A General Synthetic Approach of Spirovetivanes. The Synthesis of (±)-Solavetivone, (±)-Hinesol, and Related Compounds[1)]

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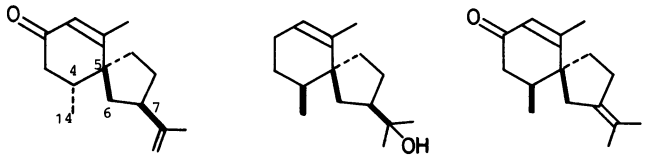
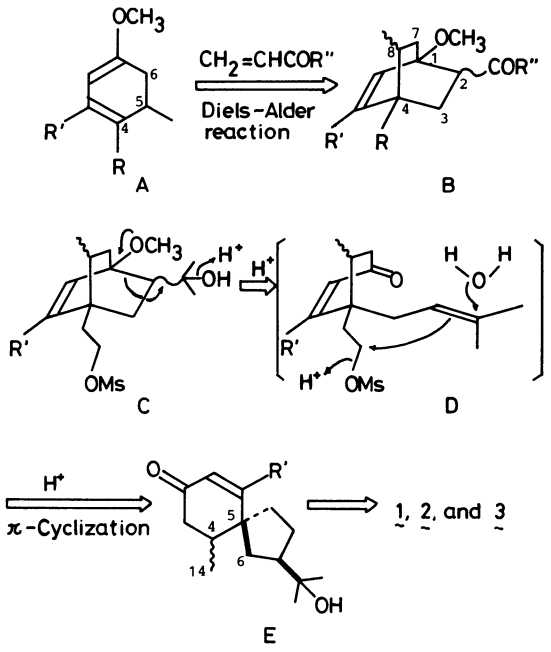
The synthetic procedure leading to preparation of representative compounds, (±)-solavetivone and (±)-hinesol, of two classes of spirovetivanes, is described. The procedure involves Diels-Alder reaction of 4-substituted 5,6-dihydro-3,5-dimethylanisoles with methyl acrylate and π-cyclization of 4-(2-mesyloxyethyl)-4-prenyl-2-cyclohexen-1-one as key steps (Scheme 1).

Naturally occurring spirovetivanes are divided into two classes based on the relative configuration between the C-4–C-14 and C-5–C-6 bonds:[2,3)] one class consists of a number of sesquiterpenes, represented by solavetivone and oxylubimin and isolated as stress compounds[4)] from diseased potato tubers, possesses the *trans* configuration concerning the relevant bonds, while the other,[3,5)] including hinesol, β-vetivone, and others isolated from vetiver oil, takes the *cis*-configuration. While considerable attention has been directed towards synthesis[3)] of these sesquiterpenes owing to the characteristic skeleton, most of the works have been limited to the preparation of spirovetivanes belonging to the latter class. Only recently, Yamada,[6)] Iwata,[7)] and coworkers reported the synthesis of (±)-solavetivone, one of the simplest spirovetivanes of the former class. We have also searched a general procedure leading to the preparation of both classes of spirovetivanes and succeeded in the synthesis of (±)-solavetivone[8)] (±)-(**1**), (±)-hinesol[5)] (±)-(**2**), (±)-β-vetivone[5)] (±)-(**3**), and close analogues. The result was published in a preliminary communication,[9)] and its details are described in this paper.



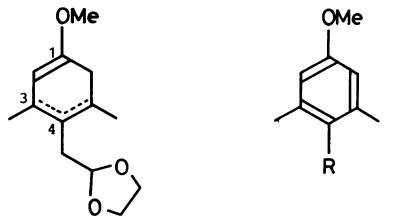
1 **2** **3**

Our synthetic plan involves two key steps as shown in Scheme 1: (i) Diels-Alder reaction of 4-substituted 3,5-dimethyl-5,6-dihydroanisoles (A) with methyl acrylate or its equivalents, giving cycloadducts (B), and (ii) π-cyclization[10)] between the primary cationic carbon atom and prenyl double bond of the intermediates (D) derived from B *via* C. The *syn*- and *anti*-configurations of the C-8-methyl group in respect to the C-2–C-3 bond in B correspond to the *cis*- and *trans*-configurations between the C-5–C-6 and C-4–C-14-bonds in the spirovetivanes (E). If each of the *syn*- and *anti*-adducts is prepared stereoselectively under suitable conditions (step i), the respective classes of spirovetivanes would be synthesized effectively. On the other hand, there seem not to be any precedents for ring closure by the relevant π-cyclization (step ii). If the cyclization proceeds smoothly, examination of the Dreiding model indicates that the desirable spirovetivones (E) with the (4*SR*,7*SR*)-isopropyl moiety would be produced stereoselectively.



Scheme 1.

The starting diene (**4**), corresponding to A in Scheme 1, was prepared as follows. 3,5-Dimethylanisole was reacted with bromine in the presence of iron metal to give its 4-bromoanisole (**5**) (85%), which on reflux with magnesium turnings and allyl bromide in ether formed its Grignard reagent. Treatment of the reagent with allyl bromide afforded 4-allyldimethylanisole (**6**) (83% from **5**), which was converted by oxidation according to the Lemieux-Johnson procedure[10)] followed by acetalization of the resulting aldehyde (**7**) into the corresponding acetal (**8**) (77% from **6**). The Birch reduction of **8** gave rise to the 3,6-dihydroanisole (**9**) (85%), which was isomerized by heating at 140 °C to yield the 5,6-dihydroanisole (**4**) (72% from **8**).



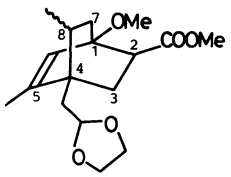
4 Δ^3, no Δ^4
9 Δ^4, no Δ^3

5 R=Br-
6 R=CH_2-CH=CH_2
7 R=CH_2CHO
8 R=CH_2CH<O, O>

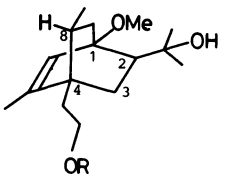
Diels-Alder reactions of the dihydroanisoles were carried out under various conditions.[11] Treatment of the 1,4-diene (**9**) with methyl acrylate in the presence of dichloromaleic anhydride (DCMA)[12] and 2,6-di-*t*-butyl-*p*-cresol (BHT) at 85 °C for 14 d produced a mixture (77% based on the recovered **9**) of four stereoisomeric cycloadducts differing in the configuration at C-2 (2-*endo*- and 2-*exo*-$COOCH_3$) and C-8 (8-*syn*- and 8-*anti*-CH_3 to the C-2–C-3 bond). The product was a 6.6:1.0 mixture of the *endo* (**10**) and exo adducts (**11**), which were separated by chromatography. Each of the adducts (**10**) and (**11**) was estimated to be a 2.0:1.0 mixture of the *syn* and *anti* isomers. The configuration of **10** and **11** was assigned on the basis of the chemical shifts of the signals due to the C-2–H [δ 2.87 (dd, J=9.5 and 5 Hz) and 2.72 (ddd, J=10, 5, and 1 Hz, long-range coupling with 7-*anti*–H=1 Hz) for the *endo* and *exo* adducts]. The ratio of the *syn* and *anti* adducts was deduced from the relative intensity of the C-8–CH_3 [δ 1.04 (d, J=6 Hz, *endo*) and 0.96 (d, J=6 Hz, *exo*) for the *syn* adducts, and δ 0.87 (d, J=6 Hz, *endo*) and 0.75 (d, J=6 Hz, *exo*) for the *anti* adducts]. The cycloaddition, when carried out in ether at 20 °C and at 15000 atm (1 atm=101325 Pa) for 2 d, afforded a 3.2:1.0 (by NMR) mixture (65% based on the recovered **9**) of the *syn-endo* and *anti-endo* adducts (**10**) as the isolable products.[11] On the other hand, treatment of the 1,3-diene (**4**) with methyl acrylate at high temperature (190 °C) afforded a 0.9:1.0 (by NMR) mixture (75%) of the *syn* and *anti* adducts, each being a 2.0:1.0 mixture of the *endo* and *exo* isomers.[11] These results indicate that (i) in contrast to exclusive production of the *anti* adducts in the reactions with 4-unsubstituted[13] and 4-methyl dines,[14] introduction of ethyl and substituted ethyl groups into C-4 of the starting diene led to formation of the *syn* isomers, and (ii) ratios of the *syn*- isomers to the corresponding *anti*-isomers in the latter reactions increased with lowering temperature.

The *endo* adducts (**10**) (a 3.2:1.0 mixture of the *syn* and *anti* adducts) were transformed by a three-step process [(i) acid hydrolysis, (ii) hydride reduction, and (iii) treatment with methyllithium] into the corresponding bicyclooctene diols, which were separated easily to give the *syn-endo* (**12**) and *anti-endo* diols (**13**) in 60 and 15% yields, respectively [δ 1.06 (3H, d, J=7 Hz, 8-CH_3) for **12**, and δ 0.74 (3H, d, J=6 Hz) for **13**]. Likewise, the aforementioned 0.9:1.0 mixture of the *syn* and *anti* adducts were separated easily by chromatography into the *endo* (**10**) and *exo* adducts (**11**), which were treated in the same manner as mentioned above to give the corresponding diols. These diols were separated by chromatography to give the *syn-endo* (**12**), and *anti-endo* isomers (**13**) in 33 and 37% yields (from **10**), and the *syn-exo* (**14**) and *anti-exo* isomers (**15**) in 30 and 33% yield (from **11**), respectively [δ 0.98 (3H, d, J=7 Hz, 8-CH_3) for **14**, and δ 0.75 (3H, d, J=7 Hz) for **15**]. These bicyclooctenediols (**12**)—(**15**) were converted by treatment with methanesulfonyl chloride into the respective methanesulfonates (**12a**)—(**15a**).

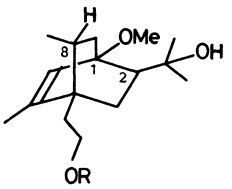
Attempts to convert the *syn-endo* mesylate (**12a**) into the spirovetivanes (**16**) and (**17**) were examined



10 2-endo-COOMe
11 2-exo-COOMe



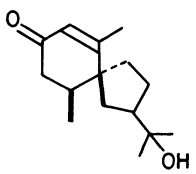
12 2-endo-$C(Me)_2OH$, R=H
12a 2-endo-$C(Me)_2OH$, R=Ms
14 2-exo-$C(Me)_2OH$, R=H
14a 2-exo-$C(Me)_2OH$, R=Ms



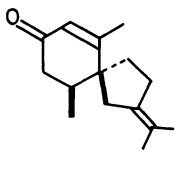
13 2-endo-$C(Me)_2OH$, R=H
13a 2-endo-$C(Me)_2OH$, R=Ms
15 2-exo-$C(Me)_2OH$, R=H
15a 2-exo-$C(Me)_2OH$, R=Ms

under various conditions: *e.g.*, tin(IV) chloride in dichloromethane at −78 °C, acetic acid at 110 °C, formic acid at 50 °C, and others. Finally, treatment of **12a** with oxalic acid (10 mol equiv) in 33% aqueous acetone at 85 °C for 4 h effected formation of the skeletone in question, giving two spirovetivanes (**16**), mp 38—41 °C, and (**17**), mp 121—123 °C, in 60 and 27% yields, respectively, in which the C-4–C-14 and C-5–C-6 bonds were oriented *cis* each other. Careful treatment of **12a** with formic acid at room temperature for 30 min gave prenylcyclohexenone (**18**), which on treatment under the same conditions as mentioned above gave **16** and **17** in 58 and 37% yields, respectively. The other *syn* adduct (**14a**) was also submitted to the same cyclization, giving **16** and **17** in 58 and 20% yields, respectively.

The π-cyclization must have taken place by attack of the prenyl double bond towards the primary cationic carbon atom formed by removal of the mesyloxyl group. It is noted that the isomer (**19**) differing from **16** in the C-7 configuration could not be detected by careful examination of IR and NMR spectra, and by GLC analysis. This high stereoselectivity for formation of the (4*SR*,7*SR*)-asymmetric center could be rationalized in terms of the relative stability of two conformers (**18A**) and (**18B**) with maximum overlap between the π-orbitals of the relevant primary cationic carbon atom and the prenyl double bond (Scheme 2). This seems to be the first example for such stereoselective ring closure.



16 (7SR)-$C(Me)_2OH$
19 (7RS)-$C(Me)_2OH$



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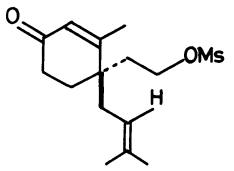

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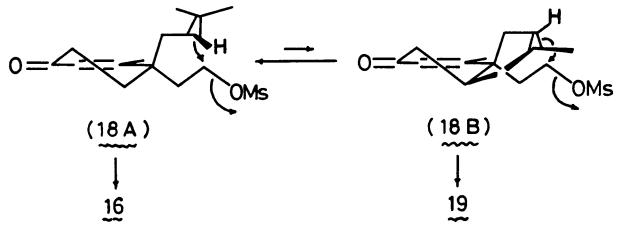
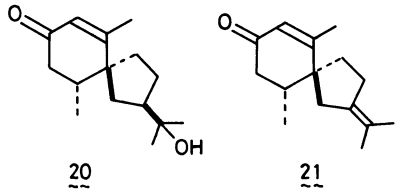
The spirovetivanes (**16**) and (**17**) were identified as authentic samples[5] of (±)-hinesolone and (±)-β-vetivone (**3**), respectively. The former could be trans-



Scheme 2.

formed according to the procedures developed by Dauben and coworkers[5] into (±)-hinesol (**2**) and (±)-β-vetispirene. The present result constitutes a new synthetic pathway to the spirovetivanes isolated from vetiver oil.

The same treatment of the *anti-endo* mesylate (**13a**) in aqueous acetone produced two spirovetivanes (**20**), oil, and (**21**), mp 52—55°C, with *trans*-oriented C-4–C-14 and C-5–C-6 bonds in 63 and 23% yields, respectively. Likewise, the *anti-exo* isomer (**15a**) afforded **20** and **21** in 69 and 26% yields, respectively. The latter (**21**) was identified as "10-epi-β-vetivone" by comparison of the spectral data with the reported ones.[15] Dehydration of **20** proceeded smoothly by heating with pyridine-modified alumina (Woelm, neutral) at 220°C for 8 min[16] to give an isopropenyl compound, oil, in 60% yield, which formed its *syn*-, mp 107.5—109°C, and *anti*-2,4-dinitrophenylhydrazones, mp 137—138°C. It is emphasized that no isopropylidene derivative was detected in the dehydration product. The compound was identified as (±)-solavetivone by direct comparison with natural solavetivone (**1**) (MS, IR, NMR, and TLC). The present synthesis of (±)-solavetivone involves 12 steps with an overall yield of 3.2% from 3,5-dimethylanisole.



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 cerium(IV) sulfate in dil sulfuric acid and/or concd sulfuric acid. The IR and NMR (100 MHz) spectra were measured in liquid state for oil and in chloroform for solid, and in [^{2}H]chloroform, respectively, unless otherwise stated. The abbreviations "s, d, t, m, and br," in the NMR spectra denote "singlet, doublet, triplet, multiplet and broad," respectively. Solvents and reagents were dried and distilled before use: diethyl ether and tetrahydrofuran (THF) (over sodium ketyl radical); benzene and carbon tetrachloride (CCl_4) (over phosphorus(V) oxide); triethylamine (over calcium hydride).

4-Bromo-3,5-dimethylanisole (5). To a solution of 3,5-dimethylanisole (82 g) in CCl_4 (600 ml) and iron powder (0.4 g) at −40—30°C was added dropwise a solution of bromine (34 ml, 0.66 mol) in CCl_4 (200 ml) over a 3 h period. The solution was stirred for 2 h at the same temperature, and poured into 400 ml of ice and water, and extracted with dichloromethane, repeatedly. The combined organic solution was washed with 5% aqueous sodium hydrogencarbonate ($NaHCO_3$) and water, dried (Na_2SO_4), and concentrated *in vacuo* to leave an oil, which was distilled under reduced pressure to give **5** (110 g, 85%); bp 123—125°C/15 Torr (1 Torr=133.322 Pa); MS, *m/z* 214 (M^+, base); IR, 1570, 1230, 1193, 1160, 1074, and 1015 cm^{-1}; NMR (CCl_4), δ 2.33 (6H, s), 3.69 (3H, s), and 6.53 (2H, s). Found: C, 50.56; H, 5.28%. Calcd for $C_9H_{11}OBr$: C, 50.26; H, 5.16%.

4-Allyl-3,5-dimethylanisole (6). To a solution of 2,6-dimethyl-4-methoxyphenylmagnesium bromide, prepared from **5** (35 g), magnesium turnings (4 g) and allyl bromide (1.2 ml) in ether (200 ml) under reflux with stirring for 18 h, was added a solution of allyl bromide (30 ml) in ether (60 ml) at room temperature under argon atmosphere. The solution was stirred under reflux for 16 h and then cooled to 0°C. To the solution was added 2M† hydrochloric acid (50 ml) to dissolve the remaining magnesium metal. The resulting mixture was poured into saturated brine (200 ml) and extracted with ether, repeatedly. The organic layer was washed with 5% aq $NaHCO_3$ and saturated brine, dried and concentrated, and the resiude was distilled to give **6** (24.09 g): bp 112—130°C/15 Torr; MS, *m/z* 176 (M^+, base); IR, 3080, 1640, 998, and 915 cm^{-1}; NMR (CCl_4), δ 2.21 (6H, s), 3.25 (2H, dt, *J*=5.5 and 1.8 Hz), 3.68 (3H, s), 4.69 (1H, ddt, *J*=17, 1.9, and 1.8 Hz), 4.82 (1H, ddt, *J*=10, 5.5, and 1.9 Hz), 5.82 (1H, ddt, *J*=17, 10, and 5.5 Hz), and 6.42 (2H, s). Found: C, 81.64; H, 9.06%. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15%.

4-(2,2-Ethylenedioxyethyl)-3,5-dimethylanisole (8). To a solution of **6** (20 g) in THF (400 ml) at room temperature was added a 0.16 M solution (4 ml) of osmium tetraoxide in THF, and the solution was stirred vigorously for 15 min. To the solution was added an aqueous solution (520 ml) containing sodium periodate (58 g) at 0°C over a 3 h period. The resulting mixture was stirred at room temperature for 10 h, and precipitates formed were removed by filtration. The filtrate was concentrated *in vacuo* to remove THF and extracted with ethyl acetate, repeatedly. The acetate solution was washed with 5% aq sodium hydrogensulfite,water and saturated brine, dried and evaporated to leave 2,6-dimethyl-4-methoxyphenylacetaldehyde (**7**) (21.57 g); IR, 2840 and 1725 cm^{-1}; NMR (CCl_4), δ 2.23 (6H, s), 3.54 (2H, d, *J*=2 Hz), 3.72 (3H, s), 6.50 (2H, s), 9.45 (1H, t, *J*=2 Hz). This compound was used for the next reaction without further purification.

The aldehyde (**7**) (21.57 g), ethylene glycol (11 g) and *p*-toluenesulfonic acid monohydrate (2 g) were dissolved in benzene (400 ml), and the solution was stirred under reflux for 15 h, water being removed continuously by a Dean-Stark tube. The reaction mixture was cooled to room temperature, and poured into saturated brine (300 ml) and extracted with ethyl acetate (EtOAc), repeatedly. The organic layer was washed with 5% aq $NaHCO_3$ and saturated brine, dried, and then evaporated. The crude residue was crystallized from hexane (350 ml), filtered, and washed with hexane–ether (1 : 1) to give **8** (11.68 g). The filtrate was concentrated and separated by chromatography over alumina (300 g) with benzene to give a crystalline substance **8** (7.17 g), mp 79—81°C (from ether); MS, *m/z* 222 (M^+); IR (Nujol), 1610, 1185, 1130, 1020, 930, 870, and 837 cm^{-1}; NMR (CCl_4), δ 2.27 (6H, s), 2.86 (2H, d, *J*=5 Hz), 3.66 (3H, s), 3.7 (4H, m), 4.82 (1H, t, *J*=5 Hz), and 6.40 (2H, s). Found: C, 79.14; H, 8.04%. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16%.

4-(2,2-Ethylenedioxyethyl)-3,5-dimethyl-3,6-dihydroanisole (9) and its 5,6-Dihydro Isomer (4). i) To a stirred mixture of **8** (7.55 g) in THF (400 ml) and liquid ammonia (700 ml), dried over potassium hydroxide pellets, was added small pieces of lithium (10 g) for 30 min. The mixture was stirred for 2 h

† 1 M=1 mol dm^{-3}.

and treated with absolute ethanol (100 ml) for 40 min. The resulting mixture, after removal of the ammonia followed by addition of ice-cooled water (500 ml), was concentrated, extracted with ether, dried, and evaporated to leave an oily residue, which on distillation gave **9** (6.475 g): bp 105—107°C/1 Torr; MS, *m/z* 224 (M^+); IR, 1701 and 1664 cm^{-1}; NMR, δ 1.08 (3H, d, J=7 Hz), 1.71 (3H, s), 3.51 (3H, s), 4.60 (1H, d, J=4 Hz), and 4.89 (1H, t, J=5 Hz).

ii) The reduction of **8** (10 g) was carrried out in the same manner as mentioned above except distillation. The crude 3,6-dihydroanisole (**9**) was heated at 140°C/29 Torr for 10 h and then distilled to give **4** (7.15 g): bp 152—160°C/13 Torr; UV (EtOH), 277 nm (ε 5000); MS, *m/z* 224 (M^+); IR, 1670, and 1645 cm^{-1}; NMR, δ 0.92 (3H, d, J=7 Hz), 1.79 (3H, s), 3.56 (3H, s), 4.77 (1H, t, J=1 Hz), and 4.88 (1H, t, J=5 Hz).

Diels-Alder Reaction. Method A; The Cycloadditon at 90°C and 1 atm: A mixture of **9** (13.32 g), DCMA (20 mg) and BHT (3 g) in methyl acrylate (80 ml) and benzene (40 ml) was heated at 90°C under argon at atmospheric pressure for 14 d. The red reaction mixture was distilled to remove excess of methyl acrylate and benzene. The syrupy residue was poured into 2M aqueous sodium hydroxide (NaOH) (300 ml), and extracted with ether (4×200 ml). The combined extracts were washed with saturated brine, dried, evaporated, and chromatographed over alumina (200 g) with benzene to give the crude starting diene (**9**, 23.6 g) and a mixture (11.79 g) of the adducts. The crude diene was distilled under reduced pressure to yield the pure starting diene (4.87 g). The crude mixture of the adducts was separated by chromatography over silica gel (400 g) with benzene and ethyl acetate (8:1) to give a mixture of the *exo*-adducts (1.20 g) and the endo-adducts (7.80 g) in 77% yield (based on the consumed starting diene): *endo* adducts (**10**); oil, MS, *m/z* 310 (M^+) and 224; IR, 1741, 1643, 1170, 1112, and 1100 cm^{-1}; NMR, δ 1.04 and 0.87 (2H, and 1H, each d, J=6 Hz), 1.87 and 1.80 (2H and 1H, each d, J=1 Hz), 2.87 (1H, dd, J=9.5 and 5 Hz), 3.32 and 3.64 (each 3H, s), 3.9 (4H, m), 4.93 and 4.98 (0.67 H and 0.33 H, each t, J=4 Hz), and 5.89 (1H, br s, W_H=7 Hz): *exo* adducts (**11**); oil, MS, *m/z* 310 (M^+) and 224; IR, 1738, 1642, 1194, 1130, and 1095 cm^{-1}; NMR, δ 0.96 (2H, d, J=6 Hz), 0.75 (1H, d, J=6 Hz), 1.81 and 1.75 (2H and 1H, each d ,J=1 Hz), 2.72 (1H, ddd, J=10, 5, and 1 Hz), 3.35 and 3.66 (each 3H, s), 3.9 (4H, m), 4.93 and 4.89 (0.67 H and 0.33 H, each t, J=5 Hz), and 6.03 (1H, br s, W_H=6 Hz).

Method B; The Cycloaddition Under High Pressure: The Teflon tube (ϕ 8.1×35 mm) filled with the 1,4-diene (**4**) (452 mg), methyl acrylate (230 mg, freshly distilled), BHT (14 mg) and ether (0.5 ml) was kept in a high pressure apparatus, and the cycloaddition was performed at 15000 atm at room temperature for 2 d. The syrupy mixture was evaporated and the residue was separated by chromatography over alumina (19 g) with benzene to give the strating diene (131 mg) and the cycloadducts (190 mg, 65% based on the recovered diene), which was a 3.2:1.0 (by NMR) inseparable mixture (**10**) of the *syn-endo* and *anti-endo* adducts: oil; MS, *m/z* 310 (M^+) and 224 (retro Diels-Alder fragment); IR, 1741, 1643, 1170, 1112, and 1100 cm^{-1}; NMR, δ 1.04 (2.29 H, d, J=6 Hz), 0.87 (0.71 H, d, J=6 Hz), 1.87 (2.29 H, d, J=1 Hz), 1.80 (0.71 H, d, J=1 Hz), 2.87 (1H, dd, J=9.5 and 5 Hz), 3.32 and 3.64 (each 3H, s), 3.9 (4H, m), 4.93 (0.76 H, t, J=4 Hz), 4.98 (0.25 H, t, J=4 Hz), and 5.89 (1H, s).

Method C; The Cycloaddition at 190°C: A mixture of **9** (147 mg), DCMA (2 mg) and BHT (5 mg) in methyl acrylate (1.4 ml) was heated at 190°C for 4 d in a sealed tube. The reaction mixture was dissolved in ethyl acetate (50 ml) and evaporated to leave a tarry residue, which was purified by chromatography over silica gel (30 g) with ethyl acetate and benzene, giving a 0.9:1.0 (by NMR) mixture (**11**, 28 mg) of *syn-exo* and *anti-exo* adducts and a 0.9:1.0 mixture (**10**, 89 mg) of *syn-endo* and *anti-endo* adducts.

*2-[2-(1-Hydroxy-1-methylethyl)-1-methoxy-5,8-dimethylbicyclo-[2.2.2]oct-5-en-4-yl]ethanols (**12**)—(**15**)[17] and their Mesylates (**12a**)—(**15a**).* i) A mixture of the *endo* adducts (**10**, 285 mg), prepared by method B, and 2M hydrochloric acid (6 ml) in ether (12 ml) was stirred at 40°C for 15 h. The aqueous layer was separated, saturated with sodium chloride and extracted with ethyl acetate (3×50 ml). The combined extracts were washed with 5% aqueous $NaHCO_3$ and saturated brine, dried and evaporated to give the corresponding bicyclooctene aldehyde (273 mg): oil, MS, *m/z* 266 (M^+); IR, 2730, 1738, 1728, 1650, 1370, 1200, 1179, and 1100 cm^{-1}; NMR (CCl_4), δ 1.16 (0.76H, d, J=6 Hz), 0.88 (0.24H, d, J=6 Hz), 1.81 (3H, s), 2.65 (1.52H, dd, J=8 and 2 Hz), 2.51 (0.48H, dd, J=8 and 1 Hz), 2.80 (1H, dd, J=9.5 and 5 Hz), 3.26 (3H, s), 3.58 (3H, s), 5.78 (0.76H, s), 5.83 (0.24H, s), 9.78 (0.76H, t, J=2 Hz), and 9.84 (0.24H, t, J=1 Hz). The aldehyde was used for the next reaction without further purification.

ii) To a solution of the aldehyde (170 mg) in methanol (5 ml) at 0°C was added sodium borohydride (100 mg). The mixture was stirred for 1 h, and evaporated to leave an oily residue, which was poured into saturated brine and extracted with ethyl acetate, repeatedly. The combined extracts were washed with 5% aqueous $NaHCO_3$ and saturated brine, dried, and evaporated to give an oil, which was purified by chromatography over silica gel (15 g) with benzene and ethyl acetate (3:1) to yield a 3.2:1.0 (by NMR) mixture of the *syn-endo* and *anti-endo* alcohols (223 mg): MS, *m/z* 268 (M^+), 182 and 151 (base): IR, 3460, 1730, 1460, 1192, 1170 1082 and 1030 cm^{-1}; NMR (CCl_4), δ 0.84 (0.7H, d, J=6 Hz), 1.00 (2.3H, d, J=6 Hz), 1.86 (2.3H, d, J=1 Hz), 1.81 (0.7H, d, J=1 Hz), 2.72 (1H, dd, J=10 and 6 Hz), 3.22 (3H, s), 3.59 (3H, s), 3.63 (1.52H, t, J=8 Hz), 3.62 (0.48H, t, J=8 Hz), 5.71 (0.76H, br s, W_H=7 Hz), and 5.72 (0.24H, br s, W_H=6 Hz).

iii) To a stirred solution of the *endo* alcohols (222 mg) in dry ether (25 ml) at room temperature was added 1.2 M methyllithium in ether (15 ml), prepared from methyl iodide (8.5 ml) and lithium (2.2 g) in ether (80 ml). After the solution was cooled at 0°C for 2 h, water (10 ml) was added carefully to the solution. The ether layer was separated, and the aqueous layer was extracted with ethyl acetate repeatedly. The combined ether and acetate extracts were washed with saturated brine, dried, and evaporated. The residue was purified by chromatography over silica gel (15 g) with benzene and ethyl acetate (3:2) to give two diols. The less polar one, which was identified as 8-*syn*-methyl-*endo* diol (**12**, 147 mg), exhibited the following physical properties: mp 101—103°C (from ether); MS, *m/z* 268 (M^+), 182, and 151 (base); IR (Nujol), 3450, 1648, 1470, 1092 and 1055 cm^{-1}; NMR, δ 0.98 (6H, s), 1.06 (3H, d, J=7 Hz), 1.81 (1H, d, J=1 Hz), 3.36 (3H, s), 3.67 (2H, t, J=8 Hz), and 5.89 (1H, br s, W_H=6 Hz). Found: C, 71.95; H, 10.33%. Calcd for $C_{16}H_{28}O_3$: C, 71.60; H, 10.52%. The more polar diol was identified as 8-*anti*-methyl-*endo* diol (**13**, 37 mg); MS, *m/z* 253 (M^+−15), 182, and 151 (base); IR, 3450, 1642, 1090, 1075 and 1040 cm^{-1}; NMR, δ 0.74 (3H, d, J=6 Hz), 0.92 (6H, s), 1.75 (3H, d, J=6 Hz), 1.88 (2H, t, J=8 Hz), 3.36 (3H, s), 3.73 (2H, t, J=8 Hz), and 5.91 (1H, br s, W_H=7 Hz). Found: *m/z* 253.1789. Calcd for $C_{15}H_{25}O_3$: M-CH_3, 253.1804.

iv) The *endo* (**10**, 7.64 g) and *exo* (**11**, 1.12 g) adducts, prepared by method A, were transformed according to the aforementioned three-step process [(i) 2M hydrochloric acid and ether (2:1), 40°C, 15 h, (ii) sodium borohydride in methanol, 0°C, 1 h, and (iii) methyllithium in ether, room temperature, 2 h] into the corresponding bicyclooctene diols, respectively. The *endo* diols were separated by chromatography to give **12** (3.559 g) and **13** (1.063 g), and the *exo* diols were likewise purified to yield *syn-exo* (**14**, 0.44 g) and *anti-exo* diols (**15**, 0.218 g). The latter compounds (**14**) and (**15**) showed the following spectra. **14**; MS, *m/z* 253 (M^+-15), 182, and 151 (base); IR, 3460, 1645, 1400, 1090 and

1043 cm^{-1}; NMR, δ 0.98 (3H, d, J=6 Hz), 1.10 and 1.26 (each 3H, s), 1.81 (3H, d, J=1 Hz), 3.33 (3H, s), 3.72 (2H, t, J=8 Hz), and 6.08 (1H, br s). Found: C, 72.03; H, 10.40%. Calcd for $C_{16}H_{28}O_3$: C, 71.60; H, 10.52%. **15**; MS, m/z 253 (M^+−15), 182, and 151 (base); IR, 3450, 1648, 1092, and 1050 cm^{-1}; NMR, δ 0.75 (3H, d, J=6 Hz), 1.02 and 1.24 (each 3H, s), 1.73 (3H, d, J=1 Hz), 3.32 (3H, s), 3.72 (2H, t, J=8 Hz), and 6.07 (1H, br s). Found: m/z 253.1819. Calcd for $C_{15}H_{25}O_3$: M-CH_3, 253.1804.

v) To a stirred solution of **12** (704 mg) in dry dichloromethane (140 ml) containing triethylamine (0.6 ml, 1.5 mol equiv) cooled at −78°C was added methanesulfonyl chloride (0.23 ml, 1.1 mol equiv) under nitrogen. The resulting mixture was stirred for 10 min, mixed with water (10 ml), and warmed to room temperature. The mixture was poured into 5% aqueous $NaHCO_3$ (10 ml) and extracted with ethyl acetate (4×30 ml). The combined extracts were washed with 5% aqueous $NaHCO_3$ and saturated brine, dried, and evaporated to give a crude *syn-endo* mesylate (**12a**) in quantitative yield (1.075 g): MS, m/z 346 (M^+), 260, 151, and 149 (base); IR, 3505, 1645, 1360, 1180, 1090, 980, and 950 cm^{-1}; NMR, δ 0.89 (6H, s), 1.08 (3H, d, J=6 Hz), 1.83 (3H, d, J=1 Hz), 2.93 and 3.39 (each 3H, s), 4.21 (2H, t, J=8 Hz), and 5.92 (1H, br s). The crude mesylate was used for the next reaction without further purification. Three other diols (**13**)—(**15**) were converted in the respective monomesylates (**13a**)—(**15a**) almost quantitatively. **13a**, oil, MS, m/z 346 (M^+), 260, 151, 149, and 136 (base); IR, 3500, 1645, 1355, 1185, 1093, 980, and 954 cm^{-1}; NMR, δ 0.78 (3H, d, J=6 Hz), 0.90 (6H, s), 1.77 (3H, d, J=1 Hz), 2.95 and 3.38 (each 3H, s), 4.24 (2H, t, J=8 Hz), and 5.94 (1H, br s): **14a**, oil, MS, m/z 346 (M^+), 260, 151, and 149 (base); IR, 3495, 1643, 1353, 1192, 1090, 976, and 948 cm^{-1}; NMR, δ 1.01 and 1.25 (each 3H, s), 1.04 (3H, d, J=7 Hz), 1.81 (3H, d, J=1 Hz), 2.92 and 3.32 (each 3H, s), 4.22 (2H, t, J=8 Hz), and 6.07 (1H, br s): **15a**, oil, MS, m/z 346 (M^+), 260, 151, 149, and 136 (base); IR, 3500, 2645, 1350, 1193, 1087, 985, and 953 cm^{-1}; NMR, δ 0.73 (3H, d, J=6 Hz), 1.08 and 1.32 (each 3H, s), 4.33 (2H, t, J=8 Hz), and 6.14 (2H, br s).

π-Cyclization Reactions. i) A mixture of **12a** (234 mg) in formic acid (99%, 14 ml) was stirred at room temperature for 30 min. The mixture was poured into ice-water (160 ml), neutralized by addition of solid sodium carbonate, and extracted with ether (4×100 ml). The organic layer was washed with 5% aq $NaHCO_3$ (2×50 ml), dried and evaporated to leave a crude prenylcyclohexenone mesylate (**18**, 220 mg): oil; IR, 1670, 1616, 1360 and 118 cm^{-1}; NMR, δ 1.06 (3H, d, J=6 Hz), 1.62 (3H, br s), 1.76 (3H, br s), 1.98 (3H, br s), 2.94 (3H, s), 4.06 (2H, t, J=8 Hz), 5.11 (1H, t, J=7 Hz), and 5.89 (1H, br s, W_H=6 Hz).

A solution of the crude **18** (142 mg) and oxalic acid dihydrate (150 mg, 10 mol equiv), water (6 ml) and acetone (3 ml) was stirred at 85°C for 4 h. The mixture was poured into 5% aqueous $NaHCO_3$ (40 ml), which was saturated with sodium chloride, and extracted with ethyl acetate (5×50 ml). The extracts were washed with 5% aq $NaHCO_3$ and saturated brine, dried, and evaporated. The residue was purified by chromatography over silica gel (5 g) with ethyl acetate and benzene to give two spirovetivanes (**16**, 41 mg) and (**17**, 23 mg), which were identified as (±)-hinesolone[5] and (±)-β-vetivone[5] (**3**) respectively. **16**, mp 121—123°C (from diisopropyl ether), and 116—120°C (from CCl_4) (lit,[5] 115—119°C); MS, m/z 218 (M^+-18, base); IR (CCl_4), 3640, 3475, 1665, and 1615 cm^{-1}; NMR (CCl_4), δ 1.01 (3H, d J=7 Hz), 1.24 (6H, s), 1.97 (3H, s), and 5.75 (1H, br s, W_H=6 Hz). Found: C, 76.15; H, 10.29%. Calcd for $C_{15}H_{24}O_2$: C, 76.22; H, 10.24%. **17** [(±)-β-vetivone], mp 38—41°C (from pentane), (lit,[7] 43.5—57°C); MS, m/z 218 (M^+, base); IR (CCl_4), 1680, 1618, 1383, 1350 and 1295 m^{-1}; NMR (CCl_4), δ 0.97 (3H, d, J=6 Hz), 1.62 and 1.64 (each 3H, br s), 1.87 (3H, s), and 5.65 (1H, br s, W_H=6 Hz). Found: C, 82.73; H, 10.11%. Calcd for $C_{15}H_{22}O$: C, 82.51; H, 10.16%.

ii) A mixture of **12a** (148 mg) in acetone (3 ml) and oxalic acid dihydrate (135 mg) in water (6 ml) was stirred at 85°C for 4 h. The reaction mixture was worked up as mentioned above to yield **16** (46 mg) and **17** (19 mg) in 60 and 27% yields, respectively.

iii) Treatment of **14a** (293 mg) with oxalic acid under the same manner as mentioned above [oxalic acid (720 mg) in water (14 ml) and acetone (7 ml), 85°C, 4 h] afforded **16** (117 mg) and **17** (54 mg) in 58 and 29% yields, respectively.

iv) A mixture of **13a** (697 mg) in acetone (12 ml) and oxalic acid dihydrate (1.58 g) in water (30 ml) was stirred at 85°C for 4.5 h. After being cooled, the mixture was concentrated to remove acetone, and extracted with ethyl acetate (4×100 ml). The combined extracts were washed with saturated brine, dried, evaporated, and purified by chromatography over silica gel (40 g) with benzene and ethyl acetate to give two spirovetivanes (**20**) and (**21**) in 63% (278 mg) and 23% (93 mg) yields, respectively, the latter (**21**) being identified as (±)-10-epi-β-vetivone.[15] **20**, oil; MS, m/z 218 (M^+−18, base); IR, 3480, 1668, 1615, 1383, and 946 cm^{-1}; NMR (CCl_4), δ 0.97 (3H, d, J=7 Hz), 1.18 and 1.95 (6H, and 3H, each s), and 5.65 (1H, br s). Found: C, 76.58; H, 10.13%. Calcd for $C_{15}H_{24}O_2$: C, 76.22; H, 10.24%. **21** [(±)-10-Epi-β-vetivone], mp 52—55°C (from pentane), (lit,[15] 53—54.5°C); MS, m/z 218 (M^+, base); IR (CCl_4), 1681, 1620, and 1386 cm^{-1}; NMR (CCl_4), δ 0.98 (3H, d, J=6 Hz), 1.61 and 1.62 (each 3H, s), and 5.66 (1H, br s). Found: C, 82.76; H, 10.05%. Calcd for $C_{15}H_{22}O$: C, 82.51; H, 10.16%.

v) The *anti-exo* mesylate (**15a**, 67 mg) was treated with oxalic acid (165 mg) in acetone (1.7 ml) and water (3.2 ml) at 85°C for 3 h to give two spirovetivanes (**20**) and (**21**) in 69 (26 mg) and 26% (9 mg) yields, respectively.

(±)-Solavetivone (1). In a glass tube, 11-hydroxysolavetivone (**20**, 50 mg) was finely mixed with pyridine-modified alumina[9] (0.2 g), prepared from neutral alumina (10 g, Woelm, activity grade I) and pyridine (0.2 ml) by stirring under reduced pressure (0.3 Torr) at room temperature for 6 h. The mixture was heated at 220°C (bath temperature) for 8 min under argon, cooled, and poured into ether (30 ml) and triethylamine (5 ml). The whole mixture was stirred for 2 h, and filtered through Celite, concentrated, and chromatographed over silica gel (3 g) with benzene to afford 26 mg (60%) of an isopropenyl compound, oil; MS, m/z 218 (M^+, base); IR, 3100, 1675, 1615, and 855 cm^{-1}; NMR, δ 1.00 (3H, d, J=7 Hz), 1.75 and 1.93 (each 3H, s), 4.74 (2H, s), and 5.74 (1H, s). Found: C, 82.67; H, 10.12%. Calcd for $C_{15}H_{22}O$: C, 82.51; H, 10.16%. The compound was identified as (±)-solavetivone (**1**) by direct comparison with natural solavetivone (MS, IR, NMR, and TLC).

To a solution of (±)-solavetivone (17 mg) in aq methanol (1 ml) at room temperature was added a solution (0.5 ml) of 2,4-dinitrophenylhydrazine (2,4-DNP), prepared from 2,4-DNP (1.0 g) in water (16 ml), 95% ethanol (18 ml), and concd sulfuric acid (3.7 ml). The mixture was stirred for 10 min, and filtrated to leave a red mass, which was dissolved in ether and filtrated. The ether filtrate was concentrated and purified by preparative TLC over silica gel with benzene followed by recrystallization from aqueous methanol to give two 2,4-dinitrophenylhydrazones (**1a**, 10 mg) and (**1b**, 5.5 mg). **1a**, mp 107.5—109°C; NMR, δ 0.99 (3H, d, J=6 Hz), 1.75 and 1.95 (each 3H, s), 4.73 (2H, s), and 6.02 (1H, s). Natural; mp 126°C, NMR, δ 0.99 (3H, d, J=6 Hz), 1.75 and 1.95 (each 3H, s), 4.73 (2H, s), and 6.04 (1H, s). **1b**, mp 137—138° C; NMR, δ 0.96 (3H, d, J=6 Hz), 1.76 and 2.03 (each 3H, s), 4.73 (2H, s), and 6.24 (1H, s). Natural; mp 137°C, NMR, δ 0.97 (3H, d, J=6 Hz), 1.76 and 2.03 (each 3H, s), 4.75 (2H, s), and 6.21 (1H, s).

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17) These compounds should be designated as 2-[3-(1-hydroxy-1-methylethyl)-4-methoxy-6,7-dimethylbicyclo[2.2.2]-oct-5-enyl]ethanols according to the IUPAC numbering rule. However, in order to avoid confusion, we used the same numbering for all bicyclo[2.2.2]octane derivatives as that for B in Scheme 1 in this paper.