SYNTHESIS OF SISAMINE AND OF PSEUDODISACCHARIDE ANALOGUES

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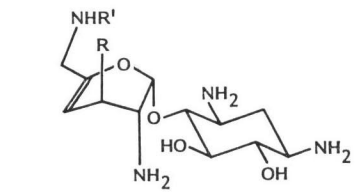
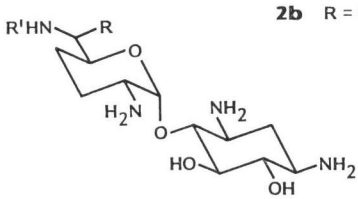
Lividamine and paromamine were converted into two key intermediate ethylenic aldehydes **10a** and **10b**. Reductive amination of the two aldehydes yielded the protected sisamine **11a** and the three analogs **11b**, **12a** and **12b**. These four derivatives were deprotected to yield the four pseudodisaccharides **1a**, **1b**, **2a** and **2b** which were less active *in vitro* than neamine against *Escherichia coli* ATCC 9637 and *Staphylococcus aureus* 209P.

The aminoglycoside antibiotics are potent agents used in clinical practice but they suffer from two major drawbacks: their toxicity and their inactivation by resistant microorganisms[1~3]. Great effort has been expended to improve their properties leading to the production of many semisynthetic compounds, some of which are now used clinically[1].

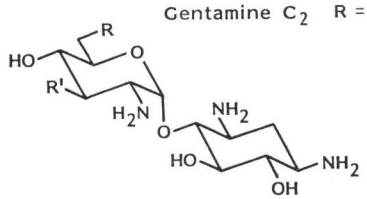
Fig. 1.



Sisamine (**1a**) R = R' = H
1b R = OH, R' = H
2a R = H, R' = CH_3
2b R = OH, R' = CH_3



Gentamines (**3**)
Gentamine C_1 R = R' = CH_3
Gentamine C_{1a} R = R' = H
Gentamine C_2 R = CH_3, R' = H



Lividamine (**4a**) R = OH, R' = H
Paromamine (**4b**) R = OH, R' = OH
Neamine R = NH_2, R' = OH

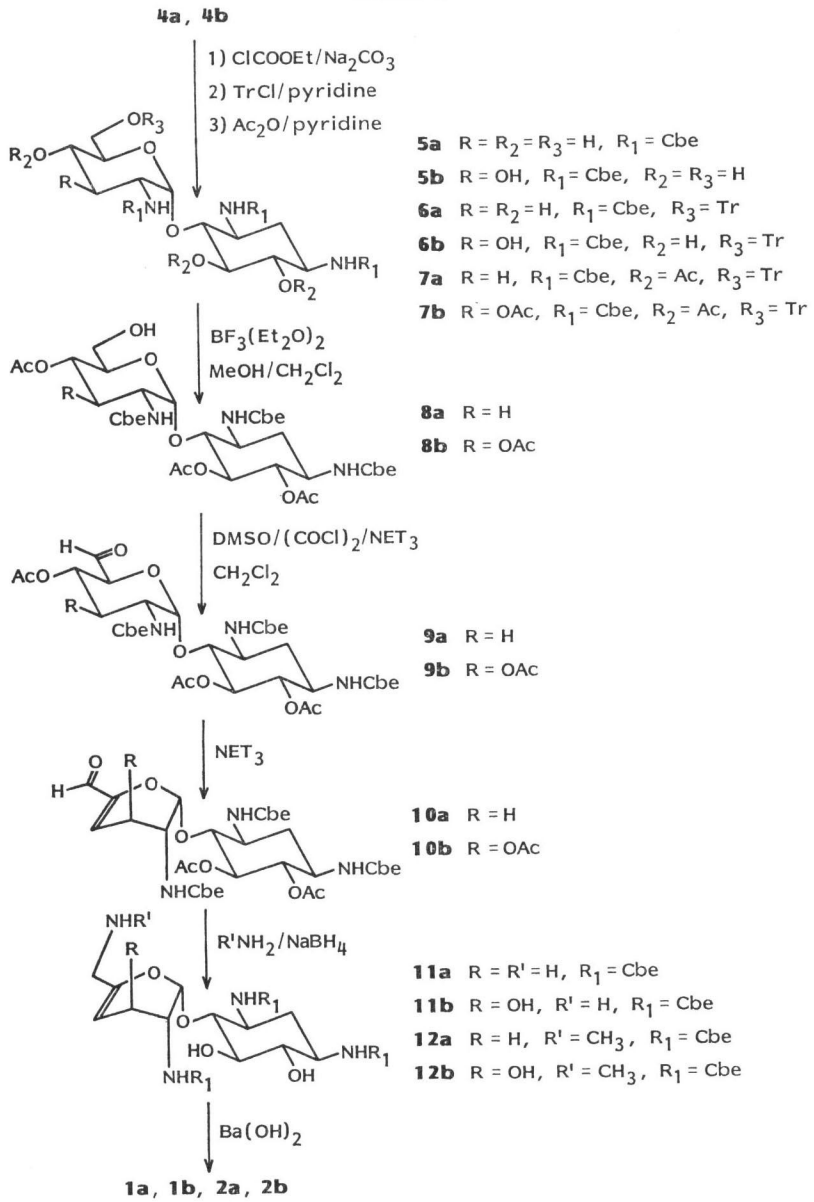
The synthesis of these new compounds has usually been done from pseudodisaccharides. The latter were obtained from their parent aminoglycoside antibiotics. Gentamine (**3**), lividamine (**4a**) and paromamine (**4b**) (Fig. 1) are readily available[4~6] and have been widely used as starting materials for the synthesis of various aminoglycoside analogues (for recent examples, see references 7~10). On the other hand, sisamine (**1a**) (Fig. 1) is not readily available[11] and has not been used as a building block for such semisyntheses. The only preparation of sisamine recently reported was that of PAULSEN[11]. In this paper, we describe an alternative efficient method for large scale synthesis of sisamine and related compounds. The use of these pseudodisaccharides for the synthesis of ribostamycin analogues is reported in the accompanying paper.

Access to sisamine (**1a**) and to the three analogues **1b**, **2a** and **2b** was provided through the two key intermediate unsaturated aldehydes

10a and **10b**, prepared from lividamine and paromamine.

We have modified the previously reported[12] synthesis of aldehyde **9a** by changing the reagents used in two crucial steps (Scheme 1, Cbe ethoxycarbonyl). First, the removal of the trityl group of 5,6,4′-tri-*O*-acetyl-6′-*O*-trityl-1,3,2′-tri-*N*-ethoxycarbonyllividamine (**7a**) to yield the 6′-hydroxyl derivative **8a** was done with boron trifluoride etherate/methanol in methylene chloride[13]. The oxidation of **8a** by the SWERN reagent[14] gave higher yields of the 6′-aldehyde **9a** than the use of the classical MOFFAT technique (dimethyl sulfoxide - dicyclohexylcarbodiimide - trifluoroacetic acid - pyridine). In our hands, drying the "hydrate form" of the aldehyde **9a** at 130°C *in vacuo* to constant weight[12] did not result in pure **9a**, but in unsaturated aldehyde **10a** by an intramolecular removal of acetic acid. The desired ethylenic aldehyde **10a** was, however, cleanly isolated by adding an excess of triethylamine to

Scheme 1.



the crude SWERN oxidation mixture.

The synthesis of the ethylenic aldehyde **10b** was performed by the same procedure starting from paromamine (**4b**) (Scheme 1). The reduction, or reductive amination of **10a** and **10b** can lead to various sisamine derivatives. For example, introduction of a primary amino group in the 6′ position with simultaneous removal of the acetyl groups was achieved by successive treatment with methanolic ammonia and sodium borohydride. Thus 1,3,2′-tri-*N*-ethoxycarbonylsisamine (**11a**), and 1,3,2′-tri-*N*-ethoxycarbonyl-3′-hydroxysisamine (**11b**) were isolated from **10a** and **10b**, respectively. 1,3,2′-Tri-*N*-ethoxycarbonyl-6′-*N*-methylsisamine (**12a**) and 1,3,2-tri-*N*-ethoxycarbonyl-3′-hydroxy-6′-*N*-methylsisamine (**12b**) were similarly obtained by successive treatment of **10a** and **10b** with methanolic methylamine and sodium borohydride. The overall yield of **11a** and **12a** from lividamine and of **11b** and **12b** from paromamine were 50% and 40%, respectively on a half mol scale.

Deprotection of the amino groups of **11a**, **12a**, **11b** and **12b** by refluxing 2 N sodium hydroxide or saturated aqueous barium hydroxide yielded sisamine (**1a**), 6′-*N*-methylsisamine (**2a**), 3′-hydroxysisamine (**1b**) and 3′-hydroxy-6′-*N*-methylsisamine (**2b**), respectively. The four pseudodisaccharides were purified by silica gel and ion exchange chromatographies and neutralized with 0.1 N sulfuric acid. Analyses were performed using the sulfate derivatives (see Table 1 and Experimental).

The antibacterial activities of **1a**, **1b**, **2a** and **2b** were compared with that of neamine and are shown in Table 2. Sisamine was found to be the most potent of the four derivatives when tested on two aminoglycoside-sensitive strains by the agar diffusion disk method (Table 2).

Table 1. ^{13}C NMR chemical shifts of the sisamine derivatives.

	6a		6b	15a	15b
	x	y	y	y	y
C-1	51.2	51.0	51.1	51.0	50.9
C-2	36.6	29.5	29.1	29.2	29.0
C-3	50.3	49.3	49.3	49.3	49.2
C-4	85.8	80.4	80.5	80.2	80.5
C-5	77.0	75.5	75.5	75.5	75.5
C-6	78.3	73.6	73.3	73.2	73.1
C-1′	101.0	97.6	97.4	97.7	97.5
C-2′	47.4	47.0	52.9	46.9	52.8
C-3′	25.5	24.0	63.5	24.1	63.5
C-4′	96.7	101.2	103.0	103.3	104.9
C-5′	150.7	144.2	147.2	142.7	145.7
C-6′	43.3	41.5	41.3	50.4	50.2
6′–NCH_3	—	—	—	33.0	33.3

x: Free base, from reference 11.
y: Sulfate 150 mg/0.5 ml D_2O.

Experimental

Evaporations were performed with a rotary evaporator under reduced pressure. The NMR spectra were recorded on with a Varian T60 spectrometer (^1H) and a Brucker WP80 spectrometer (^1H and ^{13}C). The chemical shifts are reported in ppm down field from TMS. Dioxane (67.4 ppm) was used as internal reference for ^{13}C spectra in D_2O. The optical rotations were measured with a Perkin-Elmer 141 polarimeter. The melting points were observed with a Reichert Köffler melting point apparatus and were not corrected. Microanalyses were performed with Perkin-Elmer 240 Elemental Analyzer.

The solvents were dried by distillation over an appropriate dessicating agent just prior to use. The reactions were followed by TLC monitoring (Merck, silica gel 60F254). The organic extracts

Table 2. Diameter of the zone of inhibition (in mm) (paper disk method).

	Neamine		1a		1b		2a		2b	
	30 μg	300 μg	30 μg	300 μg	30 μg	300 μg	30 μg	300 μg	30 μg	300 μg
E. coli ATCC 9637	18	23	18	30	—	21	—	20	—	12
S. aureus 209P	22	34	17	28	—	21	—	23	—	15

were dried over $MgSO_4$ or Na_2SO_4. Analytical samples were prepared by silica gel flash chromatography[16] when necessary (Riedel de Haën Kieselgel S. 31607, 230~400 mesh).

1,3,2′-Tri-*N*-ethoxycarbonylparomamine (**5b**)

The **5b** compound was synthesized as described[12] for the synthesis of the parent compound 1,3,2′-tri-*N*-ethoxycarbonyllividamine (**5a**). mp >250°C; $[\alpha]_D^{20}$ +82° (*c* 1, DMF).

Anal Calcd for $C_{21}H_{37}N_3O_{13}\cdot H_2O$: C 45.53, H 6.87, N 7.81
Found: C 45.23, H 7.05, N 7.53

5,6,3′,4′-Tetra-*O*-acetyl-1,3,2′-tri-*N*-ethoxycarbonyl-6′-*O*-tritylparomamine (**7b**)

The **7b** compound was synthesized as described[12] for the parent compound 5,6,4′-tri-*O*-acetyl-1,3,2′-tri-*N*-ethoxycarbonyl-6′-*O*-trityllividamine (**7a**).

Purification of **7a** and **7b**: After completion of the reaction, the pyridine was evaporated and toluene was added and evaporated twice. The residue was dissolved in methylene chloride, washed successively with 2 N HCl, 10% $NaHCO_3$, and water and then dried. The organic solvent was evaporated and the residue triturated with diisopropyl ether. Filtration yielded a solid product which was not further purified for the following reaction.

7b: Rf 0.53 (EtOAc - C_6H_6, 2: 1), mp 148°C, $[\alpha]_D^{20}$ +55° (*c* 1, $CHCl_3$).

Anal Calcd for $C_{48}H_{59}N_3O_{17}$: C 60.68, H 6.26, N 4.42
Found: C 61.28, H 6.06, N 4.67

5,6,4′-Tri-*O*-acetyl-1,3,2′-tri-*N*-ethoxycarbonyllividamine (**8a**)

Boron trifluoride etherate (5.6 ml, 45 mmol) was dissolved in dry methanol (18.3 ml) and added to the magnetically stirred solution of **7a** (40 g, 45 mmol) in dry dichloromethane (200 ml). The reaction mixture was stirred for 1 hour at room temperature, then washed with water until neutral and dried. The organic solvent was evaporated and the oily residue was triturated with pentane yielding a solid compound. Filtration and drying yielded solid **8a**, 22.3 g (77%). Rf 0.2 (EtOAc - toluene, 4: 1), mp 205°C, ref[12] 185°C, $[\alpha]_D^{20}$ +46° (*c* 1, $CHCl_3$), +69° (*c* 0.5, CH_3OH), ref[12] $[\alpha]_D^{13}$ +55° (*c* 0.5, CH_3OH).

Anal Calcd for $C_{27}H_{43}N_3O_{15}$: C 49.92, H 6.67, N 6.47
Found: C 49.62, H 6.43, N 6.29

5,6,3′,4,-Tetra-*O*-acetyl-1,3,2′-tri-*N*-ethoxycarbonylparomamine (**8b**)

The **8b** compound (7 g, 93%) was obtained from **7b** (10 g, 10.5 mmol) in 60 ml dichloromethane and boron trifluoride etherate (1.35 ml, 10.5 mmol) in 5 ml methanol, using the same procedure described for the preparation of **8a**. Rf 0.38 ($CHCl_3$ - EtOH, 9: 1), mp 150°C, $[\alpha]_D^{20}$ +42° (*c* 0.93, $CHCl_3$).

Anal Calcd for $C_{29}H_{45}N_3O_{17}$: C 49.22, H 6.41, N 5.94
Found: C 48.69, H 6.19, N 5.82

^{13}C NMR ($CDCl_3$) 170.8, 170.6, 169.9, OAc carbonyls; 156.3 Cbe carbonyls; 99.1 C-1′; 78.8, 75.5, 73.8, 71.2, 70.7, 69.1, C-4,5,6,3′,4′,5′; 61.2, 61.0 CH_2O (Cbe) and C-6′; 53.6, 50.6, 49.4 C-2′,1,3; 34.7 C-2; 20.6 CH_3 (OAc); 14.6 CH_3 (Cbe).

5,6,4′-Tri-*O*-acetyl-1,3,2′-tri-*N*-ethoxycarbonyl-6′-oxolividamine (**9a**) and 5,6-Di-*O*-acetyl-4-*O*-(2,3,4-trideoxy-2-ethoxycarbonylamino-α-D-glycero-1,5-hex-dialdo-4-enopyranosyl)-2-deoxy-1,3-di-*N*-ethoxycarbonylstreptamine (**10a**)

Dimethyl sulfoxide (31.25 ml, 0.44 mol) in 30 ml of dichloromethane was added slowly to a magnetically stirred solution of oxalyl chloride (18.8 ml, 0.22 mol) in 300 ml dichloromethane cooled to −50°C. The temperature was maintained between −60°C and −50°C during the dropwise addition of **8a** (140.5 g, 0.2 mol) in 300 ml of dichloromethane. Stirring was continued for 15 minutes and triethylamine (101.19 g, 1 mol) was added carefully. The solution was allowed to warm up to room temperature and, 2 hours after the triethylamine addition, the solution was evaporated to dryness.

The residue was dissolved in dichloromethane and washed with 1 N HCl, followed by water. After drying and evaporation of the organic solvent the solid obtained was finely ground up and dried under reduced pressure to yield 118.3 g (97%) of the ethylenic aldehyde **10a**. The **9a** compound was synthesized by the same procedure, but adding only two equivalents of triethylamine and working up the reaction mixture as described.

9a: Rf 0.45 ($CHCl_3$ - EtOH, 95: 5), mp >260°C, ref[12] 226.5°C (dec), $[\alpha]_D^{20}$ +48° (*c* 0.94, $CHCl_3$), ref[12] $[\alpha]_D^{16}$ +47° (*c* 1, $CHCl_3$).

Anal Calcd for $C_{27}H_{41}N_3O_{15}$: C 50.07, H 6.38, N 6.49
Found: C 49.33, H 6.71, N 6.30

^{13}C NMR ($CDCl_3$) 197.0 C-6′; 171.0, 170.2, 169.6 OAc carbonyls; 156.1, 156.0 Cbe carbonyls; 97.8 C-1′; 79.3, 75.1, 73.7, 73.6, 65.8 C-4,5,6,4′,5′; 61.2 CH_2O (Cbe); 50.2, 49.6, 48.3 C-1,3,2′; 34.7 C-2; 31.0 C-3′; 20.7 CH_3 (OAc); 14.6 CH_3 (Cbe).

10a: Rf 0.5 ($CHCl_3$ - EtOH, 95: 5), mp 160°C, $[\alpha]_D^{20}$ +67.5° (*c* 0.14, $CHCl_3$).

Anal Calcd for $C_{25}H_{37}N_3O_{13}$: C 51.10, H 6.35, N 7.15
Found: C 50.82, H 6.41, N 6.85

UV λ_{max} 252 nm (ε_{max} 5,750). ^{13}C NMR ($CDCl_3$) 186.0 C-6′; 171.0, 170.2 OAc carbonyls; 155.9, 155.7 Cbe carbonyls; 148.3 C-5′; 121.9 C-4′; 96.9 C-1′; 77.7, 74.2, 73.5 C-4,5,6,; 61.1 CH_2O (Cbe); 49.9, 49.6, 46.1, C-1,3,2′; 34.6 C-2; 29.7 C-3′; 20.6 CH_3 (OAc); 14.6 CH_3 (Cbe).

5,6,3′,4′-Tetra-*O*-acetyl-1,3,2′-tri-*N*-ethoxycarbonyl-6′-oxoparomamine (**9b**) and 5,6-Di-*O*-acetyl-4-*O*-(3-*O*-acetyl-2,4-dideoxy-2-ethoxycarbonylamino-α-D-*threo*-1,5-hex-dialdo-4-enopyranosyl)-2-deoxy-1,3-di-*N*-ethoxycarbonylstreptamine (**10b**)

The **9b** and **10b** compounds were synthesized as described for **9a** and **10a**, respectively. **9b** was too unstable to be isolated as a pure compound.

10b: Rf 0.58 ($CHCl_3$ - EtOH, 9: 1), mp 210°C, $[\alpha]_D^{20}$ +123° (*c* 1, $CHCl_3$).

Anal Calcd for $C_{27}H_{39}N_3O_{15}$: C 50.23, H 6.09, N 6.51
Found: C 50.03, H 6.31, N 6.52

UV λ_{max} 254 nm (ε_{max} 2,300). ^1H NMR ($CDCl_3$) main absorption peaks: 9.14 aldehydic proton (s, 1H); 5.8 H-4′ (d, $J_{4',3'}$=2.5 Hz, 1H); 5.5 H-3′ (d of d, $J_{3',4'}$=2.5 Hz, $J_{3',2'}$=9 Hz, 1H); 5.3 H-1′ (d, $J_{1',2'} \simeq$ 2.5 Hz, 1H); 2.1, 2.03, 2.01 $COCH_3$ (s, 3H, each). ^{13}C NMR ($CDCl_3$) 185.7 C-6′; 171.1, 170.8, 170.1 OAc carbonyls; 156.1, 155.8 Cbe carbonyls; 148.5 C-5′; 118.9 C-4′; 99.0 C-1′; 78.5, 74.4, 73.6 C-4,5,6; 67.0 C-3′; 61.4, 61.1 CH_2O (Cbe); 50.8, 49.8, 49.7 C-2′,1,3; 34.2 C-2; 20.9, 20.6 CH_3 (OAc); 14.6 CH_3 (Cbe).

1,3,2′-Tri-*N*-ethoxycarbonylsisamine (**11a**)

The **10a** compound (12 g, 12.8 mmol) was dissolved in a saturated methanolic solution of ammonia (900 ml) at room temperature. After 24 hours, sodium borohydride (1.5 g, 39.6 mmol) was added and the reaction mixture was stirred for 2 hours. The solution was evaporated to dryness and the crude product, which presented a single spot on TLC (Rf 0.62, MeOH - NH_4OH, 99: 1) was used for the following reactions without further purification. The **11a** compound was characterized as its 6′-*N*-Cbe derivative[17].

1,3,2′-Tri-*N*-ethoxycarbonyl-3′-hydroxysisamine (**11b**)

The **10b** compound (1.2 g, 1.87 mmol) was transformed into **11b** by the procedure described for the synthesis of **11a**. The **11b** compound was purified by chromatography on an Amberlite CG-50 (NH_4^+) column, eluted first with water then with 1 N NH_4OH. After evaporation, the fractions containing **11b** (Rf 0.55, MeOH - NH_4OH, 99: 1) yielded 460 mg (47%) of pure compound. mp 208°C, $[\alpha]_D^{20}$ +12° (*c* 0.42, MeOH).

Anal Calcd for $C_{21}H_{36}N_4O_{11} \cdot H_2O$: C 46.83, H 7.11, N 10.42
Found: C 46.87, H 6.70, N 10.42

^{13}C NMR (D_2O, DCl) 159.3, 158.9, 156.2 Cbe carbonyls; 149.8 C-5′; 101.7 C-4′; 99.1 C-1′; 81.1, 77.1, 75.6 C-4,5,6; 64.8 C-3′; 62.2 CH_2O (Cbe); 54.7, 51.9, 50.1 C-2′,1,3; 42.7 C-6′; 34.2 C-2; 14.6 CH_3 (Cbe).

1,3,2′-Tri-*N*-ethoxycarbonyl-6′-*N*-methylsisamine (**12a**)

The **10a** compound (7.35 g, 12.5 mmol) was dissolved in a saturated methanolic solution of methylamine (250 ml) at room temperature. After 15 hours, sodium borohydride (2 g, 50 mmol) was added and the reaction mixture was stirred for 1.5 hours. The solution was evaporated to dryness and the crude product, which presented a single spot of TLC (Rf 0.42, MeOH - NH_4OH, 99: 1) was used for the

following reactions without further purification. The **12a** compound was characterized as its 6′-*N*-Cbe derivative[17].

1,3,2′-Tri-*N*-ethoxycarbonyl-3′-hydroxy-6′-*N*-methylsisamine (**12b**)

The **10b** compound (600 mg, 0.93 mmol) was transformed into **12b** by the method described for the synthesis of **12a** from **10a**. The crude product, which showed a single spot on TLC (Rf 0.46, MeOH - NH_4OH, 99: 1), was used for the following reactions without further purification. The **12b** compound was characterized as its 6′-*N*-Cbe derivative[17].

General Method for the Hydrolysis of the Ethoxycarbonyl Groups and for the Purification of Sisamine Derivatives

The 1,3,2′-tri-*N*-Cbe derivative was added to a barium hydroxide saturated aqueous solution and refluxed for 18~48 hours. After cooling and filtration solid CO_2 was added to the filtrate which was again filtered, and the aqueous solution was evaporated. The residue was chromatographed on silica gel with methanol - concentrated aqueous ammonia (3: 1). The fractions containing the pseudodisaccharide were collected and evaporated to dryness. The solid was then chromatographed on Amberlite CG-50 (NH_4^+), washed with water, and eluted with 1 N aqueous ammonia. The fractions containing the pure sisamine derivative were collected and evaporated to dryness. The product was dissolved in water and lyophilized twice, neutralized with 0.1 N H_2SO_4 and lyophilized once more to yield the sulfate salt as a white amorphous powder.

Sisamine (**1a**): **1a**, $2H_2SO_4 \cdot 3H_2O$ (131 mg, 28%) was obtained from crude **11a** (836 mg). $[\alpha]_D^{20}$ +42° (*c* 1, H_2O), ref[11] $[\alpha]_D^{20}$ +116° (*c* 0.5, H_2O) as the free base.

Anal Calcd for $C_{12}H_{34}N_4O_{15}S_2$: C 26.76, H 6.36, N 10.40
Found: C 26.76, H 6.43, N 9.99

3′-Hydroxysisamine (**1b**): **1b**, $3H_2SO_4 \cdot 2H_2O$ (144 mg, 12%) was obtained from crude **11b** (1 g). $[\alpha]_D^{20}$ +64° (*c* 0.5, H_2O).

Anal Calcd for $C_{12}H_{34}N_4O_{19}S_3$: C 22.71, H 5.40, N 8.83
Found: C 22.61, H 5.29, N 8.41

6′-*N*-Methylsisamine (**2a**): **2a**, $2H_2SO_4 \cdot 4.5H_2O$ (208 mg, 32%) was obtained from crude **12a** (600 mg). $[\alpha]_D^{20}$ +40° (*c* 1, H_2O).

Anal Calcd for $C_{13}H_{37}N_4O_{16.5}S_2$: C 26.93, H 6.43, N 9.67
Found: C 26.84, H 7.06, N 9.42

3′-Hydroxy-6′-*N*-methylsisamine (**2b**): **2b**, $3H_2SO_4 \cdot 1.5H_2O$ (166 mg, 28%) was obtained from crude **12b** (1 g). $[\alpha]_D^{20}$ +65° (*c* 0.46, H_2O).

Anal Calcd for $C_{13}H_{35}N_4O_{18.5}S_3$: C 24.25, H 5.48, N 8.7
Found: C 24.35, H 5.42, N 8.56

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