A Direct and Efficient Stereocontrolled Synthetic Route to the Pseudopterosins, Potent Marine Antiinflammatory Agents

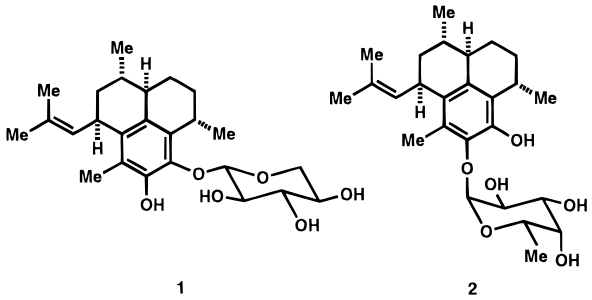
E. J. Corey* and Scott E. Lazerwith

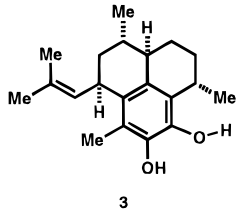
Contribution from the Department of Chemistry and Chemical Biology, Harvard University, Cambridge, Massachusetts, 02138

Received August 24, 1998

Abstract: Described herein is a new synthetic route to pseudopterosin aglycone (**3**), a key intermediate for the synthesis of a group of antiinflammatory natural products including pseudopterosin A (**1**) and E (**2**). The pathway of synthesis starts with the abundant and inexpensive (*S*)-(−)-limonene and its long-known cyclic hydroboration product (**4**) and leads to the chiral hydroxy ketone **6**. Conversion of **6** to **10** followed by a novel aromatic annulation produced **15** which underwent a highly diastereoselective cyclization to afford the protected pseudopterosin aglycone **16**. The naturally occurring pseudopterosins such as **1** and **2** are readily available from this key intermediate.

The pseudopterosins, produced by the Caribbean sea whip *Pseudopteragorgia elisabethae* and exemplified by pseudopterosins A (**1**) and E (**2**),[1] are remarkably active antiinflammatory agents[2] which were discovered by W. Fenical and collaborators. The analgesic activity of **1** (administered subcutaneously) is severalfold greater than that of indomethacin,[2] and that of **2** is some 50 times greater.[3] This potency and the fact that the biological mode of action of **1** and **2** appears to be novel[2] have made these substances (and their analogues) attractive targets for synthetic and for biological/biochemical research. Further interest in the pseudopterosins derives from their commercial use as topical antiinflammatory agents in the cosmetic field and the limited supply available from natural sources.[4] A number of laboratories have described studies on the total synthesis of pseudopterosins. The earliest syntheses were developed by C. A. Broka and co-workers[5] and in these laboratories,[6] including the first stereocontrolled enantioselective syntheses of **1** and **2** from either (+)-menthol[6a] or (*S*)-citronellal.[6b] Subsequently, a variety of additional synthetic approaches have been developed by other groups.[7−10] Although the more recent syntheses involve fascinating and elegant design, they appear to fall short of practicality. Described herein is a new process for the synthesis of pseudopterosins which has a number of advantages including (1) an inexpensive chiral starting material (limonene), (2) the use of common or readily available reagents, (3) stereocontrol, (4) simplicity of execution, (5) good yields, and (6) directness. In addition, this synthesis illustrates a number of new and potentially widely useful synthetic methods and noteworthy aspects of stereocontrol and site selectivity.





The starting material for the present synthesis of pseudopterosins was diol mixture **4** which can be obtained in nearly quantitative yield from (*S*)-(−)-limonene by cyclic hydroboration and alkaline peroxide oxidation.[11] Although this mixture of diols (nearly 1:1) is readily available in quantity, it has neither been separated nor been used as starting material in a stereocontrolled synthesis, to the best of our knowledge. Neither chromatographic nor distillation methods allow separation. Nonetheless, we found

(1) (a) Look, S. A.; Fenical, W.; Matsumoto, G.; Clardy, J. *J. Org. Chem.* **1986**, *51*, 5140−5145. (b) Fenical, W. *J. Nat. Prod.* **1987**, *50*, 1001−1008. (c) Look, S. A.; Fenical, W. *Tetrahedron* **1987**, *43*, 3363−3370.

(2) Look, S. A.; Fenical, W.; Jacobs, R. S.; Clardy, J. *Proc. Natl. Acad. Sci. U.S.A.* **1986**, *83*, 6238−6240.

(3) Personal communication from Professor William Fenical whom we thank for this information and for generously providing samples of naturally derived pseudopterosins A and E.

(4) Rouhi, A. M. *Chem. Eng. News* **1995**, November 20, 42−44.

(5) Broka, C. A.; Chan, S.; Peterson, B. *J. Org. Chem.* **1988**, *53*, 1584−1586.

(6) (a) Corey, E. J.; Carpino, P. *J. Am. Chem. Soc.* **1989**, *111*, 5472−5474. (b) Corey, E. J.; Carpino, P. *Tetrahedron Lett.* **1990**, *31*, 3857−3858.

(7) (a) McCombie, S. W.; Cox, B.; Lin, S.-I.; Ganguly, A. K.; McPhail, A. T. *Tetrahedron Lett.* **1991**, *32*, 2083−2086. (b) McCombie, S. W.; Ortiz, C.; Cox, B.; Ganguly, A. K. *Synlett* **1993**, 541−547.

(8) (a) Buszek, K. R. *Tetrahedron Lett.* **1995**, *36*, 9125−9128. (b) Buszek, K. R.; Bixby, D. L. *Tetrahedron Lett.* **1995**, *36*, 9129−9132.

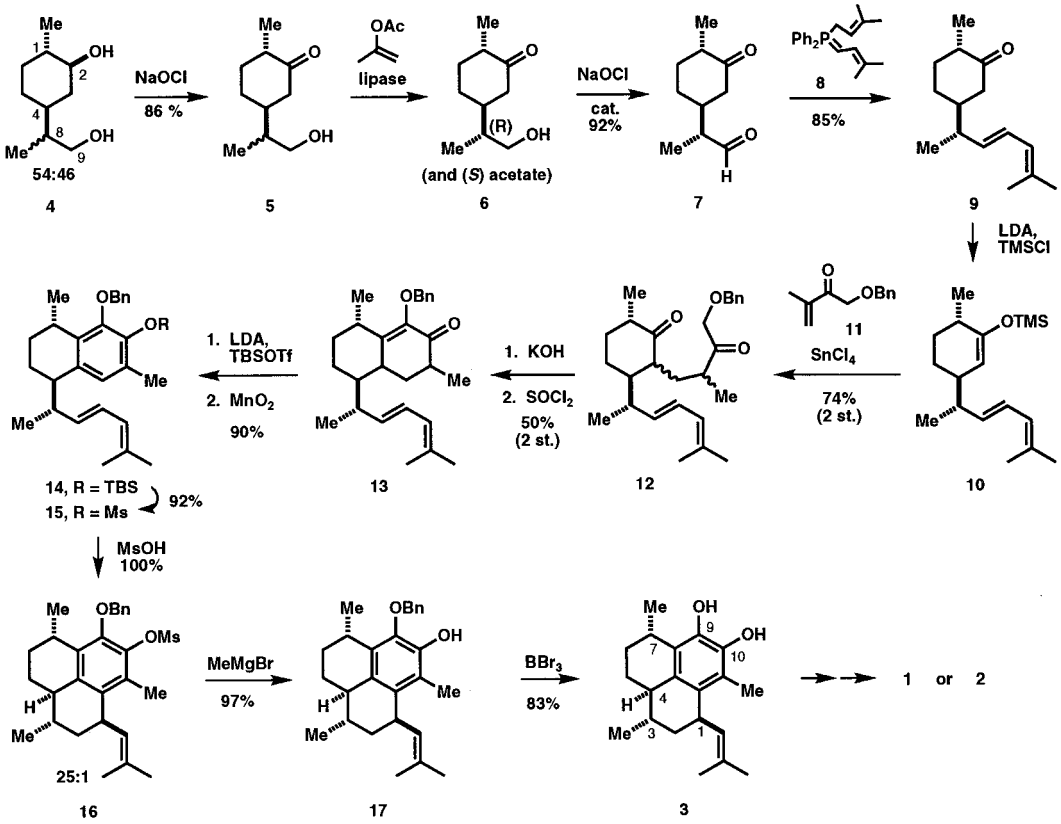
(9) Gill, S.; Kocienski, P.; Kohler, A.; Pontiroli, A.; Qun, L. *J. Chem. Soc., Chem. Commun.* **1996**, 1743−1744.

(10) (a) Majdalani, A.; Schmalz, H.-G. *Tetrahedron Lett.* **1997**, *38*, 4545−4548. (b) Majdalani, A.; Schmalz, H.-G. *Synlett.* **1997**, 1303−1305. (c) Kato, N.; Zhang, C.-S.; Matsui, T.; Iwabachi, H.; Mori, A.; Ballio, A.; Sassa, T. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2475.

(11) (a) Brown, H. C.; Pfaffenberger, C. D. *J. Am. Chem. Soc.* **1967**, *89*, 5475−5477. (b) Brown, H. C.; Negishi, E.-i. *Tetrahedron* **1977**, *33*, 2331−2357.

10.1021/ja983041s CCC: $15.00
Published on Web 11/17/1998

Chart 1



that the diastereomeric mixture could be utilized for synthesis using the novel separation process outlined in Chart 1. A 54:46 C(8) diastereomeric mixture of diols (**4**) underwent selective oxidation at C(2) upon exposure to 1.5 equiv of sodium hypochlorite[12] in aqueous acetic acid to form the diastereomeric mixture of hydroxy ketones **5** in excellent yield. Exposure of this mixture to isopropenyl acetate in isopropyl ether at 23 °C using Amano PS lipase as the catalyst resulted in selective acetylation of the (8*S*)-hydroxy ketone after 17 h. Flash chromatography of the resulting mixture on silica gel afforded the desired (8*R*)-alcohol **6** (36% based on **5**) as an oil (ratio 8*R*/8*S* = 99:1 as determined by HPLC analysis of the corresponding *p*-nitrobenzoate ester) and the acetate of the (8*S*)-diastereomer of **6**. Oxidation of **6** in a $CH_2Cl_2-H_2O$ system with sodium hypochlorite and 2,2,6,6-tetramethyl-1-piperidinyloxy radical (TEMPO) as catalyst[13] at pH 8 gave keto aldehyde **7** in 92% yield. Wittig−Vedejs *E*-selective olefination[14a] of **7** using the ylide **8**[14b] as reagent in dimethoxyethane produced the *E*-diene **9** in excellent yield, as shown in Chart 1, without the loss of stereochemical integrity at the labile C(8) position.

With the successful establishment of three of the four stereocenters of pseudopterosin aglycone (**3**), the next task called for in our strategic plan was the attachment of the aromatic ring, i.e., the conversion **9** → **14** in Chart 1. This was accomplished using a new aromatic annulation protocol starting with Mukaiyama-type Michael coupling of the enol silyl ether **10** and the functionalized α,β-enone **11**.[15,16] This coupling product was obtained in 74% yield (correcting for a small amount of recovered **9**) using 1.1 equiv of $SnCl_4$ as the catalyst in CH_2Cl_2 at −78 °C for 40 min. Treatment of **12** with ethanolic KOH at 0 °C effected aldol cyclization to a β-hydroxy ketone which was dehydrated by treatment with $SOCl_2$−pyridine at 23 °C for 1 h to form the α,β-enone **13**. The enol *tert*-butyldimethylsilyl (TBS) ether of **13** was prepared by deprotonation (alpha to methyl) and silylation with TBS−triflate, and then the resulting ether was aromatized by stirring with activated MnO_2 (Aldrich Co., Milwaukee) in methylcyclohexane at 70 °C for 36 h to provide the aromatic hydronaphthalene **14** in 90% overall yield from **13**. We discovered that the MnO_2-induced aromatization process proceeds more readily and in higher yield with methylcyclohexane as solvent than in benzene or toluene as solvent[17] and that by using the dry MnO_2−methylcyclohexane system aromatization of a wide range of 1,4- and 1,3-cyclohexadienes can be effected efficiently. A summary of these studies is presented below. In contrast to the success achieved using the MnO_2−methylcyclohexane aromatization system, a number of other oxidants that have previously been recommended for aromatization failed, including (1) Pd−C, (2) dichlorodicyanoquinone, (3) *o*-chloranil, (4) 2,6-dichloro-1,4-benzoquinone, and (5) $Cr(CO)_3 \cdot 3CH_3CN$, norbornene.[18]

Desilylation of **14** (Bu_4NF in THF) and reaction with $CH_3SO_2Cl-Et_3N$ in CH_2Cl_2 provided the mesylate **15** which upon treatment with 5 equiv of CH_3SO_3H in CH_2Cl_2 at −50 °C

(12) Stevens, R. V.; Chapman, K. T.; Stubbs, C. A.; Tam, W. W.; Albizati, K. F. *Tetrahedron Lett.* **1982**, *23*, 4647−4650.

(13) Aneli, P. L.; Banfi, S.; Montanari, F.; Quici, S. *J. Org. Chem.* **1989**, *54*, 2970−2972.

(14) (a) Vedejs, E.; Fang, H. W. *J. Org. Chem.* **1984**, *49*, 210−212. (b) Cristau, H.-J.; Ribeill, Y. *Synthesis* **1988**, 911−912.

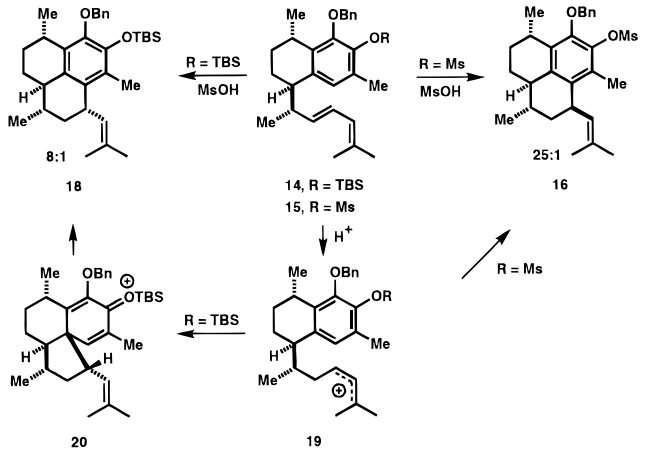
(15) The α,β-enone **11** was prepared by Swern oxidation of 1-benzyloxy-3-methylbut-3-ene-2-ol, see: Terao, S.; Shiraishi, M.; Kato, K. *Synthesis* **1979**, 467−468.

(16) For some examples of Mukaiyama-type Michael Reactions see: (a) Narasaka, K.; Soai, K.; Aikawa, Y.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 779−783. (b) Heathcock, C. H.; Norman, M. H.; Uehling, D. E. *J. Am. Chem. Soc.* **1985**, *107*, 2797−2799. (c) Ranu, B. C.; Saha, M.; Bhar, S. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2197−2199 and references therein.

(17) See (a) Mashraqui, S.; Keehn, P. *Synth. Commun.* **1982**, *12*, 637−645. (b) Sodeoka, M.; Satoh, S.; Shibasaki, M. *J. Am. Chem. Soc.* **1988**, *110*, 4823−4824.

(18) Problems with these reagents included desilylation of the starting material and interfering processes involving the diene appendage.

Chart 2



underwent highly diastereoselective cationic cyclization (25:1) to form **16** in very high yield. Reaction of **16** with MeMgBr produced cleanly the monophenol **17** which was debenzylated to give pseudopterosin aglycone (**3**). The various pseudopterosins may be accessed from **17** or **3** by procedures previously developed in these laboratories.[6] Comparison of synthetic **3** $[\alpha]^{23}_D$ −95 (c = 1, $CHCl_3$) with authentic **3**[6] revealed identical IR, ^{1}H NMR, ^{13}C NMR, and high-resolution mass spectra.

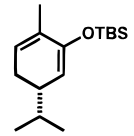
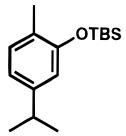
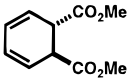
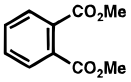
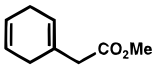
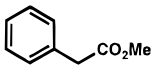
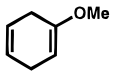
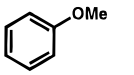
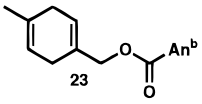
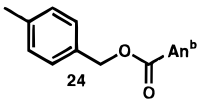
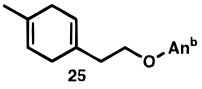
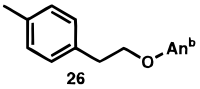
It is interesting that the methanesulfonic acid cyclization of TBS ether **14** afforded primarily (8:1) the product **18**, corresponding to **16** with the (*S*)-configuration at C(1) (Chart 2). This remarkable difference in the stereochemistry of cationic cyclization of **14** and **15**, clearly dependent on the electron-donating properties of TBSO vs MsO, is most readily explained as due to a difference in mechanistic pathway, as shown in Chart 2. The pathway from **15** to **16** probably involves direct 6-membered ring closure of allylic cation **19**. However, as shown in Chart 2, the pathway from **14** to **18** can most reasonably be explained by cyclization of allylic cation **19** to the 5-membered spiro cation **20**[19] followed by 1,2-rearrangement with 5 → 6 ring expansion. Thus, the differences in stereopreferences for formation of **16** and **18** reflect stereoelectronic preferences of the intermediate steps **19** → **16** and **19** → **20**.

We believe that the synthetic process described herein and outlined in Chart 1 provides a very direct and practical route for the synthesis of pseudopterosins in quantity. A number of the key steps are also of broader interest from the viewpoint of general synthetic methodology, including (1) the use of an inexpensive, recoverable lipase to effect separation of the diastereomers of **5**, (2) the new procedure for the aromatic annulation of **9** → **14**, (3) the remarkably stereoselective cyclizations of **15** → **16** and **14** → **18**, and (4) the superiority of MnO_2 as a mild reagent for aromatization of cyclohexadienes.

With regard to the usefulness of dry MnO_2 in methylcyclohexane as a reagent for the aromatization of cyclohexadienes, we present additional results that have been obtained with a diverse collection of substrates, as summarized in Table 1. The aromatization reactions, which were generally monitored by thin-layer chromatography, proceed at varying rates as shown in Table 1. The aromatization of dimethyl *trans*-1,2-dihydrophthalate was found to be considerably faster than that of various alkyl- or oxy-substituted dihydrobenzenes, an indication that the first step in the process may be a hydrogen atom rather than a hydride abstraction.

(19) See Corey, E. J.; Sauers, C. K. *J. Am. Chem. Soc.* **1957**, *79*, 248.

Table 1. Aromatization of Cyclohexadienes by MnO_2 at 70 °C in Methylcyclohexane

Substrate	Product	Time (yield)
		36 h (84%)
		5 h (80%)
		18 h (73%)
		16 h (43%)[a]
		36 h (83%)
		36 h (82%)

[a] Low yield due to volatility of product. [b] An = 4-methoxyphenyl.

Experimental Section

(1*S*, 4*S*, 8*R*,*S*)-Menth-2-one-9-ol (5). A solution of a 54:46 mixture of C(8) diastereomeric diols **4** (7.225 g, 41.94 mmol) in acetic acid (70 mL) was treated with aqueous sodium hypochlorite (33.1 mL, 63 mmol) dropwise over 15 min.[12] The mixture was stirred at 23 °C for 3 h. Isopropyl alcohol (10 mL) was added, and the mixture was stirred an additional 10 min. After the mixture was concentrated in vacuo to remove most of the acetic acid, water was added, and the aqueous solution was extracted three times with CH_2Cl_2. The organic layers were carefully washed with $NaHCO_3$ (saturated aqueous), and the $NaHCO_3$ was extracted twice with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. Flash chromatography (CH_2Cl_2−EtOAc 90:10 → 75:25) afforded 6.11 g (86%) of hydroxy ketone **5** as a clear oil with a diastereomeric ratio of 54:46 (determined by HPLC analysis of the *p*-nitrobenzoate ester): R_f = 0.26 (hexanes−EtOAc, 50:50); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.63−3.48 (m, 2H), 2.39−2.34 (m, 2H), 2.19−2.07 (m, 2H), 1.88−1.82 (m, 2H), 1.70−1.20 (m, 4H), 1.01 (d, J = 6.5 Hz, 3H), 0.93 (m, 3H).

(1*S*, 4*S*, 8*R*)-(+)-Menth-2-one-9-ol (6). The above mixture of keto alcohols **5** (3.89 g, 22.85 mmol) in isopropyl ether (175 mL) was treated with Amano PS lipase (1.13 g) followed by isopropenyl acetate (5.0 mL, 45.70 mmol) and stirred at 23 °C. The progress of the reaction was monitored by NMR analysis of small aliquots. After 17 h, the reaction mixture was filtered and concentrated. Flash chromatography (using as eluent hexanes−Et_2O 70:30, followed by Et_2O) afforded acetylated product and 1.412 g (36%) of the desired keto alcohol **6** as an oil of 98% de (determined by HPLC analysis of the *p*-nitrobenzoate ester): R_f = 0.26 (hexanes−EtOAc 50:50); $[\alpha]^{23}_D$ +4.0 (c 0.96, $CHCl_3$); FTIR (film) 3440, 1710 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.55 (dd, J = 10.7, 6.1 Hz, 1H), 3.47 (dd, J = 10.7, 6.3 Hz, 1H), 2.35−2.26 (m, 2H), 2.19−2.05 (m, 3H), 1.89−1.78 (m, 2H), 1.56 (sept, J = 6.2 Hz, 1H), 1.44 (dq, J = 13.0, 3.3 Hz, 1H), 1.27 (dq, J = 13.0, 3.3 Hz, 1H), 0.97 (d, J = 6.5 Hz, 3H), 0.90 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.5, 65.6, 46.3, 45.0, 41.7, 40.3, 35.0, 27.6, 14.3, 13.2; CIMS (NH_3) 188 $[M + NH_4]^+$, 170 $[M]^+$, 153 $[M - OH]^+$; HRMS calcd for $[C_{10}H_{18}O_2 + H]^+$ 171.1385, found 171.1389; HPLC

(chiral) Chiralpak at 23 °C, $\lambda = 254$ nm, hexane−isopropyl alcohol 85:15, retention times: 25.1 min (major), 33.2 min (minor) at 1 mL/min flow rate.

(1*S*, 4*S*, 8*R*)-(−)-Menthane-2,9-dione (7). A solution of keto alcohol **6** (0.404 g, 2.37 mmol) in CH_2Cl_2 (8 mL) was treated with 2,2,6,6-tetramethyl-1-piperidinyloxy, free radical (TEMPO) (0.008 g, 0.051 mmol) and potassium bromide (0.028 mL, 0.237 mmol).[13] The solution was cooled to 0 °C and treated with 6% aqueous sodium hypochlorite which had been adjusted to pH ∼8 using $NaHCO_3$ (4.0 mL, 3.8 mmol). The reaction mixture was stirred at 0 °C for 1.5 h and poured into 0.1 M HCl (30 mL). The aqueous solution was extracted three times with CH_2Cl_2, and the combined organic extracts were washed with $Na_2S_2O_3$ (saturated aqueous). The organic layer was dried over Na_2SO_4 (anhydrous), filtered, and concentrated in vacuo. Flash chromatography (hexanes−EtOAc 75:25) afforded 0.367 g (92%) of desired keto aldehyde **7** as a clear oil: $R_f = 0.30$ (hexanes−EtOAc 70:30); $[\alpha]^{23}_D$ −47.5 (*c* 1.20, $CHCl_3$); FTIR (film) 1713 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.66 (d, $J = 1.8$ Hz, 1H), 2.41−2.11 (m, 6H), 1.78 (m, 1H), 1.54 (m, 1H), 1.36 (m, 1H), 1.12 (d, $J = 7.3$ Hz, 3H), 1.03 (d, $J = 6.3$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.5, 203.8, 50.9, 45.9, 44.8, 40.0, 34.5, 27.9, 14.3, 9.8; EIMS 168$[M]^+$; HRMS calcd for $[C_{10}H_{16}O_2]^+$ 168.1150, found 168.1151.

Keto Diene 9. Diphenyldiprenylphosphonium bromide (0.956 g, 2.37 mmol)[14b] was azeotropically dried with benzene (2 × 2 mL), dissolved (mostly) in dimethoxyethane (20 mL), cooled to 0 °C, and treated with potassium *tert*-butoxide (2.37 mL, 1 M solution in DME, 2.37 mmol).[14] The mixture immediately turned red. This solution of ylide **8** was transferred dropwise via cannula to a solution of keto aldehyde **7** (0.362 g, 2.15 mmol) in DME (20 mL) at −60 °C, over 3 min (the ylide solution was washed in with an additional 3 mL DME). After 10 min NH_4Cl (saturated aqueous) was added, and the reaction mixture was partitioned between water and ether. The organic layer was separated, and the aqueous phase was extracted again with ether. The combined organic layers were washed with brine, dried over $MgSO_4$ (anhydrous), filtered, and concentrated in vacuo. Flash chromatography (hexanes−EtOAc 80:20) afforded 0.401 g (85%) of keto diene **7** as a clear oil: $R_f = 0.66$ (hexanes−EtOAc 70:30); $[\alpha]^{23}_D$ +7.21 (*c* 1.04, $CHCl_3$); FTIR (film) 1712 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.18 (dd, $J = 15.1$, 10.8 Hz, 1H), 5.78 (d, $J = 10.9$ Hz, 1H), 5.39 (dd, $J = 15.1$, 8.5 Hz, 1H), 2.41 (ddd, $J = 13.2$, 3.6, 2.3 Hz, 1H), 2.31 (sept, $J = 6.3$ Hz, 1H), 2.16, (m, 1H), 2.08 (m, 1H), 2.01 (dt, $J = 13.2$, 0.9 Hz, 1H), 1.86 (m, 1H), 1.76 (s, 3H), 1.74 (s, 3H), 1.66 (m, 1H), (dq, $J = 12.8$, 3.6 Hz, 1H), 1.30 (dq, $J = 13.1$, 3.4 Hz, 1H), 1.02 (d, $J = 6.8$ Hz, 3H), 1.00 (d, $J = 6.4$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.5, 134.2, 133.7, 126.9, 124.9, 45.8, 45.5, 44.9, 42.3, 35.0, 29.5, 25.9, 18.3, 17.8, 14.4; CIMS (NH_3) 238 $[M + NH_4]^+$, 221 $[M + H]^+$; HRMS calcd for $[C_{15}H_{24}O + NH_4]^+$ 238.2171, found 238.2171.

Diketone 12. A solution of diisopropylamine (0.084 mL, 0.6 mmol) in DME (1 mL) was cooled to 0 °C and treated dropwise with *n*-BuLi (0.232 mL, 2.59 M in hexanes, 0.6 mmol). The solution was stirred for 15 min, cooled to −78 °C, and treated with chlorotrimethylsilane (0.152 mL, 1.20 mmol). In a separate flask, keto diene **9** (0.0265 mg, 0.120 mmol) was azeotropically dried with benzene (1 mL), dissolved in DME (1 mL), and transferred dropwise via cannula to the reaction mixture (remaining **9** was washed in with an additional 0.5 mL of DME). After 5 min the reaction mixture was treated with dry triethylamine (1 mL) and $NaHCO_3$ (saturated aqueous) and warmed to 23 °C. The mixture was diluted with water and extracted three times with petroleum ether. The combined organic layers were dried over K_2CO_3 (anhydrous), filtered, and concentrated in vacuo. This afforded 0.0359 g (100%) of the enol ether **10** as an 8:1 mixture of regioisomers (as determined by ^1H NMR analysis): $R_f = 0.68$ (hexanes−EtOAc−Et_3N, 89:10:1); ^1H NMR (400 MHz, C_6D_6) δ 6.35 (dd, $J = 15.0$, 10.8 Hz, 1H), 5.94 (d, $J = 10.1$ Hz, 1H), 5.53 (dd, $J = 15.1$, 8.4 Hz, 1H), 5.00 (s, 1H), 2.2−1.9 (m, 3H), 1.80 (m, 1H), 1.66 (s, 3H), 1.65 (s, 3H), 1.63 (m, 1H), 1.3−1.1 (m, 2H), 1.16 (d, $J = 6.8$ Hz, 3H), 1.04 (d, $J = 6.7$ Hz, 3H), 0.21 (s, 9H).

Enol ether **10** and enone **11** (0.025 g, 0.132 mmol) were combined, azeotropically dried with benzene (2 × 0.5 mL), and dissolved in CH_2Cl_2 (1.2 mL). The solution was cooled to −78 °C and treated with tin tetrachloride (0.015 mL, 0.132 mmol). After 40 min the reaction mixture was treated with potassium carbonate (1 mL, 5% aqueous solution) and warmed to 23 °C. The mixture was partitioned between water and CH_2Cl_2. The organic layer was separated, and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were washed with water and brine, dried over Na_2SO_4 (anhydrous), and concentrated in vacuo. Flash chromatography (hexanes−ether 90:10) afforded 0.0058 g (22%) of the starting keto diene **9** and (hexanes−ether 80:20) 0.0284 g (58%, 74% with respect to recovered **9**) of the Michael adduct **12** as a clear oil: $R_f = 0.52$ and 0.58 (hexanes−EtOAc 70:30); FTIR (film) 1708 cm^{-1}; ^1H NMR (of the lower R_f spot) (400 MHz, $CDCl_3$) δ 7.40−7.29 (m, 5H), 6.20 (dd, $J = 15.2$, 10.7 Hz, 1H), 5.78 (d, $J = 10.8$ Hz, 1H), 5.48 (dd, $J = 15.2$, 6.9 Hz, 1H), 4.62 (m, 2H), 4.41 (d, $J = 17.5$ Hz, 1H), 4.20 (d, $J = 17.6$ Hz, 1H), 2.67 (m, 1H), 2.53 (m, 1H), 2.36 (m, 2H), 2.07 (m, 1H), 1.91 (m, 1H), 1.74 (m, 6H), 1.60−1.07 (m, 5H), 0.95 (m, 9H); EIMS 410 $[M]^+$, 392 $[M - H_2O]^+$; HRMS calcd for $[C_{27}H_{38}O_3]^+$ 410.2811, found 410.2813.

α,β-Enone 13. A solution of diketone **12** (0.214 g, 0.521 mmol) in ethanol (104 mL) was cooled to 0 °C and treated with potassium hydroxide (0.78 mL, 2 M solution in ethanol, 1.56 mmol). After 1 h, the reaction mixture was treated with pH 4 buffer (100 mL), resulting in a white precipitate. The mixture was concentrated in vacuo to remove most of the ethanol and extracted three times with ether. The combined organic layers were washed with brine, dried over $MgSO_4$ (anhydrous), filtered, and concentrated. Flash chromatography (hexanes−ether 90:10) afforded 0.150 g (70%) of aldol cyclization product (β-hydroxy ketone) as a white solid: $R_f = 0.27$ (hexanes−ether 80:20); $[\alpha]^{23}_D$ −47 (*c* 0.86, $CHCl_3$); FTIR (film) 3500, 1726 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.52−7.28 (m, 5H), 6.17 (dd, $J = 15.2$, 10.7 Hz, 1H), 5.79 (d, $J = 10.9$ Hz, 1H), 5.55 (dd, $J = 15.2$, 6.4 Hz, 1H), 4.78 (d, $J = 10.5$ Hz, 1H), 4.38 (d, $J = 10.5$ Hz, 1H), 3.85 (s, 1H), 2.51 (m, 1H), 2.39 (m, 1H), 2.30 (s, 1H), 2.01 (m, 1H), 1.75 (s, 3H), 1.74 (s, 3H), 1.69−1.20 (m, 8H), 1.10 (d, $J = 6.4$ Hz, 3H), 1.03 (d, $J = 6.6$ Hz, 3H), 0.91 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.1, 137.5, 137.0, 133.1, 128.6, 128.4, 127.9, 125.5, 125.2, 88.1, 80.8, 72.6, 45.8, 43.4, 42.3, 40.4, 35.7, 34.2, 32.3, 26.0, 25.3, 18.6, 18.3, 14.0, 11.7; CIMS (NH_3) 428 $[M + NH_4]^+$; HRMS calcd for $[C_{27}H_{38}O_3 + NH_4]^+$ 428.3165, found 428.3157.

A solution of the above β-hydroxy ketone (0.150 g, 0.365 mmol) in pyridine (20 mL) was treated with thionyl chloride (0.107 mL, 1.46 mmol) and stirred at 23 °C. After 1.5 h the solution was poured into ice−water and extracted three times with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 (anhydrous), filtered, and concentrated. Flash chromatography (hexanes−ether 95:5) afforded 0.100 g (70%) of α,β-enone **13** as a colorless powder (one diastereomer): $R_f = 0.45$ (hexanes−ether 80:20); $[\alpha]^{23}_D$ −45.3 (*c* 1.18, $CHCl_3$); FTIR (film) 1676 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.44−7.29 (m, 5H), 6.21 (dd, $J = 16.0$, 10.8 Hz, 1H), 5.79 (d, $J = 10.6$ Hz, 1H), 5.52 (dd, $J = 15.2$, 7.0 Hz, 1H), 4.92 (d, $J = 11.0$ Hz, 1H), 4.83 (d, $J = 11.0$ Hz, 1H), 2.79 (m, 1H), 2.60 (m, 1H), 2.50−2.30 (m, 2H), 2.13 (m, 1H), 1.77 (m, 6H), 1.68−1.27 (m, 6H), 1.19 (m, 6H), 0.95 (d, $J = 6.9$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.3, 154.9, 146.8, 138.1, 135.9, 133.6, 128.3, 128.1, 127.7, 125.6, 125.1, 73.1, 41.5, 40.9, 36.8, 35.9, 35.5, 31.2, 26.5, 26.0, 19.4, 18.4, 18.3, 15.3, 11.7; EIMS 392 $[M]^+$, 301 $[M - Bn]^+$; HRMS calcd for $[C_{27}H_{36}O_2]^+$ 392.2715, found 392.2708.

Phenolic Ether 14. Diisopropylamine (0.045 mL, 0.321 mmol) in THF (2 mL) was cooled to 0 °C and treated dropwise with *n*-BuLi (0.124 mL, 2.59 M solution in hexanes, 0.321 mmol). The solution was stirred for 15 min and cooled to − 78 °C. In a separate flask, α,β-enone **13** (0.0420 g, 0.107 mmol) was azeotropically dried with benzene (1 mL), dissolved in THF (1 mL), and added dropwise via cannula to the reaction mixture (residual **13** was washed in with an additional 0.5 mL of THF). The solution was stirred for 15 min and treated with *tert*-butyldimethylsilyl trifluoromethanesulfonate (0.098 mL, 0.428 mmol). The reaction mixture was stirred for 15 min at −78 °C and then warmed to 0 °C for 15 min. After the mixture was recooled to −78 °C, triethylamine (1 mL) was added, followed by $NaHCO_3$ (saturated aqueous, 1 mL), and the mixture was allowed to warm to 23 °C. Water was added, and the aqueous layer was extracted three times with petroleum ether. The combined organic layers were dried over K_2CO_3 (anhydrous), filtered, and concentrated in vacuo. The

residue was purified by flash chromatography (hexanes−ether-triethylamine 89:10:1) to afford 0.0565 g (100%) of the enol TBS ether of **13** as a clear oil: $R_f = 0.47$ (MeOH, reverse phase C_{18} plate); ^{1}H NMR (500 MHz, C_6D_6) δ 7.43 (d, $J = 7.8$ Hz, 2H), 7.19 (t, $J = 7.6$ Hz, 2H), 7.09 (t, $J = 7.5$ Hz, 1H), 6.38 (dd, $J = 15.0$, 10.7 Hz, 1H), 5.95 (d, $J = 10.8$ Hz, 1H), 5.63 (dd, $J = 15.1$, 7.0 Hz, 1H), 4.98 (d, $J = 11.8$, Hz), 4.70 (d, $J = 11.8$ Hz, 1H), 2.78 (m, 1H), 2.55 (m, 1H), 2.19 (m, 2H), 1.97 (m, 1H), 1.85 (s, 3H), 1.75 (m, 1H), 1.68 (s, 3H), 1.67 (s, 3H), 1.61 (m, 2H), 1.33 (m, 2H), 1.21 (d, $J = 7.1$ Hz, 3H), 1.02 (s, 9H), 0.89 (d, $J = 6.9$ Hz, 3H), 0.22 (s, 3H), 0.19 (s, 3H).

A solution of the above enol ether of **13** (0.0148 g, 0.0292 mmol) in methylcyclohexane (0.9 mL) was treated with activated manganese dioxide (Aldrich Co., dried by azeotroping with toluene, 0.025 g, 0.292 mmol) and heated to 70 °C with stirring for 16 h. The mixture was filtered through Celite, washed extensively with methylene chloride, and the solvent was removed in vacuo, affording crude phenolic ether **14** as a clear oil: $R_f = 0.48$ (hexanes−Et_2O 95:5); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (m, 5H), 6.73 (s, 1H), 6.15 (dd, $J = 15.2$, 10.8 Hz, 1H), 5.82 (d, $J = 10.7$ Hz, 1H), 5.60 (dd, $J = 15.2$, 6.9 Hz, 1H), 5.07 (d, $J = 12.1$ Hz, 1H), 4.77 (d, $J = 12.1$ Hz, 1H), 2.94 (m, 1H), 2.65 (m, 1H), 2.61 (m, 1H), 2.21 (s, 3H), 1.81−1.72 (m, 2H), 1.77 (s, 3H), 1.74 (s, 3H), 1.66 (m, 1H), 1.37 (m, 1H), 1.17 (d, $J = 6.9$ Hz, 3H), 1.00 (s, 9H), 0.88 (d, $J = 6.8$ Hz, 3H), 0.14 (s, 3H), 0.08 (s, 3H).

Mesylate 15. Phenolic ether **14** was dissolved in THF (1.5 mL) and treated dropwise with tetrabutylammonium fluoride (0.060 mL, 1.0 M solution in THF, 0.060 mmol). After the mixture stirred for 5 min, silica gel (0.5 mL) was added, and the mixture was concentrated in vacuo. The product absorbed on silica gel was purified by flash chromatography (hexanes−ether 95:5) to afford 0.0098 g (86% from **13**) of free phenol as a colorless powder: $R_f = 0.41$ (hexanes−ether 80:20); $[\alpha]^{23}_D$ −47 (*c* 0.80, $CHCl_3$); FTIR (film) 3510 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (m, 5H), 6.74 (s, 1H), 6.17 (dd, $J = 15.0$, 10.8 Hz, 1H), 5.83 (d, $J = 10.8$ Hz, 1H), 5.62 (dd, $J = 15.2$, 6.7 Hz, 1H), 5.39 (s, 1H), 4.99 (d, $J = 11.4$ Hz, 1H), 4.80 (d, $J = 11.4$ Hz, 1H), 3.09 (m, 1H), 2.67 (m, 2H), 2.20 (s, 3H), 1.93−1.81 (m, 2H), 1.77 (s, 3H), 1.75 (s, 3H), 1.68 (m, 1H), 1.45 (m, 1H), 1.24 (d, $J = 6.9$ Hz, 3H), 0.92 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.2, 143.4, 137.3, 133.7, 133.0, 130.5, 128.8, 128.4, 127.9, 127.2, 125.6, 125.3, 121.7, 75.6, 42.6, 41.5, 28.0, 27.8, 26.0, 22.3, 19.9, 18.3, 16.3, 15.6; CIMS (NH_3) 408 $[M + NH_4]^+$; HRMS calcd for $[C_{27}H_{34}O_2 + NH_4]^+$ 408.2903, found 408.2910.

This phenol (0.0292 g, 0.0748 mmol) was azeotropically dried with benzene (1 mL), dissolved in CH_2Cl_2 (1.9 mL), and cooled to −30 °C. This solution was treated dropwise with triethylamine (0.021 mL, 0.150 mmol), followed by methanesulfonyl chloride (0.009 mL, 0.112 mmol), and stirred for 15 min. $NaHCO_3$ (saturated aqueous, 1 mL) was added, and the mixture was warmed to 23 °C. Water was added, and the aqueous layer was extracted three times with ether. The combined organic extracts were washed with brine, dried over $MgSO_4$ (anhydrous), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (hexanes−ether 90:10) to afford 0.0337 g (96%) of mesylate **15**: $R_f = 0.41$ (hexanes−EtOAc 80:20); $[\alpha]^{23}_D$ −109 (*c* 0.97, $CHCl_3$); FTIR (film) 1368, 1170 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43−7.35 (m, 5H), 6.86 (s, 1H), 6.13 (dd, $J = 15.1$, 10.8 Hz, 1H), 5.82 (d, $J = 10.7$ Hz, 1H), 5.58 (dd, $J = 15.1$, 7.0 Hz, 1H), 5.02 (d, $J = 11.1$ Hz, 1H), 4.91 (d, $J = 11.1$ Hz, 1H), 3.10 (s, 3H), 3.06 (m, 1H), 2.69 (m, 1H), 2.61 (sex, $J = 6.4$ Hz, 1H), 2.36 (s, 3H), 1.80 (m, 2H), 1.77 (s, 3H), 1.73 (s, 3H), 1.71 (m, 1H), 1.46 (m, 1H), 1.20 (d, $J = 6.9$ Hz, 3H), 0.91 (d, $J = 6.9$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.2, 140.6, 138.8, 136.9, 136.7, 135.9, 133.5, 130.3, 128.6, 128.3, 128.1, 127.9, 126.1, 125.1, 75.7, 42.6, 41.6, 39.3, 27.7, 27.0, 26.0, 22.3, 19.3, 18.3, 17.0, 16.5; FABMS (Na) 491 $[M + Na]^+$, 359 $[M - C_8H_{13}]^+$; HRMS calcd for $[C_{28}H_{36}O_4S + Na]^+$ 491.2232, found 491.2222.

Tricycle 16. A solution of mesylate **15** (0.0337 g, 0.0719 mmol) in CH_2Cl_2 (7.2 mL) was cooled to −78 °C and treated dropwise with methanesulfonic acid (0.023 mL, 0.360 mmol). The solution was warmed to −50 °C and stirred for 10 h, and then triethylamine (0.150 mL) was added. The mixture was warmed to 23 °C, filtered through a small plug of silica gel (hexanes−EtOAc 80:20), and concentrated in vacuo to afford 0.0338 g (100%) of tricycle **16** as a clear oil: $R_f =$ 0.41 (hexanes−EtOAc 80:20); $[\alpha]^{23}_D$ −109 (*c* 0.92, $CHCl_3$); FTIR (film) 1367, 1177 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (m, 5H), 5.11 (dt, $J = 9.2$, 1.2 Hz, 1H), 4.95 (d, $J = 11.0$ Hz, 1H), 4.84 (d, $J = 11.0$ Hz, 1H), 3.63 (br d, $J = 9.1$ Hz, 1H), 3.36 (m, 1H), 3.06 (s, 3H), 2.21 (m, 1H), 2.19 (s, 3H), 2.10 (td, $J = 10.4$, 4.3 Hz, 1H), 1.95 (m, 1H), 1.75 (s, 3H), 1.70 (s, 3H), 1.69−1.50 (m, 4H), 1.24 (d, $J = 7.1$ Hz, 3H), 1.11 (tt, $J = 9.8$, 1.9 Hz, 1H), 1.05 (d, $J = 5.9$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.0, 140.6, 137.6, 137.1, 135.5, 135.1, 130.9, 129.9, 129.0, 128.7, 128.3, 127.9, 75.8, 42.4, 39.3, 39.1, 35.8, 30.1, 29.5, 27.6, 27.5, 25.8, 23.3, 21.0, 17.7, 12.8; EIMS 468 $[M]^+$; HRMS calcd for $[C_{28}H_{36}O_4S]^+$ 468.2334, found 468.2333.

Phenol 17. Tricycle **16** (0.0124 g, 0.0265 mmol) was azeotropically dried with benzene (0.5 mL), dissolved in THF (0.25 mL), and cooled to 0 °C. This solution was treated dropwise with MeMgBr (0.018 mL, 3.0 M solution in ether, 0.053 mmol) and stirred for 18 h. NH_4Cl (saturated aqueous) was added, and the aqueous layer was extracted three times with ether. The combined organic layers were dried over $MgSO_4$ (anhydrous), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (hexanes−ether 95:5) to afford 0.0100 g (97%) of tricyclic phenol **17** (25:1 mixture of diastereomers) as a clear oil: $R_f = 0.55$ (hexanes−EtOAc 80:20); $[\alpha]^{22}_D$ −104 (*c* 1.00, $CHCl_3$); FTIR (film) 3529, 1451 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (m, 5H), 5.49, (s, 1H), 5.14 (dt, $J = 9.2$, 1.2 Hz, 1H), 4.89 (d, $J = 11.2$ Hz, 1H), 4.83 (d, $J = 11.2$ Hz, 1H), 3.63 (dt, $J = 9.0$, 3.4 Hz, 1H), 3.38 (m, 1H), 2.21 (m 1H), 2.12 (dt, $J = 10.5$, 4.8 Hz, 1H), 2.05 (s, 3H), 2.00 (m, 1H), 1.76 (d, $J = 0.9$ Hz, 3H), 1.69 (s, 3H), 1.68−1.50 (m, 4H), 1.30 (d, $J = 7.1$ Hz, 3H), 1.13 (m, 1H), 1.05 (d, $J = 6.1$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.0, 141.9, 137.4, 134.8, 132.9, 130.0, 129.8, 129.3, 128.8, 128.4, 127.9, 120.5, 75.9, 42.0, 39.5, 35.6, 30.6, 29.9, 27.8, 27.6, 25.8, 23.1, 21.0, 17.8, 10.8; EIMS 390 $[M]^+$, 299 $[M - Bn]^+$; HRMS calcd for $[C_{27}H_{34}O_2]^+$ 390.2559, found 390.2563.

Pseudopterosin Aglycone 3. Phenol **17** (0.0148 g, 0.0379 mmol) was azeotropically dried with benzene (0.5 mL), dissolved in CH_2Cl_2 (1.5 mL), and cooled to 0 °C. The solution was treated dropwise with BBr_3 (0.0036 mL, 0.0379 mmol) in CH_2Cl_2 (0.100 mL). After 5 min, $NaHCO_3$ (saturated aqueous, 1 mL) was added, and the mixture was allowed to warm to room temperature. Water was added, and the aqueous layer was extracted three times with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4 (anhydrous), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (hexanes−EtOAc 90:10) to afford 0.0094 g (83%) of pseudopterosin aglycone (**3**) as an oil: $R_f = 0.28$ (hexanes−EtOAc 80:20); $[\alpha]^{23}_D$ −95 (*c* 0.94, $CHCl_3$); FTIR (film) 3449, 1448 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.11 (dt, $J = 9.2$, 1.4 Hz, 1H), 5.03 (br s, 1H), 4.82 (br s, 1H), 3.58 (m, 1H), 3.22 (m, 1H), 2.17 (m, 2H), 2.03 (s, 3H), 2.02 (m, 1H), 1.75 (d, $J = 1.1$ Hz, 3H), 1.67 (s, 3H), 1.65−1.46 (m, 4H), 1.25 (d, $J = 7.0$ Hz, 3H), 1.08 (m, 1H), 1.04 (d, $J = 6.3$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.9, 139.7, 130.3, 130.2, 129.9, 129.7, 125.9, 119.8, 43.2, 39.5, 35.4, 31.0, 30.0, 28.3, 27.4, 25.7, 23.1, 21.0, 17.7, 10.9; EIMS 300 $[M]^+$; HRMS calcd for $[C_{20}H_{28}O_2]^+$ 300.2089, found 300.2096.

α,β-Enone 11. A solution of oxalyl chloride (0.523 mL, 6.00 mmol) in CH_2Cl_2 (3 mL) was cooled to −78 °C and treated dropwise with DMSO (0.929 mL, 13.1 mmol) in CH_2Cl_2 (4 mL). After 10 min, the reaction mixture (at −78 °C) was treated dropwise with a solution of 1-benzyloxy-3-methylbut-3-ene-2-ol[15] (azeotroped with 2 mL of benzene, 1.049 g, 5.46 mmol) in CH_2Cl_2 (5 mL). The reaction mixture was stirred for 15 min and treated dropwise with diisopropylethylamine (4.76 mL, 27.3 mmol). After 15 min, the solution was warmed to 23 °C. Water was added, and the organic layer was separated. The aqueous layer was extracted again with CH_2Cl_2, and the combined organic layers were dried over Na_2SO_4 (anhydrous), filtered, and concentrated. Flash chromatography (hexanes−EtOAc 90:10) afforded 0.941 g (91%) of enone **11** as a clear oil: $R_f = 0.38$ (hexanes−EtOAc 75:25); FTIR (film) 1693 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.32 (m, 5H), 5.90 (s, 1H), 5.79 (q, $J = 1.5$ Hz, 1H), 4.62 (s, 2H), 4.50 (s, 2H), 1.90 (dd, $J = 1.5$, 1.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.6, 142.5, 137.4, 128.5, 128.0, 127.9, 124.9, 73.2, 71.7, 17.5; CIMS (NH_3) 208 $[M + NH_4]^+$, 191 $[M + H]^+$; HRMS calcd for $[C_{12}H_{14}O_2 + NH_4]^+$ 208.1338, found 208.1329.

Enol Ether 21. Diisopropylamine (0.34 mL, 2.40 mmol) in THF (10 mL) was cooled to 0 °C and treated dropwise with *n*-BuLi (0.92 mL, 2.61 M solution in hexanes, 2.40 mmol). The solution was stirred for 15 min and cooled to − 78 °C. In a separate flask, dihydrocarvone[20] (0.2434 g, 1.599 mmol) was azeotropically dried with benzene (1 mL), dissolved in THF (1 mL), and added dropwise via cannula to the reaction mixture (residual dihydrocarvone was washed in with an additional 0.5 mL of THF). The solution was stirred for 15 min. and treated with *tert*-butyldimethylsilyl trifluoromethanesulfonate (0.73 mL, 3.20 mmol). The reaction mixture was stirred for 15 min at −78 °C and then warmed to 0 °C for 15 min. Triethylamine (2 mL) was added, followed by $NaHCO_3$ (saturated aqueous, 5 mL), and the mixture was allowed to warm to 23 °C. Water was added, and the aqueous layer was extracted three times with petroleum ether. The combined organic layers were dried over K_2CO_3 (anhydrous), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (hexanes−Et_2O−triethylamine 89:10:1) to afford 0.423 g (99%) of enol ether **21** as a clear oil: $R_f = 0.73$ (hexanes−ether 90:10); $[\alpha]^{23}_D$ +62 (*c* 0.95, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.56 (m, 1H), 4.76 (d, $J = 3.3$ Hz, 1H), 2.16 (m, 1H), 2.00 (m, 2H), 1.72 (s, 3H), 1.60 (sept, $J = 6.6$ Hz, 1H), 0.94 (s, 9H), 0.86 (m, 6H), 0.17 (s, 3H), 0.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.8, 132.2, 123.7, 105.5, 40.5, 31.7, 26.4, 25.9, 25.8, 20.0, 19.9, 18.3, 17.7, −2.5, −4.3, −4.5; CIMS (NH_3) 284 $[M + NH_4]^+$, 267 $[M + H]^+$; HRMS calcd for $[C_{16}H_{30}OSi + H]^+$ 267.2144, found 267.2149.

TBS Ether 22. A solution of the enol TBS ether of dihydrocarvone **21** (0.0623 g, 0.234 mmol) in methylcyclohexane (5 mL) was treated with activated manganese dioxide (azeotroped from toluene, 0.200 g, 2.38 mmol) and heated to 70 °C. After 36 h, the mixture was filtered through Celite and washed extensively with CH_2Cl_2. The solvent was removed in vacuo, and the residue was filtered through a short plug of silica gel (hexanes−Et_2O 90:10) affording 0.0521 g (84%) of ether **22** as a clear oil: $R_f = 0.38$ (MeOH, reverse phase C_{18} plate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 (d, $J = 7.6$ Hz, 1 H), 6.73 (dd, $J = 7.7$, 1.7 Hz, 1H), 6.63 (d, $J = 1.6$ Hz, 1H), 2.81 (sept, $J = 6.9$ Hz, 1H), 2.17 (s, 3H), 1.21 (d, $J = 6.9$ Hz, 6 H), 1.02 (s, 9H), 0.22 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.8, 147.7, 130.7, 126.1, 119.0, 116.8, 33.7, 25.9, 24.1, 18.3, 16.4, −4.1; CIMS (NH_3) 282 $[M + NH_4]^+$, 265 $[M + H]^+$; HRMS calcd for $[C_{16}H_{28}OSi + NH_4]^+$ 282.2253, found 282.2251.

Anisoate 24. A solution of diene **23**[21] (0.0490 g, 0.190 mmol) in methylcyclohexane (2 mL) was treated with manganese dioxide (azeotroped from toluene, 0.207 g, 2.46 mmol), heated to 70 °C, and stirred for 36 h. The reaction mixture was filtered through Celite and washed extensively with CH_2Cl_2. The solvent was removed in vacuo to afford 0.0403 g (83%) of anisoate **24** as a clear oil: $R_f = 0.30$ (hexanes−Et_2O, 80:20); FTIR (film) 1712, 1261 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, $J = 9.0$ Hz, 2H), 7.34 (d, $J = 8.0$ Hz, 2H), 7.19 (d, $J = 7.9$ Hz, 2H), 6.91 (d, $J = 9.0$ Hz, 2H), 5.30 (s, 3H), 3.85 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 163.5, 138.0, 133.4, 131.8, 129.3, 128.3, 122.7, 113.6, 66.4, 55.5, 21.3; CIMS 256 [M]+; HRMS calcd for $[C_{16}H_{16}O_3^+]^+$ 256.1100, found 256.1099.

4-Methoxyphenyl ether 26. A solution of diene **25**[21] (0.0509 g, 0.208 mmol) in methylcyclohexane (2 mL) was treated with manganese dioxide (azeotroped from toluene, 0.228 g, 2.71 mmol), heated to 70 °C, and stirred for 36 h. The reaction mixture was filtered through Celite and washed extensively with CH_2Cl_2. The solvent was removed in vacuo, and the residue was purified by silica gel chromatography (hexanes−Et_2O 95:5) to afford 0.0412 g (82%) of ether **26** as a clear oil: $R_f = 0.45$ (hexanes−Et_2O 80:20); FTIR (film) 1509, 1232 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (d, $J = 8.0$ Hz, 2H), 7.14 (d, $J = 8.0$ Hz, 2H), 6.84 (m, 4H), 4.11 (t, $J = 7.2$ Hz, 2H), 3.77 (s, 3H), 3.05 (t, $J = 7.2$ Hz, 2H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.9, 153.0, 136.0, 135.3, 129.2, 128.9, 115.6, 114.7, 69.6. 55.8, 35.8, 21.1; EIMS 242 $[M]^+$; HRMS calcd for $[C_{16}H_{18}O_2^+]^+$ 242.1307, found 242.1302.

Acknowledgment. This research was supported by a graduate fellowship from Boehringer Ingelheim Pharmaceutical, Inc. (to S.E.L.) and by a grants from the National Institutes of Health and the National Science Foundation.

JA983041S

(20) Prepared by Mr. Steven N. Goodman, of this group, according to the procedure found in: Deslongchamps, P.; Bélanger, A.; Berney, D. J. F.; Borschberg, H.-J.; Brousseau, R.; Doutheau, A.; Durand, R.; Katayama, H.; Lapalme, R.; Leturc, D. M.; Liao, C.-C.; MacLachlan, F. N.; Maffraud, J.-P.; Marazza, F.; Martino, R.; Moreau, C.; Ruest, L.; Saint-Laurent, L.; Saintonge, R.; Soucy, P. *Can. J. Chem.* **1990**, *68*, 127−152.

(21) Corey, E. J.; Guzman-Perez, A.; Noe, M. C. *J. Am. Chem. Soc.* **1995**, *117*, 10805−10816.