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A New Synthesis of (±)-Agarospirol and (±)-Hinesol[1]

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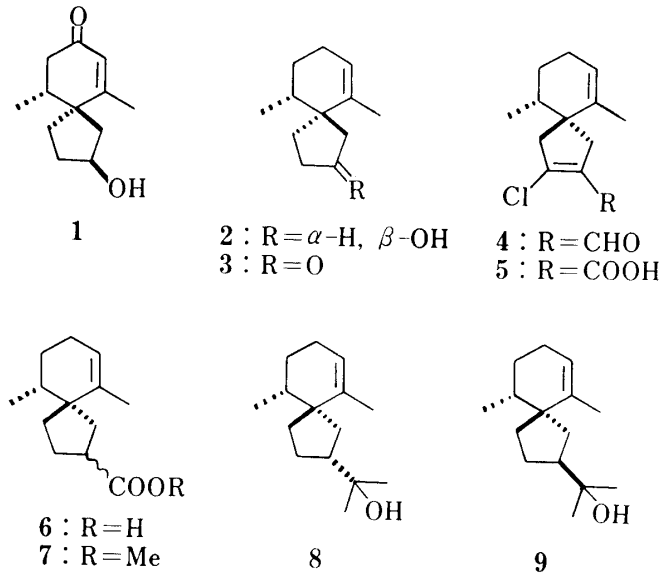
(±)-Agarospirol (**8**) and (±)-hinesol (**9**) were simultaneously synthesized *via* a useful synthon in the synthesis of spirovetivane-type sesquiterpenes, *i.e.*, (2*S**,5*S**,10*R**)-2-hydroxy-6,10-dimethylspiro[4.5]dec-6-en-8-one (**1**), which had previously been prepared from the corresponding phenolic α-diazoketone *via* the spiro-annelation reaction and subsequent stereo-controlled Birch reduction, both reported in our previous communications.

Keywords——(±)-agarospirol; (±)-hinesol; spirovetivane-type sesquiterpenes; useful synthon; (2*S**,5*S**,10*R**)-2-hydroxy-6,10-dimethylspiro[4.5]dec-6-en-8-one

A synthetic intermediate, (2*S**, 5*S**, 10*R**)-2-hydroxy-6,10-dimethyl-spiro[4.5]dec-6-en-8-one (**1**), previously prepared from the corresponding α-diazoketone by means of an effective spiro-annelation reaction[2] and subsequent stereochemically controlled Birch reduction,[3] as described in our recent communications, is a useful synthon for the synthesis of naturally occurring spirovetivane-type sesquiterpenes[4] such as β-vetivone,[5] agarospirol,[6] hinesol,[7] solavetivone,[8] and a series of phytoalexins, that is, lubimin and related compounds.[9]

In our preceding communication,[8] we described the first synthesis of (±)-solavetivone by a route *via* this synthon (**1**).



1
2 : R=α-H, β-OH
3 : R=O
4 : R=CHO
5 : R=COOH
6 : R=H
7 : R=Me
8
9

Chart 1

Several other synthetic routes for agarospirol (**8**)[10] and hinesol (**9**)[10c,11] have been reported, but in the present paper we describe a new synthetic route to **8** and **9** from the synthon (**1**) (see Chart 1).

Thioacetalization of the starting enone (**1**)[8] with ethanedithiol and a catalytic amount of boron trifluoride etherate in methanol, followed by reductive elimination with sodium in liquid ammonia,[12] afforded an alcohol (**2**) in 78% yield. The resulting alcohol was oxidized with pyridinium chlorochromate[13] in methylene chloride to give the corresponding ketone (84% yield) which was identical [infrared (IR) and proton magnetic resonance (PMR)] with the authentic Marshall–Johnson's ketone (**3**),[14a] which has also been synthesized recently by three other groups.[14b–d] On treatment with dimethylformamide and phosphoryl chloride in tetrachloroethylene,[15] **3** was converted into an α,β-unsaturated β-chloroaldehyde (**4**) (70% yield) *in a regioselective* manner. Subsequent oxidation of **4** with silver oxide in a methanol–10% aq. sodium hydroxide mixture yielded the corresponding α,β-unsaturated β-chloroacid (**5**),

which was subjected to the Birch reduction to furnish an epimeric mixture of carboxylic acids (**6**)[16] in 65% yield. After the esterification of **6** with diazomethane in the usual manner, the resulting epimeric ester (**7**) was treated with methyl lithium to give a mixture (in a ratio of *ca.* 1 : 1) of (±)-agarospirol (**8**) and (±)-hinesol (**9**) in a yield of 82%.

Separation of the mixture into each sesquiterpene component was effected by high performance liquid chromatography (HPLC), and the pure samples of (±)-agarospirol (**8**) and (±)-hinesol (**9**) isolated were identical with authentic natural agarospirol[17] and hinesol[7a] [IR (CCl_4), PMR ($CDCl_3$; 200 MHz) and mass spectra (MS), and retention times in HPLC], respectively. Furthermore, their identities were confirmed by comparison of their IR (CCl_4) and PMR ($CDCl_3$; 100 MHz) with those of authentic samples[10c] previously synthesized by an alternative route.

Experimental

Melting points were determined on a Yanagimoto micro-melting point apparatus and are uncorrected. Boiling points are also uncorrected. Ultraviolet (UV) and IR spectra were recorded on a Hitachi 124 spectrophotometer and a Hitachi EPI G-3 spectrometer, respectively. PMR spectra were measured on a Hitachi R-22 (90 MHz), a JEOL FX-100 (100 MHz), and/or a Varian XL-200 (200 MHz) instruments. Unless otherwise noted, IR spectra were taken for solutions in chloroform, and PMR spectra with $CDCl_3$ as the solvent and tetramethylsilane as an internal standard. MS and high resolution MS were measured on a Hitachi RMU-6E and/or a JEOL JMS-D 300 mass spectrometers. HPLC was carried out on a Waters Associates high-pressure liquid chromatograph with an M 6000A pump, a U6K septumless injector, and a Series R 401 differential refractometer. Two semi-micro-bonded silica packed columns [Waters Associates, μPorasil. (7.8 mm *i.d.* × 30 cm of length)] were connected and used with a flow of 3 ml/min of *n*-hexane–ethyl acetate (15: 1). For preparative thin layer chromatography (TLC), Merck Kieselgel PF_{254} was used.

Synthon (1)——The correct stereostructure for the synthon was previously established to be as shown in the formula (**1**) by X-ray crystallography,[8] and the physical constant and spectral properties are as follows; mp 85—86°C (colorless crystals from benzene–MeOH). *Anal.* Calcd for $C_{12}H_{18}O_2$: C, 74.18; H, 9.34. Found: C, 73.91; H, 9.44. IR ν_{max} cm^{-1}: 3608, 3450 (OH), 1665 (α,β-unsaturated ketone), 1618 (double bond). UV λ_{max}^{ether} nm (ε): 238 (15500). PMR (90 MHz) δ: 1.03 (3H, d, J=6.2 Hz, 10-Me), 1.5—2.8 [12H, m, including the signal at δ 1.89 (3H, s, 6-Me)], 4.42 (1H, m, 2-H), 5.71 (1H, br s, 7-H). MS *m/z*: 194 (M^+).

(2*S,5*S**,10*R**)-6,10-Dimethylspiro[4.5]dec-6-en-2-ol (2) from 1 *via* the Thioacetal**——A mixture of **1** (1.2 g), 1,2-ethanedithiol (1.5 ml), and BF_3·etherate (0.5 ml) in dry MeOH was stirred at room temperature. After the reaction was over, 5% aqueous NaOH solution was added, and the resulting mixture was extracted with CH_2Cl_2. The extract was successively washed with 5% aqueous NaOH and water, then dried over Na_2SO_4. Removal of the solvent gave the corresponding thioacetal (1.4 g; 84% yield), mp 150—151.5°C (colorless plates from MeOH). *Anal.* Calcd for $C_{14}H_{22}OS_2$: C, 62.20; H, 8.21; S, 23.67. Found: C, 61.97; H, 8.27; S, 23.87. IR ν_{max} cm^{-1}: 3613, 3450 (OH), 1645 (double bond). PMR (90 MHz) δ: 1.05 (3H, d, J=6 Hz, 10-Me), 1.1—2.4 [13H, m, including the signal at δ 1.66 (3H, d, J=1 Hz, 6-Me)], 3.0—3.6 (4H, m, $-S(CH_2)_2S-$), 4.28 (1H, m, 2-H), 5.46 (1H, br s, 7-H). MS *m/z* (%): 272 (M^++2, 13), 270 (M^+, 100), 242 (23), 237 (30), 210 (35), 209 (83), 158 (58).

The thioacetal (26 mg) obtained as above was dissolved in tetrahydrofuran (5 ml) and liquid ammonia (20 ml), and sodium (100 mg) was added to this solution at −70°C with stirring. The whole mixture was stirred for a further 10 min. After addition of EtOH (1 ml), stirring was continued until the blue mixture solution lost its color. After evaporation of the ammonia, the residual solution was diluted with water and extracted with ether. The extract was worked up as usual, and the residue was purified by preparative TLC [developed with ether–petr. ether (3: 1)] to yield **2** (13.5 mg; 78% yield) as an oil of bp 75—80°C (0.02 mmHg). *Anal.* Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 79.96; H, 11.16. IR ν_{max} cm^{-1}: 3603, 3440 (OH), 1659 (double bond). PMR (90 MHz) δ: 0.99 (3H, d, J=6 Hz, 10-Me), 1.2—2.3 (15H, m), 4.37 (1H, quintet, J=6 Hz, 2-H), 5.30 (1H, br s, 7-H). MS *m/z* (%): 180 (M^+, 33), 162 (82), 147 (93), 120 (100), 105 (85).

(5*S,10*R**)-6,10-Dimethylspiro[4.5]dec-6-en-2-one (3)**——Pyridinium chlorochromate (1.2 g) was added to a solution of **2** (600 mg) in dry CH_2Cl_2 (20 ml), and the mixture was vigorously stirred for 2 h, then diluted with ether (50 ml), and subjected to florisil column chromatography. The column was eluted with ether (200 ml) and the eluate was concentrated by evaporation. The residue was purified by preparative TLC and fractional distillation to give the ketone (**3**) (500 mg; 84% yield) as an oily substance of bp 60—64°C (0.04 mmHg). *Anal.* high resolution MS. Calcd for $C_{12}H_{18}O$ (M^+, *m/z*): 178.136. Found: 178.136. IR ν_{max} cm^{-1}: 1740 (5-membered ring ketone). PMR (90 MHz) δ: 0.94 (3H, d, J=6 Hz, 10-Me), 1.3—2.6 (14H, m), 5.42 (1H, m, 7-H). MS *m/z* (%): 178 (M^+, 67), 121 (44), 120 (67), 107 (100).

(5*S,10*R**)-3-Chloro-6,10-dimethylspiro[4.5]deca-2,6-diene-2-carbaldehyde (4)**——Phosphoryl chloride (0.9 ml) was added slowly to a solution of tetrachloroethylene (10 ml) and dimethylformamide (1.4 ml) at

0°C under a nitrogen atmosphere, and the mixture was stirred for 20 min. A solution of **3** (600 mg) in tetrachloroethylene was then added dropwise and the whole was stirred at 50—60°C for 3 h. To this mixture sodium acetate (2.24 g) in water (6 ml) was slowly added with stirring at below 25°C, and stirring was continued for a further 30 min. The resulting mixture was extracted with chloroform and the extract was washed with water, dried (Na_2SO_4) and concentrated. The residue was subjected to preparative TLC to yield the starting material (recovered) (105 mg; 17% yield) and the α,β-unsaturated β-chloroaldehyde (**4**) (533 mg; 70% yield), an oily substance. *Anal.* high resolution MS. Calcd for $C_{13}H_{17}ClO$ (M^+, m/z): 224.097. Found: 224.097. IR ν_{max} cm^{-1}: 2728, 1660 (α,β-unsaturated aldehyde), 1617 (double bond). PMR (90 MHz) δ: 0.88 (3H, d, J=6.8 Hz, 10-Me), 1.3—1.8 (6H, m), 1.8—3.2 (6H, m, allylic Hs), 5.38 (1H, m, 7-H), 9.98 (1H, s, -CHO). MS m/z (%): 226 (M^++2, 20), 224 (M^+, 51), 182 (55), 108 (98), 93 (100), 91 (63).

(5*S,10*R**)-3-Chloro-6,10-dimethylspiro[4.5]deca-2,6-diene-2-carboxylic Acid (5)**——A solution of **4** (300 mg) in MeOH (3 ml) was added to a mixture of NaOH (3.3 g) and silver oxide [freshly prepared from silver nitrate (2.7 g) and NaOH (0.8 g) in the usual manner] in distilled water (26 ml) with stirring under ice-water cooling, and the resulting mixture was stirred for a further 8 h. After removal of inorganic material by filtration, the filtrate was acidified with conc. HCl and extracted with ether. The extract was worked up as usual and the residue was purified by preparative TLC to afford the corresponding carboxylic acid (**5**) (117 mg; 57% yield) as colorless prisms, mp 125—126°C (from *n*-hexane–benzene). *Anal.* Calcd for $C_{13}H_{17}ClO_2$: C, 64.86; H, 7.12. Found: C, 64.75; H, 7.16. IR ν_{max} cm^{-1}: 3400—2100, 1691 (α,β-unsaturated carboxylic acid), 1630 (double bond). PMR (90 MHz) δ: 0.92 (3H, d, J=6.4 Hz, 10-Me), 1.1—1.8 [6H, m, including the signal at δ 1.63 (3H, d, J=1.4 Hz, 6-Me)], 1.8—2.3 (6H, m, allylic Hs), 5.37 (1H, m, 7-H). MS m/z (%): 242 (M^++2, 10), 240 (M^+, 27), 149 (33), 108 (100), 93 (61).

(2*RS*,5*R,10*R**)-6,10-Dimethylspiro[4.5]dec-6-ene-2-carboxylic Acid (6)**——A solution of **5** (150 mg) in dry tetrahydrofuran was added to a solution of lithium (60 mg) in liquid ammonia with stirring. The mixture was stirred for a further 10 min, then excess ammonium chloride was added and the ammonia was distilled off. The residual mixture was diluted with a large amount of water, acidified by addition of 10% aqueous HCl, and extracted with ether. The extract was treated in the usual manner and the residue was purified by preparative TLC to give the epimeric mixture of carboxylic acids (**6**) (100 mg; 75% yield) as a colorless oil of bp 110—115°C (0.05 mmHg). *Anal.* high resolution MS. Calcd for $C_{13}H_{20}O_2$ (M^+, m/z): 208.146. Found: 208.146. IR ν_{max} cm^{-1}: 3400—2200, 1704 (COOH). PMR (90 MHz) δ: 0.93 (3H, d, J=7.0 Hz, 10-Me), 1.1—2.3 (14H, m), 2.5—3.1 (1H, m, 2-H), 5.32 (1H, m, 7-H). MS m/z (%): 208 (M^+, 34), 149 (66), 121 (100), 105 (81), 103 (50).

Methyl (2*RS*,5*R,10*R**)-6,10-Dimethylspiro[4.5]dec-6-ene-2-carboxylate (7)**——Diazomethane in ether was added to a solution of **6** (50 mg) in dry ether (10 ml) and the solution was allowed to stand at room temperature for 10 min. After the usual work-up, the residue was purified by preparative TLC to yield an epimeric mixture of methyl esters (**7**) (52 mg; 97% yield) as a colorless oil, bp 54—58°C (0.02 mmHg). *Anal.* high resolution MS. Calcd for $C_{14}H_{22}O_2$ (M^+, m/z): 222.162. Found: 222.161. IR ν_{max} cm^{-1}: 1741, 1165 (COOMe). PMR (90 MHz) δ: 0.92 (3H, d, J=6 Hz, 10-Me), 1.1—2.3 (14H, m), 2.5—3.0 (1H, m, 2-H), 3.66 (3H, s, COOMe), 5.31 (1H, m, 7-H). MS m/z (%): 222 (M^+, 42), 162 (60), 147 (48), 121 (100), 120 (87), 95 (97), 93 (65), 91 (54).

(±)-Agarospirol (8) and (±)-Hinesol (9)——A suitable amount of methyl lithium in dry ether was added to a solution of **7** (50 mg) in dry ether, and the mixture was stirred at room temperature for 30 min. After addition of a large amount of ether saturated with water, the ether layer was separated, washed with water, dried over Na_2SO_4 and concentrated. The residue was subjected to preparative TLC and then HPLC separation (5 times recycled) to yield (±)-agarospirol (**8**) (11 mg) [high resolution MS. Calcd for $C_{15}H_{26}O$ (M^+, m/z): 222.198. Found: 222.198. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3600 (OH), 1655 (weak; double bond), 1125, 931. PMR (200 MHz) δ: 0.91 (3H, d, J=6.9 Hz, 10-Me), 1.21 (6H, s, 12- and 13-Mes), 1.68 (3H, fine splitting m, 6-Me), 5.24 (1H, br s, 7-H)] and (±)-hinesol (**9**) (10 mg) [high resolution MS. Calcd for $C_{15}H_{26}O$ (M^+, m/z): 222.198. Found: 222.198. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3600 (OH), 1665 (weak; double bond), 1125, 935. PMR (200 MHz) δ: 0.92 (3H, d, J=6.7 Hz, 10-Me), 1.21 (6H, s, 12- and 13-Mes), 1.68 (3H, fine splitting m, 6-Me), 5.31 (1H, br s, 7-H)] both in pure form. Their identification is dealt with in the main text.

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References and Notes

1) C. Iwata, Y. Ida, K. Miyashita, T. Nakanishi, and M. Yamada, *Chem. Ind.* (London), **1982**, 165.
2) C. Iwata, M. Yamada, Y. Shinoo, K. Kobayashi, and H. Okada, *Chem. Commun.*, **1977**, 888.

3) C. Iwata, K. Miyashita, Y. Ida, and M. Yamada, *Chem. Commun.*, **1981**, 461.
4) *a*) J.A. Marshall, S.F. Brady, and N.H. Andersen, *Fortschr. Chem. Org. Naturst.*, **31**, 283 (1974); *b*) A. Murai, *Yuki Gosei Kagaku Kyokai Shi*, **39**, 893 (1981).
5) J.A. Marshall and P.C. Johnson, *J. Org. Chem.*, **35**, 192 (1970) and references cited therein.
6) K.R. Varma, M.L. Maheshwari, and S.C. Bhattacharyya, *Tetrahedron*, **21**, 115 (1965).
7) *a*) I. Yosioka and T. Kimura, *Chem. Pharm. Bull.*, **17**, 856 (1969); *b*) J.A. Marshall and S.F. Brady, *J. Org. Chem.*, **35**, 4068 (1970).
8) C. Iwata, T. Fusaka, T. Fujiwara, K. Tomita, and M. Yamada, *Chem. Commun.*, **1981**, 463 and references cited therein.
9) A. Stoessl and J.B. Stother, *Can. J. Chem.*, **58**, 2069 (1980) and references cited therein.
10) *a*) M. Mongrain, J. Lafontaine, A. Bélanger, and P. Deslongchamps, *Can. J. Chem.*, **48**, 3273 (1970); *b*) M. Deighton, C.R. Hughes, and R. Ramage, *Chem. Commun.*, **1975**, 662; *c*) T. Ibuka, K. Hayashi, H. Minakata, Y. Ito, and Y. Inubushi, *Can. J. Chem.*, **57**, 1579 (1979).
11) *a*) K. Yamada, K. Aoki, H. Nagase, Y. Hayakawa, and Y. Hirata, *Tetrahedron Lett.*, **1973**, 4967; *b*) G. Büchi, D. Berthet, R. Decorzant, A. Grieder, and A. Hauser, *J. Org. Chem.*, **41**, 3208 (1976); *c*) W.G. Dauben and D.J. Hart, *J. Am. Chem. Soc.*, **99**, 7307 (1977); *d*) D.A. Chass, D. Buddhasukh, and P.D. Magnus, *J. Org. Chem.*, **43**, 1750 (1978); *e*) A. Murai, S. Sato, and T. Masamune, *Tetrahedron Lett.*, **1981**, 1033.
12) *a*) R.E. Ireland, T.I. Wrigley, and W.G. Young, *J. Am. Chem. Soc.*, **80**, 4604 (1958); *b*) D.C. Humber, A.R. Pinder, and R.A. Williams, *J. Org. Chem.*, **32**, 2335 (1967).
13) E.J. Corey and J.W. Suggs, *Tetrahedron Lett.*, **1975**, 2647.
14) *a*) J.A. Marshall and P.C. Johnson, *J. Org. Chem.*, **35**, 192 (1970); *b*) P.M. McCurry Jr., *Tetrahedron Lett.*, **1971**, 1845; *c*) K.P. Subrahamanian and W. Reusch, *Tetrahedron Lett.*, **1978**, 3789; *d*) E. Wenkert, B.L. Buckwalter, A.A. Craveiro, E.L. Sanchez, and S.S. Sathe, *J. Am. Chem. Soc.*, **100**, 1267 (1978).
15) L.A. Paquette, B.A. Johnson, and F.M. Hinga, *Org. Syn.*, **46**, 18 (1966).
16) *cf.*, *a*) R.M. Coates and J.E. Shaw, *J. Org. Chem.*, **35**, 2601 (1970); *b*) J.E. Shaw and K.K. Knutson, *J. Org. Chem.*, **36**, 1151 (1971).
17) Unpublished results. One of us (T.N.) has recently isolated and identified natural (−)-agarospirol from agarwood, and this finding will be reported in the near future.