METHODS FOR THE ESTERIFICATION OF ALCOHOLS AND COMPOUNDS USEFUL THEREFOR AS POTENTIAL ANTICANCER AGENTS

The invention relates to a method for preparing an ester, by admixing a compound having structure (I or IV) with a base and an alcohol to produce an ester, wherein the alcohol is a precursor to Taxol and its analogs. The present invention also relates to compounds having structure (I and IV) and methods of making them therefor. The invention also relates to the esterification of an alcohol by adding an alkoxide to a compound having structure (VII). The invention further relates to compounds having structure (I, IV, and VII) and methods of making them therefor. The invention further relates to alcohols, and, in particular, alcohols that are synthetic precursors to Taxol and analogs thereof.
FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

| AL | Albania           | KS | Spain          | LS | Lesotho       |
| AM | Armenia          | FI | Finland        | LT | Lithuania     |
| AT | Austria          | FR | France         | LU | Luxembourg    |
| AU | Australia        | GA | Gabon          | LV | Latvia        |
| AZ | Azerbaijan       | GB | United Kingdom | MC | Monaco        |
| BA | Bosnia and Herzegovina | GE | Georgia      | MD | Republic of Moldova |
| BB | Barbados         | GH | Ghana          | MG | Madagascar   |
| BE | Belgium          | GN | Guinea         | MK | The former Yugoslavia |
| BF | Burkina Faso     | GR | Greece         | ML | Mali          |
| BG | Bulgaria         | HU | Hungary        | MN | Mongolia      |
| BJ | Benin            | IE | Ireland        | MR | Mauritania    |
| BR | Brazil           | IL | Israel         | MW | Malawi        |
| BY | Belarus          | IS | Iceland        | MX | Mexico        |
| CA | Canada           | IT | Italy          | NE | Niger         |
| CF | Central African Republic | JP | Japan        | NL | Netherlands   |
| CG | Congo            | KE | Kenya          | NO | Norway        |
| CH | Switzerland      | KG | Kyrgyzstan     | NZ | New Zealand   |
| CI | Côte d’Ivoire    | KP | Democratic People’s | PL | Poland        |
| CM | Cameroon         | KR | Republic of Korea | PT | Portugal      |
| CN | China            | KZ | Kazakhstan     | RO | Romania       |
| CU | Cuba             | LC | Saint Lucia    | RU | Russian Federation |
| CZ | Czech Republic   | LI | Liechtenstein  | SD | Sudan         |
| DE | Germany          | LK | Sri Lanka      | SE | Sweden        |
| DK | Denmark          | LR | Liberia        | SG | Singapore     |
| EE | Estonia          | SI | Slovenia       |
| SK | Slovakia         |
| SN | Senegal          |
| SZ | Swaziland        |
| TD | Chad             |
| TG | Togo             |
| TJ | Tajikistan       |
| TM | Turkmenistan     |
| TR | Turkey           |
| TT | Trinidad and Tobago |
| UA | Ukraine          |
| UG | Uganda           |
| US | United States of America |
| UZ | Uzbekistan       |
| VN | Viet Nam         |
| VU | Yugoslavia       |
| ZW | Zimbabwe         |
METHODS FOR THE ESTERIFICATION OF ALCOHOLS AND
COMPONDS USEFUL THEREFOR AS POTENTIAL ANTICANCER
AGENTS

FIELD OF THE INVENTION

The invention relates to methods for esterifying alcohols. In particular, the
invention provides novel compounds and methods useful in the production of Taxol
and Taxol analogs.

BACKGROUND OF THE INVENTION

The esterification of alcohols is a common reaction in organic synthesis. Once
the ester is produced, the ester can undergo further reactions to produce complex
molecules. This approach is especially significant in the synthesis of natural products
and non-natural synthetic compounds that exhibit biological activity. By converting a
hydroxyl group to an ester, the chemical properties of the compound can change
dramatically. An example of this improved property is the anti-cancer drug, Taxol.

Taxol and other antitumor taxoids constitute some of the most important
discoveries in cancer chemotherapy in recent years. Taxol and Taxotere, which is a
semi-synthetic analog of Taxol, have been approved by the FDA for the treatment of
advanced ovarian and breast cancer. Additionally Taxol and Taxotere may be useful
for the treatment of non-small-cell lung cancer, head and neck cancer and several other
cancers. The structures of Taxol and Taxotere are shown below.
Taxol and Taxotere differ in their structure at the C-10 and C-3’ positions. While Taxol was first isolated from the bark of the pacific yew tree, *Taxus brevifolia*, Taxotere, a synthetic analog of Taxol, possesses better bioavailability than Taxol. Due to the limited availability of Taxol from the yew tree (1Kg from 10000 Kg of bark), different strategies including total synthesis, semisynthesis, cell and tissue culture of *taxus spp.*, have been investigated so that large amounts of Taxol can be produced. Although the total synthesis of Taxol was accomplished in 1994, lengthy multi-step sequences led to poor overall yield of Taxol. Therefore, total synthesis has not to date been a viable alternative to solve the supply problem.

One approach to a large scale production of Taxol and Taxotere is their semisynthesis from 10-deacetyl baccatin III (referred to as baccatin III or baccatin), shown below. Baccatin III can be readily obtained from the needles of the yew tree *Taxus baccata*. Importantly, yew needles can be quickly regenerated; therefore, a continuous supply of Taxol may be available without affecting the yew population.
Structure-activity relationships of Taxol derivatives indicate that the C-13 N-benzoyl-3-phenyl isoserine side chain, with the 2'R, 3'S stereochemistry, is of crucial importance for Taxol's cytotoxicity. Although there are methods in the art for the asymmetric synthesis of the C-13 side chain, coupling the side chain to the C-13 hydroxyl group is not a simple endeavor. The coupling reaction is complicated by the fact that the C-13 hydroxyl group is situated in the skeletal concavity of baccatin III, which makes this hydroxyl group sterically hindered. Furthermore, the C-13 hydroxyl group has been proposed to form a stabilizing hydrogen bond with the C-4 acetate moiety. These two factors contribute to the difficulty encountered in attaching the side chain to the C-13 hydroxyl group.

One approach to attaching the isoserine side chain to the C-13-hydroxyl group involves a condensation reaction between baccatin and an isoserine acid. Greene et al. (J. Am. Chem. Soc. 1988, 110, 5917) discloses the direct esterification reaction of a protected form of baccatin III and an isoserine acid under vigorous conditions (73°C for 4 days). International Patent Application No. WO 94/18186 to Swindell et al.; U.S. Patent No. 5,675,025 to Sisti et al.; and U.S. Patent No. 5,597,931 to Danishefsky et al. also disclose the condensation reaction between protected baccatins and isoserine acids and esters.

Another approach involves the condensation reaction between a heterocycle containing a carboxylic acid group and baccatin, followed by treatment with an acid to

Gennari et al. (Angew. Chem. Int. Ed. Engl. 1996, 35, 1723) discloses the reaction between a protected baccatin and a thioester of an oxazolidine in the presence of a base. In the case of the oxazolidine, seven steps were required to produce the oxazolidine with the thioester group, wherein the first step involves the use of chiral boron agent. The resulting oxazolidine thioester produced and subsequently coupled with baccatin is the anti isomer and not the syn isomer. The coupling reaction involves adding a base to a mixture of the protected baccatin and the oxazolidine thioester. An excess of oxazolidine thioester (3.5 equivalents) and base (4.5 equivalents) are used in the coupling reaction. Similar to the condensation reactions described above, the stereochemistry at C-2 of the oxazolidine thioester is also established.

Therefore, there remains a need for a more efficient, high yield synthesis of Taxol and other similar compounds. In addition, there exists a need for synthetic methods where the stereochemistry at C2 of the precursor to the side chain does not have to be established.
SUMMARY OF THE INVENTION

To overcome the shortcomings described above, the present invention, in one aspect, relates to a method for preparing an ester, comprising:

(a) admixing a compound having the structure I:

\[
\begin{array}{c}
\text{N} \\
\text{R}_1 \\
\text{O} \\
\text{a} \\
\text{R}_2 \\
\text{C(O)X}
\end{array}
\]

wherein,

10

\( R_1 \) and \( R_2 \) are, independently, from \( C_1 \) to \( C_{12} \) branched or straight chain alkyl; or substituted or unsubstituted aryl; and

\( X \) is a halogen or OR\(_3\), wherein \( R_3 \) is from \( C_1 \) to \( C_{12} \) branched or straight chain alkyl; substituted or unsubstituted aryl; aralkyl; acyl, or \( S(O)\_2R_{4t} \), wherein \( R_{4t} \) is \( C_1 \) to \( C_{12} \) branched or straight chain alkyl; or substituted or unsubstituted aryl,

with a base to form an intermediate; and

20

(b) admixing the intermediate of step (a) with an alcohol, an alkoxide, or a combination thereof.

The invention further relates to a method for preparing an ester, comprising:

25 admixing a compound having the structure III:
wherein,

R₁ and R₂ are, independently, from C₁ to C₁₂ branched or straight chain alkyl or substituted or unsubstituted aryl,

with an alcohol, an alkoxide or a combination thereof.

The invention further relates to a method for preparing an ester, comprising admixing:

(a) a base;

(b) an alcohol, an alkoxide or a combination thereof; and

(c) a compound having the structure I:

wherein,
R₁ and R₂ are, independently, from C₁ to C₁₂ branched or straight chain alkyl; or substituted or unsubstituted aryl; and

X is a halogen or OR₃, wherein R₃ is from C₁ to C₁₂ branched or straight chain alkyl; substituted or unsubstituted aryl; aralkyl; acyl, S(O)₂R₄₁, wherein R₄₁ is C₁ to C₁₂ branched or straight chain alkyl; or substituted or unsubstituted aryl.

The invention further relates to a method for preparing an ester, comprising admixing:

(a) a base;

(b) an alcohol, an alkoxide or a combination thereof; and

(c) a compound having the structure IV:

```
     N(R₉)(R₁₀)
      /     \
     R₁₁   C(O)Y
       /     |
      OR₁₂   IV
```

wherein,

R₉ and R₁₀ are, independently, an aralkyl or C(O)R₄₁, wherein R₄₁ is C₁ to C₁₂ straight chain or branched alkyl; substituted or unsubstituted aryl; or aralkyl;

R₁₁ is from C₁ to C₁₂ branched or straight chain alkyl or substituted or unsubstituted aryl;
R_{12} is silyl, alkyl, acyl, aryl, or aralkyl; and

Y is a halogen or OR_{13}, wherein R_{13} is from C_{1} to C_{12} branched or straight chain alkyl; or substituted or unsubstituted aryl; aralkyl; acyl; or S(O)_{2}R_{42}, wherein R_{42} is C_{1} to C_{12} straight chain or branched alkyl; or substituted or unsubstituted aryl.

The invention further relates to a method for preparing an ester, comprising admixing:

(a) an alcohol, an alkoxide, or a combination thereof; and

(b) a compound having the structure V:

\[
\begin{array}{c}
\text{N}(R_{9})(R_{10}) \\
\text{R}_{11} \quad \text{C} = \text{O} \\
\text{OR}_{12}
\end{array}
\]

wherein,

R_{9} and R_{10} are, independently, an aralkyl or C(O)R_{31}, wherein R_{31} is C_{1} to C_{12} straight chain or branched alkyl; substituted or unsubstituted aryl; or aralkyl;

R_{11} is from C_{1} to C_{12} branched or straight chain alkyl or substituted or unsubstituted aryl; and

R_{12} is silyl, alkyl, aryl, aralkyl or acyl.
The invention further relates to a method for preparing a compound having the structure I:

\[
\begin{array}{c}
\text{R}_1 \\
\text{N} \\
\text{O} \\
\text{R}_2 \\
\text{C(O)X}
\end{array}
\]

5 wherein,

\( \text{R}_1 \) and \( \text{R}_2 \) are, independently, from \( \text{C}_1 \) to \( \text{C}_{12} \) branched or straight chain alkyl or substituted or unsubstituted aryl; and

10 \( \text{X} \) is \( \text{OR}_3 \), wherein \( \text{R}_3 \) is from \( \text{C}_1 \) to \( \text{C}_{12} \) branched or straight chain alkyl; substituted or unsubstituted aryl; aralkyl; acyl, or \( \text{S(O)}_2 \text{R}_{41} \), wherein \( \text{R}_{41} \) is \( \text{C}_1 \) to \( \text{C}_{12} \) branched or straight chain alkyl; or substituted or unsubstituted aryl, and

15 \( \text{R}_2 \) and \( \text{C(O)X} \) are \( \text{cis} \) to one another,

comprising:

(a) admixing a compound having the structure VI:

\[
\begin{array}{c}
\text{OH} \\
\text{R}_2 \\
\text{C(O)X} \\
\text{R}_1 \\
\text{NH} \\
\text{O}
\end{array}
\]
wherein,

\[ R_1 \text{ and } R_2 \text{ are, independently, from } C_1 \text{ to } C_{12} \text{ branched or straight chain alkyl or substituted or unsubstituted aryl; } \]

\[ X \text{ is OR}_3, \text{ wherein } R_3 \text{ is from } C_1 \text{ to } C_{12} \text{ branched or straight chain alkyl; substituted or unsubstituted aryl; aralkyl; acyl, or } S(O)_2R_{41}, \text{ wherein } R_{41} \text{ is } C_1 \text{ to } C_{12} \text{ branched or straight chain alkyl; or substituted or unsubstituted aryl; and } \]

the hydroxyl group and amide group are cis to one another,

with a cyclization agent.

The invention further relates to a compound having the formula I:

![Chemical Structure](image)

wherein,

\[ R_1 \text{ and } R_2 \text{ are, independently, from } C_1 \text{ to } C_{12} \text{ branched or straight chain alkyl or substituted or unsubstituted aryl; } \]

\[ X \text{ is OR}_3, \text{ wherein } R_3 \text{ is halogen; } C_1 \text{ to } C_{12} \text{ branched or straight chain alkyl; substituted or unsubstituted aryl; aralkyl; acyl, aralkyl, or } \]

\[ S(O)_2R_{41}, \text{ wherein } R_{41} \text{ is } C_1 \text{ to } C_{12} \text{ branched or straight chain alkyl; or substituted or unsubstituted aryl; and } \]
$R_2$ and $C(O)X$ are *cis* to one another.

The invention further relates to a compound having the structure IV:

```
      N(R_9)(R_{10})
    /    /
R_{11}  b   \  C(O)Y
    \    /  OR_{12}
```

wherein,

- $R_9$ and $R_{10}$ are aralkyl;
- $R_{11}$ is substituted or unsubstituted aryl;
- $R_{12}$ is acyl, silyl, alkyl, aryl or aralkyl; and
- $Y$ is a halogen or OR$_{13}$, wherein $R_{13}$ is from C$_1$ to C$_{12}$ branched or straight chain alkyl; substituted or unsubstituted aryl, acyl, aralkyl or S(O)$_2$R$_{42}$, wherein $R_{42}$ is C$_1$ to C$_{12}$ branched or straight chain alkyl; or substituted or unsubstituted aryl.

The invention further relates to a method for preparing a compound having the structure IV:

```
      N(R_9)(R_{10})
    /    /
R_{11}  b   \  C(O)Y
    \    /  OR_{12}
```
wherein,

R₉ and R₁₀ are aralkyl;

R₁₁ is substituted or unsubstituted aryl;

R₁₂ is acyl, silyl, alkyl, aryl, or aralkyl; and

Y is OR₁₃, wherein R₁₃ is from C₁ to C₁₂ branched or straight chain alkyl; substituted or unsubstituted aryl; acyl, aralkyl, or S(O)₂R₄₂, wherein R₄₂ is C₁ to C₁₂ branched or straight chain alkyl or substituted or unsubstituted aryl,

comprising:

(a) admixing a base and a compound having the structure IX:

```
    N(R₉)(R₁₀)
      \   /
       R₁₁   C(O)Y
       /   /
      OH
```

wherein,

R₉ and R₁₀ are aralkyl;

R₁₁ is substituted or unsubstituted aryl; and

Y is OR₁₃, wherein R₁₃ is from C₁ to C₁₂ branched or straight chain alkyl; or substituted or unsubstituted aryl, acyl, aralkyl, or
\[ S(O)_2R_{42}, \text{ wherein } R_{12} \text{ is } C_1 \text{ to } C_{12} \text{ branched or straight chain alkyl; or substituted or unsubstituted aryl,} \]

to produce an intermediate, and

(b) admixing the intermediate of step (a) with an esterification agent,
a silylating agent, or an alkylating agent.

The invention further relates to a method for preparing an ester, comprising

admixing a compound having the structure VII:

![Chemical Structure](image)

wherein,

\[ R_{14} \text{ and } R_{16} \text{ are, independently, hydrogen, Si}(R_{21})_3 \text{ or C}(O)R_{22}, \text{ wherein each } R_{21} \text{ is, independently, branched or straight chain } C_1-C_{12} \text{ alkyl; and } R_{22} \text{ is substituted or unsubstituted aryl, aralkyl or from } C_1-C_{12} \text{ branched or straight chain alkyl;} \]

\[ R_{17} \text{ is substituted or unsubstituted aryl, aralkyl, or from } C_1-C_{12} \text{ branched or straight chain alkyl;} \]

\[ R_{18} \text{ is hydrogen; branched or straight chain } C_1-C_{12} \text{ alkyl; unsubstituted or substituted aryl; aralkyl; Si}(R_{28})_3, \text{ or C}(O)R_{29}, \text{ wherein, each } R_{28} \text{ is,} \]

\[ \text{independently, branched or straight chain } C_1-C_{12} \text{ alkyl; or aralkyl;} \]
$R_{29}$ is substituted or unsubstituted aryl, aralkyl or from C$_1$-C$_{12}$ branched or straight chain alkyl;

$R_{19}$ and $R_{20}$ are, independently, branched or straight chain C$_1$-C$_{12}$ alkyl, aryl, aralkyl, or C(O)OR$_{30}$, wherein $R_{19}$ is not hydrogen;

$R_{30}$ is branched or straight chain C$_1$-C$_{12}$ alkyl; and

$V$ and $W$ are, independently, sulfur, oxygen, or NR$_{43}$, wherein $R_{43}$ is hydrogen; branched or straight chain C$_1$-C$_{12}$ alkyl; or aralkyl, with an alkoxide.

The invention further relates to a method for preparing a compound having the structure VII:

![Chemical Structure VII](image)

wherein,

$R_{15}$ and $R_{16}$ are, independently, hydrogen, Si($R_{21}$), or C(O)R$_{22}$, wherein each $R_{21}$ is, independently, branched or straight chain C$_1$-C$_{12}$ alkyl; and $R_{22}$ is substituted or unsubstituted aryl, aralkyl or from C$_1$-C$_{12}$ branched or straight chain alkyl;
$R_{17}$ is substituted or unsubstituted aryl, aralkyl, or from $C_{1}-C_{12}$ branched or straight chain alkyl;

$R_{18}$ is branched or straight chain $C_{1}-C_{12}$ alkyl; unsubstituted or substituted aryl; aralkyl; Si($R_{28}$)$_3$ or C(O)$R_{29}$, wherein,

each $R_{28}$ is, independently, branched or straight chain $C_{1}-C_{12}$ alkyl; or aralkyl;

$R_{29}$ is substituted or unsubstituted aryl, aralkyl or from $C_{1}-C_{12}$ branched or straight chain alkyl;

$R_{19}$ and $R_{20}$ are, independently, branched or straight chain $C_{1}-C_{12}$ alkyl, aryl, aralkyl, or C(O)OR$_{30}$, wherein $R_{15}$ is not hydrogen;

$R_{30}$ is branched or straight chain $C_{1}-C_{12}$ alkyl; and

$V$ and $W$ are, independently, sulfur, oxygen, or NR$_{43}$, wherein $R_{43}$ is hydrogen; branched or straight chain $C_{1}-C_{12}$ alkyl; or aralkyl,

comprising,

(a) admixing

(i) a compound having the structure X

![Structure X](image-url)
wherein R_{18}-R_{20} are as above,

(ii) a Lewis acid; and

(iii) a base,

to produce a first intermediate;

(b) reacting the first intermediate of step (a) with a compound having the structure XI:

\[ \text{XI} \]

wherein R_{15} and R_{17} are as above,

to produce a second intermediate; and

(c) admixing the second intermediate of step (b) with a proton source.

The invention further relates to a compound having the structure VII:

\[ \text{VII} \]
wherein,

\[ R_{15} \text{ and } R_{16} \text{ are, independently, hydrogen, Si}(R_{21})_3 \text{ or } C(O)R_{22}, \text{ wherein each } R_{21} \text{ is, independently, branched or straight chain } C_1-C_{12} \text{ alkyl; and } R_{22} \text{ is substituted or unsubstituted aryl, aralkyl or from } C_1-C_{12} \text{ branched or straight chain alkyl; } \]

\[ R_{17} \text{ is substituted or unsubstituted aryl, aralkyl, or from } C_1-C_{12} \text{ branched or straight chain alkyl; } \]

\[ R_{18} \text{ is hydrogen; branched or straight chain } C_1-C_{12} \text{ alkyl; unsubstituted or substituted aryl; aralkyl; } Si(R_{28})_3 \text{ or } C(O)R_{29}, \text{ wherein, } \]

each \( R_{28} \) is, independently, branched or straight chain \( C_1-C_{12} \) alkyl; or aralkyl;

\[ R_{29} \text{ is substituted or unsubstituted aryl, aralkyl or from } C_1-C_{12} \text{ branched or straight chain alkyl; } \]

\[ R_{19} \text{ and } R_{20} \text{ are, independently, branched or straight chain } C_1-C_{12} \text{ alkyl, aryl, aralkyl, or } C(O)OR_{30}, \text{ wherein } R_{19} \text{ is not hydrogen; } \]

\[ R_{30} \text{ is branched or straight chain } C_1-C_{12} \text{ alkyl; and } \]

\[ V \text{ and } W \text{ are, independently, sulfur, oxygen, or } NR_{43}, \text{ wherein } R_{43} \text{ is hydrogen; branched or straight chain } C_1-C_{12} \text{ alkyl; or aralkyl. } \]

The invention further relates to a method for preparing a compound having the structure VII:
wherein,

$R_{15}$ and $R_{16}$ are, independently, hydrogen, Si$(R_{21})$, or C(O)OMe, wherein each $R_{21}$ is, independently, branched or straight chain C$_{1}$-C$_{12}$ alkyl; and $R_{22}$ is substituted or unsubstituted aryl, aralkyl or from C$_{1}$-C$_{12}$ branched or straight chain alkyl;

$R_{17}$ is substituted or unsubstituted aryl, aralkyl, or from C$_{1}$-C$_{12}$ branched or straight chain alkyl;

$R_{18}$ is hydrogen:

$R_{19}$ and $R_{20}$ are, independently, branched or straight chain C$_{1}$-C$_{12}$ alkyl, aryl, aralkyl, or C(O)OR$_{30}$ wherein $R_{19}$ is not hydrogen;

$R_{30}$ is branched or straight chain C$_{1}$-C$_{12}$ alkyl; and

$V$ and $W$ are, independently, sulfur, oxygen, or NR$_{43}$, wherein $R_{43}$ is hydrogen; branched or straight chain C$_{1}$-C$_{12}$ alkyl; or aralkyl,

comprising,

(a) admixing
(i) a compound having the structure XIII

![Chemical Structure XIII](attachment:structure_xiii.png)

wherein $R_{19}$-$R_{20}$ and $R_{22}$ are as above,

(ii) a Lewis acid; and

(iii) a first base,

10 to produce a first intermediate;

(b) reacting the first intermediate of step (a) with a compound having the structure XI:

![Chemical Structure XI](attachment:structure_xi.png)

wherein $R_{15}$ and $R_{17}$ are as above,

15 to produce a second intermediate; and

(c) admixing the second intermediate with a basic buffer, wherein the buffer comprises a second base.
The invention further relates a compound having the structure XIV or XV:

![Chemical structure](image1)

or

![Chemical structure](image2)

wherein,

$R_{44}$ and $R_{45}$ are, independently, hydrogen; C$_1$-C$_{12}$ branched or straight chain alkyl; or $R_{44}$ and $R_{45}$ are part of a cycloaliphatic group;

when $g$ is a single bond, $R_{46}$ is hydroxy; acetyl; or C$_1$-C$_{12}$ branched or straight chain alkoxy;
when \( g \) is a double bond, \( R_{46} \) is oxygen;

\( R_{49} \) is a C\(_{7-12}\) branched or straight chain alkyl ester; C\(_{1-12}\) branched or straight chain alkyl; carboxalkoxy; hydroxyalkyl; or derivatized or protected hydroxyalkyl;

\( R_{48} \) is C\(_{7-12}\) branched or straight chain alkyl; substituted or unsubstituted aryl; acetyl; hydroxyalkyl; or derivatized or protected hydroxyalkyl;

\( R_{49} \) and \( R_{50} \) are, independently, hydrogen; C\(_{1-12}\) branched or straight chain alkyl or alkoxy; or acetyl, provided that when one of \( R_{49} \) or \( R_{50} \) is hydrogen, the other of \( R_{49} \) and \( R_{50} \) is not hydrogen;

when \( m \) is a double bond, \( R_{51} \) is oxygen;

when \( m \) is a single bond, \( R_{51} \) is OH or OC(O)R\(_{32}\), wherein \( R_{32} \) is substituted or unsubstituted aryl; or cycloaliphatic; and

the hydroxyl group is located at carbon h or i.

The invention further relates to a method for preparing an ester, comprising admixing a compound having the structure XX:
wherein,

\( R_{60} \) is branched or straight chain \( C_1-C_{12} \) alkyl; unsubstituted or substituted aryl; aralkyl; \( \text{Si}(R_{63})_3 \) or \( \text{C}(O)R_{64} \), wherein,

each \( R_{63} \) is, independently, branched or straight chain \( C_1-C_{12} \) alkyl; or aralkyl;

\( R_{64} \) is substituted or unsubstituted aryl, aralkyl or from \( C_1-C_{12} \) branched or straight chain alkyl;

\( R_{61} \) and \( R_{62} \) are, independently, hydrogen, branched or straight chain \( C_1-C_{12} \) alkyl, aryl, aralkyl, or \( \text{C}(O)OR_{65} \);

\( R_{65} \) is branched or straight chain \( C_1-C_{12} \) alkyl; and

\( V \) and \( W \) are, independently, sulfur, oxygen, or \( NR_{66} \), wherein \( R_{66} \) is hydrogen; branched or straight chain \( C_1-C_{12} \) alkyl; or aralkyl,

with an alkoxide.

None of the references described above disclose the methods and compounds of the present invention. Additional advantages of the invention will be set forth in part in
the description which follows, and in part will be obvious from the description, or may be learned by practice of the invention. The advantages of the invention will be realized and attained by means of the elements and combinations particularly pointed out in the appended claims. It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the invention, as claimed.

DETAILED DESCRIPTION OF THE INVENTION

The present invention may be understood more readily by reference to the following detailed description of preferred embodiments of the invention and the examples included therein.

Before the present compositions of matter and methods are disclosed and described, it is to be understood that this invention is not limited to specific synthetic methods or to particular formulations, as such may, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only and is not intended to be limiting.

In this specification and in the claims which follow, reference will be made to a number of terms which shall be defined to have the following meanings:

The singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise.

Throughout the application, the term "compound" refers to all compounds embodied by the designated structure in the present application. For example, compound I refers to all compounds having the structure I as defined in the application.
The term "aralkyl" is defined as any group that has one or more aliphatic or
cycloaliphatic groups attached to an aromatic ring.

The term "cyclization agent" is defined as an agent that activates a hydroxyl
group and renders the carbon attached to it more susceptible to internal nucleophilic
attack.

The term "esterification agent" is defined as any agent that will catalyze the
formation of an ester from an alcohol or alkoxide and a carboxylic acid.

ESTERIFICATION OF ALCOHOLS-PART I

In accordance with the purpose(s) of this invention, as embodied and broadly
described herein, this invention, in one aspect, relates to a method for preparing an
ester, comprising:

(a) admixing a compound having the structure I:

\[ \text{I} \]

wherein,

R₁ and R₂ are, independently, from C₁ to C₁₂ branched or straight chain
alkyl; or substituted or unsubstituted aryl; and
X is a halogen or OR₂, wherein R₁ is from C₁ to C₁₂ branched or straight chain alkyl; substituted or unsubstituted aryl; aralkyl; acyl, or S(O)₂R₂₃, wherein R₂₃ is C₁ to C₁₂ branched or straight chain alkyl; or substituted or unsubstituted aryl,

with a base to form an intermediate; and

(b) admixing the intermediate of step (a) with an alcohol, an alkoxide, or a combination thereof.

The invention further relates to a method for preparing an ester, comprising admixing a compound having the structure III:

![Chemical Structure](image)

wherein,

R₁ and R₂ are, independently, from C₁ to C₁₂ branched or straight chain alkyl or substituted or unsubstituted aryl,

with an alcohol, an alkoxide or a combination thereof.

The invention further relates to a method for preparing an ester, comprising admixing:
(a) a base;

(b) an alcohol, an alkoxide or a combination thereof; and

(c) a compound having the structure I:

\[
\begin{array}{c}
N \\
\text{a} \\
\text{R_2} \\
\text{C(O)X}
\end{array}
\]

wherein,

10 \quad \text{R}_1 \text{ and } \text{R}_2 \text{ are, independently, from } \text{C}_1 \text{ to } \text{C}_{12} \text{ branched or straight chain alkyl; or substituted or unsubstituted aryl; and}

X \text{ is a halogen or OR}_3, \text{ wherein } \text{R}_3 \text{ is from } \text{C}_1 \text{ to } \text{C}_{12} \text{ branched or straight chain alkyl; substituted or unsubstituted aryl; aralkyl; acyl, or S(O)_2R}_4, \text{ wherein } \text{R}_4 \text{ is } \text{C}_1 \text{ to } \text{C}_{12} \text{ branched or straight chain alkyl; or substituted or unsubstituted aryl.}

The invention further relates to a method for preparing an ester, comprising admixing:

20

(a) a base;

(b) an alcohol, an alkoxide or a combination thereof; and

(c) a compound having the structure IV:
wherein,

\[ \text{IV} \]

\[ \text{N}(R_9)(R_{10}) \]

\[ R_{11} \]

\[ \text{C}(O)Y \]

\[ \text{OR}_{12} \]

R_9 and R_{10} are, independently, an aralkyl or C(O)R_{11}, wherein R_{31} is C_1 to C_{12} straight chain or branched alkyl; substituted or unsubstituted aryl; or aralkyl;

R_{11} is from C_1 to C_{12} branched or straight chain alkyl or substituted or unsubstituted aryl;

R_{12} is silyl, alkyl, acyl, aryl, or aralkyl; and

Y is a halogen or OR_{13}, wherein R_{13} is from C_1 to C_{12} branched or straight chain alkyl; substituted or unsubstituted aryl; aralkyl; acyl; or S(O)_{2}R_{42}, wherein R_{42} is C_1 to C_{12} straight chain or branched alkyl; substituted or unsubstituted aryl

The invention further relates to a method for preparing an ester, comprising admixing:

20

(a) an alcohol, an alkoxide, or a combination thereof; and

(b) a compound having the structure V:
The applicants have discovered that the combination of a base, an alcohol, and compound I or IV results in the formation of an ester. In one embodiment, the base can be added to a mixture of the alcohol and compound I and IV. In a preferred embodiment, compound I or IV is treated with a base, followed by the addition of the alcohol.

Without wishing to be bound by theory, it is believed that when the base and compound I or IV are combined together, the ketene complexes III and V are produced, respectively. It is believed that the base deprotonates a hydrogen at the \( \alpha \)-carbon (the carbon adjacent to the C(O)X group) of I and IV with concomitant loss of the leaving group, X and Y, respectively, to generate the ketene complex. The ketene complexes III and V are highly electrophilic; thus, they are susceptible to nucleophilic attack.

When a ketene is treated with an alcohol of the present invention, the alcohol reacts at C1 of the ketene to produce the corresponding ester (eq. 1). In another embodiment, an
alkoxide will react with the ketene to generate the ester. In the present invention, the ketene complexes III and V are not isolated, but generated *in situ* prior to the addition of the alcohol.

\[ \text{"ketene"} \quad \text{ROH} \quad \text{Eq. 1} \]

The bases useful for generating the ketene complexes of the present invention include, but are not limited to, an amide, a secondary amine or a tertiary amine. An amide is defined herein as \((R)_2N^+\), wherein each R is preferably an aliphatic group, a cycloaliphatic group, or a silyl group. Examples of amides useful in the present invention include, but are not limited to, potassium hexamethyldisilazide, sodium hexamethyldisilazide, lithium diisopropylamide, lithium hexamethyldisilazide, and lithium 2,2,6,6-tetramethylpiperidine. An examples of a secondary amine includes, but is not limited to, 2,2,6,6-tetramethylpiperidine. Examples of tertiary amines include, but are not limited to, dimethyl ethyl amine, triethylamine and pyridine.

One advantage of the present invention is that the stereochemistry at C2 of compounds I and IV does not have to be set. Thus, the stereochemistry at C2 can be S or R. When 1-*trans* and 1-*cis* are treated with a base (Scheme I), deprotonation at C2 and subsequent loss of X results in the formation of the ketene complex III. Thus, the applicants have discovered that the *cis* and *trans* isomers of I and IV can be used to esterify an alcohol, which is highly desirable and nowhere taught, suggested or otherwise motivated in the art.
Another advantage of the present method is that once the ketene complexes III and V are generated, nucleophilic attack by the alcohol or alkoxide can occur diastereoselectively. In one embodiment, in the case of the acyclic ketene complex V, nucleophilic attack by the alcohol or alkoxide will most likely occur opposite or anti to the adjacent R group at C_b of V. In another embodiment, in the case of the cyclic ketene complex III, nucleophilic attack by the alcohol or alkoxide can occur anti or syn to the adjacent R group at C_a; however, due to thermodynamic considerations, the trans ester is the predominant product formed. Thus, by varying the stereochemistry at C_a and C_b, it is possible to generate optically active esters using this method of the present invention. This feature of the present invention is very useful with respect to the synthesis of biologically active compounds that possess ester groups.

In one embodiment, a compound having the structure I can be used to esterify an alcohol. In the case of compound I, R_1 and R_2 are, independently, from C_1 to C_{12} branched or straight chain alkyl or substituted or unsubstituted aryl; and X is a halogen.
or OR₃, wherein R₃ is from C₁ to C₁₂ branched or straight chain alkyl; substituted or unsubstituted aryl; aralkyl; acyl, or S(O)₂R₄₁, wherein R₄₁ is C₁ to C₁₂ branched or straight chain alkyl or substituted or unsubstituted aryl. Throughout the application, the alkyl group is from C₁ to C₁₂ branched or straight chain alkyl, preferably from C₁ to C₆ branched or straight chain alkyl, and more preferably from C₁ to C₄ branched or straight chain alkyl. The term "acyl" is defined as a group having the structure R’(O)CO, wherein R’ is alkyl, aryl, or aralkyl. Acyl groups useful in the present invention include, but are not limited to, acetyl and benzoyl. The term "aralkyl" is defined as any group that has one or more aliphatic or cycloaliphatic groups attached to an aromatic ring. Examples of an aralkyl group of the present invention include, but are not limited to, benzyl and p-nitrobenzyl groups. In one embodiment, R₁ and R₂ are phenyl; R₃ is methyl; and the stereochemistry at a is S. In another embodiment, R₁ and R₂ are phenyl; R₃ is isopropyl; and the stereochemistry at a is S. In yet another embodiment, R₁ and R₂ are phenyl; R₃ is tert-butyl; and the stereochemistry at a is S.

The invention further relates to a method for preparing a compound having the structure I:

![Structure I](image)

wherein,

R₁ and R₂ are, independently, from C₁ to C₁₂ branched or straight chain alkyl or substituted or unsubstituted aryl; and
X is OR₃, wherein R₃ is from C₁ to C₁₂ branched or straight chain alkyl; substituted or unsubstituted aryl; aralkyl; acyl, or S(O)₂R₄₁, wherein R₄₁ is C₁ to C₁₂ branched or straight chain alkyl; or substituted or unsubstituted aryl, and

R₂ and C(O)X are cis to one another,

comprising:

(a) admixing a compound having the structure VI:

\[
\text{VI}
\]

wherein,

R₁ and R₂ are, independently, from C₁ to C₁₂ branched or straight chain alkyl or substituted or unsubstituted aryl;

X is OR₃, wherein R₃ is from C₁ to C₁₂ branched or straight chain alkyl; substituted or unsubstituted aryl; aralkyl; acyl, or S(O)₂R₄₁, wherein R₄₁ is C₁ to C₁₂ branched or straight chain alkyl; or substituted or unsubstituted aryl; and

the hydroxyl group and amide group are cis to one another,
with a cyclization agent.

The applicants have discovered a method for preparing a compound having the structure I, wherein \( R_2 \) and \( \text{C(O)X} \) are \textit{cis} to one another. The \textit{cis} and \textit{trans} isomers of compound I are shown in Scheme I. The art heretofore only disclosed a method for making the \textit{trans} isomer of compound I.

The use of a cyclization agent is necessary to cyclize compound VI to compound I. An example of a cyclization agent useful in the present invention is triflic anhydride with pyridine. Experimental conditions for the production of I via the cyclization of VI are outlined in the forthcoming examples.

The invention further relates to a compound having the formula I:

\[
\begin{align*}
\text{N} & \quad \text{R}_1 \\
\text{O} & \quad \text{I} \\
\text{R}_2 & \quad \text{C(O)X}
\end{align*}
\]

wherein,

\( R_1 \) and \( R_2 \) are, independently, from \( C_1 \) to \( C_{12} \) branched or straight chain alkyl or substituted or unsubstituted aryl;

\( X \) is \( \text{OR}_1 \), wherein \( R_1 \) is halogen; \( C_1 \) to \( C_{12} \) branched or straight chain alkyl; substituted or unsubstituted aryl; aralkyl; acyl, or \( S(O)_2 R_{41} \), wherein \( R_{41} \) is \( C_1 \) to \( C_{12} \) branched or straight chain alkyl; or substituted or unsubstituted aryl; and

\( R_2 \) and \( \text{C(O)X} \) are \textit{cis} to one another.
Compounds having the structure I, wherein the compound is the cis isomer, are not disclosed in the art. In one embodiment, R₁ and R₂ are phenyl; R₃ is methyl; and the stereochemistry at a is S. In another embodiment, R₁ and R₂ are phenyl; R₃ is tert-butyl; and the stereochemistry at a is S. In another embodiment, R₁ and R₂ are phenyl; R₃ is isopropyl; and the stereochemistry at a is S. In another embodiment, R₁ and R₂ are phenyl; R₃ is phenyl; and the stereochemistry at a is S. In another embodiment, R₁ and R₂ are phenyl; R₃ is 2,3-dimethyl propyl, wherein the stereochemistry at the 2-position is S; and the stereochemistry at a is S.

In another embodiment, compound IV can be used to esterify an alcohol. In this case, R₉ and R₁₀ are, independently, an aralkyl or C(O)R₃₁, wherein R₃₁ is C₁ to C₁₂ straight chain or branched alkyl; substituted or unsubstituted aryl; or aralkyl; R₁₁ is from C₁ to C₁₂ branched or straight chain alkyl or substituted or unsubstituted aryl; R₁₂ is silyl; alkyl; aryl; acyl; or aralkyl; and Y is a halogen or OR₁₃, wherein R₁₃ is from C₁ to C₁₂ branched or straight chain alkyl or substituted or unsubstituted aryl, acyl, aralkyl or S(O)₂R₄₂, wherein R₄₂ is C₁ to C₁₂ branched or straight chain alkyl or substituted or unsubstituted aryl. In one embodiment, R₉ is benzyl; R₁₀ is α-methyl benzyl; R₁₁ is phenyl; R₁₂ is C(O)Ph; R₁₃ is tert-butyl; and the stereochemistry at b is S. In another embodiment, R₉ is benzyl; R₁₀ is α-methyl benzyl; R₁₁ is phenyl; R₁₂ is C(O)Ph; R₁₃ is methyl; and the stereochemistry at b is S. In yet another embodiment, R₉ is benzyl; R₁₀ is α-methyl benzyl; R₁₁ is phenyl; R₁₂ is C(O)Ph; Y is chloride; and the stereochemistry at b is S. As described above, the stereochemistry at C2 does not have to be set; therefore, NR₉R₁₀ and OR₁₂ can be syn or anti to one another.

The invention further relates to a method for preparing a compound having the structure IV:
wherein,

Rₙ and R₁₀ are aralkyl;

R₁₁ is substituted or unsubstituted aryl;

R₁₂ is acyl, silyl, alkyl, aryl, or aralkyl; and

Y is OR₁₃, wherein R₁₃ is from C₁ to C₁₂ branched or straight chain alkyl or substituted or unsubstituted aryl, acyl, aralkyl or S(O)₂R₄₂, wherein R₄₂ is C₁ to C₁₂ branched or straight chain alkyl or substituted or unsubstituted aryl,

comprising:

(a) admixing a base and a compound having the structure IX:

wherein,
R₂ and R₁₀ are aralkyl;

R₅ is substituted or unsubstituted aryl; and

5 Y is OR₁₃, wherein R₁₃ is from C₁ to C₁₂ branched or straight chain alkyl; or substituted or unsubstituted aryl, acyl, aralkyl, or S(O)₂R₂₂, wherein R₂₂ is C₁ to C₁₂ branched or straight chain alkyl; or substituted or unsubstituted aryl, to produce an intermediate, and

(b) admixing the intermediate of step (a) with an esterification agent, a silylating agent, or an alkylating agent.

15 Treatment of compound IX with a base results in deprotonation of the hydroxyl proton to generate the corresponding alkoxide. The alkoxide is referred to as the intermediate recited above. The alkoxide is not isolated, but subsequently treated with an esterification agent, a silylating agent, or an alkylating agent to produce compound IV. The term "esterification agent" is defined as any agent that will react with an alkoxide to produce an ester. Examples of esterification agents useful in the present invention include, but are not limited to, organic anhydrides and acyl halides. In one embodiment, the esterification agent is benzoyl chloride.

The base employed is any compound capable of deprotonating a hydroxyl group. Bases used to generate the ketene compounds III and V, such as amides, secondary and tertiary amines, are suitable for deprotonation of the hydroxyl group of IX. In one embodiment, triethyl amine can be used as the base. The experimental conditions for preparing compound IV are presented in the forthcoming examples.

30 The invention further relates to a compound having the structure IV:
wherein,

R₉ and R₁₀ are aralkyl;

R₁₁ is substituted or unsubstituted aryl;

R₁₂ is acyl, silyl, alkyl, aryl or aralkyl; and

Y is a halogen or OR₁₃, wherein R₁₃ is from C₁ to C₁₂ branched or straight chain alkyl or substituted or unsubstituted aryl, acyl, aralkyl, or S(O)₂R₄₂, wherein R₄₂ is C₁ to C₁₂ branched or straight chain alkyl; or substituted or unsubstituted aryl.

In one embodiment, R₉ is benzyl; R₁₀ is α-methyl benzyl; R₁₁ is phenyl; R₁₂ is C(O)Ph; and Y is tert-butoxy. In another embodiment, R₉ is benzyl; R₁₀ is α-methyl benzyl; R₁₁ is phenyl; R₁₂ is C(O)Ph; and Y is methoxy.

Once the ketene complexes III and V have been generated, the addition of an alcohol or an alkoxide will result in the formation of an ester. The applicants have discovered that a wide variety of alcohols can be added to the ketene compounds III and V to produce the corresponding ester. Alcohols useful in the present invention include, but are not limited to, aliphatic alcohols, aromatic alcohols, cycloaliphatic alcohols, or heteroaromatic alcohols. In a preferred embodiment, the alcohol is a cycloaliphatic alcohol. In another embodiment, the alcohol is (2S)-hydroxy-3-methylbutane.
In another preferred embodiment, the alcohol is a compound having the structure II:

\[
\begin{align*}
&\text{R}_4 \text{ is acetyl or hydrogen;} \\
&\text{R}_5 \text{ is hydrogen;} \\
&\text{R}_6 \text{ is benzoyl;} \\
&\text{R}_7 \text{ is acetyl; and} \\
&\text{R}_8 \text{ is hydrogen, SiEt}_3 \text{ or } \text{C(O)CH}_2\text{CCl}_3.
\end{align*}
\]

As described above, it is advantageous to efficiently attach a side chain to the hydroxyl group at the C-13 position of baccatin and derivatives thereof. In one embodiment, for compound II, \(\text{R}_4\) and \(\text{R}_5\) are hydrogen; \(\text{R}_6\) is benzoyl; \(\text{R}_7\) is acetyl; and \(\text{R}_8\) is hydrogen, SiEt\(_3\) or C(O)CH\(_2\)CCl\(_3\). This alcohol is the precursor to taxotere. In another embodiment, \(\text{R}_4\) and \(\text{R}_5\) are acetyl; \(\text{R}_6\) is hydrogen; \(\text{R}_7\) is benzoyl; and \(\text{R}_8\) is hydrogen, SiEt\(_3\) or C(O)CH\(_2\)CCl\(_3\). This alcohol is the precursor to Taxol.
The invention further relates a compound having the structure XIV or XV:

**XIV**

**XV**

wherein,

- $R_{44}$ and $R_{45}$ are, independently, hydrogen; $C_1$-$C_{12}$ branched or straight chain alkyl; or $R_{44}$ and $R_{45}$ are part of a cycloaliphatic group;

- when $g$ is a single bond, $R_{46}$ is hydroxy; acetyl; or $C_1$-$C_{12}$ branched or straight chain alkoxy;
when g is a double bond, R_{48} is oxygen;

R_{47} is a C_{1}-C_{12} branched or straight chain alkyl ester; C_{1}-C_{12} branched or straight chain alkyl; carboalkoxy; hydroxyalkyl; or derivatized or protected hydroxyalkyl;

R_{48} is C_{1}-C_{12} branched or straight chain alkyl; substituted or unsubstituted aryl; acetyl; hydroxyalkyl; or derivatized or protected hydroxyalkyl;

R_{49} and R_{50} are, independently, hydrogen; C_{1}-C_{12} branched or straight chain alkyl or alkoxy; or acetyl, provided that when one of R_{49} or R_{50} is hydrogen, the other of R_{49} and R_{50} is not hydrogen;

when m is a double bond, R_{51} is oxygen;

when m is a single bond, R_{51} is OH or OC(O)R_{52}, wherein R_{52} is substituted or unsubstituted aryl; or cycloaliphatic; and

the hydroxyl group is located at carbon h or i.

Applicants have discovered that compounds having the structure XIV and XV are structurally simplified analogs of Taxol with incorporated structural elements of Taxol which can embody Taxol’s biological activity. Due to the difficulty in synthesizing Taxol, simplified analogs could be advantageous over semi-synthetic analogs of Taxol. The hydroxy group can be positioned at either carbon h or i, and the stereochemistry at these positions can be either R or S. In one embodiment, the hydroxyl group is at carbon h, and the stereochemistry at carbon h is S. In another embodiment, the hydroxyl group is at carbon h, and the stereochemistry at carbon h is R. In another embodiment, the hydroxyl group is at carbon i, and the stereochemistry
at carbon i is S. In another embodiment, the hydroxyl group is at carbon i, and the stereochemistry at carbon i is R.

In another embodiment, R_{44} and R_{45} of compounds XIV and XV are independently, hydrogen or methyl, preferably hydrogen and methyl. In another embodiment, R_{44} and R_{45} are part of a cycloaliphatic group, wherein the cycloaliphatic group can be cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. In one embodiment, the cycloaliphatic group is a cyclopropyl group. In another embodiment, R_{47} is methyl ester or methyl. In another embodiment, R_{48} is hydroxy, ethoxy, propoxy, or derivatized or protected hydroxy. The term "derivatized or protected hydroxy" refers to hydroxyl group that has been converted to a alkoxy group, an aryloxy group, an aralkoxy group, an acyloxy group or a silyloxy group. In another embodiment, m is a single bond and R_{32} is phenyl or cyclohexyl.

In one embodiment, when the compound has the structure XIV, R_{44} and R_{45} are hydrogen; g is a double bond; R_{47} is C(O)OMe; the stereochemistry at carbon p is R; R_{48} is methyl; the stereochemistry at carbon k is S; R_{49} is methyl; R_{9} is methyl; the stereochemistry at carbon q is R; R_{50} is hydrogen; the stereochemistry at carbon r is S; m is a single bond; R_{51} is O(C(O)Ph; the stereochemistry at carbon j is R; and the hydroxyl group is at carbon h or i. In another embodiment, the hydroxyl group is at carbon h and the stereochemistry at carbon h is R. In another embodiment, the hydroxyl group is at carbon h and the stereochemistry at carbon h is S. In another embodiment, the hydroxyl group is at carbon i and the stereochemistry is S.

In one embodiment, when the compound has the structure XIV, R_{44} and R_{45} are hydrogen; g is a double bond; R_{47} is C(O)OMe; the stereochemistry at carbon p is R; R_{48} is methyl; the stereochemistry at carbon k is S; R_{49} is methyl; the stereochemistry at carbon q is R; R_{50} is hydrogen; the stereochemistry at carbon r is S; m is a double bond; and the hydroxyl group is at carbon h or i. In another embodiment, the hydroxyl group is at carbon h and the stereochemistry at carbon h is R. In another embodiment, the
hydroxyl group is at carbon h and the stereochemistry at carbon h is S. In another embodiment, the hydroxyl group is at carbon i and the stereochemistry at carbon i is S.

Procedures for preparing compounds XIV and XV are provided in the forthcoming examples. Using the process of the present invention, compounds XIV and XV can be used to esterify alcohols.

In another embodiment, the corresponding alkoxide of the alcohols described above will also generate an ester when used in the process of the present invention. Any base that is capable of deprotonating a hydroxyl proton to produce the corresponding oxide anion is suitable in the present invention. Bases useful in the present invention include, but are not limited to, potassium hexamethyldisilazide, sodium hexamethyldisilazide, triethylamine, lithium diisopropylamide, lithium hexamethyldisilazide, dimethylethylamine, potassium hydride, sodium hydride or lithium 2,2,6,6-tetramethylpiperidine.

The present invention also provides a process for the esterification of an alcohol and/or an alkoxide that does not require the use of harsh reaction conditions (i.e., elevated temperature, extended reactions times). In one embodiment, the base is initially added to compound I or IV prior to the addition of the alcohol or alkoxide. In one embodiment, the amount of base used is less than the amount of compound I or IV. In a preferred embodiment, an excess amount of base is used relative to the amount of compound I or IV. In the case of compound I, the amount of base employed is from 1 to 10 equivalents, preferably 1 to 1.5 equivalents to 1 equivalent compound I. In another embodiment, when compound IV is used, the amount of base used is from 1 to 10 equivalents to 1 equivalent of compound IV. A slight excess of base relative to compounds I and IV is necessary in order to generate the corresponding ketene prior to the addition of the alcohol or alkoxide.
The process of the present invention typically involves the use of a solvent system. Organic solvents known in the art are useful in the present invention. Examples of organic solvents useful in the present invention include, but are not limited to, tetrahydrofuran, diethyl ether, toluene, dimethoxyethane, t-butyl methyl ether, or a mixture thereof.

Reaction temperatures and times can vary when adding the base to compounds I and IV. In one embodiment, the base is added to compound I from -50°C to 80°C. In another embodiment, the lower limit of the reaction temperature is -45°C, -40°C, -35°C, -30°C, -25°C, -20°C, or -15°C, and the upper limit is -5°C, -10°C, -15°C, -20°C, -25°C, 0°C, 20°C, 40°C, or 60°C. The base is allowed to react with compound I or IV at from 30 seconds to 3 hours. In another embodiment, the lower time limit can be 1, 5, 10, 15 minutes, and the upper limit can be 2 hours, 1 hour, 30 minutes, 15 minutes, 10 minutes, or 5 minutes.

Once the ketene complexes III and V have been generated in situ, an alcohol, alkoxide, or a combination thereof is added. The amount of the alcohol or alkoxide can be from 1 to 3 equivalents, preferably from 1 to 2 equivalents, and more preferably from 1 to 1.2 equivalents. The alcohol or alkoxide is allowed to react with the ketene at from 15 minutes to 24 hours, preferably from 15 minutes to 2 hours. In another embodiment, the lower time limit can be 20, 25, 30, 40 or 50 minutes, and the upper limit can be 1 hour, 45 minutes; 1 hour, 30 minutes; 1 hour; or 45 minutes. The temperature at which the alcohol and/or alkoxide can be added to the ketene can be from -50°C to 23°C. In another embodiment, the lower temperature limit can be -45°C, -40°C, -35°C, -30°C, -25°C or -20°C; and the lower limit can be 20°C, 15°C, 10°C, 5°C, 0°C, -5°C, -10°C or -20°C.
ESTERIFICATION OF ALCOHOLS-PART II

In accordance with the purpose(s) of this invention, as embodied and broadly described herein, this invention, in one aspect, relates to a method for preparing an ester, comprising admixing a compound having the structure VII:

![Chemical Structure](image)

wherein,

- $R_{15}$ and $R_{16}$ are, independently, hydrogen, Si($R_{21}$), or C(O)R$_{22}$, wherein each $R_{21}$ is, independently, branched or straight chain C$_{1-12}$ alkyl; and $R_{22}$ is substituted or unsubstituted aryl, aralkyl or from C$_{1-12}$ branched or straight chain alkyl;

- $R_{17}$ is substituted or unsubstituted aryl, aralkyl, or from C$_{1-12}$ branched or straight chain alkyl;

- $R_{18}$ is hydrogen; branched or straight chain C$_{1-12}$ alkyl; unsubstituted or substituted aryl; aralkyl; Si($R_{28}$) or C(O)R$_{29}$, wherein, each $R_{28}$ is, independently, branched or straight chain C$_{1-12}$ alkyl; or aralkyl;

- $R_{29}$ is substituted or unsubstituted aryl, aralkyl or from C$_{1-12}$ branched or straight chain alkyl;
$R_{19}$ and $R_{20}$ are, independently, branched or straight chain $C_7-C_{12}$ alkyl, aryl, aralkyl, or $C(O)OR_{30}$ wherein $R_{19}$ is not hydrogen;

$R_{30}$ is branched or straight chain $C_1-C_{12}$ alkyl; and

$V$ and $W$ are, independently, sulfur, oxygen, or $NR_{43}$, wherein $R_{43}$ is hydrogen; branched or straight chain $C_1-C_{12}$ alkyl; or aralkyl,

with an alkoxide.

The alkoxide is prepared \textit{in situ} by treating the corresponding alcohol with a base. Bases useful in generating the alkoxide include, but are not limited to amides, secondary and tertiary amines. In a preferred embodiment, lithium hexamethyldisilazide, sodium hexamethyldisilazide, potassium hexamethyldisilazide, n-butyllithium, sodium hydride, potassium hydride or lithium diisopropylamide can be used. Once the alkoxide is produced, it can react with compound VII to generate an ester. Nucleophilic attack at the carbamide followed by the loss of the heterocyclic ring results in the formation of the ester.

The method of the present invention has a number of advantages. First, by varying the stereochemistry of $R_{19}$ and $R_{20}$ of compound VII, it is possible to control the diastereoselectivity of the condensation reaction between the alkoxide and compound VII. Second, by varying $V$ and $W$ of compound VII, it is possible to enhance or increase the reaction between the alkoxide and compound VII. In one embodiment, $V$ and $W$ are sulfur. In another embodiment, $R_{17}$ is phenyl and $R_{18}$ is benzoyl. Finally, it is possible to recover the oxazolidine ring and reuse it after the condensation reaction.

All of the alcohols described above can be converted to the corresponding alkoxide and used in the present invention. In one embodiment, the alkoxide is a compound having the structure VIII:
wherein,

R$_{23}$ is acetyl or hydrogen;

R$_{24}$ is hydrogen;

R$_{25}$ is benzoyl;

R$_{26}$ is acetyl; and

R$_{27}$ is hydrogen, C(O)OCH$_2$Ph, SiEt$_3$ or C(O)CH$_2$CCl$_3$.

As described above, an efficient method for attaching a side chain at the C-13 position of baccatin or derivatives thereof is not known in the art; thus, the applicants have discovered another method for attaching a side chain to precursors of taxol and derivatives thereof. In one embodiment, for compound VIII, R$_{23}$ and R$_{24}$ are hydrogen; R$_{25}$ is benzoyl; R$_{26}$ is acetyl; and R$_{27}$ is hydrogen, C(O)OCH$_2$Ph, SiEt$_3$ or C(O)CH$_2$CCl$_3$. This alkoxide is the precursor to taxotere. In another embodiment, R$_{23}$ and R$_{26}$ are acetyl; R$_{24}$ is hydrogen; R$_{25}$ is benzoyl; and R$_{27}$ is hydrogen, C(O)OCH$_2$Ph, SiEt$_3$ or C(O)CH$_2$CCl$_3$. This alkoxide is a precursor to Taxol.
In another embodiment, the alkoxide is a compound having the structure XVI or XVII:

wherein,

$R_{44}$ and $R_{45}$ are, independently, hydrogen; C$_1$-C$_{12}$ branched or straight chain alkyl; or $R_{44}$ and $R_{45}$ are part of a cycloaliphatic group;

when g is a single bond, $R_{46}$ is hydroxy; acetyl; or C$_1$-C$_{12}$ branched or straight chain alkoxy;

when g is a double bond, $R_{46}$ is oxygen;
$R_{47}$ is a $C_1$-$C_{12}$ branched or straight chain alkyl ester; $C_1$-$C_{12}$ branched or straight chain alkyl; carboalkoxy; hydroxyalkyl; or derivatized or protected hydroxyalkyl;

$R_{48}$ is $C_1$-$C_{12}$ branched or straight chain alkyl; substituted or unsubstituted aryl; acetyl; hydroxyalkyl; or derivatized or protected hydroxyalkyl;

$R_{49}$ and $R_{50}$ are, independently, hydrogen; $C_1$-$C_{12}$ branched or straight chain alkyl or alkoxy; or acetyl, provided that when one of $R_{49}$ or $R_{50}$ is hydrogen, then the other of $R_{49}$ and $R_{50}$ is not hydrogen;

when $m$ is a double bond, $R_{51}$ is oxygen;

when $m$ is a single bond, $R_{51}$ is $OC(O)R_{52}$, wherein $R_{52}$ is substituted or unsubstituted aryl; or cycloaliphatic; and

the hydroxyl group is located at carbon h or i.

The invention further relates to a compound having the structure VII:

```
(R_{16})(R_{15})\ N\ O\ W\ \ N\ O\ \ V\ VII
   \ r_{17}\  \ c\ d\ e\ f\ \ R_{18}\ R_{19}\ R_{20}
```

wherein,
R₁₅ and R₁₆ are, independently, hydrogen, Si(R₂₁)₃ or C(O)R₂₂, wherein each R₂₁ is, independently, branched or straight chain C₁-C₁₂ alkyl; and R₂₂ is substituted or unsubstituted aryl, aralkyl or from C₁-C₁₂ branched or straight chain alkyl;

5

R₁₇ is substituted or unsubstituted aryl, aralkyl, or from C₁-C₁₂ branched or straight chain alkyl;

R₁₈ is hydrogen; branched or straight chain C₁-C₁₂ alkyl; unsubstituted or substituted aryl; aralkyl; Si(R₂₉)₃ or C(O)R₂₉, wherein,

10 each R₂₉ is, independently, branched or straight chain C₁-C₁₂ alkyl; or aralkyl;

R₂₉ is substituted or unsubstituted aryl, aralkyl or from C₁-C₁₂ branched or straight chain alkyl;

15 R₁₉ and R₂₀ are, independently, branched or straight chain C₁-C₁₂ alkyl, aryl, aralkyl, or C(O)ORₛ₀, wherein R₁₉ is not hydrogen;

R₃₀ is branched or straight chain C₁-C₁₂ alkyl; and

V and W are, independently, sulfur, oxygen, or NR₄₃, wherein R₄₃ is hydrogen; branched or straight chain C₁-C₁₂ alkyl; or aralkyl.

25

The invention further relates to a method for preparing a compound having the structure VII:
wherein,

R₁₅ and R₁₆ are, independently, hydrogen, Si(R₂₁), or C(O)R₂₂, wherein each R₂₁ is, independently, branched or straight chain C₁₋C₁₂ alkyl; and R₂₂ is substituted or unsubstituted aryl, aralkyl or from C₁₋C₁₂ branched or straight chain alkyl;

R₁₇ is substituted or unsubstituted aryl, aralkyl, or from C₁₋C₁₂ branched or straight chain alkyl;

R₁₈ is branched or straight chain C₁₋C₁₂ alkyl; unsubstituted or substituted aryl; aralkyl; Si(R₂₈), or C(O)R₂₉, wherein,

each R₂₈ is, independently, branched or straight chain C₁₋C₁₂ alkyl; or aralkyl;

R₂₉ is substituted or unsubstituted aryl, aralkyl or from C₁₋C₁₂ branched or straight chain alkyl;

R₁₉ and R₂₀ are, independently, branched or straight chain C₁₋C₁₂ alkyl, aryl, aralkyl, or C(O)OR₃₀, wherein R₁₉ is not hydrogen;

R₃₀ is branched or straight chain C₁₋C₁₂ alkyl; and
V and W are, independently, sulfur, oxygen, or NR_{43}, wherein R_{43} is hydrogen; branched or straight chain C_{1-12} alkyl; or aralkyl, comprising,

(a) admixing

(i) a compound having the structure X

wherein R_{18}-R_{20} are as above,

(ii) a Lewis acid; and

(iii) a base,

to produce a first intermediate;

(b) reacting the first intermediate of step (a) with a compound having the structure XI:
wherein R₁₅ and R₁₇ are as above,

to produce a second intermediate; and

5  (c) admixing the second intermediate of step (b) with a proton source.

Treatment of compound X with a Lewis acid and a base results in the formation of an enolate, which is the first intermediate recited above. In one embodiment, compound X is treated with the Lewis acid prior to the addition of the base. Bases useful for generating the enolate include, but are not limited to, potassium hexamethyldisilazide, sodium hexamethyldisilazide and lithium diisopropylamide. In a preferred embodiment, the base is lithium diisopropylamide. Once the enolate has been prepared in situ, it is treated with the imine compound XI. In a preferred embodiment, R₁₅ of the imine is C(O)Ph. The enolate reacts with the imine to generate a β-amino,α-alkoxyamide, which is the second intermediate recited above. In another embodiment, the Lewis acid facilitates the reaction between the enolate and the imine. In one embodiment, the Lewis acid is a zinc, magnesium, aluminum, boron, tin or titanium compound. In another embodiment, the Lewis acid comprises a dialkylboron triflate, stannous triflate, stannic chloride, stannous chloride or titanium tetrachloride.

Once the β-amino,α-alkoxyamide is produced, it is quenched with a proton source. Proton sources useful in the present invention include, but are not limited to, a weak acid or water.

The invention further relates to a method for preparing a compound having the structure VII:
wherein,

\( R_{13} \) and \( R_{16} \) are, independently, hydrogen, \( \text{Si}(R_{21})_3 \), or \( \text{C}(\text{O})\text{OMe} \), wherein each \( R_{21} \) is, independently, branched or straight chain \( C_1-C_{12} \) alkyl; and \( R_{22} \) is substituted or unsubstituted aryl, aralkyl or from \( C_1-C_{12} \) branched or straight chain alkyl;

\( R_{17} \) is substituted or unsubstituted aryl, aralkyl, or from \( C_1-C_{12} \) branched or straight chain alkyl;

\( R_{18} \) is hydrogen:

\( R_{19} \) and \( R_{20} \) are, independently, branched or straight chain \( C_1-C_{12} \) alkyl, aryl, aralkyl, or \( \text{C}(\text{O})\text{OR}_{30} \), wherein \( R_{19} \) is not hydrogen;

\( R_{23} \) is branched or straight chain \( C_1-C_{12} \) alkyl; and

\( V \) and \( W \) are, independently, sulfur, oxygen, or \( \text{NR}_{43} \), wherein \( R_{43} \) is hydrogen; branched or straight chain \( C_1-C_{12} \) alkyl; or aralkyl,

comprising,

(a) admixing
(i) a compound having the structure XIII

wherein $R_{19} - R_{20}$ and $R_{22}$ are as above,

(ii) a Lewis acid; and

(iii) a first base,

to produce a first intermediate;

(b) reacting the first intermediate of step (a) with a compound having the structure XI:

wherein $R_{15}$ and $R_{17}$ are as above,

to produce a second intermediate; and

(e) admixing the second intermediate with a basic buffer, wherein the buffer comprises a second base.
In a similar reaction as described above, the addition of a first base, such as an amide or secondary or tertiary amine, to compound XIII results in the formation of an enolate, which is the first intermediate recited above. Once the enolate has been produced, the imine compound XI is added to produce an β-amino,α-alkoxyamide, which is the second intermediate. The amide is then treated with a basic buffer to generate compound VII. In one embodiment, the buffer is an aqueous solution of NaHCO₃ or a phosphate. Upon treatment of the amide intermediate with the basic buffer, the C(O)R₂₂ group migrates from oxygen to nitrogen. The migration of C(O)R₂₂, and in particular, C(O)Ph, from oxygen to nitrogen under basic conditions is well known in the art.

The invention further relates to a method for preparing an ester, comprising admixing a compound having the structure XX:

![Chemical Structure](image)

wherein,

R₆₀ is branched or straight chain C₁-C₁₂ alkyl; unsubstituted or substituted aryl; aralkyl; Si(R₆₃)₃ or C(O)R₆₄, wherein,

each R₆₃ is, independently, branched or straight chain C₁-C₁₂ alkyl; or aralkyl;
R_{64} is substituted or unsubstituted aryl, aralkyl or from C_{1}-C_{12} branched or straight chain alkyl;

R_{61} and R_{62} are, independently, hydrogen, branched or straight chain C_{1}-C_{12} alkyl, aryl, aralkyl, or C(O)OR_{65};

R_{65} is branched or straight chain C_{1}-C_{12} alkyl; and

V and W are, independently, sulfur, oxygen, or NR_{66}, wherein R_{66} is hydrogen; branched or straight chain C_{1}-C_{12} alkyl; or aralkyl,

with an alkoxide.

Using the techniques described above, any alkoxide can react with compound XX to produce an ester. In one embodiment, R_{61} is not hydrogen. In another embodiment, the compound XX has the formula:

![Chemical structure](image)

**EXAMPLES**

The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how the compounds claimed
herein are made and evaluated, and are intended to be purely exemplary of the
invention and are not intended to limit the scope of what the inventors regard as their
invention. Efforts have been made to ensure accuracy with respect to numbers (e.g.,
amounts, temperature, etc.) but some errors and deviations should be accounted for.

Unless indicated otherwise, temperature is in °C or is at room temperature and pressure
is at or near atmospheric.

General Procedures

Melting points were determined on a Thomas Hoover capillary melting point
apparatus and are uncorrected. IR spectra were obtained on a Nicolet Impact 400 FT-
IR spectrometer using the OMNIC software package. ¹H NMR spectra were recorded at
either 300 MHz on a General Electric QE-300 or at 400 MHz on a Varian-400
spectrometer. ¹³C NMR were recorded at either 75 MHz on a General Electric QE-300
or at 100 MHz on a Varian-400 spectrometer. Unless otherwise stated, spectra were
recorded in deuterated chloroform (CDCl₃) with residual chloroform (¹H NMR δ 7.26
ppm, ¹³C NMR δ 77.0 ppm) taken as the internal standard. Elemental analyses were
performed by Atlantic Microlab Inc., P. O. Box 2288, Norcross, Georgia. Mass spectra
were obtained on either a VG 70-S Nier Johnson or a JEOL Mass Spectrometer,
purchased through NIH and NSF as shared instruments. Analytical Thin Layer
Chromatography (TLC) was performed on pre-coated glass backed plates purchased
from EM Science (silica gel 60 F₂₅₄, 0.25 mm thickness). Flash chromatography was
performed with silica gel 60 (230-400 mesh ASTM) from EM Science. All reactions
were performed under a dry argon atmosphere in glassware which was flame-dried
under vacuum unless otherwise indicated. Solvents were dried using activated 4Å
molecular sieves. Dry solvents were used unless otherwise indicated. Brine refers to a
saturated aqueous solution of NaCl. Saturated NH₄Cl solution refers to a saturated
aqueous solution of NH₄Cl.
Compound 1 was prepared using a slightly modified version of the procedure previously reported by Sharpless and co-workers (J. Org. Chem. 1994, 59, 5104).

\[
\begin{align*}
\text{Ph} & \quad \text{NH} & \quad \text{O} \\
\text{Ph} & \quad \text{O} & \quad \text{OMe} \\
\text{OH} & \quad 1
\end{align*}
\]

5 Synthesis of Methyl (4S,5S)-2,4-diphenyl-4,5-dihydro-oxazole-5-carboxylate (or 2,4-Diphenyl-4(S),5(S)-dihydro-oxazole-5-carboxylic acid methyl ester) (2)

\[
\begin{align*}
\text{Ph} & \quad \text{N} & \quad \text{O} \\
\text{H} & \quad \text{H} & \quad \text{Ph} & \quad \text{CO}_2\text{Me}
\end{align*}
\]

A three-necked flask was charged with 1 (2.59 g, 8.66 mmol) and dry CH\textsubscript{2}Cl\textsubscript{2} (43 mL). The suspension was cooled to -30 °C and pyridine (0.84 mL, 10.4 mmol) was added. After stirring for several minutes, trifluoromethanesulfonic anhydride (1.45 mL, 8.6 mmol) was added dropwise and the reaction mixture was gradually warmed from -30 °C to 15 °C with an acetone bath. The reaction flask was then removed from the bath and was stirred at room temperature for approximately 4 hours. The reaction mixture was then poured into a saturated NaHCO\textsubscript{3} solution (45 mL) and extracted with CH\textsubscript{2}Cl\textsubscript{2} (2x). The organic layers were washed with brine, dried over MgSO\textsubscript{4}, filtered and evaporated. Purification by silica gel chromatography (9:1 hexanes/ethyl acetate increased to 2:1 hexanes/ethyl acetate) yielded 2.11 g (87 %) of 2 as a white solid. R\textsubscript{f}
0.43 (4:1 hexanes/ethyl acetate); mp 135 °C; IR (CDCl₃) 3065, 3030, 2947, 1756, 1656, 1213, 1065, 700 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.10 (d, J = 7.14 Hz, 2 H), 7.50 (m, 3 H), 7.27 (m, 5 H), 5.74, (d, J = 10.8 Hz, 1 H), 5.38 (d, J = 10.8 Hz, 1 H), 3.20 (s, 3 H); ¹³C NMR (75 MHz, CDCl₃) δ 168.3, 164.6, 136.8, 131.8, 128.6, 128.4, 128.3, 128.0, 127.9, 127.6, 126.6, 80.9, 73.4, 51.4; HRMS (FAB): Caled for (M+H) C₁₇H₁₆NO₃, 282.1130; Found, 282.1134; EA Caled for C₁₇H₁₅NO₃: C, 72.57; H, 5.38; N, 4.98; Found: C, 72.67; H, 5.44; N, 4.94.

Synthesis of Methyl (4S,5R)-2,4-diphenyl-4,5-dihydro-oxazole-5-carboxylate (or 2,4-Diphenyl-4(S),5(R)-dihydro-oxazole-5-carboxylic acid methyl ester) (3)

\[
\begin{align*}
\text{Ph} & \quad \text{N} \quad \text{O} \\
\text{H} & \quad \text{Ph} \quad \text{H} \quad \text{CO₂Me}
\end{align*}
\]

A 15 mL three-necked flask was charged with 2 (69 mg, 0.24 mmol) and dry THF (1.3 mL). The colorless solution was cooled to -50 °C and lithium bis(trimethylsilyl)amide (0.25 mL, 1 M solution in THF, 0.25 mmol) was added. The mixture was stirred for 10 minutes during which time a bright yellow color developed. The mixture was cooled to -78 °C and quenched with saturated NH₄Cl solution (0.5 mL). The mixture was diluted with ethyl acetate and water. The aqueous layer was extracted with ethyl acetate (3 x). The combined organic layers were washed with brine, dried over MgSO₄, filtered, and evaporated to yield 69 mg (100%) of a mixture of 3 and 2. Crude ¹H NMR indicated a 2:1 ratio of 3 to 2 respectively. The spectral data obtained for 3 was consistent with previously published data. IR 3065, 3030, 2952, 1756-1735, 1656, 1452, 1069, 695 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.10 (d, J = 7.0 Hz, 2 H), 7.43 (m, 8 H), 5.45 (d, J = 6.4 Hz, 1 H), 4.93 (d, J = 6.4 Hz, 1 H), 3.87 (s, 3 H); HRMS (FAB): Caled. for (M+Li) C₁₇H₁₅NO₃Li, 288.1212; Found, 288.1222.
Synthesis tert-Butyl (4S,5R)-2,4-diphenyl-4,5-dihydro-oxazole-5-carboxylate (4)

\[
\begin{align*}
\text{Ph} & \quad \text{N} \\
\text{H} & \quad \text{O} \\
\text{Ph} & \quad \text{H} \quad \text{CO}_2\text{Bu}
\end{align*}
\]

A 25 mL three-necked flask was charged with 2 (51.9 mg, 0.18 mmol) and dry THF (1.0 mL). The solution was cooled to 0 °C and lithium tert-butoxide (0.22 mL, 1.0 M solution in THF, 0.22 mmol) was added. After stirring for 10 minutes, the ice bath was removed and the reaction warmed to 25 °C. The reaction mixture was then diluted with ethyl acetate and water. The aqueous layer was extracted with ethyl acetate (3x). The combined organic layers were washed with brine, dried over MgSO₄, filtered and evaporated to yield 45 mg (77 %) of crude 4 which was contaminated with a trace of 2 and 3. Purification by silica gel column chromatography yielded pure 4 which was consistent with previously reported spectral data for the enantiomer of this compound. $^1$H NMR (300 MHz, CDCl₃) δ 8.10 (d, J = 7.2 Hz, 2 H), 7.41 (m, 8 H), 5.38 (d, J = 6.5 Hz, 1 H), 4.70 (d, J = 6.5 Hz, 1 H), 1.55 (s, 9 H).

Esterification of Isopropanol-Synthesis of (4S,5R)-2,4-Diphenyl-4,5-dihydro-oxazole-5-carboxylic acid isopropyl ester (5)

\[
\begin{align*}
\text{Ph} & \quad \text{N} \\
\text{H} & \quad \text{O} \\
\text{Ph} & \quad \text{H} \quad \text{CO}_2\text{Pr}
\end{align*}
\]
A 15 mL three-necked flask was charged with 2 (52.9 mg, 0.19 mmol) and dry THF (0.95 mL). The colorless solution was cooled to -50 °C. After 15 minutes, lithium hexamethyldisilazide (0.22 mL, 1.0 M solution in THF, 0.22 mmol) was added and a bright yellow color developed. After 12 minutes, neat isopropanol (0.5 mL) was added and the reaction mixture was warmed gradually to 25 °C over one hour. The reaction mixture was diluted with ethyl acetate and water. The aqueous layer was extracted with ethyl acetate (3x). The combined organic layers were dried over MgSO₄, filtered and evaporated to yield 40.4 mg (69 %) of a mixture of 5a and 5b. The ratio of 5b (trans) to 5a (cis) was determined to be 6:1 by crude ¹H NMR. After purification by silica gel chromatography (5% ethyl acetate in hexanes) pure 5b was isolated as a clear oil which later became a white solid. R, 0.47 (4:1 hexanes / ethyl acetate); IR (CDCl₃) 2983, 2933, 1749, 1654, 1062 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.11 (m, 2 H), 7.43 (m, 8 H), 5.41 (d, J = 6.6 Hz, 1 H), 5.20 (m, 1 H), 4.86 (d, J = 6.6 Hz, 1 H), 1.33 (m, 6 H); ¹³C NMR (75 MHz, CDCl₃) δ 169.6, 164.1, 141.2, 131.9, 128.8, 128.7, 128.4, 128.0, 126.8, 126.5, 83.2, 74.7, 69.6, 21.7; HRMS (FAB): Calcd for (M + Li) C₁₅H₁₉NO₃Li, 316.1525; Found, 316.1519.

Using the procedure described above, t-butanol and (2S)-hydroxy-3-methylbutane were esterified as well.

Synthesis of tert-Butyl-(2S,3S,αS)-3-[N-benzyl-N-(α-methylbenzyl)amino]-2-hydroxy-3-phenyl propionate (6)

![Chemical Structure](image)
Compound 6 was prepared according to the literature procedure previously reported by Davies and co-workers (Bunnage et al., J. Chem. Soc. Perkin Trans. I, 1994, 2385). The spectral data below is consistent with the data for the enantiomer of 6 reported in the literature. IR (CDCl₃) 3495, 3023, 2977, 1724, 1494, 1454, 1369, 1112, 700 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.52 (d, J = 7.5 Hz, 4 H), 7.31 (m, 11 H), 4.43 (bs, 1 H), 4.25 (m, 2 H), 4.16, 3.86 (ABq, J = 15.0 Hz, 2 H), 2.83 (bs, 1 H), 1.24 (d, obscured, 3 H), 1.23 (s, 9 H); ¹³C NMR (75 MHz, CDCl₃) δ 172.0, 144.0, 141.8, 138.2, 129.8, 128.2, 128.0, 127.95, 127.91, 127.5, 126.8, 126.6, 82.0, 73.3, 65.5, 57.2, 52.2, 27.6, 14.1; HRMS (FAB): Calcd for (M+Li) C₂₈H₃₂NO₃Li, 438.2620; Found, 438.2639.

Synthesis of tert-Butyl-(2S,3S,αS)-3-[(N-benzyl-N-(α-methylbenzyl)amino)-2-benzoyl-oxy-3-phenylpropionate (7)

A 25 mL flask was charged with 6 (149.7 mg, 0.34 mmol). Dry triethylamine (0.1 mL, 0.71 mmol) and CH₂Cl₂ (1 mL) were added and the colorless solution was cooled to 0 °C. Benzoyl chloride (40 μL, 0.34 mmol) was added and the reaction was gradually warmed to 25 °C. After approximately 2 hours, 4-dimethylaminopyridine (49 mg, 0.40 mmol) was added along with an additional 40 μL of benzoyl chloride and 0.5 mL of CH₂Cl₂. (It was later discovered that 0.5 equivalents of DMAP and 1 equivalent of benzoyl chloride was sufficient to drive the reaction to completion in about 15 minutes.) After one hour the solvent was evaporated and the residue was
partitioned between ether (6 mL) and water (6 mL). The mixture was extracted with ether (3x) and the organic layer was dried with MgSO₄, filtered, and evaporated. The crude product was a yellow oil contaminated with white crystals (benzoic acid) which were further precipitated with hexanes and filtered from the crude product. Purification of crude 7 by silica gel column chromatography (5 % ethyl acetate in hexanes) yielded 148 mg (81 %) of pure 7 as a clear oil. R₆ 0.60 (4:1 hexanes / ethyl acetate); IR (CDCl₃) 3024, 2977, 1727 broad, 1452, 1274, 1110, 700 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.04 (d, J = 7.3 Hz, 2 H), 7.73 (d, J = 7.3 Hz, 2 H), 7.36 (m, 16 H), 5.69 (d, J = 3.9 Hz, 1 H), 4.67 (d, J = 3.9 Hz, 1 H), 4.25 (q, J = 6.7 Hz, 1 H), 4.02 (m, 2 H), 1.29 (d, J = 6.7 Hz, 3 H), 1.22 (s, 9 H); ¹³C NMR (75 MHz, CDCl₃) δ 167.5, 165.5, 143.9, 141.5, 138.2, 132.9, 129.8, 129.7, 129.6, 128.2, 128.1, 128.0, 127.9, 127.7, 127.6, 126.9, 126.3, 81.9, 73.6, 63.9, 58.4, 52.2, 27.5, 15.9; HRMS (FAB): Calcd for (M+Li) C₃₂H₃₇NO₄Li, 542.2883; Found, 542.2902.

Synthesis of (2S,3S,αS)-3-[N-Benzyl-N-(α-methylbenzyl)amino]-2-benzoyl-oxy-3-phenyl-propionic acid (8)

![Chemical Structure](image)

A 100 mL flask was charged with 7 (137 mg, 0.25 mmol) and dry CH₂Cl₂ (2.5 mL). Trifluoroacetic acid (0.8 mL) was added and the colorless solution was stirred at 25 °C for 3.5 hours. The reaction was quenched with several milliliters of a saturated NaHCO₃ solution and extracted with CH₂Cl₂ (3x). The organic layer was dried over MgSO₄, filtered, and evaporated. Purification by silica gel chromatography (4:1
hexanes/ethyl acetate increased to 1:1 hexanes/ethyl acetate) yielded 82 mg (68%) of 7 as a pure white foam. \( R_f 0.06 \) (4:1 hexanes / ethyl acetate); IR (CDCl$_3$) 3031, 2930, 1726, 1269, 1113 cm$^{-1}$; \(^1\)H NMR (300 MHz, CDCl$_3$) \( \delta \) 12.63 (bs, 1 H), 7.71 (d, \( J = 7.4 \) Hz, 2 H), 7.38 (m, 18 H), 5.97 (d, \( J = 9.8 \) Hz, 1 H), 4.88 (d, \( J = 9.8 \) Hz, 1 H), 4.34 (m, 2 H), 3.90 (d, 13.8 Hz, 1 H), 1.37 (d, \( J = 6.8 \) Hz, 3 H); \(^{13}\)C NMR (75 MHz, CDCl$_3$) \( \delta \) 171.0, 165.2, 138.0, 134.1, 133.1, 132.6, 129.7, 129.6, 129.4, 129.1, 129.0, 128.9, 128.5, 128.4, 128.1, 68.4, 62.8, 60.1, 51.8, 14.7.

**Synthesis of Methyl-(2S,3S,αS)-3-[N-benzyl-N-(α-methylbenzyl)amino]-2-benzoyloxy-3-phenylpropionate (9)**

![Chemical Structure](image)

A 10 mL flask was charged with a 40% aqueous potassium hydroxide solution (0.9 mL) and dry ether (2 mL). While stirring with a teflon stir bar, nitrosomethyl urea (NMU) (103 mg, 1 mmol) was added. After stirring for 10 minutes open to the atmosphere, the yellow ether layer containing diazomethane was pipetted into a vial charged with one KOH pellet as a desiccant. A separate flask was charged with 8 (82 mg, 0.17 mmol) and dry ether (1 mL). After 30 minutes, the diazomethane ether solution was carefully pipetted into the clear solution of 8. The clear reaction mixture stirred for 20 minutes at 25 °C open to the atmosphere. The reaction was monitored by TLC (4:1 hexanes/ethyl acetate) and had not gone to completion. Therefore, another identical batch of diazomethane was prepared exactly as described above and added dropwise to the clear reaction mixture until a yellow color persisted, indicating that the
reaction was complete. The reaction mixture and any remaining excess diazomethane were quenched with acetic acid (2 drops for the reaction mixture). The reaction mixture was extracted with ether (2x). The ether layer was dried over MgSO₄, filtered and evaporated to yield 71.6 mg (85%) of pure 9 as a white solid. Rₗ 0.47 (4:1 hexanes/ethyl acetate); IR (CDCl₃) 3064, 3028, 2952, 1752, 1724, 1276, 1116, 904, 736 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.80 (d, J = 7.7 Hz, 2 H), 7.36 (m, 18 H), 5.67 (d, J = 6.2 Hz, 1 H), 4.60 (d, J = 6.2 Hz, 1 H), 4.18 (q, J = 6.7 Hz, 1 H), 4.06, 3.85 (ABq, J = 14.5 Hz, 2 H), 3.56 (s, 3 H), 1.19 (d, J = 6.8 Hz, 3 H); ¹³C NMR (75 MHz, CDCl₃) δ 169.2, 165.4, 143.6, 140.4, 137.9, 133.1, 129.7, 129.3, 128.3, 128.2, 128.1, 127.9, 127.8, 126.9, 126.7, 73.2, 63.8, 57.2, 52.1, 51.9, 14.3; HRMS (FAB): Calcd for (M+Li) C₃₂H₃₃NO₄Li, 500.2413; Found, 500.2426.

**Synthesis of (2S,3S,αS)-3-[N-benzyl-N-(α-methylbenzyl)amino]-2-benzoyloxy-3-phenyl-propionic anhydride (10)**

![Chemical structure](image)

A 15 mL three-necked flask was charged with p-toluenesulfonyl chloride (28.5 mg, 0.15 mmol) and benzene (0.5 mL). A solution of 8 (73.3 mg, 0.15 mmol) in dry benzene (2 mL) was added to this clear solution. After stirring for 15 minutes, triethylamine (13.9 μl, 0.10 mmol) was added. TLC and IR indicated the presence of a new “anhydride” species although 8 was still present. Over a two hour period, additional triethylamine (47 μl) was added in an attempt to drive the reaction toward
anhydride and ketene formation. The reaction mixture was then heated to gentle reflux for several hours and additional triethylamine (54 µl) was added before the mixture stirred overnight at 25 °C. The reaction mixture was then evaporated and purified by column chromatography (9:1 hexane/ethyl acetate increased to 4:1 hexane/ethyl acetate) to yield 21.8 mg (15 %) of pure 10 as an oil. Identification of 10 was confirmed by the fact that upon exposure of 10 to methanol, acid 8 and methyl ester 9 were isolated. Compounds 8 and 9 had been previously fully characterized. R<sub>r</sub> 0.42 (4:1 hexanes/ethyl acetate); IR 3063, 3030, 2972, 1833, 1728, 1273, 701 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.80 (m, 4 H), 7.30 (m, 36 H), 5.45 (d, 2 H), 4.57 (d, 2 H), 4.10 (m, 2 H), 3.90 (d, 2 H), 3.70 (d, 2 H), 1.16 (d, 6 H).

**Synthesis of 2-Benzoyloxy-3-phenyl-propionic Acid (11)**

![Chemical Structure](image)

A 50 mL three-necked flask was charged with 3-phenyllactic acid (1.0 g, 6.0 mmol) and dry CH<sub>2</sub>Cl<sub>2</sub> (12 mL). To this white slurry was added benzoyl chloride (1.04 mL, 9.0 mmol) and the mixture was cooled to 0 °C. Triethylamine (0.8 mL, 6.0 mmol) was added and a light yellow solution resulted. 4-Dimethylaminopyridine (367 mg, 3.0 mmol) was added and the reaction mixture was warmed to 25 °C and stirred for 3 hours. The reaction mixture was concentrated on a rotary evaporator and ether, ethyl acetate, and water were added. The mixture was extracted with ether (3x) and ethyl
acetate, dried over MgSO\(_4\), filtered and evaporated. Purification by silica gel chromatography (4:1 hexanes/ethyl acetate increased to 1:1 hexanes/ethyl acetate) yielded 392 mg (24%) of \(11\) as a white solid. R\(_f\) 0.15 (1:1 hexanes/ethyl acetate); mp 113 °C; IR (CDCl\(_3\)) 3564-2560 (broad acid), 3028, 2924, 1720 (broad), 1452, 1268, 716 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 11.25 (s, 1 H), 8.08 (d, \(J = 7.2\) Hz, 2 H) 7.45 (m, 8 H), 5.56 (m, 1 H), 3.38 (m, 2 H); \(^13\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 175.5, 165.9, 149.9, 135.6, 133.4, 130.1, 129.7, 129.3, 128.9, 128.5, 128.4, 127.1, 72.9, 37.2; HRMS (FAB): Calcd for (M + Li) \(\text{C}_{16}\text{H}_{22}\text{O}_4\text{Li}\), 277.1052; Found, 277.1065; EA Calcd for \(\text{C}_{16}\text{H}_{14}\text{O}_4\): C, 71.10; H, 5.22; Found: C, 71.04; H, 5.24.

1,4-Dimethyl-5,8-dioxo-1,5,8,8a-tetrahydro-4H-naphthalene-4a-carboxylic acid methyl ester (12)

\[
\begin{align*}
\text{CO}_2\text{Me} & \\
\text{O} & \\
\text{O} & \\
\text{H} & \\
\end{align*}
\]

1.7 g (10 mmol) of 2,5-dihydroxymethylbezoate was stirred with 0.9 g (11 mmol) of 2,3-hexadiene in 20 ml of benzene at 10°C. 4.62 g (20 mmol) of Ag\(_2\)O was added to the reaction mixture. Cooling bath was removed and the reaction mixture was stirred overnight in darkness. The reaction mixture was deluded with 100 ml of Et\(_2\)O, filtered through 1 inch silica gel plug and concentrated to yield 2.3 g (93%) of \(12\) as an orange solid. \(^1\)H NMR (300 MHz, \(\text{C}_6\text{H}_6\)) \(\delta\) 1.06 (m, 6H), 2.32 (m, 1H), 2.88 (q, 1H), 3.24 (s, 3H), 3.64 (d, 1H), 5.39 (s, 2H), 6.13 (q, 2H); \(^13\)C NMR (75 MHz, CDCl\(_3\)): \(\delta\) 17.2, 17.8, 30.1, 34.4, 53.3, 53.5, 63.1, 128.2, 128.6, 141.8, 142.5, 171.5, 196.7, 198.1; IR (neat): 750.5, 918.8, 1259.6, 1467.7, 1680.2, 1715.6, 1746.6, 3114.6 cm\(^{-1}\); HRMS calculated for \(\text{C}_{14}\text{H}_{16}\text{O}_4^+\text{H}^+\): 249.1127, found: 249.1131.
1,4-Dimethyl-5,8-dioxo-1,5,8,8a-tetrahydro-4H-naphthalene-4a-carboxylic acid methyl ester (13)

\[
\begin{align*}
&\text{CO}_2\text{Me} \\
&\text{O} \\
&\text{O} \\
&\text{H} \\
&\text{H}
\end{align*}
\]

2.5 g (10 mmol) of 12 was dissolved in 20 ml of toluene. 1.25 g (11 mmol) of DABCO was added and the reaction mixture was stirred for 14 hours at room temperature. The reaction mixture was deluted with 100 ml of Et\textsubscript{2}O, filtered through 1 inch silica gel plug and concentrated to yield 2.4 g (93%) of 13 as an orange solid. \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}): \( \delta \) 0.96 (d, 3H, J=6.9 Hz), 1.16 (m, 3H), 2.88 (m, 1H), 3.24 (q, 1H), 3.64 (s, 4H), 5.39 (dd, 1H), 5.64 (m, 1H), 6.58 (d, 1H), 6.80 (d, 1H); \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}): \( \delta \) 17.2, 17.8, 30.1, 34.4, 53.3, 53.5, 63.1, 128.2, 128.6, 141.8, 142.5, 171.5, 196.7, 198.1; IR (neat): 750.4, 918.9, 1259.7, 1467.7, 1680.1, 1715.4, 1746.7, 3114.5 cm\textsuperscript{-1}; HRMS calculated for C\textsubscript{14}H\textsubscript{16}O\textsubscript{4}H\textsuperscript{+}: 249.112, found: 249.114.

1,4-Dimethyl-5,8-methano-9,10-dioxo-1,5,8,8a,9,9a10,10a-octahydro-4H-antracene-4a-carboxylic acid methyl ester (14)

\[
\begin{align*}
&\text{CO}_2\text{Me} \\
&\text{O} \\
&\text{O} \\
&\text{H} \\
&\text{H}
\end{align*}
\]
0.5 g (2 mmol) of 13 was stirred with 1.3 g (20 mmol) of freshly distilled cyclopentadiene in 20 ml of EtOH at room temperature for 10 hours. The reaction mixture was concentrated on rotavap to yield 0.57 g (91%) of 14 as a white solid. $^1$H NMR (300 MHz, CDCl$_3$): δ 0.86 (d, 3H, J=6.9 Hz), 1.03 (d, 3H, J=7.0 Hz), 1.37 (d, 1H), 1.45 (d, 1H), 2.08 (d, 1H), 2.73 (m, 1H), 3.11 (m, 2H), 3.24 (m, 1H), 3.39 (s, 1H), 3.59 (s, 4H), 5.32 (dd, 1H), 5.62 (m, 1H), 6.16 (m, 1H), 6.22 (m, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$): δ 17.85, 22.29, 30.49, 32.79, 49.12, 49.64, 49.83, 50.38, 50.55, 52.49, 53.27, 67.45, 129.49, 131.46, 135.60, 137.74, 169.77, 203.95, 208.66; IR (CDCl$_3$):

732.4, 914.9, 1214.9, 1247.3, 1470.4, 1705.5, 1750.1, 2982.4 cm$^{-1}$; HRMS calculated for C$_{19}$H$_{22}$O$_4$+H$: 315.159, found: 315.160.

9-Hydroxy-1,4-dimethyl-5,8-methano-10-oxo-1,5,8,8a,9,9a,10,10a-octahydro-4H-anthracene-4a-carboxylic acid methyl ester (15)

0.96 g (3 mmol) of 14 was dissolved in 5 ml of anhydrous THF and cooled to -78°C. 0.8 ml of LAH (1M, THF) was added. After 2 hours TLC indicated no 14 was left. The reaction mixture was quenched with 2 g of solid NH$_4$Cl and deluted with 50 ml of ether. The reaction mixture was washed with 10% HCl, twice with water, dried over magnesium sulfate and concentrated. Silica gel column (Hexanes:EtOAc, 4:1) yielded 0.62 g (65%) of 17. $^1$H NMR (300 MHz, CDCl$_3$): δ 0.82 (d, 3H, J=6.9 Hz), 1.23 (d, 3H, J=7.0 Hz), 1.28 (m, 2H), 1.37 (d, 1H, J=8 Hz), 1.62 (br.s, 1H), 1.78 (dd,
1H, J=8 Hz, J=3.1 Hz), 2.47 (br.m, 1H), 2.96 (m, 2H), 3.21 (s, 1H), 3.44 (m, 1H), 3.59 (s, 3H), 4.88 (br.t, 1H, J=9.2), 5.38 (dd, 1H, J=7.1 Hz, J=3.1 Hz), 5.61 (m, 1H), 6.08 (m, 1H), 6.21 (m, 1H); 13C NMR (75 MHz, CDCl3): δ 17.55, 23.53, 34.67, 35.55, 40.24, 44.06, 45.65, 48.85, 49.50, 51.63, 52.44, 71.86, 128.49, 133.42, 135.73, 137.28, 169.97, 207.56; IR (CDCl3): 732.4, 914.9, 1214.9, 1247.3, 1470.4, 1705.5, 1750.1, 2982.4, 3544.3 cm−1; HRMS calculated for C19H24O3+H+: 323.1758, found: 323.1775.

9-Benzoyloxy-1,4-dimethyl-5,8-methano-10-oxo-1,5,8,8a,9,9a,10,10a-octahydro-4H-anthracene-4a-carboxylic acid methyl ester (16)

![Chemical Structure](attachment:image)

0.15 g (0.45 mmol) of 15 was dissolved in 9 ml of 1:1:1 mixture of anhydrous CH2Cl2, triethylamine and anhydrous DMF. 0.2 ml of benzoyl chloride was added followed by catalytic amount of DMAP (0.01 g). In 24 hours the reaction mixture was quenched by pouring into 50 ml of 1:1 mixture of water and ether. The organic layer was washed with water, twice with saturated solution of ammonium chloride and with NaHCO3. Ether solution was dried over magnesium sulfate and concentrated. Silica gel column (Hexanes:EtOAc, 3:1) yielded 0.12 g (78%) of 16. 1H NMR (300 MHz, CDCl3): δ 0.82 (d, 3H, J=6.9 Hz), 1.13 (d, 3H, J=7.0 Hz), 1.23 (m, 2H), 2.16 (d, 1H, J=2.8 Hz), 2.37 (br.m, 1H), 2.86 (s, 1H), 3.01 (dd, 1H, J=3.2 Hz, J=5 Hz), 3.11 (m, 1H), 3.35 (m, 1H), 3.42 (s, 1H), 3.61 (s, 3H), 5.28 (dd, 1H, J=7.1 Hz, J=3.1 Hz), 5.61 (m, 1H), 6.12 (m, 1H), 6.22 (t, 1H, J=9.2), 6.31 (m, 1H), 7.43-8.07 (m, 5H); 13C NMR (75 MHz, CDCl3): δ 17.44, 22.93, 34.30, 35.88, 40.80, 46.83, 48.84, 48.88, 51.50, 52.74, 64.51, 75.83, 128.39, 128.65, 128.92, 129.66, 129.71, 130.19, 132.86, 133.18,
133.58, 135.83, 137.33, 166.71, 169.97, 207.35; IR (neat): 732.4, 914.9, 1214.9, 1247.3, 1470.4, 1705.5, 1712.2, 1750.1, 2982.4 cm⁻¹; HRMS calculated for C₂₀H₂₅O₃⁺H⁺: 421.1251, found: 421.1246.

5 9-Benzoyloxy-1,4-Dimethyl-6-hydroxy-5,8-methano-10-oxo-1,5,6,7,8,8a,9,9a10a-decahydro-4H-antracene-4a-carboxylic acid methyl ester (17) and 9-Benzoyloxy-1,4-Dimethyl-7-hydroxy-5,8-methano-10-oxo-1,5,6,7,8,8a,9,9a,10,10a-decahydro-4H-antracene-4a-carboxylic acid methyl ester (18)

0.42 g (1 mmol) of 16 was dissolved in 20 ml of anhydrous THF. 1.5 ml of BH₃*SMe₂ (2M, in THF, 3 eq.) was added to the solution at 0°C. The reaction mixture was stirred for 2 hours at 0°C until TLC indicated the complete consumption of 16.

After that the reaction mixture was deluted with 10 ml of MeOH. 0.1 g of NaOAc was added to the solution as a solid. Finally, 2 ml of 30% H₂O₂ was added. After two hours the reaction mixture was filtered through 1 inch silica gel plug, dried over magnesium sulfate and concentrated. Silica gel column yielded 0.44 g (82%) of 2:1 mixture of alcohols 17 and 18. 17: ¹H NMR (300 MHz, CDCl₃): δ 0.96 (d, 3H, J=6.9 Hz), 1.13 (d, 3H, J=7.0 Hz), 1.22 (m, 2H), 1.57 (d, 1H, J=9.1 Hz), 1.83 (m, 2H), 2.12 (m, 2H), 2.43 (br.m, 1H), 2.62 (m, 1H), 2.86 (m, 1H), 3.04 (m, 1H), 3.15 (m, 1H), 3.61 (s, 3H), 3.78 (d, 1H, J=3 Hz), 5.38 (dd, 1H, J=7.1 Hz, J=3.1 Hz), 5.61 (t, 1H, J=3.1 Hz), 6.29 (t, 1H,
J=9.4 Hz), 7.43-8.07 (m, 5H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 17.68, 22.62, 34.28, 34.67, 40.41, 47.72, 48.47, 49.65, 50.84, 52.83, 64.81, 75.35, 128.39, 128.65, 128.92, 129.66, 129.71, 130.19, 132.86, 133.18, 133.58, 135.83, 137.33, 165.92, 169.17, 207.28; IR (CDCl$_3$): 732.4, 914.9, 1214.9, 1247.3, 1470.4, 1705.5, 1712.2, 1750.1, 2982.4 cm$^{-1}$; HRMS calculated for C$_{26}$H$_{36}$O$_6$+Li$^+$: 445.2202, found: 445.2197. 18: $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 0.94 (d, 3H, J=6.9 Hz), 1.15 (d, 3H, J=7.0 Hz), 1.23 (m, 2H), 1.62 (d, 1H, J=9.1 Hz), 1.81 (m, 2H), 2.16 (m, 2H), 2.43 (br.m, 1H), 2.62 (m, 1H), 2.86 (m, 1H), 3.04 (m, 1H), 3.18 (t, 1H, J=7.1 Hz), 3.61 (s, 3H), 4.38 (d, 1H, J=3 Hz), 5.28 (dd, 1H, J=7.1 Hz, J=3.1 Hz), 5.61 (m, 1H), 6.22 (t, 1H, J=9.4 Hz), 7.43-8.07 (m, 5H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 17.44, 22.93, 34.30, 35.88, 40.80, 46.83, 48.84, 48.88, 51.50, 52.74, 64.51, 75.83, 128.39, 128.65, 128.92, 129.66, 129.71, 130.19, 132.86, 133.18, 133.58, 135.83, 137.33, 166.71, 169.97, 207.35; IR (CDCl$_3$): 732.4, 914.9, 1214.9, 1247.3, 1470.4, 1705.5, 1712.2, 1750.1, 2982.4 cm$^{-1}$; HRMS calculated for C$_{26}$H$_{36}$O$_6$+Li$^+$: 445.2202, found: 445.2197.

9-Benzoyloxy-1,4-Dimethyl-5,8-methano-6,10-dioxo-1,5,6,7,8,8a,9,9a10,10a-decahydro-4H-antracene-4a-carboxylic acid methyl ester (19)

```
  O
 / \   \\
O   \  \\
/    \  \\
H    CO2Me
```

0.44 g (1 mmol) of 17 was dissolved in 10 ml of dichloromethane and 0.22 g (1.1 eq) of PCC was added. After stirring for 6 hours at room temperature TLC indicated that no 17 was left. The reaction mixture was filtered through 1 inch silica gel plug, dried over magnesium sulfate and concentrated. Silica gel gravity column (Hexanes:EtOAc, 4:1) yielded 0.36 g (68%) of 19 as a white foam. $^1$H NMR (300
MHz, CDCl₃): δ 0.84 (d, 3H, J=6.9 Hz), 1.15 (d, 3H, J=7.0 Hz), 1.23 (m, 2H), 1.62 (d, 1H, J=9.1 Hz), 2.16 (m, 3H), 2.43 (br.m, 2H), 2.62 (m, 1H), 3.09 (m, 4H), 3.42 (t, 1H, J=7.1 Hz), 3.61 (s, 3H), 5.28 (dd, 1H, J=7.1 Hz, J=3.1 Hz), 5.61 (m, 1H), 6.32 (t, 1H, J=9.8 Hz), 7.43-8.07 (m, 5H); ¹³C NMR (75 MHz, CDCl₃): δ 17.58, 22.93, 34.16, 36.32, 39.73, 40.86, 47.83, 52.91, 54.76, 64.78, 74.73, 128.75, 129.06, 129.71, 132.19, 133.86, 135.83, 147.33, 166.71, 169.97, 203.35, 213.28; IR (CDCl₃): 732.4, 1064.1, 1111.3, 1274.9, 1446.5.4, 1446.5, 1712.5, 1743.1, 2847.3, 2924.4 cm⁻¹; HRMS calculated for C₂₆H₂₆O₆+Li⁺: 445.2202, found: 445.2197.

9-Benzoyloxy-1,4-Dimethyl-6-hydroxy-5,8-methano-10-oxo-1,5,6,7,8,8a,9,9a,10,10a-decahydro-4H-antracene-4a-carboxylic acid methyl ester (20)

0.44 g (1 mmol) of 19 was dissolved in 20 ml of anhydrous toluene and 1.1 ml of lithium tri tert-butoxyaluminun hydride (1M, THF) was added at 0°C. The reaction mixture was stirred for 20 hours then was quenched with 3 ml of saturated solution of ammonium chloride and deluded with 20 ml of ether. The reaction mixture was washed with water, dried over magnesium sulfate and concentrated. Preparative TLC yielded 0.41g (86%) of 20 as colorless oil. ¹H NMR (300 MHz, CDCl₃): δ 1.06 (d, 3H, J=6.9 Hz), 1.17 (d, 3H, J=7.0 Hz), 1.44 (m, 2H), 1.89 (m, 1H), 2.08 (dd, 2H, J=3.0 Hz, J=5.2 Hz), 2.31 (m, 1H), 2.39 (dd, 1H, J=9.8 Hz, J=3.8 Hz), 2.81 (m, 1H), 3.08 (m, 2H), 3.18 (m, 1H), 3.58 (m, 1H), 3.71 (s, 3H), 4.60 (m, 1H), 5.38 (m, 1H), 5.64 (m, 1H), 5.96 (dd, 1H, J=9.8 Hz, J=3.8 Hz), 7.34-8.08 (m, 5H); ¹³C NMR (75 MHz, CDCl₃): δ 19.14,
23.05, 34.34, 36.18, 37.15, 37.46, 37.88, 40.44, 41.04, 46.73, 48.53, 52.44, 57.02, 78.10, 80.97, 126.27, 128.38, 128.42, 128.54, 129.24, 129.60, 130.13, 132.63, 133.01, 166.09, 171.05, 176.39, 205.66; IR (neat): 732.4, 1064.1, 1111.3, 1274.9, 1446.4, 1446.5, 1712.5, 1743.1, 2847.3, 2924.4 cm$^{-1}$; HRMS calculated for C$_{26}$H$_{30}$O$_6$+Li$: 445.2202$, found: 445.2197.

1,4-Dimethyl-7-hydroxy-5,8-methano-9,10-dioxo-1,5,6,7,8,8a,9,9a,10,10a-decahydro-4H-antracene-4a-carboxylic acid methyl ester (21), 1,4-Dimethyl-6-hydroxy-5,8-methano-9,10-dioxo-1,5,6,7,8,8a,9,9a,10,10a-decahydro-4H-antracene-4a-carboxylic acid methyl ester (22) and 1,4-Dimethyl-5,8-methano-9,10-dioxo-1,5,6,7,8,8a,9,9a,10,10a-decahydro-4H-antracene-4a-carboxylic acid methyl ester (23)
I. Catalytic Hydroboration

0.48 g (1.5 mmol) of 20 was dissolved in 20 ml of anhydrous THF. 0.01 g of Wilkinson's catalyst was added to the solution at 0°C. After 20 min. 0.25 ml of BH₃*SMe₂ (2M, in THF) was added dropwise. Cooling bath was removed and the reaction mixture was stirred at 23°C overnight. After 24 hours the reaction mixture was deluted with 10 ml of MeOH. 2.5 ml of NaOH (3N) was added followed by 0.35 ml of 30% H₂O₂. After additional hour the reaction mixture was filtered through 1 inch silica gel plug, dried over magnesium sulfate and concentrated. Silica gel column yielded 0.37 g (70%) of 20 and 0.09 g (18%) of 2:1 mixture of alcohols 21 and 22.

II. Hydroboration with excess of BH₃*SMe₂

0.48 g (1.5 mmol) of 20 was dissolved in 20 ml of anhydrous THF at 0°C. 2.25 ml of BH₃*SMe₂ (2M, in THF, 3 eq.) was added to the solution. Reaction was stirred for 2 hours at 0°C until TLC indicated the complete consumption of 20. After that the reaction mixture was deluted with 10 ml of MeOH. 2.5 ml of NaOH (3N) was added followed by 3 ml of 30% H₂O₂. After additional hour the reaction mixture was filtered through 1 inch silica gel plug, dried over magnesium sulfate and concentrated. Silica gel column yielded 0.44 g (82%) of 2:1 mixture of alcohols 21 and 22 and 0.04 g (7%) of 23. 21: ¹H NMR (300 MHz, CDCl₃): δ 0.86 (d, 3H, J=6.9 Hz), 1.15 (d, 3H, J=7.0 Hz), 1.37 (m, 2H), 1.77 (m, 1H), 2.08 (d, 2H), 2.73 (m, 1H), 2.79 (m, 3H), 2.91 (m, 1H), 3.08 (m, 1H), 3.18 (q, 1H), 3.59 (s, 3H), 3.79 (d, 1H), 5.38 (m, 1H), 5.69 (s, 1H); ¹³C NMR (75 MHz, CDCl₃): δ 17.85, 23.29, 30.49, 32.79, 34.15, 37.55, 42.55, 49.12, 49.64, 50.38, 52.49, 53.27, 67.45, 69.55, 128.49, 131.46, 169.77, 203.95, 208.66; IR (CDCl₃): 744.4, 918.9, 1213.9, 1280.3, 1376.4, 1464.1, 1700.5, 1727.1, 2923.4 cm⁻¹; HRMS calculated for C₁₉H₂₂O₄⁺Li⁺: 339.1784, found: 339.1780. 22: ¹H NMR (300 MHz, CDCl₃): δ 0.88 (d, 3H, J=6.9 Hz), 1.11 (d, 3H, J=7.0 Hz), 1.33 (m, 2H), 1.79 (m, 1H), 2.08 (d, 2H), 2.71 (m, 1H), 2.79 (m, 3H), 2.93 (m, 1H), 3.08 (m, 1H), 3.18 (q, 1H), 3.59 (s, 3H), 3.72 (d, 1H, J=3.2 Hz), 5.38 (m, 1H), 5.69 (m, 1H); ¹³C NMR (75
MHz, CDCl₃): δ 17.85, 23.24, 30.43, 32.79, 34.15, 37.54, 42.55, 49.22, 49.64, 50.38, 52.49, 53.27, 66.45, 69.32, 128.45, 131.43, 169.77, 203.91, 208.71; IR (CDCl₃): 744.4, 918.9, 1213.9, 1280.3, 1376.4, 1464.1, 1700.5, 1727.1, 2923.4 cm⁻¹; HRMS calculated for C₁₉H₂₂O₄⁺Li⁺: 339.1784, found: 339.1780. 23: ¹H NMR (300 MHz, CDCl₃): δ

0.96 (d, 3H, J=6.9 Hz), 1.13 (d, 3H, J=7.0 Hz), 1.21-1.57 (m, 4H), 2.22 (d, 1H), 2.73-3.08 (m, 4H), 3.22 (m, 1H), 3.57 (s, 3H), 5.38 (dd, 1H), 5.68 (m, 1H); ¹³C NMR (75 MHz, CDCl₃): δ 17.93, 22.57, 24.67, 25.04, 30.77, 32.68, 39.01, 42.40, 43.49, 49.58, 50.23, 50.99, 52.48, 53.08, 67.90, 129.17, 131.53, 169.52, 205.07, 209.43; IR (neat): 733.8, 914.3, 1216.5, 1248.1, 1460.2, 1703.8, 1739.8, 2971.4 cm⁻¹; HRMS calculated for C₁₀H₁₂O₄⁺H⁺: 317.1753, found: 317.1741.

1,4-Dimethyl-5,8-methano-7,9,10-trioxo-1,5,6,7,8,8a,9,9a,10,10a-decahydro-4H-antracene-4a-carboxylic acid methyl ester (24)

0.16 g (0.5 mmol) of 22 was dissolved in 10 ml of dichloromethane and 0.11 g (1.1 eq) of PCC was added. After stirring an for 6 hours at room temperature TLC indicated that no 21 was left. The reaction mixture was filtered through 1 inch silica gel plug, dried over magnesium sulfate and concentrated. Silica gel column (Hexanes:EtOAc, 4:1) yielded 0.12 g (73%) of 24 as a white foam. ¹H NMR (300 MHz, CDCl₃): δ 0.82 (d, 3H, J=6.9 Hz), 1.12 (d, 3H, J=7.0 Hz), 1.77 (m, 2H), 1.85 (m, 2H), 2.05 (m, 2H), 2.76 (m, 1H), 3.11 (m, 3H), 3.32 (m, 1H), 3.58 (s, 3H), 5.38 (m, 1H), 5.69 (m, 1H); ¹³C NMR (75 MHz, CDCl₃): δ 17.68, 22.32, 30.75, 31.48, 32.46, 37.78, 41.43, 42.19, 49.68, 51.33, 53.26, 54.36, 67.47, 129.16, 130.92, 169.41, 200.71,
207.71, 212.73; IR (CDCl₃): 732.8, 915.6, 1075.0, 1154.7, 1220.3, 1248.4, 1464.1, 1712.5, 1750.0, 2954.7 cm⁻¹; HRMS calculated for C₁₉H₂₂O₄+Li⁺: 337.1627, found: 337.1622.

5 1,4-Dimethyl-5,8-methano-6,9,10-trioxo-1,5,6,7,8,8a,9,9a,10,10a-decahydro-4H-antracene-4a-carboxylic acid methyl ester (25)

\[
\begin{align*}
\text{O} & \quad \text{CO}_2\text{Me} \\
\text{O} & \quad \text{K} \\
\end{align*}
\]

A solution of 85 mg (1.1 mmol) of freshly dried DMSO in 1 ml of anhydrous CH₂Cl₂ was added to a solution of 70 mg (0.55 mmol) of oxalyl chloride in 1.2 ml of anhydrous CH₂Cl₂, stirred and cooled to -78°C. After stirring an additional 5 min., a solution of 0.16 g (0.5 mmol) of 22 dissolved in 1 ml of was anhydrous CH₂Cl₂ added dropwise over 10 min. After stirring an additional 15 min. at -78°C, the reaction mixture was warmed up to -10°C and 0.35 ml (2.5 mmol) of dried Et₃N was added dropwise over 30 min. Finally, cooling bath was removed and the reaction mixture was warmed up to room temperature. After 45 min. 100 ml of EtOAc was added followed by 20 ml of water. Organic layer was separated, dried over magnesium sulfate and concentrated. Silica gel column (Hexanes:EtOAc, 4:1) yielded 0.12 g (73%) of 27 as a white foam. ¹H NMR (300 MHz, CDCl₃): δ 0.92 (d, 3H, J=6.9 Hz), 1.07 (d, 3H, J=7.0 Hz), 1.77 (m, 1H), 1.85 (m, 2H), 2.08 (m, 2H), 2.76 (m, 1H), 3.08 (m, 3H), 3.32 (q, 2H), 3.59 (s, 3H), 5.38 (dd, 1H), 5.69 (m, 1H); ¹³C NMR (75 MHz, CDCl₃): δ 17.81, 21.98, 30.42, 32.47, 37.96, 40.69, 42.95, 49.15, 49.27, 50.50, 53.33, 67.45, 56.75, 68.03, 128.91, 131.16, 169.31, 204.11, 205.08, 212.63; IR (neat): 732.8, 915.6, 1075.0, 1154.7, 1220.3, 1248.4, 1464.1, 1712.5, 1750.0, 2954.7 cm⁻¹; HRMS calculated for C₁₉H₂₂O₄+Li⁺: 337.1627, found: 337.1622.
1,4-Dimethyl-6-hydroxy-5,8-methano-9,10-dioxo-1,5,6,7,8,8a,9,9a,10,10a-decahydro-4H-antracene-4a-carboxylic acid methyl ester (26)

![Chemical Structure Image]

0.08 g of 25 (0.23 mmol) was dissolved in 5 ml of anhydrous THF and 0.25 ml of DIBAL-H (1M, Hexanes) was added at 0°C. The reaction mixture was stirred at room temperature for 20 hours then was quenched with 5 ml of 10% HCl and deluted with 20 ml of ether. The reaction mixture was washed with water, dried over magnesium sulfate and concentrated. Preparative TLC yielded 0.041g (50%) of 26 as colorless oil. ¹H NMR (300 MHz, CDCl₃): δ 1.11 (m, 3H), 1.20 (m, 3H), 1.45 (m, 2H), 1.77 (m, 1H), 2.73 (m, 1H), 2.91 (m, 2H), 3.08 (m, 1H), 3.22 (m, 2H), 3.39 (d, 1H), 3.62 (s, 3H), 4.42 (m, 1H), 5.42 (m, 1H), 5.72 (m, 1H); ¹³C NMR (75 MHz, CDCl₃): δ 17.75, 23.29, 31.49, 32.79, 34.15, 37.55, 42.55, 48.12, 49.64, 50.38, 52.49, 53.27, 67.45, 73.55, 128.49, 133.46, 169.77, 205.00, 207.50; IR (neat): 744.4, 1100.9, 1228.3, 1249.6, 1382.4, 1461.9, 1700.9, 1727.1, 2923.4 cm⁻¹; HRMS calculated for C₁₉H₂₂O₄⁺H⁺: 333.1702, found: 333.1692.
Synthesis of 27

To a solution of 4-isopropyl-1,3-thiazolidine thione (1.01 g, 6.28 mmol) in
5 \( \text{CH}_2\text{Cl}_2 \) at 78 °C under \( \text{N}_2 \) was added pyridine (0.75 mL, 9.27 mmol). After stirring for
5 min at -78 °C, a solution of benzylxoyacetyl chloride (1.486, 8.05 mmol) in \( \text{CH}_2\text{Cl}_2 \)
(2 mL) was added dropwise. The reaction mixture was stirred at -78 °C for 1 hr and
then warmed to room temperature and stirred for 45 min. The reaction mixture was
diluted with \( \text{CH}_2\text{Cl}_2 \) (20 mL) and washed sequentially with \( \text{H}_2\text{O} \) (20 mL), 5% oxalic
acid (2 x 20 mL), \( \text{H}_2\text{O} \) (20 mL) and the organic layer was dried with \( \text{Na}_2\text{SO}_4 \). Removal
of solvent under vacuum followed by flash chromatography using hexanes:ethyl acetate
(10:1) yielded A (80%). \(^1\text{H}(\text{CDCl}_3, 400 \text{ MHz})\) \( \delta \) 7.30 - 7.45 (m, 5H), 5.20 (m, 1H),
5.00 (AB-q, 2H, \( J = 1.72 \text{ Hz} \)), 4.65 (AB-q, 2H, \( J = 3.2 \text{ Hz} \), \( J = 12 \text{ Hz} \)), 3.59 (dd, 1H, \( J =
8 \text{ Hz} \), \( J = 11.2 \text{ Hz} \)), 3.08 (dd, 1H, \( J = 1.2 \text{ Hz} \), \( J = 11.16 \text{ Hz} \)), 2.38 (m, 1H), 1.06 (d, 3H, \( J =
6.8 \text{ Hz} \)), 0.99 (d, 3H, \( J = 6.8 \text{ Hz} \)).
Synthesis of Compound 28

To 7-C(O)OCH₂Ph-Baccatin III (0.0512 g, 0.0711 mmol) in THF (1 mL) under N₂, 78°C was added n-BuLi (0.05 mL, 1.6 M, 0.08 mmol). The reaction mixture was slowly warmed up to 0°C to a solution of 27 (0.023 g, 0.0765 mmol) in THF (1 mL) was added dropwise. After stirring for 10 min, the reaction mixture was quenched with saturated NH₄Cl (1 mL) and diluted with H₂O (10 mL) and ether (10 mL). The layers were separated and the aqueous phase extracted with ether (2 x 10 mL). The combined organics were washed with H₂O (10 mL), brine (2 x 8 mL) and dried with Na₂SO₄.

Flash chromatography using hexanes: ethyl acetate (3:1) yielded 28 (53%). ¹H (CDCl₃, 300 MHz) δ 8.06 (d, 2H, J = 7.8), 7.3 - 7.65 (m, 13H), 6.42 (s, 1H), 6.27 (t, 1H, J = 8.4 Hz), 5.66 (d, 1H, J = 6.9 Hz), 5.53 (dd, 1H, J = 7.5 Hz, J = 10.5 Hz), 5.21 (AB-q, 2H, J = 11.7 Hz), 4.94 (d, 1H, J = 9.0 Hz), 4.69 (s, 2H), 4.30 (d, 2H, J = 8.1 Hz), 4.21 (d, 2H, J = 2.1 Hz), 4.13 (d, 1H, J = 8.7 Hz), 3.95 (d, 1H, J = 6.6 Hz), 2.64-2.52 (m, 1H), 2.3-2.2 (m, 2H), 2.21 (s, 3H), 2.19 (s, 3H), 2.04-1.92 (m, 1H, 2.00 (s, 3H), 1.79 (s, 3H), 1.23 (s, 3H), 1.17 (s, 3H).
Throughout this application, various publications are referenced. The disclosures of these publications in their entireties are hereby incorporated by reference into this application in order to more fully describe the state of the art to which this invention pertains.

Although the present methods and compounds have been described with reference to specific details of certain embodiments thereof, it is not intended that such details should be regarded as limitations upon the scope of the invention except as and to the extent that they are included in the accompanying claims.
What is claimed is:

1. A method for preparing an ester, comprising:

   (a) admixing a compound having the structure I:

   \[
   \begin{array}{c}
   \text{R}_1 \\
   \text{\textit{N}} \\
   \text{\textit{O}} \\
   \text{\textit{a}} \\
   \text{R}_2 \\
   \text{C(O)X}
   \end{array}
   \]

   wherein,

   \( \text{R}_1 \) and \( \text{R}_2 \) are, independently, from \( \text{C}_1 \) to \( \text{C}_{12} \) branched or straight chain alkyl; or substituted or unsubstituted aryl; and

   \( \text{X} \) is a halogen or \( \text{OR}_3 \), wherein \( \text{R}_3 \) is from \( \text{C}_1 \) to \( \text{C}_{12} \) branched or straight chain alkyl; substituted or unsubstituted aryl; aralkyl; acyl, or \( \text{S(O)}_2\text{R}_{41} \), wherein \( \text{R}_{41} \) is \( \text{C}_1 \) to \( \text{C}_{12} \) branched or straight chain alkyl; or substituted or unsubstituted aryl,

   with a base to form an intermediate; and

   (b) admixing the intermediate of step (a) with an alcohol, an alkoxide, or a combination thereof.

2. The method of Claim 1, wherein the base comprises an amide, a secondary amine or a tertiary amine.
3. The method of Claim 1, wherein the base comprises potassium hexamethyldisilazide, sodium hexamethyldisilazide, triethylamine, lithium diisopropylamide, lithium hexamethyldisilazide, dimethylethylamine, potassium hydride, sodium hydride or lithium 2,2,6,6-tetramethylpiperidine.

4. The method of Claim 1, wherein R₁ and R₂ are phenyl; R₃ is methyl; and the stereochemistry at a is S.

5. The method of Claim 1, wherein R₁ and R₂ are phenyl; R₃ is isopropyl; and the stereochemistry at a is S.

6. The method of Claim 1, wherein R₁ and R₂ are phenyl; R₃ is tert-butyl; and the stereochemistry at a is S.

7. The method of Claim 1, wherein the alcohol comprises an aliphatic alcohol, an aromatic alcohol, a cycloaliphatic alcohol, or a heteroaromatic alcohol.

8. The method of Claim 1, wherein the alcohol is a cycloaliphatic alcohol.

9. The method of Claim 1, wherein the alcohol is (2S)-hydroxy-3-methylbutane.

10. The method of Claim 1, wherein the alcohol is a compound having the structure II:
wherein,

\( R_4 \) is acetyl or hydrogen;

\( R_5 \) is hydrogen;

\( R_6 \) is benzoyl;

\( R_7 \) is acetyl; and

\( R_8 \) is hydrogen, SiEt, or C(OC)CH,CCL.

11. The method of Claim 10, wherein \( R_4 \) is hydrogen.

12. The method of Claim 10, wherein \( R_4 \) is acetyl.

13. The method of Claim 1, wherein the alcohol comprises a compound having the structure XIV or XV:

![Chemical Structure XIV](image)

or
wherein,

$R_{44}$ and $R_{45}$ are, independently, hydrogen; C$_{1}$-C$_{12}$ branched or straight chain alkyl; or $R_{44}$ and $R_{45}$ are part of a cycloaliphatic group;

when $g$ is a single bond, $R_{46}$ is hydroxy; acetyl; or C$_{1}$-C$_{12}$ branched or straight chain alkoxy;

when $g$ is a double bond, $R_{46}$ is oxygen;

$R_{47}$ is a C$_{1}$-C$_{12}$ branched or straight chain alkyl ester; C$_{1}$-C$_{12}$ branched or straight chain alkyl; carboalkoxy; hydroxyalkyl; or derivatized or protected hydroxyalkyl;

$R_{48}$ is C$_{1}$-C$_{12}$ branched or straight chain alkyl; substituted or unsubstituted aryl; acetyl; hydroxyalkyl; or derivatized or protected hydroxyalkyl;

$R_{49}$ and $R_{50}$ are, independently, hydrogen; C$_{1}$-C$_{12}$ branched or straight chain alkyl or alkoxy; or acetyl, wherein $R_{49}$ or $R_{50}$ is hydrogen, provided that when one of $R_{49}$ or $R_{50}$ is hydrogen, the other of $R_{49}$ and $R_{50}$ is not hydrogen;
when m is a double bond, $R_{51}$ is oxygen;

when m is a single bond, $R_{51}$ is OH or OC(O)R$_{52}$, wherein R$_{52}$ is substituted or unsubstituted aryl; or cycloaliphatic; and

the hydroxyl group is located at carbon h or i.

14. The method of Claim 13, wherein the hydroxyl group is at carbon h, and the stereochemistry at carbon h is S.

15. The method of Claim 13, wherein the hydroxyl group is at carbon h, and the stereochemistry at carbon h is R.

16. The method of Claim 13, wherein the hydroxyl group is at carbon i, and the stereochemistry at carbon i is S.

17. The method of Claim 13, wherein the hydroxyl group is at carbon i, and the stereochemistry at carbon i is R.

18. The method of Claim 13, wherein $R_{44}$ and $R_{45}$ are independently, hydrogen or methyl.

19. The method of Claim 13, wherein $R_{44}$ and $R_{45}$ are hydrogen or methyl.

20. The method of Claim 13, wherein when $R_{44}$ and $R_{45}$ are part of a cycloaliphatic group, the cycloaliphatic group is a cyclopropyl group.

21. The method of Claim 13, wherein $R_{47}$ is methyl ester or methyl.

22. The method of Claim 13, wherein $R_{49}$ is hydroxy, ethoxy, propoxy, or derivatized hydroxy.
23. The method of Claim 13, wherein m is a single bond and $R_{55}$ is phenyl or cyclohexyl.

24. The method of Claim 13,

wherein the compound has the structure XIV,

$R_{44}$ and $R_{45}$ are hydrogen;

g is a double bond;

$R_{47}$ is C(O)OMe;

the stereochemistry at carbon $p$ is S;

the stereochemistry at carbon $k$ is S;

$R_{48}$ is methyl;

$R_{49}$ is methyl;

the stereochemistry at carbon $q$ is R;

$R_{50}$ is hydrogen;

the stereochemistry at carbon $r$ is S;

m is a single bond;

$R_{55}$ is OC(O)Ph; and
the stereochemistry at carbon j is R.

25. The method of Claim 24, wherein the hydroxyl group is at carbon h and the stereochemistry at carbon h is R.

26. The method of Claim 24, wherein the hydroxyl group is at carbon h and the stereochemistry at carbon h is S.

27. The method of Claim 24, wherein the hydroxyl group is at carbon i and the stereochemistry at carbon i is S.

28. The method of Claim 13,

wherein the compound has the structure XIV,

$R_{44}$ and $R_{46}$ are hydrogen;

$g$ is a double bond;

$R_{47}$ is C(O)OMe;

the stereochemistry at carbon p is R;

the stereochemistry at carbon k is S;

$R_{48}$ is methyl;

$R_{49}$ is methyl;

the stereochemistry at carbon q is R;
$R_{so}$ is hydrogen;

the stereochemistry at carbon $r$ is $S$; and

$m$ is a double bond.

29. The method of Claim 28, wherein the hydroxyl group is at carbon $h$ and the stereochemistry at carbon $h$ is $R$.

30. The method of Claim 28, wherein the hydroxyl group is at carbon $h$ and the stereochemistry at carbon $h$ is $S$.

31. The method of Claim 28, wherein the hydroxyl group is at carbon $i$ and the stereochemistry at carbon $i$ is $S$.

32. The method of Claim 1, wherein, in step (a), one equivalent of a compound having the structure I is admixed with from 1 to 10 equivalents of a base.

33. The method of Claim 1, wherein, the admixing step (a) occurs at from -50 to 80 °C.

34. The method of Claim 1, wherein, the admixing step (a) occurs for from 30 seconds to 3 hours.

35. The method of Claim 1, wherein, in step (a) further comprises admixing a solvent with the base, the compound having the structure I or a combination thereof.

36. The method of Claim 35, wherein the solvent comprises tetrahydrofuran, diethyl ether, toluene, dimethoxyethane, t-buty1 methyl ether or a mixture thereof.
37. The method of Claim 1, wherein the admixing step (b) occurs at a temperature of from -50 to 23°C.

38. The method of Claim 1, wherein the admixing step (b) occurs for from 15 minutes to 24 hours.

39. A method for preparing an ester, comprising admixing a compound having the structure III:

![Diagram for structure III]

wherein,

R₁ and R₂ are, independently, from C₁ to C₁₂ branched or straight chain alkyl or substituted or unsubstituted aryl,

with an alcohol, an alkoxide or a combination thereof.

40. A method for preparing an ester, comprising admixing:

(a) a base;

(b) an alcohol, an alkoxide or a combination thereof; and

(c) a compound having the structure I:
wherein,

R₁ and R₂ are, independently, from C₁ to C₁₂ branched or straight chain alkyl; or substituted or unsubstituted aryl; and

X is a halogen or OR₃, wherein R₃ is from C₁ to C₁₂ branched or straight chain alkyl; substituted or unsubstituted aryl; aralkyl; acyl, S(O)₂R₄₁, wherein R₄₁ is C₁ to C₁₂ branched or straight chain alkyl; or substituted or unsubstituted aryl.

41. The method of Claim 40, wherein the compound having the structure I is first admixed with a base to produce an intermediate, and the intermediate is then admixed with an alcohol, an alkoxide or a combination thereof.

42. A method for preparing an ester, comprising admixing:

(a) a base;

(b) an alcohol, an alkoxide or a combination thereof; and

(c) a compound having the structure IV:
wherein,

R₉ and R₁₀ are, independently, an aralkyl or C(O)R₃₁, wherein R₃₁ is C₁ to C₁₅ straight chain or branched alkyl; substituted or unsubstituted aryl; or aralkyl;

R₁₁ is from C₁ to C₁₅ branched or straight chain alkyl or substituted or unsubstituted aryl;

R₁₂ is silyl, alkyl, acyl, aryl, or aralkyl; and

Y is a halogen or OR₁₃, wherein R₁₃ is from C₁ to C₁₂ branched or straight chain alkyl; substituted or unsubstituted aryl; aralkyl; acyl; or S(O)₂R₁₄₉, wherein R₁₄₉ is C₁ to C₁₂ straight chain or branched alkyl; substituted or unsubstituted aryl.

43. The method of Claim 42, wherein the compound having the structure IV is first admixed with a base to produce an intermediate, and the intermediate is then admixed with an alcohol, an alkoxide or a combination thereof.

44. The method of Claim 42, wherein R₉ is benzyl; R₁₀ is α-methyl benzyl; R₁₁ is phenyl; R₁₂ is C(O)Ph; R₁₃ is tert-butyl; and the stereochemistry at b is S.
45. The method of Claim 42, wherein R₉ is benzyl; R₁₀ is α-methyl benzyl; R₁₁ is phenyl; R₁₂ is C(O)Ph; R₁₃ is methyl; and the stereochemistry at b is S.

46. The method of Claim 42, wherein R₉ is benzyl; R₁₀ is α-methyl benzyl; R₁₁ is phenyl; R₁₂ is C(O)Ph; Y is chloride; and the stereochemistry at b is S.

47. The method of Claim 42, wherein the alcohol is an aliphatic alcohol, an aromatic alcohol, a cycloaliphatic alcohol, or a heteroaromatic alcohol.

48. The method of Claim 42, wherein the alcohol is a cycloaliphatic alcohol.

49. The method of Claim 42, wherein the alcohol is (2S)-hydroxy-3-methylbutane.

50. The method of Claim 42, wherein the alcohol is a compound having the structure II:

![Structure II](image)

wherein,

R₄ is acetyl or hydrogen;

R₅ is hydrogen;
$R_6$ is benzoyl;

$R_7$ is acetyl; and

$R_8$ is hydrogen, SiEt$_3$ or C(O)CH$_2$CCl$_3$.

51. The method of Claim 50, wherein $R_4$ is hydrogen.

52. The method of Claim 50, wherein $R_4$ is acetyl.

53. The method of Claim 1, wherein the alcohol comprises a compound having the structure XIV or XV:

![Diagram XIV](image)

or

![Diagram XV](image)
wherein,

$R_{44}$ and $R_{45}$ are, independently, hydrogen; $C_1$-$C_{12}$ branched or straight chain alkyl; or $R_{44}$ and $R_{45}$ are part of a cycloaliphatic group;

when $g$ is a single bond, $R_{46}$ is hydroxy; acetyl; or $C_1$-$C_{12}$ branched or straight chain alkoxy;

when $g$ is a double bond, $R_{46}$ is oxygen;

$R_{47}$ is a $C_1$-$C_{12}$ branched or straight chain alkyl ester; $C_1$-$C_{12}$ branched or straight chain alkyl; carboalkoxy; hydroxyalkyl; or derivatized or protected hydroxyalkyl;

$R_{48}$ is $C_1$-$C_{12}$ branched or straight chain alkyl; substituted or unsubstituted aryl; acetyl; hydroxyalkyl; or derivatized or protected hydroxyalkyl;

$R_{49}$ and $R_{50}$ are, independently, hydrogen; $C_1$-$C_{12}$ branched or straight chain alkyl or alkoxy; or acetyl, wherein $R_{49}$ or $R_{50}$ is hydrogen, provided that when one of $R_{49}$ or $R_{50}$ is hydrogen, the other of $R_{49}$ and $R_{50}$ is not hydrogen;

when $m$ is a double bond, $R_{51}$ is oxygen;

when $m$ is a single bond, $R_{51}$ is OH or OC(O)R_{52}, wherein $R_{52}$ is substituted or unsubstituted aryl; or cycloaliphatic; and

the hydroxyl group is located at carbon h or i.
54. The method of Claim 53, wherein the hydroxyl group is at carbon h, and the stereochemistry at carbon h is S.

55. The method of Claim 53, wherein the hydroxyl group is at carbon h, and the stereochemistry at carbon h is R.

56. The method of Claim 53, wherein the hydroxyl group is at carbon i, and the stereochemistry at carbon i is S.

57. The method of Claim 53, wherein the hydroxyl group is at carbon i, and the stereochemistry at carbon i is R.

58. The method of Claim 53, wherein $R_{44}$ and $R_{45}$ are independently, hydrogen or methyl.

59. The method of Claim 53, wherein $R_{44}$ and $R_{45}$ are hydrogen or methyl.

60. The method of Claim 53, wherein when $R_{44}$ and $R_{45}$ are part of a cycloaliphatic group, the cycloaliphatic group is a cyclopropyl group.

61. The method of Claim 53, wherein $R_{46}$ is methyl ester or methyl.

62. The method of Claim 53, wherein $R_{48}$ is hydroxy, ethoxy, propoxy, or derivatized hydroxy.

63. The method of Claim 53, wherein m is a single bond and $R_{52}$ is phenyl or cyclohexyl.

64. The method of Claim 53,

wherein the compound has the structure XIV,
R_{44} and R_{45} are hydrogen;

g is a double bond;

R_{47} is C(O)OMe;

the stereochemistry at carbon p is R;

the stereochemistry at carbon k is S;

R_{48} is methyl;

R_{49} is methyl;

the stereochemistry at carbon q is R;

R_{50} is hydrogen;

the stereochemistry at carbon r is S;

m is a single bond;

R_{51} is OC(O)Ph; and

the stereochemistry at carbon j is R.

65. The method of Claim 64, wherein the hydroxyl group is at carbon h and the stereochemistry at carbon h is R.

66. The method of Claim 64, wherein the hydroxyl group is at carbon h and the stereochemistry at carbon h is S.
67. The method of Claim 64, wherein the hydroxyl group is at carbon i and the stereochemistry at carbon i is S.

68. The method of Claim 53,

wherein the compound has the structure XIV,

$R_{44}$ and $R_{45}$ are hydrogen;

$g$ is a double bond;

$R_{47}$ is C(OMe);

the stereochemistry at carbon p is R;

the stereochemistry at carbon k is S;

$R_{49}$ is methyl;

$R_{50}$ is methyl;

the stereochemistry at carbon q is R;

$R_{52}$ is hydrogen;

the stereochemistry at carbon r is S; and

$m$ is a double bond.

69. The method of Claim 68, wherein the hydroxyl group is at carbon h and the stereochemistry at carbon h is R.
70. The method of Claim 68, wherein the hydroxyl group is at carbon h and the stereochemistry at carbon h is S.

71. The method of Claim 68, wherein the hydroxyl group is at carbon i and the stereochemistry at carbon h is S.

72. The method of Claim 42, wherein from one equivalent of compound having the structure IV is admixed with 1 to 10 equivalents of a base and from 1 to 3 equivalents of an alcohol.

73. The method of Claim 43, wherein the step of admixing with a base occurs at from -50 to 80 °C.

74. The method of Claim 43, wherein the step of admixing with a base occurs for from 30 seconds to 3 hours.

75. The method of Claim 42, wherein the method further comprises admixing a solvent with the base, the alcohol, the alkoxide, the compound having the structure IV or a combination thereof.

76. The method of Claim 75, wherein the solvent comprises tetrahydrofuran, diethyl ether, toluene, dimethoxymethane, t-butyl methyl ether, or a combination thereof.

77. A method for preparing an ester, comprising admixing:

(a) an alcohol, an alkoxide, or a combination thereof; and

(b) a compound having the structure V:
wherein,

R₉ and R₁₀ are, independently, an aralkyl or C(O)R₃₁, wherein R₃₁ is C₁ to C₁₂ straight chain or branched alkyl; substituted or unsubstituted aryl; or aralkyl;

R₁₁ is from C₁ to C₁₂ branched or straight chain alkyl or substituted or unsubstituted aryl; and

R₁₂ is silyl, alkyl, aryl, aralkyl or acyl.

78. A method for preparing a compound having the structure I:

wherein,

R₁ and R₂ are, independently, from C₁ to C₁₂ branched or straight chain alkyl or substituted or unsubstituted aryl; and
X is OR₃, wherein R₃ is from C₁ to C₁₂ branched or straight chain alkyl; substituted or unsubstituted aryl; aralkyl; acyl, or S(O)₂R₄₁, wherein R₄₁ is C₁ to C₁₂ branched or straight chain alkyl; or substituted or unsubstituted aryl, and

R₂ and C(O)X are cis to one another,

comprising:

(a) admixing a compound having the structure VI:

\[
\begin{array}{c}
\text{OH} \\
R₂ \\
C(O)X \\
\text{VI} \\
R₁ \\
\text{NH} \\
\end{array}
\]

wherein,

R₁ and R₂ are, independently, from C₁ to C₁₂ branched or straight chain alkyl or substituted or unsubstituted aryl;

X is OR₃, wherein R₃ is from C₁ to C₁₂ branched or straight chain alkyl; substituted or unsubstituted aryl; aralkyl; acyl, or S(O)₂R₄₁, wherein R₄₁ is C₁ to C₁₂ branched or straight chain alkyl; or substituted or unsubstituted aryl; and

the hydroxyl group and amide group are cis to one another,
with a cyclization agent.

79. A method of Claim 75, wherein the cyclization agent comprises triflic anhydride and pyridine.

80. A compound having the formula I:

![Chemical Structure](image)

wherein,

R₁ and R₂ are, independently, from C₁ to C₁₂ branched or straight chain alkyl or substituted or unsubstituted aryl;

X is OR₃, wherein R₃ is halogen; C₁ to C₁₂ branched or straight chain alkyl; substituted or unsubstituted aryl; aralkyl; acyl, or S(O)ₓR₄ₓ;

wherein R₄ₓ is C₁ to C₁₂ branched or straight chain alkyl; or substituted or unsubstituted aryl; and

R₂ and C(O)X are cis to one another.

81. The compound of Claim 80, wherein the R₁ and R₂ are phenyl; R₃ is methyl; and the stereochemistry at a is S.

82. The compound of Claim 80, wherein the R₁ and R₂ are phenyl; R₃ is tert-butyl; and the stereochemistry at a is S.
83. The compound of Claim 80, wherein the $R_1$ and $R_2$ are phenyl; $R_3$ is isopropyl; and the stereochemistry at $a$ is S.

84. The compound of Claim 80, wherein the $R_1$ and $R_2$ are phenyl; $R_3$ is phenyl; and the stereochemistry at $a$ is S.

85. The compound of Claim 80, wherein the $R_1$ and $R_2$ are phenyl; $R_3$ is 2,3-dimethyl propyl, wherein the stereochemistry at the 2-position is S; and the stereochemistry at $a$ is S.

86. A compound having the structure IV:

\[
\begin{align*}
\text{N(R}_9\text{)(R}_1\text{)}
\hspace{1cm} \text{IV} \\
\text{R}_1\hspace{1cm}
\end{align*}
\]

\[
\begin{align*}
\text{C(O)Y} \\
\text{OR}_2
\end{align*}
\]

wherein,

$R_9$ and $R_{10}$ are aralkyl;

$R_{11}$ is substituted or unsubstituted aryl;

$R_{12}$ is acyl, silyl, alkyl, aralkyl or aryl; and

$Y$ is a halogen or $\text{OR}_{13}$, wherein $R_{13}$ is from $C_1$ to $C_{12}$ branched or straight chain alkyl or substituted or unsubstituted aryl, acyl, aralkyl, or $\text{S(O)}_2\text{R}_{42}$, wherein $R_{42}$ is $C_1$ to $C_{12}$ branched or straight chain alkyl; or substituted or unsubstituted aryl.
87. The compound of Claim 86, wherein R₉ is benzyl; R₁₀ is α-methyl benzyl; R₁₁ is phenyl; R₁₂ is C(O)Ph; Y is tert-butoxy; and the stereochemistry at carbon b is S.

88. The compound of Claim 86, wherein R₉ is benzyl; R₁₀ is α-methyl benzyl; R₁₁ is phenyl; R₁₂ is C(O)Ph; Y is methoxy; and the stereochemistry at carbon b is S.

89. A method for preparing a compound having the structure IV:

```
N(R₉)(R₁₀)
\textbf{IV}
\begin{array}{c}
R₁₁ \\
\text{C(O)Y} \\
\end{array}
\begin{array}{c}
\textbf{IV} \\
OR₁₂ \\
\end{array}
```

wherein,

- R₉ and R₁₀ are aralkyl;
- R₁₁ is substituted or unsubstituted aryl;
- R₁₂ is acyl, silyl, alkyl, aryl, or aralkyl; and
- Y is OR₁₃, wherein R₁₃ is from C₁ to C₁₃ branched or straight chain aralkyl, or unsubstituted aryl, acyl, aralkyl, or S(O)₂R₁₂,
  wherein R₁₂ is C₁ to C₁₂ branched or straight chain alkyl or substituted or unsubstituted aryl,

comprising:

(a) admixing a base and a compound having the structure IX:
wherein,

R₉ and R₁₀ are aralkyl;

R₁₁ is substituted or unsubstituted aryl; and

Y is OR₁₃, wherein R₁₃ is from C₁ to C₁₂ branched or straight chain aralkyl or unsubstituted aryl, acyl, or aralkyl, S(O)₂R₄₂,
wherein R₄₂ is C₁ to C₁₂ branched or straight chain alkyl; or substituted or unsubstituted aryl,

to produce an intermediate, and

(b) admixing the intermediate of step (a) with an esterification agent, a silylating agent, or an alkylating agent.

90. The method of Claim 89, wherein the esterification agent is benzoyl chloride.

91. The method of Claim 89, wherein the base comprises an amide, a secondary amine, or a tertiary amine.

92. The method of Claim 89, wherein the base is triethylamine.

93. A method for preparing an ester, comprising admixing a compound having the structure VII:
wherein,

$R_{15}$ and $R_{16}$ are, independently, hydrogen, Si($R_{21}$), or C(O)$R_{22}$, wherein each $R_{21}$ is, independently, branched or straight chain C$_{1-12}$ alkyl; and $R_{22}$ is substituted or unsubstituted aryl, aralkyl or from C$_{1-12}$ branched or straight chain alkyl;

$R_{17}$ is substituted or unsubstituted aryl, aralkyl, or from C$_{1-12}$ branched or straight chain alkyl;

$R_{18}$ is hydrogen; branched or straight chain C$_{1-12}$ alkyl; unsubstituted or substituted aryl; aralkyl; Si($R_{29}$), or C(O)$R_{29}$, wherein, each $R_{29}$ is, independently, branched or straight chain C$_{1-12}$ alkyl; or aralkyl;

$R_{29}$ is substituted or unsubstituted aryl, aralkyl or from C$_{1-12}$ branched or straight chain alkyl;

$R_{19}$ and $R_{20}$ are, independently, branched or straight chain C$_{1-12}$ alkyl, aryl, aralkyl, or C(O)OR$_{30}$, wherein $R_{19}$ is not hydrogen;

$R_{30}$ is branched or straight chain C$_{1-12}$ alkyl; and

$V$ and $W$ are, independently, sulfur, oxygen, or NR$_{43}$, wherein $R_{43}$ is hydrogen; branched or straight chain C$_{1-12}$ alkyl; or aralkyl,
with an alkoxide.

94. The method of Claim 93, wherein the alkoxide comprises an aliphatic alkoxide, an aromatic alkoxide, a cycloaliphatic alkoxide, or a heteroaromatic alkoxide.

95. The method of Claim 93, wherein V and W are sulfur.

96. The method of Claim 93, wherein R_{17} is phenyl and R_{18} is benzoyl.

97. The method of Claim 93, wherein the alkoxide is a cycloaliphatic alkoxide.

98. The method of Claim 93, wherein the alkoxide is a compound having the structure VIII:

![Chemical structure](image)

wherein,

- $R_{23}$ is acetyl or hydrogen;
- $R_{24}$ is hydrogen;
- $R_{25}$ is benzoyl;
$R_{22}$ is acetyl; and

$R_{21}$ is hydrogen, C(O)OCH$_2$Ph, SiEt$_3$, or C(O)CH$_2$CCl$_3$.

99. The method of Claim 98, wherein $R_{21}$ is hydrogen.

100. The method of Claim 98, wherein $R_{21}$ is acetyl.

101. The method of Claim 93 wherein the alkoxide comprises a compound having the structure XVI or XVII:

![Chemical structure XVI](image1)

or

![Chemical structure XVII](image2)
wherein,

\( R_{44} \) and \( R_{45} \) are, independently, hydrogen; \( C_1-C_{12} \) branched or straight chain alkyl; or \( R_{46} \) and \( R_{47} \) are part of a cycloaliphatic group;

when \( g \) is a single bond, \( R_{44} \) is hydroxy; acetyl; or \( C_1-C_{12} \) branched or straight chain alkoxy;

when \( g \) is a double bond, \( R_{33} \) is oxygen;

\( R_{47} \) is a \( C_1-C_{12} \) branched or straight chain alkyl ester; \( C_1-C_{12} \) branched or straight chain alkyl; carboalkoxy; hydroxyalkyl; derivatized or protected hydroxyalkyl;

\( R_{48} \) is \( C_1-C_{12} \) branched or straight chain alkyl; substituted or unsubstituted aryl; acetyl; hydroxyalkyl; or derivatized or protected hydroxyalkyl;

\( R_{49} \) and \( R_{50} \) are, independently, hydrogen; \( C_1-C_{12} \) branched or straight chain alkyl or alkoxy; or acetyl, provided that when one of \( R_{49} \) or \( R_{50} \) is hydrogen, the other of \( R_{49} \) and \( R_{50} \) is not hydrogen;

when \( m \) is a double bond, \( R_{51} \) is oxygen;

when \( m \) is a single bond, \( R_{51} \) is OH or OC(O)R, wherein \( R_{52} \) is substituted or unsubstituted aryl; or cycloaliphatic; and

the hydroxyl group is located at carbon h or i.

102. The method of Claim 101, wherein the hydroxyl group is at carbon h, and the stereochemistry at carbon h is S.
103. The method of Claim 101, wherein the hydroxyl group is at carbon h, and the stereochemistry at carbon h is R.

104. The method of Claim 101, wherein the hydroxyl group is at carbon i, and the stereochemistry at carbon i is S.

105. The method of Claim 101, wherein the hydroxyl group is at carbon i, and the stereochemistry at carbon i is R.

106. The method of Claim 101, wherein $R_{44}$ and $R_{45}$ are independently, hydrogen or methyl.

107. The method of Claim 101, wherein $R_{44}$ and $R_{45}$ are hydrogen or methyl.

108. The method of Claim 101, wherein when $R_{44}$ and $R_{45}$ are part of a cycloaliphatic group, the cycloaliphatic group is a cyclopropyl group.

109. The method of Claim 101, wherein $R_{47}$ is methyl ester or methyl.

110. The method of Claim 101, wherein $R_{48}$ is hydroxy, ethoxy, propoxy or derivatized hydroxy.

111. The method of Claim 101, wherein m is a single bond and $R_{52}$ is phenyl or cyclohexyl.

112. The method of Claim 101,

wherein the compound has the structure XVI,

$R_{44}$ and $R_{45}$ are hydrogen;
g is a double bond;

$R_{47}$ is C(O)OMe;

the stereochemistry at carbon p is R;

the stereochemistry at carbon k is S;

$R_{48}$ is methyl;

$R_{49}$ is methyl;

the stereochemistry at carbon q is R;

$R_{50}$ is hydrogen;

the stereochemistry at carbon r is S;

m is a single bond;

$R_{51}$ is OC(O)Ph; and

the stereochemistry at carbon j is R.

113. The method of Claim 112, wherein the hydroxyl group is at carbon h and the stereochemistry at carbon h is R.

114. The method of Claim 112, wherein the hydroxyl group is at carbon h and the stereochemistry at carbon h is S.
115. The method of Claim 112, wherein the hydroxyl group is at carbon i and the stereochemistry at carbon i is S.

116. The method of Claim 101, wherein the compound has the structure XVI,

\[ R_{41} \text{ and } R_{45} \text{ are hydrogen; } \]
\[ g \text{ is a double bond; } \]
\[ R_{47} \text{ is } C(O)OME; \]
the stereochemistry at carbon p is R;
the stereochemistry at carbon k is S;
\[ R_{48} \text{ is methyl; } \]
\[ R_{49} \text{ is methyl; } \]
the stereochemistry at carbon q is R;
\[ R_{50} \text{ is hydrogen; } \]
the stereochemistry at carbon p is R; and
\[ m \text{ is a double bond. } \]

117. The method of Claim 116, wherein the hydroxyl group is at carbon h and the stereochemistry at carbon h is R.
118. The method of Claim 116, wherein the hydroxyl group is at carbon h and the stereochemistry at carbon h is S.

119. The method of Claim 116, wherein the hydroxyl group is at carbon i and the stereochemistry at carbon i is S.

120. A method for preparing a compound having the structure VII:

\[
\text{(R}_{16}\text{)(R}_{15}\text{)}\text{N}\text{O}\text{O} \quad \text{W} \quad \text{VII}
\]

\[
\begin{align*}
\text{R}_{17} & \quad \text{d} \\
\text{R}_{18} & \quad \text{e} \\
\text{R}_{19} & \quad \text{f} \\
\text{R}_{20} & \quad \text{V}
\end{align*}
\]

wherein,

\(\text{R}_{16}\) and \(\text{R}_{15}\) are, independently, hydrogen, Si(\(\text{R}_{21}\))\text{), or C(\text{O})\text{R}_{22}\), wherein each \(\text{R}_{21}\) is, independently, branched or straight chain C\text{\textsubscript{1}}-C\text{\textsubscript{12}} alkyl; and \(\text{R}_{22}\) is substituted or unsubstituted aryl, aralkyl or from C\text{\textsubscript{1}}-C\text{\textsubscript{12}} branched or straight chain alkyl;

\(\text{R}_{17}\) is substituted or unsubstituted aryl, aralkyl, or from C\text{\textsubscript{1}}-C\text{\textsubscript{12}} branched or straight chain alkyl;

\(\text{R}_{18}\) is branched or straight chain C\text{\textsubscript{1}}-C\text{\textsubscript{12}} alkyl; unsubstituted or substituted aryl; aralkyl; Si(\(\text{R}_{28}\))\text{), or C(\text{O})\text{R}_{29}\), wherein,

each \(\text{R}_{28}\) is, independently, branched or straight chain C\text{\textsubscript{1}}-C\text{\textsubscript{12}} alkyl; or aralkyl;
$R_{29}$ is substituted or unsubstituted aryl, aralkyl or from $C_1$-$C_{12}$ branched
or straight chain alkyl;

$R_{19}$ and $R_{20}$ are, independently, branched or straight chain $C_1$-$C_{12}$ alkyl,
aryl, aralkyl, or $C(O)OR_{30}$, wherein $R_{19}$ is not hydrogen;

$R_{30}$ is branched or straight chain $C_1$-$C_{12}$ alkyl; and

$V$ and $W$ are, independently, sulfur, oxygen, or $NR_{43}$, wherein $R_{43}$ is
hydrogen; branched or straight chain $C_1$-$C_{12}$ alkyl; or aralkyl,

comprising,

(a) admixing

(i) a compound having the structure X

\[
\begin{array}{c}
\text{O} \\
\text{N} \\
\text{e} \\
\text{f} \\
\text{X} \\
\text{O} \\
\text{R}_{18} \\
\text{R}_{19} \\
\text{R}_{20}
\end{array}
\]

wherein $R_{18}$-$R_{20}$ are as above,

(ii) a Lewis acid; and

(iii) a base,

to produce a first intermediate;
(b) reacting the first intermediate of step (a) with a compound having the structure XI:

```
    NR_{15}
   /\        \\
R_{17}  XI
```

wherein $R_{15}$ and $R_{17}$ are as above,

to produce a second intermediate; and

(c) admixing the second intermediate of step (b) with a proton source.

121. The method of Claim 120, wherein the base comprises an amide, a secondary amine or a tertiary amine.

122. The method of Claim 120, wherein a compound having the structure X is admixed with the Lewis acid prior to admixing the base.

123. The method of Claim 120, wherein the Lewis acid comprises stannous triflate, stannic chloride, stannous chloride, dialkylboron triflate, or titanium tetrachloride.

124. The method of Claim 120, wherein $R_{15}$ is $C(O)Ph$.

125. A compound having the structure VII:
wherein,

R_{15} and R_{16} are, independently, hydrogen, Si(R_{21}), or C(O)R_{22}, wherein each R_{21} is, independently, branched or straight chain C_{1-12} alkyl; and R_{22} is substituted or unsubstituted aryl, aralkyl or from C_{1-12} branched or straight chain alkyl;

R_{17} is substituted or unsubstituted aryl, aralkyl, or from C_{1-12} branched or straight chain alkyl;

R_{18} is hydrogen; branched or straight chain C_{1-12} alkyl; unsubstituted or substituted aryl; aralkyl; Si(R_{23}) or C(O)R_{24}, wherein,

each R_{23} is, independently, branched or straight chain C_{1-12} alkyl; or aralkyl;

R_{24} is substituted or unsubstituted aryl, aralkyl or from C_{1-12} branched or straight chain alkyl;

R_{19} and R_{20} are, independently, branched or straight chain C_{1-12} alkyl, aryl, aralkyl, or C(O)OR_{30}, wherein R_{19} is not hydrogen;

R_{30} is branched or straight chain C_{1-12} alkyl; and
V and W are, independently, sulfur, oxygen, or NR₄, wherein R₄ is hydrogen; branched or straight chain C₁₋₄ alkyl; or aralkyl.

126. The compound of Claim 125, wherein V and W are sulfur.

127. The compound of Claim 125, wherein R₁₇ is phenyl and R₁₈ is benzyol.

128. The compound of Claim 125, wherein R₁₈ is hydrogen.

129. The compound of Claim 125, wherein R₁₆ is C(O)Ph.

130. The compound of Claim 125, wherein R₁₆ is C(O)Ph and R₁₈ is hydrogen.

131. A method for preparing a compound having the structure VII:

![Chemical Structure](image)

wherein,

R₁₅ and R₁₆ are, independently, hydrogen, Si(R₂₁), or C(O)OMe, wherein each R₂₁ is, independently, branched or straight chain C₁₋₄ alkyl; and R₂₁ is substituted or unsubstituted aryl, aralkyl or from C₁₋₄ branched or straight chain alkyl;

R₁₇ is substituted or unsubstituted aryl, aralkyl, or from C₁₋₄ branched or straight chain alkyl;
R₁₉ is hydrogen:

R₁₉ and R₂₀ are, independently, branched or straight chain C₁-C₁₂ alkyl, aryl, aralkyl, or C(O)OR₃₀, wherein R₁₉ is not hydrogen;

R₃₀ is branched or straight chain C₁-C₁₂ alkyl; and

V and W are, independently, sulfur, oxygen, or NR₄₃, wherein R₄₃ is hydrogen; branched or straight chain C₁-C₁₂ alkyl; or aralkyl,

comprising,

(a) admixing

(i) a compound having the structure XIII

![Diagram XIII]

wherein R₁₉-R₂₀ and R₂₂ are as above,

(ii) a Lewis acid; and

(iii) a first base,

to produce a first intermediate;
(b) reacting the first intermediate of step (a) with a compound having the structure XI:

\[
\begin{array}{c}
\text{NR}_{15} \\
\text{R}_{17} \\
\text{XI}
\end{array}
\]

wherein \( R_{15} \) and \( R_{17} \) are as above,

to produce a second intermediate; and

(c) admixing the second intermediate with a basic buffer, wherein the buffer comprises a second base.

132. The method of Claim 131, wherein the first base comprises an amide, a secondary amine or a tertiary amine.

133. The method of Claim 131, wherein the compound having the structure XIII and the Lewis acid are admixed prior to admixing the base.

134. The method of Claim 131, wherein the Lewis acid comprises stannous triflate, stannic chloride, dialkylboron triflate, or titanium tetrachloride.

135. The method of Claim 131, wherein the second base comprises NaHCO\(_3\) or a phosphate.

136. A compound having the structure XIV or XV:
wherein,

$R_{44}$ and $R_{45}$ are, independently, hydrogen; C$_1$-C$_{12}$ branched or straight chain alkyl; or $R_{44}$ and $R_{45}$ are part of a cycloaliphatic group;

when g is a single bond, $R_{46}$ is hydroxy; acetyl; or C$_1$-C$_{12}$ branched or straight chain alkoxy;

when g is a double bond, $R_{46}$ is oxygen;
R_{17} is a C_{1}-C_{12} branched or straight chain alkyl ester; C_{1}-C_{12} branched or straight chain alkyl; carboalkoxy; hydroxyalkyl; or derivatized or protected hydroxyalkyl;

R_{49} is C_{1}-C_{12} branched or straight chain alkyl; substituted or unsubstituted aryl; acetyl; hydroxyalkyl; or derivatized or protected hydroxyalkyl;

R_{49} and R_{50} are, independently, hydrogen; C_{1}-C_{12} branched or straight chain alkyl or alkoxy; or acetyl, provided that when one of R_{49} or R_{50} is hydrogen, the other of R_{49} and R_{50} is not hydrogen;

when m is a double bond, R_{51} is oxygen;

when m is a single bond, R_{51} is OH or OC(O)R_{52}, wherein R_{52} is substituted or unsubstituted aryl; or cycloaliphatic; and

the hydroxyl group is located at carbon h or i.

137. The compound of Claim 136, wherein the hydroxyl group is at carbon h, and the stereochemistry at carbon h is S.

138. The compound of Claim 136, wherein the hydroxyl group is at carbon h, and the stereochemistry at carbon h is R.

139. The compound of Claim 136, wherein the hydroxyl group is at carbon i, and the stereochemistry at carbon i is S.

140. The compound of Claim 136, wherein the hydroxyl group is at carbon i, and the stereochemistry at carbon i is R.
141. The compound of Claim 136, wherein \( R_{44} \) and \( R_{45} \) are independently, hydrogen or methyl.

142. The compound of Claim 136, wherein \( R_{44} \) and \( R_{45} \) are hydrogen or methyl.

143. The compound of Claim 136, wherein when \( R_{44} \) and \( R_{45} \) are part of a cycloaliphatic group, the cycloaliphatic group is a cyclopropyl group.

144. The compound of Claim 136, wherein \( R_{45} \) is methyl ester or methyl.

145. The compound of Claim 136, wherein \( R_{45} \) is hydroxy, ethoxy, propoxy, or derivatized hydroxy.

146. The compound of Claim 136, wherein \( m \) is a single bond and \( R_{52} \) is phenyl or cyclohexyl.

147. The compound of Claim 136,

wherein the compound has the structure XIV,

\[ R_{44} \text{ and } R_{45} \text{ are hydrogen;} \]

\[ g \text{ is a double bond;} \]

\[ R_{47} \text{ is } \text{C(O)OMe;} \]

the stereochemistry at carbon \( p \) is \( R \);

the stereochemistry at carbon \( k \) is \( S \);

\[ R_{48} \text{ is methyl;} \]
R_{49} is methyl;

the stereochemistry at carbon q is R;

m is a single bond;

R_{20} is hydrogen;

the stereochemistry at carbon r is s;

R_{31} is OC(O)Ph; and

the stereochemistry at carbon j is R.

148. The compound of Claim 147, wherein the hydroxyl group is at carbon h and the stereochemistry at carbon h is R.

149. The compound of Claim 147, wherein the hydroxyl group is at carbon h and the stereochemistry at carbon h is S.

150. The compound of Claim 147, wherein the hydroxyl group is at carbon i and the stereochemistry at carbon h is S.

151. The compound of Claim 136,

wherein the compound has the structure XIV,

R_{44} and R_{45} are hydrogen;

g is a double bond;
R_{47} is C(OMe);

the stereochemistry at carbon \ p \ is \ R;

R_{48} is methyl;

the stereochemistry at carbon \ k \ is \ S;

R_{49} is methyl;

the stereochemistry at carbon \ q \ is \ R;

R_{50} is hydrogen;

the stereochemistry at carbon \ r \ is \ S; \ and

\ m \ is \ a \ double \ bond.

152. The compound of Claim 151, wherein the hydroxyl group is at carbon \ h \ and \ the \ stereochemistry \ at \ carbon \ h \ is \ R.

153. The compound of Claim 151, wherein the hydroxyl group is at carbon \ h \ and \ the \ stereochemistry \ at \ carbon \ h \ is \ S.

154. The compound of Claim 151, wherein the hydroxyl group is at carbon \ i \ and \ the \ stereochemistry \ at \ carbon \ h \ is \ S.

155. A method for preparing an ester, comprising admixing a compound having the structure XX:
wherein,

$R_{60}$ is branched or straight chain C$_{1-12}$ alkyl; unsubstituted or substituted aryl; aralkyl; Si($R_{63}$)$_3$ or C(O)$R_{64}$, wherein,

each $R_{63}$ is, independently, branched or straight chain C$_{1-12}$ alkyl; or aralkyl;

$R_{64}$ is substituted or unsubstituted aryl, aralkyl or from C$_{1-12}$ branched or straight chain alkyl;

$R_{61}$ and $R_{62}$ are, independently, hydrogen, branched or straight chain C$_{1-12}$ alkyl, aryl, aralkyl, or C(O)OR$_{65}$;

$R_{65}$ is branched or straight chain C$_{1-12}$ alkyl; and

V and W are, independently, sulfur, oxygen, or NR$_{66}$, wherein $R_{66}$ is hydrogen; branched or straight chain C$_{1-12}$ alkyl; or aralkyl,

with an alkoxide.
156. The method of Claim 155, wherein R_{61} is not hydrogen.

157. The method of Claim 155, wherein the compound XX has the formula: