TOTAL SYNTHESIS OF SELECTED DEOXYAMINO SUGARS

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This dissertation, "Total Synthesis of Selected Deoxyamino Sugars" by Suzanne R. Ellenberger, has been examined and approved by the following Examination Committee:

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Dedication

To my mother and my late father

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Abstract

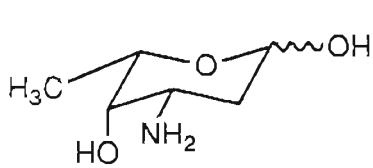
An efficient, regiospecific, high yield method for preparing racemic daunosamine, 3-epidaunosamine, ristosamine, vancosamine, and 3-epi-vancosamine from achiral precursors is described. The methodology involves preparation of a 6-carbon diene fragment with either a C-1 or C-5 hydroxyl group which is transposed to a C-3 amide through Claisen rearrangement of a imidate intermediate. C-1 of the terminal olefin is converted to a latent aldehyde group through Pummerer rearrangement of a 1-phenylthio sulfinyl group. Regio- and stereospecific functionalization of the 4,5-double bond either through cis-hydroxylation or epoxidation followed by hydrolysis with concomittant ring closure provides the desired sugars in good overall yield.

In order to demonstrate the versatility of this route, four aminopentose analogues were prepared in a similar manner through azetidinone intermediates. The β-lactams were prepared from volatile olefins using an improved procedure to provide the azetidinones in good yield (93-98%). Conversion of the azetidinones to the aminopentoses was accomplished in a straightforward manner.

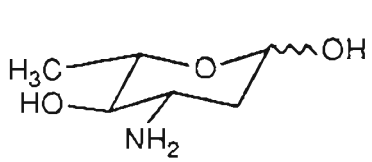
I. Introduction

In recent years there has been intense interest in the synthesis of modified 2,3,6-trideoxy-3-aminohexopyranoses possessing the several configurations, shown in Figure 1, which has been recently reviewed by Hauser and Ellenberger[1]. These syntheses have focused on the use of precursors derived from natural products and simple acyclic precursors to achieve both chiral and racemic preparations.

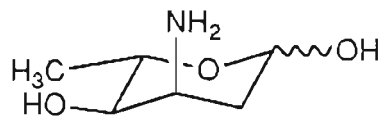
Figure 1. 2,3,6-Trideoxy-3-amino-L-hexopyranoses



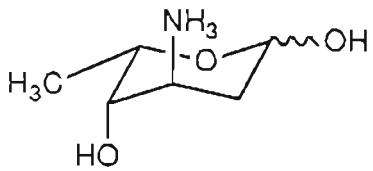
1. Daunosamine



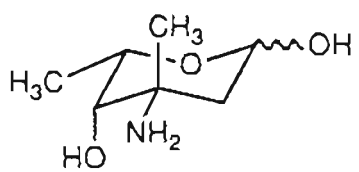
2. Acosamine



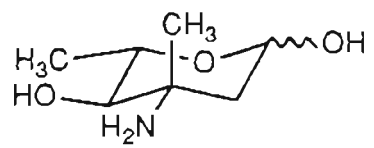
3. Ristosamine



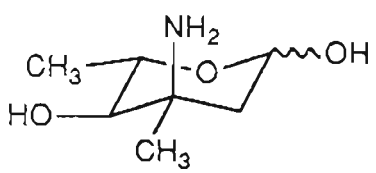
4. 3-epiDaunosamine



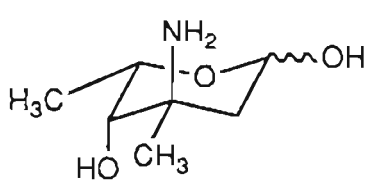
5. Vancosamine



6. 4-epiVancosamine



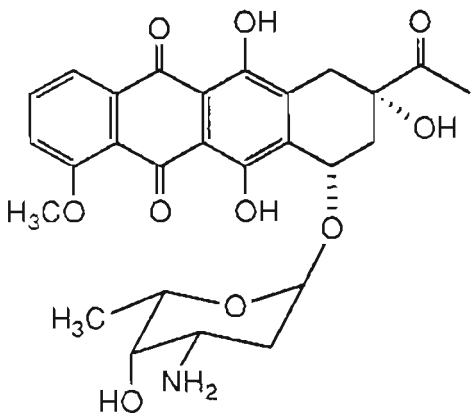
7. 2,3,6-Trideoxy-C-3-methyl-3-amino-ribo-hexopyranose



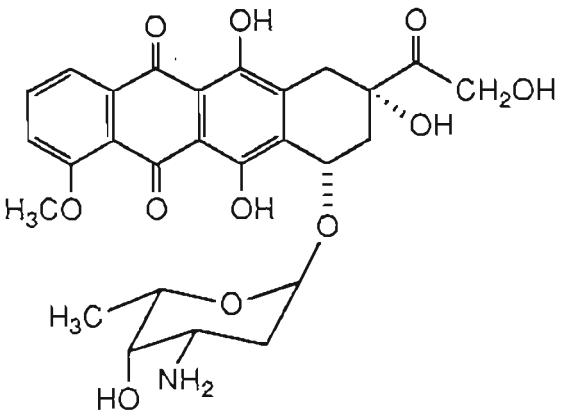
8. 3-epiVancosamine

Daunosamine (1), the most well known of the trideoxyaminohexoses, is the carbohydrate moiety in a number of naturally occurring cytotoxic anthracycline antibiotics used as antineoplastic agents. Adriamycin and daunorubicin, shown in Figure 2, are the most well known of these antineoplastic antibiotics and are clinically used in the treatment of a variey of cancers, in spite of their dose-limiting cardiotoxicity[2,3].

Figure 2. Daunorubicin and Adriamycin



Daunorubicin



Adriamycin

Daunomycin is one of the most effective agents for inducing remission of acute lymphoblastic and myeloblastic leukemia, while adriamycin is more effective against human solid tumors[4-6]. Both adriamycin and daunorubicin are known to bind with nucleic acid[7] and disrupt DNA and RNA syntheses[8,9]. The planar anthracycline nucleus fits into the DNA double helix by intercalation[10] and the hydrophobic faces of the base-pairs and

the antibiotic overlap extensively with consequent interference in biochemical utilization of the distorted DNA. The aminosugar moiety is in the large groove of the DNA and the amino residue is in close proximity to a phosphate group enabling strong hydrogen or eletrostatic bonding. The anthracycline antibiotics with the greatest antineoplastic activity have glycosides which possess a free amino group in the equatorial position; have the L-configuration; and, have an α-linkage to the anthracyclineone, all of which minimize size of the intercalation site[11].

Recently, interest in the synthesis of acosamine (2) (L-arabino), the C-4 epimer of daunosamine, and ristosamine (3) (L- and D-ribo) has intensified, since it has been determined through structure-activity relationships that substitution of acosamine or ristosamine for daunosamine in adriamycin results in reduced cardiotoxicity with no apparent loss of cytotoxic activity[12-19]. Studies are currently being conducted on the biological activity of structural analogues of these sugars such as 2-amino-4-hydroxy and 4-amino-3-hydroxy derivatives.

Daunosamine (1) was initially isolated by Arcamone et al.[20,21] from daunomycin, an antibiotic metabolite and more recently has been found as a component of other naturally occurring antibiotics[22-24]. Ristosamine (3), is a component of the water soluble glycopeptide ristomycin[25-32] which is a member of the vancomycin group of antibiotics[33]. Acosamine (2), isolated from the antibiotic actinoidin by Lomakina and coworkers[34,35], was determined to be the L-arabino isomer and the C-4 epimer of daunosamine (1). The compound with the L-xylo

configuration, 3-epidaunosamine (4), is not known to occur naturally. Vancosamine (5) is the C-3 methyl derivative of daunosamine (1) and occurs as the glycon fragment in the antibiotic vancomycin which was first isolated in 1956 by McCormick et al.[36-40]

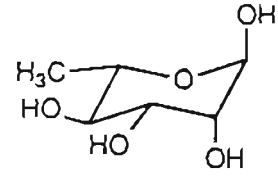
II. Literature Background

Several chiral and racemic syntheses of derivatives of 2,3,6-trideoxy-3-aminohexoses have been reported. They are based on the use of (A) D and L carbohydrates; and (B) non-carbohydrate chiral starting materials; however many approaches have exploited (C) synthons of a different origin. A feature common to these approaches is the manipulation of the chiral centers in intermediates possessing the three contiguous, optically active carbons required for assessing the necessary configurations. The presence of the traditionally problematic cis-vicinal hydroxy-amine component in daunosamine requires more steps than the trans counterparts, and thus hampers its preparation.

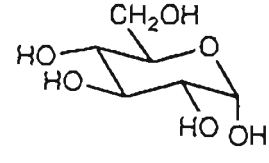
(A) Carbohydrate Derived Starting Materials

The most commonly used sugar precursors for synthesis of these trideoxyaminohexoses are rhamnose (9), glucose (10), and mannose (11) (Figure 3).

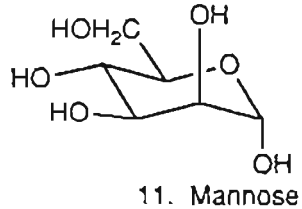
Figure 3. Commonly used sugar precursors for synthesis of 2,3,6-trideoxy-3-aminohexoses



9. Rhamnose



10. Glucose

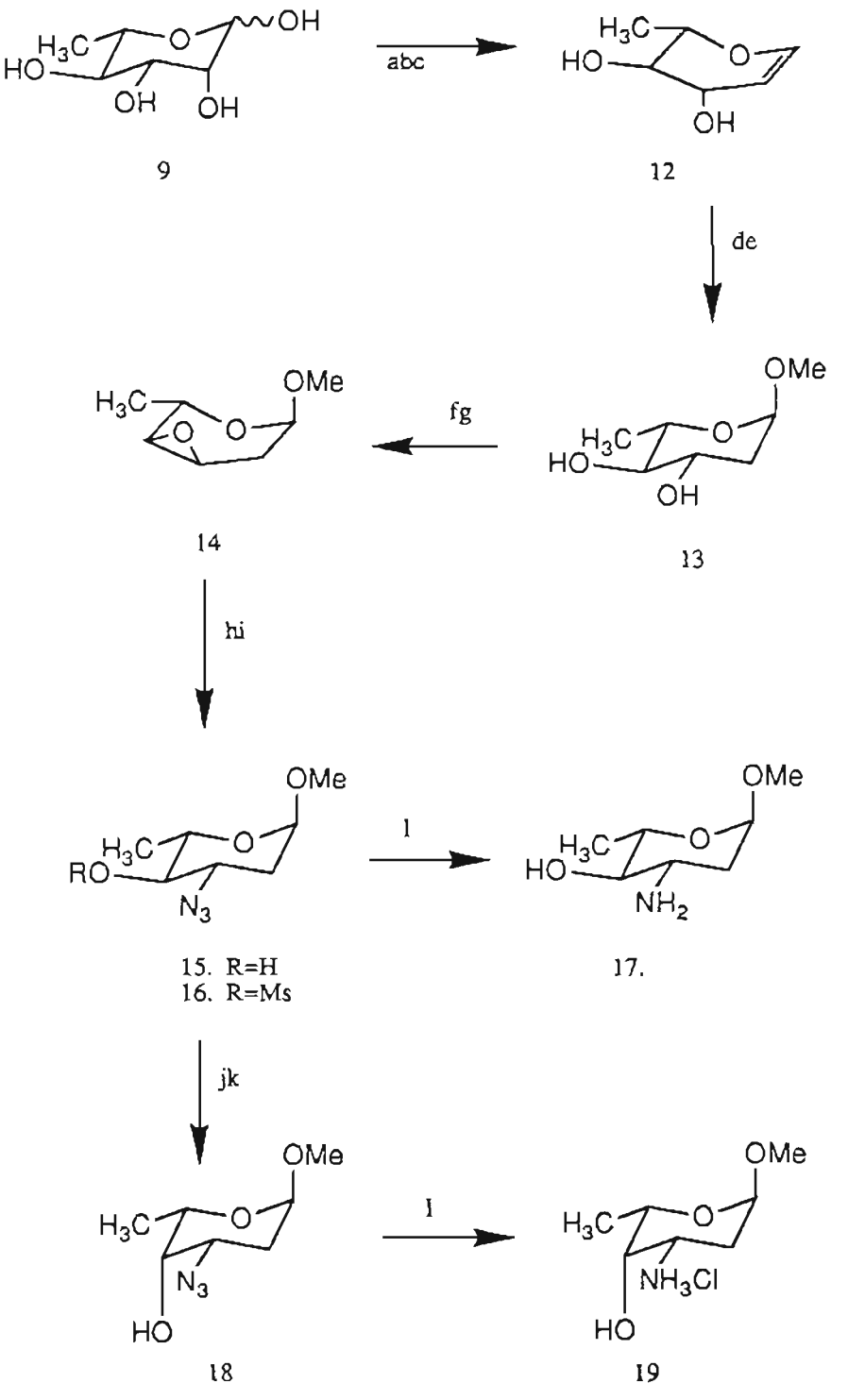


11. Mannose

All of the naturally occurring 2,3,6-trideoxy-3-aminohexoses have the L-configuration except acosamine 2 which has been isolated in both the D-[41] and L forms. Although it is relatively expensive, L-rhamnose (9) has been the most widely used starting material for synthesis of 2,3,6-trideoxy-3-aminohexoses because it has the requisite L-configuration and is devoid of a 6-hydroxyl group; glucose (10) and mannose (11) are readily available, inexpensive precursors, but the necessity exists for converting the D configuration to L. Removal of the 2-hydroxy functionality in all of the above sugars is necessary in order to produce the required 2-deoxy sugar.

In 1965, Marsh et al.[42] reported the first total synthesis of L-daunosamine (1) from rhamnose (9). This sequence is shown in Scheme 1. Conversion of 9 to L-rhamnal[43] (12) and methoxymercuration of 12 with in situ borohydride reduction of the organomercury intermediate furnished the 2,6-dideoxy sugar 13. Sulfonylation of 13 gave the 3-O-monotoluene sulfonate as the major product, which on treatment with base formed epoxide 14. The impure epoxide was reacted with sodium azide and the 3-azido sugar 15, with the L-arabino configuration, was the predominate product 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 15 generated the then unknown methyl L-acosaminide derivative 17 which was not isolated from natural sources until 1973[34,35]. The configuration of the C-4 hydroxyl in 15 was inverted through reaction of the mesylated 3-azido sugar 16 with sodium benzoate; subsequent hydrolysis produced the azido-alcohol 18 with the

Scheme 1.



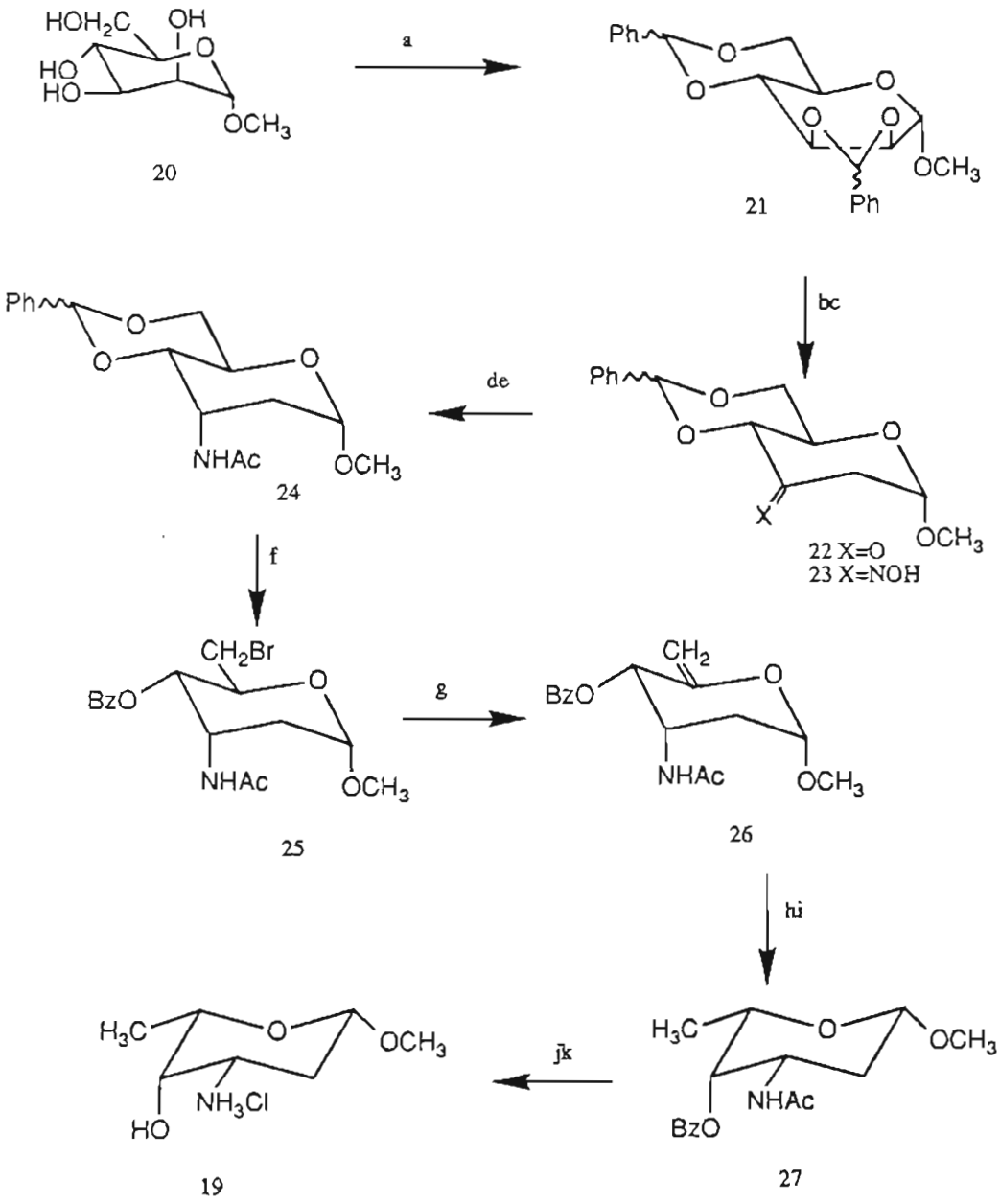
a) Ac_2O, Py b) HBr, HOAc, Ac_2O c) Zn-Cu, HOAc d) $Hg(OAc)_2$, CH_3OH
e) KBH_4 f) TsCl, Py g) $NaOCH_3$ h) NaN_3 I) MsCl, Py j) NaOBz, DMF
k) $NaOCH_3$, H_2O l) catalytic hydrogenation

L-lyxo configuration. Catalytic hydrogenation of 18 under acidic conditions gave crystalline methyl daunosaminide hydrochloride (19). Although no yields were reported by these authors, other investigators[45,46] have used this sequence to convert the epoxide 14 to daunosamine (1) in 26% 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, new solution to this problem was reported by Horton and Weckerle[47] in their total synthesis of daunosamine (1) from methyl α-D-mannoside (20). This nine step preparation, shown in Scheme 2, is one of the highest yield routes yet reported. Key elements of the synthesis are the stereoselective reduction of the oxime fragment in 23 to a C-3 amino group and the stereospecific generation of the L-lyxo stereochemistry through hydrogenation of the 5,6-olefinic entity in 26.

The 2,3:4,6-di-O-benzylidene acetal 21 was prepared through reaction of 20 with α,α-dimethoxytoluene[48]. Klemer-Rhodemeyer[49] fragmentation of the 2,3-O-benzylidene fragment with butyllithium (2 equivalents) selectively furnished the hexopyranosid-3-ulose 22, which was subsequently converted to the oxime 23[50]. Reduction of the oxime moiety with lithium aluminum hydride (LAH) followed by acetylation gave a diastereoisomeric mixture of the D-ribo (24; 87%) and D-arabino (12%) 2,3-dideoxy-N-acetyl-hexopyranoses; the difference in solubility of the isomers in ether facilitated their separation. After fragmentation

Scheme 2.



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

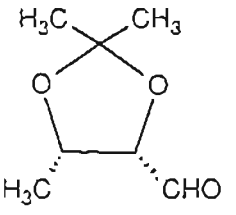
of the 4,6-O-benzylidene residue in 24 with N-bromosuccinimide (NBS) and barium carbonate[51], the resultant 4-O-benzoyl-6-bromo derivative 25 was dehydrobrominated with silver fluoride and pyridine in benzene[52] to furnish 26. Hydrolytic cleavage of the benzoyl group and then hydrogenation of the 5,6-olefinic residue in 26 stereospecifically generated the L-stereochemistry at C-5 in 27. Deacetylation of 27 gave methyl daunosaminide hydrochloride (19). The overall yield for this preparation was 40%.

(B) Non-Carbohydrate Derived Chiral Precursors

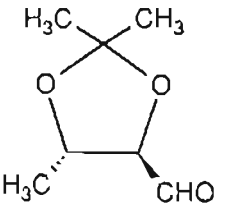
Although most of the total syntheses of optically active aminohexoses have been initiated from carbohydrate based materials, efforts have focused on the use of non-carbohydrate derived precursors. A substantial effort has focused on the use of amino acids and other low molecular weight natural products. The common use of amino acids is hampered by the fact that the readily available, naturally occurring compounds have the D-configuration which must be converted to the requisite L-configuration. Another commonly used precursor is L-tartaric acid. While this natural product contains the necessary stereochemistry, numerous steps are required to convert it to useful synthons for amino sugar syntheses.

The C-4 chiral aldehydes 28 and 29, with the respective 2S,3S and 2R,3S absolute configurations shown in Figure 4, have been the most intensely studied because they contain two of the three stereocenters and four of the six carbons of the objective aminohexoses.

Figure 4. (2S,3S)- and (2R,3S)-2,3-Dihydroxybutanal acetals.



28.

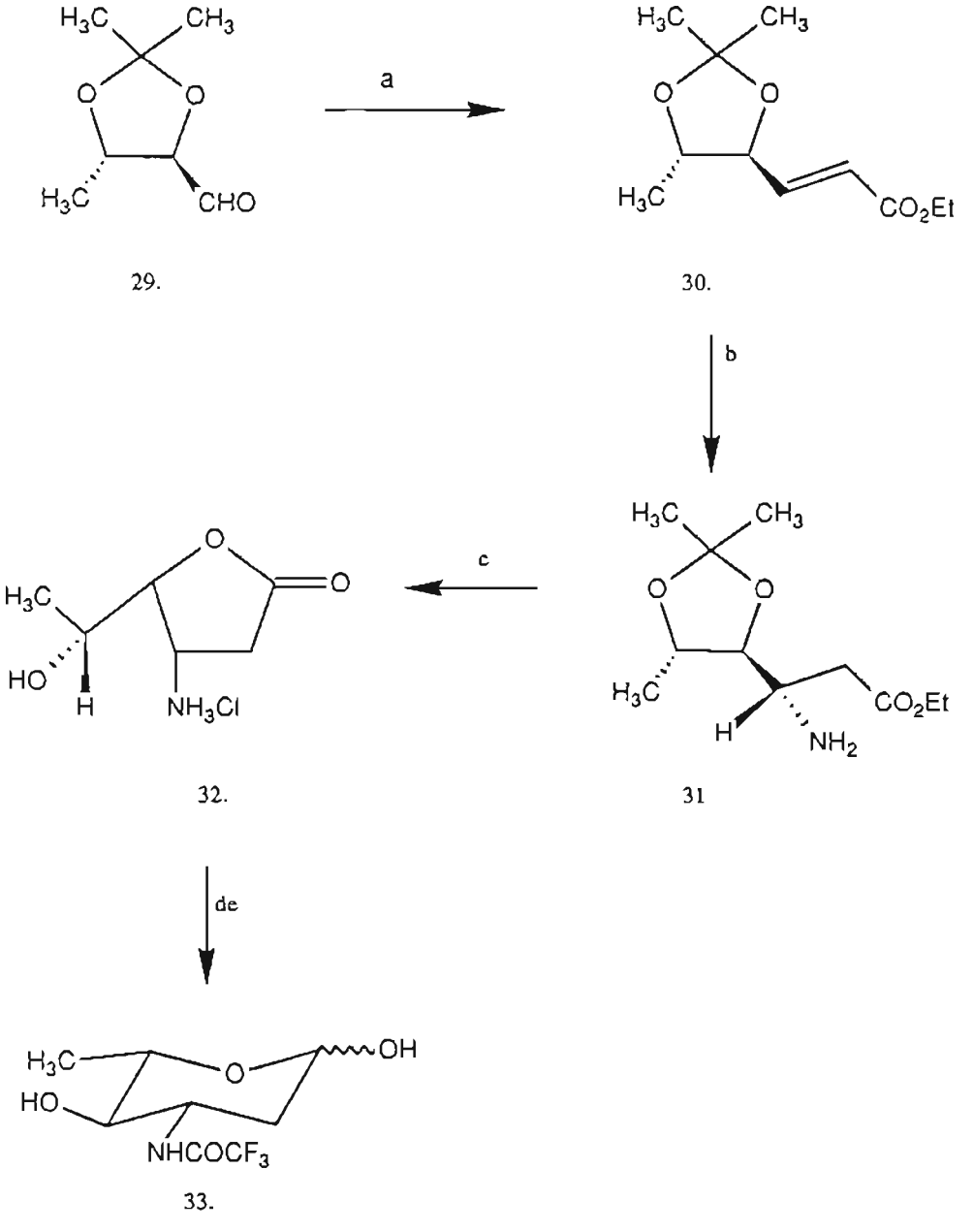


29.

Fuganti and coworkers[53,54] have reported two procedures for preparation of the protected 2S,3S-erythro-aldehyde 28 through fermentation of cinnamaldehyde with Baker's yeast. Although the four step method provided 28 in 18% yield, the authors preferred the lower yield route (8%) since it was experimentally less involved. The 2R,3S-threo-aldehyde 29 has been prepared from D-threonine[55], by epimerization of the 2S,3S-aldehyde[53,56] 28 and from L-tartaric acid[57-59]. The more direct route to 29 from D-threonine is impractical for large scale preparation due to the presently exorbitant cost of this unnatural amino acid[55].

Aldehydes 28 and 29 have served as key intermediates in several chiral syntheses of daunosamine (1) as well as in those of other configurationally related aminohexoses[60]. Transformation of these materials to the desired sugars requires stereoselective elaboration of C-1 with incorporation of a nitrogenous functionality and a two carbon homologation with the terminal carbon eventually becoming an aldehyde.

Scheme 3.



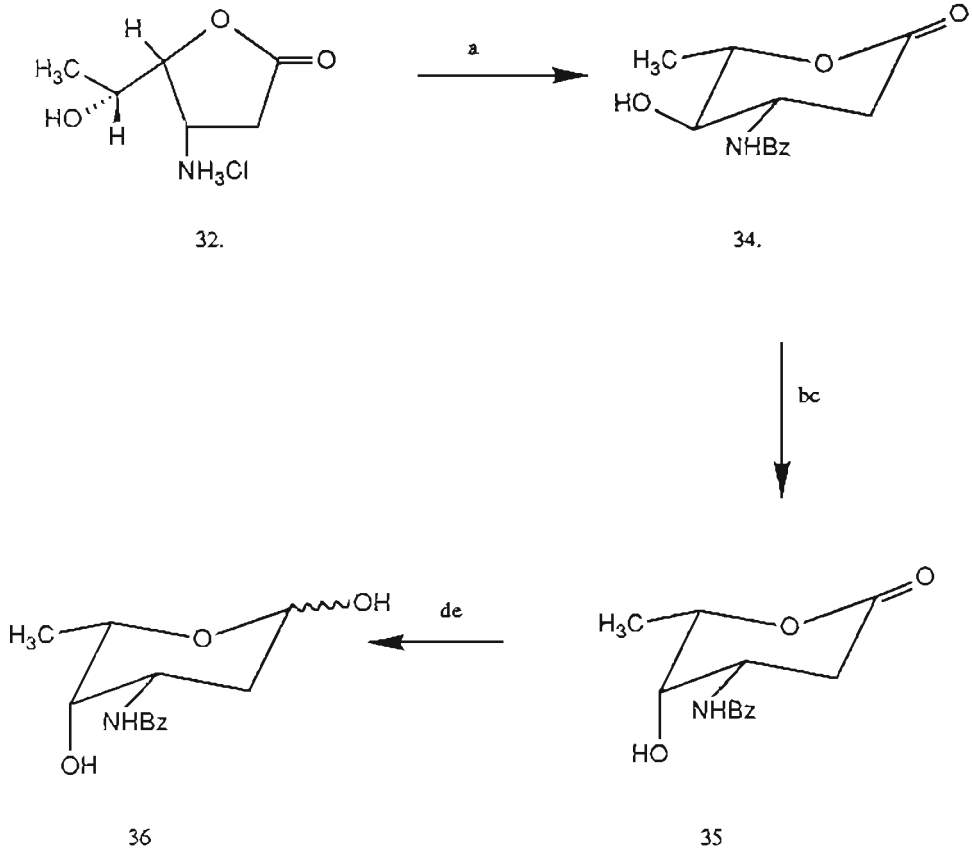
29. 30. 31 32. 33.

a) $Ph_3P{=}CHCO_2Et$ b) NH_3, MeOH c) HCl, Et_2O d) TFAA, Py
e) DIBAL, THF, -50 C

The first exploitation of these compounds as intermediates to optically active aminohexoses was reported by Fronza and coworkers[57], who used 29 as a precursor to both acosamine (2) and daunosamine (1) as shown in Scheme 3. Wittig reaction of 29 with carboethoxy methylidene triphenylphosphorane furnished the unsaturated ester 30. Conjugate addition of ammonia to 30 stereoselectively gave 31, which on acid hydrolysis of the acetonide moiety underwent intramolecular cyclization to the amino lactone 32 with the arabino configuration (70% overall yield from 29). Acetylation of 32 to the bis-N,O-trifluoroacetyl derivative followed by diisobutyl aluminum hydride (DIBAL) reduction produced N-trifluoroacetylacosamine (33) (56%).

As shown in Scheme 4, the amino lactone 32 with the arabino configuration served as an intermediate to daunosamine (1). Treatment of 32 with sodium hydroxide and benzoyl chloride effected benzoylation of the amino group and isomerization to the 6-membered lactone 34. Epimerization at C-4 of 34 to give 35 was performed in 65% overall yield through mesylation, displacement with acetate and hydrolysis. Trifluoroacetylation of 35 followed by DIBAL reduction gave N-trifluoroacetyldaunosamine (36). The yield of 36 from the aminolactone 32 was 34% (overall yield 3%).

Scheme 4.



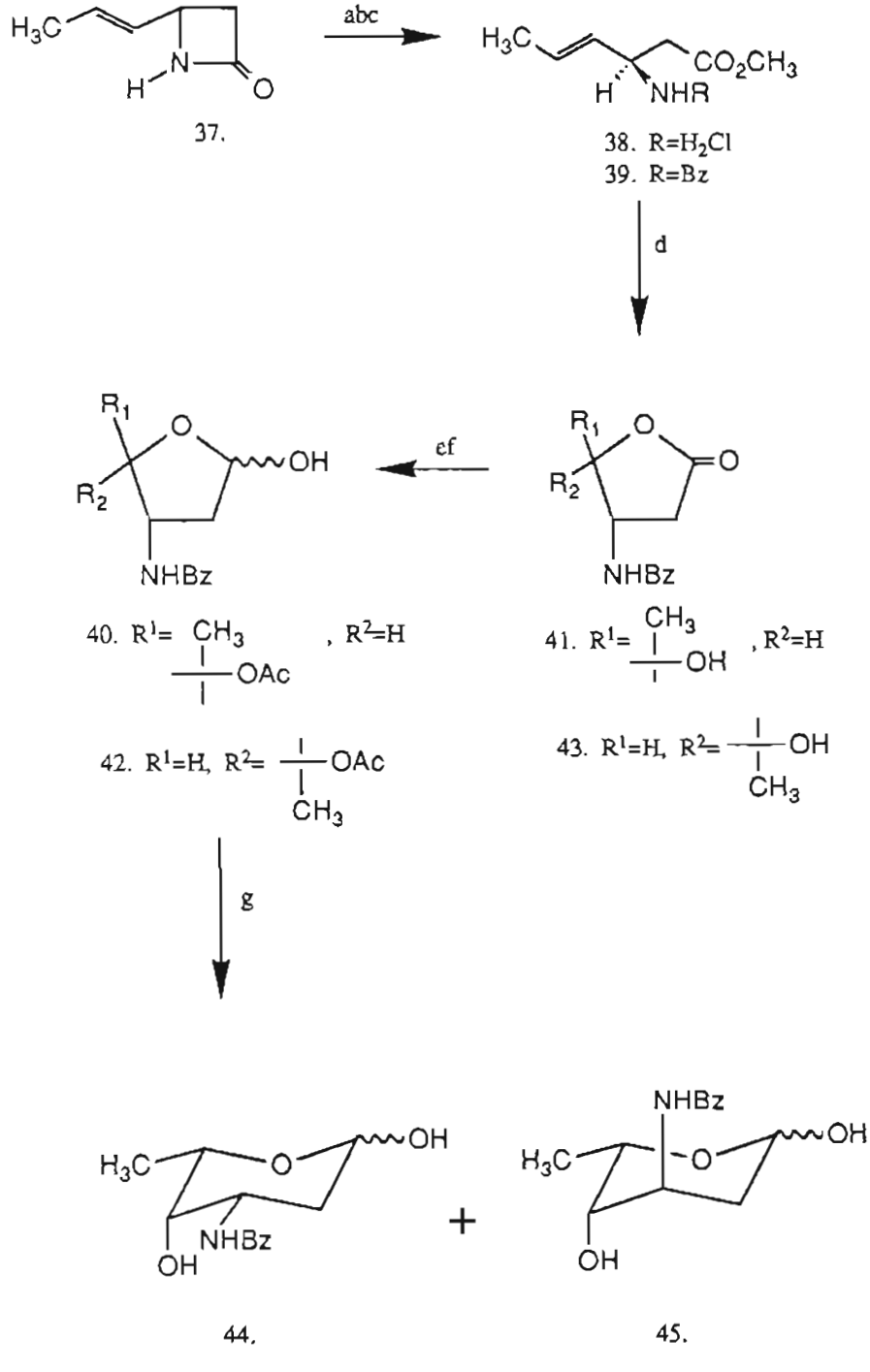
32. 34. 36 35

a) NaOH, PhCOCl b) MsCl, Py c) NaOAc d) TFAA, Py e) DIBAL

(C) Achiral Precursors

There have been many racemic and some homochiral syntheses of this group of sugars utilizing simple achiral starting materials. The origin of the starting materials of these racemic syntheses is widely varied as are the imaginative and often elegant approaches used in these preparations. Any racemic synthesis has possibility of resolution. An example of this is the initially racemic and subsequently chiral

Scheme 5.



37.

38. R=H_2Cl

39. R=Bz

40. R^1= CH_3 / OAc , R^2=H

41. R^1= CH_3 / OH , R^2=H

42. R^1=H, R^2= OAc / CH_3

43. R^1=H, R^2= OH / CH_3

44.

45.

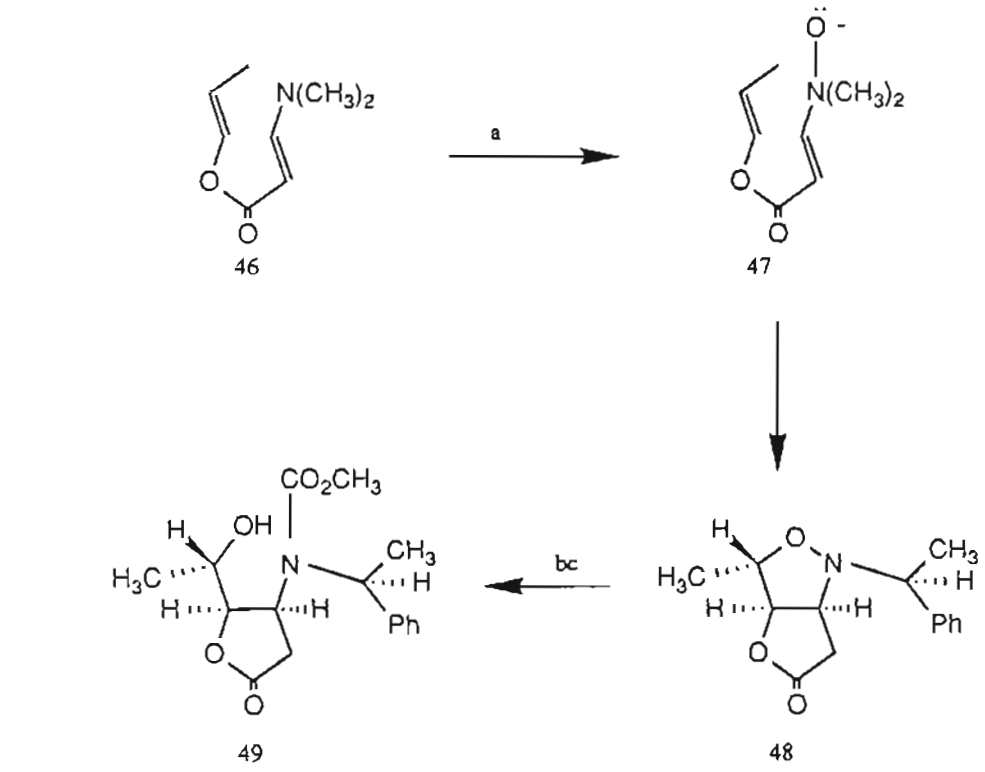
a) CH_3OH, HCl b) resolve with dibenzoyl L-tartrate or p-bromotartranilic acid
c) PhCOCl, Py d) catalytic OsO_4, TMNO e) Ac_2O, Py f) DIBAL, THF
g) NH_3, CH_3OH, 0 °C

preparation of 1 reported by Hauser and coworkers[59,60], shown in Scheme 5. Propenylazetidinone (37), prepared from cycloaddition of 1,3-pentadiene and chlorosulfonyl isocyanate[61,62], was subjected to methanolysis to give methyl 3-amino-4-(E)hexenoate hydrochloride (38). Optical resolution of the hydrochloride salt 38 with either p-bromotartranilic acid or dibenzoyl tartrate followed by hydrolysis and benzoylation (BzCl, Py) gave the optically active benzamide methyl ester 39. cis-Hydroxylation of the olefinic moiety with trimethylamine-N-oxide and a catalytic amount of osmium tetraoxide[64] directly gave the lactones 40 and 41. The hydroxyl functionalities in the lactones were acetylated to give 40a and 41b to enhance solubility in THF, the solvent required for reduction. The corresponding acetoxy furanoses 42 and 43 were obtained from DIBAL reduction and after ammonolysis, daunosamine (44) and 3-epidaunosamine (45) were obtained.

A number of imaginative routes for total syntheses of optically active daunosamine (1) from achiral precursors have been investigated. The earliest was elegantly achieved by Wovkulich and Uskokovic[65] in modest overall yield as shown in Scheme 6. 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[66] gave 46, which was heated with the oxalate salt of (S)-(-)-N-hydroxy-α-methylbenzenemethanamine[67] to form 47.

Scheme 6.



50. $R^1=CO_2CH_3$, $R^2=CHCH_3(Ph)$
51. $R^1=CO_2CH_3$, $R^2=H$
52. $R^1=R^2=H$

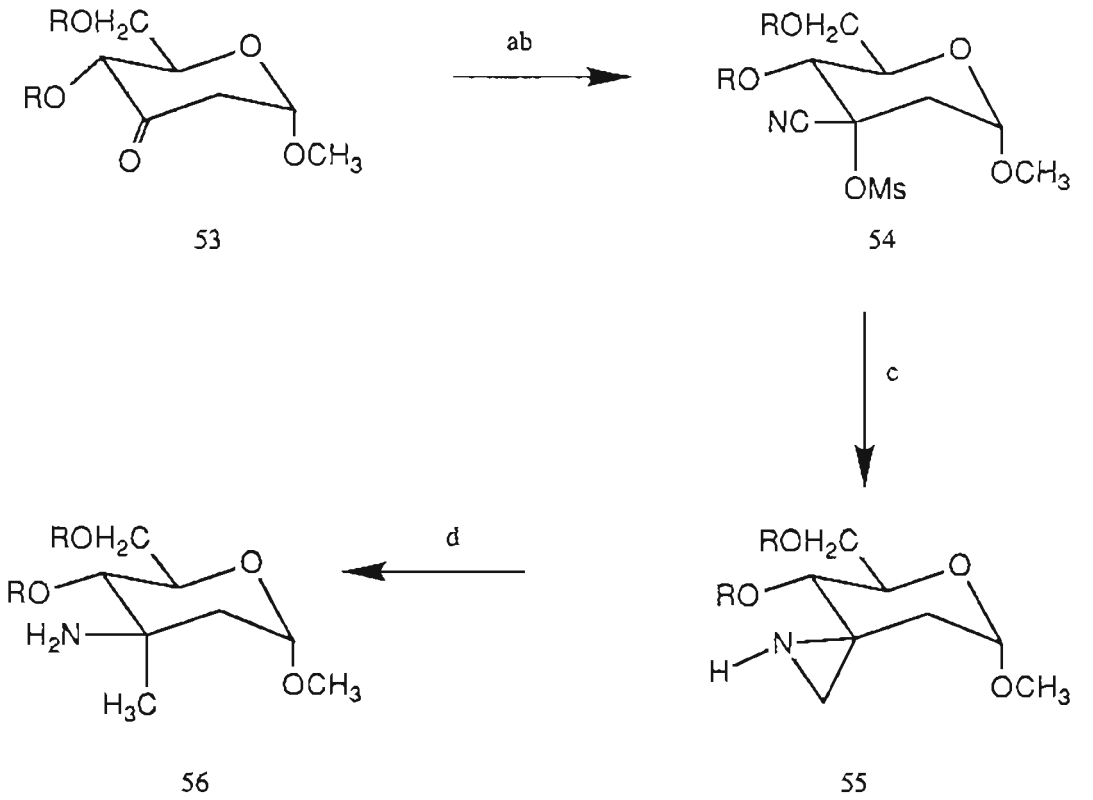
a) (s)-(-)-N-hydroxy-α-methylbenzene methanamine oxalate salt, xylene
b) Zn, HOAc, H_2O c) Na_2CO_3, CH_3OCOCl, THF d) DIBAL
e) Amberlite H^+, CH_3OH f) Na, NH_3 g) MsCl, Py h) DMF, H_2O
i) $Ba(OH)_2$, H_2O

The nitrone intermediate 47 underwent spontaneous intramolecular cyclization to give an 82:12 mixture of diastereoisomeric oxazolones that were separated by crystallization. The N-O bond of the major isomer 48 was reductively cleaved (Zn, HOAc) and the resultant amine product was reacted with methyl chloroformate to give 49. DIBAL reduction of the lactone functionality in 49, 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 51 with sodium and ammonia. The procedure of Marsh et al.[42] (Scheme 1) was used to invert the C-4 hydroxyl group stereochemistry in 51, furnishing the optically active methyl daunosaminide 52. Methyl acosaminide 17 was also produced through basic hydrolysis of the debenzylated intermediate 51.

(D) C-Methyl Sugar Syntheses

Numerous syntheses of derivatives of C-3 methyl sugars such as vancosamine (5) have been performed from both carbohydrate and non-carbohydrate derived starting materials. While several are elegantly conceived, few provide a high yield route to 5. A feature common to many branched chain amino sugar syntheses is introduction of the methyl and amino groups at C-3 by the method of Bourgeois[68-70] (Scheme 7). The procedure involves cyano-mesylation of a hexos-3-ulose (53) to give 54, reduction to give a spiro-aziridine 55 and hydrogenolysis of the aziridine ring to give the methyl substituted amino sugar 56.

Scheme 7.



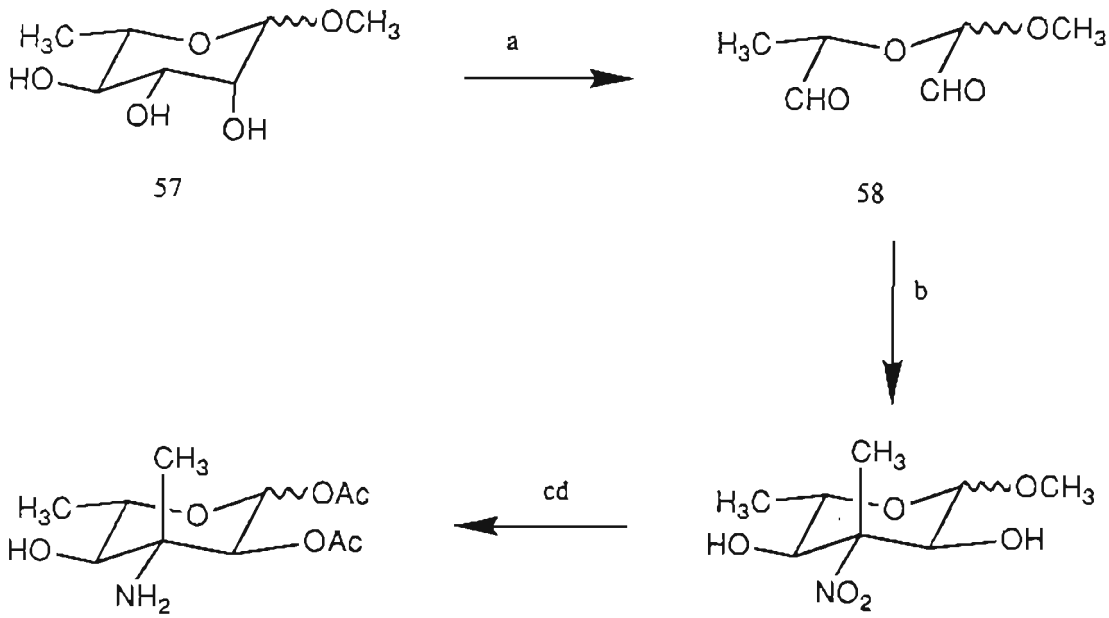
53 54 55 56

a) HCN, Py b) MsCl, Py c) LAH d) Ni(R), H_2

Another common synthetic route used to attain the requisite branching at C-3 in methyl-branched amino sugars is base catalyzed nitroethane cyclization of dialdehydes produced from oxidation of methyl glycosides[71,72] (Scheme 8). Methyl rhamnoside (57) is oxidized to the dialdehyde 58 and condensed with basic nitroethane to produce the nitrohexose 59. The methyl glycoside moiety is hydrolyzed (aqueous

HCl) and the free nitrosugar is acetylated (Ac_2O, Py) to the triacetate derivative before catalytic reduction of the nitro group to give 60.

Scheme 8.

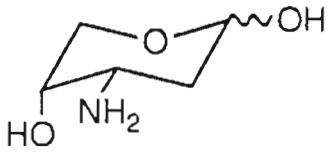


a) $NaIO_4$ b) $EtNO_2$, NaOEt C) Aq. HCl, Ac_2O, Py d) Pd, H_2

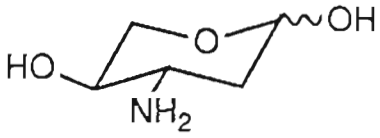
III. Synthetic Strategy

In view of the high cost and low efficiency of microbially produced antibiotics containing these sugars, an effective synthetic route to these substances is a desirable objective. The majority of the work described here has as its goal the development of efficient, regio-specific, high yield syntheses of (±)-daunosamine (1), (±)-ristosamine (3), (±)-3-epidaunosamine (4), (±)-vancosamine (5), and (±)-3-epivancos-amine (8) from inexpensive, achiral precursors. Also described is a synthesis of the (±)-2,3-dideoxy-3-aminopentoses 61 and 62 and the 3-C-methyl analogues 63 and 64 (Figure 5).

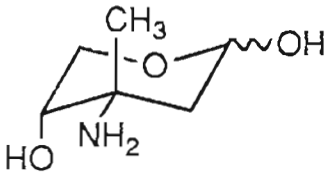
Figure 5. 2,3-Dideoxy-3-aminohexoses and 2,3-Dideoxy-3-amino-3-C-methylhexoses



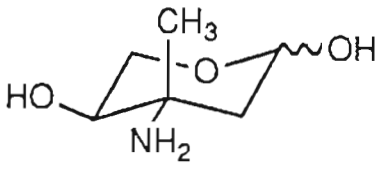
61



62



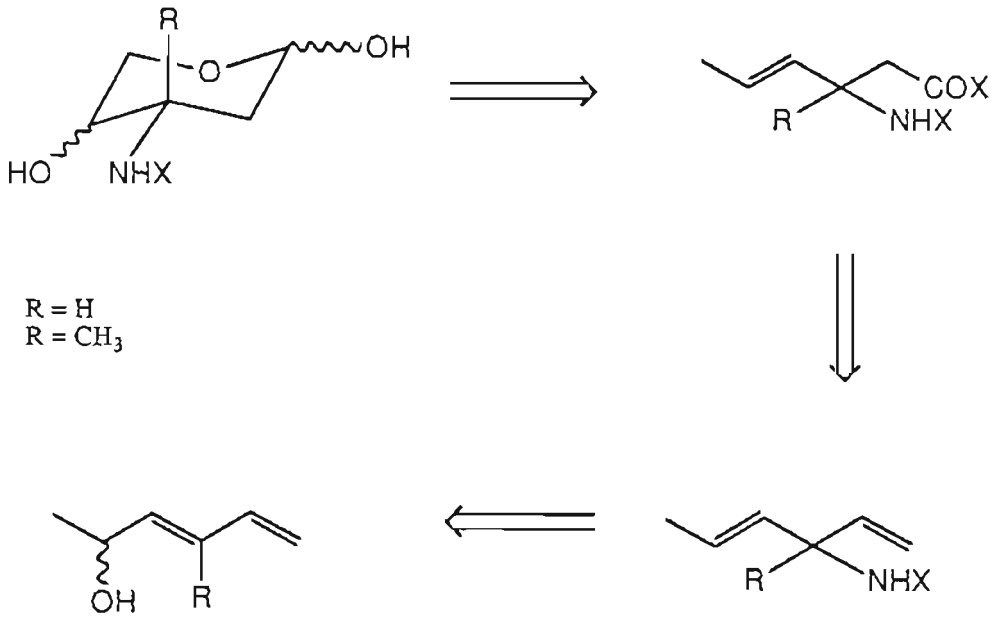
63



64

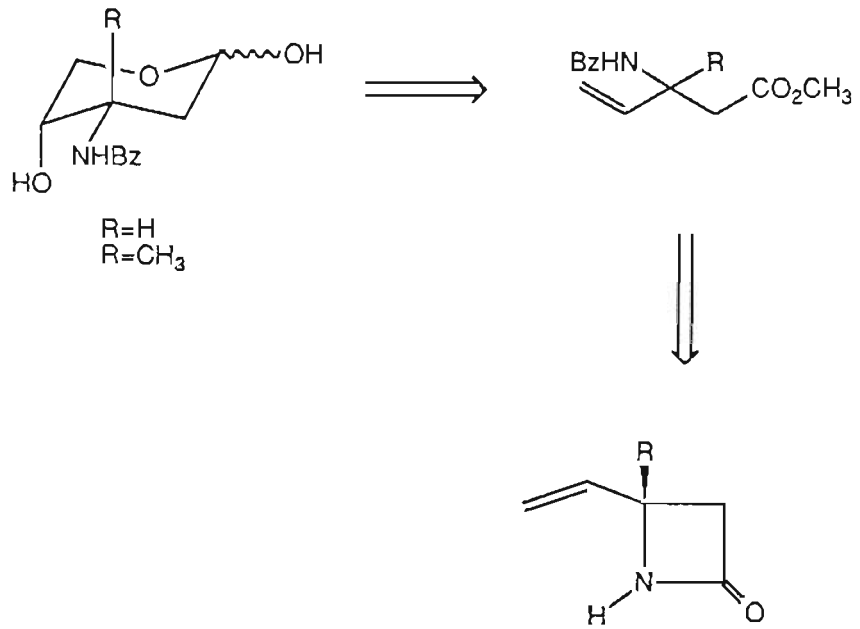
The synthetic strategy to 2,3,6-trideoxy-3-aminohexoses is based upon the use of a 6-carbon diene fragment containing a hydroxyl group at C-1 or C-5 which is transposed into a C-3 amide functionality via Claisen rearrangement of an imidate. Conversion of C-1 to an aldehyde, or its latent counterpart, followed by and regio- and stereospecific functionaliztion of the 4,5-olefin to give a diol with concomitant ring closure, provides the desired sugars as shown in the antithetic route in Scheme 9.

Scheme 9.



The synthetic strategy to 2,3-dideoxy-3-aminopentoses and C-3-methyl analogues utilizes an azetidinone intermediate which is cleaved to a 5-carbon olefinic fragment with the 3-amino moiety present from the β-lactam, and containing an ester group at C-1. Functionalization of the 4,5-olefin to a diol provides the desired sugars as shown in Scheme 10.

Scheme 10.



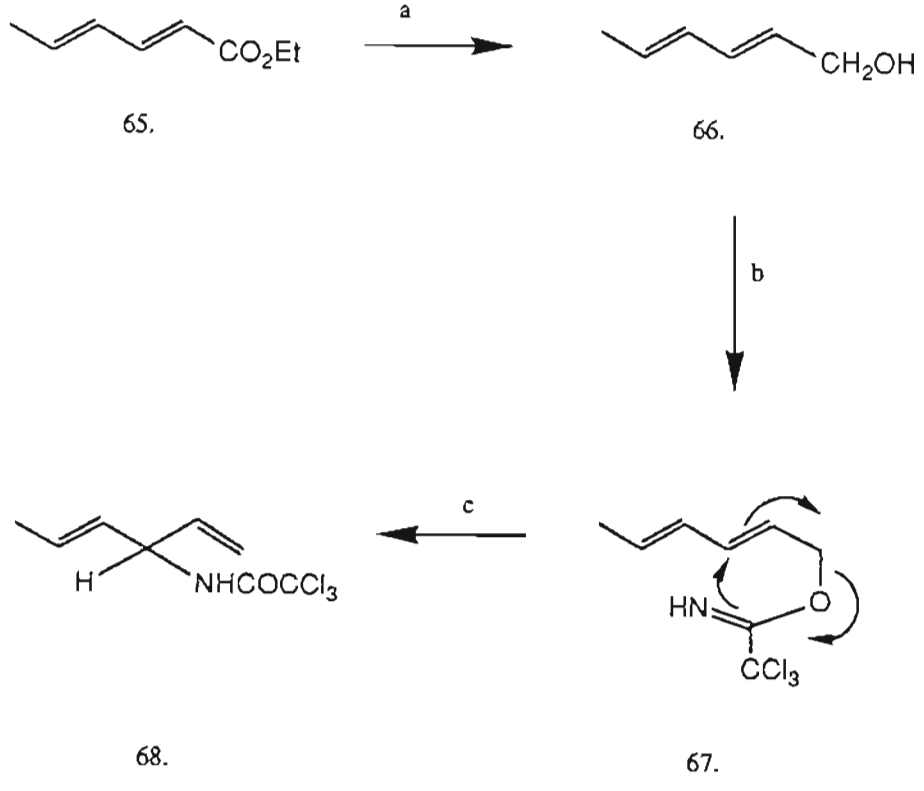
IV. Functionalization of the 4,5-olefin

A. Synthesis of (E)-1-(thiophenyl)-3-(trichloroacetamido)-4-hexene

1. Overman reaction

Two methods were employed to prepare the olefinic trichloroacetamide 68. While the origins of the allylic alcohols were quite different, both utilized the [3.3]-sigmatropic rearrangement[73,74] of an

Scheme 11.



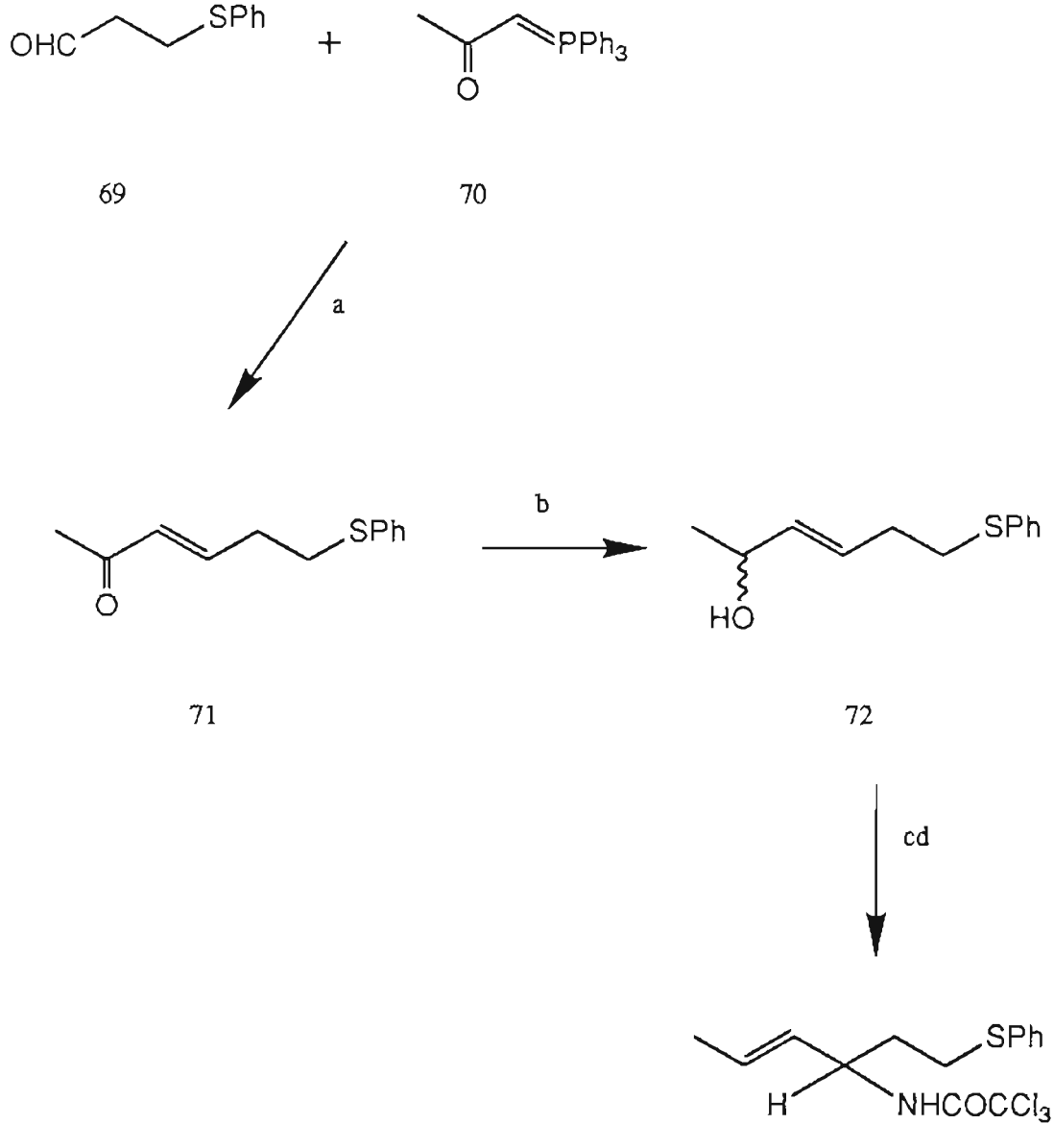
65. 66. 68. 67.

a) LAH (96%) b) NaH, Cl_3CCN c) xylenes (100%)

allyl imidate for regiospecific introduction of the amide functionality. Initially, the route shown in Scheme 11 was investigated. Commercially available ethyl sorbate (65) was reduced with lithium aluminum hydride (LAH) to sorbyl alcohol (66). Treatment of 66 with a catalytic amount of sodium hydride followed by addition of trichloroacetonitrile provided the unstable trichloroacetimidate intermediate 67, which on heating in refluxing xylenes underwent thermal rearrangement to give the deconjugated dieneamide 68 in quantitative yield. As will be shown later, 68 can be converted to 73 thereby confirming the structures of the products.

In order to confirm the structure of 68 through an alternative preparation and also to establish the conceptual potential for synthesis of objective sugars through this route, the reaction sequence shown in Scheme 12 was executed. Wittig reaction of 1-phenylthiopropanal[75] 69 with triphenylphosphoranylidene-2-propanone (70) provided the α,β-unsaturated ketosulfide 71 in 80% yield. Reduction of 71 with LAH gave 72, which on Overman rearrangement with trichloroacetonitrile and a catalytic amount of potassium hydride gave 73 as an oil in quantitative yield. Overman reaction of 72 was more difficult than of 66, and inverse addition of the alkoxide and trichloroacetonitrile was necessary for this secondary alcohol, as was a change of base from sodium to potassium hydride. In principle, this route could be used to achieve the chiral syntheses of objective sugars either through asymmetric reduction of the ketone functionality in 71 with a chiral reducing agent or through an alternative fabrication of the optically active alcohol 72.

Scheme 12.



a) benzene, Δ b) LAH (52%) c) KH, Cl_3CCN d) EtOAc, Δ (100%) 73

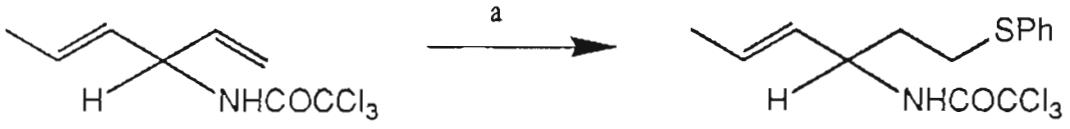
2. Sulfide preparation

The next objective in the sequence was convert C-1 in 68 to either an aldehyde or its latent counterpart. Since C-1,2 in 68 is a terminal mono-substituted olefin and C-4,5 is a trans disubstituted olefin, it was expected that C-1 could be selectively functionalized because of the greater reactivity of terminal olefins toward various reagents. Hydroboration of terminal olefins with 9-borabicyclononane (9-BBN)[76,77] followed by peroxide oxidation has been used previously to effect regiospecific conversion of terminal olefins to primary alcohols. Both commercial and freshly prepared[76] 9-BBN gave complex mixtures in which none of the desired product was discernable.

Thioalkyl radicals are known to add regiospecifically to terminal olefins with introduction of the sulfur residue at C-1[78,79]. Since thioalkyl and especially thiophenyl groups are readily converted to aldehydes via Pummerer rearrangement or through α-elimination followed by hydrolysis, this approach to selective functionalization of C-1 was investigated next.

Free radical addition of benzenethiol with a catalytic amount of azobisisobutrylnitrile (AIBN) to 68 at 80 to 90 °C proceeded regiospecifically to give the sulfide 73 (Scheme 13). However, the reaction required 24-36 h to go to completion. Attempts to increase the rate of reaction through addition of various solvents, increasing the temperature or addition a stoichiometric amount of AIBN resulted in no improvement and/or was detrimental to product formation.

Scheme 13.



68 73

a) PhSH, AIBN, 80-90 °C (88%)

3. Sulfide oxidation

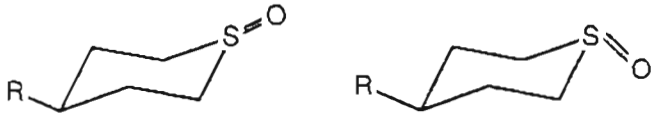
Oxidation of sulfides to sulfoxides in molecules a containing pre-existing asymmetric center has the potential for generating diastereoisomeric mixtures. Numerous reagents are available for the selective oxidation of sulfides to sulfoxides[80]. The oxidation potential of sulfides to sulfoxides is much lower than the oxidation potential of sulfoxides to sulfones. Many of these methods are potentially incompatible because of other reactive sites in 73.

While some of these methods give rise to selective formation of diastereo- and geometric isomers of cyclic substrates[80], the literature is devoid of information concerning the stereochemistry of oxidation products derived from acyclic systems. However, recent attempts for asymmetric oxidation of sulfides to sulfoxides using chiral oxidizing agents[81], such as the Sharpless reagent for asymmetric epoxidation of allylic alcohols[82,83] (titanium tetraisopropoxide, (R,R)-diethyl

tartrate, t-butyl hydroperoxide), have had variable success. A further complication in the oxidation of sulfides is that these reactions often give the sulfoxide isomers contaminated with either the sulfide starting material or the over-oxidized sulfone product. Another drawback is the relatively long reaction time needed for completion of the oxidation, especially when the oxidant is sodium metaperiodate or hydrogen peroxide.

Oxidation of organosulfides with a preexisting asymmetric center can be expected to produce diastereoisomeric mixtures. The isomer distribution from sodium metaperiodate oxidation of cyclic sulfur containing compounds has been described[80]. However, isomer distribution in corresponding oxidation of acyclic compounds as not been reported. As shown in Figure 6, with 4-substituted thianes the more stable cis-isomer 74 is more predominant than the trans-isomer 75 when R is a bulky substituent.

Figure 6. Thiacyclohexane Sulfoxides

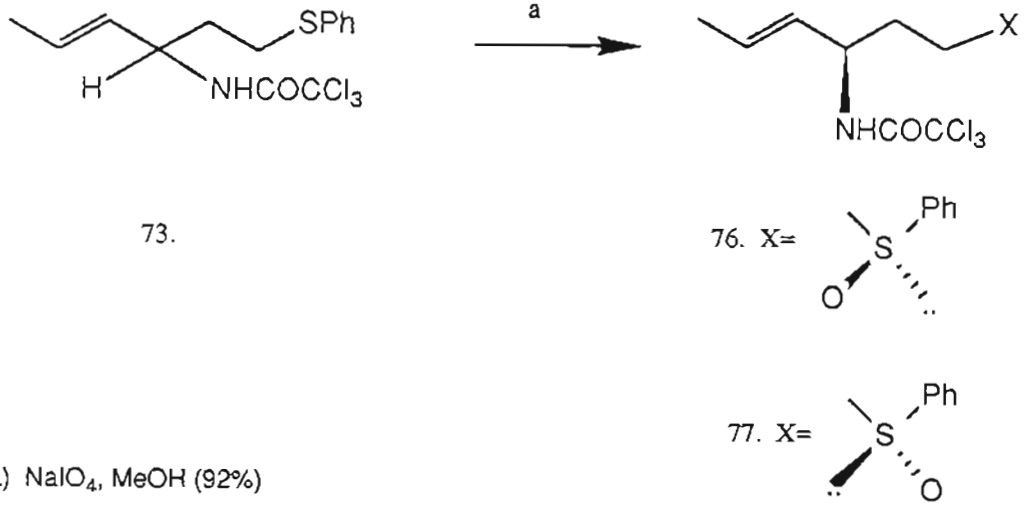


74 75

Since sodium metaperiodate[80,84] is a notably mild reagent, widely used for the selective conversion of sulfides to sulfoxides, it was used initially for oxidation of **73**. When the reaction was conducted at ambient temperature and the periodate was quickly added to the sulfide

solution, two sulfoxide diastereoisomers were clearly apparent by TLC and were isolated in the ratio 6.5 76 (nonpolar isomer):3.5 77 (polar isomer), determined by weight. However, when the oxidation reaction was run at 0 °C with incremental addition of periodate to the sulfide solution, the isomer ratio was changed dramatically to 9.2 76:0.8 77. The reaction time was quite protracted. In addition to the sulfoxide diastereoisomers, a small amount (8%) of the olefinic sulfone 78 was produced and unexpectedly, some epoxysulfone (79) (5%) was isolated, as well as a small amount (<2%) of recovered sulfide. The diastereoisomers were readily separated through a combination of fractional crystallization and column chromatography.

Scheme 14.



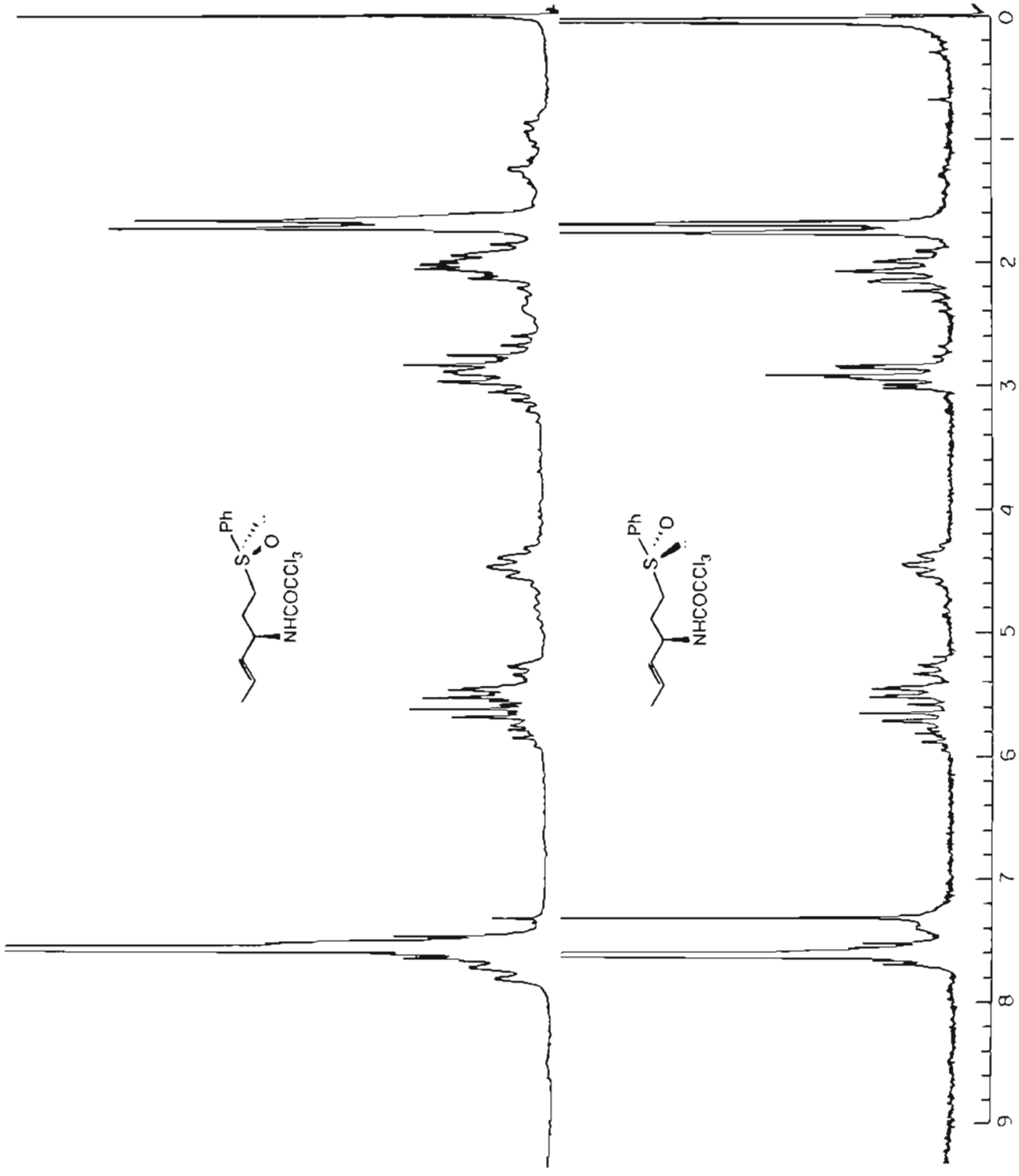
73.

76. X=

77. X=

a) $NaIO_4$, MeOH (92%)

Figure 8. NMR spectra of the sulfoxide diastereoisomers 76 and 77.

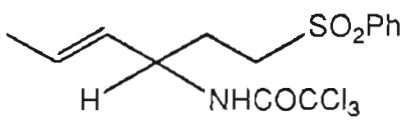


Although the ^{1}H NMR spectra of the individual diastereoisomers were distinctly different as shown in Figure 7, it was not possible to assign the relative stereochemistries present in the individual isomers.

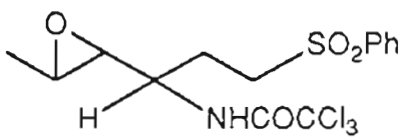
An X-ray crystallographic structure determination of the less polar sulfoxide isomer 76 was performed in collaboration with Jon Clardy and coworkers at Cornell University[85].

Authentic samples of the olefinic sulfone 78 (81%) and epoxysulfone 79 (96%) were prepared by oxidation of sulfide the 73 with 2 and 3 equivalents, respectively, of m-chloroperoxybenzoic acid (figure 8).

Figure 8. Olefinic and Epoxy Sulfones



78



79

In order to assess their effect on the diastereoselectivity, the use of other agents for the oxidation of 73 to the sulfoxides 76 and 77 was explored and these results are shown in Table 1. Although the diastereoselectivity was not exceptional, the use of N-chlorosuccinimide[86] produced the sulfoxide diastereoisomers in good yield but in

an inverted ratio relative to the sodium metaperiodate method. The use of bromine/potassium hydrogen carbonate[87] and sulfuryl chloride/wet silica gel[88] procedures for the oxidation of 73 gave only the starting sulfide (73). The titanium tetrachloride/hydrogen peroxide[89], 1,4-diazabicyclo(2,2,2)octane/bromine[90], ceric ammonium nitrate[91], and t-butyl hypochlorite[92] methods gave the starting sulfide and some sulfone (78) and none of the desired sulfoxide diastereoisomers indicating that with these systems the sulfoxide is oxidized more rapidly than the sulfide. The most dramatic effect on diastereoselectivity was observed with the selenium dioxide/hydrogen peroxide[93] procedure. Here the isomers were produced in a 1.8 76:8.2 77 ratio which is opposite that observed with sodium metaperiodate. In contrast to our experience with periodate where 5 days were required to complete the reaction, the selenium catalyzed reaction was completed in 5 minutes. Purification of the sulfoxide diastereoisomers produced by this method required only filtration through silica gel to remove the selenium impurities.

Table 1. Oxidation Methods for Sulfoxide Preparation

Reagent	Conditions	% Recovered Sulfide	% Sulfone	Sulfoxide A	Sulfoxide B	Sulfoxide %
Sodium *meta*Periodate[a]	MeOH; RT	trace		8	2	78
Sodium *meta*Periodate[a]	MeOH; 0°C-RT	trace		9.2	0.8	82
N-Chlorosuccinimide	MeOH; -5 to 0°C	-	-	4	6	90
Titanium Tetrachloride-Hydrogen Peroxide	MeOH, H_2O; RT	35	25			-
Bromine-Potassium Hydrogen Carbonate	CH_2Cl_2, H_2O; R	95	-			-
1,4-Diazabicyclo(2,2,2)-octane-Bromine	HOAc, H_2O; RT	20	40			-
Selenium Dioxide-Hydrogen Peroxide[b]	MeOH, H_2O, RT	-	10	3.5	6.5	75
Selenium Dioxide-Hydrogen Peroxide[a]	MeOH, H_2O; 0°C	-	-	1.8	8.2	85
Ceric Ammonium Nitrate	CH_3CN, H_2O; RT	trace	80			-
Sulfuryl Chloride-Silica Gel	CH_2Cl_2, H_2O; RT	93	-			-
t-Butyl Hypochlorite	MeOH; -78°C	trace	78			-

(a) Product ratios determined by weight. (b) Product ratios determined by integration of the methyl doublets in ^1H NMR.

B. Hydroxylation of the Olefin

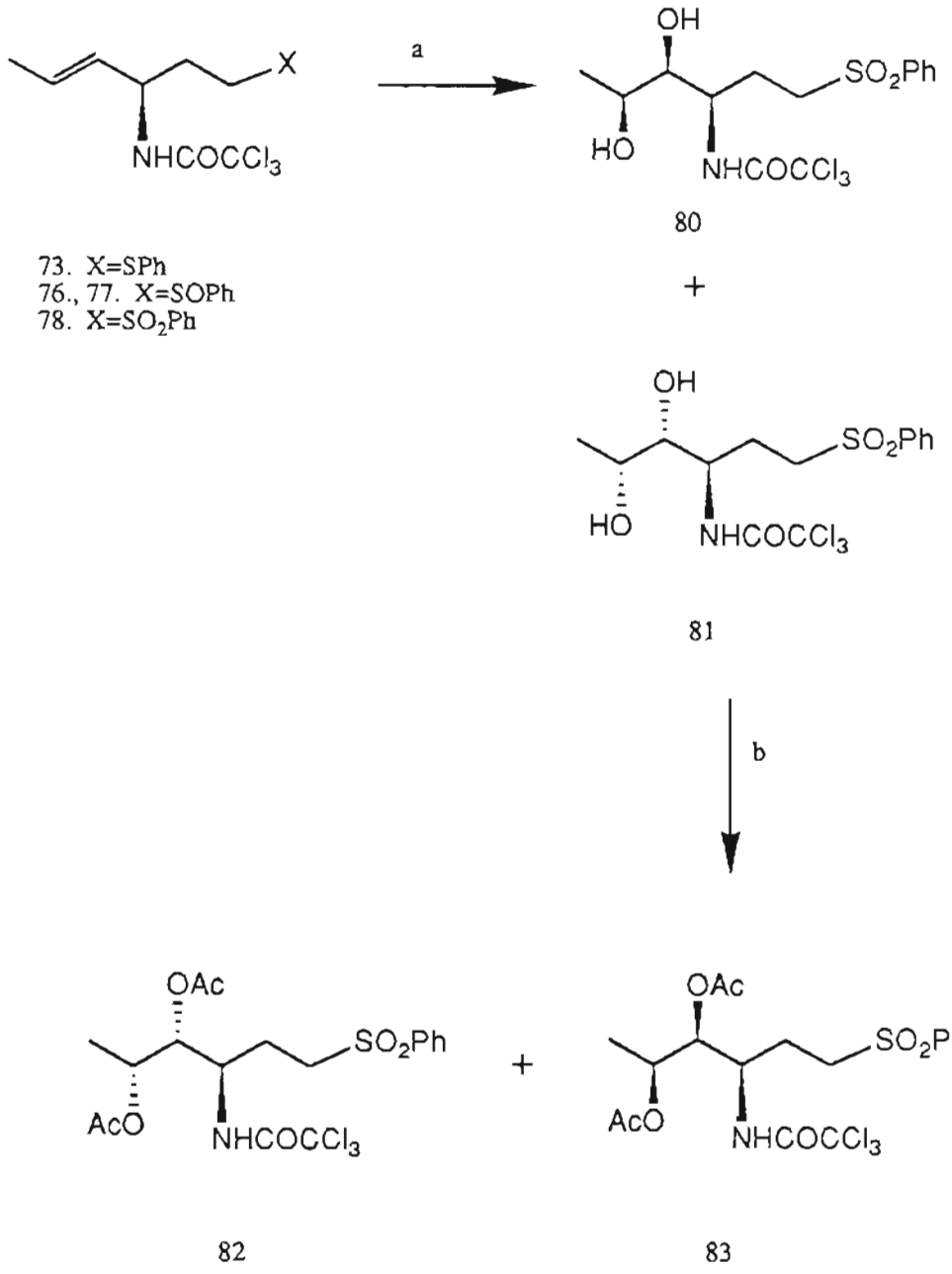
cis-Hydroxylation of allylic alcohols and amides with osmium tetraoxide generally produces a pair of diastereoisomers, since the osmium reagent can approach from both faces of the olefin. Concurrent oxidation of the sulfur entity was not expected to occur since Djerassi and Engle[94] and Henbest and Kahn[95] had stated that "sulfides are essentially inert to oxidation by osmium tetraoxide". However, sulfoxides are more reactive than sulfides toward transition-metal oxidants and good yields of the sulfone have been obtained when diphenyl or dibenzyl sulfoxide is the substrate. Furthermore, thiacyclohexane was converted to the related sulfone (58%) with osmium tetraoxide while no sulfoxide was isolated, indicating that the sulfoxide to sulfone conversion is faster than the sulfide to sulfoxide oxidation. Thus, it was anticipated that cis-hydroxylation of the olefinic moiety in the sulfide 73, sulfoxides 76 and 77 and sulfone 78 would produce identical mixtures of cis-diol products.

Due to the presence of the bulky trichloroacetamide residue in 73, a slight preponderance of the diol anti with respect to the amide was expected from simple steric hindeance. This slight stereoselectivity has been observed in several examples. Hauser and coworkers[59,60] reported an isomer ratio of 6.2:3.8 for diol products in a similar molecule with an allyl benzamide residue. Diastereoselective hydroxylation of allyl alcohols with osmium tetraoxide[96-98] has also been reported.

Oxidation of the sulfide 73 with a catalytic amount of osmium tetraoxide and two equivalents of trimethylamine N-oxide[99] resulted in an incomplete reaction providing the recovered sulfide 73 and the more polar diol products 80 and 81. Characterization of the new products was difficult due to their insolubility in solvents suitable for NMR analysis, thus the initial material was acetylated (Ac_2O, Py). Analysis of the acetylated material by TLC showed two products with similar R_f values and the product ratio, determined by both ^1H and ^{13}C NMR, was 6:4. Separation of the products either through fractional crystallization or column chromatography confirmed this product ratio and mass spectral and infrared analysis indicated the products were the diastereoisomeric diacetate sulfones 82 and 83. The IR showed a sulfone S=O asymmetric stretch at 1330 cm^{-1} and a symmetric stretch at 1140 cm^{-1}; the ^1H NMR showed that the olefinic protons at 5.5 ppm in 73 had disappeared and the appearance of two singlets which corresponded to the acetate signals at 1.7 ppm.

Reaction of the sulfide 73 with a catalytic amount of osmium tetraoxide and 4 equivalents of trimethylamine N-oxide resulted in complete conversion to the diol sulfones 80 and 81 in a stereoselective 6:4 ratio (Scheme 15). No products of intermediate oxidation, neither the diol sulfide or sulfoxide nor the olefinic sulfoxide or sulfone, were observed. cis-Hydroxylation of the olefinic sulfone 78 under the same conditions used for the sulfide 73 produced an analogous 6:4 ratio of diacetate sulfones 82 and 83.

Scheme 15.



73. X=SPh
76., 77. X=SOPh
78. $X=SO_2Ph$

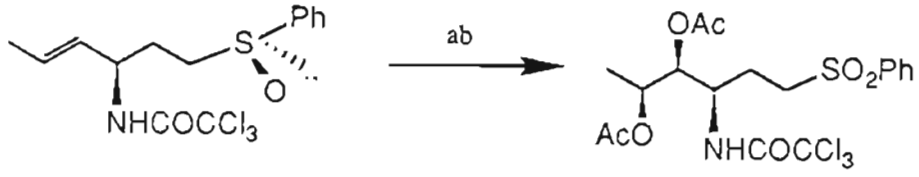
82 83

a) catalytic OsO_4, TMNO (81%) b) Ac_2O, Py (100%)

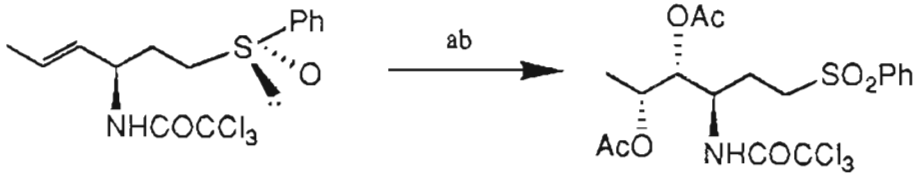
Quite unexpectedly, oxidation of mixtures of the sulfoxides 76 and 77 under the same conditions produced diol sulfone mixtures in a ratio identical to that of the starting olefinic sulfoxides rather than the expected 6:4 ratio. This finding indicated that the reaction was stereospecific.

That the conversion of the sulfoxides 76 and 77 was indeed stereospecific was demonstrated by reacting the individual sulfoxide isomers under the same conditions. In each instance, a single diol sulfone was produced (Scheme 16).

Scheme 16.



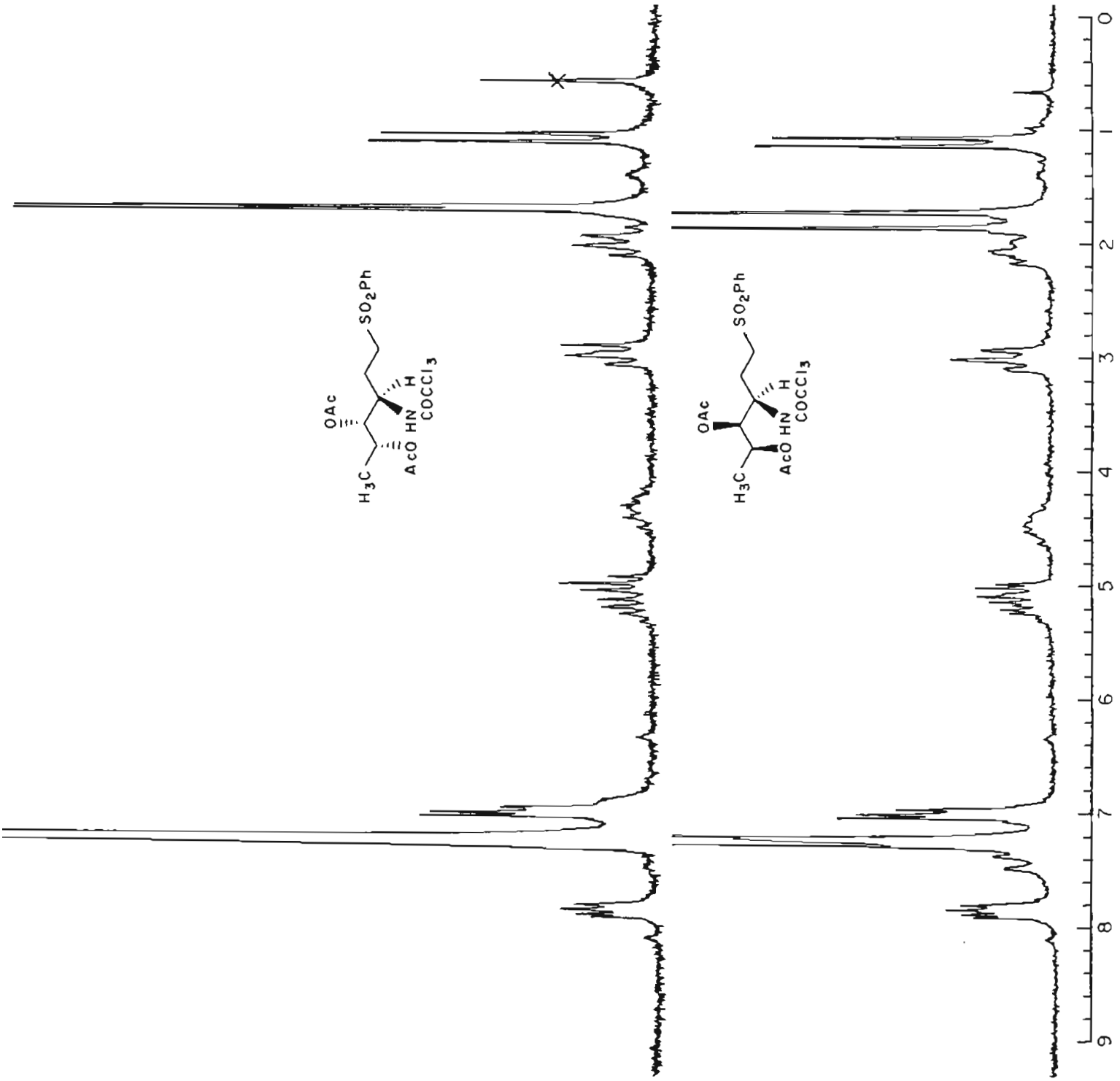
76 82



77 83

a) catalytic OsO_4, TMNO b) Ac_2O, Py

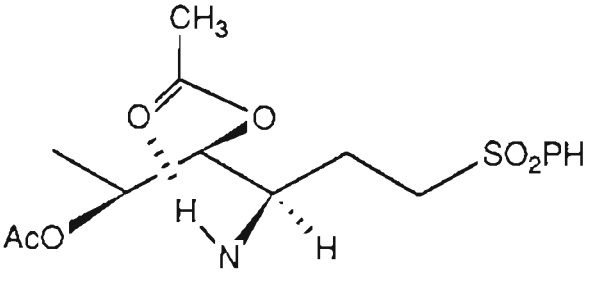
Figure 9. NMR spectra of the sulfone diacetate diastereoisomers 82 and 83.



Rigorous analysis of the diacetate sulfone products 82 and 83 with both 90 mHz and 360 mHz ^{1}H NMR spectra, ^{13}C NMR, as well as complete homonuclear decoupled proton spectra, infrared, and mass spectral data allowed tentative stereochemical assignment. The acetate methyl absorptions in the ^{1}H NMR spectrum (in benzene-d6) in 82 were closely spaced singlets (d 1.74 and 1.71) whereas in 58 they were well-separated singlets (d 1.87 and 1.74) (Figure 9).

This shift in the methyl absorption in the ^{1}H NMR spectrum of 82 was attributed to hydrogen-bonding between the amide proton and the carbonyl oxygen of the neighboring acetate to generate a seven-membered ring (84) in which the alkyl substituents are equatorial (Figure 10). The other diastereoisomer does not form a seven membered ring through hydrogen bonding since to do so would place one substituent axially, which would destabilize the ring system.

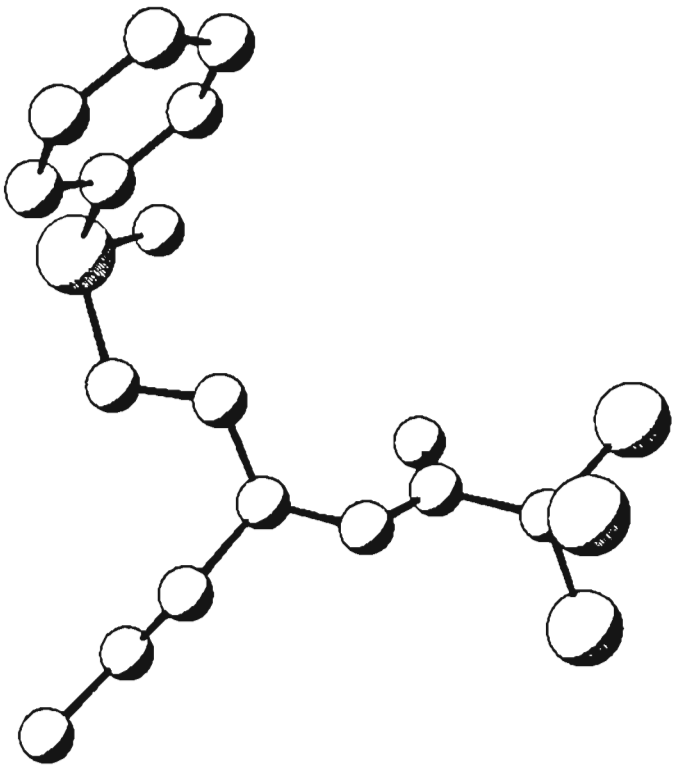
Figure 10. Seven-membered ring formed thourgh Hydrogen-bonding of the amide N-H and the neighboring acetate carbonyl.



These results demonstrate that while the amide exerts a modest steric effect favoring formation of the anti hydroxylation product (relative to the amide), complexation of the amide with the osmium is not occurring. Furthermore, the fact that hydroxylation of the sulfoxide is stereospecific and that of the sulfones is not demonstrates that oxidation of the sulfoxide to a sulfone does not take place prior to hydroxylation of the olefin. Additional evidence which indicates that a complex initially forms between the osmium an the sulfoxide group was derived from a study of the hydroxylation of the sulfoxide isomers with an amount of trimethylamine-N-oxide insufficient to cause complete reaction. No products of incomplete oxidation of hydroxylation such as the diol sulfoxide of olefinic sulfone were found. Apparently, once complexation of the osmium occurs, complete conversion to products results.

Assignment of stereochemistry to the olefinic sulfoxides 76 and 77 proved more difficult. Initially, the stereochemistry was assigned from the diol sulfone products by assuming that complexation between the oxygen of the sulfoxide and the osmium had occurred prior to hydroxylation of the olefin. The sulfoxide oxygen atom and the Os^{8+} are hard acid and hard base species, and therefore should be reaction pairs. This supposition was subsequently supported through an X-ray crystallography determination of the sulfoxide 76 (Figure 11).

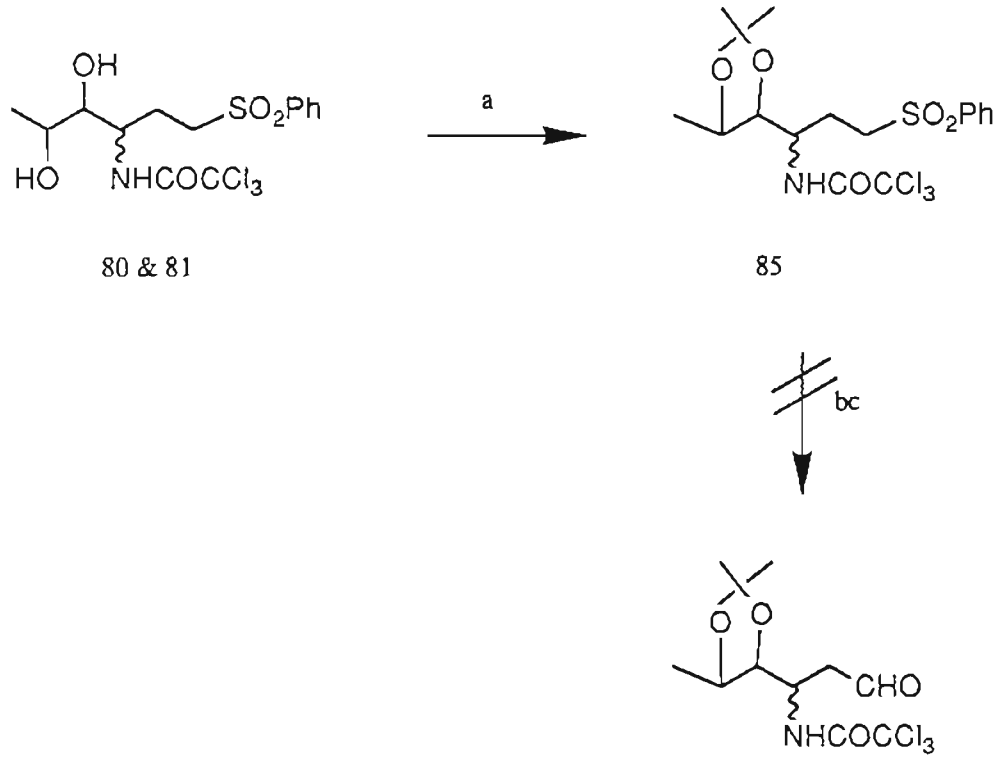
Figure 11. X-ray crystal structure of 76.



In order to utilize the stereospecificity observed for diol sulfone formation for aminosugar syntheses, conversion of the diol sulfones 80 and 81 into synthetically useful intermediates was needed. Principally, it was necessary to convert C-1 to an aldehyde functionality. Various avenues were explored to achieve this transformation. Reduction of the sulfone group to either a sulfoxide or sulfide is the most direct method for accomplishing this objective, but there is little precedence for this transformation. While the reduction of sulfoxides is straightforward[100-103], sulfone reductions generally give poor yields of sulfides. Use of lithium aluminum hydride[104] (LAH), diisobutyl aluminum hydride[105] (DIBAL), and low-valence complexes of titanium formed by reducing titanium tetrachloride with lithium hydride[106] reportedly gives

the sulfide in yields of 60 to 90%. However, use of these procedures for reduction of 80 and 81, or 82 and 83 resulted in no reduction products and only starting material was recovered. Still and Szilagi[107] have reported the reduction of sulfones to sulfoxides using sodium borohydride after the initial conversion of the sulfone to an aryloxysulfoxonium salt via arene diazonium salts[108]. This method was not investigated because the yields for this transformation are routinely quite modest (15%) and therefore not synthetically useful. A potential method for converting C-1 to an aldehyde involves oxidative desulfonylation. This route involves preparation of an unstable α-hydroxy sulfone intermediate which undergoes spontaneous cleavage to yield an aldehyde. An example of the successful use of this procedure was described by Okamura et al[109], who converted a sulfone to an aldehyde by oxidizing the α-carbanion of a sulfone with a molybdenum peroxide complex (MoOPH, oxodiperoxymolybdenum(pyridine)hexamethylphosphoramide)[110,111]. In order to use the diol sulfones in this reaction, it was necessary to first protect the diol functionality. This was accomplished by converting 80 and 81 to the acetonides 85 with dimethoxypropane and toluenesulfonic acid (95% yield). Attempted oxidative desulfonylation of the acetonides 61 was repeated several times. Each attempt resulted in the recovery of approximately 60% of the starting material and 40% of an unidentifiable black tar (Scheme 17). The use of a stronger base (butyllithium) and/or a longer reaction time gave the same results.

Scheme 17.

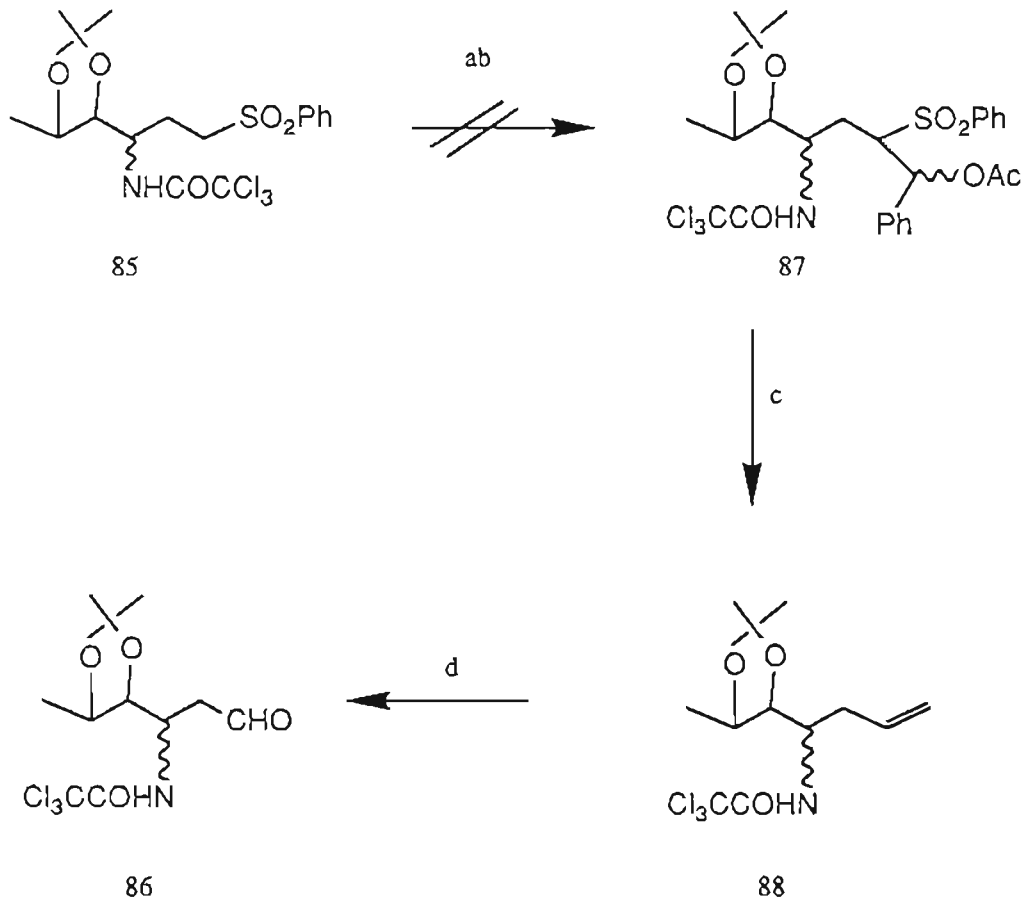


80 & 81 85 86

a) $(MeO)_2CMe_2$, TsOH b) LDA c) MoOPH

Another method of oxidative desulfonylation of sulfones involves α-alkylation of a sulfone with an aldehyde followed by acetylation of the hydroxy intermediate to an β-acetoxysulfone.[112-114] Treatment of the β-acetoxysulfone with sodium amalgam results in elimination of the acetoxy and sulfone residues to provide the olefin. Ozonolysis of the olefin then generates the aldehyde. Treatment of 85 with butyllithium and benzaldehyde followed by acetic anhydride provided, after work-up, a nearly quantitative recovery of starting material (Scheme 18). No alkylated sulfone product was detected. Numerous repetitions of the reaction with variation of the reaction conditions led to the same result.

Scheme 18.



85 87 88 86

a) n-BuLi, PhCHO b) Ac_2O c) O_3

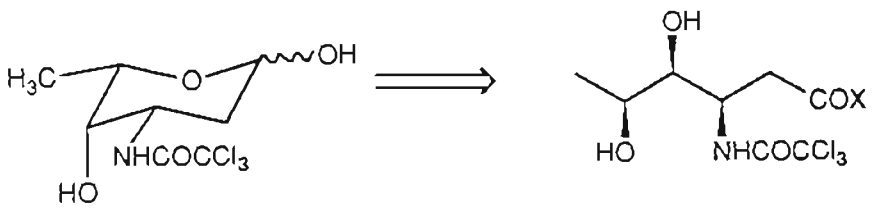
C. Epoxidation

cis-Hydroxylation of the C-4,5 olefinic moiety in the sulfide 73, sulfoxides 76 and 77, and sulfone 78 leads to diol intermediates 90 and 92 which after further manipulation would provide sugars with the lyxo (89) and xylo (91) configurations. An alternative method of functionalization leading to the trans-diol products 94 and 96 would ultimately provide sugars with either the ribo (93) or arabino (95) configurations. In order to effect trans-hydroxylation via the intermediacy of an epoxide, the route shown in Scheme 19 was investigated.

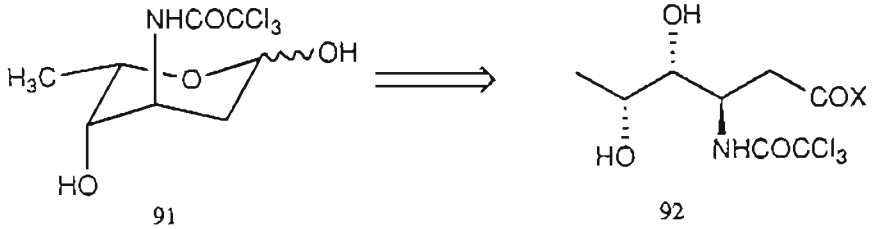
Epoxidation of the sulfide 73 with one equivalent meta-chloroperoxybenzoic[115] acid gave a 30% yield of a polar compound and a 60% yield of recovered sulfide. Mass spectral data showed that the new compound was 48 mass units higher than 73 and IR absorptions at 1340 and 1170 cm^{-1} were consistent with a symmetric and asymmetric S=O stretch. ^{1}H NMR absorptions at 2.64 and 2.16 ppm were indicative of an epoxide residue and homonuclear decoupling of the spectrum confirmed this. From this data, the structure was assigned as the epoxysulfone 79.

No intermediate oxidation products such as the olefinic sulfoxide or sulfone, nor epoxysulfide or sulfoxide were observed. Surprisingly, the ^{1}H and the ^{13}C NMR showed that only one of the two possible isomers was present. When the reaction was repeated using three equivalents of oxidant a quantitative yield of 79 was obtained. Similar reaction

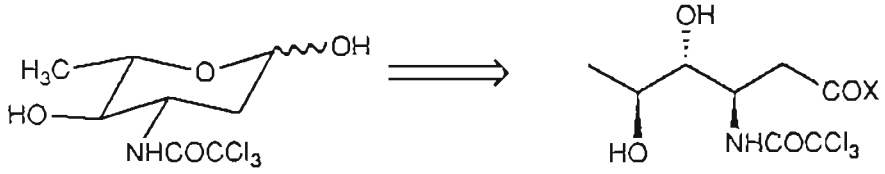
Scheme 19.



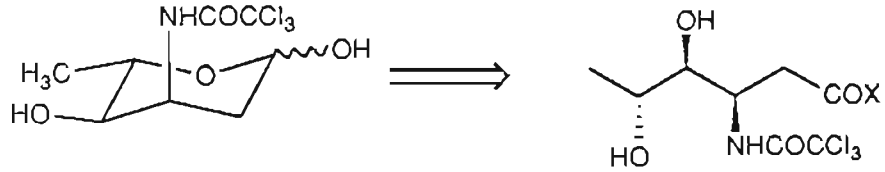
89 90



91 92



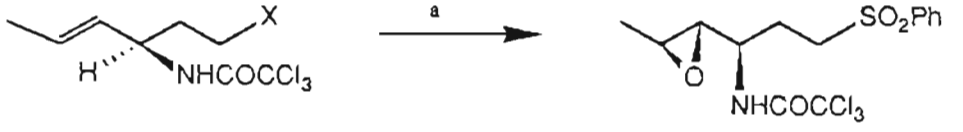
93 94



95 96

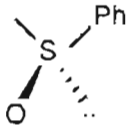
of the individual sulfoxides 76 and 77 with two equivalents, and the sulfone 78 with one equivalent of metachloroperoxybenzoic acid produced identical results (Scheme 20); formation of a single epoxysulfone. Since the sulfur did not alter the stereochemistry of the product, the amide functionality most likely was controlling the stereochemistry of the epoxidation reactions[1].

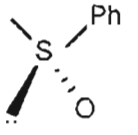
Scheme 20.



73. X=SPh

79.

76. X= 

77. X= 

78. $X=SO_2Ph$

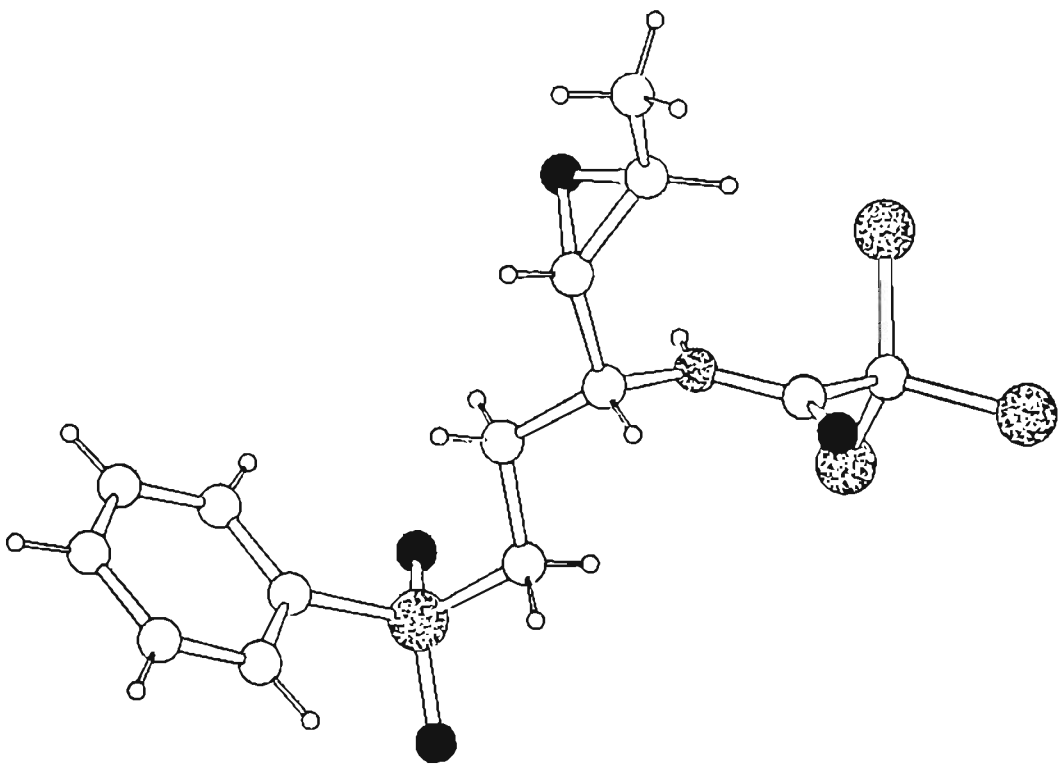
a) MCPBA, CH_2Cl_2 (95%)

[1] Our finding of a stereospecific epoxidation in an acyclic system is unprecedented and unexpected. In a private communication, Dr. William Roush at MIT has informed us that they have found that epoxidation of allyl amides is stereoselective but not stereospecific.

Although it was apparent from the NMR spectral data that only one diastereoisomer was present, the relative stereochemistry of the epoxide and amide could not be definitively assigned without an X-ray crystallographic analysis[116] (Figure 12). This was accomplished for us by Dr. J. Glusker and coworkers at Fox Chase Cancer Center (Philadelphia, Pennsylvania).

As shown in Figure 12, the crystal structure determination shows that the structure is 79 in which the epoxy residue is <u>syn</u> with respect to the trichloroacetamide group.

Figure 12. X-ray crystal structure of 79.



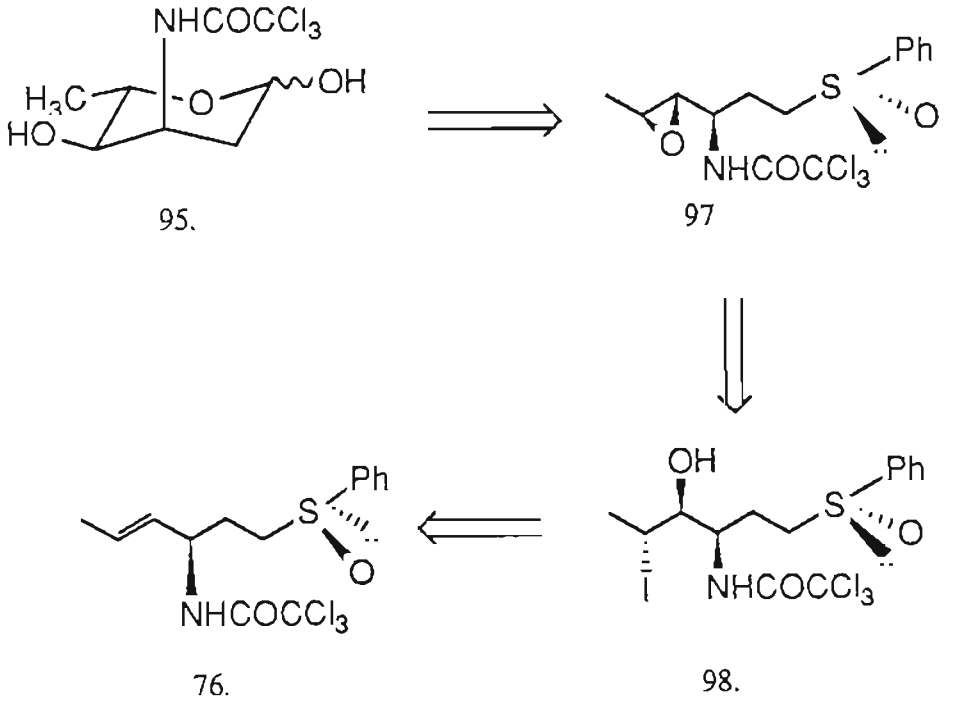
Treatment of the sulfide, sulfoxides, or sulfone with other oxidants (H_2O_2, peroxyacetic acid) produced the same results in variable yields. All attempts to produce any of the anti-epoxysulfone isomer met with failure.

D. Iodohydroxylation

Since synthesis of the anti-epoxysulfone isomer by epoxidation of 73 through conventional oxidations failed, an alternate method to this isomer was investigated. It was postulated that stereospecific or stereoselective sulfoxide directed halohydroxylation (iodine, sodium bicarbonate, water, methylene chloride) of the 4,5-double bond in either of the sulfoxide diastereoisomers would give the iodohydroxy derivatives 98 and 100. Subsequent treatment of the iodohydrins with base would produce both of the epoxide isomers 97 and 99 while conserving the sulfoxide functionality. Therefore, halohydroxylation of sulfoxide 76, generation of the epoxide and hydrolytic cleavage at C-5, would result in preparation of ristosamine 95. Corresponding reaction of the sulfoxide isomer 77 would produce acosamine 93 (Scheme 21).

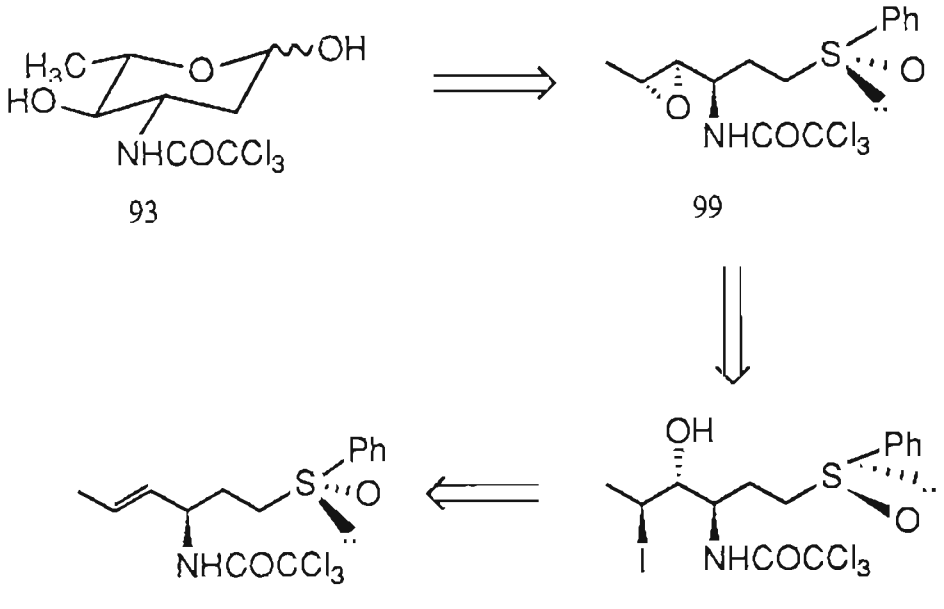
There have been several examples of neighboring-group participation by the sulfinyl oxygen in sulfoxides in the iodohydroxylation of double bond containing cyclic compounds[117-120]. The first step in the reaction involves formation of a π-complex by electrophilic attack by iodine with the double bond in 101. Neighboring group attack on the iodonium intermediate by the sulfinyl oxygen (102), and then nucleophilic attack of a water molecule on the sulfur atom, extrusion of a proton, results in inversion of configuration at the sulfoxide[118] (103). This has been elegantly demonstrated by hydrolyzing intermediate 102 with ^{18}O water and showing that the sulfur functionality in the iodohydrin product (103) contained the label[119] (Scheme 22).

Scheme 21.



95. 97

76. 98.

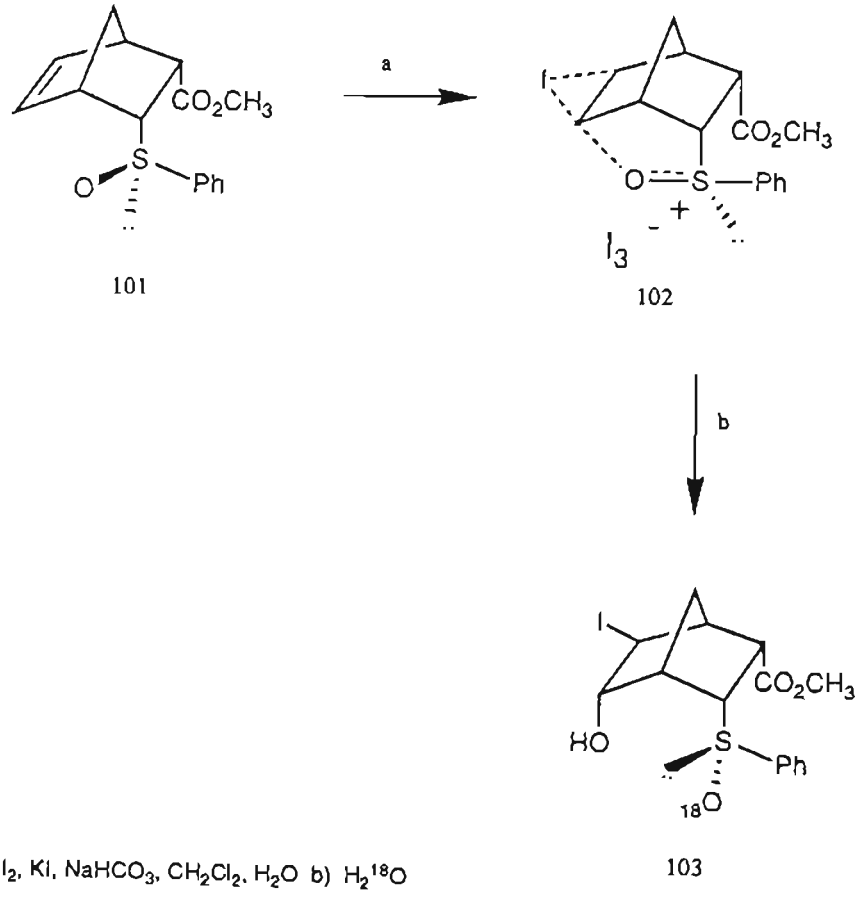


93 99

77. 100

There is precedent for the existance of intermediate 102; when the reaction is performed in ethanol or concentrated solutions of water, compound 102 can be isolated[119]. In fact, this type of transannular sulfoxide has been seen by other investigators[121,122]. However, there is no precedence for this reaction in acyclic systems as well, and the synthetic implications of this reaction have not been established.

Scheme 22.



101 102 103

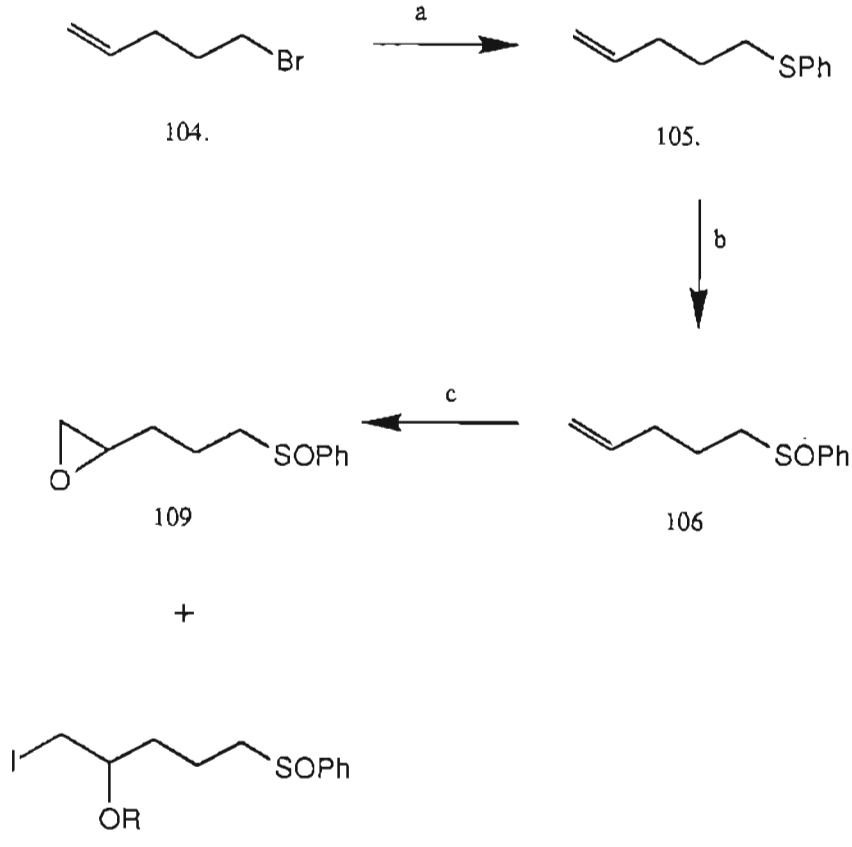
a) I_2, KI, $NaHCO_3$, CH_2Cl_2, H_2O b) $H_2{}^{18}O$

Preliminary studies on the iodohydroxylation reaction were conducted with the sulfoxide 106 which was prepared from 1-bromo-4-pentene (104) through nucleophilic replacement of the bromide with a thiophenyl group (105), followed by oxidation to the sulfoxide 106 with sodium metaperiodate. Reaction of 106 under the iodohydroxylation conditions of Ghersetti et al[118] (iodine, potassium iodide, sodium hydrogen carbonate, aqueous methylene chloride) resulted in the formation of two new compounds; one more polar than the starting sulfoxide (10% yield) and one less polar (15% yield), as well as recovered olefinic sulfoxide 106 (65%). The more polar material was assigned as the iodohydrin 107 based on spectral data. The IR spectrum showed a symmetric S=O sulfoxide stretch at 1056 cm^{-1} and a hydroxyl signal at 1.25 ppm (exchangeable with D_2O) and the disappearance of the olefinic protons at 5.69 ppm in the ^1H NMR spectra and the mass spectrum showed that the compound had a mass of 144 units greater than the starting material. In addition, the iodohydrin was acetylated to 108 to aid spectral interpretation. The less polar material was the epoxysulfoxide 109 (Scheme 23). The mass spectrum showed this compound had a mass 16 units greater than the starting sulfoxide 106 and the IR spectrum showed a sulfoxide stretch at 1062 cm^{-1}. The ^1H NMR showed new signals at 4.31 and 3.48 ppm indicative of an epoxide as well as the disappearance of the olefinic protons. Furthermore, the inter-relationship between the products was readily shown. Treatment of the acetylated iodohydrin (108) with dilute sodium hydroxide gave the epoxysulfoxide 109.

Under the iodohydroxylation conditions, the sulfoxide isomers 76 and 77 produced a small amount of the iodohydrins 98 and 100 (5%) and

recovered olefinic sulfoxides (80%). Numerous attempts to raise the yields of products by altering the experimental conditions were not successful. Apparently the reaction is general only for cyclic sulfoxides where entropic factors provide driving force for the reaction.

Scheme 23.



104.

105.

109

106

107. R=H
108. R=Ac

a) PhSH, K_2CO_3 (91%) b) $NaIO_4$ (98%) c) I_2, KI, $NaHCO_3$

IV. Stereoselective Syntheses of (±)-N-(Trichloroacetyl)daunosamine and (±)-N-(Trichloroacetyl)-3-epiDaunosamine

A. Pummerer Rearrangement

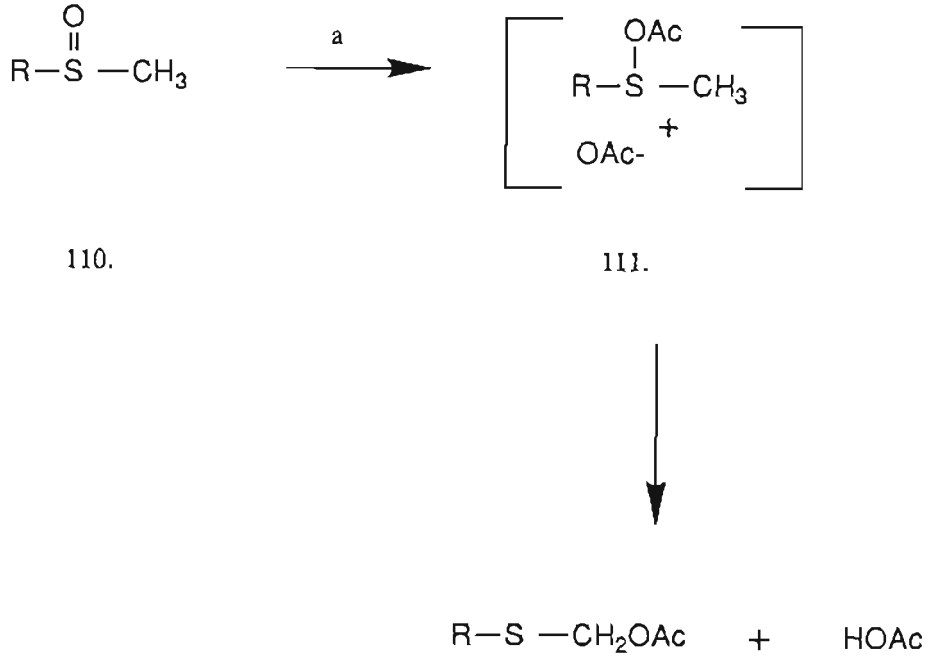
Manipulation of C-1 in one of the sulfur-containing intermediates (sulfide 73, sulfoxide 76 or 77, or sulfone 78) to an aldehyde remained a major obstacle in obtaining the desired aminosugars. Ideally, the diol sulfones 80 and 81 were the compounds of choice to manipulate, because they were readily prepared stereospecifically. However, since attempts to convert C-1 in the sulfone diols 80 and 81 or sulfone diacetate diastereoisomers 82 and 83 to an aldehyde functionality was unsuccessful, transformation of the sulfoxides 76 and 77 to an aldehyde group was attempted next.

Since α-halosulfoxides can be readily cleaved with either mercuric chloride and cadmium carbonate in aqueous carbon tetrachloride[123] or cupric chloride and cupric oxide in aqueous acetone[77], halogenation of the carbon atom alpha to the sulfoxide moiety in 76 and 77 was attempted. Reaction of 76 and 77 with N-bromosuccinimide, N-chlorosuccinimide[123,77], sulfuryl chloride with pyridine[124], potassium iodate and iodine in acetic anhydride[125] uniformly resulted in recovery of the starting sulfoxide along with trace amounts of the sulfide 73 from reduction.

Pummerer rearrangement[126,127] of sulfoxides to α-acetoxysulfides has been widely used to prepare aldehydes.

The mechanistic aspects of the Pummerer rearrangement have been studied in detail. Usually, the Pummerer rearrangement is induced by treatment of sulfoxides (110) with anhydrides in the presence of a non-nucleophilic base. It is generally accepted as shown in Scheme 24, that the first step in the reaction involves the formation of a sulfonium salt 111[128] which then undergoes base catalyzed elimination of acetate to the sulfenium intermediate. Subsequent nucleophilic attack on the sulfenium intermediate gives the acetoxysulfide. Overall, the reaction involves reduction of a sulfonium sulfur with concomitant oxidation of the α-carbon (112).

Scheme 24.

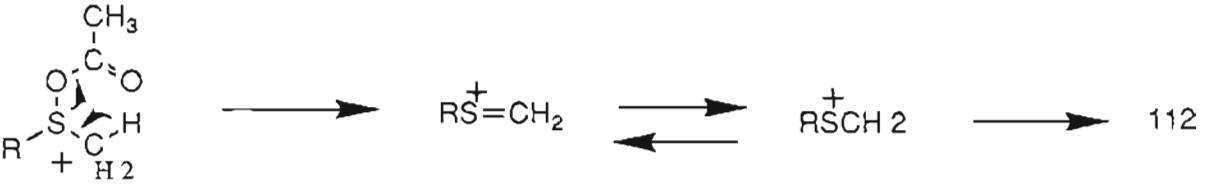


110. 111.

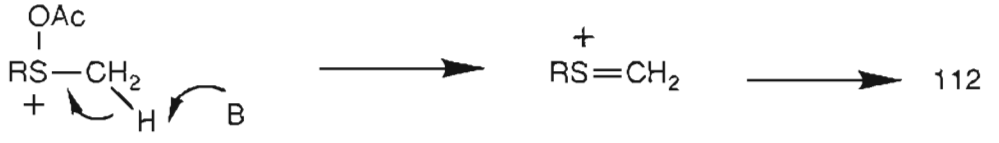
a) Ac_2O, base

The other mechanistic proposals are as shown using the sulfonium salt intermediate[129-136] (Figure 13).

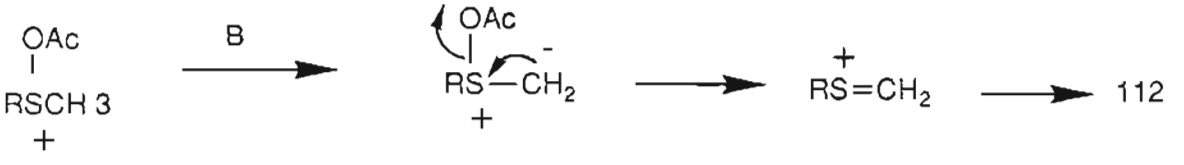
Figure 13. Reactions Mechanisms for the Pummerer Rearrangement.



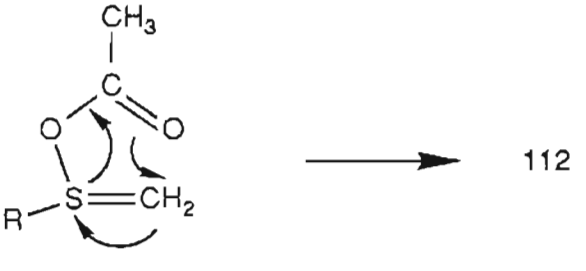
Concerted cyclic elimination of HOAc



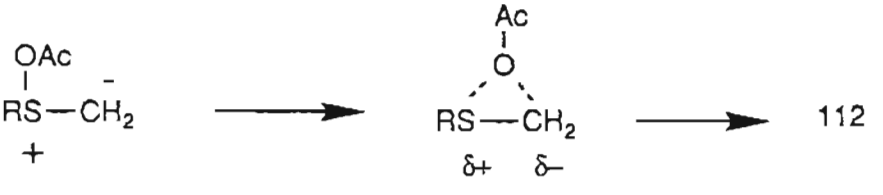
Concerted elimination of HOAc with external base



Ylide intermediate

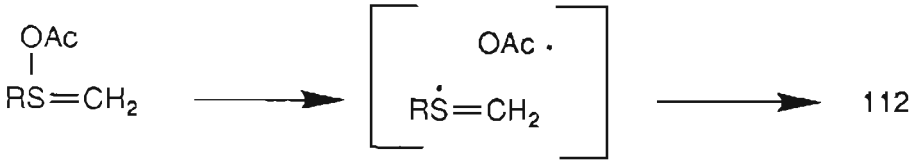


Cyclic rearrangement

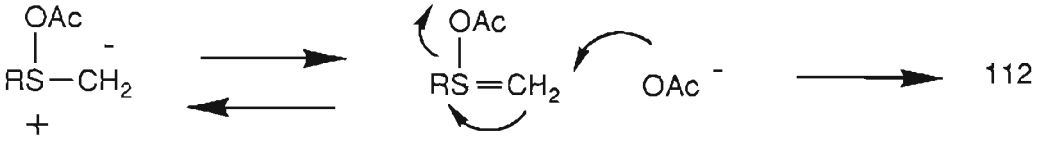


1,2-Shift

Figure 13.,continued.



Homolytic dissociation-recombination

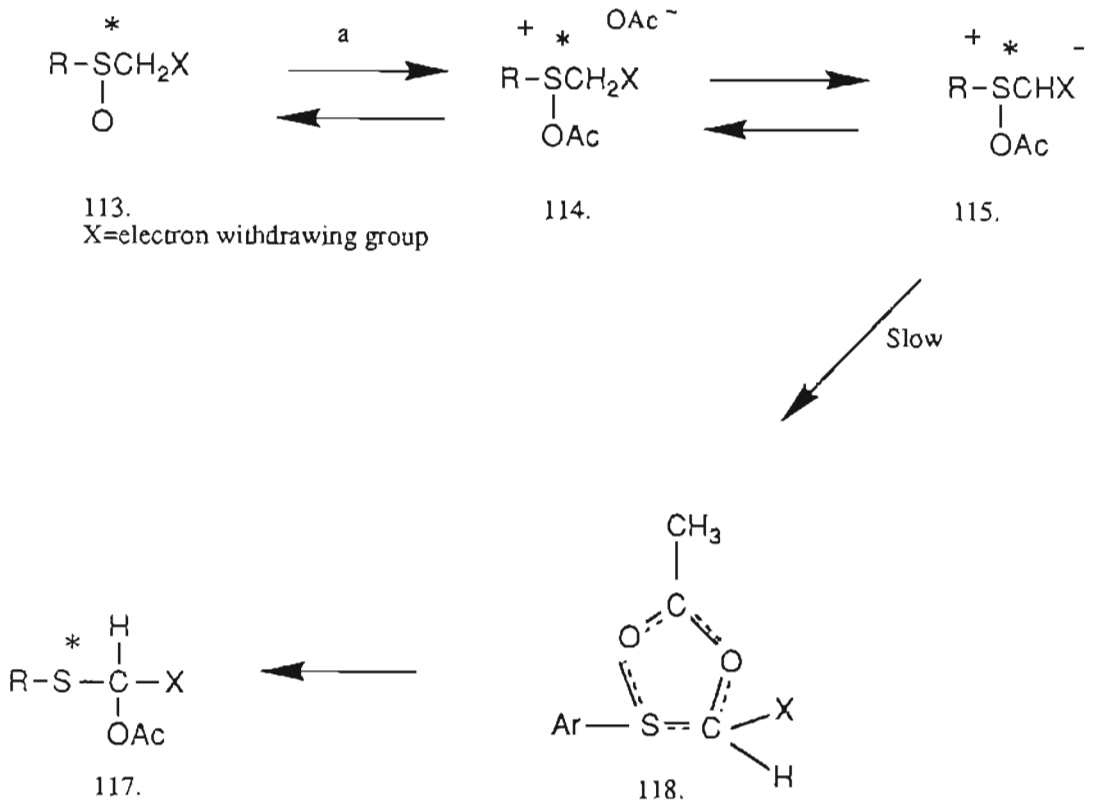


Nucleophilic displacement of ylide

There have been a number of recent examples of intramolecular 1,2-rearrangement (Figure 13.5) of the acetoxyl group based on ^{18}O-tracer experiments, stereochemistry of the Pummerer rearrangement of optically active sulfoxides, and compounds with β-electron withdrawing groups[16-23]. In these intramolecular examples, the rate determining step is the S-O bond cleavage in 115, after reversible proton removal from the acetoxylsulfonium intermediate (114). Some asymmetric induction is observed from the chiral sulfur atom to the prochiral α-carbon and is believed to be due to both the very tight nature of the α-thiocarbenium acetate ion-pair (114), and the rapid recombination

(Scheme 25). However, asymmetric induction in optically active open chain sulfoxides is minimal but in cyclic substrates it can be substantial[137].

Scheme 25.



113. X=electron withdrawing group

114.

115.

118.

117.

a) Ac_2O, base

In order to maximize the yield of acetoxysulfide, the Pummerer rearrangement was conducted under the conditions shown in Table 2. From this investigation, the mild conditions of Tanikaga et al.[138] (Ac_2O, $(F_3CCO)_2O$, lutidine) gave the highest yield (96%) of acetoxysulfide 118 and only small amounts of the sulfide reduction product. Pummerer reaction of the individual olefinic sulfoxide diastereoisomers 76 and 77 and of diastereoisomeric mixtures of the sulfoxides gave a 6:4 mixture of the α-acetoxysulfide (118). This is consistent with the finding that optically active aliphatic substrates show little if any asymmetric induction. However, when bases stronger than 2,6-lutidine such as dimethylamino pyridine (DMAP), pyridine, collidine triethylamine, and sodium acetate[139] were used, the major product was either the vinylsulfide 119 or the sulfide reduction product 73. Very little or no acetoxysulfide 118 was produced. The major product was the sulfide 73 when dicyclohexyl carbodiimide (DCC)[133] was used as an acid scavenger. No observable reaction was noted when 76 and 77 were reacted with acetic anhydride and proton sponge™[2], N,N-dimethylamino pyridine either with or without addition of trifluoroacetic anhydride, and either methane- or toluenesulfonic acid (Scheme 26).

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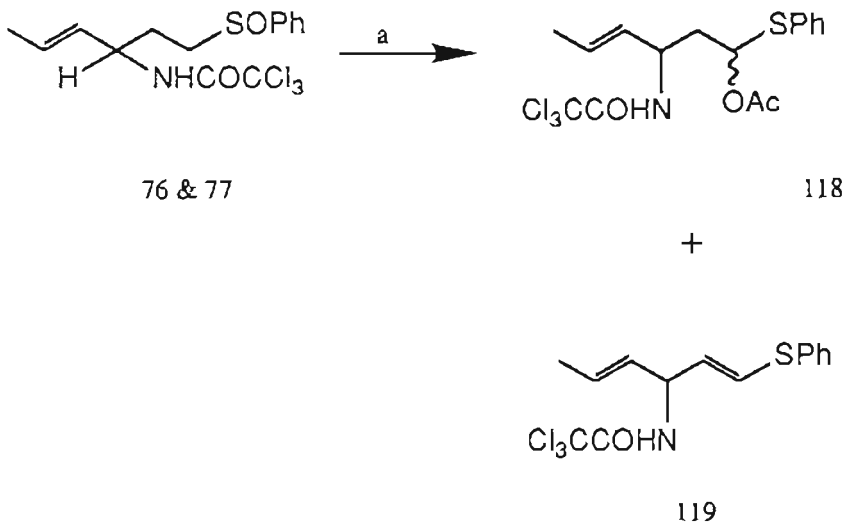
[2]Proton sponge™ (Aldrich Chemical Co.,Inc.) (1,8-bis(dimethylamino)naphthalene) is a very strong base with weak nucleophilic character due to steric effects.

Scheme 26.



76 & 77

118

+

119

a) Ac_2O,TFAA, lutidine (99%)

Table 2. Pummerer Rearrangement Reaction Conditions

Reagent	Conditions	Products			
		Acetoxysulfide	Sulfide	Vinylsulfide	Sulfoxide
NaOAc, Ac_2O	RT				100
NaOAc, Ac_2O	$PhCH_3$, h	30		70	
Ac_2O, MsOH	CH_2Cl_2, h				100
Ac_2O, TsOH	CH_2Cl_2, h				100
Ac_2O, TFAA	RT	20		80	
Ac_2O, TFAA, Lutidine	RT	70	30		
Ac_2O, TFAA, Lutidine	0°C-RT	95	1-2		3-4
Ac_2O, TFAA, Pyridine	RT				95
Ac_2O, DMAP, Pyridine	RT		20	75	
Ac_2O, TFAA, Et_3N	RT			95	
Ac_2O, TFAA, Collidine	RT	15	80		
Ac_2O, Proton Sponge™	RT				100
Ac_2O, DMAP	RT	10	20		70
Ac_2O, TFAA DMAP		70			20

Product ratios based on weight after purification by column chromatography.

B. Method 1

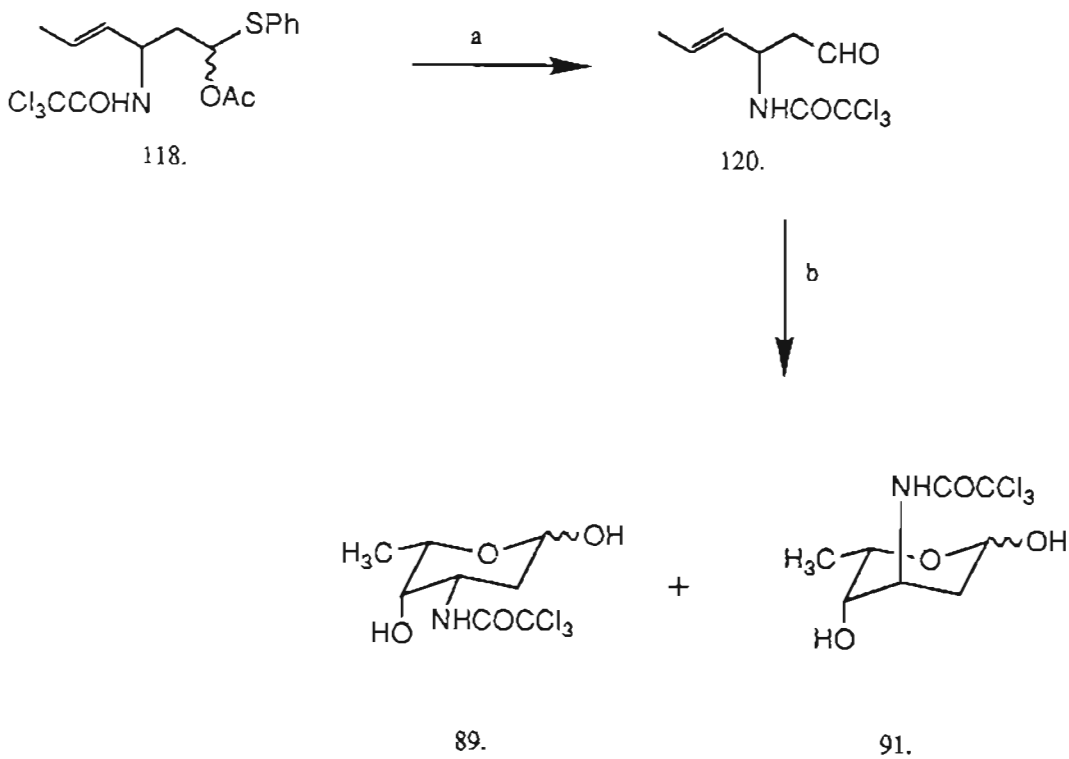
Two methods were developed for preparation of N-trichloroacetyl daunosamine (89) and N-trichloroacetyl 3-epidaunosamine (91) from the Pummerer product 118. The major difference in the two routes is the order in which the synthetic transformations were performed. In method 1 shown in Scheme 27, the acetoxysulfide moiety was cleaved to an aldehyde, followed by cis-hydroxylation with a catalytic amount of osmium tetraoxide and trimethylamine-N-oxide. In method 2 (Scheme 29), the order of the steps was inverted to produce the sugars, but with altered results.

A number of procedures for hydrolysis of the acetoxysulfide group in 118 to an aldehyde were attempted; with dilute hydrochloric acid in THF/methanol, anhydrous sodium methoxide, and dilute sodium hydroxide in methanol/THF either no reaction occurred or a complex mixture of products was obtained from which none of the desired product could be isolated. A modification of the method reported by Sugihara et al.[140] in which α-trifluoroacetoxysulfides were cleaved at room temperature with either sodium bicarbonate, cupric chloride, or mercuric chloride in aqueous acetonitrile was used. Reaction of acetoxysulfide 93 with mercuric chloride in aqueous acetonitrile at room temperature for 6 hours and then heating to reflux for an additional 6 h gave no aldehyde.

However, reaction of 118 with cupric chloride in aqueous acetonitrile at reflux led to an immediate reaction which was evidenced by a change in color of the solution from blue-green to black. Following

purification, spectral data indicated that the new component was the desired olefinic aldehyde 120. The ^1H NMR showed a band which corresponded to the aldehyde at 9.73 ppm and the aromatic signal of the phenyl sulfoxide at 7.33 ppm had vanished. cis-Hydroxylation of the olefinic moiety in 120 using trimethylamine-N-oxide and a catalytic amount of osmium tetraoxide with concomitant ring closure provided a 6:4 mixture of N-trichloroacetyldaunosamine (89) and N-trichloroacetyl-3-epidaunosamine (91) in 94% yield. The sugars were quantitatively separated through crystallization.

Scheme 27.

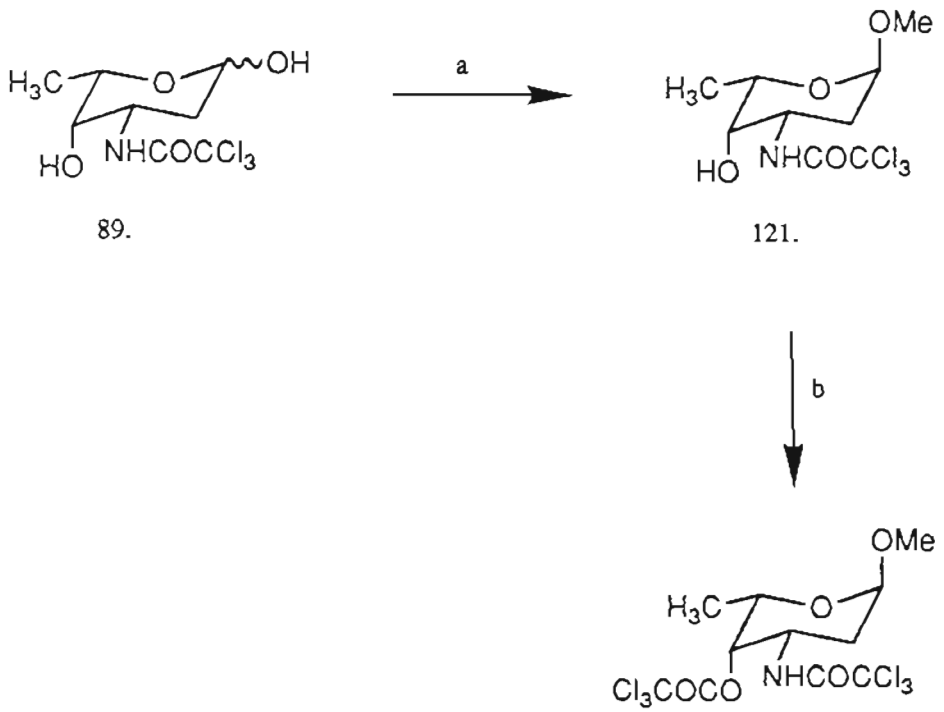


118. 120. 89. 91.

a) $CuCl_2$, CH_3CN, H_2O (86%) b) Catalytic OsO_4, TMNO (lyxo:40%; xylo:60%)

In order to establish the authenticity of the product with daunosamine, both the synthetic material 89 and an authentic sample of methyl daunosaminide hydrochloride were converted to methyl N,O-bistrichloroacetyl daunosaminide (122) (Scheme 28). The ^{1}H and ^{13}C NMR spectra of these materials were identical.

Scheme 28.



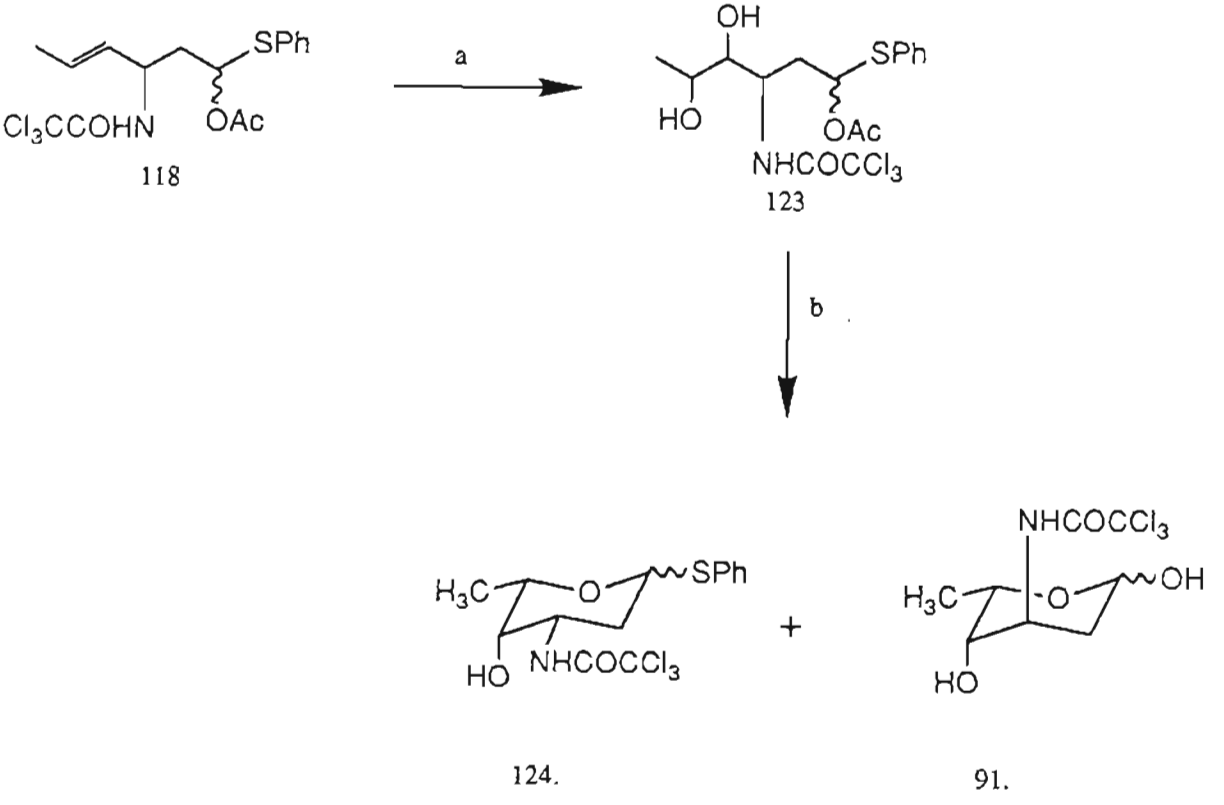
89. 121. 122.

a) HCl, CH_3OH (86%) b) Cl_3CCOCl, Py (90%)

C. Method 2

As an alternate route to these sugars, the hydrolysis and cis-hydroxylation steps were inverted. Following Pummerer rearrangement, cis-hydroxylation of the olefinic acetoxysulfides 118 and subsequent hydrolysis of the acetoxysulfide entity in 123 was performed.

Scheme 29.



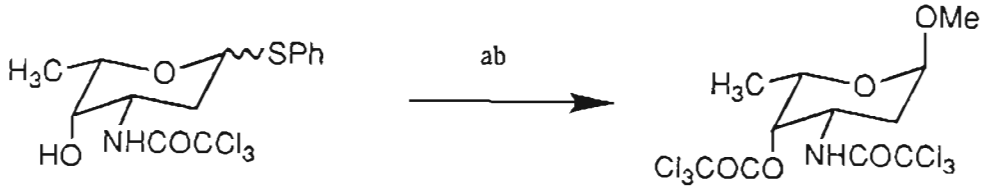
a) catalytic OsO_4, TMNO (92%) b) $CuCl_2$, CH_3CN, H_2O (xylo:40%; lyxo:60%)

Unexpectedly, the hydrolysis produced a mixture of the α and β anomers of the lyxo-thioglycoside 124 and the fully hydrolyzed xylo-sugar 91 in a 6:4 ratio. The products were readily washed apart with carbon tetrachloride since the thioglycosides (124) were soluble and the xylo-sugar (91) was not. None of the fully hydrolyzed lyxo-isomer 89 nor any of the thiophenyl derivative of the xylo- isomer was obtained (Scheme 29).

Apparently, under the hydrolytic conditions used, the acetoxysulfide diastereoisomers with the lyxo configuration can achieve transition state geometries leading to selective replacement of the acetoxy functionality, whereas those isomers with the xylo configuration could not.

The structure of 124 was confirmed through conversion to the N,O-bis-trichloroacetyl thioglycoside derivative and then to the methyl glycoside of daunosamine (122) with anhydrous methanol and hydrogen chloride (Scheme 30).

Scheme 30.



124. 122.

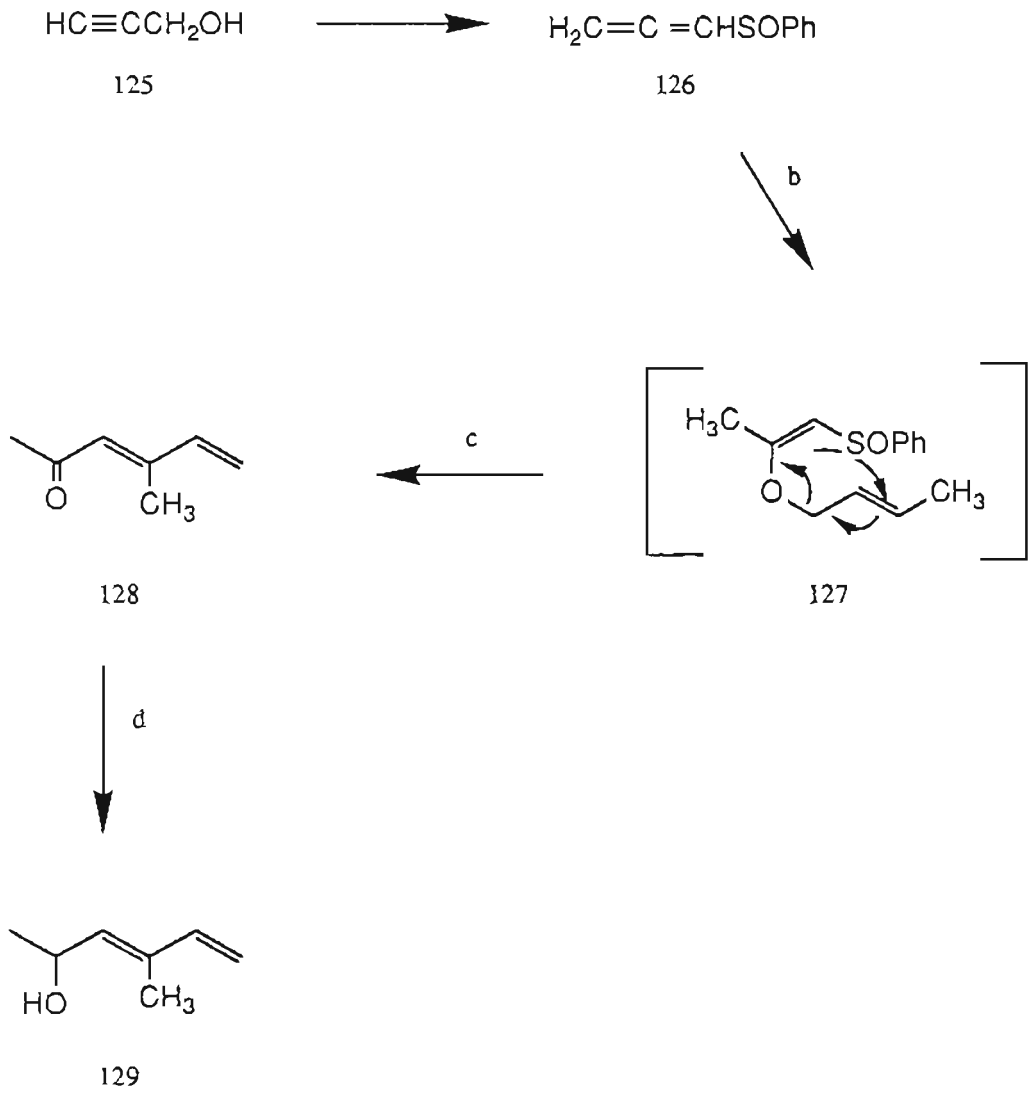
a) Cl_3CCOCl, Py (96%) b) CH_3OH, HCl (90%)

V. Stereoselective Synthesis of (±)-N-(Trichloroacetyl)vancosamine and N-(Trichloroacetyl)-3-epivancosamine

The reaction sequence for the preparation of vancosamine (5) conceptually parallels the one employed for synthesis of daunosamine (1). The dienol starting material was prepared via a modification of the procedure of Cookson and Gopalan[141]. Allenyl sulfoxide 126 was prepared by addition of phenylsulfenyl chloride[142] to propargyl alcohol (125) and triethylamine[143,144] in carbon tetrachloride; the initial adduct undergoes spontaneous Claisen rearrangement to give 126. The allenyl sulfoxide 126 was added to the sodium alkoxide ion of crotyl alcohol to produce the unstable intermediate 127 and then distilled in the presence of zinc carbonate to induce another Claisen rearrangement with subsequent elimination of phenyl sulfinate. The resultant dienone 128 was isolated in 82% yield. Reduction of the dienone 128 with lithium aluminum hydride gave the dienol 129 in quantitative yield (Scheme 31).

Overman reaction[72,73] of 129 proved unexpectedly difficult. The usual procedure for effecting Overman reaction of 129 to 130 is slow addition of trichloroacetonitrile to a cold solution of the alkoxide prepared from the alcohol 129 and sodium hydride. Reaction of 129 in the usual manner, followed by thermal rearrangement, gave poor yields. A change in base from sodium hydride to potassium hydride provided only a modest improvement, and inversion of the order of addition of the reagents, which is commonly used for secondary alcohols[72,73], resulted in no reaction. However, addition of 18-Crown-6 to the potassium hydride

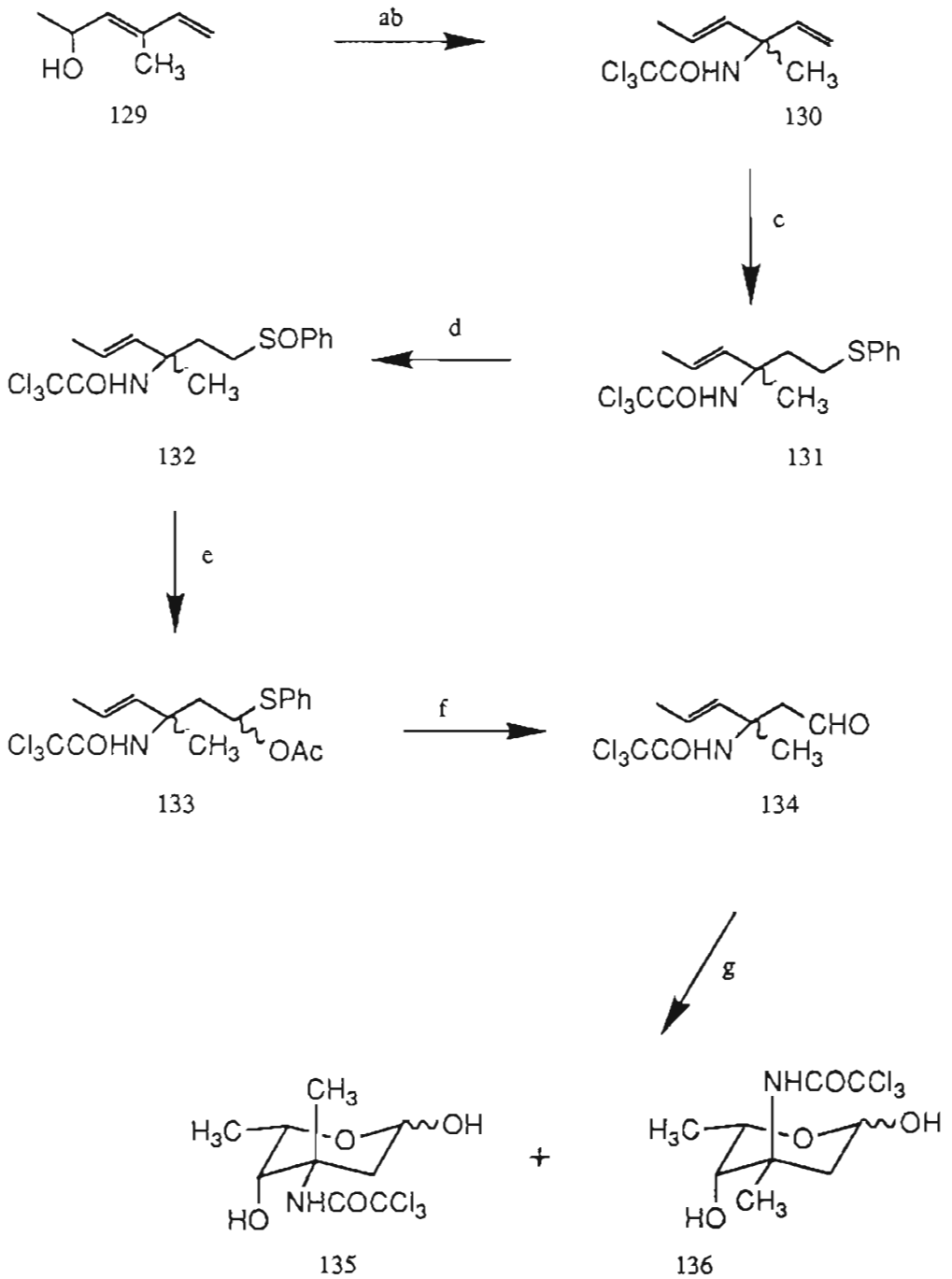
Scheme 31.



a) PhSCl, Et_3N (90%) b) NaH, crotyl alcohol ,Δ,$ZnCO_3$ (82%) d) LAH (99%)

catalyzed reaction and the use of a longer reaction time gave excellent results, producing 130 in 90% yield. Free radical addition of benzenethiol to 130 regiospecifically furnished the sulfide 131, which was oxidized with selenium dioxide and hydrogen peroxide[87] to a 1:1 mixture of the diastereoisomeric sulfoxides 132 (75%). Pummerer rearrangement[138] ($(CF_3CO)_2O$, Ac_2O, lutidine) to the acetoxysulfides 133, followed by hydrolysis ($CuCl_2$, CH_3CN, H_2O)[140] gave a 88% yield of the aldehyde 134. cis-Hydroxylation (cat. OsO_4, TMNO) of 134 proceeded stereoselectively to produce a 7:3 ratio of N-trichloroacetyl vancosamine (135) and N-trichloroacetyl epivancosamine (136) in 52% overall yield (Scheme 32). The sugars were characterized as the N,O-bistrichloroacetyl derivatives.

Scheme 32.



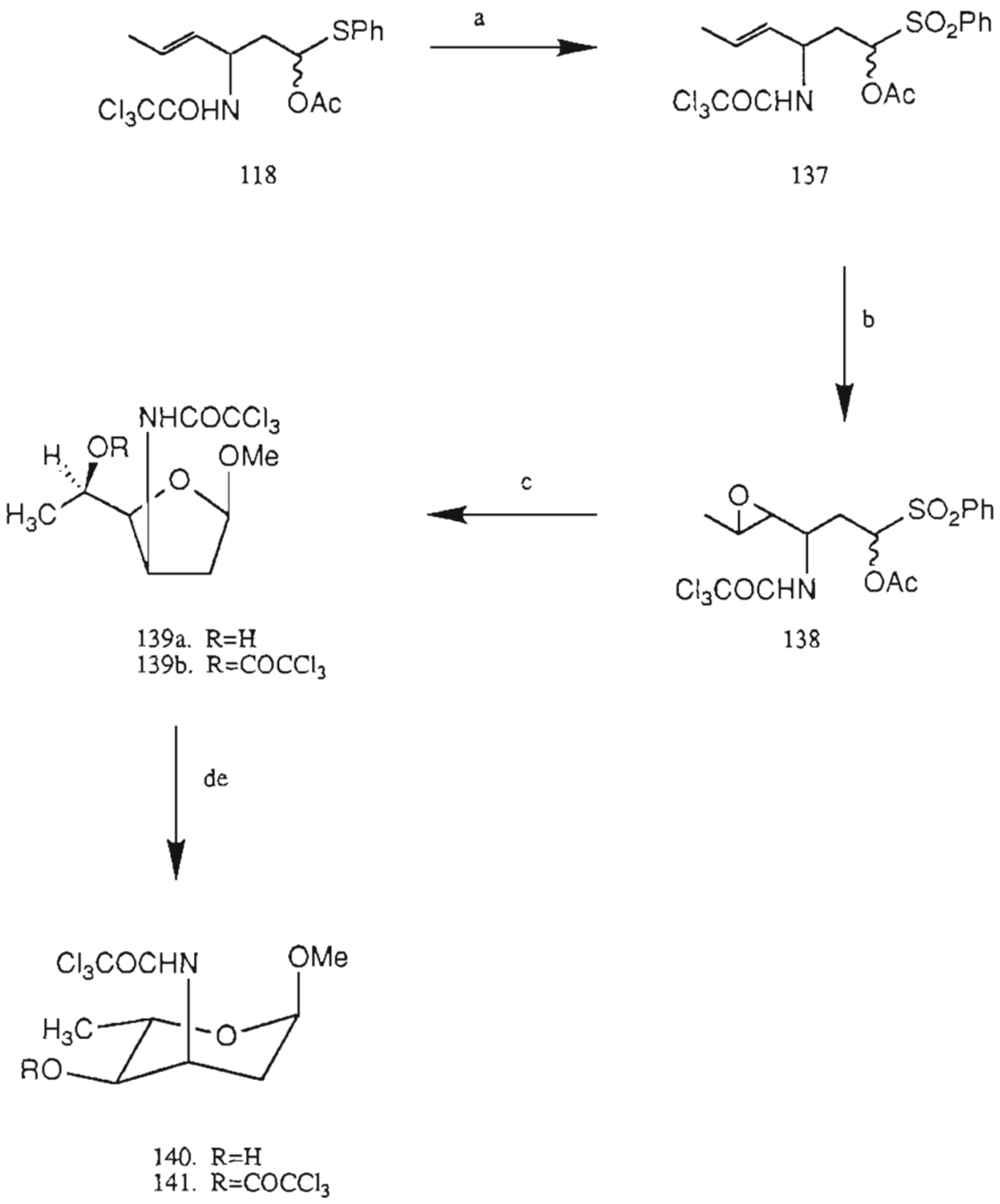
a) Cl_3CCN, KH, 18-Crown-6 b) Xylenes, Δ (89%) c) PhSH, AIBN (88%)
d) SeO_2, H_2O_2 (85%) e) Ac_2O, TFAA, Lutidine (89%) f) $CuCl_2$, CH_3CN, H_2O (99%)
g) Catalytic OsO_4, TMNO (xylo:28%; lyxo:65%)

VI. Stereospecific Synthesis of (±)-N-(Trichloroacetyl)ristosamine

In order to determine the versatility of this synthetic strategy to conveniently prepare other sugars in this class, the previous epoxidation work was utilized.

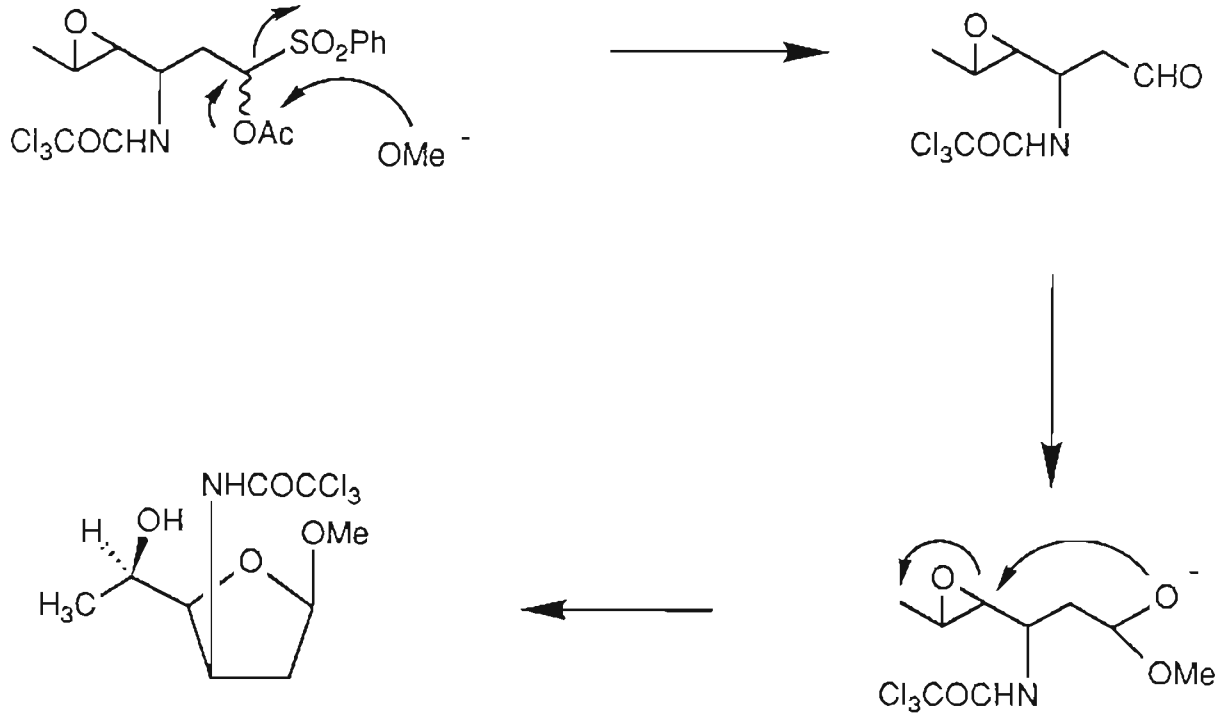
Epoxidation of the 6:4 mixture of acetoxysulfides (118) was expected to yield the possible four epoxy acetoxysulfide isomers. However, treatment of 118 with two equivalents of meta-chloroperoxybenzoic acid unexpectedly provided the olefinic acetoxysulfone (137) whose structure was determined by spectral analysis. Numerous repetitions of this reaction provided the same results. Reaction of this intermediate with another equivalent of meta-chloroperoxybenzoic acid or of 118 with three equivalents gave the epoxy acetoxysulfone 138 as a mixture of two isomers by ^{13}C NMR. Since epoxide residues are generally stable toward basic conditions, hydrolytic cleavage of 138 with aqueous sodium hydroxide was expected to give the epoxyaldehyde. However, treatment of 138 with two equivalents of sodium hydroxide in aqueous methanol at room temperature for two hours unexpectedly provided a near quantitative yield of the α-methyl ribo-hexofuranose derivative of ristosamine (139). Apparently, as shown in Scheme 34, the epoxide (138) undergoes initial hydrolysis of the acetoxysulfone to furnish the aldehyde. The aldehyde moiety then undergoes intramolecular attack by methoxide to generate a hemiacetal anion which opens to the epoxide and quantitatively gives the sugar 139. A small amount (<3%) of the β-anomer was obtained in this reaction, but no other configurational isomers were produced.

Scheme 33.



a) MCPBA b) MCPBA (97%) c) NaOAc, MeOH, H_2O (96%) d) HOAc, H_2O, e) MeOH, HCl (furanose:56%; pyranose:28%)

Scheme 34.

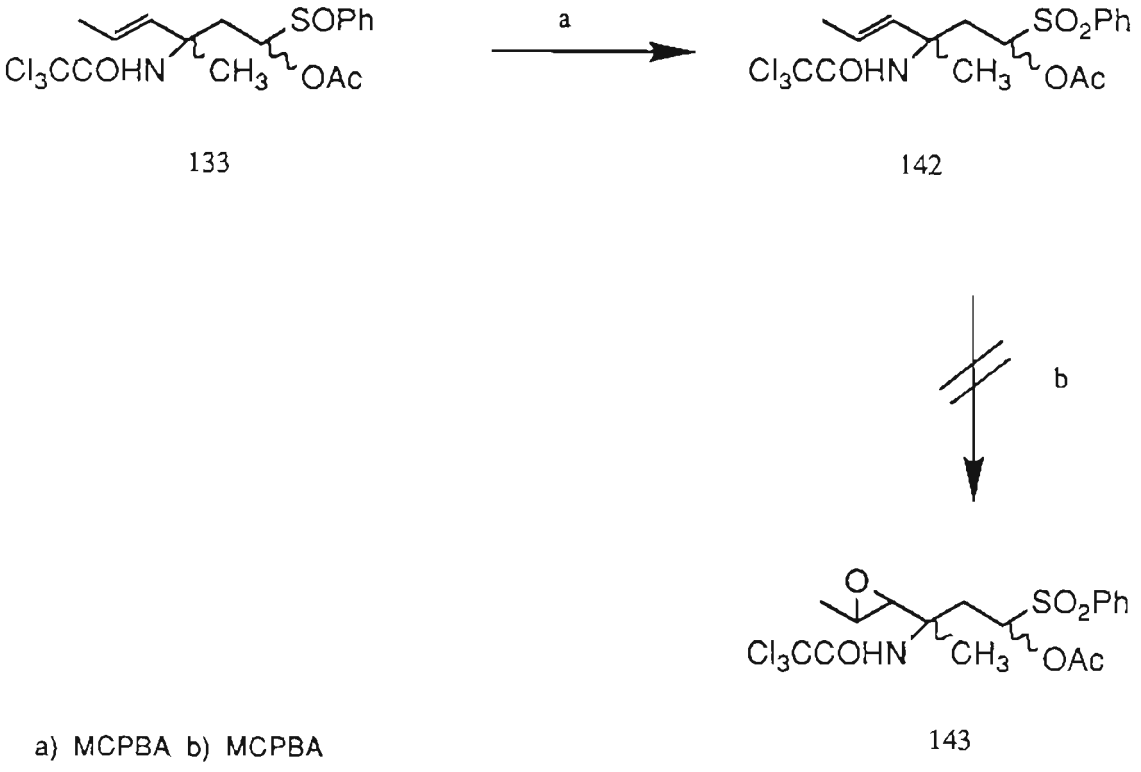


In order to prepare the pyranoside derivative (140), the furanoside 139 was hydrolyzed with hot aqueous acetic acid and subsequent methanolysis (MeOH, HCl) produced α-methyl N-trichloroacetyl ristosaminide (140) which gave a ^{1}H NMR spectrum identical to a spectrum of an authentic sample. As a further derivative, and in order to facilitate spectral interpretation, 140 was treated with trichloroacetyl chloride to give α-methyl N,O-bistrichloroacetyl ristosaminide 141.

VII. Attempted synthesis of (±)-2,3,6-Trideoxy-3-amino-3-C-methyl-ribo-hexopyranose

A synthesis of the ribo-isomer of vancosamine, analogous to the ristosamine (140) preparation from the acetoxysulfide (118) intermediate used in the daunosamine (89) synthesis, was next investigated. The acetoxysulfide 133, used in the vancosamine route, was treated with two equivalents of metachloroperoxybenzoic acid and after work-up the product was determined to be the olefinic acetoxysulfone 142 through NMR, IR and mass spectral data. No epoxide intermediate was detected. Reaction of 142 with an additional equivalent of metachloroperoxybenzoic acid did not produce the desired epoxysulfone 143, rather, recovered starting material and a dark, material was obtained from which no useful spectral data could be obtained. Repetition of the reaction with protracted reaction times and the use of other peroxy acids gave the same result.

Scheme 35.



133

142

143

a) MCPBA b) MCPBA

VIII. Synthesis of Pentose Derivatives

Heterosubstituted β-lactams comprise the fundamental nucleus of the penicillin and cephalosporin antibiotics. They have been prepared by reaction of chlorosulfonyl isocyanate (CSI) with a variety of vinyl esters[146] and olefins. The β-lactam prepared from CSI and vinyl acetate, 4-acetoxy-2-azetidinone, is particularly useful as a starting material for the synthesis of thienamycin[146] and related carbapenem[147] antibiotics. β-lactams have also been used in the synthesis of a variety of other compounds, including amino sugars[58,59].

The reaction involves a net [2 + 2] cycloaddition of CSI to a wide variety of olefins to produce β-lactams. The cycloadditions are highly stereo- and regiospecific, the cis adduct is always formed and the addition takes place so that the most stable carbonium ion is generated[148-150]. The carbon atom in CSI is strongly electrophilic due to the polar chlorosulfonyl group attached to the cumulative double bond[151]. The reaction is a concerted, thermally allowed $\pi 2_a + \pi 2_s$ cycloaddition[152] of CSI to unsaturated systems to form 1,2-cycloadducts.

Previous studies from this laboratory had shown that the propenyl-azetidinone prepared from (E)-1,3-pentadiene[58,59] could be used to accomplish an efficacious synthesis of racemic and optically active daunosamine which was described in the Literature Background section part (B) (Scheme 5). In unpublished work it was found that this approach could not be used to prepare 2,3,6-trideoxy-3-amino-3-C-methyl substituted hexoses. However, there exists the potential for use of this route in

a modified form as a method for dideoxyamino pentose syntheses. The further studies in this section demonstrate that efficient synthesis of amino pentoses from azetidinones is feasible.

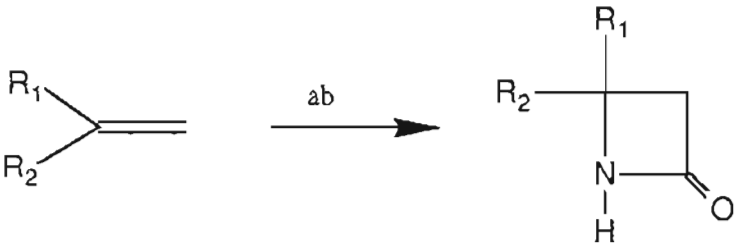
A. Azetidinone Syntheses

The azetidinone intermediates required for synthesis of these pentoses 61 and 62, and, 63 and 64 would be prepared through cycloaddition of CSI with butadiene and isoprene. While the cycloaddition reaction of CSI with nonvolatile olefins generally proceeds in high yields when volatile olefins are used, the protocol is experimentally tedious and provides low yields of the desired adducts. Thus, development of a higher yield procedure was desirable. The usual procedure for butadiene[145] involves maintaining an ether solution of CSI at the reflux temperature of butadiene (-5 °C) for several days. The yield of the azetidinone 145 after cleavage of the N-chlorosulfonyl group is only 11%[145]. The adducts prepared from isoprene[145] (144b) and isobutylene[145] (144c)have been reported in 59 and 73% yields, respectively. The preparation of 4-acetoxy-2-azetidinone[145] (145d) requires a similar procedure; however, because of the high reactivity of vinyl acetate (144d), the reaction is conducted initially at -60 °C and warmed to -20 °C for 20 minutes before work-up. The yield of 143d is 40-43%.

The procedure for the volatile olefins (144a-144c) was modified by placing the cold (-20 °C) reactants in a pressure bottle, warming to room temperature and allowing it to stand 2 days before hydrolytic work-up

provided significantly improved yields of the adducts[153] (Table 3). For vinyl acetate (144d), the same method was used except the initial reaction was performed at -78 °C, warmed to -40 °C for 2 hours and then maintained in the freezer at -17 °C for two days, rather than storing at room temperature (Scheme 36).

Scheme 36.



144. 145.

a. R_1=CH_2=CH; R_2=H (97%)
b. R_1=CH_2=CH; R_2=CH_3 (89%)
c. R_1=R_2=CH_3 (96%)
d. R_1=CH_3CO_2-; R_2=H 80%)

a) $ClSO_2NCO$ b) NaOH, $NaHSO_3$

Table 3. Yields of azetidinones prepared from volatile olefins by different procedures[145,146].

Olefin	Yield %	Lit. Yield %
Butadiene[a]	96	11, 52
Isoprene[a]	87	59
Isobutylene[a]	92	73
Vinyl Acetate[b]	84	40-43

a) Purified through column chromatography on florisil. b) No purification was necessary.

A modification of the reductive desulfonylation procedure by Durst and O'Sullivan[154] was used to cleave the N-sulfonyl residue. The cold (-78 °C) chlorosulfonyl azetidinone (145a), prepared from butadiene (144a), was transferred to a dry ice-jacketed dropping funnel with ether and added dropwise to a solution of 25% aqueous sodium bisulfite and the pH was maintained between 7 and 8 by addition of sodium hydroxide (6 N) as determined by litmus paper. Work-up of the adducts prepared from isoprene (144b) and isobutylene (144c) were similar except the chlorosulfonyl azetidinones are highly crystalline so they were chilled to -30 °C before transferring to the dropping funnel and methylene chloride washing was used. Also, the hydrolysis reactions were slower, and after addition was complete, they were stirred several hours.

As can be seen from the data given in Table 3, dramatic improvement in the yields of adducts were obtained using the modified conditions. Two factors were determined to be responsible for this: (A) performing

the reaction in a sealed container prevents loss of the volatile olefin, and, (B) cycloaddition reactions are thermal processes. By running the reaction a higher temperature, the rate of reaction was enhanced.

Transformation of the azetidinones 145a and 145b, prepared from butadiene and isoprene, respectively, to aminopentoses were accomplished in a straightforward manner[155].

B. Butadiene Adduct

As shown in Scheme 37, methanolysis (MeOH, HCl) of azetidinone 145a, prepared from butadiene, provided the methyl ester which was converted to the benzamide 146 with benzoyl chloride and pyridine. Cyclization to the lactones 147 and 148 was accomplished through cis-hydroxylation using a catalytic amount of osmium tetraoxide and trimethylamine N-oxide. The cis- (147) and trans-lactone (148) isomers, obtained in a 44:56 ratio, were separated through combined fractional crystallization and column chromatography. The less polar cis-lactone (147) was isolated as colorless plates with mp 139-141 °C and the polar trans-lactone (148) was isolated as colorless needles with mp 164-165 °C.

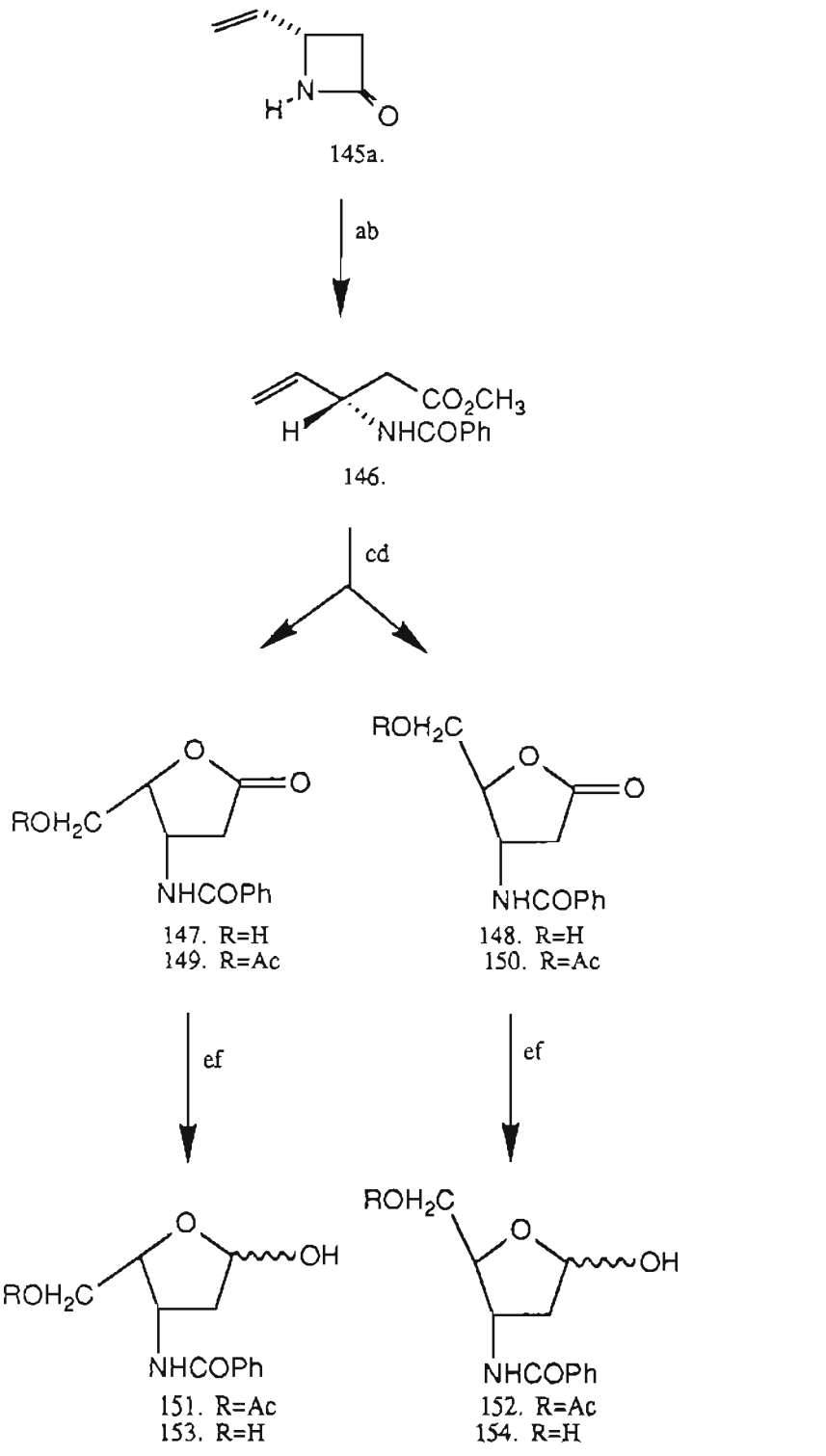
The relative stereochemistry was determined by spin-spin decoupling NMR experiments on the trans-lactone isomer 148. Irradiation of the C(5) signal at 3.87 ppm led to collapse of the C(4) quintet at 4.62 ppm to a doublet with J=3.73 Hz. Irradiation of the C(2) signal at 2.86 ppm collapsed the C(3) multiplet at 4.70 ppm to an asymmetric triplet with J=3.96 Hz. Since the dihedrahl angle between the C(3) and C(4) protons in cis-substituted five membered lactones approaches 90°, the coupling constant is small; thus, 147 has the cis-stereochemistry.

Due to insolubility of the cis- and trans-lactone isomers 147 and 148 in the solvent used for the reduction of the lactones, they were individually acetylated (Ac_2O, Py) to the acetates 149 and 150.

DIBAL reduction (THF, -80 °C, 2h) of the individual acetate derivatives 149 and 150 furnished the acetylated lactoles 151 and 152 in 85%

yield along with 10% of the deacetylated products 153 and 154. Respective ammonolysis (NH_3/MeOH, 0 °C, 1 h) gave the aminopentoses 153 and 154 quantitatively. The overall yield of the aminopentose 153 (cis) was 41% and that of the aminopentose 154 (trans) 50% (combined overall yield 81%).

Scheme 37.



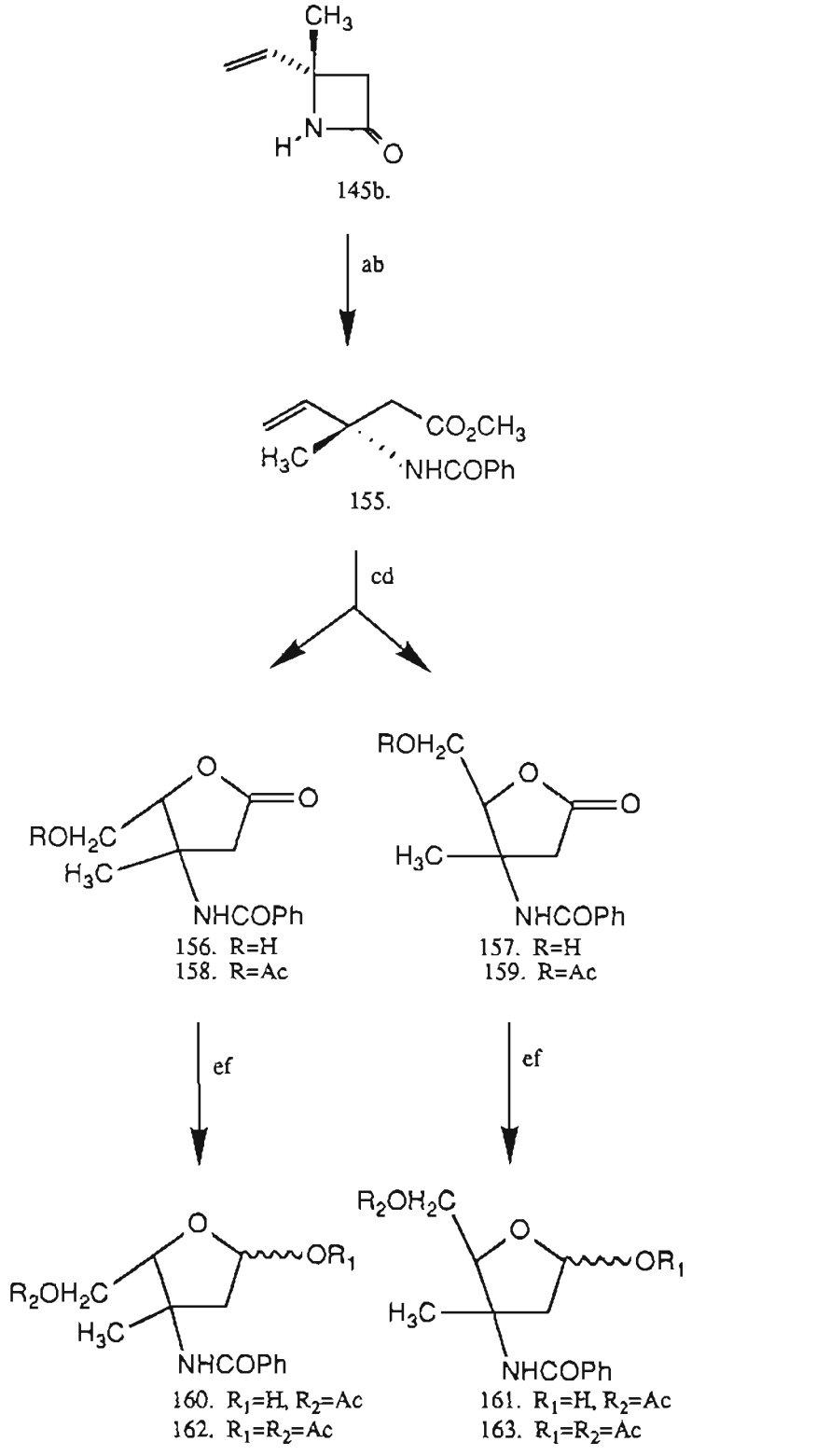
a) CH_3OH, HCl b) PhCOCl, Py (95%) c) OsO_4, TMNO (cis:44%; trans:56%)
d) $(CH_3CO)_2O$, Py (96%) e) DIBAL, THF (80%) f) NH_3, CH_3OH (93%)

C. Isoprene Adduct

Corresponding methanolysis, benzoylation, and hydroxylation of the pentenoate 155 originating from isoprene adduct 145b gave the 3-C-methyl substituted trans- and cis-lactones 156 and 157 in a 69:31 ratio, respectively. The nuclear Overhauser effect (NOE) was employed to assign stereochemistry to the individual lactones. Irradiation of the C(4) proton at 4.56 ppm in the acetate derivative 158 (cis) resulted in a 30% decrease in intensity of the methyl absorption at 1.53 ppm, demonstrating the cis relationship of the C(4) proton and the methyl group. Corresponding irradiation of the C(4) proton in the acetate derivative of the isomer 159 (trans) caused no change in the intensity of the methyl absorption.

Reduction of the individual acetate derivatives 158 and 159 with DIBAL resulted in chemoselective reduction of the lactone carbonyl group, furnishing the lactoles 160 and 161 along with a small amount of the deacetylated products and (<10%). Peracetylation (Ac_2O, Py) quantitatively furnished the triacetate C-3-methyl amino pentoses 162 and 163 as shown in scheme 38.

Scheme 38.



a) CH_3OH, HCl b) PhCOCl, Py (93%) c) OsO_4, TMNO (cis:31%; trans:69%)
d) $(CH_3CO)_2O$, Py (97%) e) DIBAL, THF (97%) f) $(CH_3CO)_2O$ 80%)

Summary

New synthetic methodology for the high yield, regiospecific and stereoselective racemic syntheses of various 2,3,6-trideoxy-3-amino hexoses and 2,6-dideoxy-3-amino pentopyranoses from simple acyclic synthons has been described.

In the preparation of daunosamine, 3-epidaunosamine, and ristosamine a 6-carbon diene fragment with either a C-1 or C-5 hydroxyl group serves as the starting material. For the syntheses of vancosamine and 3-epi-vancosamine the C-5 hydroxyl diene fragment has a C-3 methyl branch to afford the required substitution for these compounds. The hydroxyl group is transposed to a C-3 amide through Claisen rearrangement of an imidate intermediate using Overman reaction conditions. Conversion of C-1 to a latent aldehyde precursor was accomplished through free radical addition of benzenethiol to provide a sulfide which was oxidized to a sulfoxide. Pummerer rearrangement of the sulfoxide led to an α-acetoxy-sulfide which was oxidatively cleaved to an provide an aldehyde. Regio-specific and stereoselective cis-hydroxylation of individual intermediates with concomitant ring closure led to daunosamine, 3-epidaunosamine, vancosamine, and 3-epivancosamine. Stereospecific epoxidation of the α-acetoxysulfide intermediate led to ristosamine.

The efficacy of this method was demonstrated by preparing four 2,6-dideoxy-3-amino pentopyranose analogues from an azetidinone intermediate. The ß-lactam adducts, obtained through cycloaddition of chlorosulfonyl isocyanate and either butadiene or isoprene, were prepared

using an improved method which gave the desired azetidinones in 98% and 92% yields, respectively. Conversion of the azetidinone adducts to the aminopentoses was accomplished in a manner similar to the trideoxyhexoses.

IX. Experimental Section

Melting points were taken on a Kofler hot-stage microscope and are uncorrected. Infrared spectra were measured with a Perkin-Elmer 621 or 1800 FT spectrophotometer and are expressed in cm^{-1}. Proton and carbon magnetic resonance spectra were obtained with a JEOL FX-90Q and Nicolet 360 mHz (University of Oregon, Eugene) spectrometers. Chemical shifts are expressed in units. Mass spectra were obtained with a VG 7070E, DuPont CEC 21-110B, DuPont 21-491B, or Finnigan 40-21. Carbon, hydrogen, and nitrogen analyses were performed by Galbraith Laboratories, Knoxville, Tennessee.

Analytical thin-layer chromatograms (TLC) were conducted on 5 x 10 cm precoated TLC plates (silica gel 60 F 254, 0.25-mm thickness) manufactured by E. Merck and Co. Radial preparative thick layer chromatography was performed on a Chromatotron (Harrison Research) with rotors coated to 2- and 4-mm thickness (Merck silica gel 60, PF-254). Silica gel columns for chromatography utilized E. Merck silica gel 60, 70-230 mesh ASTM.

Tetrahydrofuran (THF) was dried by distillation from lithium aluminum hydride (LAH) and dioxane was distilled over calcium hydride. Methanol was dried by distillation from magnesium trunngs containing a catalytic amount of iodine. Trichloroacetonitrile and trichloroacetyl chloride were distilled before use. All other solvents were reagent grade and were not further purified. A stock solution of osmium tetraoxide (1 g in 200 mL of 3:1 $\underline{t}$-BuOH-CCl_4) was used for hydroxylations. All reactions

were run under either a nitrogen or argon atmosphere. Methyl L-daunosaminide hydrochloride was purchased from Pfanstiehl Laboratories.

A ^{1}H NMR spectrum of α-methyl N-(trichloroacetyl)ristosaminide was provided by Dr. Bert Fraser-Reid (Duke University).

(4E)-3-(Trichloroacetamido)-1,4-hexadiene (68)

Sodium hydride (50% suspension; 0.48 g, 0.01 mol), washed with hexanes (3x 5 mL) to remove the mineral oil, was suspended in ether (100 mL) and quickly added to a magnetically stirred solution of sorbyl alcohol (66) (10 g, 0.10 mol) in ether (30 mL). The resultant yellow solution was stirred at ambient temperature 15 min and then chilled to -10 to -15 °C. Trichloroacetonitrile (15.90 g, 0.11 mol) in ether (35 mL) was slowly added to the alkoxide to produce a brown solution which was stirred cold for 1 h and at room temperature 3 h. Hexanes (20 mL) and methanol (6 mL) were added to the reaction and the resultant solution was filtered through Celite. Evaporation of the solvents at reduced pressure gave the imidate intermediate (67), which was taken up in xylenes (100 mL) and heated at reflux for 12 h at which time analysis of a TLC showed the reaction to be complete. The solvent was removed at reduced pressure and the residue was filtered through silica gel (100 g; 9:1 hexanes/ethyl acetate) to give 24.09 g (100%) of the desired deconjugated diene amide 68 as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 6.97 (bs, 1H); 5.54 (m, 5H); 4.85 (m, 1H); 1.66 (d, J=5.5 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 156.37,

131.39, 124.51, 123.64, 111.89, 88.43, 50.62, 13.35; IR (neat): 3350, N-H str.; 1710, C=O str.; 1522, N-H bend; 820 cm^{-1}, C-Cl str; mass spectrum: m/z 241 ($M^{\cdot+}$), 206.

Anal. Calcd. for $C_8H_{10}Cl_3NO$: C, 39.62; H, 4.16; N, 5.78. Found: C, 39.62; H, 4.05; N, 5.71.

(E)-1-(phenylthio)-3-(trichloroacetamido)-4-hexene (73)

A magnetically stirred mixture of benzenethiol (10.95 g, 0.0996 mol), AIBN (1.64 g, .01 mol), and 68 (24.0 g, 0.0996 mol) was heated at 80-90 °C for 12 h, then cooled, and diluted with methylene chloride (100mL). The dark solution was washed with an aqueous solution of potassium hydroxide (0.5 M, 3 x 30 mL) and the combined aqueous layers were back-extracted with methylene chloride (1 x 25 mL). The combined organic solutions were dried ($MgSO_4$), filtered and evaporated at reduced pressure. The crude sulfide was chromatographed (silica gel, 150 g; 9:1 hexanes/ ethyl acetate) to give 30.70 g (88%) of the sulfide 73 as a gold oil. ^1H NMR ($CDCl_3$): δ 7.29 (m, 5H); 6.78 (bd, 2H); 5.52 (m, 2H); 4.51 (p, J=7.2 Hz, 1H); 2.95 (t, J=7.4 Hz, 2H); 1.94 (q, J=7.2 Hz, 2H); 1.71 (d, J=6.2 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 160.97, 135.56, 129.55, 129.45, 128.74, 128.46, 126.24, 92.71, 52.62, 33.99, 29.98, 17.51; IR (neat): 3411, N-H str.; 3021, C=H str., olefin; 1700 and 1517 cm^{-1}, C=O str; EI mass spectrum: m/z 351 ($M^{+\cdot}$), 316, 242, 206.

Anal. Calcd for $C_{14}H_{16}Cl_3NOS$: C, 47.68; H, 4.57; N, 3.97. Found: C, 48.00; H, 4.82; N, 4.01.

3-Phenylthiopropanal (69)

Benzenethiol (110 g, 1 mol) and morpholine (5 drops) were slowly added to a cold solution (0 °C) of acrolein (56 g, 1 mol) and an exothermic reaction immediately ensued. The resultant yellow solution was stirred 16 h before adding ether (50 mL) and quenching with aqueous hydrochloric acid (1M; 50 mL). The organic solution was dried ($MgSO_4$), filtered, and evaporated at reduced pressure. The liquid was vacuum distilled to give 107.9 g (65%) of the aldehyde 69 as a colorless liquid with bp 83-85 °C/0.35 mm. ^1H NMR ($CDCl_3$): δ 9.74 (s, 1H); 7.29 (m, 5H); 3.17 (t, $\underline{J}$=7.03 Hz, 2H); 2.74 (t, $\underline{J}$=6.59 Hz, 2H).

(E)-6-(Phenylthio)-3-hexen-2-one (71)

A magnetically stirred solution of the aldehyde 69 (20 g, 120.48 mmol), triphenylphosphoranylidene-2-propanone (70) (44.10 g, 138.55 mmol) and dry benzene (300 mL) was heated at reflux for 60 h, at which time TLC indicated the starting materials had been consumed. The reaction was cooled to ambient temperature and water (50 mL) and ethyl acetate (50 mL) were added. The layers were separated and the aqueous phase was extracted with ethyl acetate (2 x 50 mL). The combined organic solutions were dried ($MgSO_4$), filtered, and evaporated at reduced pressure to give a red-brown slushy solid. The mixture was dissolved in hot ether and chilled to effect crystallization and filtered to remove the

triphenyl phosphine. This procedure was repeated before chromatography (silica gel, 200 g; 8:2 hexanes/methylene chloride) to give 19.86 g (80%) of the hexenone 71 as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 7.29 (m, 5H); 6.80 (m, 1H); 6.01 (m, 1H); 3.02 (t, J=6.59 Hz, 2H); 2.56 (q, J=7.01 Hz, 2H); 2.20 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 197.48, 144.83, 135.56, 132.09, 129.44, 128.79, 126.14, 31.87, 26.56.

(E)-6-(phenylthio)-3-hexen-2-ol (72)

The hexenone 71 (10 g, 48.54 mmol) was added to a magnetically stirred solution of lithium aluminum hydride (1.00 g, 26.38 mmol) and ether (200 mL). The mixture was stirred 16 h before the excess LAH was destroyed with successive addition of 1 mL of water, 1 mL of 15% aqueous potassium hydroxide and 3 mL of water. The mixture was filtered and evaporated at reduced pressure to give a quantitative yield (10.08 g) of the alcohol 72. ^{1}H NMR ($CDCl_3$): δ 7.30 (m, 5H); 5.50 (m, 2H); 4.48 (p, J=5.71 Hz, 1H); 2.98 (t, J=7.25 Hz, 2H); 2.40 (m, 2H); 1.46 (bs, 1H); 1.25 (d, J=6.37 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 127.11, 125.92, 124.18, 66.44, 31.55, 30.03, 21.58.

(E)-1-(Phenylthio)-3-(trichloroacetamido)-4-hexene (73)

A modification of the Overman reaction was used to prepare 73. The imidate obtained from 72 (8.01 g, 38.51 mmol), potassium hydride (0.44 g, 3.85 mmol) (35% suspension), and trichloroacetonitrile 5.56 g (38.51

mmol) trichloroacetonitrile using inverse addition of reagents, was heated at reflux (12 h) in ethyl acetate (100 mL), to give, after chromatography (200 g silica gel, 9:1 hexanes/ethyl acetate) 13.50 g (100%) 73 as a yellow oil. The ^{1}H and ^{13}C NMR and IR spectra and the TLC behavior of this product was identical with the material prepared from 68.

(E)-1-(Phenylsulfinyl)-3-(trichloroacetamido)-4-hexene (76 and 77)

Predominant production of either diastereoisomeric sulfoxide (76 and 77) was accomplished by oxidation of the sulfide 73 with either (A) sodium metaperiodate or (B) selenium dioxide-hydrogen peroxide.

(A) Sodium metaperiodate (8.94 g, 28.49 mmol) was added in small portions to a magnetically stirred solution of 73 (10.0 g, 28.49 mmol) in methanol (75 mL) at 0 °C. The mixture was allowed to warm to room temperature and stir 2-3 d at which time, analysis of a TLC showed the reaction to be complete. The mixture was filtered to remove sodium iodate, and the filtrate was evaporated under reduced pressure to remove the methanol. The mixture was diluted with methylene chloride (75 mL), transferred to a separatory funnel, and washed with water (3 x 20 mL). The combined aqueous phases were back-extracted once with ethyl acetate (25 mL). The organic extracts were dried ($MgSO_4$), filtered and evaporated at reduced pressure.

Fractional crystallization of the residue from ethyl acetate/ hexanes gave the pure diastereoisomeric sulfoxides 76 and 77, and sulfone 78

(0.82 g, 8%) as a yellow oil, and a small amount of recovered sulfide 73. The less polar sulfoxide diastereoisomer (R_f 0.52 1:1 ethyl acetate/hexanes) 76 was obtained as colorless needles (8.93 g, 85%) with mp 110-112 °C. ^{1}H NMR ($CDCl_3$): δ 7.59 (m, 6H); 5.48 (m, 2H); 4.44 (p, J=6.1 Hz, 1H); 2.93 (m, 2H); 2.17 (m, 2H); 1.73 (d, J=5.9 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 161.46, 143.15, 131.07, 129.28, 129.01, 128.36, 123.92, 52.57, 52.40, 26.78, 17.62; IR (KBr): 3275, N-H str.; 1700, C=O str.; 1498, N-H bend; 1081 cm^{-1}, S=O str; FAB mass spectrum; m/z 368 ($M^{\cdot+}$), 243, 207.

Anal. Calcd. for $C_{14}H_{16}Cl_3NO_2S$: C, 45.60; H, 4.37; N, 3.80. Found: C, 45.47; H,4.43; N, 3.81.

The more polar sulfoxide diastereoisomer 77 (R_f 0.47 1:1 ethyl acetate/hexanes), was isolated as a pale yellow, low-melting solid (mp <50 °C) (0.73 g, 7%). ^{1}H NMR ($CDCl_3$): δ 7.50 (m, 6H); 5.56 (m, 2H); 4.43 (p, J=6.2 Hz, 1H); 2.89 (m, 2H); 1.95 (m, 2H); 1.72 (d, J=5.9 Hz, 3H); ^{13}C NMR ($CDCl_3$): 161.51, 144.05, 131.12, 129.33, 129.12, 128.30, 127.87, 124.08, 52.46, 29.65, 27.16, 17.68; IR ($CDCl_3$):δ 3419, N-H str.; 1709, C=O str.; 1507, N-H bend; 1022 cm^{-1}, S=O str.; FAB mass spectrum: m/z 368 ($M^{\cdot+}$), 243, 207.

(B) A solution of selenium dioxide (4.95 g, 44.6 mmol) and hydrogen peroxide (30%, 1.52 g, 44.6 mmol) in methanol (32 mL) and water (8 mL) was added dropwise to a magnetically stirred solution of the sulfide 73 (15.65 g, 44.6 mmol) in methanol (100 mL) at 0 °C. Immediately following addition of the oxidizing agent, analysis by TLC indicated the reaction was complete. Saturated sodium chloride solution (25 mL) was added and

the resultant solution was extracted with methylene chloride. The combined organic solutions were dried ($MgSO_4$), filtered, and evaporated under reduced pressure. Chromatography of the residue (silica gel, 150 g; 6:4 hexanes/ethyl acetate) gave 2.53 g(18%) of the less polar sulfoxide (76) and 11.51 g (82%) of the more polar diastereoisomer (77).

(E)-1-(Phenylsulfonyl)-3-trichloroacetamido-4-hexene (78)

The sulfone (78) was prepared by oxidation of the sulfide (73) or the diastereoisomeric sulfoxides (76) and (77).

(A) The sulfide (73) (4.92 g, 14.02 mmol) was dissolved in methylene chloride (100 mL) and chilled to -78 °C, and meta-chloroperoxybenzoic acid (80-85%) (3.03 g, 28.04 mmol) was added in small portions over a 10 min period. The solution was warmed to ambient temperature and stirred for 4 h. Saturated aqueous sodium bisulfite (30 mL) was added and the mixture was stirred for 30 min. The layers were separated and the aqueous solution was extracted with methylene chloride (2 x 50 mL). The combined organic solutions were washed with saturated aqueous sodium carbonate (2 x 25 mL), dried ($MgSO_4$), filtered, and evaporated at reduced pressure. Chromatography of the crude product (silica gel, 100 g; 1:9 to 3:7 ethyl acetate/hexanes) gave 0.39 g recovered sulfide.

With continued elution, there was obtained 4.32 g (80.6%) of olefinic sulfone 78 as a yellow oil. ^1H NMR ($CDCl_3$): δ 7.71 (m, 5H); 6.83 (bd, 1H); 5.51 (m, 2H); 4.39 (p, J=16.32 Hz, 1H); 3.15 (m, 2H); 2.13 (m, 2H); 1.70 (d, J=6.15 Hz, 3H).

The epoxysulfone 79 (0.43 g, 7.7%) was obtained as a colorless solid with mp 167-168 °C.

(B) From a mixture of the sulfoxide diastereoisomers 76 and 77 (5.01 g, 13.65 mmol) and metachloroperoxybenzoic acid (80-85%) (2.94 g, 13.65 mmol), dissolved in methylene chloride (100 mL) at -78 °C, there was obtained 4.86 g (93%) of olefinic sulfone 78, 0.33 g (6%) of epoxysulfone 79, and a trace of the sulfoxides (76 and 77).

1-Phenylsulfonyl-3-trichloroacetamido-4,5-di-O-acetyl hexane (82 and 83)

Hydroxylation of (A) the olefinic sulfide (73), (B) diastereoisomeric sulfoxides (76 and 77), and (C) sulfone (78) was preformed using a catalytic amount of osmium tetraoxide and trimethylamine-N-oxide dihydrate (TMNO). The resultant diol products were acetylated with acetic anhydride and pyridine.

(A) The sulfide 73 (11.36 g, 32.36 mmol) was dissolved in acetone (150 mL) and water (5 mL). Trimethylamine-N-oxide dihydrate (16.18 g, 145.62 mmol) and 1.0 mL of osmium tetraoxide stock solution were added and the mixture was magnetically stirred at ambient temperature 15 h. Saturated aqueous sodium bisulfite (30 mL) and methylene chloride (100 mL) were added and the solution was stirred 30 min. The layers were separated and the aqueous phase was extracted with methylene chloride (2 x 50 mL). The combined organic solutions were washed with brine (35 mL), dried ($MgSO_4$), filtered and evaporated at reduced pressure to give a yellow oil.

The initially received diol sulfone was directly acetylated with acetic anhydride (50 mL) and pyridine (20 mL) at ambient temperature (15 h). Methylene chloride (50 mL), saturated aqueous sodium bicarbonate (30 mL), and solid sodium bicarbonate were added as needed until foaming had ceased. The layers were separated and the aqueous phase was extracted with methylene chloride (2 x 25 mL) and the combined organic solutions were washed with hydrochloric acid (5%, 2 x 25 mL), dried ($MgSO_4$), filtered, and evaporated at reduced pressure to give a colorless solid as a 6:4 diastereoisomeric mixture (15.56 g, 96%). The two components were separated by crystallization from ethyl acetate/hexanes to give 9.34 g of the less polar isomer (R_f 0.60 in 1:1 ethyl acetate/-hexanes) 82 as a colorless solid with mp 134-136 °C. ^{1}H NMR (d6 benzene): δ 7.86 (m, 2H); 6.99 (m, 4H); 5.06 (m, 2H); 4.33 (m, 1H); 2.95 (m, 2H); 2.08 (m, 2H); 1.73 (s, 3H); 1.70 (s, 3H); 1.10 (d, J=6.37 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 170.13, 169.97, 162.22, 138.71, 134.26, 129.44, 127.97, 74.42, 68.81, 52.35, 50.24, 25.27, 20.93, 20.55, 16.44; FAB mass spectrum: m/z 502 ($M^{\cdot+}$), 442, 367.

The polar isomer (R_f 0.55 in 1:1 ethyl acetate hexanes) (83) (6.22 g) was obtained as colorless clusters of crystals with mp 149-150 °C. ^{1}H NMR (d6 benzene): δ 7.86 (m, 2H); 7.41 (bd, 1H); 7.00 (m, 3H); 5.12 (m, 2H); 4.51 (m, 1H); 3.02 (m, 2H); 2.04 (m, 2H); 1.87 (s, 3H); 1.74 (s, 3H); 1.13 (d, J=6.15 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 170.78, 169.86, 162.32, 134.04, 129.50, 127.98, 75.10, 68.87, 52.73, 50.56, 23.75, 21.09, 20.55, 16.32; FAB mass spectrum: m/e 502 ($M^{\cdot+}$), 442, 399.

(B) From 4.18 g (10.91 mmol) of the sulfone 78 there was obtained a 6:4 mixture of diastereoisomeric diacetates 82 and 83 (5.35 g, 98%).

(C) From 1.98 g (5.40 mmol) of the individual sulfoxide diastereoisomers (76 and 77) there was obtained 2.59 g (96%) of the diacetate sulfones (82 and 83), respectively.

1-(Phenylsulfonyl)-3-(trichloroacetamido)-4,5-di-O-isopropylidene hexanediol (85a and 85b)

To the diol sulfone 80 of (3.54 g, 9.19 mmol) in DMF (30 mL) was added excess dimethoxypropane (15 mL) and a catalytic amount of toluenesulfonic acid (0.25 g). The reaction was stirred for 10 h at ambient temperature, then 100 mL of 5:1 hexanes/ethyl acetate was added. The resultant solution was washed with saturated sodium bicarbonate (2 x 20 mL). The organic phase was dried ($MgSO_4$), filtered, and then evaporated at reduced pressure. The residue was crystallized from ethyl acetate/hexanes to give the acetonide 85a (3.83 g, 98%) as colorless needles with mp 142-145 °C. ^1H NMR ($CDCl_3$): δ 7.75 (m, 5H); 4.19 (m, 2H); 4.08 (m, 1H); 3.19 (m, 2H); 2.04 (m, 2H); 1.55 (m, 9H); ^{13}C NMR ($CDCl_3$): δ 162.11, 138.92, 133.94, 129.45, 127.98, 109.02, 94.68, 82.96, 74.72, 52.68, 51.65, 27.38, 26.62, 23.96, 18.49.

An analogous procedure from the diol sulfone 81 (3.00 g, 7.79 mmol) gave the acetonide 85b (3.21 g, 97%) as a yellow oil. ^1H NMR ($CDCl_3$): δ 7.41 (m, 5H); 4.35 (m, 1H); 4.08 (m, 2H); 3.22 (m, 2H); 2.04 (m, 2H);

1.45 (m, 9H); ^{13}C NMR ($CDCl_3$): δ 161.13, 138.76, 133.72, 129.28, 127.87, 107.93, 92.3, 77.81, 72.77, 52.51, 49.26, 27.54, 26.73, 23.86.

1-(Phenylsulfonyl)-3-(trichloroacetamido)-4,5-epoxyhexane (79)

The epoxysulfone (79) was prepared by oxidation of (A) the sulfide (73), (B) sulfoxide diastereoisomers (76 and 77), and (C) the olefinic sulfone (78) with metachloroperoxybenzoic acid.

(A) Methylene chloride (75 mL), m-chloroperoxybenzoic acid (80-85%) (9.22 g, 42.72 mmol), and sulfide 73 (5.00 g, 14.24 mmol) were combined and magnetically stirred 15 h at ambient temperature, at which time TLC indicated the starting material had been consumed. Saturated aqueous sodium bisulfite (35 mL) was added and the mixture was stirred 30 min. The organic phase was washed successively with saturated aqueous sodium bicarbonate (25 mL) and brine (25 mL), then dried ($MgSO_4$), filtered, and evaporated at reduced pressure. Chromatography (silica gel, 100 g; 4:6 ethyl acetate/hexanes) of the crude material gave the epoxysulfone isomer 79 (5.39 g, 95%) with mp 167-168 °C. ^{1}H NMR (d6 benzene): δ 7.87 (m, 2H); 6.99 (m, 3H); 6.94 (bd, 1H); 3.91 (dq, J=2.01 Hz, J=5.00 Hz, 1H), 3.03 (m, 2H); 2.64 (dq, J=1.99 Hz, J=5.04 Hz, 1H); 2.16 (dd, J=1.98 Hz, J=4.18 Hz, 1H); 1.95 (m, 2H); 0.90 (d, J=5.28 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 162.16, 138.70, 133.99, 129.49, 127.98, 59.28, 52.57, 51.70, 48.40, 26.46, 16.81; FAB mass spectrum: m/z 400 ($M^{\cdot+}$), 365, 275.

(B) From the diastereoisomeric sulfoxides 76 and 77 (either individually or mixed) (2.13 g, 5.80 mmol), metachloroperoxybenzoic acid

(80-85%) (2.50 g, 11.60 mmol), and methylene chloride (50 mL) there was obtained epoxysulfone 79 (2.22 g, 96%).

(C) A magnetically stirred solution of the olefinic sulfone 78 (0.84 g, 2.19 mmol), metachloroperoxybenzoic acid (80-85%) (0.48 g, 2.22 mmol), and methylene chloride (25 mL) provided the epoxysulfone 79 (0.85 g, 97%).

1-Phenylthio-4-pentene (105)

A magnetically mixture solution of 5-bromopentene (104) (14.39 g, 96.55 mmol), benzenethiol (11.02 g, 100 mmol), and potassium carbonate (13.82 g, 100 mmol) in acetone (150 mL) were heated to reflux for 1 h. The mixture was filtered, and the acetone removed by evaporation at reduced pressure. The residue was dissolved in methylene chloride (100 mL) and the resultant solution was successively washed with potassium hydroxide (0.1 N, 50 mL) and brine (50 mL). The combined organic phase was dried ($MgSO_4$), filtered, and evaporated at reduced pressure to give 15.68 g (91%) 105 as a volatile, colorless liquid. An analytical sample was purified by radial chromatography (4 mm rotor, 1:9 methylene chloride/hexanes). ^1H NMR ($CDCl_3$): δ 7.23 (m, 5H); 5.79 (m, 1H); 4.96 (m, 2H); 2.89 (t, J=7.03 Hz, 2H); 2.00 (m, 2H); 1.74 (m, 2H).

1-Phenylsulfinyl-4-pentene (106)

1-Thiophenyl-4-pentene (106) (14.10 g, 79 mmol), sodium metaperiodate (16.90 g, 79 mmol) and methanol (100 mL) were combined and stirred at ambient temperature 16 h. The sodium iodate was filtered and the methanol was removed by evaporation at reduced pressure. Methylene chloride (100 mL) was added and the resultant solution was washed with water (3 x 50 mL), dried ($MgSO_4$), filtered, and evaporated at reduced pressure to give 15.0 g of the sulfoxide 106 (98%) as a yellow oil. ^1H NMR ($CDCl_3$): δ 7.44 (m, 5H); 5.70 (m, 1H); 5.01 (m 2H); 2.80 (t, J=7.69 Hz, 2H); 2.18 (m, 2H); 1.85 (m, 2H).

1-Phenylsulfinyl-5-iodo-pentan-4-ol (107) and 1-Phenylsulfinyl-4,5-epoxy-pentane (109)

A mixture of the sulfoxide 106 (3.54 g, 18.2 mmol), iodine (6.93 g, 27.3 mmol), potassium iodide (13.59 g, 81.9 mmol), and sodium bicarbonate (3.06 g, 36.4 mmol) in methylene chloride (130 mL) and water (165 mL) were stirred for 18 h at ambient temperature. Sodium thiosulfate was added until the mixture was colorless. The reaction was transferred to a separatory funnel and the layers were separated. The aqueous phase was extracted with methylene chloride (2 x 50 mL) and the combined organic solutions were dried ($MgSO_4$), filtered, and evaporated at reduced pressure. Chromatography (150 g silica gel; 6:4 ethyl acetate/hexanes) of the residue gave 1.53 g of recovered sulfoxide 106 (43%) and 0.43 g

of the less polar epoxide 109 (11%) epoxide ^{1}H NMR ($CDCl_3$): 7.49 (m 5H); 4.24 (m, 1H); 3.42 (m, 2H); 3.05 (m, 2H); 1.85 (m, 4H).

Continued elution gave the polar iodohydrin product 107 (1.17 g, 19%) as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 7.45 (m, 5H); 3.68 (m, 1H); 3.25 (m, 2H); 2.99 (t, J=7.47 Hz, 2H); 1.94 (m, 4H).

1-Phenylsulfinyl-3-(trichloroacetamido)-5-iodo-hexan-4-ol (98 and 100)

The reaction was run identically to that using 106. From 0.60 g of the sulfoxides 76 and 77 (1.63 mmol), iodine (o.62 g, 2.45 mmol); potassium iodide (1.22 g, 7.34 mmol); sodium bicarbonate (2.74 g, 3.26 mmol), methylene chloride (65 mL) and water (75 mL), there was obtained 0.51 g of the starting olefinic sulfoxides 76 and 77 (85%) and 0.1 g of the iodohydrins 98 and 100 (12%). ^{1}H NMR ($CDCl_3$): δ 7.41 (m 5H); 4.19 (m, 3H); 2.79 (m, 2H); 2.04 (m, 2H); 1.65 (s, 1H, exchangeable with D_2O); 1.52 (d, J=5.49 Hz, 3H).

(E)-1-(phenylthio)-1-acetoxy-3-(trichloroacetamido)-4-hexene (118)

Pummerer rearrangement of either the pure sulfoxide diastereoisomer (76 or 77) or of the mixture gave identical mixtures (6:4) of diastereoisomeric acetoxysulfides 118. A typical procedure from a diastereoisomeric mixture of sulfoxides follows.

Acetic anhydride and trifluoroacetic anhydride (2:1 v/v) were mixed and allowed to stand 5 h before use. (Note: It is important that freshly mixed anhydrides be used. When the anhydrides are allowed to stand for

a long period, the trace amount of acid present catalyzes condensation reactions among the anhydrides (indicated by a brownish-gold color) and Pummerer rearrangement fails.

The diastereoisomeric sulfoxides 76 and 77 (10.0 g, 27.25 mmol) were dissolved in acetic anhydride (20 mL) and the solution of mixed anhydrides (34.69 g, 54.50 mmol TFAA) was quickly added. The colorless solution was allowed to stir 15 min at ambient temperature before slow, dropwise addition of 2,6-lutidine (11.66 g, 109 mmol). Addition of lutidine produces a slight exothermic reaction, and the initially colorless solution became a red-orange color. The reaction was stirred for 5 h, then transferred to a large Erlenmeyer flask with methylene chloride. Saturated aqueous sodium bicarbonate (50 mL) was cautiously added and then solid sodium bicarbonate was added until the reaction mixture ceased foaming. The layers were separated and the aqueous portion was extracted with methylene chloride (2 x 50 mL). The combined organic extracts were washed with 10% HCl (3 x 25 mL), dried ($MgSO_4$), filtered, and evaporated under reduced pressure. The residue was chromatographed (silica gel, 200 g; 2:8 ethyl acetate/hexanes) to give 11.03 g (99%) of 118 as a gold oil. The product, homogeneous by TLC was shown by ^1H and ^{13}C NMR to be a 6:4 mixture of diastereoisomers. Attempted separation of the isomers using a variety of chromatographic techniques was unsuccessful. ^1H NMR (benzene d-6): δ 7.60 (m, 2H); 7.05 (m, 3H); 6.32 (m, 1H); 5.26 (m, 2H); 4.60 (m, 1H); 1.96 (m, 2H); 1.73 (d, J=10.99 Hz, 3H); 1.42 (m, 3H); ^{13}C NMR ($CDCl_3$): δ 169.91, 169.20, 160.86, 134.42, 133.94, 129.01, 128.68, 128.52, 127.39, 77.65, 76.57, 50.62, 39.08,

20.98, 17.68. IR 3341, N-H str.; 1711, C=O str. (ester); 1675, C=O str. (amide); 835 cm^{-1}, C-Cl str.; FAB mass spectrum: m/z 351 ($M^{\cdot+}$-59), 300, 216.

(E)-3-(Trichloroacetamido)-4-hexenal (120)

A mixture of 118 (8.0 g, 19.56 mmol), cupric chloride dihydrate (6.69 g, 39.12 mmol), acetonitrile (150 mL), and water (10 mL) were heated at reflux 15 min. The blue solution immediately became a very dark green color and TLC indicated the reaction had gone to completion. The acetonitrile was evaporated at reduced pressure, and the mixture was transferred to a separatory funnel with methylene chloride (50 mL) and water (4 x 50 mL). The layers were separated, and the organic phase was repeatedly washed with water until the aqueous extracts were no longer green in color. The residue was chromatographed (silica gel, 250 g; 4:6 ethyl acetate/hexanes) to give 4.32 g of 120 (86%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 9.73 (bs, 1H); 7.55 (bs, 1H); 5.94 (m, 2H); 5.13 (m, 1H); 3.15 (d, J=5.27 Hz, 2H); 1.97 (d, J=4.83 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 200.03, 160.81, 129.12, 128.79, 127.60, 126.57, 92.28, 48.61, 46.99, 17.35.

(±)-N-(Trichloroacetyl)daunosamine (89) and (±)-N-(Trichloroacetyl)-3-epidaunosamine (91)

To a solution of the aldehyde 120 (4.00 g, 15.56 mmol), and trimethylamine-N-oxide monohydrate (3.46 g, 31.12 mmol), dissolved in acetone (50 mL) and water (5 mL), was added 0.5 mL of the stock solution of osmium tetraoxide. The mixture was magnetically stirred at ambient temperature for 12 h at which time saturated sodium bisulfite (25 mL) and methylene chloride (100 mL) were added. The layers were separated and the aqueous phase was extracted with methylene chloride (2 x 35 mL). The combined organic solutions were successively washed with saturated sodium bicarbonate (1 x 25 mL) and brine (1 x 25 mL), then dried ($MgSO_4$), filtered, and evaporated at reduced pressure. The residue (4.25 g, 94%) was chromatographed (silica gel, 150 g; 1:1 ethyl acetate/hexanes) to give 1.70 g (40%) of 91 (epidaunosamine) with mp 141-146 °C. ^{1}H NMR (d4 MeOH): δ 5.29 (m, 1H); 4.29 (q, J=12.75 Hz, 1H); 3.94 (q, J=6.37 Hz, 1H); 3.41 (d, J=5.27 Hz, 1H); 2.31 (dt, J=14.72 Hz, J=3.74 Hz, 1H); 1.66 (m, 1H); 1.22 (d, J=6.60 Hz, 3H); FAB mass spectrum: m/z 292 ($M^{\cdot+}$), 274, 257, 240, 207.

Continued elution gave 2.55 g (60%) (±)-N-(trichloroacetyl)daunosamine 89 as a pale yellow oil. ^{1}H NMR (d6 acetone/D_2O): δ 5.29 (m, 1H); 4.23 (dq, J=1.10 Hz, J=6.7 Hz, 1H); 4.03 (q, J=3.52 Hz, 1H); 3.43 (m, 1H); 2.29 (dt, J=4.18 Hz, J=14.06 Hz, 1H); 1.61 (m, 1H); 1.14 (d, J=6.59 Hz, 3H); FAB mass spectrum: m/z 292 ($M^{\cdot+}$), 274, 240, 207.

(±)-Methyl N-(Trichloroacetyl)daunosaminide (121)

The methyl glycoside was prepared by dissolving 89 (1.0 g, 3.44 mmol) in dry methanol (10 mL) at 0 °C and bubbling dry hydrogen chloride into the magnetically stirred solution 0.5 min. The colorless solution was warmed to ambient temperature and stirred an additional 0.5 h. The methanol was evaporated at reduced pressure in a cool bath and the residue was chromatographed (silica gel, 50 g; 6:4 ethyl acetate/hexanes) to give 1.04 g (82%) of methyl N-(trichloroacetyl)daunosaminide (121) as a yellow oil. ^{1}H NMR (d6 benzene): δ 7.00 (bs, 1H); 4.41 (d, J=3.73 Hz, 1H); 4.22 (m, 1H); 3.81 (m, 1H); 3.53 (q, J=6.60 Hz, 1H); 3.08 (s, 3H); 1.83 (dd, J=5.71 Hz, J=12.96 Hz, 1H); 1.45 (dd, J=3.29 Hz, J=12.53 Hz, 1H); 0.99 (d, J=6.60 Hz, 3H).

(±)-Methyl N,O-Bis(trichloroacetyl)daunosaminide (122)

Pyridine (1 mL) and freshly distilled trichloroacetyl chloride (0.32 g, 1.75 mmol) were added to a magnetically stirred solution of 121 (0.50 g, 1.64 mmol) in anhydrous ether (20 mL) at 0 °C. After 0.5 h, saturated aqueous sodium bicarbonate (15 mL) was added and the mixture was stirred 2 h. The layers were separated and the aqueous phase was extracted with ether (3 x 25 mL). The solvent was evaporated at reduced pressure and the residue was chromatographed (silica gel, 50 g; 4:6 ethyl acetate/hexanes) to give 0.67 g (90%) of 122 as a yellow-gold oil. ^{1}H NMR ($CDCl_3$): δ 6.58 (bd, 1H); 5.29 (m, 1H); 4.90 (m, 1H); 4.62 (dq,

J=10.0 Hz, J=1.53 Hz, 1H); 4.14 (q, J=6.40 Hz, 1H); 3.39 (s, 3H); 2.00 (m, 2H); 1.24 (d, J=6.59 Hz, 3H).

(±)-Methyl N-(Trichloroacetyl)-3-epidaunosaminide

The methyl glycoside was prepared as was described for 121. Reaction of 0.5 g (1.72 mmol) of 91 provided 0.45 g (86%) of the methyl glycoside as a yellow, low-melting solid (<50 °C). ^{1}H NMR ($CDCl_3$): δ 8.44 (bd, 1H); 4.84 (m, 1H); 4.16 (m, 2H); 3.76 (m, 1H); 3.52 (s, 3H); 2.04 (m, 2H); 1.27 (d, J=6.59 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 164.00, 78.41, 73.59, 69.32, 64.27, 54.92, 49.43, 32.74, 17.73.

(±)-Methyl N,O-Bis(trichloroacetyl)-3-epidaunosaminide

The derivatization was done analogously to 122. From 0.45 g (1.48 mmol) of the glycoside, there was obtained 0.61 g (92 %) of the bis(trichloroacetyl) derivative as a gold oil. ^{1}H NMR ($CDCl_3$): δ 8.42 (bs, 1H); 4.87 (d, J=11.2 Hz, 1H); 4.09 (m, 1H); 3.46 (m, 4H); 2.40 (dt, J=20.80 Hz, J=3.59 Hz, 1H); 1.60 (m, 1H); 1.26 (d, J=6.37 Hz, 3H).

1-(Phenylthio)-1-acetoxy-3-N-(trichloroacetamido)hexan-4,5-diol (123)

To a magnetically stirred solution of 118 (3.62 g, 8.85 mmol) in acetone (100 mL) and water (5 mL) was added 0.5 mL of the osmium tetraoxide stock solution and trimethylamine N-oxide (1.97 g, 17.70

mmol). The solution was heated at reflux for 1 h. Saturated sodium bisulfite (35 mL) and methylene chloride (50 mL) were added and the mixture was stirred until the dark color had faded. The layers were separated and the aqueous phase was extracted with methylene chloride (3 x 25 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$), filtered, and evaporated under reduced pressure. The residue was chromatographed (silica gel, 50 g; ethyl acetate) to give 123 (3.59 g, 92%) of a 6:4 mixture of isomers, as a yellow setographed (silica gel, 100 g; 6:4 ethyl acetate/hexanes) to give N-(trichloroacetyl)-3-epidaunosamine (91) (0.97 g, 38%) as colorless crystals with mp 141-146 °C.

Continued elution yielded an anomeric mixture of 1-phenyl N-(trichloroacetyl)-1-thiodaunosaminide (124) (1.91 g, 57%)as a yellow solid with mp 97-103 °C. ^1H NMR ($CDCl_3$): δ 7.73 (m, 5H); 6.90 (bd, 1H); 5.07 (m, 1H); 4.26 (m, 1H); 3.12 (m, 2H); 2.06 (d, J=2.42 Hz, 3H); 1.20 (d, J=5.94 Hz, 3H); ^{13}C NMR (d6 acetone): δ 134.51, 130.18, 128.77, 76.87, 68.64, 53.47, 52.22, 26.87, 19.66; FAB mass spectrum: m/z 384 ($M^{\cdot+}$), 275.

Phenyl Sulfenyl Chloride

Diphenyldisulfide (106.97 g, 490 mmol), triethylamine (10 mL), and freshly distilled carbon tetrachloride (500 mL) were magnetically stirred at 0 °C for 30 min. Sulfuryl chloride (71.55 g, 530 mmol) was slowly added over a two hour period, at which time the reaction became red-orange

in color. The solution was stirred 1.5 h at ambient temperature and the solvent was evaporated at reduced pressure in a cool bath (< 50 °C). The residue was vacuum distilled to yield phenyl sulfenyl chloride (127 g, 90%) bp 80 °C/11mm.

Allenyl Sulfoxide (126)

Freshly distilled propargyl alcohol (50.18g, 895 mmol), triethylamine (89.79 g, 889 mol), and distilled methylene chloride (900 mL) were chilled in a dry ice/acetone bath to an internal temperature of <-50 °C. Methylene chloride was used rather than ether as the procedure recommended, and a greater volume was used since the large amount of triethylamine hydrochloride salt produced is slightly more soluble in this solvent. Phenyl sulfinyl chloride (127 g, 889 mol) was added slowly, over a 3 h period to the alcohol solution while maintaining the internal reaction temperature at -50 °C or lower. Once the addition was completed, the mixture was allowed to warm to ambient temperature and stir an additional 2 h. The mixture was filtered to remove the triethylamine hydrochloride and the methylene chloride solution was washed with dilute hydrochloric acid (10%; 4 x 50 mL), dried ($MgSO_4$), filtered, and evaporated at reduced pressure in a cool bath (<35 °C). The residue was chromatographed (silica gel, 300 g; 8:2 to 1:1 hexanes/ ethyl acetate) and the resultant product was evaporated at reduced pressure in a cool bath (<35 °C) to give 132.10 g (90%) 126 as a pale yellow syrup. The product was stored in the refrigerator until it was used in the next

reaction; at this temperature the material was stable for at least 2 weeks. ^{1}H NMR ($CDCl_3$): δ 7.45 (m, 5H); 6.01 (t, J=6.37 Hz, 1H); 5.25 (d, J=5.93 Hz, 2H).

(3E)-4-Methyl-3,5-hexadien-2-one (128)

Crotyl alcohol (44.39 g, 616 mmol) in benzene (75 mL) was added to a suspension of sodium hydride (50% suspension in mineral oil; 31.20 g, 650 mmol; washed with hexanes to remove the mineral oil, 3 x 35 mL) in dry benzene (500 mL), chilled to 0 °C. The magnetically stirred mixture was magnetically stirred for 30 min before the allenyl sulfoxide 126 (114.09 g, 696 mmol) in benzene (300 mL) was added dropwise while maintaining an internal temperature of 0 °C. During addition of the allenyl sulfoxide 126 to the alkoxide solution, the mixture became very dark in color. The reaction was warmed to ambient temperature and stirred an additional 3 h. Water (200 mL) was cautiously added to the dark solution to destroy excess sodium hydride. The layers were separated, and the aqueous phase was extracted with methylene chloride (3 x 75 mL). The combined organic solutions were dried ($MgSO_4$), filtered, and evaporated at reduced pressure in a bath that did not exceed 30 °C. A catalytic amount of zinc carbonate (1 g) was added and the dark material was flash distilled under a water aspirator vacuum. The bath was heated to 160-175 °C to effect rearrangement of the initial adduct to the dienone 128 which distilled at 70-75 °C/15-19 mm to provide 62.71 g, 82% as a colorless liquid with a strong odor. ^{1}H NMR ($CDCl_3$): δ 7.64 (m, 1H);

5.96 (m, 3H); 2.10 (m, 6H). The dienone 128 is unstable and was reduced immediately immediately.

(3E)-4-Methyl-3,5-hexadien-2-ol (129)

The dienone 128 (30 g, 272.7 mmol) in ether (250 mL) was added dropwise to a solution of lithium aluminum hydride (5.17 g, 136.4 mmol) in ether (150 mL) and the green solution was stirred for 12 h. The excess LAH was destroyed by sequentially adding with water (5.2 mL), aqueous potassium hydroxide (15%; 5.2 mL), and water (15.6 mL) to the reaction. The mixture was filtered and the filtrate was evaporated at reduced pressure, in a cool bath (<30 °C). The residue was chromatographed (silica gel, 300 g; 8:2 hexanes/ethyl acetate) to give 129 (30.23 g, 99%) as a colorless liquid with a pleasant odor. The dienol 129, when purified, is stable at ambient temperature for several months. ^{1}H NMR ($CDCl_3$): δ 6.58 (m, 1H); 5.06 (m, 3H); 1.81 (m, 3H); 1.69 (bs, 1H); 1.26 (d, J=6.25 Hz, 3H).

(4E)-3-Methyl-3-(trichloroacetamido)-1,4-hexadiene (130)

The dienol 129 (10 g, 89.28 mmol) in ether (20 mL) was added to a solution of potassium hydride (35% suspension in mineral oil; 2.04 g, 17.84 mmol; washed with hexanes to remove the mineral oil, 3 x 10 mL) and 18-crown-6 (4.72 g, 17.84 mmol) in ether (100 mL). The solution was stirred 30 min while the color gradually turned from colorless to

brownish-gold. The reaction was then chilled to -20 °C, and freshly distilled trichloroacetonitrile (13.73 g, 95.0 mmol) in ether (25 mL) was added dropwise. During addition of the nitrile, the solution became dark brown in color. The reaction was warmed to ambient temperature and stirred for 24 h. Methanol (25 mL) and hexanes (50 mL) were added to the reaction and the suspension was filtered through Celite and evaporated at reduced pressure. The imidate was dissolved in xylenes (75 mL) and heated at reflux 12 h. The xylenes were evaporated at reduced pressure and the residue (130) was chromatographed (silica gel, 200 g; 8:2 hexanes/ethyl acetate) to give (20.39 g, 89%) of the amide 130 as a gold oil. ^{1}H NMR ($CDCl_3$): δ 6.61 (bs, 1H); 5.87 (m, 3H); 5.18 (m, 2H); 1.74 (d, J=3.52 Hz, 3H); 1.60 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 159,89, 140.33, 133.12, 126.08, 113.95, 69.85, 24.29, 17.73; IR (CH_2Cl_2): 3423, N-H str.; 3055 and 2987, C=C str.;1723, C=O str.; 1500 and 1265 cm^{-1}, N-H bend.

(E)-1-(Phenylthio)-3-methyl-3-(trichloroacetamido)-4-hexene (131)

The procedure employed to prepare 73 was used. The amide 130 (10.00 g, 38.71 mmol), AIBN (1.59 g, 9.68 mmol), and benzenethiol (4.26 g, 38.71 mmol) were heated to 88-92 °C for 24 h. Methylene chloride (50 mL) was added to the dark colored reaction mixture which was then transferred to a separatory funnel and washed with aqueous potassium hydroxide (5%; 3 x 25 mL) until the odor of benzenethiol was no longer detected. The combined organic solutions were dried ($MgSO_4$), filtered,

and evaporated at reduced pressure. The residue was chromatographed (silica gel, 200 g; 8:2 hexanes/ethyl acetate) to give the sulfide 131 as a gold oil (12.48 g, 88%) and the starting amide 130 (1.02 g, 10%). ^{1}H NMR ($CDCl_3$): δ 7.41 (m, 5H); 6.76 (bs, 1H); 5.59 (m, 2H); 2.86 (t, $\underline{J}$=7.91 Hz, 2H); 2.19 (m, 2H); 1.50 (m, 6H); ^{13}C NMR ($CDCl_3$): δ 160.53, 148.46, 136.75, 133.72, 129.22, 128.95, 126.19, 125.32, 58.20, 38.54, 29.65, 28.35, 24.45, 17.79; IR (CH_2Cl_2): 3422, N-H str.; 3033, C-H str. (olefin); 1718' C=O str.; 1507 and 1264 cm^{-1}, N-H bend.

Anal. Calcd. for $C_{15}H_{18}Cl_3NOS$: C, 49.13; H, 4.95; N, 3.82. Found: C, 50.01; H, 5.14, N, 3.79.

(E)-1-Phenylsulfinyl-3-methyl-3-(trichloroacetamido)-4-hexene (132)

The selenium dioxide-hydrogen peroxide procedure used for preparation of the sulfoxides 76 and 77 was employed. From the sulfide 131 (6.00 g, 16.37 mmol), selenium dioxide (1.82 g, 16.37 mmol), hydrogen peroxide (30%; 1.86 g, 16.37 mmol), and water (8.2 mL) there was obtained a 1:1 mixture of inseparable diastereoisomeric sulfoxides 132 as a yellow syrup (5.32 g, 85%). ^{1}H NMR ($CDCl_3$): δ 7.48 (m, 5H); 7.14 (bs, 1H); 5.52 (m, 2H); 2.84 (m, 2H); 2.16 (m, 2H); 1.69 (d, $\underline{J}$=4.84 Hz, 3H); 1.46 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 160.37, 143.04, 133.29, 133.07, 131.07, 129.22, 125.54, 123.97, 57.28, 51.10, 31.01, 24.72, 24.51, 24.43, 17.79, 17.57; IR (CH_2Cl_2): 3421 and 3239, N-H str.; 3032, C-H str. (olefin); 1718, C=O str,; 1670, C=C str.; 1509 and 1265, N-H bend; 1039 cm^{-1}, S=O str.

(E)-1-(Phenylthio)-1-acetoxy-3-methyl-3-(trichloroacetamido)-4-hexene (133)

The Pummerer rearrangement was conducted as previously described for the preparation of 118. The sulfoxides 132 (5.00 g, 13.08 mmol) were dissolved in acetic anhydride (50 mL) and a solution of the mixed anhydrides (2:1 acetic anhydride:trifluoroacetic anhydride; 16.7 mL; 5.49 g TFAA, 26.16 mmol) were quickly added. The colorless solution was stirred 30 min before careful addition of 2,6-lutidine (5.60 g, 52.32 mmol). Upon addition of the lutidine a mild exothermic reaction ensued and the color became red-orange. The solution was stirred for 5 h before adding methylene chloride (35 mL) and saturated aqueous sodium bicarbonate (25 mL). Additional solid sodium bicarbonate was added until foaming ceased. The layers were separated and the aqueous phase was extracted with methylene chloride (35 mL). The combined organic solutions were washed with aqueous hydrochloric acid (10%; 2 x 25 mL), dried ($MgSO_4$), filtered, and evaporated at reduced pressure to give 133 (4.95 g, 89%) as a yellow syrup. ^1H NMR ($CDCl_3$): δ 7.40 (m, 5H); 7.09 (bd, 1H); 6.16 (m, 1H); 5.52 (m, 2H); 2.39 (m, 2H); 2.04 (3, 3H); 2.00 (s, 3H); 1.71 m, 3H); 1.52 (d, J=1.75 Hz, 3H).

(E)-3-Methyl-3-(trichloroacetamido)-4-hexenal (134)

A mixture of the acetoxysulfide 133 (3.00 g, 7.06 mmol), acetonitrile (50 mL), water (10 mL) and cupric chloride dihydrate (2.41 g, 14.12 mmol) was heated on a steam bath until the blue colored solution became black (2 min). The solvents were evaporated under reduced pressure and the solid residue was chromatographed (silica gel, 150 g; 9:1 hexanes/ethyl acetate) to give the aldehyde 134 (1.89 g, 99%) as a colorless syrup. ^{1}H NMR ($CDCl_3$): δ 9.68 (t, J=2.2 Hz, 1H); 6.94 (bs, 1H); 5.63 (m, 2H); 2.99 (d, J=2.42, 2H); 1.69 (t, J=1.98 Hz, 3H); 1.53 (s, 3H).

(±)-Methyl N-(Trichloroacetyl)-3-epivancosaminide (136) and (±)-Methyl N-(Trichloroacetyl)vancosaminide (135)

A magnetically stirred solution of the aldehyde 134 (1.50 g, 5.54 mmol), trimethylamine N-oxide monohydrate (1.23 g, 11.08 mmol), the osmium tetraoxide stock solution (0.5 mL), acetone (30 mL), and water (3 mL) were stirred at ambient temperature 12 h. Methylene chloride (60 mL) and saturated aqueous sodium bisulfite (10 mL) were added and stirred 30 min. The layers were separated and aqueous phase was extracted with methylene chloride (2 x 30 mL). The combined organic solutions were dried ($MgSO_4$), filtered, and evaporated at reduced pressure in a cool bath (<5 °C). The inseparable sugars were dissolved in anhydrous methanol (25 mL) and chilled in an ice/salt bath 15 min. Hydrogen chloride was

bubbled through the solution (15 sec) and it was warmed to ambient temperature and stirred 1 h. The residue (3:7 mixture; 85%) was chromatographed (silica gel, 100 g; 8:2 hexanes/ethyl acetate) to give (±)-methyl N-(trichloroacetyl)-3-epivancosaminide 136 (0.49 g, 28%) as cream colored crystals with mp 92-96 °C. ^{1}H NMR ($CDCl_3$): δ 5.13 (dd, J=12.31 Hz, J=18.02 Hz, 1H); 4.12 (m, 1H); 3.37 (s, 3H); 3.04 (dd, J=9.01 Hz, J=14.72 Hz, 1H); 2.02 (m, 2H); 1.48 (d, J=4.39 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 165.48, 104.09, 84.37, 65.03, 64.97, 55.71, 44.55, 29.71, 22.83, 20.17.

Continued elution gave (±)-methyl N-(trichloroacetyl)vancosaminide 135 (1.15 g,65%) as light yellow crystals with mp 86-90 °C. ^{1}H NMR ($CDCl_3$): δ 8.44 (bs, 1H); 4.78 (d, J=3.51 Hz, 1H); 4.06 (q, J=6.37 1H); 3.46 (d, J=6.40 Hz, 1H); 3.35 (s, 3H); 1.92 (m, 2H); 1.56 (s, 3H); 1.22 (t, J=3.08 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 160.48, 97.97, 88.97, 68.50, 63.42, 55.76, 54.84, 35.12, 21.69, 16.87.

(E)-1-(Phenylsulfonyl)-1-acetoxy-3-(trichloroacetamido)-4-hexene (137)

meta-Chloroperoxybenzoic acid (80-85%; 0.53 g, 2.44 mmol) was added to a solution of the acetoxysulfide 118 (1.00 g, 2.44 mmol) in methylene chloride (35 mL). Analysis of a TLC indicated the reaction was complete in <5 min and saturated aqueous sodium bisulfite (10 mL) was added and the mixture was stirred 30 min. The layers were separated and the aqueous phase was extracted with methylene chloride (10 mL). The combined organic solutions were dried ($MgSO_4$), filtered, and evaporated at reduced

pressure. Chromatotron chromatography of the residue (2 mm rotor) with 1:1 ethyl acetate/hexanes gave the olefinic acetoxysulfone 137 as a yellow syrup. ^{1}H NMR ($CDCl_3$): δ 7.74 (m, 5H); 6.66 (bd, 2H); 5.65 (m, 3H); 4.53 (m, 1H); 2.39 (m, 2H); 1.96 (s, 3H); 1.46 (d, J=38.01 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 167.90, 161.97, 134.64, 129.55, 129.28, 127.82, 126.89, 82.91, 82.31, 50.29, 49.26, 31.93, 20.28, 20.17, 17.73; IR ($CDCl_3$): 3409, N-H str.; 1715, C=O str., ester; 1675 and 1771 C=O str., amide; 1266 and 1050, C-O-C str.; 1325, S=O str., symmetric; 1154 cm^{-1}, S=O str., asymmetric.

Anal.Calcd. for $C_{16}H_{18}Cl_3NO_6S$: C, 42.02; H, 3.95; N, 3.05. Found: C, 42.22; H, 4.15; N, 2.99.

1-(Phenylsulfonyl)-1-acetoxy-3-(trichloroacetamido)-4,5-epoxyhexane (138)

Treatment of (A) the acetoxysulfide 118 or (B) the acetoxysulfone 137 with excess metachloroperoxybenzoic acid gave the epoxide 138.

(A) From the acetoxysulfide 118 (1.02 g, 2.49 mmol), and metachloroperoxybenzoic acid (80-85%; 1.07 g, 49.80 mmol) in methylene chloride (35 mL), there was obtained the epoxysulfone 138 (1.07 g, 98%) as a colorless solid with mp 113-116 °C. ^{1}H NMR ($CDCl_3$): δ 7.76 (m, 5H); 6.76 (bm, 1H); 5.91 (dq, J=3.74 Hz, J=10.55 Hz, 1H); 4.39 (m, 1H); 2.88 (m, 1H); 2.48 (m, 1H); 1.98 (s, 3H); 1.96 (s, 3H); 1.31 (d, J=4.84 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 168.55, 167.69, 161.99, 135.24, 134.69, 129.49, 129.28, 92.06, 82.31, 59.61, 58.91, 46.72, 45.80, 30.52, 30.19, 20.33,

17.08, 16.76; IR ($CDCl_3$): 3400, N-H str.; 1770 and 1719, C=O str.; 1265 and 1050, C-O-C str., ester; 1326, S=O str., symmetric; 1156 cm^{-1}, S=O str., asymmetric.

(B) From the olefinic acetoxysulfone 137 (0.91 g, 2.14 mmol) and metachloroperoxybenzoic acid (0.46 g, 2.14 mmol), in methylene chloride (35 mL) there was obtained the epoxysulfone 138 (0.92 g, 97%).

(±)-Methyl 3-N-(Trichloroacetamido)-α-ribo-furanoside (139a)

Sodium hydroxide (0.26 g, 6.52 mmol) was added to a solution of the acetoxysulfone 138 (1.43 g, 3.24 mmol) in methanol (25 mL) and water (2 mL). After 1 h, analysis of a TLC indicated the reaction was complete. Brine (10 mL) and methylene chloride (25 mL) were added and the layers were separated. The aqueous phase was extracted with methylene chloride (2 x 15 mL) and the combined organic solutions were dried ($MgSO_4$), filtered, and evaporated at reduced pressure. The residue was chromatographed on a chromatotron (2 mm rotor) with 6:4 hexanes/ethyl acetate to give the furanoside 139a (0.94 g, 96%) as a low melting yellow solid (<50 °C). ^1H NMR ($CDCl_3$): δ 7.63 (bd, 1H); 5.19 (m, 2H); 4.64 (t, J=8.13 Hz, 1H); 4.02 (t, J=2.41 Hz, 1H); 3.40 (s, 3H); 2.42 (ddd, J=13.62 Hz, J=7.47 Hz, J=4.39 Hz, J=4.18 Hz, 1H); 1.96 (d, J=13.84 Hz, 1H); 1.50 (d, J=6.59 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 161.02, 104.95, 90.06, 67.97, 54.63, 50.67, 38.92, 18.55.

(±)-Methyl N,O-bis(trichloroacetyl)-3-amino-α-*ribo*-furanoside (139b)

From the furanoside 139a (0.50 g, 1.64 mmol), trichloroacetyl chloride (2 mL) and pyridine (2 mL), in ether (15 mL), there was obtained the bis-(trichloroacetyl) furanoside 139b (0.70 g, 95%) as a yellow syrup. ^{1}H NMR (*d*6 benzene): δ 7.56 (bd, 1H); 5.01 (dq, *J*=6.59 Hz, *J*=2.86 Hz, 1H); 4.63 (d, *J*=4.18 Hz, 1H); 4.43 (t, *J*=8.57 Hz, 1H); 3.65 (t, *J*=2.64 Hz, 1H); 3.06 (s, 3H); 1.92 (ddd, *J*=18.23 Hz, *J*=4.61 Hz, *J*=4.17 Hz, *J*=7.69 Hz, 1H); 1.47 (d, *J*=13.63 Hz, 1H); 1.22 (d, *J*=6.81 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 174.95, 161.62, 105.88, 88.48, 77.65, 55.49, 51.32, 39.08, 16.32.

Methyl N-trichloroacetyl-α-ristosaminide (140)

The furanoside 139a (0.91 g, 2.98 mmol) in aqueous acetic acid (50%, 20 mL) was heated on a steam bath for 20 min. Analysis of a TLC indicated that the hydrolysis of the methyl glycoside residue had occurred. The solvent was evaporated, and the residue was taken up in methylene chloride (25 mL) and washed with saturated aqueous sodium bicarbonate (2 x 15 mL). The organic solution was dried ($MgSO_4$), filtered and evaporated at reduced pressure. The residue was dissolved in anhydrous methanol (15 mL), chilled in an ice/salt bath for 15 min, then dry hydrogen chloride was bubbled into the reaction for 15 sec. The solution was warmed to room temperature and allowed to stand 1 h. The reaction was transferred to a separatory funnel with methylene chloride (25 mL) and

the resultant organic solution was washed with saturated aqueous sodium bicarbonate (2 x 15 mL), then dried ($MgSO_4$), filtered, and evaporated at reduced pressure. The residue (85%; 1:3 ratio) was chromatographed (silica gel, 50 g; 6:4 hexanes/ethyl acetate) to give 140 (0.26 g, 28%) as a yellow solid with mp 94-97 °C. ^{1}H NMR ($CDCl_3$): δ 8.52 (bs, 1H); 4.74 (m, 1H); 4.18 (m, 1H); 3.64 (m, 1H); 3.38 (s, 3H); 2.57 (bs, 1H); 2.01 (m, 1H); 1.65 (m, 1H); 1.28 (d, J=5.71 Hz, 3H).

Continued elution provided the starting furanoside 139a (0.51 g, 56%) as a low melting, yellow solid (<50 C).

4-Vinyl-2-azetidinone (145a)

Butadiene (144a) (approximately 17.00 g, 214 mmol) was condensed in a pressure bottle containing ether (25 mL) and immersed in a carbon tetrachloride/dry ice bath (-20 °C). Cold chlorosulfonyl isocyanate (28.30 g, 199.94 mmol) was quickly added by pipet and the bottle was sealed. The solution was allowed to slowly come to room temperature over a 3 h period, then stand undisturbed behind a safety shield for 2 d. The red solution was chilled in a dry ice/acetone bath (-78 °C) prior to careful opening of the pressure bottle. The contents were poured into a dry ice jacketed dropping funnel with ether washings and added dropwise to a mixture of 300 mL aqueous sodium bisulfite and 100 mL of ether in an ice/salt bath. A basic pH was maintained by addition of 6 N sodium hydroxide as needed by litmus paper determination. After addition was complete, the mixture was stirred 30 min. The layers were

separated and the aqueous phase was extracted with methylene chloride and ether (50 mL each), dried (Na_2SO_4), and evaporated at reduced pressure in a cool water bath to give 19.00 g (98%) of the crude azetidinone as a pale yellow liquid suitable for the next reaction. For an analytical sample, the material was purified through column chromatography (300 g florisil) with 7:3 hexanes/ethyl acetate to give 18.85 g (97%) of pure 145a as a colorless liquid. ^{1}H NMR ($CDCl_3$): δ 6.95 (bs, 1H); 5.83 (m, 1H); 5.14 (m, 2H); 4.00 (m, 1H); 3.25 (ddd, $\underline{J}$=1.76 Hz, $\underline{J}$=5.05 Hz, $\underline{J}$=14.73 Hz, 1H); 2.55 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 167.80, 137.45, 116.44, 49.10, 44.71; IR (CH_2Cl_2): 3409 and 3269, N-H str.; 3090 and 3008, C-H str.; 1758, C=O str.; 1645, C=C str.; 990 and 930 cm^{-1}, C-H bend (olefin).

4-Vinyl-4-methyl-2-azetidinone (145b)

Isoprene (144b) (14.42 g, 21.68 mmol) was added to a pressure bottle containing ether (50 mL). Cold chlorosulfonyl isocyanate (28.31 g, 200.00 mmol) was added and the bottle was sealed and allowed to stand for 2 d. The yellow solution was worked-up in a manner similar to 145a and purified on a florisil column eluting with 1:1 ethyl acetate/hexanes to give 22.78 g (89%) of **145b** as a colorless liquid. ^{1}H NMR ($CDCl_3$): δ 6.71 (bs, 1H); 5.41 (m, 1H); 3.88 (m, 2H); 2.80 (m, 2H); 1.71 (s, 3H).

4,4-Dimethyl-2-azetidinone (145c)

Isobutylene (144c) (8.91 g, 158.88 mmol) was condensed in a pressure bottle containing ether (50 mL) and immersed in a carbon tetrachloride/dry ice bath (-20 °C). To this solution was added chlorosulfonyl isocyanate (17.69 g, 125 mmol) and the bottle was then sealed and allowed to slowly warm to room temperature and stand for 2 d. The colorless reaction mixture was worked-up in a manner similar to 145a. Prior to separation and extraction the mixture was stirred an additional 2 h at room temperature due to the slow rate of hydrolysis of the N-chlorosulfonyl azetidinone intermediate. Purification on a florisil column with 1:1 ethyl acetate/hexanes provided 11.89 g (96%) of 145c as a colorless liquid. ^{1}H NMR ($CDCl_3$): δ 7.10 (bs, 1H); 2.72 (d, J=1.76 Hz, 2H); 1.43 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 167.42, 51,48, 50.02, 27.10; IR (CH_2Cl_2): 3404 and 3249, N-H str.; 1754, C=O str.; 1374 and 1352, C-H str.(gem-dimethyl); 1174 and 1154 cm^{-1}, C-H str. (gem-dimethyl).

4-Acetoxy-2-azetidinone (145d)

Vinyl acetate (144d) (14.01 g, 162.74 mmol) was added to a pressure bottle containing ether (50 mL) and immersed in a dry ice acetone bath (-20 °C). Cold chlorosulfonyl isocyanate (21.23 g, 150.00 mmol) was added, the bottle was sealed, and it was allowed to warm to -20 °C for 2 h. The bottle and its contents were then placed in a freezer (-17 °C), with a stainless steel beaker inverted over the bottle, and allowed

to stand undisturbed for 2 d. Upon warming to -17 °C the solution became a reddish color. The reaction mixture was worked-up in a manner similar to 145a. The crude product, 15.48 g (80%), was obtained as a pale yellow liquid without need for purification. ^{1}H NMR ($CDCl_3$): δ 6.62 (bs, 1H); 5.79 (dd, $\underline{J}$=1.53 Hz, $\underline{J}$=3.96 Hz, 1H); 3.13 (m, 2H); 2.08 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 171.10, 165.20, 73.04, 67.36, 44.93, 20.71. IR (neat) 3301, N-H str.; 1781, C=O str., lactone; 1749, C=O str., ester; 1267 and 1047 cm^{-1}, C-O-C str.

Methyl-(3-benzamido)-pent-4-enoate (146)

The azetidinone 145a (18.00 g, 185.57 mmol) was dissolved in 200 mL cold anhydrous methanol (ice/salt bath) and dry hydrogen chloride was bubbled into the solution 30 min. Analysis of a TLC showed no starting material remained. The methanol was evaporated at reduced pressure in a cool water bath. The crude amine hydrochloride salt was dissolved in ether (200 mL) and pyridine (45 mL) and stirred in an ice bath for 15 min. Benzoyl chloride (26.71 g, 190 mmol) was slowly added and the mixture was allowed to come to room temperature, then stir for 5 h. Saturated aqueous sodium bicarbonate (50 mL) was added and additional solid sodium bicarbonate until foaming ceased. The layers were separated and the organic phase was washed with 10% hydrochloric acid (3 x 50 mL), dried ($MgSO_4$), filtered, and evaporated at reduced pressure to give 41.07 g (95%) to 146 as a colorless, low melting solid (mp <60 °C). The material was usually not further purified. An analytical sample

was obtained through chromatography (silica gel; 1:1 ethyl acetate/hexanes). ^{1}H NMR ($CDCl_3$): δ 7.79 (m, 2H); 7.28 (m, 4H); 5.93 (m, 1H); 5.23 (m, 3H); 3.68 (s, 3H); 2.74 (d, J=5.12 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 184.70, 176.25, 136.54, 131.50, 128.52, 126.95, 115.95, 51.70, 48.02, 38.16; IR (CH_2Cl_2): 3428 and 3324, N-H str.; 1662, C=O str. (amide); 1734, C=O str. (ester); 1517 and 1265, N-H bend; 1204 and 1181, C-O-C str.; 990 and 928 cm^{-1}, C-H bend (olefin).

Anal. Calcd. for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 66.71; H, 6.47; N, 6.06.

4-hydroxymethyl-3-benzamido-γ-lactone (148 and 149)

To 16 g (68.67 mmol) of the olefin 146 in acetone (100 mL) and water (20 mL) was added trimethylamine-N-oxide monohydrate (16.78 g, 151 mmol) and the osmium tetraoxide stock solution (1 mL). The yellow solution was stirred 16 h at which time analysis of a TLC showed the starting material had been consumed. Saturated aqueous sodium bisulfite (25 mL) and methylene chloride (50 mL) were added and the layers were separated. The aqueous phase was extracted with additional methylene chloride (2 x 30 mL). The combined organic solutions were dried (Na_2SO_4), filtered, and evaporated at reduced pressure to give a yellow solid composed of the polar, trans-isomer and the less polar, cis-isomer in a 56:44 ratio in 96% yield. The trans-isomer was crystallized from the mixture with methanol/methylene chloride and recrystallized from methanol/ether to give 8.67 g of 149 as colorless needles with mp 164-165 °C. ^{1}H NMR

(MeOH d4): δ 7.67 (m, 6H); 4.76 (m, 1H); 4.62 (q, J=3.30 Hz, 1H); 3.87 (dd, J=1.10 Hz, J=2.85 Hz, 2H); 2.91 (ddd, J=4.84 Hz, J=8.79 Hz, J=22.63 Hz, 2H); ^{13}C NMR (MeOH d4): δ 177.01, 169.38, 133.99, 132.05, 128.64, 127.44, 86.98, 73.54, 62.27, 35.35; IR ($CDCl_3$): 3751, O-H str.; 3382, N-H str.; 1752, C=O str. lactone; 1640, C=O str. amide; 1605 cm^{-1}, N-H bend.

The residue was chromatographed (silica gel, 200 g; 5% methanol/methylene chloride) and the cis-lactone was recrystallized from methanol/ether to give 6.82 g of 148 as colorless plates with mp 139-141 °C. ^{1}H NMR (MeOH d4): δ 7.70 (m, 5H); 4.91 (m, 1H); 4.85 (m, 1H); 3.84 (ddd, J=3.51 Hz, J=18.14 Hz, J=3.63 Hz, 1H); 2.91 (ddd, J=8.13 Hz, J=8.13 Hz, J=5.93 Hz, J=17.58 Hz, 2H); ^{13}C NMR (MeOH d4): δ 173.66, 170.46, 133.02, 132.75, 129.56, 128.31, 83.62, 73.92, 64.49, 37.08; IR ($CDCl_3$): 3373, N-H str.; 3629, O-H str.; 1600, N-H bend; 1654, C=O str. amide; 1760 cm^{-1}, C=O str. lactone.

Anal. Calcd. for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.95. Found: C, 60.79; H, 5.69; N, 5.80.

4-Acetoxymethyl-3-benzamido-γ-lactone (150 and 151)

The lactones were individually acetylated with acetic anhydride and pyridine, stirred 16 h, and worked-up by addition of methylene chloride and successive washings with saturated aqueous sodium bicarbonate and 10% hydrochloric acid, drying with $MgSO_4$, and evaporating at reduced pressure.

cis-lactone (148): From 5 g (21.27 mmol) of 148 there was obtained 5.72 g (97 %) 150 as colorless needles after recrystallization from ethyl acetate/hexanes. ^{1}H NMR ($CDCl_3$): δ 7.60 (m, 5H); 6.86 (bd, 1H); 5.31 (m, 1H); 4.83 (m, 1H); 4.14 (m, 2H); 2.64 (m, 2H); 2.05 (s, 3H).

trans-lactone (149): From 4 g (17.02 mmol) of 149 there was obtained 4.53 g (96 %) of 151 as colorless crystals after recrystallization from acetone/hexanes. ^{1}H NMR ($CDCl_3$): δ 7.58 (m, 6H); 5.17 (m, 1H); 4.87 (m, 1H); 4.34 (m, 2H); 2.80 (ddd, J=8.35 Hz, J=4.17 Hz, J=20.44 Hz, 2H), 2.00 (s, 3H).

4-Hydroxy-3-benzamido-2,3,-dideoxy-pentopyranose (158)

The acetoxylactones were individually reduced, and hydrolyzed to the pyranose products. The cis-lactone (150) (3.0 g, 10.83 mmol) was dissolved in THF (70 mL) and chilled to -80 °C (dry ice/ether). DIBAL (1 M in THF; 32.49 mL, 32.49 mmol) was added slowly by syringe and the colorless solution was maintained at this temperature an additional 1.5 h before quenching with 75 mL 4:1 methanol/water. The solution was allowed to warm to ambient temperature and saturated aqueous sodium potassium tartrate (30 mL) was added before separating the layers. The aqueous layer was extracted with methylene chloride (2 x 25 mL) and the combined organic solutions were dried (Na_2SO_4) and evaporated at reduced pressure. The crude lactol was dissolved in dry methanol and ammonia was bubbled into the cold (0 °C) solution for 30 min to give, after evaporation of the methanol under reduced pressure, 2.05 g (80%) 158 as

a colorless oil. ^{1}H NMR (Acetone d6): δ 7.67 (m, 5H); 6.72 (bd, 1H); 5.24 (m, 1H); 4.91 (m, 1H); 4.03 (m, 1H); 3.56 (m, 2H); 1.40 (m, 2H).

From 3.0 g (10.83 mmol) of the trans-lactone 151, and DIBAL (32.49 mL, 32.49 mmol, 1 M DIBAL in THF) there was obtained after ammonolysis, 2.10 g (82 %) 159 as a low melting solid, mp <50 °C. ^{1}H NMR (Acetone d6): δ 7.68 (m, 5H); 6.81 (bd, 1H); 5.33 (m, 1H); 4.98 (m, 1H); 4.08 (m, 1H); 3.63 (m, 2H); 1.52 (m, 2H).

Methyl-(3-benzamido-3-methyl)pent-4-enoate (147)

The azetidinone 145b (15 g, 135.14 mmol) underwent hydrolysis with dry hydrogen chloride and methanol followed by amidation with benzoyl chloride (19.68 g, 140 mmol) and pyridine (40 mL) in ether (150 mL) in a manner similar to that employed for the conversion of 145a to 146. The crude solid was chromatographed on a short slug of silica gel (50 g; 6:4 ethyl acetate/hexanes) and crystallized from methylene chloride/hexanes to give 31.04 g (93%) of 147 as colorless needles with mp 86-87 °C. ^{1}H NMR ($CDCl_3$): δ 7.82 (m, 2H); 7.55 (m, 3H); 7.19 (bs, 1H); 6.12 (dd, J=10.32 Hz, J=17.35 Hz, 1H); 5.24 (d, J=5.50 Hz, 1H); 5.09 (d, J=1.76 Hz, 1H); 3.68 (s, 3H); 2.84 (d, J=1.76 Hz, 2H); 1.68 (s, 3H); ^{13}C NMR ($CDCl_3$): δ d 171.86, 166.71, 141.58, 135.34, 131.28, 128.52, 126.79, 113.08, 55.71, 43.68, 25.16, 24.94.

Anal. Calcd. for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 68.12; H, 6.95; N, 5.56.

4-Hydroxymethyl-3-benzamido-3-methyl-γ-lactone (152 and 153)

cis-Hydroxylation of 147 (12.0 g, 48.58 mmol) with trimethylamine-N-oxide (11.87 g, 106.88 mmol) and a catalytic amount of osmium tetraoxide in acetone (100 mL) and water (10 mL) provided a 69:31 mixture of cis- and trans-lactones in 95% yield. Column chromatography of the mixture (150 g silica gel; 5 to 7% methanol/methylene chloride) provided 7.93 g of the less polar cis-lactone 152 as colorless plates with mp 151-152 °C after recrystallization from methanol/hexanes. ^{1}H NMR (MeOH d4): δ 7.67 (m, 5H); 4.57 (t, J=3.74 Hz, 1H); 3.92 (d, J=3.74 Hz, 2H); 3.00 (dd, J=34.50 Hz, J=51.64 Hz, J=69.00 Hz, 2H); 1.70 (s, 3H); IR ($CDCl_3$): 3629, O-H str.; 3219, N-H str.; 1762, C=O str. lactone; 1684, C=O str. amide; 1647 cm^{-1}, N-H bend.

Anal. Calcd. for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.06; N, 5.62. Found: C, 62.27; H, 6.04; N, 5.48.

Continued elution provided 3.56 g of the more polar trans-lactone 153 as colorless needles with mp 105-107 °C after recrystallization from methanol/methylene chloride. ^{1}H NMR (MeOH d4): δ 7.56 (m, 5H); 4.98 (t, J=9.45 Hz, 1H); 3.92 (d, J=3.30 Hz, 2H); 3.03 (dd, J=53.18 Hz, J=18.46 Hz, J=36.04 Hz, 2H); 1.70 (s, 3H); IR ($CDCl_3$): 3649, O-H str.; 3434, N-H str.; 1640, N-H bend; 1654, C=O str., amide; 1744 cm^{-1}, C=O str. lactone.

4-Acetoxymethyl-3-benzamido-3-methyl-γ-lactone (154 and 155)

The lactones were individually acetylated with acetic anhydride and pyridine in a manner similar to 148 and 149.

cis-lactone: From 4.0 g (16.06 mmol) of 152 there was obtained 4.56 g (97%) 154 as colorless chunks with mp 123-124° C. ^{1}H NMR ($CDCl_3$): δ 7.42 (m, 5H); 6.86 (bs, 1H); 4.56 (dd, J=3.51 Hz, J=5.49 Hz, 1H); 4.12 (m, 2H); 2.71 (dd, J=28.12 Hz, J=62.61 Hz, J=45.26 Hz, 2H); 1.87 (s, 3H); 1.53 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 174.08, 170.18, 168.12, 131.84, 128.36, 127.00, 84.26, 62.37, 57.55, 41.84, 25.43, 20.55.

trans-lactone: From 4.0 g (16.06 mmol) of 153 there was obtained 4.56 g (97%) of 155 as colorless needles with mp 121-123 °C. ^{1}H NMR ($CDCl_3$): δ 7.60 (m, 5H); 6.33 (bs, 1H); 5.10 (dd, J=3.30 Hz, J= 5.50 Hz, 1H); 4.35 (ddd, J=3.52 Hz, J=3.1 Hz, J=12.31 Hz, 2H); 3.02 (dd, J=17.36 Hz, J=51.87 Hz, 2H); 2.08 (s, 3H); 1.58 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 173.76, 170.40, 167.58, 132.09, 128.68, 126.89, 81.71, 62.43, 58.54, 41.79, 20.66, 20.33.

2,3-Dideoxy-3-methyl-3-benzamido-4-acetoxy Pentopyranose (163)

This reaction was performed in a manner identical to that employed for the preparation of 150 and 151.

From the trans-lactone (155) (2.5 g, 8.53 mmol) and DIBAL (1 M in THF; 25.59 mL, 25.59 mmol), after ammonolysis and acetylation with acetic anhydride and pyridine there was obtained 1.95 g (78 %) of 163 as a

colorless oil. ^{1}H NMR ($CDCl_3$): δ 7.58 (m, 5H); 7.09 (bs, 1H); 5.19 (q, J=4.5 Hz, 1H); 4.99 (dd, J=4.4 Hz, J=8.13 Hz, 1H); 3.87 (m, 3H); 2.65 (m, 2H); 2.09 (s, 3H); 1.65 (s, 3H).

α-Acetyl 2,3-Dideoxy-3-methyl-3-benzamido-4-acetoxy Pentopyranoside (162)

This reaction was identical to that employed for the preparation of 150 and 151.

To 3.0 g (10.24 mmol) of the cis-lactone (154) and 30.72 mL (30.72 mmol) of DIBAL (1 M in THF) after ammonolysis and acetylation, there was obtained 2.74 g (80%) of **162** as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 7.63 (m, 5H); 7.18 (bs, 1H); 6.08 (m, 1H); 5.54 (m, 1H); 3.87 (m, 2H); 2.33 (m, 2H); 2.13 (s, 3H); 2.11 (s, 3H); 1.61 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 188.27, 185.89, 173.05, 131.72, 128.63, 126.68, 96.99, 85.29, 62.48, 60.26, 44.33, 23.11, 23.04, 21.14.

X. References

1. Hauser, F. M.; Ellenberger, S. R. Chem. Reviews 1986, 86, 35.

2. Halazun, J. F.; Wagner, H. R.; Gaeta, J. F.; Sinks, L. F. Cancer 1974, 33, 545.

3. Pettit, G. R.; Einck, J. J.; Herald, C. L.; Ode, R. H.; Von Dreele, R. B.; Brown,m P.; Brazhnikova, M. G.; Gause,, G. F. J. Am. Chem. Soc. 1975, 97, 7387.

4. Cancer Chemother. Rep. 1975, 6, Pt. 3.

5. Tan, C.; Tasaka, H.; Yu, K.; Murphey, M. L.; Karnofsky, D. A. Cancer 1967, 20, 333.

6. Boiron, M.; Jacquillar, C.; Weil, M.; Tanzer, J.; Levy, D.; Sultan, C.; Bernard, J. Lancet 1969, 330.

7. DiMarco, A.; Gaetani, M.; Orezzi, P.; Scarpinato, B.; Silvestrini, R.; Sokdati, M.; Dasdia, T.; Valentini, L. Nature 1964, 201, 706.

8. Hartmann,m G.; Goller, G.; Koschel, K.; Kersten, W.; Kersten, H. Biochem. Z. 1964, 341, 126.

9. Theologides, A.; Yarbro, J. W.; Kennedy, B. J. Cancer 1968, 21, 16.

10. Pigram, W. J.; Fuller, W.; Hamilton, L. D. Nature New Biol. 1972, 235, 17.

11. Arcamone, F. "Anticancer Agents Based on Natural Product Models"; Cassady, J. M.; Douros, J. D., Eds.; Academic Press: New York, 1980; Vol. 16, pp. 1-41.

12. Arcamone, F. "Topics in Antibiotic Chemistry"; Sammes, P. G., Ed.; Wiley: New York, 1978; Vol. 2, pp. 89-229.

13. Brown, J. R. "Progress in Medicinal Chemistry"' Ellis, G. P.; West, G. B., Eds.; Elsevier: New York, 1978; Vol 15, pp. 125-164.

14. Remers, W. A. "The Chemistry of Antitumor Antibiotics"; Wiley Interscience: New York, 1979; vol. 1; Chapter 2.

15. Henry, D. W. Cancer Treat. Rep. 1979, 63, 845.

16. Henry, D. W. "Cancer Chemotherapy"; Sartorelli, A. C., Ed.; American Chemical Society: Washington D. C., 1976.

17. Arcamone, F.; Lloydia 1977, 40, 45.

18. Arcamone, F. "International Symposium on Tumor Pharmacotherapy"; Masson: New York, 1983, pp. 79-84.

19. 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.

20. Arcamone, F.; Franceschi, G.; Orezzi, P.; Babier, W.; Mondelli, R. J. Am. Chem. Soc. 1964, 86, 5334.

21. Arcamone, F.; Cassinelli, G.; Orezzi, P.; Franceschi, G.; Mondelli, R. J. Am. Chem. Soc. 1964, 86, 5335.

22. Arcamone, F.; Franceschi, G.; Penco, S.; Selva, A. Tetrahedron Lett. 1969, 1007.

23. Carter, S. K. J. Natl. Cancer Inst. 1975, 55, 1265.

24. Skovsgaard, T.; Nissen, N. I. Dan. Med. Bull. 1975, 22, 62.

25. Gauze, G. F.; Kudrina, E. S.; Ukholina, R. S.; Gavrilina, G. V. Antibiotiki 1963, 8, 387. Chem. Abstr. 1965, 62:5843e

26. 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.

27. Bognar, R.; Sztaricskai, F.; Munk, M. E.; Tamas, J. J. Org. Chem. 1974, 39, 2971.

28. Spiridonova, I. A.; Lomakina, N. N.; Sztaricskai, F.; Bognar, R. Antibiotiki 1974, 19, 400. Chem. Abstr. 1974, 81:91882a

29. Bognar, R.; Sztaricskai, F.; Morton, M. E.; Tamas, J. Magy. Kem. Foly. 1974, 80, 385. Chem. Abstr. 1975, 82:17029g

30. Lomakina, I. A.; Spiridonova, R.; Bognar, R.; Puskas, M.; Sztaricskai, F. Antibiotiki 1968, 13, 975.

31. Sztaricskai, F.; Niszmilyi, A.; Bognar, R. Tetrahedron Lett. 1980, 21, 2983.

32. Sztaricskai, F.; Harris, C. M.; Neszmelyi, A.; Harris, T. M. J. Am. Chem Soc. 1980, 21, 2983.

33. Brazhnikova, M. G.; Lomakina, N. N.; Sztaricskai, F.; Puskas, M.; Makleit, S.; Bognar, R. Kem. Kozl. 1967, 27, 143. Chem. Abstr. 1968, 68:78165f

34. Lomakina, N. N.; Spiridonova, I. A.; Sheinker, Y. N.; Vlasova, T. F. Khim. Prir, Soedin. 1973, 9, 101. Chem. Abtr. 1973, 78:148170m

35. Spiridonova, I. A.; Yurina, M. S.; Lomakina, N. N.; Sztaricskai, F.; Bognar, F. Antibiotiki 1976, 21, 304. Chem. Abstr. 1976, 85:108925z

36. McCormick, M. H.; Stark, W. M.; Pittenger, G. E.; Pittenger, R. C.; McGuire, J. M. "Antibiotics Annual" 1955-1966, Medical Encyclopedia, Inc., New York, 1956, pp 606.

37. Weringa, W. D.; Williams, D. H.; Feeney, J.; Brown, J. P.; King, R. W. J. Chem. Soc. Perkin Trans. I 1972, 443.

38. Smith, R. M.; Johnson, A. W.; Guthrie, R. D. J. Chem. Soc. Chem. Commun. 1972, 361.

39. Johnson, A. W.; Smith, R. W.; Guthrie, R. D. J. Chem. Soc. Perkin Trans. I 1972, 2153.

40. Williams, D. H.; Kalman, J. R. J. Am. Chem. Soc. 1977, 99, 66.

41. Harada, K.-I.; Ito, S.; Suzuki, M. Carbohydr. Res. 1979, 75, C17.

42. Marsh, J. P., Jr.; Mosher, C. W.; Acton, E. M.; Goodman, L. J. Chem. Soc.Chem. Commun. 1967, 973.

43. Iselin, B.; Reichstein, T. Helv. Chim. Acta. 1944, 27, 1146.

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. Horton, D.; Weckerle, W. Carbohydr. Res. 1975, 44, 227.

48. Evans, M. E.; Carbohydr. Res. 1972, 21, 473.

49. Klemer, A.; Rhodemeyer, G. Chem. Ber. 1974, 107, 2612.

50. Benyon, P. J.; Collins, P. M.; Overend, W. G. J. Chem. Soc. C 1969, 272.

51. Hanessian, S. Carbohydr. Res. 1966, 2, 86.

52. Lehmann, J.; Weckerle, W. Carbohydr. Res. 1975, 42, 275.

53. Fronza, G.; Fuganti, C.; Grasselli, P. J. Chem. Soc. Perkin Trans. I 1980, 442.

54. Fuganti, C.; Grasselli, P. Chem. Ind. 1977, 983.

55. Fuganti, C.; Grasselli, P.; Giuseppe, P.-F. Tetrahedron Lett. 1981, 4017.

56. Fuganti, C.; Grasselli, P.; Giuseppe, P.-F. J. Org. Chem. 1983, 48, 909.

57. Fronza, G.; Fuganti, D.; Grasselli, P. J. Chem. Soc. Perkin Trans I. 1982, 885.

58. Fronza, G.; Fuganti, C.; Grasselli, P.; Marinoni, G. Tetrahedron Lett. 1979, 3883.

59. Hauser, F. M.; Rhee, R. P. J. Org. Chem. 1981, 46, 227.

60. Hauser, F. M.; Rhee,. R. P.; Ellenberger, S. R. J. Org. Chem. 1984, 49, 2236.

61. Johnston, D. B. R.; Schmett, S. M.; Bouffard, F. A.; Christensen, B. G. J. Am. Chem. Soc. 1978, 100, 313.

62. Isaacs, N. S. Chem. Soc. Rev. 1976, 5, 181.

63. Montzka, T.; Pindell, T. L.; Matiskella, D. J.; J. Org. Chem. 1968, 33, 3993.

64. Ray, R.; Matteson, D. S. Tetrahedron Lett. 1980, 449.

65. Wovkulich, P. M.; Uskokovic, M. R. J. Am. Chem. Soc. 1981, 103, 3956.

66. Bredereck, H.; Simchen, G.; Rebsdat, S.; Kantlehner, W.; Horn, P.; Wahl, R.; Hoffmann, H.; Grieschaber, P. Chem. Ber. 1968, 104, 41.

67. Polonski, T.; Chimiak, A. Tetrahedron Lett. 1974, 2453.

68. Bourgeois, J.-M. Helv. Chim. Acta. 1974, 57, 2553.

69. Bourgeois, J.-M. Helv, Chim. Acta 1975, 58, 363.

70. Bourgeois, J.-M. Helv. Chim. Acta 1976, 59, 2214.

71. Baer, H. H.; Capek, K. Can. J. Chem. 1969, 47, 99.

72. Richardson, A. C.; McLauchlan K. A. J. Chem. Soc. 1962, 2499.

73. Overman, L. E. J. Am. Chem. Soc. 1976, 98, 2901.

74. Overman, L. E. J. Am. Chem. Soc. 1974, 96, 597.

75. Sirotanovic, K.; Bajlon-Rocen, M.; Galovic, D. Glas. Hem. Drus. Beograd 1960-1961, 25/26, 509. Chemical Abs. 1963, 59, 8635d.

76. Knights, E. E.; Brown, H. C. J. Am. Chem. Soc. 1968, 90, 5280.

77. Scouten, C. G.; Brown, H. C. J. Org. Chem. 1973, 38, 4092.

78. Bakuzis, P.; Bakuzis, M. L. F. J. Org. Chem. 1976, 41, 2769.

79. Hsiao, C. N.; Shechter, H. Tetrahedron Lett. 1982, 1963.

80. Johnson, C. R.; McCants, D., Jr. J. Am. Chem. Soc. 1965, 87, 1109.

81. Pitchen, P.; Kagan, H. B. Tetrahedron Lett. 1984, 1049.

82. Sharpless, K. B.; Katsuki, T.; J. Am. Chem. Soc., 1980, 102, 5974.

83. Rossiter, B. E.; Katsuki, T.; Sharpless, K. B. J. Am. Chem. Soc. 1981, 103, 464.

84. Johnson, C. R.; Keiser, J. E.; Org. Synth. 1966, 46, 78.

85. Hauser, F. M.; Ellenberger, S. R.; Clardy, J. C.; Bass, L. S. J. Am. Chem. Soc. 1984, 106, 2458.

86. Harville, R.; Reed, S. J. Org. Chem. 1968, 33, 3976.

87. Drabowicz, J.; Midura, W.; Mikolajczyk, M. Synthesis 1979, 39.

88. Hojo, M.; Masuda, R. Tetrahedron Lett. 1976, 613.

89. Watanabe, Y.; Numata, T.; Oae, S. Synthesis 1981, 204.

90. Oae, S.; Ohnishi, Y.; Kozuka, S.; Tagaki, W. Bull. Chem. Soc. Jpn. 1966, 39, 364.

91. Ho, T.-L.; Wong, C. M.; Synthesis 1972, 561.

92. Skattebol, L.; Boulette, B.; Solomon, S. J. Org. Chem. 1967, 3111.

93. Drabowicz, J.; Mikolajczyk, M. Synthesis 1978, 758.

94. Djerassi, C.; Engle, R. R. J. Am. Chem. Soc. 1953, 75, 3838.

95. Henbest, H. B.; Kahn, S. A. J. Chem. Soc., Chem. Commun. 1968, 1036.

96. Cha, J. K.; Christ, W. J.; Kishi, Y. Tetrahedron Lett. 1983, 3943.

97. Cha, J. K.; Christ, W. J.; Kishi, Y. Tetrahedron Lett. 1983, 3947.

98. Stork, G.; Kahn, M. Tetrahedron Lett. 1983, 3951.

99. Ray, R.; Matteson, D. S. Tetrahedron Lett. 1980, 449.

100. Morrison, J. D.; Mosher, H. S. "Asymmetric Organic Reactions", Prentice-Hall, Inc., Englewood Cliffs, New Jersey, 1971, pp. 335-362.

101. Mikolajczyk, M.; Drabowicz, J. Phosphorus and Sulfur 1976, 1, 301.

102. Olah, G. A.; Gupta, B. G. B.; Narang, S. C. Synthesis 1977, 583.

103. Brown, H. C.; Ravindran, N. Synthesis 1973, 42.

104. Bordwell, F. G.; McKellin, W. H. J. Am. Chem. Soc. 1951, 73, 2251.

105. Gardner, J. N.; Kaiser, S.; Krubiner, A.; Lucas, H. Can. J. Chem. 1973, 51, 1419.

106. Dzhemilev, U. M.; Gubaidullin, L. Y.; Tolstikov, G. A.; Zelenova, L. M. Izv. Akad. Nauk SSSR, Ser. Khim. 1980, 734. Chemical Abstracts 1980, 93:25841h.

107. Still, I. W. J.; Szilagyi, S. Synthetic Commun. 1979, 9, 923.

108. Chalkley, G. R.; Snodin. D. J.; Stevens, G.; Whiting. M. C. J. Chem. Soc., (C) 1970, 682.

109. Okamura, W. H.; Peter, R. ; Reischl, W. J. Am. Chem. Soc. 1985, 107, 1034.

110. Mimoum, H.; Seree de Roche, I.; Sajus, L. Bull. Soc. Chim. France 1969, 1481.

111. Vedejs, E. Engler, D. A.; Telschow, J. E. J. Org. Chem. 1978, 43, 188.

112. Julia, M.; Paris, J.-M. Tetrahedron Lett. 1973, 4833.

113. Kocienski, P. J.; Lythgoe, B.; Ruston, S. J. Chem. Soc., Perkin Trans. I 1978, 829.

114. Little, R. D.; Myong, S. O. Tetrahedron Lett. 1980, 3339.

115. Paquette, L. A.; Barrett, J. H. Org. Synth. 1963, IV, 552.

116. Hauser, F. M.; Ellenberger, S. R.; Glusker, J. P.; Smart, C. J.; Carrell, H. L. J. Org. Chem. 1986, 51, 50.

117. Hogeveen, H.; Maccagnani, G.; Montana, F. Boll. Sci. Fac, Chim. Ind. Bologna 1963, 21, 257.

118. Ghersetti, S.; Hogeveen, H.; Maccagnani, G.; Montanari, F.; Taddei, F. J. Chem. Soc. 1963, 3718.

119. Montanari, F.; Danieli, R.; Hogeveen, H.; Maccagnani, G. Tetrahedron Lett. 1964, 2685.

120. Jones, D. N.; Saeed, M. A. Proc. Chem. Soc. 1964, 81.

121. Leonard, N. L.; Johnson, C. R. J. Am. Chem. Soc. 1962, 84, 3701.

122. Leonard, N. J.; Rippie, W. L. J. Org. Chem. 1963, 28, 1957.

123. Paquette, L. A.; Klobucar, W. D.; Snow, R. A. Synthetic. Commn. 1976, 575.

124. Oshiro, Y.; Tsuchihashi, G.-I.; Ogura, K.; Iriuchijima, S. Synthesis 1971, 89.

125. Mangoni, L.; Adinolfi, M.; Barone, G.; Parrilli, M. Tetrahedron Lett. 1973, 4485.

126. Pummerer, R. Chem. Ber. 1909, 42, 2282.

127. Pummerer, R. Chem. Ber. 1910, 43, 1401.

128. Johnson, C. R.; Phillips, W. G. J. Am. Chem. Soc. 1969, 91, 682.

129. Numata, T.; Oae, S. Tetrahedron Lett. 1977, 1337.

130. Numata, T.; Itoh, O.; Oae, S. Chem. Lett. 1977, 909.

131. Numata, T.; Itoh, O.; Oae, S. Tetrahedron Lett. 1979, 1869.

132. Numata, T.; Itoh, O.; Yoshimura, T.; Oae, S. Bull. Chem. Soc. Jpn. 1983, 56, 257.

133. Itoh, O.; Numata, T.; Yoshimura, T.; Oae, S. Bull. Chem. Soc. Jpn. 1983, 56, 266.

134. Wolfe, S.; Kazmaier, P. M. Can. J. Chem. 1979, 57, 2388.

135. Wolfe, S.; Kazmaier, P. M. Can. J. Chem. 1979, 57, 2397.

136. Iriuchijima, S.; Maniwa, K.; Tsuchihashi, G.-I. J. Am. Chem. Soc. 1974, 96, 4280.

137. Kitchin, J.; Stoodley, R. J. J. Chem. Soc., Chem. Commun. 1972, 959.

138. Tanikaga, R.; Yabuki, Y.; Ono, N.; Kaji, A. Tetrahedron Lett. 1976, 2258.

139. Iriuchijima, S. J. Am. Chem. Soc. 1974, 96, 4280.

140. Sugihara, H.; Tanikaga, R.; Kaji, A. Synthesis 1978, 881.

141. Cookson, R. C.; Gopalan, R. J. Chem. Soc., Chem. Commun. 1978, 608.

142. Harpp, D. N,; Friedlander, B. T.; Smith, R. A. Synthesis 1979, 181.

143. Horner, L.; Binder, V. Annalen 1972, 757, 33.

144. Parsons, P. J. Thesis, Southampton University, 1978.

145. Clauss, K.; Grimm, D.; Prossel, G. Justus Liebigs Ann. Chem. 1974, 539.

146. Schonberg, G. A.; Arison, B. H.; Hensens, O. D.; Hirshfield, J.; Hoogsteen, K.; Kaczka, E. A.; Rhodes, R. E.; Kahan, J. S.; Kahan, F. M.; Ratcliffe, R. W.; Walton, E.; Ruswinkle, L. J.; Morin. R. B.; Christensen, B. G. J. Am. Chem. Soc. 1978, 100, 6491.

147. Kametani, T.; Fukumoto, K.; Ihra, M. Heterocycles 1982, 17, 463.

148. Szabo, W. A. Aldrichimica Acta 1977, 10, 23.

149. Rasmussen, J. K.; Hassner, A. Chem. Rev. 1976, 76, 389.

150. Grasf, R.; Angew Chem., Int. Ed. Engl. 1968, 7, 172.

151. Moriconi, E. J.; Meyer, W. C. J Org. Chem. 1971, 36, 2841.

152. Woodward, R. B.; Hoffmann, R. Angew Chem. Int. Ed. Engl. 1969, 781.

153. Hauser, F. M.; Ellenberger, S. R. Synthesis, in press.

154. Durst, T.; O'Sullivan, M. J. J. Org. Chem. 1970, 35, 2043.

155. Hauser, F. M.; Ellenberger, S. R. Synthesis, in press.

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