pended in MeOH (12 mL), heated to reflux, and treated with pyrrolidine (0.987 mL, 11.82 mmol) whereupon the solution momentarily became homogeneous before precipitation began. The solution was cooled to 0 °C, and the precipitate was isolated by filtration and dried in vacuo to give **9α,17α-dihydroxy-16β-methyl-3-(1-pyrrolidinyl)pregna-3,5-diene (21)** (2.86 g, 82%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.89 (s, 3 H, 18-CH_3), 1.02 (s, 3 H, 19-CH_3), 1.10 (d, J = 7 Hz, 3 H, 16-CH_3), 2.21 (s, 3 H, 21-CH_3), 3.89 (br, 4 H, NCH_2), 4.56 (s, 1 H, H_4), 6.50 (d, J = 1.5 Hz, 1 H, H_6). This material was used without further purification.

Step B. Enamine **21** (1.17 g, 2.83 mmol) in EtOH (30 mL) was added to a solution of HCl (0.5 g) in EtOH (20 mL) and cooled to −55 °C. The solution was treated with Br_2 (0.22 mL, 4.25 mmol) in EtOH (10 mL), which was added over 60 min. Once addition was complete the solvent was evaporated in vacuo to give an oil. The oil was crystallized from EtOH/Et_2O to afford **1-(21-bromo-9α,17α-dihydroxy-16β-methyl-20-oxopregn-4-en-3-yl-idene)pyrrolidinium bromide (22)** (1.42 g, 87%): ^{1}H NMR δ (250 MHz, $CDCl_3$) δ 0.77 (s, 3 H, 18-CH_3), 1.06 (d, J = 7 Hz, 3 H, 16-CH_3), 1.25 (s, 3 H, 19-CH_3), 4.48 (AB q, J = 16 Hz, 21-CH_2). This material was used without further purification.

Step C. Enaminium bromide **22** (1.42 g, 2.47 mmol) in EtOH (25 mL) was treated with $KHCO_3$ (1.0 g, 9.88 mmol) in H_2O (25 mL) and stirred for 2 h. Dilution of the reaction mixture with H_2O (75 mL) precipitated a solid which was isolated by filtration and dried in vacuo to give **23** (0.77 g, 71%): mp 210–212 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.94 (s, 3 H, 18-CH_3), 1.13 (d, J = 7.2 Hz, 3 H, 16-CH_3), 1.34 (s, 3 H, 19-CH_3), 4.25 (AB q, J = 16.2 Hz, 21-CH_2), 5.90 (br, 1 H, H_4). Anal. Calcd for $C_{22}H_{31}O_4Br$: C, 60.14; H, 7.11. Found: C, 60.07; H, 6.89.

21-(Acetyloxy)-9α,17α-dihydroxy-16β-methylpregn-4-ene-3,20-dione (18). Bromide **23** (0.7 g, 1.59 mmol) in acetone (70 mL) was treated with KOAc (3.0 g, 30.46 mmol) and heated at reflux for 5 h. Evaporation of the solvent gave a solid which was recrystallized from acetone/H_2O to give **18** (0.554 g, 83%): mp 168–170 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (s, 3 H, 18-CH_3), 1.14 (d, J = 7.3 Hz, 3 H, 16-CH_3), 1.32 (s, 3 H, 19-CH_3), 2.17 (s, 3 H, OAc), 4.96 (s, 2 H, 21-CH_2) 5.87 (s, 1 H, H_4); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 13.91, 19.59, 19.91, 20.66, 25.62, 26.21, 26.83, 28.50, 31.88, 34.09, 34.81, 37.04, 42.95, 44.47, 49.02, 49.53, 69.63, 76.55, 89.80, 126.76, 169.10, 170.71, 199.89, 205.16; HRMS for $C_{24}H_{34}O_6$ calcd 418.2355, found 418.2343.

17α,21α-Bis(acetyloxy)pregna-4,9(11)-diene-3,20-dione (24). Steroid **18** (0.5 g, 1.2 mmol) in CH_2Cl_2 (10 mL) was added to an ice-cold solution of p-TSA·H_2O (0.23 g, 1.2 mmol), AcOH (2.3 mL, 40.8 mmol), and TFAA (1.9 mL, 13.2 mmol) in CH_2Cl_2 (15 mL). After 4 h the mixture was treated with H_2O (10 mL) and 5 M NaOH until pH 10 was attained. The mixture was treated with CH_2Cl_2 (50 mL), and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL), and the organic portions were combined, washed with H_2O (20 mL), dried over $MgSO_4$, filtered, and evaporated to afford **24** (0.53 g, 100%): mp 156–157 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.67 (s, 3 H, 18-CH_3), 1.31 (s, 3 H, 19-CH_3), 1.34 (d, J = 7.1 Hz, 3 H, 16-CH_3), 2.11 (s, 3 H, OAc), 2.14 (s, 3 H, OAc), 4.59 (AB q, J = 16.5 Hz, 21-CH_2), 5.55 (d, J = 5.9 Hz, 1 H, H_{11}), 5.74 (s, 1 H, H_4); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 14.08, 19.44, 20.52, 21.62, 26.01, 32.27, 32.82, 33.03, 33.80, 34.24, 36.39, 37.23, 40.97, 46.48, 47.16, 47.29, 67.76, 95.14, 118.55, 124.06, 143.61, 169.50, 170.58, 171.56, 198.93, 199.35; HRMS for $C_{26}H_{34}O_6$ calcd 442.2355, found 442.2349. Anal. Calcd for $C_{26}H_{34}O_6$: C, 70.57; H, 7.74. Found: C, 70.08; H, 7.70.

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Supplementary Material Available: X-ray crystallographic data for compound **10**, proton NMR spectra for compounds described in the Experimental Section, and computational procedures for AM1 calculations (31 pages). Ordering information is given on any current masthead page.

Asymmetric Synthesis of the Milbemycin β_3 Spiroketal Subunit

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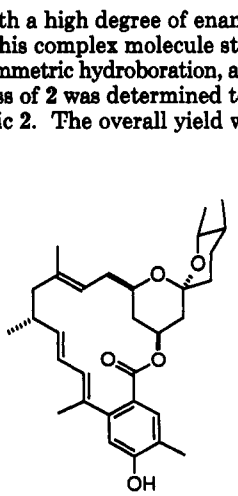
The milbemycin β_3 spiroketal subunit **2** has been prepared with a high degree of enantiomeric purity. This represents the first reagent-controlled asymmetric synthesis of this complex molecule starting from an achiral starting material. Key reactions include Sharpless epoxidation, asymmetric hydroboration, and the Birch reduction of a meta-substituted cinnamyl epoxide. The enantiomeric excess of **2** was determined to be >95% by a chiral shift ^{1}H NMR experiment with both optically active and racemic **2**. The overall yield was 1.2% from methyl *m*-toluate (**3**).

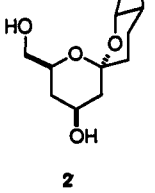
Introduction

Strategies for the construction of spiroketals are well documented, and a substantial amount of work has been reported in the past several years concerning the preparation of the avermectins, milbemycins, and their related key intermediates.[1-3] All of the previous syntheses of the milbemycin β_3 (**1**) spiroketal subunit **2** have utilized asymmetric starting materials from the chiral pool.[4,5]

We now report an enantioselective synthesis of spiroketal **2** according to the strategy outlined in retrosynthetic form in Scheme I. Spiroketal **2** was envisioned to arise from an acid-catalyzed ring closure of structure **B** with the anomeric effect governing the product's relative configu-



1 Milbemycin β_3



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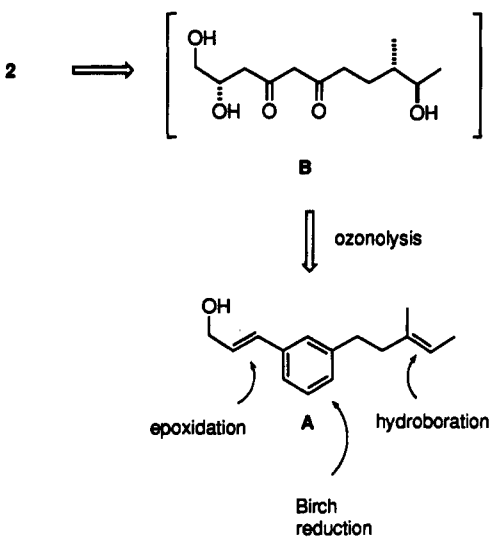
† Deceased February 17, 1989.

0022-3263/92/1957-0965$03.00/0

Scheme I



ration. The key features of our approach include the formation of β-diketo triol **B** via Birch reduction followed by ozonolysis of an aromatic precursor (**A**) and the establishment of the remote stereogenic centers by asymmetric epoxidation and asymmetric hydroboration of suitably located olefins in structure **A**. This route appeared to be attractive in that a simple meta-substituted aromatic compound was to be elaborated to structure **A** by routine functional group manipulation. A reactive 1,3-dicarbonyl system was to be stored in the form of an aromatic ring and asymmetry introduced at remote locations late in the synthesis, minimizing usage of the chiral auxiliaries utilized in the various asymmetric reagents. After this work was completed,[6a] a related application of the Birch reduction of cinnamyl epoxides followed by ozonolysis to prepare hydroxyl keto esters was reported by Evans and co-workers.[6b]

Results and Discussion

Exposure of methyl *m*-toluate (**3**) to *N*-bromosuccinimide in refluxing CCl_4 followed by treatment of the crude product with thiophenol and triethylamine yielded aromatic thioether **4** in an overall yield of 59% (Scheme II). Alcohol **5**, isolated in 82% yield from **4**, was then converted to its dianion with *n*-butyllithium and alkylated with tiglic bromide[7] to give alcohol **6** in 83% yield. The phenylthio moiety was conveniently removed with tri-*n*-butyltin hydride in refluxing benzene to give the hydroboration precursor **7** in 89% yield. Treatment of **7** with monoisopinocampheylborane[8,9] at −20 °C in a mixture of ether and tetrahydrofuran provided diol **8**, which was oxidized to benzaldehyde **9** in an overall yield of 62%.[16]

The enantiomeric excess of **9** was determined to be 54% by preparation of the corresponding *O*-methylmandelate ester **17** (Scheme III).[10] The absolute configuration of the C-2 atom was determined by the method described by Mosher, which was compatible with the theoretical result predicted by Brown.[8] Treatment of racemic **9** with (*R*)-(−)-methoxyphenylacetic acid produced a 1:1 mixture of esters. Using the Mosher model as shown in Scheme III, we can assign the absolute stereochemistry depicted in **9** to the compound possessing the more upfield C-3 methyl group resonance due to the shielding effect of the phenyl group. When this method was applied to the optically active sample of **9**, C-2 of the major enantiomer was found to be of the *R* configuration, thus establishing the C-3 center to be *S*.

Benzaldehyde **9** was converted to the epoxidation precursor **10** by treatment with vinylmagnesium bromide followed by exposure of the crude product to 3 N sulfuric acid in THF (Scheme II). Catalytic asymmetric epoxidation conditions as described by Sharpless gave diol **11** in 60% yield.[11] Because cinnamyl alcohol **10** was prepared in only 54% ee, conversion to its asymmetric epoxide **11** led to a mixture of diastereomers that was carried on through the synthesis without separation until spiroketal **14** was prepared.[12]

Attempts to convert epoxide **11** into diene **13** via Birch reduction were unsuccessful. Instead, epoxide **11** was converted to acetonide **12** in an overall yield of 70% from **11**. Acetonide **12** was then reduced and deprotected to afford triol **13** in 93% yield. After **13** was subjected to ozonolysis and acid-catalyzed spiroketalization, ketone **14** was obtained in 34% yield. The isolation of spiroketal **14** was the first opportunity to separate the diastereomeric impurity which resulted from the asymmetric epoxidation. Ketone **14** was reduced with sodium borohydride in DME (0 °C) and gave diol (+)-**2** in 50% yield along with a 27% yield of diol **15**.[13-15] Racemic diol (±)-**2** was synthesized by a similar route from **5** by employing $Me_2S{\cdot}BH_3$ (see supplementary material) and $VO(acac)_2$ in the hydroboration and epoxidation steps, respectively.

The enantiomeric excess of **2** was determined to be >95% by a ^1H NMR chiral shift study of both optically active and racemic **2**.[17] Additionally, the epimeric axial alcohol **15** was converted to spiroketal **16**.[15] The ^1H NMR spectrum and optical rotation of **16**, $[\alpha]_D$ +47.1° (*c* 0.3, $CDCl_3$), agree with those of authentic material prepared from (−)-citronellol and kindly provided by Professor

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(6) (a) This work was first described at the poster session of the 9th Annual Esther Humphrey Symposium, October 13, 1990, Burlington, VT, and subsequently at the 201st National Meeting of the American Chemical Society, April 15, 1991, Atlanta, GA, ORGN 138. (b) Evans, D. A.; Gauchet-Prunet, J. A.; Carreira, E. M.; Charette, A. B. *J. Org. Chem.* **1991**, *56*, 741–750.
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(9) Prepared from (−)-α-pinene, optical purity 98+% (Aldrich).
(10) Mosher, H. S.; Dale, J. A. *J. Am. Chem. Soc.* **1973**, *95*, 512–519.
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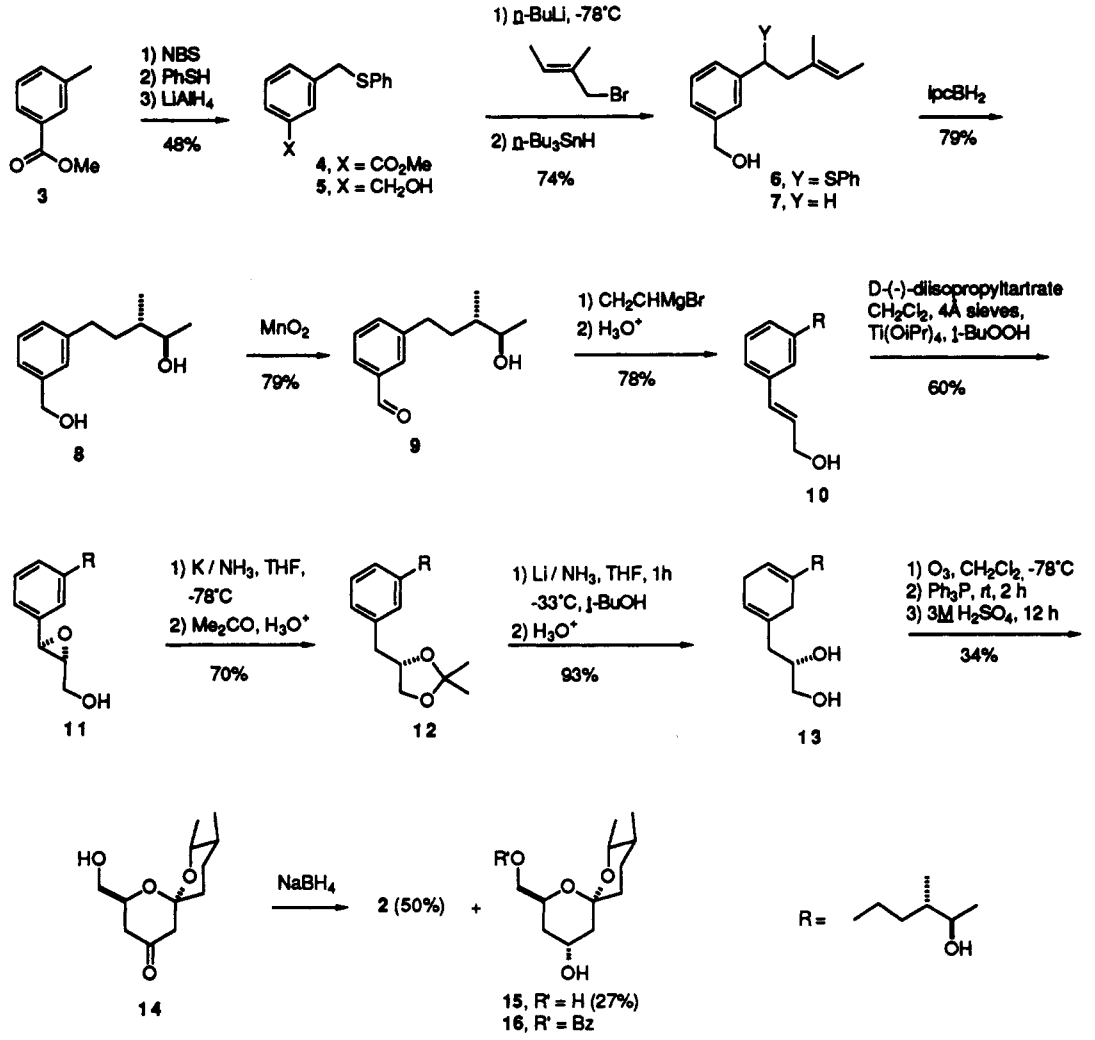
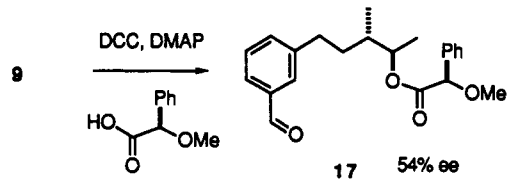
(12) Compounds **11–13** represent both the major and minor diastereomers obtained from the Sharpless epoxidation (supported by GC, HPLC, ^1H NMR shift study).
(13) Crimmons, M. T.; Bankaitis-Davis, D. M.; Hollis, W. G., Jr. *J. Org. Chem.* **1988**, *53*, 652–657.
(14) Kocienski, P. J.; Street, S. D. A.; Yeates, C.; Campbell, S. F. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2171–2181.
(15) Williams, D. R.; Barner, B. A.; Nishitani, K.; Phillips, J. G. *J. Am. Chem. Soc.* **1982**, *104*, 4708–4710.
(16) Although superior results have been reported for dilongifolylborane, treatment of **7** with this reagent gave only recovered starting material. Use of Masamune's hydroborating reagent was not investigated during this research. For examples of these reagents, see the following: Brown, H. C. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1983; Vol. 2, Chapter 1. Masamune, S.; Kim, B.; Peterson, J. S.; Sato, T.; Veenstra, S. J. *J. Am. Chem. Soc.* **1985**, *107*, 4549–4551.
(17) Although our ^1H NMR spectra data for **2** agree with the literature data, our observed optical rotation for (+)-**2** differs from the previously reported values of $[\alpha]_D$ +14.3° (*c* 0.17, $CHCl_3$) and $[\alpha]^{22}_D$ +46.3° (*c* 1.07, CH_2Cl_2). See refs 4 and 5.

Scheme II



Scheme III



Williams, $[\alpha]_D$ +46.7° (*c* 0.3, $CDCl_3$). Thus, the absolute configuration of **2** obtained from **3** by the first reagent-controlled asymmetric synthesis has been confirmed. It is noteworthy that Williams has described an efficient recycle operation that converts the undesired **16** to a derivative of **2**.

Conclusion

The milbemycin β_3 spiroketal subunit **2** has been synthesized in an overall yield of 1.2% from **3**. Complementary asymmetric induction via the hydroboration and epoxidation processes provided spiroketal **2** in high enantiomeric purity. Since Baker has previously converted **2** to milbemycin β_3 **1**, preparation of **2** also constitutes a formal enantioselective synthesis of 1.[4]

Experimental Section

General. ^1H NMR spectra were obtained at 200 MHz (Me_4Si internal standard). Melting points were determined in open capillary tubes on a Thomas Hoover apparatus and are uncorrected. Column chromatography was performed on EM Science silica gel 60 (230–400 mesh). All reactions were performed under Ar or N_2.

Diethyl ether and THF were distilled from sodium benzophenone ketyl. $BF_3{\cdot}Et_2O$, CH_2Cl_2, and pyridine were distilled over calcium hydride. Thiophenol, benzene, D-(−)-diisopropyl tartrate, titanium tetraisopropoxide, NH_3, and tri-*n*-butyltin hydride were distilled before use. TMEDA was distilled from KOH. (−)-α-Pinene of 98% ee was used for the asymmetric hydroborations and was obtained from Aldrich Chemical Co. Monoisopinocampheylborane-*N,N,N',N'*-TMEDA complex generated from (−)-α-pinene has a rotation value of $[\alpha]^{23}_D$ +64° (*c* 0.25, THF). GC analyses were performed on a 6-ft $^1/_8$-in. diameter stainless steel column packed with 3% OV-17 on Chromosorb WHP 80/100 mesh size (flame ionization detector; 300 °C). HPLC analyses were performed on either a 25-cm Partisil 5 column or a 25-cm Bakerbond chiral phase DNBPG (ionic) column.

Compounds and Procedures. 3-[(Phenylthio)methyl]-methyl Benzoate (4). A suspension of methyl *m*-toluate (**3**) (3.0 g, 20 mmol) in a solution of CCl_4 (20 mL) containing benzoyl peroxide (0.03 g, 0.1 mmol) under N_2 was stirred and heated at reflux for 3 h. After cooling to room temperature, the mixture was filtered and the crystals were washed with CCl_4. The combined filtrate was concentrated in vacuo and the crude product was dissolved in THF (20 mL) containing triethylamine (4.0 g, 0.040 mol) under N_2. The mixture was cooled to 0 °C and distilled thiophenol (2.5 g, 0.023 mol) and was added dropwise. The reaction mixture was stirred for 1.5 h at 0 °C. The mixture was partitioned with water (10 mL) and ether (10 mL). The organic phase was washed sequentially with 15% NaOH solution (10 mL) and 2 N H_2SO_4 (10 mL) and then dried (Na_2SO_4). Concentration at reduced pressure and flash chromatography (ether/hexane,

1:99) afforded 4 (3.03 g, 59%) as a clear, colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.92 (m, 2 H), 7.31 (m, 7 H), 4.13 (s, 2 H), 3.90 (s, 3 H); IR (CH_2Cl_2) 3040, 2945, 1715, 1580, 1475, 1430, 1270 cm^{-1}; CIMS m/z (rel intensity) 259 (M^+ + 1, 100), 151 (13).

Anal. Calcd for $C_{15}H_{14}O_2S$: C, 69.74; H, 5.46. Found: C, 69.80; H, 5.42.

3-[(Phenylthio)methyl]benzyl Alcohol (5). To a solution of 4 (3.03 g, 0.0120 mol) in diethyl ether (50 mL) under N_2 was added at 0 °C $LiAlH_4$ (0.70 g, 0.018 mol). The reaction was allowed to stir for 2 h. Water (0.7 mL) was slowly added followed by slow addition of 15% NaOH (0.7 mL) and water (2.1 mL), respectively. Ether (20 mL) was added, the solution was filtered, and the precipitate was washed with ether. The organic phase was dried (Na_2SO_4) and concentrated at reduced pressure. Flash chromatography (ether/hexane, 1:4) afforded 5 (2.21 g, 82%) as a colorless solid, mp 58 °C: ^{1}H NMR ($CDCl_3$) δ 7.3 (m, 9 H), 4.56 (s, 2 H), 4.12 (s, 2 H); IR (CH_2Cl_2) 3600, 3480, 3045, 2945, 2875, 1580, 1480, 1435 cm^{-1}; CIMS m/z (rel intensity) 231 (M^+ + 1, 100), 213 (34), 121 (57).

Anal. Calcd for $C_{14}H_{14}OS$: C, 73.01; H, 6.13. Found: C, 73.06; H, 6.05.

***m*-[1-(Phenylthio)-(*E*)-3-methyl-3-pentenyl]benzyl Alcohol (6).** A solution of alcohol 5 (15.34 g, 66.7 mmol) and THF (200 mL) was cooled to −78 °C and 56 mL of *n*-BuLi (2.5 M in hexane) was added. After the reaction was stirred for 15 min at −78 °C, (*E*)-1-bromo-2-methyl-2-butene (14.91 g, 100 mmol) was added. The reaction was stirred for an additional 5 min at −78 °C and was then warmed slowly to room temperature and quenched with H_2O (20 mL). The mixture was acidified with 3 M H_2SO_4, and then ether (150 mL) was added. The organic phase was washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography (ethyl acetate/hexane; 1:4) afforded 6 (16.50 g, 83%) as a clear colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.20 (m, 4 H), 5.19 (q, J = 6.6 Hz, 1 H), 4.61 (d, J = 5.8 Hz, 2 H), 4.30 (t, J = 7.9 Hz, 1 H), 2.60 (m, 2 H), 1.54 (s, 3 H), 1.50 (d, J = 6.7 Hz, 3 H); IR (CH_2Cl_2) 3600, 3050, 2920, 1580, 1480, 1440 cm^{-1}; CIMS m/z (rel intensity) 299 (M^+ + 1, 33), 281 (57), 229 (100), 189 (46), 159 (98).

Anal. Calcd for $C_{19}H_{22}OS$: C, 76.47; H, 7.43. Found: C, 76.47; H, 7.49.

***m*-[(*E*)-3-Methyl-3-pentenyl]benzyl Alcohol (7).** A solution of alcohol 6 (1.235 g, 4.14 mmol), AIBN (0.03 g, 0.2 mmol), and freshly distilled *n*-Bu_3SnH (1.5 mL, 5.7 mmol) in dry benzene (50 mL) was stirred and refluxed for 2.5 h. The reaction was cooled to room temperature and concentrated in vacuo. Flash chromatography (ether/hexane, 2:3) afforded 7 (0.69 g, 89%) as a clear colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.18 (m, 4 H), 5.23 (q, J = 6.6 Hz, 1 H), 4.67 (d, J = 5.7 Hz, 2 H), 2.70 (m, 2 H), 2.26 (m, 2 H), 1.65 (s, 3 H), 1.57 (d, J = 6.7 Hz, 3 H); IR (CH_2Cl_2) 3600, 3020, 2920, 2860, 1600, 1480, 1440 cm^{-1}; CIMS m/e (rel intensity) 173 (20), 161 (10).

Anal. Calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.53. Found: C, 81.94; H, 9.59.

***m*-[(3*S*,4*R*)-4-Hydroxy-3-methylpentyl]benzyl Alcohol (8).** To a solution of THF (7.5 mL), ethyl ether (7.5 mL), and TMED ($IpcBH_2)_2$ (1.3 g, 3.1 mmol) under N_2 was added BF_3·Et_2O (0.80 mL, 6.2 mmol). After stirring for 2 h at room temperature, the reaction was cooled to −20 °C and 7 (1.0 g, 5.3 mmol) dissolved in THF (2 mL) was added slowly. The reaction was stirred for 18 h at −20 °C and then MeOH (0.4 mL), 3 N NaOH (2.0 mL), and 30% H_2O_2 (2.0 mL) were added, respectively. After the reaction had stirred for 10 h, the aqueous layer was saturated with NaCl and the solution washed with EtOAc (4 × 20 mL). The organic phase was dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography (ethyl acetate/hexane, 1:1, followed by ethyl acetate 100%) afforded 8 (0.85 g, 79%) as a clear colorless oil; $[\alpha]^{25}_D$ −11.1° (*c* 0.9, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.08 (m, 4 H) 4.48 (s, 2 H), 3.52 (m, 1 H), 2.95 (1 H, br s, OH), 2.50 (m, 2 H), 2.15 (1 H, br s, OH), 1.66 (m, 1 H), 1.30 (m, 2 H), 0.99 (d, J = 6.35 Hz, 3 H), 0.83 (d, J = 6.59 Hz, 3 H); IR ($CHCl_3$) 3620, 2940, 2950, 1600, 1450; CIMS m/z (rel intensity) 209 (M^+ + 1, 2), 191 (85), 173 (100), 161 (32).

Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.82; H, 9.56.

***m*-[(3*S*,4*R*)-4-Hydroxy-3-methylpentyl]benzaldehyde (9).** Activated MnO_2 (6.1 g, 70 mmol) was added to 8 (1.38 g, 6.63 mmol) dissolved in $CHCl_3$ (100 mL), and the suspension was stirred for 18 h under N_2. The mixture was filtered through Celite, and flash chromatography (ethyl acetate/hexane, 1:4) afforded 9 (1.14 g, 79%) and 0.193 g of recovered starting material: $[\alpha]^{25}_D$ −9.7° (*c* 3.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 9.97 (s, 1 H), 7.7 (m, 2 H), 7.44 (m, 2 H), 3.67 (m, 1 H), 2.7 (m, 2 H), 1.83 (m, 1 H), 1.58 (s, 1 H), 1.50 (m, 2 H), 1.13 (d, J = 6.3 Hz, 3 H), 0.95 (d, J = 6.6 Hz, 3 H); IR ($CHCl_3$) 3600, 2950, 1695; CIMS m/z (rel intensity) 207 (M^+ + 1, 37), 189 (100), 161 (81).

Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.79. Found: C, 75.80; H, 8.68.

The enantiomeric excess was judged to be 54% by preparing the corresponding Mosher ester 17.[10]

3-[*m*-((3*S*,4*R*)-3-Methyl-4-hydroxypentyl)phenyl]-(*E*)-2-propen-1-ol (10). Vinylmagnesium bromide (1.2 mL, 1.2 mmol, 1 M in THF) was slowly added to a stirred mixture of 9 (91 mg, 0.40 mmol) in THF (3 mL) at room temperature. The reaction was quenched after 1 h by adding 3 M H_2SO_4 (5 mL). The mixture was washed with EtOAc (5 × 3 mL) and the combined organic phase was washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography (ethyl acetate/hexane, 1:1, followed by ethyl acetate) afforded 91 mg (88%) of the conjugated and unconjugated reaction product. The combined reaction products were then dissolved in THF (8 mL) and 3 M H_2SO_4 (3 mL) and stirred for 4 days. The mixture was then exhaustively extracted into EtOAc, and the combined organic phase was washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography (ethyl acetate/hexane, 1:1, followed by ethyl acetate) afforded 10 (80 mg, 78%) as a clear yellow oil: $[\alpha]^{22}_D$ −8.8° (*c* 1.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.2 (m, 4 H), 6.63 (d, J = 15.9 Hz, 1 H), 6.35 (dt, J = 15.9 Hz, 5.5 Hz, 1 H), 4.30 (d, J = 4.5 Hz, 2 H), 3.68 (m, 1 H), 2.6 (m, 2 H), 1.5 (m, 5 H), 1.13 (d, J = 6.4 Hz, 3 H), 0.95 (d, J = 6.6 Hz, 3 H); IR ($CHCl_3$) 3610, 3450, 3010, 2950, 1400; EIMS m/e (rel intensity) 234 (M^+, 6), 216 (2), 187 (12), 160 (18), 117 (100).

Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.64; H, 9.38.

(2*R*,3*R*)-3-[*m*-((3*S*,4*R*)-4-Hydroxy-3-methylpentyl)-phenyl]-*trans*-2,3-epoxy-1-propanol (11). A solution of (−)-diisopropyltartrate (7 mg, 0.03 mmol) and CH_2Cl_2 (4.3 mL) was stirred and cooled to −20 °C and 4-Å activated molecular sieves powder (24 mg) was added. Titanium tetraisopropoxide (0.006 mL, 0.02 mmol) and *t*-BuOOH (0.3 mL, 0.8 mmol, 3 M in isooctane) were added. The contents were stirred at −20 °C for 1 h and 10 (100 mg, 0.4 mmol) dissolved in CH_2Cl_2 (1 mL) was added over 60 min. The reaction was allowed to stir at −20 °C for 4 h. The mixture was quenched with 10% NaOH saturated with NaCl (0.06 mL) and then ethyl ether (0.8 mL) was added. The mixture was allowed to warm to 10 °C and $MgSO_4$ (0.06 g) and Celite (0.006 g) were added. The contents of the flask were stirred for 15 min and then vacuum filtered through a bed of Celite. Toluene was added, and the mixture was concentrated in vacuo. CH_2Cl_2 was added and flash chromatography (ethyl acetate/hexane, 1:1) afforded 11 (64.7 mg, 60%) as a clear colorless oil. An NMR shift study with Resolve-Al-PrFod indicated a de of 40%: ^{1}H NMR ($CDCl_3$) δ 7.16 (m, 4 H), 4.01 (ddd, J = 12.7, 5.3, 2.7 Hz, 1 H), 3.90 (d, J = 2.2 Hz, 1 H), 3.75 (d, J = 2.2 Hz, 1 H), 3.66 (m, 1 H), 3.21 (m, 1 H), 2.60 (m, 3 H), 1.78 (m, 1 H), 1.46 (m, 2 H), 1.12 (d, J = 6.3 Hz, 3 H), 0.93 (d, J = 6.45 Hz, 3 H); IR ($CHCl_3$) 3620, 3450, 3010, 2940, 1225, 880; CIMS m/z (rel intensity) 251 (M^+ + 1, 7), 233 (45), 215 (100), 203 (59).

Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.87; H, 8.88.

(2*R*,3*S*)-5-[*m*-[(2*S*)-2,3-(Isopropylidenedioxy)propyl]-phenyl]-3-methyl-2-pentanol (12). A solution of 11 (0.458 g, 1.80 mmol) in THF (20 mL) and *t*-BuOH (0.51 mL, 5.4 mmol) was stirred and cooled at −78 °C as NH_3 (100 mL) was distilled into the flask, and an excess of potassium metal (0.70 g, 18 mmol) was added portionwise until a blue coloration was obtained. The reaction was stirred for 30 min at −78 °C and then quenched by slowly adding excess NH_4Cl. The NH_3 was evaporated and 3 M H_2SO_4 (5 mL) was added. The mixture was extracted into EtOAc (5 × 5 mL), dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography (EtOAc/hexane, 1:1, followed by ethyl acetate) afforded the desired triol (0.359 g, 80%) as a clear colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.12 (m, 4 H), 3.91 (m, 1 H), 3.65 (dd, J =

10.7, 4.1 Hz, 1 H), 3.65 (m, 1 H), 3.5 (dd, J = 11.0, 7.0 Hz, 1 H), 2.60 (m, 4 H), 1.78 (m, 3 H), 1.40 (m, 3 H), 1.11 (d, J = 6.31 Hz, 3 H), 0.93 (d, J = 6.5 Hz, 3 H); IR (CH_2Cl_2) 3600, 3400, 2950; CIMS m/z (rel intensity) 253 (M^+ + 1, 10), 217 (46), 199 (100), 173 (42).

Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.17; H, 9.47.

To a well-stirred mxiture of the triol (0.352 g, 1.40 mmol) and acetone (50 mL) were added four drops of 3 M H_2SO_4. The reaction was allowed to stir for 12 h, concentrated in vacuo, and flash chromatography (EtOAc/hexane, 1:1) afforded **12** (0.359 g, 88%) as a clear colorless oil: ^1H NMR ($CDCl_3$) δ 7.1 (m, 4 H), 4.31 (m, 1 H), 3.95 (dd, J = 8.2, 5.9 Hz, 1 H), 3.64 (m, 1 H), 3.67 (m, 1 H), 3.00 (dd, J = 13.7, 6.0 Hz, 1 H), 2.74 (dd, J = 13.6, 7.3 Hz, 1 H), 2.60 (m, 3 H), 1.78 (m, 3 H), 1.43 (s, 3 H), 1.35 (s, 3 H), 1.13 (d, J = 6.3 Hz, 3 H), 0.94 (d, J = 6.6 Hz, 3 H); IR ($CDCl_3$) 3615, 2933; CIMS m/z 293 (M^+ + 1, 25), 235 (7), 217 (32), 199 (100).

Anal. Calcd for $C_{18}H_{28}O_3$: C, 73.93; H, 9.65. Found: C, 74.07; H, 9.77.

(2*S*)-3-[5-((3*S*,4*R*)-4-Hydroxy-3-methylpentyl)-1,4-cyclohexadien-1,5-yl]-1,2-propanediol (13). A solution of **12** (0.235 g, 0.805 mmol) in THF (20 mL) and *t*-BuOH (0.22 mL, 2.3 mmol) was stirred and cooled at −78 °C as NH_3 (100 mL) was distilled into the flask, lithium wire (1.4 g, 0.20 mol) was added portionwise, and the reaction was allowed to warm to −33 °C after a blue coloration was obtained. After 1 h the mixture was cooled to −78 °C and quenched with excess NH_4Cl. The NH_3 was allowed to evaporate and 3 N H_2SO_4 (5 mL) was added. The mixture was extracted with ether (5 × 10 mL) and the organic phase was dried (Na_2SO_4). Concentration in vacuo and flash chromatography (ether/hexane, 1:1) afforded the desired diene (0.22 g, 94%) as a clear colorless oil: ^1H NMR ($CDCl_3$) δ 5.49 (m, 1 H), 5.41 (m, 1 H), 4.22 (m, 1 H), 4.03 (dd, J = 7.9, 5.9 Hz, 1 H), 3.66 (m, 1 H), 3.54 (m, 1 H), 2.60 (m, 4 H), 2.33 (d, J = 6.4 Hz, 1 H), 2.16 (dd, J = 13.3, 7.1 Hz, 1 H), 2.00 (m, 3 H), 1.65 (m, 2 H), 1.41 (s, 3 H), 1.35 (s, 3 H), 1.13 (d, J = 6.3 Hz, 3 H), 0.88 (d, J = 6.7 Hz, 3 H); IR ($CDCl_3$) 3617, 2932; CIMS m/z (rel intensity) 295 (M^+ + 1, 15), 237 (100), 219 (42), 199 (26).

Anal. Calcd for $C_{18}H_{30}O_3$: C, 73.43; H, 10.27. Found: C, 73.25; H, 10.09. To a stirred mixture of the diene (0.36 g, 1.2 mmol) and THF (10 mL) were added 1 N HCl (5 mL). After the reaction stirred for 90 min, ether (2 mL) was added and enough NaCl was added to saturate the aqueous layer. The product was extracted with EtOAc (5 × 10 mL) and the combined organic phase was washed with brine. Concentration in vacuo and flash chromatography (ethyl acetate) yielded **13** (0.31 g, 99%) as clear colorless oil: ^1H NMR ($CDCl_3$) δ 5.55 (m, 1 H), 5.43 (m, 1 H), 3.85 (m, 1 H), 3.65 (m, 2 H), 3.45 (m, 1 H), 2.60 (m, 3 H), 2.10 (m, 6 H), 1.55 (m, 5 H), 1.12 (d, J = 6.3 Hz, 3 H), 0.87 (d, J = 6.7 Hz, 3 H); IR ($CDCl_3$) 3600, 3400, 2950; EIMS m/e (rel intensity) 254 (M^+, 0.1), 236 (0.1), 218 (0.3), 200 (0.2), 194 (0.4), 185 (0.8), 175 (1.3), 167 (2.4).

Anal. Calcd for $C_{15}H_{26}O_3$: C, 70.83; H, 10.30. Found: C, 70.97; H, 10.12.

(2*S*,6*S*,8*R*,9*S*)-4-Oxo-8,9-dimethyl-1,7-dioxaspiro[5.5]undecane-2-methanol (14). A solution of **13** (157 mg, 0.618 mmol) and CH_2Cl_2 (17 mL) was cooled to −78 °C and ozone was bubbled into the solution until a light blue coloration persisted. Ph_3P (0.413 g, 1.58 mmol) was added, and the reaction was allowed to warm to room temperature. After stirring for 2 h, two drops of 3 M H_2SO_4 was added and stirring was continued overnight. Concentration in vacuo and flash chromatography (ethyl acetate/hexane, 1:4) yielded **14** (33 mg, 34%, corrected for diastereomeric impurity in starting material): ^1H NMR ($CDCl_3$) δ 3.95 (m, 1 H), 3.80 (dd, J = 11.5, 2.5 Hz, 1 H), 3.62 (dd, J = 11.8, 5.4 Hz, 1 H), 3.27 (dq, J = 9.6, 6.4 Hz, 1 H), 2.55–2.25 (m, 4 H), 1.86 (m, 1 H), 1.56 (m, 3 H), 1.26 (m, 1 H), 1.09 (d, J = 6.3 Hz, 3 H), 0.83 (d, J = 6.6 Hz, 3 H); IR (CH_2Cl_2) 3683, 3598, 3062, 2957, 1723; CIMS m/z (rel intensity) 229 (M^+ + 1, 100), 211 (22), 129 (28), 101 (22).

(2*S*,4*S*,6*S*,8*R*,9*S*)-4-Hydroxy-8,9-dimethyl-1,7-dioxaspiro[5.5]undecane-2-methanol (2). To a dry 50-mL round-bottom flask under N_2 were added DME (21 mL) and $NaBH_4$ (0.02 g, 0.5 mmol). The flask was cooled to 0 °C and **14** (49 mg, 0.21 mmol) was added. After the reaction had stirred for 3 h an additional 13 mg of $NaBH_4$ was added. After one additional hour, another 10 mg was added. After stirring for an additional 15 min, the mixture was slowly quenched with a saturated solution of NH_4Cl. The mixture was concentrated in vacuo, and the residue was partitioned between ether and water. The aqueous layer was extracted with ether (5×) and flash chromatography (ether) afforded 23 mg (50%) of alcohol **2** as a colorless solid, mp 88–90 °C, and 13 mg (27%) of alcohol **15**. A chiral shift experiment with tris[(3-heptafluoropropyl)hydroxymethylene)-(+)-camphorato]-praseodymium(III) derivative indicated that **2** was obtained in an enantiomeric excess of ≥95%; the minor enantiomer was undetectable. **2**: $[\alpha]^{23}_D$ +74.7° (*c* 0.79, CH_2Cl_2);[17] ^1H NMR δ 4.18 (m, 1 H), 3.6 (m, 3 H), 3.25 (dq, J = 9.5, 6.1 Hz, 1 H), 2.00 (ddd, J = 10.7, 4.8, 1.9 Hz, 1 H), 1.85 (m, 1 H), 1.4–1.7 (m, 6 H), 1.3 (m, 3 H), 1.09 (d, J = 6.3 Hz, 3 H), 0.81 (d, J = 6.4 Hz, 3 H); IR (CH_2Cl_2) 3852, 3599, 3053, 2930, 1456, 1380 cm^{-1}; CIMS m/z (rel intensity) 231 (M^+ + 1, 100), 213 (47), 153 (13), 127 (11). **15**: $[\alpha]^{22}_D$ +56.8° (*c* 0.44, $CHCl_3$); ^1H NMR δ 4.24 (d, J = 9.6 Hz, 1 H), 4.01 (m, 2 H), 3.69 (dd, J = 11.5, 3.18 Hz, 1 H), 3.55 (dd, J = 11.5, 6.6 Hz, 1 H), 3.40 (m, 1 H), 1.86 (dt, J = 14.28, 4.69, 2.71 Hz, 1 H), 1.73–1.20 (m, 9 H) 1.15 (d, J = 6.24 Hz, 3 H), 0.82 (d, J = 6.45 Hz, 3 H); IR (CH_2Cl_2) 3599, 3497, 2932 cm^{-1}; IR (CH_2Cl_2) 3599, 3497, 2932 cm^{-1}; CIMS m/z (rel intensity) 231 (M^+ + 1, 100), 213 (18).

(2*S*,4*S*,6*S*,8*R*,9*S*)-2-[(Benzoyloxy)methyl]-8,9-dimethyl-1,7-dioxaspiro[5.5]undecan-4-ol (16). To a dry 5-mL round-bottom flask were added alcohol **15** (8.2 mg, 0.36 mmol), triethylamine (7.0 mg, 0.07 mmol), benzoyl chloride (7 mg, 0.05 mmol), and CH_2Cl_2 (1 mL). The mixture was allowed to stir for 2 h and was then added directly to a packed column of silica gel. Flash chromatography (ether/hexane, 1:1) afforded **16** (4 mg, 34%) and recovered **15** (5 mg, 61%): $[\alpha]^{22}_D$ +47.1° (*c* 0.34, $CDCl_3$); ^1H NMR δ 8.07 (m, 2 H), 7.5 (m, 3 H), 4.3 (m, 5 H), 3.46 (m, 1 H), 1.87 (m, 2 H), 1.55 (m, 3 H), 1.60 (d, J = 6.2 Hz, 3 H), 0.72 (d, J = 6.5 Hz, 3 H); IR ($CDCl_3$) 3495, 2956, 1717; CIMS m/z (rel intensity) 335 (M^+ + 1, 26), 317 (100).

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Supplementary Material Available: Experimental procedures and data for (±)-**8**, **17**, and racemic **11** (7 pages). Ordering information is given on any current masthead page.