Total Synthesis of (±)-Lubimin and (±)-Oxylubimin. I. Synthesis of (±)-15-Norsolavetivone and Related Compounds[1]

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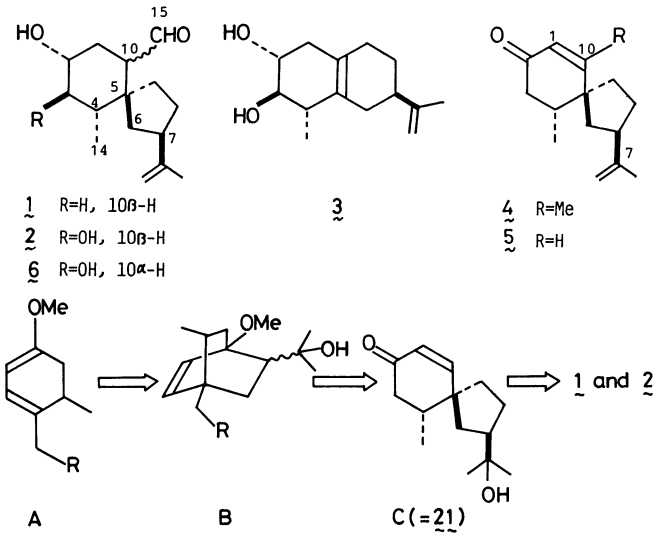
(Received February 6, 1984)

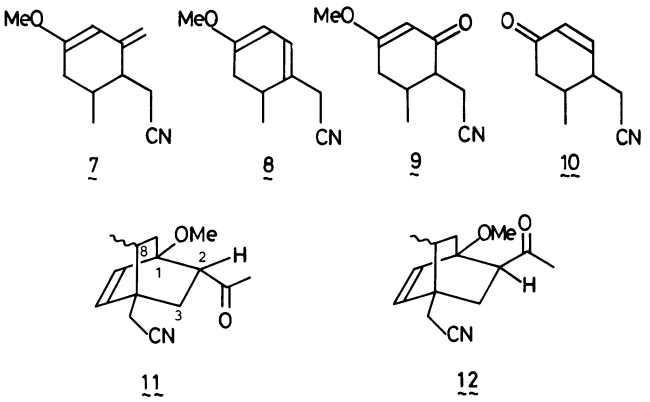
The total synthesis of (±)-15-norsolavetivone, a key intermediate in the synthesis of oxygenated spirovetivane stress metabolites, is described.

The title compounds, lubimin[2] (**1**) and oxylubimin[2] (**2**), are representative members of a group of the spirovetivane sesquiterpenes, which are produced with rishitin[3] (**3**) by potato tubers infected with fungi and qualified as phytoalexins.[4,5] These stress metabolites are biosynthetic intermediates[6] in the major pathway from acetic acid to **3** *via* solavetivone (**4**) and are characterized structurally by the presence of five and six asymmetric centers in the spiro[4.5]decane system as well as the *trans*-disposed C-4–C-14 and C-5–C-6 bonds. Total synthesis of these highly oxygenated spirovetivane phytoalexins has recently been performed according to the synthetic plan shown in Scheme 1, which is divided into two parts: Synthesis of (±)-15-norsolavetivone (±)-(**5**) and related compounds (C in Scheme 1) as key intermediates, and their transformation into (±)-**1**, (±)-**2**, and related compounds such as (±)-10-epioxylubimin[7] (±)-(**6**). The result was published in two preliminary communications.[8] In the present paper the details of the synthesis of (±)-**5** are described.



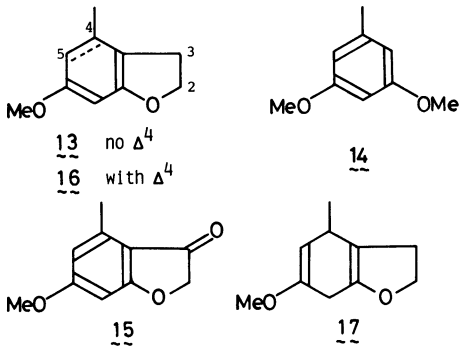
Scheme 1.

In the preceding paper[1] we reported efficient synthesis of (±)-**4**, which started with cycloaddition of 4-methoxy-6-methyl-2-methylene-3-cyclohexenylacetonitrile (**7**) with methyl vinyl ketone. The successful result led us consider that 4-methoxy-6-methyl-1,3-cyclohexadienylacetonitrile (**8**) would be one of the suitable starting materials for the present synthesis. The compound (**8**) was prepared as follows. Reduction of 4-methoxy-6-methyl-2-oxo-3-cyclohexenylacetonitrile[1] (**9**) with sodium hydrotrimethoxyborate[9] followed by acid treatment afforded 4-oxo-6-methyl-2-cyclohexenylacetonitrile (**10**) (70%), which on treatment with 2,2-dimethoxypropane and *p*-toluenesulfonic acid (TsOH) in *N*,*N*-dimethylformamide[10] (DMF) formed the aimed dihydroanisole (**8**) in 55% yield. Cycloaddition of **8** with methyl vinyl ketone at 150°C furnished a mixture of four stereoisomeric adducts, which was separated by chromatography to give the *endo* (**11**) and *exo* adducts (**12**) in 54 and 13% yields, respectively. The NMR spectra revealed that each of the adducts consisted of a 2.5:1.0 mixture of *anti* and *syn* isomers (see Experimental). These results indicated that the overall yield of the expected *anti*-bicyclooctene (B in Scheme 1) was only 18% from 3-methoxy-5-methyl-2-cyclohexenone,[1] a precursor of **9**. The low yield and low stereoselectivity in cycloaddition prompted us to search for another starting material.



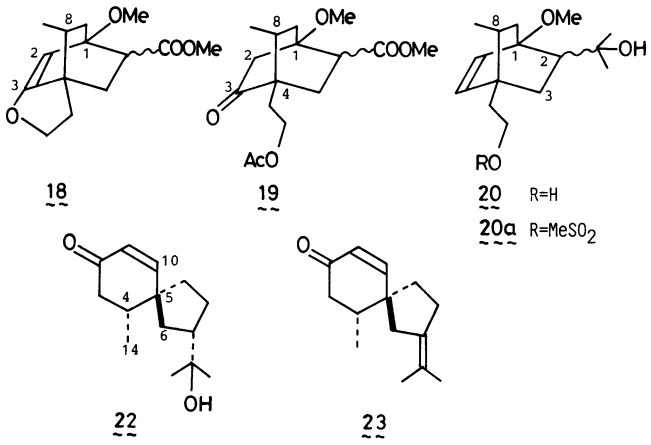
Our previous study[11] indicated that the cycloaddition of 4-substituted 3,5-dimethyldihydroanisoles with methyl acrylate varied, depending on the bulkiness of the 4-substituents. Thus 6-methoxy-4-methyl-2,3,4,5-tetrahydrobenzofuran (**13**) was selected as another suitable diene (A in Scheme 1) for the relevant cycloaddition. The compound (**13**) was prepared from commercially available orcinol dimethyl ether (**14**) as follows. Friedel-Crafts acylation of **14** with chloroacetyl chloride and aluminium chloride gave 2,3-dihydrobenzofuran-3-one (**15**), which on reduction with sodium borohydride ($NaBH_4$) in a mixture of tetrahydrofuran (THF) and methanol followed by hydrogenolysis over 10% palladium–charcoal in the same solvent mixture afforded 6-methoxy-4-methyl-2,3-dihydrobenzofuran (**16**) in 99% yield. The benzofuran (**16**), when submitted to the Birch reduction, was converted into its dihydro derivative (**17**), equivalent to the conjugate diene (**13**), in 81% yield.

The cycloaddition of **17** with methyl acrylate at 150°C in the presence of dichloromaleic anhydride (DCMA) proceeded as expected, giving only a 3:2 mixture of *syn*-8-methyl-6-*endo*-methoxycarbonyl- and *syn*-8-methyl-6-*exo*-methoxycarbonylbicyclo[2.2.2] oc-

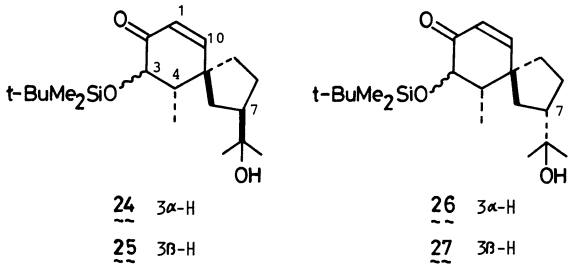


tene adducts (**18**) in 70% yields: *syn-endo* isomer, δ 0.83 (1.8H, s, 8-CH_3) and 4.91 (0.6H, s, 2-H); *syn-exo* isomer, δ 0.86 (1.2H, s) and 5.12 (0.4H, s). Hydrolysis of the mixture (**18**) with oxalic acid in aqueous methanol followed by acetylation furnished keto acetates (**19**) in 70% yield. Treatment of **19** with *p*-tolylsulfonylhydrazine and concd hydrochloric acid in THF under reflux gave its tosylhydrazones (~100%), which were converted under the Shapiro conditions[12] with excess of methylithium into *anti*-8-methylbicyclo[2.2.2]octene diols (**20**) in 71% yield.

Treatment of the diols (**20**), after monomesylation under the usual conditions, with oxalic acid (10 mol equiv) in a 1:5 heterogeneous mixture of water and methyl isobutyl ketone at 130°C for 8 h effected successive cleavage of the C-1–C-2 bond and ring closure[13] to give a mixture of three 15-norsolavetivanes with the *trans*-oriented C-4–C-14 and C-5–C-6 bonds, from which 11-hydroxy-15-norsolavetivane (**21**=C) with a (4*SR*, 7*SR*)-isopropyl moiety was isolated in 35% yield along with its (4*SR*, 7*RS*)-epimer (**22**) (25%) and a 7-isopropylidene derivative (**23**) (30%) by preparative HPLC over μ-Porasil. The relevant reactions, when carried out under the same conditions as those for solavetivones[13] (oxalic acid in a 2:1 homogeneous mixture of water and acetone) led to formation of **21**, **22**, and **23** in 16, 38, and 16% yields, respectively. These results strongly suggested that the bulkiness of the methyl group at C-10 controls conformations of the transition state in the ring closure[14] in question. The spirovetivane (**21**) underwent smooth dehydration on treatment with pyridine-modified alumina[16] to give (±)-15-norsolavetivone (±)-**5** in 68% yield. The synthesis of (±)-5 involved 11 steps and the overall yield was 5.7% from the orcinol (**14**).



The relative configuration at C-7 in the 15-norspirovetivanes (**21**) and (**22**) was assigned tentatively on the basis of the following facts. Treatment of **21** with lithium diisopropylamide (LDA) in a mixture of THF and hexamethylphosphoric triamide (HMPA) and then with *t*-butyldimethylsilyl chloride in THF, followed by oxidation with perbenzoic acid in hexane,[15] furnished a mixture of the 3,4-diequatorial 3-silyl ether (**24**) and its 3-epimer (**25**), which were separated easily by chromatography in 51 and 25% yields, respectively: **24**, δ 3.89 (1H, d, J=11 Hz, 3-H), 5.78 and 6.80 (each 1H, d, J=10 Hz, 1- and 10-H); **25**, δ 4.40 (1H, d, J=4 Hz), 5.81 and 6.60 (each 1H, d, J=10 Hz). The same treatment of **22** afforded the corresponding 3,4-diequatorial 3-silyl ether (**26**) and its 3-epimer (**27**) in 50 and 26% yields, respectively: **26**, δ 3.90 (1H, d, J=11 Hz, 3-H), 5.72 and 6.67 (each 1H, J=10 Hz, 1- and 10-H); **27**, δ 4.41 (1H, d, J=11 Hz), 5.81 and 6.62 (each 1H, d, J=10 Hz). The observed difference in chemical shift (Δδ 0.13) of the proton at C-10 between **24** and **26** was explained well by the difference of the configuration at C-7; namely, the cyclohexane rings in **24** and **26** would take a half-chair conformation owing to the bulky 3-silyloxyl group (equatorial). Thus the hydroxyl group in the C-7 isopropyl moiety would be situated near the hydrogen atom at C-10 only in **24** and hence would deshield the proton in question. A definite assignment was provided by transformation of the 10-hydroxy-15-norspirovetivanes (**21**) and (**24**) into natural spirovetivanes.[16]



Experimental

All the melting and boiling points were uncorrected. The homogeneity of each compound was always checked by TLC over silica gel (Wakogel B-5F) with various solvent systems, and the spots were developed with concd sulfuric acid (H_2SO_4). The IR and NMR (100 MHz) spectra were measured in liquid state for oil and chloroform for solid, and in [^{2}H]-chloroform, respectively, unless otherwise stated. The preparative HPLC was carried out on Waters Associates Model 6000 A, and the column chromatography over silica gel (Kieselgel 60) or aluminium oxide (Aluminumoxide 90), respectively. The following solvents were dried and distilled before use: diethyl ether and THF (from sodium ketyl radical), benzene, carbon tetrachloride, carbon disulfide, and hexane (from phosphorus (V) oxide); triethylamine, DMF, 1,2-dimethoxyethane (DME), HMPA, and dimethyl sulfoxide (DMSO) (from calcium hydride), and ethanol (from magnesium).

4-Oxo-6-methyl-3-cyclohexenylacetonitrile (10). To a suspension of sodium hydride (3.4 g, 60% in oil) in refluxing THF (120 ml) was added freshly distilled methyl borate (7.31 ml, 64 mmol) under nitrogen over a 20 min period. The mixture was stirred for 30 min and cooled to room temperature. A solution of 4-methoxy-6-methyl-2-oxo-3-cyclo-

hexenylacetonitrile (**9**) (2.86 g, 16 mmol), prepared in the preceding paper,[1] in THF (20 ml) was added to the mixture, and stirred for an additional 24 h. To the reaction mixture at 0 °C was added 10% aq H_2SO_4 (20 ml). The whole mixture was stirred for 20 min, concentrated *in vacuo*, poured into 50 ml of saturated brine, and extracted with ethyl acetate (4×100 ml). The combined extracts were washed with 10% aq H_2SO_4 and saturated brine, dried, evaporated, and separated by chromatography over silica gel (120 g) with benzene to give **10** (1.463 g, 70% yield, based on the consumed **9**), oil; MS, *m/z* 149 (M^+); IR, 2220, 1685, and 1615 cm^{-1}; NMR, δ 1.17 (3H, d, J=6 Hz), 6.08 and 6.80 (each 1H, d, J=10 Hz). Found: 149.0844. Calcd for $C_9H_{11}NO$: M, 149.0841.

4-Methoxy-6-methyl-1,3-cyclohexadienylacetonitrile (8). A mixture of **10** (1.412 g), 2,2-dimethoxypropane (12 ml), *p*-TsOH (20 mg), methanol (0.2 ml) and DMF (12 ml) was refluxed under nitrogen for 19 h. The mixture was cooled, poured into aqueous sodium hydrogencarbonate ($NaHCO_3$) (30 ml), and extracted with ether (3×100 ml). The combined extracts were washed with 5% aq $NaHCO_3$, saturated brine, and dried over potassium carbonate and sodium sulfate. The extracts was concentrated and separated by chromatography over alumina (120 g) with benzene to give **8** [559 mg, 36% yield (55% yield, based on the recovered **10**)], oil; MS, *m/z* 163 (M^+), 148, and 108 (base): IR, 2225, 1670, 1610, and 1255 cm^{-1}; NMR, δ 1.04 (3H, d, J=6 Hz), 1.96 (1H, dd, J=16, 4 Hz), 2.3~2.8 (2H, m), 3.01 (2H, s), 3.54 (3H, s), 4.82 and 5.84 (each 1H, d, J=7 Hz). Found: *m/z* 163.0990. Calcd for $C_{10}H_{13}NO$: M, 163.0994.

Cycloaddition of 8. A mixture of **8** (160 mg) and 2,6-di-*t*-butyl-*p*-cresol (BHT) (5 mg) in methyl vinyl ketone (1 ml) was heated in a sealed tube at 150 °C for 2 d. The reaction mixture was cooled and evaporated to leave an oily residue, which was dissolved in ethyl acetate (50 ml). The mixture was washed with 2 M† hydrochloric acid (HCl) (2×20 ml), 5% aq $NaHCO_3$, saturated brine, dried, evaporated, and separated by chromatography over silica gel (20 g) with benzene–ethyl acetate to give a mixture of *anti*- and *syn-endo* adducts (**11**) (122 mg, 54%) and a mixture of the corresponding *exo*-adducts (**12**) (29 mg, 13%), each being a 2.5:1.0 mixture of *anti*- and *syn*-8-methylbicyclooctenes: **11**; MS, *m/z* 233 (M^+); IR, 2225, 1716, 1180, and 1110 cm^{-1}; NMR, δ 0.84 and 1.04 (2.14H and 0.86H, each d, J=6 Hz), 2.16 (3H, s), 2.62 and 2.48 (1.43H and 0.57, each s), 3.08 and 2.98 (0.72H and 0.28H, each dd, J=10 and 6 Hz), 3.32 (3H, s), 5.83 and 6.27 (each 0.72H, d, J=9 Hz), 6.18 and 6.24 (each 0.28H, d, J=9 Hz); **12**, oil; MS, *m/z* 233 (M^+); IR 2230, 1713, 1180, and 1108 cm^{-1}; NMR, δ 0.78 and 1.11 (2.14H and 0.86H, each d, J=6 Hz), 2.23 and 2.21 (2.14H and 0.86H, each s), 3.34 and 3.32 (2.14H and 0.86H, each s), 5.89 and 6.45 (each 0.72H, d, J=8 Hz), 6.17 and 6.45 (each 0.28H, d, J=8 Hz).

6-Methoxy-4-methyl-2,3-dihydrobenzofuran (16). To a solution of orcinol dimethyl ether (16.74 g, 0.11 mmol) in carbon disufide (110 ml) was added at 0 °C carefully powdered aluminium chloride (14.8 g, 0.11 mmol) with vigorous stirring and then at room temperature a solution of chloroacetyl chloride (9 ml, 0.11 mmol) in carbon disulfide (55 ml) over a 1 h period. The mixture was stirred under reflux for 7 h, distilled to remove the solvent, and cooled with an ice-water bath. To the residue were added chloroform (200 ml), ice-water (100 ml) and 2 M HCl, successively. The mixture was stirred for 40 min at 0 °C, when the residue was dissolved. The aqueous layer was separated and the chloroform extracts were washed with 2 M HCl (100 ml) and water (2×100 ml), dried, and concentrated to leave an oily residue, which crystallized on addition of diisopropyl ether (200 ml). Recrystallization from diisopropyl ether gave 6-methoxy-4-methyl-2,3-dihydrobenzofuran-3-one (**15**). (12.09 g, 62%), mp 123—124 °C; MS, *m/z* 178 (M^+, base); IR (Nujol), 1702, 1620, 1590, 1280, 1190, 1150, and 1080 cm^{-1}; NMR, δ 2.55 (3H, s), 3.85 (3H, s), 4.57 and 6.36 (each 2H, s). Found: C, 67.33%; H, 5.82%. Calcd for $C_{10}H_{10}O_3$: C, 67.40%; H, 5.66%. The filtrate was concentrated and purified by chromatography over silica gel (300 g) with benzene and ethyl acetate to give the starting orcinol dimethyl ether (0.52 g, 3%), **15** (2.25 g, 8.1%), and 3,5-dimethoxy-2-(chloroacetyl)toluene (2.05 g, 8.1%), mp 69—70.5 °C (from diisopropyl ether); MS, *m/z* 230 (M^++2), 228 (M^+), and 179 (base); IR (Nujol), 1701, 1605, 1575, 1330, 1155, and 1102 cm^{-1}; NMR, δ 2.27 and 3.80 (3H and 6H, each s), 4.49 (2H, s), 6.27 and 6.31 (each 1H, d, J=1 Hz). Found: C, 57.72; H, 5.71%. Calcd for $C_{11}H_{13}O_3Cl$: C, 57.77; H, 5.73%.

The chloroacetyl compound was transformed into **15** as follows. A mixture of the compound (13.3 g, 0.058 mmol) and powdered aluminium chloride (8.6 g) in carbon disulfide (150 ml) was heated under reflux for 22 h. After removal of the solvent and cooling at 0 °C, the residue was worked up as described above to give **15** (10.06 g, 97%).

ii) To a solution of **15** (12.09 g) in THF (250 ml) and methanol (150 ml) was added $NaBH_4$ (8 g) in four portions at 0 °C, and the mixture was stirred for an additional 1.5 h. To the reaction mixture was added acetone (100 ml), and the mixture was concentrated *in vacuo*. The residue was poured into a mixture of saturated brine (200 ml) and 5% aq $NaHCO_3$ (100 ml), and extracted with ethyl acetate (3×200 ml) and the combined extracts were washed with water (3×50 ml), dried, and evaporated to give a crystalline residue. Recrystallization from methanol afforded an analytical sample: mp 67—68 °C; MS, *m/z*, 180 (M^+) and 162 (base); IR (Nujol), 3240, 1623, 1603, 1200, and 1141 cm^{-1}; NMR, δ 2.35 and 3.74 (each 3H, s), 4.43 (1H, d, J=3 Hz), 4.45 (1H, d, J=5 Hz), 5.23 (1H, dd, J=5 and 3 Hz), 6.23 and 6.26 (each 1H, s). Found: C, 66.75; H, 6.70%. Calcd for $C_{10}H_{12}O_3$: C, 66.56; H, 6.71%. The crude residue was used for the next reaction without further purification.

A solution of the crude alcohol in THF (200 ml) and ethanol (200 ml) was treated with hydrogen over 4 g of 10% palladium on charcoal at room temperature under atmospheric pressure, until uptake of hydrogen ceased. The solution was filtered through Celite and concentrated under reduced pressure. The residue was recrystallized from methanol to give **16** (8.366 g), mp 54.5—56.5 °C; MS, *m/z* 164 (M^+, base); IR (Nujol), 1628, 1605, 1204, and 1140 cm^{-1}; NMR, δ 2.22 (3H, s), 3.05 (2H, t, J=8 Hz), 3.75 (3H, s), 4.57 (2H, t, J=8 Hz), and 6.23 (2H, s). Found: C, 73.34; H, 7.25%. Calcd for $C_{10}H_{12}O_2$: C, 73.14; H, 7.37%.

6-Methoxy-4-methyl-2,3,4,7-tetrahydrobenzofuran (17). To a mixture of **16** (15 g) in dry ether (700 ml) and liquid NH_3 (2 l) at −33 °C was added small pieces of lithium (28 g) over a 30 min period. The mixture was stirred for 2 h, and, after addition of 260 ml of ethanol over a 1 h period, was warmed to evaporate ammonia. The residue was mixed with water (1.4 l) at 0 °C, saturated with sodium chloride, and extracted with ether (5×300 ml). The combined ether extracts were washed with water (2×200 ml), dried, evaporated, and separated by chromatography over alumina (300 g) with benzene to leave **17** (12.3 g, 81%), oil; MS, *m/z* 166 (M^+) and 151 (base); IR, 1732, 1664, 1404, 1232, and 1164 cm^{-1}; NMR (CCl_4), δ 1.05 (3H, d, J=7 Hz), 3.50 (3H, s), 4.27 (2H, t, J=9 Hz), 4.47 (1H, d, J=4 Hz). Found: *m/z* 166.0982. Calcd for $C_{10}H_{14}O_2$: M, 166.0994.

*2-(1-Methoxy-6-methoxycarbonyl-8-*syn*-methyl-3-oxobicyclo-[2.2.2]oct-4-yl)ethyl Acetate (19).*[17] i) A mixture of **17** (50 g), methyl acrylate (120 ml), dichloromaleic anhydride (1 g), and BHT (2.5 g) was heated in an autoclave at 150 °C under argon atmosphere for 5 d. The mixture was dissolved in benzene

† 1 M=1 mol dm^{-3}.

(100 ml), concentrated, and separated by chromatography over alumina (2.4 kg) with benzene to afford a mixture of adducts (**18**) (52.90 g, 70%), oil; MS, *m/z* 252 (M^+), 221, 166, and 151 (base); IR, 1733, 1680, 1207, and 1172 cm^{-1}; NMR, δ 0.83 and 0.86 (1.8H and 1.2H, each d, J=6 Hz, 8-CH_3), 2.92 (1H, m, 6-H), 3.33 and 3.37 (1.8H and 1.2H, each s, 1-OCH_3), 4.91 and 5.12 (0.6H and 0.4H, each s, *endo*- and *exo*-2-H). The mixture of the adducts was used for the next reaction without further purification.

ii) A mixture of the adducts (**18**) (52.90 g), oxalic acid (300 g as dihydrate) in methanol (850 ml) and water (1.7 l) was stirred at room temperature for 2 h, and neutralized with solid sodium carbonate. The mixture was stirred for an additional 30 min, and concentrated *in vacuo*. The residue was saturated with sodium chloride, and extracted with ethyl acetate (4×500 ml). The combined acetate extracts were washed with saturated brine, dried, evaporated, and separated by chromatography over silica gel (2.0 kg) with benzene–ethyl acetate (3:2) to give keto alcohols (39.18 g). The mixture of *endo* and *exo* keto alcohols was used for the next reaction without further separation. However, an analytical sample of each alcohol was obtained by careful column chromatography. *exo*-Keto alcohol, oil; MS, *m/z* 270 (M^+), 184, 166, and 151 (base); IR, 3480, 1730, 1720, 1202, 1183, and 1116 cm^{-1}; NMR, δ 0.84 (3H, d, J=6 Hz), 3.06 (1H, ddd, J= 10, 6, and 3 Hz), 3.28 (3H, s), 3.66 (2H, t, J=7 Hz), and 3.75 (3H, s). Found: C, 61.85; H, 8.25%. Calcd for $C_{14}H_{22}O_5$: C, 62.20; H, 8.20%. *endo*-Keto alcohol, oil; MS, *m/z* 270 (M^+), 184, 166, and 151 (base); IR, 3476, 1725, 1200, 1174, and 1113 cm^{-1}; NMR, δ 0.85 (3H, d, J=6 Hz), 2.92 (1H, dd, J=8 and 5 Hz), 3.25 (3H, s), 3.63 (2H, t, J=7 Hz), and 3.71 (3H, s). Found: C, 61.77; H, 8.26%. Clacd for $C_{14}H_{22}O_5$: C, 62.20; H, 8.20%.

iii) A mixture of the keto alcohols (30.2 g) in dry pyridine (300 ml) and acetic anhydride (120 ml) was stirred at 20°C under nitrogen for 23 h. The mixture was mixed with ethanol (100 ml) stirred for 30 min at 20°C, and concentrated at 50 °C *in vacuo* (15 Torr) (1 Torr=133.322 Pa). The residue was poured into ice-water (200 ml), and extracted with ethyl acetate (3×250 ml). The combined acetate extracts were washed with 2 M HCl (4×100 ml), dried, evaporated, and saparated by column chromatography over silica gel (200 g) with benzene–ethyl acetate (7:1) afforded **19** (30.54 g, 97% based on the recovered starting material), oil; MS, *m/z* 312 (M^+); IR, 1732, 1249, 1205, 1117, and 1115 cm^{-1}; NMR, δ 2.02 (3H, s), 3.25 and 3.24 (1.8H and 1.2H, each s), 3.70 and 3.73 (1.8H and 1.2H, each s), and 4.06 (2H, t, J=7 Hz).

*2-[2-(1-Hydroxy-1-methylethyl]-1-methoxy-8-*anti*-methylbicyclo-[2.2.2]oct-3-en-4-yl]ethanol (**20**)*[17] *and its monomesylate (**20a**).* i) A mixture of **19** (4.303 g, 0.014 mmol), *p*-tolylsulfonylhydrazine (2.73 g, 0.015 mmol) and concd HCl (0.5 ml) in THF (190 ml) was stirred under reflux for 20 h. The reaction mixture was cooled, concentrated *in vacuo*, and dried at 20°C for 10 h under reduced pressure (3 Torr), giving the crude hydrazone (7.30 g), amorphous: IR ($CHCl_3$), 3540, 3225, 1728, 1598, 1440, 1374, 1340, 1248, 1168, 1098, 1040, and 815 cm^{-1}.

To a solution of the crude tosyl hydrazone (7.30 g) in dry THF (600 ml) at 0°C under nitrogen was added a 1 M solution of methyllithium in ether (210 ml, 15 mol equiv), prepared from methyl iodide (160 ml) and lithium (40 g) in ether (250 ml), over a 1 h period. The mixture was heated at 35°C for 19 h, cooled, mixed carefully with water (100 ml) at 0°C, and concentrated to remove THF *in vacuo*. The residue was poured into saturated brine (400 ml), and extracted with ethyl acetate (4×200 ml). The combined extracts were washed with saturated brine (2×100 ml), dried, evaporated, and separated by chromatography over silica gel (250 g) with benzene–ethyl acetate (2:1) to yield **20** (2.479 g, 71% from **19**), oil; MS, *m/z* 254 (M^+), 239, and 236; IR, 3473, 1384, 1173, 1101, and 1050 cm^{-1}; NMR, δ 0.78 and 0.76 (1.8H and 1.2H, each d, J= 7 Hz), 1.00 (3.6H, s), 1.10 and 1.34 (total 2.4H, each s), 3.39 and 3.37 (1.8H and 1.2H, each s), 3.75 (2H, t, J=7.5 Hz), 5.82 and 6.28 (each 0.6H, d, J=9 Hz), 5.74 and 6.44 (each 0.4H, d, J=9 Hz).

ii) To a solution of **20** (13.70 g, 0.054 mol), and triethylamine (12.8 ml, 1.7 mol equiv) in dichloromethane (270 ml) at −78°C under nitrogen was added methanesulfonyl chloride (4.7 ml, 1.1 mol equiv). The mixture was stirred for 15 min, mixed with 5% aq $NaHCO_3$ (20 ml), and warmed to room temperature. The mixture was again poured into 5% aq $NaHCO_3$ (200 ml), when the dichloromethane layer was separated. The aqueous layer was extracted with ethyl acetate (3×20 ml). The dichloromethane and acetate extracts were combined, washed with 5% aq $NaHCO_3$ (70 ml) and saturated brine (70 ml), dried, and concentrated to give crude monomesylates (**20a**), which were used for the next reaction.

*Norsolavetivanes (**21**), (**22**), and (**23**).* i) A mixture of **20a** (71 mg) and oxalic acid dihydrate (252 mg) in methyl isobutyl ketone (20 ml) and water (4 ml) was stirred at 130°C for 8 h. After being cooled and neutralized with solid sodium carbonate at 0°C, the mixture was poured into saturated brine and extracted with ethyl acetate (4×50 ml). The extracts were washed, dried, concentrated, and separated by chromatography over silica gel (6 g) with benzene–ethyl acetate (2:1) to give a mixture (18 mg, 60% based on the consumed starting material) of 15-nor-11-hydroxy-solavetivanes (**21**) and (**22**) and its isopropylidene analogue (**23**) (8.1 mg, 30%), oil; MS, *m/z* 204 (M^+); IR, 1685, 1362, and 1182 cm^{-1}; NMR, δ 0.99 (3H, d, J=7 Hz), 1.63 (6H, s), 5.85 and 6.71 (each 1H, d, J=10 Hz). Found: *m/z* 204.1550. Calcd for $C_{14}H_{20}O$: M, 204.1515. A mixture of **21** and **22** was separated by HPLC [Waters, μ-Porasil, eluted with hexane–ether (1:1) 5 ml/min] to give **21** (10.3 mg, 35%) and **22** (7.4 mg, 25%): **21**, R_t=28 min, oil; MS, *m/z* 222 (M^+); IR, 3495, 1678, 1383, 1362, 1178, and 944 cm^{-1}; NMR, δ 1.00 (3H, d, J=6 Hz), 1.21 (6H, s), 5.78 and 6.74 (each 1H, d, J=10 Hz). Found: *m/z* 222.1617. Calcd for $C_{14}H_{22}O_2$: M, 222.1620. **22**, R_t=23 min, oil; MS, *m/z* 222 (M^+); IR, 3490, 1680, 1614, 1387, 1140, and 940 cm^{-1}; NMR, δ 1.01 (3H, d, J=6 Hz), 1.22 (6H, s), 5.79 and 6.76 (each 1H, d, J=10 Hz). Found: *m/z* 222.1624. Calcd for $C_{14}H_{22}O_2$: M, 222.1620.

ii) A mixture of **20a** (106 mg) and oxalic acid dihydrate (282 mg) in acetone (3 ml) and water (6 ml) was stirred at 90°C for 8 h. The reaction mixture was worked up as described above to give a mixture (81 mg, 54%) of **21**, **22**, and **23** (21 mg, 16%). The mixture was separated by HPLC as described above to give **21** (24 mg, 16%) and **22** (57 mg, 38%).

*15-Norsolavetivone (**5**).* Compound **21** (165 mg) was mixed with pyridine-modified alumina (0.5 g), prepared from neutral alumina (Woelm, activity grade I) and pyridine withstirring under reduced pressure (0.3 Torr) at room temperature for 6 h. The mixture was heated in a glass tube at 220°C (bath temperature) for 8 min under argon, cooled, poured into ether (100 ml) and triethylamine (15 ml), and stirred for 3 h. The mixture was filtrated through Celite, concentrated, and separated by chromatography over silica gel (10 g) with benzene to afford **5** (75 mg, 68% yield based on the recovered starting material), oil; MS, *m/z* 204 (M^+) and 162; IR, 3090, 1687, 1650, and 890 $^{-1}$; NMR, δ 1.01 (3H, d, J=6 Hz), 1.73 (3H, s), 4.70 (2H, s), 5.78 and 6.70 (each 1H, d, J=10 Hz). Found: *m/z* 204.1499. Calcd for $C_{14}H_{20}O$: M, 204.1502.

*3-t-Butyldimethylsiloxy-11-hydroxy-2-oxo-15-nor-$\Delta^{1(10)}$-solavetivanes (**24**)—(**27**).* i) To a solution of LDA (1.5 mmol), prepared from diisopropylamine (0.21 ml, 1.51 mmol) in THF (5 ml) and 1.5 M butyllithium (1.5 mmol) in hexane (1 ml), was added **21** (134 mg, 0.6 mmol) in THF (3 ml) and

HMPA (0.26 ml) at −78°C under nitrogen, and the mixture was stirred for 30 min. A solution of *t*-butyldimethylchlorosilane (226 mg, 1.5 mmol) in THF (1 ml) was added to the mixture, and the whole mixture was warmed to room temperature and stirred for an additional 1 h. The mixture was shaken with ether (20 ml) and water (0.5 ml), dried, and concentrated to give an oily residue (426 mg). On the other hand, a solution of perbenzoic acid (96 mg, 0.72 mmol) in dry hexane was stirred at 0°C for 20 min. To this solution was added a solution of the oily residue (426 mg) in hexane (5 ml) at −15 °C. The mixture was warmed to room temperature, stirred for 1.5 h, poured into 30 ml of saturated brine, and extracted with ethyl acetate (4×50 ml). The combined extracts were washed with 5% aq $NaHCO_3$ (2×20 ml), dried, and evaporated to leave an oily residue, which was separated by chromatography over silica gel (10 g) with benzene–ethyl acetate (15:1) to afford **24** (91.5 mg) and **25** (45 mg) in 51 and 25% yields (based on the consumed starting material), respectively. **24**, oil; MS, *m/z* 337 (M^+-15); IR, 3620, 3450, 1698, 1615, 1257, 1145, 867, and 840 cm^{-1}; NMR, δ 1.08 (3H, d, J=7 Hz), 1.24 (6H, s), 3.89 (1H, d, J=11 Hz), 5.78 and 6.80 (each 1H, d, J=10 Hz). Found: C, 68.32; H, 10.13%. Calcd for $C_{20}H_{36}O_3Si$: C, 68.13; H, 10.29%. **25**, oil; MS, *m/z* 337 (M^+-15); IR, 3500, 1700, and 1260 cm^{-1}; NMR, δ 0.99 (3H, d, J=6 Hz), 1.23 (6H, s), 4.40 (1H, d, J=6 Hz), 5.81 and 6.60 (each 1H, d, J=10 Hz). Found: C, 68.45; H, 10.11%. Calcd for $C_{20}H_{36}O_3Si$: C, 68.13; H, 10.29%.

ii) Siloxylation of **21** (122 mg) was carried out under the same conditions as descrived above to give **26** (97 mg, 50%), and **27** (50 mg, 26%). **26**, oil; MS, *m/z* 337 (M^+-15); IR, 3625, 3470, 1700, 1620, 1150, 870, and 840 m^{-1}; NMR, δ 1.09 (3H, d, J=7 Hz), 1.22 (6H, s), 3.90 (1H, d, J=11 Hz), 5.72 and 6.67 (each 1H, d, J=10 Hz). Found: C, 68.41; H, 10.11%. Calcd for $C_{20}H_{36}O_3Si$: C, 68.13; H, 10.29%. **27**, oil; MS, *m/z* 337 (M^+-15), IR, 3495, 1700, 1260, 1150, 880, and 840 cm^{-1}; NMR, δ 0.94 (3H, d, J=6 Hz), 1.23 (6H, s), 4.41 (1H, d, J=4 Hz), 5.81 and 6.62 (each 1H, d, J=10 Hz). Found: C, 68.35; H, 10.15%. Calcd for $C_{20}H_{36}O_3Si$: C, 68.13; H, 10.29%.

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17) Compounds **19** and **20** should be designated as 2-(4-methoxy-5-methoxycarbonyl-7-*syn*-methyl-2-oxobicyclo-[2.2.2]octyl)ethyl acetate and 2-[3-(1-Hydroxy-4-methylethyl)-7-*anti*-methylbicyclo[2.2.2]oct-5-enyl]ethanol, respectively according to the IUPAC numbering rule. However, in this paper we used the same numbering for these compounds as that for 16 (C-1, carbon atom bearing the methoxyl group).