Stereoselective Syntheses of 3-Acetyl-1,2-dimethyl-1-cyclopentanols. Syntheses of *dl*-Plinols A, B, and C

Takeshi IMAGAWA, Kazuyuki MATSUURA, Nobuyuki MURAI, Tetsuo AKIYAMA, and Mituyosi KAWANISI*

Department of Industrial Chemistry, Faculty of Engineering, Kyoto University, Sakyo-ku, Kyoto 606

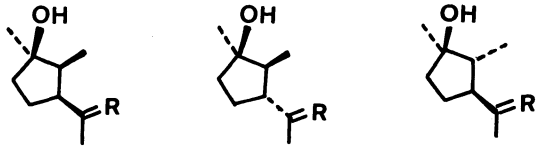
(Received May 9, 1983)

c- and *t*-3-Acetyl-1,*c*-2-dimethyl-*r*-1-cyclopentanols and *c*-3-acetyl-1,*t*-2-dimethyl-*r*-1-cyclopentanol are synthesized stereoselectively and *dl*-plinols A, B, and C are prepared therefrom.

Isomeric 3-acetyl-1,2-dimethyl-1-cyclopentanols have been obtained by ozonolysis of four isomeric plinols separated gas-chromatographically from a mixture of A, B, C, and D, which was derived from linalool by ene reaction.[1] Meanwhile, the title cyclopentanols have been recognized[2] as the key substance for synthesis of a variety of terpenoids. For instance, cyclonerodiol, a biogenetically important fungal metabolite, has been synthesized from an isomer of the cyclopentanols.[3] However, procurement of the aforementioned plinols in stereochemically pure state is not necessarily easy task. Therefore, facile preparation of each cyclopentanol isomer seems highly desirable.

In this report we wish to describe a streoselective synthesis of *c*- and *t*-acetyl-1,*c*-2-dimethyl-*r*-1-cyclopentanols (**1** and **2**, respectively) and *c*-3-acetyl-1,*t*-2-dimethyl-*r*-1-cyclopentanol (**3**) by a methodology based on Wagner-Meerwein rearrangement of 7-oxabicyclo[2.2.1]hept-2-yl cation to 2-oxabicyclo[2.2.1]hept-3-yl cation employing anodic oxidative decarboxylation.[4]

Additionally the transformation of the cyclopentanols into *dl*-plinols A, B, and C is described.



1 : R = O 2 : R = O 3 : R = O

6 : R = CH_2 4 : R = CH_2 5 : R = CH_2

Results and Discussion

The anhydride **8**,[5] obtained from the Diels-Alder adduct (**7**) of maleic anhydride and 2,5-dimethylfuran followed by hydrogenation, was reduced by sodium borohydride to give lactone **9**. Lactone **9** was treated with benzenethiolate anion to afford carboxylic acid **10**. Raney nickel desulfurization of **10** gave *exo*-methyl carboxylic acid **11** in 31% overall yield from **7**.

Acid **11** was electrolyzed in methanolic solution with addition of sodium methanolate using graphite electrodes to give cyclic acetal **12**.[4] Addition of aqueous acetic acid to this mixture gave ketone **1** in 84% yield. The configuration of this compound was obvious from consideration of the reaction course as well as from comparison with the reported data.[1] It was further established by transformation into *dl*-plinol C (**6**) as follows.

Methylenation of **1** with dibromomethane–zinc–titanium tetrachloride[6] gave exclusively *dl*-plinol C (**6**) in 50% yield. Its structure was confirmed by comparison with the reported spectral data.[1]

Alternatively the methyl ketone **1** was efficiently epimerized[1,3] to isomeric ketone **2** which was a synthetic intermediate for cyclonerodiol.[3] Methylenation of ketone **2** in the same manner yielded *dl*-plinol A (**4**) in 66% yield.

The *endo*-anhydride **17** obtained from the Diels-Alder adduct (**13**) of 2,5-dimethylfuran and dimethyl acetylenedicarboxylate gave lactone **18** by sodium borohydride reduction. Cleavage of lactone **18** by benzenethiolate anion, followed by desulfurization gave *endo*-methyl carboxylic acid **20** isomeric to **11** in 77% yield.

Similarly, electrolysis of **20** followed by hydrolysis gave stereoselectively *trans*-methyl ketone **3** in 63% yield. Methylenation of **3** gave *dl*-plinol B (**5**) in 51% yield.

In summary three isomeric 3-acetyl-1,2-dimethyl-1-cyclopentanols were prepared in stereochemically pure form and it was demonstrated that they are useful starting materials for synthesis of natural products.

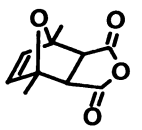
Experimental

All mp's were uncorrected. Distillation was performed on a Buchi Kugelrohr apparatus. ^{1}H-NMR spectra were obtained with a Varian EM-360 or EM-390 spectrometer using tetramethylsilane as an internal standard. ^{13}C-NMR spectra were obtained with a Varian CFT-20 spectrometer in $CDCl_3$ solution unless otherwise noted, using tetramethylsilane as an internal standard. IR spectra were recorded with a Shimazu IR-27 spectrophotometer as Nujol mull.

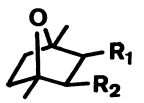
Synthesis of c-3-Acetyl-1,c-2-dimethyl-r-1-cyclopentanol (1).

(a) Hydrogenation of 7: Hydrogenation of 5.23 g (26.9 mmol) of **7** in 30 ml of ethyl acetate using palladium black catalyst (0.5 g) gave 5.03 g (95%) of the product **8** after filtration, removal of the solvent and distillation; mp 126.2—126.7 °C (lit,[5] 121.5 °C); ^{1}H-NMR ($CDCl_3$): δ=3.16 (s, 2H), 1.81 (s, 4H), 1.64 (s, 6H).

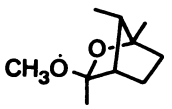
(b) exo-3-Hydroxymethyl-1,4-dimethyl-7-oxabicyclo[2.2.1]heptane-exo-2-carboxylic Lactone (9): To an ice-cooled and stirred solution of 2.8 g (73.7 mmol)of $NaBH_4$ in 100 ml of dry EtOH 9.03 g (46.0 mmol) of the anhydride **8** was added slowly. After the evolution of the reaction heat subsided, the reaction mixture was kept for 3 h at room temp and 35 ml of 5 M hydrochloric acid (1 M=1 mol dm^{-3}) was added with cooling in an ice bath. The solution was diluted with water and extracted with dichloromethane. The organic layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Distillation gave 7.41 g (88%) of **9**; bp 116—117 °C/3 kPa; ^{1}H-NMR ($CDCl_3$): δ=4.5—4.1 (m, 2H), 2.2—2.9 (2H), 1.74 (m, 4H), 1.59 (s, 3H), 1.47 (s, 3H); ^{13}C-NMR: δ=176.6 (s), 85.8 (s),



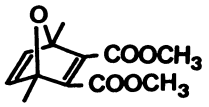
7



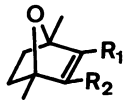
8 : R_1,R_2 = -COOCO-
9 : R_1,R_2 = $-CH_2OCO-$
10 : R_1 = CH_2SPh, R_2 = COOH
11 : R_1 = CH_3, R_2 = COOH



12



13



14 : R_1 = R_2 = COOMe
15 : R_1 = R_2 = COOH

16 : R_1 = R_2 = COOH
17 : R_1 = R_2 = -COOCO-
18 : R_1 = R_2 = $-CH_2OCO-$
19 : R_1 = CH_2SPh, R_2 = COOH
20 : R_1 = CH_3, R_2 = COOH

85.0 (s), 68.7 (t), 52.7 (d), 48.0 (d), 38.7 (t), 37.5 (t), 18.0 (q), 17.4 (q); MS: *m/e* 182 (M^+, 1), 124, 98 (100), 97, 43. Found: C, 66.20; H, 7.83%. Calcd for $C_{10}H_{14}O_3$: C, 65.92; H, 7.74%.

*(c) 1,4-Dimethyl-*exo*-3-phenylthiomethyl-7-oxabicyclo[2.2.1]-heptane-*exo*-2-carboxylic Acid (**10**)*: Sodium benzenethiolate, freshly prepared from 0.74 g (32 mmol) of Na and 3.5 ml (34 mmol) of benzenethiol by stirring overnight at room temp. and evaporation of the solvent (THF), and 2.374 g (13.03 mmol) of **9** were dissolved in 25 ml of DMF. The solution was heated at 130 °C for 16 h. After having been cooled to room temp, the reaction mixture was acidified with 20 ml of 2 M hydrochloric acid and extracted with dichloromethane. The organic layer was extracted with 2% aq NaOH four times (30 ml×2, 20 ml×2). The combined aqueous layer was acidified and extracted with diethyl ether. The organic layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Crude crystals thus obtained were recrystallized from benzene to give 2.468 g (65%) of pure **10**; mp 122.0—124.0 °C; ^{1}H-NMR ($CDCl_3$): δ=7.4 (m, 5H), 3.3—2.9 (3H), 2.42 (m, 1H), 1.70 (bs, 4H), 1.52 (s, 3H), 1.48 (s, 3H); ^{13}C-NMR: δ 177.4 (s), 135.7 (s), 129.9 (d), 128.9 (d), 126.3 (d), 85.2 (s), 84.9 (s), 56.1 (d), 49.8 (d), 39.3 (t), 38.7 (t), 33.0 (t), 18.3 (q), 17.8 (q) Found: C, 65.57; H, 6.98; S, 11.13%. Calcd for $C_{16}H_{20}O_3S$: C, 65.73; H, 6.89; S, 10.96%.

*(d) 1,*exo*-3,4-Trimethyl-7-oxabicyclo[2.2.1]heptane-*exo*-2-carboxylic Acid (**11**)*: To a solution of 6.04 g of NaOH and 612 mg (2.093 mmol) of **10** in 40 ml of water, 3.06 g of Ni–Al alloy was added slowly with cooling with running water. After addition of the alloy the suspension was stirred for 1 h and refluxed for 2.5 h. The Raney nickel was removed by filtration and the filtrate was acidified with hydrochloric acid. Extraction with diethyl ether, drying over Na_2SO_4, removal of the solvent, and distillation gave 364 mg (94%) of **11**; mp 67.5—68.5 °C; ^{1}H-NMR ($CDCl_3$): δ=9.1 (COOH), 2.95 (d, 1H), 2.3 (m, 1H), 1.70 (bs, 4H), 1.54 (s, 3H), 1.37 (s, 3H), 0.98 (d), 3H); ^{13}C-NMR: δ=174.6 (s), 85.8(s), 84.5 (s), 58.4 (d), 44.0 (d), 39.3 (t), 38.4 (t), 18.6 (q), 17.4 (q), 13.3 (q); MS: *m/e* 184 (M^+, 15), 169, 139, 123, 109, 97 (100). Found: C, 64.93; H, 8.79%. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75%.

*(e) Electrolysis of **11***: A solution of 351 mg (1.906 mmol) of **11** and 30 mg of NaOMe in 25 ml of dry MeOH was electrolyzed using graphite electrode in an undivided cell with ice cooling. After **11** had been consumed, 4 ml of water and 1 ml of AcOH were added to the reaction mixture. The solution was kept overnight at room temp. and concentrated *in vacuo*. The residue was diluted with water, neutralized with $NaHCO_3$ and extracted with dichloromethane. The organic layer was washed with sat. aq NaCl, dried over Na_2SO_4, concentrated, and distilled to give 250 mg (84%) of **1**; ^{13}C-NMR: δ=216.4 (s), 79.3 (s), 54.9 (d), 46.4 (d), 41.6 (t), 32.4 (q), 26.6 (t), 24.8 (q), 9.1 (q); other spectral data of **1** were in accord with those previously reported.[1]

Synthesis of dl-*Plinol C (**6**)*. To a suspension of 779 mg (11.9 mmol) of zinc powder in 10 ml of dry THF, 756 mg (4.35 mmol) of CH_2Br_2 was added under argon atmosphere. At 0 °C 3.0 ml of 1 M solution of $TiCl_4$ in CH_2Cl_2 was added and stirring was continued for 20 min. A solution of 44.4 mg of **1** in 2 ml of THF was added to this solution. After having been stirred overnight at r.t., the mixture was diluted with 10 ml of diethyl ether and 20 ml of 1 M hydrochloric acid and stirring was continued for an additional hour. Ether extract of the solution was washed with sat. aq NaCl, dried over Na_2SO_4, concentrated, and distilled to give 21.9 mg (50%) of *dl*-plinol C (**6**); ^{13}C-NMR: δ=148.2 (s), 110.6 (t), 80.3 (s), 48.9 (d), 45.7 (d), 39.5 (t), 29.4 (q), 25.5 (t), 23.3 (q), 9.3 (q); other spectra were identical with the reported full spectra.[1] (−)-Plinols C and B are reported to be crystals[1] but *dl*-plinols C and B were obtained as oils.

Preparation of t-*3-Acetyl-1,*c-*2-dimethyl-*r-*1-cyclopentanol (**2**)*. Isomerization of **1** (123 mg; 0.787 mmol) was performed by the published procedure[3] to give 107 mg (87%) of **2**; ^{13}C-NMR: δ=211.3 (s), 80.7 (s), 57.8 (d), 46.2 (d), 40.2 (t), 29.8 (q), 25.8 (q), 11.6 (q); other spectral data were consistent with those previously reported.[1]

Synthesis of dl-*Plinol A (**4**)*. *dl*-Plinol A (**4**) was prepared from **2** (31.6 mg; 0.203 mg) according to the method described above for plinol C as a liquid (20.7 mg; 66%); ^{13}C-NMR: δ=147.2 (s), 110.3 (t), 80.4 (s), 52.9 (d), 47.2 (d), 40.2 (t), 27.6 (t), 26.6 (q), 19.1 (q), 10.6 (q); other spectra were identical with the reported full spectra.[1]

Synthesis of c-*3-Acetyl-1,*t-*2-dimethyl-*r-*1-cyclopentanol (**3**)*.

*(a) 1,4-Dimethyl-7-oxabicyclo[2.2.1]heptane-*endo*-2,3-dicarboxylic Anhydride (**17**)*: A mixture of 3.34 g (34.8 mmol) of 2,5-dimethylfuran and 4.47 g (31.5 mmol) of dimethyl acetylenedicarboxylate was heated in a pressure bottle at 100 °C

for 21 h. The reaction mixture was dissolved in 30 ml of acetone and hydrogenated over 0.82 g of 10% Pd/C. Removal of the catalyst and of the solvent gave **14** in quantitative yield; mp 158—160 °C; ^{1}H-NMR ($CDCl_3$): δ=3.81 (s, 6H), 1.76 (bs, 4H), 1.68 (s, 6H).

To a solution of 3.461 g (14.4 mmol) of **14** in 2.5 ml of THF, 6 ml of 20 M KOH solution was added . After stirring for 2 h at r.t., the reaction mixture was acidified to pH 1 and concentrated. The residue was extracted with diethyl ether. Drying over Na_2SO_4 and removal of the solvent gave 3.003 g (98%) of **15**; mp 158—160 °C; ^{1}H-NMR (CD_3COCD_3): δ=1.72 (bs, 4H), 1.68 (s, 6H).

Hydrogenation of **15** (1.156 g; 5.45 mmol) (Pd black; EtOH) gave quantitiatively **16**; mp 155—158 °C; ^{1}H-NMR (CD_3COCD_3): δ=3.00 (s, 2H), ≈1.5 (4H), 1.47 (s, 6H).

A solution of 656 mg (3.06 mmol) of **16** in 8 ml of acetyl chloride was heated under reflux for 3 h. Removal of the volatile material by evaporation and washing the residue with ligroine gave 549 mg (92%) of **17**; mp 140—143 °C; ^{1}H-NMR (CD_3COCD_3): δ=3.62 (s, 2H), 1.82 (s, 4H), 1.59 (s, 6H). Found: C, 60.98; H, 5.87%. Calcd for $C_{10}H_{12}O_4$: C, 61.21; H, 6.17%.

endo-*3-Hydroxymethyl-1,4-dimethyl-7-oxabicyclo[2.2.1]heptane*-endo-**2**-*carboxylic Lactone (***18***)*. According to the procedure for the reduction of **8**, 278 mg (1.42 mmol) of **17** was reduced to the lactone **18** (246 mg; 95%); mp 103.0—104.5 °C. ^{1}H-NMR (CD_3COCD_3): δ=4.21 (m, 2H), 2.97 (m, 2H), ≈1.7 (4H), 1.46 (s, 3H), 1.37 (s, 3H); ^{13}C-NMR (CD_3COCD_3): δ=177.1 (s), 87.3 (s), 86.6 (s), 67.6 (t), 56.3 (d), 52.4 (d), 35.2 (t), 31.4 (t), 21.4 (q), 21.0 (q); MS: *m/e* 182 (M^+, 9), 125. 124, 108 (100), 107; IR: 1760 cm^{-1}. Found: C, 65.74; H, 7.78%. Calcd for $C_{10}H_{14}O_3$: C, 65.92; H, 7.74%.

1,4-Dimethyl-endo-*3-phenylthiomethyl-7-oxabicyclo[2.2.1]heptane*-endo-*2-carboxylic Acid (**19**)*. As described above, 545 mg (2.99 mmol) of **18** yielded 777 mg (89%) of **19**; ^{1}H-NMR ($CDCl_3$): δ=7.2 (5H), 2.7—3.5 (3H), 1.5—2.5 (5H), 1.42 (s, 3H), 1.32 (s, 3H); ^{13}C-NMR: δ=177.2 (s), 135.8 (s), 130.0 (d), 129.0 (d), 126.4 (d), 87.1 (s), 86.4 (s), 54.1 (d), 49.8 (d), 33.2 (t), 31.7 (t), 31.7 (t), 21.2 (q), 20.4 (q). IR: 3000, 1725, 1580, 1450 cm^{-1}. Found: C, 65.46; H, 6.61; S, 11.13%. Calcd for $C_{16}H_{20}O_3S$: C, 65.73; H, 6.89; S, 10.96%.

*1,*endo-*3,4-Trimethyl-7-oxabicyclo[2.2.1]heptane*-endo-*2-carboxylic Acid (**20**)*. As described above, 145 mg (0.496 mmol) of **19** gave 82 mg (90%) of **20**; mp 102.9—104.2 °C; ^{1}H-NMR ($CDCl_3$): δ=9.6 (COOH), 2.93 (d, 1H), 2.6—1.8 (5H), 1.51 (s, 3H), 1.40 (s, 3H), 1.05 (d, 3H); ^{13}C-NMR: δ=177.2 (s), 87.8 (s), 85.7 (s), 55.4 (d), 44.2 (d), 32.7 (t), 31.2 (t), 21.4 (q), 20.1 (q), 12.5 (q); MS: *m/e* 184 (M^+), 166, 139, 97 (100); IR: 2900, 1740 cm^{-1}. Found: C, 65.38; H, 9.01%. Calcd for $C_{10}H_{16}O_3$; C, 65.19; H, 8.75%.

Electrolysis of **20** (114 mg; 0.619 mmol) gave 61 mg (63%) of **3** after hydrolysis; ^{13}C-NMR: δ=211.8 (s), 81.2 (s), 58.8 (d), 47.4 (d), 40.0 (t), 29.4 (q), 25.6 (t), 23.1 (q), 16.4 (q); other spectral characteristics were consistent with those previously reported.[1]

Synthesis of dl-*Plinol B (**5**)*. Similar methylenation of 50.2 mg (0.321 mmol) of **3** gave 25.4 mg (51%) of *dl*-plinol B (**5**): ^{13}C-NMR: δ=135.4 (s), 110.2 (t), 80.4 (s), 53.3 (d), 48.0 (d), 40.6 (t), 27.0 (t), 23.5 (q), 19.0 (q), 12.8 (q); other spectra were in accord with the reported full spectra.[1]

References

1) H. Strickler, G. Ohloff, and E. sz. Kováts, *Helv. Chim. Acta*, **50**, 759 (1967).

2) A. F. Thomas, "The Total Synthesis of Natural Products," ed by J. ApSimon, Wiley-interscience, New York (1973), Vol. 2, p. 60, and references cited therein.

3) S. Nozoe, N. Morisaki, and M. Goi, *Tetrahedron Lett.*, **1971**, 3701.

4) T. Akiyama, T. Fujii, H. Ishiwari, T. Imagawa, and M. Kawanisi, *Tetrahedron Lett.*, **1978**, 2165; T. Imagawa, T. Nakagawa, K. Matsuura, T. Akiyama, and M. Kawanisi, *Chem. Lett.*, **1981**, 903; T. Imagawa, S. Sugita, T. Akiyama, and M. Kawanisi, *Tetrahedron Lett.*, **22**, 2564 (1981); T. Imagawa, N. Murai, T. Akiyama, and M. Kawanisi, *ibid.*, **1979**, 1961; T. Imagawa, T. Sonobe, H. Ishiwari, T. Akiyama, and M. Kawanisi, *J. Org. Chem.*, **45**, 2005 (1980).

5) O. Diels and S. Olsen, *J. Prakt. Chem.*, **156**, 285 (1940).

6) K. Takai, Y. Hotta, K. Oshima, and H. Nozaki, *Bull. Chem. Soc. Jpn.*, **53**, 1698 (1980).