Pseudo-Sugars. XVI. Facile Synthesis of Pseudo-α-D and L-Glucopyranoses[1]

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Synopsis. Optically active pseudo-α-glucopyranoses have been synthesized from enantiomeric (1,3,5/2,4)-2,3-diacetoxy-4,5-dibromo-1-cyclohexanecarboxylic acids, obtained by optical resolution of the racemic modification using (+)- and (−)-α-methylbenzylamines.

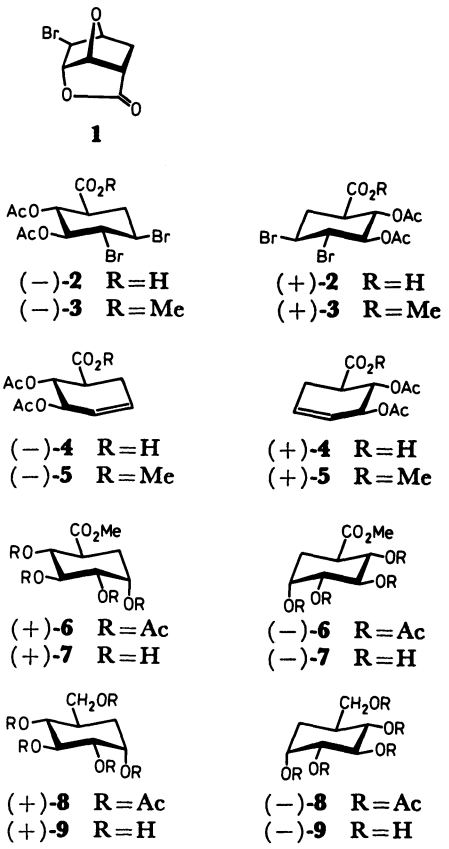
Recently, pseudo-α-DL-glucopyranose[2] has been shown to inhibit glucokinase activity and glucose-stimulated insulin release.[3] Accordingly, it has become necessary to provide quantities of the pseudo-sugars, as optically active forms, for a further biological and biochemical studies. We now describe a facile synthesis of pseudo-α-D and L-glucopyranoses, starting from (−) and (+)-enantiomers of (1,3,5/2,4)-2,3-diacetoxy-4,5-dibromo-1-cyclohexanecarboxylic acid (**2**), respectively, obtained by an optical resolution[4] of the racemic modification.[5]

Pseudo-α-D-glucopyranose has already been synthesized from D-glucose by two research groups.[6,7] The sequence of the present synthesis could readily be conducted with a high selectivity and a high overall yield, and has an advantage to furnish both D- and L-enantiomers with ease.

The racemic acid (±)-**2** was successfully resolved by use of commercially available (+)- and (−)-α-methylbenzylamines. Thus, a mixture of (*R*)-(+)-amine salts of (−)-**2** and (+)-**2** was fractionally crystallized from ethanol to give, in 54% yield, the pure (*R*)-(+)-amine salt of (−)-**2**, from which the free acid (−)-**2** ($[\alpha]_D$ −5.1°) was obtained by treatment with sodium carbonate followed by hydrochloric acid. Similarly, the acid (+)-**2** ($[\alpha]_D$ +5.2°) was obtained by use of the (*S*)-(−)-amine. The absolute configuration of (−)-**2** could be estabilised as shown in Scheme by identification with the authetic sample derived from (3*S*)-(+)-2-*exo*-bromo-4,8-dioxatricyclo[4.2.1.0^{3,7}]nonan-5-one[8] (**1**) by treatment with hydrogen bromide in acetic acid.

The present synthesis of **9** was carried out in the following sequence,[5] previously used for the preparation of the racemic modification.

Treatment of the acid (−)-**2** with methanol and acetyl chloride gave the methyl ester (−)-**3** in 91% yield. Compound (−)-**2** was debrominated with zinc dust in acetic acid to give 96% yield of the olefin (−)-**4**. Similarly, (−)-**3** was converted into the olefin (−)-**5** in 92% yield. Oxidation of (−)-**5** with osmium tetraoxide and hydrogen peroxide in *t*-butyl alcohol, followed by acetylation, afforded selectively the tetraacetate (+)-**6** in 85% yield.[9] *O*-Deacetylation of (+)-**6** with methanolic sodium methoxide gave the methyl ester (+)-**7** ($[\alpha]_D$ +48°) quantitatively. Reduction of (+)-**6** with lithium aluminum hydride in tetrahydrofuran, followed by acetylation, gave the pentaacetate (+)-**8** ($[\alpha]_D$ +57°) in 98% yield. *O*-Deacetylation of (+)-**8** gave pseudo-α-D-glucopyranose (+)-**9** ($[\alpha]_D$ +67°)[10] quantitatively. The overall yield of (+)-**9** from (−)-**2** was about 70%.



Likewise, pseudo-α-L-glucopyranose (−)-**9** ($[\alpha]_D$ −67°) was obtained from (+)-**2**.

The structures of **8** and **9** were established on the basis of the ^{1}H NMR spectra.[2,11]

Experimental

Melting points were determined on a MEL-TEMP capillary melting-point apparatus and are uncorrected. Optical rotations were measured on a Jasco DIP-4 polarimeter. The ^{1}H NMR spectra were recorded on a Varian EM-390 (90 MHz) spectrometer for solution of chloroform-*d* or deuterium oxide. The silica gel used for column chromatography was Wakogel C-300 (Wako Co., Osaka). The structures of the optically active compounds synthesized were confirmed by comparison of the ^{1}H NMR spectra with those of the corresponding racemic modifications.[2,5,11]

Optical Resolution of DL-(1,3,5/2,4)-2,3-Diacetoxy-4,5-dibromo-1-cyclohexanecarboxylic Acid[2] [(±)-2]. To a solution of the acid (±)-**2** (20 g, 50 mmol) in ethanol (200 ml) was

added (*R*)-(+)-α-methylbenzylamine[12] (7.7 ml, 60 mmol), and the mixture was kept in a refrigerator (0—5 °C) overnight. The precipitates, a mixture of the salts, were collected by filtration and washed with 2-propanol. The salts were fractionally crystallized from ethanol to give the pure (*R*)-(+)-amine salt of (−)-**2** (6.8 g, 52%) as white needles: Mp 187—190 °C; $[\alpha]_D^{20}$ +8.7° (*c* 1.0, MeOH).

Found: C, 43.68; H, 4.74; N, 2.67%. Calcd for $C_{19}H_{25}Br_2NO_6$: C, 43.62; H, 4.82; N, 2.67%.

Similarly, by use of (*S*)-(−)-α-methylbenzylamine, the (*S*)-(−)-amine salt of (+)-**2** was obtained in 47% yield, needles (from EtOH): Mp 187—190 °C; $[\alpha]_D^{21}$ −8.6° (*c* 0.90, MeOH).

Found: C, 43.58; H, 4.75; N, 2.55%.

A portion (1.46 g, 3.13 mmol) of (*R*)-(+)-amine salt of (−)-**2** was treated with 2 M aqueous sodium carbonate (40 ml) (1 M=1 mmol dm^{-3}) at room temperature for 2 h, and then the solution was extracted with ether (20 ml×3). The solvent was removed to leave recovered (*R*)-(+)-amine (0.36 g 92%). The aqueous layer was acidified with 1 M hydrochloric acid and extracted with ether (100 ml×3). The extracts were dried over anhydrous sodium sulfate and concentrated to give a crystalline residue. Recrystallization from 2-propanol gave the acid (−)-**2** (1.19 g, 95%) as prisms: Mp 180—181 °C; $[\alpha]_D^{19}$ −5.1° (*c* 0.90, EtOH).

Found: C, 33.10; H, 3.69; Br, 39.45%. Calcd for $C_{11}H_{14}Br_2O_6$: C, 32.86; H, 3.51; Br, 39.75%.

From (*S*)-(−)-amine salt of (+)-**2**, the acid (+)-**2** was obtained in 93% yield, prisms (from *i*-PrOH): Mp 180—181 °C; $[\alpha]_D^{21}$ +5.2° (*c* 1.8, EtOH).

Found: C, 31.99; H, 3.21%. Calcd for $C_{11}H_{14}Br_2O_6 \cdot 0.5\,H_2O$: C, 32.14: H, 3.68%.

Preparation of (−)-2 from (3*S*)-(+)-2-*exo*-Bromo-4,8-dioxatricyclo[4.2.1.$0^{3,7}$]nonan-5-one[7] (1). The bromolactone **1** (1.0 g, 4.6 mmol) was heated with 20% hydrogen bromide–acetic acid (6 ml) in a sealed tube at 85 °C for 42 h. The reaction mixture was poured into ice-water (70 ml) containing sodium hydrogencarbonate (2 g) and the precipitates, after standing overnight in a refrigerator, were collected by filtration. Recrystallization from ethanol gave (−)-**2** (0.86 g, 44%) as prisms: Mp 182—183 °C; $[\alpha]_D^{23}$ −4.7° (*c* 0.72, EtOH).

Methyl (1*S*)-(−) [(−)-3] and (1*R*)-(+)-(1,3,5/2,4)-2,3-Diacetoxy-4,5-dibromo-1-cyclohexanecarboxylate [(+)-3]. A mixture of (−)-**2** (0.91 g, 2.3 mmol), acetyl chloride (0.1 ml), and methanol (10 ml) was heated at reflux for 2 h, and then neutralized with sodium hydrogencarbonate. The reaction mixture was concentrated and the residue was acetylated with acetic anhydride (5 ml) and pyridine (5 ml) overnight at room temperature. The mixture was concentrated, the residue was taken up in ethyl acetate (30 ml), and the solution was washed with 1 M hydrochloric acid, saturated aqueous sodium hydrogencarbonate, and water, dried, and concentrated. Recrystallization of the residue from ethanol gave (−)-**3** (0.85 g, 91%) as needles: Mp 140—141 °C; $[\alpha]_D^{20}$ −15.5° (*c* 1.4, $CHCl_3$).

Found: C, 34.48; H, 3.88; Br, 38.53%. Calcd for $C_{12}H_{16}Br_2O_6$: C, 34.64; H, 3.88; Br, 38.41%.

Similarly, (+)-**2** was converted into the ester (+)-**3**; needles (from EtOH): Mp 140—141 °C; $[\alpha]_D^{20}$ +15.4° (*c* 0.85, $CHCl_3$).

Found: C, 34.97; H, 3.89%.

(1*S*)-(−) [(−)-4] and (1*R*)-(+)-(1,3/2)-2,3-Diacetoxy-4-cyclohexene-1-carboxylic Acid [(+)-4]. To a solution of (−)-**2** (0.93 g, 2.3 mmol) in acetic acid (20 ml) was added zinc dust (1.5 g, 23 matom) in portions at 70 °C for 0.5 h. The insoluble material was filtered and the filtrate was concentrated. The residue was taken up in ethyl acetate (20 ml) and the solution was washed with saturated aqueous sodium hydrogencarbonate and water, dried, and concentrated. Recrystallization of the residue from carbon tetrachloride gave (−)-**4** (0.54 g, 96%) as prisms: Mp 113—115 °C; $[\alpha]_D^{17}$ −2.5° (*c* 1.9, EtOH).

Found: C, 54.32; H, 5.70%. Calcd for $C_{11}H_{14}O_6$: C, 54.54; H, 5.83%.

Similarly, (+)-**4** was obtained from (+)-**2**; prisms (from CCl_4): Mp 113—115 °C; $[\alpha]_D^{17}$ +2.7° (*c* 2.7, EtOH).

Found: C, 54.38; H, 5.73%.

Methyl (1*S*)-(−) [(−)-5] and (1*R*)-(+)-(1,3/2)-2,3-Diacetoxy-4-cyclohexene-1-carboxylate [(+)-5]. The ester (−)-**3** (0.50 g, 1.2 mmol) was treated with zinc dust in acetic acid as described for the preparation of (−)-**4** to give (−)-**5** (0.28 g, 92%) as needles (from ether): Mp 45—47 °C; $[\alpha]_D^{18}$ −22° (*c* 1.6, $CHCl_3$).

Found: C, 55.87; H, 5.96%. Calcd for $C_{12}H_{16}O_6$: C, 56.25; H, 6.29%.

Similarly, the ester (+)-**3** was converted into (+)-**5**; needles (from ether): Mp 45—47 °C; $[\alpha]_D^{17}$ +21° (*c* 0.96, $CHCl_3$).

Found: C, 55.98; H, 6.07%.

Methyl (1*S*)-(+) [(+)-6] and (1*R*)-(−)-(1,3/2,4,5)-2,3,4,5-Tetraacetoxy-1-cyclohexanecarboxylate [(−)-6]. A mixture of (−)-**5** (0.51 g, 2.0 mmol), *t*-butyl alcohol (11 ml) containing 30% hydrogen peroxide (2 ml), and *t*-butyl alcohol (3.8 ml) containing osmium tetraoxide (19 mg) was stirred at room temperature for 24 h. Excess peroxide was decomposed by addition of sodium sulfite and the mixture was concentrated. The residue was acetylated in a usual way and the product was eluted from a column of silica gel (30 g) with 2-butanone–toluene (1:8) to give (+)-**6** (0.63 g, 85%) as prisms (from EtOH): Mp 79—80 °C; $[\alpha]_D^{23}$ +56° (*c* 1.1, $CHCl_3$).

Found: C, 51.30; H, 5.87%. Calcd for $C_{16}H_{22}O_{10}$: C, 51.34; H, 5.92%.

Similarly, (−)-**6** was obtained from (+)-**5**; prisms (from EtOH): Mp 79—80 °C; $[\alpha]_D^{22}$ −58° (*c* 1.1, $CHCl_3$).

Found: C, 51.08; H, 5.77%.

Methyl (1*S*)-(+) [(+)-7] and (1*R*)-(−)-(1,3/2,4,5)-2,3,4,5-Tetrahydroxy-1-cyclohexanecarboxylate [(−)-7]. Compound (+)-**6** (45 mg, 0.12 mmol) was treated with 0.1 M methanolic sodium methoxide (2 ml) at room temperature for 2 h, and then the mixture was neutralized by passage through a short column of Amberlite IR 120B (H^+) resin. The eluate was concentrated to give (+)-**7** (25 mg, 100%) as a syrup: $[\alpha]_D^{20}$ +48° (*c* 0.71, MeOH).

Found: C, 45.59; H, 6.66%. Calcd for $C_8H_{14}O_6 \cdot 0.25H_2O$: C, 45.60; H, 6.94%.

Similarly, (−)-**7** was obtained from (−)-**6**; syrup: $[\alpha]_D^{20}$ −48° (*c* 0.98, MeOH).

Found; C, 46.61; H, 6.58%. Calcd for $C_8H_{14}O_6$: C, 46.60; H, 6.84%.

(1*S*)-(+) [(+)-8] and (1*R*)-(−)-(1,3/2,4,5)-2,3,4,5-Tetraacetoxycyclohexanmethanol [(−)-8]. The ester (+)-**6** (100 mg, 0.27 mmol)was treated with lithium aluminum hydride (55 mg, 1.4 mmol) in tetrahydrofuran (2 ml) at room temperature for 8 h. The mixture was processed in a usual way to give a hydroxy compound, which was acetylated with acetic anhydride in pyridine. The product was purified by passage through a short column of alumina with chloroform to give (+)-**8** (103 mg, 98%) as a syrup: $[\alpha]_D^{21}$ +57° (*c* 0.90, $CHCl_3$) [lit,[6] $[\alpha]_D^{22}$ +37° ($CHCl_3$)] (Found: C, 52.44; H, 6.01%).

Similarly, (−)-**8** was obtained from (−)-**6**; syrup: $[\alpha]_D^{20}$ −56° (*c* 1.1, $CHCl_3$).

(1*S*)-(+) [(+)-9] and (1*R*)-(−)-(1,3/2,4,5)-2,3,4,5-Tetrahydroxycyclohexanemethanol [(−)-9]. Compound (+)-**8** (56 mg, 0.14 mmol) was treated with 0.1 M methanolic sodium methoxide (2 ml) at room temperature for 3 h. The mixture was neutralized with Amberlite IR 120B (H^+) resin to give (+)-**9** (27 mg, 100%) as a syrup: $[\alpha]_D^{21}$ +67° (*c* 0.50, MeOH) [lit,[6] $[\alpha]_D^{25}$ +30° (MeOH)].

Similarly, the pentol (−)-**9** was obtained from (−)-**8**:

syrup: $[\alpha]_D^{21}$ −67° (*c* 1.5, MeOH).

Found: C, 47.32; H, 7.66%. Calcd for $C_7H_{14}O_5$: C, 47.18; H, 7.92%.

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References

1) Part XV, see T. Suami, S. Ogawa, Y. Uematsu, and A. Suga, *Bull. Chem. Soc. Jpn.*, **59**, 1261 (1986).

2) S. Ogawa, Y. Tsukiboshi, Y. Iwasawa, and T. Suami, *Carbohydr. Res.*, **136**, 77 (1985).

3) I. Miwa, H. Hara, J. Okuda, T. Suami, and S. Ogawa, *Biochem Int.*, **11**, 809 (1985).

4) Since the yield of the reaction producing **2** was rather low, an optical resolution of (±)-**2** seemed to be more effective for the present synthesis.

5) S. Ogawa, Y. Yato, K. Nakamura, M. Takata, and T. Takagaki, *Carbohydr. Res.*, **148**, 249 (1986).

6) T. Suami, K. Tadano, Y. Kameda, and Y. Iimura, *Chem. Lett.*, **1984**, 1919.

7) J. Cleophax, S. D. Gero, P. Krausz, A. S. Machado, M. Philippe, B. Sire, C. Tachdjian, and G. Vass, 3rd European Symposium on Carbohydrates, Grenoble-France, September 1985, Abstr., No. B.2-5.

8) S. Ogawa, Y. Iwasawa, T. Nose, T. Suami, S. Ohba, M. Ito, and Y. Saito, *J. Chem. Soc., Perkin Trans. 1*, **1985**, 903.

9) The oxidation of **5** has been found to be more selective reaction than that of the correspondind bromomethyl compound, giving a pseudo-sugar derivative with the α-gluco configuration, see Ref. 11.

10) The remarkable discrepancy between the values of optical rotation of (+)-**9** and that of an authentic sample[6] might be explained by their homogeneity rather than by optical purity. The present results seem to be convincing, because optical rotations of both enantiomers synthesized are equal and opposite.

11) S. Ogawa, T. Toyokuni, T.Kondoh, Y. Hattori, S. Iwasaki, M. Suetsugu, and T. Suami, *Bull. Chem. Soc. Jpn.*, **54**, 2739 (1981).

12) (*R*)-(+) and (*S*)-(−)-α-methylbenzylamine were perchased from Tokyo Kasei Kogyo Co. Ltd. and showed specific rotations of +38.4 and −38.4° (neat), respectively, corresponding to ca. 96% optical purity.