

# A Novel Synthesis of Methyl $\alpha$ ,L-Garosaminide Which Illustrates a Stereocontrolled Approach to the *cis*-Hydroxyamino Moiety of Amino Sugars

Sir:

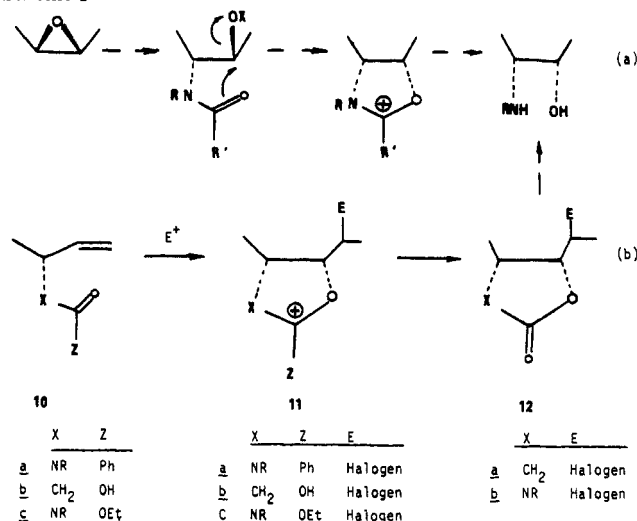
The branched-chain sugar garosamine, shown here as its methyl glycoside **1**, is a key component of a number of clinically important<sup>1,2</sup> aminocyclitol antibiotics including the gentamycins,<sup>3</sup> sisomycin,<sup>4</sup> and their potent, recently discovered congeners XK-62-2<sup>5</sup> and G-52.<sup>6</sup> Two syntheses of **1** beginning with 1,2:5,6-di-*O*-isopropylidene-D-glucose have been reported,<sup>7,8</sup> and the tortuous paths employed emphasize the magnitude of the challenge presented by (a) the tertiary hydroxyl group and (b) the *cis*-hydroxyamino moiety. In this communication we outline a synthesis of **1** in which both stereochemical problems are solved simultaneously.

The synthesis of a *cis*-hydroxyamino moiety which occurs frequently among antibiotic amino sugars is traditionally troublesome, and a standard solution is depicted in eq a<sup>9</sup> (Scheme I). However, application of this protocol to a synthesis of garosamine would be compromised by the fact that **2**, the logical starting material, undergoes azidolysis indiscriminately at C-2 and C-3.<sup>10</sup> It occurred to us that the simple strategy of using the allyl epoxide **4** should prove auspicious, since the desired stereo- and regioselectivity of nucleophilic attack at C-3 would thereby be ensured, and, in addition, the *exo*-methylene group would constitute the rudiments of the troublesome tertiary alcohol of **1**.

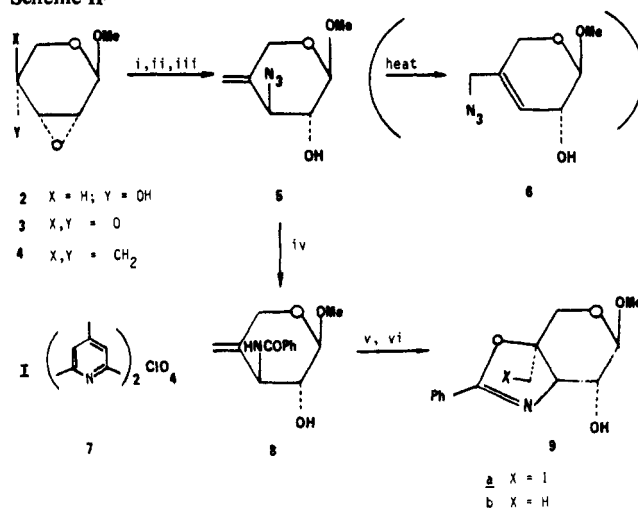
Accordingly, azidolysis of the allyl epoxide **4** at room temperature gave **5**<sup>11</sup> in 70% isolated yield (Scheme II). (The isomer **6** was formed quantitatively when the azidolysis was done at reflux or when **5** was allowed to stand at room temperature.) The benzamide **8** obtained from **5** in the usual way is reminiscent of a  $\gamma,\delta$ -unsaturated carboxylic acid as emphasized in the prototypes **10a** and **10b** (Scheme I, eq b), and the efficiency of haloactonization of the latter (i.e., **10b**  $\rightarrow$  **11b**  $\rightarrow$  **12a**) suggested that the same technique could be applied to **10a** ( $\equiv$  **8**). Iodonium dicollidine perchlorate<sup>7,12</sup> was adopted since in our experience<sup>13</sup> it is a superior source of iodonium ions.<sup>14</sup> Indeed its use<sup>16</sup> led to an 80% yield of the iodoazolidine **9a** which, because of its tendency to lose iodine, was reduced with tri-*n*-butyltin hydride to **9b**.

Compound **9b** is well on the way to **1**, but an intermediate bearing the *N*-methyl group would clearly have been preferred. In addition, further contemplation of eq b suggested that a urethane, **10c**, should serve better than **10a**, since the intermediate **11c** should readily scavenge water giving **12b**. Indeed the urethane **13** obtained in 65% overall yield from **4**, upon

Scheme I

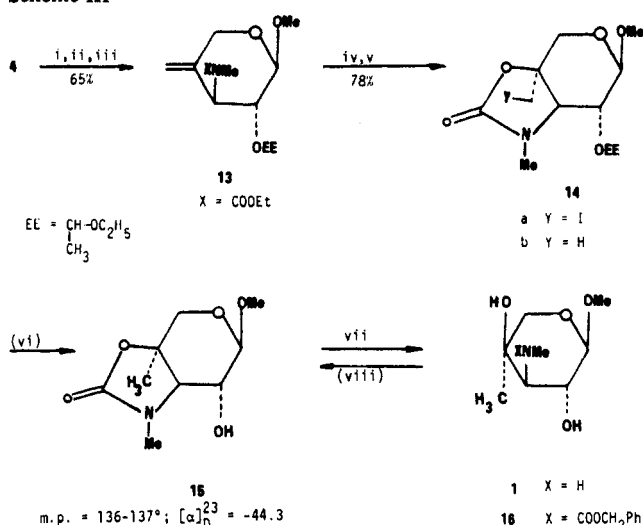


Scheme II<sup>a</sup>



<sup>a</sup> (i) PCC (85%); (ii) Ph<sub>3</sub>PCH<sub>2</sub>Br, *n*-BuLi, DME, N<sub>2</sub> (60%); (iii) NaN<sub>3</sub>, H<sub>2</sub>O-EtOH, 25 °C, 20 min (70%); (iv) LiAlH<sub>4</sub>, PhCOCl (86%); (v) ref 16 (80%); (vi) *n*-Bu<sub>3</sub>SnH, AIBN, C<sub>6</sub>H<sub>6</sub>, reflux (84%).

Scheme III<sup>a</sup>



<sup>a</sup> (i) MeNH<sub>2</sub>, EtOH, 100 °C, 1 h; (ii) EtOCOCI, CHCl<sub>3</sub>, NaHCO<sub>3</sub>, 23 °C; (iii) EtOCH=CH<sub>2</sub>Cl<sub>2</sub>, PPTS,<sup>18</sup> 23 °C, 12 h; (iv) ref 16 (82%); (v) H<sub>2</sub>, Pd/C, KOH (trace), EtOH; (vi) PPTS,<sup>18</sup> EtOH, reflux, 1 h; (vii) 15% KOH, 80 °C, 6 h (82%); (viii) NaH, DMF, 0 °C (quantitative).

treatment<sup>16</sup> with the iodonium salt **7**, gave a product assigned as **14a**<sup>17</sup> (Scheme III) in 82% yield, which was immediately reduced to **9b**. Removal of the ethoxy ethyl group gave **15** as a crystalline substance which was prepared alternatively by treating the urethane **16**,<sup>19</sup> obtained from authentic<sup>8</sup> methyl  $\alpha$ ,L-garosaminide **1**, with sodium hydride in DMF. Both compounds had identical <sup>1</sup>H NMR spectra<sup>20</sup> and their melting points were undepressed by admixture. Hydrolysis of **15** with potassium hydroxide afforded compound **1** as a syrup having identical <sup>1</sup>H NMR and IR spectra with those of the authentic material obtained from the Schering Corporation.

The application of this methodology to the stereocontrolled synthesis of other amino sugars is currently being investigated.

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Schering Corporation, New Jersey, gave us generous samples of **1** and **16**.

## References and Notes

- (1) P. L. J. Daniels in "Drug Action and Resistance in Bacteria", S. Mitsuhashi, Ed., University Park Press, Tokyo, 1975, pp 75-111.
- (2) "Drugs of Choice", W. Modell, Ed., C. V. Mosby Co., St. Louis, Mo., 1976.
- (3) M. J. Weinstein, G. M. Leukemann, G. E. M. Oden, C. H. Wagman, J. P. Rosselet, J. A. Marquez, C. T. Coniglio, W. Charney, H. L. Herzog, and J. Black, *J. Med. Chem.*, **6**, 463 (1963).
- (4) H. Reinmann, R. S. Jaret, and D. J. Cooper, *J. Chem. Soc., Chem. Commun.*, 924 (1971).
- (5) R. S. Egan, R. L. DeVault, S. L. Mueller, M. I. Levenberg, A. C. Sinclair, and R. S. Stanaszek, *J. Antibiot.*, **28**, 29 (1975).
- (6) P. L. J. Daniels, R. S. Jaret, T. L. Nagabhushan, and W. N. Turner, *J. Antibiot.*, **29**, 488 (1976).
- (7) W. Meyer zu Rechenhof and E. Bischof, *Chem. Ber.*, **105**, 2546 (1972).
- (8) J. S. Wright and C. L. Luce, *J. Org. Chem.*, **43**, 1968 (1978).
- (9) See, for example, D. Horton in "The Amino Sugars Ia", R. Jeanloz, Ed., Academic Press, New York, 1976.
- (10) D. J. Cooper, H. Davies, A. K. Mallans, and A. S. Yehaskel, *J. Chem. Soc., Perkin Trans. 1*, 785 (1975).
- (11) The structure of **5** was evident from the presence of the *exo*-methylene group in the IR (3050  $\text{cm}^{-1}$ ) and  $^1\text{H}$  NMR (5.12 ppm, 2 H).
- (12) R. U. Lemieux and A. R. Morgan, *Can. J. Chem.*, **43**, 2199 (1965).
- (13) (a) D. E. Iley and B. Fraser-Reid, *J. Am. Chem. Soc.*, **97**, 2563 (1975); (b) B. Fraser-Reid and D. E. Iley, *Can. J. Chem.*, **57**, 645 (1979).
- (14) Interestingly, in spite of (1) the resemblances emphasized in eq b (Scheme I) and (2) the fact that Weinstein had effected cyclization of 3-benzamidocyclohexene with NBS,<sup>15</sup> our systems failed to react under comparable conditions. Thus compounds **8** and **13** failed to cyclize with  $\text{I}_2$ -THF- $\text{H}_2\text{O}$ , NBS- $\text{CH}_2\text{Cl}_2$ , or NBS- $\text{Me}_2\text{SO}$ - $\text{H}_2\text{O}$ .
- (15) S. Weinstein, L. Goodman, and R. Boschan, *J. Am. Chem. Soc.*, **72**, 2311 (1950).
- (16) **7** (1 equiv) is added to a solution of the starting material in chloroform (1 mmol in 7 mL) and the solution is stirred in the dark until completion (TLC and/or NMR). Further additions of **7** were usually required. The workup procedure was as previously described by us.<sup>13b</sup>
- (17) The two protons at 5.12 ppm<sup>11</sup> disappear giving rise to sharp singlets (at 60 MHz) at 3.49 and 3.54 ppm ascribed to the diastereotopic protons of the iodomethyl group of **9a**.
- (18) PPTS = pyridinium *p*-toluenesulfonate; M. Miyashita, A. Yoshikoshi, and P. A. Grieco, *J. Org. Chem.*, **42**, 3772 (1977).
- (19) We are grateful to Dr. J. Wright of the Schering Corporation for this sample.
- (20)  $^1\text{H}$  NMR (60 MHz,  $\text{CDCl}_3$ ,  $\text{Me}_4\text{Si}$ ): 4.22 (d, H-1), 3.22-3.67 (n, H-2, H-5, H-5'), 2.28 (d, H-3), 1.17 (s,  $\text{CH}_3$ ), 2.47 (s,  $\text{NCH}_3$ ), 3.50 ppm (s,  $\text{OCH}_3$ ).

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## Mesomeric Stabilization of Carbonium Ions by $\alpha$ -Cyano Groups. A Theoretical Evaluation of Inductive vs. Resonance Effects of the Cyano Moiety

Sir:

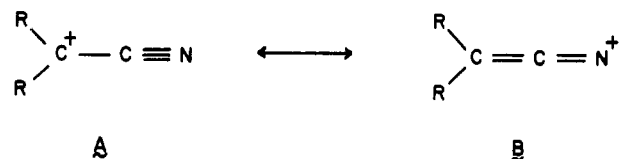
For generations, students have been taught that mechanisms of organic reactions which require the intermediacy of species having positively charged carbon attached to strong electron-withdrawing groups are to be rigorously avoided. Thus, postulated reaction mechanisms which involve the presence of a carbonium-ion center adjacent to carbonyl, sulfonyl, nitro, trifluoromethyl, or cyano functions are extremely rare. The basis for these teachings is reasonably well founded. Both Hammett<sup>1</sup> and Taft<sup>2</sup> have demonstrated the importance of considering the inductive effect of substituent groups, and Brown<sup>3</sup> has emphasized the importance of these principles when carbonium ions are involved. It is known<sup>4</sup> that placing a cyano function  $\beta$  to an incipient carbonium-ion center provides a rate-retarding effect on ionization of  $10^3$ - $10^7$ . In addition, Koshy and Tidwell have demonstrated that the presence of an  $\alpha$ -trifluoromethyl group leads to a  $\text{H}/\alpha\text{-CF}_3$  rate ratio of  $10^6$  for the solvolysis of simple sulfonate esters.<sup>5</sup> Using standard extrapolations,<sup>2,6</sup> it might be predicted that the related  $\text{H}/\alpha\text{-CN}$  rate ratio would be somewhere between  $10^9$  and

**Table I.** Calculated Bond Lengths and Bond Orders for Acetonitrile and for  $\alpha$ -Cyano and  $\beta$ -Cyano Substituted Carbonium Ions

compd or ion	bond length, Å		bond order	
	C-C <sup>a</sup>	C-N	C-C	C-N
$\text{CH}_3\text{CN}$ ( <b>1</b> )	1.456	1.155	1.038	2.939
$^+\text{CH}_2\text{CN}$ ( <b>2</b> )	1.366	1.197	1.418	2.522
$\text{CH}_3\text{CHCN}$ ( <b>3</b> )	1.384	1.187	1.310	2.627
$(\text{CH}_3)_2\text{CCN}$ ( <b>4</b> )	1.401	1.179	1.232	2.707
$(\text{CH}_3)_3\text{CCCN}$ ( <b>5</b> )	1.401 <sup>b</sup>	1.179 <sup>b</sup>	1.224	2.705
$^+\text{CH}_2\text{CH}_2\text{CN}$ ( <b>6</b> )	1.456	1.160	0.977	2.925
$(\text{CH}_3)_2\text{C}^+\text{CCN}$ ( <b>7</b> )	1.456 <sup>c</sup>	1.160 <sup>c</sup>	0.979	2.927

<sup>a</sup> Refers to the interatomic distance between the  $\alpha$  carbon and the carbon of the cyano function. <sup>b</sup> Values not optimized, but taken from 4. <sup>c</sup> Values not optimized, but taken from 6.

$10^{18}$ . Surprisingly, when this  $\text{H}/\alpha\text{-CN}$  rate ratio was measured for three different simple systems, a value of  $(2.7 \pm 0.8) \times 10^3$  was observed.<sup>7,8</sup> This discrepancy between expectations and observations prompted us to suggest that  $\alpha$ -cyano cations of general formula **A** are significantly stabilized by charge delocalization through resonance structures such as **B**, even



though this requires a portion of the charge to reside on a divalent nitrogen.<sup>7</sup> In view of the implications of these findings, we have utilized PRDDO<sup>9</sup> and full ab initio calculation in order to evaluate theoretically the implications of our experimental results. We now report the results of these calculations.

Table I lists the compounds for which PRDDO calculations have been completed. PRDDO is a method which incorporates all electrons in a minimum basis set of Slater-type orbitals. Exponents for atoms were taken from the work of Hehre, Stewart, and Pople.<sup>10</sup> Localized molecular orbitals for the valence space were calculated using Boys' criteria<sup>11</sup> as described previously.<sup>12</sup> Bond orders were calculated according to the procedure of Armstrong, Perkins, and Stewart.<sup>13</sup> All calculations were carried out assuming a planar configuration for the carbonium-ion center. Since we desired to study the changes which might occur in terms of bond lengths and bond orders, we calibrated our calculations by first examining acetonitrile (**1**). The C-H bond lengths were set at 1.10 Å and all angles were set at the tetrahedral value ( $109^\circ 28'$ ). After optimization, the  $\text{C}_\alpha\text{-C}_\text{N}$  and  $\text{C}\equiv\text{N}$  values derived were 1.456 and 1.155 Å, respectively. When compared with the experimental values<sup>14</sup> of 1.458 and 1.157 Å, our calculated values show excellent agreement. The bond order for the C-C bond was found to be 1.04 and that for the  $\text{C}\equiv\text{N}$  bond was 2.94. These can be compared with the idealized values of 1.00 and 3.00, respectively.

While some geometry optimization was carried out for most of the molecules studied, the geometry for  $^+\text{CH}_2\text{CN}$  (**2**) was fully optimized.<sup>15</sup> Only the  $\text{C}_\alpha\text{-C}_\text{N}$  and  $\text{C}\equiv\text{N}$  bonds were optimized<sup>16</sup> for **3** and **4**. For **6** the  $\text{C}_\alpha\text{-C}_\beta$  bond distance and the  $\text{C}_\beta\text{-C}_\alpha\text{-C}_\text{N}$  and  $\text{H-C}_\beta\text{-H}$  angles were also optimized.<sup>17</sup> For **5** and **7**, the C-C and  $\text{C}\equiv\text{N}$  bonds were taken from **4** and **6**, respectively.<sup>18</sup>

As can be seen from Table I, the  $\text{C}_\alpha\text{-C}_\text{N}$  bond length for **2** is considerably shorter than the  $\text{C}_\alpha\text{-C}_\text{N}$  bond length of