SYNTHESIS OF DEF RING SYNTHONS TO NOGAROL ANTHRACYCLINES

William Paul Ellenberger
M. S., San Jose State University, 1981
B. A., San Jose State University, 1974

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This dissertation, "Synthesis of DEF Ring Synthons to Nogarol Anthracyclines" by William P. Ellenberger, has been examined and approved by the following Examination Committee:

Frank M. Hauser, Thesis Advisor and
External Examiner
Professor of Chemistry
State University of New York
Albany, New York

James K. Hurst
Professor

William L. Pengelly
Associate Professor

David H. P. Thompson
Assistant Professor

Dedication

To my mother and my late father

Acknowledgements

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Abstract

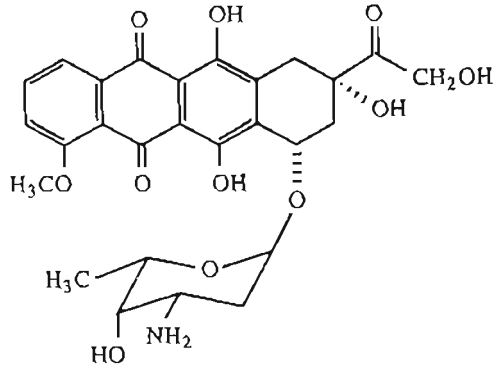
An expedient, regio- and stereospecific route for the construction of sugar analogs of 2,6-epoxy-1(2H)-benzoxocins is described. The methodology involves the oxidation of furancarbinols followed by acidic hydrolysis to afford 2,6-epoxy-1(2H)-ketobenzoxocin. Further functionalization affords sugar analogs with the manno, talo, altro and galacto configurations and aminosugar analogs with the ribo and arabino configurations.

The preparation of benzoxocin DEF ring synthons to nogarol anthracyclines is also described. Oxidation of furancarbinols containing variously substituted benzene rings were converted to methyl hexenulose derivatives by acidic methanolysis. Functionalization of the hexenuloses afforded gluco configurated amino sugars. These highly functionalized gluco-2,6-epoxy-1(2H)-benzoxocin analogues are suitable as synthons for the DEF ring system in nogarol anthracyclines.

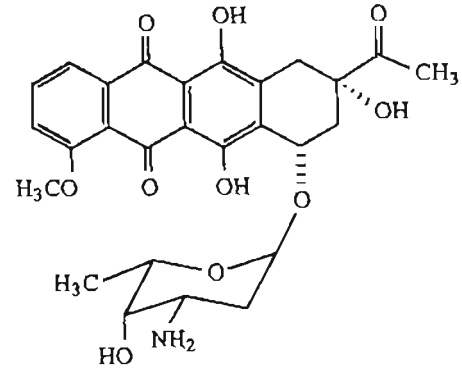
I. Introduction

The anthracycline antibiotics adriamycin (1) and daunorubicin (2), shown in Figure 1, are effective therapeutic agents for the treatment of cancer.[1-4] Adriamycin is the most widely used antineoplastic agent due to its broad spectrum of activity. Their mode of action was determined through x-ray analysis of daunorubicin complexed with DNA.[5] The aromatic fragment of the anthracycline lies in the major grove of DNA and the sugar is electrostatically bound to a phosphate residue.

Figure 1. Adriamycin and Daunorubicin



1.



2.

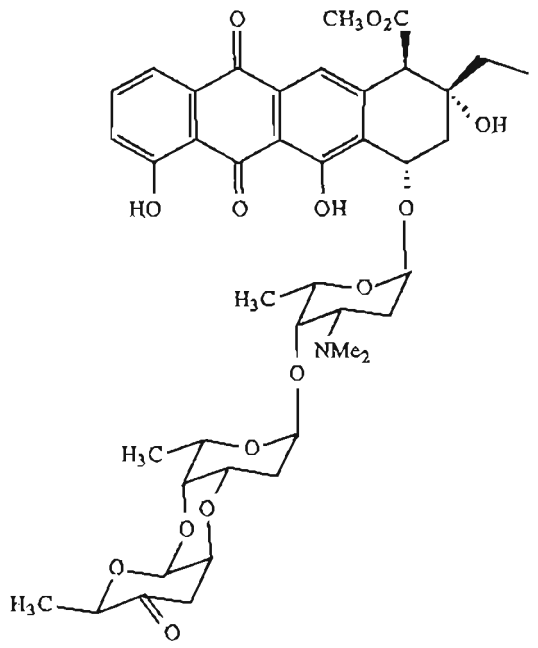
The principal disadvantage of these chemotherapeutic agents is their cumulative cardiotoxicity[7], which limits the total dose that can ever be administered. Oki and coworkers[8-10] have isolated a new anthracycline antibiotic, aclacinomycin (3), shown in Figure 2 which

is currently undergoing clinical evaluation. Preliminary results indicate that it is significantly less cardiotoxic than adriamycin or daunorubicin, but it is also a less effective chemotherapeutic agent.

Wiley and coworkers at Upjohn[11-15] isolated the anthracycline antibiotic, nogalamycin (4) shown in Figure 2, which exhibits prominent antitumor activity and reduced cardiotoxicity when compared with adriamycin and daunorubicin. A unique structural feature of nogalamycin is the presence of a hydroxyamino epoxybenzoxocin fragment. Conceptually this fragment originates from the dual attachment of a single deoxyamino sugar residue through both carbon-carbon and carbon-oxygen bonds. Determination of the absolute stereochemistry of nogalamycin was hampered by the presence of the complex epoxybenzoxocin ring system. The absolute stereochemistry was finally determined by Arora[16] in 1983 using x-ray crystallographic techniques.

Acidic methanolysis[14] of nogalamycin, as shown in Scheme 1, replaces the nogalose residue with a methoxyl group to furnish 7-con-O-methylnogalarol (5). Decarbomethoxylation of 5 through alkaline hydrolysis (0.53 N KOH at room temperature) followed by refluxing in dimethylformamide gave 7-con-O-methylnogarol (6). The antitumor activity of this semi-synthetic derivative is superior to that of nogalamycin.

Figure 2. Aclacinomycin and Nogalamycin



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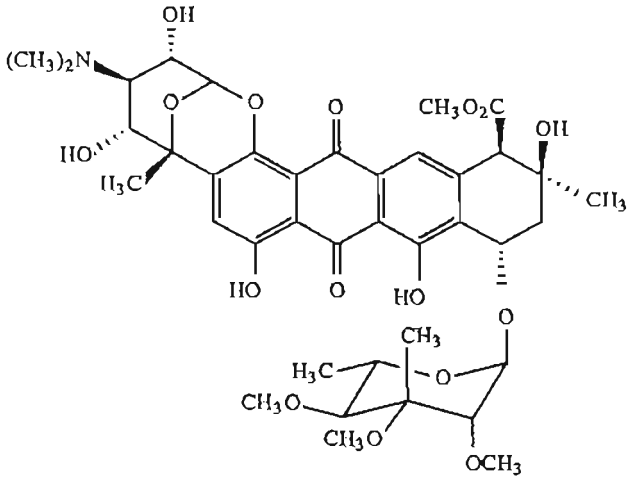

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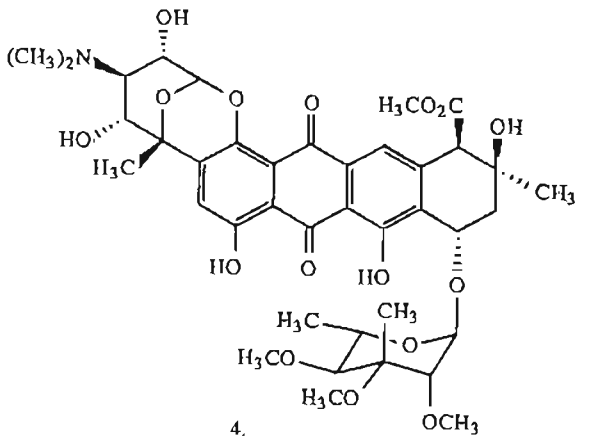
Scheme 1.



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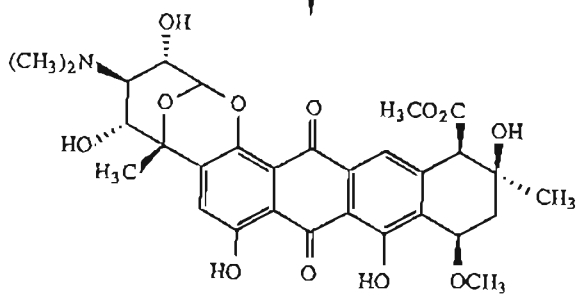
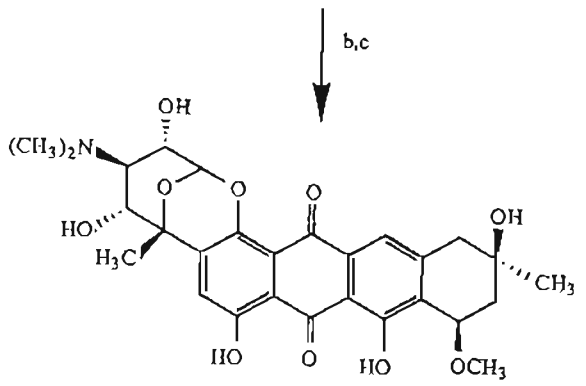


5.



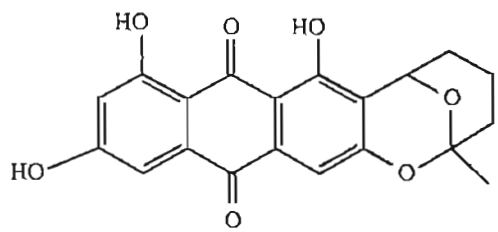
6.

a) HCl, MeOH b) KOH, H_2O c) DMF, reflux

Nogalamycin is the only natural product to contain a perfunctionalized epoxybenzoxocin ring system. However, averufin (7)[17], shown in Figure 3, an intermediate in aflatoxin biosynthesis, does contain an unfunctionalized epoxybenzoxocin system. Its synthesis, with[18-20] and without[21,22] radiolabelling, has been well documented.

This thesis describes studies directed towards the synthesis of nogalamycin and 7-con-O-methylnogarol.

Figure 3. Averufin



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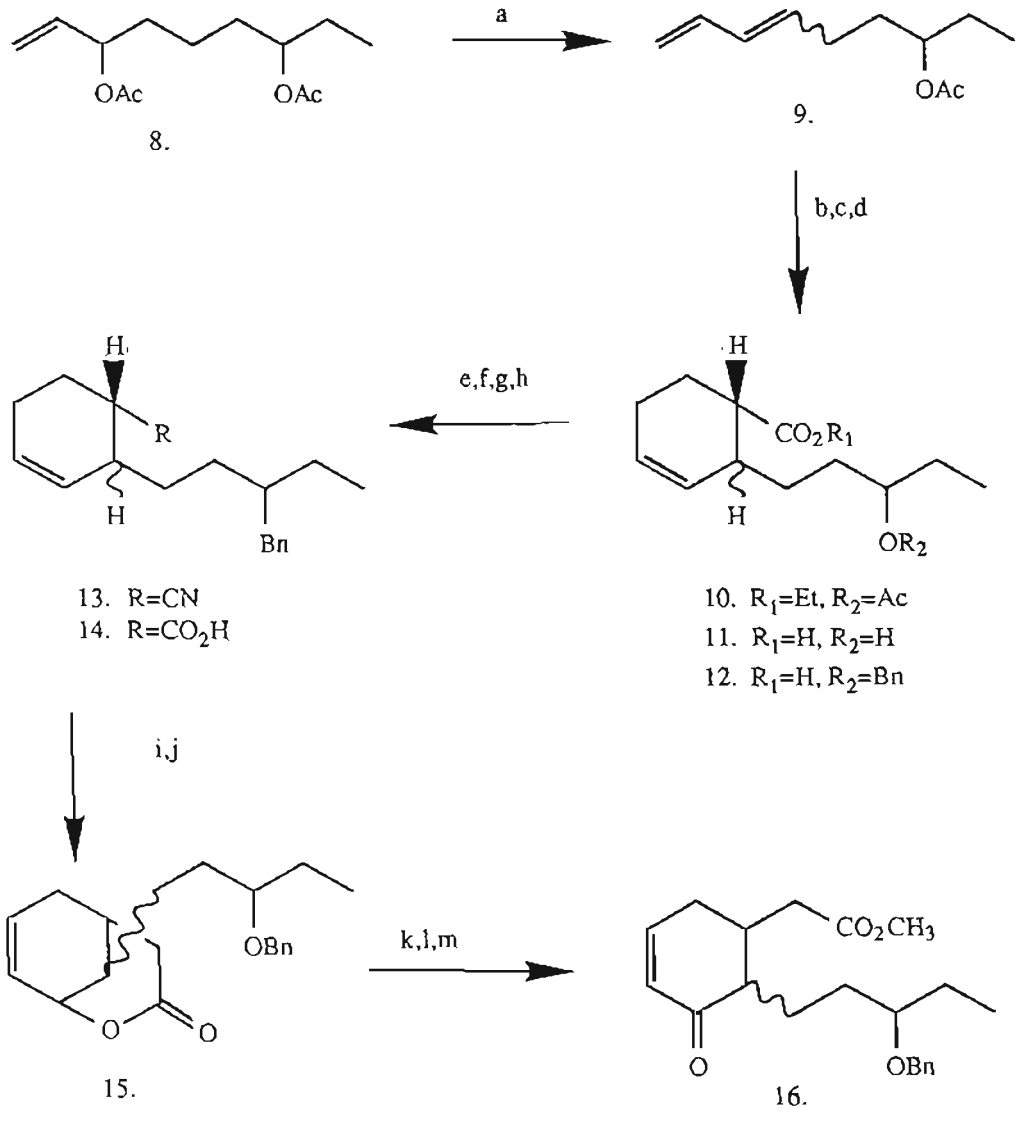
II. Literature Background

An efficient total synthesis of nogalamycin and 7-con-O-methylnogarol must address two key problems: Stereospecific synthesis of the epoxybenzoxocin sugar fragment and regiospecific fabrication of the polycyclic aromatic ring system.

Several years ago, a general, efficient and regiospecific synthesis of anthracyclinones was developed in these laboratories.[22,24] During the course of this thesis, this methodology was extended to include precedents for the synthesis of nogalamycin and 7-con-O-methylnogarol. In conjunction with syntheses of aclacinomycinone and pyrromycinone,[25] the total synthesis of an aromatic fragment analogous to that found in nogalamycin was preformed and is shown in Scheme 2.

Treatment of the diacetate 8[26] with a catalytic amount of palladium acetate and triphenylphosphine in refluxing dioxane led to chemospecific elimination of the allylic acetoxy group[27]. The resultant diene acetate 9 was isolated in 82% yield as a 78:22 mixture of E and Z isomers. The E isomer selectively underwent Diels-Alder reaction with ethyl acrylate to regiospecifically form 10 in 92% yield based on E diene. Basic hydrolysis of 10 (NaOH, EtOH) gave the hydroxyacid 11, which was selectively benzylated (NaH, BnBr, THF) to the benzyl ether 12 in 82% overall yield.

Scheme 2.

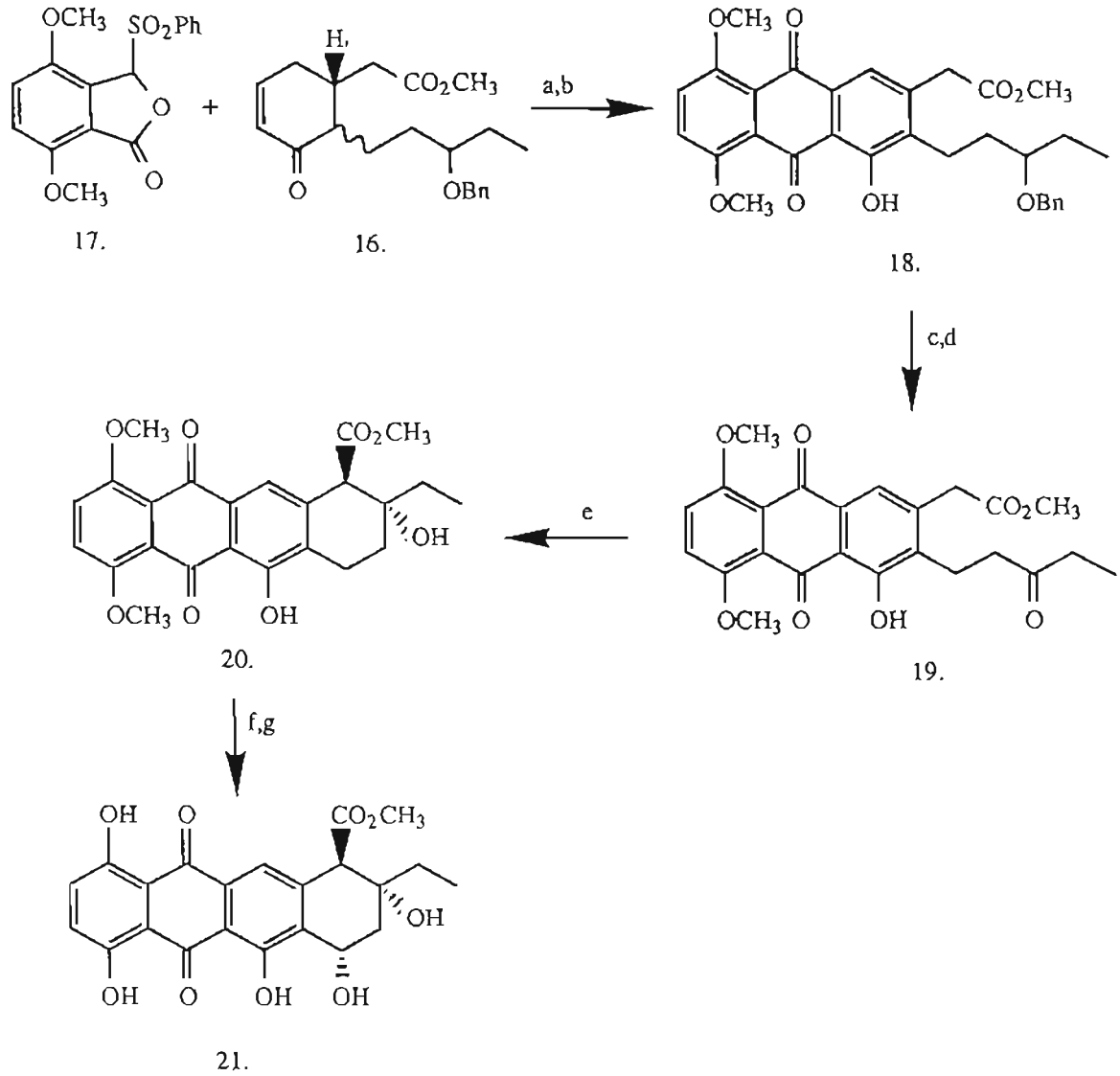


a) $Pd(OAc)_2$, PPh_3, dioxane, reflux, 82% b) EtOAc, hydroquinone, 155°C, 72% c) KOH, EtOH, H_2O, reflux, 100% d) NaH, BnBr, THF, reflux, 83% e) LAH, Et_2O, reflux, 97% f) MsCl, Py g) NaCN, NaI, DMF, 100°C, 92% h) KOH, EtOH, H_2O, reflux, 95% i) I_2, collidine, CH_3CN, 81% j) DBU, PhH, reflux, 96% k) KOH, MeOH, H_2O, 100°C, 95% l) CH_3I, DBU, CH_3CN m) ClCOCOCl, DMSO, Et_3N, CH_2Cl_2, 82%

Reduction of 12 (LAH, Et_2O), followed by mesylation (MsCl, Py) of the resultant alcohol intermediate, and then displacement of the mesylate group with cyanide (NaCN, DMF) gave the nitrile 13. Hydrolysis of 13 (NaOH, EtOH) furnished the acid 14 in 91% overall yield from 12. Iodolactonization[28] of 14 (I_2, collidine, CH_3CN) followed by dehydrohalogenation (DBU, PhH) afforded the olefin 15 in 83% overall yield. Hydrolysis of the lactone 15 (KOH, MeOH, H_2O), followed by chemospecific methylation of the carboxyl functionality (MeI, DBU, CH_3CN)[29] and oxidation of the alcohol functionality with Swern's reagent (ClCOCOCl, DMSO, Et_3N)[30] furnished the ketone 16 in 82% overall yield.

Condensation of the cyclohexenone 16 with the anion of the dimethoxyphthalidsulfone 17, followed by aromatization (O_2, DMF, 100°C)[31] of the hydroanthracene intermediate, afforded the anthraquinone 18 in 86% overall yield as shown in Scheme 3. Debenzylation of 18 (5% Pd/C, H_2, MeOH) and oxidation of the resultant alcohol with pyridinium chlorochromate[32] in methylene chloride gave the ketone 19 in 83% overall yield. Intramolecular aldol cyclization of 19 to 20 with magnesium methoxide gave a 3.5 to 1 mixture of isomers in which the desired isomer predominated. Demethylation of the phenolic ethers in 20 ($AlCl_3$, CH_2Cl_2, room temperature) followed by homolytic bromination[33] (Br_2, AIBN, CCl_4) and solvolysis in water-THF furnished pure (±)-purromycinone in 92% overall yield.

Scheme 3.



a) Li t-butoxide, THF b) O_2, DMF, 70°C, 82% c) Pd/C, HCl, MeOH, H_2, 93% d) PCC, CH_2Cl_2, 96%
e) Triton B, MeOH, CH_2Cl_2, 0°C f) $AlCl_3$, CH_2Cl_2, 94% g) Br_2, AIBN, CCl_4; THF, H_2O, 96%

In conjunction with the development of general methodology for the total syntheses of 9-alkyl-9-hydroxy aklavinones[31] and pyrromycinones, a brief regiospecific route to a 7-con-O-methylnogarol analog was demonstrated (Scheme 4). Boron trifluoride catalyzed Diels-Alder reaction between cyclohexenone and isoprene afforded the ketone 22 in 67% yield. The 2,3-unsaturation in naphthalenone 23 was introduced through kinetic deprotonation (lithium cyclohexyliospropyl amide, THF, -78°C)[34] of ketone 22 followed by reaction with phenyl-benzenethiosulfate furnished the α-phenylthio ether intermediate in 90% yield. Oxidation ($NaIO_4$, MeOH) of the thioether moiety to a sulfoxide and then pyrolysis (CCl_4, $CaCO_3$) furnished the naphthalenone 23 in 60% overall yield.

Condensation of the anion of the phthalidesulfone 17 with the decalenone 23, followed by selective acetylation (Ac_2O, Py, room temperature) afforded the tetrahydronaphthacenone 24 in 80% overall yield. Reaction of 24 with mercuric nitrate[35], followed by reductive demercuration with sodium hydroxide and sodium borohydride, selectively gave the alcohol 25 in 81% yield. Deacetylation, aromatization of the B-ring and oxidation of the C-ring to a quinone was accomplished in a single step by bubbling oxygen through an ethanolic potassium hydroxide solution of 25. Selective acetylation of the tertiary alcohol was accomplished by generating the bis-acetate (Ac_2O Et_3N, DMAP), then selectively hydrolyzing (KOH, DME, H_2O, room temperature) the phenolic acetate. The resultant acetoxyalcohol 26 was obtained in 63% overall yield from 25. Homolytic bromination and solvolysis[33]

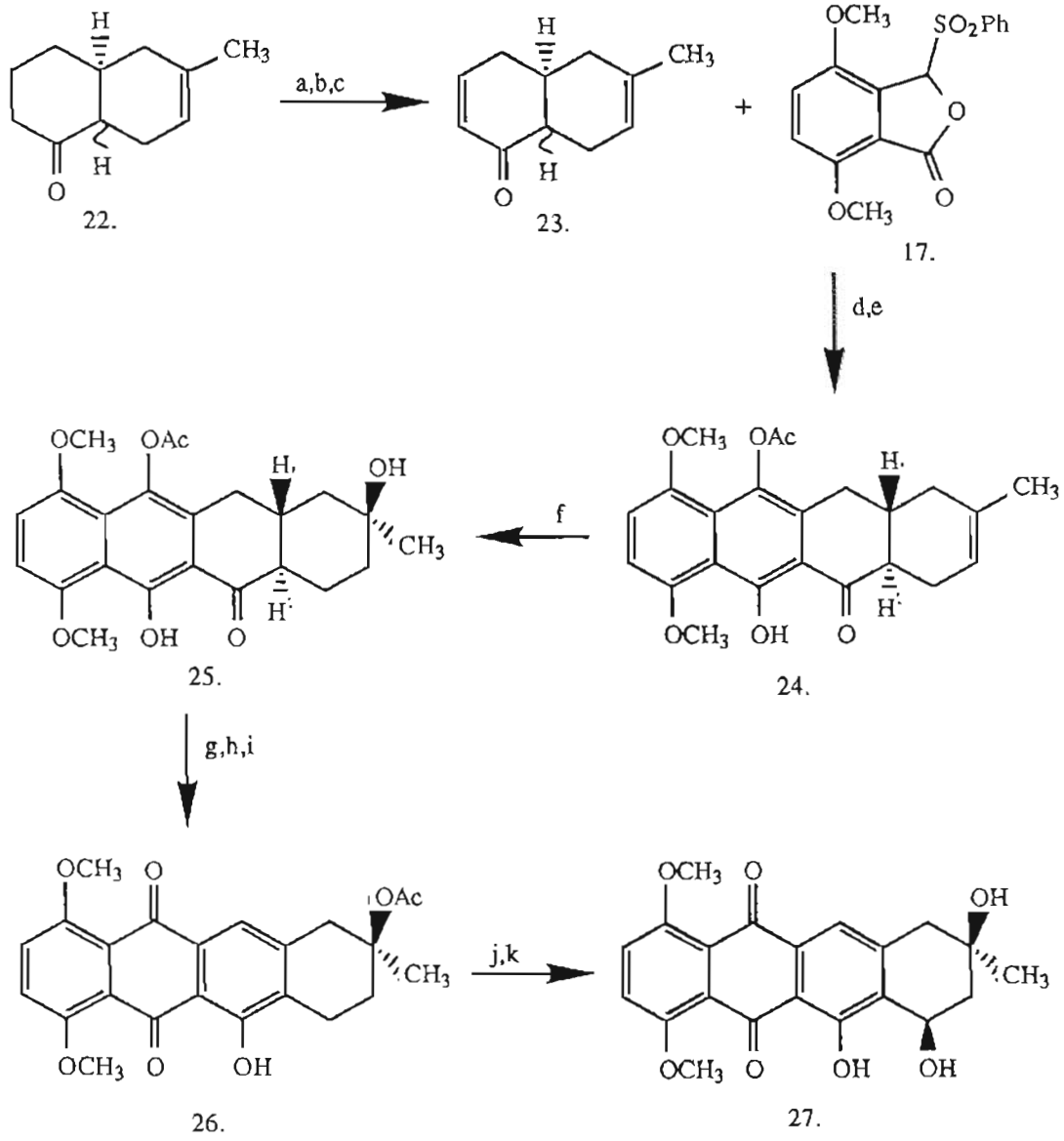
(Br_2, AIBN, CCl_4, H_2O, 67%) of 26 followed by deacetylation (KOH, DME, H_2O, 65°C, 88%) afforded the aglycone 27, analogous to that found in 7-con-O-methylnogarol.

At the time the work in this thesis was initiated there existed no literature precedence for the preparation of functionalized epoxybenzoxocins. During the course of this work, four papers appeared in the literature. The first originated from this laboratory[36] and described the synthesis of functionalized epoxybenzoxocins from phenolic furan carbinols. This work was accomplished in conjunction with the research described in this thesis and will be described in detail in subsequent sections. The second paper, a chiral synthesis of perhydroxylated epoxybenzoxocins with the D-gluco and L-ido configurations, was reported from this group by Hauser and Adams[37] and is described in Scheme 5.

Treatment of the aldehydo sugar 28 with methyl magnesium bromide, followed by Collins[38] oxidation gave the methyl ketone 29. Addition of the Grignard reagent, formed from the benzyl ether derivative of 2-bromo-4-methylphenol, gave the D-gluco configurated tertiary carbinol 30 stereospecifically in 80% yield.

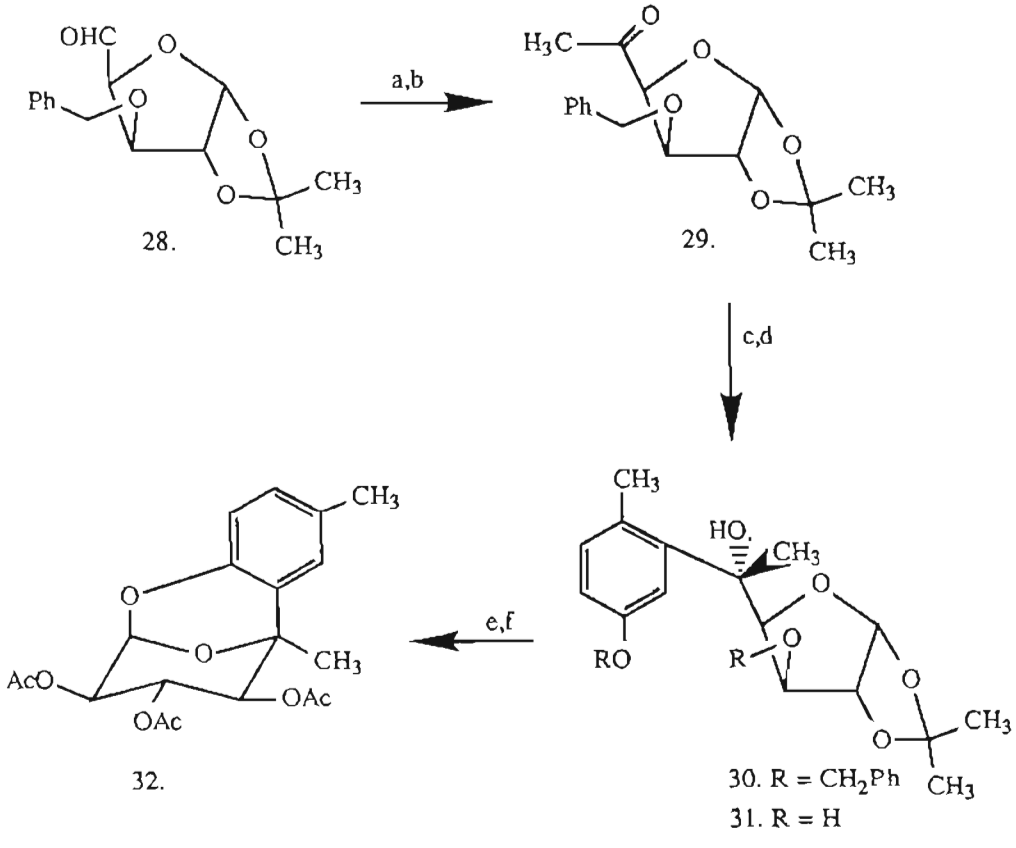
Hydrogenolysis of the benzyl protecting groups (Pd/C, EtOAc) gave the phenol 31 in 96% yield. Hydrolysis of 31 with acidic ion exchange resin[39] (Amberlite IR-20), followed by acetylation (Ac_2O, pyridine), gave a modest yield of the D-gluco (32) and the L-ido (33) isomers in 16% and 17%, respectively.

Scheme 4.



a) lithiun cyclohexylisopropylamide, THF, $PhSSO_2Ph$, -78°C, 90% b) $NaIO_4$, 92% c) CCl_4, $CaCO_3$, reflux, 70% d) LiOtBu, THF, 86% e) Ac_2O, Py, 92% f) $Hg(NO_3)$, NaOH, $NaBH_4$, 81% g) NaOH, O_2, 83% h) Ac_2O, Et_3N, DMAP, 82% i) KOH, DME, H_2O, 93% j) NBS, CCl_4, H_2O, 67% k) KOH, DME, H_2O, 88%

Scheme 5.

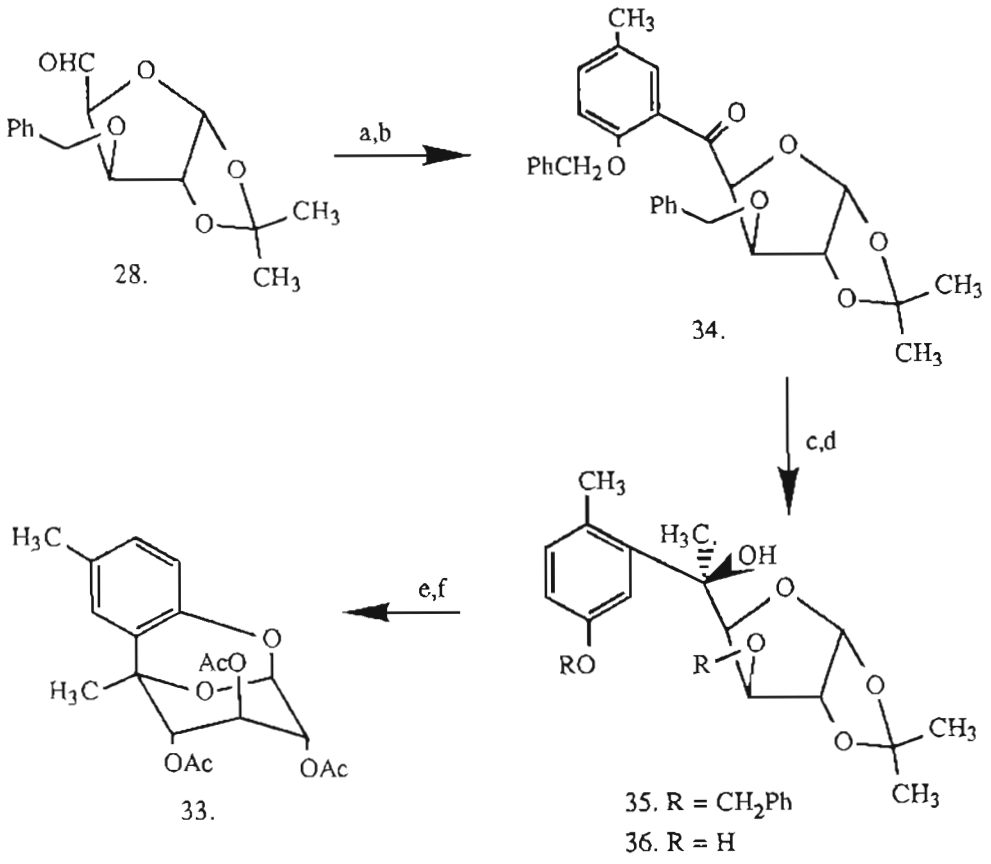


a) MeMgBr b) CrO_3, Py c) 1-benzyloxy-4-methylphenyl-2-magnesium bromide, 80% d) Pd/C, H_2, EtOAc, 96% e) Amberlite IR-20 f) Ac_2O, Py, (32., 16%; 33., 17%)

By inverting the order of Grignard additions to the aldehyde 28, as shown in Scheme 6, the L-ido isomer was prepared stereoselectively. Addition of the Grignard reagent formed from the benzyl ether derivative of 2-bromo-4-methylphenol to 28, followed by Collins[38] oxidation,

gave the ketone 34 in 58% overall yield. Reaction of methyllithium (THF,-78°C) with 34 furnished the tertiary carbinol 35 stereo-specifically in 82% yield.

Scheme 6.



a) 1-benzyloxy-4-methylphenyl-2-magnesium bromide b) CrO_3, Py, 58% c) MeLi, ether, -78°C, 82% d) Pd/C, H_2, EtOH, 95% e) Amberlite IR-20 f) Ac_2O, Py, (32., 4%; 33., 57%)

Hydrogenolysis of 35 (Pd/C, EtOAc) gave a 95% yield of the phenol 36. Hydrolysis of 36 with acidic ion exchange resin[39] (Amberlite IR-120), followed by acetylation, furnished the L-ido (33) and the D-gluco (32) isomers in 57% and 4% yields, respectively.

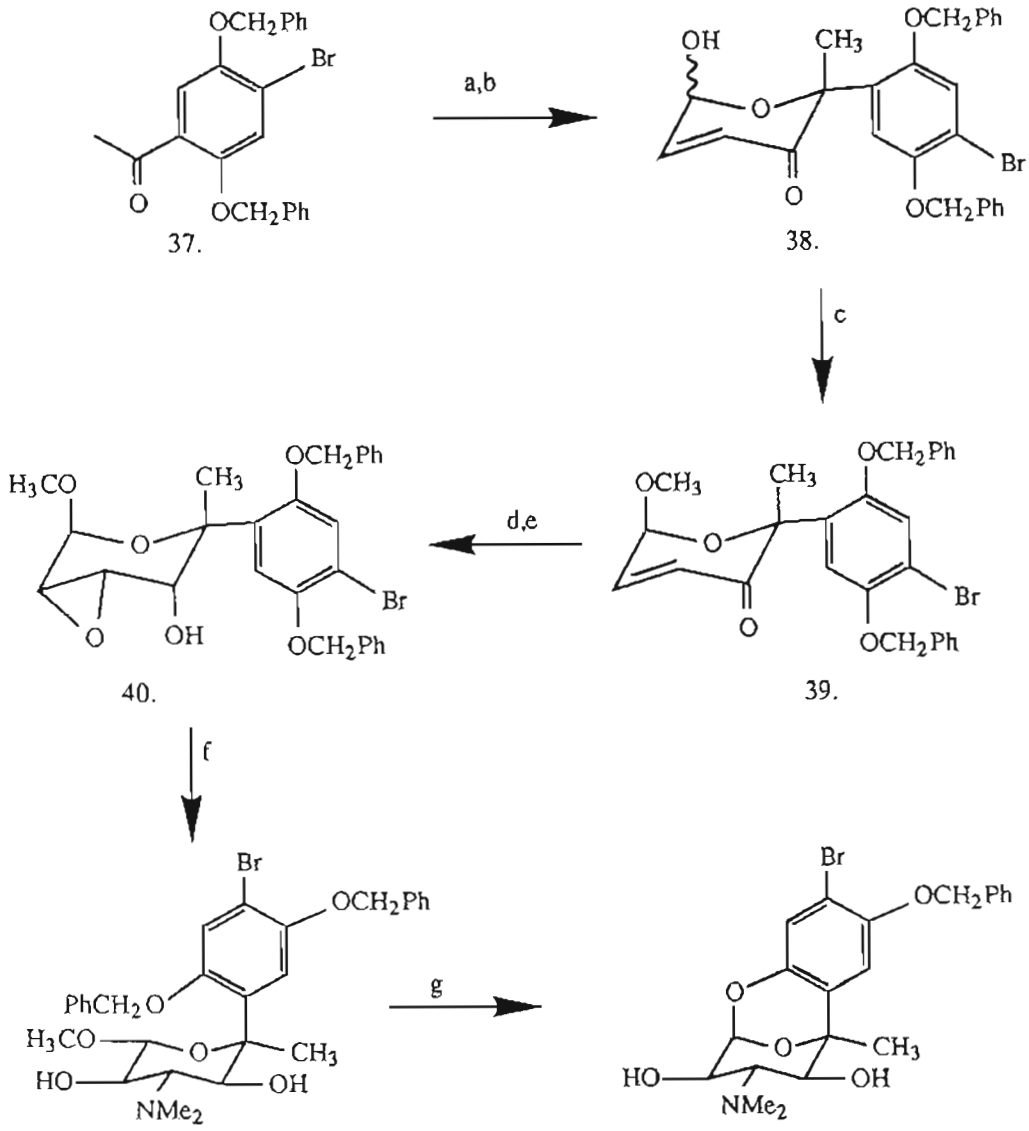
While these preparations were successful, the loss of stereochemical control during ring closure to the epoxybenzoxocin presents a serious drawback to the use of this approach. Moreover, modification of the plan to overcome the problem, likely would result in a protracted sequence.

Following publication of our work on the use of furan carbionls as intermediates to epoxybenzoxocins, Bates an Sammes[40] reported the use of this reaction to prepare a gluco-configurated amino-epoxybenzoxocin as a DEF ring synthon to nogalamycin. Their approach, which explored the use of a hexenulose intermediate is shown in Scheme 7.

The addition of 2-furyllithium[41] to 4-bromo-2,5-dibenzyloxyacetophenone (37) gave a furancarbinol which was oxidized with m-chloroperoxybenzoic acid[42] to the hexenulose 38 in 75% overall yield. Methylation of the anomeric hydroxyl with methyl iodide-silver nitrate[43] to give a 65% yield of the α-glycoside 39 and a 10% yield of the analogous β-glycoside.

Epoxidation of the α-glycoside 39 with alkaline t-butylhydroperoxide[44] (no yield given), followed by reduction of the ketone with sodium borohydride (94%) gave the epoxyalcohol 40. The epoxide ring was opened with dimethylamine[45] in 58% yield to give the amino pyranose 41.

Scheme 7.



a) 2-furyllithium b) mCPBA, 75% c) $AgNO_3$,CH_3I, 65% α-anomer d) t-BuOOH, base e) $NaBH_4$, 94% f) $(CH_3)_2NH$, 58% g) $(CH_3)_3SiI$, $(CH_3)_3SiCl$, 40%

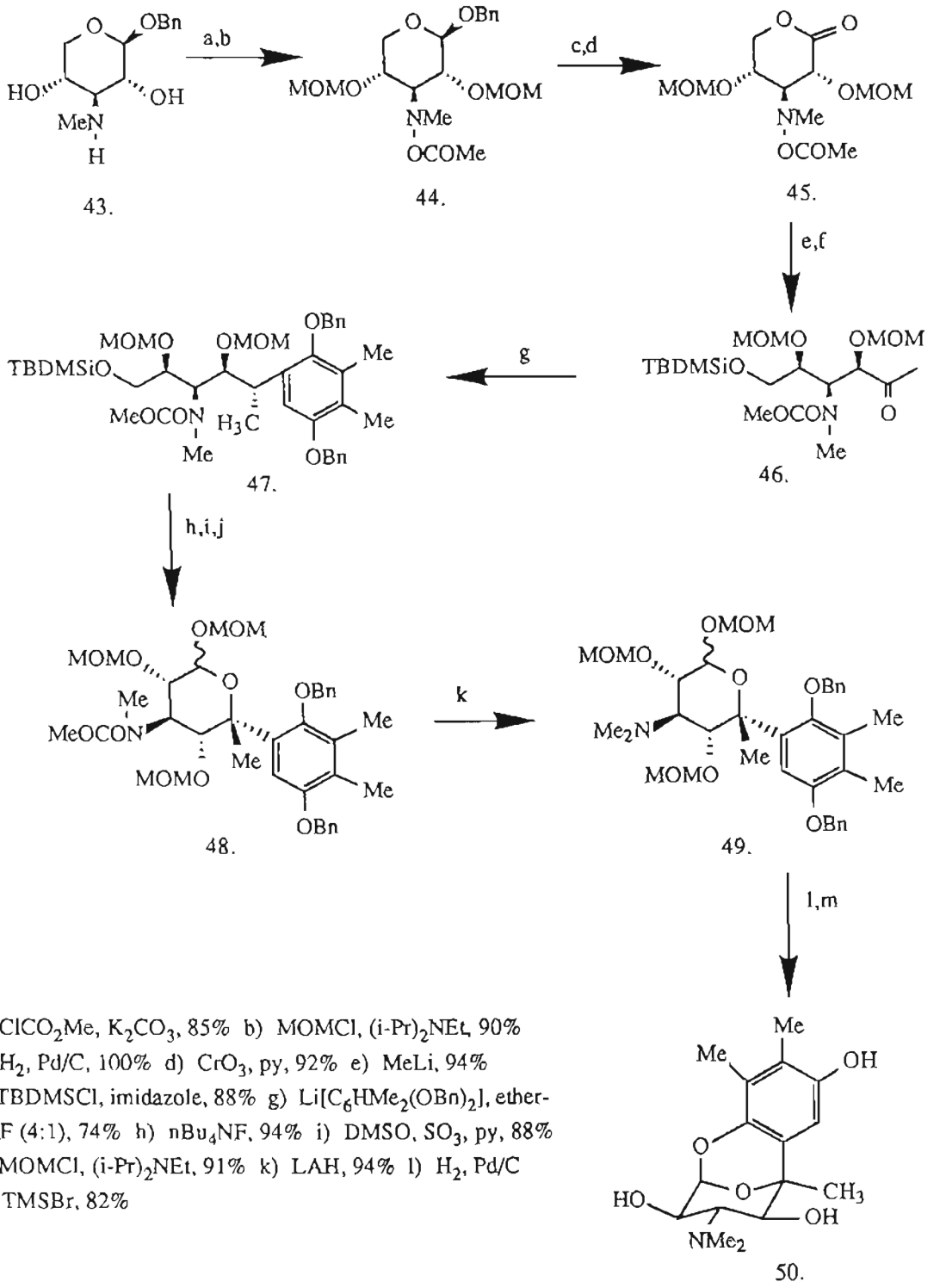
Cleavage (trimethylsilyl iodide/trimethylsilyl chloride[46]) of the benzyloxy protective group and the methyl acetal, followed by concomitant ring closure gave the desired DEF ring synthon 42 in 40% yield.

A chiral synthesis of a DEF ring synthon to Nogalamycin, developed by Terashima, et al.[47], was the fourth paper to appear. The synthesis began with an amino sugar, benzyl β-D-gentosaminide[48,49] (43), that already contained all the desired stereochemistry required in the final synthon (50).

As shown in Scheme 8, the methylamino group in 43 was protected as a urethane through acylation with methylchloroformate[50] and the alcohols were protected as methoxymethyl ethers[51] (methoxymethyl chloride, diisopropylethylamine). The product 44, obtained in 77% overall yield, was hydrogenolyzed (Pd/C EtOH) to cleave the benzyl protective group. Collins[18] oxidation of the lactol gave the lactone 45 in 92% overall yield. Treatment of 45 with methyllithium followed by silylation (t-butyldimethylsilyl chloride, imidazole[52]) furnished the acyclic methyl ketone 46 in 83% overall yield.

The aryllithium generated from 1,4-dibenzyloxy-5-bromo-2,3-dimethylbenzene was added to 46 to give a 66% yield of the alcohol 47 with the desired stereochemistry. Desilylation[53] (tetra-n-butyl ammonium fluoride) of 47, followed by oxidation of the resulting alcohol (DMSO, SO_3[54]) and protection of the lactol (methoxymethyl chloride, diisopropylethylamine[51]) gave the methoxymethyl acetal 48 in 76% overall yield.

Scheme 8.



a) $ClCO_2Me$, K_2CO_3, 85% b) MOMCl, $(i\text{-}Pr)_2NEt$, 90%
c) H_2, Pd/C, 100% d) CrO_3, py, 92% e) MeLi, 94%
f) TBDMSCl, imidazole, 88% g) $Li[C_6HMe_2(OBn)_2]$, ether-THF (4:1), 74% h) nBu_4NF, 94% i) DMSO, SO_3, py, 88%
j) MOMCl, $(i\text{-}Pr)_2NEt$, 91% k) LAH, 94% l) H_2, Pd/C
m) TMSBr, 82%

Lithium aluminum hydride reduction of the urethane in 48 afforded the dimethylamino compound 49 in 94% yield. Removal of the benzyl ethers (Pd/C, H_2, EtOH) and cleavage of the three methoxymethyl ethers (trimethylsilyl bromide[55]), with simultaneous ring closure, gave the desired tricyclic intermediate 50 in 82% yield.

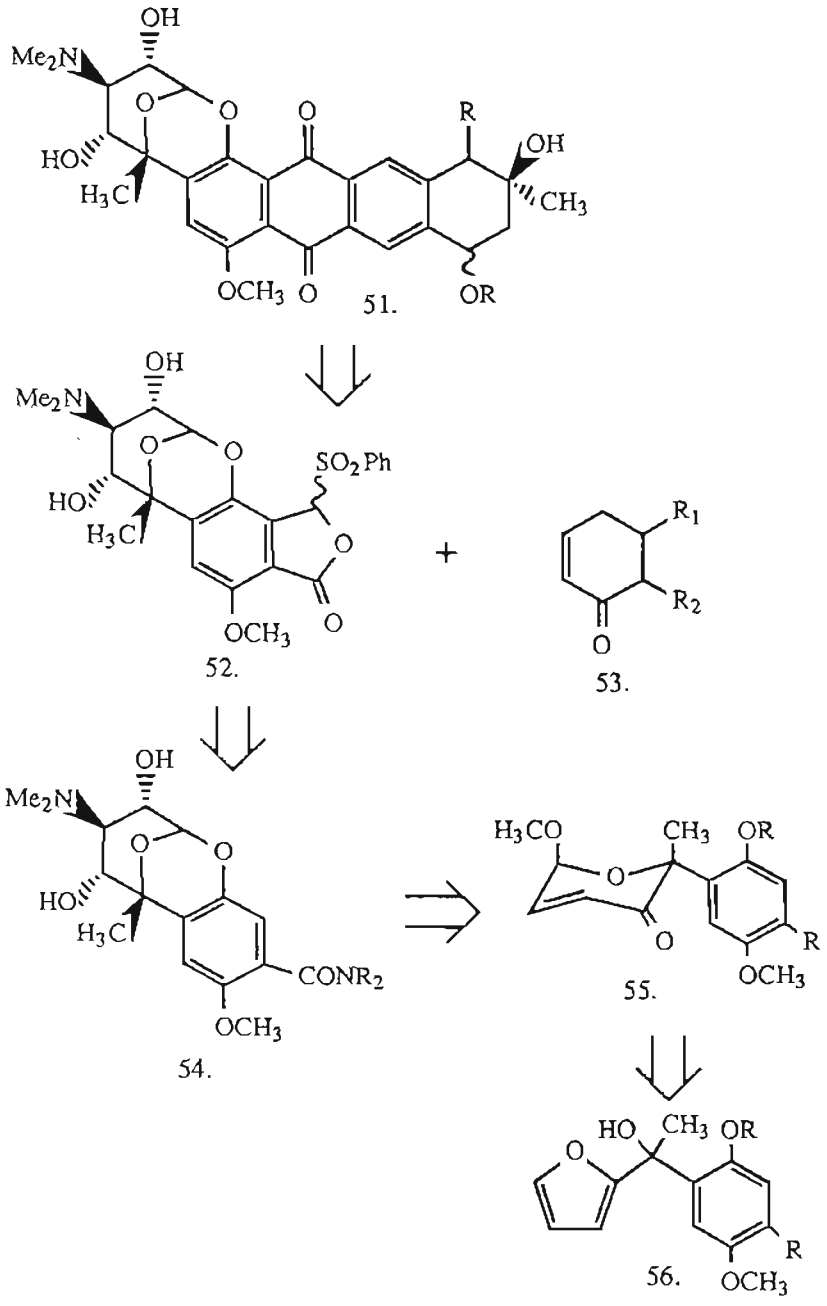
The DEF ring synthons prepared by Bates and Sammes[40] (7 steps, <10% overall yield) and Terashima, et al.[47] (13 steps 22% overall yield, based on benzyl β-D-gentosaminide) are excellent examples of building synthons to perform convergent organic syntheses. However, it is not clear how either investigator proposes to construct the remaining aromatic fragment present in nogalamycin and 7-con-O-methylnogarol. Furthermore, a total synthesis of noglamycin or 7-con-O-methylnogarol has yet to appear in the literature. Thus, there exists the need to prepare different synthons to complete the task of synthesizing these important antitumor agents.

III. Synthetic Strategy

The ultimate objective of this synthetic work was to prepare nogalamycin and 7-con-O-methylnogarol by an efficient, regio- and stereospecific method. The synthetic strategy to realize this goal is outlined in the antithetic analysis shown in Scheme 9. The generalized structure 51 for the desired anthracyclinones can be divided through the C ring to give a functionalized phthalidesulfone (52) and an appropriately substituted hexenone (53). The requisite hexenones, their condensation with phthalide sulfones and the subsequent steps needed to convert the intermediates to final products was discussed in the Literature Background section of this thesis.

The phthalidesulfone portion of the required sugar substituted epoxybenzoxocin can be readily prepared through ortho-metallation of a dialkylbenzamide moiety (54). The dialkylbenzamide can be synthesized from a suitably substituted hexenulose (55) through functionalization of the hexenone fragment followed by regiospecific deprotection of a phenol and acid catalyzed cyclization. The hexenulose 55 can be obtained by oxidation of a furan ring bound to an appropriately functionalized aromatic ring such as 56.

Scheme 9.


OH
Me2N
HO
H3C
O
O
O
R
OH
CH3
OCH3
O
OR
51.
SO2Ph
52.
R1
R2
53.
CONR2
54.
H3CO
CH3
OR
55.
HO
56.

IV. Synthesis of 2,6-Epoxy-1(2H)-benzoxocin Sugar Analogues

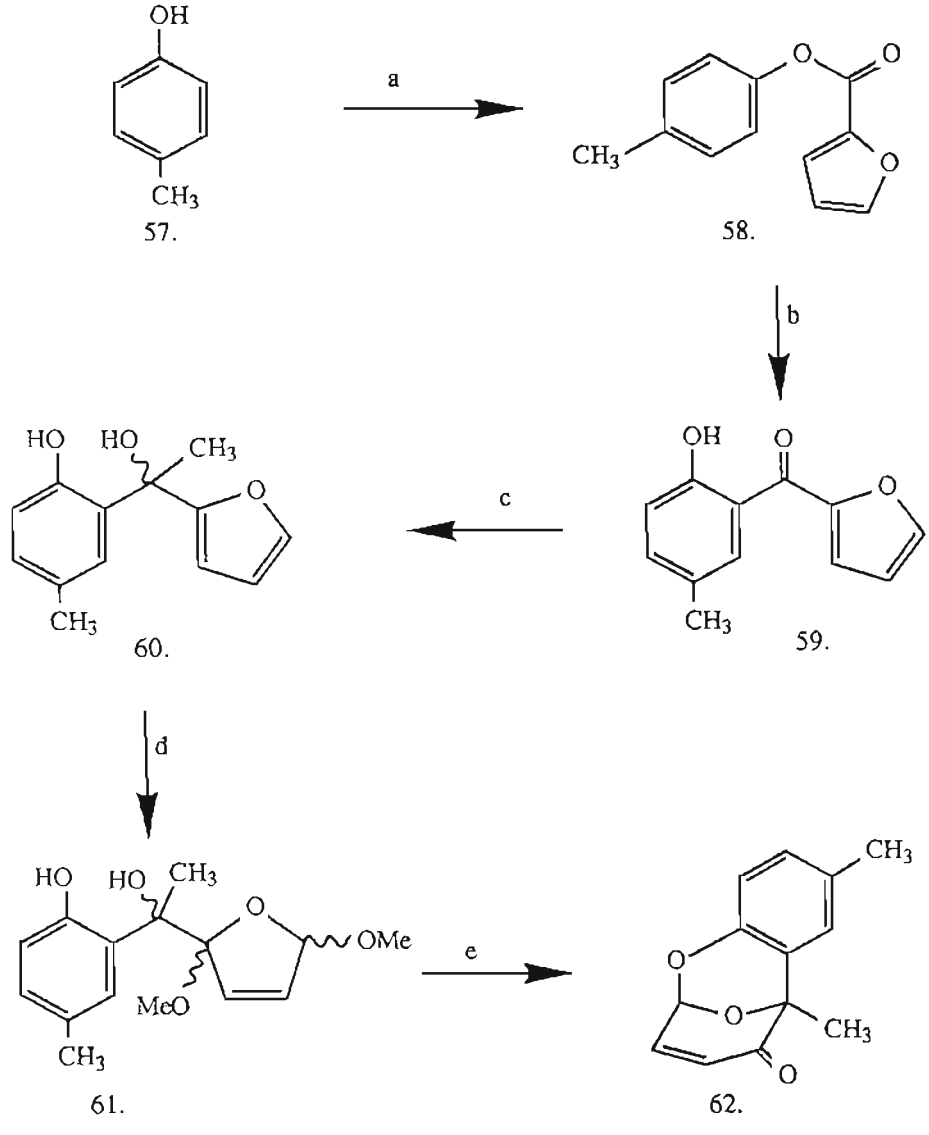
A. Synthesis of D,L-6,8-Dimethyl-2,6-epoxy-1(2H)benzoxocin-5-(6H)-one (62)

The preparation of ketooxocin 62 was accomplished as shown in Scheme 6. Acylation of p-cresol (57) with 2-furoyl chloride afforded the ester 58 in 94% yield, which on Fries rearrangement in molten aluminum chloride (2 equiv., 165°C) furnished the ketone 59 in 87% yield[56]. Reaction of 59 with excess methyllithium (3 equiv.) gave the tertiary alcohol 60 in 92-95% yield. Although 60 was reasonably stable, on chromatography it underwent dehydration and therefore was not purified but directly used in the next step.

Oxidation of the furan ring in 60 by the method of Achmatowicz, et al.[57] (bromine in methanol, followed by neutralization with ammonia) afforded the methanol adduct 61 as a mixture of diastereoisomers. This material was not purified but directly hydrolyzed in acetic acid containing dilute sulfuric acid to furnish the crystalline ketobenzoxocin 62 in 79% yield.

The optimal conditions for the oxidation, hydrolysis and intramolecular cyclization of 60 to 62 were obtained only after a lenghty study. Hydrolysis of 61 in refluxing tetrahydrofuran containing a catalytic amount of 5% hydrochloric acid afforded variable yields of 62 (0 to 45%).

Scheme 10.

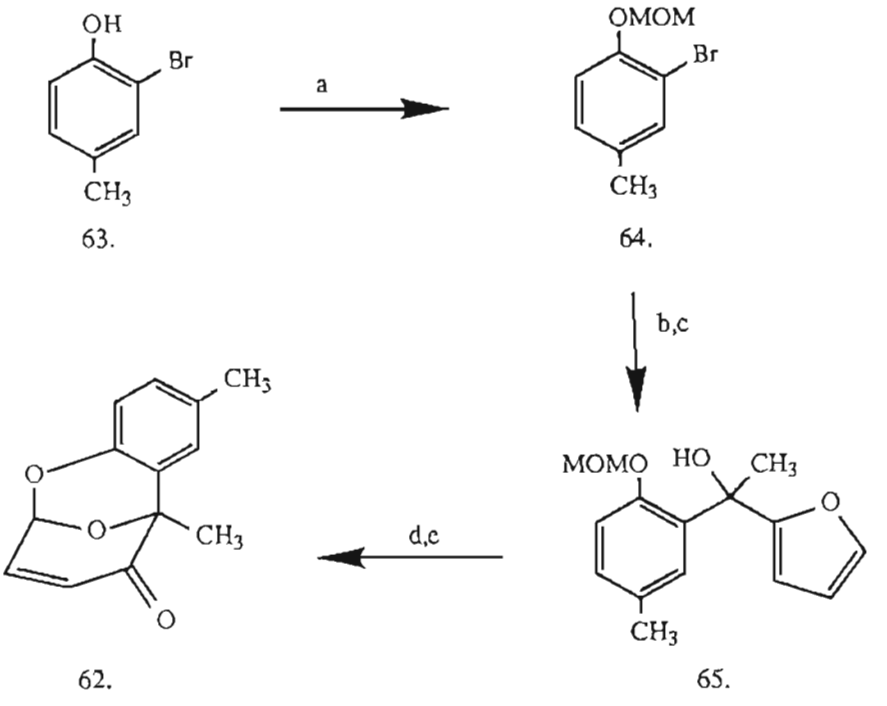


a) 2-furoyl chloride, Py, CH_2Cl_2, 94% b) $AlCl_3$, 165° C, 30 min., 87%
c) CH_3Li, Et_2O, 95% d) Br_2, MeOH, -78° C e) H_2SO_4 (0.5 N), HOAc, 50° C, 79%

The use of aqueous bromine[58] to perform both the oxidation and subsequent hydrolysis gave a complex product mixture containing less than 5% of 62. Oxidation of 60 with m-chloroperoxybenzoic acid[42], followed by cyclization with either aqueous acid or toluenesulfonic acid in refluxing benzene afforded 62 in 17% yield. The optimized method, bromine/methanol oxidation of the furan moiety[57], followed by acetic acid-dilute sulfuric acid hydrolysis afforded an experimentally simple procedure which consistently, furnished 62 in greater than 75% yield.

The alternative procedure to 62, shown in Scheme 11 was investigated in order to avoid the experimentally tedious use of molten aluminum chloride. Commercially available 2-bromo-4-methylphenol (63) was converted to the methoxymethyl ether derivative 64 in 87% yield through treatment with sodium hydride and methoxymethyl chloride[52]. Reaction of the Grignard reagent (magnesium, tetrahydrofuran, reflux) derived from 64 with 2-acetylfuran gave the furanmethanol 65 in 70% yield. Oxidation of 65 (bromine, methanol) followed by hydrolysis with concomitant intramolecular cyclization (acetic acid, 0.5 N sulfuric acid) using the previously optimized procedures gave 62 in 55% yield. Although this method is shorter and avoids the use of aluminum chloride, the overall yield (4 steps, 33% overall yield) is less than that obtained in the previous sequence (5 steps, 60% overall yield). Therefore, large scale preparations of 62 were performed using the Fries rearrangement procedure.

Scheme 11.



63. 64. 65. 62.

a) NaH, MOMCl, THF, 87% b) Mg, THF, reflux c) 2-acetylfuran, 70%
d) Br_2, MeOH; NH_3 HOAc, H_2SO_4 (aq), 55%

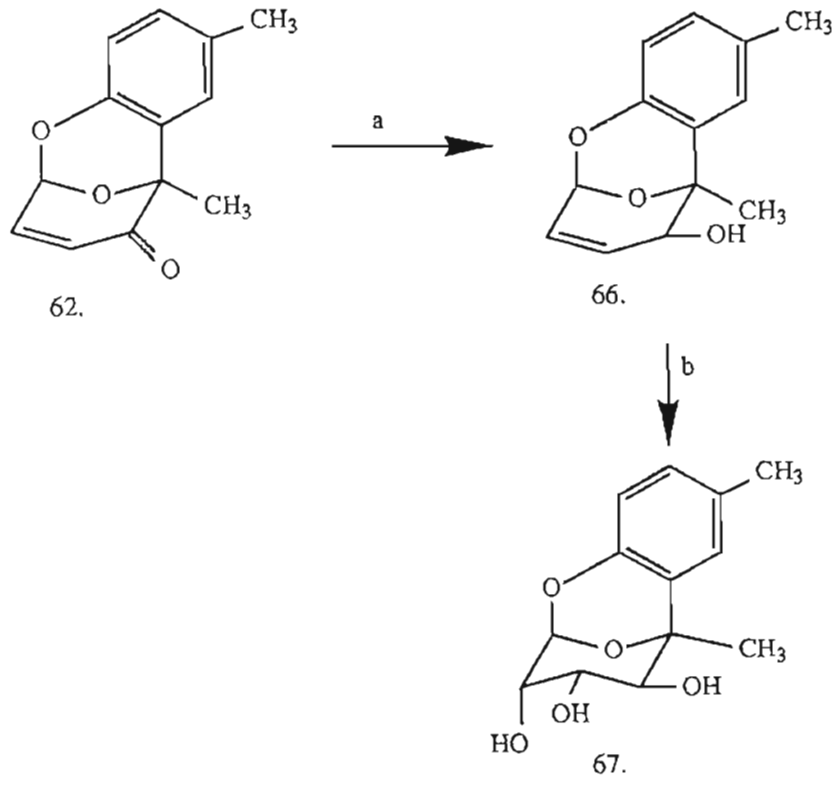
B. Synthesis of 1,2'-Anhydro-6-deoxy-5-C-(2'-hydroxy-5'-methylphenyl-α-D,L-mannopyranose (67)

The presence of the phenyl group and the rigidity of the bicyclic epoxybenzoxocin ring system creates a strong diastereofacial bias in the enone fragment in 62. Thus, reactions should occur predominantly, if not exclusively from the less hindered exo face of the molecule. As a consequence, further transformation of 62 to sugar analogues through manipulation of the enone fragment was anticipated to occur in a highly stereoselective, if not stereospecific manner.

The conversion of 62 to the benzoxocin sugar analogue 67 with the manno configuration was readily accomplished as shown in Scheme 12. Reduction of 62 with either lithium aluminum hydride of cerium borohydride[59] furnished the endo alcohol 66 stereospecifically in 97% yield. cis-Hydroxylation of the olefinic moiety in 66 with trimethylamine N-oxide and a catalytic amount of osmium tetroxide[60] also proceeded stereospecifically and gave the triol 67 in 92% yield.

The chemical shifts for the individual protons on carbons C-2 through C-5 were well separated in the ^{1}H NMR spectrum of 67. Analysis of the spin-spin couplings permitted definitive assignment of the stereochemistry. A notable feature of the spectrum was the upfield location of the C-4 proton (dd, J=9.7 Hz) at 3.24 ppm which is a consequence of its proximity to the shielding cone of the aromatic ring.

Scheme 12.



62. 66. 67.

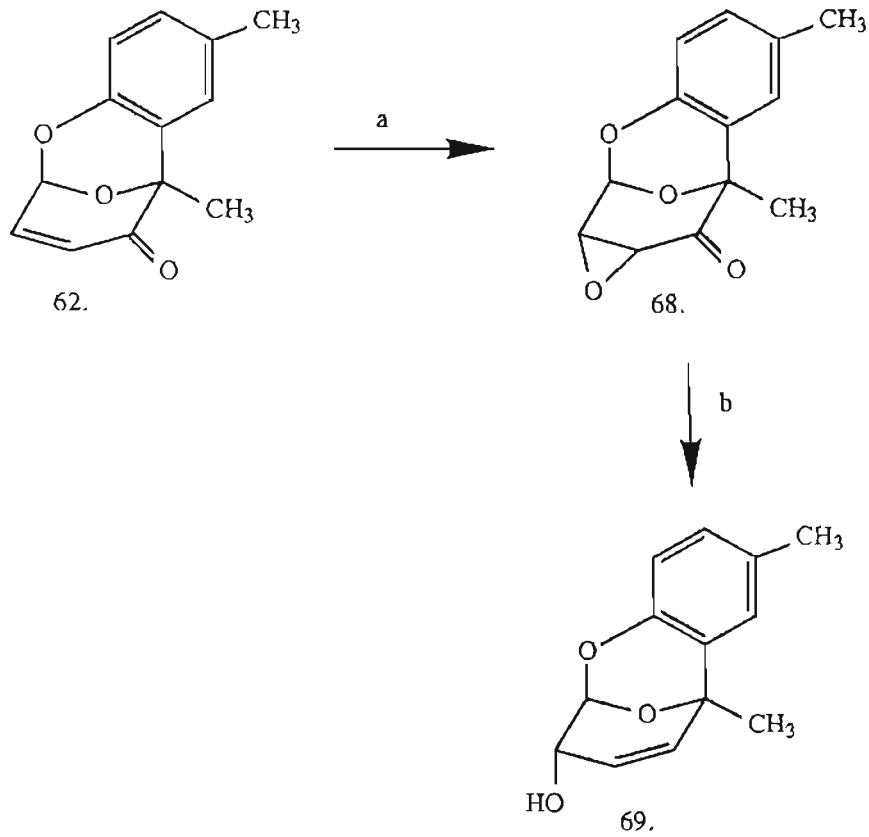
a) LAH, Et_2O, 96% b) catalytic OsO_4, TMNO, 92%

C. Synthesis of 1,2'-Anhydro-6-deoxy-5-C-(2'-hydroxy-5'-methylphenyl) α-D,L-talopyranose (75) and 1,2'-Anhydro-6-deoxy-5-C-(2'-hydroxy-5'-methylphenyl)-α-D,L-altropyranose (76)

Due to the stereochemical bias generated by the presence of the phenyl ring in the ketoepoxybenzoxocin ring system, other sugar analogs could not be attained without inversion of the regiochemistry of functionalization in the system. Initially, the route shown in Scheme 13 was investigated. The olefinic entity in 62 proved resistant to epoxidation with a variety of reagents, (Triton-B/tert-butylhydroperoxide[44], hydrogen peroxide/sodium hydroxide[61], and m-chloroperoxybenzoic acid[62]). However, reaction with sodium hypochlorite in dioxane[63] produced the desired epoxide (68) though in modest yield (45%). Subsequent Wharton fragmentaton[64,65] of 68 gave only a 5% yield of the desired allyl alcohol (69). However, the experimental result could not be reproduced or optimized.

Since the yield from the Wharton procedure was not synthetically useful, the alternate sequence shown in Scheme 14 was investigated for inverting the regiochemistry of the allyl alcohol system. This plan utilizes the finding by Evans et al.[66] that in refluxing methanol in the presence of trimethyl phosphite, allyl sulfoxides undergo thermal [3.3]-sigmatropic rearrangement with subsequent reductive cleavage to allyl alcohols.

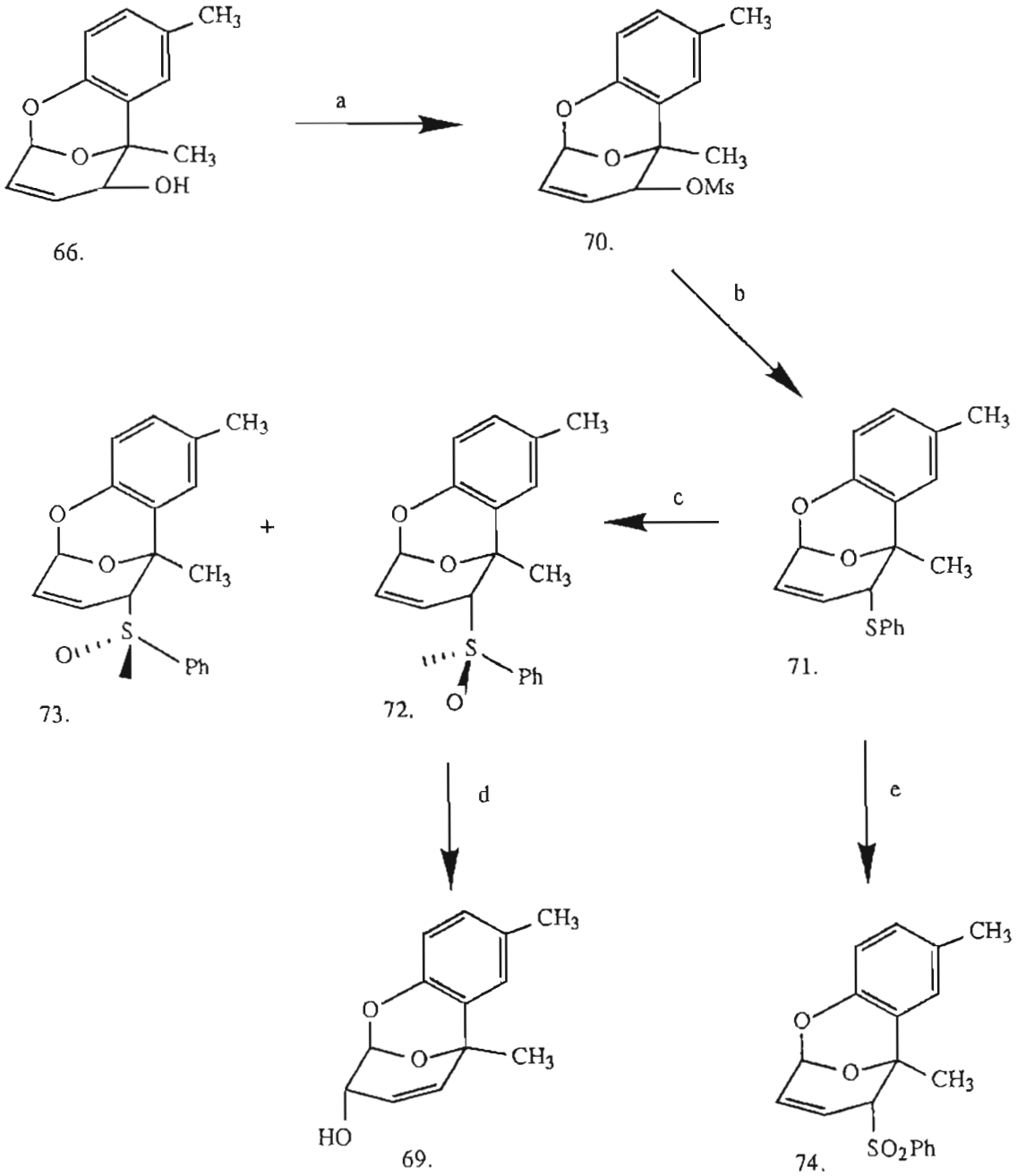
Scheme 13.



62. 68. 69.

a) NaOCl, dioxane, 36% b) H_2NNH_2, HOAc, <5%

Scheme 14.



a) MsCl, Py, 86% b) PhSH, K_2CO_3, DMF, 48% c) mCPBA, 50, 49%; 51, 40%
d) $P(OMe)_3$, MeOH, 88% e) mCPBA, 94%

Treatment of allyl alcohol 66 with methanesufonyl chloride and pyridine afforded the mesylate 70 in 86% yield. Displacement of the mesylate group with thiophenoxide anion (potassium carbonate, dimethylformamide) gave the sulfide 71 in 48% yield. Oxidation of 71 with m-chloroperoxybenzoic acid (methylene chloride, -78°C) gave a 5:4 ratio of the readily separable diastereomeric sulfoxides 72 and 73 in 89% yield.

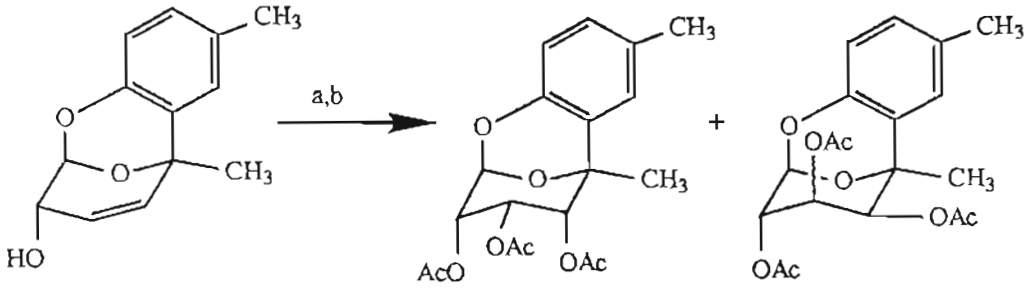
Although the ^{1}H NMR spectra of the sulfoxide diastereoisomers were distinctly different, it was not possible to assign the relative stereochemistry. However, the dichotomy in chemical behavior uniquely permitted assignment of the stereochemistry at sulfur. The more polar sulfoxide smoothly underwent [3,3]sigmatropic rearrangement and reductive cleavage at reflux in methanol containing trimethyl phosphite and gave the allyl alcohol 69 in 88% yield. Under the same conditions, the less polar sulfoxide failed to undergo any reaction and the starting material was recovered. Based on its ability to readily attain a transition state geometry that furnishes 69, the more polar isomer was assigned structure 72. Since the transition state geometry of the less polar sulfoxide results in a severe steric interaction between the ring methyl and the sulfoxide phenyl group, this isomer fails to undergo reaction and was assigned structure 73.

Attempts to enhance the formation of the sulfoxide diastereoisomer 72, by oxidizing 71 with sodium periodate[67], ceric ammonium nitrate[68], N-chlorosuccinimide[69], titanium trichloride-hydrogen peroxide[70], and selenium dioxide-hydrogen peroxide[71] were not successful. Moreover,

efforts to racemize 73 with hydrochloric acid[72] in dioxane or to invert the configuration of 73 through alkylation with Merwein's reagent (trimethyloxonium tetrafluoroborate) followed by hydrolysis[73] were also unsuccessful. However, reduction of 73 with lithium aluminum hydride resulted in a 50% yield of the reoxidizable sulfide starting material 71. To confirm that the sulfoxide diastereoisomer 73 was not the sulfone 74, an authentic sample of 74 was prepared by oxidation of 71 with m-chloroperoxybenzoic acid (2 equiv) in 94% yield.

cis-Hydroxylation of the olefinic entity in the allyl alcohol 69, was performed with the trimethylamine N-oxide/osmium tetroxide reagent combination as shown in Scheme 15. The resultant triols were separated only after conversion to the peracetate derivatives. Analysis of the ^{1}H NMR spectrum established that the major product 75 (47%) had the talo configuration. This isomer results from hydroxylation of the less hindered exo olefinic face. The minor isomer with the altro configuration (76) was identified from its striking ^{1}H NMR spectrum; the methyl of the 4-acetoxyl group was shifted upfield to 1.40 ppm since it lies directly in the shielding cone of the phenyl ring. Although the exo olefinic face in 69 is less hindered, the presence of the C-3 axial alcohol presents a significant steric impediment to hydroxylation from this direction.

Scheme 15.



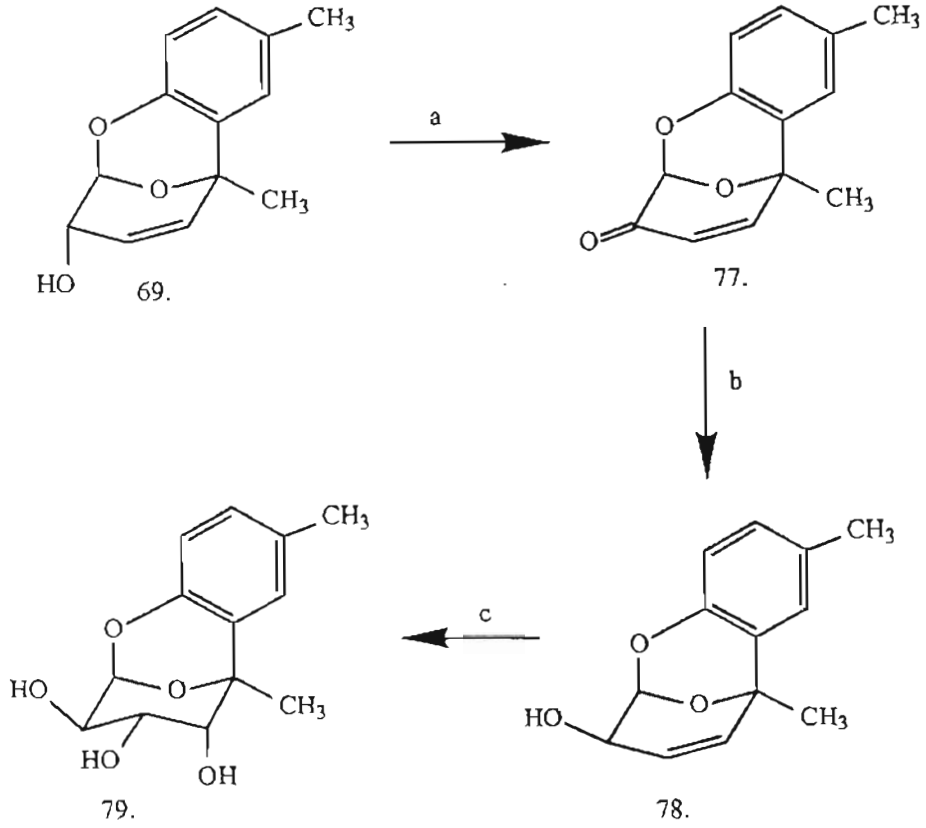
69. 75. 76.

a) cat. OsO_4, TMNO b) Ac_2O, Py, 54., 47%; 55., 18%

D. Synthesis of 1,2'-Anhydro-6-deoxy-5-C-(2-hydroxy-5-methylphenyl)-α-D,L-galactopyranose (79)

The allylic alcohol (69) was also employed as shown in Scheme 16 to prepare the epoxyoxocin sugar analog with the galacto configuration. Inversion of the stereochemistry of the C-2 alcohol in 69 was accomplished by oxidation with Swern's reagent[30] (oxalyl chloride, dimethyl sulfoxide, triethylamine, 74% yield) followed by reduction with lithium aluminum hydride (94% yield) to the epimerized alcohol 78. This reduction was stereospecific resulting from hydride attack on the less hindered exo face. cis-Hydroxylation of 78 with catalytic osmium tetroxide/ trimethylamine N-oxide gave stereospecifically the sugar analog 79 with the galacto configuration in 74% yield.

Scheme 16.

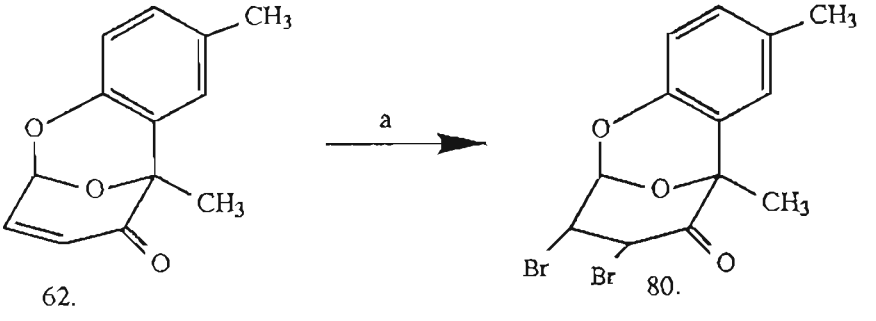


a) ClCOCOCl, Me_2SO, Et_3N, 74% b) LAH, Et_2O, 94% c) OsO_4, TMNO, 72%

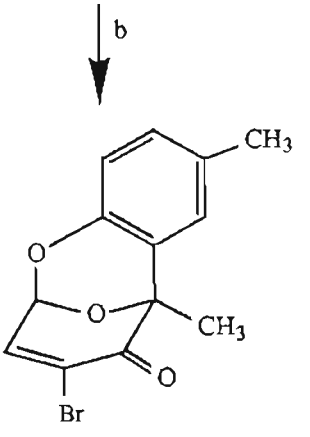
E. Synthesis of 1,2'-Anhydro-2,6-dideoxy-3-bromo-5-C-(2'-hydroxy-5'-methylphenyl)-α-D,L-hex-2-en-4-ulose (81)

The strong diastereofacial bias observed in the synthesis of the benzoxocin sugar analogs prompted the examination of other addition reactions of the olefinic entity. Bromination of olefins is known to occur by a trans diaxial mechanism via a bromonium ion intermediate. Treatment of 62 with bromine, shown in Scheme 17, resulted in the dibromide 80 in quantitative yield. Analysis of the coupling constants in the ^{1}H NMR (J_{AB}=3.6 Hz and J_{BC}=12.2 Hz) of 80 showed that the pyranose ring was in a "twist boat" rather than a chair conformation. This is a consequence of the flexibility added to the ring by the sp^2 hybridized carbon at C-4 and the steric repulsion caused by interaction of the axial C-3 bromine and the phenyl ring. Attempted purification of 80 by silica gel chromatography resulted in dehydrohalogenation to the unsaturated bromoketone 81.

Scheme 17.



62. 80.



a) Br_2, CCl_4, 99% b) silica gel, 60% 81.

V. Synthesis of 2,6-epoxy-1(2H)-benzoxocin Deoxyamino Sugar Analogs

A. Synthesis of 1,2'-Anhydro-2,3,6-trideoxy-(3-acetamido)-(4-acetoxy)-5-C-(2'-hydroxy-5'-methylphenyl)-α-D,L-ribohexopyranose (85)

While the preceding studies demonstrated that electrophilic hydroxylation of the olefinic moiety provides convenient access to a wide variety of epoxybenzoxocin sugar analogs, construction of a C-3 amino epoxybenzoxocin with the gluco configuration would likely require introduction of the amine group through nucleophilic replacement of the C-3 oxygen functionality. To this point, only one nucleophilic replacement on the epoxybenzoxocin ring system had been performed; preparation of the thiophenyl intermediate from the 4-O-mesylate (70).

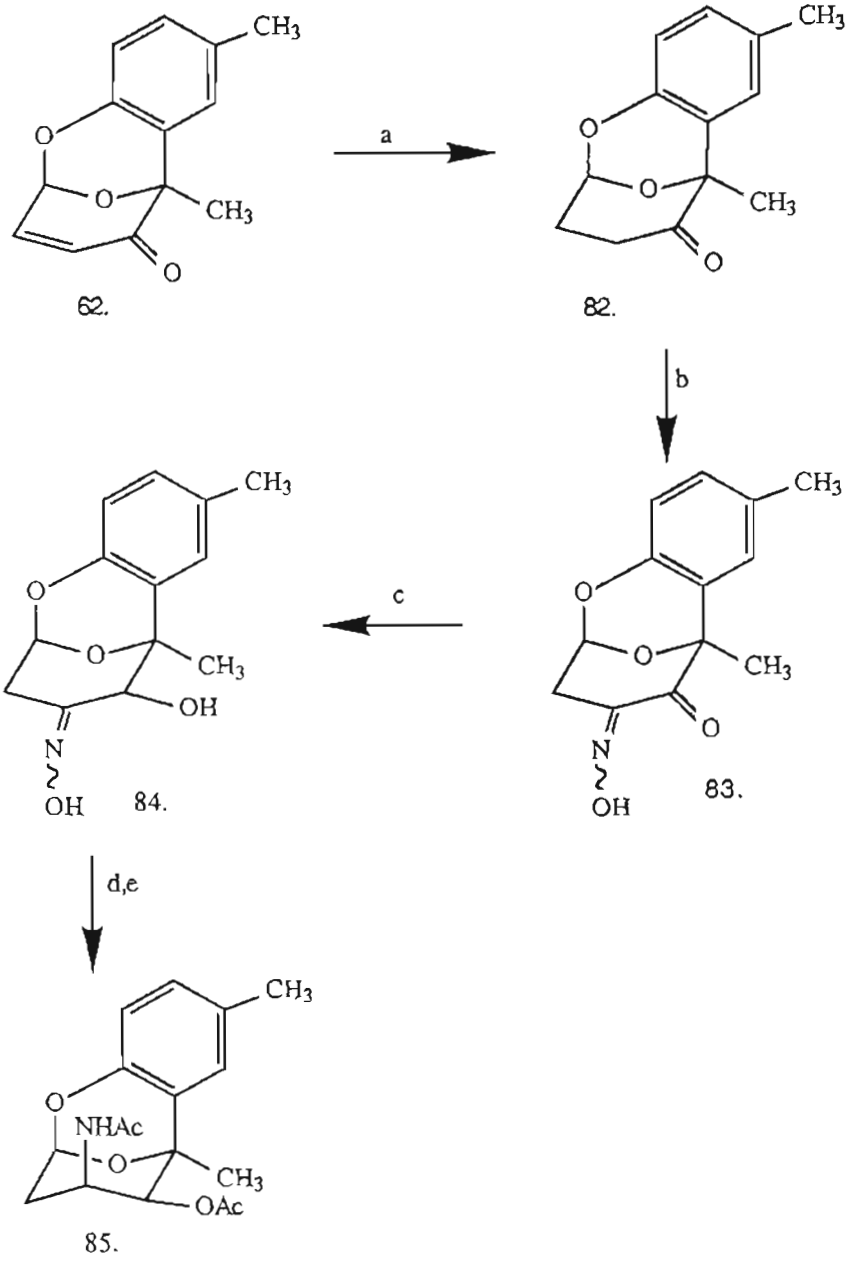
In order to explore the feasibility of conducting nucleophilic replacement of functionality on the pyran ring, the reaction sequences shown in Schemes 18 through 22 were investigated. The decision to use a less highly functionalized ring system for this study was based on several considerations; selective manipulation of functionality would be simplified, the sequences provide deoxyamino isomers which would permit direct comparison of the products, and spectral interpretations would be simplified due to the absence of interfering functionality. An added feature of these routes is that they provide deoxyamino epoxybenzoxocin sugar analogs for structure-activity studies.

The deoxyamino epoxybenzoxocin sugar analog with the ribo configuration was prepared as shown in Scheme 18. Catalytic

hydrogenation (palladium on carbon, ethyl acetate) of 62 gave the saturated ketone 82 in quantitative yield. Addition of a solution of 82 and isoamylnitrite[74] to a solution of sodium methoxide routinely furnished the α-oximinoketone 83 in 88% yield. These conditions were established only after considerable study; the use of other reagents or protocols gave little or none of the desired product. Sodium borohydride reduction of 83 gave the oximino alcohol 84 in 96% yield. Catalytic hydrogenation (palladium on carbon, ethyl acetate) of 84 gave the aminoalcohol as an intractable oil, which after acetylation (acetic anhydride, pyridine), gave the diacetate 85 with the ribo configuration in 69% yield.

The overall preparation of 85 was stereospecific since both reduction steps occurred exclusively from the exo face due the diastereofacial bias of the benzoxocin ring system.

Scheme 18.



62. 82. 83. 84. 85.

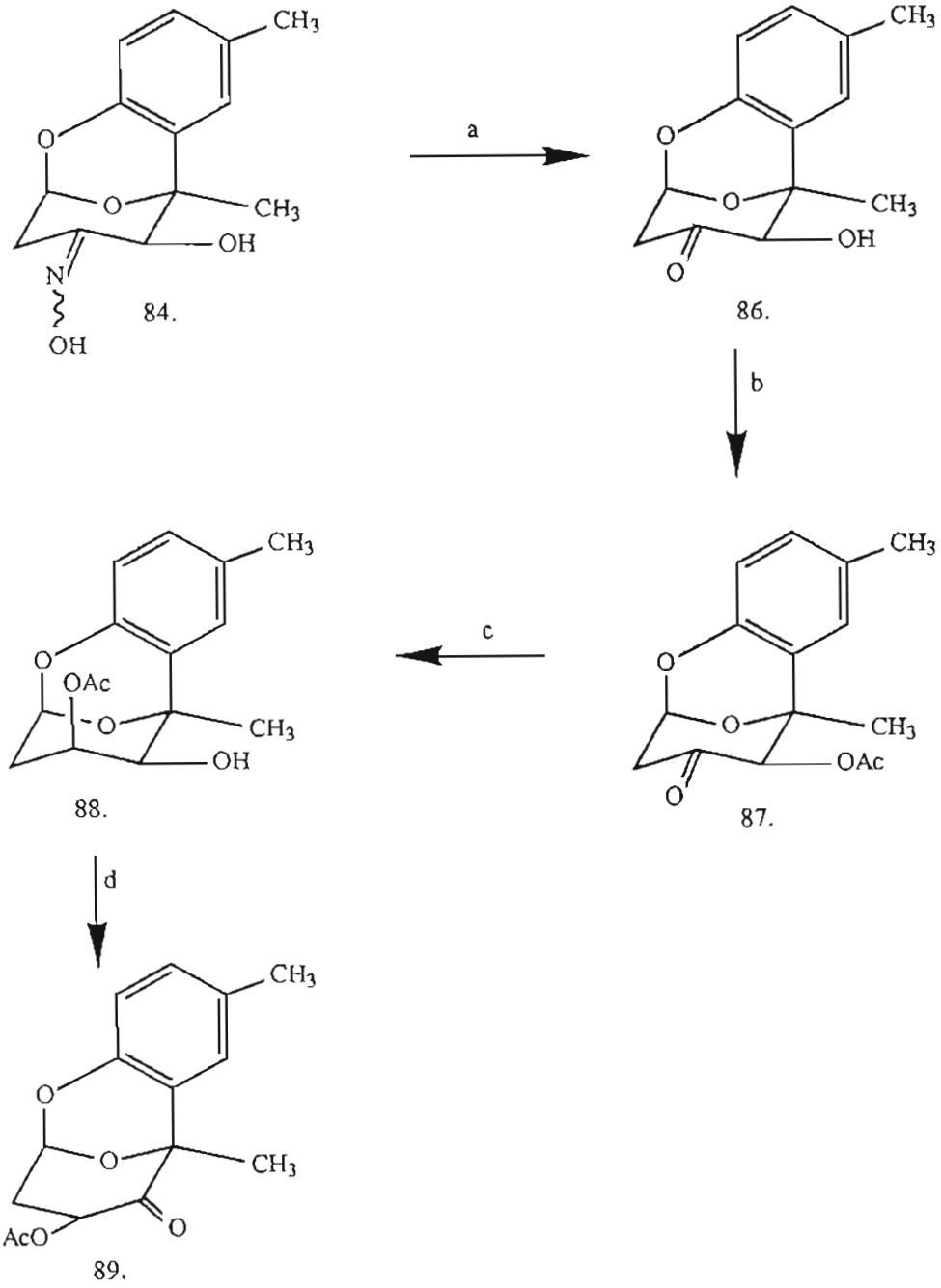
a) H_2, Pd/C, EtOAc, 99% b) NaOMe, MeOH, isoamyl nitrite, 88% c) $NaBH_4$, IPA, 96%
d) H_2, Pd/C, HOAc e) Ac_2O, Py, 69%

B. Synthesis of 1,2'-Anhydro-2,3,6-trideoxy-3-acetamido-4-hydroxy-5-C-(2'-hydroxy-5'-methylphenyl)-α-D,L-arbinohexopyranose (98)

In order to prepare the deoxyamino epoxybenzoxocin sugar analog with the arabino configuration, the oxime functionality in (84) must be hydrolysed to a ketone. Reduction of the ketone would only proceed stereospecifically to yield an endo alcohol. Displacement of the C-3 endo alcohol with a nitrogen nucleophile would provide the desired arabino configurated sugar analog.

Cleavage of the oxime group in 84 through exchange with pyruvate[75,77], followed by acetylation (acetic anhydride, pyridine) of the keto alcohol intermediate 86 gave the acetoxyketone 87 in 92% overall yield (Scheme 19). Reduction of the ketone moiety in 87 with a variety of reducing agents (sodium borohydride, lithium tri-tert-butoxyaluminohydride[78], L-selectride[79], diisobutylaluminum hydride[80,81]) proceeded stereospecifically and in high yield (92-98%). However, in each instance, the reduction product was the acetoxy alcohol 88 resulting from migration of the acetate group from the equatorial to the newly formed axial hydroxyl group. Evidence for this migration was the observed upfield shift of the acetate methyl absorption from 2.2 ppm in the ^{1}H NMR spectrum of 87 to 1.5 ppm in the ^{1}H NMR in 88. This shift was attributed to the proximity of the acetate methyl in 88 to the deshielding cone of the aromatic ring. This observation was confirmed by oxidizing 88 with chromium trioxide-pyridine[38] to the ketone 89, which had different physical and spectral properties than 87.

Scheme 19.



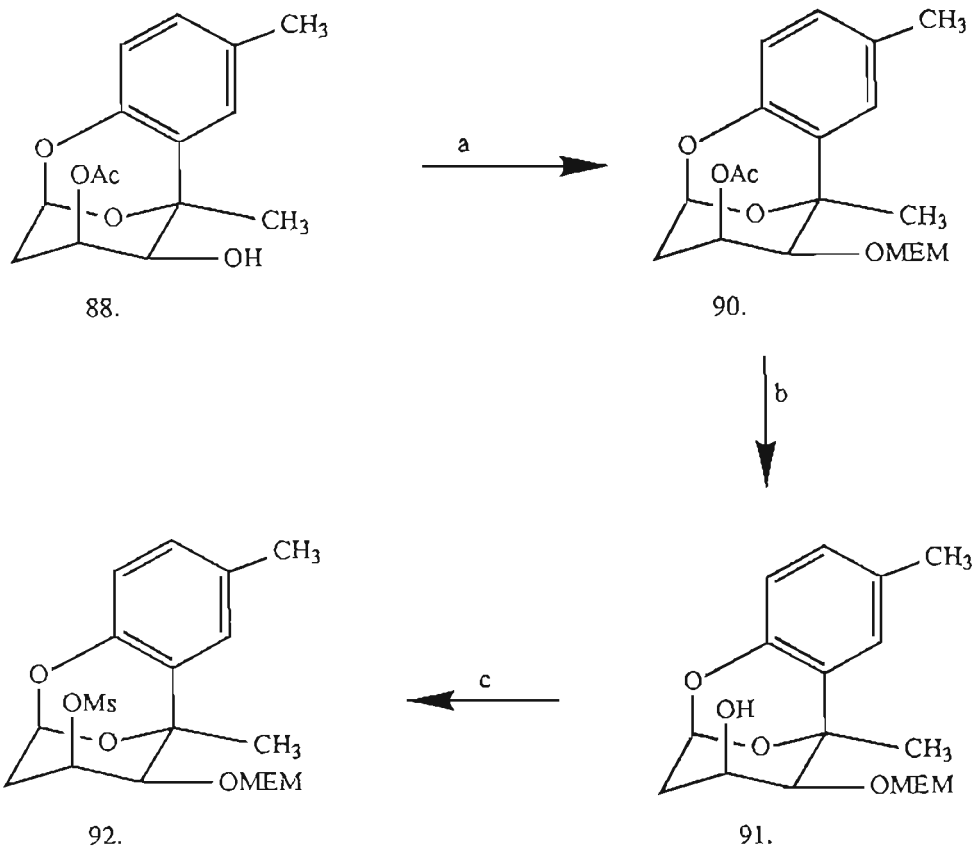
a) CH_3COCO_2H, HCl (1.5 N), THF, 96% b) Ac_2O, Py, 96% c) $NaBH_4$, IPA, 94% d) CrO_3, Py, 68%

The ^{1}H NMR absorption of the acetate methyl singlet in 89 was observed at 2.1 ppm and the ring hydrogen attached to the acetoxy moiety was observed as a doublet of doublets at 5.65 ppm (J=13.1 Hz and 7.6 Hz). These observations indicate that 89 exists in the "twist boat" conformation and that the acetate functionality is attached to the oxygen at C-4.

The acetate migration, initially viewed as a problem, was used advantageously to selectively protect the C-5 alcohol group as shown in Scheme 20. Thus, reaction of 88 with methoxyethoxymethyl chloride and diisopropylethylamine gave the MEM ether 90 in 92% yield. Subsequent reductive cleavage of the acetate functionality in 90 with lithium aluminum hydride furnished the alcohol 91 in 85% yield. Repeated attempts to construct a nitrogen containing arabino intermediate via nucleophilic displacement of the C-4 oxygen functionality with azide through either Mitsunobu reaction[82] of 91 or conversion to the mesylate 92 (methanesulfonyl chloride, pyridine, 61%) and subsequent displacement with azide in refluxing dimethylformamide were unsuccessful.

An alternative approach, utilizing the intermediacy of a bromo intermediate was attempted as shown in Scheme 21. Reduction of the ketone 81 with cerium borohydride[59] gave allyl alcohol 93 in 87% yield, which was acetylated (acetic anhydride, pyridine) to give the acetate 94 in quantitative yield. Attempted hydrogenation of 94 to the C-4 endo bromide resulted in either no reaction or concomitant cleavage of the carbon-bromine bond.

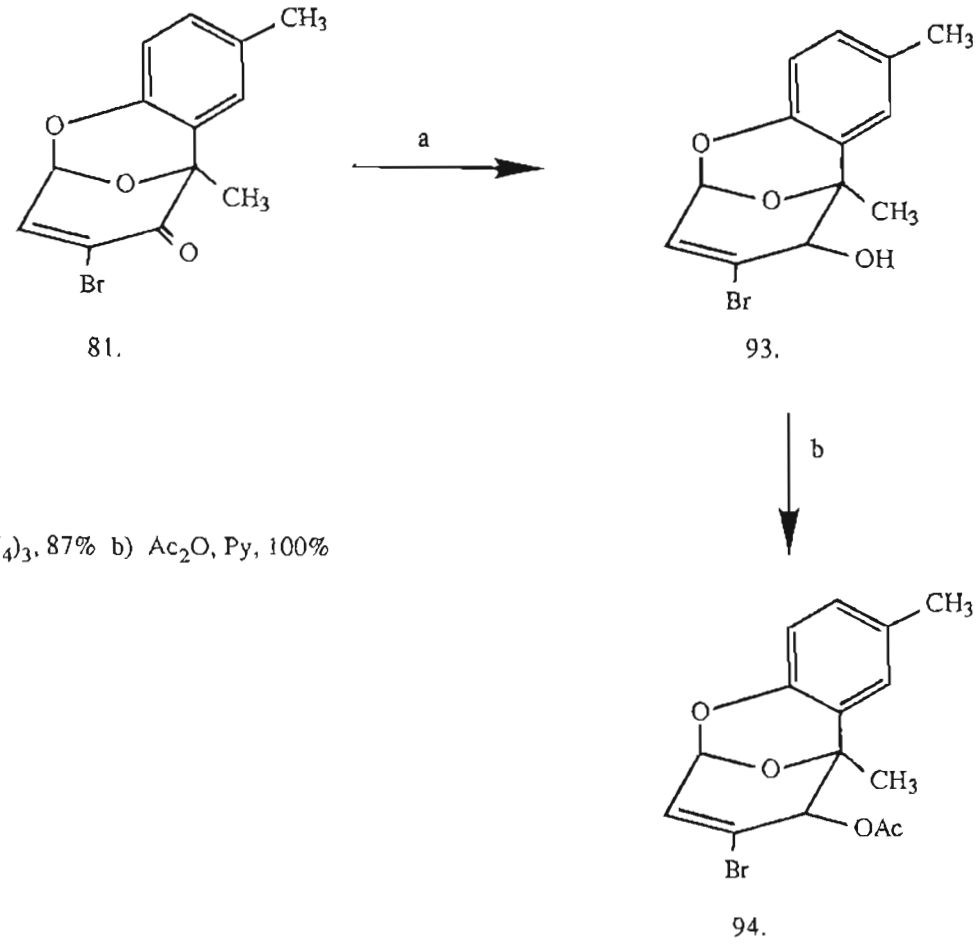
Scheme 20.



88. 90. 91. 92.

a) MEMCl, $(iPr)_2NEt$, 92% b) LAH, 85% c) MsCl, Py, 61%

Scheme 21.



81.

93.

94.

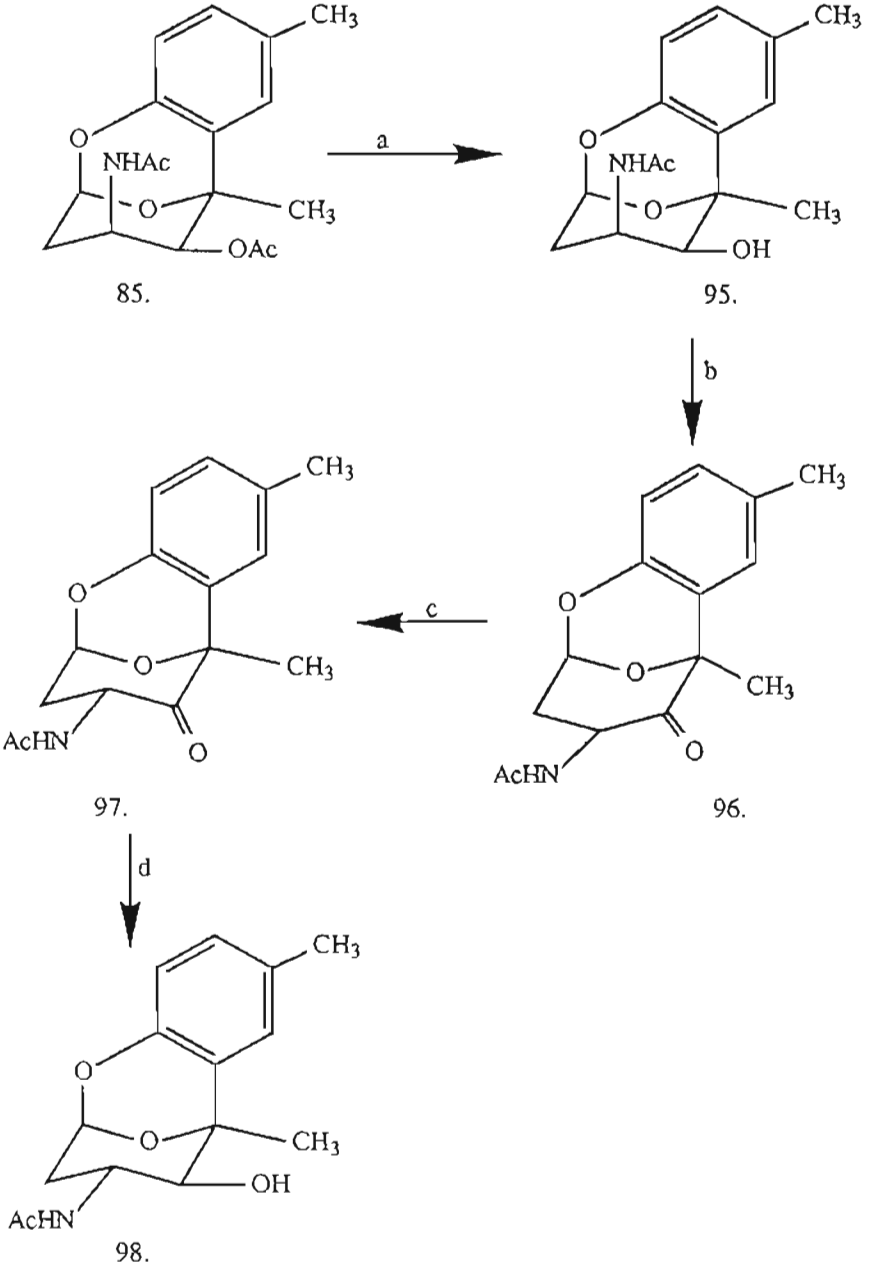
a) $Ce(BH_4)_3$, 87% b) Ac_2O, Py, 100%

The inability to effect nucleophilic replacement of the C-3 oxygen functionality led us to explore the feasibility of epimerization of the C-3 acetamido functionality in the ribo isomer. Although the driving force for this epimerization would be relief of steric congestion, it was unclear if protonation would occur on the highly hindered endo face. The intermediacy of an α-acetamido ketone was necessary to perform the desired epimerization as shown in Scheme 22.

Ammonolysis of 85 afforded the alcohol 95 in quantitative yield. Swern[30] oxidation of 95 furnished the ketone 96 in 88% yield. The presence of the C-5 keto functionality gave sufficient flexibility to the ring for conversion to the "twist boat" conformation as evidenced by the acetamido methyl absorption at 1.99 ppm.

Attempted epimerization with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) or triethylamine in tetrahydrofuran gave only decomposition products. However, epimerization with triethylamine in methylene chloride gave a quantitative yield of the epimerized ketone 97. Reduction of the ketone with sodium borohydride gave 98 with the arabino configuration in 95% yield. The arabino configuration was confirmed from the ^{1}H NMR spectrum which showed the acetamido methyl singlet at 2.05 ppm as compared to 1.49 ppm in the sugar with the ribo configuration.

Scheme 22.



85. 95. 96. 97. 98.

a) NH_3, MeOH, 100% b) ClCOCOCl, DMSO, Et_3N, 88% c) Et_3N, CH_2Cl_2, 100% d) $NaBH_4$, 95%

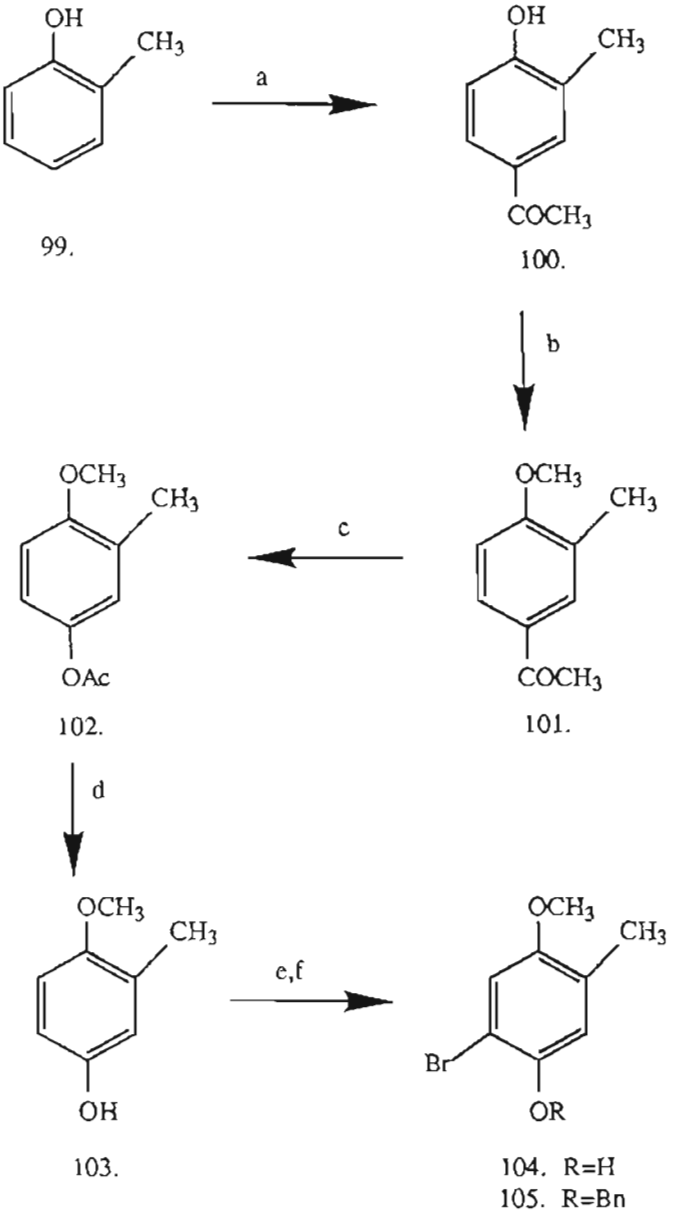
VI. Synthesis of 1,2'-Anhydro-3,6-dideoxy-3-dimethylamino-5-C-(2'-hydroxy-4'-diethylcarbamyl-5'-methoxyphenyl)-α-D,L-gluco-pyranoside 127

A. Synthesis via an Arylmethyl Oxidation

The preceding studies establish the scope and limitations of using the intact epoxybenzoxocin ring system for construction of amino sugar analogs. While preparation of sugar analogs with a variety of configurations can be straightforwardly accomplished, the preparation of amino analogs through nucleophilic introduction of a nitrogen functionality was unsuccessful. An alternative route, via the intermediacy of a hexenulose intermediate (Scheme 9), was undertaken. In this approach, the hexenulose intermediate prepared from the furan carbinol is converted to a pyranose with the gluco configuration, then ring closed to an epoxybenzoxocin.

The requisite benzenoid starting material was synthesized as shown in Scheme 23. Friedel Crafts acylation of O-cresol (99) with acetyl chloride (aluminum chloride, nitromethane, 100°C) gave the acetophenone 100 in 86% yield[83]. Methylation of 100 with dimethylsulfate (potassium carbonate, acetone, reflux) furnished the anisole 101 (84-%)[84-86]. Baeyer-Villiger oxidation of 101 with m-chloroperoxybenzoic acid gave 102 which was hydrolyzed to the phenol 103 in 85% overall yield. Alternatively, the four step synthesis of 103 could be performed without purification of the intermediates in 75% overall yield.

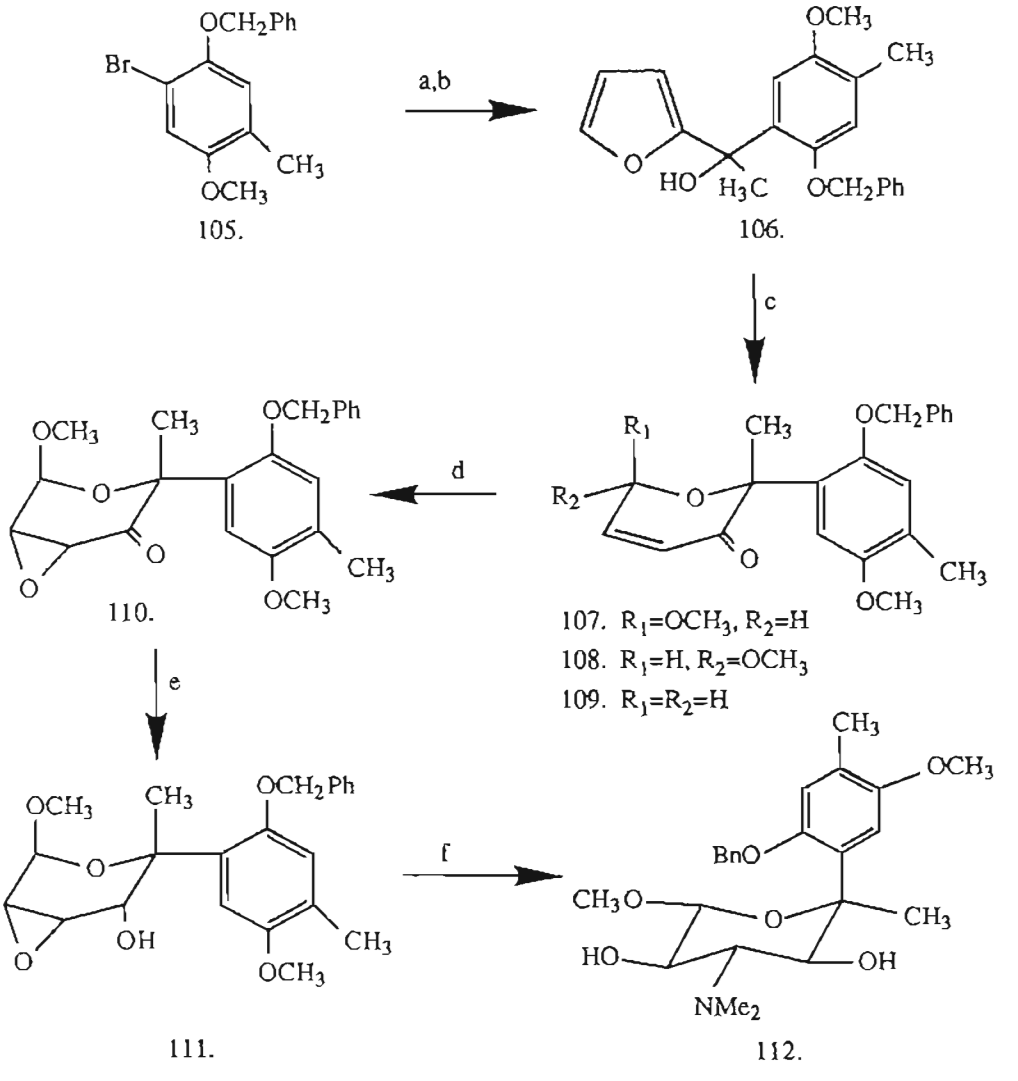
Scheme 23.



a) $AlCl_3$, AcCl, CH_3NO_2, 88% b) Me_2SO_4, K_2SO_4, Acetone, 84%
c) mCPBA, CH_2Cl_2, 86% d) 3N HCl, THF, 98% e) Br_2, CCl_4, 97%
f) NaH, $PhCH_2Br$, THF, 90%

Bromination of 103 (Br_2, CCl_4) gave the unstable bromophenol 104[87-89], which without purification was converted to the benzyl ether (benzyl bromide, potassium carbonate, acetone, reflux) derivative 105 (87% overall yield). Grignard addition of 105 (magnesium, tetrahydrofuran, reflux) to 2-acetylfuran, as shown in Scheme 24, gave the furan carbinol 106 in 85% yield (93% based on recovered starting material).

Scheme 24.



a) Mg, THF, reflux b) 2-acetylfuran (85%) c) Br_2, MeOH; HCO_2H, MeOH (107 50%, 108 12%, 109 12%) d) t-BuOOH, Triton B, CH_2Cl_2, 94% e) $NaBH_4$, IPA, 99% f) Me_2NH, sealed tube, 150°C, 78%

Treatment of 106 with bromine[57] and methanol followed by hydrolysis of the 1,4-dimethoxyfuran intermediate with formic acid[58] in methanol gave a 4:1:1 mixture of the methyl α-hexenulose 107, the methyl β-hexenulose 108 and the free sugar 109 in 74% combined yield. In the α-anomer, the methyl acetal and aryl substituents are trans-oriented with respect to the pyranulose ring. This relative configuration was assigned on the basis of ^{1}H NMR spectroscopic studies. In the α-anomer, shielding by the aromatic ring caused the anomeric proton to resonate at 5.06 ppm as compared to 5.33 ppm for the β-anomer. Epimerization of the β-anomer into the synthetically useful α-anomer (anhydrous hydrochloric acid, methanol[90]; Dowex 50 H^{+}, methanol[91,92]; titanium tetrachloride, methylene chloride[93]) was investigated without success. However, treatment of the free sugar 109 with stannic chloride and trimethylorthoformate[94] gave a 89% yield of the α- and β-anomers in a 4:1 ratio.

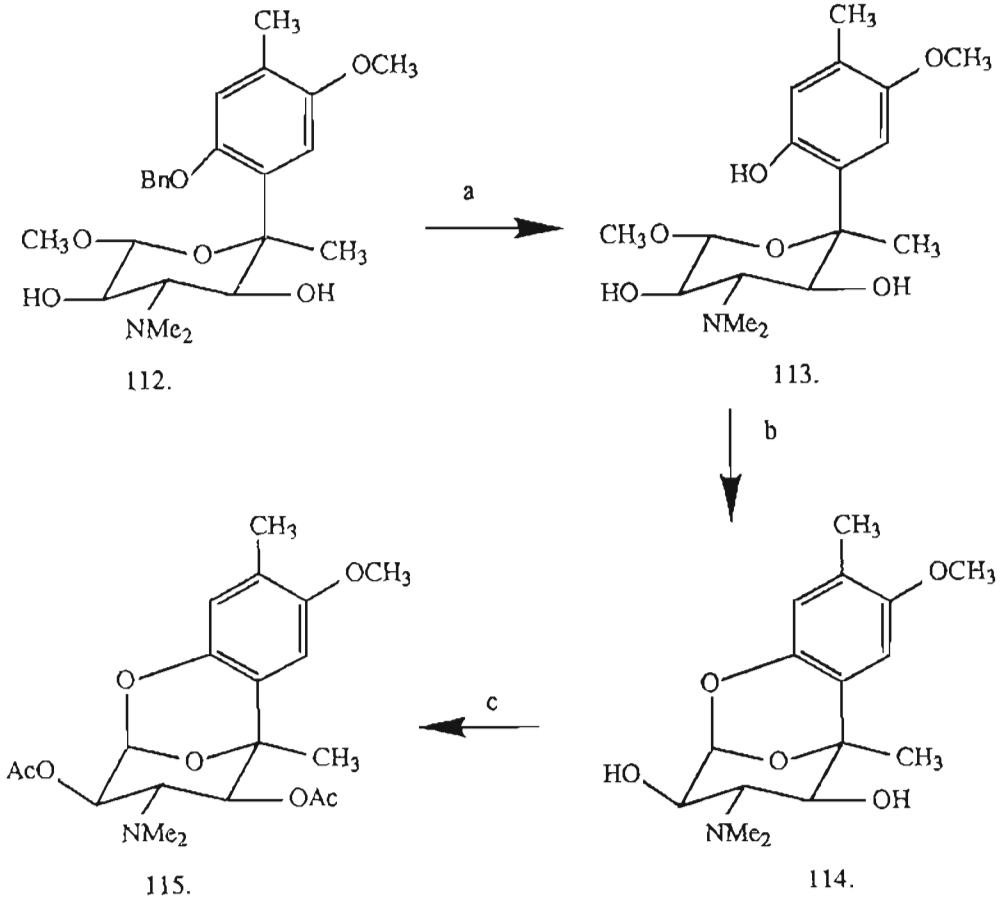
Epoxidation[44] of the unsaturated enone fragment in 107 with tert-butylhydroperoxide and Triton-B gave the epoxyketone 110 in 94% yield, which on treatment with sodium borohydride underwent stereospecific reduction to the epoxyalcohol 111 in quantitative yield. The hydride delivery to the ketone occurred exclusively from the α-face of the sugar ring due to the adjacent β-face aryl group. Opening of the epoxide in 111 with dimethylamine[95] also proceeded stereospecifically and furnished the dimethylamino substituted pyran 112 in 78% yield. The dimethylamino pyranose underwent a conformational inversion to the more stable conformer in which the dimethylamino and alcohol

functionalities are in equitorial positions. This conformational change was ascertained from the coupling constants and the very high field position of the axial anomeric proton (4.12 ppm) caused by shielding by the aromatic ring.

Reductive cleavage (palladium on carbon, hydrogen) of the benzyl protective group in 112 (Scheme 25) gave the phenol 113 in 88% yield. Hydrolysis of the anomeric methyl acetal (acetic acid, 3 N hydrochloric acid, 100°C) with concomitant intramolecular ring closure gave the epoxybenzoxocin 114 in 87% yield. The alcohol groups in 114 were protected as the acetates, prior to undertaking oxidation of the aryl methyl substituent. The synthetic transformations required to convert the methyl α-hexenulose 107 to the acetylated epoxybenzoxocin 115 was routinely performed on a 10 to 15 gram scale without purification of the intermediates in 80 to 88% overall yield.

While oxidation of aryl methyl groups is normally straightforward and can be performed with a variety of reagents, oxidation of the aryl methyl substituent in 115 proved to be vexing. A variety of oxidizing agents were attempted (N-bromosuccinimide; cobalt acetate bromide/oxygen[96]; potassium permanganate/18-Crown-6[97]; 2,3-dichloro-5,6-dicyano-1,4-benzoquinone[98]; bromine/azobisisobutyronitrile[31]; ceric ammonium nitrate[99]; chromyl chloride[100]) without success. The model study shown in Scheme 26 was undertaken to determine the cause of the failed oxidations. Sodium borohydride reduction of the ketone group in 82 gave the alcohol 116 stereospecifically, which was acetylated (Ac_2O, Py) to 117 in 95% overall yield.

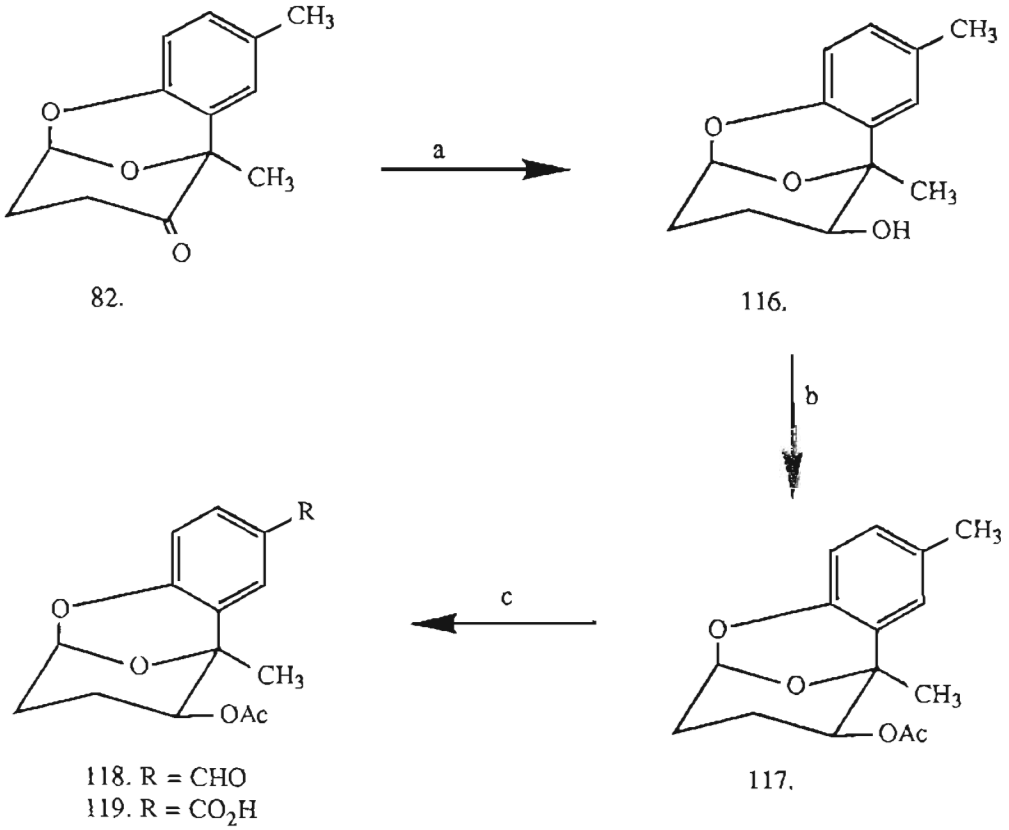
Scheme 25.



a) H_2, Pd/C, EtOAc, 88% b) HOAc, HCl, H_2O, 87% c) Ac_2O, Et_3N, 89%

Oxidation of 117 with cobalt (II) acetate bromide and oxygen[96] gave a mixture of oxidation products; aldehyde 118 in 45% and carboxylic acid 119 in 30% yield. The dimethylamino functionality appeared to be the culprit in the failed oxidations, probably acting as a free radical scavenger.

Scheme 26.



82.

116.

118. R = CHO
119. R = CO_2H

117.

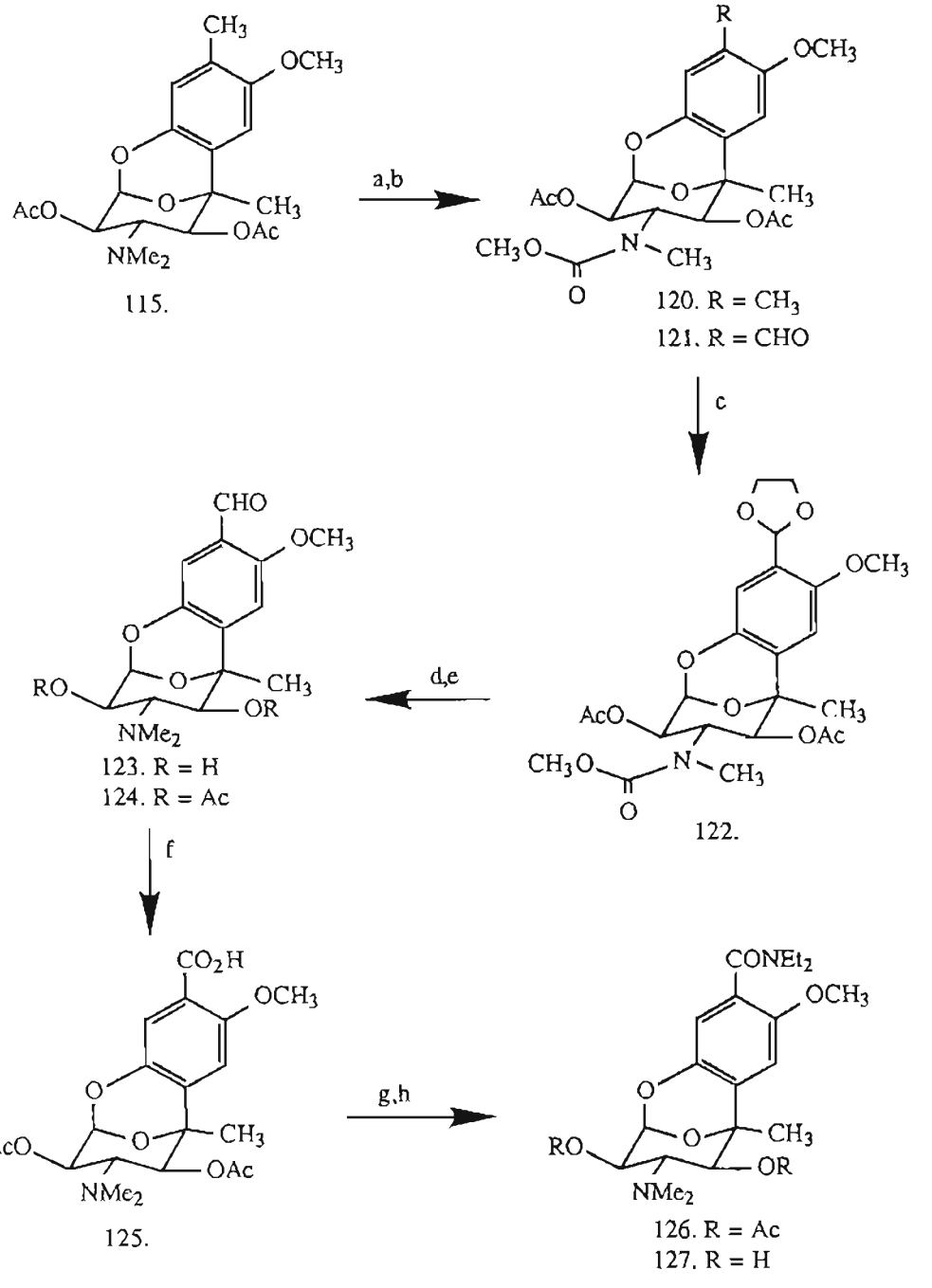
a) $NaBH_4$, IPA, 98% b) Ac_2O, Py, 97% c) CoBrOAc, HOAc, O_2, 100°C, (118., 45%; 119., 30%)

Protection of the dimethylamino functionality prior to oxidation of the arylmethyl moiety was accomplished as shown in Scheme 27. Treatment of 115 with methyl chloroformate[101] afforded the demethylated urethane 120 in quantitative yield. Oxidation of the aryl methyl functionality with copper (II) sulfate and sodium persulfate[102,103] gave the aldehyde 121 in 58% yield. Regeneration of the dimethylamino moiety with conservation of the aldehyde group was accomplished by

protecting the aldehyde in 121 as its 1,3-dioxolane 122 (ethylene glycol, pyridinium p-toluenesulfonate, 100%). The urethane moiety in 122 was reduced with lithium aluminum hydride and the dioxolane protecting group was cleaved during the acidic workup to afford the dimethylamino aldehydobenzoxocin 123 in 79% yield.

The alcohol groups in 123 were protected through acetylation (acetic anhydride, pyridine, 95%) to 124 prior to oxidation of the aldehyde moiety. Treatment of 124 with sodium chlorite, using sulfamic acid to scavenge[104] chlorine dioxide, furnished the carboxylic acid 125 in 88% yield. Conversion of 125 to the diethylamide derivative 126 was accomplished through reaction with dicyclohexylcarbodiimide[105], dimethylamino pyridine and diethylamine in 96% yield. Treatment of 126 with ammonia in methanol afforded the deacetylated diethylamide 127 in 98% yield.

Scheme 27.



a) $ClCO_2CH_3$, $NaHCO_3$, $CHCl_3$, 100% b) $CuSO_4$, $Na_2S_2O_8$, CH_3CN, H_2O, 56% c) $(CH_2OH)_2$, PPTs, PhH, 100% d) LAH, 79% e) Ac_2O, Et_3N, 95% f) $NaClO_3$, H_2NSO_3H, 88% g) DCC, DMAP, Et_2NH, 96% h) MeOH, NH_3, 98%

B. Synthesis via an Aryl Deprotonation

The accomplished preparation just described for the synthesis of 127 via an arylmethyl oxidation is not only regio- and stereospecific, but provides varied functionalization patterns on the benzenoid system appropriate for subsequent construction of the remaining hydroaromatic system. However, the synthetic route to 127 involved 22 steps and although most of the steps were accomplished in high yield, the overall yield was only 5%. A shorter, more expedient route was envisioned for the synthesis of 127 based on findings of Swenton and coworkers[106]. They observed that 2,5-dimethoxybenzaldehyde, when protected as the dimethyl acetal, metalated para to the acetal instead of ortho as predicted by the pioneering work of Snieckus, et al.[107] The new abbreviated route to 127 is outlined in Scheme 28.

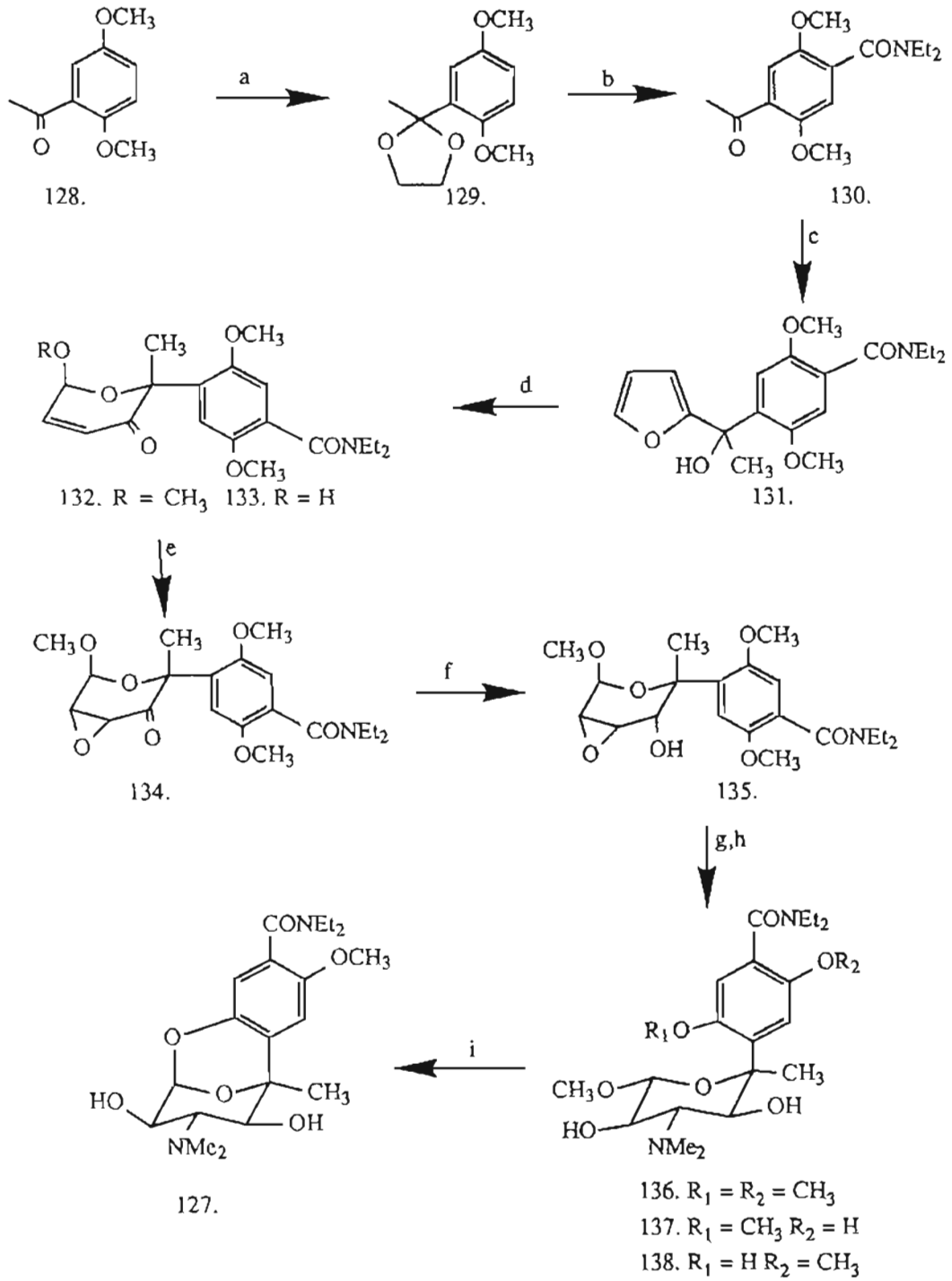
Commercially available 2,5-dimethoxyacetophenone (128) was converted to the ethylene ketal 129 (ethylene glycol, pyridinium p-toluenesulfonate, benzene, reflux) in 92% yield. The benzene ring in 129 was metallated[106] at the 4-position (sec-butyllithium, tetramethylethylenediamine, tetrahydrofuran, -78°C) then condensed with diethylcarbamyl chloride. Acidic workup afforded the ketone 130 in 61% yield. Reaction of 130 with one equivalent of 2-furyllithium[108] resulted in poor yields (30-45%) of 131. However, when 130 was reacted with two equivalents of 2-furyllithium, the furancarbinol 131 was obtained in 93% yield. This anomaly was apparently due to complexation of one equivalent of 2-furyllithium with the diethylcarboxamide

functionality and the adjacent methyl ether.

Oxidation of the furan ring by the Achmatowicz[57] procedure (bromine, methanol) followed by hydrolysis[58] (formic acid, methanol) gave the methyl-α-hexenulose 132 in 83% yield and the free sugar 133 in 15% yield. Epoxidation of 132 with alkaline tert-butylhydroperoxide[44] furnished the epoxyketone 134 in 91% yield. Stereospecific reduction of the ketone in 134 with sodium borohydride gave a 97% yield of epoxyalcohol 135. Opening of the oxirane ring with dimethylamine[95] (sealed tube, 150°C) gave the dimethylamino sugar 136 in 88% yield which has the ring inverted conformation. Cleavage of the appropriate methyl ether was accomplished regioselectively using sodium thioethoxide[109] in hot dimethylformamide and afforded the phenol 138 in 73% yield. A small amount (4%) of the other regioisomer 137 was also obtained and no trace of a bisphenol was observed. Hydrolysis of the methylacetal and cyclization of 138 by treatment with hot 3 N hydrochloric acid in acetic acid gave benzoxocin 127 in 76% yield.

The aryl deprotonation methodology afforded the early introduction of the diethylamide functionality in 127 thus avoiding the protection, oxidation and deprotection steps in the arylmethyl oxidation procedure. The accomplished synthesis afforded a short (9 step), efficient (19% overall yield) method for the production of the highly functionalized epoxybenzoxocin 127.

Scheme 28.

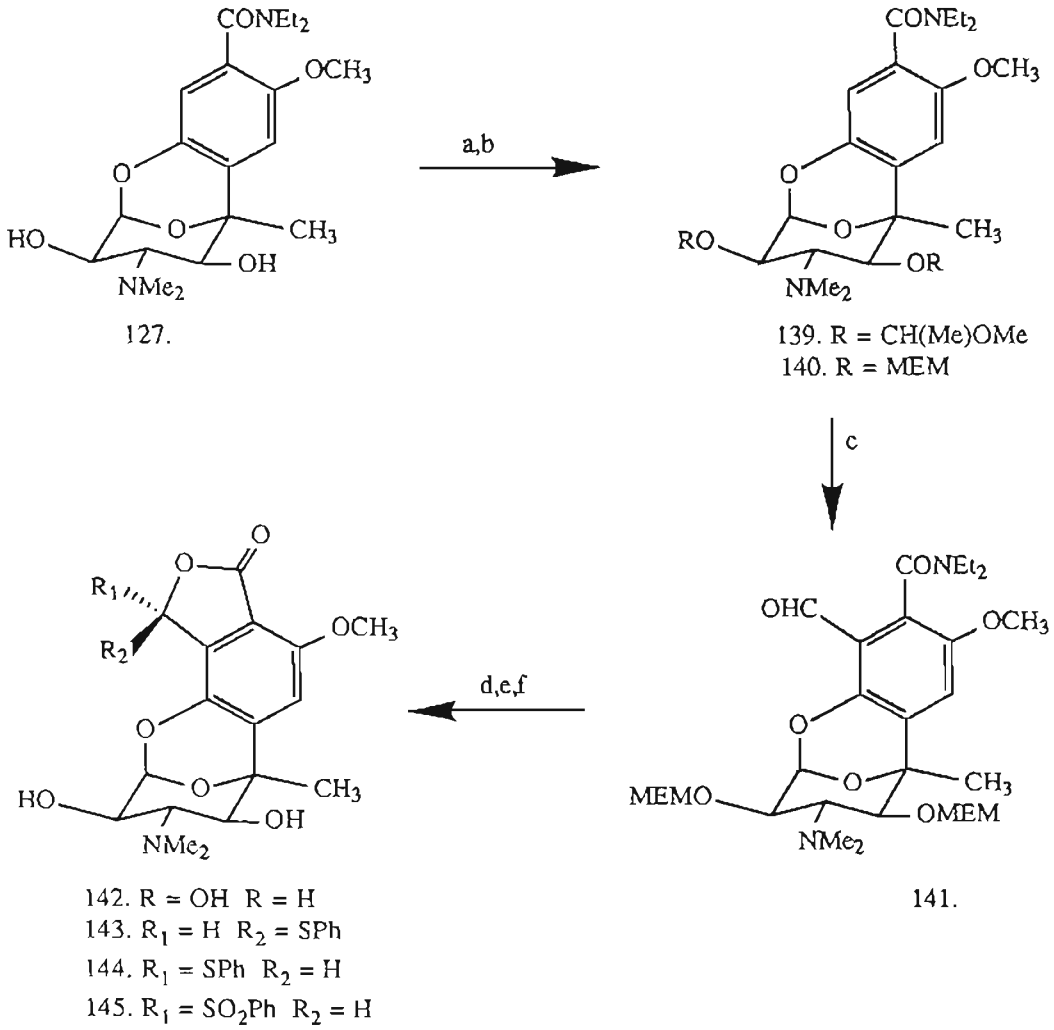


a) $(CH_2OH)_2$, PPTs, PhH, 92% b) s-BuLi, TMEDA, $ClCO_2NEt_2$, 61% c) 2-furyllithium (2 equiv.), THF, 93% d) Br_2, MeOH; HCO_2H, MeOH, (132. 83%; 133. 15%) e) tBuOOH, Triton B, CH_2Cl_2, 91% f) $NaBH_4$, IPA, 97% g) Me_2NH, 150°C, 88% h) EtSNa, DMF, 100°C, 73% i) HOAc, 3N HCl, 76%

VII. D,L-4-(Dimethylamino)-3β,4α,5β,6α-tetrahydro-3,5-dihydroxy-8-methoxy-6-methyl-11β-(phenylsulfonyl)-2α,6-methano-2H-furo[3,4-j]-1-benzoxocin-9(11H)-one (145)

The synthesis of a phthalide sulfone[23,24] benzoxocin intermediate capable of undergoing condensation with a suitably substituted AB ring synthon is outlined in Scheme 29. Initially, metallation[107] of 127 ortho to the diethylcarboxamide moiety was attempted without protection of the two hydroxyl functionalities (3 equiv sec-butyllithium, tetramethylethylenediamine, tetrahydrofuran) and resulted in only recovered starting material. Protection of the alcohols as the bis-ethoxyethylether 139 (ethylvinyl ether, p-toluenesulfonic acid, methylene chloride, 69% yield)[110] followed by ring metallation was also unsuccessful. The MEM-ether protected compound (140) (methoxyethoxymethyl chloride, sec-butyllithium, tetrahydrofuran, 85% yield), also failed to undergo metallation (1 equiv sec-butyllithium-tetramethylethylenediamine, tetrahydrofuran, -78°C). Ultimately, metallation was accomplished by treating a -78°C solution of 140, tetramethylethylenediamine (2.5 equiv) and tetrahydrofuran with six equivalents of sec-butyllithium. The reaction mixture went from a light yellow color to orange and finally to a deep red color as the sec-butyllithium was slowly added. The anion was quenched with dimethylformamide and after acidic workup, afforded the aldehyde 141 in 50% yield (88% yield based on recovered 140).

Scheme 29.



127.

139. R = CH(Me)OMe
140. R = MEM

141.

142. R = OH R = H
143. R_1 = H R_2 = SPh
144. R_1 = SPh R_2 = H
145. R_1 = SO_2Ph R_2 = H

a) ethyl vinyl ether, TsOH, CH_2Cl_2, 69% b) s-BuLi, THF, MEMCl, 85% c) s-BuLi (6 equiv.), TMEDA (2.5 equiv.), THF, -78°C; DMF, 50% (88% based on recovered starting material)
d) HOAc, 3N HCl, 100°C e) PhSH, TsOH, PhH, reflux, (122, 31%; 123, 69%)
f) H_2O_2, HOAc, 100°C, 18%

Hydrolysis of 141 (acetic acid; hydrochloric acid, water, 100°C) gave 142 as an intractable oil which was refluxed overnight with thiophenol, p-toluenesulfonic acid and benzene to give a quantitative yield of the diastereoisomeric thiophenyl acetals 143 and 144 in a 1:2 ratio. The two isomers were readily separated by silica gel chromatography. The thiophenyl acetal proton absorption in the ^{1}H NMR spectrum of the less polar isomer 143, was observed at 6.78 ppm and at 6.66 ppm in the more polar isomer 144. This shift can be explained by assigning the more polar isomer (144) the exo configuration where the proton is shifted slightly upfield due to partial shielding by the benzoxocin phenyl ring. Oxidation of 144 with hydrogen peroxide in acetic acid furnished the phthalidesulfone 145 in 18% yield.

SUMMARY

An expedient, regio- and stereospecific synthesis of benzoxocin DEF ring synthons to nogarol anthracyclines has been described.

Model studies directed toward the synthesis of 2,6-epoxy-1(2H)-benzoxocin sugar analogs having a gluco configuration showed that this configuration could not be attained if functionalization was attempted after formation of the benzoxocin system. However, sugar analogs with the manno, talo, altro and galacto configurations were prepared. In addition, 2,3,6-trideoxy-3-amino sugar analogs with the ribo and arabino configurations were synthesized for possible structure-activity relationship studies.

Synthesis of 2,6-epoxy-1(2H)-benzoxocins containing benzene rings with a variety of functionalization and a 3,6-dideoxy-3-dimethylamino sugar ring with a gluco configuration accomplished by oxidation and methanolysis of functionalized furancarbinols to afford methyl hexenuloses. Epoxidation of the hexenuloses followed by stereospecific reduction of the ketone, opening of the epoxide with dimethylamine and hydrolysis formed gluco configurated 2,6-epoxy-1(2H)-benzoxocins capable of serving as DEF ring synthons for nogarol anthracycline total synthesis.

VIII. 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 spectrometer. Chemical shifts are expressed in δ units. Mass spectra were obtained with a VG 7070E, DuPont CEC 21-110B, DuPont 21-491B, or Finnigan 40-21 mass spectrometers. 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 either 2- or 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 methanol was dried by distillation from magnesium turnings containing a catalytic amount of iodine. All other solvents were reagent grade and were not further purified. A stock solution of osmium tetroxide (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.

4'-Methylphenyl-2-furoate (58)

To a stirred solution of p-cresol (50 mL, 0.48 mol), methylene chloride (500 mL), and pyridine (45 mL, 0.55 mol) was slowly added 2-furoyl chloride (47 mL, 0.48 mol) in methylene chloride (100 mL) at 0°C under a nitrogen atmosphere. When the addition of the acid chloride was completed, the reaction was stirred for 2 h, then quenched with water (300 mL) and the layers separated. The organic phase was washed successively with 1 N hydrochloric acid (3 x 200 mL), 1 N sodium hydroxide (3 x 200 mL) and water (200 mL) then dried ($MgSO_4$), filtered, and evaporated at reduced pressure. The residue was filtered through silica (300 g, methylene chloride) to give 91.1 g (94%) of 58 as a cream colored solid with mp 57-58°C. ^1H NMR ($CDCl_3$) δ 2.35 (s, 3H); 6.56 (dd, J=3.5 Hz, J=1.7 Hz, 1H); 7.15 (m, 4H); 7.35 (dd, J=3.5 Hz, J=0.8 Hz, 1H); 7.65 (t, J=0.8 Hz, 1H).

1-(2'-Hydroxy-5'-methylphenyl_2-furanone (59)

A stirred mixture of p-tolyl-2-furoate (58) (29.1 g, 0.14 mol) and aluminum chloride (38.7 g, 0.29 mol) under N_2 was immersed in a wax bath at 180°C and maintained at 160-165°C for 30 min. After approximately 20 min, the initially molten slurry solidified. After cooling, the flask was chilled in an ice bath and the solid was manually dissolved in 10% hydrochloric acid (500 mL) and methylene chloride (500 mL). The aqueous mixture was extracted with methylene chloride

(3 x 200 mL) and the combined extracts were dried ($MgSO_4$), filtered, and evaporated under vacuum. The residue was purified by column chromatography (300 g, silica gel, CH_2Cl_2) and furnished 25.4 g (87%) of pure 37 as yellow needles: mp 66-67 °C (lit.[39] mp 74-75°C); ^1H NMR ($CDCl_3$) δ 2.33 (s, 3H); 6.61 (dd, J=1.6 Hz, J=3.6 Hz, 1H); 6.93 (d, J=8.4 Hz, 1H); 7.33 (d, J=10.3 Hz, 1H); 7.35 (s, 1H); 7.73 (d, J=1.6 Hz, 1H); 8.02 (d, J=3.4 Hz, 1H).

α-Methyl-α-(2'-hydroxy-5'-methylphenyl)-2-furanmethanol (60)

Methyllithium (23 mL, 1.6 M, 36.8 mmol) was added over a 15 min period to a magnetically stirred, cold (0°C) solution of 59 (2.5 g, 12.2 mmol) in anhydrous ether (25 mL) under N_2. The reaction was stirred for an additional 20 min, then quenched with saturated aqueous ammonium chloride (50 mL). The aqueous phase was extracted with ether (3 x 50 mL) and the combined extracts were dried ($MgSO_4$), filtered, and evaporated at reduced pressure to yield 2.5 g (93%) of 60 as a colorless oil, which was used in the next step without purification due to its tendency to dehydrate: ^1H NMR ($CDCl_3$) δ 1.91 (s, 3H); 2.16 (s, 3H); 3.84 (s, 1H); 6.29 (m, 2H); 6.48 (d, J=2.0 Hz, 1H); 6.75 (d, J=8.2 Hz, 1H); 6.95 (dd, J=2.1 Hz, J=8.3 Hz, 1H); 7.37 (m, 1H); 8.70 (s, 1H).

D,L-6,8-Dimethyl-2,6-epoxy-2H-1-benzoxocin-5(6H)-one (62)

A solution of bromine (0.6 mL), 11.7 mmol) in methanol (10 mL) was added dropwise over a 15 min addition period to a magnetically stirred, cold (-60°C) solution of carbinol 60 (2.5 g, 11.4 mmol) in methanol (50 mL) under N_2. The reaction was continued for 30 min, then saturated with ammonia gas with gradual warming to 0°C. The methanol was removed at reduced pressure and the residue was taken up in benzene (100 mL). The benzene solution was washed with water (50 mL) and brine (50 mL), then dried ($MgSO_4$), filtered, and evaporated to give the methanol adduct of 61 as an oil.

The adduct 61 was dissolved in acetic acid (15 mL), containing sulfuric acid (6 mL of 0.5 N), and heated at 50°C overnight with stirring. The reaction was cooled, then poured slowly into a slurry of potassium carbonate hydrate (21 g) in water (50 mL). When the carbon dioxide evolution subsided, the aqueous mixture was extracted with ethyl acetate (3 x 50 mL). The combined extracts were dried ($MgSO_4$), filtered, and evaporated under vacuum. Purification of the residue by column chromatography (silica gel, 100 g, 8:2 hexanes/ ethyl acetate) gave 1.95 g (79% based on 60) of 62 as large colorless crystals after recrystallization from hexanes: mp 111-111.5°C; ^1H NMR ($CDCl_3$) δ 1.73 (s, 3H); 2.25 (s, 3H); 5.93 (d, J=3.7 Hz, 1H); 6.15 (d, J=10.1 Hz, 1H); 6.76 (d, J=9.4 Hz, 1H); 6.81 (dd, J=10.3 Hz, J=3.6 Hz, 1H); 6.91 (d, J=2.0 Hz, 1H); 7.05 (dd, J=8.4 Hz, J=2.0 Hz, 1H).

Anal. Calcd. for $C_{13}H_{12}O_3$: C, 72.21; H, 5.59. Found: C, 72.44,

H, 5.70.

2-Bromo-4-methylphenyl methoxymethyl ether (64)

To a stirred mixture of sodium hydride (0.23 g, 50% dispersion, 4.7 mmol) in tetrahydrofuran (20 mL) and dimethylformamide (20 mL) was slowly added a solution of the phenol **63** (0.88 g, 4.7 mmol) in tetrahydrofuran (10 mL). The mixture was stirred for 20 minutes, then chloromethyl methyl ether (2 mL, 26.3 mmol) was added. The reaction mixture was stirred overnight, then quenched with water (40 mL) and extracted with ether (3 x 50 mL). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated at reduced pressure. Purification of the residue by radial chromatography (Chromatotron, 10% ethyl acetate/ hexanes) furnished 0.94 g (87%) of **64** as an oil. ^1H NMR ($CDCl_3$) δ 2.26 (s, 3H); 3.50 (s, 3H); 5.19 (s, 2H); 7.01 (s, 1H): 7.03 (s, 1H); 7.35 (bs, 1H).

α-Methyl-α-(2-methoxymethyloxy-5-methylphenyl)-2-furanmethanol (65)

A stirred mixture of **64** (2.40 g, 10.4 mmol), tetrahydrofuran (80 mL), magnesium turnings (0.33 g, 13.6 mmol) and iodine (0.20 g) was refluxed under nitrogen for three hours. The reaction was cooled to room temperature and 2-acetylfuran (1.05 mL, 10.5 mmol) in tetrahydrofuran (10 mL) was added slowly. The reaction was stirred for one hour, the quenched with saturated ammonium chloride (100 mL) and

extracted with ether (3 x 100 mL). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated at reduced pressure. The residue was purified by column chromatography (80 g silica, 8:2 hexanes/ethyl acetate) to furnish 1.92 g (70%) of 65 as an oil. ^1H NMR ($CDCl_3$) δ 1.91 (s, 3H); 2.28 (s, 3H); 3.33 (s, 3H); 4.37 (s, 1H); 5.03 (s, 2H); 6.14 (d, J=3.3 Hz, 1H); 6.28 (dd, J=3.3 Hz, J=1.8 Hz, 1H); 7.03 (m, 3H); 7.29 (m, 1H).

D,L-6,8-Dimethyl-2,6-epoxy-2H-1-benzoxocin-5(6H)-one (62)

To a stirred -60°C solution of 65 (8.22g, 31.3 mmol) in methanol (20 mL) was added slowly a solution of bromine (5.0 g, 31.3 mmol) in methanol (20 mL). The reaction was stirred for 30 minutes, then saturated with ammonia while warming to room temperature. The mixture was evaporated at reduced pressure and the residue was taken up in water (80 mL) and extracted with methylene chloride (3 x 100 mL). The combined organic extracts were evaporated at reduced pressure. The residue was dissolved in acetic acid (20 mL) and 10% hydrochloric acid (5 mL) and heated to 55°C for 6 h. The reaction was cooled, neutralized with saturated sodium carbonate (100 mL) and extracted with methylene chloride (3 x 100 mL). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated at reduced pressure. The residue was purified by column chromatography (silica, 150 g, 8:2 hexanes/ethyl acetate) to give 3.74 g (55%) of 62 as a white solid. The mp 111-112°C and ^1H NMR were identical with that given previously.

D,L-5,6-Dihydro-6,8-dimethyl-2,6-epoxy-2H-1-benzoxocin-5β-ol (66)

To a magnetically stirred mixture of lithium aluminum hydride (0.17 g, 4.5 mmol) in anhydrous ether (50 mL) under nitrogen was added a solution of 62 (0.65 g, 3.0 mmol) in anhydrous ether (20 mL). The reaction was stirred for 2 h, then cooled in an ice bath and the excess hydride was cautiously decomposed by sequential dropwise addition of water (0.2 mL), 15% NaOH (0.6 mL), and water (0.6 mL). The resulting slurry was filtered through celite, and the ether was filtrate dried ($MgSO_4$), filtered, and evaporated under vacuum. Radial chromatography of the residue (Chromatotron, 6:4 hexanes/methylene chloride) gave 0.61 g (97%) of pure 66 as a white crystalline solid: mp 105-108°C; ^{1}H NMR ($CDCl_3$) δ 1.63 (s, 3H); 1.75 (s, 1H); 2.2 (s, 3H); 4.24 (d, J=5.7 Hz, 1H); 5.68 (m, 3H); 7.20 (m, 3H).

Anal. Calcd. for $C_{13}H_{14}O_3$: C, 71.54; H, 6.46. Found: C, 71.35; H, 6.47.

1,2'-Anhydro-6-deoxy-5-C-(2'-hydroxy-5'-methylphenyl)-α-D,L-manno-pyranose (67)

A mixture of 66 (0.40 g, 1.8 mmol), acetone (6 mL), water (1 mL), trimethylamine-N-oxide dihydrate (0.43 g, 3.9 mmol), and osmium tetroxide stock solution (1.0 mL) was stirred magnetically overnight at room temperature. The reaction mixture was chilled in an ice bath,

quenched with saturated sodium bisulfite (30 mL), and extracted with ethyl acetate (3 x 30 mL). The combined extracts were dried ($MgSO_4$), filtered, and evaporated under vacuum. The residue was recrystallized from ethyl acetate to furnish 0.42 g (92%) of pure 67 as colorless plates: mp 238-240°C; ^1H NMR (CD_3OD) δ 1.64 (s, 3H); 2.28 (s, 3H); 3.24 (dd, J=9.9 Hz, J=3.7 Hz, 1H); 3.78 (d, J=9.9 Hz, 1H); 3.97 (dd, J=3.7 Hz, J=1.8 Hz, 1H); 5.42 (d, J=1.8 Hz, 1H); 6.80 (m, 3H).

Anal. Calcd. for $C_{13}H_{16}O_5$: C, 61.89; H, 6.39. Found: C, 61.98; H, 6.48.

1,2'-Anhydro-6α-deoxy-2α,3α-epoxy-5-C-(2'-hydroxy-5'-methylphenyl)-α-D,L-hex-4-ulose (68)

A mixture of 62 (0.37 g, 1.7 mmol), dioxane (20 mL) and sodium hypochlorite (7 mL, 5.25% aqueous solution) was stirred overnight at ambient temperature. The reaction was diluted with brine (30 mL) and extracted with ether (4 x 30 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and evaporated at reduced pressure. The residue was purified by radial chromatography (Chromatotron, 15% ethyl acetate/hexanes) to furnish 0.18 g (45%) of 68 as a colorless solid with mp 100-101°C. ^1H NMR ($CDCl_3$) δ 1.70 (s, 3H); 2.24 (s, 3H); 3.22 (d, J=3.5 Hz, 1H); 3.57 (dd, J=3.4 Hz, J=1.2 Hz, 1H); 5.91 (d, J=1.3 Hz, 1H); 6.84 (m, 3H).

D,L-5,6-Dihydro-6,8-dimethyl-2,6-epoxy-2H-1-benzoxocin-5β-methanesulfonate (70)

To a cold (0°C) solution of 66 (0.61 g, 2.9 mmol) in ether (75 mL) and pyridine (0.8 mL, 9.9 mmol) under N_2 was added methanesulfonyl chloride (0.5 mL, 6.5 mmol) and the mixture was stirred at room temperature for 2 h. Hydrochloric acid (25 mL of 2%) was added to the reaction and the aqueous phase was separated and extracted with ether (4 x 30 mL). The combined ether extracts were dried ($MgSO_4$), filtered, and evaporated at reduced pressure. The residue was taken up in ether and filtered through silica to give 0.75 g (86%) of 70 as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.70 (s, 3H); 2.30 (s, 3H); 3.11 (s, 3H); 5.40 (d, J=2.6 Hz, 1H); 5.75 (s, 1H); 5.88 (dd, J=2.6 Hz, J=1.8 Hz, 1H); 5.95 (d, J=1.8 Hz, 1H); 6.90 (m, 3H).

D,L-5,6-Dihydro-6,8-dimethyl-2,6-epoxy-5α-(phenylthio)-2H-1-benzoxocin (71)

A mixture of 70 (0.62 g, 2.1 mmol), dimethylformamide (15 mL), thiophenol (0.4 mL, 3.9 mmol), and potassium carbonate (0.7 g, 5.0 mmol) was stirred overnight at 75°C. The reaction mixture was cooled, diluted with water (50 mL), and extracted with 1:1 ether/hexanes (4 x 50 mL). The combined extracts were washed with water (3 x 50 mL), dried ($MgSO_4$), filtered, and evaporated under vacuum. Radial chromatography (Chromatotron, 8:2 hexanes/methylene chloride) of the residue furnished 0.31 g (48%) of pure 71 as an oil: ^{1}H NMR ($CDCl_3$) δ 1.71 (s, 3H); 2.23 (s, 3H); 3.68 (dd, J=5.4 Hz, J=0.9 Hz, 1H); 5.63 (dd,

J=2.0 Hz, J=1.4 Hz, 1H); 5.72 (dd, J=3.4 Hz, J=1.0 Hz, 1H); 6.12 (m, 1H); 6.84 (m, 3H); 7.36 (m, 5H).

D,L-5,6-Dihydro-6,8-dimethyl-2,6-epoxy-5α-(phenylsulfinyl)-2H-1-benzoxocins (72 and 73)

To a mixture of 71 (1.77 g, 5.7 mmol) in methylene chloride (50 mL) at -78°C under N_2 was added solid m-chloroperoxybenzoic acid (1.85 g, 8.6 mmol) and the reaction was stirred for 2 h. Saturated sodium bisulfite (40 mL) was added to the cold reaction and the mixture was allowed to come to room temperature. The methylene chloride layer was separated, washed with saturated sodium bicarbonate (40 mL) and water (40 mL), then dried ($MgSO_4$), filtered, and evaporated at reduced pressure. Column chromatography of the residue (silica gel, 200 g, 6:4 hexanes/ethyl acetate) gave 0.91 g (49%) of 72 as colorless needles (mp 145-146°C) and with continued elution 0.76 g (40%) of 73 as an oil.

72: ^{1}H NMR ($CDCl_3$) δ 2.08 (s, 3H); 2.26 (s, 3H); 3.09 (dd, J=5.4 Hz, J=1.0 Hz, 1H); 5.45 (dd, J=9.9 Hz, J=5.3 Hz, 1H); 5.86 (d, J=3.3 Hz, 1H); 6.17 (ddd, J=9.9 Hz, J=3.3 Hz, J=0.9 Hz, 1H); 6.84 (m, 3H); 7.55 (m, 5H).

73: ^{1}H NMR ($CDCl_3$) δ 1.74 (s, 3H); 2.26 (s, 3H); 3.34 (dd, J=5.5 Hz, J=0.9 Hz, 1H); 5.06 (m, 1H); 5.68 (t, J=1.5 Hz, 1H); 5.76 (dd, J=3.5 Hz, J=0.9 Hz, 1H); 6.80 (m, 3H); 7.60 (m, 5H).

Anal. (72) Calcd. for $C_{19}H_{18}O_3S$: C, 69.93; H, 5.56. Found: C, 69.79; H, 5.68.

D,L-(2α,5β,6α)-5,6-Dihydro-6,8-dimethyl-2,6-epoxy-2H-1-benzoxocin-3α-ol (69)

A mixture of 72 (0.56 g, 1.7 mmol) and trimethyl phosphite (0.8 mL, 6.8 mmol) in methanol (50 mL) was heated at reflux under N_2 for 2 h. The reaction mixture was cooled, quenched with dilute NH_4OH (50 mL of 5%), and extracted with ether (4 x 60 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and evaporated under vacuum. Radial chromatography of the residue (Chromatotron 8:2 hexanes/ethyl acetate) furnished 0.32 g (88%) of 69 as an oil: ^1H NMR ($CDCl_3$) δ 1.72 (s, 3H); 1.79 (s, 1H); 2.27 (s, 3H); 3.92 (m, 1H); 5.78 (br s, 1H); 5.95 (m, 2H); 6.85 (m, 3H).

D,L-5,6-Dihydro-6,8-dimethyl-2,6-epoxy-5α-(phenylsulfonyl)-2H-1-benzoxocin (74)

A solution of 71 (0.12 g, 0.4 mmol) and m-chloroperoxybenzoic acid (85%, 0.20g, 1.0 mmol) in methylene chloride (30 mL) was stirred overnight at room temperature. The reaction mixture was washed with 1 N sodium hydroxide (3 x 30 mL), dried ($MgSO_4$), filtered and evaporated at reduced pressure. The residue was recrystallized from ethyl acetate to give 0.12 g (94%) of 74 as colorless crystals with mp 152-155°C. ^1H NMR ($CDCl_3$) δ 1.99 (s, 3H); 2.26 (s, 3H); 3.75 (dd, J=2.2 Hz, J=1.0 Hz, 1H); 5.44 (d, J=2.0 Hz, 1H); 5.92 (d, J=0.9 Hz, 1H); 5.96 (s, 1H); 6.82 (m, 3H); 7.60 (m, 3H); 7.91 (m, 2H).

D,L-5,6-Dihydro-6,8-dimethyl-2,6-epoxy-5-(phenylthio)-2H-1-benzoxocin (71)

To a stirred mixture of lithium aluminum hydride (0.17 g, 45 mmol) in tetrahydrofuran (25 mL) was slowly added a solution of 73 (0.19 g, 0.58 mmol) in tetrahydrofuran (15 mL). After stirring for 1 h, the reaction was cautiously decomposed by sequential dropwise addition of water (0.2 mL), 15% sodium hydroxide (0.2 mL) and water (0.6 mL). The resultant slurry was filtered through celite, and the filtrate was dried ($MgSO_4$), filered and evaporated under vacuum. The residue was purified by radial chromatography (chromatotron, 8:2 hexanes/ethyl acetate) to give 0.09 g (50%) of 71 as an oil. ^1H NMR ($CDCl_3$) δ 1.71 (s, 3H); 2.23 (s, 3H); 3.68 (dd, J=5.4 Hz, J=0.9 Hz, 1H); 5.63 (dd, J=2.0 Hz, J=1.4 Hz, 1H); 5.72 (dd, J=3.4 Hz, J=1.0 Hz, 1H); 6.12 (m, 1H); 6.84 (m, 3H); 7.36 (m, 5H).

1,2'-Anhydro-6-deoxy-5-C-(2-hydroxy-5'-methylphenyl)-α-D,L-talopyranose (75) and 1,2'-Anhydro-6-deoxy-5-C-(2'-hydroxy-5'-methylphenyl)-α-D,L-altropyranose (76)

A mixture of 69 (0.10 g, 0.5 mmol), acetone (6 mL), ether (1 mL), trimethylamine-N-oxide (0.20g, 1.8 mmol), and osmium tetroxide (1 mL) was stirred overnight at room temperature. The reaction mixture was quenched with saturated sodium bisulfite (30 mL). The combined extracts

were dried ($MgSO_4$), filtered, and evaporated under vacuum. In order to effect separation of the diol mixture the initial product was acetylated. The residue (0.06 g) from the hydroxylation was taken up in acetic anhydride (2 mL) and pyridine (5 mL), then stirred overnight under N_2. Saturated sodium bicarbonate solution (25 mL) was added to the reaction, which was then extracted with ethyl acetate (4 x 25 mL). The combined extracts were washed with 1 N HCl (2 x 50 mL) and water (50 mL), then dried ($MgSO_4$), filtered, and evaporated under vacuum. Radial chromatography (Chromatotron, 8:2 hexanes/ethyl acetate) furnished 82 mg (47%) of 75, mp 180.5-182°C, and with continued elution 31 mg (18%) of 76 as an oil.

75: ^{1}H NMR ($CDCl_3$) δ 1.59 (s, 3H); 1.91 (s, 3H); 2.17 (s, 3H); 2.21 (s, 3H); 2.28 (s, 3H); 5.00 (m, 1H); 5.28 (m, 2H); 5.62 (d, J=1.7 Hz, 1H); 6.94 (m, 3H).

76: ^{1}H NMR ($CDCl_3$) δ 1.40 (s, 3H); 1.57 (s, 3H); 2.03 (s, 3H); 2.18 (s, 3H); 2.28 (s, 3H); 5.04 (br s, 1H); 5.22 (br s, 1H); 5.33 (br s, 1H); 5.47 (br s, 1H); 6.86 (m, 3H).

Anal. (75) Calcd. for $C_{19}H_{22}O_8$: C, 60.31; H, 5.86. Found: C, 60.51; H, 6.06.

D,L-6,8-Dimethyl-2,6-epoxy-2H-1-benzoxocin-3(6H)-one (77)

A mixture of oxalyl chloride (0.15 mL, 1.7 mmol) in methylene chloride (15 mL) was cooled to -78°C under N_2. Dimethyl sulfoxide

(0.25 mL, 3.5 mmol) was added and the reaction was stirred for 10 min. A mixture of 69 (0.23 g, 1.05 mmol) in methylene chloride (5 mL) was added dropwise over 15 min, then stirred for an additional 30 min. Triethylamine (1.2 mL, 8.6 mmol) was next added dropwise and after 15 min, the cooling bath was removed and the reaction was allowed to come to room temperature over 1 h. The reaction was quenched with saturated sodium bicarbonate (30 mL) and extracted with methylene chloride (3 x 30 mL). The combined extracts were washed with 2% hydrochloric acid (2 x 50 mL), then dried ($MgSO_4$), filtered and evaporated under vacuum. Radial chromatography of the residue (Chromatotron, 8:2 hexanes/ethyl acetate) furnished 0.17 g (74%) of pure 77 as colorless needles: mp 75-76°C; ^1H NMR ($CDCl_3$) δ 1.78 (s, 3H); 2.28 (s, 3H); 5.57 (d, $\underline{J}$=0.8 Hz, 1H); 5.18 (dd, $\underline{J}$=10.2 Hz, $\underline{J}$=0.8 Hz, 1H); 6.88 (m, 3H); 6.12 (d, $\underline{J}$=10.2 Hz, 1H).

Anal. Calcd. for $C_{13}H_{12}O_3$: C, 72.21; H, 5.59. Found: C, 72.42; H, 5.71.

D,L-5,6-Dihydro-6,8-dimethyl-2,6-epoxy-2H-1-benzoxocin-3-ol (78)

A mixture of 77 (0.17 g, 0.8 mmol) in ether (10 mL) was added to lithium aluminum hydride (60 mg, 1.6 mmol) in ether (15 mL) at room temperature under N_2. The reaction was stirred at room temperature for 1 h, then quenched with 3 N hydrochloric acid (40 mL), and extracted with ether (4 x 30 mL). The combined extracts were dried ($MgSO_4$), filtered, and evaporated under vacuum. Radial chromatography

(Chromatotron, 7.5:2.5 hexanes/ethyl acetate) of the residue furnished 0.16 g (94%) of 78 as an oil: ^{1}H NMR ($CDCl_3$) δ 1.68 (s, 3H); 2.03 (d, J=11.6 Hz, 1H) 2.27 (s, 3H); 4.26 (dd, J=11.7 Hz, J=3.8 Hz, 1H); 5.73 (m, 2H); 6.89 (m, 3H).

1,2'-Anhydro-6-deoxy-5-C-(2'-hydroxy-5'-methylphenyl)-α-D,L-galactopyranose (79)

A mixture of 78 (0.07 g, 0.3 mmol), acetone (6 mL), water (1 mL), trimethylamine-N-oxide (0.08 g, 0.7 mmol), and osmium tetroxide stock solution (1 mL) was stirred overnight at room temperature. The reaction was quenched with saturated sodium bisulfite (30 mL) and extracted with ethyl acetate (4 x 30 mL). The combined extracts were dried ($MgSO_4$), filtered, and evaporated under vacuum. The residue was purified by radial chromatography (Chromatotron, ethyl acetate as eluent) to furnish 0.06 g (72%) of pure 79 as a colorless solid: mp 159-160°C; ^{1}H NMR (CD_3OD) δ 1.62 (s, 3H); 2.28 (s, 3H); 3.49 (dd, J=10.1 Hz, J=3.5 Hz, 1H); 3.75 (d, J=3.5 Hz, 1H); 3.95 (dd, J=10.1 Hz, J=3.6 HZ, 1H); 5.47 (d, J=3.6 Hz, 1H); 6.89 (m, 3H).

Anal. Calcd. for $C_{13}H_{16}O_5$: C, 61.89; H, 6.39. Found: C, 62.01; H, 6.54.

1,2'-Anhydro-2,3,6α-trideoxy-2α,3β-dibromo-5-C-(2'-hydroxy-5'-methylphenyl)-α-D,L-hex-4-ulose (80) and 1,2'-Anhydro-2,6α-dideoxy-3-bromo-5-C-(2'hydroxy-5'-methylphenyl)-α-D,L-hex-2-en-4-ulose (81)

To a magnetically stirred, cold (0°C) solution of 62 (0.33 g, 1.5 mmol) in methylene chloride (30 mL) was slowly added a solution of bromine (0.1 mL) in methylene chloride (5 mL) until the orange color of bromine persisted. The reaction was continued for 15 min then quenched with saturated sodium bisulfite (30 mL). The phases were separated and the aqueous phase was extracted with methylene chloride (30 mL). The combined organic phases were dried ($MgSO_4$), filtered and evaporated at reduced pressure to give 0.55 g (99%) of 80 as a pale yellow oil. Crude ^1H NMR ($CDCl_3$) δ 1.74 (s, 3H); 2.26 (s, 3H); 4.36 (dd, J=12.2 Hz, J=3.6 Hz, 1H); 5.02 (d, J=12.2 Hz, 1H); 6.15 (d, J=3.7 Hz, 1H); 6.93 (m, 3H). Purification of the residue by radial chromatography (Chromatotron, 8.5:1.5 hexanes/ ethyl acetate) gave 0.26 g (60%) of 81 as colorless crystals, which after recrystallization from hexanes had mp 132-134°C. ^1H NMR ($CDCl_3$) δ 1.78 (s, 3H); 2.25 (s, 3H); 5.87 (d, J=4.2 Hz, 1H); 6.89 (m, 3H); 7.15 (d, J=4.2 Hz, 1H).

1,2'-Anhydro-2,3,6α-trideoxy-5-C-(2'-hydroxy-5'-methylphenyl)-α-D,L-hex-4-ulose (82)

A mixture of 62 (2.68 g, 12.2 mmol), 5% palladium on carbon (250 mg) and ethyl acetate (100 mL) was shaken at 40 psi H_2 for 12 h at ambient temperature. The mixture was filtered and the ethyl acetate was evaporated at reduced pressure to give 2.67 g (99%) of 82 as a colorless solid with mp 75-77°C. ^{1}H NMR ($CDCl_3$) δ 1.65 (s, 3H); 2.25 (s, 3H); 2.39 (m, 4H); 5.82 (m, 1H); 6.80 (m, 3H). ^{13}C NMR ($CDCl_3$) δ 208.2, 148.0, 130.7, 130.2, 125.8, 122.1, 116.8, 92.8, 79.0, 31.1, 29.5, 20.9, 20.6.

1,2'-Anhydro-2,6α-dideoxy-3-oximino-5-C-(2'hydroxy-5'methylphenyl)-α-D,L-hex-4-ulose (83)

To a cold (0°C) solution of sodium methoxide (3.7 mL of a 2.6 M solution in methanol) in methanol (25 mL) was rapidly added a solution containing 82 (2.11 g, 9.5 mmol), isoamyl nitrite (4 mL, 30 mmol) and methanol (10 mL). After stirring overnight at ambient temperature, the reaction was quenched with 1 N hydrochloric acid (50 mL) and extracted with methylene chloride (3 x 100 mL). The combined extracts were dried ($MgSO_4$), filtered and evaporated at reduced pressure. The residue was purified by column chromatography (100 g silica, 8:2 hexanes/ethyl acetate) to give 2.07 g (88%) 83 as a light yellow solid with mp 167-169°C. ^{1}H NMR ($CDCl_3$) δ 1.77 (s, 3H); 2.23 (s, 3H); 2.95

(dd, J=20.1 Hz, J= 1.0 Hz, 1H), 3.54 (dd, J= 20.2 Hz, J= 7.0 Hz, 1H); 5.87 (dd, J=7.0 Hz, J=1.1 Hz, 1H); 6.89 (m, 3H). Mass spectrum: m/z 247 ($m^{\cdot +}$), 202.

1,2'-Anhydro-2,6α-dideoxy-3-oximino-4β-hydroxy-5-C-(2'-hydroxy-5'-methylphenyl)-α-D,L-hexopyranose (84)

To a solution of **83** (1.89 g, 7.6 mmol) in isopropyl alcohol (50 mL) was added sodium borohydride (0.3 g, 7.9 mmol) and the reaction was stirred for 1h at ambient temperature. The solvent was evaporated at reduced pressure and the residue was taken up in water (50 mL) and extracted with methylene chloride (3 x 50 mL). The combined extracts were dried ($MgSO_4$), filtered and evaporated at reduced pressure. The residue was purified by column chromatography (silica, 50 g, 8:2 hexanes/ethyl acetate) to give 1.83 g (96%) of **84** as a white solid with mp 101-104°C. ^1H NMR ($CDCl_3$) δ 1.74 (s, 3H); 2.27 (s, 3H); 2.43 (dd, J=15.6 Hz, J=4.8 Hz, 2H); 3.22 (bs, 1H); 3.59 (d, J=15.8 Hz, 1H); 4.30 (d, J=5.5 Hz, 1H); 5.73 (d, J=4.4 Hz, 1H); 6.92 (m, 3H). Mass Spectrum: m/z 249 ($M^{\cdot +}$), 232.

1,2'-Anhydro-2,3,6α-tridoexy-(3-acetamido-4-acetoxy)-5-C-(2'hydroxy-5'-methylphenyl)-α-D,L-*ribo*-hexopyranose (85)

A mixture of **84** (0.50 g, 2.0 mmol), 5% palladium on carbon (0.10 g) and acetic acid (30 mL) was shaken at 40 psi H_2 for 12 h at ambient temperature. The reaction was filtered through celite and

the filtrate was evaporated at reduced pressure. The residue was dissolved in methylene chloride (50 mL) and acetic anhydride (2 mL) and pyridine (5 mL) were added. The resulting solution was stirred for 4 h at ambient temperature, then quenched with saturated sodium bicarbonate. The layers were separated and the aqueous phase was extracted with methylene chloride (2 x 50 mL). The combined organic solutions were dried ($MgSO_4$), filtered and evaporated at reduced pressure. Radial chromatography of the residue (6:4 hexanes/ ethyl acetate) gave 0.44 g (69%) of **85** as a white solid with mp 121-122°C. ^1H NMR ($CDCl_3$) δ 1.47 (s, 3H); 1.56 (s, 3H); 2.08 (s, 3H); 2.27 (m, 2H); 2.33 (s, 3H); 4.61 (m, 1H); 4.75 (bs, 1H); 5.09 (d, $\underline{J}$=5.0 Hz, 1H); 5.65 (dd, $\underline{J}$=3.5 HZ, $\underline{J}$=2.0 Hz, 1H); 6.97 (m, 3H). Mass spectrum: m/z 319 ($M^{\cdot+}$), 276.

Anal. calcd for $C_{17}H_{21}NO_5$: C, 63.94; H, 6.63; N, 4.39. Found: C, 63.71; H, 6.93; N, 4.11.

1,2'-Anhydro-2,6α-dideoxy-4β-hydroxy-5-C-(2'hydroxy-5'-methylphenyl)-α-$\underline{D}$,$\underline{L}$-hex-3-ulose (86)

A mixture of **84** (0.92 g, 3.8 mmol), pyruvic acid (3.5 g, 40 mmol), tetrahydrofuran (25 mL) and 1.5 N hydrochloric acid (25 mL) was stirred for 16 h at ambient temperature. The reaction was extracted with methylene chloride (4 x 50 mL) and the combined extracts were dried ($MgSO_4$), filtered and evaporated at reduced pressure. Radial chromatography of the residue (8:2 hexanes/ethyl acetate) gave 0.85 g

(96%) of **86** as a white solid with mp 151-152°C. ^{1}H NMR ($CDCl_3$) δ 1.76 (s, 3H); 2.24 (s, 3H); 2.86 (d, J=1.4 Hz, 1H); 2.95 (dd, J=4.8 Hz, J=1.2 Hz, 1H); 3.47 (d, J=5.0 Hz, 1H); 4.30 (dd, J=5.0 Hz, J=1.2 Hz, 1H); 5.97 (dd, J=4.8 Hz, J=1.4 Hz, 1H); 6.91 (m, 3H). Mass spectrum: m/z 234 ($M^{\cdot+}$).

1,2'-Anhydro-2,6α-dideoxy-4β-acetoxy-5-C-(2'-hydroxy-5'-methylphenyl)-α-D,L-hex-3-ulose (87)

A mixture of **86** (1.50 g 6.4 mmol), acetic anhydride (0.5 mL), pyridine (0.7 mL) and methylene chloride (60 mL) was stirred overnight at ambient temperature under nitrogen. The reaction was quenched with saturated sodium bicarbonate (50 mL). The layers were separated and the aqueous phase was extracted with methylene chloride (2 x 50 mL). The combined organic solutions were dried ($MgSO_4$), filtered and evaporated at reduced pressure. The residue was purified by column chromatography (75 g silica, 6:4 hexanes/ ethyl acetate) to give 1.68 g (96%) of **87** as a white solid with mp 179-182°C. ^{1}H NMR ($CDCl_3$) δ 1.69 (s, 3H); 2.20 (s, 3H); 2.25 (s, 3H); 2.84 (d, J=1.4 Hz, 1H); 2.94 (dd, J=5.1 Hz, J=1.3 Hz, 1H); 5.32 (d, J=1.3 Hz, 1H); 5.95 (dd, J=5.1 Hz, J=1.4 Hz, 1H); 6.93 (m, 3H). Mass spectrum: m/z 276 ($M^{\cdot+}$), 234.

1,2'-Anhydro-2,6-dideoxy-3-acetoxy-4-hydroxy-5-C-(2'-hydroxy-5'-methylphenyl)-α-D,L-ribo-hexopyranose (88)

To a solution of 87 (1.73 g, 6.3 mmol) in 2-propanol (75 mL) was rapidly added sodium borohydride (0.36 g, 9.5 mmol) and the mixture was stirred at room temperature for 2 h. The solvent was removed at reduced pressure and the residue was dissolved in water (50 mL) and extracted with methylene chloride (3 x 50 mL). The combined extracts were dried (Na_2SO_4), filtered and evaporated at reduced pressure. The residue was purified by column chromatography (80 g silica, 7:3 hexanes/ethyl acetate) to give 1.65 g (94%) of 88 as a colorless solid with mp 161-163°C. ^1H NMR ($CDCl_3$) δ 1.48 (s, 3H); 1.64 (s, 3H); 2.18 (t, J=2.0 Hz, 1H); 2.26 (s, 3H); 2.31 (m, 1H); 3.80 (dd, J=10.0 Hz, J=4.0 Hz, 1H); 5.08 (m, 1H); 5.60 (dd, J=4.0 Hz, J=2.0 Hz, 1H); 6.80 (m, 3H). Mass spectrum: m/z 278 ($M^{\cdot+}$).

1,2'-Anhydro-2,6α-dideoxy-3β-acetoxy-5-C-(2'hydroxy-5'methylphenyl)-α-D,L-hex-4-ulose (89)

To a solution of pyridine (1.1 mL) in methylene chloride (20 mL) was added chromium trioxide (0.65 g, 6.5 mmol) and the resulting mixture was stirred for 15 min. A solution of 88 (0.06 g, 0.22 mmol) in methylene chloride (10 mL) was rapidly added and the resulting mixture was stirred for 30 min. The reaction mixture was diluted with ether (100 mL), filtered through a bed of celite, and evaporated at reduced pressure. The residue was purified by radial chromatography (Chromato-

tron, 8:2 hexanes/ethyl acetate) to furnish 0.04 g (68%) of 89 as an oil. ^{1}H NMR ($CDCl_3$) δ 1.67 (s, 3H); 2.10 (s, 3H); 2.12 (m, 1H); 2.25 (s, 3H); 2.84 (dt, J=13.1 Hz, J=8.8 Hz, 1H); 5.65 (dd, J=13.1 Hz, J=7.6 Hz, 1H); 5.96 (dd, J=8.8 Hz, J=4.8 Hz, 1H); 6.87 (m, 3H).

1,2'-Anhydro-2,6-dideoxy-3-acetoxy-4-methoxyethoxymethoxy-5-C-(2'-hydroxy-5'-methylphenyl)-α-D,L-ribo-hexopyranose (90)

A mixture of 88 (0.10 g, 0.36 mmol), diisopropylethylamine (1.0 mL), 2-methoxyethoxymethyl chloride (1.0 mL) and methylene chloride (25 mL) was stirred overnight at ambient temperature. The reaction was quenched with 1 N hydrochloric acid (25 mL), the phases were separated and the aqueous layer was extracted with methylene chloride (2 x 25 mL). The combined organic phases were dried (Na_2SO_4), filtered and evaporated under reduced pressure. The residue was purified by radial chromatography (Chromatotron, 8:2 hexanes/ethyl acetate) to give 0.12 g (92%) of 90 as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.48 (s, 3H); 1.60 (s, 3H); 2.18 (m, 2H); 2.25 (s, 3H); 3.38 (s, 3H); 3.58 (m, 4H); 3.86 (d, J=3.7 Hz, 1H); 4.75 (q, J=7.4 Hz, 2H); 5.29 (m, 1H); 5.60 (m, 1H); 6.89 (m, 3H).

1,2'-Anhydro-2,6-dideoxy-3-hydroxy-4-methoxyethoxymethoxy-5-C-(2'-hydroxy-5'-methylphenyl)-α-D,L-ribo-hexoyranose (91)

A mixture of 90 (0.12 g, 0.33 mmol), ether (30 mL) and lithium aluminum hydride (20 mg, 0.53 mmol) was stirred for 2 h at ambient temperature. The reaction was quenched by the slow addition of 1 N sodium hydroxide (20 mL) then extracted with ether (3 x 30 mL). The combined organic phases were dried (Na_2SO_4), filtered and evaporated at reduced pressure. The residue was purified by radial chromatography (Chromatotron, 6:4 hexanes/ethyl acetate to furnish 0.09 g (85%) of 91 as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.59 (s, 3H); 2.25 (s, 3H); 2.30 (m, 2H); 3.30 (s, 3H); 3.36 (s, 1H); 3.54 (m, 2H); 3.75 (m, 2H); 4.23 (bs, 1H); 4.81 (s, 1H); 4.87 (d, J=2.9 Hz, 1H); 5.60 (dd, J=2.4 Hz, J=0.9 Hz, 1H); 6.80 (m, 3H).

1,2'-Anhydro-2,6-dideoxy-3-methanesulfonyl-4-methoxyethoxymethoxy-5-C-(2'-hydroxy-5'-methylphenyl)-α-D,L-ribo-hexopyranose (92)

A mixture of 91 (0.09 g, 0.28 mmol), ether (30 mL), methanesulfonyl chloride (0.5 mL) and pyridine (1.0 mL) was stirred overnight at ambient temperature. The solvent was evaporated at reduced pressure and the residue was purified by radial chromatography (Chromatotron, 8:2 hexanes/ethyl acetate) to give 0.07 g (61%) of 92 as a pale yellow oil. ^{1}H NMR ($CDCl_3$) δ 1.64 (s, 3H); 2.25 (s, 3H); 2.43 (s, 3H); 2.45 (m, 2H); 3.38 (s, 1H); 3.40 (s, 3H); 3.60 (m, 2H); 3.89 (m, 2H); 4.87

(q, J=7.0 Hz, 2H); 5.20 (m, 1H); 5.65 (d, J=2.9 Hz, 1H); 6.83 (m, 3H).

1,2'-Anhydro-2,3,6α-trideoxy-3-bromo-4β-hydroxy-5-C-(2'-hydroxy-5'-methylphenyl)-α-D,L-hex-2-enopyranose (93)

To a mixture of **81** (0.07 g, 0.24 mmol) and cerium (III) chloride heptahydrate (0.85 g, 0.24 mmol) in methanol (5 mL) was rapidly added a solution of sodium borohydride (0.01 g, 0.24 mmol) in methanol (5 mL). The reaction was stirred for 15 min, then quenched with 0.1 N hydrochloric acid (10 mL) and extracted with methylene chloride (3 x 30 mL). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated at reduced pressure. The residue was purified by radial chromatography (Chromatotron, 8:2 hexanes/ethyl acetate) to furnish 0.06 g (87%) of **93** as a colorless solid with mp 132-134°C. ^{1}H NMR ($CDCl_3$) δ 1.74 (s, 3H); 2.30 (s, 3H); 4.28 (m, 1H); 5.65 (d, J=3.7 Hz, 1H); 6.14 (dd, J=4.0 Hz, J=2.0 Hz, 1H); 6.89 (m, 3H).

1,2'-Anhydro-2,3,6α-trideoxy-3-bromo-4β-acetoxy-5-C-(2'-hydroxy-5'-methylphenyl)-α-D,L-hex-2-enopyranose (94)

A solution of **93** (0.05 g, 0.18 mmol), acetic anhydride (1 mL), pyridine (1 mL) and methylene chloride (10 mL) was stirred overnight. Methanol (5 mL) was added and the mixture was stirred for 2 h, then evaporated at reduced pressure. Chromatograhy of the residue (Chromatotron, 8:2 hexanes/ethyl acetate) furnished a quantitative yield

of 94 (0.06 g) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.58 (s, 3H); 2.22 (s, 3H); 2.30 (s, 3H); 5.68 (d, J=3.7 Hz, 1H); 5.78 (d, J=2.0 Hz, 1H); 6.19 (dd, J=3.7 Hz, J=2.1 Hz, 1H); 6.85 (m, 3H). Mass spectrum: m/z 338 ($M^{\cdot+}$), 259, 217.

1,2'-Anhydro-2,3,6-trideoxy-3-acetamido-4-hydroxy-5-C-(2'-hydroxy-5'-methylphenyl)-α-D,L-ribo-hexopyranose (95)

A cold (0°C) solution of 85 (0.10 g, 0.31 mmol) in methanol was saturated with ammonia, then stirred for 1 h. The solvent was removed under reduced pressure and the residue was purified by radial chromatography (Chromatotron, ethyl acetate) to give a quantitative yield of 95 (0.09 g) as a colorless solid with mp 180-184°C. ^{1}H NMR ($CDCl_3$) δ 1.49 (s, 3H); 1.63 (s, 3H); 2.19 (t, J=2.0 Hz, 1H); 2.29 (s, 3H); 2.31 (m, 1H); 3.50 (bs, 1H); 3.91 (d, J=5.1 Hz, 1H); 4.47 (m, 1H); 5.05 (bs, 1H); 5.64 (dd, J=3.6 Hz, J=1.4 Hz, 1H); 6.91 (m, 3H).

1,2'-Anhydro-2,3,6α-trideoxy-3β-acetamido-5-C-(2'hydroxy-5'-methylphenyl)-α-D,L-hex-4-ulose (96)

To a mixture of oxalyl chloride (0.44 mL, 5.0 mmol) in methylene chloride (30 mL) at -78°C under nitrogen was added dimethyl sulfoxide (0.71 mL, 10.0 mmol) and the reaction was stirred for 10 min. A mixture of 95 (0.80 g, 2.9 mmol) in methylene chloride (10 mL) was slowly added, then stirred for 30 min. Triethylamine (4.2 mL, 30.1 mmol)

was added dropwise and after 15 min, the cooling bath was removed and the reaction was allowed to come to room temperature for 1 h. The reaction was quenched with saturated sodium bicarbonate (30 mL) and the phases were separated. The aqueous phase was extracted with methylene chloride (3 x 40 mL). The combined organic solutions were washed with 2% hydrochloric acid (2 x 40 mL), then dried (Na_2SO_4), filtered and evaporated at reduced pressure. Radial chromatography of the residue (Chromatotron, ethyl acetate) furnished 0.70 g (88%) of **96** as a colorless solid which sublimes at 160°C. ^{1}H NMR ($CDCl_3$) δ 1.62 (m, 1H); 1.69 (s, 3H); 1.99 (s, 3H); 2.29 (s, 3H); 3.26 (ddd, J=14.5 Hz, J=8.6 Hz, J=7.2 Hz, 1H); 4.86 (ddd, J=13.1 Hz, J=7.2 Hz, J=6.4 Hz, 1H); 5.95 (bs, 1H); 5.98 (dd, J=8.6 Hz, J=5.1 Hz, 1H); 6.93 (m, 3H). ^{13}C NMR ($CDCl_3$) δ 209.3, 170.2, 146.1, 131.4, 130.6, 126.0, 122.2, 117.5, 92.3, 79.3, 49.2, 31.7, 23.0, 22.0, 20.7. Mass spectrum: m/z 275 ($M^{\cdot+}$), 232.

1,2'-Anhydro-2,3,6α-trideoxy-3α-acetamido-5-C-(2'-hydroxy-5'-methyl-phenyl)-α-D,L-hex-4-ulose (97)

A solution of **96** (0.45 g, 1.6 mmol), triethylamine (2 mL) and methylene chloride (30 mL) was stirred overnight at room temperature. The solvent was removed at reduced pressure and the residue was purified by radial chromatography (Chromatotron, ethyl acetate) to give a quantitative yield of **97** (0.45 g) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.64 (s, 3H); 1.96 (s, 3H); 2.27 (s, 3H); 2.35 (m, 1H); 3.57 (m,

2H); 5.40 (bs, 1H); 5.61 (dd, J=5.1 Hz, J=2.6 Hz, 1H); 6.84 (m, 3H). Mass spectrum: m/z 275 ($M^{\cdot+}$), 232.

1,2'-Anhydro-2,3,6-trideoxy-3-acetamido-4-hydroxy-5-C-(2'hydroxy-5'-methylphenyl)-α-D,L-arabino-hexopyranose (98)

To a cold (0°C) mixture of sodium borohydride (0.10 g, 2.6 mmol) in isopropyl alcohol (20 mL) was rapidly added a solution of 97 (0.38 g, 1.4 mmol) in isopropyl alcohol (10 mL). The reaction was stirred for 2 h and the solvent was removed at reduced pressure. The residue was suspended in water (30 mL) and extracted with methylene chloride (3 x 50 mL). The combined extracts were dried (Na_2SO_4), filtered and evaporated at reduced pressure. The residue was purified by radial chromatography (Chromatotron, ethyl acetate) to furnish 0.37 g (95%) of 98 as a colorless solid with mp 193-198°C. ^1H NMR ($CDCl_3$) δ 1.65 (s, 3H); 1.87 (m, 1H); 1.98 (s, 3H); 2.28 (s, 3H); 2.31 (m, 1H); 3.46 (d, J=10.1 Hz, 1H); 3.75 (m, 1H); 5.44 (bs, 1H); 5.62 (d, J=2.2 Hz, 1H); 6.85 (m, 3H). Mass spectrum: M/z 277 ($M^{\cdot+}$).

Anal. calcd for $C_{15}H_{19}NO_4$: C, 64.97; H, 6.91; N, 5.05. Found: C, 64.31; H, 6.88; N, 4.74.

4-Hydroxy-3-methylacetophenone (100)

To a mixture of aluminum chloride (80.0 g, 0.60 mol) in nitromethane (150 mL) was slowly added a solution of o-cresol (50.0 mL,

0.50 mL) and acetyl chloride (40.0 mL, 0.56 mol). Once the addition had been completed, the reaction was heated on a steam bath for 1 h. The reaction was cooled to room temperature, quenched with 3 N HCl (200 mL) and extracted with ethyl acetate (3 x 200 mL). The combined organic extracts were washed with water (2 x 250 mL) and brine (250 mL), then dried ($MgSO_4$), filtered and evaporated at reduced pressure. The residue was distilled under vacuum (bp 151-156°C/8 mm) to give 65.1 g (86%) of 100. ^1H NMR ($CDCl_3$) δ 2.30 (s, 3H); 2.56 (s, 3H); 6.79 (s, 1H); 6.87 (s, 1H); 7.79 (s, 1H).

4-Methoxy-3-methylacetophenone (101)

A mixture of 100 (64.8 g, 0.43 mol), dimethyl sulfate (47 mL, 0.50 mol), potassium carbonate (90 g, 0.65 mol) and acetone (750 mL) was refluxed overnight. The reaction was cooled to room temperature, then filtered. The solvent was evaporated under reduced pressure and the residue was distilled under vacuum (132-134°C/7mm) to give 59.3 g (84%) of 101. ^1H NMR ($CDCl_3$) δ 2.25 (s, 3H); 2.55 (s, 3H); 3.89 (s, 3H); 6.74 (s, 1H); 6.89 (s, 1H); 7.77 (s, 1H).

4-Methoxy-3-methylphenyl Acetate (102)

A mixture of 101 (59.1 g, 0.35 mol), m-chloroperoxybenzoic acid (90.0 g, 0.44 mol) and methylene chloride (500 mL) was refluxed overnight. The reaction was cooled to room temperature and filtered.

The filtrate was washed with saturated sodium bicarbonate (3 x 300 mL), then dried ($MgSO_4$), filtered and evaporated at reduced pressure. The residue was distilled under vacuum (136-138°C/20 mm) to give 54.2 g, (86%) of **102**. ^1H NMR ($CDCl_3$) δ 2.20 (s, 3H); 2.26 (s, 3H); 3.81 (s, 3H); 6.82 (m, 3H).

4-Hydroxy-2-methylanisole (103)

A mixture of **102** (58.8 g, 0.32 mol), tetrahydrofuran (400 mL) and 3 N hydrochloric acid (200 mL) was refluxed overnight. The reaction was cooled to room temperature and extracted with ether (3 x 250 mL). The combined extracts were dried ($MgSO_4$), filtered and evaporated at reduced pressure. The residue was distilled under vacuum (bp 103-106°C, 3 mm) to give 38.8 g (98%) of **103**. ^1H NMR ($CDCl_3$) δ 2.18 (s, 3H); 3.77 (s, 3H); 4.70 (s, 1H); 6.65 (m, 3H). IR (neat) 3356, 1505, 1222 cm^{-1}.

5-Bromo-4-hydroxy-2-methylanisole (104)

To a solution of **103** (10.0 g, 72.4 mmol) in carbon tetrachloride (120 mL) was slowly added bromine (11.8 g, 73.2 mmol) at ambient temperature, stirred for 1 h, then quenched with saturated sodium bisulfite (100 mL). The layers were separated and the aqueous phase was extracted with methylene chloride (2 x 100 mL). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated at reduced pressure to give a crude yield of 15.2 g (97%) of **104** as a light yellow

oil. All attempts at purification resulted in decomposition. ^{1}H NMR ($CDCl_3$) δ 2.16 (s, 3H); 3.76 (s, 3H); 4.72 (s, 1H); 6.64 (s, 1H); 6.96 (s, 1H).

2-Bromo-4-methoxy-5-methylphenyl Benzyl Ether (105)

A mixture of 104 (15.1 g, 69.6 mmol), benzyl bromide (12.8 g, 75.0 mmol) and acetone (250 mL) was refluxed overnight. The reaction was cooled to room temperature, filtered and the filtrate evaporated at reduced pressure. Column chromatography of the residue (silica, 200 g, 9.5:5 hexanes/ethyl acetate) furnished 19.2 g (90%) of 105 as a low melting solid (mp <60°C). ^{1}H NMR ($CDCl_3$) δ 2.13 (s, 3H); 3.76 (s, 3H); 5.04 (s, 2H); 6.78 (s, 1H); 6.98 (s, 1H); 7.37 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 152.7, 149.0, 137.0, 128.5, 127.8, 127.2, 126.8, 118.1, 117.8, 115.5, 109.5, 72.2, 56.0, 16.2. Mass spectrum: m/z 306 ($m^{\cdot+}$).

α-Methyl-α-(2'-benzyloxy-5'-methoxy-4'-methylphenyl)-2-furanmethanol (106)

A mixture of 105 (22.1 g, 71.9 mmol), magnesium (2.6 g, 107 mmol), tetrahydrofuran (400 mL) and iodine (4 crystals) was refluxed overnight. The Grignard solution was cooled to room temperature and a solution of 2-acetylfuran (7.9 g, 71.7 mmol) in tetrahydrofuran (50 mL) was rapidly added. The reaction was stirred for 3 h, then quenched with saturated ammonium chloride (100 mL) and extracted with ether (2 x

200 mL). The combined extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (silica, 300 g; 8.5:1.5 hexanes/ethyl acetate) to give 1.9 g of recovered 105. With continued elution, there was obtained 20.7 g of 106 (85%, 93% based on recovered 105) as a colorless solid which after recrystallization from hexanes had mp 81-84°C. ^1H NMR ($CDCl_3$) δ 1.90 (s, 3H); 2.18 (s, 3H); 3.75 (s, 3H); 4.51 (s, 1H); 4.92 (s, 2H); 6.19 (dd, $\underline{J}$=3.4 Hz, $\underline{J}$=1.3 Hz, 1H); 6.77 (dd, $\underline{J}$=3.1 Hz, $\underline{J}$=1.3 Hz, 1H), 7.30 (m, 7H). ^{13}C NMR ($CDCl_3$) δ 159.7, 152.0, 149.8, 141.4, 141.1, 136.7, 131.7, 128.6, 128.0, 127.5, 126.8, 116.4, 116.2, 110.2, 110.0, 105.2, 72.8, 71.5, 56.0, 27.4, 16.0.

Methyl α-5-(2'-Benzyloxy-5'-methoxy-4'-methylphenyl)-6-deoxyhex-2-en-4-ulose (107) and Methyl β-5-(2'-Benzyloxy-5'-methoxy-4'-methylphenyl)-6-deoxyhex-2-en-4-ulose (108) and 5-(2'-Benzyloxy-5'-methoxy-4'-methylphenyl)-6-deoxyhex-2-en-4-ulose (109)

To a -78°C solution 106 (5.81 g, 17.1 mmol) in methanol (75 mL) was slowly added a solution of bromine (2.73 g, 17.1 mmol) in methanol (25 mL). The mixture was stirred for 30 min, then saturated with ammonia while warming to ambient temperature. The solvent was removed at reduced pressure and the residue was taken up in ether (200 mL). The ethereal solution was washed with water (2 x 100 mL) and brine (100 mL), then dried ($MgSO_4$), filtered and evaporated at reduced pressure. The residue was dissolved in methanol (15 mL) and formic

acid (98%, 45 mL) and stirred for 45 min. The reaction was neutralized with saturated sodium carbonate (100 mL) followed by solid sodium bicarbonate until carbon dioxide evolution ceased. The aqueous mixture was extracted with ether (3 x 100 mL) and the combined extracts were dried ($MgSO_4$), filtered and evaporated at reduced pressure. The residue was purified by column chromatography (silica, 150 g, 8:2 hexanes/ethyl acetate) to furnish 3.17 g (50%) of the α anomer 107 as a crystalline solid with mp 113-114°C. ^{1}H NMR ($CDCl_3$) δ 1.85 (s, 3H); 2.18 (s, 3H); 3.46 (s, 3H); 3.82 (s, 3H); 4.88 (d, J=2.2 Hz, 2H); 5.06 (dd, J=2.9 Hz, J=1.3 Hz, 1H); 5.86 (dd, J=10.4 Hz, J=2.9 Hz, 1H); 6.44 (dd, J=10.3 Hz, J=2.9 Hz, 1H); 6.78 (s, 1H); 6.92 (s, 1H); 7.32 (s, 5H). ^{13}C NMR ($CDCl_3$) δ 196.9, 151.9, 149.9, 141.3, 136.8, 129.8, 128.3, 127.9, 127.3, 116.9, 116.7, 110.5, 110.3, 94.7, 80.7, 71.7, 56.0, 55.4, 24.6, 24.5, 16.1, 15.9.

Anal calcd for $C_{22}H_{24}O_5$: C, 71.72; H, 6.57. Found: C, 71.60; H, 6.61.

Continued elution gave 0.75 g (12%) of the β anomer 108 as a crystalline solid with mp 122-123°C. ^{1}H NMR ($CDCl_3$) δ 1.77 (s, 3H); 2.18 (s, 3H); 3.28 (s, 3H); 3.81 (s, 3H); 4.89 (d, J=5.5 Hz, 2H); 5.38 (t, J=1.6 Hz, 1H); 5.89 (dd, J=10.5 Hz, J=1.5 Hz, 1H); 6.53 (dd, J=10.5 Hz, J=1.5 Hz, 1H); 6.76 (s, 1H); 6.92 (s, 1H); 7.33 (s, 5H). ^{13}C NMR ($CDCl_3$) δ 197.2, 151.8, 149.7, 143.2, 136.9, 128.8, 128.6, 128.5, 128.2, 117.1, 116.8, 110.7, 110.4, 94.2, 94.1, 79.9, 71.9, 56.1, 54.8, 54.7, 21.6, 16.2.

Anal calcd for $C_{22}H_{24}O_5$: C, 71.72; H, 6.57. Found: C, 71.76;

H, 6.61.

Continued elution gave 0.73 g (12%) of the free sugar **109** as a crystalline solid with mp 140-145°C. ^{1}H NMR ($CDCl_3$) δ 1.80 (s, 3H); 2.18 (s, 3H); 3.80 (s, 3H); 4.88 (s, 2H); 5.43 (dt, $\underline{J}$=7.1 Hz, $\underline{J}$=1.6 Hz, 1H); 5.93 (dd, $\underline{J}$=10.3 Hz, $\underline{J}$=1.5 Hz, 1H); 6.48 (dd, $\underline{J}$=10.2 Hz, $\underline{J}$=2.1 Hz, 1H); 6.77 (s, 1H); 6.89 (s, 1H); 7.34 (s, 5H). ^{13}C NMR ($CDCl_3$) δ 196.3, 152.4, 149.7, 143.3, 143.1, 136.9, 128.6, 128.4, 127.9, 127.2, 117.5, 112.3, 110.5, 88.8, 81.2, 72.1, 56.1, 25.8, 25.6, 16.1.

Anal calcd for $C_{21}H_{22}O_5$: C, 71.17; H, 6.26. Found: C, 70.90; H, 6.11.

Methyl α-5-(2'-Benzyloxy-5'-methoxy-4'-methylphenyl)-6-deoxyhex-2-en-4-ulose (107) and Methyl β-5-(2'-Benzyloxy-5'-,methoxy-4'-methylphenyl)-6-deoxyhex-2-en-4-ulose (108)

To a mixture of **109** (2.56 g, 7.2 mmol) and trimethylorthoformate (2.5 mL, 22.9 mmol) in tetrahydrofuran (75 mL) was added dropwise anhydrous stannic chloride (0.9 mL, 7.6 mmol). The reaction was stirred for 1 h then quenched with triethylamine (4.0 mL). The mixture was filtered and the solvent was evaporated at reduced pressure. Column chromatography (silica, 100 g, 8:2 hexanes/ethyl acetate) of the residue gave 1.91 g (72%) of the α anomer **107** as a crystalline solid with mp 113-115°C. ^{1}H NMR ($CDCl_3$) δ 1.84 (s, 3H); 2.18 (s, 3H); 3.46 (s, 3H); 3.81 (s, 3H); 4.88 (d, $\underline{J}$=2.0 Hz, 2H); 5.05 (dd, $\underline{J}$=2.9 Hz, $\underline{J}$=1.3 Hz,

1H); 5.86 (dd, J=10.5 Hz, J=1.3 Hz, 1H); 6.44 (dd, J=10.4 Hz, J=2.7 Hz, 1H); 6.78 (s, 1H); 6.92 (s, 1H); 7.32 (s, 5H).

Continued elution gave 0.45 g (17%) of the β anomer 108 as a crystalline solid with mp 118-120°C. ^{1}H NMR ($CDCl_3$) δ 1.77 (s, 3H); 2.17 (s, 3H); 3.28 (s, 3H); 3.81 (s, 3H); 4.89 (d, J=5.5 Hz, 2H); 5.37 (t, J=1.5 Hz, 1H); 5.87 (dd, J=10.4 Hz, J=1.6 Hz, 1H); 6.53 (dd, J=10.2 Hz, J=1.4 Hz, 1H); 6.76 (s, 1H); 6.92 (s, 1H); 7.33 (s, 5H).

Methyl α-6-Deoxy-2,3-anhydro-5-(2'-benzyloxy-5'-methoxy-4'-methyl-phenyl)-hexos-4-ulose (110)

A mixture of 107 (6.61 g, 17.9 mmol), methylene chloride (100 mL), tert-butylhydroperoxide (10 mL, 3.0 M in toluene) and Triton B (3 mL, 40% solution in methanol) was stirred overnight. The reaction mixture was washed with water (3 x 50 mL), then dried ($MgSO_4$), filtered and evaporated at reduced pressure. Column chromatography (silica, 150 g; 8:2 hexanes/ethyl acetate) of the residue furnished 6.47 g (94%) of 110 as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.72 (s, 3H); 2.15 (s, 3H); 3.38 (d, J=4.4 Hz, 1H); 3.51 (s, 3H); 3.55 (m, 1H); 3.81 (s, 3H); 4.96 (s, 2H); 5.12 (d, J=1.1 Hz, 1H); 6.72 (s, 1H); 6.99 (s, 1H); 7.39 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 201.7, 152.3, 148.3, 137.0, 128.5, 128.0, 127.7, 127.3, 117.1, 116.8, 110.1, 109.8, 96.4, 96.3, 80.5, 72.0, 57.4, 56.3, 55.9, 53.8, 26.8, 15.9.

Methyl α-6-Deoxy-2,3-anhydro-5-(2'-benzyloxy-5'-methoxy-4'-methyl-

phenyl)-lyxo-hexopyranoside (111)

To a solution of 110 (5.56 g, 14. mmol) in isopropyl alcohol (100 mL) was added sodium borohydride (0.3 g, 7.9 mmol) and the reacton was stirred for 1 h. The solvent was evaporated at reduced pressure and the residue was taken up in water (50 mL) and extracted with methylene chloride (3 x 75 mL). The combined extracts were dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residue was purified by column chromatography (silica, 100 g; 8:2 hexanes/ethyl acetate) to give 5.56 g (99%) of 111 as a white solid with mp 157-158°C. ^1H NMR ($CDCl_3$) δ 1.56 (s, 3H); 2.15 (s, 3H); 2.31 (s, 1H); 3.29 (d, J=3.7 Hz, 1H); 3.51 (s, 3H); 3.59 (m, 1H); 3.77 (s, 3H); 4.67 (dd, J=10.3 Hz, J=6.1 Hz, 1H); 5.03 (s, 2H); 6.75 (s, 1H); 7.22 (s, 1H); 7.37 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 151.9, 148.2, 137.3, 130.0, 128.5, 127.8, 127.6, 126.0, 115.7, 115.4, 110.3, 109.9, 96.5, 77.3, 71.3, 64.7, 56.0, 55.5, 51.8, 23.8, 16.0. Mass spectrum: m/z 386 ($m^{\cdot+}$), 296.

Anal calcd for $C_{22}H_{26}O_6$: C, 68.20; H, 6.76. Found: C, 68.20; H, 7.25.

Methyl α-6-Dideoxy-3-dimethylamino-5-(2'-benzyloxy-5'-methoxy-4'-methyl-phenyl)-gluco-hexopyranoside (112)

A mixture of 111 (5.56g, 14.4 mmol) and dimethylamine (60 mL) were combined in a sealed tube and heated at 150°C overnight. The cooled

tube was opened and the excess dimethylamine was allowed to evaporate. The residue was purified by column chromatography (silica, 100 g; 9:1 methylene chloride/methanol) to give 0.44 g of recovered starting material. With continued elution there was obtained 4.83 g (78%, 85% based on consumed starting material) of 112 as a yellow solid with mp 178-180°C. ^{1}H NMR ($CDCl_3$) δ 1.78 (s, 3H); 2.22 (s, 3H); 2.44 (s, 6H); 3.39 (s, 3H); 3.57 (m, 3H); 3.79 (s, 3H); 4.12 (d, J=7.5 Hz, 1H); 5.10 (s, 2H); 6.85 (s, 1H); 7.40 (m, 5H); 7.57 (s, 1H).

Anal calcd for $C_{28}H_{33}NO_6$: C, 70.13; H, 6.94; N, 2.92. Found: C, 69.96; H, 7.09; N, 3.18.

Methyl α-3,6-Dideoxy-3-dimethylamino-5-(2'-hydroxy-5'-methoxy-4'-methylphenyl)-gluco-hexopyranoside (113)

A mixture of 112 (4.41 g, 10.2 mmol), and 10% palladium on charcoal (0.5 g) in acetic acid (60 mL) was shaken overnight under 40 psi of hydrogen. The mixture was filtered through celite and the solvent was evaporated at reduced pressure. Column chromatography (silica, 100 g; 9:1 methylene chloride/methanol) of the residue gave 0.16 g of recovered starting material and 1.49 g (88%; 93% based on consumed starting material) of 113 as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.69 (s, 3H); 2.17 (s, 3H); 2.52 (s, 6H); 3.48 (d, J=1.8 Hz, 1H); 3.59 (s, 3H); 3.75 (s, 3H); 3.79 (m, 2H); 4.32 (d, J=7.5 Hz, 1H); 6.67 (s, 1H); 7.18 (s, 1H).

1,2'-Anhydro-3,6-dideoxy-3-dimethylamino-5-C-(2'-hydroxy-4'-methyl-5'-methylphenyl)-α-D,L-gluco-hexopyranoside (114)

A mixture of 113 (7.0 g, 20.5 mmol), acetic acid (45 mL) and 3 N hydrochloric acid (15 mL) was heated on a steam bath for 3 h. The reaction was then cooled, neutralized with saturated sodium carbonate (50 mL) and solid sodium bicarbonate was added until gas evolution ceased. The mixture was extracted with ether (4 x 75 mL) and the combined organic extracts were dried (Na_2SO_4), filtered and evaporated at reduced pressure. The residue was purified by column chromatography (silica, 50 g; 9:1 methylene chloride/methanol) to give 5.5 g (87%) of 114 as a low melting (<50°C) solid. ^1H NMR ($CDCl_3$) δ 1.67 (s, 3H); 2.19 (s, 3H); 2.46 (s, 6H); 3.50 (d, J=10.3 Hz, 1H); 3.80 (s, 3H); 4.03 (m, 2H); 5.47 (d, J=3.7 Hz, 1H); 6.57 (s, 1H); 6.70 (s, 1H). Mass spectrum: m/z 310 ($m^{\cdot+}$).

1,2'-Anhydro-3,6-dideoxy-2,4-diacetoxy-3-dimethylamino-5-C-(2'-hydroxy-4'-methyl-5'-methoxyphenyl)-α-D,L-gluco-hexopyranoside (115)

A mixture of 114 (4.6 g, 14.9 mmol), acetic anhydride (3.8 mL), triethylamine (5.5 mL) and methylene chloride (75 mL) was stirred overnight. The reaction was quenched with saturated sodium bicarbonate (100 mL) and extracted with ether (3 x 50 mL). The combined extracts were dried (Na_2SO_4), filtered and evaporated at reduced pressure. Column chromatography (silica, 100 g; 7:3 hexanes/ethyl acetate) of

the residue gave 5.2 g (89%) of 115 as a crystalline solid with mp 166-168°C. ^{1}H NMR ($CDCl_3$) δ 1.51 (s, 3H); 2.07 (s, 3H); 2.10 (s, 3H); 2.18 (s, 3H); 2.24 (s, 6H); 2.73 (d, J=10.7 Hz, 1H); 3.76 (s, 3H); 5.03 (d, J=10.7 Hz, 1H); 5.11 (dd, J=10.7 Hz, J=4.0 Hz, 1H); 5.57 (d, J=4.0 Hz, 1H); 6.42 (s, 1H); 6.69 (s, 1H).

Anal calcd for $C_{20}H_{27}NO_7$: C, 61.06; H, 6.92; N, 3.56. Found: C, 60.31; H, 7.02; N, 3.41.

1,2'-Anhydro-2,3,6α-trideoxy-4β-hydroxy-5-C-(2'hydroxy-5'-methylphenyl)-α-D,L-hexopyranose (116)

A mixture of 82 (2.34 g, 10.7 mmol), isopropyl alcohol (50 mL) and sodium borohydride (0.41 g, 10.7 mmol) was stirred for two hours. The solvent was evaporated at reuced pressure and the residue was taken up in water (50 mL) and extracted with methylene chloride (3 x 70 mL). The combined extracts were dried ($MgSO_4$), filtered and evaporated at reduced pressure. Column chromatography (silica, 100 g; 8:2 hexanes/ethyl acetate) of the residue gave 2.31 g (98%) of 116 as an oil. ^{1}H NMR ($CDCl_3$) δ 1.66 (s, 3H); 1.98 (m, 4H); 2.28 (s, 3H); 3.64 (m, 1H); 3.77 (d, J=4.6 Hz, 1H); 5.53 (t, J=1.8 Hz, 1H); 6.90 (m, 3H).

1,2'-Anhydro-2,3,6α-trideoxy-4β-acetoxy-5-C-(2'-hydroxy-5'-methylphenyl)-α-D,L-hexopyranose (117)

A solution of 116 (0.34 g, 1.5 mmol), acetic anhydride (1.0 mL), pyridine (1.0 mL) and methylene choride (20 mL) was stirred overnight. Methanol (5 mL) was added to the reacton and the solution was stirred for 2 h. Evaporation of the solvent at reduced pressure, followed by radial chroatography (Chromatotron, 8:2 hexanes/ethyl acetate) of the residue gave 0.38 g (97%) of 117 as an oil. ^{1}H NMR ($CDCl_3$) δ 1.55 (s, 3H); 2.02 (m, 4H); 2.06 (s, 3H); 2.23 (s, 3H); 5.00 (d, J=4.4 Hz, 1 H); 5.52 (t, J=1.8 Hz, 1H); 6.82 (m, 3H).

1,2'-Anhydro-2,3,6α-trideoxy-4β-acetoxy-5-C-(2'hydroxy-5'-aldehydo-phenyl)-α-D,L-hexopyranose (118) and 1,2'-Anhydro-2,3,6α-trideoxy-4β-acetoxy-5-C-(2'-hydroxy-5'-carboxyphenyl)-α-D,L-hexopyranose (119)

A mixture of 117 (0.21 g, 0.80 mmol), cobalt (II) acetate tetra-hydrate (0.10 g, 0.40 mmol), hydrobromic acid (30% in acetic acid, 0.03 g, 0.11 mmol), and acetic acid (12 mL) was heated at 70°C with constant addition of oxygen through a dispersion tube for 3 h. The solvents were evaporated at reduced pressure, the residue taken up in methylene chloride (10 mL) and filtered. Radial chromatography (Chromatotron, 8:2 hexanes/ethyl acetate) of the residue gave 0.10 g (45%) of aldehyde 118 as an oil. ^{1}H NMR ($CDCl_3$) δ 1.79 (s, 3H); 2.24 (s, 3H); 2.33 (m, 4H); 5.22 (d, J=4.6 Hz, 1H); 5.81 (m, 1H); 7.12 (d, J=8.4 Hz, 1H); 7.86 (m, 2H); 9.88 (s, 1H). Mass spectrum: m/z 277 ($M^{=\cdot}$), 261, 233, 217.

With continued elution was obtained 0.07 g (30%) of acid 119 as an oil. ^{1}H NMR ($CDCl_3$) δ 1.62 (s, 3H); 2.06 (m, 4H); 2.08 (s, 3H);

5.06 (m, 1H); 5.66 (m, 1H); 6.89 (d, J=8.3 Hz, 1H); 7.91 (m, 2H).

Methyl [3,5-bis(acetyloxy)-9-methyl-3β,4α,5β,6α-tetrahydro-8-methoxy-6-methyl-2α,6-methano-2H-1-benzoxocin-4-yl]methylcarbamate (120)

A mixture of 115 (0.74 g, 1.9 mmol), methyl chloroformate (20 mL), sodium bicarbonate (5 g) and chloroform (40 mL) was refluxed overnight. The reaction was filtered and the filtrate was evaporated at reduced pressure. Radial chromatography (Chromatotron, 7:3 hexanes/ethyl acetate) of the residue furnished 0.89 g (100%) of 120 as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.55 (s, 3H); 2.03 (s, 3H); 2.07 (s, 3H); 2.1 (s, 3H); 2.70 (s, 3H); 3.59 (s, 3H); 3.75 (s, 3H); 4.42 (m, 1H); 5.04 (d, J=3.7 Hz, 1H); 5.16 (d, J=3.9 Hz, 1H); 5.61 (d, J=3.8 Hz, 1H); 6.40 (s, 1H); 6.72 (s, 1H). Mass spectrum: m/z ($m^{\cdot+}$), 409.

Methyl [3,5-bis(acetyloxy)-9-aldehydo-methyl-3β,4α,5β,6α-tetrahydro-methoxy-6-methyl-2α,6-methano-2H-1-benzoxocin-4-yl] methylcarbamate (121)

A mixture of 120 (0.82 g, 1.9 mmol), cupric sulfate pentahydrate (0.47 g, 1.9 mmol) and potassium persulfate (1.52 g, 5.6 mmol) in water (30 mL) and acetonitrile (30 mL) was refluxed for 30 min. The reaction was cooled, then extracted with methylene chloride (3 x 60 mL). The combined extracts were dried (Na_2SO_4), filtered and evaporated at reduced pressure. The residue was purified by radial chromatography

(Chromatotron, 6:4 hexanes/ethyl acetate) to give 0.47 g (56%) of 121 as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.60 (s, 3H); 2.05 (s, 3H); 2.08 (s, 3H); 2.70 (s, 3H); 3.59 (s, 3H); 3.86 (s, 3H); 4.45 (m, 1H); 5.07 (m, 1H); 5.20 (m, 1H); 5.66 (d, J=3.6 Hz, 1H); 6.61 (s, 1H); 7.38 (s, 1H); 10.39 (s, 1H).

Methyl [3,5-bis(acetyloxy)-9-(1,3-dioxolan-2-yl)-methyl-3β,4α,5β,6α-tetrahydro-methoxy-6-methyl-2α,6-methano-2H-1-benzoxocin-4-yl] methyl-carbamate (122)

A mixture of 121 (0.44 g, 1.0 mmol), ethylene glycol (0.1 mL), pyridinium p-toluenesulfonate (50 mg), and benzene (50 mL) was refluxed overnight with a Dean-Stark trap. The reaction was cooled, then transferred to a separatory funnel and washed with saturated sodium carbonate (2 x 50 mL). The organic layer was dried (Na_2SO_4/ Na_2CO_3), filtered and evaporated at reduced pressure. Radial chromatography (Chromatotron, 6:4 hexanes/ethyl acetate) of the residue furnished 0.49 g (100%) of 122 as a colorless oil. ^1H NMR ($CDCl_3$) δ 1.58 (s, 3H); 2.06 (s, 3H); 2.10 (s, 3H); 2.75 (s, 3H); 3.58 (s, 3H); 3.83 (s, 3H); 4.11 (m, 4H); 4.41 (m, 1H); 4.86 (m, 1H); 5.09 (m, 1H); 5.21 (m, 1H); 5.66 (d, J=3.5 Hz, 1H); 6.13 (s, 1H); 6.53 (s, 1H).

1,2'-Anhydro-3,6-dideoxy-3-dimethylamino-5-C-(2'-hydroxy-4'-aldehydo-5'-methoxyphenyl)-α-D,L-gluco-hexopyranoside (123)

To a mixture of lithium aluminum hydride (0.10 g, 2.6 mmol) in tetrahydrofuran (40 mL) was slowly added a solution of 122 (0.47 g, 0.95 mmol) in tetrahydrofuran (10 mL). The reaction was stirred for 2 h, then quenched by slow addition of 1 N hydrochloric acid (20 mL). The mixture was stirred for 1 h, then made basic by addition of 50% sodium hydroxide solution. The mixture was extracted with ether (4 x

50 mL), and the combined extracts were dried (Na_2SO_4), filtered and evaporated at reduced pressure. The residue was purified by radial chromatography (Chromatotron, 9:1 methylene chloride/methanol) to give 0.21 g (79%) of 123 as a colorless oil. ^1H NMR ($CDCl_3$) δ 1.71 (s, 3H); 2.21 (t, J=10.3 Hz, 1H); 2.48 (s, 6H); 2.75 (bs, 2H); 3.53 (d, J=10.1 Hz, 1H); 3.90 (s, 3H); 4.04 (dd, J=10.5 Hz, J=3.6 Hz, 1H); 5.50 (d, J=3.5 Hz, 1H); 6.77 (s, 1H); 7.31 (s, 1H); 10.39 (s, 1H).

1,2'-Anhydro-3,6-dideoxy-3-dimethylamino-2,4-diacetoxy-5-C-(2'hydroxy-4'-aldehydo-5'-methoxyphenyl)-α-D,L-gluco-hexopyranoside (124)

A mixture of 123 (0.22 g, 0.68 mmol), acetic anhydride (0.2 mL, 2.1 mmol), triethylamine (0.3 mL, 2.2 mmol) and methylene chloride (20 mL) was stirred overnight. The reaction was evaporated at reduced pressure and the residue was purified by radial chromatography (Chromatotron, 6:4 hexanes/ethyl acetate) to give 0.26 g (95%) of 124 as a colorless solid with mp 216-218°C. ^1H NMR ($CDCl_3$) δ 1.58 (s, 3H); 2.11 (s, 3H); 2.14 (s, 3H); 2.27 (s, 6H); 2.63 (t, J=10.6 Hz, 1H); 3.90 (s, 3H); 5.08 (d, J=10.6 Hz, 1H); 5.15 (dd, J=10.6 Hz, J=3.6 Hz, 1H); 5.63 (d, J=3.6 Hz, 1H); 6.64 (s, 1H); 7.37 (s, 1H); 10.44 (s, 1H).

1,2'-Anhydro-3,6-dideoxy-3-dimethylamino-2,4-diacetoxy-5-C-(2'-hydroxy-4'-carboxy-5'-methoxyphenyl)-α-D,L-gluco-hexopyranoside (125)

To a solution of 124 (0.24 g, 0.59 mmol) and sulfamic acid (0.09 g, 0.93 mmol) in water (10 mL) and tetrahydrofuran (10 mL) was added a solution of sodium chlorite (0.08 g, 0.93 mmol) in water (5 mL). The mixture was stirred for 30 min, then extracted with methylene chloride (3 x 25 mL). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated at reduced pressure. Radial chromatography (Chromatotron, 9:1 methylene chloride/methanol) of the residue furnished 0.22 g (88%) of 125 as a colorless oil. ^1H NMR ($CDCl_3$) δ 1.59 (s, 3H); 2.11 (s, 3H); 2.14 (s, 3H); 2.29 (s, 6H); 2.70 (d, J=10.8 Hz, 1H); 4.05 (s, 3H); 5.10 (d, J=10.8 Hz, 1H); 5.17 (dd, J=10.8 Hz, J= 4.0 Hz, 1H); 5.66 (d, J=4.0 Hz, 1H); 6.70 (s, 1H); 7.72 (s, 1H).

1,2'-Anhydro-3,6-dideoxy-3-dimethylamino-2,4-diacetoxy-5-C-(2'-hydroxy-4'-N,N-dimethylcarbamyl-5'-methoxyphenyl)-α-D,L-gluco-hexopyranoside (126)

A solution of 125 (0.20 g, 0.47 mmol), dicyclohexylcarbodiimide (0,12 g, 0.60 mmol), dimethylaminopyridine (0.08 g, 0.65 mmol) and diethylamine (0.1 mL, 0.97 mmol) in methylene chloride (25 mL) was stirred overnight. The reaction mixture was evaporated at reduced pressure and the residue was purified by radial chromatography (Chromatotron, 6:4 hexanes/ethyl acetate) to give 0.22 g (96%) of 126

as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.04 (t, J=7.1 Hz, 3H); 1.22 (t, J=7.1 Hz, 3H); 1.54 (s, 3H); 2.04 (s, 3H); 2.08 (s. 3H); 2.25 (s, 6H); 2.70 (t, J=10.2 Hz, 1H); 3.15 (q, J=7.1 Hz, 2H); 3.54 (q, J=7.1 Hz, 2H); 3.75 (s, 3H); 5.02 (d, J=10.2 Hz, 1H); 5.10 (dd, J=10.2 Hz, J=4.0 Hz, 1H); 5.59 (d, J=4.0 Hz, 1H); 6.50 (s, 1H); 6.74 (s, 1H). Mass spectrum: m/z 478 ($m^{\cdot+}$), 418.

Anal calcd for $C_{24}H_{34}N_2O_8$: C, 60.24; H, 7.16; N, 5.85. Found: C, 60.09; H, 7.29; N, 6.04.

(±)-N,N-Diethyl-4-(dimethylamino)-3β,4α,5β,6α-tetrahydro-8-methoxy-3,5-bishydroxy-6-methyl-2α,6-methano-2H-1-benzoxocin-9-carboxamide (127)

A cold (0°C) solution of 126 (10.2 g, 21.2 mmol) in methanol (100 mL) was saturated with ammonia, then stirred overnight at room temperature. The solvent was removed at reduced pressure and the residue was purified by column chromatography (silica, 150 g; 9:1 methylene chloride/ methanol) to furnish 8.2 g (98%) of 127 as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.05 (t, J=7.2 Hz, 3H); 1.21 (t, J=7.2 Hz, 3H); 1.67 (s, 3H); 2.58 (s, 6H); 3.16 (q, J=7.2 Hz, 3H); 3.58 (m, 4H); 3.76 (s, 3H); 4.01 (dd, J=11.2 Hz, J=3.8 Hz, 1H); 5.46 (d, J=3.5 Hz, 1H); 6.66 (s, 1H); 6.74 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 168.0, 148.9, 144.6, 127.6, 124.7, 114.4, 110.4, 95.5, 74.9, 72.9, 70.1, 67.1, 56.3, 42.9, 41.6, 38.9, 23.5, 13.9, 12.8. Mass spectrum: m/z 394 ($m^{\cdot+}$), 335.

2-Methyl-2-(2',5'-dimethoxyphenyl)-1,3-dioxolane (129)

A mixture of 2,5-dimethoxyacetophenone (47.3 g, 0.26 mol), ethylene glycol (30 mL, 0.54 mol) and pyridinium p-toluenesulfonate (0.25 g, 1 mmol) in benzene (750 mL) was refluxed for 16 h with a Dean-Stark trap under nitrogen. The mixture was cooled, then washed with saturated sodium carbonate (3 x 100 mL). The organic layer was dried (Na_2SO_4/Na_2CO_3), filtered and evaporated under reduced pressure. The residue was distilled (bp 100-102°C/0.2 mm) to yield 52.9 g (92%) of 129. ^1H NMR ($CDCl_3$) δ 1.79 (s, 3H); 3.80 (s, 3H); 3.86 (s, 3H); 3.92 (m, 2H); 4.05 (m, 2H); 6.85 (m, 2H); 7.13 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 153.3, 151.3, 131.9, 113.4, 113.0, 108.3, 64.6, 56.5, 55.7, 25.3. IR (neat) 2910, 1450, 1369, 1220, 1040, 730 cm^{-1}.

N,N-Diethyl-2,5-dimethoxy-4-acetyl Benzamide (130)

To a -78°C solution of 129 (34.4 g, 0.15 mol) and tetramethyl-ethylene diamine (23 mL, 0.15 mol) in tetrahydrofuran (600 mL) was added dropwise sec-butyllithium (110 mL of a 1.4 M solution in hexane). The reaction was stirred for 1 h, then diethylcarbamyol chloride (21.0 mL, 0.15 mol) was rapidly added. The solution was stirred overnight at ambient temperature, then quenched with 200 mL of 3 N hydrochloric acid. The layers were separated and the aqueous phase was extracted with methylene chloride (2 x 200 mL). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated under reduced pressure.

Purification of the residue by column chromatography (silica, 250 g; gradient elution methylene chloride to 9:1 methylene chloride/ tetrahydrofuran) gave 12.5 g (35%) of 2,5-dimethoxyacetophenone (128) and 25.9 g (61%) of the amide 130 which had bp 173-176°C at 0.4 mm. ^{1}H NMR ($CDCl_3$) δ 1.03 (t, J=7.0 Hz, 3H); 1.23 (t, J=7.1 Hz, 3H); 2.60 (s, 3H); 3.13 (q, J=7.0 Hz, 2H); 3.56 (m, 2H); 3.80 (s, 3H); 3.86 (s, 3H); 6.83 (s, 1H); 7.29 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 198.8, 153.5, 148.9, 131.9, 128.4, 112.6, 111.6, 56.1, 42.7, 38.9, 31.8, 13.9. IR (neat) 2960, 1670, 1630, 1460, 1390, 1220, 1040 cm^{-1}. Mass spectrum: m/z 279 ($m^{\cdot+}$), 264, 248.

α-Methyl-α-(2,5-dimethoxy-4-N,N-diethylcarbamyl)-2-furanmethanol (131)

To a cold (0°C) solution of furan (17.9 mL, 0.25 mol) in tetrahydrofuran (500 mL) was added dropwise n-butyllithium (98 mL of a 2.5 M solution in hexane). The solution was stirred for 1 h, then chilled to -78°C and a solution of 130 (34.3 g, 0.12 mol) in tetrahydrofuran (100 mL) was rapidly added. The reaction was stirred for 2 h, then quenched with saturated ammonium chloride (250 mL). The layers were separated and the aqueous phase was extracted with methylene chloride (2 x 200 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under vacuum. Purification of the residue by column chromatography (silica, 250 g; 9.5:5 methylene chloride/ tetrahydrofuran) gave 39.7 g (93%) of 131 which was recrystallized from acetone to give colorless crystals with mp 147-

148°C. ^{1}H NMR ($CDCl_3$) δ 1.05 (t, J=7.1 Hz, 3H); 1.24 (t, J=7.2 Hz, 3H); 1.91 (s, 3H); 3.17 (q, J=7.1 Hz, 2H); 3.56 (q, J=7.2 Hz, 2H); 3.72 (s, 3H); 3.75 (s, 3H); 4.51 (s, 1H); 6.33 (m, 2H); 6.79 (s, 1H); 7.35 (bs, 1H). ^{13}C NMR ($CDCl_3$) δ 168.1, 151.0, 149.1, 134.8, 126.6, 111.8, 111.2, 110.0, 87.7, 73.0, 56.4, 56.3, 42.8, 38.9, 27.1, 14.0, 12.9.

Methyl α-5-(2',5'-dimethoxy-4'-N,N-diethylcarbamylphenyl)-6-deoxyhex-2-en-4-ulose (132) and Methyl β-5-(2',5',-dimethoxy-4'-N,N-diethyl-carbamylphenyl)-6-deoxyhex-2-en-4-ulose (133)

Bromine (4.5 mL, 87.8 mmol) was rapidly added to a solution of 131 (27.8 g, 80.0 mmol) in methanol (250 mL) at -78°C. The reaction was stirred for 30 min, then neutralized with ammonia. The methanol was removed under vacuum and the residue was taken up in water (100 mL) and extracted with methylene chloride (3 x 150 mL). The combined extracts were dried (Na_2SO_4), filtered and evaporated under reduced pressure. The residue was dissolved in methanol (20 mL) and formic acid (120 mL) was added. The reaction was stirred for 30 min, then poured into saturated sodium carbonate (300 mL). Solid sodium bicarbonate was added until foaming ceased. The mixture was extracted with methylene chloride (3 x 250 mL) and the combined organic solutions were dried (Na_2SO_4), filtered and evaporated under reduced pressure. Column chromatography (silica, 250 g; 9.5:5 methylene chloride/tetrahydrofuran) of the residue gave 25.1 g (83%) of 132 as a colorless

oil. ^{1}H NMR ($CDCl_3$) δ 1.05 (t, J=7.1 Hz, 3H); 1.24 (t, J=7.2 Hz, 3H); 1.84 (s, 3H); 3.17 (q, J=7.1 Hz, 2H); 3.59 (m, 2H); 3.65 (s, 3H); 3.80 (s, 3H); 5.15 (dd, J=2.6 Hz, J=1.3 Hz, 1H); 6.22 (dd, J=10.3 Hz, J=1.5 Hz, 1H); 6.77 (s, 1H); 6.97 (bs, 1H). Mass spectrum: m/z 377 ($m^{\cdot+}$), 345.

With continued elution there was obtained 4.4 g (15%) of 133 as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.03 (t, J=7.2 Hz, 3H); 1.21 (t, J=7.2 Hz, 3H); 1.74 (s, 3H); 3.14 (q, J=7.2 Hz, 2H); 3.49 (m, 2H); 3.61 (s, 3H); 3.76 (s, 3H); 5.41 (m, 1H); 6.16 (dd, J=1.2 Hz, J=1.5 Hz, 1H); 6.73 (m, 2H); 6.98 (m, 1H).

Methyl α-6-Deoxy-2,3-anhydro-5-(2',5'-dimethoxy-4'-N,N-diethylcarbamyl-phenyl)hexopyran-4-ulose (134)

A solution of 132 (14.1 g, 37.3 mmol), tert-butylhydroperoxide (25 mL of a 3 M solution in toluene), Triton B (2 mL of a 40% solution in methanol) and methylene chloride (200 mL) was stirred for 16 h at ambient temperature. The reaction was washed with water (3 x 100 mL) and the organic layer was dried (Na_2SO_4), filtered and evaporated under reduced pressure. Column chromatography (silica, 150 g; 9.5:5 methylene chloride/tetrahydrofuran) of the residue gave 13.3 g (91%) of 134 as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.03 (t, J=7.0 Hz, 3H); 1.22 (t, J=7.1 Hz, 3H); 1.68 (s, 3H); 3.16 (q, J=7.1 Hz, 2H); 3.54 (s, 3H); 3.61 (m, 4H); 3.69 (s, 3H); 3.79 (s, 3H); 5.16 (s, 1H); 6.73 (s, 1H); 7.07 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 201.4, 167.9, 149.9, 149.5,

127.8, 112.5, 111.5, 96.4, 80.3, 57.0, 56.7, 56.5, 53.5, 42.8, 38.8, 26.3, 14.0, 12.9. IR (neat) 2950, 1730, 1625, 1465, 1390, 1210, 1065, 1040 cm^{-1}.

Methyl α-6-Deoxy-2,3-anhydro-5-(2',5'-dimethoxy-4'-N,N-diethylcarbamyl-phenyl)-lyxo-hexopyranoside (135)

A mixture of **134** (12.1 g, 30.8 mmol), sodium borohydride (1.13 g, 0.03 mol), and isopropyl alcohol (100 mL) was stirred at room temperature for 2 h. The reaction mixture was evaporated at reduced pressure and the residue was taken up in water (100 mL) and extracted with methylene chloride (3 x 100 mL). The combined extracts were dried (Na_2SO_4), filtered and evaporated at reduced pressure. The residue was purified by column chromatography (silica, 100 g; 9:1 methylene chloride/tetrahydrofuran) to give 11.8 g (97%) of 135 as a colorless oil. ^1H NMR ($CDCl_3$) δ 1.04 (t, J=7.1 Hz, 3H); 1.23 (t, J=7.1 Hz, 3H); 1.55 (s, 3H); 3.18 (q, J=7.1 Hz, 2H); 3.36 (q, J=7.1 Hz, 2H); 3.54 (s, 3H); 3.65 (m, 2H); 3.78 (s, 3H); 3.81 (s, 3H); 4.74 (dd, J=10.2 Hz, J=6.2 Hz, 1H); 5.08 (s, 1H); 6.74 (s, 1H); 7.30 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 163.4, 149.5, 149.0, 133.3, 125.8, 110.9, 96.4, 77.4, 64.6, 56.2, 55.9, 55.5, 51.8, 51.5, 42.7, 38.6, 30.2, 23.6, 13.9, 12.8. IR (neat) 3490, 2938, 2241, 1620, 1504, 1475, 1464, 1391. Mass spectrum: m/z 395 ($m^{\cdot+}$), 364.

Methyl α-3,6-Dideoxy-3-dimethylamino-5-(2',5'-dimethoxy-4'-N,N-diethylcarbamylphenyl)-gluco-hexopyranoside (136)

A mixture of 135 (10.1 g, 25.5 mmol) and dimethylamine (60 mL) were combined in a sealed tube and heated to 150°C overnight. After cooling to 0°C, the tube was opened and the excess dimethylamine was allowed to evaporate. Column chromatography (silica, 150 g; 9:1 methylene chloride/methanol) of the residue furnished 9.9 g (88%) of 136 as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.06 (t, J=7.0 Hz, 3H); 1.22 (t, J=7.0 Hz, 3H); 1.67 (s, 3H); 2.68 (s, 6H); 3.10 (m, 3H); 3.45 (s, 3H); 3.62 (m, 4H); 3.73 (s, 3H); 3.81 (s, 3H); 4.07 (d, J=7.3 Hz, 1H); 6.77 (s, 1H); 7.60 (s, 1H).

Methyl α-3,6-Dideoxy-3-dimethylamino-5-(2'-methoxy-4'-N,N-diethylcarbamyl-5-hydroxyphenyl)-gluco-hexopyranoside (137) and Methyl α-3,6-Dideoxy-3-dimethylamino-5-(2'-hydroxy-4'-N,N-diethylcarbamyl-5'-methoxyphenyl)-gluco-hexopyranoside (138)

To a room temperature mixture of sodium hydride (1.9 g, 60% suspension, 47.5 mmol) in dimethylformamide (50 mL) was slowly added ethanethiol (4.0 mL, 95%, 50.8 mmol) and the mixture was stirred for 10 min. A solution of 136 (9.5 gm, 21.6 mmol) in dimethylformamide (25 mL) was rapidly added to the ethanethiolate anion solution and the reaction was heated on a steam bath for 3 h. The reaction was cooled, neutralized with acetic acid (2.8 mL, 47.5 mmol) and evaporated at

reduced pressure. The residue was taken up in water (100 mL) and extracted with methylene chloride (3 x 100 mL). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated at reduced pressure. The residue was purified by column chromatography (silica, 150 g; 9:1 methylene chloride/methanol) to give 0.35 g (4%) of 137 as a colorless oil. ^1H NMR ($CDCl_3$) δ 1.06 (t, J=7.2 Hz, 3H); 1.22 (t, J=7.3 Hz, 3H); 1.68 (s, 3H); 2.59 (s, 6H); 2.87 (m, 1H); 3.18 (q, J=7.2 Hz, 2H); 3.50 (m, 4H); 3.57 (s, 3H); 3.76 (s, 3H); 4.65 (d, J=7.5 Hz, 1H); 6.71 (s, 1H); 7.12 (s, 1H).

With continued elution there was obtained 6.5 g (73%) of 117 as a colorless oil. ^1H NMR ($CDCl_3$) δ 1.09 (t, J=7.0 Hz, 3H); 1.23 (t, J=7.0 Hz, 3H); 1.65 (s, 3H); 2.54 (s, 6H); 2.85 (m, 1H); 3.22 (q, J=7.0 Hz, 2H); 3.58 (s, 3H); 3.62 (m, 4H); 3.73 (s, 3H); 4.30 (d, J=7.5 Hz, 1H); 6.73 (s, 1H); 7.27 (s, 1H).

(±)-N,N-Diethyl-4-(dimethylamino)-3β,4α,5β,6α-tetrahydro-8-methoxy-3,5-bishydroxy-6-methyl-2α,6-methano-2H-1-benzoxocin-9-carboxamide (127)

A mixture of 138 (6.4 g, 15.6 mmol), acetic acid (50 mL) and 3 N hydrochloric acid (25 mL) was heated on a steam bath for 3 h. The reaction was cooled, then neutralized with solid sodium carbonate until gas evolution ceased. The mixture was extracted with methylene chloride (4 x 70 mL) and the combined organic extracts were dried (Na_2SO_4), filtered and evaporated at reduced pressure. Column chromatography (silica, 100 g; 9:1 methylene chloride/methanol) of

the residue furnished 4.7 g (76%) of 127 as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.05 (t, J=7.2 Hz, 3H); 1.21 (t, J=7.4 Hz, 3H); 1.67 (s, 3H); 2.58 (s, 6H); 3.16 (q, J=7.2 Hz, 2H); 3.58 (m, 4H); 3.76 (s, 3H); 4.01 (dd, J=11.2 Hz, J=3.5 Hz, 1H); 5.46 (d, J=3.5 Hz, 1H); 6.66 (s, 1H); 6.74 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 168.0, 148.9, 144.6, 127.6, 124.7, 114.4, 110.4, 95.5, 74.9, 72.9, 70.1, 67.1, 56.3, 42.9, 41.6, 38.9, 23.5, 13.9, 12.8.

Anal calcd for $C_{20}H_{30}N_2O_6$: C, 60.90; H, 7.67; N, 7.10. Found: C, 60.35; H, 7.72: N, 6.59.

(±)-N,N-Diethyl-4-dimethylamino-3β,4α,5β,6α-tetrahydro-8-8methoxy-3,5-bis[(2-ethoxy)ethoxy]-6-methyl-2α,6-methano-2H-1-benzoxocin-9-carboxamide (139)

A solution of 127 (0.19 g, 0.48 mmol), ethyl vinyl ether (6 mL) and toluene sulfonic acid monohydrate (50 mg) in methylene chloride (25 mL) was stirred overnight. The reaction was diluted with ether (75 mL) and washed with 1 N sodium hydroxide (2 x 25 mL). The ether extracts were dried (Na_2SO_4), filtered and evaporated at reduced pressure. The residue was purified by radial chromatography (Chromatotron, 9.5:5 methylene chloride/ methanol) to give 0.18 g (69%) of 139 as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.19 (m, 18H); 1.65 (s, 3H); 2.41 (s, 6H); 3.14 (q, J=7.3 Hz, 2H); 3.48 (m, 9H); 3.74 (s, 3H); 4.12 (dd, J=10.5 Hz, J=3.5 Hz, 1H); 4.87 (m, 1H); 5.67 (d, J=3.5 Hz, 1H); 6.63 (s, 1H); 6.69 (s, 1H).

(±)-N,N-Diethyl-4-dimethylamino-3β,4α,5β,6α-tetrahydro-3,5-bis[(2-methoxyethoxy)methoxy]-6-methyl-2α,6-methano-2H-1-benzoxocin-9-carboxamide (140)

To a -78°C solution of 127 (0.94 g, 2.4 mmol) in tetrahydrofuran (60 mL) was slowly added sec-butyllithium (3.4 mL of a 1.4 M solution in hexanes). The solution was stirred for 15 min, then 2-methoxyethoxymethyl chloride (1.0 mL, 8.8 mmol) was added rapidly. The reaction was stirred to room temperature overnight, then quenched with saturated sodium bicarbonate (50 mL) and extracted with ether (3 x 50 mL). The combined ether extracts were dried (Na_2SO_4), filtered and evaporated at reduced pressure. Radical chromatography of the residue (Chromatotron, 9.5:5 methylene chloride/methanol) furnished 1.16 g (85%) of 140 as an colorless oil. ^1H NMR ($CDCl_3$) δ 1.02 (t, J=7.2 Hz, 3H); 1.18 (t, J=7.2 Hz, 3H); 1.61 (s, 3H); 2.33 (s, 6H); 2.58 (d, J=10.3 Hz, 1H); 3.14 (q, J=7.2 Hz, 2H); 3.36 (s, 6H); 3.57 (m, 10 H); 3.72 (s, 3H); 3.96 (m, 2H); 4.82 (m, 4H); 5.68 (d, J=3.7 Hz, 1H); 6.60 (s, 1H); 6.67 (s, 1H).

(±)-N,N-Diethyl-4-(dimethylamino)-10-formyl-3β,4α,5β,6α-tetrahydro-8-methoxy-3,5-bis[(2-methoxyethoxy)methoxy]-6-methyl-2α,6-methano-2H-1-benzoxocin-9-carboxamide (141)

To a -78°C solution of 140 (0.66 g, 1.2 mmol), tetramethylene ethylenediamine (0.4 mL, 2.7 mmol) and tetrahydrofuran (50 mL) was

slowly added sec-butyllithium (5.0 mL of 1.4 M solution in hexanes) until a deep orange color persisted. The reaction mixture was stirred for 1 h. then dimethylformamide (1 mL) was added. The mixture was stirred at room temperature for 3 h, then quenched with saturated sodium bicarbonate (50 mL) and extracted with ether (4 x 50 mL). The combined extracts were dried (Na_2SO_4), filtered and evaporated at reduced pressure. Radial chromatography (Chromatotron, 9.5:5 methylene chloride/methanol) of the residue gave 0.29 g of recovered starting material 141 and with continued elution, 0.34 g (50%, 88% based on consumed starting material) of 120 as a yellow oil. ^1H NMR ($CDCl_3$) δ 1.00 (t, J=7.0 Hz, 3H); 1.30 (t, J=7.3 Hz, 3H); 1.66 (s, 3H); 2.37 (s, 6H); 2.61 (t, J=10.1 Hz, 1H); 3.07 (q, J=7.0 Hz, 2H); 3.39 (s, 6H); 3.59 (m, 10 H); 3.77 (s, 3H); 3.92 (m, 2H); 4.86 (m, 4H); 5.87 (d, J=3.9 Hz, 1H); 6.93 (s, 1H); 10.38 (s, 1H). Mass Spectrum: m/z 508 (M-88).

Anal calcd for $C_{29}H_{46}N_2O_{11}$: C, 58.18; H, 7.74; N, 4.70. Found: C, 57.80; H, 7.93; N, 4.18.

(±)-4-(Dimethylamino)-3β,4α,5β,6α-tetrahydro-3,5-dihydroxy-8-methoxy-6-methyl-11α-(thiophenyl)-2α,6-methano-2H-furo[3,4-j]-1-benzoxocin-9(11H)-one (143) and (±)-4-(Dimethylamino)-3β,4α,5β,6α-tetrahydro-3,5-dihydroxy-8-methoxy-6-methyl-11β-(thiophenyl)-2α,6-methano-2H-furo[3,4-j]-1-benzoxocin-9(11H)-one (144)

A mixture of 141 (0.21 g, 0.35 mmol), acetic acid (10 mL) and 3 N hydrochloric acid (10 mL) was heated on a steam bath for 3 h. The reaction mixture was cooled and evaporated at reduced pressure. The intractable residue was combined with thiophenol (1 mL), p-toluene-sulfonic acid (0.1 g) and benzene (40 mL) and refluxed overnight with a Dean-Stark trap. The mixture was cooled and diluted with ether (60 mL). The ether solution was washed with saturated sodium bicarbonate (2 x 50 mL), then dried (Na_2SO_4), filtered and evaporated at reduced pressure. The residue was purified by radial chromatography (Chromatotron, 9:1 methylene chloride/methanol) to give 0.05g (31%) of 143 as a yellow oil. ^1H NMR ($CDCl_3$) δ 1.75 (s, 3H); 2.18 (t, J=12.3 Hz, 1H); 2.49 (s, 6H); 3.52 (d, J=10.3 Hz, 1H); 3.73 (bs, 2H); 3.94 (s, 3H); 4.19 (m, 1H); 5.64 (d, J=3.9 Hz, 1H); 6.59 (s, 1H); 6.78 (s, 1H); 7.38 (m, 5H). Mass spectrum: m/z 459 ($M^{\cdot+}$), 350.

With continued elution there was isolated, 0.11 g (69%) of 144 as a yellow oil. ^1H NMR ($CDCl_3$) δ 1.69 (s, 3H); 2.34 (m, 1H); 2.50 (s, 6H); 3.49 (d, J=10.6 Hz, 1H); 3.72 (bs, 2H); 3.82 (s, 3H); 4.11 (dd, J=10.6 Hz, J=3.8 Hz, 1H); 5.69 (d, J=3.8 Hz, 1H); 6.61 (s, 1H); 6.66 (s, 1H); 7.38 (m, 5H). Mass spectrum: m/z 459 ($M^{\cdot+}$), 350.

Anal calcd for $C_{23}H_{25}NO_7S$: C, 60.12; H, 5.48; N, 3.05. Found: C, 60.13; H, 5.63; N, 2.67.

(±)-4-(Diethylamino)-3β,4α,5β,6α-tetrahydro-3,5-dihydroxy-8-methoxy-6-methyl-11β-(phenylsylfonyl)-2α,6-methano-2H-furo[3,4-j]-1-benzoxocin-9(11H)-one (145)

A mixture of 144 (0.05 g, 0.11 mmol), hydrogen peroxide (0.2 mL, 30% in water) and acetic acid (5 mL) was heated on a steam bath for 1 h. The reaction was cooled, then quenched with solid sodium bicarbonate and diluted with ethyl acetate (20 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated at reduced pressure. Radial chromatography of the residue (Chromatotron, 9:1 methylene chloride/methanol) furnished 0.01 g (18%) of 145 as a dark yellow oil. ^1H NMR ($CDCl_3$) δ 1.68 (s, 3H); 2.36 (m, 1H); 2.52 (s, 6H); 3.48 (d, J=10.4 Hz, 1H); 3.70 (bs, 2H); 3.84 (s, 3H); 4.07 (dd, J=10.4 Hz, J=3.6 Hz, 1H); 5.73 (s, J=3.6 Hz, 1H); 6.60 (s, 1H); 6.98 (s, 1H); 7.38 (m, 5H).

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VITA

The author, William P. Ellenberger, was born in San Mateo, California on October 17, 1951. He attended San Jose State University in California and earned the degrees of Bachelor of Arts in biochemistry in 1974 and Masters of Science in chemistry in 1981. In 1982, he joined the Oregon Graduate Center in Beaverton, Oregon and began work toward a doctoral degree in organic chemistry under the direction of Dr. Frank M. Hauser. He is currently employed as a research associate at Nova Pharmaceutical Corporation in Baltimore, Maryland.

William Ellenberger is married to Suzanne Ellenberger and they have a daughter, Dana Noel.