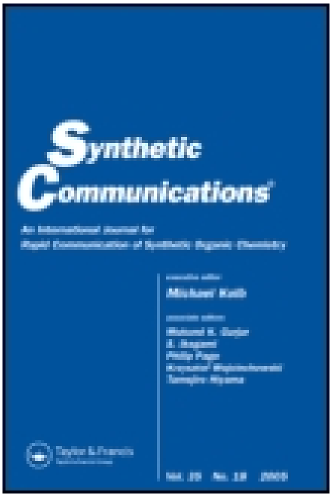

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A Concise Synthesis of (±)-Sporochnol A

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ABSTRACT

A concise synthesis of (±)-sporochnol A (**5**) by a reaction sequence starting from geraniol is described in 23.0% overall yield.

Key Words: Geraniol; Sporochnol.

Sporochnol is monoterpene-substituted phenol isolated from the Caribbean marine alga *sporochnus bolleanus*.[1] It is known to be a chemical defense substance and to show significant feeding deterrence toward herbivorous fish. The synthesis of racemic or optically active sporochnol has recently been reported by several groups.[2] We describe here a concise synthesis of (±)-sporochnol A from geraniol with three to four steps in 23.0% overall yield (Sch. 1).

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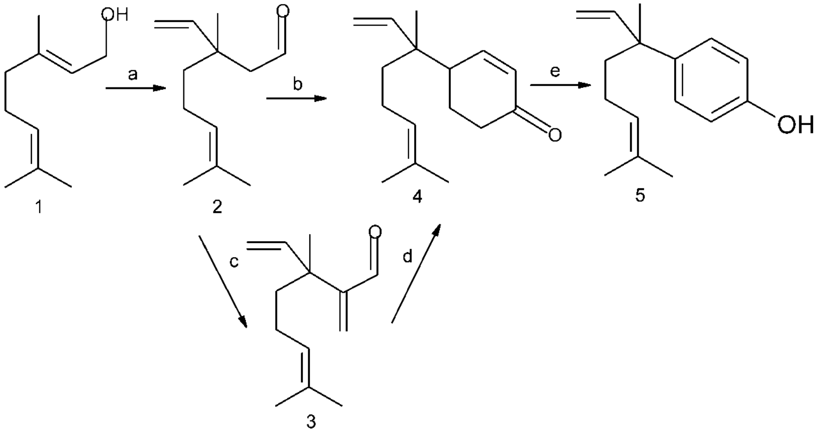

Scheme 1. ***Reagents and conditions:*** **(a) i)** vinyl ethyl ether, $Hg(OAc)_2$, 30°C, 21 h; **ii)** 180°C, 0.5 h; **(b)** piperidine, K_2CO_3,$CH_3COCH{=}CH_2$, HOAc; **(c)** HCHO, piperidine acetate; **(d)** ethylacetoacetate, EtOH, EtONa, rt; **(e)** $PdCl_2$, tert-butanol, rt.

Geraniol and vinyl ethyl ether is stirred for 21 h at room temperature under a nitrogen atmosphere, then the excess vinyl ethyl ether is removed. The residue is heated under a nitrogen atmosphere at 180°C for 0.5 h to afford aldehyde **2** in 52.1% yield. The α,β-unsaturated ketone **4** is obtained from aldehyde **2** using Stork's enamines method.[3] The compound 4 is also made by the aldehyde **2** to an aldol condensation to yield the α,β-unsaturated aldehyde **3**, which on further refluxing with ethylacetoacetate, yields **4**.[4] The α,β-unsaturated ketone is then treated with $PdCl_2$ to give (±)-sporochnol A in 65.7% yield.[5]

EXPERIMENTAL

Preparation of 3-Vinyl-Citronellal (2). Geraniol (15.4 g, 0.1 mol) and $Hg(OAc)_2$ (9.5 g, 0.03 mol) were added to freshly distilled vinyl ethyl ether (72 g, 1 mol). The reaction mixture was then stirred for 21 h at room temperature under a nitrogen atmosphere, after which it was cooled (0°C) and treated (0.5 h) with ice-cold 10% $NaCO_3$ aq (40 mL). The organic phase was separated, washed with cold 10% $NaCO_3$ aq, ice-water, brine, and dried (K_2CO_3). The excess vinyl ethyl ether and ethanol formed in the reaction were distilled off under reduced pressure. The crude residue was then heated under a nitrogen atmosphere at 180°C for 0.5 h. The resultant crude oil was chromatographed on silica gel with petroleum ether-$CHCl_3$ (1 : 2) as eluent to furnish aldehyde **2**. Yield: 52.1% (9.38 g). IR (film): 1722, 1452, 1378, 1004, 917 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.15 (s, 3H), 1.40 (t, 2H), 1.59 (s, 3H), 1.66 (s, 3H), 1.90 (m, 2H), 2.36 (d, 2H), 5.08 (t, 1H), 5.86–4.96 (m, 3H), 9.70 (t, 1H); ^{13}C NMR ($CDCl_3$): 202.5, 144.7, 131.1, 123.8, 112.7, 52.6, 41.0, 38.6, 25.3, 22.3, 17.2 ppm; MS (m/e): 180 (M^+).

Preparation of 4-(1,5-dimethyl-1-ethenyl-4-hexene)cyclohex-2-enone (4). To an ice-cooled mixture of piperidine (7.5 g, 0.1 mol) and anhydrous K_2CO_3 was added dropwise aldehyde **2** (9 g, 0.05 mol). After stirring an additional 2 h the solution was filtered, then the residue washed with anhydrous ether and added to the original filtrate. The excess piperidine was removed under reduced pressure. Freshly distilled methyl vinyl ketone was added to the above residue in nitrogen atmosphere. After stirring for 24 h at room temperature under a nitrogen atmosphere, the mixture was refluxed with 4 mL glacial acetic acid for 4 h, then it was diluted with water and isolated by ether extraction. The organic layer was dried and the solvent removed. The crude oil was chromatographed on silica gel with hexane-ether (20 : 1) as eluent to give the α,β-unsaturated ketone **4**. Yield: 67.2% (7.79 g). IR (film): 1687, 1620, 1450, 1380, 1141, 1002, 916, 835 cm^{-1}; ^1H NMR ($CDCl_3$):δ 0.96 (d, 3H), 1.33 (t, 2H), 1.51 (s, 3H), 1.60 (s, 3H), 1.80 (m, 2H), 2.06 (m, 2H), 2.26 (m, 2H), 2.43 (m, 1H), 5.67–4.90 (m, 3H), 5.14 (t, 1H), 5.94 (dd, 1H), 6.88 (tt, 1H); ^{13}C NMR ($CDCl_3$): 199.8, 153.1, 144.6, 131.5, 129.9, 124.2, 114.2, 44.2, 44.8, 38.7, 37.7, 25.5, 23.8 ppm; MS (m/e): 232 (M^+).

Preparation of α,β-unsaturated aldehyde (3). A solution of 9 g (0.05 mol) of the aldehyde **2** and 7.5 g (0.1 mol) of 40% HCHO aq in 50 mL of ethanol containing 0.5 mL of piperidine and 0.5 mL of acetic acid was refluxed for 2 h. The ethanol was removed under reduced pressure. The residue was chromatographed on silica gel with acetone-petroleum ether (1 : 50) to obtain compound **3**. Yield: 94.3% (9.1 g). IR (film): 1698, 1452, 1373, 1008, 917, 873 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.25 (s, 3H), 1.52 (s, 3H), 1.60 (s, 3H), 1.82-1.57 (m, 4H), 5.05 (t, 1H), 5.99–4.93 (m, 3H), 6.01 (s, 1H), 6.25 (s, 1H), 9.51 (s, 1H); ^{13}C NMR ($CDCl_3$): 194.1, 154.8, 144.2, 134.6, 131.3, 124.2, 112.6, 43.0, 37.8, 25.5, 23.1, 22.6, 17.5 ppm; MS (m/e):192 (M^+).

Preparation of 4-(1,5-dimethyl-1-ethenyl-4-hexene)cyclohex-2-enone (4). The α,β-unsaturated aldehyde **3** (7.7 g, 0.04 mol), ethylacetoacetate (6.5 g, 0.05 mol), EtONa (2.18 g, 0.032 mol) and ethanol (150 mL) were refluxed in a 250 mL round-bottom flask for 6 h. Upon cooling to room temperature, the mixture was quenched with 1 M HCl solution, diluted with a 1 : 1 mixture of ether and benzene, washed with 1 M NaOH solution and brine. The separated organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was chromatographed on silica gel with hexane-ether (20 : 1) to give the α,β-unsaturated ketone **4**. Yield: 64.1% (5.95 g).

Preparation of (±)-sporochnol A (5). The ketone **4** (0.464 g, 0.002 mol), $PdCl_2$ (0.354 g, 0.002 mol) and anhydrous Na_2CO_3 (1.06 g, 0.01 mol) in tert-butanol (50 mL) was refluxed for 10 h under a nitrogen atmosphere. Then the reaction mixture was filtered and the solvent removed under reduced pressure. The residue was chromatographed on silica gel with AcOEt-hexane (1 : 8) as eluent to afford (+)-sporochnol A. Yield: 65.7% (0.302 g). IR (film): 3372, 1612,1511, 1459, 1375, 914, 829 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.33 (s, 3H), 1.50 (s, 3H), 1.66 (s, 3H),1.77–1.64 (m, 4H), 4.65 (s, 1H), 5.08–4.98 (m, 3H), 6.02 (dd, 1H), 6.76 (d, 2H), 7.17 (d, 2H); ^{13}C NMR ($CDCl_3$): 153.5, 147.2, 139.6, 131.3, 127.8, 124.7, 114.8, 111.4, 43.6, 41.2, 25.6, 25.0, 23.3, 17.5 ppm; MS (m/e): 230 (M^+).

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