Enantioselective Total Synthesis of Eunicenone A

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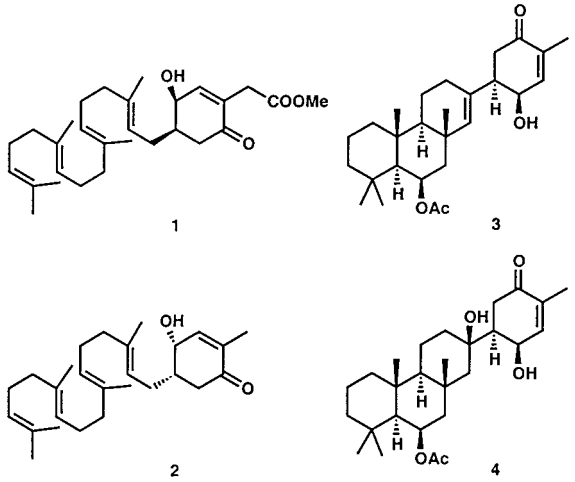
Abstract: An enantioselective, stereocontrolled total synthesis of eunicenone A (**1**) is described starting from geranylgeranylacetylene (**9**) in 14 steps via intermediates **10**−**20**. The most critical construction in the synthesis is the highly effective Diels−Alder combination of the achiral components 2-bromoacrolein and diene **13** in the presence of the chiral Lewis acid catalyst **14** to form **15** (85% yield, 97% ee, >98:2 endo−exo ratio). The synthesis utilizes a novel reagent (**12**) for introduction of silicon, which serves to activate and direct the diene **13** for Diels−Alder reaction and to provide for eventual oxygen functionality of homoallylic alcohol **17** under mild conditions. Other noteworthy steps include the position selective and diastereoselective epoxidation **17** → **18**, the methoxycarbonylation with allylic transposition **19** → **20**, and the α,β-enone unmasking **20** → **1**.

Eunicenone A (**1**) and the corresponding free acid/acetate ester derivative (eunicenone B) are novel tetraprenylated 2-cyclohexenones which have been isolated by Shin and Fenical from a chemically distinct *Eunicea* species (CI86-183) found offshore in the Tobago Cays of the eastern Caribbean sea.[1] The structure of **1** was determined by ^{1}H, ^{13}C, COSY, XHCORR, and COLOC NMR analysis together with IR, mass spectral, and chemical data. The absolute configuration was clarified by circular dichroism measurement with the benzoate of **1**.[1] It has been proposed that **1** is biosynthesized by coupling of a geranylgeraniol derivative with a phenylalanine precursor.[1] Several other known marine natural products may originate from the same type of coupling reaction, including sarcodictyenone (**2**)[2] and suberitenones A and B (**3** and **4**).[3] While no data on biological activity were reported for eunicenones, suberitenone B was shown to inhibit the cholesteryl ester transfer protein (CETP), which mediates the transfer of cholesteryl ester and triglyceride between high-density lipoproteins (HDLs) and low-density lipoproteins (LDLs or VLDLs).[4] Studies have shown an inverse correlation between HDL and the incidence of atherosclerotic cardiovascular diseases.[5] CETP is a possible therapeutic target for atherosclerotic diseases. The structures of eunicenones A and B suggest that they might show bioactivity, for example, as inhibitors of prenyltransferases since they contain both a tetraprenyl side chain and an electrophilic headgroup. Prenyltransferases (such as farnesyltransferases or geranylgeranyltransferases) mediate the functionally important posttranslational prenylation of proteins with polyisoprenoids and have been implicated in processes such as RAS activation which underlie certain proliferative diseases.[6]



The catalytic enantioselective total synthesis of eunicenone A presents a challenge to contemporary synthesis especially because of the paucity of examples and methods for the asymmetric synthesis of such polysubstituted 2-cyclohexenones. Most of the syntheses of chiral 2-cyclohexenones previously reported employ naturally occurring chiral starting materials, enzymatically produced chiral compounds, or chiral auxiliaries.[7,8] We were encouraged to attempt the synthesis of **1** using a catalytic asymmetric Diels−Alder approach because of excellent results obtained previously in our laboratory on the

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(1) Shin, J.; Fenical, W. *Tetrahedron* **1993**, *49*, 9277.

(2) D'Ambrosio, M.; Guerriero, A.; Fabbri, D.; Pietra, F. *Helv. Chim. Acta* **1986**, *69*, 1581.

(3) Shin, J.; Seo, Y.; Rho, J.-R.; Baek, E.; Kwon, B.-M.; Jeong, T.-S.; Bok, S.-H. *J. Org. Chem.* **1995**, *60*, 7582.

(4) Lagrost, L. *Biochim. Biophys. Acta* **1994**, *1215*, 209 and references therein.

(5) (a) Marotti, K. R.; Castle, C. K.; Boyle, T. P.; Lin, A. H.; Murray, R. W.; Melchior, G. W. *Nature* **1993**, *364*, 73. (b) Brown, M. L.; Inazu, A.; Hesler, C. B.; Agellon, L. B.; Mann, C.; Whitlock, M. E.; Marcel, Y. L.; Milne, R. W.; Koizumi, J.; Mabuchi, H.; Takeda, R.; Tall, A. R. *Nature* **1989**, *342*, 448. (c) Inazu, A.; Brown, M. L.; Hesler, C. B.; Agellon, L. B.; Koizumi, J.; Takata, K.; Maruhama, Y.; Mabuchi, H.; Tall, A. R. *N. Engl. J. Med.* **1990**, *323*, 1234.

(6) (a) Leonard, D. M. *J. Med. Chem.* **1997**, *40*, 2971. (b) Casey, P. J.; Solski, P. A.; Der, C. J.; Buss, J. E. *Proc. Natl. Acad. Sci. U.S.A.* **1989**, *86*, 8323. (c) Hancock, J. F.; Magee, A. I.; Chilad, J. E.; Marshall, C. J. *Cell* **1989**, *57*, 1167. (d) Schafer, W. R.; Kim, R.; Sterne, R.; Thorner, J.; Kim, S.-H.; Rine, J. *Science* **1989**, *245*, 379.

(7) For recent collections of references to this literature, see: (a) Hareau, G. P.-J.; Koiwa, M.; Hikichi, S.; Sato, F. *J. Am. Chem. Soc.* **1999**, *121*, 3640. (b) Meyers, A. I.; Brengel, G. P. *J. Chem. Soc., Chem. Commun.* **1997**, 1.

(8) For two other interesting synthetic routes to chiral 2-cyclohexenones using Diels−Alder reactions without a chiral catalyst, see: (a) Kozmin, S. A.; Rawal, V. H. *J. Am. Chem. Soc.* **1997**, *119*, 7165. (b) Stoltz, B. M.; Kano, T.; Corey, E. J. *J. Am. Chem. Soc.* **2000**, *122*, 9044.

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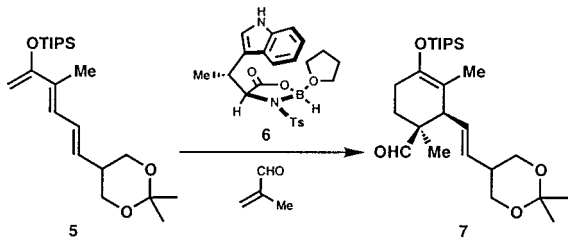
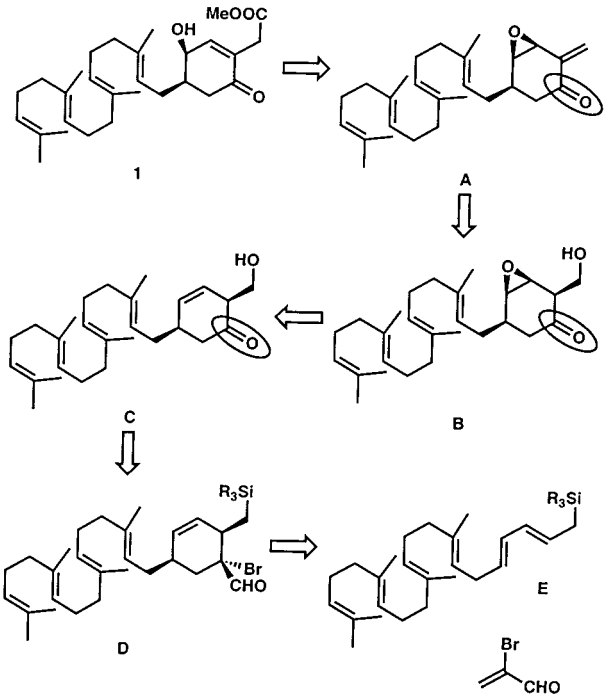
enantioselective total synthesis of the potent, naturally occurring antiulcer agent cassiol.[9] The key Diels−Alder step in that case was the reaction of 2-methylacrolein with diene **5** in the presence of a catalytic amount of the oxazaborolidine **6** to form the adduct **7** in 83% yield and 97% ee.



The retrosynthetic plan devised for the enantioselective synthesis of eunicenone A (**1**) is outlined in Scheme 1. The

Scheme 1



retrosynthetic search was guided by the establishment of the retron for Diels−Alder disconnection of intermediate **D** to the diene **E** and 2-bromoacrolein (as a ketene equivalent). In this design, the silyl group serves to activate and direct diene **E** for Diels−Alder reaction and to provide for eventual oxygen functionality of homoallylic alcohol **C**. The retrosynthetic connection between **1** and the key Diels−Alder adduct **D** was established via the retrosynthetic sequence of target offspring **A** ⇒ **B** ⇒ **C** ⇒ **D**.

The sequence of reactions that were used for the enantioselective synthesis of eunicenone A is outlined in Scheme 2. The acetylenic tetraene **9** was prepared in 83% yield from geranylgeraniol[10] by mesylation followed by ethynylation (1 equiv of *n*-BuLi, then 1.1 equiv of MsCl in THF at −78 °C for 1.5 h, followed by 2.5 equiv of ethynylmagnesium chloride and 1.25 equiv of CuCN at 0 °C for 12 h). Hydrozirconation of **9** with 1.1 equiv of Cp_2ZrHCl in THF at 23 °C for 45 min, subsequent addition of 1.2 equiv of $ZnCl_2$, 5 mol % of $Pd(PPh_3)_4$, and methyl *E*-3-iodoacrylate, and further reaction for 1 h at 23 °C gave stereospecifically the *E,E*-α,*β*,*γ*,*δ*-unsaturated ester **10** (75% yield).[11] Reduction of ester **10** with 3 equiv of DIBAL-H in THF for 40 min at 0 °C gave the corresponding primary alcohol that was benzoylated (1.25 equiv of PhCOCl and 1.5 equiv of pyridine in CH_2Cl_2 at 23 °C for 2 h) to form the all-*E*-hexaene benzoate **11** (96%).

The next step in the synthesis involved a novel disilane reagent (**12**)[12] and a challenging Si−C bond-forming reaction, **11** → **13**. Reaction of **12** with methyllithium (1.05 equiv) in 4:1 THF−hexamethylphosphoric triamide (HMPA)[13a] at −50 °C for 5 h gave dimethyl-2-methoxyphenylsilyllithium, which was treated with 0.5 equiv of CuCN[13b] at 0 °C over 45 min to give a silylmetallic reagent that was then allowed to react with benzoate **11** (ratio of silyl reagent to **11**, 4:1) to provide the all-*E*-hexaene silane **13** (70%). The conversion of **12** (or the chloride) to the corresponding silyllithium reagent could not be effected by other methods previously used for preparing dimethylphenylsilyllithium.[14]

Diels−Alder addition of **13** to 2-bromoacrolein (5 equiv) in the presence of 0.5 equiv of oxazaborolidine **14**[9,15] as catalyst in CH_2Cl_2 at −78 °C for 48 h proceeded smoothly to form bromo aldehyde **15** of 97% ee in 80% yield (endo−exo ratio, >98:2) (85% yield based on recovered diene component).[16] Reduction of bromo aldehyde **15** with 1 equiv of sodium borohydride in THF containing 2% H_2O at 23 °C for 5 min produced cleanly the corresponding bromohydrin, which was transformed in 77% overall yield into the epoxide **16** by treatment with 5 equiv of NaOMe in isopropyl alcohol at −30 to 0 °C over 30 h. Silyl epoxide **16** was converted into the hydroxy ketal **17** by the following sequence: (1) epoxide hydrolysis by exposure to 3 N LiOH in EtOH-*i*-PrOH at 70 °C for 72 h, (2) Si-2-methoxyphenyl cleavage by reaction with 2.5 equiv of trifluoroacetic acid at 23 °C for 3.5 h and subsequent treatment with 5 equiv of potassium fluoride, 5 equiv of $KHCO_3$, and excess H_2O_2 in THF−CH_3OH at 23 °C for 24 h to give a 1,3,4-triol (71% yield for 2 steps), and (3) ketalization with 3 equiv of 1,1-dimethoxycyclopentane and 0.5 equiv of camphorsulfonic acid (CSA) in THF at 23 °C for 14 h to form **17** selectively as the only ketal (87% yield from the corresponding 1,3,4-triol). The facile replacement of the 2-methoxyphenyldimethylsilyl group by hydroxyl under mild conditions is critical to the successful formation of **17** from **16**. In comparison, serious problems were encountered with the hydroxy-desilylation reaction when the conventional phenyldimethylsilyl group, which requires more drastic conditions for this process, was used.[17]

(9) Corey, E. J.; Guzman-Perez, A.; Loh, T.-P. *J. Am. Chem. Soc.* **1994**, *116*, 3611.

(10) We are grateful to Dr. Takashi Onishi, Kuraray Co., Ltd., for a generous gift of *E,E,E*-geranylgeraniol.

(11) The Pd-catalyzed coupling reaction proceeded more rapidly in the presence of $ZnCl_2$, presumably because of prior Zr → Zn transmetallation. See: Panek, J. S.; Hu, T. *J. Org. Chem.* **1997**, *62*, 4912. For reviews on the hydrozirconation−Pd coupling sequence, see: Wipf, P.; Jahn, H. *Tetrahedron* **1996**, *52*, 12853.

(12) Disilane **12** is a very useful reagent whose broader application in synthesis will be described in a separate publication. It is readily prepared by reaction of 2-methoxyphenyllithium with commercially available dichlorotetramethyldisilane (Aldrich).

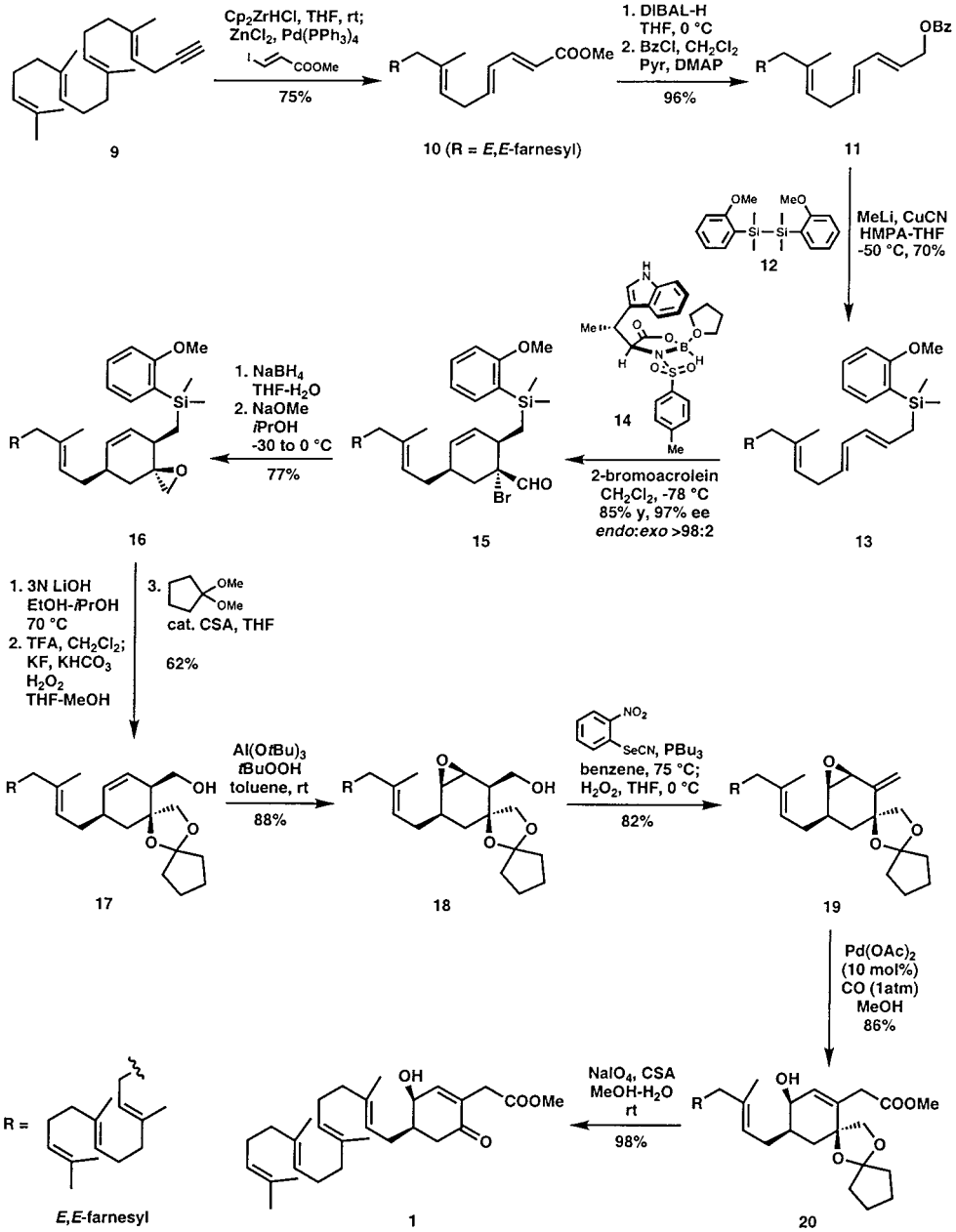
(13) (a) Still, W. C. *J. Org. Chem.* **1976**, *41*, 3063. (b) Fleming, I. In *Organocopper Reagents*; Oxford University Press: Oxford, 1994; pp 257−292.

(14) Rahman, N. A.; Fleming, I.; Zwicky, A. B. *J. Chem. Res. (M)* **1992**, 2401.

(15) (a) Corey, E. J.; Loh, T.-P.; Roper, T. D.; Azimioara, M. D.; Noe, M. C. *J. Am. Chem. Soc.* **1992**, *114*, 8290. (b) Corey, E. J.; Loh, T.-P. *J. Am. Chem. Soc.* **1991**, *113*, 8966. (c) Corey, E. J.; Loh, T.-P. *Tetrahedron Lett.* **1993**, *34*, 3979.

(16) The Diels−Alder reaction of 2-bromoacrolein with dienes of type **13** proceeded more rapidly and with higher enantioselectivity than with analogues in which the 2-methoxyphenyl group was replaced by phenyl.

Scheme 2



The ketal homoallylic alcohol **17** was subjected to selective hydroxyl-directed epoxidation using 1 equiv of Al(O*t*-Bu)$_3$ and 1.5 equiv of *t*-BuOOH in toluene at 23 °C for 2 h to afford the epoxide **18** in 88% yield.[18,19] Dehydration of the epoxy alcohol **18** was effected by using 1.5 equiv of 2-nitrophenylselenocyanate and 1.8 equiv of tri-*n*-butylphosphine[20] in C_6H_6 at 75 °C for 2 h followed by 5 equiv of 30% H_2O_2 in THF at 0 °C for 7 h to form the corresponding methylenecyclohexane derivative **19** in 82% yield. Methoxycarbonylation of **19** to form ketal ester **20** in 86% yield was accomplished by reaction with 1 atm of CO in MeOH at 23 °C for 24 h in the presence of 10 mol % of $Pd(OAc)_2$.[21] When the ketal ester **20** was exposed to a solution of 5 equiv of sodium periodate and 5% CSA in 9:1 MeOH−H_2O at 23 °C for 7 h concomitant ketal hydrolysis and 1,2-glycol cleavage occurred to form eunicenone A (**1**) in 98% overall yield. The identity of totally synthetic **1** with natural eunicenone A was established by comparison of ^{1}H, ^{13}C NMR, IR, and high-resolution mass spectra and optical rotation, $[a]_D^{23}$ +38 (*c* 0.42, $CHCl_3$); lit.[1] $[a]_D^{23}$ +40 (*c* 1.3, $CHCl_3$).

In addition to the key step in the synthesis, the catalytic enantioselective formation of bromo aldehyde **15**, the synthesis

(17) For a review of silyl-to-hydroxy conversion in organic synthesis see: Fleming, I. *Chemtracts-Org. Chem.* **1996**, *9*, 1. The 2-methoxyphenyldimethylsilyl reagents and derivatives used herein were arrived at after extensive experimentation with several alternatives, as will be described in a separate publication (see ref 12).

(18) (a) Takai, K.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1980**, *21*, 1657. (b) Overman, L. E.; Pennington, L. D. *Org. Lett.* **2000**, *2*, 2683.

(19) Attempted epoxidation of **17** with *t*-BuOOH and VO(O*i*-Pr)$_3$, even under optimal conditions (at 23 °C for 22 h in CH_3CN), afforded lower yields (<60%) of **18** due partly to competing epoxidation at the other double bonds.

(20) Grieco, P. A.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1976**, *41*, 1485.

(21) During this process Pd(II) is reduced to a black species that is probably a Pd(0)-active catalyst. When $Pd(PPh_3)_4$ is used as catalyst, high pressures of CO (ca. 60 atm) are required. See: Kiji, J.; Okano, T.; Higashimae, Y.; Fukui, Y. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 1029.

(22) Buchwald, S. L.; LaMaire, S. J.; Nielsen, R. B.; Watson, B. T.; King, S. M. *Tetrahedron Lett.* **1987**, *28*, 3895.

(23) (a) Carpita, A.; Neri, D.; Rossi, R. *Gazz. Chim. Ital.* **1987**, *117*, 481. (b) Biougne, J.; Theron, F. *C. R. Acad. Sci. Paris (Ser. C)* **1971**, *272*, 858.

described above contains a number of noteworthy transformations including the following: **9** → **10**, *E,E*-1,3-diene synthesis; **11** → **13**, copper-catalyzed allylic silane formation using the new reagent **12**; **16** → **17**, mild hydroxy desilylation and selective ketal formation; **17** → **18**, selective monoepoxidation of a reactive pentaene; **19** → **20**, novel methoxycarbonylation of a 1,2-epoxy-1,3-diene with allylic transposition; and **20** → **1**, extremely efficient ketal unmasking and glycol cleavage. The synthesis is both stereo- and regiocontrolled as well as enantioselective.

Experimental Section

Geranylgeranylacetylene (9). To a solution of geranylgeraniol (501 mg, 1.72 mmol, dried by azeotropic removal of water with benzene) in 8 mL of THF at −78 °C was added *n*-BuLi (1.91 M solution in hexanes, 948 μL, 1.81 mmol) dropwise over 2 min. After 15 min, methanesulfonyl chloride (147 μL, 217 mg, 1.90 mmol) was added and the reaction mixture was stirred at −78 °C for 1.5 h. Meanwhile, ethynylmagnesium bromide (0.50 M solution in THF, 8.62 mL, 4.31 mmol) was added to a suspension of CuCN (193 mg, 2.16 mmol, briefly flame-dried in vacuo) in 20 mL of THF at −40 °C. After being warmed to 0 °C for 1 h, the cuprate solution was recooled to −78 °C and the mesylate solution was added via cannula. The resulting mixture was stirred at 0 °C for 12 h and then quenched with 30 mL of saturated NH_4Cl solution (adjusted to pH ∼8 with concentrated NH_4OH). The heterogeneous mixture was stirred vigorously at room temperature for 1 h, poured into 100 mL of water, and extracted with three 120-mL portions of hexanes. The organic phases were combined, dried over $MgSO_4$, filtered, and concentrated to afford a crude pale yellow oil. Purification by flash chromatography on silica gel (elution with 1% EtOAc−hexanes) afforded 427 mg (83%) of geranylgeranylacetylene **9** as a colorless oil.

Methyl (*2E,4E,7E,11E,15E*)-8,12,16,20-Tetramethylheneicosa-2,4,7,11,15,19-hexaenoate (10). To a suspension of Cp_2ZrHCl (522 mg, 2.02 mmol) in 3.1 mL of THF was added a solution of geranylgeranylacetylene **9** (549 mg, 1.84 mmol) in 3.0 mL of THF. The resulting suspension was stirred at room temperature for 45 min and a dark red solution was observed. Zinc chloride (301 mg, 2.21 mmol, fused before used) was added in 4.4 mL of THF. After 5 min, a solution of (*E*)-methyl β-iodoacrylate (354 mg, 1.67 mmol) and $Pd(PPh_3)_4$ (96.6 mg, 0.0836 mmol) in 6.0 mL of THF was added via cannula. The resulting clear brown solution was stirred at room temperature for 1 h, poured into 100 mL of water, and extracted with two 150-mL portions of Et_2O. The organic phases were combined, dried over $MgSO_4$, filtered, and concentrated to afford a crude yellow oil. Purification by flash chromatography on silica gel (elution with 2.5% EtOAc−hexanes) afforded 484 mg (75%) of hexaenyl ester **10** as a pale yellow oil.

(*2E,4E,7E,11E,15E*)-8,12,16,20-Tetramethylheneicosa-2,4,7,11,15,19-hexaenyl Benzoate (11). To a solution of hexaenyl ester **10** (480 mg, 1.25 mmol) in 12.5 mL of THF at −78 °C was slowly added DIBAL-H (1.0 M in toluene, 3.74 mL, 3.74 mmol) dropwise over 3 min. The resulting mixture was warmed to 0 °C for 40 min and quenched with methanol (3.00 mL, 2.37 g, 74.8 mmol), $Na_2SO_4 \cdot 10H_2O$ (24.1 g, 74.8 mmol) and Celite. The crude suspension was warmed to room temperature and stirred vigorously for 30 min. The resulting mixture was diluted with 50 mL of Et_2O and filtered and the filter cake was washed with 300 mL of Et_2O. The organic filtrate was dried over $MgSO_4$, filtered, and concentrated to afford the intermediate crude alcohol that was used without further purification: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.22 (dd, 1H, J = 10.3, 15.3 Hz), 6.05 (dd, 1H, J = 11.0, 15.0 Hz), 5.72 (m, 2H), 5.13 (m, 4H), 4.16 (br s, 2H), 2.79 (app. t, 2H, J = 7.0 Hz), 2.04 (m, 13H), 1.68 (s, 3H), 1.61 (s, 3H), 1.60 (s, 9H).

The crude alcohol (dried by azeotropic removal of water with benzene) was dissolved in 5 mL of CH_2Cl_2 and cooled to 0 °C. Pyridine (151 μL, 148 mg, 1.87 mmol), benzoyl chloride (181 μL, 219 mg, 1.56 mmol), and 4-DMAP (ca. 5 mg) were added, respectively. The reaction mixture was warmed to room temperature for 2 h, poured into 40 mL of water, and extracted with two 60-mL portions of CH_2Cl_2. The combined organic phases were washed with 40 mL of saturated NaCl solution, dried over Na_2SO_4, filtered, and concentrated to afford a pale yellow oil. Purification by flash chromatography on silica gel (elution with 5% EtOAc−hexanes) afforded 550 mg (96%) of hexaenyl benzoate **11** as a pale yellow oil: R_f 0.53 (EtOAc−hexanes 1:9); FTIR (thin film) 2967, 2917, 2854, 1722 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (dd, 2H, J = 1.6, 8.4 Hz), 7.55 (t, 1H, J = 7.4 Hz), 7.43 (t, 2H, J = 7.4 Hz), 6.36 (dd, 1H, J = 10.0, 14.8 Hz), 6.08 (dd, 1H, J = 10.4, 15.2 Hz), 5.76 (m, 2H), 5.13 (m, 4H), 4.83 (d, 2H, J = 7.2 Hz), 2.80 (app. t, 2H, J = 6.8 Hz), 2.04 (m, 12H), 1.68 (s, 3H), 1.62 (s, 3H), 1.60 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 136.7, 135.1, 135.0, 134.9, 134.8, 132.8, 131.1, 130.2, 129.5, 128.7, 128.2, 124.3, 124.12, 124.09, 124.0, 120.9, 65.4, 39.76, 39.75, 39.73, 31.2, 26.8, 26.7, 26.6, 25.8, 17.8, 16.12, 16.11, 16.09; HMRS (CI) calcd for $[C_{32}H_{44}O_2]$ ($[M + NH_4]^+$) 478.3685, found 478.3681.

((*2E,4E,7E,11E,15E*)-8,12,16,20-Tetramethylheneicosa-2,4,7,11,-15,19-hexaenyl)(2-methoxyphenyl)dimethylsilane (13). To a 0.15 M solution of bis(2-methoxyphenyl)tetramethyldisilane **12**[12] (1.10 mL, 1.13 g, 3.43 mmol, dried by azeotropic removal of water with benzene) in 22.9 mL of HMPA−THF (20% v/v) at −50 °C was added methyllithium (1.56 M solution in Et_2O, 2.31 mL, 3.60 mmol). After 5 h, a suspension of CuCN (154 mg, 1.71 mmol, briefly flame-dried in vacuo) in 6 mL of THF was added to the orange silyllithium solution. The resulting mixture was stirred at 0 °C for 45 min. The resulting brownish yellow silyl cuprate solution was recooled to −50 °C and hexaenyl benzoate **11** (395 mg, 0.857 mmol) was added with the aid of 3 mL of THF. The reaction mixture was quenched after 16 h with 10 mL of saturated NH_4Cl solution and stirred vigorously at room temperature for 2 h. The crude mixture was poured into a solution of 200 mL of water and 1 mL of concentrated NH_4OH and extracted with two 250-mL portions of hexanes. The combined organic phases were dried over Na_2SO_4, filtered, and concentrated to afford a crude yellow oil. Purification by flash chromatography on silica gel (brief filtration with 5% CH_2Cl_2−hexanes) followed by reverse-phase silica gel column chromatography (elution with MeOH) afforded 305 mg (70%) of hexaenylsilane **13** as a colorless oil: R_f 0.52 (EtOAc−hexanes 1:19), 0.26 (MeOH, reverse phase TLC plate); FTIR (thin film) 3008, 2963, 2916, 2855, 1589, 1573 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (m, 2H), 6.95 (t, 1H, J = 7.3 Hz), 6.83 (d, 1H, J = 8.0 Hz), 5.97 (dd, 1H, J = 10.5, 14.0 Hz), 5.90 (dd, 1H, J = 10.5, 14.5 Hz), 5.56 (dt, 1H, J = 8.0, 14.5 Hz), 5.43 (dt, 1H, J = 7.0, 14.5 Hz), 5.12 (m, 4H), 3.80 (s, 3H), 2.74 (app. t, 2H, J = 7.0 Hz), 2.07 (m, 6H), 1.99 (m, 6H), 1.81 (d, 2H, J = 8.5 Hz), 1.69 (s, 3H), 1.60 (s, 12H), 0.25 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.0, 135.8, 135.1, 134.9, 134.7, 131.1, 130.7, 130.5, 129.2, 129.1, 128.4, 126.2, 124.3, 124.12, 124.07, 121.8, 120.3, 109.3, 55.0, 39.81, 39.80, 39.79, 31.2, 26.9, 26.8, 26.7, 25.8, 22.2, 17.8, 16.18, 16.16, 16.15, −2.9; HMRS (EI) calcd for $[C_{34}H_{52}OSi]$ ($[M]^+$) 504.3788, found 504.3798.

Diels−Alder Adduct 15. A suspension of (*R*)-*N*-*p*-Toluenesulfonyl-β-methyltryptophan[15] (112 mg, 0.302 mmol, dried by azeotropic removal of water with benzene) in 5 mL of CH_2Cl_2 at 23 °C was treated dropwise with $BH_3 \cdot$THF (0.746 M, 404 μL, 0.302 mmol) and stirred for 15 min. The resulting homogeneous mixture was briefly concentrated in vacuo (<2 min),[25] redissolved in 3.7 mL of CH_2Cl_2, and cooled to −78 °C. 2-Bromoacrolein (244 μL, 408 mg, 3.02 mmol) and a solution of hexaenyl silane **13** (305 mg, 0.603 mmol, dried by azeotropic removal of water with benzene) in 1 mL of CH_2Cl_2 were added slowly dropwise respectively to the catalyst solution at −78 °C. The reaction mixture was maintained at −78 °C for 48 h and then quenched with 750 μL of Et_3N. After warming to room temperature, the reaction mixture was diluted with hexanes, dried over Na_2SO_4, and filtered. The solvent was removed in vacuo and the residue was purified by flash chromatography on silica gel (gradient elution with 0.2−0.5% EtOAc−hexanes) to give 18.2 mg (6%) of recovered **13** and 309 mg (80%, 97% ee, >98:2 endo:exo) of cycloadduct **15** as a colorless oil: $[\alpha]^{23}_D$ −108.1 (*c* 0.50, $CHCl_3$, 97% ee); R_f 0.33 (EtOAc−hexanes 1:19); FTIR (thin film) 2961, 2917, 2854, 1727, 1589, 1572 cm^{-1}; ^{1}H NMR (400

(24) Coulson, D. R. In *Inorganic Syntheses*; McGraw-Hill: New York, 1972; Vol. XIII, pp 121−124.

(25) A more active Diels−Alder catalyst was obtained after removal of excess THF from the catalyst mixture.

MHz, $CDCl_3$) δ 9.29 (s, 1H), 7.37 (m, 2H), 6.97 (app. t, 1H, J = 7.2 Hz), 6.84 (d, 1H, J = 8.4 Hz), 5.54 (s, 2H), 5.16 (m, 1H), 5.10 (m, 3H), 3.81 (s, 3H), 2.76 (d, 1H, J = 12.8 Hz), 2.46 (m, 1H), 2.06 (m, 15H), 1.69 (dd, 1H, J = 10.4, 15.2 Hz), 1.68 (s, 3H), 1.61 (s, 3H), 1.60 (s, 9H), 0.98 (dd, 1H, J = 2.8, 13.6 Hz), 0.75 (dd, 1H, J = 12.4, 13.6 Hz), 0.34 (s, 3H), 0.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.4, 163.9, 137.1, 135.13, 135.06, 134.8, 131.3, 131.2, 130.0, 127.5, 125.3, 124.3, 124.2, 124.0, 121.4, 120.7, 109.5, 75.1, 54.9, 39.9, 39.79, 39.76, 39.6, 35.2, 33.4, 30.0, 26.9, 26.8, 26.7, 25.8, 23.4, 17.8, 16.4, 16.14, 16.11, −1.5, −1.8; HMRS (ESI) calcd for [$C_{37}H_{55}BrO_2Si$] ([M + H]$^+$) 639.3233, found 639.3204. Diastereoselectivity, the exo/endo ratio, was determined by ^{1}H NMR analysis of the crude mixture. Enantioselectivity was determined by reduction with $NaBH_4$ to the corresponding alcohol (vide infra), conversion to the (*R*)-MTPA ester derivative, and ^{1}H NMR integration (500 MHz, CD_3CN): δ 4.74 (d, 1H, major), 4.68 (d, 1H, minor).

Conversion of 15 to Epoxide 16. To a solution of Diels−Alder adduct **15** (305 mg, 0.477 mmol) in 6 mL of THF at room temperature was added 100 μL of water and $NaBH_4$ (18.0 mg, 0.477 mmol). After 5 min, the reaction mixture was poured into 100 mL of water and extracted with three 125-mL portions of Et_2O. The organic phases were combined and dried over $MgSO_4$, filtered, and concentrated to afford the intermediate crude alcohol, which was used without further purification: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (m, 2H), 6.95 (app. t, 1H, J = 7.0 Hz), 6.82 (d, 1H, J = 8.0 Hz), 5.55 (ddd, 1H, J = 2.4, 4.9, 10.1 Hz), 5.47 (d, 1H, J = 10.1 Hz), 5.15 (m, 1H), 5.11 (m, 3H), 3.82 (d, 1H, J = 12.5 Hz), 3.80 (s, 3H), 3.70 (d, 1H, J = 12.5 Hz), 2.78 (br d, 1H, J = 12.0 Hz), 2.49 (m, 1H), 1.97 (m, 16H), 1.68 (s, 3H), 1.60 (s, 12H), 1.39 (dd, 1H, J = 10.0, 13.5 Hz), 1.31 (dd, 1H, J = 3.5, 13.5 Hz), 0.59 (app. t, 1H, J = 12.8 Hz), 0.33 (s, 3H), 0.29 (s, 3H).

The crude alcohol was dissolved in 8 mL of 2-propanol and cooled to −30 °C. Sodium methoxide (129 mg, 2.39 mmol) was added, and the resulting mixture was stirred at −30 °C for 24 h and then warmed to 0 °C over 6 h. H_2O (10 mL) was added and the resulting mixture was concentrated to remove most of the 2-propanol. The crude material was poured into 100 mL of water and extracted with three 125-mL portions of Et_2O. The organic phases were combined, dried over $MgSO_4$, filtered, and concentrated to afford a colorless oil. Purification by flash chromatography on silica gel (elution with 25−33% benzene−hexanes with 0.1% Et_3N) afforded 207 mg (77%) of epoxide **16** as a colorless oil: $[\alpha]^{23}_D$ −67.4 (*c* 0.69, $CHCl_3$, 97% ee); R_f 0.49 (benzene−hexanes 1:1); FTIR (thin film) 2916, 2853, 1588 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (dd, 1H, J = 1.8, 7.3 Hz), 7.34 (ddd, 1H, J = 1.8, 7.3, 8.2 Hz), 6.94 (app. td, 1H, J = 1.0, 7.3 Hz), 6.81 (d, 1H, J = 8.2 Hz), 5.57 (ddd, 1H, J = 2.6, 4.8, 9.9 Hz), 5.43 (br d, 1H, J = 10.3 Hz), 5.12 (m, 4H), 3.79 (s, 3H), 2.62 (d, 1H, J = 5.1 Hz), 2.60 (dd, 1H, J = 1.3, 5.1 Hz), 2.32 (m, 1H), 2.03 (m, 14H), 1.91 (app. t, 1H, J = 11.7 Hz), 1.79 (m, 1H), 1.69 (s, 3H), 1.61 (s, 6H), 1.60 (s, 6H), 1.32 (dd, 1H, J = 3.7, 14.3 Hz), 1.18 (dd, 1H, J = 5.7, 12.6 Hz), 0.94 (dd, 1H, J = 11.4, 14.3 Hz), 0.32 (s, 3H), 0.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.1, 136.7, 135.1, 134.9, 134.8, 131.5, 131.1, 130.6, 130.0, 126.8, 124.3, 124.1, 124.0, 121.8, 120.3, 109.3, 61.5, 56.0, 54.9, 39.9, 39.8, 39.7, 38.4, 37.9, 34.3, 32.5, 26.84, 26.75, 26.71, 25.8, 19.3, 17.8, 16.3, 16.11, 16.08, −1.56, −1.64; HMRS (FAB) calcd for [$C_{37}H_{56}O_2Si$] ([M + Na]$^+$) 583.3947; found 583.3941.

Transformation of Epoxide 16 to the Corresponding Glycol. To a solution of epoxide **16** (97.6 mg, 0.174 mmol) in 10.6 mL of EtOH−*i*-PrOH (4:1) was added LiOH solution (3.00 N in water, 5.80 mL, 17.4 mmol). The resulting solution was heated to 70 °C under a N_2 atmosphere for 72 h, poured into 100 mL of water, and extracted with five 100-mL portions of EtOAc. The organic phases were combined, dried over Na_2SO_4, filtered, and concentrated to afford a colorless oil, which was redissolved in 4 mL of CH_2Cl_2 and treated with trifluoroacetic acid (33.5 μL, 49.6 mg, 0.435 mmol). After 3.5 h, the reaction mixture was concentrated and sparged with two 4-mL portions of CH_2Cl_2 to remove excess TFA. The crude mixture was then redissolved in 4 mL of THF−MeOH (1:1). KF (50.5 mg, 0.870 mmol), $KHCO_3$ (87.1 mg, 0.870 mmol), and H_2O_2 (aqueous solution, 30% w/v, 197 μL, 1.74 mmol) were added and the resulting mixture was stirred vigorously for 24 h. The reaction mixture was then diluted with 100 mL of water, dried over Na_2SO_4, filtered, and concentrated in vacuo to afford a clear crude oil. Purification by column chromatography (gradient elution with 25−67% EtOAc−hexanes) afforded 53.1 mg (71%) of the corresponding glycol intermediate as a colorless oil: $[\alpha]^{23}_D$ +1.6 (*c* 0.90, $CHCl_3$, 97% ee); R_f 0.58 (EtOAc); FTIR (thin film) 3382, 2961, 2923, 2854 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.59 (d, 1H, J = 9.9 Hz), 5.42 (ddd, 1H, J = 2.4, 4.9, 9.9 Hz), 5.11 (m, 4H), 3.75 (dd, 1H, J = 9.2, 11.4 Hz), 3.64 (br d, 1H, J = 11.4 Hz), 3.54 (d, 1H, J = 11.0 Hz), 3.47 (d, 1H, J = 11.0 Hz), 3.19 (br s, 1H), 3.02 (br s, 1H), 2.42 (m, 1H), 2.12 (m, 1H), 2.03 (m, 15H), 1.82 (dd, 1H, J = 5.7, 12.8 Hz), 1.68 (s, 3H), 1.60 (s, 12H), 1.50 (dd, 1H, J = 11.0, 12.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.1, 135.1, 135.0, 132.8, 131.3, 124.6, 124.4, 124.2, 124.1, 121.5, 75.5, 67.8, 64.4, 43.1, 39.8, 39.71, 39.70, 35.8, 34.5, 33.9, 26.7, 26.64, 26.63, 25.7, 17.7, 16.3, 16.03, 16.00; HMRS (ESI) calcd for [$C_{28}H_{46}O_3$] ([M + H]$^+$) 431.3525, found 431.3540.

Ketal 17. To triol intermediate above (53.1 mg, 0.123 mmol) in 2.05 mL of THF was added CSA (14.3 mg, 0.0616 mmol) and 1,1-dimethoxycyclopentane (51.4 μL, 48.2 mg, 0.370 mmol). After being stirred at room temperature for 14 h, the reaction mixture was poured into 50 mL of a half-saturated solution of $NaHCO_3$ and extracted with three 50-mL portions of Et_2O. The combined organic phases were washed with 50 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford a colorless oil. Purification by flash chromatography on silica gel (elution with 5% EtOAc−hexanes) afforded 53.3 mg (87%) of ketal **17** as a colorless oil: $[\alpha]^{23}_D$ −4.5 (*c* 1.1, $CHCl_3$, 97% ee); R_f 0.56 (EtOAc−hexanes 1:3); FTIR (thin film) 3533, 2963, 2925, 2854 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.57 (d, 1H, J = 9.9 Hz), 5.45 (ddd, 1H, J = 2.2, 5.1, 9.9 Hz), 5.10 (m, 4H), 3.81 (d, 1H, J = 8.8 Hz), 3.73 (dd, 1H, J = 9.2, 11.7 Hz), 3.69 (d, 1H, J = 8.8 Hz), 3.57 (ddd, 1H, J = 2.9, 10.3, 11.7 Hz), 3.44 (d, 1H, J = 10.3 Hz), 2.42 (m, 1H), 2.19 (m, 1H), 2.02 (m, 14H), 1.83 (m, 5H), 1.69 (m, 5H), 1.68 (s, 3H), 1.60 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.2, 135.1, 134.9, 133.3, 131.3, 124.9, 124.4, 124.2, 124.0, 121.3, 119.1, 83.4, 74.3, 65.0, 46.0, 39.8, 39.71, 39.70, 37.03, 36.99, 36.6, 34.4, 33.9, 26.7, 26.6 (2C), 25.7, 23.3, 23.2, 17.7, 16.3, 16.00, 15.99; HMRS (ESI) calcd for [$C_{33}H_{52}O_3$] ([M + H]$^+$) 497.3994, found 497.4013.

Epoxy Alcohol 18. To homoallylic alcohol **17** (38.1 mg, 0.0767 mmol) was added a solution of aluminum *tert*-butoxide (18.9 mg, 0.0767 mmol) in 380 μL of toluene followed by anhydrous *tert*-butylhydroperoxide (11.6 μL, 10.4 mg, 0.115 mmol). After being stirred at room temperature for 2 h, the reaction crude was purified directly by flash chromatography on silica gel (gradient elution with 10−15% EtOAc−hexanes) to afford 34.4 mg (88%) of epoxy alcohol **18** as a colorless oil: $[\alpha]^{23}_D$ −1.4 (*c* 0.56, $CHCl_3$, 97% ee); R_f 0.18 (EtOAc−hexanes 1:3); FTIR (thin film) 3455, 2964, 2925, 2870, 2856 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.17 (m, 1H), 5.10 (m, 3H), 3.98 (dd, 1H, J = 7.3, 11.4 Hz), 3.86 (m, 1H), 3.75 (d, 1H, J = 8.4 Hz), 3.63 (d, 1H, J = 8.4 Hz), 3.25 (dd, 1H, J = 3.7, 5.1 Hz), 3.07 (d, 1H, J = 3.7 Hz), 2.75 (br d, 1H, J = 7.0 Hz), 2.25 (m, 2H), 2.06 (m, 10H), 1.97 (m, 4H), 1.85 (m, 2H), 1.83−1.65 (m, 7H), 1.68 (s, 3H), 1.64 (s, 3H), 1.59 (s, 9H), 1.33 (dd, 1H, J = 4.4, 12.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.8, 135.1, 135.0, 131.3, 124.4, 124.2, 124.0, 121.0, 119.3, 81.4, 74.4, 61.7, 54.5, 54.1, 42.0, 39.8, 39.7 (2C), 37.0, 36.8, 35.1, 32.4, 31.8, 26.7, 26.63, 26.60, 25.7, 23.4, 23.0, 17.7, 16.1, 16.01, 15.99; HMRS (ESI) calcd for [$C_{33}H_{52}O_4$] ([M + Na]$^+$) 535.3763, found 535.3745.

Transformation of Alcohol 18 to Exocyclic Olefin 19. To a solution of epoxy alcohol **18** (34.4 mg, 0.0671 mmol) and *o*-nitrophenylselenocyanate (22.9 mg, 0.101 mmol) in 1.34 mL of benzene was added tributylphosphine (30.1 μL, 24.4 mg, 0.121 mmol). The resulting dark red solution was heated at 75 °C and became orange in color within 5 min. After 2 h, the reaction mixture was cooled to room temperature, diluted with 2.7 mL of THF, and cooled to 0 °C. H_2O_2 (aqueous solution, 30% w/v, 38.0 μL, 11.4 mg, 0.335 mmol) was added. After being stirred at 0 °C for 7 h, the reaction mixture was poured into 60 mL of H_2O and extracted with two 60-mL portions of CH_2Cl_2. The organic phases were combined, dried over Na_2SO_4, filtered, and concentrated to afford a yellow oil. Purification by flash chromatography on silica gel (elution with 5% EtOAc−hexanes) afforded 27.1 mg (82%)

of exocyclic olefin **19** as a pale yellow oil: $[\alpha]^{23}_{D}$ +30.1 (*c* 0.38, $CHCl_3$, 97% ee); R_f 0.60 (EtOAc−hexanes 1:4); FTIR (thin film) 2963, 2926, 2870, 2854 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.66 (d, 1H, J = 1.0 Hz), 5.49 (s, 1H), 5.20 (m, 1H), 5.11 (m, 3H), 3.77 (d, 1H, J = 8.3 Hz), 3.61 (d, 1H, J = 8.3 Hz), 3.51 (d, 1H, J = 3.9 Hz), 3.27 (d, 1H, J = 3.9 Hz), 2.28 (m, 1H), 2.05 (m, 15H), 1.92 (m, 1H), 1.80 (m, 2H), 1.76−1.62 (m, 5H), 1.68 (s, 3H), 1.64 (s, 3H), 1.60 (s, 9H), 1.51 (dd, 1H, J = 4.9, 12.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.8, 137.7, 135.1, 134.9, 131.3, 124.4, 124.2, 124.0, 121.1, 119.6, 119.5, 80.1, 75.0, 55.6, 54.6, 39.8, 39.7 (2C), 37.2, 36.5, 34.5, 34.4, 31.9, 26.7, 26.6 (2C), 25.7, 23.8, 23.2, 17.7, 16.2, 16.02, 16.00; HMRS (ESI) calcd for $[C_{33}H_{50}O_3]$ ($[M + Na]^+$) 517.3658, found 517.3678.

Methoxycarbonylation of Epoxide 19 To Form 20. To a mixture of vinyl epoxide **19** (10.7 mg, 0.0216 mmol) and $Pd(OAc)_2$ (0.5 mg, 0.002 mmol) under 1 atm of CO (balloon pressure) was added 80 μL of methanol. A heterogeneous mixture with black Pd precipitate was observed instantaneously. After being stirred vigorously at room temperature for 24 h, the reaction mixture was filtered through a cotton plug with CH_2Cl_2 and concentrated to afford a colorless oil. Purification by flash chromatography on silica gel (elution with 10% EtOAc−hexanes) afforded 10.3 mg (86%) of hydroxyester **20** as a colorless oil: $[\alpha]^{23}_{D}$ +33.7 (*c* 0.32, $CHCl_3$, 97% ee); R_f 0.23 (EtOAc−hexanes 1:3); FTIR (thin film) 3432, 2961, 2926, 2872, 1741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.88 (d, 1H, J = 5.1 Hz), 5.18 (m, 1H), 5.10 (m, 3H), 4.00 (m, 1H), 3.78 (d, 1H, J = 8.8 Hz), 3.74 (d, 1H, J = 8.8 Hz), 3.68 (s, 3H), 3.11 (d, 1H, J = 15.7 Hz), 3.07 (d, 1H, J = 15.7 Hz), 2.21 (m, 1H), 2.02 (m, 14H), 1.82 (m, 6H), 1.75−1.65 (m, 3H), 1.68 (s, 3H), 1.64 (s, 3H), 1.60 (s, 9H), 1.55 (m, 1H), 1.42 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 137.6, 137.2, 135.2, 134.9, 131.3, 131.2, 124.4, 124.2, 124.1, 121.7, 119.8, 81.4, 72.2, 65.1, 51.9, 39.9, 39.72, 39.71, 38.2, 37.5, 36.6, 36.3, 35.6, 30.1, 26.8, 26.7, 26.6, 25.7, 23.7, 23.2, 17.7, 16.2, 16.01, 16.00; HMRS (ESI) calcd for $[C_{35}H_{54}O_5]$ ($[M + NH_4]^+$) 572.4315, found 572.4294.

Eunicenone A (1). To a mixture of hydroxyester **20** (10 mg, 0.019 mmol) and $NaIO_4$ (20 mg, 0.093 mmol) was added 11 mL of a solution of 5% CSA (w/v) in MeOH−H_2O (9:1). After being stirred at room temperature for 7 h, the reaction mixture was quenched with 10 mL of saturated $NaHCO_3$ solution and concentrated to remove most of the MeOH. The concentrate was poured into 50 mL of saturated $NaHCO_3$ solution and extracted with three 60-mL portions of EtOAc. The organic phases were combined, dried over Na_2SO_4, filtered, and concentrated to afford a colorless oil. Purification by flash chromatography on silica gel (gradient elution with 15−20% EtOAc−hexanes) afforded 8.3 mg (98%) of eunicenone A (**1**) as a colorless oil with physical and spectral characteristics identical with those reported:[1] $[\alpha]^{23}_{D}$ +37.8 (*c* 0.42, $CHCl_3$, 97% ee); R_f 0.51 (EtOAc−hexanes 1:1); FTIR (thin film) 3417, 2950, 2921, 2853, 1743, 1681 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.81 (d, 1H, J = 4.4 Hz), 5.15 (m, 1H), 5.10 (m, 3H), 4.48 (app. br q, 1H, J = 4.8 Hz), 3.68 (s, 3H), 3.22 (s, 2H), 2.56 (dd, 1H, J = 9.9, 16.7 Hz), 2.41 (dd, 1H, J = 4.0, 16.7 Hz), 2.30 (m, 1H), 2.24 (m, 1H), 2.15−1.90 (m, 13H), 1.80 (d, 1H, J = 6.2 Hz, OH), 1.68 (s, 3H), 1.63 (s, 3H), 1.60 (s, 9H); ^{13}C NMR (100 MHz, C_6D_6) δ 196.7, 171.0, 146.3, 137.4, 135.2, 135.0, 134.1, 131.1, 124.9, 124.8, 124.6, 122.1, 66.5, 51.5, 40.6, 40.3, 40.21, 40.18, 39.2, 35.0, 28.2, 27.2, 27.1, 26.9, 25.8, 17.7, 16.14 (2C), 16.11; HMRS (ESI) calcd for $[C_{29}H_{44}O_4]$ ($[M + Na]^+$) 479.3137, found 479.3157.

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Supporting Information Available: Full procedures and characterization for compounds **9** and **10** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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