Formal Synthesis of *dl*-Plinol B

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The highly functionalized cyclopentenone (3), obtainable by facile silica-gel-catalyzed air oxidation of the cyclopentenone (2), was converted to the key intermediate for the synthesis of *dl*-plinol B.

Keywords plinol B; selective reduction; air oxidation; pyridinium dichromate-oxidation; lactone formation; trisubstituted cyclopentane

Previously, we reported that the cyclopentenone (**2**) obtained by base-catalyzed cyclization of the 1,4-diketone (**1**) underwent facile air-oxidation during silica-gel column chromatography to afford two oxygenated products, **3** and **4**, in 48% and 21% yields, respectively.[1] The highly functionalized **3** seems to have attractive functional groups for the synthesis of natural products containing a five-membered ring. That is to say, this compound has a conjugated enone (required for 1,4-addition), and a quaternary carbon with two substituents (alcohol and ester), which may be converted to the carbonyl function *via* reduction of the ester function and subsequent oxidation with $NaIO_4$. It is also possible to introduce appropriate substituents at each position on the five-membered ring. Furthermore, optically active **3** can be prepared by microbial reduction (*Rhodotorula rubra* CCY 20-7-1). The above structural advantages were confirmed by the syntheses of α- and β-cuparenones, cuparene, laurene,[2] and prostaglandin E[3] from **3** or its analogues.

Now, we describe the synthesis of plinol B from **3**. Plinols A, B, C, and D have been prepared from (3*R*)-(−)-linalool *via* the ene reaction (heating at 650 °C) and subsequent isolation by gas chromatography, and it was found that the fraction of higher boiling point obtained from camphor oil consists of plinol D.[4] The Pd-catalyzed hydrogenation of (±)-**3** proceeded in stereocontrolled fashion to afford a single stereoisomer (**5**)[5] after treatment with CH_2N_2; the stereochemistry of **5** is appropriate for the synthesis of plinol B.

Treatment of **5** with ethanedithiol/BF_3–etherate afforded the dithioacetal (**6**) in 85% yield, and subsequent desulfurization with Raney Ni afforded the diester (**7**) in 92% yield. Selective reduction[6] of only the α-hydroxy ester in the presence of two methyl esters to the diol (**8**) was accomplished by using borane–methyl sulfide complex (BH_3–Me_2S) in 50% yield, and **8** was converted to the monotosylate (**9**) in a usual manner. Reduction of **9** with $LiEt_3BH$[7] afforded the dimethyl compound (**10**) (64% from **8**), in which the *cis* configuration of the dimethyl function, as assumed from the stereochemistry of **5**, was supported by the nuclear Overhauser effect difference spectrum (NOEDS). Oxidation of **10** with pyridinium dichromate (PDC) gave two products, the aldehyde (**11**) (22%) and the lactone (**12**) (28%). The lactone **12** may be formed from **11**

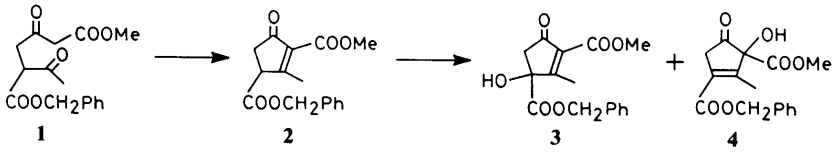


Chart 1

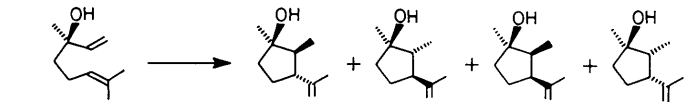
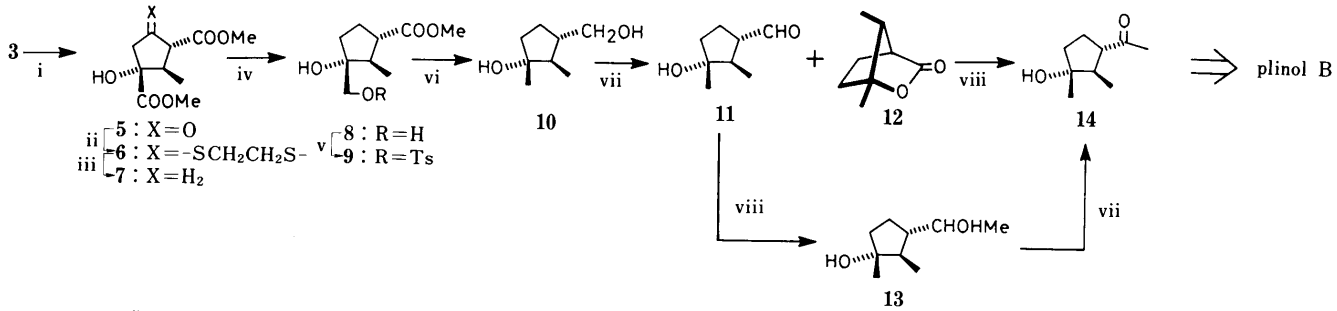


Chart 2



reagents; i) a; H_2/10% Pd–C, b; CH_2N_2, ii) ethanedithiol/BF_3, iii) Raney Ni, iv) BH_3–Me_2S, v) TsCl, vi) $LiEt_3BH$, vii) PDC, viii) MeLi

Chart 3

via the facile lactol formation between the aldehyde and the tertiary alcohol, which should be *cis*. Treatment of **11** with MeLi followed by PDC oxidation afforded the key intermediate (**14**)[4c,8] for the synthesis of *dl*-plinol B ((1*RS*,2*RS*,3*SR*)-1,2-dimethyl-3-isopropenyl-1-cyclopentanol). Similarly, compound **12** was also converted to **14**. Compound (−)-**3**,[1] which is obtainable from (±)-**3** by using a microbial procedure, should be similarly convertible to (−)-plinol B.

Experimental

Infrared (IR) spectra were measured on a JASCO A-202 spectrometer, and proton nuclear magnetic resonance (^{1}H-NMR) spectra were measured on a JEOL JNM-PS-100 or JEOL JNM-FX-100 spectrometer. Mass spectra (MS) were taken on a JEOL JMS-D 300 spectrometer. For column chromatography, silica gel (Merck, Kieselgel 60, 70—230 mesh) was used. Thin layer chromatography (TLC) was performed on Silica gel F_{254} plates (Merck). All organic solvent extracts were washed with brine and dried over anhydrous sodium sulfate. The percentage composition of solvent systems in column chromatography refers to v/v.

(2*RS*,3*RS*,4*RS*)-4-Hydroxy-2,4-bis(methoxycarbonyl)-3-methylcyclopentanone (5) A solution of **3** (420 mg) in MeOH (10 ml) was hydrogenated in the presence of 10% Pd–C (0.42 g) under an H_2 atmosphere at 0 °C. The catalyst was filtered off and the filtrate was concentrated *in vacuo* to afford an oily residue, which was treated with CH_2N_2 in the usual manner. The crude product was purified by column chromatography on silica gel. The fraction eluted with 20% AcOEt in hexane afforded **5** (206 mg, 65%) as colorless needles, mp 103—104 °C (acetone–hexane).[1] IR (Nujol): 3440, 1715, 1455 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.07 (3H, d, J=7 Hz, Me), 2.73, 2.81 (1H each, d, J=18 Hz, C_5-H), 3.79, 3.84 (3H each, s, COOMe). MS *m/z*: 230 (M^+), 212, 180.

(2*SR*,3*RS*,4*RS*)-4-Hydroxy-2,4-bis(methoxycarbonyl)-3-methyl-1-cyclopentanone Ethylene Dithioacetal (6) Ethanedithiol (910 mg) was added to a stirred solution of **5** (1.48 g) in CH_2Cl_2 (15 ml) in the presence of BF_3–etherate (0.4 ml) at 0 °C, and the whole was stirred for 4 h at room temperature. The reaction mixture was diluted with water, and extracted with ether. The ether extract was washed with 5% aqueous $NaHCO_3$, and brine, then dried. Removal of the solvent *in vacuo* afforded an oily residue, which was purified by silica-gel column chromatography. The fraction eluted with 10—20% AcOEt in hexane afforded **6** (1.65 g, 85%) as a colorless oil. IR (neat): 3500, 1730 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.94 (3H, d, J=7 Hz, Me), 2.64, 3.08 (1H each, d, J=15 Hz, C_5-H), 3.15—3.39 (5H, m), 3.76, 3.84 (3H each, s, COOMe). MS *m/z*: 306 (M^+), 279, 137.

(1*RS*,2*RS*,3*SR*)-1,3-Bis(methoxycarbonyl)-2-methyl-1-cyclopentanol (7) Raney Ni (W-2, 15 ml) was added to a stirred solution of **6** (1.38 g) in MeOH (15 ml) at room temperature, and the whole was heated under reflux for 2 h. The precipitate was filtered off, and the filtrate was concentrated *in vacuo* to leave an oily residue, which was subjected to column chromatography on silica gel. The fraction eluted with 10—20% AcOEt in hexane afforded **7** (896 mg, 92%) as a colorless oil. IR (neat): 3500, 1730 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.93 (3H, d, J=7 Hz, Me), 3.70, 3.80 (3H each, s, COOMe). MS *m/z*: 216 (M^+), 157, 97.

(1*RS*,2*RS*,3*SR*)-1-Hydroxymethyl-3-methoxycarbonyl-2-methyl-1-cyclopentanol (8) BH_3–Me_2S (0.54 ml, 6.08 mmol) was added to a stirred solution of **7** (620 mg, 2.87 mmol) in tetrahydrofuran (THF) (25 ml) at 0 °C under an Ar atmosphere. After being stirred for 2 h at room temperature, the reaction mixture was diluted with MeOH. Removal of the solvent *in vacuo* afforded an oily residue, which was purified by column chromatography on silica gel. The fraction eluted with 70% AcOEt in hexane afforded **8** (269 mg, 50%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.02 (3H, d, J=7 Hz, Me), 3.55, 3.60 (1H each, d, J=11 Hz, CH_2O), 3.72 (3H, s, COOMe) (the IR spectrum and MS were not measured).

(1*RS*,2*RS*,3*SR*)-3-Methoxycarbonyl-2-methyl-1-*p*-toluenesulfonyloxymethyl-1-cyclopentanol (9) *p*-Toluenesulfonyl chloride (*p*-TsCl) (435 mg, 2.28 mmol) and 4-dimethylaminopyridine (DMAP) (28 mg, 0.23 mmol) were successively added to a stirred solution of **8** (214 mg, 1.14 mmol) in pyridine (3 ml) at 0 °C, and the whole was stirred for 22 h at room temperature. The reaction mixture was diluted with 5% aqueous $NaHCO_3$, and extracted with ether. The ether extract was successively washed with 3% aqueous HCl, 5% aqueous $NaHCO_3$, and brine, then dried. Removal of the solvent *in vacuo* afforded an oily residue, which was subjected to column chromatography on silica gel. The fraction eluted with 10—20% AcOEt in hexane afforded **9** (311 mg, 80%) as a colorless oil. IR (neat): 3500, 1730, 1360, 1175 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.95 (3H, d, J=7 Hz, Me), 3.68 (3H, s, COOMe), 3.99 (2H, s, CH_2O), 7.33, 7.81 (2H each, d, J=8 Hz, Ar-H). MS *m/z*: 342 (M^+), 312, 228, 91.

(1*RS*,2*RS*,3*SR*)-1,2-Dimethyl-3-hydroxymethyl-1-cyclopentanol (10) $LiEt_3BH$ (1.0 M in THF, 3.5 ml, 3.5 mmol) was added to a stirred solution of **9** (300 mg, 0.88 mmol) in THF (5 ml) at 0 °C under an Ar atmosphere, and the whole was heated under reflux for 3 h. The reaction mixture was diluted with water, and extracted with AcOEt. The AcOEt extract was dried, and concentrated *in vacuo* to afford an oily residue, which was purified by column chromatography on silica gel. The fraction eluted with 30% AcOEt in hexane afforded **10** (100 mg, 79%) as a colorless oil. IR (neat): 3610, 3375, 1450, 1110 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.94 (3H, d, J=7 Hz, C_2-Me), 1.20 (3H, s, C_1-Me), 3.63 (2H, d, J=4.0 Hz, CH_2). MS *m/z*: 144 (M^+), 126, 108.

(1*RS*,2*RS*,3*SR*)-1,2-Dimethyl-3-formyl-1-cyclopentanol (11) and (1*RS*,4*SR*,7*RS*)-1,7-Dimethyl-2-oxabicyclo[2.2.1]heptan-3-one (12) PDC (1.05 g, 2.77 mmol) was added portionwise to a stirred solution of **10** (100 mg, 0.69 mmol) in CH_2Cl_2 (3 ml) at 0 °C. The mixture was stirred for 5 h at room temperature, then the excess reagent was decomposed with isopropanol (0.3 ml), and the reaction mixture was diluted with ether. The precipitate was filtered off, and the filtrate was concentrated *in vacuo* to leave an oily residue, which was subjected to silica-gel column chromatography. The fraction eluted with 10% AcOEt in hexane afforded **12** (27 mg, 28%) as a colorless oil. IR ($CHCl_3$): 1765, 1390, 1045 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.92 (3H, d, J=7 Hz, C_7-Me), 1.47 (3H, s, C_1-Me), 1.75—1.82 (3H, m), 2.07 (1H, m), 2.17 (1H, q, J=7 Hz), 2.60 (1H, d, J=4 Hz). MS *m/z*: 140 (M^+), 112, 95, 79. The fraction eluted with 20% AcOEt in hexane afforded **11** (22 mg, 22%) as a colorless oil. IR ($CHCl_3$): 3600, 1715, 1380 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.00 (3H, d, J=7 Hz, C_2-Me), 1.23 (3H, s, C_1-Me), 1.50—2.20 (6H, m), 2.37 (1H, m), 9.67 (1H, d, J=2 Hz, CHO). MS *m/z*: 142 (M^+), 124, 109.

(1*RS*,2*RS*,3*SR*)-1,2-Dimethyl-3-(1-hydroxyethyl)-1-cyclopentanol (13) MeLi (1.04 M in ether, 0.3 ml, 0.3 mmol) was added to a stirred solution of **11** (17 mg, 0.12 mmol) in ether at 0 °C under an Ar atmosphere. After 3 h, the reaction mixture was diluted with 5% aqueous NH_4Cl, and the precipitate was filtered off. The filtrate was concentrated *in vacuo* to leave an oily residue, which was purified by preparative TLC, and the alcohol **13** (12 mg) was obtained as a colorless oil. IR ($CHCl_3$): 3610, 3420 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.93, 0.94 (1.5H each, d, J=7 Hz, C_2-Me), 1.16, 1.20 (1.5H each, d, J=6 Hz, Me), 1.22 (3H, s, C_1-Me), 2.47 (1H, br, OH), 3.80, 3.94 (0.5H each, dq, J=3, 6 Hz, C<u>H</u>(OH)). MS *m/z*: 158 (M^+), 140, 122.

(1*RS*,2*RS*,3*SR*)-3-Acetyl-1,2-dimethyl-1-cyclopentanol (14) Compound **13** (10 mg) was oxidized to **14** (8 mg) in a manner similar to that described for oxidation of **10**. **14**: Colorless oil. IR ($CHCl_3$): 3420, 1695, 1360, 1175, 1110 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.96 (3H, d, J=7 Hz, C_2-Me), 1.19 (3H, s, C_1-Me), 1.61—1.97 (6H, m), 2.20 (3H, s, COMe), 2.61 (1H, m). MS *m/z*: 156 (M^+), 138, 95. High-MS for $C_9H_{16}O_2$ (M^+): Calcd *m/z*: 156.11494. Found: 156.11512. Alkylation of **12** (11 mg) with MeLi, in a manner similar to that described for alkylation of **11**, also afforded **14** (7 mg).

References and Notes

1) K. Okano, Y. Mizuhara, H. Suemune, H. Akita and K. Sakai, *Chem. Pharm. Bull.*, **36**, 1358 (1988).
2) K. Okano, H. Suemune and K. Sakai, *Chem. Pharm. Bull.*, **36**, 1379 (1988).
3) K. Okano, H. Suemune and K. Sakai, *Chem. Pharm. Bull.*, **37**, 1995 (1989).
4) *a*) H. Strickler, G. Ohloff and E. sz. Kovats, *Helv. Chim. Acta*, **50**, 759 (1967); *b*) For the synthesis of plinols A and C, see S. Tanimori, Y. Mitani, M. Chikai, S. Ohira and M. Nakayama, *Agric. Biol. Chem.*, **51**, 2861 (1987); *c*) T. Imagawa, K. Matsuura, N. Murai, T. Akiyama and M. Kawanishi, *Bull. Chem. Soc. Jpn.*, **56**, 3020 (1983).
5) The relative configuration in the optically active (−)-**5** was determined as 2*R**,3*R**,4*R** by X-ray analysis. See reference 1.
6) Selective reduction of only the α-hydroxy ester in the presence of the two other esters may be a result of neighboring-group assistance by the OH function.
7) Reduction with $(Bu)_3SnH$ resulted in the formation of a complex mixture.
8) The spectral data for **14** were identical with the reported values. See reference 4*a*.