The Magnesium-ene Cyclization Stereochemically Directed by an Allylic Oxyanionic Group and Its Application to a Highly Stereoselective Synthesis of (±)-Matatabiether. Allylmagnesium Compounds by Reductive Magnesiation of Allyl Phenyl Sulfides

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Supporting Information

General Description. NMR spectra were recorded on a Bruker AF-300 or DPX-300 (^{1}H: 300 MHz, ^{13}C: 75 MHz) NMR spectrometer at ambient temperature. Chemical shift data are reported in units of δ (ppm) relative to solvents ($CDCl_3$ δ 7.27 for ^{1}H NMR and $CDCl_3$ δ 77.00 or C_6D_6 δ 125.00 for ^{13}C NMR) or to tetramethylsilane (δ 0.00 for ^{1}H NMR) as internal standards. The $CDCl_3$ solvent for NMR spectroscopy was filtered through alumina or anhydrous K_2CO_3 to prevent possible acid induced decomposition of tertiary alcohols and ethers. High resolution mass spectra were recorded on a CH-5 double focusing Varian MAT or on a VG 70-SE mass spectrometer. Column chromatography (low-pressure) was performed with EM Science silica gel 60 (230-400 mesh ASTM) unless otherwise stated. TLC analysis was carried out on Anatech 250 micron glass-backed silica gel GF plates and were visualized by using 7% phosphomolybdic acid in ethanol or 5% *p*-anisaldehyde in ethanol or by using UV light. Reactions were performed under a dry argon atmosphere in flame-dried glassware with magnetic stirring unless otherwise stated. Methylene chloride, acetonitrile, and pyridine were distilled from CaH_2, diethyl ether and THF from sodium/benzophenone, hexanes from sodium and pentane from P_2O_5. Other chemicals were from commercial sources and were used without further purification, unless otherwise stated. Commercial organolithium reagents were titrated before use. Magnesium powder was quickly washed with 1% HCl, filtered, washed with EtOH and diethyl ether and dried in vacuum before use.

Typical Formation of Lithium 4,4'-Di-*tert*-butylbiphenylide (LDBB). To a flame-dried three-necked flask, equipped with a glass-coated stirring bar, rubber septum and argon inlet,

were added 4,4'-di-*tert*-butylbiphenyl (DBB, 1.604 g, 6.02 mmol) as a solution in THF (20 mL). Lithium ribbon was prepared by scraping the dark oxide coating off the surface while it was immersed in mineral oil. The shiny metal was dipped in hexanes in order to remove the oil and then weighed (49.5 mg, 7.13 mmol) in a tared beaker containing mineral oil. The metal was sliced into small pieces while it was still immersed in mineral oil. The lithium pieces were dipped again in hexanes prior to addition to the mixture of THF and DBB, while the flask was rapidly being purged with argon. The reaction mixture was stirred at room temperature for about 5 min until a dark-blue color appeared on the lithium surface, and then cooled to 0 °C and stirred for 5 h. The resulting dark-blue LDBB solution was ready for reductive lithiation (~3.0 mmol scale). A solution of a known amount of phenyl thioether in THF (~9 mL) was added dropwise to the LDBB solution until the color of the solution changed from dark blue to dark red. The amount of the phenyl thioether used could be thus calculated.

Procedure for Cyclization by Reductive Lithiation with LDBB/THF Followed by Transmetallation with $MgBr_2$. 3,7-Dimethyl-6-phenylthio-1,7-octadien-3-ol (**1**)[1] (262 mg, 1.00 mmol) was dissolved in dry THF (6.0 mL) in a 3-necked flask (25 mL). To this solution at -78 °C with stirring, was added MeLi (1.10 M in ether, 1.2 mL, 1.3 mmol) via syringe and the reaction mixture was cannulated into an LDBB solution (formed with polished lithium (16 mg, 2.3 mmol), 4,4'-di-*tert*-butylbiphenyl (670 mg, 2.52 mmol) in dry THF (10 mL) for 5 h at 0 °C) at -78 °C. After 10 min, anhydrous $MgBr_2$ (4.0 mmol in 12.0 mL of THF; see next experiment for its method of preparation) was added via syringe. After 1 h at -30 °C, the reaction mixture was warmed to and maintained at 40 °C over night. Diphenyl diselenide (624 mg, 2.0 mmol) was added as a solution in THF (6 mL) and the mixture was stirred for 2 h before water (50 mL) and ether (100 mL) were added. The separated organic phase was washed with NaOH (1.0 N aqueous, 2x40 mL) and water (50 mL) and dried with anhydrous K_2CO_3. Evaporation of the solvents gave a crude mixture whose ^1H NMR spectrum suggested the presence of **2** and **3a** in an approximately 3:1 ratio; the characterizations of these products are described below.

Procedure for Cyclization by Reductive Lithiation with LDMAN/Me_2O Followed by Transmetallation with $MgBr_2$. To a stirred solution of the same alcohol **1**[1] (1.10

g, 4.2 mmol) dissolved in dry ether (15.0 mL) in a 3-necked flask (50 mL) at -78 °C was added via syringe MeLi (1.10 M in ether, 4.2 mL, 4.6 mmol) . After 10 min, the reaction mixture was cannulated into an LDMAN solution (formed with polished lithium (80 mg, 11.5 mmol), *N,N*-dimethyl-1-naphthylamine (2.06 g, 12.0 mmol) and dry Me_2O (20 mL) for 5 h at -70 °C with stirring) at –70 °C. After 10 min, a solution of anhydrous $MgBr_2$ (20 mmol in 60 mL of ether, taken from a solution formed by stirring Mg (1.20 g, 50 mmol) with 1,2-dibromoethane (5.64 g, 30 mmol) in refluxing ether (90 mL) for 4 h) was added via syringe. After 1 h at -30 °C, the reaction mixture was warmed to and maintained at room temperature for 15 h. Diphenyl diselenide (2.81 g, 9.0 mmol) was added and the mixture was stirred for 2 h before water (60 mL) was added. The separated organic phase was washed with NaOH (1.0 N aqueous, 2x60 mL) and water (60 mL) and dried with anhydrous K_2CO_3. Evaporation of ether solvent and column chromatography (hexanes / ethyl acetate = 7 / 1, 0.5% NEt_3) gave the cyclized selenide **2** (830 mg, 64%) as an oil: ^{1}H NMR ($CDCl_3$) δ 7.55-7.42 (m, 2 H), 7.30-7.20 (m, 3 H), 4.88 (m, 1 H), 4.76 (m, 1 H), 2.93 (dd, *J*= 9.8, 11.9 Hz, 1 H), 2.79 (dd, *J*= 4.2, 12.0 Hz, 1 H), 2.62-2.55 (m, 1 H), 2.22-2.12 (m, 1 H), 2.11 (s, 1 H, OH), 1.93-1.76 (m, 2 H), 1.75-1.52 (m, 2 H), 1.65 (s, 3 H), 1.41 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 145.3, 132.7, 130.7, 129.0, 126.9, 112.0, 80.3, 50.8, 50.5, 40.4, 31.5, 26.7, 25.3, 23.1; exact mass calcd. for $C_{16}H_{22}OSe$ 310.0836, found 310.0838.

The same cyclization procedure was repeated except with water (50 mL) as the quenching reagent. The separated organic phase was washed with NaOH (1.0 N aqueous, 2x60 mL) and water (60 mL) and dried with anhydrous K_2CO_3. Evaporation of ether solvent gave a mixture containing the three isomers **3a**, **3b**, and **3c** of 1,2-dimethyl-3-isopropenyl-cyclopentan-1-ol in the ratio of approximately 3.3 to 1.0 to 0.23, as determined by integration of the ^{1}H NMR methyl doublets (see below).

Formation of Cyclic Alcohols 3a (Isopropenyl and Methyl cis) and 3b (Isopropenyl and Methyl trans) by Li-ene Cyclization. To a solution of **1**[1] (390 mg, 1.49 mmol) dissolved in 6.0 mL of dry THF in a 3-necked 25 mL flask at -78 °C with stirring was added via syringe MeLi (1.10 M in ether, 1.50 mL, 1.65 mmol).. This reaction mixture was cannulated into an

LDBB solution (formed with polished lithium (28 mg, 4.0 mmol), 4,4'-di-*tert*-butylbiphenyl (1.08 g, 4.05 mmol) and dry THF (16 mL) for 5 h at 0 °C) maintained at -78 °C. The reaction mixture was allowed to warm to room temperature over night (dry ice in acetone evaporated naturally) and the reaction was quenched with water (20 mL). After being diluted with ether (80 mL), the mixture was separated and the organic phase was washed with NaOH (1.0 N aqueous, 50 mL) and water (50 mL) and dried with anhydrous K_2CO_3. Column chromatography (eluent: hexanes / ethyl acetate=5 / 1, 0.5% triethylamine) gave **3a** (48 mg, 21%, oil) and **3b** (122 mg, 54%, oil).

3a: ^{1}H NMR ($CDCl_3$) δ 4.85 (m, 1 H), 4.71 (m, 1 H), 2.70-2.55 (m, 1 H), 2.00-1.55 (m, 5 H), 1.74 (s, 3 H), 1.36 (s, 1 H, OH), 1.35 (s, 3 H), 0.78 (d, J = 7.4 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 146.6, 110.5, 80.3, 48.7, 45.5, 39.3, 29.3, 25.2, 23.3, 9.2; exact mass calcd. for $C_{10}H_{18}O$ 154.1358, found 154.1356.

3b: ^{1}H NMR ($CDCl_3$) δ 4.72 (m, 2 H), 2.15-2.00 (m, 1 H), 1.85-1.55 (m, 5 H), 1.71 (s, 3 H), 1.40 (s, 1 H, OH), 1.17 (s, 3 H), 0.86 (d, J = 6.9 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 147.0, 110.3, 80.2, 53.1, 47.8, 40.5, 26.8, 23.4, 18.8, 12.6; exact mass calcd. for $C_{10}H_{18}O$ - H_2O 136.1252, found 136.1251.

4-Phenylthio-2-pentene 4b.[2] To a solution of mainly trans 3-penten-2-ol (6.3 mL, 61.7 mmol) and diphenyl disulfide (13.9 g, 63.7 mmol) in acetonitrile (90 mL), was added Bu_3P at ambient temperature and the mixture was stirred for 4 h. The mixture was treated with 5% aq NaOH, the ether extract from which was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography (1% ethyl acetate / hexane R_f 0.61) gave 4-phenylthio-2-pentene (**4b**) as a colorless oil (6.2 g, 57%) consisting of a single isomer, presumably trans: ^{1}H NMR ($CDCl_3$) δ 7.39-7.36 (m, 2 H), 7.30-7.20 (m, 3 H), 5.48-5.30 (m, 2 H), 3.78-3.68 (m, 1 H), 1.59 (d, J = 5.4 Hz, 3 H), 1.35 (d, J = 6.6 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 135.2, 132.8, 129.5, , 128.6, 127.1, 125.0, 45.8, 20.7, 17.6.

3-Methyl-1-phenylthio-2-butene 4c. To a solution of sodium ethoxide (6.1 g, 91 mmol) in ethanol (95 mL), thiophenol (6.5 mL, 63.0 mmol) was added at rt and the mixture was stirred for 30 min. A solution of 1-bromo-3-methyl-2-butene (7.0 mL, 60 mmol) in ethanol (10 mL) was added

dropwise and the solution was stirred for 8 h at rt. After work-up with 5% aq NaOH, ethanol was removed under reduced pressure. The residue was dissolved in ether, washed with 1 N aq NaOH and brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography (200 : 1 hexanes : ethyl acetate R_f 0.36) gave the desired product (**4c**) as a colorless oil (8.9 g, 83%): ^1H NMR ($CDCl_3$) δ 7.34 - 7.14 (m, 5 H), 5.30 (m, 1 H), 3.53 (d, J = 7.8 Hz, 2 H), 1.70 (s, 3 H), 1.58 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 136.8, 136.3, 129.6, 128.7, 125.9, 119.3, 32.2, 35.6, 17.7; exact mass calcd. for $C_{11}H_{14}O$ 178.0816, found 178.0815.

3-Phenylthio-4-phenyl-1-butene 4d.[3] To a solution of allyl phenyl sulfide (3.75 g, 25 mmol) in THF (75 mL) at -78 °C was added *sec*-BuLi (20 mL, 1.43 M in cyclohexane, 28 mmol) . The solution was stirred for 2 h and 15 min. A solution of benzyl bromide (2.8 mL, 23 mmol) in THF (25 mL) was then added dropwise and the solution was stirred for 3.5 h at -78 °C. The reaction was quenched with saturated aqueous NH_4Cl. The mixture was extracted with ether and the extract was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography (1.5% ethyl acetate / hexanes, R_f 0.62) afforded 1.74 g (72%) of the title compound **4d** as a colorless oil: ^1H NMR ($CDCl_3$) δ 7.39-7.15 (m, 10 H), 5.70 (m, 1 H), 4.80 (dd, J = 10.2 Hz, 18 Hz), 3.8-3.78 (m, 1 H), 3.07-2.85 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 138.5, 137.8, 134.6, 132.7, 129.3, 128.7, 128.2, 127.1, 126.5, 116.4, 53.5, 40.8.

3-Phenylthio-1,7-octadiene 4e. To a stirred solution of allyl phenyl sulfide **4a** (1.14 g, 7.60 mmol) in THF (40 mL) at -78 °C was added dropwise *n*-BuLi (1.6 M in hexanes, 4.90 mL, 7.84 mmol). After 30 min of stirring at that temperature, 5-bromo-1-pentene (1.16 g, 7.79 mmol) was added via syringe and the reaction mixture was stirred for an additional 2 h. A saturated solution of $NaHCO_3$ (30 mL) was added. The product was extracted with ether (2 x 40 mL). The combined organic layers were washed with water and then with saturated NaCl solution (40 mL) and dried with $MgSO_4$. The solvents were removed by rotary evaporation. The crude product was purified by column chromatography (hexanes), yielding diene **4e** (1.40 g, 85%) as an oil: ^1H NMR ($CDCl_3$) δ 7.45–7.18 (m, 5 H), 5.85–5.60 (m, 2 H), 5.10–4.85 (m, 4 H), 3.59 (m, 1 H), 2.15–2.00 (m, 2 H), 1.85–1.45 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 138.7, 138.2, 134.7, 132.6, 128.5, 126.9, 115.5, 114.7,

52.1, 33.5, 33.3, 26.4; exact mass calcd. for $C_{14}H_{18}S$ 218.1129, found 218.1115.

Reductive Magnesiation of Allyl Phenyl Sulfide 4a. After several trials, the following conditions proved most effective. To a mixture of magnesium powder (70-80 mesh, 240 mg, 10 mmol), anthracene (35.0 mg, 0.20 mmol) in THF (20 mL) was added 1,2-dibromoethane (0.10 mL. 1.1 mmol) at ambient temperature. The mixture was sonicated at ambient temperature (sonicator temperature controlled by a cooling apparatus) for 8 h. Allyl phenyl sulfide (**4a**, 0.3 mL, 2.0 mmol) was added dropwise at -30 °C. The mixture was stirred at 48 °C for 16 h and the reaction was quenched with *p*-anisaldehyde (0.43 mL, 3.5 mmol) at 0 °C. The mixture was stirred at ambient for 1 h and at 45 °C for 1.5 h. Aq 5% NaOH was added and the mixture was extracted with ether. The organic extract was washed with 5% aq NaOH and brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatograph (30% EtOAc / hexanes, $R_f = 0.42$) gave alcohol **5a** as a colorless liquid (326 mg, 92%): IR (neat) 3407, 3074, 3001, 2934, 2836, 1640, 1611, 1513, 1463, 1441, 1302, 1247, 1175, 1105, 1035, 917, 871, 768; ^{1}H NMR ($CDCl_3$) δ 7.20 (d, J = 8.4 Hz, 2 H), 6.82 (d, J = 8.4 Hz, 2 H), 5.78-5.69 (m, 1 H), 5.11-5.05 (m, 2 H), 4.58 (t, J = 6.6 Hz, 1 H), 3.74 (s, 3 H), 2.84 (b, 1 H, OH), 2.46-2.41 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 158.7, 136.0, 134.6, 126.9, 117.7, 113.5, 72.9, 55.1, 43.5) . When the reaction with Mg was carried out at 25 °C, instead of 48 °C, for 16 h, the yield decreased to 82%.

Reductive Magnesiation of 4-Phenylthio-2-pentene 4b. The procedure was the same as that for reductive magnesiation of **4a** except that a 50% larger scale was used and the **4b** was added at -65 °C. After the 16 h heating period at 48 °C, the reaction was quenched with chlorodiphenylmethylsilane (1.3 mL, 6.0 mmol) at -30 °C. The mixture was stirred at -30 °C for 1 h, at 0 °C for 1 h, and at rt for 30 min. Aq 5% NaOH was added and the mixture was extracted with ether. The organic extract was washed with 5% aq NaOH and brine, dried over $MgSO_4$ and concentrated under reduced pressure. Analysis by ^{1}H NMR ($CDCl_3$, 1,1,2,2-tetrabromoethane as the internal standard) of the crude product indicated 53% of silane **5b**. Purification by flash chromatography (0 to 1% ethyl acetate / hexanes) (1% ethyl acetate / hexanes R_f 0.51) gave the silane **5b** as a colorless liquid: ^{1}H NMR ($CDCl_3$) δ 7.54-7.51 (m, 4 H), 7.39-7.31 (m, 6 H), 5.53-5.20 (m,

2 H), 2.21-2.14 (m, 1 H), 1.62 (d, J = 6.3 Hz, 3 H), 1.10 (d, J = 7.2 Hz, 3 H), 0.50 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 136.2, 135.0, 133.1, 129.2, 127.8, 122.2, 24.2, 18.3, 14.4, -6.23; MS (EI) m / z (relative intensity) 266 (M^+, 65), 197 (100), 181 (35), 119 (23), 105 (55), 93 (20); exact mass calcd. for $C_{18}H_{22}Si$ 266.149, found 266.150.

Reductive Magnesiation of 3-Methyl-1-phenylthio-2-butene 4c. The procedure and scale were the same as those for reductive magnesiation of **4b** except that after the reaction had been quenched with silylating reagent, the mixture was stirred at 0 °C for 2 h and for 30 min at rt. After the same work-up procedure, except omitting the nmr analysis of crude product, the silane **5c** (R_f 0.51 in 1% ethyl acetate / hexane) was obtained as a colorless liquid (472.0 mg, 59%): ^{1}H NMR ($CDCl_3$) δ 7.57-7.54 (m, 4 H), 7.43-7.35 (m, 6 H), 5.21 (t with further minor splitting, J = 8.4, 1 H), 1.98 (d, J = 8.4 Hz, 2 H), 1.69 (s, 3 H), 1.49 (s, 3 H), 0.55 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 137.2, 134.6, 130.5, 129.2, 127.8, 118.8, 25.9, 17.7, 16.3, -4.5; MS (EI) m/z (relative intensity) 266 (M^+, 60), 197 (100), 181 (30), 165 (15), 119 (15), 105 (35), 93 (10); exact mass calcd. for $C_{18}H_{22}Si$ 266.1491, found 266.1489.

Reductive Magnesiation of 3-Phenylthio-4-phenyl-1-butene 4d. The procedure and scale were the same as those for reductive magnesiation of **4b**. Similar analysis by ^{1}H NMR of the crude product indicated 76% of silane **6d**. Purification by flash chromatograph (0% - 20% EtOAc / hexanes) (TLC 1% AcOEt / hexanes R_f 0.38) gave a mixture of two stereoisomer (3 : 1) of the silane **6d** as a yellow oil (708 mg, 72%): ^{1}H NMR ($CDCl_3$) δ 7.57-7.07 (m, 15 H, Ph), 5.53-5.47 (m, 2 H), 3.29,3.26 (2d, J = 5.7 Hz, 6.9 Hz, 2 H), 2.16 (d, J = 7.8 Hz, 0.49 H, $CH_2SiMePh$, minor-isomer), 2.05 (d, J = 6.6 Hz, 1.51 H, $CH_2SiMePh$, *major*-isomer), 0.59 (s, 1 H, $SiCH_3Ph$, *minor*-isomer), 0.56 (s, 2 H, $SiCH_3Ph$, *major*-isomer). ^{13}C NMR ($CDCl_3$) δ 141.2, 136.7, 134.6, 129.4, 129.3, 128.9, 128.4, 128.3, 128.1, 127.7, 127.4, 126.8, 125.8, 125.4, 39.2, 33.3, 29.7, 20.4, -4.51. MS (EI) m/z (relative intensity) 328 (M^+, 15), 250 (60), 197 (100), 181 (20), 165 (13), 130 (10), 119 (24), 105 (50), 91 (30), 77 (10); exact mass calc for $C_{23}H_{24}Si$ 328.1647, found 328.1649.

Reductive Magnesiation of Benzyl Phenyl Sulfide. (a) Silylation quench. The procedure and scale were the same as that for reductive magnesiation of **4b** except that after the reaction

had been quenched with silylating reagent, the mixture was stirred at 0 °C for 2 h and over night at rt. The same work-up procedure indicated a crude yield of benzyl methyl diphenylsilane of 57%. After the same chromatography procedure, the silane (R_f 0.54 in 1% ethyl acetate / hexane) was obtained as a white powder (321 mg, 37%) mp 64 - 66 °C (lit[4] mp 64 °C): ^{1}H NMR ($CDCl_3$) δ 7.47-6.86 (m, 15 H), 2.62 (s, 2 H), 0.46 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 138.9, 136.4, 134.7, 129.4, 129.1, 128.7, 128.1, 127.8, 124.3, 24.5, -4.7. **(b) Aqueous quench.** The procedure and scale were the same as in part (a) above except that the reaction was quenched with water at 0 °C. After the same work-up procedure, a 2 mL aliquot of the above solution (total volume 39 mL) was analyzed by gas chromatography. The solution was found to contain a total of 226 mg (2.4 mmol) of toluene (yield: 82%) determined by the addition of 62.9 mg of chlorobenzene as an internal standard to 2 mL of the above solution. The response factor ($f^A_{\text{toluene / chlorobenzene}} = 0.76$) was determined by analysis of a known mixture of chlorobenzene and toluene.

Reductive Magnesiation of 3-Phenylthio-1,7-octadiene 4e Followed by Aqueous Quench. The procedure and scale were the same as that for reductive magnesiation of benzyl phenyl sulfide (b) with aqueous quench. The solution contained a total of 268 mg (2.4 mmol, 81%) of hydrocarbon as determined by the addition of 16.4 mg of chlorobenzene to the 2 mL aliquot. The response factor ($f^A_{\text{1,7-octadiene / chlorobenzene}} = 0.64$) was determined by GC analysis of a known mixture of chlorobenzene and 1,7-octadiene. The yield can only be approximate since the hydrocarbon could contain several isomers of 1,7-octadiene, including cyclized material, with slightly different response factors.

Reductive Magnesiation of 3-Phenylthio-1,7-octadiene 4e Followed by Magnesium-ene Cyclization. To a mixture of 0.267 g (11.0 mmol) of magnesium (70–80 mesh) and 1.78 g (10.0 mmol) of anthracene in 30 mL of THF was added 0.10 mL (1.2 mmol) of 1,2-dibromoethane. The reaction mixture was sonicated in a cleaning sonicator at 25 °C (controlled by a cooling apparatus) for 24 h to produce a green solution of magnesium anthracene complex. The solution was cooled to -65 °C and 3-phenylthio-1,7-octadiene (1.97 g, 9.00 mmol) was added. The reaction mixture was warmed to 65 °C and stirred at that temperature for 16 h. The reaction mixture

was cooled to -65 °C and a solution of 2.94 g (13.5 mmol) of diphenyl disulfide in 10 mL of THF was added. The reaction mixture was warmed to 65 °C and stirred further for 1 h. A dilute solution of HCl was added after the reaction mixture had cooled to rt. The organic layer was separated and the aqueous phase was extracted with ether. The organic portions were combined and washed with 5% $NaHCO_3$ solution and brine and dried over $MgSO_4$. The solvent was removed by rotary evaporation. Anthracene was removed by crystallization from ethanol and excess diphenyl disulfide was removed by stirring the mixture of the crude product and *n*-Bu_3P in 40 mL of ether for 4 h. The product was purified by flash chromatography (1% EtOAc / hexanes) yielding 1.71 g (87%) of *cis*-2-(vinylcyclopentyl)methyl phenyl sulfide **7**. ^1H NMR ($CDCl_3$) δ 7.32–7.12 (m, 5 H), 5.84–5.72 (m, 1 H), 5.09–4.93 (m, 2 H), 2.98 (dd, J_1 = 12.3 Hz, J_2 = 6.2 Hz, 1 H), 2.76–2.66 (m, 1 H), 2.18–1.31 (m, 8 H); ^{13}C NMR ($CDCl_3$) δ 138.7, 128.9, 128.7, 128.6, 125.4, 115.2, 46.9, 43.0, 35.5, 30.8, 30.3, 22.8; IR (neat, NaCl) 3058 (m), 2938 (s), 2861 (m), 1576 (m), 1472 (m), 733 (s) cm^{-1}; exact mass calcd. for $C_{14}H_{18}S$ 218.1129, found 218.1129.

Reductive Magnesiation of the Magnesium Bromo Salt of 3,7-Dimethyl-6-phenylthio-1,7-octadien-3-ol 1 Followed by Cyclization. To a mixture of 600 mg (25.0 mmol) of magnesium (~50 mesh, 99+%, Aldrich), anthracene (890 mg, 5.0 mmole) and dry THF (8 mL) in a Schlenk tube topped with a condenser was added 1,2-dibromoethane (545 mg, 0.25 mL, 2.9 mmole) and the mixture was sonicated in a water bath for 8 h (between rt and 38 °C). A dark green mixture was produced. To a solution of **1** (1.31 g, 5 mmol) in THF (18 mL) at about -20 °C was added MeMgBr (3.0 M in ether, 3.0 mL) and the mixture was warmed to room temperature and stirred for 15 min before it was cannulated into the activated Mg / THF mixture at -30 °C. The resulting mixture was heated at reflux for 6 h and then cooled to 0 °C. Diphenyl diselenide (4.50 g, 14.4 mmole) was added as a solution in THF (16 mL) and the mixture was stirred over night. The mixture was decanted into aqueous NaOH solution (0.5 N, 100 mL), the Schlenk tube was washed with ether (200 mL), and the two phases were separated. The aqueous phase was extracted with ether (80 mL) and the combined organic phase was washed with NaOH (0.5 N, 100 mL) and water (100 mL) and dried with anhydrous K_2CO_3. Evaporation of the solvents followed by column chromatography

(eluent: hexanes / ethyl acetate = 7 / 1, 1% NEt_3) gave **2** (1.21 g, 78%) as an oil. Quenching the reaction mixture instead with water, after 5 h at reflux, followed by a similar work-up procedure, gave a mixture containing **3a**, **3b**, and **3c** in the ratio of approximately 95 : 2.6 : 2.4.

Preparation of Diol 8 by Hydroboration of Seleninated Cyclization Product 2. To a solution of **2** (1.647 g, 5.31 mmol) in dry THF (15 mL) at 0 °C with stirring was added 9-BBN (9-borabicyclo[3,3,1]nonane, 0.5 M in THF, 20 mL, 10 mmol) and the mixture was stirred at room temperature for 3 h. Then it was cooled to 0 °C and a mixture of NaOH (5.1 g in 25 mL of water) and H_2O_2 (30%, 5 mL) was added. After the mixture had been stirred at room temperature for 60 min, saturated $NaHCO_3$ solution (50 mL) was added and the mixture was shaken with ether (120 mL). The organic phase was washed with $Na_2S_2O_3$ (10%, 60 mL) and water (60 mL), and dried with K_2CO_3. Evaporation gave an oily mixture which was subjected to column chromatography (eluent: hexanes / ethyl acetate = 1 / 1, 0.5% NEt_3) to give diol **8** (980 mg, 56%) as an oil: ^1H NMR ($CDCl_3$) δ 7.60-7.48 (m, 2 H, aromatic), 7.30-7.20 (m, 3 H, aromatic), 3.62 (dd, *J* = 6.0, 10.8 Hz, 1 H), 3.41 (dd, *J* = 5.4, 10.7 Hz, 1 H), 3.15-3.00 (m, 2 H), 2.75 (bs, 1 H, OH), 2.47 (bs, 1 H, OH), 2.15-1.45 (m, 7 H), 1.36 (s, 3 H), 0.84 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 132.7, 131.0, 129.0, 126.8, 80.6, 65.6, 51.2, 45.3, 40.1, 35.3, 29.7, 24.8, 24.3, 17.4; exact mass calcd. for $C_{16}H_{24}O_2Se$ 328.0942, found 328.0949. The other isomer, which was likely the diastereomer of the hydroboration, was also obtained (40 mg, 2.3%) by chromatography.

Preparation of Bicyclic Ether 9 from Diol 8. To a solution of compound **8** (630 mg, 1.92 mmol) in dry pyridine (5 mL) at 0 °C was added *p*-toluenesulfonyl chloride (440 mg, 2.31 mmol) and the mixture was stirred at room temperature for 6 h. Ether (120 mL) was added and the organic phase was washed with aq Na_2CO_3 (8%, 60 mL), $CuSO_4$ (10%, 3x60 mL) and water (60 mL), and then dried with K_2CO_3. Evaporation and chromatography through a short column (eluent: hexanes / ethyl acetate = 2 : 1, 0.5% NEt_3) gave the tosylate intermediate as an oil, which was immediately dissolved in dry THF (50 mL). NaH (60% in mineral oil, 120 mg, 3.0 mmol) was added and the mixture was heated at reflux for 2 h. It was cooled to room temperature and filtered, the residue being washed with ether. After evaporation of the solvents, the residue

was subjected to chromatography through a short column (eluent, hexanes / ethyl acetate = 8 / 1, 0.5% NEt_3) to give the bicyclic ether **9** (540 mg, 91%) as an oil: ^{1}H NMR ($CDCl_3$) δ 7.55-7.45 (m, 2 H, aromatic), 7.30-7.20 (m, 3 H, aromatic), 3.63 (dd, J = 6.0, 11.5 Hz, 1 H), 3.33-3.07 (m, 3 H), 2.20-2.12 (m, 1 H), 2.10-1.96 (m, 1 H), 1.90-1.46 (m, 5 H), 1.17 (s, 3 H), 0.68 (d, J = 6.6 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 132.1, 130.9, 129.0, 126.6, 80.2, 67.2, 49.5, 42.9, 35.2, 26.1, 23.6, 22.9, 21.6, 14.6; exact mass calcd. for $C_{16}H_{22}OSe$ 310.0836, found 310.0831.

(±)-Matatabiether 10. To a solution of bicyclic seleninyl ether **9** (454 mg, 1.46 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added 3-chloroperoxybenzoic acid (50-60%, 606 mg, at least 1.76 mmol) and the mixture was stirred at room temperature for 20 min before it was diluted with CH_2Cl_2 (50 mL), washed with NaOH (1.0 N, 2x30 mL) and $Na_2S_2O_3$ (3%, 50 mL) and dried with K_2CO_3. After evaporation, the residue was mixed with pyridine (1 mL), and the mixture was heated to and maintained at 85 °C for 15 min. The cooled mixture was subjected to column chromatography (eluent: CH_2Cl_2) to give **(±)-matatabiether 10** (197 mg, 89%) as an oil: ^{1}H NMR ($CDCl_3$) δ 4.75 (m, 2 H, vinyl), 3.67 (dd, J = 5.7, 11.6 Hz, 1 H), 3.38 (dd, $J_1 = J_2$ =11.5 Hz, 1 H), 2.55-2.45 (m, 1 H), 2.20-1.55 (m, 5 H), 1.32 (s, 3 H), 0.77 (d, J = 6.7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 158.6, 98.7, 78.7, 67.0, 47.8, 39.1, 33.9, 21.2, 20.2, 14.7; exact mass calcd. for $C_{10}H_{16}O$ 152.1201, found 152.1203.

Cyclization of the Transmetallated Reductive Lithiation Product of the des-Methyl Analogue 11 of 1. The procedure was same as that for reductive lithiation of **1** in dimethyl ether, followed by transmetallation and cyclization except that 7-methyl-6-phenylthio-1,7-octadien-3-ol (**11**)[1] was the substrate (1.2 mmol scale) and the cyclized organometallic was treated with water (30 mL) instead of being seleninated. The reaction mixture was shaken with ether (30 mL) and the separated organic phase was washed with NaOH (1.0 N aqueous, 40 mL) and water (50 mL) and dried with anhydrous $MgSO_4$. After evaporation, the residue was subjected to column chromatography to give an oily mixture (121 mg, 73%) which was composed of compounds **12a** and **12b** in a ratio of 94 to 6. The major distinguishing characteristics in the proton nmr spectra were the methyl doublets which for **12a** appeared as two doublets (area ratio 46 : 54) at δ 0.71 (J = 7.1 Hz) and δ 0.65 (J = 7.2 Hz)

and for **12b** as a doublet at δ 1.00 (J = 6.6 Hz). In this series of alcohols and ketones, the peaks of methyl groups that are cis to the isopropenyl group are consistently at higher fields than those of the methyl groups that are trans to this group; it is expected that the cis methyl groups are in the shielding region of the alkene function since the isopropenyl group must approach an angle of 90° with the plane of the ring because of steric crowding in the planar conformer. However the main evidence that the two isomers of **12a** have cis methyl and isopropenyl groups is the ketone isomerization experiments below.

Oxidation of Alcohols 12 to Ketones cis- and trans-3-Isopropenyl-2-methylcyclopentanone 13. The diastereomeric alcohol mixture obtained above containing **12a** and **12b** was oxidized using a literature procedure[5] to give ketones **13a** and **13b** in approximately the ratio 94 : 6.

^{1}H NMR ($CDCl_3$) **13a** δ 4.94-4.84 (m, 1 H), 4.77-4.67 (m, 1 H), 2.90-2.78 (m, 1 H), 2.50-2.20 (m, 3 H), 2.15-1.85 (m, 2 H), 1.71 (s, 3 H), 0.89 (d, J = 7.5 Hz, 3 H). Control tests indicated that the ketones were not subject to epimerization when treated with pyridine, one of the constituents of the oxidizing mixture, under similar conditions.

Epimerization under Basic Conditions of the 14.5 : 1 Ketone Mixture of 13a to 13b. The above ketone mixture (50 mg, 0.36 mmol) was stirred with a solution of KOH (10 mg, 0.18 mmol) in MeOH (10 mL) for 60 min. The mixture was shaken with ether (60 mL) and water (30 mL) and the organic phase was washed with water (3x30 mL) and dried with $MgSO_4$. Evaporation of the solvents gave a residue containing mainly **13b** (**13a / 13b** = 11 : 89): ^{1}H NMR ($CDCl_3$) **13b** δ 4.90–4.80 (m, 2 H), 2.50-2.00 (m, 5 H), 1.76 (s, 3 H), 1.75-1.65 (m, 1 H), 1.04 (d, J = 6.9 Hz, 3 H).

Addition of MeLi to Ketone 13a. MeLi (1.1 M in ether, 0.6 mL, 1.8 mmol) was added dropwise via syringe with stirring to a solution of the ketone mixture (**13a / 13b** = 94 : 6; 50 mg, 0.36 mmol), obtained in the above oxidation, dissolved in dry ether (10 mL) at -78 °C. The mixture was warmed to 0 °C and quenched with water (10 mL). The organic phase was separated, washed with water (10 mL) and dried with $MgSO_4$. Evaporation of the solvent gave a residue containing mainly **3a**.

Column chromatography (eluent: hexanes / ethyl acetate = 5 / 1, 0.5% triethylamine) gave a compound (37 mg, 68%) which had an identical ^{1}H NMR spectrum to **3a**. Traces of unreacted ketones were also detected in the ^{1}H NMR spectrum of the mixture; this may be due to enolization competing with addition. No other methyl doublets were clearly visible.

Addition of MeLi to Ketone 13b. MeLi (1.1 M in ether, 0.4 mL, 1.2 mmol) was added dropwise via syringe with stirring to a solution in dry ether (10 mL) of the ketone mixture obtained upon base equilibration (**13b / 13a** = 14.2; 40 mg, 0.29 mmol) at -78 °C. The mixture was warmed to 0 °C and quenched with water (5 mL). The organic phase was separated, washed with water (10 mL) and dried with $MgSO_4$. Evaporation of the solvent gave a residue containing two major products with characteristic ^{1}H NMR signals (δ 0.87, d, J = 6.7 Hz, **3d** and δ 0.86, d, J = 6.9 Hz, **3b**). The methyl doublet of the adduct **3a** of methyllithium to **13a** was also present to the extent of about 11%.

References

(1) Cheng, D.; Knox, R. K.; Cohen, T. *J. Am. Chem. Soc.*, **2000**, *122*, 412-3

(2) Vedejs, E.; McClure, C. K. *J. Am. Chem. Soc.* **1986**, *108*, 1094-1096.

(3) Takeda, T.; Miura, I.; Horikawa, Y.; Fujiwara, T. *Tetrahedron Lett.* **1995**, *36*, 1495-1498.

(4) Hosomi, A.; Sakurai. H. Bull. Chem. Soc. Jpn. **1972**, *45*, 248-50.

(5) Ratcliffe, R.; Rodehorst, R. *J. Org. Chem.* **1970**, *35*, 4000-02.