

# Syntheses of 2,3,6-Trideoxy-3-amino- and 2,3,6-Trideoxy-3-nitrohexoses

FRANK M. HAUSER\* and SUZANNE R. ELLENBERGER

Oregon Graduate Center, Department of Chemical, Biological, and Environmental Sciences, Beaverton, Oregon 97006

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Frank M. Hauser is professor of chemistry at the Oregon Graduate Center. He received his B.S. degree in 1965 and his Ph.D. degree in 1969 from the University of North Carolina. His postdoctoral work with the late William Wildman at Iowa State University involved X-ray crystallographic structure elucidation on *Amaryllidacea* alkaloids with Jon Clardy. In 1970, he joined the Research Triangle Institute as a postdoctoral associate and subsequently became a staff chemist. In 1974, he moved to the Oregon Graduate Center. From 1976 to 1981 he was an NIH Career Development Awardee, and in 1984 was a visiting professor of chemistry at the University of Oregon. His research interests are the total syntheses of anthracycline antibiotics and amino sugars.



Suzanne Ellenberger received her B.S. degree in 1979 at San Jose State University and is currently completing her doctoral studies at the Oregon Graduate Center under the direction of Professor Frank Hauser. Her doctoral work has focused on the synthesis of aminohexoses.

## I. Introduction

Figure 1 shows the naturally occurring 2,3,6-trideoxy-3-amino- and -3-nitrohexoses as well as the configurational isomers prepared in conjunction with syn-

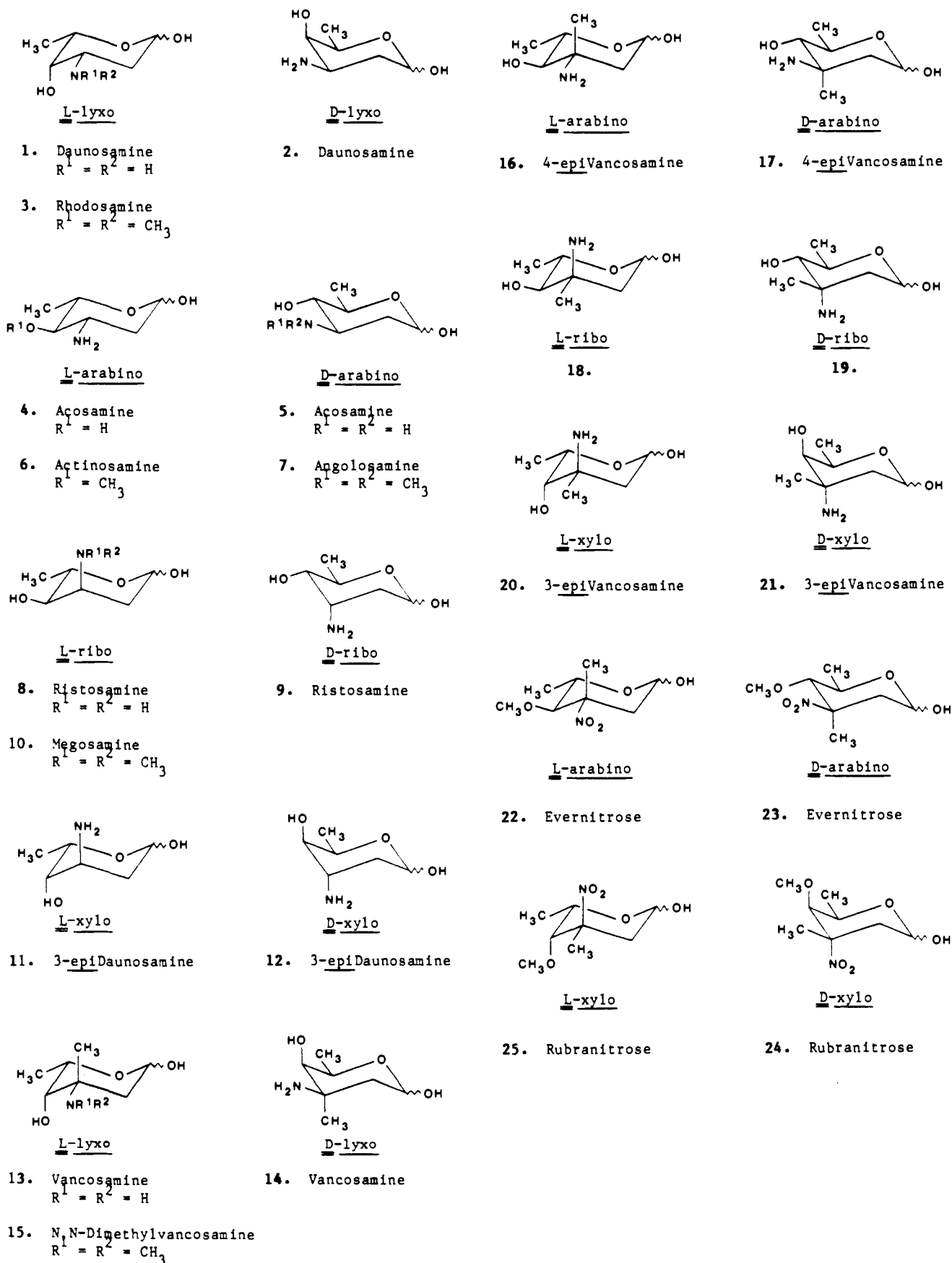


Figure 1. Naturally occurring and synthetic 2,3,6-trideoxy-3-amino- and -3-nitrohexoses.

thetic studies on this class of compounds. Those sugars that occur naturally are not found as distinct entities, but as structural components of glycosidic and polysaccharide antibiotics. All were originally isolated

through hydrolysis of parent antibiotics from which they take their trivial names. Most have the L absolute stereochemistry at C-5; however, angolosamine (7) and rubranitrose (24) occur only as the D isomer. Acosamine

(4 and 5) is unique in that it has been isolated in both L and D forms.

Although rhodosamine (3) was the first of these aminohexoses to be isolated,<sup>1,2</sup> it was not until the discovery of L-evernitrose (22)<sup>3,4</sup> that any synthetic work on these nitrogenous sugars was reported. The initial preparative interest in evernitrose (22) was largely of an intellectual nature, stemming from the fact that it was the first known naturally occurring nitro sugar. The isolation of the therapeutically useful anticancer antibiotics daunomycin<sup>5-8</sup> and adriamycin,<sup>8,9</sup> containing L-daunosamine (1) as the sugar fragment, provided practical impetus for the present strong synthetic interest in this class of sugars.

## II. Scope and Limitations

It is the intent of this article to objectively document the diverse synthetic strategies, and their present capacities, for preparation of 2,3,6-trideoxy-3-amino- and -3-nitrohexoses. The literature through December 1984 is covered. Many of the approaches have clearly undergone evolutionary development, and similar change can be expected for other routes that are currently in a preliminary form. In most instances, we have given overall yields. However, the reader is cautioned: Such numerical values are a reflection only of the efficiency of a particular preparation from a given starting material. Other factors, such as the number of steps, expense of reagents, and difficulty of procedures, are also important considerations. Since starting materials and/or their secondary syntheses are often major factors in assessing the utility of a particular route, we have thus commented upon or shown the best method to these materials. Finally, that ethereal quality of elegance—an individual matter subject to one's personal prejudices—is to many the most important property of a preparation, regardless of yield or practicality. The reader's indulgence is requested when we use this term.

The basic presentation is organized according to the individual hexose configuration. Secondary arrangement of each section is based on (a) chiral total syntheses from sugars, (b) chiral syntheses from other natural products and achiral precursors, and then (c) racemic preparations. An exception to this format was necessary in the section dealing with daunosamine (1) since the C-4 epimer, L-acosamine (4), has often been employed as an intermediate to 1.

A number of excellent articles on structure-activity relationships<sup>10-17</sup> and spectral interpretations<sup>18-21</sup> for these sugars have appeared; therefore, these topics will not be discussed.

Although this presentation is limited to syntheses of the title amino- and nitrohexoses, in a broader context, the described concepts and procedures are applicable to chemical syntheses in general.

## III. Nomenclature<sup>263</sup>

As might be expected, the majority of the syntheses have been achieved from other carbohydrates. Although the revised "Rules of Carbohydrate Nomenclature"<sup>22</sup> have been followed in describing many of these compounds, they have been interchanged with the general nomenclature of organic chemistry in order to facilitate readability. The convention used for denoting the conformations of pyranoid compounds (<sup>1</sup>C<sub>4</sub>,

<sup>4</sup>C<sub>1</sub>) is in accord with the rules established by Stodart.<sup>23</sup>

## IV. 2,3,6-Trideoxy-3-aminohexopyranoses

### A. Daunosamine (L- and D-lyxo)

L-Daunosamine (1) is the glycosidic component of a number of important anthracycline antibiotics that exhibit impressive activity against a broad range of solid tumors and soft tissue sarcomas.<sup>9,24,25</sup> It is by far the most well-known of the trideoxyaminohexoses and was first isolated by Arcamone et al.<sup>5,6</sup> from the antibiotic daunorubicin. The structure and absolute configuration were determined mainly from its spectral similarity to rhodosamine (3) and 2-deoxy-L-fucose, both of which have the L-lyxo configuration.<sup>1,2</sup> A key step in the structure elucidation was the oxidative degradation of the N-benzoyl derivative of 1 to L-aspartic acid.

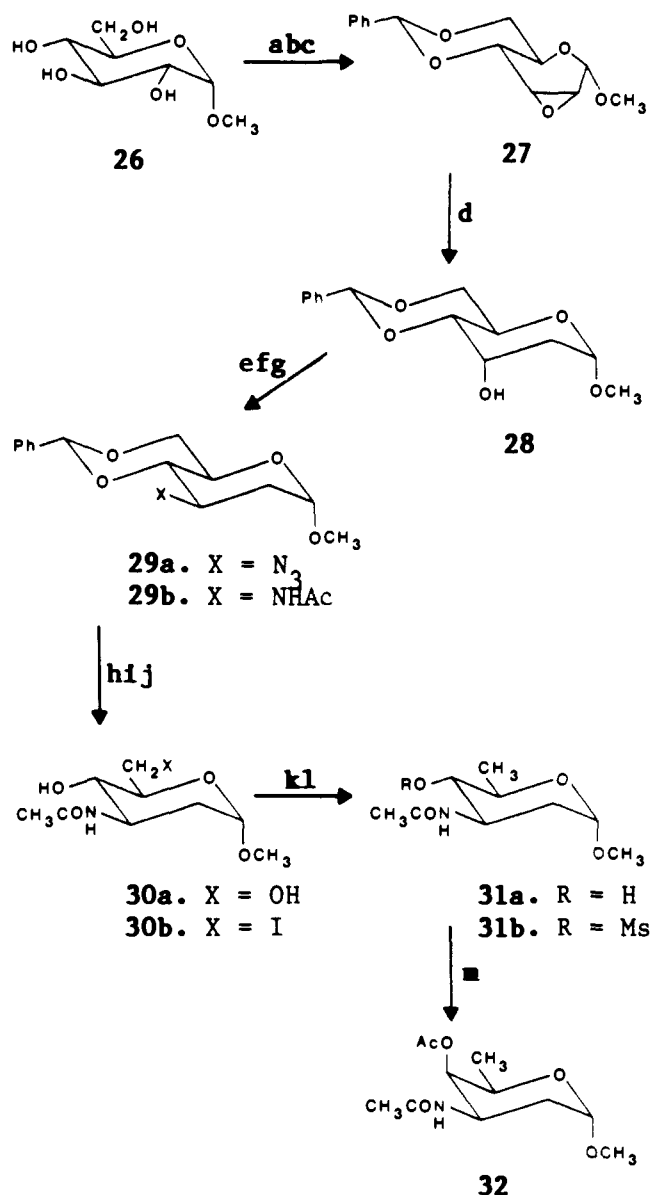
The importance of the anthracycline antibiotics as antineoplastic agents and the associated need for large quantities of daunosamine (1) for structure-activity studies have been major factors contributing to the strong synthetic interest in this sugar. Also, in view of the high cost of microbially produced antibiotics containing 1, a practical synthetic route is a desirable objective.

The synthesis of L-daunosamine (1) is hampered by the presence of a cis vicinal hydroxyamine component that is traditionally problematic and requires more steps for construction than the trans counterpart. Most of the syntheses of derivatives of 1 have been initiated from D and L carbohydrates or amino acids, but recently emphasis has been placed on developing approaches in which other types of starting materials are used. A feature common to all the approaches is that manipulation of the chiral centers in intermediates possessing the three contiguous optically active carbons is required in order to obtain the "all down" L-lyxo configuration.

#### 1. Chiral Syntheses from Carbohydrate Precursors

Although D-daunosamine (2) is the unnatural enantiomorph, it was prepared first in order to confirm the assigned structure and stereochemistry of L-daunosamine. The initial synthesis of the D isomer (2) was accomplished by Richardson<sup>26,27</sup> from methyl β-D-glucoside (26) as shown in Scheme I. Reaction of 26 with zinc chloride and benzaldehyde gave the 4,6-O-benzylidene derivative which on sequential treatment with toluenesulfonyl chloride and sodium methoxide<sup>51,135</sup> furnished the *allo*-mannoside 27<sup>28</sup> in 45% overall yield. Reduction of 27 with lithium aluminum hydride (LAH) proceeded through axial addition of hydride to the 2-position and selectivity provided the 2-deoxyhexose 28.<sup>28</sup> The 3-hydroxyl moiety in 28 was mesylated (MsCl, Py) and the mesylate group displaced with sodium azide in *N,N*-dimethylformamide (DMF)<sup>29</sup> to furnish the azidohexose 29a in 49% yield from 27. Catalytic hydrogenation (Raney nickel) of the azide functionality in 29a in the presence of acetic anhydride resulted in situ acetylation of the amine group, furnishing 29b. Hydrolysis of the benzylidene moiety with methanolic hydrogen chloride generated the *N*-acetyl glycoside 30a (71% yield).

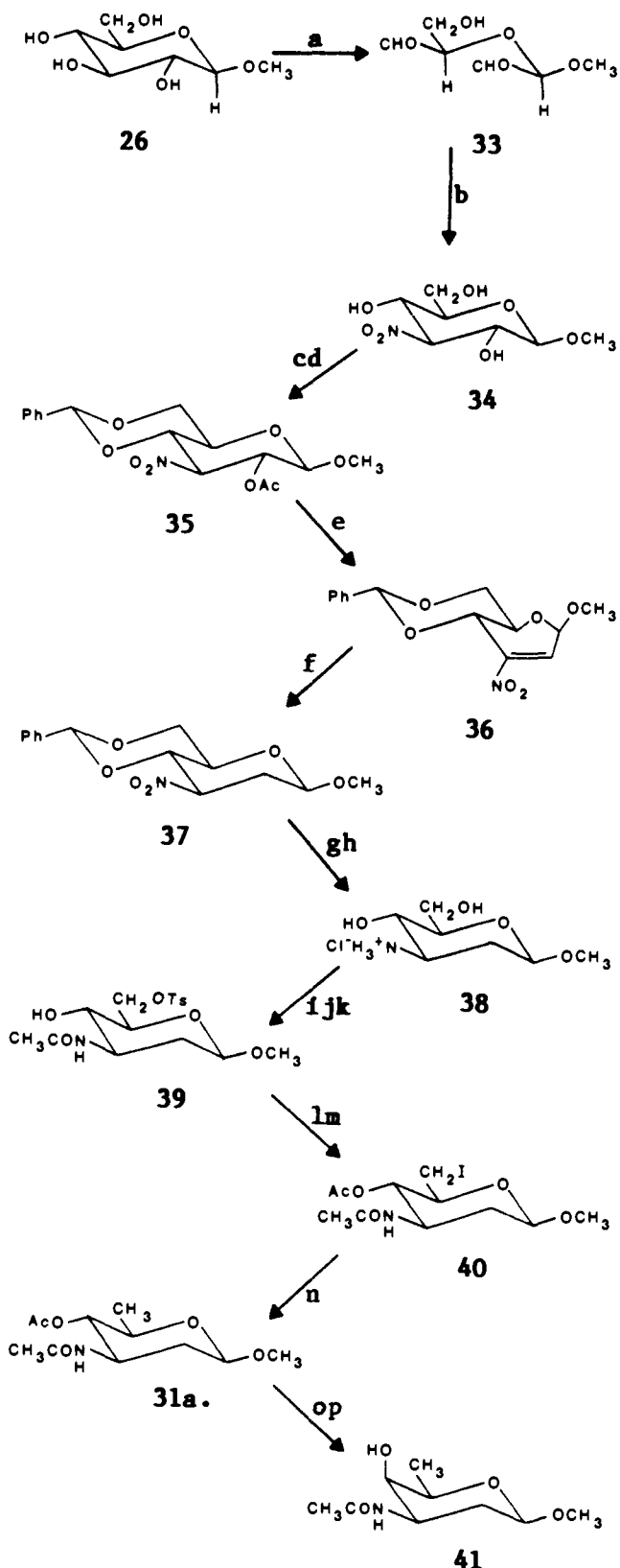
A standard reaction sequence was used to convert the 6-hydroxymethyl group in 30a to a methyl functionality.

SCHEME I<sup>a</sup>

<sup>a</sup> (a) ZnCl<sub>2</sub>, PhCHO; (b) TsCl, Py; (c) NaOMe; (d) LAH; (e) MsCl, Py; (f) NaN<sub>3</sub>, DMF; (g) Ni(R), H<sub>2</sub>, Ac<sub>2</sub>O; (h) MeOH, HCl; (i) TsCl, Py; (j) NaI; (k) Ni(R), H<sub>2</sub>; (l) MsCl, Py; (m) NaOAc.

Selective monotosylation of the 6-hydroxyl group, followed by replacement of the tosyl group with iodide, furnished the corresponding 6-iodo product **30b**. Reductive dehalogenation with Raney nickel and hydrogen produced the *N*-acetyl-D-acosaminide derivative **31a** in 80% yield. Solvolysis of the derived 4-methanesulfonate **31b** with hot aqueous sodium acetate<sup>30,31</sup> inverted the configuration of the C-4 hydroxyl group and gave methyl *N,O*-diacetyl-D-daunosaminide (**32**) in 42% overall yield from **31a**. Using a route similar to Richardson's,<sup>26,27</sup> Boivin et al.<sup>32</sup> subsequently prepared D-daunosamine (**2**), as well as D-acosamine (**5**) and L-risotamine (**8**).

Baer and co-workers<sup>33</sup> have extensively investigated the condensation of nitroalkanes with dialdehydes, derived from partial oxidative degradation of carbohydrates, as a general strategy for construction of both amino- and nitrohexoses. In conjunction with these studies, they achieved the synthesis of D-daunosamine (**2**) shown in Scheme II. Sodium metaperiodate oxidation of either methyl β-D-glucoside (**26**)<sup>34</sup> or methyl

SCHEME II<sup>a</sup>

<sup>a</sup> (a) NaIO<sub>4</sub>; (b) CH<sub>3</sub>NO<sub>2</sub>, NaOMe; (c) ZnCl<sub>2</sub>, PhCHO; (d) Ac<sub>2</sub>O, Py; (e) NaHCO<sub>3</sub>; (f) Pd/C, H<sub>2</sub>; (g) Dowex-H<sup>+</sup>, CH<sub>3</sub>OH; (h) PtO<sub>2</sub>, HCl, H<sub>2</sub>; (i) Dowex-OH<sup>-</sup>; (j) Ac<sub>2</sub>O, MeOH; (k) TsCl, Py; (l) Ac<sub>2</sub>O, Py; (m) NaI, NaHCO<sub>3</sub>; (n) Ni(R), H<sub>2</sub>, Et<sub>3</sub>N, CH<sub>3</sub>OH; (o) MsCl, Py; (p) NaOAc, H<sub>2</sub>O.

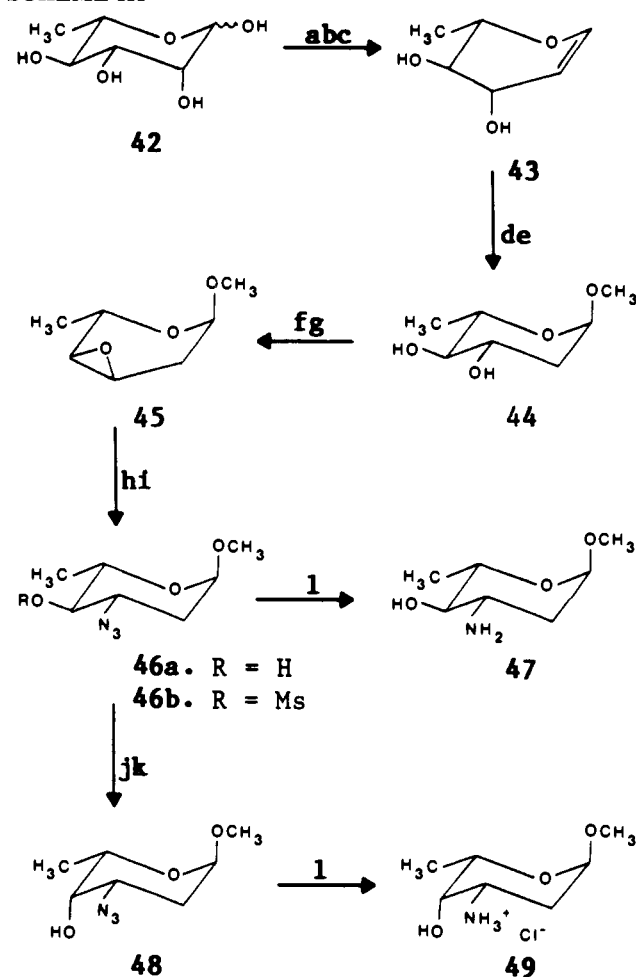
β-D-galactoside<sup>35,36</sup> produced the dialdehyde **33**, which on treatment with nitromethane in methanol<sup>37</sup> in the presence of added base gave the 3-deoxynitroglycoside **34** in 15% overall yield. Although the yield of **34** was

modest (25%), the product was isolated directly through crystallization. Reaction of **34** with benzaldehyde and zinc chloride furnished the 4,6-*O*-benzylidene derivative which was acetylated to the 2-acetoxy product **35**. Deoxygenation at C-2, through elimination of acetic acid, occurred when **35** was treated with sodium bicarbonate in refluxing benzene. The olefinic moiety in the resultant hexos-2-enide **36** was catalytically hydrogenated (Pd/C, H<sub>2</sub>), giving **37** with the *D*-arabino configuration.<sup>38</sup> Hydrolytic removal of the benzylidene protective group with cation exchange resin in methanol-water, followed by catalytic hydrogenation (PtO<sub>2</sub>, HCl) of the nitro group, produced **38** in 23% yield from **34**. The amine hydrochloride salt **38** was treated with anion-exchange resin and then sequentially *N*-acetylated (Ac<sub>2</sub>O, MeOH) and monotosylated (TsCl, Py) to furnish **39**. After acetylation (Ac<sub>2</sub>O, Py) of the 4-hydroxyl functionality in **39**, the 6-tosyl group was displaced with iodide (NaI, NaHCO<sub>3</sub>, butanone) to give **40**; sodium bicarbonate was added to the displacement reaction to prevent anomerization from trace amounts of liberated acid. Reductive replacement of the 6-iodo functionality through hydrogenation with Raney nickel in the presence of triethylamine generated methyl *N,O*-diacetylacosaminide (**31a**) (28% yield from **38**). The previously described procedure of Richardson<sup>26,27</sup> was used to invert the C-4 hydroxy group in **31a**, producing methyl *N*-acetyl-β-*D*-daunosaminide (**41**).

L-Rhamnose (**42**) has been the most widely used starting material for synthesis of 2,3,6-trideoxy-3-amino- and -3-nitrohexoses because it has the requisite L-configuration and is devoid of a 6-hydroxyl group. It should be noted, however, that this deoxy sugar is relatively expensive; this precludes its use as a practical intermediate.

In 1965, Marsh et al.<sup>39</sup> reported the first total synthesis of L-daunosamine (**1**) from L-rhamnose (**42**), and this sequence is shown in Scheme III. Conversion of L-rhamnose (**42**) to L-rhamnol (**43**)<sup>40</sup> and methoxymercuration of **43** with in situ borohydride reduction of the organomercury intermediate furnished the 2,6-dideoxy sugar **44**. Sulfonation of **44** gave the 3-*O*-monotoluenesulfonate as the major product, which on treatment with base formed epoxide **45**. When the impure epoxide was reacted with sodium azide, the 3-azido sugar **46a** with the *L*-arabino configuration was predominately formed as a consequence of trans-diaxial opening of the epoxide in the <sup>4</sup>C<sub>1</sub> conformation from the least hindered direction. Catalytic hydrogenation of the crude azide **46a** generated the then unknown methyl L-acosaminide derivative **47**. (Although this preparation represents a formal total synthesis of L-acosamine (**4**), the sugar was not isolated from natural sources until 1973.<sup>42,43</sup>) The configuration of the C-4 hydroxyl in **46a** was inverted through reaction of the mesylated 3-azido sugar **46b** with sodium benzoate;<sup>44</sup> subsequent hydrolysis produced the azido alcohol **48** with the *L*-lyxo configuration. Catalytic hydrogenation of **48** under acidic conditions gave the crystalline hydrochloride salt of methyl daunosaminide (**49**). Although no yields were reported by these authors, other investigators<sup>45,46</sup> have used this sequence to convert the epoxide **45** to daunosamine (**1**) in 26% yield.

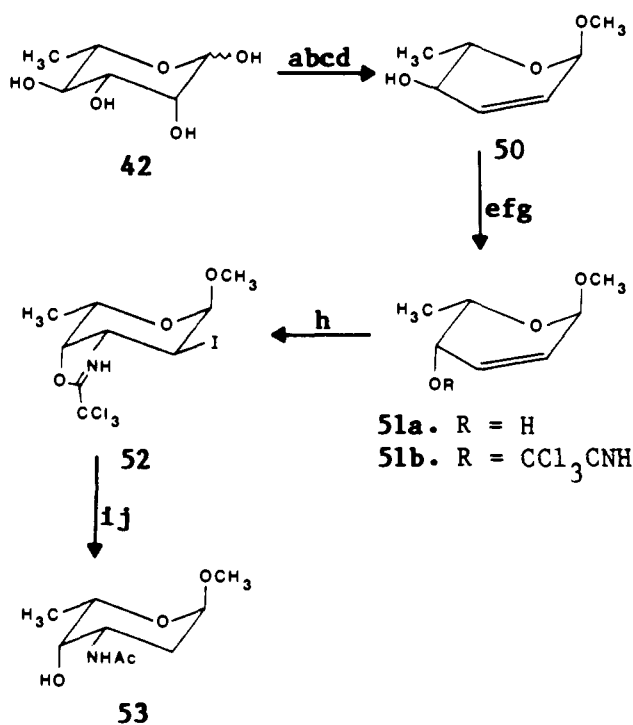
An elegant, efficient synthesis of **1** from L-rhamnose (**42**) was reported by Pauls and Fraser-Reid<sup>47</sup> in 1983.

SCHEME III<sup>a</sup>

<sup>a</sup> (a) Ac<sub>2</sub>O, Py; (b) HBr, HOAc, Ac<sub>2</sub>O; (c) Zn-Cu, HOAc; (d) Hg(OAc)<sub>2</sub>, CH<sub>3</sub>OH; (e) KBH<sub>4</sub>; (f) TsCl, Py; (g) NaOCH<sub>3</sub>; (h) NaN<sub>3</sub>; (i) MsCl, Py; (j) NaOBz, DMF; (k) NaOCH<sub>3</sub>, H<sub>2</sub>O; (l) catalytic hydrogenation.

In this sequence, shown in Scheme IV, rhamnose (**42**) was initially converted to rhamnol (**43**),<sup>40,48</sup> which was solvolyzed in acidic methanol to the hex-2-enopyranoside **50**<sup>49-51</sup> (53% yield from **42**). Epimerization of the 4-hydroxyl group in **50** through Mitsunobu reaction<sup>52</sup> (DEAD, PPh<sub>3</sub>, PhCO<sub>2</sub>H) followed by basic hydrolysis of the benzoate group provided **51a**. The C-4 alcohol moiety in **51a** was used to effect stereospecific introduction of the vicinal nitrogen via neighboring group participation. The trichloromethyl imidate ester **51b** was prepared from **51a** by a modified Overman method<sup>53</sup> (Cl<sub>3</sub>CCN, NaH) and underwent iodonium ion induced cyclization to **52**. Dehalogenation (Bu<sub>3</sub>SnH) and hydrolysis of the dihydroxazole moiety in **52** furnished the optically active methyl *N*-acetyl-daunosaminide (**53**) in 59% yield from **50**. The overall yield was 31%. Using a procedure nearly identical with that of Pauls and Fraser-Reid, Cardillo and co-workers<sup>54</sup> also prepared **49**.

Brimacombe and co-workers<sup>55</sup> reported the preparation of daunosamine (**1**) from L-rhamnose (**42**) shown in Scheme V; as in numerous other sequences, an acosaminide derivative served as an intermediate. Sequential protection of the 2,3-hydroxyl functionality in the methyl glycoside **54** of L-rhamnose (**42**) as the benzylidene derivative ( $\alpha,\alpha$ -dimethoxytoluene, TsOH, DMF; 72%)<sup>56-59</sup> and of the 4-hydroxyl group as the meth-

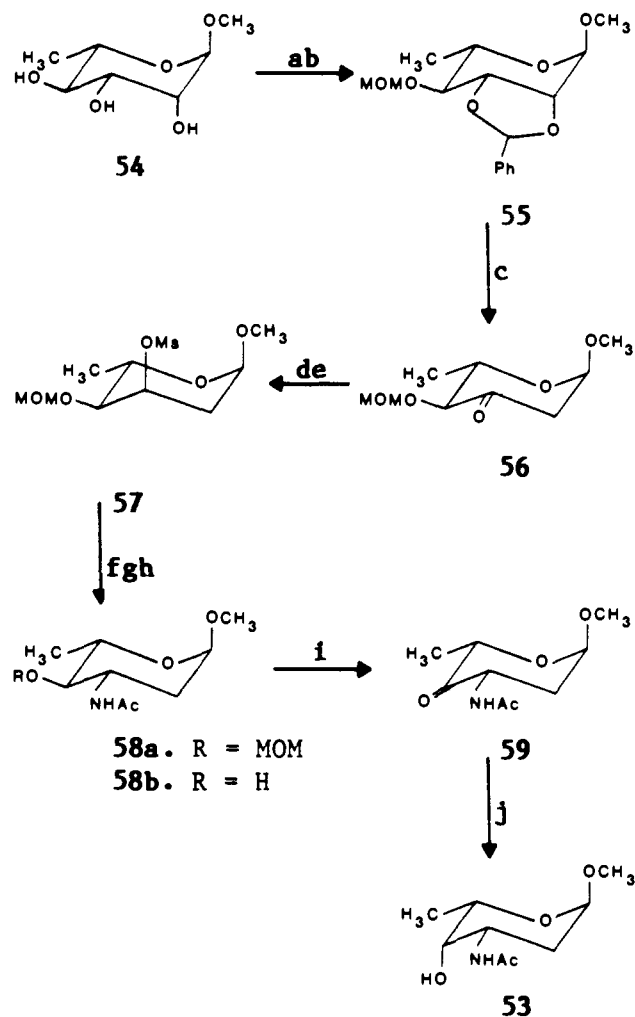
SCHEME IV<sup>a</sup>

<sup>a</sup> (a) Ac<sub>2</sub>O, Py; (b) HBr, HOAc, Ac<sub>2</sub>O; (c) Zn-Cu, HOAc; (d) BF<sub>3</sub>, CH<sub>3</sub>OH; (e) Ph<sub>3</sub>P, EtO<sub>2</sub>CN=NCO<sub>2</sub>Et, PhCO<sub>2</sub>H; (f) NaOCH<sub>3</sub>; (g) NaH, Cl<sub>3</sub>CCN; (h) I(2,4,6-trimethylpyridine)<sub>2</sub>ClO<sub>4</sub>; (i) (*n*-Bu)<sub>3</sub>SnH, AIBN; (j) TsOH, Py, H<sub>2</sub>O.

oxymethyl (MOM) derivative provided 55. Modified Klemmer-Rhodemeyer fragmentation<sup>60-62</sup> of the 2,3-*O*-benzylidene moiety in 55 with butyllithium furnished the hexos-3-ulose 56 (29% yield). The ketone group in 56 was reduced with sodium borohydride and the alcohol product was mesylated (MsCl, Py) to give 57 in 86% overall yield. Following displacement of the mesylate group in 57 with sodium azide in *N,N*-dimethylformamide (DMF), catalytic hydrogenation of the azide moiety in the presence of acetic anhydride generated the methyl *N*-acetylacosaminide derivative 58a in 66% yield. Hydrolysis of the MOM protective group (MeOH, HCl) furnished the alcohol 58b. The method of Richardson<sup>27</sup> was used to transform 58b to daunosamine (1) in 50% overall yield.

An alternative and slightly better overall yield procedure for configurational inversion of the C-4 hydroxyl group was developed by these investigators.<sup>55</sup> Oxidation of the 4-hydroxyl moiety in 58b with either pyridinium chlorochromate (PCC)<sup>63</sup> or trifluoroacetic anhydride-dimethyl sulfoxide<sup>64</sup> gave the ketohexose 59 in 63% yield. L-Selectride (Aldrich) reduction<sup>65,66</sup> of 59 stereoselectivity produced methyl *N*-acetyl-daunosaminide (53) in 90% yield.

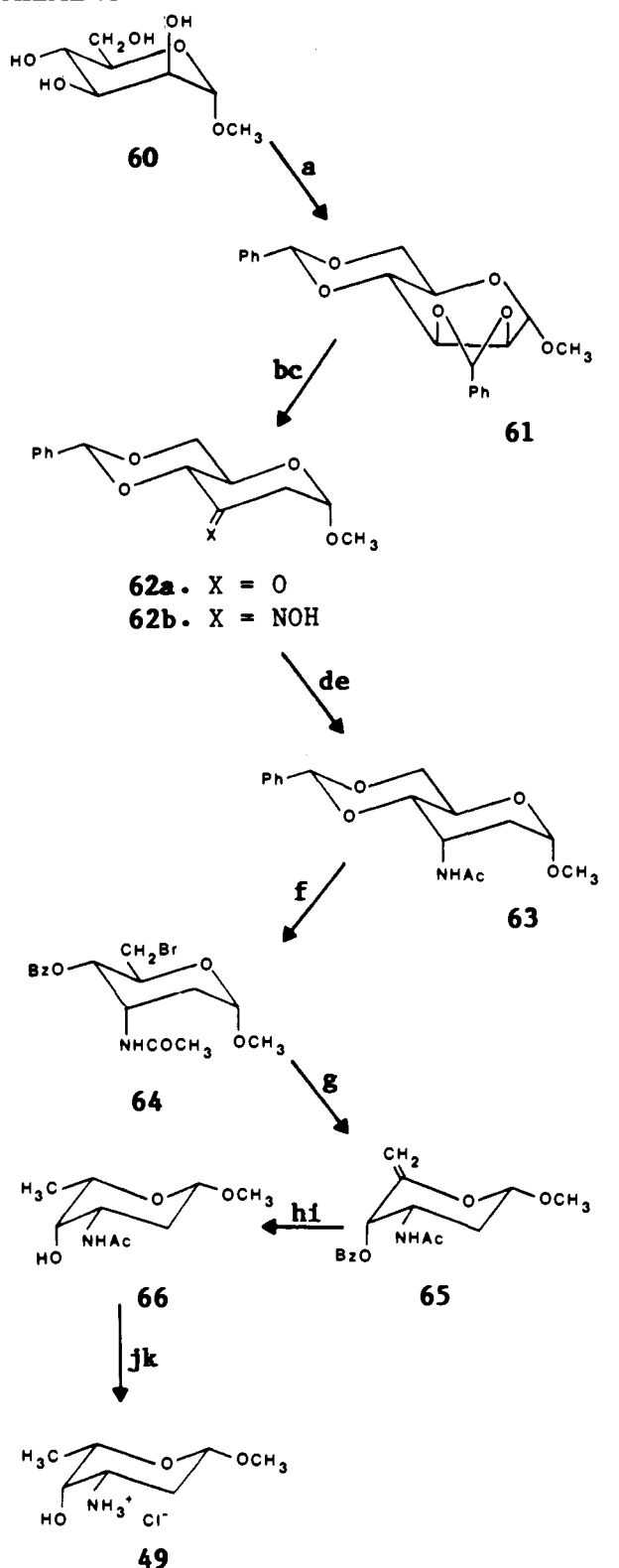
D-Hexoses comprise a larger and much cheaper pool of chiral starting materials; however, an inherent limitation to their use is that inversion of C-5 is required in order to obtain the L stereochemistry. An elegant solution to this problem was first reported by Horton and Weckerle<sup>58</sup> in their total synthesis of daunosamine (1) from methyl  $\alpha$ -D-mannoside (60). This 11-step preparation, shown in Scheme VI, is one of the highest yield routes yet reported and can be conducted on a large scale. Key elements of the synthesis are the stereoselective reduction of the oxime fragment in 62b to a C-3 amino group and the stereospecific generation of

SCHEME V<sup>a</sup>

<sup>a</sup> (a) PhCH(OCH<sub>3</sub>)<sub>2</sub>, TsOH, DMF; (b) CH<sub>3</sub>OCH<sub>2</sub>Cl, *N*(*i*-Pr)<sub>2</sub>Et; (c) THF, BuLi; (d) NaBH<sub>4</sub>; (e) MsCl, Py; (f) NaN<sub>3</sub>, DMF; (g) PtO<sub>2</sub>, H<sub>2</sub>, Ac<sub>2</sub>O; (h) CH<sub>3</sub>OH, HCl; (i) PCC, CH<sub>2</sub>Cl<sub>2</sub>; (j) L-Selectride, THF.

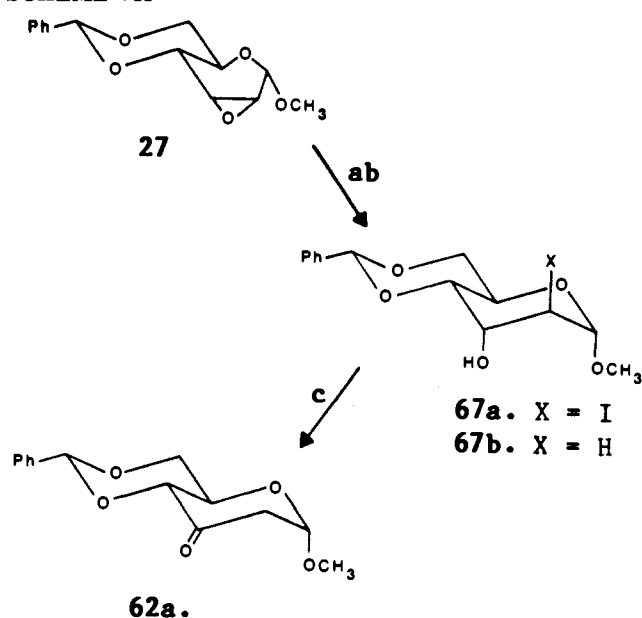
the *L-lyxo* stereochemistry through hydrogenation of the 5,6-olefinic entity in 65. Another feature that significantly contributes to the practicality of this approach is the absence of chromatographic separations.

The 2,3,4,6-di-*O*-benzylidene acetal 61 was prepared through reaction of 60 with  $\alpha,\alpha$ -dimethoxytoluene.<sup>59</sup> Klemmer-Rhodemeyer fragmentation<sup>60</sup> of the 2,3-*O*-benzylidene fragment with butyllithium (2 equiv) selectivity furnished the hexopyranosid-3-ulose 62a, which was subsequently converted to the oxime 62b.<sup>67</sup> Reduction of the oxime moiety with lithium aluminum hydride (LAH) followed by acetylation gave a diastereoisomeric mixture of the *D-ribo* (63; 87%) and *D-arabino* (12%) *N*-acetylhexopyranoses; the difference in solubility of the isomers in ether facilitated separation of the *D-ribo* isomer 63. After fragmentation of the 4,6-*O*-benzylidene residue in 63 with *N*-bromosuccinimide (NBS) and barium carbonate,<sup>68</sup> the resultant 4-*O*-benzoyl-6-bromo derivative 64 was dehydrobrominated with silver fluoride and pyridine in benzene<sup>69</sup> to furnish 65. Hydrolytic cleavage of the benzoyl group and then hydrogenation of the 5,6-olefinic residue in 65 stereospecifically generated the L stereochemistry at C-5 in 66. Deacetylation of 66 gave daunosamine hydrochloride (49), and the overall yield for this preparation was 40%.

SCHEME VI<sup>a</sup>

<sup>a</sup> (a)  $\text{PhCH}(\text{OCH}_3)_2$ , TsOH, DMF; (b) BuLi, THF; (c)  $\text{H}_2\text{NOH}\cdot\text{HCl}$ , NaOH, EtOH; (d) LAH,  $\text{Et}_2\text{O}$ ; (e)  $\text{Ac}_2\text{O}$ , Py; (f) NBS,  $\text{CCl}_4$ ,  $\text{BaCO}_3$ ; (g) AgF, Py; (h)  $\text{NaOCH}_3$ ; (i) Pd/ $\text{BaCO}_3$ ,  $\text{CH}_3\text{OH}$ ,  $\text{H}_2$ ; (j)  $\text{Ba}(\text{OH})_2$ ,  $\text{H}_2\text{O}$ ; (k) HCl.

Gurjar et al.<sup>70</sup> have described a synthesis of the ketone intermediate **62a** used by Horton and Weckerle<sup>58</sup> and this is shown in Scheme VII. This procedure is practical and has potential for use on a large scale. The *allo*-mannoside (**27**), prepared from methyl  $\alpha$ -D-glucoside,<sup>71</sup> was reacted with magnesium iodide etherate to effect trans-diaxial opening of the epoxide group,

SCHEME VII<sup>a</sup>

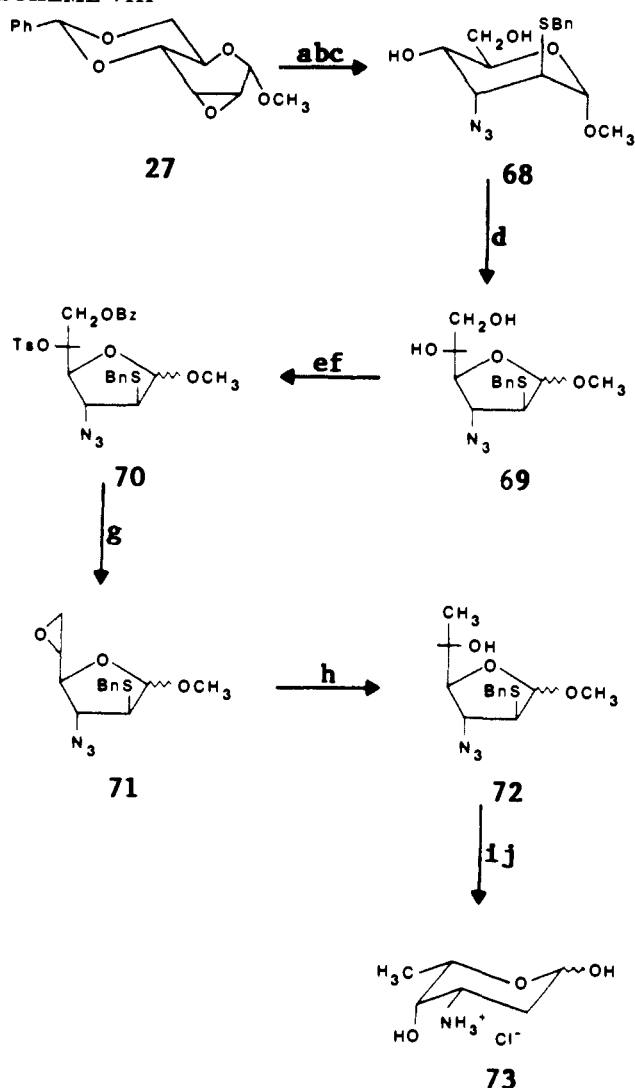
<sup>a</sup> (a)  $\text{MgI}_2$ ,  $\text{Et}_2\text{O}$ ; (b)  $(n\text{-Bu})_3\text{SnCl}$ , NaBH<sub>4</sub>; (c) PDC,  $\text{CH}_2\text{Cl}_2$ .

regiospecifically furnishing the 2-iodo pyranoside **67a** in 97% yield. Reductive dehalogenation of **67a** with tri-*n*-butyltin chloride and sodium borohydride<sup>72</sup> quantitatively generated the 2-deoxy product **67b**, which was oxidized to the ketone **62a** with pyridinium dichromate (70%). Although the number of steps is greater than that in the Horton sequence, the overall yield is comparable. A definite advantage of this route is that the hazardous use of large quantities of butyllithium is avoided.

The only total synthesis of L-daunosamine (**1**) in which the L stereochemistry was generated by direct nucleophilic inversion at C-5 of a D sugar was reported by Yamaguchi and Kojima.<sup>73</sup> The synthetic route, shown in Scheme VIII, evolved from their earlier finding<sup>74,75</sup> that hexopyranosides with a 2-thio substituent isomerize to anomeric mixtures of furanosides, which provides manipulative access to the C-5 and C-6 hydroxyl functionalities.

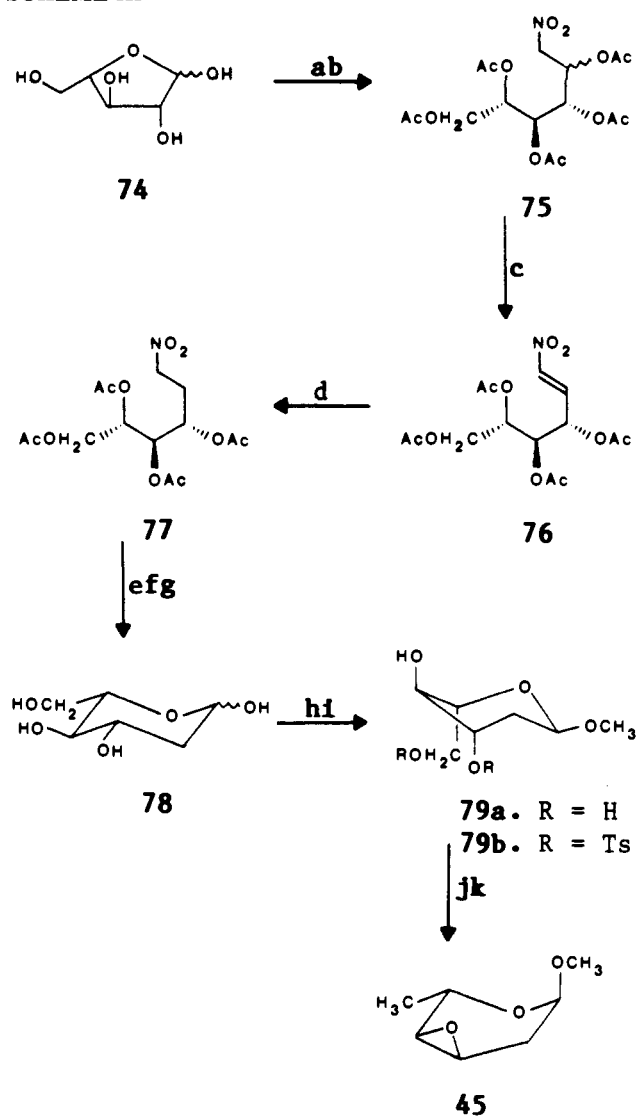
The starting material, 2-thiobenzyl-3-azido-*altro*-pyranoside (**68**), was prepared originally by Christensen and Goodman<sup>76</sup> in three steps (42% overall yield) from the *allo*-mannoside **27**. Isomerization of **68** with an acidic ion-exchange catalyst in methanol produced a complex mixture for which the anomeric furanosides **69** were chromatographically separated. The primary C-6 hydroxyl group in **69** was protected as its benzoate derivative and the C-5 hydroxyl group was tosylated to give **70**. Methoxide cleavage of the 6-benzoate functionality in **70** generated the 6-alkoxide which displaced the neighboring 5-tosylate group and formed the epoxide **71** with the L stereochemistry at C-5. Reduction of **71** with LAH gave the 6-deoxy-3-amino product **72**, which was desulfurized with Raney nickel (48% yield) and subsequently hydrolyzed to L-daunosamine hydrochloride (**73**). The overall yield was low, and extensive chromatography was required.

Whereas hexoses with the L configuration are uncommon, certain L-pentoses occur naturally, are relatively inexpensive, and can be readily homologated to 2-deoxy-L-hexoses. These properties were exploited by Grethe et al.<sup>45</sup> in their total synthesis of **1** in which

SCHEME VIII<sup>a</sup>

<sup>a</sup> (a) NaOCH<sub>3</sub>, BnSH, CH<sub>3</sub>OH; (b) TsCl, Py; (c) NaN<sub>3</sub>, CH<sub>3</sub>OC-H<sub>2</sub>CH<sub>2</sub>OH; (d) Amberlite-H<sup>+</sup>, CH<sub>3</sub>OH-H<sub>2</sub>O; (e) BzCl, Py; (f) TsCl, Py; (g) NaOCH<sub>3</sub>, CHCl<sub>3</sub>; (h) LAH, THF; (i) Ni(R), dioxane; (j) HCl-H<sub>2</sub>O.

L-arabinose (74), containing two of the requisite chiral centers with the correct absolute stereochemistry, was used as the starting material. The reaction sequence, shown in Scheme IX, eventually merges with the one employed by Marsh et al.<sup>39</sup> A modification of the procedure originally reported by Sowden and Fischer<sup>77,78</sup> was used first to homologate L-arabinose (74) to the 2-deoxy-L-hexose 78. Methoxide-catalyzed condensation of 74 with nitromethane, followed by acetylation with acetic anhydride and boron trifluoride, gave the crystalline pentacetate 75 in 70% yield. Treatment of 75 with sodium bicarbonate in toluene quantitatively furnished the (*E*)-nitro olefin 76, which was selectively reduced over palladium to the saturated nitro compound 77. A modified Nef reaction<sup>79,80</sup> (Ba(OH)<sub>2</sub>, H<sub>2</sub>SO<sub>4</sub>) transformed 77 to a mixture of anomeric L-arabino-hexoses 78. Since selective manipulation of the 3,4-hydroxyl groups was dependent upon the generation and use of intermediates with the <sup>4</sup>C<sub>1</sub> conformation, 78 was converted to the methyl α-glycoside 79a. Reaction of 78 with an acidic ion-exchange resin in methanol gave an anomeric mixture of methyl glycosides from which the pure α-anomer 79a was isolated by crystallization.

SCHEME IX<sup>a</sup>

<sup>a</sup> (a) CH<sub>3</sub>NO<sub>2</sub>, NaOCH<sub>3</sub>; (b) BF<sub>3</sub>·Et<sub>2</sub>O, Ac<sub>2</sub>O; (c) NaHCO<sub>3</sub>, PhCH<sub>3</sub>; (d) Pd/C, H<sub>2</sub>, EtOAc; (e) Ba(OH)<sub>2</sub>; (f) H<sub>2</sub>SO<sub>4</sub>; (g) BaCO<sub>3</sub>; (h) CH<sub>3</sub>OH, Amberlite-H<sup>+</sup>; (i) TsCl, Py; (j) NaBH<sub>4</sub>, DME; (k) Amberlite-OH<sup>-</sup>, CH<sub>3</sub>OH.

Complete conversion of the β-anomer to the desired α-anomer 79a through repeated equilibrations achieved maximum use of material.

Two routes from 79a to the epoxide intermediate 45 were developed. In the preferred sequence, 79a was converted to the ditosylate 79b (2 equiv of TsCl; 51%), which was separated from other mono- and ditosylate products by high-pressure liquid chromatography (HPLC). (The byproducts were recycled in order to improve material utilization.) Although 79b could be transformed to the epoxide 45 in a one-pot process through reduction with sodium borohydride followed by addition of methanol, better results (75% yield) were obtained when the 6-deoxy product from the borohydride reduction was isolated and then treated with basic ion-exchange resin. The epoxide 45 is the same intermediate used by Marsh et al.<sup>39</sup> (Scheme III), and it was converted to daunosamine (1) through an identical reaction sequence (26% from 45). In additional work, described in a later section, Grethe et al.<sup>46</sup> reported an elegant total synthesis of the optically active epoxide 45 from achiral precursors.





**80a.** R,R = CH<sub>3</sub>                      **81a.** R,R = CH<sub>3</sub>  
**80b.** R-R = -(CH<sub>2</sub>)<sub>5</sub>-            **81b.** R-R = -(CH<sub>2</sub>)<sub>5</sub>-

**Figure 2.** (2*S*,3*S*)- and (2*S*,3*S*)-2,3-dihydroxybutanal acetals.

## 2. Chiral Syntheses from Non-Carbohydrate Precursors

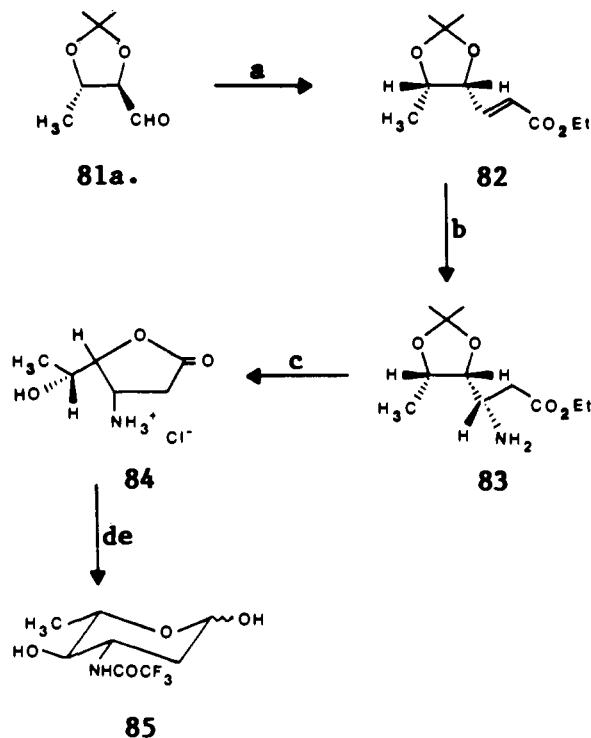
Although most of the total syntheses of optically active aminohexoses have been initiated from carbohydrate based materials, substantial efforts have focused on the use of non-carbohydrate derived precursors. The C-4 chiral aldehydes **80** and **81**, with the respective 2*S*,3*S* and 2*R*,3*S* absolute configurations shown in Figure 2, have been the most intensely studied because they contain two of the three stereocenters and four of the six carbons of the objective aminohexoses.

Fuganti and co-workers<sup>81,82</sup> have reported two procedures for preparation of the protected (2*S*,3*S*)-*erythro*-aldehyde **80a** through fermentation of cinnamaldehyde with Baker's yeast. Although the four-step method provided **80a** in 18% yield, the authors preferred the lower yield route (8%) since it was experimentally less involved. The (2*R*,3*S*)-*threo*-aldehyde **81a** has been prepared from D-threonine,<sup>83</sup> from epimerization of the (2*S*,3*S*)-aldehyde **80a**<sup>81,84</sup> and from L-tartaric acid.<sup>85-87</sup> The more direct route to **81a** from D-threonine is impractical for large scale preparation due to the exorbitant cost of this unnatural amino acid.<sup>83</sup> Of the two routes from L-tartaric acid,<sup>85-87</sup> the sequence reported by Mukaiyama et al.<sup>87</sup> is preferred because of its better overall yield and less involved experimental procedures.

Aldehydes **80** and **81** have served as key intermediates in several chiral syntheses of daunosamine (**1**) as well as in those of other configurationally related aminohexoses.<sup>18</sup> Transformation of these materials to the desired sugars requires stereoselective elaboration of C-3 with incorporation of a nitrogenous functionality and a two-carbon homologation with the terminal carbon eventually becoming an aldehyde. The first exploitation of these compounds as intermediates to optically active aminohexoses was reported by Fronza and co-workers,<sup>85</sup> who used **81a** as a precursor to both acosamine (**4**) and daunosamine (**1**). Their sequence largely followed a route established earlier by Dyong and Bendlin<sup>88</sup> for racemic syntheses and its use for preparation of an acosamine derivative is shown in Scheme X. Wittig reaction of **81a** with (carbethoxymethylene)triphenylphosphorane furnished the unsaturated ester **82**. Conjugate addition of ammonia to **82** stereoselectivity gave **83**, which on acid hydrolysis of the acetonide moiety underwent intramolecular cyclization to the amino lactone **84** with the *arabino* configuration (70% overall yield from **81a**). Acetylation of **84** to the bis-(*N,O*-trifluoroacetyl) derivative followed by diisobutylaluminum hydride (DIBAL) reduction produced *N*-(trifluoroacetyl)acosamine (**85**) (56%).

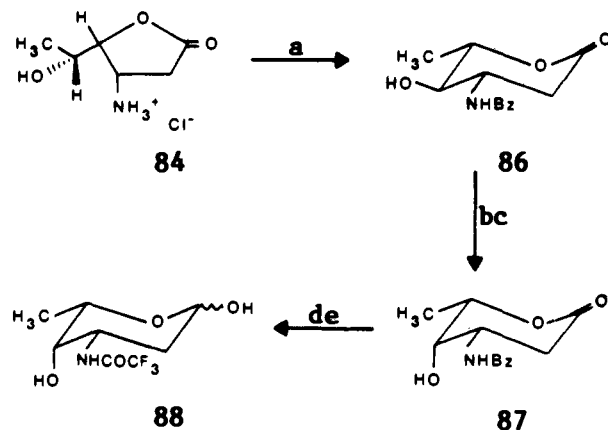
As shown in Scheme XI, the amino lactone **84** with the *arabino* configuration served as an intermediate to daunosamine (**1**). Treatment of **84** with sodium hy-

### SCHEME X<sup>a</sup>



<sup>a</sup> (a) Ph<sub>3</sub>P=CHCO<sub>2</sub>Et; (b) NH<sub>3</sub>, CH<sub>3</sub>OH; (c) HCl, Et<sub>2</sub>O; (d) TFAA, Py; (e) THF, DIBAL, -50 °C.

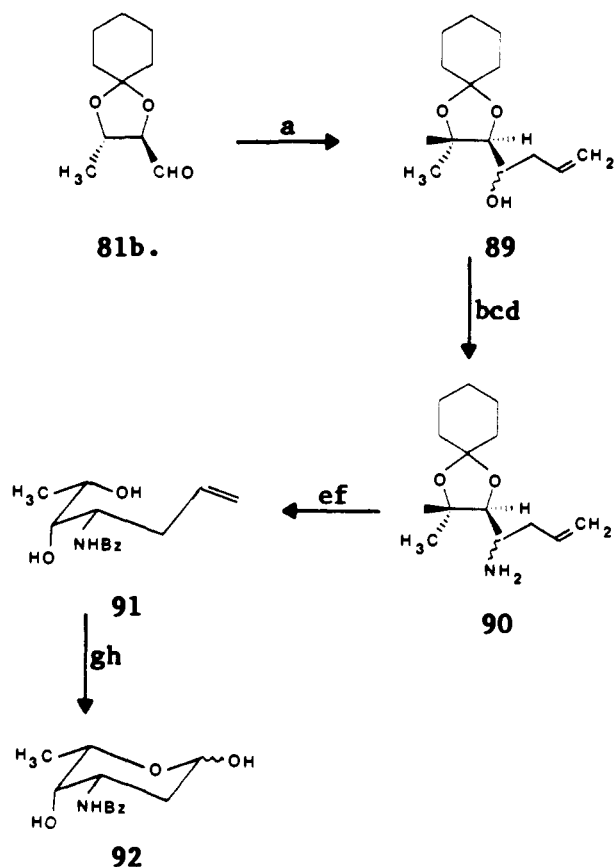
### SCHEME XI<sup>a</sup>



<sup>a</sup> (a) NaOH, PhCOCl; (b) MsCl, Py; (c) NaOAc; (d) TFAA, Py; (e) DIBAL.

dride and benzoyl chloride effected benzylation of the amino group and isomerization to the six-membered lactone **86**. C-4 epimerization of **86** to **87** was performed in 65% overall yield through mesylation, neighboring group displacement, and hydrolysis. Trifluoroacetylation of **87** followed by DIBAL reduction gave *N*-(trifluoroacetyl)daunosamine (**88**). The yield of **88** from the amino lactone **84** was 34% (overall yield 3%).

The (2*R*,3*S*)-aldehyde **81b** was employed by Fuganti and co-workers<sup>83</sup> in the stereoselective, direct total synthesis of daunosamine (**1**) shown in Scheme XII. Reaction of **81b** with allylmagnesium bromide (THF, -78°C) stereoselectively produced an 8:2 mixture (75% yield) of alcohols **89**; the diastereoisomer with the *xylo* configuration was the major product. Since the isomers were inseparable, subsequent steps were conducted on the mixture. Tosylation of the alcohol group in **89**, followed by azide displacement of the tosylate and then reduction of the azide functionality with LAH, gave the

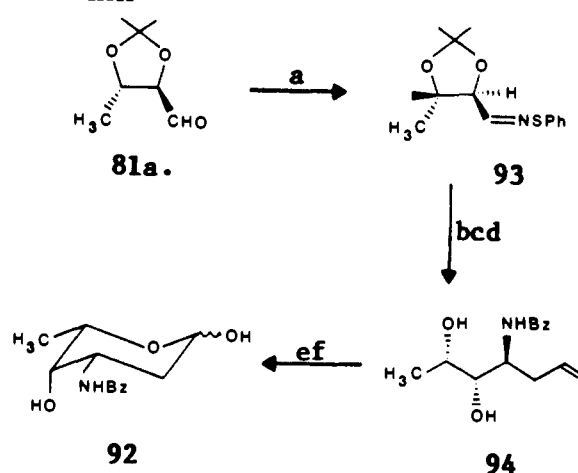
SCHEME XII<sup>a</sup>

<sup>a</sup> (a)  $\text{BrMgCH}_2\text{CH}=\text{CH}_2$ , THF,  $-78^\circ\text{C}$ ; (b)  $\text{TsCl}$ , Py; (c)  $\text{NaN}_3$ ,  $\text{NH}_4\text{Cl}$ , DMF; (d) LAH,  $\text{Et}_2\text{O}$ ; (e)  $\text{HOAc}$ ,  $\text{H}_2\text{O}$ ; (f)  $\text{PhCOCl}$ ,  $\text{K}_2\text{CO}_3$ ; (g)  $\text{O}_3$ ,  $\text{CH}_3\text{OH}$ ; (h)  $(\text{CH}_3)_2\text{S}$ .

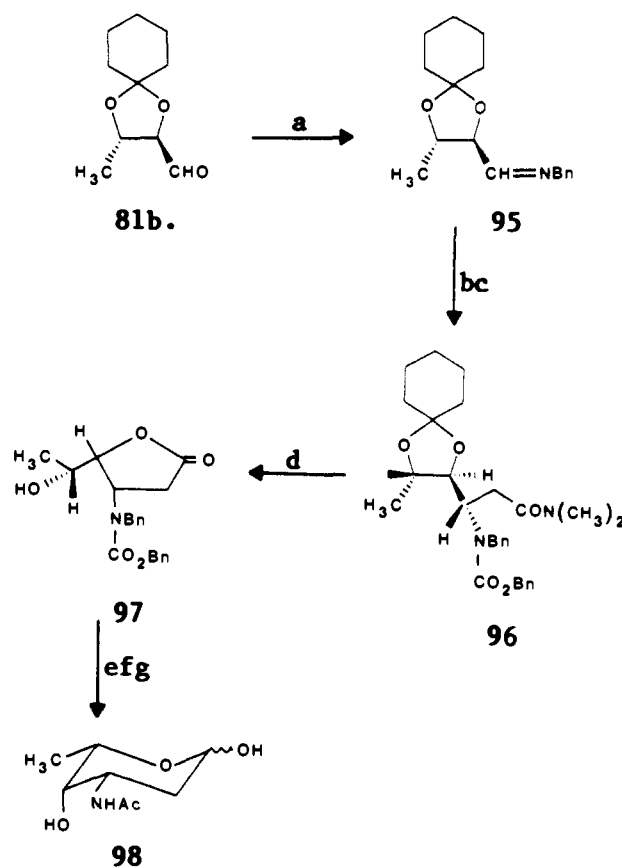
amine **90**. Hydrolysis of the acetonide and selective benzylation of the amine group furnished the benzamide alcohol **91**. The configurational isomers were separated at this point by preferential crystallization, and the yield of the *lyxo* isomer **91** from **81b** was 18%. Ozonolysis of the terminal olefin in **91** with reductive workup furnished *N*-benzoyldaunosamine (**92**). The seven-step sequence was accomplished with reasonably high efficiency (16% yield).

Although the previous syntheses in which **80** and **81** served as precursors were accomplished with moderate to good stereoselectivity, an inherent limitation was that stereochemistries other than *lyxo* were initially generated. As a consequence, additional manipulative steps were required to generate the configuration present in daunosamine (**1**). Elegant solutions to this problem were independently reported by Fuganti<sup>84</sup> and Mukaiyama<sup>87</sup> and their respective co-workers. Exceptionally high stereoselectivities and a modest number of steps resulting from direct generation of the *lyxo* stereochemistry are noteworthy characteristics of these preparations.

In the route employed by Fuganti et al.<sup>84</sup> and shown in Scheme XIII, the sulfenimine **93** was prepared from **81a** ( $(\text{PhS})_2$ ,  $\text{AgNO}_3$ )<sup>89</sup> initially. Addition of diallylzinc to **93** was highly *erythro* selective (75:1) and furnished, after acidic hydrolysis and benzylation, the intermediate **94**. The stereoselectivity observed for addition of the zinc reagent to **93** is in marked contrast with the result obtained when allylmagnesium bromide was used (5.5 *erythro*:4.5 *threo*). Ozonolysis of **94** with reductive work-up gave a 75:1 mixture of the *lyxo* (**92**) and *xylo*

SCHEME XIII<sup>a</sup>

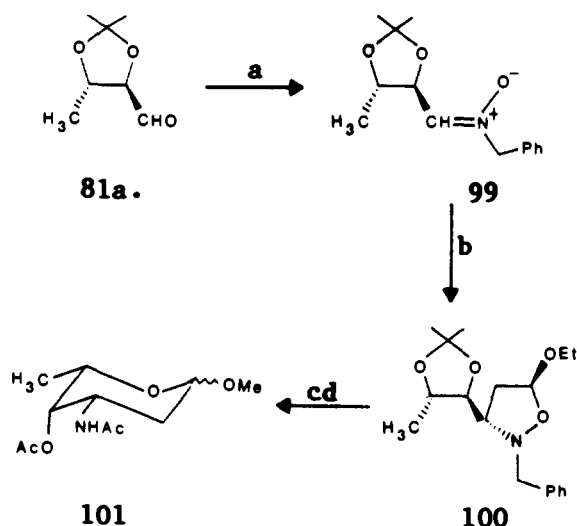
<sup>a</sup> (a)  $\text{PhSSPh}$ ,  $\text{AgNO}_3$ ,  $\text{NH}_3$ ,  $\text{CH}_3\text{OH}$ ; (b)  $(\text{CH}_2=\text{CHCH}_2)_2\text{Zn}$ ; (c)  $\text{H}_3\text{O}^+$ ; (d)  $\text{PhCOCl}$ ,  $\text{NaHCO}_3$ ; (e)  $\text{O}_3$ ,  $\text{CH}_3\text{OH}$ ; (f)  $(\text{CH}_3)_2\text{S}$ .

SCHEME XIV<sup>a</sup>

<sup>a</sup> (a)  $\text{PhCH}_2\text{NH}_2$ ,  $\text{Et}_2\text{O}$ ; (b)  $\text{LiCH}_2\text{CON}(\text{CH}_3)_2$ ,  $\text{ZnBr}_2$ , THF; (c)  $\text{PhCH}_2\text{OCOC}$ ,  $\text{NaHCO}_3$ ; (d)  $\text{HOAc}$ ,  $\text{H}_2\text{O}$ ; (e) DIBAL; (f)  $\text{Pd/C}$ ,  $\text{H}_2$ ,  $\text{HCO}_2\text{H}$ ; (g)  $\text{Ac}_2\text{O}$ .

isomers; the yield of *N*-benzoyldaunosamine (**92**) from **81a** was 38%. A parallel sequence using the (2*S*,3*S*)-aldehyde **80a** produced *L*-ristosamine (**8**).

In the sequence employed by Mukaiyama and co-workers<sup>87</sup> and shown in Scheme XIV, the (2*R*,3*S*)-aldehyde **81b** was reacted with benzylamine to generate the imine **95**. Condensation of **95** with  $\alpha$ -lithio-*N,N*-dimethylacetamide in the presence of zinc bromide proceeded stereoselectively and furnished, after benzyloxycarbonylation of the amine group, the nearly diastereomerically pure *lyxo*  $\beta$ -aminoamide **96** (50% yield from **81b**). Without zinc bromide, the stereo-

SCHEME XV<sup>a</sup>

<sup>a</sup>(a) PhCH<sub>2</sub>NHOH; (b) EtOCH=CH<sub>2</sub>; (c) Pd(OH)<sub>2</sub>, H<sub>2</sub>, HCl, CH<sub>3</sub>OH; (d) Py, DMAP, Ac<sub>2</sub>O.

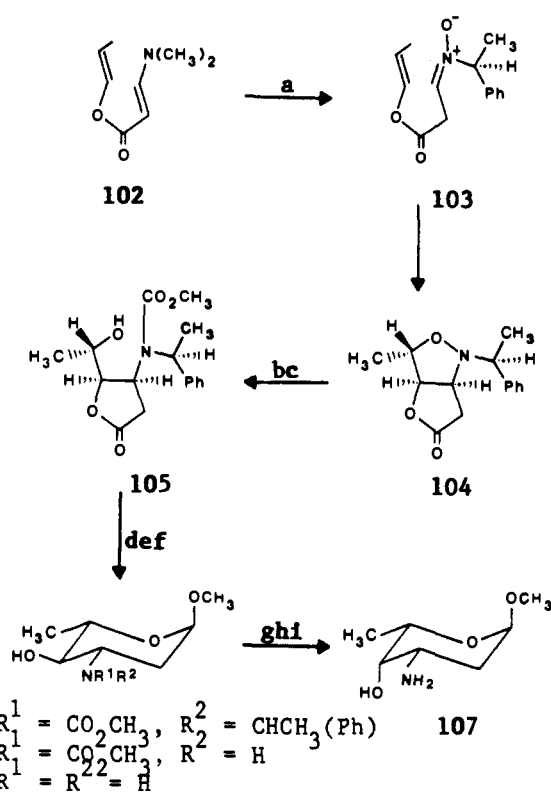
chemical outcome was altered so that the amide with the desired *lyxo* configuration was the minor product. The lactone 97, prepared through acidic hydrolysis of 96, was reduced with DIBAL to the aminoheptose. Deprotection of the amino group by catalytic hydrogenation and acetylation of the resultant free amino compound produced *N*-acetyl daunosamine (98) in 42% yield from 96 (21% yield overall).

DeShong and Leginus<sup>90</sup> used the achiral aldehyde with the same relative stereochemistry as 81a to synthesize racemic daunosamine. The reaction sequence which is shown in Scheme XV is stereospecific and is the highest yield route yet reported to racemic product from this aldehyde intermediate. Reaction of the racemic acetonide 81a with benzylhydroxylamine gave exclusively the *Z*-nitron 99, which underwent diastereospecific and regioselective cycloaddition with ethyl vinyl ether to the isoxazolidene 100 with an anti relative stereochemistry at C-3 and C-5. The N-O bond in 100 proved unusually resistant to cleavage; ultimately, hydrogenolysis over Pearlman's catalyst<sup>91</sup> provided the racemic *N,O*-diacetyl derivative 101 of methyl daunosaminide. Although only the achiral aldehyde obtained from crotonic acid<sup>92,93</sup> has been employed in this sequence, in principle, the aldehyde prepared from tartaric acid<sup>85-87</sup> could be used for an optically active preparation.

### 3. Chiral Syntheses from Achiral Precursors

A number of imaginative routes for optically active total syntheses of daunosamine (1) from achiral precursors have been investigated. The earliest was elegantly achieved by Wovkulich and Uskokovic<sup>94</sup> in modest overall yield as shown in Scheme XVI. Key elements of this preparation were the use of an optically active hydroxylamine as an auxiliary for asymmetric induction and the use of an intramolecular cyclization to invert the usual product regiochemistry obtained from nitron cycloadditions with enol ethers.

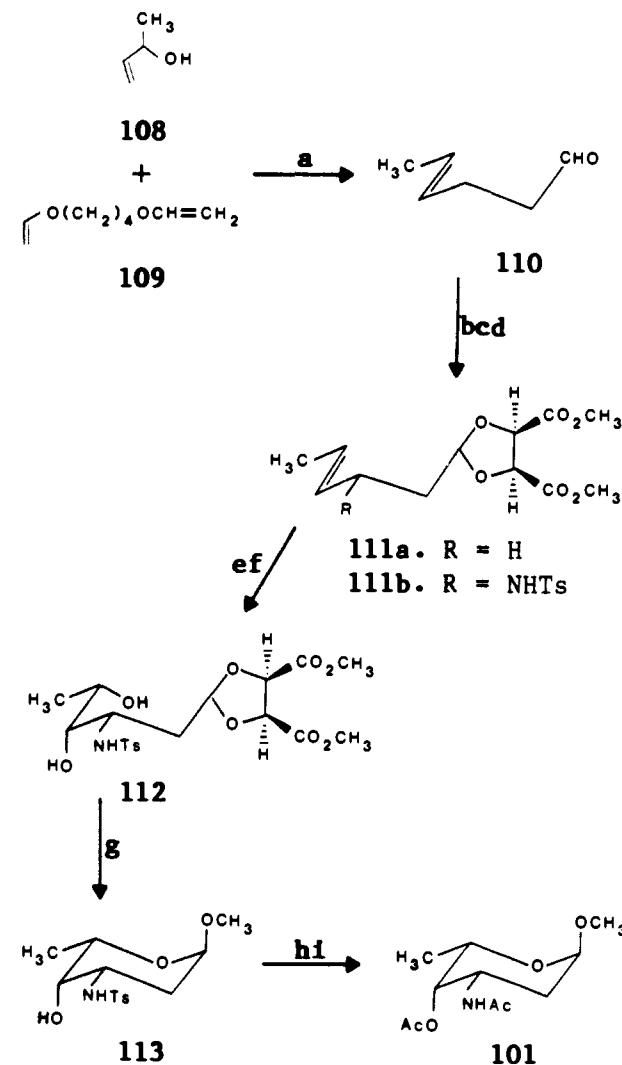
Formylation of *trans*-propenyl acetate with bis(dimethylamino)-*tert*-butoxymethane<sup>95</sup> gave 102, which was heated with the oxalate salt of (*S*)-(-)-*N*-hydroxy- $\alpha$ -methylbenzenemethanamine<sup>96</sup> to form 103. The nitron intermediate 103 underwent spontaneous intra-

SCHEME XVI<sup>a</sup>

<sup>a</sup>(a) (*S*)-(-)-*N*-hydroxy- $\alpha$ -methylbenzenemethanamine oxalate salt, xylene; (b) Zn, HOAc-H<sub>2</sub>O; (c) Na<sub>2</sub>CO<sub>3</sub>, CH<sub>3</sub>OCOC<sub>2</sub>H<sub>5</sub>, THF; (d) DIBAL; (e) Amberlite-H<sup>+</sup>, CH<sub>3</sub>OH; (f) Na/NH<sub>3</sub>; (g) MsCl, Py; (h) DMF-H<sub>2</sub>O; (i) Ba(OH)<sub>2</sub>, H<sub>2</sub>O.

molecular cyclization to an 82:12 mixture of diastereoisomeric oxazolones that were separated by crystallization. The N-O bond of the major isomer 104 was reductively cleaved (Zn, HOAc), and the resultant amine product was reacted with methyl chloroformate to give 105. DIBAL reduction of the lactone functionality in 105, followed by reaction with methanol in the presence of an acidic ion-exchange resin, furnished a 4:1 mixture of  $\alpha$ - and  $\beta$ -methyl acosaminide anomers. The major anomer was reductively debenzylated to 106b with sodium and ammonia. The procedure of Marsh et al.<sup>39</sup> was used to invert the C-4 hydroxyl group stereochemistry in 106b, furnishing the optically active methyl daunosaminide 107. Methyl acosaminide 47 was also produced through basic hydrolysis of the debenzylated intermediate 106b.

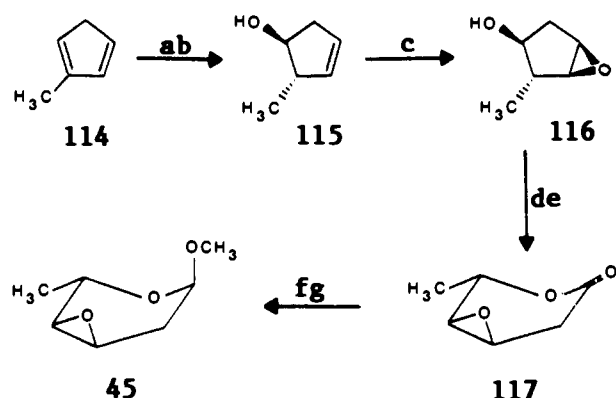
Using a modification of their racemic synthesis,<sup>97</sup> Dyong and co-workers<sup>98,99</sup> developed a novel chiral route to 1 from commercially available 3-buten-2-ol (108) and 1,4-bis(vinyl)butane (109) (Scheme XVII). Mercuric acetate catalyzed reaction of 108 with 109<sup>100</sup> followed by Claisen rearrangement of the allyl vinyl ether intermediate, gave the aldehyde 110, which was converted to the acetal derivative 111a with methyl *L*-tartrate. Allylic amination of the 4-olefinic entity with the reagent formed from selenium and chloramine-T<sup>101</sup> produced the tosylamide 111b in 53% overall yield. Cis hydroxylation of 111b with osmium tetroxide and *N*-methylmorpholine *N*-oxide<sup>102</sup> resulted in a 4:1 mixture of *xylo* and *lyxo* (112) diols. In contrast, cis hydroxylation carried out with *N*-bromoacetamide and silver acetate,<sup>103,104</sup> followed by deacetylation with sodium methoxide, produced a 1:8 ratio of *xylo* and *lyxo* (112) isomers. After 112 was treated with methanolic hy-

SCHEME XVII<sup>a</sup>

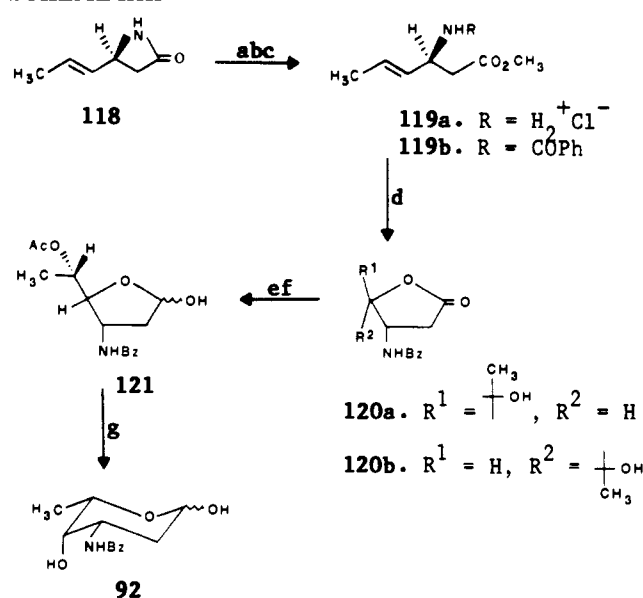
<sup>a</sup> (a) Hg(OAc)<sub>2</sub>; (b) NaOH, (H<sub>3</sub>CO)<sub>2</sub>SO; (c) (2*R*,3*R*)-(+)-di-methyltartrate, TsOH, PhH; (d) Se(NTs)<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>; (e) CH<sub>3</sub>CONHBr, AgOAc; (f) NaOCH<sub>3</sub>; (g) CH<sub>3</sub>OH, HCl; (h) Na/NH<sub>3</sub>; (i) Ac<sub>2</sub>O, Py.

drogen chloride, the toluenesulfonamide entity in the methyl pyranoside 113 was cleaved with sodium in ammonia and the resultant amino alcohol was acetylated to provide the chiral diacetyl methyl glycoside 101 of daunosamine in 17% overall yield. Notable features of this synthesis are the stereoselective *cis* hydroxylation of key intermediate 111b, the use of inexpensive starting materials, and the reasonable yield.

An elegant, albeit low yield, chiral, stereospecific total synthesis of 45, the epoxide intermediate to acosamine (4) and daunosamine (1), from achiral precursors was recently reported by Grethe et al.<sup>45</sup> (Scheme XVIII). Asymmetric hydroboration of 2-methylcyclopentadiene (114) with the optically active borane derived from diborane and pinene gave the chiral alcohol 115 in 50% yield (95% enantiomeric excess).<sup>105</sup> Epoxidation of 115 was guided by the homoallylic hydroxyl group and stereospecifically introduced the remaining two chiral centers in 116. Collins oxidation of 116 followed by Baeyer-Villiger ring enlargement furnished the lactone 117, which on DIBAL reduction and subsequent glycosidation with methanol-boron trifluoride gave the  $\alpha$ -anomer of 45 (10%). The remaining transformations were performed according to Marsh's procedure<sup>39,45</sup> and

SCHEME XVIII<sup>a</sup>

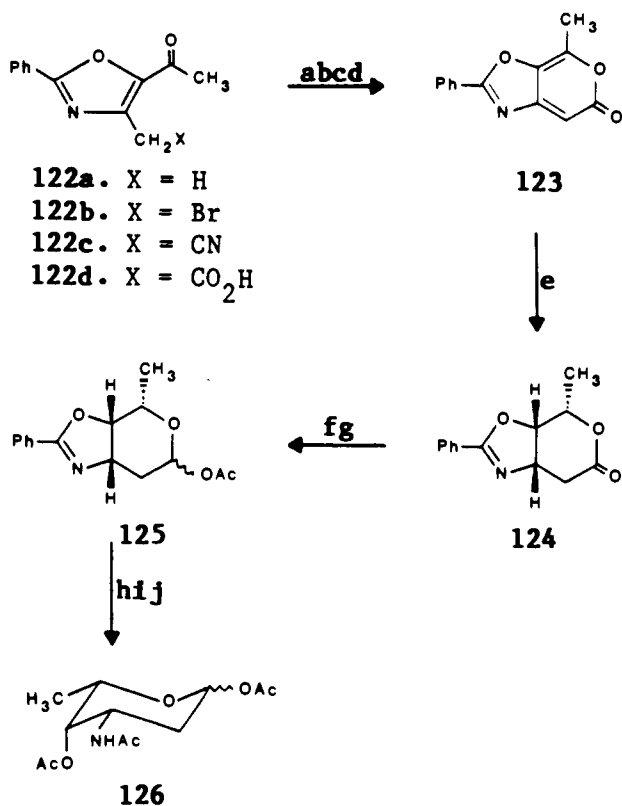
<sup>a</sup> (a) (-)-Di-3-pinanylborane; (b) H<sub>2</sub>O<sub>2</sub>, NaOH; (c) MCPBA, NaHCO<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>; (d) CrO<sub>3</sub>-2Py, CH<sub>2</sub>Cl<sub>2</sub>; (e) MCPBA; (f) DIBAL, PhCH<sub>3</sub>, -70 °C; (g) CH<sub>3</sub>OH, BF<sub>3</sub>.

SCHEME XIX<sup>a</sup>

<sup>a</sup> (a) CH<sub>3</sub>OH, HCl; (b) Resolve with dibenzoyl-L-tartaric acid or *p*-bromotartranilic acid; (c) PhCOCl, Py, CH<sub>2</sub>Cl<sub>2</sub>; (d) catalytic OsO<sub>4</sub>, TMNO; (e) Ac<sub>2</sub>O, Py; (f) DIBAL, THF; (g) NH<sub>3</sub>, CH<sub>3</sub>OH, 0 °C.

provided 1 in 4% overall yield.

Hauser and co-workers<sup>106</sup> accomplished a brief, racemic synthesis of the *N*-benzoyl derivative of 1 from simple acyclic starting materials and later modified it to achieve the chiral preparation<sup>107</sup> of daunosamine shown in Scheme XIX. The azetidinone 118, a key intermediate in the synthesis, was prepared through cycloaddition of chlorosulfonyl isocyanate and (*E*)-1,3-pentadiene.<sup>108,109</sup> Methanolysis cleaved the  $\beta$ -lactam and gave the racemic methyl ester amine hydrochloride salt 119a. This intermediate was resolved through crystallization of the diastereoisomeric salts formed from either dibenzoyltartaric acid or *p*-bromotartranilic acid;<sup>110</sup> the efficiencies were 68 and 71%, respectively. The optically active amine 119a was benzoylated to the amide 119b, which underwent diastereoselective *cis* hydroxylation (OsO<sub>4</sub>, TMNO)<sup>111</sup> to give predominantly the lactone 120 with the *lyxo* configuration. The lactone was acetylated and the resultant acetate was reduced with DIBAL to the hexofuranose 121, which on ammonolysis formed *N*-benzoyldaunosamine (92) in 9% overall yield. An identical sequence performed on the

SCHEME XX<sup>a</sup>

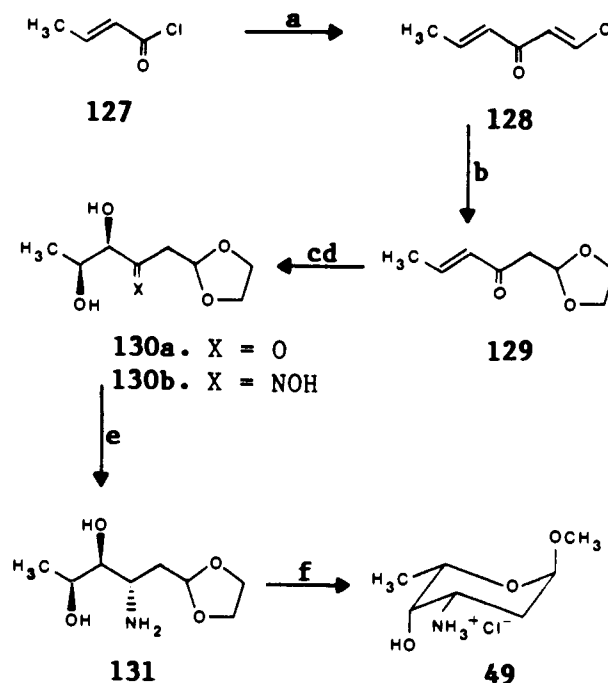
<sup>a</sup>(a) NBS; (b) KCN, HCN, Et<sub>2</sub>O, 75 °C, 36 h, (sealed tube); (c) HCl, HOAc; (d) SOCl<sub>2</sub>, CHCl<sub>3</sub>; (e) Rh/Al<sub>2</sub>O<sub>3</sub>, H<sub>2</sub>; (f) Na(OCH<sub>3</sub>)<sub>2</sub>-AlH; (g) Ac<sub>2</sub>O, Py; (h) Rh/Al<sub>2</sub>O<sub>3</sub>, H<sub>2</sub>; (i) H<sub>3</sub>O<sup>+</sup>; (j) Ac<sub>2</sub>O, Py.

lactone **120b** provided the *xylo* isomer in 8% yield overall. Important aspects of this preparation are the use of inexpensive precursors and the relative ease of the chemical manipulations.

## 4. Racemic Syntheses

The earliest racemic total synthesis of daunosamine (**1**,**2**) was reported by Wong et al.<sup>112</sup> and it is shown in Scheme XX. This preparation is quite novel in that it is the only reported route to have used a nitrogen heterocycle as a starting material. Although the oxazole **122a**<sup>113</sup> had 5 of the 6 carbons, the nitrogen, and two of the three oxygens, its transformation to daunosamine (**1**) was hampered by unstable intermediates. Homolytic bromination of **122a** gave the bromomethyl derivative **122b**, but introduction of the remaining carbon atom through displacement of the bromine in **122b** with cyanide proved difficult, and ultimately, required the use of exceptional reaction conditions (liquid HCN, Et<sub>2</sub>O, KCN; sealed tube; 75 °C; 36 h). Hydrolysis of the nitrile in **122c** produced the unstable acid **122d** that was immediately transformed to the oxazole- $\gamma$ -pyrone **123** with thionyl chloride. Reduction of **123** with rhodium on alumina gave the thermally unstable *cis*-oxazolinopyrone **124**, which was reduced with L-Selectride. The lactol product was acetylated to **125**, and a second hydrogenation with rhodium on alumina cleaved the oxazoline moiety. The racemic daunosamine product was isolated as the triacetate derivative **126**.

A very brief, stereoselective total synthesis of **1** was accomplished from crotonoyl chloride (**127**) by Iwataki et al.<sup>114</sup> using the reaction sequence shown in Scheme XXI. Friedel-Crafts reaction of **127** with vinyl chloride furnished the 1-chlorohexadienone **128** in 53% yield.

SCHEME XXI<sup>a</sup>

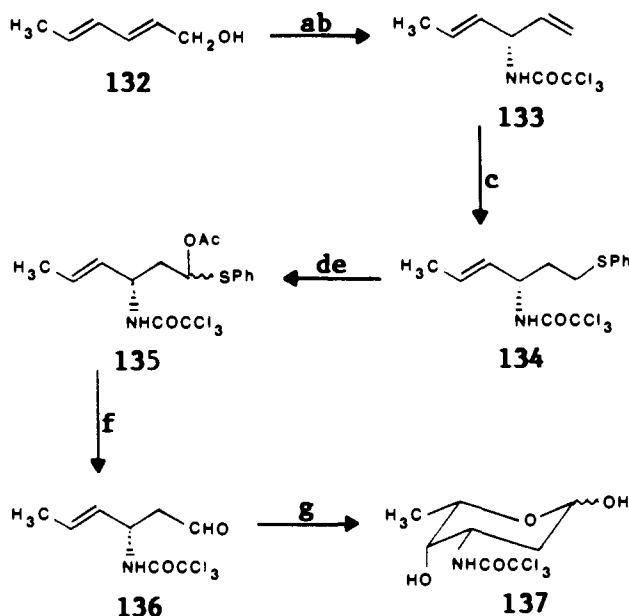
<sup>a</sup>(a) CH<sub>2</sub>=CHCl; (b) HOCH<sub>2</sub>CH<sub>2</sub>OH, K<sub>2</sub>CO<sub>3</sub>; (c) KMnO<sub>4</sub>, acetone, -40 °C; (d) HONH<sub>2</sub>-HCl, NaOEt; (e) PtO<sub>2</sub>, H<sub>2</sub>, HOAc; (f) CH<sub>3</sub>OH, HCl.

Transformation of the  $\beta$ -chloroenone fragment to a  $\beta$ -keto acetal through reaction of **128** with potassium carbonate and ethylene glycol gave **129** in only 14% yield. The 4,5-olefinic entity in **129** was *cis* hydroxylated with potassium permanganate (-40 °C, acetone; 35%), and the resultant keto alcohol **130a** was reacted with hydroxylamine to produce the oxime **130b** (56% yield). Catalytic hydrogenation of the oxime moiety in **130b** over platinum oxide stereoselectively produced the amino glycol **131**, which was hydrolyzed in acidic methanol to methyl daunosaminide hydrochloride (**49**).

Hauser et al.<sup>116</sup> have reported a brief procedure for the preparation of **137**, the trichloroacetamide derivative of racemic daunosamine, from commercially available sorbyl alcohol (**132**) (Scheme XXII). Overman reaction (NaH, CCl<sub>3</sub>CN)<sup>53</sup> of **132** furnished a quantitative yield of the deconjugated trichloroactamide **133**, and free radical addition of benzenethiol<sup>117</sup> to **133** provided the latent functionalization required for subsequent conversion of C-1 to an aldehyde functionality. The regioselectively formed thiophenyl adduct **134** was oxidized to the sulfoxide,<sup>118</sup> which on Pummerer rearrangement ((CF<sub>3</sub>CO)<sub>2</sub>O, Ac<sub>2</sub>O, lutidine)<sup>119</sup> gave **135**. After hydrolysis (CuCl<sub>2</sub>, H<sub>2</sub>O)<sup>120</sup> of the acetoxy sulfide moiety in **135**, *cis* hydroxylation of the olefinic moiety in the unsaturated aldehyde **136** led to a 60:40 ratio of **137** (38%) and the *xylo* isomer (overall yield of 59%). Alternatively, *cis* hydroxylation of **135** and then hydrolysis produced the *xylo* isomer and the 1-thiophenyl glycoside of **137** in the same ratio. The thiophenyl glycoside is useful in coupling reactions with anthracyclines.<sup>121</sup> Important features of this route are its brevity, the use of inexpensive materials, and the high yield.

## B. Rhodosamine (L-lyxo)

L-Rhodosamine (**3**), the *N,N*-dimethylamino derivative of daunosamine (**1**), was the first 2,3,6-trideoxy-3-

SCHEME XXII<sup>a</sup>

<sup>a</sup> (a) NaH, Cl<sub>3</sub>CCN; (b) xylene, Δ; (c) PhSH, AIBN; (d) NaIO<sub>4</sub>, CH<sub>3</sub>OH; (e) Ac<sub>2</sub>O, TFAA, Lutidine; (f) CuCl<sub>2</sub>, CH<sub>3</sub>CN-H<sub>2</sub>O; (g) catalytic OsO<sub>4</sub>, TMNO, acetone-H<sub>2</sub>O.

aminohexose to be isolated, and was originally obtained from rhodomycin-isorhodomycin mixtures by Brockmann and co-workers.<sup>1,2</sup> Subsequently, it was shown to be the lead sugar in numerous anthracycline antibiotics<sup>122,123</sup> and occurs as such in aclacinomycin, which is currently undergoing clinical evaluation as an anticancer agent. The structure and absolute configuration of **3** were determined largely from its <sup>1</sup>H NMR spectrum and that of its hydrazone and diacetate derivatives.

Rhodosamine (**3**) is the most abundant aminohexose in anthracycline antibiotics, and its preparation from daunosamine (**1**) is a conceptually trivial synthetic step. Because of this, no total synthesis of this sugar has been reported.

### C. Acosamine (L- and D-*arabino*)

L-Acosamine (**4**) and its 4-*O*-methyl derivative, actinosamine (**6**), were isolated from the antibiotic actinoidin by Lomakina and co-workers.<sup>42,43</sup> Based on the IR and NMR spectra of the acetate and methyl glycoside derivatives, both were shown to be *L-arabino* isomers. The D enantiomorph (**5**) of acosamine was later obtained from the basic antibiotic *N*-acetylsporavidin by Harada et al.<sup>124</sup> and its structure established through mass spectral, <sup>13</sup>C NMR, and <sup>1</sup>H NMR data and comparison of the optical rotation with that of L-acosamine (**4**).

The present strong synthetic interest in L-acosamine (**4**) results from structure activity studies on daunorubicin and adriamycin. Replacement of daunosamine (**1**) with acosamine (**4**) produces analogues which are nearly devoid of cardiotoxicity, but retain the anticancer activity.<sup>15,16,42</sup> Acosamine (**4**) has often served as an intermediate in syntheses of daunosamine (**1**)<sup>18,39,45,46,55,81,83,84,94</sup> and has also been isolated as a minor product in other preparations of aminohexoses.<sup>125,126</sup> (Where acosamine has played a role in the synthesis of another sugar, it has been dealt with in that section.) All of the numerous reported syntheses

of **4** are chiral, and except for two, have used carbohydrates as starting materials. The D isomer **5** has also been prepared from carbohydrate precursors and has been a byproduct in syntheses of D-daunosamine (**2**).<sup>26,27,33</sup>

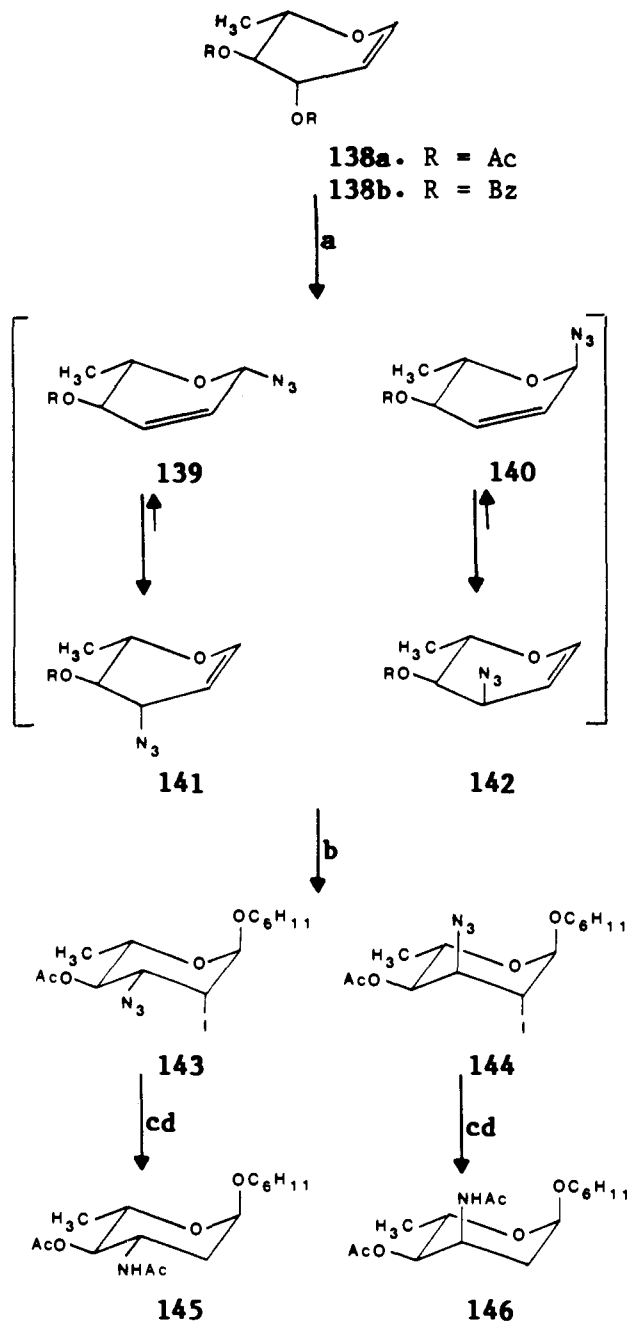
#### 1. Chiral Syntheses from Carbohydrate Precursors

In order to confirm the assigned structure, Gupta<sup>127</sup> and Lee et al.<sup>128</sup> independently reported preparations of L-acosamine (**4**). Both preparations were accomplished from the azido intermediate **46a** that Marsh et al.<sup>39</sup> used in the synthesis of daunosamine (**1**) and were identical with the earlier established sequence.

Heyns et al.<sup>129,130</sup> and Boivin and Monneret<sup>131</sup> developed the Lewis acid catalyzed addition of azide to *O*-acyl derivatives of rhamnal (**43**) as a route for generating pyranose intermediates with a nitrogenous functionality at C-3. In the sequence employed by Heyns et al.<sup>129,130</sup> and shown in Scheme XXIII, the diacetate derivative **138a** of rhamnal (**43**) was reacted with sodium azide and boron trifluoride in ether.<sup>132</sup> The generated mixture of the C-1 (**139a** and **140a**) and C-3 (**141a** and **142a**) azide epimers was shown to be in equilibrium through [3,3]-sigmatropic rearrangement. Reaction of the mixture with hexanol and *N*-iodosuccinimide<sup>133</sup> produced a 7:3 ratio of iodoazides **143** (*L-arabino*) and **144** (*L-ribo*), which were separated by chromatography. <sup>1</sup>H NMR studies showed that **143** existed solely in the <sup>1</sup>C<sub>4</sub> conformation whereas **144** was a mixture of <sup>1</sup>C<sub>4</sub> and <sup>4</sup>C<sub>1</sub> conformers. Concomitant reduction of the azide group and reductive dehalogenation of **143** were accomplished with nickel(II) chloride and sodium borohydride;<sup>134</sup> subsequent acetylation (Ac<sub>2</sub>O, Py) of the reduction product gave the hexyl *N,O*-diacetyl- $\alpha$ -L-acosaminide (**145**) in 12% overall yield. An identical sequence from the *ribo* azide isomer **144** produced the ristosamine derivative **146** in 7% overall yield.

In their work, which is shown in Scheme XXIV, Boivin and Monneret<sup>131</sup> made several additional contributions to the employed azide chemistry. They demonstrated that while the ratio of 3-azido-hexoses (**141b** and **142b**) from rhamnal dibenzoate (**138b**)<sup>135</sup> was altered by the use of different solvents, the isomer **141b** with the *arabino* configuration was always predominant and was produced in the highest percentage when ether was the solvent. The individual 3-azido isomers **141b** and **142b** were separated and shown to undergo re-equilibration through [3,3]sigmatropic rearrangement to the corresponding C-1 anomers **139b** and **140b**. Independent reduction with LAH of the separated C-3 isomers **141b** and **142b** produced the respective amines **147** and **148**, which were *N*-trifluoroacetylated and then *O-p*-nitrobenzoylated. Reaction of **149** and **150** with toluenesulfonic acid and an alcohol (MeOH or C<sub>6</sub>H<sub>11</sub>OH) furnished the corresponding glycosides; the methyl acosinimide derivative **151a** and the methyl ristosaminide **152a** were obtained in 13% and 7% overall yield, respectively, from rhamnose.

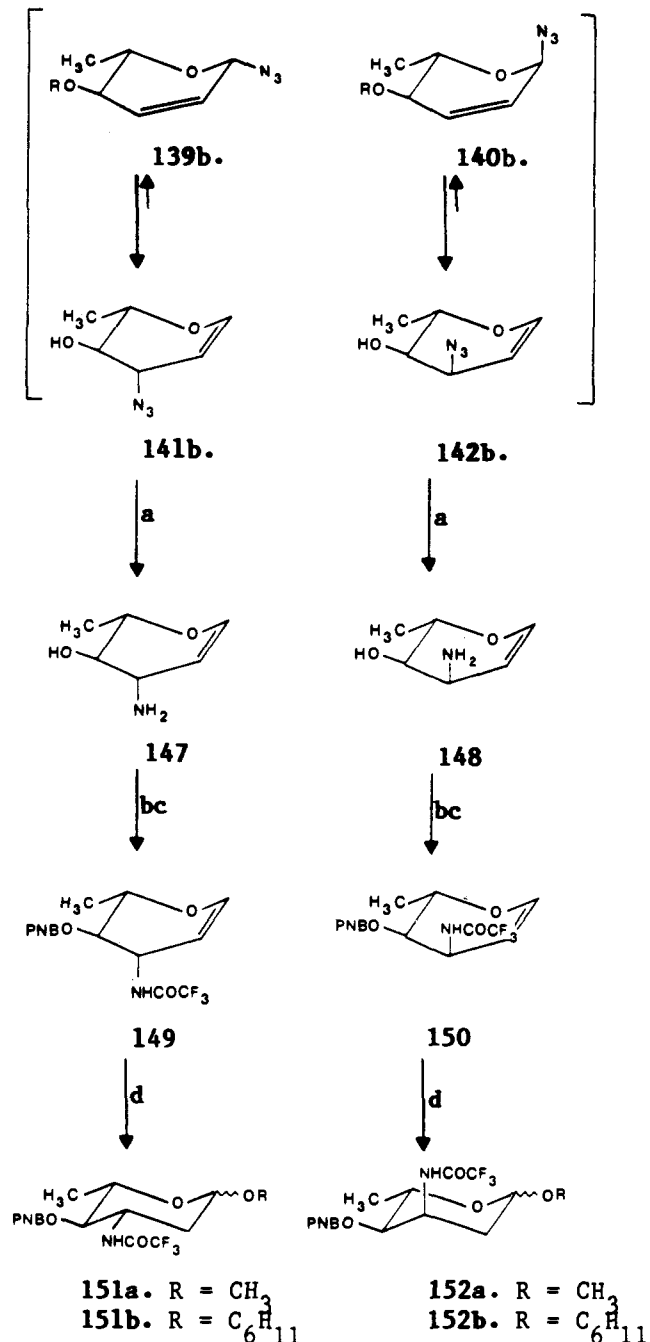
Using a sequence developed in their earlier work on ristosamine (**8**),<sup>136</sup> Pelyvas et al.<sup>137</sup> reported the synthesis of **4** and its 1-thiobenzyl derivative **155b** from rhamnal (**43**) (Scheme XXV). Oxidation of L-rhamnal (**43**) to the enone **153** with Fetizon's reagent<sup>138</sup> (silver carbonate on Celite) and then glycosidation through

SCHEME XXIII<sup>a</sup>

<sup>a</sup> (a)  $\text{NaN}_3$ ,  $\text{BF}_3 \cdot \text{Et}_2\text{O}$ ,  $\text{CH}_3\text{CN}$ ; (b)  $\text{C}_6\text{H}_{11}\text{OH}$ , NIS; (c)  $\text{NiCl}_2$ ,  $\text{NaBH}_4$ ; (d)  $\text{Ac}_2\text{O}$ , Py.

conjugate addition of sodium methoxide to the olefinic moiety<sup>139</sup> furnished **154a** as a 15:1 mixture of  $\alpha$ - and  $\beta$ -anomers (49% overall yield). The oxime **154b**, obtained by reaction of **154a** with methanolic hydroxylamine, was acetylated to the oxime acetate **154c**. Reduction of **154c** with diborane stereoselectively produced the amine intermediate,<sup>139</sup> which was acetylated to methyl *N,O*-diacetylacosaminide (**155a**) in 28% overall yield from **43**. In contrast, catalytic hydrogenation of the oxime **154b** inverted the stereochemical outcome, producing a 39:7 mixture of ristosaminide and acosaminide acetate derivatives **155a**.<sup>136</sup> A similar preparation of the thioglycoside analogue **155b** of acosamine was accomplished from the conjugate addition product of benzyl mercaptan and the hexen-3-ulose **153**.

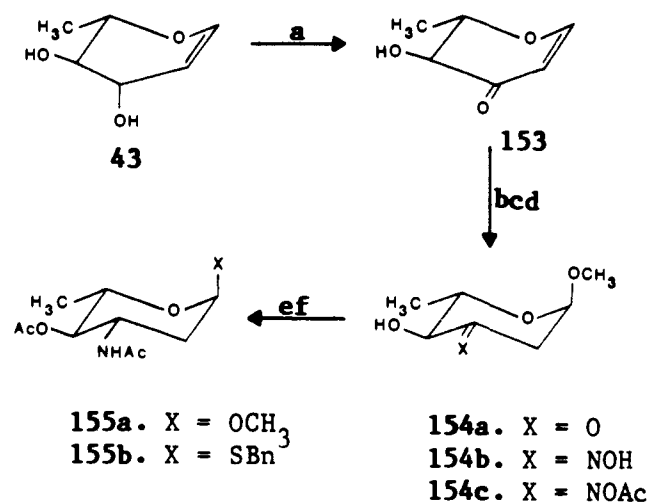
Suami et al.<sup>140</sup> recently reported the preparation of acosamine (**4**) and the *ribo* (**8**) and *xylo* (**11**) configu-

SCHEME XXIV<sup>a</sup>

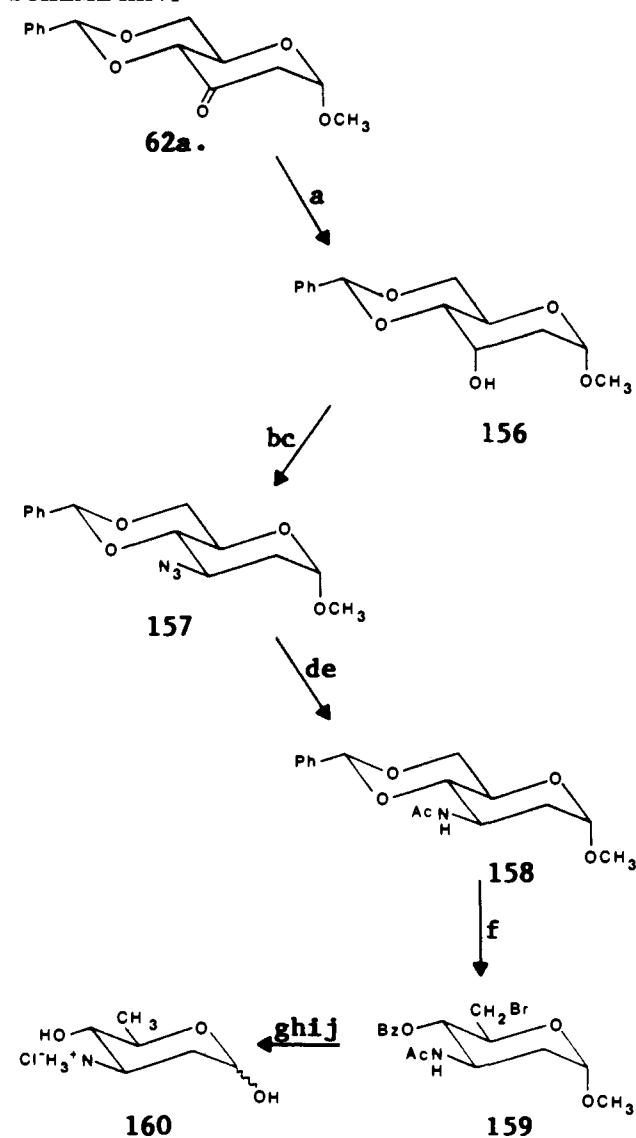
<sup>a</sup> (a) LAH; (b) TFAA,  $\text{Et}_3\text{N}$ ; (c) *p*- $\text{NO}_2\text{C}_6\text{H}_4\text{COCl}$ , Py; (d) TsOH,  $\text{CH}_3\text{OH}$  or TsOH,  $\text{C}_6\text{H}_{11}\text{OH}$ .

rational isomers from a *D*-mannitol derivative. This long sequence, some 22 steps, gave only a modest yield (0.8%) of product.

The *D*-enantiomorph **5** of acosamine was prepared by Horton et al.<sup>141</sup> using an intermediate from their earlier daunosamine synthesis<sup>58</sup> (Scheme XXVI). The keto sugar intermediate **62a**, obtained from methyl-*D*-mannoside (**60**),<sup>58</sup> was reduced with LAH to produce a 10:1 mixture of *D-ribo* (**156**) and *-arabino* diastereoisomers that were readily separated by recrystallization. After **156** was mesylated, azide displacement of the mesylate group inverted the configuration at C-3,<sup>26,27,29</sup> providing the azido sugar **157**. Reduction of **157**, followed by acetylation, furnished **158** in 40% overall yield from **62a**. Cleavage of the benzylidene group in the glycoside **158** with NBS<sup>68</sup> produced the 4-*O*-benzoyl-6-

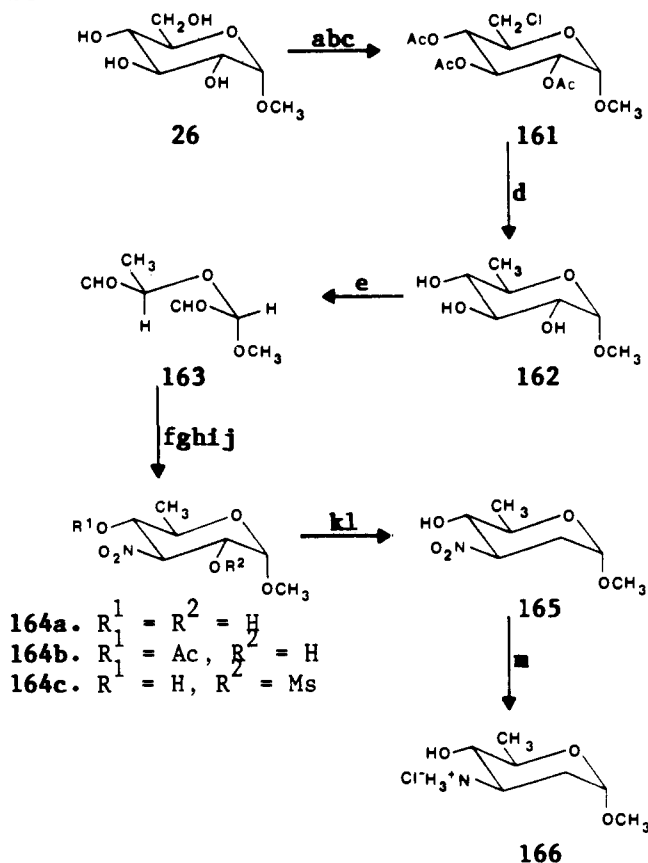
SCHEME XXV<sup>a</sup>

<sup>a</sup> (a) Ag<sub>2</sub>CO<sub>3</sub>/Celite, PhH; (b) NaOCH<sub>3</sub>, CH<sub>3</sub>OH; (c) NH<sub>2</sub>OH, CH<sub>3</sub>OH; (d) Ac<sub>2</sub>O, Py; (e) BH<sub>3</sub>; (f) TFAA, Py.

SCHEME XXVI<sup>a</sup>

<sup>a</sup> (a) LAH, Et<sub>2</sub>O; (b) MsCl, Py; (c) NaN<sub>3</sub>, DMF; (d) Ni(R)/H<sub>2</sub>, CH<sub>3</sub>OH; (e) Ac<sub>2</sub>O; (f) NBS, CCl<sub>4</sub>, BaCO<sub>3</sub>; (g) Ni(R)/H<sub>2</sub>, Et<sub>3</sub>N; (h) NaOCH<sub>3</sub>; (i) Ba(OH)<sub>2</sub>; (j) HCl-H<sub>2</sub>O.

bromo analog 159 which was shown by <sup>1</sup>H NMR to have the <sup>4</sup>C<sub>1</sub> conformation. Following reductive dehalogen-

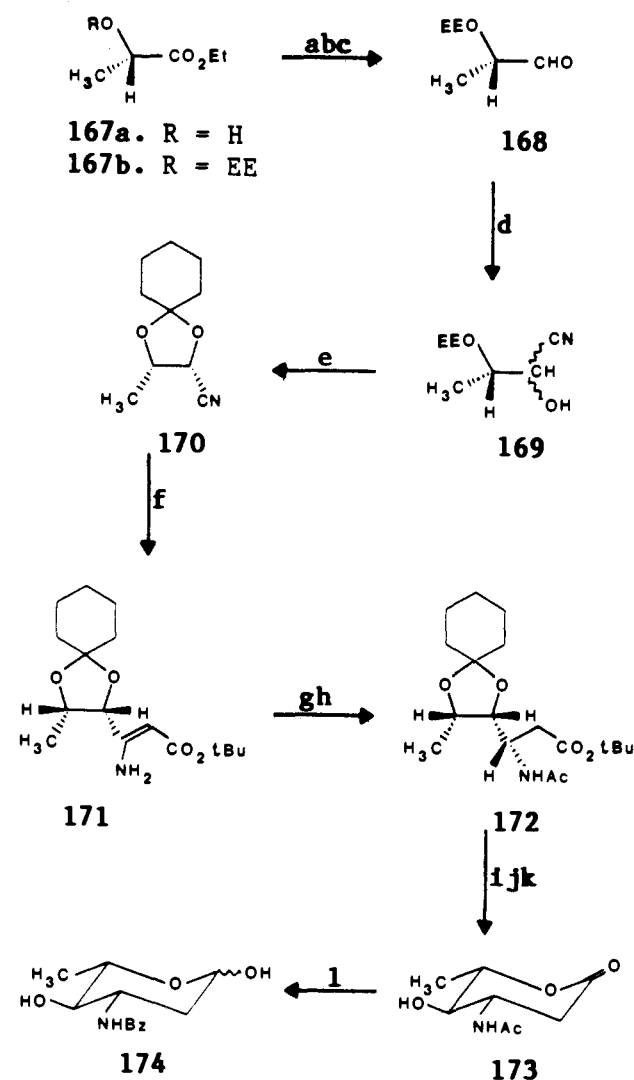
SCHEME XXVII<sup>a</sup>

<sup>a</sup> (a) MsCl, DMF; (b) 2-propanol/H<sub>2</sub>O; (c) Ac<sub>2</sub>O, Py; (d) LAH, Et<sub>2</sub>O; (e) NaIO<sub>4</sub>; (f) CH<sub>3</sub>NO<sub>2</sub>, NaOCH<sub>3</sub>; (g) BF<sub>3</sub>·Et<sub>2</sub>O, Ac<sub>2</sub>O; (h) NaOH, acetone, AcCl; (i) MsCl, Py; (j) CH<sub>3</sub>OH, HCl; (k) NaHCO<sub>3</sub>; (l) NaBH<sub>4</sub>; (m) PtO<sub>2</sub>, H<sub>2</sub>, HCl, CH<sub>3</sub>OH.

ation of 159 with Raney nickel and triethylamine, the benzoyl groups were cleaved with sodium methoxide and the *N*-acetyl moiety was removed with barium hydroxide. Acidic hydrolysis of the glycosidic bond furnished *D*-acosamine hydrochloride (160) in 29% overall yield.

Baer and Georges<sup>142</sup> used the procedure shown in Scheme XXVII to synthesize *D*-acosamine (5) from methyl *D*-glucoside (26) in 6% overall yield. Like their earlier work,<sup>33</sup> this sequence is keyed to the condensation of nitromethane with a sugar-derived aldehyde intermediate. Reaction of 26 with methanesulfonyl chloride, followed by cleavage of the secondary mesylate groups with 2-propanol and then by acetylation (Ac<sub>2</sub>O, Py), produced the 6-chloro sugar 161.<sup>143,144</sup> Reduction of 161 with LAH furnished 162, which was oxidized with sodium metaperiodate to the dialdehyde 163. Aldol condensation of 163 with nitromethane<sup>145,146</sup> gave the nitro sugar 164a in 29% overall yield from 26. Boron trifluoride catalyzed acetylation of 164a and selective 2-de-O-acetylation<sup>147</sup> (MeOH, AcCl) of the diacetate produced 164b. Following methanesulfonylation of 164b, the 4-acetoxy functionality was de-O-acetylated with methanolic hydrogen chloride<sup>148</sup> to give 164c in 35% yield from 164a. The mesylate in 164c was eliminated with sodium bicarbonate and the resultant olefinic nitro intermediate was conjugately reduced to the 2-deoxypyranoside 165. Hydrogenation of 165 with Adams' catalyst in the presence of anhydrous hydrogen chloride gave methyl *D*-acosaminide hydrochloride 166.

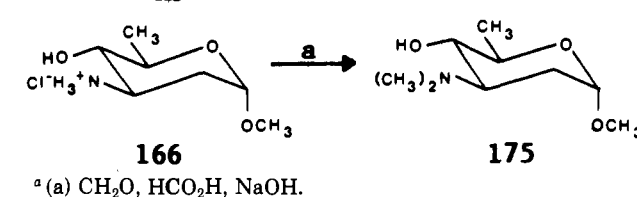


SCHEME XXVIII<sup>a</sup>

## 2. Chiral Syntheses from Non-Carbohydrate Precursors

Fronza et al.<sup>149</sup> have reported the syntheses of both racemic and chiral L-acosamine (4) from cinnamaldehyde and of several C-methyl sugars from  $\alpha$ -methylcinnamaldehyde. The sequence they used was nearly identical with their previous route in which acosamine (4) served as an intermediate to daunosamine (1) (Scheme X).<sup>81</sup>

A chiral synthesis of 4 from ethyl L-lactate (167a) was recently documented by Hiyama et al.<sup>150</sup> and is shown in Scheme XXVIII. The key intermediate, (2R,3S)-butanenitrile 170, is similar to the (2R,3S)-aldehydes 80 and 81 used by Fuganti and co-workers,<sup>83,84,86</sup> Mukaiyama et al.,<sup>87</sup> and Deshong and Leginus<sup>90</sup> to prepare both 1 and 4; however, the reaction sequence required to convert 170 to 4 is quite different. The ethyl vinyl ether derivative 167b of ethyl (S)-lactate (167a) was reduced with LAH, and the alcohol product was oxidized with the Swern reagent<sup>84,151</sup> to produce the protected lactaldehyde 168. Treatment of 168 with acetone cyanohydrin and a catalytic amount of triethylamine gave the cyanohydrin 169. Reaction of 169 with cy-

SCHEME XXIX<sup>a</sup>

clohexanone dimethyl acetal and a catalytic amount of bis(trimethylsilyl) sulfate furnished a 45:55 mixture (94% yield) of the cyclohexylidene butanenitriles with the 2S,3S and 2R,3S (170) configurations. The isomers were separated by column chromatography and the desired nitrile 170 was condensed with the magnesium enolate of *tert*-butyl acetate<sup>152</sup> to give the unsaturated amino ester 171 as an 8:2 ratio of *Z* and *E* isomers (54% yield). Acetylation ( $\text{Ac}_2\text{O}$ , Py) of the vinylamine moiety in 171, followed by catalytic hydrogenation over rhodium ( $70\text{ kg/cm}^2$ ,  $55^\circ\text{C}$ , 24 h), gave the saturated ester 172 as the sole product in 12% overall yield from 167b. Acid hydrolysis of 172, benzoylation, and then lactonization with hydrochloric acid furnished 173. DIBAL reduction of the lactone moiety produced *N*-benzoylacosamine (174) in 9% overall yield.

## D. Actinosamine (L-arabino)

L-Actinosamine (6) is the *O*-methyl derivative of L-acosamine (4) and was isolated from the same antibiotic from which 4 was obtained.<sup>42,43</sup> The assigned structure was confirmed by Lee et al.,<sup>153</sup> who methylated L-acosamine (4) with silver oxide and methyl iodide.

## E. Angolosamine (D-arabino)

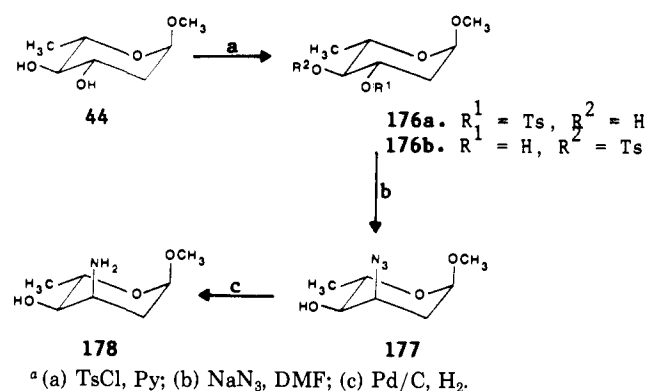
Angolosamine (7), the *N,N*-dimethyl derivative of D-acosamine (5), is one of three glycosidic components of the macrolide antibiotic angolomycin and also occurs as a C-glycoside residue in a number of anthra[1,2-*b*]pyran antibiotics.<sup>154</sup> The structure of 7 was originally determined from the similarity of its <sup>1</sup>H NMR spectrum to that of D-acosamine (5).<sup>155</sup>

The only reported preparation of angolosamine (7) was performed by Baer and Georges<sup>142</sup> in conjunction with their total synthesis of optically active D-acosamine derivative 166. As shown in Scheme XXIX, Eschweiler-Clarke methylation<sup>156</sup> ( $\text{CH}_2\text{O}$ ,  $\text{HCO}_2\text{H}$ , NaOH) of 166 furnished methyl angolosaminide (175).

## F. Ristosamine (L- and D-ribo)

L-Ristosamine (8) is a component of the water-soluble glycoprotein ristomycin,<sup>157,158</sup> which is a member of the vancomycin group of antibiotics.<sup>159</sup> Its structure was determined through chemical degradation and extensive <sup>1</sup>H NMR and <sup>13</sup>C NMR spectroscopy by Bogнар, Sztaricskai, and co-workers.<sup>160-165</sup> Some early confusion about the exact physical properties of ristosamine (8) was caused by the hygroscopic nature of the free sugar and its hydrochloride salt.

Synthetic interest in the *ribo* isomer was heightened by the finding of Arcamone et al.<sup>166</sup> that the coupling of L-ristosamine (8) with daunosmycinone produced an analogue with anticancer activity. Horton et al.<sup>167,168</sup> subsequently obtained similar results when D-ristosamine was used. There have been numerous preparations of both L- (8) and D-ristosamine (9) as well as those

SCHEME XXX<sup>a</sup>

accomplished in conjunction with the preparation of other hexoses.<sup>32,84,87,88,128-131,137,140</sup> (When ristosamine was used as an intermediate or was a byproduct, it is discussed as such in other sections.)

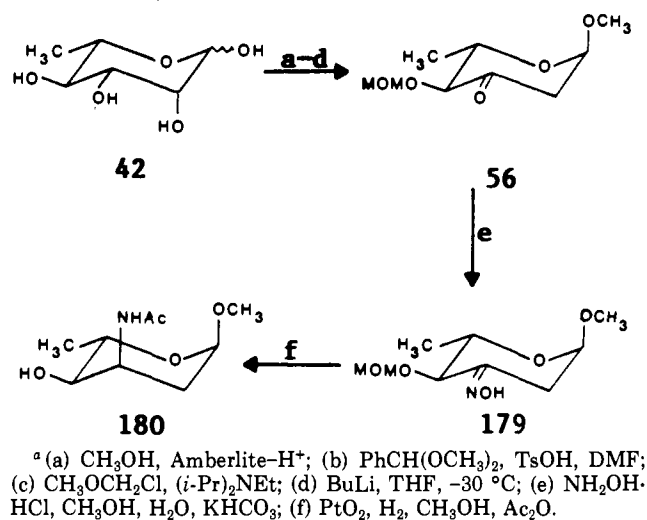
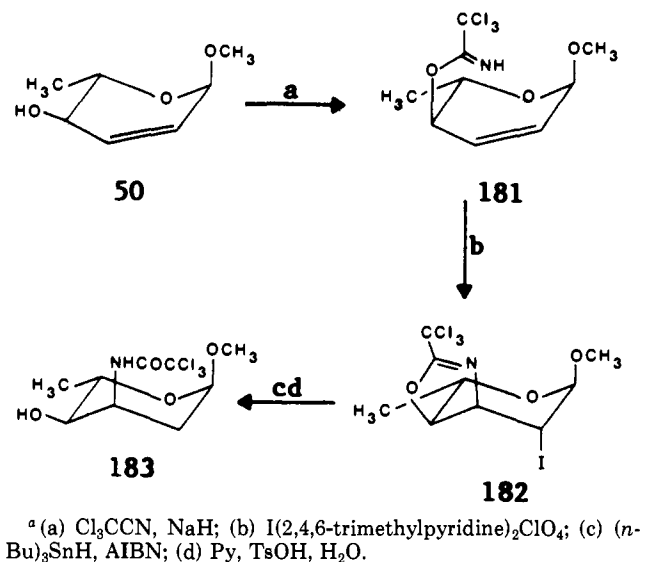
## 1. Chiral Syntheses from Carbohydrate Precursors

All but one of the reported chiral total syntheses of L-ristosamine (8) were accomplished from rhamnol (43). Shortly after elucidation of the structure of 8, Lee et al.<sup>153</sup> and Sztaricskai et al.<sup>169</sup> concurrently reported almost identical preparations from the diol pyranoside 44 that served as a key intermediate in the synthesis of daunosamine (1) reported by Marsh et al.<sup>39</sup> Sztaricskai et al.<sup>170,171</sup> subsequently reported the complete details of their work, which is outlined in Scheme XXX. Methoxymercuration (Hg(OAc)<sub>2</sub>, methanol) of L-rhamnol (43), followed by reductive cleavage of the organomercury intermediate with sodium borohydride, furnished the methyl pyranoside 44 (50% overall yield). Tosylation of 44 (TsCl, Py, 0 °C; 5 days) gave an inseparable 4:1 mixture of the 3-*O*- and 4-*O*-arabinomonotosylates 176a and 176b in 51% yield along with 5% of the ditosylate. After the mixture was reacted with sodium azide in dimethylformamide (DMF), the resultant *ribo* 3-azido compound 177 was isolated, purified by crystallization (36% yield), and then catalytically hydrogenated to methyl ristosaminide (178).

A higher yielding sequence (18%) to L-ristosamine (8) from L-rhamnol (43) was subsequently reported by Pelyvas et al.<sup>136</sup> The work paralleled that employed for the synthesis of D-acosamine (5)<sup>137</sup> and was presented in that section.

Brimacombe and co-workers<sup>56,172</sup> performed the total synthesis of L-ristosamine (8) shown in Scheme XXXI from the keto sugar 56 that they originally prepared from L-rhamnose (42) in conjunction with their preparation of daunosamine (1).<sup>55</sup> Reaction of 56 with aqueous hydroxylamine hydrochloride furnished the oxime derivative 179, which on catalytic reduction over Adams' catalyst in the presence of acetic anhydride gave methyl *N*-acetylristosaminide (180) in 62% yield (13% from 42).

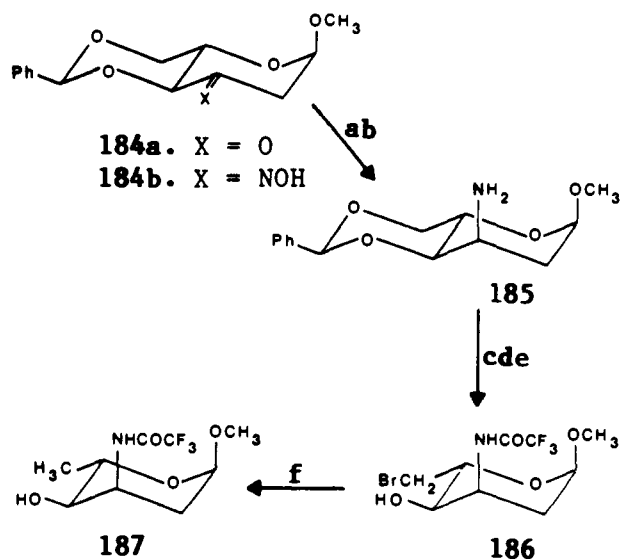
The shortest route to L-ristosamine (8) from rhamnol (43) was accomplished by Pauls and Fraser-Reid,<sup>173</sup> who used the reaction sequence shown in Scheme XXXII. The synthetic plan conceptually paralleled their preparation of daunosamine<sup>47</sup> in that the appended imidate functionality in 181, prepared from the alcohol 50, was employed to stereospecifically introduce the vicinal amino group. Halogenation of 181 with cyclization of

SCHEME XXXI<sup>a</sup>SCHEME XXXII<sup>a</sup>

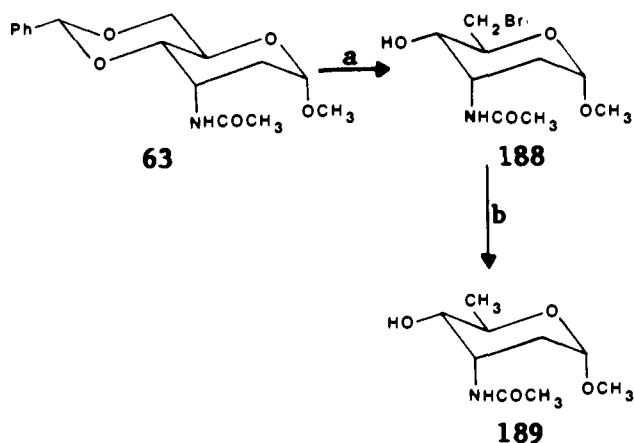
the neighboring imidate gave 182, which on dehalogenation with tri-*n*-butyltin hydride, furnished the methyl ristosaminide derivative 183. Subsequently, Bogini et al.<sup>174</sup> reported an almost identical preparation of this sugar.

The only synthesis of L-ristosamine (8) which did not originate with rhamnol was reported by Arcamone et al.<sup>166</sup> and is shown in Scheme XXXIII. The keto acetal starting material 184a was prepared according to the method of Williams et al.<sup>175</sup> and was obtained in 10% overall yield from L-arabinose in 10 steps. (With minor modification, this sequence is the same as that employed by Grethe et al.<sup>45</sup> in their synthesis of daunosamine (1), which was shown in Scheme IX.) The oxime derivative 184b was reduced with LAH to the amine 185. After the acetal functionality in 185 was hydrolyzed and the amine *N*-trifluoroacetylated, the product was reacted with triphenylphosphine and NBS.<sup>68,176</sup> The resultant 6-bromo compound 186 was catalytically reduced to methyl *N*-(trifluoroacetyl)-L-ristosaminide (187). No yields were reported.

The large number of chiral total syntheses of D-ristosamine (9) can be partially accounted for by its straightforward access from the large pool of D-hexoses. The first preparation of 9 was reported by Horton and

SCHEME XXXIII<sup>a</sup>

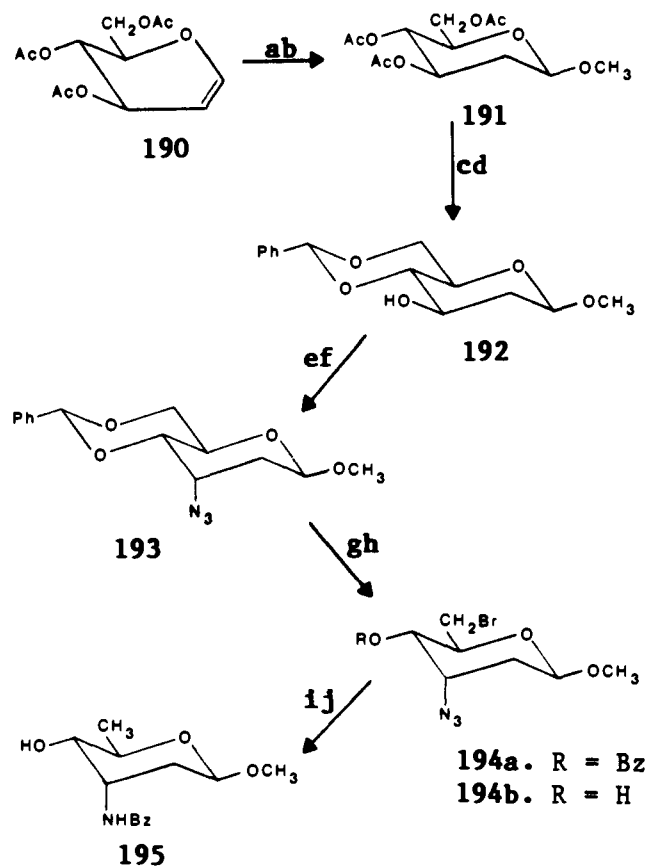
<sup>a</sup> (a) H<sub>2</sub>NOH·HCl, NaOH, EtOH; (b) LAH, Et<sub>2</sub>O; (c) H<sub>3</sub>O<sup>+</sup>; (d) TFAA, Py; (e) Ph<sub>3</sub>P, NBS, DMF; (f) catalytic hydrogenation.

SCHEME XXXIV<sup>a</sup>

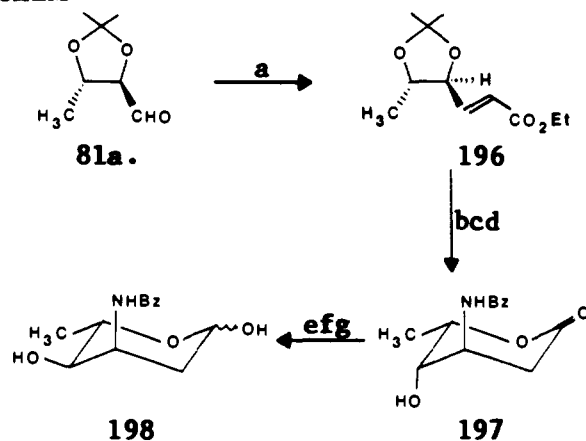
<sup>a</sup> (a) NBS, CCl<sub>4</sub>, BaCO<sub>3</sub>; (b) Ni(R), H<sub>2</sub>.

co-workers<sup>167,168</sup> and was derived directly from the sequence they employed for preparation of methyl daunosaminide hydrochloride (49)<sup>58</sup> from methyl mannoside (60) (Scheme XXXIV). The amide 63 with the *ribo* configuration was prepared as previously discussed and shown in Scheme VI. Fragmentation of the 4,6-*O*-benzylidene moiety through treatment with NBS and barium carbonate<sup>68</sup> gave the 6-bromo-4-benzoate product 188, which on catalytic reduction (H<sub>2</sub>, Raney Ni) furnished methyl *N*-acetyl-D-ristosaminide (189) in 49% overall yield from 60.

Both Pelyvas et al.<sup>177,178</sup> and Baer et al.<sup>179</sup> reported virtually identical sequences to D-ristosamine (9) from triacetyl-D-glucal (190) (Scheme XXXV). Treatment of 190<sup>48,49</sup> with dry hydrogen chloride, followed by silver carbonate induced methanolysis of the 1-chloro intermediate, gave the methyl glycoside 191. Basic hydrolysis of the acetoxy functionality in 191 and then selective protection of the 4,6-hydroxyl groups as the benzylidene derivative produced 192 in 42% yield from 190. After the 3-hydroxyl group in 192 was mesylated and displaced with sodium azide in hexamethylphosphoric triamide, the 3-azido pyranoside 193 was treated with NBS and barium carbonate,<sup>68</sup> the 4-benzoate functionality in the resultant 194a was se-

SCHEME XXXV<sup>a</sup>

<sup>a</sup> (a) HCl, PhH; (b) Ag<sub>2</sub>CO<sub>3</sub>, CH<sub>3</sub>OH; (c) NaOCH<sub>3</sub>; (d) PhCHO, ZnCl<sub>2</sub>; (e) MsCl, Py; (f) NaN<sub>3</sub>, HMPPT, 100 °C; (g) NBS, BaCO<sub>3</sub>, CCl<sub>4</sub>; (h) NaOCH<sub>3</sub>; (i) Ni(R), H<sub>2</sub>, CH<sub>3</sub>OH, Et<sub>3</sub>N; (j) PhCOCl, Py.

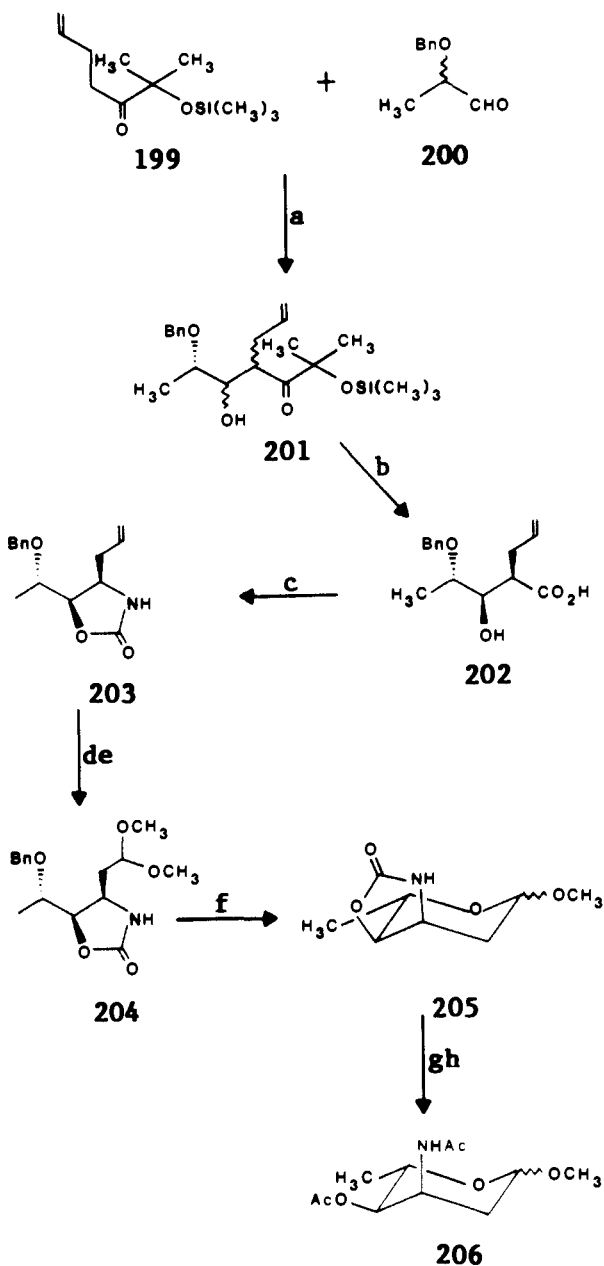
SCHEME XXXVI<sup>a</sup>

<sup>a</sup> (a) Ph<sub>3</sub>P=CHCO<sub>2</sub>Et; (b) NH<sub>3</sub>, CH<sub>3</sub>OH; (c) HCl, EtOH; (d) NaOH, PhCOCl; (e) MsCl, Py; (f) NaOAc; (g) DIBAL, THF, -40 °C.

lectively cleaved with sodium methoxide to furnish 194b. Reduction of the azide group in 194b to an amine and reductive replacement of the 6-bromine were simultaneously accomplished through hydrogenation with Raney nickel.<sup>179</sup> Benzoylation of the reduction product furnished methyl *N*-benzoyl-D-ristosaminide (195) in 13% overall yield.

## 2. Chiral Syntheses from Non-Carbohydrate Precursors

The only chiral total synthesis of L-ristosamine (8) from noncarbohydrate precursors was reported by

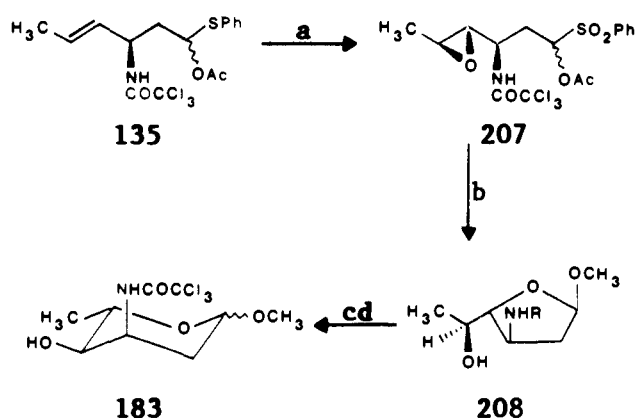
SCHEME XXXVII<sup>a</sup>

<sup>a</sup> (a) LDA, THF; (b) HIO<sub>4</sub>, THF; (c) diphenylphosphorazidate, Et<sub>3</sub>N; (d) OsO<sub>4</sub>, NaIO<sub>4</sub>; (e) CH<sub>3</sub>OH, HCl; (f) Catalytic hydrogenation; (g) Ba(OH)<sub>2</sub>; (h) HCl-H<sub>2</sub>O.

Fronza et al.<sup>86</sup> and is shown in Scheme XXXVI. As in their previously described work,<sup>18,81</sup> the aldehyde acetonide 81a with the 2*R*,3*S* configuration was first converted to the unsaturated ester 196 through Wittig reaction. Conjugate addition of ammonia,<sup>88</sup> acidic hydrolysis of the acetonide, and benzylation gave predominantly the  $\delta$ -lactone 197 with the *L*-xylo configuration. To convert 197 to the *L*-ribo configuration, the C-4 hydroxyl group was mesylated and then displaced with acetate. DIBAL reduction of the lactone functionality furnished *N*-benzoyl-*L*-ristosamine (198).

### 3. Racemic Syntheses

In conjunction with their development of elegant methods for diastereoselective aldol condensation, Heathcock and Montgomery<sup>180</sup> described the stereoselective total synthesis of racemic ristosamine which is shown in Scheme XXXVII. The enolate of the ketone

SCHEME XXXVIII<sup>a</sup>

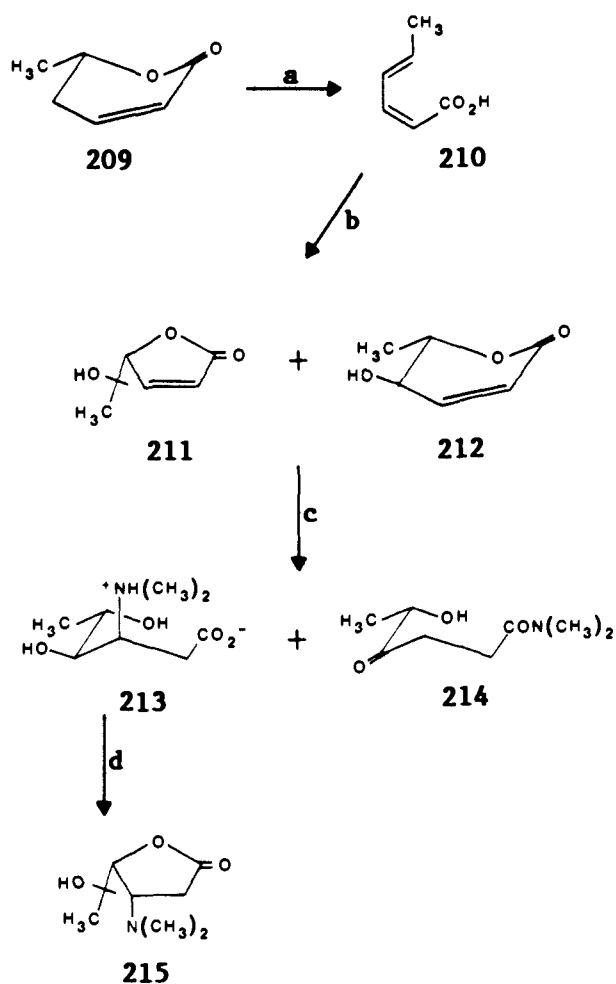
<sup>a</sup> (a) MCPBA, CH<sub>2</sub>Cl<sub>2</sub>; (b) NaOCH<sub>3</sub>, CH<sub>3</sub>OH; (c) HOAc-H<sub>2</sub>O; (d) CH<sub>3</sub>OH, HCl.

199,<sup>181</sup> generated with lithium diisopropylamide (LDA), was reacted with racemic 2-(benzyloxy)propionaldehyde (200) to produce a 78:22 mixture (97% yield) of the diastereoisomers 201; in order to obtain this ratio, it was necessary to use 2 equiv of the ketone 199 for each one of the aldehyde 200. Their finding that the desired diastereoisomer of 201 reacted 2.5 times faster with periodic acid<sup>182</sup> than the undesired isomer was elegantly exploited to enhance the proportion of the acid product 202 (96% yield). After chromatographic separation of the isomers, modified Curtius degradation<sup>183</sup> of 202 produced the oxazolidone 203 in 69% yield. Lemieux-Johnson oxidative cleavage<sup>184</sup> (OsO<sub>4</sub>, NaIO<sub>4</sub>) of the olefinic entity in 203 to an aldehyde and then treatment with acidic methanol furnished the dimethyl acetal 204 (87% yield). Cleavage of the benzyl ether group by hydrogenolysis afforded a 68:32 equilibrium mixture of  $\alpha$  and  $\beta$  anomers which was hydrolyzed with barium hydroxide to the oxazolidine 205. Acid hydrolysis furnished methyl *N*,*O*-diacetylristosaminide (206) in 33% overall yield.

Hauser et al.<sup>116</sup> achieved a stereospecific synthesis of racemic ristosamine from the acetoxy sulfide 135, which also served as an intermediate to daunosamine. As shown in Scheme XXXVIII, epoxidation of 135 with 3 equiv of *m*-chloroperbenzoic acid gave the epoxy-acetoxy sulfone 207 in quantitative yield. Conversion of 207 to the methyl furanoside of *N*-trichloroacetylristosaminide (208) was accomplished in a single pot by cleaving the acetoxy sulfone moiety in 208 with sodium methoxide. The resultant aldehyde intermediate underwent a second addition of methoxide generating a hemiacetoxime that intramolecularly cyclized through nucleophilic ring opening of the epoxide at C-4. Subsequent methanolysis furnished D,L-183. This synthesis of racemic ristosamine was accomplished in 74% overall yield and is the highest yield route reported for the racemate.

### G. Megosamine (*L*-ribo)

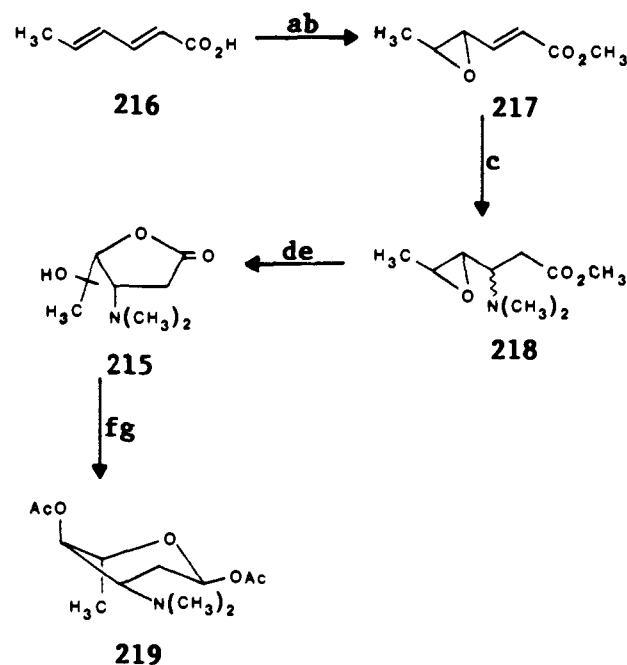
Megosamine (10), the *N,N*-dimethylamino derivative of *L*-ristosamine (8), was isolated from the macrolide antibiotics meglamycins and was originally assigned as D-rhosamine (D-lyxo) by Mallams<sup>185,186</sup> and Nourse and Roberts.<sup>187</sup> When it was later shown by X-ray crystallography to have the *L*-ribo configuration, it was renamed megosamine.<sup>186</sup>

SCHEME XXXIX<sup>a</sup>

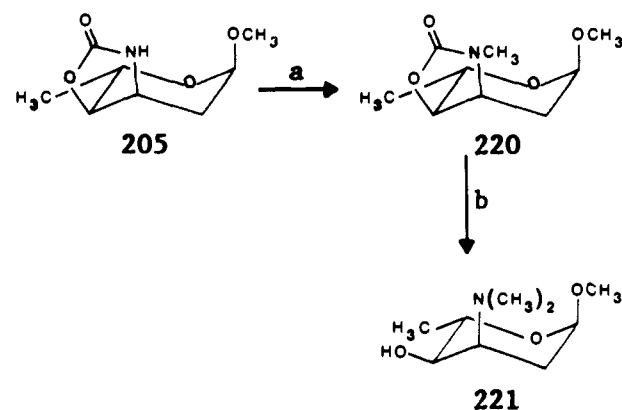
<sup>a</sup> (a) NaOCH<sub>3</sub>; (b) MCPBA, CH<sub>2</sub>Cl<sub>2</sub>; (c) (CH<sub>3</sub>)<sub>2</sub>NH, H<sub>2</sub>O, 2 weeks; (d) HCl-H<sub>2</sub>O.

All of the total syntheses of 10 have been racemic and have been initiated from non-carbohydrate derived materials. Jensen and Torssell<sup>188</sup> reported the preparation of the  $\gamma$ -lactone 211 shown in Scheme XXXIX as an intermediate to 10, but were unable to effect its further transformation to the desired hexose product. Parasorbic acid (209) was treated with a cold solution of sodium methoxide to give a 75% yield of *cis,trans*-sorbic acid<sup>189</sup> (210) along with an 8% yield of methyl sorbate. Reaction of 210 with *m*-chloroperbenzoic acid (0 °C, 4 days) resulted in a 3:1 mixture (90% yield) of the desired  $\gamma$ - and undesired  $\delta$ -Osrunonda lactones 211 and 212, respectively. Direct reaction of the mixture with aqueous dimethylamine gave the acid 213 and the keto amide 214 in a 1.1:1 ratio (77% yield). The acid 213 was readily separated from the amide 214 through bicarbonate extraction, then treated with dilute hydrochloric acid to effect cyclization to the lactone 215. DIBAL reduction of 215 to 10 under a variety of conditions was unsuccessful, resulting in either recovery of the lactone starting material, the tetrahydrofuran product, or the  $\alpha,\beta$ -elimination product 211.

Dyong and Bendlin<sup>190</sup> successfully carried out DIBAL reduction of the lactone intermediate 215 in their total synthesis of racemic 10, which is shown in Scheme XL. Their preparation of 215 was initiated from (*E,E*)-sorbic acid (216). The 3,4-olefinic entity in 216 was selectively epoxidized with buffered peracetic acid<sup>191</sup> and the resultant epoxyacid intermediate was esterified, furnish-

SCHEME XL<sup>a</sup>

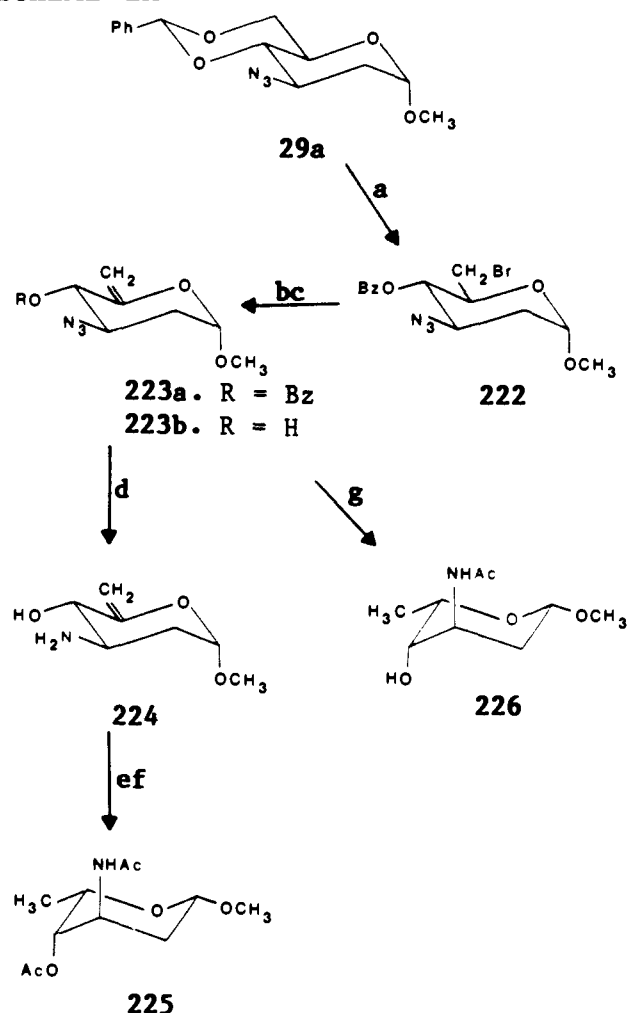
<sup>a</sup> (a) HOOAc, NaOAc, CHCl<sub>3</sub>; (b) CH<sub>2</sub>N<sub>2</sub>; (c) (CH<sub>3</sub>)<sub>2</sub>NH; (d) NaOH; (e) HCl-H<sub>2</sub>O; (f) DIBAL; (g) Ac<sub>2</sub>O, Py.

SCHEME XLI<sup>a</sup>

<sup>a</sup> (a) KH, CH<sub>3</sub>I; (b) LAH.

ing the methyl ester 217. Conjugate addition of dimethylamine (-10 °C) to the olefinic moiety in 217 produced an inseparable 3.4:1 mixture of the *lyxo*- and *xylo*-hexonates 218 in 92% yield. The mixture was successively treated with sodium hydroxide and hydrochloric acid to form the  $\gamma$ -lactones from which the *ribo* isomer 215 was isolated in 75% yield through crystallization. DIBAL reduction of the lactone 215 produced the unstable sugar, which was then acetylated to diacetyl megosamine (219) in 29% overall yield. <sup>1</sup>H NMR studies of 219 showed that this sugar prefers the <sup>4</sup>C<sub>1</sub> conformation in which the bulky dimethylamino moiety is equatorial.

Heathcock and Montgomery<sup>180</sup> used the  $\alpha$ -anomer of 205, which was a key intermediate in their synthesis of ristosamine (Scheme XXXVII), as a precursor to racemic megosamine 10 as shown in Scheme XLI. Alkylation of 205 with potassium hydride and methyl iodide furnished 220 (85% yield), which was reduced with LAH to give a 7:3 mixture of  $\alpha$ - and  $\beta$ -anomers of methyl megosaminide (221).

SCHEME XLII<sup>a</sup>

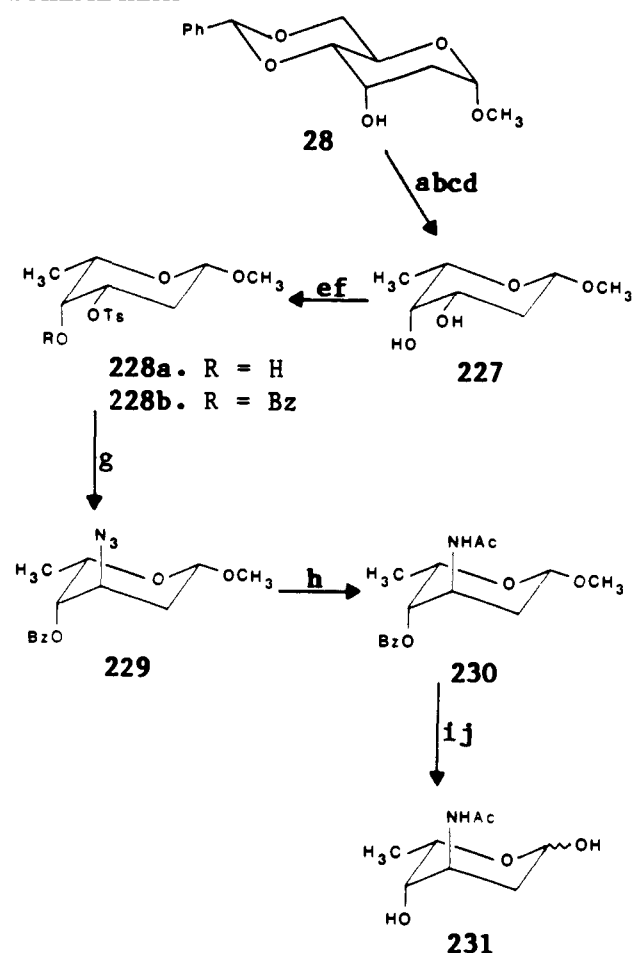
<sup>a</sup> (a) NBS, BaCO<sub>3</sub>, CCl<sub>4</sub>; (b) AgF, Py; (c) NaOH, CH<sub>3</sub>OH, H<sub>2</sub>O; (d) LAH; (e) Pd, H<sub>2</sub>, TsOH; (f) Ac<sub>2</sub>O, Py; (g) Ni(R), H<sub>2</sub>, EtOH.

H. 3-*epi*-Daunosamine (L- and D-*xylo*)

The L- and D-aminohexoses with the *xylo* configuration (11 and 12) are the C-3 epimers of L- and D-daunosamine (1 and 2) and often have been referred to as 3-*epi*-daunosamine. They are not naturally occurring isomers, and most usually, have been prepared as minor products in conjunction with the synthesis of one of the other sugars.<sup>82-84,86,94,97,98,105-107,116,150,151,170,171</sup> Of the five total syntheses in which D- or L-3-*epi*-daunosamine (11 or 12) was the primary objective, four were chiral and three used methyl D-glucoside (26) as a starting material.

## 1. Chiral Syntheses from Carbohydrate Precursors

The first total syntheses of L-3-*epi*-daunosamine (11) were reported by Cheung et al.<sup>126</sup> and Boivin et al.<sup>32</sup> The initial steps in these sequences, shown in Scheme XLII, were identical. The starting material for both was the 4,6-*O*-benzylidene-3-azido-hexose 29a, which was prepared in six steps from  $\alpha$ -D-glucopyranoside (26) as discussed in the D-daunosamine<sup>26-28,71,73</sup> and D-acosamine<sup>141</sup> sections (Schemes I and XXVI). The 6-bromo derivative 222, formed by treatment of 29a with NBS and barium carbonate,<sup>68</sup> was dehydrohalogenated with silver fluoride in pyridine<sup>192</sup> to give the 5,6-unsaturated enopyranoside 223a. The benzoate ester in 223a was

SCHEME XLIII<sup>a</sup>

<sup>a</sup> (a) PhCOCl, Py; (b) NBS, BaCO<sub>3</sub>, CCl<sub>4</sub>; (c) Ni(R), H<sub>2</sub>, Et<sub>3</sub>N; (d) NaOCH<sub>3</sub>; (e) TsCl, Py; (f) PhCOCl, Py; (g) NaN<sub>3</sub>, Me<sub>2</sub>SO; (h) Pd/C, H<sub>2</sub>, HOAc; (i) NaOCH<sub>3</sub>; (j) HOAc, H<sub>2</sub>O.

removed by catalytic transesterification (NaOH, MeOH) to furnish the glycoside 223b.

At this stage, different reaction sequences were employed to complete the respective syntheses. Cheung et al.<sup>126</sup> reduced the azido entity in 223b to the amine 224 with LAH. Subsequent catalytic hydrogenation (Pd, H<sub>2</sub>, TsOH) of the olefinic entity, followed by acetylation, produced the *N,O*-diacetyl derivative 225 (44% yield from 29a) and the D-*arabino* isomer in an 18:1 ratio. In the sequence used by Boivin et al.,<sup>32</sup> catalytic hydrogenation with Raney nickel simultaneously reduced the azide and olefinic moieties in 223b to provide the unprotected *xylo*-hexose 226 in 57% overall yield from 29a.

Cheung et al.<sup>193</sup> reported another synthesis of 11 (Scheme XLIII) in which the *N*-acetyl derivative was prepared from the deoxyhexose 28 in 10 steps (10% overall yield). Benzoylation of the 3-hydroxyl group in 28, followed by cleavage of the 4,6-*O*-benzylidene entity with NBS,<sup>68</sup> gave the 6-bromo derivative. Catalytic hydrogenation (Raney Ni) effected reductive replacement of the 6-bromo functionality, and subsequent removal of the benzoate groups through treatment with sodium methoxide furnished 227 in 46% overall yield.<sup>194</sup> Selective tosylation of the equatorial 3-hydroxyl group in 227 and benzoylation gave 228b. Azide displacement of the tosyl group produced the azido intermediate 229, which was reduced (Pd/C, H<sub>2</sub>) and acetylated to the *N*-acetyl-*O*-benzoyl product 230. Debenzylation of 223

with sodium methoxide and then acid hydrolysis gave the *N*-acetyl *xylo* product **231**.

## 2. Chiral Syntheses from Achiral Precursors

Fronza et al.<sup>18,85</sup> reported a chiral synthesis for both the *L*- and *D*-*xylo*-pyranoses **11** and **12** from achiral precursors. For the synthesis of *L*-3-*epi*-daunosamine (**11**), the starting material was the (2*R*,3*S*)-aldehyde **81a**, which was prepared from natural tartaric acid.<sup>195</sup> This preparation paralleled their work that used the (2*R*,3*S*)-aldehyde **81a** was used for the synthesis of daunosamine (**1**) and was shown in Schemes X and XXXVI.<sup>81</sup>

The same sequence was used to prepare the *D*-*xylo*-hexose (**12**) in approximately the same overall yield (1%). The 2*S*,3*R*-aldehyde employed in this route was prepared from *L*-threonine in 45% yield.<sup>85,196</sup>

## 3. Racemic Syntheses

In their racemic synthesis of *xylo*-hexoses (**11** and **12**), Dyong and Wiemann<sup>197</sup> reported a route analogous to that used in their racemic and chiral syntheses of *L*-daunosamine (**1**)<sup>97-99</sup> shown in Scheme XVII. The *xylo* isomer, which was a minor product in the *cis* hydroxylation of the tosylamide **111b**, was carried through the same reaction sequence to obtain racemic 3-*epi*-daunosamine in 28% overall yield.

## V. 2,3,6-Trideoxy-3-C-methyl-3-aminohexopyranoses

### A. Vancosamine (*L*- and *D*-*lyxo*)

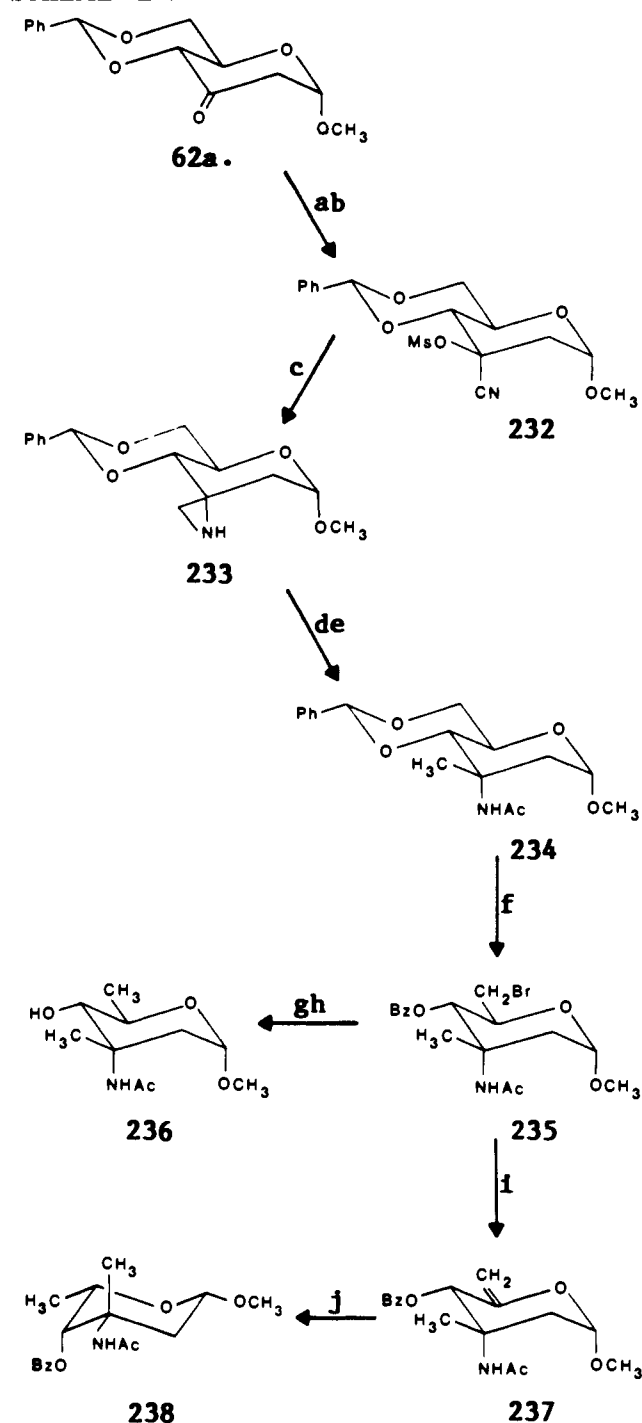
Vancosamine (**13**), the C-3 methyl analogue of daunosamine (**1**), was isolated by McCormick et al.<sup>198</sup> in 1956 following methanolysis of the parent antibiotic, vancomycin.<sup>199-202</sup> A variety of spectroscopic techniques, including high-resolution mass spectroscopy, NMR, and circular dichroism, were employed to elucidate the structure. Vancosamine, in the form of its *N,N*-dimethyl derivative (**15**), is also found as a C-sugar residue in the anthra[1,2-*b*]pyran antibiotics, kidamycin,<sup>203</sup> pluramycin A,<sup>204</sup> and hedamycin.<sup>205</sup>

Numerous syntheses of derivatives of vancosamine (**13** and **14**) have been performed from both carbohydrate and non-carbohydrate starting materials; while several are elegantly conceived, few provide a high yield route. A commonly employed strategy to this amino sugar from other sugar precursors has been to introduce the methyl and amino groups at C-3 by the method of Bourgeois,<sup>206-208</sup> which involves cyanomesylation of a hexose-3-ulose, reduction of the cyanomesylate to a spiroaziridine, and then hydrogenolysis of the aziridine ring.

Another frequently used synthetic approach from hexose precursors has been to construct the requisite branching at C-3 through base catalyzed aldol condensation of nitroethane with dialdehydes produced from partial oxidative degradation of methyl glycosides.<sup>145,146</sup> This methodology has also been established as a general procedure for preparing nitro sugars.

The several optically active and racemic total syntheses from non-carbohydrate precursors have paralleled earlier preparations of the configurationally related daunosamine (**1**). In part, these syntheses were

### SCHEME XLIV<sup>a</sup>

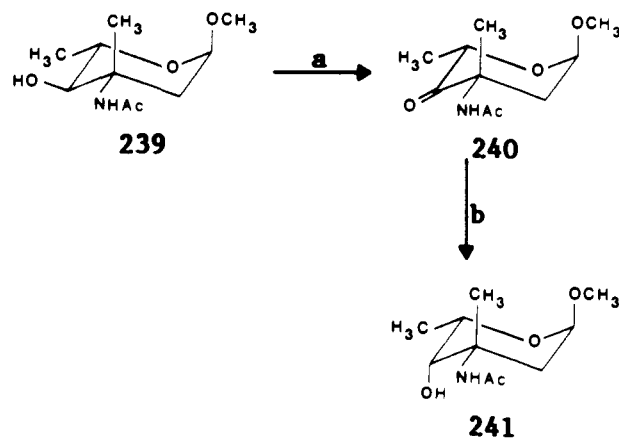


<sup>a</sup> (a) KCN, CH<sub>2</sub>Cl<sub>2</sub>, NaHCO<sub>3</sub>, H<sub>2</sub>O; (b) MsCl, Py; (c) LAH; (d) Ni(R), H<sub>2</sub>; (e) Ac<sub>2</sub>O, Py; (f) NBS, BaCO<sub>3</sub>, CCl<sub>4</sub>; (g) Catalytic hydrogenation; (h) base hydrolysis; (i) AgF, DBU; (j) Ni(R), H<sub>2</sub>.

performed to establish the generality of the earlier routes.

### 1. Chiral Syntheses from Carbohydrate Precursors

In the first reported total synthesis of *L*-vancosamine (**13**), Thang et al.<sup>209</sup> used the method of Bourgeois<sup>206-208</sup> to introduce the amino-methyl branching at C-3 (Scheme XLIV). The starting material, hexulose **62a**, was prepared from either methyl glucoside (**26**)<sup>70</sup> or methyl mannose (**60**).<sup>58</sup> Addition of alkaline potassium cyanide<sup>206</sup> to **62a** under thermodynamic conditions, followed by mesylation of the cyanohydrin intermediate, furnished the *arabino*-benzylidene **232** in

SCHEME XLV<sup>a</sup>

<sup>a</sup> (a) PCC, CH<sub>2</sub>Cl<sub>2</sub>, molecular sieves; (b) L-Selectride, THF, -15 °C.

76% yield. Reduction of the cyano moiety with LAH resulted in configurational inversion at C-3<sup>210</sup> and directly produced the spiroaziridine 233.<sup>211</sup> (The C-4 epimer of 233 was also synthesized to aid in structural and stereochemical assignments.<sup>211</sup>) The aziridine ring in 233 was hydrogenolyzed (Raney nickel, H<sub>2</sub>), and the resultant amino-methyl product was acetylated to give 234, which was treated with NBS and barium carbonate<sup>68</sup> to cleave the benzylidene group. Catalytic hydrogenation of the 6-bromo derivative 235, followed by basic hydrolysis, furnished the *D*-ribo-hexose 236 in 39% overall yield from 62a.

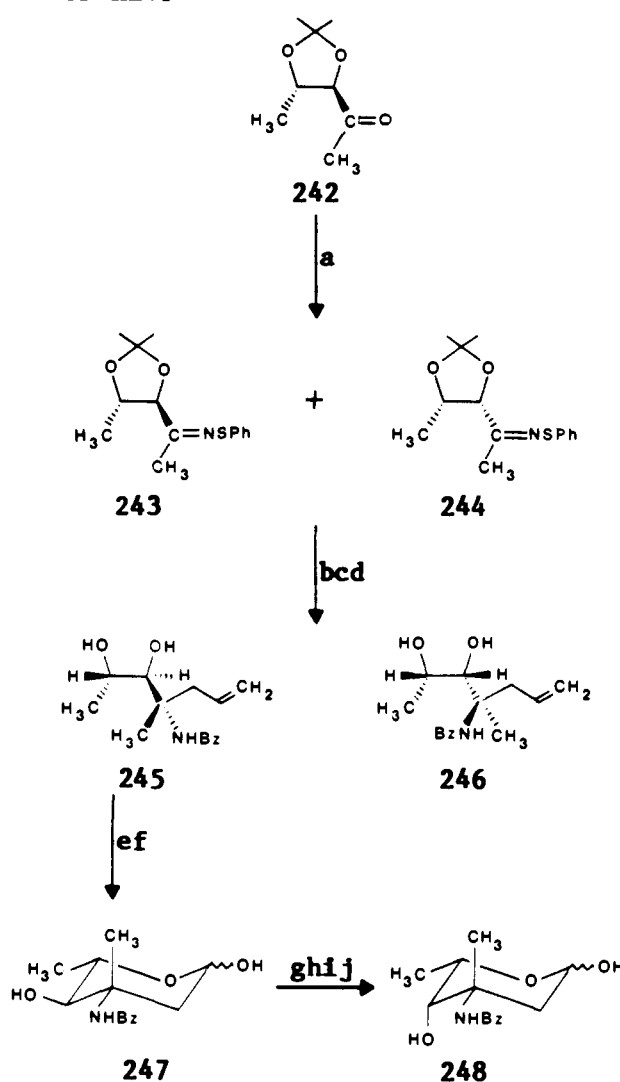
In the same study, the 6-bromo compound 235 was used to prepare a derivative of *L*-vancosamine (13). Dehydrohalogenation (AgF, DBU)<sup>58</sup> of 235 gave 237 in 95% yield, and subsequent hydrogenation of the olefinic moiety with Raney nickel produced methyl *N*-acetyl-*O*-benzoylvancosaminide (238) and the *D*-ribo isomer 236 in 78% and 8% yield, respectively.

Using the precedent established for the preparation of daunosamine (1) through C-4 inversion of acosamine (4), Ahmad et al.<sup>212</sup> similarly inverted the configuration of C-4 in 4-*epi*-vancosamine (239)<sup>213</sup> to obtain methyl *N*-acetylvancosaminide (241) (Scheme XLV). The oxidation of 239 proved sensitive to the choice of oxidizing agents; ruthenium tetroxide gave only a 45% yield, whereas pyridinium chlorochromate<sup>214,215</sup> produced the 4-hexulose 240 in 66% yield. Reduction of the ketone moiety with L-Selectride (-15 °C) furnished methyl *N*-acetylvancosaminide (241) and the arabino starting material 239 as a 6.6:1 mixture that was chromatographically separated.

## 2. Chiral Syntheses from Non-Carbohydrate Precursors

Fronza and co-workers<sup>19,216</sup> reported the total synthesis of three configurational isomers from non-carbohydrate starting materials as shown in Scheme XLVI. The preparations paralleled their earlier work<sup>84</sup> on daunosamine (1), and the reaction sequences are virtually identical. The *xylo*- and *arabino*-hexoses were prepared directly, and vancosamine (13) was obtained through C-4 epimerization of the arabino isomer.

The (2*R*,3*S*)-ketone 242, the methyl ketone analogue of the aldehyde 81a, was prepared in 18% overall yield by reaction of  $\alpha$ -methylcinnamaldehyde, acetaldehyde, and baker's yeast with subsequent protection of the diol

SCHEME XLVI<sup>a</sup>

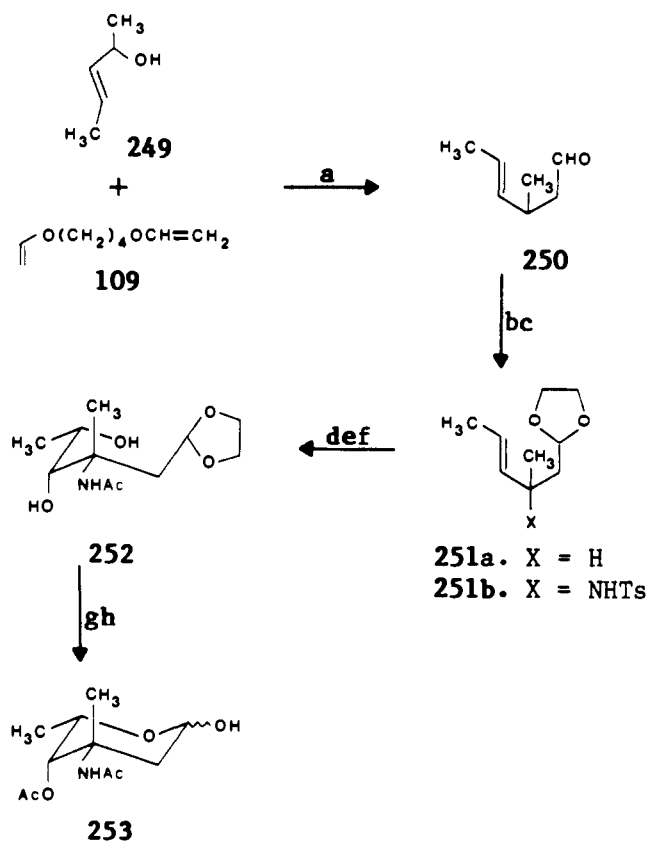
<sup>a</sup> (a) NH<sub>3</sub>, CH<sub>3</sub>OH, PhSSPh, AgNO<sub>3</sub>; (b) CH<sub>2</sub>=CHCH<sub>2</sub>MgBr, THF, -78 °C; (c) HCl; (d) PhCOCl, K<sub>2</sub>CO<sub>3</sub>; (e) O<sub>3</sub>, CH<sub>3</sub>OH, -20 °C; (f) (CH<sub>3</sub>)<sub>2</sub>S; (g) CH<sub>3</sub>OH, HCl; (h) MsCl, Et<sub>3</sub>N; (i) NaOAc; (j) HCl.

entity as an acetonide.<sup>82</sup> Treatment of 242 with ammonia, diphenyl disulfide, and silver nitrate resulted in an inseparable mixture of *erythro*- (243) and *threo*- (244) sulfinimines (65% yield). Formation of the *threo* isomer 244 was attributed to  $\alpha$ -epimerization, which resulted from the basic reaction conditions. Addition of allylmagnesium bromide<sup>83</sup> to the imine entity in 243 and 244, followed by sequential acidic hydrolysis and benzoylation, gave a 7:3 ratio of 245 and 246 in 50% yield. After the isomer 245 was chromatographically separated, the terminal olefinic moiety was ozonized with reductive workup to furnish the *N*-benzoyl-*arabino*-hexose 247 in 80% yield (13% from 242). The *xylo*-hexose was prepared in 85% yield by treating 246 analogously to 245. C-4 inversion of the *arabino* isomer 247 through mesylation, displacement with sodium acetate, and acidic hydrolysis produced *N*-benzoylvancosamine (248). Attempted preparation of the *ribo* isomer through C-4 epimerization of the *xylo*-hexose was unsuccessful due to the instability and decomposition of the mesylate intermediate.

## 3. Racemic Syntheses

Two racemic syntheses of vancosamine (13 and 14) from asymmetric starting materials have been reported.

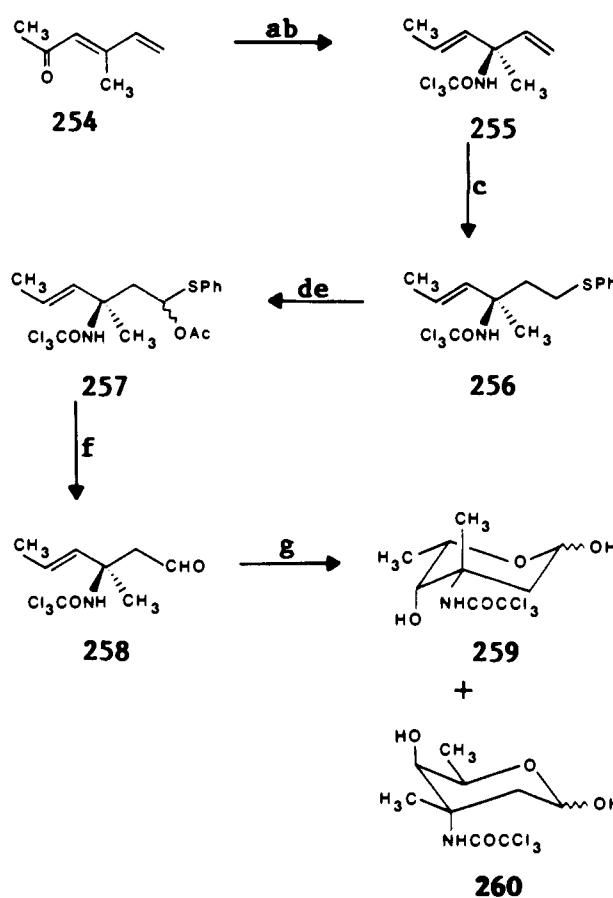


SCHEME XLVII<sup>a</sup>

<sup>a</sup> (a)  $Hg(OAc)_2$ ; (b) TsOH,  $HOCH_2CH_2OH$ ; (c) Se, Chloramine T; (d) Na,  $NH_3$ ; (e)  $Ac_2O$ , Py; (f)  $OsO_4$ , NMO; (g) HCl; (h)  $Ac_2O$ , Py.

Using a reaction sequence that paralleled their earlier work<sup>97-99</sup> on daunosamine (1), Dyong and co-workers<sup>21,217</sup> prepared racemic vancosamine in 2% overall yield. As shown in Scheme XLVII, mercuric acetate catalyzed reaction of **249** with **109**, followed by Claisen rearrangement of the allyl vinyl ether intermediate, gave the aldehyde **250**, which was converted ( $HOCH_2CH_2OH$ , TsOH) to the acetal derivative **251a**. In contrast to the result obtained with the nor-methyl analogue **111b** used in the daunosamine preparation,<sup>97,99</sup> the regiochemical outcome for the introduction of the 3-amino functionality through allylic amination of the olefinic entity in **251a** (selenium and Chloramine-T)<sup>101</sup> was reversed. The terminal 6-tosylamino regioisomer was the major product (44% yield), and the desired allyl tosylamide **251b** was obtained in only 22% yield. Reductive detosylation of **251b** (Na,  $NH_3$ ), acetylation ( $Ac_2O$ , Py) of the amine intermediate, and then osmium tetroxide<sup>102</sup> catalyzed cis hydroxylation gave a mixture of the *lyxo* (**252**) and *xylo* diols in 78% yield. Acid hydrolysis of the acetal in **252**, followed by peracetylation and chromatographic separation, furnished *N,O*-diacetylvancosamine (**253**) in 15% yield (2% overall).

Hauser et al.<sup>116</sup> successfully extrapolated their earlier work on daunosamine to achieve a brief preparation of a derivative of racemic vancosamine from acyclic precursors (Scheme XLVIII). Reduction (LAH) of the dienone **254**<sup>218</sup> to the diol, followed by Overman reaction<sup>53</sup> ( $Cl_3CCN$ , NaH; xylene, reflux), furnished the deconjugated trichloroacetamide **255** in 85% yield. Free radical addition of benzenethiol (AIBN, 80–90 °C)<sup>117</sup> to **255** regioselectively gave the terminal sulfide **256**

SCHEME XLVIII<sup>a</sup>

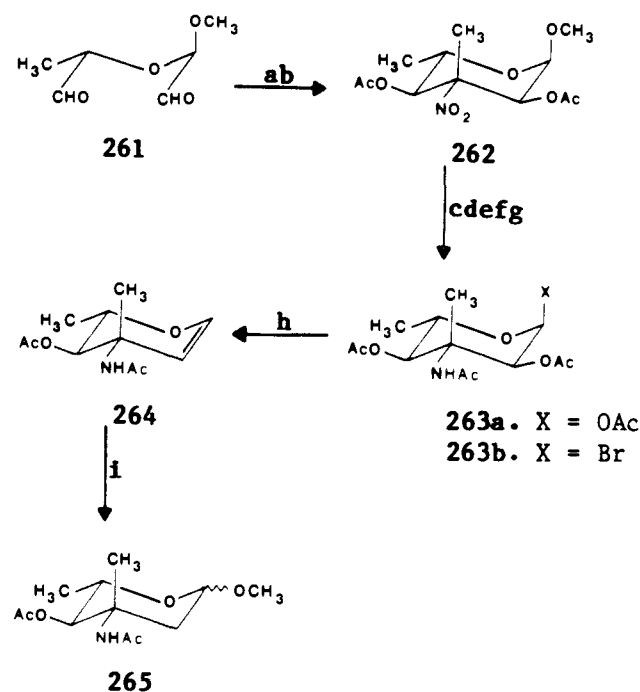
<sup>a</sup> (a) LAH,  $Et_2O$ ; (b) NaH,  $Cl_3CCN$ , xylene; (c) AIBN, PhSH; (d)  $NaIO_4$ ,  $CH_3OH$ ; (e) TFAA,  $Ac_2O$ , Lutidine; (f)  $CuCl_2$ ,  $CH_3CN-H_2O$ ; (g) catalytic  $OsO_4$ , TMNO, acetone,  $H_2O$ .

(73% yield) with the latent functionalization needed for subsequent transformation of C-1 to an aldehyde functionality. Oxidation of the sulfide entity in **256** to a sulfoxide ( $NaIO_4$ , MeOH),<sup>118</sup> Pummerer rearrangement ( $(F_3CCO)_2O$ ,  $Ac_2O$ , lutidine)<sup>119</sup> to the acetoxy sulfide **257**, and then hydrolysis ( $CuCl_2$ ,  $H_2O$ ,  $CH_3CN$ )<sup>120</sup> produced the aldehyde **258**. Osmium tetroxide catalyzed cis hydroxylation of the olefinic entity in **258** gave a 3:7 ratio of the *xylo* isomer **260** and *N*-(trichloroacetyl)vancosamine (**259**). The overall yield of vancosamine was 37%.

B. 4-*epi*-Vancosamine (L- and D-*arabino*)

4-*epi*-Vancosamine (**16**) is the 3-*C*-methyl sugar with the *arabino* configuration, and although it has not been isolated from natural sources, a number of preparations have been reported. Some of these syntheses were accomplished in conjunction with that of vancosamine (**13**)<sup>19,212,216</sup> and were discussed in the previous section. All of the total syntheses have been initiated from carbohydrate starting materials.

Brimacombe and co-workers<sup>213,214</sup> reported a synthesis of L-4-*epi*-vancosamine (**16**) (Scheme XLIX) in which the dialdehyde **261**, obtained by oxidation of rhamnose (**42**) with sodium metaperiodate,<sup>145,146</sup> was condensed with basic nitroethane<sup>219</sup> to produce the nitrohexose **262** in 12% yield. In the preferred route, the methyl glycoside moiety in **262** was hydrolyzed with dilute hydrochloric acid, and the free nitro sugar was peracetylated to the triacetate derivative. Catalytic re-

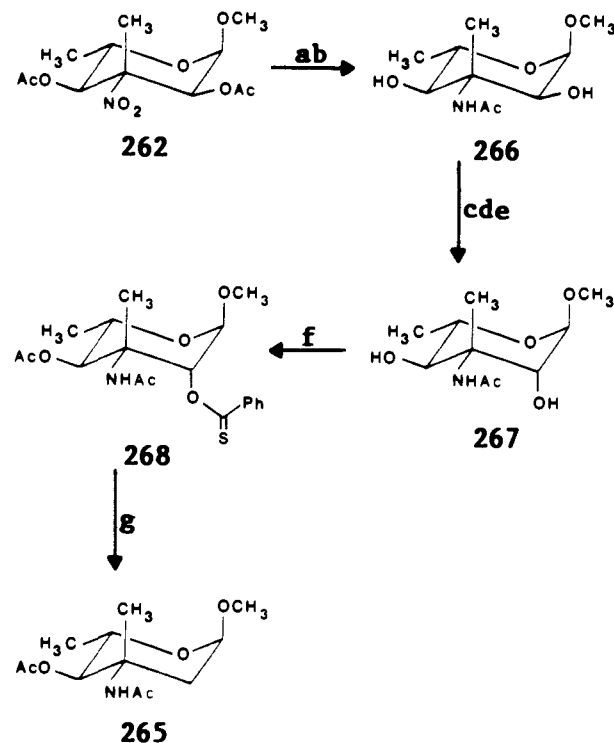
SCHEME XLIX<sup>a</sup>

<sup>a</sup> (a) EtNO<sub>2</sub>, NaOEt; (b) Ac<sub>2</sub>O, Py; (c) HCl; (d) Ac<sub>2</sub>O, Py; (e) Pd/C, H<sub>2</sub>; (f) Ac<sub>2</sub>O, Py; (g) HBr, HOAc, Ac<sub>2</sub>O; (h) Zn-Cu, NaOAc, HOAc, H<sub>2</sub>O, -10 °C; (i) BF<sub>3</sub>·Et<sub>2</sub>O, CH<sub>3</sub>OH, CH<sub>2</sub>Cl<sub>2</sub>.

duction (Pd, H<sub>2</sub>) of the nitro group to an amine and subsequent acetylation gave the amide **263a** in 56% overall yield. After **263a** was treated with hydrogen bromide (HOAc, Ac<sub>2</sub>O), the resultant 1-bromo compound **263b** was reacted with zinc-copper couple, producing the glycol **264** (48% yield from **263a**). Boron trifluoride catalyzed addition of methanol to the glycol gave the methyl 4-*epi*-vancosaminide derivative **265** as a 3:1 mixture of  $\alpha$ - and  $\beta$ -anomers (4% yield from **42**).

Using a similar sequence, Brimacombe and Menges<sup>20</sup> reported the preparation of **16** shown in Scheme L. The nitrohexose **262** starting material was produced as in the preceding sequence<sup>213,214</sup> and then catalytically hydrogenated over Raney nickel to the amine, which was N-acetylated to give **266** in 68% yield. Phase transfer catalyzed reaction<sup>221</sup> of **266** with 1 equiv of tosyl chloride provided the 2-monotosylate which was acetylated; displacement of the tosylate group and subsequent hydrolysis to **267** was accomplished with sodium acetate in wet diglyme (61% yield overall). Reaction of **267** with *N,N*-dimethyl- $\alpha$ -chlorobenzylideneammonium chloride and then with hydrogen sulfide in pyridine<sup>222</sup> gave **268** (31% yield). Removal of the 2-thiobenzoate group in **268** by radical-induced cleavage with tri-*n*-butyltin hydride in refluxing toluene furnished 4-*epi*-vancosamine (**265**) (30% yield). Since low yields were encountered in the formation and cleavage of the thiobenzoate in **268**, the authors concluded that the glycol route, presented in the previous scheme, was the preferred method for the conversion of **262** to the 2-deoxyhexose **265**.<sup>213</sup>

In a series of papers, Yoshimura and co-workers<sup>211,223,224</sup> reported the synthesis of the L- (**16**) and D- (**17**) *arabino*-hexoses from L- and D-hexos-3-ulose intermediates. Different routes were used to prepare the keto sugar intermediates; however, the subsequent conversion to hexoses with the *arabino* configuration

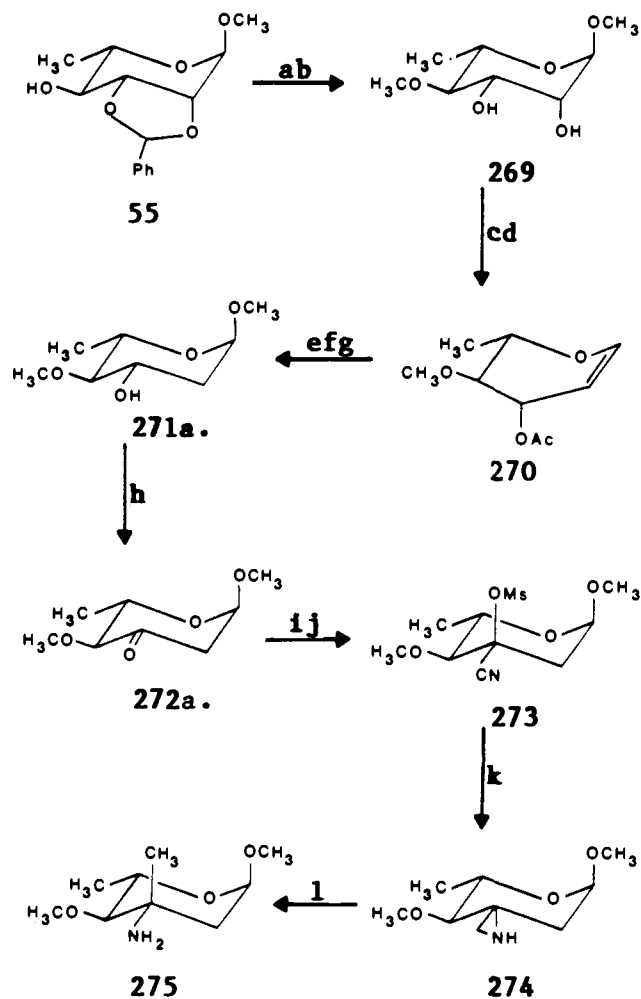
SCHEME L<sup>a</sup>

<sup>a</sup> (a) Ni(R), H<sub>2</sub>; (b) Ac<sub>2</sub>O, CH<sub>3</sub>OH; (c) TsCl, NaOH; (d) Ac<sub>2</sub>O, Py; (e) NaOAc, diglyme; (f) *N,N*-dimethyl- $\alpha$ -chlorobenzylideneammonium chloride, H<sub>2</sub>S, Py; (g) Bu<sub>3</sub>SnH, PhCH<sub>3</sub>.

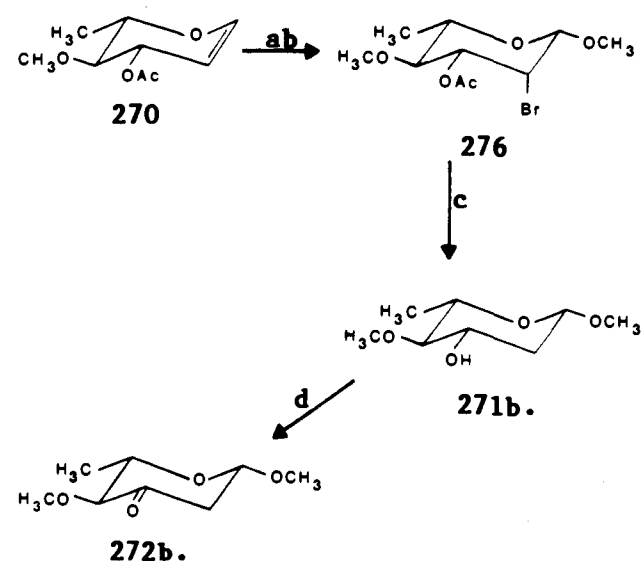
followed the same cyanomesylation procedure.

In the synthesis of the L isomer **16** shown in Scheme LI,<sup>224</sup> the initial steps leading to the hexulose intermediate **272a** essentially paralleled a procedure originally described by Clode and co-workers.<sup>57</sup> Methylation (NaH, CH<sub>3</sub>I) of the 4-hydroxyl group in the 2,3-*O*-benzylidene starting material **55**, prepared from rhamnose (**42**), was followed by hydrolytic removal of the 2,3-*O*-benzylidene group (HOAc, 95 °C, 1 h), furnishing **269** in 96% yield. After acylation of the diol moiety, the resultant acetate product was sequentially treated with hydrogen bromide and zinc-copper couple to produce the glycol **270** (62% yield).<sup>40</sup> The methyl 2-bromoglycoside generated through reaction of **270** with NBS was reduced with tributylstannane,<sup>225</sup> and then deacetylated (NaOMe) to give a 9:2 ratio of  $\alpha$ - and  $\beta$ -anomers **271**. The isomers were chromatographically separated and the  $\alpha$ -anomer **271** was oxidized (CrO<sub>3</sub>, Py) to the  $\alpha$ -hexos-3-ulose **272a** (41% overall yield from **270**). Reaction of the  $\alpha$ -anomer **272a** with basic hydrogen cyanide, followed by mesylation (MsCl),<sup>206-208</sup> furnished exclusively the cyanomesylate **273** with the *ribo* configuration. Lithium aluminum hydride reduction of **273** produced the spiroaziridine<sup>209</sup> **274** (71% yield), which on catalytic hydrogenolysis over Raney nickel was converted in 96% yield to the aminohexose **275** with the *L-arabino* configuration (15% yield from **42**).

Subsequently, Yoshimura et al.<sup>224</sup> described a selective preparation of the hexulose  $\beta$ -anomer **272b** and explored its conversion to 3-*C*-methyl-substituted aminohexoses (Scheme LII). Addition of bromine to **270**, followed by silver carbonate assisted solvolysis in methanol of the glycosyl bromide group, gave the  $\beta$ -methyl 2-bromo-pyranoside **276** (88% yield) as a mixture of four diastereoisomers. Hydrogenation of **276**

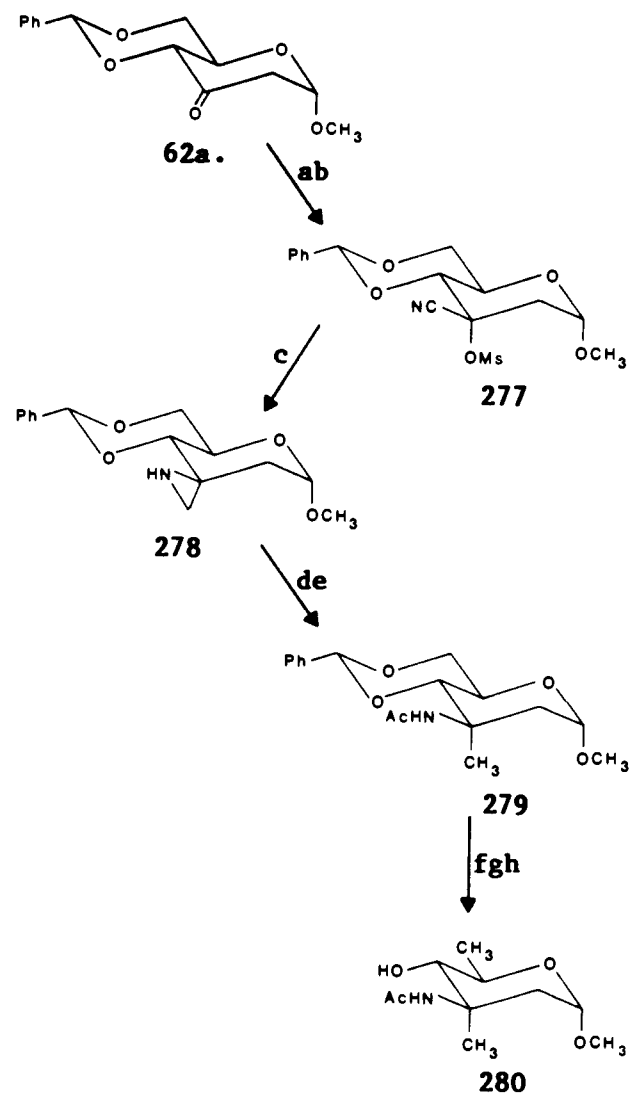
SCHEME LI<sup>a</sup>

<sup>a</sup> (a)  $\text{CH}_3\text{I}$ ,  $\text{NaH}$ ,  $\text{DMF}$ ; (b)  $\text{HOAc}$ ,  $\text{CH}_3\text{OH}$ ; (c)  $\text{HOAc}$ ,  $\text{H}_2\text{SO}_4$ , 3 days; (d)  $\text{HOAc}$ ,  $\text{Ac}_2\text{O}$ ,  $\text{HBr}$ ,  $-10^\circ\text{C}$ ,  $\text{Zn}$ ,  $\text{CuSO}_4$ ; (e)  $\text{CH}_3\text{OH}$ ,  $\text{CH}_3\text{-CN}$ ,  $\text{NBS}$ ,  $0^\circ\text{C}$ ; (f)  $\text{Bu}_3\text{SnH}$ ,  $\text{PhH}$ ,  $\text{AIBN}$ ; (g)  $\text{NaOCH}_3$ ; (h)  $\text{CrO}_3$ ,  $\text{Py}$ ,  $\text{CH}_2\text{Cl}_2$ ; (i)  $\text{HCN}$ ,  $\text{Py}$ ,  $0^\circ\text{C}$ ; (j)  $\text{MsCl}$ ,  $\text{Py}$ ; (k)  $\text{LAH}$ ; (l)  $\text{Ni(R)}$ ,  $\text{H}_2$ .

SCHEME LII<sup>a</sup>

<sup>a</sup> (a)  $\text{Br}_2$ ,  $\text{CHCl}_3$ ,  $0^\circ\text{C}$ ; (b)  $\text{Ag}_2\text{CO}_3$ ,  $\text{CH}_3\text{OH}$ ; (c)  $\text{Pd/C}$ ,  $\text{H}_2$ ,  $\text{CH}_3\text{-OH}$ ,  $\text{H}_2\text{O}$ ,  $\text{Et}_3\text{N}$ ; (d)  $\text{CrO}_3$ ,  $\text{Py}$ ,  $\text{CH}_2\text{Cl}_2$ .

( $\text{Pd/C}$ ,  $\text{MeOH}$ ,  $\text{Et}_3\text{N}$ )<sup>226</sup> produced a 1:4 mixture of  $\alpha$ - and  $\beta$ -anomers of 271 in 62% yield. The isomers were separated and 271b was oxidized to the keto hexose

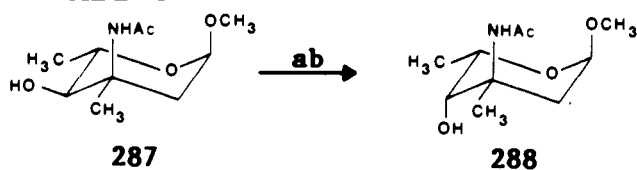
SCHEME LIII<sup>a</sup>

<sup>a</sup> (a)  $\text{HCN}$ ,  $\text{Py}$ ,  $0^\circ\text{C}$ ; (b)  $\text{MsCl}$ ,  $\text{Py}$ ; (c)  $\text{LAH}$ ,  $\text{Et}_2\text{O}$ ; (d)  $\text{Ni(R)}$ ,  $\text{H}_2$ ,  $\text{CH}_3\text{OH}$ ,  $40^\circ\text{C}$ ; (e)  $\text{Ac}_2\text{O}$ ,  $\text{Py}$ ; (f)  $\text{NBS}$ ,  $\text{BaCO}_3$ ,  $\text{CCl}_4$ ; (g)  $\text{Ni(R)}$ ,  $\text{H}_2$ ,  $\text{CH}_3\text{OH}$ ,  $\text{Et}_3\text{N}$ ; (h)  $\text{CH}_3\text{OH}$ ,  $\text{NH}_3$ .

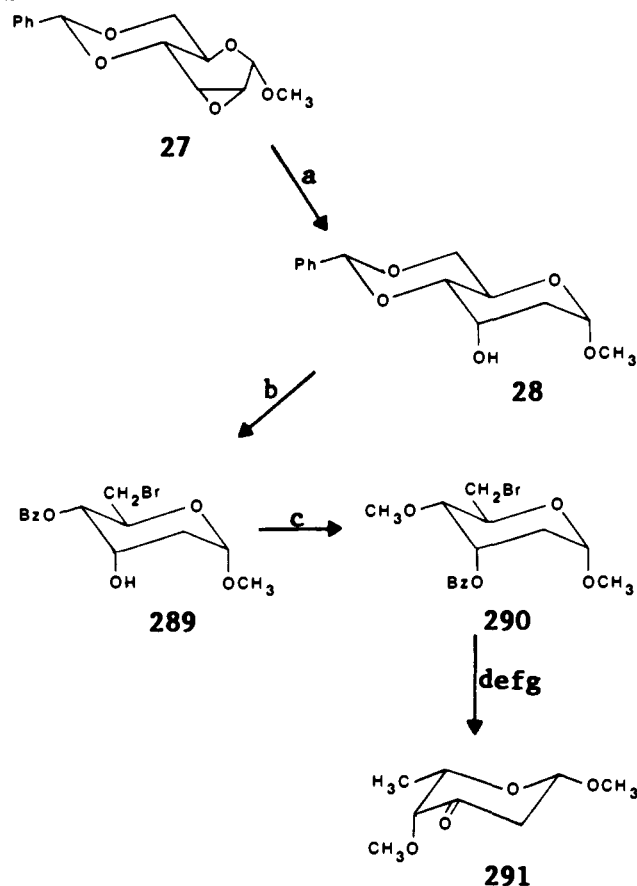
272b (4% overall yield) with chromium trioxide and pyridine. Cyanomesylation<sup>206-209</sup> of the  $\beta$ -anomer 272b was only stereoselective and furnished a 1:2 mixture of *ribo* (273) and *arabino* isomers. This result contrasted sharply with the stereospecific reaction previously observed for the  $\alpha$ -isomer and was attributed to the absence of hydrogen bonding between the C-3 hydroxyl and the C-1 methoxyl in the cyanohydrin intermediate formed during cyanomesylation of 272b. The conversion of the *ribo* (273) and *arabino* isomer to the corresponding L-aminohexoses was performed as described in Scheme LI.

The same authors used an analogous cyanomesylation of a keto sugar intermediate for the preparation of the D enantiomer of 4-*epi*-vancosamine (1) shown in Scheme LIII.<sup>211,223</sup> The 4,6-*O*-benzylidene 62a, employed by Horton et al.<sup>58,141</sup> to synthesize daunosamine (1), was cyanomesylated<sup>206-208</sup> to furnish a 95:5 ratio of the *ribo*- (277) and *arabino*-hexoses (64% *ribo*; 3% *arabino*). Reduction of 277 with lithium aluminum hydride produced the spiroaziridine 278, which was further reduced (Raney nickel) and then acetylated to the *N*-acetyl derivative 279. The 6-bromo compound, obtained on reaction of 279 with NBS and barium



SCHEME LVII<sup>a</sup>

<sup>a</sup> (a) PCC, molecular sieves; (b) L-Selectride.

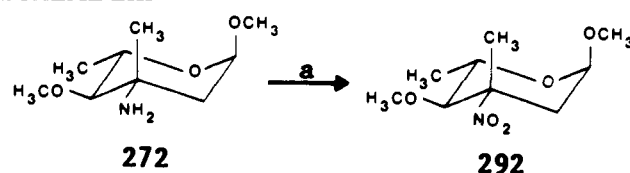
SCHEME LVIII<sup>a</sup>

<sup>a</sup> (a) LiAlH<sub>4</sub>, THF; (b) NBS, BaCO<sub>3</sub>, CCl<sub>4</sub>; (c) Ag<sub>2</sub>O, CH<sub>3</sub>I, DMF; (d) AgF, Py; (e) catalytic hydrogenation; (f) de-O-benzoylation; (g) PCC, CH<sub>2</sub>Cl<sub>2</sub>.

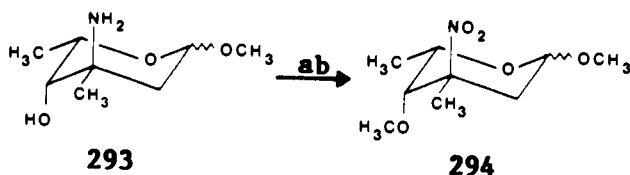
parcin.<sup>234,235</sup> The structure of **20** was assigned from its <sup>1</sup>H NMR spectrum, and the absolute stereochemistry was confirmed by applying Hudson's rule,<sup>236</sup> the optical rotation of the  $\alpha$ -anomer was more negative than the  $\beta$ -anomer.

Almost all of the syntheses of the *L*-xylo isomer (**20**) have been incidental to the preparation of other sugars, and most often as a minor product in syntheses of vancosamine (**13**).<sup>19,21,116,216,217</sup> The only other reported synthesis was performed by Brimacombe et al.<sup>230,232</sup> as shown in Scheme LVII. Oxidation of the *ribo*-hexose **287** with pyridinium chlorochromate (PCC), followed by reduction of the ketone intermediate with L-Selectride, inverted the C-4 hydroxyl group, furnishing the *xylo*-hexose **288** in 71% yield.

The *D*-xylo-hexopyranose **21** has been prepared several times as an intermediate in the synthesis of kijanose (2,3,4,6-tetradeoxy-4-[(methoxycarbonyl)amino]-3-*C*-methyl-3-nitro-*D*-xylo-hexose).<sup>237-239</sup> A formal synthesis was performed by Yoshimura and co-workers<sup>240</sup> and is shown in Scheme LVIII. The 2,3-anhydropyranoside **27**,<sup>45,76</sup> prepared from methyl glu-

SCHEME LIX<sup>a</sup>

<sup>a</sup> (a) MCPBA, CH<sub>2</sub>Cl<sub>2</sub>.

SCHEME LX<sup>a</sup>

<sup>a</sup> (a) CH<sub>3</sub>I, NaH, DMF; (b) MCPBA, CH<sub>2</sub>Cl<sub>2</sub>.

coside **26**, was reduced with lithium aluminum hydride<sup>45,76</sup> to furnish the 2-deoxy sugar **28**. Reaction of **28** with NBS and barium carbonate<sup>68</sup> produced the 6-bromo derivative **289**. Concurrent migration of the benzoyl group and 4-*O*-methylation were accomplished by treating **289** with silver oxide and methyl iodide in DMF and gave **290** in 76% yield. Dehydrohalogenation of **290** with silver fluoride in pyridine produced an inseparable 3:2 mixture of the desired 5-enopyranoside and the 6-fluoro derivative. Catalytic hydrogenation of the 5,6-olefinic residue, followed by *O*-debenzoylation and oxidation of the 3-hydroxyl moiety (PCC), furnished the hexopyranosid-3-ulose **291** (34% yield). Conversion of **291** to the *xylo*-aminohexose **21** was accomplished via the spiroaziridine route established previously<sup>209,211,223,224,230-232</sup> and shown in Scheme LI.

## VI.

**2,3,6-Trideoxy-3-*C*-methyl-3-nitrohexopyranoses****A. Evernitrose (*L*- and *D*-arabino)**

Evernitrose (**22**), with the *L*-arabino configuration, was the first naturally occurring nitro sugar to be isolated. It is a constituent of the oligosaccharide antibiotics evernimycin B, C, and D<sup>3,4</sup> and is liberated upon acidic hydrolysis. Spectroscopic and chemical degradation studies<sup>242</sup> led to an initial assignment of the *L*-ribo configuration; however, a later X-ray analysis of the methyl  $\alpha$ -glycoside of the 3-acetamido derivative **189** established that the configuration was *L*-arabino.

All of the syntheses of *L*- and *D*-evernitrose (**22** and **23**) have used the corresponding amino sugars **272** and **280** as precursors. As shown in Scheme LIX, Yoshimura and co-workers<sup>211,223,224</sup> oxidized the amine moiety in **272** with *m*-chloroperbenzoic acid and obtained *L*-evernitrose **292** in 50% yield. The *D*-isomer **23** was analogously prepared from **280**.<sup>211,223</sup>

**B. Rubranitrose (*D*- and *L*-xylo)**

*D*-Rubranitrose (**24**), a component of the antibiotic rubradirin,<sup>244-248</sup> was first reported to be 4-*O*-methyl-3-nitro-*L*-xylo-hexopyranose.<sup>249</sup> Recently, comparison of its circular dichroism spectrum and optical rotation with that of *D*-kijanose indicated that the configuration of **24** was *D*.<sup>250</sup>

Although there has been no published synthesis of the natural *D*-rubranitrose (**24**), two preparations of the

unnatural L-enantiomorph **25** have been reported. These preparations, by Yoshimura et al.<sup>240</sup> and Brimacombe et al.,<sup>251</sup> were initiated from the methyl-L-xylo-aminohexose **293**.<sup>230,240</sup> As shown in Scheme LX, methylation of **293** (MeI, NaH)<sup>252</sup> and oxidation of the amine entity with *m*-chloroperbenzoic acid gave the nitro sugar **294** in 57% overall yield.

### VII. Summary and Conclusions

The discovery that L-daunosamine (1), the glycosidic fragment in the therapeutically useful anticancer antibiotics daunorubicin and adriamycin, was essential for activity initiated interest not only in its preparation, but also that of the other configurationally related 2,3,6-trideoxy-3-amino- and 3-nitro-hexoses. Daunosamine (1) has been the most often synthesized; however, there have been nearly an equal number of acosamine (4) preparations, since it has a more synthetically accessible configuration and can be readily transformed to daunosamine (1). Added impetus for singular preparations of acosamine (4) stems from structure activity studies that have shown that replacement of daunosamine (1) with acosamine (4) or ristosamine (8) produced analogues which are nearly as active, but are less cardiotoxic.

As might be expected from their structural similarity to the amino and nitro sugars, commercially available D- and L-hexoses and L-pentoses have been the most commonly used starting materials for optically active syntheses. Since the objective sugars are less highly functionalized, removal and manipulation of functionality from the starting carbohydrate are necessary; thus the reaction sequences are rather long. Nevertheless, reasonably efficient preparations of all the configurational isomers have been accomplished by using this approach. The employment of carbohydrates as starting materials will likely remain a significant strategy for synthesis of the title sugars as even more efficient methods for manipulating functionality are developed.

An increasingly common method for synthesis of these sugars is based on the use of acyclic intermediates. Initially, this approach took advantage of the significant advances made in diastereoselective fabrication of acyclic intermediates and asymmetric synthesis. More recently, synthetic efforts on the sugars themselves have resulted in contributions to new chemical methodology. In particular, asymmetric introduction of functionality in an acyclic system through the use of existing groups was largely developed from efforts directed at the preparation of these aminohexoses. A significant advantage of the acyclic strategy is that the need for protective groups is minimized.

No class of compounds is immune from the persistent curiosity of synthetic chemists, and these amino and nitro sugars are no exception. Given the importance of these compounds, the advances being made in synthetic methodology, and especially the imaginations of synthetic chemists, new routes to these sugars will likely be investigated for many years to come.

### VIII. Addendum

Since this review was closed to additions, a number of publications on the synthesis of the title amino and

nitro sugars have appeared, and these are briefly described below.

Hamada and co-workers have reported novel, parallel syntheses of optically active daunosamine<sup>253</sup> (1) and vancosamine<sup>254</sup> (13) from L-lactic acid. Noteworthy aspects of these stereoselective preparations are the direct C-acylation of a protected lactic acid derivative with methyl isocynoacetate to generate an oxazole and the production of a lyxo-configured  $\gamma$ -lactone via stereoselective hydrogenation of the amino reductone from hydrolysis of the oxazole moiety. Dibal reduction of the lactone, Wittig reaction of the resultant lactol with (methoxymethylene)triphenylphosphorane, and then hydrolysis were employed to introduce C-1. Daunosamine (1) was prepared in nine steps in 24% overall yield. Alkylation of the  $\gamma$ -lactone with methyl iodide and 3 equiv of LDA gave the corresponding methyl substituted lactone with the *lyxo* configuration (96% stereoselectivity, 67% yield), which was homologated to vancosamine (13).

Methyl *N,O*-dibenzoyldaunosaminide was prepared by Gurjar and co-workers<sup>255</sup> from a methyl-D-glucosamine derivative in nine steps and in 7% overall yield. Migration of the 2-amino moiety in a 2-amino-2-deoxyglucoside derivative to C-3 was accomplished through an aziridine intermediate. Hydrogenation of a 5,6-enoside intermediate was used to effect configurational inversion to the L stereochemistry.

Hanessian and Kloss<sup>256</sup> described a stereoselective route to either D- or L-3-amino-2,3,6-trideoxyhexoses. Aldol condensation of methyl 3-nitropropionate with *O*-benzyl-D- or -L-lactaldehyde stereoselectivity gave the *ribo*-configured acyclic product, which was subsequently cyclized to the  $\gamma$ -lactone precursor to D-ristosamine (9) (44% yield). The mesylate derivative of the D-ristosamine intermediate was used to effect configurational inversion to the L-*lyxo*- $\gamma$ -lactone precursor to L-daunosamine (1) (19% yield). Small amounts of the *arabino*- and *xylo*- $\gamma$ -lactones were also prepared as byproducts.

A conceptually novel synthesis of D,L-daunosamine has been reported by Danishefsky and Maring.<sup>257</sup> The 1,4-alkoxy-2-siloxy-substituted diene starting material was prepared in four steps as a three-component *E,Z* mixture and underwent Lewis acid catalyzed cycloaddition with acetaldehyde to give a 3.1:1 mixture of desired *cis*- and undesired *trans*-2-alkoxy-1-methyl-1,2-dihydro-3-pyrones. Oxymercuration of the *cis*-dihydropyrone with in situ sodium cyanoborohydride reduction of the organomercurial furnished the methyl glycoside of the hexosulose. Reduction of the acetyl-oxime derivative of the hexosulose provided a 2:1 mixture of methyl *N,O*-diacetyldaunosaminide and the *epi*-daunosaminide isomer in 20% overall yield.

In the first of two papers, Hiramata et al.<sup>258</sup> reported highly diastereoselective preparations of D,L-acosamine and ristosamine from the 3,4-*erythro*-diol obtained from epoxidation of commercially available ethyl sorbate. The parallel preparations are based on their recent finding that intramolecular Michael additions of  $\gamma$ - and  $\delta$ -carbamoyloxy unsaturated esters occur with high 1,2- and 1,3-*syn* asymmetric induction. In the acosamine synthesis, the carbamoyloxy group is in the  $\gamma$ -position, while in the ristosamine preparation it is  $\delta$  to the ester function. Following hydrolysis and reduction, acos-

amine was obtained in 15% and ristosamine in 11% overall yield.

In the second paper,<sup>260</sup> the concepts and procedures established for acosamine and ristosamine were further refined to perform syntheses of daunosamine and *epi*-daunosamine from the *threo*-diol obtained through cis hydroxylation of ethyl sorbate with osmium tetroxide. The diastereofacial selectivity in the kinetically controlled intramolecular conjugate addition of the carbamate to the unsaturated ester is due to steric and stereoelectronic factors. In the 1,2- and 1,3-*syn* additions, steric factors are more important, while in the 1,3-*anti* selection, the contribution from stereoelectronic stabilization is only slightly larger than that from steric factors and lower stereoselectivity is observed.

Using a sequence similar to that shown in Scheme XXIII for the synthesis of L-acosamine,<sup>129,130</sup> Thiem and Springer<sup>261</sup> reported preparations of ristosamine and 3-*epi*-daunosamine from L-rhamnal. The 4-hydroxyl group in the isomeric iodo azide intermediates (143 and 144) was oxidized to give azido enosidulose isomers which were converted to L-ristosamine and L-3-*epi*-daunosamine. The overall yields were modest (2% and 0.7%, respectively).

An additional preparation of D-daunosamine from D-glucose has been reported by Stewart and Williams.<sup>262</sup> The major difference between their route and the one shown in Scheme I<sup>26,27</sup> is that the order of the steps is slightly rearranged.

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## IX. References and Notes

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- (263) Bn and Bz have been used as abbreviations for benzyl and benzoate, respectively. Less well-known abbreviations used for reagents: BnSH, benzyl mercaptan; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; DEAD, diethyl azodicarboxylate; DI-BAL, diisobutylaluminum hydride; DMAP, 4-(dimethylamino)pyridine; NIS, *N*-iodosuccinimide; NMO, *N*-methylmorpholine *N*-oxide; PCC, pyridinium chlorochromate; PDC, pyridinium dichromate; Py, pyridine; TFAA, trifluoroacetic anhydride; TMNO, trimethylamine *N*-oxide.
- (264) Except for the protecting group on the C-4 hydroxyl moiety, 56 is the same precursor used by Yoshimura and co-workers<sup>211,223</sup> for the synthesis of 4-*epi*-vancosamine (6). These authors reported that reaction of 56 with alkaline cyanide gave a product with the *ribo* configuration.