Pergamon

Tetrahedron: *Asymmetry* 10 (1999) 1153–1162

TETRAHEDRON: *ASYMMETRY*

# Total synthesis of (−)-sporochnol A, the fish deterrent, from a chiral malonate

Antoine Fadel * and Lucie Vandromme

*Laboratoire des Carbocycles (Associé au CNRS), Institut de Chimie Moléculaire d'Orsay, Bât. 420, Université de Paris-Sud, 91405 Orsay, France*

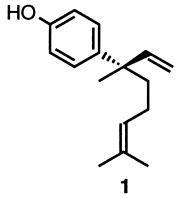
Received 15 February 1999; accepted 8 March 1999

**Abstract**

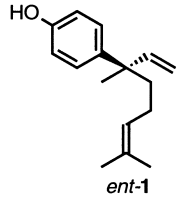
From a single chiron, the homochiral benzylic malonic acid ester (*R*)-(+)-**2** available with high enantiomeric excess by enzymatic hydrolysis (PLE acetonic powder), enantiomerically pure (−)-sporochnol A **1** was prepared. This versatile method allows preparation of sporochnol **1**, via aldehydes **7** and **15**, in good overall yield. 

## 1. Introduction

(+)-Sporochnol A **1**, isolated from the Caribbean marine alga *Sporochnus bolleanus*, has been shown to exhibit significant feeding deterrence towards herbivorous fish.[1]




**1**
(*S*)-(+)-sporochnol A



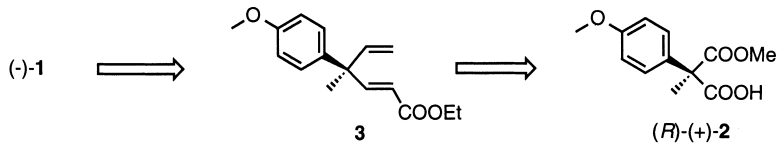

*ent*-**1**
(*R*)-(-)-sporochnol A

The structure was determined by spectral and chemical methods[1] and the absolute configuration assigned to be (*S*) for the natural (+)-sporochnol A **1**. Few methods for the enantioselective synthesis have been investigated.[2,3] In previous papers, we have described the asymmetric construction of quaternary benzylic carbons from chiral malonates[4–6] and their subsequent transformation into both enantiomers of (−)-aphanorphine and (+)-eptazocine.[7,8] Herein we wish to describe a total synthesis of (−)-sporochnol

* Corresponding author. Fax: +33(1)69156278; e-mail: antfadel@icmo.u-psud.fr

0957-4166/99/$ - see front matter 
*PII:* S0957-4166(99)00086-5

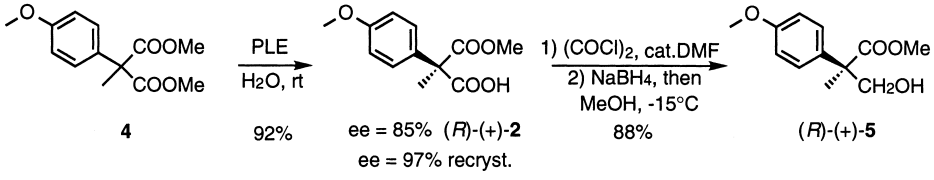
A **1** from a chiral acid ester **2**, obtained on a large scale by enantiomeric hydrolysis via the conjugated ester **3**.




## 2. Results and discussions

The prochiral dimethyl malonate **4**, obtained in 92% yield from methyl 4-methoxyphenylacetate by successive alkylation with methyl iodide and methyl chloroformate, was submitted to enantioselective enzymatic hydrolysis by pig liver esterase (PLE) to provide (*R*)-(+)-**2** (yield, 93%) in the acid ester.† The enantiomeric excess of **2**, determined from the $^1$H NMR spectra of its salt with (*R*)-(+)-1-naphthylethylamine, was 85% and was raised to 97% after recrystallisation (see Experimental) [$[\alpha]_D^{20}$=+12 (c=1, $CHCl_3$), ee=97%].

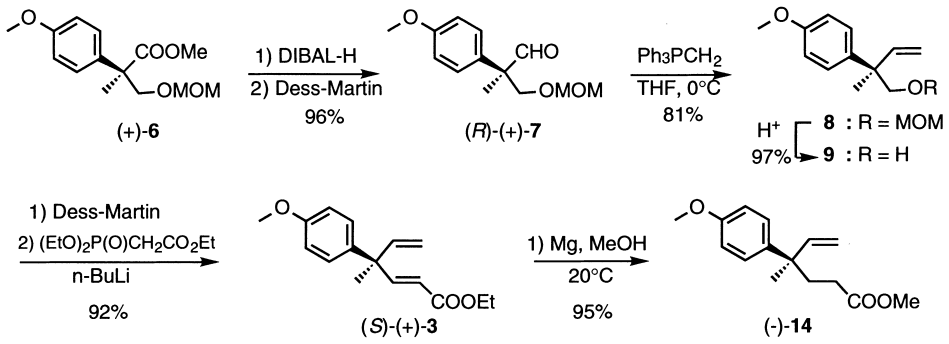
We have previously reported on the chemoselective reduction of acid esters such as **2**.[6] Thus, reaction of (*R*)-(+)-**2** with $(COCl)_2$-cat. DMF,[9] followed by reduction of the resulting acyl chloride ($NaBH_4$, THF then MeOH)[10] gave the β-hydroxy ester (*R*)-(+)-**5** in 88% overall yield, $[\alpha]_D^{20}$=+65.5 (c=1, $CHCl_3$).



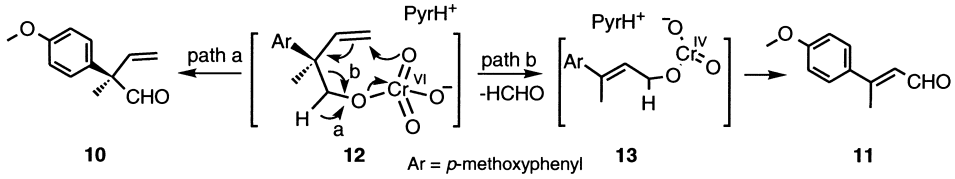

Hydroxy ester (+)-**5** was found to be a key intermediate for the preparation of conjugated ester (+)-**3**. Thus its protection with chloromethyl methyl ether in the presence of diisopropylethylamine led to the ester (+)-**6** [98% yield; $[\alpha]_D^{20}$=+31 (c=1, $CHCl_3$)]. Its reduction with 2 equiv. of diisobutylaluminium hydride (DIBAL-H in toluene)‡ at −78°C gave the corresponding alcohol, which was submitted to the Dess–Martin oxidation[11] to furnish aldehyde **7** in 96% overall yield. This aldehyde **7**, without further purification, was treated with methylenetriphenylphosphorane to give olefin **8** [81% yield, $[\alpha]_D^{20}$=−9.5 (c=1, $CHCl_3$)]. At this stage the deprotection of alcohol was carried out in EtOH at 65°C in the presence of concentrated HCl to afford alcohol **9** in 97% yield. Oxidation with the Dess–Martin reagent,[11] followed by Horner–Emmons reaction of the resulting aldehyde, led to α,β-unsaturated ester (+)-**3** in 92% overall yield. However, oxidation of alcohol **9** with PCC[12] furnished, in 92% yield, the expected aldehyde **10** and the byproduct **11**[13] in a 91:9 ratio.

† The absolute configuration (*R*)-(+)-**2** was assigned by comparison to other aryl malonic acid ester obtained with PLE,[4–6] and was confirmed, vide infra, by comparison of the sign of (*R*)-(−)-sporochnol A with that of the literature.[2]

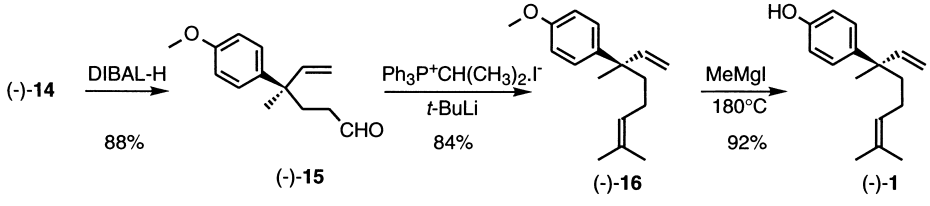
‡ Use of 1 equiv. of DIBAL-H gave a mixture of alcohol, aldehyde and unreacted ester.




We believe that we have first formation in the chromium(VI) oxidation of chromate ester **12**, which undergoes a normal oxidation to aldehyde **10** (path a), or an unexpected rearrangement via a seven-membered transition state (path b) to rearranged ester **13**. This latter is oxidised to rearranged aldehyde **11**. Such rearrangement was known in the oxidation of allyl alcohol using $CrO_3$.[14–16] Chemoselective reduction of the conjugated ester (+)-**3** with magnesium in methanol,[17–19] gave methyl ester (*R*)-(−)-**14** in 95% yield. A simple reduction of ester **14** by 1.3 equiv. of DIBAL-H in toluene at −78°C led to aldehyde (*R*)-(−)-**15** (88% yield) and corresponding alcohol (5%): $[[\alpha]_D^{20}=-12.5$ (c=1, $CHCl_3$), lit.[2] $[\alpha]_D^{20}=-8.7$ (c=1.9, $CHCl_3$)].




The aldehyde (*R*)-(−)-**15** underwent the Wittig reaction with isopropyltriphenylphosphorane ($Ph_3P^+CH(Me)_2\cdot I^-$, *t*-BuLi) to furnish (*R*)-(−)-*O*-methylsporochnol A **16** in 84% yield as a single product. Finally, to cleave the ether bond, the methyl ether **16** was heated at 180°C with methylmagnesium iodide[20,21] to give (−)-*ent*-sporochnol A **1** (92% yield). The sign of the specific rotation of (−)-**1** indicated that the configuration is (*R*) as reported,[2] and consequently confirmed our assignment ((*R*)-configuration) of acid (+)-**2** prepared by enzymatic hydrolysis.




In conclusion, from a readily available chiron **2** (ee >97%), we have developed, by a 10-step reaction sequence, a rapid and competitive total synthesis of (−)-*ent*-sporochnol A **1** with 33% overall yield. Furthermore, we can also emphasise that asymmetric synthesis of the natural product (*S*)-(+)-**1** is conceivable from the same precursor **2**, by converting aldehyde (*R*)-(+)-**7** into ester (*R*)-(−)-**3** just by inverting the order of the Wittig, Dess–Martin, and Horner–Emmons reactions through the same sequence proposed herein.

## 3. Experimental

Except as otherwise indicated, reactions were carried out under argon, with magnetic stirring. All reactions were monitored by thin layer chromatography (TLC) using 0.25 mm E. Merck precoated silica gel plates. Flash chromatography was performed with silica gel 60 (particle size 0.040–0.063 mm). Yields refer to chromatographically and spectroscopically pure compounds, except as noted. Proton and $^{13}C$ NMR spectra were recorded on a Bruker AM250 spectrometer in deuteriochloroform using the solvent signal as an internal standard, 7.27 ppm. Chemical shifts (δ) are expressed in parts per million and the coupling constants (J) are given in hertz. IR spectra were recorded on a Perkin–Elmer 682 spectrophotometer. Mass spectra were recorded at an ionising voltage of 70 eV by EI. High resolution mass spectra were obtained with a MAT 95S spectrometer. Melting points were determined on a Mettler FP51 capillary melting point apparatus and are uncorrected. Specific rotations were obtained at 20°C using a Perkin–Elmer 341 polarimeter. Enantiomeric excesses were performed on a GC (Fisons 9130) chiral column Cydex B (SGE) (25 m, 110°C, 0.8 bar). Elemental analyses were performed by the microanalytical laboratory of CNRS at Gif (France).

### 3.1. *Dimethyl 2-(4-methoxyphenyl)-2-methylmalonate **4***

Prepared from 2-(4-methoxyphenyl)acetic acid (24.9 g, 0.15 mol) following the procedure described in the literature,[6] with 93% overall yield as a colourless oil (35 g).

*Data for **4***: $R_f$=0.56 (EtOAc:petroleum ether, 3:7); IR (film, $cm^{-1}$): 1745, 1620, 1590, 1260; $^1H$ NMR ($CDCl_3$) δ: 7.35–7.23 (m, 2H), 6.44–6.82 (m, 2H), 3.80 (s, 3H), 3.75 (s, 3H, $Me_{ester}$), 1.85 (s, 3H); $^{13}C$ NMR ($CDCl_3$) δ: 172.0 (2s), [6 arom C: 158.7 (s), 129.8 (s), 128.3 (2d), 113.3 (2d)], 57.8 (s, $C_2$), 54.9 (q), 52.5 (2q), 22.0 (q); MS (EI) *m/z*: 253 ($M^+$+1, 5), 252 ($M^+$, 27), 251 (43), 193 (53), 192 (93), 165 (20), 164 (22), 134 (27), 133 (91), *132* (100), 91 (23), 90 (24). HRMS calcd for $C_{13}H_{16}O_5$: 252.0998. Found: 252.0999. Anal. calcd for $C_{13}H_{16}O_5$: C, 61.90; H, 6.39. Found: C, 62.14; H, 6.58.

### 3.2. *(*R*)-(+)-2-(Methoxycarbonyl)-2-(4-methoxyphenyl)propionic acid **2***

Following the procedure described in the literature:[6] to a stirred solution of malonate **4** (25.2 g, 0.1 mol) in water (100 mL) was added, at 25°C, pig liver esterase (5 g, acetonic powder purchased from Sigma L 8251). The pH of the reaction was kept at 7.0 by regular addition of 2 N aqueous NaOH via a syringe pump interfaced with a pH controller. After a stirring period of 3 h another portion of PLE (2×5 g) was added. When 50 mL of aqueous 2 N NaOH (60 h) was added, the enzyme was eliminated by filtration (addition of Celite to the mixture facilitates the filtration). The precipitate was washed with water (60 mL) and with ether (100 mL). After separation, the aqueous layer was acidified (2 N aqueous HCl) until pH=3 and the malonate monoester **2** was extracted with ethyl acetate (6×250 mL). The combined organic extracts were washed with brine, dried and evaporated ($T$<35°C) to give 23.2 g (97.5%) of crude acid. Product purification was achieved by flash chromatography on silica gel (elution with EtOAc:petroleum ether, 3:7 to 6:4). Then 22.1 g (92.8%) acid ester (+)-**2**, was isolated as a colourless oil, $[\alpha]_D^{20}$=+10.3 (c=1, $CHCl_3$); ee=85% from $^1H$ NMR spectra in the presence of (*R*)-(+)-1-naphthylethylamine. Crystallisation of 22 g acid ester from ether:pentane gave 3 g of a solid mixture of (*S*):(*R*) (9:2) and concentration of the mother liquor furnished 19 g (80% yield) of pure acid (+)-**2**.

*Data for (*R*)-(+)-**2***: $[\alpha]_D^{20}$=+12 (c=1, $CHCl_3$); ee=97%. $R_f$=0.16 (EtOAc:petroleum ether, 1:1); IR (film, $cm^{-1}$): 3600, 3500, 3200, 1745, 1720, 1620, 1590; $^1H$ NMR ($CDCl_3$, 250 MHz) δ: 10.15 (br s, $1H_{acid}$), 7.40–7.25 (m, 2H), 6.95–6.80 (m, 2H), 3.82 (s, 3H), 3.80 (s, 3H, $Me_{ester}$), 1.90 (s, 3H); $^{13}C$

NMR ($CDCl_3$, 50.29 MHz) δ: 177.0 (s, $C_1$ acid), 172.2 (s, $C_3$), [6 arom C: 159.1 (s), 129.3 (s), 128.5 (2d), 113.6 (2d)], 57.8 (s, $C_2$), 55.1 (q), 52.9 (q), 21.7 (q). Anal. calcd for $C_{12}H_{14}O_5$: C, 60.50; H, 5.92. Found: C, 60.50; H, 5.92.

### 3.3. *Methyl (*R*)-(+)-3-hydroxy-2-(4-methoxyphenyl)-2-methylpropionate* ***5***

To a stirred solution of acid ester (+)-**2** (11.9 g, 50 mmol, 97% ee) and 2 drops of DMF[9] in dry $CH_2Cl_2$ (90 mL) was added dropwise $(COCl)_2$ (9.6 mL, 110 mmol, 2.2 equiv.). The mixture was stirred at room temperature for 2 h (complete reaction as evidenced by TLC). The solvent was evaporated to dryness, which quantitatively gave the corresponding acyl chloride. This was used in the next step without further purification.

*Data for acyl chloride*: $^1$H NMR ($CDCl_3$, 250 MHz) δ: 7.42–7.20 (m, 2H), 7.00–6.80 (m, 2H), 3.85 (s, 3H), 3.83 (s, 3H, $Me_{ester}$), 2.00 (s, 3H); $^{13}$C NMR ($CDCl_3$, 62.86 MHz) δ: 173.4 (s, $C_1$), 169.9 (s, $C_3$), [6 arom C: 159.7 (s), 128.9 (2d), 127.6 (s), 114.0 (2d)], 67.0 (s, $C_2$), 55.3 (q), 53.3 (q), 22.4 (q).

To a cold (−30°C) stirred solution of acyl chloride (50 mmol) in dry THF was added $NaBH_4$ (5.7 g, 150 mmol, 3 equiv.) in one portion, and then MeOH (15 mL)[7] was added dropwise over 1 h 30 min. After stirring at −30°C for 1 h, then at room temperature for 2 h, the reaction mixture was hydrolysed with 6 N aq. HCl (to pH 2). The hydroxy ester was extracted with $CH_2Cl_2$ (4×150 mL). The combined organic extracts were washed with brine, dried and concentrated. Product purification was achieved by flash chromatography on silica gel (eluent: ethyl acetate:petroleum ether, 1:9 to 6:4). There was 9.85 g (88% overall yield from acid **2**) hydroxy ester (+)-**5** isolated as a colourless oil.

*Data for (*R*)-(+)-**5***: $R_f$=0.27 (AcOEt:petroleum ether, 3:7); $[\alpha]_D^{20}$=+65.5 (c=1, $CHCl_3$); ee=97%; IR (film, $cm^{-1}$): 3500, 1735, 1615, 1590, 1520; $^1$H NMR ($CDCl_3$, 200 MHz) δ: 7.30–7.15 (m, 2H), 6.95–6.80 (m, 2H), 3.82 [AB part of ABM system, $\Delta\nu_{AB}$=87 Hz, 4.05 (dd, A part, $J_{AB}$=13.6 Hz, $J_{AM}$=6.3 Hz, 1H), 3.58 (dd, B part, $J_{AB}$=13.6 Hz, $J_{BM}$=8.4 Hz, 1H)], 3.80 (s, 3H), 3.72 (s, 3H, $Me_{ester}$), 2.50 (dd, M part, $J_{AM}$=6.3 Hz, $J_{BM}$=8.4 Hz, OH), 1.64 (s, 3H); $^{13}$C NMR ($CDCl_3$, 62.86 MHz) δ: 176.4 (s, $C_1$), [6 arom C: 158.5 (s), 132.3 (s), 127.1 (2d), 113.4 (2d)], 69.3 (t, $C_3$), 55.0 (q), 52.0 (q), 51.7 (s, $C_2$), 19.9 (q); MS (EI) *m/z*: 225 ($M^+$+1, 5.2), 224 ($M^+$, 24), 194 (84), 193 (60), 165 (43), 135 (27), 134 (26), *133* (100), 132 (22), 91 (32), 77 (17), 65 (16), 43 (36). HRMS calcd for $C_{12}H_{16}O_4$: 224.1048. Found: 224.1038.

### 3.4. *Methyl (*R*)-(+)-3-(methoxymethoxy)-2-(4-methoxyphenyl)-2-methylpropionate* ***6***

To a stirred solution of alcohol (+)-**5** (8.96 g, 40 mmol) and diisopropylethylamine (21 mL, 120 mmol) in $CH_2Cl_2$ (150 mL) was added chloromethyl methyl ether (MOMCl, 6.06 mL, 80 mmol) at 0°C. The mixture was stirred at 0°C for 2 h and at room temperature overnight. After addition of water (80 mL) the mixture was extracted with EtOAc (3×200 mL). The organic layer was dried and concentrated and the residue purified by flash chromatography on silica gel (using ether:petroleum ether 1:9 to 6:4 as eluent). Then 10.5 g (98%) of the protected ester **6** was isolated.

*Data for (*R*)-(+)-**6***: $[\alpha]_D^{20}$=+31.4 (c=1, $CHCl_3$); ee=97%; $R_f$=0.64 (EtOAc:petroleum ether, 3:7); IR (film, $cm^{-1}$): 1740, 1615, 1595, 1520; $^1$H NMR ($CDCl_3$, 250 MHz) δ: 7.30–7.15 (m, 2H), 6.95–6.80 (m, 2H), 4.65 (A′B′ system like q, $J_{A'B'}$=6.4 Hz, 2H), 3.90 [AB system, $\Delta\nu_{AB}$=95 Hz, $J_{AB}$=9.5 Hz, 4.12 (d, A part, $J_{AB}$=9.5 Hz, 1H), 3.71 (d, B part, $J_{AB}$=9.5 Hz, 1H)], 3.79 (s, 3H), 3.70 (s, 3H, $Me_{ester}$), 3.31 (s, 3H), 1.65 (s, 3H); $^{13}$C NMR ($CDCl_3$, 62.86 MHz) δ: 175.0 (s, $C_1$), [6 arom C: 158.5 (s), 132.9 (s), 127.0 (2d), 113.7 (2d)], 96.5 (t), 73.4 (t, $C_3$), 55.1 (q), 52.0 (q), 50.4 (s, $C_2$), 21.0 (q); MS (EI) *m/z*: 269 ($M^+$+1, 4), 268 ($M^+$, 12), 238 (11), 206 (11), 194 (20), *193* (100), 192 (12), 177 (10), 165 (13), 151 (11), 134 (17), 133 (61), 45 (71), 44 (17). HRMS calcd for $C_{14}H_{20}O_5$: 268.1311. Found: 268.1300.

### 3.5. (R)-(+)-3-(Methoxymethoxy)-2-(4-methoxyphenyl)-2-methylpropanal **7**

*Preparation of alcohol*: To a stirred solution of ester **6** (9.11 g, 34 mmol), in dry $CH_2Cl_2$ (100 mL) was slowly added via cannula at −78°C, a solution of DIBAL-H (1 M solution in toluene, 102 mL, 3 equiv.). The mixture was stirred for 1 h at −78°C before quenching with MeOH (7 mL) then allowed to warm to room temperature. The solution was poured into a 6:1 mixture of ethyl acetate:potassium sodium tartrate (140 mL). The organic layer was dried and concentrated to give 7.95 g (97.5%) of alcohol (*R*)-(+)-3-(methoxymethoxy)-2-(4-methoxyphenyl)-2-methylpropanol, which was used in the next step without further purification.

*Data for (R)-(+)-3-(methoxymethoxy)-2-(4-methoxyphenyl)-2-methylpropanol*: $[\alpha]_D^{20}$=+4 (c=1, $CHCl_3$); ee=97%; $R_f$=0.27 (EtOAc:petroleum ether, 3:7); IR (film, $cm^{-1}$): 3500, 1620, 1590, 1520; $^1H$ NMR ($CDCl_3$, 200 MHz) δ: 7.40–7.23 (m, 2H), 6.98–6.82 (m, 2H), 4.64 (s, 2H), 3.96–3.65 (m, 2H), 3.81 (s, 3H), 3.79 (AB system, $\Delta\nu_{AB}$=34.8 Hz, $J_{AB}$=9.4 Hz, 2H), 3.35 (s, 3H), 2.17 (m, OH), 1.34 (s, 3H); $^{13}C$ NMR ($CDCl_3$, 62.86 MHz) δ: [6 arom C: 157.9 (s), 135.3 (s), 127.4 (2d), 113.6 (2d)], 96.6 (t), 74.2 (t, $C_3$), 69.4 (t, $C_1$), 55.2 (q), 55.0 (q), 43.0 (s, $C_2$), 20.8 (q); MS (EI) *m/z*: 241 ($M^+$+1, 1.9), 240 ($M^+$, 11), 177 (17), 165 (70), 164 (24), 149 (10), 148 (71), 147 (30), 135 (14), 121 (27), 91 (19), 90 (12), 57 (15), *45* (100), 44 (30). HRMS calcd for $C_{13}H_{20}O_4$: 240.1361. Found: 240.1370.

To a stirred suspension of periodinane (Dess–Martin's reagent)[11] (19.1 g, 1.5 equiv.) in $CH_2Cl_2$ (120 mL), was added dropwise a solution of crude alcohol (7.2 g, 30 mmol) in 20 mL of $CH_2Cl_2$. The mixture was stirred at room temperature. The reaction was monitored by TLC and was completed after 20 h. Ether (60 mL) was added and the precipitate was filtered and washed with ether (50 mL). The filtrate was successively washed with $Na_2S_2O_3$ solution (50 mL), $NaHCO_3$ saturated solution (5 mL) and brine (5 mL). The organic layer was dried, filtered, and concentrated to give 7.07 g of aldehyde **7** (99%) used in the next step without further purification.

*Data for (R)-(+)-**7***: $[\alpha]_D^{20}$=+0.3 (c=1, $CHCl_3$); ee=97%; $R_f$=0.61 (EtOAc:petroleum ether, 3:7); IR (film, $cm^{-1}$): 1740, 1620, 1590, 1520; $^1H$ NMR ($CDCl_3$, 200 MHz) δ: 9.57 (s, 1H), 7.30–7.10 (m, 2H), 7.00–6.82 (m, 2H), 4.60 (m, AB system, 2H), 3.95 [AB system, $\Delta\nu_{AB}$=60.8 Hz, $J_{AB}$=9.5 Hz, 4.10 (d, A part, $J_{AB}$=9.5 Hz, 1H), 3.79 (d, B part, $J_{AB}$=9.5 Hz, 1H)], 3.81 (s, 3H), 3.31 (s, 3H), 1.54 (s, 3H); $^{13}C$ NMR ($CDCl_3$, 62.86 MHz) δ: 201.2 (d, $C_1$), [6 arom C: 158.8 (s), 129.6 (s), 128.0 (2d), 114.2 (2d)], 96.5 (t), 71.1 (t, $C_3$), 55.2 (q), 55.1 (q), 53.8 (s, $C_2$), 17.8 (q); MS (EI) *m/z*: 239 ($M^+$+1, 1.1), 238 ($M^+$, 5), 179 (14), 177 (11), 163 (23), 148 (20), 135 (20), *45* (100). HRMS calcd for $C_{13}H_{18}O_4$: 238.1205. Found: 238.1194.

### 3.6. (R)-(+)-4-(Methoxymethoxy)-3-(4-methoxyphenyl)-2-methylbut-1-ene **8**

To a stirred suspension of methyltriphenylphosphonium bromide (15 g, 42 mmol) in dry THF (100 mL), was added *n*-BuLi (1.6 M, 24.3 mL, 38.9 mmol) at 0°C. The resulting yellow suspension was stirred at room temperature for 1 h. To this suspension was added a solution of crude aldehyde **7** (6.66 g, 28 mmol) in THF (50 mL) at 0°C. The solution was kept at 0°C for 30 min, then allowed to warm to rt (4 h). The solvent was evaporated and the resulting solid was diluted in ether (200 mL) then filtered on Celite and the precipitate washed with ether (3×150 mL). The filtrate was concentrated and the resulting residue purified by flash chromatography on silica gel (elution, EtOAc:petroleum ether, 1:19 to 4:6). There was 5.35 g (81%) of a pure olefin **8** isolated as a colourless oil and 865 mg (13%) of the unreacted aldehyde **7**.

*Data for (R)-(+)-**8***: $R_f$=0.75 (AcOEt:petroleum ether, 3:7); $[\alpha]_D^{20}$=−9.4 (c=1, $CHCl_3$); ee=97%; IR (film, $cm^{-1}$): 3080, 2940, 1630 ($\nu_{C=C}$), 1610, 1580, 1515, 1255, 1115, 1050, 920; $^1H$ NMR ($CDCl_3$, 250

MHz) δ: 7.35–7.20 (m, 2H), 6.92–6.80 (m, 2H), 6.08 (dd, $J_{cis}$=10.5 Hz, $J_{trans}$=17.7 Hz, $H_a$), 5.18 (dd, $J_{cis}$=10.5 Hz, $J_{gem}$=2.6 Hz, $H_b$), 5.11 (dd, $J_{gem}$=2.6 Hz, $J_{trans}$=17.7 Hz, $H_c$), 4.61 (s, like AB system, 2H), 3.80 (s, 3H), 3.73 (m, AB system, 2H), 3.30 (s, 3H), 1.45 (s, 3H); $^{13}$C NMR ($CDCl_3$, 62.86 MHz) δ: [6 arom C: 157.8 (s), 137.0 (s), 127.8 (2d), 113.4 (2d)], 144.4 (d, $C_2$), 113.0 (t, $C_1$), 96.6 (t), 75.2 (t, $C_4$), 55.2 (q), 55.1 (q), 44.7 (s, $C_3$), 23.2 (q); MS (EI) *m/z*: 237 ($M^+$+1, 1), 236 ($M^+$, 6), 162 (16), *161* (100), 121 (14), 91 (12), 45 (51). HRMS calcd for $C_{14}H_{20}O_3$: 236.1412. Found: 236.1402.

### 3.7. Ethyl (S)-(+)-4-(4-methoxyphenyl)-4-methylhexa-2,5-dienoate *3*

*Deprotection*: A stirred solution of olefin **8** (4.72 g, 42 mmol) in ethanol (40 mL) and concentrated HCl (1 mL), was heated at 65°C for 16 h. After addition of $Na_2CO_3$ (solid) to pH=7, the solution was filtered through $Na_2CO_3$ (solid) and the precipitate was washed with ether (2×50 mL). The filtrate was concentrated and the resulting residue was diluted with ether (50 mL). The organic layer was again filtered through a silica gel pad. Evaporation of the solvent furnished 3.73 g (97%) crude alcohol **9**, used in the next step without further purification.

*Data from crude alcohol **9***: $^1$H NMR ($CDCl_3$) δ: 7.35–7.20 (m, 2H), 6.95–6.80 (m, 2H), 6.07 (dd, $J_{cis}$=10.5 Hz, $J_{trans}$=17.9 Hz, $H_a$), 5.25 (dd, $J_{cis}$=10.5 Hz, $J_{gem}$=2.2 Hz, $H_b$), 5.15 (dd, $J_{trans}$=17.9 Hz, $J_{gem}$=2.2 Hz, $H_c$), 3.81 (s, 3H), 3.77 (m, 2H), 1.42 (s, 3H).

*Oxidation by periodinane*: Aldehyde **10** was prepared following the procedure described above for **7**, from a mixture of crude alcohol **9** (3.07 g, 16 mmol), periodinane (10.2 g, 24 mmol) in $CH_2Cl_2$ (80 mL). Usual workup quantitatively gave the corresponding aldehyde **10** which was used in the next step without further purification.

*Data from the crude aldehyde **10***: $^1$H NMR ($CDCl_3$) δ: 9.55 (s, 1H), 7.42–7.22 (m, 2H), 7.03–6.80 (m, 2H), 6.22 (dd, $J_{cis}$=10.5 Hz, $J_{trans}$=17.4 Hz, 1H), 5.41 (d, $J_{cis}$=10.5 Hz, 1H), 5.18 (d, $J_{trans}$=17.4 Hz, 1H), 3.81 (s, 3H), 1.51 (s, 3H).

*Wittig–Horner reaction*: Conjugate ester **3** was prepared following the procedure described in the literature,[8] from a mixture of crude aldehyde **10** (3.04 g, 16 mmol), triethyl phosphonoacetate (4.3 g, 19.2 mmol) and *n*-BuLi (12.4 mL of a 1.55 N solution, 19.2 mmol). Chromatography on silica gel (EtOAc:petroleum ether, 1:19) furnished 3.83 g (92% overall yield from the olefin **8**) as a colourless oil of the *trans*-(+)-**3**.

*Data for (S)-(+)-**3***: $R_f$=0.70 (AcOEt:petroleum ether, 3:7); $[\alpha]_D^{20}$=+19.6 (c=1, $CHCl_3$); ee=97%; IR (film, $cm^{-1}$): 3070, 2970, 1720 ($\nu_{C=O}$), 1645 ($\nu_{C=C}$ conjugated), 1630 ($\nu_{C=C}$), 1610, 1580, 1515, 1260, 1185, 1040; $^1$H NMR ($CDCl_3$, 200 MHz) δ: 7.30–7.10 (m, 2H), 7.18 (d, $J_{trans}$=16.1 Hz, 1H conjugated olefin), 6.06 (dd, $J_{cis}$=10.6 Hz, $J_{trans}$=17.8 Hz, 1H), 5.79 (d, $J_{trans}$=16.1 Hz, 1H conjugated olefin), 5.20 (dd, $J_{cis}$=10.6 Hz, $J_{gem}$=0.8 Hz, 1H), 5.05 (dd, $J_{trans}$=17.8 Hz, $J_{gem}$=0.8 Hz, 1H), 4.20 (q, $J$=7.3 Hz, 2H), 3.80 (s, 3H), 1.54 (s, 3H), 1.30 (t, $J$=7.3 Hz, 3H); $^{13}$C NMR ($CDCl_3$, 62.86 MHz) δ: 166.7 (s, $C_1$), 158.2 (s), 154.4 (d, $C_3$), 143.5 (d, $C_5$), 136.2 (s), 128.1 (2d), 119.5 (d, $C_2$), 113.9 (t, $C_6$), 113.6 (2d), 60.3 (t), 55.1 (q), 47.2 (s, $C_4$), 24.8 (q), 14.2 (q); MS (EI) *m/z*: 261 ($M^+$+1, 7), 260 ($M^+$, 32), *187* (100), 186 (92), 185 (36), 172 (55), 171 (72), 159 (32), 158 (34), 128 (37), 127 (36), 126 (33), 79 (36), 78 (40), 77 (53), 76 (38). HRMS calcd for $C_{16}H_{20}O_3$: 260.1412. Found: 260.1410.

*N.B. Oxidation by PCC*: Aldehyde **10** was prepared following the procedure described in the literature,[6] from crude alcohol **9** (307 mg, 1.6 mmol), PCC[12] (690 mg, 3.2 mmol), $Na_2HPO_4$ (0.4 g), Celite (1 g) and $CH_2Cl_2$ (20 mL). After 16 h at room temperature, the usual workup gave 280 mg (92%) as a mixture of expected aldehyde **10** and conjugated aldehyde **11** in a 9:1 ratio.

The $^1$H NMR spectrum of conjugated aldehyde **11** read from the mixture ($CDCl_3$) δ: 10.16 (d, J=8 Hz,

1H), 7.56 (br d, *J*=9 Hz, 2H), 6.95 (br d, *J*=9 Hz, 2H), 6.41 (dd, *J*=8 Hz, *J*=1.2 Hz, 1H), 3.87 (s, 3H), 2.57 (d, *J*=1.2 Hz, 3H). Spectral data are identical with those reported.[11]

### 3.8. *Methyl (*R*)-(−)-4-(4-methoxyphenyl)-4-methylhex-5-enoate* ***14***

A suspension of conjugated ester **3** (3.38 g, 13 mmol) and Mg (1.56 g, 65 m.atm g) in methanol (50 mL) was stirred at room temperature for 4 h. The cloudy mixture was neutralised with 2 N HCl and extracted with EtOAc (3×150 mL). The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated under vacuum. The resulting residue (3.13 g, 87.2% yield) was purified by chromatography ($SiO_2$, 70 g, eluent: EtOAc:petroleum ether, 1:19) to furnish ester **14** (3.06 g, 95%) as a colourless oil.

*Data for (*R*)-(−)-**14***: $[\alpha]_D^{20}$=−11 (c=1, $CHCl_3$); ee=97%; $R_f$=0.5 (ether:pentane, 1:3); IR (film, $cm^{-1}$): 3075, 2960, 1740 ($\nu_{C=O}$), 1630 ($\nu_{C=C}$), 1610, 1580, 1515, 1255, 1185, 1040; $^1$H NMR ($CDCl_3$, 250 MHz) δ: 7.35–7.12 (m, 2H), 6.94–6.74 (m, 2H), 5.98 (dd, $J_{cis}$=10.6 Hz, $J_{trans}$=16.8 Hz, 1H), 5.13 (d, $J_{cis}$=10.6 Hz, 1H), 5.07 (d, $J_{trans}$=16.8 Hz, 1H), 3.80 (s, 3H), 3.63 (s, 3H, $Me_{ester}$), 2.32–1.92 (m, 4H), 1.35 (s, 3H); $^{13}$C NMR ($CDCl_3$, 62.86 MHz) δ: 174.1 (s, $C_1$), [6 arom C: 157.6 (s), 138.1 (s), 127.4 (2d), 113.4 (2d)], 146.0 (d, $C_5$), 112.0 (t, $C_6$), 54.9 (q), 51.3 (q), 43.0 (s, $C_4$), 35.4 (t, $C_2$), 29.6 (t, $C_3$), 24.7 (q); MS (EI) *m/z*: 249 ($M^+$+1, 2), 248 ($M^+$, 7.8), 162 (16), *161* (100), 160 (61), 146 (7), 145 (6), 91 (6). HRMS calcd for $C_{15}H_{20}O_3$: 248.1412. Found: 248.1408.

### 3.9. *(*R*)-(−)-4-(4-methoxyphenyl)-4-methylhex-5-en-1-al* ***15***

To a stirred solution of ester **14** (2.48 g, 10 mmol) in dry $CH_2Cl_2$ (20 mL) was slowly added a solution of DIBALH (1 M in hexane, 13 mL, 13 mmol, 1.3 equiv.) at −78°C. The mixture was stirred for 30 min at −78°C before quenching with MeOH (5 mL) then allowed to warm to room temperature. The solution was poured into a 6:1 mixture of EtOAc:potassium sodium tartrate (350 mL). The organic layer was dried and concentrated and the residue purified by flash chromatography ($SiO_2$, eluent: ether:pentane, 15:85) to yield 1.92 g (88%) of pure aldehyde (*R*)-(−)-**15** as a colourless oil and the corresponding alcohol (110 mg, 5%).

*Data for (*R*)-(−)-**15***: $[\alpha]_D^{20}$=−12.5 (c=1, $CHCl_3$); ee=97%; [lit.[2] $[\alpha]_D^{20}$=−8.7 (c=1.9, $CHCl_3$)]; $R_f$=0.5 (ether:pentane, 1:3); IR (film, $cm^{-1}$): 2960, 1720 ($\nu_{C=O}$), 1630 ($\nu_{C=C}$), 1608, 1580, 1510, 1255, 1185, 1035; $^1$H NMR ($CDCl_3$, 250 MHz) δ: 9.70 (t, *J*=1.5 Hz, 1H), 7.30–7.17 (m, 2H), 6.92–6.80 (m, 2H), 5.99 (dd, $J_{trans}$=17.2 Hz, $J_{cis}$=10.8 Hz, 1H), 5.14 (dd, $J_{cis}$=10.8 Hz, *J*=1 Hz, 1H), 5.08 (dd, $J_{trans}$=17.2 Hz, *J*=1 Hz, 1H), 3.79 (s, 3H), 2.50–2.25 (m, 2H), 2.25–1.95 (m, 2H), 1.35 (s, 3H); $^{13}$C NMR ($CDCl_3$, 62.86 MHz) δ: 202.1 (d, $C_1$), [6 arom C: 157.7 (s), 138.1 (s), 127.4 (2d), 113.5 (2d)], 146.1 (d, $C_5$), 112.1 (t, $C_6$), 55.0 (q), 42.9 (s, $C_4$), 39.7 (t), 32.3 (t), 24.9 (q); MS (EI) *m/z*: 219 ($M^+$+1, 2), 218 ($M^+$, 8), 162 (17), *161* (100), 160 (57), 146 (8), 145 (7), 91 (7). HRMS calcd for $C_{14}H_{18}O_2$: 218.1306. Found: 218.1304. All spectral data are identical with those reported.[2]

*Data for 4-(4-methoxyphenyl)-4-methylhex-5-en-1-ol*: $^1$H NMR ($CDCl_3$, 250 MHz) δ: 7.30–7.15 (m, 2H), 6.91–6.75 (m, 2H), 6.02 (dd, $J_{trans}$=17.3 Hz, $J_{cis}$=10.7 Hz, 1H), 5.18–5.05 (m, 2H), 3.79 (s, 3H), 3.60 (t, *J*=6.5 Hz, 2H), 1.92–1.65 (m, 2H), 1.60–1.25 (m, 2H and OH), 1.35 (s, 3H).

### 3.10. *(*R*)-(−)-3,7-Dimethyl-3-(4-methoxyphenyl)octa-1,6-diene (*ent-O-*methylsporochnol A)* ***16***

To a stirred solution of isopropyltriphenylphosphonium iodide (2.16 g, 5 mmol) in anhydrous THF (20 mL) was added *t*-BuLi (1.5 M in pentane, 3.3 mL, 5 mmol) at 0°C and, after 2 h (deep red solution),

aldehyde **15** (435 mg, 2 mmol) in THF (5 mL) was added at 0°C and the reaction mixture was stirred at 0°C for 1 h then at room temperature for 10 h. After addition of a saturated aqueous solution of $NH_4Cl$ (20 mL), the mixture was extracted with ether (3×40 mL). The combined extracts were dried and concentrated under reduced pressure. Purification by flash chromatography ($SiO_2$, 40 g, eluent, toluene:hexane, 25:75) furnished diene **16** (410 mg, 84%) as a colourless oil.

*Data for (*R*)-(−)-**16***: $[\alpha]_D^{20}$=−3.7; $[\alpha]_{365}^{20}$=−15.2 (c=1, $CHCl_3$); ee=97%; [lit.[2] $[\alpha]_D^{29}$=−2.3 (c=1.1, $CHCl_3$)]; $R_f$=0.42 (toluene:hexane, 3:7); IR (film, $cm^{-1}$): 2960, 1630 ($\nu_{C=C}$), 1610, 1580, 1510, 1250, 1180, 1040; $^1H$ NMR ($CDCl_3$, 250 MHz) δ: 7.25 (br d, *J*=9 Hz, 2H), 6.85 (br d, *J*=9 Hz, 2H), 6.03 (dd, $J_{trans}$=17.4 Hz, $J_{cis}$=10.8 Hz, 1H), 5.10 (dd, $J_{cis}$=10.8 Hz, *J*=1.2 Hz, 1H), 5.05 (dd, $J_{trans}$=17.4 Hz, *J*=1.2 Hz, 1H), 5.18–5.04 (m, 1H), 3.80 (s, 3H), 2.00–1.60 (m, 4H), 1.68 (br s, 3H), 1.04 (br s, 3H), 1.37 (s, 3H); $^{13}C$ NMR ($CDCl_3$, 62.86 MHz) δ: [6 arom C: 157.5 (s), 139.5 (s), 127.6 (2d), 113.3 (2d)], 147.2 (d, $C_2$), 131.2 (s, $C_7$), 124.7 (d, $C_6$), 111.4 (t, $C_1$), 55.1 (q), 43.6 (s, $C_3$), 41.2 (t), 25.7 (q), 25.0 (t), 23.3 (q), 17.5 (q); MS (EI) *m/z*: 245 ($M^+$+1, 1.5), 244 ($M^+$, 6), 162 (27), *161* (100), 160 (33), 146 (7), 91 (9), 83 (9), 55 (17). HRMS calcd for $C_{17}H_{24}O_1$: 244.1827. Found: 244.1820.

All spectral data are identical with those reported.[2]

### *3.11. (*R*)-(−)-3,7-Dimethyl-3-(4-hydroxyphenyl)octa-1,6-diene (*ent*-(*R*)-(−)-sporochnol)* ent-***1***

Prepared following the literature:[2] To a stirred solution of MeMgI [20,21] (2 M in $Et_2O$: 5 mL, 10 mmol) was added ether **16** (125 mg, 0.5 mmol) and the solution was evaporated under reduced pressure. The residue was heated at 180°C for 10 min. The reaction mixture was cooled to 0°C and diluted with ether (10 mL), then carefully hydrolysed with 1.5 N HCl, and extracted with ether (3×50 mL). The organic layer was washed with brine (10 mL), dried ($MgSO_4$), and concentrated. The residue was purified by flash chromatography ($SiO_2$, 30 g, eluent: ether:pentane, 1:9) to give *ent*-(*R*)-sporochnol A *ent*-**1** (106 mg, 92%) as a colourless oil.

*Data for (*R*)-(−)-*ent-***1***: $[\alpha]_D^{20}$=−2.5 and $[\alpha]_{365}^{20}$=−10.3 (c=1, $CHCl_3$); ee=97%; [lit.[2] $[\alpha]_D^{29}$=−1.3 (c=0.5, $CHCl_3$), natural[1] $[\alpha]_D$=+10 (c=1, $CHCl_3$)]; $R_f$=0.48 (ether:pentane, 1:3); IR (film, $cm^{-1}$): 3365, 2980, 1630 ($\nu_{C=C}$), 1608, 1590, 1510, 1240, 1176, 930; $^1H$ NMR ($CDCl_3$, 250 MHz) δ: 7.19 (br d, *J*=9 Hz, 2H), 6.77 (br d, *J*=9 Hz, 2H), 6.01 (dd, $J_{trans}$=17.2 Hz, $J_{cis}$=10.8 Hz, 1H), 5.09 (dd, $J_{cis}$=10.8 Hz, *J*=1.4 Hz, 1H), 5.03 (dd, $J_{trans}$=17.2 Hz, *J*=1.4 Hz, 1H), 5.18–5.00 (m, 1H), 4.78 (br s, OH), 2.00–1.58 (m, 4H), 1.66 (br s, 3H), 1.53 (br s, 3H), 1.35 (s, 3H); $^{13}C$ NMR ($CDCl_3$, 62.86 MHz) δ: [6 arom C: 153.3 (s), 139.7 (s), 127.8 (2d), 114.8 (2d)], 147.1 (d, $C_2$), 131.3 (s, $C_7$), 124.7 (d, $C_6$), 111.4 (t, $C_1$), 43.6 (s, $C_3$), 41.1 (t), 25.6 (q), 25.0 (t), 23.2 (q), 17.5 (q); MS (EI) *m/z*: 231 ($M^+$+1, 2.3), 230 ($M^+$, 9), 148 (31), *147* (100), 146 (26), 120 (11), 107 (10), 83 (18), 55 (38), 54 (23), 41 (45). HRMS calcd for $C_{16}H_{22}O_1$: 230.1671. Found: 230.1661.

All spectral data are identical with those reported.[2]

## References


1. Shen, Y.-C.; Tsai, P. I.; Fenical, W.; Hay, M. E. *Phytochemistry* **1993**, *52*, 71.
2. Takahashi, M.; Shioura, Y.; Murakami, T.; Ogasawara, K. *Tetrahedron: Asymmetry* **1997**, *8*, 1235.
3. Kamikubo, T.; Shimizu, M.; Ogasawara K. *Enantiomer* **1998**, *2*, 297.
4. Fadel, A.; Garcia-Argote, S. *Tetrahedron: Asymmetry* **1996**, *7*, 1159.
5. Fadel, A.; Canet, J. L.; Salaün, J. *Tetrahedron: Asymmetry* **1993**, *4*, 27.
6. Canet, J. L.; Fadel, A.; Salaün, J. *J. Org. Chem*. **1992**, *57*, 3463 and references cited therein.
7. Fadel, A.; Arzel, Ph. *Tetrahedron: Asymmetry* **1997**, *8*, 371.
8. Fadel, A.; Arzel, Ph. *Tetrahedron: Asymmetry* **1995**, *6*, 893.

9. Wissner, A.; Grudzinskas, C. V. *J. Org. Chem*. **1978**, *43*, 3972.
10. Soai, K.; Yokoyoma, S.; Moshida, K. *Synthesis* **1987**, 647.
11. Dess, D. B.; Martin, J. C. *J. Org. Chem*. **1983**, *48*, 4156.
12. (a) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett*. **1975**, 2650. (b) Bortolussi, M. Unpublished results, private communication, Orsay, 1984.
13. Gulyi, S. E.; Erman, M. B.; Novikov, N. A.; Aul'chenko, I. S.; Vol'pin, M. E. *J. Org. Chem. Russ (Engl. Transl.)* **1983**, *19*, 715.
14. Sundararaman, P.; Herz, W. *J. Org. Chem*. **1977**, *42*, 813.
15. Dauben, W. G.; Michno, D. M. *J. Org. Chem*. **1977**, *42*, 682.
16. Schlecht, M. F.; Kim, H.-J. *J. Org. Chem*. **1989**, *54*, 583.
17. Profitt, J. A.; Watt, D. S.; Corey, E. J. *J. Org. Chem*. **1975**, *40*, 127.
18. Takano, S.; Yamada, S.; Numata, H.; Ogasawara, K. *J. Chem. Soc., Chem. Commun*. **1983**, 761.
19. Hudlicky, T.; Sinai-Zingde, G.; Natchus, M. G. *Tetrahedron Lett*. **1987**, *28*, 5287.
20. Grignard, V. *C.R. Acad. Sci. (Fr)* **1910**, *151*, 3225.
21. Takano, S.; Shimazaki, Y.; Ogasawara, K. *Tetrahedron Lett*. **1990**, *23*, 3325.