Ac_2O/pyr and allowed to stand at room temperature for 6–8 h. Concentration and purification by preparative TLC (silica gel, 10% MeOH/CH_2Cl_2) then afforded 59 mg (48%) of the hexaacetate derivative of **16** as a very pale yellow oil, R_f 0.70 (silica gel, 10% MeOH/CH_2Cl_2). The material thus obtained was identical in all respects with an authentic sample and was readily converted to (±)-saxitoxin (**3**) following the published procedure.[7,20]

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Stereoselection in Acyclic Systems. The Synthesis of Amino Sugars via Nitrone Cycloadditions‡

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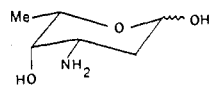
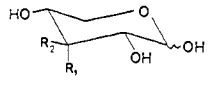
Abstract: Nitrones react with electron-rich dipolarophiles to yield isoxazolidines in which substituents have been placed in a regio- and stereoselective fashion on the periphery of the five-membered ring. Subsequent reductive cleavage of the N,O bond of these isoxazolidines results in release of a β-amino aldehyde (a Mannich system). The regioselectivity and stereoselectivity of the nitrone cycloaddition with various dipolarophiles is discussed, and the application of the method to the synthesis of the amino sugars daunosamine and 3-epigentosamine is reported.

The application of cycloaddition reactions as a means to control the stereochemistry in acyclic systems has been an area of intense activity.[1] Recently, we reported a total synthesis of the amino sugar daunosamine (**1**)[2] in which the stereochemistry of the sugar backbone was established by [3 + 2] dipolar cycloaddition of a nitrone and ethyl vinyl ether.[3] In this paper, we present full experimental details of the daunosamine synthesis and, in addition, will describe results which demonstrate that a variety of β-amino aldehyde systems can be prepared by the nitrone approach. This method is exceptionally suited for the synthesis of 3-amino-3-deoxypyranoses and has been applied to the stereoselective total synthesis of 3-epigentosamine-(*N*-methyl-3-xylosamine (**2**)).



DAUNOSAMINE **1**

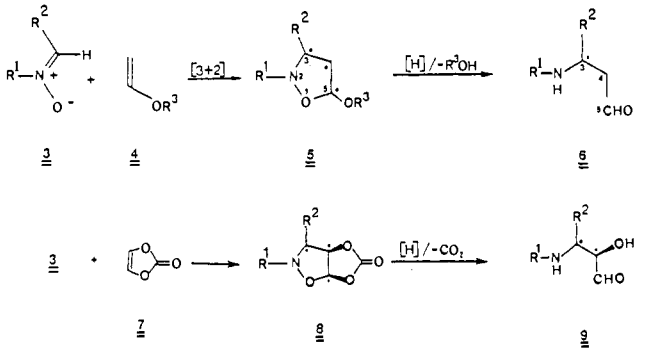


3-EPI-GENTOSAMINE, **2**: R_1 = MeNH, R_2 = H
GENTOSAMINE, : R_1 = H, R_2 = MeNH

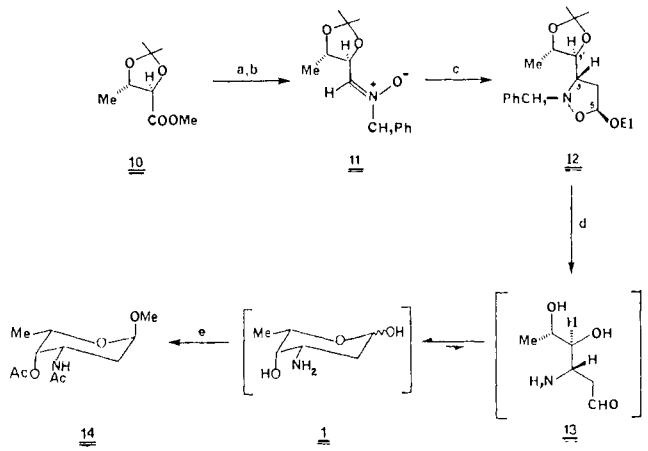
The amino sugars daunosamine (**1**) and 3-epigentosamine (**2**) are examples of the 3-amino-2,3,6-trideoxy- and 3-amino-3-deoxypyranoses, respectively, and are thus related to a wide variety of amino sugars which play critical roles in modern medicinal chemistry.[4] We decided to embark upon a project to develop a general synthetic approach to these classes of amino sugars *from non-carbohydrate precursors*. The strategy devised is shown in Scheme I and depended upon employing an isoxazolidine (**5** or **8**) as a masked form of the β-amino aldehyde moieties **6** and **9**, respectively. We had previously demonstrated[5,6] that nitrones (**3**) react with vinyl ethers and vinyl esters (**4**, R = alkyl or acyl, respectively) to produce *exclusively* isoxazolidine regioisomer **5**. Reductive cleavage of the N,O bond in isoxazolidine **5** and jettison of R^3OH liberated β-amino aldehyde **6**. Introduction of an α-hydroxyl onto **6** was to be accomplished by replacing the vinyl dipolarophile **4** with vinylene carbonate, **7**.

Traditionally, β-amino carbonyl systems are prepared by the Mannich reaction or one of its modern variants. However, the Mannich reaction fails when the systems such as **6** (or **9**) are the desired products since under Mannich conditions **6** is an effective

Scheme I



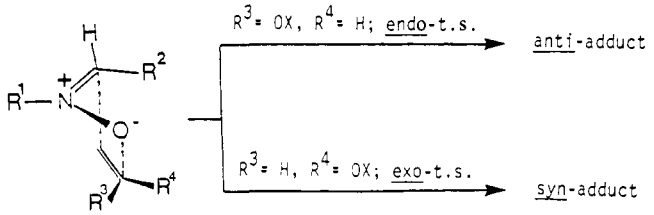
Scheme II



‡Presented in part at the 183rd National Meeting of the American Chemical Society in Las Vegas, NV, April, 1982. A preliminary communication of these results has appeared: DeShong, P.; Leginus, J. M. *J. Am. Chem. Soc. 1983, 105*, 1686.

0002-7863/84/1506-5598$01.50/0

Scheme III



intermediate for further reaction with excess starting reagents.[7] Therefore, an alternative strategy to the Mannich reaction had to be developed for the synthesis of the amino sugars **1** and **2**.

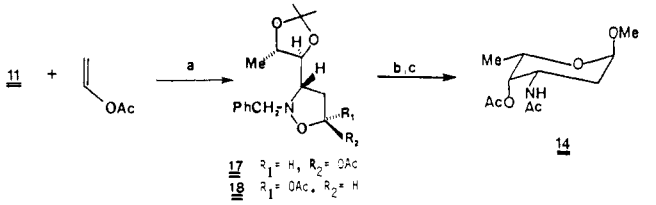
Results and Discussion

Daunosamine. Racemic ester **10**[8] was converted to nitrone **11** (84%) by DIBAL reduction followed by treatment with benzylhydroxylamine[9] (Scheme II). A single nitrone isomer was obtained which was assigned the *Z* configuration by nuclear Overhauser effect difference spectroscopy (NOEDS).[6] This configuration was expected since most of the nitrones prepared in this manner exist exclusively in the *Z* configuration.

Cycloaddition of nitrone **11** with excess ethyl vinyl ether gave a single isoxazolidine isomer **12**. Two new asymmetric centers were generated in the reaction and, therefore, four diastereomeric cycloadducts were possible. As shown in Scheme III, cycloaddition of the *Z* nitrone via and endo transition state results in the formation of the *anti*-isoxazolidine. Cycloaddition through the exo transition state would give the syn isomer. However, since R^2 is chiral in **11**, the faces of the nitrone are diastereotopic and thus formation of two anti products is possible. *Nitrone **11** has displayed high diastereofacial selectivity and high stereoselectivity for the endo transition state in the cycloaddition with ethyl vinyl ether.*

The relative stereochemistry of **12** at C-3/C-5 on the isoxazolidine ring was determined from its ^{1}H NMR spectrum. As

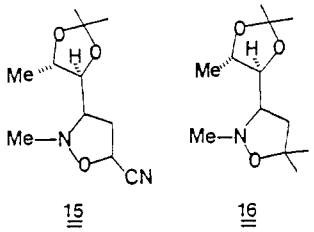
Scheme IV



(a) 72 °C, 36 h. (b) 10% HCl in MeOH, $Pd(OH)_2$, H_2, 50 psi, 48 h. (c) Ac_2O, pyridine, DMAP, 25 °C, 24 h.

we have shown in a series of similar isoxazolidines,[6] the spin multiplicity of the proton at C-5 is diagnostic for the relative stereochemistry between the substituents at C-3 and C-5. The relative stereochemistry of C-1′ and C-3 could not be determined by physical methods, but it was proven by conversion of **12** to daunosamine (vide infra).

Initial attempts to cleave the N,O bond of isoxazolidine **12** and free the Mannich system by reductive means were unsuccessful. Isoxazolidine **12** was remarkably stable and withstood prolonged treatment with reagents which successfully cleave related isoxazolidine systems.[10] For instance, sodium amalgam, aluminum amalgam, diimide, or a variety of catalytic hydrogenation conditions had no effect upon **12**, and the starting material was recovered unchanged. The stability displayed by **12** is especially noteworthy since treatment of isoxazolidines **15** and **16** with the reagents listed above resulted in rapid reduction and formation of the acyclic amino alcohols. The reluctance of the 5-heteroatom-substituted isoxazolidines, such as **12**, to undergo reductive cleavage of the N,O bond is a general phenomenon and has been observed in several systems (vide infra).



Hydrogenation of cycloadduct **12** over Pearlman's catalyst[11] in methanolic HCl/50 psi H_2/2 days resulted in reduction of the N,O bond and removal of the acetonide protecting group to produce the methyl glycoside of daunosamine via **13** and **1** in quantitative yield.[12] Acetylation of the methyl glycoside gave diacetate **14** which was identical by TLC, IR, and ^{1}H NMR with a sample prepared from authentic daunosamine. With use of this methodology, methyl daunosaminide was prepared in a stereospecific fashion in four steps from **10** in an overall yield of 78%.

Nitrone **11** displays diastereofacial selectivity in reactions with other dipolarophiles, such as vinyl acetate. Dipolar cycloaddition of **11** with vinyl acetate gave a 70% yield of two adducts, **17** and **18**, in a ratio of 1:4 (scheme IV). The relative configurations were proven by taking the individual cycloadducts to **14** by the methodology developed above. *Therefore, **17** and **18** must be epimeric only at C-5, and the cycloaddition between nitrone **11** and vinyl acetate must have occurred with complete diastereofacial selectivity, and with a preference for endo transition state geometry.*

3-Epigentosamine. Having established that the nitrone strategy could be exploited for the synthesis of 3-amino-2,3,6-trideoxy-

(1) Wovkulich, P. M.; Uskokovič, M. R. *J. Am. Chem. Soc.* **1981**, *103*, 3956 and references cited therein. Belzecki, C.; Panfil, C. *J. Org. Chem.* **1979**, *44*, 1212. Vasella, A.; Voeffray, R. *Helv. Chim. Acta* **1982**, *65*, 1134 and references cited therein. Koizumi, T.; Hirai, H.; Yashii, E. *J. Org. Chem.* **1982**, *47*, 4005. Kozikowski, A. P.; Chen, Y. Y. *Tetrahedron Lett.* **1982**, *23*, 2081. Kozikowski, A. P.; Ghosh, A. K. *J. Am. Chem. Soc.* **1982**, *104*, 5788. Jäger, V.; Schwab, W.; Buss, V. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 601 and references cited therein. Jäger, V.; Schobe, R.; Paulus, E. *Angew. Chem.*, in press, and references cited therein. Curran D. *J. Am. Chem. Soc.* **1982**, *104*, 4024 and references cited therein. Weinreb, S. M.; Garigipati, R. *Ibid.* **1983**, *105*, 4499 and references cited therein. McGarvey, G. J.; Hiner, R. N.; Matsubara, G.; Oh, T. *Tetrahedron Lett.* **1983**, *24*, 2733 and references cited therein. Masamune, S., et al. *J. Am. Chem. Soc.* **1982**, *104*, 5528. Heathcock, C. H., et al. *J. Org. Chem.* **1980**, *45*, 3846. Bartlett, P. A. *Tetrahedron* **1980**, *36*, 2. Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1–115. Schreiber, S. L.; Liew, W. F. *Tetrahedron Lett.* **1983**, *24*, 2363 and references cited therein. Martin, S. F.; Dupre, B. *Tetrahedron Lett.* **1983**, *24*, 1337 and references cited therein.

(2) For recent syntheses of daunosamine (3-amino-2,3,6-trideoxy-L-lyxo-hexose) and its derivatives, see: Wovkulich, P. M.; Uskokovič, M. R. *J. Am. Chem. Soc.* **1981**, *103*, 3956 and references cited therein. Hauser, F. M.; Rhee, R. P. *J. Org. Chem.* **1981**, *46*, 227. Dyong, I.; Wiemann, R. *Chem. Ber.* **1980**, *113*, 2666. Fronza, G.; Fuganti, C.; Grasselli, P. *J. Chem. Soc., Chem. Commun.* **1980**, 442. Iwataki, I.; Nakamura, Y.; Takahashi, K.; Natsumoto, T. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 2731. Overall yields range from <5% to a maximum of 42% with the number of reaction steps varying from 5 to >10.

(3) DeShong, P.; Leginus, J. M. *J. Am. Chem. Soc.* **1983**, *105*, 1686.

(4) Jäger, V.; Müller, I. *Tetrahedron Lett.* **1982**, *23*, 4777. Kunieda, T.; Abe, Y.; Iitaka, Y.; Hirobe, M. *J. Org. Chem.* **1982**, *47*, 4291. Sammes, P. G.; Bates, M. A. *J. Chem. Soc., Chem. Commun.* **1983**, 896.

(5) DeShong, P.; Dicken, C. M. *J. Org. Chem.* **1982**, *47*, 2047.

(6) DeShong, P.; Dicken, C. M.; Staib, R. R.; Freyer, A. J.; Weinreb, S. M. *J. Org. Chem.* **1982**, *47*, 4397.

(7) Blicke, F. F. "Organic Reactions"; John Wiley and Son: New York, 1942; Vol. 1, pp 303–369. Tramontini, M. *Synthesis* **1973**, 703.

(8) Hatch, R. P.; Shringarpure, J.; Weinreb, S. M. *J. Org. Chem.* **1978**, *43*, 4172. Although racemic **10** was utilized in the synthesis, optically active **10** (either enantiomer) can be prepared from tartaric acid by literature procedures: Fronza, G.; Fuganti, C.; Grasselli, P.; Marinoni, G. *Tetrahedron Lett.* **1979**, 3883.

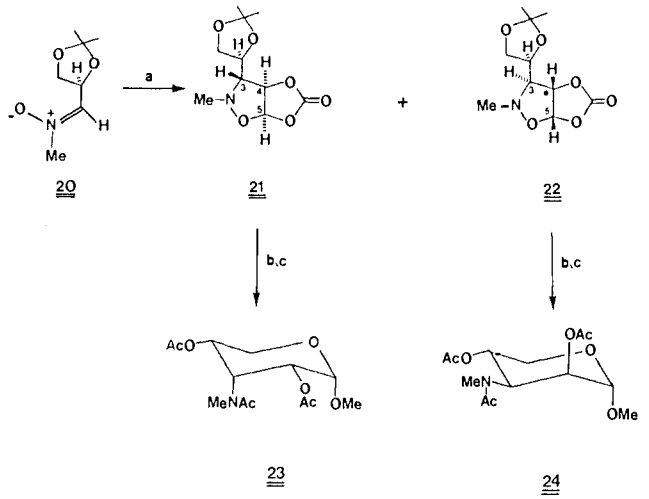
(9) Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2897.

(10) House, H. O.; Wichman, P. P.; Müller, H. C. *J. Am. Chem. Soc.* **1962**, *84*, 3139. Adams, R.; Marshall, J. R. *Ibid.* **1928**, *50*, 1970. Keck, G. E. *Synth. Commun.* **1979**, *9*, 281. Siegal, S.; Foreman, M.; Fisher, R. P.; Johnson, S. E. *J. Org. Chem.* **1975**, *40*, 3599.

(11) Pearlman, W. M. *Tetrahedron Lett.* **1967**, *17*, 1663.

(12) Authentic daunosamine was purchased from Pfanstiehl Laboratories, Inc., Waukegan, IL, and was converted to the β-glycoside by standard procedures. Authentic α-methyldaunosaminide was donated by Hoffmann-LaRoche, Nutley, NJ.

Scheme V



(a) benzene, vinylene carbonate, 45–50 °C, 48 h, 85%. (b) H_2, $Pd(OH)_2$, 10% HCl in MeOH, 50 psi, 90%. (c) Ac_2O, pyridine DMAP, room temperature, 12 h, quantitative.

pyranoses such as daunosamine, we attempted to extend the utility of the method by preparing gentosamine, a compound which incorporates an α-hydroxy function into the Mannich system. The additional oxygen atom was to be introduced by using vinylene carbonate (**7**) as the dipolarophile as illustrated in **7-9** in Scheme I. The vinylene carbonate cycloaddition posed an additional stereochemical problem because another asymmetric center would be introduced at C-4 of the isoxazolidine ring (see **8**). However, if the cycloaddition with vinylene carbonate proceeded with comparable diastereofacial and stereochemical selectivity to the vinyl ether system, then it would be feasible to employ the nitrone strategy for the preparation of the α-hydroxy Mannich system also.

Condensation of (*R*)-glyceraldehyde acetonide[13] and methylhydroxylamine produced nitrone **20**. As before, only the *Z* isomer was obtained as evidenced by ^1H NMR.[6] Dipolar cycloaddition of nitrone **20** and vinylene carbonate (**7**) resulted in the formation of a 1:1 mixture of adducts **21** and **22** in 85% yield. The relative configurations of C-3, C-4, and C-5 in the adducts were clearly indicated by the ^1H NMR spectra. The protons at C-4 and C-5 must be syn in **21** and **22** and their coupling constants are indicative of this stereochemical relationship, $J_{4,5}$ = 5 Hz.[14] There is no coupling between the C-3 and C-4 protons in either **21** or **22** ($J_{3,4}$ = 0 Hz) and *this can only occur when the dihedral angle between the protons is approximately 90°. From inspection of molecular models it is clear that a dihedral angle of 90° can only be achieved when the protons have an anti relationship.*

The relative stereochemistry between C-3 and C-1′ in the cycloadducts could not be determined by spectroscopic means; therefore, the structure of **21** was determined by a single-crystal X-ray diffraction study (see supplementary material for details).

Both cycloadducts, **21** and **22**, have arisen from reaction of *Z* nitrone (**20**) through an endo transition state (see Scheme III). However, unlike nitrone **11** which exhibits high diastereofacial selectivity in the cycloaddition reaction, *nitrone **20** displays no diastereofacial selectivity in reaction with vinylene carbonate.*

Hydrogenation of isoxazolidine **21** under the conditions developed in the daunosamine synthesis resulted in the formation of 3-epigentosamine (**2**) which was analyzed as **23**.[15]

(13) The *R* enantiomer is readily prepared according to modified procedures of Baer and Fischer. The racemic aldehyde is also available from glycerol by standard procedures.

(14) Jackman, L. M.; Sternhell, S. "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2nd ed.; Pergamon Press: Oxford, 1969.

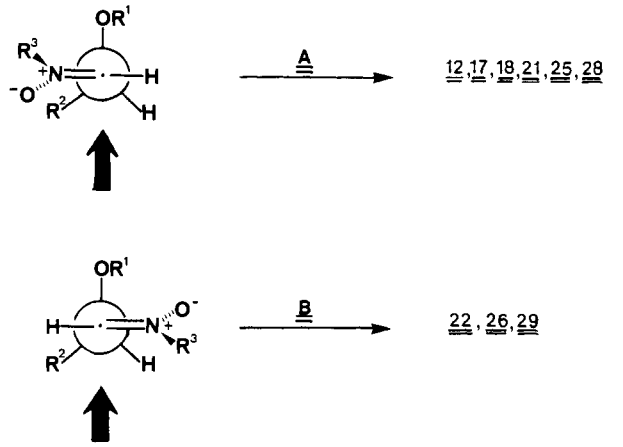
(15) Synthetic **23** was identical by ^1H NMR, IR, and MS with a sample of **23** prepared from authentic xylosamine by standard methods. We thank Dr. A. Mallams for furnishing a sample of xylosamine.

Table I. Diastereofacial Selectivity Observed in the Dipolar Cycloaddition Reaction

nitrone	dipolarophile	isoxazolidine(s)	diastereofacial selectivity[a]
11	**4**, R^3 = Et	**12**	100:0
11	**4**, R^3 = Ac	**17, 18**	100:0
11	**7**	**25, 26**	9:1[b]
20	**7**	**21, 22**	1:1
27	**7**	**28, 29**	2:1[b]

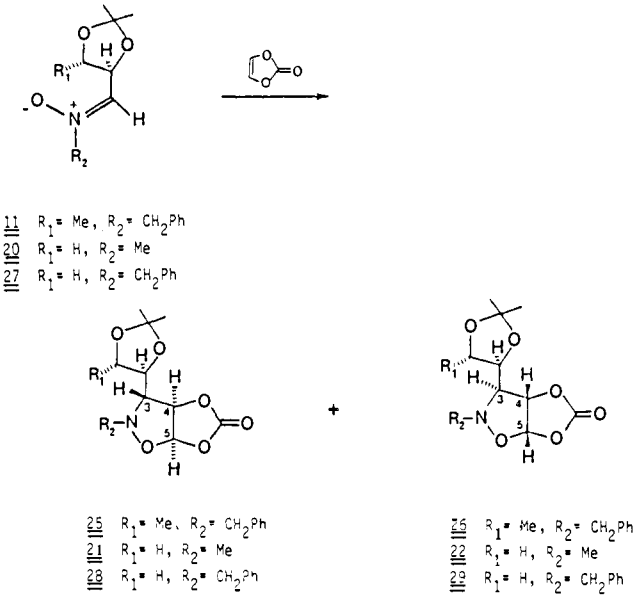
[a] Ratio measured by HPLC isolation of isomers. [b] Tentative structure assignments based upon analysis of the ^1H NMR spectrum.

Scheme VI



Similarly, hydrogenation of **22** followed by acetylation resulted in formation of the 2-epigentosamine derivative **24**.

Diastereofacial Selectivity. The diastereofacial selectivity observed in the cycloaddition of nitrones **11**, **20**, and **27** with a variety of dipolarophiles is summarized in Table I. Clearly, nitrone **11** displays greater diastereofacial selectivity than either nitrone **20** or **27**.



The observed diastereofacial selectivity in the cycloaddition of nitrone **11** with vinyl ethers or esters (see Schemes II and IV) can be explained by assuming that conformation A is the reactive conformation of the cycloaddition (see Scheme VI). Conformations A and B are the major conformations available to the nitrone in the Felkin–Anh[16,17] model for asymmetric induction.

(16) Chērest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2201.
(17) Anh, N. T.; Eisentein, O. *Nouv. J. Chim.* **1977**, *1*, 61.

Calculations of Anh[17] suggest that the polarized carbon–oxygen bond occupies a position orthogonal to the plane of the nitrone, thereby eliminating any conformation where R^2 is perpendicular to the C,N double bond. According to the Felkin–Anh rationale, *A* is expected to be the more reactive conformer because as the dipolarophile approaches the sp^2-hybridized carbon it avoids interactions with the bulky R^2 substituent. This is analogous to the situation addressed by Anh regarding attack at a carbonyl group. The argument is supported by the fact that as R^2 increases in steric bulk (**20** vs. **11**) the diastereofacial selectivity dramatically increases.

The stereochemical assignments of **25**, **26**, **21**, **22**, **28**, and **29** were delineated from the ^1H NMR spectra of the respective compounds. As discussed above, the C-3, C-4, C-5 anti,syn relationship of protons in all of these products was obvious from the coupling constants: $J_{3,4} = 0$ Hz, requiring an anti relationship between these protons. The coupling constant for the protons at C-3 and C-1′ of **21**, whose structure had been confirmed by X-ray (see supplementary material for details) analysis, was 8 Hz. Isomer **22** displayed $J_{3,1'} = 3$ Hz. Similar trends in coupling constants between the C-3 and C-1′ protons in the series **25**/**26** and **28**,**29** led us to assign stereochemistries as shown above.

Conclusion

We have demonstrated that nitrones carrying a chiral substituent on carbon (R^2 is chiral, Scheme I) react with electron-rich dipolarophiles to yield isoxazolidines with high diastereofacial selectivity. These isoxazolidines are valuable intermediates in the preparation of 3-amino-2,3-dideoxy and 3-amino-3-deoxy amino sugars. We are currently investigating further extensions of this methodology to the synthesis of natural products.

Experimental Section

Benzyl Nitrone (11). Methyl ester **10** was prepared following the procedure of Weinreb.[8] Diisobutyl aluminum hydride (101 mL, 1.0 M in hexane, 101 mmol) was added over 30 min to a solution of methyl ester **10** (5.0 g, 29 mmol) in diethyl ether (90 mL) at −78 °C. The mixture was stirred for 1 h and then quenched with H_2O (10 mL). The reaction mixture was allowed to warm to room temperature and stirred for an additional 45 min, whereupon it was filtered and the filter cake was washed thoroughly with ether. The ether filtrates were dried (Na_2SO_4) and concentrated leaving a cloudy residue which was distilled (58–62 °C, 23 mm) yielding 3.75 g (90%) of a clear liquid. The product was found to exist as a 59:41 mixture of the aldehyde and its hydrate as evidenced by the relative integration of the aldehydic proton (δ 9.73) in the 360-MHz NMR. IR (neat) 3600–3200 (b), 2965 (s), 1725 (m) cm^{-1}; NMR ($CDCl_3$) δ 1.4 (m, 9 H), 3.87 (dd, *J* = 2.4, 7.9 Hz, 1 H), 4.14 (dq, *J* = 6.1, 7.9 Hz, 1 H), 9.73 (d, *J* = 2.4 Hz, 1 H); mass spectrum, *m/z* (relative intensity, %) 145 ($M^+ + 1$, 2), 129 (17), 115 (44). The aldehyde was used directly for the formation of nitrone **11**. To a cooled (0 °C) mixture of benzylhydroxylamine[9] (4.5 g, 28.8 mmol) and $CaCl_2$ (2.0 g) was added the aldehyde (4.0 g, 27.7 mmol) in ether. The reaction mixture was stirred at 0 °C for 2 h, filtered, and concentrated in vacuo. Chromatography (85:15, EtOAc/MeOH) afforded 6.4 g (93%) of the *Z* nitrone.[6] IR (neat) 3050 (w), 2920 (s), 1590 (m) cm^{-1}; NMR ($CDCl_3$) δ 1.39 (d, 6 H), 1.48 (d, *J* = 6.1 Hz, 3 H), 4.04 (dq, *J* = 6.1, 7.3 Hz, 1 H), 4.84 (dd, *J* = 7.3, 6.0 Hz, 1 H), 4.89 (s, 2 H), 6.78 (d, *J* = 6.0 Hz, 1 H), 7.41 (s, 5 H); mass spectrum, *m/z* (relative intensity, %) 250 ($M^+ + 1$, 0.4), 205 (48), 91 (100). Anal. Calcd for $C_{14}H_{19}NO_3$: C, 67.45; H, 7.68; N, 5.62. Found: C, 67.05; H, 7.57; N, 5.28.

Isoxazolidine 12. Isoxazolidine 12 was prepared by refluxing nitrone **11** (378 mg, 1.52 mmol) in an excess of ethyl vinyl ether (10 mL) for a period of 72 h. The ethyl vinyl ether was then removed in vacuo and the product isolated by flash chromatography (10% ethyl acetate–hexane). A single diastereomer (**12**) (454 mg, 93%) was obtained where the protons at C-3 and C-5 maintain the anti configuration.[6] IR (CCl_4) 3040 (w), 2980 (m), 2880 (s), 1690 (w), 1425 (s) cm^{-1}; NMR ($CDCl_3$) δ 1.13 (t, *J* = 7.0 Hz, 3 H), 1.28 (s, 3 H), 1.30 (s, 3 H), 1.35 (d, *J* = 5.8 Hz, 3 H), 2.46 (m, 2 H), 3.40 (q, *J* = 7.0 Hz, 2 H), 3.68–3.82 (m, 3 H), 4.00 (s, 2 H), 5.23 (dd, *J* = 5.8, 1.5 Hz, 1 H), 7.27–7.38 (m, 5 H); mass spectrum, *m/z* (relative intensity, %) 321 (M^+, 0.6), 277 (5), 206 (69); mass spectrum, *m/z* 321.1934 (M^+, calcd for $C_{18}H_{27}NO_4$ 321.1940).

***N*,*O*-Diacetyl-α-daunosaminide (14).** Isoxazolidine **12** (100 mg, 0.31 mmol) was hydrogenated in 10% HCl in MeOH and 100 mg $Pd(OH)_2$ under 50 psi of H_2 for 48 h. Catalyst removal was affected by filtering the solution through Celite and the filtrates were concentrated. Acetylation was carried out directly on the crude product by treatment with 1 mL of acetic anhydride, 1 mL of pyridine, and 25 mg of dimethylaminopyridine. Stirring was continued for 24 h, the mixture was diluted with 10 mL of EtOAc, and the insoluble salts were filtered. Flash chromatography (EtOAc) provided crystals which were sublimed (140 °C, 0.1 mm) to yield 56 mg (74%) of white crystals (mp 156–159 °C). Authentic *N*,*O*-diacetyl-α-daunosaminide mp 163–165 °C (optically active): IR (CH_2Cl_2) 3440 (m), 2900 (m), 1740 (m), 1680 (s) cm^{-1}; NMR ($CDCl_3$) δ 1.11 (d, *J* = 6.4 Hz, 3 H), 1.81 (m, 2 H), 1.94 (s, 3 H), 2.19 (s, 3 H), 3.34 (s, 3 H), 4.05 (q, *J* = 6.4 Hz, 1 H), 4.56 (m, 1 H), 4.81 (d, *J* = 2.1 Hz, 1 H), 5.10 (d, *J* = 2.4 Hz, 1 H), 5.36 (d, *J* = 7.9 Hz, 1 H); mass spectrum, *m/z* (relative intensity, %) 245 (M^+, 0.3), 214 (8), 185 (10), 101 (47). Spectral data of authentic *N*,*O*-diacetyl-α-daunosaminide are identical with those obtained for **14**.

Cycloadducts 17 and 18. The cycloaddition was performed by refluxing nitrone **11** (3.0 g, 12 mmol) in 50 mL of vinyl acetate for 36 h in the dark. Excess vinyl acetate was removed in vacuo and the residue was purified by flash chromatography (2:1 hexane–ethyl acetate). A 4:1 mixture of diastereomeric isoxazolidines (3.2 g, 70%) was obtained differing only in their configuration at C-5.[6] Major isomer **18** (R_f 0.39): IR (CCl_4) 3040 (m), 2995 (s), 1750 (m), 1235 (s) cm^{-1}; NMR ($CDCl_3$) δ 1.28 (s, 6 H), 1.29 (d, *J* = 5.2 Hz, 3 H), 2.10 (s, 3 H), 2.62 (ddd, *J* = 13.7, 7.3, 2.4 Hz, 1 H), 2.76 (ddd, *J* = 13.7, 6.1, 1.2 Hz, 1 H), 3.36 (dt, *J* = 7.3, 5.2 Hz, 1 H), 3.42 (t, *J* = 7.3 Hz, 1 H), 3.55 (m, 1 H), 4.00 (d, *J* = 12.8 Hz, 1 H), 4.30 (d, *J* = 12.8 Hz, 1 H), 6.44 (dd, *J* = 6.1, 2.4 Hz, 1 H), 7.34 (d, 5 H); mass spectrum, *m/z* (relative intensity, %) 355 (M^+, 4), 320 (7), 220 (61); mass spectrum, *m/z* 335.1740 (M^+, calcd for $C_{18}H_{25}NO_5$ 335.1733). Minor isomer **17** (R_f 0.42): IR (CCl_4) 3040 (m), 2995 (s), 1750 (m), 1235 (s) cm^{-1}; NMR ($CDCl_3$) δ 1.30 (s, 6 H), 1.34 (m, 3 H), 2.07 (s, 3 H), 2.56 (m, 2 H), 3.17 (m, 1 H), 3.54 (dt, *J* = 5.8, 2.1 Hz, 1 H), 3.70 (dd, *J* = 7.9, 6.7 Hz, 1 H), 3.98 (d, *J* = 13.4 Hz, 1 H), 4.10 (d, *J* = 13.4 Hz, 1 H), 6.44 (dd, *J* = 5.4, 1.5 Hz, 1 H), 7.33 (d, 5 H); mass spectrum, *m/z* (relative intensity, %) 335 (M^+, 4), 320 (7), 220 (61); mass spectrum, *m/z* 335.1711 (M^+, calcd for $C_{18}H_{25}NO_5$ 335.1733).

***Isoxazolidines* 21 and 22.** Nitrone **20** (1.06 g, 6.67 mmol) was added to vinylene carbonate (1.50 g, 17.4 mmol) and heated to 45 °C for 48 h. Flash chromatography (2:1 hexane/EtOAc) gave **21** and **22** as a 1:1 mixture of trans isomers (1.36 g, 83%) which could be separated by column chromatography (2:1 hexane/EtOAc). High R_f isomer **21**: IR (CCl_4) 2980 (w), 1835 (vs), 1370 (m), 1280 (s), 1150 (s); NMR ($CDCl_3$) δ 1.34 (s, 3 H), 17.4 (s, 3 H), 2.97 (s, 3 H), 3.40 (d, 1 H, *J* = 8 Hz), 3.85 (dd, 1 H, *J* = 4, 9 Hz), 3.94 (ddd, 1 H, *J* = 4, 6, 8 Hz), 4.16 (dd, 1 H, *J* = 6, 9 Hz), 5.53 (d, 1 H, *J* = 5 Hz), 6.20 (d, 1 H, *J* = 5 Hz); ^{13}C NMR ($CDCl_3$, ORD) δ 24.81 (q), 26.94 (q), 68.20 (t), 72.37 (d), 72.44 (d), 78.46 (q), 87.01 (d), 103.95 (d), 110.42 (s), 152.60 (s); mass spectrum, *m/z* (relative intensity, %) 245 (M^+, 17), 230 (80), 140 (85), 101 (100), 43 (100); mass spectrum, *m/z* 245.0895 (M^+, calcd for $C_{10}H_{15}NO_6$ 245.0899); [α] +11.5° (*c* 6, MeOH); mp 115–118 °C. Anal. Calcd for $C_{10}H_{15}NO_6$: C, 48.98; H, 6.17; N, 5.71. Found: C, 48.60; H, 6.11; N, 5.39. Low R_f isomer **22**: IR (CCl_4) 2980 (w), 1835 (vs), 1370 (m), 1280 (s), 1150 (s); NMR ($CDCl_3$) δ 1.35 (s, 3 H), 1.44 (s, 3 H), 2.98 (s, 3 H) 3.55 (d, 1 H, *J* = 5 Hz), 3.73 (dd, 1 H, *J* = 6, 9 Hz), 4.07 (dd, 1 H, *J* = 7, 9 Hz), 4.29 (ddd, 1 H, *J* = 5, 6, 7 Hz), 5.32 (d, 1 H, *J* = 5 Hz), 6.11 (d, 1 H, *J* = 5 Hz); mass spectrum, *m/z* (relative intensity, %) 245 (M^+, 21), 230 (100), 144 (90), 101 (100), 43 (100); mass spectrum, *m/z* 245.0910 (M^+, calcd for $C_{10}H_{15}NO_6$ 245.0899); [α] −93.3° (*c* 1, MeOH); mp 135–138 °C.

***N*,*O*,*O*-Triacetyl-α-epigentosaminide (23).** Isoxazolidine **21** (0.10 g, 0.41 mmol) was hydrogenated in 10% HCl in MeOH and 0.10 g of $Pd(OH)_2$ under H_2 for 48 h. Catalyst removal was affected by filtering the solution through Celite; the filtrates were concentrated, and the crude product was acetylated by treatment with 1 mL of acetic anhydride, 1 mL of pyridine, and 25 mg of dimethylaminopyridine. Stirring was continued for 24 h at room temperature. The reaction mixture was dissolved in an aqueous $CuSO_4$ solution and extracted with EtOAc (4 × 50 mL). The EtOAc extracts were washed with brine and dried over Na_2SO_4. PLC (2.0-mm plate, EtOAc, four elutions) afforded amino sugar **23** (yellow oil, 0.11 g, 90%). IR (CCl_4) 2960 (m), 1740 (vs), 1660 (s), 1370 (s), 1220 (vs), 1080 (vs); NMR ($CDCl_3$) δ 2.10 (s, 3 H), 2.16 (s, 3 H), 2.20 (s, 3 H), 3.07 (s, 3 H), 3.51 (s, 3 H), 3.73 (dd, 1 H, *J* = 9, 12 Hz), 4.15 (dd, 1 H, *J* = 5, 12 Hz), 4.44 (d, 1 H, *J* = 2 Hz), 5.03

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(ddd, 1 H, J = 3, 5, 9 Hz), 5.11 (t, 1 H, J = 3 Hz), 5.42 (dd, 1 H, J = 2, 3Hz); mass spectrum, m/z (relative intensity, %) 303 (M^+, 1), 272 (6), 243 (11), 200 (43), 43 (100).

Benzyl Isoxazolidines 25 and 26. Nitrone **11** (0.11 g, 0.44 mmol) and excess vinylene carbonate (2.0 mL) were heated to 95 °C for 72 h. Flash chromatography (5:1 hexane/EtOAc) to remove excess vinylene carbonate, followed by PLC (2.0-mm plate, 3:1 hexane/EtOAc, two elutions), gave a 9:1 ratio of trans isomers **25** and **26** (0.12 g, 80%). High R_f isomer **25**: IR (CCl_4) 3030 (w), 2980 (m), 1830 (vs), 1140 (s), 1050 (s); NMR ($CDCl_3$) δ 1.25 (d, 3 H, J = 6 Hz), 1.27 (s, 3 H), 1.36 (s, 3 H), 3.39 (dd, 1 H, J = 7, 8 Hz), 3.47 (dq, 1 H, J = 6, 7 Hz), 3.54 (d, 1 H, J = 8 Hz), 4.02 (d, 1 H, J = 12 Hz), 4.42 (d, 1 H, J = 12 Hz), 5.55 (d, 1 H, J = 5 Hz), 6.24 (d, 1H, J = 5 Hz), 7.35 (m, 5 H); mass spectrum, m/z (relative intensity, %) 335 (M^+, 1), 320 (2), 115 (11), 90 (100), 59 (13). Low R_f isomer **26**: IR (CCl_4) 3020 (w), 2980 (m), 1830 (vs), 1370 (m), 1140 (vs), 1050 (vs); NMR ($CDCl_3$) δ 0.85 (d, 3 H, J = 6 Hz), 1.34 (s, 3 H), 1.37 (s, 3 H), 3.48 (dq, 1 H, J = 3, 8 Hz), 3.61 (d, 1 H, J = 3 Hz), 3.87 (dq, 1 H, J = 6, 8 Hz), 3.96 (d, 1 H, J = 12 Hz), 4.53 (d, 1 H, J =12 Hz), 5.48 (d, 1 H, J = 5 Hz), 6.22 (d, 1 H, J = 5 Hz); mass spectrum, m/z (relative intensity, %) 335 (M^+, 1), 320 (3), 220 (2), 115 (10), 91 (100), 59 (13).

***N*-Benzyl Nitrone 27.** To a cooled mixture (0 °C) of benzylhydroxylamine (4.5 g, 28 mmol) and $CaCl_2$ (2.0 g) was added aldehyde **19** (4.0 g, 28 mmol) in ether (100 mL). The reaction mixture was stirred at 0 °C for 2 h, filtered and concentrated in vacuo. Column chromatography (85:15 EtOAc/MeOH) afforded the Z nitrone **27** (6.4 g, 93%). IR (neat) 3050 (w), 2920 (s), 1590 (m); NMR ($CDCl_3$) δ 1.37 (s, 3 H), 1.41 (s, 3 H), 1.48 (d, 3 H, J = 6 Hz), 4.04 (dq, 1 H, J = 6, 7 Hz), 4.38 (dd, 1 H, J = 6, 7 Hz), 4.89 (s, 2 H), 6.78 (d, 1 H, J = 6 Hz), 7.41 (s, 5 H); mass spectrum, m/z (relative intensity, %) 250 (M^+, 1), 205 (48), 91 (100).

Benzyl Isoxazolidines 28 and 29. Nitrone **27** (0.10 g, 0.43 mmol) and excess vinylene carbonate (2.0 mL) were heated at 90 °C for 72 h. Flash chromatography (3:1 hexane/EtOAc) yielded isoxazolidines **28** and **29** (0.11 g, 81%) as a 2:1 mixture of trans isomers which could be separated by HPLC (cyano column, 9:1 hexane/EtOAc). High R_f isomer **29**: IR (CCl_4) 3030 (w) 2960 (m), 1835 (vs), 1250 (s), 1100 (vs); NMR ($CDCl_3$) δ 1.34 (s, 3 H), 1.47 (s, 3 H), 3.40 (d, 1 H, J = 5 Hz), 3.89 (m, 2 H), 4.20 (m, 3 H), 5.30 (d, 1 H, J = 5 Hz), 6.11 (d, 1 H, J = 5 Hz), 7.35 (m, 5 H); mass spectrum, m/z (relative intensity, %) 321 (M^+, 1), 220 (15), 101 (23), 91 (100). Low R_f isomer **28**. IR (CCl_4) 3030 (w), 2960 (m), 1835 (vs), 1250 (s), 1100 (vs); NMR ($CDCl_3$) δ 1.35 (s, 3 H), 1.44 (s, 3 H), 3.42 (d, 1 H, J = 9 Hz), 3.79 (dd, 1 H, J = 6, 9 Hz), 4.01 (d, 1 H, J = 14 Hz), 4.22 (d, 1 H, J = 14 Hz), 4.27 (m, 2 H), 5.54 (d, 1 H, J = 5 Hz), 6.18 (d, 1 H, J = 5 Hz), 7.40 (m, 5 H); mass spectrum, m/z (relative intensity, %) 321 (M^+, 1) 220 (10), 101 (25), 91 (100).

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Supplementary Material Available: Experimental details, table of bond angles and lengths, and an ORTEP drawing of **21** (5 pages). Ordering information is given on any current masthead page.

Stereochemical Effects in Cyclopropane Ring Openings: Biomimetic Ring Openings of All Isomers of 22,23-Methylenecholesterol Acetate

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Abstract: By using the unique stereochemistry of the side chain in cholesterol, the dynamic influence of proximate chiral centers on the acid-promoted isomerizations of cyclopropanes is defined. Unexpectedly, when the cyclopropane is placed in the 22,23 position, either a backbone rearrangement is induced or a priori unanticipated side-chain olefins arise, each dependent on the stereochemistry of the cyclopropane starting material. The synthesis and sterochemical assignments of the four possible 22,23-methylenecholesterol acetates [22*R*,23*R* (**22**), 22*S*,23*S* (**23**), 22*S*,23*R* (**24**), 22*R*,23*S* (**25**)] are reported as well as the effect of stereochemistry on the acid-promoted isomerization of these compounds. Isomers **22** and **23** under the conditions of ring opening yield unexpected backbone rearrangement products of the 3β-acetoxy-(17*S*)-17,23-dimethyl-18-normethylcholest-5,13(14)-diene type (**32-35**), which can also be obtained from rearrangement of the $\Delta^{5,20(22)}$- and $\Delta^{5,17(20)}$-23-methylcholestadien-3β-ol acetates (**42**, **44**, **53**, **54**). The stereochemical criteria governing the course of these isomerizations are discussed.

The recent isolation[1] of 22(*R*),23(*R*)-methylenecholesterol (**1**) offers indirect support for the hypothesis that naturally occurring 23-methyl[2-4] and 22-methylene[5] substituted cholesterols may arise by enzymic isomerization of the corresponding 22,23-cyclopropane analogues. The involvement of an enzyme in the conversion of cycloeucalenol (**2**) to obtusifoliol (**3**) has been described.[6] Several

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