SHORT PAPER

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A facile synthesis of (±)-sporochnol A†

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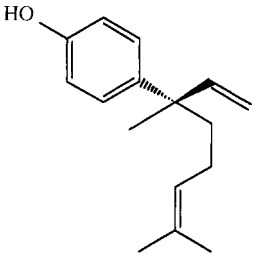
A facile synthesis of (±)-sporochnol A, starting from readily available monoketal of 1,4-cyclohexanedione in high overall yield, is described. The key step is the alkylation of monoketal of 1,4-cyclohexadione with geranyl bromide mediated by chromium(II).

(+)-Sporochnol A (**1**), first isolated by Fenical and co-workers in 1993 from the Caribbean marine alga *Sporochnus bolleanus*,[1] has been shown to exhibit significant feeding deterrence towards herbivorous fish.



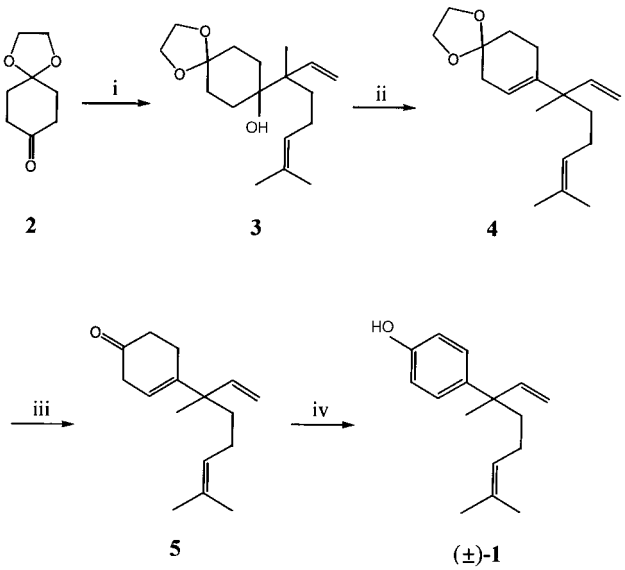
(+)-(*S*)-Sporochnol A (**1**)

(+)-Sporochnol A (**1**) has a novel structure containing a prenylated phenol and an asymmetric quarternary carbon. The chemical structure and absolute stereochemistry were determined by spectral and chemical methods. Its absolute configuration assigned to be (*S*) by synthetic method.[2] Recently enatioselective synthesis of **1** by Fadel[2,3] and Ogasawara[4] has been investigated. Herein we report a facile synthesis of (±)-**1** from the monoketal of 1,4-dicyclohexanedione and geranyl bromide.

The synthetic route of (±)-**1** is outlined in Scheme 1.

Reagents and conditions: (i) 1) $CrCl_3$, $LiAlH_4$, THF, 0°C, 2) geranyl bromide, DMF, r.t. 6h, 74%; (ii) $SOCl_2$, pyridine, benzene, 0°C, 10min, 92%; (iii) *p*-TsOH (cat.), acetone, reflux, 3h, 90%; (iv) $PdCl_2$, Na_2CO_3, *tert*-butanol, 70°C, 10h, 79%.

1,4-Cyclohexanedione monoketal **2**,[5] readily obtained by selective ketalization of 1,4-cyclohexanedione, was alkylated with geranyl bromide mediated by chromium(II)[6] in DMF to give the alcohol **3** in 74% yield.[7] The alcohol **3** was converted into the corresponding alkene **4** by dehydration with $SOCl_2$ in pyridine.[8] Deprotection of ketal **4** by normal acidic hydrolysis to give ketone **5**, which was exposed[9] to $PdCl_2$ in *tert*-butanol containing 4 equivalent of Na_2CO_3 at 70°C to afford (±)-sporochnol A (**1**) in 79% yield, and in 48% overall yield from monoketal **2**. The synthesis decribed here is short, and efficient.



Scheme 1

Experimental

^{1}H NMR spectra were recorded on a Varian FT-80A or a Bruker AM-400 spectrometer in $CDCl_3$ solution using TMS as the internal reference. IR spectra were obtained on a Nicolet AVATAR 360 FT-IR (film) spectrometer. Mass spectra were measured on a VG ZAB-HS spectrometer by direct inlet at 70 eV. Melting points were measured on a Kofler hot stage and uncorrected. All solvents were freshly purified and dried by standard techniques prior to use. All reactions were routinely carried out under an inert atmosphere of Ar, and monitored by TLC. Purification of products were conducted by flash column chromatography on silica gel (200–300 mesh) purchased from Yan Tai Yuan Bo Silica Gel Co. or Al_2O_3 purchased from Shang Hai Wu Si Chemical Reagents Company, China.

8-(1-Ethyl-1,5-dimethyl-4-hexenyl)-1,4-dioxaspiro[4,5]dec-8-ol (**3**): Lithium aluminum hydride (0.49 g, 12.8 mmol) was added portionwise to a suspension of chromium(III) chloride (4.0 g, 25.6 mmol) in THF (30 ml) at 0°C over 15 minutes. After the gas evolution had ceased, the reaction mixture was concentrated under reduced pressure, and the resulting residue was taken up in DMF (20 ml). To the above chromium(II) reagent was added the monoketal **2** (1.0 g, 6.4 mmol) and then a DMF (10 ml) solution of geranyl bromide (2.78 g, 12.8 mmol) at room temperature. After 3h the reaction mixture was treated with brine (30 ml) and extracted thoroughly with ether (3×100 ml). The organic phases were dried over anhydrous $MgSO_4$, and concentrated. The crude product was chromatographed on Al_2O_3 eluting with pet. ether:ethyl ether (v/v 15:1) to afford alcohol **3** (1.39 g, 74%) as white solid. m.p. 64–65°C; IR (film):υ_{max}/cm^{-1} 3499, 3079, 2966, 1634, 1375, 1101, 1037, 889; ^{1}H NMR ($CDCl_3$, 400MHz) δ(ppm): 5.9 (dd, J_{trans} = 17.2 Hz, J_{cis} = 10.8 Hz, 1H), 5.31 (d, J_{cis} = 10.8 Hz, 1H), 5.15 (d, J_{trans} = 17.2 Hz, 1H), 5.09 (t, 3H), 3.95 (s, 4H), 2.0–1.4 (m, 12H), 1.67 (br s, 3H), 1.58 (br s, 3H), 1.06 (s, 3H); EIMS (*m/z*): 294 (M^+, 0.1), 276 (M^+-18, 0.4), 194 (6.6), 169 (9), 157 (31), 138 (17), 123 (25), 100 (20), 95 (100), 69 (48).

8-(1-Ethyl-1,5-dimethyl-4-hexenyl)-1,4-dioxaspiro[4,5]dec-7-ene (**4**)*:* Thionyl chloride (0.41 ml, 5.65 mme) was added dropwise to a stirred solution of alcohol **3** (1.37 g, 4.65 mmol) in anhydrous benzene (25 ml) and pyridine (5 ml) at 0°C and the reaction mixture was stirred at 0°C for 10 minutes. It was then treated with ice water (20 ml) and extracted thoroughly with ether (3×50 ml). The organic phases were washed with 5% HCl (3×10 ml), saturated $NaHCO_3$ (10 ml), H_2O and brine, and dried. Evaporation of the solvent gave the

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† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M)*.

residue, which was chromatographed on Al_2O_3 eluting with pet. ether:ethyl acetate (v/v 30:1) to afford **4** (1.18 g, 92%) as a colourless oil. IR (film): υ_{max}/cm^{-1} 3080, 3053, 2966, 1633, 1375, 1258, 1116; ^1H NMR ($CDCl_3$, 80MHz) δ(ppm): 5.9 (dd, J_{trans} = 17.2 Hz, J_{cis} = 10.8 Hz, 1H), 5.42 (t, 1H), 5.10 (t, 1H), 5.06 (d, J_{cis} = 10.8 Hz, 1H), 4.9 (d, J_{trans} = 17.2 Hz), 3.98 (s, 4H), 2.3–1.4 (m, 10H), 1.7 (br s, 3H), 1.6 (br s, 3H), 1.13 (s, 3H); EIMS (*m/z*): 276 (M^+, 4), 233 (4), 194 (54), 149 (8), 131 (13), 105 (2), 99 (57), 86 (100), 55 (22), 41 (18). HRMS calcd for $C_{18}H_{28}O_2$: 276.2090; Found: 276.2066.

4-(1-Ethyl-1,5-dimethyl-4-hexenyl)-3-cyclohexen-1-one (**5**)*:* A mixture of ketal **4** (1.16 g, 4.22 mmol) and a catalytic amount *p*-TsOH in dry acetone (30 ml) was refluxed for 3h. The mixture was evaporated *in vacuo* and the residue was chromatographed on silica gel eluting with pet. ether:ethyl acetate (v/v 30:1) to give the ketone **5** (0.88 g, 90%) as a colourless oil. IR (film): υ_{max}/cm^{-1} 3080, 2968, 2936, 1720, 1633, 1193; ^1H NMR ($CDCl_3$, 400MHz) δ(ppm): 5.87 (dd, J_{trans} = 17.2 Hz, J_{cis} = 10.8 Hz, 1H), 5.59 (t, 1H), 5.11 (t, 1H), 5.06 (d, J_{cis} = 10.8 Hz, 1H), 4.78 (d, J_{trans} = 17.2 Hz, 1H), 2.93 (d, 2H), 2.42 (br s, 4H), 2.0–1.6 (m, 4H), 1.71 (s, 3H), 1.61 (s. 3H), 1.18 (s 3H); EIMS (*m/z*): 232 (M^+, 4), 189 (12), 161 (5), 150 (41), 121 (14), 105 (35), 93 (44), 91 (43), 83 (58), 55 (100), 41 (77). HRMS calcd for $C_{16}H_{24}O$: 232.1827; Found: 232.1857.

(±)-Sporochnol A (**1**). A mixture of ketone (**5**). (200 mg, 0.86 mmol), $PdCl_2$ (150 mg, 0.86 mmol), and anhydrous Na_2CO_3 (360 mg, 3.44 mmol) in *tert*-butanol (20 ml) was refluxed for 8h. The reaction mixture was quenched with water (10 ml) and extracted with ether (3×50 ml). The organic phases were washed with H_2O, brine, and dried. Evaporation of the solvent gave the residue, which was chromatographed on silica g. Elution with pet. ether:ethyl acetate (v/v 20:1) afforded (±)–**1** (150 mg, 79%) as a colourless oil. IR (film): υ_{max}/cm^{-1} 3386, 2924, 1635, 1608, 1594, 1512, 1440, 1242, 1178, 913, 830; ^1H NMR ($CDCl_3$, 400MHz): δ(ppm) 7.18 (d, *J* = 6.6 Hz, 2H), 6.76 (d, *J* = 6.6 Hz, 2H), 6.0 (dd, J_{trans} = 17.7 Hz, J_{cis} = 10.7 Hz, 1H), 5.08 (t, 1H), 5.06 (d, J_{cis} = 10.7, 1H), 5.02 (d, J_{trans} = 17.7 Hz, 1H), 4.75 (br s, 1H, OH), 1.8–1.6 (m, 4H), 1.67 (br s, 3H), 1.51 (br s, 3H), 1.34 (s, 3H); EIMZ (*m/z*): 231 (M^++1,1), 230 (M^+, 6), 187 (4), 148 (22), 147 (100), 120 (13), 107 (17), 91 (14), 83 (12), 41 (24). HRMS calcd for $C_{16}H_{22}O$: 230.1664; Found: 230.1681.

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