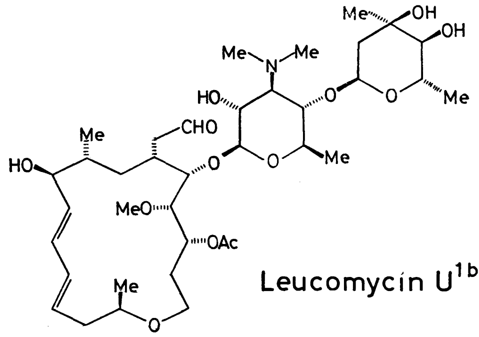
# Synthesis of Anomeric Methyl 6-*O*-(L-Mycarosyl)-β-D-glucosaminides and 4-*O*-(L-Mycarosyl)-β-D-mycaminosides

Shinkiti Koto, Kazuo Yago, Shonosuke Zen, and Satoshi Ōmura*
*School of Pharmaceutical Sciences, Kitasato University, Shirokane, Minato-ku, Tokyo 108*
**The Kitasato Institute, Shirokane, Minato-ku, Tokyo 108*

(Received September 27, 1972)

Condensation of 3,4-*O*-carbonyl-2,6-dideoxy-3-*C*-methyl-L-*ribo*hexopyranosyl chloride (III) with methyl 2-deoxy-2-(2,4-dinitroanilino)-β-D-glucopyranoside and the subsequent removal of blocking groups gave the anomeric isomers of methyl 6-*O*-(2,6-dideoxy-3-*C*-methyl-L-*ribo*hexopyranosyl)-2-amino-2-deoxy-β-D-glucopyranoside (VIIa, VIIb). On the other hand, the condensation of III with methyl 3,6-dideoxy-3-(*N*-methylcarboethoxyamino)-2-*O*-*p*-phenylazobenzoyl-β-D-glucopyranoside (XI) followed by removal of the acyl groups and *N*-methylation afforded the anomeric forms of methyl 4-*O*-(2,6-dideoxy-3-*C*-methyl-L-*ribo*hexopyranosyl)-3,6-dideoxy-3-dimethylamino-β-D-glucopyranoside (XVa, XVb).

Some 16-membered macrolide antibiotics such as magnamycin,[1] leucomycins,[2] spiramycin,[3] B-58945[4] and tylosin[5] have a unique structural feature. They contain a disaccharide moiety in which the neutral branched-chain sugar is linked glycosidically to the 3,6-dideoxy-3-dimethylamino-D-glucopyranose, D-mycaminose. Concerning the structural-activity relationship of macrolide antibiotics,[6] it was surmised that the sugar moiety could be important for antibiotic activity. Attempts to obtain the disaccharide moiety of leucomycins, 4-*O*-(2,6-dideoxy-3-*C*-methyl-α-L-*ribo*hexopyranosyl)-3,6-dideoxy-3-dimethylamino-β-L-glycopyranose, and confirm whether the moiety itself has any activity at all, failed, since 2,6-dideoxy-3-*C*-methyl-L-*ribo*hexopyranose, L-mycarose was preferentially released by acid hydrolysis from the disaccharide, which was expected to be cleaved from the lactone moiety. Thus as a part of chemical studies of macrolide sugar,[7] the syntheses of two model disaccharides have been carried out.[8] This paper deals with the preparation of 3,4-*O*-carbonyl-2,6-dideoxy-3-*C*-methyl-L-*ribo*hexopyranosyl chloride (III) and methyl 4-*O*-(2,6-dideoxy-3-*C*-methyl-L-*ribo*hexopyranosyl)-3,6-dideoxy-3-dimethylamino-β-D-glucopyranoside (XVa, XVb), as well as other related glycosides.



Leucomycin U[1b]

Methyl 3,4-*O*-carbonyl-2,6-dideoxy-3-*C*-methyl-α-L-*ribo*hexopyranosyl[9] (Ia) was hydrolyzed and converted into *p*-nitrobenzoyl derivative (II), which was then subjected to Zorbach's procedure[10] to generate III. The chloride was methanolyzed in the presence of silver oxide to give an anomeric mixture of Ia and Ib; β-anomer was predominant (α : β=2 : 3).

At first, the primary hydroxyl group of methyl 2-deoxy-2-(2,4-dinitroanilino)-β-D-glucopyranoside[11] was condensed with III. Condensation in nitromethane in the presence of mercuric cyanide gave an anomeric mixture (IVa and IVb); α-anomer was predominant (α : β=7 : 3). Condensation products (IVa and IVb) were characterized as the di-*O*-benzoate (Va and Vb). A similar condensation was performed in the presence of 2,6-lutidine,[12] and the predominant formation of the α-anomer was also observed (α : β= 5 : 3). The glycosidation at the C–6 position of 2-amino-2-deoxy-D-glucose was checked by PMR spectra of IVa and IVb in comparison with those of V's: signal of methine protons of C–3 and C–4 of glucosamine moiety shifted toward the lower field by *O*-benzoylation. The preferential glycosidation of the primary hydroxyl group in hexopyranoside has been reported.[13] Removal of the blocking groups of Va and Vb by successive methanolysis and hydrolysis gave methyl

---

[1] a) R. B. Woodward, L. S. Weiler, and P. C. Dutta, *J. Amer. Chem. Soc.*, **87**, 4662 (1965); b) N. E. Kuehe and B. W. Benson, *ibid.*, **87**, 4460 (1965).

[2] a) S. Ōmura, A. Nakagawa, M. Katagiri, T. Hata, M. Hiramatsu, T. Kimura, and K. Naya, *Chem. Pharm. Bull.* (Tokyo), **18**, 1501 (1970); b) S. Ōmura, M. Katagiri, A. Nakagawa, H. Yamane, I. Umezawa, K. Komiyama, and T. Hata, Progress in Antimicrobial and Anticancer Chemotherapy-Proceedings of the 6th International Congress of Chemotherapy, University of Tokyo Press, (1970), p. 1043.

[3] a) R. Paul and S. Tchelitheff, *Bull. Soc. Chim. Fr.*, **1965**, 650; b) S. Ōmura, A. Nakagawa, M. Otani, T. Hata, H. Ogura, and K. Furuhata, *J. Amer. Chem. Soc.*, **91**, 3401 (1969).

[4] T. Suzuki, This Bulletin, **43**, 292 (1970).

[5] R. B. Morin, M. Gorman, R. L. Hamil, and P. V. Darmaco, *Tetrahedron Lett.*, **1970**, 4737.

[6] S. Ōmura, M. Tichler, A. Nakagawa, Y. Hironaka, and T. Hata, *J. Med. Chem.*, **15**, 1011 (1972).

[7] S. Koto, S. Zen, S. Ōmura, and T. Hata, This Bulletin, **45**, 532 (1972).

[8] a) S. Koto, K. Yago, S. Zen, S. Ōmura, and T. Hata, *Chem. Lett.*, **1972**, 731; b) S. Koto, K. Yago, S. Zen, and S. Ōmura, *ibid.*, **1972**, 1091.

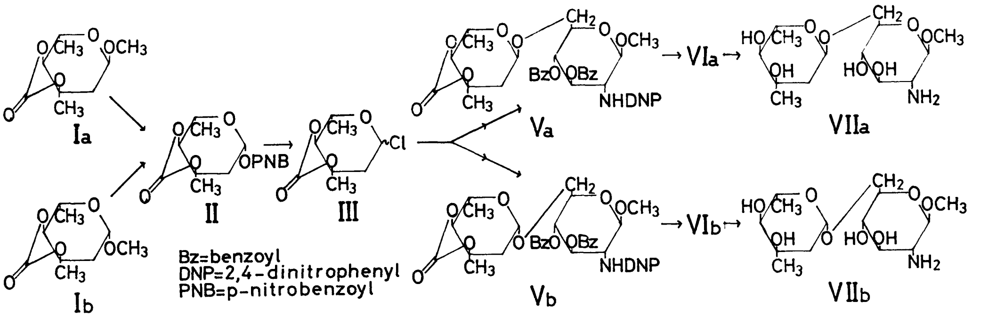
[9] W. Hofheinz, H. Grisebach, and H. Friebolin, *Tetrahedron*, **18**, 1265 (1962).

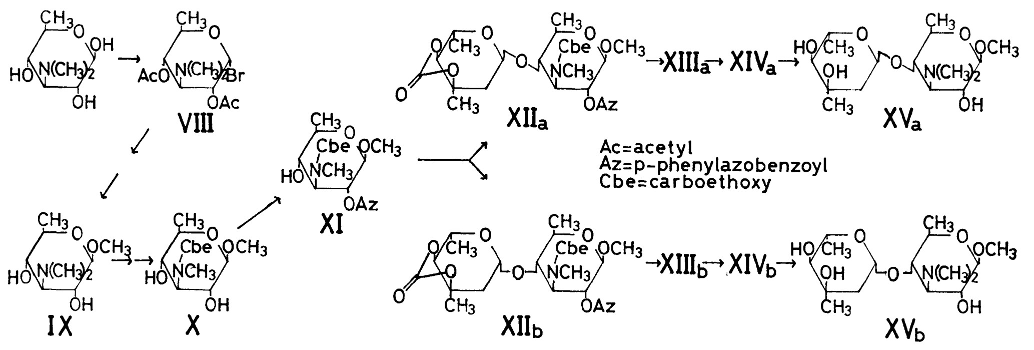
[10] W. W. Zorbach and K. V. Bhat, *Adv. Carbohydrate Chem.*, **21**, 273 (1966).

[11] W. Yu and T. Hsing, *Acta Chim. Sinica*, **24**, 368 (1958); R. F. Lloyd and M. Stacey, *Tetrahedron*, **9**, 116 (1960).

[12] S. Koto, T. Uchida, and S. Zen, *Chem. Lett.*, **1972**, 1049.

[13] A. M. Bills and J. W. Green, *J. Chem. Soc., B*, **1967**, 716.





6-*O*-(2,6-dideoxy-3-*C*-methyl-α-L-*ribo*hexopyranosyl)-3, 6-dideoxy-3-dimethylamino-β-D-glucopyranoside (VIIa) and its anomer (VIIb).

Finally, the synthesis of methyl 4-*O*-(2,6-dideoxy-3-*C*-methyl-α-L-*ribo*hexopyranosyl)-3,6-dideoxy-3-dimethylamino-β-D-glucopyranoside (XVa) was carried out. 3,6-Dideoxy-3-dimethyl-amino-β-D-glucopyranoside hydrochloride monohydrate[14] was treated with acetyl bromide[15] to give 2,4-di-*O*-acetyl-3,6-dideoxy-3-dimethyl-amino-α-D-glucopyranosyl bromide hydrobromide (VIII), which was methanolyzed, in the presence of silver oxide, to afford methyl 3,6-dideoxy-3-dimethyl-amino-β-D-glucopyranoside (IX).[16] Compound IX was treated with ethyl chloroformate in the presence of sodium carbonate[17] and ethanolyzed to give methyl 3,6-dideoxy-3-(*N*-methylcarboethoxyamino)-β-D-glucopyranoside (X). Partial acylation of the hydroxyl groups of X with a molar *p*-phenylazobenzoyl chloride in pyridine and subsequent chromatographical separation gave methyl 3,6-dideoxy-3-(*N*-methylcarboeth oxyamino)-2-*O*-(*p*-phenylazobenzoyl)-β-D-glucopyranoside (XI) in about 40% yield. The C-2-substitution of compound XI was checked by PMR. Direct partial acylation of IX gave no good results.

Chloride III was condensed with the partialy blocked XI in nitromethane in the presence of mercuric cyanide to afford two products, the α-glycoside XIIa and its β-anomer XIIb; α-glycoside was predominantly formed (α : β=3 : 2). The main product XIIa was converted into *O*-deblocked compound XIIIa which was then hydrolyzed into a free base XIVa. The reductive *N*-methylation with formaldehyde over palladium furnished desired methyl 4-*O*-(2,6-dideoxy-3-*C*-methyl-α-L-*ribo*hexopyranosyl)-3, 6-dideoxy-3-dimethylamino-β-D-glucopyranoside (XVa). The minor product XIIb was subjected to the above sequence of reactions to give the β-glycoside XVb.

The anomeric configuration of the synthesized mycarosides VIIa, VIIb, XVa, and XVb was confirmed by the observation of their optical rotation and PMR spectra. PMR data of these compounds indicated that the in mycarosyl moiety had the normal $C_4{}^1$ conformation in water (Table 1). In each disaccharide-synthesis, predominant formation of α-glycoside was observed; this is often the case with the glycosidation of the 2-deoxy sugar.[10]

MIC's of the free base, VIIa, VIIb, XVa, and XVb, against *Bacillus subtilis* PCI 219, *Staphylococcus aureus* FDA 209P, *Sarcine Lutea* PCI, 1001, *Escherichia coli* NIHJ, and *Klebsiella pneumoniae* were more than 100 μg/ /ml.

## Experimental

*General Procedure.* The solvent system used for tlc (Silica Gel No. 7731, Merck) and column chromatography over silica gel (Kanto Kagaku, Co.) was as follows : benzene : 2-butanone=(SA30) 30 : 1, (SA20) 20 : 1, (SA10) 10 : 1, (SA5) 5 : 1; benzene : acetone=(SB3) 3 : 1, (SB2) 2 : 1; acetone : methanol=(SC4) 4 : 1, (SC2) 2 : 1, by volume.

Melting points were determined with a Yanagimoto micromelting point apparatus; uncorrected values are given. Optical rotations were measured with an Atago Polux apparatus in 1-dm tube and IR spectra with a JASCO IRA-1 spectrometer, absorptions being given in $cm^{-1}$. PMR spectra were determined with a Varian S-60T spectrometer. Elemental analyses were made with a Perkin-Elmer Model 240 Analyser apparatus.

---

[14] F. A. Hochstein and K. Murai, *J. Amer. Chem. Soc.*, **76**, 5080 (1954).

[15] Y. Ito, S. Koto, and S. Umezawa, This Bulletin **35**, 1618 (1962).

[16] F. A. Hochstein and D. Regna, *J. Amer. Chem. Soc.*, **77**, 3353 (1955).

[17] J. Newman, *J. Org. Chem.*, **30**, 1287 (1965).

TABLE 1. PMR DATA OF H'-1 AND H'-4 OF MYCAROSIDES

| Compound | Configuration | Solvent | H'-1 (ppm) | $J_{1',2'e}$ (Hz) | $J_{1',2'a}$ (Hz) | H'-4 (ppm) | $J_{4',5'}$ (Hz) |
|---|---|---|---|---|---|---|---|
| IVa | $\alpha$ | C | 4.96 | 5.5 | 5.5 | — | — |
| IVb | $\beta$ | C | 4.88 | 4.5 | 10.5 | — | — |
| VIa | $\alpha$ | C | 4.92 | 2.0 | 2.0 | 3.02 | 10.0 |
| VIb | $\beta$ | C | 4.88 | 2.0 | 9.0 | 3.09 | 9.5 |
| VIIa | $\alpha$ | W | 4.94 | 2.0 | 4.0 | 3.14 | 10.0 |
| VIIb | $\beta$ | W | 4.90 | 2.0 | 10.0 | 3.08 | 10.0 |
| XIIa | $\alpha$ | C | 4.98 | 2.0 | 3.5 | 2.92 | 10.0 |
| XIIb | $\beta$ | C | 4.67 | 4.0 | 8.5 | 2.90 | 9.5 |
| XVa | $\alpha$ | W | 5.21 | 2.0 | 4.0 | 3.15 | 10.0 |
| XVb | $\beta$ | W | 5.05 | 3.0 | 9.5 | 3.07 | 9.5 |

C=$CDCl_3$/TMS, W=$D_2O$/TMSS

*Methyl 3,4-*O*-Carbonyl-2,6-dideoxy-3-*C*-methyl-β-*L-ribo*hexopyranoside (Ib).* Cold phosgene solution in toluene (25%; 17 ml) was added to a solution of methyl 2,6-dideoxy-3-*C*-methyl-β-L-*ribo*hexopyranoside[18] (0.69 g) in a mixture of chloroform (30 ml) and pyridine (7 ml). The resulting mixture was stirred at room temperature overnight. Chloroform-extract was chromatographed with the solvent SA10 to give Ib (0.73 g; 92%), bp 110—115 °C/0.003 mmHg, mp 53—54 °C, $[\alpha]_D^{25}+6.7°$ ($c$ 1.0, $CHCl_3$), $\nu_{max}^{KBr}$: 1795 (carbonate)

Found: C, 53.24; H, 6.99%. Calcd for $C_9H_{14}O_5$: C, 53.46; H, 6.84%.

*3,4-*O*-Carbonyl-2,6-dideoxy-3-*C*-methyl-1-*O*-(*p*-nitrobenzoyl)-β-*L-ribo*hexopyranose (II).* Cold concd hydrochloric acid (21 ml) was added to a solution of Ia[9] (0.74 g) in a mixed solvent of dioxane (35 ml) and water (35 ml). The solution was kept standing at room temperature for 3 days, neutralized with sodium bicarbonate to pH 5.5, concentrated and then extracted with chloroform. The extract (0.48 g) treated with *p*-nitrobenzoyl chloride (0.53 g) in pyridine (4.0 ml) gave a crude product (1.2 g), which was crystallized with isopropyl alcohol to give II (0.51 g; 41%); mp 153—154 °C; $[\alpha]_D^{25}+8°$ ($c$ 2.6, $CHCl_3$); $\nu_{max}^{KBr}$: 1785 (carbonate); 1730, (*p*-nitrobenzoyl); $\delta_{CDCl3}^{TMS}$: 1.45 (3H, doublet; $CH_3$-5, $J$=6.0 Hz, 1.65 (3H, singlet; $CH_3$-3), 2.15 (1H, quartet; H-2a, $J_{1,2a}$=7.5 Hz, $J_{2e,2a}$=15.5 Hz), 2.70 (1H, quartet; H-2e, $J_{1,2e}$=4.0 Hz), 6.30 (1H, quartet; anomeric H).

Found: C, 53.45; H, 4.43; N, 4.16%. Calcd for $C_{15}H_{15}NO_8$: C, 53.42; H, 4.48; N, 4.15%.

*3,4-*O*-Carbonyl-2,6-dideoxy-3-*C*-methyl-*L-ribo*hexopyranosyl Chloride (III) and Its Methanolysis.* II (0.750 g) was dissolved in dichloromethane (40 ml) saturated with hydrogen chloride at 0 °C and the mixture was kept standing at 5 °C for 40 min. *p*-nitrobenzoic acid (0.36 g; 97%) was filtered off, the resulting solution evaporated to dryness and co-evaporated with toluene three times to give III,[19] which was immediately used for the following glycosidation.

Freshly prepared III from II (216 mg) was stirred in methanol (2.0 ml) in the presence of silver oxide (152 mg) at room temperature for one hour in the dark, filtered and chromatographed with the solvent SA20 to give Ia (39 mg; 30%) and Ib (60 mg; 46%), which were identified by means of elemental analyses, mixed melting points and IR spectra (KBr), respectively.

*Methyl 6-*O*-(3,4-O-Carbonyl-2,6-dideoxy-3-*C*-methyl-α-*L-ribo*hexopyranosyl)-3,4-*O*-benzoyl-2-deoxy-2-(2,4-dinitroanilino)-β-*D*-glucopyranoside (Va) and Methyl 6-*O*-(3,4-*O*-Carbonyl-2,6-dideoxy-3-*C*-methyl-β-*L-ribo*hexopyranosyl)-3,4-*O*-benzoyl-2-deoxy-2-(2,4-dinitroanilino)-β-*D*-glucopyranoside (Vb).* By condensation with mercuric cyanide. III, prepared from II (0.75 g) was stirred with methyl 2-deoxy-2-(2,4-dinitroanilino) β-D-glucopyranoside[11] (1.00 g) in nitromethane (10 ml) in the presence of mercuric cyanide (0.750 g) at room temperature for 20 hr. The mixture was diluted with chloroform, filtered, and then chromatographed with the solvent SB3. After elution of high $R_f$ substances, a compound (IVb) of $R_f$ 0.33 (0.095 g; 8.1% from II) and that (IVa) of $R_f$ 0.25 (0.220g; 19%) were obtained. IVa (200mg) was treated with benzoyl chloride (0.2 g) in pyridine (2 ml), chromatographed with the solvent SA20 and crystallized with ethanol to give yellow Va (187 mg; 67%), mp 123—124 °C, $[\alpha]_D^{25}-13.5°$ ($c$ 0.9, $CHCl_3$), $\nu_{max}^{KBr}$: 1800 (carbonate); 1730 (benzoyl); 1620, 1530, 1345 (dinitrophenyl). Similarly, IVb (90 mg) was benzoylated to give yellow Vb (95 mg; 76%), mp 118—120 °C, $[\alpha]_D^{25}+16°$ ($c$ 0.9, $CHCl_3$), $\nu_{max}^{KBr}$: 1810 (carbonate); 1733 (benzoyl); 1620, 1525, 1340 (dinitrophenyl). PMR spectra of Va and Vb had multiplets of a couple of methine protons at $\delta$ 5.6—6.0, whereas those of IVa and IVb had no signal in this region.

Found: (Va) C, 56.78; H, 4.74; N, 5.96%. (Vb) C, 56.85; H, 4.75; N, 5.46%. Calcd for $C_{35}H_{35}N_3O_{15}$: C, 56.99; H, 4.78; N, 5.70%.

Methanolysis of IVa and IVb with methanolic hydrochloric acid[18] gave Ia and Ib and methyl 2-deoxy-2-(2,4-dinitroanilino)-β-D-glucopyranoside which were detected by tlc.

By condensation with 2,6-lutidine. III, prepared from II (0.78 g) was condensed with the methyl glucosaminide (1.1 g) in nitromethane (10 ml) in the presence of 2,6-lutidine (0.29 ml) for 20 hr at room temperature to yield IVa (0.170 g 14%) and IVb (0.095 g; 7.8%). Each compound was successively benzoylated to give Va and Vb, respectively. These compounds were identified with the above Va and Vb, respectively, by means of elemental analyses and mixed melting points.

*Methyl 6-*O*-(2,6-Dideoxy-3-*C*-methyl-α-*L-ribo*hexopyranosyl)-2-deoxy-(2,4-dinitroanilino)-β-*D*-glucopyranoside (VIa).* Va (104 mg) was treated with diluted sodium methoxide (0.14 M; 0.7 ml) at room temperature overnight, neutralized with dil. acetic acid (1% in methanol), purified by chromatography with the solvent SB2, and crystallized with benzene to give yellow VIa (51 mg; 72%), mp 116—118 °C, $[\alpha]_D^{25}$ −13° ($c$ 1.3, $CHCl_3$). The characteristic bands of carbonate and benzoyl were absent in the IR spectrum (KBr), $\delta_{CDCl3}^{TMS}$: 1.25

---

[18] S. Ōmura, M. Katagiri, H. Ogura, and T. Hata, *Chem. Pharm. Bull.* (Tokyo), **15**, 1529 (1967).

[19] Optical rotation could not be observed because of rapid formation of some dark green substance.

singlet; $CH_3$-3′), 1.31 (3H, doublet; $CH_3$-5′, $J$=6.0 Hz), 3.45 (3H, singlet; $OCH_3$), 4.42 (1H; H-1, $J_{1,2}$=6.5 Hz).

Found: C, 47.87; H, 5.77; N, 8.26%. Calcd for $C_{20}H_{29}N_3O_{12}$: C, 47.71; H, 5.81; N, 8.35%.

*Methyl 6-O-(2,6-Dideoxy-3-C-methyl-β-L-*ribo*hexopyranosyl)-2-deoxy-2-(2,4-dinitroanilino)-β-D-glucopyranoside (VIb).* Vb (58 mg) was treated with dil. sodium methoxide to give VIb (32 mg; 81%), mp 114—116 °C, $[\alpha]_D^{25}$ −4° (*c* 0.7, $CHCl_3$). $\delta_{\mathrm{CDCl3}}^{\mathrm{TMS}}$: 1.31 (3H, singlet; $CH_3$-3′), 1.33 (3H, doublet; $CH_3$-5′, $J$=6.5 Hz), 3.56 (3H, singlet; $OCH_3$), 4.36 (1H, doublet; H-1, $J_{1,2}$=6.0 Hz).

Found: C, 48.23; H, 6.01; N, 7.76%. Calcd for $C_{20}H_{29}N_3O_{12}$: C, 47.71; H, 5.81; N, 8.35%.

*Methyl 6-O-(2,6-Dideoxy-3-C-methyl-α-L-*ribo*hexopyranosyl)-2-amino-2-deoxyl-β-D-glucopyranoside (VIIIa).* VIa (50 mg) was treated with Dowex 1X2 (OH) (*ca.* 1 ml) in moist acetone[20] and a crude syrup was chromatographed over the same resin to give a ninhydrin-positive hard syrup of VIIa (27 mg; 81%), which was taken up with a small amounts of methanol and precipitated from isopropyl alcohol, diisopropyl ether, and *n*-hexane to give colorless hygroscopic powder, mp 100 °C; $[\alpha]_D^{25}$ −91° (*c* 1.1, $H_2O$); $\delta_{\mathrm{D_2O}}^{\mathrm{TMSS}}$: 1.22 (3H, singlet; $CH_3$-3′), 1.28 (3H, doublet; $CH_3$-5′, $J$=6.5 Hz), 3.54 (3H, singlet; $OCH_3$), 4.27 (1H; doublet; H-1, $J_{1,2}$=8.5 Hz).

Found: C, 48.38; H, 8.22; N, 3.94%. Calcd for $C_{14}H_{27}NO_8\cdot 1/2H_2O$: C, 48.54; H, 8.14; N, 4.04%.

*Methyl 6-O-(2,6-Dideoxy-3-C-methyl-β-L-*ribo*hexopyranosyl)-2-amino-2-deoxy-β-D-glucopyranoside (VIIb).* VIb (20 mg) was treated as above to give a hard syrup of VIIb (9.2 mg; 69%); which was treated with *n*-hexane to afford colorless hygroscopic powder, mp 100 °C, $[\alpha]_D^{25}$ −19° (*c* 0.4, $H_2O$). $\delta_{\mathrm{CDCl_3}}^{\mathrm{TMS}}$: 1.25 (3H, singlet; $CH_3$-3′), 1.26 (3H, doublet; $CH_3$-5′, $J$=6.0 Hz), 3.55 (3H, singlet; $OCH_3$), 4.28 (1H, doublet; H-1, $J$=8.0 Hz).

Found: C, 47.25; H, 8.31; N, 3.78%. Calcd for $C_{14}H_{27}NO_8\cdot H_2O$: C, 47.31; H, 8.22; N, 3.94%.

*2,4-Di-O-Acetyl-3,6-dideoxy-3-dimethylamino-α-D-glucopyranosyl Bromide Hydrobromide (VIII).* 3,6-Dideoxy-3-dimethylamino-β-D-glucopyranose hydrochloride monohydrate[14] (2.32 g) was added to ice-cooled acetyl bromide (5 ml). The mixture was kept standing in a sealed vessel at room temperature overnight, evaporated and co-evaporated thrice with toluene to give crystalline residue, which was triturated with *n*-hexane to give VIII (3.85 g; 97%), mp 72—76 °C, $[\alpha]_D^{25}$ +100° (*c* 0.7, $CHCl_3$); $\delta_{\mathrm{CDCl_3}}^{\mathrm{TMS}}$: 1.27 (3H, doublet, $CH_3$-5), 2.35 (6H, singlet; $OCOCH_3$), 3.03 (6H, broad, $\overset{+}{N}CH_3$), 6.66 (1H, doublet; H-1, $J_{1,2}$=4.0 Hz).

Found: C, 33.51; H, 4.83; N, 3.22%. Calcd for $C_{12}H_{20}NO_5Br\cdot HBr$: C, 34.39; H, 5.05; N, 3.34%.

*Methyl 3,6-Dideoxy-3-dimethylamino-β-D-glucopyranoside (IX).* VIII (1.91 g) was stirred in methanol (67 ml) in the presence of silver oxide (2.4 g) and anhydrous magnesium sulfate (5 g) at room temperature for 2 hr, filtered, and concentrated to give a residue which was treated with dil. sodium methoxide (0.05 M; 40 ml) for 2 hr at room temperature. The mixture was evaporated below 20 °C and then chromatographed with the solvent SC4 to give IX (0.74 g; 79%), mp 117—119 °C, which was used for the subsequent reaction. Sublimation at 95—100 °C under 0.02 mmHg gave an analytical sample,[21] mp 123—125 °C, $[\alpha]_D^{25}$ −35° (*c* 1.4, $H_2O$). Lit,[16] mp 126—126.5 °C, $[\alpha]_D^{25}$ −39° (*c* 1, $H_2O$).

*Methyl 3,6-Dideoxy-3-(N-methylcarboethoxyamino)-β-D-glucopyranoside (X).* IX (0.44 g) was stirred in ethyl chloroformate (10 ml) in the presence of powdery sodium carbonate (4.2 g) at room temperature for five days, filtered, evaporated, and co-evaporated thrice with toluene at 80 °C to give a syrup which was ethanolyzed with dil. sodium ethoxide (0.1 M, 38 ml) at room temperature overnight. The mixture was neutralized with acetic acid, evaporated and chromatographed with the solvent SB2 to give a homogeneous oil of X (0.47 g; 83%), $[\alpha]_D^{25}$ −1° (*c* 1.5, $CHCl_3$); $\delta_{\mathrm{CDCl_3}}^{\mathrm{TMS}}$: 1.27 (3H, triplet; $C\underline{H}_3CH_2O$–, $J$=7.0 Hz), 1.36 (3H, doublet; $CH_3$-5, $J$=5.7 Hz), 2.89 (3H, singlet; N-$CH_3$), 3.55 (3H, singlet; $OCH_3$), 4.14 (2H, quartet; $CH_3C\underline{H}_2O$–), 4.27 (1H, doublet; anomeric H, $J_{1,2}$=7.3 Hz).

After the elution of X, a small quantity of IX was recovered with the solvent SC4.

*Methyl 3,6-Dideoxy-3-(N-methylcarboethoxyamino)-2-O-p-phenylazobenzoyl-β-D-glucopyranoside (XI).* A well stirred mixture of *p*-phenylazobenzoyl chloride (2.7 g) in pyridine (60 ml) was added to a solution of X (27 g) in pyridine (40 ml) for 80 min at 2 °C under vigorous agitation and then the temperature was allowed to rise gradually up to 17 °C. The mixture was further stirred for 2 days at the same temperature, treated with a small amount of water, evaporated and then chromatographed with the solvent SA5. The fraction having $R_f$ 0.35 was crystallized with diisopropyl ether to give orange XI (1.8 g; 37%), mp 127—131 °C. Recrystallization form the same solvent gave a single product, mp 134—136 °C. $[\alpha]_D^{25}$ +57° (*c* 1.3, $CHCl_3$); 3410 (OH), 1727 (ester), 1680 (urethane); $\delta_{\mathrm{CDCl_3}}^{\mathrm{TMS}}$: 0.75 (3H, triplet; $C\underline{H}_3CH_2O$–, $J$=7.0 Hz), 1.53 (3H, doublet; $CH_3$-5, $J$=5.7 Hz), 2.83 (3H, singlet; $NCH_3$), 3.37 (3H, singlet; $OCH_3$), 4.72 (1H, doublet; anomeric H, $J$=7.5 Hz), 4.93 (1H, quasi-triplet; H-3, $J_{2,3}$=$J_{3,4}$=11.0 Hz), 5.57 (1H, quartet; H-2), Assignments of H-1, H-2, and H-3 were checked by the measurement at 100 MHz (Varian HA-100).

Found: C, 61.27; H, 6.22; N, 8.96%. Calcd for $C_{24}H_{29}N_3O_7$: C, 61.14; H, 6.20; N, 8.91%.

From the mother liquor, a second crop (0.4 g) having a melting point of 100—114 °C was obtained, but this gave no crystals when dissolved in diisopropyl ether. In this PMR spectrum, the quartet at δ 5.57 was entirely deformed by the appearance of new broad signals at δ 5.05—5.20, probably coming form H-4 of a 4-*O*-substituted minor product.

*Methyl 4-O-(3,4-O-Carbonyl-2,6-dideoxy-3-C-methyl-α-L-*ribo*hexopyranosyl-3,6-dideoxy-3-(N-methylcarboethoxyamino)-2-O-(p-phenylazobenzoyl)-β-D-glucopyranoside (XIIIa) and Methyl 4-O-3,4-Carbonyl-3,6-dideoxy-3-C-methyl-β-L-*ribo*hexopyranosyl)-3,6-dideoxy-3-(N-methylcarboethoxyamino)-2-O-phenylazobenzoyl-β-D-glucopyranoside (XIIb).* Chloride III, prepared from II (0.70 g) was stirred with XI (0.70 g) in nitromethane (5 ml) in the presence of mercuric cyanide (0.70 g) for 2 days at room temperature, diluted with chloroform filtered and evaporated, and then chromatographed with the solvent SA1O to give two crude products; a glass of $R_f$ 0.45 and that of $R_f$ 0.33. The main product $R_f$ 0.33 was refined by preparative tlc with the solvent SA20 with the multiple development technique, and triturated with diisopropyl ether containing *n*-hexane to give orange amorphous XIIa (0.15 g; 11%), mp 97—99 °C, $[\alpha]_D^{25}$ +2° (*c* 1.0, $CHCl_3$); $\nu_{\max}^{\mathrm{KBr}}$: 1805 (carbonate), 1733 (ester), 1700 (urethane); $\delta_{\mathrm{CDCl_3}}^{\mathrm{TMS}}$: 1.04 (3H, triplet; $C\underline{H}_3CH_2O$-, $J$=7.0 Hz), 1.52 (3H, singlet; $CH_3$-3′), 2.87 (3H, singlet; $NCH_3$), 3.48 (3H, singlet; $OCH_3$), 4.55 (1H, doublet; H-1, $J_{1,2}$=8.0 Hz).

The minor product was worked up as above with the solvent SA30 to give orange crystalline XIIb (0.095 g; 7%), 176—178 °C, $[\alpha]_D^{25}$ +105° (*c* 1.0, $CHCl_3$); $\nu_{\max}^{\mathrm{KBr}}$: 1805 (carbonate), 1720 (ester), 1705 (urethane); $\delta_{\mathrm{CDCl_3}}^{\mathrm{TMS}}$: 1.12 (3H, triplet; $C\underline{H}_3CH_2O$-, $J$=7.0 Hz), 1.51 (3H, singlet;

---

20) *cf.* S. Umezawa and S. Koto, This Bulletin, **39**, 2014 (1966).

21) Found: C, 52.88; H, 9.44; N, 6.50%.

$CH_3$-3′), 2.86 (3H, singlet; $NCH_3$), 3.50 (3H, singlet; $OCH_3$), 4.56 (1H, doublet; H-1, $J_{1,2}$=7.5 Hz).

Found: (XIIa) C, 59.20; H, 5.98; N, 6.16%. (XIIb) C, 59.78; H, 6.10; N, 6.53%. Calcd for $C_{32}H_{39}N_3O_{11}$: C, 59.90; H, 6.13; N, 6.55%.

*Methyl 4-O-(2,6-Dideoxy-3-*C*-methyl-α-*L*-*ribo*hexopyranosyl)-3,6-dideoxy-3-(*N*-methylcarboethoxyamino-β-*D*-glucopyranoside (XIIIa).* XIIa (65 mg) was treated with dil. sodium ethoxide (0.1 M; 20 ml), neutralized with dil. acetic acid (1%, in ethanol), dried up, chromatographed with the solvent SB3, and then crystallized with diisopropyl ether to give colorless XIIIa (27 mg; 65%), mp 94—96 °C, $[\alpha]_D^{25}$ −77° (*c* 1.0, $CHCl_3$), $\nu_{max}^{KBr}$: 1690, 1655 (urethane); $\delta_{CDCl_3}^{TMS}$ 2.94 (3H, singlet; $NCH_3$), 3.57 (3H, singlet; $OCH_3$), 4.20 (1H, doublet; H-1, $J_{1,2}$=7.5 Hz).

Found: C, 52.24; H, 8.12; N, 3.37%. Calcd for $C_{18}H_{33}NO_9$: C, 53.06; H, 8.16; N, 3.44%.

*Methyl 4-O-(2,6-Dideoxy-3-*C*-methyl-β-*L*-*ribo*hexopyranosyl)-3,6-dideoxy-3-(*N*-methylcarboethoxyamino)-α-*D*-glucopyranoside (XIIb).* XIIb (26 mg) was ethanolyzed in the same manner as above to give colorless XIIb (11 mg; 67%), mp 137—139 °C; $[\alpha]_D^{25}$ +17° (*c* 1.0, $CHCl_3$); $\nu_{max}^{KBr}$: 1690 (urethane); $\delta_{CDCl_3}^{TMS}$: 2.89 (3H, singlet, $NCH_3$), 3.56 (3H, singlet; $OCH_3$).

Found: C, 52.77; H, 8.18; N, 3.49%. Calcd for $C_{18}H_{33}NO_9$: C, 53.06; H, 8.16; N, 3.44%.

*Methyl 4-O-(2,6-Dideoxy-3-*C*-methyl-α-*L*-*ribo*hexopyranosyl)-3,6-dideoxy-3-methylamino-β-*D*-glucopyranoside (XIVa).* XIIIa (17 mg) was hydrolyzed with aqueous barium hydroxide (8%; 4 ml) at 95 °C for 10 hr, neutralized with carbon dioxide, filtered and then chromatographed over Dowex 1X2 (OH) with carbon dioxide-free water to give a ninhydrin-positive hard syrup of XIVa (11 mg; 79%), which was crystallized with diisopropyl ether to afford colorless crystals, mp 164—167 °C (sintered at 155 °C), $[\alpha]_D^{25}$ −68° (*c* 0.7, $CH_3OH$).

Found: C, 53.14; H, 8.74; N, 4.03%. Calcd for $C_{15}H_{29}NO_7$: C, 53.72; H, 8.71; N, 4.18%.

*Methyl 4-O-(2,6-Dideoxy-3-*C*-methyl-β-*L*-*ribo*hexopyranosyl)-3,6-dideoxy-3-methylamino-β-*D*-glucopyranoside (XIVb).* XIIIb (12 mg) was hydrolyzed as above to give a hard syrup of XIVb (8.0 mg; 81%), which was crystallized with diisopropyl ether to give colorless crystals, mp 195—197 °C, $[\alpha]_D^{25}$ +8° (*c* 0.7, $CH_3OH$).

Found: C, 53.17; H, 8.68; N, 4.12%. Calcd for $C_{15}H_{29}NO_7$: C, 53.72; H, 8.71; N, 4.18%.

*Methyl 4-O-(2,6-Dideoxy-3-*C*-methyl-α-*L*-*ribo*hexopyranosyl)-3.6-dideoxy-3-dimethylamino-β-*D*-glucopyranoside (XVa).* XIVa (11 mg) was dissolved in ethanol (2 ml) containing formaline (37%; 0.1 ml), hydrogenated over palladium black (10 mg) under hydrogen pressure of 50 lb/in$^2$ (initial) for 18 hr at room temperature, filtered, evaporated to dryness and then chromatographed over Dowex 1X2 (OH), irrigated with carbon dioxide-free water to give a homogenous ninhydrin-negative syrup of XVa (11 mg; 96%),[22] which could not be crystallized by any treatment; $[\alpha]_D^{25}$ −93° (*c* 1.1, $C_2H_5OH$); $\delta_{D_2O}^{TMSS}$: 1.22 (3H, singlet; $CH_3$-3′), 1.30 6H, doublet; $CH_3$-5, $CH_3$-5′, *J*=6.5 Hz), 2.48 (6H, singlet; $NCH_3$), 3.54 (3H, singlet; $OCH_3$), 4.24 (1H, doublet; H-1, $J_{1,2}$=8.0 Hz).

*Methyl 4-O-(2,6-Dideoxy-3-*C*-methyl-β-*L*-*ribo*hexopyranosyl)-3,6-dideoxy-3-dimethylamino-β-*D*-glucopyranoside (XVb).* XIVb 9.0 mg) was *N*-methylated as above to give a ninhydrin-negative glass of XVb (8.5 mg; 91%), $[\alpha]_D^{25}$ +14° (*c* 0.9, $C_2H_5OH$); $\delta_{D_2O}^{TMSS}$: 1.26 (3H, singlet; $CH_3$-3′), 2.43 (6H, singlet; $NCH_3$), 3.53 (3H, singlet; $OCH_3$), 4.31 (1H, doublet; H-1, $J_{1,2}$=8.0 Hz). Trituration with *n*-hexane turned XVb into powder, mp 134—136 °C (sintered at 125 °C).

Found: C, 53.23; H, 8.72; N, 3.82%. Calcd for $C_{16}H_{31}NO_7 \cdot 1/2H_2O$: C, 53.61; H, 9.00; N, 3.91%.

When a sample of XVa and XVb was methanolyzed with dil. methanolic hydrochloric acid,[18] formation of methyl 2,6-dideoxy-3-*C*-methyl-α- and β-*ribo*hexopyranoside was observed by tlc with the solvent SB2. Hot hydrolysis of XVa and XVb with dil. hydrochloric acid[18] gave 3,6-dideoxy-3-dimethylamino-D-glucopyranose, which was detected by tlc with the solvent SC2.

The authors wish to thank Toyo Jozo Co. for the supply of Leucomycin bulk, and Mr. K. Kushida of Nichiden-Varian for measurement of the 100 MHz PMR spectrum.

---

[22] A sample of methyl 2,6-dideoxy-3-*C*-methyl-α- and β-*ribo*hexopyranoside was subjected to hydrolysis with hot aqueous barium hydroxide and subsequent reductive *N*-methylation. Its perfect stability under this treatment was confirmed by observation of tlc. On the other hand, Compound X gave IX by this treatment, with no by-products.