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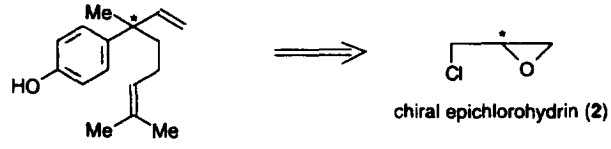
The absolute configuration of (+)-sporochnol A, the fish deterrent from the Caribbean marine alga *Sporochnus bolleanus*

Michiyasu Takahashi, Yoko Shioura, Taku Murakami and Kunio Ogasawara *
Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980-77, Japan

Abstract: The absolute configuration of (+)-sporochnol A, the fish deterrent from the Caribbean marine alga *Sporochnus bolleanus*, has been established as *S* based on the stereocontrolled synthesis of its (*R*)-(−)-enantiomer from (*S*)-epichlorohydrin. © 1997 Elsevier Science Ltd

(+)-Sporochnol A **1** was isolated from the Caribbean marine alga *Sporochnus bolleanus* and it was shown to exhibit significant feeding deterrence toward herbivorous fishes.[1] Its structure was determined by spectral and chemical methods but left the absolute configuration uncertain. Since we are interested in its functions in chemical defense, we investigated its asymmetric synthesis using optically active epichlorohydrin **2** which are practically available in both enantiomeric forms.[2] We now disclose the enantiocontrolled synthesis of the unnatural (*R*)-(−)-enantiomer *ent*-**1** which determined unambiguously the absolute configuration of natural (+)-sporochnol A **1** as *S* by correlation to the configuration of (*S*)-epichlorohydrin **2** (Scheme 1).



(+)-sporochnol A (1)

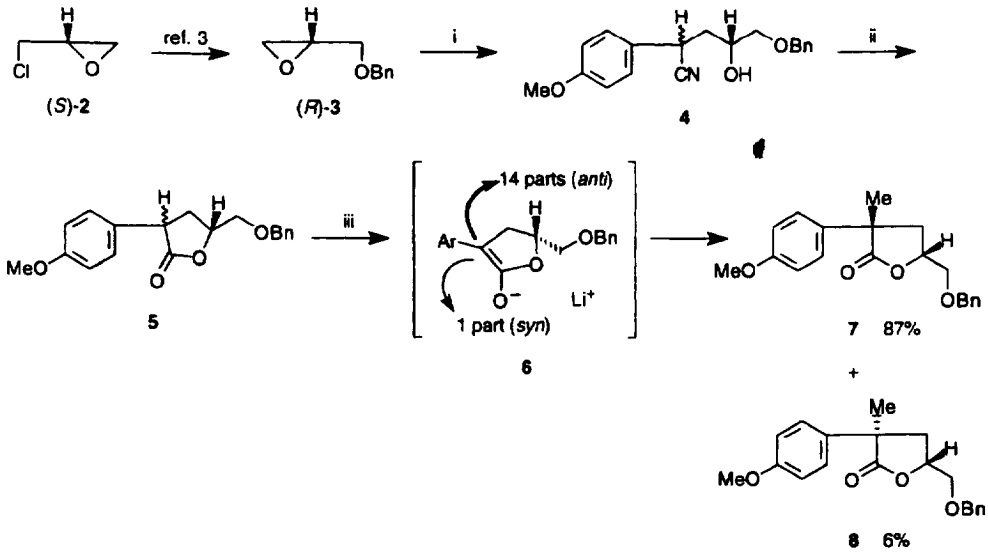
chiral epichlorohydrin (2)

Scheme 1.

(*S*)-Epichlorohydrin **2** was first transformed into (*R*)-*O*-benzylglycidol **3** (>98% ee) by the established procedure.[3,4] The (*R*)-glycidol ether **3** was then condensed with 4-methoxyphenylacetonitrile and the resulting γ-hydroxynitrile **4** was hydrolyzed under alkaline conditions to give the γ-lactone **5** in 70% overall yield as a separable epimeric mixture after acid workup.[5] Kinetic alkylation of the lactone mixture **5** at the α-center with iodomethane in the presence of lithium diisopropylamide (LDA) at −78°C occurred stereoselectively from the less hindered *anti*-face of the γ-benzyloxymethyl group in a 14:1 ratio to give the 1,4-*anti*-product **7** in 86% yield accompanied by the readily separable *syn*-product **8** in 6% yield. Stereochemistry of the major product was easily confirmed by an n.O.e. experiment which showed significant interaction between α-methyl and γ-proton supporting their *syn* relationship. The enantiomeric excess of the major product as well as that of the minor product was determined at this stage to be >98% ee by hplc using a chiral column (CHIRALCEL OD, elution with hexane/*i*-PrOH, 4:1) (Scheme 2).

Having constructed the quaternary stereogenic center in a highly stereoselective manner, the major *anti*-γ-lactone **7** thus obtained was reduced with diisobutylaluminum hydride (DIBAL) to give the lactol (**9**) which was treated with methylenetriphenylphosphorane to give the vinyl alcohol **10** in 93% overall yield. Since the glycol **11** generated from **10** under the Birch conditions, though it proceeded excellently, was accompanied by a trace of an inseparable over reduced product, the debenzylation was

* Corresponding author. Fax: +81-22-217-6845; Email konol@mail.cc.tohoku.ac.jp



Scheme 2. *Reagents and conditions*: i) LDA, 4-methoxyphenylacetonitrile, THF, −78°C (76%); ii) KOH, EtOH, reflux then 1N HCl, EtOH (92%); iii) LDA, MeI, THF, −78°C (92%).

carried out using boron tribromide to give the pure glycol **11** in 78% yield. To construct the requisite homoprenyl functionality, the glycol **11** was cleaved with sodium periodate to give the aldehyde **12** in 98% yield. Horner–Emmons reaction of **12** followed by chemoselective reduction of the resulting α,β-unsaturated ester **13** with magnesium in methanol[6,7] afforded the methyl ester **14** in 57% overall yield. Treatment of **14** with an excess methyllithium[7,8] gave the tertiary alcohol **15** which afforded an inseparable mixture of (*R*)-*O*-methylsporochnol A **16** and the *exo*-methylene isomer on treatment with methanesulfonyl chloride in the presence of 4-(*N*,*N*-dimethylamino)pyridine[7] (2.6:1) or with a copper sulfate–silica gel mixture (1:1) in toluene at 120°C[10] (5:1). On the other hand, **12** was first transformed into the vinyl ether **17** by Wittig reaction in 76% yield. **17** was then acid hydrolyzed to give the homologated aldehyde **18** in 93% yield. This compound afforded (*R*)-*O*-methylsporochnol A **16** in 75% yield as a single product on reaction with isopropylidenetriphenylphosphorane. Finally, the methyl ether **16** was heated with methylmagnesium iodide[7,8] at 180°C to cleave the ether bond to give (−)-*ent*-sporochnol A *ent*-**1** whose spectroscopic data, except the sign of the specific rotations, were identical with those of the natural product. This indicated that the synthetic (−)-*ent*-sporochnol A *ent*-**1** was the unnatural enantiomer having *R*-configuration based on the starting (*S*)-epichlorohydrin (*S*)-**2** and, consequently, the natural (+)-sporochnol A **1** possessed *S* configuration[9] (Scheme 3).

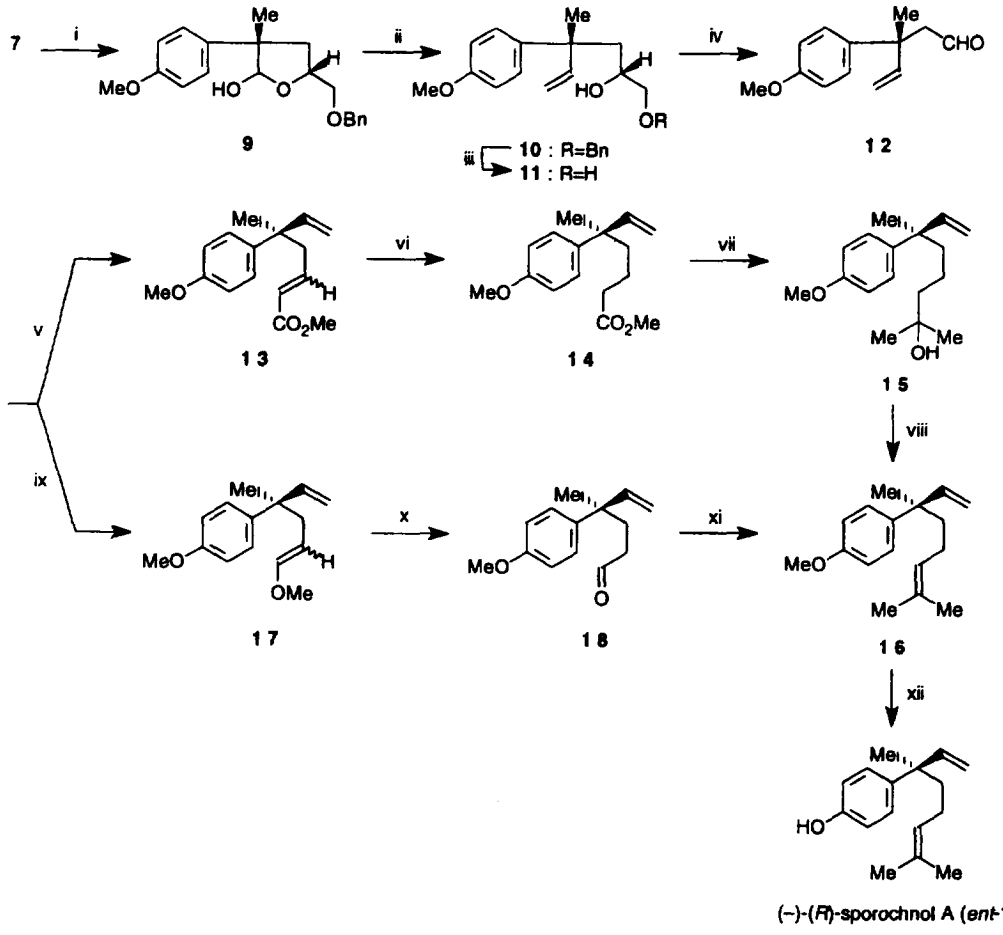
In summary, we have determined the absolute configuration of (+)-sporochnol A **1**, the fish deterrent from the Caribbean marine alga *Sporochnus bolleanus*, as *S* by enantiocontrolled synthesis of the unnatural enantiomer *ent*-**1** starting from (*S*)-epichlorohydrin.

Experimental

M.p.s were determined on a Yanagimoto hotstage instrument and are uncorrected. IR spectra were recorded on a JASCO-IR 700 spectrometer. ^{1}H NMR spectra were recorded on a Varian Gemini-2000 (300 MHz) spectrometer. Optical rotations were measured with a JASCO-DIP-370 digital polarimeter. Optical purities were determined on a Gilson Model-307 instrument equipped with a chiral column.

(2R,4R/S)-1-Benzyloxy-4-cyano-4-(4-methoxyphenyl)butan-2-ol **4**

To a stirred solution of LDA [prepared *in situ* by treating *i*-Pr_2NH (0.78 ml, 5.6 mmol) in THF (7 ml) with *n*-BuLi (1.56 M in hexane; 3.4 ml, 5.3 mmol) at −78°C for 10 min] was added dropwise 4-methoxyphenylacetonitrile (648 mg, 4.4 mmol) in THF (2 ml) at −78°C for and the mixture was



Scheme 3. *Reagents and conditions*: i) DIBAL, CH_2Cl_2, −78°C (95%); ii) $Ph_3P^+CH_3Br^-$, *n*-BuLi, THF (98%); iii) BBr_3, CH_2Cl_2, −30°C (78%); iv) $NaIO_4$, H_2O–EtOH (98%); v) $(MeO)_2P(O)CH_2CO_2Me$, NaH, THF (95%); vi) Mg, MeOH (60%); vii) MeLi, THF (76%); viii) $MeSO_2Cl$, Et_3N, DMAP (75% as 2.6:1 mixture) or $CuSO_4$–SiO_2 (1:1), toluene, reflux, 1 h (quantitative, 5:1 mixture); ix) $Ph_3P^+CH_2OMeCl^-$, *n*-BuLi, THF (76%); x) 70% $HClO_4$, THF (93%); xi) $Ph_3P^+CH(Me)_2I^-$, *n*-BuLi, THF (75%); xii) MeMgI, 180°C (62%).

raised to room temperature. After 10 min, the mixture was cooled to −78°C and a solution of (*R*)-(−)-*O*-benzylglycidol (*R*)-**3** (791 mg, 4.8 mmol) in THF (2 ml) was added dropwise to the mixture at the same temperature. After stirring for 30 min, the temperature was raised to room temperature and the reaction was quenched by addition of saturated aqueous NH_4Cl (2 ml). The mixture was extracted with ether (5 ml x 3) and the combined organic layer was washed with brine (2 ml), dried ($MgSO_4$), evaporated under reduced pressure, and chromatographed (SiO_2, 20 g, eluent: AcOEt–hexane, 1:2) to give the nitrile **4** (1.04 g, 76.0%) as a colorless oil. IR (film): ν=3460, 2238 cm^{-1}. ^1H NMR ($CDCl_3$): δ=7.40–7.23 (7H, m), 6.89 (2H, br d, *J*=8.5 Hz), 4.55 (1.75H, s), 4.51 (0.75H, s), 4.20–4.08, 4.07–3.99, 3.61–3.50, 3.46–3.30 (4H, m), 2.95–2.55 (2H, m), 2.54 (1.25H, d, *J*=3.8 Hz, exchangeable with D_2O), 2.38 (0.75H, d, *J*=4.4 Hz, exchangeable with D_2O), 2.23–2.12 (0.75H, m), 2.00–1.81 (1.25H, m). ^{13}C NMR ($CDCl_3$): δ=159.49 (s), 159.36 (s), 137.69 (s), 137.62 (s), 129.01 (d), 128.52 (d), 128.36 (d), 128.01 (s), 127.93 (d), 127.82 (d), 126.96 (s), 121.84 (s), 120.90 (s), 114.49 (d), 114.10 (d), 73.90 (t), 73.76 (t), 73.35 (t), 73.30 (t), 67.76 (d), 66.38 (d), 55.21 (q), 39.54 (t), 38.61 (t), 33.00 (d), 31.95 (d). MS: *m/z*=311 (M^+), 160 (100%). HRMS: calcd for $C_{19}H_{21}NO_3$: 311.1522 (M^+). Found: 311.1541.

(3R/S,5R)-5-(Benzyloxymethyl)-3-(4-methoxyphenyl)tetrahydrofuran-2-one **5**

A mixture of **4** (5.98 g, 19.2 mmol) and KOH (8.5 g, 151 mmol) in EtOH (100 ml) was refluxed for 16 h. After cooling, the solvent was evaporated under reduced pressure, the residue was diluted with H_2O (50 ml) and the aqueous solution, after washing with ether (50 ml x 2), was made acidic by addition of conc. HCl and the mixture was extracted with CH_2Cl_2 (50 ml x 3), washed with brine (50 ml), and dried ($MgSO_4$). After evaporation of the solvent under reduced pressure, the residue was stirred in a mixture of 1N HCl (50 ml) and EtOH (50 ml) at room temperature for 10 h. The solvent was evaporated under reduced pressure and the residue, dissolved in AcOEt (150 ml), was washed with 5% aqueous $NaHCO_3$ (50 ml), dried ($MgSO_4$), evaporated under reduced pressure, and chromatographed (SiO_2, 300g, eluent: AcOEt–hexane, 1:3) to give the lactone **5** (5.49 g, 91.6%) as a 1:1 diastereomeric mixture. A part of the product was separated by silica gel column chromatography to give the (3*S*,5*R*)-isomer **5** and the (3*R*,5*R*)-isomer **5** both as crystals: (3*S*,5*R*)-**5**: colorless needles, mp 54–55°C, $[\alpha]_D^{26}$ −37.6 (*c* 1.0, $CHCl_3$). IR (film): ν=1768 cm^{-1}. ^1H NMR ($CDCl_3$): δ=7.41–7.27 (5H, m), 7.19 (2H, br d, *J*=8.5 Hz), 6.89 (2H, br d, *J*=8.8 Hz), 4.79–4.71 (1H, m), 4.63 (1H, d, *J*=12.1 Hz), 4.58 (1H, d, *J*=12.1 Hz), 4.01 (1H, t, *J*=9.3 Hz), 3.79 (3H, s), 3.65–3.76 (1H, dd, *J*=10.7, 3.3 Hz, 3.65 (1H, dd, *J*=10.7, 3.6 Hz), 2.65 (1H, ddd, *J*=12.9, 9.6, 3.6 Hz), 2.44 (1H, ddd, *J*=12.9, 9.1, 8.5 Hz). MS: *m/z*=312 (M^+), 91 (100%). *Anal.* Calcd for $C_{19}H_{20}O_4$: C 73.06, H 6.45. Found: C 73.26, H 6.48. (3*R*,5*R*)-**5**: colorless needles, mp 94–95°C, $[\alpha]_D^{27}$ +3.8 (*c* 2.2, $CHCl_3$). IR (film): ν=1759 cm^{-1}. ^1H NMR ($CDCl_3$): δ=7.40–7.28 (5H, m), 7.20 (2H, br d, *J*=8.5 Hz), 6.87 (2H, br d, *J*=9.1 Hz), 4.72–4.61 (1H, m), 4.63 (2H, s), 3.84 (1H, dd, *J*=12.4, 9.1 Hz), 3.79 (3H, s), 3.77 (1H, dd, *J*=11.0, 3.3 Hz), 3.68 (1H, dd, *J*=11.0, 4.9 Hz), 2.66 (1H, ddd, *J*=12.9, 9.1, 6.0 Hz), 2.28 (1H, dt, *J*=12.6, 12.4 Hz). MS: *m/z*=312 (M^+, 100%). *Anal.* Calcd for $C_{19}H_{20}O_4$: C 73.06, H 6.45. Found: C 73.20, H 6.47.

(3S,5R)-5-(Benzyloxymethyl)-3-(4-methoxyphenyl)-3-methyltetrahydrofuran-2-one **7** *and (3R,5R)-5-(benzyloxymethyl)-3-(4-methoxyphenyl)-3-methyltetrahydrofuran-2-one* **8**

To a stirred solution of LDA [prepared *in situ* by treating *i*-Pr_2NH (0.42 ml, 3.0 mmol) in THF (20 ml) with *n*-BuLi (1.56 M in hexane; 1.9 ml, 3.0 mmol)] was added **5** (624 mg, 2.0 mmol) in THF (14 ml) at −78°C and after 20 min, the mixture was added MeI (0.36 ml, 6.0 mmol) dropwise at the same temperature and the stirring was continued for 30 min. The mixture, after raising to room temperature, was treated with saturated aqueous NH_4Cl (2 ml) and extracted with AcOEt (20 ml x 3). The extract was washed with brine (20 ml), dried ($MgSO_4$), evaporated under reduced pressure, and chromatographed (SiO_2, 100 g, eluent: AcOEt–hexane, 1:10) to give the *anti*-3*S*,5*R*-product **7** (560 mg, 85.9%) and the *syn*-3*R*,5*R*-product **8** (40 mg, 6.1%) both as colorless oil. (3*S*,5*R*)-**7**: $[\alpha]_D^{30}$ −18.4 (*c* 0.4, $CHCl_3$). IR (film): ν=1764 cm^{-1}. ^1H NMR ($CDCl_3$): δ=7.39–7.26 (7H, m), 6.86 (2H, br d, *J*=9.1 Hz), 4.77–4.67 (1H, m), 4.58 (1H, d, *J*=12.1 Hz), 4.54 (1H, d, *J*=12.1 Hz), 3.79 (3H, s), 3.62 (1H, dd, *J*=10.7, 4.1 Hz), 3.58 (1H, dd, *J*=10.7, 5.2 Hz), 2.53 (1H, dd, *J*=12.9, 8.8 Hz), 2.39 (1H, dd, *J*=12.9, 6.9 Hz), 1.62 (3H, s). ^{13}C NMR ($CDCl_3$): δ=179.94 (s), 158.75 (s), 137.78 (s), 134.69 (s), 128.57 (d), 127.93 (d), 127.85 (d), 127.37 (d), 114.04 (d), 75.78 (d), 73.59 (t), 71.01 (t), 55.25 (q), 47.12 (s), 40.12 (t), 25.47 (q). MS: *m/z*=326 (M^+), 91 (100%). HRMS: calcd for $C_{20}H_{22}O_4$: 326.1518 (M^+). Found: 326.1562. HPLC (CHIRALCEL OD, elution: hexane–*i*-PrOH, 4:1): >98% ee. (3*R*,5*R*)-**8**: $[\alpha]_D^{31}$ +38.3 (*c* 0.6, $CHCl_3$). IR (film): ν=1764 cm^{-1}. ^1H NMR ($CDCl_3$): δ=7.38–7.25 (7H, m), 6.87 (2H, br d, *J*=9.1 Hz), 4.58 (2H, s), 4.46–4.36 (1H, m), 3.77 (3H, s), 3.67 (1H, dd, *J*=11.0, 3.6 Hz), 3.60 (1H, dd, *J*=11.0, 5.2 Hz), 2.62 (1H, dd, *J*=12.9, 5.5 Hz), 2.18 (1H, dd, *J*=12.9, 10.4 Hz), 1.56 (3H, s). MS: *m/z*=326 (M^+), 161 (100%). HRMS: calcd for $C_{20}H_{22}O_4$: 326.1518 (M^+). Found: 326.1496.

(2R/S,3S,5R)-5-(Benzyloxymethyl)-2-hydroxy-3-(4-methoxyphenyl)-3-methyltetrahydrofuran **9**

To a stirred solution of **7** (500 mg, 1.53 mmol) in CH_2Cl_2 (8 ml) was added diisobutylaluminum hydride (1.5 M in toluene: 1.02 ml, 1.53 mmol) dropwise at −78°C and the mixture was stirred for 1.5 h at the same temperature. The reaction was quenched by addition of saturated aqueous NH_4Cl (6

ml) and the mixture was extracted with CH_2Cl_2 (20 ml x 3). The extract was washed with brine (10 ml), dried ($MgSO_4$), evaporated under reduced pressure, and chromatographed (SiO_2, 20 g, eluent: Et_2O–hexane, 1:1) to give the lactol **9** (477 mg, 95%) as a colorless oil. IR (film): ν=3414 cm^{-1}. ^1H NMR ($CDCl_3$): δ=7.38–7.14 (7H, m), 6.90–6.82 (2H, m), 5.45 (0.33H, d, *J*=6.3 Hz), 5.31 (0.67H, d, *J*=7.1 Hz), 4.64 (1H, d, *J*=12.1 Hz), 4.60–4.47 (1H, m), 4.58 (1H, d, *J*=12.1 Hz), 3.79 (3H, s), 3.68 (0.67H, dd, *J*=9.9, 3.0 Hz), 3.53 (0.67H, dd, *J*=9.9, 3.6 Hz), 3.53–3.44 (0.67H, m), 3.20 (0.67H, d, *J*=7.4 Hz, exchangeable with D_2O), 2.89 (0.33H, d, *J*=6.3 Hz, exchangeable with D_2O), 2.46 (0.67H, dd, *J*=11.8, 9.3 Hz), 2.19 (0.67H, d, *J*=7.7 Hz), 2.04 (0.67H, dd, *J*=12.1, 7.1 Hz), 1.35 (0.67H, s), 1.32 (1.33H, s). ^{13}C NMR ($CDCl_3$): δ=158.04 (s), 157.87 (s), 138.54 (s), 138.25 (s), 137.57 (s), 137.21 (s), 128.54 (d), 128.40 (d), 128.05 (d), 127.93 (d), 127.90 (s), 127.73 (d), 127.63 (d), 127.11 (d), 113.75 (d), 113.66 (d), 103.73 (d), 103.55 (d), 77.69 (d), 74.99 (d), 73.44 (t), 73.29 (t), 72.94 (t), 71.97 (t), 55.12 (q), 52.41 (s), 48.36 (s), 40.45 (t), 34.79 (t), 27.73 (q), 22.40 (q). MS: *m/z*=328 (M^+), 91 (100%). HRMS: calcd for $C_{20}H_{24}O_4$: 328.1675 (M^+). Found: 328.1720.

(2R,4R)-1-Benzyloxy-4-(4-methoxyphenyl)-4-methyl-5-hexen-2-ol ***10***

To a solution of methyltriphenylphosphonium bromide (1.60 g, 4.83 mmol) in THF (30 ml) was added *n*-BuLi (1.56 M in hexane; 2.7 ml, 4.2 mmol) at 0°C and, after 30 min, a solution of the lactol **9** (287 mg, 0.88 mmol) in THF (6 ml) was added at the same temperature and the stirring was continued for 13 h at room temperature. The reaction was quenched by addition of saturated aqueous NH_4Cl (8 ml) and the mixture was extracted with AcOEt (30 ml x 3). The extract was washed with brine (30 ml), dried ($MgSO_4$), evaporated under reduced pressure, and chromatographed (SiO_2, 100 g, eluent: AcOEt–hexane, 1:10) to give the olefin **10** (280 mg, 97.7%) as a colorless oil, $[\alpha]_D^{27}$ −2.6 (*c* 1.1, $CHCl_3$). IR (film): ν=3462 cm^{-1}. ^1H NMR ($CDCl_3$): δ=7.38–7.14 (7H, m), 6.82 (2H, br d, *J*=8.8 Hz), 6.07 (1H, dd, *J*=17.6, 10.7 Hz), 5.07 (1H, dd, *J*=10.7, 1.1 Hz), 5.03 (1H, dd, *J*=17.6, 1.1 Hz), 4.47 (2H, s), 3.80–3.71 (1H, m), 3.79 (3H, s), 3.28–3.18 (2H, m), 2.23 (1H, br d, *J*=2.7 Hz, exchangeable with D_2O), 1.89 (2H, d, *J*=5.2 Hz), 1.47 (3H, s). ^{13}C NMR ($CDCl_3$): δ=157.82 (s), 147.88 (d), 138.66 (s), 138.03 (s), 128.40 (d), 127.76 (d), 127.69 (d), 127.54 (d), 113.51 (d), 111.24 (t), 75.05 (t), 73.03 (t), 67.70 (d), 55.03 (q), 44.20 (t), 42.85 (s), 25.12 (q). MS: *m/z*=326 (M^+), 161 (100%). HRMS: calcd for $C_{21}H_{26}O_3$: 326.1882 (M^+). Found: 326.1926.

(2R,4R)-4-(4-Methoxyphenyl)-4-methyl-5-hexene-1,2-diol ***11***

To a stirred solution of **11** (652 mg, 2 mmol) in CH_2Cl_2 (10 ml) was added BBr_3 (1.0 M solution in CH_2Cl_2: 2 ml, 2 mmol) dropwise at −30°C and the mixture was stirred for 30 min at the same temperature. The reaction was quenched by addition of 5% aqueous $NaHCO_3$ (2 ml) and extracted with CH_2Cl_2 (30 ml x 3). The extract was washed with brine, dried ($MgSO_4$), evaporated under reduced pressure, and chromatographed (SiO_2, 100 g, eluent: AcOEt–hexane, 1:1) to give the diol **11** (367 mg, 77.8%) as a colorless oil, $[\alpha]_D^{29}$ −9.7 (*c* 0.6, $CHCl_3$). IR (film): ν=3374 cm^{-1}. ^1H NMR ($CDCl_3$): δ=7.25 (2H, br d, *J*=8.8 Hz), 6.86 (2H, br d, *J*=9.1 Hz), 6.13 (1H, dd, *J*=17.6, 10.7 Hz), 5.16 (1H, dd, *J*=10.3, 0.8 Hz), 5.11 (1H, dd, *J*=17.6, 1.1 Hz), 3.79 (3H, s), 3.78–3.68 (1H, m), 3.49–3.31 (2H, m), 2.17 (2H, br s, exchangeable with D_2O), 1.92–1.88 (2H, m), 1.46 (3H, s). ^{13}C NMR ($CDCl_3$): δ=157.91 (s), 147.58 (d), 138.80 (s), 127.67 (d), 113.67 (d), 111.73 (t), 69.62 (d), 67.26 (t), 55.15 (q), 44.19 (t), 42.82 (s), 25.22 (q). MS: *m/z*=236 (M^+), 161 (100%). HRMS: calcd for $C_{14}H_{20}O_3$: 236.1413 (M^+). Found: 236.1392.

(R)-3-(4-Methoxyphenyl)-3-methyl-4-pentenal ***12***

To a stirred solution of the diol **11** (108 mg, 0.46 mmol) in 90% EtOH (2 ml) was added $NaIO_4$ (388 mg, 1.84 mmol) in H_2O (1 ml) at room temperature. After 30 min, the mixture was extracted with AcOEt (20 ml x 3) and the extract was washed with brine (20 ml), dried ($MgSO_4$), evaporated under reduced pressure, and chromatographed (SiO_2, 10 g, eluent: AcOEt–hexane, 1:10) to give the aldehyde **12** (92 mg, 97.6%) as a colorless oil, $[\alpha]_D^{23}$ +2.9 (*c* 2.0, $CHCl_3$). IR (film): ν=1719 cm^{-1}. ^1H NMR ($CDCl_3$): δ=9.58 (1H, t, *J*=3.0 Hz), 7.25 (2H, br d, *J*=9.1 Hz), 6.90 (2H, br d, *J*=9.1 Hz),

6.08 (1H, dd, *J*=17.6, 10.7 Hz), 5.19 (1H, dd, *J*=10.7, 0.8 Hz), 5.10 (1H, dd, *J*=17.6, 0.8 Hz), 3.80 (3H, s), 2.81 (1H, dd, *J*=15.4, 3.0 Hz), 2.72 (1H, dd, *J*=15.4, 3.0 Hz), 1.51 (3H, s). ^{13}C NMR ($CDCl_3$): δ=203.20 (d), 158.31 (s), 145.47 (d), 137.51 (s), 127.47 (d), 113.93 (d), 112.87 (t), 55.19 (q), 53.31 (t), 42.21 (s), 26.13 (q). MS: *m/z*=204 (M^+), 161 (100%). HRMS: calcd for $C_{13}H_{16}O_2$: 204.1150 (M^+). Found: 204.1111.

Methyl (E/Z)-(5R)-5-(4-Methoxyphenyl)-4-methyl-2,6-heptadienoate ***13***

To a stirred solution of NaH (60% in oil: 135 mg, 3.38 mmol) in THF (8 ml) was added methyl diethylphosphonoacetate (0.56 ml, 3.38 mmol), followed by the aldehyde **12** (344 mg, 1.69 mmol) in THF (2 ml) at 0°C. After stirring for 15 min at the same temperature and for 12 h at room temperature, the reaction was quenched by addition of brine (10 ml) and the mixture was extracted with AcOEt (20 ml x 3). The extract was washed with brine, dried ($MgSO_4$), evaporated under reduced pressure, and chromatographed (SiO_2, 50 g, eluent: AcOEt–hexane, 1:9) to give the α,β-unsaturated ester **13** (415 mg, 94.5%) as a colorless oil. IR (film): ν=1721, 1642, 1609 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ=7.22 (2H, br d, *J*=8.8 Hz), 6.86 (2H, br d, *J*=8.8 Hz), 6.78 (0.75H, dt, *J*=15.7, 7.7 Hz), 6.14–5.94 (1.25H, m), 5.85–5.76 (1H, m), 5.16–5.00 (2H, m), 3.80 (3H, s), 3.71 (0.75H, s), 3.69 (2.25H, s), 3.27–3.06 (0.5H, m), 2.72–2.56 (1.5H, m), 1.37 (0.75H, s), 1.36 (2.25H, s). MS: *m/z*=260 (M^+), 161 (100%). HRMS: calcd for $C_{16}H_{20}O_3$: 260.1412 (M^+). Found: 260.1453.

Methyl (R)-5-(4-Methoxyphenyl)-5-methyl-6-heptenoate ***14***

A suspension of the α,β-unsaturated ester **13** (250 mg, 0.96 mmol) and Mg metal (234 mg, 9.62 matom) in MeOH (5 ml) was stirred at room temperature for 3.5 h. The clear mixture was treated with 3N HCl and extracted with AcOEt (30 ml x 3). The extract was washed with saturated aqueous $NaHCO_3$, brine, dried ($MgSO_4$), evaporated under reduced pressure, and chromatographed (SiO_2, 10 g, eluent: AcOEt–hexane, 1:9) to give the ester **14** (150 mg, 59.6%) as a colorless oil, $[\alpha]_D^{29}$ −5.7 (*c* 1.0, $CHCl_3$). IR (film): ν=1737 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ=7.22 (2H, br d, *J*=8.5 Hz), 6.85 (2H, br d, *J*=8.5 Hz), 6.00 (1H, dd, *J*=17.6, 10.7 Hz), 5.08 (1H, dd, *J*=10.7, 1.1 Hz), 5.03 (1H, dd, *J*=17.6, 1.1 Hz), 3.79 (3H, s), 3.63 (3H, s), 2.26 (2H, t, *J*=7.4 Hz), 1.84–1.39 (4H, m), 1.35 (3H, s). ^{13}C NMR ($CDCl_3$): δ=173.93 (s), 157.70 (s), 146.92 (d), 139.10 (s), 127.52 (d), 113.40 (d), 111.62 (s), 54.93 (q), 51.20 (q), 43.38 (s), 40.39 (t), 34.27 (t), 24.86 (q), 19.97 (t). MS: *m/z*=262 (M^+), 161 (100%). HRMS: calcd for $C_{16}H_{22}O_3$: 262.1569 (M^+). Found: 262.1596.

(R)-6-(4-Methoxyphenyl)-2,6-dimethyl-7-octen-2-ol ***15***

To a stirred solution of the ester **14** (162 mg, 0.62 mmol) in THF (3 ml) was added MeLi (1.4 M in Et_2O: 4.4 ml, 6.2 mmol) dropwise at −30°C and the mixture was stirred for 18 h at the same temperature. The reaction was quenched by addition of brine and the mixture was extracted with AcOEt (10 ml x 3). The extract was washed with brine, dried ($MgSO_4$), evaporated under reduced pressure, and chromatographed (SiO_2, 10 g, eluent: AcOEt–hexane, 1:4) to give the alcohol **15** (124 mg, 76.3%) as a colorless oil, $[\alpha]_D^{27}$ −7.1 (*c* 1.0, $CHCl_3$). IR (film): ν=3404 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ=7.22 (2H, br d, *J*=9.1 Hz), 6.84 (2H, br d, *J*=9.1 Hz), 6.00 (1H, dd, *J*=17.6, 10.7 Hz), 5.07 (1H, dd, *J*=10.7, 1.3 Hz), 5.02 (1H, dd, *J*=17.6, 1.4 Hz), 3.79 (3H, s), 1.82–1.60 (2H, m), 1.48–1.06 (5H, m), 1.35 (3H, s), 1.15 (6H, s). ^{13}C NMR ($CDCl_3$): δ=157.43 (s), 147.16 (d), 139.58 (s), 127.47 (d), 113.38 (d), 111.45 (s), 70.88 (s), 55.15 (q), 44.56 (t), 43.74 (t), 41.71 (t), 29.25 (q), 25.16 (q), 19.32 (t). MS: *m/z*=262 (M^+), 161 (100%). HRMS: calcd for $C_{17}H_{26}O_2$: 262.1933 (M^+). Found: 262.1980.

Dehydration of the Tertiary Alcohol ***15***

(a) To a stirred solution of **15** (145 mg, 0.55 mmol) in CH_2Cl_2 (3 ml) was added methanesulfonyl chloride (0.13 ml, 1.66 mmol), Et_3N (0.23 ml, 1.66 mmol) and 4-(*N*,*N*-dimethylaminopyridine (0.67 mg, 5.5 μmol) at room temperature and the mixture was stirred for 3 h at the same temperature. The mixture after treatment with 5% $NaHCO_3$ was dissolved in CH_2Cl_2 (30 ml). The organic layer was washed with 1N HCl, 5% $NaHCO_3$, brine, dried ($MgSO_4$), evaporated under reduced pressure, and

chromatographed (SiO_2, 20 g, eluent: AcOEt–hexane, 1:50) to give the olefin mixture consisted of sporochnol methyl ether **16** and its *exo*-olefin isomer (*endo*/*exo*=2.6:1: 101 mg, 75%).

(b) A suspension of **15** (28 mg, 0.11 mmol) and $CuSO_4$–SiO_2 (1:1, 0.1 g) in toluene (3 ml) was reflux for 1 h. The mixture, after removal of the insoluble material was evaporated to give a mixture of **16** and the *exo*-olefin isomer (26 mg, 100%) as a 5 (*endo*):1 (*exo*) mixture. The mixture ratio was determined by ^1H NMR spectrum [*exo*-olefin δ=5.13–5.06 (m):*endo*-olefin δ=4.67 (br s), 4.63 (br s)].

(E/Z)-(R)-6-Methoxy-3-(4-methoxyphenyl)-3-methyl-1,5-hexadiene ***17***

To a stirred solution of methoxymethyltriphenylphosphonium chloride (1.37 g, 4 mmol) in THF (20 ml) was added *n*-BuLi (1.56 M in hexane: 2.2 ml, 3.4 mmol) at 0°C and, after 30 min, the aldehyde **12** (136 mg, 0.67 mmol) in THF (4 ml) at the same temperature. The mixture was then stirred at room temperature for 16 h and was treated with saturated aqueous NH_4Cl (8 ml). The mixture was extracted with AcOEt (30 ml x 3), washed with brine (30 ml), dried ($MgSO_4$), evaporated under reduced pressure, and chromatographed (SiO_2, 20 g, eluent: AcOEt–hexane, 1:40) to give the enol ether **17** (117 mg, 75.6%) as a colorless oil. IR (film): ν=1662, 1609 cm^{-1}. ^1H NMR ($CDCl_3$): δ=7.28–7.20 (2H, m), 6.87–6.81 (2H, m), 6.22 (0.6H, br d, *J*=12.6 Hz), 6.02 (0.6H, dd, *J*=17.6, 10.7 Hz), 6.01 (0.4H, dd, *J*=17.3, 10.7 Hz), 5.88 (1H, ddd, *J*=6.3, 1.6, 1.4 Hz), 5.12–4.97 (2H, m), 4.51 (0.6H, dt, *J*=12.6, 7.7 Hz), 4.24–4.14 (0.4H, m), 3.80 (1.8H, s), 3.79 (1.2H, s), 3.55 (1.2H, s), 3.43 (1.8H, s), 2.61–2.45 (0.8H, m), 2.41–2.26 (1.2H, m), 1.34 (1.2H, s), 1.31 (1.8H, s). ^{13}C NMR ($CDCl_3$): δ=157.78 (s), 157.75 (s), 148.74 (d), 147.41 (d), 147.12 (d), 139.44 (s), 139.38 (s), 132.33 (d), 132.29 (d), 131.65 (d), 131.53 (d), 128.78 (d), 128.63 (d), 127.90 (d), 127.84 (d), 113.46 (d), 113.40 (d), 111.85 (t), 111.67 (t), 103.11 (d), 99.25 (d), 59.43 (q), 55.91 (q), 55.19 (q), 43.78 (s), 39.56 (t), 35.08 (t), 25.19 (q), 24.78 (q). MS: *m/z*=232 (M^+), 161 (100%). HRMS: calcd for $C_{15}H_{20}O_2$: 232.1463 (M^+). Found: 232.1455.

(R)-4-(4-Methoxyphenyl)-4-methyl-5-hexenal ***18***

A solution of the enol ether **17** (139 mg, 0.60 mmol) in THF (10 ml) was stirred with 70% $HClO_4$ (2.5 ml) at room temperature for 1.5 h. The reaction was quenched by addition of 5% $NaHCO_3$ (4 ml) at 0°C and the mixture was extracted with AcOEt (20 ml x 3). The extract was washed with brine (20 ml), dried ($MgSO_4$), evaporated under reduced pressure, and chromatographed (SiO_2, 30 g, eluent: AcOEt–hexane, 1:6) to give the aldehyde **18** (122 mg, 93.4%) as a colorless oil, $[\alpha]_D^{22}$ −8.7 (*c* 1.9, $CHCl_3$). IR (film): ν=1721 cm^{-1}. ^1H NMR ($CDCl_3$): δ=9.70 (1H, t, *J*=1.6 Hz), 7.22 (2H, br d, *J*=9.1 Hz), 6.85 (2H, br d, *J*=9.1 Hz), 5.98 (1H, dd, *J*=17.6, 10.7 Hz), 5.13 (1H, dd, *J*=10.7, 1.1 Hz), 5.07 (1H, dd, *J*=17.6, 1.1 Hz), 3.79 (3H, s), 2.42–2.20 (2H, m), 2.18–1.96 (2H, m), 1.35 (3H, s). ^{13}C NMR ($CDCl_3$): δ=202.57 (d), 158.04 (s), 146.35 (d), 138.36 (s), 127.70 (d), 113.70 (d), 112.38 (t), 55.19 (q), 43.00 (s), 39.84 (t), 32.43 (t), 25.00 (q). MS: *m/z*=218 (M^+), 161 (100%). HRMS: calcd for $C_{14}H_{18}O_2$: 218.1307 (M^+). Found: 218.1305.

(R)-3-(4-Methoxyphenyl)-3,7-dimethyl-1,6-octadiene (ent-O-*Methylsporochnol A)* ***16***

To a stirred solution of isopropyltriphenylphosphonium iodide (618 mg, 1.43 mmol) in THF (9 ml) was added *n*-BuLi (1.56 M in hexane: 0.78 ml, 1.20 mmol) at 0°C and, after 1.5 h, the aldehyde **18** (52 mg, 0.24 mmol) in THF (2 ml) was added at the same temperature and the mixture was stirred for 12 h at room temperature. The reaction was quenched by addition of saturated aqueous NH_4Cl (2 ml) and the mixture was extracted with AcOEt (20 ml x 3). The extract was washed with brine (20 ml), dried ($MgSO_4$), evaporated under reduced pressure, and chromatographed (SiO_2, 40 g, eluent: hexane) to give the diene **16** (44 mg, 75.1%) as a colorless oil, $[\alpha]_D^{29}$ −2.3 (*c* 1.1, $CHCl_3$) [lit.[9]: $[\alpha]_D^{30}$ +2.8 (*c* 0.9, $CHCl_3$)]. IR (film): ν=1609 cm^{-1}. ^1H NMR ($CDCl_3$): δ=7.23 (2H, br d, *J*=9.1 Hz), 6.84 (2H, br d, *J*=9.1 Hz), 6.01 (1H, dd, *J*=17.6, 10.7 Hz), 5.13–4.98 (3H, m), 3.79 (3H, s), 1.89–1.67 (4H, m), 1.66 (3H, br s), 1.52 (3H, br s), 1.35 (3H, s). ^{13}C NMR ($CDCl_3$): δ=157.78 (s), 147.44 (d), 139.73 (s), 131.50 (s), 127.78 (d), 124.91 (d), 113.52 (d), 111.58 (t), 55.25 (q), 43.68 (s), 41.21 (t), 25.68 (q), 25.00 (q), 23.28 (t), 17.56 (q). MS: *m/z*=244 (M^+), 161 (100%). HRMS: calcd for

$C_{17}H_{24}O$: 244.1827 (M^+). Found: 244.1811. Spectral data were identical with those of the authentic material obtained by the different procedure.[9]

ent-*(−)-(R)-Sporochnol A* ent-***1***

To a stirred solution of MeMgBr (1.83 M in Et_2O: 2.4 ml, 4.4 mmol) was added the ether **16** (43 mg, 0.18 mmol) and the solution was evaporated under reduced pressure and the residue was heated at 180°C for 9 min. The reaction mixture was diluted with ether and then 5% HCl was added. The organic layer, after separation, was washed with brine (20 ml), dried ($MgSO_4$), evaporated under reduced pressure, and chromatographed (SiO_2, 20 g, eluent: AcOEt–hexane, 1:9) to give *ent-(R)*-sporochnol A *ent-***1** (25 mg, 61.5%) as a colorless oil, $[\alpha]_D^{31}$ −1.3 (*c* 0.5, $CHCl_3$) [natural[1]: $[\alpha]_D$ +10 (*c* 1, $CHCl_3$); lit.[9]: $[\alpha]_D^{30}$ +2.9 (*c* 0.5, $CHCl_3$)]. IR (film): ν=3336 cm^{-1}. ^1H NMR ($CDCl_3$): δ=7.18 (2H, br d, *J*=8.8 Hz), 6.77 (2H, br d, *J*=8.8 Hz), 6.00 (1H, dd, *J*=17.3, 10.7 Hz), 5.12–4.98 (3H, m), 4.63 (1H, br s), 1.88–1.68 (4H, m), 1.66 (3H, br s), 1.51 (3H, br s), 1.35 (3H, s). MS: *m/z*=230 (M^+), 147 (100%). HRMS: calcd for $C_{16}H_{22}O$: 230.1671 (M^+). Found: 230.1671. Spectral data were identical with those of an authentic material.[9]

References

1. Shen, Y.-C.; Tsai, P. I.; Fenical, W.; Hay, M. E. *Phytochemistry* **1993**, *52*, 71–75.
2. Optically pure epichlorohydrin is commercially available in both enantiomeric forms from DAISO Corporation, Osaka, Japan. We thank DAISO for the donation of optically pure epichlorohydrin (>98% ee).
3. Takano, S.; Sekiguchi, Y.; Setoh, M.; Yoshimitsu, T.; Inomata, K.; Takahashi, M.; Ogasawara, K. *Heterocycles* **1990**, *31*, 1715–1719.
4. Pertinent reviews utilizing optically active *O*-benzylglycidol in chiral syntheses, see: Takano, S.; Ogasawara, K. *J. Syn. Org. Chem. Jpn.* **1989**, *47*, 813–830: Hanson, R. M. *Chem. Rev.* **1991**, 437–475.
5. Takano, S.; Imamura, Y.; Ogasawara, K. *Tetrahedron Lett.* **1981**, *22*, 4479–4482. Takano, S.; Goto, E.; Hirama, M.; Ogasawara, K. *Chem. Pharm. Bull.* **1982**, *30*, 2641–2643; Takano, S.; Goto, E.; Ogasawara, K. *Tetrahedron Lett.* **1982**, *23*, 5567–5570.
6. Profitt, J. A.; Watt, D. S.; Corey, E. J. *J. Org. Chem.* **1975**, *40*, 127–128: Takano, S.; Yamada, S.; Numata, H.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1983**, 761–763.
7. Takano, S.; Shimazaki, Y.; Ogasawara, K. *Tetrahedron Lett.* **1990**, *23*, 3325–3326.
8. Carnduff, J.; Miller, J. A. *J. Chem. Soc., Chem. Commun.* **1967**, 606–607: *idem J. Chem. Soc. (C)* **1968**, 2671–2673.
9. Recently, we have completed an alternative asymmetric synthesis of (+)-sporochnol A by employing the fundamentally different procedure which also supported the present conclusion, see: Kamikubo, T.; Shimizu, M.; Ogasawara, K. *Enantiomer*, in press.
10. Nishiguchi, T.; Machida, E.; Yamamoto, E. *Tetrahedron Lett.* **1987**, *28*, 4565–4568.

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