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Synthesis of Sporochnol A, a Marine Fish Deterrent

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Abstract: A synthesis of the methyl ether of the fish-deterrent sporochnol A is described. The route involves the application of Claisen ortho-ester rearrangement to generate the key quaternary carbon.

Keywords: Claisen ortho-ester rearrangement, fish deterrent, sporochnols

INTRODUCTION

Sporochnol A **1**, along with its congeners sporochnol B and C, **2**, **3**, constitute a group of substituted monoterpenoid phenolic constitutents isolated from the Caribbean marine alga *Sporochnus bolleanus*.[1] These have been reported to significantly deter feeding by herbivorous fish. The structural assignment of sporochnol A relied on chemical and spectroscopic analysis.[1] However, the absolute configuration of the lone asymmetric centre as *S* was based on the asymmetric synthesis of the *ent*-isomer.[2] The pronounced biological activity of **1** has prompted its many synthesis in both racemic and optically active forms.[3] We report a facile synthesis of **1** employing Claisen ortho-ester rearrangement[4] to generate the key quaternary carbon center.

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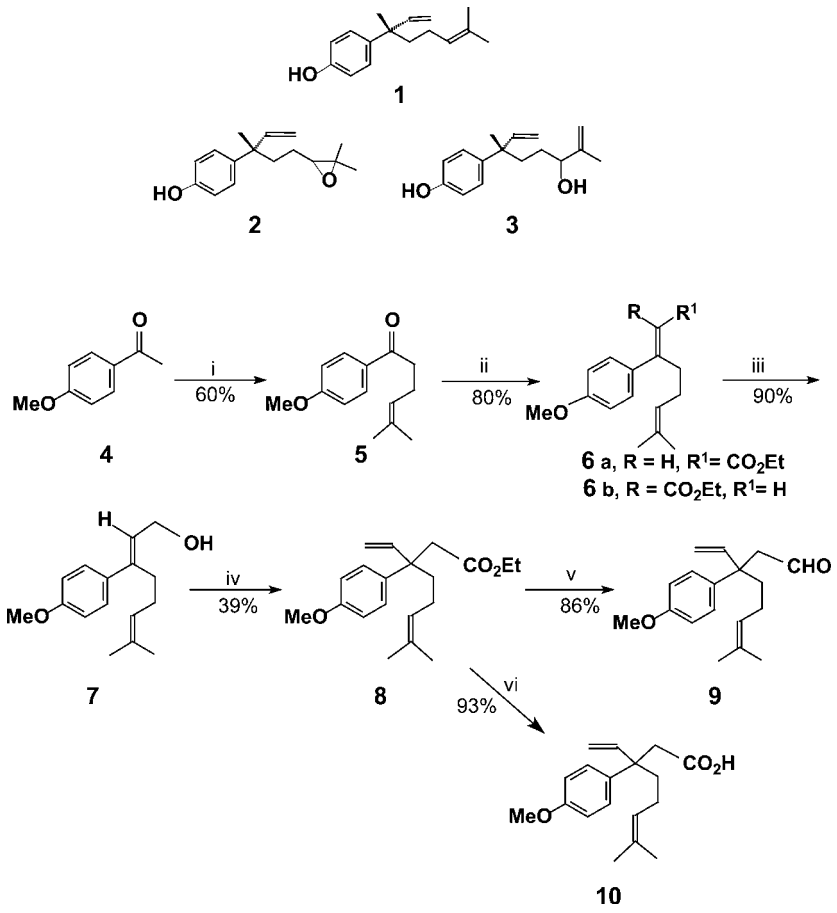
RESULTS AND DISCUSSION

Alkylation of the lithium enolate of 4-methoxy acetophenone **4** with prenyl bromide furnished the prenylated ketone **5** in 60% yield. Condensation of this ketone with triethyl phosphonoacetate afforded the α,β-unsaturated ester(s) **6** in very good yield as a mixture of geometrical isomers. Although there was no need to separate the isomers in view of the subsequent steps, chromatographic purification to recover the traces of the starting ketone **5** led to an efficient separation affording the isomers **6a** and **6b** in 2 : 1 proportion. The structural assignment followed from spectral characteristics of the isomers. In the ^{1}H NMR of **6a**, the methylene protons adjacent to the styrenoid double bond appeared as a triplet at δ3.02, the ester function causing a downfield shift compared with the same protons in **6b** appearing at δ2.37. The olefinic proton, proximal to the aromatic ring, experiencing a deshielding effect, appeared at δ5.92 (br s) as against the same proton in **6b** appearing at δ5.77. Furthermore, the *peri*-hydrogen in the benzene ring of isomer **6b** showed a pronounced upfield shift consequent on the shielding by the ester function and showed as a doublet at δ7.04 compared with the same hydrogen in **6a**, a doublet at δ7.32. The protons of the ethyl group in isomer **6b** also displayed a similar upfield shift compared with the same protons in **6a**. Reduction of the major ester **6a** with lithium aluminium hydride produced the allylic alcohol **7**. This allylic alcohol, on refluxing with triethyl orthoacetate in presence of a catalytic amount of propionic acid, underwent a facile Claisen ortho-ester rearrangement to afford the diene-ester **8** in a moderate yield. In subsequent experiments the combined mixture of isomers **6a** and **6b** was reduced with lithium aluminium hydride and subjected to the Claisen ortho-ester rearrangement and furnished the same diene-ester **8.** This ester incorporated all the requisite features of the target compound and it was anticipated that a ready decarboxylative degradation of the acetate side chain would yield the methyl ether of sporochnol A. However, all efforts to effect this degradation proved futile. The efforts involved decarbonylation experiments of the corresponding aldehyde **9**, obtained from hydride reduction of the ester **8** to an alcohol followed by oxidation. Decarbonylation attempts were carried out employing Wilkinson's catalyst and also photolytic conditions. Direct decarboxylation of the corresponding acid **10**, obtained from hydrolysis of **8**, was also attempted under photolytic conditions. In all cases only a complex product profile resulted and no product corresponding to the desired *O*-methyl sporochnol A could be traced (Scheme 1).

In view of these failures in the final phase of the synthesis, the approach was modified at the initial stage, but once again using the Claisen ortho-ester rearrangement to generate the quaternary carbon center. The starting point was the α,β-unsaturated ester **11**, obtained as a mixture of isomers in excellent yield on condensation of 4-methoxy acetophenone with triethyl phosphonoacetate following the reported procedure.[5] This ester was expeditiously reduced with lithium aluminiumhydride to the allylic alcohol(s) **12**.



Scheme 1. Reagents and conditions: (i) LDA, $(CH_3)_2C{=}CHCH_2Br$, THF, $-20^\circ C$; (ii) $(C_2H_5O)_2P(O)CH_2CO_2Et$, NaH, THF, reflux, 20 h; (iii) LAH, Et_2O, $-20^\circ C$, 4 h; (iv) $CH_3C(OEt)_3$, $C_2H_5CO_2H$, $Hg(OAc)_2$, $200^\circ C$, 24 h; (v) a. LAH, THF, reflux, 2 h; b. $(COCl)_2$, DMSO, Et_3N, $-78^\circ C$; (vi) KOH, EtOH, reflux, 12 h.

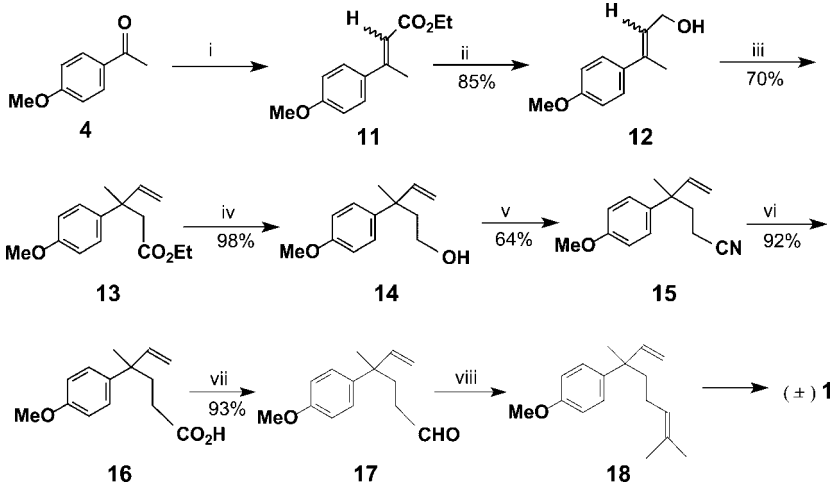
Treatment of this alcohol(s) with triethyl orthoacetate at reflux temperature in the presence of a catalytic amount of propionic acid effected a facile ortho-ester rearrangement to afford the olefinic ester **13** in very good yield, incorporating the elusive geminal vinyl and methyl groups and an acetate side chain for further elaboration. This was readily achieved through a one-carbon homologation. Lithium aluminium hydride–induced reduction of the ester **13** yielded the alcohol **14** in near quantitative yield. The corresponding tosylate, obtained from interaction with toluene-*p*-sulfonyl chloride, on treatment with potassium cyanide in dimethyl sulfoxide afforded the nitrile **15** in an overall yield of 64%. Alkaline hydrolysis of this nitrile furnished the carboxylic

acid **16**. This acid had previously been synthesized by Ohira et al.[3g] and taken to sporochnol A. However, for the purpose of spectral comparison, we carried out the reported steps and converted this acid to the aldehyde **17**, which was subjected to a Wittig reaction with isopropylidene triphenylphosphorane to finally afford *O*-methyl sporochnol A **18** (Scheme 2). The spectral data (^{1}H NMR and ^{13}C NMR) of our **18** fully matched the reported values.[2,3b] Deprotection of **18** to sporochnol A **1** has already been carried out[3b] and hence, the present efforts concluded a synthesis of this marine antifeedent. Because sporochnol A has been converted to sporochnols B **2** and C **3**,[3g] this also constitutes a formal synthesis of these compounds.

In summary, we have described a synthesis of the important fish deterrent sporochnol A, employing readily available materials and simple reaction conditions. The crucial step of generating the quaternary carbon center involved the application of Claisen ortho-ester rearrangement.

EXPERIMENTAL

Melting points are uncorrected. Purity of the products was routinely monitored by TLC. Preparative TLC was performed with silica-gel 60 HF_{254} plates of 1 mm in thickness. The petroleum ether that was used has a bp 60–80°C.



Scheme 2. Reagents and conditions: (i) $(C_2H_5O)_2P(O)CH_2CO_2C_2H_5$, NaH, THF, reflux, 6 h; (ii) LAH, Et_2O, −20°C, 2 h; (iii) $CH_3C(OEt)_3$, $C_2H_5CO_2H$, 138–142°C, 5 h; (iv) LAH, THF, reflux, 3 h; (v) a. *p*-TsCl, Py, 12 h, rt, 2 h, 60–70°C; b. KCN, DMSO, 160°C, 14 h; (vi) KOH, $CH_2(OH)CH_2OH$, 180°C, 24 h; (vii) a. LAH, THF, reflux, 8 h; b. $(COCl)_2$, DMSO, Et_3N, −78°C; (viii) $(CH_3)_2CHPPh_3I$, *n*-BuLi, THF, 0°C.

Na_2SO_4 was used to dry organic extracts. The IR spectra are of $CHCl_3$ solutions. ^1H NMR spectra of $CDCl_3$ solutions were recorded at 300 MHz and ^{13}C NMR spectra at 75 MHz.

4-Methoxy-(3-methyl)-but-2-enyl acetophenone (5). To a well-stirred solution of LDA [prepared from *n*-butyllithium (1.4 mL of 1.6 M solution in hexane, 2.24 mmol) and diisopropylamine (0.32 mL, 2.3 mmol)] in THF at -20°C, a solution of *p*-methoxyacetophenone **4** (300 mg, 2.00 mmol) in THF (2 mL) was added in drops. After 30 min, prenyl bromide (0.28 mL, 2.41 mmol) was added and stirring was continued at -20°C for 45 min and at rt for 4 h. The reaction mixture was then quenched with saturated aqueous NH_4Cl solution and extracted with ether (15 mL × 2). The combined ethereal extracts were washed with water, dried, and the solvent removed. The residual oil was subjected to column chromatography over silica gel. Elution with ethyl acetate–petroleum ether (1 : 49) afforded the prenylated ketone **5** as colorless oil (260 mg, 60%). IR 1678 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.64 (s, 3H), 1.70 (s, 3H), 2.38–2.45 (m, 2H), 2.95 (t, $J = 7.4$ Hz, 2H), 3.87 (s, 3H), 5.18 (t, $J = 7.1$ Hz, 1H), 6.93 (d, $J = 8.7$ Hz, 2H), 7.95 (d, $J = 8.7$ Hz, 2H); δ_C (75 MHz, $CDCl_3$) 18.0, 23.5, 26.1, 38.8, 55.8, 113.9, 122.1, 123.5, 130.7, 133.0, 163.7, 199.0. Anal. calcd. for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 77.15; H, 8.27.

Ethyl 3-(4-methoxyphenyl)-7-methyl-octa-2,6-dienoate(s) (6a and 6b). Triethyl phosphonoacetate (0.72 mL, 3.60 mmol) was added dropwise to a stirred slurry of sodium hydride (72 mg, 3.00 mmol, freed from oil) in THF (4 mL) and stirring continued at rt for 40 min. The ketone **5** (200 mg, 0.92 mmol) in THF (2 mL) was then added dropwise and stirring continued for 2 h at ambient temperature. Then, the reaction mixture was refluxed for 20 h. It was then cooled and poured into saturated aqueous NH_4Cl solution and extracted with ether (5 mL × 2). The combined ethereal extracts were washed with brine, dried, and concentrated. The residual oil was purified by column chromatography over silica gel. Elution with ethyl acetate–petroleum ether (1 : 49) furnished the diene-ester **6a** (110 mg, 42%) as colorless oil. IR 1712 cm^{-1}; δ_H (300 MHz, $CDCl_3$): 1.21 (t, $J = 7.1$ Hz, 3H), 1.44 (s, 3H), 1.56 (s, 3H), 1.99–2.07 (m, 2H), 3.02 (t, $J = 7.4$ Hz, 2H), 3.73 (s, 3H), 4.11 (q, $J = 7.1$ Hz, 2H), 5.07 (t, $J = 7.2$ Hz, 1H), 5.92 (s, 1H), 6.79 (d, $J = 8.8$ Hz, 2H), 7.32 (d, $J = 8.8$ Hz, 2H); δ_C (75 MHz, $CDCl_3$) 14.7, 18.0, 26.0, 28.2, 31.2, 55.6, 60.0, 114.2, 116.0, 124.0, 128.4, 132.4, 133.7, 159.8, 160.7, 167.0. Anal. calcd for $C_{18}H_{24}O_3$: C, 74.97; H, 8.39. Found: C, 74.93; H, 8.41.

Continued elution afforded starting material **5** (40 mg, 20%). Further elution with ethyl acetate–petroleum ether (1 : 19) afforded the isomer **6b** (60 mg, 23%) as colorless liquid. IR 1712 cm^{-1}; δ_H (300 MHz, $CDCl_3$): 1.04 (t, $J = 7.1$ Hz, 3H), 1.44 (s, 3H), 1.59 (s, 3H), 1.94–2.01 (m, 2H), 2.37 (t, $J = 7.2$ Hz, 2H), 3.73 (s, 3H), 3.94 (q, $J = 7.1$ Hz, 2H), 4.98

(t, $J = 7.2$ Hz, 1H), 5.77 (s, 1H), 6.79 (d, $J = 8.7$ Hz, 2H), 7.04 (d, $J = 8.7$ Hz, 2H); δ_C (75 MHz, $CDCl_3$) 14.4, 18.1, 26.0, 26.6, 40.8, 55.5, 60.1, 113.6, 117.1, 123.3, 129.1, 132.2, 132.9, 159.4, 159.6, 166.6. Anal. calcd for $C_{18}H_{24}O_3$: C, 74.97; H, 8.39. Found: C, 74.81; H, 8.37.

3-(4-Methoxyphenyl)-7-methyl-octa-2,6-dien-1-ol (7). A suspension of LAH (180 mg, 4.74 mmol) in ether (8 mL) was stirred for 0.5 h and allowed to settle. The clear solution (7 mL) was removed via syringe and added dropwise to a stirred and cooled (-20°C) solution of the ester **6a** (0.70 g, 2.43 mmol) in ether (8 mL). After stirring for 4 h at this temperature, the reaction mixture was quenched by addition of aqueous saturated Na_2SO_4 solution. The ether layer was carefully decanted and concentrated, and the residue subjected to column chromatography. Elution with ethyl acetate–petroleum ether (1 : 1) furnished the alcohol **7** (540 mg, 90%) as a gummy oil. δ_H (300 MHz, $CDCl_3$) 1.53 (s, 3H), 1.69 (s, 3H), 2.00–2.07 (m, 2H), 2.55 (t, $J = 7.4$ Hz, 2H), 3.83 (s, 3H), 4.31 (d, $J = 7.0$ Hz, 2H), 5.12 (t, $J = 7.4$ Hz, 1H), 5.86 (t, $J = 7.0$ Hz, 1H), 6.88 (d, $J = 8.7$ Hz, 2H), 7.33 (d, $J = 8.7$ Hz, 2H); δ_C (75 MHz, $CDCl_3$) 18.1, 26.0, 27.5, 30.3, 55.7, 60.0, 114.1, 124.0, 126.1, 127.9, 133.0, 134.7, 142.8, 159.3. Anal. calcd for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00. Found: C, 78.12; H, 8.91.

Ethyl 3-(4-methoxyphenyl)-7-methyl-3-vinyl-oct-7-enoate (8). A mixture of the alcohol **7** (200 mg, 0.81 mmol), triethyl orthoacetate (1.48 mL, 8.1 mmol), propionic acid (6 mg, 0.08 mmol), and mercuric acetate (20 mg) was placed in a sealed tube and heated at 200°C for 24 h. Then, it was cooled and the excess orthoester and propionic acid were removed by distillation under reduced pressure (~50–60°C at 20 mmHg) and the residue purified by column chromatography over silica gel. Elution with ethyl acetate–petroleum ether (1 : 19) furnished the diene-ester **8** (100 mg, 39%) as colorless oil; IR 1732 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.09 (t, $J = 7.1$ Hz, 3H), 1.52 (s, 3H), 1.65 (s, 3H), 1.82–2.03 (m, 4H), 2.77 (s, 2H), 3.78 (s, 3H), 3.97 (q, $J = 7.1$ Hz, 2H), 5.05–5.11 (m, 2H), 5.20 (d, $J = 10.9$ Hz, 1H), 6.03 (dd, $J = 10.9$, 17.4 Hz, 1H), 6.83 (d, $J = 8.7$ Hz, 2H), 7.20 (d, $J = 8.7$ Hz, 2H); δ_C (75 MHz, $CDCl_3$) 14.5, 17.9, 23.3, 26.1, 37.9, 42.9, 46.5, 55.6, 60.4, 113.3, 113.7, 124.6, 128.4, 132.0, 137.0, 145.0, 158.2, 171.8. Anal. calcd for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92. Found: C, 75.73; H, 8.89.

3-(4-Methoxyphenyl)-7-methyl-3-vinyl-oct-6-enal (9). To a magnetically stirred suspension of LAH (20 mg, 0.53 mmol) in THF (2 mL), the ester **8** (120 mg, 0.38 mmol) in THF (2 mL) was added dropwise at 0°C. Then, it was brought to room temperature and stirred for 30 min. The reaction mixture was then refluxed for 2 h. It was cooled and decomposed with saturated aqueous Na_2SO_4 solution. The organic layer was separated and the aqueous layer extracted with ether (5 mL × 2). The combined organic extracts were dried and concentrated. The residue after purification over

silica-gel column chromatography and eluting with ethyl acetate–petroleum ether (2 : 5) furnished alcohol (100 mg, 96%) as a very viscous liquid; δ_H (300 MHz, $CDCl_3$) 1.53 (s, 3H), 1.68 (s, 3H), 1.73–1.82 (m, 4H), 2.04–2.16 (m, 2H), 3.52 (t, $J = 7.5$ Hz, 2H), 3.79 (s, 3H), 5.10–5.17 (m, 2H), 5.22 (d, $J = 10.9$ Hz, 1H), 5.95 (dd, $J = 10.9$, 17.6 Hz, 1H), 6.86 (d, $J = 8.8$ Hz, 2H), 7.23 (d, $J = 8.8$ Hz, 2H); δ_C (75 MHz, $CDCl_3$) 17.9, 23.1, 26.0, 38.5, 40.4, 46.1, 55.5, 59.8, 113.1, 113.8, 124.8, 128.3, 131.8, 137.7, 145.7, 158.0. Anal. calcd for $C_{18}H_{26}O_2$: C, 78.79; H, 9.55. Found: C, 78.81; H, 9.52

To a magnetically stirred and cooled (−78°C) solution of oxalyl chloride (0.11 mL, 1.26 mmol) in dichromethane (2 mL), a solution of DMSO (0.2 mL, 2.81 mmol) in dichloromethane (1 mL) was added dropwise. After stirring at −78°C for 15 min, a solution of this alcohol (180 mg, 0.66 mmol) in dichloromethane (2 mL) was added and stirred for 45 min at this temperature. Triethylamine (0.64 mL, 4.59 mmol) was then added and the reaction mixture allowed to attain rt and was stirred for 2 h. The reaction mixture was poured into cold water and the organic layer separated. The aqueous part was extracted with dichloromethane (5 mL × 2). The combined organic layers were washed with water, dried, and concentrated. The residual oil was subjected to column chromatography. Elution with ethyl acetate–petroleum ether (1 : 19) afforded the aldehyde **9** (160 mg, 90%) as a colorless oil; IR 1720 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.50 (s, 3H), 1.64 (s, 3H), 1.78–1.87 (m, 4H), 2.76 (dd, A of ABX, $J_{AB} = 15.3$ Hz, 1H), 2.80 (dd, B of ABX, $J_{BA} = 15.3$ Hz, 1H), 3.78 (s, 3H), 5.03–5.16 (m, 2H), 5.29 (d, $J = 10.7$ Hz, 1H), 6.08 (dd, $J = 10.7$, 17.4 Hz, 1H), 6.86 (d, $J = 8.7$ Hz, 2H), 7.22 (d, $J = 8.7$ Hz, 2H), 9.52 (t, X of ABX, $J_{AX} = J_{BX} = 3.0$ Hz, 1H); δ_C (75 MHz, $CDCl_3$) 17.9, 23.0, 26.0, 39.7, 45.9, 50.7, 55.5, 114.1, 114.4, 124.1, 128.3, 132.3, 136.3, 144.2, 158.4, 203.7. Anal. calcd for $C_{18}H_{24}O_2$: C, 79.37; H, 8.88. Found: C, 79.28; H, 8.91.

3-(4-Methoxyphenyl)-7-methyl-3-vinyl-oct-6-enoic acid (10). The ester **8** (100 mg, 0.32 mmol) was taken in 20% ethanolic KOH (3 mL) and heated under reflux for 12 h. The reaction mixture was then diluted with ice-cold water and extracted once with ether. The aqueous part was acidified with cold dilute HCl (6 N) and extracted with ether (5 mL × 2). The combined ethereal extracts were washed with saturated brine, dried, and concentrated to afford the acid **10** (85 mg, 93%) as a thick mass; IR 1708 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.50 (s, 3H), 1.65 (s, 3H), 1.77–2.00 (m, 4H), 2.82 (s, 2H), 3.79 (s, 3H), 5.06–5.12 (m, 2H), 5.21 (d, $J = 10.7$ Hz, 1H), 6.04 (dd, $J = 10.7$, 17.4 Hz, 1H), 6.83 (d, $J = 8.7$ Hz, 2H), 7.20 (d, $J = 8.7$ Hz, 2H); δ_C (75 MHz, $CDCl_3$) 17.9, 23.3, 26.0, 38.0, 42.6, 46.3, 55.5, 113.5, 113.8, 124.5, 128.3, 132.1, 136.7, 144.8, 158.2, 176.9. Anal. calcd. for $C_{18}H_{24}O_3$: C, 74.97; H, 8.39. Found: C, 74.89; H, 8.41.

3-(4-Methoxyphenyl)-but-2-en-1-ol(s) (12). A suspension of LAH (170 mg, 4.47 mmol) in ether (10 mL) was stirred for 0.5 h and was allowed to settle. The clear solution (9 mL) was removed via syringe and was added dropwise

to a stirred and cooled (−20°C) solution of the ester **11** (500 mg, 2.27 mmol) in ether (10 mL). After stirring for 2 h at this temperature, the reaction mixture was quenched by dropwise addition of saturated Na_2SO_4 solution. The ether layer was carefully decanted and concentrated, and residue subjected to column chromatography over silica gel. Elution with ethyl acetate–petroleum ether (1 : 3) furnished the alcohol **12** as a white crystalline solid. Crystallised from ether–petroleum ether (340 mg, 85%), mp 59–60°C; δ_H (300 MHz, $CDCl_3$) 1.98 (s, 3H), 3.74 (s, 3H), 4.27 (d, $J = 6.6$ Hz, 2H), 5.83 (t, $J = 6.6$ Hz, 1H), 6.79 (d, $J = 8.7$ Hz, 2H), 7.28 (d, $J = 8.7$ Hz, 2H); δ_C (75 MHz, $CDCl_3$) 16.3, 55.7, 60.3, 114.0, 125.2, 127.2, 135.6, 137.8, 159.3. Anal. calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.24; H, 8.02.

Ethyl 3-(4-methoxyphenyl)-3-methylpent-4-enoate (13). A mixture of the allylic alcohol **12** (710 mg, 3.98 mmol), triethyl orthoacetate (7.29 mL, 39.8 mmol), and propionic acid (29 mg, 0.39 mmol) was heated with stirring to keep the temperature of the liquid at 138–142°C. Heating was continued for 5 h; the reaction mixture was allowed to cool to rt and excess orthoacetate was removed by distillation under reduced pressure (~50–60°C at 20 mmHg). The residue was purified by column chromatography. Elution with ethyl acetate–petroleum ether (1 : 19) afforded the ester **13** (690 mg, 70%) as colorless oil. IR 1734 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.13 (t, $J = 7.1$ Hz, 3H), 1.56 (s, 3H), 2.74, 2.78 (AB_q, $J = 13.9$ Hz, 2H), 3.80 (s, 3H), 4.02 (q, $J = 7.1$ Hz, 2H), 5.08 (d, $J = 17.5$ Hz, 1H), 5.14 (d, $J = 10.7$ Hz, 1H), 6.15 (dd, $J = 10.7$, 17.5 Hz, 1H), 6.86 (d, $J = 8.8$ Hz, 2H), 7.26 (d, $J = 8.8$ Hz, 2H); δ_C (75 MHz, $CDCl_3$) 14.5, 25.9, 43.2, 46.2, 55.6, 60.4, 112.3, 113.8, 127.8, 138.4, 146.2, 158.2, 171.7. Anal. calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.76; H, 8.03.

3-(4-Methoxyphenyl)-3-methyl-pent-4-en-1-ol (14). To a magnetically stirred suspension of LAH (40 mg, 1.05 mmol) in THF (3 mL), the ester **13** (220 mg, 0.89 mmol) in THF (5 mL) was added dropwise at 0°C. Then, it was brought to rt and stirred for 30 min. The reaction mixture was then refluxed for 3 h, cooled, and quenched with saturated aqueous solution of Na_2SO_4. The organic layer was decanted, dried, and concentrated and the residue purified by column chromatography. Elution with ethyl acetate–petroleum ether (1 : 3) afforded the alcohol **14** (180 mg, 98%) as a colorless viscous liquid. δ_H (300 MHz, $CDCl_3$) 1.38 (s, 3H), 1.99–2.13 (m, 2H), 3.54–3.63 (m, 2H), 3.78 (s, 3H), 5.06 (d, $J = 17.4$ Hz, 1H), 5.10 (d, $J = 10.7$ Hz, 1H), 6.02 (dd, $J = 10.7$, 17.4 Hz, 2H), 6.85 (d, $J = 8.8$ Hz, 2H), 7.24 (d, $J = 8.8$ Hz, 2H); δ_C (75 MHz, $CDCl_3$) 25.8, 42.9, 43.8, 55.6, 60.3, 112.1, 113.9, 127.8, 139.3, 147.2, 158.1. Anal. calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.58; H, 8.91.

4-(4-Methoxyphenyl)-4-methyl-hex-5-enonitrile (15). To a cold solution of the alcohol **14** (220 mg, 1.07 mmol) in pyridine (5 mL), toluene-*p*-sulphonyl chloride (244 mg, 1.28 mmol) was added and the mixture stirred overnight

at rt. Then, it was warmed at 60–70°C for 2 h. The reaction mixture was diluted with ice water, saturated with NaCl, and extracted with ether. The ethereal extract was washed with an ice-cold solution of HCl (10%) and brine, and then dried. The residue after evaporation was chromatographed over silica gel. Elution with ethyl acetate–petroleum ether (1 : 4) afforded the corresponding tosylate as a gummy liquid (290 mg, 76%). δ_H (300 MHz, $CDCl_3$) 1.31 (s, 3H), 2.07–2.17 (m, 2H), 2.44 (s, 3H), 3.78 (s, 3H), 3.91–3.97 (m, 2H), 4.98 (d, $J = 17.4$ Hz, 1H), 5.07 (d, $J = 10.7$ Hz, 1H), 5.88 (dd, $J = 10.7$, 17.4 Hz, 1H), 6.79 (d, $J = 8.8$ Hz, 2H), 7.11 (d, $J = 8.8$ Hz, 2H), 7.31 (d, $J = 8.2$ Hz, 2H), 7.72 (d, $J = 8.2$ Hz, 2H); δ_C (75 MHz, $CDCl_3$) 22.0, 25.8, 39.5, 42.7, 55.6, 68.4, 112.7, 114.0, 127.6, 128.2, 130.2, 133.5, 138.1, 145.1, 146.0, 158.3.

A solution of tosylate (240 mg, 0.67 mmol) in DMSO (3 mL) was added dropwise to a stirred suspension of KCN (53 mg, 0.80 mmol) in DMSO (3 mL) maintained at 130–135°C. The reaction mixture was then heated at 160°C for 14 h. Then, it was cooled and poured into cold water (30 mL) and extracted with ether (15 mL × 3). The combined ethereal extracts were washed with brine, dried, and concentrated. The residual oil was subjected to column chromatography over silica gel. Elution with ethyl acetate–petroleum ether (1 : 7) furnished the nitrile **15** as a viscous oil (120 mg, 84%); IR 2246 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.37 (s, 3H), 2.06–2.20 (m, 4H), 3.79 (s, 3H), 5.07 (d, $J = 17.4$ Hz, 1H), 5.18 (d, $J = 10.7$ Hz, 1H), 5.95 (dd, $J = 10.7$, 17.4 Hz, 1H), 6.86 (d, $J = 8.8$ Hz, 2H), 7.19 (d, $J = 8.8$ Hz, 2H); δ_C (75 MHz, $CDCl_3$) 13.3, 25.0, 36.8, 43.7, 55.6, 113.4, 114.2, 120.6, 127.8, 137.3, 145.4, 158.5. Anal. calcd. for $C_{14}H_{17}NO$: C, 78.10; H, 7.96; N, 6.51. Found: C, 77.94; H, 7.92; N, 6.49.

4-(4-Methoxyphenyl)-4-methyl-hex-5-enoic acid (16). A mixture of the nitrile **15** (120 mg, 0.56 mmol) and potassium hydroxide in ethylene glycol (3 mL, 20%) was heated under reflux for 24 h. The cooled reaction mixture was diluted with ice-cold water and extracted once with ether. The aqueous alkaline portion was acidified with cold dilute HCl (6 N) and extracted with ether (10 mL × 3). The combined ethereal extracts were washed with brine, dried, and concentrated to afford the acid **16** as a gummy liquid (120 mg, 92%); IR 1708 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.35 (s, 3H), 2.02–2.26 (m, 4H), 3.79 (s, 3H), 5.07 (d, $J = 17.4$ Hz, 1H), 5.13 (d, $J = 10.7$ Hz, 1H), 5.98 (dd, $J = 10.7$, 17.4 Hz, 1H), 6.85 (d, $J = 8.8$ Hz, 2H), 7.23 (d, $J = 8.8$ Hz, 2H); δ_C (75 MHz, $CDCl_3$) 25.3, 30.2, 35.7, 43.5, 55.6, 112.7, 114.0, 127.9, 138.6, 146.4, 158.2, 180.6. Anal. calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.65; H, 7.63.

4-(4-Methoxyphenyl)-4-methyl-hex-5-en-1-al (17). A solution of the acid **16** (120 mg, 0.51 mmol) in THF (3 mL) was added to magnetically stirred slurry of LAH (60 mg, 1.58 mmol) in THF (4 mL). After addition the reaction mixture was refluxed for 8 h. The reaction mixture was then cooled and

decomposed with saturated aqueous Na_2SO_4 solution. The organic layer was separated and the aqueous layer extracted with ether (10 mL × 2). The combined ethereal extracts were washed with saturated $NaHCO_3$ and brine and dried. The residual oil after removal of solvent was chromatographed over silica gel. Elution with ethyl acetate–petroleum ether (1 : 3) furnished the corresponding alcohol (110 mg, 97%) as a viscous liquid. δ_H (300 MHz, $CDCl_3$) 1.36 (s, 3H), 1.38–1.51 (m, 2H), 1.68–1.84 (m, 2H), 3.58 (t, $J = 6.5$ Hz, 2H), 3.78 (s, 3H), 5.03 (d, $J = 17.4$ Hz, 1H), 5.08 (d, $J = 10.7$ Hz, 1H), 6.01 (dd, $J = 10.7$, 17.4 Hz, 1H), 6.84 (d, $J = 8.8$ Hz, 2H), 7.23 (d, $J = 8.8$ Hz, 2H); δ_C (75 MHz, $CDCl_3$) 25.4, 28.4, 37.5, 43.7, 55.6, 63.8, 112.0, 113.8, 127.9, 139.6, 147.4, 158.0. Anal. calcd for $C_{14}H_{20}O_2$: C, 76.32; H, 9.15. Found: C, 75.89; H, 9.35.

To a magnetically stirred and cooled (−78°C) solution of oxalyl chloride (0.08 mL, 0.91 mmol) in dichloromethane (1 mL), a solution of DMSO (0.14 mL, 1.97 mmol) in dichloromethane (1 mL) was added dropwise. After stirring at −78°C for 15 min, a solution of this alcohol (100 mg, 0.45 mmol) in dichloromethane (2 mL) was added and stirred for 45 min. Triethylamine (0.4 mL, 2.86 mmol) was then added and the reaction mixture allowed to attain rt and stirred for 4 h. The reaction mixture was poured into cold water and the organic layer separated. The aqueous part was extracted with dichloromethane (5 mL × 2). The combined organic layers were washed with water, dried, and concentrated. The residue after column chromatography over silica gel using ethyl acetate–petroleum ether (1 : 5) afforded the aldehyde **17** (95 mg, 96%) as a colorless oil. IR 1720 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.35 (s, 3H), 1.98–2.16 (m, 2H), 2.27–2.35 (m, 2H), 3.79 (s, 3H), 5.06 (d, $J = 17.4$ Hz, 1H), 5.12 (d, $J = 10.7$ Hz, 1H), 5.98 (dd, $J = 10.4$, 17.4 Hz, 1H), 6.84 (d, $J = 8.8$ Hz, 2H), 7.21 (d, $J = 8.8$ Hz, 2H), 9.69 (t, $J = 1.5$ Hz, 1H); δ_C (75 MHz, $CDCl_3$) 25.4, 32.9, 40.3, 43.4, 55.6, 112.7, 113.8, 127.9, 138.6, 146.5, 158.2, 202.7. Anal. calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 76.98; H, 8.25.

3-(4-Methoxyphenyl)-3,7-dimethyl-1,6-octadiene (*O*-methylsporochnol A) (18). The aldehyde **17** was converted to *O*-methylsporochnol A **18** following literature procedure[3b] and was obtained in 76% yield as a colorless oil. δ_H (300 MHz, $CDCl_3$) 1.28 (s, 3H), 1.44 (s, 3H), 1.58 (s, 3H), 1.61–1.75 (m, 4H), 3.72 (s, 3H), 4.92–5.02 (m, 3H), 5.93 (dd, $J = 10.7$, 17.5 Hz, 1H), 6.76 (d, $J = 8.8$ Hz, 2H), 7.15 (d, $J = 8.8$ Hz, 2H). δ_C (75 MHz, $CDCl_3$) 16.5, 22.3, 24.0, 24.6, 40.2, 42.6, 54.2, 110.4, 112.3, 123.7, 126.7, 130.3, 138.5, 146.2, 156.5.

The spectral data of **18** were identical with the reported values.[2,3b]

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