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A short and efficient synthesis of (*R*)-(−)-sporochnol A

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Dedicated to the memory of Professor Marcial Moreno-Mañas✠

Abstract—A short and efficient synthesis of (*R*)-(−)-sporochnol A in five steps and 9% overall yield has been developed. The sequence uses as starting material the easily available enantiopure monoketal derived from 1,4-cyclohexanedione and (*R*,*R*)-hydrobenzoin that serves as a chiral auxiliary.

1. Introduction

Nature presents many examples of chemical defenses and much attention has been paid to the role of secondary metabolites in defending plants from herbivores. There are many examples of phenolic derivatives implicated as defensive agents against herbivores.[1] Among them, (*S*)-(+)-sporochnol A, (*S*)-(+)-**1**, a prenylated phenol, which was isolated in 1993 from the Caribbean marine alga *Sporochnus bolleanus*, collected near Hunting Cay in Belize, has been found to show significant feeding deterrence toward herbivorous fishes (Fig. 1).[2]

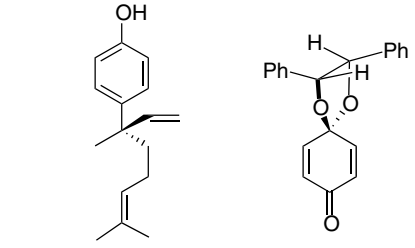

Figure 1.

Six syntheses of this natural product in enantiopure form have been reported: one describes access to each enantiomer,[3] two report the synthesis of the natural isomer,[4,5] and three that of the unnatural (*R*)-(−)-enantiomer.[6–8] All of these stereocontrolled synthetic sequences present severe disadvantages: five require 12 or more synthetic steps when using the commercially available compounds as the starting materials,[3–7] and the sixth, although significantly shorter in a number of steps, requires the difficult preparation of peptide-based enantiopure ligands and reports only an 82% ee.[8]

Already in this century, other six total or formal syntheses of racemic sporochnol have been published.[9–14] By far, the shortest and most competitive synthesis of racemic sporochnol A is the one published by Li and co-workers[9] in 2000, which requires only four steps from the commercially available ethylenglycol monoketal of 1,4-cyclohexanedione, having an overall yield of 48%, and, most relevant, using conventional reagents. The only drawback of this synthesis is that a racemic mixture of sporochnol A is obtained.

In recent years we have extensively studied the use of the enantiopure monoketal of *p*-benzoquinone (+)-**2** in stereocontrolled processes.[15] In this ketal, the diol unit is (*R*,*R*)-hydrobenzoin, a C_2-symmetric chiral auxiliary, a class of chiral auxiliaries that present several advantages. Therefore, we envisaged the possibility of developing a synthesis of enantiopure sporochnol A using the approach of Li's group, but starting from the (*R*,*R*)-hydrobenzoin

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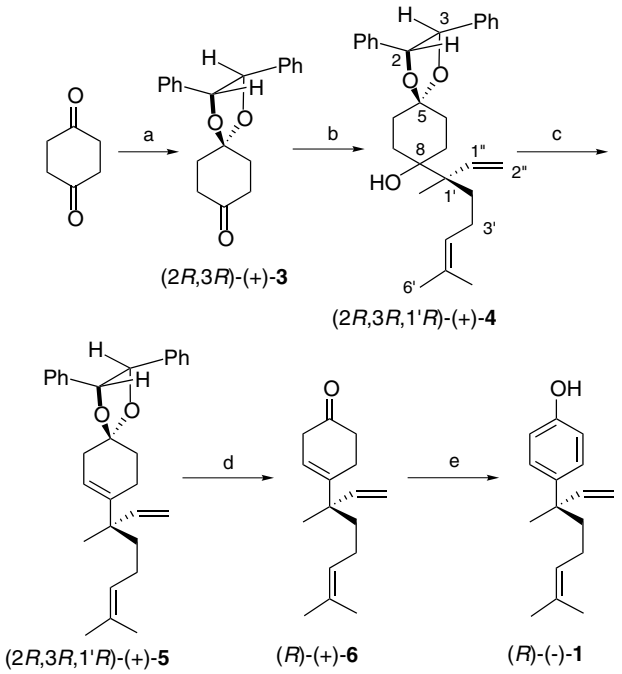
monoketal of 1,4-cyclohexanedione, (*R*,*R*)-(+)-**3**. This strategy is reported herein (Scheme 1).



Scheme 1. Reagents and conditions: (a) (*R*,*R*)-hydrobenzoin, *p*-TsOH, benzene, reflux, 6 h, 52%; (b) (i) $CrCl_3$, $LiAlH_4$, THF, 0 °C, (ii) geranyl bromide, DMF, rt, 3 h, 61%, (iii) separation of diastereoisomers, 42%; (c) $SOCl_2$, py, 0 °C, 15 min, 97%; (d) montmorillonite K-10, CH_2Cl_2, reflux, 7 h, 98%; (e) $PdCl_2$, Na_2CO_3, ^tBuOH, reflux, 6 h, 74%.

2. Results and discussion

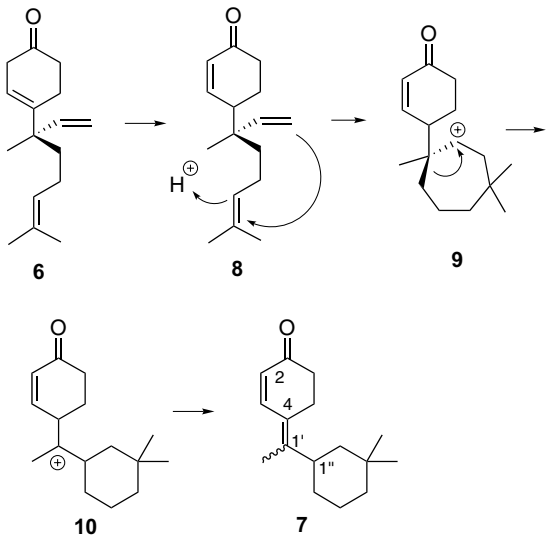
The first goal was to achieve an easy method for preparing ketal (*R*,*R*)-(+)-**3**. Three different syntheses of ketal (*R*,*R*)-(+)-**3** are already published. The first one was reported by Konopelski et al.[16] and uses 1,4-cyclohexanediol as a starting material. Ducrot and co-workers[17] prepared it starting from 1,4-cyclohexanedione by a multistep sequence, and we have described it by the olefin reduction of ketal **2**.[15e] Since all of these sequences require several steps, we decided to attempt the direct monoketalization of 1,4-cyclohexanedione with (*R*,*R*)-hydrobenzoin and we were pleased to observe that this reaction, using a twofold excess of commercially available diketone, afforded the desired compound (*R*,*R*)-(+)-**3** in one step and 52% yield (Scheme 1), along with the corresponding diketal. The synthesis was continued with the Nozaki–Hiyama alkylation between geranyl bromide and **3** promoted by chromium(II). This reaction yielded alcohol **4** as a ca. 1:1 mixture of both possible diastereoisomers in a 61% yield. The advantage of using a C_2-symmetric chiral auxiliary becomes apparent here: only two stereoisomers may be formed in this reaction. We were able to separate them by repeated crystallizations from pentane solution. By this way, we obtained isomer (+)-(2*R*,3*R*,1′*R*)-**4** in a 26% yield from **3**, with a diastereoisomeric ratio, determined by chiral HPLC, of 99:1.

The absolute configuration of the newly generated stereocenter at C-1′ could not be determined at this stage, but it has been unequivocally established by the successful synthesis of enantiopure sporochnol A (vide infra). The analysis of the ^{13}C NMR spectrum of the samples of **4** was useful in the purification process, since the less soluble diastereoisomer shows signals at δ 32.7, 31.7, 30.0, and 28.8 corresponding to four methylene carbon atoms, whereas the more soluble one presents signals at δ 32.5, 31.9, 29.6, and 29.2. Thus, highly diastereoisomerically enriched amounts of **4** was accessible.

The dehydration of alcohol (2*R*,3*R*,1′*R*)-(+)-**4** by treatment with thionyl chloride in the presence of pyridine gave olefin (2*R*,3*R*,1′*R*)-(+)-**5** in a 97% yield (Scheme 1). Its 500 MHz proton NMR spectrum revealed the presence of five olefinic protons, which demonstrated that the newly formed double bond has not migrated. The three vinylic hydrogen atoms absorb as an ABX system at δ 5.87, 5.07, and 5.05. The new olefinic proton H-7 resonates at δ 5.55 as a broad singlet, while H-4′ appears as a broad triplet at δ 5.15. Using two-dimensional NMR techniques we have been able to assign all the proton and carbon atom signals.

The synthesis continued with the deprotection of the ketal moiety of **5** (Scheme 1). After several attempts, using standard acidic conditions, removal of the chiral auxiliary from **5** was best achieved using montmorillonite K-10,[15d,e,18] although at a lower concentration and using a higher ratio of clay to the substrate than that used previously in our group. Unconjugated ketone (*R*)-(+)-**6** was isolated in a 98% yield considering the recovered starting material, and the formation of the carbonyl group without olefin migration is demonstrated by the presence of a signal at δ 211.7 in its ^{13}C NMR. The hydrolysis of the ketal functionality did not work using other known mild deprotection procedures, like cerium ammonium nitrate in acetonitrile/water[19] or the system of cerium trichloride/sodium iodide.[20]

In one experiment, run in the presence of montmorillonite K-10, but with a longer reaction time, we isolated a different compound, identified as the conjugated and rearranged ketone **7** in a ca. 1:1 mixture of the (*E*)- and (*Z*)-isomers, respectively, in a 59% yield (Scheme 2). Its structural elucidation is based on spectroscopic data. Thus, the ^1H NMR spectrum shows two AB systems at δ 7.46 and 5.84 and δ 7.52 and 5.83 corresponding to the olefinic protons H-2 and H-3 of both the (*E*)- and (*Z*)-isomers, respectively, and no other signals attributable to olefinic protons. Nevertheless, in ^{13}C NMR spectrum there are four pairs of signals, two corresponding to CH groups and two to carbon atoms not bonded to hydrogen, assignable to olefinic carbon atoms. The proton NMR spectrum also reveals that only one of the three observed methyl groups corresponds to an allylic methyl group (δ 1.80) and the absorption at δ 200.6 in ^{13}C NMR indicates the presence of a conjugated ketone. The proposed mechanism for the formation of this thermodynamically more stable compound is shown in Scheme 2. The initially formed compound **6** could isomerize to the conjugated ketone **8** and protonation of the trisubstituted olefin followed by the attack of the terminal olefin would form a cycloheptyl



Scheme 2.

cation **9**. Now, a ring contraction process would deliver a stable tertiary cation **10**, which would eliminate a proton, giving rise to **7**. The identification of **7** guided us to reduce the reaction time of the hydrolysis process.

The treatment of ketone (*R*)-(+)-**6** with $PdCl_2$ in *tert*-butanol containing four equivalents of Na_2CO_3 afforded (*R*)-(−)-sporochnol **1** in a 74% yield (Scheme 1), whose spectroscopic data matched that reported in the literature,[2,4,5,7] and whose negative specific rotation, $[\alpha]_D^{20} = -4.5$ (*c* 0.4, $CHCl_3$), indicated that we had achieved the synthesis of the unnatural enantiomer of sporochnol A. The low value of specific rotation found for (*R*)-(−)-sporochnol A is consistent with previous literature values for both enantiomers of synthetic sporochnol A,[21] considering our sample with 98% of ee determined by HPLC in the above mentioned intermediate (vide supra).

3. Conclusion

(*R*)-(−)-Sporochnol has been prepared via a short sequence involving only five synthetic steps with an overall yield of 9%, 4.5% without considering recovered materials in steps 4 and 5, and an ee of 98%.

4. Experimental

4.1. General

The reaction mixtures were stirred magnetically. The organic extracts were dried over anhydrous sodium sulfate. The reaction solutions were concentrated using a rotary evaporator at 5–10 Torr. Flash chromatographies were performed using Merck silica gel (230–400 mesh). Infrared spectra were recorded on a Bruker Tensor 2000 spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker AC-250-WB instrument at 250 and 62.5 MHz, respectively, in $CDCl_3$ solutions (δ 7.26 and 77.2, respectively), unless otherwise indicated. ^1H NMR spectra were also recorded on a Bruker ARX 500 instrument at 500 MHz. Mass spectra were performed on a Bruker Esquire 3000 instrument using the electrospray technique. Specific rotation values were measured on a Jasco J-715 UV–vis spectropolarimeter and in a Propol Automatisches model, Dr. Kernchen polarimeter. The diastereoisomeric mixtures of **4** were analyzed by chiral HPLC on a column CHIRACEL OD 250 × 4.6 mm: eluent hexane/*i*-PrOH 9:1, flow rate 1.0 mL/min, t_R 20.7 and 23.4 min.

4.2. (2*R*,3*R*)-(+)-2,3-Diphenyl-1,4-dioxaspiro[4.5]decan-8-one, (2*R*,3*R*)-(+)-3

A solution of 1,4-cyclohexanedione (15.11 g, 134.6 mmol), (*R*,*R*)-hydrobenzoin (14.35 g, 67.0 mmol), and *p*-toluenesulfonic acid (34 mg, 0.20 mmol) in benzene (300 mL) was stirred at the reflux temperature in a reaction flask equipped with a Dean–Stark azeotropic separator for 6 h. The solvent was removed and the crude material was purified by flash chromatography (hexane/ethyl acetate 6:1) to afford the following fractions: (i) 7.35 g (14.6 mmol, 43% yield) of (2*R*,3*R*,10*R*,11*R*)-2,3,10,11-tetraphenyl-1,4,9,12-tetraoxadispiro[4.2.4.2]tetradecane, (+)-**11**, as a white solid; and (ii) 10.74 g (34.86 mmol, 52% yield) of (2*R*,3*R*)-(+)-**3**[17] as a white solid. Compound (+)-**11**: with a mp of 152–153 °C (hexane); IR (ATR) 3030, 2955, 2881, 1496, 1357, 1261, 1127, 1044, 765, 697 cm^{-1}; ^1H NMR δ 7.42–7.20 (m, 20H), 4.83 (s, 4H), 2.29 (s, 8H); ^{13}C NMR δ 137.2, 128.5, 128.4, 127.2, 109.3, 85.4, 33.8; MS (ESI+) *m*/*z* 527 ($[M+Na]^+$, 100); $[\alpha]_D^{20} = +55.4$ (*c* 1.0, $CHCl_3$). Compound (2*R*,3*R*)-(+)-**3**: mp 75–77 °C (ether/hexane); IR (ATR) 3060, 3029, 2941, 2884, 1715, 1492, 1447, 1414, 1358, 1304, 1265, 1132, 1017, 924, 758, 699 cm^{-1}; ^1H NMR δ 7.42–7.20 (m, 10H), 4.85 (s, 2H), 2.68 (br t, $J = 7.0$ Hz, 4H), 2.45–2.25 (m, 4H); ^{13}C NMR δ 210.2, 136.3, 128.7, 126.8, 108.0, 85.7, 38.3, 35.5; MS (ESI+) *m*/*z* 331 ($[M+Na]^+$, 100), 242 (18); $[\alpha]_D^{20} = +62.6$ (*c* 2.3, $CHCl_3$), lit.[17] $[\alpha]_D^{20} = +52.2$ (*c* 2.28, $CHCl_3$).

4.3. (2*R*,3*R*,1′*R*)-(+)-8-(1,5-Dimethyl-1-vinyl-4-hexenyl)-2,3-diphenyl-1,4-dioxaspiro[4.5]decan-8-ol, (2*R*,3*R*,1′*R*)-(+)-4

Lithium aluminum hydride (0.23 g, 5.95 mmol) was added portionwise to a suspension of chromium(III) chloride (1.85 g, 11.72 mmol) in THF (24 mL) at 0 °C over 10 min and the mixture was stirred for 20 min. The reaction mixture was concentrated and dry DMF (10 mL) was added. To the above solution, monoketal (2*R*,3*R*)-(+)-**3** (1.00 g, 3.27 mmol) dissolved in dry DMF (1 mL) was added over 5 min. Geranyl bromide (1.1 mL, 5.84 mmol) was then added dropwise and the mixture was stirred for 3 h at room temperature. Brine (15 mL) and ethyl acetate (20 mL) were added to the reaction mixture and the organic layer was extracted with ethyl acetate (2 × 10 mL). The solvent was removed and the remaining crude material was purified by flash chromatography (hexane/ethyl acetate 8:1) to afford 0.89 g (2.00 mmol, 61% yield) of a ca. 1:1 diastereoisomeric mixture of (2*R*,3*R*,1′*RS*)-**4** as a white solid. Repeated crystallizations from pentane allowed the isolation of the less soluble isomer, (2*R*,3*R*,1′*R*)-(+)-**4**, in 26% yield from

3: mp 115–117 °C (pentane); IR (ATR) 3554, 3085, 3033, 2969, 2927, 1630, 1453, 1360, 1263, 1121, 1040, 987, 764, 695 cm^{-1}; ^1H NMR δ 7.40–7.20 (m, 10H), 5.94 (dd, $J = 17.6$, 10.9 Hz, 1H), 5.31 (dd, $J = 10.9$, 1.3 Hz, 1H), 5.12 (dd, $J = 17.6$, 1.3 Hz, 1H), 5.12 (m, 1H), 4.79 (d, $J = 8.6$ Hz, 1H), 4.74 (d, $J = 8.6$ Hz, 1H), 2.40–2.15 (m, 2H), 2.10–1.40 (m, 10H), 1.69 (br s, 3H), 1.60 (br s, 3H), 1.11 (s, 3H); ^{13}C NMR δ 143.8 (CH, C-1″), 137.4 (C), 137.3 (C), 131.4 (C, C-5′), 128.6 (CH), 128.5 (CH), 128.4 (CH), 128.3 (CH), 127.0 (CH), 126.9 (CH), 125.1 (CH, C-4′), 116.2 (CH_2, C-2″), 109.9 (C), 85.42 (CH), 85.41 (CH), 74.3 (C), 47.7 (C, C-1′), 35.3 (CH_2, C-2′), 32.7 (CH_2), 31.7 (CH_2), 30.0 (CH_2), 28.8 (CH_2), 25.8 (CH, C-6′), 23.6 (CH_2), 17.8 (CH, Me), 16.6 (CH, Me); MS (ESI+) m/z 469 ($[M+Na]^+$, 100); $[\alpha]_D^{20} = +19.2$ (c 0.6, $CHCl_3$); ee $\geqslant$98% by chiral HPLC. Anal. Calcd for $C_{30}H_{38}O_3$: C, 80.68; H, 8.58. Found: C, 80.72; H, 8.59. Observable signals of the more soluble isomer in pentane from the mixture of diastereoisomers: ^{13}C NMR δ 32.5, 31.9, 29.6, 29.2.

4.4. (2*R*,3*R*,1′*R*)-(+)-8-(1,5-Dimethyl-1-vinyl-4-hexenyl)-2,3-diphenyl-1,4-dioxaspiro[4.5]dec-7-ene, (2*R*,3*R*,1′*R*)-(+)-5

Thionyl chloride (0.20 mL, 2.75 mmol) was added dropwise to a solution of (2*R*,3*R*,1′*R*)-(+)-**4** (600 mg, 1.34 mmol) and pyridine (1.4 mL, 17.30 mmol) in dry toluene (9 mL) at 0 °C and the mixture was stirred for 15 min. The solvent was removed and the oily residue was washed with hexane/ethyl acetate 1:1 (3 × 20 mL). The solid formed was filtered and washed with the same solvent (3 × 10 mL). The solvent was removed and the remaining material was purified by flash chromatography (hexane/ethyl acetate 10:1) to afford 559 mg (1.30 mmol, 97% yield) of (2*R*,3*R*,1′*R*)-(+)-**5** as a white solid: mp 60–62 °C; IR (ATR) 3058, 3031, 2919, 1630, 1602, 1448, 1211, 1109, 1065, 749, 699 cm^{-1}; ^1H NMR (500 MHz) δ 7.40–7.20 (m, 10H), 5.87 (dd, $J = 17.5$, 10.8 Hz, 1H), 5.55 (br s, 1H, H-7), 5.15 (br t, $J = 7.1$ Hz, 1H, H-4′), 5.07 (dd, $J = 10.8$, 1.4 Hz, 1H), 5.05 (dd, $J = 17.5$, 1.4 Hz, 1H), 4.84 (d, $J = 8.5$ Hz, 1H), 4.81 (d, $J = 8.5$ Hz, 1H), 2.72 (br d, $J = 17.6$ Hz, 1H, H-6), 2.64 (br d, $J = 17.6$ Hz, 1H, H-6), 2.42 (m, 1H, H-9), 2.32 (m, 1H, H-9), 2.14 (m, 1H, H-10), 2.03 (m, 1H, H-10), 1.95–1.85 (m, 2H, 2H-3′), 1.70 (br s, 3H), 1.62 (m, 1H, H-2′), 1.57 (br s, 3H), 1.47 (m, 1H, H-2′), 1.20 (s, 3H); ^{13}C NMR δ 146.6 (CH, C-1″), 141.8 (C, C-8), 137.4 (C), 137.1 (C), 131.2 (C, C-5′), 128.5 (CH), 128.4 (CH), 128.3 (CH), 127.0 (CH), 126.9 (CH), 125.1 (CH, C-4′), 118.6 (CH, C-7), 111.8 (CH_2, C-2″), 109.1 (C), 85.5 (CH), 85.3 (CH), 45.1 (C, C-1′), 38.2 (CH_2, C-2′), 37.7 (CH_2, C-6), 33.4 (CH_2, C-10), 25.9 (CH, C-6′), 24.3 (CH_2, C-9), 23.3 (CH_2, C-3′), 22.9 (CH, Me), 17.7 (CH, Me); MS (ESI+) m/z 451 ($[M+Na]^+$, 100); $[\alpha]_D^{20} = +36.4$ (c 1.0, $CHCl_3$). Anal. Calcd for $C_{30}H_{36}O_2$: C, 84.07; H, 8.47. Found: C, 83.86; H, 8.32.

4.5. (*R*)-(+)-4-(1,5-Dimethyl-1-vinyl-4-hexenyl)-3-cyclohexenone, (*R*)-(+)-6

A mixture of ketal (2*R*,3*R*,1′*R*)-(+)-**5** (187 mg, 0.44 mmol) and montmorillonite K-10 (1.5 g) in CH_2Cl_2 (45 mL) and water (0.1 mL) was stirred at reflux for 7 h. The reaction mixture was filtered and the solid washed twice with hot ethyl acetate (40 mL) for 15 min. The solvent was removed and the remaining material was purified by flash chromatography (hexane/ethyl acetate 10:1) to afford the following fractions: (i) 67 mg (0.16 mmol) of starting ketal **5**; and (ii) 64 mg (0.28 mmol, 98% yield considering the recovered starting material) of (*R*)-(+)-**6**[9] as an oil: ^1H NMR δ 5.77 (dd, $J = 17.5$, 10.8 Hz, 1H), 5.58 (t, $J = 3.8$ Hz, 1H, H-3), 5.08 (m, 1H, H-4′), 5.04 (dd, $J = 10.8$, 1.2 Hz, 1H), 4.99 (dd, $J = 17.5$, 1.2 Hz, 1H), 2.89 (d, $J = 3.8$ Hz, 2H), 2.45–2.25 (m, 4H), 2.05–1.70 (m, 2H), 1.67 (br s, 3H), 1.70–1.35 (m, 2H), 1.57 (br s, 3H), 1.14 (s, 3H); ^{13}C NMR δ 211.7, 145.7, 144.0, 131.6, 124.8, 118.2, 112.5, 45.4, 40.1, 39.1, 38.0, 25.9, 25.2, 23.4, 22.7, 17.8; $[\alpha]_D^{20} = +42.1$ (c 0.4, $CHCl_3$).

4.6. (*E*)- and (*Z*)-4-[1-(3,3-Dimethylcyclohexyl)ethylidene]-2-cyclohexenone, 7

A mixture of ketal (2*R*,3*R*,1′*R*)-(+)-**5** (249 mg, 0.58 mmol) and montmorillonite K-10 (2.0 g) in CH_2Cl_2 (30 mL) was stirred at reflux for 15 h. The same work-up procedure described in Section 4.5 was applied and flash chromatography (hexane/ethyl acetate 10:1) of the crude material afforded 80 mg (0.34 mmol, 59% yield) of a ca. 2:1 diastereoisomeric mixture of (*E*)- and (*Z*)-**7**, respectively, as an oil: IR (ATR) 2918, 2848, 1668, 1602, 1209, 820, 754 cm^{-1}; ^1H NMR δ 7.52 (d, $J = 10.2$ Hz, 1H, isomer *Z*), 7.46 (d, $J = 10.0$ Hz, 1H, isomer *E*), 5.84 (d, $J = 10.0$ Hz, 1H, isomer *E*), 5.83 (d, $J = 10.0$ Hz, 1H, isomer *Z*), 2.93 (tt, $J = 11.7$, 4.7 Hz, 1H, H-1″, isomer *Z*), 2.80 (tt, $J = 11.7$, 4.7 Hz, 1H, H-1″, isomer *E*), 2.77–2.60 (m, 2H), 2.50–2.40 (m, 2H), 1.80 (s) + 1.76 (s) (3H), 1.70–1.00 (m, 8H), 0.98 (s) + 0.96 (s) + 0.92 (s) (6H); ^{13}C NMR δ 200.6 (C), 148.4/148.3 (C, C-1′), 145.0/143.0 (CH, C-3), 125.9/125.8 (C, C-4), 125.0/124.8 (CH, C-2), 44.0 (CH_2), 43.7 (CH_2), 38.94 (CH_2), 38.88 (CH_2), 37.7 (CH, C-1″), 37.5 (CH_2, C-6), 37.4 (CH_2, C-6), 36.7 (CH, C-1″), 33.6 (CH), 31.0 (C), 30.7 (CH_2), 30.4 (CH_2), 26.3 (CH_2), 25.1 (CH_2), 24.82 (CH, Me), 24.77 (CH, Me), 22.4 (CH_2), 22.3 (CH_2), 15.2 (CH, C-2′), 14.0 (CH, C-2′).

4.7. (*R*)-(−)-4-(1,5-Dimethyl-1-vinyl-4-hexenyl)phenol, (*R*)-(−)-1

A mixture of ketone (*R*)-(+)-**6** (30 mg, 0.13 mmol), $PdCl_2$ (31 mg, 0.18 mmol), and anhydrous Na_2CO_3 (61 mg, 0.58 mmol) in *tert*-butanol (3 mL) was heated at the reflux temperature for 6 h. Water (2 mL) was added and the mixture was extracted with ether (3 × 15 mL) and ethyl acetate (10 mL). The solvent was removed and the remaining material was purified by flash chromatography (hexane/ethyl acetate 30:1) affording the following fractions: (i) 8 mg (0.03 mmol) of starting ketone **6**; and (ii) 16 mg (0.07 mmol, 74% yield considering the recovered material) of (*R*)-(−)-**1** as an oil: ^1H NMR δ 7.25–7.10 (m, 2H), 6.85–6.70 (m, 2H), 6.01 (dd, $J = 17.4$, 10.7 Hz, 1H), 5.07 (dd, $J = 10.7$, 1.3 Hz, 1H), 5.06 (m, 1H), 5.02 (dd, $J = 17.4$, 1.3 Hz, 1H), 4.86 (br s, 1H), 1.92–1.57 (m, 4H), 1.66 (br s, 3H), 1.52 (br s, 3H), 1.35 (br s, 3H); ^{13}C NMR δ 153.7, 147.4, 139.9, 131.5, 128.0, 124.9, 115.0,

111.6, 43.9, 41.4, 25.8, 25.2, 23.5, 17.7; $[\alpha]_D^{20} = -4.5$ (*c* 0.4, $CHCl_3$).[21]

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References

1. (a) Harborne, J. B. *Nat. Prod. Rep.* **2001**, *18*, 361–379, and references cited therein; (b) Hay, M. E. *J. Exp. Mar. Biol. Ecol.* **1996**, *200*, 103–134.
2. Shen, Y.-C.; Tsai, P. I.; Fenical, W.; Hay, M. E. *Phytochemistry* **1993**, *32*, 71–75.
3. Ohira, S.; Kuboki, A.; Hasegawa, T.; Kikuchi, T.; Kutsukake, T.; Nomura, M. *Tetrahedron Lett.* **2002**, *43*, 4641–4644.
4. Kamikubo, T.; Shimizu, M.; Ogasawara, K. *Enantiomer* **1997**, *2*, 297–301.
5. Kita, Y.; Furukawa, A.; Futamura, J.; Ueda, K.; Sawama, Y.; Hamamoto, H.; Fujioka, H. *J. Org. Chem.* **2001**, *66*, 8779–8786.
6. Takahashi, M.; Shioura, Y.; Murakami, T.; Ogasawara, K. *Tetrahedron: Asymmetry* **1997**, *8*, 1235–1242.
7. Fadel, A.; Vandromme, L. *Tetrahedron: Asymmetry* **1999**, *10*, 1153–1162.
8. Luchaco-Cullis, C. A.; Mizutani, H.; Murphy, K. E.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2001**, *40*, 1456–1460.
9. Li, Y.; Yuan, H.; Lu, B.; Li, Y.; Teng, D. *J. Chem. Res. (S)* **2000**, 530–531.
10. Bassindale, M. J.; Hamley, P.; Harrity, J. P. A. *Tetrahedron Lett.* **2001**, *42*, 9055–9057.
11. Shan, S.; Ha, C. *Synth. Commun.* **2004**, *34*, 4005–4008.
12. Ávila-Zárraga, J. G.; Barroso, M.; Covarrubias-Zúñiga, A.; Romero-Ortega, M. *Synth. Commun.* **2005**, *35*, 389–395.
13. Srikrishna, A.; Satyanarayana, G.; Prasad, M. R. *Synth. Commun.* **2005**, *35*, 1687–1698.
14. Biswas, B.; Venkateswaran, R. V. *Synth. Commun.* **2005**, *35*, 1769–1779.
15. (a) de March, P.; Escoda, M.; Figueredo, M.; Font, J.; Álvarez-Larena, A.; Piniella, J. F. *J. Org. Chem.* **1995**, *60*, 3895–3897; (b) de March, P.; Escoda, M.; Figueredo, M.; Font, J.; Álvarez-Larena, A.; Piniella, J. F. *J. Org. Chem.* **1997**, *62*, 7781–7787; (c) de March, P.; Figueredo, M.; Font, J.; Rodríguez, S. *Tetrahedron* **2000**, *56*, 3603–3609; (d) de March, P.; Escoda, M.; Figueredo, M.; Font, J.; García-García, E.; Rodríguez, S. *Tetrahedron: Asymmetry* **2000**, *11*, 4473–4483; (e) Busqué, F.; Cantó, M.; de March, P.; Figueredo, M.; Font, J.; Rodríguez, S. *Tetrahedron: Asymmetry* **2003**, *14*, 2021–2032.
16. Konopelski, J. P.; Deng, H.; Schiemann, K.; Keane, J. M.; Olmstead, M. M. *Synlett* **1998**, 1105–1107.
17. Boyer, F.-D.; Prangé, T.; Ducrot, P.-H. *Tetrahedron: Asymmetry* **2003**, *14*, 1153–1159.
18. (a) Gautier, E. C. L.; Graham, A. E.; McKillop, A.; Standen, S. P.; Taylor, R. J. K. *Tetrahedron Lett.* **1997**, *38*, 1881–1884; (b) Alibés, R.; Bayón, P.; de March, P.; Figueredo, M.; Font, J.; Marjanet, G. *Org. Lett.* **2006**, *8*, 1617–1620.
19. (a) Markó, I. E.; Ates, A.; Gautier, A.; Leroy, B.; Plancher, J.-M.; Quesnel, Y.; Vanherck, J.-C. *Angew. Chem., Int. Ed.* **1999**, *38*, 3207–3209; (b) Ates, A.; Gautier, A.; Leroy, B.; Plancher, J.-M.; Quesnel, Y.; Markó, I. E. *Tetrahedron Lett.* **1999**, *40*, 1799–1802.
20. Marcantoni, E.; Nobili, F.; Bartoli, G.; Bosco, M.; Sambri, L. *J. Org. Chem.* **1997**, *62*, 4183–4184.
21. The literature values of the specific rotation of sporochnol A are the following: lit.[2] $[\alpha]_D^{20} = +10.0$ (*c* 1.0, $CHCl_3$), lit.[3] $[\alpha]_D^{25} = +5.8$ (*c* 0.95, $CHCl_3$), lit.[4] $[\alpha]_D^{30} = +2.9$ (*c* 0.80, $CHCl_3$), and lit.[5] $[\alpha]_D^{20} = +2.0$ (*c* 1.13, $CHCl_3$) for the natural isomer; and lit.[3] $[\alpha]_D^{25} = -5.4$ (*c* 1.48, $CHCl_3$), lit.[6] $[\alpha]_D^{31} = -1.3$ (*c* 0.50, $CHCl_3$), and lit.[7] $[\alpha]_D^{20} = -2.5$ (*c* 1.0, $CHCl_3$) for the unnatural isomer.