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Trisubstituted phenyl derivatives having retinoid agonist, antagonist or inverse agonist type biological activity

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(21) International Application Number: PCT/US98/07394 (22) International Filing Date: 13 April 1998 (13.04.98) (30) Priority Data: 08/845,019 19 April 1997 (19.04.97) US (71) Applicant: ALLERGAN SALES, INC. [US/US]; 2525 Dupont Drive, Irvine, CA 92612 (US). (72) Inventors: SONG, Tae, K.; Apartment 26, 8 Ethan Allen Avenue, Colchester, VT 05446 (US). TENG, Min; 5185 Sea Chase Street, San Diego, CA 92130 (US). CHAN-DRARATNA, Roshantha, A.; 25841 Empresa, Mission Viejo, CA 92691 (US). (74) Agents: BARAN, Robert, J. et al.; Allergan Sales, Inc., 2525 Dupont Drive, Irvine, CA 92612 (US).		(81) Designated States: AU, CA, JP, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i> <i>With amended claims.</i>	
(54) Title: TRISUBSTITUTED PHENYL DERIVATIVES HAVING RETINOID AGONIST, ANTAGONIST OR INVERSE AGONIST TYPE BIOLOGICAL ACTIVITY			
(57) Abstract Compounds of formula (I) where the symbols have the meaning defined in the specification, have retinoid, retinois antagonist or retinoid inverse agonist type biological activity. (I)			

1 TRISUBSTITUTED PHENYL DERIVATIVES HAVING RETINOID
2 AGONIST, ANTAGONIST OR INVERSE AGONIST TYPE BIOLOGICAL
3 ACTIVITY

4
5 BACKGROUND OF THE INVENTION

6 1. Field of the Invention

7 The present invention relates to novel compounds having
8 retinoid-like, retinoid antagonist and/or retinoid inverse-agonist-like
9 biological activity. More specifically, the present invention relates to
10 trisubstituted phenyl derivatives which have retinoid-like, retinoid
11 antagonist or retinoid inverse agonist-like biological activity.

12 2. Background Art

13 Compounds which have retinoid-like activity are well
14 known in the art, and are described in numerous United States and
15 other patents and in scientific publications. It is generally known and
16 accepted in the art that retinoid-like activity is useful for treating
17 animals of the mammalian species, including humans, for curing or
18 alleviating the symptoms and conditions of numerous diseases and
19 conditions. In other words, it is generally accepted in the art that
20 pharmaceutical compositions having a retinoid-like compound or
21 compounds as the active ingredient are useful as regulators of cell
22 proliferation and differentiation, and particularly as agents for treating
23 skin-related diseases, including, actinic keratoses, arsenic keratoses,
24 inflammatory and non-inflammatory acne, psoriasis, ichthyoses and
25 other keratinization and hyperproliferative disorders of the skin,
26 eczema, atopic dermatitis, Darriers disease, lichen planus, prevention
27 and reversal of glucocorticoid damage (steroid atrophy), as a topical
28 anti-microbial, as skin anti-pigmentation agents and to treat and reverse
29 the effects of age and photo damage to the skin. Retinoid compounds
30 are also useful for the prevention and treatment of cancerous and

1 precancerous conditions, including, premalignant and malignant
2 hyperproliferative diseases such as cancers of the breast, skin, prostate,
3 cervix, uterus, colon, bladder, esophagus, stomach, lung, larynx, oral
4 cavity, blood and lymphatic system, metaplasias, dysplasias, neoplasias,
5 leukoplakias and papillomas of the mucous membranes and in the
6 treatment of Kaposi's sarcoma. In addition, retinoid compounds can be
7 used as agents to treat diseases of the eye, including, without limitation,
8 proliferative vitreoretinopathy (PVR), retinal detachment, dry eye and
9 other corneopathies, as well as in the treatment and prevention of
10 various cardiovascular diseases, including, without limitation, diseases
11 associated with lipid metabolism such as dyslipidemias, prevention of
12 post-angioplasty restenosis and as an agent to increase the level of
13 circulating tissue plasminogen activator (TPA). Other uses for retinoid
14 compounds include the prevention and treatment of conditions and
15 diseases associated with human papilloma virus (HPV), including warts
16 and genital warts, various inflammatory diseases such as pulmonary
17 fibrosis, ileitis, colitis and Krohn's disease, neurodegenerative diseases
18 such as Alzheimer's disease, Parkinson's disease and stroke, improper
19 pituitary function, including insufficient production of growth hormone,
20 modulation of apoptosis, including both the induction of apoptosis and
21 inhibition of T-Cell activated apoptosis, restoration of hair growth,
22 including combination therapies with the present compounds and other
23 agents such as Minoxidil^R, diseases associated with the immune system,
24 including use of the present compounds as immunosuppressants and
25 immunostimulants, modulation of organ transplant rejection and
26 facilitation of wound healing, including modulation of chelosis.

27 Several United States Patents assigned to the same assignee as
28 the present application and patents and publications cited therein
29 describe or relate to substituted phenyl derivatives having retinoid like
30 biological activity. Examples of such patents are:

1 4,980,369; 4,992,468; 5,006,550; 5,013,744; 5,015,658; 5,068,252;
2 5,130,355; 5,134,159; 5,162,546; 5,202,471; 5,231,113; 5,278,318;
3 5,324,744; 5,324,840; 5,326,898; 5,346,915; 5,348,975; 5,349,105;
4 5,391,753; 5,414,007; 5,434,173; 5,498,755; 5,498,795; 5,534,641, and
5 5,556,996. Still further, several co-pending applications and recently
6 issued patents which are assigned to the assignee of the present
7 application, are directed to further compounds having retinoid-like
8 activity.

9 Although pharmaceutical compositions containing retinoids have
10 well established utility (as is demonstrated by the foregoing citation of
11 patents and publications from the voluminous literature devoted to this
12 subject) retinoids also cause a number of undesired side effects at
13 therapeutic dose levels, including headache, teratogenesis,
14 mucocutaneous toxicity, musculoskeletal toxicity, dyslipidemias, skin
15 irritation, headache and hepatotoxicity. These side effects limit the
16 acceptability and utility of retinoids for treating disease.

17 It is now general knowledge in the art that two main types of
18 retinoid receptors exist in mammals (and other organisms). The two
19 main types or families of receptors are respectively designated the
20 RARs and RXRs. Within each type there are subtypes; in the RAR
21 family the subtypes are designated RAR α , RAR β and RAR γ , in RXR
22 the subtypes are: RXR α , RXB β and RXR γ . It has also been established
23 in the art that the distribution of the two main retinoid receptor types,
24 and of the several sub-types is not uniform in the various tissues and
25 organs of mammalian organisms. Moreover, it is generally accepted in
26 the art that many unwanted side effects of retinoids are mediated by
27 one or more of the RAR receptor subtypes. Accordingly, among
28 compounds having agonist-like activity at retinoid receptors, specificity
29 or selectivity for one of the main types or families, and even specificity
30 or selectivity for one or more subtypes within a family of receptors, is

1 considered a desirable pharmacological property. Some compounds
2 bind to one or more RAR receptor subtypes, but do not trigger the
3 response which is triggered by agonists of the same receptors. A
4 compound that binds to a biological receptor but does not trigger an
5 agonist-like response is usually termed an antagonist. Accordingly, the
6 "effect" of compounds on retinoid receptors may fall in the range of
7 having no effect at all, (inactive compound, neither agonist nor
8 antagonist), the compound may elicit an agonist-like response on all
9 receptor subtypes (pan-agonist), or a compound may be a partial agonist
10 and/or partial antagonist of certain receptor subtypes if the compound
11 binds to but does not activate certain receptor subtype or subtypes but
12 elicits an agonist-like response in other receptor subtype or subtypes.
13 A pan-antagonist is a compound that binds to all known retinoid
14 receptors but does not elicit an agonist-like response in any of the
15 receptors.

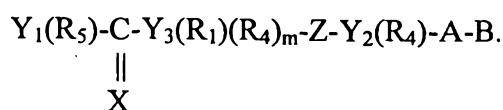
16 Recently a two-state model for certain receptors, including the
17 above-mentioned retinoid receptors, have emerged. In this model, an
18 equilibrium is postulated to exist between inactive receptors and
19 spontaneously active receptors which are capable of coupling with a G
20 protein in the absence of a ligand (agonist). In this model, so-called
21 "inverse agonists" shift the equilibrium toward inactive receptors, thus
22 bringing about an overall inhibitory effect. Neutral antagonists do not
23 effect the receptor equilibrium but are capable of competing for the
24 receptors with both agonists (ligands) and with inverse agonists.

25 It has been recently discovered and described in pending
26 applications assigned to the same assignee as the present application
27 that the above mentioned retinoid antagonist and/or inverse agonist-
28 like activity of a compound is also a useful property, in that such
29 antagonist or inverse agonist-like compounds can be utilized to block
30 certain undesired side effects of retinoids, to serve as antidotes to

retinoid overdose or poisoning, and may lend themselves to other pharmaceutical applications as well. More particularly, regarding the published scientific and patent literature in this field, published PCT application WO 94/14777 describes certain heterocyclic carboxylic acid derivatives which bind to RAR retinoid receptors and are said in the application to be useful for treatment of certain diseases or conditions, such as acne, psoriasis, rheumatoid arthritis and viral infections. A similar disclosure is made in the article by Yoshimura et al. J Med. Chem. 1995, 38, 3163-3173. Kaneko et al. Med. Chem Res. (1991) 1:220-225; Apfel et al. Proc. Natl. Acad. Sci. USA Vol 89 pp 7129-7133 August 1992 Cell Biology; Eckhardt et al. Toxicology Letters, 70 (1994) 299-308; Keidel et al. Molecular and Cellular Biology, Vol 14, No. 1, Jan. 1994, p 287-298; and Eyrolles et al. J. Med. Chem. 1994, 37, 1508-1517 describe compounds which have antagonist like activity at one or more of the RAR retinoid subtypes.

SUMMARY OF THE INVENTION

The present invention relates to compounds of Formula 1



Formula 1

where X is O, S, C(R₂) or NOR*,

R* is H, C₁₋₆ alkyl, C₃₋₆ cycloalkyl or phenyl;

R₁ is H, lower alkyl of 1 to 10 carbons, cycloalkyl of 3 to 10 carbons, F, Cl, Br, I, CF₃, OR₂, SR₂, OCH₂OC₁₋₆ alkyl or CF₂CF₃;

R₂ is independently H, lower alkyl of 1 to 10 carbons, lower cycloalkyl of 3 to 10 carbons, R₃Si, or COR₃ where R₃ is independently H, lower alkyl of 1 to 6 carbons, cycloalkyl of 3 to 6 carbons or phenyl;

R₄ is lower alkyl of 1 to 6 carbons, cycloalkyl of 3 to 6 carbons, F, Cl, Br, I, CF₃, CF₂CF₃, NO₂, N(R₆)₂, CN, COR₃ or N(R₆)-COR₃;



m is integer between 0 and 3;

Y_1 is phenyl, naphthyl or heteroaryl selected from a group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiazolyl, oxazolyl, imidazolyl and pyrrazolyl, said phenyl, naphthyl and heteroaryl groups being unsubstituted or substituted with one to three R_5 groups, where R_5 is alkyl of 1 to 10 carbons, cycloalkyl of 3 to 10 carbons, fluoro-substituted cycloalkyl of 3 to 10 carbons, fluoro-substituted alkyl of 1 to 10 carbons, alkenyl of 2 to 10 carbons and having 1 to 3 double bonds, cycloalkenyl of 3 to 10 carbons, alkynyl having 2 to 10 carbons and 1 to 3 triple bonds, F, Cl, Br, I, NO_2 , CN, COOH, $COOC_{1-6}alkyl$, N_3 , $N(R_6)_2$, OH, OR_3 , SR_3 , $OCOR_3$, or $SCOR_3$;

Z is

- C $\equiv$ C-
- N=N-,
- N(O)=N-,
- N=N(O)-,
- N=CR₆-,
- CR₆=N,
- (CR₆=CR₆)_n-where n is an integer having the value 0 - 5,
- CO-NR₆-,
- CS-NR₆,
- NR₆-CO,
- NR₆-CS,
- COO-,
- OCO-;
- CSO-;
- OCS-;
- CO-CR₆=CR₆-

R_6 is independently H, lower alkyl of 1 to 6 carbons, or cycloalkyl of 3 to 6 carbons;

Y_2 is a phenyl or naphthyl group, or heteroaryl selected from a group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiazolyl, oxazolyl, imidazolyl and pyrrazolyl, said phenyl and heteroaryl groups being unsubstituted or substituted with one or two R_4 groups, or



when Z is $-(CR_6=CR_6)_n$ and n is 3, 4 or 5 then Y_2 represents a direct valence bond between said $(CR_6=CR_6)_n$ group and B;

Y_3 is phenyl, pyridyl, thienyl or furyl unsubstituted or substituted with up to 3 R_1 groups and unsubstituted or substituted with up to 3 R_4 groups;

A is $(CH_2)_q$ where q is 0-5, lower branched chain alkyl having 3-6 carbons, cycloalkyl having 3-6 carbons, alkenyl having 2-6 carbons and 1 or 2 double bonds, cycloalkenyl of 3 to 6 carbons, alkynyl having 2-6 carbons and 1 or 2 triple bonds;

B is COOH or a pharmaceutically acceptable salt thereof, $COOR_8$, $CONR_9R_{10}$, $-CH_2OH$, CH_2OR_{11} , CH_2OCOR_{11} , CHO, $CH(OR_{12})_2$, $CH(OR_{13}O)$, $-COR_7$, $CR_7(OR_{12})_2$, $CR_7(OR_{13}O)$, or $Si(C_{1-6}alkyl)_3$, where R_7 is an alkyl, cycloalkyl or alkenyl group containing 1 to 5 carbons, R_8 is an alkyl group of 1 to 10 carbons or (trimethylsilyl)alkyl where the alkyl group has 1 to 10 carbons, or a cycloalkyl group of 5 to 10 carbons, or R_8 is phenyl or $C_1 - C_6$ lower alkylphenyl, R_9 and R_{10} independently are hydrogen, an alkyl group of 1 to 10 carbons, or a cycloalkyl group of 5-10 carbons, or phenyl, hydroxyphenyl or $C_1 - C_6$ lower alkylphenyl, R_{11} is lower alkyl, lower cycloalkyl, phenyl or $C_1 - C_6$ lower alkylphenyl, R_{12} is lower alkyl or lower cycloalkyl, and R_{13} is divalent alkyl radical of 2-5 carbons.

In a second aspect, this invention relates to the use of the compounds of Formula 1 for the treatment of skin-related diseases, including, without limitation, actinic keratoses, arsenic keratoses, inflammatory and non-inflammatory acne, psoriasis, ichthyoses and other keratinization and hyperproliferative disorders of the skin, eczema, atopic dermatitis, Darriers disease, lichen planus, prevention and reversal of glucocorticoid damage (steroid atrophy), as a topical anti-microbial, as skin anti-pigmentation agents and to treat and reverse the effects of age and photo damage to the skin. The compounds are



1 also useful for the prevention and treatment of cancerous and
2 precancerous conditions, including, premalignant and malignant
3 hyperproliferative diseases such as cancers of the breast, skin, prostate,
4 cervix, uterus, colon, bladder, esophagus, stomach, lung, larynx, oral
5 cavity, blood and lymphatic system, metaplasias, dysplasias, neoplasias,
6 leukoplakias and papillomas of the mucous membranes and in the
7 treatment of Kaposi's sarcoma. In addition, the present compounds can
8 be used as agents to treat diseases of the eye, including, without
9 limitation, proliferative vitreoretinopathy (PVR), retinal detachment, dry
10 eye and other corneopathies, as well as in the treatment and prevention
11 of various cardiovascular diseases, including, without limitation, diseases
12 associated with lipid metabolism such as dyslipidemias, prevention of
13 post-angioplasty restenosis and as an agent to increase the level of
14 circulating tissue plasminogen activator (TPA). Other uses for the
15 compounds of the present invention include the prevention and
16 treatment of conditions and diseases associated with Human papilloma
17 virus (HPV), including warts and genital warts, various inflammatory
18 diseases such as pulmonary fibrosis, ileitis, colitis and Krohn's disease,
19 neurodegenerative diseases such as Alzheimer's disease, Parkinson's
20 disease and stroke, improper pituitary function, including insufficient
21 production of growth hormone, modulation of apoptosis, including both
22 the induction of apoptosis and inhibition of T-Cell activated apoptosis,
23 restoration of hair growth, including combination therapies with the
24 present compounds and other agents such as Minoxidil^R, diseases
25 associated with the immune system, including use of the present
26 compounds as immunosuppressants and immunostimulants, modulation
27 of organ transplant rejection and facilitation of wound healing, including
28 modulation of chelosis.

29 Alternatively, those compounds of the invention which act as
30 antagonists or inverse agonists of one or more retinoid receptor

1 subtypes are useful to prevent certain undesired side effects of retinoids
2 which are administered for the treatment or prevention of certain
3 diseases or conditions. For this purpose the retinoid antagonist and/or
4 inverse agonist compounds of the invention may be co-administered
5 with retinoids. The retinoid antagonist and inverse agonist compounds
6 of the present invention are also useful in the treatment of acute or
7 chronic toxicity resulting from overdose or poisoning by retinoid drugs
8 or Vitamin A.

9 This invention also relates to a pharmaceutical formulation
10 comprising a compound of **Formula 1** in admixture with a
11 pharmaceutically acceptable excipient, said formulation being adapted
12 for administration to a mammal, including a human being, to treat or
13 alleviate the conditions which were described above as treatable by
14 retinoids, to be co-administered with retinoids to eliminate or reduce
15 side effects of retinoids, or to treat retinoid or Vitamin A overdose or
16 poisoning.

17 BIOLOGICAL ACTIVITY, MODES OF ADMINISTRATION

18 Assays of Retinoid-like or Retinoid Antagonist and Inverse Agonist- 19 like Biological Activity

20 A classic measure of retinoic acid activity involves measuring the
21 effects of retinoic acid on ornithine decarboxylase. The original work
22 on the correlation between retinoic acid and decrease in cell
23 proliferation was done by *Verma & Boutwell, Cancer Research, 1977, 37,*
24 *2196-2201.* That reference discloses that ornithine decarboxylase
25 (ODC) activity increased precedent to polyamine biosynthesis. It has
26 been established elsewhere that increases in polyamine synthesis can be
27 correlated or associated with cellular proliferation. Thus, if ODC
28 activity could be inhibited, cell hyperproliferation could be modulated.
29 Although all cases for ODC activity increases are unknown, it is known
30 that 12-0-tetradecanoylphorbol-13-acetate (TPA) induces ODC activity.

1 Retinoic acid inhibits this induction of ODC activity by TPA. An assay
2 essentially following the procedure set out in **Cancer Research**:
3 1662-1670,1975 may be used to demonstrate inhibition of TPA induction
4 of ODC by compounds of this invention. "IC₆₀" is that concentration of
5 the test compound which causes 60% inhibition in the ODC assay. By
6 analogy, "IC₈₀", for example, is that concentration of the test compound
7 which causes 80% inhibition in the ODC assay.

8 Other assays described below, measure the ability of the
9 compounds of the present invention to bind to, and/or activate various
10 retinoid receptor subtypes. When in these assays a compound binds to
11 a given receptor subtype and activates the transcription of a reporter
12 gene through that subtype, then the compound is considered an **agonist**
13 of that receptor subtype. Conversely, a compound is considered an
14 **antagonist** of a given receptor subtype if in the below described
15 co-transfection assays the compound does not cause significant
16 transcriptional activation of the receptor regulated reporter gene, but
17 nevertheless binds to the receptor with a K_d value of less than
18 approximately 1 micromolar. In the below described assays the ability
19 of the compounds to bind to RAR_α, RAR_β, RAR_γ, RXR_α, RXR_β and
20 RXR_γ receptors, and the ability or inability of the compounds to
21 activate transcription of a reporter gene through these receptor subtypes
22 can be tested.

23 Specifically, a **chimeric receptor transactivation assay** which tests
24 for agonist-like activity in the RAR_α, RAR_β, RAR_γ, RXR_α receptor
25 subtypes, and which is based on work published by Feigner P. L. and
26 Holm M. (1989) Focus, 112 is described in detail in United States
27 Patent No. 5,455,265 the specification of which is hereby expressly
28 incorporated by reference.

29 A **holoreceptor transactivation assay** and a **ligand binding assay**
30 which measure the antagonist/agonist like activity of the compounds of

1 the invention, or their ability to bind to the several retinoid receptor
2 subtypes, respectively, are described in published PCT Application No.
3 WO WO93/11755 (particularly on pages 30 - 33 and 37 - 41) published
4 on June 24, 1993, the specification of which is also incorporated herein
5 by reference. A detailed experimental procedure for holoreceptor
6 transactivations has been described by *Heyman et al.* *Cell* 68, 397 - 406,
7 (1992); *Allegretto et al.* *J. Biol. Chem.* 268, 26625 - 26633, and
8 *Mangelsdorf et al.* *The Retinoids: Biology, Chemistry and Medicine*, pp
9 319 - 349, Raven Press Ltd., New York, which are expressly
10 incorporated herein by reference. The results obtained in this assay are
11 expressed in EC₅₀ numbers, as they are also in the chimeric receptor
12 transactivation assay. The results of ligand binding assay are expressed
13 in K_d numbers. (See *Cheng et al.* *Biochemical Pharmacology* Vol. 22 pp
14 3099-3108, expressly incorporated herein by reference.)

15 Still another transactivation assay, the "PGR assay" is described in
16 the publication *Klein et al.* *J. Biol. Chem.* 271, 22692-22696 (1996) which
17 is expressly incorporated herein by reference, and a detailed description
18 is also provided below. The results of the PGR assay are also
19 expressed in EC₅₀ numbers (nanomolar concentration).

20 **RAR-P-GR holoreceptor Transactivation Assay**

21 CV-1 cells (4 x 10⁵ cells/well) were transiently transfected with the
22 luciferase reporter plasmid MTV-4(R5G)-Luc (0.7 µg/well) containing
23 four copies of the R5G retinoid DNA response element along with the
24 RXRα expression plasmid pRS-hRXRα (0.1 µg/well) and one of the
25 RAR-P-GR expression plasmids (0.05 µg/well) in 12 well plates via
26 calcium phosphate precipitation *Chen et al.* (1987) *Mol. Cell. Biol.* 7,
27 2745-2752, as described by *Klein et al.* in *J. Biol. Chem.* 271, 22692,
28 referenced above. The three different RAR-P-GR expression plasmids,
29 pRS-RARα-P-GR, pcDNA3-RARβ-P-GR and pcDNA3-RARγ-P-GR,
30 express RARα, RARβ and RARγ receptors, respectively, which contain

1 modified DNA binding domains such that their "P-boxes" have been
2 altered to that of the glucocorticoid receptor. These RAR-P-GR
3 receptors bind to DNA as heterodimeric complexes with RXR.
4 Specifically, the RAR-P-GR receptors bind retinoic acid response
5 elements designated R5G, comprised of two RAR half sites (nucleotide
6 sequence 5'-GGTTCA-3') separated by 5 base pairs in which the 3'-half
7 site has been modified to that of a glucocorticoid receptor half site, 5'-
8 AGAACA-3'. To allow for various in transfection efficiency a β -
9 galactosidase expression plasmid (0.01 ug/well) was used as an internal
10 control. Alternatively, the assay was performed in a 96-well microtiter
11 plate format (5000 cells/well) in a manner which was identical to that
12 described above except 1/5 of the amount of the DNA-calcium
13 phosphate precipitant (20 μ l instead of 100 μ l) was applied to each well.
14 Eighteen hours after introduction of the DNA precipitants, cells were
15 rinsed with phosphate buffered saline (PBS) and fed with D-MEM
16 (Gibco-BRL) containing 10% activated charcoal extracted fetal bovine
17 serum (Gemini Bio-Products). Cells were treated for 18 hours with the
18 compounds indicated in the figures. After rinsing with PBS, cells were
19 lysed and luciferase activity was measured as previously described in *de*
20 *Wet et al.* (1987) Mol. Cell. Biol. 7, 725-737. Luciferase values represent
21 the mean $\pm$ SEM of triplicate determinations normalized to β -
22 galactosidase activity.

23 **Table 1** below shows the results of the **PGR assay** for certain
24 exemplary compounds of the invention for the receptor subtypes in the
25 RAR group and **Table 2** shows the results of the **ligand binding assay**
26 for the same compounds. As it can be seen from the Tables, these
27 exemplary compounds do not transactivate but bind to the receptor and
28 therefore have retinoid antagonist (or inverse agonist) effects.

TABLE 1
PGR Assay Data (transactivation)

Compound No.	EC ₅₀ (nanomolar)			% Efficiency ¹		
	RAR _α	RAR _β	RAR _γ	RAR _α	RAR _β	RAR _γ
5	NA ²	NA	NA	1	3	1
8	NA	NA	NA	1	3	3
9	NA	NA	NA	1	3	5
12	NA	NA	NA	0	1	5
13	NA	NA	NA	0	0	0
20	NA	NA	NA	9	5	1
22	NA	NA	NA	0	0	0
25	NA	NA	NA	0	2	0
28	NA	NA	NA	0	0	1
29	NA	NA	NA	0	0	1
31	NA	NA	NA	0	4	2

¹ "% Efficiency" is percentage of efficiency of the test compounds in this assay relative to all-*trans*-retinoic acid.

² "NA" stands for NOT ACTIVE (>10,000 nM)

TABLE 2

Ligand Binding Assay

Compound No.	Kd (nanomolar)		
	RAR _α	RAR _β	RAR _γ
5	339	98	897
8	8205	1315	5218
9	942	152	730
12	1447	193	394
13	1187	487	902
20	>1000	224	>1000
22	1597	763	1498
25	1154	217	1960
28	2094	538	949
29	1160	233	817
31	3289	488	366

Inverse agonists are ligands that are capable of inhibiting the basal receptor activity of unliganded receptors. Recently, retinoic acid receptors (RARs) have been shown to be responsive to retinoid inverse agonists in regulating basal gene transcriptional activity. Moreover, the biological effects associated with retinoid inverse agonists are distinct from those of retinoid agonists or antagonists. For example, RAR inverse agonists, but not RAR neutral antagonists, cause a dose-dependent inhibition of the protein MRP-8 in cultured human keratinocytes differentiated with serum. MRP-8 is a specific marker of cell differentiation, which is also highly expressed in psoriatic epidermis,

1 but is not detectable in normal human skin. Thus, retinoid inverse
2 agonists may offer a unique way of treating diseases such as psoriasis.

3 The activity of retinoid inverse agonists can be tested by the
4 procedure of *Klein et al. J. Biol. Chem.* 271, 22692 - 22696 (1996) which
5 is expressly incorporated herein by reference.

6 In this assay, retinoid inverse agonists are able to repress the
7 basal activity of a RAR γ -VP-16 chimeric receptor where the
8 constitutively active domain of the herpes simplex virus (HSV) VP-16 is
9 fused to the N-terminus of RAR γ . CV-1 cells are cotransfected with
10 RAR γ -VP-16, an ER-RXR α chimeric receptor and an ERE-tk-Luc
11 chimeric reporter gene to produce a basal level of luciferase activity, as
12 shown by *Nagpal et al. EMBO J.* 12, 2349 -2360 (1993) expressly
13 incorporated herein by reference. Retinoid inverse agonists are able to
14 inhibit the basal luciferase activity in these cells in a dose dependent
15 manner and IC₅₀s measured.

16 Modes of Administration

17 The compounds of this invention may be administered
18 systemically or topically, depending on such considerations as the
19 condition to be treated, need for site-specific treatment, quantity of
20 drug to be administered, and numerous other considerations.

21 In the treatment of dermatoses, it will generally be preferred to
22 administer the drug topically, though in certain cases such as treatment
23 of severe cystic acne or psoriasis, oral administration may also be used.
24 Any common topical formulation such as a solution, suspension, gel,
25 ointment, or salve and the like may be used. Preparation of such
26 topical formulations are well described in the art of pharmaceutical
27 formulations as exemplified, for example, by Remington's
28 *Pharmaceutical Science*, Edition 17, Mack Publishing Company, Easton,
29 Pennsylvania. For topical application, these compounds could also be
30 administered as a powder or spray, particularly in aerosol form. If the

1 drug is to be administered systemically, it may be confected as a
2 powder, pill, tablet or the like or as a syrup or elixir suitable for oral
3 administration. For intravenous or intraperitoneal administration, the
4 compound will be prepared as a solution or suspension capable of being
5 administered by injection. In certain cases, it may be useful to
6 formulate these compounds by injection. In certain cases, it may be
7 useful to formulate these compounds in suppository form or as extended
8 release formulation for deposit under the skin or intramuscular
9 injection.

10 Other medicaments can be added to such topical formulation for
11 such secondary purposes as treating skin dryness; providing protection
12 against light; other medications for treating dermatoses; medicaments
13 for preventing infection, reducing irritation, inflammation and the like.

14 Treatment of dermatoses or any other indications known or
15 discovered to be susceptible to treatment by retinoic acid-like
16 compounds will be effected by administration of the therapeutically
17 effective dose of one or more compounds of the instant invention. A
18 therapeutic concentration will be that concentration which effects
19 reduction of the particular condition, or retards its expansion. In
20 certain instances, the compound potentially may be used in prophylactic
21 manner to prevent onset of a particular condition.

22 A useful therapeutic or prophylactic concentration will vary from
23 condition to condition and in certain instances may vary with the
24 severity of the condition being treated and the patient's susceptibility to
25 treatment. Accordingly, no single concentration will be uniformly
26 useful, but will require modification depending on the particularities of
27 the disease being treated. Such concentrations can be arrived at
28 through routine experimentation. However, it is anticipated that in the
29 treatment of, for example, acne, or similar dermatoses, that a
30 formulation containing between 0.01 and 1.0 milligrams per milliliter of

1 formulation will constitute a therapeutically effective concentration for
2 total application. If administered systemically, an amount between 0.01
3 and 5 mg per kg per day of body weight would be expected to effect a
4 therapeutic result in the treatment of many diseases for which these
5 compounds are useful.

6 The partial or pan retinoid antagonist and/or retinoid inverse
7 agonist compounds of the invention, when used to take advantage of
8 their antagonist and/or inverse agonist property, can be co-administered
9 to mammals, including humans, with retinoid agonists and, by means of
10 pharmacological selectivity or site-specific delivery, preferentially
11 prevent the undesired effects of certain retinoid agonists. The
12 antagonist and/or inverse agonist compounds of the invention can also
13 be used to treat Vitamin A overdose, acute or chronic, resulting either
14 from the excessive intake of vitamin A supplements or from the
15 ingestion of liver of certain fish and animals that contain high levels of
16 Vitamin A. Still further, the antagonist and/or inverse agonist
17 compounds of the invention can also be used to treat acute or chronic
18 toxicity caused by retinoid drugs. It has been known in the art that the
19 toxicities observed with hypervitaminosis A syndrome (headache, skin
20 peeling, bone toxicity, dyslipidemias) are similar or identical with
21 toxicities observed with other retinoids, suggesting a common biological
22 cause, that is RAR activation. Because the antagonist or inverse agonist
23 compounds of the present invention block or diminish RAR activation,
24 they are suitable for treating the foregoing toxicities.

25 Generally speaking, for therapeutic applications in mammals, the
26 antagonist and/or inverse agonist compounds of the invention can be
27 administered enterally or topically as an antidote to vitamin A, or
28 antidote to retinoid toxicity resulting from overdose or prolonged
29 exposure, after intake of the causative factor (vitamin A, vitamin A
30 precursor, or other retinoid) has been discontinued. Alternatively, the

1 antagonist and/or inverse agonist compounds of the invention are
2 co-administered with retinoid drugs, in situations where the retinoid
3 provides a therapeutic benefit, and where the co-administered
4 antagonist and/or inverse agonist compound alleviates or eliminates one
5 or more undesired side effects of the retinoid. For this type of
6 application the antagonist and/or inverse agonist compound may be
7 administered in a site-specific manner, for example as a topically
8 applied cream or lotion while the co-administered retinoid may be given
9 enterally. For therapeutic applications the antagonist compounds of
10 the invention, like the retinoid agonists compounds, are incorporated
11 into pharmaceutical compositions, such as tablets, pills, capsules,
12 solutions, suspensions, creams, ointments, gels, salves, lotions and the
13 like, using such pharmaceutically acceptable excipients and vehicles
14 which *per se* are well known in the art. For topical application, the
15 antagonist and/or inverse agonist compounds of the invention could also
16 be administered as a powder or spray, particularly in aerosol form. If
17 the drug is to be administered systemically, it may be confected as a
18 powder, pill, tablet or the like or as a syrup or elixir suitable for oral
19 administration. For intravenous or intraperitoneal administration, the
20 compound will be prepared as a solution or suspension capable of being
21 administered by injection. In certain cases, it may be useful to
22 formulate these compounds by injection. In certain cases, it may be
23 useful to formulate these compounds in suppository form or as extended
24 release formulation for deposit under the skin or intramuscular
25 injection.

26 The antagonist and/or inverse agonist compounds also, like the
27 retinoid agonists of the invention, will be administered in a
28 therapeutically effective dose. A therapeutic concentration will be that
29 concentration which effects reduction of the particular condition, or
30 retards its expansion. When co-administering the compounds of the

1 invention to block retinoid-induced toxicity or side effects, the
2 antagonist and/or inverse agonist compounds of the invention are used
3 in a prophylactic manner to prevent onset of a particular condition, such
4 as skin irritation.

5 A useful therapeutic or prophylactic concentration will vary from
6 condition to condition and in certain instances may vary with the
7 severity of the condition being treated and the patient's susceptibility to
8 treatment. Accordingly, no single concentration will be uniformly
9 useful, but will require modification depending on the particularities of
10 the chronic or acute retinoid toxicity or related condition being treated.
11 Such concentrations can be arrived at through routine experimentation.
12 However, it is anticipated that a formulation containing between 0.01
13 and 1.0 milligrams of the active compound per milliliter of formulation
14 will constitute a therapeutically effective concentration for total
15 application. If administered systemically, an amount between 0.01 and 5
16 mg per kg per day of body weight would be expected to effect a
17 therapeutic result.

18 GENERAL EMBODIMENTS AND SYNTHETIC METHODOLOGY

19 Definitions

20 The term alkyl refers to and covers any and all groups which are
21 known as normal alkyl, branched-chain alkyl and cycloalkyl. The term
22 alkenyl refers to and covers normal alkenyl, branch chain alkenyl and
23 cycloalkenyl groups having one or more sites of unsaturation. Similarly,
24 the term alkynyl refers to and covers normal alkynyl, and branch chain
25 alkynyl groups having one or more triple bonds.

26 Lower alkyl means the above-defined broad definition of alkyl
27 groups having 1 to 6 carbons in case of normal lower alkyl, and as
28 applicable 3 to 6 carbons for lower branch chained and cycloalkyl
29 groups. Lower alkenyl is defined similarly having 2 to 6 carbons for
30 normal lower alkenyl groups, and 3 to 6 carbons for branch chained and

1 cyclo- lower alkenyl groups. Lower alkynyl is also defined similarly,
2 having 2 to 6 carbons for normal lower alkynyl groups, and 4 to 6
3 carbons for branch chained lower alkynyl groups.

4 The term "ester" as used here refers to and covers any compound
5 falling within the definition of that term as classically used in organic
6 chemistry. It includes organic and inorganic esters. Where B of
7 **Formula 1** is -COOH, this term covers the products derived from
8 treatment of this function with alcohols or thiols preferably with
9 aliphatic alcohols having 1-6 carbons. Where the ester is derived from
10 compounds where B is -CH₂OH, this term covers compounds derived
11 from organic acids capable of forming esters including phosphorous
12 based and sulfur based acids, or compounds of the formula
13 -CH₂OCOR₁₁ where R₁₁ is any substituted or unsubstituted aliphatic,
14 aromatic, heteroaromatic or aliphatic aromatic group, preferably with
15 1-6 carbons in the aliphatic portions.

16 Unless stated otherwise in this application, preferred esters are
17 derived from the saturated aliphatic alcohols or acids of ten or fewer
18 carbon atoms or the cyclic or saturated aliphatic cyclic alcohols and
19 acids of 5 to 10 carbon atoms. Particularly preferred aliphatic esters are
20 those derived from lower alkyl acids and alcohols. Also preferred are
21 the phenyl or lower alkyl phenyl esters.

22 Amides has the meaning classically accorded that term in organic
23 chemistry. In this instance it includes the unsubstituted amides and all
24 aliphatic and aromatic mono- and di- substituted amides. Unless stated
25 otherwise in this application, preferred amides are the mono- and
26 di-substituted amides derived from the saturated aliphatic radicals of ten
27 or fewer carbon atoms or the cyclic or saturated aliphatic-cyclic radicals
28 of 5 to 10 carbon atoms. Particularly preferred amides are those
29 derived from substituted and unsubstituted lower alkyl amines. Also
30 preferred are mono- and disubstituted amides derived from the

1 substituted and unsubstituted phenyl or lower alkylphenyl amines.

2 Unsubstituted amides are also preferred.

3 Acetals and ketals include the radicals of the formula-CK where
4 K is $(-OR)_2$. Here, R is lower alkyl. Also, K may be $-OR_7O-$ where R,
5 is lower alkyl of 2-5 carbon atoms, straight chain or branched.

6 A pharmaceutically acceptable salt may be prepared for any
7 compounds in this invention having a functionality capable of forming a
8 salt, for example an acid functionality. A pharmaceutically acceptable
9 salt is any salt which retains the activity of the parent compound and
10 does not impart any deleterious or untoward effect on the subject to
11 which it is administered and in the context in which it is administered.

12 Pharmaceutically acceptable salts may be derived from organic or
13 inorganic bases. The salt may be a mono or polyvalent ion. Of
14 particular interest are the inorganic ions, sodium, potassium, calcium,
15 and magnesium. Organic salts may be made with amines, particularly
16 ammonium salts such as mono-, di- and trialkyl amines or ethanol
17 amines. Salts may also be formed with caffeine, tromethamine and
18 similar molecules. Where there is a nitrogen sufficiently basic as to be
19 capable of forming acid addition salts, such may be formed with any
20 inorganic or organic acids or alkylating agent such as methyl iodide.

21 Preferred salts are those formed with inorganic acids such as
22 hydrochloric acid, sulfuric acid or phosphoric acid. Any of a number of
23 simple organic acids such as mono-, di- or tri- acid may also be used.

24 Some of the compounds of the present invention may have *trans*
25 and *cis* (E and Z) isomers. In addition, the compounds of the present
26 invention may contain one or more chiral centers and therefore may
27 exist in enantiomeric and diastereomeric forms. The scope of the
28 present invention is intended to cover all such isomers *per se*, as well as
29 mixtures of *cis* and *trans* isomers, mixtures of diastereomers and
30 racemic mixtures of enantiomers (optical isomers) as well.

1 Generally speaking, compounds of the invention where **Z** is an
2 ethyne function are obtained in a sequence of reactions which initially
3 involve the synthesis of a halogenated, preferably brominated, phenyl
4 derivative, that has in the position *meta* to the halogene (preferably
5 bromo) group an $Y(R_5)$ -CO ketone function and which may be obtained
6 as a result of a *Friedel-Crafts* or like reaction. The bromo compound is
7 reacted with (trimethylsilyl)acetylene to provide a [1-(2-
8 trimethylsilyl)ethynyl]phenyl derivative, from which the trimethylsilyl
9 group is removed by treatment with base. The $Y(R_5)$ -CO ketone
10 function may be subjected to a Grignard reaction, followed by
11 dehydration of the resulting tertiary alcohol to provide compounds of the
12 invention where **X** is CH_2 . The ethyne compounds are coupled with a
13 reagent of the formula $X_2-Y_2(R_4)$ -**A-B** where X_2 is a halogen and the
14 remaining symbols are defined in connection with **Formula 1**.

15 Compounds of the invention where **Z** is other than the above-
16 described ethyne function, are obtained by utilizing the reactive nature
17 of the bromo group, either to couple the bromo phenyl ketone
18 compound (bromine is in the phenyl group) directly, such as in a *Heck*
19 reaction, to provide compounds where the $Y_2(R_4)$ **A-B** group is attached
20 directly to the phenyl group. Alternatively the bromo function may be
21 converted into other reactive groups, such as NH_2 , SH, or COOH which
22 is then coupled to a reagent that together with the NH_2 , SH, or COOH
23 completes the moiety designated **Z** in **Formula 1**, and which also
24 introduces the $Y_2(R_4)$ -**A-B** moiety of the compounds of the invention.
25 Compounds of the invention where **Z** represents an ester, amide,
26 thioester, thioamide, or azo linkage can, for example, be prepared in
27 accordance with this general synthetic methodology. During the
28 synthetic manipulation the OH or SH function in the *para* position of
29 the phenyl ring may be protected by appropriate acid or base labile
30 protecting groups, such as methoxymethyl (MOM), acetyl or trialkylsilyl.

1 Still further, the $Z-Y_2(R_4)-A-B$ moiety can be formed in multiple
2 steps starting with the introduction of a two-carbon moiety (such as the
3 CH_3CO group) in place of the reactive bromo group of the substituted
4 phenyl nucleus. This type of reaction sequence is suitable, for example,
5 for the preparation of compounds of the invention where Z is
6 $-(CR_6=CR_6)_n-$, n is 3, 4 or 5 and Y_2 represents a direct valence bond
7 between the $(CR_6=CR_6)_n$ group and B . Details of the above-outlined
8 generalized synthetic schemes are provided below in connection with the
9 description of the specific embodiments and specific examples.

10 The synthetic methodology employed for the synthesis of the
11 compounds of the present invention may also include transformations of
12 the group designated $-A-B$ in Formula 1. Generally speaking, these
13 transformations involve reactions well within the skill of the practicing
14 organic chemist. In this regard the following well known and published
15 general principles and synthetic methodology are briefly described.

16 Carboxylic acids are typically esterified by refluxing the acid in a
17 solution of the appropriate alcohol in the presence of an acid catalyst
18 such as hydrogen chloride or thionyl chloride. Alternatively, the
19 carboxylic acid can be condensed with the appropriate alcohol in the
20 presence of dicyclohexylcarbodiimide (DCC) and 4-
21 (dimethylamino)pyridine (DMAP). The ester is recovered and purified
22 by conventional means. Acetals and ketals are readily made by the
23 method described in March, "Advanced Organic Chemistry," 2nd
24 Edition, McGraw-Hill Book Company, p 810). Alcohols, aldehydes and
25 ketones all may be protected by forming respectively, ethers and esters,
26 acetals or ketals by known methods such as those described in McOmie,
27 Plenum Publishing Press, 1973 and Protecting Groups, Ed. Greene,
28 John Wiley & Sons, 1981.

29 To increase the value of q in the compounds of the invention
30 (or precursors thereof) before affecting the coupling or linkage with the

1 phenyl nucleus (where such compounds are not available from a
2 commercial source) aromatic or heteroaromatic carboxylic acids are
3 subjected to homologation by successive treatment under Arndt-Eistert
4 conditions or other homologation procedures. Alternatively, derivatives
5 which are not carboxylic acids may also be homologated by appropriate
6 procedures. The homologated acids can then be esterified by the
7 general procedure outlined in the preceding paragraph.

8 Compounds of the invention as set forth in **Formula 1** (or
9 precursors thereof) where A is an alkenyl group having one or more
10 double bonds can be made for example, by synthetic schemes well
11 known to the practicing organic chemist; for example by Wittig and like
12 reactions, or by introduction of a double bond by elimination of halogen
13 from an alpha-halo-arylalkyl-carboxylic acid, ester or like carbox-
14 aldehyde. Compounds of the invention or precursors thereof, where
15 the A group has a triple (acetylenic) bond, can be made by reaction of a
16 corresponding aromatic methyl ketone with strong base, such as lithium
17 diisopropylamide, reaction with diethyl chlorophosphate and subsequent
18 addition of lithium diisopropylamide.

19 The acids and salts derived from compounds of the invention are
20 readily obtainable from the corresponding esters. Basic saponification
21 with an alkali metal base will provide the acid. For example, an ester of
22 the invention may be dissolved in a polar solvent such as an alkanol,
23 preferably under an inert atmosphere at room temperature, with about
24 a three molar excess of base, for example, lithium hydroxide or
25 potassium hydroxide. The solution is stirred for an extended period of
26 time, between 15 and 20 hours, cooled, acidified and the hydrolysate
27 recovered by conventional means.

28 The amide may be formed by any appropriate amidation means
29 known in the art from the corresponding esters or carboxylic acids. One
30 way to prepare such compounds is to convert an acid to an acid chloride

1 and then treat that compound with ammonium hydroxide or an
2 appropriate amine. For example, the ester is treated with an alcoholic
3 base solution such as ethanolic KOH (in approximately a 10% molar
4 excess) at room temperature for about 30 minutes. The solvent is
5 removed and the residue taken up in an organic solvent such as diethyl
6 ether, treated with a dialkyl formamide and then a 10-fold excess of
7 oxalyl chloride. This is all effected at a moderately reduced
8 temperature between about -10 degrees and +10 degrees C. The last
9 mentioned solution is then stirred at the reduced temperature for 1-4
10 hours, preferably 2 hours. Solvent removal provides a residue which is
11 taken up in an inert organic solvent such as benzene, cooled to about 0
12 degrees C and treated with concentrated ammonium hydroxide. The
13 resulting mixture is stirred at a reduced temperature for 1 - 4 hours.
14 The product is recovered by conventional means.

15 Alcohols are made by converting the corresponding acids to the
16 acid chloride with thionyl chloride or other means (J. March, "Advanced
17 Organic Chemistry", 2nd Edition, McGraw-Hill Book Company), then
18 reducing the acid chloride with sodium borohydride (March, Ibid, pg.
19 1124), which gives the corresponding alcohols. Alternatively, esters may
20 be reduced with lithium aluminum hydride at reduced temperatures.
21 Alkylating these alcohols with appropriate alkyl halides under
22 Williamson reaction conditions (March, Ibid, pg. 357) gives the
23 corresponding ethers. These alcohols can be converted to esters by
24 reacting them with appropriate acids in the presence of acid catalysts or
25 dicyclohexylcarbodiimide and dimethylaminopyridine.

26 Aldehydes can be prepared from the corresponding primary
27 alcohols using mild oxidizing agents such as pyridinium dichromate in
28 methylene chloride (Corey, E. J., Schmidt, G., Tet. Lett., 399, 1979), or
29 dimethyl sulfoxide/oxalyl chloride in methylene chloride (Omura, K.,
30 Swern, D., Tetrahedron, 1978, 34, 1651).

1 Ketones can be prepared from an appropriate aldehyde by
2 treating the aldehyde with an alkyl Grignard reagent or similar reagent
3 followed by oxidation.

4 Acetals or ketals can be prepared from the corresponding
5 aldehyde or ketone by the method described in March, Ibid, p 810.

6 Compounds of the invention, or precursors thereof, where B is
7 H can be prepared from the corresponding halogenated aromatic or
8 heteroaromatic compounds, preferably where the halogen is I.

9 SPECIFIC EMBODIMENTS

10 With reference to the symbol Y_1 in Formula 1, the preferred
11 compounds of the invention are those where Y_1 is phenyl, pyridyl,
12 thienyl, furyl and thiazolyl. Among these the phenyl group and
13 particularly methyl substituted phenyl are more preferred. Furthermore,
14 substitution of the Y_1 phenyl group with the carbonyl group and the
15 methyl group is preferred in the 1,4 (*para*) and 1,3 (*meta*) positions.

16 The X group is preferably O (carbonyl function) or $=CH_2$.

17 The preferred Z (linker) groups are $-C\equiv C-$, $-CH=CH-$, $-CONH-$
18 , $-COO-$, $-OCO-$, $-NHCO-$, $-(CR_6=CR_6)_n-$ and n is 3, or the Z group
19 is absent (n is zero and Y is directly attached to the phenyl ring).
20 Among the foregoing even more preferred are the following: $-C\equiv C-$,
21 $-C=C-$, and $-CONH-$. Presently $-C\equiv C-$ is most preferred.

22 The Y_2 group is preferably phenyl, naphthyl, pyridyl, thienyl or
23 furyl. Even more preferred are compounds where Y_2 is phenyl. As far
24 as substitutions on the Y_2 (phenyl), Y_2 (pyridyl) and (Y_2) naphthyl
25 groups are concerned, compounds are preferred where the phenyl group
26 is 1,4 (*para*) substituted, the naphthyl group is 2,6 substituted and where
27 the pyridine ring is 2,5 substituted. (Substitution in the 2,5 positions in
28 the "pyridine" nomenclature corresponds to substitution in the 6-position
29 in the "nicotinic acid" nomenclature.) In the preferred compounds of
30 the invention there is no or only one optional R_4 substituent on the Y_2

1 group, and the preferred R_4 substituent is fluoro (F).

2 Y_3 is preferably phenyl. The Y_3 phenyl group is preferably
3 substituted in the 1,3 (*meta*) positions by the $Y_1(R_5)CX$ and Z groups.

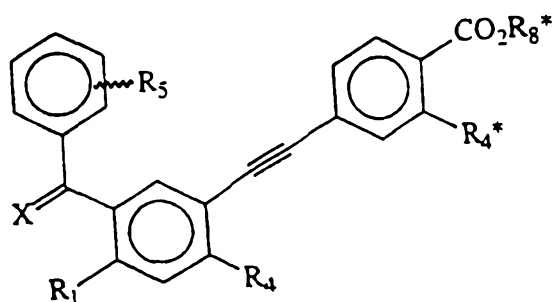
4 The R_1 group is preferably in the 4 (*para*) position relative to the Z, and
5 in the 2 (*ortho*) position relative to the $Y_1(R_5)CX$ group.

6 The A-B group of the preferred compounds is $(CH_2)_qCOOH$ or
7 $(CH_2)_q-COOR_8$, where R_8 is defined as above. Even more preferably q
8 is zero and R_8 is lower alkyl.

9 In the preferred compounds of the invention m is 0, that is, there
10 is no R_4 substituent on the phenyl ring.

11 The R_1 group of the preferred compounds of the invention is OH,
12 or OR_2 where R_2 is preferably H, lower alkyl of 1 to 10 carbons,
13 methoxymethyl or dimethyl-*t*-butylsilyl. Among the R_2 alkyl groups
14 methyl and isopropyl are especially preferred.

15 The most preferred compounds in accordance with Formula 1 are
16 listed below in Table 3 for Formula 2 and with reference to that
17 formula.



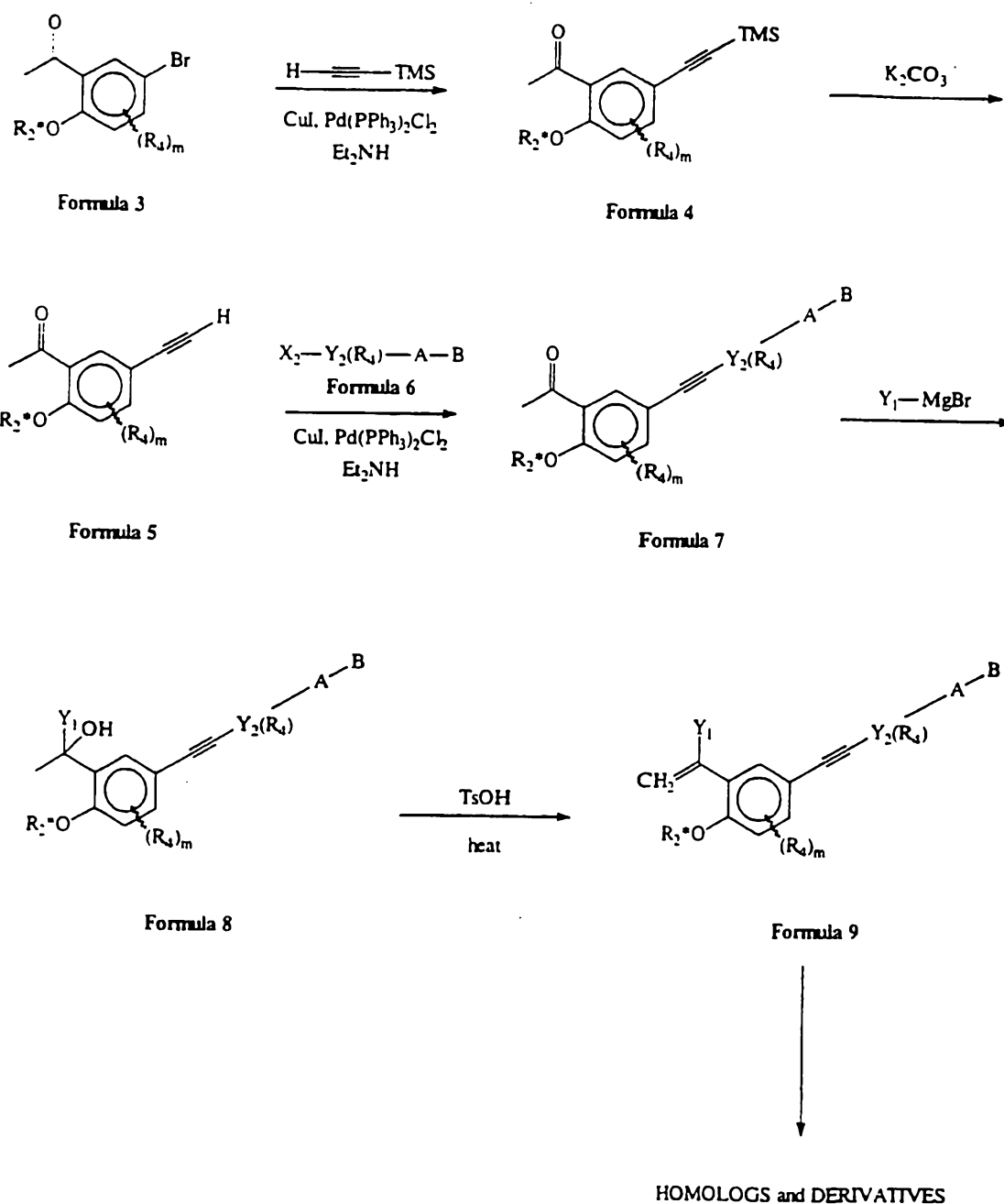
30 Formula 2

TABLE 3

Compound No.	R ₁	R ₄	X	R ₅	R ₄ '	R ₈ '
3	OCH ₂ OCH ₃	H	O	4-methyl	H	Et
4	OH	H	O	4-methyl	H	Et
5	OH	H	O	4-methyl	H	H
6	CH ₃ COO-	H	CH ₂	4-methyl	H	Et
7	OCH ₂ OCH ₃	H	CH ₂	4-methyl	H	Et
8	OH	H	CH ₂	4-methyl	H	H
9	OCH ₂ OCH ₃	H	CH ₂	4-methyl	H	H
11	OCH ₃	H	CH ₂	4-methyl	H	Et
12	OCH ₃	H	CH ₂	4-methyl	H	H
13	OCH ₂ OCH ₃	H	O	4-methyl	H	H
15	O- <i>n</i> -heptyl	H	CH ₂	4-methyl	H	Et
16	O- <i>n</i> -heptyl	H	CH ₂	4-methyl	H	H
19	H	H	CH ₂	4-methyl	H	Et
20	H	H	CH ₂	4-methyl	H	H
21	-OCH ₃	H	O	4-methyl	H	Et
22	-OCH ₃	H	O	4-methyl	H	H
23	OCH ₂ OCH ₃	CH ₃	O	4-methyl	F	Et
24	OH	CH ₃	O	4-methyl	F	Et
25	OH	CH ₃	O	4-methyl	F	H
26	OCH(CH ₃) ₂	H	CH ₂	4-methyl	H	Et
27	OCH(CH ₃) ₂	H	CH ₂	4-methyl	F	Et
28	OCH(CH ₃) ₂	H	CH ₂	4-methyl	H	H
29	OCH(CH ₃) ₂	H	CH ₂	4-methyl	F	H
30	OCH(CH ₃) ₂	H	CH ₂	3-methyl	H	Et
31	OCH(CH ₃) ₂	H	CH ₂	3-methyl	H	H

1	32	OSi(CH ₃) ₂ - <i>t</i> -butyl	H	CH ₂	4-methyl	H	Et
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2
3 The compounds of this invention can be made by the general
4 procedures outlined above under the title ""GENERAL
5 EMBODIMENTS AND SYNTHETIC METHODOLOGY". The
6 following chemical pathways represent the presently preferred synthetic
7 routes to certain classes of the compounds of the invention and to
8 certain specific exemplary compounds. However, the synthetic chemist
9 will readily appreciate that the conditions set out here for these specific
10 embodiments can be generalized to any and all of the compounds
11 represented by **Formula 1**.



1 Referring now to **Reaction Scheme 1** a synthetic process is
2 disclosed whereby exemplary compounds of the invention are obtained
3 in which, with reference to **Formula 1**, the **Z** group is ethynyl ($-C\equiv C-$)
4 and the **X** group is CH_2 . The compounds shown in this reaction
5 scheme and in the other reactions schemes of this specification, include
6 an OR_2^* substituent where the R_2^* group represents the moieties defined
7 as R_2 in connection with **Formula 1**. However, for the purposes of the
8 reaction schemes the R_2^* moiety is distinguished from the R_2 group of
9 the "final" biologically active compounds of the invention, because the
10 synthetic steps involved in the synthesis of the compounds of the
11 invention may require the R_2^* to act as protecting group, and not all of
12 the R_2 groups are necessarily suitable for this purpose. Therefore,
13 during the synthetic steps which are only generally described in
14 connection with the reaction schemes, removal and attachments of the
15 various R_2^* groups may become necessary as protection and
16 deprotection of the OH or SH groups. However, these protection and
17 deprotection steps and how to perform them will be readily apparent to
18 those skilled in the art in light of the present disclosure. The synthetic
19 processes disclosed in the reaction schemes of this specification can also
20 be applied for the preparation of compounds where, with reference to
21 **Formula 1** the R_1 group is other than OR_2 , or SR_2 .

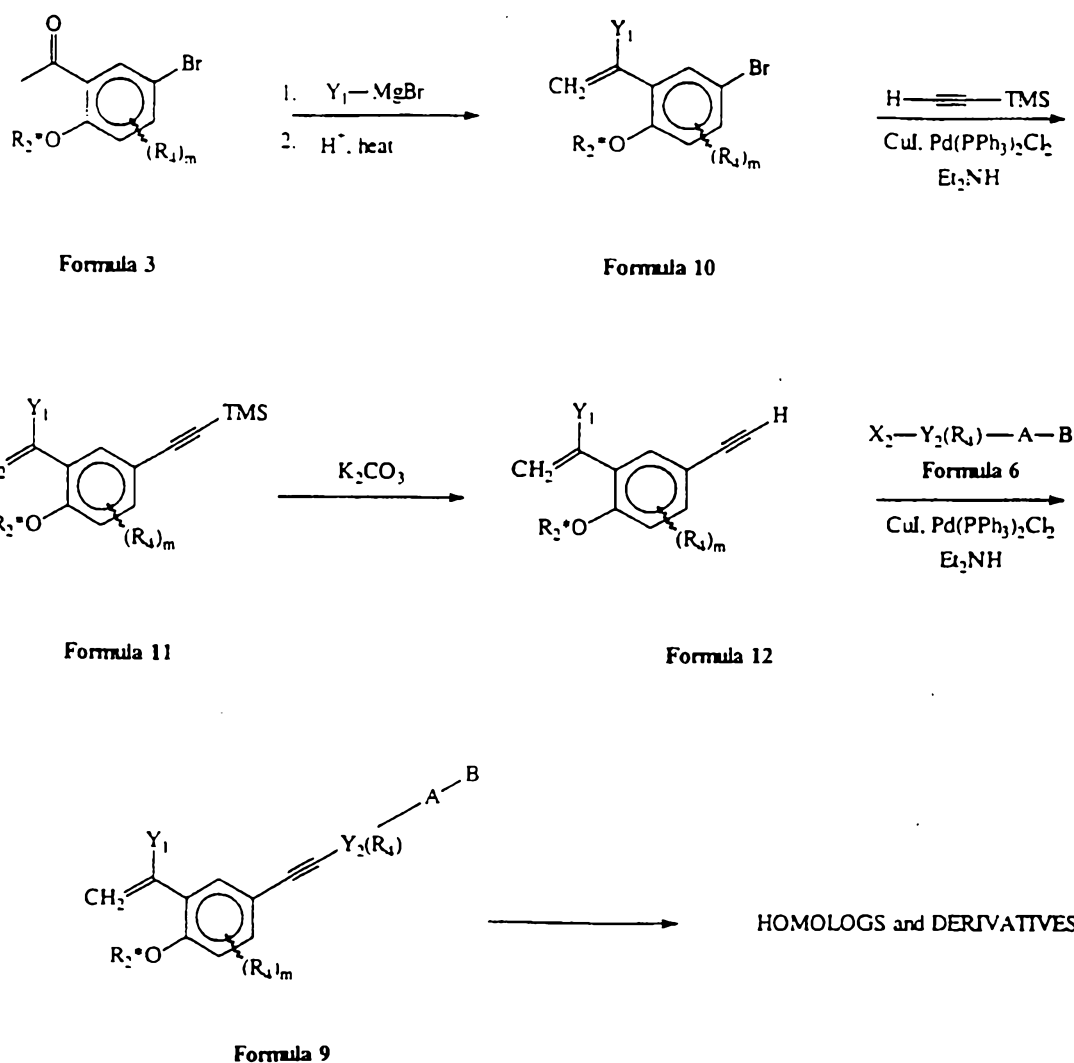
22 The compounds of **Formula 3** in **Reaction Scheme 1** may be
23 available commercially or can be obtained in synthetic steps which are
24 well known in the chemistry of benzene derivatives. An example for a
25 compound of **Formula 3** is 5-bromo-2-methoxyacetophenone, which can
26 be obtained through a *Friedel Crafts* reaction from 4-bromoanisole, as is
27 described in detail in the Specific Examples. Another example is 5-
28 bromo-2-methoxymethoxyacetophenone which can be obtained from 5-
29 bromo-2-hydroxyacetophenone by treatment with chloromethyl methyl
30 ether in the presence of base. As is shown in **Reaction Scheme 1**,

1 compounds of **Formula 3** are reacted with (trimethylsilyl)acetylene in
2 the presence of copper(I)iodide, diethylamine and
3 bis(triphenylphosphine)palladium(II) chloride to yield the acetophenone
4 derivatives substituted in the *meta* position with the
5 (trimethylsilyl)ethynyl group (**Formula 4**). The trimethylsilyl group is
6 removed from the compounds of **Formula 4** by treatment with base,
7 such as potassium carbonate, in alcoholic solvent (eg. methanol), to
8 yield the ethynyl substituted acetophenone derivatives of **Formula 5**.
9 The ethynyl substituted acetophenone derivatives of **Formula 5** are
10 then coupled with the reagent of the formula $X_2-Y_2(R_4)-A-B$ (**Formula**
11 **6**), where X_2 is halogen and the remaining symbols are defined in
12 connection with **Formula 1**. The coupling reaction is conducted in the
13 presence of copper(I)iodide, diethylamine and
14 bis(triphenylphosphine)palladium(II) chloride to provide the
15 disubstituted acetylene compounds of **Formula 7**. Examples for the
16 reagent $X_2-Y_2(R_4)-A-B$ (**Formula 6**) are ethyl 4-iodobenzoate, ethyl 6-
17 bromo-2-naphthoate, ethyl 6-iodonicotinate, ethyl 2-iodofuran-5-
18 carboxylate, and ethyl 2-iodothiophen-5-carboxylate. Precise conditions
19 of the reactions leading from compounds of **Formula 3** to the
20 compounds of **Formula 7** are described in connection with the specific
21 examples. These reactions are analogous to the reaction described in
22 several United States Letters Patent, such as United States Patent Nos.
23 5,348,972 and 5,346,915, assigned to the assignee of the present
24 application, where introduction of an ethynyl group into a heteroaryl
25 nucleus and subsequent coupling with a halogenated aryl or heteroaryl
26 function are described. The specifications of United States Patent
27 Nos. 5,348,972 and 5,346,915 are specifically incorporated herein by
28 reference.

29 The disubstituted acetylene compounds of **Formula 7** are then
30 reacted with a Grignard (or similar organometal) reagent having the

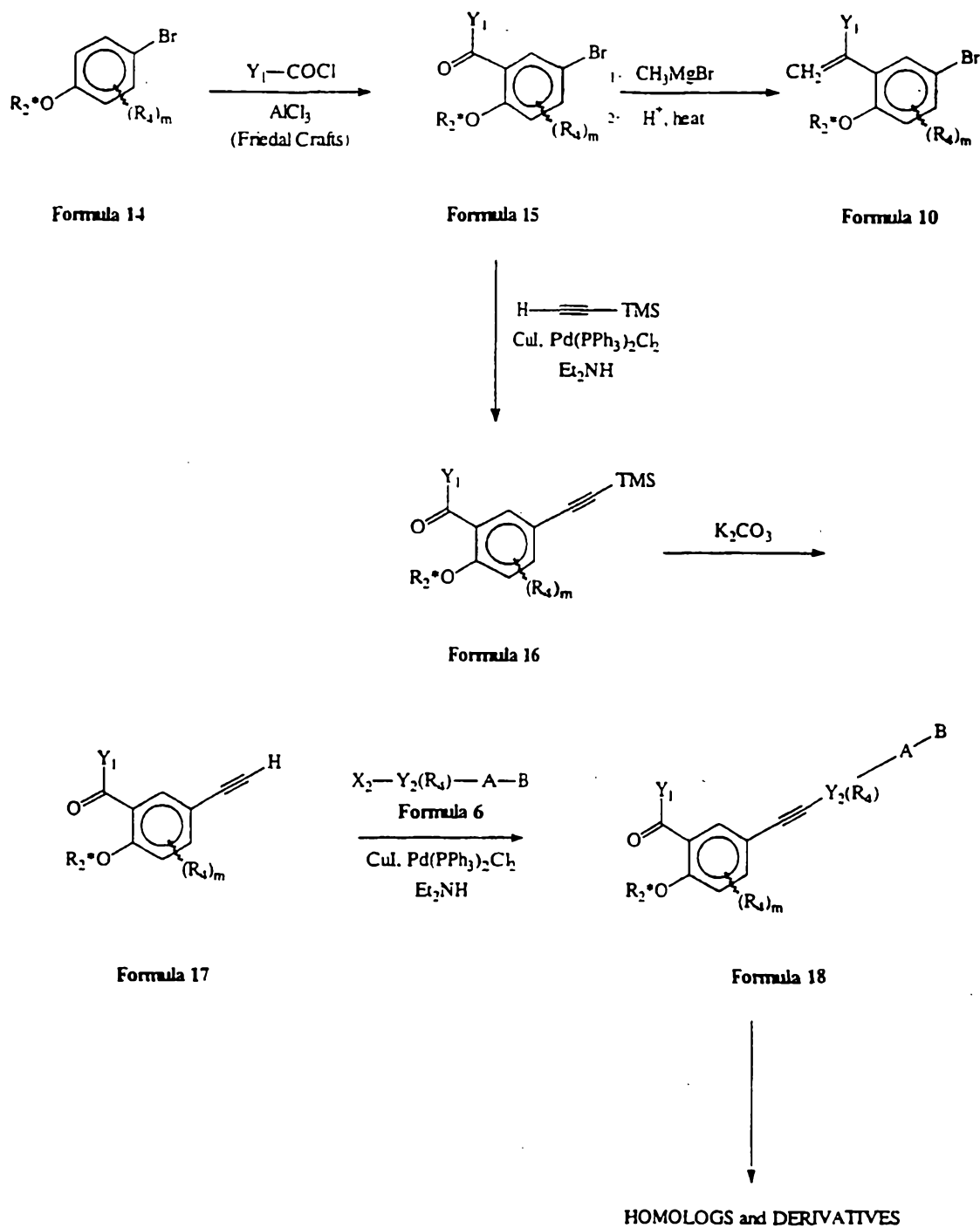
1 formula Y_1 -MgBr, where Y_1 is defined as in connection with **Formula 1**.
2 An example for the Y_1 -MgBr reagent is the Grignard reagent obtained
3 from *para*-tolylbromide, other examples are Grignard or organometal
4 reagents obtained from halogenated heteroaryl compounds. The
5 product of the Grignard (or like) reaction is a tertiary alcohol of
6 **Formula 8**, which is dehydrated by treatment with acid, to provide
7 compounds of **Formula 9**. The compounds of **Formula 9** are within the
8 scope of the invention ($X = CH_2$), and can be converted into further
9 homologs and derivatives in reactions of the type generally described
10 above. A frequently used reaction in this regard is saponification
11 whereby an ester function (represented in **Formula 9** by the symbol **B**)
12 is converted into a carboxylic acid function. Similarly the R_2^* group
13 may represent an acyl function that can be removed by saponification,
14 or R_2^* may represent an acid labile group (such as methoxymethyl) that
15 can be removed to yield compounds of the invention where R_2 is H.

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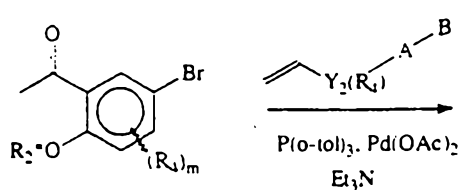
Reaction Scheme 2

1 **Reaction Scheme 2** discloses another process for synthesizing
2 exemplary compounds of the invention where, with reference to
3 **Formula 1**, X represents CH₂. The reactions in this scheme differ from
4 the reactions illustrated in **Scheme 1** primarily in the sequence in which
5 they are conducted. As is shown in **Reaction Scheme 2**, the
6 brominated acetophenone derivative of **Formula 3** is reacted with the
7 Grignard (or similar organometal) reagent having the formula Y₁-MgBr,
8 to provide a tertiary alcohol that is dehydrated by treatment with acid,
9 to yield the brominated vinylphenyl compounds of **Formula 10**. The
10 brominated vinylphenyl compounds of **Formula 10** are then coupled
11 with (trimethylsilyl)acetylene, the resulting the
12 (trimethylsilyl)ethynylphenyl compounds (**Formula 11**) are reacted with
13 base to give ethynylphenyl compounds (**Formula 12**) which are then
14 coupled with the reagent X₂-Y₂(R₄)-A-B (**Formula 6**), in a series of
15 reactions of the type described above in connection with **Reaction**
16 **Scheme 1**. The product of the coupling reaction with the reagent X₂-
17 Y₂(R₄)-A-B (**Formula 6**) is the disubstituted ethynyl derivative of
18 **Formula 9** that is within the scope of **Formula 1** (X = CH₂). The
19 compounds of **Formula 9** can be converted to further homologs and
20 derivatives, as described above and indicated in the reaction scheme.

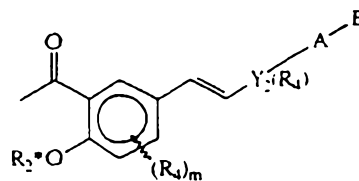


1 **Reaction Scheme 3** discloses a process for synthesis of exemplary
2 compounds of the invention where **X** of **Formula 1** is O. Starting
3 material for this synthesis is a halogen, preferably bromo-substituted
4 phenol derivative of **Formula 14** that is protected in the phenolic
5 hydroxyl group. An example is 4-bromoanisole. The compound of
6 **Formula 14** is subjected to a *Friedel Crafts* (or like) reaction with a
7 reagent of the formula $Y_1\text{-COCl}$. An example for this reagent, used for
8 the preparation of several preferred compounds of the invention, is
9 *para*-toluoyl chloride. Other examples are acid chlorides formed from
10 such acids as benzoic acid, nicotinic acid, thiophene-2-carboxylic acid,
11 and furan-2-carboxylic acid. The result of the *Friedel Crafts* reaction is a
12 ketone compound of **Formula 15**; in the preferred example where the
13 reagent is *para*-toluoyl chloride the compound of **Formula 15** is a
14 benzophenone derivative. Thereafter, the ketone compound of **Formula**
15 **15** is subjected to the sequence of reactions described above, namely
16 coupling with (trimethylsilyl)acetylene, followed by treatment with base,
17 and followed by coupling with the reagent $X_2\text{-Y}_2(R_4)\text{-A-B}$ (**Formula 6**),
18 to provide, through the intermediates of **Formulas 16** and **17**, the
19 ketone compounds within the scope of the invention (**Formula 18**).
20 The compounds of **Formula 18** can be converted into further homologs
21 and derivatives, as described above.

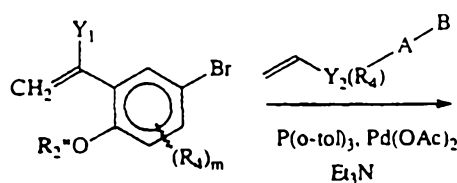
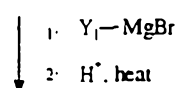
22 The intermediate brominated benzophenone (or like) derivatives
23 of **Formula 15** can also be subjected to a Grignard reaction with
24 methylmagnesium bromide, to provide, after dehydration of the
25 intermediary tertiary alcohol the brominated vinylphenyl compounds of
26 **Formula 10**. As is described above, the compounds of **Formula 10**
27 serve as intermediates in accordance with **Reaction Scheme 2** in the
28 synthesis of exemplary compounds of the invention where **X** of **Formula**
29 **1** is CH_2 .



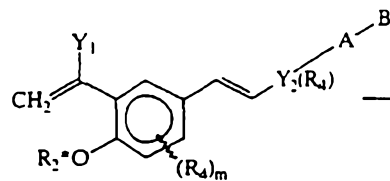
Formula 3



Formula 19

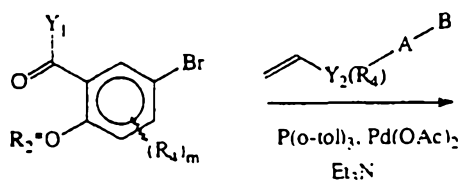


Formula 10

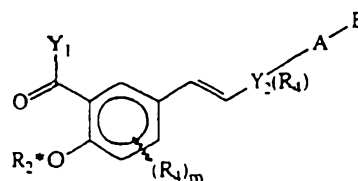


Formula 20

HOMOLOGS
and DERIVATIVES



Formula 15



Formula 21

HOMOLOGS
and DERIVATIVES

Reaction Scheme 4

Reaction Scheme 4 discloses synthetic processes for obtaining certain exemplary compounds of the invention in which, with reference to Formula 1, the Z group is -CH=CH-. In accordance with this process brominated acetophenone derivatives of Formula 3 are reacted

1 in a *Heck* reaction with vinylaryl compounds of the formula
2 $\text{CH}_2=\text{CH}-\text{Y}_2(\text{R}_4)-\text{A}-\text{B}$. Examples for suitable vinylaryl compounds are
3 ethyl 4-vinylbenzoate, ethyl 6-vinyl nicotinate, ethyl 5-vinylfuran-2-
4 carboxylate and ethyl 5-vinylthiophen-2-carboxylate. The *Heck* reaction
5 is typically conducted in the presence of triethylamine, copper(I)iodide,
6 palladium(II)acetate and tri-(*o*-tolyl)phosphine. The *Heck* reaction
7 provides compounds of **Formula 19** which are within the scope of the
8 present invention. Depending on the precise nature of the starting
9 compound of **Formula 3**, its ketone function may need to be protected
10 before the *Heck* coupling reaction is performed, and the protective
11 group is then removed after the *Heck* reaction. Suitable protective
12 groups for this purpose are ketal groups, such as the ketal formed under
13 acidic condition with ethyleneglycol. Protection and deprotection of
14 the ketone group of **Formula 3** is not shown in the scheme, but will
15 become readily apparent to those skilled in the art in light of the nature
16 of the compound of **Formula 3** and the present disclosure. The need
17 for protection and deprotection of the ketone group in the form of a
18 ketal, may also arise in connection with other reactions described in this
19 specification. After the *Heck* reaction (and deprotection of the ketone
20 function if necessary) the compounds of **Formula 19** are reacted in a
21 Grignard (or like organometal) reaction with the reagent $\text{Y}_1\text{-MgBr}$ (or
22 other suitable organometal reagent, $\text{Y}_1\text{-Me}$ where Me is metal such as
23 lithium) to provide after dehydration of the intermediary tertiary alcohol
24 the aryl vinylphenyl compounds of **Formula 20** which are within the
25 scope of the invention. The compounds of **Formula 20** can be
26 converted to further homologs and derivatives still within the scope of
27 the present invention, as described above.

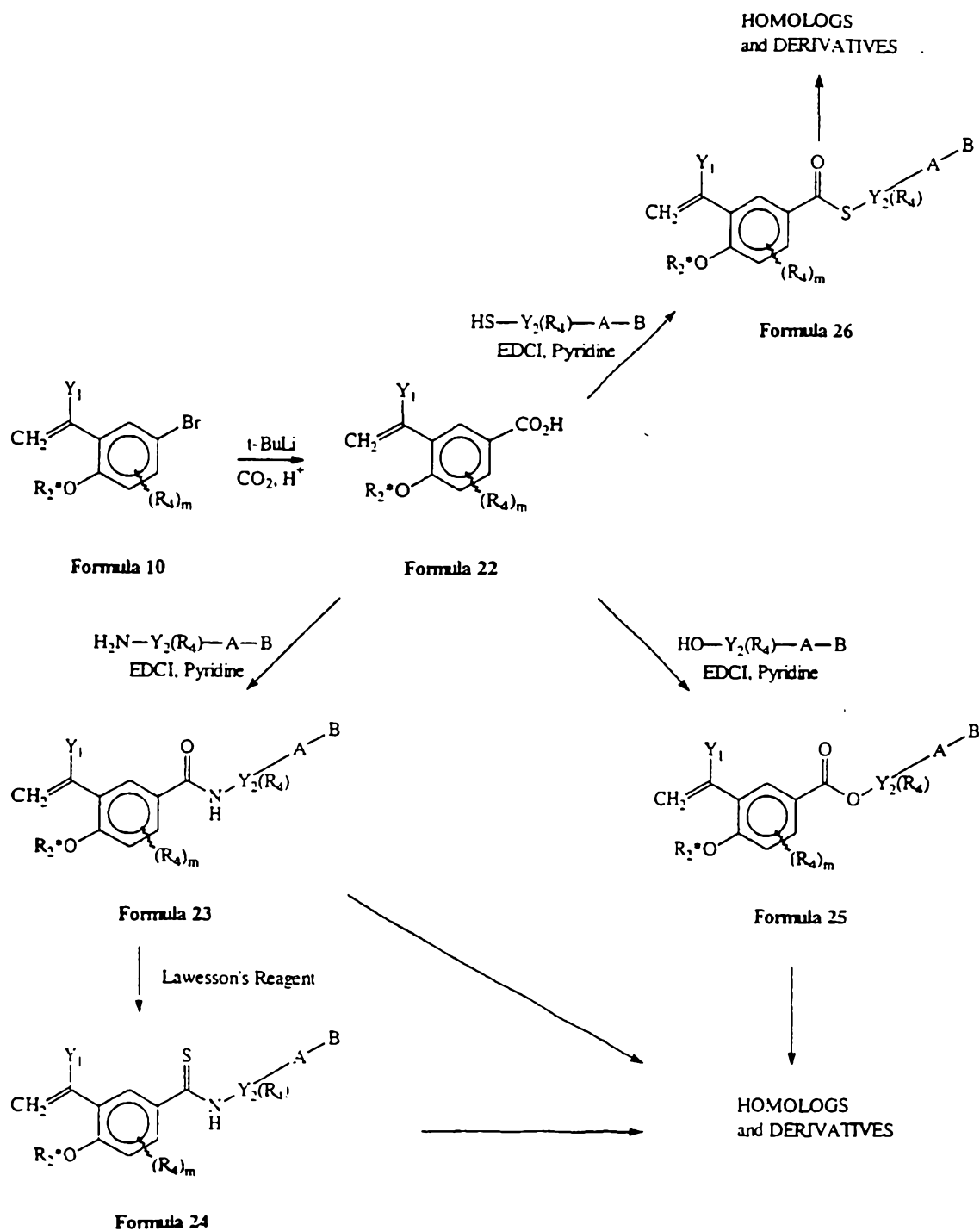
28 As is further disclosed in **Reaction Scheme 4** the *Heck* reaction
29 can also be performed on the intermediate brominated arylvinylphenyl
30 compounds of **Formula 10**, and on the brominated diaryl ketone

1 compounds of **Formula 15**, which are obtained in accordance with
2 **Reaction Schemes 2** and **3**, respectively. The products of the *Heck*
3 reaction of the compounds of **Formula 10** with the reagent of the
4 formula $\text{CH}_2=\text{CH}-\text{Y}_2(\text{R}_4)-\text{A}-\text{B}$ are the arylvinylphenyl compounds of the
5 invention of **Formula 20**. The products of the *Heck* reaction of the
6 compounds of **Formula 15** with the reagent of the formula $\text{CH}_2=\text{CH}-$
7 $\text{Y}_2(\text{R}_4)-\text{A}-\text{B}$ are the diaryl ketone compounds of the invention of
8 **Formula 21**, and the latter can be converted into compounds of
9 **Formula 20** by reaction with the Grignard reagent CH_3MgBr , followed
10 by dehydration of the tertiary alcohol.

11 The following **Reaction Schemes 5, 6, 7** and **8** describe
12 synthetic processes to provide exemplary compounds of the invention
13 starting with the brominated aryl vinylphenyl compounds of **Formula 10**.

14 However, those skilled in the art will readily understand that the
15 herein described synthetic steps and processes can be applied with such
16 modifications that are within the skill of the practicing organic chemist,
17 to the brominated acetophenone derivatives of **Formula 3** and to the
18 brominated diaryl ketone compounds of **Formula 15**, and by extension
19 of the herein described generic principles to still further compounds of
20 the invention as well.

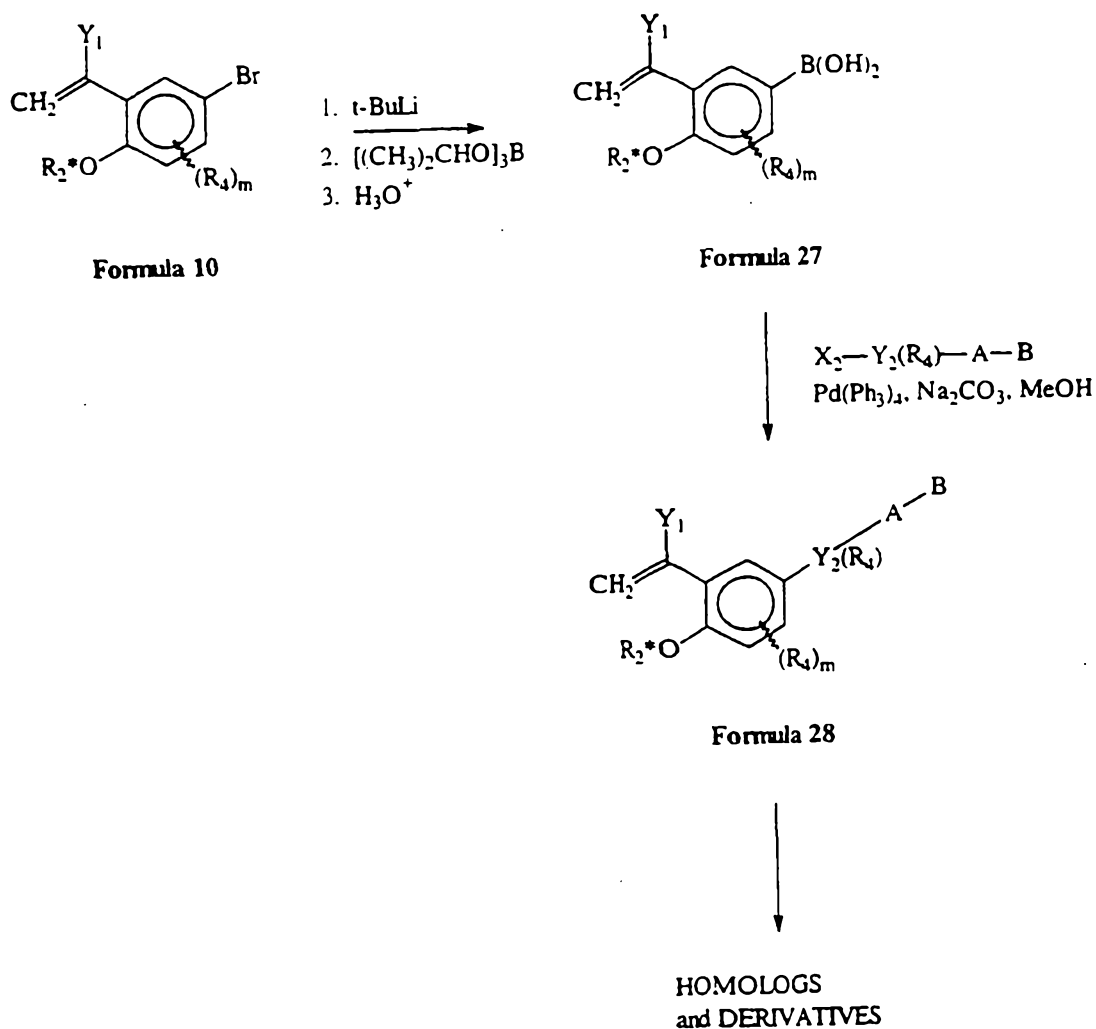
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Reaction Scheme 5

Referring now specifically to **Reaction Scheme 5**, it discloses synthetic routes to compounds of the invention where, with reference to **Formula 1**, Z is -CONH- (amides), -COO- (esters) -COS- (thioesters) and -CSNH- (thioamides). In accordance with this scheme the brominated aryl vinylphenyl compounds of **Formula 10** are reacted with *n*-butyl lithium and carbon dioxide to "capture" the carbon dioxide and to provide the aryl vinylbenzoic acid derivatives of **Formula 22**. The aryl vinylbenzoic acid derivatives of **Formula 22** can be converted into amides of **Formula 23** by reaction with reagents of the formula $H_2N-Y_2(R_4)-A-B$, into esters of **Formula 25** by reaction with reagents of the formula $HO-Y_2(R_4)-A-B$, and into thioesters of **Formula 26** by reaction with reagents of the formula $HS-Y_2(R_4)-A-B$, where the symbols are defined as in connection with **Formula 1**. Examples for the reagents of formula $H_2N-Y_2(R_4)-A-B$ are ethyl 4-aminobenzoate and ethyl 6-aminonicotinate, for the reagents of the formula $HO-Y_2(R_4)-A-B$ ethyl 4-hydroxybenzoate and ethyl 6-hydroxynicotinate, and for the reagents of the formula $HS-Y_2(R_4)-A-B$ ethyl 4-mercaptobenzoate and ethyl 6-mercaptonicotinate. The reactions between the carboxylic acids of **Formula 22** and the reagents of the formulas $H_2N-Y_2(R_4)-A-B$, $HO-Y_2(R_4)-A-B$ and $HS-Y_2(R_4)-A-B$, can be performed in several ways in which amides, esters and thioesters are normally prepared. For example, the carboxylic acids of **Formula 22** can be activated to form an acid chloride or an activated ester which is thereafter reacted with the amines, alcohols or thioalcohols of the above formulas. More advantageously, however, the formation of the amides, esters or thioesters is performed by condensation of the carboxylic acid of **Formula 22** with the amines, alcohols or thiols in a suitable aprotic solvent, such as pyridine, in the presence of a condensing agent such as dicyclohexylcarbodiimide (DCC) or more preferably 1-(3-dimethylaminopropyl)-3-ethylcarbodiimidehydrochloride (EDCI). The

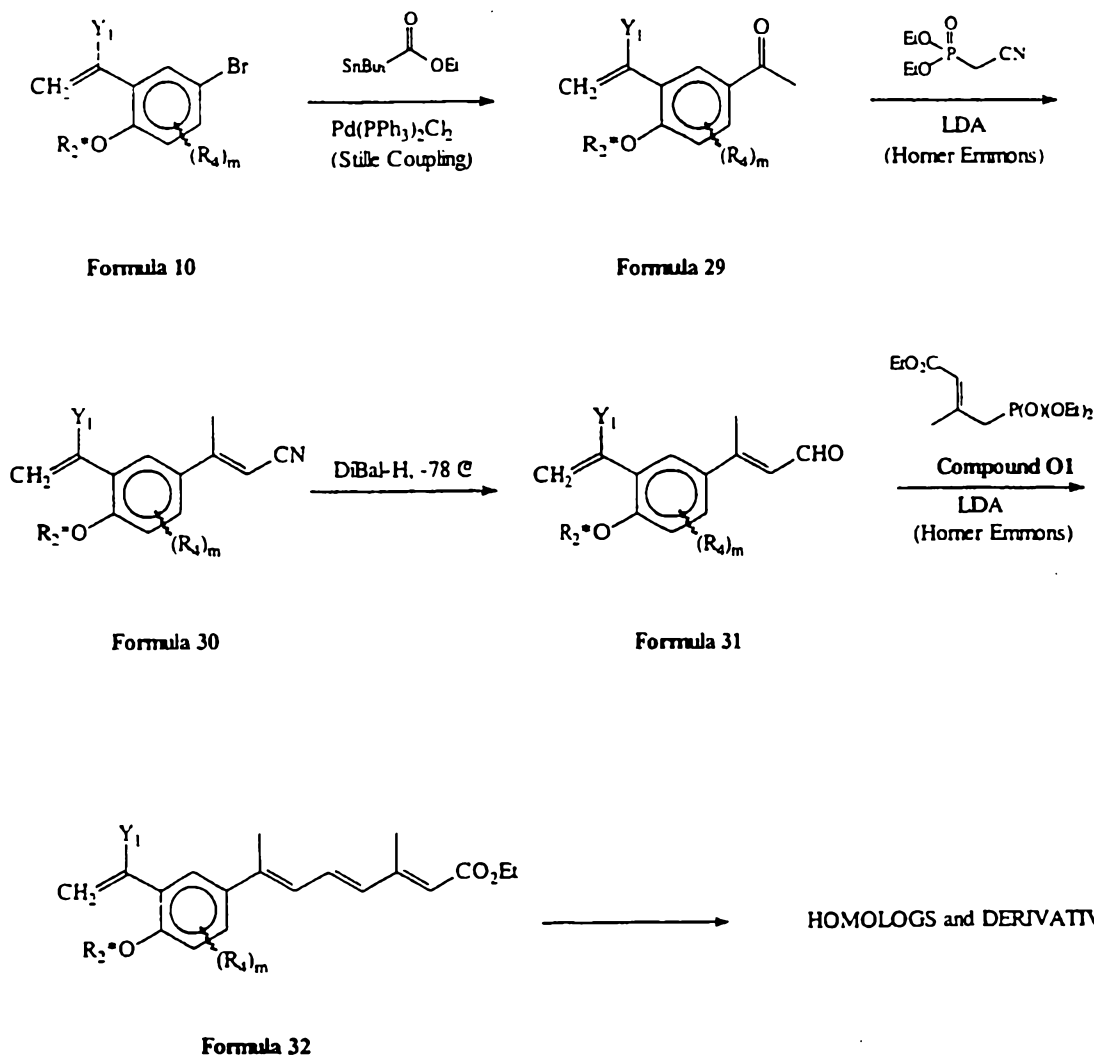
1 amide derivatives of Formula 23 can be readily converted to the
2 thioamides of Formula 24 by reaction with [2,4-bis(4-methoxyphenyl)-
3 1,3-dithia-2,4-diphosphetane-2,4-disulfide] (Lawesson's reagent). The
4 amide derivatives of Formula 23 where the symbol **B** represents an ester
5 function (such as COOEt) can be readily saponified by treatment with
6 aqueous base, for example LiOH, to yield the corresponding amide
7 derivatives where **B** represents a free carboxylic acid or its salt. Similar
8 saponification of the esters of Formula 25, or of the thioesters of
9 Formula 26, however is problematic because of the lability of the
10 internal ester and thioester functions. The free acids of these
11 derivatives (where **B** is COOH or a salt thereof) can be obtained by
12 hydrogenation of the corresponding benzyl esters in which **B** represents
13 COOCH₂C₆H₅.



Reaction Scheme 6

27 **Reaction Scheme 6** discloses a synthetic process for preparing
 28 compounds of the invention where, with reference to **Formula 1**, the **Z**
 29 group is $-(\text{CR}_6=\text{CR}_6)_n-$ and n is 0. In other words, this is a reaction
 30 scheme for obtaining compounds of the invention where the $-\text{Y}_2(\text{R}_4)-\text{A}-\text{B}$

1 moiety is directly linked to the position of the phenyl ring which is
2 *meta* to the $Y_1-C(CH_2)-$ moiety. Pursuant to this reaction scheme, the
3 brominated aryl vinylphenyl compounds of **Formula 10** are reacted with
4 *t*-butyl lithium and subsequently with triisopropylborate to provide the
5 boronic acid derivative intermediates of **Formula 27**. The boronic acid
6 derivatives of **Formula 27** react with compounds of the formula X_2--
7 $Y_2(R_4)-A-B$ (where the symbols are defined as above and X_2 is
8 preferably bromine) in the presence of
9 tetrakis[triphenylphosphine]palladium $[Pd(PPh_3)_4]$ and a base, such as
10 sodium carbonate, to yield compounds of **Formula 28**. Examples of
11 preferred reagents of formula $X_2-Y_2(R_4)-A-B$ are ethyl 6-bromo-2-
12 naphthoate, ethyl 4-iodobenzoate, ethyl 6-iodonicotinate, ethyl 2-
13 iodofuran-5-carboxylate, and ethyl 2-iodothiophen-5-carboxylate. The
14 compounds of **Formula 28** can be converted into further compounds of
15 the invention by the reactions described above, such as saponification,
16 amide formation, homologation and the like.



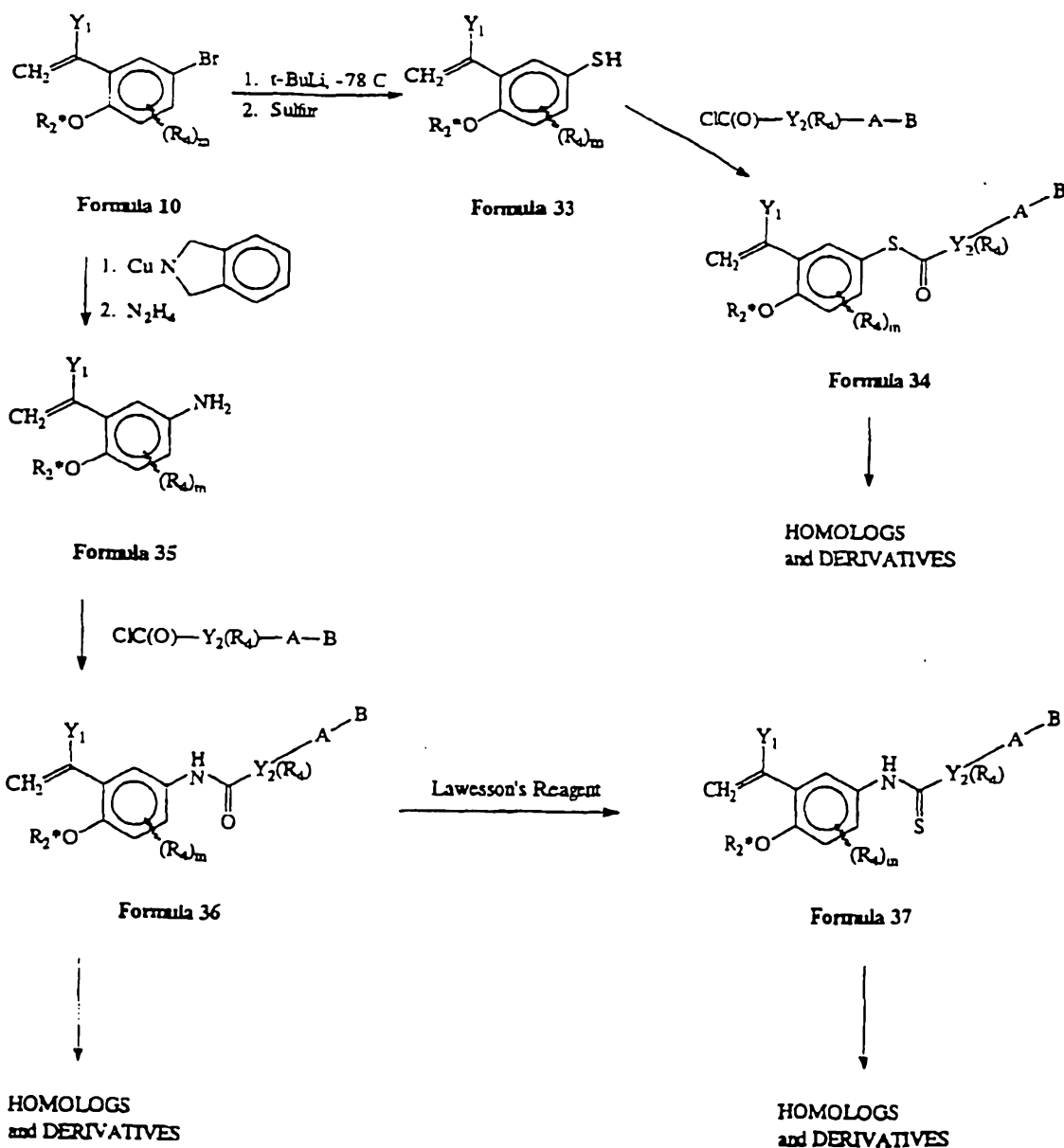
Reaction Scheme 7

Reaction Scheme 7 discloses a synthetic route for the preparation of compounds where, with reference to **Formula 1**, **Z** is $-(\text{CR}_6=\text{CR}_6)_n-$, **n** is 3 and the **B** group is directly attached to the **Z** group. Thus, in accordance with this scheme the brominated aryl vinylphenyl

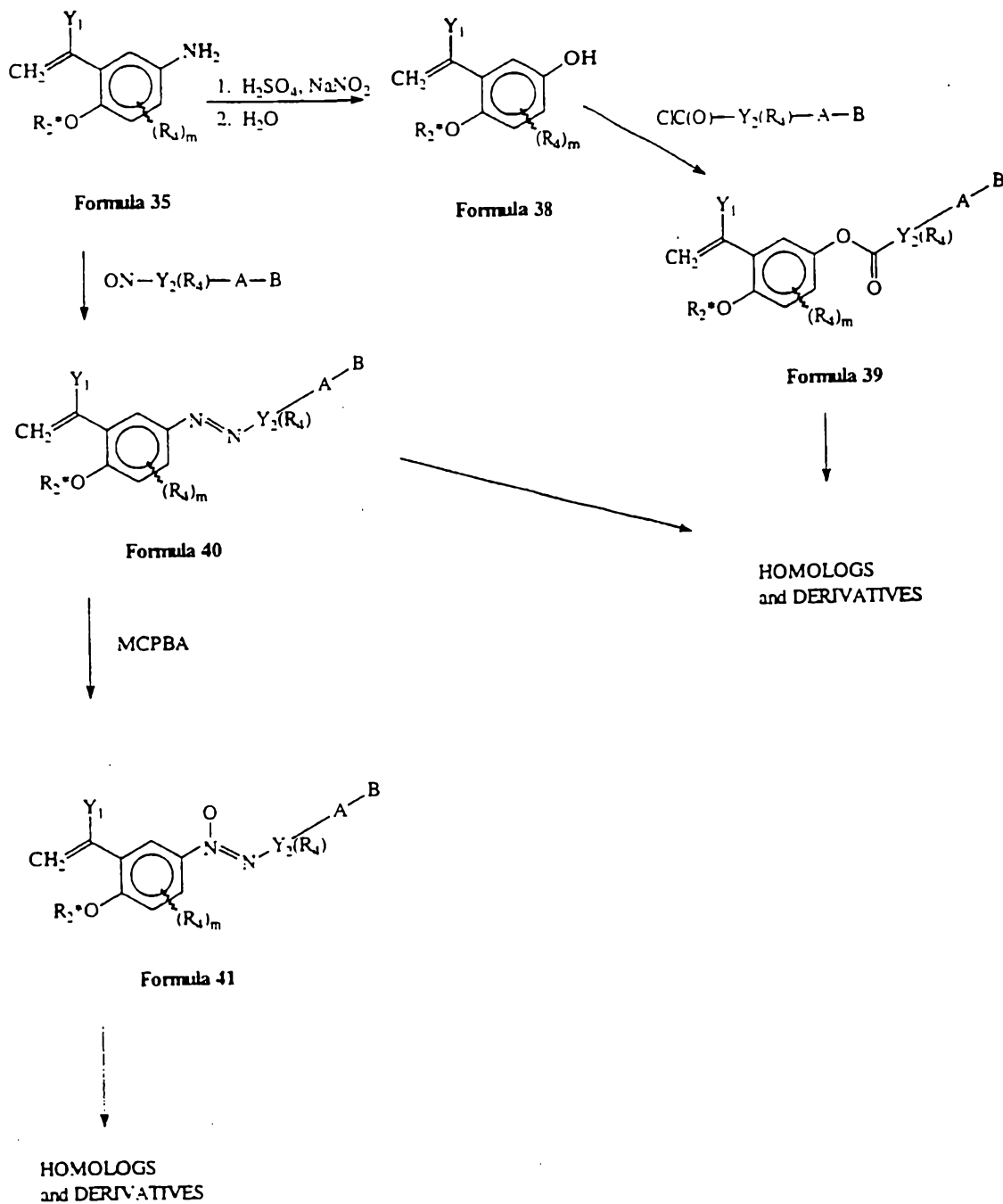
1 compounds of **Formula 10** are reacted with (1-ethoxyvinyl)tributyltin in
2 the presence of bis(triphenylphosphine)palladium(II) chloride to
3 introduce the acetyl group into the position of the phenyl ring which is
4 *meta* to the $Y_1-C(CH_3)_2$ - moiety, and yield the acetophenone derivatives
5 of **Formula 29**. The latter reaction is known in the art as a *Stille*
6 coupling. The acetophenone derivatives of **Formula 29** are then
7 reacted in a *Horner Emmons* reaction, in the presence of strong base
8 such as lithium diisopropylamide (LDA), with diethylcyanomethyl
9 phosphonate. The latter reagent is commercially available. The
10 product of the *Horner Emmons* reaction is an arylvinylphenyl compound
11 of **Formula 30** that is substituted in the *meta* position with a 1-methyl-2-
12 cyanoethenyl group. Those skilled in the art will readily understand that
13 instead of a *Horner Emmons* reaction the compounds of **Formula 30**
14 can also be obtained as a result of an analogous *Wittig* reaction.

15 Referring still to **Reaction Scheme 7**, the cyano function of the
16 compounds of **Formula 30** is reduced with a mild reducing agent, such
17 as diisobutylaluminum hydride (Dibal-H) to provide the aldehyde
18 compounds of **Formula 31**. Another *Horner Emmons* reaction
19 performed on the aldehydes of **Formula 31** with the reagent diethyl(E)-
20 3-ethoxycarbonyl-2-methylallylphosphonate (**Compound O1**) provides
21 compounds of **Formula 32** which are within the scope of the present
22 invention. **Compound O1** can be prepared from commercially available
23 ethyl (2)-3-formyl-2-butenate according to the literature of *Corey et al.*
24 *J. Org. Chem.* 1974, 39, 921. It will be readily apparent to those skilled
25 in the art that the herein described exemplary synthetic process can be
26 readily adapted or modified by utilizing analogous phosphonate or
27 phosphonium salt reagents in *Horner Emmons* or *Wittig* reactions,
28 respectively, to obtain additional compounds within the scope of
29 **Formula 1** in which **Z** is $-(CR_6=CR_6)_n-$, and **n** is 3 - 5. The
30 compounds of **Formula 32** can be converted into further compounds

1 within the scope of the invention by reactions such as saponification,
 2 amide formation, reduction to the aldehyde or alcohol stage, and the
 3 like. This is indicated in the reaction scheme by conversion to
 4 "homologs and derivatives".



Reaction Scheme 8



1 Synthetic routes for the preparation of compounds of **Formula 1**
2 where the **Z** is -SCO- (thioester), -NHCO- (amide) -NHCS- (thioamide)
3 -OCO- (ester) of the order "reverse" to the one described in connection
4 with **Reaction Scheme 5**, as well as where **Z** is -N=N- (azo) and -
5 N=N(=O)- (azoxide) are disclosed in **Reaction Schemes 8 and 9**. As is
6 first shown in **Reaction Scheme 8** the brominated aryl vinylphenyl
7 compounds of **Formula 10** are reacted with *t*-butyl lithium, and
8 thereafter with sulfur to provide the (arylvinyl)thiophenol compounds
9 of **Formula 33**. The thiophenol compounds of **Formula 33** are reacted
10 with a carboxylic acid, or an activated form of the carboxylic acid, which
11 forms a thioester and introduces the -CO-Y₂(R₄)-A-B moiety into the
12 molecules. Those skilled in the art will understand that just as it is
13 described in connection with the amide, ester and thioester formations
14 in **Reaction Scheme 5**, various activated forms of carboxylic acids are
15 suitable for this purpose. The instant reaction scheme illustrates the
16 method of using acid chlorides of the formula ClCO-Y₂(R₄)-A-B in these
17 reactions. Examples for the acid chlorides of formula ClCO-Y₂(R₄)-A-B
18 are ClCOC₆H₄COOEt ClCOC₆H₄COOCH₂C₆H₅ (the monochlorides of
19 terephthalic acid ethyl and benzyl esters), and ClCOC₅NH₃COOEt and
20 ClCOC₅NH₃COOCH₂C₆H₅ (the monochlorides of pyridine 3,6,-
21 dicarboxylic acid ethyl and benzyl esters). The thioesters of **Formula**
22 **34** are within the scope of the present invention. In order to obtain
23 compounds within the scope of **Formula 34** where the **B** group is a free
24 carboxylic acid (or salt thereof), the thioester is prepared first where the
25 **B** group is -COOCH₂C₆H₅. The benzyl group is then removed by
26 hydrogenation to provide the free acid.

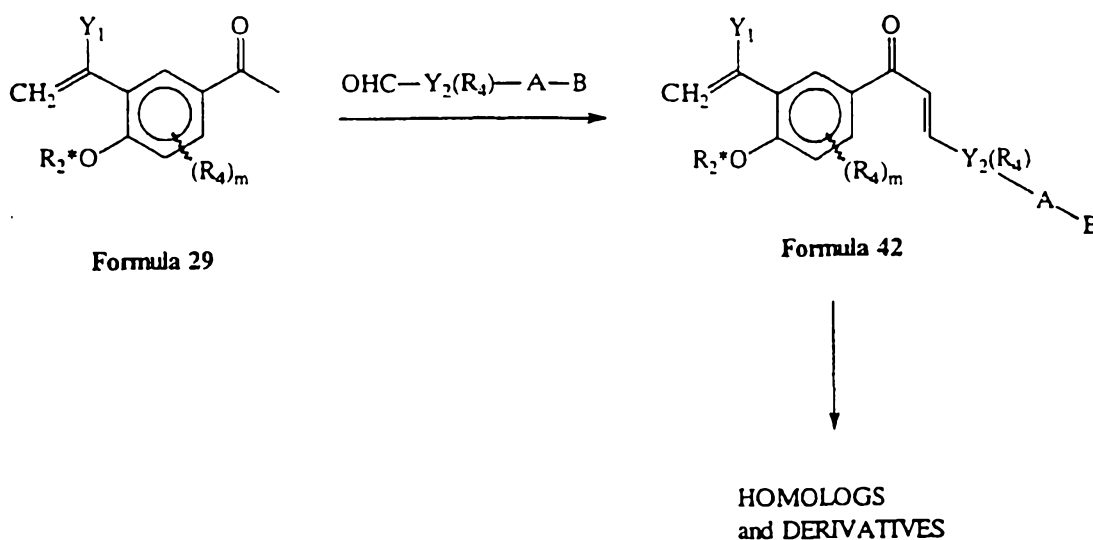
27 As is shown further in **Reaction Scheme 8**, the brominated aryl
28 vinylphenyl compounds of **Formula 10** are reacted with the cuprous salt
29 of phthalimide and thereafter with hydrazine to provide the
30 (arylvinyl)aniline derivatives of **Formula 35**. These are reacted with

1 the acid chlorides of formula $\text{ClCO-Y}_2(\text{R}_4)\text{-A-B}$ to yield the amides of
2 **Formula 36** which are within the scope of the invention. The amides of
3 **Formula 36** are converted into thioamides of **Formula 37** by treatment
4 with [2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-
5 disulfide] (Lawesson's reagent). The amides and thioamides of **Formula**
6 **36** and **37** can be subjected to transformations (including saponification
7 of an ester group when **B** is COOR_8) to yield further compounds within
8 the scope of the present invention.

9 Referring now to **Reaction Scheme 9**, the (arylviny)aniline
10 derivatives of **Formula 35** are converted to diazonium salt and
11 thereafter to (arylviny)phenol derivatives of **Formula 38**. The
12 (arylviny)phenol derivatives of **Formula 38** are then converted into
13 esters of **Formula 39** by reaction with the acid chlorides of the formula
14 $\text{ClCO-Y}_2(\text{R}_4)\text{-A-B}$ or with other activated forms of the carboxylic acids
15 of the general formula $\text{HOCO-Y}_2(\text{R}_4)\text{-A-B}$. As it is described in
16 connection with **Reaction Scheme 5**, the ester formation may be affected
17 with the free carboxylic acid in an aprotic solvent, such as pyridine, in
18 the presence of dicyclohexylcarbodiimide (DCC) or more preferably 1-
19 (3-dimethylaminopropyl)-3-ethylcarbodiimidehydrochloride (EDCI). In
20 order to obtain free carboxylic acids within the scope of **Formula 39**
21 (compounds where **B** is COOH or a salt thereof) the benzyl ester (**B** =
22 $\text{COOCH}_2\text{C}_6\text{H}_5$) is prepared first, and the benzyl protecting group is
23 thereafter removed by hydrogenation.

24 In order to obtain compounds of **Formula 1** where the **Z** group is
25 -N=N- (azo) or -N(O)=N- (azoxy) the (arylviny)aniline derivatives of
26 **Formula 35** are reacted with nitroso compounds of the formula ON-
27 $\text{Y}_2(\text{R}_4)\text{-A-B}$. Examples for reagents of formula $\text{ON-Y}_2(\text{R}_4)\text{-A-B}$ are ethyl
28 4-nitrosobenzoate, ethyl 6-nitroso-2-naphthoate, ethyl 4-nitrosobenzoate,
29 ethyl 6-nitroso-nicotinate, ethyl 2-nitroso-furan-5-carboxylate, and ethyl
30 2-nitroso-thiophen-5-carboxylate. The azo compounds of **Formula 40**

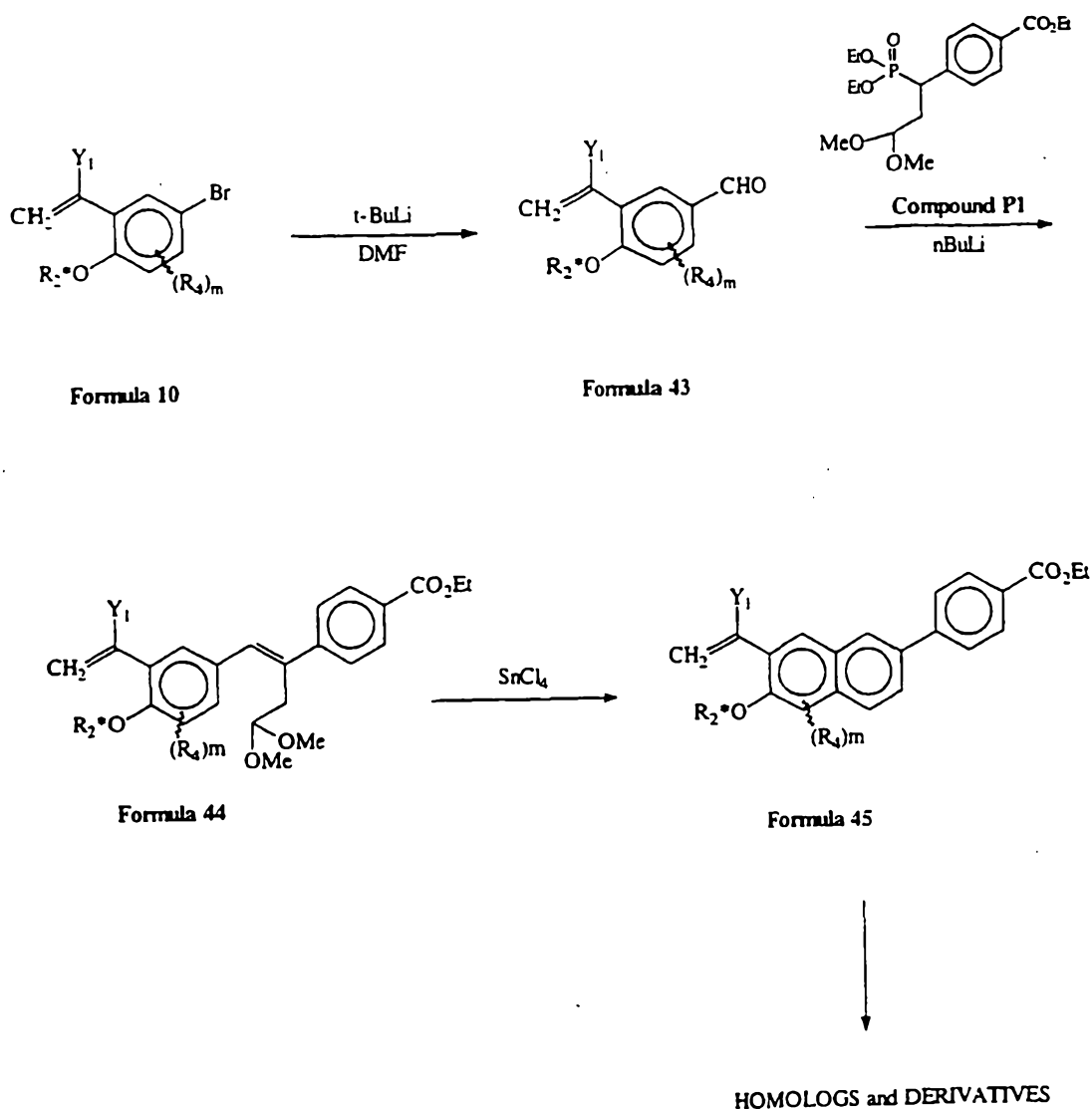
1 can be converted to the azoxy compounds of **Formula 41** by oxidation
 2 with oxidizing agents known in the art, for example with *meta*-
 3 chloroperoxybenzoic acid (MCPBA).



24 Reaction Scheme 10

25 **Reaction Scheme 10** discloses a synthetic route for the
 26 preparation of exemplary compounds where, with reference to **Formula**
 27 **1**, **Z** is $-\text{CO}-\text{CR}_6=\text{CR}_6-$, that is the preparation of compounds which are
 28 α -unsaturated ketone derivatives (chalcones). In accordance with this
 29 scheme the acetophenone derivatives of **Formula 29** (obtained by
 30 *Stille* coupling as shown in **Reaction Scheme 7**) are reacted in a

1 condensation reaction with a reagent of the formula $\text{OHC--Y}_2(\text{R}_4)\text{-A-B}$
2 to yield compounds of **Formula 42** which are within the scope of the
3 invention. An example for the reagent $\text{OHC--Y}_2(\text{R}_4)\text{-A-B}$ is
4 4-carboxybenzaldehyde that is available commercially. Examples of
5 other reagents suitable for the condensation reaction and for the
6 synthesis of compounds of **Formula 42** are:
7 5-carboxy-pyridine-2-aldehyde, 4-carboxy-pyridine-2-aldehyde,
8 4-carboxy-thiophene-2-aldehyde, 5-carboxy-thiophene-2-aldehyde,
9 4-carboxy-furan-2-aldehyde, 5-carboxy-furan-2-aldehyde,
10 4-carboxyacetophenone, 2-acetyl-pyridine-5-carboxylic acid,
11 2-acetyl-pyridine-4-carboxylic acid, 2-acetyl-thiophene-4-carboxylic acid,
12 2-acetyl-thiophene-5-carboxylic acid, 2-acetyl-furan-4-carboxylic acid, and
13 2-acetyl-furan-5-carboxylic acid. The latter compounds are available in
14 accordance with the chemical literature; see for example *Decroix et al. J.*
15 *Chem Res. (S)*, 1978, 4, 134; *Dawson et al. J. Med. Chem.*, 1983, 29,
16 1282; and *Queguiner et al., Bull. Spc. Chimique de France*, 1969, No. 10,
17 pp 3678 - 3683. The condensation reaction between the compounds of
18 **Formula 29** and the aldehyde of the formula $\text{OHC--Y}_2(\text{R}_4)\text{-A-B}$ (or an
19 analogous ketone compound) is conducted in the presence of base in
20 an alcoholic solvent. Preferably, the reaction is conducted in ethanol in
21 the presence of sodium hydroxide. Those skilled in the art will
22 recognize this condensation reaction as an aldol condensation, and in
23 case of the herein described preferred examples (condensing a ketone
24 of **Formula 29** with an aldehyde) as a Claisen-Schmidt reaction. (See
25 March: *Advanced Organic Chemistry: Reactions, Mechanisms, and*
26 *Structure*, pp 694 695 McGraw Hill (1968). The compounds of
27 **Formula 42** are within the scope of the present invention, and can also
28 be subjected to further transformations resulting in additional
29 compounds of the invention designated in the scheme as "homologs and
30 derivatives".



Reaction Scheme 11

Reaction Scheme 11 provides an example for synthesis of compounds of the invention where the Y_3 group is naphthyl substituted in the 1,7 positions by the $Y_1(R_5)CX$ and Z groups, and where Z is $-(CR_6=CR_6)_n-$, and n is 0. More specifically, Reaction Scheme 11 provides an example for synthesis of compounds of the invention where the Y_3 naphthyl group is directly attached to the Y_2 -A-B group. In

1 accordance with this reaction scheme, the bromo compounds of
2 **Formula 10** are reacted with dimethylformamide in the presence of *t*-
3 butyl lithium to yield the benzaldehyde derivatives of **Formula 43**.
4 The benzaldehyde derivatives of **Formula 43** are subjected to a *Horner*
5 *Emmons* type reaction, in the presence of strong base such as *n*-butyl
6 lithium in hexane, with a 1-aryl or 1-heteroaryl 1-diethoxyphosphoryl-
7 3,3-dimethoxypropane derivative, such as ethyl 4-(diethoxyphosphoryl-
8 3,3-dimethoxypropyl)benzoate (**Compound P1**). Ethyl 4-
9 (diethoxyphosphoryl-3,3-dimethoxypropyl)benzoate (**Compound P1**) is
10 available in accordance with the procedure of EPO Application No. 0
11 210 929 (published on February 4, 1987, *Shroot et al.*) which is
12 incorporated herein by reference. In accordance with the *Shroot et al.*
13 reference the reagent ethyl 4-(diethoxyphosphoryl-3,3-
14 dimethoxypropyl)benzoate is made starting with ethyl 4-bromobenzoate
15 that is reacted with dimethyl acetal of acryl aldehyde, the product is
16 hydrogenated and subsequently brominated (with *N*-bromo succinimide)
17 and thereafter reacted with triethylphosphite. Examples for
18 phosphonates analogous to **Compound P1** in that they are suitable for a
19 *Horner Emmons* reaction with the benzaldehyde derivatives of **Formula**
20 **43** are ethyl 2-(diethoxyphosphoryl-3,3-dimethoxypropyl)pyridine-5-
21 carboxylate, ethyl 2-(diethoxyphosphoryl-3,3-dimethoxypropyl)pyridine-
22 6-carboxylate, ethyl 2-(diethoxyphosphoryl-3,3-
23 dimethoxypropyl)thiophene-4-carboxylate, ethyl 2-(diethoxyphosphoryl-
24 3,3-dimethoxypropyl)thiophene-5-carboxylate, ethyl 2-
25 (diethoxyphosphoryl-3,3-dimethoxypropyl)furan-4-carboxylate, ethyl 2-
26 (diethoxyphosphoryl-3,3-dimethoxypropyl)furan-5-carboxylate. These
27 and analogous phosphonate reagents can be obtained by appropriate
28 modification of the procedure described in the *Shroot et al.* reference.
29 The product of the *Horner Emmons* reaction between the
30 benzaldehyde derivatives of **Formula 43** and ethyl 4-

(diethoxyphosphoryl-3,3-dimethoxypropyl)benzoate (**Compound P1**) is a disubstituted ethene compound of **Formula 44**. Those skilled in the art will readily understand that instead of a *Horner Emmons* reaction, a *Wittig* reaction can also be employed, utilizing the appropriate phosphonium derivative, to provide compounds of **Formula 44**. The disubstituted ethene compounds of **Formula 44** are cyclized, for example by heating in a neutral solvent (such as dichloromethane), in the presence of SnCl_4 or other suitable *Friedel Crafts* type catalyst, to form the "B ring" of the naphthalene derivatives of the invention, as shown in **Formula 45**. The compounds of **Formula 45** can be converted into further compounds of the invention by reaction well known to the synthetic organic chemist, such as saponification, esterification, amide formation and homologation. This is indicated in **Reaction Scheme 11** as conversion to "homologs and derivatives".

SPECIFIC EXAMPLES

Ethyl 4-iodobenzoate (Compound A)

To a suspension of 24.9 g (100.4 mmol) of 4-iodobenzoic acid in 46.25 g (58.9 mL, 1.0 mol) of ethanol was added 3 mL of c. sulfuric acid. The resulting mixture was refluxed for 60 minutes, distilled until a clear, homogeneous solution was obtained and then allowed to cool to room temperature. The reaction mixture was extracted and partitioned between pentane (250 mL) and water (250 mL) and the layers were separated. The aqueous phase was washed with 3 x 100 mL-portions of pentane. All organic phases were combined, washed with brine, dried over MgSO_4 , filtered and concentrated *in vacuo* to a dark yellow oil. Purification by flash chromatography (silica, 10% ethyl acetate in hexane) yielded the title compound as a clear, light yellow oil. PMR (CDCl_3): δ 1.39 (3H, t, $J = 7.2$ Hz), 4.37 (2H, q, $J = 7.2$ Hz), 7.73-7.82 (4H, m).

2-Fluoro-4-iodobenzoic acid (Compound B)

1 A round bottom (RB) flask containing a solution of 8.0 g (27.0
2 mmol) of sodium dichromate in 44 mL of glacial acetic acid was placed
3 in an external water bath (21 °C) and left exposed to air. To the
4 resultant orange slurry was added 3.2 g (13.6 mmol) of 2-fluoro-4-
5 iodotoluene followed by the dropwise addition of 22 mL of c. sulfuric
6 acid via syringe (caution: if added too quickly there is a tendency for
7 the mixture to erupt). After the addition of approximately 8 mL of
8 sulfuric acid, a green solid precipitated and the water bath temperature
9 had risen (25 °C). The green reaction mixture was heated in an oil bath
10 (90 °C) for one hour, allowed to cool to ambient temperature, diluted
11 with 1N NaOH solution (aq.) and ethyl acetate (500 mL) and then
12 quenched with sat. NaHCO₃ (aq.) solution. The organic phase was
13 separated and washed with water and brine, dried over MgSO₄, filtered
14 and concentrated *in vacuo* to an orange oil. Residual acetic acid was
15 removed by further extraction between ethyl acetate and sat. NaHCO₃
16 (aq.) solution and washing of the organic phase with water and brine.
17 The organic phase was dried over MgSO₄, filtered and concentrated *in*
18 *vacuo* to give the title compound as an orange solid.

19 PMR (DMSO-d₆): δ 7.61 (1H, t, J = 8.0 Hz, J (C-F) = 8.0 Hz), 7.67
20 (1H, dd, J = 1.5, 8.2 Hz), 7.78 (1H, dd, J = 1.5 Hz, J (C-F) = 8.9 Hz).
21 Ethyl 2-fluoro-4-iodobenzoate (Compound C)

22 To a solution of 2.5 g (27.0 mmol) of 2-fluoro-4-iodobenzoic acid
23 (Compound B) in 11 mL (8.6 g, 187.5 mmol) of ethanol was added 0.3
24 mL of c. sulfuric acid. The reaction mixture was heated to reflux in an
25 oil bath (90 °C) for 1.75 hours, fitted with a short path distillation
26 apparatus, distilled and then allowed to cool to ambient temperature.
27 The reaction mixture was extracted and partitioned between pentane
28 and water and the layers were separated. The aqueous phase was
29 washed with pentane and the organic phases were combined. The
30 combined organic phase was washed sequentially with sat. NaHCO₃

1 (aq.) solution, water and brine, dried over MgSO_4 , filtered and
2 concentrated *in vacuo* to a purple oil. Purification by flash
3 chromatography (silica, 10% ethyl acetate in hexane) gave the title
4 compound as an orange oil.

5 PMR (CDCl_3): δ 1.39 (3H, t, $J = 7.1$ Hz), 4.39 (2H, q, $J = 7.1$ Hz),
6 7.52-7.67 (3H, m).

7 4-bromophenyl acetate (Compound D)

8 To a solution of 10.0 g (57.8 mmol) of 4-bromophenol in 100 mL
9 of acetonitrile was added 9.6 g (69.5 mmol) of potassium carbonate. A
10 white slurry was obtained to which was added 8.6 mL (121.0 mmol) of
11 acetyl chloride and the resultant reaction mixture was stirred at ambient
12 temperature for 17.5 hours. The reaction mixture was filtered, washed
13 with ethyl acetate and the filtrate was concentrated *in vacuo* to a yellow
14 oil. Purification by flash chromatography (silica, 10% ethyl acetate in
15 hexane) gave the title compound as a clear, nearly colorless oil.
16 PMR (CDCl_3): δ 2.30 (3H, s), 6.98 (2H, d, $J = 8.9$ Hz), 7.49 (2H, d, J
17 $= 8.9$ Hz).

18 4-Bromo-1-methoxy-3-methylbenzene (Compound E)

19 To a solution of 0.8 g (4.4 mmol) of 4-bromo-3-methylphenol in
20 20 mL of acetone was added 1.5 g (10.9 mmol) of potassium carbonate.
21 A yellow slurry was obtained to which was added 0.55 mL (1.25 g, 8.8
22 mmol) of methyl iodide. The resultant reaction mixture was stirred at
23 ambient temperature for 12.25 hours, filtered and extracted between
24 ethyl ether and water. The layers were separated and the organic phase
25 was washed with sat. Na_2SO_3 (aq.) solution, dried over MgSO_4 , filtered
26 and then concentrated *in vacuo* to a yellow oil. Purification by flash
27 chromatography (silica, 10% ethyl acetate in hexane) gave the title
28 compound as a yellow oil.
29 PMR (CDCl_3): δ 2.36 (3H, s), 6.63 (1H, dd, $J = 3, 8.8$ Hz), 6.79 (H, d,
30 $J = 3$ Hz), 7.40 (1H, d, $J = 8.8$ Hz).

1 5-Bromo-2-hydroxyacetophenone (Compound F)

2 Under a blanket of argon, an amalgam of 10.0 g (46.4 mmol) of
3 4-bromophenyl acetate (**Compound D**) and 6.9 g (51.8 mmol) of
4 aluminum chloride was heated in an oil bath (130 °C) for 30 minutes to
5 give a yellow slurry. The slurry was cooled to 0 °C in an ice bath,
6 diluted with 200 mL of crushed ice and extracted with dichloromethane
7 (twice). The organic phases were combined and then washed with water
8 and brine, dried over MgSO₄, filtered and concentrated *in vacuo* to give
9 a yellow-green solid. Purification by flash chromatography (silica, 5%
10 ethyl acetate in hexane) gave the title compound as a white solid.
11 PMR (CDCl₃): δ 2.63 (3H, s), 6.90 (1H, d, J = 8.9 Hz), 7.54 (1H, dd, J
12 = 2.5, 8.9 Hz), 7.84 (1H, d, J = 2.5 Hz), 12.17 (1H, s).

13 5-Bromo-2-methoxyacetophenone (Compound G)

14 To a slurry of 8.55 g (64.2 mmol) of aluminum chloride in 75 mL
15 of dichloromethane cooled to 0 °C (under a blanket of argon) was
16 added dropwise a solution of 10.0 g (53.5 mmol) of 4-bromoanisole and
17 4.6 mL (64.2 mmol) of acetyl chloride in 25 mL of dichloromethane.
18 After the addition was complete, the clear yellow solution was stirred at
19 0 °C for 15 minutes, poured into 200 mL of 10% HCl (aq.) solution,
20 cooled to 0 °C in an ice bath and then extracted with dichloromethane
21 (3 x 200-mL portions). The organic phases were combined and then
22 washed with water and brine, dried over MgSO₄, filtered and
23 concentrated *in vacuo* to give a yellow semi-solid. Purification by flash
24 chromatography (silica, 10% ethyl acetate in hexane) gave the title
25 compound as a white solid.
26 PMR (CDCl₃): δ 2.60 (3H, s), 3.91 (3H, s), 6.86 (1H, d, J = 8.9 Hz),
27 7.55 (1H, dd, J = 2.7, 8.9 Hz), 7.84 (1H, d, J = 2.7 Hz).

28 5-Bromo-2-methoxy-4'-methylbenzophenone (Compound H)

29 Employing the same general procedure as for the preparation of
30 5-bromo-2-methoxyacetophenone (**Compound G**), 1.3 mL (1.7 g, 9.2

1 mmol) of 4-bromoanisole was converted into the title compound using
2 1.5 g (11.3 mmol) of aluminum chloride, 1.3 mL (1.6 g, 10.1 mmol) of
3 *p*-toluoyl chloride and 20 mL of dichloromethane. Deviations from the
4 general procedure involved continued overnight stirring (ambient
5 temperature, 16.75 hours) following stirring at 0 °C for 35 minutes and
6 using a 10% solution of c. H₂SO₄ in crushed ice (v/v) instead of cold
7 10% HCl (aq.) solution during the subsequent workup procedure.
8 Purification by flash chromatography (silica, 10% ethyl acetate in
9 hexane) gave the title compound as a white solid.
10 PMR (CDCl₃): δ 2.42 (3H, s), 3.72 (3H, s), 6.87 (1H, d, J = 8.9 Hz),
11 7.24 (2H, d, J = 8 Hz), 7.43 (1H, d, J = 2.6 Hz), 7.54 (1H, dd, J = 2.6,
12 8.9 Hz), 7.70 (2H, d, J = 8 Hz).

13 5-Bromo-2-methoxy-4-methyl-4'-methylbenzophenone (Compound I)

14 Employing the same general procedure as for the preparation 5-
15 bromo-2-methoxy-4'-methylbenzophenone (Compound H), 780 mg (3.9
16 mmol) of 4-bromo-1-methoxy-3-methylbenzene (Compound E) was
17 converted into the title compound using 260 mg (1.9 mmol) of
18 aluminum chloride, 0.6 mL (0.7 g, 4.7 mmol) of *p*-toluoyl chloride and
19 17 mL of dichloromethane. Purification by flash chromatography (silica,
20 5% ethyl acetate in hexane) gave the title compound as a white solid.
21 PMR (CDCl₃): δ 2.40 (3H, s), 2.44 (3H, s), 3.69 (3H, s), 6.86 (1H, s),
22 7.22 (2H, d, J = 8.2 Hz), 7.48 (1H, s), 7.69 (2H, d, J = 8.2 Hz).

23 5-Bromo-2-methoxy-3'-methylbenzophenone (Compound J)

24 Employing the same general procedure as for the preparation 5-
25 bromo-2-methoxy-4'-methylbenzophenone (Compound H), 1.0 mL (1.5
26 g, 8.0 mmol) of 4-bromoanisole was converted into the title compound
27 using 0.5 g (4.0 mmol) of aluminum chloride, 1.3 mL (1.5 g, 9.6 mmol)
28 of *m*-toluoyl chloride and 20 mL of dichloromethane. Purification by
29 flash chromatography (silica, 10% ethyl acetate in hexane) gave the title

1 compound as a white solid.

2 PMR (CDCl₃): δ 2.40 (3H, s), 3.72 (3H, s), 6.88 (1H, d, J = 8.8 Hz),
3 7.29-7.36 (1H, m), 7.36-7.42 (1H, m), 7.43 (1H, d, J = 2.5 Hz), 7.52-7.58
4 (2H, m), 7.65 (1H, br s).

5 5-Bromo-2-hydroxy-4'-methylbenzophenone (Compound K)

6 To a solution of 190 mg (0.6 mmol) of 5-bromo-2-methoxy-4'-
7 methylbenzophenone (Compound H) in 15 mL of dichloromethane was
8 added 0.9 mL (0.9 mmol) of boron tribromide (1M in dichloromethane)
9 at ambient temperature. The orange solution was stirred at ambient
10 temperature for 3 hours under a blanket of argon. The reaction
11 mixture was cooled to -78 °C, quenched with methanol and then
12 extracted between ethyl acetate and sat. NaHCO₃ (aq.) solution. The
13 layers were separated and the organic phase was dried over MgSO₄,
14 filtered and concentrated *in vacuo* to give a pale yellow solid.
15 Purification by flash chromatography (silica, 5% ethyl acetate in hexane)
16 gave the title compound as a white solid.

17 PMR (CDCl₃): δ 2.47 (3H, s), 6.97 (1H, d, J = 8.8 Hz), 7.33 (2H, d, J
18 = 8.2 Hz), 7.54-7.62 (3H, m), 7.72 (1H, d, J = 2.5 Hz), 11.93 (1H, s).

19 5-Bromo-2-hydroxy-3'-methylbenzophenone (Compound L)

20 Employing the same general procedure as for the preparation 5-
21 bromo-2-hydroxy-4'-methylbenzophenone (Compound K), 533 mg (1.7
22 mmol) of 5-bromo-2-methoxy-3'-methylbenzophenone (Compound J)
23 was converted into the title compound using 2.6 mL (2.6 mmol) of
24 boron tribromide (1M in dichloromethane) and 15 mL of
25 dichloromethane. Purification by flash chromatography (silica, 10%
26 ethyl acetate in hexane) gave the title compound as a white solid.
27 PMR (CDCl₃): δ 2.45 (3H, s), 6.98 (1H, d, J = 8.9 Hz), 7.36-7.52 (4H,
28 m), 7.58 (1H, dd, J = 2.4, 8.9 Hz), 7.70 (1H, d, J = 2.4 Hz), 11.94 (1H,
29 s).

1 5-Bromo-2-hydroxy-4-methyl-4'-methylbenzophenone (Compound M)

2 Employing the same general procedure as for the 5-bromo-2-
3 hydroxy-4'-methylbenzophenone (Compound K), 319 mg (1.0 mmol) of
4 5-bromo-2-methoxy-4-methyl-4'-methylbenzophenone (Compound I) was
5 converted into the title compound using 2.4 mL (2.4 mmol) of boron
6 tribromide (1M in dichloromethane) and 10 mL of dichloromethane.
7 Purification by flash chromatography (silica, 10% ethyl acetate in
8 hexane) gave the title compound as a pale yellow solid.
9 PMR (CDCl₃): δ 2.42 (3H, s), 2.46 (3H, s), 6.97 (1H, s), 7.33 (1H, d, J
10 = 8.0 Hz), 7.58 (1H, d, J = 8.0 Hz), 7.74 (1H, s), 11.93 (1H, s).

11 4-Bromo-2-[(1-m-tolyl)vinyl]phenol (Compound N)

12 To a cold solution (-78 °C) of 99 mg (0.3 mmol) of 5-bromo-2-
13 hydroxy-3'-methylbenzophenone (Compound L) in 5 mL of
14 tetrahydrofuran (under a blanket of argon) was added 1.0 mL (3.0
15 mmol) of methyl magnesium chloride (3M in tetrahydrofuran). With
16 the addition, the solution turned yellowish-orange in color. The -78 °C
17 bath was removed and the solution was allowed to warm to ambient
18 temperature and stirred for 2 hours. The reaction mixture was
19 concentrated *in vacuo*, extracted between ethyl acetate and sat. NH₄Cl
20 (aq.) solution and the layers were separated. The organic phase was
21 washed with water and brine, dried over MgSO₄, filtered and
22 concentrated *in vacuo* to give crude 4-bromo-2-[(1-m-tolyl-1-
23 hydroxy)ethyl]phenol as a yellow oil. The crude alcohol was dissolved in
24 2 mL of toluene, placed under a blanket of argon and 5.9 mg of p-
25 toluene sulfonic acid monohydrate was added. The resultant mixture
26 was heated at 70 °C for 45 minutes, cooled to ambient temperature and
27 purified by flash chromatography (silica, 5% ethyl acetate in hexane) to
28 give the title compound as a clear, colorless oil.
29 PMR (CDCl₃): δ 2.34 (3H, s), 5.09 (1H, s), 5.40 (1H, br s), 5.84 (1H, br

1 s), 6.83 (1H, d, $J = 8.6$ Hz), 7.11-7.20 (3H, m), 7.22-7.30 (1H, m), 7.35
2 (1H, dd, $J = 2.5, 8.6$ Hz).

3 2-Acetoxy-5-bromo-4'-methylbenzophenone (Compound O)

4 To a yellow solution of 229 mg (0.8 mmol) of 5-bromo-2-hydroxy-
5 4'-methylbenzophenone (Compound K) in 15 mL of dichloromethane
6 (under a blanket of argon) was added 0.07 mL (69 mg, 0.9 mmol) of
7 pyridine followed by 0.07 mL (74 mg, 0.9 mmol) of acetyl chloride. The
8 resultant reaction mixture was stirred at ambient temperature overnight
9 (16.75 hours), poured into 10% HCl (aq.) solution and extracted with
10 ethyl acetate. The layers were separated and the aqueous phase was
11 washed with ethyl acetate. The organic phases were combined and then
12 sequentially washed with sat. NaHCO_3 (aq.) solution, water and brine,
13 dried over MgSO_4 , filtered and concentrated *in vacuo* to give a yellow
14 oil. Purification by flash chromatography (silica, 20% ethyl acetate in
15 hexane) gave the title compound as a clear, colorless oil.

16 PMR (CDCl_3): δ 1.95 (3H, s), 2.43 (3H, s), 7.09 (1H, d, $J = 8.1$ Hz),
17 7.27 (2H, d, $J =$ approximately 8 Hz), 7.60-7.70 (4H, m).

18 5-Bromo-2-methoxymethoxyacetophenone (Compound P)

19 To a cold solution (0 °C) of 4.5 g (21.0 mmol) of 5-bromo-2-
20 hydroxyacetophenone (Compound F) in 160 mL of dichloromethane
21 (under a blanket of argon) was added 22 mL (16.3 g, 126.3 mmol) of
22 *N,N*-diisopropylethylamine followed by 2.6 mL (2.8 g, 34.2 mmol) of
23 chloromethyl methyl ether and 52 mg of tetrabutylammonium iodide.
24 The resultant yellow solution was heated to reflux in an oil bath (45 °C)
25 overnight (14.75 hours), cooled to ambient temperature, concentrated *in*
26 *vacuo* and then extracted and partitioned between ethyl acetate and sat.
27 NaHCO_3 (aq.) solution. The layers were separated and the organic
28 phase was washed with water and brine, dried over MgSO_4 , filtered and
29 concentrated *in vacuo* to a yellow oil. Purification by flash

1 chromatography (silica, 10% ethyl acetate in hexane) gave the title
2 compound as a yellow oil.

3 PMR (CDCl₃): δ 2.62 (3H, s), 3.51 (3H, s), 5.26 (2H, s), 7.10 (1H, d, J
4 = 8.7 Hz), 7.51 (1H, dd, J = 2.6, 8.7 Hz), 7.81 (1H, d, J = 2.6 Hz).

5 5-Bromo-2-methoxymethoxy-4-methyl-4'-methylbenzophenone

6 (Compound Q)

7 Employing the same general procedure as for the preparation 5-
8 bromo-2-methoxymethoxyacetophenone (Compound P), 250 mg (0.8
9 mmol) 5-bromo-2-hydroxy-4-methyl-4'-methylbenzophenone (Compound
10 M) was converted into the title compound using 0.2 mL (0.2 g, 2.5
11 mmol) of chloromethyl methyl ether, 0.85 mL (0.6 g, 4.9 mmol) of *N,N*-
12 diisopropylethylamine, 10 mL of dichloromethane and a catalytic
13 amount of tetrabutylammonium iodide (< 5 mg). Purification by flash
14 chromatography (silica, 10% ethyl acetate in hexane) gave the title
15 compound as a white solid.

16 PMR (CDCl₃): δ 2.42 (3H, s), 2.44 (3H, s), 3.32 (3H, s), 5.03 (2H, s),
17 7.11 (1H, s), 7.24 (2H, d, J = 8.2 Hz), 7.49 (1H, s), 7.72 (2H, d, J = 8.2
18 Hz).

19 4-Bromo-2-[(1-*p*-tolyl)vinyl]phenol (Compound R)

20 To a solution of 2.2 g (8.5 mmol) of 5-bromo-2-
21 methoxymethoxyacetophenone (Compound P) in 25 mL of ethyl ether
22 (under a blanket of argon) was added 25.5 mL (25.5 mmol) of *p*-
23 tolylmagnesium bromide (1M in ether) via syringe. The yellow solution
24 effervesced as the Grignard reagent was being added. The reaction
25 mixture was allowed to stir at ambient temperature for 17 hours, poured
26 into 75 mL of ice water and extracted and partitioned between 10%
27 HCl (aq.) solution and ethyl ether. The layers were separated and the
28 organic phase was washed with water and brine, dried over MgSO₄,
29 filtered and concentrated *in vacuo* to give an inseparable mixture of

1 tertiary alcohols (4-bromo-2-[(1-hydroxy-1-*p*-tolyl)ethyl]phenol and 4-
2 bromo-1-methoxymethoxy-2-[(1-hydroxy-1-*p*-tolyl)ethyl]benzene
3 (approximately 2.5 to 1 ratio, respectively) following flash
4 chromatography. The mixture was dissolved in 15 mL of ethanol (under
5 a blanket of argon) and 5 mL of 10% HCl (aq) solution was added.
6 The resultant reaction mixture was stirred at ambient temperature for 4
7 hours, heated in an oil bath (90 °C) for 2 hours, cooled to ambient
8 temperature and stirred overnight (14 hours). The reaction mixture was
9 concentrated *in vacuo*, extracted and partitioned between ethyl acetate
10 and sat. NaHCO₃ (aq.) solution and the layers were separated. The
11 organic phase was washed with water and brine, dried over MgSO₄,
12 filtered and concentrated *in vacuo* to a yellow oil. Purification by flash
13 chromatography (silica, 10% ethyl acetate in hexane) gave the title
14 compound as a clear oil.

15 PMR (CDCl₃): δ 2.35 (3H, s), 5.15 (1H, s), 5.35 (1H, br s), 5.81 (1H, br
16 s), 6.81 (1H, d, J = 8.6 Hz), 7.15 (2H, d, J = 8.2 Hz), 7.23 (2H, d, J =
17 8.2 Hz), 7.27 (1H, d, J = 2.5 Hz), 7.33 (1H, dd, J = 2.5, 8.6 Hz).

18 4-Bromo-1-isopropoxy-2-[(1-*p*-tolyl)vinyl]benzene (Compound S)

19 To a cold solution (0 °C) of 125 mg (0.4 mmol) of 4-bromo-2-[(1-
20 *p*-tolyl)vinyl]phenol (Compound R) in 5 mL of tetrahydrofuran was
21 added 125 mg (0.5 mmol) of triphenylphosphine and 0.04 mL (31 mg,
22 0.5 mmol) of isopropanol followed by 0.07 mL (82 mg, 0.5 mmol) of
23 diethylazodicarboxylate. The dark yellow solution was removed from
24 the ice bath, allowed to warm to ambient temperature on its own and
25 stirred overnight (22.5 hours). The reaction mixture was concentrated
26 *in vacuo* to a gummy yellow solid. Purification by flash chromatography
27 (silica, 1% ethyl acetate in hexane) gave the title compound as a yellow
28 oil.

29 PMR (CDCl₃): δ 0.98 (6H, d, J = 6.1 Hz), 2.33 (3H, s), 4.30 (1H,
30 heptet, J = 6.1 Hz), 5.25 (1H, d, J = 1.3 Hz), 5.58 (1H, d, J = 1.3 Hz),

1 6.74 (1H, d, J = 8.6 Hz), 7.07 (2H, d, J = 8.2 Hz), 7.14 (2H, d, J = 8.2
2 Hz), 7.36 (1H, dd, J = 2.5, 8.6 Hz), 7.39 (1H, d, J = 2.5 Hz).

3 4-Bromo-1-isopropoxy-2-[(1-*m*-tolyl)vinyl]phenol (Compound T)

4 Employing the same general procedure as for the preparation of
5 4-bromo-1-isopropoxy-2-[(1-*p*-tolyl)vinyl]benzene (Compound S), 81.5
6 mg (0.3 mmol) of 4-bromo-2-[(1-*m*-tolyl)vinyl]phenol (Compound N)
7 was converted into the title compound using 164 mg (0.6 mmol) of
8 triphenylphosphine, 0.10 mL (108 mg, 0.6 mmol) of
9 diethylazodicarboxylate, 0.05 mL (39 mg, 0.6 mmol) of isopropanol and
10 3 mL of tetrahydrofuran. The reaction was sluggish necessitating
11 addition (after 23 hours of stirring at ambient temperature) of another
12 equivalent of reagents (initially only 1/2 of the above amounts were
13 added) and stirring for 4 additional days. Purification by flash
14 chromatography (silica, 10% ethyl acetate in hexane) gave the title
15 compound as a pink oil.

16 PMR (CDCl₃): δ 0.97 (6H, d, J = 6.0 Hz), 2.30 (3H, s), 4.31 (1H,
17 heptet, J = 6.0 Hz), 5.29 (1H, d, J = 1.4 Hz), 5.59 (1H, d, J = 1.4 Hz),
18 6.73 (1H, d, J = 8.6 Hz), 7.02-7.10 (3H, m), 7.12-7.20 (1H, m), 7.36
19 (1H, dd, J = 2.6, 8.6 Hz), 7.40 (1H, d, J = 2.6 Hz).

20 4-Bromo-1-*tert*-butyldimethylsilyloxy-2-[(1-*p*-tolyl)vinyl]benzene
21 (Compound U)

22 To a solution of 82 mg (0.3 mmol) of 4-bromo-2-[(1-*p*-
23 tolyl)vinyl]phenol (Compound R) in 3 mL of dichloromethane (under a
24 blanket of argon) was added 0.05 mL (36 mg, 0.34 mmol) of
25 triethylamine followed by 0.3 mL (0.3 mmol) of *tert*-
26 butyldimethylsilylchloride (1M in dichloromethane). The resultant
27 yellow solution was stirred at ambient temperature overnight (23.7
28 hours), concentrated *in vacuo* and purified by flash chromatography
29 (silica, 100% hexane) to give the title compound as a clear, colorless oil.
30 PMR (CDCl₃): δ 0.03 (6H, s), 0.71 (9H, s), 2.32 (3H, s), 5.22 (1H, br

1 s), 5.69 (1H, br s), 6.69 (1H, d, J = 8.5 Hz), 7.07 (2H, d, J = 8.2 Hz),
2 7.16 (2H, d, J = 8.2 Hz), 7.30 (1H, dd, J = 2.6, 8.5 Hz), 7.34 (1H, d, J
3 = 2.56 Hz).

4 4-Bromo-2-[(1-*p*-tolyl)vinyl]phenyl acetate (Compound V)

5 To a solution of 1.3 g (4.6 mmol) of 4-bromo-2-[(1-*p*-
6 tolyl)vinyl]phenol (Compound R) in 15 mL of dichloromethane (under a
7 blanket of argon) was added 0.77 mL (0.6 g, 5.6 mmol) of triethylamine
8 and 0.4 mL (0.4 g, 5.6 mmol) of acetyl chloride. A white precipitate
9 immediately formed upon addition of acetyl chloride. The reaction
10 mixture was stirred at ambient temperature for 14.5 hours and then
11 concentrated *in vacuo*. Purification by flash chromatography (silica,
12 10% ethyl acetate in hexane) gave the title compound as a clear,
13 colorless oil.

14 PMR (CDCl₃): δ 2.34 (3H, s), 5.29 (1H, br s), 5.64 (1H, d, J = 1.1 Hz),
15 6.96 (1H, d, J = 8.6 Hz), 7.08-7.17 (4H, m), 7.47 (1H, dd, J = 2.5, 8.6
16 Hz), 7.51 (1H, d, J = 2.5 Hz).

17 2-Methoxy-5-trimethylsilanylethynyl acetophenone (Compound W)

18 To a sparged solution (a stream of argon was bubbled vigorously
19 into the solution for several minutes) of diethylamine (5 mL) in a
20 pressure tube vessel was added a solution of 1.85 g (8.1 mmol) of 5-
21 bromo-2-methoxyacetophenone (Compound G) in 20 mL of
22 diethylamine. After sparging with argon for 5 minutes, 0.4 g (2.0 mmol)
23 of cuprous iodide was added to the solution and the resultant mixture
24 was sparged with argon for 2 minutes. To this reaction mixture was
25 then added 1.4 g (2.0 mmol) of bis(triphenylphosphine)palladium(II)
26 chloride. After sparging with argon for 3 minutes, 4.3 mL (40.4 mmol)
27 of trimethylsilyl acetylene was added to the reaction mixture. The
28 pressure tube was then sealed and heated in an oil bath (55 °C) for 5
29 days. The reaction mixture was filtered through celite and washed with
30 ethyl ether (400 mL). The filtrate was extracted with water (3 x 200

1 mL-portions) and brine, dried over MgSO_4 , filtered and concentrated *in vacuo* to give a dark brown residue. Purification by flash chromatography (preabsorbed onto silica with chloroform, 10% ethyl acetate in hexane) gave the title compound as a yellow solid. PMR (CDCl_3): δ 0.24 (9H, s), 2.01 (2H, t, $J = 7.1$ Hz), 2.59 (3H, s), 3.92 (3H, s), 6.90 (1H, d, $J = 8.6$ Hz), 7.55 (1H, dd, $J = 2.2, 8.6$ Hz), 7.84 (1H, d, $J = 2.2$ Hz).

8 2-Acetoxy-5-trimethylsilanylethynyl-4'-methylbenzophenone (Compound
9 X)

10 Employing the same general procedure as for the preparation of
11 2-methoxy-5-trimethylsilanylethynyl acetophenone (Compound W), 228.5
12 mg (0.7 mmol) of 2-acetoxy-5-bromo-4'-methylbenzophenone
13 (Compound O) was converted into the title compound using 120 mg
14 (0.2 mmol) of bis(triphenylphosphine)palladium (II) chloride, 33 mg
15 (0.2 mmol) of cuprous iodide, 0.73 mL (670 mg, 6.9 mmol) of
16 trimethylsilyl acetylene and 10 mL of triethylamine (heated at 75°C).
17 Purification by flash chromatography (silica, 5% ethyl acetate in hexane)
18 gave the title compound as an oil.
19 PMR (CDCl_3): δ 0.23 (9H, s), 1.98 (3H, s), 2.43 (3H, s), 7.14 (1H, d, J
20 $= 8.2$ Hz), 7.27 (2H, d, $J = 8.1$ Hz), 7.57-7.63 (2H, m), 7.67 (2H, d, $J =$
21 8.1 Hz).

22 4-Trimethylsilanylethynyl-2-[(1-*p*-tolyl)vinyl]phenyl acetate (Compound
23 Y)

24 Employing the same general procedure as for the preparation of
25 2-methoxy-5-trimethylsilanylethynyl acetophenone (Compound W), 515
26 mg (1.6 mmol) of 4-bromo-2-[(1-*p*-tolyl)vinyl]phenyl acetate (Compound
27 V) was converted into the title compound using 219 mg (0.3 mmol) of
28 bis(triphenylphosphine)palladium (II) chloride, 58 mg (0.3 mmol) of
29 cuprous iodide, 1.66 mL (1.5 g, 15.6 mmol) of trimethylsilyl acetylene

1 and 10 mL of triethylamine (heated at 75 °C). Purification by flash
2 chromatography (silica, 5% ethyl acetate in hexane) gave the title
3 compound as a tan solid.

4 PMR (CDCl₃): δ 0.27 (9H, s), 1.80 (3H, s), 2.36 (3H, s), 5.31 (1H, br
5 s), 5.65 (1H, br s), 7.04 (1H, d, J = 8.3 Hz), 7.10-7.19 (4H, m), 7.47
6 (1H, dd, J = 2.0, 8.3 Hz), 7.52 (1H, d, J = 2.0 Hz).

7 3-Trimethylsilyl ethynyl acetophenone (Compound Z)

8 Employing the same general procedure as for the preparation of
9 2-methoxy-5-trimethylsilyl ethynyl acetophenone (Compound W), 0.66
10 mL (1.0 g, 5.0 mmol) of 3-bromoacetophenone was converted into the
11 title compound using 0.9 g (1.3 mmol) of
12 bis(triphenylphosphine)palladium (II) chloride, 0.2 g (1.0 mmol) of
13 cuprous iodide, 5.4 mL (5.0 g, 50.7 mmol) of trimethylsilyl acetylene and
14 12 mL of triethylamine (heated at 75 °C). Purification by flash
15 chromatography (silica, 5% ethyl acetate in hexane) gave the title
16 compound as a yellow oil.

17 PMR (CDCl₃): δ 0.27 (9H, s), 2.61 (3H, s), 7.38-7.44 (1H, m), 7.62-7.67
18 (1H, m), 7.84-7.86 (1H, m), 8.10-8.25 (1H, m).

19 2-Methoxymethoxy-4-methyl-5-trimethylsilyl ethynyl-4'-
20 methylbenzophenone (Compound A1)

21 Employing the same general procedure as for the preparation of
22 2-methoxy-5-trimethylsilyl ethynyl acetophenone (Compound W), 264
23 mg (0.76 mmol) of 5-bromo-2-methoxymethoxy-4-methyl-4'-
24 methylbenzophenone (Compound Q) was converted into the title
25 compound using 133 mg (0.2 mmol) of
26 bis(triphenylphosphine)palladium (II) chloride, 36 mg (0.2 mmol) of
27 cuprous iodide, 0.8 mL (0.7 g, 7.6 mmol) of trimethylsilyl acetylene and
28 10 mL of triethylamine (heated at 75 °C). Purification by flash
29 chromatography (silica, 5% ethyl acetate in hexane) gave the title
30 compound as a yellow oil.

1 PMR (CDCl₃): δ 0.23 (9H, s), 2.41 (3H, s), 2.48 (3H, s), 3.32 (3H, s),
2 5.06 (2H, s), 7.04 (1H, s), 7.21 (2H, d, J = 8.2 Hz), 7.43 (1H, s), 7.70
3 (2H, d, J = 8.2 Hz).

4 1-Isopropoxy-4-trimethylsilanylethynyl-2-[(1-*p*-tolyl)vinyl]benzene
5 **(Compound B1)**

6 Employing the same general procedure as for the preparation of
7 2-methoxy-5-trimethylsilanylethynyl acetophenone (**Compound W**), 64
8 mg (0.2 mmol) of 4-bromo-1-isopropoxy-2-[(1-*p*-tolyl)vinyl]benzene
9 (**Compound S**) was converted into the title compound using 33.5 mg
10 (0.05 mmol) of bis(triphenylphosphine)palladium (II) chloride, 9 mg
11 (0.05 mmol) of cuprous iodide, 0.3 mL (0.3 g, 2.8 mmol) of
12 trimethylsilyl acetylene and 5 mL of triethylamine (heated at 75 °C).
13 Purification by flash chromatography (silica, 2% ethyl acetate in hexane)
14 gave the title compound as a yellow oil.

15 PMR (CDCl₃): δ 0.26 (9H, s), 0.99 (6H, d, J = 6.0 Hz), 2.34 (3H, s),
16 4.37 (1H, heptet, J = 6.0 Hz), 5.26 (1H, d, J = 1.5 Hz), 5.58 (1H, d, J
17 = 1.5 Hz), 6.79 (1H, d, J = 8.4 Hz), 7.05-7.18 (4H, m), 7.38-7.46 (2H,
18 m).

19 1-Isopropoxy-4-trimethylsilanylethynyl-2-[(1-*m*-tolyl)vinyl]benzene
20 **(Compound C1)**

21 Employing the same general procedure as for the preparation of
22 2-methoxy-5-trimethylsilanylethynyl acetophenone (**Compound W**), 37
23 mg (0.1 mmol) of 4-bromo-1-isopropoxy-2-[(1-*m*-tolyl)vinyl]benzene
24 (**Compound T**) was converted into the title compound using 20 mg
25 (0.03 mmol) of bis(triphenylphosphine)palladium (II) chloride, 6 mg
26 (0.03 mmol) of cuprous iodide, 0.12 mL (111 mg, 1.1 mmol) of
27 trimethylsilyl acetylene and 3 mL of triethylamine (heated at 75 °C).
28 Purification by flash chromatography (silica, 1% ethyl acetate in hexane)
29 gave the title compound as a yellow oil.

30 PMR (CDCl₃): δ 0.24 (9H, s), 0.95 (6H, d, J = 6.1 Hz), 2.29 (3H, s),

1 4.37 (1H, heptet, J = 6.1 Hz), 5.28 (1H, d, J = 1.5 Hz), 5.57 (1H, d, J
2 = 1.5 Hz), 6.77 (1H, d, J = 8.4 Hz), 7.00-7.10 (3H, m), 7.10-7.20 (1H,
3 m), 7.40 (1H, dd, J = 2.2, 8.4 Hz), 7.43 (1H, d, J = 2.2 Hz).

4 1-tert-Butyldimethylsilyloxy-4-trimethylsilylethynyl-2-[(1-p-
5 tolyl)vinyl]benzene (Compound D1)

6 Employing the same general procedure as for the preparation of
7 2-methoxy-5-trimethylsilylethynyl acetophenone (Compound W), 43.4
8 mg (0.1 mmol) of 1-tert-butyldimethylsilyloxy-4-bromo-2-[(1-p-
9 tolyl)vinyl]benzene (Compound U) was converted into the title
10 compound using 19 mg (0.03 mmol) of
11 bis(triphenylphosphine)palladium (II) chloride, 6.8 mg (0.03 mmol) of
12 cuprous iodide, 0.11 mL (101 mg, 1.1 mmol) of trimethylsilyl acetylene
13 and 4 mL of triethylamine (heated at 75 °C). Purification by flash
14 chromatography (silica, 2% ethyl acetate in hexane) gave the title
15 compound as a yellow oil.

16 PMR (CDCl₃): δ 0.04 (6H, s), 0.24 (9H, s), 0.71 (9H, s), 2.32 (3H, s),
17 5.22 (1H, d, J = 1.3 Hz), 5.68 (1H, d, J = 1.3 Hz), 6.74 (1H, d, J = 8.3
18 Hz), 7.02-7.10 (2H, m), 7.12-7.20 (2H, m), 7.33 (1H, dd, J = 2.2, 8.3
19 Hz), 7.38 (1H, d, J = 2.2 Hz).

20 5-Ethynyl-2-methoxyacetophenone (Compound E1)

21 To a solution of 990 mg (4.0 mmol) of 2-methoxy-5-
22 trimethylsilylethynylacetophenone (Compound W) in 100 mL of
23 methanol was added 144 mg (1.0 mmol) of potassium carbonate. The
24 mixture was stirred for 2.5 hours at ambient temperature (under a
25 blanket of argon). The dark brown solution was concentrated *in vacuo*
26 to a brown residue, diluted with dichloromethane (5 mL) and sat.
27 NaHCO₃ (aq.) solution (100 mL), and then stirred at ambient
28 temperature for approx. 30 minutes. The mixture was extracted
29 between dichloromethane and water, the layers were separated and the
30 aqueous phase was washed with dichloromethane. The organic phases

1 were combined and sequentially washed with water and brine, dried
2 over MgSO_4 , filtered and concentrated *in vacuo*. Purification by column
3 chromatography (silica, 10% ethyl acetate in hexane) yielded the title
4 compound as a white solid.

5 PMR (CDCl_3): δ 2.60 (3H, s), 3.01 (1H, s), 3.93 (3H, s), 6.92 (1H, d, J
6 = 8.5 Hz), 7.58 (1H, dd, J = 2.1, 8.5 Hz), 7.86 (1H, d, J = 2.1 Hz).

7 5-Ethynyl-2-hydroxy-4'-methylbenzophenone (Compound F1)

8 To a solution of 100 mg (0.3 mmol) of 2-acetoxy-5-
9 trimethylsilanylethynyl-4'-methylbenzophenone (Compound X) in 5 mL
10 of tetrahydrofuran (under a blanket of argon) was added 0.86 mL (0.86
11 mmol) of tetrabutylammonium fluoride (1M in tetrahydrofuran). The
12 resultant yellow solution was stirred at ambient temperature for 30
13 minutes, diluted with water (1 mL), extracted between ethyl ether and
14 10% HCl (aq.) solution, the layers separated and the aqueous phase
15 washed with ethyl ether. The organic phases were combined, dried over
16 MgSO_4 , filtered and concentrated *in vacuo*. Purification by flash
17 chromatography (silica, 3% ethyl acetate in hexane) gave the title
18 compound as an oil.

19 PMR (CDCl_3): δ 2.46 (3H, s), 2.96 (1H, s), 7.03 (1H, d, J = 8.6 Hz),
20 7.33 (2H, d, J = 7.8 Hz), 7.58-7.64 (3H, m), 7.78 (1H, d, J = 2.0 Hz),
21 12.17 (1H, s).

22 5-Ethynyl-2-methoxymethoxy-4'-methylbenzophenone (Compound G1)

23 Employing the same general procedure as for the preparation of
24 5-bromo-2-methoxymethoxyacetophenone (Compound P), 70 mg (0.3
25 mmol) of 5-ethynyl-2-hydroxy-4'-methylbenzophenone (Compound F1)
26 was converted into the title compound using 0.3 mL (1.7 mmol) of *N,N*-
27 diisopropylethylamine, 0.7 mL (0.9 mmol) of chloromethyl methyl ether,
28 a catalytic amount of tetrabutylammonium iodide (< 5 mg) and 5 mL of
29 dichloromethane. The yellow residue obtained was of sufficient purity

1 to be used without further purification.

2 PMR (CDCl₃): δ 2.41 (3H, s), 3.01 (1H, s), 3.31 (3H, s), 5.07 (2H, s),
3 7.16 (1H, d, J = 8.7 Hz), 7.23 (2H, d, J = approximately 8 Hz), 7.46
4 (1H, d, J = 2.1 Hz), 7.55 (1H, dd, J = 2.1, 8.7 Hz), 7.71 (2H, d, J =
5 approximately 8 Hz).

6 4-Ethynyl-2-[(1-*p*-tolyl)vinyl]phenyl acetate (Compound H1) and 4-
7 Ethynyl-2-[(1-*p*-tolyl)vinyl]phenol (Compound I1)

8 Employing the same general procedure as for the preparation of
9 5-ethynyl-2-hydroxy-4'-methylbenzophenone (Compound F1), 500 mg
10 (1.4 mmol) of 4-trimethylsilanylethynyl-2-[(1-*p*-tolyl)vinyl]phenyl acetate
11 (Compound Y) was converted into the title compounds using 3.2 mL
12 (3.2 mmol) of tetrabutylammonium fluoride (1M in tetrahydrofuran)
13 and 20 mL of tetrahydrofuran. Purification by flash chromatography
14 (silica, 10% ethyl acetate in hexane) gave the title compounds as clear
15 oils in a 1:1 ratio.

16 PMR: 4-Ethynyl-2-[(1-*p*-tolyl)vinyl]phenyl acetate (Compound H1):
17 (CDCl₃): δ 1.78 (3H, s), 3.07 (1H, s), 5.29 (1H, br s), 5.63 (1H, br s),
18 7.03 (1H, d, J = 8.2 Hz), 7.10-7.16 (4H, m), 7.47 (1H, dd, J = 2.0, 8.2
19 Hz), 7.52 (1H, d, J = 2.0 Hz).

20 PMR: 4-Ethynyl-2-[(1-*p*-tolyl)vinyl]phenol (Compound I1): (CDCl₃): δ
21 2.36 (3H, s), 2.98 (1H, s), 5.31 (1H, s), 5.37 (1H, br s), 5.84 (1H, br s),
22 6.89 (1H, d, J = 8.4 Hz), 7.20, (2H, d, J = 8 Hz), 7.24 (2H, d, J = 8
23 Hz), 7.32 (1H, d, J = 2.1 Hz), 7.39 (1H, dd, J = 2.1, 8.4 Hz).

24 4-Ethynyl-1-methoxymethoxy-2-[(1-*p*-tolyl)vinyl]benzene (Compound J1)

25 Employing the same general procedure as for the preparation of
26 5-bromo-2-methoxymethoxy acetophenone (Compound P), 109 mg (0.5
27 mmol) of 4-ethynyl-2-[(1-*p*-tolyl)vinyl]phenol (Compound I1) was
28 converted into the title compound using 0.11 mL (117 mg, 1.45 mmol)
29 of chloromethyl methyl ether, 0.49 mL (360 mg, 2.8 mmol) of *N, N*-
30 diisopropylethylamine, a catalytic amount of tetrabutylammonium iodide

1 (< 5 mg) and 5 mL of dichloromethane. Purification by flash
2 chromatography (silica, 10% ethyl acetate in hexane) gave the title
3 compound as a clear, colorless oil.
4 PMR (CDCl₃): δ 2.32 (3H, s), 3.01 (1H, s), 3.17 (3H, s), 4.96 (2H, s),
5 5.25 (1H, s), 5.68 (1H, br s), 7.00-7.10 (3H, m), 7.17 (2H, d, J =
6 approximately 8 Hz), 7.41-7.46 (2H, m).

7 3-Ethynylacetophenone (Compound K1)

8 Employing the same general procedure as for the preparation of
9 5-ethynyl-2-methoxyacetophenone (Compound E1), 1.1 g (5.0 mmol) of
10 3-trimethylsilanylethynyl acetophenone (Compound Z) was converted
11 into the title compound using 172 mg (1.25 mmol) of potassium
12 carbonate and 10 mL of methanol. Purification by flash
13 chromatography (silica, 10% ethyl acetate in hexane) gave the title
14 compound as a yellow solid.
15 PMR (CDCl₃): δ 2.61 (3H, s), 3.15 (1H, s), 7.40-7.50 (1H, m), 7.65-7.68
16 (1H, m), 7.90-7.95 (1H, m), 8.05-8.08 (1H, m).

17 5-Ethynyl-2-methoxymethoxy-4-methyl-4'-methylbenzophenone
18 (Compound L1)

19 Employing the same general procedure as for the preparation of
20 5-ethynyl-2-methoxyacetophenone (Compound E1), 260 mg (0.8 mmol)
21 of 2-methoxymethoxy-4-methyl-5-trimethylsilanylethynyl-4'-
22 methylbenzophenone (Compound A1) was converted into the title
23 compound using 26 mg (0.2 mmol) of potassium carbonate and 5 mL of
24 methanol. Purification by flash chromatography (silica, 5% ethyl acetate
25 in hexane) gave the title compound as a white solid.
26 PMR (CDCl₃): δ 2.41 (3H, s), 2.50 (3H, s), 3.22 (1H, s), 3.32 (3H, s),
27 5.07 (2H, s), 7.06 (1H, s), 7.23 (2H, d, J = 8.4 Hz), 7.46 (1H, s), 7.71
28 (2H, d, J = 8.4 Hz).

29 4-Ethynyl-1-isopropoxy-2-[(1-p-tolyl)vinyl]benzene (Compound M1)

1 Employing the same general procedure as for the preparation of
2 5-ethynyl-2-methoxyacetophenone (**Compound E1**), 53 mg (0.15 mmol)
3 1-isopropoxy-4-trimethylsilanylethynyl-2-[(1-*p*-tolyl)vinyl]benzene
4 (**Compound B1**) was converted into the title compound using 8 mg (0.06
5 mmol) of potassium carbonate and 4 mL of methanol. Purification by
6 flash chromatography (silica, 5% ethyl acetate in hexane) gave the title
7 compound as a yellow oil.
8 PMR (CDCl₃): δ 0.99 (6H, d, J = 6.0 Hz), 2.33 (3H, s), 3.00 (1H, s),
9 4.37 (1H, heptet, J = 6.0 Hz), 5.25 (1H, d, J = 1.5 Hz), 5.57 (1H, d, J
10 = 1.5 Hz), 6.79 (1H, d, J = 8.7 Hz), 7.06 (2H, d, J = 8.2 Hz), 7.14 (2H,
11 d, J = 8.2 Hz), 7.40-7.45 (2H, m).

12 4-Ethynyl-1-isopropoxy-2-[(1-*m*-tolyl)vinyl]benzene (**Compound N1**)

13 Employing the same general procedure as for the preparation of
14 5-ethynyl-2-methoxyacetophenone (**Compound E1**), 22 mg (0.07 mmol)
15 1-isopropoxy-4-trimethylsilanylethynyl-2-[(1-*m*-tolyl)vinyl]benzene
16 (**Compound C1**) was converted into the title compound using 3 mg (0.02
17 mmol) of potassium carbonate and 3 mL of methanol. Purification by
18 flash chromatography (silica, 1% ethyl acetate in hexane) gave the title
19 compound as a yellow oil.
20 PMR (CDCl₃): δ 0.98 (6H, d, J = 6.0 Hz), 2.30 (3H, s), 3.01 (1H, s),
21 4.37 (1H, heptet, J = 6.0 Hz), 5.29 (1H, br s), 5.58 (1H, d, J = 1.5 Hz),
22 6.79 (1H, d, J = 8.5 Hz), 7.00-7.10 (3H, m), 7.10-7.20 (1H, m), 7.40-7.50
23 (2H, m).

24 1-*tert*-Butyldimethylsilanyloxy-4-ethynyl-2-[(1-*p*-tolyl)vinyl]benzene
25 (**Compound O1**)

26 Employing the same general procedure as for the preparation of
27 5-ethynyl-2-methoxyacetophenone (**Compound E1**), 25 mg (0.06 mmol)
28 1-*tert*-butyldimethylsilanyloxy-4-trimethylsilanylethynyl-2-[(1-*p*-
29 tolyl)vinyl]benzene (**Compound D1**) was converted into the title
30 compound using 4 mg (0.03 mmol) of potassium carbonate and 1 mL of

1 ethanol. Purification by flash chromatography (silica, 5% ethyl acetate
2 in hexane) gave the title compound as a yellow oil.
3 PMR (CDCl₃): δ 0.05 (6H, s), 0.71 (9H, s), 2.31 (3H, s), 3.00 (1H, s),
4 5.22 (1H, br s), 5.68 (1H, br s), 6.75 (1H, d, J = 8.2 Hz), 7.06 (2H, d, J
5 = 8.2 Hz), 7.16 (2H, d, J = 8.2 Hz), 7.35 (1H, dd, J = 2.1, 8.2 Hz), 7.38
6 (1H, d, J = 2.1 Hz).

7 Ethyl 4-[(3'-acetyl-4'-methoxy)phenylethynyl]benzoate (Compound 1)

8 To a sparged solution of 10 mL of diethylamine (a stream of
9 argon was bubbled vigorously into the solution for several minutes) was
10 added a mixture of 440 mg (2.5 mmol) of 5-ethynyl-2-
11 methoxyacetophenone (Compound E1), 770 mg (2.8 mmol) of ethyl 4-
12 iodobenzoate (Compound A) and 10 mL of diethylamine. After
13 sparging with argon for 5 minutes, 96 mg (0.5 mmol) of cuprous iodide
14 was added to the solution and the resultant mixture was sparged with
15 argon for 3 minutes. The mixture was cooled to 0 °C in an ice bath and
16 then 440 mg (0.6 mmol) of bis(triphenylphosphine)palladium (II)
17 chloride was added. The reaction mixture was stirred at 0 °C for 30
18 minutes (initial 5 minutes performed under sparging conditions),
19 allowed to warm to ambient temperature and then stirred at ambient
20 temperature for 27 hours. The reaction mixture was filtered through
21 celite, washed with ethyl ether (250 mL) and the collected filtrate
22 washed with water (3 x 200 mL-portions) and brine (150 mL). The
23 organic phase was dried over MgSO₄, filtered and concentrated *in vacuo*
24 to a solid residue. Purification by flash chromatography (preabsorbed
25 onto silica with chloroform, 10% ethyl acetate in hexane) gave the title
26 compound as a pale yellow solid.
27 PMR (CDCl₃): δ 1.41 (3H, t, J = 7.1 Hz), 2.63 (3H, s), 3.96 (3H, s),
28 4.39 (2H, q, J = 7.1 Hz), 6.98 (1H, d, J = 8.6 Hz), 7.56 (2H, d, J = 8.4
29 Hz), 7.64 (1H, dd, J = 2.2, 8.6 Hz), 7.93 (1H, d, J = 2.2 Hz), 8.02 (2H,
30 d, J = 8.4 Hz).

1 4-[(3'-Acetyl-4'-methoxy)phenylethynyl]benzoic acid (Compound 2)

2 To a solution of 102.5 mg (0.3 mmol) of ethyl 4-[(3'-acetyl-4'-
3 methoxy)phenylethynyl]benzoate (**Compound 1**) in 15 mL of
4 tetrahydrofuran was added 3.2 mL (3.2 mmol) of LiOH solution (1M in
5 water). The reaction mixture was allowed to stir at ambient
6 temperature for 3 days, concentrated *in vacuo*, and extracted between
7 hexane and water. The layers were separated and the aqueous phase
8 was diluted with ethyl ether, cooled to 0 °C in an ice bath and acidified
9 with 1N H₂SO₄ (aq.) solution to pH 3-4. The solution was diluted with
10 brine and the organic phase was separated. The organic phase was
11 dried over Na₂SO₄, filtered and concentrated *in vacuo* to give the title
12 compound as a white solid.

13 PMR (DMSO-d₆): δ 2.54 (3H, s), 3.93 (3H, s), 7.25 (1H, d, J = 9 Hz),
14 7.65 (2H, d, J = approximately 8 Hz), 7.73-7.78 (2H, m), 7.95 (2H, d, J
15 = approximately 8 Hz).

16 Ethyl 4-[[4'-methoxymethoxy-3'-(4''-
17 methyl)benzoyl]phenylethynyl]benzoate (Compound 3)

18 Employing the same general procedure as for the preparation of
19 ethyl 4-[(3'-acetyl-4'-methoxy)phenylethynyl]benzoate (**Compound 1**), 44
20 mg (0.2 mmol) of 5-ethynyl-2-methoxymethoxy-4'-methylbenzophenone
21 (**Compound G1**) was converted into the title compound using 46 mg (0.2
22 mmol) of ethyl 4-iodobenzoate (**Compound A**), 22 mg (0.03 mmol) of
23 bis(triphenylphosphine)palladium (II) chloride, 6 mg (0.03 mmol) of
24 cuprous iodide and 6 mL of triethylamine. Purification by flash
25 chromatography (silica, 10-20% ethyl acetate in hexane) gave the title
26 compound as a yellow solid.

27 PMR (CDCl₃): δ 1.40 (3H, t, J = 7.1 Hz), 2.42 (3H, s), 3.33 (3H, s),
28 4.38 (2H, q, J = 7.1 Hz), 5.10 (2H, s), 7.22 (1H, d, J = 8.6 Hz), 7.25
29 (2H, d, J = 8.2 Hz), 7.52-7.58 (3H, m), 7.61 (1H, dd, J = 2.1, 8.6 Hz),

1 7.74 (2H, d, J = 8.3 Hz), 8.01 (2H, d, J = 8.3 Hz).

2 Ethyl 4-[[4'-hydroxy-3'-(4''-methyl)benzoyl]phenylethynyl]benzoate

3 (Compound 4)

4 To a solution of 34 mg (0.08 mmol) of ethyl 4-[[4'-
5 methoxymethoxy-3'-(4''-methyl)benzoyl]phenylethynyl]benzoate
6 (Compound 3) in 3 mL of ethanol (under a blanket of argon) was
7 added 3 drops of c. HCl via pipet. The reaction mixture was heated to
8 reflux in an oil bath (95 °C) for 35 minutes, cooled to ambient
9 temperature and concentrated *in vacuo*. The residue was extracted and
10 partitioned between ethyl acetate and sat. NaHCO₃ (aq.) solution. The
11 layers were separated and the organic phase was washed with water and
12 brine, dried over MgSO₄, filtered and concentrated *in vacuo* to a yellow
13 solid. Purification by flash chromatography (silica, 10% ethyl acetate in
14 hexane) gave the title compound as a yellow solid.

15 PMR (CDCl₃): δ 1.41 (3H, t, J = 7.1 Hz), 2.48 (3H, s), 4.39 (2H, q, J
16 = 7.1 Hz), 5.10 (2H, s), 7.09 (1H, d, J = 8.7 Hz), 7.36 (2H, d, J = 8.0
17 Hz), 7.54 (2H, d, J = 8.5 Hz), 7.63-7.69 (3H, m), 7.83 (1H, d, J = 2.1
18 Hz), 8.01 (2H, d, J = 8.5 Hz), 12.22 (1H, s).

19 4-[[4'-hydroxy-3'-(4''-methyl)benzoyl]phenylethynyl]benzoic acid

20 (Compound 5)

21 To a solution of 16.5 mg (0.04 mmol) of ethyl 4-[[4'-hydroxy-3'-
22 (4''-methyl)benzoyl]phenylethynyl]benzoate (Compound 4) in 2 mL of
23 ethanol and 0.4 mL of tetrahydrofuran (under a blanket of argon) was
24 added 0.4 mL (0.4 mmol) of NaOH solution (1M in water). The yellow
25 solution was stirred at ambient temperature for 20 hours, concentrated
26 *in vacuo*, acidified with 0.6 mL of 1N (aq) H₂SO₄ solution and then
27 extracted between ethyl ether and brine. The layers were separated and
28 the organic phase was dried over MgSO₄, filtered and concentrated *in*
29 *vacuo* to a yellow solid. Recrystallization from methanol gave the title

1 compound as a yellow needles.

2 PMR (CDCl₃): δ 2.48 (3H, s), 5.10 (2H, s), 7.09 (1H, d, J = 8.7 Hz),
3 7.37 (2H, d, J = 8.1 Hz), 7.57 (2H, d, J = 8.4 Hz), 7.63-7.69 (3H, m),
4 7.84 (1H, d, J = 2.1 Hz), 8.06 (2H, d, J = 8.4 Hz), 12.23 (1H, s).

5 Ethyl 4-[[4'-acetoxy-3'-(1-*p*-tolyl)vinyl]phenylethynyl]benzoate

6 (Compound 6)

7 Employing the same general procedure as for the preparation of
8 ethyl 4-[(3'-acetyl-4'-methoxy)phenylethynyl]benzoate (Compound 1),
9 128 mg (0.5 mmol) of 4-ethynyl-2-[(1-*p*-tolyl)vinyl]phenyl acetate
10 (Compound H1) was converted into the title compound using 128 mg
11 (0.5 mmol) of ethyl 4-iodobenzoate (Compound A), 65 mg (0.09 mmol)
12 of bis(triphenylphosphine)palladium (II) chloride, 17 mg (0.09 mmol) of
13 cuprous iodide and 6 mL of triethylamine. Purification by flash
14 chromatography (silica, 10% ethyl acetate in hexane) gave the title
15 compound as a clear, colorless oil which solidified upon standing to a
16 waxy, white solid.

17 PMR (CDCl₃): δ 1.41 (3H, t, J = 7.1 Hz), 1.81 (3H, s), 2.35 (3H, s),
18 4.39 (2H, q, J = 7.1 Hz), 5.33 (1H, br s), 5.66 (1H, br s), 7.07-7.19 (5H,
19 m), 7.52-7.60 (4H, m), 8.03 (2H, d, J = 8.1 Hz).

20 Ethyl 4-[[4'-methoxymethoxy-3'-(1-*p*-tolyl)vinyl]phenylethynyl]benzoate

21 (Compound 7)

22 Employing the same general procedure as for the preparation of
23 ethyl 4-[(3'-acetyl-4'-methoxy)phenylethynyl]benzoate (Compound 1), 87
24 mg (0.3 mmol) of 4-ethynyl-1-methoxymethoxy-2-[(1-*p*-
25 tolyl)vinyl]benzene (Compound J1) was converted into the title
26 compound using 94 mg (0.3 mmol) of ethyl 4-iodobenzoate (Compound
27 A), 42 mg (0.06 mmol) of bis(triphenylphosphine)palladium (II)
28 chloride, 12 mg (0.06 mmol) of cuprous iodide and 6 mL of
29 triethylamine. Purification by flash chromatography (silica, 5% ethyl

1 acetate in hexane) gave the title compound as a white solid.
2 PMR (CDCl₃): δ 1.40 (3H, t, J = 7.1 Hz), 2.33 (3H, s), 3.19 (3H, s),
3 4.39 (2H, q, J = 7.1 Hz), 5.00 (2H, s), 5.30 (1H, br s), 5.72 (1H, br s),
4 7.06-7.12 (3H, m), 7.20 (2H, d, J = 8.2 Hz), 7.46-7.52 (2H, m), 7.57
5 (2H, d, J = 8.4 Hz), 8.02 (2H, d, J = 8.4 Hz).
6 4-[[4'-Hydroxy-3'-(1-p-tolyl)vinyl]phenylethynyl]benzoic acid (Compound
7 8)

8 Employing the same general procedure as for the preparation of
9 4-[[4'-hydroxy-3'-(4''-methyl)benzoyl]phenylethynyl]benzoic acid
10 (Compound 5), 84 mg (0.2 mmol) of ethyl 4-[[4'-acetoxy-3'-(1-p-
11 tolyl)vinyl]phenylethynyl]benzoate (Compound 6) was converted into the
12 title compound (pale yellow solid) using 2.0 mL (2.0 mmol) of NaOH
13 solution (1M in water), 8 mL of ethanol and 1 mL of tetrahydrofuran.
14 PMR (Aceton-d₆): δ 2.31 (3H, s), 5.32 (1H, d, J = 1.4 Hz), 5.77 (1H,
15 br s), 6.96 (1H, d, J = 8.3 Hz), 7.12 (2H, d, J = 7.9 Hz), 7.23 (2H, d, J
16 = 8.3 Hz), 7.35 (1H, d, J = 2.1 Hz), 7.44 (1H, dd, J = 2.1, 8.4 Hz), 7.62
17 (2H, d, J = 8.4 Hz), 8.03 (2H, d, J = 8.4 Hz), 8.52 (1H, br s).
18 4-[[4'-methoxymethoxy-3'-(1-p-tolyl)vinyl]phenylethynyl]benzoic acid
19 (Compound 9)

20 Employing the same general procedure as for the preparation of
21 4-[[4'-hydroxy-3'-(4''-methyl)benzoyl]phenylethynyl]benzoic acid
22 (Compound 5), 18 mg (0.04 mmol) of ethyl 4-[[4'-methoxymethoxy-3'-(1-
23 p-tolyl)vinyl]phenylethynyl]benzoate (Compound 7) was converted into
24 the title compound using 0.4 mL (0.4 mmol) of NaOH solution (1M in
25 water), 2 mL of ethanol and 0.8 mL of tetrahydrofuran.
26 PMR (Aceton-d₆): δ 2.30 (3H, s), 3.14 (3H, s), 5.05 (2H, s), 5.27 (1H,
27 br s), 5.73 (1H, br s), 7.12 (2H, d, J = 7.9 Hz), 7.15-7.22 (3H, m), 7.43
28 (1H, d, J = 2.1 Hz), 7.56 (1H, dd, J = 2.1, 8.4 Hz), 7.65 (2H, d, J = 8.3
29 Hz), 8.05 (2H, d, J = 8.3 Hz).

1 Ethyl 4-[[4'-methoxy-3'-(1-hydroxy-1-*p*-tolyl)ethyl]phenylethynyl]benzoate
2 **(Compound 10)**

3 To a cold solution (-78 °C) of 132.5 mg (0.4 mmol) of ethyl 4-[(3'-
4 acetyl-4'-methoxy)phenylethynyl]benzoate (**Compound 1**) in 5 mL of
5 tetrahydrofuran (under a blanket of argon) was added 0.6 mL (0.6
6 mmol) of *p*-tolylmagnesium bromide (1M in ethyl ether). The clear,
7 colorless solution immediately turned orange-reddish in color. The -78
8 °C bath was removed, the reaction mixture was allowed to slowly warm
9 on its own to ambient temperature, stirred at ambient temperature for
10 2.25 hours, and concentrated *in vacuo*. Purification by flash
11 chromatography (silica, 10% ethyl acetate in hexane) gave the title
12 compound as a white solid.

13 PMR (CDCl₃): δ 1.41 (3H, t, J = 7.1 Hz), 1.85 (3H, s), 2.31 (3H, s),
14 3.64 (3H, s), 4.39 (2H, q, J = 7.1 Hz), 4.43 (1H, s), 6.86 (1H, d, J = 8.5
15 Hz), 7.07 (2H, d, J = 8.1 Hz), 7.19 (2H, d, J = 8.1 Hz), 7.50 (1H, dd, J
16 = 2.1, 8.5 Hz), 7.59 (2H, d, J = 8.4 Hz), 7.67 (1H, d, J = 2.1 Hz), 8.03
17 (2H, d, J = 8.4 Hz).

18 Ethyl 4-[[4'-methoxy-3'-(1-*p*-tolyl)vinyl]phenylethynyl]benzoate
19 **(Compound 11)**

20 To a solution of 40.5 mg (0.1 mmol) of ethyl 4-[[4'-methoxy-3'-(1-
21 hydroxy-1-*p*-tolyl)ethyl]phenylethynyl]benzoate (**Compound 10**) in 2 mL
22 of toluene (under a blanket of argon) was added approximately 8 mg of
23 *p*-toluene sulfonic acid monohydrate. The reaction mixture was heated
24 at 70 °C for 20 minutes, cooled to ambient temperature and then
25 concentrated *in vacuo*. Purification by flash chromatography (silica,
26 10% ethyl acetate in hexane) gave the title compound as a white solid.
27 PMR (CDCl₃): δ 1.40 (3H, t, J = 7.1 Hz), 2.34 (3H, s), 3.68 (3H, s),
28 4.38 (2H, q, J = 7.1 Hz), 5.28 (1H, d, J = 1.3 Hz), 5.73 (1H, br s), 6.89
29 (1H, d, J = 8.6 Hz), 7.09 (2H, d, J = 8.2 Hz), 7.19 (2H, d, J = 8.2 Hz),

1 7.45 (1H, d, J = 2.1 Hz), 7.50-7.58 (3H, m), 8.01 (2H, d, J = 8.5 Hz).

2 4-[[4'-Methoxy-3'-(1-p-tolyl)vinyl]phenylethynyl]benzoic acid (Compound
3 **12)**

4 Employing the same general procedure as for the preparation of
5 4-[[4'-hydroxy-3'-(4''-methyl)benzoyl]phenylethynyl]benzoic acid
6 (**Compound 5**), 25 mg (0.06 mmol) of ethyl 4-[[4'-methoxy-3'-(1-p-
7 tolyl)vinyl]phenylethynyl]benzoate (**Compound 11**) was converted into
8 the title compound (white solid) using 0.6 mL (0.6 mmol) of NaOH
9 solution (1M in water), 2.5 mL of ethanol and 0.5 mL of
10 tetrahydrofuran.

11 PMR (Aceton-d₆): δ 2.30 (3H, s), 3.69 (3H, s), 5.24 (1H, d, J = 1.5
12 Hz), 5.72 (1H, br s), 7.08-7.16 (3H, m), 7.17 (2H, d, J = 8.4 Hz), 7.39
13 (1H, d, J = 2.2 Hz), 7.58 (1H, dd, J = 2.2, 8.7 Hz), 7.64 (2H, d, J = 8.3
14 Hz), 8.04 (2H, d, J = 8.3 Hz).

15 4-[[4'-methoxymethoxy-3'-(4''-methyl)benzoyl]phenylethynyl]benzoic acid
16 (**Compound 13**)

17 Employing the same general procedure as for the preparation of
18 4-[[4'-hydroxy-3'-(4''-methyl)benzoyl]phenylethynyl]benzoic acid
19 (**Compound 5**), 14 mg (0.03 mmol) of ethyl 4-[[4'-methoxymethoxy-3'-
20 (4''-methyl)benzoyl]phenylethynyl]benzoate (**Compound 3**) was
21 converted into the title compound (white solid) using 0.3 mL (0.3
22 mmol) of NaOH solution (1M in water), 3.2 mL of ethanol and 0.2 mL
23 of tetrahydrofuran. The white solid obtained was rinsed with 2 mL of
24 20% ethyl acetate in hexane to give the title compound.

25 PMR (Aceton-d₆): δ 2.41 (3H, s), 3.27 (3H, s), 5.16 (2H, s), 7.31-7.38
26 (3H, m), 7.53 (1H, d, J = 2.1 Hz), 7.64-7.73 (5H, m), 8.05 (2H, d, J =
27 8.4 Hz).

28 Ethyl 4-[(3'-acetyl-4'-methoxymethoxy)phenylethynyl]benzoate
29 (**Compound 14**)

1 5-bromo-2-methoxymethoxyacetophenone (**Compound P**) was
2 converted into the title compound in a step-wise set of reaction
3 conditions resulting in the final isolation of the title compound as a
4 white solid. Employing the same general procedure as for the
5 preparation of 2-methoxy-5-trimethylsilanylethynyl acetophenone
6 (**Compound W**), 598 mg (2.3 mmol) of 5-bromo-2-
7 methoxymethoxyacetophenone (**Compound P**) was converted into 2-
8 methoxymethoxy-5-trimethylsilanylethynyl acetophenone using 405 mg
9 (0.6 mmol) of bis(triphenylphosphine)palladium (II) chloride, 90 mg
10 (0.5 mmol) of cuprous iodide, 2.5 mL (2.7 g, 27.6 mmol) of
11 trimethylsilyl acetylene and 6 mL of triethylamine (heated at 75 °C).
12 The reaction proceeded slowly and after 3 days of heating, an additional
13 2.5 mL (27.6 mmol) of trimethylsilyl acetylene and 406 mg (0.6 mmol)
14 of bis(triphenylphosphine)palladium (II) chloride was added to the
15 sealed tube (careful to keep the contents under a positive stream of
16 argon) and the resultant mixture heated for 3 additional days (6 days
17 total). Purification by flash chromatography (silica, 5-10% ethyl acetate
18 in hexane) gave crude 2-methoxymethoxy-5-trimethylsilanylethynyl
19 acetophenone. Employing the same general procedure as for the
20 preparation of 5-ethynyl-2-methoxyacetophenone (**Compound E1**), the
21 crude TMS-acetylene derivative was then converted to 5-ethynyl-2-
22 methoxymethoxy acetophenone using 104 mg (0.75 mmol) of K₂CO₃ and
23 10 mL of methanol, and was isolated by flash chromatography (silica,
24 5% ethyl acetate in hexane) in >80% purity. Employing the same
25 general procedure as for the preparation of ethyl 4-[(3'-acetyl-4'-
26 methoxy)phenylethynyl]benzoate (**Compound 1**), the crude acetylene
27 was converted into the title compound using 277 mg (1.0 mmol) of ethyl
28 4-iodobenzoate (**Compound A**), 137 mg (0.2 mmol) of
29 bis(triphenylphosphine)palladium (II) chloride, 36 mg (0.2 mmol) of
30 cuprous iodide and 6 mL of triethylamine. Purification by flash

1 chromatography (silica, 10-20% ethyl acetate in hexane) gave the title
2 compound as a white solid.

3 PMR (CDCl₃): δ 1.41 (3H, t, J = 7.2 Hz), 2.65 (3H, s), 3.53 (3H, s),
4 4.37 (2H, t, J = 7.2 Hz), 4.38 (2H, q, J = 7.1 Hz), 5.32 (2H, s), 7.20
5 (1H, d, J = 8.7 Hz), 7.56 (2H, d, J = 8.4 Hz), 7.60 (1H, dd, J = 2.2, 8.7
6 Hz), 7.91 (1H, d, J = 2.2 Hz), 8.03 (2H, d, J = 8.4 Hz).

7 Ethyl 4-[[4'-heptyloxy-3'-(1-p-tolyl)vinyl]phenylethynyl]benzoate
8 (Compound 15)

9 Ethyl 4-[(3'-acetyl-4'-methoxymethoxy)phenylethynyl]benzoate
10 (Compound 14) was converted in a step-wise set of reaction conditions
11 resulting in the final isolation of the title compound as a white solid.
12 Employing the same general procedure as for the preparation of ethyl
13 4-[[4'-methoxy-3'-(1-hydroxy-1-p-tolyl)ethyl]phenylethynyl]benzoate
14 (Compound 10), 0.4 mL (0.4 mmol) of p-tolylmagnesium bromide (1M
15 in ethyl ether) was used to convert a solution of 100 mg (0.3 mmol) of
16 ethyl 4-[(3'-acetyl-4'-methoxymethoxy)phenylethynyl]benzoate
17 (Compound 14) in 3 mL of tetrahydrofuran into a 3:2 mixture of ethyl
18 4-[[4'-methoxymethoxy-3'-(1-hydroxy-1-p-
19 tolyl)ethyl]phenylethynyl]benzoate and ethyl 4-[[4'-hydroxy-3'-(1-hydroxy-
20 1-p-tolyl)ethyl]phenylethynyl]benzoate following flash chromatography
21 (silica, 15% ethyl acetate in hexane). To a yellow solution of the crude
22 mixture in 3 mL of ethanol (under a blanket of argon) was added 1 mL
23 of 10% HCl (aq.) solution. The resultant reaction mixture was stirred
24 at ambient temperature for 6.5 hours, heated at 55 °C overnight and
25 quenched with water followed by sat. NaHCO₃ (aq.) solution. The
26 resultant mixture was extracted into ethyl acetate and the layers were
27 separated. The organic phase was washed with water and brine, dried
28 over MgSO₄, filtered and concentrated *in vacuo* to a yellow residue.
29 Purification by flash chromatography (silica, 50% ethyl acetate in

1 hexane) gave crude ethyl 4-[[4'-hydroxy-3'-(1-*p*-
2 tolyl)vinyl]phenylethynyl]benzoate. The crude material was converted
3 into the title compound using the same general procedure as for the
4 preparation of 4-bromo-1-methoxy-3-methylbenzene (**Compound E**),
5 except using 30 mg (0.2 mmol) of potassium carbonate, 0.025 mL (32
6 mg, 0.1 mmol) of *n*-heptyl iodide and 5 mL of acetone. After stirring at
7 ambient temperature for 22 hours, the reaction mixture was
8 concentrated *in vacuo* and purified by flash chromatography (silica, 5%
9 ethyl acetate in hexane) to give the title compound as a white solid.
10 PMR (CDCl₃): δ 0.87 (3H, t, J = 7.3 Hz), 0.95-1.02 (2H, m), 1.08-1.30
11 (6H, m), 1.34-1.40 (5H, m), 2.33 (3H, s), 3.80 (2H, t, J = 7.1 Hz), 4.38
12 (2H, q, J = 7.1 Hz), 5.28 (1H, d, J = 1.5 Hz), 5.63 (1H, d, J = 1.5 Hz),
13 6.83 (1H, d, J = 9.0 Hz), 7.07 (2H, d, J = 8.2 Hz), 7.17 (2H, d, J = 8.2
14 Hz), 7.47-7.52 (2H, m), 7.56 (2H, d, J = 8.4 Hz), 8.01 (2H, d, J = 8.4
15 Hz).

16 4-[[4'-Heptyloxy-3'-(1-*p*-tolyl)vinyl]phenylethynyl]benzoic acid
17 (**Compound 16**)

18 Employing the same general procedure as for the preparation of
19 4-[[4'-hydroxy-3'-(4''-methyl)benzoyl]phenylethynyl]benzoic acid
20 (**Compound 5**), 8.5 mg (0.02 mmol) of ethyl 4-[[4'-heptyloxy-3'-(1-*p*-
21 tolyl)vinyl]phenylethynyl]benzoate (**Compound 15**) was converted into
22 the title compound (white solid) using 0.2 mL (0.2 mmol) of NaOH
23 solution (1M in water), 0.8 mL of ethanol and 0.2 mL of
24 tetrahydrofuran. The white solid obtained was rinsed with 1 mL of 10%
25 ethyl acetate in hexane to give the title compound.
26 PMR (CDCl₃): δ 0.86 (3H, t, J = 7.2 Hz), 0.90-1.45 (10H, m), 2.31
27 (3H, s), 3.87 (2H, t, J = 6.1 Hz), 5.26 (1H, br s), 5.65 (1H, br s), 7.03
28 (1H, d, J = 8.5 Hz), 7.11 (2H, d, J = 8.3 Hz), 7.16 (2H, d, J = 8.3 Hz),
29 7.45 (1H, d, J = 2.1 Hz), 7.56 (1H, dd, J = 2.1, 8.5 Hz), 7.65 (2H, d, J

1 = 8.4 Hz), 8.05 (2H, d, J = 8.4 Hz).

2 Ethyl 4-[(3'-acetyl)phenylethynyl]benzoate (Compound 17)

3 Employing the same general procedure as for the preparation of
4 ethyl 4-[(3'-acetyl-4'-methoxy)phenylethynyl]benzoate (Compound 1),
5 600 mg (4.2 mmol) of 3-ethynylacetophenone (Compound K1) was
6 converted into the title compound using 1.3 g (4.6 mmol) of ethyl 4-
7 iodobenzoate (Compound A), 585 mg (0.8 mmol) of
8 bis(triphenylphosphine)palladium (II) chloride, 156 mg (0.8 mmol) of
9 cuprous iodide and 16 mL of triethylamine. Purification by flash
10 chromatography (silica, 10% ethyl acetate in hexane) gave the title
11 compound as a yellow solid.

12 PMR (CDCl₃): δ 1.40 (3H, t, J = 7.1 Hz), 2.62 (3H, s), 4.38 (2H, q, J
13 = 7.1 Hz), 7.44-7.51 (2H, m), 7.59 (2H, d, J = 8.3 Hz), 7.69-7.75 (1H,
14 m), 7.91-7.97 (1H, m), 8.03 (2H, d, J = 8.3 Hz), 8.10-8.14 (1H, m).

15 Ethyl 4-[[3'-(1-hydroxy-1-*p*-tolyl)ethyl]phenylethynyl]benzoate
16 (Compound 18)

17 To a cold solution (0 °C) of 112 mg (0.4 mmol) of ethyl 4-[(3'-
18 acetyl)phenylethynyl]benzoate (Compound 17) in 3 mL of
19 tetrahydrofuran (under a blanket of argon) was added 0.6 mL (0.6
20 mmol) of *p*-tolylmagnesium bromide (1M in ethyl ether). The solution
21 immediately turned orange and was stirred at 0 °C for 3 hours at which
22 time an additional 0.3 mL (0.3 mmol) of *p*-tolylmagnesium bromide (1M
23 in ethyl ether) was added. The reaction mixture was stirred at 0 °C for
24 an additonal 15 minutes, quenched by adding sat. NH₄Cl (aq.) solution
25 and extracted into ethyl acetate. The layers were separated and the
26 organic phase was washed with water and brine, dried over MgSO₄,
27 filtered and concentrated *in vacuo* to a yellow oil. Purification by flash
28 chromatography (silica, 5-10% ethyl acetate in hexane) gave the title
29 compound as a clear film.

1 PMR (CDCl₃): δ 1.40 (3H, t, J = 7.1 Hz), 1.95 (3H, s), 2.24 (1H, s),
2 2.33 (3H, s), 4.38 (2H, q, J = 7.1 Hz), 7.14 (2H, d, J = 7.9 Hz), 7.25-
3 7.33 (3H, m), 7.39-7.43 (2H, m), 7.56 (2H, d, J = 8.5 Hz), 7.63-7.65
4 (1H, m), 8.01 (2H, d, J = 8.5 Hz).

5 Ethyl 4-[[3'-(1-*p*-tolyl)vinyl]phenylethynyl]benzoate (Compound 19)

6 Employing the same general procedure as for the preparation of
7 ethyl 4-[[4'-methoxy-3'-(1-*p*-tolyl)vinyl]phenylethynyl]benzoate
8 (Compound 11), 47 mg (0.1 mmol) of ethyl 4-[[3'-(1-hydroxy-1-*p*-
9 tolyl)ethyl]phenylethynyl]benzoate (Compound 18) was converted into
10 the title compound using 8.5 mg of *p*-toluene sulfonic acid monohydrate
11 and 2 mL of toluene. Purification by flash chromatography (silica, 10%
12 ethyl acetate in hexane) gave the title compound as a white solid.

13 PMR (CDCl₃): δ 1.40 (3H, t, J = 7.1 Hz), 2.37 (3H, s), 4.38 (2H, q, J
14 = 7.1 Hz), 5.43 (1H, d, J = 1.1 Hz), 5.47 (1H, br s), 7.16 (2H, d, J =
15 8.2 Hz), 7.23 (2H, d, J = 8.2 Hz), 7.32-7.35 (2H, m), 7.47-7.51 (1H, m),
16 7.53-7.60 (3H, m), 8.01 (2H, d, J = 8.4 Hz).

17 4-[[3'-(1-*p*-Tolyl)vinyl]phenylethynyl]benzoic acid (Compound 20)

18 Employing the same general procedure as for the preparation of
19 4-[[4'-hydroxy-3'-(4''-methyl)benzoyl]phenylethynyl]benzoic acid
20 (Compound 5), 36 mg (0.1 mmol) of ethyl 4-[[3'-(1-*p*-
21 tolyl)vinyl]phenylethynyl]benzoate (Compound 19) was converted into
22 the title compound (white solid) using 1.0 mL (1.0 mmol) of NaOH
23 solution (1M in water), 4.0 mL of ethanol and 0.5 mL of
24 tetrahydrofuran.

25 PMR (DMSO-*d*₆): δ 2.33 (3H, s), 5.50-5.54 (2H, m), 7.19-7.23 (4H, br
26 s), (1H, d, J = 1.1 Hz), 5.47 (1H, br s), 7.19-7.22 (4H, m), 7.36-7.40
27 (1H, m), 7.44-7.50 (2H, m), 7.56-7.61 (1H, m), 7.67 (2H, d, J = 8.5 Hz),
28 7.96 (2H, d, J = 8.5 Hz).

29 Ethyl 4-[[4'-methoxy-3'-(4''-methyl)benzoyl]phenylethynyl]benzoate

1 (Compound 21)

2 Employing the same general procedure as for the preparation of
3 ethyl 4-[(3'-acetyl-4'-methoxymethoxy)phenylethynyl]benzoate
4 (Compound 14), a crude sample of 5-bromo-2-methoxy-4'-
5 methylbenzophenone (Compound H) was converted into the title
6 compound (white needles) in a series of reactions. A crude sample
7 (approximately 50% purity) of approximately 195 mg (0.6 mmol) of 5-
8 bromo-2-methoxy-4'-methylbenzophenone (Compound H) was converted
9 into crude 2-methoxy-5-trimethylsilanylethynyl-4'-methylbenzophenone
10 using 112 mg (0.2 mmol) of bis(triphenylphosphine)palladium (II)
11 chloride, 30 mg (0.2 mmol) of cuprous iodide, 0.7 mL (0.6 g, 6.4 mmol)
12 of trimethylsilyl acetylene 10 mL of triethylamine (heated at 75 °C).
13 After purification by flash chromatography (silica, 3% ethyl acetate in
14 hexane), the crude TMS-acetylene derivative obtained was converted
15 into crude 5-ethynyl-2-methoxy-4'-methylbenzophenone using 10 mg
16 (0.07 mmol) of K₂CO₃ and 10 mL of methanol. Purification by flash
17 chromatography (silica, 5% ethyl acetate in hexane) gave the acetylene
18 derivative in >90% purity. The crude acetylene was converted into the
19 title compound using 86 mg (0.3 mmol) of ethyl 4-iodobenzoate
20 (Compound A), 50 mg (0.07 mmol) of bis(triphenylphosphine)palladium
21 (II) chloride, 13 mg (0.07 mmol) of cuprous iodide and 6 mL of
22 triethylamine. Purification by flash chromatography (silica, 15% ethyl
23 acetate in hexane) followed by recrystallization from methanol gave the
24 title compound as white needles.

25 PMR (CDCl₃): δ 1.40 (3H, t, J = 7.1 Hz), 2.43 (3H, s), 3.78 (3H, s),
26 6.99 (1H, d, J = 8.7 Hz), 7.25 (2H, d, J = ~ 8 Hz), 7.52 (1H, d, J =
27 2.1 Hz), 7.54 (2H, d, J = 8.4 Hz), 7.64 (1H, dd, J = 2.1, 8.7 Hz), 7.73
28 (2H, d, J = 8.3 Hz), 8.01 (2H, d, J = 8.3 Hz).

29 4-[[4'-methoxy-3'-(4''-methyl)benzoyl]phenylethynyl]benzoic acid

1 (Compound 22)

2 Employing the same general procedure as for the preparation 4-
3 [(3'-acetyl-4'-methoxy)phenylethynyl]benzoic acid (Compound 2), 46 mg
4 (0.1 mmol) ethyl 4-[[4'-methoxy-3'-(4''-
5 methyl)benzoyl]phenylethynyl]benzoate (Compound 21) was converted
6 into the title compound (white solid) using 1.2 mL (1.2 mmol) of LiOH
7 solution (1M in water) and 5 mL of tetrahydrofuran. The white solid
8 obtained was rinsed with 3 mL of 5% ethyl acetate in hexane to give the
9 title compound.

10 PMR (Aceton-d₆): δ 2.38 (3H, s), 3.73 (3H, s), 7.26 (1H, d, J = 8.8
11 Hz), 7.33 (2H, d, J = 7.8 Hz), 7.50 (1H, d, J = 2.1 Hz), 7.59-7.65 (4H,
12 m), 7.60 (1H, dd, J = 2.1, 8.6 Hz), 7.94 (2H, d, J = 8.6 Hz).

13 Ethyl 4-[[4'-methoxymethoxy-2'-methyl-5'-(4''-
14 methyl)benzoyl]phenylethynyl]-2-fluoro-benzoate (Compound 23)

15 Employing the same general procedure as for the preparation of
16 ethyl 4-[(3'-acetyl-4'-methoxy)phenylethynyl]benzoate (Compound 1),
17 123 mg (0.4 mmol) of 5-ethynyl-4-methyl-2-methoxymethoxy-4'-
18 methylbenzophenone (Compound L1) was converted into the title
19 compound using 136 mg (0.5 mmol) of ethyl 2-fluoro-4-iodobenzoate
20 (Compound C), 74 mg (0.1 mmol) of bis(triphenylphosphine)palladium
21 (II) chloride, 20 mg (0.1 mmol) of cuprous iodide and 5.0 mL of a 4:1
22 mixture of triethylamine:*N,N*-dimethylformamide. Purification by flash
23 chromatography (silica, 10% ethyl acetate in hexane) gave the title
24 compound as a yellow solid.

25 PMR (CDCl₃): δ 1.40 (3H, t, J = 7.1 Hz), 2.42 (3H, s), 2.56 (3H, s),
26 3.34 (3H, s), 4.40 (2H, q, J = 7.1 Hz), 5.09 (2H, s), 7.11 (1H, s), 7.20-
27 7.35 (4H, m), 7.51 (1H, s), 7.73 (2H, d, J = 8.2 Hz), 7.90 (1H, t, J = 7.9
28 Hz, J (C-F) = 7.9 Hz).

29 Ethyl 4-[[4'-hydroxy-2'-methyl-5'-(4''-methyl)benzoyl]phenylethynyl]-2-

1 fluoro-benzoate (Compound 24)

2 Employing the same general procedure as for the preparation of
3 ethyl 4-[[4'-hydroxy-3'-(4''-methyl)benzoyl]phenylethynyl]benzoate
4 (Compound 4), 13 mg (0.03 mmol) of ethyl 4-[[4'-methoxymethoxy-2'-
5 methyl-5'-(4''-methyl)benzoyl]phenylethynyl]-2-fluoro-benzoate
6 (Compound 23) was converted into the title compound (yellow oil)
7 using 1 drop of c. HCl and and 2 mL of ethanol. Purification by flash
8 chromatography (silica, 10% ethyl acetate in hexane) gave the title
9 compound as a yellow oil.

10 PMR (CDCl₃): δ 1.40 (3H, t, J = 7.1 Hz), 2.47 (3H, s), 2.53 (3H, s),
11 4.39 (2H, q, J = 7.1 Hz), 6.97 (1H, s), 7.22 (1H, dd, J = 1.5 Hz, J (C-F)
12 = 9.1 Hz), 7.31 (1H, dd, J = 1.5, 8.1 Hz), 7.35 (2H, d, J = 8.1 Hz), 7.62
13 (2H, d, J = 8.1 Hz), 7.78 (1H, s), 7.89 (1H, t, J = 7.9 Hz, J (C-F) = 7.8
14 Hz), 12.27 (1H, s).

15 4-[[4'-Hydroxy-2'-methyl-5'-(4''-methyl)benzoyl]phenylethynyl]-2-fluoro-
16 benzoic acid (Compound 25)

17 Employing the same general procedure as for the preparation of
18 4-[[4'-hydroxy-3'-(4''-methyl)benzoyl]phenylethynyl]benzoic acid
19 (Compound 5), 10 mg (0.025 mmol) of
20 ethyl 4-[[4'-hydroxy-2'-methyl-5'-(4''-methyl)benzoyl]phenylethynyl]-2-
21 fluoro-benzoate (Compound 24) was converted into the title compound
22 (yellow crystals) using 0.25 mL (0.25 mmol) of NaOH solution (1M in
23 water), 1.0 mL of ethanol and 0.2 mL of tetrahydrofuran.
24 Recrystallization from acetonitrile gave the title compound as yellow
25 needles.

26 PMR (Aceton-d₆): δ 2.46 (3H, s), 2.57 (3H, s), 7.04 (1H, s), 7.37-7.46
27 (4H, m) 7.80 (1H, s), 7.62-7.70 (2H, d, J = 8.3 Hz), 7.96 (1H, t, J = 7.5
28 Hz, J (C-F) = 8.0 Hz).

29 Ethyl 4-[[4'-isopropoxy-3'-(1-p-tolyl)vinyl]phenylethynyl]benzoate

1 (Compound 26)

2 Employing the same general procedure as for the preparation of
3 ethyl 4-[(3'-acetyl-4'-methoxy)phenylethynyl]benzoate (Compound 1), 20
4 mg (0.07 mmol) 4-ethynyl-1-isopropoxy-2-[(1-*p*-tolyl)vinyl]benzene
5 (Compound M1) was converted into the title compound using 24 mg
6 (0.09 mmol) of ethyl 4-iodobenzoate (Compound A), 13 mg (0.02 mmol)
7 of bis(triphenylphosphine)palladium (II) chloride, 4 mg (0.02 mmol) of
8 cuprous iodide and 3.5 mL of triethylamine. Purification by flash
9 chromatography (silica, 5% ethyl acetate in hexane) gave the title
10 compound as a white solid.

11 PMR (CDCl₃): δ 1.00 (6H, d, J = 6.0 Hz), 1.40 (3H, t, J = 7.0 Hz),
12 2.34 (3H, s), 4.32-4.44 (3H, m), 5.29 (1H, d, J = 1.4 Hz), 5.60 (1H, br
13 s), 6.85 (1H, d, J = 8.2 Hz), 7.08 (2H, d, J = 8.2 Hz), 7.16 (2H, d, J =
14 8.2 Hz), 7.45-7.52 (2H, m), 7.56 (2H, d, J = 8.4 Hz), 8.01 (2H, d, J =
15 8.4 Hz).

16 Ethyl 4-[[4'-isopropoxy-3'-(1-*p*-tolyl)vinyl]phenylethynyl]-2-fluoro-
17 benzoate (Compound 27)

18 Employing the same general procedure as for the preparation of
19 ethyl 4-[(3'-acetyl-4'-methoxy)phenylethynyl]benzoate (Compound 1), 16
20 mg (0.06 mmol) 4-ethynyl-1-isopropoxy-2-[(1-*p*-tolyl)vinyl]benzene
21 (Compound M1) was converted into the title compound using 17.5 mg
22 (0.06 mmol) of ethyl 2-fluoro-4-iodobenzoate (Compound C), 10 mg
23 (0.015 mmol) of bis(triphenylphosphine)palladium (II) chloride, 3.2 mg
24 (0.02 mmol) of cuprous iodide and 3.5 mL of triethylamine.
25 Purification by flash chromatography (silica, 5% ethyl acetate in hexane)
26 gave the title compound as a yellow oil which later solidified to a yellow
27 solid.

28 PMR (CDCl₃): δ 1.00 (6H, d, J = 6.0 Hz), 1.40 (3H, t, J = 7.1 Hz),
29 2.34 (3H, s), 4.3-4.5 (3H, m), 5.28 (1H, d, J = 1.4 Hz), 5.60 (1H, d, J =

1 1.4 Hz), 6.85 (1H, d, J = 8.3 Hz), 7.08 (2H, d, J = 8.1 Hz), 7.15 (2H, d,
2 J = 8.1 Hz), 7.25 (1H, dd, J = 1.5 Hz, J (C-F) = 11.4 Hz), 7.31 (1H,
3 dd, J = 1.5, 8.1 Hz), 7.44-7.50 (2H, m), 7.90 (1H, t, J = 7.9 Hz, J (C-F)
4 = 7.8 Hz).

5 4-[[4'-Isopropoxy-3'-(1-p-tolyl)vinyl]phenylethynyl]benzoic acid

6 (Compound 28)

7 Employing the same general procedure as for the preparation of
8 4-[[4'-hydroxy-3'-(4''-methyl)benzoyl]phenylethynyl]benzoic acid
9 (Compound 5), 17 mg (0.04 mmol) of ethyl 4-[[4'-isopropoxy-3'-(1-p-
10 tolyl)vinyl]phenylethynyl]benzoate (Compound 26) was converted into
11 the title compound (white crystals) using 0.4 mL (0.4 mmol) of NaOH
12 solution (1M in water), 1.6 mL of ethanol and 0.4 mL of
13 tetrahydrofuran. Recrystallization from acetonitrile gave the title
14 compound as white crystals.

15 PMR (Aceton-d₆): δ 0.99 (6H, d, J = 6.0 Hz), 2.31 (3H, s), 4.54 (1H,
16 heptet, J = 6.0 Hz), 5.24 (1H, d, J = 1.5 Hz), 5.61 (1H, d, J = 1.5 Hz),
17 7.05 (1H, d, J = 8.5 Hz), 7.07-7.20 (4H, m), 7.43 (1H, d, J = 2.2 Hz),
18 7.54 (1H, dd, J = 2.2, 8.4 Hz), 7.64 (2H, d, J = 8.5 Hz), 8.04 (2H, d, J
19 = 8.5 Hz).

20 4-[[4'-Isopropoxy-3'-(1-p-tolyl)vinyl]phenylethynyl]-2-fluoro-benzoic acid

21 (Compound 29)

22 Employing the same general procedure as for the preparation of
23 4-[[4'-hydroxy-3'-(4''-methyl)benzoyl]phenylethynyl]benzoic acid
24 (Compound 5), 10 mg (0.02 mmol) of ethyl 4-[[4'-isopropoxy-3'-(1-p-
25 tolyl)vinyl]phenylethynyl]-2-fluoro-benzoate (Compound 27) was
26 converted into the title compound (white solid) using 0.2 mL (0.2
27 mmol) of NaOH solution (1M in water), 1.0 mL of ethanol and 0.2 mL
28 of tetrahydrofuran. The white solid obtained was rinsed with a small
29 amount of 5% ethyl acetate in hexane to give the title compound.

1 PMR (Aceton- d_6): δ 0.99 (6H, d, $J = 6.0$ Hz), 2.31 (3H, s), 4.55 (1H,
2 heptet, $J = 6.0$ Hz), 5.24 (1H, br s), 5.62 (1H, d, $J = 1.6$ Hz), 7.03-7.20
3 (5H, m), 7.36-7.60 (3H, m), 7.55 (1H, dd, $J = 2.2, 8.5$ Hz), 7.97 (1H, t, J
4 $= 8.0$ Hz, J (C-F) $= 7.8$ Hz).

5 Ethyl 4-[[4'-isopropoxy-3'-(1-*m*-tolyl)vinyl]phenylethynyl]benzoate
6 (Compound 30)

7 Employing the same general procedure as for the preparation of
8 ethyl 4-[(3'-acetyl-4'-methoxy)phenylethynyl]benzoate (Compound 1), 14
9 mg (0.05 mmol) of 4-ethynyl-1-isopropoxy-2-[(1-*m*-tolyl)vinyl]benzene
10 (Compound N1) was converted into the title compound using 14 mg
11 (0.04 mmol) of ethyl 4-iodobenzoate (Compound A), 9 mg (0.01 mmol)
12 of bis(triphenylphosphine)palladium (II) chloride, 2 mg (0.01 mmol) of
13 cuprous iodide and 3 mL of triethylamine. Purification by flash
14 chromatography (silica, 1% ethyl acetate in hexane) gave the title
15 compound as a clear oil which later solidified to a white solid.
16 PMR (CDCl₃): δ 0.99 (6H, d, $J = 6.0$ Hz), 1.40 (3H, t, $J = 7.1$ Hz),
17 2.30 (3H, s), 4.33-4.46 (3H, m), 5.32 (1H, d, $J = 1.5$ Hz), 5.61 (1H, br
18 s), 6.84 (1H, d, $J = 8.4$ Hz), 7.05-7.20 (4H, m), 7.45-7.52 (2H, m), 7.57
19 (2H, d, $J = 8.4$ Hz), 8.02 (2H, d, $J = 8.4$ Hz).

20 4-[[4'-Isopropoxy-3'-(1-*m*-tolyl)vinyl]phenylethynyl]benzoic acid
21 (Compound 31)

22 Employing the same general procedure as for the preparation of
23 4-[[4'-hydroxy-3'-(4''-methyl)benzoyl]phenylethynyl]benzoic acid
24 (Compound 5), 10 mg (0.02 mmol) of ethyl 4-[[4'-isopropoxy-3'-(1-*m*-
25 tolyl)vinyl]phenylethynyl]benzoate (Compound 30) was converted into
26 the title compound (white solid) using 0.3 mL (0.3 mmol) of NaOH
27 solution (1M in water), 1.2 mL of ethanol and 0.3 mL of
28 tetrahydrofuran. The white solid obtained was rinsed with 1.5 mL of 5%
29 ethyl acetate in hexane to give the title compound.

PMR (Aceton- d_6): δ 0.97 (6H, d, $J = 6.0$ Hz), 2.28 (3H, s), 4.54 (1H, heptet, $J = 6.0$ Hz), 5.29 (1H, d, $J = 1.5$ Hz), 5.67 (1H, br s), 7.02-7.22 (5H, m), 7.46 (1H, d, $J = 2.2$ Hz), 7.54 (1H, dd, $J = 2.2, 8.4$ Hz), 7.65 (2H, d, $J = 8.4$ Hz), 8.05 (2H, d, $J = 8.4$ Hz).

Ethyl 4-[[4'-*tert*-butyldimethylsilanyloxy-3'-(1-*p*-tolyl)vinyl]phenylethynyl]benzoate (Compound 32)

Employing the same general procedure as for the preparation of ethyl 4-[(3'-acetyl-4'-methoxy)phenylethynyl]benzoate (Compound 1), 12 mg (0.04 mmol) of 1-*tert*-butyldimethylsilanyloxy-4-ethynyl-2-[(1-*p*-tolyl)vinyl]benzene (Compound O1) was converted into the title compound using 10 mg (0.04 mmol) of ethyl 4-iodobenzoate (Compound A), 6 mg (0.01 mmol) of bis(triphenylphosphine)palladium (II) chloride, 1.5 mg (0.01 mmol) of cuprous iodide and 2 mL of triethylamine. Purification by flash chromatography (silica, 1% ethyl acetate in hexane) gave the title compound as a yellow oil.

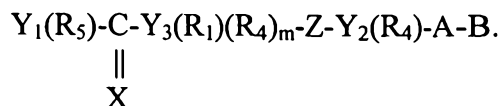
PMR ($CDCl_3$): δ 0.07 (6H, s), 0.73 (9H, s), 1.40 (3H, t, $J = 7.0$ Hz), 2.32 (3H, s), 4.38 (2H, q, $J = 7.0$ Hz), 5.25 (1H, d, $J = 1.2$ Hz), 5.71 (1H, d, $J = 1.2$ Hz), 6.80 (1H, d, $J = 8.2$ Hz), 7.08 (2H, d, $J = 8.4$ Hz), 7.18 (2H, d, $J = 8.4$ Hz), 7.38-7.48 (2H, m), 7.55 (2H, d, $J = 8.2$ Hz), 8.01 (2H, d, $J = 8.2$ Hz).

The reference to any prior art in this specification is not, and should not be taken as, an acknowledgment or any form of suggestion that that prior art forms part of the common general knowledge in Australia.



The claims defining the invention are as follows:

1. A compound of the formula



where X is O, S, C(R₂) or NOR*,

R* is H, C₁₋₆ alkyl, C₃₋₆ cycloalkyl or phenyl;

R₁ is H, lower alkyl of 1 to 10 carbons, cycloalkyl of 3 to 10 carbons, F, Cl, Br, I, CF₃, OR₂, SR₂, OCH₂OC₁₋₆ alkyl or CF₂CF₃;

R₂ is independently H, lower alkyl of 1 to 10 carbons, lower cycloalkyl of 3 to 10 carbons, R₃Si, or COR₃ where R₃ is independently H, lower alkyl of 1 to 6 carbons, cycloalkyl of 3 to 6 carbons or phenyl;

R₄ is lower alkyl of 1 to 6 carbons, cycloalkyl of 3 to 6 carbons, F, Cl, Br, I, CF₃, CF₂CF₃, NO₂, N(R₆)₂, CN, COR₃ or N(R₆)-COR₃;

m is integer between 0 and 3;

Y₁ is phenyl, naphthyl or heteroaryl selected from a group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiazolyl, oxazolyl, imidazolyl and pyrrolazolyl, said phenyl, naphthyl and heteroaryl groups being unsubstituted or substituted with one to three R₅ groups, where R₅ is alkyl of 1 to 10 carbons, cycloalkyl of 3 to 10 carbons, fluoro-substituted cycloalkyl of 3 to 10 carbons, fluoro-substituted alkyl of 1 to 10 carbons, alkenyl of 2 to 10 carbons and having 1 to 3 double bonds, cycloalkenyl of 3 to 10 carbons, alkynyl having 2 to 10 carbons and 1 to 3 triple bonds, F, Cl, Br, I, NO₂, CN, COOH, COOC₁₋₆alkyl, N₃, N(R₆)₂, OH, OR₃, SR₃, OCOR₃, or SCOR₃;

Z is -C≡C-

-N=N-,

-N(O)=N-,

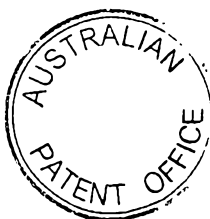
-N=N(O)-,

-N=CR₆-,

-CR₆=N,

-(CR₆=CR₆)_n-where n is an integer having the value 0 - 5,

-CO-NR₆-,



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-CS-NR₆,
 -NR₆-CO,
 -NR₆-CS,
 -COO-,
 -OCO-;
 -CSO-;
 -OCS-;
 -CO-CR₆=CR₆-

R₆ is independently H, lower alkyl of 1 to 6 carbons, or cycloalkyl of 3 to 6 carbons;

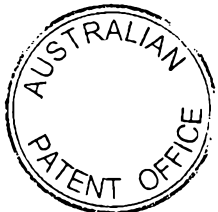
Y₂ is a phenyl or naphthyl group, or heteroaryl selected from a group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl, piazinyl, thiazolyl, oxazolyl, imidazolyl and pyrazolyl, said phenyl and heteroaryl groups being unsubstituted or substituted with one or two R₄ groups, or

when Z is -(CR₆=CR₆)_n and n is 3, 4 or 5 then Y₂ represents a direct valence bond between said (CR₆=CR₆)_n group and B;

Y₃ is phenyl, pyridyl, thienyl or furyl unsubstituted or substituted with up to 3 R₁ groups and unsubstituted or substituted with up to 3 R₄ groups;

A is (CH₂)_q where q is 0-5, lower branched chain alkyl having 3-6 carbons, cycloalkyl having 3-6 carbons, alkenyl having 2-6 carbons and 1 or 2 double bonds, cycloalkenyl of 3 to 6 carbons, alkynyl having 2-6 carbons and 1 or 2 triple bonds;

B is COOH or a pharmaceutically acceptable salt thereof, COOR₈, CONR₉R₁₀, -CH₂OH, CH₂OR₁₁, CH₂OCOR₁₁, CHO, CH(OR₁₂)₂, CH(OR₁₃O), -COR₇ CR₇(OR₁₂)₂, CR₇(OR₁₃O), or Si(C₁₋₆alkyl)₃, where R₇ is an alkyl, cycloalkyl or alkenyl group containing 1 to 5 carbons, R₈ is an alkyl group of 1 to 10 carbons or (trimethylsilyl)alkyl where the alkyl group has 1 to 10 carbons, or a cycloalkyl group of 5 to 10 carbons, or R₈ is phenyl or C₁ - C₆ -lower alkylphenyl, R₉ and R₁₀ independently are hydrogen, an alkyl group of 1 to 10 carbons, or a cycloalkyl group of 5-10 carbons, or phenyl, hydroxyphenyl or C₁ - C₆ lower alkylphenyl, R₁₁ is lower alkyl, lower cycloalkyl, phenyl or C₁ - C₆ lower alkylphenyl, R₁₂ is lower alkyl or lower cycloalkyl, and R₁₃ is divalent alkyl radical of 2-5 carbons.



2. A compound in accordance with Claim 1 where X is S.

3. A compound in accordance with Claim 1 where Z is selected from the group consisting of $-C\equiv C-$, $-CH=CH-$, $-CONH-$, $-COO-$, $-OCO-$, $-NHCO-$, and $-(CR_6=CR_6)_n$ where n is zero or 3.

4. A compound in accordance with Claim 1 where the A-B group is $(CH_2)_qCOOH$ or $(CH_2)_qCOOR_8$.

5. A compound in accordance with Claim 1 where R_1 is OH, or OR_2 .

6. A compound of Claim 1 wherein X is O, or CH_2 ;

R_1 is H, lower alkyl of 1 to 10 carbons, OCH_2OCH_3 , or OR_2 ;

R_2 is H, lower alkyl of 1 to 10 carbons, tri-(C_{1-6} alkyl)silyl, or COR_3 ;

R_4 is lower alkyl or 1 to 6 carbons, F, Cl, Br, I, or CF_3 ;

m is integer between 0 and 3;

Y_1 is phenyl, naphthyl or heteroaryl selected from a group consisting of pyridyl, thienyl, furyl, or thiazolyl, said phenyl, naphthyl and heteroaryl groups being unsubstituted or substituted with one to three R_5 groups, where R_5 is alkyl of 1 to 10 carbons, or fluoro-substituted alkyl of 1 to 10 carbons, F, Cl, Br, I, NO_2 , CN, COOH, or $COOC_{1-6}$ alkyl;

Z is $-C\equiv C-$

$-(CR_6=CR_6)_n-$ where n is an integer having the value 0 – 5,

$-CO-NR_6-$,

$-CS-NR_6-$,

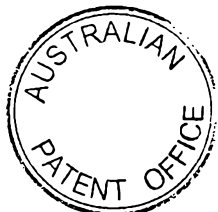
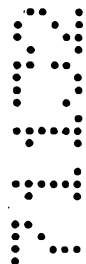
$-NR_6-CO$,

$-NR_6-CS$,

$-COO-$,

$-OCO-$;

Y_2 is a phenyl or naphthyl group, or heteroaryl selected from a group consisting of pyridyl, thienyl, or furyl, said phenyl and heteroaryl groups be unsubstituted or substituted



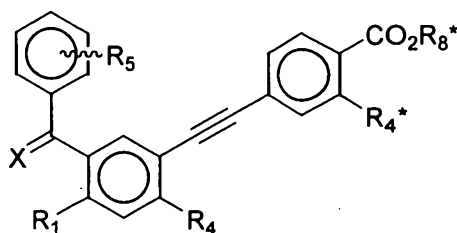
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with one or two R_4 groups, or

when Z is $-(CR_6=CR_6)_n$ and n is 3, 4 or 5 then Y_2 represents a direct valence bond between said $(CR_6=CR_6)_n$ group and B and Y_3 is phenyl.

7. A compound in accordance with Claim 6 where Y_2 is phenyl and Z is $-C\equiv C-$.

8. A compound of the formula



wherein X is O , or CH_2 ;

R_1 is H , OCH_2OCH_3 , or OR_2 ;

R_2 is H , lower alkyl or 1 to 10 carbons, cycloalkyl of 3 to 10 carbons, tri- $(C_{1-6}alkyl)silyl$, or COR_3 where R_3 is H , lower alkyl or lower cycloalkyl;

R_4 is H , lower alkyl of 1 to 6 carbons or cycloalkyl of 3 to 6 carbons;

R_4^* is H or F ;

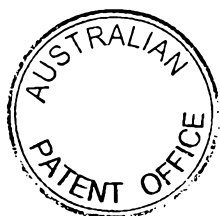
R_5 is H , F , lower alkyl of 1 to 6 carbons or cycloalkyl of 3 to 6 carbons,

R_8^* is H , lower alkyl or 1 to 6 carbons, cycloalkyl of 3 to 6 carbons, or a pharmaceutically acceptable salt thereof.

9. A compound in accordance with Claim 8 where X is CH_2 and R_5 is 4-methyl.

10. A compound in accordance with Claim 9 where R_4 is H .

11. A compound in accordance with Claim 10 where R_1 is H .



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12. A compound in accordance with Claim 11 where R_4^* is H and R_8^* is H or ethyl.
13. A compound in accordance with Claim 10 where R_1 is CH_3OCH_2O- .
14. A compound in accordance with Claim 13 where R_4^* is H and R_8^* is H or ethyl.
15. A compound in accordance with Claim 10 where R_1 is OH.
16. A compound in accordance with Claim 15 where R_4^* is H and R_8^* is H or ethyl.
17. A compound in accordance with Claim 10 where R_1 is OCH_3 .
18. A compound in accordance with Claim 17 where R_4^* is H and R_8^* is H or ethyl.
19. A compound in accordance with Claim 10 where R_1 is $OCH(CH_3)_2$.
20. A compound in accordance with Claim 19 where R_4^* is H and R_8^* is H or ethyl.
21. A compound in accordance with Claim 19 where R_4^* is F and R_8^* is H or ethyl.
22. A compound in accordance with Claim 8 where X is CH_2 and R_5 is 3-methyl.
23. A compound in accordance with Claim 22 where R_4 is H, R_1 is $OCH(CH_3)_2$

3
7
N

3
3
3
3



R_4^* is H and R_8^* is H or ethyl.

24. A compound in accordance with Claim 8 where X is O and R_5 is 4-methyl.
25. A compound in accordance with Claim 24 where R_4 is H.
26. A compound in accordance with Claim 25 where R_1 is $\text{CH}_3\text{OCH}_2\text{O}-$.
27. A compound in accordance with Claim 26 where R_4^* is H and R_8^* is H or ethyl.
28. A compound in accordance with Claim 25 where R_1 is OH.
29. A compound in accordance with Claim 28 where R_4^* is H and R_8^* is H or ethyl.
30. A compound in accordance with Claim 25 where R_1 is OCH_3 .
31. A compound in accordance with Claim 24 where R_4 is CH_3 .
32. A compound in accordance with Claim 31 where R_1 is OH.
33. A compound in accordance with Claim 32 where R_4^* is F.
34. A compound in accordance with Claim 1, compositions containing same, uses thereof and/or methods for their preparation substantially as herein described.

DATED this 30th day of March 2001

Allergan Sales Inc.

By its Patent Attorneys

DAVIES COLLISON CAVE

