Preparation of (*R*)-(2-Cyclopentenyl)methanol and the First Total Synthesis of (8*R*,11*R*)-Precapnelladiene

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Synopsis. Enantiometrically pure (*R*)- (2- cyclopentenyl)methanol (**2**) was prepared from ethyl 2-oxocyclopentanecarboxylate. Coupling of **2** with 4,4-dimethyl-3-phenylthio-2-cyclohexenone gave an enol ether, which was converted into (8*R*,11*R*)-precapnelladiene, $[\alpha]_D^{19}=-70.7°$, in 6 steps.

Due to the unique characteristics of an 8-membered ring,[1] various methodologies have been developed for the construction of 8-membered ring natural products.[2] Precapnelladiene (**1**), isolated from the soft coral *Capnella imbricata*,[3] is one such typical terpenoid, and has been synthesized by four groups[4—7] as a *dl*-form. Although the relative stereochemistry of **1** was thus established unambiguously by these syntheses, the absolute stereochemistry has remained uncertain. And although we have no information concerning the absolute configuration of **1**,[8] it is worth synthesizing any enantiomer of **1** in order to clarify its chirotropic properties.

Our strategy concerning the construction of an 8-membered ring system is a cleavage of the C_1–C_6 bond of 6-alkoxybicyclo[4.2.0]octan-2-one (see **5** in Scheme 1) which, in turn, can be derived by the [2+2]photocycloaddition of 3-(3-alkenyloxy)-2-cyclohexenone. Along this line, we have succeeded in a formal total synthesis of (*dl*)-**1**.[7] Since the stereochemistry of **1** can be easily controlled by that of C_1 of (2-cyclopentenyl)methanol (**2**), an asymmetric synthesis of **1** will become possible if optically active **2**[9,10] is available.

The reduction of ethyl 2-oxocyclopentanecaboxylate (**8**) with Baker's yeast[11] (*Saccharomyces cerevisiae*) gave ethyl (1*R*,2*S*)-2-hydoxycyclopentanecaboxylate (**9**) (Scheme 2). The pyrolysis of the xanthate (**10**) afforded ethyl 2-cyclopentene-1-caboxylate (**11**) exclusively in 73% yield. An $LiAlH_4$ reduction of the ester **11** gave (*R*)-(2-cylopentenyl)methanol (**2**), $[\alpha]_D^{24}=+158.9°$ (*c* 1.47, $CHCl_3$). A NMR analysis of the (*S*)-α-methoxy-α-trifluoromethyl-α-phenylacetate (MTPA ester) of **2** showed the presence of no trace of diastereoisomers.

Coupling of the chiral alcohol **2** with a thioenol ether **3** gave quantitatively a regiospecific enol ether **4**. The conversion of **4** to a methylene ketone **7** was performed by following the procedure for *dl*-analogues.[7] The final conversion of **7** to a chiral precapnelladiene (**1**) was carried out according to known procedures,[5] with a slight modification. (8*R*,11*R*)-Precapnelladiene (**1**), thus obtained, showed identical IR and ^1H NMR spectra with those of (*dl*)-analogue, and $[\alpha]_D^{19}=-70.7°$ (*c* 1.1, $CHCl_3$).

Experimental

The melting points are uncorrected. The IR spectra were taken on a JASCO IR Report-100 spectrophotometer. ^1H and ^{13}C NMR spectra were measured in $CDCl_3$, except when otherwise stated, either on a JEOL FX90Q (90 MHz) or on a Brucker AM500 (500 MHz) spectrometer; the chemical shifts were recorded relative to TMS as an internal standard. Specific rotations were observed on a JASCO DIP-181 polarimeter in chloroform. Column chromatographies were performed using either Merck silica gel 60 or Merck aluminium oxide 90, while flash chromatographies using a Wakogel C-300 with the stated solvent. Chiral compounds **1**,**2**, **4**—**7**, and **11** obtained in the present study show identical IR (solution), ^1H and ^{13}C NMR spectra with those of *dl*-analogues.[7] Micro analyses were performed at the Analytical Center, University of Tsukuba.

Ethyl (1*R*,2*S*)-(+)-2-Hydroxycyclopentanecarboxylate (9). According to the Rauk's conditions,[11] ethyl (1*R*,2S)-(+)-2-hydroxycyclopentanecarboxylate (**9**) was prepared from ethyl 2-oxocyclopentanecarboxylate (**8**) by a reduction with dried Baker's yeast, *Saccharomyces cerevisiae* (from S. I. Lesaffre Co.). After removal of the unreacted **8**, **9** was obtained by a Kugelrohr distillation [bath temp: 70—75 °C/1.5 mmHg (1 mmHg=133.322 Pa)] in 64% yield.

9: $[\alpha]_D^{20}=+15.0°$ (*c* 1.59, $CHCl_3$) [Lit,[11] +15.1° (*c* 1.57, $CHCl_3$)].

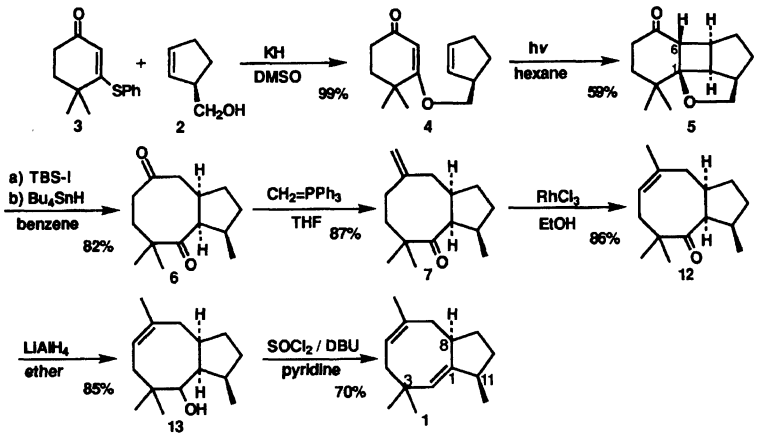
Xanthate 10. A solution of **9** (966 mg, 6.1 mmol) in dry DMSO (5 ml) was treated at room temperature successively with DBU (1.0 ml, 6.7 mmol, 1 h), CS_2 (2.4 ml, excess, 2 h), and methyl iodide (0.8 ml, 12.2 mmol, 1 h). After the solution had been concentrated, it was diluted with ethyl acetate and the organic layer was washed with water and brine. Flash chromatography (benzene–AcOEt=10 : 1) of the residue gave a pure **10** (1.36 g, 90%).

10: IR (CCl_4) 1740, 1220, 1185, and 1060 cm^{-1}; $[\alpha]_D^{24}=-2.9°$ (*c* 1.56). Found: C, 48.12; H, 6.46%. Calcd for $C_{10}H_{16}O_3S_2$: C, 48.36; H, 6.49%.

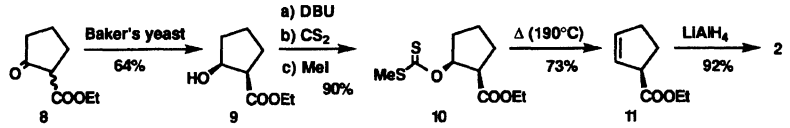
Ethyl (*R*)-2-Cyclopentene-1-carboxylate (11). The xanthate **10** (5.1 g) was placed in a round-bottomed flask equipped with a reflux condenser and heated at 190 °C for 4 h. After cooling to room temperature, the residue was purified by a Kugelrohr distillation (bath temp: 90—105 °C/145 mmHg) to give an ester **11** (2.1 g, 73%).

11: IR (CCl_4) 3060, 1735, and 1180 cm^{-1}; $[\alpha]_D^{25}=+188.5°$ (*c* 1.69).

(*R*)-(+)-(2-Cyclopentenyl)methanol (2). A solution of the ester **11** (2.06 g) in dry ether (5 ml) was added slowly to the suspension of $LiAlH_4$ (800 mg) in ether (30 ml) at 0 °C. The mixture was warmed to room temperature and stirred for 3.5 h. After the usual workup, the residue was purified by a Kugelrohr distillation (bath temp: 90—100 °C/19 mmHg) to afford an alcohol **2** (1.33 g, 92%).



Scheme 1.



Scheme 2.

2: IR (CCl_4) 3630, 3350br, 3050, and 1025 cm^{-1}; $[\alpha]_D^{24}=+158.9°$ (*c* 1.47).

(+)-4,4-Dimethyl-3-[(*R*)-(2-cyclopentenyl)methoxy]-2-cyclohexenone (4). To a suspension of KH (activity 74.7%, 214 mg, 5.33 mmol) in dry DMSO (10 ml), a solution of **2** (359 mg, 3.65 mmol) in DMSO (7 ml) was slowly added, and the mixture was stirred at room temperature for 1 h. A solution of 4,4-dimethyl-3-phenylthio-2-cyclohexenone (**3**, 850 mg, 3.65 mmol) in DMSO (8 ml) was added, and the whole was stirred for 1 h. After pouring into ice water, the products were extracted with ether. The organic layer was washed with water and brine, and dried over Na_2SO_4. Evaporation of the solvent and flash chromatography (CH_2Cl_2–ether=9 : 1) of the residue gave an enol ether **4** (796 mg, 99%).

4: Oil; IR (CCl_4) 1660, 1595, 1195, and 1160 cm^{-1}; $[\alpha]_D^{17}=+129.3°$ (*c* 1.40).

Photocyclization of 4. A solution of **4** (1.61 g) in 840 ml of hexane was degassed and irradiated in a Pyrex test tube with a 400 W high-pressure mercury arc lamp. The reaction was monitored by GLC and stopped when two thirds of the starting material disappeared. After evaporating the solvent, the residue was chromatographed on 10% $AgNO_3/SiO_2$ with CH_2Cl_2–ether (9 : 1) to afford a photoadduct **5** and the starting **4**. The recovered **4** was again irradiated and the combined yield of **5** was 942 mg (59%).

5: Oil; IR (CCl_4) 1695 and 1060 cm^{-1}; $[\alpha]_D^{18}=-53.0°$ (*c* 1.48).

(1*R*,8*R*,11*R*)-(−)-3,3,11-Trimethylbicyclo[6.3.0]-undecane-2,6-dione (6). To a solution of **5** (194 mg, 0.881 mmol) in 2 ml of dry benzene, there was added trimethylsilyl iodide (126 µl, 0.881 mmol); the mixture was then stirred at room temperature. When the starting **5** had been unrecognized on TLC (after 4 h), tributyltin hydride (356 µl, 1.32 mmol) was added and the whole was stirred for 2.5 h. Hexane (3 ml) was added to the mixture and products were adsorbed on alumina. After washing well with hexane, 160 mg (82%) of a diketone **6** was eluted with hexane–benzene (1 : 1).

6: Mp 97—99 °C (from pentane); IR (KBr) 1690 cm^{-1}; $[\alpha]_D^{20}=-73.7°$ (*c* 1.09). Found: C, 75.20; H, 9.63%. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97%.

(1*R*,8*R*,11*R*)-(−)-6-Methylene-3,3,11-trimethylbicyclo[6.3.0]undecan-2-one (7). Butyllithium hexane solution (1.61 M, 348 µl, 0.56 mmol, 1 M=1 mol dm^{-3}) was added at −78 °C to a suspension of methyltriphenylphosphonium bromide (214 mg, 0.60 mmol) in dry THF (2.2 ml); the mixture was then stirred at room temperature for 2 h. A solution of the diketone **6** (89 mg, 0.40 mmol) in THF (2 ml) was added, and the whole was stirred for 1.5 h. After diluting with pentane, the organic layer was washed with water and brine, and dried over Na_2SO_4. Evaporation of the solvent and chromatography of the residue on alumina (benzene) gave **7** (77 mg, 87%).

7: Mp 96—98 °C (from MeOH); IR(KBr) 3060, 1680, 1635, and 890 cm^{-1}; $[\alpha]_D^{20}=-51.8°$ (*c* 0.93). Found: C, 81.48; H, 11.05%. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98%.

Erratum: 40.2(d) should be read as 40.2(t) in ^{13}C NMR spectrum reported in Ref. 7.

(8*R*,11*R*)-(−)-Precapnelladiene (1). A solution of **7** (110 mg, 0.50 mmol) and $RhCl_3 \cdot 3H_2O$ (55 mg, 2.5 mmol) in dry ethanol (10 ml) was refluxed for 6 h. After the removal of reagents by passing through a short alumina column, the products were chromatographed on alumina (hexane–benzene=2 : 1) to give an isomeric olefin **12** (95 mg, 86%); oil; IR (CCl_4): 1690 cm^{-1}; ^1H NMR δ=5.41 (br.t, 1H, J=8.1 Hz), 3.21 (t, 1H, J=6.3 Hz), 1.74 (br.s, 3H), 1.19 (s, 3H), 1.05 (s, 3H), and 0.88 (d, 3H, J=7.2 Hz).

A solution of **12** (72 mg) in dry ether was added to the suspension of $LiAlH_4$ (32 mg) in ether cooled with ice water; the mixture was then stirred for 1.5 h at room temperature. After the usual workup, the products were purified by chromatography on alumina (hexane–benzene=2 : 1) to afford an alcohol **13** (62 mg, 85%); oil; IR (CCl_4) 3640 and 1045 cm^{-1}; ^1H NMR δ=5.35 (br.t, 1H, J=8.1 Hz), 3.48 (d, 1H, J=6.3 Hz), 1.74 (br.s, 3H), 1.02 (s, 3H), 0.96 (d, 3H, J=7.2 Hz),

and 0.85 (s, 3H).

To a solution of **13** (53 mg, 0.1 mmol) in dry pyridine (2.7 ml) cooled at 0 °C, DBU (286 μl, 1.9 mmol) and thionyl chloride (87 μl, 0.5 mmol) were added successively. After stirring for 30 min at room temperature, pentane and a 1 M NaOH solution were added; the products were then extracted with pentane. The organic layer was washed with saturated $CuSO_4$, saturated $NaHCO_3$, brine and dried over Na_2SO_4. The solvent was removed and the residue was chromatographed on alumina (hexane–benzene=2:1) to afford (8*R*,11*R*)-precapnelladiene (**1**) (34 mg, 70%).

1: Oil; $[\alpha]_D^{19}=-70.7°$ (*c* 1.11); ^{1}H NMR (500 MHz) δ=5.328 (1H, br.t, J=8.5 Hz), 5.016 (1H, br.s), 3.506 (1H, dt, J=12.9 and 6.5 Hz), 2.894 (1H, dd, J=13.8 and 8.8 Hz), 2.385 (1H, m), 2.364 (1H, br. dd, J=16.0 and 6.6 Hz), 1.745 (1H, m), 1.720 (1H, dd, J=16.0 and 12.9 Hz), 1.699 (1H, m), 1.625 (3H, br.s), 1.555 (1H, dd, J=13.8 and 8.8 Hz), 1.405 (1H, dd, J=10.8 and 6.5 Hz), 1.223 (1H, m), 1.036 (3H, d, J=6.9 Hz), 0.981 (3H, s), and 0.966 (3H, s); ^{13}C NMR (125 MHz) δ=22.1 (q), 26.7 (q), 29.9 (q), 31.4 (q), 31.5 (t), 33.7 (t), 38.8 (t), 38.9 (d), 39.7 (s), 40.5 (d), 42.5 (t), 121.9 (d), 130.4 (d), 136.4 (s), and 145.6 (s). Found: *m/z* 204.1883. Calcd for $C_{15}H_{24}$: M, 204.1879.

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