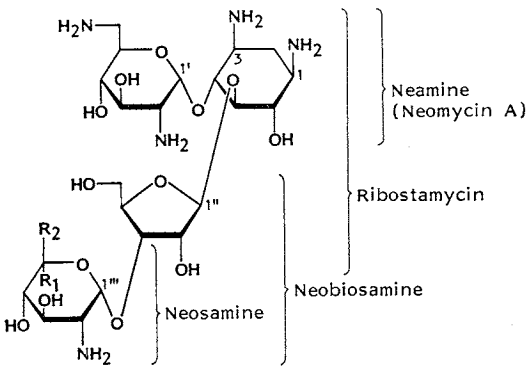
TOTAL SYNTHESIS OF NEOMYCIN B†

Sir:

Neomycin B is a main component of the neomycin complex which was independently discovered by UMEZAWA *et al.*[1] and WAKSMAN and LECHEVALIER[2]. Neomycin group is a representative of pseudo-tetrasaccharide antibiotics, which provide some fascinating problems in carbohydrate chemistry[3,4]. Complete structures and absolute stereochemistry of neomycins were elucidated by HICHENS and RINEHART, Jr.[5]. Total synthesis of neomycin C, another component of the neomycin complex, has been achieved by UMEZAWA and NISHIMURA[6] and UMEZAWA *et al.*[7]. Neamine (neomycin A), a pseudo-disaccharide portion common to neomycins, was synthesized also by UMEZAWA *et al.* first[8] through conversion of paromamine and later[9] by glycosylation of the aminocyclitol component. On the other hand, because of the difficulty associated with glycosylation by 2,6-diamino-2,6-dideoxy-L-idose (neosamine B) which distinguishes neomycin B from C, total synthesis of neomycin B has not been successful[10]. In this communication we wish to report the first total synthesis of neomycin B.

In order to solve the above-mentioned problem, we have reported the synthesis of 3-*O*-acetyl-2,6-diazido-4-*O*-benzyl-2,6-dideoxy-L-idopyranosyl chloride (**1**)[11] as a key intermediate for the preparation of 1,2-*cis*(β-L-) linked neosamine B. The present approach to neomycin B is characterized by stepwise glycosylation reactions: 1) Glycosylation of the 3-OH of a protected ribose (**2**)[12] with glycosyl chloride (**1**) to yield a masked disaccharide (**3**) corresponding to neobiosamine B, 2) glycosylation of the 5-OH of a selectively protected neamine (**10**) with the disaccharide portion to yield a masked pseudo-tetrasaccharide (**11**), and subsequent transformation of **11** into neomycin B.



Neomycin B $R_1 = CH_2NH_2$ $R_2 = H$

Neomycin C $R_1 = H$ $R_2 = CH_2NH_2$

Reaction of **1** with **2** was performed under modified KOENIGS-KNORR condition (mercuric cyanide, mercuric bromide, Molecular sieves 4A, CH_2Cl_2, room temp overnight), yielding the desired β-L-connected disaccharide **3** in 70% yield, based on **2**, and the α-L anomer (**4**, 7%). The anomeric configurations were assigned on the basis of the more dextro-rotating specific rotation†† of **3** (+139°; **4** +28°) and their NMR spectra[13]. ^1H NMR ($CDCl_3$, 250 MHz); **3**: δ 5.11 (d, $J_{1',2'}$=2.0 Hz, 1'-H); **4**: δ 4.87 (d, $J_{1',2'}$=3.4 Hz, 1'-H). ^{13}C NMR ($CDCl_3$, 62.9 MHz); **3**: δ 97.5 (C-1'); **4**: δ 100.1 (C-1'). Deisopropylidenation (AcOH - 2 N HCl, 2:1) of **3** followed by conventional acetylation (Ac_2O - pyridine) gave an anomeric mixture (**5**, α:β ~ 1:3) of glycosyl acetates, 92%; $[\alpha]_D$ +82°, a neobiosamine B equivalent duly masked and functionalized for the coupling with protected neamine.

A new neamine derivative, in which all the functional groups except the 5-hydroxyl are protected, was prepared. Selective cyclohexylidenation of tetrakis(*N*-benzyloxycarbonyl)-neamine (**6**)[14] by a modified literature procedure gave **7**[15], the two hydroxyl groups of which were then acylated with *o*-methoxybenzoyl group to give a fully protected neamine **8**, 72% from **6**; $[\alpha]_D$ +22.5°. Decyclohexylidenation (AcOH - H_2O - THF, 3:1:1) gave the diol **9**, 98%; $[\alpha]_D$ +59°. Treatment of **9** with sodium hydride in DMF in the presence of benzyltriethylammonium chloride gave cyclic 1,6-carbamate **10**, 78%; $[\alpha]_D$ +80°; ^1H NMR ($CDCl_3$+D_2O, 250 MHz) δ 1.55 (1H, q, J=~12 Hz, 2-H_{ax}), 2.15 (1H, m, 2-H_{eq}), 3.65 and 3.68 (each 3H, s, OCH_3). Addition of the quaternary ammonium salt was found to improve the yield.

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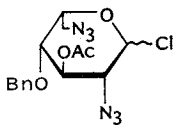
†† Optical rotations were measured, unless otherwise noted, at 20~22°C for solutions (*c* 0.7~1.1) in $CHCl_3$. All new compounds gave satisfactory elemental analyses.



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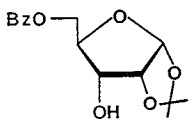

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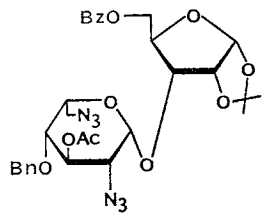

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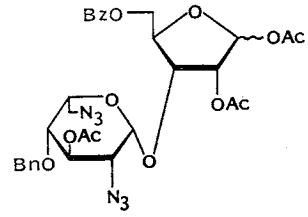

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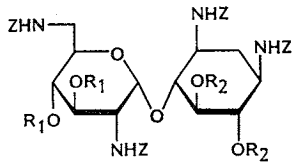
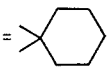
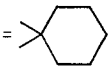
Bn = $PhCH_2$

Bz = PhC=O

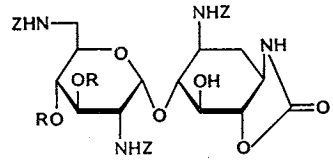


6 $R_1 = R_2 = H$

7 $R_1 = H$ $R_2 =$ 

8 $R_1 = (OCH_3)Bz$ $R_2 =$ 

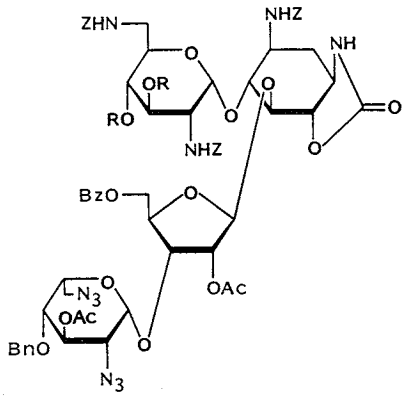
9 $R_1 = (OCH_3)Bz$ $R_2 = H$



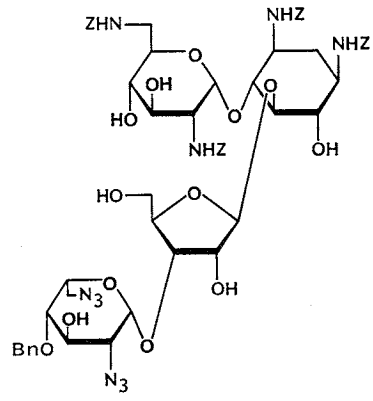
10 $R = (OCH_3)Bz$

$(OCH_3)Bz$ = o-Methoxybenzoyl

Z = $COOCH_2Ph$



11 $R = (OCH_3)Bz$



12

Coupling of the two portions was best effected by use of trimethylsilyl triflate (TMSOTf)[16]. Reaction of **10** with **5** (1.5 equivalent to **10**) in the presence of TMSOTf (benzene, room temp 4 hours) gave pseudo-tetrasaccharide **11** as a sole isolable product, 60%; $[\alpha]_D$ +55°. Treatment of **11** with sodium benzyl alcoholate gave partially deprotected **12**, 85%; $[\alpha]_D$ +40°.

Table 1. Antibacterial spectra of synthetic and natural neomycin B.

Test organisms*	MIC (μg/ml)	
	Synthetic	Natural
Staphylococcus aureus FDA 209P	0.78	0.78
Micrococcus luteus PCI 1001	1.56	0.78
Bacillus subtilis NRRL B-558	0.20	0.39
Escherichia coli K-12	0.78	0.39
E. coli K-12 ML1629	100	100
E. coli K-12 LA 290 R 55	1.56	1.56
E. coli K-12 LA 290 R 56	1.56	0.78
E. coli K-12 W 677	0.78	0.39
E. coli K-12 JR 66/W 677	100	100
Klebsiella pneumoniae PCI 602	0.78	0.78
K. pneumoniae type 22 #3038	100	100
Mycobacterium smegmatis ATCC 607**	0.78	0.78

* Agar dilution streak method (nutrient agar, 37°C, 17 hours).
** 48 hours.

Finally catalytic hydrogenation (4 kg/cm^2 H_2, 10% Pd-C) of **12** gave neomycin B, 65% (as free base). ^1H[17] and ^{13}C NMR[18] spectra of the free base (in D_2O) and the specific rotation[19] of the hydrochloride [+54° (*c* 1.1, H_2O)] agreed well with those reported. The identity of the synthetic and natural specimens was further established by the antibacterial spectra as shown in Table 1.

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