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# SYNTHESIS OF NOVEL BRANCHED-CHAIN AMINO SUGARS: METHYL L-SIBIROSAMINIDE AND *N*-ACYLKANSOSAMINE

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ABSTRACT

Methyl L-sibirosaminide and *N*-acylkansosamine were synthesized *via* the same intermediate, methyl 4-amino-4,6-dideoxy-2,3-*O*-isopropylidene-3-*C*-methyl-α-L-mannopyranoside (**7**), from L-rhamnose in 7 and 10 steps, respectively. Conversion of **7** into the title compounds was performed by *N*-methylation or *N*-(2-methoxypropanoyl)ation followed by appropriate derivatization.

## INTRODUCTION

Sibirosamine[1] (**1**) and *N*-acylkansosamine[2] (**2**) form a unique class of branched-chain amino sugars. The former is a component sugar of an antibiotic, sibiromycin[3], which has remarkable antitumor activity. Among the benzodiazepinone antitumor antibiotics, sibiromycin undergoes the most rapid reaction with DNA and forms the most stable adduct. It was at first proposed that the structure of methyl sibirosaminide is methyl 4,6-dideoxy-3-*C*-methyl-4-(methylamino)-β-D-altropyranoside, this being based on chemical degradation, and $^1$H-n.m.r.-spectral and optical data, by Mestensev and Kuljaeva[4] in 1973. Since that proposal, various groups[5] have reported the preparation of supposed sibirosamine derivatives which were, however, not comparable with those from the natural product. In 1982, Parker and Babine[6] revised the configuration of sibirosamine to be L-*manno*, by synthesis of an *N*-tosylsibirosamine derivative which was directly compared with that from sibiromycin.

The other compound, *N*-acylkansosamine (**2**) is a component sugar of the antigenic trehalose-containing lipo-oligosaccharides of *Mycobacterium kansasii* and exists in the distal nonreducing terminus. For the structure of this novel branched-chain amino sugar, which is regarded as exclusive to *M. kansasii* and as its primary cell-wall immunodeterminant, Hunter *et al.*[7] proposed 4,6-dideoxy-4-(2-methoxypropanamido)-3-*C*-methyl-2-*O*-methyl-L-mannopyranose from $^1$H- and $^{13}$C-n.m.r.-spectral and mass-spectrometric data. However, the decision as to the absolute

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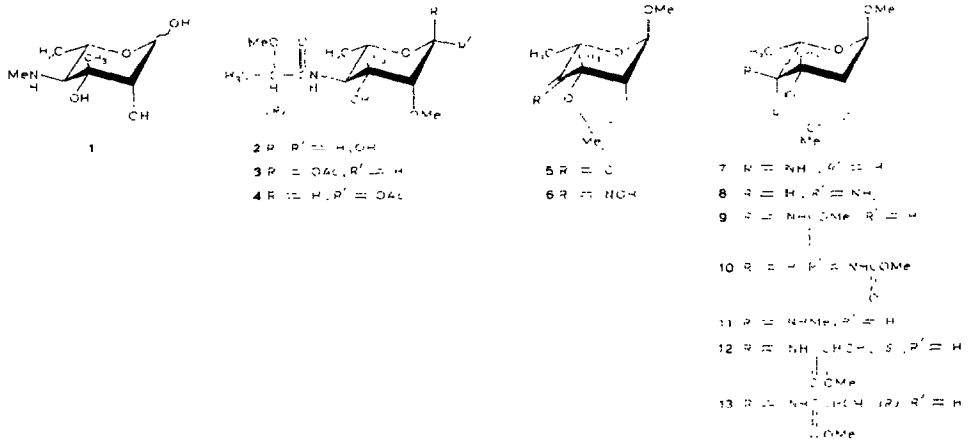
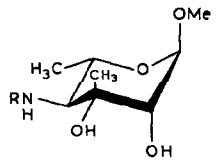
configuration was tentative, and the configuration of the side-chain on C-4 remained to be clarified. In a previous paper[8], we communicated an efficient approach to the synthesis of sibirosaminide from L-rhamnose, and thereafter extended it to the synthesis of *N*-acylkansosamine[9]. The details of both syntheses are given herein. The later synthesis disclosed the absolute configurations of the hexose and *N*-acyl moieties to be L-*manno* and *R*, respectively.

## RESULTS AND DISCUSSION

Considering the known stereoselectivity in the reactions of methylmagnesium iodide, methyllithium, and diazomethane with D-*arabino*-hexopyranosid-3-uloses[10], use of other methods is necessary for the synthesis of branched-chain hexoses having an axial methyl group at C-3, such as sibirosamine and *N*-acylkansosamine. Methylation of aldulose enolates, reported by Klemer *et al.*[11], provided a suitable synthetic intermediate, namely, methyl 6-deoxy-2,3-*O*-isopropylidene-3-*C*-methyl-α-L-*lyxo*-hexopyranosid-4-ulose (**5**). Treatment of **5** with hydroxylamine hydrochloride in 1:1 pyridine–ethanol at 80° gave a mixture of the *syn* and *anti* forms of oxime **6** in almost quantitative yield. Catalytic reduction of the mixture **6** in the presence of palladium–charcoal in ethanol–acetic acid gave exclusively the 4-amino derivative **8** having the undesired L-*talo* configuration, as would generally be expected from the bicyclic structure of the oxime **6**. However, reduction of the mixture **6** with lithium aluminum hydride in oxolane gave the amino derivatives as a 1:1 mixture of the L-*manno* (**7**) and L-*talo* (**8**) isomers. Although these 4-epimers could be separated on a column of silica gel, separation after *N*-(methoxycarbonyl)ation proved to be more efficient. Treatment of a mixture of **7** and **8** with methyl chloroformate at room temperature gave a mixture of **9** and **10** in 94% yield, from which only the desired isomer **9** was obtained in pure form by crystallization from hexane–ethyl acetate.



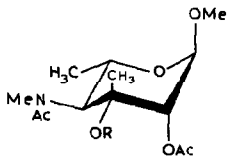
The carbamate **9** was converted into the *N*-methyl derivative in excellent yield (92%) by reduction with lithium aluminum hydride in ether. Selective hydrolysis of the isopropylidene group of **11** with 80% acetic acid at 90° gave methyl sibirosaminide (**14**) in 69% yield. Acetylation of **14** with acetic anhydride in pyridine gave the crystalline *N*-acetyl-*O*-acetyl derivative **17**. Furthermore, acetylation of **17** with acetic anhydride in pyridine containing a catalytic amount of 4-(dimethylamino)pyridine afforded crystalline *N*-acetyl-di-*O*-acetyl derivative **18** in 71% yield. The physical data for **17** and **18** were in accord with those reported for the compounds from the natural product. Attempted hydrolysis in 2M HCl at 90° of **14** to yield the free sugar **1** was unsuccessful, resulting in decomposition[12].




**14** R = Me

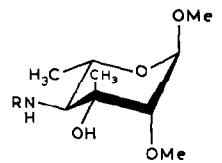
**15** R = $-\overset{\overset{O}{\|}}{C}CHCH_3$ *(S)*
OMe

**16** R = $-\overset{\overset{O}{\|}}{C}CHCH_3$ *(R)*
OMe




**17** R = H

**18** R = Ac




**19** R = $-\overset{\overset{O}{\|}}{C}CHCH_3$ *(S)*
OMe

**20** R = $-\overset{\overset{O}{\|}}{C}CHCH_3$ *(R)*
OMe

The synthesis of *N*-acylkansosamine was achieved as follows. Large-scale preparation of **7** in 95% yield was performed by hydrolysis of **9** by heating with aqueous potassium hydroxide in ethylene glycol. The amine **7** was coupled with (*S*)-2-methoxypropanoic acid in dichloromethane, using 3-(3-dimethylaminopropyl)-1-ethylcarbodiimide hydrochloride, to give the corresponding *N*-acyl derivative **12**. *O*-Deisopropylidenation of **12** afforded syrupy methyl 4,6-dideoxy-4-[(*S*)-2-methoxypropanamido]-3-*C*-methyl-α-L-mannopyranoside (**15**) in 87% yield.

The secondary hydroxyl group of **15** was selectively methylated with sodium hydride–methyl iodide in *N*,*N*-dimethylformamide at −5°, to yield the crystalline 2-*O*-methyl derivative **19** in 53% yield. However, the $^1$H-n.m.r. data found for **19** were not identical with those reported for the natural product.

Thereafter, coupling of **7**, as already described but with (*R*)-2-methoxypropanoic acid, prepared by optical resolution of the racemic acid, gave the corresponding *N*-acyl derivative **13** in quantitative yield. As for **12**, *O*-deisopropylidenation of **13**, followed by 2-*O*-methylation, gave methyl 4,6-dideoxy-4-[(*R*)-2-methoxypropanamido]-3-*C*-methyl-2-*O*-methyl-α-L-mannopyranoside (**20**). Alternatively, 2-*O*-methylation of **16** with silver oxide–methyl iodide in toluene also gave, in 93% yield, crystalline **20**, whose $^1$H-n.m.r. spectrum was exactly superposable on that of derived from the natural product. Hydrolysis of the methyl glycoside with 0.5M sulfuric acid for 4 h at 90° gave syrupy free *N*-acylkansosamine

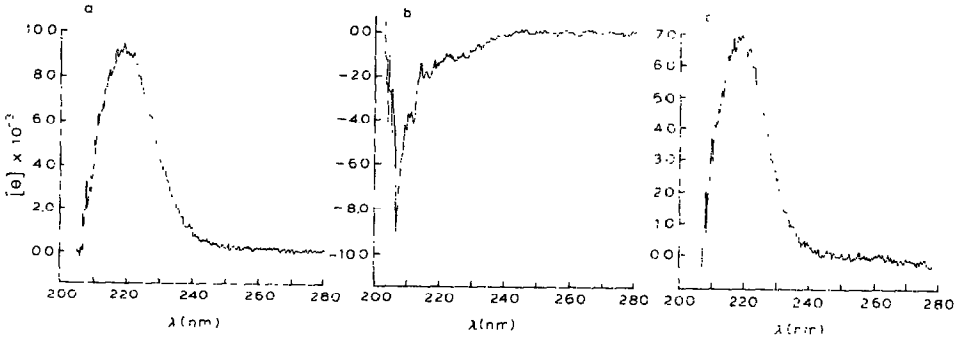



Fig. 1. C.d. spectra of compounds **20** (Fig. 1a), **19** (1b), and **2** (1c) in methanol. **20**: $[\theta]_{220}$ +9100 (0.34 mmol/L); **19** $[\theta]_{217}$ −9400 (0.34 mmol/L); **2**: $[\theta]_{220}$ +6900 (0.22 mmol/L).

(**2**). Furthermore, acetylation of **2** with acetic anhydride in pyridine gave the α-1-*O*-acetyl (**3**) and β-1-*O*-acetyl (**4**) derivatives, whose $^1$H- and $^{13}$C-n.m.r. data were also identical with those already reported (in Tables I and II in a preliminary communiation[9]). Thus, the structure of *N*-acylkansosamine was clearly ascertained to be 4,6-dideoxy-4-[(*R*)-2-methoxypropanamido]-3-*C*-methyl-2-*O*-methyl-L-mannopyranose or its enantiomer, *i.e.*, 4,6-dideoxy-4-[(*S*)-2-methoxypropanamido]-3-*C*-methyl-2-*O*-methyl-D-mannopyranose, which, of course, cannot be distinguished by n.m.r. spectroscopy.

The question still remaining, regarding the absolute stereochemistry, could not be answered from the optical rotation, owing to its small value, but was clarified by measurement of c.d. spectra. C.d. spectra of the methyl *N*-acylkansosaminides having the (*R*)-acyl moiety (**20**) and the (*S*)-acyl one (**19**) respectively show positive and negative Cotton effects (see Fig. 1a and 1b). Because both the synthetic (see Fig. 1c) and the natural* *N*-acylkansosamine show positive Cotton effect at 220 nm, the structure of *N*-acylkansosamine was unequivocally proved to be 4,6-dideoxy-4-[(*R*)-2-methoxypropanamido]-3-*C*-methyl-2-*O*-methyl-L-mannopyranose. The present work provided an efficient short-step synthetic approach to these novel branched-chain amino sugars and led to assignment of the absolute configuration of *N*-acylkansosamine.

## EXPERIMENTAL

*General methods.* — All melting points are uncorrected. Solutions were evaporated under diminished pressure at 35° (bath). Optical rotations were measured with a Jasco DIP-4 polarimeter at 20° ±5°. C.d. spectra were recorded with a Jasco J-500 C spectropolarimeter. $^1$H-N.m.r. and $^{13}$C-n.m.r. spectra were respectively recorded with a JEOL PS-100 spectrometer and a JEOL FX-90

*The c.d. spectrum of synthetic *N*-acylkansosamine was well superposable on that of the natural compound, which showed a slightly lower value of $[\theta]_{220}$.

spectrometer, for solutions in $CDCl_3$ (internal $Me_4Si$) unless otherwise stated. Chromatography was performed on Wakogel C-200, and preparative t.l.c. on silica gel 60 (Merck).

*Methyl 6-deoxy-2,3-*O*-isopropylidene-3-*C*-methyl-α-*L*-lyxo-hexopyranosid-4-ulose oxime* (**6**). — To a solution of **5** (8.52 g, 37 mmol) in 1:1 pyridine–ethanol (100 mL) was added hydroxylamine hydrochloride (7.7 g, 111 mmol), and the mixture was kept for 3 h at 80° with stirring. The mixture was cooled and evaporated to give a residue which, after coevaporation with toluene to remove any traces of pyridine, was dissolved in dichloromethane. The solution was thoroughly washed with water, dried (magnesium sulfate), and evaporated *in vacuo*, to afford a *syn–anti* mixture of the corresponding oxime as a syrup (9.0 g, 96%). The ratio of the geometrical isomers was 2–3:1. A small portion thereof was purified by t.l.c. in 4:1 hexane–ethyl acetate; $[\alpha]_D$ −110° (*c* 1.0, $CHCl_3$); $^1$H-n.m.r.: δ 9.90 (bs, 0.7 H, NOH), 4.93 (s, 0.7 H, H-1), 4.37 (q, 0.7 H, $J_{5,6}$ 6.0 Hz, H-5), 3.77 (s, 0.7 H, H-2), 3.44 (s, 2.1 H, OMe); minor isomer: 9.15 (bs, 0.3 H, NOH), 4.48 (q, 0.3 H, $J_{5,6}$ 6.0 Hz, H-5), 4.60 (s, 0.3 H, H-1), 3.97 (s, 0.3 H, H-2), 3.40 (s, 0.9 H, OMe), and 1.60–1.40 (m, 9 H, H-6 and CMe).

*Anal.* Calc. for $C_{11}H_{19}NO_5$: C, 53.86; H, 7.81; N, 5.71. Found: C, 53.91; H, 7.63; N, 6.03.

*Methyl 4,6-dideoxy-2,3-*O*-isopropylidene-4-(methoxycarbonylamino)-3-*C*-methyl-α-*L*-mannopyranoside* (**9**) *and the* L-talo *isomer* (**10**). — A solution of **6** (8.0 g, 32.6 mmol) in dry oxolane (20 mL) was gradually added to a stirred suspension of lithium aluminum hydride (3.66 g, 97.8 mmol) in oxolane (200 mL). The mixture was heated under reflux for 24 h, cooled, and the excess of hydride decomposed by careful addition of ethyl acetate followed by water. The precipitates were filtered off, and washed with ethyl acetate. The filtrate and washings were combined, dried, and evaporated, to give a crude syrupy mixture of the L-*manno* (**7**) and L-*talo* isomer (**8**) (1:1; 7.5 g). This mixture (5.0 g, 21.6 mmol) was dissolved in methanol (50 mL) and to the solution were added sodium hydrogencarbonate (5.44 g, 64.8 mmol) and the methyl chloroformate (3.06 g, 32.4 mmol), with stirring. After 1 h, the solids were removed by filtration, and the filtrate was evaporated. The residue was dissolved in chloroform, and the solution washed with water, dried (magnesium sulfate), and evaporated under diminished pressure, to yield a mixture of **9** and **10** (6.23 g). The L-*manno* derivative **9** crystallized on trituration with hexane, and was recrystallized from hexane–ethyl acetate, to give fine needles (2.86 g, 46%). The residual syrup obtained from the first filtrate was purified on a column of silica gel with 1:4 ethyl acetate–hexane, to give **10** (3.0 g, 48%).

Compound **9** had m.p. 184–185°; $[\alpha]_D$ −57.8° (*c* 1.0, $CHCl_3$); $^1$H-n.m.r.: δ 4.90 (s, 1 H, H-1), 4.60 (bd, $J_{NH,4}$ 10.0 Hz, NH), 3.91 (t, 1 H, $J_{NH,4} = J_{4,5} = 10.0$ Hz, H-4), 3.83 (s, 1 H, H-2), 3.72 (s, 3 H, $CO_2Me$), 3.60 (dq, 1 H, $J_{5,6}$ 6.2 Hz, H-5), 3.40 (s, 3 H, OMe), 1.63, 1.37, and 1.32 (each s, 9 H, CMe), and 1.26 (d, 3 H, H-6).

*Anal.* Calc. for $C_{13}H_{23}NO_6$: C, 53.96; H, 8.01; N, 4.84. Found: C, 53.81; H, 7.74, N, 4.59.

Compound **10** was syrup; $[\alpha]_D$ −39.8° (*c* 1.5, $CHCl_3$); $^1$H-n.m.r.: δ 5.13 (bd, 1 H, $J_{NH,4}$ 10.0 Hz, NH), 4.87 (s, 1 H, H-1), 4.00 (dq, 1 H, $J_{4,5}$ 1.4, $J_{5,6}$ 6.4 Hz, H-5), 3.74 (s, 1 H, H-2), 3.71 (s, 3 H, $CO_2Me$), 3.52 (bd, 1 H, H-4), 3.39 (s, 3 H, OMe), 1.47 and 1.38 (each s, 3 H, CMe), and 1.23 (d, 3 H, H-6).

*Anal.* Calc. for $C_{13}H_{23}NO_6$: C, 53.96; H, 8.01; N, 4.84. Found: C, 53.78; H, 7.94; N, 4.75.

*Methyl 4-amino-4,6-dideoxy-2,3-*O*-isopropylidene-3-C-methyl-α-*L*-mannopyranoside* (**7**). — A stirred solution of **9** (1.0 g, 0.35 mmol) in ethylene glycol (10 mL) containing potassium hydroxide (200 mg) in water (5 mL) was kept overnight at 100°, cooled, extracted with chloroform, and the extract washed with water, dried (magnesium sulfate), and evaporated: purification of the residue on a short column of silica gel with 9:1 chloroform–methanol gave **7** (0.76 g, 95%) as a syrup: $[\alpha]_D$ −53.3° (*c* 2.1, $CHCl_3$); $^1$H-n.m.r.: δ 4.86 (s, 1 H, H-1), 3.79 (s, 1 H, H-2), 3.50 (dq, 1 H, $J_{4,5}$ 10, $J_{5,6}$ 6.5 Hz, H-5), 3.38 (s, 3 H, OMe), 2.82 (d, 1 H, H-4), 1.49, 1.36, and 1.29 (each s, 9 H, CMe), 1.26 (d, 3 H, H-6), and 1.11 (bs, 2 H, $NH_2$).

*Anal.* Calc. for $C_{11}H_{21}NO_4$: C, 57.12; H, 9.15; N, 6.06. Found: C, 57.04; H, 8.77; N, 6.23.

*Methyl 4-amino-4,6-dideoxy-2,3-*O*-isopropylidene-3-C-methyl-α-*L*-talopyranoside* (**8**). — *A. N-Demethoxycarbonylation of* **10**. Treatment of **10** (100 mg, 0.35 mmol) with potassium hydroxide (20 mg) in ethylene glycol (3 mL) and water (2 mL), as described for **7**, gave **8** (71 mg, 86%).

*B. Catalytic reduction of* **6**. Hydrogen was bubbled through a solution of **6** (100 mg) in ethanol (10 mL) containing acetic acid (2 drops) and palladium–charcoal (10%) in catalytic amount. After 8 h, the undissolved materials were filtered off, and the filtrate was evaporated, to give **8** (83 mg, 88%) of sufficient purity, as a syrup; $[\alpha]_D$ −48.7° (*c* 1.7, $CHCl_3$); $^1$H-n.m.r.: δ 4.87 (s, 1 H, H-1), 3.96 (dq, 1 H, $J_{4,5}$ 1.0, $J_{5,6}$ 6.0 Hz, H-5), 3.74 (s, 1 H, H-2), 3.38 (s, 3 H, OMe), 2.37 (bs, 1 H, H-4), 1.51, 1.40, and 1.36 (each s, 11 H, CMe and $NH_2$), and 1.34 (d, 3 H, H-6).

*Anal.* Calc. for $C_{11}H_{21}NO_4$: C, 57.12; H, 9.15; N, 6.06. Found: C, 57.46; H, 8.83; N, 6.17.

*Methyl 4,6-dideoxy-2,3-*O*-isopropylidene-4-[(*S*)-2-methoxypropanamido]-3-C-methyl-α-*L*-mannopyranoside* (**12**). — (*S*)-2-Methoxypropanoic acid (500 mg, 4.8 mmol) was added to a solution of **7** (1.04 g, 4.49 mmol) in dichloromethane (30 mL) containing 3-(3-dimethylaminopropyl)-1-ethylcarbodiimide hydrochloride (0.85 g, 4.8 mmol) at room temperature. After stirring for 2 h, the mixture was washed well with water, dried (magnesium sulfate), and evaporated. Column chromatography of the residue on silica gel with 1:4 ethyl acetate–hexane gave syrupy **12** (1.37 g, quantitative); $[\alpha]_D$ −78.6° (*c* 1.0, $CHCl_3$); $^1$H-n.m.r.: δ 6.46 (bd, $J_{NH,4}$ 10.3 Hz, NH), 4.90 (s, 1 H, H-1), 4.23 (t, 1 H, $J_{4,5}$ 10.3 Hz, H-4), 3.81 (q, 1 H, $J_{1',2'}$ 6.4 Hz, H-1'), 3.80 (s, 1 H, H-2), 3.66 (dq, 1 H, $J_{5,6}$ 6.0 Hz, H-5), 3.40 and 3.37 (each s, 6 H, OMe), 1.61 and 1.34 (each s, 9 H, CMe), 1.36 (d, 3 H, H-2'), and 1.19 (d, 3 H, H-6).

*Anal.* Calc. for $C_{15}H_{27}NO_6$: C, 56.76; H, 8.58; N, 4.41. Found: C, 56.49; H, 8.63; N, 4.07.

*Methyl 4,6-dideoxy-2,3-O-isopropylidene-4-[(R)-2-methoxypropanamido]-3-C-methyl-α-L-mannopyranoside* (**13**). — Treatment of **7** (980 mg, 4.23 mmol) with (*R*)-2-methoxypropanoic acid (470 mg, 4.5 mmol) in dichloromethane (30 mL) containing 3-(3-dimethylaminopropyl)-1-ethyl carbodiimide hydrochloride (749 mg, 4.23 mmol), and isolation as for **12**, yielded **13** (1.29 g, quantitative) as a syrup; $[\alpha]_D$ −40.8° (*c* 1.4, $CHCl_3$); $^1$H-n.m.r.: δ 6.44 (bd, 1 H, $J_{NH,4}$ 10.0 Hz, NH), 4.90 (s, 1 H, H-1), 4.16 (t, 1 H, $J_{4,5}$ 10.0 Hz, H-4), 3.80 (s, 1 H, H-2), 3.70 (q, 1 H, $J_{1',2'}$ 6.5 Hz, H-1'), 3.86–3.55 (m, 1 H, H-5), 3.40 (s, 6 H, OMe), 1.58 and 1.34 (each s, 9 H, CMe), 1.39 (d, 3 H, H-2'), and 1.20 (d, 3 H, H-6).

*Anal.* Calc. for $C_{15}H_{27}NO_6$: C, 56.76; H, 8.58; N, 4.41. Found: C, 56.99; H, 8.61; N, 4.54.

*Methyl 4,6-dideoxy-4-[(S)-2-methoxypropanamido]-3-C-methyl-α-L-mannopyranoside* (**15**). — A mixture of **12** (450 mg, 1.41 mmol) and 60% acetic acid (10 mL) was kept for 8 h at 70°, evaporated under diminished pressure, and then coevaporated with toluene. After purification on a short column of silica gel with 20:1 chloroform–methanol, compound **15** (340 mg) was obtained as a syrup in 87% yield; $[\alpha]_D$ −119.5° (*c* 0.8, $CHCl_3$); $^1$H-n.m.r.: δ 6.54 (bd, 1 H, $J_{NH,4}$ 7.0 Hz, NH), 4.77 (bs, 1 H, H-1), 3.87 (t, 1 H, $J_{4,5}$ 7.0 Hz, H-4), 4.15–3.64 (m, 2 H, H-1',5), 3.57 (bs, 1 H, H-2), 3.44 and 3.38 (each s, 6 H, OMe), 1.38 (d, 3 H, $J_{1',2'}$ 6.5 Hz, H-2'), 1.24 (d, 3 H, $J_{5,6}$ 6.0 Hz, H-6), and 1.25 (s, 3 H, CMe).

*Anal.* Calc. for $C_{12}H_{23}NO_6$: C, 51.97; H, 8.36; N, 5.05. Found: C, 52.08; H, 8.45; N, 5.11.

*Methyl 4,6-dideoxy-4-[(R)-2-methoxypropanamido]-3-C-methyl-α-L-mannopyranoside* (**16**). — Treatment of **13** (1.0 g) with 60% acetic acid (15 mL) overnight at 70°, and isolation and purification as described for **15**, gave syrupy **16** (850 mg, 98%); $[\alpha]_D$ −118° (*c* 0.5, $CHCl_3$); $^1$H-n.m.r.: δ 6.54 (bd, 1 H, $J_{NH,4}$ 8.0 Hz, NH), 4.79 (bs, 1 H, H-1), 4.58 (bs, 2 H, OH), 3.85 (t, 1 H, $J_{4,5}$ 8.0 Hz, H-4), 4.02–3.61 (m, 2 H, H-1'), 3.57 (bs, 1 H, H-2), 3.42 and 3.39 (each s, 6 H, OMe), 1.42 (d, 3 H, $J_{1',2'}$ 7.0 Hz, H-2'), 1.30 (d, 3 H, $J_{5,6}$ 6.0 Hz, H-6), and 1.24 (s, 3 H, CMe).

*Anal.* Calc. for $C_{12}H_{23}NO_6$: C, 51.97; H, 8.36; N, 5.05. Found: C, 51.88; H, 8.57; N, 5.27.

*Methyl 4,6-dideoxy-4-[(S)-2-methoxypropanamido]-3-C-methyl-2-O-methyl-α-L-mannopyranoside* (**19**). — To an efficiently stirred solution of compound **15** (0.41 g, 1.5 mmol) in dry *N,N*-dimethylformamide (5 mL) at −5° were added sodium hydride (55%; 65 mg, 1.5 mmol), and, after 4 h, methyl iodide (629 mg, 4.4 mmol). The stirring was continued overnight and then the mixture was poured into ice–water, and extracted with ethyl acetate. The extract was thoroughly washed with water, dried (magnesium sulfate), and evaporated, to give a crystalline residue. Recrystallization from hexane gave **19** (228 mg, 53%) as needles; m.p. 134–136° (hexane), $[\alpha]_D$ −77.3° (*c* 0.8, $CHCl_3$); $^1$H-n.m.r. data in Table I of the preliminary communication[9].

*Anal.* Calc. for $C_{13}H_{25}NO_6$: C, 53.59; H, 8.65; N, 4.81. Found: C, 53.83; H, 8.74; N, 4.77.

*Methyl 4,6-dideoxy-4-[(R)-2-methoxypropanamido]-3-C-methyl-2-O-methyl-α-*L*-mannopyranoside* (**20**). — Treatment of **16** (850 mg, 3.07 mmol) in dry *N,N*-dimethylformamide (30 mL) with sodium hydride (147 mg, 6.13 mmol) and methyl iodide (1.3 g, 9.19 mmol), as described for **19**, gave crystalline **20** (427 mg, 48%); m.p. 121–122° (hexane), $[\alpha]_D$ −35.6° (*c* 0.5, $CHCl_3$); $^1$H-n.m.r. data in Table I of the communication[9].

*Anal.* Calc. for $C_{13}H_{25}NO_6$: C, 53.59; H, 8.65; N, 4.81. Found: C, 53.71; H, 8.50; N, 4.77.

Alternatively, to a solution of **16** (1.0 g, 3.6 mmol) in dry toluene (20 mL) were added silver oxide (1.66 g, 7.2 mmol) and methyl iodide (1.53 g, 10.8 mmol). After stirring overnight at room temperature, the solid material was filtered off, and the filtrate was evaporated, to give crystalline **20**. Recrystallization from hexane gave needles (0.98 g, 93%).

N-*Acylkansosamine* (**2**). — A mixture of methyl glycoside **16** (100 mg) and 0.5M sulfuric acid (2 mL) was kept for 8 h at 85°, cooled, and the acid neutralized with barium carbonate. Inorganic material was filtered off, and washed thoroughly with water, and the filtrate and washings were combined and evaporated under diminished pressure. Purification on a column of silica gel with 10:1 chloroform–methanol gave **2** (86 mg, 91%) as syrup, $[\alpha]_D$ +5.6° (*c* 1.1, $H_2O$); lit.[7] $[\alpha]_D$ +14.7° (*c* 0.02, $H_2O$); $^1$H-n.m.r.: δ 6.37 (bs, 1 H, NH), 5.29 (bs, 0.6 H, H-1α), 4.81 (bs, 0.4 H, H-1β), 4.2–3.7 (m, H-4,5,2'), 3.69 (s, 1.2 H, OMe-2β), 3.51 (s, 1.8 H, OMe-2α), 3.40 (s, 3 H, OMe-2'), 3.19 (bs, 0.4 H, H-2β), 3.12 (bs, 0.6 H, H-2α), and 1.45–1.15 (m, 9 H, CMe).

*Anal.* Calc. for $C_{12}H_{23}NO_6$: C, 51.97; H, 8.36; N, 5.05. Found: C, 51.72; H, 8.48; N, 5.34.

*1-O-Acetyl-4,6-dideoxy-4-[(R)-2-methoxypropanamido]-3-C-methyl-2-O-methyl-α- and -β-*L*-mannopyranose* (**3** and **4**). — Compound **2** (95 mg) was acetylated with 1:1 acetic anhydride–pyridine (2 mL) in the conventional manner to give a syrupy anomeric mixture (α:β = 1.3:1), which was separated by t.l.c. with 9:1 ether–acetone, to give pure α-acetate **3** (46 mg) and β-acetate **4** (37 mg) in 76% combined yield.

Compound **3** was a syrup; $[\alpha]_D$ −38.6° (*c* 1.5, $CHCl_3$): $^1$H-n.m.r. and $^{13}$C-n.m.r. data in Tables I and II of the communication[9], respectively.

*Anal.* Calc. for $C_{14}H_{25}NO_7$: C, 52.65; H, 7.89; N, 4.39. Found: C, 52.88; H, 7.51; N, 4.23.

Compound **4** was a syrup; $[\alpha]_D$ +6.8° (*c* 1.4, $CHCl_3$); $^1$H-n.m.r. data in Table I of the communication[9]; $^{13}$C-n.m.r.: δ 174.3 and 169.1 (C=O), 92.2 (C-1), 84.1 (C-5), 72.9 (C-2), 71.2 (C-3), 62.1 (C-2), 57.3 and 55.5 (OMe), 55.3 (C-4), 21.0, 18.3, and 18.1 (CMe).

*Anal.* Calc. for $C_{14}H_{25}NO_7$: C, 52.65; H, 7.89; N, 4.39. Found: C, 52.70; H, 7.67; N, 4.41.

*Methyl 4,6-dideoxy-2,3-*O*-isopropylidene-3-*C*-methyl-4-(methylamino)-α-*L*-mannopyranoside* (**11**). — A suspension of lithium aluminum hydride (52 mg, 1.4 mmol) in ether (10 mL) containing **9** (200 mg, 0.69 mmol) was refluxed overnight. After cooling in an ice bath, the excess of the reagent was carefully decomposed by addition of moist ethyl acetate. The undissolved material was filtered off, and washed with ether (10 mL × 3). The filtrate and washings were combined, washed twice water, dried (magnesium sulfate), and evaporated. The residue was placed on a short column of silica gel and eluted with 10:1 chloroform–methanol, to give **11** (155 mg, 92%) as a syrup, $[\alpha]_D$ −69.5° (*c* 1.7, $CHCl_3$); $^1$H-n.m.r. ($CDCl_3$): δ 4.83 (s, 1 H, H-1), 3.75 (s, 1 H, H-2), 3.50 (dq, 1 H, $J_{4,5}$ 10.0, $J_{5,6}$ 6.2 Hz, H-5), 3.37 (s, 3 H, OMe), 2.54 (s, 3 H, NMe), 2.48 (d, 1 H, H-4), 1.53, 1.35, and 1.30 (each s, 9 H, $CMe_2$ and CMe), and 1.29 (d, 3 H, H-6).

*Anal.* Calc. for $C_{12}H_{23}NO_4$: C, 58.75; H, 9.45; N, 5.71. Found: C, 59.01; H, 9.33; N, 5.47.

*Methyl 4,6-dideoxy-3-*C*-methyl-4-(methylamino)-α-*L*-mannopyranoside* (**14**). — A solution of **11** (50 mg) in 80% acetic acid (2 mL) was kept at 90° until the starting material had disappeared (24 h), cooled, and evaporated under diminished pressure; the residue was dissolved in chloroform, and the solution washed with a saturated solution of sodium hydrogencarbonate. The usual processing, and purification by preparative t.l.c. with 10:1 chloroform–methanol, afforded **14** (29 mg, 69%) as a syrup, which was characterized only by $^1$H-n.m.r. data: δ 4.71 (d, 1 H, $J_{1,2}$ 1.4 Hz, H-1), 3.80 (dq, 1 H, $J_{4,5}$ 10.0, $J_{5,6}$ 6.2 Hz, H-5), 3.57 (d, 1 H, H-2), 3.37 (s, 3 H, OMe), 2.68 (s, 3 H, NMe), 2.74 (d, 1 H, H-4), 1.36 (s, 3 H, CMe), and 1.40 (d, 3 H, H-6).

*Methyl 4-*N*-acetyl-2-*O*-acetyl-4,6-dideoxy-3-*C*-methyl-4-(methylamino)-α-*L*-mannopyranoside* (**17**). — Conventional acetylation of **14** (20 mg) with acetic anhydride (1 mL) and dry pyridine (1 mL) overnight at room temperature gave a crystalline solid which on recrystallization (ethyl acetate–hexane), afforded pure **17** (23 mg, 82%); m.p. 132–133°, $[\alpha]_D$ −65° (*c* 0.5, MeOH); lit.[6] m.p. 135–136°, $[\alpha]_D$ −70° (*c* 0.4, MeOH); $^1$H-n.m.r.: δ 4.75 (bs, 1 H, H-1), 4.69 (d, 1 H, $J_{4,5}$ 10.0 Hz, H-4), 4.64 (bs, 1 H, H-2), 3.99 (dq, 1 H, $J_{5,6}$ 6.2 Hz, H-5), 3.40 (s, 3 H, OMe), 2.97 (s, 3 H, NMe), 2.16 (s, 6 H, OAc and NAc), 1.37 (s, 3 H, CMe), and 1.23 (d, 3 H, H-6).

*Anal.* Calc. for $C_{13}H_{23}NO_6$: C, 53.96; H, 8.01; N, 4.84. Found: C, 53.77; H, 7.83; N, 4.59.

*Methyl 4-*N*-acetyl-2,3-di-*O*-acetyl-4,6-dideoxy-3-*C*-methyl-4-(methylamino)-α-*L*-mannopyranoside* (**18**). — A solution of **17** (15 mg) in 1:1 pyridine–acetic anhydride (2 mL) containing 4-(dimethylamino)pyridine in catalytic amount was kept for 2 days at room temperature; conventional processing then gave a crystalline residue. Recrystallization (ethyl acetate–hexane) afforded **18** (12 mg, 71%); m.p. 130–131°, $[\alpha]_D$ −23° (*c* 0.7, MeOH); lit.[6] m.p. 127–128°, $[\alpha]_D$ −25° (*c* 0.3, MeOH); $^1$H-n.m.r.: δ 5.59 (d, 1 H, $J_{1,2}$ 1.5 Hz, H-2), 4.69 (d, 1 H, H-1), 4.16

(dq, $J_{4,5}$ 10.0, $J_{5,6}$ 5.4 Hz, H-5), 3.97 (d, 1 H, H-4), 3.42 (s, 3 H, OMe), 2.86 (s, 3 H, NMe), 2.28, 2.07, and 1.97 (each s, 9 H, OAc and NAc), and 1.24 (d, 3 H, H-6).

*Anal.* Calc. for $C_{15}H_{25}NO_7$: C, 54.37; H, 7.61; N, 4.23. Found: C, 54.22; H, 7.74; N, 4.10.

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REFERENCES

1 M. G. BRAZHNIKOVA, N. N. KONSTANTINOVA, AND A. S. MESENTEV, *J. Antibiot.*, 25 (1972) 668–673.
2 S. W. HUNTER, R. C. MURPHY, K. CLAY, M. GOREN, AND P. J. BRENNAN, *J. Biol. Chem.*, 258 (1983) 10,481–10,487.
3 L. H. HURLEY, C. GAIROLA, AND M. ZMIJEWSKI, *Biochim. Biophys. Acta*, 475 (1977) 521–535.
4 A. S. MSTENSEV AND V. V. KULJAEVA, *Tetrahedron Lett.*, (1973) 2225–2228.
5 I. DYONG AND G. SCHULTE, *Chem. Ber.*, 114 (1981) 1484–1502; J. YOSHIMURA, N. HONG, A. U. RAHMAN, AND K. SATO, *Chem. Lett.*, (1980) 777–778; M. GEORGES, D. MACKAY, AND B. FRASER-REID, *J. Am. Chem. Soc.*, 104 (1982) 1101–1103.
6 K. A. PARKER AND R. E. BABINE, *Tetrahedron Lett.*, (1982) 1763–1766; *J. Am. Chem. Soc.*, 104 (1982) 7330–7331.
7 S. W. HUNTER, T. FUJIWARA, R. C. MURPHY, AND P. J. BRENNAN, *J. Biol. Chem.*, 259 (1984) 9729–9734.
8 J. YOSHIMURA, K. SATO, AND R. B. SINGH, *Chem. Lett.*, (1985) 69–70.
9 J. YOSHIMURA, K. SATO, A. AQEEL, R. B. SINGH, AND H. HASHIMOTO, *Carbohydr. Res.*, 144 (1985) c15–c17.
10 J. YOSHIMURA, *Adv. Carbohydr. Chem. Biochem.*, 42 (1984) 69–134.
11 A. KLEMER AND H. BEERMAN, *J. Carbohydr. Chem.*, 2 (1983) 457–459; A. KLEMER AND H. THIEMEYER, *Justus Liebigs Ann. Chem.*, (1984) 1094–1099.
12 P. J. MAURER, C. G. KNUDSEN, A. D. PALKOWITZ, AND H. RAPOPORT, *J. Org. Chem.*, 50 (1985) 325–332.