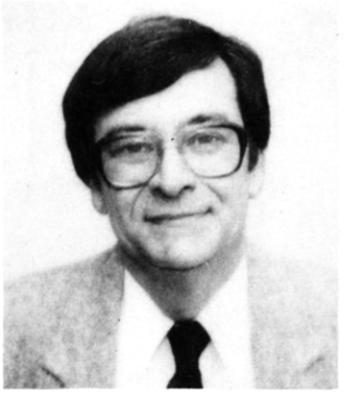
Syntheses of 2,3,6-Trideoxy-3-amino- and 2,3,6-Trideoxy-3-nitrohexoses

FRANK M. HAUSER* and SUZANNE R. ELLENBERGER

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

Received July 7, 1985 (Revised Manuscript Received October 25, 1985)

Contents



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

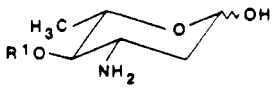
Figure 1 shows the naturally occurring 2,3,6-trideoxy-3-amino- and -3-nitrohexoses as well as the configurational isomers prepared in conjunction with syn-

0009-2665/86/0786-0035$06.50/0

L-lyxo

1. Daunosamine
$R^1 = R^2 = H$

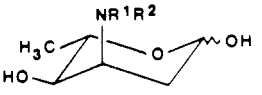
3. Rhodosamine
$R^1 = R^2 = CH_3$



L-arabino

4. Acosamine
$R^1 = H$

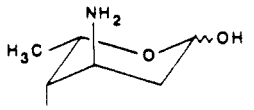
6. Actinosamine
$R^1 = CH_3$



L-ribo

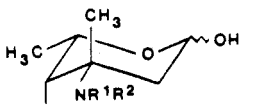
8. Ristosamine
$R^1 = R^2 = H$

10. Megosamine
$R^1 = R^2 = CH_3$



L-xylo

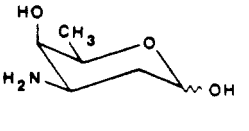
11. 3-epiDaunosamine



L-lyxo

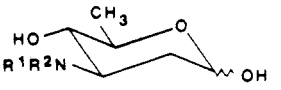
13. Vancosamine
$R^1 = R^2 = H$

15. N,N-Dimethylvancosamine
$R^1 = R^2 = CH_3$



D-lyxo

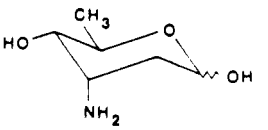
2. Daunosamine



D-arabino

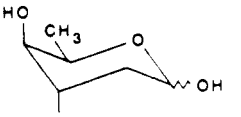
5. Acosamine
$R^1 = R^2 = H$

7. Angolosamine
$R^1 = R^2 = CH_3$



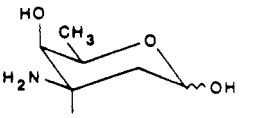
D-ribo

9. Ristosamine



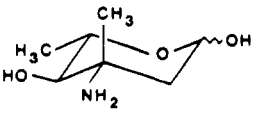
D-xylo

12. 3-epiDaunosamine



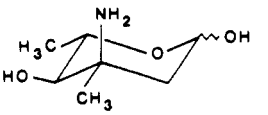
D-lyxo

14. Vancosamine



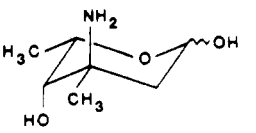
L-arabino

16. 4-epiVancosamine



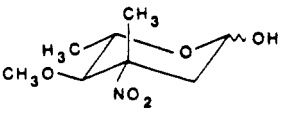
L-ribo

18.



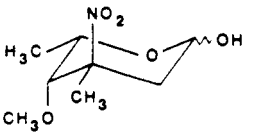
L-xylo

20. 3-epiVancosamine



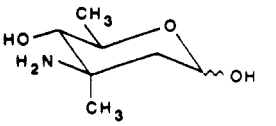
L-arabino

22. Evernitrose



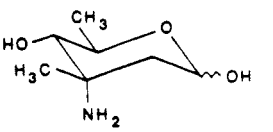
L-xylo

25. Rubranitrose



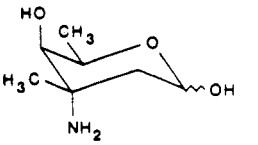
D-arabino

17. 4-epiVancosamine



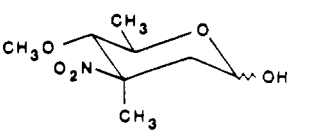
D-ribo

19.



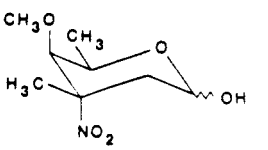
D-xylo

21. 3-epiVancosamine



D-arabino

23. Evernitrose



D-xylo

24. Rubranitrose

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,[1,2] it was not until the discovery of L-evernitrose (22)[3,4] 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[5-8] and adriamycin,[8,9] 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[10-17] and spectral interpretations[18-21] 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[263]

As might be expected, the majority of the syntheses have been achieved from other carbohydrates. Although the revised "Rules of Carbohydrate Nomenclature"[22] 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 ($^1C_4$, $^4C_1$) is in accord with the rules established by Stoddart.[23]

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.[9,24,25] It is by far the most well-known of the trideoxyaminohexoses and was first isolated by Arcamone et al.[5,6] 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.[1,2] 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.

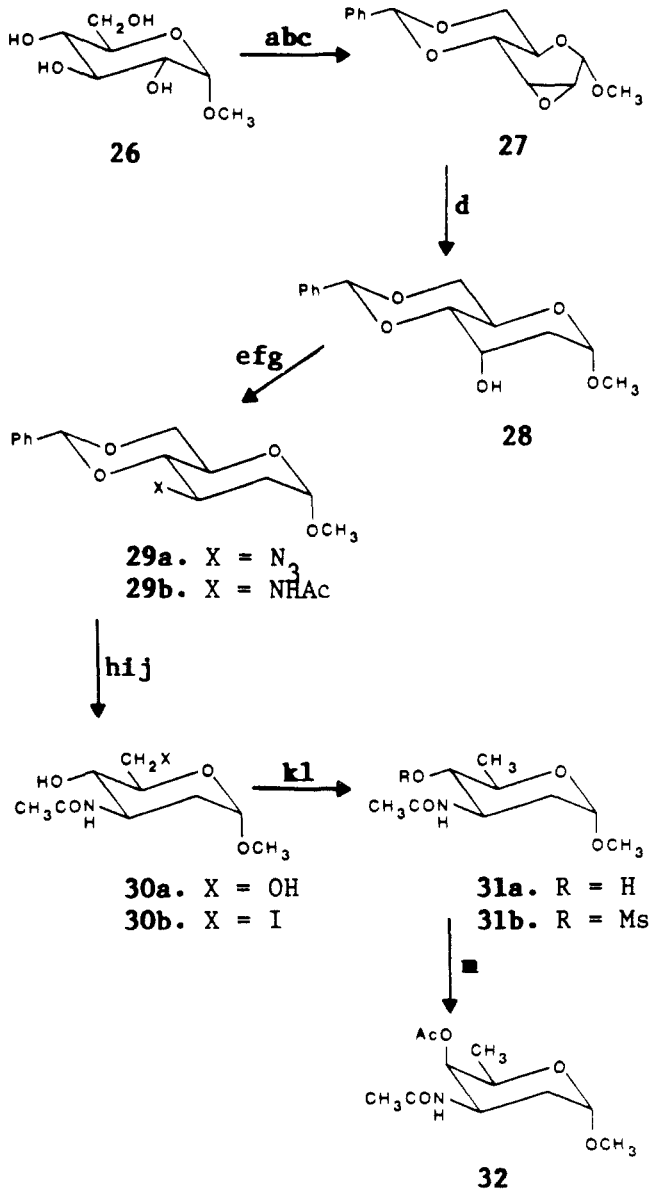
The synthesis of L-daunosamine (1) is hampered by the presence of a cis vicinal hydroxyamine component that is traditionally problematic and requires more steps for construction than the trans counterpart. Most of the syntheses of derivatives of 1 have been initiated from D and L carbohydrates or amino 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[26,27] 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[51,135] furnished the *allo*-mannoside **27**[28] 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**.[28] The 3-hydroxyl moiety in **28** was mesylated (MsCl, Py) and the mesylate group displaced with sodium azide in *N*,*N*-dimethylformamide (DMF)[29] 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 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[a]

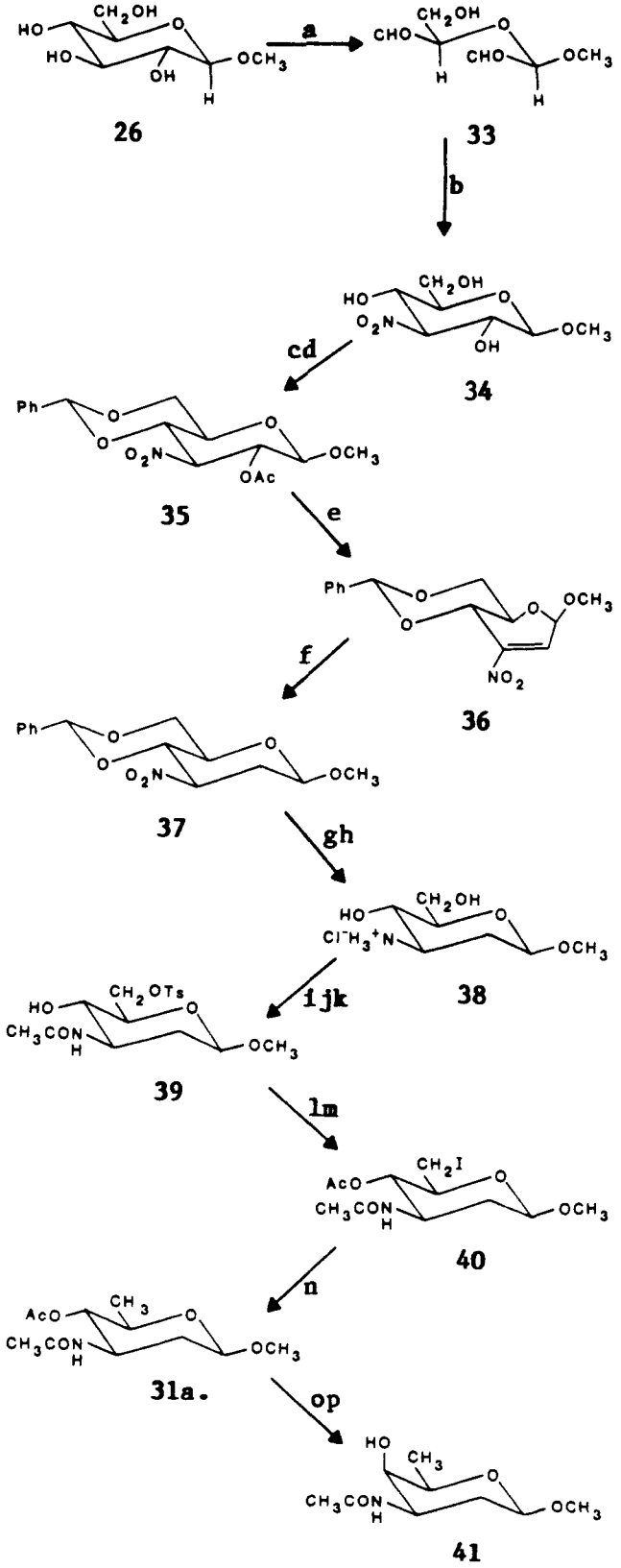


[a] (a) $ZnCl_2$, PhCHO; (b) TsCl, Py; (c) NaOMe; (d) LAH; (e) MsCl, Py; (f) NaN_3, DMF; (g) Ni(R), H_2, Ac_2O; (h) MeOH, HCl; (i) TsCl, Py; (j) NaI; (k) Ni(R), H_2; (l) MsCl, Py; (m) NaOAc.

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[30,31] 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,[26,27] Boivin et al.[32] subsequently prepared D-daunosamine (**2**), as well as D-acosamine (**5**) and L-ristosamine (**8**).

Baer and co-workers[33] 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**)[34] or methyl

SCHEME II[a]



[a] (a) $NaIO_4$; (b) CH_3NO_2, NaOMe; (c) $ZnCl_2$, PhCHO; (d) Ac_2O, Py; (e) $NaHCO_3$; (f) Pd/C, H_2; (g) Dowex-H^+, CH_3OH; (h) PtO_2, HCl, H_2; (i) Dowex-OH^-; (j) Ac_2O, MeOH; (k) TsCl, Py; (l) Ac_2O, Py; (m) NaI, $NaHCO_3$; (n) Ni(R), H_2, Et_3N, CH_3OH; (o) MsCl, Py; (p) NaOAc, H_2O.

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

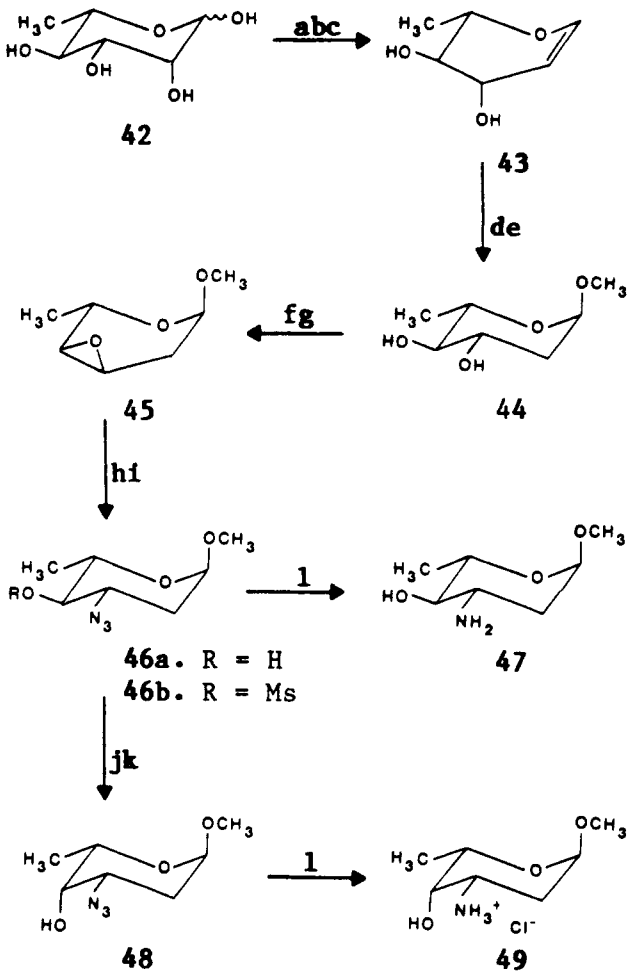
modest (25%), the product was isolated directly through crystallization. Reaction of **34** with benzaldehyde and zinc chloride furnished the 4,6-*O*-benzylidene derivative which was acetylated to the 2-acetoxy product **35**. Deoxygenation at C-2, through elimination of acetic acid, occurred when **35** was treated with sodium bicarbonate in refluxing benzene. The olefinic moiety in the resultant hexos-2-enide **36** was catalytically hydrogenated (Pd/C, H_2), giving **37** with the D-*arabino* configuration.[38] Hydrolytic removal of the benzylidene protective group with cation exchange resin in methanol–water, followed by catalytic hydrogenation (PtO_2, 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_2O, MeOH) and monotosylated (TsCl, Py) to furnish **39**. After acetylation (Ac_2O, Py) of the 4-hydroxyl functionality in **39**, the 6-tosyl group was displaced with iodide (NaI, $NaHCO_3$, 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[26,27] 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.[39] 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-rhamnal (**43**)[40] and methoxymercuration of **43** with in situ borohydride reduction of the organomercury intermediate furnished the 2,6-dideoxy sugar **44**. Sulfonylation 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 $^4C_1$ 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.[42,43]) The configuration of the C-4 hydroxyl in **46a** was inverted through reaction of the mesylated 3-azido sugar **46b** with sodium benzoate;[44] 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[45,46] 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[47] in 1983.

SCHEME III[a]

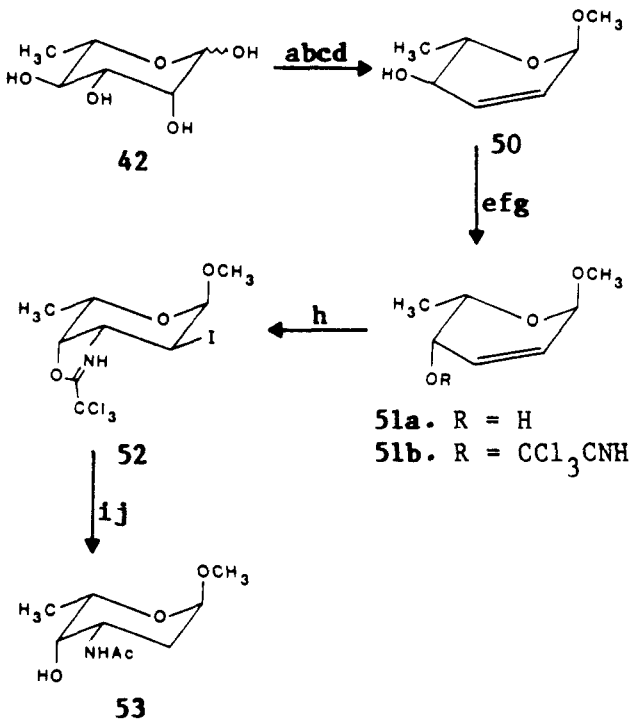


[a] (a) Ac_2O, Py; (b) HBr, HOAc, Ac_2O; (c) Zn–Cu, HOAc; (d) $Hg(OAc)_2$, CH_3OH; (e) KBH_4; (f) TsCl, Py; (g) $NaOCH_3$; (h) NaN_3; (i) MsCl, Py; (j) NaOBz, DMF; (k) $NaOCH_3$, H_2O; (l) catalytic hydrogenation.

In this sequence, shown in Scheme IV, rhamnose (**42**) was initially converted to rhamnal (**43**),[40,48] which was solvolyzed in acidic methanol to the hex-2-enopyranoside **50**[49–51] (53% yield from **42**). Epimerization of the 4-hydroxyl group in **50** through Mitsunobu reaction[52] (DEAD, PPh_3, $PhCO_2H$) 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[53] (Cl_3CCN, NaH) and underwent iodonium ion induced cyclization to **52**. Dehalogenation (Bu_3SnH) and hydrolysis of the dihydroxazole moiety in **52** furnished the optically active methyl *N*-acetyldaunosaminide (**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[54] also prepared **49**.

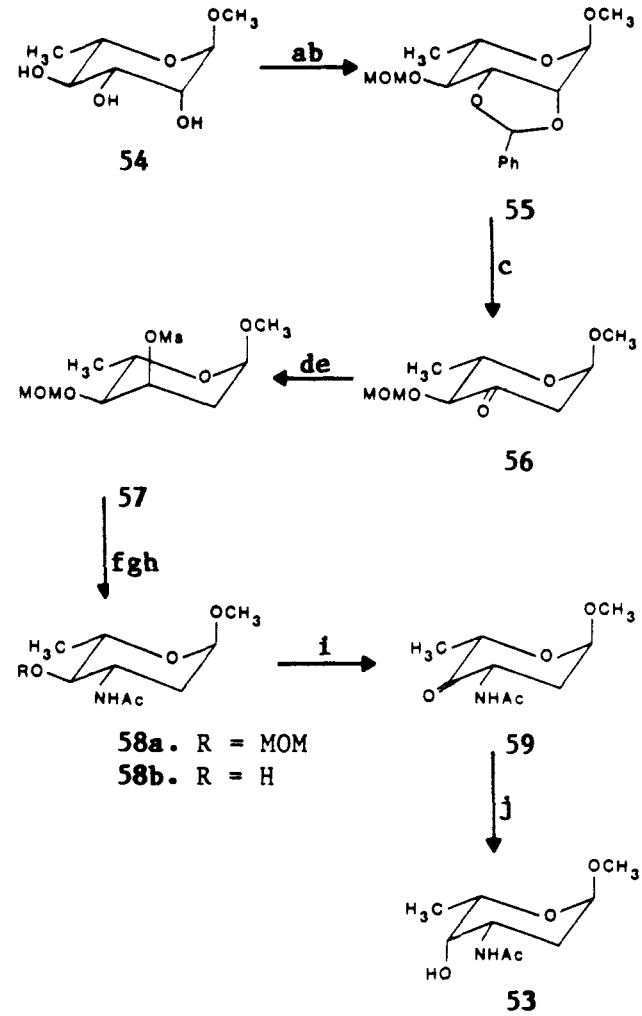
Brimacombe and co-workers[55] reported the preparation of daunosamine (**1**) from L-rhamnose (**42**) shown in Scheme V; as in numerous other sequences, an acosamine derivative served as an intermediate. Sequential protection of the 2,3-hydroxyl functionality in the methyl glycoside **54** of L-rhamnose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

SCHEME IV[a]



[a] (a) Ac_2O, Py; (b) HBr, HOAc, Ac_2O; (c) Zn–Cu, HOAc; (d) BF_3, CH_3OH; (e) Ph_3P, $EtO_2CN{=}NCO_2Et$, $PhCO_2H$; (f) $NaOCH_3$; (g) NaH, Cl_3CCN; (h) I(2,4,6-trimethylpyridine)$_2ClO_4$; (i) $(n\text{-}Bu)_3SnH$, AIBN; (j) TsOH, Py, H_2O.

SCHEME V[a]



[a] (a) $PhCH(OCH_3)_2$, TsOH, DMF; (b) CH_3OCH_2Cl, $N(i\text{-}Pr)_2Et$; (c) THF, BuLi; (d) $NaBH_4$; (e) MsCl, Py; (f) NaN_3, DMF; (g) PtO_2, H_2, Ac_2O; (h) CH_3OH, HCl; (i) PCC, CH_2Cl_2; (j) L-Selectride, THF.

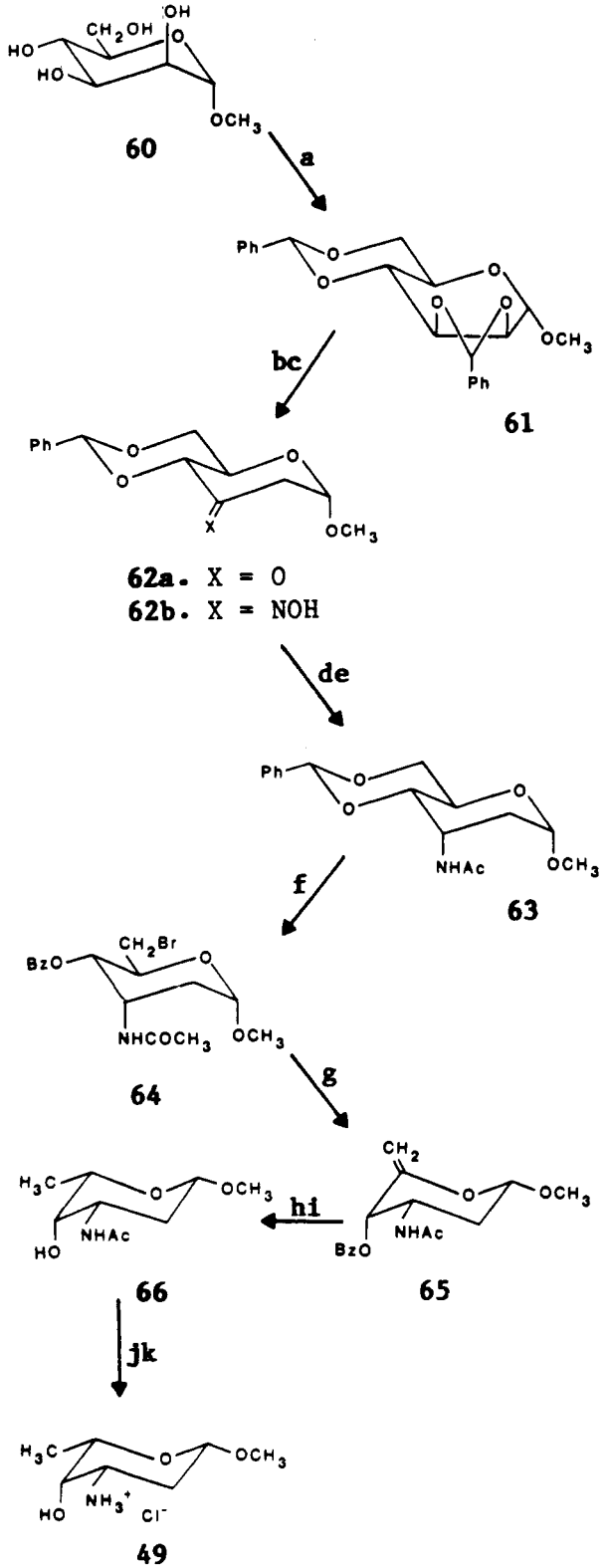
oxymethyl (MOM) derivative provided **55**. Modified Klemer–Rhodemeyer fragmentation[60–62] of the 2,3-*O*-benzylidene moiety in **55** with butyllithium furnished the hexos-3-ulose **56** (29% yield). The ketone group in **56** was reduced with sodium borohydride and the alcohol product was mesylated (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[27] 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.[55] Oxidation of the 4-hydroxyl moiety in **58b** with either pyridinium chlorochromate (PCC)[63] or trifluoroacetic anhydride–dimethyl sulfoxide[64] gave the ketohexose **59** in 63% yield. L-Selectride (Aldrich) reduction[65,66] of **59** stereoselectivity produced methyl *N*-acetyldaunosaminide (**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[58] in their total synthesis of daunosamine (**1**) from methyl α-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 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 α,α-dimethoxytoluene.[59] Klemer–Rhodemeyer fragmentation[60] 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**.[67] 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,[68] the resultant 4-*O*-benzoyl-6-bromo derivative **64** was dehydrobrominated with silver fluoride and pyridine in benzene[69] 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%.

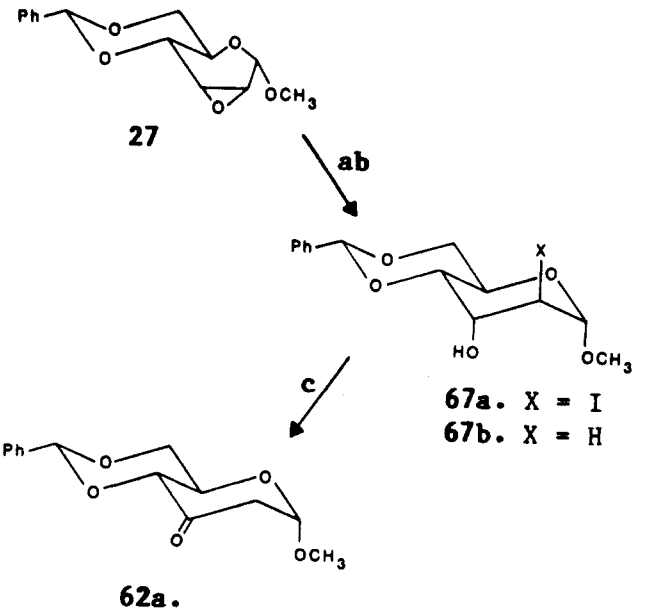
SCHEME VI[a]



[a] (a) $PhCH(OCH_3)_2$, TsOH, DMF; (b) BuLi, THF; (c) $H_2NOH \cdot HCl$, NaOH, EtOH; (d) LAH, Et_2O; (e) Ac_2O, Py; (f) NBS, CCl_4, $BaCO_3$; (g) AgF, Py; (h) $NaOCH_3$; (i) $Pd/BaCO_3$, CH_3OH, H_2; (j) $Ba(OH)_2$, H_2O; (k) HCl.

Gurjar et al.[70] have described a synthesis of the ketone intermediate **62a** used by Horton and Weckerle[58] 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 α-D-glucoside,[71] was reacted with magnesium iodide etherate to effect trans-diaxial opening of the epoxide group,

SCHEME VII[a]



[a] (a) MgI_2, Et_2O; (b) $(n\text{-}Bu)_3SnCl$, $NaBH_4$; (c) PDC, CH_2Cl_2.

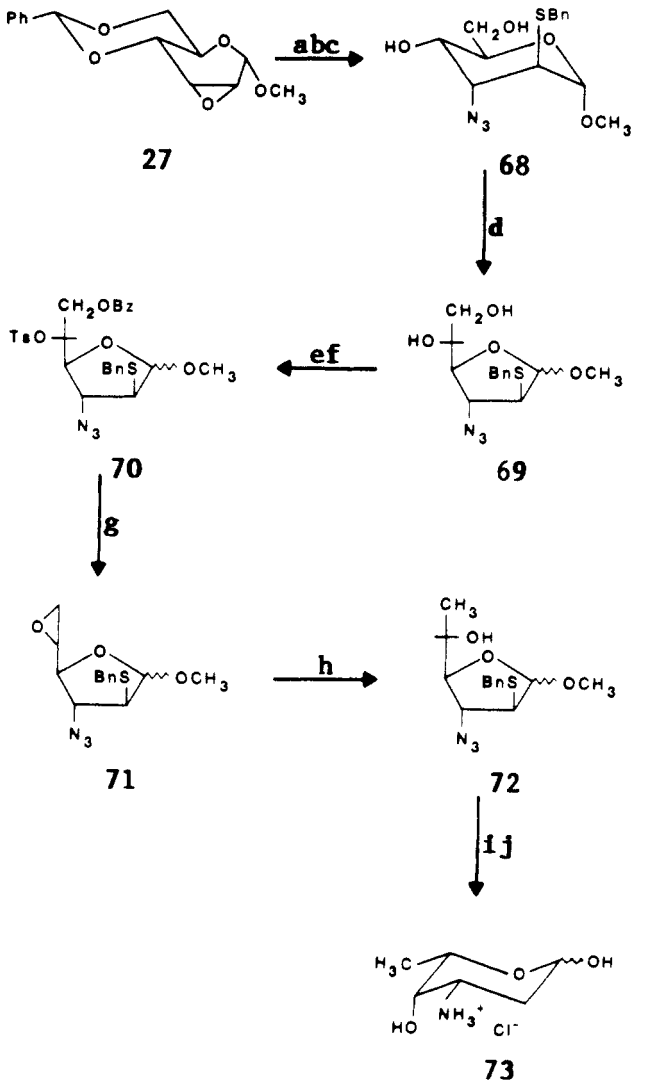
regiospecifically furnishing the 2-iodo pyranoside **67a** in 97% yield. Reductive dehalogenation of **67a** with tri-*n*-butyltin chloride and sodium borohydride[72] quantitatively generated the 2-deoxy product **67b**, which was oxidized to the ketone **62a** with pyridinium dichromate (70%). Although 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.[73] The synthetic route, shown in Scheme VIII, evolved from their earlier finding[74,75] 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[76] 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.

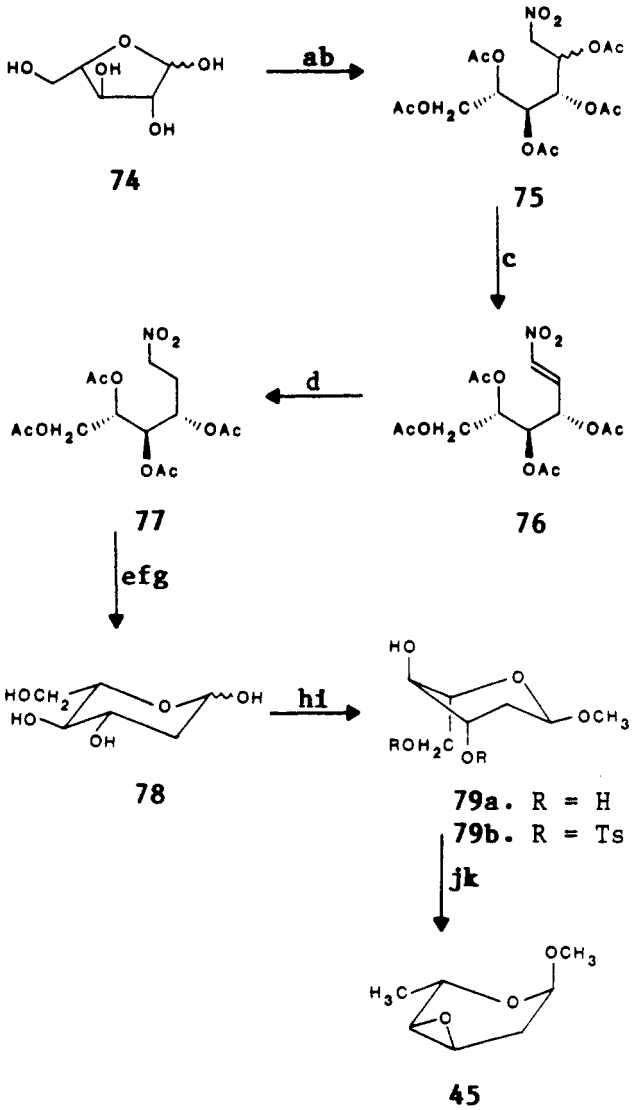
Whereas hexoses with the L configuration are uncommon, certain L-pentoses occur naturally, are relatively inexpensive, and can be readily homologated to 2-deoxy-L-hexoses. These properties were exploited by Grethe et al.[45] in their total synthesis of **1** in which

SCHEME VIII[a]



[a] (a) $NaOCH_3$, BnSH, CH_3OH; (b) TsCl, Py; (c) NaN_3, $CH_3OCH_2CH_2OH$; (d) Amberlite-H^+, CH_3OH–H_2O; (e) BzCl, Py; (f) TsCl, Py; (g) $NaOCH_3$, $CHCl_3$; (h) LAH, THF; (i) Ni(R), dioxane; (j) HCl–H_2O.

SCHEME IX[a]



[a] (a) CH_3NO_2, $NaOCH_3$; (b) BF_3·Et_2O, Ac_2O; (c) $NaHCO_3$, $PhCH_3$; (d) Pd/C, H_2, EtOAc; (e) $Ba(OH)_2$; (f) H_2SO_4; (g) $BaCO_3$; (h) CH_3OH, Amberlite-H^+; (i) TsCl, Py; (j) $NaBH_4$, DME; (k) Amberlite-OH^-, CH_3OH.

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.[39] A modification of the procedure originally reported by Sowden and Fischer[77,78] 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[79,80] ($Ba(OH)_2$, H_2SO_4) 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 $^4C_1$ 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. 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.[39] (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.[46] reported an elegant total synthesis of the optically active epoxide **45** from achiral precursors.

80a. R,R = CH_3 **81a.** R,R = CH_3
80b. R-R = $-(CH_2)_5-$ **81b.** R-R = $-(CH_2)_5-$

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.

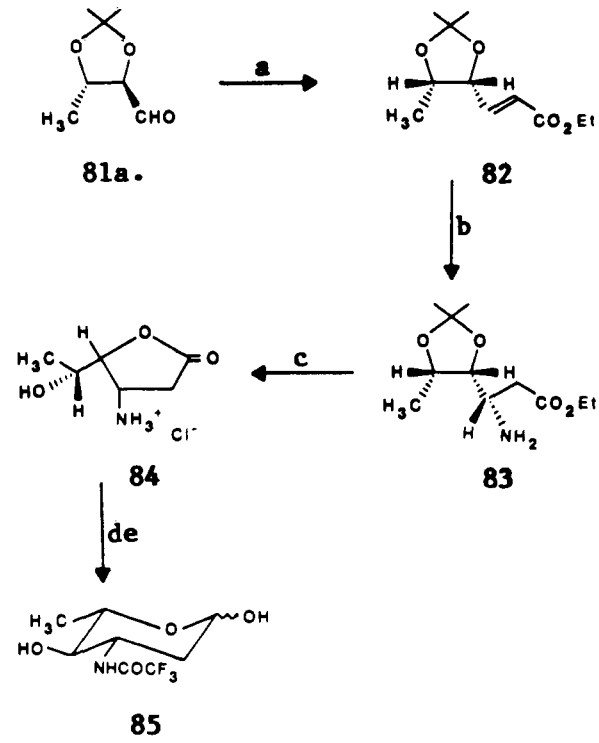
Fuganti and co-workers[81,82] have reported two procedures for preparation of the protected (2*S*,3*S*)-*erythro*-aldehyde **80a** through fermentation of cinnamaldehyde with Baker's yeast. Although the four-step method provided **80a** in 18% yield, the authors preferred the lower yield route (8%) since it was experimentally less involved. The (2*R*,3*S*)-*threo*-aldehyde **81a** has been prepared from D-threonine,[83] from epimerization of the (2*S*,3*S*)-aldehyde **80a**[81,84] and from L-tartaric acid.[85-87] 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.[83] Of the two routes from L-tartaric acid,[85-87] the sequence reported by Mukaiyama et al.[87] 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.[18] 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,[85] 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[88] 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 hydroxide and benzoyl chloride effected benzoylation 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%).

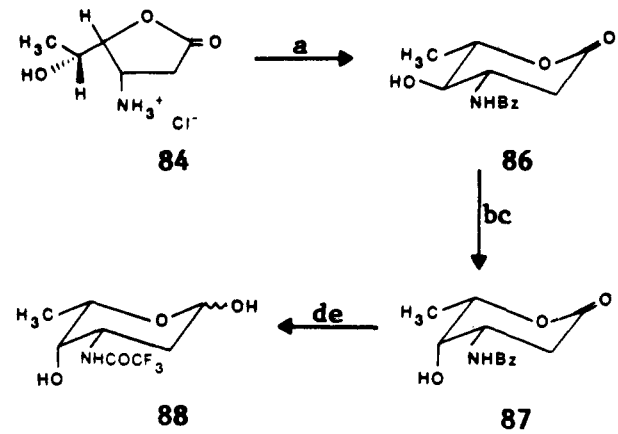
The (2*R*,3*S*)-aldehyde **81b** was employed by Fuganti and co-workers[83] in the stereoselective, direct total synthesis of daunosamine (**1**) shown in Scheme XII. Reaction of **81b** with allylmagnesium bromide (THF, −78°C) stereoselectively produced an 8:2 mixture (75% yield) of alcohols **89**; 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 X[a]



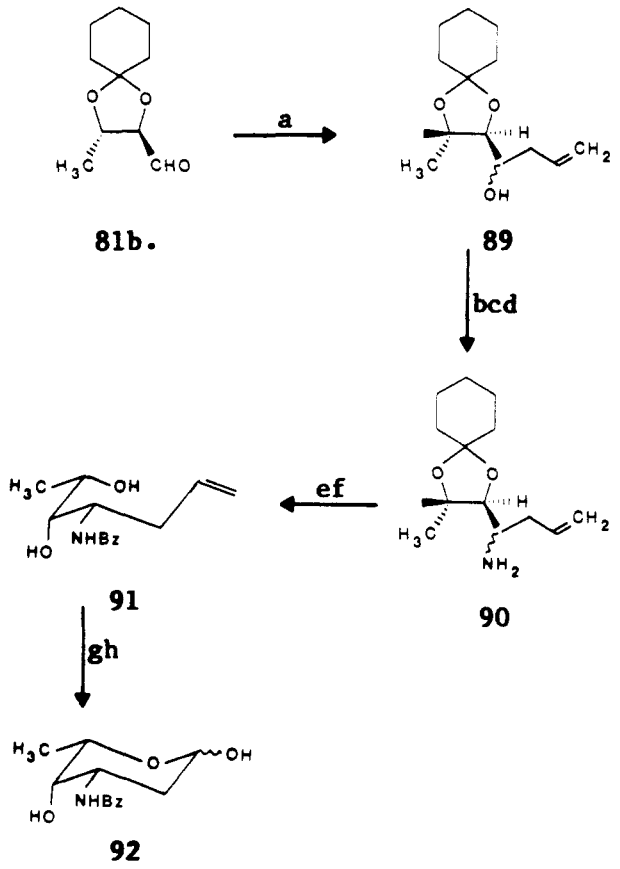
[a] (a) $Ph_3P{=}CHCO_2Et$; (b) NH_3, CH_3OH; (c) HCl, Et_2O; (d) TFAA, Py; (e) THF, DIBAL, −50 °C.

SCHEME XI[a]



[a] (a) NaOH, PhCOCl; (b) MsCl, Py; (c) NaOAc; (d) TFAA, Py; (e) DIBAL.

SCHEME XII[a]



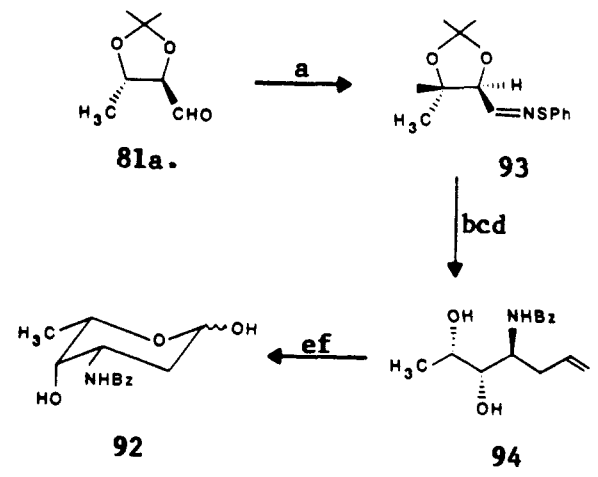
[a] (a) $BrMgCH_2CH{=}CH_2$, THF, −78 °C; (b) TsCl, Py; (c) NaN_3, NH_4Cl, DMF; (d) LAH, Et_2O; (e) HOAc, H_2O; (f) PhCOCl, K_2CO_3; (g) O_3, CH_3OH; (h) $(CH_3)_2S$.

amine **90**. Hydrolysis of the acetonide and selective benzoylation 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[84] and Mukaiyama[87] 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.

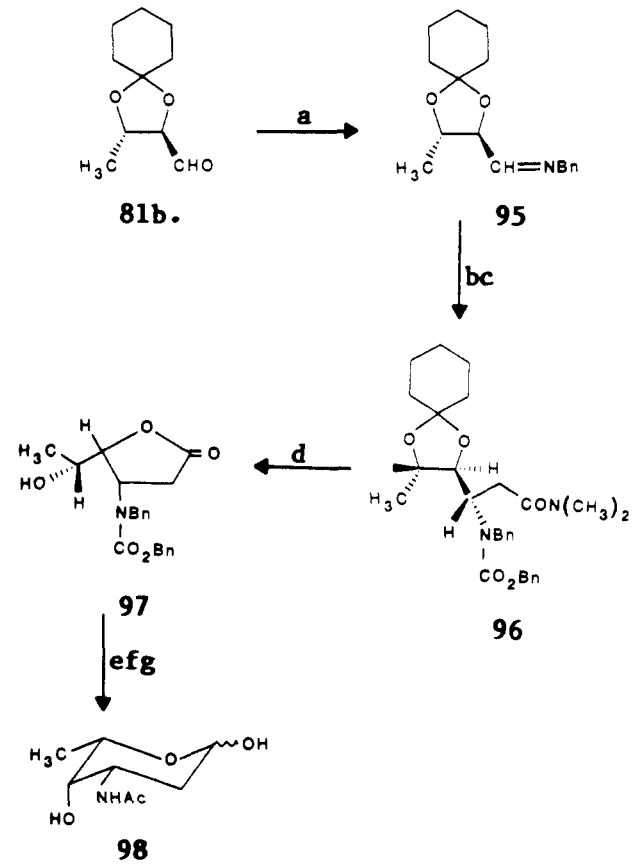
In the route employed by Fuganti et al.[84] and shown in Scheme XIII, the sulfenimine **93** was prepared from **81a** ($(PhS)_2$, $AgNO_3$)[89] initially. Addition of diallylzinc to **93** was highly *erythro* selective (75:1) and furnished, after acidic hydrolysis and benzoylation, the intermediate **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[a]



[a] (a) PhSSPh, $AgNO_3$, NH_3, CH_3OH; (b) $(CH_2{=}CHCH_2{-})_2Zn$; (c) H_3O^+; (d) PhCOCl, $NaHCO_3$; (e) O_3, CH_3OH; (f) $(CH_3)_2S$.

SCHEME XIV[a]

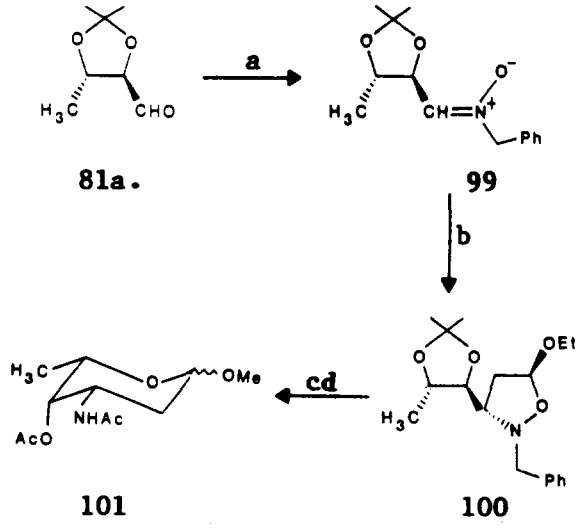


[a] (a) $PhCH_2NH_2$, Et_2O; (b) $LiCH_2CON(CH_3)_2$, $ZnBr_2$, THF; (c) $PhCH_2OCOCl$, $NaHCO_3$; (d) HOAc, H_2O; (e) DIBAL; (f) Pd/C, H_2, HCO_2H; (g) Ac_2O.

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 coworkers[87] 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 α-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* β-aminoamide **96** (50% yield from **81b**). Without zinc bromide, the stereo-

SCHEME XV[a]



[a] (a) $PhCH_2NHOH$; (b) $EtOCH{=}CH_2$; (c) $Pd(OH)_2$, H_2, HCl, CH_3OH; (d) Py, DMAP, Ac_2O.

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 aminohexose. Deprotection of the amino group by catalytic hydrogenation and acetylation of the resultant free amino compound produced *N*-acetyldaunosamine (**98**) in 42% yield from **96** (21% yield overall).

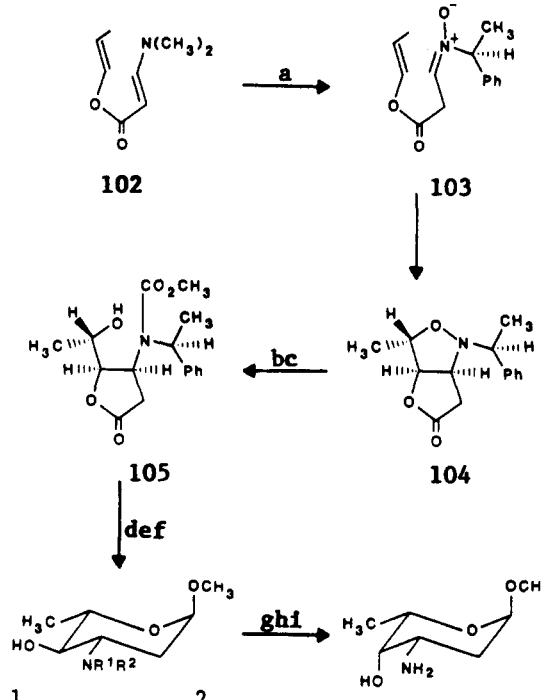
DeShong and Leginus[90] used the achiral aldehyde with the same relative stereochemistry as **81a** to synthesize racemic daunosamine. The reaction sequence which is shown in Scheme XV is stereospecific and is the highest yield route yet reported to racemic product from this aldehyde intermediate. Reaction of the racemic acetonide **81a** with benzylhydroxylamine gave exclusively the *Z*-nitrone **99**, which underwent diastereo- and regiospecific 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[91] provided the racemic *N,O*-diacetyl derivative **101** of methyl daunosaminide. Although only the achiral aldehyde obtained from crotonic acid[92,93] has been employed in this sequence, in principle, the aldehyde prepared from tartaric acid[85–87] 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[94] 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 nitrone cycloadditions with enol ethers.

Formylation of *trans*-propenyl acetate with bis(dimethylamino)-*tert*-butoxymethane[95] gave **102**, which was heated with the oxalate salt of (*S*)-(−)-*N*-hydroxy-α-methylbenzenemethanamine[96] to form **103**. The nitrone intermediate **103** underwent spontaneous intramolecular 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 α- and β-methyl acosaminide anomers. The major anomer was reductively debenzylated to **106b** with sodium and ammonia. The procedure of Marsh et al.[39] 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**.

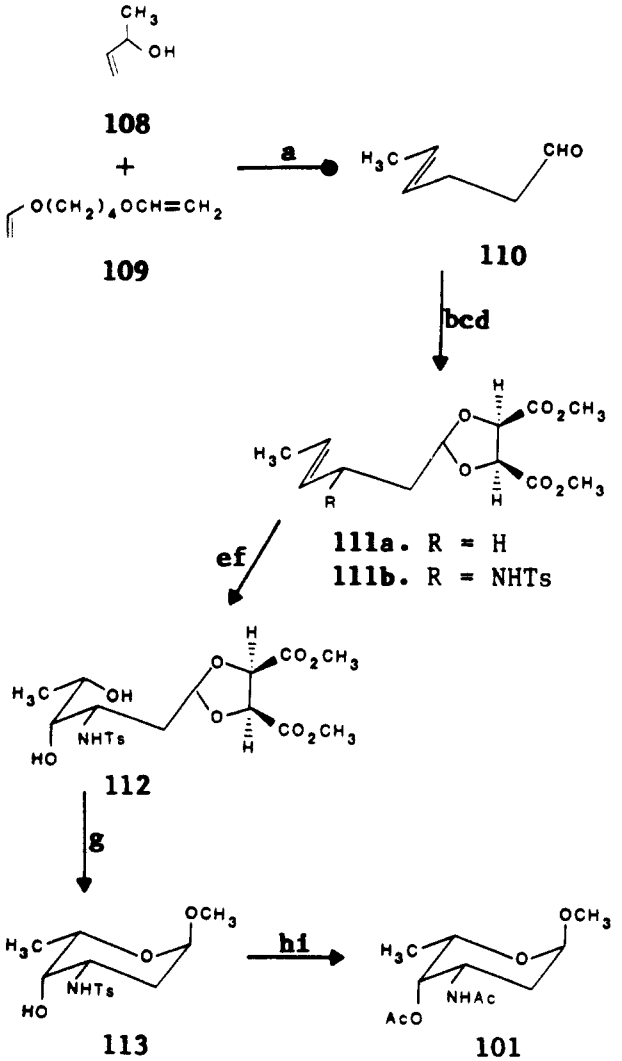
SCHEME XVI[a]



[a] (a) (S)-(−)-*N*-hydroxy-α-methylbenzenemethanamine oxalate salt, xylene; (b) Zn, HOAc–H_2O; (c) Na_2CO_3, CH_3OCOCl, THF; (d) DIBAL; (e) Amberlite-H^+, CH_3OH; (f) Na/NH_3; (g) MsCl, Py; (h) DMF–H_2O; (i) $Ba(OH)_2$, H_2O.

Using a modification of their racemic synthesis,[97] Dyong and co-workers[98,99] developed a novel chiral route to **1** from commerically available 3-buten-2-ol (**108**) and 1,4-bis(vinyloxy)butane (**109**) (Scheme XVII). Mercuric acetate catalyzed reaction of **108** with **109**,[100] 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[101] produced the tosylamide **111b** in 53% overall yield. Cis hydroxylation of **111b** with osmium tetroxide and *N*-methylmorpholine *N*-oxide[102] resulted in a 4:1 mixture of *xylo* and *lyxo* (**112**) diols. In contrast, cis hydroxylation carried out with *N*-bromoacetamide and silver acetate,[103,104] 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[a]

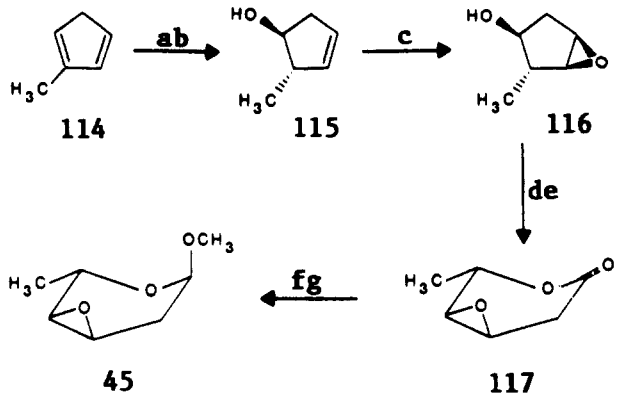


[a] (a) $Hg(OAc)_2$; (b) NaOH, $(H_3CO)_2SO$; (c) (2*R*,3*R*)-(+)-dimethyltartrate, TsOH, PhH; (d) $Se(NTs)_2$, CH_2Cl_2; (e) $CH_3CONHBr$, AgOAc; (f) $NaOCH_3$; (g) CH_3OH, HCl; (h) Na/NH_3; (i) Ac_2O, Py.

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.

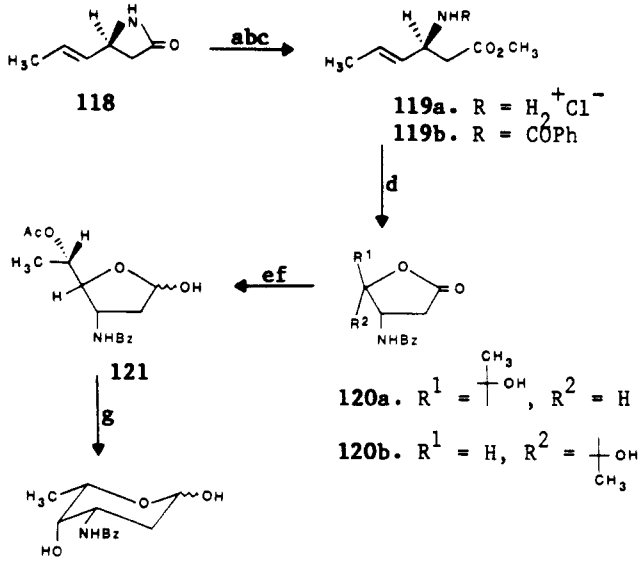
An elegant, albeit low yield, chiral, stereospecific total synthesis of **45**, the epoxide intermediate to acosamine (**4**) and daunosamine (**1**), from achiral precursors was recently reported by Grethe et al.[45] (Scheme XVIII). Asymmetric hydroboration of 2-methylcyclopentadiene (**114**) with the optically active borane derived from diborane and pinene gave the chiral alcohol **115** in 50% yield (95% enantiomeric excess).[105] 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 α-anomer of **45** (10%). The remaining transformations were performed according to Marsh's procedure[39,45] and

SCHEME XVIII[a]



[a] (a) (−)-Di-3-pinanylborane; (b) H_2O_2, NaOH; (c) MCPBA, $NaHCO_3$, CH_2Cl_2; (d) CrO_3-2Py, CH_2Cl_2; (e) MCPBA; (f) DIBAL, $PhCH_3$, −70 °C; (g) CH_3OH, BF_3.

SCHEME XIX[a]

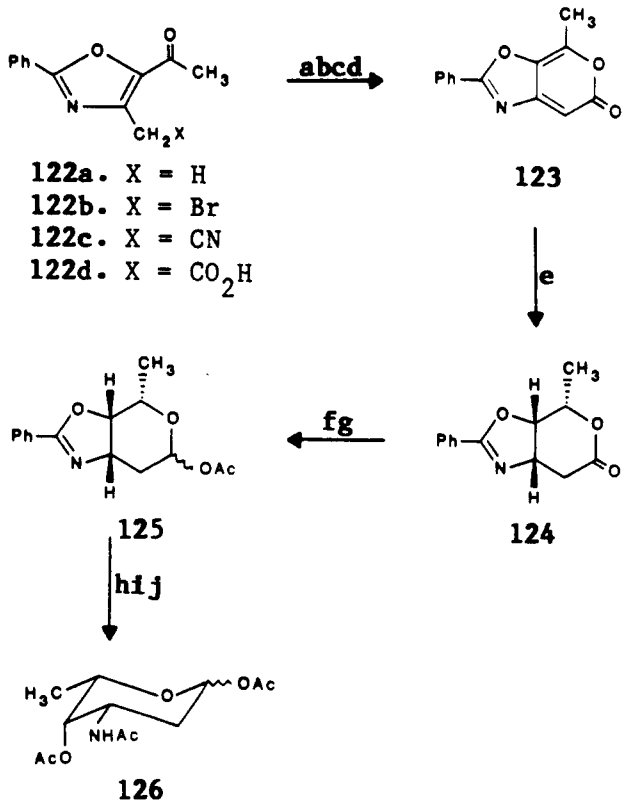


[a] (a) CH_3OH, HCl; (b) Resolve with dibenzoyl-L-tartaric acid or *p*-bromotartranilic acid; (c) PhCOCl, Py, CH_2Cl_2; (d) catalytic OsO_4, TMNO; (e) Ac_2O, Py; (f) DIBAL, THF; (g) NH_3, CH_3OH, 0 °C.

provided **1** in 4% overall yield.

Hauser and co-workers[106] 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[107] 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.[108,109] Methanolysis cleaved the β-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;[110] the efficiencies were 68 and 71%, respectively. The optically active amine **119a** was benzoylated to the amide **119b**, which underwent diastereoselective cis hydroxylation (OsO_4, TMNO)[111] 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[a]



[a] (a) NBS; (b) KCN, HCN, Et_2O, 75 °C, 36 h, (sealed tube); (c) HCl, HOAc; (d) $SOCl_2$, $CHCl_3$; (e) Rh/Al_2O_3, H_2; (f) $Na(OCH_3)_2AlH$; (g) Ac_2O, Py; (h) Rh/Al_2O_3, H_2; (i) H_3O^+; (j) Ac_2O, Py.

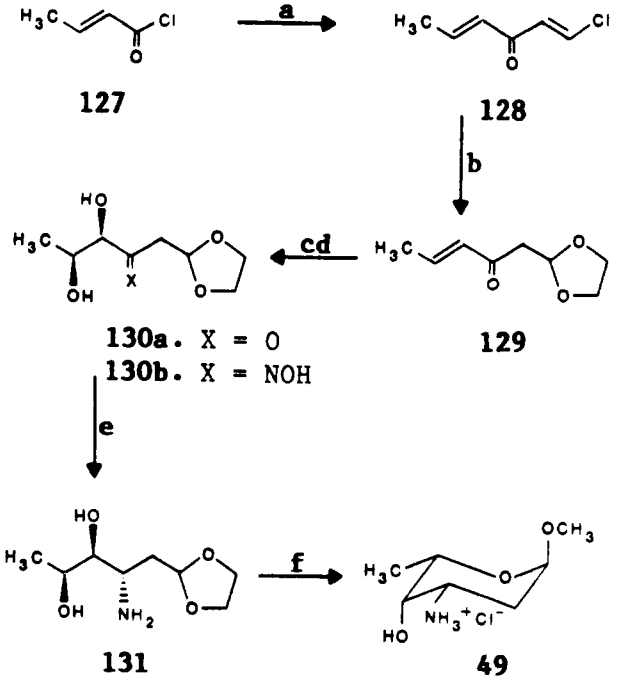
lactone **120b** provided the *xylo* isomer in 8% yield overall. Important aspects of this preparation are the use of inexpensive precursors and the relative ease of the chemical manipulations.

4. Racemic Syntheses

The earliest racemic total synthesis of daunosamine (**1**,**2**) was reported by Wong et al.[112] 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**[113] 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_2O, KCN; sealed tube; 75 °C; 36 h). Hydrolysis of the nitrile in **122c** produced the unstable acid **122d** that was immediately transformed to the oxazolo-γ-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.[114] 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[a]



[a] (a) CH_2=$CHCl$; (b) $HOCH_2CH_2OH$, K_2CO_3; (c) $KMnO_4$, acetone, −40 °C; (d) $HONH_2$·HCl, NaOEt; (e) PtO_2, H_2, HOAc; (f) CH_3OH, HCl.

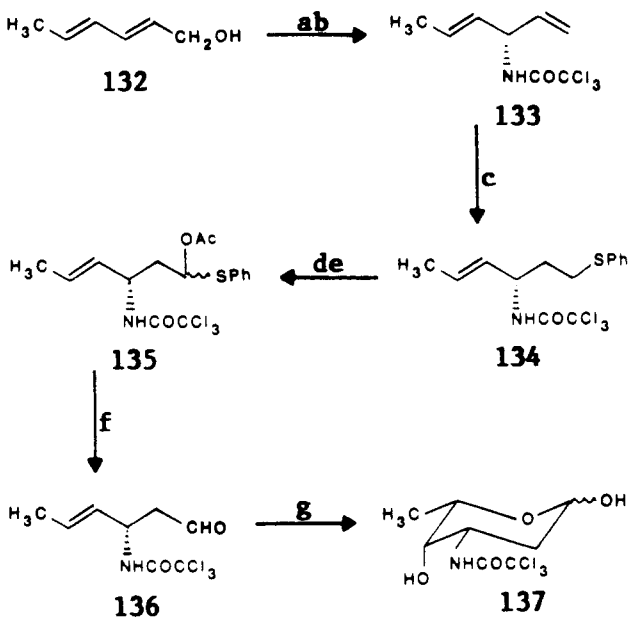
Transformation of the β-chloroenone fragment to a β-keto acetal through reaction of **128** with potassium carbonate and ethylene glycol gave **129** in only 14% yield. The 4,5-olefinic entity in **129** was cis hydroxylated with potassium permanganate (−40 °C, acetone; 35%), and the resultant keto alcohol **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.[116] 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_3CN)[53] of **132** furnished a quantitative yield of the deconjugated trichloroactamide **133**, and free radical addition of benzenethiol[117] to **133** provided the latent functionalization required for subsequent conversion of C-1 to an aldehyde functionality. The regiospecifically formed thiophenyl adduct **134** was oxidized to the sulfoxide,[118] which on Pummerer rearrangement ($(CF_3CO)_2O$, Ac_2O, lutidine)[119] gave **135**. After hydrolysis ($CuCl_2$, H_2O)[120] 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.[121] 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[a]



[a] (a) NaH, Cl_3CCN; (b) xylene, Δ; (c) PhSH, AIBN; (d) $NaIO_4$, CH_3OH; (e) Ac_2O, TFAA, Lutidine; (f) $CuCl_2$, CH_3CN–H_2O; (g) catalytic OsO_4, TMNO, acetone–H_2O.

aminohexose to be isolated, and was originally obtained from rhodomycin–isorhodomycin mixtures by Brockmann and co-workers.[1,2] Subsequently, it was shown to be the lead sugar in numerous anthracycline antibiotics[122,123] 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 ^1H 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.[42,43] 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*-acetylsporaviridin by Harada et al.[124] and its structure established through mass spectral, ^{13}C NMR, and ^1H 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.[15,16,42] Acosamine (**4**) has often served as an intermediate in syntheses of daunosamine (**1**)[18,39,45,46,55,81,83,84,94] and has also been isolated as a minor product in other preparations of aminohexoses.[125,126] (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**).[26,27,33]

1. Chiral Syntheses from Carbohydrate Precursors

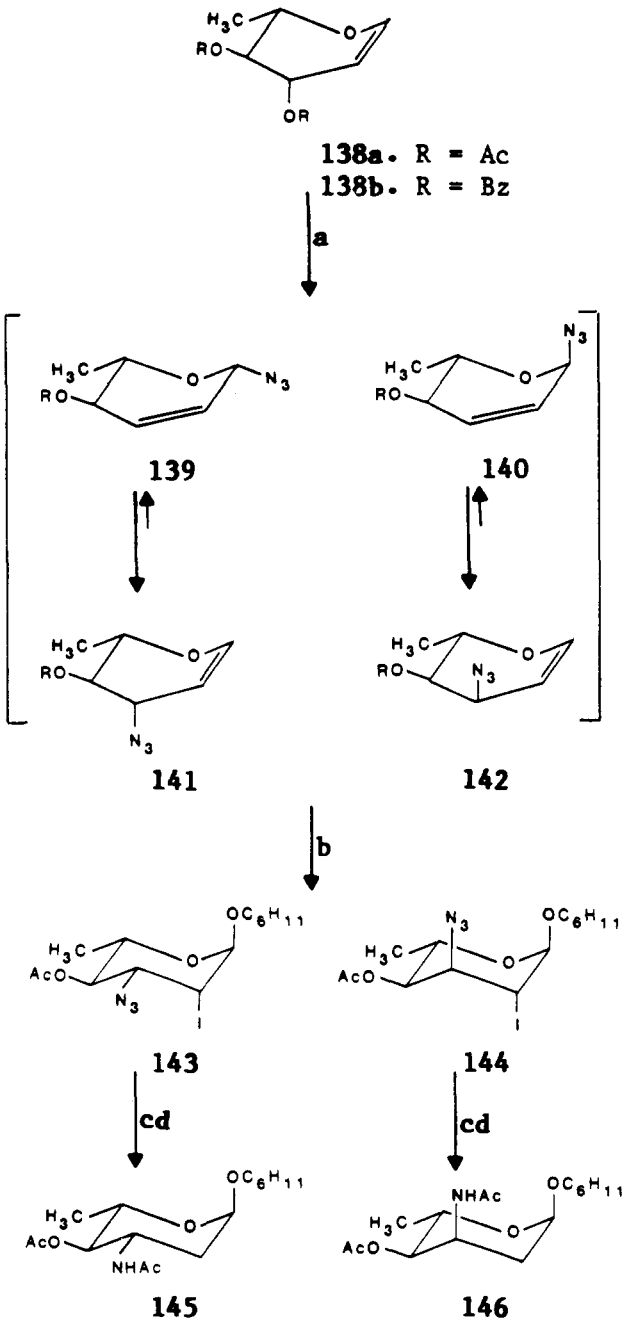
In order to confirm the assigned structure, Gupta[127] and Lee et al.[128] independently reported preparations of L-acosamine (**4**). Both preparations were accomplished from the azido intermediate **46a** that Marsh et al.[39] used in the synthesis of daunosamine (**1**) and were identical with the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

Heyns et al.[129,130] and Boivin and Monneret[131] 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.[129,130] and shown in Scheme XXIII, the diacetate derivative **138a** of rhamnal (**43**) was reacted with sodium azide and boron trifluoride in ether.[132] 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[133] produced a 7:3 ratio of iodoazides **143** (L-*arabino*) and **144** (L-*ribo*), which were separated by chromatography. ^1H NMR studies showed that **143** existed solely in the $^1C_4$ conformation whereas **144** was a mixture of $^1C_4$ and $^4C_1$ conformers. Concomitant reduction of the azide group and reductive dehalogenation of **143** were accomplished with nickel(II) chloride and sodium borohydride;[134] subsequent acetylation (Ac_2O, Py) of the reduction product gave the hexyl *N*,*O*-diacetyl-α-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[131] made several additional contributions to the employed azide chemistry. They demonstrated that while the ratio of 3-azidohexoses (**141b** and **142b**) from rhamnal dibenzoate (**138b**)[135] 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 reequilibration 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 $C_6H_{11}OH$) 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.

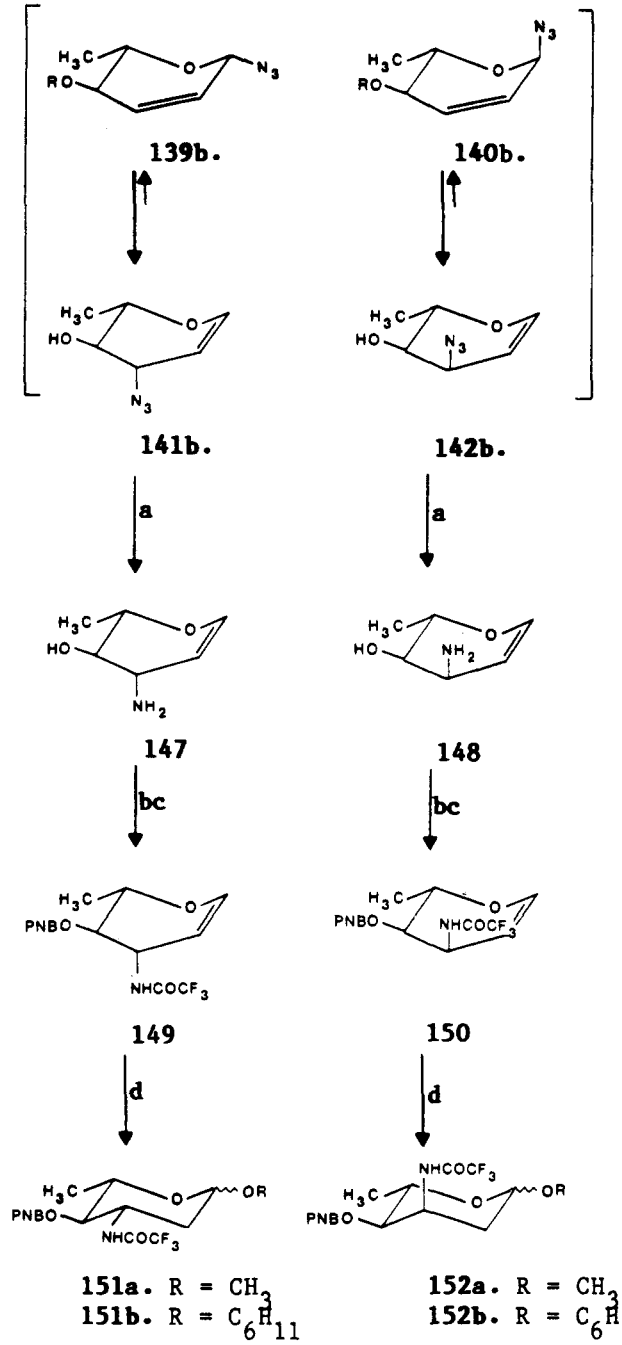
Using a sequence developed in their earlier work on ristosamine (**8**),[136] Pelyvas et al.[137] reported the synthesis of **4** and its 1-thiobenzyl derivative **155b** from rhamnal (**43**) (Scheme XXV). Oxidation of L-rhamnal (**43**) to the enone **153** with Fetizon's reagent[138] (silver carbonate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

SCHEME XXIII[a]



[a] (a) NaN_3, BF_3-Et_2O, CH_3CN; (b) $C_6H_{11}OH$, NIS; (c) $NiCl_2$, $NaBH_4$; (d) Ac_2O, Py.

SCHEME XXIV[a]



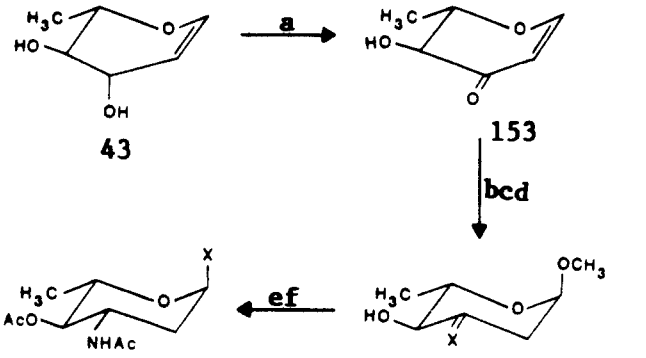
[a] (a) LAH; (b) TFAA, Et_3N; (c) p-$NO_2C_6H_4COCl$, Py; (d) TsOH, CH_3OH or TsOH, $C_6H_{11}OH$.

conjugate addition of sodium methoxide to the olefinic moiety[139] furnished **154a** as a 15:1 mixture of α- and β-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,[139] 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**.[136] 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.[140] recently reported the preparation of acosamine (**4**) and the *ribo* (**8**) and *xylo* (**11**) configurational isomers from a D-mannitol derivative. This long sequence, some 22 steps, gave only a modest yield (0.8%) of product.

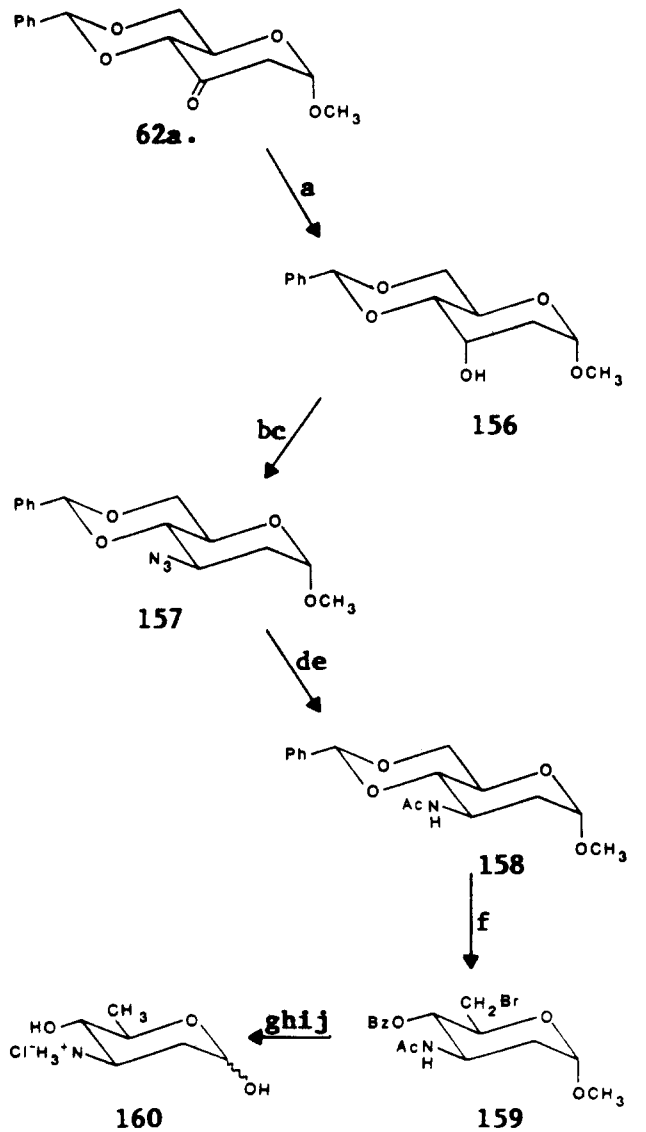
The D-enantiomorph **5** of acosamine was prepared by Horton et al.[141] using an intermediate from their earlier daunosamine synthesis[58] (Scheme XXVI). The keto sugar intermediate **62a**, obtained from methyl-D-mannoside (**60**),[58] was reduced with LAH to produce a 10:1 mixture of D-*ribo* (**156**) 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,[26,27,29] 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[68] produced the 4-*O*-benzoyl-6-

SCHEME XXV[a]



[a] (a) Ag_2CO_3/Celite, PhH; (b) $NaOCH_3$, CH_3OH; (c) NH_2OH, CH_3OH; (d) Ac_2O, Py; (e) BH_3; (f) TFAA, Py.

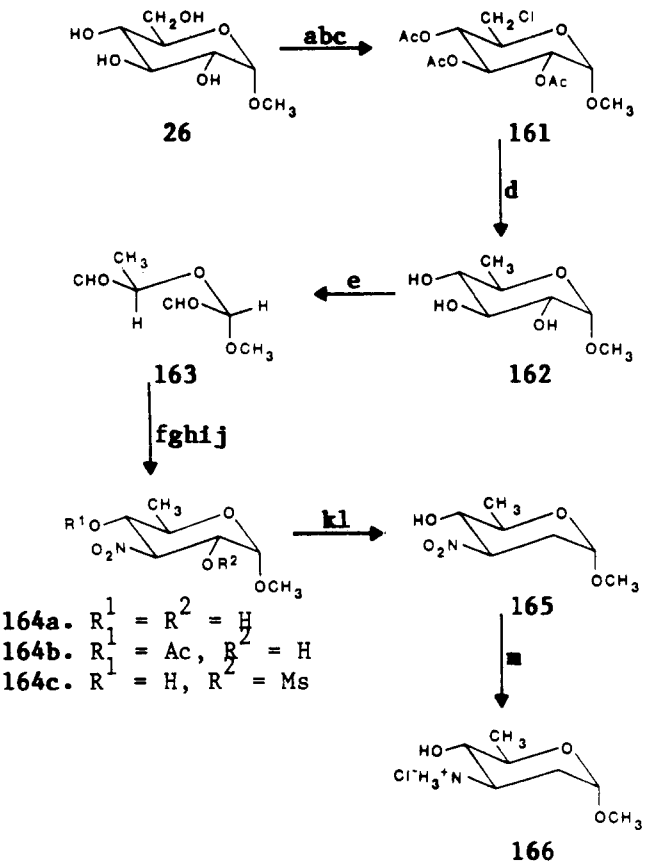
SCHEME XXVI[a]



[a] (a) LAH, Et_2O; (b) MsCl, Py; (c) NaN_3, DMF; (d) Ni(R)/H_2, CH_3OH; (e) Ac_2O; (f) NBS, CCl_4, $BaCO_3$; (g) Ni(R)/H_2, Et_3N; (h) $NaOCH_3$; (i) $Ba(OH)_2$; (j) HCl–H_2O.

bromo analog **159** which was shown by ^1H NMR to have the $^4C_1$ conformation. Following reductive dehalogenation 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.

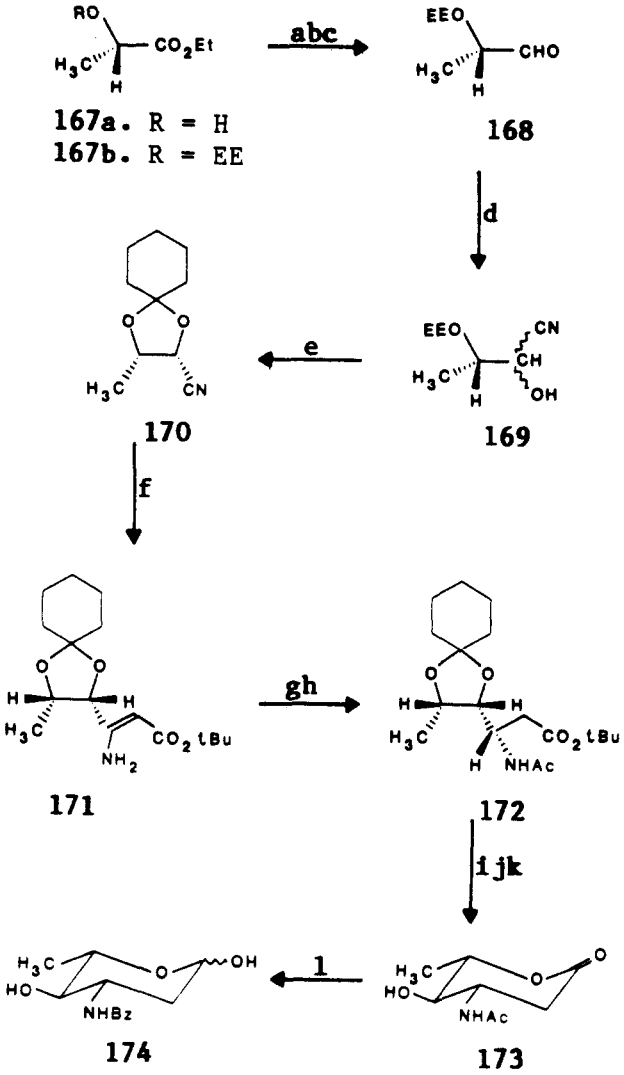
SCHEME XXVII[a]



[a] (a) MsCl, DMF; (b) 2-propanol/H_2O; (c) Ac_2O, Py; (d) LAH, Et_2O; (e) $NaIO_4$; (f) CH_3NO_2, $NaOCH_3$; (g) $BF_3{\cdot}Et_2O$, Ac_2O; (h) NaOH, acetone, AcCl; (i) MsCl, Py; (j) CH_3OH, HCl; (k) $NaHCO_3$; (l) $NaBH_4$; (m) PtO_2, H_2, HCl, CH_3OH.

Baer and Georges[142] 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,[33] 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_2O, Py), produced the 6-chloro sugar **161**.[143,144] Reduction of **161** with LAH furnished **162**, which was oxidized with sodium metaperiodate to the dialdehyde **163**. Aldol condensation of **163** with nitromethane[145,146] gave the nitro sugar **164a** in 29% overall yield from **26**. Boron trifluoride catalyzed acetylation of **164a** and selective 2-de-O-acetylation[147] (MeOH, AcCl) of the diacetate produced **164b**. Following methanesulfonylation of **164b**, the 4-acetoxyl functionality was de-O-acetylated with methanolic hydrogen chloride[148] 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[a]



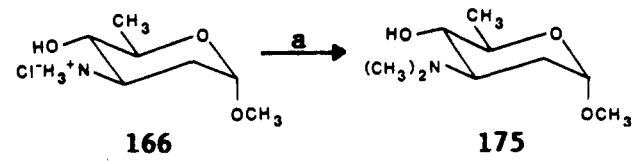
[a] (a) CH_2=CHOEt, Py, TsOH; (b) LAH, Et_2O; (c) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2; (d) $(CH_3)_2C(OH)CN$, Et_3N; (e) $(CH_2)_5C(OMe)_2$, $(Me_3SiO)_2SO_2$; (f) $BrMgCH_2CO_2t$-Bu, Et_2O; (g) Ac_2O, Py; (h) Rh/C, H_2, THF, 55 °C; (i) HCl–H_2O; (j) PhCOCl, $NaHCO_3$, acetone–water; (k) HCl–H_2O; (l) DIBAL, THF, -55 °C.

2. Chiral Syntheses from Non-Carbohydrate Precursors

Fronza et al.[149] have reported the syntheses of both racemic and chiral L-acosamine (4) from cinnamaldehyde and of several *C*-methyl sugars from α-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).[81]

A chiral synthesis of 4 from ethyl L-lactate (**167a**) was recently documented by Hiyama et al.[150] and is shown in Scheme XXVIII. The key intermediate, (2*R*,3*S*)-butanenitrile **170**, is similar to the (2*R*,3*S*)-aldehydes **80** and **81** used by Fuganti and co-workers,[83,84,86] Mukaiyama et al.,[87] and Deshong and Leginus[90] 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[64,151] 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 cyclohexanone dimethyl acetal and a catalytic amount of bis(trimethylsilyl) sulfate furnished a 45:55 mixture (94% yield) of the cyclohexylidene butanenitriles with the 2*S*,3*S* and 2*R*,3*S* (**170**) configurations. The isomers were separated by column chromatography and the desired nitrile **170** was condensed with the magnesium enolate of *tert*-butyl acetate[152] to give the unsaturated amino ester **171** as an 8:2 ratio of *Z* and *E* isomers (54% yield). Acetylation (Ac_2O, Py) of the vinylamine moiety in **171**, followed by catalytic hydrogenation over rhodium (70 kg/cm^2, 55 °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.

SCHEME XXIX[a]



[a] (a) CH_2O, HCO_2H, NaOH.

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.[42,43] The assigned structure was confirmed by Lee et al.,[153] 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.[154] The structure of 7 was originally determined from the similarity of its ^{1}H NMR spectrum to that of D-acosamine (5).[155]

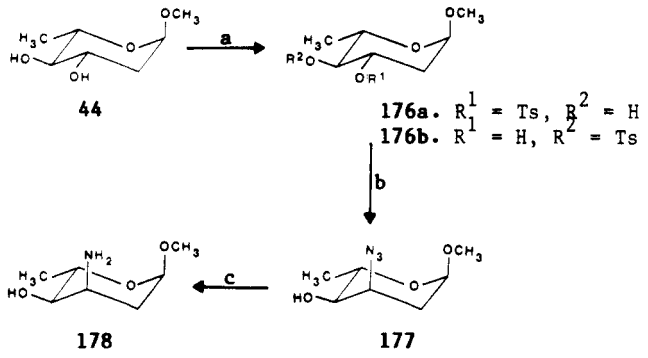
The only reported preparation of angolosamine (7) was performed by Baer and Georges[142] in conjunction with their total synthesis of optically active D-acosamine derivative **166**. As shown in Scheme XXIX, Eschweiler–Clarke methylation[156] (CH_2O, HCO_2H, NaOH) of **166** furnished methyl angolosaminide (**175**).

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

L-Ristosamine (8) is a component of the water-soluble glycoprotein ristomycin,[157,158] which is a member of the vancomycin group of antibiotics.[159] Its structure was determined through chemical degradation and extensive ^{1}H NMR and ^{13}C NMR spectroscopy by Bognar, Sztaricskai, and co-workers.[160–165] 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.[166] that the coupling of L-ristosamine (8) with daunomycinone produced an analogue with anticancer activity. Horton et al.[167,168] 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[a]



[a] (a) TsCl, Py; (b) NaN_3, DMF; (c) Pd/C, H_2.

accomplished in conjunction with the preparation of other hexoses.[32,84,87,88,128-131,137,140] (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

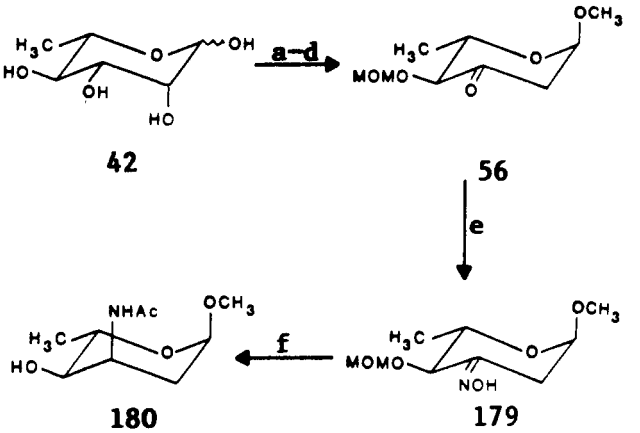
All but one of the reported chiral total syntheses of L-ristosamine (8) were accomplished from rhamnal (43). Shortly after elucidation of the structure of 8, Lee et al.[153] and Sztaricskai et al.[169] concurrently reported almost identical preparations from the diol pyranoside 44 that served as a key intermediate in the synthesis of daunosamine (1) reported by Marsh et al.[39] Sztaricskai et al.[170,171] subsequently reported the complete details of their work, which is outlined in Scheme XXX. Methoxymercuration ($Hg(OAc)_2$, methanol) of L-rhamnal (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*-*arabino*-monotosylates **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-rhamnal (43) was subsequently reported by Pelyvas et al.[136] The work paralleled that employed for the synthesis of D-acosamine (5)[137] and was presented in that section.

Brimacombe and co-workers[56,172] 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).[55] 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).

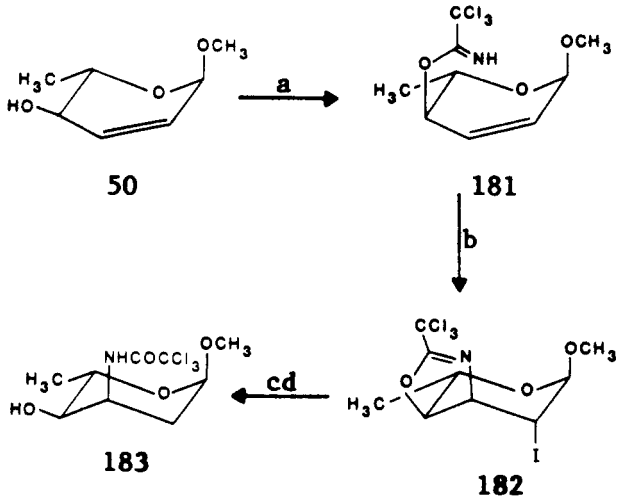
The shortest route to L-ristosamine (8) from rhamnal (43) was accomplished by Pauls and Fraser-Reid,[173] who used the reaction sequence shown in Scheme XXXII. The synthetic plan conceptually paralleled their preparation of daunosamine[47] in that the appended imidate functionality in **181**, prepared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

SCHEME XXXI[a]



[a] (a) CH_3OH, Amberlite-H^+; (b) $PhCH(OCH_3)_2$, TsOH, DMF; (c) CH_3OCH_2Cl, $(i\text{-}Pr)_2NEt$; (d) BuLi, THF, -30 °C; (e) $NH_2OH\cdot HCl$, CH_3OH, H_2O, $KHCO_3$; (f) PtO_2, H_2, CH_3OH, Ac_2O.

SCHEME XXXII[a]



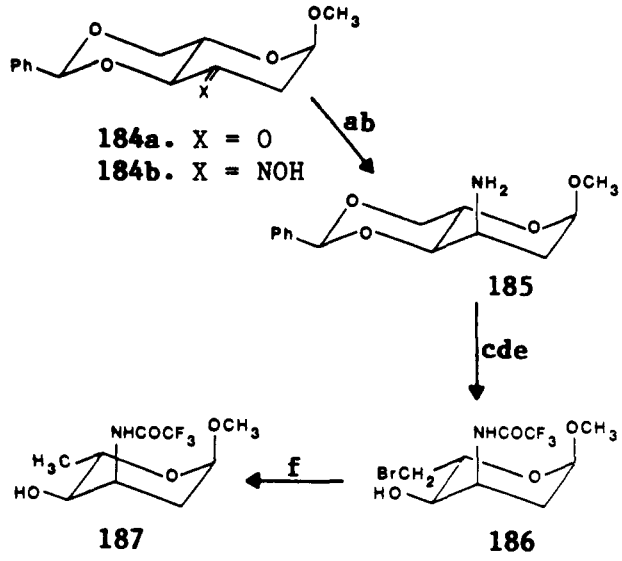
[a] (a) Cl_3CCN, NaH; (b) $I(2,4,6\text{-trimethylpyridine})_2ClO_4$; (c) $(n\text{-}Bu)_3SnH$, AIBN; (d) Py, TsOH, H_2O.

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

The only synthesis of L-ristosamine (8) which did not originate with rhamnal was reported by Arcamone et al.[166] and is shown in Scheme XXXIII. The keto acetal starting material **184a** was prepared according to the method of Williams et al.[175] 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.[45] 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.[68,176] The resultant 6-bromo compound **186** was catalytically reduced to methyl *N*-(trifluoroacetyl)-L-ristosaminide (**187**). No yields were reported.

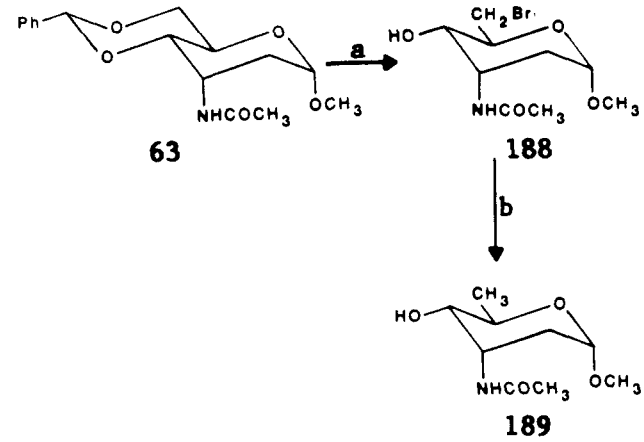
The large number of chiral total syntheses of D-ristosamine (9) can be partially accounted for by its straightforward access from the large pool of D-hexoses. The first preparation of 9 was reported by Horton and

SCHEME XXXIII[a]



[a] (a) H_2NOH·HCl, NaOH, EtOH; (b) LAH, Et_2O; (c) H_3O^+; (d) TFAA, Py; (e) Ph_3P, NBS, DMF; (f) catalytic hydrogenation.

SCHEME XXXIV[a]

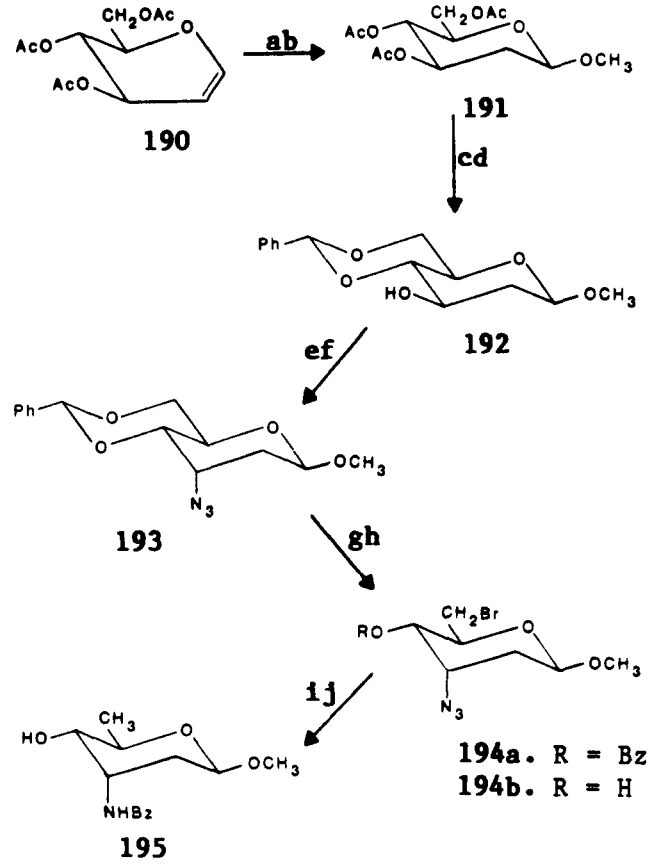


[a] (a) NBS, CCl_4, $BaCO_3$; (b) Ni(R), H_2.

co-workers[167,168] and was derived directly from the sequence they employed for preparation of methyl daunosaminide hydrochloride (**49**)[58] 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*-benzylidine moiety through treatment with NBS and barium carbonate[68] gave the 6-bromo-4-benzoate product **188**, which on catalytic reduction (H_2, Raney Ni) furnished methyl *N*-acetyl-D-ristosaminide (**189**) in 49% overall yield from **60**.

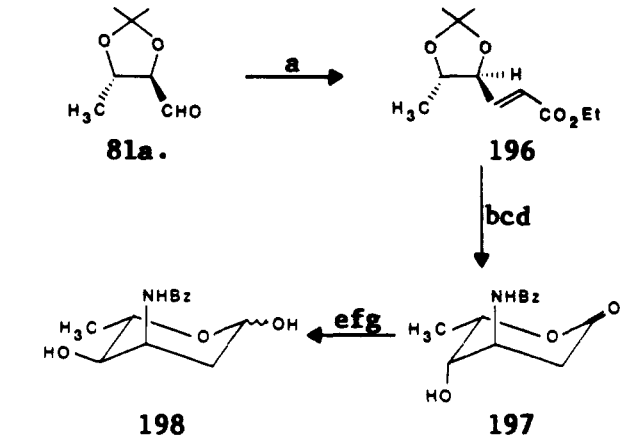
Both Pelyvas et al.[177,178] and Baer et al.[179] reported virtually identical sequences to D-ristosamine (**9**) from triacetyl-D-glucal (**190**) (Scheme XXXV). Treatment of **190**[48,49] with dry hydrogen chloride, followed by silver carbonate induced methanolysis of the 1-chloro intermediate, gave 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;[68] the 4-benzoate functionality in the resultant **194a** was selectively 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.[179] Benzoylation of the reduction product furnished methyl *N*-benzoyl-D-ristosaminide (**195**) in 13% overall yield.

SCHEME XXXV[a]



[a] (a) HCl, PhH; (b) Ag_2CO_3, CH_3OH; (c) $NaOCH_3$; (d) PhCHO, $ZnCl_2$; (e) MsCl, Py; (f) NaN_3, HMPT, 100 °C; (g) NBS, $BaCO_3$, CCl_4; (h) $NaOCH_3$; (i) Ni(R), H_2, CH_3OH, Et_3N; (j) PhCOCl, Py.

SCHEME XXXVI[a]

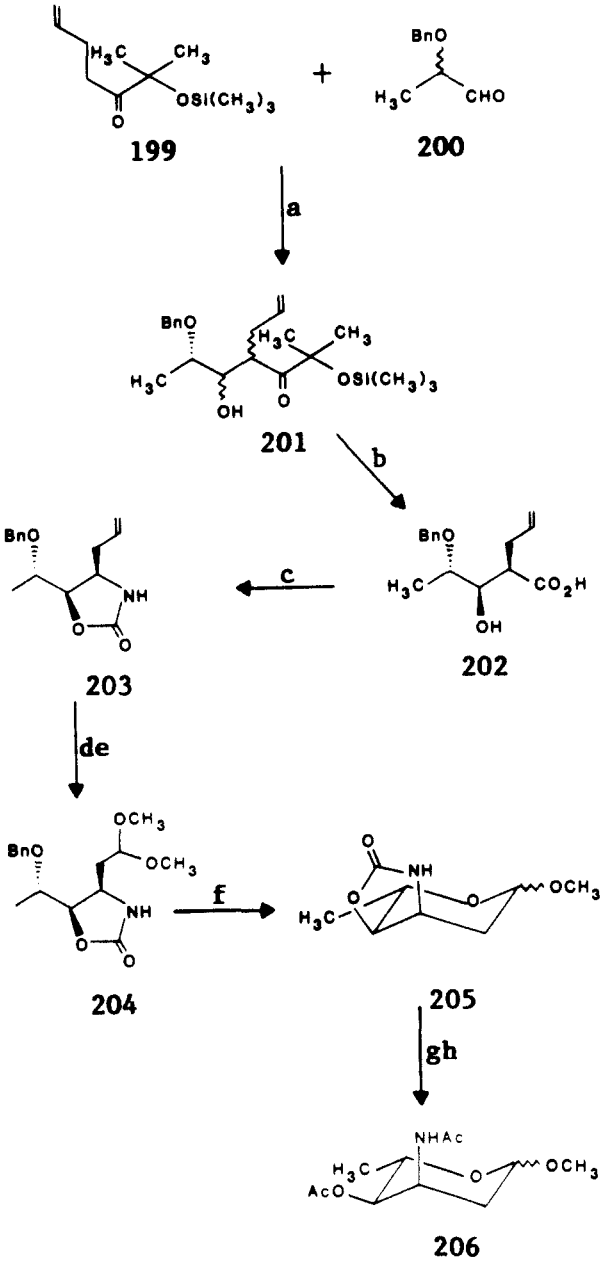


[a] (a) $Ph_3P{=}CHCO_2Et$; (b) NH_3, CH_3OH; (c) HCl, EtOH; (d) NaOH, PhCOCl; (e) MsCl, Py; (f) NaOAc; (g) DIBAL, THF, −40 °C.

2. Chiral Syntheses from Non-Carbohydrate Precursors

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

SCHEME XXXVII[a]



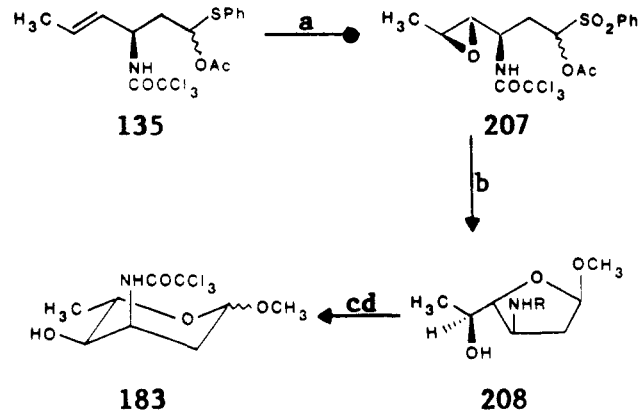
[a] (a) LDA, THF; (b) HIO_4, THF; (c) diphenylphosphorazidate, Et_3N; (d) OsO_4, $NaIO_4$; (e) CH_3OH, HCl; (f) Catalytic hydrogenation; (g) $Ba(OH)_2$; (h) $HCl-H_2O$.

Fronza et al.[86] and is shown in Scheme XXXVI. As in their previously described work,[18,81] the aldehydo acetonide **81a** with the 2*R*,3*S* configuration was first converted to the unsaturated ester **196** through Wittig reaction. Conjugate addition of ammonia,[88] acidic hydrolysis of the acetonide, and benzoylation gave predominantly the δ-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[180] described the stereoselective total synthesis of racemic ristosamine which is shown in Scheme XXXVII. The enolate of the ketone

SCHEME XXXVIII[a]



[a] (a) MCPBA, CH_2Cl_2; (b) $NaOCH_3$, CH_3OH; (c) $HOAc-H_2O$; (d) CH_3OH, HCl.

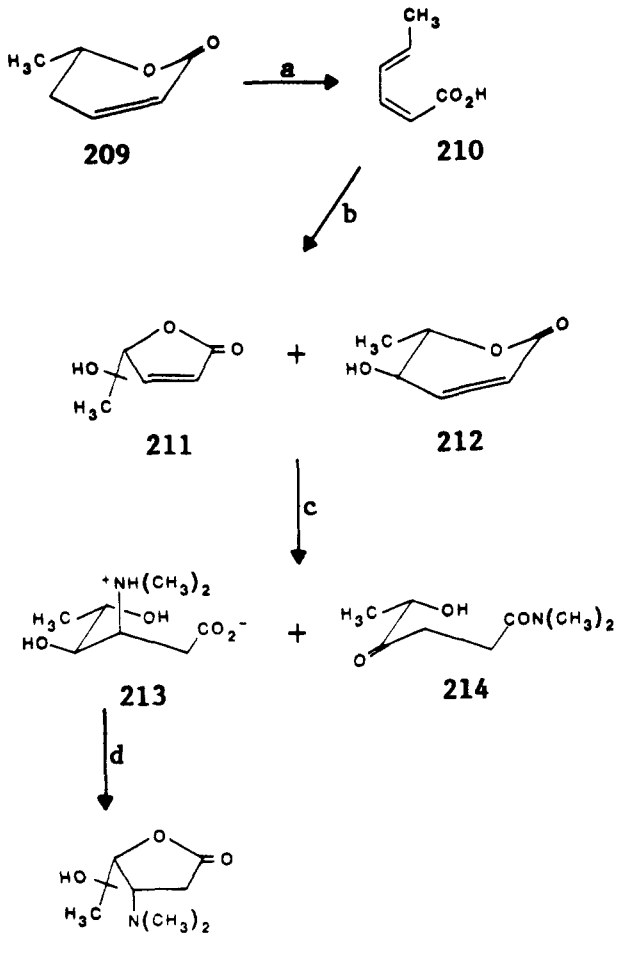
199,[181] generated with lithium diisopropylamide (LDA), was reacted with racemic 2-(benzyloxy)propionaldehyde (**200**) to produce a 78:22 mixture (97% yield) of the diastereoisomers **201**; in order to obtain this ratio, it was necessary to use 2 equiv of the ketone **199** for each one of the aldehyde **200**. Their finding that the desired diastereoisomer of **201** reacted 2.5 times faster with periodic acid[182] 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[183] of **202** produced the oxazolidone **203** in 69% yield. Lemieux–Johnson oxidative cleavage[184] (OsO_4, $NaIO_4$) 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 α and β 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.[116] 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 epoxyacetoxy 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 hemiacetoxide 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-rhodosamine (D-*lyxo*) by Mallams[185,186] and Nourse and Roberts.[187] When it was later shown by X-ray crystallography to have the L-*ribo* configuration, it was renamed megosamine.[186]

SCHEME XXXIX[a]

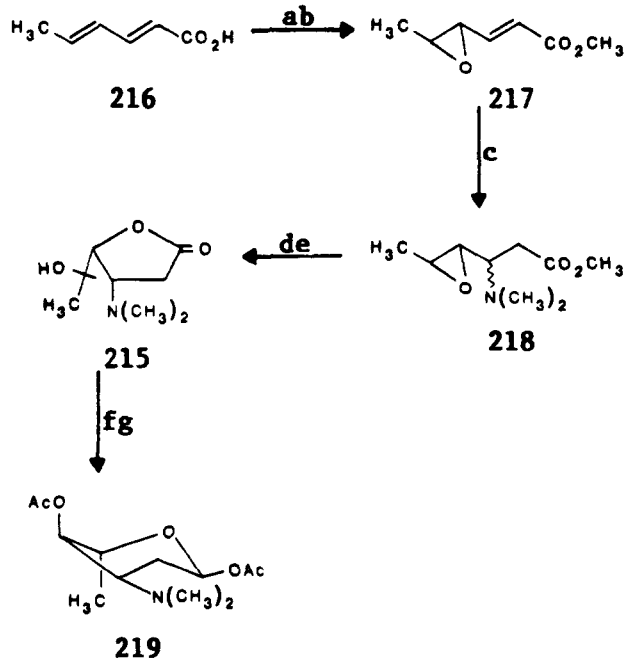


[a] (a) $NaOCH_3$; (b) MCPBA, CH_2Cl_2; (c) $(CH_3)_2NH$, H_2O, 2 weeks; (d) HCl–H_2O.

All of the total syntheses of **10** have been racemic and have been initiated from non-carbohydrate derived materials. Jensen and Torssell[188] reported the preparation of the γ-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[189] (**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 γ- and undesired δ-Osr ıunda 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 α,β-elimination product **211**.

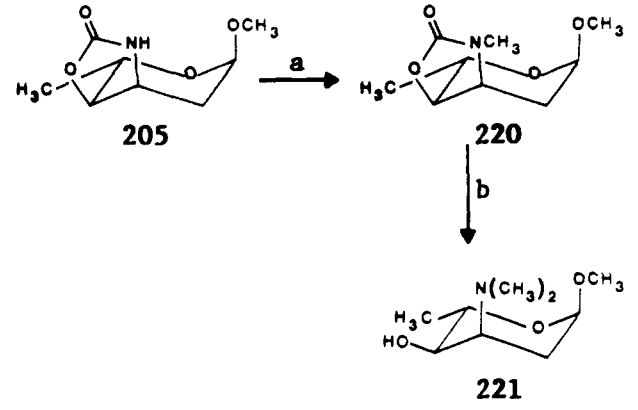
Dyong and Bendlin[190] successfully carried out DIBAL reduction of the lactone intermediate **215** in their total synthesis of racemic **10**, which is shown in Scheme XL. Their preparation of **215** was initiated from (*E,E*)-sorbic acid (**216**). The 3,4-olefinic entity in **216** was selectively epoxidized with buffered peracetic acid[191] and the resultant epoxyacid intermediate was esterified, furnishing 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 γ-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. ^1H NMR studies of **219** showed that this sugar prefers the $^4C_1$ conformation in which the bulky dimethylamino moiety is equatorial.

SCHEME XL[a]



[a] (a) HOOAc, NaOAc, $CHCl_3$; (b) CH_2N_2; (c) $(CH_3)_2NH$; (d) NaOH; (e) HCl–H_2O; (f) DIBAL; (g) Ac_2O, Py.

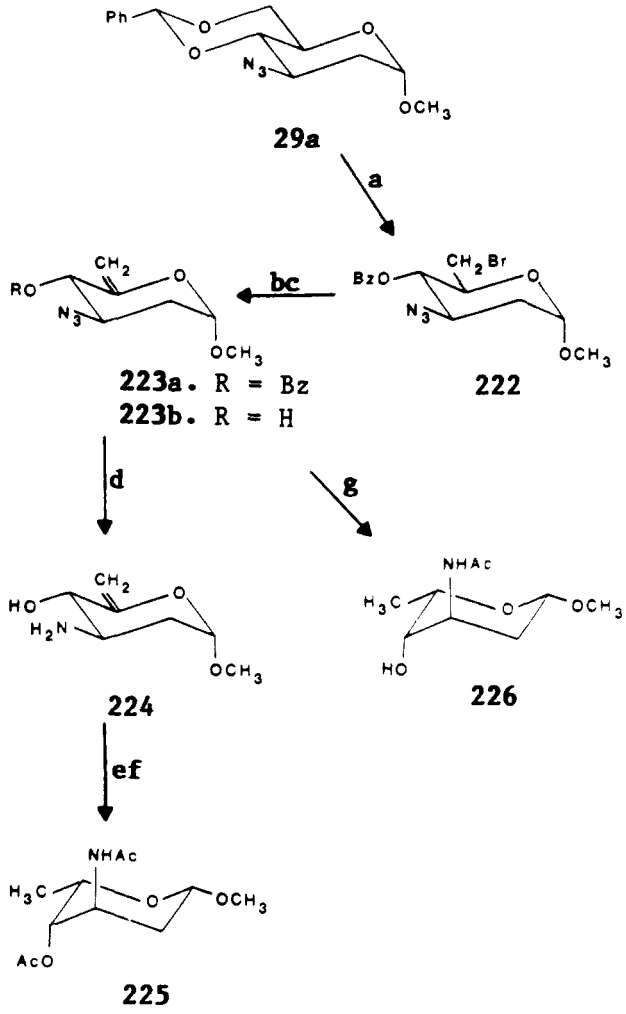
SCHEME XLI[a]



[a] (a) KH, CH_3I; (b) LAH.

Heathcock and Montgomery[180] used the α-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 α- and β-anomers of methyl megosaminide (**221**).

SCHEME XLII[a]



[a] (a) NBS, $BaCO_3$, CCl_4; (b) AgF, Py; (c) NaOH, CH_3OH, H_2O; (d) LAH; (e) Pd, H_2, TsOH; (f) Ac_2O, Py; (g) Ni(R), H_2, EtOH.

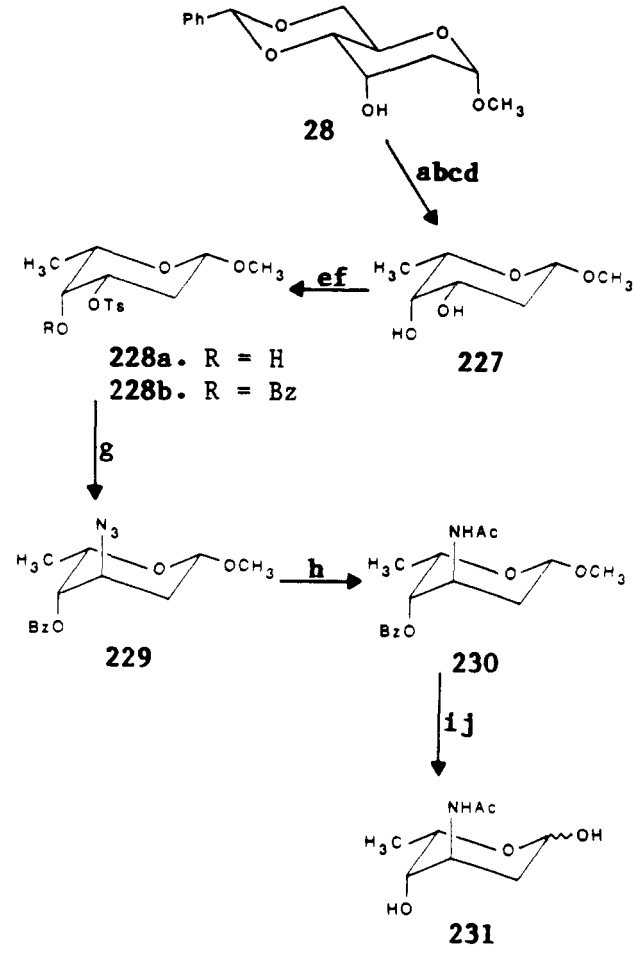
H. 3-*epi*-Daunosamine (L- and D-*xylo*)

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.[82-84,86,94,97,98,105-107,116,150,151,170,171] 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.[126] and Boivin et al.[32] The initial steps in these sequences, shown in Scheme XLII, were identical. The starting material for both was the 4,6-*O*-benzylidene-3-azidohexose **29a**, which was prepared in six steps from α-D-glucopyranoside (**26**) as discussed in the D-daunosamine[26-28,71,73] and D-acosamine[141] sections (Schemes I and XXVI). The 6-bromo derivative **222**, formed by treatment of **29a** with NBS and barium carbonate,[68] was dehydrohalogenated with silver fluoride in pyridine[192] to give the 5,6-unsaturated enopyranoside **223a**. The benzoate ester in **223a** was removed by catalytic transesterification (NaOH, MeOH) to furnish the glycoside **223b**.

SCHEME XLIII[a]



[a] (a) PhCOCl, Py; (b) NBS, $BaCO_3$, CCl_4; (c) Ni(R), H_2, Et_3N; (d) $NaOCH_3$; (e) TsCl, Py; (f) PhCOCl, Py; (g) NaN_3, Me_2SO; (h) Pd/C, H_2, HOAc; (i) $NaOCH_3$; (j) HOAc, H_2O.

At this stage, different reaction sequences were employed to complete the respective syntheses. Cheung et al.[126] reduced the azido entity in **223b** to the amine **224** with LAH. Subsequent catalytic hydrogenation (Pd, H_2, 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.,[32] 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.[193] 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,[68] 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.[194] 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_2) and acetylated to the *N*-acetyl-*O*-benzoyl product **230**. Debenzoylation 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.[18,85] 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.[195] 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.[81]

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.[85,196]

3. Racemic Syntheses

In their racemic synthesis of *xylo*-hexoses (**11** and **12**), Dyong and Wiemann[197] reported a route analagous to that used in their racemic and chiral syntheses of L-daunosamine (**1**)[97-99] 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*)

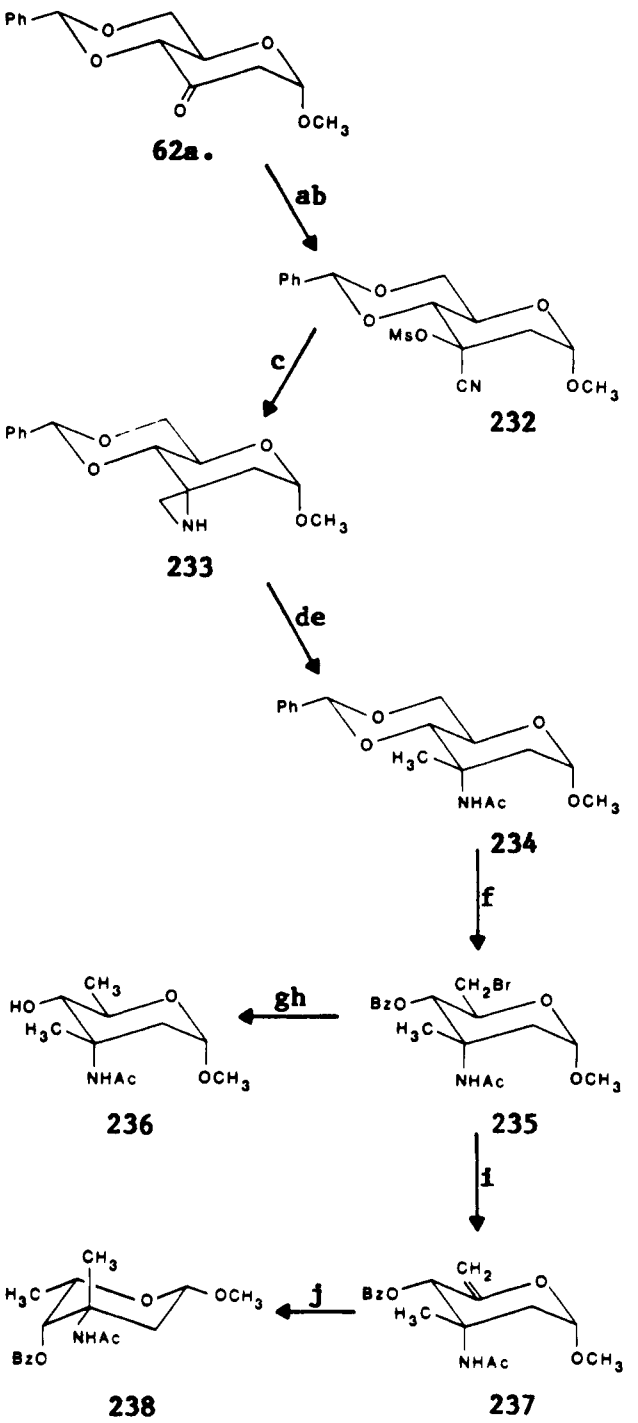
Vancosamine (**13**), the C-3 methyl analogue of daunosamine (**1**), was isolated by McCormick et al.[198] in 1956 following methanolysis of the parent antibiotic, vancomycin.[199-202] A variety of spectroscopic techniques, including high-resolution mass spectroscopy, NMR, and circular dichroism, were 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,[203] pluramycin A,[204] and hedamycin.[205]

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,[206-208] which involves cyanomesylation of a hexos-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.[145,146] 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 performed to establish the generality of the earlier routes.

SCHEME XLIV[a]

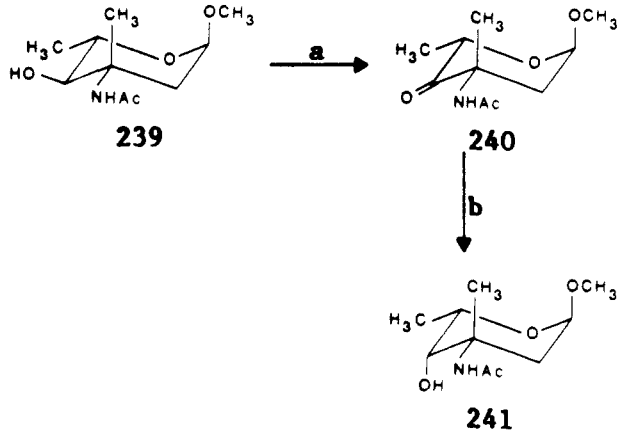


[a] (a) KCN, CH_2Cl_2, $NaHCO_3$, H_2O; (b) MsCl, Py; (c) LAH; (d) Ni(R), H_2; (e) Ac_2O, Py; (f) NBS, $BaCO_3$, CCl_4; (g) Catalytic hydrogenation; (h) base hydrolysis; (i) AgF, DBU; (j) Ni(R), H_2.

1. Chiral Syntheses from Carbohydrate Precursors

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

SCHEME XLV[a]



[a] (a) PCC, CH_2Cl_2, molecular sieves; (b) L-Selectride, THF, −15 °C.

76% yield. Reduction of the cyano moiety with LAH resulted in configurational inversion at C-3[210] and directly produced the spiroaziridine **233**.[211] (The C-4 epimer of **233** was also synthesized to aid in structural and stereochemical assignments.[211]) The aziridine ring in **233** was hydrogenolyzed (Raney nickel, H_2), and the resultant amino–methyl product was acetylated to give **234**, which was treated with NBS and barium carbonate[68] 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)[58] 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.

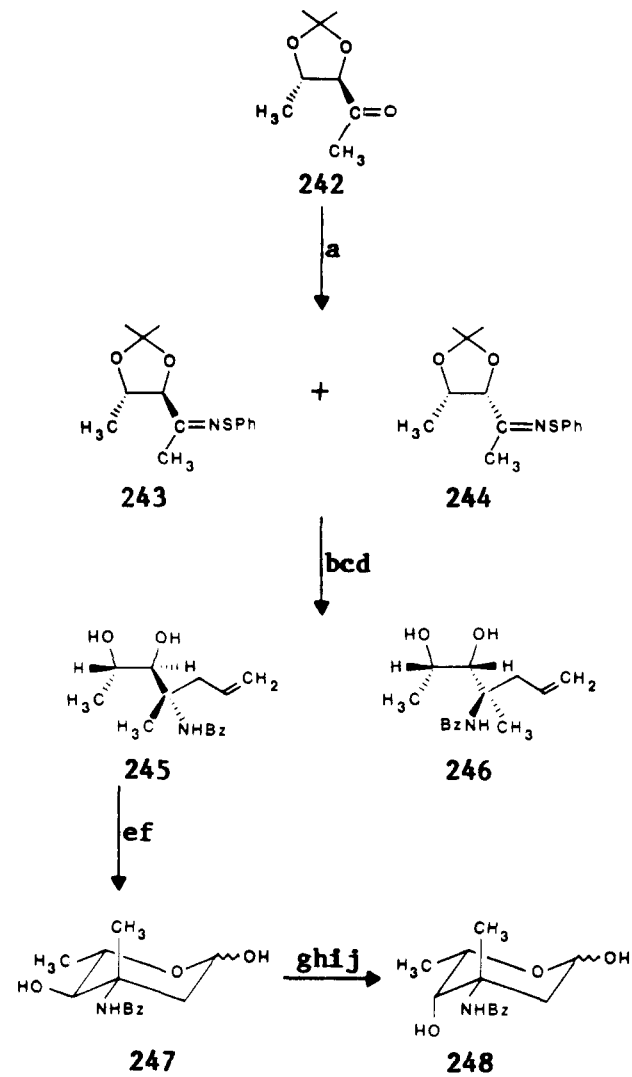
Using the precedent established for the preparation of daunosamine (**1**) through C-4 inversion of acosamine (**4**), Ahmad et al.[212] similarly inverted the configuration of C-4 in 4-*epi*-vancosamine (**239**)[213] to obtain methyl *N*-acetylvancosaminide (**241**) (Scheme XLV). The oxidation of **239** proved sensitive to the choice of oxidizing agents; ruthenium tetroxide gave only a 45% yield, whereas pyridinium chlorochromate[214,215] 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[19,216] reported the total synthesis of three configurational isomers from non-carbohydrate starting materials as shown in Scheme XLVI. The preparations paralleled their earlier work[84] 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 α-methylcinnamaldehyde, acetaldehyde, and baker's yeast with subsequent protection of the diol

SCHEME XLVI[a]



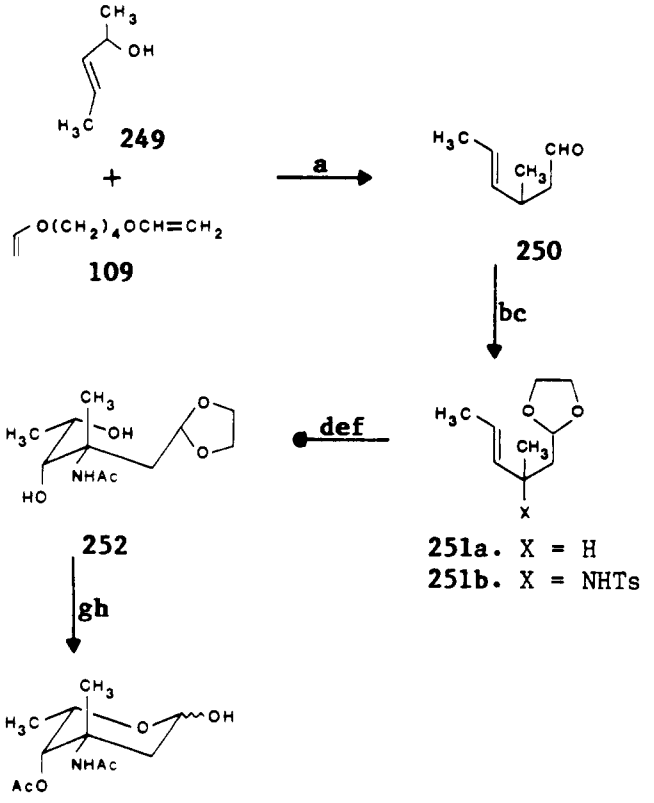
[a] (a) NH_3, CH_3OH, PhSSPh, $AgNO_3$; (b) CH_2=$CHCH_2MgBr$, THF, −78 °C; (c) HCl; (d) PhCOCl, K_2CO_3; (e) O_3, CH_3OH, −20 °C; (f) $(CH_3)_2S$; (g) CH_3OH, HCl; (h) MsCl, Et_3N; (i) NaOAc; (j) HCl.

entity as an acetonide.[82] Treatment of **242** with ammonia, diphenyl disulfide, and silver nitrate resulted in an inseparable mixture of *erythro*- (**243**) and *threo*- (**244**) sulfenimines (65% yield). Formation of the *threo* isomer **244** was attributed to α-epimerization, which resulted from the basic reaction conditions. Addition of allylmagnesium bromide[83] 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[a]

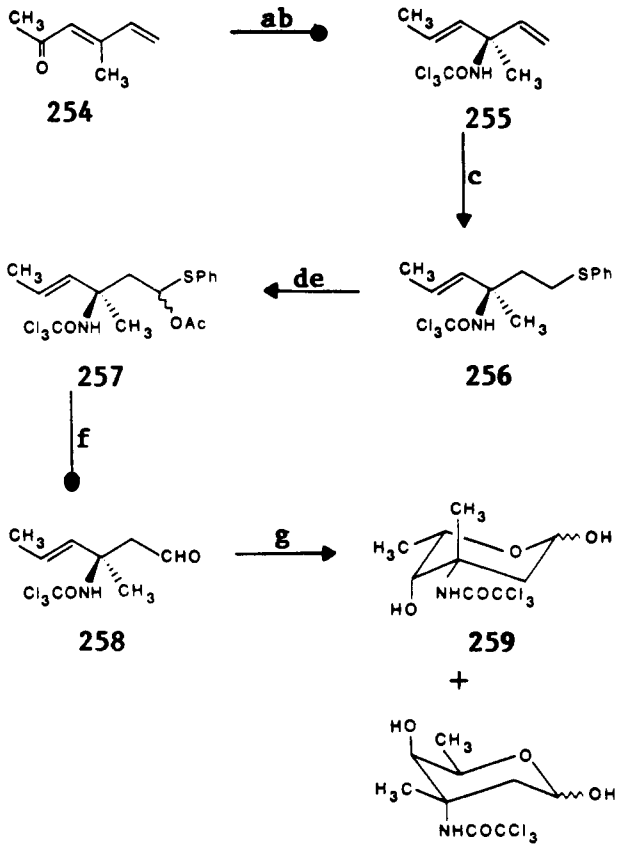


[a] (a) $Hg(OAc)_2$; (b) TsOH, $HOCH_2CH_2OH$; (c) Se, Chloramine T; (d) Na, NH_3; (e) Ac_2O, Py; (f) OsO_4, NMO; (g) HCl; (h) Ac_2O, Py.

Using a reaction sequence that paralled their earlier work[97-99] on daunosamine (1), Dyong and co-workers[21,217] 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,[97,99] the regiochemical outcome for the introduction of the 3-amino functionality through allylic amination of the olefinic entity in **251a** (selenium and Chloramine-T)[101] 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[102] 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.[116] 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**[218] to the dienol, followed by Overman reaction[53] (Cl_3CCN, NaH; xylene, reflux), furnished the deconjugated trichloroacetamide **255** in 85% yield. Free radical addition of benzenethiol (AIBN, 80–90 °C)[117] to **255** regiospecifically gave the terminal sulfide **256**

SCHEME XLVIII[a]



[a] (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.

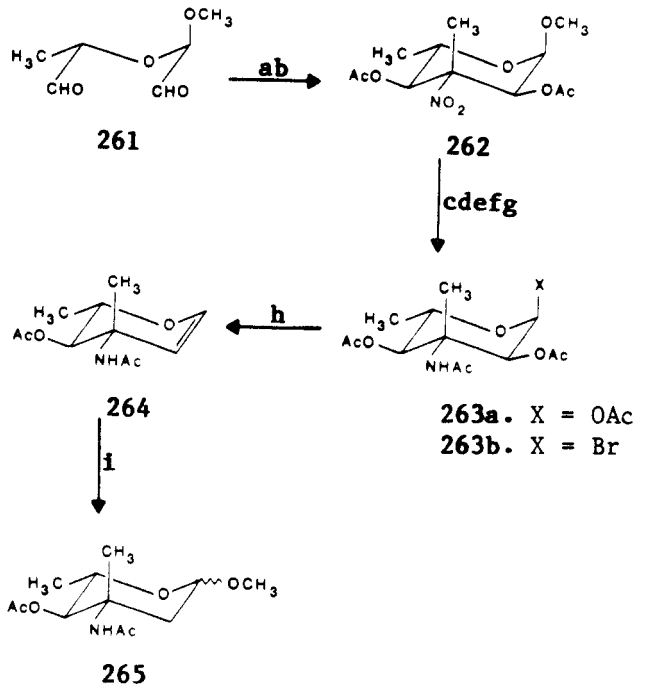
(73% yield) with the latent functionalization needed for subsequent transformation of C-1 to an aldehyde functionality. Oxidation of the sulfide entity in **256** to a sulfoxide ($NaIO_4$, MeOH),[118] Pummerer rearrangement ($(F_3CCO)_2O$, Ac_2O, lutidine)[119] to the acetoxy sulfide **257**, and then hydrolysis ($CuCl_2$, H_2O, CH_3CN)[120] 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**)[19,212,216] and were discussed in the previous section. All of the total syntheses have been initiated from carbohydrate starting materials.

Brimacombe and co-workers[213,214] 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,[145,146] was condensed with basic nitroethane[219] 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[a]



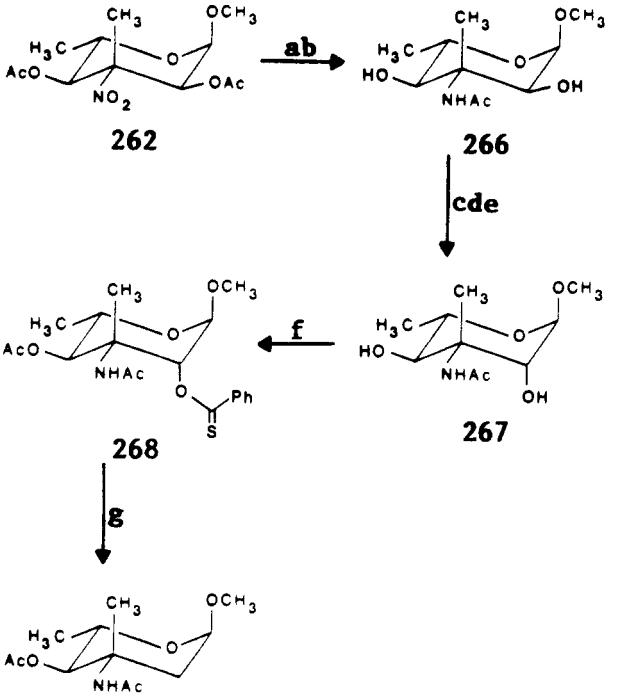
[a] (a) $EtNO_2$, NaOEt; (b) Ac_2O, Py; (c) HCl; (d) Ac_2O, Py; (e) Pd/C, H_2; (f) Ac_2O, Py; (g) HBr, HOAc, Ac_2O; (h) Zn–Cu, NaOAc, HOAc, H_2O, −10 °C; (i) BF_3·Et_2O, CH_3OH, CH_2Cl_2.

duction (Pd, H_2) 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_2O), the resultant 1-bromo compound **263b** was reacted with zinc–copper couple, producing the glycal **264** (48% yield from **263a**). Boron trifluoride catalyzed addition of methanol to the glycal gave the methyl 4-*epi*-vancosaminide derivative **265** as a 3:1 mixture of α- and β-anomers (4% yield from **42**).

Using a similar sequence, Brimacombe and Mengech[220] reported the preparation of **16** shown in Scheme L. The nitrohexose **262** starting material was produced as in the preceding sequence[213,214] and then catalytically hydrogenated over Raney nickel to the amine, which was N-acetylated to give **266** in 68% yield. Phase transfer catalyzed reaction[221] 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-α-chlorobenzylideneammonium chloride and then with hydrogen sulfide in pyridine[222] 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 glycal route, presented in the previous scheme, was the preferred method for the conversion of **262** to the 2-deoxyhexose **265**.[213]

In a series of papers, Yoshimura and co-workers[211,223,224] 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[a]



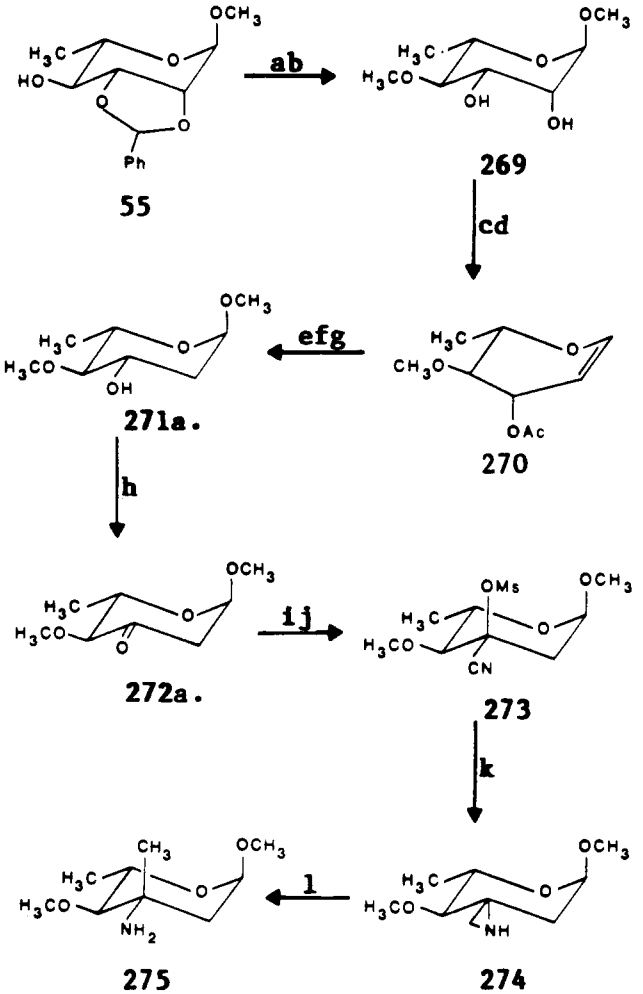
[a] (a) Ni(R), H_2; (b) Ac_2O, CH_3OH; (c) TsCl, NaOH; (d) Ac_2O, Py; (e) NaOAc, diglyme; (f) *N*,*N*-dimethyl-α-chlorobenzylideneammonium chloride, H_2S, Py; (g) Bu_3SnH, $PhCH_3$.

followed the same cyanomesylation procedure.

In the synthesis of the L isomer **16** shown in Scheme LI,[224] the initial steps leading to the hexulose intermediate **272a** essentially paralleled a procedure originally described by Clode and co-workers.[57] Methylation (NaH, CH_3I) 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 glycal **270** (62% yield).[40] The methyl 2-bromoglycoside generated through reaction of **270** with NBS was reduced with tributylstannane,[225] and then deacetylated (NaOMe) to give a 9:2 ratio of α- and β-anomers **271**. The isomers were chromatographically separated and the α-anomer **271** was oxidized (CrO_3, Py) to the α-hexos-3-ulose **272a** (41% overall yield from **270**). Reaction of the α-anomer **272a** with basic hydrogen cyanide, followed by mesylation (MsCl),[206-208] furnished exclusively the cyanomesylate **273** with the *ribo* configuration. Lithium aluminum hydride reduction of **273** produced the spiroaziridine[209] **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**).

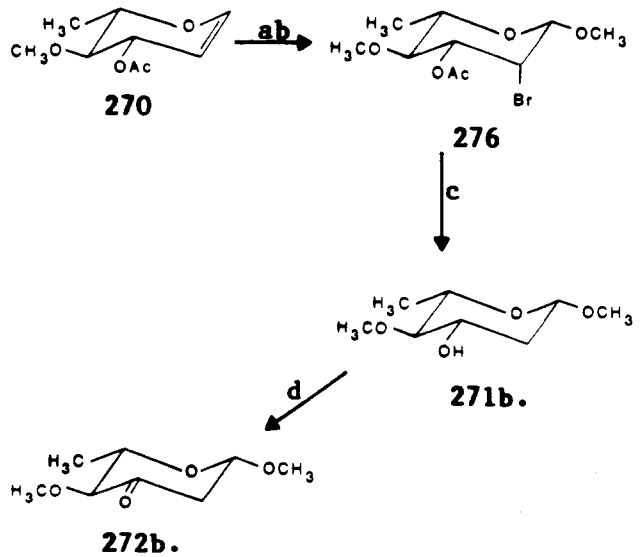
Subsequently, Yoshimura et al.[224] described a selective preparation of the hexulose β-anomer **272b** and explored its conversion to 3-*C*-methyl-substituted aminohexoses (Scheme LII). Addition of bromine to **270**, followed by silver carbonate assisted solvolysis in methanol of the glycosyl bromide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

SCHEME LI[a]



[a] (a) CH_3I, NaH, DMF; (b) HOAc, CH_3OH; (c) HOAc, H_2SO_4, 3 days; (d) HOAc, Ac_2O, HBr, −10 °C, Zn, $CuSO_4$; (e) CH_3OH, CH_3CN, NBS, 0 °C; (f) Bu_3SnH, PhH, AIBN; (g) $NaOCH_3$; (h) CrO_3, Py, CH_2Cl_2; (i) HCN, Py, 0 °C; (j) MsCl, Py; (k) LAH; (l) Ni(R), H_2.

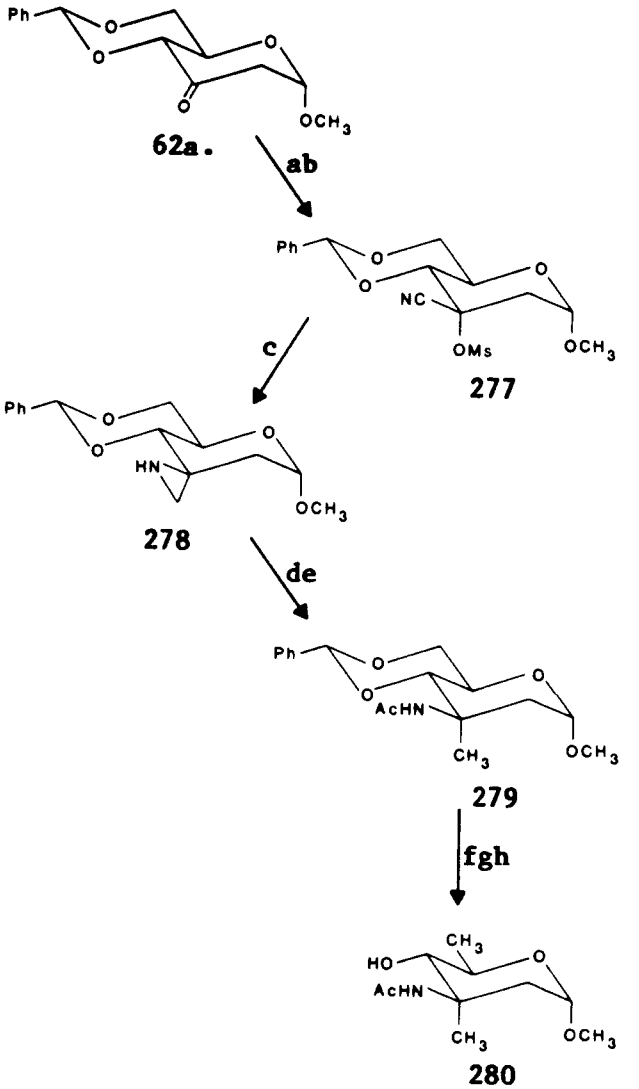
SCHEME LII[a]



[a] (a) Br_2, $CHCl_3$, 0 °C; (b) Ag_2CO_3, CH_3OH; (c) Pd/C, H_2, CH_3OH, H_2O, Et_3N; (d) CrO_3, Py, CH_2Cl_2.

(Pd/C, MeOH, Et_3N)[226] produced a 1:4 mixture of α- and β-anomers of **271** in 62% yield. The isomers were separated and **271b** was oxidized to the keto hexose

SCHEME LIII[a]

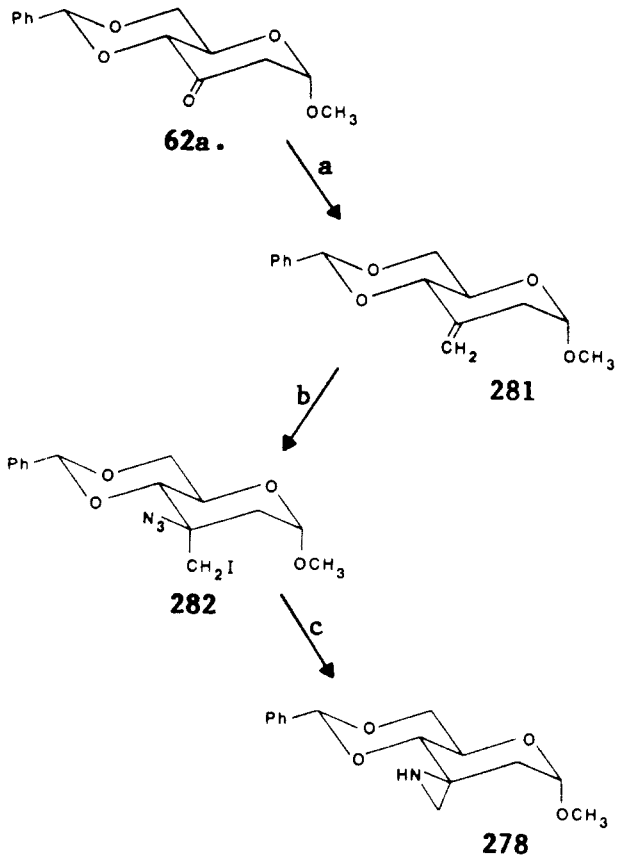


[a] (a) HCN, Py, 0 °C; (b) MsCl, Py; (c) LAH, Et_2O; (d) Ni(R), H_2, CH_3OH, 40 °C; (e) Ac_2O, Py; (f) NBS, $BaCO_3$, CCl_4; (g) Ni(R), H_2, CH_3OH, Et_3N; (h) CH_3OH, NH_3.

272b (4% overall yield) with chromium trioxide and pyridine. Cyanomesylation[206-209] of the β-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 α-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 (**17**) shown in Scheme LIII.[211,223] The 4,6-*O*-benzylidene **62a**, employed by Horton et al.[58,141] to synthesize daunosamine (**1**), was cyanomesylated[206-208] 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 LIV[a]



[a] (a) $Ph_3P{=}CH_2$; (b) NaN_3, ICl, CH_3CN; (c) LAH, Et_2O, 0 °C.

carbonate,[68] was hydrogenated with Raney nickel and de-O-benzoylated to **280** (26% yield from **62a**).

Another preparation of the D isomer **17** through the spiroaziridine intermediate **278** was reported by Brimacombe et al.[227] and is shown in Scheme LIV. Wittig reaction with methylenetriphenylphosphorane transformed **62a**[58,141,211,223] to the *C*-methylene sugar **281** in 72% yield.[175] Addition of iodine azide[228,229] to **281** gave the iodo azide **282** (24% yield), which was reduced with LAH to the spiroaziridine **278** in 84% yield (15% overall). The remaining transformations required to produce **17** were identical with those used by Yoshimura et al.[211,223,224] in Scheme LI.

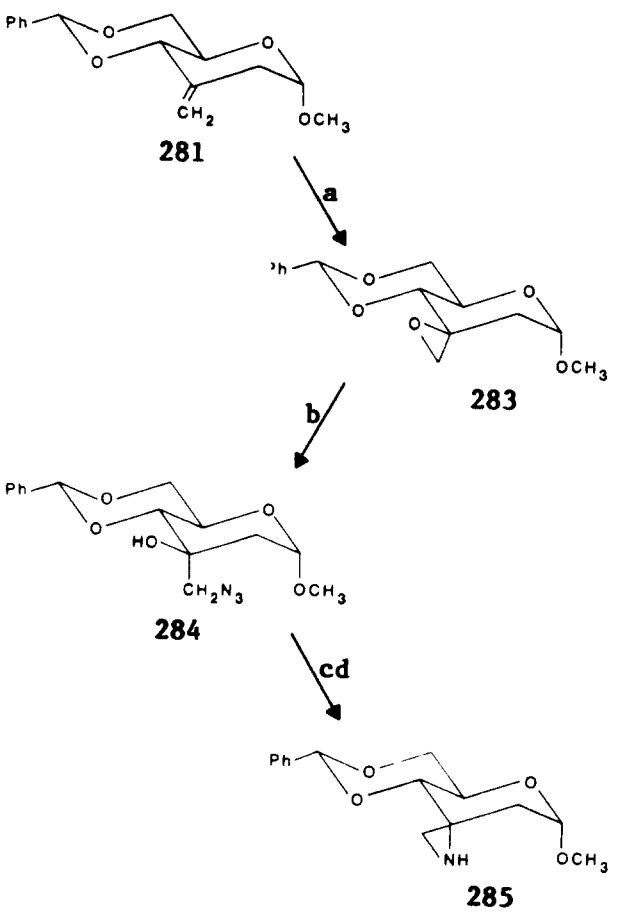
C. 2,3,6-Trideoxy-3-*C*-methyl-3-aminohexoses (L- and D-*ribo*)

Although the 3-*C*-methyl sugar (**18** and **19**) with the *ribo* configuration does not occur naturally, it has been synthesized on several occasions in conjunction with the preparation of other sugars.[19,216,230-232]

In the first of the two formal syntheses by Brimacombe et al.[230,231] the starting material was the hexos-3-ulose **56** that had been used previously by this group for syntheses of L-ristosamine (**8**)[172] and L-daunosamine (**1**) (Scheme V).[56] Hexulose **56** was first cyanomesylated with alkaline potassium cyanide[206-208] and the resultant arabino[264] product was transformed to the *ribo*-hexopyranoside **18** (17% overall yield) through the procedures[209,211,223,224] established in Scheme LI.

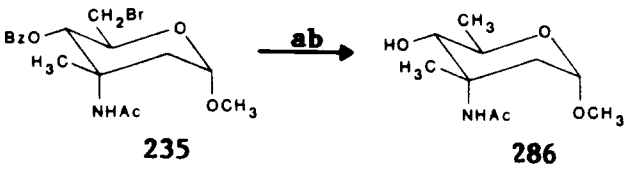
The more recent synthesis by Brimacombe et al.[232] featured the preparation of the spiroaziridine **285** with the D-*ribo* configuration (Scheme LV). Epoxidation of the unsaturated sugar **281**[227] with *m*-chloroperbenzoic

SCHEME LV[a]



[a] (a) MCPBA, $ClCH_2CH_2Cl$; (b) NaN_3, DMF, 100 °C; (c) MsCl, Py; (d) PtO_2, H_2, CH_3OH.

SCHEME LVI[a]



[a] (a) Catalytic hydrogenation; (b) base.

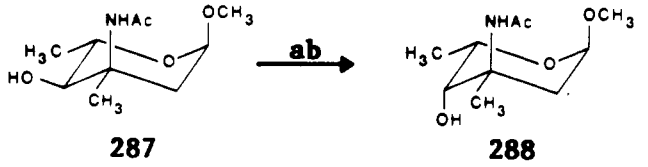
acid[233] furnished the anhydrohexose **283**; subsequent opening of the epoxide with sodium azide (DMF, 100 °C) gave the azidomethyl derivative **284** in 37% overall yield. Mesylation (MsCl, Py) of the hydroxyl moiety in **284**, followed by catalytic hydrogenation (Adams' catalyst, MeOH) of the azide entity to an amine, resulted in spontaneous ring closure, producing the spiroaziridine **285** along with a small amount of the 3-azido methylene derivative. The further conversion of **285** to the methyl-*N*-acetyl-*ribo*-hexose **286** was carried out as described in Scheme LI.[209,211,223,224,230,231]

Using an intermediate from their synthesis of vancosamine (**13**), Thang et al.[209] also prepared the D-*ribo* isomer **19**. As shown in Scheme LVI, catalytic hydrogenation of **235**, followed by basic hydrolysis, provided the methyl-*N*-acetyl-D-*ribo*-hexose **286** in 85% overall yield.

D. 3-*epi*-Vancosamine (L- and D-*xylo*)

The *xylo*-aminohexose, L-3-*epi*-vancosamine (**20**), was isolated from the gram-positive antibiotic A35512B, which is related to vancomycin, ristocetin, and avo-

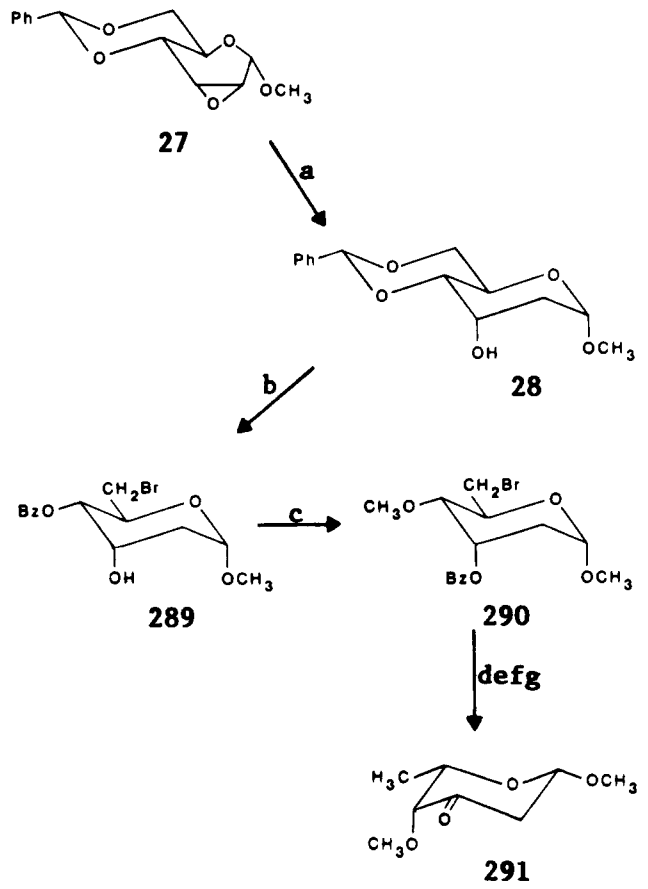
SCHEME LVII[a]



287 288

[a] (a) PCC, molecular sieves; (b) L-Selectride.

SCHEME LVIII[a]



27 28 289 290 291

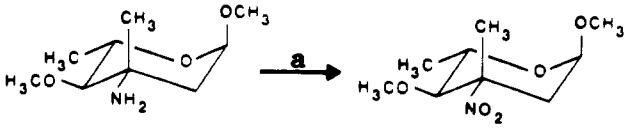
[a] (a) $LiAlH_4$, THF; (b) NBS, $BaCO_3$, CCl_4; (c) Ag_2O, CH_3I, DMF; (d) AgF, Py; (e) catalytic hydrogenation; (f) de-O-benzoylation; (g) PCC, CH_2Cl_2.

parcin.[234,235] The structure of **20** was assigned from its ^1H NMR spectrum, and the absolute stereochemistry was confirmed by applying Hudson's rule;[236] the optical rotation of the α-anomer was more negative than the β-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**).[19,21,116,216,217] The only other reported synthesis was performed by Brimacombe et al.[230,232] 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).[237-239] A formal synthesis was performed by Yoshimura and co-workers[240] and is shown in Scheme LVIII. The 2,3-anhydropyranoside **27**,[45,76] prepared from methyl glucoside **26**, was reduced with lithium aluminum hydride[45,76] to furnish the 2-deoxy sugar **28**. Reaction of **28** with NBS and barium carbonate[68] 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[209,211,223,224,230-232] and shown in Scheme LI.

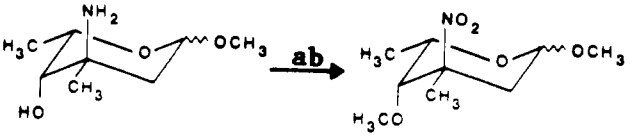
SCHEME LIX[a]



272 292

[a] (a) MCPBA, CH_2Cl_2.

SCHEME LX[a]



293 294

[a] (a) CH_3I, NaH, DMF; (b) MCPBA, CH_2Cl_2.

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 everninomycin B, C, and D[3,4] and is liberated upon acidic hydrolysis. Spectroscopic and chemical degradation studies[242] led to an initial assignment of the L-*ribo* configuration; however, a later X-ray analysis of the methyl α-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[211,223,224] 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**.[211,223]

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

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

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.[240] and Brimacombe et al.,[251] were initiated from the methyl-L-*xylo*-aminohexose **293**.[230,240] As shown in Scheme LX, methylation of **293** (MeI, NaH)[252] 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, commerically 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[253] (**1**) and vancosamine[254] (**13**) from L-lactic acid. Noteworthy aspects of these stereoselective preparations are the direct C-acylation of a protected lactic acid derivative with methyl isocyanoacetate to generate an oxazole and the production of a lyxo-configurated γ-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 γ-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[255] 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[256] 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*-configurated acyclic product, which was subsequently cyclized to the γ-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*-γ-lactone precursor to L-daunosamine (**1**) (19% yield). Small amounts of the *arabino*- and *xylo*-γ-lactones were also prepared as byproducts.

A conceptually novel synthesis of D,L-daunosamine has been reported by Danishefsky and Maring.[257] 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 acetyloxime 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, Hirama et al.[258] 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 γ- and δ-carbamoyloxy unsaturated esters occur with high 1,2- and 1,3-*syn* asymmetric induction. In the acosamine synthesis, the carbamoyloxy group is in the γ-position, while in the ristosamine preparation it is δ to the ester function. Following hydrolysis and reduction, acos-

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

In the second paper,[260] 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,[129,130] Thiem and Springer[261] 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.[262] The major difference between their route and the one shown in Scheme I[26,27] is that the order of the steps is slightly rearranged.

Acknowledgments. We express our sincere appreciation to Harriet Hauser for proofreading and to the Institute for General Medical Sciences of the National Institutes of Health for partial support (GM 26574) of our research on the subject matter in this review.

IX. References and Notes

(1) Brockmann, H.; Spohler, E.; Waehneldt, T. *Chem. Ber.* **1963**, *96*, 2925.
(2) Brockmann, H.; Waeneldt, T. *Naturwissenschaften* **1963**, *50*, 92.
(3) Ganguly, A. K.; Saksena, A. K. *J. Antibiot.* **1975**, *28*, 707.
(4) Ganguly, A. K.; Szmulewicz, S. *J. Antibiot.* **1975**, *28*, 710.
(5) Arcamone, F.; Franceschi, G.; Orezzi, P.; Babier, W.; Mondelli, R. *J. Am. Chem. Soc.* **1964**, *86*, 5334.
(6) Arcamone, F.; Cassinelli, G.; Orezzi, P.; Franceschi, G.; Mondelli, R.. *J. Am. Chem. Soc.* **1964**, *86*, 5335.
(7) Arcamone, F.; Cassinelli, G.; Franceschi, G.; Mondelli, R.; Orezzi, P.; Penco, S. *Gazz. Chim. Ital.* **1970**, *100*, 949.
(8) DiMarco, A.; Arcamone, F.; Zunino, F. In "Antibiotics"; Corcoran, J. W., Hahn, F. S., Eds.; Springer Verlag: New York, 1975; Vol. III, pp 101–128.
(9) Arcamone, F.; Franceschi, G.; Penco, S.; Selva, A. *Tetrahedron Lett.* **1969**, 1007.
(10) Arcamone, F. In "Topics in Antibiotic Chemistry"; Sammes, P. G., Ed.; Wiley: New York, 1978; Vol. 2, pp 89–229.
(11) Brown, J. R. In "Progress in Medicinal Chemistry"; Ellis, G. P., West, G. B., Eds.; Elsevier: New York, 1978; Vol. 15, pp 125–164.
(12) Remers, W. A. "The Chemistry of Antitumor Antibiotics"; Wiley Interscience: New York, 1979; Vol. 1; Chapter 2.
(13) Henry, D. W. *Cancer Treat. Rep.* **1979**, *63*, 845.
(14) Henry, D. W. In "Cancer Chemotherapy"; Sartorelli, A. C., Ed.; American Chemical Society: Washington DC, 1976.
(15) Arcamone, F.; *Lloydia* **1977**, *40*, 45.
(16) Arcamone, F. "International Symposium on Tumor Pharmacotherapy"; Masson: New York, 1983; pp 79–84.
(17) Arcamone, F.; Penco, S.; Vigevani, A.; Redaelli, S.; Franchie, G.; DiMarco, A.; Casazza, A. M.; Dosdia, T.; Formelli, F.; Nacio, A.; Soranzo, C. *J. Am. Chem. Soc.* **1975**, *18*, 703.
(18) Fronza, G.; Fuganti, D.; Grasselli, P. *J. Chem. Soc., Perkin Trans. 1* **1982**, 885.
(19) Fronza, G.; Fuganti, C.; Grasselli, P.; Guiseppi, P.-F. *J. Carbohydr. Chem.* **1983**, *2*, 225.
(20) Luckas, G.; Smith, R. M. *Bull. Chim. Soc. Fr.* **1972**, *10*, 3995.
(21) Dyong, I.; Friege, H.; Luftmann, H.; Merten, H. *Chem. Ber.* **1981**, *114*, 2669.
(22) "Rules of Carbohydrate Chemistry". Report by the Division of Carbohydrate Chemistry of the American Chemical Society under the chairmanship of Dr. M. L. Wolfrom and a British Committee on Carbohydrate Nomenclature. The report was approved by the Committee of Nomenclature, Spelling and Pronunciation of the American Chemical Society and by the Council of the American Chemical Society in March 1962. *J. Org. Chem.* **1963**, *28*, 281.
(23) Stoddart, J. F. "Stereochemistry of Carbohydrates"; Wiley Interscience: New York, 1971; p 54.
(24) Carter, S. K. *J. Natl. Cancer Inst.* **1975**, *55*, 1265.
(25) Skovsgaard, T.; Nissen, N. I. *Dan. Med. Bull.* **1975**, *22*, 62.
(26) Richardson, A. C. *J. Chem. Soc., Chem. Commun.* **1965**, 1627.
(27) Richardson, A. C. *Carbohydr. Res.* **1967**, *4*, 422.
(28) Prins, D. A. *J. Am. Chem. Soc.* **1948**, *70*, 3955.
(29) Guthrie, R. D.; Murphy, D. *J. Chem. Soc.* **1965**, 6956.
(30) Baker, B. R.; Schaub, R. E. *J. Org. Chem.* **1954**, *19*, 646.
(31) Richardson, A. C.; McLauchlan, K. A. *J. Chem. Soc.* **1962**, 2499.
(32) Boivin, J.; Pais, M.; Monneret, C. *Carbohydr. Res.* **1978**, *64*, 271.
(33) Baer, H. H.; Capek, K.; Cook, M. C. *Can. J. Chem.* **1969**, *47*, 89.
(34) Baer, H. H. *J. Am. Chem. Soc.* **1961**, *83*, 1882.
(35) Baer, H. H.; Kienzle, F.; Neilson, T. *Can. J. Chem.* **1965**, *43*, 1829.
(36) Baer, H. H.; Kienzle, F. *Can. J. Chem.* **1965**, *43*, 3074.
(37) Baer, H. H.; Kienzle, F. *Can. J. Chem.* **1963**, *41*, 1606.
(38) Baer, H. H.; Neilson, T. *Can. J. Chem.* **1965**, *43*, 840.
(39) Marsh, J. P., Jr.; Mosher, C. W.; Acton, E. M.; Goodman, L. *J. Chem. Soc., Chem. Commun.* **1967**, 973.
(40) Iselin, B.; Reichstein, T. *Helv. Chim. Acta.* **1944**, *27*, 1146.
(41) Inglis, G. R.; Schwarz, J. C. P.; McLaren, L. *J. Chem. Soc.* **1962**, 1017.
(42) Lomakina, N. N.; Spiridonova, I. A.; Sheinker, Y. N.; Vlasova, T. F. *Khim. Prir., Soedin.* **1973**, *9*, 101; *Chem. Abstr.* **1973**, *78*, 148170m.
(43) Spiridonova, I. A.; Yurina, M. S.; Lomakina, N. N.; Sztaricskai, F.; Bognar, F. *Antibiotiki* **1976**, *21*, 304; *Chem. Abstr.* **1976**, *85*, 108925z.
(44) Reist, E. J.; Goodman, L.; Spencer, R. R.; Baker, B. R. *J. Am. Chem. Soc.* **1958**, *80*, 3962.
(45) Grethe, G.; Mitt, T.; Williams, T. H.; Uskokovic, R. *J. Org. Chem.* **1983**, *48*, 5309.
(46) Grethe, G.; Sereno, J.; Williams, T. H.; Uskokovic, M. R. *J. Org. Chem.* **1983**, *48*, 5315.
(47) Pauls, H. W.; Fraser-Reid, B. *J. Chem. Soc., Chem. Commun.* **1983**, 1031.
(48) Roth, W.; Pigman, W. *Methods Carbohydr. Chem.* **1963**, *2*, 405.
(49) Paulsen, H.; Koebernick, W. *Carbohydr. Res.* **1977**, *56*, 53.
(50) (a) Ferrier, R. J. *Adv. Carbohydr. Chem.* **1965**, *20*, 67. (b) Ferrier, R. J. *Adv. Carbohydr. Chem.* **1969**, *24*, 199.
(51) Brimacombe, J. S.; Donner, L. W.; Rollins, A. J. *J. Chem. Soc., Perkin Trans. 1* **1972**, 2977.
(52) Mitsunobu, O. *Synthesis* **1981**, 1.
(53) Overman, L. E. *J. Am. Chem. Soc.* **1976**, *98*, 2091.
(54) Cardillo, G.; Orena, M.; Sandri, S.; Tomasini, C. *J. Org. Chem.* **1984**, *49*, 3951.
(55) Brimacombe, J. S.; Hanna, R.; Tucker, L. C. N. *Carbohydr. Res.* **1985**, *136*, 419.
(56) Brimacombe, J. S.; Hanna, R.; Saeed, M. S.; Tucker, L. C. N. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2583.
(57) Clode, D. M.; Horton, D.; Weckerle, W. *Carbohydr. Res.* **1976**, *49*, 305.
(58) Horton, D.; Weckerle, W. *Carbohydr. Res.* **1975**, *44*, 227.
(59) Evans, M. E.; *Carbohydr. Res.* **1972**, *21*, 473.
(60) Klemer, A.; Rhodemeyer, G. *Chem. Ber.* **1974**, *107*, 2612.
(61) Klemer, A.; Balkau, D. *J. Chem. Res.* **1978**, S, 303.
(62) Klemer, A.; Balkaum, D. *J. Chem. Res.* **1978**, M, 3823.
(63) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647.
(64) Mancuso, A. J.; Swern, L. *Synthesis* **1981**, 165.
(65) Brown, H. C.; Krishnamurthy, S. *J. Am. Chem. Soc.* **1972**, *94*, 7159.
(66) Krishnamurthy, S. *Aldrichimica Acta* **1974**, *7*, 55.
(67) Benyon, P. J.; Collins, P. M.; Overend, W. G. *J. Chem. Soc. C* **1969**, 272.
(68) Hanessian, S. *Carbohydr. Res.* **1966**, *2*, 86.
(69) Lehmann, J.; Weckerle, W. *Carbohydr. Res.* **1975**, *42*, 275.
(70) Gurjar, M. K.; Yadav, J. S.; Rao, A. V. R. *Indian J. Chem.* **1983**, *22*, 1139.
(71) Richtmyer, N. K. *Methods Carbohydr. Chem.* **1962**, *1*, 107.
(72) Corey, E. J.; Suggs, J., W. *J. Org. Chem.* **1975**, *40*, 2554.
(73) Yamaguchi, T.; Kojima, M. *Carbohydr. Res.* **1977**, *59*, 343.
(74) Yamaguchi, T.; Kojima, M. *Carbohydr. Res.* **1977**, *59*, 129.
(75) Kojima, M.; Watanabe, M.; Yamaguchi, T.; Ishimaru, S.; Toguchi, T. *Yakugaku Zasshi* **1976**, *96*, 1241.

(76) Christensen, J. E.; Goodman, L.; *J. Am. Chem. Soc.* **1961**, *83*, 3827.
(77) Sowden, J. C.; Fischer, H. O. L. *J. Am. Chem. Soc.* **1947**, *69*, 1963.
(78) Sowden, J. C.; Fischer, H. O. L. *J. Am. Chem. Soc.* **1947**, *69*, 1048.
(79) Satoh, C.; Kiyomoto, A. *Chem. Pharm. Bull. Tokyo* **1964**, *12*, 615.
(80) Perr, M. B.; Webb, A. C. *Can. J. Chem.* **1969**, *47*, 1245.
(81) Fronza, G.; Fuganti, C.; Grasselli, P. *J. Chem. Soc., Perkin Trans. 1* **1980**, 442.
(82) Fuganti, C.; Grasselli, P. *Chem. Ind.* **1977**, 983.
(83) Fuganti, C.; Grasselli, P.; Giuseppe, P.-F. *Tetrahedron Lett.* **1981**, 4017.
(84) Fuganti, C.; Grasselli, P.; Giuseppe, P.-F. *J. Org. Chem.* **1983**, *48*, 909.
(85) Fronza, G.; Fuganti, C.; Grasselli, P.; Marinoni, G. *Tetrahedron Lett.* **1979**, 3883.
(86) Fronza, G.; Fuganti, C.; Grasselli, P. *Tetrahedron Lett.* **1980**, 2999.
(87) Mukaiyama, T.; Yukishia, G.; Shoda, S.-I. *Chem. Lett.* **1983**, 671.
(88) Dyong, I.; Bendlin, H. *Chem. Ber.* **1978**, *111*, 1677.
(89) Davis, F. A.; Slegeir, W. A. R.; Evans, S.; Schwartz, A.; Goff, D. L.; Palmer, R. *J. Org. Chem.* **1973**, *38*, 2809.
(90) DeShong, P.; Leginus, J. M. *J. Am. Chem. Soc.* **1983**, *103*, 1686.
(91) Pearlman, W. M. *Tetrahedron Lett.* **1967**, 1663.
(92) Hatch, R. P.; Shringarpure, J.; Weinreb, S. M. *J. Org. Chem.* **1978**, *43*, 4172.
(93) Bachelor, F. W.; Miana, G. A. *Can. J. Chem.* **1969**, *47*, 4089.
(94) Wovkulich, P. M.; Uskokovic, M. R. *J. Am. Chem. Soc.* **1981**, *103*, 3956.
(95) Bredereck, H.; Simchen, G.; Rebsdat, S.; Kantlehner, W.; Horn, P.; Wahl, R.; Hoffmann, H.; Grieschaber, P. *Chem. Ber.* **1968**, *104*, 41.
(96) Polonski, T.; Chimiak, A. *Tetrahedron Lett.* **1974**, 2453.
(97) Dyong, I.; Wiemann, R. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 682.
(98) Dyong, I.; Wiemann, R. *Chem. Ber.* **1980**, *113*, 2666.
(99) Dyong, I.; Friege, H.; Hone, T. *Chem. Ber.* **1982**, *115*, 256.
(100) Watanabe, W. H.; Conlon, L. E. *J. Am. Chem. Soc.* **1957**, *79*, 2828.
(101) Sharpless, K. B.; Hori, T.; Truesdale, L. K.; Dietrich, C. O. *J. Am. Chem. Soc.* **1976**, *98*, 269.
(102) VanReenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, 1973.
(103) Woodward, R. B.; Brutcher, F. V. *J. Am. Chem. Soc.* **1958**, *80*, 209.
(104) Jasserand, D.; Girard, J. P.; Rossi, J. C.; Granger, R. *Tetrahedron Lett.* **1976**, 1581.
(105) Partridge, J. J.; Chadha, N. K.; Uskokovic, M. R. *J. Am. Chem. Soc.* **1973**, *95*, 532.
(106) Hauser, F. M.; Rhee, R. P. *J. Org. Chem.* **1981**, *46*, 227.
(107) Hauser, F. M.; Rhee, R. P.; Ellenberger, S. R. *J. Org. Chem.* **1984**, *49*, 2236.
(108) Johnston, D. B. R.; Schmett, S. M.; Bouffard, F. A.; Christensen, B. G. *J. Am. Chem. Soc.* **1978**, *100*, 313.
(109) Isaacs, N. S. *Chem. Soc. Rev.* **1976**, *5*, 181.
(110) Montzka, T.; Pindell, T. L.; Matiskella, D. J. *J. Org. Chem.* **1968**, *33*, 3993.
(111) Ray, R.; Matteson, D. S. *Tetrahedron Lett.* **1980**, 449.
(112) Wong, C. M.; Ho, T.-L.; Niemczura, W. P. *Can. J. Chem.* **1975**, *53*, 3144.
(113) Jakobsen, H. J.; Larsen, E. H.; Madsen, P.; Lawesson, S.-O. *Ark. Kemi.* **1965**, *24*, 519.
(114) Iwataki, I.; Nakamura, Y.; Takahashe, K.; Matsumoto, T. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 2731.
(115) Roth, W.; Pigman, W.; Danishefsky, I. *Tetrahedron* **1964**, *20*, 1675.
(116) Hauser, F. M.; Ellenberger, S. R.; Glusker, J. P.; Smart, C. J.; Carroll, H. C. *J. Org. Chem.* **1985**, in press.
(117) Hsiao, C.-N.; Shechter, H. *Tetrahedron Lett.* **1982**, 1963.
(118) Hauser, F. M.; Ellenberger, S. R.; Clardy, J. C.; Bass, L. S. *J. Am. Chem. Soc.* **1984**, *106*, 2458.
(119) Tanikaga, R.; Yabuki, Y.; Ono, N.; Kaji, A. *Tetrahedron Lett.* **1976**, 2258.
(120) Sugihara, H.; Tanikaga, R.; Kaju, A. *Synthesis* **1978**, *12*, 881.
(121) Nicolaou, K. C.; Seitz, S. P.; Papahatjis, D. P. *J. Am. Chem. Soc.* **1983**, *105*, 2430.
(122) Brockmann, H.; Lenk, W. *Chem. Ber.* **1959**, *92*, 1904.
(123) Ettlinger, E.; Gaumann, E.; Hutler, R.; Keller-Schierlein, W.; Kradolfer, P.; Neipp, L.; Prelog, V.; Reusser, P.; Zahner, H. *Chem. Ber.* **1959**, *92*, 1867.
(124) Harada, K.-I.; Ito, S.; Suzuki, M. *Carbohydr. Res.* **1979**, *75*, C17.
(125) Pelyvas, I.; Sztaricskai, F.; Bognar, R. *Carbohydr. Res.* **1979**, *76*, 257.
(126) Cheung, T.-M.; Horton, D.; Sorensen, R. J.; Weckerle, W. *Carbohydr. Res.* **1979**, *63*, 77.
(127) Gupta, S. K.; *Carbohydr. Res.* **1974**, *37*, 381.
(128) Lee, W. W.; Wu, H. Y.; Christensen, J. E.; Goodman, L.; Henry, D. W. *J. Med. Chem.* **1975**, *18*, 768.
(129) Heyns, K.; Lim, H. J.; Park, J. I. *Tetrahedron Lett.* **1976**, *18*, 1477.
(130) Heyns, K.; Feldman, J.; Hadamczyk, D.; Schwentner, J.; Thiem, J. *Chem. Ber.* **1981**, *114*, 232.
(131) Boivin, J.; Monneret, M. C. P. *Carbohydr. Res.* **1980**, *79*, 193.
(132) Heyns, K.; Hohlweg, R. *Chem. Ber.* **1978**, *111*, 1632.
(133) Thiem, J.; Karl, H.; Schwentner, J. *Synthesis* **1978**, 696.
(134) Boar, R. B.; Hawkins, D. W.; McGhie, J. F.; Barton, D. H. R. *J. Chem. Soc., Perkin Trans. 1* **1973**, *1*, 654.
(135) Ness, R. K.; Fletcher, H. G., Jr.; Hudson, C. S. *J. Am. Chem. Soc.* **1951**, *73*, 296.
(136) Pelyvas, I.; Sztaricskai, F.; Bognar, R. *Carbohydr. Res.* **1979**, *76*, 257.
(137) Pelyvas, I.; Whistler, R. L. *Carbohydr. Res.* **1980**, *84*, C5.
(138) Fetizon, M.; Golfier, M. *C. R. Acad. Sci., Ser. 3* **1968**, *267*, 900.
(139) Thiem, J.; Elvers, J. *Chem. Ber.* **1978**, *111*, 3484.
(140) Suami, T.; Tadano, K.-I.; Suga, A.; Ueno, Y. *J. Carbohydr. Chem.* **1984**, *3*, 429.
(141) Horton, D.; Sorenson, R. J.; Weckerle, W. *Carbohydr. Res.* **1977**, *58*, 125.
(142) Baer, H. H.; Georges, F. F. Z. *Can. J. Chem.* **1977**, *55*, 1100.
(143) Evans, M. E.; Parish, F. W. *Methods Carbohydr. Chem.* **1972**, *6*, 177.
(144) Evans, M. E.; Parish, F. W. *Methods Carbohydr. Chem.* **1972**, *6*, 193.
(145) Baer, H. H.; Capek, K. *Can. J. Chem.* **1969**, *47*, 99.
(146) Richardson, A. C.; McLauchlan, K. A. *J. Chem. Soc.* **1962**, 2499.
(147) Baer, H. H.; Chiu, C. W. *Can. J. Chem.* **1974**, *52*, 111.
(148) Baer, H. H.; Georges, F. F. Z. *J. Org. Chem.* **1976**, *41*, 3474.
(149) Fronza, G.; Fuganti, C.; Grasselli, P.; Majori, L.; Pedrocchi-Fantoni, G.; Spreafico, F. *J. Org. Chem.* **1982**, *47*, 3289.
(150) Hiyama, T.; Nishide, K.; Kobayashi, K. *Tetrahedron Lett.* **1984**, 569.
(151) Okamura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651.
(152) Hiyama, T.; Kobayashi, K. *Tetrahedron Lett.* **1982**, 1597.
(153) Lee, W. W.; Wu, H. Y.; Christensen, J. E.; Goodman, L.; Henry, D. W. *J. Med. Chem.* **1975**, *18*, 767.
(154) Brufani, M.; Keller-Scherlein, W. *Helv. Chim. Acta* **1966**, *49*, 1962.
(155) Kinumaki, T.; Suzuki, M. *J. Antibiot.* **1972**, *25*, 480.
(156) Clark, H. T.; Gillespie, H. B.; Weisshaus, S. S. *J. Am. Chem. Soc.* **1933**, *55*, 4571.
(157) Gauze, G. F.; Kudrina, E. S.; Ukholina, R. S.; Gavrilina, G. V. *Antibiotiki* **1963**, *8*, 387; *Chem. Abstr.* **1965**, *62*, 5843e.
(158) Brazhnikova, M. G.; Lomakina, N. N.; Lavrova, M. F.; Tolstykh, I. V.; Yurina, M. S.; Kluyeva, L. M. *Antibiotiki* **1963**, *8*, 392; *Chem. Abstr.* **1965**, *62*, 8045h.
(159) Brazhnikova, M. G.; Lomakina, N. N.; Sztaricskai, F.; Puskas, M.; Makleit, S.; Bognar, R. *Kem. Kozl.* **1967**, *27*, 143; *Chem. Abstr.* **1968**, *68*, 78165f.
(160) Bognar, R.; Sztaricskai, F.; Munk, M. E.; Tamas, J. *J. Org. Chem.* **1974**, *39*, 2971.
(161) Spiridonova, I. A.; Lomakina, N. N.; Sztaricskai, F.; Bognar, R. *Antibiotiki* **1974**, *19*, 400; *Chem. Abstr.* **1974**, *81*, 91882a.
(162) Bognar, R.; Sztaricskai, F.; Morton, M. E.; Tamas, J. *Magy. Kem. Foly.* **1974**, *80*, 385; *Chem. Abstr.* **1975**, *82*, 17029g.
(163) Lomakina, I. A.; Spiridonova, R.; Bognar, R.; Puskas, M.; Sztaricskai, F. *Antibiotiki* **1968**, *13*, 975.
(164) Sztaricskai, F.; Niszmilyi, A.; Bognar, R. *Tetrahedron Lett.* **1980**, *21*, 2983.
(165) Sztaricskai, F.; Harris, C. M.; Neszmelyi, A.; Harris, T. M. *J. Am. Chem. Soc.* **1980**, *21*, 2983.
(166) Arcamone, F.; Bargiotti, A.; Cassinelli, G.; Penco, S.; Hanessian, S. *Carbohydr. Res.* **1976**, *46*, C3.
(167) Horton, D.; Nicol, R. G.; Weckerle, W.; Winter-Mihaly, E. *Carbohydr. Res.* **1979**, *76*, 269.
(168) Horton, D.; Weckerle, W. *Carbohydr. Res.* **1976**, *46*, 227.
(169) Sztaricskai, F.; Pelyvas, I.; Bognar, R. *Tetrahedron Lett.* **1975**, 1111.
(170) Sztaricskai, F.; Pelyvas, I.; Szilogyi, L.; Bognar, R. *Carbohydr. Res.* **1978**, *65*, 193.
(171) Sztaricskai, F.; Pelyvas, I.; Szilagyi, L.; Bognar, R.; Tamas, J.; Neszmelyi, A. *Magy. Kem. Foly.* **1978**, *84*, 320; *Chem. Abstr.* **1978**, 89, 180262f.
(172) Brimacombe, J. S.; Hanna, R.; Saeed, M. S.; Tucker, L. C. N. *Carbohydr. Res.* **1982**, *100*, C10.
(173) Pauls, H. W.; Fraser-Reid, B. *J. Org. Chem.* **1983**, *48*, 305.
(174) Bogini, A.; Cardillo, G.; Orena, M.; Sandri, S.; Tomasini, C. *Tetrahedron* **1983**, *39*, 3801.
(175) Williams, E. H.; Szarek, W. A.; Jones, J. K. N. *Can. J. Chem.* **1969**, *47*, 4467.
(176) Hanessian, S.; Pompipom, M. M.; Lavallee, P. *Carbohydr. Res.* **1972**, *24*, 45.
(177) Pelyvas, I.; Sztaricskai, F.; Bognar, R. *Carbohydr. Res.* **1977**, *53*, C17.

(178) Pelyvas, I.; Sztaricskai, F.; Szilagyi, L.; Bognar, R. *Carbohydr. Res.* **1979**, *68*, 321.
(179) Baer, H. H.; Georges, F. F. Z. *Carbohydr. Res.* **1977**, *55*, 253.
(180) Heathcock, C. H.; Montgomery, S. H. *Tetrahedron Lett.* **1983**, 4637.
(181) Seebach, D.; Pohmakotr, M. *Tetrahedron*, **1981**, *37*, 4047.
(182) Ireland, R. E.; Newbould, J. *J. Org. Chem.* **1963**, *28*, 23.
(183) Ninmiya, K.; Shjioiri, T.; Yamada, S. *Tetrahedron Lett.* **1974**, 2151.
(184) Pappo, R.; Allen, D. S., Jr.; Lemieux, R. U.; Johnson, W. S. *J. Org. Chem.* **1956**, *21*, 478.
(185) Mallams, A. K. *J. Am. Chem. Soc.* **1969**, *91*, 7505.
(186) Mallams, A. K. *J. Chem. Soc., Perkin Trans. 1* **1973**, 1369.
(187) Nourse, J. G.; Roberts, J. D. *J. Am. Chem. Soc.* **1975**, *97*, 4584.
(188) Jensen, J. E.; Torssell, K. *Acta Chim. Scand., Ser. B* **1978**, *32*, 457.
(189) Torssell, K.; Tyagi, M. P. *Acta Chim. Scand., Ser. B* **1977**, *31*, 297.
(190) Dyong, I.; Bendlin, H. *Chem. Ber.* **1979**, *112*, 717.
(191) Dyong, I.; Jersch, N. *Chem. Ber.* **1976**, *109*, 896.
(192) Helferich, B.; Himmen, E. *Chem. Ber.* **1928**, *61*, 1825.
(193) Cheung, T.-M.; Horton, D.; Weckerle, W. *Carbohydr. Res.* **1979**, *74*, 93.
(194) Cheung, T.-M.; Horton, D.; Weckerle, W. *Carbohydr. Res.* **1977**, *58*, 139.
(195) Musich, J. A.; Rapoport, H. *J. Am. Chem. Soc.* **1978**, *100*, 4865.
(196) Meyer, C. E.; Rose, W. C. *J. Biol. Chem.* **1936**, *115*, 721.
(197) Dyong, I.; Wiemann, R. *Chem. Ber.* **1980**, *113*, 1592.
(198) McCormick, M. H.; Stark, W. M.; Pittenger, G. E.; Pittenger, R. C.; McGuire, J. M. "Antibiotics Annual"; Medical Encyclopedia, Inc.: New York, 1956; p 606.
(199) Weringa, W. D.; Williams, D. H.; Feeney, J.; Brown, J. P.; King, R. W. *J. Chem. Soc., Perkin Trans. 1* **1972**, 443.
(200) Smith, R. M.; Johnson, A. W.; Guthrie, R. D. *J. Chem. Soc., Chem. Commun.* **1972**, 361.
(201) Johnson, A. W.; Smith, R. W.; Guthrie, R. D. *J. Chem. Soc., Perkin Trans. 1* **1972**, 2153.
(202) Williams, D. H.; Kalman, J. R. *J. Am. Chem. Soc.* **1977**, *99*, 66.
(203) Furukawa, M. I.; Hayakawa, I.; Ohta, G.; Iitaka, Y. *Tetrahedron*, **1975**, *31*, 2989.
(204) Kondo, S.; Miyamoto, M.; Naganawa, H.; Takeuchi, T.; Umezawa, H. *J. Antibiot.* **1977**, *30*, 1143.
(205) Seguin, U. *Tetrahedron* **1978**, *34*, 761.
(206) Bourgeois, J.-M. *Helv. Chim. Acta* **1974**, *57*, 2553.
(207) Bourgeois, J.-M. *Helv. Chim. Acta* **1975**, *58*, 363.
(208) Bourgeois, J.-M. *Helv. Chim. Acta* **1976**, *59*, 2214.
(209) Thang, T. T.; Winternitz, F.; Olesker, A.; Lagrange, A.; Lukacs, G. *J. Chem. Soc., Chem. Commun.* **1979**, 153.
(210) Brimacombe, J. S.; Miller, J. A.; Zakir, U. *Carbohydr. Res.* **1976**, *49*, 233.
(211) Yoshimura, J.; Matsuzawa, M.; Sato, K.-I.; Funabashi, M. *Chem. Lett.* **1977**, 1403.
(212) Ahmad, H. I.; Brimacombe, J. S.; Mengech, A. S.; Tucker, L. C. N. *Carbohydr. Res.* **1981**, *93*, 288.
(213) Brimacombe, J. S.; Doner, L. W. *J. Chem. Soc., Perkin Trans. 1* **1974**, 62.
(214) Brimacombe, J. S.; Mengech, A. S.; Saeed, M. S. *Carbohydr. Res.* **1979**, *75*, C5.
(215) Herscovici, J.; Antonakis, K. *J. Chem. Soc., Chem. Commun.* **1980**, 561.
(216) Fronza, G.; Fuganti, C.; Grasselli, P.; Pedrocchi-Fantoni, G. *Tetrahedron Lett.* **1981**, 5073.
(217) Dyong, I.; Friege, H. *Chem. Ber.* **1979**, *112*, 3273.
(218) Cookson, R.; Gopalan, R. *J. Chem. Soc., Chem. Commun.* **1978**, 608.
(219) Gunner, S. W.; Overend, W. G.; Williams, N. R. *Chem. Ind.* **1964**, 1523.
(220) Brimacombe, J. S.; Mengech, A. S. *J. Chem. Soc., Perkin Trans. 1* **1980**, 204.
(221) Garegg, P. J.; Iversen, T.; Oscarson, S. *Carbohydr. Res.* **1977**, *53*, C5.
(222) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574.
(223) Yoshimura, J.; Matsuzawa, M.; Funabashi, M. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 2064.
(224) Yoshimura, J.; Matsuzawa, M.; Sato, K.-I.; Nagasawa, Y. *Carbohydr. Res.* **1979**, *76*, 67.
(225) Tatsuta, K.; Fujimoto, K.; Umezawa, S. *Carbohydr. Res.* **1977**, *54*, 85.
(226) Lemieux, R. U.; Fraser-Reid, B. *Can. J. Chem.* **1964**, *42*, 532.
(227) Brimacombe, J. S.; Saeed, M. S.; Weakley, T. J. R. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2061.
(228) Hassner, A.; Levy, L. A. *J. Am. Chem. Soc.* **1965**, *87*, 4203.
(229) Fowler, F. W.; Hassner, A.; Levy, L. A. *J. Am. Chem. Soc.* **1967**, *89*, 2077.
(230) Brimacombe, J. S.; Hanna, R.; Tucker, L. C. N. *Carbohydr. Res.* **1982**, *105*, C1.
(231) (a) Brimacombe, J. S.; Hanna, R.; Tucker, L. C. N. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2277. (b) Brimacombe, J. S.; Rahamn, K. M. M. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1067.
(232) (a) Brimacombe, J. S.; Rahman, K. M. M. *Carbohydr. Res.* **1983**, *113*, C6. (b) Brimacombe, J. S.; Rahman, K. M. M. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1073.
(233) Funabashi, M.; Hong, N.-G.; Kodama, H.; Yoshimura, J. *Carbohydr. Res.* **1978**, *67*, 139.
(234) Debono, M.; Molloy, R. M. *J. Org. Chem.* **1980**, *45*, 4685.
(235) Michael, K.; Shah, R. M.; Hamill, R. L. "A35512, A Complex of New Antibacterial Agents and Chemotherapy"; New York, October 14, 1977; Abstr. 41.
(236) Hudson, C. S. *J. Am. Chem. Soc.* **1909**, *31*, 66.
(237) Mallams, A. K.; Puar, M. S.; Rossman, R. R. *J. Am. Chem. Soc.* **1981**, *103*, 3938.
(238) Tomita, F.; Tamaoki, K.; Shiragata, K.; Kasai, M.; Morimoto, M.; Ohkubo, S.; Mineura, K.; Ishii, S. *J. Antibiot.* **1980**, *33*, 668.
(239) Tamaoki, T.; Kasai, M.; Shirahata, K.; Ohkubo, S.; Morimoto, M.; Mineura, K.; Ishii, S.; Tomita, F. *J. Antibiot.* **1980**, *33*, 946.
(240) (a) Yoshimura, J.; Yasumoi, T.; Kondo, T.; Sato, K.-I. *Carbohydr. Res.* **1982**, *106*, C1. (b) Yoshimura, J.; Yasumori, T.; Kondo, T.; Sato, K.-I. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2535. (c) Yasumori, T.; Sato, K.-I.; Hashimoto, H.; Yoshimura, J. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2538.
(241) Rosenthal, A.; Catsoulacos, P. *Can. J. Chem.* **1968**, *46*, 2868.
(242) Ganguly, A. K.; Sarre, O. Z.; Reimann, H. *J. Am. Chem. Soc.* **1968**, *90*, 7129.
(243) Ganguly, A. K.; Sarre, O. Z.; McPhail, A. T.; Onan, K. D. *J. Chem. Soc., Chem. Commun.* **1977**, 313.
(244) Bhuan, B. K.; Owen, S. P.; Dietz, A. *Antimicrob. Agents Chemother.* **1965**, 91.
(245) Meyer, C. E. *Antimicrob. Agents Chemother.* **1965**, 97.
(246) Reusser, F. *Biochemistry* **1973**, *12*, 1136.
(247) Hoekema, H.; Chidester, C.; Mizsak, S. A.; Baczynskj, J. *J. Antibiot.* **1978**, *31*, 1067.
(248) Kozikowski, A. P.; Sugiyama, K.; Springer, J. P. *Tetrahedron Lett.* **1980**, 3257.
(249) Mizsak, S. A.; Hoeksema, H.; Pschigoda, L. M. *J. Antibiot.* **1979**, *32*, 771.
(250) Mallams, A. K.; Puar, M. S.; Rossman, R. H. *J. Am. Chem. Soc.* **1981**, *103*, 3938.
(251) Brimacombe, J. S.; Rahman, K. M. M. *Carbohydr. Res.* **1983**, *114*, C1.
(252) Brimacombe, J. S.; Jones, B. D.; Stacey, M.; Willard, J. J. *Carbohydr. Res.* **1966**, *2*, 167.
(253) Hamada, Y.; Kawai, A.; Shioiri, T. *Tetrahedron Lett.* **1984**, 5409.
(254) Hamada, Y.; Kawai, A.; Shioiri, T. *Tetrahedron Lett.* **1984**, 5413.
(255) Gurjar, M. K.; Patil, V. J.; Yadav, J.; Rao, A. V. R. *Carbohydr. Res.* **1984**, *129*, 267.
(256) Hanessian, S.; Kloss, J. *Tetrahedron Lett.* **1985**, 1261.
(257) Danishefsky, S. J.; Maring, C. J. *J. Am. Chem. Soc.* **1985**, *107*, 1269.
(258) Hirama, M.; Shigemoto, T.; Yamazaki, Y.; Ito, S. *Tetrahedron Lett.* **1985**, 4133.
(259) Hirama, M.; Ahigemoto, T.; Yamazaki, Y.; Ito, S. *J. Am. Chem. Soc.* **1985**, *107*, 1797.
(260) Hirama, M.; Shigemoto, T.; Ito, S. *Tetrahedron Lett.* **1985**, 4137.
(261) Thiem, J.; Springer, D. *Carbohydr. Res.* **1985**, *136*, 325.
(262) Stewart, A. O.; Williams, R. M. *Carbohydr. Res.* **1984**, *135*, 167.
(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; DIBAL, 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[211,223] 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.