Pseudo-sugars. IX. Synthesis of Three (Hydroxymethyl)-cyclohexanepentols[1]

Seiichiro OGAWA, Toshinobu NAKAMURA, Noritaka CHIDA, and Tetsuo SUAMI*

Department of Applied Chemistry, Faculty of Science and Technology, Keio University, Hiyoshi, Kohoku-ku, Yokohama 223

(Received November 11, 1982)

Synopsis. Three new DL-(hydroxymethyl)cyclohexanepentols, of which configurations are related to biologically important *chiro*- and *myo*-inositols, have been synthesized as hexaacetates from DL-tri-*O*-acetyl-(1,3/2,4)-4-benzoyloxymethyl-5-cyclohexene-1,2,3-triol by osmium tetraoxide-oxidation or peroxy acid-oxidation followed by acid hydrolysis, and their structures have been established by ^{1}H NMR spectroscopy.

During the course of synthetic studies of hydroxyvalidamine and valienamine,[2] three new (hydroxymethyl)cyclohexanepentols have been prepared and characterized as hexaacetates. These branched-chain cyclitols are useful not only as reference compounds for structural elucidation of new cyclitols by ^{1}H NMR spectroscopy, but also as biologically interesting inositol analogs with *chiro*- and *myo*-configurations.

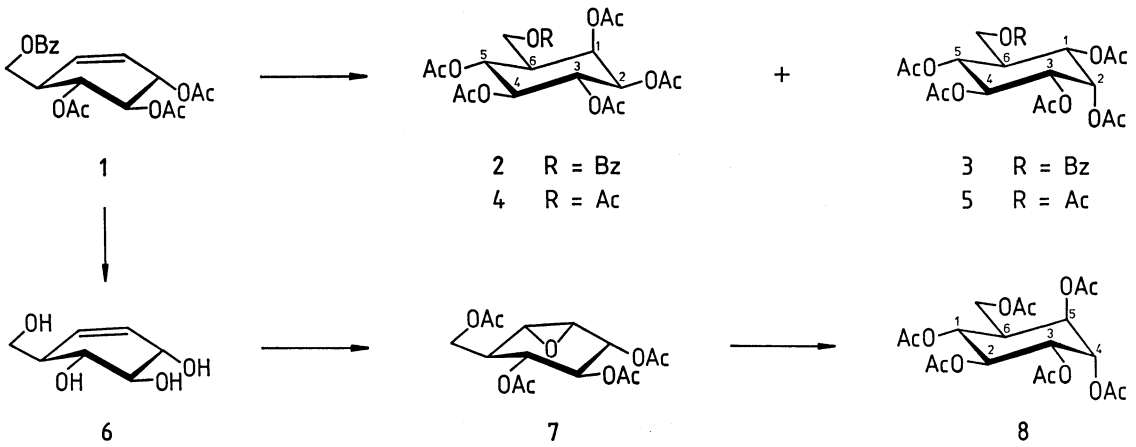
Treatment of DL-tri-*O*-acetyl-(1,3/2,4)-4-benzoyloxymethyl-5-cyclohexene-1,2,3-triol (**1**)[2] with osmium tetraoxide in aqueous *t*-butyl alcohol containing 3% hydrogen peroxide at 40 °C for 120 h, followed by conventional acetylation, gave, after chromatography on silica gel, two peracyl (hydroxymethyl)cyclohexanepentols **2** and **3** in 24 and 24% yields, respectively. The assigned structures were established on the basis of their ^{1}H NMR spectra. Thus, in the spectrum of **2**, the signals for H-1, H-2, H-3, H-4, and H-5 appear as a triplet (δ=5.67, J=3 Hz), a doublet of doublets (δ=4.95, J=3 and 10.2 Hz), a triplet (δ=5.43, J=10.2 Hz), a doublet of doublets (δ=5.22, J=9 and 10.2 Hz), and a doublet of doublets (δ=5.34, J=10.2 and 10.5 Hz), respectively, indicating equatorial-axial-axial-axial-axial conformations for H-1, H-2, H-3, H-4, and H-5. The spectrum of **3** exhibits the signal for H-4 as a triplet (J=10 Hz) at δ=5.42, which seems deshielded by 0.2 ppm relative to that of **2** by the C-2 acetoxyl group in the 1,3-diaxial disposition. *O*-Deacylation of **2** and **3** with methanolic sodium methoxide in methanol followed by acetylation gave crystalline hexaacetates **4** and **5** in 43 and 59% yields, respectively.

On the other hand, the epoxide **7** prepared specifically by peroxy acid-oxidation of the tetrahydroxy compound **6** derived from **1**[2] was hydrolyzed by refluxing in aqueous 2-methoxyethanol containing 0.7% sulfuric acid for 2 h. The product was successively acetylated to give a single crystalline hexol hexaacetate **8** in 70% yield. The structure was assigned as shown in the scheme by ^{1}H NMR spectroscopy. The spectrum indicated the signals for two acetoxyl groups to be as a 6-proton singlet in the regions characteristic of axial groups (δ=2.13),[3] supporting that the reaction involves trans-diaxial opening of the oxirane ring.

Experimental

Melting points were determined on a Mitamura Riken micro hot stage and are uncorrected. ^{1}H NMR spectra were taken on a Varian EM-390 (90 MHz) spectrometer in chloroform-*d* with reference to tetramethylsilane as an internal standard. TLC was performed on precoated silica gel 60 F-254 plates (Merck, Darmstadt; 0.25 mm thickness). The silica gel used for column chromatography was Wakogel C-300 (Wako Pure Chemical Industries, Ltd.).

Oxidation of DL-*Tri*-O-*acetyl-(1,3/2,4)-4-benzoyloxymethyl-5-cyclohexene-1,2,3-triol (**1**) with Osmium Tetraoxide.* To a solution of **1** (0.20 g) in aqueous *t*-butyl alcohol (3 ml) containing 3% hydrogen peroxide was added osmium tetraoxide (5 mg) in *t*-butyl alcohol (1 ml), and the mixture was stirred at 40 °C for 120 h. The reaction mixture was concentrated and the residue was treated with acetic anhydride (1 ml) and pyridine (1 ml) at room temperature overnight. Evaporation of the excess reagent gave crude



Scheme 1.

products, which were fractionated on a silica-gel column (8.5 g) with 2-butanone–toluene (1: 12) as an eluent. The first fraction [R_f 0.45, 2-butanone–toluene (1: 5)] gave an oil (61 mg, 24%), which was crystallized from ethanol to give 15 mg of DL-1,2,3,4,5-penta-*O*-acetyl-7-*O*-benzoyl-(1,2,4,6/3,5)-6-hydroxymethyl-1,2,3,4,5-cyclohexanepentol (**2**) as prisms: mp 156—158 °C; ^{1}H NMR ($CDCl_3$) δ=1.95 (3H, s), 1.99 (6H, s), 2.01 (3H, s), and 2.10 (3H, s) (OAc), 2.45 (1H, m, H-6), 4.08 (1H, dd, $J_{6,7}$=9 Hz, J_{gem}=11 Hz) and 4.35 (1H, dd, $J_{6,7'}$=4.5 Hz) ($C\underline{H}_2OBz$), and 7.33—8.03 (5H, m, phenyl).

Found: C, 56.85; H, 5.30%. Calcd for $C_{24}H_{28}O_{12}$: C, 56.69; H, 5.55%.

Compound **2** (160 mg) was treated with 0.3 M (1 M= 1 mol dm^{-3}) methanolic sodium methoxide (3 ml) at room temperature for 1 h, and the reaction mixture was neutralized by 1 M hydrochloric acid and concentrated. The residual product was acetylated in the usual way and the product was crystallized from ethanol to give 68 mg (43%) of the hexaacetate **4** as prisms: mp 158—159 °C; ^{1}H NMR ($CDCl_3$) δ=1.96 (3H, s), 1.98 (3H, s), 2.00 (6H, s), 2.01 (3H, s), and 2.12 (3H, s) (OAc), 3.85 (1H, dd, $J_{6,7}$=4.5 Hz, J_{gem}=10.8 Hz) and 4.04 (1H, dd, $J_{6,7'}$=9 Hz) ($C\underline{H}_2OAc$), 4.87 (1H, dd, $J_{1,2}$=3 Hz, $J_{2,3}$=10.2 Hz, H-2), and 5.51 (1H, dd, $J_{1,6}$=2.3 Hz, H-1).

Found: C, 51.11; H, 5.80%. Calcd for $C_{19}H_{26}O_{12}$: C, 51.12; H, 5.87%.

The second fraction (R_f 0.40) gave an oil (63 mg, 24%), which was crystallized from ethanol to give 18 mg of DL-1,2,3,4,5-penta-*O*-acetyl-7-*O*-benzoyl-(1,2,3,5/4,6)-6-hydroxymethyl-1,2,3,4,5-cyclohexanepentol (**3**) as prisms: mp 146—148 °C; ^{1}H NMR ($CDCl_3$) δ=1.97 (6H, s), 2.01 (3H, s), 2.06 (3H, s), and 2.16 (3H, s) (OAc), 2.60 (1H, br t, $J_{1,6}$ =$J_{5,6}$=10 Hz, H-6), 4.28 (2H, br s, $C\underline{H}_2OBz$), 5.18 (1H, t, $J_{4,5}$=10 Hz, H-5), 5.42 (1H, t, $J_{3,4}$=10 Hz, H-4), 5.57 (1H, t, $J_{1,2}$=$J_{2,3}$=2.5 Hz, H-2), and 7.25—8.07 (5H, m, phenyl).

Found: C, 56.56; H, 5.57%. Calcd for $C_{24}H_{28}O_{12}$: C, 56.69; H, 5.55%.

Compound **3** (230 mg) was *O*-deacylated similarly as described above and acetylated to give a crystalline product, which was recrystallized from ethanol to give 135 mg (59%) of the hexaacetate **5** as prisms: mp 180—182 °C; ^{1}H NMR ($CDCl_3$) δ=1.99 (6H, s), 2.01 (3H, s), 2.04 (6H, s), and 2.16 (3H, s) (OAc), 4.00 (2H, br d, J=2 Hz, $C\underline{H}_2OBz$), 5.37 (1H, t, $J_{3,4}$=$J_{4,5}$=10.5 Hz, H-4), and 5.87 (1H, t, $J_{1,2}$=$J_{2,3}$=3 Hz, H-2).

Found: C, 51.10; H, 5.78%. Calcd for $C_{19}H_{26}O_{12}$: C, 51.12; H, 5.87%.

DL-*Hexa*-O-*acetyl-(1,3,4/2,5,6)-6-hydroxymethyl-1,2,3,4,5-cyclohexanepentol (**8**).* A mixture of DL-tetra-*O*-acetyl-1,2-anhydro-(1,2,3,5/4,6)-6-hydroxymethyl-1,2,3,4,5-cyclohexanepentol (**7**)[2] (83 mg) in 2-methoxyethanol (2 ml) and 1% sulfuric acid (5 ml) was refluxed for 1.5 h. The reaction mixture was neutralized with sodium hydrogencarbonate and concentrated. The residue was acetylated and the product was purified by passage through a short column of alumina with chloroform. The crystalline product was recrystallized from ethyl acetate–hexane to give 75 mg (70%) of **8** as prisms: mp 102—105 °C; ^{1}H NMR ($CDCl_3$) δ=1.96 (3H, s), 2.00 (3H, s), 2.01 (3H, s), and 2.13 (6H, s) (OAc), 2.52 (1H, m, H-6), 3.93 (1H, dd, $J_{6,7}$=4.5 Hz, J_{gem}=11.3 Hz) and 4.19 (1H, dd, $J_{6,7'}$=8.3 Hz) ($C\underline{H}_2OAc$), 5.16 (1H, dd, $J_{2,3}$=9 Hz, $J_{3,4}$=3.2 Hz, H-3), 5.28 (1H, t, $J_{1,2}$=$J_{1,6}$=9 Hz, H-1), 5.38 (1H, t, $J_{4,5}$=3.2 Hz, H-4), and 5.41 (1H, t, H-2).

Found: C, 51.35; H, 5.88%. Calcd for $C_{19}H_{26}O_{12}$: C, 51.12; H, 5.88%.

The authors wish to express their thanks to Mr. Saburo Nakada for elemental analyses.

References

1) The preceding paper of this series: S. Ogawa, M. Oya, T. Toyokuni, N. Chida, and T. Suami, *Bull. Chem. Soc. Jpn.*, **56**, 1441 (1983). The nomenclature and numbering of cyclitols used in this paper follow the IUPAC and IUB Tentative Rules for Cyclitol Nomenclature [*J. Biol. Chem.*, **243**, 5809 (1968)]. All compounds described in this paper are racemic and the formulas depict only one of the respective enantiomers.

2) S. Ogawa, N. Chida, and T. Suami, *J. Org. Chem.*, in press.

3) F. W. Lichtenthaler and P. Emig, *Carbohydr. Res.*, **7**, 121 (1968); F. W. Lichtenthaler, G. Bambach, and P. Emig, *Chem. Ber.*, **102**, 994 (1969).