  Bull. Chem. Soc. Jpn., 57, 2535—2537 (1984)

Branched-chain Sugars. XXXV. The Synthesis of L-Rubranitrose (2,3,6-trideoxy-3-*C*-methyl-4-*O*-methyl-3-nitro-L-*xylo*-hexopyranose)[1]

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(Received April 16, 1984)

The title compound was stereoselectively synthesized from methyl 2,6-dideoxy-4-*O*-methyl-β-L-*threo*-hexopyranosid-3-ulose (**11**) through the successive conversions; cyanomesylation, reductive spiro aziridine formation, reductive ring-opening to the methyl-branched amino sugar, oxidation to the corresponding nitro sugar.

For rubranitrose, a component of the antibiotic rubradirin,[2] the structure was reprtred to be 2,3,6-trideoxy-3-*C*-methyl-4-*O*-methyl-3-nitro-L-*xylo*-hexopyranose (**1**) from X-ray analysis and the CD spectrum,[3] in which a positive Cotton effect was observed, opposite in sign to that of L-evernitrose (**2**).[4] However, Mallams *et al.*[5] pointed out that **1** should have D-configuration, from comparison of the CD spectrum and rotational value with D-kijanose (**3**), of which the configuration was assigned by the application of Hudson's Rules of Isorotation. In a previous communication,[6] we proved the correctness of the deduction of Mallams *et al.*, by the synthesis of **1** from D-glucose. This paper describes it in detail. In our synthesis, hexopyranosid-3-ulose was converted successively into the corresponding methyl-branched nitro sugar; *i.e.* cyanomesylation of the carbonyl group, reductive spiro aziridine formation by intramolecular S_N2 substitution, reductive ring-opening into methyl-branched amino sugar, and oxidation into the corresponding nitro sugar. The series of conversions was previously used for the synthesis of **2**[7] and its enantiomer.[8] Recently, Brimacombe *et al.*[9] communicated the synthesis of **1** and its enantiomer through the inversion of configuration of *C*-4 of methyl 3-trifluoroacetamido-2,3,6-trideoxy-3-*C*-methyl-α-L- and D-*ribo*-hexopyranoside (**4**), respectively.

Results and Discussion

For the synthesis of **1** through the aforementioned pathway, methyl 2,6-dideoxy-4-*O*-methyl-β-L-*threo*-hexopyranosid-3-ulose (**11**) was considered to be the most suitable key intermediate. Treatment of methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*ribo*-hexopyranoside,[10] which was obtained from D-glucose through five-step conversions, with *N*-bromosuccinimide and barium carbonate in carbon tetrachloride gave unstable methyl 4-*O*-benzoyl-6-bromo-2,6-dideoxy-α-D-*ribo*-hexopyranoside (**5**) in 92% yield. It was found that *O*-methylation of **5** in *N*,*N*-dimethylformamide with methyl iodide and silver(I) oxide is nicely accomapnied with benzoyl migration to give the corresponding 3-*O*-benzoyl-4-*O*-methyl derivative (**6**) in 90% yield. Treatment of **6** in pyridine with silver(I) fluoride[11] gave a 3:2 mixture of the corresponding hex-5-enopyranoside (**8**) and 6-fluoro-6-deoxy derivative (**7**). The mixture could not be separated, and the presence of **7** was confirmed only by ^{19}F-NMR. Compound **8** was separated, after conversion into methyl 2,6-dideoxy-4-*O*-methyl-β-L-*lyxo*-hexopyranoside (**10**) *via* the corresponding 3-benzoate (**9**) in 49% yield. Oxidation of **10** with pyridinium chlorochromate gave the crystalline key intermediate (**11**) in 65% yield.

One-flask cyanomesylation of **11** by treatment overnight with hydrogen cyanide in dry pyridine, and then with methanesulfonyl chloride for 2 d at room temperature gave methyl 3-*C*-cyano-2,6-dideoxy-3-*O*-methylsulfonyl-4-*O*-methyl-β-L-*lyxo*-hexopyranoside (**12**) as crystals in 65% yield. In order to examine the stereoselectivity of cyanomesylation under the thermodynamic conditions,[12] cyanohydrine formation was

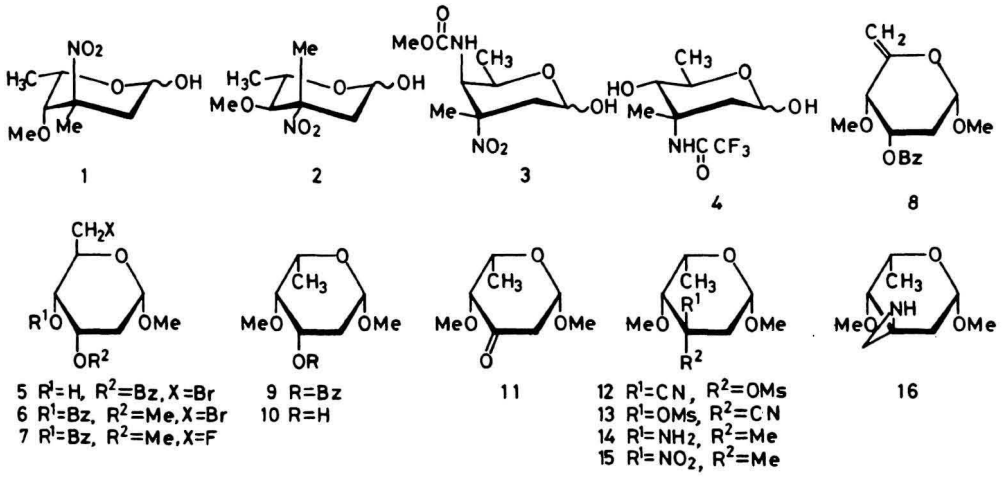

TABLE 1. ^{1}H AND ^{13}C-NMR DATA OF **1**

	Chemical shift (δ) and coupling constant (Hz) in ^{1}H-NMR							
	H-1 ($J_{1,2a}$)	H-2a ($J_{1,2e}$)	H-2e ($J_{2a,2e}$)	H-4 ($J_{4,5}$)	H-5 ($J_{5,6}$)	H-6	CMe	OMe
α-**1**	5.30 dd (2.5)	2.07 dd (3.5)	2.68 dd (14.5)	3.61 bs (1.0)	4.40 bq (6.5)	1.33 d	1.67 s	3.64 s
(Reported for α-D-**1**)	5.28 dd (2.5)	2.05 dd (3.5)	2.67 dd (14.5)	3.62 bs (<1)	4.40 bq (6.5)	1.33 d	1.67 s	3.62 s
	Chemical shift (ppm) of carbons in ^{13}C-NMR							
	C-1	*C*-2	*C*-3	*C*-4	*C*-5	*C*-6	*C*Me	OMe
α-**1**	92.51	37.17	63.45	79.65	69.84	16.79	25.84	62.69
β-**1**	90.58	34.46	62.96	79.43	69.84	16.36	25.14	62.58

carried out by treatment of **11** in dichloromethane with aqueous potassium cyanide and sodium hydrogencarbonate, followed by mesylation of the product in pyridine, to give a 1:4 mixture of **12** and its L-*xylo* isomer (**13**) in 83% yield. Reduction of **12** with lithium aluminium hydride gave the corresponding spiro aziridine (**16**) in 65% yield, which was converted into the methyl glycoside (**15**) of L-rubranitrose *via* the corresponding methyl-branched amino sugar (**14**) in 56% yield, by successive catalytic hydrogenolysis and oxidation with *m*-chloroperoxybenzoic acid. Hydrolysis of **15** in 0.05 M (1 M=1 mol dm^{-3}) sulfuric acid gave **1** {mp 147—148 °C, $[\alpha]_D$ −76° (*c* 0.48, ethanol, after 3 h); lit,[3] α-D-**1**: mp 150—153°, $[\alpha]_D$ +127°→ +86° (*c* 1.0, ethanol)} quantitatively. As shown in Table 1, ^{1}H-NMR parameters reveal the relative structure, and ^{13}C-NMR data indicate the presence of an equatorial *C*-methyl group.[13] Both the opposite sign of the optical rotational values and of the Cotton effect (the molar ellipticity at 285 nm of **1** in methanol was −1580; lit,[3] for β-acetate of the natural compound, +2500) between **1** and the natural product proved that the latter has the D-configuration.

Experimental

Melting points are uncorrected. Optical rotations were measured with a JASCO DIP-4 polarimeter in chloroform, and ^{1}H and ^{13}C-NMR were recorded in chloroform-*d* with JEOL PS-100 and JEOL FX-100 spectrometers, respectively, with tetramethylsilane as an internal standard, unless otherwise stated. Chemical shifts and coupling constants were recorded in δ and Hz units, respectively, and IR frequencies in cm^{-1}.

*Methyl 4-O-Benzoyl-6-bromo-2,6-dideoxy-α-D-*ribo*-hexopyranoside (5).* A suspension of methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*ribo*-hexopyranoside (20 g, 75.2 mmol), *N*-bromosuccinimide (14.72 g, 82.7 mmol), and barium carbonate (80 g) in carbon tetrachloride (1.2 l) was refluxed for 2 h. The solution colored once red and then changed to colorless. The cooled reaction mixture was filtered, and the filtrate was evaporated to a half, poured into ice-water, then extracted with chloroform. The usual work-up of the extract, and purification of the product on a short column of silica gel gave **5** (22.7 g) as a sirup in 92.0% yield.

$[\alpha]_D$ +93.0° (*c* 1.0); NMR: δ=8.15—8.00 and 7.70—7.20 (m, 5H, Ph), 4.95 (dd, 1H, $J_{3,4}$=3.0, $J_{4,5}$=10.0, H-4), 4.95 (dd, 1H, $J_{1,2e}$=1.0, $J_{1,2a}$=3.6, H-1), 4.62—4.18 (m, 2H, H-3 and 5), 3.70—3.40 (m, 2H, H-6 and 6'), 3.50 (s, 3H, OMe), 2.22 (ddd, 1H, $J_{2e,3}$=3.6, H-2e), 2.04 (dt, 1H, $J_{2a,3}$=3.6, H-2a), and 1.75 (bs, 1H, OH).

Anal. ($C_{14}H_{17}O_5Br$) C, H, Br.

*Methyl 3-O-Benzoyl-6-bromo-2,6-dideoxy-4-O-methyl-α-D-*ribo*-hexopyranoside (6).* To a solution of **5** (13.8 g, 42.0 mmol) in *N*,*N*-dimethylformamide (50 ml) was added methyl iodide (17.9 g, 126 mmol) and silver(I) oxide (11.67 g, 50.4 mmol), and the mixture was stirred for 24 h at room temperature in the dark. After monitoring the disappearance of **5**, the mixture was filtered, and the filtrate was evaporated. The residual sirup was purified on a silica-gel column (benzene–aceonte 16:1) to give **6** (13.57 g) as a pale yellow sirup in 90.0% yield. $[\alpha]_D$+70.0° (*c* 1.9); NMR: δ=8.15—8.00 and 7.60—7.20 (m, 5H, Bz), 5.70 (dt, 1H, $J_{3,4}$=3.5, H-3), 4.83 (bd, $J_{1,2a}$=4.0, $J_{1,2e}$=1.0, H-1), 3.44 (dd, 1H, $J_{4,5}$=10.0, H-4), 4.24 (ddd, 1H, $J_{5,6}$=4.5, H-5), 3.90—3.60 (m, 2H, H-6 and 6'), 3.47 and 3.44 (each s, 6H, 2x OMe), 2.26 (ddd, 1H, $J_{2e,3}$=3.6, H-2e), and 1.98 (dt, 1H, $J_{2a,2e}$=15.5, $J_{2a,3}$=4.0, H-2a).

Anal. ($C_{15}H_{19}O_5Br$) C, H, Br.

Conversion of 6 into the Corresponding L-Sugar. A suspension of **6** (3.1 g, 8.64 mmol) and powdered silver(I) fluoride (3.1 g, 24.4 mmol) in dry pyridine (60 ml) was stirred for 40 h in the dark, then filtered. The filtrate was poured into ice–water, and extracted with chloroform. The extract was evaporated to give a yellow sirup, which was a 3:2 mixture of methyl 3-*O*-benzoyl-2,6-dideoxy-α-D-*erythro*-hex-5-enopyranoside (**8**) and methyl 3-*O*-benzoyl-2,6-dideoxy-6-fluoro-4-*O*-methyl-α-D-*ribo*-hexopyranoside (**7**). Because the mixture could not be separated, a solution of the mixture in methanol (36 ml) containing a few drops of acetic acid was hydrogenated in the presence of 10% palladium–carbon (383 mg) overnight, and then filtered. The filtrate was evaporated, and the dried residue was dissolved in 2M sodium hydroxide (30 ml). After stirring the solution at room temperature for 3 h, it was extracted with chloroform. Evaporation of the extract gave a yellow sirup which was fractionally crystallized from ethanol to give methyl 2,6-dideoxy-4-*O*-methyl-β-L-*lyxo*-hexopyranoside (**10**,739 mg) as white crystals in 48.6% overall yield. Mp 142.8—144 °C (ethanol); $[\alpha]_D$ +34.2° (*c* 1.0); NMR: 4.28 (dd, 1H, $J_{1,2a}$=10.0, $J_{1,2e}$=2.0, H-1), 3.90—3.30 (m, 2H, H-3 and 5), 3.64 and 3.51 (each s, 6H, 2×OMe), 3.16 (bd, 1H, $J_{3,4}$=3.6, $J_{4,5}$=<1, H-4), 2.00 (ddd, 1H, $J_{2e,3}$=5.0, $J_{2a,2e}$=12.0, H-2e), 1.67 (dt, 1H, $J_{2a,3}$= 10.0, H-2a), and 1.28 (d, 3H, H-6).

Anal. ($C_8H_{16}O_4$) C, H.

*Methyl 2,6-Dideoxy-4-O-methyl-β-L-*threo*-hexopyranosid-3-ulose (11).* A solution of **10** (500 mg, 2.84 mmol) and pyridinium chlorochromate (2.5 g, 11.6 mmol) in dichloromethane (12.5 ml) was stirred overnight at room temperature, and then evaporated roughly to dryness. The porduct was

purified directly on a silica-gel column (benzene–acetone 16:1) to give **11** (380 mg) as white crystals in 76.0% yield. Mp 38.8—40.4 °C (ethanol–hexane); $[\alpha]_D$ +92.0° (*c* 1.1); NMR: δ=4.57 (dd, 1H, $J_{1,2a}$=8.0, $J_{1,2e}$=3.0, H-1), 3.74 (dq, 1H, $J_{4,5}$=3.0, $J_{5,6}$=6.4, H-5), 3.56 and 3.41 (each s, 6H, 2×OMe), 3.37 (m, 1H, H-4), 2.87 (dd, 1H, $J_{2a,2e}$=13.0, H-2a), 2.57 (ddd, 1H, $J_{2e,4}$=1.0, H-2e), and 1.42 (d, 3H, H-6).

Anal. ($C_8H_{14}O_4$) C, H.

Cyanomesylation of 11. i) A solution of **11** (722 mg, 4.15 mmol) and hydrogen cyanide (170 mg, 6.19 mmol) in dry pyridine was kept at room temperature overnight, and then methanesulfonyl chloride (4.19 ml, 24.9 mmol) was added dropwise to it. The resulting solution was stirred for 2 d, diluted with chloroform, poured into ice–water, and then extracted with chloroform. The usual work-up of the extract, and purification of the product on a silica-gel column (benzene–acetone 8:1) gave methyl 3-*C*-cyano-2,6-dideoxy-3-*O*-methylsulfonyl-4-*O*-methyl-β-L-*lyxo*-hexopyranoside (**12**, 750 mg) as white plates in 64.8% yield. Mp 94.2—94.6 °C (ethanol); $[\alpha]_D$ −2.28° (*c* 1.0); NMR: δ=4.61 (dd, 1H, $J_{1,2a}$=9.0, $J_{1,2e}$=3.0, H-1), 3.91 (dq, 1H, $J_{4,5}$=1.4, $J_{5,6}$=6.4, H-5), 3.25 (s, 3H, SMe), 3.67 (bs, 1H, H-4), 3.17 and 3.54 (each s, 6H, 2×OMe), 2.47 (ddd, 1H, $J_{2a,2e}$=12.4, $J_{2e,4}$=1.0, H-2e), 2.27 (dd, 1H, H-2a), and 1.37 (d, 3H, H-6).

Anal. ($C_{10}H_{17}O_6NS$) C, H, N, S.

ii) To a solution of **11** (210 mg, 1.2 mmol) in dichloromethane (2.8 ml) was added a solution of potassium cyanide (157 mg, 2.14 mmol) and sodium hydrogencarbonate (101 mg, 1.20 mmol) in water (1.5 ml) at 0 °C and the solution was stirred at room temperature overnight. The usual work-up of the solution gave a product, which was treated with methanesulfonyl chloride (553 mg, 4.83 mmol) to give a product, which was fractionally crystallized from ethanol to give crystals of L-*xylo* isomer (**13**) of **12**. The component in the filtrate was separated on a silica-gel column (benzene–acetone 8:1). Compound **13** and **12** were obtained in 68.3% (230 mg) and 13.7% (46 mg) yield, respectively.

13: mp 91.2—92 °C (ethanol); $[\alpha]_D$ +0.57 °C (*c* 1.5); NMR: δ=4.67 (dd, 1H, $J_{1,2a}$=9.0, $J_{1,2e}$=3.0, H-1), 4.03 (dq, 1H, $J_{4,5}$=1.4, $J_{5,6}$=6.8, H-5), 3.76 and 3.54 (each s, 6H, 2×OMe), 3.33 (s, 3H, SMe), 3.57 (bs, 1H, H-4), 2.46 (ddd, 1H, $J_{2e,4}$=1.0, H-2e), 2.30 (dd, 1H, $J_{2a,2e}$=15.0, H-2a), 1.36 (d, 3H, H-6).

Anal. ($C_{10}H_{17}NO_6S$) C, H, N, S.

Spiro[aziridine-2,3′-(methyl 2,3,6-trideoxy-4-O-methyl-β-L-xylo-hexopyranoside)](16). To a solution of **12** (200 mg, 0.717 mmol) in anhydrous ether (24 ml) was added lithium aluminium hydride (140 mg, 1.05 mmol), and the resulting suspension was refluxed for 2 h. The excess reagent was decomposed by addition of a small amount of water to the reaction mixture and filtered, and the precipitate was washed with ethanol. The filtrate and washings were combined and extracted with chloroform. Evaporation of the extract and purification of the product on a silica-gel column (ethanol) gave **16** (96.7 mg) as a sirup in 65.2% yield. $[\alpha]_D$ 0° (*c* 1.0); NMR: δ=4.60 (dd, 1H, $J_{1,2a}$=9.6, $J_{1,2e}$=2.5, H-1), 3.89 (dq, 1H, $J_{4,5}$=1.4, $J_{5,6}$=6.4, H-5), 3.54 (bs, 1H, H-4), 3.52 and 3.45 (each s, 6H, 2×OMe), 2.32 (dd, 1H, $J_{2a,2e}$=13.5, H-2a), 2.35 (bs, 1H, NH), 1.90 and 1.83 (each s, 2H, NCH_2), 1.31 (d, 3H, H-6), and 1.05 (ddd 1H, $J_{2e,4}$=1.0, H-2e).

Anal. ($C_9H_{17}NO_3$) C, H, N.

Methyl 2,3,6-Trideoxy-3-C-methyl-4-O-methyl-3-nitro-β-L-xylo-hexopyranoside (15). A solution of **16** (187 mg, 1.0 mmol) in methanol (100 ml) was hydrogenolyzed under 120 atm hydrogen in the presence of Raney nickel (1.0 g) for 2 d, filtered, and then evaporated to give 3-amino-2,3,6-trideoxy-3-*C*-methyl-4-*O*-methyl-β-L-*xylo*-hexopyranoside (**14**) as a sirup, quantitatively. To a solution of the sirup in dichloromethane (3.0 ml) was added a solution of *m*-chloroperoxybenzoic acid (518 g, 3.0 mmol) in dichloromethane (3.0 ml) portionwise under refluxing, and the resulting solution was refluxed for 40 min, poured into 10% sodium sulfite solution, and then extracted with chloroform. The usual work-up of the extract, and purification of the product on a silica-gel column (benzene–acetone 6:1) gave **15** (123 mg) as a pale yellow sirup in 56.2% overall yield.

$[\alpha]_D$ −15.9° (*c* 0.8); NMR: δ=4.46 (dd, 1H, $J_{1,2a}$=9.6 $J_{1,2e}$=2.2, H-1), 3.80—3.50 (m, 2H, H-4 and 5), 3.68 and 3.54 (each s, 6H, 2×OMe), 2.56 (ddd, 1H, $J_{2a,2e}$=14.6, $J_{2e,4}$=1.4, H-2e), 1.82 (dd, 1H, H-2a), 1.68 (s, 3H, CMe) and 1.36 (d, 3H, $J_{5,6}$=6.0, H-6).

Anal. ($C_9H_{17}NO_5$) C, H, N.

L-Rubranitrose (1). A solution of **15** (56.7 mg, 0.26 mmol) in aq dioxane (1:1, 10.0 ml) of 0.05 M sulfuric acid was warmed at 90—95 °C for 2 h, neutralized with barium carbonate, and then filtered. The filtrate was evaporated, and the resulting sirup was purified on a silica-gel column (benzene–acetone 5:1) to give **1** (53.0 mg) as crystals in 98.0% yield. Physical properties of **1** were mentioned in Result and Discussion.

Anal. ($C_8H_{15}NO_5$) C, H, N.

References

1) Part XXXIV. J. Yoshimura, K. Hara, and M. Matsuzawa, *Bull. Chem. Soc. Jpn.*, **56**, 2189 (1983).

2) B. K. Bhuyan, S. P. Owen, and A. Dietz, *Antimicrob. Agents Chemother.*, **1965**, 91; C. E. Meyer, *ibid.*, **1965**, 97; F. Reusser, *Biochemistry*, **12**, 1136 (1973); H. Hoeksema, C. Chidester, S. A. Mizsak, and L. Bacznski, *J. Antibiot.*, **31**, 1067 (1978); A. P. Kozikowski, K. Sugiyama, and J. P. Springer, *Tetrahedron Lett.*, **1980**, 3257.

3) S. A. Mizsak, H. Hoeksema, and L. M. Pschigoda, *J. Antibiot.*, **32**, 771 (1979).

4) A. K. Ganguly, O. Z. Sarre, A. T. McPhall, and K. D. Onan, *J. Chem. Soc., Chem. Commun.*, **1977**, 313.

5) A. K. Mallams, M. S. Puar, and R. H. Rossman, *J. Am. Chem. Soc.*, **103**, 3938 (1981).

6) J. Yoshimura, T. Yasumori, T. Kondo, and K. Sato, *Carbohydr. Res.*, **106**, c1 (1982).

7) J. Yoshimura, M. Matsuzawa, K. Sato, and Y. Nagasawa, *Carbohydr. Res.*, **76**, 67 (1979).

8) J. Yoshimura, M. Matsuzawa, and M. Funabashi, *Bull. Chem. Soc. Jpn.*, **51**, 2064 (1978).

9) J. S. Brimacombe and K. M. M. Rahman, *Carbohydr. Res.*, **114**, c1 (1983).

10) A. Rosenthal and P. Catsoulacos, *Can. J. Chem.*, **46**, 2868 (1968).

11) T. M. Cheung, D. Horton, and W. Weckerle, *Carbohydr. Res.*, **58**, 139 (1977).

12) T. T. Thang, F. Winternitz, A. Lagranes, A. Olesker, and G. Lukacs, *Tetrahedron Lett.*, **21**, 4495 (1980); T. T. Thang and F. Winternitz, *J. Chem. Soc., Chem. Commun.*, **1979**, 153.

13) M. Miljković, M. Gligorijević, T. Sato, and D. Miljković, *J. Org. Chem.*, **39**, 1379 (1974); S. Omura, A. Nakagawa, A. Neszmelyi, S. D. Gero, A.-M. Sepulchre, F. Piriou, and G. Lukacs, *J. Am. Chem. Soc.*, **97**, 4001 (1975); K. Sato, K. Kubo, N. Hong, H. Kodama, and J. Yoshimura, *Bull. Chem. Soc. Jpn.* **55**, 938 (1982).