), 7.11–7.08 (m, 2 H), 6.92–6.81 (m, 4 H), 6.29 (d, *J* = 16.0 Hz, 1 H), 5.36 (dd, *J* = 8.0, 4.8 Hz, 1 H), 5.23 (s, 2 H), 5.19 (s, 2 H), 5.17 (s, 2 H), 5.16 (s, 2 H), 3.71 (s, 3 H), 3.18 (dd, *J* = 14.4, 5.0 Hz, 1 H), 3.11 (dd, *J* = 14.4, 8.4 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.1, 166.0, 150.8, 148.6, 148.5, 147.7, 145.5, 141.2, 141.1, 140.7, 140.5, 127.9, 127.2, 127.2, 127.1, 125.8, 125.4, 125.3, 125.3, 123.3, 122.7, 122.2, 116.2, 115.2, 114.9, 114.0, 113.5, 72.8, 70.5, 70.3, 69.9, 52.2, 36.9; HRMS (FAB) calcd for $C_{51}H_{38}F_{12}O_8^+$ [M^+] 1006.2375, found 1006.2424.

Dienophile 28 and Chiral Alcohol 29. Solid NaOMe (0.057 g, 1.05 mmol, 1 equiv) was added in a single portion to a solution of **27** (1.06 g, 1.05 mmol) in methanol:CH_2Cl_2 (1:1, 16 mL) at 25 °C, and the reaction was stirred at 25 °C for 2 h. Upon completion, the reaction contents were quenched with 1 M aqueous HCl (10 mL), poured into water (10 mL), and extracted with EtOAc (2 × 20 mL). The combined organic layers were then washed with saturated aqueous NH_4Cl (20 mL) and brine (20 mL), dried ($MgSO_4$), and concentrated. The

resultant crude yellow solid was purified by flash column chromatography (silica gel, hexanes:EtOAc, 7:3) to afford the desired dienophile **28** (0.493 g, 92% yield) as a white amorphous solid alongside chiral alcohol **29** (0.498 g, 90% yield) as a white amorphous solid. **28**: R_f = 0.66 (silica gel, hexanes:EtOAc, 3:2); IR (film) ν_{max} 3004, 2918, 1713, 1422, 1363, 1222, 1126, 665 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.66-7.47 (m, 9 H), 7.13-7.09 (m, 2 H), 6.91 (d, *J* = 8.8 Hz, 1 H), 6.27 (d, *J* = 16.2 Hz, 1 H), 5.24 (s, 2 H), 5.22 (s, 2 H), 3.79 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.4, 150.4, 148.5, 144.1, 140.8, 140.6, 128.2, 127.2, 127.2, 127.1, 127.1, 127.1, 125.5, 125.5, 125.4, 125.4, 123.0, 116.1, 114.0, 113.4, 70.3, 70.0, 51.5; HRMS (FAB) calcd for $C_{26}H_{20}F_6O_4^+$ [M^+] 510.1266, found 510.1261.

29: R_f = 0.34 (silica gel, hexanes:EtOAc, 3:2); $[\alpha]^{22}_D$ = +11.0° (*c* = 0.79, $CHCl_3$); IR (film) ν_{max} 3417, 1720, 1632, 1519, 1421, 1330, 1271, 1239, 1217, 1159, 1142, 1115, 1105, 1068, 1037, 1021, 823 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.64-7.53 (m, 8 H), 6.85 (d, *J* = 8.4 Hz, 1 H), 6.84 (s, 1 H), 6.75 (dd, *J* = 8.4, 2.0 Hz, 1 H), 5.19 (s, 2 H), 5.17 (s, 2 H), 4.40 (dd, *J* = 6.6, 4.2 Hz, 1 H), 3.73 (s, 3 H), 3.04 (dd, *J* = 14.2, 4.2 Hz, 1 H), 2.87 (dd, *J* = 14.0, 6.4 Hz, 1 H), 2.69 (br s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.4, 148.4, 147.6, 141.3, 141.2, 130.2, 129.8, 127.3, 127.2, 125.9, 125.5, 125.4, 122.8, 116.5, 115.0, 71.2, 70.5, 70.5, 52.4, 39.9; HRMS (FAB) calcd for $C_{26}H_{22}F_6O_5^+$ [M^+] 528.1371, found 528.1392.

Phenol 32. EDC•HCl (1.41 g, 7.34 mmol, 2.0 equiv) and 4-DMAP (0.448 g, 3.67 mmol, 1.0 equiv) were added

sequentially in single portions to a solution of TBS-protected acid **31** (2.26 g, 7.34 mmol, 2.0 equiv) and chiral alcohol **29** (1.94 g, 3.67 mmol, 1.0 equiv) in CH_2Cl_2 (20 mL) at 25 °C, and the resulting mixture was stirred at 25 °C for 3 h. Upon completion, the reaction contents were diluted with EtOAc (30 mL), poured into water (40 mL), and extracted with EtOAc (2 × 50 mL). The combined organic layers were then washed with 1 M aqueous HCl (3 × 30 mL) and brine (30 mL), dried ($MgSO_4$), and concentrated to afford the desired ester as a yellow oil which was carried forward without any additional purification. Next, AcOH (0.6 mL) and TBAF (1.0 M in THF, 7.34 mL, 7.34 mmol, 2.0 equiv) were added sequentially and dropwise over the course of several minutes to a solution of the newly formed ester in THF (20 mL) at 0 °C. After 5 min of stirring at 0 °C, the reaction contents were poured into 1 M aqueous HCl (30 mL) and extracted with EtOAc (2 × 30 mL). The combined organic layers were then washed with brine (30 mL), dried ($MgSO_4$), and concentrated. The resultant crude yellow solid was purified by flash column chromatography (silica gel, hexanes:EtOAc, 7:3) to afford phenol **32** (2.43 g, 94% yield over 2 steps) as a white amorphous solid. **32**: R_f = 0.35 (silica gel, hexanes:EtOAc, 3:2); $[\alpha]^{23}_D$ = +36.2° (*c* = 0.65, $CHCl_3$); IR (film) ν_{max} 3413, 3004, 1716, 1422, 1366, 1218, 1092, 902 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 16.4 Hz, 1 H), 7.62-7.58 (m, 4 H), 7.54-7.49 (m, 4 H), 7.06 (dd, *J* = 8.0, 1.6 Hz, 1 H), 7.00 (d, *J* = 1.6 Hz, 1 H) 6.92-6.82 (m, 4 H), 6.31 (d, *J* = 16.0 Hz, 1 H), 5.95 (s, 1 H), 5.37 (ddd, *J* = 8.0, 4.8, 1.2 Hz, 1 H) 5.16 (s, 2 H), 5.15 (s, 2 H), 3.93 (s, 3 H), 3.87 (s, 3 H), 3.18 (dd, *J* = 14.4, 4.8 Hz, 1 H), 3.12 (dd, *J* = 14.4, 8.4 Hz, 1 H); ^{13}C NMR (75 MHz,

$CDCl_3$) δ 170.2, 166.2, 148.4, 148.4, 147.6, 146.8, 146.2, 141.1, 141.0, 129.7, 127.2, 127.1, 126.5, 125.3, 125.2, 125.2, 123.2, 122.7, 116.1, 114.9, 114.7, 114.0, 109.4, 72.7, 70.4, 70.3, 55.6, 52.2, 36.9; HRMS (FAB) calcd for $C_{36}H_{30}F_6O_8^+$ [M^+] 704.1845, found 704.1864.

Carboxylic Acid 31. *i*-Pr_2NEt (8.07 mL, 46.3 mmol, 3.0 equiv) and TBSCl (5.82 g, 38.6 mmol, 2.5 equiv) were added sequentially in single portions to a solution of 3-methoxy-4-hydroxydihydrocinnamic acid (**30**, 3.00 g, 15.4 mmol, 1.0 equiv) in CH_2Cl_2 (20 mL) at 25 °C, and the reaction mixture was stirred at 25 °C for 14 h. Upon completion, the reaction contents were diluted with EtOAc (60 mL), poured into water (15 mL), washed with 1 M aqueous HCl (2 × 30 mL) and brine (30 mL), dried ($MgSO_4$) and concentrated to afford the desired bis-silylated product as a light yellow oil which was carried forward without any additional purification. Next, the newly formed intermediate was taken up in wet THF (20 mL), solid K_2CO_3 (2.00 g, excess) was added at 25 °C in a single portion, and the resultant slurry was stirred vigourously for 2 h at 25 °C. Upon completion, the reaction contents were diluted with EtOAc (60 mL), poured into water (40 mL), washed with 1 M aqueous HCl (30 mL) and brine (30 mL), dried ($MgSO_4$), and concentrated. The resultant white solid was then dried under high vacuum in a 60 °C oil bath for 3 h to drive off TBSOH and afford the desired carboxylic acid **31** (4.74 g, 99% yield) as a white amorphous solid. **31**: R_f = 0.40 (silica gel, hexanes:EtOAc, 3:2); IR (film) ν_{max} 2956, 2931, 2858, 1679, 1625, 1509, 1418, 1283, 1265, 1205, 1160, 1123, 906, 839, 824, 783 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 11.4 (br s, 1

H), 7.72 (d, J = 16.0 Hz, 1 H), 7.07-7.04 (m, 2 H), 6.86 (d, J = 8.8 Hz, 1 H), 6.31 (d, J = 16.0 Hz, 1 H), 3.85 (s, 3 H), 1.00 (s, 9 H), 0.18 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.0, 151.2, 148.0, 147.1, 127.9, 122.7, 121.1, 115.0, 111.1, 55.4, 25.6, 18.5, -4.6; HRMS (FAB) calcd for $C_{16}H_{25}O_4Si^+$ [M + H^+] 309.1522 and $C_{16}H_{23}O_3Si^+$ [M - OH^+] 291.1416, found 309.1503 and 291.1424.

Diels-Alder Dimer 33. MeOH (10 mL) and $PhI(OAc)_2$ (0.444 g, 1.38 mmol, 1.05 equiv) were added sequentially to a solution of phenol **32** (0.925 g, 1.31 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL) at 0 °C. The resulting yellow solution was allowed to slowly warm to 25 °C, and then stirred for 14 h. Upon completion, the reaction contents were concentrated directly and purified by flash column chromatography (silica gel, hexanes:EtOAc, 7:3) to afford a 1:1 mixture of diastereomeric **33** (0.959 g, 99% yield) as a light yellow amorphous solid. **33**: R_f = 0.22 (silica gel, hexanes:EtOAc, 3:2); IR (film) ν_{max} 3059, 1731, 1718, 1631, 1512, 1421, 1326, 1267, 1220, 1165, 1126, 1065, 1018, 825 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 1:1 mixture of diastereomers) δ 7.63-7.52 (m, 32 H), 7.24 (d, J = 14.0 Hz, 1 H), 7.21 (d, J = 15.2 Hz, 1 H), 7.03 (d, J = 16.0 Hz, 1 H), 6.97 (d, J = 15.6 Hz, 1 H), 6.91-6.84 (m, 8 H), 6.80-6.76 (m, 4 H), 6.17 (app dt, J = 6.8, 3.4 Hz, 2 H), 6.13-5.96 (m, 7 H), 5.92 (d, J = 10.4 Hz, 1 H), 5.30-5.18 (m, 20 H), 3.70 (s, 3 H), 3.69 (s, 3 H), 3.66 (s, 3 H), 3.63 (s, 3 H), 3.40 (m, 10 H), 3.37 (br s, 1 H), 3.32 (m, 5 H), 3.30 (s, 1 H), 3.23 (d, J = 6.8 Hz, 1 H), 3.21 (s, 3 H), 3.17 (s, 3 H), 3.15-3.08 (m, 8 H), 3.02 (s, 3 H), 2.98 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, 1:1 mixture of diastereomers) δ 198.8, 191.1, 170.1, 169.8,

165.6, 165.3, 164.9, 149.2, 149.1, 148.5, 147.7, 145.7, 133.1, 132.8, 130.7, 130.3, 129.9, 129.6, 129.5, 128.7, 128.4, 127.3, 127.2, 125.9, 125.5, 122.9, 122.8, 122.3, 121.0, 120.9, 119.4, 119.0, 116.3, 116.1, 115.1, 97.7, 94.3, 94.2, 77.2, 73.3, 70.5, 58.3, 57.9, 52.3, 52.2, 50.7, 50.6, 50.4, 50.1, 50.0, 49.9, 49.0, 48.9, 43.5, 43.3, 40.7, 36.9; LRMS (MALDI) calcd for $C_{74}H_{63}F_{12}O_{18}Na^+$ [M - H + Na^+] 1490.37, found 1490.46.

Mixed Diels-Alder Product 34. A solution of **33** (1.07 g, 0.728 mmol, 1.0 equiv) and dienophile **27** (4.90 g, 4.87 mmol, 6.7 equiv) in mesitylene (3.0 mL) was carefully degassed 3 times using the freeze-pump-thaw method, and then sealed under argon in a tube equipped with a magnetic stir bar. The reaction mixture was then stirred at 220 °C (oil bath) for 35 min. After cooling the reaction contents to 25 °C, the reaction mixture was purified directly by flash column chromatography (silica gel, hexanes:EtOAc:CH_2Cl_2, 8:1:1→5:4:1) to provide recovered **27** (4.12 g) along with **34** (0.960 g, 38% yield, 71% yield based on recovered starting material) as a light yellow solid. [Note: compound **34** is produced as a 1:1 mixture of chromatographically separable diastereomers; only data pertaining to the diastereomer which leads to the final natural products is provided here]. **34**: R_f = 0.24 (silica gel, hexanes:EtOAc:CH_2Cl_2, 3:1:1); $[\alpha]^{25}_D$ = +63.5° (*c* = 0.45, $CHCl_3$); IR (film) ν_{max} 1740, 1435, 1367, 1325, 1228, 1246, 1112, 1065, 824 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.55-7.43 (m, 24 H), 7.34 (d, *J* = 16.0 Hz, 1 H), 6.87-6.69 (m, 8 H), 6.58-6.55 (m, 2 H), 6.18 (d, *J* = 15.6 Hz, 1 H), 5.29 (dd, *J* = 7.6, 5.2 Hz, 1 H), 5.18-5.02 (m, 13 H), 4.97 (app s, 2

H), 3.66 (s, 3 H), 3.57 (s, 3 H), 3.37 (app s, 2 H), 3.30 (s, 3 H), 3.28 (s, 3 H), 3.13 (dd, J = 14.4, 5.2 Hz, 1 H), 3.08 (dd, J = 14.2, 7.8 Hz, 1 H), 3.02 (dd, J = 14.2, 4.6 Hz, 1 H), 2.92 (dd, J = 14.8, 8.0 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.5, 172.2, 169.3, 165.9, 148.6, 148.5, 148.3, 147.8, 147.8, 142.4, 141.2, 141.0, 140.4, 134.3, 134.1, 130.4, 129.9, 129.5, 127.4, 127.3, 127.2, 127.1, 125.8, 125.5, 122.7, 122.6, 122.3, 120.7, 118.3, 116.1, 114.9, 114.7, 93.9, 77.2, 73.3, 73.0, 70.5, 70.4, 70.3, 55.3, 52.3, 52.3, 51.0, 49.7, 46.7, 44.9, 42.1, 40.0, 36.7; HRMS (FAB) calcd for $C_{88}H_{70}F_{18}O_{17}^{+}$ [M^{+}] 1740.43, found 1739.98.

Helisorin (3). Water (0.012 mL, 0.645 mmol, 5.0 equiv) and $BF_3 \cdot OEt_2$ (0.487 mL, 3.88 mmol, 30 equiv) were added in single portions to a solution of Diels-Alder adduct **34** (0.225 g, 0.129 mmol, 1.0 equiv) in benzene (6 mL) at 0 °C. The resulting yellow solution was then warmed slowly to 25 °C and stirred for an additional 16 h. Upon completion, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (10 mL), poured into water (10 mL), and extracted with EtOAc (3 × 20 mL). The combined organic layers were then washed with brine (10 mL), dried ($MgSO_4$), and concentrated. The crude orange solid was purified by flash column chromatography (silica gel, toluene:acetone, 19:1) to afford recovered **34** (0.080 g) alongside the protected natural product (0.116 g, 53% yield, 82% yield based on recovered starting material) as a colorless glass. Next, BBr_3 (1.0 M in CH_2Cl_2, 0.283 mL, 0.283 mmol, 20 equiv) was added in a single portion to a solution of this newly formed intermediate (0.024 g, 0.014 mmol, 1.0 equiv) in CH_2Cl_2 (1 mL) at −78 °C, and the reaction was stirred at −78

°C for 30 min. Upon completion, the reaction mixture was quenched at −78 °C with saturated aqueous $NaHCO_3$ (1 mL), re-acidified with 1.0 M HCl (1 mL), warmed to 25 °C, poured into water (10 mL), and extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), and concentrated. The resultant crude yellow solid was triturated with CH_2Cl_2 (3 × 1 mL) to afford helisorin (**3**, 9.2 mg, 89% yield) as a white solid. [Note: significant decomposition of helisorin (**3**) was observed following its application to silica gel, exposure to air, and/or temperatures above 25 °C]. **3**: R_f = 0.13 (silica gel, CH_2Cl_2:MeOH, 9:1); $[\alpha]^{25}_D$ = +28.3° (*c* = 0.15, MeOH); IR (film) ν_{max} 3415, 1728, 1631, 1515, 1444, 1261, 1160, 1044 cm^{-1}; ^1H NMR (500 MHz, acetone-d_6) δ 7.71 (br s, 4 H), 7.25 (d, *J* = 16.0 Hz, 1 H), 6.80 (s, 1 H), 6.74 (br s, 2 H), 6.72 (d, *J* = 9.0 Hz, 1 H), 6.72 (d, *J* = 3.5 Hz, 1 H), 6.71 (br s, 1 H), 6.68 (d, *J* = 8.0 Hz, 1 H), 6.57 (dd, *J* = 8.0, 2.0 Hz, 1 H), 6.56 (dd, *J* = 8.0, 2.0 Hz, 1 H), 6.04 (d, *J* = 16.0 Hz, 1 H), 5.15 (dd, *J* = 9.2, 6.8 Hz, 1 H), 4.97 (dd, *J* = 9.2, 4.3 Hz, 1 H), 3.97 (br s, 1 H), 3.62 (s, 3 H), 3.64–3.59 (m, 1 H), 3.55 (s, 3 H), 3.51 (d, *J* = 5.0 Hz, 1 H), 6.57 (dd, *J* = 8.0, 2.0 Hz, 1 H), 3.57 (s, 3 H), 3.37 (app s, 2 H), 3.30 (s, 3 H), 3.28 (s, 3 H), 3.05 (dd, *J* = 13.7, 4.3 Hz, 1 H), 3.01 (br s, 1 H), 2.98 (dd, *J* = 14.7, 6.7 Hz, 1 H), 2.97 (dd, *J* = 14.5, 4.5 Hz, 1 H), 2.82 (dd, *J* = 14.0, 9.5 Hz, 1 H); ^{13}C NMR (125 MHz, acetone-d_6) δ 204.7, 170.9, 170.7, 170.3, 166.7, 147.3, 145.9, 145.9, 145.8, 145.0, 145.1, 142.8, 140.7, 138.0, 137.6, 134.8, 128.7, 128.7, 121.9, 121.8, 118.2, 117.4, 117.4, 116.3, 116.2, 111.4, 111.0, 82.0, 75.0, 74.3, 57.5, 53.0, 52.9, 52.7, 52.5, 43.7, 37.6, 37.6; HRMS (FAB) calcd for $C_{38}H_{35}O_{16}^+$ [M + H^+]

747.4531, found 747.4528. All spectroscopic data for this synthetic material match those reported by Tezuka and co-workers for natural helisorin (**3**); see Table S1 at the end of this section for a direct comparison [1a].

Hydroxyketal 35. $NaBH_4$ (0.090 g, 2.38 mmol, 2.0 equiv) was added in a single portion to a solution of bicyclic ketone **21** (0.550 g, 1.19 mmol, 1.0 equiv) in MeOH:CH_2Cl_2 (5:1, 6 mL) at 0 °C, and the resultant mixture was stirred at 0 °C for 1 h. Upon completion, the reaction contents were diluted with EtOAc (20 mL), poured into water (20 mL), washed with 1 M aqueous HCl (20 mL), saturated aqueous $NaHCO_3$ (20 mL), and brine (20 mL), dried ($MgSO_4$), and concentrated to afford hydroxyketal **35** (0.551 g, 99% yield) as a white amorphous solid. **35**: R_f = 0.51 (silica gel, hexanes:EtOAc, 3:7); IR (film) ν_{max} 3548, 2949, 1717, 1630, 1517, 1436, 1310, 1237, 1194, 1119, 1086, 1056, 911, 868 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, *J* = 15.6 Hz, 1 H), 6.94-6.92 (m, 2 H), 6.80 (d, *J* = 8.8 Hz, 1 H), 6.68 (d, *J* = 6.8 Hz, 1 H), 6.01 (d, *J* = 16.0 Hz, 1 H), 3.89 (s, 3 H), 3.84 (s, 3 H), 3.75 (s, 3 H), 3.70 (d, *J* = 1.2 Hz, 1 H), 3.61 (s, 3 H), 3.58 (ddd, *J* = 8.8, 3.2, 1.2 Hz, 1 H), 3.55 (s, 3 H), 3.42 (dd, *J* = 6.2, 2.2 Hz, 1 H), 3.39 (app d, *J* = 7.6 Hz, 1 H), 3.21 (dt, *J* = 6.8, 0.2 Hz, 1 H), 3.12 (s, 3 H), 2.21 (d, *J* = 8.8 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.7, 167.5, 148.9, 147.6, 142.6, 139.7, 137.6, 133.6, 119.0, 117.3, 111.7, 111.1, 98.9, 72.2, 55.8, 55.7, 52.1, 51.5, 48.9, 48.8, 46.5, 41.6, 41.1, 40.3; HRMS (FAB) calcd for $C_{24}H_{30}O_9^+$ [M^+] 462.1890, found 462.1897.

Hydroxyketone 36. To a solution of alcohol **35** (0.026 g, 0.056 mmol, 1.0 equiv) in toluene (2 mL) at 0 °C was sequentially added water (0.050 mL) and HCl (4.0 M in dioxane, 0.100 mL). The resultant biphasic solution was then stirred vigorously at 0 °C for 20 h. Upon completion, the reaction contents were quenched with saturated aqueous $NaHCO_3$ (10 mL), poured into water (10 mL), and extracted with EtOAc (3 × 15 mL). The combined organic layers were then washed with brine (10 mL), dried ($MgSO_4$), and concentrated. The resultant crude oil was purified by flash column chromatography (silica gel, hexanes:EtOAc, 1:1) to afford hydroxyketone **36** (0.020 g, 86% yield) as a colorless oil. **36**: R_f = 0.22 (silica gel, hexanes:EtOAc, 2:3); IR (film) ν_{max} 3727, 3475, 2947, 1730, 1631, 1517, 1435, 1313, 1237, 1172, 1146, 1026, 803 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, *J* = 15.6 Hz, 1 H), 6.93 (d, *J* = 7.2 Hz, 1 H), 6.83-6.79 (m, 3 H), 6.03 (d, *J* = 16.0 Hz, 1 H), 4.05 (app t, *J* = 2.2 Hz, 1 H), 3.88 (s, 3 H), 3.88-3.85 (m, 1 H) 3.85 (s, 3 H), 3.77 (s, 3 H), 3.64 (s, 3 H), 3.64-3.61 (m, 1 H), 3.57-3.54 (m, 2 H), 2.08 (d, *J* = 5.2 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.9, 171.8, 167.0, 149.0, 148.1, 140.8, 140.6, 135.1, 131.8, 119.5, 118.9, 111.9, 110.9, 72.2, 55.9, 52.6, 51.8, 49.3, 47.3, 46.3, 42.5; HRMS (FAB) calcd for $C_{22}H_{24}O_8$ [M^+] 416.1471, found 416.1489.

Hydroxyketone 37. Water (0.050 mL) and HCl (4.0 M in dioxane, 0.750 mL) were added sequentially to a solution of alcohol **35** (0.102 g, 0.220 mmol, 1.0 equiv) in THF (5 mL) at 25 °C to obtain a final acid concentration of 0.5 M. The resultant solution was stirred at 25 °C for 14 h. Upon completion, the reaction was poured into EtOAc (30 mL),

washed with saturated aqueous $NaHCO_3$ (15 mL) and brine (15 mL), dried ($MgSO_4$), and concentrated. The resultant crude solid was purified by flash column chromatography (silica gel, hexanes:EtOAc, 3:2) and crystallized from Et_2O to afford the desired hydroxyketone **37** (0.077 g, 84% yield) as a white crystalline solid. **37**: R_f = 0.51 (silica gel, hexanes:EtOAc, 3:7); m.p. = 170.0–170.3 °C; IR (film) ν_{max} 3727, 3456, 2947, 1730, 1629, 1518, 1436, 1312, 1194, 1173, 1026, 811 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, J = 15.6 Hz, 1 H), 6.78–6.77 (m, 3 H), 6.65 (dd, J = 6.4, 2.0 Hz, 1 H), 6.13 (d, J = 15.6 Hz, 1 H), 3.87 (dt, J = 3.2, 2.0 Hz, 1 H), 3.83 (s, 6 H), 3.78 (s, 3 H), 3.64 (s, 3 H), 3.61 (dd, J = 7.6, 2.4 Hz, 1 H), 3.57 (dd, J = 7.2, 2.0 Hz, 1 H), 3.28 (dd, J = 6.4, 2.4 Hz, 1 H), 3.23 (d, J = 2.0 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.2, 173.7, 167.2, 148.8, 148.1, 140.8, 140.2, 134.7, 132.3, 120.1, 118.6, 111.4, 111.1, 69.8, 55.7, 52.3, 51.8, 49.1, 41.8, 41.8; HRMS (FAB) calcd for $C_{22}H_{24}O_8^+$ [M^+] 416.1471, found 416.1489.

Ketone 39. AcOH (0.3 mL) and tetramethylammonium triacetoxyborohydride (0.146 g, 0.555 mmol, 3.0 equiv) were added sequentially to a solution of hydroxyketone **37** (0.077 g, 0.185 mmol, 1.0 equiv) in MeCN (3 mL) at 0 °C. The resultant solution was then warmed to 25 °C, and the reaction contents were stirred at 25 °C for 3 h. A second portion of tetramethylammonium triacetoxyborohydride (0.097 g, 0.370 mmol, 2.0 equiv) was then added, and stirring was continued at 25 °C for 2 h. Upon completion, the reaction contents were diluted with EtOAc (30 mL), poured into water (20 mL), and extracted with EtOAc (3 × 20 mL). The combined organic layers were then washed with saturated aqueous

$NaHCO_3$ (2 × 20 mL) and brine (20 mL), dried ($MgSO_4$), and concentrated. The resultant crude yellow solid was purified by flash column chromatography (silica gel, hexanes:EtOAc, 3:7) to afford the desired *anti*-disposed diol (0.066 g, 75% yield) as a white solid. With this step complete, Et_3N (0.110 mL, 0.789 mmol, 5.0 equiv) and TBSOTf (0.036 mL, 0.158 mmol, 1.0 equiv) were added sequentially to a solution of this newly formed *anti*-disposed diol (0.066 g, 0.158 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL) at -78 °C. The reaction contents were then slowly warmed to 25 °C over 1 h with constant stirring. Upon completion, the reaction contents were diluted with EtOAc (30 mL), poured into water (20 mL), and extracted with EtOAc (3 × 20 mL). The combined organic layers were then washed with saturated aqueous $NaHCO_3$ (20 mL) and brine (20 mL), dried ($MgSO_4$), and concentrated to afford the desired mono-silylated diol as a white solid which was used directly without any additional purification. With this operation complete, solid $NaHCO_3$ (0.132 g, 1.58 mmol, 10 equiv) and Dess-Martin periodinane (0.134 g, 0.315 mmol, 2.0 equiv) were added sequentially in single portions to a solution of this newly formed intermediate in CH_2Cl_2 (2 mL) at 25 °C. The resultant suspension was stirred at 25 °C for 1 h. Upon completion, saturated aqueous Na_2SO_3 (2 mL) was added and the resultant biphasic mixture was stirred vigorously for 1 h to quench any remaining oxidizing agents. The reaction contents were then diluted with EtOAc (30 mL), poured into water (20 mL), and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (20 mL) and brine (20 mL), dried ($MgSO_4$), and concentrated. The crude product was purified by flash column chromatography (silica

gel, hexanes:EtOAc, 7:3) to afford ketone **39** (0.079 g, 94% yield over 2 steps, 71% overall yield from **37**) as a light yellow solid. **39**: R_f = 0.69 (silica gel, hexanes:EtOAc, 3:7); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (d, *J* = 15.5 Hz, 1 H), 6.88 (d, *J* = 6.5 Hz, 1 H), 6.85 (d, *J* = 8.5 Hz, 1 H), 6.77 (d, *J* = 7.5 Hz, 1 H), 6.02 (d, *J* = 15.5 Hz, 1 H), 3.95 (s, 1 H), 3.91 (d, *J* = 2.0 Hz, 1 H), 3.89 (s, 3 H), 3.88 (s, 3 H), 3.76 (s, 3 H), 3.65 (s, 3 H), 3.51 (dd, *J* = 7.0, 2.5 Hz, 1 H), 3.36 (dd, *J* = 6.8, 1.8 Hz, 1 H), 3.08 (dt, *J* = 6.0, 2.5 Hz, 1 H), 0.76 (s, 9 H), -0.08 (s, 3 H), -0.10 (s, 3 H).

Hydroxyketone 40. AcOH (0.012 mL, 0.196 mmol, 2.0 equiv) and TBAF (1.0 M in THF, 0.196 mL, 0.196 mmol, 2.0 equiv) were added sequentially in single portions to a solution of **39** (0.052 g, 0.098 mmol, 1.0 equiv) in THF (2 mL) at 25 °C, and the resultant solution was stirred at 25 °C for 2 h. Upon completion, the reaction contents were poured into EtOAc (20 mL) and washed with saturated aqueous NH_4Cl (15 mL) and brine (15 mL), dried ($MgSO_4$), and concentrated. The resultant crude yellow solid was purified by flash column chromatography (silica gel, hexanes:EtOAc, 3:2) to afford recovered **39** (0.015 g) alongside hydroxyketone **40** (0.022 g, 54% yield, 76% yield based on recovered starting material) as a white amorphous solid. **40**: R_f = 0.32 (silica gel, hexanes:EtOAc, 3:7); IR (film) ν_{max} 3728, 3460, 1731, 1631, 1518, 1436, 1313, 1238, 1172, 1089, 1026, 808 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, *J* = 16.0 Hz, 1 H), 6.91 (d, *J* = 6.8 Hz, 1 H), 6.86-6.79 (m, 3 H), 6.06 (d, *J* = 15.6 Hz, 1 H), 4.03 (t, *J* = 1.6 Hz, 1 H), 3.98 (s, 1 H), 3.89 (s, 3 H), 3.88 (s, 3 H), 3.77 (s, 3 H), 3.64 (s, 3 H), 3.55 (dd,

J = 7.2, 2.8 Hz, 1 H), 3.41 (dd, *J* = 7.2, 2.0 Hz, 1 H), 3.30 (dt, *J* = 6.4, 2.4 Hz, 1 H), 2.55 (d, *J* = 1.6 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.4, 172.2, 167.0, 149.3, 148.4, 141.6, 140.4, 133.0, 131.3, 119.1, 118.5, 111.7, 111.3, 66.9, 56.0, 52.7, 51.8, 46.1, 44.2, 41.6; HRMS (FAB) calcd for $C_{22}H_{25}O_8^+$ [M+H$^+$] 417.1549, found 417.1548.

Hydroxyketal 42. HCl (4.0 M in dioxane, 0.3 mL) was added to a solution of ketone **39** (0.027 g, 0.051 mmol, 1.0 equiv) in MeOH:$CH(OMe)_3$ (4:1, 2.5 mL) at 25 °C, and the resultant solution was stirred at 25 °C for 14 h. Upon completion, the reaction contents were concentrated directly and the resultant crude yellow solid was purified by flash column chromatography (silica gel, hexanes:EtOAc, 3:2) to afford monomer **42** (0.022 g, 93% yield) as a light yellow solid. **42**: R_f = 0.45 (silica gel, hexanes:EtOAc, 3:7); IR (film) ν_{max} 3525, 2950, 1717, 1628, 1516, 1436, 1240, 1171, 1123, 1083, 1027, 733 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, *J* = 15.6 Hz, 1 H), 6.90–6.83 (m, 3 H), 6.78 (d, *J* = 7.2 Hz, 1 H), 6.01 (d, *J* = 16.0 Hz, 1 H), 3.92 (dd, *J* = 6.6, 2.2 Hz, 1 H), 3.90 (s, 3 H), 3.77 (s, 3 H), 3.76 (app s, 1 H), 3.60 (s, 3 H), 3.53 (dd, *J* = 6.8, 2.0 Hz, 1 H), 3.32 (s, 3 H), 3.31 (s, 3 H), 3.26 (dd, *J* = 6.8, 2.8 Hz, 1 H), 2.92 (dt, *J* = 6.8, 2.6 Hz, 1 H), 2.86 (d, *J* = 6.4 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.8, 167.4, 149.0, 147.9, 142.5, 141.4, 136.8, 132.5, 120.0, 116.4, 111.8, 111.2, 101.9, 68.3, 55.9, 55.8, 52.1, 51.6, 49.8, 49.6, 48.2, 44.3, 41.6, 41.5; HRMS (FAB) calcd for $C_{24}H_{30}O_9^+$ [M$^+$] 462.1890, found 462.1889.

Unsymmetrical Dimer 43. Solid NaH (60% dispersion in mineral oil, 5.8 mg, 0.144 mmol, 10 equiv) was added in a

single portion to a solution of hydroxyketone **40** (6.0 mg, 0.014 mmol, 1.0 equiv) in THF (0.5 mL) at 0 °C. The resultant slurry was then warmed to 25 °C and stirred for 20 min. Upon completion, the reaction mixture was carefully quenched with saturated aqueous NH_4Cl (10 mL), poured into water (10 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layers were then washed with brine (10 mL), dried ($MgSO_4$), and concentrated. The resultant crude off-white solid was purified by flash column chromatography (silica gel, hexanes:EtOAc, 1:1) to afford unsymmetrical dimer **43** (6.0 mg, 99% yield) which was recrystallized from $CHCl_3$:Et_2O (2:1) as white needles. **43**: R_f = 0.17 (silica gel, hexanes:EtOAc, 3:7); m.p. = 189.0–189.3 °C; IR (film) ν_{max} 3426, 2904, 1720, 1632, 1518, 1436, 1311, 1238, 1196, 1027, 810 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.52 (d, *J* = 16.0 Hz, 1 H), 7.28 (d, *J* = 16.5 Hz, 1 H), 7.00–6.97 (m, 2 H), 6.89 (d, *J* = 8.0 Hz, 1 H), 6.85–6.80 (m, 3 H), 6.71 (d, *J* = 6.5 Hz, 1 H), 6.59 (d, *J* = 6.0 Hz, 1 H), 5.96 (d, *J* = 15.5 Hz, 1 H), 5.80 (d, *J* = 15.5 Hz, 1 H), 5.43 (br s, 1 H), 4.14 (d, *J* = 3.0 Hz, 1 H), 3.88 (s, 6 H), 3.84 (s, 3 H), 3.79 (s, 3 H), 3.79 (s, 3 H), 3.79–3.76 (m, 2 H), 3.73 (s, 3 H), 3.58 (s, 3 H), 3.57 (s, 3 H), 3.53 (dd, *J* = 6.0, 2.0 Hz, 1 H), 3.45 (dd, *J* = 5.8, 2.7 Hz, 1 H), 3.34 (dd, *J* = 6.5, 2.0 Hz, 1 H), 3.25 (dd, *J* = 6.5, 2.5 Hz, 1 H), 3.16 (s, 1 H), 3.12 (dt, *J* = 6.5, 3.0 Hz, 1 H), 2.91 (dt, *J* = 6.5, 2.8 Hz, 1 H), 2.51 (br s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.4, 173.3, 167.2, 149.0, 148.0, 142.0, 141.5, 138.6, 138.2, 137.7, 136.9, 132.4, 132.2, 120.4, 119.6, 118.1, 117.5, 112.3, 111.4, 111.3, 111.2, 106.6, 80.7, 71.5, 55.9, 55.9, 55.8, 52.3, 51.6, 51.5, 47.4, 45.0, 44.4,

44.2, 43.9, 43.1, 42.9, 41.7; HRMS (FAB) calcd for $C_{44}H_{48}O_{16}^{+}$ [M^{+}] 832.2942, found 832.2975.

Ketone 44. Anhydrous HCl gas (1 atm, generated in another flask linked via rubber tubing by slowly adding concentrated H_2SO_4 to solid NaCl) was ducted into a round-bottom flask containing alcohol **42** (0.7 mg, 0.0015 mmol) and immersed in a 100 °C oil bath. A positive pressure of HCl was maintained in the reaction flask for 5 min, after which time no further HCl was added. The reaction was then maintained at 100 °C for an additional 40 min. Upon completion, the reaction contents were cooled to 25 °C, affording ketone **44** (0.6 mg, 99% yield) as a light yellow amorphous solid. **44**: R_f = 0.38 (silica gel, hexanes:EtOAc, 3:2); IR (film) ν_{max} 2953, 1715, 1631, 1518, 1436, 1264, 1170, 1101, 1026, 811 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, J = 16.0 Hz, 1 H), 6.86 (d, J = 1.6 Hz, 1 H), 6.83-6.77 (m, 2 H), 6.65 (d, J = 6.4 Hz, 1 H), 6.13 (d, J = 15.6 Hz, 1 H), 3.91 (app s, 1 H), 3.85 (s, 3 H), 3.85 (s, 3 H), 3.79 (s, 3 H), 3.71 (s, 3 H), 3.66 (s, 3 H), 3.57 (dd, J = 7.4, 2.2 Hz, 1 H), 3.49 (dd, J = 6.8, 2.0 Hz, 1 H), 3.37 (d, J = 3.6 Hz, 1 H), 3.24 (dd, J = 6.6, 2.6 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.0, 173.7, 167.1, 165.3, 148.9, 148.1, 140.9, 139.8, 135.4, 133.0, 120.3, 118.5, 111.2, 59.0, 56.4, 55.8, 52.3, 51.8, 48.3, 42.8, 39.9; HRMS (FAB) calcd for $C_{23}H_{26}O_8^{+}$ [M^{+}] 430.1628, found 430.1635.

Enol Triflate 45. KHMDS (0.5 M in toluene, 0.604 mL, 0.302 mmol, 1.3 equiv) was added dropwise to a solution of Tf_2NPh (0.216 g, 0.604 mmol, 2.6 equiv) and ketone **44** (0.100 g, 0.232 mmol, 1.0 equiv) in THF (5 mL) at -78 °C, and the

reaction was stirred at -78 °C for 10 min. Upon completion, the reaction contents were quenched sequentially at -78 °C with water (10 mL) and saturated aqueous $NaHCO_3$ (10 mL). After warming to 25 °C, the mixture was extracted with EtOAc (2 × 20 mL). The combined organic layers were then washed with brine (20 mL), dried ($MgSO_4$) and concentrated. The resultant crude yellow solid was purified by flash column chromatography (silica gel, hexanes:EtOAc, 7:3) to afford enol triflate **45** (0.097 g, 74% yield) as a white amorphous solid. **45**: R_f = 0.37 (silica gel, hexanes:EtOAc, 3:2); IR (film) ν_{max} 2953, 1718, 1632, 1516, 1420, 1205, 1138, 1085, 1027, 878 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34 (d, J = 16.0 Hz, 1 H), 6.92 (d, J = 5.5 Hz, 1 H), 6.81 (d, J = 9.0 Hz, 1 H), 6.72-6.71 (m, 2 H), 6.00 (d, J = 16.0 Hz, 1 H), 4.28 (app s, 1 H), 3.88 (s, 1 H), 3.87 (s, 6 H), 3.77 (s, 3 H), 3.62 (s, 3 H), 3.56 (dd, J = 6.5, 2.0 Hz, 1 H), 3.44 (dd, J = 5.0, 2.0 Hz, 1 H), 3.04 (dd, J = 5.0, 2.5 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9, 167.1, 149.7, 149.2, 148.3, 142.6, 140.5, 140.1, 133.8, 127.8, 119.3, 117.4, 111.4, 110.5, 58.4, 55.9, 55.8, 52.2, 51.7, 48.5, 47.9, 42.2; HRMS (FAB) calcd for $C_{24}H_{26}O_{10}F_3S^+$ [M^+] 563.1199, found 563.1191.

Ketone 47. Alcohol **42** (3.5 mg, 0.008 mmol, 1.0 equiv) was heated neat under an argon atmosphere at 160 °C for 4 h. Upon completion, the reaction contents were cooled to 25 °C, concentrated, and purified by flash column chromatography (silica gel, hexanes:EtOAc, 3:2) to afford recovered **42** (1.8 mg) alongside **47** (0.5 mg, 15% yield, 32% yield based on recovered starting material) as a colorless oil. **47**: R_f = 0.55 (silica gel, hexanes:EtOAc, 3:7); ^1H NMR

(400 MHz, $CDCl_3$) δ 7.40 (d, *J* = 16.0 Hz, 1 H), 6.79 (d, *J* = 8.4 Hz, 1 H), 6.70-6.64 (m, 3 H), 6.08 (d, *J* = 15.6 Hz, 1 H), 3.90 (s, 1 H), 3.85 (s, 6 H), 3.78 (s, 3 H), 3.71 (s, 3 H), 3.61 (dd, *J* = 6.2, 2.2 Hz, 1 H), 3.58 (s, 3 H), 3.54 (d, *J* = 2.8 Hz, 1 H), 3.49 (dd, *J* = 6.8, 2.4 Hz, 1 H), 3.01 (dd, *J* = 6.4, 2.0 Hz, 1 H); LRMS (FAB) calcd for $C_{23}H_{26}O_8^+$ [M^+] 430.2, found 430.1.

Helicterin A Core 48. $BF_3 \cdot OEt_2$ (0.057 mL, 0.450 mmol, 4.0 equiv) was added in a single portion under strictly anhydrous conditions to a solution of monomer **42** (0.052 g, 0.112 mmol, 1.0 equiv) in CH_2Cl_2 (1 mL) at 0 °C, and the reaction was stirred at 0 °C for 30 min. Upon completion, the reaction contents were quenched at 0 °C with saturated aqueous $NaHCO_3$ (10 mL), poured into water (10 mL), and extracted with EtOAc (2 × 20 mL). The combined organic layers were then washed with brine (20 mL), dried ($MgSO_4$), and concentrated. The resultant crude yellow solid was purified by flash column chromatography (silica gel, hexanes:EtOAc, 3:2) and recrystallized from Et_2O:hexanes (3:1) to afford dimer **48** (0.038 g, 79% yield) as a white crystalline solid. **48**: R_f = 0.51 (silica gel, hexanes:EtOAc, 3:7); m.p. = 215.0-215.8 °C; IR (film) ν_{max} 2950, 1705, 1632, 1517, 1435, 1362, 1234, 1170, 1145, 1026 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, *J* = 15.2 Hz, 2 H), 6.95-6.91 (m, 4 H), 6.80 (d, *J* = 8.4 Hz, 2 H), 5.88 (d, *J* = 15.6 Hz, 2 H), 3.88 (s, 6 H), 3.86 (s, 6 H), 3.80 (s, 6 H), 3.63 (d, *J* = 3.2 Hz, 2 H), 3.57 (s, 6 H), 3.29 (s, 6 H), 3.24 (dd, *J* = 6.4, 2.8 Hz, 2 H), 3.14 (dd, *J* = 6.4, 1.6 Hz, 2 H), 2.79 (dt, *J* = 6.4, 1.6 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.6, 167.7, 148.8, 147.7, 142.9, 139.7, 135.7, 133.0, 120.0,

116.1, 112.2, 111.1, 100.1, 69.1, 55.8, 52.1, 51.6, 49.0, 44.4, 43.2, 42.2, 40.1; HRMS (FAB) calcd for $C_{46}H_{52}O_{16}^{+}$ [M^{+}] 860.3255, found 860.3262.

Hydroxyketone 49. $NaBH_4$ (0.022 g, 0.586 mmol, 1.5 equiv) was added in a single portion to a solution of Diels-Alder adduct **34** (0.680 g, 0.390 mmol, 1.0 equiv) in MeOH:THF (4:1, 7.5 mL) at -30 °C. The reaction was then stirred at -30 °C for 1 h. Upon completion, the reaction mixture was carefully quenched at -30 °C with 1 M aqueous HCl (15 mL), poured into water (10 mL), and extracted with EtOAc (3 × 30 mL). The combined organic layers were then washed with saturated aqueous $NaHCO_3$ (15 mL) and brine (15 mL), dried ($MgSO_4$), and concentrated. The resultant crude material was then purified by flash column chromatography (silica gel, toluene:acetone, 9:1) to afford the desired intermediate alcohol as a yellow solid. Next, this newly formed alcohol was taken up in MeCN (5 mL), and water (0.050 mL) and HCl (4.0 M in dioxane, 0.750 mL) were then added sequentially at 25 °C to obtain a final acid concentration of 0.5 M. The resultant solution was stirred at 25 °C for 14 h. Upon completion, the reaction contents were diluted with EtOAc (30 mL), poured into water (10 mL), and extracted with EtOAc (3 × 10 mL). The combined organic layers were then washed with saturated aqueous $NaHCO_3$ (15 mL) and brine (15 mL), dried ($MgSO_4$), and concentrated. The resultant crude material was purified by flash column chromatography (silica gel, toluene:acetone, 19:1) to afford **49** (0.370 g, 56% yield over 2 steps) as a light yellow solid. **49**: R_f = 0.44 (silica gel, toluene:acetone, 9:1); $[\alpha]^{25}_{D}$ = +49.2° (*c* = 0.19, $CHCl_3$); IR (film) ν_{max} 3628, 2928, 1734, 1513, 1324,

1161, 1110, 1066, 1017, 824 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.63-7.43 (m, 24 H), 7.32 (d, *J* = 15.6 Hz, 1 H), 6.86-6.78 (m, 5 H), 6.70-6.65 (m, 3 H), 6.61 (dd, *J* = 6.4, 1.2 Hz, 1 H), 6.53 (dd, *J* = 8.4, 2.0 Hz, 1 H), 6.21 (d, *J* = 15.6 Hz, 1 H), 5.30 (dd, *J* = 7.6, 5.2 Hz, 1 H), 5.15-5.01 (m, 13 H), 3.88 (d, *J* = 2.8 Hz, 1 H), 3.69 (d, *J* = 3.6 Hz, 1 H), 3.66 (s, 3 H), 3.53 (s, 3 H), 3.51 (app d, *J* = 1.6 Hz, 1 H), 3.42 (dd, *J* = 7.6, 2.4 Hz, 1 H), 3.25 (dd, *J* = 6.4, 2.0 Hz, 1 H), 3.14 (dd, *J* =14.4, 5.2 Hz, 1 H), 3.07 (dd, *J* = 14.4, 8.0 Hz, 1 H), 3.00 (dd, *J* = 14.4, 4.4 Hz, 1 H), 2.89 (dd, *J* = 14.8, 8.4 Hz, 1 H), 2.71 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.6, 172.6, 169.9, 169.3, 165.9, 148.5, 147.9, 147.8, 147.7, 141.4, 141.0, 140.4, 134.9, 133.3, 130.8, 130.3, 129.9, 129.5, 129.2, 127.3, 127.3, 127.2, 127.1, 125.8, 125.5, 122.7, 122.5, 122.2, 121.3, 118.7, 116.2, 116.0, 115.0, 114.8, 77.2, 73.3, 73.0, 70.6, 70.4, 70.4, 70.1, 54.7, 52.3, 49.0, 41.8, 41.5, 36.9, 36.7; HRMS (FAB) calcd for $C_{86}H_{67}F_{18}O_{16}^+$ [M + H^+] 1697.41, found 1697.77.

Hydroxyketal 50. AcOH (0.2 mL) and tetramethylammonium triacetoxyborohydride (0.239 g, 0.912 mmol, 3.0 equiv) were added sequentially to a solution of hydroxyketone **49** (0.515 g, 0.303 mmol, 1.0 equiv) in MeCN (10 mL) at 0 °C. The resultant solution was then warmed to 25 °C, and the reaction contents were stirred at 25 °C for 10 h. A second portion of tetramethylammonium triacetoxyborohydride (0.159 g, 0.606 mmol, 2.0 equiv) was then added, and stirring was continued at 25 °C for 4 h. Upon completion, the reaction contents were diluted with EtOAc (20 mL), poured into water (15 mL), and extracted with EtOAc (2 × 20 mL). The combined organic layers were then washed with saturated aqueous

$NaHCO_3$ (2 × 20 mL) and brine (20 mL), dried ($MgSO_4$), and concentrated. The resultant crude orange solid was purified by flash column chromatography (silica gel, toluene:acetone, 9:1) to afford recovered **49** (0.162 g) alongside the desired *anti*-disposed diol product (0.270 g, 52% yield, 76% yield based on recovered starting material) as a colorless, glassy solid. Next, Et_3N (0.082 mL, 0.585 mmol, 5.0 equiv) and TBSOTf (0.028 mL, 0.123 mmol, 1.05 equiv) were added sequentially to a solution of a portion of this newly formed *anti*-disposed diol (0.199 g, 0.117 mmol, 1.0 equiv) in CH_2Cl_2 (3 mL) at -78 °C. The reaction was then slowly warmed to 25 °C over 1 h with constant stirring. Upon completion, the reaction contents were diluted with EtOAc (20 mL), poured into water (15 mL), and extracted with EtOAc (2 × 20 mL). The combined organic layers were then washed with saturated aqueous $NaHCO_3$ (20 mL) and brine (20 mL), dried ($MgSO_4$), and concentrated to afford the desired mono-silylated diol as a white solid which was used directly without any additional purification. With this operation complete, $NaHCO_3$ (0.986 g, 1.17 mmol, 10 equiv) and Dess-Martin periodinane (0.074 g, 0.176 mmol, 1.5 equiv) were added sequentially in single portions to a solution of this newly formed intermediate in CH_2Cl_2 (2 mL) at 25 °C. The resultant suspension was then stirred at 25 °C for 1 h. Upon completion, saturated aqueous Na_2SO_3 (2 mL) was added and the resultant biphasic mixture was stirred vigorously for 1 h to quench any remaining oxidizing agents. The reaction contents were then diluted with EtOAc (20 mL), poured into water (15 mL), and extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (2 × 20 mL)

and brine (20 mL), dried ($MgSO_4$), and concentrated to afford the desired crude ketone as a light yellow solid which was carried forward without any additional purification. Finally, HCl (0.3 mL) was added to a solution of the newly formed crude ketone in MeOH:$CH(OMe)_3$ (4:1, 2.5 mL) at 25 °C, and the resultant solution was stirred at 25 °C for 14 h. Upon completion, the reaction contents were diluted with EtOAc (20 mL), poured into water (15 mL), and extracted with EtOAc (2 × 20 mL). The combined organic layers were then washed with saturated aqueous $NaHCO_3$ (20 mL) and brine (20 mL), dried ($MgSO_4$), and concentrated. The resultant crude yellow solid was purified by flash column chromatography (silica gel, toluene:acetone, 19:1) to afford the desired alcohol **50** (0.148 g, 73% yield over the final 3 steps, 43% overall from **49**) as a light yellow solid. **50**: R_f = 0.28 (silica gel, toluene:acetone, 9:1); $[\alpha]^{25}_D$ = +14.2° (*c* = 0.38, $CHCl_3$); IR (film) ν_{max} 3727, 2953, 1743, 1715, 1623, 1513, 1420, 1324, 1161, 1118, 1066, 824 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.63-7.35 (m, 25 H), 6.93-6.73 (m, 8 H), 6.64-6.61 (m, 2 H), 6.41 (dd, *J* = 8.0, 1.6 Hz, 1 H), 6.14 (d, *J* = 15.6 Hz, 1 H), 5.28 (dd, *J* = 7.2, 5.6 Hz, 1 H), 5.16-4.98 (m, 13 H), 3.82 (app d, *J* = 6.4 Hz, 1 H), 3.72 (s, 1 H), 3.65 (s, 3 H), 3.57 (s, 3 H), 3.54 (app d, *J* = 7.2 Hz, 1 H), 3.26 (s, 3 H), 3.17 (s, 3 H), 3.10 (dd, *J* = 6.8, 4.0 Hz, 1 H), 3.00-2.87 (m, 5 H), 2.85 (d, *J* = 6.4 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.8, 170.0, 169.5, 166.2, 148.7, 148.5, 148.3, 147.7, 147.6, 147.5, 143.3, 141.4, 141.1, 141.0, 137.3, 133.8, 130.3, 129.9, 129.6, 129.4, 129.1, 127.3, 127.2, 127.1, 127.1, 125.8, 125.4, 122.7, 122.7, 122.2, 121.0, 116.5, 116.2, 115.9, 115.4, 114.9, 114.7, 101.9, 77.2, 73.0, 70.5, 70.4, 70.3,

68.6, 52.2, 49.9, 49.7, 47.3, 44.5, 41.7, 41.1, 37.0, 36.6; HRMS (FAB) calcd for $C_{88}H_{72}F_{18}O_{17}^{+}$ [M^{+}] 1742.45, found 1742.67.

Helicterin B (2). $BF_3 \cdot OEt_2$ (0.033 mL, 0.262 mmol, 8.0 equiv) was added in a single portion under rigorously anhydrous conditions to a solution of monomer **50** (0.057 g, 0.033 mmol, 1.0 equiv) in CH_2Cl_2 (0.2 mL) at 0 °C, and the resultant solution was stirred at 0 °C for 30 min. Upon completion, the reaction contents were quenched at 0 °C with saturated aqueous $NaHCO_3$ (10 mL) and extracted with EtOAc (2 × 15 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), and concentrated. The resultant crude yellow solid was purified by flash column chromatography (silica gel, toluene:acetone, 19:1) to afford protected helicterin A (0.038 g, 67% yield) as a white amorphous solid. Next, BBr_3 (1.0 M in CH_2Cl_2, 0.126 mL, 0.126 mmol, 18 equiv) was added in a single portion to a solution of protected helicterin A (0.024 g, 0.007 mmol, 1.0 equiv) in CH_2Cl_2 (0.5 mL) at −78 °C, and the resultant solution was stirred at −78 °C for 45 minutes. Upon completion, the reaction mixture was quenched at −78 °C with saturated aqueous $NaHCO_3$ (1 mL), re-acidified with 1.0 M HCl (1 mL), warmed to 25 °C, poured into water (10 mL), and extracted with EtOAc (2 × 10 mL). The combined organic layers were then washed with brine (10 mL), dried ($MgSO_4$), and concentrated. The crude yellow solid was then triturated with CH_2Cl_2 (3 × 1 mL) to afford helicterin B (**2**) (8.0 mg, 76% yield) as a white solid. The natural product was further purified by preparative TLC (silica gel, CH_2Cl_2:MeOH, 4:1). [Note: some decomposition was observed on silica gel]. **2**: R_f = 0.05 (silica gel, CH_2Cl_2:MeOH, 4:1);

$[\alpha]^{25}_D$ = +6.5° (*c* = 0.15, CH_3OH); IR (film) ν_{max} 3412, 2924, 1730, 1701, 1627, 1521, 1442, 1363, 1284, 1174, 1117, 816 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 7.26 (d, *J* = 15.5 Hz, 1 H), 7.25 (d, *J* = 15.5 Hz, 1 H), 6.88 (d, *J* = 1.0 Hz, 1 H), 6.82 (d, *J* = 2.5 Hz, 1 H), 6.73 (d, *J* = 8.5 Hz, 1 H), 6.71 (d, *J* = 8.5 Hz, 1 H), 6.71 (br s, 2 H), 6.70 (d, *J* = 7.0 Hz, 1 H), 6.695 (d, *J* = 8.0 Hz, 1 H), 6.64-6.58 (m, 6 H), 6.53 (d, *J* = 1.5 Hz, 1 H), 6.39 (dd, *J* = 8.0, 1.0 Hz, 1 H), 6.34 (d, *J* = 5.0 Hz, 1 H), 6.32 (dd, *J* = 7.8, 1.7 Hz, 1 H), 6.29 (d, *J* = 6.0 Hz, 1 H), 5.93 (d, *J* = 15.5 Hz, 1 H), 5.92 (d, *J* = 15.5 Hz, 1 H), 5.28 (dd, *J* = 8.3, 4.3 Hz, 1 H), 5.27 (dd, *J* = 8.8, 4.3 Hz, 1 H), 4.99 (dd, *J* = 7.5, 4.5 Hz, 1 H), 4.97 (dd, *J* = 8.0, 4.0 Hz, 1 H), 3.83 (d, *J* = 2.0 Hz, 1 H), 3.73 (s, 3 H), 3.71 (s, 3 H), 3.58 (br d, *J* = 1.5 Hz, 2 H), 3.54 (s, 3 H), 3.53 (s, 3 H), 3.48 (dd, *J* = 6.8, 1.8 Hz, 1 H), 3.28 (br s, 1 H), 3.24 (s, 3 H), 3.12-3.08 (m, 3 H), 3.03 (dd, *J* = 14.5, 8.5 Hz, 2 H), 2.99 (dd, *J* = 6.2, 3.7 Hz, 2 H), 2.93 (dd, *J* = 14.8, 3.8 Hz, 1 H), 2.89 (dd, *J* = 14.5, 4.5 Hz, 1 H), 2.80 (dd, *J* = 13.8, 8.7 Hz, 1 H), 2.80 (dd, *J* = 14.0, 8.0 Hz, 1 H), 2.75-2.72 (m, 1 H), 2.66 (dt, *J* = 6.5, 2.8 Hz, 1 H); ^{13}C NMR (75 MHz, CD_3OD) δ 175.8, 175.3, 170.3, 170.3, 172.3, 172.2, 169.3, 169.3, 147.1, 147.,1 146.9, 146.9, 146.9, 146.9, 146.8, 146.6, 146.1, 146.1, 146.1, 146.0, 146.0, 145.8, 143.3, 141.7, 139.3, 137.8, 134.4, 134.3, 129.6, 129.6, 129.3, 129.2, 122.7, 122.6, 122.6, 122.6, 121.7, 121.6, 118.2, 118.0, 117.9, 117.9, 117.4, 117.4, 117.4, 117.2, 117.2, 117.2, 117.2, 117.2, 117.2, 117.2, 102.4, 98.8, 75.8, 75.6, 75.5, 75.4, 71.1, 70.9, 53.5, 53.5, 53.5, 53.5, 50.0, 50.0, 48.0, 46.9, 46.9, 45.5, 45.1, 44.8, 43.8, 42.0, 38.6, 38.6, 38.4, 38.4. All spectroscopic data for this synthetic material match

those reported by Tezuka and co-workers for natural helicterin B (**2**); see Table S2 at the end of this section for a direct comparison [1b].

Helisterculin A (4). A solution of **17** (0.190 g, 0.129 mmol, 1.0 equiv) and dienophile **27** (0.441 g, 0.864 mmol, 6.7 equiv) in mesitylene (1.0 mL) was carefully degassed 3 times using the freeze-pump-thaw method, and then sealed under argon in a tube equipped with a magnetic stir bar. The reaction mixture was then stirred at 225 °C (oil bath) for 35 min. After cooling the reaction contents to 25 °C, the reaction mixture was purified directly by flash column chromatography (silica gel, hexanes:EtOAc:CH_2Cl_2, 8:1:1→5:4:1) to provide recovered **27** (1.22 g) alongside the desired Diels-Alder adduct (0.142 g, 44% yield, 78% based on recovered starting material) as a light yellow solid. Next, a portion of this newly formed ketone (0.128 g, 0.103 mmol, 1.0 equiv) was taken up in MeOH:THF (4:1, 5.0 mL) and $NaBH_4$ (6.0 mg, 0.154 mmol, 1.5 equiv) was added in a single portion at 0 °C. The reaction was then stirred at 0 °C for 30 minutes. Upon completion, the reaction mixture was carefully quenched at 0 °C with 1 M aqueous HCl (10 mL), poured into water (10 mL), and extracted with EtOAc (3 × 10 mL). The combined organic layers were then washed with saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL), dried ($MgSO_4$), and concentrated. The resultant crude material was then purified by flash column chromatography (silica gel, hexanes:EtOAc, 3:2) to afford the desired intermediate alcohol (0.111 g, 79% yield) as a yellow solid. Next, this newly formed alcohol was taken up in MeCN (2 mL) and a solution of HCl (4.0 M in dioxane, 0.133 mL) was then added

at 25 °C to obtain a final acid concentration of 0.2 M. The resultant solution was stirred at 25 °C for 2 h. Upon completion, the reaction contents were diluted with EtOAc (10 mL), poured into water (10 mL), and extracted with EtOAc (3 × 10 mL). The combined organic layers were then washed with saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL), dried ($MgSO_4$), and concentrated. The resultant crude material was purified by flash column chromatography (silica gel, hexanes:EtOAc, 3:2) to afford the desired hydroxyketone (0.037 g, 33% yield) as a white amorphous solid. Finally, BBr_3 (1.0 M in CH_2Cl_2, 0.140 mL, 0.140 mmol, 8.0 equiv) was added to a solution this newly formed intermediate (0.021 g, 0.017 mmol, 1.0 equiv) in CH_2Cl_2 (0.5 mL) at -78 °C, and the reaction was stirred at -78 °C for 30 min. Upon completion, the reaction mixture was quenched at -78 °C with water (1 mL), warmed to 25 °C, poured into water (10 mL), and extracted with EtOAc (2 × 10 mL). The combined organic layers were then washed with brine (10 mL), dried ($MgSO_4$), and concentrated. The resultant crude yellow solid was triturated with CH_2Cl_2 (3 × 1 mL) to afford a 1:1 diastereomeric mixture of helisterculin A (**4**, 8.8 mg, 92% yield, 12% overall yield from **17**) as a white solid. [Note: some decomposition was observed on silica gel]. **4**: R_f = 0.50 (silica gel, CH_2Cl_2:MeOH, 4:1); IR (film) ν_{max} 3412, 2918, 1701, 1627, 1521, 1438, 1284, 1165, 1066, 816 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6) δ 7.64 (br s, 4 H), 7.34 (d, J = 15.6 Hz, 1 H), 6.85 (dd, J = 7.0, 1.8 Hz, 1 H), 6.82 (br s, 1 H), 6.79 (d, J = 2.0 Hz, 1 H), 6.74 (d, J = 8.0 Hz, 1 H), 6.70 (d, J = 8.0 Hz, 1 H), 6.66 (dd, J = 8.2, 1.8 Hz, 1 H), 6.61 (dd, J = 8.0, 2.0 Hz, 1 H), 6.12 (d, J = 15.6 Hz, 1 H), 5.18 (dd, J = 8.6, 4.6 Hz, 1 H), 3.82 (d, J = 2.4 Hz, 1

H), 3.78 (d, J = 3.2 Hz, 1 H), 3.68 (s, 3 H), 3.59 (s, 3 H), 3.56 (dd, J = 7.2, 2.0 Hz, 1 H), 3.46 (dd, J = 7.2, 2.4 Hz, 1 H), 3.17 (dd, J = 6.6, 2.6 Hz, 1 H), 3.07 (dd, J = 14.6, 4.6 Hz, 1 H), 3.00 (dd, J = 14.2, 5.4 Hz, 1 H); ^{13}C NMR (75 MHz, acetone-d_6) δ 207.3, 175.1, 171.0, 166.9, 146.2, 146.1, 145.3, 143.5, 141.6, 138.1, 134.1, 129.0, 121.9, 121.1, 118.4, 117.7, 116.7, 116.4, 116.3, 74.5, 70.2, 57.7, 52.7, 52.7, 49.6, 44.2, 43.5, 37.8; HRMS (FAB) calcd for $C_{29}H_{29}O_{12}$ [M+H$^+$] 569.1659, found 569.1656. All spectroscopic data for this synthetic material match those reported by Tezuka and co-workers for natural helisterculin A (**4**); see Table S3 at the end of this section for a direct comparison [1a].

51. Thiocarbonyl diimidazole (0.069 g, 0.389 mmol, 6.0 equiv) and 4-DMAP (0.012 g, 0.097 mmol, 1.5 equiv) were added sequentially to a solution of alcohol **35** (0.030 g, 0.065 mmol, 1.0 equiv) in CH_2Cl_2 (1 mL) at 25 °C, and the reaction mixture was stirred at 40 °C in a sealed tube for 48 h. Upon completion, the reaction contents were poured into saturated aqueous NH_4Cl (15 mL) and extracted with EtOAc (2 × 10 mL). The combined organic layers were then washed with saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL), dried ($MgSO_4$), and concentrated. The resultant thick orange oil was purified by flash column chromatography (silica gel, hexanes:EtOAc, 2:3) to afford compound **51** (0.032 g, 91% yield) as a white amorphous solid. **51**: R_f = 0.17 (silica gel, hexanes:EtOAc, 3:7); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (s, 1 H), 7.39 (d, J = 16.0 Hz, 1 H), 7.18 (s, 1 H), 6.82 (m, 2 H), 6.73 (m, 2 H), 6.61 (d, J = 8.5 Hz, 1 H), 6.07 (d, J = 16.0 Hz, 1 H), 5.21 (d, J = 3.0 Hz, 1 H),

3.94 (dt, J = 15.0, 3.0 Hz, 1 H), 3.81 (s, 3 H), 3.79 (s, 3 H), 3.78 (s, 3 H), 3.71 (s, 3 H), 3.71 (m, 1 H), 3.68 (s, 3 H), 3.42 (s, 3 H), 3.35 (d, J = 7.5 Hz, 1 H), 3.10 (s, 3 H).

52. Oxygen gas passed through a drying tube was bubbled into a solution of **51** (5.0 mg, 0.009 mmol, 1.0 equiv), Et_3B (1.0 M in hexanes, 0.046 mL, 0.046 mmol, 5.0 equiv) and *n*-Bu_3SnH (0.012 mL, 0.046 mmol, 5.0 equiv) in CH_2Cl_2 (1 mL) at 0 °C for 30 min. The resultant solution was then stirred at 0 °C for an additional 30 min. Upon completion, the reaction was quenched with 1 M aqueous HCl (10 mL) and extracted with EtOAc (2 × 10 mL). The combined organic layers were then washed with saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL), dried ($MgSO_4$), and concentrated. The crude was purified by flash column chromatography (silica gel, hexanes:EtOAc, 2:3) to afford compound **52** (3.5 mg, 72% yield) as a white amorphous solid. **52**: R_f = 0.14 (silica gel, hexanes:EtOAc, 3:7); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (s, 1 H), 7.37 (d, J = 15.5 Hz, 1 H), 6.87 (m, 2 H), 6.83 (s, 1 H), 6.80 (s, 1 H), 6.73 (d, J = 7.0 Hz, 1 H), 6.69 (d, J = 8.0 Hz, 1 H), 6.05 (d, J = 15.5 Hz, 1 H), 4.77 (d, J = 3.0 Hz, 1 H), 3.82 (s, 3 H), 3.78 (s, 3 H), 3.77 (m, 2 H), 3.76 (s, 3 H), 3.71 (m, 2 H), 3.67 (s, 3 H), 3.42 (s, 3 H), 3.34 (d, J = 6.0 Hz, 1 H), 3.17 (s, 3 H).

Xanthate Ester 53. NaH (60% dispersion in mineral oil, 0.086 g, 2.16 mmol, 5.0 equiv) and carbon disulfide (1 mL) were added in single portions to a solution of alcohol **35** (0.200 g, 0.432 mmol, 1.0 equiv) in THF (4 mL) at 0 °C, and the resultant mixture was stirred at 0 °C for 30 min. MeI

(1 mL, gross excess) was then added and the reaction contents were stirred at 40 °C for an additional 15 h. Upon completion, the reaction mixture was diluted with ether (20 mL), extracted with saturated aqueous NH_4Cl (20 mL), dried ($MgSO_4$), and concentrated. The crude was purified by flash column chromatography (silica gel, hexanes:EtOAc, 7:3) to afford xanthate ester **53** (0.225 g, 94% yield) as a yellow amorphous solid. **53**: R_f = 0.59 (silica gel, hexanes:EtOAc, 3:7); ^1H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, *J* = 16.0 Hz, 1 H), 7.03 (d, *J* = 2.0 Hz, 1 H), 6.85 (d, *J* = 9.2 Hz, 1 H), 6.78 (d, *J* = 8.4 Hz, 1 H), 6.77 (d, *J* = 6.8 Hz, 1 H), 6.03 (d, *J* = 16.0 Hz, 1 H), 5.48 (d, *J* = 3.2 Hz, 1 H), 3.93 (s, 3 H), 3.84 (s, 3 H), 3.77 (s, 3 H), 3.66 (m, 1 H), 3.64 (s, 3 H), 3.53 (dt, *J* = 5.6, 3.2 Hz, 1 H), 3.43 (s, 3 H), 3.30 (d, *J* = 6.4 Hz, 1 H), 3.13 (s, 3 H), 2.23 (s, 3 H).

Thiol 54. A solution of **53** (0.027 g, 0.049 mmol, 1.0 equiv), AIBN (0.032 g, 0.195 mmol, 4.0 equiv), *n*-Bu_3SnH (0.078 mL, 0.293 mmol, 6.0 equiv) and PhSeSePh (0.061 g, 0.195 mmol, 4.0 equiv) in freshly degassed wet toluene (2 mL) was stirred in a sealed tube at 80 °C for 15 min. Upon completion, the reaction contents were concentrated directly and purified by flash column chromatography (silica gel, hexanes:EtOAc, 4:1) to afford thiol **54** (0.021 g, 84% yield) which was recrystallized from hexanes:Et_2O (1:1). **54**: R_f = 0.59 (silica gel, hexanes:EtOAc, 3:7); ^1H NMR (500 MHz, $CDCl_3$) δ 7.35 (d, *J* = 15.5 Hz, 1 H), 6.98 (d, *J* = 7.0 Hz, 1 H), 6.97 (s, 1 H), 6.77 (d, *J* = 8.0 Hz, 1 H), 6.68 (d, *J* = 7.0 Hz, 1 H), 6.02 (d, *J* = 15.5 Hz, 1 H), 4.32 (dd, *J* = 11.5, 8.5 Hz, 1 H), 4.03 (dd, *J* = 8.0, 7.0 Hz, 1 H), 3.90 (s, 3 H), 3.83 (s, 3 H), 3.81 (m, 1 H), 3.76 (s, 3

H), 3.71 (app s, 1 H), 3.60 (s, 3 H), 3.57 (dd, *J* = 7.0, 1.5 Hz, 1 H), 3.51 (s, 3 H), 3.22 (m, 1 H), 3.20 (s, 3 H), 3.19 (m, 1 H), 1.69 (dd, *J* = 10.5, 9.0 Hz, 1 H).

Heterocycle 55. HCl (4.0 M in dioxane, 0.1 mL) was added to a solution of thiol **54** (4.0 mg, 0.008 mmol, 1.0 equiv) in THF (0.5 mL) at 25 °C to obtain a final acid concentration of 0.7 M. The resultant solution was stirred at 25 °C for 3 h. The reaction contents were concentrated directly and purified by preparative TLC (silica gel, hexanes:EtOAc, 2:3) to afford heterocycle **55** (2.5 mg, 66% yield) as a thick colorless oil. **55**: R_f = 0.69 (silica gel, hexanes:EtOAc, 3:7); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (d, *J* = 15.5 Hz, 1 H), 6.96 (s, 1 H), 6.93 (d, *J* = 8.5 Hz, 1 H), 6.79 (d, *J* = 8.0 Hz, 1 H), 6.78 (d, *J* = 7.5 Hz, 1 H), 6.01 (d, *J* = 15.5 Hz, 1 H), 4.87 (AB, *J* = 29.5, 6.5 Hz, 2 H), 4.04 (d, *J* = 7.5 Hz, 1 H), 4.02 (app s, 1 H), 3.89 (s, 3 H), 3.84 (s, 3 H), 3.83 (m, 1 H), 3.77 (s, 3 H), 3.75 (d, *J* = 3.5 Hz, 1 H), 3.62 (s, 3 H), 3.41 (m, 1 H), 3.38 (s, 3 H), 3.25 (d, *J* = 7.5 Hz, 1 H).

Thiocarbonyl 56. A solution of **53** (0.030 g, 0.054 mmol, 1.0 equiv), AIBN (0.011 g, 0.065 mmol, 1.2 equiv), *n*-Bu_3SnH (0.019 mL, 0.109 mmol, 3.0 equiv) and PhSeSePh (0.022 g, 0.072 mmol, 2.0 equiv) in freshly degassed toluene (1 mL) was stirred in a sealed tube at 80 °C for 3 h. Upon completion, the reaction contents were concentrated directly and purified by flash column chromatography (silica gel, hexanes:EtOAc, 4:1) to afford recovered **53** (0.027 g) alongside **56** (2.0 mg, 7% yield, 72% yield based on recovered starting material) as a colorless solid. **56**:

R_f = 0.49 (silica gel, hexanes:EtOAc, 3:7); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (s, 1 H), 7.35 (d, *J* = 16.0 Hz, 1 H), 6.98 (d, *J* = 2.0 Hz, 1 H), 6.93 (d, *J* = 8.5 Hz, 1 H), 6.78 (d, *J* = 8.0 Hz, 1 H), 6.70 (d, *J* = 6.5 Hz, 1 H), 6.03 (d, *J* = 16.0 Hz, 1 H), 4.77 (app s, 1 H), 3.89 (s, 3 H), 3.85 (s, 3 H), 3.84 (m, 1 H), 3.78 (s, 3 H), 3.76 (m, 1 H), 3.62 (s, 3 H), 3.60 (d, *J* = 6.5 Hz, 1 H), 3.48 (s, 3 H), 3.30 (d, *J* = 6.5 Hz, 1 H), 3.12 (s, 3 H).

Boronate 57. Oxygen gas passed through a drying tube was bubbled into a solution of **53** (8.0 mg, 0.014 mmol, 1.0 equiv) and Et_3B (1.0 M in hexanes, 0.087 mL, 0.087 mmol, 6.0 equiv) in CH_2Cl_2 (1 mL) at 0 °C for 30 min. The resultant solution was then stirred at 25 °C for an additional 48 h under an O_2 atmosphere. Upon completion, the reaction contents were concentrated directly and purified by preparative TLC (silica gel, hexanes:EtOAc, 2:3) to afford recovered **53** (5.0 mg) alongside boronate **57** (2.0 mg, 29% yield, 75% yield based on recovered starting material) as a colorless solid. **57**: R_f = 0.58 (silica gel, hexanes:EtOAc, 3:7); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (d, *J* = 15.5 Hz, 1 H), 7.00 (d, *J* = 2.0 Hz, 1 H), 6.91 (d, *J* = 8.0 Hz, 1 H), 6.78 (d, *J* = 8.5 Hz, 1 H), 6.69 (d, *J* = 7.0 Hz, 1 H), 6.01 (d, *J* = 15.5 Hz, 1 H), 4.45 (d, *J* = 3.0 Hz, 1 H), 3.91 (app s, 1 H), 3.86 (m, 2 H), 3.85 (s, 3 H), 3.77 (s, 3 H), 3.72 (app s, 1 H), 3.62 (s, 3 H), 3.60 (dd, *J* = 7.5, 2.0 Hz, 1 H), 3.46 (s, 3 H), 3.41 (m, 1 H), 3.25 (d, *J* = 7.0 Hz, 1 H), 3.14 (s, 3 H), 1.05 (app t, *J* = 7.0 Hz, 3 H); LRMS (FAB) calcd for $C_{26}H_{36}BO_9$ [M+H$^+$] 503.2, found 503.7.

Phosphinate 58. Diphenylphosphinic chloride (0.020 mL, 0.108 mmol, 5.0 equiv), Et_3N (0.030 mL, 0.216 mmol, 10 equiv) and 4-DMAP (catalytic) were sequentially added to a solution of alcohol **35** (0.010 g, 0.022 mmol, 1.0 equiv) in 1,2-dichloroethane:THF (1:1, 1 mL) at 25 °C, and the resultant reaction mixture was stirred at 60 °C in a sealed tube for 48 h. Upon completion, the reaction contents were quenched with 1 M aqueous HCl (10 mL) and extracted with EtOAc (2 × 10 mL). The combined organic layers were then washed with saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL), dried ($MgSO_4$), and concentrated. The crude was purified by flash column chromatography (silica gel, hexanes:EtOAc, 3:7) to afford phosphinate **58** (0.013 g, 89% yield) as a white amorphous solid. **58**: R_f = 0.22 (silica gel, hexanes:EtOAc, 3:7); ^1H NMR (300 MHz, $CDCl_3$) δ 7.63 (m, 2 H), 7.49-7.32 (m, 5 H), 7.29 (d, *J* = 15.6 Hz, 1 H), 7.28-7.18 (m, 2 H), 7.03-6.97 (m, 4 H), 6.60 (d, *J* = 7.5 Hz, 1 H), 6.57 (d, *J* = 6.9 Hz, 1 H), 5.96 (d, *J* = 15.6 Hz, 1 H), 4.57 (dd, *J* = 12.0, 3.0 Hz, 1 H), 3.78 (m, 1 H), 3.77 (s, 3 H), 3.75 (s, 3 H), 3.74 (s, 3 H), 3.69 (app s, 1 H), 3.59 (s, 3 H), 3.56 (dd, *J* = 7.2, 2.1 Hz, 1 H), 3.43 (s, 3 H), 3.26 (d, *J* = 6.9 Hz, 1 H), 3.11 (s, 3 H), 2.96 (dt, *J* = 6.9, 2.4 Hz, 1 H); LRMS (FAB) calcd for $C_{36}H_{40}O_{10}P$ $[M+H^+]$ 663.2, found 663.0.

Mesylate 59. Et_3N (0.023 mL, 0.162 mmol, 15 equiv) and MsCl (0.008 mL, 0.108 mmol, 10 equiv) were added sequentially to a solution of alcohol **35** (5.0 mg, 0.011 mmol, 1.0 equiv) in THF (0.5 mL) at 0 °C, and the mixture was stirred at 25 °C for 6 h. The reaction contents were then concentrated directly and purified by preparative TLC (silica gel,

hexanes:EtOAc, 2:3) to afford mesylate **59** (1.2 mg, 20% yield) as a white amorphous solid. **59**: R_f = 0.41 (silica gel, hexanes:EtOAc, 2:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, J = 16.0 Hz, 1 H), 7.08 (d, J = 2.0 Hz, 1 H), 6.96 (d, J = 8.0 Hz, 1 H), 6.81 (d, J = 8.4 Hz, 1 H), 6.64 (d, J = 7.6 Hz, 1 H), 6.02 (d, J = 16.0 Hz, 1 H), 4.56 (d, J = 3.2 Hz, 1 H), 3.92 (s, 3 H), 3.86 (s, 3 H), 3.78 (s, 3 H), 3.76 (app s, 1 H), 3.62 (s, 3 H), 3.58 (dd, J = 7.4, 2.0 Hz, 1 H), 3.51 (s, 3 H), 3.48-3.30 (m, 4 H), 3.21 (s, 3 H), 2.28 (s, 3 H).

Triflates 61 and 62. A solution of alcohol **35** (0.050 g, 0.108 mmol, 1.0 equiv) in pyridine (0.3 mL) was added dropwise over 10 min to a solution of Tf_2O (0.073 mL, 0.432 mmol, 4.0 equiv) in pyridine (0.7 mL) at 0 °C. The resultant reaction mixture was stirred at 25 °C for 1 h and then at 35 °C for another 1 h. Upon completion, the reaction contents were diluted with EtOAc (20 mL) and washed repeatedly with 0.3 M aqueous HCl (10 mL) until the aqueous layer remained acidic. The organic layer was then washed with brine (10 mL), dried ($MgSO_4$), and concentrated. The resultant crude material was purified by flash column chromatography (silica gel, hexanes:EtOAc, 3:2) to afford recovered **35** (0.036 g) alongside **61** (8.0 mg, 13% yield, 22% yield based on recovered starting material) as a colorless solid and **62** (4.0 mg, 7% yield, 46% yield based on recovered starting material) as a colorless solid. **61**: R_f = 0.58 (silica gel, hexanes:EtOAc, 2:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, J = 16.0 Hz, 1 H), 7.12 (d, J = 8.4 Hz, 1 H), 7.10 (d, J = 2.0 Hz, 1 H), 6.98 (dd, J = 8.4, 1.6 Hz, 1 H), 6.68 (d, J = 7.2 Hz, 1 H), 6.00 (d, J = 16.0 Hz, 1 H),

3.92 (s, 3 H), 3.76 (s, 3 H), 3.72 (d, J = 1.6 Hz, 1 H), 3.64 (s, 3 H), 3.61 (dd, J = 6.8, 2.8 Hz, 1 H), 3.56 (s, 3 H), 3.43 (d, J = 5.6 Hz, 1 H), 3.34 (dd, J = 6.4, 2.0 Hz, 1 H), 3.29 (dt, J = 6.8, 2.8 Hz, 1 H), 3.12 (s, 3 H), 2.38 (d, J = 7.2 Hz, 1 H); LRMS (FAB) calcd for $C_{24}H_{27}F_3O_{11}S$ [M^+] 580.1, found 580.4.

62: R_f = 0.64 (silica gel, hexanes:EtOAc, 2:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, J = 16.0 Hz, 1 H), 6.74 (d, J = 8.4 Hz, 1 H), 6.73 (s, 1 H), 6.63 (m, 2 H), 6.18 (d, J = 16.0 Hz, 1 H), 5.02 (d, J = 3.6 Hz, 1 H), 3.94 (app s, 1 H), 3.85 (s, 3 H), 3.83 (s, 3 H), 3.82 (s, 3 H), 3.70 (s, 3 H), 3.61 (d, J = 8.0 Hz, 1 H), 3.32 (s, 3 H), 3.30 (s, 3 H), 3.18 (m, 1 H), 2.36 (dd, J = 8.4, 1.6 Hz, 1 H).

63. A solution of *i*-Bu_2AlO*i*-Pr (0.93 M in toluene) was prepared by adding *i*-PrOH (0.38 mL, 5.0 mmol, 1.0 equiv) dropwise to a commercial solution of *i*-Bu_2AlH (1.0 M in toluene, 5.0 mL, 5.0 mmol, 1.0 equiv) at 25 °C, and the resultant solution was stirred at 25 °C for 30 min until the evolution of H_2 gas was no longer observed. Next, freshly prepared *i*-Bu_2AlO*i*-Pr (0.93 M in toluene, 0.028 mL, 0.026 mmol, 1.1 equiv) was added to a solution of ketone **21** (0.011 g, 0.024 mmol, 1.0 equiv) in toluene (0.5 mL) at 25 °C, and the reaction contents were stirred at 60 °C in a sealed tube for 48 h. Upon completion, the reaction mixture was concentrated directly and purified by preparative TLC (silica gel, hexanes:EtOAc, 3:2) to afford recovered **21** (7.0 mg) alongside **63** (2.0 mg, 17% yield, 46% yield based on recovered starting material) as a thick colorless oil. **63**: R_f = 0.40 (silica gel, hexanes:EtOAc, 3:2); ^{1}H NMR (500

MHz, $CDCl_3$) δ 7.36 (d, *J* = 15.5 Hz, 1 H), 6.83 (s, 1 H), 6.80 (d, *J* = 8.0 Hz, 1 H), 6.63 (d, *J* = 5.0 Hz, 1 H), 6.10 (d, *J* = 15.5 Hz, 1 H), 3.97 (dd, *J* = 7.0, 3.5 Hz, 1 H), 3.94 (app s, 1 H), 3.86 (s, 3 H), 3.85 (s, 3 H), 3.84 (m, 1 H), 3.68 (s, 3 H), 3.59 (dd, *J* = 6.5, 2.0 Hz, 1 H), 3.49 (s, 3 H), 3.45 (dd, *J* = 7.0, 2.0 Hz, 1 H), 3.35 (s, 3 H), 3.30 (dd, *J* = 7.0, 2.0 Hz, 1 H), 2.00 (app t, *J* = 6.5 Hz, 1 H), 0.98 (s, 3 H), 0.97 (s, 3 H).

Analogues **64-80** were prepared according to the methods described hereinabove.

64. ^1H NMR ($CDCl_3$, 400 MHz): 8.06 (s, 1 H), 7.89 (s, 1 H), 7.38 (d, *J* = 15.6 Hz, 1 H), 6.82 (m, 1 H), 6.73 (m, 2 H), 6.62 (m, 1 H), 6.07 (d, *J* = 15.6 Hz, 1 H), 5.29 (d, *J* = 3.2 Hz, 1 H), 3.93 (m, 1 H), 3.81 (m, 1 H), 3.79 (s, 3 H), 3.78 (s, 3 H), 3.72 (s, 3 H), 3.69 (m, 1 H), 3.68 (s, 3 H), 3.47 (s, 3 H), 3.39 (m, 1 H), 3.12 (s, 3 H).

65. ^1H NMR ($CDCl_3$, 300 MHz): 8.38 (s, 1 H), 7.68 (s, 1 H), 7.03 (m, 3 H), 5.74 (d, *J* = 6.6 Hz, 1 H), 5.23 (d, *J* = 3.3 Hz, 1 H), 3.67 (s, 3 H), 3.63 (s, 3 H), 3.29 (m, 1 H), 3.05 (s, 3 H), 2.98 (m, 1 H), 2.81 (s, 1 H), 2.49 (m, 4 H), 2.13 (m, 1 H), 1.62 (m, 1 H).

66. ^1H NMR ($CDCl_3$, 300 MHz): 8.30 (s, 1 H), 7.62 (s, 1 H), 7.03 (s, 1 H), 5.68 (d, *J* = 5.7 Hz, 1 H), 5.46 (d, *J* = 2.7 Hz, 1 H), 3.68 (s, 3 H), 3.63 (s, 3 H), 3.30 (m, 1 H), 3.25 (s, 3 H), 3.16 (s, 3 H), 2.82 (m, 2 H), 2.53 (m, 4 H), 2.09 (m, 1 H), 1.51 (m, 1 H).

67. ^{1}H NMR ($CDCl_3$, 400 MHz): 8.36 (s, 1 H), 7.65 (s, 1 H), 7.06 (s, 1 H), 5.91 (d, J = 6.4 Hz, 1 H), 5.23 (d, J = 3.2 Hz, 1 H), 3.70 (s, 3 H), 3.29 (m, 1 H), 3.28 (s, 3 H), 3.05 (s, 3 H), 3.04 (s, 1 H), 2.90 (app s, 1 H), 2.54 (s, 1 H), 2.31 (m, 1 H), 1.52 (m, 1 H).

68. ^{1}H NMR ($CDCl_3$, 400 MHz): 8.29 (s, 1 H), 7.60 (s, 1 H), 7.03 (s, 1 H), 5.84 (d, J = 6.0 Hz, 1 H), 5.39 (d, J = 3.2 Hz, 1 H), 3.71 (s, 3 H), 3.26 (m, 1 H), 3.25 (s, 3 H), 3.19 (s, 3 H), 2.92 (m, 2 H), 2.61 (s, 4 H), 2.31 (m, 1 H), 1.42 (m, 1 H).

69. ^{1}H NMR ($CDCl_3$, 400 MHz): 7.39 (d, J = 15.6 Hz, 1 H), 7.15 (m, 2 H), 6.90 (s, 1 H), 6.72-6.67 (m, 5 H), 6.08 (d, J = 15.6 Hz, 1 H), 5.39 (br s, 1 H), 5.31 (d, J = 3.6 Hz, 1 H), 3.91 (s, 3 H), 3.89 (m, 1 H), 3.71 (app s, 6 H), 3.70 (m, 1H), 3.68 (m, 1 H), 3.67 (s, 3 H), 3.52 (s, 3 H), 3.38 (s, 3 H), 3.20 (app s, 3 H), 3.18 (app s, 1 H).

70. ^{1}H NMR ($CDCl_3$, 400 MHz): 7.37 (d, J = 15.6 Hz, 1 H), 6.98 (m, 1 H), 6.86 (d, J = 7.6 Hz, 1 H), 6.83 (d, J = 2.0 Hz, 1 H), 6.73 (d, J = 6.8 Hz, 1 H), 6.61 (d, J = 8.4 Hz, 1 H), 6.60 (m, 1 H), 6.03 (d, J = 15.6 Hz, 1 H), 6.02 (m, 1 H), 4.78 (d, J = 3.2 Hz, 1 H), 3.81 (s, 3 H), 3.79 (m, 1 H), 3.78 (s, 3 H), 3.74 (s, 3 H), 3.71 (m, 1 H), 3.69 (s, 3 H), 3.62 (m, 1 H), 3.41 (s, 3 H), 3.32 (d, J = 6.4 Hz, 1 H), 3.17 (s, 3 H).

71. ^{1}H NMR ($CDCl_3$, 400 MHz): 7.38 (d, J = 15.6 Hz, 1 H), 6.92 (m, 2 H), 6.80 (d, J = 8.4 Hz, 1 H), 6.73 (m, 2 H), 6.60 (d, J = 8.0 Hz, 1 H), 6.04 (d, J = 15.6 Hz, 1 H), 6.01 (app s, 1 H), 5.31 (d, J = 2.8 Hz, 1 H), 3.91 (m, 1 H),

3.78 (s, 3 H), 3.77 (s, 3 H), 3.72 (m, 1 H), 3.69 (s, 3 H), 3.68 (m, 1 H), 3.67 (s, 3 H), 3.39 (s, 3 H), 3.34 (m, 1 H), 3.13 (m, 1 H), 3.11 (s, 3 H).

72. ^{1}H NMR ($CDCl_3$, 400 MHz): 7.36 (d, J = 15.6 Hz, 1 H), 6.89 (d, J = 1.6 Hz, 1 H), 6.73 (m, 3 H), 5.98 (d, J = 15.6 Hz, 1 H), 5.32 (d, J = 2.8 Hz, 1 H), 4.11 (m, 1 H), 3.88 (s, 3 H), 3.87 (m, 1 H), 3.84 (s, 3 H), 3.76 (s, 3 H), 3.70 (s, 1 H), 3.67 (s, 3 H), 3.58 (dd, J = 7.2, 1.6 Hz, 1 H), 3.47 (m, 1 H), 3.33 (s, 3 H), 3.31 (m, 2 H), 3.09 (s, 3 H), 2.57 (m, 1 H), 1.40-1.52 (m, 3H), 1.19-1.10 (m, 2 H).

73. ^{1}H NMR ($CDCl_3$, 400 MHz): 8.33 (s, 1 H), 7.64 (s, 1 H), 7.05 (s, 1 H), 5.71 (d, J = 6.4 Hz, 1 H), 5.51 (d, J = 2.8 Hz, 1 H), 5.21 (d, J = 3.2 Hz, 1 H), 4.99 (sept, J = 6.4 Hz, 1 H), 3.72 (s, 3 H), 3.31 (m, 1 H), 3.30 (s, 3 H), 2.89 (s, 1 H), 2.79 (dd, J = 7.6, 1.6 Hz, 1 H), 2.56 (s, 4 H), 2.11 (m, 1 H), 1.52 (m, 1 H), 1.28 (m, 6 H).

74. ^{1}H NMR ($CDCl_3$, 400 MHz): 7.76 (s, 2 H), 7.41 (d, J = 16.0 Hz, 2 H), 7.20 (s, 2 H), 6.87-6.76 (m, 12 H), 6.65 (d, J = 8.4 Hz, 2 H), 6.11 (d, J = 16.0 Hz, 1 H), 6.10 (d, J = 16.0 Hz, 1 H), 5.35 (dd, J = 7.6, 5.2 Hz, 2 H), 5.24 (d, J = 3.6 Hz, 2 H), 3.97-3.94 (m, 2 H), 3.91 (s, 3 H), 3.91 (s, 3 H), 3.90 (s, 3 H), 3.89 (s, 3 H), 3.86-3.81 (m, 2 H), 3.82 (s, 6 H), 3.78 (s, 3 H), 3.76 (s, 3 H), 3.74 (s, 6 H), 3.69 (s, 3 H), 3.64 (s, 3 H), 3.59 (t, J = 2.8 Hz, 2 H), 3.46 (s, 6 H), 3.40-3.35 (m, 2 H), 3.25-3.15 (m, 4 H), 3.12 (s, 6 H).

75. ^{1}H NMR ($CDCl_3$, 400 MHz): 7.76 (s, 1 H), 7.41 (d, J = 15.6 Hz, 1 H), 7.20 (s, 1 H), 6.86 (br s, 2 H), 6.76 (br s,

2 H), 6.64 (d, J = 8.4 Hz, 1 H), 6.09 (d, J = 16.0 Hz, 1 H), 5.93-5.85 (m, 1 H), 5.32 (d, J = 1.6 Hz, 1 H), 5.29-5.23 (m, 2 H), 4.59 (dd, J = 6.0, 4.8 Hz, 2 H), 3.98-3.66 (m, 1 H), 3.85 (s, 1 H), 3.81 (s, 6 H), 3.74 (s, 3 H), 3.74-3.70 (m, 1 H), 3.45 (s, 3 H), 3.39 (d, J = 6.4 Hz, 1 H), 3.13 (s, 3 H).

76. ^{1}H NMR ($CDCl_3$, 400 MHz): 8.32 (s, 1 H), 7.62 (s, 1 H), 7.05 (s, 1 H), 5.89 (m, 1 H), 5.71 (m, 1 H), 5.50 (m, 1 H), 5.31 (m, 1 H), 5.28 (m, 2 H), 4.59 (m, 2 H), 3.71 (m, 4 H), 3.38 (m, 1 H), 3.30 (m, 4 H), 3.21 (s, 3 H), 3.29 (m, 2 H), 2.56 (m, 4 H), 2.50 (app s, 1 H), 2.15 (m, 1 H), 1.52 (m, 1 H).

77. ^{1}H NMR ($CDCl_3$, 400 MHz): 8.41 (s, 1 H), 7.71 (s, 1 H), 7.07 (s, 1 H), 5.77 (d, J = 2.8 Hz, 1 H), 5.27 (d, J = 2.6 Hz, 1 H), 4.08 (m, 2 H), 3.70 (s, 3 H), 3.32 (m, 1 H), 3.30 (s, 1 H), 3.08 (s, 3 H), 2.91 (m, 1 H), 2.82 (s, 1 H), 2.52 (m, 1 H), 2.51 (s, 4 H), 2.13 (m, 1 H), 1.71-1.52 (m, 5 H), 1.32 (m, 3 H).

78. ^{1}H NMR ($CDCl_3$, 400 MHz): 7.72 (s, 1 H), 7.69 (s, 1 H), 7.38 (d, J = 15.6 Hz, 1 H), 7.37 (d, J = 15.6 Hz, 1 H), 7.15 (s, 2 H), 6.92-6.55 (m, 20 H), 6.23 (d, J = 16.0 Hz, 1 H), 5.92 (d, J = 15.6 Hz, 1 H), 5.36-5.32 (m, 2 H), 5.24-5.20 (m, 3 H), 5.15 (dd, J = 8.4, 4.4 Hz, 1 H), 4.01-3.95 (m, 2 H), 3.95-3.55 (m, 4 H, buried signals), 3.89 (s, 9 H), 3.88 (s, 3 H), 3.86 (s, 6 H), 3.85 (s, 3 H), 3.82 (s, 3 H), 3.81 (s, 3 H), 3.77 (s, 3 H), 3.75 (s, 6 H), 3.70 (s, 3 H), 3.67 (s, 3 H), 3.43 (s, 3 H), 3.33 (s, 3 H), 3.20-3.13 (m, 4 H), 3.12 (s, 3 H), 3.08 (s, 3 H), 3.03-2.93 (m, 4 H).

79. ^{1}H NMR ($CDCl_3$, 400 MHz, 1:1 mix of diastereomers): $CDCl_3$ (400 MHz): 8.34 (s, 1 H), 7.62 (s, 1 H), 7.08 (s, 1 H), 5.76 (d, *J* = 8.4 Hz, 1 H), 5.42 (d, *J* = 3.6 Hz, 1 H), 3.71 (s, 9 H), 3.52 (m, 4 H), 3.31 (s, 3 H), 3.22 (s, 3 H), 3.20 (m, 1 H), 2.91 (m, 2 H), 2.61 (s, 4 H), 2.07 (m, 1 H), 1.50 (m, 1 H).

80. ^{1}H NMR ($CDCl_3$, 400 MHz, 1:1 mix of diastereomers): $CDCl_3$ (400 MHz): 8.41 (s, 1 H), 8.32 (s, 1 H), 7.72 (s, 1 H), 7.63 (s, 1 H), 7.09 (s, 1 H), 7.03 (s, 1 H), 6.48 (app t, *J* = 8.0 Hz, 1 H), 6.41 (app t, *J* = 7.6 Hz, 1 H), 6.18 (app t, *J* = 7.6 Hz, 1 H), 6.12 (app t, *J* = 8.0 Hz, 1 H), 5.51 (d, *J* = 3.6 Hz, 1 H), 5.31 (d, *J* = 3.6 Hz, 1 H), 3.69 (s, 3 H), 3.68 (s, 3 H), 3.46 (m, 2 H), 3.31 (s, 3 H), 3.28 (s, 3 H), 3.26 (s, 3 H), 3.13 (s, 3 H), 3.05 (m, 2 H), 2.98 (m, 1 H), 2.91 (m, 1 H), 2.20 (m, 2 H), 1.72 (m, 1 H), 1.63 (m, 1 H).

Table S1. NMR Spectral Data Comparison of Natural and Synthetic Helisorin (3); Coupling Constants (*J*) in Hz.

^1H		^{13}C	
Natural helisorin	Synthetic helisorin	Natural helisorin	Synthetic helisorin
7.88 (s, 2 H)	7.71 (br s)	204.6	204.7
7.81 (s)		170.8	170.9
7.68 (s)		170.5	170.7
7.61 (s, 2 H)		170.2	170.3
7.24 (d, J = 15.5)	7.25 (d, J = 16.0)	166.7	166.7
6.78 (s)	6.80 (s)	147.2	147.3
6.74 (s)	6.74 (br s)	145.9	145.9
6.735 (d, J = 2.0)		145.8	145.9
6.73 (d, J = 8.0)	6.72 (d, J = 9.0)	145.8	145.8
6.727 (d, J = 2.0)	6.72 (d, J = 3.5)	145.0	145.1
6.70 (dd, J = 6.5, 2.0)	6.71 (br s)	145.0	145.0
6.68 (d, J = 8.0)	6.68 (d, J = 8.0)	142.8	142.8
6.56 (dd, J = 8.0, 2.0)	6.57 (dd, J = 8.0, 2.0)	140.6	140.7
6.55 (dd, J = 8.0, 2.0)	6.56 (dd, J = 8.0, 2.0)	137.9	138.0
6.03 (d, J = 15.5)	6.04 (d, J = 16.0)	137.4	137.6
5.15 (dd, J = 7.5, 5.0)	5.15 (dd, J = 9.2, 6.8)	134.6	134.8
4.96 (dd, J = 9.5, 4.0)	4.97 (dd, J = 9.2, 4.3)	128.6	128.7
3.97 (dd, J = 3.5, 1.5)	3.97 (br s)	128.6	128.7
3.66 (s, 3 H)	3.62 (s, 3 H)	121.8	121.9
3.62 (dd, J = 6.5, 5.0)	3.64 - 3.59 (m)	121.8	121.8
3.58 (s, 3 H)	3.55 (s, 3 H)	118.2	118.2
3.54 (d, J = 5.0)	3.51 (d, J = 5.0)	117.3	117.4
3.04 (dd, J = 14.0, 5.0)	3.05 (dd, J = 13.7, 4.3)	117.3	117.4
3.02 (dd, J = 3.5, 1.0)	3.01 (br s)	116.3	116.3
2.98 (dd, J = 14.0, 7.5)	2.98 (dd, J = 14.7, 6.7)	116.2	116.2
2.98 (dd, J = 14.0, 4.0)	2.97 (dd, J = 14.5, 4.5)	111.3	111.4
2.82 (dd, J = 14.0, 9.5)	2.82 (dd, J = 14.0, 9.5)	111.0	111.0
		82.0	82.0
		75.0	75.0
		74.3	74.3
		57.4	57.5
		52.8	53.0
		52.8	52.9
		52.7	52.7
		52.7	52.5
		43.7	43.7
		37.7	37.6
		37.6	37.6

Table S2. NMR Spectral Data Comparison of Natural and Synthetic Helicterin B (2); Coupling Constants (*J*) in Hz.

^{1}H		^{13}C	
Natural helicterin B	**Synthetic helicterin B**	**Natural helicterin B**	**Synthetic helicterin B**
7.26 (d, *J* = 15.5)	7.26 (d, *J* = 15.5)	175.8	175.8
7.25 (d, *J* = 15.5)	7.25 (d, *J* = 15.5)	175.3	175.3
6.89 (d, *J* = 2.0)	6.88 (d, *J* = 1.0)	173.0	173.0
6.83 (d, *J* = 2.0)	6.82 (d, *J* = 2.5)	173.0	
6.74 (d, *J* = 8.0)	6.73 (d, *J* = 8.5)	172.2	172.3
6.71 (d, *J* = 8.0)	6.71 (d, *J* = 8.5)	172.2	172.2
6.71 (d, *J* = 2.0)	6.71 (br s)	169.3	169.3
6.71 (d, *J* = 2.0)		169.3	
6.700 (d, *J* = 8.0)	6.70 (d, *J* = 7.0)	147.0	147.1
6.695 (d, *J* = 8.0)	6.695 (d, *J* = 8.0)	147.0	
6.69 (dd, *J* = 8.0, 2.0)	6.71 - 6.67 (m)	146.9	146.9
6.63 (dd, *J* = 8.0, 2.0)	6.64 - 6.58 (m)	146.9	
6.62 (d, *J* = 8.0)		146.9	
6.61 (dd, *J* = 8.0, 2.0)		146.9	
6.61 (dd, *J* = 8.0, 2.0)		146.7	146.8
6.60 (d, *J* = 8.0)		146.5	146.6
6.59 (d, *J* = 2.0)		146.0	146.1
6.54 (d, *J* = 2.0)	6.53 (d, *J* = 1.5)	146.0	
6.39 (dd, *J* = 8.0, 2.0)	6.39 (dd, *J* = 8.0, 1.0)	146.0	
6.34 (d, *J* = 6.5)	6.34 (d, *J* = 5.0)	146.0	146.0
6.33 (dd, *J* = 8.0, 2.0)	6.32 (dd, *J* = 7.8, 1.7)	146.0	
6.29 (d, *J* = 6.5)	6.29 (d, *J* = 6.0)	145.7	145.8
5.94 (d, *J* = 15.5)	5.93 (d, *J* = 15.5)	143.2	143.3
5.93 (d, *J* = 15.5)	5.92 (d, *J* = 15.5)	141.7	141.7
5.28 (dd, *J* = 8.5, 6.0)	5.28 (dd, *J* = 8.3, 4.3)	139.3	139.3
5.27 (dd, *J* = 8.5, 5.0)	5.27 (dd, *J* = 8.8, 4.3)	137.8	137.8
4.99 (dd, *J* = 8.5, 5.0)	4.99 (dd, *J* = 7.5, 4.5)	134.4	134.4
4.97 (dd, *J* = 8.5, 5.0)	4.97 (dd, *J* = 8.0, 4.0)	134.3	134.3
3.83 (d, *J* = 3.0)	3.83 (d, *J* = 2.0)	129.6	129.6
3.72 (s, 3 H)	3.73 (s, 3 H)	129.6	
3.71 (s, 3 H)	3.71 (s, 3 H)	129.3	129.3
3.59 (br s)	3.58 (br d, *J* = 1.5)	129.2	129.2
3.58 (d, *J* = 3.0)		122.7	122.7
3.54 (s, 3 H)	3.54 (s, 3 H)	122.6	122.6
3.53 (s, 3 H)	3.53 (s, 3 H)	122.6	
3.49 (dd, *J* = 6.5, 2.0)	3.48 (dd, *J* = 6.8, 1.8)	122.6	
3.28 (br s)	3.28 (br s)	121.7	121.7
3.24 (s, 3 H)	3.24 (s, 3 H)	121.7	121.6
3.11 (dd, *J* = 6.5, 2.0)	3.12 - 3.08 (m)	118.2	118.2
3.11 (dd, *J* = 14.5, 5.0)		118.0	118.0
3.09 (dd, *J* = 14.5, 5.0)		117.9	117.9

3.03 (dd, J = 14.5, 8.5)	3.03 (dd, J = 14.5, 8.5)	117.9	117.9
3.03 (dd, J = 14.5, 8.5)		117.4	117.4
2.995 (dd, J = 6.5, 3.0)	2.99 (dd, J = 6.2, 3.7)	117.3	
2.99 (dd, J = 6.5, 3.0)		117.3	
2.93 (dd, J = 14.5, 5.0)	2.93 (dd, J = 14.8, 3.8)	117.2	117.2
2.89 (dd, J = 14.5, 5.0)	2.89 (dd, J = 14.5, 4.5)	117.2	
2.81 (dd, J = 14.5, 8.5)	2.80 (dd, J = 13.8, 8.7)	117.2	
2.80 (dd, J = 14.5, 8.5)	2.80 (dd, J = 14.0, 8.0)	117.2	
2.74 (dt, J = 6.5, 3.0)	2.75 - 2.72 (m)	117.2	
2.66 (dt, J = 6.5, 3.0)	2.66 (dt, J = 6.5, 2.8)	117.2	
		117.1	
		102.3	102.4
		98.8	98.8
		75.7	75.8
		75.6	75.6
		75.4	75.5
		75.3	75.4
		71.0	71.1
		70.8	70.9
		53.6	53.5
		53.6	
		53.5	53.5
		53.5	
		50.0	50.0
		50.0	
		47.9	48.0
		46.9	46.9
		46.8	
		45.5	45.5
		45.1	45.1
		44.8	44.8
		43.8	43.8
		42.0	42.0
		38.5	38.6
		38.5	
		38.4	38.4
		38.4	

Table S3. NMR Spectral Data Comparison of Natural and Synthetic Helisterculin A (4); Coupling Constants (*J*) in Hz.

^{1}H		^{13}C	
Natural helisterculin A	Synthetic helisterculin A	Natural helisterculin A	Synthetic helisterculin A
7.75 (br s, 4H)	7.64 (br s, 4H)	207.3	207.3
7.34 (d, *J* = 15.5)	7.34 (d, *J* = 15.6)	175.1	175.1
6.83 (dd, *J* = 6.5, 2.0)	6.85 (dd, *J* = 7.0, 1.8)	171.0	171.0
6.81 (d, *J* = 2.0)	6.82 (br s)	166.9	166.9
6.78 (d, *J* = 2.0)	6.79 (d, *J* = 2.0)	146.2	146.2
6.74 (d, *J* = 8.0)	6.74 (d, *J* = 8.0)	146.1	146.1
6.71 (d, *J* = 8.0)	6.70 (d, *J* = 8.0)	145.3	145.3
6.66 (dd, *J* = 8.0, 2.0)	6.66 (dd, *J* = 8.2, 1.8)	145.3	
6.61 (dd, *J* = 8.0, 2.0)	6.61 (dd, *J* = 8.0, 2.0)	143.5	143.5
6.12 (d, *J* = 15.5)	6.12 (d, *J* = 15.6)	141.5	141.6
5.18 (dd, *J* = 8.5, 4.5)	5.18 (dd, *J* = 8.6, 4.6)	138.1	138.1
3.82 (dd, *J* = 3.0, 2.0)	3.82 (br d, *J* = 2.4)	134.1	134.1
3.78 (d, *J* = 3.0)	3.78 (d, *J* = 3.2)	129.0	129.0
3.69 (s, 3 H)	3.68 (s, 3 H)	121.9	121.9
3.59 (s, 3 H)	3.59 (s, 3 H)	121.1	121.1
3.56 (dd, *J* = 7.5, 3.0)	3.56 (dd, *J* = 7.2, 2.0)	118.4	118.4
3.47 (dd, *J* = 7.5, 2.5)	3.46 (dd, *J* = 7.2, 2.4)	117.7	117.7
3.18 (dd, *J* = 6.5, 2.5)	3.18 (dd, *J* = 6.6, 2.6)	116.7	116.7
3.08 (*J* = 14.5, 4.5)	3.07 (*J* = 14.6, 4.6)	116.4	116.4
2.99 (*J* = 14.5, 4.5)	3.00 (*J* = 14.2, 5.4)	116.3	116.3
		74.5	74.5
		70.2	70.2
		57.5	57.7
		52.8	52.7
		52.8	52.7
		49.6	49.6
		44.2	44.2
		43.5	43.5
		37.9	37.8

Results and Discussion

In efforts to temper the latter of the reactivity issues desribed in the background of the invention by using an *ortho*-quinone monoketal as a surrogate for the needed diene as provided upon oxidation of model compound **14** by $PhI(OAc)_2$ in MeOH, the resultant molecule underwent a Diels-Alder-based homodimerization that afforded **15** in 87% yield no matter how many equivalents of dienophile **13** were present in solution [7] (see Figure 3). Only through major structural alteration, such as removal of the conjugated olefin and the use of a smaller dienophile, were it possible to achieve direct [4+2] reactions, though, as illustrated with a reaction between acrylonitrile and the oxidized form of **16**, the resultant products (such as **17**) possessed regiochemistry opposite that found in the helicterin family. The regiochemistry of this product matches that reported by several other investigators [8]. In the same vein, attempts to achieve controlled radical-based dimerizations of **14** using single-electron transfer (SET) reagents, such as AgOAc, consistently led to a combinatorial array of products from which only dihydrofuran **18**, which is a known oxidation product of methyl ferulate [10], has been isolated and characterized. Despite the absence of control in endeavors to dimerize this substrate, others have reported a number of instances where high levels of selectivity can be achieved using SET agents [9].

Overarching Synthetic Approach and Initial Model Studies

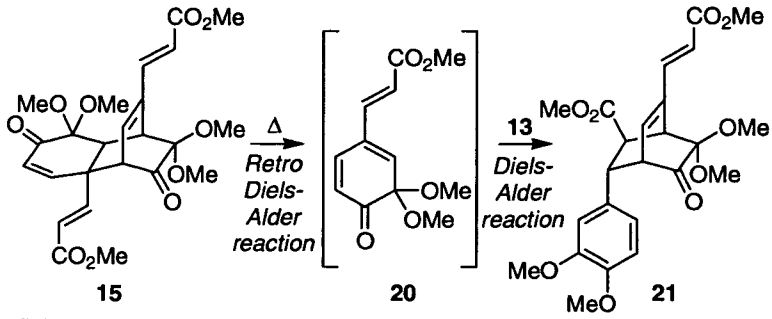
Given the inability to temper the reactive pathways of model compounds related to rosmarinic acid (**5**, Figure 4), it was wondered whether the varied architectural complexity

of the helicterin family could be controllably accessed from a different starting material. Such an idea was inspired by previous studies with the resveratrol-based collection of natural products where exposure of a common precursor, one distinct from Nature's building block, to a variety of simple reagents enabled creation of a variety of structurally unique natural products and analogs with complete selectivity [11]. Specifically, it was postulated that **19**, a fully functionalized form of the Diels-Alder homodimer (**15**) discussed above, could constitute that starting material based on the notion that it could be funneled into a protected version of the desired core structure (**8**, cf. Figure 2) by heating it at a high enough temperature in the presence of the requisite dienophile (**9**). In other words, it was hypothesized that the Diels-Alder reaction modeled earlier with phenol **14** provided a kinetic outcome (i.e. **15**), while the desired product (**21**, Figure 5) might represent a thermodynamic sink reachable by breaking apart that material (**15**) through a retro Diels-Alder reaction and inducing its participation in a [4+2]-cycloaddition reaction with dienophile **13**. Examples of the reaction concept using masked *ortho*-benzoquinones have been described. It is important to note that in all these examples, only mono-substituted dienophiles were employed; none has explored a substrate as complex as that reported here. Also, the regiochemistry observed in these cases is in line with that observed for compound **17** [12].

Given this idea, this model system was re-explored, and pleasingly, compound **21** was produced in 83% yield based on recovered starting material (43% isolated yield) following 30 min of heating a mixture of **15** and **13** at 220 °C in

mesitylene in a sealed tube; its structure was verified by X-ray crystallographic analysis. As shown in Table 1, this unique retro Diels-Alder/Diels-Alder sequence was not effectively promoted by microwave radiation irrespective of reaction solvent (entries 1-3), did not appear to benefit from any "on-water" effect under thermal activation (entry 4 and entry 6 versus entry 7) [13], and required slightly more than 5 equivalents of dienophile to obtain a maximal yield (entries 7-11). It also required significant activation as no product was observed under thermal conditions if the reaction temperature was below 160 °C. As such, the general harshness of this protocol appears to implicate the role of an enzyme if Nature employs a direct Diels-Alder reaction in her synthetic approach to these neolignans, as a retro-based pathway would be highly unlikely. At a strategic level, however, the outcome validated the general concept of using **19** (Figure 4) as a starting material to fashion **1**-**4**.

Table 1. Screening of conditions to form Diels-Alder product **21**.



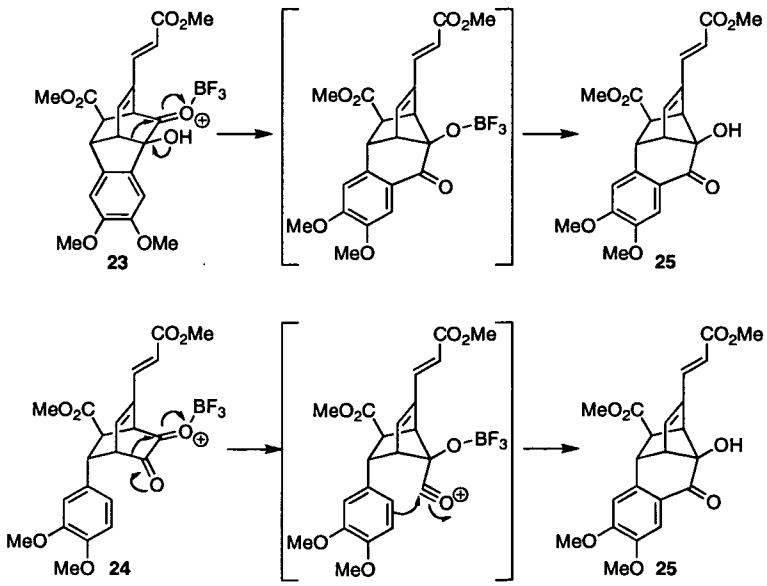
15 20 21

Entry	Heating source	Conditions	Yield (%)
1	μwave	EtOH, 200 °C, 5 min, 5.0 equiv **13**	0
2	μwave	ethylene glycol, 210 °C, 10 min, 5.0 equiv **13**	16
3	μwave	toluene/*i*-PrOH, 190 °C, 35 min, 5.0 equiv **13**	11
4	oil bath[a]	H_2O/LiCl, 160 °C, 60 min, 5.0 equiv **13**	23
5	oil bath[a]	DMA, 220 °C, 30 min, 5.0 equiv **13**	26
6	oil bath[a]	mesitylene/H_2O, 220 °C, 30 min, 5.0 equiv **13**	34
7	oil bath[a]	mesitylene, 220 °C, 30 min, 5.0 equiv **13**	40
8	oil bath[a]	mesitylene, 220 °C, 30 min, 3.3 equiv **13**	33
9	oil bath[a]	mesitylene, 220 °C, 30 min, 6.7 equiv **13**	43
10	oil bath[a]	mesitylene, 220 °C, 30 min, 10 equiv **13**	42
11	oil bath[a]	mesitylene, 220 °C, 30 min, 20 equiv **13**	44

[a] Reaction performed in a sealed tube. DMA = *N,N*-dimethylacetamide

From this new compound (**21**, Figure 5), performance of an additional model study was sought, namely a search for conditions that could achieve a Friedel-Crafts-like union between C-6 and the C-4' carbonyl as required to create the core of helisorin (**3**). Compound **21** was exposed to a variety of protic acids in an array of reaction solvents (such as HCl or TFA in wet THF and *p*-TsOH in acetone) in hopes of effecting both acetal cleavage as well as the desired C-C bond construction. However, the starting material was consistently recovered in near quantitative yield from all these experiments. Fortunately, select Lewis acids provided the needed activation. For instance,

controlled exposure of **21** to 6 equivalents of $BF_3 \cdot OEt_2$ in CH_2Cl_2 at 0 °C, followed by slow warming to ambient temperature and 16 h of additional stirring, accomplished the desired event in 82% yield. Others, such as $FeCl_3 \cdot SiO_2$ [14], also provided **23**, but in significantly reduced yield (13%). Mechanistically, it was postulate that this step leading to **23** proceeded via initial Friedel-Crafts cyclization (generating intermediate **22**), followed by acetal cleavage. This statement is not based on the direct observation or isolation of any **22**. Rather, it reflects the fact that when the putative diketone intermediate (**24**) that would arise from the alternate order of events was exposed separately to the same reaction conditions involving $BF_3 \cdot OEt_2$, only the unique rearranged adduct **25** was obtained. The structure of **25** was confirmed by X-ray crystallographic analysis. As indicated below, it is believed that the formation of this product follows a Pinacol-like mechanism, with slightly different pathways depending upon whether the sequence commences with **23** or **24**.



Moreover, **23** could be converted into the same material only through far more forcing conditions (20 equivalents of $BF_3 \cdot OEt_2$). As a final and more general note, if more powerful Lewis acids were employed in attempts to convert **21** into **23**, unexpected reaction products were typically obtained; for instance, the use of 6 equivalents of BBr_3 at -78 °C in CH_2Cl_2 smoothly provided halogenated intermediate **26** in 82% yield. The existence of such bromoacetals has been documented previously [15]. Several other Lewis acids, such as $In(OTf)_3$, $TiCl_4$ and Me_2AlCl in CH_2Cl_2 at 25 °C, did not induce any reactions with **21** despite several hours of stirring and their use in superstoichiometric amounts (10-15 equivalents).

Protecting Group Selection, Synthesis of Fully Functionalized Starting Materials, and Total Synthesis of Helisorin (3)

Although the above studies were promising in revealing that the core motifs of at least one of the target molecules could be accessed (i.e. **3**), the main issue for their translation to fully functional materials was the identification of an appropriate protecting group for the phenols. Though such an issue is a standard concern for any synthetic plan [16], these natural products, and the developed conditions up to this point for the critical C-C bond constructions, presented a unique array of combined challenges. First, under no circumstance could the chosen protecting group require aqueous acid to cleave as such conditions could rupture the acetal linkage in the two helicterins (**1** and **2**); aqueous base would presumably be just as deleterious as it could hydrolyze the ester linkages within all the target molecules and/or racemize

their chiral centers. Moreover, given the oxidation potential of the 3,4-diphenoxy ring systems within all of the targets (each was isolated from the plant extracts in less than 30 min in a cold room; ambient temperatures, light, and oxygen caused their decomposition), every member of the phenol protecting group array would have to be cleaved quickly and cleanly so as to avoid over-manipulation of the final product, especially during purification. Finally, based on a series of additional model studies (not shown), it became evident that both the Diels-Alder reaction leading to **21**, as well as the Friedel-Crafts reaction that afforded **24** (cf. Figure 5), required an electron-donating protecting group to proceed.

Given these collated criteria, it was anticipated that the ideal protective group would likely need to be an ether, one with just the right balance of stability versus reactivity so as to be able to survive exposure to stoichiometric amounts of mild Lewis acids (such as $BF_3 \cdot OEt_2$) at 25 °C over several hours, but which could be ruptured quickly in the presence of more powerful Lewis acids (such as BBr_3) at much lower temperatures. Based on literature precedent, benzyl ethers appeared ideal in this regard [17]; however, simple model studies (not shown) quickly demonstrated that this group was sensitive to prolonged exposure to $BF_3 \cdot OEt_2$. Thus, substituted benzyl ethers were explored, in hopes that the addition of a mildly electron withdrawing group, such as a *p*-CF_3 group, which has a σ value of 0.54 as determined by a known method [18] and the reactivity of which has previously been explored [19], could deactivate the protecting group enough

to survive exposure to $BF_3 \cdot OEt_2$ while still permitting the Diels-Alder and Friedel-Crafts reactions to succeed. While *p*-CF_3-benzyl ethers have been used to protect aliphatic alcohols on a select number of occasions, they have never been employed to protect phenols.

This conjecture was tested by preparing the differentially protected rosmarinic acid derivatives **27** and **32** as shown in Figure 6. Starting from commercially-available **5**, initial chemoselective methylation of its free carboxylic acid was achieved through treatment with 0.95 equivalents of $TMSCH_2N_2$ and was followed by a subsequent alkylation of the four phenol residues using *p*-CF_3-benzyl bromide under Finkelstein conditions. Elements of the sequence leading to this piece were inspired by the work of O'Malley et al [20]. These operations completed the synthesis of **27** in 84% overall yield. Methanolysis of the internal ester linkage within this new product then provided both **28** and **29**, the latter of which was coupled with carboxylic acid **31** under standard conditions (EDC, 4-DMAP, CH_2Cl_2, 25 °C) to afford, following silyl ether cleavage, the differentially-protected intermediate **32**. These operations set the stage to explore the key sequence of steps that would hopefully lead to a total synthesis of helisorin (**3**).

As indicated in Figure 7, the first of these operations, oxidative homodimerization of **32** via a Diels-Alder reaction, proceeded quickly and cleanly in near quantitative yield (99%) with $PhI(OAc)_2$ in MeOH at 25 °C. Next, in a test of the robustness of the retro Diels-Alder/Diels-Alder sequence that worked so effectively in model systems, this intermediate (**33**) was then heated in

mesitylene in a sealed tube at 220 °C in the presence of 6.7 equivalents of dienophile **27**, and the desired Diels-Alder product (**34**) was obtained in 71% yield based on recovered **27**. Interestingly, though both fragments contained a single chiral center, this new product (**34**) was generated as a 1:1 mixture of diastereomers, indicating that such stereochemical information was too remote to control the facial presentation of the two partners in this key event. Again, such an outcome supports the intervention of an enzyme in Nature's synthesis of such a framework if a Diels-Alder reaction [21] is involved, since only a single natural product enantiomer has been isolated thus far. Recently, some very unique approaches have been developed to create chiral masked *ortho*-benzoquinones that could conceivably afford a diastereoselective solution to this key step [22].

Given the uncertainty regarding some of the stereochemistry of the final natural products as mentioned in the Background, the two Diels-Alder diastereomers (**34**) were separated at this stage via standard column chromatography, and then subjected separately to $BF_3 \cdot OEt_2$ in hopes of creating the remaining C-C bond of the helisorin core. Fortunately, this step proceeded smoothly in 82% yield based on recovered **34** if the original model conditions ($BF_3 \cdot OEt_2$ in CH_2Cl_2) were slightly adjusted in terms of solvent and water content (benzene and 5 equivalents of added water). Finally, controlled exposure to BBr_3 in CH_2Cl_2 at -78 °C quickly and cleanly cleaved all six *p*-CF_3-benzyl ethers in 30 min, providing a synthetic sample of **3** in 77% yield that was identical to naturally-derived helisorin (**3**) in all respects (^1H and ^{13}C NMR, IR, HRMS, α_D).

As such, the first laboratory synthesis of this neolignan was complete and a definitive assignment of this molecule's relative stereochemistry and the connection of the family to **5** and/or **6** could finally be made. As a concluding note for this synthesis, if the final deprotection was stirred for prolonged periods (greater than 1 h), executed at reaction temperatures above -50 °C, and/or left unprotected from atmospheric oxygen and light (especially upon purification), significant decomposition was observed.

Final isolations of each synthetic natural product were handled with extreme care so as to minimize exposure to heat and air. Typically, upon completion of the BBr_3-induced deprotection, the reaction would be quenched while still cold, quickly engaged in an extractive work-up, and concentrated via rotary evaporation using an ice-cold water bath (all performed in less than 5 min). The crude product was then loaded onto a preparative TLC plate, with the separation performed in the dark using an argon-purged chamber and degassed solvents (typically in less than 30 min).

Total Synthesis of Helicterin B (2)

With these successes in hand, the most complex members of the family, helicterins A and B (**1** and **2**), beginning with model studies seeking to create the acetal core of these rosmarinic acid tetramers, were targeted next. The initial goal was to convert compound **21** into either hydroxyketone **40** or hydroxyketal **42** (Figure 8) given literature precedent indicating that such systems in [2.2.1]-bicyclic frameworks could be induced to dimerize simply upon standing or upon exposure to anhydrous acids [23]. As such, efforts began

with attempts to achieve a stereoselective reduction of the ketone within **21** to generate **42** directly. Unfortunately, no condition screened, including several that can accomplish such a reaction in [2.2.1]-systems (such as Meerwein-Pondorff-Verley reduction, samarium-based reducing agents, or $NaBH_4/CeCl_3$) [24], rose to the occasion. Instead, **35** was formed consistently, and proved resistant to all efforts at inversion (either under standard Mitsunobu conditions or attempted displacement of a triflate with KO_2 or $NaNO_2$) [25]. The same inversion challenge was also observed with hydroxyketone **36**, formed from **35** in 86% yield via its controlled exposure to aqueous HCl in toluene at 0 °C.

As such, an indirect approach to **40** and **42** was developed wherein **35** was first exposed to 0.5 M HCl in a more polar solvent (THF) to effect both acetal cleavage as well as an equilibrative rearrangement which ultimately provided hydroxyketone **37**, the core of the natural product helisterculin A (**4**). This compound, formed in 84% yield, was the most likely of the four possible hydroxyketone isomers to be produced based on the mechanism drawn in Figure 8, since it would result from proton capture by enol **38** from the least hindered face [26] at the most accessible position; it also happens to be the most thermodynamically stable (1.7 kcal/mol) based on DFT calculations. These calculations were performed at the DFT-B3LYP(1)/6-31+G* level in acetonitrile and THF continuum solvents. All four possible isomers were subjected to conformational searching within MacroModel 6.0 using the OPLS 2001 force field. The lowest energy structures for each possible isomer were then optimized in the gas phase at the B3LYP/6-31+G* level

within Jaguar 7.0. Single-point solvation calculations, including first-shell correction terms and activation energy, were then performed in acetonitrile and THF continuum solvents [27].

From here, compound **39** was accessed via 1) directed reduction of the remaining ketone as mediated by $Me_4NBH(OAc)_3$, [28] 2) selective silyl protection of the resultant C-4' hydroxyl, and 3) oxidation of the remaining alcohol. Desilylation under basic conditions (TBAF, THF) then completed the synthesis of **40** in 76% yield, while controlled treatment of **39** with a solution of 0.5 M HCl in a 4:1 mixture of $MeOH/CH(OMe)_3$ led to **42** in 93% yield. It is important to note that in the latter of these two operations the added $CH(OMe)_3$ ensured initial acetal formation followed by silyl ether cleavage, thereby preventing any equilibration back to **37** by way of an intermediate hydroxyketone.

At this juncture, it was expected that both compounds **40** and **42** would dimerize readily to generate the core of helicterin A (**1**) based upon the precedent mentioned above [23]. However, as quickly revealed by pilot experiments (Figure 9), no such facility was observed. Despite the facility of forming such dimers from [2.2.1]-bicyclic monomers, no examples of successfully employing [2.2.2]-systems exist. In fact, there are several examples that reveal failed attempts to forge such dimeric cores [29]. For instance, exposure of **42** to anhydrous HCl afforded only **44** (likely though a mechanism similar to the one leading to **37**, vide supra), while treatment with acids such as CSA in toluene led to **44** alongside an unsymmetrical dimer (**43**,

verified by X-ray crystallography) whose connectivity reflects the core structure of yunnaneic acid C [30], a member of a related group of natural products. Similarly, heating **42** neat at 160 °C for several hours primarily generated **47**, while efforts to dimerize hydroxyketone **40** under both acidic and basic protocols (NaH/THF or HCl/MeOH) delivered **43** exclusively in near quantitative yield (99%). Even efforts to utilize a more circuitous route, such as attempts to convert **44** into enol triflate **45** as part of an effort to generate a different dimerization precursor (i.e. epoxide **46**), were thwarted, in this case by the relative ease with which **45** underwent a retro Diels-Alder reaction upon its exposure to various Pd(II) sources in attempts to replace the triflate group with a hydrogen atom. Once again, as with the Friedel-Crafts reaction leading to helisorin (**3**, cf. Figure 7)., only a Lewis acid would prove capable of forging the requisite bond constructions. That reagent was $BF_3 \cdot OEt_2$, which delivered a model helicterin A core (**48**) in 79% yield when used in CH_2Cl_2 at 0 °C for 30 min. The structure of **48** was verified by X-ray crystallography. Interestingly, exposure of hydroxyketone **40** to a number of different Lewis acids did not afford a helicterin A-like core.

Pleasingly, these explorations were readily transferred to fully functionalized intermediates, as compound **32** was smoothly advanced to intermediate **50** via the same reaction sequence as shown in Figure 10. The only major surprise came two steps later, as following the formation of the desired acetal core of helicterin A (**1**) with $BF_3 \cdot OEt_2$, subsequent exposure of the resultant product to BBr_3 in CH_2Cl_2 not only cleaved all 12 *p*-CF_3-benzyl ethers, but also

led to the replacement of one of the methyl ethers in the acetal core with a hydroxyl group. As such, the first total synthesis of helicterin B (**2**) had been achieved. Thus far, all efforts to convert helicterin B (**2**) into helicterin A (**1**), such as exposure to anhydrous MeOH under acidic catalysis, have led solely to the recovery of **2**. It was hypothesized that the difficulty in executing this conversion, as well as the general ease of forming **2** in the absence of obtaining even trace amounts of **1** in the final deprotection, emanates from the additional intramolecular hydrogen bond that is obtained from the exchange.

Total Synthesis of Helisterculin A (4)

As a final demonstration of the robustness and utility of the developed sequences, the remaining dimeric member of the family, helisterculin A (**4**), was prepared using a number of the critical steps discussed earlier. As shown in Figure 11, the common dimeric starting material (**33**) was subjected to the same retro Diels-Alder/Diels-Alder cascade, this time using a different dienophile (**28**) to yield the bicyclic core of the target molecule. This intermediate was then subjected to reduction followed by an acid-catalyzed acetal cleavage and equilibrative rearrangement, as discussed above in the context of Figure 8, to afford the thermodynamic hydroxyketone product. Global phenol deprotection with BBr_3 then smoothly converted this compound into the natural product (**4**), completing the sequence in a final, overall yield of 42%.

An efficient approach capable of controllably accessing the major architectures within this neolignan family, culminating here in total syntheses of three natural

products as well as providing the first route to the core of several others (the yunnaneic acids), have been developed. In the process, the stereochemical ambiguities of the side-chains have been resolved and their connection to rosmarinic acid established. Each route proceeds in good overall yield, requiring 14 or fewer steps from commercially available materials. Key features of these sequences include some of the most complex retro Diels-Alder/Diels-Alder reactions to date, an unconventional protecting group to achieve the proper balance of chemical reactivity on sensitive scaffolds, several carefully developed reaction conditions that effectively balanced competing reaction pathways, and the illustration that Lewis acids were typically needed to accomplish the biomimetic steps of the sequence. This synthesis also reaffirms a synthetic principle previously expressed: diverse, oligomeric natural products can be easily accessed by way of common precursors that differ from Nature's presumed building block (i.e. **33**) [10]. The intermediates described herein are useful for the synthesis of the structurally unique natural products helicterin B (**2**), helisorin (**3**), and helisterculin A (**4**), which all have established inhibitory activity against avian myeloblastosis virus reverse transcriptase [1].

Synthesis of Analogs

Beyond the importance of synthesizing the natural products themselves given their established biological activity, pathways to a number of analogs with which far broader biological screening through collaborative effort could be attempted are desirable.

Additional monomeric and oligomeric neolignan analogs can be synthesized using the synthetic sequences described above. The requisite precursor used in the formation of the Diels-Alder homodimer may comprise carbogenic chains of various lengths and saturation between the phenyl ring and the carboxyl group, which may be in the form of a carboxylic acid or an ester. The precursor for the Diels-Alder homodimer may be obtained commercially with carbogenic chains of various lengths and saturation, as well as various substituents on the ester group already in place. However, when the desired precursors are not readily available, substituents can be installed on the phenyl ring of the molecule using standard aryl substitution reactions well known in organic synthesis and the ester may be formed using esterification or transesterfication reactions well known to the skilled artisan.

Furthermore, modifications can be made to the dienophile that is used in the retro-Diels-Alder step. For example, the desired 3-phenylacrylic acid or its ester may have various substituents on the phenyl ring as well as the ester. When the desired 3-phenylacrylic acid dienophile or ester thereof is not readily available, substituents are installed on the phenyl ring using standard aryl substitution reactions and the ester group can be formed using esterification or transesterfication reactions well known in organic synthesis.

It is also understood that the skilled artisan may choose a starting material having a specific chirality in order to arrive at a product having the desired chirality. For example, while the choice of naturally-occurring (R)-

rosmarinic acid as a starting material results in the synthesis of natural helisorin, helicterin B, and helisterculin A as described above, the choice of (S)-rosmarinic acid as a starting material would result in the synthesis of non-natural stereoisomers of helisorin, helicterin B, and helisterculin A.

Nucleophilic substituents, such as hydroxyl, mercapto, and amino groups, may also be modified through nucleophilic substitution reactions by exposure to electrophilic compounds. For example, free hydroxyl groups may be alkylated by exposure to an alkyl halide or silylated by exposure to a trialkylsilyl halide or triflate.

Figures 12 and 13 provide examples of representative sequences that have been used thus far to create analogs **51-63**. The majority of these sequences are based on standard functionalization chemistry, as well as some unique radical-based rearrangement to create a diversity of architectures [31].

Similarly, compounds **64-80** (see Figures 15-20) are synthesized according to the respresentative sequences shown on Figures 12 and 13.

Preliminary Biological Screening

Screening structural analogs in PC12 cell-based alamar blue assay:

A mother plate of the hit compound and the structural analogs was prepared in a Greiner 384-well plate. In this

mother plate, 50 µL of DMSO were added to the wells in the outer two rows while ten different concentrations of each compound in DMSO were added to the inner wells. To make the ten different dilutions of each compound, a 20 mg/mL stock solution of each compound was first prepared by dissolving 2.0 mg of the compound in 100 µL of DMSO. Each stock solution was then diluted down by a factor of 2 nine times using 50 µL of DMSO for each dilution to result in a 2-fold, 10 point dilution. Once the various concentrations of each compound were added to their respective wells, the mother plate was tightly sealed and thawed in a desiccator overnight.

For the PC12 screen, cell stock solutions for uninduced and induced PC12 cells were prepared with 3 mL of trypsin to remove the cells from the surface of the container and 7 mL of PC12 cell media. These solutions were then further diluted so that the volume of cell stock solution delivered to each well in the assay plates would contain 7500 cells.

Using the Biomek (Figure 21), 2 µL of each compound solution from the mother plate were added to individual wells containing 98 µL of PC12 cell media in a Greiner deep well daughter plate for a 1:50 compound to cell media dilution. Immediately before preparation of the assay plates, 20 µL of tebufenozide was added to the induced cell stock solution. A protocol on the Biomek was then designed to add in triplicate 3 µL of compound from the daughter plate to assay plates with wells containing 57 µL of PC12 cell media, resulting in an overall 1:1000 dilution of compound to cell media. The assay plates were placed in the incubator (39°C, 9.5% CO_2) for 48 hours.

Using the Biomek, 20 µL of a solution of 40% alamar blue and 60% PC12 cell media were added to each well in every assay plate. The assay plates were then incubated (39°C, 9.5% CO_2) for 16 hours. Each assay plate was read using the wsyAB setting on the plate reader.

As evidence for the value of this initial compound collection, preliminary screens of it, along with many of the molecules presented above, have revealed that compound **51** possesses the capability to rescue cells infected with the human huntingtin gene containing mutant polyglutamine repeats with no real cytotoxic effect on uninduced cells. (see Figure 14). Therefore, compound **51** is shown to be useful for reducing cell death in conditions where cells express mutant huntingtin genes, the expression of which result in mutant huntingtin proteins having abnormal numbers of N-terminal polyglutamine repeats, such as Huntington's disease.

Analogs of compound **51** may be made according to the synthetic sequences and principles described above. Diversity around active compound **51** is generated by varying the substituents on the phenyl ring of the Diels-Alder homodimer precursor as well as the substituents on the dienophile utilized in the retro-Diels-Alder step. Further diversity may be accessed by derivatization of nucleophilic groups, such as free hydroxyl groups, using well-known nucleophilic substitution chemistry. The substituents are chosen and resulting analogs are evaluated according to principles well known in the art of medicinal and pharmaceutical chemistry, such as quantification of

structure-activity relationships, optimization of biological activity and ADMET (absorption, distribution, metabolism, excretion, and toxicity) properties.

Compounds **64-80** (see Figures 15-20) were synthesized according to the synthetic sequences and principles described above. Diversity around the bicyclo[2.2.2]octane core is generated by varying the substituents on the phenyl ring of the Diels-Alder homodimer precursor as well as the substituents on the dienophile utilized in the retro-Diels-Alder step. For example, acrylonitrile, alkyl acrylates, or acrylamides, among others, may be used as the dienophile. Further diversity may be accessed by derivatization of nucleophilic groups, such as free hydroxyl groups, using well-known nucleophilic substitution chemistry.

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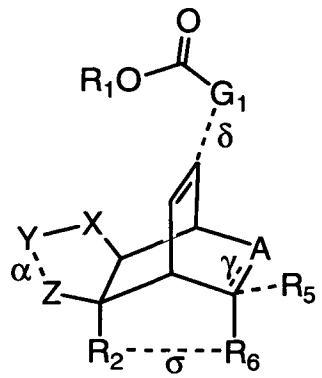
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Claims

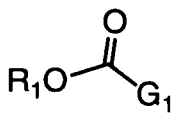
What is claimed is:

1. A compound having the structure

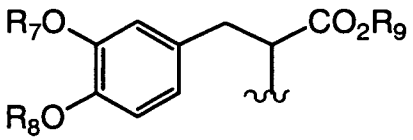


wherein

α, γ, δ and σ are each, independently, present or absent;

wherein when δ is absent,  is absent;

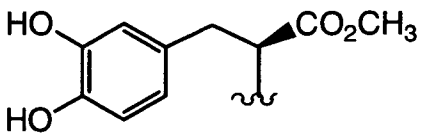
G_1 is C_{1-10} alkylene, C_{2-10} alkenylene, or C_{2-10} alkynylene;

R_1 is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or ,

wherein R_7 and R_8 are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; or $-SO_2R_{10}$,

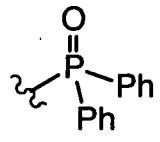
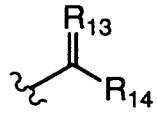
wherein R_{10} is C_{1-10} alkyl, or unsubstituted or substituted aryl;

R_9 is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

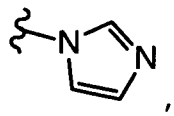
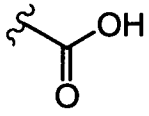
when R_7 and R_8 are H and R_9 is CH_3, then R_1 is ; and

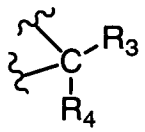
when γ is present; R_5 is absent and A is C-R_4,

wherein R_4 is H, halogen, or OR_{11},

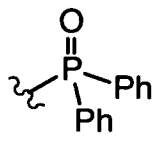
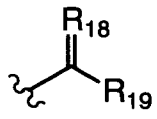
wherein R_{11} is H, C_{1-10} alkyl, $-CH_2SH$, $-BHCH_2CH_3$, -CH=SH, , $-SO_2R_{12}$, , or $-Si(R_{15})_3$;

wherein R_{12} and each occurrence of R_{15} is C_{1-10} alkyl; or unsubstituted or substituted aryl; and

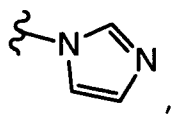
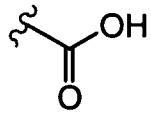
R_{13} is S or O; and R_{14} is $-SCH_3$, , or ; and

when γ is absent; R_5 is present and A is a direct bond or ;

wherein R_3 and R_4 are each, independently, H, halogen, or OR_{16};

wherein R_{16} is H, C_{1-10} alkyl, $-CH_2SH$, $-BHCH_2CH_3$, -CH=SH, , $-SO_2R_{17}$, , or $-Si(R_{20})_3$;

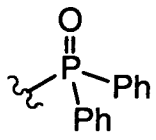
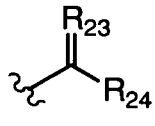
wherein R_{17} and each occurrence of R_{20} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

R_{18} is S or O; and R_{19} is $-SCH_3$, , or ; or

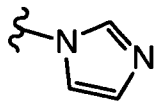
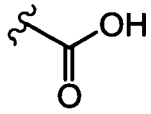
R_3 and R_4 taken together form =O; and

wherein R_5 is H, halogen, or OR_{21},

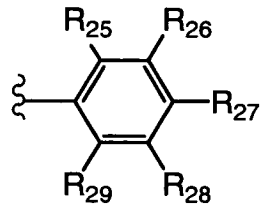
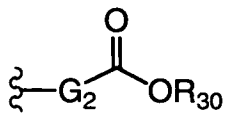
wherein R_{21} is H, C_{1-10} alkyl, $-CH_2SH$, $-BHCH_2CH_3$, $-CH{=}SH$,


, $-SO_2R_{22}$,

, or $-Si(R_{25})_3$,

wherein R_{22} and each occurrence of R_{25} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

R_{23} is S or O; and R_{24} is $-SCH_3$,

, or

; and

when σ is absent;

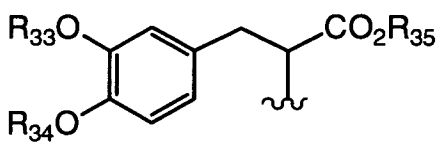
R_2 is H,

, or

;

wherein R_{25}, R_{26}, R_{27}, R_{28}, and R_{29} are each, independently, H, halogen, $-NO_2$, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; $-OR_{31}$, $-SR_{31}$, $-OSO_2R_{31}$, or $-NR_{31}R_{32}$,

wherein R_{31} and R_{32} are each, independently, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or unsubstituted or substituted aryl;

wherein G_2 is C_{1-10} alkylene, C_{2-10} alkenylene, or C_{2-10} alkynylene; and

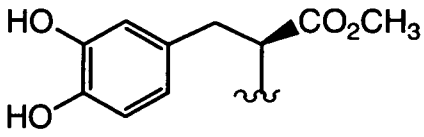
R_{30} is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or


,

wherein R_{33} and R_{34} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; or $-SO_2R_{36}$,

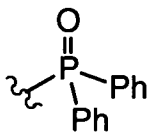
wherein R_{36} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

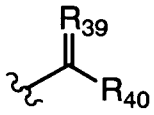
wherein R_{35} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

when R_{33} and R_{34} are H and R_{35} is CH_3, then R_{30} is 

; and

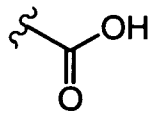
R_6 is H, halogen, or OR_{37};

wherein R_{37} is H, C_{1-10} alkyl, $-CH_2SH$, $-BHCH_2CH_3$, $-CH=SH$, 

, $-SO_2R_{38}$, 

, or $-Si(R_{41})_3$;

wherein R_{38} and each occurrence of R_{41} is C_{1-10} alkyl; or unsubstituted or substituted aryl;

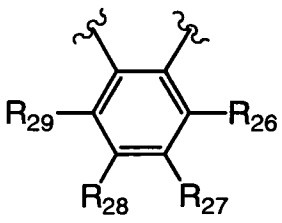
R_{39} is S or O; and R_{40} is $-SCH_3$; -NH-aryl, heteroaryl, heterocyclyl; or 

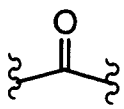
; or

R_5 when present and R_6 taken together form =O; or

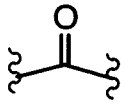
R_4 joined to R_6 form a 5-membered heterocyclic ring; and

when σ is present;

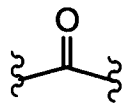
R_2 is 

; and R_6 is a direct bond or 

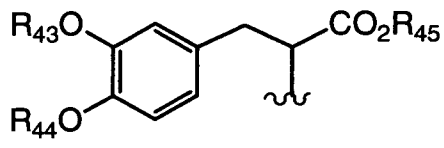
; and

wherein X is a direct bond, 

, or $C(OMe)_2$;

Y is H or OR_{42}; or when α is present, Y is ;

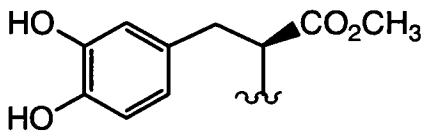
wherein R_{42} is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl,

or ,

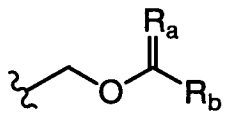
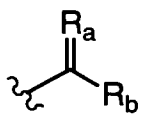
wherein R_{43} and R_{44} are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; or $-SO_2R_{46}$,

wherein R_{46} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

R_{45} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and when R_{43} and R_{44} are H and R_{45} is CH_3, then R_{42} is

; or

wherein each occurrence of alkyl, alkylene, alkenyl, alkenylene, alkynyl, or alkynylene is branched or unbranched, unsubstituted or substituted;

Z is H, CN,  or ,

wherein R_a is S or O; R_b is $-O-(C_1-C_{10})$alkyl, $-O-(C_2-C_{10})$alkenyl, heterocyclyl, or heteroaryl; or

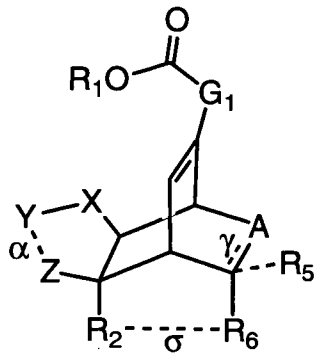
when α is present, Z is -CH=CH-;

and

when α is present, R_1 is other than methyl;

or a salt thereof.

2. The compound of claim 1 having the structure

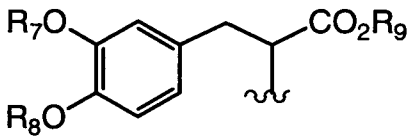


wherein

α, γ, and σ are each, independently, present or absent;

G_1 is C_{1-10} alkylene, C_{2-10} alkenylene, or C_{2-10} alkynylene;

R_1 is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or



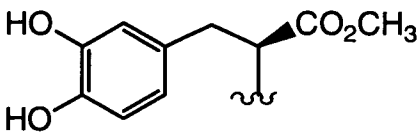
,

wherein R_7 and R_8 are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; or $-SO_2R_{10}$,

wherein R_{10} is C_{1-10} alkyl, or unsubstituted or substituted aryl;

R_9 is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

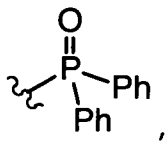
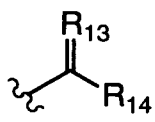
when R_7 and R_8 are H and R_9 is CH_3, then R_1 is



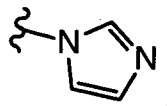
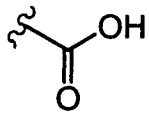
; and

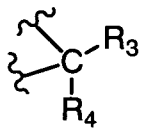
when γ is present; R_5 is absent and A is C-R_4,

wherein R_4 is H, halogen, or OR_{11},

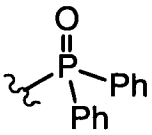
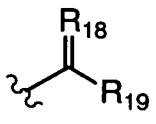
wherein R_{11} is H, C_{1-10} alkyl, $-CH_2SH$, $-BHCH_2CH_3$, $-CH{=}SH$, , $-SO_2R_{12}$, , or $-Si(R_{15})_3$;

wherein R_{12} and each occurrence of R_{15} is C_{1-10} alkyl; or unsubstituted or substituted aryl; and

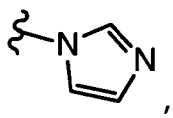
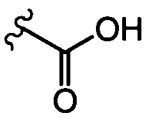
R_{13} is S or O; and R_{14} is $-SCH_3$, , or  ; and

when γ is absent; R_5 is present and A is a direct bond or  ;

wherein R_3 and R_4 are each, independently, H, halogen, or OR_{16};

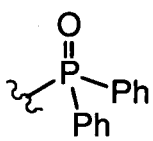
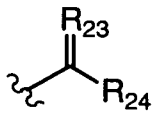
wherein R_{16} is H, C_{1-10} alkyl, $-CH_2SH$, $-BHCH_2CH_3$, $-CH{=}SH$, , $-SO_2R_{17}$, , or $-Si(R_{20})_3$;

wherein R_{17} and each occurrence of R_{20} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

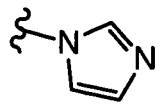
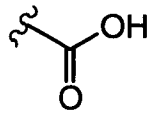
R_{18} is S or O; and R_{19} is $-SCH_3$, , or  ; or

R_3 and R_4 taken together form =O; and

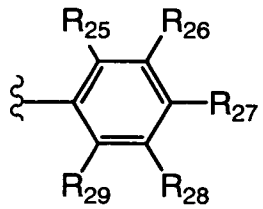
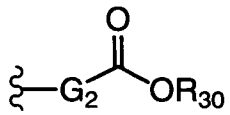
wherein R_5 is H, halogen, or OR_{21},

wherein R_{21} is H, C_{1-10} alkyl, $-CH_2SH$, $-BHCH_2CH_3$, $-CH{=}SH$, , $-SO_2R_{22}$, , or $-Si(R_{25})_3$,

wherein R_{22} and each occurrence of R_{25} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

R_{23} is S or O; and R_{24} is $-SCH_3$, , or ; and

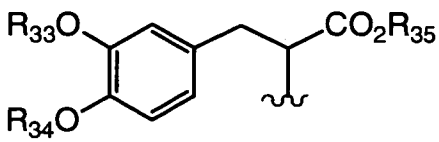
when σ is absent;

R_2 is H, , or ;

wherein R_{25}, R_{26}, R_{27}, R_{28}, and R_{29} are each, independently, H, halogen, $-NO_2$, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; $-OR_{31}$, $-SR_{31}$, $-OSO_2R_{31}$, or $-NR_{31}R_{32}$,

wherein R_{31} and R_{32} are each, independently, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or unsubstituted or substituted aryl;

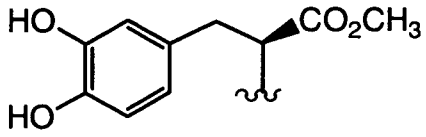
wherein G_2 is C_{1-10} alkylene, C_{2-10} alkenylene, or C_{2-10} alkynylene; and

R_{30} is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or ,

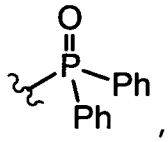
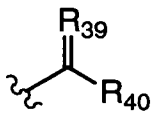
wherein R_{33} and R_{34} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; or $-SO_2R_{36}$,

wherein R_{36} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

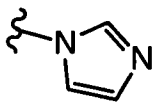
wherein R_{35} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

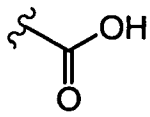
when R_{33} and R_{34} are H and R_{35} is CH_3, then R_{30} is  ; and

R_6 is H, halogen, or OR_{37};

wherein R_{37} is H, C_{1-10} alkyl, $-CH_2SH$, $-BHCH_2CH_3$, $-CH{=}SH$, , $-SO_2R_{38}$, , or $-Si(R_{41})_3$;

wherein R_{38} and each occurrence of R_{41} is C_{1-10} alkyl; or unsubstituted or substituted aryl;

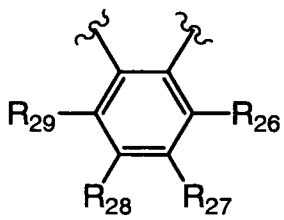
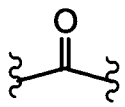
R_{39} is S or O; and R_{40} is $-SCH_3$;  ; or

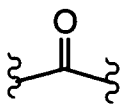
 ; or

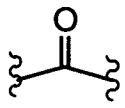
R_5 when present and R_6 taken together form =O; or

R_4 joined to R_6 form a 5-membered heterocyclic ring; and

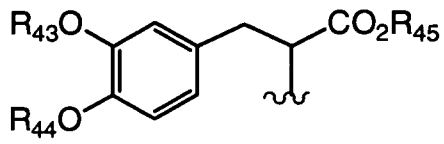
when σ is present;

R_2 is  ; and R_6 is a direct bond or  ; and

wherein X is a direct bond, , or $C(OMe)_2$;

Y is H or OR_{42}; or when α is present, Y is  ;

wherein R_{42} is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl,

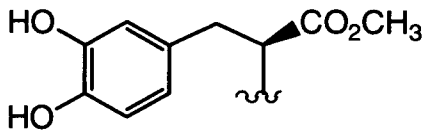


or ,

wherein R_{43} and R_{44} are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; or $-SO_2R_{46}$,

wherein R_{46} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

R_{45} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and when R_{43} and R_{44} are H and R_{45} is CH_3, then R_{42} is



; or

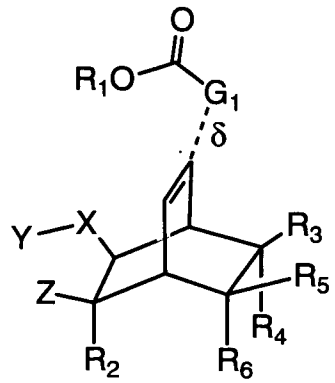
wherein each occurrence of alkyl, alkylene, alkenyl, alkenylene, alkynyl, or alkynylene is branched or unbranched, unsubstituted or substituted;

Z is H or CN; or when α is present, Z is -CH=CH-; and

when α is present, R_1 is other than methyl;

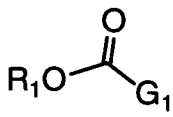
or a salt thereof.

3. The compound of claim 1 having the structure

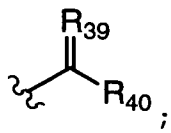


wherein

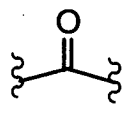
δ is present or absent;

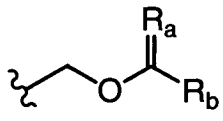
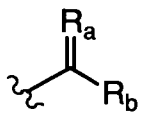
wherein when δ is absent,  is absent;

R_6 is OR_{37};

wherein R_{37} is ;

wherein R_{39} is S or O; and R_{40} is -NH-aryl, heteroaryl, heterocyclyl; or

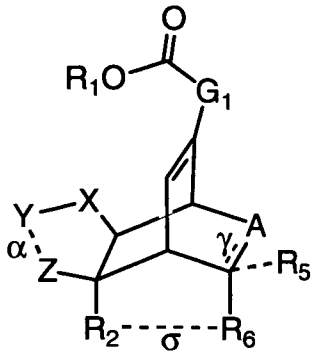
X is a direct bond or ;

Z is H, CN,  or ,

wherein R_a is S or O; R_b is -O-(C_1-C_{10})alkyl, -O-(C_2-C_{10})alkenyl, heterocyclyl, or heteroaryl; or

or a salt thereof.

4. The compound of claim 2 having the structure

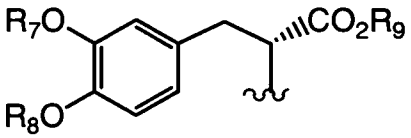


wherein

α, γ, and σ are each, independently, present or absent;

G_1 is C_{1-10} alkylene, C_{2-10} alkenylene, or C_{2-10} alkynylene;

R_1 is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or



,

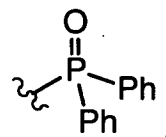
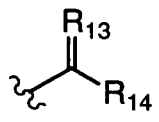
wherein R_7 and R_8 are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; or $-SO_2R_{10}$,

wherein R_{10} is C_{1-10} alkyl, or unsubstituted or substituted aryl;

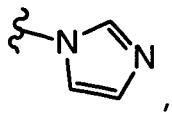
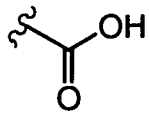
R_9 is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and at least one of R_7 and R_8 is other than H; and

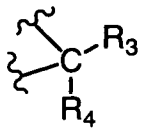
when γ is present; R_5 is absent and A is C-R_4,

wherein R_4 is H, halogen, or OR_{11},

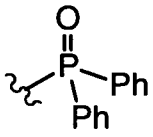
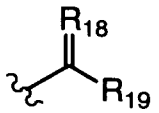
wherein R_{11} is H, C_{1-10} alkyl, $-CH_2SH$, $-BHCH_2CH_3$, $-CH{=}SH$, , $-SO_2R_{12}$, , or $-Si(R_{15})_3$;

wherein R_{12} and each occurrence of R_{15} is C_{1-10} alkyl; or unsubstituted or substituted aryl; and

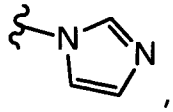
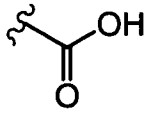
R_{13} is S or O; and R_{14} is $-SCH_3$, , or ; and

when γ is absent; R_5 is present and A is a direct bond or ;

wherein R_3 and R_4 are each, independently, H, halogen, or OR_{16};

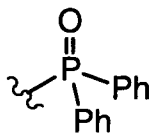
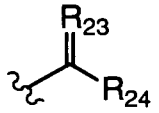
wherein R_{16} is H, C_{1-10} alkyl, $-CH_2SH$, $-BHCH_2CH_3$, $-CH{=}SH$, , $-SO_2R_{17}$, , or $-Si(R_{20})_3$;

wherein R_{17} and each occurrence of R_{20} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

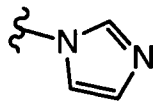
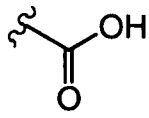
R_{18} is S or O; and R_{19} is $-SCH_3$, , or ; or

R_3 and R_4 taken together form =O; and

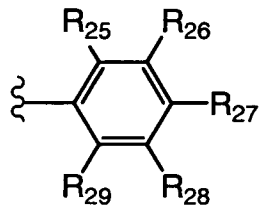
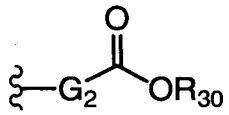
wherein R_5 is H, halogen, or OR_{21},

wherein R_{21} is H, C_{1-10} alkyl, $-CH_2SH$, $-BHCH_2CH_3$, $-CH{=}SH$, , $-SO_2R_{22}$, , or $-Si(R_{25})_3$,

wherein R_{22} and each occurrence of R_{25} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

R_{23} is S or O; and R_{24} is $-SCH_3$, , or ; and

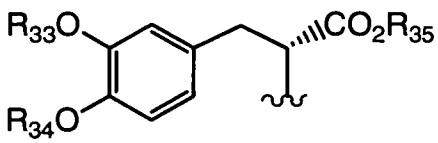
when σ is absent;

R_2 is H, , or ;

wherein R_{25}, R_{26}, R_{27}, R_{28}, and R_{29} are each, independently, H, halogen, $-NO_2$, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; $-OR_{31}$, $-SR_{31}$, $-OSO_2R_{31}$, or $-NR_{31}R_{32}$,

wherein R_{31} and R_{32} are each, independently, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or unsubstituted or substituted aryl;

wherein G_2 is C_{1-10} alkylene, C_{2-10} alkenylene, or C_{2-10} alkynylene; and

R_{30} is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or ,

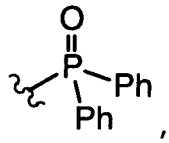
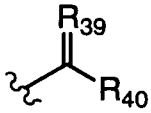
wherein R_{33} and R_{34} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; or $-SO_2R_{36}$,

wherein R_{36} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and at least one of R_{33} and R_{34} is other than H; and

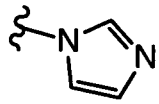
wherein R_{35} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

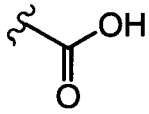
R_6 is H, halogen, or OR_{37};

wherein R_{37} is H, C_{1-10} alkyl, $-CH_2SH$, $-BHCH_2CH_3$, $-CH=SH$,


, $-SO_2R_{38}$, 
, or $-Si(R_{41})_3$;

wherein R_{38} and each occurrence of R_{41} is C_{1-10} alkyl; or unsubstituted or substituted aryl;

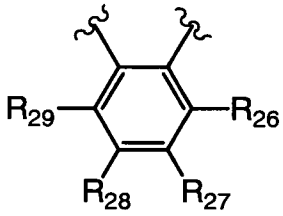
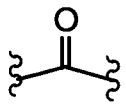
R_{39} is S or O; and R_{40} is $-SCH_3$; 
; or

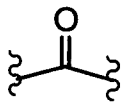

; or

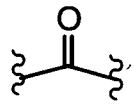
R_5 when present and R_6 taken together form =O; or

R_4 joined to R_6 form a 5-membered heterocyclic ring; and

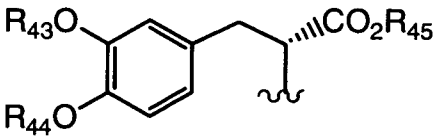
when σ is present;

R_2 is 
; and R_6 is a direct bond or 
; and

wherein X is a direct bond, 
, or $C(OMe)_2$;

Y is H or OR_{42}; or when α is present, Y is 
;

wherein R_{42} is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl,

or 
,

wherein R_{43} and R_{44} are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; or $-SO_2R_{46}$,

wherein R_{46} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

R_{45} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and at least one of R_{43} and R_{44} is other than H; or

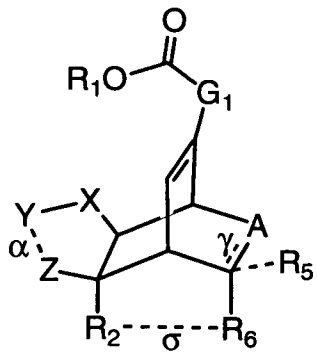
wherein each occurrence of alkyl, alkylene, alkenyl, alkenylene, alkynyl, or alkynylene is branched or unbranched, unsubstituted or substituted;

Z is H or CN; or when α is present, Z is -CH=CH-; and

when α is present, R_1 is other than methyl;

or a salt thereof.

5. The compound of claim 2 having the structure

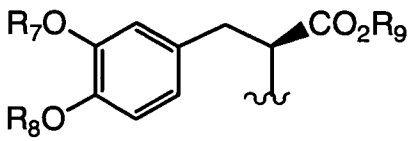


wherein

α, γ, and σ are each, independently, present or absent;

G_1 is C_{1-10} alkylene, C_{2-10} alkenylene, or C_{2-10} alkynylene;

R_1 is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or



,

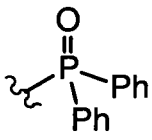
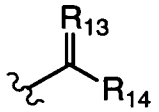
wherein R_7 and R_8 are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; or $-SO_2R_{10}$,

wherein R_{10} is C_{1-10} alkyl, or unsubstituted or substituted aryl;

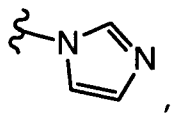
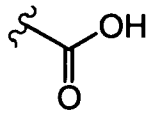
R_9 is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

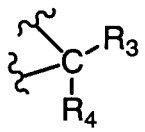
when γ is present; R_5 is absent and A is C-R_4,

wherein R_4 is H, halogen, or OR_{11},

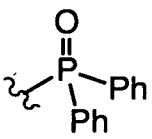
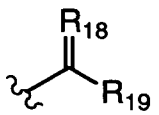
wherein R_{11} is H, C_{1-10} alkyl, $-CH_2SH$, $-BHCH_2CH_3$, $-CH{=}SH$, , $-SO_2R_{12}$, , or $-Si(R_{15})_3$;

wherein R_{12} and each occurrence of R_{15} is C_{1-10} alkyl; or unsubstituted or substituted aryl; and

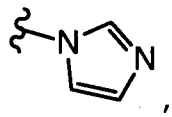
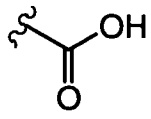
R_{13} is S or O; and R_{14} is $-SCH_3$, , or ; and

when γ is absent; R_5 is present and A is a direct bond or ;

wherein R_3 and R_4 are each, independently, H, halogen, or OR_{16};

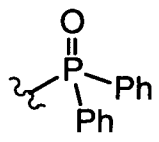
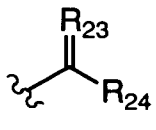
wherein R_{16} is H, C_{1-10} alkyl, $-CH_2SH$, $-BHCH_2CH_3$, $-CH{=}SH$, , $-SO_2R_{17}$, , or $-Si(R_{20})_3$;

wherein R_{17} and each occurrence of R_{20} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

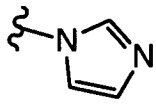
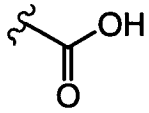
R_{18} is S or O; and R_{19} is $-SCH_3$, , or ; or

R_3 and R_4 taken together form =O; and

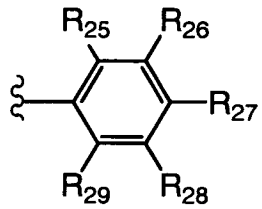
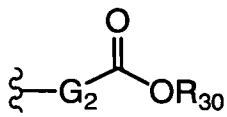
wherein R_5 is H, halogen, or OR_{21},

wherein R_{21} is H, C_{1-10} alkyl, $-CH_2SH$, $-BHCH_2CH_3$, $-CH{=}SH$, , $-SO_2R_{22}$, , or $-Si(R_{25})_3$,

wherein R_{22} and each occurrence of R_{25} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

R_{23} is S or O; and R_{24} is $-SCH_3$, , or ; and

when σ is absent;

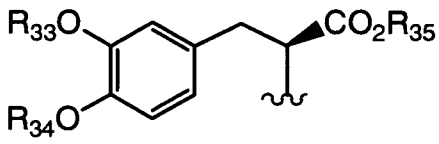
R_2 is H, , or ;

wherein R_{25}, R_{26}, R_{27}, R_{28}, and R_{29} are each, independently, H, halogen, $-NO_2$, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; $-OR_{31}$, $-SR_{31}$, $-OSO_2R_{31}$, or $-NR_{31}R_{32}$,

wherein R_{31} and R_{32} are each, independently, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or unsubstituted or substituted aryl;

wherein G_2 is C_{1-10} alkylene, C_{2-10} alkenylene, or C_{2-10} alkynylene; and

R_{30} is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or



,

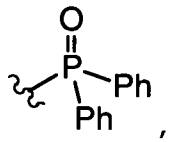
wherein R_{33} and R_{34} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; or $-SO_2R_{36}$,

wherein R_{36} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

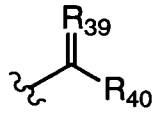
wherein R_{35} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

R_6 is H, halogen, or OR_{37};

wherein R_{37} is H, C_{1-10} alkyl, $-CH_2SH$, $-BHCH_2CH_3$, $-CH{=}SH$,



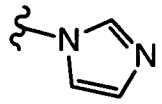
, $-SO_2R_{38}$,



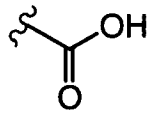
, or $-Si(R_{41})_3$;

wherein R_{38} and each occurrence of R_{41} is C_{1-10} alkyl; or unsubstituted or substituted aryl;

R_{39} is S or O; and R_{40} is $-SCH_3$;



; or



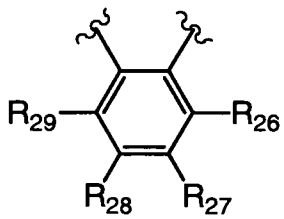
; or

R_5 when present and R_6 taken together form =O; or

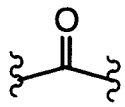
R_4 joined to R_6 form a 5-membered heterocyclic ring; and

when σ is present;

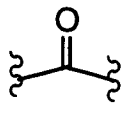
R_2 is

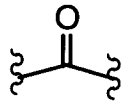


; and R_6 is a direct bond or

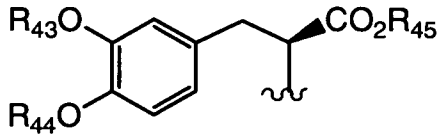


; and

wherein X is a direct bond, , or $C(OMe)_2$;

Y is H or OR_{42}; or when α is present, Y is ;

wherein R_{42} is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl,

or ,

wherein R_{43} and R_{44} are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; or $-SO_2R_{46}$,

wherein R_{46} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

R_{45} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; or

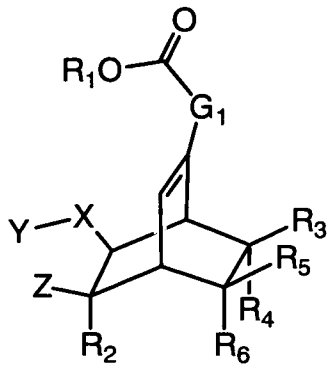
wherein each occurrence of alkyl, alkylene, alkenyl, alkenylene, alkynyl, or alkynylene is branched or unbranched, unsubstituted or substituted;

Z is H or CN; or when α is present, Z is -CH=CH-; and

when α is present, R_1 is other than methyl;

or a salt thereof.

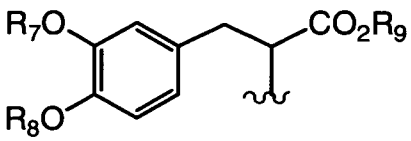
6. The compound of claim 1, 2, 4, or 5 having the structure



wherein

G_1 is C_{1-10} alkylene, C_{2-10} alkenylene, or C_{2-10} alkynylene;

R_1 is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or



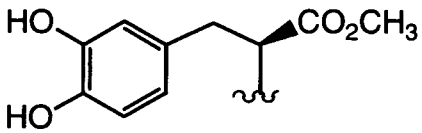
,

wherein R_7 and R_8 are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; or $-SO_2R_{10}$,

wherein R_{10} is C_{1-10} alkyl, or unsubstituted or substituted aryl;

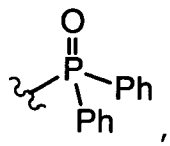
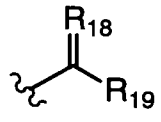
R_9 is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

when R_7 and R_8 are H and R_9 is CH_3, then R_1 is

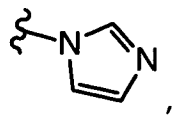
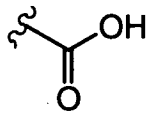


; and

wherein R_3 and R_4 are each, independently, H, halogen, or OR_{16};

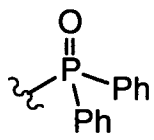
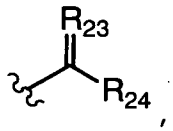
wherein R_{16} is H, C_{1-10} alkyl, $-CH_2SH$, $-BHCH_2CH_3$, $-CH{=}SH$, , $-SO_2R_{17}$, , or $-Si(R_{20})_3$;

wherein R_{17} and each occurrence of R_{20} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

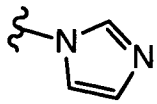
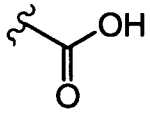
R_{18} is S or O; and R_{19} is $-SCH_3$, , or ; or

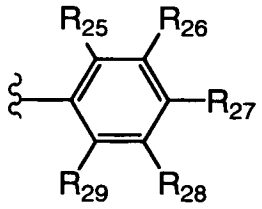
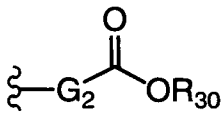
R_3 and R_4 taken together form =O; and

wherein R_5 is H, halogen, or OR_{21},

wherein R_{21} is H, C_{1-10} alkyl, $-CH_2SH$, $-BHCH_2CH_3$, $-CH=SH$, , $-SO_2R_{22}$, , or $-Si(R_{25})_3$,

wherein R_{22} and each occurrence of R_{25} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

R_{23} is S or O; and R_{24} is $-SCH_3$, , or ; and

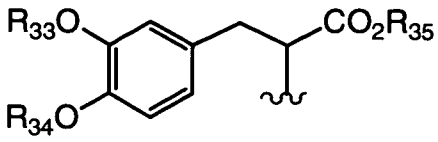
R_2 is H, , or ;

wherein R_{25}, R_{26}, R_{27}, R_{28}, and R_{29} are each, independently, H, halogen, $-NO_2$, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; $-OR_{31}$, $-SR_{31}$, $-OSO_2R_{31}$, or $-NR_{31}R_{32}$,

wherein R_{31} and R_{32} are each, independently, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or unsubstituted or substituted aryl;

wherein G_2 is C_{1-10} alkylene, C_{2-10} alkenylene, or C_{2-10} alkynylene; and

R_{30} is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or



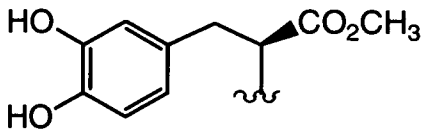
,

wherein R_{33} and R_{34} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; or $-SO_2R_{36}$,

wherein R_{36} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

wherein R_{35} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

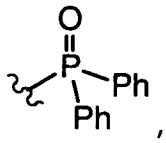
when R_{33} and R_{34} are H and R_{35} is CH_3, then R_{30} is



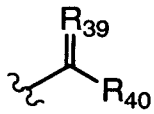
; and

R_6 is H, halogen, or OR_{37};

wherein R_{37} is H, C_{1-10} alkyl, $-CH_2SH$, $-BHCH_2CH_3$, $-CH{=}SH$,



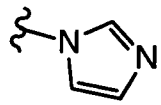
, $-SO_2R_{38}$,



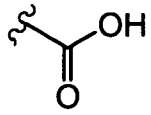
, or $-Si(R_{41})_3$;

wherein R_{38} and each occurrence of R_{41} is C_{1-10} alkyl; or unsubstituted or substituted aryl;

R_{39} is S or O; and R_{40} is $-SCH_3$;



; or

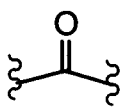


; or

R_5 when present and R_6 taken together form =O; or

R_4 joined to R_6 form a 5-membered heterocyclic ring; and

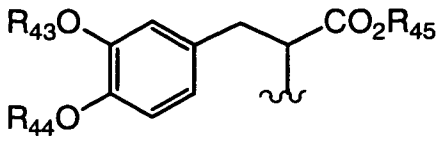
wherein X is a direct bond or



; and

Y is H or OR_{42},

wherein R_{42} is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl,



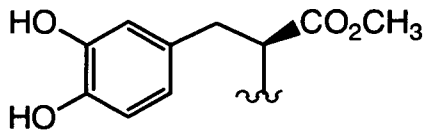
or ,

wherein R_{43} and R_{44} are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; or $-SO_2R_{46}$,

wherein R_{46} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

R_{45} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl;

and when R_{43} and R_{44} are H and R_{45} is CH_3, then R_{42} is



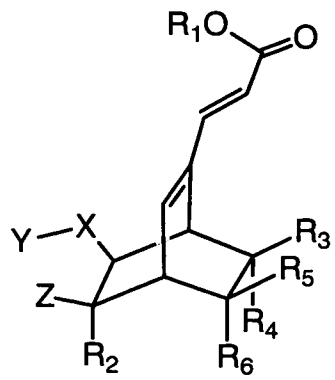
; or

wherein each occurrence of alkyl, alkylene, alkenyl, alkenylene, alkynyl, or alkynylene is branched or unbranched, unsubstituted or substituted;

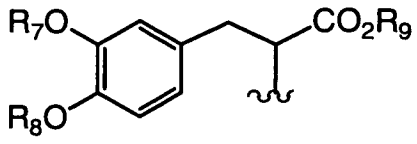
Z is H or CN;

or a salt thereof.

7. The compound of claim 6 having the structure



wherein

R_1 is H, CH_3, or ,

wherein R_7 and R_8 are p-trifluoromethylbenzyl; and

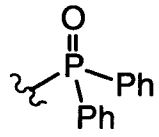
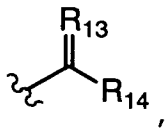
R_9 is CH_3; and

wherein R_3 is H, OCH_3, Br, $-OSO_2CF_3$, or -OiPr;

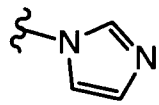
R_4 is H, OH, or OCH_3;

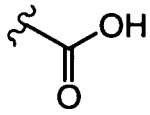
R_5 is H, OH, $-OSO_2CF_3$, or $-OSi(CH_3)_2$(t-butyl); and

R_6 is H or OR_{11},

wherein R_{11} is H, $-CH_2SH$, $-BHCH_2CH_3$, -CH=SH, , -SO_2R_{12}, or ,

wherein R_{12} is CH_3 or CF_3;

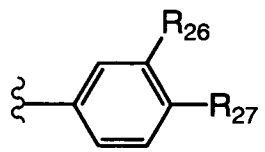
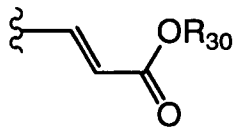
R_{13} is S or O; and R_{14} is $-SCH_3$; ; or

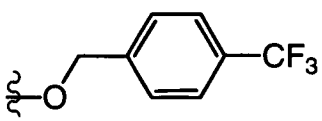
; or

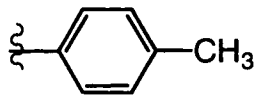
R_5 and R_6 together form =O; or

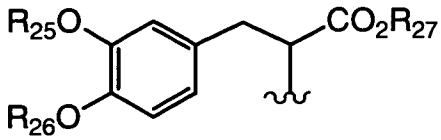
R_3 and R_4 together form =O; or

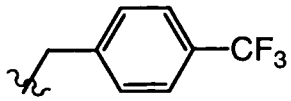
R_4 joined to R_6 form a 5-membered heterocyclic ring; and

wherein R_2 is H, , or ,

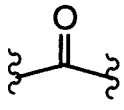
wherein R_{26} and R_{27} are each, independently, $-OCH_3$, , or $-OSO_2R_{24}$,

wherein R_{24} is ;

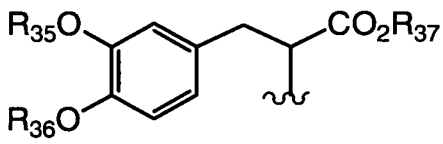
wherein R_{30} is CH_3 or ,

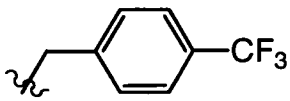
wherein R_{25} and R_{26} are each ;

wherein R_{27} is CH_3; and

wherein X is a direct bond, , or $C(OMe)_2$;

Y is H or OR_{34},

wherein R_{34} is CH_3 or ,

wherein R_{35} and R_{36} are each ; and

R_{37} is CH_3; and

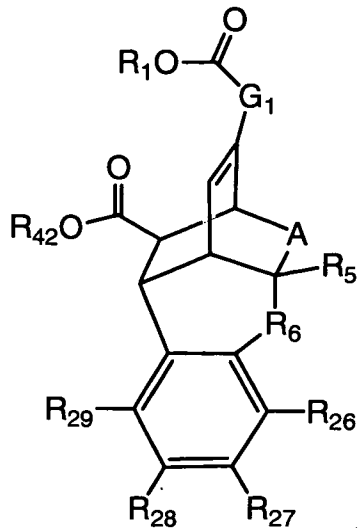
Z is H or CN;

or a salt thereof.

8. The compound of claim 7 selected from the group consisting of Compound 17, 21, 24, 26, 33, 34, 36, 36, 37, 39, 40, 42, 44, 45, 47, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63.

9. The compound of claim 8 selected from the group consisting of Compound 51.

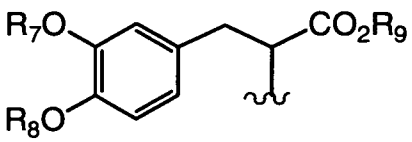
10. The compound of claim 1, 2, 4, or 5 having the structure



wherein

G_1 is C_{1-10} alkylene, C_{2-10} alkenylene, or C_{2-10} alkynylene;

R_1 is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or



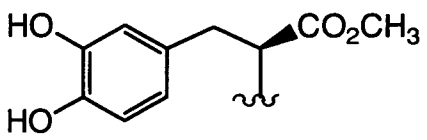
,

wherein R_7 and R_8 are independently H; C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, unsubstituted or substituted aryl(C_{1-10})alkyl, or $-SO_2R_{10}$,

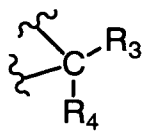
wherein R_{10} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

R_9 is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

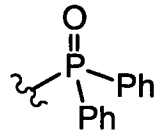
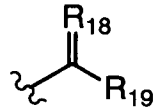
when R_7 and R_8 are H and R_9 is CH_3, then R_1 is



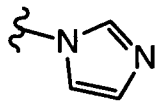
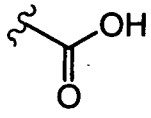
;

A is a direct bond or  ;

wherein R_3 and R_4 are each, independently, H, halogen, or OR_{16};

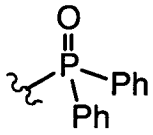
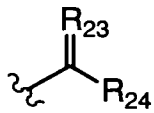
wherein R_{16} is H, C_{1-10} alkyl, $-CH_2SH$, $-BHCH_2CH_3$, $-CH{=}SH$, , $-SO_2R_{17}$, , or $-Si(R_{20})_3$;

wherein R_{17} and each occurrence of R_{20} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

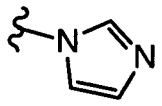
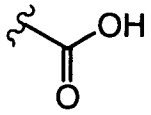
R_{18} is S or O; and R_{19} is $-SCH_3$, , or ; or

R_3 and R_4 taken together form =O; and

wherein R_5 is H, halogen, or OR_{21},

wherein R_{21} is H, C_{1-10} alkyl, $-CH_2SH$, $-BHCH_2CH_3$, $-CH{=}SH$, , $-SO_2R_{22}$, , or $-Si(R_{25})_3$,

wherein R_{22} and each occurrence of R_{25} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

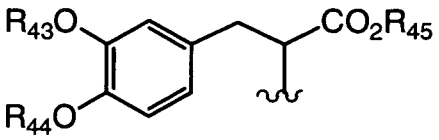
R_{23} is S or O; and R_{24} is $-SCH_3$, , or ; and

wherein R_6 is a direct bond or ; and

wherein R_{26}, R_{27}, R_{28}, and R_{29} are each, independently, H, halogen, $-NO_2$, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; $-OR_{31}$, $-SR_{31}$, $-OSO_2R_{31}$, or $-NR_{31}R_{32}$,

wherein R_{31} and R_{32} are each, independently, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or unsubstituted or substituted aryl;

wherein R_{42} is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or



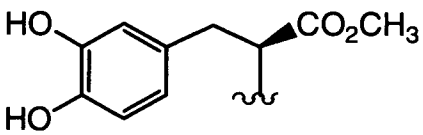
,

wherein R_{43} and R_{44} are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; or $-SO_2R_{46}$,

wherein R_{46} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

R_{45} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl;

and when R_{43} and R_{44} are H and R_{45} is CH_3, then R_{42} is

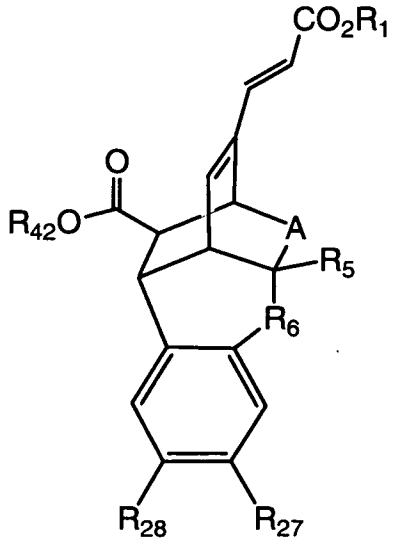


; or

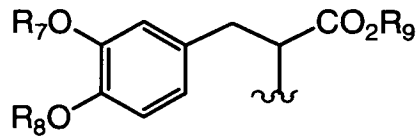
wherein each occurrence of alkyl, alkylene, alkenyl, alkenylene, alkynyl, or alkynylene is branched or unbranched, unsubstituted or substituted;

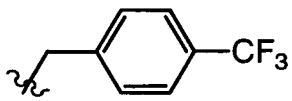
or a salt thereof.

11. The compound of claim 10 having the structure

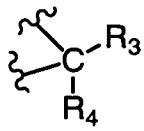


wherein

R_1 is CH_3 or ,

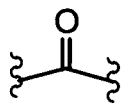
wherein R_7 and R_8 are ; and

R_9 is CH_3;

A is a direct bond or ;

wherein R_3 and R_4 taken together form =O;

R_5 is H or OH;

R_6 is a direct bond or ;

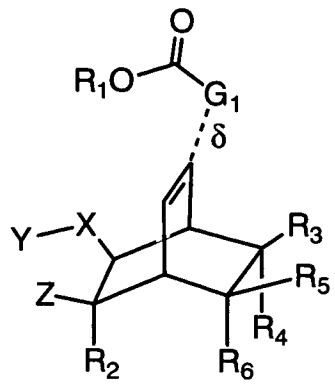
R_{27} and R_{28} are each $-OCH_3$; and

wherein R_{42} is CH_3; or

a salt thereof.

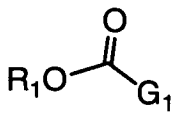
12. The compound of claim 11 selected from the group consisting of: Compound 23 and 25.

13. The compound of claim 3 having the structure

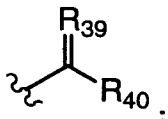


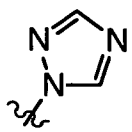
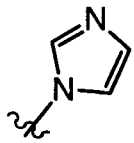
wherein

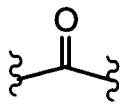
δ is present or absent;

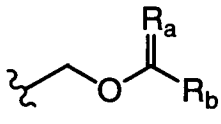
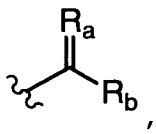
wherein when δ is absent,  is absent;

R_6 is OR_{37};

wherein R_{37} is ;

wherein R_{39} is S; and R_{40} is  or ;

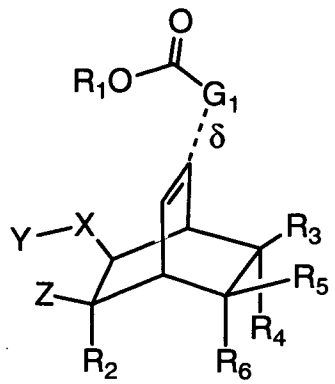
X is a direct bond or ;

Z is H, CN,  or ,

wherein R_a is S or O; R_b is -O-(C_1-C_{10})alkyl, -O-(C_2-C_{10})alkenyl, heterocyclyl, or heteroaryl; or

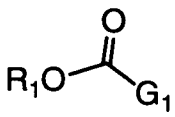
or a salt thereof.

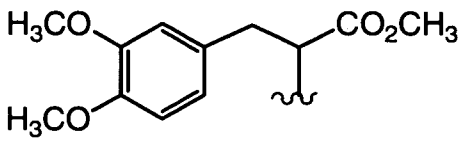
14. The compound of claim 13 having the structure

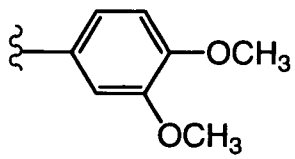


wherein

δ is present or absent;

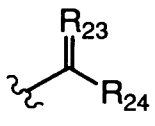
wherein when δ is absent,  is absent;

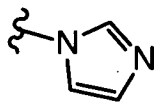
R_1 is H, methyl or ;

R_2 is H or ;

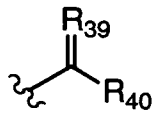
R_3 and R_4 are each $-OCH_3$;

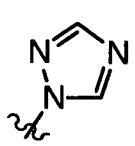
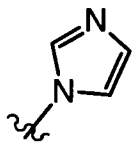
R_5 is H or OR_{21},

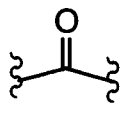
wherein R_{21} is ,

wherein R_{23} is S; and R_{24} is ; and

R_6 is OR_{37};

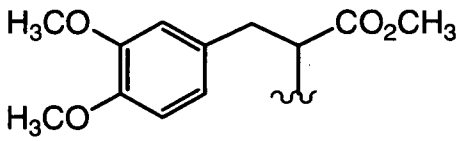
wherein R_{37} is ;

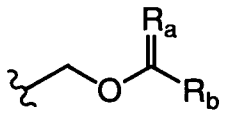
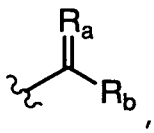
wherein R_{39} is S; and R_{40} is  or ;

X is a direct bond or ;

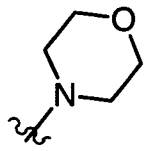
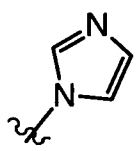
Y is H or OR_{42};

wherein R_{42} is methyl, $-CH_2CH=CH_2$ or

;

Z is H, CN,  or ,

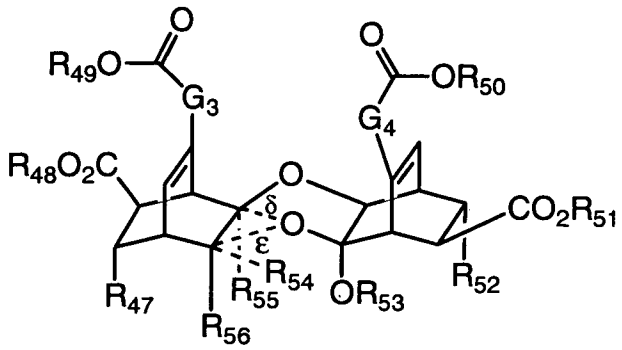
wherein R_a is S or O; R_b is $-OCH_3$, $-OCH(CH_3)_2$, $-OCH_2CH=CH_2$,

$-OCH_2CH_2CH_2CH_3$, , or ;

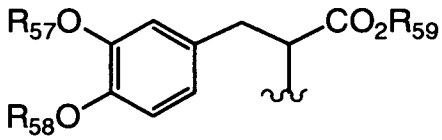
or a salt thereof.

15. The compound of claim 14 selected from the group consisting of Compound 64, 65, 66, 67, 68, 73, 74, 75, 76, 77, 78, 79, 80, and a pharmaceutically acceptable salt thereof.

16. A compound having the structure

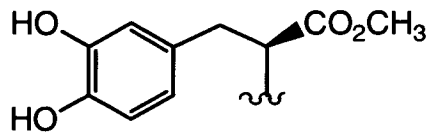


wherein ε and δ are present or absent;
wherein R_{54} and R_{55} are present or absent; and
when ε is present; δ and R_{54} are absent, and R_{55} is present; and
when δ is present; ε and R_{55} are absent, and R_{54} is present;

wherein G_3 and G_4 are each, independently, is C_{1-10} alkylene, C_{2-10} alkenylene, or C_{2-10} alkynylene;
R_{48}, R_{49}, R_{50}, and R_{51} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; or ,

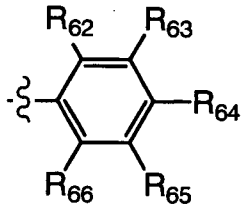
wherein R_{57} and R_{58} are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, unsubstituted or substituted aryl(C_{1-10})alkyl, or $-SO_2R_{60}$,

wherein R_{60} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

wherein R_{59} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and when R_{57} and R_{58} are H and R_{59} is CH_3, then R_{48}, R_{49}, R_{50}, or R_{51} is ; and

wherein R_{53} is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, unsubstituted or substituted aryl(C_{1-10})alkyl, or $-SO_2R_{61}$,

wherein R_{61} is C_{1-10} alkyl, or unsubstituted or substituted aryl;

R_{47} and R_{52} are each H, CN, or ,

wherein R_{62}, R_{63}, R_{64}, R_{65}, and R_{66} are each, independently, H, halogen, $-NO_2$, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; $-OR_{67}$, $-SR_{67}$, $-OSO_2R_{67}$, or $-NR_{67}R_{68}$,

wherein R_{67} and R_{68} are each, independently, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or unsubstituted or substituted aryl; and

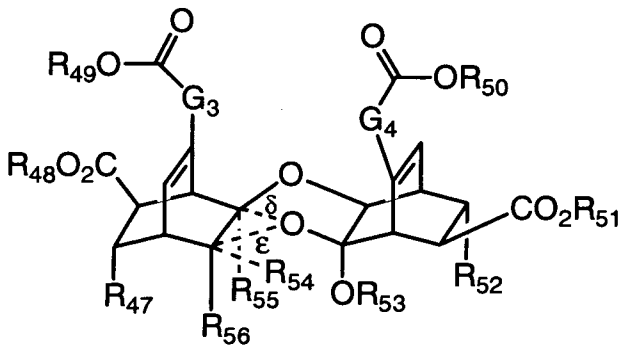
wherein R_{54} when present, R_{55} when present, and R_{56} are each, independently, H or OR_{69},

wherein R_{69} is H or C_{1-10} alkyl; or

wherein each occurrence of alkyl, alkylene, alkenyl, alkenylene, alkynyl, alkynylene is branched or unbranched, unsubstituted or substituted;

or a salt thereof.

17. The compound of claim 16 having the structure



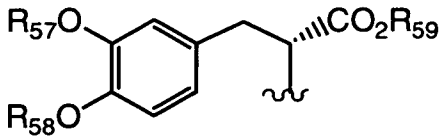
wherein ε and δ are present or absent;

wherein R_{54} and R_{55} are present or absent; and

when ε is present; δ and R_{54} are absent, and R_{55} is present; and

when δ is present; ε and R_{55} are absent, and R_{54} is present;

wherein G_3 and G_4 are each, independently, is C_{1-10} alkylene, C_{2-10} alkenylene, or C_{2-10} alkynylene;

R_{48}, R_{49}, R_{50}, and R_{51} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; or 

,

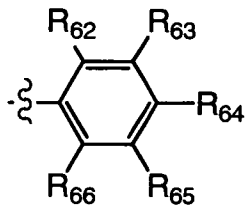
wherein R_{57} and R_{58} are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, unsubstituted or substituted aryl(C_{1-10})alkyl, or $-SO_2R_{60}$,

wherein R_{60} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

wherein R_{59} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and at least one of R_{57} and R_{58} is other than H; and

wherein R_{53} is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, unsubstituted or substituted aryl(C_{1-10})alkyl, or $-SO_2R_{61}$,

wherein R_{61} is C_{1-10} alkyl, or unsubstituted or substituted aryl;

R_{47} and R_{52} are each H, CN, or 

,

wherein R_{62}, R_{63}, R_{64}, R_{65}, and R_{66} are each, independently, H, halogen, $-NO_2$, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; $-OR_{67}$, $-SR_{67}$, $-OSO_2R_{67}$, or $-NR_{67}R_{68}$,

wherein R_{67} and R_{68} are each, independently, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or unsubstituted or substituted aryl; and

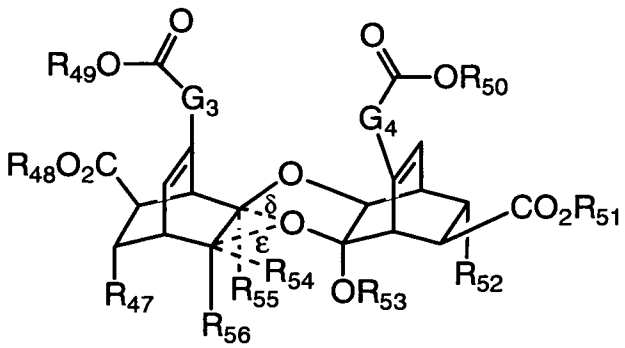
wherein R_{54} when present, R_{55} when present, and R_{56} are each, independently, H or OR_{69},

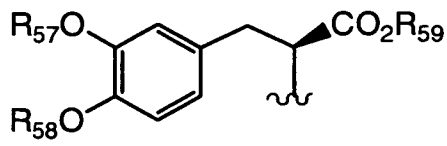
wherein R_{69} is H or C_{1-10} alkyl; or

wherein each occurrence of alkyl, alkylene, alkenyl, alkenylene, alkynyl, alkynylene is branched or unbranched, unsubstituted or substituted;

or a salt thereof.

18. The compound of claim 16 having the structure



wherein ε and δ are present or absent;
wherein R_{54} and R_{55} are present or absent; and
when ε is present; δ and R_{54} are absent, and R_{55} is present; and
when δ is present; ε and R_{55} are absent, and R_{54} is present;
wherein G_3 and G_4 are each, independently, is C_{1-10} alkylene, C_{2-10} alkenylene, or C_{2-10} alkynylene;
R_{48}, R_{49}, R_{50}, and R_{51} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; or 

,

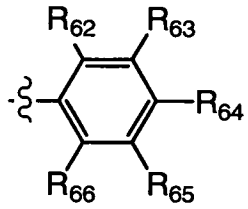
wherein R_{57} and R_{58} are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, unsubstituted or substituted aryl(C_{1-10})alkyl, or $-SO_2R_{60}$,

wherein R_{60} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

wherein R_{59} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

wherein R_{53} is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, unsubstituted or substituted aryl(C_{1-10})alkyl, or $-SO_2R_{61}$,

wherein R_{61} is C_{1-10} alkyl, or unsubstituted or substituted aryl;

R_{47} and R_{52} are each H, CN, or 

,

wherein R_{62}, R_{63}, R_{64}, R_{65}, and R_{66} are each, independently, H, halogen, $-NO_2$, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; $-OR_{67}$, $-SR_{67}$, $-OSO_2R_{67}$, or $-NR_{67}R_{68}$,

wherein R_{67} and R_{68} are each, independently, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or unsubstituted or substituted aryl; and

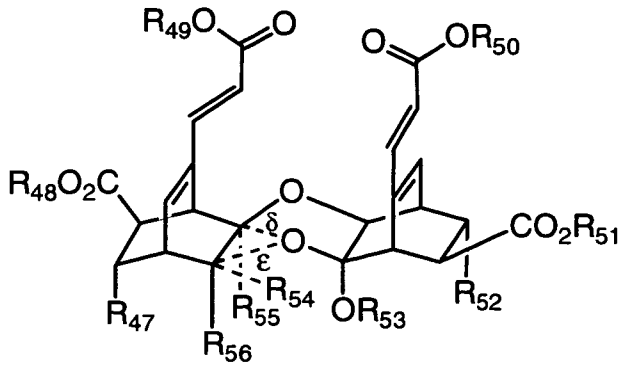
wherein R_{54} when present, R_{55} when present, and R_{56} are each, independently, H or OR_{69},

wherein R_{69} is H or C_{1-10} alkyl; or

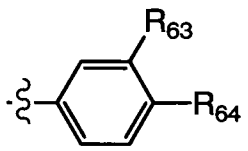
wherein each occurrence of alkyl, alkylene, alkenyl, alkenylene, alkynyl, alkynylene is branched or unbranched, unsubstituted or substituted;

or a salt thereof.

19. The compound of claim 16, 17, or 18 having the structure



wherein ε and δ are present or absent;
wherein R_{54} and R_{55} are present or absent; and
when ε is present; δ and R_{54} are absent, and R_{55} is present; and
when δ is present; ε and R_{55} are absent, and R_{54} is present;
R_{48}, R_{49}, R_{50}, and R_{51} are each CH_3;
R_{53} is H or CH_3;

R_{47} and R_{52} are each ,

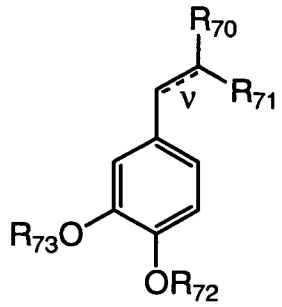
wherein R_{63} and R_{64} are each $-OCH_3$; and
wherein R_{54} when present, R_{55} when present, and R_{56} are each, independently, H or OR_{69},
wherein R_{69} is H or CH_3;

wherein each occurrence of alkyl, alkylene, alkenyl, alkenylene, alkynyl, alkynylene is branched or unbranched, unsubstituted or substituted;

or a salt thereof.

20. The compound of claim 19 selected from the group consisting of: Compound 43 and 48.

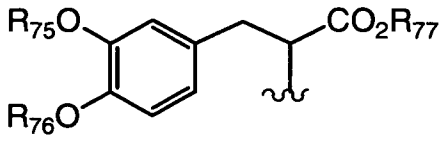
21. A compound having the structure



wherein ν is present or absent;

wherein R_{70} and R_{71} are each, independently, H, OH, $-CO_2R_{74}$,

wherein R_{74} is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl,



or ,

wherein R_{75} and R_{76} are independently H; C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; or $-SO_2R_{78}$,

wherein R_{78} is C_{1-10} alkyl; or unsubstituted or substituted aryl; and

wherein R_{77} is H; C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and at least one of R_{75} and R_{76} is other than H;

wherein R_{72} and R_{73} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; $-SO_2R_{79}$, or $-Si(R_{80})_3$,

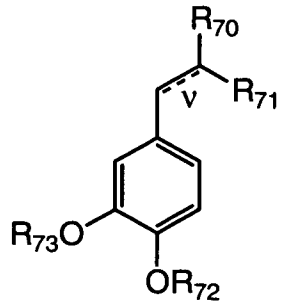
wherein R_{79} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

wherein each occurrence of R_{80} is, independently, C_{1-10} alkyl, or unsubstituted or substituted aryl; and when R_{74} is H or CH_3, R_{73} is other than H or Me; and

wherein each occurrence of alkyl, alkylene, alkenyl, alkenylene, alkynyl, or alkynylene is branched or unbranched, unsubstituted or substituted;

or a salt thereof.

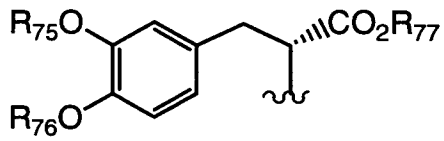
22. The compound of claim 21 having the structure



wherein ν is present or absent;

wherein R_{70} and R_{71} are each, independently, H, OH, $-CO_2R_{74}$,

wherein R_{74} is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl,

or ,

wherein R_{75} and R_{76} are independently H; C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; or $-SO_2R_{78}$,

wherein R_{78} is C_{1-10} alkyl; or unsubstituted or substituted aryl; and

wherein R_{77} is H; C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and at least one of R_{75} and R_{76} is other than H;

wherein R_{72} and R_{73} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; $-SO_2R_{79}$, or $-Si(R_{80})_3$,

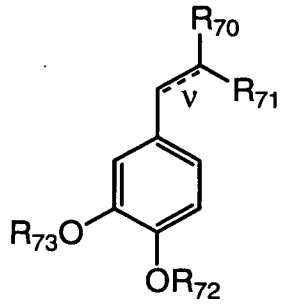
wherein R_{79} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

wherein each occurrence of R_{80} is, independently, C_{1-10} alkyl, or unsubstituted or substituted aryl; and when R_{74} is H or CH_3, R_{73} is other than H or Me; and

wherein each occurrence of alkyl, alkylene, alkenyl, alkenylene, alkynyl, or alkynylene is branched or unbranched, unsubstituted or substituted;

or a salt thereof.

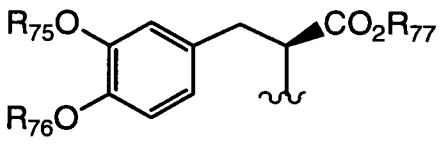
23. The compound of claim 22 having the structure



wherein ν is present or absent;

wherein R_{70} and R_{71} are each, independently, H, OH, $-CO_2R_{74}$,

wherein R_{74} is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl,



or ,

wherein R_{75} and R_{76} are independently H; C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; or $-SO_2R_{78}$,

wherein R_{78} is C_{1-10} alkyl; or unsubstituted or substituted aryl; and

wherein R_{77} is H; C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and at least one of R_{75} and R_{76} is other than H;

wherein R_{72} and R_{73} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; $-SO_2R_{79}$, or $-Si(R_{80})_3$,

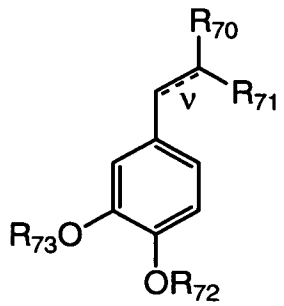
wherein R_{79} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

wherein each occurrence of R_{80} is, independently, C_{1-10} alkyl, or unsubstituted or substituted aryl; and when R_{74} is H or CH_3, R_{73} is other than H or Me; and

wherein each occurrence of alkyl, alkylene, alkenyl, alkenylene, alkynyl, or alkynylene is branched or unbranched, unsubstituted or substituted;

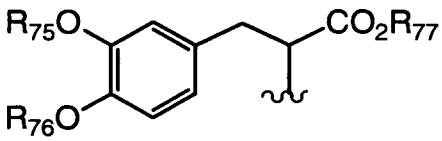
or a salt thereof.

24. The compound of claim 21, 22, or 23 having the structure

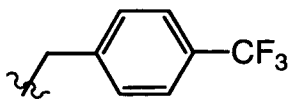


wherein ν is present or absent;

wherein R_{70} and R_{71} are each, independently, H, OH, $-CO_2R_{74}$,



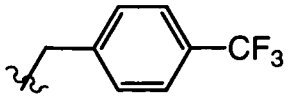
wherein R_{74} is H, CH_3, or ,



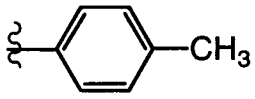
wherein R_{75} and R_{76} are each ; and

wherein R_{77} is CH_3;

wherein R_{72} and R_{73} are each, independently, H, CH_3,



, $-SO_2R_{79}$, or $-Si(R_{80})_3$,

wherein R_{79} is  ; and

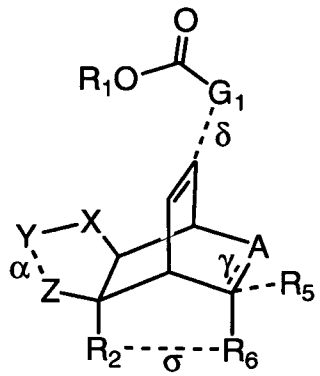
wherein each occurrence of R_{80} is, independently, CH_3 or t-butyl; and

wherein each occurrence of alkyl, alkylene, alkenyl, alkenylene, alkynyl, or alkynylene is branched or unbranched, unsubstituted or substituted;

or a salt thereof.

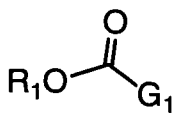
25. The compound of claim 24 selected from the group consisting of: Compound 14, 27, 28, 29, 31, and 32.

26. A process for preparing a compound having the structure



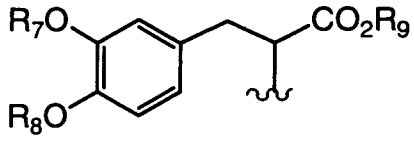
wherein

α, γ, δ and σ are each, independently, present or absent;

wherein when δ is absent,  is absent;

G_1 is C_{1-10} alkylene, C_{2-10} alkenylene, or C_{2-10} alkynylene;

R_1 is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or



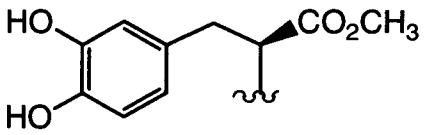
,

wherein R_7 and R_8 are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; or $-SO_2R_{10}$,

wherein R_{10} is C_{1-10} alkyl, or unsubstituted or substituted aryl;

R_9 is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

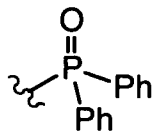
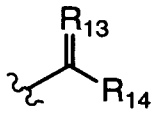
when R_7 and R_8 are H and R_9 is CH_3, then R_1 is



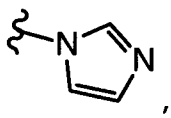
; and

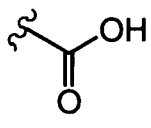
when γ is present; R_5 is absent and A is C-R_4,

wherein R_4 is H, halogen, or OR_{11},

wherein R_{11} is H, C_{1-10} alkyl, $-CH_2SH$, $-BHCH_2CH_3$, $-CH{=}SH$, , $-SO_2R_{12}$, , or $-Si(R_{15})_3$;

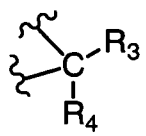
wherein R_{12} and each occurrence of R_{15} is C_{1-10} alkyl; or unsubstituted or substituted aryl; and

R_{13} is S or O; and R_{14} is $-SCH_3$, , or



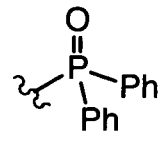
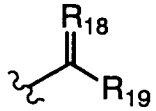
; and

when γ is absent; R_5 is present and A is a direct bond or

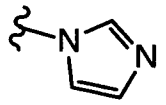
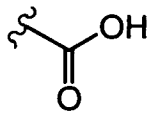


;

wherein R_3 and R_4 are each, independently, H, halogen, or OR_{16};

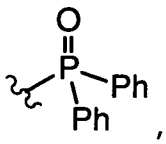
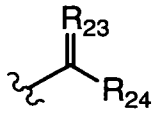
wherein R_{16} is H, C_{1-10} alkyl, $-CH_2SH$, $-BHCH_2CH_3$, $-CH{=}SH$, , $-SO_2R_{17}$, , or $-Si(R_{20})_3$;

wherein R_{17} and each occurrence of R_{20} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

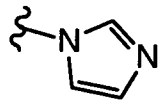
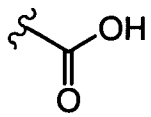
R_{18} is S or O; and R_{19} is $-SCH_3$, , or ; or

R_3 and R_4 taken together form =O; and

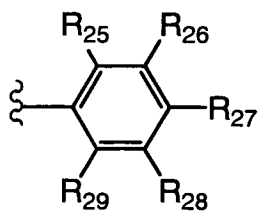
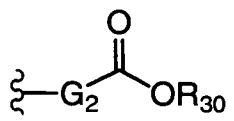
wherein R_5 is H, halogen, or OR_{21},

wherein R_{21} is H, C_{1-10} alkyl, $-CH_2SH$, $-BHCH_2CH_3$, $-CH{=}SH$, , $-SO_2R_{22}$, , or $-Si(R_{25})_3$,

wherein R_{22} and each occurrence of R_{25} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

R_{23} is S or O; and R_{24} is $-SCH_3$, , or ; and

when σ is absent;

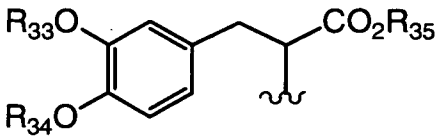
R_2 is H, , or ;

wherein R_{25}, R_{26}, R_{27}, R_{28}, and R_{29} are each, independently, H, halogen, $-NO_2$, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; $-OR_{31}$, $-SR_{31}$, $-OSO_2R_{31}$, or $-NR_{31}R_{32}$,

wherein R_{31} and R_{32} are each, independently, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or unsubstituted or substituted aryl;

wherein G_2 is C_{1-10} alkylene, C_{2-10} alkenylene, or C_{2-10} alkynylene; and

R_{30} is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or



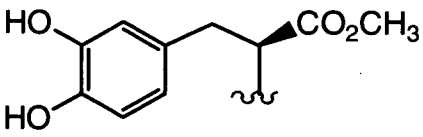
,

wherein R_{33} and R_{34} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; or $-SO_2R_{36}$,

wherein R_{36} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

wherein R_{35} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

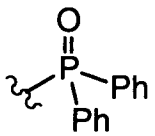
when R_{33} and R_{34} are H and R_{35} is CH_3, then R_{30} is



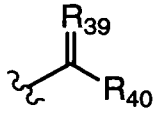
; and

R_6 is H, halogen, or OR_{37};

wherein R_{37} is H, C_{1-10} alkyl, $-CH_2SH$, $-BHCH_2CH_3$, $-CH{=}SH$,



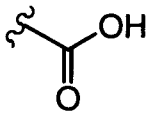
, $-SO_2R_{38}$,



, or $-Si(R_{41})_3$;

wherein R_{38} and each occurrence of R_{41} is C_{1-10} alkyl; or unsubstituted or substituted aryl;

R_{39} is S or O; and R_{40} is $-SCH_3$; -NH-aryl, heteroaryl,

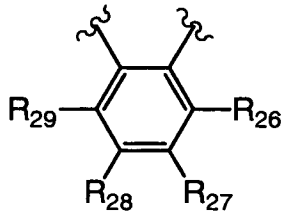


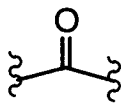
heterocyclyl; or ; or

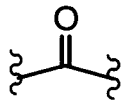
R_5 when present and R_6 taken together form =O; or

R_4 joined to R_6 form a 5-membered heterocyclic ring; and

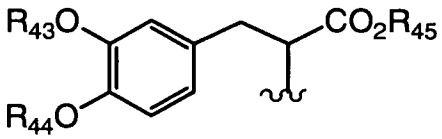
when σ is present;

R_2 is  ; and R_6 is a direct bond or ; and

wherein X is a direct bond, , or $C(OMe)_2$;

Y is H or OR_{42}; or when α is present, Y is ;

wherein R_{42} is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl,



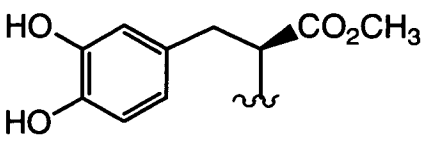
or ,

wherein R_{43} and R_{44} are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; or $-SO_2R_{46}$,

wherein R_{46} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

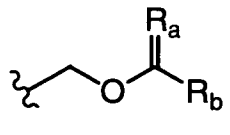
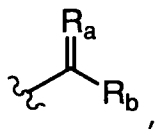
R_{45} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl;

and when R_{43} and R_{44} are H and R_{45} is CH_3, then R_{42} is



; or

wherein each occurrence of alkyl, alkylene, alkenyl, alkenylene, alkynyl, or alkynylene is branched or unbranched, unsubstituted or substituted;

Z is H, CN,  or ,

wherein R_a is S or O; R_b is -O-(C_1-C_{10})alkyl, -O-(C_2-C_{10})alkenyl, heterocyclyl, or heteroaryl; or

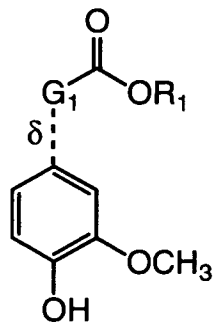
when α is present, Z is -CH=CH-;

and

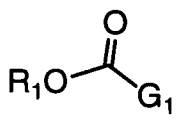
when α is present, R_1 is other than methyl;

comprising:

a) contacting a compound having the structure

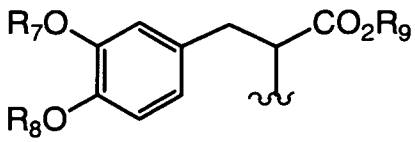
,

wherein

when δ is absent,  is absent;

G_1 is C_{1-10} alkylene, C_{2-10} alkenylene, or C_{2-10} alkynylene;

R_1 is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or

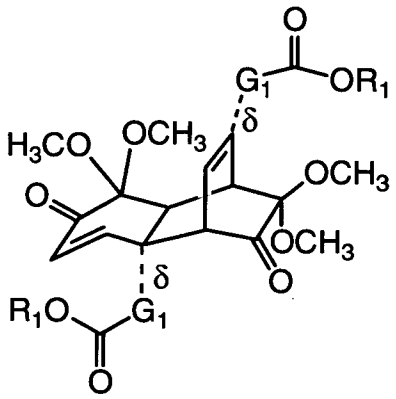
,

wherein R_7 and R_8 are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; or $-SO_2R_{10}$,

wherein R_{10} is C_{1-10} alkyl, or unsubstituted or substituted aryl;

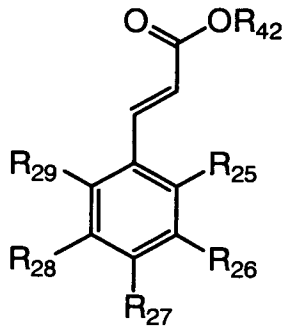
R_9 is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl;

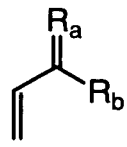
with a first suitable oxidizing agent in the presence of methanol so as to form the compound having the structure



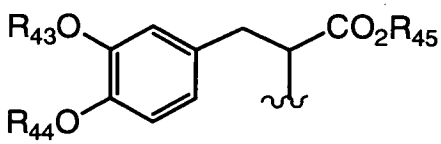
;

b) contacting the product of step a) with a compound having the structure



, NC-CH=CH_2, or 

wherein R_{42} is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl,



or

,

wherein R_{43} and R_{44} are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; or $-SO_2R_{46}$,

wherein R_{46} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

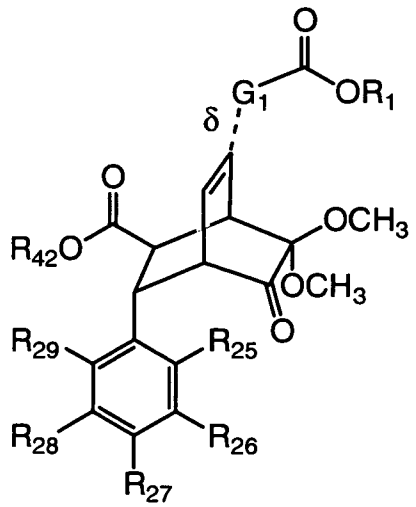
R_{45} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl;

R_{25}, R_{26}, R_{27}, R_{28}, and R_{29} are each, independently, H, halogen, $-NO_2$, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; $-OR_{31}$, $-SR_{31}$, $-OSO_2R_{31}$, or $-NR_{31}R_{32}$,

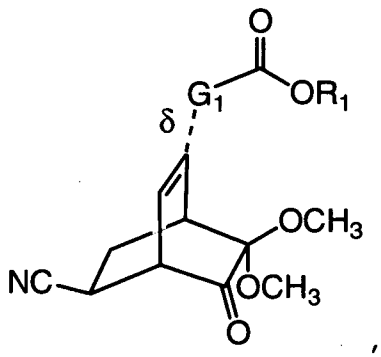
wherein R_{31} and R_{32} are each, independently, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or unsubstituted or substituted aryl; and

wherein R_a is S or O; R_b is -O-(C_1-C_{10})alkyl, -O-(C_2-C_{10})alkenyl, heterocyclyl, or heteroaryl;

in the presence of a first suitable energy source so as to form the compound having the structure

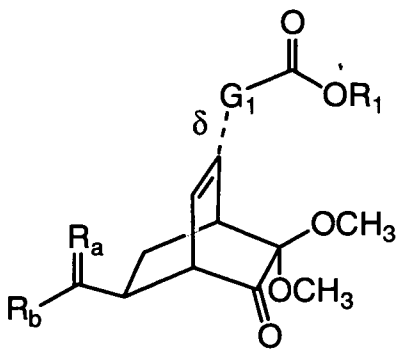


,



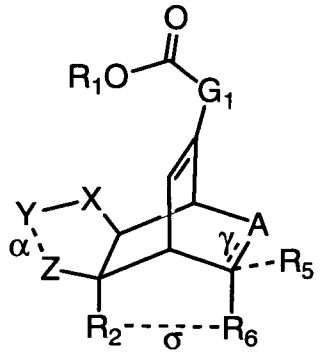
,

or



.

27. The process of claim 26 for preparing a compound having the structure

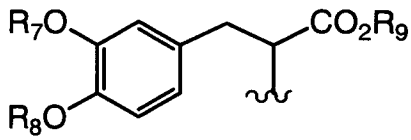


wherein

α, γ, and σ are each, independently, present or absent;

G_1 is C_{1-10} alkylene, C_{2-10} alkenylene, or C_{2-10} alkynylene;

R_1 is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or



,

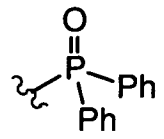
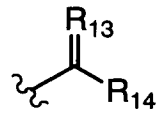
wherein R_7 and R_8 are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; or $-SO_2R_{10}$,

wherein R_{10} is C_{1-10} alkyl, or unsubstituted or substituted aryl;

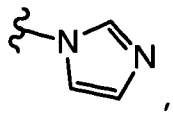
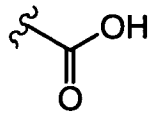
R_9 is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

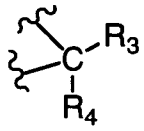
when γ is present; R_5 is absent and A is C-R_4,

wherein R_4 is H, halogen, or OR_{11},

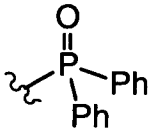
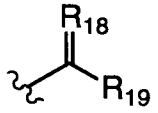
wherein R_{11} is H, C_{1-10} alkyl, $-CH_2SH$, $-BHCH_2CH_3$, $-CH{=}SH$,  , $-SO_2R_{12}$,  , or $-Si(R_{15})_3$;

wherein R_{12} and each occurrence of R_{15} is C_{1-10} alkyl; or unsubstituted or substituted aryl; and

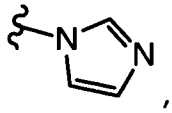
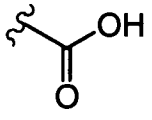
R_{13} is S or O; and R_{14} is $-SCH_3$, , or ; and

when γ is absent; R_5 is present and A is a direct bond or ;

wherein R_3 and R_4 are each, independently, H, halogen, or OR_{16};

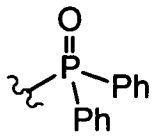
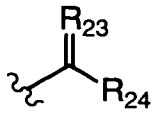
wherein R_{16} is H, C_{1-10} alkyl, $-CH_2SH$, $-BHCH_2CH_3$, $-CH{=}SH$, , $-SO_2R_{17}$, , or $-Si(R_{20})_3$;

wherein R_{17} and each occurrence of R_{20} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

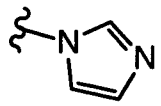
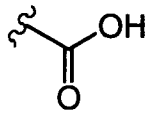
R_{18} is S or O; and R_{19} is $-SCH_3$, , or ; or

R_3 and R_4 taken together form =O; and

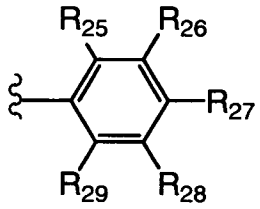
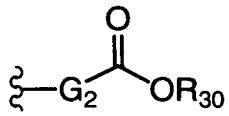
wherein R_5 is H, halogen, or OR_{21},

wherein R_{21} is H, C_{1-10} alkyl, $-CH_2SH$, $-BHCH_2CH_3$, $-CH{=}SH$, , $-SO_2R_{22}$, , or $-Si(R_{25})_3$,

wherein R_{22} and each occurrence of R_{25} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

R_{23} is S or O; and R_{24} is $-SCH_3$, , or ; and

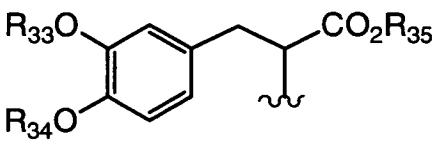
when σ is absent;

R_2 is H, , or ;

wherein R_{25}, R_{26}, R_{27}, R_{28}, and R_{29} are each, independently, H, halogen, $-NO_2$, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; $-OR_{31}$, $-SR_{31}$, $-OSO_2R_{31}$, or $-NR_{31}R_{32}$,

wherein R_{31} and R_{32} are each, independently, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or unsubstituted or substituted aryl;

wherein G_2 is C_{1-10} alkylene, C_{2-10} alkenylene, or C_{2-10} alkynylene; and

R_{30} is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or ,

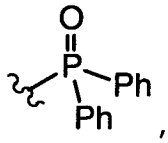
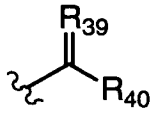
wherein R_{33} and R_{34} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; or $-SO_2R_{36}$,

wherein R_{36} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

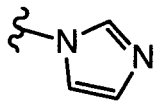
wherein R_{35} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

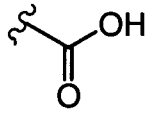
R_6 is H, halogen, or OR_{37};

wherein R_{37} is H, C_{1-10} alkyl, $-CH_2SH$, $-BHCH_2CH_3$, $-CH=SH$,


, $-SO_2R_{38}$, 
, or $-Si(R_{41})_3$;

wherein R_{38} and each occurrence of R_{41} is C_{1-10} alkyl; or unsubstituted or substituted aryl;

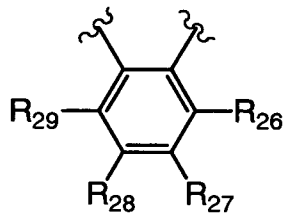
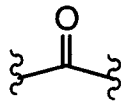
R_{39} is S or O; and R_{40} is $-SCH_3$; 
; or


; or

R_5 when present and R_6 taken together form =O; or

R_4 joined to R_6 form a 5-membered heterocyclic ring; and

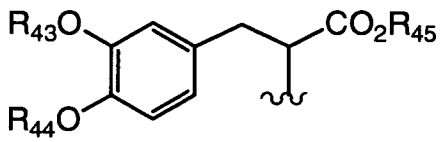
when σ is present;

R_2 is 
; and R_6 is a direct bond or 
; and

wherein X is a direct bond, 
, or $C(OMe)_2$;

Y is H or OR_{42}; or when α is present, Y is 
;

wherein R_{42} is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl,

or 
,

wherein R_{43} and R_{44} are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; or $-SO_2R_{46}$,

wherein R_{46} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

R_{45} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; or

wherein each occurrence of alkyl, alkylene, alkenyl, alkenylene, alkynyl, or alkynylene is branched or unbranched, unsubstituted or substituted;

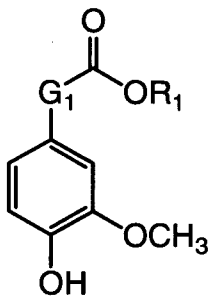
Z is H or CN; or when α is present, Z is -CH=CH-; and

when α is present, R_1 is other than methyl;

or a salt thereof;

comprising:

a) contacting a compound having the structure

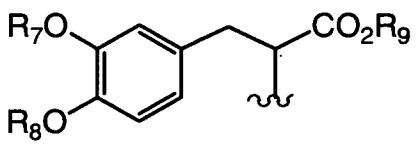


,

wherein

G_1 is C_{1-10} alkylene, C_{2-10} alkenylene, or C_{2-10} alkynylene;

R_1 is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or



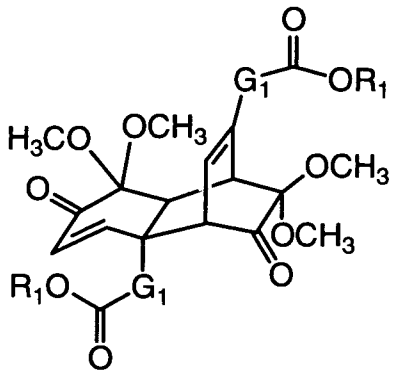
,

wherein R_7 and R_8 are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; or $-SO_2R_{10}$,

wherein R_{10} is C_{1-10} alkyl, or unsubstituted or substituted aryl;

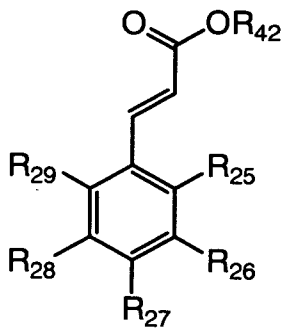
R_9 is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl;

with a first suitable oxidizing agent in the presence of methanol so as to form the compound having the structure

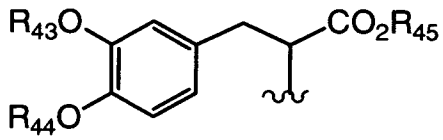


;

b) contacting the product of step a) with a compound having the structure



wherein R_{42} is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl,



or ,

wherein R_{43} and R_{44} are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; or $-SO_2R_{46}$,

wherein R_{46} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

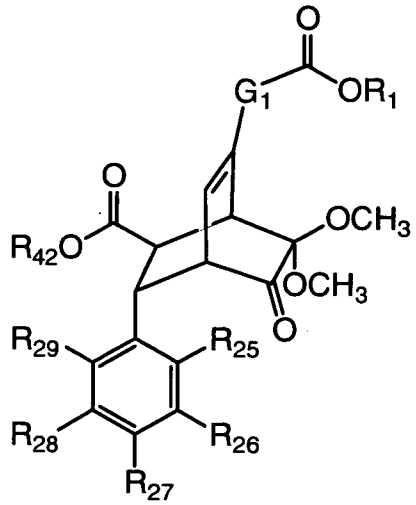
R_{45} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl;

R_{25}, R_{26}, R_{27}, R_{28}, and R_{29} are each, independently, H, halogen, $-NO_2$, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl;

unsubstituted or substituted aryl(C_{1-10})alkyl; $-OR_{31}$, $-SR_{31}$, $-OSO_2R_{31}$, or $-NR_{31}R_{32}$,

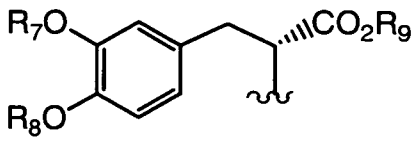
wherein R_{31} and R_{32} are each, independently, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or unsubstituted or substituted aryl;

in the presence of a first suitable energy source so as to form the compound having the structure



28. The process of claim 27,

wherein R_1 is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or



,

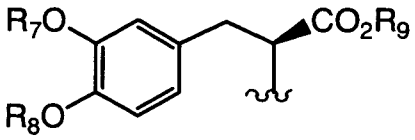
wherein R_7 and R_8 are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, unsubstituted or substituted aryl(C_{1-10})alkyl, or $-SO_2R_{10}$,

wherein R_{10} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

R_9 is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl.

29. The process of claim 27,

wherein R_1 is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or



,

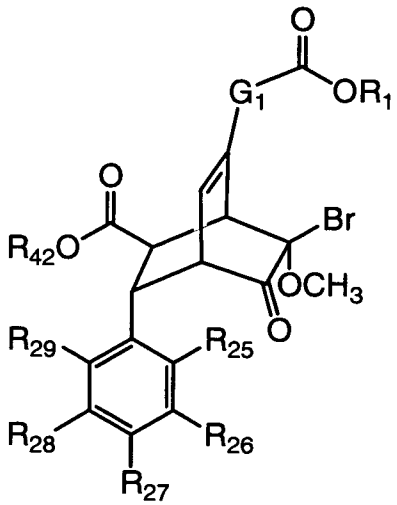
wherein R_7 and R_8 are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, unsubstituted or substituted aryl(C_{1-10})alkyl, or $-SO_2R_{10}$,

wherein R_{10} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

R_9 is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl.

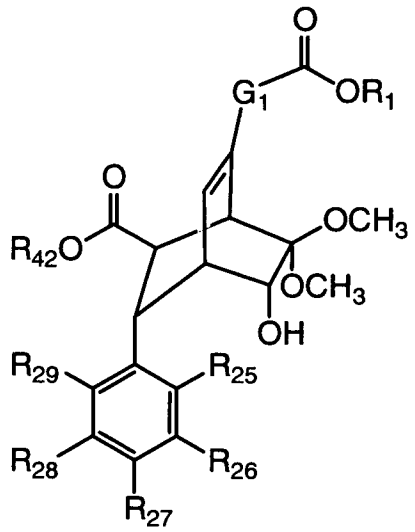
30. The process of claim 27, 28, or 29, further comprising:

c) contacting the product of step b) with BBr_3 so to form a compound having the structure



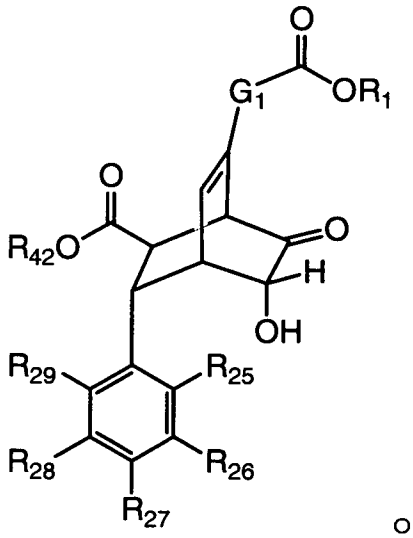
31. The process of claim 27, 28, or 29, further comprising:

c) contacting the product of step b) with a first suitable hydride reducing agent so as to form a compound having the structure

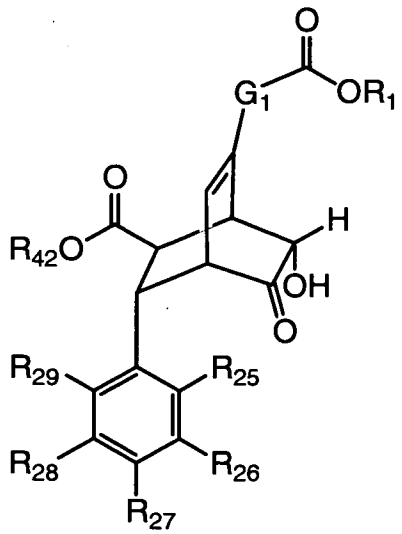


32. The process of claim 31 further comprising:

d) exposing the product of step c) to a first suitable Bronsted acid so as to form a compound having the structure

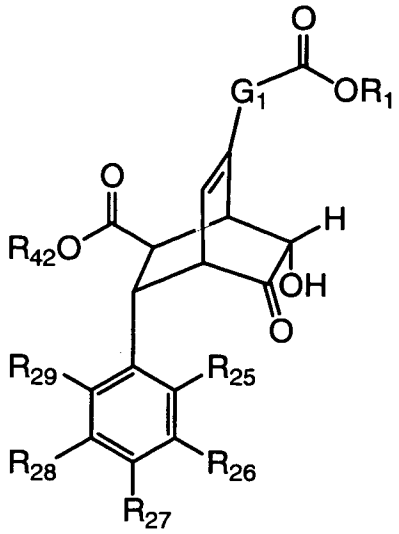


or



33. The process of claim 32 further comprising:

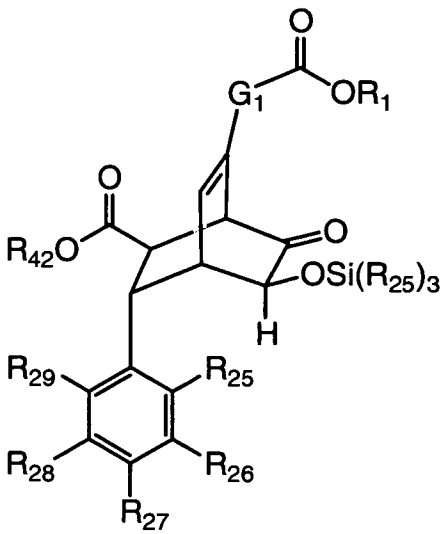
e) contacting the product of step d) having the structure



with a second suitable hydride reducing agent;

f) contacting the product of step e) with a suitable silylating agent;

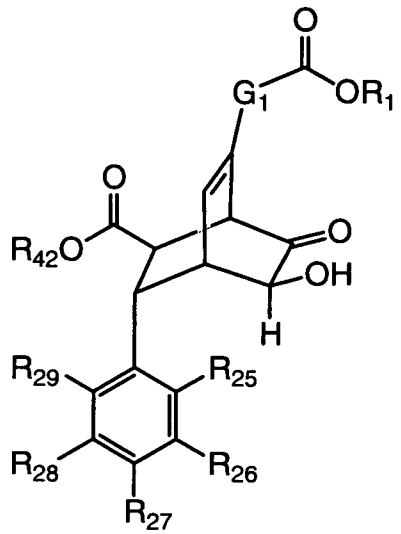
g) contacting the product of step f) with a second suitable oxidizing agent so as to form a compound having the structure



, wherein each occurrence of R_{25} is C_{1-10} alkyl; or unsubstituted or substituted aryl.

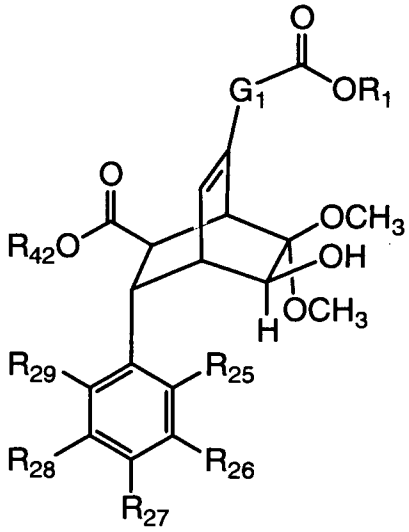
34. The process of claim 33 further comprising

h) exposing the product of step g) to tetra-n-butylammonium fluoride so as to form a compound having the structure



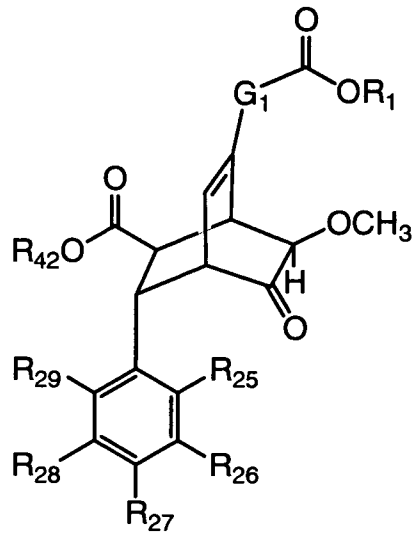
35. The process of claim 33 further comprising

h) exposing the product of step g) to a second suitable Bronsted acid in the presence of methanol so as to form a compound having the structure



36. The process of claim 35 further comprising:

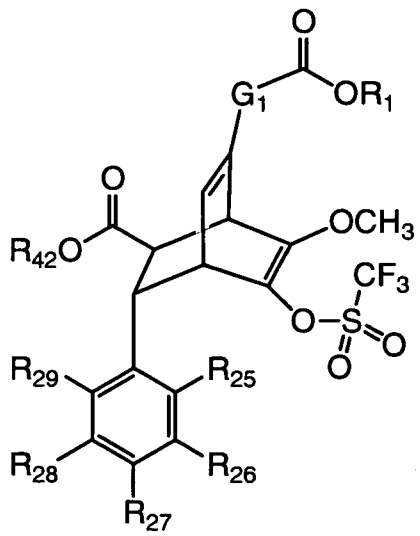
i) exposing the product of step h) to a second suitable energy source so as to form a compound having the structure



37. The process of claim 35 further comprising:

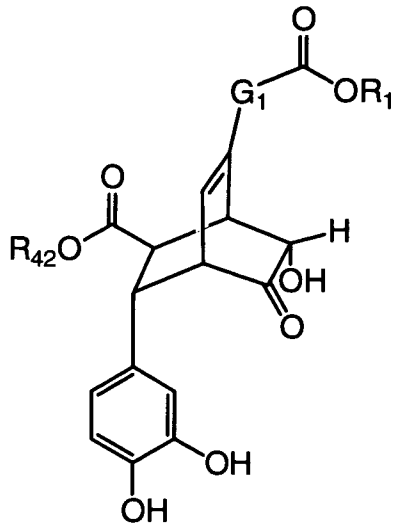
i) exposing the product of step h) to a third suitable Bronsted acid;

j) contacting the product of step i) with Tf_2NPh in the presence of a base so as to form a compound having the structure

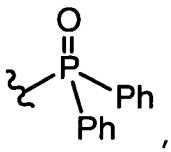
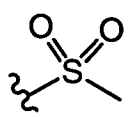
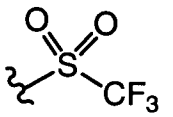
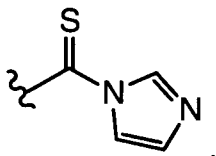
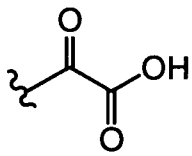
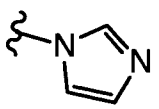
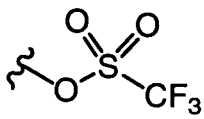


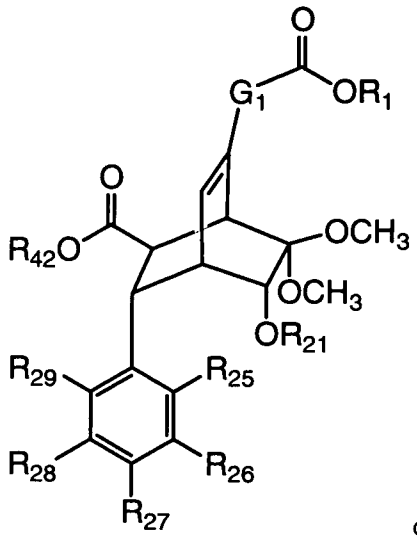
38. The process of claim 32 further comprising:

e) exposing the product of step d) to a first suitable Lewis acid so as to from a compound having the structure

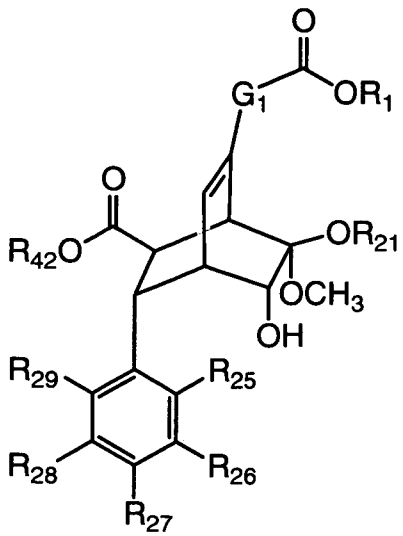


39. The process of claim 31 further comprising:

d) exposing the product of step c) to a compound having the structure R_{21}-L, wherein R_{16} is , , , , or ; and L is Cl, , or ; in the presence of a base so as to form a compound having the structure



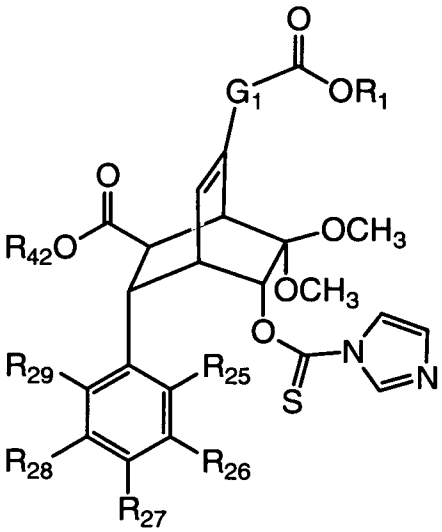
or



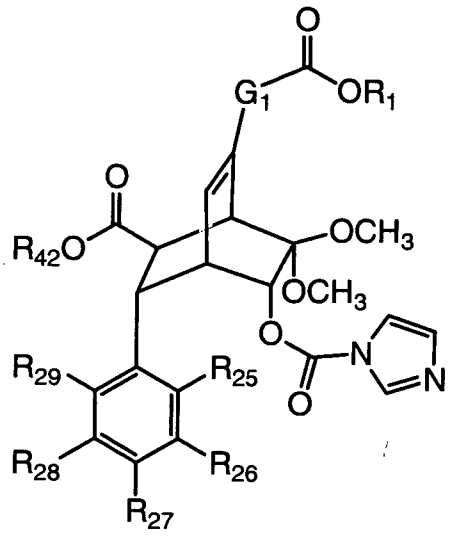
.

40. The process of 39 further comprising:

e) contacting the product of step d) having the structure

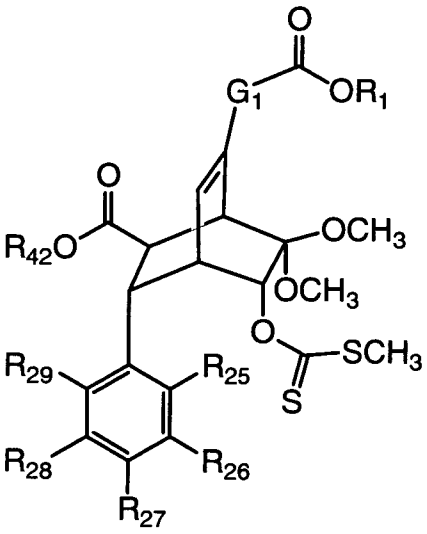


with Et_3B and nBu_3SnH in the presence of O_2 so as to form a compound having the structure



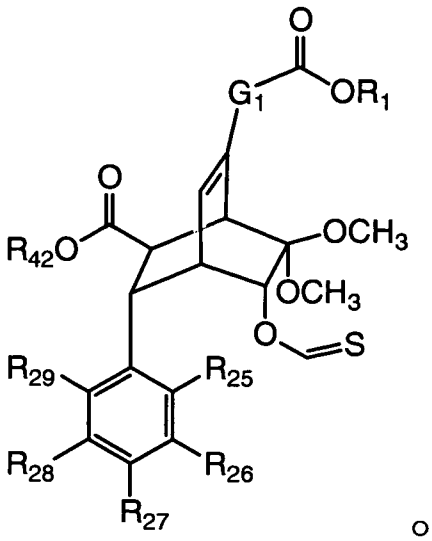
41. The process of claim 31 further comprising:

d) exposing the product of step c) to a base and carbon disulfide followed by methyl iodide so as to form a compound having the structure

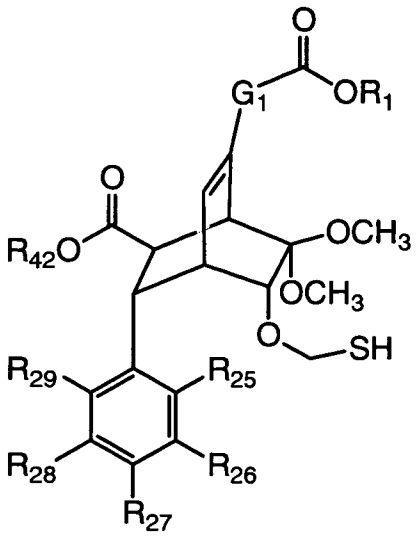


42. The process of claim 41 further comprising:

e) exposing the product of step d) to PhSeSePh in the presence of AIBN and nBu_3SnH so as to form a compound having the structure



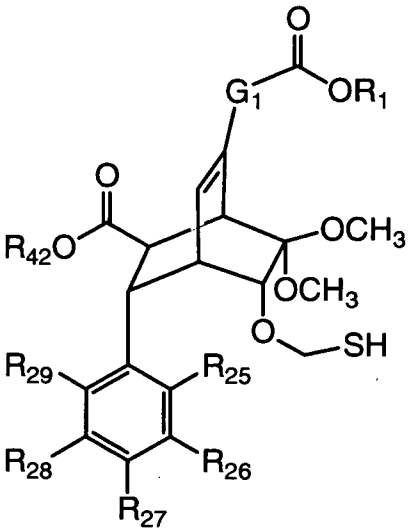
or



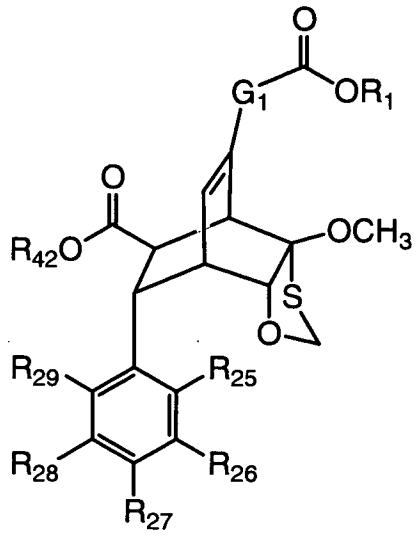
.

43. The process of 42 further comprising:

f) exposing the product of step e) having the structure

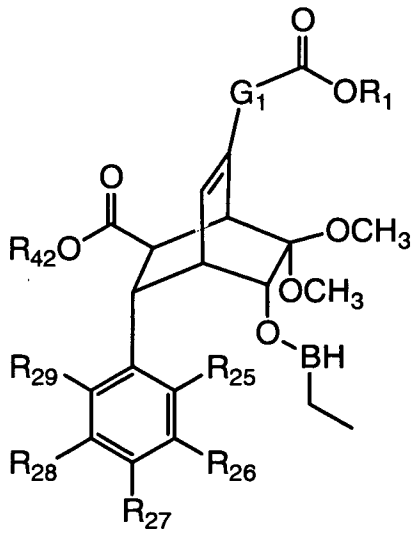


to HCl so as to form a compound having the structure



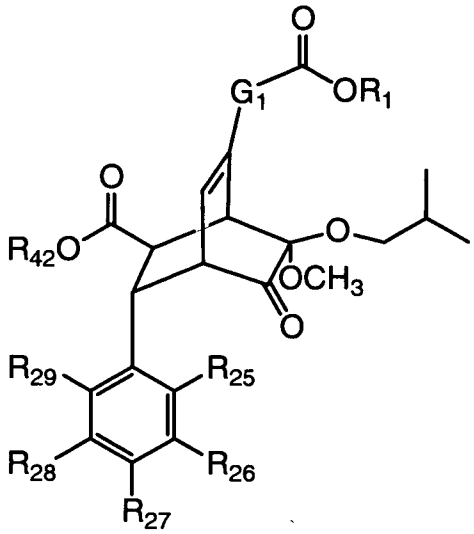
44. The process of claim 41 further comprising:

e) contacting the product of step d) with Et_3B in the presence of O_2 so as to form a compound having the structure



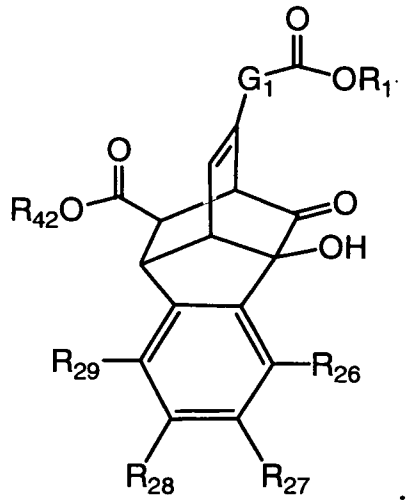
45. The process of claim 27, 28, or 29, further comprising:

c) contacting the product of step b) with i-$Bu_2Al(OiPr)$ so as to form a compound having the structure



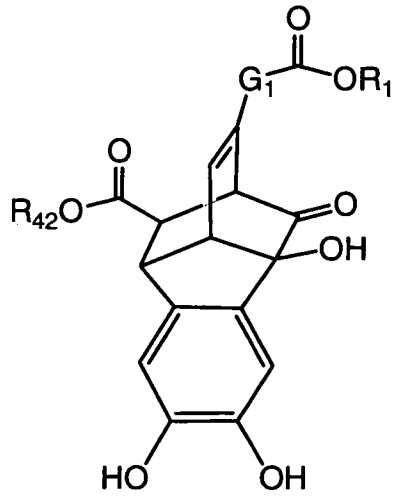
46. The process of claim 27, 28, or 29, further comprising:

c) exposing the product of step b) to a first suitable Lewis acid so as to form a compound having the structure



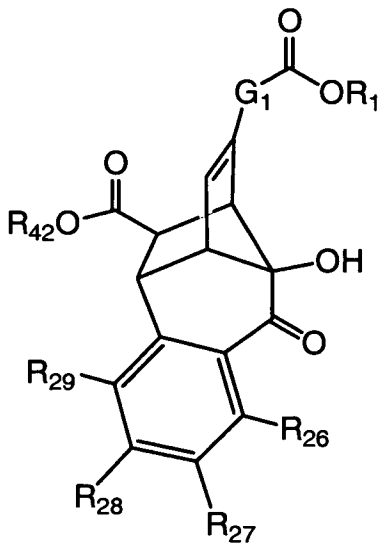
47. The process of claim 46 further comprising:

d) contacting the product of step c) with a second suitable Lewis acid so as to form a compound having the structure



48. The process of claim 46 further comprising:

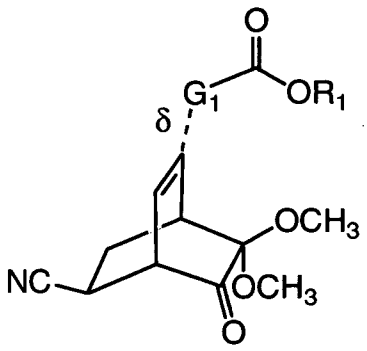
d) contacting the product of step c) with a second suitable Lewis acid so as to form a compound having the structure



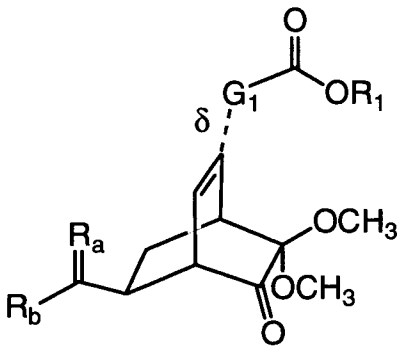
49. The process of any one of claims 27, 28, or 30-48 wherein the compound prepared is selected from a group consisting of: Compound 3, 4, 21, 23, 24, 25, 26, 33, 34, 35, 36, 37, 39, 40, 42, 44, 45, 47, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, and 63.

50. The process of claim 26 further comprising:

c) contacting the product of step b) having the structure



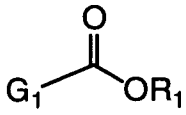
or



,

wherein

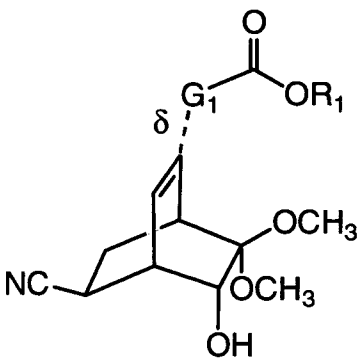
δ is present or absent;

wherein when δ is present, 

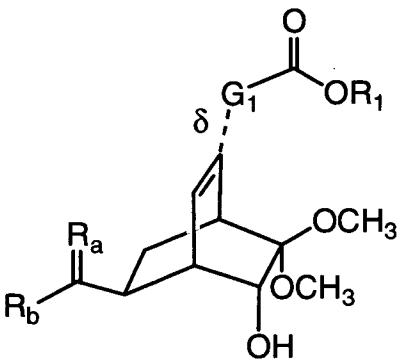
is present;

R_a is S or O; R_b is -O-(C_1-C_{10})alkyl, -O-(C_2-C_{10})alkenyl, heterocyclyl, or heteroaryl;

with a first suitable hydride reducing agent so as to form a compound having the structure



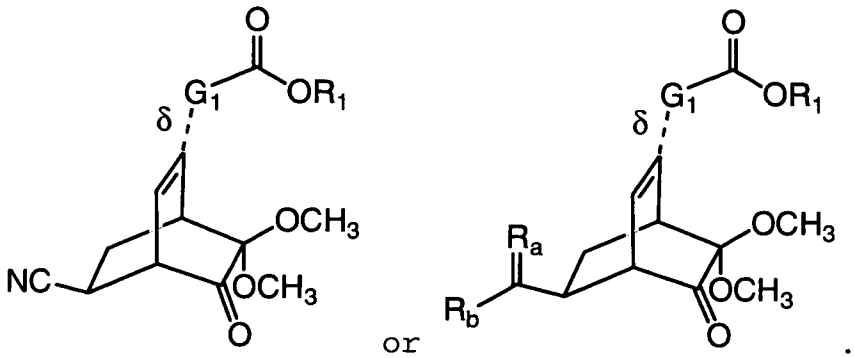
or



.

51. The process of claim 50 further comprising:

d) exposing the product of step c) to a first suitable Bronsted acid so as to form a compound having the structure

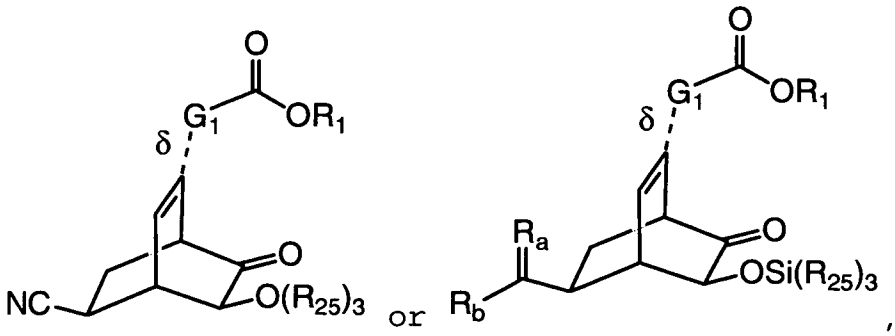


52. The process of claim 51 further comprising:

e) contacting the product of step d) with a second suitable hydride reducing agent;

f) contacting the product of step e) with a suitable silylating agent;

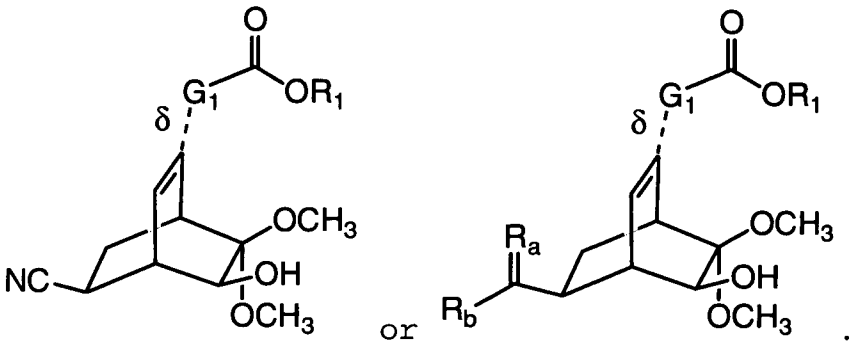
g) contacting the product of step f) with a second suitable oxidizing agent so as to form a compound having the structure



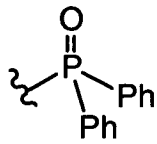
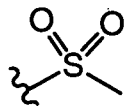
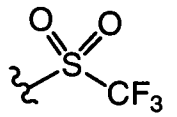
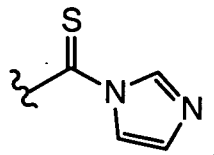
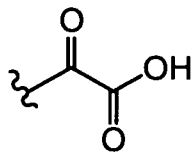
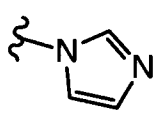
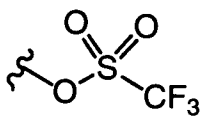
wherein each occurrence of R_{25} is C_{1-10} alkyl; or unsubstituted or substituted aryl.

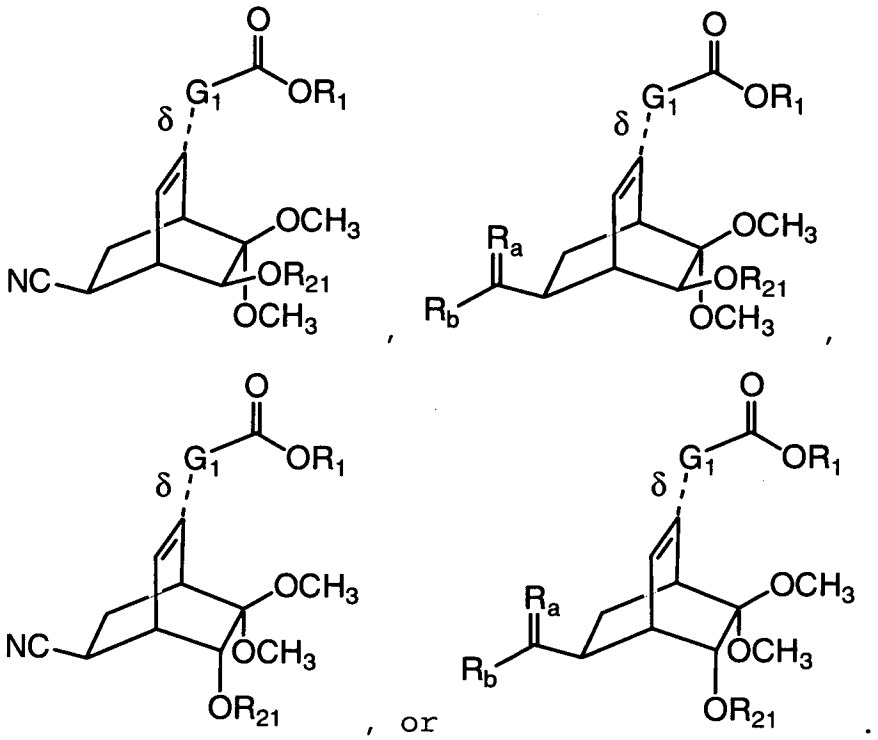
53. The process of claim 52 further comprising

h) exposing the product of step g) to a second suitable Bronsted acid in the presence of methanol so as to form a compound having the structure

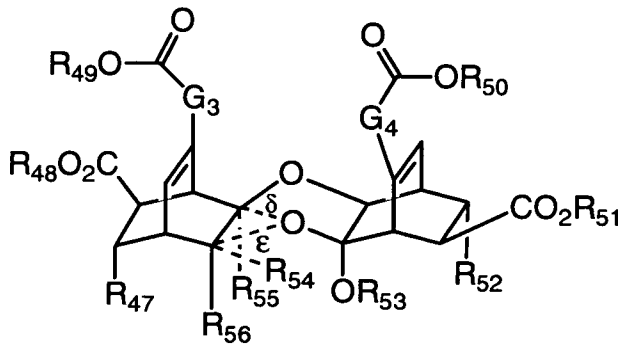


54. The process of claim 50 or 53 further comprising:

exposing the final product to a compound having the structure R_{21}-L, wherein R_{16} is , , , , or ; and L is Cl, , or ; in the presence of a base so as to form a compound having the structure



55. A process for preparing a compound having the structure



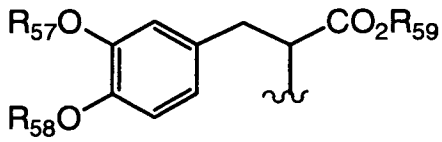
wherein ε and δ are present or absent;

wherein R_{54} and R_{55} are present or absent; and

when ε is present; δ and R_{54} are absent, and R_{55} is present; and

when δ is present; ε and R_{55} are absent, and R_{54} is present;

wherein G_3 and G_4 are each, independently, is C_{1-10} alkylene, C_{2-10} alkenylene, or C_{2-10} alkynylene;

R_{48}, R_{49}, R_{50}, and R_{51} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; or ,

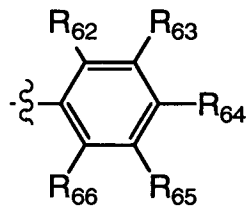
wherein R_{57} and R_{58} are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, unsubstituted or substituted aryl(C_{1-10})alkyl, or $-SO_2R_{60}$,

wherein R_{60} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

wherein R_{59} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

wherein R_{53} is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, unsubstituted or substituted aryl(C_{1-10})alkyl, or $-SO_2R_{61}$,

wherein R_{61} is C_{1-10} alkyl, or unsubstituted or substituted aryl;

R_{47} and R_{52} are each H, CN, or ,

wherein R_{62}, R_{63}, R_{64}, R_{65}, and R_{66} are each, independently, H, halogen, $-NO_2$, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; $-OR_{67}$, $-SR_{67}$, $-OSO_2R_{67}$, or $-NR_{67}R_{68}$,

wherein R_{67} and R_{68} are each, independently, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or unsubstituted or substituted aryl; and

wherein R_{54} when present, R_{55} when present, and R_{56} are each, independently, H or OR_{69},

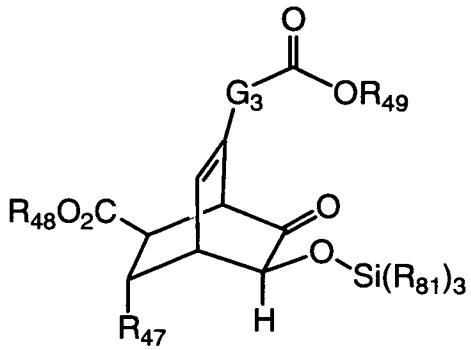
wherein R_{69} is H or C_{1-10} alkyl; or

wherein each occurrence of alkyl, alkylene, alkenyl, alkenylene, alkynyl, alkynylene is branched or unbranched, unsubstituted or substituted;

or a salt thereof;

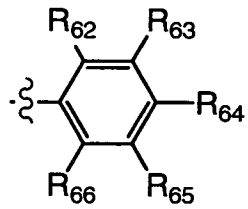
comprising:

a) contacting a compound having the structure



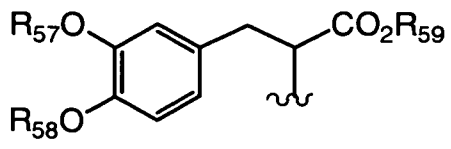
,

wherein G_3 is C_{1-10} alkylene, C_{2-10} alkenylene, or C_{2-10} alkynylene;

R_{47} is H, CN, or ,

wherein R_{62}, R_{63}, R_{64}, R_{65}, and R_{66} are each, independently, H, halogen, $-NO_2$, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; $-OR_{67}$, $-SR_{67}$, $-OSO_2R_{67}$, or $-NR_{67}R_{68}$,

wherein R_{67} and R_{68} are each, independently, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or unsubstituted or substituted aryl;

R_{48} and R_{49} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; or ,

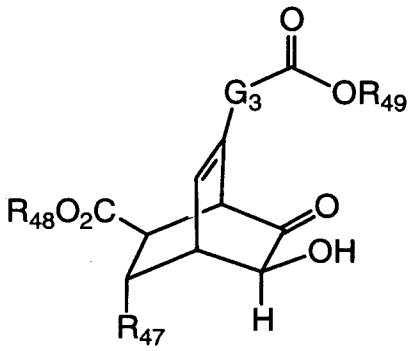
wherein R_{57} and R_{58} are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, unsubstituted or substituted aryl(C_{1-10})alkyl, or $-SO_2R_{60}$,

wherein R_{60} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

wherein R_{59} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

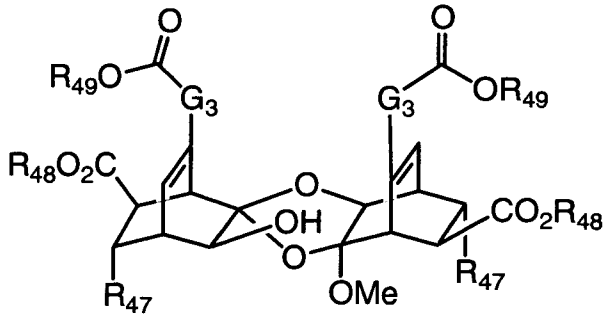
wherein each occurrence of R_{81} is, independently, C_{1-10} alkyl, or unsubstituted or substituted aryl;

with tetra-n-butylammonium fluoride so as to form a compound having the structure



;

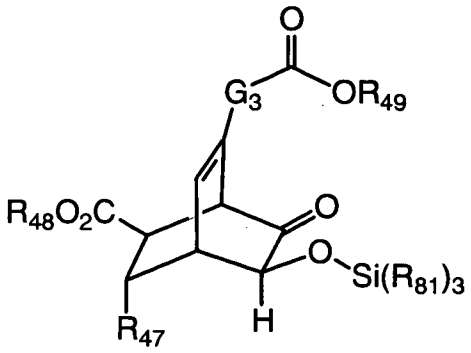
b) contacting the product of step a) with sodium hydride so as to form a compound having the structure



;

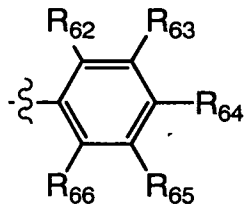
or

a') contacting a compound having the structure



,

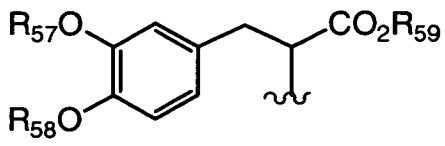
wherein G_3 is C_{1-10} alkylene, C_{2-10} alkenylene, or C_{2-10} alkynylene;



R_{47} is H, CN, or , ,

wherein R_{62}, R_{63}, R_{64}, R_{65}, and R_{66} are each, independently, H, halogen, $-NO_2$, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; $-OR_{67}$, $-SR_{67}$, $-OSO_2R_{67}$, or $-NR_{67}R_{68}$,

wherein R_{67} and R_{68} are each, independently, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or unsubstituted or substituted aryl;

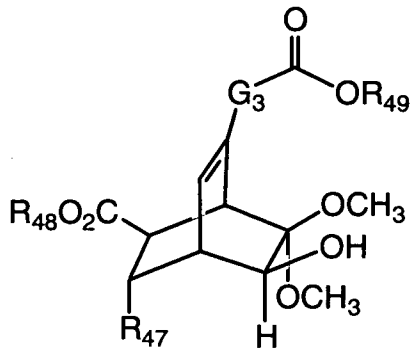
R_{48} and R_{49} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; or  ,

wherein R_{57} and R_{58} are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, unsubstituted or substituted aryl(C_{1-10})alkyl, or $-SO_2R_{60}$,

wherein R_{60} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

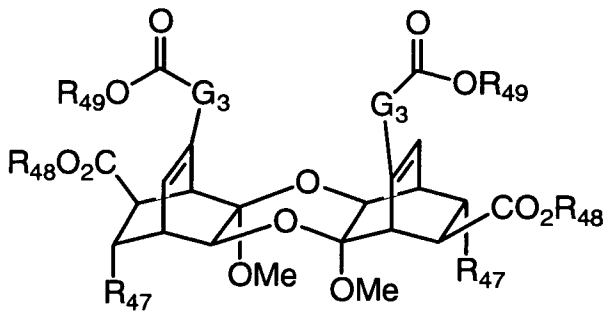
wherein R_{59} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

wherein each occurrence of R_{81} is, independently, C_{1-10} alkyl, or unsubstituted or substituted aryl;
with a first suitable Bronsted acid in the presence of methanol so as to form a compound having the structure



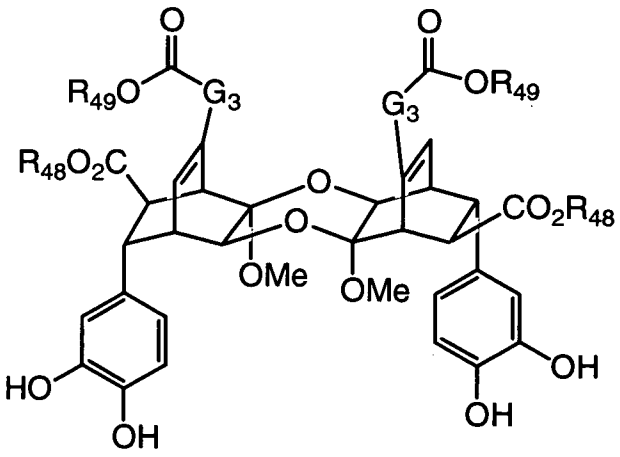
;

b') contacting the product of a') with a first suitable Lewis acid so as to form a compound having the structure



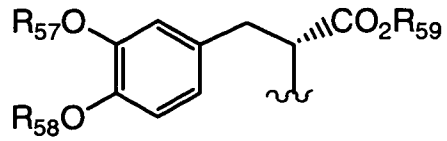
;

c') contacting the product of step b') with a second suitable Lewis acid so as to form a compound having the structure



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56. The process of claim 55,

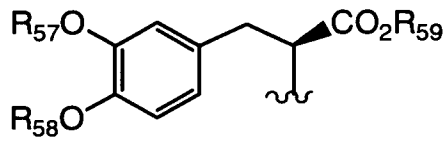
wherein R_{48} and R_{49} are each, independently, H, C_{1-10} alkyl, , C_{2-10} alkenyl, C_{2-10} alkynyl; or ,

wherein R_{57} and R_{58} are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, unsubstituted or substituted aryl(C_{1-10})alkyl, or $-SO_2R_{60}$,

wherein R_{60} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

wherein R_{59} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl.

57. The process of claim 55,

wherein R_{48} and R_{49} are each, independently, H, C_{1-10} alkyl, , C_{2-10} alkenyl, C_{2-10} alkynyl; or ,

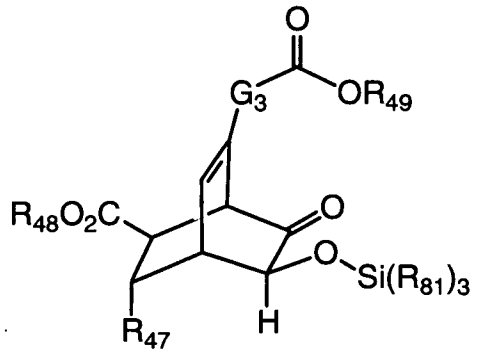
wherein R_{57} and R_{58} are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, unsubstituted or substituted aryl(C_{1-10})alkyl, or $-SO_2R_{60}$,

wherein R_{60} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

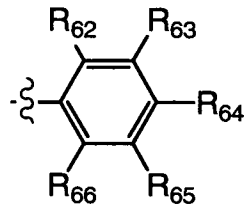
wherein R_{59} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl.

58. The process of claim 55, 56, or 57, comprising:

a) contacting a compound having the structure

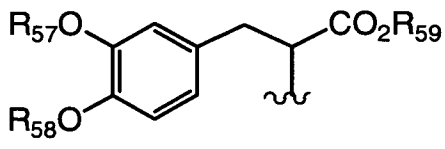


wherein G_3 is C_{1-10} alkylene, C_{2-10} alkenylene, or C_{2-10} alkynylene;

R_{47} is H, CN, or ,

wherein R_{62}, R_{63}, R_{64}, R_{65}, and R_{66} are each, independently, H, halogen, $-NO_2$, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; $-OR_{67}$, $-SR_{67}$, $-OSO_2R_{67}$, or $-NR_{67}R_{68}$,

wherein R_{67} and R_{68} are each, independently, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or unsubstituted or substituted aryl;

R_{48} and R_{49} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; or ,

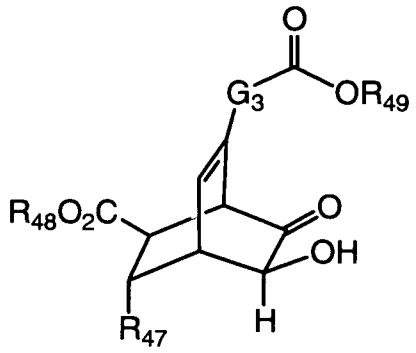
wherein R_{57} and R_{58} are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, unsubstituted or substituted aryl(C_{1-10})alkyl, or $-SO_2R_{60}$,

wherein R_{60} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

wherein R_{59} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

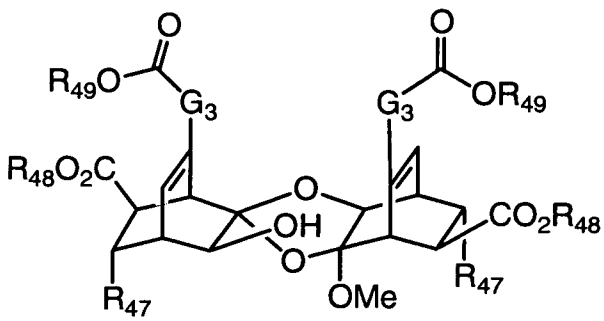
wherein each occurrence of R_{81} is, independently, C_{1-10} alkyl, or unsubstituted or substituted aryl;

with tetra-n-butylammonium fluoride so as to form a compound having the structure



;

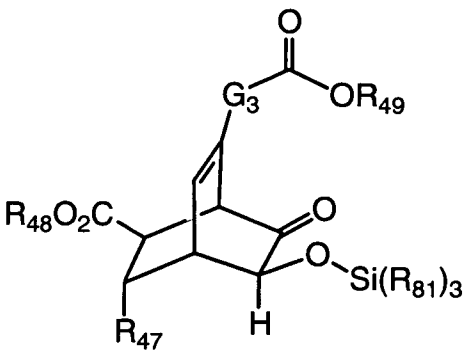
b) contacting the product of step a) with sodium hydride so as to form a compound having the structure



.

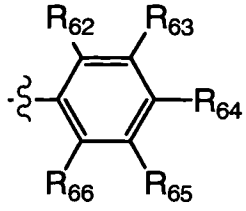
59. The process of claim 55, 56, or 57, comprising:

a') contacting a compound having the structure



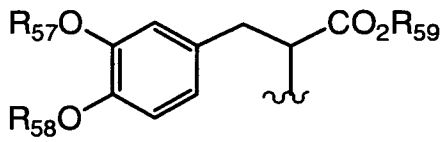
,

wherein G_3 is C_{1-10} alkylene, C_{2-10} alkenylene, or C_{2-10} alkynylene;

R_{47} is H, CN, or ,

wherein R_{62}, R_{63}, R_{64}, R_{65}, and R_{66} are each, independently, H, halogen, $-NO_2$, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; $-OR_{67}$, $-SR_{67}$, $-OSO_2R_{67}$, or $-NR_{67}R_{68}$,

wherein R_{67} and R_{68} are each, independently, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or unsubstituted or substituted aryl;

R_{48} and R_{49} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; or ,

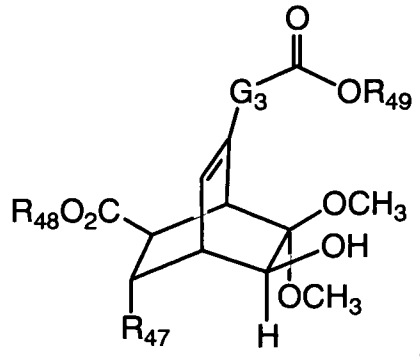
wherein R_{57} and R_{58} are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, unsubstituted or substituted aryl(C_{1-10})alkyl, or $-SO_2R_{60}$,

wherein R_{60} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

wherein R_{59} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

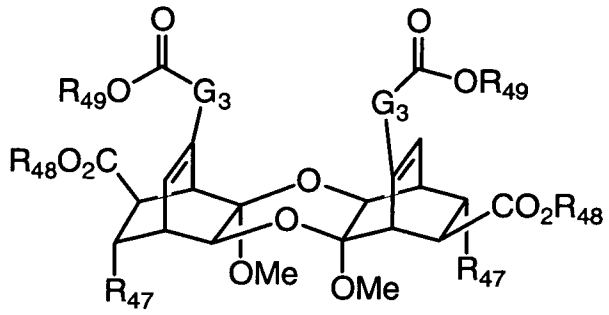
wherein each occurrence of R_{81} is, independently, C_{1-10} alkyl, or unsubstituted or substituted aryl;

with a first suitable Bronsted acid in the presence of methanol so as to form a compound having the structure



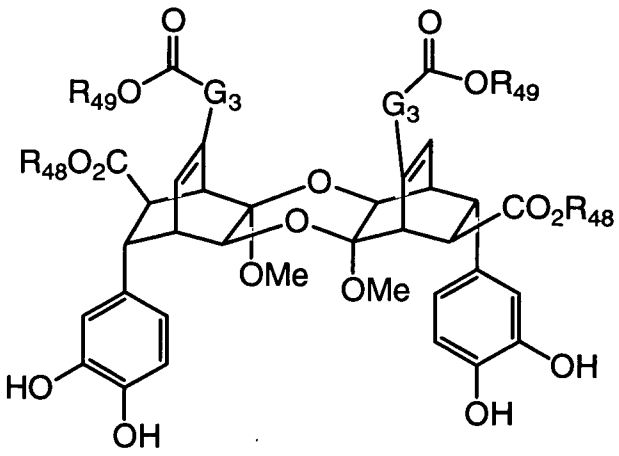
;

b') contacting the product of a') with a first suitable Lewis acid so as to form a compound having the structure



;

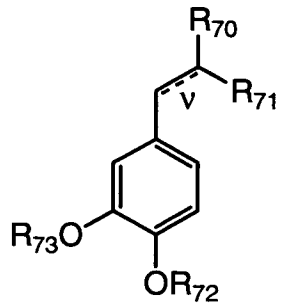
c') contacting the product of step b') with a second suitable Lewis acid so as to form a compound having the structure



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60. The process of claims 55, 56, 58, or 59 wherein the compound prepared is selected from the group consisting of: Compound 2, 43, and 48.

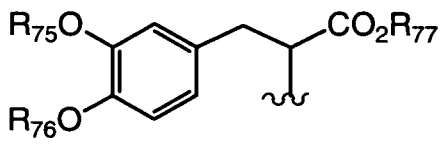
61. A process for preparing a compound having the structure



wherein ν is present or absent;

wherein R_{70} and R_{71} are each, independently, H, OH, $-CO_2R_{74}$,

wherein R_{74} is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl,

or ,

wherein R_{75} and R_{76} are independently H; C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; or $-SO_2R_{78}$,

wherein R_{78} is C_{1-10} alkyl; or unsubstituted or substituted aryl; and

wherein R_{77} is H; C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl;

wherein R_{72} and R_{73} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; $-SO_2R_{79}$, or $-Si(R_{80})_3$,

wherein R_{79} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

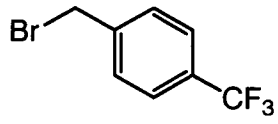
wherein each occurrence of R_{80} is, independently, C_{1-10} alkyl, or unsubstituted or substituted aryl; and

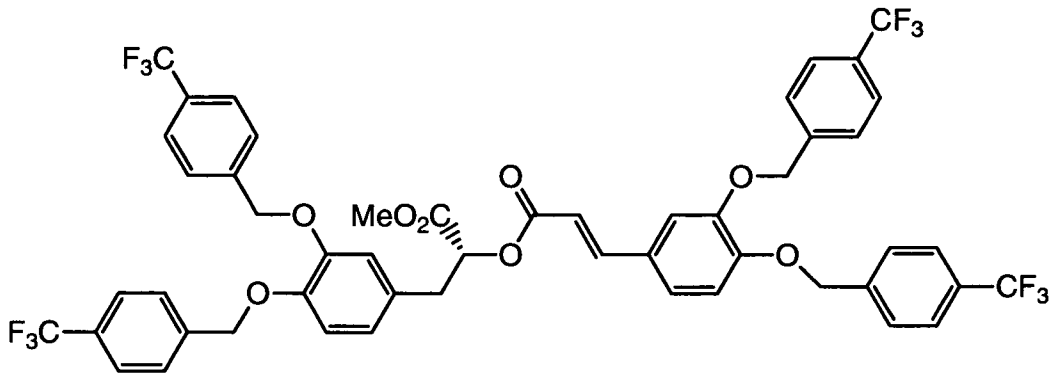
wherein each occurrence of alkyl, alkylene, alkenyl, alkenylene, alkynyl, or alkynylene is branched or unbranched, unsubstituted or substituted;

or a salt thereof;

comprising:

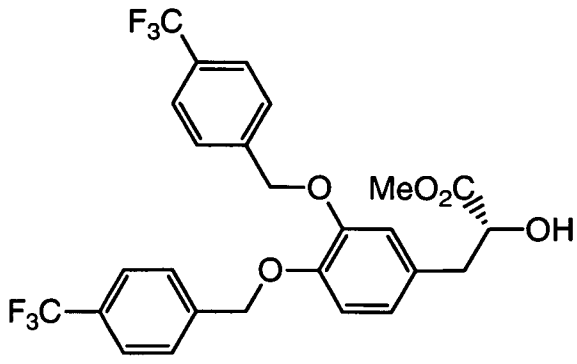
a) contacting rosmarinic acid with $TMSCHN_2$;

b) contacting the product of step a) with a compound having the structure  in the presence of a first suitable base so as to form a compound having the structure



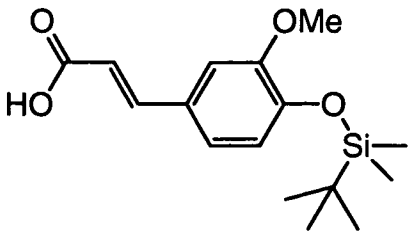
62. The process of claim 61 further comprising:

c) contacting the product of step b) with a second suitable base so as to form a compound having the structure



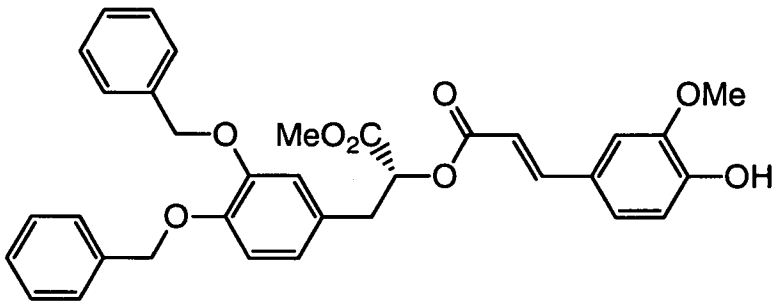
;

d) contacting the product of step c) with a compound having the structure

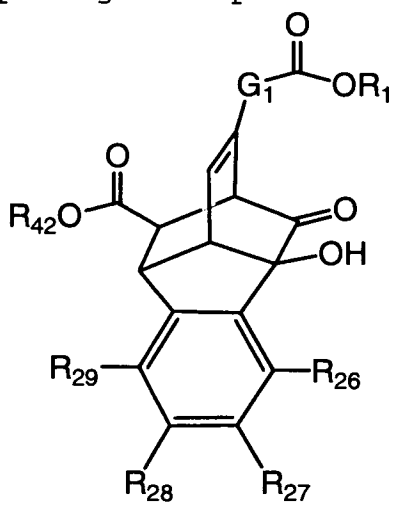


in the presence of *N*-ethyl-*N'*-(3-dimethylaminopropyl)carbodiimide and a third suitable base;

e) contacting the product of step d) with tetra-n-butylammonium fluoride so as to form a compound having the structure

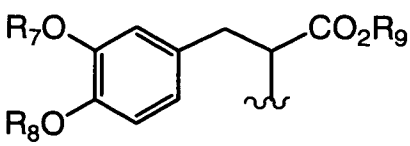


63. A process for preparing a compound having the structure



wherein G_1 is C_{1-10} alkylene, C_{2-10} alkenylene, or C_{2-10} alkynylene;

R_1 is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or



wherein R_7 and R_8 are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; or $-SO_2R_{10}$,

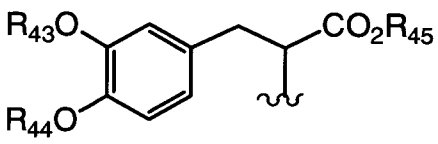
wherein R_{10} is C_{1-10} alkyl, or unsubstituted or substituted aryl;

R_9 is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl;

R_{26}, R_{27}, R_{28}, and R_{29} are each, independently, H, halogen, $-NO_2$, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; $-OR_{31}$, $-SR_{31}$, $-OSO_2R_{31}$, or $-NR_{31}R_{32}$,

wherein R_{31} and R_{32} are each, independently, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or unsubstituted or substituted aryl; and

R_{42} is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or



,

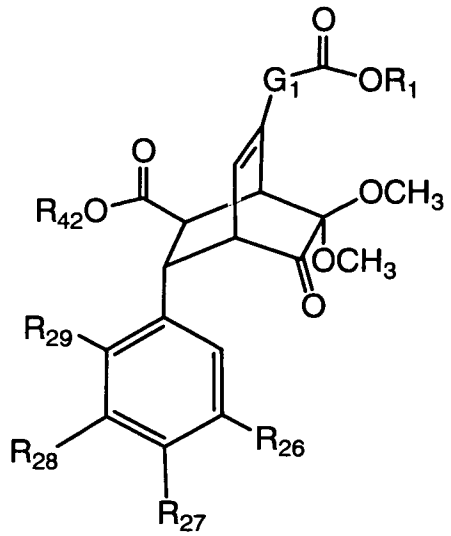
wherein R_{43} and R_{44} are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; or $-SO_2R_{46}$,

wherein R_{46} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

R_{45} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl;

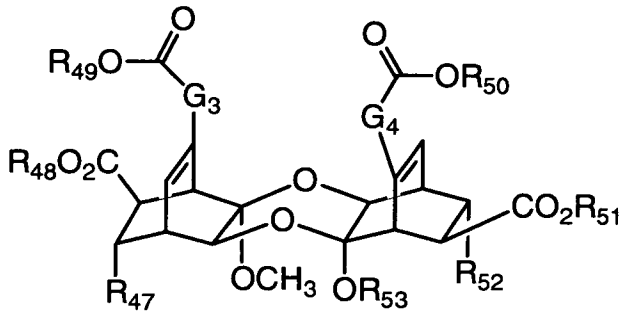
comprising:

a) exposing a compound having the structure

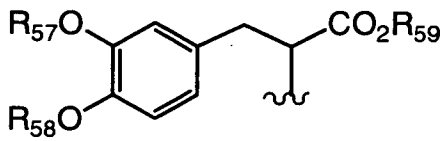


to a suitable Lewis acid so as to form the compound.

64. A process for preparing a compound having the structure



wherein G_3 and G_4 are each, independently, is C_{1-10} alkylene, C_{2-10} alkenylene, or C_{2-10} alkynylene;

R_{48}, R_{49}, R_{50}, and R_{51} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; or ,

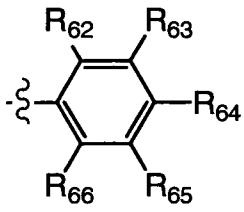
wherein R_{57} and R_{58} are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, unsubstituted or substituted aryl(C_{1-10})alkyl, or $-SO_2R_{60}$,

wherein R_{60} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

wherein R_{59} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

wherein R_{53} is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, unsubstituted or substituted aryl(C_{1-10})alkyl, or $-SO_2R_{61}$,

wherein R_{61} is C_{1-10} alkyl, or unsubstituted or substituted aryl;



R_{47} and R_{52} are each H, CN, or ,

wherein R_{62}, R_{63}, R_{64}, R_{65}, and R_{66} are each, independently, H, halogen, $-NO_2$, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; $-OR_{67}$, $-SR_{67}$, $-OSO_2R_{67}$, or $-NR_{67}R_{68}$,

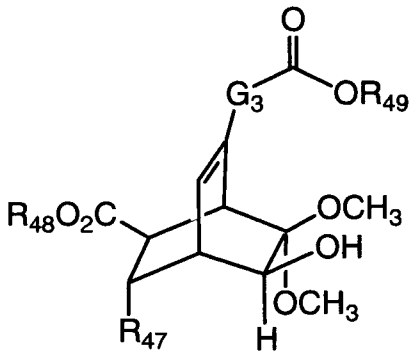
wherein R_{67} and R_{68} are each, independently, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or unsubstituted or substituted aryl; or

wherein each occurrence of alkyl, alkylene, alkenyl, alkenylene, alkynyl, alkynylene is branched or unbranched, unsubstituted or substituted;

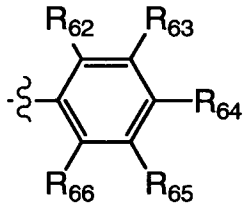
or a salt thereof;

comprising:

a) contacting a compound having the structure

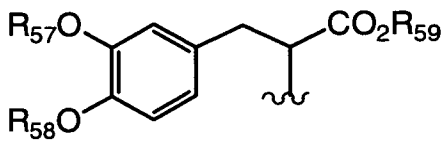


wherein G_3 is C_{1-10} alkylene, C_{2-10} alkenylene, or C_{2-10} alkynylene;

R_{47} is H, CN, or ,

wherein R_{62}, R_{63}, R_{64}, R_{65}, and R_{66} are each, independently, H, halogen, $-NO_2$, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; $-OR_{67}$, $-SR_{67}$, $-OSO_2R_{67}$, or $-NR_{67}R_{68}$,

wherein R_{67} and R_{68} are each, independently, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or unsubstituted or substituted aryl;

R_{48} and R_{49} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; or ,

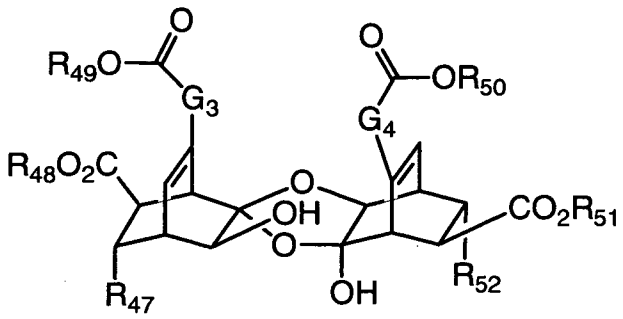
wherein R_{57} and R_{58} are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, unsubstituted or substituted aryl(C_{1-10})alkyl, or $-SO_2R_{60}$,

wherein R_{60} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

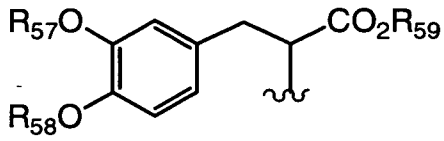
wherein R_{59} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl;

with a suitable Lewis acid so as to form the compound.

65. A process for preparing a compound having the structure



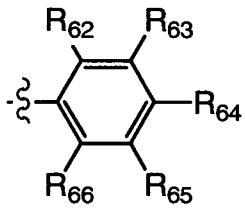
wherein G_3 and G_4 are each, independently, is C_{1-10} alkylene, C_{2-10} alkenylene, or C_{2-10} alkynylene;

R_{48}, R_{49}, R_{50}, and R_{51} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; or ,

wherein R_{57} and R_{58} are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, unsubstituted or substituted aryl(C_{1-10})alkyl, or $-SO_2R_{60}$,

wherein R_{60} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

wherein R_{59} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

R_{47} and R_{52} are each H, CN, or ,

wherein R_{62}, R_{63}, R_{64}, R_{65}, and R_{66} are each, independently, H, halogen, $-NO_2$, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; $-OR_{67}$, $-SR_{67}$, $-OSO_2R_{67}$, or $-NR_{67}R_{68}$,

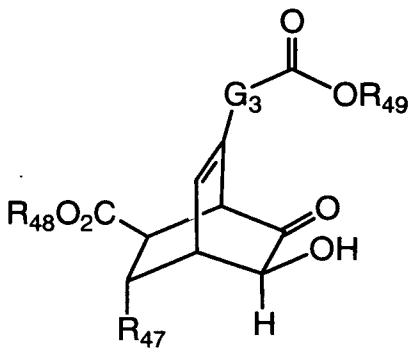
wherein R_{67} and R_{68} are each, independently, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or unsubstituted or substituted aryl; or

wherein each occurrence of alkyl, alkylene, alkenyl, alkenylene, alkynyl, alkynylene is branched or unbranched, unsubstituted or substituted;

or a salt thereof;

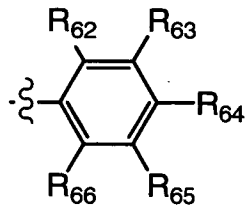
comprising:

a) contacting a compound having the structure



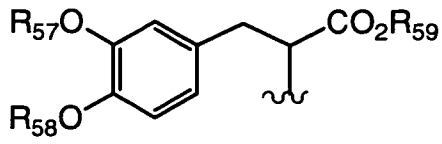
,

wherein G_3 is C_{1-10} alkylene, C_{2-10} alkenylene, or C_{2-10} alkynylene;

R_{47} is H, CN, or  ,

wherein R_{62}, R_{63}, R_{64}, R_{65}, and R_{66} are each, independently, H, halogen, $-NO_2$, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; $-OR_{67}$, $-SR_{67}$, $-OSO_2R_{67}$, or $-NR_{67}R_{68}$,

wherein R_{67} and R_{68} are each, independently, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or unsubstituted or substituted aryl;

R_{48} and R_{49} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; or ,

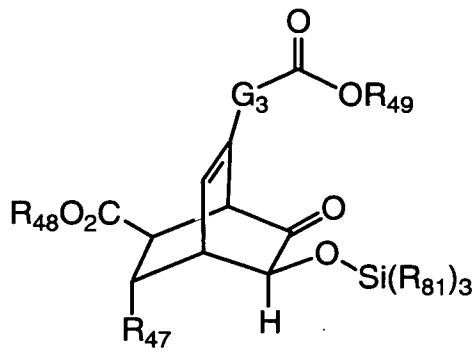
wherein R_{57} and R_{58} are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, unsubstituted or substituted aryl(C_{1-10})alkyl, or $-SO_2R_{60}$,

wherein R_{60} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

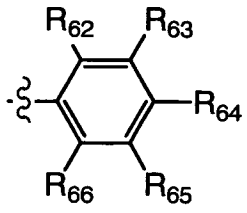
wherein R_{59} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl;

with a suitable base so as to form the compound.

66. A process for preparing a compound having the structure

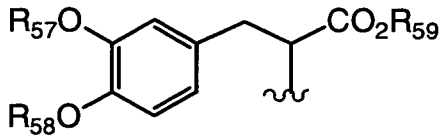


wherein G_3 is C_{1-10} alkylene, C_{2-10} alkenylene, or C_{2-10} alkynylene;

R_{47} is H, CN, or ,

wherein R_{62}, R_{63}, R_{64}, R_{65}, and R_{66} are each, independently, H, halogen, $-NO_2$, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; $-OR_{67}$, $-SR_{67}$, $-OSO_2R_{67}$, or $-NR_{67}R_{68}$,

wherein R_{67} and R_{68} are each, independently, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or unsubstituted or substituted aryl;

R_{48} and R_{49} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; or 

,

wherein R_{57} and R_{58} are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, unsubstituted or substituted aryl(C_{1-10})alkyl, or $-SO_2R_{60}$,

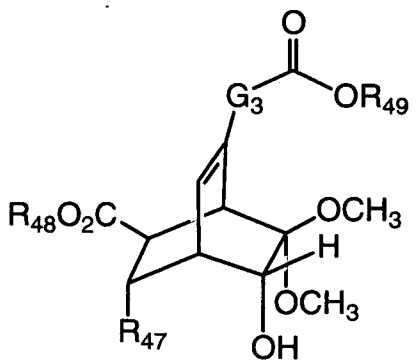
wherein R_{60} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

wherein R_{59} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

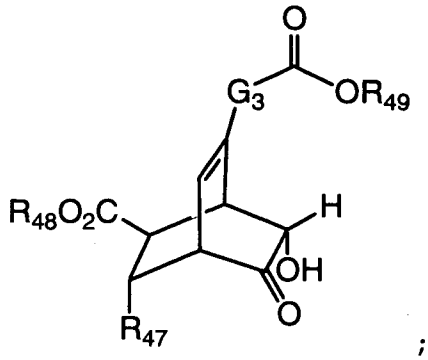
wherein each occurrence of R_{81} is, independently, C_{1-10} alkyl, or unsubstituted or substituted aryl;

comprising:

a) contacting a compound having the structure



with a suitable Bronsted acid so as to form a compound having the structure



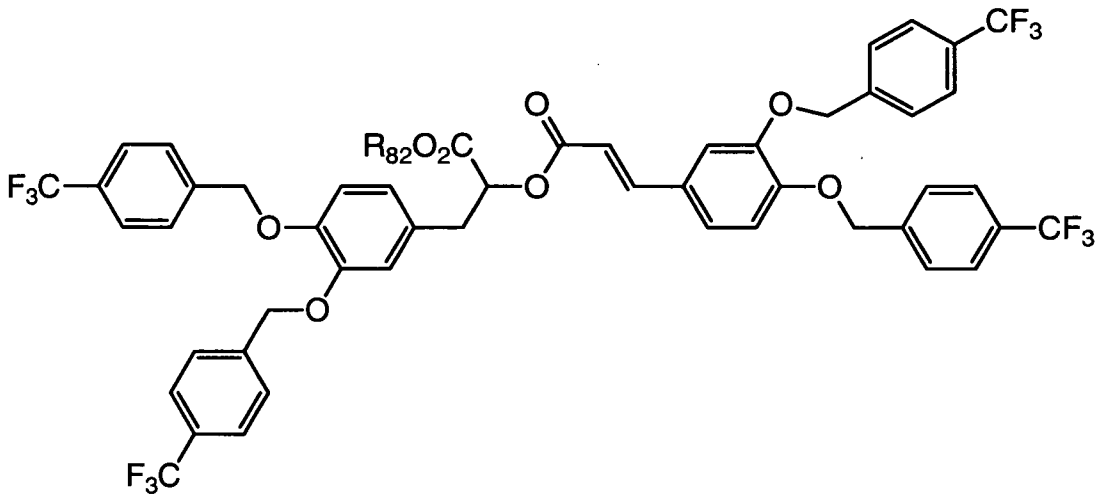
;

b) contacting the product of step a) with a suitable hydride reducing agent;

c) contacting the product of step b) with a suitable silylating agent;

d) contacting the product of step c) with a suitable oxidizing agent so as to form the compound.

67. A process for preparing a compound having the structure



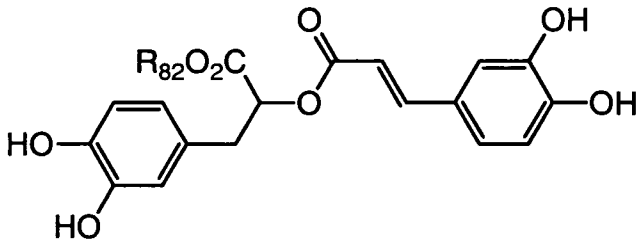
wherein R_{82} is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl;

wherein each occurrence of alkyl, alkylene, alkenyl, alkenylene, alkynyl, or alkynylene is branched or unbranched, unsubstituted or substituted;

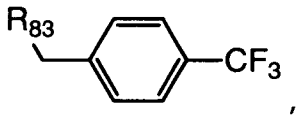
or a salt thereof;

comprising:

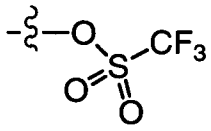
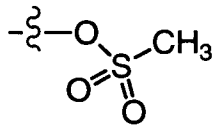
a) contacting a compound having the structure

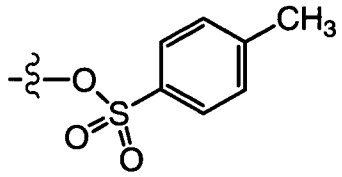


with a compound having the structure



,

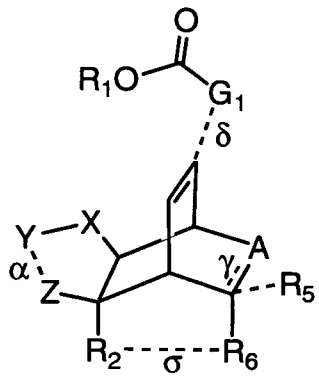
wherein R_{83} is halogen, -OH, , ,



or ;

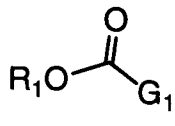
in the presence of a suitable base so as to form the compound.

68. A composition, free of plant extract, comprising a compound having the structure

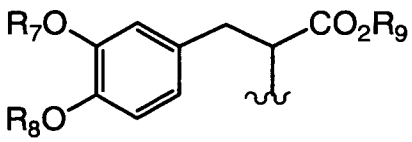


wherein

α, γ, δ and σ are each, independently, present or absent;

wherein when δ is absent,  is absent;

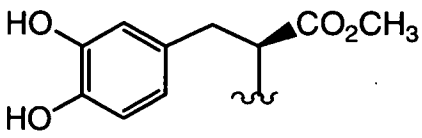
G_1 is C_{1-10} alkylene, C_{2-10} alkenylene, or C_{2-10} alkynylene;

R_1 is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or ,

wherein R_7 and R_8 are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; or $-SO_2R_{10}$,

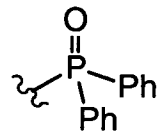
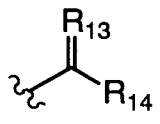
wherein R_{10} is C_{1-10} alkyl, or unsubstituted or substituted aryl;

R_9 is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

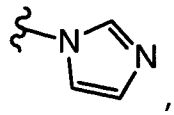
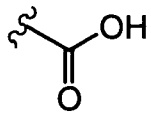
when R_7 and R_8 are H and R_9 is CH_3, then R_1 is ; and

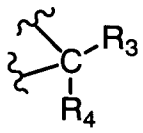
when γ is present; R_5 is absent and A is C-R_4,

wherein R_4 is H, halogen, or OR_{11},

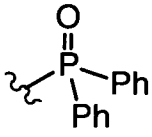
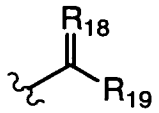
wherein R_{11} is H, C_{1-10} alkyl, $-CH_2SH$, $-BHCH_2CH_3$, $-CH{=}SH$, , $-SO_2R_{12}$, , or $-Si(R_{15})_3$;

wherein R_{12} and each occurrence of R_{15} is C_{1-10} alkyl; or unsubstituted or substituted aryl; and

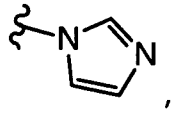
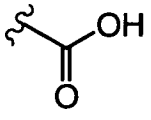
R_{13} is S or O; and R_{14} is $-SCH_3$, , or ; and

when γ is absent; R_5 is present and A is a direct bond or ;

wherein R_3 and R_4 are each, independently, H, halogen, or OR_{16};

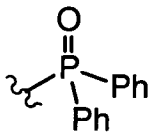
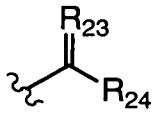
wherein R_{16} is H, C_{1-10} alkyl, $-CH_2SH$, $-BHCH_2CH_3$, $-CH{=}SH$, , $-SO_2R_{17}$, , or $-Si(R_{20})_3$;

wherein R_{17} and each occurrence of R_{20} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

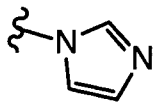
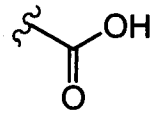
R_{18} is S or O; and R_{19} is $-SCH_3$, , or ; or

R_3 and R_4 taken together form =O; and

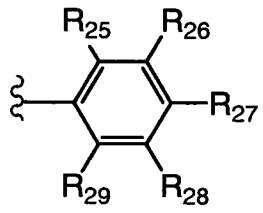
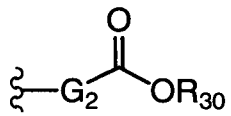
wherein R_5 is H, halogen, or OR_{21},

wherein R_{21} is H, C_{1-10} alkyl, $-CH_2SH$, $-BHCH_2CH_3$, $-CH{=}SH$, , $-SO_2R_{22}$, , or $-Si(R_{25})_3$,

wherein R_{22} and each occurrence of R_{25} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

R_{23} is S or O; and R_{24} is $-SCH_3$, , or ; and

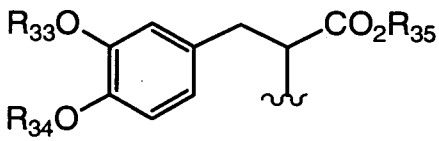
when σ is absent;

R_2 is H, , or ;

wherein R_{25}, R_{26}, R_{27}, R_{28}, and R_{29} are each, independently, H, halogen, $-NO_2$, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; $-OR_{31}$, $-SR_{31}$, $-OSO_2R_{31}$, or $-NR_{31}R_{32}$,

wherein R_{31} and R_{32} are each, independently, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or unsubstituted or substituted aryl;

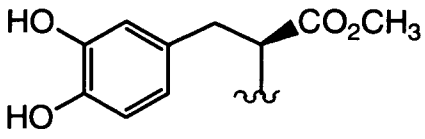
wherein G_2 is C_{1-10} alkylene, C_{2-10} alkenylene, or C_{2-10} alkynylene; and

R_{30} is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or ,

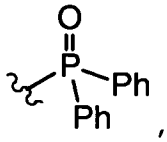
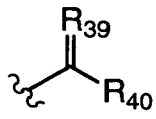
wherein R_{33} and R_{34} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; or $-SO_2R_{36}$,

wherein R_{36} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

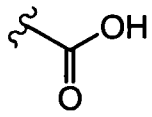
wherein R_{35} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

when R_{33} and R_{34} are H and R_{35} is CH_3, then R_{30} is  ; and

R_6 is H, halogen, or OR_{37};

wherein R_{37} is H, C_{1-10} alkyl, $-CH_2SH$, $-BHCH_2CH_3$, $-CH=SH$,  , $-SO_2R_{38}$,  , or $-Si(R_{41})_3$;

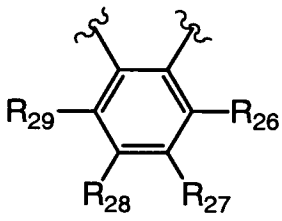
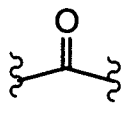
wherein R_{38} and each occurrence of R_{41} is C_{1-10} alkyl; or unsubstituted or substituted aryl;

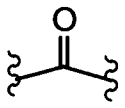
R_{39} is S or O; and R_{40} is $-SCH_3$; -NH-aryl, heteroaryl, heterocyclyl; or  ; or

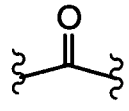
R_5 when present and R_6 taken together form =O; or

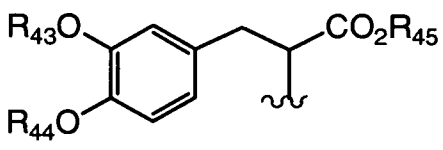
R_4 joined to R_6 form a 5-membered heterocyclic ring; and

when σ is present;

R_2 is  ; and R_6 is a direct bond or  ; and

wherein X is a direct bond,  , or $C(OMe)_2$;

Y is H or OR_{42}; or when α is present, Y is  ;

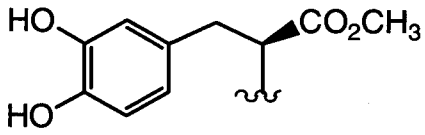
wherein R_{42} is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or  ,

wherein R_{43} and R_{44} are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; or $-SO_2R_{46}$,

wherein R_{46} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

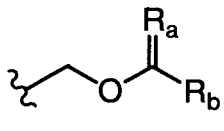
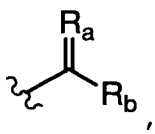
R_{45} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl;

and when R_{43} and R_{44} are H and R_{45} is CH_3, then R_{42} is



; or

wherein each occurrence of alkyl, alkylene, alkenyl, alkenylene, alkynyl, or alkynylene is branched or unbranched, unsubstituted or substituted;

Z is H, CN,  or ,

wherein R_a is S or O; R_b is $-O-(C_1-C_{10})$alkyl, $-O-(C_2-C_{10})$alkenyl, heterocyclyl, or heteroaryl; or

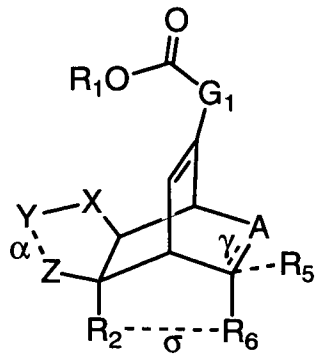
when α is present, Z is $-CH=CH-$;

and

when α is present, R_1 is other than methyl;

or a salt thereof.

69. The composition of claim 68 comprising a compound having the structure

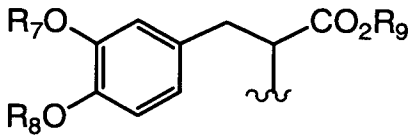


wherein

α, γ, and σ are each, independently, present or absent;

G_1 is C_{1-10} alkylene, C_{2-10} alkenylene, or C_{2-10} alkynylene;

R_1 is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or



,

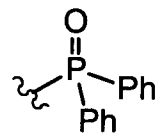
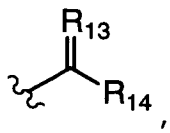
wherein R_7 and R_8 are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; or $-SO_2R_{10}$,

wherein R_{10} is C_{1-10} alkyl, or unsubstituted or substituted aryl;

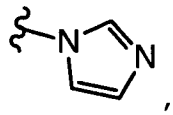
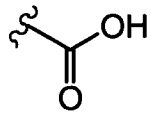
R_9 is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

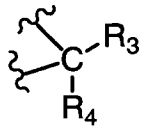
when γ is present; R_5 is absent and A is C-R_4,

wherein R_4 is H, halogen, or OR_{11},

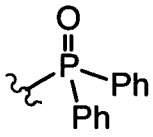
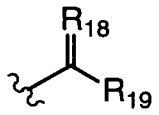
wherein R_{11} is H, C_{1-10} alkyl, $-CH_2SH$, $-BHCH_2CH_3$, $-CH{=}SH$, , $-SO_2R_{12}$, , or $-Si(R_{15})_3$;

wherein R_{12} and each occurrence of R_{15} is C_{1-10} alkyl; or unsubstituted or substituted aryl; and

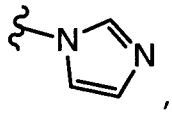
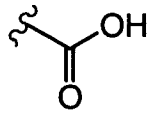
R_{13} is S or O; and R_{14} is $-SCH_3$, , or ; and

when γ is absent; R_5 is present and A is a direct bond or ;

wherein R_3 and R_4 are each, independently, H, halogen, or OR_{16};

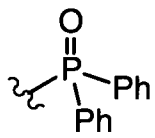
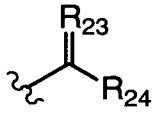
wherein R_{16} is H, C_{1-10} alkyl, $-CH_2SH$, $-BHCH_2CH_3$, $-CH{=}SH$, , $-SO_2R_{17}$, , or $-Si(R_{20})_3$;

wherein R_{17} and each occurrence of R_{20} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

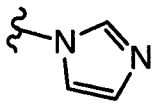
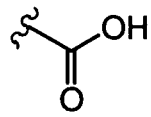
R_{18} is S or O; and R_{19} is $-SCH_3$, , or ; or

R_3 and R_4 taken together form =O; and

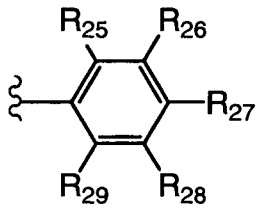
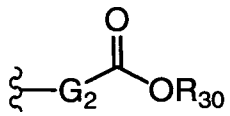
wherein R_5 is H, halogen, or OR_{21},

wherein R_{21} is H, C_{1-10} alkyl, $-CH_2SH$, $-BHCH_2CH_3$, $-CH{=}SH$, , $-SO_2R_{22}$, , or $-Si(R_{25})_3$,

wherein R_{22} and each occurrence of R_{25} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

R_{23} is S or O; and R_{24} is $-SCH_3$, , or ; and

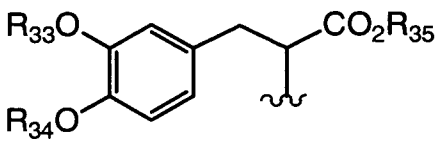
when σ is absent;

R_2 is H, , or ;

wherein R_{25}, R_{26}, R_{27}, R_{28}, and R_{29} are each, independently, H, halogen, $-NO_2$, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; $-OR_{31}$, $-SR_{31}$, $-OSO_2R_{31}$, or $-NR_{31}R_{32}$,

wherein R_{31} and R_{32} are each, independently, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or unsubstituted or substituted aryl;

wherein G_2 is C_{1-10} alkylene, C_{2-10} alkenylene, or C_{2-10} alkynylene; and

R_{30} is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or ,

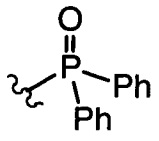
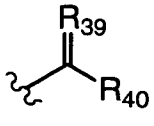
wherein R_{33} and R_{34} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; or $-SO_2R_{36}$,

wherein R_{36} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

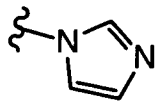
wherein R_{35} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

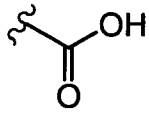
R_6 is H, halogen, or OR_{37};

wherein R_{37} is H, C_{1-10} alkyl, $-CH_2SH$, $-BHCH_2CH_3$, $-CH=SH$,


, $-SO_2R_{38}$, 
, or $-Si(R_{41})_3$;

wherein R_{38} and each occurrence of R_{41} is C_{1-10} alkyl; or unsubstituted or substituted aryl;

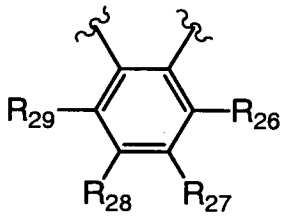
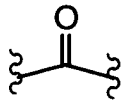
R_{39} is S or O; and R_{40} is $-SCH_3$; 
; or

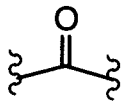

; or

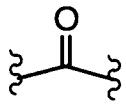
R_5 when present and R_6 taken together form =O; or

R_4 joined to R_6 form a 5-membered heterocyclic ring; and

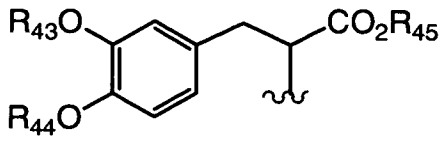
when σ is present;

R_2 is 
; and R_6 is a direct bond or 
; and

wherein X is a direct bond, 
, or $C(OMe)_2$;

Y is H or OR_{42}; or when α is present, Y is 
;

wherein R_{42} is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl,

or 
,

wherein R_{43} and R_{44} are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; or $-SO_2R_{46}$,

wherein R_{46} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

R_{45} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; or

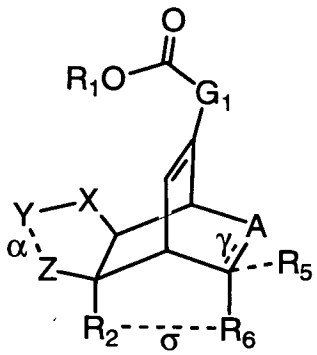
wherein each occurrence of alkyl, alkylene, alkenyl, alkenylene, alkynyl, or alkynylene is branched or unbranched, unsubstituted or substituted;

Z is H or CN; or when α is present, Z is -CH=CH-; and

when α is present, R_1 is other than methyl;

or a salt thereof.

70. The composition of claim 69, wherein the compound has the structure

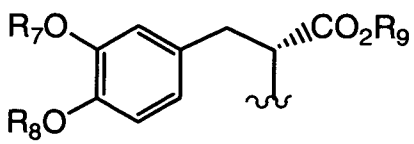


wherein

α, γ, and σ are each, independently, present or absent;

G_1 is C_{1-10} alkylene, C_{2-10} alkenylene, or C_{2-10} alkynylene;

R_1 is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or



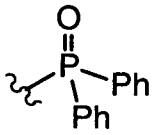
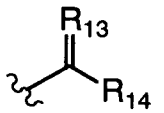
wherein R_7 and R_8 are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; or $-SO_2R_{10}$,

wherein R_{10} is C_{1-10} alkyl, or unsubstituted or substituted aryl;

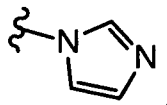
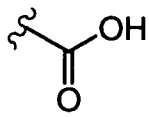
R_9 is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

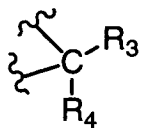
when γ is present; R_5 is absent and A is C-R_4,

wherein R_4 is H, halogen, or OR_{11},

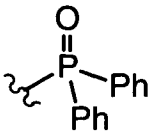
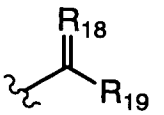
wherein R_{11} is H, C_{1-10} alkyl, $-CH_2SH$, $-BHCH_2CH_3$, $-CH{=}SH$, , $-SO_2R_{12}$, , or $-Si(R_{15})_3$;

wherein R_{12} and each occurrence of R_{15} is C_{1-10} alkyl; or unsubstituted or substituted aryl; and

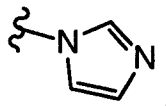
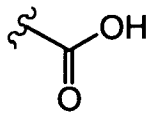
R_{13} is S or O; and R_{14} is $-SCH_3$, , or ; and

when γ is absent; R_5 is present and A is a direct bond or ;

wherein R_3 and R_4 are each, independently, H, halogen, or OR_{16};

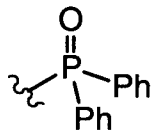
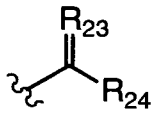
wherein R_{16} is H, C_{1-10} alkyl, $-CH_2SH$, $-BHCH_2CH_3$, $-CH{=}SH$, , $-SO_2R_{17}$, , or $-Si(R_{20})_3$;

wherein R_{17} and each occurrence of R_{20} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

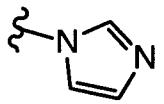
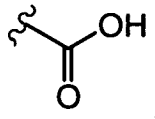
R_{18} is S or O; and R_{19} is $-SCH_3$, , or ; or

R_3 and R_4 taken together form =O; and

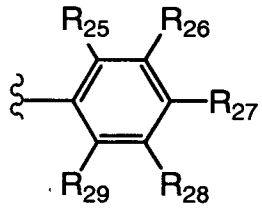
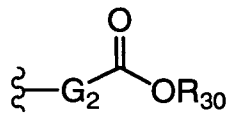
wherein R_5 is H, halogen, or OR_{21},

wherein R_{21} is H, C_{1-10} alkyl, $-CH_2SH$, $-BHCH_2CH_3$, $-CH{=}SH$, , $-SO_2R_{22}$, , or $-Si(R_{25})_3$,

wherein R_{22} and each occurrence of R_{25} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

R_{23} is S or O; and R_{24} is $-SCH_3$, , or ; and

when σ is absent;

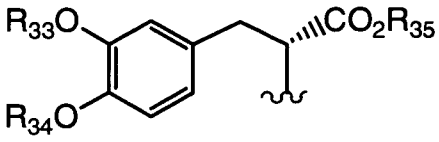
R_2 is H, , or ;

wherein R_{25}, R_{26}, R_{27}, R_{28}, and R_{29} are each, independently, H, halogen, $-NO_2$, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; $-OR_{31}$, $-SR_{31}$, $-OSO_2R_{31}$, or $-NR_{31}R_{32}$,

wherein R_{31} and R_{32} are each, independently, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or unsubstituted or substituted aryl;

wherein G_2 is C_{1-10} alkylene, C_{2-10} alkenylene, or C_{2-10} alkynylene; and

R_{30} is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or



,

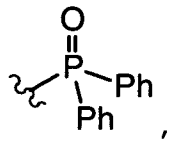
wherein R_{33} and R_{34} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; or $-SO_2R_{36}$,

wherein R_{36} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

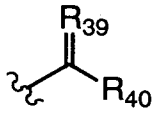
wherein R_{35} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

R_6 is H, halogen, or OR_{37};

wherein R_{37} is H, C_{1-10} alkyl, $-CH_2SH$, $-BHCH_2CH_3$, $-CH=SH$,



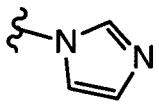
, $-SO_2R_{38}$,



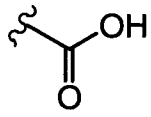
, or $-Si(R_{41})_3$;

wherein R_{38} and each occurrence of R_{41} is C_{1-10} alkyl; or unsubstituted or substituted aryl;

R_{39} is S or O; and R_{40} is $-SCH_3$;



; or



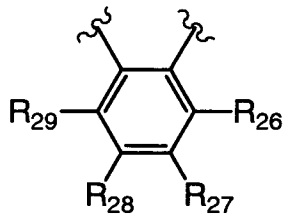
; or

R_5 when present and R_6 taken together form =O; or

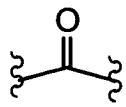
R_4 joined to R_6 form a 5-membered heterocyclic ring; and

when σ is present;

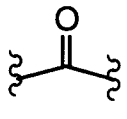
R_2 is



; and R_6 is a direct bond or

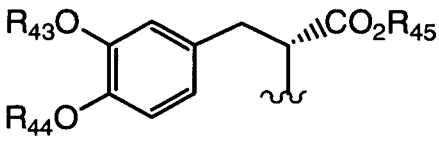


; and

wherein X is a direct bond, , or $C(OMe)_2$;

Y is H or OR_{42}; or when α is present, Y is ;

wherein R_{42} is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl,

or ,

wherein R_{43} and R_{44} are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; or $-SO_2R_{46}$,

wherein R_{46} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

R_{45} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; or

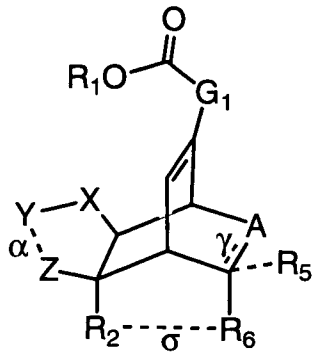
wherein each occurrence of alkyl, alkylene, alkenyl, alkenylene, alkynyl, or alkynylene is branched or unbranched, unsubstituted or substituted;

Z is H or CN; or when α is present, Z is -CH=CH-; and

when α is present, R_1 is other than methyl;

or a salt thereof.

71. The composition of claim 69, wherein the compound has the structure

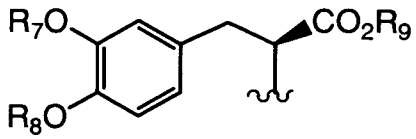


wherein

α, γ, and σ are each, independently, present or absent;

G_1 is C_{1-10} alkylene, C_{2-10} alkenylene, or C_{2-10} alkynylene;

R_1 is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or



,

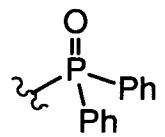
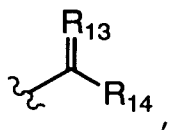
wherein R_7 and R_8 are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; or $-SO_2R_{10}$,

wherein R_{10} is C_{1-10} alkyl, or unsubstituted or substituted aryl;

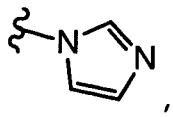
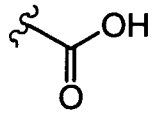
R_9 is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

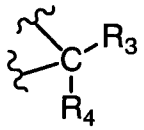
when γ is present; R_5 is absent and A is C-R_4,

wherein R_4 is H, halogen, or OR_{11},

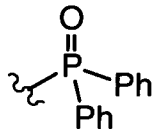
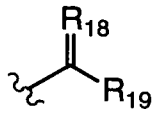
wherein R_{11} is H, C_{1-10} alkyl, $-CH_2SH$, $-BHCH_2CH_3$, $-CH{=}SH$, , $-SO_2R_{12}$, , or $-Si(R_{15})_3$;

wherein R_{12} and each occurrence of R_{15} is C_{1-10} alkyl; or unsubstituted or substituted aryl; and

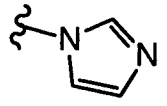
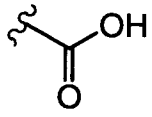
R_{13} is S or O; and R_{14} is $-SCH_3$, , or ; and

when γ is absent; R_5 is present and A is a direct bond or ;

wherein R_3 and R_4 are each, independently, H, halogen, or OR_{16};

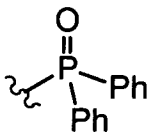
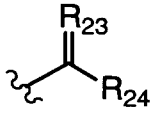
wherein R_{16} is H, C_{1-10} alkyl, $-CH_2SH$, $-BHCH_2CH_3$, $-CH{=}SH$, , $-SO_2R_{17}$, , or $-Si(R_{20})_3$;

wherein R_{17} and each occurrence of R_{20} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

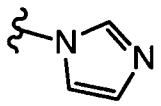
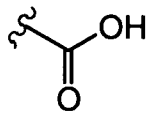
R_{18} is S or O; and R_{19} is $-SCH_3$, , or ; or

R_3 and R_4 taken together form =O; and

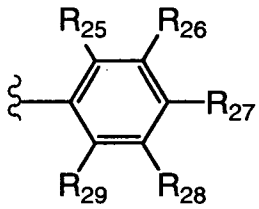
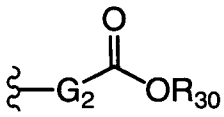
wherein R_5 is H, halogen, or OR_{21},

wherein R_{21} is H, C_{1-10} alkyl, $-CH_2SH$, $-BHCH_2CH_3$, $-CH{=}SH$, , $-SO_2R_{22}$, , or $-Si(R_{25})_3$,

wherein R_{22} and each occurrence of R_{25} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

R_{23} is S or O; and R_{24} is $-SCH_3$, , or ; and

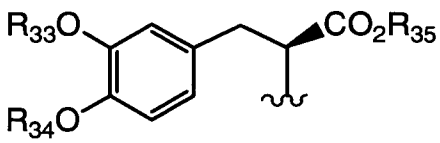
when σ is absent;

R_2 is H, , or ;

wherein R_{25}, R_{26}, R_{27}, R_{28}, and R_{29} are each, independently, H, halogen, $-NO_2$, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; $-OR_{31}$, $-SR_{31}$, $-OSO_2R_{31}$, or $-NR_{31}R_{32}$,

wherein R_{31} and R_{32} are each, independently, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or unsubstituted or substituted aryl;

wherein G_2 is C_{1-10} alkylene, C_{2-10} alkenylene, or C_{2-10} alkynylene; and

R_{30} is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or ,

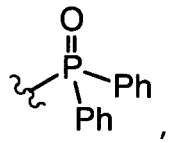
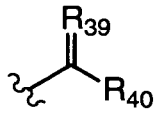
wherein R_{33} and R_{34} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; or $-SO_2R_{36}$,

wherein R_{36} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

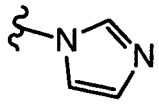
wherein R_{35} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

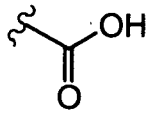
R_6 is H, halogen, or OR_{37};

wherein R_{37} is H, C_{1-10} alkyl, $-CH_2SH$, $-BHCH_2CH_3$, $-CH=SH$,


, $-SO_2R_{38}$, 
, or $-Si(R_{41})_3$;

wherein R_{38} and each occurrence of R_{41} is C_{1-10} alkyl; or unsubstituted or substituted aryl;

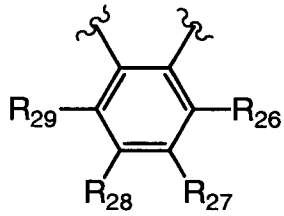
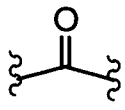
R_{39} is S or O; and R_{40} is $-SCH_3$; 
; or

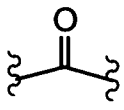

; or

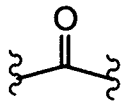
R_5 when present and R_6 taken together form =O; or

R_4 joined to R_6 form a 5-membered heterocyclic ring; and

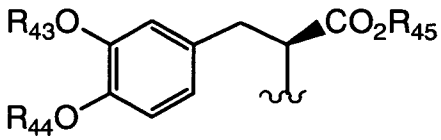
when σ is present;

R_2 is 
; and R_6 is a direct bond or 
; and

wherein X is a direct bond, 
, or $C(OMe)_2$;

Y is H or OR_{42}; or when α is present, Y is 
;

wherein R_{42} is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl,

or 
,

wherein R_{43} and R_{44} are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; or $-SO_2R_{46}$,

wherein R_{46} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

R_{45} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; or

wherein each occurrence of alkyl, alkylene, alkenyl, alkenylene, alkynyl, or alkynylene is branched or unbranched, unsubstituted or substituted;

Z is H or CN; or when α is present, Z is -CH=CH-; and

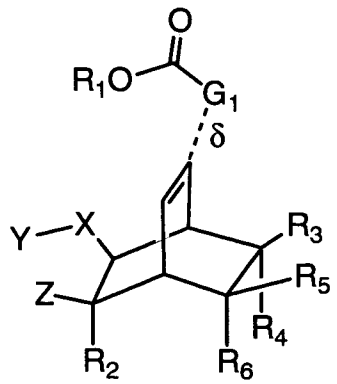
when α is present, R_1 is other than methyl;

or a salt thereof.

72. The composition of claim 69 or 70 wherein the compound is selected from the group consisting of: Compound 3, 4, 21, 23, 24, 25, 26, 33, 34, 35, 36, 37, 39, 40, 42, 44, 45, 47, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, and 63.

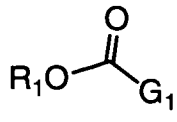
73. The composition of claim 69 or 70 wherein the compound is compound 51.

74. The composition of claim 68 comprising a compound having the structure

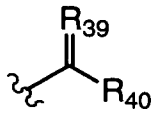


wherein

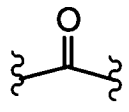
δ is present or absent;

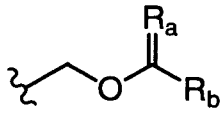
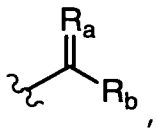
wherein when δ is absent,  is absent;

R_6 is OR_{37};

wherein R_{37} is ;

wherein R_{39} is S or O; and R_{40} is -NH-aryl, heteroaryl, heterocyclyl; or

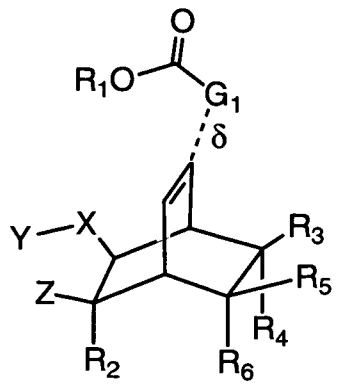
X is a direct bond or ;

Z is H, CN,  or ,

wherein R_a is S or O; R_b is -O-(C_1-C_{10})alkyl, -O-(C_2-C_{10})alkenyl, heterocyclyl, or heteroaryl; or

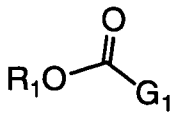
or a salt thereof.

75. The composition of claim 74 comprising a compound having the structure

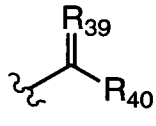


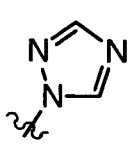
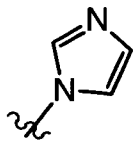
wherein

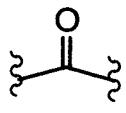
δ is present or absent;

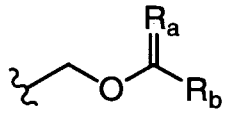
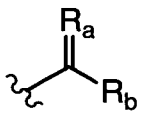
wherein when δ is absent,  is absent;

R_6 is OR_{37};

wherein R_{37} is ;

wherein R_{39} is S; and R_{40} is  or ;

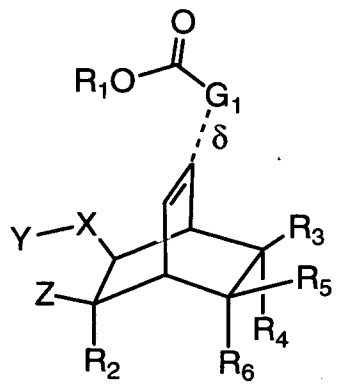
X is a direct bond or ;

Z is H, CN,  or ,

wherein R_a is S or O; R_b is -O-(C_1-C_{10})alkyl, -O-(C_2-C_{10})alkenyl, heterocyclyl, or heteroaryl; or

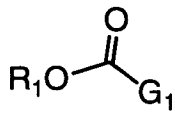
or a salt thereof.

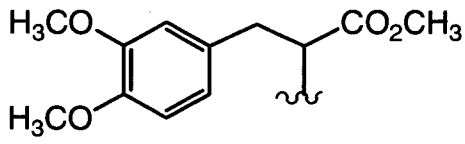
76. The composition of claim 75 comprising a compound having the structure

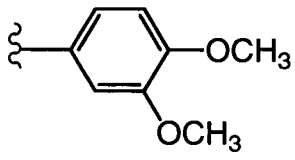


wherein

δ is present or absent;

wherein when δ is absent,  is absent;

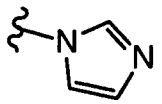
R_1 is H, methyl or ;

R_2 is H or ;

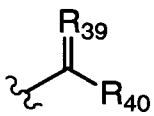
R_3 and R_4 are each $-OCH_3$;

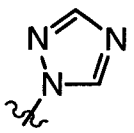
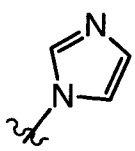
R_5 is H or OR_{21},

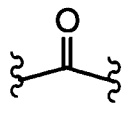
wherein R_{21} is ,

wherein R_{23} is S; and R_{24} is ; and

R_6 is OR_{37};

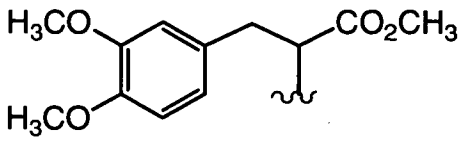
wherein R_{37} is ;

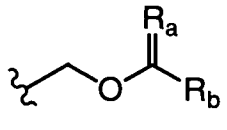
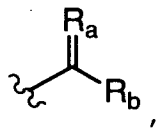
wherein R_{39} is S; and R_{40} is  or ;

X is a direct bond or ;

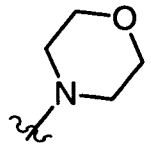
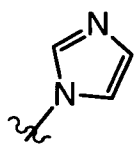
Y is H or OR_{42};

wherein R_{42} is methyl, $-CH_2CH=CH_2$ or

;

Z is H, CN,  or ,

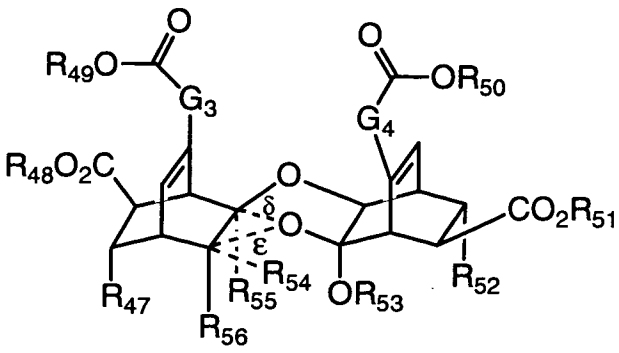
wherein R_a is S or O; R_b is $-OCH_3$, $-OCH(CH_3)_2$, $-OCH_2CH=CH_2$,

$-OCH_2CH_2CH_2CH_3$, , or ;

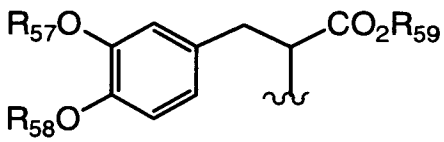
or a salt thereof.

77. The composition of claim 76 comprising a compound selected from the group consisting of Compound 64, 65, 66, 67, 68, 73, 74, 75, 76, 77, 78, 79, 80, and a pharmaceutically acceptable salt thereof.

78. A composition, free of plant extract, comprising a compound having the structure



wherein ε and δ are present or absent;
wherein R_{54} and R_{55} are present or absent; and
when ε is present; δ and R_{54} are absent, and R_{55} is present; and
when δ is present; ε and R_{55} are absent, and R_{54} is present;

wherein G_3 and G_4 are each, independently, is C_{1-10} alkylene, C_{2-10} alkenylene, or C_{2-10} alkynylene;
R_{48}, R_{49}, R_{50}, and R_{51} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; or ,

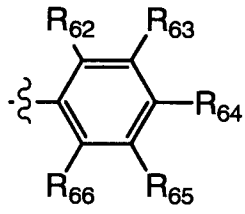
wherein R_{57} and R_{58} are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, unsubstituted or substituted aryl(C_{1-10})alkyl, or $-SO_2R_{60}$,

wherein R_{60} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

wherein R_{59} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

wherein R_{53} is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, unsubstituted or substituted aryl(C_{1-10})alkyl, or $-SO_2R_{61}$,

wherein R_{61} is C_{1-10} alkyl, or unsubstituted or substituted aryl;



R_{47} and R_{52} are each H, CN, or ,

wherein R_{62}, R_{63}, R_{64}, R_{65}, and R_{66} are each, independently, H, halogen, $-NO_2$, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; $-OR_{67}$, $-SR_{67}$, $-OSO_2R_{67}$, or $-NR_{67}R_{68}$,

wherein R_{67} and R_{68} are each, independently, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or unsubstituted or substituted aryl; and

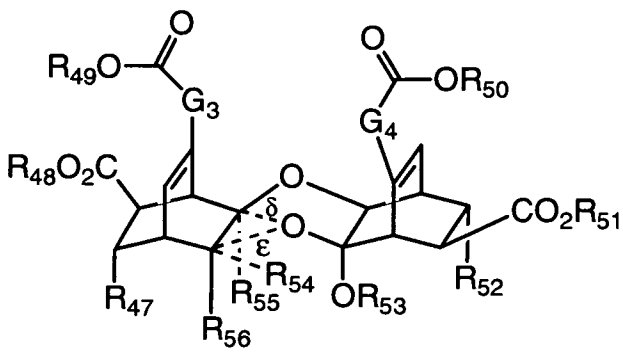
wherein R_{54} when present, R_{55} when present, and R_{56} are each, independently, H or OR_{69},

wherein R_{69} is H or C_{1-10} alkyl; or

wherein each occurrence of alkyl, alkylene, alkenyl, alkenylene, alkynyl, alkynylene is branched or unbranched, unsubstituted or substituted;

or a salt thereof.

79. The composition of claim 78, wherein the compound has the structure

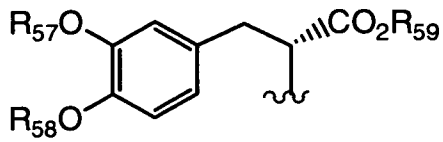


wherein ε and δ are present or absent;

wherein R_{54} and R_{55} are present or absent; and

when ε is present; δ and R_{54} are absent, and R_{55} is present; and when δ is present; ε and R_{55} are absent, and R_{54} is present;

wherein G_3 and G_4 are each, independently, is C_{1-10} alkylene, C_{2-10} alkenylene, or C_{2-10} alkynylene;

R_{48}, R_{49}, R_{50}, and R_{51} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; or 

,

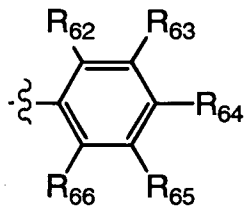
wherein R_{57} and R_{58} are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, unsubstituted or substituted aryl(C_{1-10})alkyl, or $-SO_2R_{60}$,

wherein R_{60} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

wherein R_{59} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

wherein R_{53} is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, unsubstituted or substituted aryl(C_{1-10})alkyl, or $-SO_2R_{61}$,

wherein R_{61} is C_{1-10} alkyl, or unsubstituted or substituted aryl;

R_{47} and R_{52} are each H, CN, or 

,

wherein R_{62}, R_{63}, R_{64}, R_{65}, and R_{66} are each, independently, H, halogen, $-NO_2$, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; $-OR_{67}$, $-SR_{67}$, $-OSO_2R_{67}$, or $-NR_{67}R_{68}$,

wherein R_{67} and R_{68} are each, independently, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or unsubstituted or substituted aryl; and

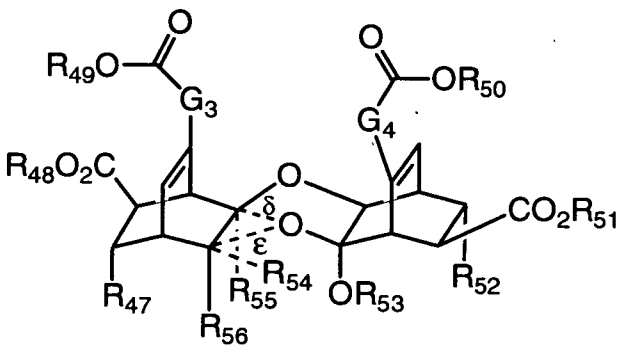
wherein R_{54} when present, R_{55} when present, and R_{56} are each, independently, H or OR_{69},

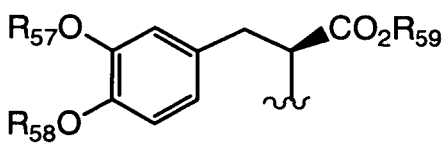
wherein R_{69} is H or C_{1-10} alkyl; or

wherein each occurrence of alkyl, alkylene, alkenyl, alkenylene, alkynyl, alkynylene is branched or unbranched, unsubstituted or substituted;

or a salt thereof.

80. The composition of claim 79, wherein the compound has the structure



wherein ε and δ are present or absent;
wherein R_{54} and R_{55} are present or absent; and
when ε is present; δ and R_{54} are absent, and R_{55} is present; and
when δ is present; ε and R_{55} are absent, and R_{54} is present;
wherein G_3 and G_4 are each, independently, is C_{1-10} alkylene, C_{2-10} alkenylene, or C_{2-10} alkynylene;
R_{48}, R_{49}, R_{50}, and R_{51} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; or ,

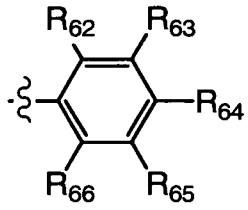
wherein R_{57} and R_{58} are independently H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, unsubstituted or substituted aryl(C_{1-10})alkyl, or $-SO_2R_{60}$,

wherein R_{60} is C_{1-10} alkyl, or unsubstituted or substituted aryl; and

wherein R_{59} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

wherein R_{53} is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, unsubstituted or substituted aryl(C_{1-10})alkyl, or $-SO_2R_{61}$,

wherein R_{61} is C_{1-10} alkyl, or unsubstituted or substituted aryl;



R_{47} and R_{52} are each H, CN, or ,

wherein R_{62}, R_{63}, R_{64}, R_{65}, and R_{66} are each, independently, H, halogen, $-NO_2$, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl; unsubstituted or substituted aryl(C_{1-10})alkyl; $-OR_{67}$, $-SR_{67}$, $-OSO_2R_{67}$, or $-NR_{67}R_{68}$,

wherein R_{67} and R_{68} are each, independently, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or unsubstituted or substituted aryl; and

wherein R_{54} when present, R_{55} when present, and R_{56} are each, independently, H or OR_{69},

wherein R_{69} is H or C_{1-10} alkyl; or

wherein each occurrence of alkyl, alkylene, alkenyl, alkenylene, alkynyl, alkynylene is branched or unbranched, unsubstituted or substituted;

or a salt thereof.

81. The composition of claim 79 or 80 wherein the compound is selected from the group consisting of: Compound 2, 43, and 48.

82. The composition of any one of claims 68-81 further comprising a pharmaceutically acceptable carrier.

83. A method of treating a cell expressing a mutant human huntingtin gene, wherein the expression of the mutant huntingtin gene results in a huntingtin protein having a polyglutamine N-terminal, comprising contacting the cell with the composition of any one of claims 68-82 so as to treat the cell.

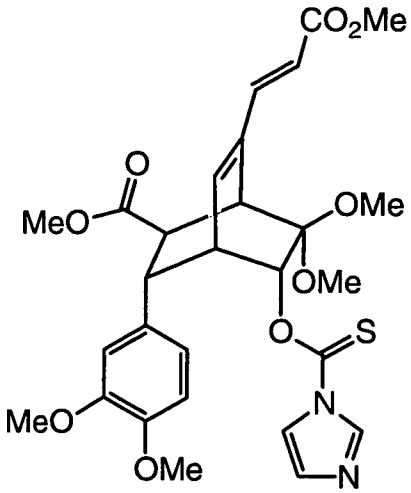
84. A method of treating a cell expressing a mutant human huntingtin gene, wherein the expression of the mutant huntingtin gene results in a huntingtin protein having a polyglutamine N-terminal, comprising contacting the cell with the compound of any one of claims 1 to 20 so as to treat the cell.

85. A method of reducing cell death in a population of cells expressing a mutant human huntingtin gene, wherein the expression of the mutant huntingtin gene results in a huntingtin protein having a polyglutamine N-terminal, comprising contacting the population of cells with the composition of any one of claims 68-82 so as to reduce cell death in the population of cells.

86. A method of reducing cell death in a population of cells expressing a mutant human huntingtin gene, wherein the expression of the mutant huntingtin gene results in a huntingtin protein having a polyglutamine N-terminal, comprising contacting the population of cells with the compound of any one of claims 1 to 20 so as to reduce cell death in the population of cells.

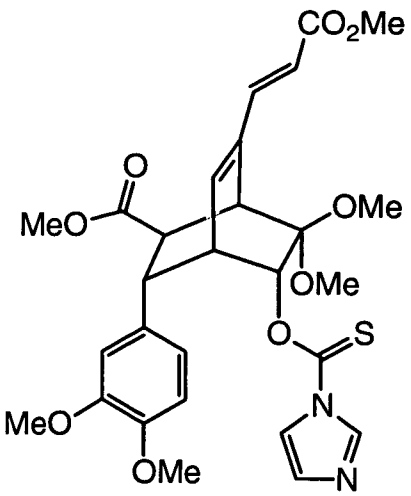
87. The method of claim 83 or 84, wherein the cell is a mammalian nerve cell.

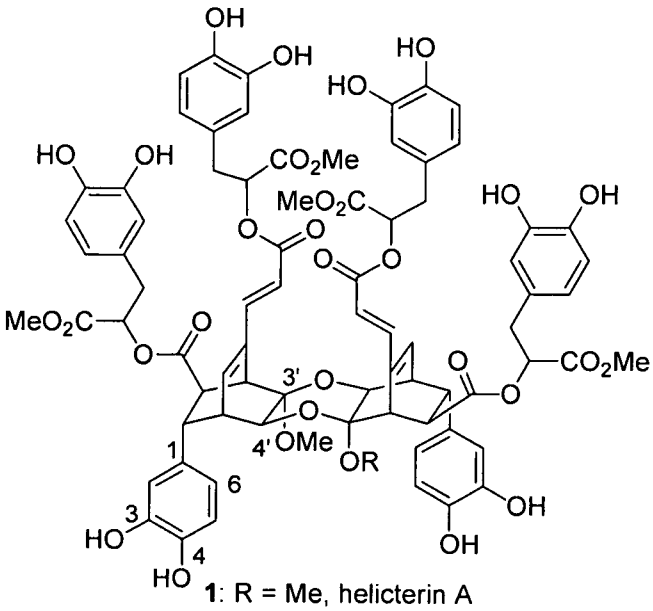
88. The method of claim 83 or 85, wherein the composition comprises a compound having the structure



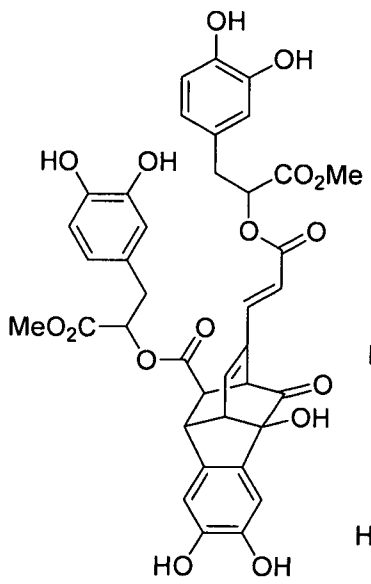
89. The method of claim 85 or 86, wherein the population of cells is a population of mammalian nerve cells.

90. The method of claim 84 or 86, wherein the compound has the structure

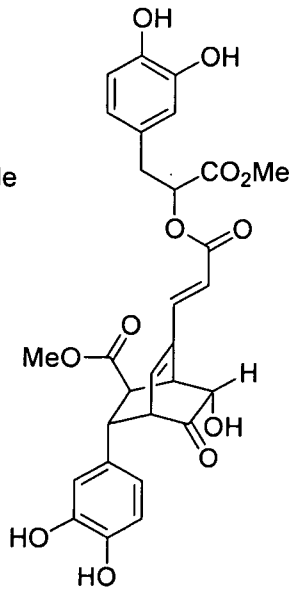




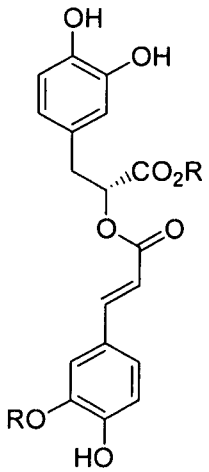
1: R = Me, helicterin A
2: R = H, helicterin B



3: helisorin



4: helisterculin A



5: R = H
6: R = Me

Figure 1.

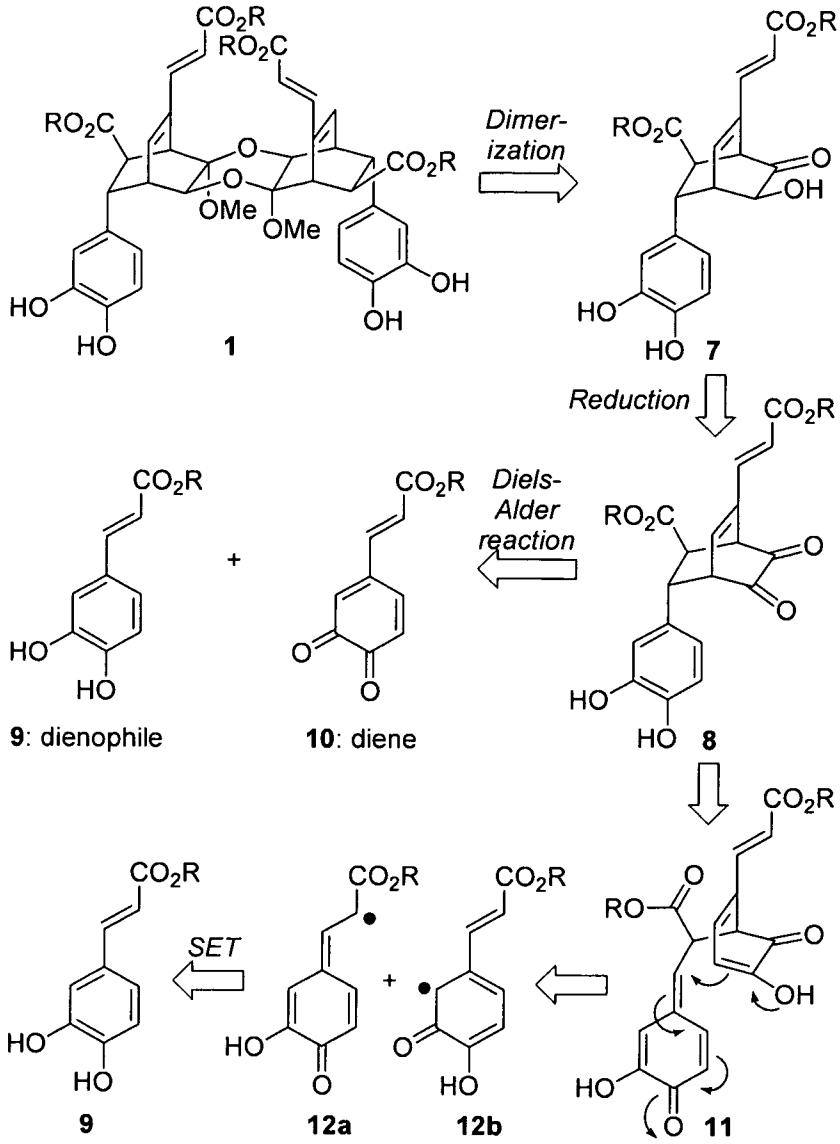

CO2R
RO2C
RO2C
CO2R
OMe
OMe
OH
OH
HO
HO
1
Dimer-
ization
RO2C
CO2R
O
OH
HO
HO
7
Reduction
CO2R
RO2C
O
O
HO
HO
8
Diels-
Alder
reaction
CO2R
HO
HO
9: dienophile
+
CO2R
O
O
10: diene
CO2R
RO
O
O
OH
HO
O
11
SET
CO2R
HO
HO
9
CO2R
HO
O
12a
+
CO2R
O
HO
12b

Figure 2.

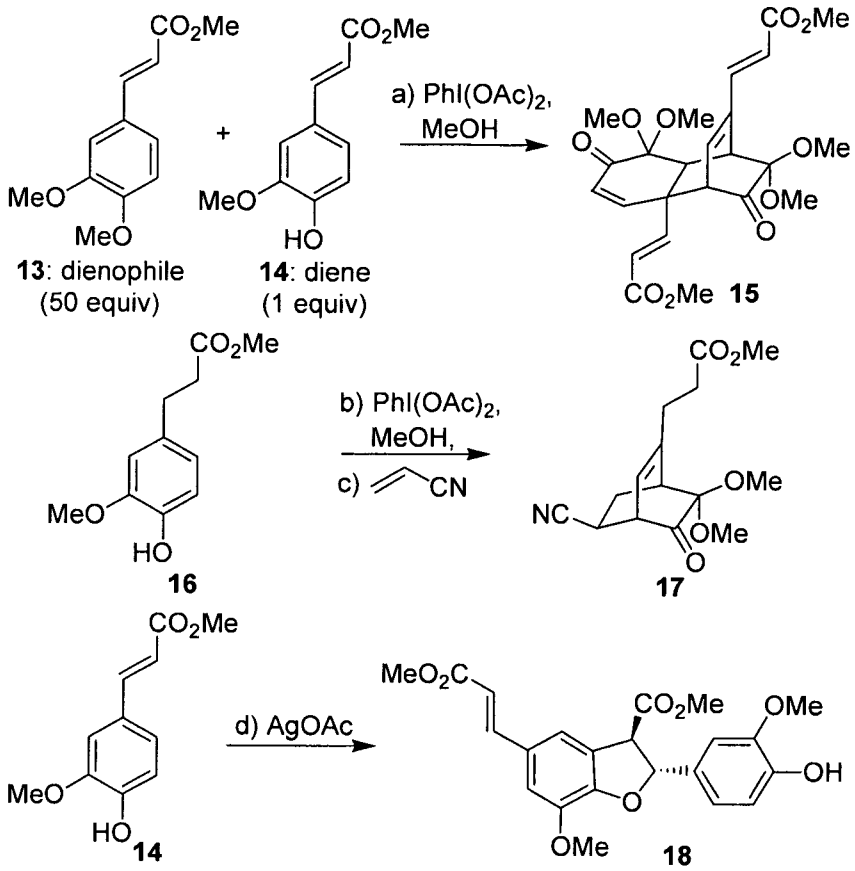

CO2Me
MeO
MeO
13: dienophile
(50 equiv)
+
CO2Me
MeO
HO
14: diene
(1 equiv)
a) PhI(OAc)2,
MeOH
MeO OMe
O
OMe
OMe
O
CO2Me 15
CO2Me
MeO
HO
16
b) PhI(OAc)2,
MeOH,
c) CN
CO2Me
NC
OMe
OMe
O
17
CO2Me
MeO
HO
14
d) AgOAc
MeO2C
CO2Me
OMe
OH
O
OMe
18

Figure 3.

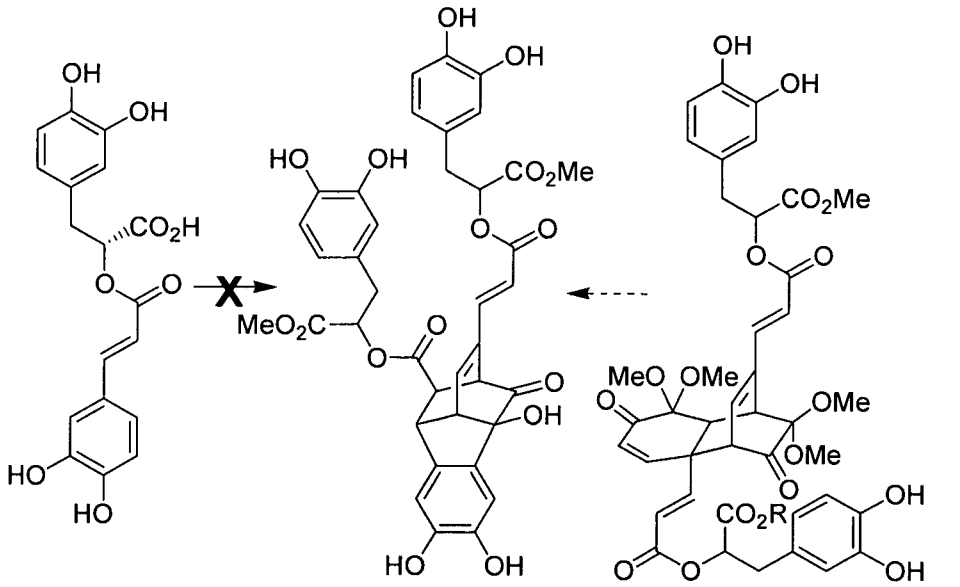

OH
OH
CO2H
O
O
HO
HO
5: rosmarinic acid
MeO2C
HO
OH
CO2Me
4: helisorin
MeO
OMe
OMe
OMe
CO2R
19: R = Me, potential precursor?

Figure 4.

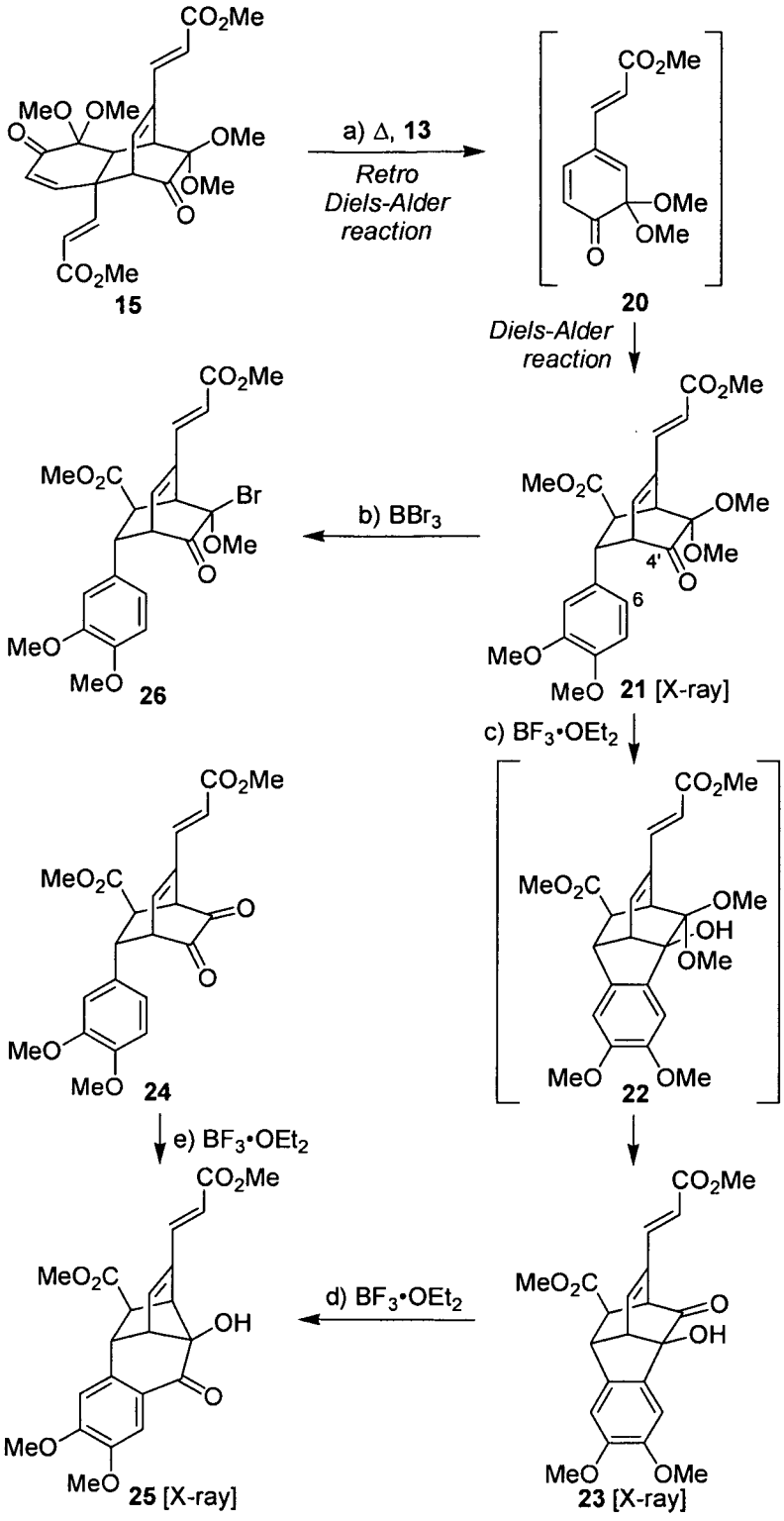

CO2Me
MeO OMe
OMe
OMe
CO2Me
15
a) Δ, 13
Retro
Diels-Alder
reaction
CO2Me
OMe
OMe
20
Diels-Alder
reaction
CO2Me
MeO2C
OMe
OMe
4'
6
MeO
MeO
21 [X-ray]
b) BBr3
CO2Me
MeO2C
Br
OMe
MeO
MeO
26
c) BF3•OEt2
CO2Me
MeO2C
OMe
OH
OMe
MeO
OMe
22
CO2Me
MeO2C
O
O
MeO
MeO
24
e) BF3•OEt2
CO2Me
MeO2C
OH
O
MeO
MeO
25 [X-ray]
d) BF3•OEt2
CO2Me
MeO2C
O
OH
MeO
OMe
23 [X-ray]

Figure 5.

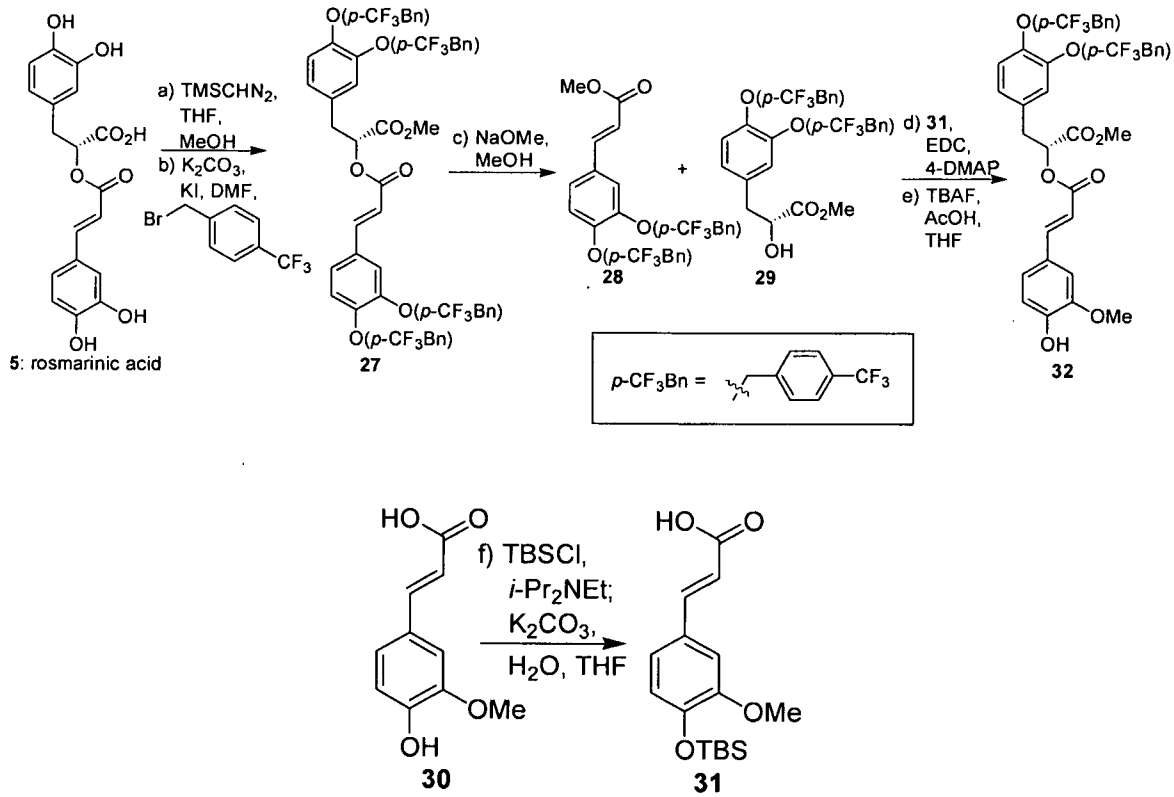

OH
OH
CO2H
O
O
OH
OH
5: rosmarinic acid
a) TMSCHN2, THF, MeOH
b) K2CO3, KI, DMF,
Br
CF3
O(p-CF3Bn)
O(p-CF3Bn)
CO2Me
O
O
O(p-CF3Bn)
O(p-CF3Bn)
27
c) NaOMe, MeOH
MeO
O
O(p-CF3Bn)
O(p-CF3Bn)
28
+
O(p-CF3Bn)
O(p-CF3Bn)
CO2Me
OH
29
d) 31, EDC, 4-DMAP
e) TBAF, AcOH, THF
O(p-CF3Bn)
O(p-CF3Bn)
CO2Me
O
O
OMe
OH
32
p-CF3Bn =
CF3
HO
O
OH
OMe
30
f) TBSCl, i-Pr2NEt; K2CO3, H2O, THF
HO
O
OTBS
OMe
31

Figure 6.

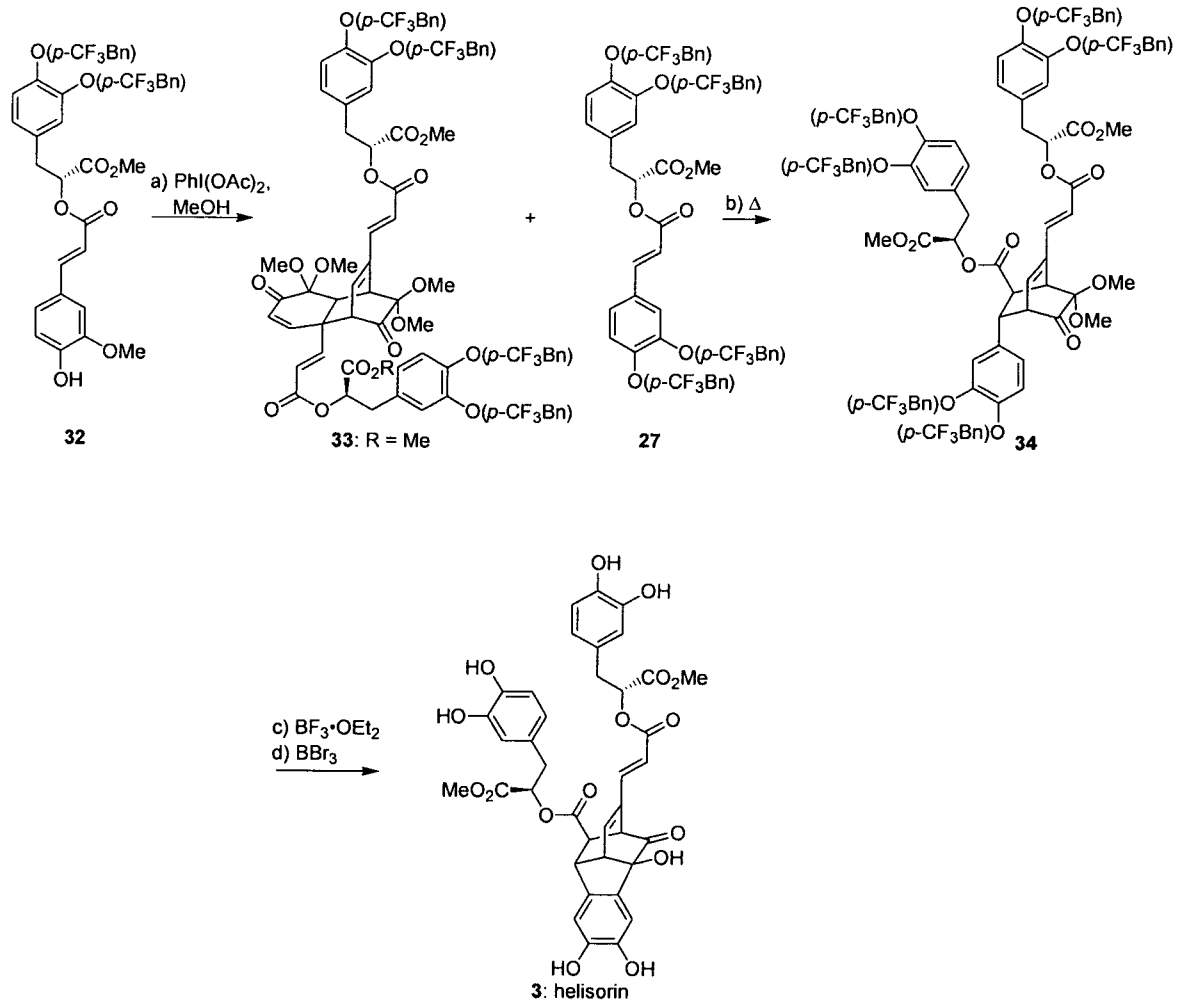
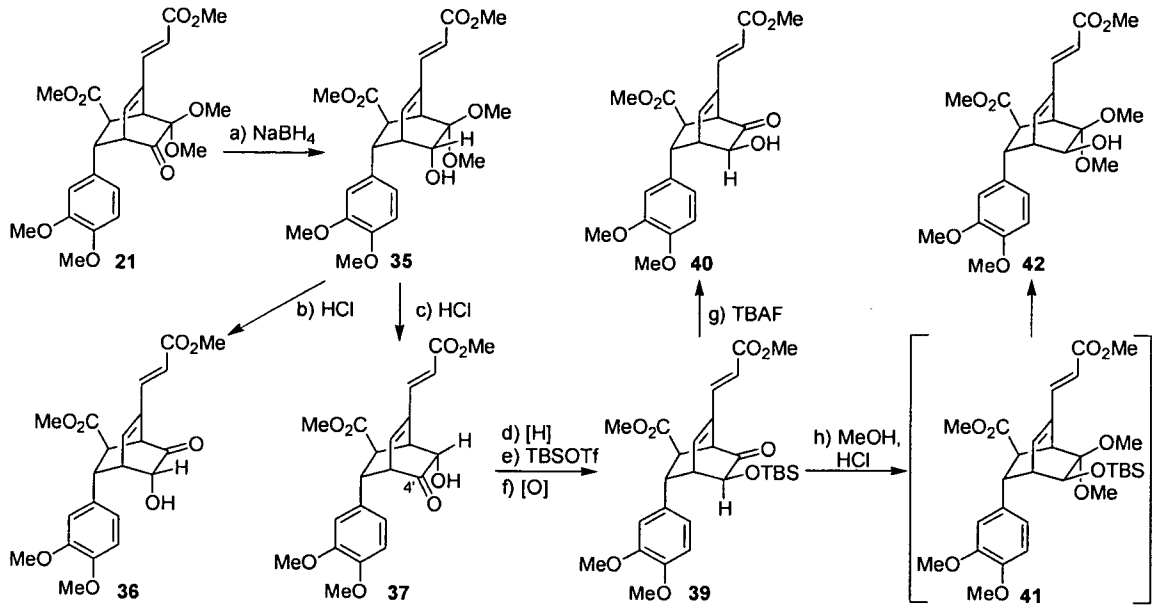


Figure 7.


a) NaBH4
b) HCl
c) HCl
d) [H]
e) TBSOTf
f) [O]
g) TBAF
h) MeOH, HCl
21
35
36
37
39
40
41
42

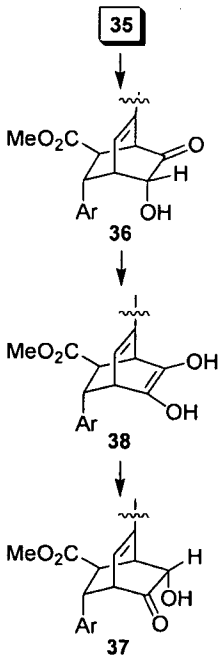

35
36
38
37

Figure 8.

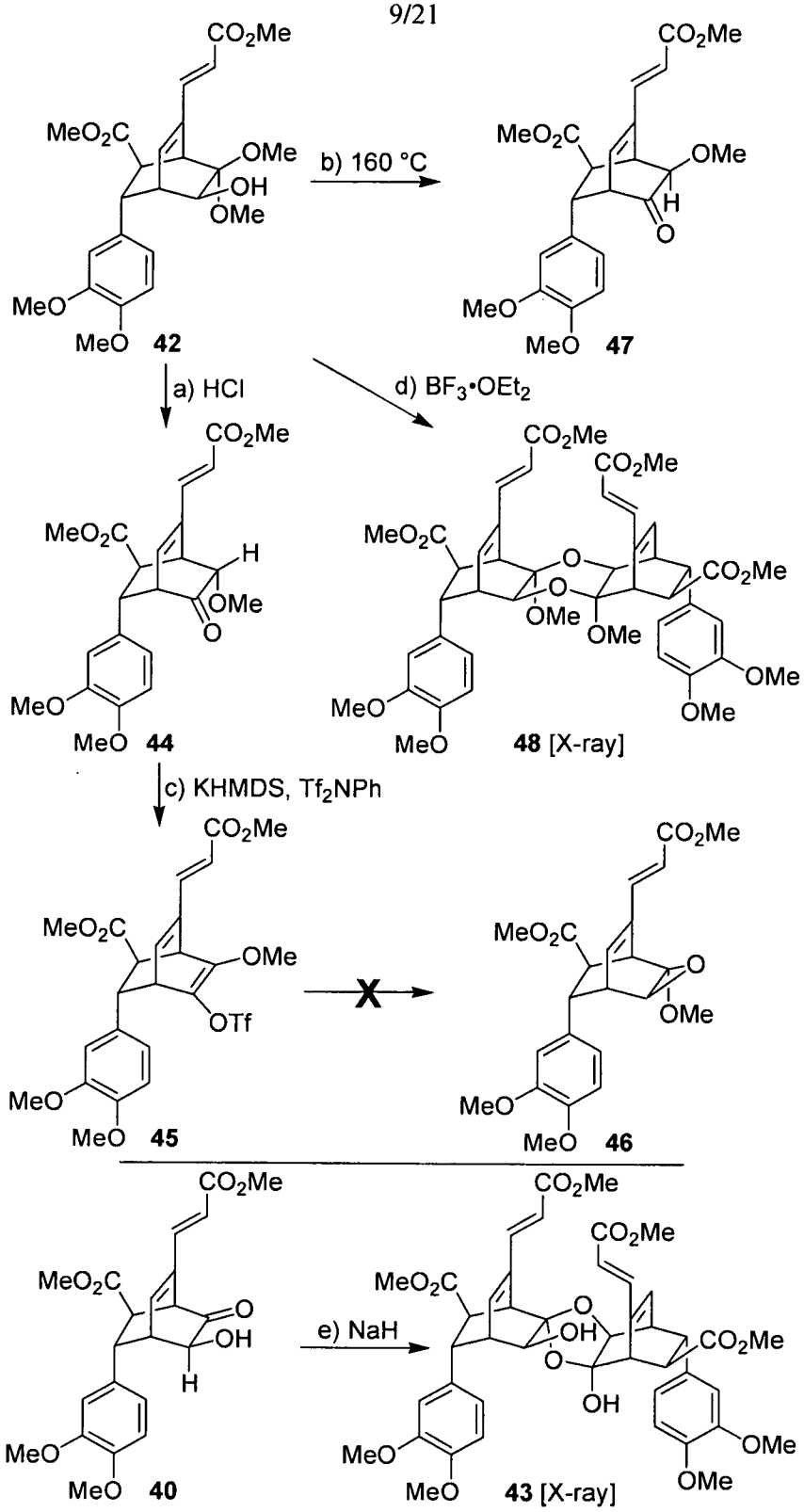

CO2Me
MeO2C
OMe
OH
OMe
MeO
MeO
42
b) 160 °C
47
a) HCl
d) BF3•OEt2
44
48 [X-ray]
c) KHMDS, Tf2NPh
OTf
45
46
e) NaH
40
43 [X-ray]

Figure 9.

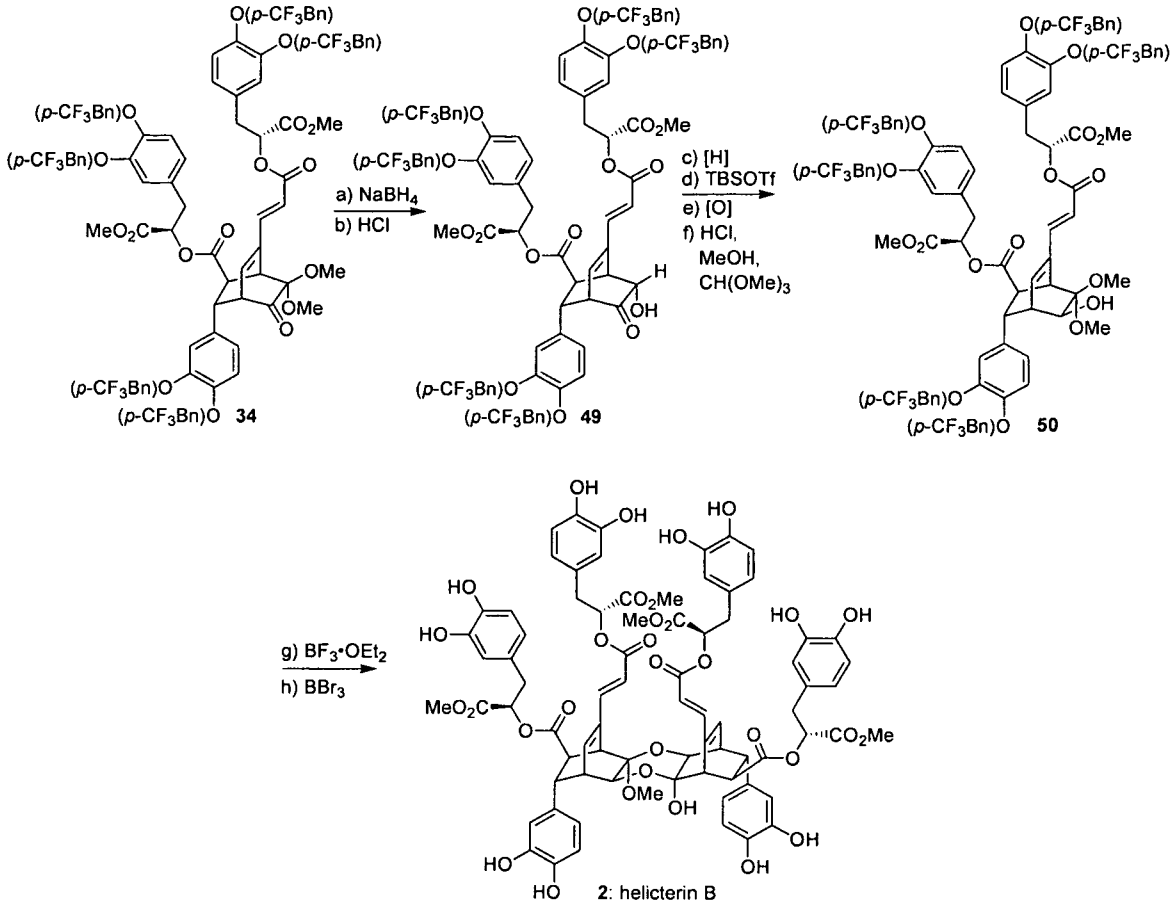

a) NaBH4
b) HCl
c) [H]
d) TBSOTf
e) [O]
f) HCl, MeOH, CH(OMe)3
g) BF3•OEt2
h) BBr3
34
49
50
2: helicterin B

Figure 10.

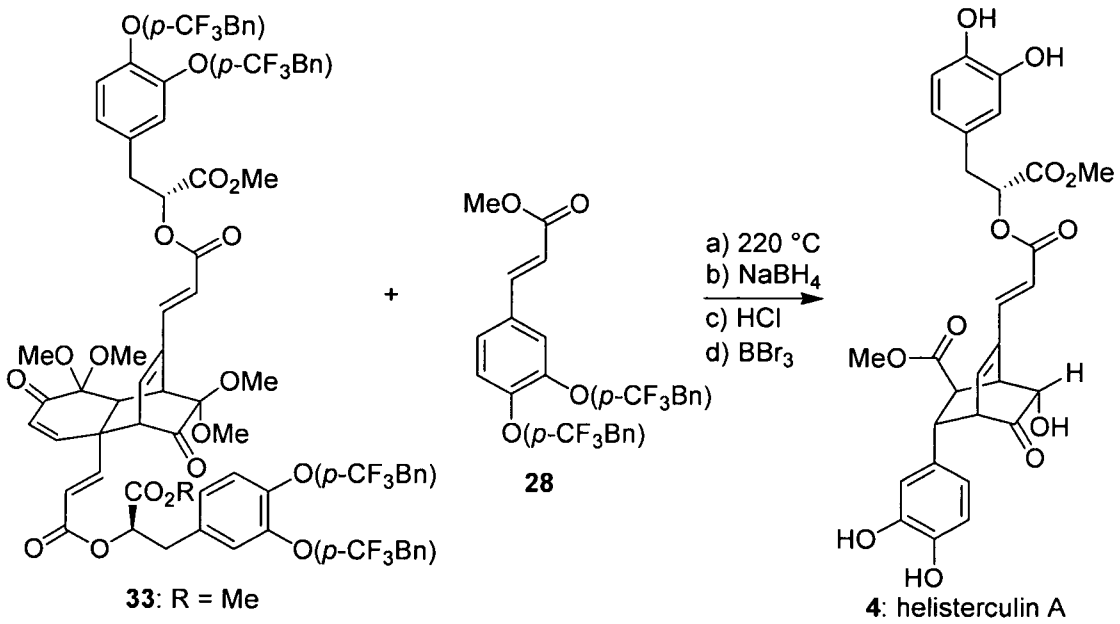

O(p-CF3Bn)
O(p-CF3Bn)
CO2Me
MeO
OMe
OMe
OMe
CO2R
O(p-CF3Bn)
O(p-CF3Bn)
33: R = Me
+
MeO
O(p-CF3Bn)
O(p-CF3Bn)
28
a) 220 °C
b) NaBH4
c) HCl
d) BBr3
OH
OH
CO2Me
MeO
H
OH
HO
HO
4: helisterculin A

Figure 11.

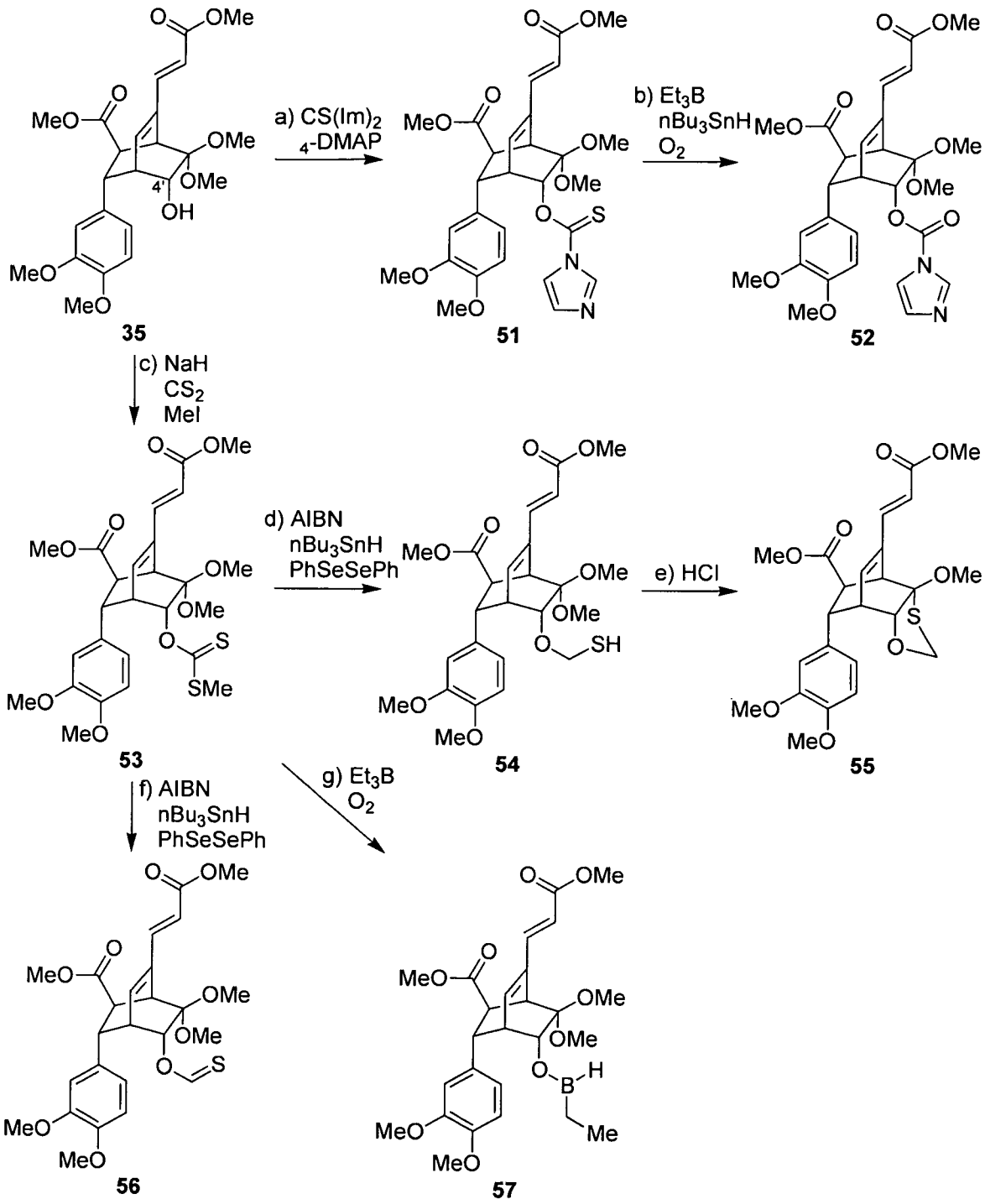

a) CS(Im)2
4-DMAP
b) Et3B
nBu3SnH
O2
c) NaH
CS2
MeI
d) AIBN
nBu3SnH
PhSeSePh
e) HCl
f) AIBN
nBu3SnH
PhSeSePh
g) Et3B
O2
35
51
52
53
54
55
56
57

Figure 12.

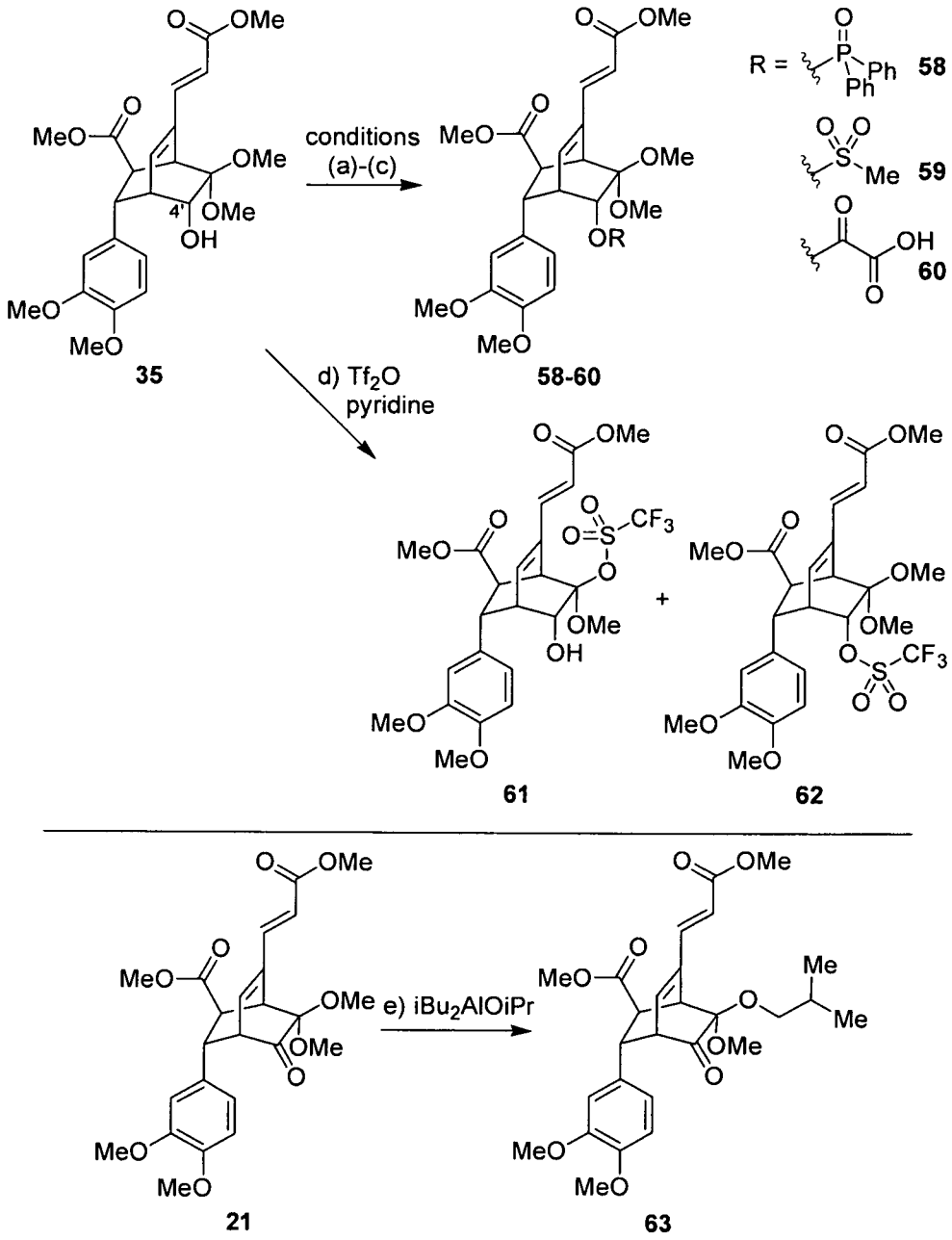

conditions
(a)-(c)
d) Tf2O
pyridine
e) iBu2AlOiPr
R =
58
59
60
35
58-60
61
62
21
63

Figure 13.

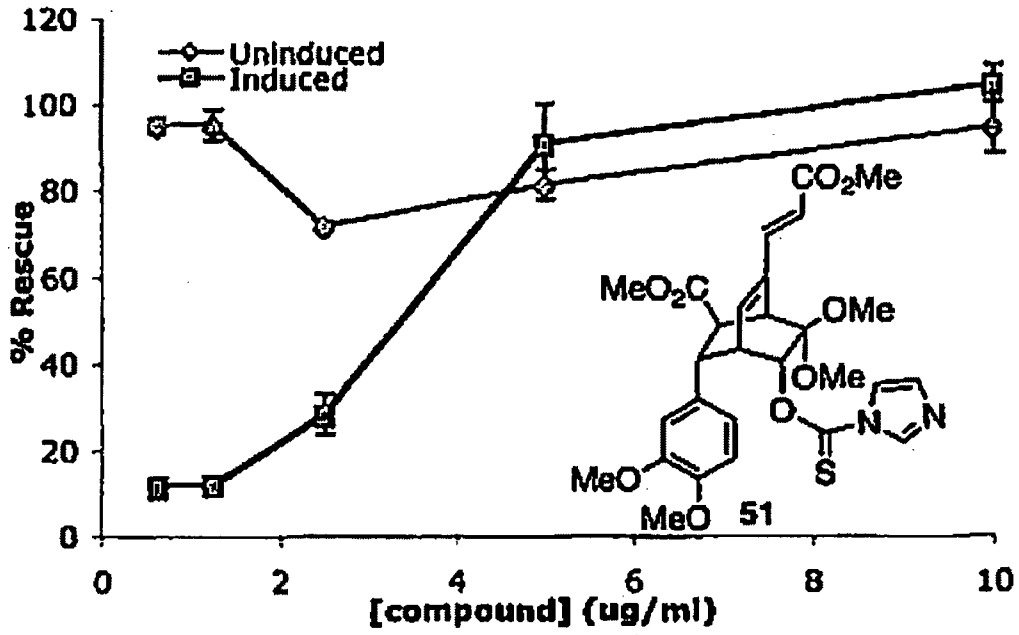
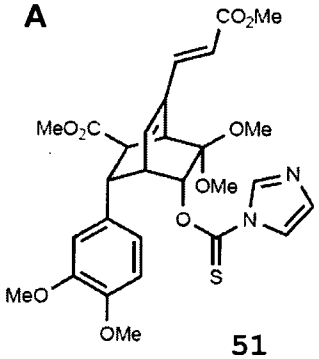
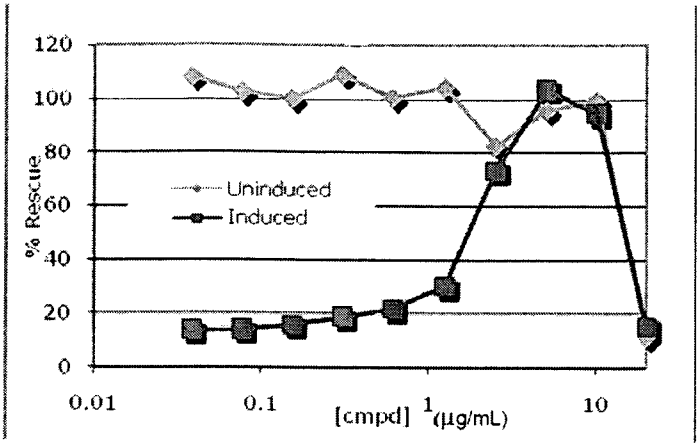

120
100
80
60
40
20
0
% Rescue
Uninduced
Induced
0
2
4
6
8
10
[compound] (ug/ml)
CO2Me
MeO2C
OMe
OMe
O
N
N
S
MeO
MeO
51

Figure 14.

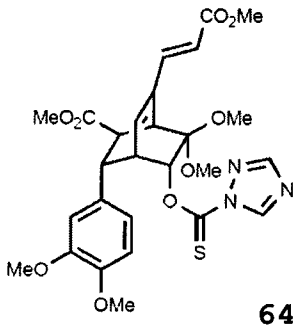
A



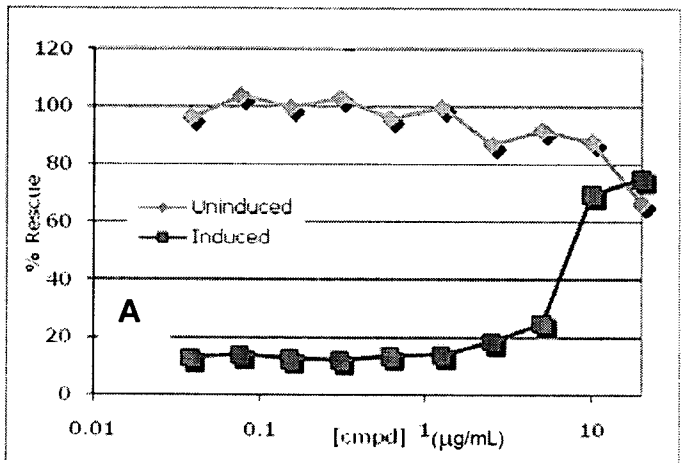
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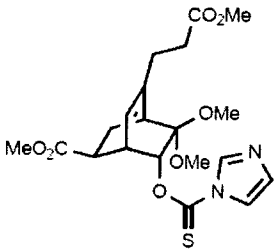
B



64



C



65

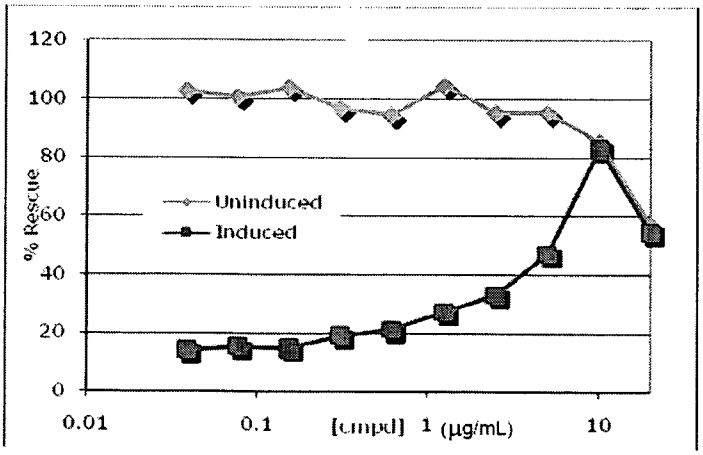
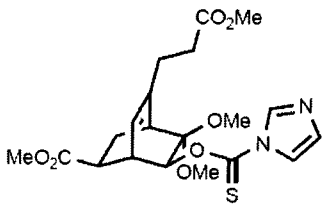
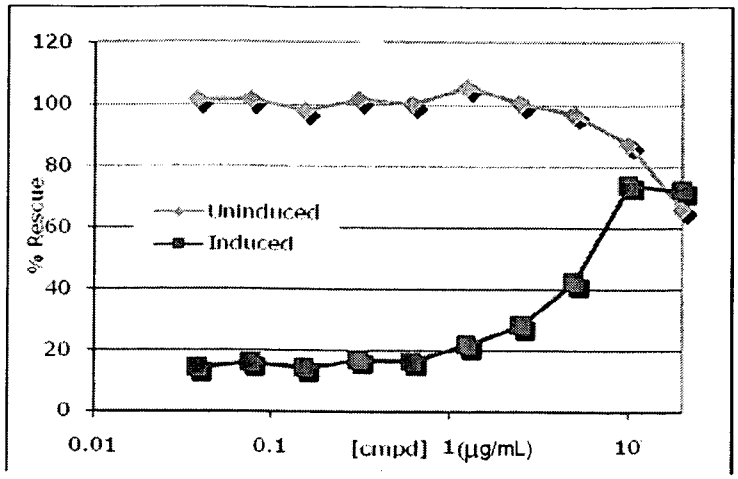


Figure 15.

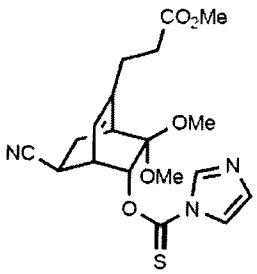
A



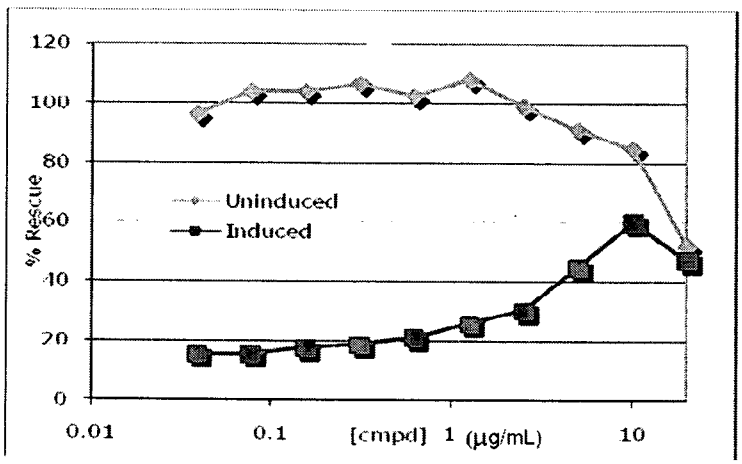
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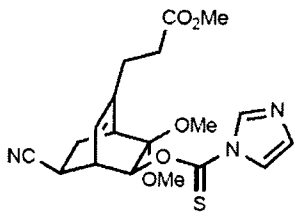
B



67



C



68

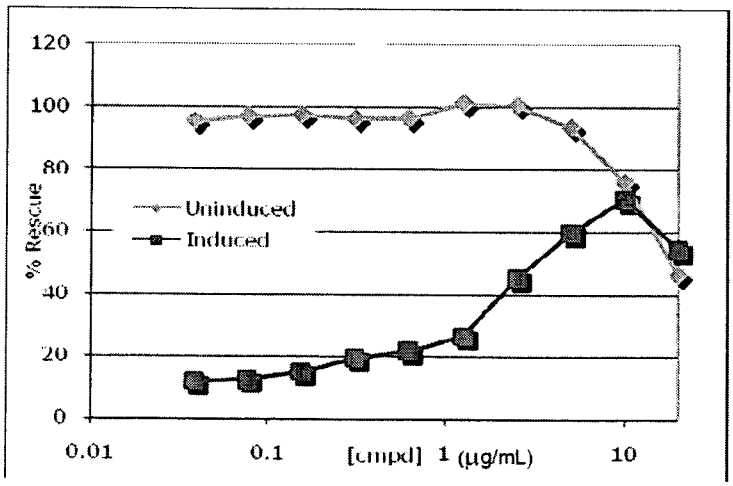
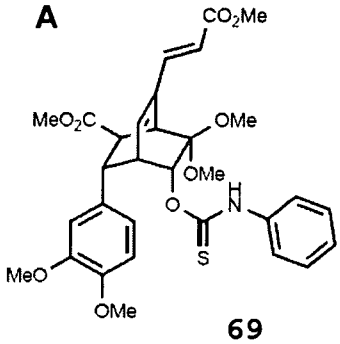
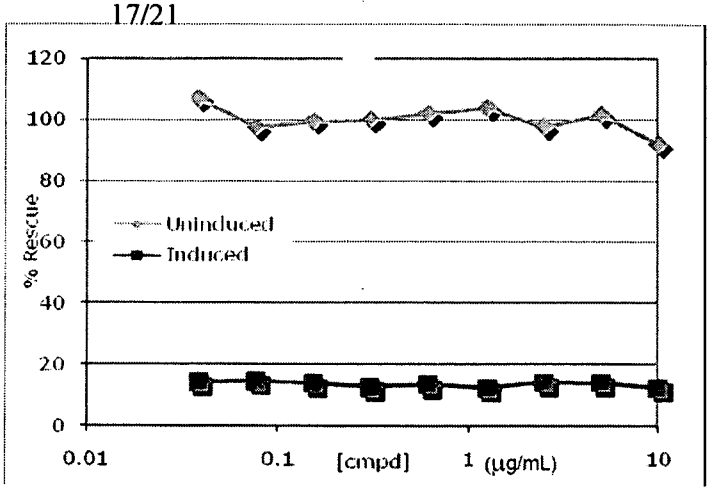


Figure 16.

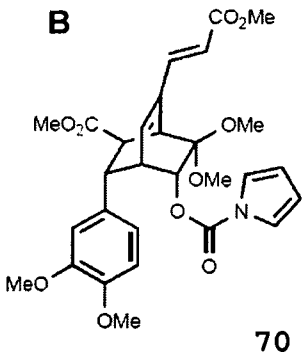
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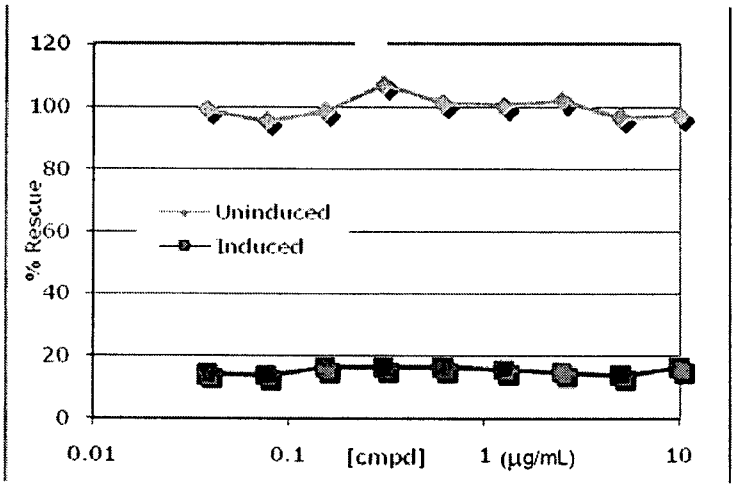
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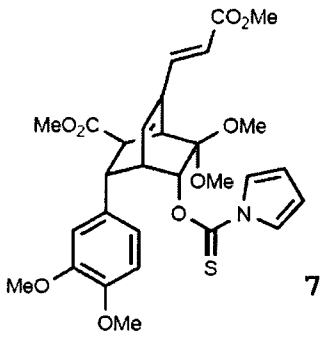
B



70



C



71

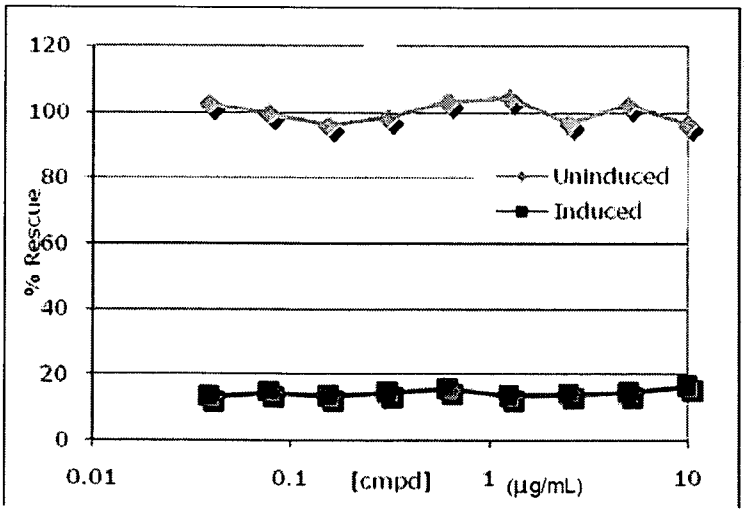
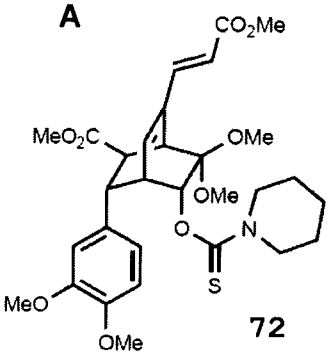
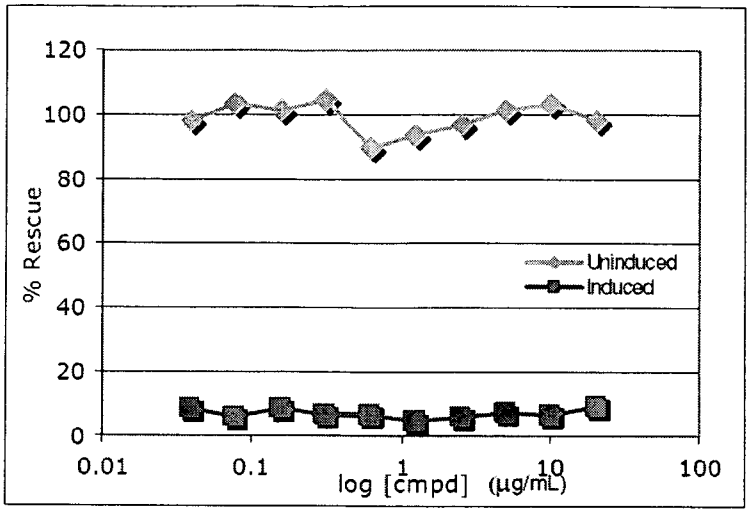


Figure 17.

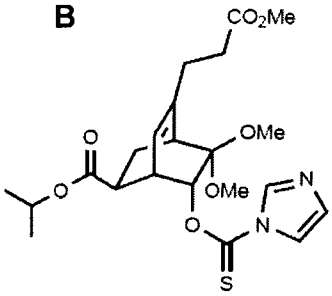
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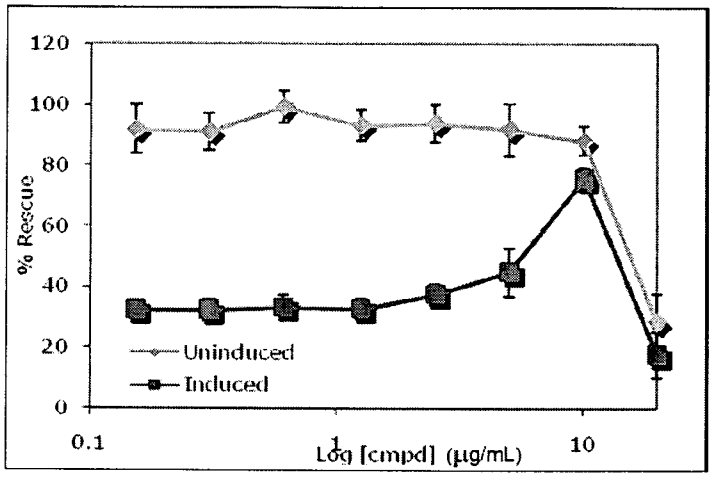
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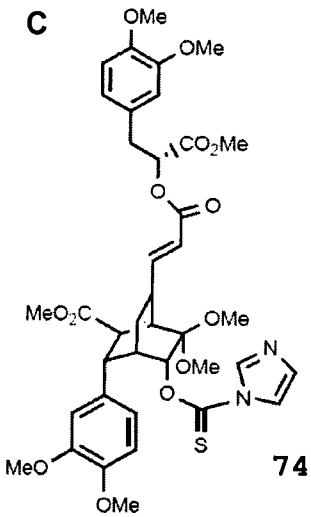
B



73



C



74

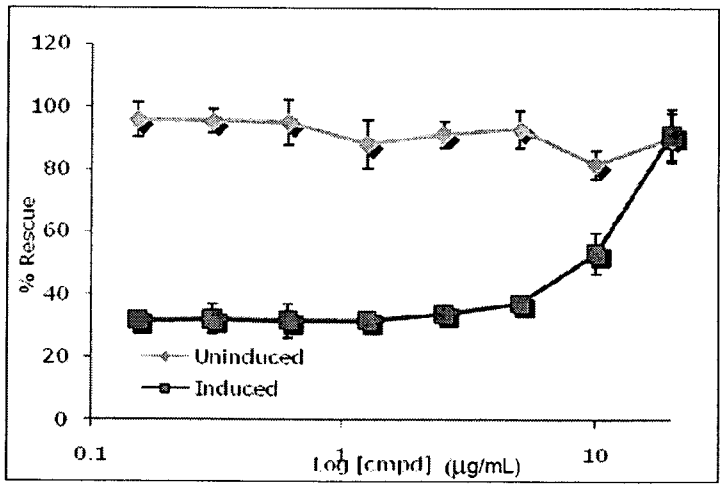
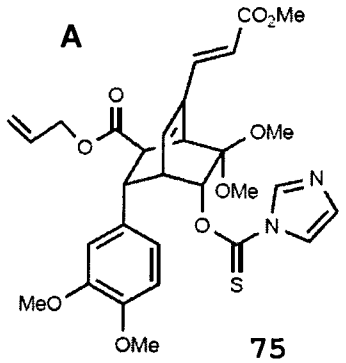
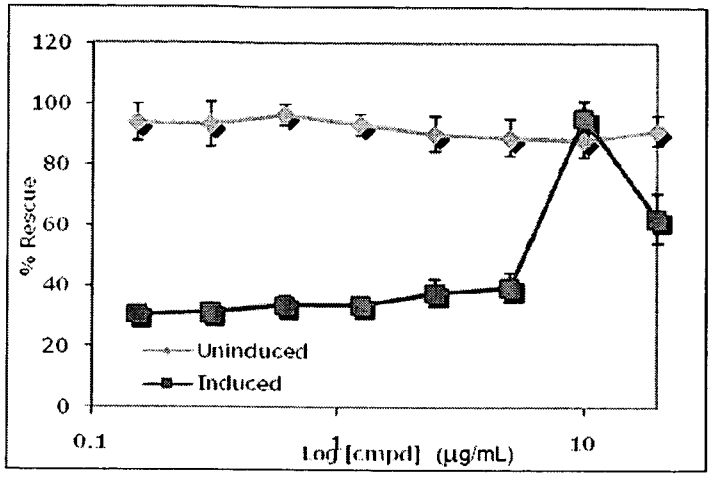
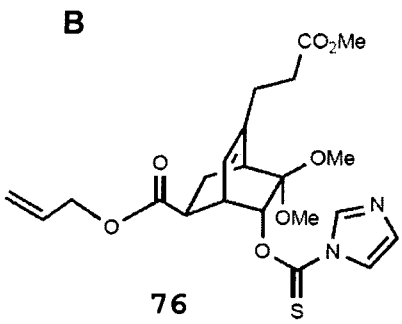
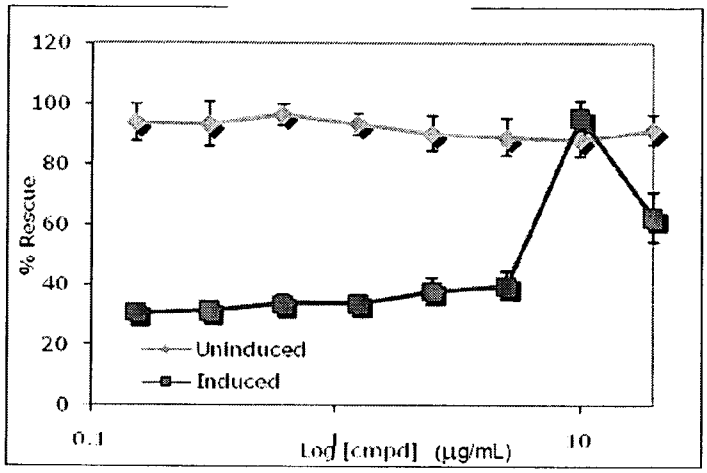


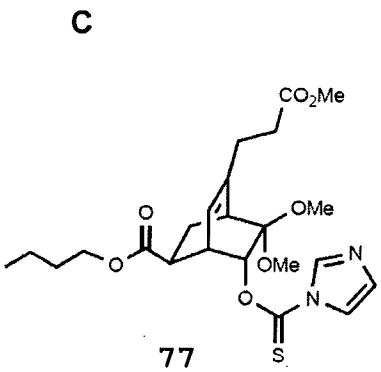
Figure 18.


A
CO2Me
O
O
OMe
OMe
N
N
O
S
MeO
OMe
75


120
100
80
60
40
20
0
% Rescue
Uninduced
Induced
0.1
Log [cmpd] (µg/mL)
10


B
CO2Me
O
OMe
OMe
N
N
O
S
76


120
100
80
60
40
20
0
% Rescue
Uninduced
Induced
0.1
Log [cmpd] (µg/mL)
10


C
CO2Me
O
OMe
OMe
N
N
O
S
77

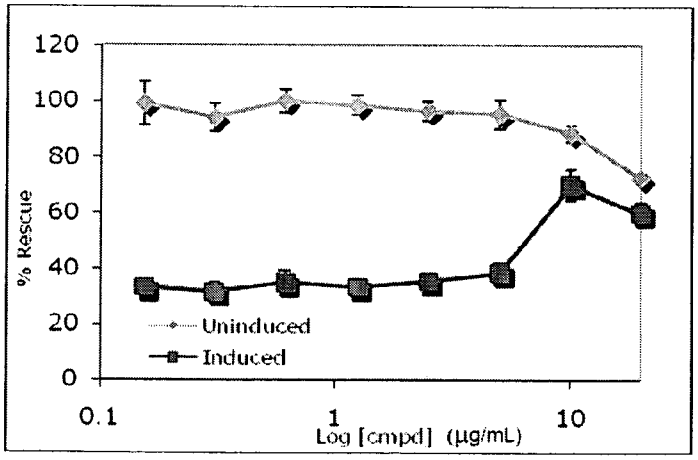
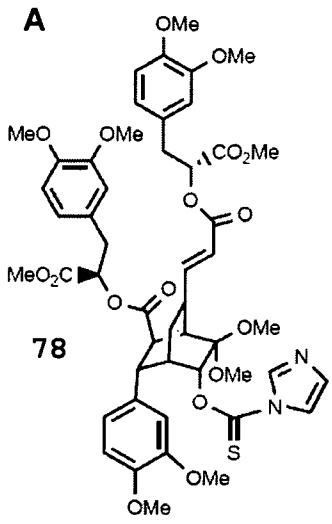
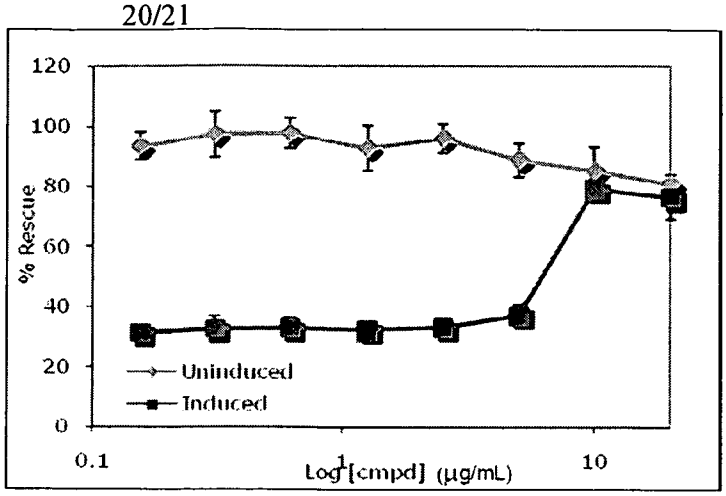

120
100
80
60
40
20
0
% Rescue
Uninduced
Induced
0.1
1
Log [cmpd] (µg/mL)
10

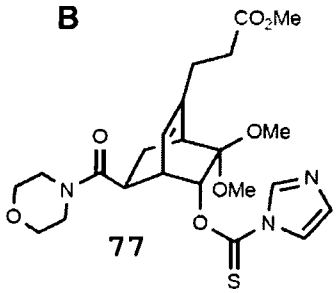
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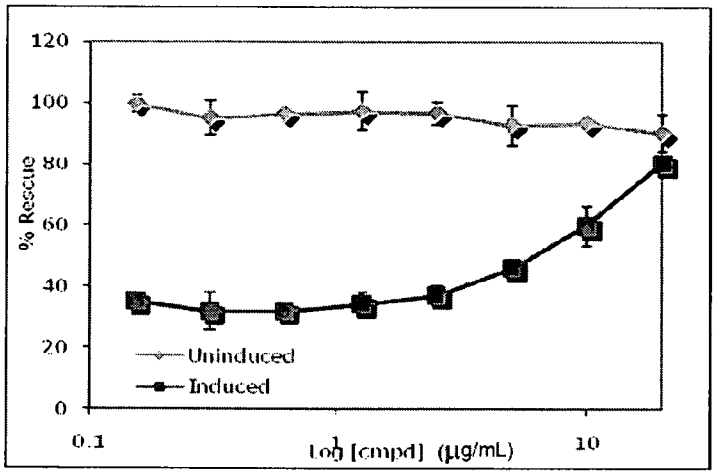
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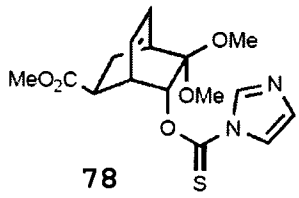


B





C



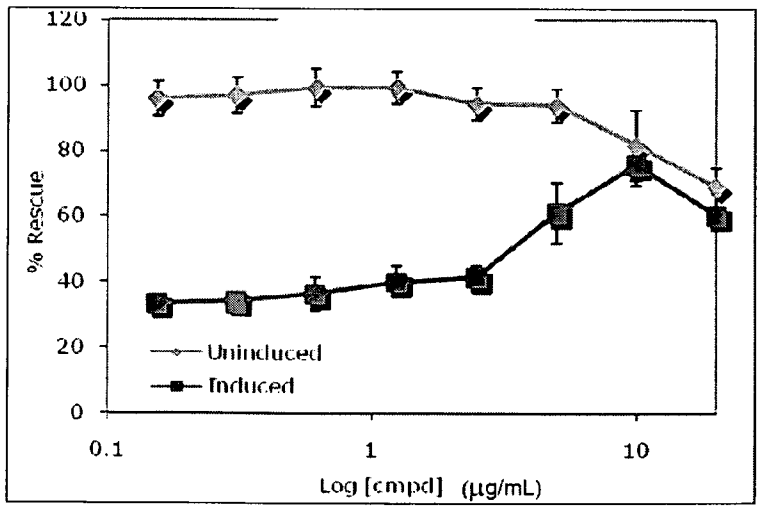


Figure 20.

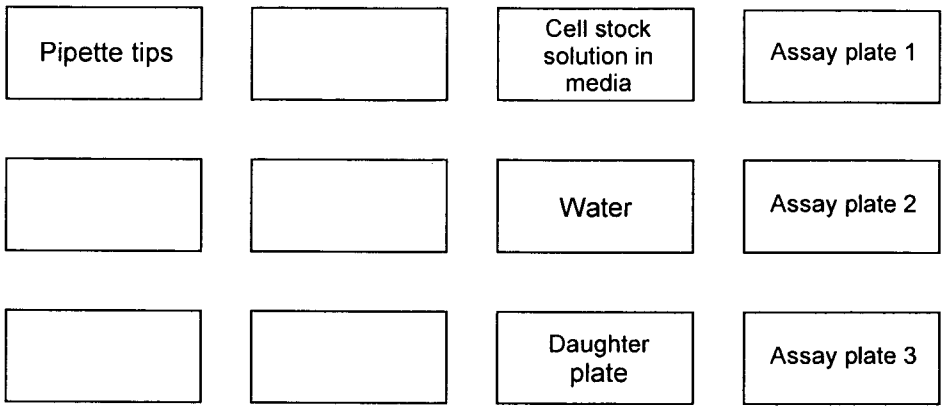

Pipette tips
Cell stock solution in media
Assay plate 1
Water
Assay plate 2
Daughter plate
Assay plate 3

Figure 21.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 09/06713

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A01N 65/00; A61K 36/00 (2010.01)
USPC - 424/725
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
USPC: 424/725

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 514/284-286 (see keywords below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
WEST: DB=PGPB,USPT,USOC,EPAB,JPAB
Google: Scholar/WEST: lithospermic acid oligomeric neolignans helisterculin helicterin helisorin analogs synthesis neolignans lignans diels alder oxidation hydride

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	TEZUKA et al. Helicterins A-F, Six New Dimeric (7.5', 8.2')-Neolignans From the Indonesian Medicinal Plant Helicteres Isora. Helvitica Chimica Acta, 2000, Vol 83, pP 2908-2919; pg 2909, Compounds 7, 8 and 9; pg 2917	1-15, 26-48, 50-54, 63, 66, 68-77
Y	O'MALLEY et al. Total Synthesis of (+)-Lithospermic Acid by Asymmetric Intramolecular Alkylation via Catalytic C-H Bond Activation. Journal of American Chemical Society, 2005, Vol 127, pp 13496-13497; pg 13497, Schemes 3 and 4	1-15, 26-48, 50-54, 63, 66, 68-77
Y	WARD. Lignans, neolignans, and related Compounds. Natural Product Reports, 1995, Vol 12, pp 43-74; pg 56, Scheme 6, compound 170; pg 59, col 2, para 1; pg 61, Scheme 18, compounds 206 to 208; pg 50, Scheme 2, compounds 96 to 97; pg 54, Reaction 20; pg 71, Scheme 29; pg 59, col 2, para 1; pg 61, Scheme 18	31-48, 50-54, 63, 66

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
08 April 2010 (08.04.2010)	23 APR 2010
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 09/06713

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 49, 60 and 82-90
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
see extra sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-15, 26-48, 50-54, 63, 66 and 68-77

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 09/06713

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I: claims 1-15, 26-48, 50-54, 63, 66 and 68-77, directed to compounds of the structure as shown in claim 1, and related methods of making.

Group II: claims 16-20, 55-59, 64-65 and 78-81, directed to compounds of the structure as shown in claim 16, and related methods of making.

Group III: claims 21-25 and 61-62, directed to compounds of the structure as shown in claim 21, and related methods of making.

Group IV: claim 67, directed to a compound of the structure as shown in said claim.

The inventions listed as Groups I-IV do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The claims of the various groups I-IV as defined above do not share any special technical feature. The compounds of the formulae as shown in claims 1, 16, 21 and 67 are distinct and do not share any special technical feature. As such, they would be expected to exhibit different physical, chemical, biological and pharmacological properties. While some of the compounds of the various groups may be precursors of the the compounds of other groups, they would not necessarily be limited to such use.

Thus, the inventions listed as Groups I-IV do not relate to a single general inventive concept under PCT Rule 13.1 because under PCT Rule 13.2 they lack the same or corresponding special technical feature. According to PCT Rule 13.2, unity of invention exists only when the same or corresponding technical feature is shared by all claimed inventions.

In this case the first named invention that will be searched without additional fees is Group I represented by claims 1-15, 26-48, 50-54, 63, 66 and 68-77.

Claims 49, 60 and 82-90 are improper multiple dependent claims because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).