A Novel Synthesis of Methyl α,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[1,2] aminocyclitol antibiotics including the gentamycins,[3] sisomycin,[4] and their potent, recently discovered congeners XK-62-2[5] and G-52.[6] Two syntheses of **1** beginning with 1,2:5,6-di-*O*-isopropylidene-D-glucose have been reported,[7,8] 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.

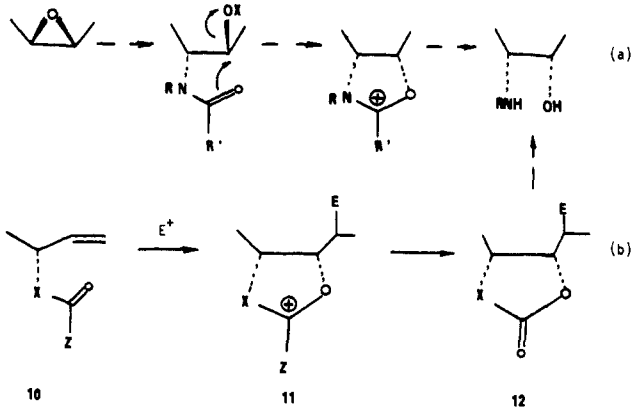
The synthesis of a *cis*-hydroxyamino moiety which occurs frequently among antibiotic amino sugars is traditionally troublesome, and a standard solution is depicted in eq a[9] (Scheme I). However, application of this protocol to a synthesis of garosamine would be compromised by the fact that **2**, the logical starting material, undergoes azidolysis indiscriminately at C-2 and C-3.[10] 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 consititute the rudiments of the troublesome tertiary alcohol of **1**.

Accordingly, azidolysis of the allyl epoxide **4** at room temperature gave **5**[11] 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 γ,δ-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** → **11b** → **12a**) suggested that the same technique could be applied to **10a** (≡**8**). Iodonium dicollidine perchlorate **7**[12] was adopted since in our experience[13] it is a superior source of iodonium ions.[14] Indeed its use[16] led to an 80% yield of the iodooxazolidine **9a** which, because of its tendency to lose iodine, was reduced with tri-*n*-butyltin hydride to **9b**.

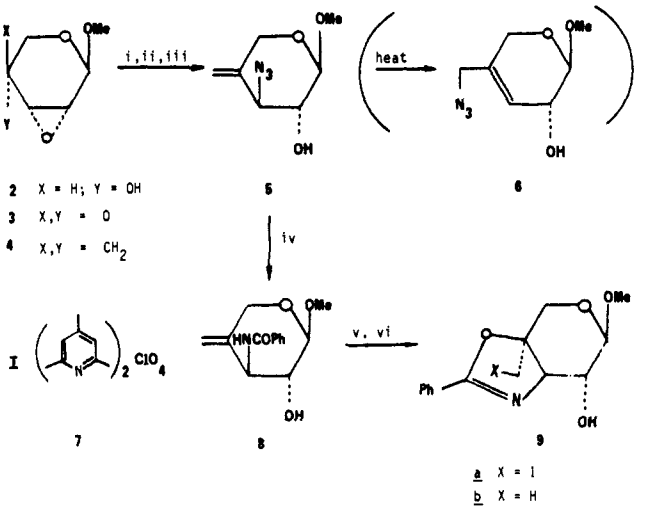
Compound **9b** is well on the way to **1**, but an intermediate bearing the *N*-methyl group would clearly have been preferred. In addition, *further contemplation of eq b suggested that a urethane,* **10c**, *should serve better than* **10a**, *since the intermediate* **11c** *should readily scavenge water giving* **12b**. Indeed the urethane **13** obtained in 65% overall yield from **4**, upon treatment[16] with the iodonium salt **7**, gave a product assigned as **14a**[17] (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**,[19] obtained from authentic[8] methyl α,L-garosaminide **1**, with sodium hydride in DMF. Both compounds had identical ^{1}H NMR spectra[20] and their melting points were undepressed by admixture. Hydrolysis of **15** with potassium hydroxide afforded compound **1** as a syrup having identical ^{1}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.

Scheme I

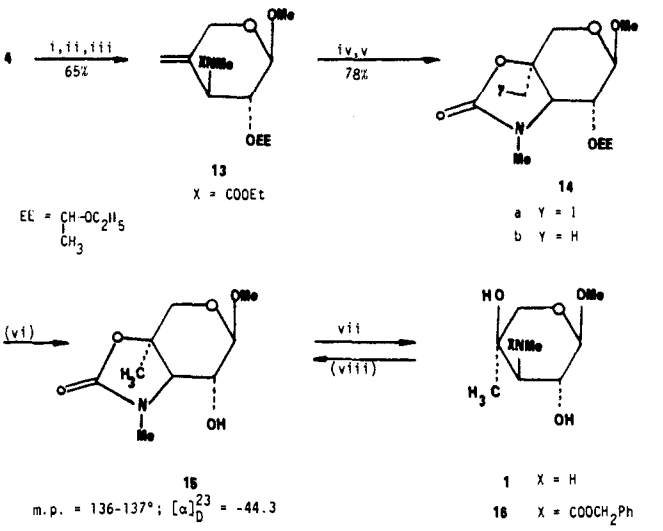


Scheme II[a]



[a] (i) PCC (85%); (ii) Ph_3PCH_3Br, *n*-BuLi, DME, N_2 (60%); (iii) NaN_3, H_2O–EtOH, 25 °C, 20 min (70%); (iv) $LiAlH_4$, PhCOCl (86%); (v) ref 16 (80%); (vi) *n*-Bu_3SnH, AIBN, C_6H_6, reflux (84%).

Scheme III[a]



[a] (i) $MeNH_2$, EtOH, 100 °C, 1 h; (ii) EtOCOCl, $CHCl_3$, $NaHCO_3$, 23 °C; (iii) $EtOCH{=}CH_2Cl_2$, PPTS,[18] 23 °C, 12 h; (iv) ref 16 (82%); (v) H_2, Pd/C, KOH (trace), EtOH; (vi) PPTS,[18] EtOH, reflux, 1 h; (vii) 15% KOH, 80 °C, 6 h (82%); (viii) NaH, DMF, 0 °C (quantitative).

Acknowledgments. We are grateful to the National Science and Engineering Research Council of Canada and Bristol Laboratories (Syracuse) for financial support for this work. Helpful advice was received from our colleague Professor Donald Mackay and Drs. Marcel Menard and Ivo Monkovic of Bristol Laboratories, Montreal. Dr. J. Wright of the

0002-7863/80/1502-3956$01.00/0

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 Rechendorf 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 cm^{-1}) and ^1H 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 Winstein had effected cyclization of 3-benzamidocyclohexene with NBS,[15] our systems failed to react under comparable conditions. Thus compounds **8** and **13** failed to cyclize with I_2–THF–H_2O, NBS–CH_2Cl_2, or NBS–Me_2SO–H_2O.
(15) S. Winstein, 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.[13b]
(17) The two protons at 5.12 ppm[11] 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 = pyridimium *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) ^1H NMR (60 MHz, $CDCl_3$, Me_4Si): 4.22 (d, H-1), 3.22–3.67 (n, H-2, H-5, H-5'), 2.28 (d, H-3), 1.17 (s, CH_3), 2.47 (s, NCH_3), 3.50 ppm (s, OCH_3).

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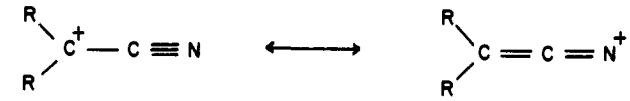
Received December 17, 1979

Mesomeric Stabilization of Carbonium Ions by α-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[1] and Taft[2] have demonstrated the importance of considering the inductive effect of substituent groups, and Brown[3] has emphasized the importance of these principles when carbonium ions are involved. It is known[4] that placing a cyano function β 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 α-trifluoromethyl group leads to a H/α-CF_3 rate ratio of 10^6 for the solvolysis of simple sulfonate esters.[5] Using standard extrapolations,[2,6] it might be predicted that the related H/α-CN rate ratio would be somewhere between 10^9 and 10^{18}. Surprisingly, when this H/α-CN rate ratio was measured for three different simple systems, a value of $(2.7 \pm 0.8) \times 10^3$ was observed.[7,8] This discrepancy between expectations and observations prompted us to suggest that α-cyano cations of general formula A are significantly stabilized by charge delocalization through resonance structures such as B, even



A B

though this requires a portion of the charge to reside on a divalent nitrogen.[7] In view of the implications of these findings, we have utilized PRDDO[9] 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. Calculated Bond Lengths and Bond Orders for Acetonitrile and for α-Cyano and β-Cyano Substituted Carbonium Ions

compd or ion	bond length, Å		bond order	
	C–C[a]	C–N	C–C	C–N
CH_3CN (1)	1.456	1.155	1.038	2.939
$^+CH_2CN$ (2)	1.366	1.197	1.418	2.522
$CH_3\overset{+}{C}HCN$ (3)	1.384	1.187	1.310	2.627
$(CH_3)_2\overset{+}{C}CN$ (4)	1.401	1.179	1.232	2.707
$(CH_3)_2C\overset{+}{C}CN$ (5)	1.401[b]	1.179[b]	1.224	2.705
CH_3				
$^+CH_2CH_2CN$ (6)	1.456	1.160	0.977	2.925
CH_3				
$(CH_3)_2\overset{+}{C}CCN$ (7)	1.456[c]	1.160[c]	0.979	2.927
CH_3				

[a] Refers to the interatomic distance between the α carbon and the carbon of the cyano function. [b] Values not optimized, but taken from **4**. [c] Values not optimized, but taken from **6**.

Table I lists the compounds for which PRDDO calculations[9] 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.[10] Localized molecular orbitals for the valence space were calculated using Boys' criteria[11] as described previously.[12] Bond orders were calculated according to the procedure of Armstrong, Perkins, and Stewart.[13] 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° 28′). After optimization, the C_α—C_N and C≡N values derived were 1.456 and 1.155 Å, respectively. When compared with the experimental values[14] 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 C≡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 $^+CH_2CN$ (**2**) was fully optimized.[15] Only the C_α—C_N and C≡N bonds were optimized[16] for **3** and **4**. For **6** the C_α—C_β bond distance and the C_β–C_α–C_N and H–C_β–H angles were also optimized.[17] For **5** and **7**, the C—C and C≡N bonds were taken from **4** and **6**, respectively.[18]

As can be seen from Table I, the C_α—C_N bond length for **2** is considerably shorter than the C_α—C_N bond length of

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