Efficient Synthesis of (±)-Solavetivone and (±)-[8,8-$^2H_2$]Solavetivone[1]

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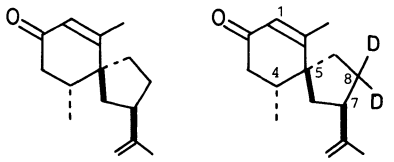
(Received February 6, 1984)

An alternative and efficient synthesis of the title compounds is described. The synthesis involves cycloaddition of 2-methylene-4-methoxy-6-methyl-4-cyclohexenylacetonitrile with methyl vinyl ketone as a key step.

The title sesquiterpene, solavetivone[2] (**1**) is a representative member of the spirovetivane phytoalexins in the genus *Solanum* and has been considered to play an important role in the biosynthetic pathway[3] leading to formation of rishitin, one of the major phytoalexins in the family Solanaceae.[4] While attempts to elucidate this biosynthetic pathway have been made by several groups,[4] the requisite studies with labelled solavetivone have not been performed yet. In the preceding paper we described a general synthetic procedure leading to preparation of representative compounds, (±)-**1** and (±)-hinesol, of two classes of natural spirovetivanes.[1] However the overall yield (3.2%) of (±)-**1** was not always satisfactory for the present biosynthetic studies. This synthetic procedure involved cycloaddition of 4-substituted 3,5-dimethyldihydroanisoles with methyl acrylate, which controlled the relative configuration between the C-4–C-14 and C-5–C-6 bonds in spirovetivanes.[1,5] This stereochemical control in cycloaddition for preferential preparation of (±)-**1** has been improved by introducing a cyanomethyl group to C-4 of the relevant dihydroanisole. The group was less bulky than an ethyl group and converted into desirable functional groups. The result was recently published in preliminary communications,[6] and its details are described in the present paper.

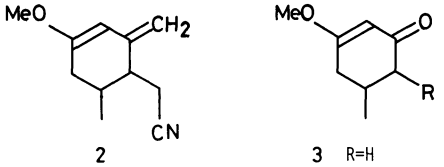


1 [8,8-$^2H_2$] **1**

The dihydroanisole (**2**) in question, equivalent to 4-methoxy-2,6-dimethyl-3-cyclohexenylacetonitrile, was prepared from readily available 3-methoxy-5-methyl-2-cyclohexenone[7] (**3**). Treatment of **3** with lithium diisopropylamide in tetrahydrofuran (THF) followed by addition of chloroacetonitrile in a 1:1 mixture of THF and hexamethylphosphoric triamide (HMPA) afforded 4-methoxy-6-methyl-2-oxo-3-cyclohexenylacetonitrile (**4**), which on the Wittig reaction with methylenetriphenylphosphorane in dimethyl sulfoxide (DMSO) was converted into **2** in 80% yield (from **3**).

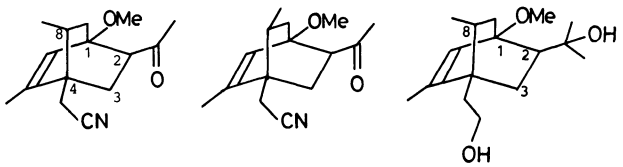
The cycloaddition of **2** was carried out with methyl vinyl ketone in benzene in the presence of dichloromaleic anhydride (DCMA) and 2,6-di-*t*-butyl-*p*-cresol (BHT) under reflux for 3 d, when a mixture of four stereoisomeric cycloadducts differing in the configurations at C-2 and C-8 was obtained in 76% yield (based on the recovered **2**). The mixture was estimated by the NMR spectrum[1] to consist of a 2.7:1.0 mixture of the *endo* and *exo* adducts, each being a 3.5:1.0 mixture of the 8-*anti*- and 8-*syn*-methyl (in respect to the C-2–C-3 bond) isomers. Indeed, the mixture was separated by repeated chromatography over silica gel to give the *anti-endo* (**5**) [δ 0.79 (3H, d, J=6 Hz, 8-CH_3) and 3.02 (1H, dd, J=10 and 6 Hz, 2-H)], *anti-exo* (**6**) [δ 0.73 (3H, d, J=6 Hz) and 2.87 (1H, ddd, J=11, 6, and 1 Hz, long-range coupling between 2-*endo*-H and 7-*anti*-H=1 Hz)], *syn-endo* (**7**) [δ 1.06 (3H, d, J=6 Hz) and 2.99 (1H, dd, J=10 and 6 Hz)], and *syn-exo* adducts (**8**) [δ 1.14 (3H, d, J=6 Hz) and 2.87 (1H, ddd, J=11, 6, and 1 Hz)] in 43, 16, 12, and 4.5% yields, respectively. The result evidently indicated that the cycloaddition proceeded with predominant formation of the desirable *anti* isomers.

The *anti-endo* (**5**) and *anti-exo* adducts (**6**) were transformed by a three-step process [(i) treatment with methyllithium in ether, (ii) reduction with diisobutylaluminium hydride (DIBAH) in ether, and (iii) reduction with sodium borohydride ($NaBH_4$) in THF–water (2:1)] into the corresponding diols (**9**) and (**10**) in 96 and 75% yields, respectively. These diols were identified as the known intermediates[8] for synthesis of (±)-**1** and were smoothly converted into (±)-solavetivone by the procedure described into the preceding paper.[1] The present synthesis involved 9 steps and the overall yield was 16.6%.



2

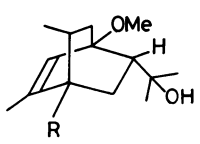
3 R=H
4 R=CH_2CN

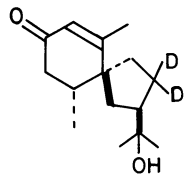


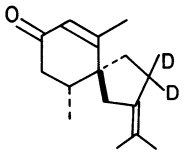
5 2-endo-Ac
6 2-exo-Ac
7 2-endo-Ac
8 2-exo-Ac
9 2-endo-$C(Me)_2OH$
10 2-exo-$C(Me)_2OH$

Preparation of the title deuterium-labelled (±)-solavetivone (±)-[8,8-$^2H_2$] (**1**) started with oxidation of the *anti-endo* bicyclooctene diol (**9**) with Jones reagent[9] into the corresponding acid (**11**) (88%). The acid (**11**) was transformed into the corresponding deuterated diol (**12**) according to the following procedure [(i) ethyl chloroformate and triethylamine in THF and (ii) reduction with sodium borodeuteride ($NaBD_4$, ^2H-content, over 98%) in water].[10] The resulting diol (**12**) exhibited the spectra practically identical with those of **9** with exception of the parent peaks

in the mass spectrum and the C-D stretching bands near 2200 cm^{-1} in the IR spectrum. The diol (**12**) was converted with methanesulfonyl chloride and triethylamine in dichloromethane into the monomesylate (**12a**), which was submitted to ring opening and ring closure (π-cyclization) under the reported conditions[1] [10 mol equiv oxalic acid in 33% aq acetone, 85°C, 4 h], giving two spirovetivanes (**13**) and (**14**) in 58 and 13% yields (from **12**), respectively. The former underwent dehydration by heating with pyridine-modified alumina[11] to give its isopropenyl compound (±)-[8,8-$^2H_2$](**1**) in 64% yield. The deuterated compound revealed the spectra differing from those of (±)-solavetivone only in the following: MS, *m/z* 220 (M^+, 57%) and 218 (M^+−2, 0%) [8,8-$^2H_2$ content, *ca.* 100%]; IR, 2200 and 2100 cm^{-1}. This compound with two deuterium atoms at the inactive site (C-8) of (±)-solavetivone has been found to be effective for elucidation of the relevant biosynthetic pathway.[6b]







11 R=CH_2COOH
12 R=CH_2CD_2OH
12a R=CH_2CD_2OMs

13 **14**

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. 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.

4-Methoxy-6-methyl-2-oxo-3-cyclohexenylacetonitrile (4). To a solution of lithium diisopropylamide, prepared from diisopropylamine (11.5 ml) and 1.5 M butyllithium in hexane (55 ml), in THF (75 ml) at −78°C was added 3-methoxy-5-methyl-2-cyclohexenone (**3**) (10.5 g) in THF (80 ml) under nitrogen over a 20 min period. After being stirred for 15 min, the mixture was added to a solution of HMPA (19.5 ml) and THF (20 ml), and the whole mixture was again stirred for 15 min. To the mixture was added chloroacetonitrile (7.5 ml), and the mixture was warmed gradually to room temperature over a 12 h period under stirring. The solution was poured into saturated brine (200 ml), and extracted with ethyl acetate (EtOAc). The combined extracts were washed with water (200 ml), dried, and concentrated to leave an oily residue, which was separated by chromatography over silica gel (120 g) with benzene and ethyl acetate. The material eluted was recrystallized from ether to give **4** (7.78 g, 58%, 94% based on the recovered starting material), mp 95—97°C; MS, *m/z* 179 (M^+); IR, 2225, 1650, 1610, 1390, 1235, 1168, 1006, and 840 cm^{-1}; NMR (CCl_4), δ 1.18 (2.5H, d, J=6 Hz), 0.96 (0.5H, d, J=6 Hz), 3.64 (3H, s), 5.30 (0.83H, s), and 5.22 (0.17H, s). Found: *m/z* 179.0956. Calcd for $C_{10}H_{13}NO_2$: M, 179.0946.

4-Methoxy-6-methyl-2-methylene-3-cyclohexenylacetonitrile (2). A solution of sodium methylsulfinylmethanide in DMSO was prepared by heating a mixture of sodium hydride (1.07 g as a 60% oil dispersion), washed with hexane, and DMSO (12 ml) at 75—80°C for 30 min under nitrogen. To this solution was added dropwise methyltriphenylphosphonium iodide (8.14 g) in DMSO (20 ml) at 10°C for 10 min, and the mixture was stirred at room temperature for 20 min. Compound **4** (3.00 g) in DMSO (15 ml) was added to this mixture at room temperature during 10 min. The whole suspension was stirred at room temperature for 14 h and then at 45°C for 7.5 h under stirring. The reaction mixture was cooled, poured into 5% aq sodium hydrogencarbonate ($NaHCO_3$, 100 ml) and extracted with ether (4×100 ml). The ether solution was washed with 5% aq $NaHCO_3$, dried, and evaporated to give a reddish syrup, which was separated by chromatography over alumina (180 g) with benzene to afford **2** [1.757 g, 71% based on the recovered starting material (0.505 g)], oil; MS, *m/z* 177 (M^+) and 162 (base); IR, 3080, 2220, 1646, 1608, 1220, 1167, 873 cm^{-1}; NMR (CCl_4), δ 0.99 (3H, d, J=6 Hz), 3.54 (3H, s), 4.72 (2H, s), and 5.17 (1H, s). Found: *m/z* 177.1158. Calcd for $C_{11}H_{15}NO$: M, 177.1153.

(2-Acetyl-1-methoxy-5,8-dimethylbicyclo[2.2.2]oct-5-en-4-yl)-acetonitrile (5)—(8).[12] Compound **2** (1.57 g) was refluxed with methyl vinyl ketone (20 ml), DCMA (10 mg) and BHT (0.1 g) in benzene (20 ml) for 3 d under argon atmosphere. The reaction mixture was concentrated *in vacuo*, and dissolved in ethyl acetate (300 ml). The solution was washed with 2M hydrochloric acid (HCl) (2×40 ml) and 5% aq $NaHCO_3$, dried, and evaporated. The residue was separated by careful chromatography over silica gel (200 g) with benzene and ethyl acetate to give three fractions (total 1.317 g, 60%; 76% based on the recovered starting material).

The first fraction (161 mg) eluted early was a 1:1 (by NMR) mixture of the *syn-exo* and *anti-exo* adducts, and was recrystallised from diisopropyl ether to afford the *syn-exo* adduct (**8**) (47 mg), and the filtrate concentrated gave the *anti-exo* adduct (**6**), (75 mg). The second fraction (296 mg) was a 2:1 (by NMR) mixture of the *anti-exo* and *anti-endo* adducts. The third fraction (850 mg) was a 3:1 (by NMR) mixture of the *anti-endo* and *syn-endo* adducts, and again purified by rechromatography over silica gel (30 g) with benzene–ether (10:1) to afford the *anti-endo* (**5**) (442 mg) and *syn-endo* adducts (**7**) (75 mg).

Each of the adducts exhibited the following physical properties: **8**, mp 103—109°C (from ether); MS, *m/z* 247 (M^+), 177, and 162 (base); IR, 2230, 1710, and 1095 cm^{-1}; NMR, δ 1.14 (3H, d, J=6 Hz), 1.91 (3H, d, J=1 Hz), 2.19 (3H, s), 2.40 (2H, s), 2.87 (1H, ddd, J=11, 6, and 1 Hz), 3.30 (3H, s), 6.07 (1H, br s, W_H=7 Hz). Found: *m/z* 247.1581. Calcd for $C_{15}H_{21}NO_2$: M, 247.1571. **6**, oil; MS, *m/z* 247 (M^+), 177, and 162 (base); IR, 2230, 1718, and 1100 cm^{-1}; NMR, δ 0.73 (3H, d, J=6 Hz), 1.82 (3H, d, J=1 Hz), 2.22 (3H, s), 2.48 and 2.67 (each 1H, d, J=16 Hz), 2.96 (1H, ddd, J=12, 5, and 1.5 Hz), 3.34 (3H, s), 6.12 (1H, br s, W_H=7 Hz). Found: *m/z* 247.1569. Calcd for $C_{15}H_{21}NO_2$: M, 247.1571. **5**, mp 64—67°C (from diisopropyl ether); MS, *m/z* 247 (M^+), 177, and 162 (base); IR, 2230, 1715, 1650, and 1095 cm^{-1}; NMR, δ 0.79 (3H, d, J=6 Hz), 1.78 (3H, d, J=1 Hz), 2.14 (3H, s), 2.63 (2H, s), 3.02 (1H, dd, J=10 and 6 Hz), 3.30 (3H, s), 5.88 (1H, br s, W_H=7 Hz). Found *m/z* 247.1571. Calcd for $C_{15}H_{21}NO_2$: M, 247.1571. **7**, mp 66—67°C (from diisopropyl ether); MS, *m/z* 247 (M^+), 177, and 162 (base); IR, 2225, 1715, 1645, and 1097 cm^{-1}; NMR, δ 1.06 (3H, d, J=6 Hz), 1.95 (3H, d, J=6 Hz), 2.13 (3H, s), 2.40, and 2.56 (each 1H, d, J=16 Hz), 2.99 (1H, dd, J=10 and 6 Hz), 3.30 (3H, s), and 5.82 (1H, br s, W_H=7 Hz). Found: *m/z* 247.1588. Calcd for $C_{15}H_{21}NO_2$: M, 247.1571.

2-[2-(1-Hydroxy-1-methylethyl)-1-methoxy-5,8-dimethylbiocyclo-[2.2.2]oct-5-en-4-yl]ethanols (9) and (10).[12] i) To a stirred solution of the *anti-endo* keto nitrile (**5**) (300 mg) in dry ether (16 ml) at −78°C was added a 1.0 M† methyllithium solution

† 1 M=1 mol dm^{-3}.

in ether (1.82 ml), prepared from methyl iodide (1.6 ml) and lithium (0.4 g) in ether (25 ml). The mixture was stirred for 1 h, poured into water (30 ml), and extracted with ethyl acetate (4×50 ml). The organic layer was washed with saturated brine, dried, and concentrated. The residue was separated by chromatography over silica gel (15 g) with benzene–ethyl acetate (5:1) to afford the starting ketone (59 mg) and hydroxy nitrile (258 mg), oil; MS, *m/z* 263 (M^+), 248, 245, and 177 (base); IR, 3520, 2225, and 1090 cm^{-1}; NMR, δ 0.88 (3H, d, J=6 Hz), 1.00 (6H, s), 1.78 (3H, d, J=1 Hz), 2.58 (2H, s), 3.37 (3H, s), and 6.03 (1H, br s, W_H=7 Hz).

To a stirred solution of the hydroxy nitrile (248 mg, 0.94 mmol) in ether (20 ml) at 0°C under nitrogen was added a 1.55 M solution of DIBAH in hexane (2.44 ml). The mixture was stirred at 0°C for 1 h, mixed with 2 M HCl (5 ml), and stirred for 15 min. The mixture was extracted with ethyl acetate and then worked up as usual to give hydroxy aldehyde (276 mg); IR, 3525 and 1722 cm^{-1}. The aldehyde was used for the next reaction without further purification.

To a mixture of the aldehyde (276 mg) in THF (10 ml) and water (5 ml) at 0°C was added $NaBH_4$ (50 mg) with stirring, and the mixture was stirred for 15 min and then nuetralized with 2 M HCl. The mixture was concentrated *in vacuo* to remove THF, poured into saturated brine, and extracted with ethyl acetate (3×60 ml). The combined extracts were washed with 2 M HCl, 5% aq $NaHCO_3$ and saturated brine, dried, and evaporated to leave an oily residue, which was separated by chromatography over silica gel (14 g) with benzene–ethyl acetate (3:2) to give the starting hydroxy nitrile (83 mg, 33%) and **9** (159 mg, 63%), the latter being identical with the *anti-endo* diol prepared in the previous paper.[1]

ii) The keto nitrile (**6**), (78 mg, 0.316 mmol) was transformed into hydroxy nitrile (64 mg, 77%) in the same manner as mentioned above, oil; MS, *m/z* 263 (M^+), 248, and 177 (base); IR, 3520, 2240, 1645, and 1072 cm^{-1}; NMR, δ 0.87 (3H, d, J=6 Hz), 1.11, and 1.34 (each 3H, s), 1.75 (3H, d, J=1 Hz), 2.56 (2H, s), 3.33 (3H, s) , and 6.17 (1H, br s, W_H=7 Hz).

To a solution of the hydroxy nitrile (63 mg, 0.24 mmol) in ether (6 ml) at 0°C under nitrogen was added a 1.5 M DIBAH solution in hexane (0.7 ml). The mixture was stirred for 2.5 h and worked up as usual to give crude aldehyde (63 mg).

The reduction of the aldehyde (63 mg) under the same conditions as mentioned above [$NaBH_4$ (10 mg) in THF (2.5 ml) and water (1 ml), 0°C, 15 min] afforded crude diol (66 mg), which was separated by chromatography over silica gel (4 g) with benzene–ethyl acetate (3:2) to afford an oily *anti-exo* diol (**10**), (50 mg, 78%). The *exo* diol (**10**) was identical with the *anti-exo* diol, prepared in the previous paper.[1]

(±)-[8.8-$^2H_2$]solavetivone (±)-[8.8-$^2H_2$] (1). i) To a solution of bicyclooctene diol (**9**) (1.67 g) in acetone (100 ml) at 0°C was added Jones reagent (10 ml), and the mixture was stirred for 2 h. When isopropyl alcohol (10 ml) was added to the mixture, green precipitates appeared and were removed by filtration through Celite. The filtrate was concentrated *in vacuo* to leave an oily residue, which was dissolved in ether (100 ml), and washed with 5% aq $NaHCO_3$ (3×30 ml), dried, and concentrated to give the starting diol (**9**) (233 mg). On the other hand, the aq $NaHCO_3$ solution was acidified to pH 2 with 2 M HCl and extracted with chloroform (3×100 ml). The chloroform extracts were dried and evaporated to afford crude acid (1.25 g), oil; IR, 3450, 1730, 1650, 1400, 1390, 1160, and 1090 cm^{-1}; NMR, δ 0.89 (3H, d, J=6 Hz), 1.01 and 1.74 (6H, and 3H, each s), 2.50 and 2.64 (each 1H, d, J=15 Hz), 3.34 and 5.93 (3H and 1H, each s). The acid was used for the next reaction without further purification.

ii) To a mixture of the acid (2.46 g) in THF (50 ml) and triethylamine (Et_3N) (1.5 ml, 1.2 mol equiv) at 0°C was added a solution of ethyl chloroformate (1.0 ml, 1.2 mol equiv) in THF (5 ml) over a 15 min period. The mixture was stirred for 4 h, and the precipitates were removed by filtration and washed with dry THF. The filtrate and THF washings were used for the next reaction.

iii) To a solution of $NaBD_4$ (0.87 g) (^2H content, over 98%) in water (20 ml) at 20°C was added the aforementioned, combined, THF solution over a 50 min period. The mixture was stirred for 5 h, neutralized with 2 M HCl, and concentrated. The residue was extracted with ethyl acetate (4×100 ml), washed with 10% aq sodium hydroxide, dried, evaporated, and separated by chromatography over silica gel (80 g) with benzene–ethyl acetate (1:1) to afford deuterated diol (**12**) (1.65 g), oil; MS, *m/z* 270 (M^+), 255, 184, and 151 (base); IR, 3475, 2190, 2098, 1648, 1400, 1385, 1098, and 1085 cm^{-1}; NMR, δ 0.74 (3H, d, J=6 Hz), 0.98 and 1.74 (6H and 3H, each s), 3.36 (3H, s), and 5.95 (1H, s).

iv) To a mixture of **12** (553 mg) and Et_3N (0.43 ml, 1.5 mol equiv) in dichloromethane (10 ml) at −78°C under nitrogen was added methanesulfonyl chloride (0.17 ml, 1.1 mol equiv) and the solution was stirred for 20 min. The mixture was poured into 5% aq $NaHCO_3$ (50 ml) and extracted with ether (4×70 ml). The ether solution was washed with 5% aq $NaHCO_3$ and saturated brine, dried, and evaporated *in vacuo* to give the corresponding mesylate (705 mg), which was immediatedly used for the next reaction.

v) A mixture of the mesylate (705 mg) and oxalic acid dihydrate (1.66 g) in water (33 ml) and acetone (12 ml) was heated at 85°C for 4 h under stirring. The mixture was neutralized with solid $NaHCO_3$, concentrated, and extracted with ethyl acetate (4×70 ml). The acetate solution was worked up as usual to leave an oily residue, which was separated by chromatography over silica gel (24 g) with benzene–ethyl acetate (3:1) to afford **13** (281 mg) and **14** (60 mg): **13**, oil; MS, *m/z* 238 (M^+), 220 (M^+−18, 28%), and 218 (0%); IR, 3450, 2200, 2100, 1670, 1615, and 1385 cm^{-1}; NMR, δ 0.96 (3H, d, J=7 Hz), 1.22 and 1.94 (6H and 3H, each s), 5.72 (1H, s).

A mixture of **13** (52 mg) and pyridine-modified alumina (0.2 g), prepared from alumina (Woelm, neutral, activity II-III, 10 g) and pyridine (0.2 ml) with stirring at room temperature at 1.6 Torr (1 Torr≈133.322 Pa) for 5 h, was heated in a glass tube at 220°C for 8 min under argon. The residue was dissolved in ether (40 ml) and Et_3N (5 ml), and stirred for 5 h under nitrogen. The mixture was concentrated and purified by chromatography over silica gel (3 g) with benzene–ethyl acetate (20:1) to afford (±)-[8.8-$^2H_2$]**1** (31 mg), oil; MS, *m/z* 220 (M^+, 57.1%), 218 (M^+−2, ~0%), 205 (12.7%), 192 (12.2%), 178 (44.2%), and 136 (base); IR, 3090, 2200, 2100, 1680, 1654, 1619, and 885 cm^{-1}; NMR, δ 1.00 (3H, d, J=7 Hz), 1.76 and 1.94 (each 3H, s), 4.73 (2H, s), and 5.75 (1H, s).

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12) Compounds (**5**)—(**8**) should be designated as (3-acetyl-4-methoxy-6,7-dimethylbicyclo[2.2.2]oct-5-enyl)acetonitrile, and those (**9**) and (**10**) as 2-[3-(1-hydroxy-1-methylethyl)1-4-methoxy-6,7-dimethylbicyclo[2.2.2]oct-5-enyl]-ethanols, respectively, according to the IUPAC numbering rule. However, in this paper we used the same numbering for these bicyclo[2.2.2]octane derivatives as that for the corresponding compounds in the preceding paper.