Synthesis of the Four Stereoisomers of Enprostil[1,2]

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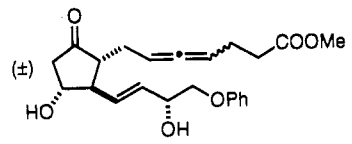
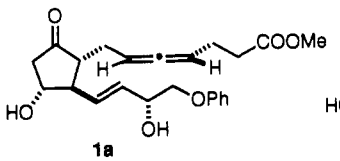
The four stereoisomeric components of enprostil (**1a–d**) were prepared using an orthoester Claisen rearrangement of individual propargylic alcohol intermediates **8** to generate the required allene upper chain stereochemistry, followed by one-carbon homologation. All four of the key propargylic alcohols **8** were prepared by addition of ethynyl Grignard reagent to aldehyde **7** (and to its enantiomer) and chromatographic separation of the diastereomers. Isomer **8a** was also prepared by asymmetric reduction of propargylic ketone **10**, which was in turn efficiently prepared by the opening of lactone **3** with dichlorocerium acetylide followed by silylation. Propargylic alcohol **8a** was stereospecifically converted to enprostil isomer **1a** via reaction of the inverted propargylic bromide **21** with the three-carbon functionalized organocuprate **22**, easily prepared from methyl 3-bromopropionate.

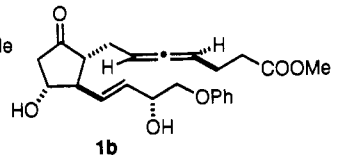
Enprostil (**1**), a C-4 allenic 16-phenoxy-17,18,19,20-tetranor PGE analog, is a potent inhibitor of gastric acid secretion[3] and an effective agent for the treatment of gastrointestinal disease.[4,5] The presence of the unresolved asymmetric allene moiety in this racemic compound gives rise to the four stereoisomeric components **1a–d**, which are present in approximately equimolar amounts. Samples of the individual stereoisomers were needed to assess their relative stabilities in a soft elastic gelatin capsule formulation (an asymmetric environment!)[6] and to determine their relative activities in various pharmacological studies. We describe here the synthesis of each of the four stereoisomers and the development of an efficient route to a single isomer, both starting with the known lactones **2** and **3**.[8]



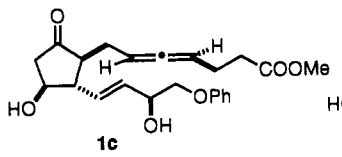
1 Enprostil



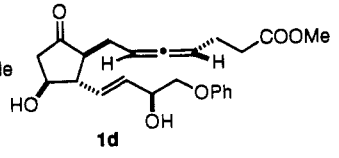
1a



1b



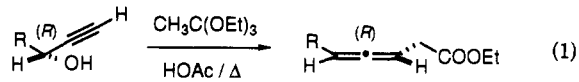
1c



1d

Results and Discussion

The pivotal intermediates for the preparation of the allene epimers **1a** and **1b** were the enantiomerically pure propargylic alcohols **8a** and **8b**.[9] Preparation of a pure propargylic alcohol epimer of known configuration allowed the preparation of a pure allene epimer of known configuration via the stereospecific orthoester Claisen rearrangement (eq 1).



(1)

This transformation was key to the success of the synthesis of the pheromone of the male dried bean beetle by K. Mori et al.[10] A 3:2 mixture of **8a** and **8b** was prepared as shown in Scheme I from the known lactones **2** and **3**.[8] A one-pot conversion of **3** into **4** began with saponification of **3** in methanol with aqueous KOH followed by concentration and azeotropic removal of water, giving a dry, toluene-soluble potassium salt. Silylation with excess *tert*-butyldimethylchlorosilane/imidazole in DMF[11] gave an intermediate disilylated compound which was hydrolyzed *in situ* with water to the silyl ether carboxylic acid **4** in 97.5% overall yield. Conversion of **4** to the aldehyde **7** was effected in three high-yielding steps. Esterification with methyl iodide/$NaHCO_3$ in DMF gave **5**, which was

† Institute of Organic Chemistry.
‡ División de Investigación.
(1) Dedicated to John A. Edwards, Director of the Institute of Organic Chemistry, on the occasion of his retirement from Syntex.

(2) Contribution No. 872 from the Institute of Organic Chemistry.
(3) Carpio, H.; Cooper, G. F.; Edwards, J. A.; Fried, J. H.; Garay, G. L.; Guzman, A.; Mendez, J. A.; Muchowski, J. M.; Roszkowski, A. P.; Van Horn, A. R.; Wren, D. *Prostaglandins* **1987**, *33*, 169.
(4) Mahachai, V.; Walker, K.; Sevelius, H.; Thomson, A. B. R. *Gastroenterology* **1985**, *89*, 555.
(5) Bright-Asare, P.; Giannikopoulos, I. G.; Mayberry, C.; Brand, D. L.; Krejs, G. J.; Tesler, M.; Van Zuiden, P. E. A.; Park, S.; Bynum, L. *Gastroenterology* **1986**, *90*, 1357.
(6) Kenley, R. A.; Fleitman, J. S.; Partridge, I. W. *J. Pharm. Sci.* **1986**, *75*, 842.
(7) (a) Rosenkranz, R. P.; Fisher, P. E.; Turke, M. L.; Perry, M. R.; Wong, A. G.; Wren, D. L.; Cooper, G. F.; Smith, W. L. *Arzneim.-Forsch.* **1989**, *39*, 1568. (b) Eglen, R. M.; Whiting, R. L. *Br. J. Pharmacol.* **1989**, *98*, 1335.
(8) (a) Schaaf, T. K.; Bindra, J. S.; Eggler, J. F.; Plattner, J. J.; Nelson, J.; Johnson, M. R.; Constantine, J. W.; Hess, H.-J. *J. Med. Chem.* **1981**, *24*, 1353. (b) For a stereoselective synthesis of an immediate precursor of **2** from the Corey lactone see: Bansal, R.; Cooper, G. F.; Corey, E. J. *J. Org. Chem.* **1991**, *56*, 1329.
(9) The following discussion is illustrated by the preparation of the two isomers with the natural prostaglandin absolute stereochemistry, **1a** and **1b**. The same synthetic schemes were used to prepare the enantiomeric isomers **1c** and **1d**, *vide infra*.
(10) Mori, K.; Nukada, T.; Ebata, T. *Tetrahedron* **1981**, *37*, 1343.
(11) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.

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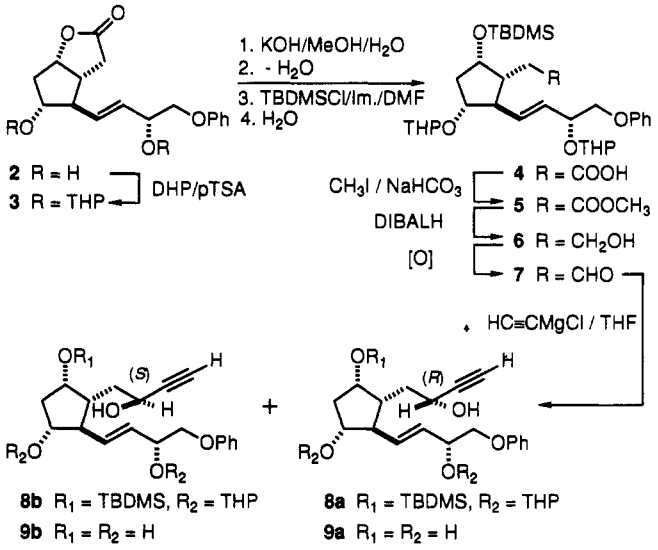
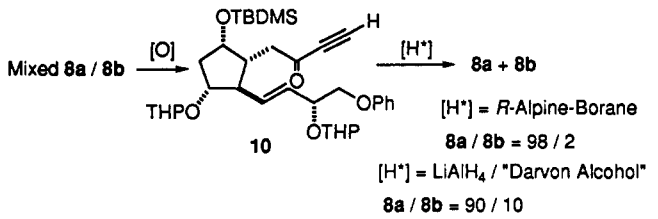
Scheme I



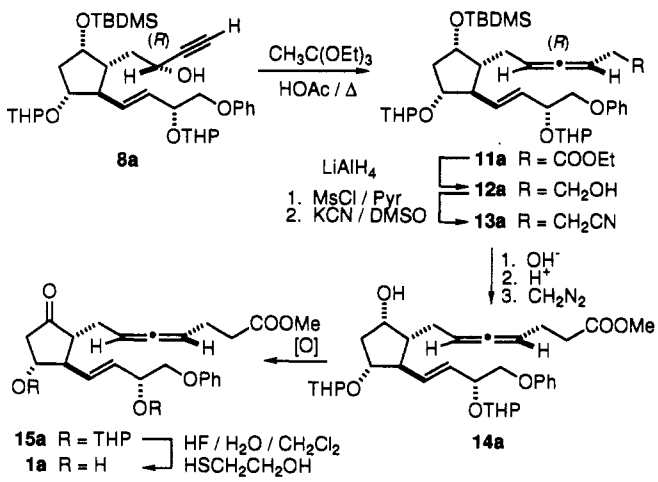
Scheme II



reduced with DIBALH in toluene at room temperature to the primary alcohol **6**. Collins oxidation of **6** gave the aldehyde **7** which was sufficiently pure to be used without chromatography. Direct reduction of ester **5** to aldehyde **7** with DIBALH at low temperature, although a shorter route, gave **7** contaminated with **5** and **6**. Since it was desired to use aldehyde **7** rapidly, without chromatography, the longer, but much cleaner, three-step procedure was used. On reaction with excess ethynylmagnesium chloride in THF at reflux, **7** gave a mixture of **8a** and **8b**. Careful TLC analysis showed eight closely spaced, but distinct, spots corresponding to the eight stereoisomers present in **8a**/**8b**. Fortuitously, the four least-polar spots corresponded to the four THP epimers of one of the propargylic alcohols and the four most-polar spots to those of the other. HPLC analysis showed that the two propargylic alcohols occurred in a 3:2 ratio. Careful chromatography on silica gel gave pure samples of **8a** and **8b**. Removal of all protecting groups from samples of each with acetic acid/THF/H_2O at 40 °C gave the pure tetraols **9a** and **9b**, which were shown to be pure by ^{13}C NMR and HPLC.

In order to make assignments of the configuration of the propargylic alcohol centers in **8a** and **8b** advantage was taken of the considerable knowledge in the literature concerning the asymmetric reduction of propargylic ketones.[12] A mixed **8a**/**8b** fraction was oxidized with chromium trioxide/3,5-dimethylpyrazole[13] to ketone **10** (Scheme II). Reduction of **10** with Mosher's $LiAlH_4$/"Darvon alcohol" reagent,[14] known to reduce propargylic ketones predominantly to carbinols having the *R* configuration,[12c] gave a 9:1 mixture of more-polar to less-polar **8** isomers. Reduction of **10** with *B*-(3-pinanyl)-9-borabicyclo[3.3.1]nonane (*R*-Alpine-Borane)[15] gave a 98:2 mixture of the same isomers. This reagent is also known to give *R* propargylic alcohols.[12a] Since the *R*-Alpine-Borane used had an optical purity of only 92% (ee), the observed 96% diasteromeric excess suggested that structural features of **10** were directing hydride reagents to the β face of the ynone, amplifying any other stereoselection. In agreement with this, the mismatched reagent *S*-Alpine-Borane (88% ee) reacted only sluggishly with **10** to give a 23.8:76.2 ratio of **8a**/**8b** (52.4% de). A similar effect has been noted by Midland in a steroidal acetylenic ketone reduction.[16] Thus, it seemed likely that *R*-Alpine-Borane and Mosher's $LiAlH_4$/"Darvon alcohol" reagents were acting in their normal preferred modes, leading predominantly to the *R* propargylic alcohol and thus, that the more polar propargylic alcohol had the *R* configuration (i.e. **8a**). These assignments, supported by $[\alpha]_D$ measurements on the isomers of **1** prepared from more-polar and less-polar **8** fractions (*vide infra*), were subsequently confirmed by a synthesis of **1a** in which the allene chirality was unambiguously obtained from the chiral pool.[17]

Scheme III



Scheme III depicts the conversion of a propargylic alcohol **8** isomer to the target prostaglandin **1** isomer, exemplified for **8a**. The same chemistry converted alcohol **8b** to isomer **1b** in similar yield. Orthoester Claisen rearrangement[18] of **8a** with triethyl orthoacetate gave, stereospecifically, allenic ester **11a** as a result of *syn* elimination.[10,19] A small amount of conjugated diene **16** was also formed. It was found that extended heating of the reaction mixture favored the production of diene **16**. A short reaction-period procedure that gave good conversion of **8a** into **11a** (70%), minimizing formation of **16** and allowing recovery of unreacted **8a** for recycle, was devised. After one recycle the overall conversion of **8a** to

(12) (a) Midland, M. M.; Tramontano, A.; Kazubski, A.; Graham, R. S.; Tsai, D. J. S.; Cardin, D. B. *Tetrahedron* **1984**, *40*, 1371. (b) Noyori, R.; Tomino, I.; Yamada, M.; Nishizawa, M. *J. Am. Chem. Soc.* **1984**, *106*, 6717. (c) Brinkmeyer, R. S.; Kapoor, V. M. *J. Am. Chem. Soc.* **1977**, *99*, 8339. (d) Vigneron, J.-P.; Bloy, V. *Tetrahedron Lett.* **1979**, 2683. *Ibid.* **1980**, 1735.

(13) Corey, E. J.; Fleet, G. W. J. *Tetrahedron Lett.* **1973**, 4499.

(14) Yamaguchi, S.; Mosher, H. S.; Pohland, A. *J. Am. Chem. Soc.* **1972**, *94*, 9254. Yamaguchi, S.; Mosher, H. S. *J. Org. Chem.* **1973**, *38*, 1870.

(15) *R*-Alpine-Borane and *S*-Alpine-Borane are registered trademarks of their supplier Aldrich Chemical Co.

(16) Midland, M. M.; Kwon, Y. C. *Tetrahedron Lett.* **1984**, *25*, 5981.

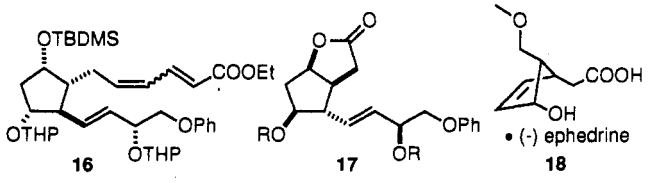
(17) Gooding, O. W.; Beard, C. C.; Cooper, G. F.; Jackson, D. Y. *J. Org. Chem.*, in press.

(18) Crandall, J. K.; Tindell, G. L. *J. Chem. Soc., Chem. Commun.* **1970**, 1411.

(19) Ziegler, F. E. *Acc. Chem. Res.* **1977**, *10*, 227.

11a was on the order of 85%. As 11a was unstable toward conjugation it was reduced to the primary alcohol 12a as the first step in a five-step, one-carbon homologation procedure similar to that used by Mori.[10] Mesylation of 12a followed immediately by displacement of the mesylate with KCN in DMSO gave nitrile 13a as an oil (65% overall from 11a). During the course of this procedure conjugated impurity 16 was lost, presumably due to base catalyzed 1,6-elimination of methanesulfonic acid. Base-catalyzed hydrolysis of nitrile 13a under vigorous conditions was accompanied by hydrolysis of the silyl protecting group. Careful acidification of the resulting potassium salt followed by esterification with diazomethane gave hydroxy ester 14a as an oil. Oxidation of 14a with chromium trioxide/3,5-dimethylpyrazole[13] in CH_2Cl_2 gave the oily protected ketone 15a. Deprotection to give 1a was accomplished with a two-phase aqueous HF/CH_2Cl_2 system. HF was found to be a sufficiently strong acid to accomplish THP hydrolysis without effecting excessive dehydration of the sensitive β-hydroxy ketone. Mercaptoethanol was added to drive the deprotection to completion, presumably by tying up the 5-hydroxypentanal as a thioacetal.[20]

To prepare the isomers in the enantiomeric series the same two sequences were carried out starting with 17, the antipode of 2, prepared by the Corey synthesis via the *l*-(−)-ephedrine salt 18.[21]

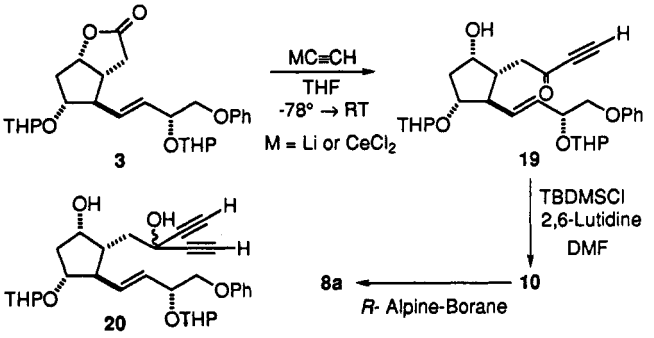


Isomers 1a and 1c were nicely crystalline compounds having mp = 69–70 °C. Recrystallization of each from ethyl acetate/hexanes gave 1a and 1c completely free of allene epimers 1b and 1d. We were unable to produce crystals suitable for X-ray crystallography due to the fine needle morphology of these materials. Pure isomers 1b and 1d were obtained as oils by repeated flash column chromatography.[22]

Support for the allene, and thus propargylic alcohol, stereochemical assignments was obtained from $[\alpha]_D$ measurements of 1a and 1b. The isomer prepared from the more polar propargylic alcohol (*R* allene from the *R* alcohol) 1a had $[\alpha]_D = -123°$. The other isomer (1b) had $[\alpha]_D = -3°$. The Lowe–Brewster rules[23] predict that a 1,3-disubstituted allene of the *R* configuration will have a more negative rotation at the sodium D line than the corresponding *S* isomer, in agreement with the observed results. This analysis, of course, assumes that the allenic moiety does not interact with other parts of the molecule in a manner which affects the rotation contribution of either part.

Subsequent studies of the antisecretory activities of the isomers[7a] and their binding to PG receptors,[7b] which showed that isomer 1a was by far the most potent of the four, made the directed synthesis of this isomer a desirable goal. Previous experience with reduction of ketone 10 by *R*-Alpine-Borane, which gave almost exclusively the needed propargylic alcohol 8a, encouraged a search for a shorter route to this ketone.

Scheme IV

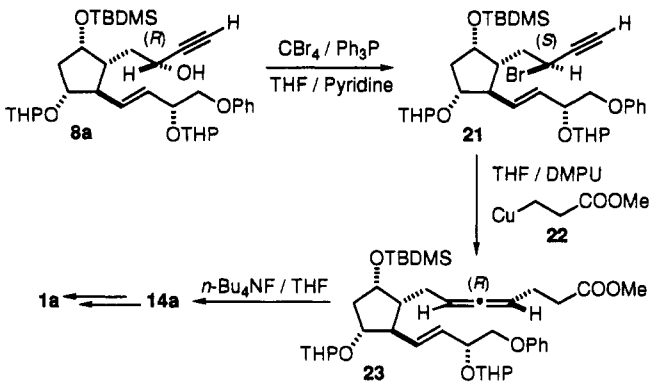


While there were many literature references to the monoaddition of higher homologs of metal acetylides to γ-lactones,[24] we could find no examples which employed the ethynyl parent. We found that lithium acetylide, prepared *in situ* from acetylene and *n*-butyllithium/hexane in THF at −78 °C according to Midland,[25] reacted with 3 during warmup to room temperature giving 19 in as high as 42% yield as shown in Scheme IV. Although not well characterized, the polar sideproducts which accounted for the remainder of the yield, seemed to involve two molecules of 3. Reasoning that the modest yield was related to the basicity of the reagent and the relative acidity of any terminal acetylene hydrogen, we sought a less basic acetylide. The ethynyl Grignard reagent gave predominantly the tertiary alcohol 20. Dichlorocerium acetylide,[26] prepared by addition of lithium acetylide to an anhydrous $CeCl_3$ slurry in THF at−78 °C, gave the desired adduct 19 in 95% yield with only a trace of 20. Although NMR indicated that 19 existed as a mixture of the cyclic hemiacetals and the hydroxy ynone, silylation to give 10 was accomplished in 90% yield using standard procedures[11] with the substitution of the non-nucleophilic base 2,6-lutidine for imidazole, which was found to add to the ynone. On a larger scale, the reduction of 10 with *R*-Alpine-Borane was best accomplished with 2.3 equiv of the neat reagent at room temperature.[27] The ketone was dissolved in the commercially available 0.5 M THF solution of the reagent[15] under nitrogen and concentrated at room temperature to a viscous oil. After standing for 3 days the reaction was worked up using the literature procedure[28] affording alcohol 8a in 90.1% yield after chromatography. HPLC analysis showed 8a/8b = 97.8/2.2 in the crude and 98.9/1.1 after chromatography.

Elaboration of the *R*-propargylic alcohol 8a to the *R*-allene 1a as described above benefitted from the completely stereospecific nature of the orthoester Claisen rearrangement allene formation, but suffered from the need to add one carbon to the chain. Although the homologation proceeded in good overall yield (60%), it required five synthetic steps to add the equivalent of one

(20) Hurd, C. D.; Saunders, W. H., Jr. *J. Am. Chem. Soc.* **1952**, *74*, 5324.
(21) Corey, E. J.; Schaaf, T. K.; Huber, W.; Koelliker, U.; Weinshenker, N. M. *J. Am. Chem. Soc.* **1970**, *92*, 397.
(22) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
(23) Lowe, G. *J. Chem. Soc., Chem. Commun.* **1965**, 411. Brewster, J. H. *Topics Stereochem.* **1967**, *2*, 1.
(24) See footnote 9 in: Cavicchioli, S.; Savoia, D.; Trombini, C.; Umani-Ronchi, A. *J. Org. Chem.* **1984**, *49*, 1246.
(25) Midland, M. M. *J. Org. Chem.* **1975**, *40*, 2250.
(26) Imamoto, T.; Sugiura, Y.; Takiyama, N. *Tetrahedron Lett.* **1984**, *25*, 4233.
(27) Brown, H. C.; Pai, G. G. *J. Org. Chem.* **1982**, *47*, 1606.
(28) Midland, M. M.; McLoughlin, J. I.; Gabriel, J. *J. Org. Chem.* **1989**, *54*, 159.

Scheme V



methylene unit. We devised cuprate-based three-carbon homologation/allene-forming chemistry, on which we have already published,[29] to solve this problem (Scheme V). Since the S_N2' displacement which generates the allene in this chemistry proceeds with inversion of configuration, it was necessary to convert the alcohol center of **8a** to a propargylic leaving group with another inversion of configuration in order to go from *R* alcohol to *R* allene. This was accomplished by treatment of **8a** with triphenylphosphine/carbon tetrabromide[30] in the presence of pyridine to give **21** in 88.8% yield. Reaction with the cuprate reagent **22**[29] gave **23** with the desired seven-carbon upper side chain in 88.3% yield. Deprotection of **23** with tetrabutylammonium fluoride (TBAF) in THF gave **14a** in 93.8% yield. Use of commercial TBAF/THF, which contained 5% water, gave a small amount of ester hydrolysis. Drying the commercial reagent over 3A molecular sieves to less than 0.5% water content eliminated this side reaction. Oxidation and deprotection, as before, completed the synthesis of **1a**.

In conclusion, the four stereoisomers of enprostil have been prepared from **2** using an orthoester Claisen rearrangement to generate allene moieties of known configuration from propargylic alcohols of known configuration. The path from **2** to each enprostil isomer involved 14 synthetic transformations. Subsequent refinements, including the high yield generation of a γ-hydroxy propargylic ketone from a γ-lactone using dichlorocerium acetylide, and the efficient, stereospecific, three-carbon homologation/allene formation from a propargylic bromide, reduced the path to eight synthetic transformations.

Experimental Section

NMR spectra were measured in $CDCl_3$ solution with Me_4Si as internal standard. Due to the presence of two tetrahydropyranyl groups in most compounds, resonances were compounded and fine structure was lost. Most peak assignments are given as m (multiplet) reflecting this. ^{13}C NMR spectra were measured at 75.5 MHz and peak assignments are given by the position number of a carbon atom as it appears in the final product using normal prostaglandin numbering where appropriate. Thin-layer chromatography was performed on Analtech silica gel plates visualized with phosphomolybdic acid/heat. Column chromatography was performed on Merck silica gel 60. Solvents are removed *in vacuo* on a rotary evaporator at 40 °C unless otherwise specified. Melting points are not corrected. $[\alpha]_D$ measurements were made in methanol.

(3*R*)- and (3*S*)-4-[(1*R*,2*R*,3*R*,5*S*)-5-[(*tert*-Butyldimethylsilyl)oxy]-2-[(*E*)-(3*R*)-4-phenoxy-3-[(tetrahydro-2*H*-pyran-2-yl)oxy]-1-butenyl]-3-[(tetrahydro-2*H*-pyran-2-yl)oxy]cyclopentyl]but-1-yn-3-ol (8a and 8b). Preparation via Reaction of Aldehyde 7 with Ethynylmagnesium Chloride. A solution of 20 g (42.3 mmol) (3a*R*,4*R*,5*R*,6a*S*)-hexahydro-4-[(*E*)-(3*R*)-4-phenoxy-3-[(tetrahydro-2*H*-pyran-2-yl)oxy]-1-butenyl]-5-[(tetrahydro-2*H*-pyran-2-yl)oxy]-2*H*-cyclopenta[*b*]furan-2-one (**3**) in 100 mL of THF was treated with 15.28 mL of 2.91 M aqueous potassium hydroxide (44.5 mmol) and refluxed under nitrogen for 1 h. The solvents were removed by evaporation at 50 °C, and the toluene-soluble potassium salt was dried by evaporation from 100 mL of toluene twice. The crude hydroxy acid salt was suspended in 100 mL of dry DMF and treated sequentially with 17.28 g (254 mmol) of imidazole and 19.12 g (127 mmol) of *tert*-butyldimethylchlorosilane. After being stirred overnight at room temperature, the reaction mixture was treated with 20 mL of water, stirred vigorously for 45 min, and partitioned between water and diethyl ether. The aqueous phase was extracted once with diethyl ether. The combined ether phase was washed with saturated NaCl solution, dried (Na_2SO_4), filtered, and evaporated, and the residue was chromatographed (10% EtOAc/hexanes followed by EtOAc) to give 24.96 g (97.5%) of **4** as a very viscous plastic: ^1H NMR: δ 7.27 (m, 2), 6.92 (m, 3), 5.76–5.47 (m, 2), 4.50 (m, 1), 4.25 (m, 1), 4.10 (m, 1).

A solution of 24.9 g (41.2 mmol) of **4** in 200 mL of dry DMF was treated with 12 g (143 mmol) of $NaHCO_3$ and 50.2 g (353 mmol) of CH_3I and stirred under nitrogen at 40–43 °C for 24 h. The reaction mixture was poured into water and extracted with diethyl ether. The ether extract was washed with half-saturated NaCl solution, dried (Na_2SO_4), filtered, and evaporated. The crude product was chromatographed (5% EtOAc/hexanes) to give 17.4 g (68.3%) of **5** as a colorless oil: ^1H NMR δ 3.62 (s, 3).

A solution of 17.0 g (27.5 mmol) of **5** in 170 mL of dry toluene at ice-bath temperature was treated with 82.5 mL of 1 M DIBALH in toluene (82.5 mmol) under nitrogen. The ice bath was removed and the reaction allowed to stir for 2.5 h. It was then cooled to ice-bath temperature, diluted with 83 mL of hexanes and, with vigorous stirring, treated sequentially with 13.86 g (330 mmol) of powdered NaF and 4.46 mL of water (248 mmol).[31] After being stirred for 30 min the mixture was filtered and the filter cake washed well with CH_2Cl_2. The filtrate was evaporated and chromatographed (20% EtOAc/hexanes) to give 14.9 g (91.8%) of **6** as a colorless oil.

A slurry of 18.02 g (180 mmol) of CrO_3 in 454 mL dry CH_2Cl_2 was cooled to 5–10 °C and, with stirring, 29.3 mL (360 mmol) of pyridine was added slowly keeping the temperature below 15 °C. After the mixture was stirred 30 min, 14.9 g of Celite was added. After the mixture was stirred an additional 5 min, 14.9 g (25.2 mmol) of **6** dissolved in 56 mL of dry CH_2Cl_2 was added at 15 °C and stirred for 1 h. Solid $NaHSO_4$ hydrate (37.8 g, 274 mmol) was added and stirring was continued for 30 min. The reaction mixture was filtered through Celite and the filter cake washed well with CH_2Cl_2. The filtrate was washed three times with water, once with saturated NaCl solution, dried (Na_2SO_4), filtered, and evaporated to give crude aldehyde **7** which was used directly in the next step: ^1H NMR δ 9.74 (bs, 1).

Crude aldehyde **7** was dissolved in 93 mL of dry THF and heated to reflux under nitrogen. To it was added, over 15 min, 55 mL of approximately 0.67 M ethynylmagnesium chloride in THF (37 mmol).[32] After the reaction was cooled to room temperature, 10 g of Celite and 50 mL of saturated aqueous NH_4Cl were added. The mixture was filtered through Celite and washed in well with CH_2Cl_2. The filtrate was washed with saturated aqueous NaCl, dried (Na_2SO_4), filtered, and evaporated to give a crude mixture of **8a** and **8b**. TLC (17.5-cm plate developed with 20% EtOAc/hexanes) showed eight spots: R_f 0.32, 0.35, 0.38, 0.40 corresponding to the THP isomers of **8a** and R_f 0.43, 0.46, 0.48, 0.50 corresponding to the THP isomers of **8b**. The mixture was chromatographed (5, 10, and 15% EtOAc/hexanes) with rechromatography of mixed fractions (10 and 15% EtOAc/hexanes) to give ultimately 5.83 g (37.6%) of the more-

(29) Gooding, O. W.; Beard, C. C.; Jackson, D. Y.; Wren, D. L.; Cooper, G. F. *J. Org. Chem.* **1991**, *56*, 1083.
(30) For a review of this reagent see: Appel, R. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 801.
(31) Yamamoto, H.; Maruoka, K. *J. Am. Chem. Soc.* **1981**, *103*, 4186.
(32) Skattebøl, L.; Jones, E. R. H.; Whiting, M. C. *Organic Syntheses*; Wiley: New York, 1963; Collect. Vol. IV, p 792.

polar isomer **8a**, 3.86 g (24.9%) of the less-polar isomer **8b**, and 3.66 g (23.6%) of mixed fractions (86.1% total yield).

For **8a**: IR ($CHCl_3$) 3285 cm^{-1}; ^1H NMR δ 7.27 (m, 2), 6.93 (m, 3), 5.49–5.80 (m, 2), 4.52 (m, 1), 4.41 (bm, 1), 2.41 (m, 1), 0.90 (bs, 9), 0.054, 0.058 (s, 6). Anal. Calcd for $C_{35}H_{54}O_7Si$: C, 68.37; H, 8.85. Found: C, 68.17; H, 9.01.

For **8b**: IR ($CHCl_3$) 3295 cm^{-1}; ^1H NMR δ 7.27 (m, 2), 6.93 (m, 3), 5.49–5.94 (m, 2), 4.50 (m, 1), 4.41 (bm, 1), 2.41, 2.39 (d, 1 combined), 0.90 (bs, 9), 0.054, 0.058 (s, 6). Anal. Calcd for $C_{35}H_{54}O_7Si$: C, 68.37; H, 8.85. Found: C, 68.10; H, 8.77.

Ethyl (3,4,5*R*)-6-[(1*R*,2*R*,3*R*,5*S*)-5-[(*tert*-Butyldimethylsilyl)oxy]-2-[(*E*)-(3*R*)-4-phenoxy-3-[(tetrahydro-2*H*-pyran-2-yl)oxy]-1-butenyl]-3-[(tetrahydro-2*H*-pyran-2-yl)oxy]cyclopentyl]-3,4-hexadienoate (11a). A solution of 5.7 g (9.27 mmol) of **8a** in 32 mL of triethyl orthoacetate containing 0.31 mL of glacial acetic acid was heated in a 170 °C oil bath for 30 min while simultaneously adding dropwise a total of 21 mL more triethyl orthoacetate containing 0.31 mL of glacial acetic acid and distilling out an equal volume of volatiles using a nitrogen sparge. Bath temp = 150–170 °C, pot temp = 105–122 °C, head temp = 92–111 °C. The warm solution was then evaporated to dryness *in vacuo* and relieved of residual acetic acid by evaporation of a toluene solution twice. Chromatography (4–20% gradient of EtOAc/hexanes) gave 4.70 g (77.3%) of **11a** as an oil and 1.17 g of recovered **8a**, which was recycled through the same process giving an additional 0.65 g (10.7%) of **11a** and 0.46 g (8.17%) of **8a**. Total yield = 5.35 g (84.2%) of **11a** as an oil: IR (neat) 1965, 1738 cm^{-1}; ^1H NMR δ 7.27 (m, 2), 6.92 (m, 3), 5.45–5.77 (m, 2), 5.20 (m, 2), 4.14 (q, 2, J = 7 Hz), 2.99 (m, 2), 1.26 (t, 3, J = 7 Hz), 0.89 (bs, 9), 0.04–0.06 (s, 6). Anal. Calcd for $C_{39}H_{60}O_8Si$: C, 68.38; H, 8.83. Found: C, 68.59; H, 8.97.

Ethyl (3,4,5*S*)-6-[(1*R*,2*R*,3*R*,5*S*)-5-[(*tert*-Butyldimethylsilyl)oxy]-2-[(*E*)-(3*R*)-4-phenoxy-3-[(tetrahydro-2*H*-pyran-2-yl)oxy]-1-butenyl]-3-[(tetrahydro-2*H*-pyran-2-yl)oxy]cyclopentyl]-3,4-hexadienoate (11b). Starting with 3.76 g (6.11 mmol) of the *S*-propargylic alcohol **8b**, the process described above for **11a** was carried out to give 2.50 g (59.7%) of **11b** as an oil: IR (neat) 1970, 1935 cm^{-1}; ^1H NMR δ 7.27 (m, 2), 6.92 (m, 3), 5.40–5.81 (m, 2), 5.22 (m, 2), 4.52 (m, 1), 4.14 (q, 2, J = 7 Hz), 3.00 (m, 2), 1.26 (t, 3, J = 7 Hz), 0.89 (bs, 9), 0.04–0.06 (s, 6). Anal. Calcd for $C_{39}H_{60}O_8Si$: C, 68.38; H, 8.83. Found: C, 68.53; H, 9.10.

(3,4,5*R*)-6-[(1*R*,2*R*,3*R*,5*S*)-5-[(*tert*-Butyldimethylsilyl)oxy]-2-[(*E*)-(3*R*)-4-phenoxy-3-[(tetrahydro-2*H*-pyran-2-yl)oxy]-1-butenyl]-3-[(tetrahydro-2*H*-pyran-2-yl)oxy]cyclopentyl]-3,4-hexadien-1-ol (12a). A solution of 5.35 g (7.81 mmol) of **11a** in 20 mL of anhydrous diethyl ether was added over 20 min to a slurry of 0.26 g of $LiAlH_4$ in 50 mL of anhydrous diethyl ether keeping the temperature below 10 °C. After 30 min, acetone (2-4 mL) was added dropwise (cautiously!) and stirring continued for 10 min. Saturated aqueous NaK tartrate (2 mL) was added dropwise and stirring continued for 20 min. The reaction mixture was treated with 23 mL of NaK tartrate and stirred 10 min and the aqueous layer extracted with EtOAc. The extract was washed with water, dried (Na_2SO_4), filtered, treated with 0.4 mL of triethylamine, and evaporated to give 5.29 g (105%) of crude **12a** which was used without purification in the next step: IR 3440, 1965 cm^{-1}; ^1H NMR: δ 7.27 (m, 2), 6.92 (m, 3), 5.43–5.83 (m, 2), 5.15 (m, 1), 5.05 (m, 1), 4.51 (m, 1), 3.67 (bq, 2), 0.90 (bs, 9), 0.04–0.06 (s, 6). Anal. Calcd for $C_{37}H_{58}O_7Si$: C, 69.12; H, 9.09. Found: C, 69.29; H, 9.01.

(3,4,5*S*)-6-[(1*R*,2*R*,3*R*,5*S*)-5-[(*tert*-Butyldimethylsilyl)oxy]-2-[(3*R*)-4-phenoxy-3-[(tetrahydro-2*H*-pyran-2-yl)oxy]-1-butenyl]-3-[(*E*)-(tetrahydro-2*H*-pyran-2-yl)oxy]cyclopentyl]-3,4-hexadien-1-ol (12b). Starting with 2.50 g (3.65 mmol) of the *S*-allene **11b**, the process described above for **11a** was carried out to give 2.44 g (104%) of crude **12b** which was used without purification in the next step: IR 3450, 1968 cm^{-1}; ^1H NMR δ 7.27 (m, 2), 6.92 (m, 3), 5.40–5.83 (m, 2), 5.20 (m, 1), 5.08 (m, 1), 4.52 (m, 1), 3.67 (q, 2, J = 7 Hz), 0.90 (bs, 9), 0.04–0.06 (s, 6). Anal. Calcd for $C_{37}H_{58}O_7Si$: C, 69.12; H, 9.09. Found: C, 69.12; H, 9.06.

(4,5,6*R*)-7-[(1*R*,2*R*,3*R*,5*S*)-5-[(*tert*-Butyldimethylsilyl)oxy]-2-[(*E*)-(3*R*)-4-phenoxy-3-[(tetrahydro-2*H*-pyran-2-yl)oxy]-1-butenyl]-3-[(tetrahydro-2*H*-pyran-2-yl)oxy]cyclopentyl]-4,5-heptadienenitrile (13a). Crude alcohol **12a** from 5.35 g (7.81 mmol) of **11a** was dissolved in 46 mL of dry CH_2Cl_2, treated with 3.34 g (33 mmol) of dry triethylamine, and cooled under nitrogen to −30 °C. Methanesulfonyl chloride (1.61 g, 14.0 mmol), dissolved in 9.7 mL of dry CH_2Cl_2, was added dropwise at such a rate as to maintain the temperature below −20 °C. After being stirred for 20 min at −20 to −30 °C, the reaction was allowed to reach room temperature and was diluted with 1.3 mL of triethylamine in 13.7 mL of CH_2Cl_2 followed by 13.7 mL of saturated aqueous $NaHCO_3$. After 5 min of vigorous stirring, the aqueous layer was extracted with CH_2Cl_2 and the combined organic phase was washed with half-saturated aqueous $NaHCO_3$, dried (Na_2SO_4), filtered, and evaporated to give 5.96 g (106%) of crude mesylate which was used immediately without purification. Crude mesylate was dissolved in 13.7 mL of dry DMSO and added to a slurry of 3.2 g of KCN (49.1 mmol) in 11.3 mL of dry DMSO being stirred in a 79–80 °C oil bath. After being stirred for 1 h at 70–80 °C, the reaction mixture was cooled to 40 °C and diluted with 100 mL of CH_2Cl_2. The mixture was washed with water twice, and the aqueous washes were back-extracted with CH_2Cl_2. The combined organic layer was dried (Na_2SO_4 + trace Et_3N) and evaporated. Crude nitrile **13a** was chromatographed (5%, 10% EtOAc/hexanes) to give 3.3 g of pure **13a** (64.8% from **11a**) as an oil: IR (neat) 2260, 1963 cm^{-1}; ^1H NMR δ 7.27 (m, 2), 6.91 (m, 3), 5.45–5.82 (m, 2), 5.26 (m, 1), 5.09 (m, 1), 4.51 (m, 1), 2.36 (m, 2), 0.89, (bs, 9), 0.04–0.05 (s, 6). Anal. Calcd for $C_{38}H_{57}NO_6Si$: C, 70.01; H, 8.81; N, 2.15. Found: C, 69.90; H, 8.92; N, 2.24.

(4,5,6*S*)-7-[(1*R*,2*R*,3*R*,5*S*)-5-[(*tert*-Butyldimethylsilyl)oxy]-2-[(*E*)-(3*R*)-4-phenoxy-3-[(tetrahydro-2*H*-pyran-2-yl)oxy]-1-butenyl]-3-[(tetrahydro-2*H*-pyran-2-yl)oxy]cyclopentyl]-4,5-heptadienenitrile (13b). Starting with the crude alcohol **12b** from 2.50 g (3.65 mmol) of **11b**, the process described above for **13a** was carried out to give 1.57 g (66.0%) of **13b** as an oil: IR (neat) 2260, 1965 cm^{-1}; ^1H NMR δ 7.28 (m, 2), 6.91 (m, 3), 5.45–5.83 (m, 2) 5.31 (m, 1), 5.12 (m, 1), 4.51 (m, 1), 2.36 (m, 2), 0.90 (bs, 9), 0.04–0.06 (s, 6). Anal. Calcd for $C_{38}H_{57}NO_6Si$: C, 70.01; H, 8.81; N, 2.15. Found: C, 70.38; H, 8.95; N, 2.07.

Methyl (4,5,6*R*)-7-[(1*R*,2*R*,3*R*,5*S*)-5-Hydroxy-2-[(*E*)-(3*R*)-4-phenoxy-3-[(tetrahydro-2*H*-pyran-2-yl)oxy]-1-butenyl]-3-[(tetrahydro-2H-pyran-2-yl)oxy]cyclopentyl]-4,5-heptadienoate (14a). Preparation by Hydrolysis of 13a. A solution of 3.3 g of **13a** (5.06 mmol) was dissolved in 35 mL of 2-methoxyethanol, treated with 1.7 g of KOH dissolved in 5.8 mL of water, and refluxed under nitrogen for 96 h. The reaction mixture was cooled to room temperature, and the solvents were evaporated. Residual 2-methoxyethanol was removed by evaporation of a toluene solution three times. The crude hydroxy acid salt was dissolved in 14 mL of water, cooled to ice-bath temperature, and carefully acidified to pH = 2 with 10% hydrochloric acid, with good stirring. The mixture was extracted with EtOAc four times, and the combined extract was washed with water, dried (Na_2SO_4), filtered, evaporated, and dried by evaporation of a toluene solution. The crude was dissolved in diethyl ether, cooled to 0 °C, and esterified with excess ethereal diazomethane. Evaporation of solvents gave crude **14a** which was chromatographed (10, 15, 20, 25% EtOAc/hexanes) to give 2.51 g (87.1%) of **14a** as an oil: IR (neat) 1966 cm^{-1}; ^1H NMR δ 7.27 (m, 2), 6.92 (m, 3), 5.44–5.81 (m, 2), 5.18 (bm, 2), 4.51 (m, 1), 4.22 (bm, 1), 3.66 (s, 3). Anal. Calcd for $C_{33}H_{46}O_8$: C, 69.45; H, 8.12. Found: C, 69.82; H, 8.08.

Methyl (4,5,6*S*)-7-[(1*R*,2*R*,3*R*,5*S*)-5-Hydroxy-2-[(*E*)-(3*R*)-4-phenoxy-3-[(tetrahydro-2*H*-pyran-2-yl)oxy]-1-butenyl]-3-[(tetrahydro-2*H*-pyran-2-yl)oxy]cyclopentyl]-4,5-heptadienoate (14b). Starting with 1.57 g (2.41 mmol) of **13b**, the process described above for **14a** was repeated to give 1.20 g (87.1%) of **14b** as an oil: IR (neat 1966 cm^{-1}; ^1H NMR δ 7.27 (m, 2), 6.92 (m, 3), 5.45–5.82 (m, 2), 5.15 (bm, 2), 4.51 (m, 1), 4.22 (m, 1), 3.66 (s, 3). Anal. Calcd for $C_{33}H_{46}O_8$: C, 69.45; H, 8.12. Found: C, 69.51; H, 8.29.

Methyl (4,5,6*R*)-7-[(1*R*,2*R*,3*R*)-2-[(*E*)-(3*R*)-4-Phenoxy-3-[(tetrahydro-2*H*-pyran-2-yl)oxy]-1-butenyl]-3-[(tetrahydro-2*H*-pyran-2-yl)oxy]-5-oxocyclopentyl]-4,5-heptadienoate (15a). A suspension of 3.88 g (38.8 mmol) of CrO_3 in 125 mL of dry CH_2Cl_2 was treated at −20 °C under nitrogen with 3.82 g

(39.7 mmol) 3,5-dimethylpyrazole. After 30 min of being stirred, a solution of 2.51 g (4.40 mmol) of **14a** in 75 mL of dry CH_2Cl_2 was added. After 30 min of being stirred, 37.5 silica gel was added and the solvents were evaporated. The dry adsorbate was placed atop a column of silica gel and eluted with 10 and 20% EtOAc/hexanes to give 1.75 g (70%) **15a** as an oil: IR (neat) 1966, 1740 cm^{-1}; ^1H NMR δ 7.28 (m, 2), 6.92 (m, 3), 5.56–5.94 (m, 2), 5.23 (m, 1), 5.17 (m, 1), 3.66 (s, 3). Anal. Calcd for $C_{38}H_{44}O_8$: C, 69.70; H, 7.80. Found: C, 69.74; H, 7.97.

Methyl (4,5,6*S*)-7-[(1*R*,2*R*,3*R*)-2-[(*E*)-(3*R*)-4-Phenoxy-3-[(tetrahydro-2*H*-pyran-2-yl)oxy]-1-butenyl]-3-[(tetrahydro-2*H*-pyran-2-yl)oxy]-5-oxocyclopentyl]-4,5-heptadienoate (15b). Starting with 1.0 g (1.75 mmol) of **14b**, the process described above for **15a** was carried out to give 0.70 g (70%) of **15b** as an oil: IR (neat) 1967, 1738 cm^{-1}; ^1H NMR δ 7.28 (m, 2), 6.92 (m, 3), 5.58–5.95 (m, 2), 5.10 (bm, 2), 3.67 (s, 3). Anal. Calcd for $C_{38}H_{44}O_8$: C, 69.70; H, 7.80. Found: C, 70.10; H, 7.65.

Methyl (4,5,6*R*)-7-[(1*R*,2*R*,3*R*)-3-Hydroxy-2-[(*E*)-(3*R*)-3-hydroxy-4-phenoxy-1-butenyl]-5-oxocyclopentyl]-4,5-heptadienoate (1a). A solution of 1.75 g (3.08 mmol) of **15a** in 70 mL of CH_2Cl_2, stirred vigorously at room temperature, was treated with 0.35 mL of 48% hydrofluoric acid (10.1 mmol) followed by slow addition over 1 h of 26.3 mL of 0.217 M 2-mercaptoethanol in CH_2Cl_2 (5.71 mmol). When addition was complete, the mixture was neutralized with saturated aqueous $NaHCO_3$ (vigorous stirring). The aqueous phase was extracted with CH_2Cl_2, and the combined organic phase was washed with water, dried (Na_2SO_4), and evaporated. The crude product was chromatographed (20, 50, 75, and 100% EtOAc/hexanes) to give 0.77 g (62.4%) of **1a** as an oil which solidified. Recrystallization from ethyl acetate/hexanes gave white needles: mp 70–70.5 °C; $[\alpha]_D$ = −123° (*c* = 0.25); ^1H NMR δ 7.29 (m, 2), 6.95 (m, 3), 5.78 (m, 2), 5.07 (m, 1), 5.12 (m, 1), 4.55 (m, 1), 4.11 (m, 1), 3.98 (m, 2), 3.64 (s, 3), 2.75 (d of d, 1, *J* = 7, 18 Hz), 2.56 (m, 1), 2.39 (m, 2); ^{13}C NMR δ 173.58 (C-1), 33.08 (C-2), 23.70 (C-3), 90.37 (C-4), 204.75 (C-5), 88.77 (C-6), 26.70 (C-7), 53.34 (C-8), 213.62 (C-9), 45.94 (C-10), 71.94 (C-11), 54.13 (C-12), 131.90 (C-13), 133.49 (C-14), 70.86 (C-15), 71.54 (C-16), 158.39 (O-arom), 114.63 (*ortho*-arom), 129.62 (*meta*-arom), 121.40 (*para*-arom) 51.63 (OCH_3). Anal. Calcd for $C_{23}H_{28}O_6$: C, 68.98; H, 7.05. Found: C, 69.15; H, 7.05.

Methyl (4,5,6*S*)-7-[(1*R*,2*R*,3*R*)-3-Hydroxy-2-[(*E*)-(3*R*)-3-hydroxy-4-phenoxy-1-butenyl]-5-oxocyclopentyl]-4,5-heptadienoate (1b). Starting with 0.70 g (1.23 mmol) of **15b**, the process described above for **1a** was carried out to give 0.43 g (87.2%) of **1b** as an oil. Repeated flash column chromatography (EtOAc) gave pure **1b** free from the very slightly less-polar **1a** by HPLC analysis: $[\alpha]_D$ = −3° (*c* = 0.532); ^1H MMR δ 7.30 (m, 2), 6.95 (m, 3), 5.81 (m, 2), 5.06 (m, 1), 5.12 (m, 1), 4.58 (m, 1), 4.14 (m, 1), 3.99 (m, 1), 3.64 (s, 3), 2.78 (d of d, 1, *J* = 7, 18 Hz), 2.60 (m, 1), 2.41 (m, 2); ^{13}C NMR 173.53 (C-1), 33.24 (C-2), 23.83 (C-3), 90.26 (C-4), 204.71 (C-5), 88.74 (C-6), 26.75 (C-7), 53.46 (C-8), 213.37 (C-9), 46.02 (C-10), 71.98 (C-11), 54.19 (C-12), 131.90 (C-13), 133.23 (C-14), 70.79 (C-15), 71.58 (C-16), 158.39 (O-arom), 114.65 (*ortho*-arom), 129.63 (*meta*-arom), 121.42 (*para*-arom), 51.65 (OCH_3). Anal. Calcd for $C_{23}H_{28}O_6$: C, 68.98; H, 7.05. Found: 69.04; H, 7.00.

Methyl (4,5,6*S*)-7-[(1*S*,2*S*,3*S*)-3-Hydroxy-2-[(*E*)-(3*S*)-3-hydroxy-4-phenoxy-1-butenyl]-5-oxocyclopentyl]-4,5-heptadienoate (1c), and Methyl(4,5,6*R*)-7-[(1*S*,2*S*,3*S*)-3-Hydroxy-2-[(*E*)-(3*S*)-3-hydroxy-4-phenoxy-1-butenyl]-5-oxocyclopentyl]-4,5-heptadienoate (1d). The processes described above for the preparation of **1a** and **1b** from **3** were repeated starting with **17**, the antipode of **3**.

For **1c**: mp = 68–70 °C, $[\alpha]_D$ = +126° (*c* = 0.138); ^1H NMR δ 7.30 (m, 2), 6.97 (m, 3), 5.81 (m, 2), 5.08 (m, 1), 5.13 (m, 1), 4.58 (m, 1), 4.17 (m, 1), 3.99 (m, 2), 3.66 (s, 3), 2.77 (d of d, 1, *J* = 7, 18 Hz), 2.62 (m, 1), 2.41 (m, 2); ^{13}C NMR δ 33.14 (C-2), 23.79 (C-3), 90.42 (C-4), 88.78 (C-6), 26.86 (C-7), 53.13 (C-8), 46.12 (C-10), 72.19 (C-11), 54.17 (C-12), 132.12 (C-13), 132.32 (C-14), 70.63 (C-15), 71.76 (C-16), 114.73 (*ortho*-arom), 129.64 (*meta*-arom), 121.47 (*para*-arom). Anal. Calcd for $C_{23}H_{28}O_6$: C, 68.98; H, 7.05. Found: C, 68.79; H, 6.65.

For **1d**: $[\alpha]_D$ = +2.6° (*c* = 0.192); ^1H NMR δ 7.29 (m, 2), 6.95 (m, 3), 5.79 (m, 2), 5.06 (m, 1), 5.12 (m, 1), 4.56 (m, 1), 4.12 (m, 1), 3.99 (m, 2), 3.64 (s, 3), 2.76 (d of d, 1, *J* = 7, 18 Hz), 2.57 (m, 1), 2.39 (m, 2); ^{13}C NMR δ 33.29 (C-2), 23.87 (C-3), 90.27 (C-4), 88.77 (C-6), 26.82 (C-7), 53.46 (C-8), 46.08 (C-10), 72.04 (C-11), 54.23 (C-12), 131.98 (C-13), 133.05 (C-14), 70.78 (C-15), 71.69 (C-16), 114.72 (*ortho*-arom), 129.64 (*meta*-arom), 121.45 (*para*-arom), 51.62 (OCH_3). Anal. Calcd for $C_{23}H_{28}O_6$: C, 68.98; H, 7.05. Found: C, 68.72; H, 7.09.

4-[(1*R*,2*R*,3*R*,5*S*)-5-[(*tert*-Butyldimethylsilyl)oxy]-2-[(*E*)-(3*R*)-4-phenoxy-3-[(tetrahydro-2*H*-pyran-2-yl)oxy]-1-butenyl]-3-[(tetrahydro-2*H*-pyran-2-yl)oxy]cyclopentyl]but-1-yn-3-one (10). Preparation by Oxidation of 8a/8b. Mixed **8a/8b**, 0.50 g (0.813 mmol), dissolved in 1 mL of dry CH_2Cl_2, was added to a −20 °C solution of 0.50 g (5.0 mmol) of CrO_3 and 0.489 g (5.09 mmol) of 3,5-dimethylpyrazole in 6.5 mL of dry CH_2Cl_2. After 1 h at −20 °C the mixture was allowed to warm to room temperature. Silica gel (2.2 g) was added, and the solvents were evaporated. Evaporation of a hexane slurry of the adsorbate removed residual CH_2Cl_2. Chromatography of the adsorbate on more silica gel (10% EtOAc/hexanes) gave 0.30 g (60%) of **10** as a colorless oil: IR 2100, 1690 cm^{-1}; ^1H NMR δ 7.27 (m, 2), 6.91 (m, 3), 5.47–5.75 (m, 2), 3.13 (m, 1), 0.89 (bs, 9), −0.02, 0.02, 0.03 (s, 6). Anal. Calcd for $C_{35}H_{52}O_7Si$: C, 68.59; H, 8.55. Found: C, 68.94; H, 8.79.

4-[(1*R*,2*R*,3*R*,5*S*)-5-Hydroxy-2-[(*E*)-(3*R*)-4-phenoxy-3-[(tetrahydro-2*H*-pyran-2-yl)oxy]-1-butenyl]-3-[(tetrahydro-2*H*-pyran-2-yl)oxy]cyclopentyl]but-1-yn-3-one (19). Cerium trichloride heptahydrate (51.56 g, 138.4 mmol) was dried under high vacuum at 140–145 °C for 2 h and 15 min and cooled to room temperature under nitrogen. Dry THF (450 mL) was added and the resulting slurry was stirred for 2.5 h at room temperature and then cooled to −78 °C. Meanwhile, lithium acetylide was prepared as described below from 2986 mL of purified acetylene gas (133.3 mmol, calculated volume at STP) in 300 mL of dry THF and 79.35 mL of 1.60 M *n*-butyllithium in hexane at −78 °C. After the lithium acetylide had stirred for 30 min, it was rapidly transferred by cannulation to the cold $CeCl_3$/THF slurry and stirring was continued for 30 min. Lactone **3** (30.0 g, 63.5 mmol) dissolved in 100 mL of dry THF was added over 20 min keeping the internal temperature below −68 °C. The reaction was allowed to warm to −40 °C over 10 min and held there for 3 h. The reaction mixture was added to 2.25 L of saturated aqueous NH_4Cl and washed in with 100 mL of the same and 2 × 50 mL of diethyl ether. After 10 min of being stirred, 67.5 g of Celite was added and the mixture was filtered through 22.5 g of Celite in a sintered glass filter. The filter cake was washed with 5 × 100 mL of diethyl ether and the aqueous phase extracted with a further 2 × 100 mL of diethyl ether. The combined organic phase was dried ($MgSO_4$), filtered, and evaporated to give 34.00 g of crude product. The crude was absorbed on 34 g of silica gel in CH_2Cl_2 solution, evaporated, and placed atop a column of 650 g of silica gel packed in 5% acetone/hexanes. Elution with 5 and 10% of the same solvents gave 30.6 g (96.6%) of **19** as a very viscous plastic: IR ($CHCl_3$) 3310, 2105, 1680 cm^{-1}; ^1H NMR δ 3.20 (narrow m, ynone acetylene), 2.60 and 2.57 (narrow m, hemiacetal acetylene isomers). Anal. Calcd for $C_{29}H_{38}O_7$: C, 69.86; H, 7.68. Found: C, 70.15; H, 7.88.

(±)-4-[(1*R,2*R**,3*R**,5*S**)-5-Hydroxy-2-[(*E*)-(3*R**)-4-phenoxy-3-[(tetrahydro-2*H*-pyran-2-yl)oxy]-1-butenyl]-3-[(tetrahydro-2*H*-pyran-2-yl)oxy]cyclopentyl]but-1-yn-3-one ((±)-19). Preparation by Addition of Lithium Acetylide to the Model Substrate (±)-3.** To 10 mL of dry THF stirring under nitrogen in a −78 °C bath was injected 63 mL of purified acetylene gas (2.81 mmol, calculated volume at STP) below the surface from a gas-tight syringe. Over 8 min was added 1.65 mL of 1.55 M *n*-butyllithium in hexane (2.56 mmol) dropwise and stirring continued for 17 min. To this over 9 min was added 1.00 g of racemic lactone **3** dissolved in 4 mL of THF. After stirring at −78 °C bath temperature for 25 min, the bath temperature was raised to −50 °C and held for 10 min and then raised to −20 °C and held for 45 min. The reaction was quenched at −20 °C by the addition of 10 mL of saturated aqueous NH_4Cl, the cold bath was removed, 5 mL of diethyl ether was added, and the mixture was stirred for 5 min. Just enough water was added to dissolve precipitated salts, and the aqueous layer was extracted with diethyl ether. The combined ether layer was washed with water and brine, dried (Na_2SO_4), and evaporated. The crude product was purified by flash column chromatography (25% EtOAc/CH_2-

Cl_2, 2.5 and 4% MeOH/CH_2Cl_2) giving 0.45 g (42.4%) (±)-**19**, identical spectroscopically to **19**, as a colorless plastic.

4-[(1*R*,2*R*,3*R*,5*S*)-5-[(*tert*-Butyldimethylsilyl)oxy]-2-[(*E*)-(3*R*)-4-phenoxy-3-[(tetrahydro-2*H*-pyran-2-yl)oxy]-1-butenyl]-3-[(tetrahydro-2*H*-pyran-2-yl)oxy]cyclopentyl]but-1-yn-3-one (10). Preparation by Silylation of 19. *tert*-Butyldimethylchlorosilane (23.94 g, 158.8 mmol) and 2,6-lutidine (21.28 g, 198.6 mmol) were dissolved in 100 mL of dry DMF. After the mixture had stirred at room temperature for 45 min, 39.60 g of **19** (79.42 mmol) dissolved in 190 mL of DMF was added. After being stirred overnight, the mixture was cooled in an ice bath for 15 min and 76 mL of water was added. After a further 15 min of being stirred in the ice bath, the mixture was allowed to warm to room temperature and stirred for 45 min. The mixture was partitioned between 700 mL of water and 700 mL of diethyl ether. The organic layer was combined with 2 × 100 mL of diethyl ether extracts of the aqueous layer and washed with water, 1 N HCl, water, saturated aqueous $NaHCO_3$, water, and brine. After being dried (Na_2SO_4), crude **10** was obtained by evaporation of solvents. Chromatography (5, 10, and 15% EtOAc/hexanes) gave 47.93 g (98.5%) of **10** as a viscous oil.

(3*R*)-4-[(1*R*,2*R*,3*R*,5*S*)-5-[(*tert*-Butyldimethylsilyl)oxy]-2-[(*E*)-(3*R*)-4-phenoxy-3-[(tetrahydro-2*H*-pyran-2-yl)oxy]-1-butenyl]-3-[(tetrahydro-2*H*-pyran-2-yl)oxy]cyclopentyl]-but-1-yn-3-ol (8a). Preparation by Reduction of 10 with *R*-Alpine-Borane. To 25.42 g (41.48 mmol) of ynone **10** in a nitrogen-purged flask was added 190.8 mL of 0.5 M *R*-Alpine-Borane (95.40 mmol) in THF. The THF was evaporated at 20 °C on a nitrogen-purged rotary evaporator and the residue allowed to stand under nitrogen for 3 d. The reaction mixture was diluted with 25 mL of dry diethyl ether, cooled in an ice bath, and treated with 7.4 mL of freshly distilled acetaldehyde in 1-mL portions. The ice bath was removed and the mixture stirred at room temperature for 1 h. After stripping the volatiles at 40 °C on a rotary evaporator, the flask was brought to atmospheric pressure with nitrogen, 125 mL dry diethyl ether was added, and the solution was cooled in an ice bath to 0 °C. Ethanolamine (6.31 mL) was added and the mixture stirred for 1 h at 0 °C. It was then filtered and the filter cake washed with 3 × 75 mL of diethyl ether. The filtrate was evaporated to give 34.42 g of crude **8a** as an oil: HPLC showed **8a**/**8b** = 97.8/2.2. Chromatography (5–20% EtOAc/hexanes in 1% increments) gave 22.98 g (90.1%) of **8a** as an oil: HPLC showed **8a**/**8b** = 98.9/1.1.

(3*S*)-3-Bromo-4-[(1*R*,2*R*,3*R*,5*S*)-5-[(*tert*-butyldimethylsilyl)oxy]-2-[(*E*)-(3*R*)-4-phenoxy-3-[(tetrahydro-2*H*-pyran-2-yl)oxy]-1-butenyl]-3-[(tetrahydro-2*H*-pyran-2-yl)oxy]cyclopentyl]but-1-yne (21). Triphenylphosphine (60.0 g, 228.7 mmol), pyridine (8.7 g, 110 mmol), and alcohol **8a** (58.8 g, 95.7 mmol) were added to 527 mL of dry THF under nitrogen. The mixture was stirred vigorously in a 20 °C water bath while adding as rapidly as possible carbon tetrabromide (36.5 g 109.4 mmol), dissolved in 116 mL of dry THF containing 4.9 g of pyridine. A brown precipitate formed as the reaction proceeded. After 30 min the reaction was diluted with 1 L of diethyl ether, stirred 10 min, and filtered. The filtrate and 2 × 100 mL diethyl ether washes of the filter cake were combined and evaporated. Chromatography (hexanes, 5, 10, 20% EtOAc/hexanes) gave 57.5 g of **21** (88.8%) as an oil: IR (neat) 3290 and 2120 cm^{-1}; ^1H NMR δ 7.28 (m, 2), 6.93 (m, 3), 5.51–5.83 (m, 2), 4.52 (m, 2), 2.59 (m, 1), 0.90 (bs, 9), 0.054, 0.058 (s, 6). Anal. Calcd for $C_{35}H_{53}BrO_5Si$: C, 62.02; H, 7.88; Br, 11.79. Found: C, 62.22; H, 7.92; Br, 11.80.

Methyl (4,5,6*R*)-7-[(1*R*,2*R*,3*R*,5*S*)-5-[(*tert*-Butyldimethylsilyl)oxy]-2-[(*E*)-(3*R*)-4-phenoxy-3-[(tetrahydro-2*H*-pyran-2-yl)oxy]-1-butenyl]-3-[(tetrahydro-2*H*-pyran-2-yl)oxy]-cyclopentyl)]-4,5-heptadienoate (23). Methyl 3-iodopropionate (39.0 g, 181.1 mmol) was reacted with zinc–copper couple (Aldrich) (18.6 g, 286 mmol) in a mixture of 561 mL of dry toluene and 31 mL of dry dimethylacetamide (DMAC) stirred vigorously in a 45 °C oil bath. After 80 min, 35.2 g (170.7 mmol) of finely powdered copper bromide–dimethyl sulfide (Aldrich) was added in one portion, followed by 19.2 mL of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU). Vigorous stirring was continued for 40 min. Bromide **21** (54.2 g, 80.0 mmol), dissolved in a mixture of 70 mL of toluene and 7 mL of DMAC, was added and stirring in a 45 °C oil bath continued for 40 min. After the reaction was cooled to 20 °C, 50 g of Celite was added. The reaction was quenched by the dropwise addition of 50 mL of saturated aqueous NH_4Cl with vigorous stirring, filtered through a pad of Celite, and washed in with 300 mL of EtOAc. The filtrate was washed with water and half-saturated brine, dried (Na_2SO_4), and evaporated. Chromatography (hexanes, 5, 10, 20% EtOAc/hexanes) gave 48.4 g (88.3%) of **23** as an oil: IR (neat) 1960 cm^{-1}; ^1H NMR δ 7.27 (m, 2), 6.92 (m, 3), 5.46–5.81 (m, 2), 5.13 (bm, 1), 5.09 (bm, 1), 4.50 (m, 1), 3.61 (s, 3). Anal. Calcd for $C_{39}H_{60}O_8Si$: C, 68.39; H, 8.83. Found: C, 68.58; H, 9.17.

Methyl (4,5,6*R*)-7-[(1*R*,2*R*,3*R*,5*S*)-5-Hydroxy-2-[(*E*)-(3*R*)-4-phenoxy-3-[(tetrahydro-2*H*-pyran-2-yl)oxy]-1-butenyl]-3-[(tetrahydro-2*H*-pyran-2-yl)oxy]cyclopentyl]-4,5-heptadienoate (14a). Preparation by Desilylation of 23. Commercial (Aldrich Chemical Co.) *n*-Bu_4NF in THF, 1.1 M containing ca. 5% water, was dried to 0.42% water (Karl Fischer) over 3A molecular sieves and filtered. A solution of 77.51 g (113.2 mmol) of **23** in 257.3 mL (283.1 mmol) of this solution was stirred at room temperature for 24 h. The reaction mixture was poured into 600 mL of water and extracted with 4 × 250 mL of diethyl ether. The combined extract was washed with water and brine, dried (Na_2SO_4), and evaporated. Chromatography (hexanes, 10, 20, 30, and 40% EtOAc/hexanes) gave 60.7 g (93.8%) of **14a** as an oil.