1988

Synthetic approaches to anthracycline antibiotics

Tim On Man
Iowa State University

Order Number 8825417

Synthetic approaches to anthracycline antibiotics

Man, Tim On, Ph.D.

Iowa State University, 1988

U·M·I
300 N. Zeeb Rd.
Ann Arbor, MI 48106

PLEASE NOTE:

In all cases this material has been filmed in the best possible way from the available copy. Problems encountered with this document have been identified here with a check mark __✓__.

1. Glossy photographs or pages _____
2. Colored illustrations, paper or print _____
3. Photographs with dark background _____
4. Illustrations are poor copy _____
5. Pages with black marks, not original copy ✓
6. Print shows through as there is text on both sides of page _____
7. Indistinct, broken or small print on several pages _____
8. Print exceeds margin requirements _____
9. Tightly bound copy with print lost in spine _____
10. Computer printout pages with indistinct print _____
11. Page(s) _____ lacking when material received, and not available from school or author.
12. Page(s) _____ seem to be missing in numbering only as text follows.
13. Two pages numbered _____. Text follows.
14. Curling and wrinkled pages _____
15. Dissertation contains pages with print at a slant, filmed as received _____
16. Other _____

_____

_____

Synthetic approaches to anthracycline antibiotics

by

Tim On Man

A Dissertation Submitted to the
Graduate Faculty in Partial Fulfillment of the
Requirements for the Degree of
DOCTOR OF PHILOSOPHY

Department: Chemistry
Major: Organic Chemistry

Approved:

Signature was redacted for privacy.

In Charge of Major Work

Signature was redacted for privacy.

For the Major Department

Signature was redacted for privacy.

For the Graduate College

Iowa State University
Ames, Iowa

1988

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

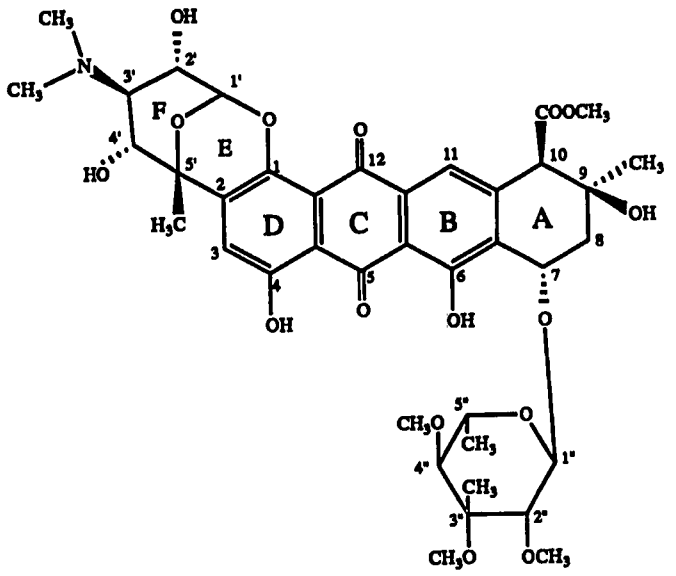
INTRODUCTION

Nogalamycin and Its Analogs: History and Chemistry

Nogalamycin (1), an anthracycline antibiotic produced by Streptomyces nogalater,[1,2] was isolated 20 years ago at The Upjohn Company.[3] It exhibits inhibitory activity against a variety of gram-positive bacteria in vitro and several tumors in vivo.

During the period of interest in nogalamycin, structural studies were continued and the analogs obtained were tested for biological activity. At the early stage of the investigation, the gross structure of nogalamycin was established based on chemical studies and spectral analyses.[4-6] However, there were some uncertainties regarding the absolute stereochemistry of the amino sugar and absolute stereochemistry at C-7, C-9, and C-10 of nogalamycin. Arora[7] later carried out a crystallographic study of nogalamycin and established the absolute stereochemistry and complete structure of the compound (Figure 1). In addition to revealing the molecular structure, he also proposed models for the probable mode of interaction with DNA.

In the course of investigating the antitumor activity of nogalamycin, a large number of nogalamycin analogs have been prepared from the degradation of nogalamycin.[4] Almost all of these can be included in two series: the nogalarol



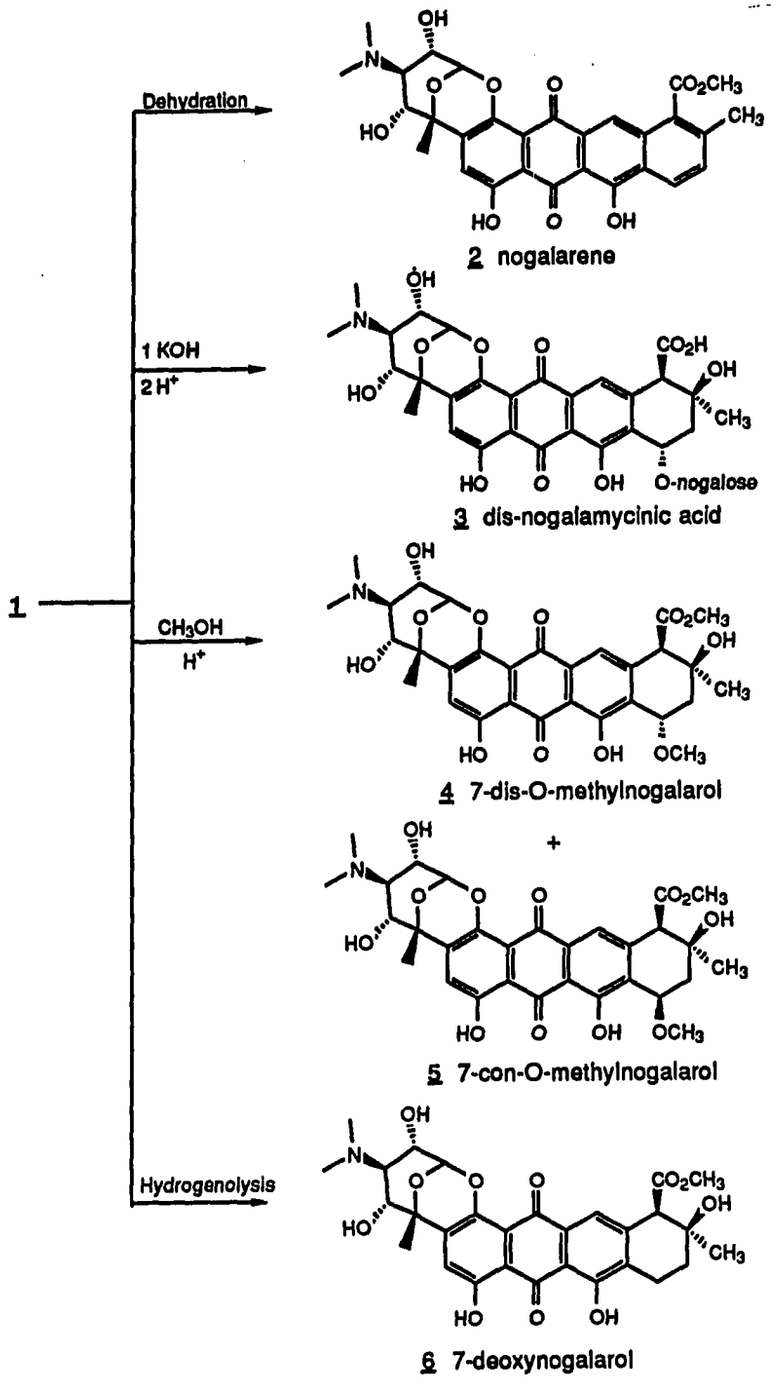
1

Figure 1. Nogalamycin

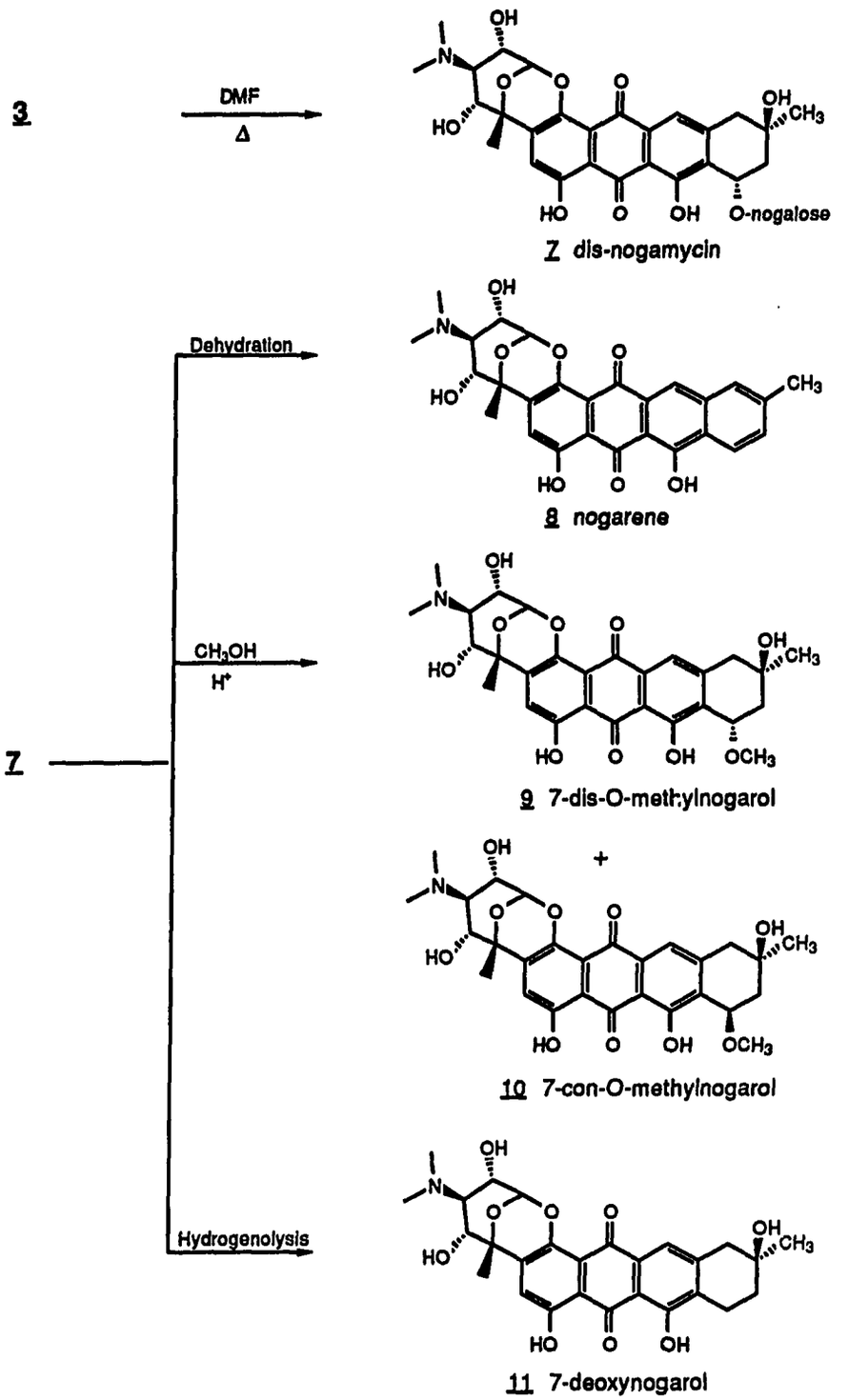
series and the nogarol series. The difference between the two is the presence of the carbomethoxyl group at C-10 in the nogalarol series and its absence in the nogarol series. Scheme I and Scheme II summarize the preparation, structure and nomenclature of the major nogalamycin analogs.

Dehydration of nogalamycin with triethylamine in refluxing methanol gave nogalarene (2). At room temperature, nogalamycin was hydrolyzed in 0.5 N potassium hydroxide to dis-nogalamycinic acid (3). The unionized form of acid 3 is indicated, but it exists as the zwitterion.

Scheme I


1
Dehydration
1 KOH
2 H+
CH3OH
H+
Hydrogenolysis
2 nogalarene
3 dis-nogalamycinic acid
4 7-dis-O-methylnogalarol
+
5 7-con-O-methylnogalarol
6 7-deoxynogalarol

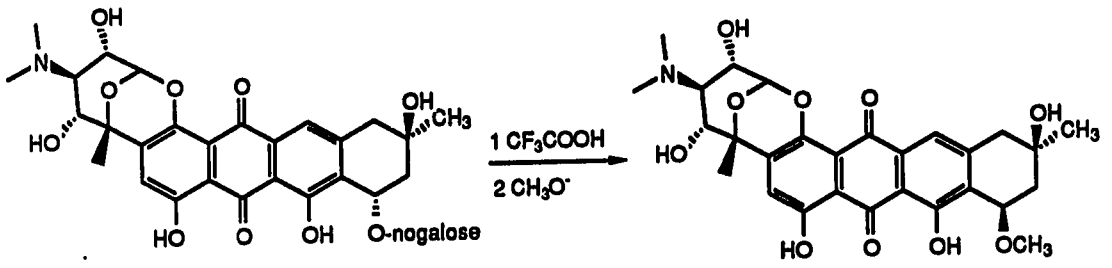
Scheme II


3
DMF
Δ
7 dis-nogamycin
Dehydration
8 nogarene
CH3OH
H+
9 7-dis-O-methylnogarol
7
+
10 7-con-O-methylnogarol
Hydrogenolysis
11 7-deoxynogarol

The acid 3 is readily decarboxylated upon dissolving in DMF to give dis-nogamycin (7). Acidic methanolysis of nogalamycin (1) resulted a pair of 7-con- and 7-dis-O-methylnogalarols (4, 5). Similarly, dis-nogamycin gave 7-con- and 7-dis-O-methylnogarols (9, 10) when treated with acidic methanol. The ratio of compounds 9 and 10 formed in the reaction was 4:6. Separation of 9 and 10 was quite difficult, as aromatization of ring A occurred readily to form nogarene (8), which was prepared independently by heating dis-nogamycin in aqueous acid. Catalytic hydrogenation of nogalamycin and dis-nogamycin replaced the nogalose at C-7 by hydrogen to form 7-deoxnogalarol (6) and 7-deoxynogarol (11), respectively.

The isomerization of various anthracyclines at C-7 by reaction with trifluoroacetic acid followed by hydrolysis has been reported.[8] Dis-nogamycin was found to give a somewhat similar reaction. It reacted with trifluoroacetic acid under mild condition to replace the nogalose moiety. The resulting intermediate was not characterized but reacted with nucleophiles to introduce the nucleophile at C-7 with essentially complete stereospecificity.[9] The products had the opposite chirality at C-7 to that of dis-nogamycin. The reaction in which the nucleophile was methoxide is indicated in Scheme III.

Scheme III



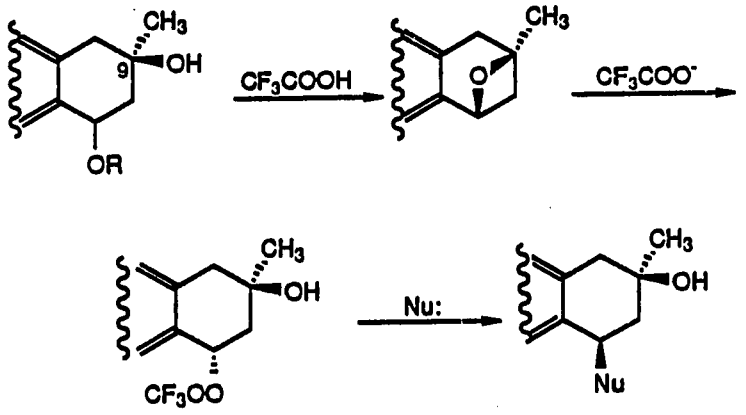
7 10

The reaction shown in Scheme III appears to be entirely general for alkoxides, mercaptides, acid anions, ammonia, primary and secondary amines, azides, and carbanions. The product in all cases was the con isomer. It is interesting to find that 7-con-O-methylnogarol reacted with trifluoroacetic acid to give a product which subsequently reacted with sodium ethoxide to form 7-con-O-ethylnogarol. This suggests that the overall reaction always results in a con product regardless of chirality at C-7 in the initial reactant.

The nature of the product obtained in the first step is somewhat uncertain, as purification difficulties prevented its characterization. It seems probable that during the course of the reaction a trifluoroacetate is formed at C-7,

and this intermediate is attacked by the nucleophile (Scheme IV). In order to produce the observed chirality, the

Scheme IV



hydroxyl group at C-9 must influence the stereochemistry of the intermediate via an oxetane ring or its ion pair equivalent. Only ring A is indicated in Scheme IV. This procedure allowed the preparation of a large number of nogalamycin analogs in which only con isomers could be obtained.

Antitumor Activity of Nogalamycin and Its Analogs

About 60 analogs of nogalamycin have been prepared, and most of them showed considerable activity as antitumor agents. Of all the nogalamycin analogs, 7-con-O-methyl-nogarol (10) has been found to be superior to its parent compound in tests of its antitumor activity.[9-14]

The in vitro L-1210 leukemia growth inhibitory activity and the in vivo antitumor activity of analogs of several structural types are shown in Table 1. There was some correlation between the in vitro and in vivo activity. Analogs with high ID_{50} values were not very active in vivo; however, a low ID_{50} value (<0.2 μM) did not necessarily indicate high in vivo activity.

The most active compounds against P-388 leukemia were, in decreasing order, 7-con-O-methylnogarol, dis-nogamycin, 7-con-O-methylnogalarol, 7-dis-O-methylnogarol, 7-con-O-ethylnogarol, and 7-dis-O-methylnogalarol. Against the B-16 melanoma the most active compounds were 7-con-O-methylnogarol, dis-nogamycin, 7-dis-O-methylnogarol, nogalamycin, and 7-dis-O-methylnogalarol. Thus, except for dis-nogamycin, the most active analogs did not contain the nogalose moiety.

The 7-deoxy compounds, 7-deoxynogalarol and 7-deoxynogarol, were only marginally active against P-388 leukemia and the optimum doses were high (50-100 mg kg^{-1}) compared to the other analogs. Neither of the aromatized analogs (nogalarene and nogarene) showed much activity against P-388 leukemia.

Dis-nogamycin was more active than con-nogamycin against both P-388 leukemia and B-16 melanoma. However, 7-con-O-methylnogarol and 7-con-O-methylnogalarol were considerably

Table 1. In vitro and in vivo antitumor activity of nogalamycin and its analogs

Compound	L-1210 leukemia vitro ID^a_{50} (μM)	P-388 leukemia ILS	L-1210 leukemia ILS	B-16 melanoma ILS
Nogalamycin	0.078	49	38	72-157
Dis-nogalamycin acid	1.00	56	18	NT
Dis-nogalarol	0.89	0	0	NT
7-Dis-O-methylnogalarol	0.27	60	12	84
7-Con-O-methylnogalarol	0.13	98(1/6)[b]	NT	35
7-Deoxynogalarol	0.58	27	4	NT
Nogalarene	0.24	50	2	NT
Dis-nogamycin	0.18	93	27	61-260
Con-nogamycin	0.56	44	NT	28
7-Dis-O-methylnogarol	0.41	76	NT	105
7-Con-O-methylnogarol	0.061	197(3/6)	140(1/6)	60-114
7-Dis-O-ethylnogarol	0.43	NT[c]	NT	34
7-Con-O-ethylnogarol	0.16	63	NT	25
7-Deoxynogarol	0.94	21	NT	NT
Nogarene	0.22	17	NT	NT

[a] ID_{50} = Concentrations required for 50% inhibition.

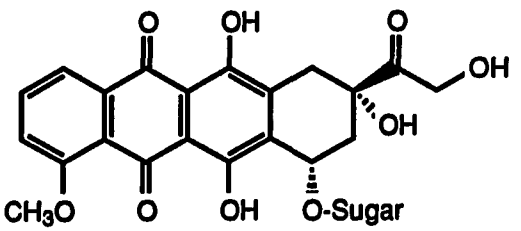
[b] Numbers in parentheses = Number of cures/total Number treated.

[c] NT = Not tested.

more active than their corresponding 7-dis isomers against P-388 leukemia. Against B-16 melanoma, no difference was apparent between 7-con- and 7-dis-O-methylnogarol; 7-con-O-methylnogalarol was less active than 7-dis-O-methyl-nogalarol.

Of the analogs, 7-con-O-methylnogarol and dis-nogamycin were considered the best compounds for further investigation. Despite strong activity against P-388 leukemia and B-16 melanoma, dis-nogamycin was only marginally active against L-1210 leukemia and was inactive when tested further in the colon 26, colon 38 and $CD8F_1$ mammary tumors, and in the Lewis lung carcinoma. 7-Con-O-methylnogarol has a rather broad spectrum of activity in mouse tumors. In addition to activity in the P-388 and L-1210 leukemias and in B-16 melanoma, 7-con-O-methylnogarol was significantly active against the murine colon 26 and colon 38 tumors, as well as the $CD8F_1$ mammary tumor. It was not considered effective against Lewis lung carcinoma, although 38% ILS value was achieved in the experiment (40% ILS is the criterion of activity).

Adriamycin (12) has been one of the major drugs for cancer treatment in the past decade. However, the success of adriamycin is limited by its cumulative cardiotoxicity.[15,16] The largest amount of adriamycin which



12

can be given to a patient is about 500 mgm^{-2} of body surface without danger of irreversible, fatal cardiotoxicity. Two adriamycin analogs[17] currently in clinical trials are also known to induce rubidazone, which has been reported to be cardiotoxic in humans at cumulative doses of greater than 1500 mgm^{-2}. As the consequence of this cardiotoxicity property of adriamycin and its analogs, any new anthracycline analog proposed for clinical use must be evaluated for its cardiotoxic potential. 7-Con-O-methylnogarol is of no exception, and the compound was investigated by the standard procedures using rabbits as the testing animal.[18]

All adriamycin-treated control rabbits died of drug-induced cardiomyopathy and congestive heart failure at 222 to 277 mgm^{-2}. No 7-con-O-methylnogarol-treated rabbits died from cardiotoxicity at doses up to 3700 mgm^{-2}, thus 7-con-O-methylnogarol is at least 15 times less potent than

is adriamycin in inducing cardiotoxicity, and the compound could possess a therapeutic advantage over adriamycin.

The Molecular Basis of Antitumor Activity

To understand the mechanistic aspects of the antitumor activity of the antitumor nogalamycin analogs, the molecular basis of antibiotic action of anthracyclines has been extensively studied. The anthracyclines form complexes with deoxyribonucleic acid (DNA) with stability constants in the range of 10^5 to 10^6 M^{-1}. Because the main biochemical effects of the antitumor anthracyclines are concerned with nucleic acid synthesis and function, this type of molecular association has been studied in detail. On the basis of the physicochemical properties of the complex, including changes in the spectroscopic and polarographic properties of the antibiotic induced by native DNA,[19] as well as changes in DNA sedimentation rate, viscosity, or denaturation profile induced by the antibiotics,[19,20] an intercalative mode of association was proposed.

The intercalation complex is a type of non covalent binding of small molecules to double-helical DNA, originally suggested by Lerman[21] for explaining the molecular association of acridine dyes and DNA, and subsequently accepted as the mode of interaction of a wide range of different drugs with a DNA receptor.[22] According to the model, a planar molecule is intercalated between two

adjacent base pairs of the biopolymer, the distance between the same base pairs become 6.8 A, in order to allow normal Van der Waals contact with the intercalating molecule. In anthracyclines, stabilization of the complex was ascribed to several factors. Because of the close contact of the electron-deficient quinone chromophore with the electron-rich purine and pyrimidine bases, insured by the intercalation, the conditions for the formation of a DNA complex should be fulfilled. Such an electron donor-acceptor complex is typical of the quinones.

Different methods for the study of the DNA complexation reaction were employed in the early investigations. The interaction of the anthracycline with DNA can be monitored spectrophotometrically or by equilibrium dialysis.[23] A fluorometric method based on the quenching of the typical anthracycline fluorescence by DNA has also been developed.[24] Other useful information can be obtained by circular dichroism spectroscopy,[25,26] calorimetric measurements,[27] thermal denaturation of DNA, and viscosimetric determinations.[23] An additional promising technique for the study of anthracycline interactions with biological macromolecules or with metal ions is offered by Raman spectroscopy.[28]

A direct consequence of DNA complexation is the inhibition exerted by anthracyclines on the template activity of DNA in vitro. The detailed mechanism of this

inhibition remains to be established: both prevention of separation of the DNA strands and hindrance to the attachment of the polymerase due to distortion of the DNA structure have been proposed as possible causes.[22]

Taking account of the DNA intercalation model as the most widely accepted candidate for the representation of the main drug-receptor complex, a number of structural and configurational features of the anthracyclines have to be considered as necessary conditions for complex formation and, therefore, for the exhibition of biological activity. Among these, the planar, electron-withdrawing quinone chromophore should be taken as an obvious requirement. The relationship between the ability to form intercalation complexes and the pharmacological activities is not clear, because of the different biological effects of the intercalating agent.[29]

Nogalamycin interacts with DNA by intercalation of the chromophore between adjacent base pairs of the helix.[30-35] The formation of the intercalation complex was shown by the reversal of supercoiling in supercoiled DNA,[36] an increase in Tm of DNA and in the viscosity of DNA solution.[20] Further evidence for the intercalation complex formation was shown by a decrease in the sedimentation coefficient of DNA and removal of kinks from T7 DNA in the presence of nogalamycin.[37] Dichroism studies had shown that the plane

of the nogalamycin chromophore is perpendicular to the helix axis when the antibiotic is bound to DNA, and nogalamycin cannot be reduced polarographically when it forms a complex with DNA. Competitive fluorescence polarization using DNAs of differing base composition indicated that nogalamycin analogs containing the nogalose moiety generally prefer adenine and thymine.[38]

To further study the biological properties of the nogalamycin analogs, their effect on macromolecular synthesis and DNA binding was investigated in L-1210 leukemia cells.[14] Nogalamycin strongly inhibits RNA synthesis, and to a somewhat lesser degree, DNA synthesis. The results with 7-con-O-methylnogarol (Table 2) against DNA and RNA synthesis in L-1210 cells were quite surprising. It almost totally failed to inhibit either RNA or DNA synthesis. The dis isomer was much less active than nogalamycin in the inhibition of both RNA and DNA synthesis. In the case of the other two pairs of con and dis isomers, the con was much less active than was the dis.

The interaction of calf thymus DNA with nogalamycin and its analogs was measured by circular dichroism (CD) and by Tm determination (Table 3). The difference between CD curves at 465 nm of DNA and of the compound taken separately and the CD curve of the mixture was determined and expressed as millidegrees of ellipticity. The values shown are

Table 2. Inhibition of macromolecular synthesis by nogalamycin and its analogs

Compound	ID_{50} (nmol/ml) DNA	RNA
Nogalamycin	3.3	0.4
Dis-Nogalamycinic acid	15	3.6
Dis-Nogamycin	3	0.5
7-Dis-O-Methylnogalarol	3.8	0.5
7-Con-O-Methylnogalarol	7-17	0.5
7-Dis-O-Methylnogarol	11.6	7.8
7-Con-O-Methylnogarol	37.2	46
7-Dis-O-Ethylnogarol	3.2	0.8
7-Con-O-Ethylnogarol	10.6	5.2

Table 3. Interaction between DNA and nogalamycin and its analogs

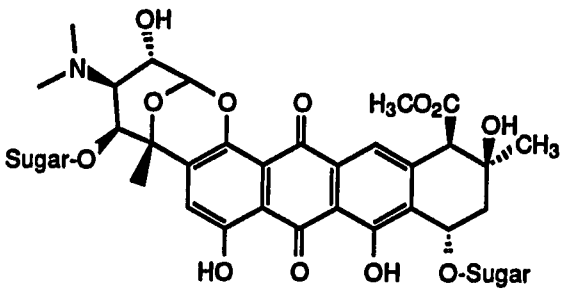
Compound	CD (millidegrees of ellipticity)	ΔTm (°C)
Nogalamycin	12	15.0
Dis-Nogalamycinic acid	8	4.4
Dis-Nogamycin	11	11.7
7-Dis-O-Methylnogalarol	8	5.0
7-Con-O-Methylnogalarol	6	3.1
7-Dis-O-Methylnogarol	8	4.0
7-Con-O-Methylnogarol	2	0
7-Dis-O-Ethylnogarol	8	3.9
7-Con-O-Ethylnogarol	2	-2.5

proportional to drug-DNA interaction. The results indicate that nogalamycin and dis-nogalamycin had a much stronger binding affinity to calf thymus DNA than did dis-nogalamycinic acid, and the two compounds in the con-nogarol series interacted much less strongly in the dis series. The binding effect in the nogarol series (con vs. dis) was much less pronounced.

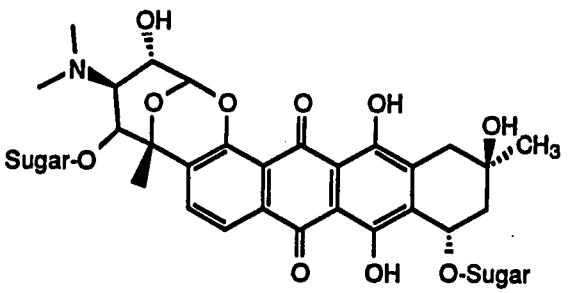
7-Con-O-methylnogarol was the most cytotoxic analog tested, and it was also found to be the most active analog against both P-388 and L-1210 leukemia.[39] This analog, surprisingly, neither interacted strongly with DNA nor markedly inhibited DNA and RNA synthesis. These results collectively suggest that the biological activities of 7-con-O-methylnogarol is probably mediated through some mechanism other than the interaction with DNA, the mechanism suggested to explain antitumor activities for most anthracycline antibiotics.[29] Because of the superior biological activity and the unique biochemical characteristics of 7-con-O-methylnogarol, further investigation on the properties is proceeding.

LITERATURE SURVEY

Nogalamycin and its analogs are structurally different from the classical anthracyclines in that the amino sugar residue is joined to the aromatic D-ring via both glycoside and C-C bonds forming a benzoxocin ring system. Additional examples of anthracyclines containing this structural feature, namely, arugomycin (13a) and decilorubicin (13b), have been reported recently.[40,41]



13 a Arugomycin



13 b Decilorubicin

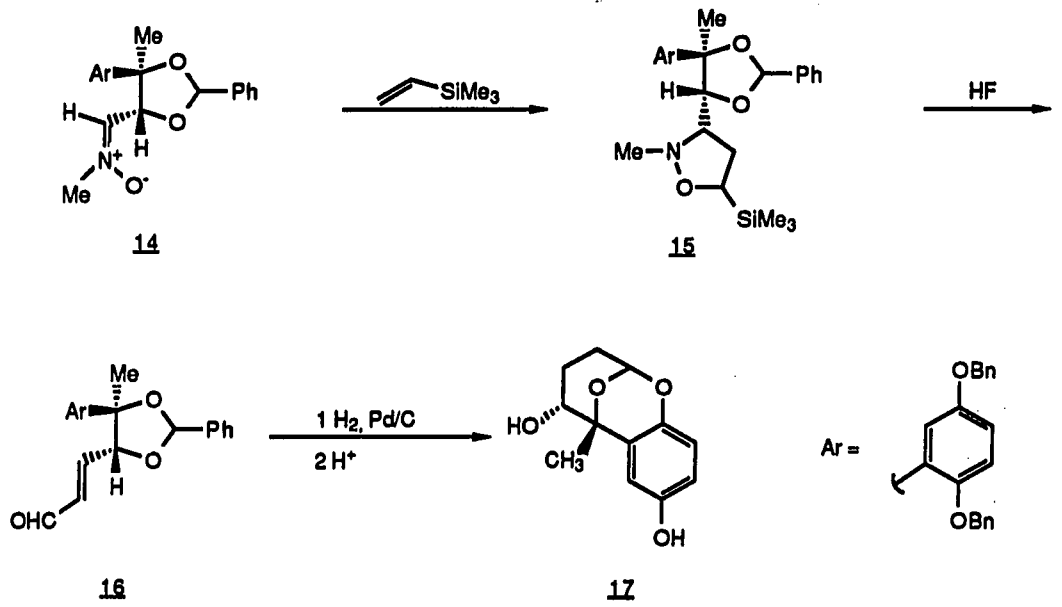
Nogalamycin and its analogs have been the subject of interest in recent years because of their potential

therapeutic value in cancer chemotherapy. Of all the analogs, 7-con-O-methylnogarol has the most outstanding antitumor properties. Its biochemical properties differ greatly from those of the other anthracyclines. The fact that 7-con-O-methylnogarol is a likely clinically-effective chemotherapeutic agent, coupled with the remarkable structure of the analog (presence of benzoxocin ring system), make it an interesting and challenging synthetic target for our group. In order to supply a framework of reference for the discussion presented in the latter sections of this thesis, a brief review of the previous synthetic attempts on nogalamycin analogs is given below.

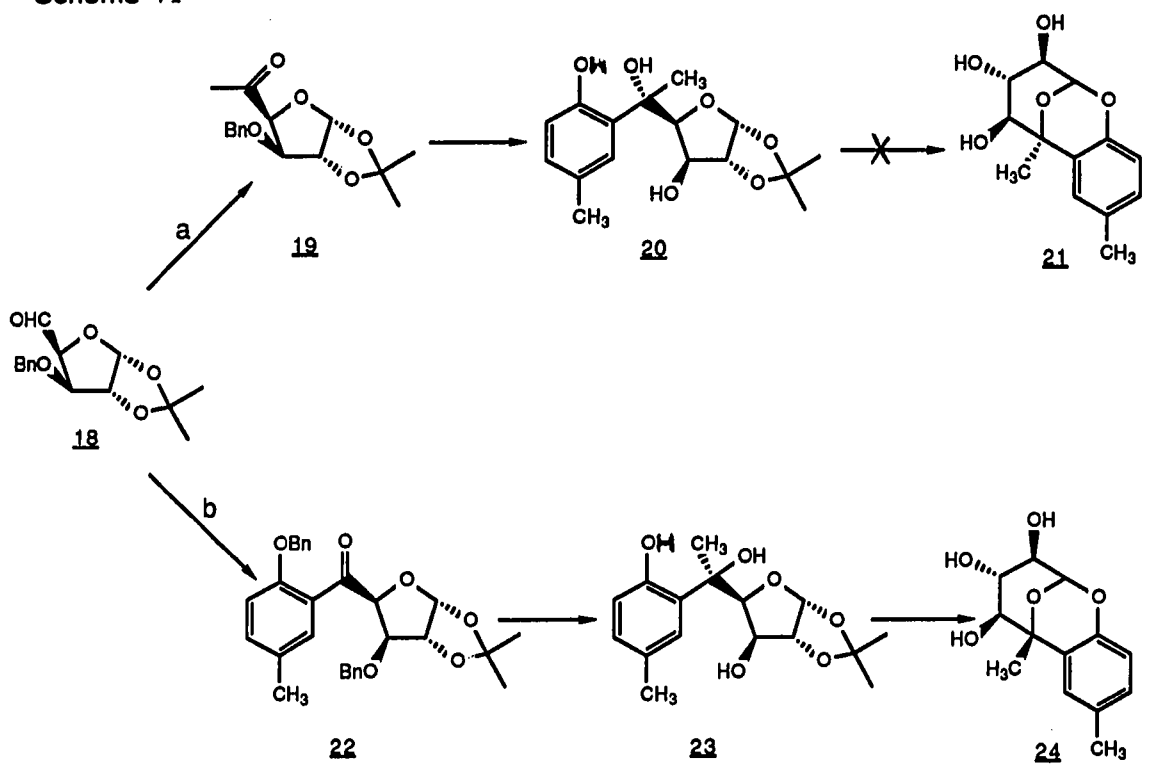
DeShong and Leginus[42] have synthesized benzoxocin 17, a model system of the glycosidic portion of 7-con-O-methylnogarol. The key step in the reaction sequence involved the cycloaddition of nitrone 14 with vinyltrimethylsilane to produce isoxazolidines 15, followed by fluoride-induced fragmentation of 15 to give unsaturated aldehyde 16. Catalytic hydrogenation of 16 and subsequent mild acid hydrolysis furnished the benzoxocin 17. The overall transformations are summarized in Scheme V.

Hauser and Adams[43] developed a methodology to construct a more highly functionalized benzoxocin ring system, which is shown in Scheme VI. For both paths a and b, the aldehydofuranose 18 served as a chiral synthon for

Scheme V



Scheme VI



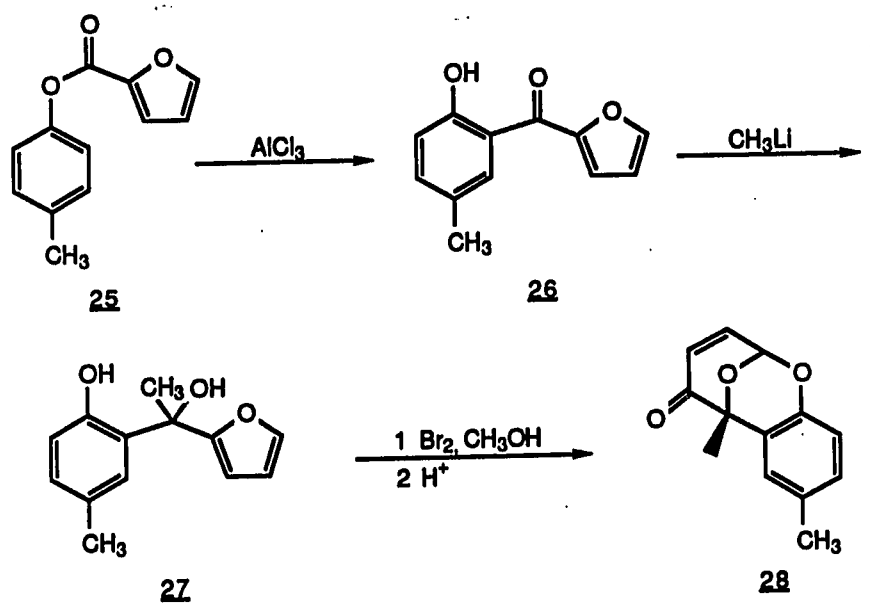
constructing the optically active benzoxocins 21 and 24. In path a, reaction of methyl ketone 19 with the Grignard reagent formed from the benzyl ether derivative of 2-bromo-4-methyl phenol, followed by careful hydrogenation gave debenzylated product 20. However, attempted hydrolysis of 20 and rearrangement to benzoxocin 21 only produced a complex mixture.

In path b, reaction of ketone 22 with methyllithium, followed by hydrogenolysis gave alcohol 23. In contrast to the unsuccessful conversion of intermediate 20 to oxocin 21, the transformation of 23 to the corresponding oxocin 24 with L-ido configuration proceeded smoothly and with high stereoselectivity.

Hauser et al.[44] also prepared the racemic ketobenzoxocin 28, which can be converted to racemic sugar analogues. The transformation to 28 is shown in Scheme VII.

Fries rearrangement of ester 25, followed by reacted with excess of methyl lithium furnished the tertiary alcohol 27. Treatment of 27 with bromine in methanol, and subsequent acid hydrolysis in acetic acid containing a trace of sulfuric acid gave the rigid bicyclic benzoxocin 28 in good yield. Other sugar analogues with the manno-, talo-, altro- and galacto- configurations can be derived from the resulting benzoxocin 28.

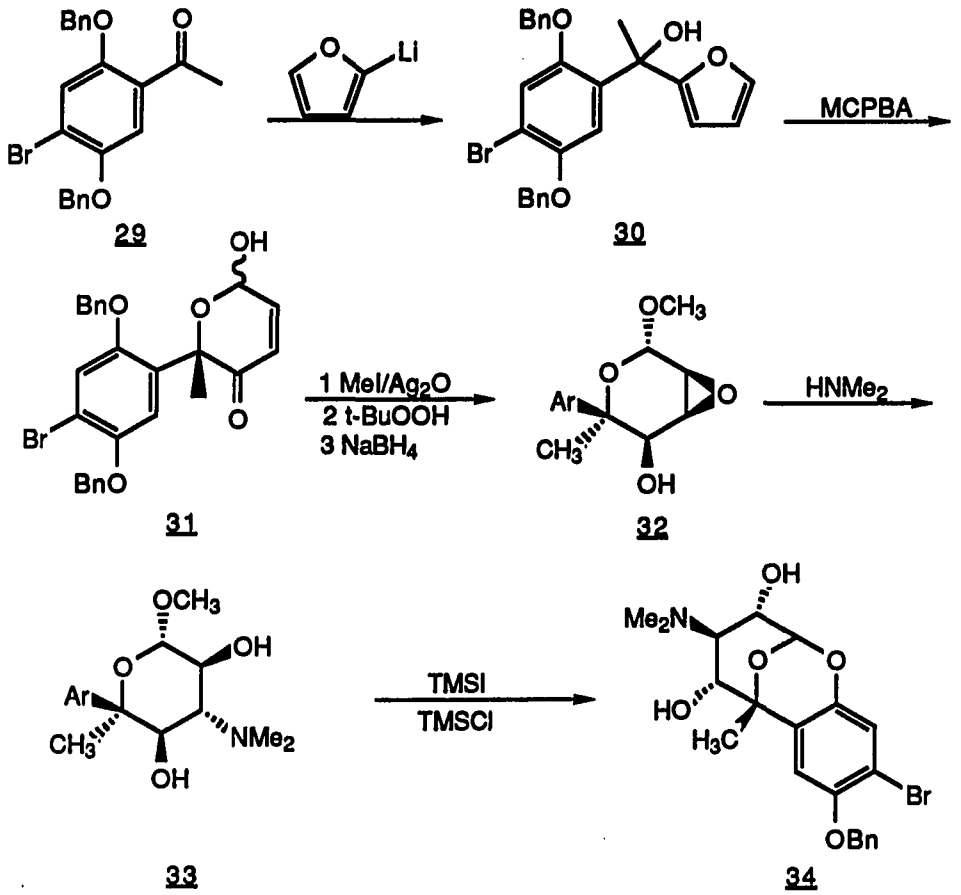
Scheme VII



25 26 27 28

Bates and Sammes[45] reported a flexible method for the construction of a benzoxocin ring which is exemplified by the preparation of the DEF ring system of nogalamycin (Scheme VIII). Reaction of acetophenone 29 with 2-furyl-lithium gave the alcohol 30. The resulting adduct 30 was oxidized with m-chloroperoxybenzoic acid to yield diastereomeric pyranuloses 31. Methylation of 31 with methyl iodide-silver oxide afforded two methyl acetals. Epoxidation of the major diastereomer with t-butylhydroperoxide, followed by reduction with sodium borohydride produced epoxy-alcohol 32 as the only product. Treatment of 32 with dimethylamine gave amino alcohol 33, and the

Scheme VIII



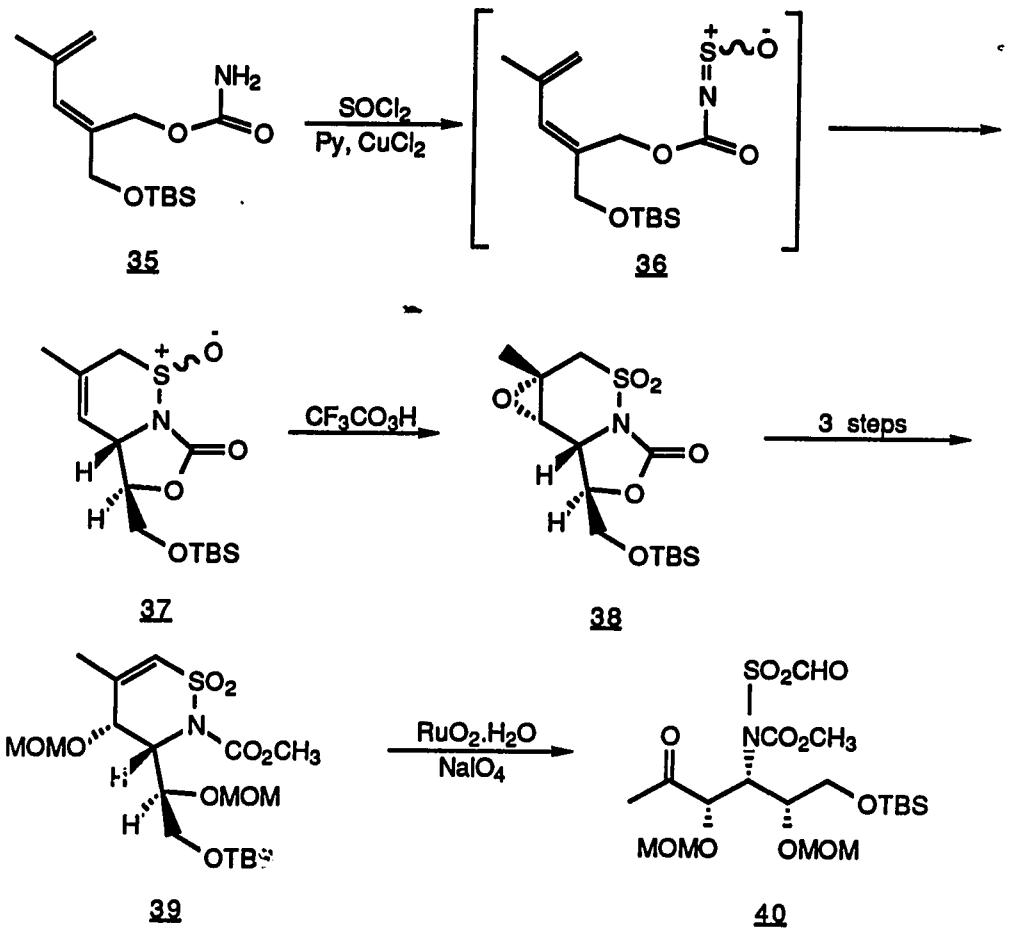
resulting nucleophilic addition was regio- and stereo-specific. Selective debenzylation and demethylation, followed by cyclization to produce benzoxocin 34 was achieved by treatment of 33 with trimethylsilyl iodide and trimethylsilyl chloride.

Joyce et al.[46] foresaw a strategy involving an important intermediate ketone 40, which bears three of the chiral

centers of nogalamycin (C-2', 3', 4'). That intermediate has the key components of the benzoxocin portion of nogalamycin analogs.

The approach to ketone 40 centered on an intramolecular N-sulfinyl dienophile Diels-Alder cycloaddition (Scheme IX). Treatment of carbamate 35 with thionyl chloride/pyridine and

Scheme IX

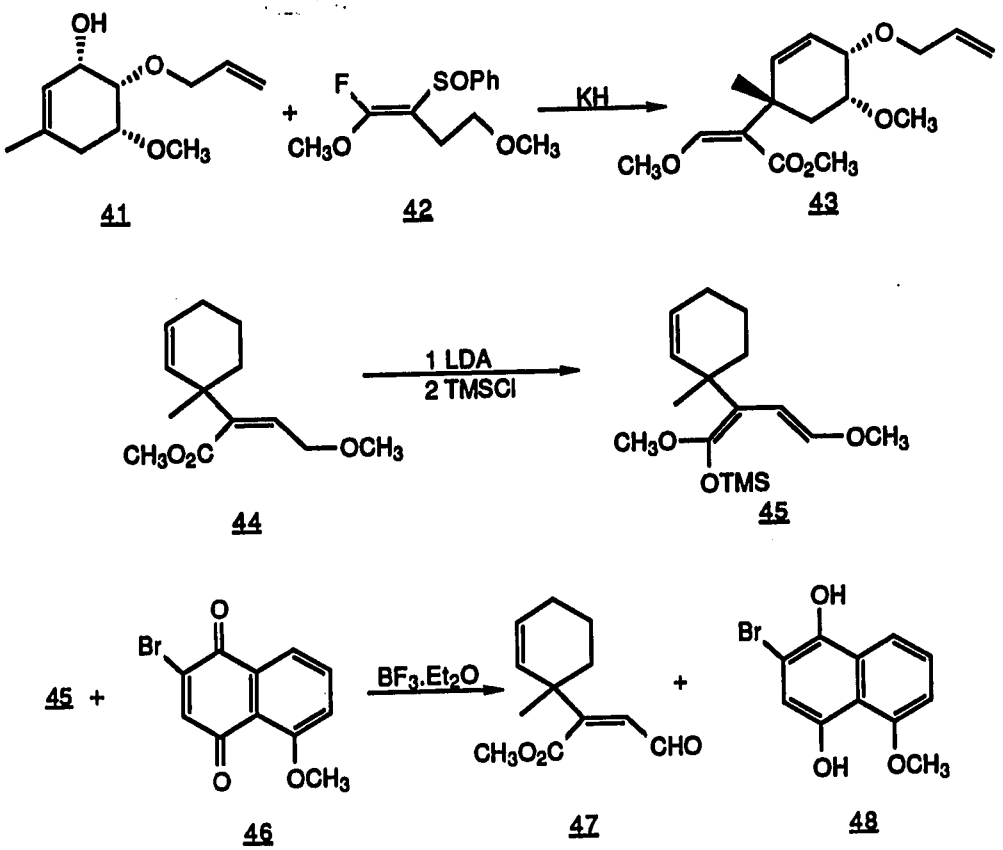


catalytic amount of copper(II) chloride produced a reactive N-sulfinyl carbamate 36, which cyclized to give bicyclic dihydrothiazine oxide 37. Oxidation of 37 with trifluoroperacetic acid provided epoxysultam 38 with high selectivity. Transformation of 38 into ether 39 was achieved via three steps. Cleavage of the double bond of 39 with ruthenium tetroxide yielded ketone 40, which will be used in approaches to nogalamycin.

Vatele[47] proposed an interesting strategy towards the benzoxocin ring system of nogalamycin analogs. The strategy involves stereospecific formation of the quaternary center at C-5' by a Claisen rearrangement and construction of D ring by a Diels-Alder reaction (Scheme X).

Precursor 41 was prepared from D-glucose via several steps. Reaction between alcohol 41 and the sulfoxide derivative 42, in the presence of potassium hydride, gave smoothly the α-β-unsaturated ester 43 in moderate yield with exclusive formation of the Z-isomer. This novel step involved a Michael addition of alkoxide, derived from alcohol 41, to the unsaturated sulfoxide 42 with elimination of fluoride anion. The resulting adduct then underwent Claisen rearrangement, followed by sulfoxide elimination in situ to give ester 43. This step demonstrates a unique formation of the quaternary center by Claisen rearrangement stereospecifically.

Scheme X

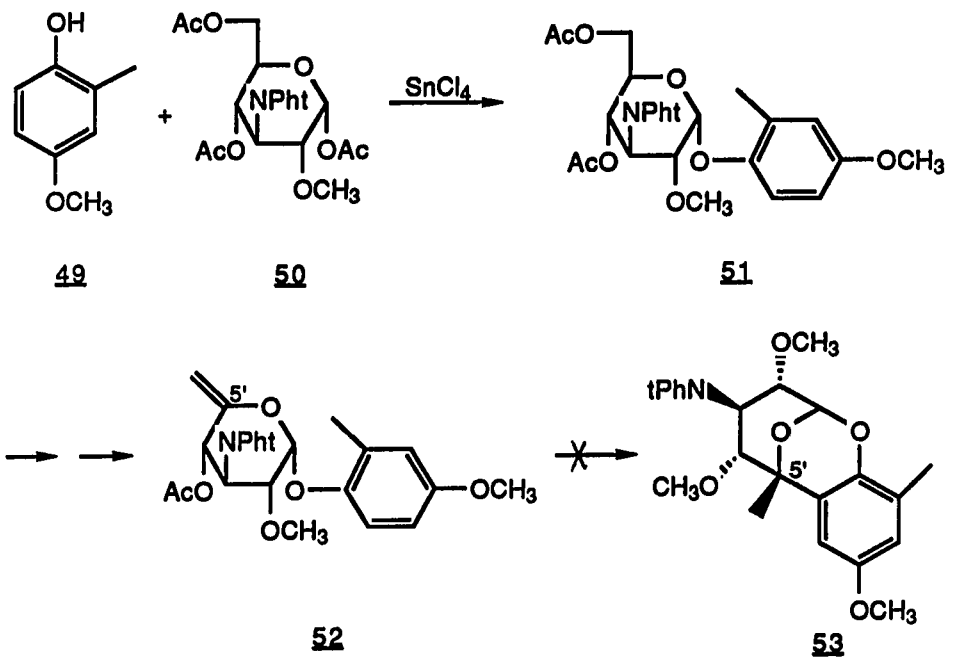


In order to investigate the possibility of constructing ring D of nogalamycin by a Diels-Alder reaction, a model diene 45 was made from ester 44. Surprisingly, Diels-Alder reaction between 45 and 2-bromo-5-methoxy-1,4-naphthoquinone (46) did not proceed even in boiling toluene. In the presence of boron trifluoride-etherate, no cycloadduct was formed, but instead aldehyde 47 and hydroquinone 48 were

isolated. Because of the unsuccessful Diels-Alder reaction in the model system, the investigation was terminated.

Smith[48] reported a different approach towards the synthesis of benzoxocin ring system. Their approach involved the synthesis of a suitable amino sugar and a D-ring synthon, followed by stereoselective glycosidation of the D-ring synthon with the amino sugar, and finally adjustment of the functionality of the resulting adduct to allow C-C bond formation between C-2 and C-5' (Scheme XI).

Scheme XI

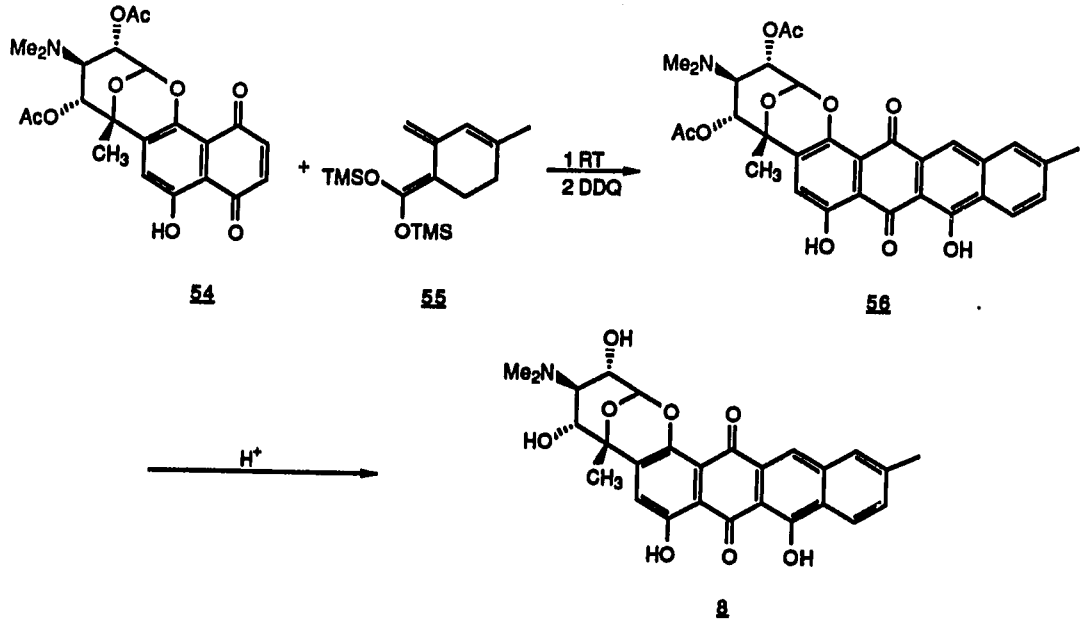


Glycosidation of phenol 49 with the sugar 50 could be achieved under $SnCl_4$-catalyzed conditions.

Functionalization of the adduct 51 gave enol ether 52, which was subjected to cyclization. In order to achieve the cyclization, it is necessary to develop a positive charge at C-5' of the vinyl ether 52, which will then react with the electron rich aromatic ring. In practice, a proton source like trifluoroacetic acid, or a positive halogen species like N-bromosuccinimide, or iodonium dicollidine perchlorate, was tried. Each of the above reagents could generate the positive charge at C-5'; however, none afforded the required cyclization product.

Kawasaki et al.[49] accomplished a total synthesis of (+)-nogarene (8) by a convergent approach. The key step in the synthesis involved a regioselective Diels-Alder reaction of quinone 54 with diene 55 at room temperature. The resulting cycloadduct was treated with DDQ to give quinone 56, which underwent acid hydrolysis to complete the total synthesis (Scheme XII).

Scheme XII



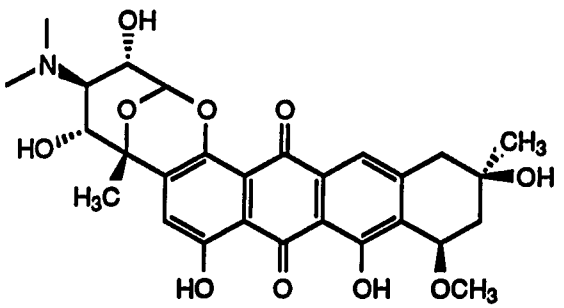
54 55 56

8

RESULTS AND DISCUSSION

Retrosynthetic Analysis and General Strategy

7-Con-O-methylnogarol (10), an analog of the antibiotic nogalamycin, has been found to exhibit superior antitumor activity to its parent compound.[13] Since 7-con-O-methylnogarol is a potentially effective chemotherapeutic agent with remarkable structural features, we initiated a



10

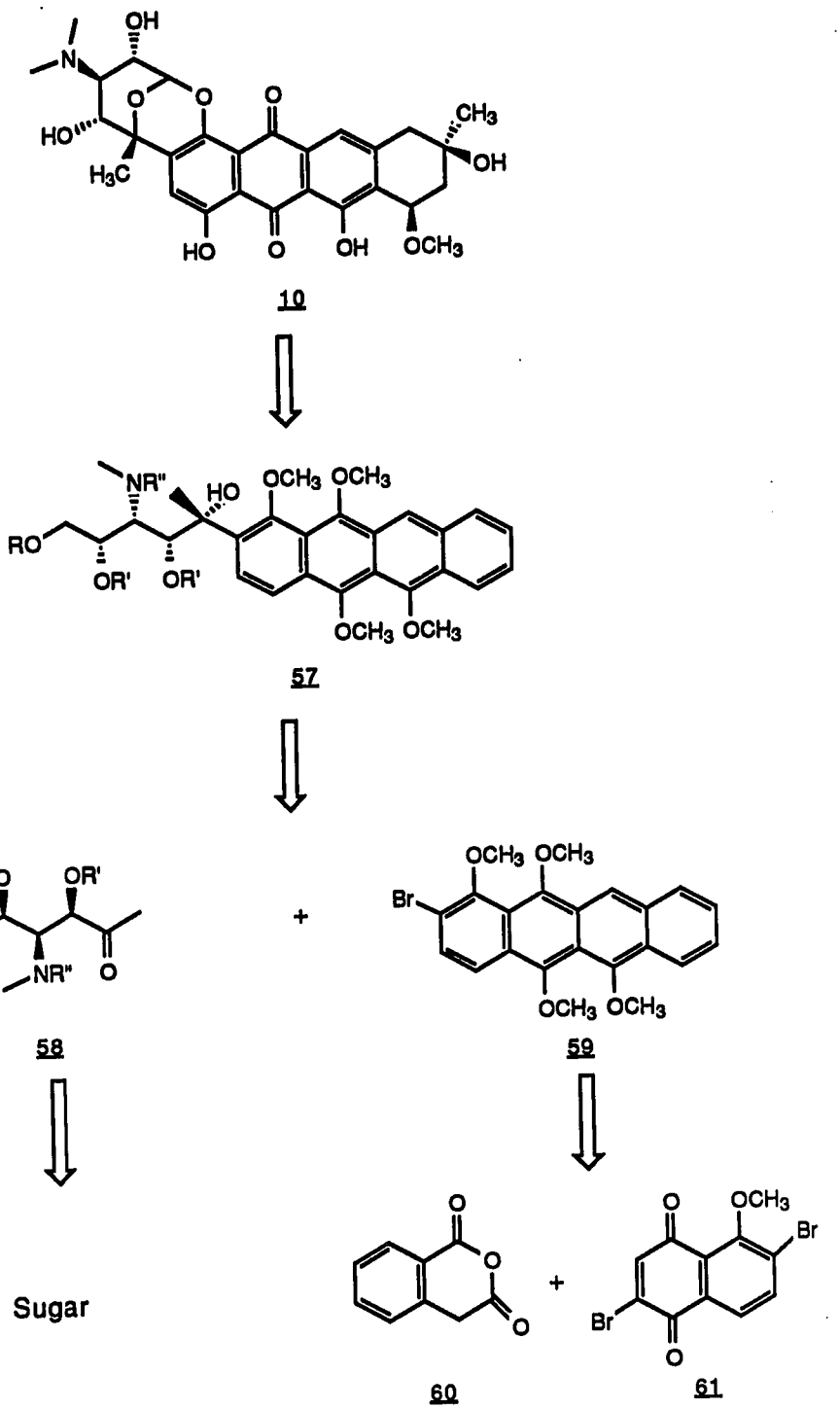
a synthetic effort toward that molecule and the corresponding analogs. The most noticeable feature of the target molecule which differs from the normal anthracyclines, is the presence of a benzoxocin ring system. The benzoxocin ring contains an amino sugar residue joined to the aromatic D ring. Different synthetic approaches toward this interesting ring system have been reviewed in the previous section, but most of them cannot be elaborated to the total synthesis of nogalamycin. The only successful

total synthesis of a nogalamycin analog (nogarene), which exhibits no significant biological activity, was completed by Kawasaki et al.[49]

In the course of our investigation, we devised an efficient route to 7-con-O-methylnogarol. The approach is threefold: (1) preparation of the ketone 58 with three contiguous stereogenic centers which could be converted into C-2', 3', 4' of the target molecule; (2) synthesis of a suitable tetracyclic moiety such as 59, which could be transformed into ABCD rings of the synthetic target; and (3) combination of the above two pieces and further functionalization to finish 7-con-O-methylnogarol. The retrosynthetic analysis is shown in Scheme XIII.

To synthesize the highly functionalized acyclic ketone 58 in a specific manner presents a great challenge. There are two general strategies for synthesizing acyclic skeletons. First, we can modify an already existing linear chain or combine two smaller acyclic pieces. Second, we can start from a cyclic precursor and cleave it to give the linear molecule, a process which is simply a retrosynthesis of cyclic compounds from linear precursors. We envisioned that the synthesis of ketone 58 could be accomplished through the second strategy by using a cyclic carbohydrate as a chiron. The reasons are evident. With carbohydrates as starting materials, one has the option of using a cyclic

Scheme XIII


OH
N
O
O
O
HO
H3C
CH3
OH
HO
O
OH
OCH3
10
NR"
HO
OCH3 OCH3
RO
OR'
OR'
OCH3 OCH3
57
R'O
OR'
RO
NR"
O
58
+
OCH3 OCH3
Br
OCH3 OCH3
59
Sugar
O
O
O
+
O
OCH3
Br
Br
O
60
61

carbon atom framework consisting of 5-7 carbon atoms and various asymmetric centers. This provides the flexibility to modify the chiron chemically and stereochemically and finally leads to the synthesis of ketone 58.

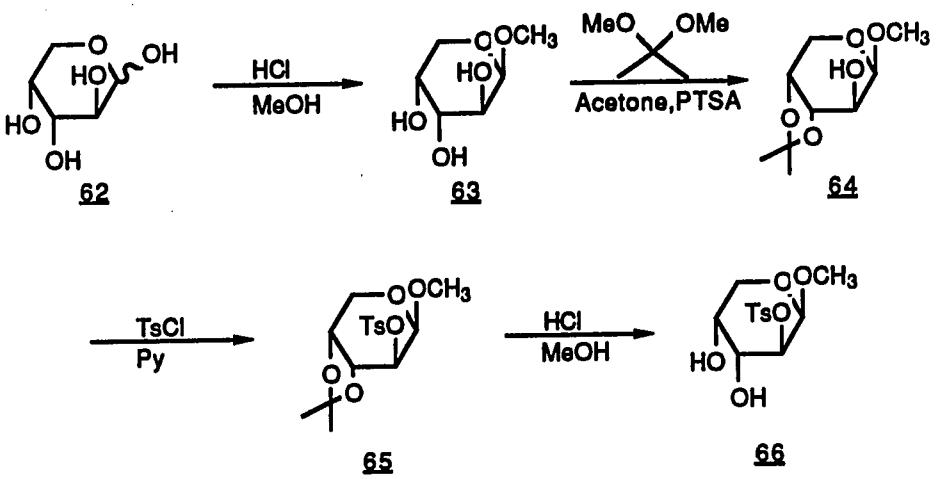
In the construction of the tetracyclic moiety, we foresaw that the presence of a bromine atom at C-2 of the naphthacene derivative 59 would be crucial. This allows us to transmetallate 59 regiospecifically, and then react with ketone 58 to give 57. We also expected the tetracyclic compound 59 would be readily available from anhydride 60 and bromoquinone 61 followed by a reductive methylation procedure developed in our laboratory.[50] With key intermediates 58 and 59 in hand, it was hoped that a Cram chelation-controlled addition of an aryl lithium (from transmetallation of 59) to ketone 58 would generate both the requisite C-5' chirality and incipient C-glycosidic bond. The resulting adduct 57 could be transformed into the final target 10 with functional group manipulation.

Ketosugar Preparation

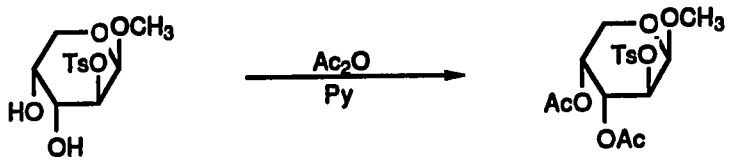
With the exception of Kawasaki's work, the chemical synthesis of nogalamycin and its analogs is a largely unexplored area. Our objective was to devise a practical and flexible route to these systems. In order to test our projected synthetic scheme in a workable manner, it was very

important that the key intermediate 58 be obtained in manageable quantities.

In the course of our investigation, we chose cheap, commercially available D-arabinose (62) as the starting material. Treatment of 62 in refluxing acidic methanol[51] yielded methyl pyranoside 63, which was selectively protected as isopropylidene 64. Tosylation[52] of 64 in pyridine gave 65. The isopropylidene group of compound 65 was selectively removed in refluxing acidic methanol to give alcohol 66.

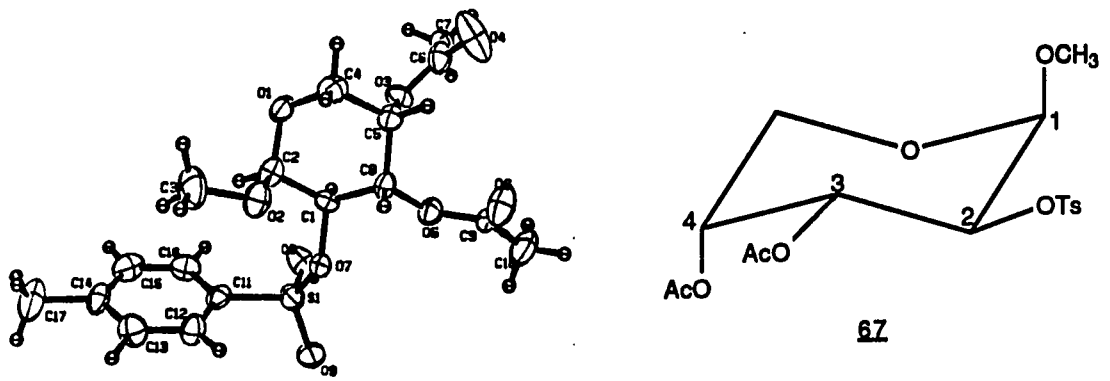


At that stage, although we were confident about the configuration of alcohol 66, we still wanted to reaffirm the structure of 66 without any ambiguity. To achieve this, we prepared compound 67 by treating 66 with acetic anhydride in pyridine. Compound 67 was crystalline and could be used for



66 67

X-ray analysis. The X-ray structure determination showed that the configuration of compound 67 was what we expected. More importantly, the conformation of pyranoside 67 was also established from the data we obtained. As shown in Figure 2, the methoxyl group and acetate group at C-1 and C-4,



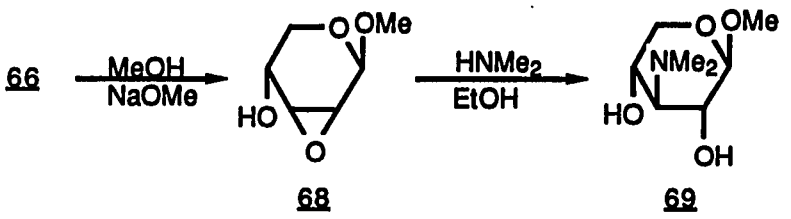
67

Figure 2. Conformation of pyranoside 67

respectively, are all in axial positions, while the other functional groups at C-2 and C-3 are located equatorially.

Continuing our synthesis, we displaced a tosyl group intramolecularly in compound 66 to afford epoxide 68 in 72%

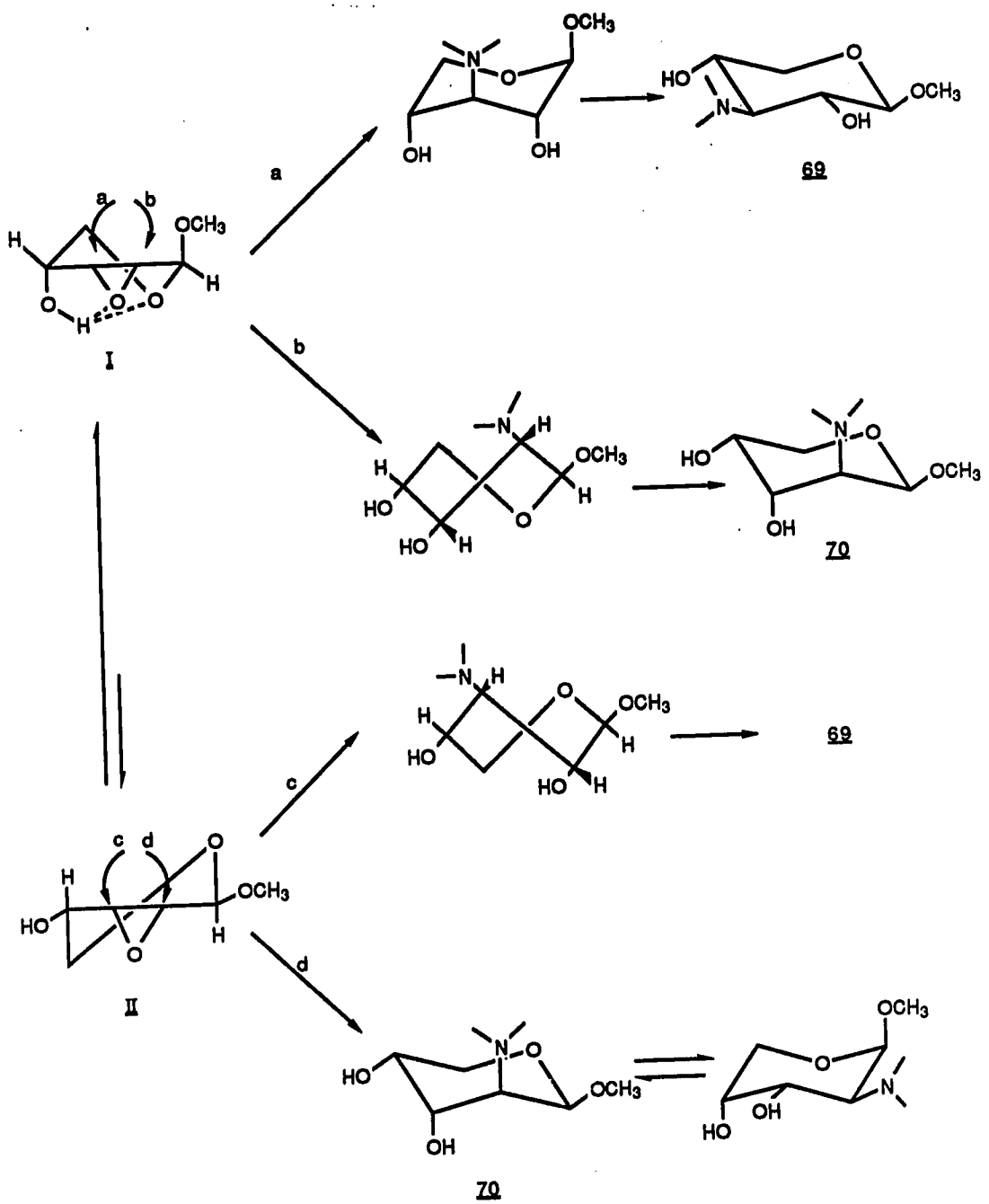
yield. Opening of the epoxide ring in 68 with dimethylamine in ethanol yielded amino alcohol 69 exclusively.



68 69

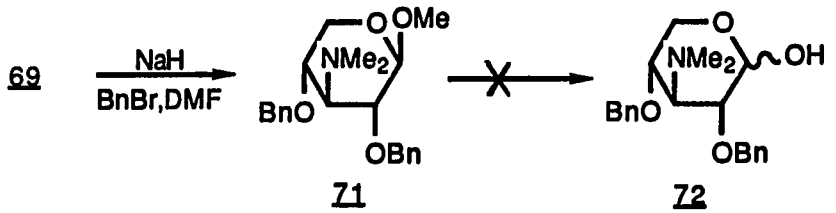
To account for the regiospecific ring opening of epoxide 68 by the amine, we have to analyze the probable conformations of the epoxide 68 and the transition states of the intermediates.[53] As shown in Scheme XIV, the epoxide 68 can exist as two half-chair conformations. In conformation I, the hydroxyl and methoxyl groups are in pseudoaxial positions, while in conformation II, both groups are located pseudoequatorially. The former conformation should be relatively more stable than conformation II, because of the anomeric effect and extra stabilization by intramolecular hydrogen bonding, which can overcome the unfavorable diaxial non-bonding interaction. Hence, in order to explain the exclusive 69 formation, we need to consider conformation I only. There are two possible pathways of the ring opening reaction in conformation I. In path a, the reaction at C-3 gives chair intermediate with epoxide ring opening and thence 69. In path b, the electronically controlled

Scheme XIV



stereochemistry of the transition state in SN_2 reaction requires that the reaction at C-2 must give the twist-boat intermediate which then produces compound 70 after a conformational change. The formation of the transition state to produce twist-boat intermediate is a higher energy process than that in path a. Product 69 is thus formed in preference to 70 under kinetically controlled conditions. Indeed, it is well known that the epoxide opening gives the trans-diaxial products.

After we obtained the desired amino sugar 69, the alcohol group in 69 was protected as benzyl ether[54] on treatment of 69 with sodium hydride and benzyl bromide in DMF. With the protected compound 71 in hand, we were ready

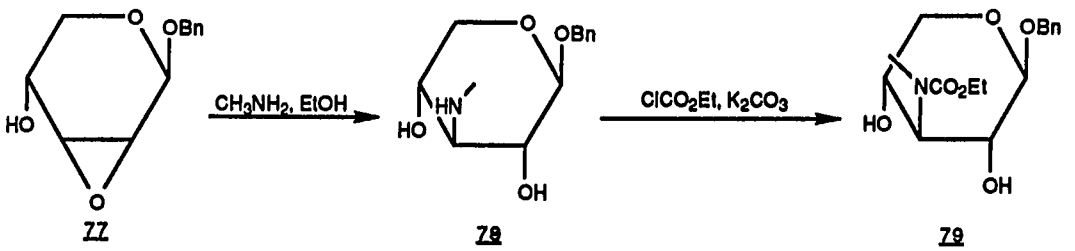


to cleave the acetal to give hemiacetal 72. Several reaction conditions were attempted, including acid hydrolysis at different concentrations and temperatures, trimethylsilyl iodide in methylene chloride, and boron trifluoride etherate in THF. None of the conditions gave a

satisfactory result. We either recovered starting material or observed non-selective debenzylated products.

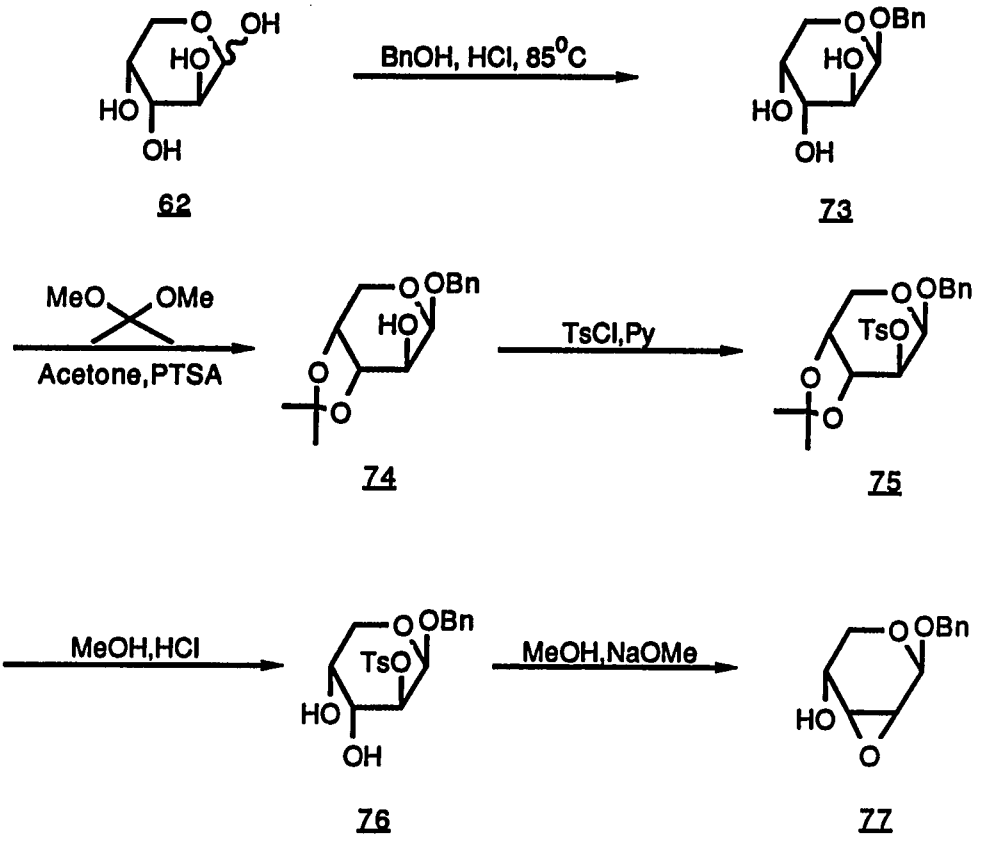
As a result of the difficulties with compound 71, we shifted our attention to different protecting groups but retained our initial strategy. Instead of using methyl-β-D-arabinopyranoside (63) as starting material, benzyl-β-D-arabinopyranoside (73) was our next option. Under the same reaction sequence, with only slight modifications in experimental conditions, the analogous sugar intermediates 73-77 were obtained in good yields and summarized in Scheme XV.

Epoxide 77 underwent nucleophilic ring-opening by methylamine in ethanol at 110°C to give amino alcohol 78 exclusively. The amino group of compound 78 was protected as carbamate by treating 78 with ethyl chloroformate and

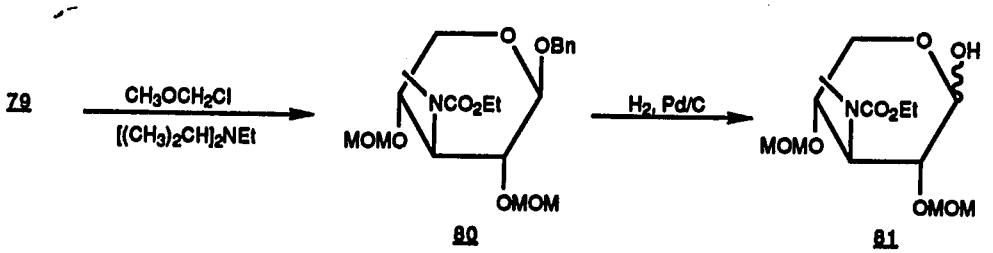


anhydrous potassium carbonate in boiling acetone.[55]

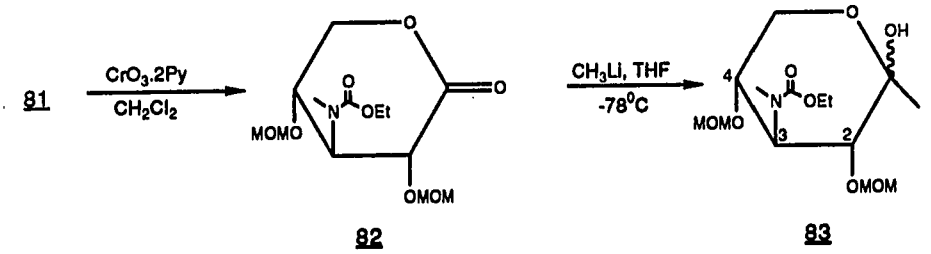
Scheme XV



The two hydroxyl groups in carbamate 79 were protected as methoxymethyl ethers by reacting 79 with chloromethyl methyl ether and diisopropylethylamine in THF.[56] At that stage, all the sensitive functionalities have been protected. Debenzylation of 80 occurred smoothly with catalytic hydrogenation.[57] The resulting cyclic hemiacetal 81 existed as a mixture of anomers.



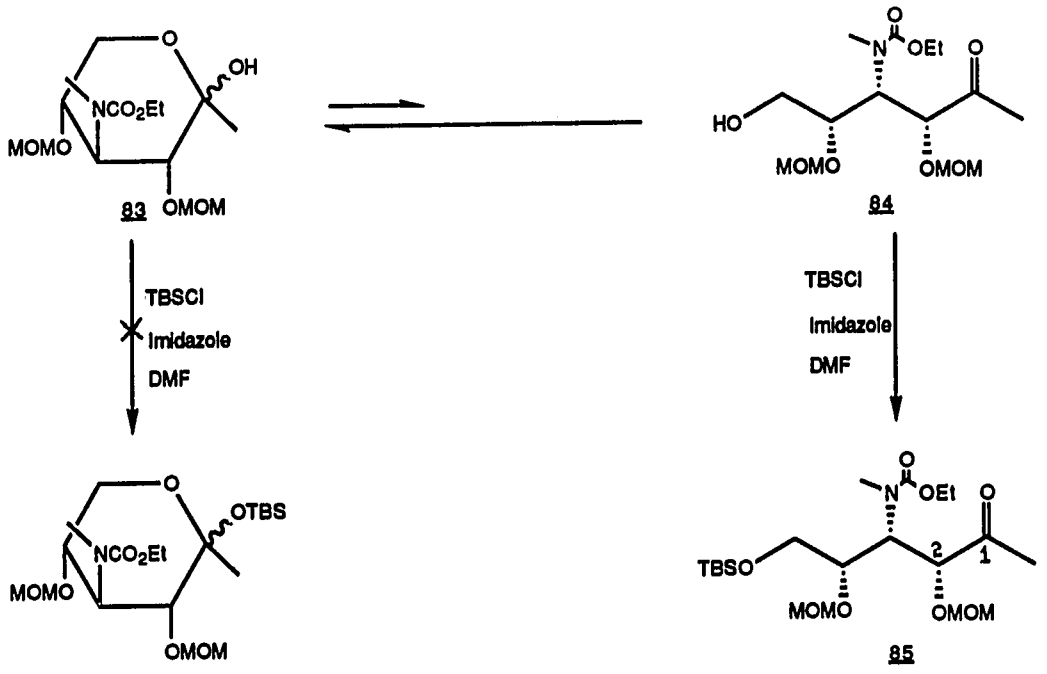
Mixture 81 was oxidized to lactone 82 by Collins reagent.[58] Addition of methyl lithium to lactone 82 at -78°C yielded cyclic hemiketal 83, which was also a mixture similar to hemiacetal 81. At that point, we have



successfully prepared compound 83 in reasonable quantity. The stereogenic centers at C-2, C-3 and C-4 of 83 will become the groups at C-2', C-3', and C-4' respectively of the benzoxocin ring system in nogalamycin analogs.

According to our strategy, the next move is to cleave the cyclic precursor into an acyclic ketosugar. We envisioned that there is a tremendous difference between the reaction rates of primary alcohols and tertiary alcohols, when reacted with tert-butyldimethylsilyl chloride to form

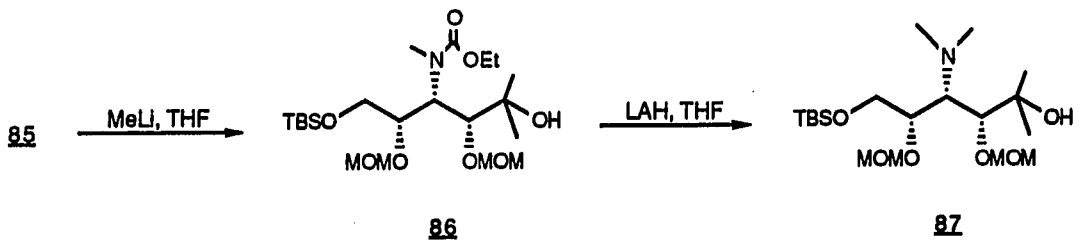
the corresponding silyl ethers.[59] To achieve our goal (converting cyclic sugar 83 into acyclic ketosugar 85), we treated 83 with tert-butyldimethylsilyl chloride and imadazole in DMF. We got the desired linear ketosugar 85 via the acyclic ketoalcohol 84.



There were a few things worth comment. In the proton NMR of 85, we saw two distinct singlets (2.17, 2.22 ppm) corresponding to the methyl protons adjacent to the carbonyl group. In the corresponding C-13 NMR, we observed two carbonyl signals (205.18, 205.28 ppm) corresponding to the

carbon atom at C-1. We were curious about these observations and wanted to figure out whether it was due to epimerization at C-2 of 85 to form two diastereomers, or to the restricted rotation on the carbamate group, which leads to the formation of two rotamers.

To prove which hypothesis is correct, we treated ketosugar 85 with methyl lithium at -78°C to form alcohol 86. The resulting 86 was reduced with lithium aluminum hydride to give amino alcohol 87.

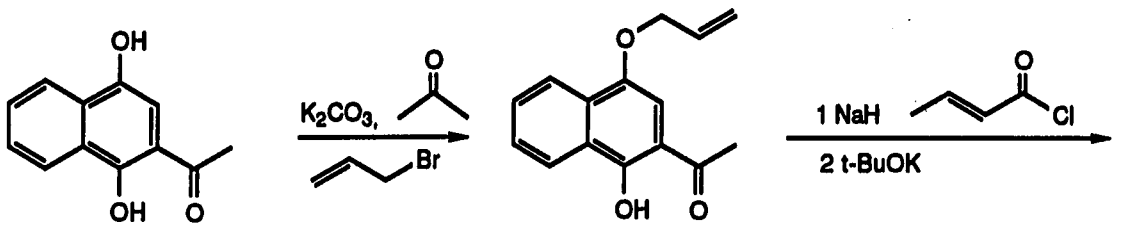


86 87

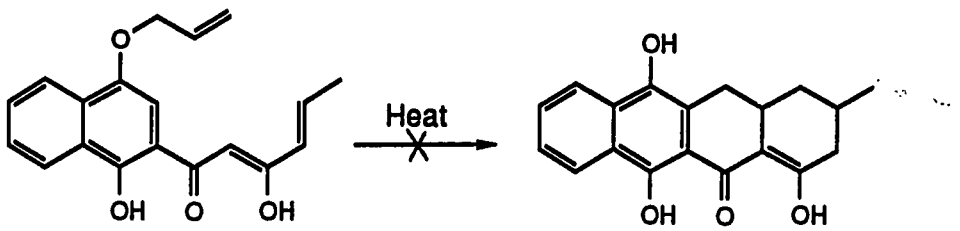
Spectroscopic data on compound 87 suggested that it was a single isomer, which supported our second hypothesis, i.e., the presence of two methyl signals on compound 85 is due to the restricted rotation of the carbamate group. As a result, we can declare that we have synthesized the highly functionalized ketosugar 85, which is one of our key intermediates toward the total synthesis of nogalamycin analogs.

Synthesis of the Tetracyclic Moiety

There are numerous different approaches toward the construction of ABCD ring portions of anthracyclines. At the early stage of our investigation, our approach featured a tandem Claisen-Diels-Alder reaction, which was developed by our colleagues.[60]



88 89

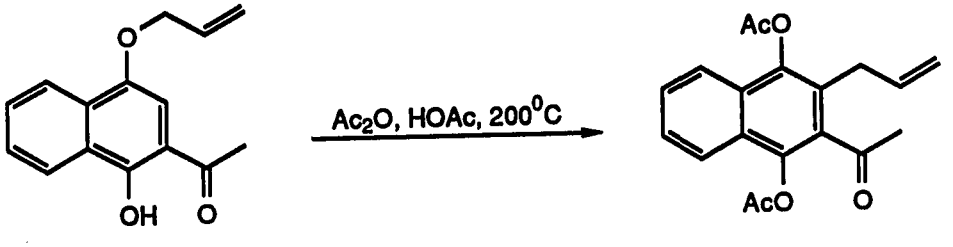


90 91

In the preliminary studies, the readily available dihydroxyketone 88 was regioselectively alkylated with allyl bromide in the presence of potassium carbonate in refluxing acetone.[61] The ortho-hydroxyketone 89 was then acylated by reacting 89 with sodium hydride followed by the acid

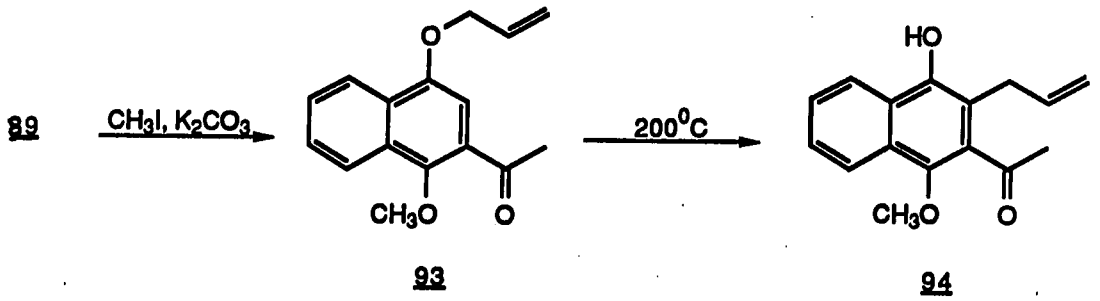
chloride. The resulting acylated compound was not isolated but treated with potassium tert-butoxide directly and stirred for an additional hour.[62] The one pot process afforded ketone 90 in 62% yield. The next step involved the tandem Claisen-Diels-Alder reaction sequence, but the result was disappointing. When we prepared 0.01 M solution of 90 and heated it to 180°C, no reaction occurred. At higher temperatures, it led to decomposition of the starting material.

To identify the best reaction conditions for the Claisen rearrangement, we heated compound 89 in toluene at various temperatures between 150°C and 230°C, but only decomposition occurred at prolonged heating above 200°C. However, when 89 was heated in a solution of acetic anhydride and acetic acid at 200°C, Claisen rearrangement proceeded smoothly with the formation of diacetate 92.



89 92

The hydroxyl group of 89 was protected as a methyl ether on treatment with excess methyl iodide and potassium carbonate,[63] methoxyketone 93 was rearranged to 94 when



93 94

heated at 200°C. Compound 94 could be a useful intermediate for further elaboration to the tetracyclic moiety.

During the investigation of tandem Claisen-Diels-Alder reaction in the naphthalene system, we also directed our attention toward the protection of the quinone moiety. In addition to their presence as subunits in a variety of natural products, quinones are useful building blocks for natural product synthesis. Because of the high reactivity of quinones, protection of the quinone moiety is often required. The protection of a quinone usually involves reduction to a hydroquinone followed by protection of the hydroquinone. For most compounds the hydroquinone is not actually isolated but is treated in situ with an acylating agent,[64] a methylating agent,[65] or a silylating agent.[66] The acylated or trimethylsilylated hydroquinones are too unstable for multistep sequences. Consequently, the reductive methylation technique has become the method of choice. The value of this technique is evidenced by several recent publications.[65] However, with quinones bearing

hydroxyl or alkoxyl groups, the standard reductive methylation conditions ($Na_2S_2O_4$, Me_2SO_4, K_2CO_3) generally proceed poorly. A modification of the standard procedure which constitutes a general one for the reductive methylation of quinones is thus described.

The modification involved the use of a phase transfer catalyst to improve the solubility of the anion of the reduced quinone. As shown in Table 4, even quinones bearing hydroxyl or methoxyl groups afforded good yields of the reductively methylated products. Notably, a bromine substituent was not reduced, as evidenced by entries 4, 5, and 9. The only limitation that we have observed is that aromatic amines were not compatible with the reaction conditions. The reductive methylation of 1,8-dimethoxy-anthraquinone and 1,4-dihydroxyanthraquinone is significant in that the other reductive methylation conditions failed to produce any of the respective tetramethoxyanthracene. As the example illustrated below indicates, ketones are also compatible with the reaction conditions. Protection of the reactive hydroxyanthraquinone moiety permits further elaboration of the A ring.

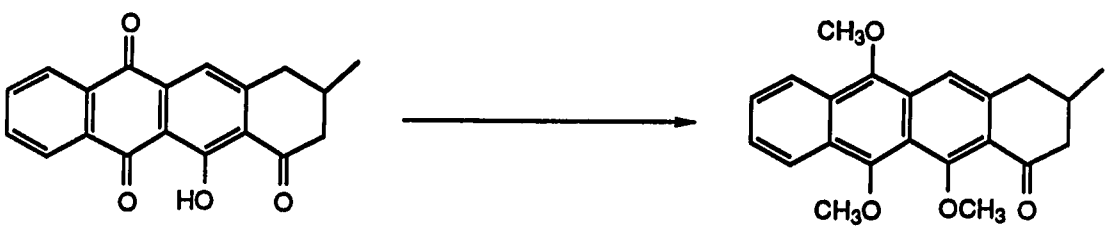
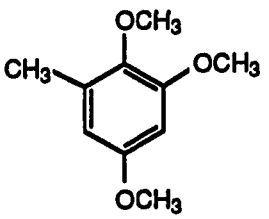


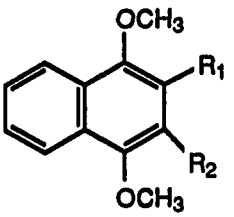
Table 4. Reductive methylation of quinones

Entry	Quinone	% Yield	Product[a]
1	1-methoxy-6-methylbenzoquinone	82	95
2	1,4-naphthoquinone	94	96
3	2-hydroxy-1,4-naphthoquinone	67	97
4	2-bromo-3-methyl-1,4-naphthoquinone	88	98
5	2-bromo-1,4-naphthoquinone	85	99
6	anthraquinone	92	100
7	1,4-dihydroxy-9,10-anthraquinone	66	101
8	1-hydroxy-4-amino-9,10-anthraquinone	--	--
9	1-methoxy-3-bromo-9,10-anthraquinone	69	102
10	1,8-dimethoxy-9,10-anthraquinone	77	103

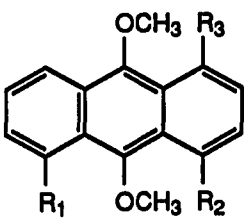
a



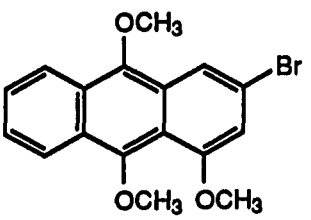
95



96 R_1=R_2=H
97 R_1=OCH_3, R_2=H
98 R_1=Br, R_2=CH_3
99 R_1=Br, R_2=H



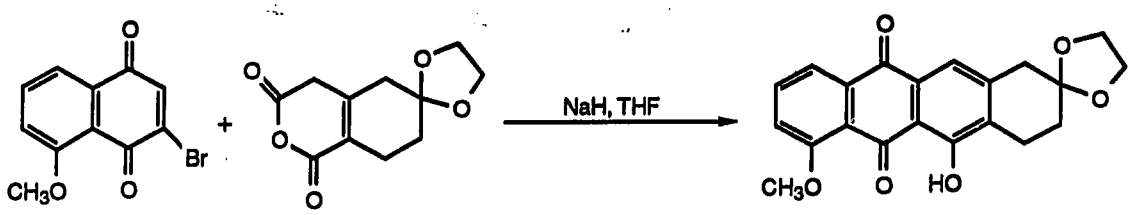
100 R_1=R_2=R_3=H
101 R_1=H, R_2=R_3=OCH_3
103 R_1=R_2=OCH_3, R_3=H



102

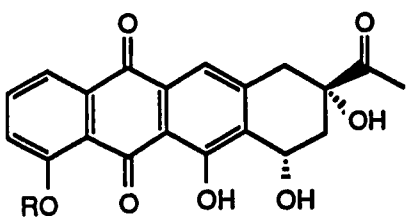
Coupled with the mild conditions for oxidation of hydroquinone dimethyl ethers to quinones developed by Rapoport,[67] this procedure will generate new pathways for the synthesis of quinonoid compounds.

As a result of the successful phase transfer reductive methylation technique on different kinds of quinones, our attention was turned to the preparation of tetracyclic compound 59. Of several possible alternatives, Tamura's work using strong base-induced cycloaddition of acid anhydrides with different naphthoquinones seemed to be very attractive.[68] For example, the key tetracyclic quinone 106,



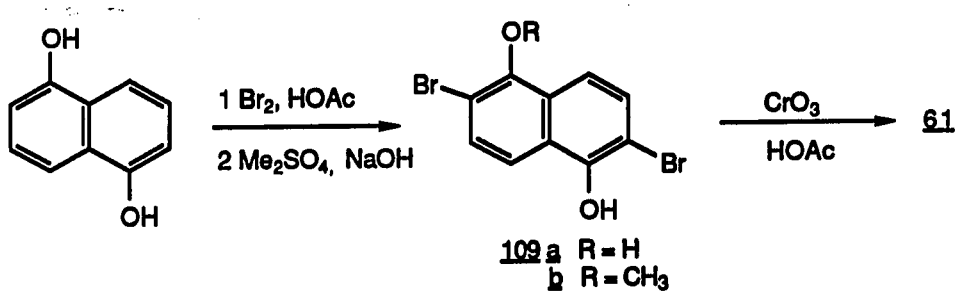
104 105 106

which can be converted into 11-deoxydaunomycinone (107) and 11-deoxycarminomycinone (108), was synthesized in only one step from naphthoquinone 104 and anhydride 105.

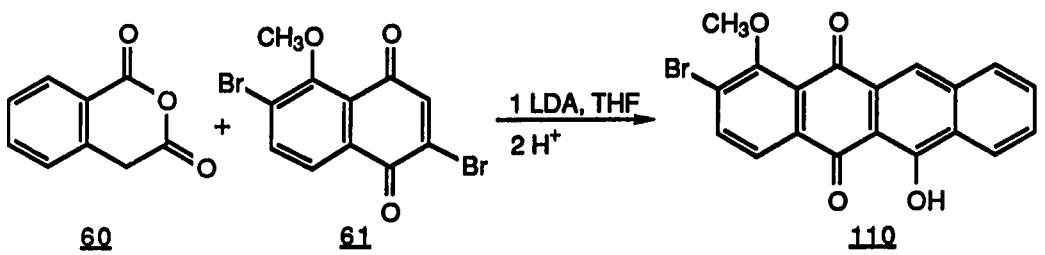


107 R = CH_3
108 R = H

In our synthesis, we started with commercially available homophthalic anhydride (60), and naphthoquinone 61, whose preparation can be accomplished in three steps from modified literature procedures.[69] Bromination of 1,5-dihydroxy-naphalene in acetic acid at 80°C gave 2,6-dibromo-1,5-dihydroxynaphthalene in 75% yield. The resulting bromo compound was monomethylated to yield compound 109b. Oxidation of 109b with chromium trioxide led to quinone 61 in 55% yield.

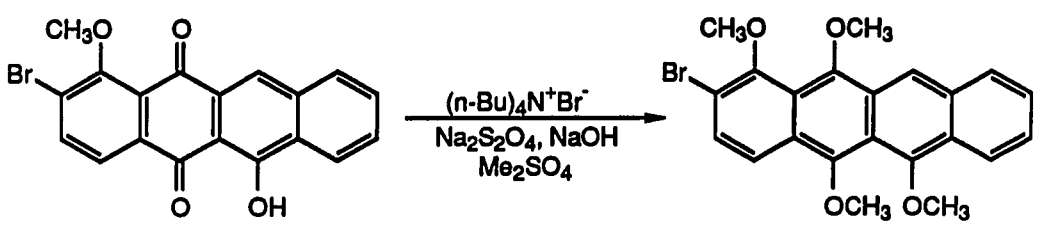


After the preparation of quinone 61, we attempted to conduct the Tamura reaction by adding homophthalic anhydride (60) into an LDA solution at -78°C, followed by the addition of quinone 61. The reaction proceeded smoothly and the resulting adduct 110 was obtained in 75% yield.



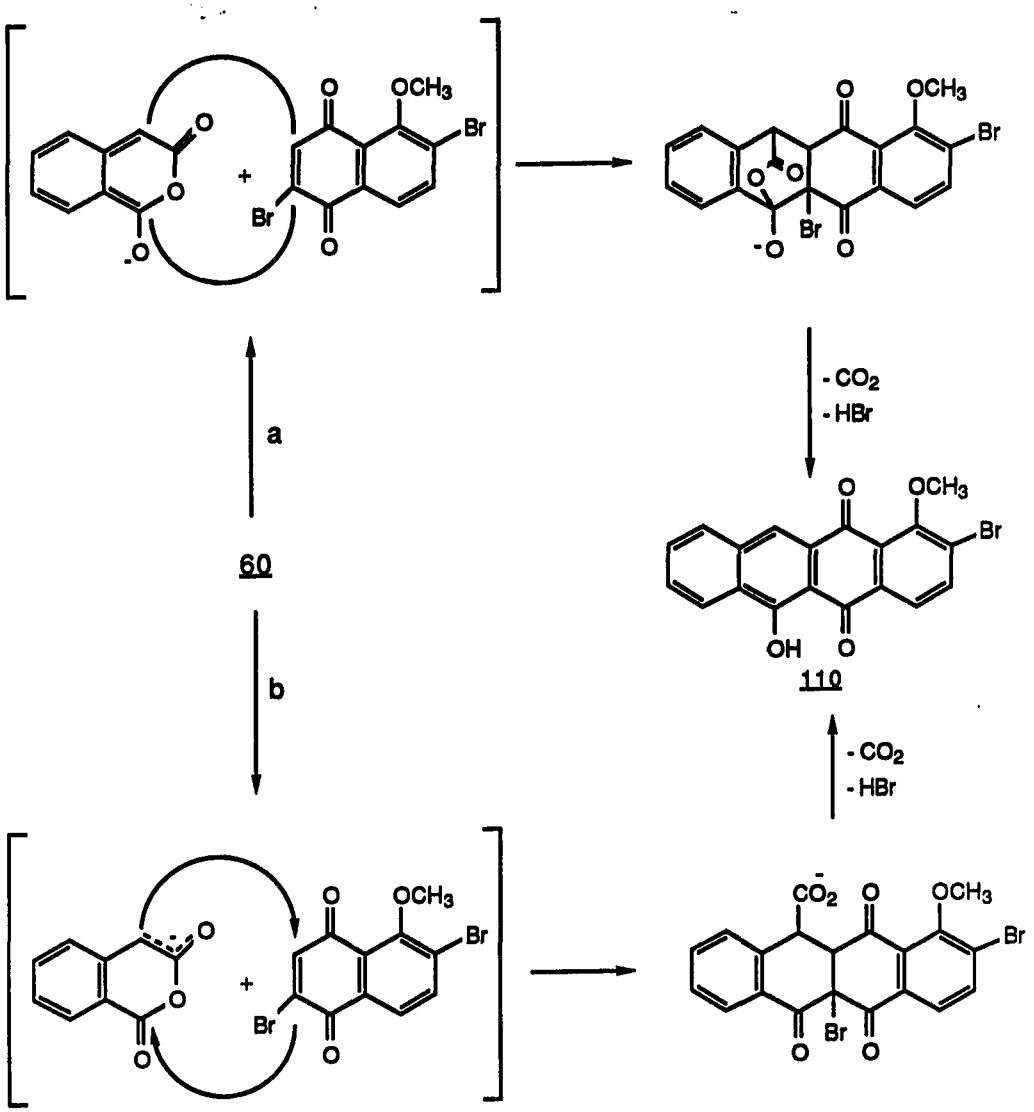
Mechanistically, the path involving a Diels-Alder type reaction of anhydride to dienophile (path a) is more probable than another path involving a Michael addition of anhydride to the electron deficient olefin (path b) as exemplified in the reaction of the alkaline salt of 60 with 61 leading to 110 (Scheme XVI), although it is not rigorously defined. The attractive feature of the reaction is that cycloadduct was obtained in a highly regioselective manner, no other regioisomer was isolated. Another interesting feature of the reaction is that the intermediate underwent spontaneous elimination of CO_2 and HBr in situ to form 110.

After quinone 110 was obtained, we proceeded to the phase transfer reductive methylation procedure. Treatment of quinone 110 with $Na_2S_2O_4$, NaOH, and Me_2SO_4 in the presence of the phase transfer reagent resulted in the formation of tetramethoxynapthacene 59 in 55% yield.



110 59

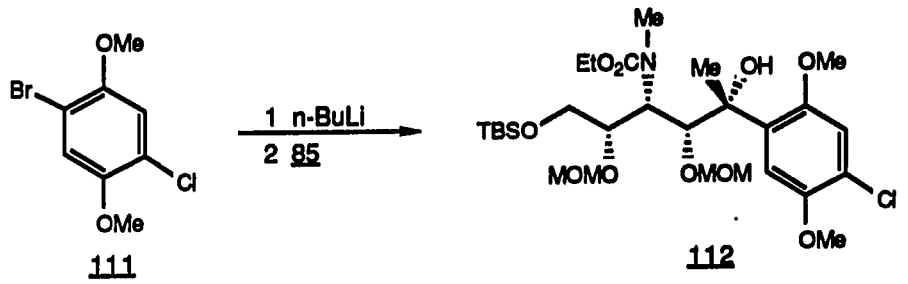
Scheme XVI



Studies of the Coupling Reaction

With ketosugar 85 and tetramethoxynapthacene 59 in hand, we proceeded to the coupling reaction. A model study showed that an aryl lithium was formed by transmetallation of bromo compound 111. Ketosugar 85 was added and the solution was

then warmed to 0°C for 20 min. The coupling reaction between the aryl lithium and 85 occurred, and the corresponding tertiary alcohol 112 was formed.



111 112

Although we cannot absolutely prove the configuration of the tertiary carbon in 112 at present, based on the Cram chelation model,[70] the lithium cation should interact with the two oxygen atoms of the MOM group adjacent to the carbonyl group of 85 more effectively than the oxygen atom of methyl ether in the aromatic ring. Therefore, the usual chelation model (Figure 3) should afford the desired product.

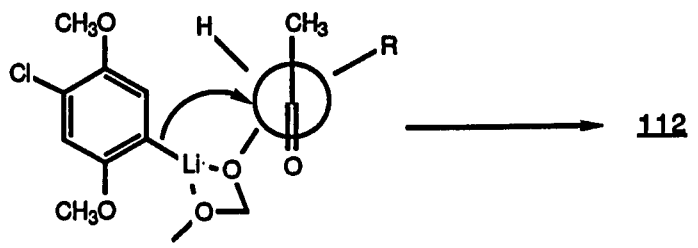
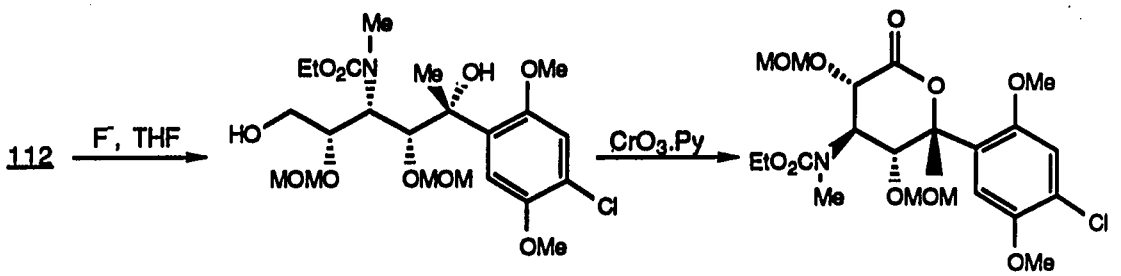


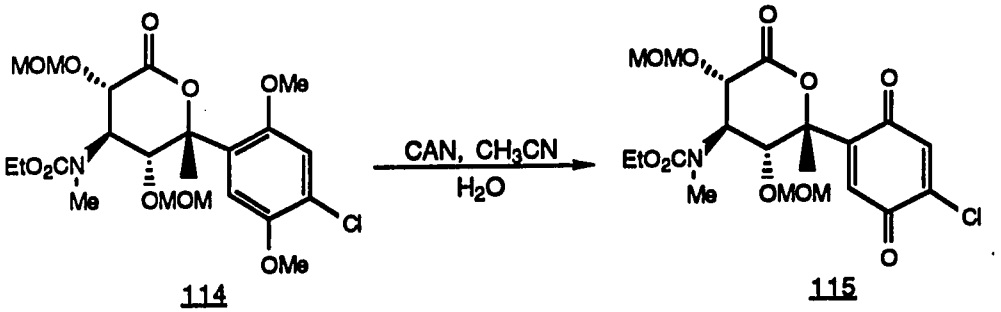
Figure 3. Chelation model

Removal of the silyl protecting group in 112 was done by treating 112 with tetrabutylammonium fluoride in THF. The resulting diol 113 was oxidized by Collins reagent to give the corresponding lactone 114.



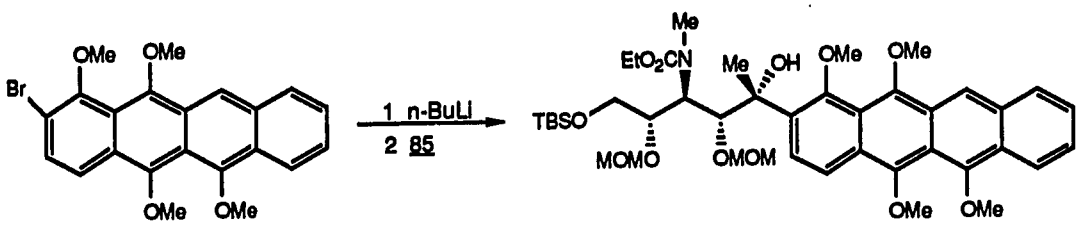
113 114

The lactone 114 can be oxidized by ceric ammonium nitrate in aqueous CH_3CN to form an unstable quinone 115 which is a useful dienophile in Diels-Alder reaction.



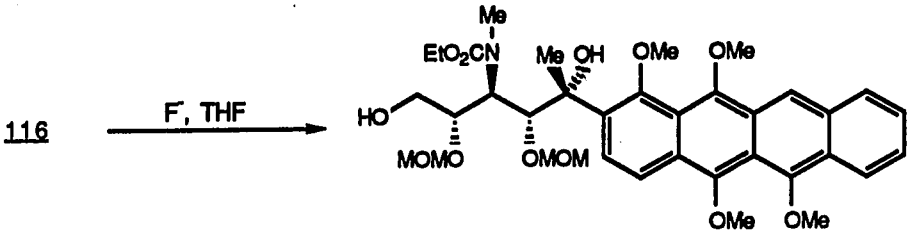
114 115

In the real system, coupling reaction occurred in the similar manner, compound 59 was transmetallated with n-butyl lithium, followed by addition of ketosugar 85 to the resulting aryl lithium to form tertiary alcohol 116. With

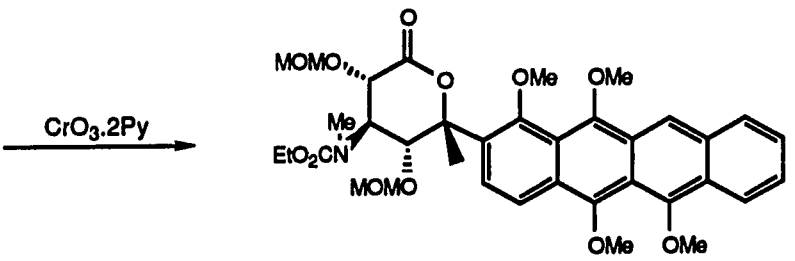


59 116

116 in hand, we expected desilylation of compound 116 followed by the oxidation of the resulting product, should give lactone 118.



117



118

CONCLUSION

Based on our initial strategy to the synthesis of nogalamycin analogs, we have achieved some of our goals. These include:

(1) An effective method for synthesizing highly functionalized ketosugar from cheap, commercially available D-arabinose. This ketosugar contained three contiguous stereogenic centers which could be converted into C-2', 3' and 4' of the target molecule.

(2) An approach to the tetracyclic moiety using the Tamura reaction, followed by a one pot reductive methylation has been developed. This tetracyclic moiety could be transformed into ABCD ring of our synthetic target.

(3) A Cram chelation-controlled coupling reaction between the ketosugar and the tetracyclic moiety has been achieved.

EXPERIMENTAL

General

Unless otherwise noted, materials were obtained from commercial suppliers and were used without purification. Tetrahydrofuran (THF) and diethyl ether were distilled from sodium benzophenone ketyl prior to usage. Acetone and dichloromethane were distilled from phosphorous pentoxide. Benzene was distilled from lithium aluminum hydride. Pyridine was distilled from calcium hydride. All reactions were conducted under a nitrogen atmosphere, and all extracts were dried over anhydrous magnesium sulfate. Apparatus for experiments requiring anhydrous conditions was flame-dried under a steam of nitrogen or was dried in an oven at 150°C for 12 hours. Flash chromatography was performed on Grace silica gel, grade 62, mesh 60-200. Melting points were determined on a Fischer-Johns melting point apparatus and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer 1320 or Beckman IR-4250 infrared spectrophotometer. Nuclear magnetic resonance spectra were determined on a Varian EM-360 spectrometer. High field (300 MHz) proton spectra were obtained using a Nicolet Magnetics Corporation NMC-1280 spectrometer. All chemical shifts are reported in ppm relative to tetramethylsilane as an internal standard. Splitting patterns are designated as s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet);

addition of b indicates a broadened pattern. C-13 NMR spectra were determined on a JOEL FQ-90Q or Nicolet NMC-1280 spectrometer and are reported in ppm relative to the central peak of $CDCl_3$ (77.06 ppm) or D_6-acetone (27.0 ppm). High resolution mass spectra were recorded on an AEI-MS 902 high resolution mass spectrometer. Low resolution mass spectra were recorded on a Finnegan 4023 mass spectrometer. Elemental analyses were determined by Galbraith Laboratories, Inc.

Acetonide 64

To a stirred solution of sugar 63 (5.0 g, 3.05 mmol) in acetone (30 mL) at room temperature was added 2,2-dimethoxypropane (10 mL) and PTSA (0.19 g, 1.0 mmol). After stirring for 12 h, triethylamine (1 mL) was added, and stirring was continued for 5 min. The solution was concentrated in vacuo. To the residue was added 10 mL of water, and the resulting suspension was repeatedly extracted with dichloromethane. The combined extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo to give a yellow oily liquid, which was purified via flash column chromatography using 1:1 hexanes:ethyl acetate as eluent to obtain compound 64 (4.7 g, 75%) as an oil. NMR ($CDCl_3$) δ 4.68 (d, 1 H, J = 3.6 Hz), 4.10-4.21 (m, 2 H), 3.80-3.90 (m, 2 H), 3.74 (dd, 1 H, J = 3.6 and 6.3 Hz), 3.41 (s, 3 H), 2.33 (bs, 1 H), 1.50 (s, 3

H), 1.33 (s, 3 H). IR (neat) 3450, 2920, 1465, 1450, 1260, 1030, 906 cm^{-1}. High resolution mass spectrum for $C_9H_{15}O_5$ (M^+-H) requires 203.09195; measured 203.09161. C-13 NMR ($CDCl_3$) δ 108.83, 98.90, 75.93, 72.89, 70.01, 59.12, 55.46, 27.85, 25.88.

Tosylate 65

To a vigorously stirred solution of compound 64 (10.0 g, 49.0 mmol) in pyridine (100 mL) at room temperature was added p-toluenesulfonyl chloride (14.0 g, 73.5 mmol) in one portion. After stirring for 48 h, the resulting reaction mixture was concentrated in vacuo. To the residue was added 100 mL of water, and the resulting suspension was repeatedly extracted with dichloromethane. The combined extracts were washed with water and brine, dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo to give a white solid. Recrystallization of this substance from 1:1 hexanes:ethanol afforded 65 (16.1 g, 92%) as colorless crystals (mp 136-137°C). NMR ($CDCl_3$) δ 7.83 (d, 2 H, J = 8.4 Hz), 7.32 (d, 2 H, J = 8.4 Hz), 4.85 (d, 1 H, J = 3.0 Hz), 4.15-4.31 (m, 3 H), 3.85-3.97 (m, 2 H), 3.36 (s, 3 H), 2.42 (s, 3 H), 1.23 (s, 3 H), 1.10 (s, 3 H). IR (film) 2930, 1585, 1370, 1195, 1172, 1020, 945 cm^{-1}. High resolution mass spectrum for $C_{16}H_{22}O_7S$ requires 358.10863; measured 358.10885. C-13 NMR ($CDCl_3$) δ 144.68, 132.93, 129.41, 127.97, 108.83, 97.36, 78.85, 73.64, 72.31, 57.87,

55.53, 27.17, 25.85, 21.30. Elemental analysis calculated for $C_{16}H_{22}O_7S$: C, 53.62; H, 6.19. Found: C, 53.37; H, 6.05.

Alcohol 66

A mixture of compound 65 (6.0 g, 16.8 mmol), methanol (200 mL), water (5 mL) and 6 N hydrochloric acid (8 mL) was heated at reflux with stirring for 12 h. The mixture was cooled to room temperature, pyridine (10 mL) was added and the reaction mixture was concentrated in vacuo. The residue was dissolved in dichloromethane (250 mL), washed with brine, dried over anhydrous magnesium sulfate and concentrated in vacuo to give a yellow oil, which was purified via flash column chromatography using 1:1 hexanes:ethyl acetate as eluent to afford compound 66 (4.7 g, 88%) as a viscous oil. NMR ($CDCl_3$) δ 7.84 (d, 2 H, J = 8 Hz), 7.36 (d, 2 H, J = 8 Hz), 4.63 (bs, 1 H), 4.60 (m, 1 H), 3.96-4.09 (m, 2 H), 3.66-3.81 (m, 2 H), 3.29 (s, 3 H), 2.46 (s, 3 H). IR (neat) 3450, 3050, 2960, 1590, 1350, 1185, 1170, 1130, 1005, 940 cm^{-1}. Mass spectrum m/e 318, 269, 155, 131, 103, 61. High resolution mass spectrum for $C_{13}H_{19}O_7S$ (MH^+) requires 319.08516; measured 319.08549. C-13 NMR ($CDCl_3$) δ 144.78, 133.16, 129.50, 127.58, 97.34, 78.07, 69.34, 66.50, 61.77, 55.08, 21.26.

Acetate 67

To a stirred solution of compound 66 (9.5 g, 29.9 mmol) in pyridine (40 mL) at room temperature was added acetic anhydride (20 mL). After stirring for 12 h the reaction mixture was cooled to 0°C, methanol (20 mL) was added to destroy the unreacted acetic anhydride. Stirring was continued for 10 min. The solution was concentrated in vacuo. To the residue was added 100 mL of water, and the resulting suspension was repeatedly extracted with dichloromethane. The combined extracts were washed with water and brine, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to give a white solid. Recrystallization of this substance from 1:1 hexanes:ethyl acetate afforded pure 67 (11.3 g, 94%) as colorless crystals (mp 112-114°C). NMR ($CDCl_3$) δ 7.76 (d, 2 H, J = 8 Hz), 7.31 (d, 2 H, J = 8 Hz), 5.23-5.26 (m, 2 H), 4.74-4.82 (m, 2 H), 3.84 (d, 1 H, J = 13 Hz), 3.58 (dd, 1 H, J = 1.5 and 13 Hz), 3.29 (s, 3 H), 2.41 (s, 3 H), 2.06 (s, 3 H), 1.74 (s, 3 H). IR (film) 3020, 2930, 1740, 1590, 1360. Mass spectrum m/e 402, 247, 187, 155, 127, 85. High resolution mass spectrum for $C_{17}H_{23}O_9S$ (MH^+) requires 403.10629; measured 403.10629. C-13 NMR ($CDCl_3$) δ 170.02, 169.49, 144.99, 133.78, 129.67, 127.82, 98.04, 74.44, 69.39, 66.51, 60.13, 55.74, 21.61, 20.83, 20.38.

Epoxide 68

A freshly prepared 1.0 N solution of sodium methoxide in methanol (75 mL) was poured into a flask containing compound 66 (6.0 g, 18.9 mmol) and methanol (25 mL) at room temperature. After stirring for 12 h, the basic solution was neutralized with acetic acid. The resulting solution was concentrated in vacuo. The residue was washed thoroughly with diethyl ether and filtered. The filtrate was concentrated in vacuo to give an oil, which was purified via flash column chromatography using 2:1 hexanes:ethyl acetate as eluent to obtain compound 68 (2.4 g, 87%) as a colorless oil. NMR ($CDCl_3$) δ 4.80 (bs, 1 H), 3.87 (m, 1 H), 3.73 (dd, 1 H, J = 3 and 12 Hz), 3.50 (t, 1 H, J = 4 Hz), 3.43 (s, 3 H), 3.39 (d, 1 H, J = 12 Hz), 3.71 (d, 1 H, J = 4 Hz). IR (neat) 3450, 2920, 1400, 1240, 1082, 1058, 1025, 970 cm^{-1}. Mass spectrum m/e 146, 115, 85, 69, 58. High resolution mass spectrum for $C_6H_{10}O_4$ requires 146.05791; measured 146.05792. C-13 NMR ($CDCl_3$) δ 95.43, 61.75, 61.70, 55.79, 51.79.

Amine 69

To a stirred solution of epoxide 68 (1.0 g, 6.8 mmol) in ethanol (20 mL) at 0°C in a culture tube was added dimethyl amine (2 mL). The solution was deoxygenated and heated at 110°C for 20 h. The reaction mixture was cooled to room temperature and concentrated in vacuo. The crude product

was dissolved in hot chloroform (10 mL), followed by the addition of hexanes (30 mL). The resulting mixture was refrigerated and the product (1.1 g, 84%) was collected through suction filtration as white powder (mp 79-81°C). NMR ($CDCl_3$) δ 4.13 (d, 1 H, J = 7.5 Hz), 4.04 (dd, 1 H, J = 5 and 11 Hz), 3.43-3.64 (m, 4 H), 3.22 (t, 1 H, J = 11 Hz), 2.52 (s, 6 H), 2.40 (t, 1 H, J = 10 Hz). IR (film) 3050, 2940, 1075, 1030 cm^{-1}. Mass spectrum m/e 191, 159, 129, 117, 87, 72, 58. High resolution mass spectrum for $C_8H_{17}NO_4$ requires 119.11576; measured 119.11553. C-13 NMR ($CDCl_3$) δ 105.66, 70.47, 69.75, 67.09, 65.05, 56.87, 41.64.

Ether 71

To a suspension of hexane-washed sodium hydride (0.41 g, 17.1 mmol) in DMF (20 mL) at 0°C under nitrogen atmosphere was added compound 69 (1.0 g, 5.2 mmol). The reaction mixture was stirred at 0°C for 10 min and benzyl bromide (1.97 g, 12.5 mmol) was added. The reaction mixture was warmed to room temperature. After stirring for 8 h, the reaction mixture was poured into ice water and was repeatedly extracted with dichloromethane. The combined extracts were washed with water and brine, dried over anhydrous sodium sulfate, filtered, concentrated in vacuo to give a yellow oil. The crude product was purified via flash column chromatography using 4:1 hexanes:ethyl acetate as eluent to afford compound 71 (1.8 g, 92%) as a viscous

liquid. NMR ($CDCl_3$) δ 7.24-7.40 (m, 10 H), 4.85 (d, 1 H, J = 11 Hz), 4.71 (d, 1 H, J = 11 Hz), 4.68 (d, 1 H, J = 11 Hz), 4.59 (d, 1 H, J = 11 Hz), 4.24 (d, 1 H, J = 7 Hz), 3.93 (dd, 1 H, J = 5 and 11 Hz), 3.45-3.56 (m, 1 H), 3.50 (s, 3 H), 3.29 (dd, 1 H, J = 7 and 10 Hz), 3.20 (dd, 1 H, J = 10 and 11 Hz), 2.47 (s, 6 H). IR (neat) 3020, 1590, 1350, 1170, 1010, 930 cm^{-1}. Mass spectrum m/e 371, 280, 188, 148, 91, 58. High resolution mass spectrum for $C_{22}H_{29}NO_4$ requires 371.20967; measured 371.20974. C-13 NMR ($CDCl_3$) δ 138.82, 138.50, 128.38, 128.23, 128.08, 127.92, 127.72, 127.46, 106.21, 77.64, 73.66, 73.34, 72.53, 69.52, 64.96, 56.77, 42.05.

Acetonide 74

To a stirred solution of compound 73 (20.0 g, 83.3 mmol) in acetone (150 mL) at room temperature was added 2,2-dimethoxypropane (30 mL) and PTSA (0.5 g, 2.6 mmol). After stirring for 12 h, triethylamine (1 mL) was added and stirring was continued for 5 min. The solution was concentated in vacuo. To the residue was added 30 mL of water, and the resulting suspension was repeatedly extracted with dichloromethane. The combined extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo to give a yellow oily liquid, which was purified via flash column chromatography using 2:1 hexanes:ethyl acetate as eluent to obtain compound 74 (20.7

g, 89%) as a viscous oil. NMR ($CDCl_3$) δ 7.25-7.50 (m, 5 H), 4.92 (d, 1 H, J = 3.6 Hz), 4.78 (d, 1 H, J = 12 Hz), 4.54 (d, 1 H, J = 12 Hz), 4.16-4.22 (m, 2 H), 3.88-4.03 (m, 2 H), 3.76-3.81 (m, 1 H), 1.52 (s, 3 H), 1.35 (s, 3 H), IR (neat) 3450, 3020, 2910, 1443, 1370, 1240, 1210, 848 cm^{-1}. Mass spectrum m/e 280, 265, 189, 156, 131, 91, 59. High resolution mass spectrum for $C_{15}H_{20}O_5$ requires 280.13108; measured 280.13172. C-13 NMR ($CDCl_3$) δ 136.88, 128.21, 128.12, 127.68, 108.80, 96.90, 75.69, 72.76, 69.83, 69.39, 59.40, 27.71, 25.76.

Tosylate 75

To a vigorously stirred solution of compound 74 (19.0 g, 67.9 mmol) in pyridine (150 mL) at room temperature was added p-toluenesulfonyl chloride (19.4 g, 101.8 mmol) in one portion. After stirring for 48 h, the resulting suspension was concentrated in vacuo. To the residue was added 150 mL of water, and the suspension was repeatedly extracted with dichloromethane. The combined extracts were washed with water and brine, dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo to give a syrup, which was purified via flash column chromatography using 3:1 hexanes:ethyl acetate as eluent to yield compound 75 (27.1 g, 92%) as a viscous liquid. NMR ($CDCl_3$) δ 7.78 (d, 2 H, J = 8 Hz), 7.33 (m, 5 H), 7.28 (d, 2 H, J = 8 Hz), 5.04 (d, 1 H, J = 1.5 Hz), 4.68 (d, 1 H, J = 12 Hz), 4.48 (d, 1 H, J =

12 Hz), 4.30-4.32 (m, 2 H), 4.15-4.19 (m, 1 H), 3.95 (m, 2 H), 2.41 (s, 3 H), 1.25 (s, 3 H), 1.14 (s, 3 H). IR (neat) 3020, 2975, 2920, 1590, 1490, 1447, 1360, 1305, 1240, 1130, 1065, 1010, 940, 830 cm^{-1}. Mass spectrum m/e 434, 419, 359, 315, 279, 239, 204, 174, 143, 91, 65. High resolution mass spectrum for $C_{22}H_{26}O_7S$ requires 434.13993; measured 434.13909. C-13 NMR ($CDCl_3$) δ 144.73, 136.66, 133.19, 129.60, 128.40, 128.23, 127.90, 127.72, 109.19, 95.84, 78.84, 72.66, 70.04, 58.59, 27.47, 26.16, 21.61.

Alcohol 76

To a solution of compound 75 (15.0 g, 34.6 mmol) in methanol (200 mL) was added 6 N hydrochloric acid (5 mL). The solution was refluxed for 8 h, cooled to room temperature, and pyridine (10 mL) was added. Stirring was continued for 10 min. The solution was concentrated in vacuo. To the residue was added 50 mL of water, and the resulting mixture was repeatedly extracted with dichloromethane. The combined extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo to give a syrup. Chromatography on silica gel using 1:2 diethyl ether:ethyl acetate as eluent afforded compound 76 (12.9 g, 95%) as a sticky substance. NMR ($CDCl_3$) δ 7.72 (d, 2 H, J = 8 Hz), 7.27-7.40 (m, 5 H), 7.25 (d, 2 H, J = 8 Hz), 4.80 (d, 1 H, J = 3.6 Hz), 4.66 (d, 1 H, J = 12 Hz), 4.63 (dd, 1 H, J = 3.6 and 10 Hz), 4.37 (d,

1 H, J = 12 Hz), 4.12 (dd, 1 H, J = 3.6 and 10 Hz), 4.01 (t, 1 H, J = 1.5 Hz), 3.84 (d, 1 H, J = 13 Hz), 3.71 (dd, 1 H, J = 1.5 and 13 Hz), 3.102 (bs, 1 H), 2.90 (bs, 1 H), 2.41 (s, 3 H). IR (neat) 3350, 3020, 2920, 1590, 1448, 1350, 1170, 1133, 1060, 1010, 940, 860 cm^{-1}. Mass spectrum m/e 394, 377, 317, 269, 245, 173, 155, 91. High resolution mass spectrum for $C_{19}H_{23}SO_7$ (MH^+) requires 395.11646; measured 395.11657. C-13 NMR ($CDCl_3$) δ 144.87, 136.75, 133.10, 129.68, 128.23, 127.74, 127.66, 95.82, 78.06, 69.43, 66.88.

Epoxide 77

To a well stirred solution of alcohol 76 (5.6 g, 14.2 mmol) in methanol (50 mL) was added sodium methoxide (2.3 g, 42.6 mmol) at room temperature. After stirring for 12 h, the basic solution was neutralized with acetic acid. The solution was concentrated in vacuo. To the residue was added 30 mL of water, and the resulting mixture was repeatedly extracted with dichloromethane. The combined extracts were washed with water and brine, dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo to give a yellow solid, which was purified via column chromatography using 2:1 hexanes:ethyl acetate as eluent to obtain compound 77 (2.7 g, 86%) as a white powder (mp 77-79°C). NMR ($CDCl_3$) δ 7.25-7.42 (m, 5 H), 5.02 (s, 1 H), 4.78 (d, 1 H, J = 12 Hz), 4.58 (d, 1 H, J = 12 Hz), 3.80-3.95 (m, 2 H), 3.50 (t, 1 H, J = 4 Hz), 3.42 (d, 1 H, J

= 12 Hz), 3.22 (d, 1 H, J = 4 Hz), 3.10 (bd, 1 H, J = 10 Hz). IR (neat) 3450, 3040, 2960, 1490, 1445, 1397, 1260, 1145, 1120, 1080, 1052, 1015, 972 cm^{-1}. Mass spectrum m/e 222, 161, 133, 107, 91, 73, 65. High resolution mass spectrum for $C_{12}H_{14}O_4$ requires 222.08921; measured 222.08966. C-13 NMR ($CDCl_3$) δ 136.92, 128.41, 128.00, 127.91, 93.53, 69.98, 62.04, 61.64, 51.85, 51.83.

Amine 78

To a solution of epoxide 77 (4.5 g, 20.3 mmol) in ethanol (50 mL) in a culture tube was saturated with methylamine. The solution was heated at 110°C for 18 h. After cooling to room temperature, the resulting mixture was concentrated in vacuo. The residue was dissolved in hot chloroform (20 mL). To the resulting hot solution was added hexanes (100 mL) and refrigerated. The amine 78 (4.6 g, 90%) was collected through suction filtration as a white solid (mp 150-151°C). NMR ($CDCl_3$) δ 7.25-7.42 (m, 5 H), 4.87 (d, 1 H, J = 11 Hz), 4.56 (d, 1 H, J = 11 Hz), 4.40 (d, 1 H, J = 6.6 Hz), 4.06 (dd, 1 H, J = 4.5 and 11 Hz), 3.64 (m, 1 H), 3.50 (dd, 1 H, J = 6.5 and 8.9 Hz), 3.30 (dd, 1 H, J = 8.7 and 11 Hz), 2.48 (t, 1 H, J = 8.7 Hz), 2.44 (s, 3 H). IR (film) 3400, 3020, 2940, 1600, 1480, 1240, 1115, 960 cm^{-1}. Mass spectrum m/e 253, 191, 145, 91. High resolution mass spectrum for $C_{13}H_{19}O_4N$ requires 253.13141; measured 253.13124. C-13 NMR ($CDCl_3$) δ 137.11, 128.58, 128.15,

70.06, 66.80, 66.24, 64.36, 32.13. Elemental analysis calculated for $C_{13}H_{19}O_4N$: C, 61.64; H, 7.56. Found: C, 61.52; H, 7.29.

Carbamate 79

To a stirred suspension of amine 78 (6.8 g, 26.9 mmol) in acetone (50 mL) was added anhydrous potassium carbonate 8.2 g, 50.1 mmol) and ethyl chloroformate (2.8 mL, 29.6 mmol). The reaction mixture was refluxed for 8 h, cooled to room temperature, filtered and concentrated in vacuo. The crude product was dissolved in chloroform (20 mL). To the resulting solution was added hexanes (150 mL) and refrigerated. The carbamate 79 (8.1 g, 93%) was collected through suction filtration as a white powder (mp 119-120°C). NMR ($CDCl_3$) δ 7.26-7.43 (m, 5 H), 4.91 (d, 1 H, J = 11 Hz), 4.61 (d, 1 H, J = 11 Hz), 4.36 (d, 1 H, J = 7.5 Hz), 4.00-4.20 (m, 4 H), 3.77 (m, 1 H), 3.52 (m, 1 H), 3.26 (t, 1 H, J = 10 Hz), 2.88 (s, 3 H), 2.65 (bs, 1 H), 1.26 (t, 3 H, J = 7 Hz). IR (film) 3450, 3020, 2960, 1650, 1480, 1420, 1335, 1280, 1233, 1145, 1050, 970 cm^{-1}. Mass spectrum m/e 325, 310, 217, 188, 170, 91. High resolution mass spectrum for $C_{16}H_{23}NO_6$ requires 325.15254; measured 325.15301. C-13 NMR ($CDCl_3$) δ 158.86, 136.95, 128.46, 128.04, 127.96, 103.21, 70.96, 68.96, 67.38, 65.77, 62.95, 61.96, 28.64.

Ether 80

To a well stirred solution of compound 79 (8.1 g, 24.9 mmol) in THF (30 mL) and diisopropylethylamine (17.3 mL, 99.6 mmol) at room temperature was added chloromethyl methyl ether (5.7 mL, 74.8 mmol). After stirring for 24 h, 50 mL of water was added and the resulting suspension was repeatedly extracted with dichloromethane. The combined extracts were washed with water and brine, dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo to give an orange oil. The crude product was purified via flash column chromatography to afford compound 80 (9.8 g, 95%) as a slight yellow liquid. NMR ($CDCl_3$) δ 7.20-7.26 (m, 5 H), 4.96 (d, 1 H, J = 7 Hz), 4.88 (d, 1 H, J = 12 Hz), 4.51-4.65 (m, 5 H), 4.45 (d, 1 H, J = 7 Hz), 4.00-4.23 (m, 4 H), 3.30-3.40 (m, 2 H), 3.31 (s, 3 H), 3.27 (s, 3 H), 2.90 (s, 3 H), 1.20-1.29 (m, 3 H). IR (neat) 3010, 2940, 1680, 1449, 1400, 1370, 1320, 1215, 1145, 915 cm^{-1}. Mass spectrum m/e 413, 322, 289, 246, 222, 189, 170, 116, 91, 59. High resolution mass spectrum for $C_{20}H_{31}O_8N$ requires 413.20498; measured 413.20424. C-13 NMR ($CDCl_3$) δ 156.59, 136.88, 136.78, 127.74, 127.03, 103.09, 96.33, 96.29, 95.56, 73.28, 70.68, 70.25, 70.21, 64.81, 60.68, 60.49, 59.53, 54.93, 54.68, 54.57, 27.16, 14.17.

Hemiacetal 81

To a suspension of compound 80 (9.5 g, 23.0 mmol) and activated 10% Pd/C (0.6 g) in ethanol (100 mL) was hydrogenated at 50 psi for 8 h at room temperature. The resulting suspension was filtered through celite. The filter cake was washed thoroughly with methanol (3 x 20 mL) and the combined filtrate was concentrated in vacuo. The crude product was purified via flash column chromatography using 1:1 hexanes:ethyl acetate as eluent to yield compound 81 (7.1 g, 96%) as a viscous liquid. NMR ($CDCl_3$) δ 5.3 (m, 1 H), 4.45-4.70 (m, 5 H), 3.39-4.22 (m, 4 H), 3.60-3.81 (m, 3 H), 3.33-3.41 (m, 2 H), 3.32, 3.30, 3.27 and 3.26 (s, 6 H), 2.89 (bs, 3 H), 1.16-1.32 (m, 3 H). IR (neat) 3450, 2940, 1690, 1441, 1405, 1372, 1320, 1135, 1097, 1025, 915 cm^{-1}. Mass spectrum m/e 323, 292, 278, 246, 216, 202, 148, 116, 72. High resolution mass spectrum for $C_{13}H_{25}O_8N$ required 323.15802; measured 323.15778. C-13 NMR ($CDCl_3$) δ 157.40, 98.31, 96.91, 96.37, 96.24, 96.11, 92.50, 91.23, 91.09, 75.66, 73.63, 71.57, 71.15, 71.08, 70.67, 65.42, 65.32, 61.49, 61.27, 61.11, 60.46, 60.33, 60.18, 55.57, 55.44, 55.38, 55.22, 27.80, 14.60.

Lactone 82

To a well stirred solution of dry pyridine (23.1 mL, 286 mmol) in dichloromethane (300 mL) at 0°C was added chromium trioxide (14.3 g, 143 mmol) in portions under nitrogen

atmosphere. Stirring was continued for 10 min at room temperature after complete addition. Compound 81 (7.7 g, 23.8 mmol) in dichloromethane (50 mL) was added to the freshly prepared Collins reagent solution and the reaction mixture was stirred for 60 min. The dark mixture was passed through a column containing silica gel with ethyl acetate as solvent and the combined solution was concentrated in vacuo. The resulting crude product was purified via flash column chromatography using 1:1 hexanes:ethyl acetate as eluent to yield compound 82 (7.0 g, 95%) as an oily liquid. NMR ($CDCl_3$) δ 5.09 (d, 1 H, J = 11 Hz), 4.90 (m, 1 H), 4.62-4.78 (m, 4 H), 4.30-4.45 (m, 2 H), 4.09-4.25 (m, 3 H), 3.39 (s, 3 H), 3.35 (s, 3 H), 3.11 (s, 3 H), 1.29 (t, 3 H, J = 7 Hz). IR (neat) 2940, 1758, 1682, 1460, 1395, 1340, 1300, 1252, 1210, 1171, 1148, 1120, 1095, 1023, 913 cm^{-1}. Mass spectrum m/e 321, 276, 202, 160, 114, 70. High resolution mass spectrum for $C_{13}H_{23}O_8N$ requires 321.14237; measured 321.14228. C-13 NMR ($CDCl_3$) δ 170.79, 155.58, 95.69, 95.25, 75.14, 69.44, 67.78, 66.41, 61.20, 55.23, 37.64, 14.27.

Hemiketal 83

To a stirred solution of lactone 82 (7.0 g, 21.8 mmol) in THF (40 mL) at -78°C was added methyl lithium (28.3 mL, 28.3 mmol) slowly. After stirring at -78°C for 5 h, the reaction mixture was quenched with 2 N ammonium chloride (20 mL). The resulting mixture was repeatedly extracted with

dichloromethane. The combined extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo to give a yellow oil, which was purified via flash column chromatography using 1:1 hexanes:ethyl acetate as eluent to yield compound 83 (6.4 g, 87%) as a viscous liquid. NMR ($CDCl_3$) δ 4.45-4.75 (m, 5 H), 4.18-4.27 (m, 3 H), 3.70-3.86 (m, 2 H), 3.40-3.42 (m, 1 H), 3.36 (bs, 3 H), 3.31 (bs, 3 H), 2.88 (bs, 3 H), 3.48 and 3.45 (s, 3 H), 1.26 (t, 3 H, J = 7 Hz). IR (neat) 3450, 2922, 1675, 1460, 1440, 1400, 1370, 1305, 1145, 1090, 1024, 915 cm^{-1}. High resolution mass spectrum for $C_{14}H_{27}O_8N$ requires 337.17371; measured 337.17382. C-13 NMR ($CDCl_3$) δ 157.57, 99.65, 98.03, 97.67, 97.42, 97.20, 96.60, 96.34, 96.23, 96.16, 79.07, 78.14, 77.94, 77.79, 72.97, 71.74, 71.20, 65.09, 62.22, 61.88, 61.81, 61.49, 61.40, 61.15, 57.92, 56.39, 56.11, 55.68, 55.44, 55.30, 40.53, 27.96, 26.44, 14.70.

Ketone 85

To a stirred solution of hemiketal 83 (6.5 g, 19.3 mmol) in DMF (50 mL) was added imidazole (3.9 g, 57.9 mmole) and tert-butyldimethylsilyl chloride (3.8 g, 25.2 mmol). After stirring at room temperature for 24 h, 30 mL of water was added and the resulting mixture was repeatedly extracted with dichloromethane. The combined extracts were washed with water and brine, dried over anhydrous magnesium

sulfate, filtered and concentrated in vacuo to give a yellow oily liquid, which was purified via flash column chromatography using 4:1 hexanes:ethyl acetate as eluent to yield compound 85 (8.7 g, 100%) as a colorless oil. NMR ($CDCl_3$) δ 5.15 and 4.98 (dd, 1 H), 4.38-4.82 (m, 4 H), 4.05-4.18 (m, 2 H), 3.73-3.97 (m, 3 H), 3.37 (s, 3 H), 3.35 (s, 3 H), 3.35-3.39 (m, 1 H), 2.92 and 2.90 (s, 3 H), 2.22 and 2.17 (s, 3 H), 1.17-1.30 (m, 3 H), 0.93 (s, 9 H), 0.11, 0.10, 0.09 and 0.08 (s, 6 H). IR (neat) 2920, 1725, 1700, 1470, 1440, 1400, 1317, 1250, 1210, 1150, 1025, 920, 835 cm^{-1}. Mass spectrum 451, 394, 334, 274, 232, 190, 158, 116, 89. High resolution mass spectrum for $C_{20}H_{40}O_8NSi$ (M^+-H) requires 450.25233; measured 450.25312. C-13 NMR ($CDCl_3$) δ 205.28, 205.18, 157.38, 156.97, 99.26, 96.60, 96.42, 96.19, 81.84, 81.71, 75.36, 75.29, 62.34, 61.71, 61.25, 56.33, 55.67, 55.21, 55.10, 30.76, 30.54, 26.56, 26.19, 25.67, 25.63, 18.00, 17.96, 17.68, 14.42, -5.73, -5.59.

Alcohol 86

To a solution of compound 85 (1.0 g, 2.2 mmol) in THF (15 mL) at -78°C was added methyl lithium (2.9 mL, 4.4 mmol) slowly. After stirring at -78°C for 5 h, the reaction mixture was quenched with 2 N ammonium chloride (10 mL). The resulting mixture was repeatedly extracted with dichloromethane. The combined extracts were washed with water and brine, dried over anhydrous magnesium sulfate,

filtered and concentrated *in vacuo* to give an oil, which was purified via flash column chromatography using 3:1 hexanes:ethyl acetate as eluent to afford compound **86** (0.9 g, 88%) as a colorless oil. NMR ($CDCl_3$) δ 4.51-4.80 (m, 5 H), 4.07-4.19 (m, 2 H), 3.50-3.91 (m, 4 H), 3.44 and 3.42 (s, 3 H), 3.33 (s, 3 H), 2.92 and 2.91 (s, 3 H), 1.60 (bs, 1 H), 1.17-1.25 (m, 9 H), 0.88 (s, 9 H), 0.06 (s, 3 H), 0.04 (s, 3 H). IR (neat) 3460, 2900, 1675, 1465, 1310, 1250, 1210, 830 cm^{-1}. Mass spectrum m/e 467, 436, 410, 334, 232, 190, 161, 116, 89, 73. High resolution mass spectrum for $C_{21}H_{46}O_8NSi$ (MH^+) requires 468.29929; measured 468.29881. C-13 NMR ($CDCl_3$) δ 157.52, 157.20, 99.75, 99.53, 96.21, 95.85, 89.25, 88.96, 76.71, 75.96, 72.34, 72.24, 63.03, 62.01, 60.98, 55.71, 55.56, 55.33, 55.03, 54.89, 31.15, 30.92, 25.51, 25.24, 25.12, 24.07, 17.88, 17.83, 14.44, 14.23, -5.79.

Amine **87**

To a stirred suspension of lithium aluminum hydride (182 mg, 4.8 mmol) in diethyl ether (10 mL) was added compound **86** (560 mg, 1.2 mmol) in diethyl ether (2 mL) at 0°C. The reaction mixture was heated at reflux for 5 h, cooled to -78°C, diluted with ether (20 mL) and quenched with 2 N ammonium chloride (4 mL). The reaction mixture was filtered through celite and the filter cake was washed thoroughly with ether (4 x 20 mL). The combined filtrate was washed

with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo* to give a yellow oil, which was purified via flash column chromatography using 3:1 hexanes:ethyl acetate as eluent to afford compound **87** (407 mg, 83%) as a viscous liquid. NMR ($CDCl_3$) δ 4.81 (d, 1 H, J = 7 Hz), 4.80 (d, 1 H, J = 7 Hz), 4.74 (d, 1 H, J = 7 Hz), 4.00 (m, 2 H), 4.86 (dd, 1 H, J = 2.5 and 12 Hz), 3.44 (s, 3 H), 3.38 (s, 3 H), 3.16 (d, 1 H, J = 2 Hz), 2.58 (s, 6 H), 2.55-2.57 (m, 1 H), 1.23 (s, 3 H), 1.15 (s, 3 H), 0.87 (s, 9 H), 0.06 (s, 3 H), 0.04 (s, 3 H). IR (neat) 3460, 2920, 1462, 1250, 1145, 1025, 957 cm^{-1}. Mass spectrum 409, 352, 276, 190, 100, 73, 58. High resolution mass spectrum for $C_{19}H_{42}O_6NSi$ (M^+-H) requires 408.27815; measured 408.27890. C-13 NMR ($CDCl_3$) δ 100.29, 96.83, 85.25, 79.59, 73.79, 62.37, 62.13, 56.43, 56.29, 43.31, 29.76, 29.05, 27.64, 25.98, 18.34, -5.34.

Ketone **89**

To a stirred suspension of compound **88** (265 mg, 1.31 mmol) and anhydrous potassium carbonate (181 mg, 1.31 mmol) in acetone (10 mL) at room temperature was added allyl bromide (169 mg, 1.40 mmol). The reaction mixture was heated at reflux for 7 h, poured into ice water and acidified with 2 N hydrochloric acid. The aqueous mixture was repeatedly extracted with dichloromethane. The combined extracts were washed with water and brine, dried over

anhydrous sodium sulfate, filtered and concentrated in vacuo to give a brown residue, which was purified via flash column chromatography using 3:1 hexanes:ethyl acetate as eluent to yield compound 89 (267 mg, 84%) as a bright yellow powder (mp 103-105°C). NMR ($CDCl_3$) δ 13.74 (s, 1 H), 8.44 (d, 1 H, J = 8 Hz), 8.23 (d, 1 H, J = 8 Hz), 7.66 (t, 1 H, J = 8 Hz), 7.57 (t, 1 H, J = 8 Hz), 6.88 (s, 1 H), 6.18 (m, 1 H), 5.52 (bd, 1 H, J = 17 Hz), 5.36 (bd, 1 H, J = 11 Hz), 4.69 (bd, 2 H, J = 5.4 Hz), 2.66 (s, 3 H). IR (film) 3300, 3020, 2936, 1670, 1480, 1160 cm^{-1}. Mass spectrum m/e 242, 230, 201, 183, 173, 155, 127, 102, 77, 51. High resolution mass spectrum for $C_{15}H_{14}O_3$ requires 242.09430; measured 242.09427. C-13 NMR ($CDCl_3$) δ 203.66, 157.52, 146.27, 133.37, 130.58, 129.79, 126.64, 126.02, 124.43, 122.04, 117.60, 112.00, 102.82, 69.60, 27.07.

Diketone 90

To a suspension of hexane-washed sodium hydride (34 mg, 1.42 mmol) in THF (2 mL) was added compound 89 (341 mg, 1.41 mmol) in THF (1 mL). The resulting solution was stirred for 10 min at 0°C. Sorboyl chloride (184 mg, 1.41 mmol) in THF (1 mL) was then added dropwise, and the solution was stirred at 0°C for 30 min. A complex of t-BuOK/t-BuOH (528 mg, 2.84 mmol) was then added in one portion. The reaction mixture was diluted with water and ether and acidified with 6 N hydrochloric acid to pH 6. The aqueous layer was repeatedly

extracted with ether. The combined extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo* to give a brown solid, which was purified via flash column chromatography using 4:1 ether:ethyl acetate as eluent to yield compound **90** (332 mg, 70%) as an orange powder (mp 128-130°C). NMR ($CDCl_3$) δ 14.69 (s, 1 H), 13.58 (s, 1 H), 8.39 (d, 1 H, J = 8 Hz), 8.18 (d, 1 H, J = 8 Hz), 7.49-7.63 (m, 2 H), 7.22 (dd, 1 H, J = 10 and 15 Hz), 6.75 (s, 1 H), 6.06-6.26 (m, 3 H), 6.05 (s, 1 H), 5.91 (d, 1 H, J = 15 Hz), 5.52 (dd, 1 H, J = 1.2 and 17 Hz), 5.35 (dd, 1 H, J = 1.1 and 11 Hz), 4.64 (bd, 2 H, J = 5 Hz), 1.86 (d, 3 H, J = 6 Hz). IR (film) 3300, 3020, 2965, 1620, 1532, 1470, 1420, 1250, 920 cm^{-1}. Mass spectrum m/e 336, 295, 226, 185, 129, 95, 67. High resolution mass spectrum for $C_{21}H_{20}O_4$ requires 336.13616; measured 336.13613. C-13 NMR ($CDCl_3$) δ 194.73, 174.54, 157.33, 146.46, 140.29, 138.89, 133.42, 130.61, 129.33, 126.44, 126.31, 124.13, 123.46, 121.91, 117.47, 111.10, 101.36, 96.67, 69.56, 18.89.

Acetate **92**

To a stirred solution of compound **89** (100 mg, 0.41 mmol) in acetic acid (2 mL) was added acetic anhydride (4 mL) in a culture tube. The reaction mixture was deoxygenated and heated to 200°C for 1 h. The reaction mixture was cooled to room temperature and diluted with ether (60 mL). The

organic layer was extracted with 0.2 N potassium hydroxide twice, washed with water and brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo* to give a yellow solid. The crude product was purified via flash column chromatography using 4:1 hexanes:ethyl acetate as eluent to afford compound **92** (120 mg, 90%) as a white solid (mp 115-118°C). NMR ($CDCl_3$) δ 7.67-7.73 (m, 2 H), 7.46-7.56 (m, 2 H), 5.76-5.91 (m, 1 H), 4.99-5.08 (m, 2 H), 3.43 (bd, 2 H, J = 6 Hz), 2.52 (s, 3 H), 2.43 (s, 3 H), 2.39 (s, 3 H). IR (film) 3025, 2960, 1765, 1685, 1480, 1180, 960 cm^{-1}. Mass spectrum m/e 326, 284, 242, 224, 181, 152, 105, 51. High resolution mass spectrum for $C_{19}H_{18}O_5$ requires 326.11543; measured 326.11508. C-13 NMR ($CDCl_3$) δ 202.20, 169.01, 168.65, 143.32, 143.29, 141.00, 134.84, 132.55, 127.98, 127.90, 127.16, 126.33, 124.81, 121.98, 121.72, 116.92, 32.28, 31.61, 20.61.

Ether **93**

To a stirred solution of compound **81** (1.0 g, 4.1 mmol) in acetone (15 mL) was added methyl iodide (1.8 g, 12.6 mmol) and anhydrous potassium carbonate (1.2 g, 8.7 mmol). The reaction mixture was refluxed for 7 h and then diluted with water (50 mL). The aqueous layer was repeatedly extracted with methylene chloride. The combined extracts were washed with water and brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo* to

give a brown oil. The crude product was purified via flash column chromatography using 5:1 hexanes:ethyl acetate as eluent to yield compound 93 (1.0 g, 95%) as a yellow oil. NMR ($CDCl_3$) δ 8.28-8.36 (m, 1 H), 8.13-8.19 (m, 1 H), 7.53-7.63 (m, 2 H), 7.09 (s, 1 H), 6.10-6.23 (m, 1 H), 5.52 (qd, 1 H, J = 1.5 and 17 Hz), 5.34 (qd, 1 H, J = 1.5 and 11 Hz), 4.73 (bd, 2 H, J = 5 Hz), 3.96 (s, 3 H), 2.79 (s, 3 H). IR (neat) 3060, 2980, 2920, 1660, 1578, 1450, 1405, 1370, 1215, 1090 cm^{-1}. Mass spectrum m/e 256, 244, 215, 201, 183, 173, 155, 127, 101, 51. High resolution mass spectrum for $C_{16}H_{16}O_3$ requires 256.10995; measured 256.10972. C-13 NMR ($CDCl_3$) δ 199.50, 151.83, 150.50, 132.97, 129.13, 128.70, 127.69, 127.03, 126.99, 123.15, 122.56, 117.47, 103.27, 69.04, 63.73, 30.86.

Ketone 94

A solution of ether 93 (1.0 g, 3.9 mmol) in benzene (40 mL) was deoxygenated in a culture tube. It was heated at 210°C for 12 h. The reaction mixture was cooled, concentrated in vacuo, and purified by flash column chromatography to afford compound 94 (0.95 g, 95%) as a yellow oil. NMR ($CDCl_3$) δ 8.14-8.22 (m, 1 H), 8.01-8.07 (m, 1 H), 7.50-7.57 (m, 2 H), 5.95-6.09 (m, 1 H), 5.49 (bs, 1 H), 5.15-5.24 (m, 2 H), 3.87 (s, 3 H), 3.45 (td, 2 H, J = 1.7 and 6 Hz), 2.61 (s, 3 H). IR (neat) 3475, 3060, 2920, 1680, 1580, 1445, 1417, 1366, 1212, 1193, 1070, 990 cm^{-1}.

Mass spectrum m/e 256, 241, 226, 210, 198, 181, 165, 152, 115, 77, 51. High resolution mass spectrum for $C_{16}H_{16}O_3$ requires 256.10995; measured 256.10998. C-13 NMR ($CDCl_3$) δ 205.83, 146.82, 146.39, 135.49, 132.71, 127.21, 126.56, 126.14, 122.07, 121.99, 116.95, 114.07, 63.76, 33.01, 31.54.

General procedure for the reductive methylation

To a mixture of quinone (2 mmol) and tetrabutylammonium bromide (75 mg) in THF (5 mL) and water (2 mL) was added aqueous sodium dithionate (12 mmol). After 15 min at ambient temperature, aqueous potassium hydroxide (46 mmol) was added. After 5 min, dimethyl sulfate (4 mL) was added and the mixture was stirred for 10 h. The product was isolated by partitioning between water and methylene chloride. The crude product was purified by silica gel chromatography.

Ether 95: NMR ($CDCl_3$) δ 6.28 (bs, 2 H), 3.80 (s, 3 H), 3.75 (s, 6 H), 2.24 (s, 3 H). IR (film) 1605, 1500, 1336, 1220, 826, 764 cm^{-1}. Mass spectrum m/e 182, 167, 139, 124, 107. High resolution mass spectrum for $C_{10}H_{14}O_3$ requires 182.0943; measured 182.0943. C-13 NMR ($CDCl_3$) δ 155.78, 155.23, 141.47, 131.94, 106.04, 97.86, 60.16, 55.66, 55.39, 16.01.

Ether 96: NMR ($CDCl_3$) δ 8.05-8.30 (m, 2 H), 6.61 (s, 2 H), 3.92 (s, 6 H). IR (film) 3060, 2930, 1580, 1438, 1380, 1221, 1072 cm^{-1}. Mass spectrum m/e 188, 173, 145, 130, 115,

102, 91, 76. High resolution mass spectrum for $C_{12}H_{12}O_2$ requires 188.0837; measured 188.0835. C-13 NMR ($CDCl_3$) δ 149.599, 126.412, 125.817, 121.808, 103.280, 55.716.

Ether 97: NMR ($CDCl_3$) δ 7.90-8.30 (m, 2 H), 7.15-7.70 (m, 2 H), 6.56 (s, 1 H), 3.97 (s, 3 H), 3.94 (s, 3 H), 3.90 (s, 3 H). IR (film) 1620, 1590, 1445, 1360, 1205, 998, 760 cm^{-1}. Mass spectrum m/e 218, 203, 175, 160, 102. High resolution mass spectrum for $C_{13}H_{14}O_3$ requires 218.0943; measured 218.0944. C-13 NMR ($CDCl_3$) δ 152.42, 148.14, 136.87, 129.34, 126.74, 123.27, 121.97, 121.48, 120.89, 95.59, 61.03, 57.23, 55.55.

Ether 98: NMR ($CDCl_3$) δ 8.02-8.10 (m, 2 H), 7.42-7.58 (m, 2 H), 3.96 (s, 3 H), 3.86 (s, 3 H), 2.52 (s, 3 H). IR (film) 1580, 1459, 1358, 1000, 750 cm^{-1}. Mass spectrum m/e 282, 280, 267, 265, 171, 143, 115, 69. High resolution mass spectrum for $C_{13}H_{13}O_2Br$ requires 280.00949; measured 280.00989. C-13 NMR ($CDCl_3$) δ 150.57, 149.92, 127.93, 127.66, 127.33, 126.52, 126.20, 122.46, 117.26, 61.62, 61.30, 16.66.

Ether 99: NMR ($CDCl_3$) δ 8.01-8.21 (m, 2 H), 7.44-7.59 (m, 2 H), 6.83 (s, 1 H), 3.96 (s, 3 H), 3.85 (s, 3 H). IR (film) 3060, 2912, 1618, 1570, 1452, 1355, 1210, 1100 cm^{-1}. Mass spectrum m/e 268, 266, 253, 251, 225, 223, 188, 157, 129, 101, 75. High resolution mass spectrum for $C_{12}H_{11}O_2Br$ requires 265.99424; measured 265.99426. C-13 NMR ($CDCl_3$) δ

152.28, 146.79, 129.02, 127.37, 127.28, 125.80, 122.61, 121.84, 111.90, 107.96, 61.43, 55.93.

Ether 100: NMR ($CDCl_3$) δ 8.05-8.34 (m, 4 H), 7.22-7.54 (m, 4 H), 4.07 (s, 6 H). IR (film) 3042, 2910, 1621, 1568, 1360, 1220, 1100, 980 cm^{-1}. Mass spectrum m/e 238, 223, 208, 180, 152, 136, 109, 87, 59. High resolution mass spectrum for $C_{16}H_{14}O_2$ requires 238.0994; measured 238.0996. C-13 NMR ($CDCl_3$) δ 148.57, 125.38, 125.00, 122.62, 63.19.

Ether 101: NMR ($CDCl_3$) δ 8.20-8.50 (m, 2 H), 7.26-7.68 (m, 2 H), 6.58 (s, 2 H), 3.98 (s, 12 H). IR (film) 1620, 1450, 1355, 1252, 1080 cm^{-1}. Mass spectrum m/e 298, 283, 252, 225, 149. High resolution mass spectrum for $C_{18}H_{18}O_4$ requires 298.1205; measured 298.1208. C-13 NMR ($CDCl_3$) δ 150.52, 148.90, 126.85, 125.93, 122.95, 119.86, 104.20, 63.46, 56.91.

Ether 102: NMR ($CDCl_3$) δ 8.18-8.40 (m, 2 H), 8.05 (d, 1 H, J = 2 Hz), 7.43-7.55 (m, 2 H), 6.81 (d, 1 H, J = 2 Hz), 4.05 (s, 6 H), 3.98 (s, 3 H). IR (film) 1590, 1300, 1055, 755 cm^{-1}. Mass spectrum m/e 348, 346, 333, 331, 209, 151. High resolution mass spectrum for $C_{17}H_{15}O_3Br$ requires 346.0204; measured 346.0205. C-13 NMR ($CDCl_3$) δ 157.24, 149.60, 147.16, 128.85, 127.71, 127.12, 126.52, 125.93, 125.60, 123.43, 122.08, 119.37, 117.04, 107.61, 63.57, 62.97, 56.37.

Ether 103: NMR ($CDCl_3$) δ 7.81 (d, 2 H, J = 8 Hz), 7.16-7.46 (m, 2 H), 6.68 (d, 2 H, J = 7 Hz), 4.02 (s, 9 H), 3.88 (s, 3 H). IR (film) 3020, 2920, 1640, 1462, 1350, 1251, 1080 cm^{-1}. Mass spectrum m/e 298, 283, 268, 253. High resolution mass spectrum for $C_{18}H_{18}O_4$ requires 298.1205; measured 298.1207. C-13 NMR ($CDCl_3$) δ 157.51, 150.95, 147.43, 127.55, 125.76, 119.10, 114.66, 104.31, 63.62, 62.43, 56.31.

Phenol 109a

To a well stirred suspension of 1,5-dihydroxynaphthalene (20.0 g, 120 mmol) in glacial acetic acid (500 mL) at 80° was added bromine (13 mL, 240 mmol) in acetic acid (50 mL) slowly. After addition, the reaction mixture was stirred for 15 min. On standing at room temperature, the green needles were separated. Recrystallization of this substance from acetic acid afforded 109a (30.9 g, 81%) as pale green crystals (mp 223-225°C). NMR ($CDCl_3$) δ 8.55 (s, 2 H), 7.73 (d, 2 H, J = 9 Hz), 7.56 (d, 2 H, J = 9 Hz. IR (film) 3400, 3060, 1620, 1570, 1375, 1220, 1105, 975 cm^{-1}. Mass spectrum m/e 320, 318, 316, 241, 239, 211, 209, 129, 102, 75. High resolution mass spectrum for $C_{10}H_6O_2Br_2$ requires 315.87345; measured 315.87350. C-13 NMR (D_6-acetone) δ 150.68, 130.87, 127.28, 116.73, 106.39.

Phenol 109b

To a stirred solution of compound 109a (10.0 g, 31.4 mmol) and sodium hydroxide (3.8 g, 94.3 mmol) in water (60 mL) was added dimethyl sulfate (7.8 g, 62.0 mmol). The reaction mixture was stirred for 2 h at room temperature and filtered. The alkaline filtrate was acidified with 6 N hydrochloric acid and a white precipitate was separated. Recrystallization of this precipitate from alcohol afforded 109b (5.2 g, 50%) as colorless needles (mp 148-150°C). NMR ($CDCl_3$) δ 7.88 (d, 1 H, J = 9 Hz), 7.59 (d, 2 H, J = 9 Hz), 7.52 (d, 1 H, J = 9 Hz), 5.99 (s, 1 H), 3.98 (s, 3 H). IR (film) 3350, 3040, 1530, 1140, 965 cm^{-1}. Mass spectrum m/e 334, 332, 330, 319, 317, 315, 291, 289, 287, 178, 129, 100, 74. High resolution mass spectrum for $C_{11}H_8O_2Br_2$ requires 329.88910; measured 329.88933. C-13 NMR ($CDCl_3$) δ 153.09, 148.59, 130.53, 129.64, 129.42, 124.91, 119.80, 115.66, 114.10, 104.98, 61.56.

Quinone 61

To a well stirred suspension of compound 109b (0.5 g, 1.5 mmol) in glacial acetic acid (5 mL) at 0°C was added chromium trioxide (1.1 g, 11.0 mmol) in water (3 mL). The reaction mixture was allowed to stir at room temperature for 6 h, diluted with water (20 mL), and filtered through sinter glass funnel. The yellow precipitate was washed thoroughly with distilled water and dried under vacuum.

Recrystallization of the precipitate from aqueous alcohol afforded quinone 61 (325 mg, 63%) as bright yellow needles (mp 174-176°C). NMR ($CDCl_3$) δ 7.97 (d, 1 H, J = 8 Hz), 7.87 (d, 1 H, J = 8 Hz), 7.44 (s, 1 H), 3.94 (s, 3 H). IR (film) 3035, 2962, 1665, 1325, 1120 cm^{-1}. Mass spectrum m/e 348, 346, 344, 330, 328, 326, 317, 267, 265, 237, 209, 87, 53. High resolution mass spectrum for $C_{11}H_6O_3Br_2$ requires 343.86836; measured 343.86845. C-13 NMR ($CDCl_3$) δ 180.43, 177.23, 156.97, 141.46, 138.45, 137.80, 131.77, 128.23, 125.04, 124.92, 61.70.

Quinone 110

To diisopropylamine (0.06 mL, 0.38 mmol) in dry THF (3 mL) at -78°C under nitrogen was added n-BuLi (0.13 mL, 0.32 mmol) dropwise. The solution was stirred for 15 min and a solution of anhydride 60 (46.8 mg, 0.29 mmol) in THF (1 mL) was added dropwise. After addition, the reaction mixture was stirred for 5 min and a solution of quinone 110 (100 mg, 0.29 mmol) in THF (1 mL) was added. The resulting mixture was allowed to warm to room temperature and stirred for 4 h. The reaction mixture was then added water (5 mL), acidified with 6 N hydrochloric acid and extracted repeatedly with chloroform. The combined extracts were washed with water and brine, dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo. The crude product was recrystallized from acetone (2 mL) to give compound 110

(78.0 mg, 70%) as orange solid (mp 257-259°C). NMR ($CDCl_3$) δ 14.28 (s, 1 H), 8.44 (d, 1 H, J = 8 Hz), 8.19 (s, 1 H), 8.05 (d, 1 H, J = 8 Hz), 7.95 (d, 1 H, J = 8 Hz), 7.92 (d, 1 H, J = 8 Hz), 7.59-7.71 (m, 2 H), 4.04 (s, 3 H). IR (film) 3360, 3020, 2965, 1665, 1320, 1140 cm^{-1}. Mass spectrum m/e 384, 382, 274, 257, 189, 95. High resolution mass spectrum for $C_{19}H_{11}O_4Br$ requires 381.98407; measured 381.98331. C-13 NMR ($CDCl_3$) δ 186.61, 163.48, 157.91, 136.63, 135.43, 131.42, 130.38, 129.41, 128.92, 128.15, 127.41, 124.84, 124.31, 121.92, 121.82, 115.61, 111.88, 109.09, 61.82.

Napthacene (59)

To a mixture of quinone 110 (100 mg, 0.26 mmol) and tetrabutylammonium bromide (20 mg) in THF (5 mL) and water (2 mL) was added aqueous sodium dithionate (455 mg, 2.6 mmol). After 15 min at ambient temperature, aqueous potassium hydroxide 756 mg, 13.5 mmol) was added. After 2 min, dimethyl sulfate (4 mL) was added and the mixture was stirred for 10 h. The product was isolated by partitioning between water and methylene chloride. The crude product was purified by silica gel chromatography to afford compound 59 (56 mg, 51%). NMR ($CDCl_3$) δ 8.89 (s, 1 H), 8.60 (d, 1 H, J = 8 Hz), 8.00-8.09 (m, 2 H), 7.38-7.58 (m, 3 H), 4.13 (s, 3 H), 4.12 (s, 3 H), 4.08 (s, 3 H), 4.01 (s, 3 H). IR (film) 3025, 2912, 1610, 1572, 1320, 1240, 1105 cm^{-1}. High resolution mass spectrum for $C_{22}H_{19}O_4Br$ requires 426.04667;

measured 426.04648. C-13 NMR ($CDCl_3$) δ 157.30, 151.40, 149.60, 147.26, 128.76, 128.52, 127.81, 127.36, 127.10, 126.59, 125.90, 125.48, 123.50, 122.42, 120.35, 119.92, 117.18, 109.30, 63.49, 62.56, 57.48, 56.93.

Alcohol 112

To a stirred solution of compound 111 (2.83 g, 11.24 mmol) in THF (25 mL) and ether (15 mL) at -78°C under nitrogen atmosphere was added n-butyllithium (4.5 mL, 11.24 mmol) dropwise. The reaction mixture was stirred for 30 min at -78°C. Ketone 85 (3.90 g, 8.65 mmol) in THF (5 mL) was added slowly. After addition, the solution was warmed slowly to 0°C and stirred for 15 min. The resulting mixture was quenched with 2 N ammonium chloride (30 mL) and extracted repeatedly with dichloromethane. The combined extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo to give a yellow residue, which was purified via flash column chromatography using 4:1 hexanes:ethyl acetate as eluent to afford compound 112 (3.25 g, 60%) as a viscous liquid. NMR ($CDCl_3$) δ 7.38 (s, 1 H), 6.86 (bs, 1 H), 4.45-4.85 (m, 5 H), 4.10-4.23 (m, 3 H), 3.87 (s, 3 H), 3.78 (s, 3 H), 3.60-3.77 (m, 2 H), 3.36 (s, 3 H), 3.33 (s, 2 H), 2.99 (s, 3 H), 1.61 (s, 3 H), 1.25 (t, 3 H, J = 7 Hz), 0.88 (s, 9 H), 0.06 (s, 3 H), 0.04 (s, 3 H). IR (neat) 3450, 2930, 1665, 1485, 1370, 1250, 1200, 830 cm^{-1}. High resolution mass spectrum for

$C_{28}H_{50}O_{10}ClNSi$ requires 623.2884; measured 623.2892. C-13 NMR ($CDCl_3$) δ 157.60, 157.49, 153.52, 151.43, 147.25, 130.43, 125.42, 115.29, 113.48, 97.48, 96.21, 89.42, 88.65, 84.76, 79.50, 75.66, 75.42, 65.07, 63.87, 62.95, 56.79, 55.19, 55.08, 31.56, 31.20, 26.79, 26.03, 17.80, 17.12, 14.45, 14.30, -5.71, -5.61.

Alcohol 113

To a stirred solution of compound 112 (2.82 g, 4.53 mmol) in THF (9 mL) at room temperature was added tetrabutylammonium fluoride (4.53 mL, 4.53 mmol). After stirring for 3 h, 2 N ammonium chloride (10 mL) was added and the resulting mixture was repeatedly extracted with dichloromethane. The combined extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo to give an oil, which was purified via flash column chromatography using 1:1 hexanes:ethyl acetate as eluent to afford compound 113 (2.23 g, 97%) as a colorless oil. NMR ($CDCl_3$) δ 7.12 (s, 1 H), 7.00 (bs, 1 H), 4.95-5.21 (m, 2 H), 4.51-4.80 (m, 4 H), 4.17 (bq, 2 H, J = 7 Hz), 3.90 (s, 3 H), 3.82 (m, 2 H), 3.79 (s, 3 H), 3.38 (s, 3 H), 3.32 (m, 1 H), 3.25 (bs, 3 H), 3.00 (s, 3 H), 1.92 (bs, 3 H), 1.29 (bt, 3 H, J = 7 Hz). IR (neat) 3450, 3022, 2940, 1680, 1490, 1400, 1370, 1262, 1210, 915 cm^{-1}. High resolution mass spectrum for $C_{22}H_{36}O_{10}ClN$ requires 509.20188; measured 509.20176. C-13 NMR ($CDCl_3$) δ 157.69,

157.38, 153.50, 151.49, 131.27, 128.60, 127.69, 124.05, 119.87, 99.87, 99.10, 97.36, 95.60, 89.30, 88.73, 77.71, 76.05, 73.01, 72.56, 67.21, 65.40, 63.23, 62.51, 60.75, 55.61, 55.43, 55.10, 54.62, 31.18, 30.92, 26.71, 26.42, 24.18, 14.45.

Lactone 114

To a well stirred solution of dry pyridine (10 mL, 100 mmol) in dichloromethane (100 mL) at 0°C was added chromium trioxide (5.0 g, 50 mmol) in portions under nitrogen atmosphere. Stirring was continued for 10 min at room temperature after complete addition. Compound 113 (2.5 g, 5.1 mmol) was added to the freshly prepared Collins reagent solution and the reaction mixture was stirred for 1 h. The dark mixture was passed through a column containing silica gel with ethyl acetate as solvent and the combined solution was concentrated in vacuo. The resulting crude product was purified via flash column chromatography using 2:1 hexanes:ethyl acetate as eluent to yield compound 114 (2.1 g, 81%) as a viscous liquid. NMR ($CDCl_3$) δ 7.02 (s, 1 H), 6.95 (s, 1 H), 4.97-5.21 (m, 2 H), 4.60-4.75 (m, 2 H), 4.55 (m, 1 H), 4.17 (bq, 2 H, J = 7 Hz), 3.87 (s, 3 H), 3.78 (s, 3 H), 3.38 (s, 3 H), 3.35 (m, 1 H), 3.25 (bs, 3 H), 3.01 (s, 3 H), 1.93 (bs, 3 H), 1.27 (bt, 3 H, J = 7 Hz). IR (neat) 2925, 1740, 1685, 1495, 1460, 1375, 1210, 1150, 1030, 905 cm^{-1}. High resolution mass spectrum for $C_{22}H_{32}O_{10}ClN$

requires 505.17056; measured 505.17102. C-13 NMR ($CDCl_3$) δ 169.94, 155.81, 150.05, 148.43, 122.36, 113.98, 113.63, 112.23, 96.92, 96.59, 84.79, 79.50, 75.77, 70.09, 63.99, 62.05, 56.72, 56.19, 55.77, 34.82, 27.75, 14.50.

Quinone 115

To a solution of ceric ammonium nitrate (3.3 g, 6.0 mmol) in water (4 mL) and acetonitrile (2 mL) at 0°C was added compound 114 (500 mg, 1.0 mmol) in acetonitrile (5 mL) and potassium acetate (394 mg, 4.0 mmol). After addition, the reaction mixture was allowed to warm to room temperature and stirred for 1 h. The resulting mixture was repeatedly extracted with dichloromethane. The combined extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo to give crude product 115 (432 mg, 91%) as an orange substance. NMR ($CDCl_3$) δ 7.13 (s, 1 H), 6.97 (s, 1 H), 5.45 (d, 1 H, J = 7 Hz), 5.19 (m, 1 H), 4.72 (d, 1 H, J = 7 Hz), 4.68 (m, 1 H), 4.21 (bq, 2 H, J = 7 Hz), 3.34 (m, 1 H), 3.38 (s, 3 H), 3.27 (s, 3 H), 1.89 (bs, 3 H), 1.31 (t, 3 H, J = 7 Hz). IR (film) 2920, 2840, 1750, 1670, 1660, 1475, 1370, 1020, 915 cm^{-1}. High resolution mass spectrum for $C_{20}H_{26}O_{10}ClN$ requires 475.12358; measured 475.12381. C-13 NMR ($CDCl_3$) δ 181.43, 177.65, 170.90, 156.77, 153.59, 140.59, 137.45, 136.90, 98.70, 96.33, 76.24, 69.50, 68.78, 65.41, 60.20, 57.23, 56.42, 38.50, 27.89, 14.30.

Alcohol 116

To a stirred solution of compound 59 (100 mg, 0.23 mmol) in THF (1 mL) at -78°C under nitrogen atmosphere was added n-butyllithium (0.10 mL, 0.23 mmol) dropwise. The reaction mixture was stirred for 30 min at -78°C. Ketone 85 (104 mg, 0.23 mmol) in THF (1 mL) was added slowly. After addition, the solution was warmed slowly to 0°C and stirred for 15 min. The resulting mixture was quenched with 2 N ammonium chloride (10 mL) and extracted repeatedly with dichloromethane. The combined extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo to give an orange residue, which was purified via flash column chromatography using 4:1 hexanes:ethyl acetate as eluent to afford compound 116 (96 mg, 52%) as an orange liquid. NMR ($CDCl_3$) δ 8.18-8.25 (m, 3 H), 7.43-7.62 (m, 4 H), 4.56-4.89 (m, 4 H), 4.04-4.21 (m, 6 H), 4.00, 3.99 and 3.97 (s, 12 H), 3.36, 3.31 and 3.29 (s, 6 H), 3.01 and 2.98 (s, 3 H), 1.79 (s, 3 H), 1.10-1.31 (m, 3 H), 0.90 and 0.88 (s, 9 H), 0.04 and 0.03 (s, 6 H). IR (film) 3440, 3020, 2975, 1670, 1435, 1220, 1160, 916 cm^{-1}. Mass spectrum m/e 799 (M^+), 761, 629, 601, 432, 351, 173.

Alcohol 117

To a stirred solution of compound 116 (65 mg, 0.08 mmol) in THF (1 mL) at room temperature was added tetrabutylammonium fluoride (0.08 mL, 0.08 mmol). After

stirring for 3 h at room temperature, 2 N ammonium chloride (5 mL) was added and the resulting mixture was repeatedly extracted with dichloromethane. The combined extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo to give an orange residue, which was purified via flash column chromatography using 2:1 hexanes:ethyl acetate as eluent to afford compound 117 (53 mg, 97%) as an orange oil. NMR ($CDCl_3$) δ 8.25 (d, 1 H, J = 8 Hz), 7.98 (d, 1 H, J = 8 Hz), 7.41-7.58 (m, 5 H), 4.21-4.80 (m, 6 H), 4.02-4.09 (m, 2 H), 4.01, 4.00, 3.98, 3.96 (s, 12 H), 3.32 (s, 3 H), 3.26 (s, 3 H), 2.96, 2.94 (s, 3 H), 1.79 (s, 3 H), 1.22 (t, 3 H, J = 7 Hz). IR (neat) 3450, 3020, 2975, 1665, 1220, 1150, 945 cm^{-1}. Mass spectrum m/e 685 (M^+), 660, 547, 479, 243.

REFERENCES

1. Bhuyan, B. K.; Smith, C. G. Proc. Natl. Acad. Sci. U.S.A. 1965, 54, 566.

2. Bhuyan, B. K.; Dietz, A. Antimicrob. Agents Chemother. 1965, 836.

3. Wiley, P. F.; MacKellar, F. A.; Caron, E. L. Tetrahedron Lett. 1968, 663.

4. Wiley, P. F.; Elrod, D. W.; Houser, D. J.; Johnson, J. L.; Pschigoda, L. M.; Krueger, W. C. J. Org. Chem. 1979, 44, 4030.

5. Wiley, P. F.; Kelly, R. B.; Caron, E. L.; Wiley, V. H.; Johnson, J. H.; MacKellar, F. A.; Mizsak, S. A. J. Am. Chem. Soc. 1977, 99, 542.

6. Wiley, P. F.; Duchamp, D. J., Hsiung, V.; Chidester, C. G. J. Org. Chem. 1971, 36, 2670.

7. Arora, S. K. J. Am. Chem. Soc. 1983, 105, 1328.

8. Brockman, H.; Niemeyer, J. Chem. Ber. 1967, 100, 3578.

9. Wiley, P. F. J. Nat. Prod. 1979, 42, 570.

10. Wiley, P. F.; Johnson, J. L.; Houser, D. J. J. Antibiot. 1977, 30, 628.

11. Eckle, E.; Stezowski, J. J. Tetrahedron Lett. 1980, 21, 507.

12. Bhuyan, B. K.; Reusser, F. Cancer Res. 1970, 30, 984.

13. Neil, G. L.; Kuentzel, S. L.; McGovren, J. P. Cancer Treat. Rep. 1979, 63, 1971.

14. Li, L. H.; Kuentzel, S. L.; Murch, L. L.; Pschigoda, L. M.; Krueger, W. C. Cancer Res. 1979, 39, 4816.

15. Lenaz, L.; Page, J. A. Cancer Treat. Rev. 1976, 39, 111.

16. Minow, R. A.; Benjamin, R. S.; Gottlieb, J. A. Cancer Chemother. Rep. 1975, 6, 195.

17. Benjamin, R. S.; Mason, J. W.; Billingham, M. E. Cancer Treat. Rep. 1978, 62, 975.

18. McGovren, J. P.; Neil, G. L.; Denlinger, R. H.; Thomas, L. H.; Crampton, S. L.; Swenberg, J. A. Cancer Res. 1979, 39, 4849.

19. Calendi, E.; Di Marco, A.; Reggiani, M.; Scarpinato, M. B.; Valentini, L. Biochim. Biophys. Acta 1965, 103, 25.

20. Kersten, W.; Kersten, H.; Szybalski, W. Biochemistry 1966, 5, 236.

21. Lerman, L. S. J. Mol. Biol. 1961, 3, 18.

22. Waring, M. J. Nature (London) 1968, 219, 1320.

23. Zunino, F.; Gambetta, R.; Di Marco, A.; Zaccara, A. Biochim. Biophys. Acta 1972, 277, 489.

24. Zunino, F.; Gambetta, R.; Di Marco, A.; Luoni, G.; Zaccara, A. Biochim. Biophys. Res. Commun. 1976, 69, 744.

25. Barthelemy-Clavey, V.; Maurizot, J. C.; Sicard, P. J. Biochimie 1973, 55, 859.

26. Dalgleish, D. G.; Fey, G.; Kersten, W. Biopolymers 1974, 13, 1757.

27. Quadrifoglio, F.; Crescenzi, V. Biophys. Chem. 1974, 2, 64.

28. Hillig, K. W.; Morris, M. D. Biochim. Biophys. Res. Commun. 1976, 71, 1228.

29. Neidle, S. Prog. Med. Chem. 1979, 16, 196.

30. Plumbridge, T. W.; Brown, J. R. Biochem. Pharmcol. 1979, 28, 3231.

31. Chowdhury, K.; Chowdhury, I.; Biswas, N.; Neogy, R. K. Indian J. Biochem. Biophys. 1978, 15, 373.

32. Saunders, G. F.; Reese, W. N.; Saunders, P. P. Biochim. Biophys. Acta 1969, 190, 406.

33. Neogy, R. K.; Chowdhury, K.; Thakurta, G. G. Biochim. Biophys. Acta 1973, 299, 241.

34. Ellem, K. A. O.; Rhode, III, S. L. Biochim. Biophys. Acta 1970, 209, 415.

35. Arrighi, F. E. J. Cell. Physiol. 1967, 69, 45.

36. Waring, M. J. Mol. Biol. 1970, 54, 247.

37. Sinha, R. K.; Talapatra, P.; Mitra, A.; Mazumder, S. Biochim. Biophys. Acta 1977, 474, 199.

38. Richardson, C. L.; Grant, A. D.; Schpok, S. L.; Krueger, W. C.; Li, L. H. Cancer Res. 1981, 41, 2235.

39. Neil, G. L.; Blowers, C. L.; Houser, D. J.; Wiley, P. F. Proc. Am. Assoc. Cancer Res. 1977, 18, 2.

40. Ishi, K.; Kondo, S.; Nishimura, Y.; Hamada, M.; Takeuchi, T.; Umezawa, H. J. Antibiot. 1983, 36, 1569.

41. Kawai, H.; Hayakawa, Y.; Nakagawa, M.; Imamura, K.; Tanabe, K.; Shimazu, A.; Seto, H.; Otake, N. J. Antibiot. 1983, 36, 1569. Kawai, H.; Hayakawa, Y.; Nakagawa, M.; Furihata, K.; Seto, H.; Otake, N. Tetrahedron Lett. 1984, 25, 1937. Kawai, H.; Hayakawa, Y.; Nakagawa, M.; Furihata, K.; Seto, H.; Otake, N. Tetrahedron Lett. 1984, 25, 1941.

42. DeShong, P.; Leginus, J. M. Tetrahedron Lett. 1984, 25, 5355.

43. Hauser, F. M.; Adams, T. C., Jr. J. Org. Chem. 1984, 49, 1169.

44. Hauser, F. M.; Ellenberger, W. P.; Adams, T. C., Jr. J. Org. Chem. 1984, 49, 2296.

45. Bates, M. A.; Sammes, P. G. J. Chem. Soc., Chem. Commun. 1983, 896.

46. Joyce, R. P.; Parvez, M.; Weinreb, S. M. Tetrahedron Lett. 1986, 27, 4885.

47. Vatele, J. M. Tetrahedron 1986, 42, 4443.

48. Smith, T. H. J. Org. Chem. 1987, 52, 3566.

49. Kawasaki, M.; Matsuda, F.; Terashima, S. Tetrahedron Lett. 1986, 27, 2145.

50. Kraus, G. A.; Man, T. O. Synth. Commun. 1986, 16, 1037.

51. Hudson, C. S. J. Am. Chem. Soc. 1925, 47, 265.

52. Jones, J. K. N.; Kent, P. W.; Stacey, M. J. Chem. Soc. 1947, 1341.

53. Valls, J.; Toromanoff, E. Bull. Soc. Chim. Fr. 1961, 758. Shoppee, C. W.; Jones, D. N.; Summers, G. H. R. J. Chem. Soc. 1957, 3100. Parker, R. E.; Isaacs, N. S. Chem. Rev. 1959, 59, 737.

54. Czernecki, S.; Georgoulis, C.; Provelenghiou, C. Tetrahedron Lett. 1976, 3535.

55. Corey, E. J.; Bock, M. G.; Kozikowski, A. P.; Rama Rao, A. V.; Floyd, D.; Lipshutz, B. Tetrahedron Lett. 1978, 1051.

56. Stork, G.; Takahashi, T. J. Am. Chem. Soc. 1972, 94, 7827.

57. Heathcock, C. H.; Ratcliffe, R. J. Am. Chem. Soc. 1971, 93, 1746.

58. Collins, C.; Hess, W. W. Org. Synth. 1972, 52, 5.

59. Corey, E. J.; Venkateswarlu, A. J. Am. Chem. Soc. 1972, 94, 6190.

60. Kraus, G. A.; Fulton, B. S. J. Org. Chem. 1985, 50, 1782. Kraus, G. A.; Fulton, B. S. Tetrahedron 1984, 40, 4777. Kraus, G. A.; Woo, S. H. J. Org. Chem. 1987, 52, 4841.

61. Baker, W.; Lothian, D. M. J. Chem. Soc. 1936, 274.

62. Kraus, G. A.; Fulton, B. S.; Woo, H. S. J. Org. Chem. 1984, 49, 3212. Hauser, C. R. Org. React. (N.Y.) 1954, 8, 168.

63. Vyas, G. N.; Shah, N. M. Org. Synth., Coll. Vol. IV 1963, 836.

64. Manecke, G.; Storck, W. Chem. Ber. 1961, 94, 3246 and references therein.

65. Kraus, G. A.; Roth, B. J. Org. Chem. 1978, 43, 4923. Gonzalez, A. G.; Alvarez, M. A.; Martin, J. D.; Norte, M.; Perez, C.; Rovirosa, J. Tetrahedron 1982, 38, 719. Chorn, T. A.; Giles, R. G. F.; Green, I. R.; Mitchell, P. R. K. J. Chem. Soc., Perkin Trans. I 1983, 1249. Giles, R. G. F.; Green, I. R.; Hugo, V. I.; Mitchell, P. R. K.; Yorke, S. C. J. Chem. Soc., Perkin Trans. I 1984, 2383.

66. Neumann, G.; Neumann, W. P. J. Organometal. Chem. 1972, 42, 277.

67. Snyder, C. D.; Rapoport, H. J. Am. Chem. Soc. 1972, 94, 277.

68. Tamura, Y.; Sasho, M.; Nakagawa, K.; Tsugoshi, T.; Kita, Y. J. Org. Chem. 1984, 49, 473. Tamura, Y.; Wada, A.; Sasho, M.; Fukunaga, K.; Maeda, H.; Kita, Y. J. Org. Chem. 1982, 47, 4376. Tamura, Y.; Akai, S.; Sasho, M.; Kita, Y. Tetrahedron Lett. 1984, 1167. Tamura, Y.; Mohri, S.; Maeda, H.; Tsugoshi, T.; Sasho, M.; Kita, Y. Tetrahedron Lett. 1984, 309. Tamura, Y.; Sasho, M.; Akai, S.; Wada, A.; Kita, Y. Tetrahedron 1984, 40, 4539.

69. Carter, A. H.; Race, E.; Rowe, F. M. J. Chem. Soc. 1942, 236.

70. Cram, D. J.; Wilson, D. R. J. Am. Chem. Soc. 1963, 85, 1245.

ACKNOWLEDGMENTS

"Art is I; science is we."

Claude Bernard,
French Physiologist (1813-1878)

I would like to express my deepest gratitude to my advisor, Dr. Kraus, for his invaluable guidance and enthusiastic encouragement throughout the course of this investigation. His continuous enthusiasm and pleasant personality have helped me to eliminate the "graduate student syndrome" at the early stage of my research.

Secondly, I would like to thank all the members of my family and my friends in Hong Kong for their support, love and encouragement throughout my life.

Thirdly, I want to thank all the members of Kraus' group and my friends at Iowa State University for their amiable friendship. The sharing of experiences with them in different areas was really enjoyable.

Last, but not least, I want to thank Nancy Qvale for preparing this manuscript. Her professional and skillful typing is greatly appreciated.