Stereocontrolled routes to *cis*-hydroxyamino sugars. Part VI. A synthesis of garosamine[1]

HENRY W. PAULS[2,3] AND BERT FRASER-REID[3]

Department of Chemistry, University of Waterloo, Waterloo, Ont., Canada N2L 3G1

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The exocyclic olefin, **5**, obtained from the known epoxy uloside, methyl 2,3-anhydro-β-D-*erythro*-pentopyranosid-4-ulose, **3**, reacts with ammonia or methylamine to give the 3-amino-3-deoxy or 3-methylamino-3-deoxy derivatives respectively. The benzamide, **8***c*, obtained from the former, reacts with iodonium ion to give an oxazoline in which the *cis* relationship between the tertiary alcohol and the 3-amino group of garosamine is secured. Deiodination is followed by a one-pot *N*-methylation and reduction. A hydrolysis gives methyl α-L-garosamimide **2**. In a second route, the urethane, **16***c*, reacts with iodonium ion to give an oxazolidone **17***a*. This reaction establishes the *cis*-hydroxyamino moiety and circumvents the *N*-methylation/reduction steps. Deiodination followed by deprotection yields methyl α-L-garosaminide **2**. Both routes require eight steps from **3** with overall yields of 14% and 11%, respectively.

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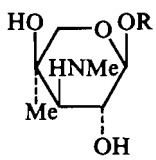
L'oléfine exocyclique, **5**, qui est obtenue de l'époxy uloside connu, anhydro-2,3 β-D-*érythro*-pentopyrannoside ulose-4 de méthyle, **3**, réagit avec l'ammoniac ou la méthylamine pour donner, suivant le cas, soit le dérivé amino-3 déoxy-3 ou méthylamino-3 déoxy-3. Le benzamide **8***c*, obtenu à partir du premier de ces dérivés, réagit avec l'ion iodonium pour donner une oxazoline dans laquelle on a fixé, entre l'alcool tertiaire et le groupe amino-3, la relation *cis* qui existe dans la garosamine. Après l'élimination de l'iode, on effectue, dans le même ballon, une *N*-méthylation suivie d'une réduction. Une hydrolyse conduit à la α-L-garosamimide de méthyle, **2**. Dans une deuxième voie de synthèse, on fait réagir l'uréthane **16***c* avec l'ion iodonium pour obtenir une oxazolidone **17***a*. Cette réaction permet d'établir la relation *cis* de la portion amino-alcool et évite les étapes de *N*-méthylation/réduction. L'élimination de l'iode, suivie d'une déprotection, conduit au produit **2**. Chacune des voies requiert huit étapes à partir du produit **3** et leurs rendements respectifs sont de 14% et 11%.

[Traduit par le journal]

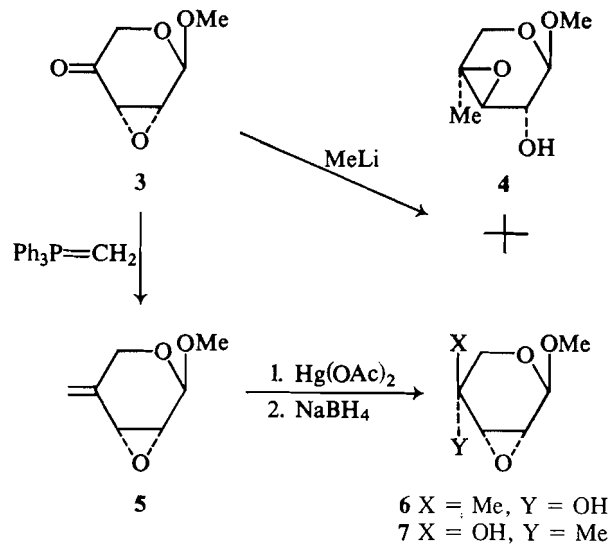
Introduction

The *C*-gentamycins are the principle components of an antibiotic complex produced by *Micromonospora purpurea* NRRL 2953 and *Micromonospora echinospora* NRRL 2985 under anaerobic conditions (1). Widespread clinical use has established them as major broad-spectrum antibiotics, and the advent of semi-synthetic methods has raised the possibility of obtaining novel, more potent modifications (2). A common, essential subunit of all three is the amino sugar garosamine, **1**, which occurs also in a number of other potent aminocyclitol antibiotics, sisomycin (3), G-52 (4), and XK-62-2 (5). Accordingly, a reliable synthetic route to **1** has been of interest for some time, and was the reason for our entry into the area of amino sugar synthesis (6–10).[4]



1 R = H
2 R = Me

Two structural features, the tertiary alcohol and the *cis*-hydroxyamino moiety, had posed challenges for earlier syn-



3 **4** **5**

6 X = Me, Y = OH
7 X = OH, Y = Me

SCHEME 1

thesis of garosamine (11, 12). The first of these by zu Reckendorf and Bishop (11), served to establish the correct structure of **1**; but major problems were encountered which caused low yields. The synthesis of the Schering group led by Wright (12) employed a clever solution to the problematic tertiary alcohol. However, this did not constitute a general solution to *cis*-hydroxyamino features.

From these publications (11, 12) it is apparent that the tertiary alcohol is a major obstacle, and some early exploratory investigations in our group convinced us that there would be no easy solutions. Thus the known epoxy uloside **3** seemed to be a plausible intermediate. Paulsen and Eberstein had shown that methyllithium addition to **3** gave virtually equal amounts of **4** and **6** (13). We decided to examine the hydration of the exo-

[1]Part I is the preliminary account of this work, ref. 6. Part II is the preliminary account of the accompanying paper, ref. 7. Part III, see ref. 8; Part IV, see ref. 9; Part V, see ref. 10.

[2]Holder of NSERC Postgraduate Scholarship, 1981–1982.

[3]Present address: Gross Chemical Laboratory, Duke University, Durham, NC 27706, U.S.A. Correspondence may be addressed to B.F-R.

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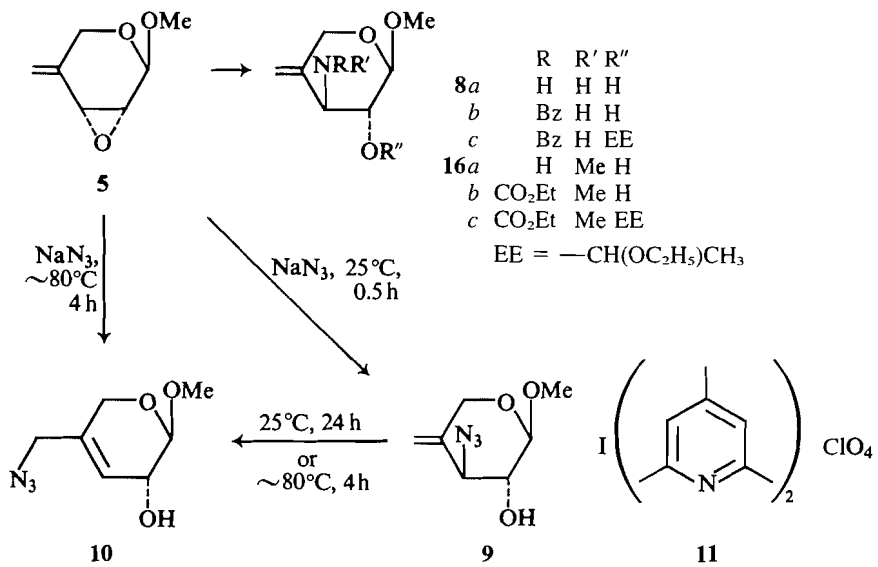
cyclic olefin **5**, which could be obtained cleanly by a Wittig reaction of **3**. However, the yield of **5** was variable because of the high volatility of the material. We had hoped that, in keeping with our studies on frontalin (14), hydration of the double bond would lead to the desired lyxoside **7**. Unfortunately, the single product obtained from oxymercuration–demercuration of **5** proved to be the riboside **6**.

With regard to the second problem, the *cis*-hydroxyamino moiety, we were interested in developing a general methodology for this structural feature. Winstein *et al.* had achieved the halolactonization of simple allylic amides to afford oxazolines (5). Application of this methodology to **8***b* would not only establish the *cis*-hydroxyamino component, but would simultaneously secure the troublesome tetiary hydroxyl group. In this and the accompanying manuscript (16) we give full details of some of our results.

Results and discussion



	R	R′	R″
8*a*	H	H	H
b	Bz	H	H
c	Bz	H	EE
16*a*	H	Me	H
b	CO_2Et	Me	H
c	CO_2Et	Me	EE

EE = —$CH(OC_2H_5)CH_3$

SCHEME 2

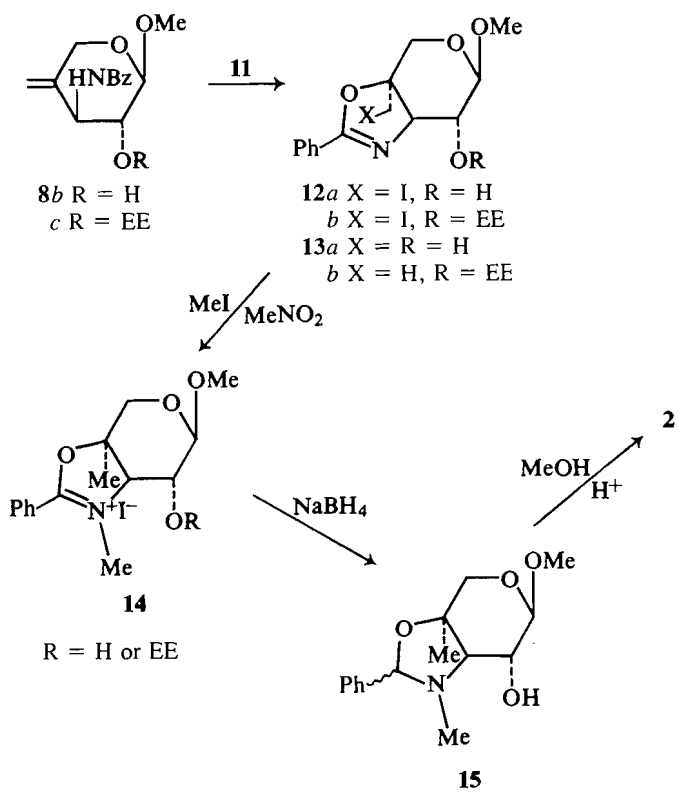
Route I

The appropriate precursor would be the amine **8***a*, obtainable by S_N2 attack at the allylic position of **5**. Azidolysis was examined initially, and some pertinent data relating to this are summarized in Scheme 2. At low temperatures, a clean S_N2 reaction occurred at the allylic site, C-3, to give the azido alcohol **9**, there being only traces of the S_N2' product **10**, barely detectable by tlc. With refluxing aqueous ethanol, compound **10** was the sole product after 4 h. The latter could be obtained alternatively by heating **9** in ethanol, or by allowing **9** to stand at room temperature for 24 h.

The sigmatropic rearrangement to the thermodynamically more stable **10** detracted from **9** as an intermediate and hence ammonolysis was examined. The best procedure was to saturate an ice-cold ethanol solution of the epoxide **5**, contained in a pressure vessel, with the amine, seal and place the vessel in an oil bath, and gradually raise the temperature to 80°C. Under these conditions, the primary amine **8***a* was obtained in 97% yield.

The benzamide **8***b* was prepared, but in contrast to Winstein's case (5), no reaction could be induced with *N*-bromosuccinimide. Typical iodolactonization conditions (I_2/KI/H_2O/THF) were also unsuccessful.

Iodonium dicollidine perchlorate (17) **11** was adopted, since in our experience this salt is a reliable source of iodonium ions (18). Indeed, treatment of the benzamides **8***b* or **8***c* with the salt in chloroform (Scheme 3) yielded the iodo-oxazolines **12***a* or **12***b* respectively, which were smoothly deiodinated by treatment with tri-n-butyltin hydride to **13***a* and **13***b* respectively.

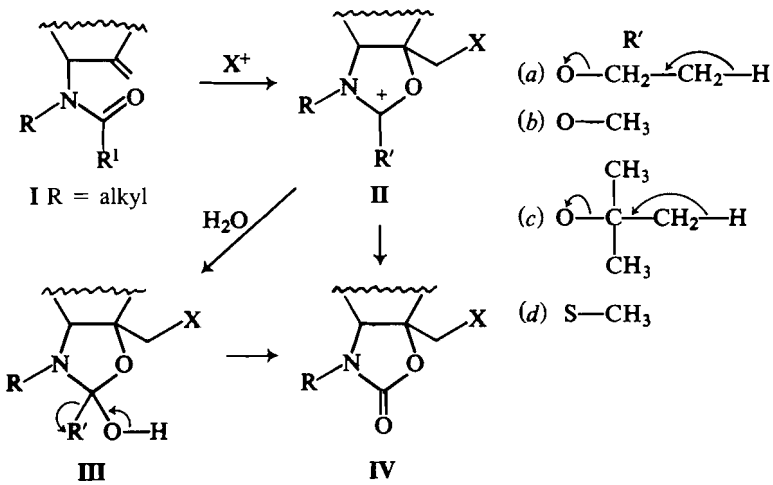


SCHEME 3

Since *cis*-fusion is expected for 6/5 heterocyclic systems (19) the product was expected to establish the desired orientation at C-4 stereospecifically.

Quaternization of the nitrogen of **13***b* required heating with methyl iodide in nitromethane for 48 h (tlc). The resulting salt, presumably **14**, was reduced directly with sodium borohydride in methanol. During these two steps, the C-2 protecting group was lost, giving **15** as the product. Strangely, the unprotected alcohol **13***a* could not be *N*-methylated under identical conditions.

Hydrolysis of the oxazolidine **15** was achieved with methanol and hydrogen chloride and the resulting material had infrared and ^{1}H nmr spectra identical with those of an authentic sample of methyl α-L-garosaminide **2** (*vide infra*).



SCHEME 4

Mechanistic considerations

In spite of the success of the above route, some economy of steps was desired. An intermediate such as **I** (Scheme 4, R = Me) was preferable since the extra steps of *N*-methylation and reduction would be circumvented. The urethane group emerged as the nitrogen substituent of choice since the corresponding cationic intermediate, **II**, is stablized by three heteroatoms, and should react further to give cyclic urethane **IV** (i.e. a 2-oxazolidone).

It is appropriate to comment on the possible modes of decomposition of the carbocation intermediates in Scheme 4. These species ought to react readily with traces of water to give **III**, which should eject an alcohol to give the cyclic urethane **IV**. This mode of decomposition should not be greatly affected by the nature of the substitutent R′. However, subsequent to our preliminary report, Parker and O'Fee (20) found that methyl urethanes, for example **II***b*, gave little, if any, oxazolidone, whereas *tert*-butyl analogs, for example **II***c*, reacted very smoothly. The results with **II***a* and **II***c* are accommodated by the alternate mode of decomposition depicted in Scheme 4, in which ethylene and isobutylene, respectively, are ejected. This is more satisfying than involvement of **III**, since our work was carried out under rigorously anhydrous conditions.

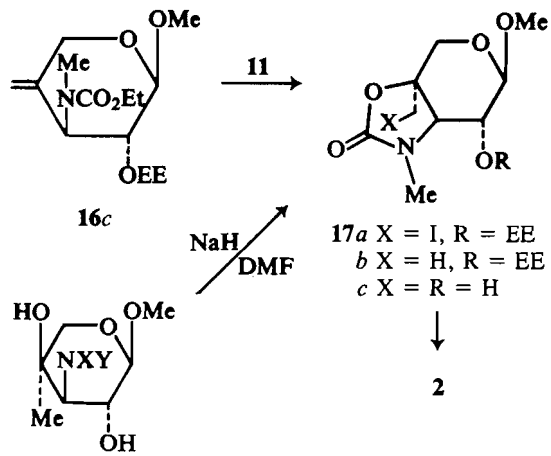
The foregoing notwithstanding, it should be noted that Knapp and Patel have obtained excellent results from bromocyclization of methylurethanes and methylthiourethanes, such as **II***b* and **II***d* respectively (21).

Route 2

The *N*-methyl amino alcohol **16***a*, prepared in a manner similar to **8***a*, was treated with ethyl chloroformate, followed by ethyl vinyl ether, to yield **16***c*. Reaction of **16***c* with the iodonium salt, **11**, afforded the desired product **17***a* in 82% yield. Deiodination was effected by hydrogenolysis over palladium, and subsequent hydrolysis with pyridinium *p*-toluenesulfonate led to oxazolidone **17***c* as a crystalline substance. This material was alternatively prepared by treating urethane **18** (obtained from authentic methyl α-L-garosaminide[4]) with sodium hydride in dimethyl formamide. The two samples had identical physical constants. Hydrolysis of **17***c* with potassium hydroxide gave the previously described garosamide **2**.

Summary

The syntheses described above are reasonably successful in terms of economy of steps and overall yield. The oxazoline route yields methyl α-L-garosaminide **2** from the known epoxy uloside **3** in 8 steps with 14% overall yield. The overall yield of **2** from **3** for the oxazolidone route (Scheme 5) is 11% in 8 steps. Further use of the oxy-amination procedure is reported in the accompanying paper (16).



SCHEME 5

Experimental

General methods

Melting points were determined in capillary tubes in a Buchi model SMP-20 melting point apparatus, and are uncorrected. Elemental analyses were performed by Guelph Chemical Laboratories Ltd., 500 York Road, Guelph, Ont., N1H 3J4. Nuclear magnetic resonance (^{1}H nmr) spectra were determined in deuteriochloroform containing 1% tetramethylsilane (TMS) as internal standard with a Perkin– Elmer R-12B (60 MHz) or, when specifically stated, with a Varian HR-220 spectrometer. Coupling constants were obtained by measuring the spacings of spectra judged to be first order. Infrared (ir) spectra were determined on a Beckman model IR-10 spectrometer using 0.1-mm sodium chloride cells and chloroform as solvent for solids, or sodium chloride plates for thin film smears. Low resolution mass spectra were determined on a Varian MAT CH7 mass spectrometer. High resolution mass spectra (hrms) were determined on a VG 7070F.

Optical rotations were measured on a Carl Zeiss model LEP nür 370740 Lichtelektrisches Präzisionspolarimeter at 23°C.

The progress of all reactions was monitored by thin layer chromatography (tlc) which was performed on 1.3 cm × 6.6 cm aluminum sheets precoated with silica gel 60 (HF-245, E. Merck) to a thickness of 0.25 mm. The following solvent systems were used to develop the plates: (A) ethyl acetate – petroleum ether (30–60°C), (1:1); (B) diethyl ether – methylene chloride (1:19); (C) ethyl acetate. The chromatograms were viewed under an ultraviolet light, sprayed with concentrated sulfuric acid, and heated to a temperature greater than 100°C under a hot air gun. For column chromatography E. Merck Kieselgel 60 (230–400 mesh A.S.T.M.) was used. The columns were eluted under pressure.

*Methyl 2,3-anhydro-4-*C*-methylene-β-*D*-*erythro*-pentopyranoside (**5**)*

To a stirred mixture of (methyl) triphenylphosonium bromide (6.50 g, 18.2 mmol) and 50 mL dry DME under argon was added 2.2 molar n-butyllithium in hexane (6.04 mL, 13.3 mmol). The resulting suspension was stirred for 15 min, placed in an ice bath, and stirred an additional 15 min. The ketone, **3** (10) (1.74 g, 12.1 mmol), dissolved in 15 mL dry dimethoxyethane, was added dropwise. After the addition was complete the resulting mixture was stirred for 5 min, then quenched with wet diethyl ether (300 mL). The resulting slurry was filtered through Celite and washed several times with diethyl ether. The filtrate was evaporated under reduced pressure at room temperature and the residue was chromatographed with solvent system B. Epoxy olefin **5**, the only carbohydrate product, was isolated as a mobile oil (0.88 g, 51.3%); R_f 0.51 (solvent B); $[\alpha]_D^{23}$ −123.7° (*c* 1.0, chloroform); ir ν_{max}: 1450 (terminal alkene C—H bend) cm^{-1}; ^{1}H nmr δ: 3.15 (dd, 1, $J_{2,3}$ = 3.5 Hz, H-3), 3.4 (s, 3, —OCH_3), 3.62 (d, 1, H-3), 4.07–4.18 (complex ABq, 2, H-5, H-5′), 4.92 (bs, 1, H-1), 5.20–5.35 (dm, 2, =CH_2).

*Methyl 2,3-anhydro-4-*C*-methyl-β-*D*-*ribopyranoside (**6**)*

Epoxy olefin **5** (0.197 g, 1.39 mmol) was dissolved in 5 mL THF and 6 mL water, to which was added mercuric acetate (0.493 g, 1.56 mmol). The mixture was stirred at room temperature until the starting material had disappeared – typically 10 h. At this time 3.5 mL of 3 *M* aqueous sodium hydroxide and 2 mL of freshly prepared aqueous sodium borohydride (0.5 *M*, 1.0 mmol) in 3 *M* sodium hydroxide were added in quick succession. The resulting mixture was extracted 3 times with methylene chloride. The organic layers were combined, filtered to remove suspended mercury, dried over sodium sulfate, and evaporated. The sole product **6** (0.176 g, 79%) was obtained as a white solid. Recrystallization from chloroform/hexane yielded white crystals which showed mp 99–101°C; $[\alpha]_D^{23}$ −72° (*c* 1.1, chloroform). The literature (13) reports mp 103°C; $[\alpha]_D^{23}$ −79°.

*Methyl 3-azido-3,4-dideoxy-4-*C*-methylene-α-*L*-threo-pentopyranoside, (**9**)*

The starting material **5** (0.10 g, 0.70 mmol) was dissolved in 4 mL of a 3:1 ethanol/water mixture, sodium azide (0.14 g, 2.1 mmol) was added, and the mixture was stirred at room temperature. After 30 min, tlc indicated that the epoxy olefin had been consumed and replaced by **9** with trace amounts of **10**, showing R_f 0.47 and 0.32 respectively in solvent A. The reaction mixture was poured into ice water and the aqueous layer was extracted three times with methylene chloride. The combined organic washings were dried over sodium sulfate and evaporated to yield 0.92 g of a white solid (71%). The crude product exhibited the following physical data; ir ν_{max}: 3300–3500 (OH), 2120 (N_3), 1625 (C=C) cm^{-1}; ^{1}H nmr δ: 3.1 (bs, 1, OH), 3.30–4.47 (m, 5, H-1, H-2, H-3, H-5, H-5′), 3.50 (s, 3, —OCH_3), 5.15–5.30 (dm, 2, =CH_2).

*Methyl 4-*C*-azidomethyl-3,4-dideoxy-β-*D*-*glycero*-pent-3-enopyranoside (**10**)*

(a) Epoxy olefin **5** (1.0 g, 7.04 mmol) was dissolved in 25 mL of ethanol, to which was added 7.5 mL water, sodium azide (0.52 g, 8.1 mmol), and ammonium chloride (0.53 g, 9.8 mmol). The mixture was refluxed with stirring for 4 h, at which time tlc revealed **10** as the only product. The solvent was evaporated and the residue was partitioned between water and methylene chloride. The aqueous layer was separated and washed once more with methylene chloride, then the organic layers were combined, dried, and evaporated. Product **10** was obtained as a pale brown syrup (0.88 g, 67.5%); $[\alpha]_D^{23}$ −175.1° (*c* 0.6, chloroform); ir ν_{max}: 3440–3460 (OH), 2100 (N_3) cm^{-1}; ^{1}H nmr δ: 2.8 (bs, 1, —OH), 3.53 (s, 3, —OCH_3), 3.8 (s, 2, H-4a, H-4b), 3.9 (m, 1, H-2), 4.13 (s, 2, H-5, H-5′), 4.6 (d, 1, $J_{1,2}$ = 2.5 Hz, H-1), 5.9 (bs, 1, H-3); *m/e*: 143 ($M^+ - N_3$), 125 ($M^+ - N_3 - H_2O$), 94 ($M^+ - N_3 - H_2O$ – OMe).

(b) Azide **9**, upon standing at room temperature for about 24 h, or when refluxed in ethanol/water for 4 h, was converted into azide **10**.

*Methyl 3-amino-3,4-dideoxy-4-*C*-methylene-α-*L*-threo-pentapyranoside (**8**a)*

The epoxy olefin **5** (0.389 g, 2.74 mmol) was dissolved in absolute ethanol (20 mL) and placed in a pressure vessel. The vessel was cooled in an ice bath and the solution saturated with a stream of ammonia. The pressure vessel was sealed, placed in an oil bath, and heated to 80°C. After 30 min the vessel was removed, cooled to room temperature, and the solvent was removed on a rotary evaporator. A brown solid, **8***a* (0.42 g, 96.8%), was obtained, which was suitable for subsequent manipulations. After two recrystallizations from ethanol white crystals of **8***a* were obtained with the following physical constants: mp 170.0–170.5°C; $[\alpha]_D^{23}$ −65.5° (*c* 0.7, chloroform); ir ν_{max}: 3400–3600 (NH and OH) cm^{-1}; ^{1}H nmr δ: 3.54 (s, 3, OCH_3), 3.90–4.32 (m, 3, H-1, H-5, H-5′), 5.10 (dm, 2, =CH_2). *Anal.* calcd. for $C_7H_{13}O_3N$: C 52.82, H 8.23, N 8.80; found: C 53.13, H 8.51, N 8.69.

*Methyl 3-benzamido-3,4-dideoxy-4-*C*-methylene-α-*L*-threo-pentopyranoside (**8**b)*

The allylic amine **8***a* (0.360 g, 2.26 mmol) was dissolved in 20 mL dry chloroform. To this was added sodium bicarbonate (0.190 g, 2.26 mmol) and benzoyl chloride (0.30 mL, 2.6 mmol). After stirring for 1 h at room temperature, 20 mL of water was added, and the mixture was stirred another 15 min. The mixture was poured into a separatory funnel and the organic layer was removed. The aqueous layer was saturated with sodium chloride and extracted twice more with methylene chloride. The organic layers were combined, dried, and evaporated to dryness to give a white solid **8***b* (0.494 g, 83%) which, after recrystallization from ethanol, gave the following data: mp 202–203°C; $[\alpha]_D^{23}$ −131.3° (*c* 1.6, chloroform); ir ν_{max}: 1660 (C=O stretch) cm^{-1}; ^{1}H nmr (220 MHz) δ: 2.62 (d, 1, $J_{2,3}$ = 8 Hz, H-3), 3.50 (s, 3, —OCH_3), 3.65 (m, 1, —OH), 4.10 (ABq, 2, $J_{5,5'}$ = 13.5 Hz, H-5, H-5′), 4.60 (d, 1, $J_{1,2}$ = 4 Hz, H-1), 4.8 (dd, 1, H-2), 5.23 (d, 2, =CH_2), 7.42 (m, 3, *meta* and *para* phenyl protons), 7.75 (m, 2, *ortho* phenyl protons). *Anal.* calcd. for $C_{14}H_{17}O_5N$: C 63.87, H 6.51, N 5.32; found: C 64.10, H 6.55, N 5.25.

*2′-Phenyl-(methyl 3,4-dideoxy-4-*C*-iodomethyl-α-*L*-arabinopyranosido)-[3,4:4′,5′]-Δ$^{2'}$-oxazoline (**12**a)*

Compound **8***b* (0.128 g, 0.49 mmol) was dissolved in 20 mL

chloroform to which was added iodonium dicollidine perchlorate **11** (17) (0.342 g, 0.735 mmol). The solution was stirred at room temperature in the dark for 4 h. Diethyl ether (100 mL) was added and the unreacted reagent was removed by filtration. The filtrate was evaporated and the residue was redissolved in methylene chloride. The methylene chloride phase was washed with 10% sodium thiosulfate, 5% hydrochloric acid, and, finally, water. The aqueous layers were washed successively with two fresh aliquots of methylene chloride. The organic layers were combined, dried over sodium sulfate, and evaporated. The crude syrup obtained was chromatographed on silica gel with solvent A to yield product **12***a* as a foam (0.147 g, 93%); R_f 0.33 (Solvent A); ir ν_{max}: 1730 (oxazoline C=N stretch), 3400 (OH) cm^{-1}; ^1H nmr δ: 3.48 (s, 3, $-OCH_3$), 3.52 (s, 2, $-CH_2I$), 4.54 (d, 1, $J_{1,2}$ = 5 Hz, H-1), 7.48 (m, 3, *meta* and *para* phenyl protons), 7.95 (m, 2, *ortho* phenyl protons). *Exact Mass* calcd. for $M^+ - OCH_3$: 357.9942; found (hrms): 357.9940; calculated for $M^+ - I$: 262.1079; found (hrms): 262.1078.

*2'-Phenyl-(methyl 3,4-dideoxy-4-*C*-methyl-α-L-arabinopyranosido)-[3,4:4',5']-Δ$^{2'}$-oxazoline (**13**a)*

Iodide **12***a* (0.347 g, 0.89 mmol) was dissolved in 20 mL reagent benzene to which was added tri-n-butyltin hydride (0.30 mL, 0.10 mmol). The reaction mixture was heated to reflux for 4 h, at which time the benzene was removed by evaporation. The resultant residue was partitioned between hexane and acetonitrile. The acetonitrile layer was washed twice more with hexane, then evaporated to give product **13***a* (0.155 g, 66%), which after one recrystallization from ethyl acetate had the following physical data: mp 208–209°C; $[\alpha]_D^{23}$ −0.6° (*c* 1.3, chloroform); ^1H nmr δ: 1.40 (s, 3, $-\overset{|}{C}CH_3$), 3.54 (s, 3, $-OCH_3$), 3.87 (ABq, 2, $J_{5,5'}$ = 11 Hz, H-5, H-5'), 4.49 (d, 1, $J_{1,2}$ = 5 Hz, H-1), 4.05 (bs, 1, —OH), 7.55 (m, 3, *meta* and *para* phenyl protons), 8.10 (m, 2, *ortho* phenyl protons). Satisfactory elemental analysis of **13***a* could not be obtained.[5]

*Methyl 3-benzamido-3,4-dideoxy-2-*O*-α-ethoxyethyl-4-*C*-methylene-α-L-*threo*-pentopyranoside (**8**c)*

The starting material **8***b* (0.116 g, 0.44 mmol) was dissolved in dry methylene chloride (40 mL) to which was added ethyl vinyl ether (0.12 mL, 1.2 mmol) and pyridinium *p*-toluenesulfonate (0.30 g, 0.13 mmol). The solution was stirred at room temperature and the reaction progress was followed by tlc. Upon completion, typically 4 h, the reaction mixture was poured into an equal volume of brine, shaken, and separated. The aqueous layer was washed twice with methylene chloride. The organic layers were combined, dried over sodium sulfate, and evaporated to yield impure **8***c*. After chromatography, in solvent A, the product **8***c* was obtained as a white solid (0.156 g, quantitative yield); it showed mp 154–155°C; R_f 0.30 (solvent A); ir ν_{max}: 1730 (amide C=O stretch) cm^{-1}; ^1H nmr δ: 1.05–1.5 (m, 6, $-OCH(CH_2)OCH_2CH_3$), 3.54 (s, 3, $-OCH_3$), 5.1 (m, 2, $=CH_2$), 7.30–8.0 (m, 5, phenyl protons). *Anal.* calcd. for $C_{18}H_{25}O_5N$: C 64.46, H 7.51, N 4.18; found: C 64.14, H 7.47, N 4.11.

*2'-Phenyl-(methyl 3,4-dideoxy-2-*O*-α-ethoxyethyl-4-*C*-iodomethyl-α-L-arabinopyranosido)-[3,4:4',5']-Δ$^{2'}$-oxazoline (**12**b)*

Compound **8***b* (0.047 g, 0.14 mmol) was treated with iodonium dicollidine perchlorate **11** (0.098 g, 0.21 mmol) as described for **12***a* above. The crude product was chromatographed with solvent A to yield compound **12***b* as an amber syrup (0.077 g, quantitative yield); R_f 0.5 (solvent A); ir ν_{max}: 1665 (oxazoline C=N stretch) cm^{-1}; ^1H nmr δ: 1.05–1.55 (m, 6, $-OCH(CH_3)OCH_2CH_3$), 3.50 (s, OCH_3), 3.65 (bs, 2, $-CH_2I$), 4.6 (m, 1, H-1), 4.95 (m, 1, $-OCH(CH_3)OCH_2CH_3$), 7.55 (m, 3, *meta* and *para* phenyl protons), 8.0 (m, 2, *ortho* phenyl protons).

[5]Compound **13***a* was hydrolysed on standing to give the crystalline amide **19**, mp 222–223°C. *Anal.* calcd. for $C_{14}H_{19}O_5N$: C 59.72, H 6.67, N 4.70; found: C 59.66, H 6.83, N 4.81.

*2'-Phenyl-(methyl 3,4-dideoxy-2-*O*-α-ethoxyethyl-4-*C*-methyl-α-L-arabinopyranosido)-[3,4:4,4'5')-Δ$^{2'}$-oxazoline (**13**b)*

Iodide **12***b* (0.214 g, 0.48 mmol) was dissolved in 20 mL reagent benzene to which was added tri-n-butyltin hydride (0.15 mL, 0.50 mmol). The reaction was heated to reflux for 4 h in the presence of AIBN (1–2 mg). The benzene was removed by rotary evaporation and the resultant residue was chromatographed using solvent A. Product **13***b* was isolated as a syrup (0.127 g, 83%); it showed R_f 0.5 (solvent A); ir ν_{max}: 1645 (oxazoline C=stretch) cm^{-1}; ^1H nmr δ: 1.0–1.45 (m, 6, $-OCH(CH_3)OCH_2CH_3$), 1.45 (s, 3, $-\overset{|}{C}-CH_3$), 3.36 (s, 3, $-OCH_3$), 4.60 (two d, 1, H-1), 4.90 (two q, 1, $-OCH(CH_3)-CH_2CH_3$).

*3'-*N*-Methyl-2'-phenyl-(methyl 3,4-dideoxy-4-*C*-methyl-α-L-arabinopyranosido)-[3,4:4',5')-oxazolidine (**15**)*

The starting material **13***b* (0.395 g, 1.18 mmol) was dissolved in nitromethane (10 mL) to which was added methyl iodide (0.20 mL, 2.36 mmol). The reaction flask was fitted with a reflux condenser and heated with stirring at 70–80°C for 24 h. At this time more methyl iodide was added (0.20 mL, 2.36 mmol), and the reaction mixture was heated an additional 24 h. Analysis by tlc indicated the replacement of starting material by a new, uv active spot at the base line. Solvent and remaining reagent were removed under reduced pressure to yield a syrupy residue, presumably **14**.

The residue was redissolved in absolute methanol (15 mL) and the solution was cooled in an ice bath. To this was added sodium borohydride (0.045 g, 1.18 mmol) and the mixture was stirred for 1 h at 5°C, with the exclusion of moisture. At this time tlc indicated that the base line material had been replaced by a more mobile compound having R_f 0.58 (solvent A). The reaction vessel was allowed to warm to room temperature and, after slow addition of small amounts of water, the contents were partitioned between equal volumes of water and methylene chloride. The layers were separated and the aqueous layer was extracted twice more with methylene chloride. The organic layers were combined, dried over sodium sulfate, and evaporated. Chromatography of the residue (solvent A) yielded solid oxazolidine **15** (0.201 g, 61.5%). Recrystallization from ethyl acetate gave pure **15** which showed mp 101.5–102.5°C; $[\alpha]_D^{23}$ −3.3° (*c* 0.6, chloroform); ir ν_{max}: 3300–3650 (OH stretch) cm^{-1}; ^1H nmr δ: 1.43 (s, 3, $-\overset{|}{C}CH_3$), 2.34 (s, 3, $-NCH_3$), 2.60 (d, 1, $J_{2,3}$ = 5 Hz, H-3), 3.10 (bs, 1, —OH), 3.31–4.10 (m, 3, H-2, H-5, H-5'), 3.43 (s, 3, $-OCH_3$), 4.58 (d, 1, $J_{1,2}$ = 4 Hz), 4.90 (s, 1, benzylidine-methine), 7.40–7.70 (m, 5, aromatic protons). *Anal.* calcd. for $C_{15}H_{21}O_4H$: C 64.50, H 7.58, N 5.01; found: C 64.75, H 7.95, N 5.41.

*Methyl 3,4-dideoxy-3-(*N*-ethoxycarbonyl-*N*-methylamino)-4-*C*-methylene-α-L-*threo*-pentopyranoside (**16**b)*

The epoxy olefin **5** (0.77 g, 5.4 mmol) was dissolved in absolute ethanol (30 mL) and placed in a pressure vessel. The vessel was cooled in an ice bath and gaseous methylamine was bubbled through the ethanol solution for 15 min. The vessel was then sealed, placed in an oil bath, and heated to 80°C. After 30 min the vessel was removed, cooled to room temperature, and the contents concentrated. The product, obtained as a heavy brown oil, was dissolved in 10 mL of chloroform. To this was added sodium bicarbonate (0.361 g, 2.2 mmol) and ethyl chloroformate (0.39 mL, 2.5 mmol). After stirring for 15 min, saturated sodium bicarbonate solution (20 mL) was added and the mixture was stirred for an additional 15 min. The aqueous and organic layers were separated and the aqueous phase was washed three times with methylene chloride. The organic layers were combined, dried, and evaporated to dryness. The product **16***b* was obtained as a beige solid (0.287 g, 55%) which, upon recrystallization from ethanol, gave the following physical data: mp 132.5–133°C; $[\alpha]_D^{23}$ −63.3° (*c* 1.0, chloroform); ir ν_{max}: 1695 (urethane C=O stretch), 3300–3600 (OH stretch) cm^{-1}; ^1H nmr δ: 1.25 (t, 2, $-OCH_2CH_3$), 2.89 (s, 3,

—NHCH_3), 3.58 (s, 3, —OCH_3), 4.9 (bd, 3, =CH_2, H-1); *m/e*: 245 (M^+), 227 ($M^+ - H_2O$), 214 (M^+ – OMe), 185 ($M^+ - C_2O_2H_4$). *Anal.* calcd. for $C_{11}H_{19}O_5N$: C 53.87, H 7.81, N 5.71; found: C 53.88, H 8.05, N 5.68.

*Methyl 3,4-dideoxy-3-(*N*-ethoxycarbonyl-*N*-methyl amino)-2-O-ethoxyethyl-4-C-methylene-α-*L*-threo-pentopyranoside (**16***c*)*

Urethane **16***b* (0.082 g, 0.33 mmol) was treated with ethyl vinyl ether in a similar manner as used in the preparation of **8***c*. The crude syrup obtained was chromatographed on silica gel using solvent A. Compound **16***c* (0.092 g, 86%) was obtained as a thick oil; R_f 0.52 (solvent A); ir ν_{max}: 1690 (urethane C=O stretch) cm^{-1}; ^1H nmr δ: 1.0–1.5 (m, 9, —$OCH(CH_3)OCH_2CH_3$, —OCH_2CH_3), 2.78, 2.81 (two s, 3, —NCH_3), 3.5 (two, s, 3, —OCH_3), 4.93 (bd, 4, =CH_2, H-1, —$OCH(CH_3)OCH_2CH_3$).

*3′-*N*-Methyl-2′-oxo-(methyl 3,4-dideoxy-2-O-α-ethoxyethyl-4-C-iodomethyl-α-*L*-arabinopyranosido)-[4,4:4′5′]-oxazolidone (**17**a)*

The starting material **16***c* (0.162 g, 0.051 mmol) was dissolved in chloroform, to which was added one equivalent of iodonium dicollidine perchlorate (0.202 g, 0.051 mmol). The resulting solution was stirred in the dark for five days, a fresh equivalent of iodonium dicollidine perchlorate being added per 24 h of reaction time. The reaction mixture was worked up by addition of diethyl ether. Unreacted reagent was filtered off and the filtrate was concentrated under vacuum. The residue was dissolved in methylene chloride and washed with 10% sodium thiosulfate, then 5% hydrochloric acid and, finally, water. The aqueous layers were washed successively with two fresh aliquots of methylene chloride. The organic layers were combined, dried over sodium sulfate, and evaporated to dryness to yield **17***a* (0.174 g, 82%); it showed R_f 0.46 (solvent A); ir ν_{max}: 1740 (urethane C=O stretch) cm^{-1}; ^1H nmr δ: 1.20–1.40 (m, 6, —$OCH(CH_3)OCH_2CH_3$), 2.84, 2.93 (two s, 3, —NCH_3), 3.38, 3.40 (two s, 3, —OCH_3), 3.51, 3.54 (two s, 2, —CH_2I), 4.58, 4.69 (two d, 1, H-1), 4.86 (d, 1, —$OCH(CH_3)OCH_2CH_3$).

*3-*N*-Methyl-2′-oxo-(methyl 3,4-dideoxy-2-O-ethoxyethyl-4-C-methyl-α-*L*-arabinopyranosido)-[3,4:4′,5′]-oxazolidone (**17**b)*

Compound **17***a* (0.238 g) was placed in a Parr hydrogenation flask, then dissolved in methanol/water, 9:1 (20 mL). One pellet of potassium hydroxide and 10% palladium on carbon (50 mg) were added. The mixture was shaken under 20 atm of hydrogen for 24 h (1 atm = 101.3 kPa). The reaction mixture was filtered and the filtrate was partitioned between water and methylene chloride. The organic layer was separated and washed with 5% hydrochloric acid followed by water. The aqueous layers were washed successively with two portions of methylene chloride. The combined organic layers were dried over sodium sulfate and evaporated to yield **17***b* (0.162 g, 76.8%); ir ν_{max}: 1750 (urethane C=O stretch) cm^{-1}; ^1H nmr δ: 1.1–1.45 (m, 6, —$OCH(CH_3)OCH_2CH_3$), 1.51 (s, 3, —$C(CH_3)$—), 2.92, 2.98 (two s, 3, —$N(CH_3)$—), 3.4 (s, 3, —OCH_3), 4.60, 4.72 (two d, 1, H-1), 4.90 (two q, 1, —$OCH(CH_3OCH_2CH_3)$).

*3-*N*-Methyl-2′-oxo-(methyl 3,4-dideoxy-4-C-methyl-α-*L*-arabinopyranosido)-[3,4:4′,5′]-oxazolidone (**17**c)*

(a) Starting material **17***b* (0.162 g, 0.561 mmol) was dissolved in ethanol (10 mL) to which was added pyridinium *p*-toluene sulfonate (22) (0.017 g, 0.056 mmol). The solution was warmed on a steam bath until all the starting material had reacted. The ethanol was evaporated and the residue was taken up in methylene chloride (40 mL) and brine (15 mL). The layers were separated and the aqueous portion was washed twice more with methylene chloride. The organic layers were dried and evaporated to yield solid **17***c* (0.112 g, 92.1%). Recrystallization from ethyl acetate, followed by chloroform and hexane, yielded the following physical constants: mp 136–137°C; $[\alpha]_D^{23}$ −44.3° (*c* 0.5 chloroform); ir ν_{max}: 1750 (C=O stretch) cm^{-1}; ^1H nmr (220 MHz) δ: 1.48 (s, 3, —CCH_3), 3.03 (s, 4, —NCH_3, —OH), 3.40 (d, 1, $J_{2,3}$ = 6 Hz), 3.50 (s, 3, —OCH_3), 3.75 (m, 1, H-2), 3.81 (ABq, 2, $J_{5,5'}$ = 12.5 Hz, H-5, H-5′), 4.39 (d, 1, $J_{1,2}$ = 5.5 Hz). *Anal.* calcd. for $C_9H_{15}O_5N$: C 49.76, H 6.96, N 6.45; found: C 49.66, H 6.84, N 6.33.

(b) Compound **18** (0.240 g, 0.738 mmol), derived from authentic methyl α-*L*-garosaminide (12), was dissolved in dry DMF (15 mL) and cooled in an ice bath. A small amount of 50% sodium hydride dispersion in oil (0.040 g, 0.833 mmol) was washed three times with petroleum ether (bp 30–60°C) and added to the reaction vessel. The mixture was stirred at 0°C with exclusion of moisture until tlc indicated that compound **18**, R_f 0.45 (Solvent C), had been replaced by a new, more polar product. The flask contents were partitioned between water, added slowly, and methylene chloride. The organic layer was separated, dried, and evaporated to yield a white solid (0.112 g, 70%). The material was recrystallized from ethyl acetate, followed by chloroform and hexane, to give oxazolidone **17***c* of part (a); it showed a mixture mp 134.5–136°C.

*Methyl α-*L*-garosaminide (**2**)*

(a) The starting material **15** (0.111 g, 0.398 mmol) was dissolved in absolute methanol (30 mL) to which was added methanolic hydrochloric acid (13.5%, 5 mL). The solution was stirred at room temperature, with exclusion of moisture, for 24 h, at which time tlc (solvent A) indicated the replacement of **15** by a new material at the base line. The methanol was removed under vacuum and the resulting residue was partitioned between 5% hydrochloric acid (40 mL) and methylene chloride (40 mL). The aqueous layer was separated, neutralized with 5% sodium hydroxide, and evaporated to dryness. The solid obtained was extracted three times with hot ethyl acetate. The ethyl acetate was evaporated to yield amorphous, solid methyl α-garosaminide **2** (0.054 g, 70.1%). This material refused recrystallization from ethanol, but its nmr, ir, and tlc behavior matched that of the authentic sample (12).

(b) The starting oxazolidone **17***c* (0.112 g, 0.516 mmol) was added to 15% KOH (20 mL) and the reaction vessel was fitted with a condenser. The mixture was heated to 50–60°C for 6 h, at which time tlc (solvent A) indicated the replacement of **17***c* by a new material at the base line. The solution was acidified with 10% sulfuric acid and washed once with methylene chloride. The aqueous layer was neutralized with 5% sodium hydroxide and then evaporated to dryness. The solid remaining was extracted three times with hot ethyl acetate, which was removed under vacuum to yield **2** (0.067 g, 72%) as a thick syrup. The physical constants were identical with those of the material described in part (a).

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