DISSERTATION

SYNTHESIS OF CARBOCYCLIC AND 4'-DISUBSTITUTED NUCLEOSIDE ANALOGS AND PROGRESS TOWARDS THE SYNTHESIS OF BIPYRIMIDINE-BRIDGED BIS-DIOXOCYCLAMS

Submitted by

Lisa K. Geisler

Department of Chemistry

In partial fulfillment of the requirements

For the Degree of Doctor of Philosophy

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WE HEREBY RECOMMEND THAT THE DISSERTATION PREPARED UNDER OUR SUPERVISION BY LISA KAY GEISLER ENTITLED SYNTHESIS OF CARBOCYCLIC AND 4'-DISUBSTITUTED NUCLEOSIDE ANALOGS AND PROGRESS TOWARDS THE SYNTHESIS OF BIPYRIMIDINE-BRIDGED BIS-DIOXOCYCLAMS BE ACCEPTED AS FULFILLING IN PART REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY.

Committee on Graduate Work

Ellen R. Fisher

Alan J. Kennan

Richard G. Finke

Julia M. Inamine

Louis S. Hegedus/Advisor

C. Michael Elliott/Department Head/Director

ABSTRACT OF DISSERTATION

SYNTHESIS OF CARBOCYCLIC AND 4'-DISUBSTITUTED NUCLEOSIDE ANALOGS AND PROGRESS TOWARDS THE SYNTHESIS OF BIPYRIMIDINE-BRIDGED BIS-DIOXOCYCLAMS

(-)-5-Benzyloxymethyl-5-ethoxy-5*H*-furan-2-one has been synthesized using chromium carbene chemistry; this versatile nucleoside template was then used for the total synthesis of (+)-neplanocin A. This synthesis showcased the development of a new reaction, a one-pot ring opening, intramolecular Wadsworth-Emmon reaction and was the first total synthesis of (+)-neplanocin A. During the synthesis insight was gained in the stereoselectivity of the *cis*-dihydroxylation of 5-benzyloxymethyl-5-ethoxy-5*H*-furan-2-one.

Benzyloxymethyl-5-ethoxy-5*H*-furan-2-one was also utilized in the *de novo* synthesis a series of 4'-disubstituted nucleoside analogs. The 4'-ethoxy-dideoxy- and 4'-ethoxy-dideoxydidehydronucleoside analogs were synthesized in good overall yield. Studies were performed on the synthesis of 4'-ethoxythymidine and 4'-ethoxy-2'-deoxythymidine to give the correct stereochemistry at the 2'- and 3'-positions. However, the desired diol could not be formed selectively. Synthesis of "unnatural" 2',3'-α-OH diastereomers was examined but the synthesis was hindered by the instability of the intermediates during formation of the glycosidic bond.

Chromium carbene chemistry was also used to synthesize novel 5,12-dioxocyclams and studies were performed on the synthesis of bipyrimidine-bridged bis-dioxocyclams. The tetrakis(bromomethyl)bipyrimidine bridge was synthesized. Attempts were made to synthesize bipyrimidine-bridged bis-dioxocyclams; however, the reaction was hindered by low yields or purification problems.

Lisa Kay Geisler
Chemistry Department
Colorado State University
Fort Collins, CO 80523
Fall 2002

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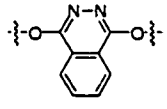
LIST OF ABBREVIATIONS

AIBN	azobisisobutyronitrile
AD mix $\alpha^{®}$	contains $K_3Fe(CN)_6$, K_2CO_3, chiral ligand $(DHQ)_2$-PHAL, and $K_2OsO_2(OH)_4$
AD mix $\beta^{®}$	which contains $K_3Fe(CN)_6$, K_2CO_3, chiral ligand $(DHQD)_2$-PHAL, and $K_2OsO_2(OH)_4$
CBz	phenylmethoxycarbonyl
CEM cells	central nucleus medial cells
COSY	correlation spectroscopy referring to the homonuclear proton-proton correlation
Cp	cyclopentadiene
CSA	camphorsulfonic acid
DDC	1,3-dicyclohexyl carbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DHQ	dihydroquinine
DHQD	dihydroquinidine
DI	deionized
DMAP	N,N-dimethyl 4-pyridinamine
DMF	N,N-dimethylformamide
DMSO	dimethyl sulfoxide
dppf	1,1-bis(diphenylphosphino)ferrocene
EC_{50}	50% effective concentration

exact mass	calculations are based on the exact mass of only the most abundant isotopes for each element
FAB-HRMS	Fast Atom Bombardment-High Resolution Mass Spectrometry referring to the use of a Cs ion gun and can also be called FIB-HRMS
FCC	flash column chromatography
HSQC	Heteronuclear Single Quantum Coherence
Hunig's base	N,N-diisopropylethyl amine
m-CPBA	*meta*-chloro peroxybenzoic acid
IC_{50}	50% inhibitory concentration
MOM	methoxymethyl chloride
molecular weight	calculations are based on the average of the exact masses for all naturally occurring isotopes weighted by their percent abundance for each element
NBS	N-bromosuccinimide
NMO	N-methyl morpholine N-oxide
NMR	Nuclear Magnetic Resonance
nOe	nuclear Overhauser enhancement
PBM	peripheral blood mononuclear
PDC	pyridinium dichromate
PHAL	
PPTS	pyridinum p-toluene sulfonate
PPh_3	triphenylphosphine
PTLC	Preparative Thin Layer Chromatography
Rochelle's Salt	saturated, aqueous sodium potassium tartrate
$RuCl_3$	"$RuCl_3 \cdot xH_2O$" – a mixture of mono- and polymetallic oxides,

	hydroxides, and chlorides of ruthenium (III) and –(IV)
SAH	s-adenosylhomocysteine
SM	starting material
TBAF	tetrabutylammonium fluoride
TBS or TBDPS	*tert*-butyldiphenylsilane
TES	triethylsilyl
TMS	trimethylsilyl
TsOH	*para*-toluenesulfonic acid
TsCl	4-methyl benzenesulfonyl chloride
Vero Cells	african green monkey kidney cells

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PREFACE

There are two main aspects of synthesis in organic chemistry: (1) total synthesis and (2) methodology. The main goal of total synthesis is completion of a final compound. Efficiency and design are factors in the synthesis but can be sacrificed to complete the molecule. The second aspect of synthetic organic chemistry, methodology, focuses on the design and understanding of new organic reactions, as well as understanding the scope and limitation of these systems. Synthetic organic research can combine both aspects by performing total synthesis of a compound in which a new reaction is being developed. Finishing the compound becomes secondary and the total synthesis becomes a place to showcase new and interesting chemistry. An additional feature of synthetic organic chemistry is the synthesis of complex molecular systems. These systems can be used in the development of new materials with a wide range of applications. This thesis describes three projects that address each of these aspects of synthetic organic chemistry.

The total synthesis of neplanocin A is presented in the first chapter. The goal of this project was the synthesis of (-)-neplanocin A with the focus being the design of a new reaction, a one-pot ring opening, intramolecular Wadsworth-Emmon reaction. (-)-Neplanocin A has been synthesized before and the question becomes "Why synthesize a compound that has been synthesized before?" The answer to this question lies in the work on neplanocin A. Since a known

literature compound was being synthesized, the total synthesis process can be evaluated by matching the data of the final compound to the literature data. Upon completion of neplanocin A, the wrong optical rotation was obtained. Therefore, (+)-neplanocin A was synthesized instead of (-)-neplanocin A and problems with the synthesis came to light that would not have been known otherwise.

The total synthesis of a series of 4′-ethoxy nucleoside analogs is presented in the second chapter. The goal of this research was the synthesis of 4′-ethoxy-2′,3′-dideoxythymidine, 4′-ethoxy-2′,3′-dideoxydidehydrothymidine, 4′-ethoxy-2′-deoxythymidine, and 4′-ethoxythymidine. *De novo* synthesis of 4′-disubstituted nucleoside analogs with a heteroatom in the 4′-position is unprecedented. In addition, 4′-ethoxy nucleosides are potently biologically active, giving this total synthesis its importance.

The synthesis of bipyrimidine-bridged bis-dioxocyclams is presented in the third chapter and this work bridges the gap between synthetic organic chemistry and materials science. With the use of organic chemistry, complex molecular systems can be synthesized for use in materials development. Bipyrimidine-bridged bis-dioxocyclams are macrocycles that have three defined cavities that can complex transition metals. The application of this research could be widespread but the foremost challenge lies in its synthesis and characterization of a bipyrimdine-bridged bis-dioxocyclam.

CHAPTER ONE

TOTAL SYNTHESIS OF (+)-NEPLANOCIN A FROM CHROMIUM-CARBENE COMPLEX-DERIVED OPTICALLY ACTIVE CYCLOBUTANONE

I. Introduction and Background

Interest in nucleoside analogs and their synthesis has dramatically increased with the emergence of drug-resistant strains of HIV and the need for viable treatments for AIDS patients. Nucleosides are compounds that contain a purine or pyrimidine base and a sugar residue (Figure 1.1). Nucleotides, the phosphate ester of a nucleoside, play essential roles in nearly all biochemical processes. The roles of nucleotides include the following: activated precursors of DNA and RNA, activated intermediates in many biosyntheses, constituents of

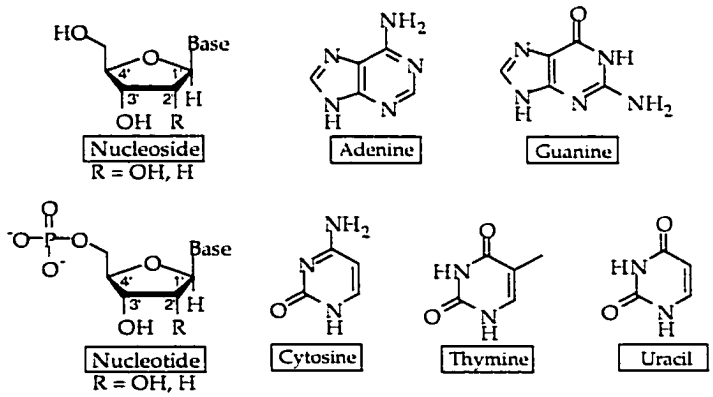


Figure 1.1 Natural Nucleosides

three major coenzymes (NAD^+, FAD, and CoA), sources of energy (ATP), and constituents of metabolic regulators.[1,2]

Nucleosides and their analogs are prodrugs. When phosphorylated to make nucleotides, they exhibit a wide range of biological activity, including but not limited to the treatment of AIDS. These compounds also have potent antitumor, anticancer, and antifungal activity.[1] For example, AZT (**1**) is one of

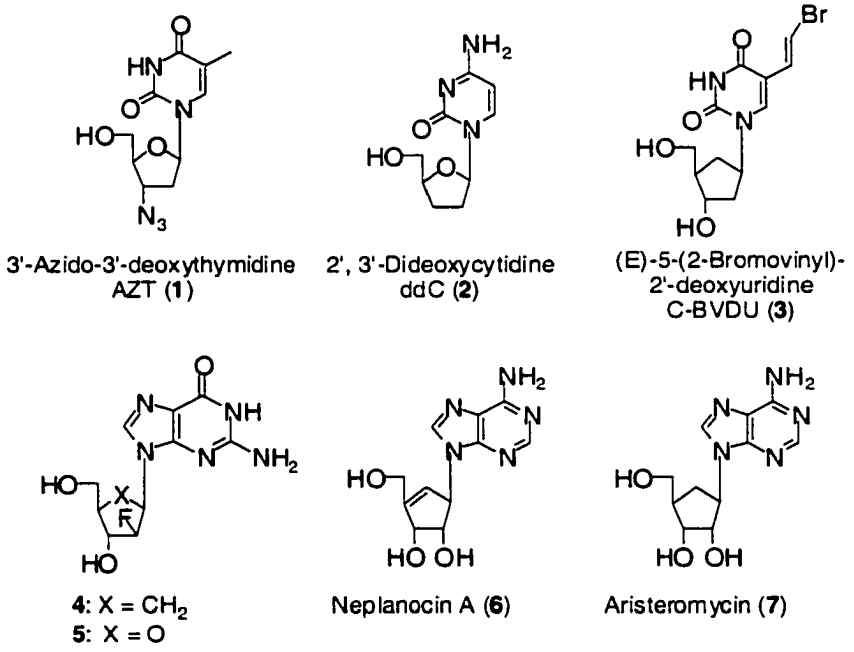


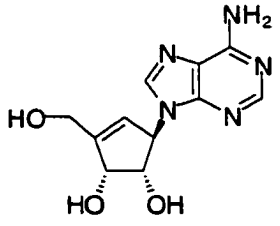
Figure 1.2 Examples of Nucleoside Analogs with Biological Activity.

the most widely known nucleoside analogs and was the first antiretroviral agent approved for treatment of patients with HIV infection.[3] The nucleoside, ddC (**2**), another antiretroviral agent, is currently being used in combination therapies with AZT.[3,4] C-BVDU (**3**) is an inhibitor of the herpes simplex virus (HSV) and is especially interesting because both (+) and (-)-enantiomers show impressive anti-HSV activity.[5] (-)-Neplanocin A (**6**) and aristeromycin (**7**) have antitumor and antiviral activity. (-)-Neplanocin A was the first cyclopentene carbocyclic

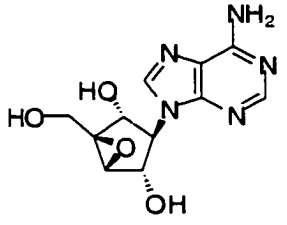
nucleoside to show enhanced potency and specificity compared to its saturated counterpart **7** (Figure 1.2).[6]

Modifications of nucleosides to the ring, substituents on the ring, and the nucleoside base have been performed extensively to give molecules with enhanced stability and biological activity. The natural nucleoside base can be altered, as shown with C-BVDU (**3**). The substituents at the 2′-, 3-′, and 4′-positions can be removed or replaced with unnatural functionality (**1**, **2**, **4**, **5**). In addition, the furanose oxygen of the nucleoside core can be replaced with a methylene group (**4**, **6**, **7**) to produce a carbocyclic nucleoside analog. The nucleoside's furanose oxygen weakens the 1′ N-C bond facilitating its cleavage by phosphorylases and hydrolases. Thus, carbocyclic nucleoside analogs have increased metabolic stability.[2]

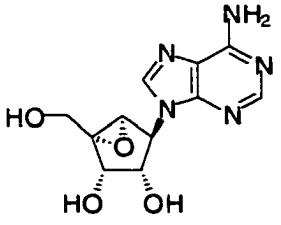
The cyclopentane ring of carbocyclic nucleoside analogs can be further modified to a 4′-5′ cyclopentene ring, as with (-)-neplanocin A (**6**). (-)-Neplanocin A was identified in 1981[7] as one of the 5 antibiotics produced by the soil fungus, *Ampullariella regularis*; it is coproduced with aristeromycin by



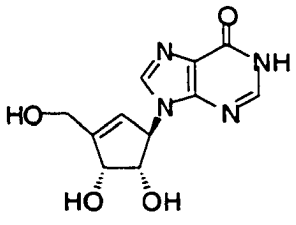
(-)-Neplanocin A (**6**)



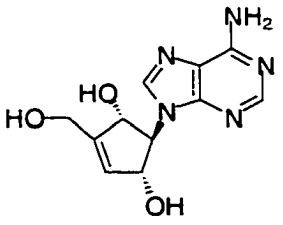
Neplanocin B



Neplanocin C



Neplanocin D



Neplanocin F

Figure 1.3 The Neplanocins.

Streptomyces citricolor.[8] Among the neplanocins, A, B, C, D, and F[9], (-)-neplanocin A has sparked the most interest because of its significant antitumor and potent antiviral activity (Figure 1.3).

(-)-Neplanocin A's antiviral activity is attributed to its ability to inhibit *S*-adenosylhomocysteine (SAH) hydrolase, a key enzyme in the methylation reactions that are required for the maturation of viral mRNA, in viral replicative cycles and in viral protein synthesis (Figure 1.4). Compounds that block this enzyme are active against a broad spectrum of viruses e.g. vaccinia (a poxvirus), rhabodo and paramyxo [(-)RNA viruses] and reovirus [a (±)RNA viruses].[10,11]

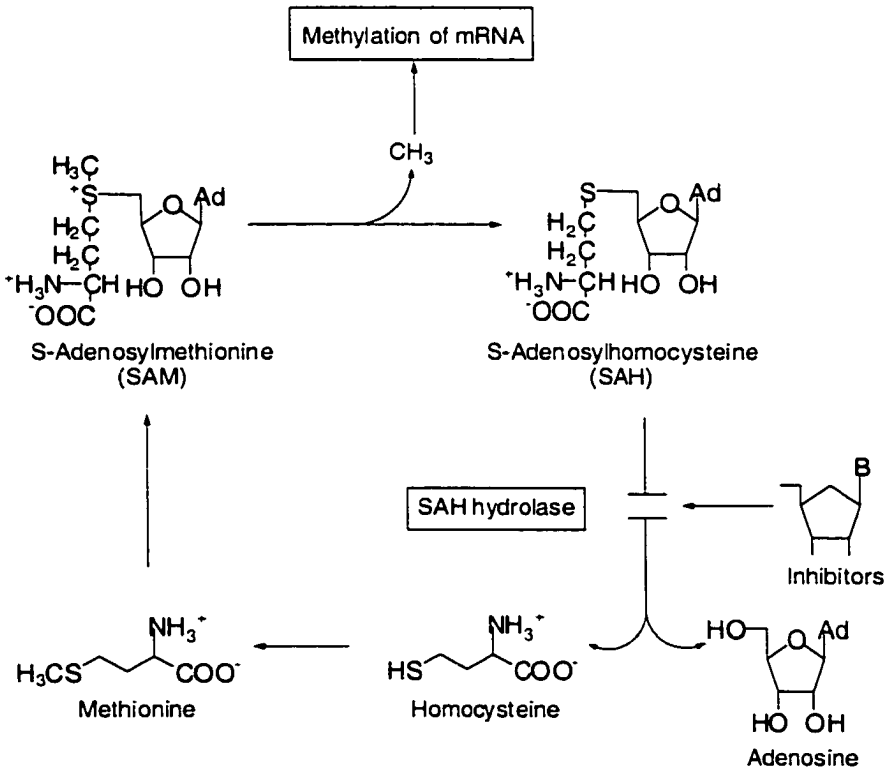


Figure 1.4 Inhibition of S-Adenosylhomocysteine Hydrolase.

(-)-Neplanocin A has remarkable antitumor activity against murine leukemias such as L1210 and P388 and the CD8F mammary tumor but is inactive

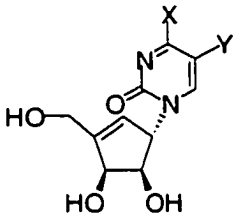
against B16 melanoma and Lewis lung carcinoma. The precise nature of this activity remains to be determined but there is evidence that its inhibitory effect on SAH is *not* the primary mechanism. It is known that (-)-neplanocin A is activated by adenosine kinase and suppresses RNA synthesis to a significantly greater extent than DNA synthesis.[12]

The therapeutic utility of (-)-neplanocin A as an antiviral agent is limited because of its significant cytotoxicity. This can be attributed to phosphorylation of the primary hydroxyl group at the 6'-position by adenosine kinase and subsequent formation of the triphosphate. The triphosphate is believed to inhibit cellular polymerases and/or be incorporated into the host cells. (-)-Neplanocin A is also rapidly deaminated by adenosine deaminase, forming the therapeutically inactive inosine congener.[13]

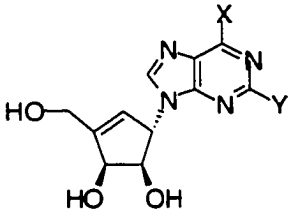
It has been shown that one enantiomer of a drug candidate can have enhanced biological activity and reduced toxicity. Therefore, it is of interest to test both (+) and (-) enantiomers. In 2001, (+)-neplanocin A's antiviral activity against HIV and the West Nile virus (Flavivirus family, genus *Flavivirus*, which includes yellow fever, dengue, and Japanese encephalitis viruses) was tested. Its cytotoxicity was also tested, along with a variety of D- and L-cyclopentenyl nucleosides (Table 1.1). It was found that (+)-neplanocin A (**13**) did not exhibit antiviral activity with an EC_{50} >100 μM against the HIV virus and an EC_{50} >200 μM against the West Nile virus. For comparison, the natural enantiomer, (-)-neplanocin A, has an EC_{50} = 0.1μM against the HIV virus and EC_{50} >51 μM against the West Nile virus. These studies also showed that (+)-neplanocin A had significant toxicity with an IC_{50} greater than 100 for all tests, compared to

(-)-neplanocin A's cytotoxicity with an IC_{50} of 44.6, 3.5, and 1.2 for PBM, Vero and CEM cells respectively. Interestingly, most of the L-(+)-nucleoside series gave poor results with only analogue **15** exhibiting weak antiviral activity (EC_{50} = 58.9 μM for the HIV virus).[13]

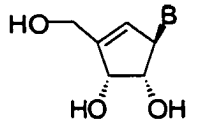
Table 1.1 Anti-HIV and Anti-West Nile Virus Activities of D- and L-Cyclopentenyl Nucleosides.



8: X = OH, Y = H
9: X = OH, Y = CH_3
10: X = OH, Y = F
11: X = NH_2, Y = H
12: X = NH_2, Y = F



13: X = NH_2, Y = H
14: X = O=, Y = H
15: X = O=, Y = NH_2



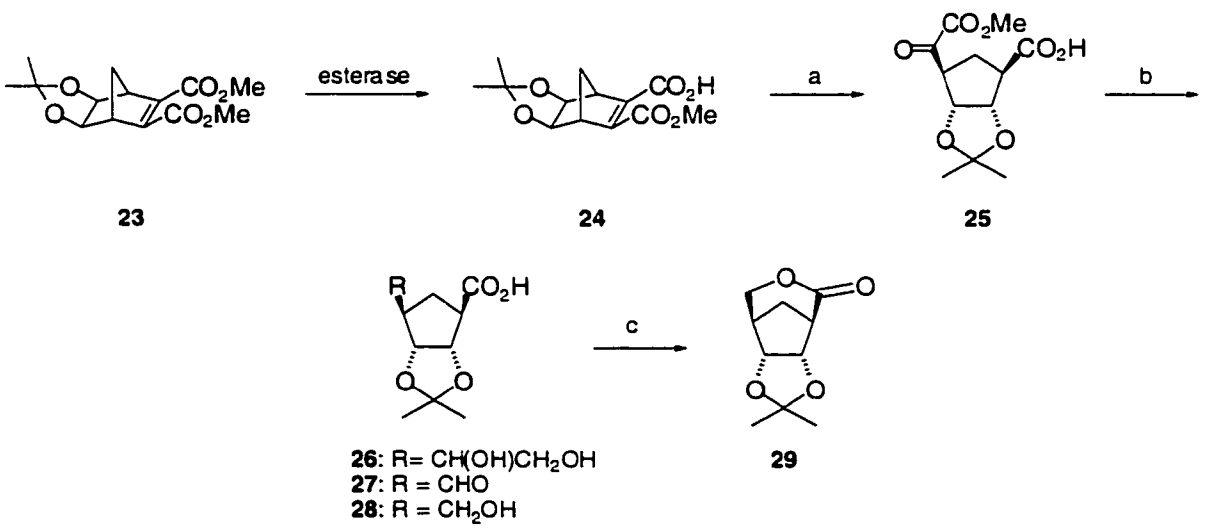
6: B = Adenine
16: B = Hypoxanthine
17: B = Guanine
18: B = Uracil
19: B = Thymine
20: B = 5-Fluorouracil
21: B = Cytosine
22: B = 5-Fluorocytosine

	EC_{50}, μM		cytotoxicity (IC_{50}, μM)		
compound	HIV-1	West Nile virus	PBM cells	Vero cells	CEM cells
8	>100	>200	>100	>100	>100
9	>100	>200	>100	>100	>100
10	>100	>200	>100	>100	>100
11	58.9	>200	>100	>100	>100
12	>100	>200	>100	>100	>100
13	>100	>200	>100	>100	>100
14	>100	>200	>100	>100	>100
15	>100	>200	>100	>100	>100
6	0.1	>51	44.6	3.5	1.2
16	>100	>200	>100	>100	>100
17	>100	>200	>100	>100	>100
18	>100	>200	>100	>100	>100
19	>100	>200	>100	>100	>100
20	93.1	>200	>100	>100	>100
21	0.06	0.2 (3)[a]	6.5	1.95	0.08
22	5.34	15 (20)	73.7	27.4	51.8
AZT[b]	0.004	ND	>100	29.0	14.3
6-azauridine[b]	ND	1.2	ND	>100	ND

(-)-Neplanocin A (**6**) has been synthesized over twenty five times[14] and these approaches can be placed into six main classes. The first class uses chemoenzymatic methods. Ohno used this method in the first total enantioselective synthesis of (-)-neplanocin A.[9] As shown in Scheme 1.1, the key intermediate, optically active half-ester **24**, was produced almost quantitatively

in 80% ee from the readily available symmetric unsaturated diester **23** using pig liver esterase.

With half-ester **24** in hand, a long and tedious route to (-)-neplanocin A was accomplished. Half-ester **24** was subjected to ozonolysis to give α-keto ester acid **25** in quantitative yield. Reduction with sodium borohydride, cleavage of the vicinal glycol with sodium periodate and 2N HCl, followed by reduction with sodium borohydride afforded alcohol **28**. Treatment of alcohol **28** with acetic anhydride and pyridine gave lactone **29** in 60% overall yield from **25**.

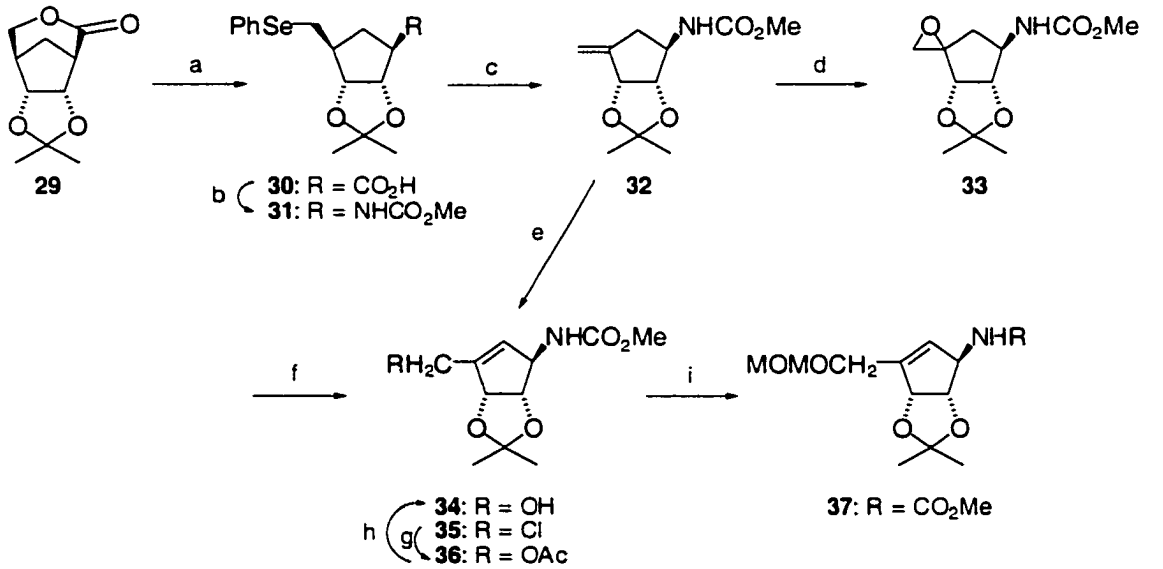


Scheme 1.1 Initial Steps of Ohno's Synthesis of (-)-Neplanocin A (**6**). (a) O_3, AcOEt, -78 °C; (b) 1. $NaBH_4$, 2. $NaIO_4$, HCl, 3. $NaBH_4$; (c) Ac_2O, pyr.

Lactone **29** was treated with PhSeNa, generated *in situ*, to afford selenide **30** in 93% yield. Conversion to methyl carbamate **31** in 91% overall yield was accomplished by a one-pot four-step sequence (Scheme 1.2). Ozonolysis of **31**, followed by removal of the selenoxide with pyridine gave exo-methylene **32** in 95% yield.

Since formation of allyl alcohol **34** from **32** was the most crucial step in this approach, three routes were investigated. The first route converted exo-

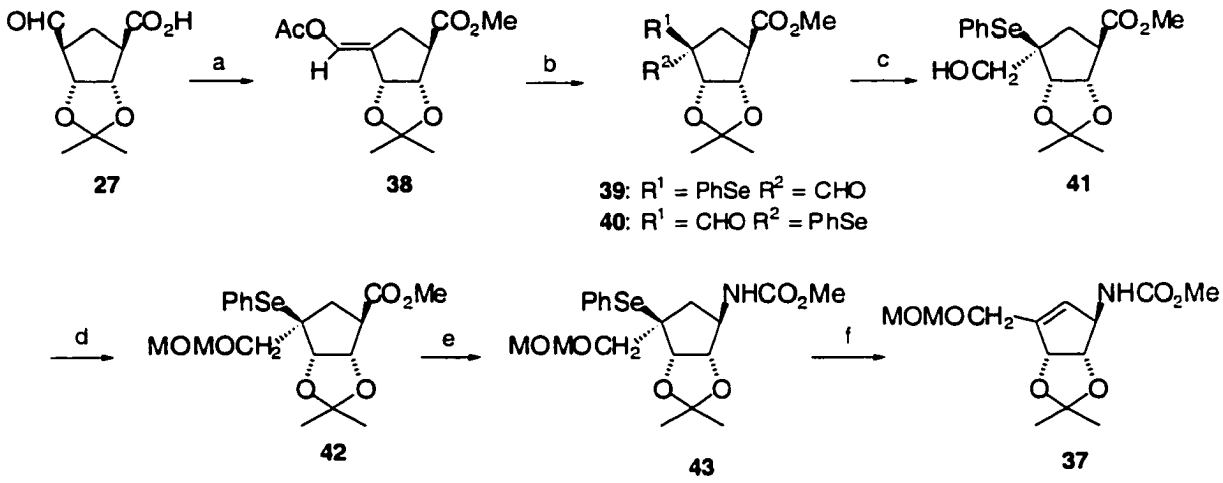
methylene **32** to epoxide **34** in 91% yield with *m*-CPBA. Using Noyori's procedure, cyclopentane alcohol **34** was obtained in 28% yield from epoxide **33**. The second route subjected **32** to *t*-butylhypochlorite to regioselectively give allyl chloride **35**. This was converted to allyl acetate **36** with sodium acetate in the presence of potassium iodide. Allyl acetate **36** was then hydrolyzed with sodium carbonate to give **34** in 48% overall yield. Alcohol **34** was protected with MOMCl to give **37** in quantitative yield.



Scheme 1.2 Ohno's First and Second Routes. (a) Ph_2Se_2, $NaBH_4$; (b) 1. $ClCO_2Et/NEt_3$, 2. NaN_3, 3. Δ in C_6H_6, 4. MeOH; (c) 1. O_3, 2. cat. Pyr.; (d) *m*-CPBA; (e) 1. *t*-BuOCl/HCO_2Me; (f) 1. Me_3SiOTf/2,6-lutidine, 2. DBU, d. K_2CO_3; (g) NaOAc/KI; (h) Na_2CO_3; (i) $MeOCH_3Cl/i\text{-}Pr_2NEt$.

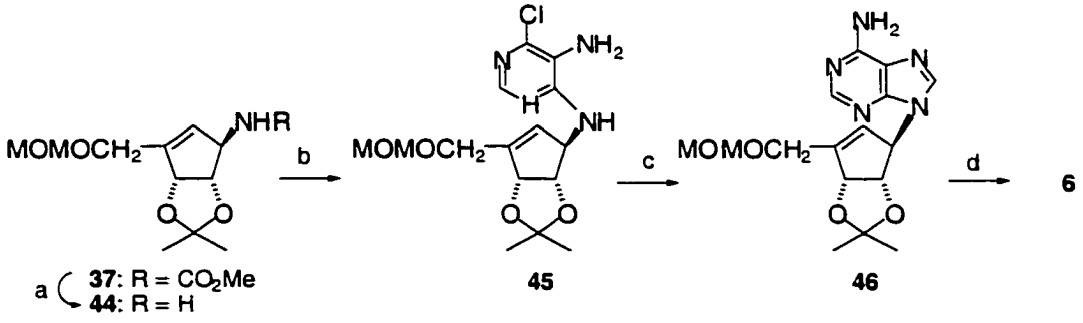
The third route to intermediate **37** converted acid **27** into the methyl ester with diazomethane, as shown in Scheme 1.3. Enol acetate **38** was then formed with Ac_2O in 73% yield to give a 1:5 mixture of E to Z isomers. Both isomers of **38** were treated with phenylselenyl trifluoroaceate to give predominately **39** at –78 °C (73% of **39**, 12% **40**). Selenide **39** was reduced to alcohol **41** in 95% yield with sodium borohydride. Protection of the alcohol followed by hydrolysis with

sodium hydroxide and Curtius rearrangement afforded methyl carbamate **43** in 62% overall yield. Oxidative removal of the phenylseleno group with ozone and addition of triethylamine gave **37** in 98% yield.



Scheme 1.3 Ohno's Third Route. (a) 1. CH_2N_2, Ac_2O/DMAP; (b) $PhSeOCOCF_3$, -78 °C; (c) $NaBH_4$; (d) $MeOCH_2Cl$/*i*-Pr_2NEt; (e) 1. NaOH, 2. $ClCO_2Et/NEt_3$, 3. NaN3, 4. Δ inC_6H_6, 5. MeOH; (f) 1. O_3, 3. NEt_3.

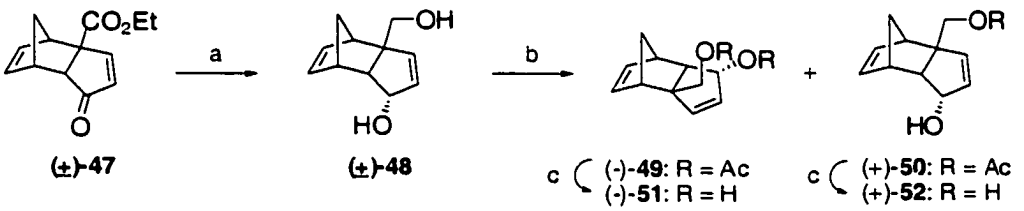
Unsaturated methyl carbonate **37** was then converted to (-)-neplanocin A as follows (Scheme 1.4). Carbamate **37** was hydrolyzed with KOH in aqueous methanol to afford cyclopentenaneamine **44** in quantitative yield. Amine **44** was subjected to a three-step sequence of reactions to synthesize the adenine base (**46**)



Scheme 1.4 Ohno's Completion of (-)-Neplanocin A. (a) KOH; (b) 5-amino-4,6-dichloropyrimidine/NEt_3, ; (c) 1. $HC(OEt)_3/Ac_2O$ 2. NH_3; (d) 2N HCl/MeOH.

and then deprotection of the MOM group with 2N HCl gave (-)-neplanocin A (**6**) in 42% overall yield from **34**.

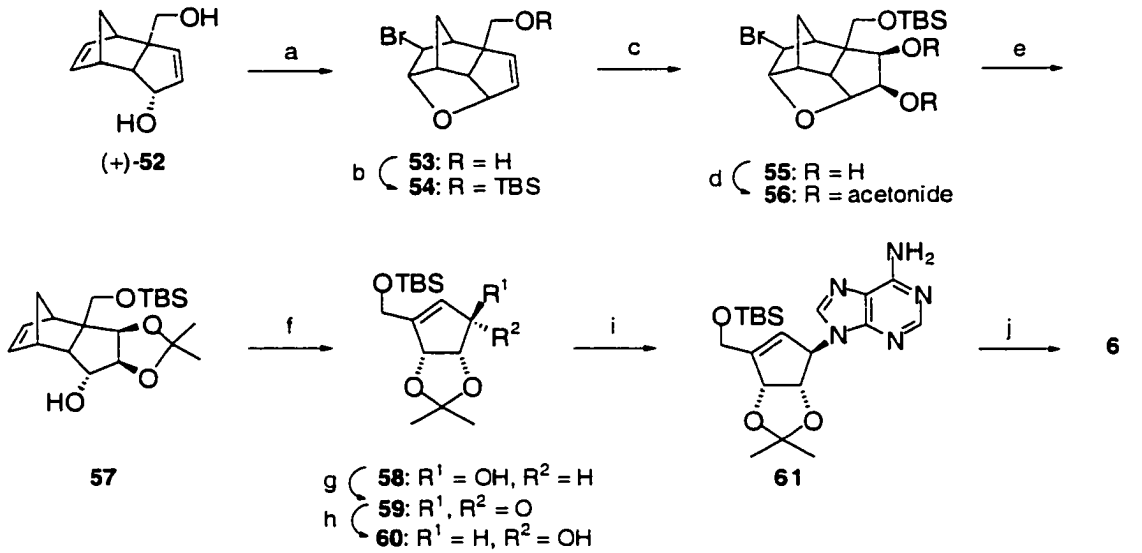
Another noteworthy synthesis of (-)-neplanocin A, using chemoenzymatic methods, is a concise synthesis by Ogasawara[15] (Scheme 1.5). Starting from tricylic ester **47**, which is available in 2 steps in 65% yield from the Diels-Alder adduct of benzoquinone and cyclopentadiene, reduction with diisobutylaluminumhydride (DIBAL) gave racemic diol **48** in 65% yield. Treatment of diol **48** with vinyl acetate in *t*-BuOMe in the presence of Lipase LIP (Toyobo) furnished (-)-diacetate **49** and (+)-monoacetate **50** in 41% yield/92% ee and 46% yield/>99% ee respectively. Alkaline methanolysis gave enantiomeric diols (-)-**51** and (+)-**52** quantitatively.



Scheme 1.5 Ogasawara's Concise Synthesis. (a) DIBAL, -78 °C; (b) lipase LIP, vinyl acetate, *t*-BuOMe; (c) K_2CO_3, MeOH.

Unfortunately, only (+)-**52** can be used for the synthesis. As shown in Scheme 1.6, (+)-**52** was treated with NBS to differentiate one of the two double bonds giving bromoether **53** in quantitative yield. Formation of silyl ether **54** followed by dihydroxylation, with attack occurring on the convex face, gave glycol **55** exclusively. Protection of the diol gave acetonide **56** in 92% overall yield. The double bond was unmasked with zinc and acetic acid to give olefin **57** in 95% yield. Thermolysis in diphenylether at reflux afforded cyclopentenol **58** in 97% yield. Inversion of the secondary alcohol by a PDC/DIBAL

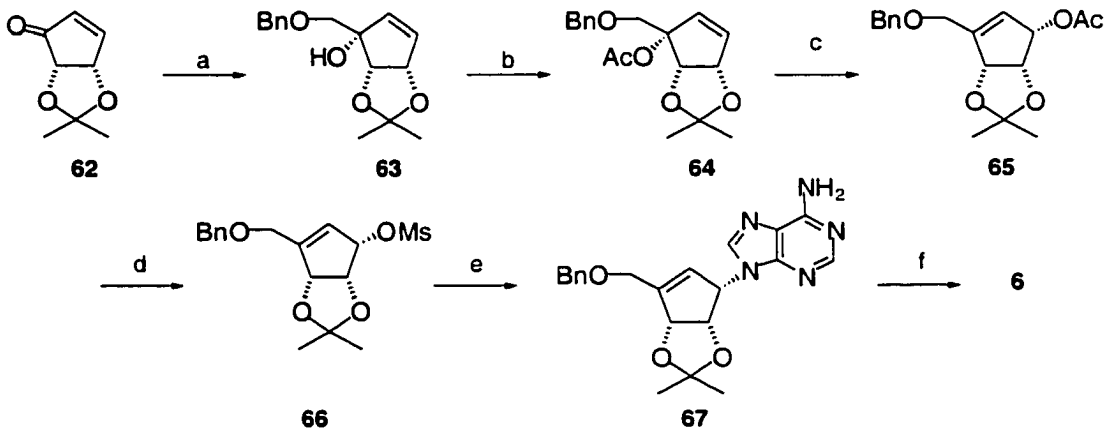
oxidation/reduction sequence gave epimer **60** in 83% overall yield. Mitsunobu conditions coupled the adenine base and gave penultimate **61** in 84% yield. Treatment of **61** with aqueous acid gave (-)-neplanocin A (**6**) in 10 steps and 45% overall yield.



Scheme 1.6 Ogasawara's Concise Synthesis Continued. (a) NBS; (b) TBSCl, imidazole; (c) OsO_4 (cat.), NMO, 70% aq. THF; (d) 2,2-dimethoxypropane, PPTS, acetone; (e) Zn, AcOH (cat.), MeOH; (f) Ph_2O. reflux; (g) PDC (h) DIBAL, -78 °C; (i) adenine, diisopropyl azodicarboxylate, PPh_3; (j) 1N HCl-MeOH.

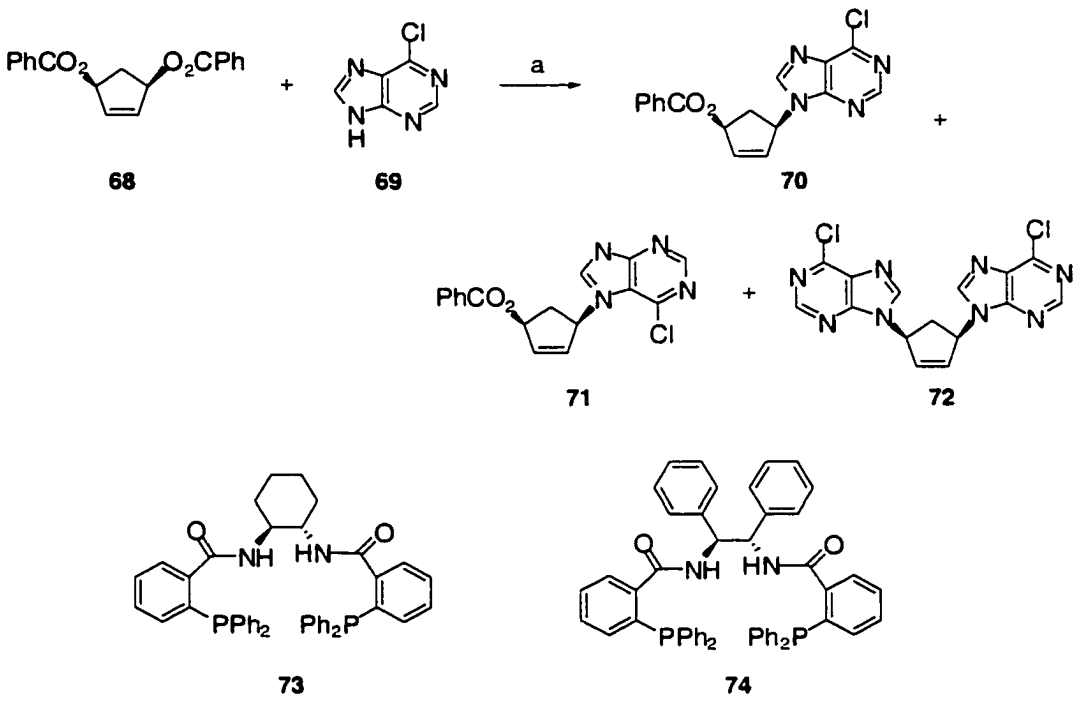
The second class of (-)-neplanocin A syntheses uses a palladium-mediated rearrangement as the key step. As shown in Scheme 1.7, Medich[16] began with (+)-cyclopentanone **62** which was previously prepared in their lab in 36% yield.[17] Treatment of **62** with (benzyloxymethyl)lithium afforded allylic alcohol **63** in 86% yield and acetylation gave acetate **64** in quantitative yield. Rearrangement of the acetate with a catalytic amount of $PdCl_2(CH_3CN)_2$ gave **65** in 92% yield in the presence of benzoquinone. Removal of the acetate with potassium carbonate followed by treatment with mesyl chloride and triethylamine gave mesylate **66** in 98% yield. Coupling with adenine, potassium carbonate, and 18-crown-6 gave

protected (-)-neplanocin A **67** in 46% yield. Removal of the protecting groups (87% yield) gave (-)-neplanocin A (**6**) in 36% overall yield from cyclopentenone **62.**



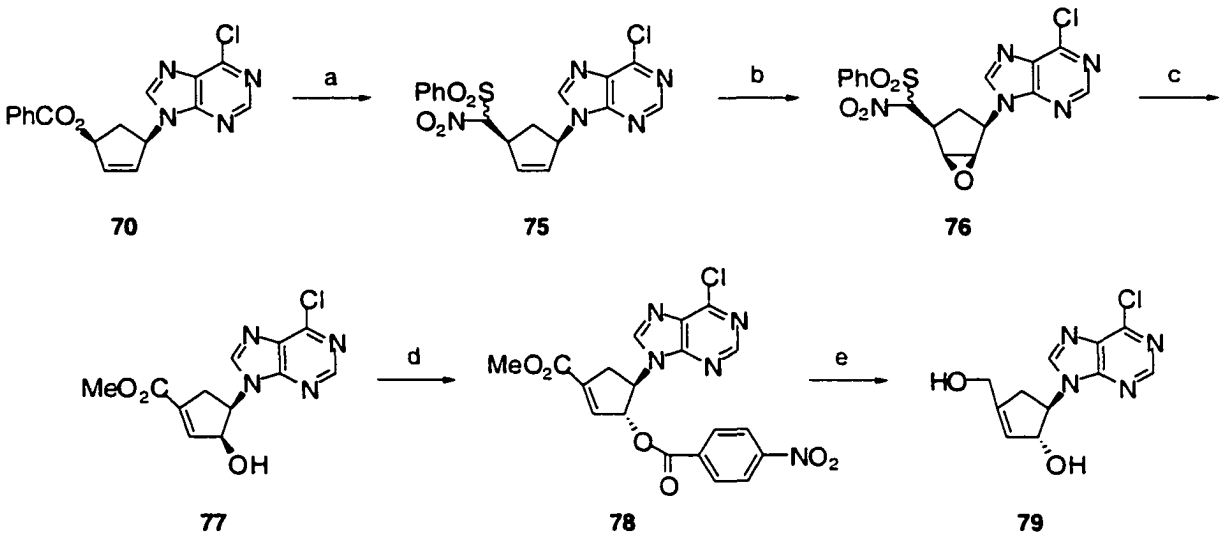
Scheme 1.7 Medich's Synthesis. (a) n-Bu_2SnCH_2OBn, n-BuLi, -78 °C; (b) Ac_2O, Et_3N, cat. DMAP; (c) 3 mol% $PdCl_2(CH_3CN)_2$, 0.4 eq. benzoquinone, reflux; (d) 1. K_2CO_3, MeOH 2. MsCl, Et_3N, 0 °C; (e) 2 eq. adenine, 2 eq. K_2CO_3, 1 eq. 18-crown-6, DMF, 75 °C; (f) 1. $Pd(OH)_2$, cyclohexene, EtOH, 80 °C 2. 2N HCl/MeOH.

The third class of syntheses of (-)-neplanocin A also employes palladium in the key step. Trost utilized a palladium-catalyzed allylic amination to desymmetrize cyclopentene derivatives. Starting from diester **68**,[18,19] initial experiments with ligand **73** and triethylamine gave poor yields and low enantiomeric excesses (ee) of desired amination product **70** (Scheme 1.8). The use of ligand **74** solved these problems by giving **70** in 53% yield (76% based on recovered SM) and 94% ee.



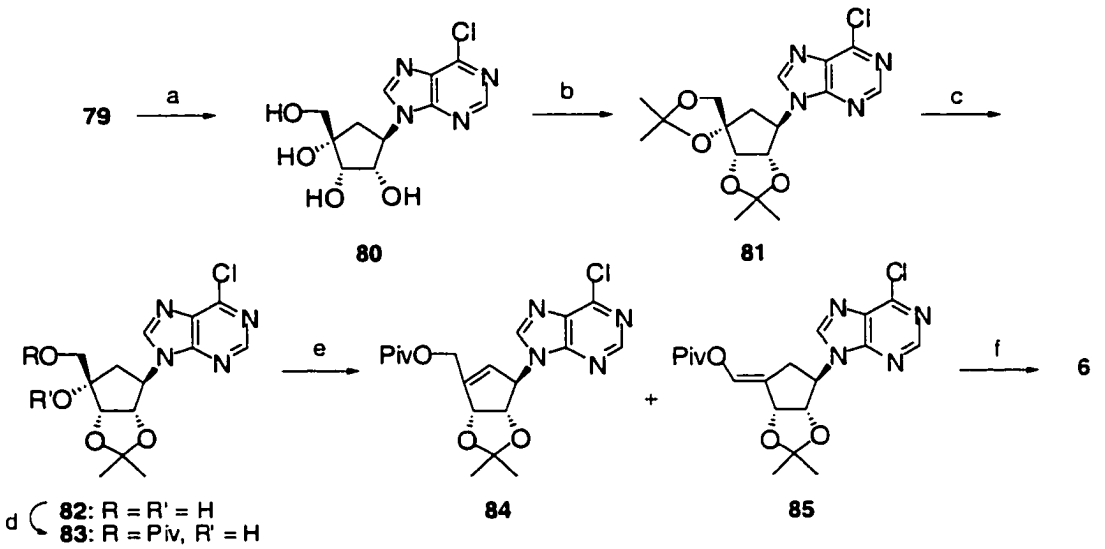
Scheme 1.8 Trost's Asymetric Alkyaltion with an Adenine Equivalent. (a) 1% $Pd_2dba_3{\cdot}CHCl_3$, 3% **74**, Et_3N, THF, rt.

With the key intermediate in hand, a rather elaborate synthesis of (-)-neplanocin A was established. As shown in Scheme 1.9, a second Pd(0)-catalyzed alkylation of **70** gave nitrosulfone **75** in 95% yield, as a 1:1 mixture of diastereomers. Epoxidation of both diastereomers with *m*-CPBA occurred from a single face to give **76** in 67% yield, showing the stereoselectivity of the epoxidation. Unfortunately this was not the desired epoxide. Therefore, ozonolysis gave alcohol **77** and esterification using a Mitsunobu reaction gave nitrobenzoate **78**. DIBAL reduction and transesterifcation with MeOH gave diol **79** in 79% yield.



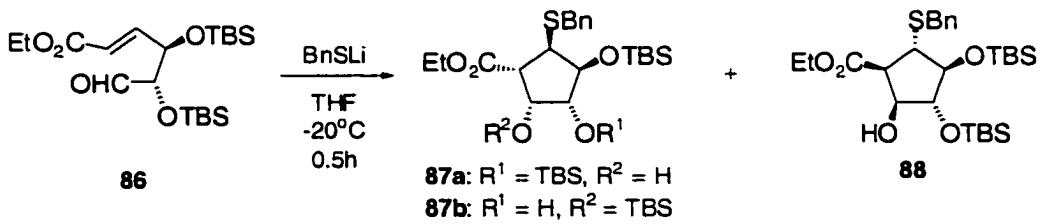
Scheme 1.9 Trost's Work Towards (-)-Neplanocin A. (a) 0.5% $Pd_2dba_3{\cdot}CHCl_3$, 3% PPh_3, $PhSO_2CH_2NO_2$, Et_3N, THF, rt; (b) *m-CPBA* (c) O_3, DBU, MeOH, THF, -78 °C; (d) *p*-$NO_2C_6H_4COOH$, PPh_3, DEAD, 0 °C; (e) DIBAL, -78 °C then Et_3N, MeOH, rt.

Dihydroxylation of **79** with osmium tetroxide gave only tetraol **80** (attack from the α face) in 89% yield, and bis-acetonide **81** was obtained in 71% yield from standard conditions (Scheme 1.10). Chemoselective removal of one acetonide from **81** required the use of $FeCl_3$ to give diol **82** in 91% yield. Protection of the primary alcohol with the bulky pivalate group gave **83** in 95% yield. This large protecting group was required to prevent elimination to exocyclic olefin **85** in the subsequent reaction. Thionyl chloride in pyridine gave the best results for formation of protected neplanocin A **84** with a 68% yield of a 8:1 ratio of **84**:**85**. Deprotection with aqueous acid gave (-)-neplanocin A (**6**) in 13 steps from bis-benzoate **68**.



Scheme 1.10 Trost's Synthesis. (a) OsO_4, NMO, acetone, H_2O; (b) $(MeO)_2CMe_2$, TsOH; (c) $FeCl_3{\cdot}H_2O$ on silica gel; (d) Me_2CCOCl, pyr; (e) $SOCl_2$, DMF, pyr; (f) aq. HCl, 80 °C.

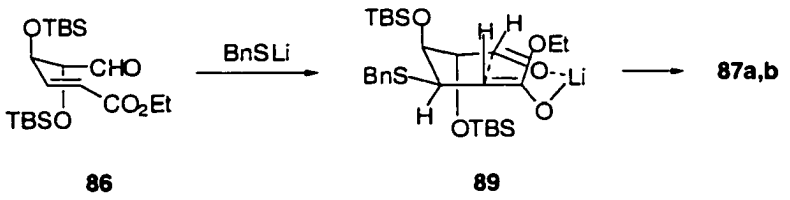
The fourth class of (-)-neplanocin A syntheses constructs the ring using an intramolecular aldol reaction. Tomioka[20] employed α,β-unsaturated ester **86**, an intermediate previously established in the group,[20,21] to examine the key cyclization reaction with lithium thiolate (Scheme 1.11). The best result was obtained with 1.2 eq. of lithium benzylthiolate in THF at -20 °C, giving three cyclization products **87a**, **87b**, and **88** in 34%, 28% and 11% yield respectively.



Scheme 1.11 Tomioka's Aldol Reaction.

Compound **87b** is a silyl-migrated product from **87a**, therefore the selectivity of the thiolate conjugate addition in the first step was 85:15 for **87**:**88**. As seen in Scheme 1.12, this is rationalized by the anti-orientation of the large TBS ethers. Furthermore, the selectivity of the aldol cyclization was perfect with the addition

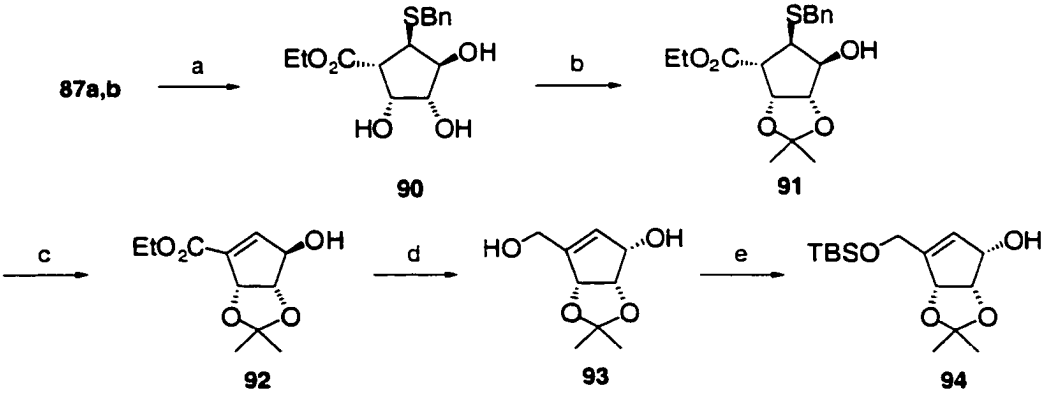
of lithium thiolate taking place only from the face opposite the aldehyde to generate the lithium enolate **89**.



86 **89**

Scheme 1.12 Model for diastereoselectivity.

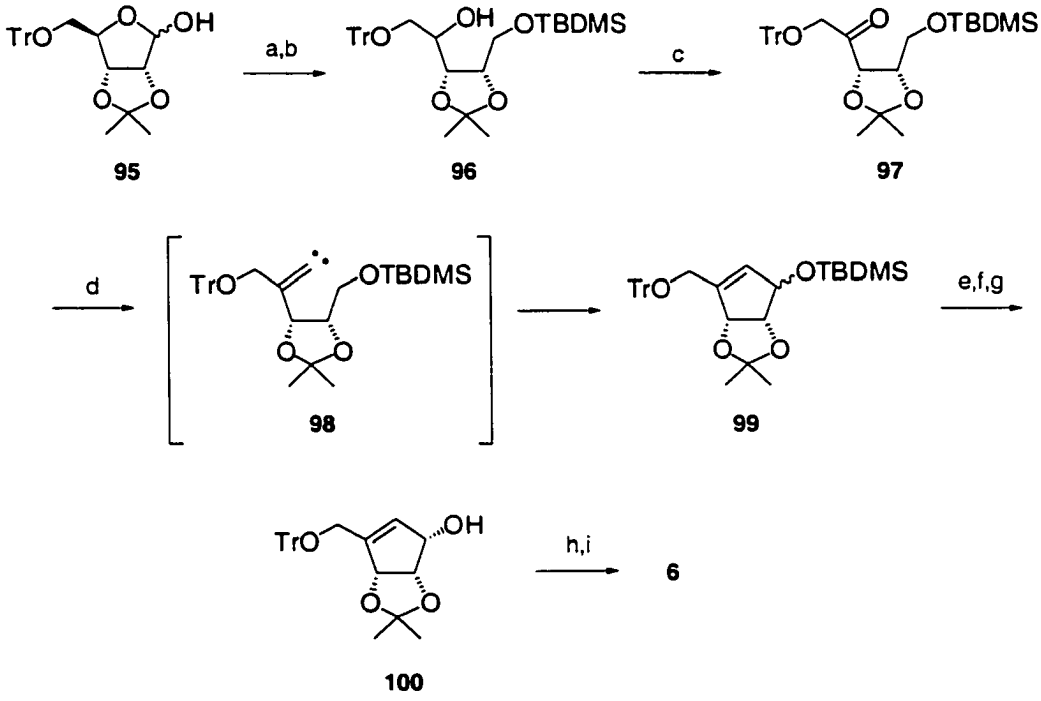
Compounds **87a** and **87b** were deprotected with aqueous hydrogen fluoride to afford triol **90** in 99% yield (Scheme 1.13). The vicinal hydroxyl groups were selectively protected as acetonide **91** in 89% yield. Oxidation to the sulfoxide with sodium metaperiodate in aq. ethanol, followed by thermal syn elimination in decalin at 180 °C, gave olefin **92** in 68% yield. At this point the secondary alcohol had to be inverted by an oxidation/reduction sequence and the primary alcohol was protected with TBSCl to give alcohol **94** in 53% yield over the three steps. This is the same synthetic intermediate used in Ogasawara's synthesis (Scheme 1.6, **60**) and therefore completes the formal synthesis of (-)-neplanocin A (**6**) in 15% overall yield from **86**.



90 **91** **92** **93** **94**

Scheme 1.13 Completion of Tomioka's Formal Synthesis of (-)-Neplanocin A. (a) aq. HF, CH_3CN, rt; (b) *p*-TsOH, acetone, rt; (c) 1. $NaIO_4$, aq. EtOH, rt. 2. decalin, 180 °C; (d) 1. PDC 2. DIBAL, -78 °C; (e) TBSCl, Et_3N, DMAP.

The fifth class of syntheses produces (-)-neplanocin A via a C-H insertion reaction to form the cyclopentene ring. Ohira and coworkers[22] reported a concise synthesis of neplanocin A utilizing this method with alkylidenecarbene **98** (Scheme 1.14). Reduction of protected D-ribose **95** with lithium aluminum hydride gave the corresponding diol in 85% yield. Protection of the primary alcohol as the TBDMS ether gave secondary alcohol **96** in 97% yield and Swern oxidation furnished unstable ketone **97** in 89% yield.



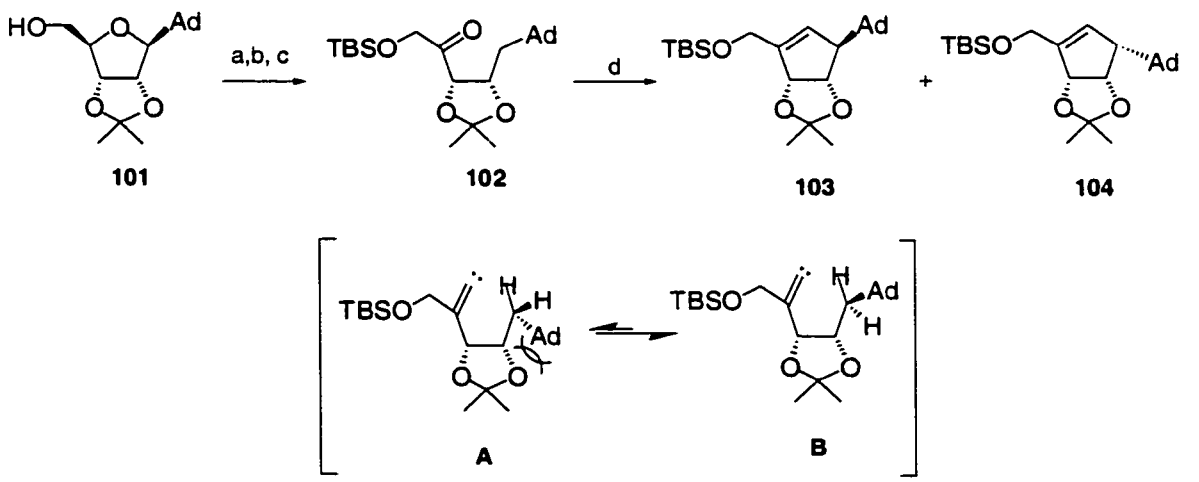
95 **96** **97** **98** **99** **100**

Scheme 1.14 Ohira's Synthesis. (a) $LiAlH_4$, Et_2O; (b) TBDMSCl, imidazole, DMF; (c) $(COCl)_2$, DMSO then Et_3N, CH_2Cl_2; (d) $TMSC(Li)N_2$, THF, 0 °C, 1 hr; (e) Bu_4NF, THF; (f) PDC, CH_2Cl_2; (g) $LiAlH_4$, THF; (h) adenine, DEAD, Ph_3P, THF; (i) HCl, MeOH.

Immediate treatment of ketone **97** with 3 eq. of lithiotrimethylsilyl-diazomethane generated alkylidenecarbene **98**, which inserted into the C-H bond adjacent to the protected hydroxyl group. Cyclopentene **99** was obtained in 55-65% yield as a 2.7:1 mixture of diastereomers. Unfortunately, because of the bulky siloxy and acetonide group, the major product had the undesired

stereochemistry. Therefore, the *t*-butyldimethylsilyl group was removed with TBAF in 69% yield, followed by an oxidation/reduction sequence which gave alcohol **100** in 70% yield as a single epimer. Treatment of alcohol **100** with adenine under Mitsunobu conditions gave the coupled product in 52% yield. Removal of the protecting groups with acid gave (-)-neplanocin A (**6**) quantitatively in 9 steps and in overall 9-12% yield.

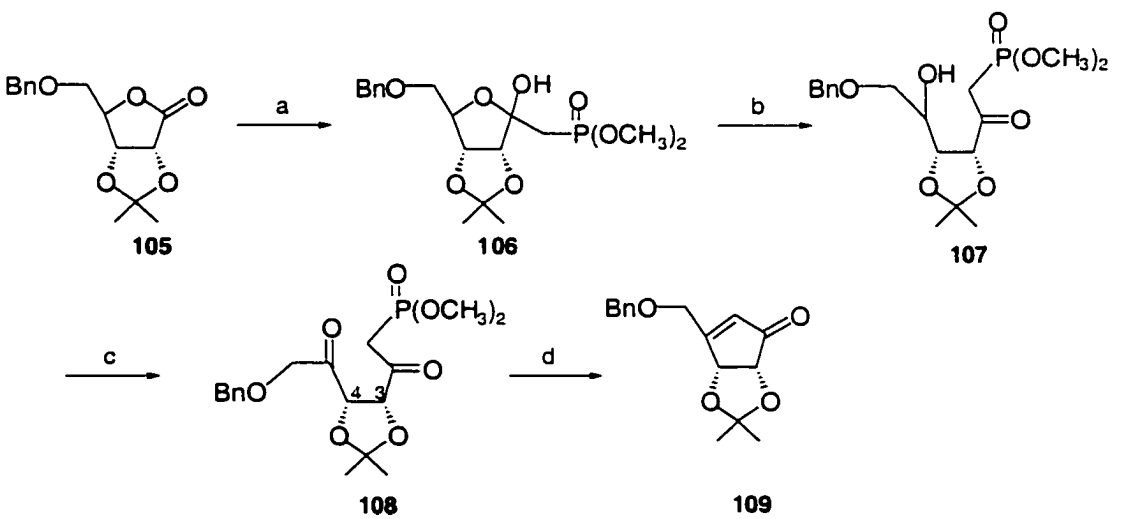
Niizuma[23] altered this procedure by modifying the substrate for C-H insertion, as shown in Scheme 1.15. Protected adenosine **101** was reduced with DIBAL, the primary alcohol was protected as the *t*-butyldimethylsilyl ether, and Dess-Martin oxidation of the secondary alcohol gave adenine derivative **102**. Treatment of **102** with lithiotrimethylsilyldiazomethane gave protected (-)-neplanocin A, as a 4:1 mixture of diastereomers in 21% yield. Fortunately, the major diastereomer was the desired β-epimer (Scheme 1.15) and Niizuma



Scheme 1.15 Niizuma's C-H Insertion with an Adenine Derivative. Ad = Adenine. (a) DIBAL; (b) TBSCl, imidazole; (c) Dess-Martin ox.; (d) $TMSC(Li)N_2$.

proposed that intermediate A, which would give the undesired α-epimer, was disfavored due to the steric interactions of adenine with the protected hydroxyl group.

The sixth class of (-)-neplanocin A syntheses utilized a Horner-Wadsworth-Emmons/Wittig reaction. Marquez[6] began with protected D-ribonic acid lactone (**105**) and treated it with lithium dimethyl methyl-phosphonate in THF (Scheme 1.16). This gave hemiketal **106** in quantitative yield. Subsequent opening of the hemiketal intermediate to its tautomer, keto phosphonate **107**, was accomplished with sodium methoxide in methanol in 90% yield. Oxidation of **107** with modified Collins reagent produced diketo phosphonate **108** in 80% yield. Treatment of **108** with potassium carbonate and 18-crown-6 gave cyclopentenone **109** in only 42% yield due to base-catalyzed epimerization at C-3 and C-4 of diketone **108**.

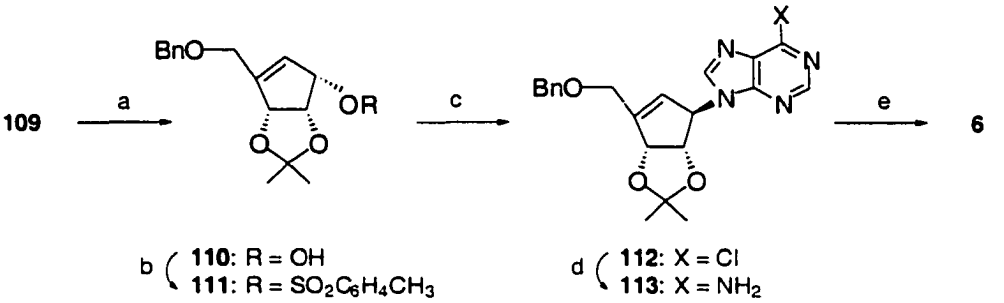


Scheme 1.16 Marquez's Stepwise Horner-Wadsworth-Emmons Reaction.

(a) $LiCH_2P(O)(OMe)_2$; (b) $NaOCH_3$; (c) CrO_3, pyr.; (d) K_2CO_3, 18-crown-6.

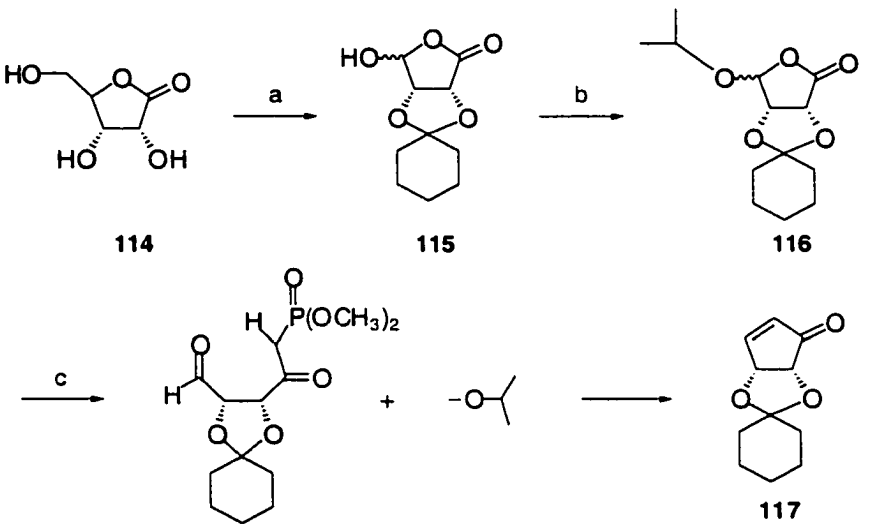
Completion of the synthesis from the key intermediate (**109**) consisted of formation of the glycosidic bond (Scheme 1.17). Cyclopentene **109** was reduced

with sodium borohydride and cerium trichloride to give a single diastereomer, alcohol **110**, which was then tosylated to produce **111**. Alkylation of 6-chloropurine sodium salt with tosylate **111** afforded cyclopentenyl-6-chloropurine **112** in 30% yield. Treatment of **112** with methanolic ammonia and deprotection with boron trichloride gave (-)-neplanocin A (**6**) in 9 steps in 2% overall yield.



Scheme 1.17 Marquez's Completion of (-)-Neplanocin A. (a) $NaBH_4$, $CeCl_3$; (b) *p*-CH_3PhSO_2Cl; (c) 6-chloropurine, NaH; (d) NH_3, MeOH; (e) BCl_3.

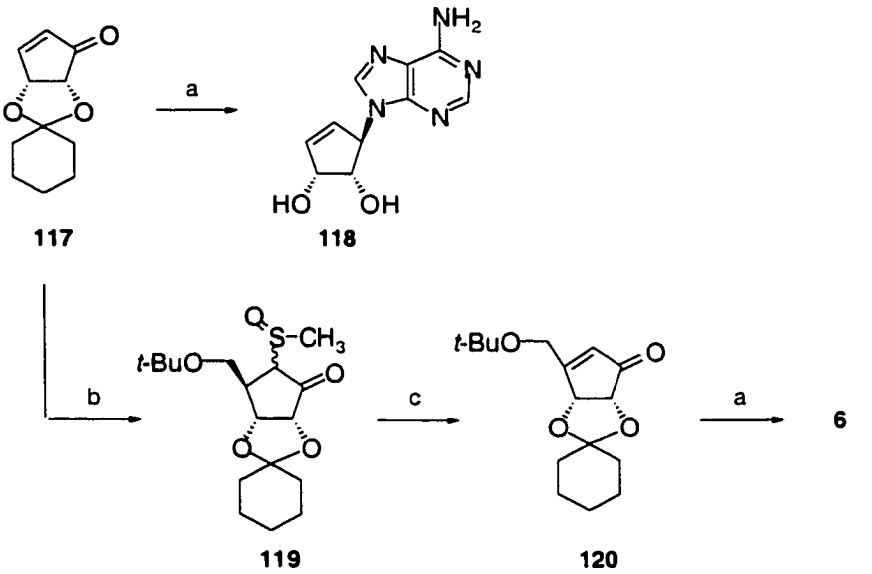
This methodology has been extended to synthesize (-)-neplanocin A (**6**) and analog (**118**) which lacks the 4'-hydroxymethyl substituent, as shown in Scheme 1.18.[24] Starting from D-ribonolactone **114**, Borchardt used $FeCl_3$ and cylcohexanone to protect the 3,4-diol. Oxidation with sodium periodate gave protected lactone **115** in 85% yield over two steps. Conversion of the hydroxyl to an isopropoxide leaving group with 2-propanol and PPTS gave L-glycoside **116** in 95% yield. Treatment of **116** with lithium dimethyl methylphosphonate prompted the ring to open with loss of the isopropoxide group. This base, formed *in situ*, promoted an intramolecular cyclization to give **117** in 80% yield. This one-pot, cascade process occurred without detectable racemization.



Scheme 1.18 Borchardt's Synthesis of Cyclopentenone **117** by a One-pot Cascade Reaction.

(a) 1. Cyclohexanone, $FeCl_3$ 2. H_2O, NaOH, $NaIO_4$; (b) 2-propanol, PPTS, Δ ; (c) $LiCH_2P(O)(OMe)_2$.

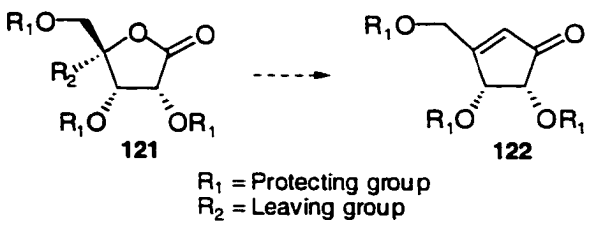
Using a procedure similar to Marquez's approach[6] (see (a) in Scheme 1.19), neplanocin A analog **118** was synthesized in 29% overall yield from **117**.[25] In addition, an organocuprate reaction was employed to install the 4-hydroxymethyl substituent on **117** to synthesize (-)-neplanocin A (**6**).[26] $(t\text{-BuOCH}_2)_2\text{CuLi}$ was added to **117** and the reaction was transferred to a flask containing methanesulfinyl chloride. β-Keto sulfoxide **119** was produced as a mixture of four diastereomers, with the variable chirality at the sulfur and α-carbons atoms, and underwent pyrolytic *syn*-elimination in toluene at reflux with calcium carbonate to produce cyclopentenone **120** in an overall 64% yield from **117**. The calcium carbonate assisted in the epimerization of the diastereomers of **119**, converting all four diastereomers to the desired cyclopentenone. Compound **120** was then converted to (-)-neplanocin A (see (a) in Scheme 1.19) in 11 steps and 11% yield from **114**.



Scheme 1.19 Borchardt's Completion of (-)-Neplanocin A (**6**) and Analog (**118**). (a) 1. DIBAL 2. $(CF_3SO_2)O$, pyr. 3. adenine, NaH, 18-crown-6 4. H_3O^+; (b) 1. $(t\text{-}BuOCH_2)_2CuLi$ 2. MeS(O)Cl; (c) toluene, $CaCO_3$, Δ.

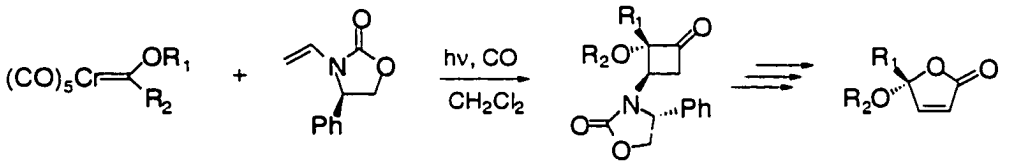
II. Rationale

An appropriate intermediate can be envisioned combining the two strategies in the sixth class of syntheses of (-)-neplanocin A, the utilization of a Wadsworth-Emmons reaction. If the 4'-hydroxymethyl group and a leaving group were installed on the lactone core, such as **121** as shown in Scheme 1.20, treatment with lithium dimethyl methylphosphonate should give cyclopentenone **122**. This would provide a direct method to synthesize (-)-neplanocin A from a novel one pot ring opening, Wadsworth-Emmons reaction.



Scheme 1.20

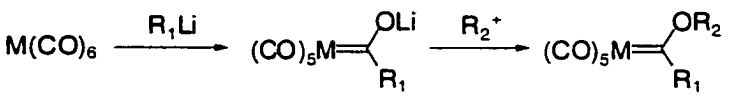
Access to 5-disubstituted diols such as **121** is not straightforward. Fortunately, methodology to synthesize such compounds has been established in the Hegedus group. Optically active functionalized cyclobutanones (**125**) have been synthesized via photolysis of heteroatom-stabilized chromium carbene complexes with chiral, electron-rich olefins (Scheme 1.21). The cyclobutanones have been converted to butenolides (**126**) which have been used as nucleoside templates,[27-29] in the syntheses of other natural products,[30,31] or have been *cis*-dihydroxylated to give 5-disubstituted diols.



123 **124** **125** **126**

Scheme 1.21

Heteroatom-stabilized or Fischer carbene complexes have been frequently used in organic synthesis. They are usually synthesized by one of two methods. In the first method, developed by Fischer,[32] one of the CO ligands on chromium hexacarbonyl (**127**) is attacked by an organolithium to produce an anionic lithium acyl "ate" complex (**128**) which undergoes *O*-alkylation with a variety of hard alkylating reagents (Scheme 1.22). The alkyl substituent on the carbene is limited to available organolithium reagents, as well as the stability of the other functionality to this reagent.

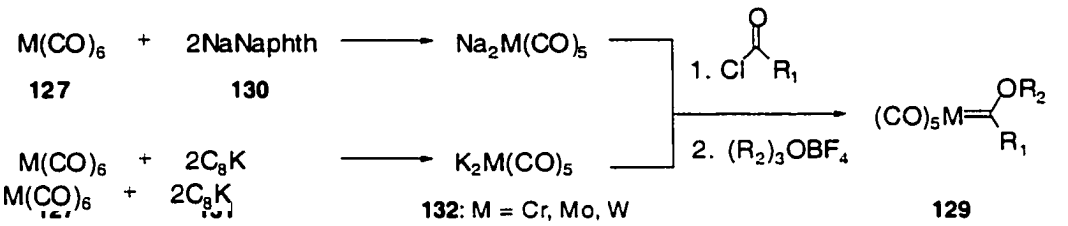


127 **128** **129**

M = Cr, Mo, W; R_1 = Me, Ph, etc.; R_2 = Me, Et, etc.

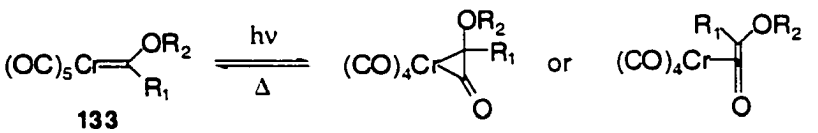
Scheme 1.22

The second method to synthesize Fischer carbene complexes was developed by Semmelhack and extended by Hegedus. Reduction of a metal hexacarbonyl (**127**) with either sodium naphthalenide (**130**)[33] or a potassium/graphite intercolate (**131**)[34] gave chromium pentacarbonyl dianion **132**. This nucleophilic dianion reacted with a variety of acyl transfer agents and, upon *O*-alkylation with a hard alkylating agent, gave the desired alkoxycarbene complex **129** (Scheme 1.23).



Scheme 1.23

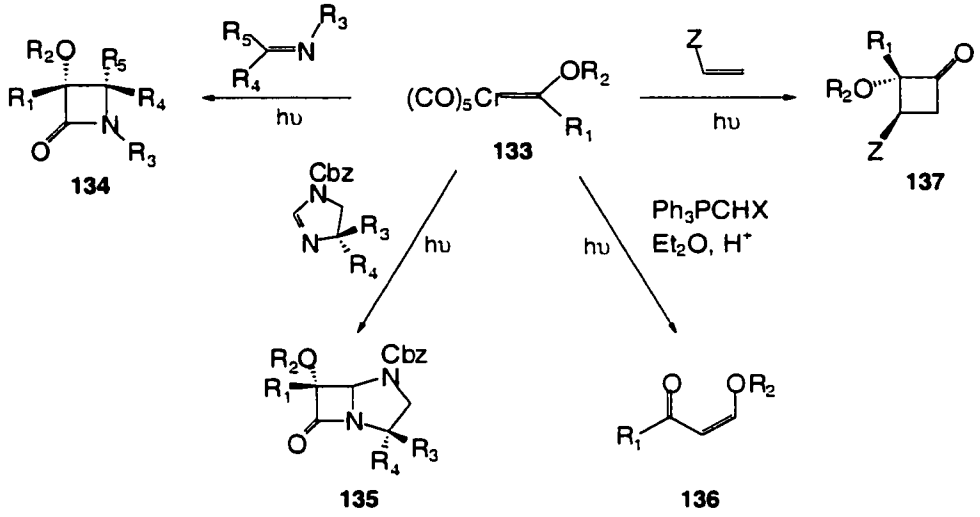
It is postulated that irradiation into the metal-to-ligand charge transfer band (350 – 400 nm) of chromium carbene complexes, such as **133**, promotes an electron from the chromium metal to the carbene carbon. This formal oxidation of the metal center is believed to cause a reversible insertion of CO into the metal carbon double bond, generating a metallacyclopropanone or a metal bound ketene, as shown in Scheme 1.24. These intermediates have not been observed



Scheme 1.24

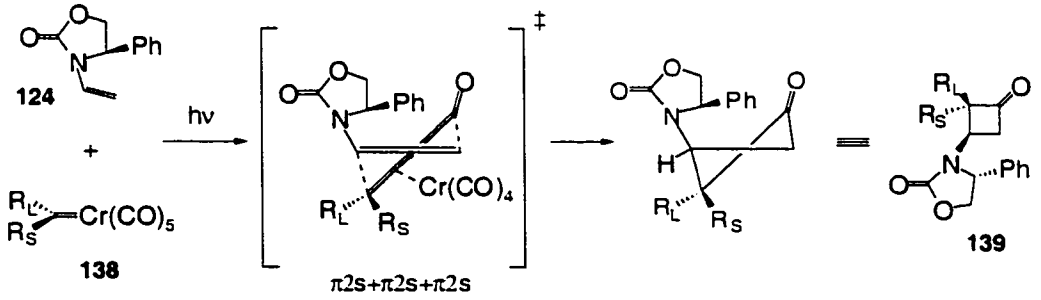
spectroscopically but are inferred from their reactivity. As shown in Scheme 1.25,[35] this ketene-like species can react with a variety of reagents to synthesize compounds such as β-lactams (**134**) and cyclobutanones (**137**). Since the CO insertion is reversible for this process, and the ketene intermediate is bound by

the chromium, there is never a high concentration of the ketene-like species present. Therefore, this chemistry is not plagued by dimerization as is free ketene chemistry.



Scheme 1.25

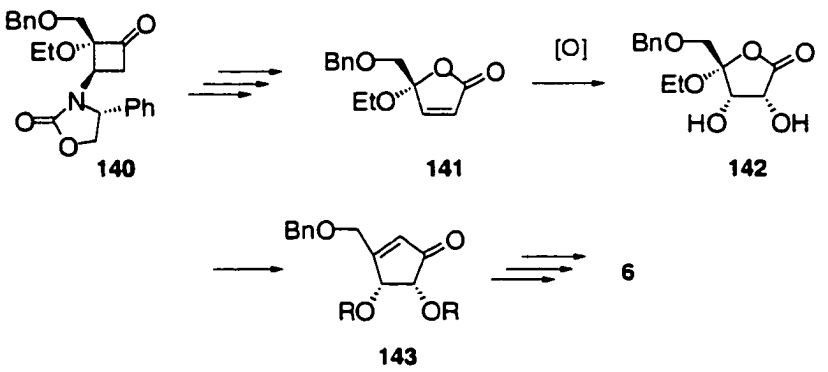
The cycloaddition of chromium carbene complexes with electron-rich alkenes (Scheme 1.25, **133** → **137**), proceeds with high regio- and stereoselectivity to give cyclobutanones. The use of an optically active alkene results in nearly perfect diastereoselectivity.[36,37] The stereochemistry of the cyclobutanone can be rationalized by steric constraints in the transition state, with the alkene attacking



Scheme 1.26

over the smaller ketene substituent and the chiral auxiliary oriented to reduce unfavorable interactions (Scheme 1.26).[38,39]

As shown in Scheme 1.27, previous work in the Hegedus group established the conversion of cyclobutanones to 5-disubstituted diols (**140** → **142**). With diol **142** in hand, the Wadsworth-Emmon reaction could be probed to see if a one-pot ring opening, intramolecular cyclization would occur to give the key intermediate (**143**) for the synthesis of (-)-neplanocin A (**6**). Since enone **143** is

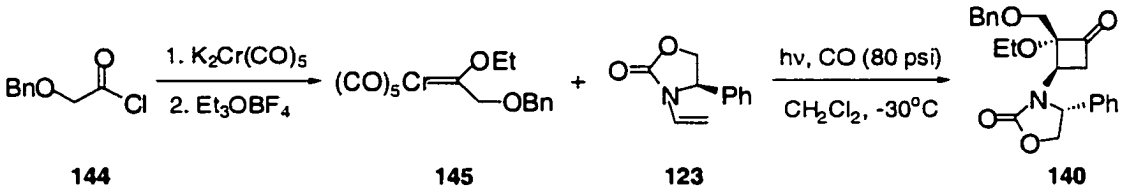


Scheme 1.27

the key intermediate in the synthesis of a number of carbocyclic nucleoside analogs,[40,41] its asymmetric synthesis by this route may streamline those syntheses as well.

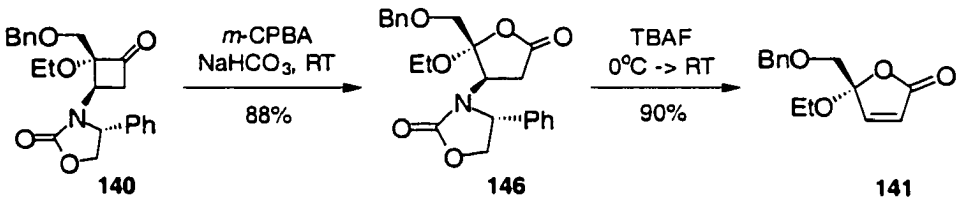
III. Results and Discussion

Optically active cyclobutanone **140** was synthesized following protocol previously established in the Hegedus group. Treatment of the potassium salt of the chromium pentacarbonyl dianion with benzyloxyacetyl chloride (**144**) and triethyloxonium tetrafluoroborate gave chromium carbene complex **145** in 78% yield (Scheme 1.28). Irradiation of this complex in the presence of (R)-vinyl carbamate **123** at -30 °C under carbon monoxide for 6 days produced only one diastereomer, cyclobutanone **140** in 68% yield.



Scheme 1.28

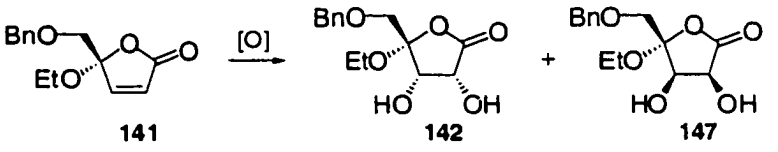
Baeyer Villiger oxidation of cyclobutanone **140** with *m*-CPBA and sodium bicarbonate gave lactone **146** in 88% yield. At this point the chiral auxiliary could be removed with TBAF (and recycled), giving butenolide **141** in 90% yield (Scheme 1.29).[31]



Scheme 1.29

cis-Dihydroxylation of butenolide **141** with potassium permanganate /dicyclohexano-18-crown-6 (DCH-18-c-6) at –40 °C produced a single *cis*-diol in 72% yield at 70% conversion (50% isolated yield of **142**), as shown in Scheme 1.30.[42] The use of sodium periodate in the presence of a catalytic amount of ruthenium(III) chloride at 0 °C[43] gave a 3:1 mixture of *cis*-diols in overall 65% yield, at 80% conversion (40% and 12% isolated yields of **142** and **147**, respectively). The use of catalytic amounts of osmium tetraoxide and NMO at 0 °C to room temperature gave a lower yield of both diastereomers, 9% and 4% respectively at 30% conversion.[31,42] The *cis*-dihydroxylation reactions were not run to completion or at higher temperatures because both butenolide **141**, diol **142**, and diol **147** decompose under the reaction conditions. Therefore, the

reaction was monitored and quenched when the undesired side products began to form, making it possible to recycle **141**.

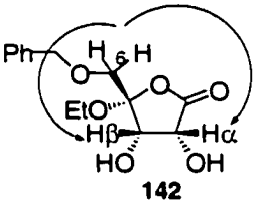


141 **142** **147**

$KMnO_4$/DCH-18-C-6	50%	0%
$NaIO_4/RuCl_3$	40%	12%
OsO_4/NMO	9%	5%

Scheme 1.30

The two diastereoisomeric diols could be separated using column chromatography and the post doctoral fellow, Andrew Riches, who was working on the oxidation determined the diols' stereochemistry by nOe studies. He found that irradiation of the C-6 methylene protons of **142** resulted in a perceptibly greater enhancement of the Hα and Hβ resonances than did the same irradiation of **147** (Figure 1.5). Therefore, it was concluded that major



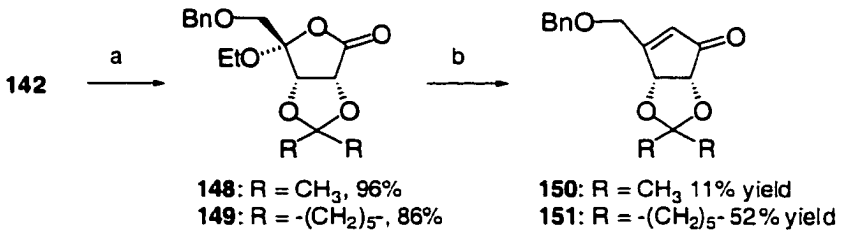
142

Figure 1.5 Major Diol **142**'s nOe Data.

diastereomer **142** was from *cis*-hydroxylation of the α-face of the butenolide, giving the diol *syn* to the alkoxy group. It was postulated that the selectivity was due to the steric hindrance of the benzyloxymethyl substituent. This stereoselectivity was consistent with previous studies, in which nOe data were used to determine that *cis*-dihydroxylation from the face bearing the alkoxy group is favored for other 4-alkoxy-4-alkyl-butenolides.[31,42] In retrospect, the evidence was not strong for an assignment of the diastereotopic diols **142** and

147, especially with the known problems plaguing five member rings and nOe data because five membered rings due not exist predominately as one conformer.[44] However, with the excitement of having a direct route to a versatile nucleoside template, certain details were overlooked.

For the synthesis of (-)-neplanocin A, what was believed to be diol **142** from previous work was protected as acetonide **148** in 60% yield using 2,2-dimethoxy-propane and TsOH. The one-pot ring-opening, intramolecular Wadsworth-Emmons reaction could be problematic, therefore precautions were taken. One equivalent of the lithium salt of dimethyl methylphosphonate was made at -78 °C from freshly titrated *n*-BuLi and freshly distilled dimethyl methylphosphonate. This was to assure that no excess reagent was produced to avoid its addition to the enone product. A solution of acetonide **148** was added dropwise down the side arm of the flask to precool the solution and assure complete addition of phosphonate reagent to acetonide **148**. Even with these precautions taken only an 11% yield of cyclopentenone **150** was obtained (Scheme 1.31). The crude material was extremely clean by ^{1}H NMR



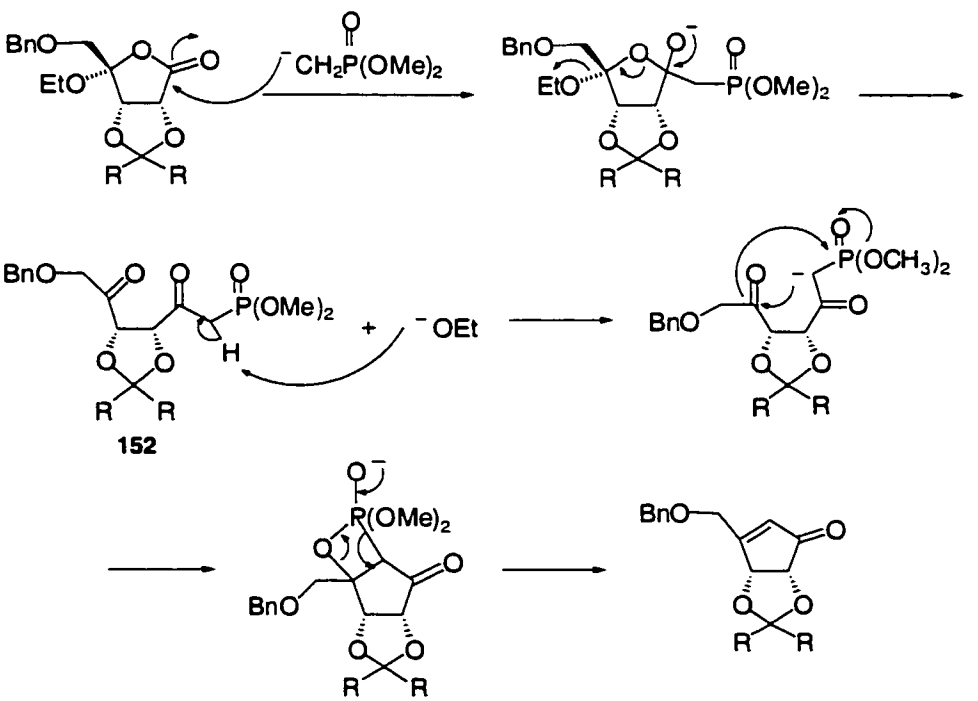
Scheme 1.31 Novel Ring Opening, Wadsworth Emmons Reaction. (a) **148**: 2,2-Dimethoxypropane, TsOH. **149**: 1,1-Dimethyloxycyclohexane, TsOH; (b) nBuLi, $CH_3P(O)(OCH_3)_2$, then **148**/**149**.

spectroscopy but there was a very poor mass balance. It was envisioned that the low yield of enone **150** was due to a problem with the phosphonate anion. In an

attempt to improve formation of the phosphonate anion, a stock solution was made. Unfortunately, this did not improve the yield of enone **150**. Inverse addition of the phosphonate anion to acetonide **148** was also attempted with no success.

It was believed that enone **150** was volatile causing the low yield. Therefore, diol **142** was protected with a larger protecting group. Cyclohexanone ketal **149** was synthesized in 86% yield and subjected to the conditions for the one-pot ring-opening, intramolecular Wadsworth-Emmons reaction. The yield increased from 11% for **150** to 52% (and 60% based on recovered starting material) for **151** (Scheme 1.31). Once again, the crude material was very clean by H^1 NMR spectroscopy but the mass balance was low.

It was postulated that a water-soluble intermediate was not converting to product, causing the low mass balance. As shown by the mechanism in



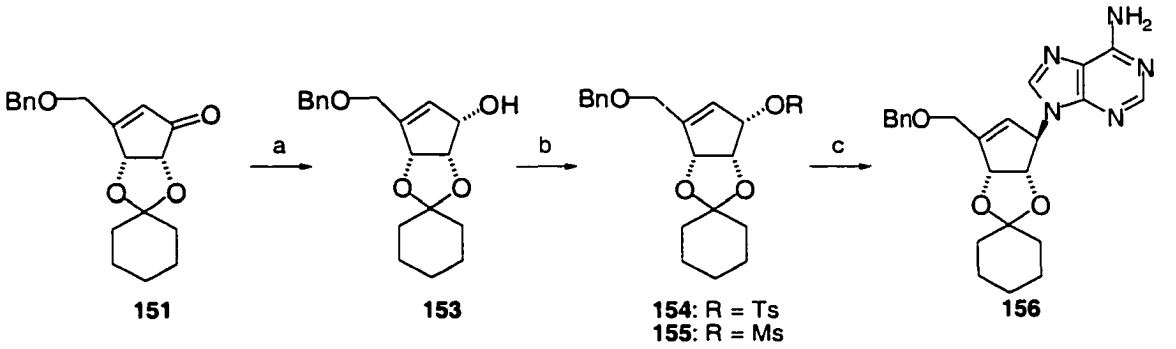
Scheme 1.32 Postulated Mechanismfor One-pot Ring-opening, Intramolecular Wadsworth-Emmons Reaction.

Scheme 1.32, if the base formed *in situ* was quenched during the reaction, the intramolecular ring closing reaction could not occur. Therefore, a build up of intermediate **152** would occur, which may be water soluble and cause loss of material upon workup. Additional base was not added to the reaction to test this hypothesis due to the known racemization and subsequent poor yield that can occur.[6]

Reduction of enone **151** with sodium borohydride and cerium trichloride[6,45] occurred exclusively from the face opposite the protected diol, giving alcohol **153** in 96% yield (Scheme 1.33). A number of approaches for the direct introduction of adenine into allylic alcohols, such as **153**, have been reported with Mitsunobu coupling[15] being the most direct approach. However, when alcohol **153** was subjected to Mitsunobu conditions at room temperature in THF no reaction occurred, perhaps because adenine is poorly soluble in the reaction medium. Heating the reaction to 100 °C in a pressure tube resulted in extensive decomposition.

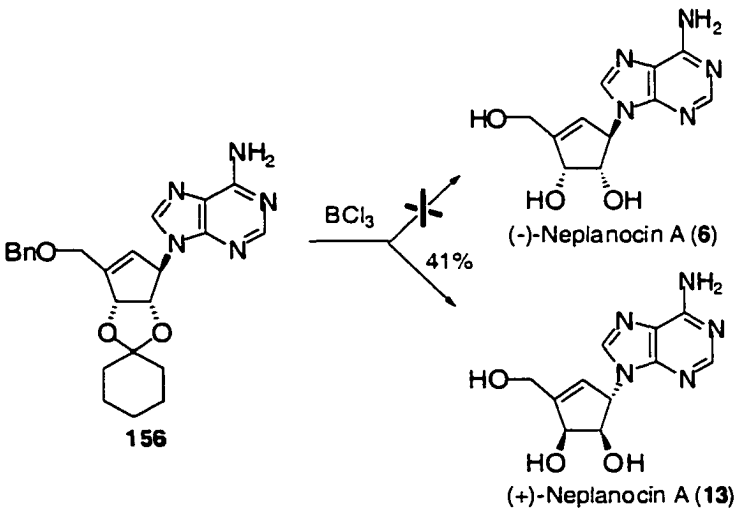
Formation of the glycosidic bond can also be accomplished by S_N2 displacement of a leaving group with adenine. Therefore, alcohol **153** was converted to tosylate **154** with tosyl chloride and triethylamine. Removal of excess TsCl from the product was problematic and the coupling was intolerant to the TsCl.[22,24] In contrast, mesylation of **153** with mesyl chloride and triethylamine proceeded in 86% yield without complications. Coupling of **155** with adenine, potassium carbonate, and 18-crown-6 in DMF[16] gave protected neplanocin A (**156**) in 54% yield, accompanied by small amounts (≈4%) of the N-7 isomer,

results comparable to other reported couplings with adenine[45] as shown in Scheme 1.33.



Scheme 1.33 (a) $NaBH_4/CeCl_3$; (b) **154**: TsCl, Et_3N **155**: MsCl, Et_3N: (c) adenine, K_2CO_3, 18-crown-6, DMF.

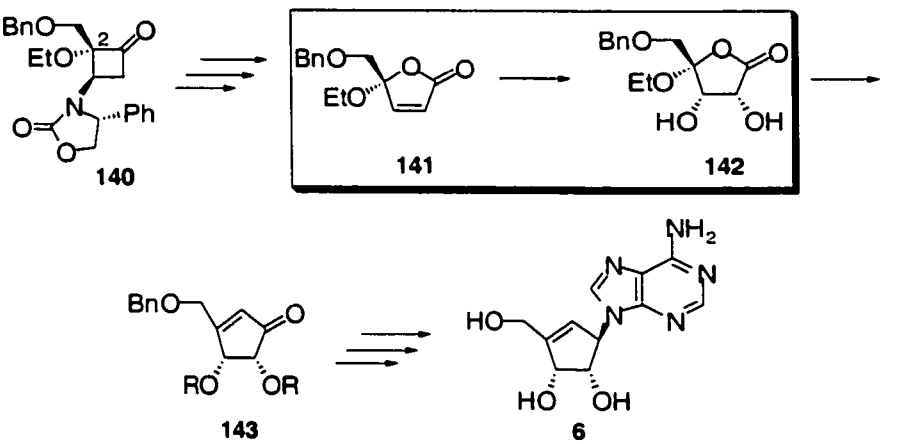
Removal of both protecting groups with BCl_3 should have given (-)-neplanocin A (**6**). Product was obtained in 41% yield that spectroscopically matched the data for neplanocin A. It was only when the optical rotation was determined that a problem arose. Surprisingly, the rotation was positive instead of negative, indicating the wrong enantiomer (**13**) was synthesized (Scheme 1.34).



Scheme 1.34

Intermediate **156** could not produce (+)-neplanocin A (**13**) with the addition of BCl_3. Therefore, there was a problem with the stereochemistry of the

proposed synthetic route. A solution to this puzzle required reevaluation of work performed, both past and present. As stated previously, the stereochemistry of cyclobutanone **140** is established in the photoreaction by the use of (R)-vinyl carbamate **123** and this has been confirmed by an X-ray crystal structure. The stereochemistry at the C-2 center is carried on to butenolide **141** (and this center is destroyed in the synthesis of enone **143**), therefore the stereochemistry of butenolide **141** is valid. Accordingly, synthesis of the



Scheme 1.35

wrong enantiomer of neplanocin A could only occur if the stereochemistry of diol **142** was assigned incorrectly, since the *cis*-hydroxylation step sets the remaining 1'-, 2'-, and 3'-stereocenters for (-)-neplanocin A (**6**). The major diol must result from *cis*-hydroxylation of the β-face of the butenolide, the face *opposite* the ethoxy group (Scheme 1.35). Therefore, the attempts to establish the stereochemistry of the two diastereomeric diols using nOe data failed, as is often the case in five-membered ring systems.[44]

To investigate the reasons why the nOe data were misinterpreted, new spectroscopic data were collected. For the assignment of the ^{1}H NMR spectra for diol **142** and **147**, it was believed that the proton alpha to the carbonyl (Hα) for

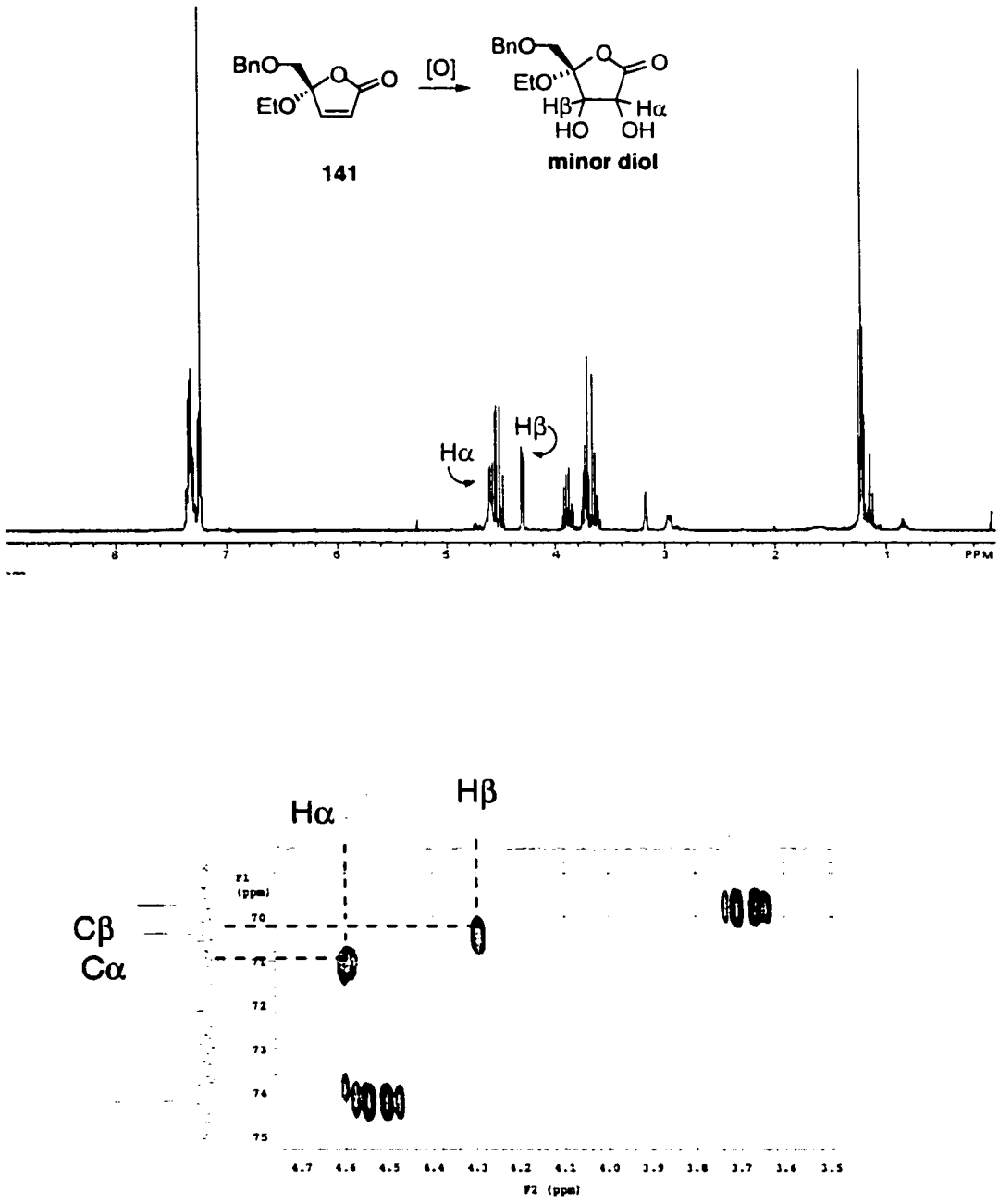
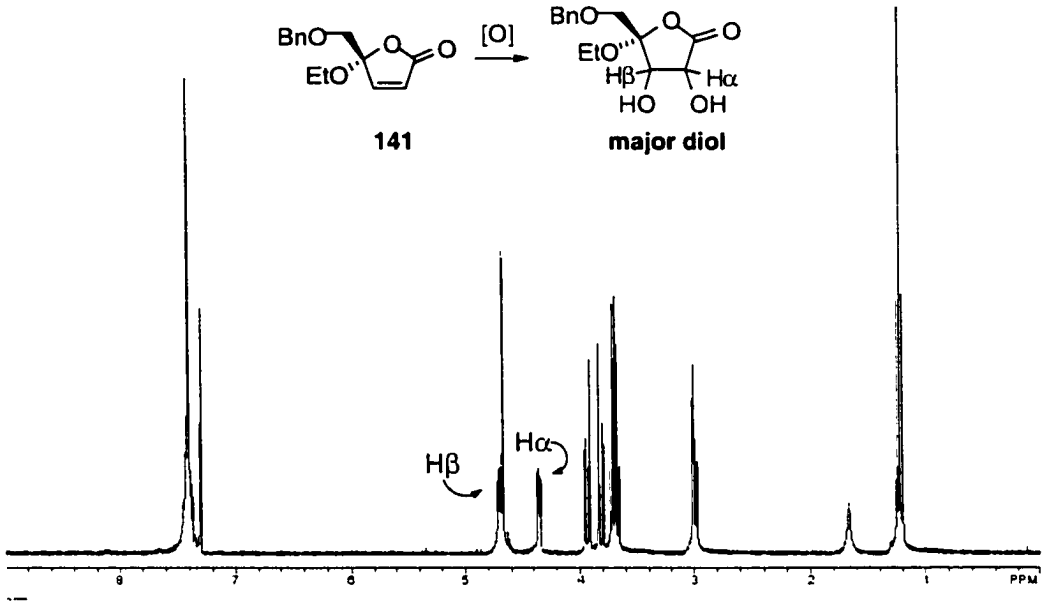


Figure 1.6 ^{1}H NMR and HSQC Data for Minor Diol.

each diastereomer would be further downfield than the proton beta to the carbonyl (Hβ). The key experiment to test this assumption is a 2D NMR technique; a HSQC experiment. This experiment is composed of only cross-

peaks with the ^{1}H NMR spectrum on the x-axis and the ^{13}C NMR spectrum on the y-axis, each crosspeak relating a carbon to its directly bonded proton or protons.



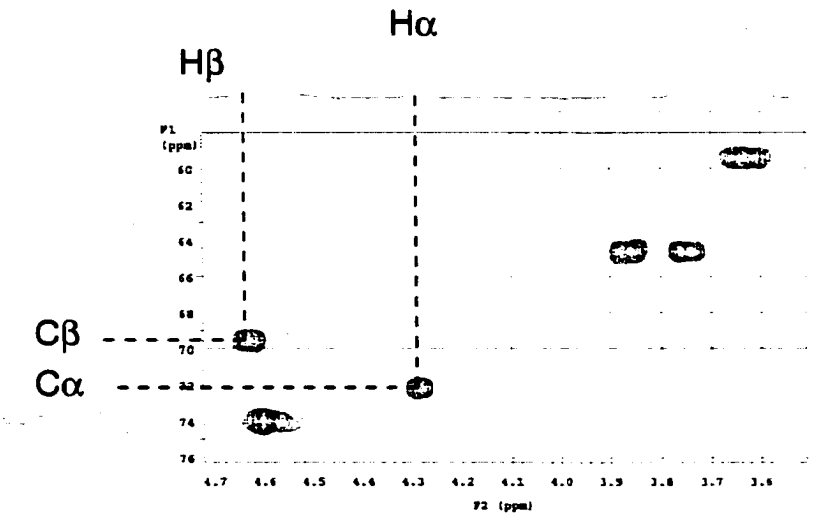


Figure 1.7 ^{1}H NMR and HSQC Data for Major Diol.

As shown in Figure 1.6, by interpreting the HSQC experiment it was found that the assumption for the assignment of Hα and Hβ in the ^{1}H NMR spectrum was correct for the minor diol, with Hβ appearing at δ 4.3 and Hα at δ 4.6. However by interpreting the HSQC data for the major diol, the assumption was found to be incorrect. In its ^{1}H NMR spectrum Hβ appeared at δ 4.6 while Hα appeared at δ 4.3, as shown in Figure 1.7. This exchange of the signals for α- and β-protons for the two diols was surprising.

With the correct assignment of the ^{1}H NMR spectra, new nOe data were taken to see if it could shed some light on the stereochemistry of the diols. The only significant nOe interactions that could be used to determine the stereochemistry of the diols were interactions of Hβ of *both* isomers with C-6 methylene protons (Figure 1.8). Therefore, no assignment could be made.

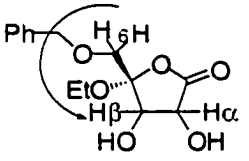
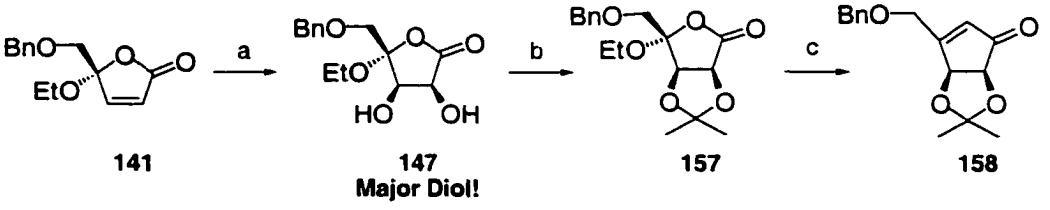


Figure 1.8 Both Major and Minor Diol's nOe Data.

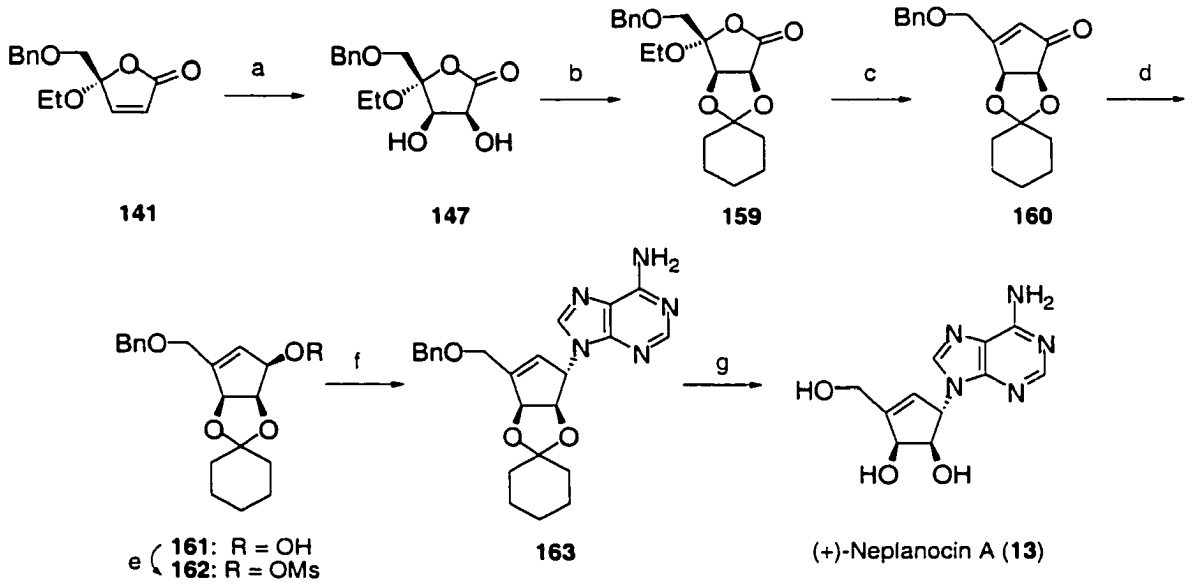
To confirm that the major diol was indeed **147** and not **142**, it was converted to acetonide **158** (Scheme 1.36) which had an $[\alpha]_D$ of +8° (c = 0.06, $CHCl_3$), in comparison to the reported $[\alpha]_D$ of -7.2° (c = 1.1, $CHCl_3$) for the α-isomer.[45]



141 **147** **Major Diol!** **157** **158**

Scheme 1.36 (a) $KMnO_4$, 18-crown-6; (b) 2,2-dimethoxypropane, TsOH; (c) *n*-BuLi, dimethyl methyl phosphonate.

With the correct stereochemistry known for the *cis*-dihydroxylation, the synthesis of (+)-neplanocin A (**13**) is straightforward. The true stereochemistry of the previously established synthesis is shown in Scheme 1.37 and it is the first published synthesis of (+)-neplanocin A.[29] (-)-Neplanocin A (**6**) should be



Scheme 1.37 (a) $KMnO_4$, 18-crown-6; (b) 1,1-dimethoxy-cyclohexane, TsOH; (c) *n*-BuLi, dimethyl methylphosphonate; (d) $NaBH_4/CeCl_3$; (e) MsCl, Et_3N; (f) adenine, K_2CO_3, 18-crown-6, DMF; (g) BCl_3.

available by the same route, starting with the (+)-enantiomer of **141** which is readily available using S-phenyl glycine and in-house chromium carbene chemistry.[31]

IV. Conclusion

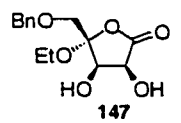
The first total synthesis of (+)-neplanocin A was accomplished with the development of the novel one-pot ring-opening, intramolecular Wadsworth-Emmons reaction. Insight was gained in the oxidation of butenolide **141**, for which previous work in the group assigned the incorrect stereochemistry of the

two diastereotopic diols (**142** and **147**). The Hegedus group has been working on a variety of nucleoside analogs that use this oxidation chemistry. Therefore, correct assignment of the diastereomers was also crucial to their development.

V. Experimental

Materials. The following compound was synthesized according to literature procedure: butenolide **141**.[46] Its purity was confirmed by NMR spectroscopy and optical rotation datum.

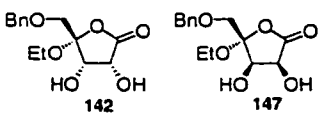
General Methods. THF was distilled from sodium-benzophenone ketyl; CH_2Cl_2, DMF, and Et_3N were distilled from CaH_2. Commercially available reagents were used as received except as indicated and dimethyl methylphosphonate and $RuCl_3 x H_2O$ were stored in a desiccator. ^1H NMR, nOe, COSY (300 MHz), ^{13}C NMR (75 MHz), and HSQC (400 ^1H MHz) spectra were recorded in $CDCl_3$ unless otherwise noted and chemical shifts are given in ppm relative to $CDCl_3$ (7.24 ppm). Column chromatography was performed with ICN 32-66 nm, 60 Å silica gel using flash column techniques unless otherwise noted. Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ. FAB-High Resolution Mass Spectrometry (HRMS) was obtained with a Fisons VG AutoSpec mass spectrometer with a Cs ion gun, *m*-nitrobenzyl alcohol was used for the matrix, and the resolution was set to 10,000. All reactions were performed in flame-dried glassware under an atmosphere of Ar unless otherwise noted.



147
$C_{14}H_{18}O_5$
Exact Mass: 282.11
Mol. Wt.: 282.29
C, 59.57; H, 6.43; O, 34.01

(3S, 4R, 5R)-5-Benzyloxymethyl-5-ethoxy-3,4-dihydroxy-dihydro-furan-2-one (147). (-)-Butenolide **141** (0.900 g, 3.62 mmol) was dissolved in 30 mL of CH_2Cl_2 and

cis-dicyclohexano-18-crown-6 (0.135 g, 0.362 mmol) was added. The solution was cooled to -40 °C in a dry ice/acetonitrile bath and $KMnO_4$ (0.744 g, 4.71 mmol) was added in five portions over 45 minutes. The mixture was stirred at -40 °C until side products were visible (~ 2-3 hours) by TLC (silica gel, hexane/EtOAc, 3:1). Solid $NaHSO_3$, DI H_2O, and two drops of 1M H_2SO_4 were added and the mixture was transferred to a separatory funnel. The mixture was shaken vigorously and additional solid $NaHSO_3$ was added until the solution decolorized upon shaking. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The crude yellow oil was purified by flash column chromatography (5:1 - 3:1 hexane/Et_2O - 100% Et_2O gradient elution) to yield diol **147** as a clear oil (0.514 g, 1.82 mmol, 50%) and recovered butenolide **141** (0.256 g). **147**: $[\alpha]_D^{25}$ -17° (*c* = 1.83, EtOH); ^1H NMR δ 7.35 (m, 5H), 4.63 (m, 1H), 4.60 (s, 2H), 4.29 (dd, *J*=2.7 Hz, *J*=4.8 Hz, 2H), 3.87 (d, *J*=11.1 Hz, 1H), 3.75 (d, *J*=10.8 Hz, 1H), 3.63 (q, *J*=7.1 Hz, 2H), 2.93 (m, 2H), 1.15 (t, *J*=7.1 Hz, 3H); ^{13}C NMR δ 175.4, 136.9, 128.5, 128.1, 128.0, 107.4, 73.7, 71.9, 69.4, 64.2, 59.1, 15.3; IR (neat) 3421, 1793 cm^{-1}; FAB-HRMS calcd for $C_{14}H_{19}O_6$ (M+H): 283.1182, found 283.1174.

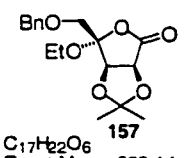


$C_{14}H_{18}O_6$
Exact Mass: 282.11
Mol. Wt.: 282.29
C, 59.57; H, 6.43; O, 34.01

5-Benzyloxymethyl-5-ethoxy-3,4-dihydroxy-dihydro-furan-2-ones (142 and 147). Method A: (-)-Butenolide **141** (52.5 mg, 0.211 mmol) was dissolved in 2 mL of EtOAc and 2 mL of CH_3CN. The solution was cooled to 0 °C. $RuCl_3 \cdot xH_2O$ (3.1 mg, 0.015 mmol) and $NaIO_4$ (67.8 mg, 0.317 mmol) were dissolved in 0.75 mL of H_2O and added to the butenolide solution via syringe. The reaction was stirred vigorously for 5 minutes and then poured into sat. aq. $Na_2S_2O_3$. The organic layer was extracted with EtOAc, combined,

dried over $MgSO_4$, filtered, and concentrated. The crude brown residue was purified by flash column chromatography (4:1 - 3:1 hexane/EtOAc gradient elution) to yield diol **142** (7 mg, 0.02 mmol, 12%) and **147** (24 mg, 0.085 mmol, 40%) as clear oils along with recovered butenolide **141** (11 mg). **142**: ^{1}H NMR (400 MHz) δ 7.31 (m, 5H), 4.61 (m, 1H), 4.57 (d, *J*=12.4 Hz, 1H), 4.49 (d, *J*=11.6 Hz, 1H), 4.30 (d, *J*=5.6 Hz, 1H), 3.90 (m, 1H), 3.73 (d, *J*=9.6 Hz, 1H), 3.68 (m, 1H), 3.66 (d, *J*=10.4 Hz, 1H), 3.17 (s, 1H), 2.96 (d, *J*=8.4 Hz, 1H), 1.24 (t, *J*=7.2, 3H); ^{13}C NMR δ 174.0, 136.4, 128.7, 128.3, 128.0, 127.8, 103.6, 74.0, 70.8, 70.2, 69.5, 61.0, 15.4.

Method B: (-)-Butenolide **141** (16.5 mg, 0.0644 mmol) was dissolved in 1 mL of a 1:1 mixture of acetone and DI H_2O. OsO_4 (0.2 mL, 0.033 mmol) was added via syringe. $(CH_3)_3NO$ (18.4 mg, 0.166 mmol) and pyridine (2 drops) were added respectively and the reaction flask was wrapped in foil to exclude light. The reaction was quenched when undesirable side products were present by TLC (silica gel, 1:1 hexane/EtOAc) with 10% sat. aq. $Na_2S_2O_3$. The organic layer was extracted with CH_2Cl_2, dried with $MgSO_4$, and concentrated. Purification by preparative TLC (1:1 hexane/EtOAc) gave major diol **147** (2.6 mg, 0.0092, 9%) and minor diol **142** (1.4 mg, 0.0049 mmol, 5%) along with butenolide **141** (13.3 mg, 0.084 mmol).

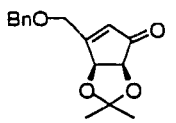


157

$C_{17}H_{22}O_6$
Exact Mass: 322.14
Mol. Wt.: 322.35
C, 63.34; H, 6.88; O, 29.78

(3*S*, 4*R*, 5*R*)-5-Benzyloxymethyl-3,4-diol-5-ethoxydihydrofuran-2-one Acetonide (157). A flask, equipped with reflux condenser and Soxhlett extractor containing 4 Å molecular sieves, was charged with diol **147** (32.3 mg, 0.114 mmol), 2,2-dimethoxypropane (0.25 mL, 2.9 mmol), and 15 mL benzene. The solution was warmed to reflux and a few crystals of TsOH were added. The reaction was kept at reflux for 30 minutes and then cooled to room temperature. The organic layer was washed with sat. aq. $NaCO_3$ (x2), DI H_2O

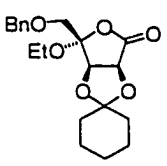
(x2), dried, and concentrated to give pure acetonide **157** (35.5 mg, 0.110 mmol, 96%) as a colorless oil: $[\alpha]_D^{25}$ +12° (*c* = 0.72, $CHCl_3$); IR (thin film) 1799 cm^{-1}; ^1H NMR δ 7.37 (m, 5H), 4.90 (d, *J*=5.1 Hz, 1H), 4.70 (d, *J*=12.1 Hz, 1H), 4.61 (d, *J*=4.8 Hz, 1H), 4.60 (d, *J*=12.5 Hz, 1H), 3.85 (d, *J*=11.0 Hz, 1H), 3.72 (d, *J*=11.0 Hz, 1H), 3.69 (q, *J*=7.0 Hz, 2H), 1.44 (s, 3H), 1.41 (s, 3H), 1.18 (t, *J*=7.0 Hz, 3H); ^{13}C NMR δ 173.6, 137.3, 127.9, 127.8, 114.5, 106.3, 79.3, 75.8, 73.6, 64.1, 59.0, 26.8, 26.1, 15.1; Anal. Calcd for $C_{16}H_{22}O_6$: C, 63.34; H, 6.88. Found: C, 63.16; H, 7.00.



$C_{16}H_{18}O_4$ **158**
Exact Mass: 274.12
Mol. Wt.: 274.31
C, 70.06; H, 6.61; O, 23.33

(4S, 5S)-3-Benzyloxymethyl-4,5-diol acetonide-cyclopent-2-enone (158). Following the general procedure of Borcherding *et al*[24], a two-necked flask was charged with freshly distilled dimethyl methylphosphonate (7.4 μL, 0.069 mmol) dissolved in 0.4 ml THF. The solution was cooled to -78 °C with an acetone/dry ice bath. Freshly titrated *n*-butyllithium (1.14 M in hexane, 0.06 ml, 0.069 mmol) was added via syringe over a 15 minute period, down the side arm of the flask to precool the solution. The solution was stirred for an additional 15 minutes after the addition was complete. Acetonide **157** (19 mg, 0.059 mmol), dissolved in a minimal amount of THF, was added down the side arm via syringe. The solution was stirred at -78 °C for 3 hours. The acetone/dry ice bath was removed and the solution was warmed to room temperature for 2 hours. The solution was partitioned between Et_2O and brine. The organic layer was separated and the aqueous layer was extracted with Et_2O. The combined ethereal layers were dried over $MgSO_4$, filtered, and concentrated. The crude oil was purified by flash column chromatography (3:1 pentane:ether) to afford enone **158** as a yellow oil (11 mg, 0.040 mmol, 11%). ^1H NMR (300 Hz, $CDCl_3$): δ 7.36-7.30 (m, 5H), 6.18 (s, 1H,), 5.07 (d, 1H, J=5.5 Hz), 4.62 (d, 2H, J=1.8 Hz), 4.48 (d, 1H, J=5.5 Hz), 4.45-4.29 (m, 2H), 1.41 (s, 3H), 1.38 (s, 3H). ^{13}C NMR (300 Hz,

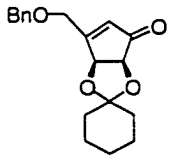
$CDCl_3$): δ 201.91, 173.88, 128.80, 128.72, 128.30, 127.97, 115.96, 78.25, 77.94, 73.61, 67.72, 27.65, 26. 42. IR (neat) 1723, 1626 cm^{-1}.



159

$C_{20}H_{26}O_6$
Exact Mass: 362.17
Mol. Wt.: 362.42
C, 66.28; H, 7.23; O, 26.49

(3*S*, 4*R*, 5*R*)-5-Benzyloxymethyl-3,4-diol-5-ethoxy-dihydrofuran-2-one Cyclohexanonide (159). Cyclohexanonide **159** was prepared using the procedure for acetonide **157** except 1,1-dimethoxycyclohexane (0.15 ml, 0.96 mmol, 10 eq.) was used. The crude material was purified by flash column chromatography (25:1 hexane/EtOAc) to give **159** as a clear oil (30 mg, 0.083 mmol, 86%): $[\alpha]_D^{25}$ -15° (*c* = 1.38, EtOH); ^{1}H NMR δ 7.30 (m, 5H), 4.87 (d, *J*=4.8 Hz, 1H), 4.65 (d, *J*=12.3 Hz, 1H), 4.60 (d, *J*=12.6 Hz, 1H), 4.56 (d, *J*=5.1 Hz, 1H), 3.84 (d, *J*=10.8 Hz, 1H), 3.71 (d, *J*=10.5 Hz, 1H), 3.68 (m, 2H), 1.57 (m, 10H), 1.16 (t, *J*=6.9 Hz, 3H); ^{13}C NMR δ 173.8, 137.3, 128.3, 127.8, 115.1, 106.4, 78.9, 75.5, 73.6, 64.2, 59.0, 36.5, 35.6, 24.7, 23.8, 15.2; IR (neat) 1801 cm^{-1}; FAB-HRMS calcd for $C_{20}H_{27}O_6$ (M+H): 363.1808, found 363.1804.

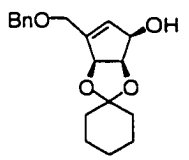


160

$C_{19}H_{22}O_4$
Exact Mass: 314.15
Mol. Wt.: 314.38
C, 72.59; H, 7.05; O, 20.36

(4S, 5S)-3-Benzyloxymethyl-4,5-diol cyclohexanonide-cyclopent-2-enone (160). Enone **160** was prepared using the procedure for enone **158**. The crude material was purified by flash column chromatography (25:1 - 10:1 hexane/EtOAc gradient elution) to give enone **160** as a yellow oil (56 mg, 0.18 mmol, 52%) and recovered starting material **159** (17.5 mg). **160**: $[\alpha]_D^{25}$ +7° (*c* = 0.855, EtOH); ^{1}H NMR δ 7.38 (m, 5H), 6.16 (m, 1H), 5.05 (d, *J*=5.7 Hz, 1H), 4.64 (d, *J*=11.7 Hz, 1H), 4.60 (d, *J*=12.0 Hz, 1H), 4.50 (dd, *J*=1.8 Hz, *J*=17.4 Hz, 1H), 4.46 (d, *J*=6.0 Hz, 1H), 4.33 (dd, *J*=1.2 Hz, *J*=17.7 Hz, 1H), 1.58 (m, 10H); ^{13}C NMR δ 201.7, 173.9, 137.1, 128.5, 128.3, 128.0, 127.6, 116.2, 77.6, 77.4, 73.3, 67.6, 37.3, 35.8, 25.0, 23.9, 23.6; IR (neat) 1724 cm^{-1}; FAB-HRMS calcd for

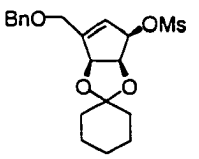
$C_{19}H_{23}O_4$ (M+H): 315.1596, found 315.1600; Anal. Calcd for $C_{19}H_{22}O_4$: C, 72.56; H, 7.05; Found: C, 72.32; H, 6.91.



161

$C_{19}H_{24}O_4$
Exact Mass: 316.17
Mol. Wt.: 316.39
C, 72.13; H, 7.65; O, 20.23

(1R, 4S, 5R)-3-Benzyloxymethyl-4,5-diol cyclohexanonide-cyclopent-2-enol (161). Enone **160** (67 mg, 0.21 mmol) was dissolved in 0.2 mL of MeOH (stored over 3 Å molecular sieves). The solution was cooled to 0 °C and $CeCl_3 \cdot 7H_2O$ (66.7 mg, 0.179 mmol) was added. $NaBH_4$ (12.1 mg, 0.32 mmol) was added in 3 portions and the reaction was stirred at 0 °C for 10 minutes. Glacial acetic acid was added via syringe until pH ~ 5, brine was added, and the mixture was extracted with Et_2O. The combined ethereal layers were dried over $MgSO_4$, filtered, and concentrated by rotary evaporation. The crude oil was purified by flash column chromatography (25:1 hexane/EtOAc gradient elution) to yield alcohol **161** as a clear film (64 mg, 0.20 mmol, 96%): $[\alpha]_D^{25}$ -28° (*c* = 1.69, EtOH); ^{1}H NMR δ 7.28 (m, 5H), 5.77 (s, 1H), 4.95 (d, *J*=5.4 Hz, 1H), 4.73 (t, *J*=5.4 Hz, 1H), 4.54 (m, 2H), 4.13 (s, 2H), 2.76 (d, *J*=9.9 Hz, 1H) 1.58 (m, 10H); ^{13}C NMR δ 173.8, 137.3, 128.3, 127.8, 115.2, 106.4, 78.9, 75.5, 73.6, 64.2, 59.0, 36.5, 35.7, 24.7, 23.8, 23.7, 15.2; IR (neat) 3540 cm^{-1}; FAB-HRMS calcd for $C_{19}H_{25}O_4$ (M+H): 317.1753, found 317.1740.

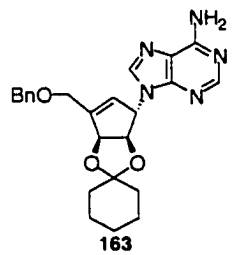


162

$C_{20}H_{26}O_6S$
Exact Mass: 394.15
Mol. Wt.: 394.48
C, 60.89; H, 6.64; O, 24.33; S, 8.13

(1R, 4S, 5R)-Methanesulfonic acid 3-benzyloxymethyl-4,5-diol cyclohexanonide-cyclopent-2-enyl ester (162). Alcohol **161** (40 mg, 0.126 mmol) was dissolved in 3 mL of CH_2Cl_2 and cooled to 0 °C. NEt_3 (0.02 mL, 0.164 mmol) and then MsCl (0.01 mL, 0.164 mmol) were added via syringe. The reaction was stirred at 0 °C for 10 minutes

and quenched with water. The aqueous layer was separated and extracted with CH_2Cl_2. The combined organic layers were washed with sat. aq. $NaHCO_3$, dried over $MgSO_4$, and concentrated by rotary evaporation. The crude oil was purified by flash column chromatography (4:1 hexane/EtOAc) to yield mesylate **162** as a clear oil (43 mg, 0.109 mmol, 86%): $[\alpha]_D^{25}$ +15° (*c* = 1.96, EtOH); ^{1}H NMR (400 MHz) δ 7.30 (m, 5H), 5.78 (d, *J*=0.8 Hz, 1H), 5.39 (dd, *J*=2.0 Hz, *J*=5.2 Hz, 1H), 4.94 (d, *J*=5.6 Hz, 1H), 4.89 (t, *J*=5.4 Hz, 1H), 4.57 (d, *J*=12.0 Hz, 1H), 4.54 (d, *J*=12.0 Hz, 1H), 4.20 (d, *J*=14.0 Hz, 1H), 4.15 (d, *J*=14.4 Hz, 1H), 3.12 (s, 3H), 1.54 (m, 10H); ^{13}C NMR (400 MHz) δ 147.3, 137.7, 128.4, 127.8, 127.6, 125.0, 114.2, 82.6, 80.9, 76.8, 73.0, 66.1, 39.0, 37.1, 36.4, 24.9, 23.9; IR (neat) 1350, 1175 cm^{-1}; FAB-HRMS calcd for $C_{20}H_{26}O_6S$: 394.1450, found 394.1438.

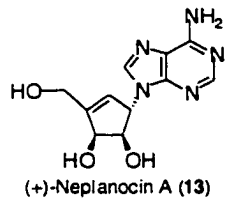


163

$C_{24}H_{27}N_5O_3$
Exact Mass: 433.21
Mol. Wt.: 433.50
C, 66.49; H, 6.28; N, 16.16; O, 11.07

(1S, 4S, 5R)-9-(3-Benzyloxymethyl-4,5-diol cyclohexanonide-cyclopent-2-enyl)-9*H*-purin-6-ylamine (163). K_2CO_3 (36.4 mg, 0.264 mmol) and 18-crown-6 (34.8 mg, 0.132 mmol) were dissolved in 1.8 mL of DMF. Adenine (35.6 mg, 0.264 mmol) was added and the solution was stirred for 10 minutes. Mesylate **162** (52 mg, 0.13 mmol), dissolved in a minimal amount of DMF, was added dropwise to the solution. The solution was warmed to ~70 °C for 18 hours and then cooled to room temperature. The DMF was removed by rotary evaporation. The resulting tan residue was dissolved in CH_2Cl_2, filtered through Celite to remove any solid particles, and concentrated. The resulting yellow oil was purified by flash column chromatography (6:1 hexane/EtOAc - 100% CH_2Cl_2 - 3% MeOH/CH_2Cl_2

gradient elution) to first give a clear oil, which was triturated with CH_2Cl_2 to remove any inorganic impurities. Concentration of the triturating solvent gave **163** as a clear oil (31 mg, 0.072 mmol, 54%): $[\alpha]_D^{25}$ +102° (*c* = 1.34, EtOH); ^1H NMR δ 8.34 (s, 1H), 7.64 (s, 1H), 7.31 (m, 5H), 6.07 (bs, 2H), 5.78 (s, 1H), 5.55 (s, 1H), 5.38 (d, *J*=4.2 Hz, 1H), 4.70 (d, *J*=4.5 Hz, 1H), 4.63 (d, *J*=9.3 Hz, 1H), 4.54 (d, *J*=18.3 Hz, 1H), 4.50 (d, *J*=18.6 Hz, 1H), 4.24 (d, *J*=11.4 Hz, 1H), 1.59 (m, 10H); ^{13}C NMR (400 MHz) δ 155.3, 152.7, 149.8, 149.6, 138.9, 137.8, 128.4, 127.8, 127.6, 122.8, 120.1, 113.4, 83.9, 83.6, 72.9, 66.5, 64.7, 37.2, 35.6, 24.9, 24.0, 23.6; IR (neat) 3319, 3156, 1648, 1596 cm^{-1}; FAB-HRMS calcd for $C_{24}H_{28}N_5O_3$ (M+H): 434.2192, found 434.2195. The column then gave the N-7 isomer (2 mg, 0.005 mmol, 4%): ^1H NMR δ 8.49 (s, 1H), 7.85 (s, 1H), 7.34 (m, 5H), 6.02 (s, 1H), 5.76 (s, 1H), 5.53 (d, *J*=1.5 Hz, 1H), 5.25 (d, *J*=14.7 Hz, 1H), 4.72 (d, *J*=6.0 Hz, 1H), 4.65 (s, 2H), 4.31 (d, *J*=15.0 Hz, 1H), 4.26 (d, *J*=15.0 Hz, 1H), 1.65 (m, 10H).



(+)-Neplanocin A (**13**)
$C_{11}H_{13}N_5O_3$
Exact Mass: 263.10
Mol. Wt.: 263.25
C, 50.19; H, 4.98; N, 26.60; O, 18.23

(+)-Neplanocin A (13). Protected (+)-neplanocin A **163** (20 mg, 0.0461 mmol) was dissolved in 0.5 mL of CH_2Cl_2 and cooled to -78 °C. BCl_3 (0.5 mL, 0.461 mmol) was added slowly via syringe down the side of the flask to precool the solution. The mixture was stirred until no starting material was observed (~ 10 minutes) by TLC (silica gel, 10% MeOH in CH_2Cl_2). The solution was warmed to room temperature, quenched with MeOH, and concentrated. MeOH (2 mL) was added and the solution was concentrated. This addition/evaporation process was repeated twice more, followed by the addition of 1 mL of NH_3 in MeOH (satd at 0 °C). The solution was concentrated

and purified by flash column chromatography (10% EtOH/CH_2Cl_2 - 20% MeOH/CH_2Cl_2 gradient elution) to give a white solid, which was triturated with EtOH to remove any inorganic impurities. Concentration of the triturating solvent gave **13** as a white solid (4.9 mg, 0.0186 mmol, 41%): $[\alpha]_D$ +35° (c = 0.5, H_2O). The ^1H, ^{13}C, and mass spectra of this compound were identical to those previously reported.[24]

VI. References

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CHAPTER TWO

DE NOVO SYNTHESIS OF 4′-ETHOXY NUCLEOSIDE ANALOGS

I. Introduction and Background

Since the discovery of nucleocidin (**1**), a 4′-fluororibonucleoside with potent antibiotic activity,[1,2] numerous biologically active 4′-disubstituted nucleoside analogs have been discovered (Figure 2.1). For example, 5′-deoxy-4′,5-difluorouridine (**2**) has anticancer activity[3] and 4'-methyl adenine **3** has agonistic activity toward adenosine receptors.[4]

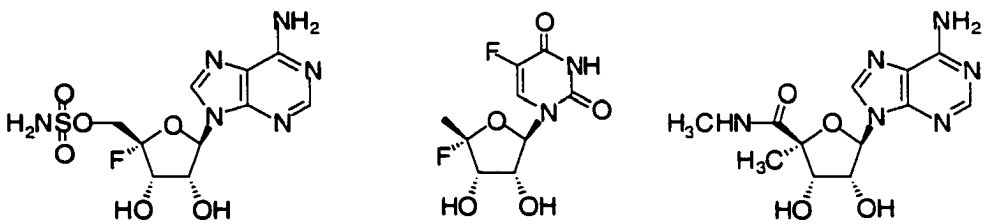


Figure 2.1 4′-Ethoxy Nucleoside Analogs.

A number of synthetic 4′-disubstituted nucleoside analogs (**4-8**) have anti-HIV activity, as shown in Figure 2.2.[5,6] Many anti-HIV active nucleoside analogs function as chain terminators and therefore must lack the 3′-hydroxy group. However, anti-HIV active 4′-disubstituted nucleoside analogs *required* a

3′-hydroxy group, indicating a fundamentally different mode of action for this class[7-9].

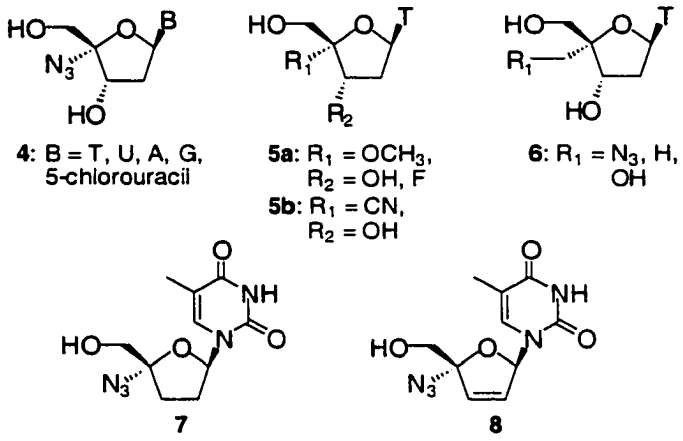


Figure 2.2 Synthetic 4′-Nucleoside Analogs.

The structure/activity relationships of 4′-disubstituted nucleoside analogs have been classified.[6] It was found that modifying the nucleoside base did not improve or diminish the nucleosides' biological activity, while substitution at the 2′-, 3′-, and 4′-position greatly affected it (Figure 2.3).

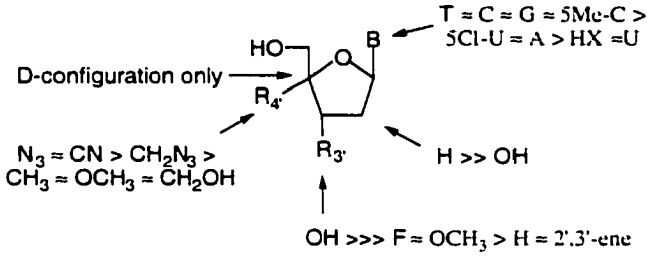
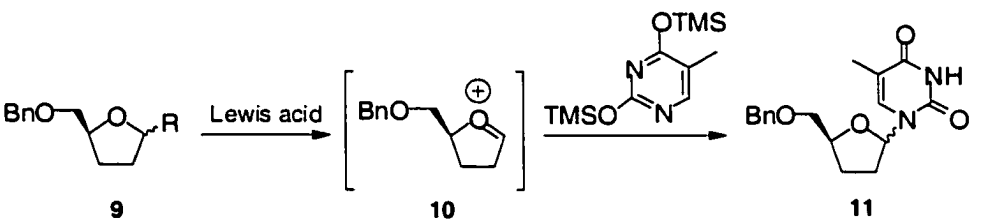


Figure 2.3 Structure/Activity Relationships of 4′-Disubstituted Nucleoside Analogs.

Most of 4′-disubstituted nucleosides have been synthesized from existing nucleosides[10-13] or carbohydrates.[14-18] With these methods it is difficult to control the stereochemistry at the 4′-position. In addition, these approaches are restricted to the naturally occurring D-nucleosides. However, the recent availability of L-ribose from L-xylose[19] should provide access to the unnatural

L-series of nucleosides, which may have antiviral activity, reduced toxicity,[20] and can be precursors to stable L-RNA building blocks.[21]

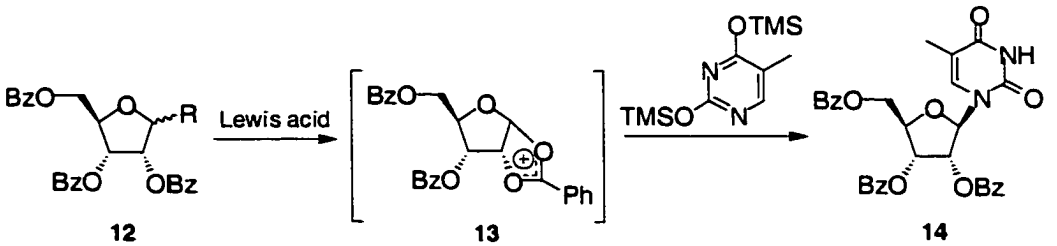
When carbohydrates or other non-nucleoside substrates are used as starting material for 4′-disubstituted nucleoside analogs, the glycosidic bond needs to be formed. Vorbrüggen coupling is the standard method and uses a Lewis acid to ionize compounds such as **9**, forming an oxonium ion (**10**). When the oxonium ion is treated with a silylated nucleoside base, which can be formed *in situ* or isolated, the glycosidic bond is formed (**11**). In the synthesis of 2′-deoxy-, 2′,3′-dideoxy-, and 2′,3′-dideoxydidehydronucleoside analogs, Vorbrüggen coupling is nonselective, giving a 1:1 mixture of α:β anomers (Scheme 2.1). Selectivity is seen only in the synthesis of



9 **10** **11**

Scheme 2.1 R = Leaving group = Br, Cl, OAc, OCO_2Me, OBz, OTs, OMs, etc.

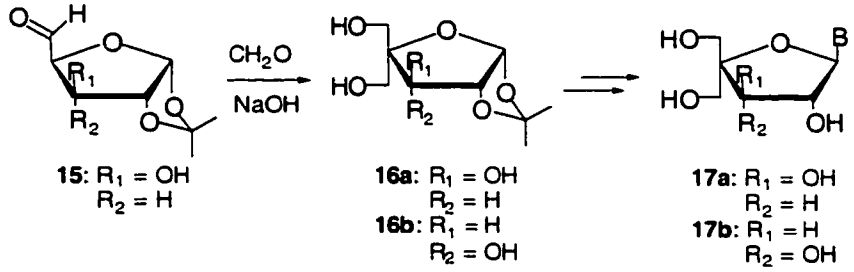
2′-hydroxynucleoside analogs, in which the 2′-hydroxyl protecting group, such as benzoyl and acetate, can participate in the oxonium ion (**13**). Exclusive formation of the β-anomer is obtained by the oxonium ion **13** blocking the α-face of the molecule (Scheme 2.2).[22]



12 **13** **14**

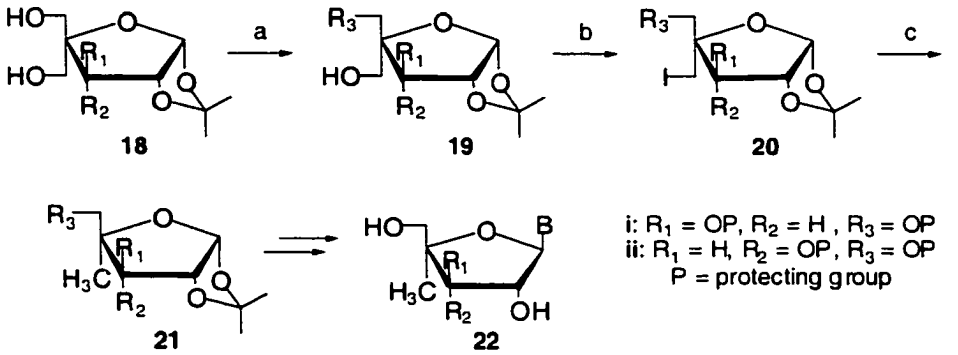
Scheme 2.2 R = Br, Cl, OAc, OCO_2Me, OBz, OTs, OMs, etc.

Most 4′-disubstituted nucleoside syntheses that use existing nucleosides or carbohydrates as the starting material were inspired by a seminal paper published in 1959 by Schaffer.[23] In this breakthrough work, aldehyde **15** was allowed to react with formaldehyde and aqueous sodium hydroxide to give 4′-bis(hydroxymethyl)ribose **16a** in 75% yield (Scheme 2.3) via a mixed aldol condensation and Cannizzaro reduction of the resulting hydroxyaldehyde. Later work showed that the product contained 12% of isomeric triol **16b**, which could be separated by chromatography.[18] Leland and Youssefyeh completed the synthesis of 4′-bis(hydroxymethyl)nucleoside analogs **17a** by acetolysis of **16a,b** and coupling with a variety of nucleoside bases.[17,18]



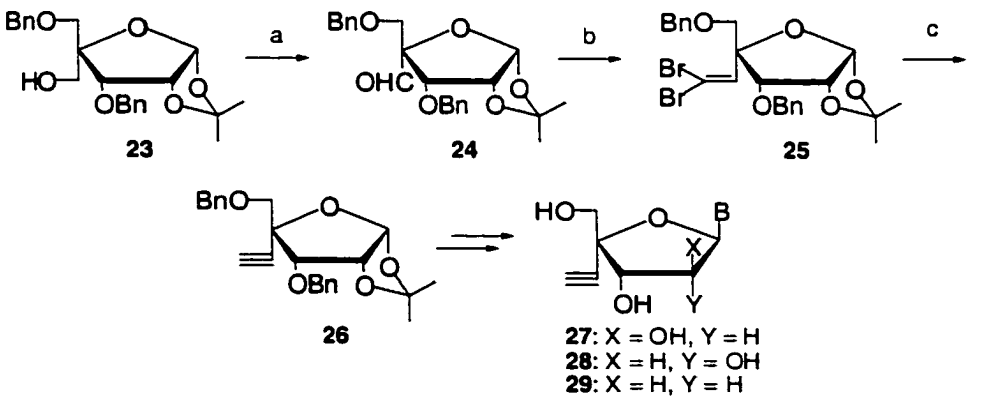
Scheme 2.3 B = adenine, 6-methoxyadenine, 6-methylthioadenine, 5-fluorouridine-6-aza-2-thiouracil, and 1,2,3-triazole-3-carboxamide.

In 1993, Ohrui utilized Schaffer's method to synthesize protected carbohydrates **18** and developed a synthesis of 4′-methyl nucleoside analogs **22** (Scheme 2.4).[16] This was accomplished by selectively protecting the 4-β-OH to give **19**. Ribose **19** was then converted to iodide **20** by Garreg's method and reduced to give methyl ribose **21**. Acetolysis, Vorbrüggen coupling with a variety of nucleoside bases, and deprotection gave a series of 4′-methyl nucleoside analogs **22**.



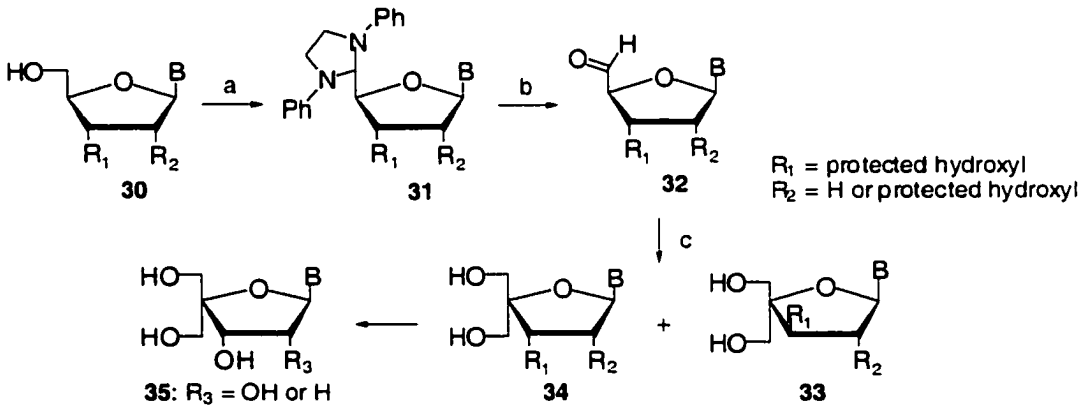
Scheme 2.4 B = adenine, thymine, uracil, cytidine, or guanine. (a) 1 eq. NaH and BnBr, 66% yield or DDQ, 53% yield; (b) imidazole, PPh_3, I_2, toluene/CH_3CN, reflux, 80% yield; (c) Bu_3SnH, AIBN, 74% or 90% yield.

Ohrui also developed a synthesis of 4′-ethynyl nucleoside analogs (**27-29**) from ribose **23** in 2000, as shown in Scheme 2.5.[15] Oxidation of **23** gave aldehyde **24**, which was converted to ethynyl analog **26**. Acetolysis, Vorbrüggen coupling, manipulation of the resulting 3′-hydroxyl, and deprotection gave 2′-deoxy, 2′-arabino, and 4′-ethynyl nucleoside analogs **27-29**. Several of the 2′-deoxy- and arabino-nucleoside analogs had impressive anti-HIV activity, with EC_{50} values ranging from 0.0003 to 0.03 μM.



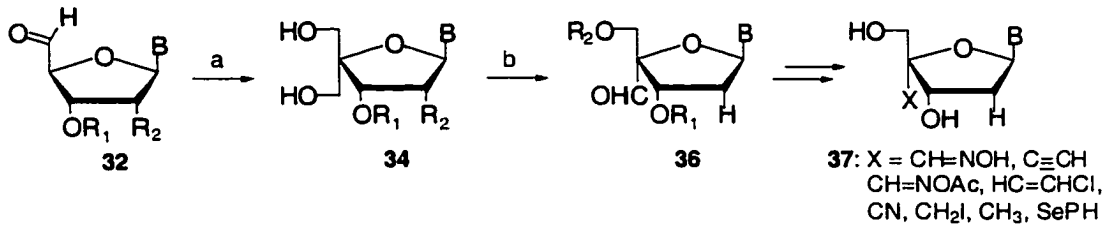
Scheme 2.5 B = thymidine, uridine, cytosine, inosine, guanosine, adenine, 5-halouridine, 5-halocytidine. (a) $(COCl)_2$, DMSO, ET_3N; (b) CBr_4, PPh_3, 95% yield; (c) *n*-BuLi, 90% yield; (d) 10% trifluoroacetic acid in 70% HOAc, 90% yield.

Schaffer's breakthrough also opened the door for the synthesis of 4'-disubstituted nucleoside analogs from existing nucleosides. In 1979, Jones synthesized the 5'-aldehyde nucleoside **32** by oxidation of **30** with DCC and DMSO, formation of the N,N'-phenylimidazolidine derivative **31** (for purification purposes), and hydrolysis (Scheme 2.6).[10] Schaffer's method was used to form 4'-dihydroxylmethyl nucleosides **34** in 62% yield, as a separable 1:1 mixture of **33**:**34**. Nucleoside **34** was deprotected to give a series of 4'-disubstituted nucleoside analogs **35**.[10]



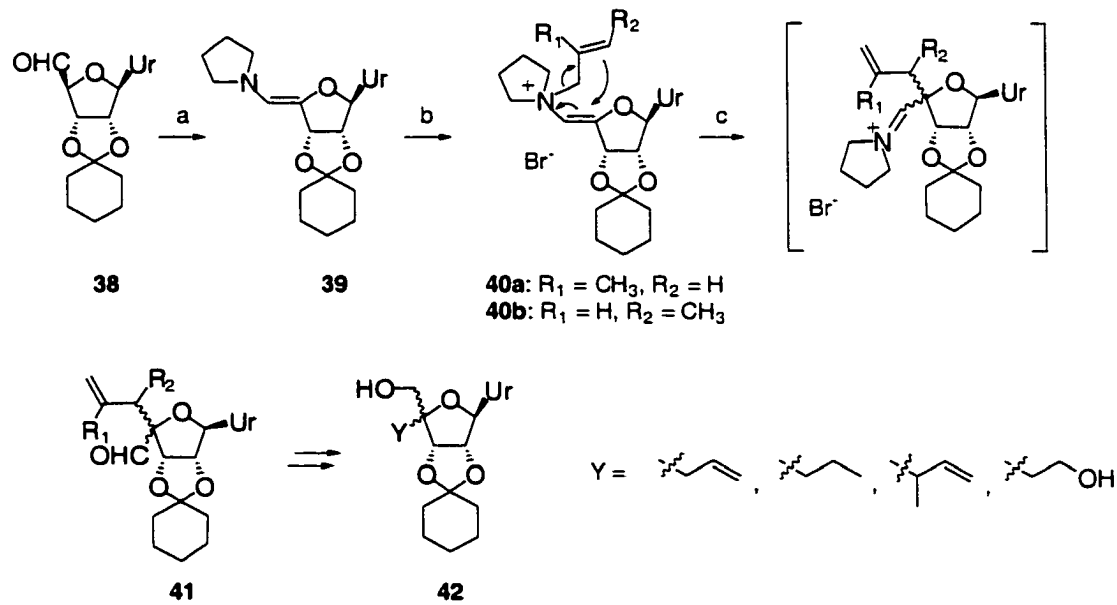
Scheme 2.6 B = adenine, cytidine, thymidine, uridine. (a) 1. DMSO, DCC 2. H^+, 3. $(PhNHCH_2)_2$ (b) Dowex 50 (H^+) resin, H_2O:THF, 53% yield over two steps; (c) CH_2O, NaOH, 62% yield.

Nomura improved the synthesis of **34** by adapting Schaffer's methods. Aldehyde **32** was reacted with formaldehyde and sodium hydroxide. The resulting hydroxymethyl aldehyde was reduced directly with sodium borohydride, instead of allowing the Cannizzaro reduction to occur, giving **34** in 44% yield (Scheme 2.7). After manipulation of the protecting groups, oxidation gave 5'-aldehyde **36**. The aldehyde was converted to a variety of substituents and deprotection gave 4'-disubstituted nucleoside analogs (**37**).[12]



Scheme 2.7 (a) CH_2O, NaOH, $NaBH_4$, 44% yield; (b) 1. DMTrCl, pyr. 2. TBDPSCl, imidazole, 48% yield 3. Swern oxidation, 82% yield.

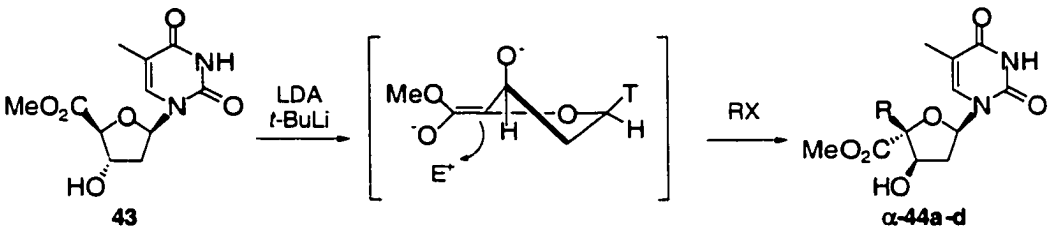
Using 5'-aldehyde nucleoside **38**, Secrist[24] developed a synthesis of 4'-(carbon)-substituted nucleoside analogs from 4',5'-enamines. Treatment of **38** with pyrrolidine gave 4',5'-enamine **39**. Alkylation at nitrogen (**40**), subsequent aza-Claisen rearrangement, and hydrolysis gave 4'-substituted aldehyde **41**. Further manipulation of the R group is possible and/or the aldehyde can be reduced to give protected 4'-disubstituted nucleosides **42**, as shown in Scheme 2.8.



Scheme 2.8 (a) pyrrolidine, 1:1 benzene:acetonitrile, 50 °C, quant. yield; (b) allyl bromide, methylallyl bromide or crotyl bromide, 80 °C; (c) 80 °C, then aq. H^+.

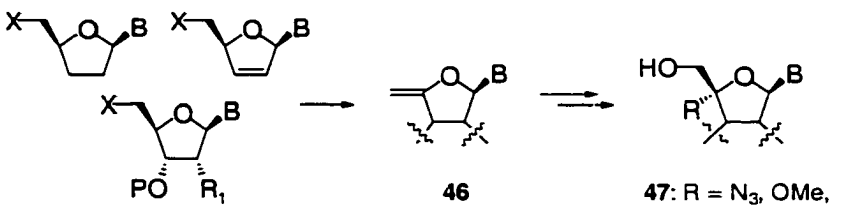
4'-Disubstituted nucleoside analogs can also be synthesized by electrophilic addition to 5'-esters **43**, as shown by Jung (Table 2.1). Nucleoside **43** was treated with excess LDA, *t*-BuLi and an electrophile, to give 4'-disubstituted nucleoside analogs (**44a-d**). Unfortunately, the major product was the undesired α-diastereomer due to the 3'-exo-configuration of the intermediate and subsequent attack of the electrophile opposite the hydroxyl group.[25]

Table 2.1



Compound	RX	R	α-product	β-product	% yield
44a	PhSeCl	SePh	9.3	1	62
44b	Allyl-Br	Allyl	7.3	1	22
44c	MeI	Me	8.7	1	58
44d	NFSI	F	1	0	30

4'-Disubstituted nucleoside analogs have also been synthesized from existing nucleosides via addition into a 3',4'- or 4',5'- double bond. 4',5'-Unsaturated nucleosides **46** are commonly obtained from elimination of a 5'-leaving group (Scheme 2.9). Halogenation or addition reactions of **46** gave 4'-azido, halo, or methoxy compounds (**47**). The reactions are often unselective



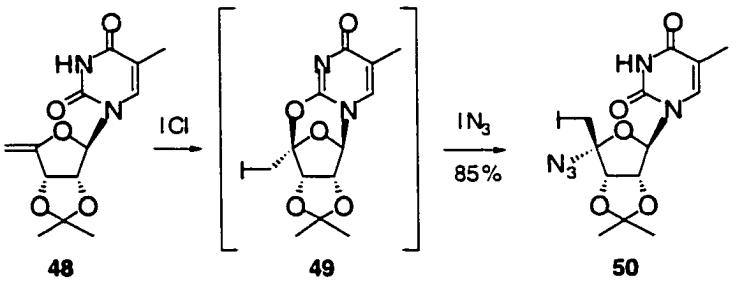
45: X = tosylate, mesylate, sulfoxide, selenoxide
R_1 = OP, H
P = Protecting group

46

47: R = N_3, OMe, halogens

Scheme 2.9

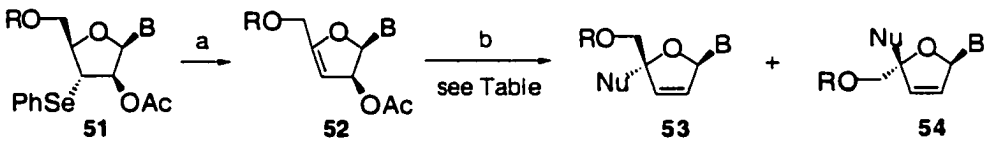
unless a bicyclic intermediate is formed, such as **49** which gave nucleoside analog **50** exclusively in 85% yield (Scheme 2.10).[13]



Scheme 2.10

Haraguchi developed the synthesis of 4'-(carbon)-disubstituted dideoxydidehydronucleoside analogs **53** from 3',4'-unsaturated nucleosides **52**. Oxidative elimination of selenide **51** gave 3'4-unsaturated nucleosides **52** which underwent allylic substitution by a variety of organosilicon reagents to give **53** and **54** in good yield, favoring the desired diastereomer **53** (Table 2.2). It is

Table 2.2

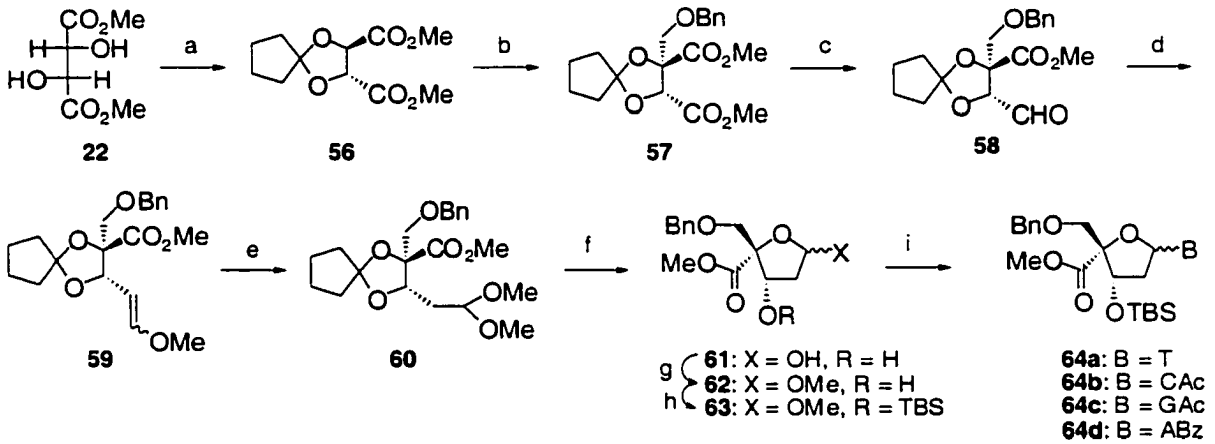


Entry	Reagent	Nu	R	% Yield	Ratio **53** : **54**
1	CH_2=$CHCH_2SiMe_3$	-CH_2CH=CH_2	TBDPS	79	15:1
2	CH_2=$C(Me)OSiMe_3$	-$CH_2C(O)CH_3$	TBDPS	51	6:1
3	CH_2=$C(Ph)OSiMe_3$	-$CH_2C(O)Ph$	TBDPS	64	6:1
4	1-[trimethylsilyl)-oxy]cyclopentene		TBDPS	70	34:1
5	$NCSiMe_3$	-CN	Ac	64	2:1

R = TBDPS (a) *m*-CPBA, 30-40 °C, 90% yield; (b) All reactions were carried out at -78 °C with 5 eq. $SnCl_4$ and 10 eq. of the appropriate silicon reagent.

interesting to note that inverting the stereochemistry of the acetate at the 2'-position of **52** does not affect the stereochemical outcome of the reaction.[26,27]

A few *de novo* syntheses of 4'-disubstituted nucleoside analogs have been developed. These methods offer more control of stereochemistry at the 4'-position, easier access to both L- and D-nucleosides, and increased functionality. Unfortunately, not many different subtitutents have been employed at the 4'-position: methyl ester, [28] methyl,[29-31] heptyl, benzyl, and 3-hydroxylpropyl substitutents.[32]

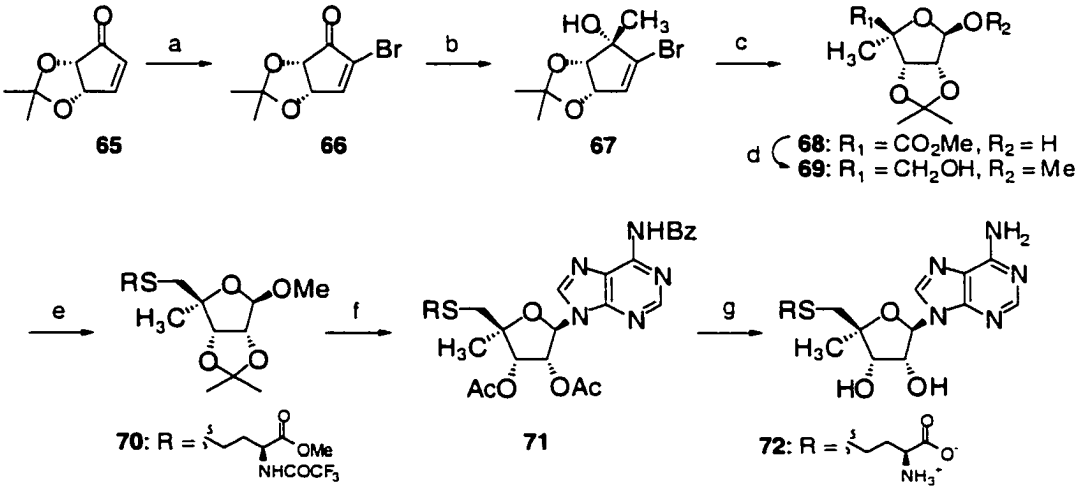


Scheme 2.11 Crich's Synthesis. (a) cyclopentanone dimethyl acetal, TsOH, 90% yield; (b) 1. LDA, THF/HMPA 2. BOMCl, 60% yield; (c) 1. DIBAL, 2. Swern Ox., 60% yield; (d) $Ph_3P^+CH_2OMe$, LDA, 62% yield; (e) 1. $Hg(OAc)_2$, MeOH 2. $NaBH_4$, 85% yield; (f) 3N HCl; (g) TsOH, MeOH, 85% yield over 2 steps; (h) TBDMSOTf, 96%; (i) nucleoside base, $SnCl_4$, MeCN, 40-90% yield.

A *de novo* method that gave a series of protected 4'-carboxylic methyl ester nucleoside analogs **64a-d** has been developed by Crich (Scheme 2.11).[28] Starting from L-tartaric acid, dimethyl ester **55** was formed and converted to **58** by protection of the diol, addition of the benzyloxymethyl group with enolate chemistry, and reduction. Formation of diacetal **60** from aldehyde **58** and hydrolysis unmasked the ribose framework giving **61**. Manipulation of the

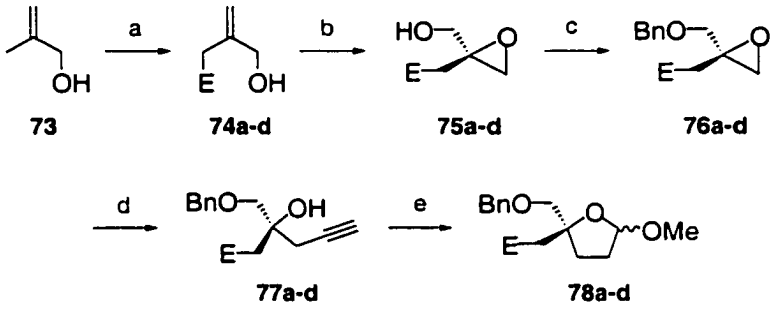
resulting free hydroxyl groups gave ribofuranose **63**. Vorbrüggen coupling with a variety of nucleoside bases gave protected 4′-carboxylic methyl ester nucleoside analogs **64a-d** in low anomeric ratios (1:1 – 1:3 favoring the unnatural α-anomer).

Johnson developed an interesting *de novo* method to synthesize S-adenosyl-L-homocysteine analog **72**.[29] As shown in Scheme 2.12, elaboration of enone (+)-**65** gave the substituted vinyl bromide **67**. Ozonolysis followed by reductive workup with dimethylsulfide unveiled the ribose framework to give alcohol **68** as a single anomer. Formation of the methoxy leaving group and amino acid side chain was followed by manipulation of the protecting groups. Vorbrüggen coupling with adenine and deprotection gave S-(4′-methyladenosyl)-L-homocysteine (**72**) in 44% overall yield from **65**.



Scheme 2.12 (a) Br_2, then Et_3N, 99% yield; (b) MeMgBr, 97% yield; (c) O_3, MeOH, pyr., -78 °C-0 °C then Me_2S, 91% yield; (d) 1. MeOH, acetone, TsOH, Δ 2. $LiBH_4$, 85% yield; (e) 1. Tf_2O, Et_3N, -78 °C 2. *N*-(trifluoroacetyl)-L-homocysteine, methyl ester, NaH, DMF, 95% yield; (f) 1. MeOH, HCl 2. Ac_2O, TEA 3. N^6-benzoyladenine, TMSOTf, 64% yield; (g) 1. 0.2 M LiOH, 3 hrs. 2. NH_3, MeOH, 12 hrs., 98% yield.

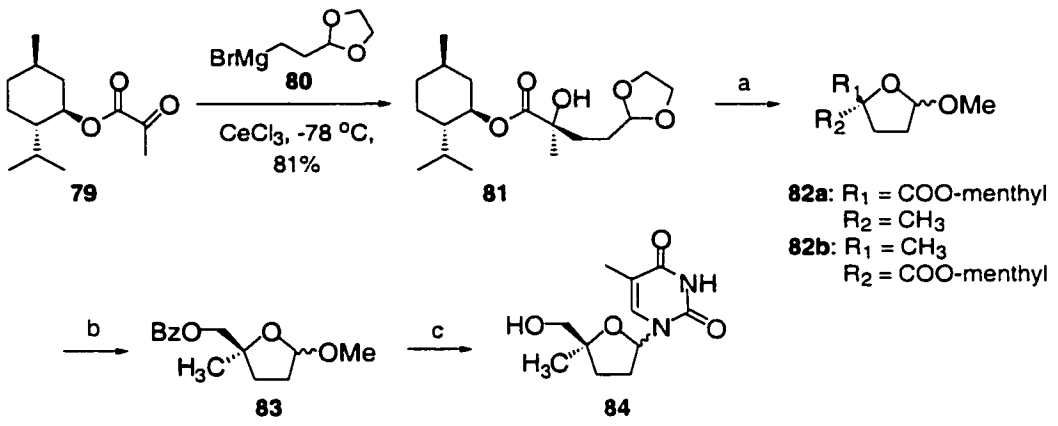
Lipshutz has published a *de novo* asymmetric synthesis of C-4 alkylated dideoxyribosides **78a-d** that are potential precursors to 4'-disubstituted nucleoside analogs (Scheme 2.13).[32] Alcohol **73** was alkylated with a variety of reagents, epoxidized using Sharpless's method, and protected to give **76a-d**. The epoxides were ring-opened to give alkynes **77a-d**, which were converted to riboses **78a-d** in a one-pot process. Unfortunately, their conversion to 4'-disubstituted nucleosides has not been reported.



a: E = n-C_7H_{15} ; **b**: E = CH_2Ph; **c**: E = $CH_2CH_2OTBDPS$; **d**: E = H

Scheme 2.13 (a) 1. n-BuLi, TMEDA, -78 °C to rt. 2. **74a**: n-$C_7H_{15}I$, **74b**: $PhCH_2Br$, **74c**: t-$BuPh_2SiOCH_2CH_2I$, 68-84% yield; (b) (+)-DET/$Ti(O\text{-}i\text{-}Pr)_4$, 4Å molecular sieves, t-BuOOH, CH_2Cl_2, -20 °C, 63-81% yield, 87-98% ee; (c) NaH, BnBr, 79-87% yield; (d) $LiC{\equiv}CH$, $BF_3{\cdot}Et_2O$, 73-77% yield; (e) 1. diisoamylborane, 78 °C to rt. 2. H_2O_2, NaOH, H_2O (pH 8), 0 °C 3. HCl, MeOH, 68-77% yield.

A *de novo* synthesis of 4'-methyl-2',3'-dideoxythymidine (**84**) has been completed by Luzzio[30] which was, however and unfortunately, plagued by racemization (Scheme 2.14). Buchi-Wiest Grignard **80** was used to make an organocerium reagent which chemoselectively added to (-)-menthyl pyruvate **79** to give (-)-menthyl hydroxyester **81**, as a single enantiomer. Manipulation of **81** to menthyl ester glycoside **82a** also gave **82b** in a 2:1 ratio due to partial racemization at C-4. Formation of the glycosidic bond and deprotection completed the synthesis of 4'-methyl nucleoside **84**.



Scheme 2.14 Luzzio's Synthesis. (a) 1. aq. HOAc 2. methanolic HCl, **82a:b**, 76%; (b) 1. $LiAlH_4$ 2. BzCl, DMAP, 92%; (c) 1. bis(trimethylsilyloxy)-5-methylpyrimidine, TBDMSOTf, CH_3CN, 81% 2. methanolic NaOH, 39% α-**84**, 55% β-**84**.

II. Rationale

De novo synthesis of 4'-disubstituted nucleoside analogs in which the 4'-substitutent is a heteroatom is unprecedented. A versatile nucleoside template, butenolide **85**,[33] has been developed by the Hegedus group (see Chapter One). It was envisioned that butenolide **85** would be a common intermediate in the synthesis of several 4'-ethoxy nucleoside analogs (**88-91**), as shown in Figure 2.4. The 2',3'-dideoxy- and 2',3'-dideoxydidehydronucleoside analogs (**88** and **89**) could be obtained from acetate **86**. Nucleoside **88** could be obtained from **86** by formation of the glycoside bond, reduction of the double bond and removal of the benzyl protecting group. Nucleoside **89** could be obtained from **86** by formation of the glycoside bond and removal of the benzyl protecting group. 4'-Ethoxy and 4'-ethoxy-2'-deoxythymidine nucleoside analogs (**90** and **91**) would be available from another common intermediate, diol **87**. Formation of the glycosidic bond and deprotection would give **90**. Further

manipulation of the 3′-hydroxyl group of **87**, then formation of the glycoside bond and deprotection would give **91**.

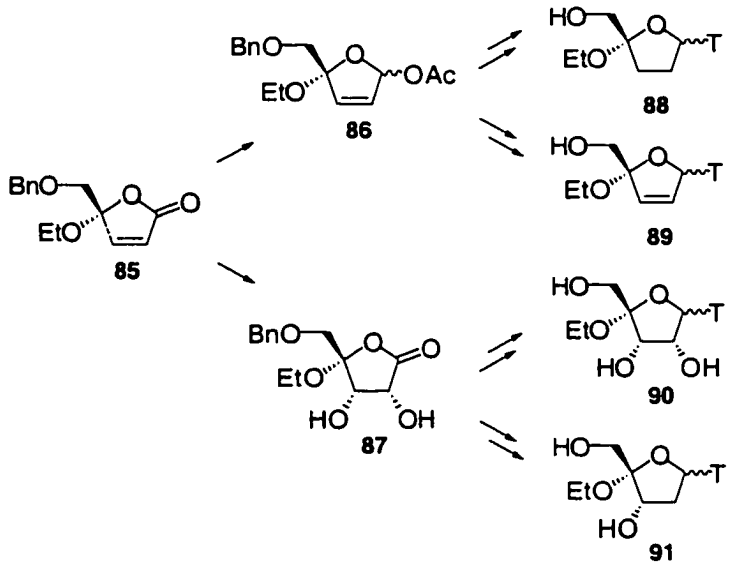
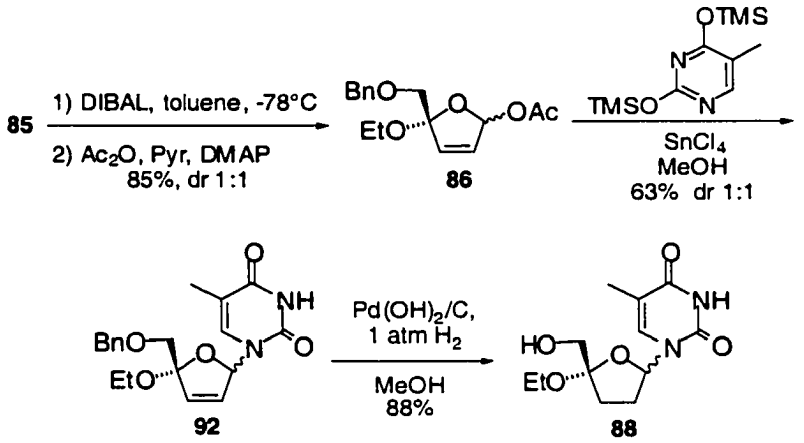


Figure 2.4 4′-Ethoxy Nucleoside Analog Series.

III. Results and Discussion

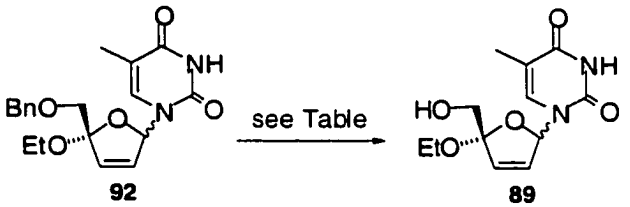
The synthesis of 4′-ethoxy-2′,3′-dideoxythymidine (**88**) had been previously established in the Hegedus group. Butenolide **85** was reduced with DIBAL and the lactol aluminate was trapped *in situ* with acetic anhydride in the presence of pyridine and DMAP, to give acetate **86** in 85% yield as a 1:1 mixture of C-1 anomers (Scheme 2.15). Vorbrüggen coupling[22] with silylated thymine gave **92** in 63% yield, but with no diastereoselectivity, as expected for Vorbrüggen couplings of 2′-deoxyribose systems. Reduction (Pearlman's catalyst/H_2) both debenzylated the 5′-position and reduced the double bond, giving 4′-ethoxy-2′,3′-dideoxythymidine **88** in 88% yield, again as an inseparable 1:1 mixture of C-1 anomers.



Scheme 2.15 Synthesis of 4'-Ethoxy-2',3'-dideoxythymidine **6**

Access to 4'-ethoxy-2',3'-dideoxydehydrothymidine **89** was envisioned to be straightforward from intermediate **92**, by deprotection of the

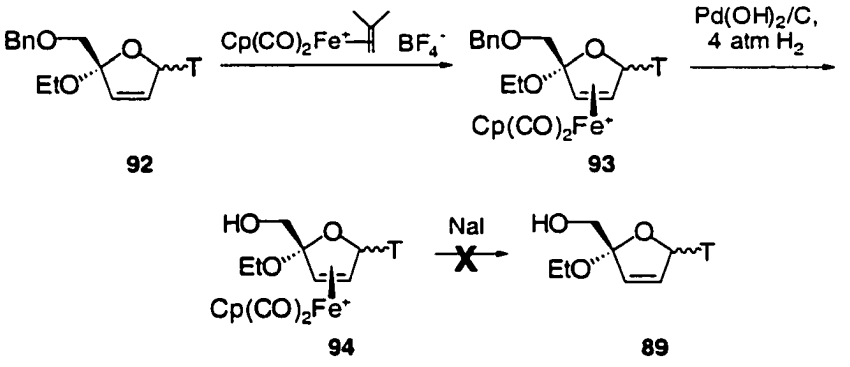
Table 2.3



Reagent	Result
Na/NH_3	Decomp.
Ca/NH_3	Decomp.
$PhCBF_4$	Decomp.
Oxone	SM
Pd/C 1,4-cyclohexadiene	SM
BCl_3	Free thymine
$BCl_3 \cdot SMe_2$	Free thymine
$TiCl_4$	SM and decomp
DDQ	SM and Decomp.
DDQ/pH7 buffer	SM and Decomp.
$ZnCl_2$, Toluene	Decomp.

benzyloxymethyl substituent while leaving the double bond intact (Table 2.3). Unfortunately, this proved to be unsuccessful with all methods giving either decomposition, free thymine, or starting material.

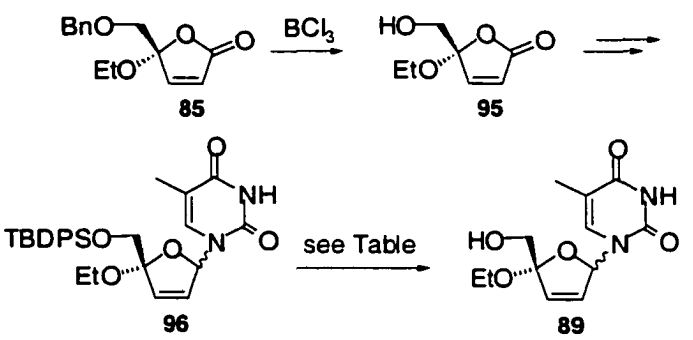
Since it was impossible to debenzylate **92** without reducing the 2′,3′-double bond, this double bond was protected (Scheme 2.16). Thymidine **92** was allowed to react with [CpFe(CO)$_2$(isobutylene)]BF_4 to give a red oil.[34] The crude mixture was hydrogenated (Pearlman's catalyst/H_2) and the $FeCp^+$ was removed with sodium iodide. Unfortunately, this gave only uncharacterizable products.



Scheme 2.16

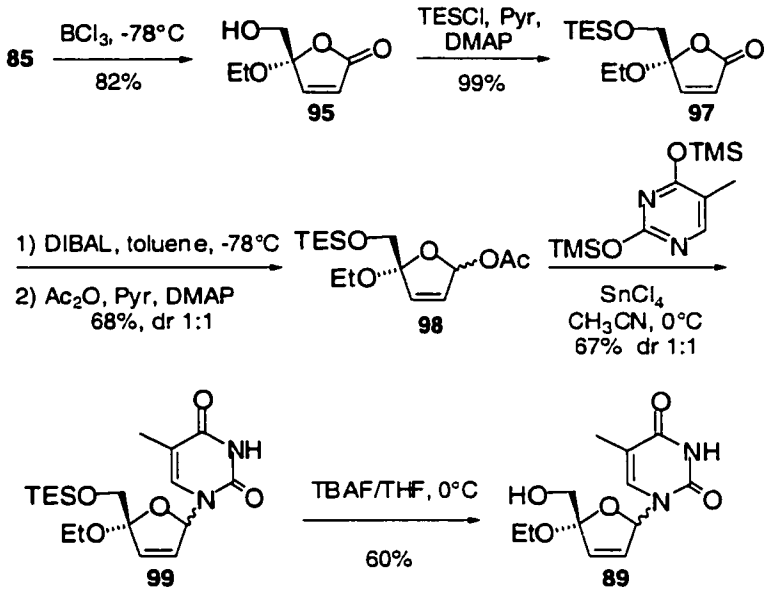
Since deprotection of the benzyl group was unsuccessful without removing the double bond, a more labile protecting group was needed. The benzyl group was removed from butenolide **85** with BCl_3 to give alcohol **95** and other protecting groups were surveyed. Previous work in the group established that a TBDPS group could be removed with TBAF to give 4′-ethoxy nucleoside **89** in 16% yield (Table 2.4). The TES protecting group is more base labile

Table 2.4



Reagent	Result
TBAF	16% yield
PPTS, 60 °C	Decomp.
HF/pyr	Decomp.
KF/18-Crown-6	SM
CsF	Decomp.
$LiBF_4$	Decomp.
DAST	SM

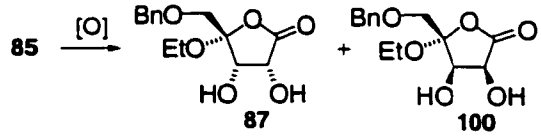
than the TBDPS group.[35] Therefore, it was anticipated that the TES group could be removed at the end of the synthesis if its analog to **96** could be synthesized. Treatment of alcohol **95** with triethylsilyl chloride, pyridine, and DMAP gave TES protected butenolide **97** in 99% yield. Reduction and acylation gave acetate **98** in 68% yield, as a 1:1 mixture of diastereomers. Vorbrüggen coupling gave the protected 4′-ethoxy-2′,3′-dideoxydidehydrothymidine **99** in 67% yield. The TES group was removed with TBAF at 0 °C to give 4′-ethoxy-2′,3′-dideoxydidehydrothymidine (**89**) in 60% yield, as a 1:1 mixture of C-1 anomers, which could be separated by preparative TLC (Scheme 2.17).



Scheme 2.17

With the dideoxy- and dideoxydidehydronucleoside analogs (**88** and **89**) in hand, attention was turned to the remaining two nucleoside analogs in the 4'-ethoxy series. Synthesis of 4'-ethoxy- and 4'-ethoxy-2'-deoxythymidine (**90** and **91**) required that butenolide **85** be *cis*-dihydroxylated from the α-face of the butenolide, the same face as the ethoxy substituent. However, it was shown in the total synthesis of neplanocin A[36] (Chapter 1) that a variety of oxidants gave diol **100** exclusively or as the major product (Table 2.5). In addition, no conversion was seen with the treatment of AD mix α® and AD mix β® on butenolide **85**.

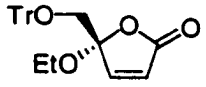
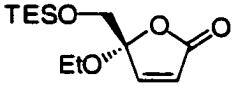
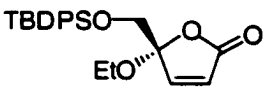
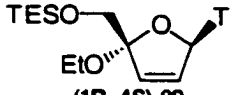
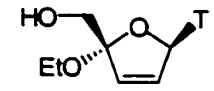
Table 2.5 *cis*-Dihydroxylation of Butenolide **85**.



	87	**100**
$KMnO_4$	0%	50%
$NaIO_4/RuCl_3$	12%	40%
OsO_4/NMO	5%	9%

When Andrew Riches was working on the *cis*-dihydroxylation, it was theorized that the benzyloxymethyl group might favor formation of the α-diol by sterically blocking the β-face. However with the true stereochemistry known, it was shown that the benzyloxymethyl substituent does not cause this desired steric interaction. Therefore, it was attempted to increase the diastereoselectivity of the *cis*-dihydroxylation to favor the α-diol by synthesizing substrates with larger 6-*O*-protecting groups (Table 2.6). Unfortunately, in all cases, the use of $KMnO_4$ or OsO_4 gave low conversions. With the use of $RuCl_3$ and $NaIO_4$,[37] the best diastereoselectivities and conversions were obtained with butenolide **97** and **102**. Unfortunately, the desired α-diol was still not the major product and the

Table 2.6 *cis*-Dihydroxylation Studies.

	$KMnO_4$	OsO_4, NMO	$RuCl_3$, $NaIO_4$
85	50% β	14% 70%[a] 2:1 β:α	52% 3:1 β:α
 **101**	10% 18%[a]	Low conversion	Low conversion 1:1 β:α
 **97**	-	1% 75%[a]	39% 67%[a] 1.5:1 β:α
 **102**	-	-	54% 84%[a] 1.3:1 mixture
 **(1R, 4S)-99**	SM Decomp.	SM	<30% 1:1 mixture
 **(1R, 4S)-89**	-	SM Decomp.	-

[a] percent yield based on recovered starting material

TES and TBDPS groups were not stable to the following DIBAL reduction and acylation steps for the synthesis of 4'-disubstituted nucleoside analogs.

In an attempt to increase the steric bias even further and change the electronic properties of the alkene, the *cis*-dihydroxylation was attempted on thymine analogs **99** and **89**. No reaction was observed with $KMnO_4$ or OsO_4 and $RuCl_3/NaIO_4$ gave a very low conversion. Therefore, increasing the steric bulk on the β-face and/or changing the electronic properties of the butenolide did not improve the diastereoselectivity to favor the α-diol, but in fact inhibited the oxidation reaction.

To understand the reasons why there was lack of control in the *cis*-dihydroxylation, the mechanism needs to be addressed. For *cis*-dihydroxylation reactions, there is a debate over the exact mechanism of addition.[38] As shown in Figure 2.5 for the ligand-assisted oxidation of an alkene by OsO_4, there are two proposed mechanisms. Based on his work in 1936 on a ligand-accelerated version of the dihydroxylation, Creigee[39] proposed a concerted [3+2] addition which is supported by Corey.[38] More recently, Sharpless argued that the alkene first

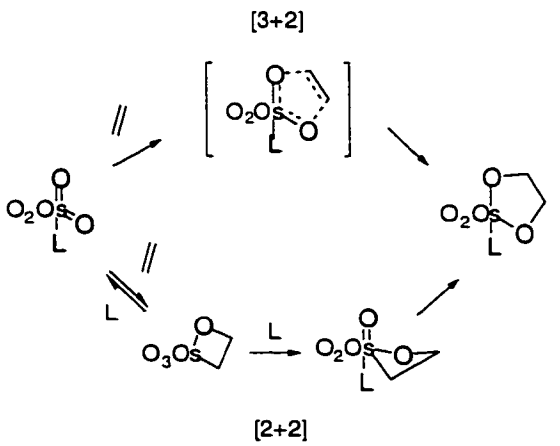


Figure 2. 5 Proposed Mechanisms for the Ligand-assisted Oxidation an Alkene with OsO_4.

coordinates to the electron-deficient osmium, the electrophilic center, then forms an osmaoxetane which is a formal [2+2] addition.[40-42] There is evidence that supports both mechanisms and the debate continues.[38]

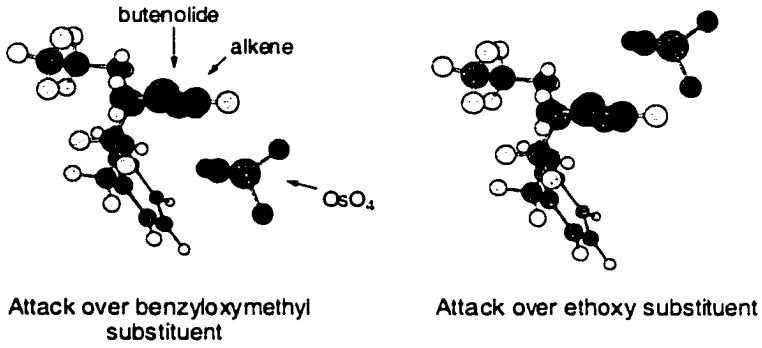


Figure 2.6 3D model of the *cis*-Dihydroxylation of Benzyl-protected Butenolide **85** with OsO_4.

However, with either mechanism the lack of control in the stereoselectivity of the *cis*-dihydroxylation can be rationalized by a 3D model. For example, in Figure 2.6 a 3D model of OsO_4 approaching butenolide **85** is shown. The approach of the oxidant can occur from either face of the alkene without large steric interactions with the ethoxy or the benzyloxymethyl substituent. A similar 3D model of OsO_4 approaching trityl-protected butenolide **101** is as shown in Figure 2.7. This model demonstates that OsO_4 can also approach either face of the alkene even when the large trityl protecting group is used.

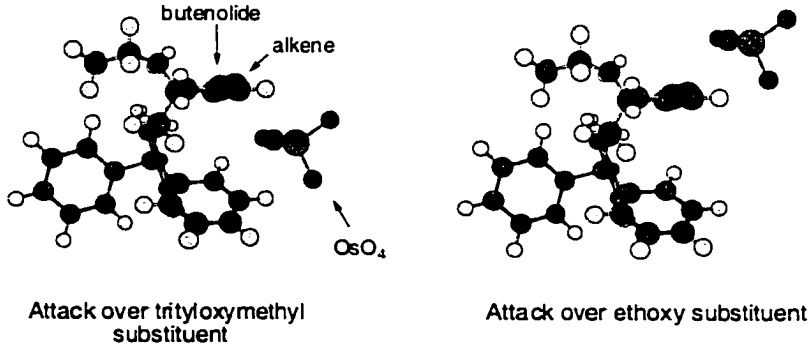
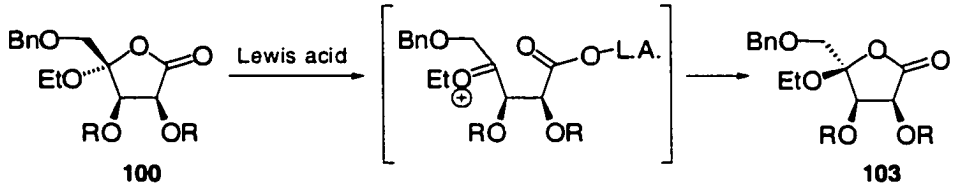


Figure 2.7 3D model of the *cis*-Dihydroxylation of Trityl-protected Butenolide **101** with OsO_4.

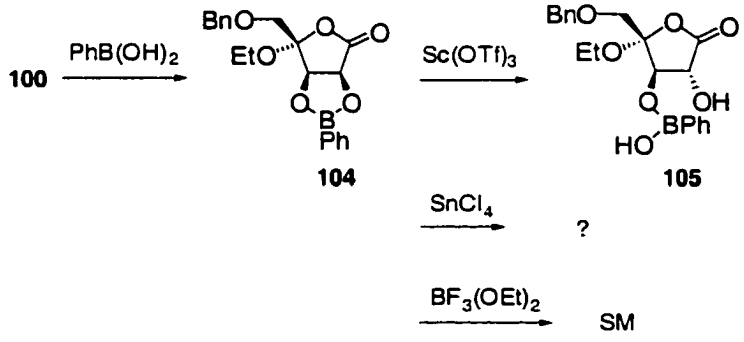
Epimerization of the 4'-position of protected diol **100** would lead to the correct relative stereochemistry (**103**: diol moiety *anti* to the CH_2OBn group), as shown in Scheme 2.18. Therefore, diol **100** was protected with a variety of protecting groups and a range of Lewis acids were screened.



100 **103**

Scheme 2.18

Protection of diol **100** with phenylboronic acid[43] gave boronate ester **104** in quantitative yield (Scheme 2.19). Treatment of **104** with BF_3 etherate as the Lewis acid gave recovered starting material. The use of scandium triflate gave partly hydrolyzed *trans*-diol **105**. Tin tetrachloride gave complete conversion to an unstable product, which could not be isolated. The NMR spectrum of this reaction mixture was different from *trans*-diol **105** and starting material, suggesting that it was either the desired epimerized product or a starting material:tin complex.



Scheme 2.19

Treatment of diol **100** with dimethoxytoluene and a catalytic amount of anhydrous tin dichloride gave benzylidene acetal **106** in 77% yield, as a separable

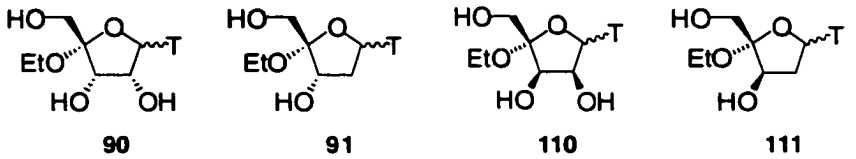
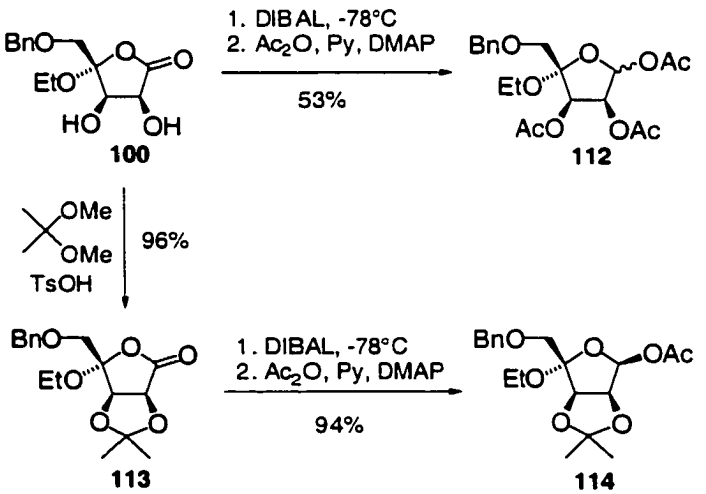


Figure 2.8

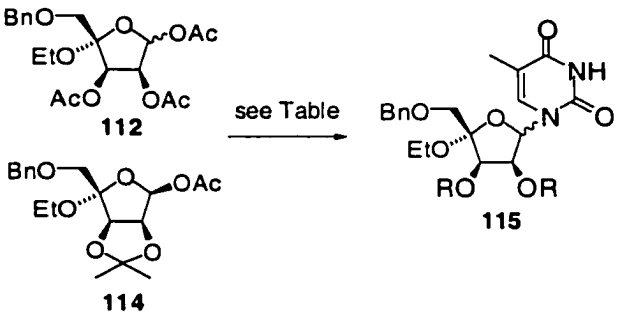
For the synthesis of thymidine **110**, triacetate **112** was synthesized following protocol previously established in the Hegedus group. Treatment of **100** with DIBAL, then acetic anhydride, pyridine, and DMAP gave lactol triacetate **112** in modest yield as a 1:1 mixture of C-1 anomers (Scheme 2.22). The major by-product of this process was the 2′,3′-diacetate of **100**, from acetylation of unreduced **100**, and it was formed even when a large excess of DIBAL was used. To suppress this reaction, **100** was protected as acetonide **113**. Reduction and acylation of **113** gave acetate **114**, in 94% yield as a single diastereomer.



Scheme 2.22

Vorbrüggen coupling of acetates **112** and **114** proved problematic. Starting material was recovered under mild conditions, while harsher conditions caused extensive ring opening and decomposition (Table 2.7).

Table 2.7 Attempted Vorbrüggen Coupling.



SM	Base	Lewis Acid	Temp.	Solvent	Result
112	Thymine BSA	3 eq. TMSOTf	0 °C - RT	CH_3CN	Decomp. one diastereomer
112	Thymine BSA	1.1 eq. $SnCl_4$	0 °C - RT	CH_3CN	Decomp.
114	Thymine BSA	1.1 eq. $SnCl_4$	0 °C	CH_3CN	SM & Decomp.
114	Thymine BSA	4 eq. Et_2AlCl	0 °C - 50 °C	CH_3CN	Decomp.
114	Thymine BSA	3 eq. TMSOTf	0 °C - 60 °C	CH_3CN	Decomp.
114	Silylated Thymine	3 eq. TMSOTf	0 °C - RT	CH_3CN	Decomp.
114	Silylated Thymine	3 eq. TMSOTf	0 °C - RT	$ClCH_2CH_2Cl$	Epimerization & Decomp.
114	Silylated Thymine	2 eq. $Sc(OTf)_3$	0 °C - RT	$ClCH_2CH_2Cl$	Epimerization & Decomp.
114	Silylated Thymine	2 eq. $Sc(OTf)_3$ 1.8 eq. TBAF	0 °C - RT	$ClCH_2CH_2Cl$	Decomp.
114	Silylated Thymine	2 eq. Et_2AlCl	0 °C - 50 °C	$ClCH_2CH_2Cl$	Decomp.

There is no literature precedent for a *de novo* synthesis of a 4′-disubstituted nucleoside analog with a heteroatom in the 4′-position. All syntheses of these types of compounds used existing nucleosides as their starting material. Therefore, formation of a glycosidic bond from compounds such as acetate **112** or **114** has not be address. It is unclear why the Vorbrüggen coupling was

unsuccessful with acetates **112** and **114**, while there was success in the synthesis of 4'-ethoxy-2',3'-deoxy- and 4'-ethoxy-2',3'-deoxy-2',3'-didehydronucleoside analogs **88** and **89** using this method. It is not believed that steric interactions caused the failure of the Vorbrüggen coupling because the α-face of the oxonium ion should be available for attack of the nucleoside base, as shown in the 3D model in Figure 2.9.

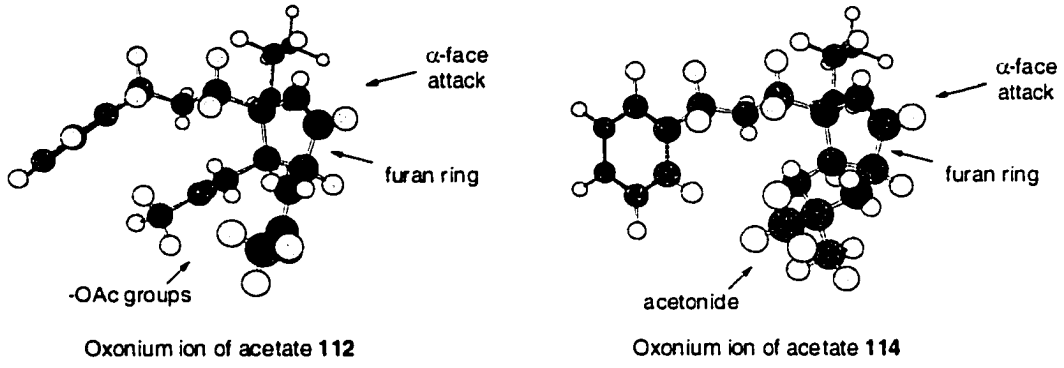
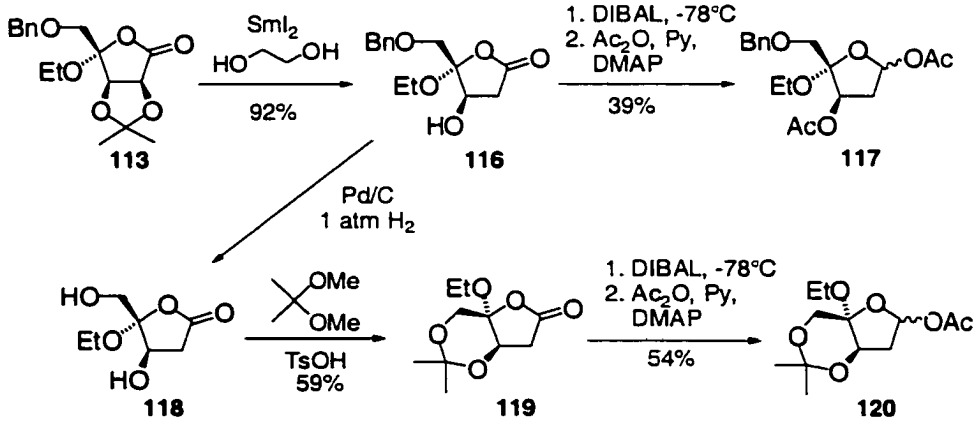


Figure 2.9 3D Models of the Oxonium Ion Intermediates for Acetates **112** and **114**.

In an attempt to synthesize the "unnatural" 3'-β-OH diastereomer **111**, acetonide **113** was treated with samarium iodide and ethylene glycol[44,45] to give α-deoxygenated lactone **116** in 92% yield (Scheme 2.23). Reduction and acylation gave lactol diacetate **117** in 39% yield, as a 5:1 mixture of anomers. With this substrate, small amounts of ring-opened, reduced material was always observed,

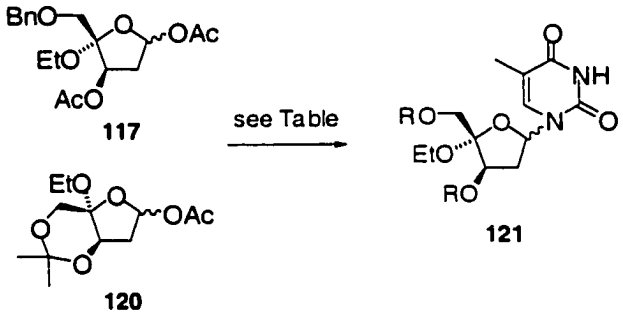


Scheme 2.23

and easily removed. α-Deoxygenated lactone **116** could also be reduced (Pd/C and 1 atm H_2) to give a quantitative yield of diol **118**. Conversion to acetonide **119** occurred in an unoptimized 59% yield, and reduction/acylation conditions gave acetate **120** in fair yield, as a 1:1 mixture of diastereomers.

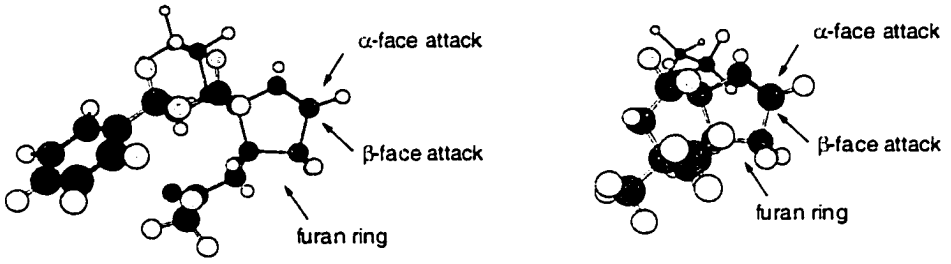
Vorbrüggen coupling of acetates **117** and **120** was unsuccessful. Starting material was recovered with mild conditions (5 eq. Lewis acid, 0 °C → room temperature) and ring opening was seen when a larger excess of the Lewis acid and higher temperatures were used (Table 2.8).

Table 2.8 Attempted Vorbrüggen coupling.



SM	Base	Lewis Acid	Temp.	Solvent	Result
117	Thymine BSA	3 eq. TMSOTf	0 °C - RT	CH_3CN	Decomp.
117	Thymine BSA	5 eq. Me_2AlCl	0 °C - RT	CH_3CN	SM
117	Thymine BSA	5 eq. Me_2AlCl	0 °C - RT	1:1 CH_3CN: $ClCH_2CH_2Cl$	SM
117	Silylated Thymine	3 eq. Et_2AlCl	RT	$ClCH_2CH_2Cl$	SM
117	Silylated Thymine	6 eq. Et_2AlCl	50 °C	$ClCH_2CH_2Cl$	Decomp.
120	Silylated Thymine	5 eq. Et_2AlCl	0 °C - RT	$ClCH_2CH_2Cl$	Decomp.
120	Silylated Thymine	1.5 eq. Me_2AlCl	0 °C - RT	1:1 CH_3CN: $ClCH_2CH_2Cl$	SM
120	Silylated Thymine	5 eq. Me_2AlCl	RT	1:1 CH_3CN: $ClCH_2CH_2Cl$	Decomp.

As with the Vorbrüggen coupling of acetates **112** and **114**, it is unclear why the Vorbrüggen coupling was not successful with acetates **117** and **120**. As stated earlier, it is not believed that steric interactions caused the failure of the Vorbrüggen coupling because both the α- and β-face of the oxonium ion should be available for attack of the nucleoside base, as shown in the 3D model in Figure 2.10.



Oxonium ion of acetate **117** Oxonium ion of acetate **120**

Figure 2.10 3D Models of the Oxonium Ion Intermediates for Acetates **117** and **120**.

IV. Conclusion

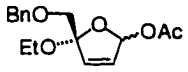
Using chromium carbene chemistry, both enantiomers of butenolide **85** were synthesized and used as optically active templates for the *de novo* synthesis of 4′-disubstituted nucleoside analogs. 4′-Ethoxy-2′,3′-dideoxythymidine (**88**) and 4′-ethoxy-2′,3′-dideoxydidehydrothymidine (**89**) were synthesized and became the first *de novo* synthesis of a 4′-disubstituted nucleoside with a heteroatom in the 4′-position.[46] Unfortunately, 4′-ethoxy and 4′-ethoxy-2′-deoxythymidine (**90** and **91**) could not be synthesized by a variety of methods from the butenolide template (**85**) because the diol could not be formed stereoselectively. In addition, "unnatural" diastereomers **110** and **111** could not be synthesized because the glycosidic bond could not be formed.

V. Experimental

Materials. The following compounds were synthesized according to literature procedures: butenolide **85**,[33], diol **87**, diol **100**.[47,48] Their purity was confirmed by NMR spectroscopy and optical rotation data.

General Methods. The general methods described for Chapter One were followed with the exceptions that ^{1}H NMR, NOE, COSY (300MHz), ^{13}C NMR (75MHz), and HSQC (400 ^{1}H MHz) spectra were recorded in $CDCl_3$ unless otherwise noted and chemical shifts are given in ppm relative to $CDCl_3$ (7.27 ppm). In addition, toluene and acetonitrile were distilled from CaH_2.

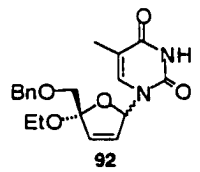
General Procedure for DIBAL Reductions. The starting material was dissolved in CH_2Cl_2 (0.1M – 0.02M) and dried with $MgSO_4$. The mixture was filtered through Celite into a flame-dried flask. The solution was purged with argon and then cooled to -78 °C. DIBAL (1.3 eq.) was added dropwise via syringe. The reaction was stirred at -78 °C for 1 hour. The reaction was monitored by TLC and more DIBAL was added, as needed, in portions of 0.5 eq. until there was no starting material present by TLC. Pyridine (3 eq.), DMAP (2 eq.), and Ac_2O (4 eq.) were added and the reaction was warmed to 0 °C. The ice bath was allowed to warm to room temperature overnight and then the solution was quenched with Rochelle's salt, extracted with CH_2Cl_2, dried and concentrated.



86

$C_{16}H_{20}O_5$
Exact Mass: 292.13
Mol. Wt.: 292.33
C, 65.74; H, 6.90; O, 27.37

(5*S*)-2-Acetoxy-5-benzyloxymethyl-5-ethoxy-2,5-dihydrofuran (86). Acetate **86** was prepared from butenolide **85** (66 mg, 0.266 mmol, ~0.02M) by using the general procedure. Purification by flash column chromatography (10:1 hexane/EtOAc) gave **86** (66 mg, 0.23 mmol, 85%) as a 1:1 mixture of diastereomers and as a yellow oil: ^{1}H NMR δ 7.38-7.26 (m, 5H), 6.89 (s, 0.5H), 6.75 (s, 0.5H), 6.23-6.11 (m, 2H), 4.64 (s, 1H), 4.6 (s, 1H), 3.77 (d, J=12.5 Hz, 0.5H), 3.73 (d, J=12.3 Hz, 0.5H), 3.56 (d, J=15.9 Hz, 0.5H), 3.53 (d, J=16.2 Hz, 0.5H), 3.65-3.3 (m, 2H), 2.1 (s, 1.5H), 2.03 (s, 1.5H), 1.19 (t, J=7 Hz, 3H); ^{13}C NMR δ 170.5, 170.1, 138.4, 138.2, 134.5, 133.7, 130.3, 130.2, 128.5, 128.4, 127.8, 127.6, 115.2, 114.2, 100.7, 99, 74.1, 73.8, 73.7, 73.6, 58.8, 58.4, 21.3, 21.2, 15.5, 15.4; IR (neat) 2975, 2932, 2866, 2358, 2336, 1748 cm^{-1}; FAB-LRMS calcd for $C_{14}H_{17}O_3$ (M-OAc): 233.13, found 233.13.

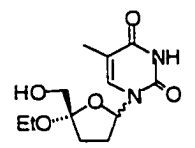


92

$C_{19}H_{22}N_2O_5$
Exact Mass: 358.15
Mol. Wt.: 358.39
C, 63.67; H, 6.19; N, 7.82; O, 22.32

(4′*S*)-5′-*O*-Benzyl-4′-ethoxy-2′,3′-dideoxy-didehydrothymidine (92). A two necked flask was charged with thymine (16.6 mg, 0.132 mmol) and 2.5 mL CH_3CN. N,O-Bis(trimethylsilyl) acetamide (65 μL, 0.26 mmol) was added via syringe and the mixture was stirred for 30 minutes. The solution went from a cloudy white suspension to a clear solution. Acetate **86** (35 mg, 0.12 mmol) was added dissolved in 1 mL CH_3CN and the solution was cooled to 0 °C. $SnCl_4$ (15 μL, 0.13 mmol) was added via syringe down the sidearm of the flask to precool the solution. The solution was stirred at 0 °C for ~20 minutes until no starting material was present by TLC (silica gel, 4:1

hexane/EtOAc). The reaction was quenched cold with sat. aq. $NaHCO_3$, extracted with CH_2Cl_2, dried with $MgSO_4$, and concentrated. The crude residue was purified by flash column chromatography (100% EtOAc - 100% MeOH gradient elution). The fractions were collected, concentrated, dissolved in CH_2Cl_2 and filtered to removed any silica particles. Coupled **92** (27 mg, 0.075 mmol, 63%) was obtained as a clear film and as a separable mixture of anomers. α-Anomer: ^{1}H NMR δ 9.74 (s, 1H), 7.4-7.25 (m, 5H), 6.93 (s, 1H), 6.38 (dd, *J*=1.1 Hz, 5.6 Hz, 1H), 6.02 (dd, *J*=0.8 Hz, 5.8 Hz, 1H), 4.61 (d, *J*=12 Hz, 1H), 4.56 (d, *J*=12 Hz, 1H), 3.83 (d, *J*=10.5 Hz, 1H), 3.7-3.35 (m, 2H), 3.48 (d, *J*=10.5 Hz, 1H), 1.9 (s, 3H), 1.18 (t, *J*=7.1 Hz, 3H); ^{13}C NMR δ 164.2, 151.3, 137.7, 136.1, 133.9, 129, 128.6, 128, 127.8, 112.5, 111.4, 87.86, 73.69, 70.71, 58.86, 15.53, 12.57. β-Anomer: ^{1}H NMR δ 9.69 (s, 1H), 7.53 (s, 1H), 7.4-7.25 (m, 5H), 7.13 (s, 1H), 6.12 (s, 2H), 4.56 (s, 2H), 3.73 (s, 2H), 3.7-3.35 (m, 2H), 1.47 (s, 3H), 1.16 (t, *J*=7.1 Hz, 3H); ^{13}C NMR δ 164.2, 151.1, 137.4, 136.4, 135.5, 131.3, 128.7, 128.2, 127.9, 114.2, 111.2, 88.67, 73.74, 72.9, 57.85, 15.33, 11.93. IR (neat) 1695 cm^{-1}. Anal. Calcd for $C_{19}H_{22}N_2O_5$: C, 63.67; H, 6.18; N, 7.82. Found: C, 63.62; H, 6.07; N, 7.58.

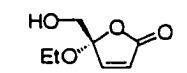


88

$C_{12}H_{18}N_2O_5$
Exact Mass: 270.12
Mol. Wt.: 270.28
C, 53.33; H, 6.71; N, 10.36; O, 29.60

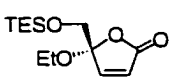
(4'*S*)-4'-Ethoxy-2',3'-dideoxythymidine (88). A solution of coupled **92** (11 mg, 0.030 mmol) in MeOH (2 mL) was stirred over 20% $Pd(OH)_2$ /C (4 mg) under an H_2 atmosphere (1 atm) for 1 hour. Argon was bubbled through the solution. Filtration of the reaction mixture through Celite and removal of solvent afforded **88** as a white solid and as a 1:1 mixture of diastereomers (7.0 mg, 0.047 mmol, 88%): ^{1}H NMR δ 9.1 (s, 1H), 9.05 (s, 1H), 7.43

(d, *J*=1.1 Hz, 1H), 7.34 (d, *J*=1.1 Hz, 1H), 6.45 (t, *J*=6.6 Hz, 1H), 6.26 (d, *J*=4.2 Hz, 0.5H), 6.24 (d, *J*=3.8 Hz, 0.5H), 3.9-3.5 (m, 8H), 2.7-2 (m, 8H), 1.95 (s, 1.5H), 1.9 (s, 1.5H), 1.24 (t, *J*=6.9 Hz, 1.5H), 1.17 (t, *J*=7 Hz, 1.5H)); ^{13}C NMR (400 MHz) δ 163.8, 163.7, 150.8, 150.4, 136.0, 135.8, 111.4, 109.9, 109.8, 86.3, 86.1, 63.0, 62.6, 57.7, 57.6, 33.1, 31.6, 30.8, 30.0, 15.7, 15.6, 12.6; IR (neat) 3430, 1692 cm^{-1}; FAB-HRMS calcd for $C_{12}H_{18}N_2O_5$ (M+H): 271.1294, found 271.1289.



95
$C_7H_{10}O_4$
Exact Mass: 158.06
Mol. Wt.: 158.15
C, 53.16; H, 6.37; O, 40.47

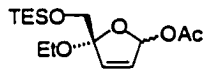
(5*S*)-5-Ethoxy-5-hydroxymethyl-5H-furan-2-one (95). (-)-5-Benzyloxymethyl-5-ethoxy-5*H*-furan-2-one (**85**) (16 mg, 0.064 mmol) was dissolved in 1.5 mL CH_2Cl_2 and cooled to -78 °C. BCl_3 (0.2 mL, 0.2 mmol) was added via syringe and the solution was stirred for 20 minutes. The reaction was quenched cold with MeOH and sat. aq. $Na_2S_2O_3$ was added. The mixture was extracted with CH_2Cl_2, dried, and concentrated. The crude residue was purified by flash column chromatography (2:1 hexane/EtOAc) to yield alcohol **95** as a clear film (8.4 mg, 0.053 mmol, 82%): $[\alpha]_D^{25}$ -59° (*c* = 1.13, $CHCl_3$); ^{1}H NMR δ 7.27 (d, *J*=6.8 Hz, 1H), 6.27 (d, *J*=5.6 Hz, 1H), 3.87 (dd, *J*=6.4 Hz, *J*=11.6 Hz, 1H), 3.73 (dd, *J*=7.2 Hz, *J*=11.6 Hz, 1H), 3.54, (m, 1H), 3.39 (m, 1H), 2.02 (t, *J*=7.2 Hz, 1H), 1.19 (t, *J*=6.8 Hz, 3H); ^{13}C NMR δ 169.6, 152.4, 125.8, 109.5, 65.4, 60.0, 15.1; IR (neat) 3432, 1765 cm^{-1}; FAB-HRMS calcd for $C_7H_{11}O_4$ (M+H): 159.0657, found 159.0653.



97
$C_{13}H_{24}O_4Si$
Exact Mass: 272.14
Mol. Wt.: 272.41
C, 57.32; H, 8.88; O, 23.49; Si, 10.31

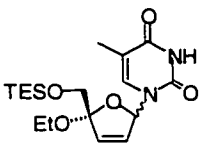
(5*S*)-5-Ethoxy-5-(triethylsilanyloxymethyl)-5H-furan-2-one (97). Alcohol **95** (20.5 mg, 0.130 mmol) was dissolved in 2 mL DMF. DMAP (15.8 mg, 0.130 mmol),

imidazole (21.2 mg, 0.311 mmol), and TESCl (0.030 mL, 0.16 mmol) were added and the mixture was stirred at room temperature for 12 hours. The reaction was quenched with sat. aq. NH_4Cl, extracted with CH_2Cl_2, washed with brine, dried with $MgSO_4$, and concentrated. The crude oil was purified by flash column chromatography (10:1 hexane/EtOAc) to yield TES protected alcohol **97** (34.9 mg, 0.128 mmol, 99%) as a yellow oil: $[\alpha]_D^{25}$ -55° (*c* = 0.74, CH_2Cl_2); ^1H NMR δ 7.16 (d, *J*=6.0 Hz, 1H), 6.21 (d, *J*=5.4 Hz, 1H), 3.89 (d, *J*=10.8 Hz, 1H), 3.77 (d, *J*=10.8 Hz, 1H), 3.52, (m, 1H), 3.38 (m, 1H), 1.17 (t, *J*=6.9 Hz, 3H), 0.90 (t, *J*=3.7 Hz, 9H), 0.55 (q, *J*=7.7 Hz, 6H); ^{13}C NMR δ 169.8, 152.4, 125.5, 110.1, 65.1, 59.9, 15.2, 6.7, 4.4; IR (neat) 1772, 1082 cm^{-1}; FAB-HRMS calcd for $C_{13}H_{24}O_4Si$ (M+H): 273.1522, found 273.1518.



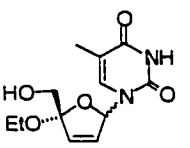
$C_{15}H_{28}O_5Si$ **98**
Exact Mass: 316.17
Mol. Wt.: 316.47
C, 56.93; H, 8.92; O, 25.28; Si, 8.87

(5S)-2-Acetoxy-5-ethoxy-5-(triethylsilanyl-oxymethyl)-2,5-dihydrofuran (98). Acetate **98** was prepared from butenolide **97** (16.5 mg, 0.0605 mmol, 0.06M) by using the general procedure. Purification by flash column chromatograhy (15:1 hexane/EtOAc) gave **98** (12.9 mg, 0.0408 mmol, 68%) as a yellow oil and as a 1:1 mixture of diastereomers: ^1H NMR δ 6.84 (s, 1H), 6.63 (s, 1H), 6.10 (m, 4H), 3.80 (m, 2H), 3.61, (m, 3H), 3.37 (m, 3H), 2.07 (s, 3H), 2.05 (s, 3H), 1.16 (t, *J*=6.9 Hz, 3H), 1.15 (t, *J*=6.9 Hz, 3H), 0.92 (m, 18H), 0.58 (m, 12H); ^{13}C NMR δ 170.5, 170.1, 134.4, 133.6, 130.1, 129.9, 115.8, 114.8, 100.6, 99.0, 67.3, 66.5, 58.7, 58.2, 53.9, 21.2, 15.3, 15.2, 6.7, 4.4, 4.4.; IR (neat) 1751 cm^{-1}; FAB-LRMS calcd for $C_{13}H_{26}O_3Si$ (M-OAc): 257.17, found 257.15.



$C_{18}H_{30}N_2O_5Si$ **99**
Exact Mass: 382.19
Mol. Wt.: 382.53
C, 56.52; H, 7.90; N, 7.32; O, 20.91; Si, 7.34

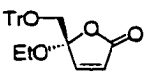
(5′*S*)-5′-Ethoxy-5′-*O*-triethylsilanyl-2′,3′-dideoxydidehydrothymidine (99). Protected nucleoside analog **99** (80.8 mg, 0.211 mmol, 67%) was prepared by using the procedure for protected nucleoside analog **92**. The anomers were separated by preparative TLC (2:1 hexane/EtOAc X2). The stereochemistry of the anomers was studied by 2D spectroscopy and nOe data. High R_f anomer: ^{1}H NMR δ 8.24 (bs, 1H), 7.27 (s, 1H), 6.87 (s, 1H) 6.33 (dd, *J*=1.2 Hz, *J*=5.7 Hz, 1H), 6.04 (dd, *J*=0.9 Hz, *J*=5.4 Hz 1H), 3.93 (d, *J*=10.5 Hz, 1H), 3.65 (m, 3H), 1.91 (s, 3H), 1.12 (t, *J*=6.9 Hz, 3H), 0.96 (t, *J*=7.8 Hz, 9H), 0.62 (q, *J*=7.8 Hz, 6H). Low R_f anomer: ^{1}H NMR δ 8.70 (bs, 1H), 7.50 (s, 1H), 7.06 (s, 1H) 6.14 (d, *J*=6.0 Hz, 1H), 6.06 (d, *J*=6.3 Hz, 1H), 3.84 (s, 2H), 3.50 (m, 1H), 3.39 (m, 1H), 1.91 (s, 3H), 1.19 (t, *J*=6.9 Hz, 3H), 0.96 (t, *J*=8.1 Hz, 9H), 0.63 (q, *J*=7.8 Hz, 6H); ^{13}C NMR δ 163.5, 150.6, 135.8, 133.7, 130.8, 115.2, 110.7, 88.7, 65.8, 57.9, 15.3, 12.6, 6.8, 4.3. Both anomers: ^{13}C NMR δ 163.9, 150.9, 150.7, 135.9, 135.8, 135.0, 133.5, 130.9, 128.9, 115.1, 113.3, 111.1, 110.7, 88.7, 87.7, 65.8, 64.1, 58.7, 57.8, 15.5, 15.3, 12.5, 6.8, 6.7, 4.4, 4.3; IR (neat) 3187, 3058, 1699 cm^{-1}; FAB-HRMS calcd for $C_{18}H_{31}N_2O_5Si$ (M+H): 383.2002, found 383.2004.



89
$C_{12}H_{16}N_2O_5$
Exact Mass: 268.11
Mol. Wt.: 268.27
C, 53.73; H, 6.01; N, 10.44; O, 29.82

(4′*S*)-4′-Ethoxy-2′,3′-dideoxydidehydro-thymidine (89). Protected nucleoside analog **15** (42.8 mg, 0.112 mmol) was dissolved in 4 mL THF and then cooled to 0 °C. 1M TBAF in THF (0.12 mL, 0.12 mmol) was added via syringe. The reaction was stirred at 0 °C until no starting material was present (~10 minutes) by TLC (silica gel, EtOAc). The reaction was

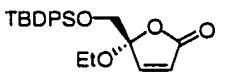
concentrated and purified by preparative TLC (100% EtOAc) to yield both anomers of **89** as clear oils. The stereochemistry of the anomers was determined by 2D NMR spectroscopy and nOe studies. (1R, 4S)-Anomer: (8.7 mg, 0.032mmol, 29%): $[\alpha]_D^{25}$ +88° (*c* = 0.35, $CHCl_3$); ^1H NMR δ 8.30 (bs, 1H), 7.35 (s, 1H), 7.12 (s, 1H), 6.23 (dd, *J*=6.0 Hz, *J*=1.8 Hz, 1H), 6.16 (d, *J*=5.7 Hz, 1H), 3.87 (d, *J*=11.7 Hz, 1H), 3.78 (d, *J*=12.9 Hz, 1H), 3.52 (m, 1H), 3.41 (m, 1H), 2.29 (bs, 1H), 1.88 (s, 3H), 1.20 (t, *J*=7.5 Hz, 3H); ^{13}C NMR δ 163.4, 150.6, 135.8, 134.4, 130.8, 114.7, 111.2, 89.0, 65.9, 58.2, 15.2, 12.4; IR (neat) 3447, 3177, 3057, 1695 cm^{-1}; FAB-HRMS calcd for $C_{12}H_{17}N_2O_5$ (M+H): 269.1137, found 269.1138. (1S, 4S)-Anomer: (9.2 mg, 0.034 mmol, 30%): $[\alpha]_D^{25}$ -66° (*c* = 0.31, $CHCl_3$); ^1H NMR (400 MHz) δ 8.92 (bs, 1H), 7.21 (d, *J*=1.2 Hz, 1H), 6.94 (d, *J*=1.6 Hz, 1H), 6.37 (dd, *J*=6.0 Hz, *J*=2.0 Hz, 1H), 6.11 (dd, *J*=5.6 Hz, *J*=1.6 Hz, 1H), 3.84 (dd, *J*=5.6 Hz, *J*=11.6 Hz, 1H), 3.75 (dd, *J*=5.2 Hz, *J*=11.6 Hz, 1H), 3.62 (q, *J*=7.2 Hz, 2H), 2.35 (t, *J*=5.6 Hz, 1H), 1.92 (d, *J*=1.2 Hz, 3H), 1.20 (t, *J*=6.8 Hz, 3H); ^{13}C NMR δ 163.6, 150.8, 135.7, 135.2, 129.3, 113.4, 111.4, 87.7, 64.2, 59.0, 15.5, 12.5; IR (neat) 3421, 1696 cm^{-1}; FAB-HRMS calcd for $C_{12}H_{17}N_2O_5$ (M+H): 269.1137, found 269.1135; Anal. Calcd for $C_{12}H_{16}N_2O_5$: C, 53.73; H, 6.01; N, 10.44. Found: C, 53.96; H, 6.07; N, 10.21.



$C_{26}H_{24}O_4$ **101**
Exact Mass: 400.17
Mol. Wt.: 400.47
C, 77.98; H, 6.04; O, 15.98

(5S)-5-Ethoxy-5-(trityloxymethyl)-5H-furan-2-one (101). Alcohol **95** (17.4 mg, 0.11 mmol) was dissolved in 1 mL CH_2Cl_2. DMAP (0.7 mg, 0.006 mmol), triethylamine (0.03 mL, 0.2 mmol), and TrCl (23.5 mg, 0.121 mmol) were added and the mixture was stirred at room temperature for 3 days. The reaction was quenched with sat. aq. $NaHCO_3$, extracted with CH_2Cl_2, dried with $MgSO_4$, and concentrated. The

crude oil was purified by flash column chromatography (10:1 hexane/EtOAc) to give recovered starting material and trityl protected alcohol **13** (20.8 mg, 0.0519 mmol, 47%) as a yellow oil: $[\alpha]_D^{25}$ -39° (*c* = 1.04, $CHCl_3$); ^1H NMR δ 7.33 (m, 15H), 7.12 (d, *J*=6.0 Hz, 1H), 6.30 (d, *J*=6.0 Hz, 1H), 3.51 (m, 1H), 3.50 (d, *J*=9.6 Hz, 1H), 3.40 (d, *J*=9.6 Hz, 1H), 1.17 (t, *J*=6.9 Hz, 3H); ^{13}C NMR δ 170.0, 152.8, 143.2, 128.6, 127.9, 127.2, 125.2, 109.6, 86.9, 65.2, 59.6, 15.1; IR (neat) 1773 cm^{-1}; FAB-HRMS calcd for $C_{26}H_{24}O_4$: 400.1675, found 400.1669.

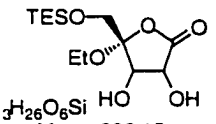


$C_{23}H_{28}O_4Si$ **102**
Exact Mass: 396.18
Mol. Wt.: 396.55
C, 69.66; H, 7.12; O, 16.14; Si, 7.08

(5*S*)-5-Ethoxy-5-(*t*-butyldiphenyl-silanyloxymethyl)-5H-furan-2-one (102). Butenolide **102** was prepared from alcohol **95** (140.7 mg, 0.8896 mmol) by following the procedure for TES protected butenolide **97**. Purification by flash column chromatography (30:1 hexane/EtOAc) gave **102** (335 mg, 0.845 mmol, 95% yield): $[\alpha]_D^{25}$ -29° (*c* = 0.27, $CHCl_3$); ^1H NMR (400 MHz) δ 7.62 (m, 4H), 7.41 (m, 6H), 7.13 (d, *J*=6.0 Hz, 1H), 6.28 (d, *J*=5.6 Hz, 1H), 3.90 (d, *J*=10.8 Hz, 1H) 3.88 (d, *J*=11.2 Hz, 1H), 3.56 (m, 1H), 3.40 (m, 1H), 1.16 (t, *J*=8.0 Hz, 1H), 1.02 (s, 9H); ^{13}C NMR δ 170.0, 152.4, 135.6, 135.6, 132.8, 132.4, 129.9, 127.8, 127.7, 125.7, 110.1, 65.4, 59.8, 26.6, 19.1, 15.1; IR (neat) 1773 cm^{-1}; FAB-HRMS calcd for $C_{23}H_{29}O_4Si$ (M+H): 397.1835, found 397.1843.

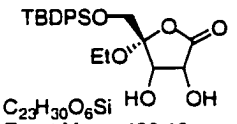
General Procedure for $RuCl_3/NaIO_4$ Oxidations. The butenolide was dissolved in a 1:1 mixture of EtOAc:CH_3CN (0.053M). The solution was cooled to 0 °C. $RuCl_3 \cdot xH_2O$ (0.07 eq.) and $NaIO_4$ (1.5 eq.) were dissolved in DI H_2O (0.02M in respect to $RuCl_3$) and added to the butenolide solution via syringe. The

reaction was stirred vigorously for 5 minutes and then poured into sat. aq. $Na_2S_2O_3$. The organic layer was extracted with EtOAc, combined, dried over $MgSO_4$, filtered, and concentrated to give the crude material.



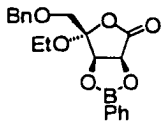
$C_{13}H_{26}O_6Si$
Exact Mass: 306.15
Mol. Wt.: 306.43
C, 50.95; H, 8.55; O, 31.33; Si, 9.17

Oxidation of (5*S*)-5-Ethoxy-5-(triethylsilanyloxymethyl)-5H-furan-2-one (97). Oxidation of butenolide **97** (28.6 mg, 0.0747 mmol) with $RuCl_3/NaIO_4$ was performed using the general procedure. Purification by flash column chromatography (5:1 hexane/EtOAc) gave a high R_f diol (5.2 mg, 0.017 mmol, 23%), a low R_f diol (3.7 mg, 0.012 mmol, 16%) and recovered starting material **97** (11.5 mg, 0.03 mmol). The stereochemistry of the diols was studied by 2D NMR spectroscopy and nOe data and tentatively assigned. High R_f diol (diol syn to the benzyloxymethyl group): ^{1}H NMR (400 MHz) δ 4.64 (d, *J*=4.8 Hz, 1H), 4.30 (d, *J*=4.8 Hz, 1H), 4.05 (d, *J*=11.2 Hz, 1H), 3.97 (d, *J*=11.2 Hz, 1H), 3.70 (m, 2H), 3.41 (bs, 1H), 3.08 (bs, 1H), 1.18 (t, *J*=7.2 Hz, 3H), 0.98 (t, *J*=7.6 Hz, 9H), 0.66 (q, *J*=7.6 Hz, 6H); ^{13}C NMR 175.3, 107.4, 72.2, 69.6, 59.2, 59.0, 15.3, 6.6, 4.2; IR (neat) 3444, 1790 cm^{-1}. Low R_f diol (diol syn to the ethoxy group): ^{1}H NMR (400 MHz) δ 4.62 (dd, *J*=5.6 Hz, *J*=10.0 Hz, 1H), 4.31 (d, *J*=5.6 Hz, 1H), 3.96 (d, *J*=10.8 Hz, 1H), 3.95 (m, 1H), 3.78 (m, 1H), 3.78 (d, *J*=10.8 Hz, 1H), 3.23 (bs, 1H), 3.10 (d, *J*=10.4 Hz, 1H), 1.27 (t, *J*=7.2 Hz, 3H), 0.95 (t, *J*=8.4 Hz, 9H), 0.62 (q, *J*=7.6 Hz, 6H); IR (neat) 3448, 1793 cm^{-1}.



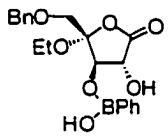
$C_{23}H_{30}O_6Si$
Exact Mass: 430.18
Mol. Wt.: 430.57
C, 64.16; H, 7.02; O, 22.30; Si, 6.52

Oxidation of (5*S*)-5-Ethoxy-5-(*t*-butyldiphenylsilanyloxymethyl)-5H-furan-2-one (102). Oxidation of butenolide **102** (335 mg, 0.845 mmol) with $RuCl_3/NaIO_4$ was performed using the general procedure. Purification by flash column chromatography (6:1 hexane/EtOAc) gave a high R_f diol (108.2 mg, 0.251 mmol, 30%), a low R_f diol (85.9 mg, 0.200 mmol, 24%), and recovered starting material **102** (123 mg, 0.310 mmol). The stereochemistry of the diols was studied by 2D NMR spectroscopy and nOe data and tentatively assigned. High R_f diol (diol syn to the benzyloxymethyl group): $[\alpha]_D^{25}$ -11° (*c* = 0.69, $CHCl_3$); ^1H NMR (400 MHz) δ 7.67 (m, 4H), 7.44 (m, 6H), 4.69 (bt, *J*=5.6 Hz, 1H), 4.35 (dd, *J*=4.4 Hz, *J*=1.6 Hz, 1H), 4.03 (d, *J*=12.0 Hz, 1H), 4.00 (d, *J*=11.6 Hz, 1H), 3.54 (m, 2H), 3.10 (d, *J*=6.8 Hz, 1H), 2.96 (d, *J*=2.0 Hz, 1H), 1.14 (t, *J*=6.8 Hz, 3H), 1.10 (s, 9H); ^{13}C NMR 175.5, 135.6, 132.5, 130.2, 127.9, 127.9, 107.7, 72.0, 69.5, 59.1, 58.8, 26.7, 19.3, 15.2; IR (neat) 3443, 1786 cm^{-1}; FAB-HRMS calcd for $C_{23}H_{31}O_6Si$ (M+H): 431.1890, found 431.1885. Low R_f diol (diol syn to the ethoxy group): $[\alpha]_D^{25}$ -2° (*c* = 0.92, $CHCl_3$); ^1H NMR δ 7.64 (m, 4H), 7.45 (m, 6H), 4.67 (dd, *J*=5.6 Hz, *J*=10.0 Hz, 1H), 4.41 (d, *J*=5.6 Hz, 1H), 3.90 (d, *J*=11.2 Hz, 1H), 3.85 (m, 1H), 3.77 (d, *J*=11.2 Hz, 1H), 3.63 (s, 1H), 3.29 (bs, 1H), 3.14 (d, *J*=10.0 Hz, 1H), 1.20 (t, *J*=6.8 Hz, 3H), 1.06 (s, 9H); ^{13}C NMR 174.0, 135.5, 135.4, 131.9, 131.4, 130.3, 128.1, 104.3, 70.9, 70.0, 63.8, 60.9, 26.7, 19.1, 15.3; IR (neat) 3446, 1792 cm^{-1}; FAB-HRMS calcd for $C_{23}H_{31}O_6Si$ (M+H): 431.1890, found 431.1894.



$C_{20}H_{21}BO_6$ **104**
Exact Mass: 368.14
Mol. Wt.: 368.19
C, 65.24; H, 5.75; B, 2.94; O, 26.07

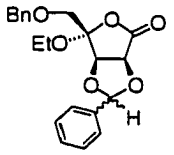
(3*S*, 4*R*, 5*R*)-5-Benzyloxymethyl-3,4-diol-5-ethoxy-dihydrofuran-2-one Boronate Ester (104). Diol **100** (23 mg, 0.081 mmol) was dissolved in 10 mL benzene and transferred to a flask equipped with Soxhlet extractor containing 4Å molecular sieves and reflux condenser. $PhB(OH)_2$ (9.9 mg, 0.0814 mmol) was added and the solution was warmed to reflux. After 5 hours the solution was cooled to room temperature, filtered, and concentrated to yield **104** (29.9 mg, 0.0812 mmol, 100%) as a clear oil: $[\alpha]_D^{25}$ -18° (*c* = 0.755, $CHCl_3$); ^1H NMR δ 7.54 (m, 10H), 6.85 (s, 1H), 6.67 (s, 1H), 6.13 (m, 4H), 4.60 (s, 2H), 4.57 (s, 2H), 3.52 (m, 8H), 2.07 (s, 3H), 2.00 (s, 3H), 1.16 (t, *J*=6.9 Hz, 2H); ^{13}C NMR δ 171.9, 138.0, 136.0, 135.5, 133.1, 132.8, 128.9, 128.4, 128.3, 109.1, 81.9, 76.8, 74.3, 65.5, 60.0, 15.6; IR (neat) 1801 cm^{-1}.



$C_{20}H_{23}BO_7$ **105**
Exact Mass: 386.15
Mol. Wt.: 386.20
C, 62.20; H, 6.00; B, 2.80; O, 29.00

(3*R*, 4*R*, 5*R*)-5-Benzyloxymethyl-3,4-diol-5-ethoxy-dihydrofuran-2-one Boronic Acid (105). A dry NMR tube was charged with boronate ester **104** (16 mg, 0.043 mmol), $Sc(OTf)_3$ (21.4 mg, 0.043 mmol) and 2 mL CD_2Cl_2. The reaction was monitored by ^1H NMR spectroscopy for 60 hours until no starting material was present. The solution was transferred to a round bottom and stripped to dryness. The solid was taken up in $CHCl_3$, filtered through Celite, and stripped to yield **105** (14.6 mg, 0.0397 mmol, 91%) as a clear oil: ^1H NMR (400 MHz) δ 7.85 (m, 3H), 7.39 (m, 7H), 5.11 (s, 2H), 4.58 (m, 2H), 4.11 (m, 2H), 3.80 (d, *J*=10.5 Hz, 1H), 3.66 (d, *J*=10.8 Hz, 1H), 1.19 (t, *J*=7.5 Hz, 3H); ^{13}C NMR δ 168.7, 137.4, 135.1, 134.5, 132.1, 131.6, 128.4, 127.9, 127.6, 101.2, 73.9, 72.9,

72.7, 62.1, 14.0. The data of this compound did not match the data collected of the desired epimerized product of boronate ester **104**, which was synthesized by a known method.[49] ^{1}H NMR δ 8.22 (d, *J*=6.6 Hz, 1H), 7.83 (d, *J*=6.6 Hz, 2H), 7.49 (t, *J*=7.8 Hz, 2H), 7.40 (m, 5H), 5.06 (d, *J*=6.0 Hz, 1H), 5.03 (d, *J*=6.0 Hz, 1H), 4.58 (d, *J*=11.7 Hz, 1H), 4.49 (d, *J*=11.7 Hz, 1H), 3.38 (m, 4H), 1.19 (t, *J*=6.9 Hz, 3H); ^{13}C NMR δ 168.8, 137.4, 135.1, 134.5, 132.2, 131.6, 127.9, 127.6, 101.2, 73.9, 72.9, 72.7, 62.2, 14.0; FAB-HRMS calcd for $C_{20}H_{22}BO_6$ (M+H): 369.1509, found 369.1511.

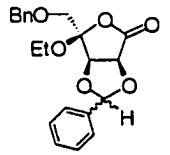


106

$C_{21}H_{22}O_6$
Exact Mass: 370.14
Mol. Wt.: 370.40
C, 68.10; H, 5.99; O, 25.92

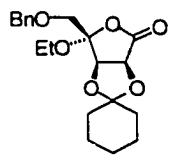
(3*S*, 4*R*, 5*R*)-5-Benzyloxymethyl-3,4-diol-5-ethoxy-dihydrofuran-2-one Benzylidene Acetonide (106). A 5 mL flask equipped with reflux condenser was charged with diol **100** (15.6 mg, 0.0552 mmol) and 2-3 mL toluene. Dimethoxytoluene (10 *u*L, 0.066 mmol) was added via syringe, along with a few crystals of anhydrous tin dichloride. The solution was heated to reflux for 30 minutes. The reaction was then cooled to room temperature, quenched with sat. aq. $Na_2S_2O_3$, washed with brine, dried with $MgSO_4$, and concentrated. The crude material was purified by preparative TLC (2:1 – 1:1 hexane/EtOAc) to yield two diastereomers of benzylidene acetonide **107** as clear oils. Major diastereomer: (11.6 mg, 0.0313 mmol, 57%): $[\alpha]_D^{25}$ -2° (*c* = 0.58, $CHCl_3$); ^{1}H NMR δ 7.43 (s, 5H), 7.36 (s, 5H), 6.12 (s, 1H), 5.07 (d, *J*=5.1 Hz, 1H), 4.60 (d, *J*=5.1 Hz, 1H), 4.70 (d, *J*=12.0 Hz, 1H), 4.60 (d, *J*=12.0 Hz, 1H), 3.94 (d, *J*=11.3 Hz, 1H), 3.78 (d, *J*=11.4 Hz, 1H), 3.77 (d, *J*=6.6 Hz, 1H), 3.73 (d, *J*=6.9 Hz, 1H), 1.25 (t, *J*=6.9 Hz, 3H); ^{13}C NMR δ 172.4, 137.2, 135.3, 130.0, 128.4, 128.4, 128.0, 127.9, 126.8, 107.8, 105.9, 80.7, 75.8, 73.6, 64.0, 59.0; IR (neat) 1798 cm^{-1}; FAB-HRMS calcd for $C_{21}H_{23}O_6$ (M+H):

371.1495, found 371.1489. Minor diastereomer: (4.1 mg, 0.0111 mmol, 20%): ^{1}H NMR δ 7.43 (m, 5H), 7.34 (m, 5H), 5.89 (s, 1H), 5.19 (d, *J*=5.1 Hz, 1H), 4.69 (d, *J*=12.0 Hz, 1H), 4.67 (d, *J*=5.4 Hz, 1H), 4.61 (d, *J*=12.0 Hz, 1H), 3.95 (d, *J*=10.5 Hz, 1H), 3.79 (d, *J*=10.8 Hz, 1H), 3.73 (q, *J*=6.9 Hz, 2H), 1.21 (t, *J*=6.9 Hz, 3H); IR (neat) 1793 cm^{-1}; FAB-HRMS calcd for $C_{21}H_{23}O_6$ (M+H): 371.1495, found 371.1493.



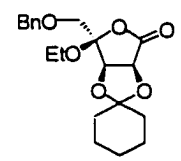
$C_{21}H_{22}O_6$ **107**
Exact Mass: 370.14
Mol. Wt.: 370.40
C, 68.10; H, 5.99; O, 25.92

(3*S*, 4*R*, 5*S*)-5-Benzyloxymethyl-3,4-diol-5-ethoxy-dihydrofuran-2-one Benzylidene Acetonide (107). Dry minor product **106** (4.1 mg, 0.011 mmol) was dissolved in 0.3 mL of CH_2Cl_2 and cooled to -78 °C. Et_2AlCl (22 μL, 0.022 mmol) was added via syringe and the mixture was warmed to room temperature for 1 day. Starting material was still present by TLC (silica gel, 4:1 hexane/EtOAc). Two drops of Et_2AlCl were added via syringe and the reaction was stirred at room temperature for 5 hours. The reaction was quenched with sat. aq. $NaHCO_3$, extracted with CH_2Cl_2, dried with $MgSO_4$, and concentrated to give crude material that was a 1:1.4 mixture of **107**:**106** (1.0 mg, 0.0027 mmol, 24%). The ^{1}H NMR spectrum of **107** matched the spectrum of its enantiomer synthesized by a known method:[50] ^{1}H NMR δ 7.49 (m, 5H), 7.38 (m, 5H), 6.01 (s, 1H), 5.00 (d, *J*=6.0 Hz, 1H), 4.82 (d, *J*=5.7 Hz, 1H), 4.61 (d, *J*=11.2 Hz, 1H), 4.51 (d, *J*=11.7 Hz, 1H), 3.93 (m, 1H), 3.82 (m, 1H), 3.74 (d, *J*=9.6 Hz, 1H), 3.72 (d, *J*=9.7 Hz, 1H), 1.19 (t, *J*=6.9 Hz, 1H).



$C_{20}H_{26}O_6$ **108**
Exact Mass: 362.17
Mol. Wt.: 362.42
C, 66.28; H, 7.23; O, 26.49

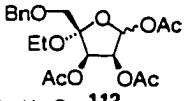
(3*S*, 4*R*, 5*R*)-5-Benzyloxymethyl-3,4-diol-5-ethoxy-dihydrofuran-2-one Cyclohexanonide (108). A flask, equipped with reflux condenser and Soxhlet extractor containing 4 Å molecular sieves, was charged with diol **100** (27 mg, 0.096 mmol), 1,1-dimethoxycyclohexanone (0.15 mL, 0.96 mmol), and 8 mL of benzene. The solution was warmed to reflux and then a few crystals of TsOH were added. The mixture was kept at reflux for until no starting material was present (~ 30 minutes) by TLC (silica gel, 4:1hexane/EtOAc). The mixture was cooled to room temperature and quenched with sat. aq. Na_2CO_3. The separated organic layer was washed with sat. aq. Na_2CO_3 and water. The organic layer was then dried over $MgSO_4$, filtered, and concentrated by rotary evaporation. The crude oil (37 mg) was purified by flash column chromatography (25:1 hexane/EtOAc) to yield protected diol **108** as a clear oil (30 mg, 0.083 mmol, 86%): $[\alpha]_D^{25}$ -15° (*c* = 1.38, EtOH); ^{1}H NMR δ 7.30 (m, 5H), 4.87 (d, *J*=4.8 Hz, 1H), 4.65 (d, *J*=12.3 Hz, 1H), 4.60 (d, *J*=12.6 Hz, 1H), 4.56 (d, *J*=5.1 Hz, 1H), 3.84 (d, *J*=10.8 Hz, 1H), 3.71 (d, *J*=10.5 Hz, 1H), 3.68 (m, 2H), 1.57 (m, 10H), 1.16 (t, *J*=6.9 Hz, 3H); ^{13}C NMR δ 173.8, 137.3, 128.3, 127.8, 115.1, 106.4, 78.9, 75.5, 73.6, 64.2, 59.0, 36.5, 35.6, 24.7, 23.8, 15.2; IR (neat) 1801 cm^{-1}; FAB-HRMS calcd for $C_{20}H_{27}O_6$ (M+H): 363.1808, found 363.1804.



$C_{20}H_{26}O_6$ **109**
Exact Mass: 362.17
Mol. Wt.: 362.42
C, 66.28; H, 7.23; O, 26.49

(3*S*, 4*R*, 5*S*)-5-Benzyloxymethyl-3,4-diol-5-ethoxy-dihydrofuran-2-one Cyclohexanonide (109). Dry acetonide **108** (4.3 mg, 0.012 mmol) was dissolved in 0.5 mL CH_2Cl_2 and cooled to -78 °C. Et_2AlCl (0.02 mL, 0.024 mmol) was added

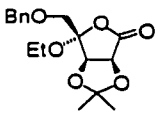
via syringe. The solution was stirred at -78 °C for 2 hours. The reaction was quenched with cold sat. aq. $NaHCO_3$, extracted with CH_2Cl_2, dried, and concentrated. Purification by preparative TLC (10:1 hexane/EtOAc X2) gave recovered starting material **108** (3.3 mg, 0.0090 mmol, 75%) and epimerized **109** (1.0 mg, 0.0027 mmol, 23%). ^{1}H NMR spectrum of **109** matches the spectrum for its enantiomer synthesized by a known method:[51] ^{1}H NMR δ 7.40 (m, 3H), 7.25 (m, 2H), 4.90 (d, *J*=6.0 Hz, 1H), 4.71 (d, *J*=5.7 Hz, 1H), 4.60 (d, *J*=11.7 Hz, 1H), 4.50 (d, *J*=11.7 Hz, 1H), 4.00 (m, 1H), 3.85 (m, 1H), 3.72 (d, *J*=9.9 Hz, 1H), 3.69 (d, *J*=9.6 Hz, 1H), 1.70 (m, 10H), 1.23 (t, *J*=6.9 Hz, 3H).



$C_{20}H_{26}O_9$ **112**
Exact Mass: 410.16
Mol. Wt.: 410.42
C, 58.53; H, 6.39; O, 35.09

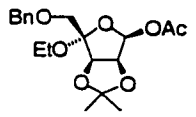
(3*S*, 4*R*, 5*R*)-5-Benzyloxymethyl-5-ethoxy-2,3,4-triacetoxytetrahydrofuran (112). Acetate **112** was prepared from diol **100** (43.6 mg, 0.1545 mmol, 0.03M) by using the general procedure with the exceptions that 3.3 eq. of DIBAL were added at the beginning of the reaction and then pyridine (6 eq.), DMAP (2.2 eq.), and Ac_2O (8 eq.) were added. The crude ^{1}H NMR spectrum indicated a 0.6:1 mixture of anomeric acetates which were separated by flash chromatography (5:2 hexane/EtOAc) to give **112**. Anomer 1 (14 mg, 0.034 mmol, 22%): ^{1}H NMR δ 7.30 (m, 5H), 6.18 (d, *J*=4.1 Hz, 1H), 5.71 (dd, *J*=4.9, *J*=4.1 Hz, 1H), 5.43 (d, *J*=4.9 Hz, 1H), 4.58 (d, *J*=12.2 Hz, 1H), 4.43 (d, *J*=12.2 Hz, 1H), 3.63 (d, *J*=10.7 Hz, 1H), 3.60 (m, 2H), 3.54 (d, *J*=10.7 Hz, 1H), 2.09 (s, 3H), 2.01 (s, 3H), 1.93 (s, 3H), 1.20 (t, *J*=7.1 Hz, 3H). Anomer 2 of **112** (20 mg, 0.049 mmol, 31%): ^{1}H NMR δ 7.27-7.38 (m, 6H), 6.34 (d, *J*=5.0 Hz, 1H), 5.55 (t, *J*=5.0 Hz, 1H), 5.42 (d, *J*=5.0 Hz, 1H), 4.58 (d, *J*=12.2 Hz, 1H), 4.45 (d, *J*=12.2 Hz, 1H), 3.68 (d, *J*=10.6 Hz, 1H), 3.59 (d, *J*=10.6

Hz, 1H), 3.54-3.65 (m, 2H), 2.05 (s, 3H), 2.02 (s, 3H), 1.97 (s, 3H), 1.18 (t, *J*=7.1 Hz, 3H); IR (thin film) 2933, 1753 cm^{-1}; Anal. Calcd. for $C_{20}H_{26}O_9$; C, 58.53; H, 6.39. Found; C, 58.35; H, 6.15. Also obtained was 2,3-diacetoxy lactone (6.0 mg, 0.016 mmol, 15%) as a colorless oil: ^1H NMR δ 7.37-7.27 (m, 5H), 5.94 (d, *J*=4.9 Hz, 1H), 5.53 (d, *J*=4.9 Hz, 1H), 4.60 (d, *J*=12.1 Hz, 1H), 4.46 (d, *J*=12.1 Hz, 1H), 3.83 (d, *J*=10.8 Hz, 1H), 3.71 (m, 2H), 3.65 (d, *J*=10.8 HZ, 1H), 2.11 (s, 3H), 1.93 (s, 3H), 1.22 (t, *J*=7.1 Hz, 3H).



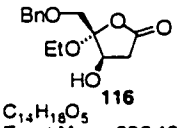
$C_{17}H_{22}O_6$ **113**
Exact Mass: 322.14
Mol. Wt.: 322.35
C, 63.34; H, 6.88; O, 29.78

(3*S*, 4*R*, 5*R*)-5-Benzyloxymethyl-3,4-diol-5-ethoxydihydrofuran-2-one Acetonide (113). A flask, equipped with reflux condenser and Soxhlet extractor containing 4 Å molecular sieves, was charged with diol **100** (32.3 mg, 0.114 mmol), 2,2-dimethoxypropane (0.25 mL, 2.9 mmol), and 15 mL benzene. The solution was warmed to reflux and a few crystals of TsOH were added. The reaction was kept at reflux for 30 minutes and then cooled to room temperature. The organic layer was washed with sat. aq. Na_2CO_3 (x2), DI H_2O (x2), dried, and concentrated to give pure acetonide **113** (35.5 mg, 0.110 mmol, 96%) as a colorless oil: $[\alpha]_D^{25}$ +12° (*c* = 0.72, $CHCl_3$); ^1H NMR δ 7.37 (m, 5H), 4.90 (d, *J*=5.1 Hz, 1H), 4.70 (d, *J*=12.1 Hz, 1H), 4.61 (d, *J*=4.8 Hz, 1H), 4.60 (d, *J*=12.5 Hz, 1H), 3.85 (d, *J*=11.0 Hz, 1H), 3.72 (d, *J*=11.0 Hz, 1H), 3.69 (q, *J*=7.0 Hz, 2H), 1.44 (s, 3H), 1.41 (s, 3H), 1.18 (t, *J*=7.0 Hz, 3H); IR (thin film) 1799 cm^{-1}; ^{13}C NMR δ 173.6, 137.3, 127.9, 127.8, 114.5, 106.3, 79.3, 75.8, 73.6, 64.1, 59.0, 26.8, 26.1, 15.1; Anal. Calcd for $C_{17}H_{22}O_6$: C, 63.34; H, 6.88. Found: C, 63.16; H, 7.00.



$C_{19}H_{26}O_7$ **114**
Exact Mass: 366.17
Mol. Wt.: 366.41
C, 62.28; H, 7.15; O, 30.57

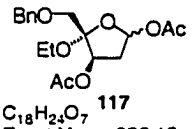
(2*S*, 3*S*, 4*R*, 5*R*)-2-Acetoxy-5-benzyloxymethyl-3,4-diol-5-ethoxytetrahydrofuran Acetonide (114). Acetate **114** was prepared from acetonide **113** (35.5 mg, 0.110 mmol, 0.02M) by using the general procedure. Purification by flash column chromatography (6:1 hexane/EtOAc) gave **114** (37.8 mg, 0.103 mmol, 94% yield): $[\alpha]_D^{25}$ +19° (*c* = 0.655, $CHCl_3$); ^1H NMR δ 7.34 (m, 5H), 5.94 (d, *J*=4.0 Hz, 1H), 4.92 (dd, *J*=3.4 Hz, *J*=5.4 Hz, 1H), 4.68 (d, *J*=12.3 Hz, 1H), 4.59 (d, *J*=5.4 Hz, 1H), 4.58 (d, *J*=12.9 Hz, 1H), 3.74 (d, *J*=10.8 Hz, 1H), 3.68 (d, *J*=10.5 Hz, 1H), 3.58 (m, 2H), 2.15 (s, 3H), 1.49 (s, 3H), 1.38 (s, 3H), 1.18 (t, *J*=6.9 Hz, 3H); ^{13}C NMR δ 168.9, 137.7, 128.2, 127.9, 127.6, 113.8, 105.6, 96.6, 82.5, 78.5, 73.4, 65.0, 57.1, 26.0, 25.7, 20.9, 15.4; IR (neat) 1748.5 cm^{-1}; FAB-HRMS calcd for $C_{19}H_{27}O_7$ (M+H): 367.1757, found 367.1758.



$C_{14}H_{18}O_5$
Exact Mass: 266.12
Mol. Wt.: 266.29
C, 63.15; H, 6.81; O, 30.04

(4*R*, 5*R*)-5-Benzyloxymethyl-5-ethoxy-4-hydroxydihydrofuran-2-one (116). Acetonide **113** (50 mg, 0.16 mmol) was dissolved in THF (2 mL) and dry ethylene glycol (0.1 mL) was added. This solution was degassed by freeze-pump-thaw (3 cycles). A degassed solution of SmI_2 (9 mL, 0.17 M in THF) was added via cannula and the resulting mixture was stirred at room temperature for 0.5 h before quenching by addition of sat. aq. $NaHCO_3$. The mixture was extracted with Et_2O (2 x 40 mL). The organic phase was washed with 10% $Na_2S_2O_3$ solution, washed with brine, dried, and evaporated to give a pale brown oil. Flash column chromatography of the crude product (4:1 hexane/EtOAc) gave alcohol **116** (38.1 mg, 0.143 mmol, 92%) as a colorless oil: $[\alpha]_D^{25}$ -20° (*c* = 0.44, $CHCl_3$); ^1H NMR δ 7.39 (m, 5H), 4.64 (d, *J*=12.1 Hz, 1H), 4.58 (d, *J*=11.8 Hz, 1H),

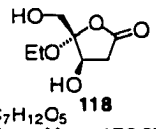
4.37 (ddd, *J*=1.5 Hz, , *J*=3.7 Hz , *J*=6.2 Hz, 1H), 3.95 (d, *J*=10.6 Hz, 1H), 3.76 (d, *J*=10.6 Hz, 1H), 3.60 (m, 2H), 2.96 (ddd, *J*=1.1, *J*=6.2 Hz, *J*=18.0 Hz, 1H), 2.67 (dd, *J*=1.1 Hz, *J*=3.7 Hz, 1H), 2.46 (dd, *J*=1.5 Hz, *J*=18.3 Hz, 1H), 1.18 (t, *J*=7.0 Hz, 3H); ^{13}C NMR δ 174.6, 136.8, 128.7, 128.4, 128.0, 109.4, 73.7, 72.6, 65.2, 58.7, 36.6, 15.3; IR (neat) 3455, 1795 cm^{-1}; FAB-HRMS calcd for $C_{14}H_{20}O_5$ (M+H): 267.1232, found 267.1239.



117
$C_{18}H_{24}O_7$
Exact Mass: 352.15
Mol. Wt.: 352.38
C, 61.35; H, 6.86; O, 31.78

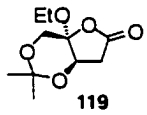
(4*R*, 5*R*)-5-Benzyloxymethyl-2,4-diacetoxy-5-ethoxytetrahydrofuran (117). Acetate **117** was prepared from alcohol **116** (28 mg, 0.11 mmol, 0.03M) by using the general procedure with the exceptions that DIBAL (2.3 eq.) was only added at the beginning of the reaction, the reaction stirred at -78 °C for 3 hours, and then pyridine (4 eq.), DMAP (2 eq.), and Ac_2O (8 eq.) were added. Flash column chromatography of the crude product (8:1 hexane/EtOAc) gave the impure diacetate **117** (14 mg, 0.040 mmol, 39%) as a colorless oil (5:1 mixture of anomers). Major anomer: ^{1}H NMR δ 7.33 (m, 5H), 6.27 (d, *J*=5.9 Hz, 1H), 5.18 (d, *J*=5.1 Hz, 1H), 4.61 (d, *J*=12.1 Hz, 1H), 4.50 (d, *J*=12.4 Hz, 1H), 3.72 (d, *J*=10.3 Hz, 1H), 3.64 (d, *J*=10.6 Hz, 1H), 3.60 (m, 2H), 2.75 (dt, *J*=5.5 Hz, *J*=15.0 Hz, 1H), 2.05 (s, 3H), 1.96 (s, 3H), 1.17 (t, *J*=7.0 Hz, 3H). Minor anomer: ^{1}H NMR δ 6.38 (dd, *J*=6.3 Hz, *J*=4.5 Hz, 1H), 5.33 (dd, *J* = 5.7 Hz, *J*=1.7 Hz, 1H), 2.56 (ddd, *J*=14.7 Hz, *J*=5.7 Hz, *J*=4.5 Hz, 1H), 2.31 (ddd, *J*=14.7 Hz, *J*=6.3 Hz, *J*=1.7 Hz, 1H), 2.07 (s, 3H), 1.91 (s, 3H). Both anomers: ^{13}C NMR δ 169.8, 169.4, 137.7, 127.9, 127.7, 127.6, 109.6, 109.1, 97.5, 97.3, 74.7, 74.5, 73.5, 65.4, 65.1, 57.1, 57.0, 37.9, 37.3, 21.2, 21.0, 21.0,

20.8, 15.4, 15.2; IR (thin film) 1749 cm^{-1}; FAB-LRMS calcd for $C_{16}H_{21}O_5$ (M-OAc): 293.15, found 293.14.



118
$C_7H_{12}O_5$
Exact Mass: 176.07
Mol. Wt.: 176.17
C, 47.72; H, 6.87; O, 45.41

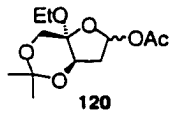
(4*R*, 5*R*)-5-Ethoxy-4-hydroxy-5-hydroxymethyl-dihydrofuran-2-one (118). Alcohol **117** (30.3 mg, 0.114 mmol) was dissolved in 2.5 mL EtOH and stirred over 10% Pd/C (15 mg) under a H_2 atmosphere (1 atm) until no starting material was present (~1 hour) by TLC (silica gel, 1:1 hexane/EtOAc). Argon was bubbled through the solution. The solution was filtered through Celite and then concentrated to give dialcohol **118** (20 mg, 0.11 mmol) in quantitative yield as a colorless oil: $[\alpha]_D^{25}$ -3° (*c* = 0.5, $CHCl_3$); ^1H NMR δ 4.44 (ddd, *J*=1.6 Hz, *J*=3.6 Hz, *J*=5.6 Hz, 1H), 4.11 (dd, *J*=4.0 Hz, *J*=12.0 Hz, 1H), 3.97 (dd, *J*=7.6 Hz, *J*=12.0 Hz, 1H), 3.70 (m, 2H), 3.01 (dd, *J*=6.4 Hz, *J*=18.0 Hz, 1H), 2.83 (d, *J*=3.6 Hz, 1H), 2.52 (dd, *J*=1.6 Hz, *J*=18.4 Hz, 1H), 1.97 (t, *J* =4.9 Hz, 1H), 1.22 (t, *J*=7.0 Hz, 3H); ^{13}C NMR δ 174.9, 109.7, 72.5, 59.0, 58.8, 37.1, 15.4 cm^{-1}; IR (neat) 3421, 1772; FAB-HRMS calcd for $C_7H_{13}O_5$ (M+H): 177.0763, found 177.0756.



119
$C_{10}H_{16}O_5$
Exact Mass: 216.10
Mol. Wt.: 216.23
C, 55.55; H, 7.46; O, 37.00

(4*R*, 5*R*)-4,6-Diol-5-ethoxydihydrofuran-2-one Acetonide (119). Acetonide **119** was prepared from diol **118** (15.8 mg, 0.0896 mmol) by using the procedure for acetonide **113**. Acetonide **119** (11.4 mg, 0.0527 mmol, 59%) was obtained as a clear oil: $[\alpha]_D^{25}$ +5° (*c* = 0.57, CH_2Cl_2); ^1H NMR δ 4.27 (d, *J*=5.4 Hz, 1H), 4.07 (d, *J*=12.9 Hz, 1H), 3.99 (d, *J*=12.3 Hz, 1H), 3.65 (m, 2H), 2.94 (dd, *J*=5.4 Hz, *J*=18.0 Hz, 1H), 2.46 (d, *J*=18.0 Hz, 1H), 1.48 (s, 3H), 1.38 (s, 3H), 1.20 (t, *J*=7.2 Hz, 3H); ^{13}C NMR δ

175.0, 103.7, 99.2, 70.8, 61.6, 58.6, 35.2, 26.4, 21.0, 15.5; IR (neat) 1799 cm^{-1}; FAB-HRMS calcd for $C_{10}H_{17}O_5$ (M+H): 217.1076, found 217.1073.



120

$C_{12}H_{20}O_6$
Exact Mass: 260.13
Mol. Wt.: 260.28
C, 55.37; H, 7.74; O, 36.88

(4*R*, 5*R*)-2-Acetoxy-4,6-diol-5-ethoxydihydrofuran-2-one Acetonide (120). Acetate **120** was prepared from acetonide **119** (32 mg, 0.1479 mmol, ~0.02M) by using the general procedure. Purification by flash column chromatography (4.5:1 hexane/EtOAc) gave **120** (20.7 mg, 0.0795 mmol, 54% yield) as a 1:1 mixture of diastereomers and as a clear oil: ^{1}H NMR δ 6.53 (dd, *J* =4.8 Hz, *J* =6.2 Hz, 1H), 6.35 (d, *J*=5.7 Hz, 1H), 4.24 (d, *J*=5.1 Hz, 1H), 4.15 (d, *J* =5.4 Hz, 1H), 3.97 (d, *J* =12.5 Hz, 1H), 3.97 (s, 2H), 3.91 (d, *J* =12.5 Hz, 1H), 3.63 (m, 2H), 3.48 (m, 2H), 2.58 (dt, *J* =5.5 Hz, *J* =20.1 Hz, 1H), 2.38 (m, 3H), 2.13 (s, 3H), 2.10 (s, 3H), 1.47 (s, 3H), 1.46 (s, 3H), 1.41 (s, 3H), 1.37 (s, 3H), 1.18 (t, *J* =6.0 Hz, 3H), 1.16 (t, *J* =7.0 Hz, 3H); ^{13}C NMR δ 170.1, 104.9, 103.5, 99.0, 98.7, 98.4, 98.3, 74.7, 73.1, 63.2, 62.5, 57.3, 56.9, 38.0, 37.3, 27.5, 27.0, 21.4, 21.2, 20.7, 20.1, 15.7, 15.5; IR (neat) 1749 cm^{-1}; FAB-HRMS calcd for $C_{10}H_{17}O_4$ (M-OAc): 201.1127, found 201.1127.

V. References

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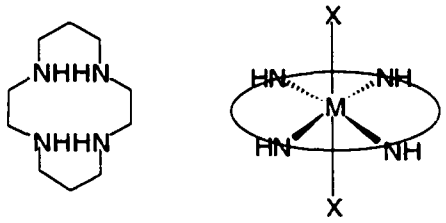
(47) *Diol **87** and **100** correspond to diol **142** and **147** respectively in Chapter One.*
(48) Reed, A. D. *Ph.D. Dissertation, Colorado State University* **1996**.
(49) *The boronate ester of diol **87** was synthesized using the procedure for **104**.*
(50) *The benzylidene acetal of diol **87** was synthesized using the procedure for **106**.*
(51) *The enantiomer of acetonide **109** was synthesized from diol **87** using the procedure for **108**.*

CHAPTER THREE

PROGRESS TOWARDS THE SYNTHESIS OF BIPYRIMIDINE-BRIDGED BIS-DIOXOCYCLAMS

I. Introduction and Background

Cyclams are 14-membered tetraazamacrocycles (**1**). They have mainly been used for metal coordination chemistry because of their ability to coordinate strongly to a variety of first and second row transition metals. Complexation usually involves all four nitrogens and the coordination geometry of the metal is square planar (**2**), with the two *trans*-coordination sites open (Figure 3.1). In



Cyclam **1** *trans*-Geometry (**2**)

Figure 3.1 Cyclam **1** and Coordination Geometry.

addition, the cyclam ring is flexible and can accommodate a variety of atomic radii and coordination geometries forming complexes with lanthanides and main group metals.

Dioxocyclams (**4-7**) differ from cyclams in that they contain two amine and two amide moieties (Figure 3.2). Upon complexation (such as **8**), the amide

protons become acidic and can be removed under basic conditions. Thus, when divalent metals are used the resulting complex is neutral. Dioxocyclams complex metals more selectively than cyclams. Copper(II), nickel(II), palladium(II),[1,2] cobalt(II),[2,3] and platinum (II)[1] form stable complexes. Metal complexation of dioxocyclams can be monitored by IR spectroscopy because the stretching frequency of the amide carbonyls usually decreases 80 cm^{-1}.

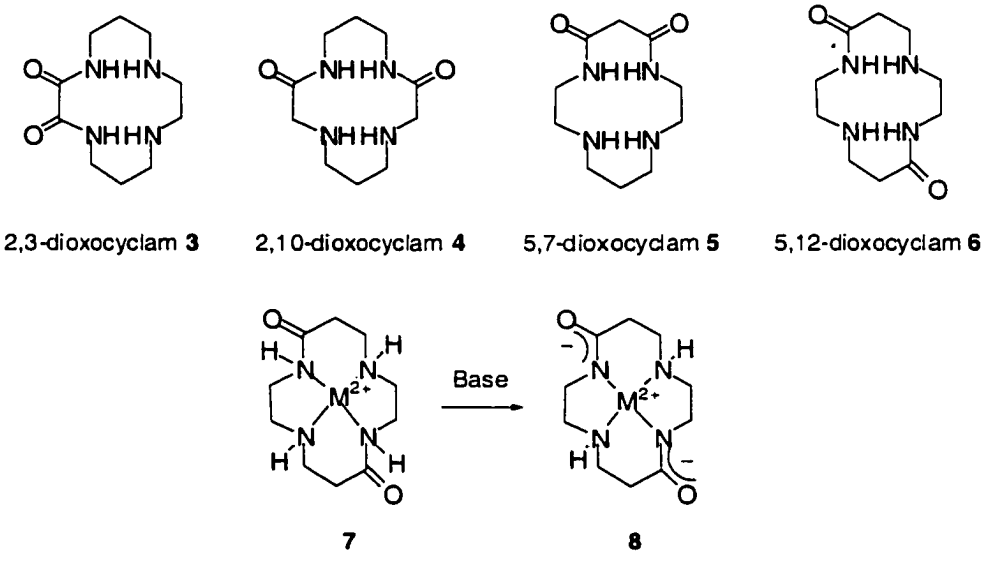
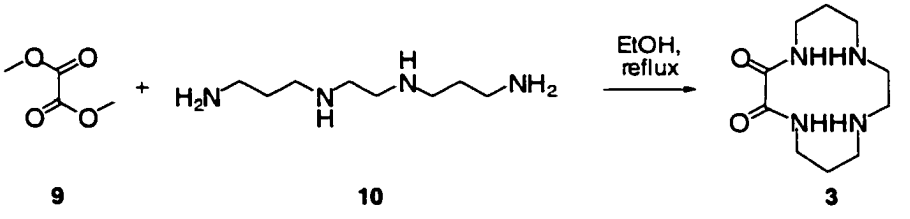


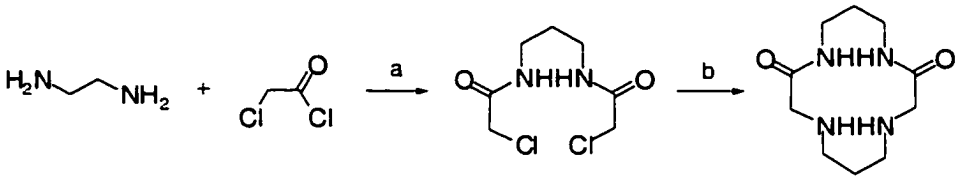
Figure 3.2 Dioxocyclams and Metal Complexation.

There are only few methods to synthesize dioxocyclams and most syntheses give unsubstituted products. Robertson published the only synthesis of a 2,3-dioxocyclam (Scheme 3.1).[4] Under high dilution conditions, dimethyloxalate (**9**) and N,N'-bis(3-aminopropyl)-ethylenediamine (**10**) were heated to reflux for over 32 hours to give 2,3-dioxocyclam **3** in 60% yield.



Scheme 3.1 Robertson's Synthesis of 2,3-Dioxocyclams.

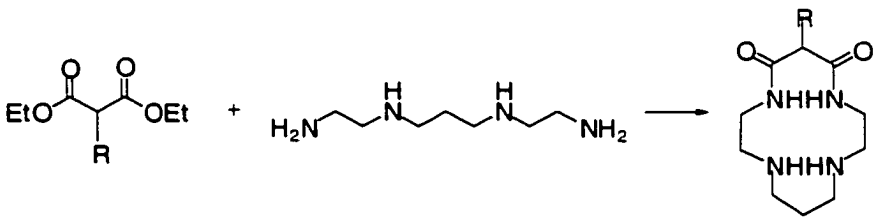
Tempkin developed the only synthesis of a 2,10-dioxocyclam (Scheme 3.2).[5,6] The reaction of ethylenediamine **11** and chloroacetyl chloride **12** gave dichloride **13**. 2,10-Dioxocyclam **4** was obtained after cyclization of **13** with another equivalent of **11**.



11 **12** **13** **4**

Scheme 3.2 Tempkin's Synthesis of 2,10-Dioxocylam **4**. (a) K_2CO_3, CH_2Cl_2:H_2O, -10 °C to rt.; (b) ethylenediamine, Na_2CO_3, acetonitrile, reflux.

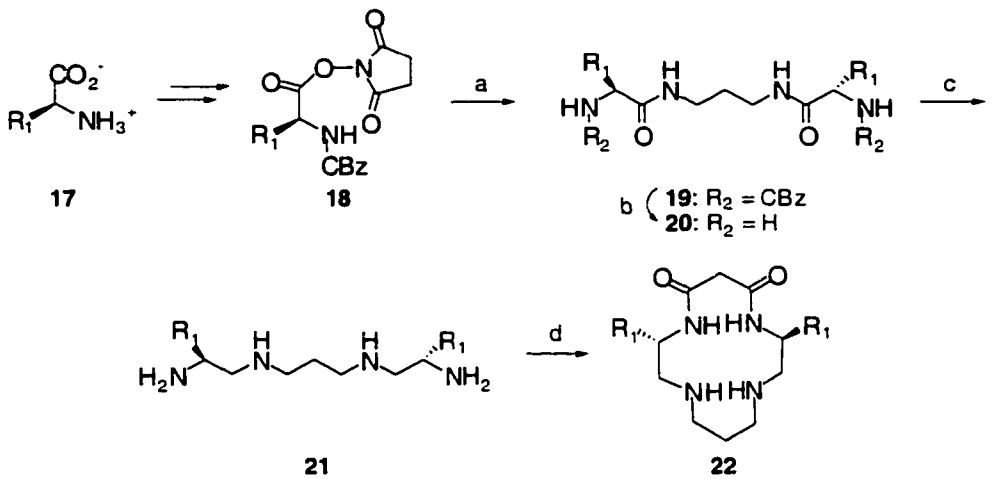
Tabushi developed the synthesis of functionalized 5,7-dioxocyclams **16**. The reaction of malonate ester **14** with N,N'-bis-(2-aminoethyl)-propane-1,3-diamine (**15**) gave **16** in 25-40% yield (Scheme 3.3).[7] This methodology was



14 **15** **16**

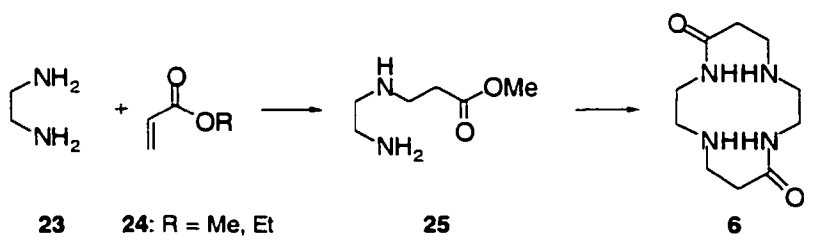
Scheme 3.3 Tabushi's 5,7-Dioxocyclam Synthesis. R = H, $CH_2C_6H_5$, CH_2CH_2OH, $CH_2CH_2CH_2CH_3$, $CH_2CH_2CH_2CN$, $CH_2CH{=}CH_2$.

expanded to synthesize optically active 5,7-dioxocyclams. Starting from phenylalanine, leucine, and valine, Burrows used Tabushi's method to synthesize 3,9-disubstituted 5,7-dioxocyclams **22** in 2-6% overall yield from **18** (Scheme 3.4).[8]



Scheme 3.4 Burrow's Optically Active 5,7-Dioxocyclam Synthesis. R_1 = H, $CH_2C_6H_5$, $CH_2CH(CH_3)_2$, $CH(CH_3)_2$. (a) ethylenediamine, DME, >80%; (b) 5% Pd/C, 40 psi H_2; (c) BH_3/THF, 37-62% from **15**; (d) MeOH, reflux, dimethyl malonate, 8-12% yield.

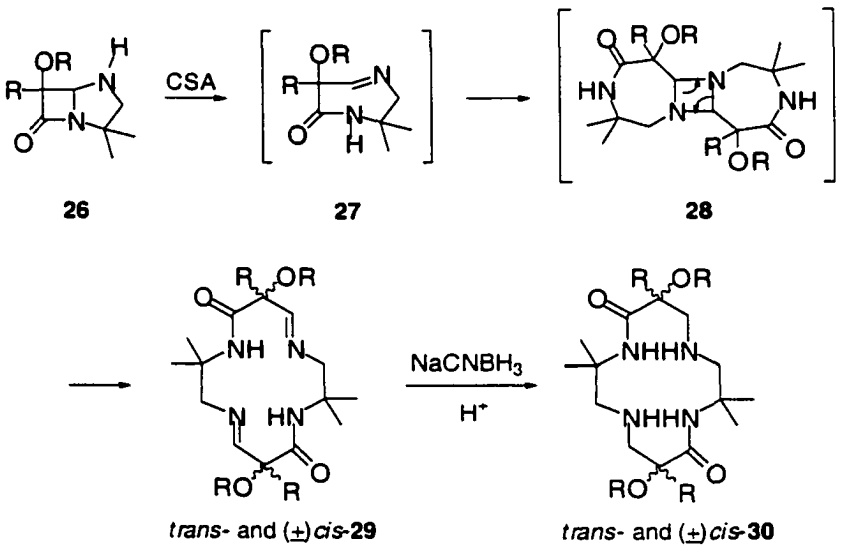
There are two methods to synthesize 5,12-dioxocylams. The first method was developed Tomalia and Wilson for the Dow Chemical Company (Scheme 3.5). Methyl acrylate (**24**) and ethylene diamine (**23**) were condensed and upon cyclization gave dioxocyclam **6** in 2% yield.[9] When ethyl acrylate was used dioxocyclam **6** was obtained in 9% yield.[10] This method suffers from low yield and lack of functionality but the reactions can be scaled up and the reagents are inexpensive.



Scheme 3.5 Tomalia's Synthesis.

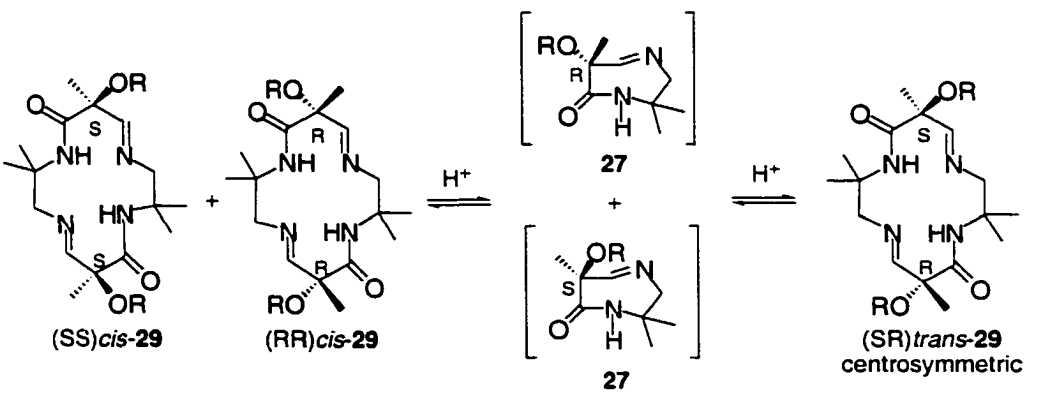
The second method to synthesize 5,12-dioxocyclams was developed by Hegedus. While researching the synthesis of penicillin analogs, azapenam **26** was treated with CSA and surprisingly gave imine **29** in 82-96% yield, as a

mixture of *trans*- and (±)*cis*-isomers. Imine **29** is believed to be formed via acid-promoted ring opening of **26**. The seven membered imine **27** then dimerizes to give **28**, which metathesizes to the 14-membered macrocycle **29** (Scheme 3.6).[11] Imine **29** can be reduced with sodium cyanoborohydride to give *trans*- and (±)*cis*-dioxocyclam **30** in high yield.[12]



Scheme 3.6 Hegedus's Synthesis of 5,12-Dioxocyclams.

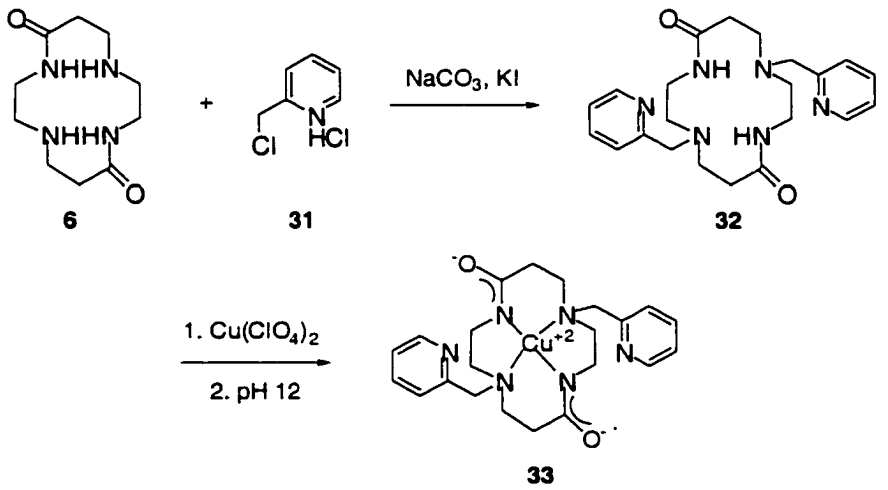
With this method the yields are high and the products are functionalized. However, stereochemistry is an issue and two diastereomers (**29**) are obtained. Racemic azapenam **26** affords racemic **27**, which upon dimerization gives



Scheme 3.7 Conformational Isomers of **29**.

(RR)*cis*-**29** and (SS)*cis*-**29** (Scheme 3.7), as well as (SR)*trans*-**29** (an achiral compound). With the use of an optically pure azapenam, this methodology was expanded to synthesize optically active dioxocyclams.[1]

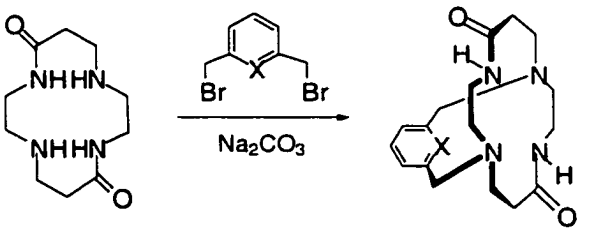
Alkylation of the amine nitrogens on 5,12-dioxocyclams has been reported. Williams[10] synthesized N,N-disubstituted 5,12-dioxocyclam **32**, anticipating that the pendant pyridyl groups would be additional coordination sites for a metal. Treatment of dioxocyclam **6** with 2-(chloromethyl)pyridine hydrochloride (**31**), sodium carbonate, and a catalytic amount of potassium iodide gave dialkylated **32** in 75% yield (Scheme 3.8). When **32** was treated with copper(II)perchlorate under basic conditions, copper complex **33** was obtained. The data from the X-ray crystal structure showed that the pyridyl nitrogens were weakly coordinated to the copper because the average nitrogen-copper distance was 2.721 Å.



Scheme 3.8

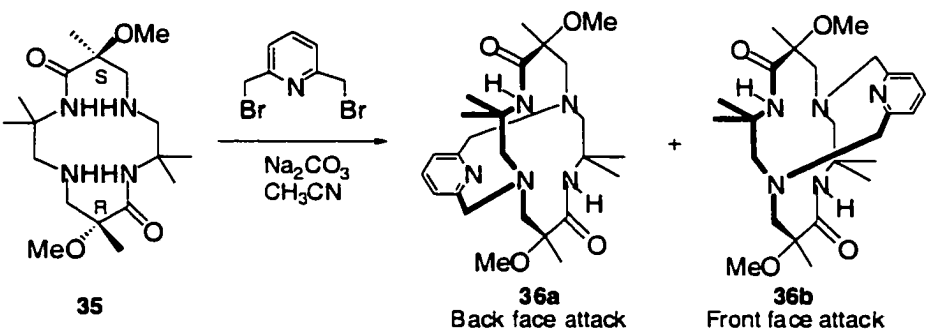
Alkylation of a 5,12-dioxocyclam with a bidentate alkylating agent was performed by Guilard. Treatment of **6** with α,α′-dibromo-*m*-xylene or 2,6-bis(bromomethyl)pyridine gave capped dioxocyclam **34a** and **34b** in 90% and

84% yield respectively (Scheme 3.9).[13] Metal complexation of **34a** or **34b** has not been reported.



Scheme 3.9

Highly functionalized capped 5,12-dioxocyclams have been synthesized in the Hegedus group. Work has been performed on two series, the (methyl)(methyoxy)- and (methyl)(benzyloxy)dioxocyclams. For clarification the (methyl)(methoxy) series is referred to below. *trans*-Dioxocyclam **35** was treated with bis(bromomethyl)pyridine and sodium carbonate to give capped dioxocyclam **36** in 81% yield, as a mixture of enantiomers (Scheme 3.10). Substitution on *trans*-dioxocyclam **35** can occur from either face, giving **36a** (back face attack) or **36b** (front face attack). The mirror image relationship of **36a** to



Scheme 3.10

36b is shown in Figure 3.3, noting that once *trans*-cyclam **35** is capped, the amine nitrogens cannot invert and become stereocenters.[A]

[A] See the Appendix for the priorities for R/S assignment of the stereogenic amines.

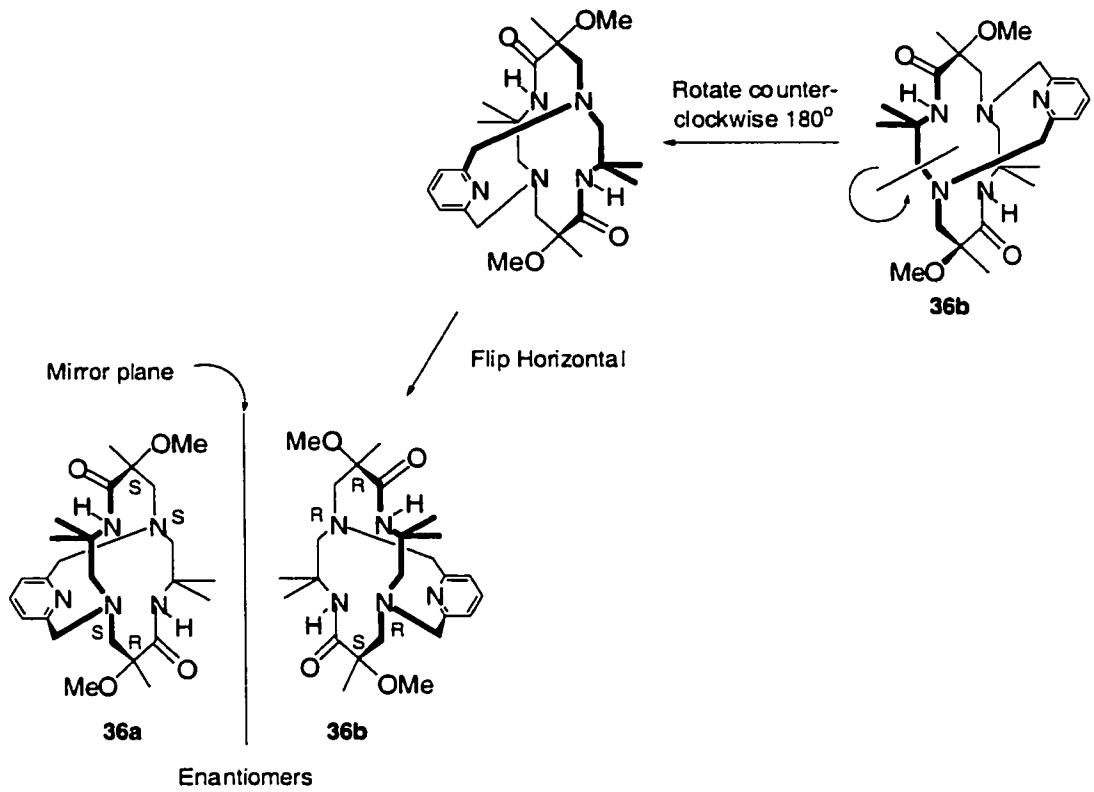
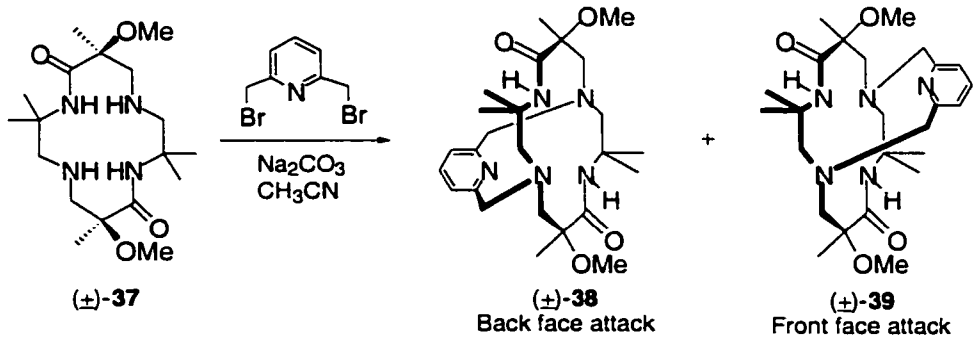


Figure 3.3

When (±)-*cis*-dioxocyclam **37** is used in the capping reaction, the stereochemistry becomes more complex. (±)-*cis*-Dioxocyclam **37** was treated with bis(bromomethyl)pyridine and sodium carbonate to give capped cyclam (±)-**38** in 25% yield and (±)-**39** in 56% yield, as a mixture of racemic diastereomers (Scheme 3.11).[12] As before, substitution can occur from either face, giving (±)-**38**



Scheme 3.11

(back face attack) and (±)-**39** (front face attack). As seen in Figure 3.4, these compounds are diastereomers (the [S,S]-enantiomer is shown for clarity).

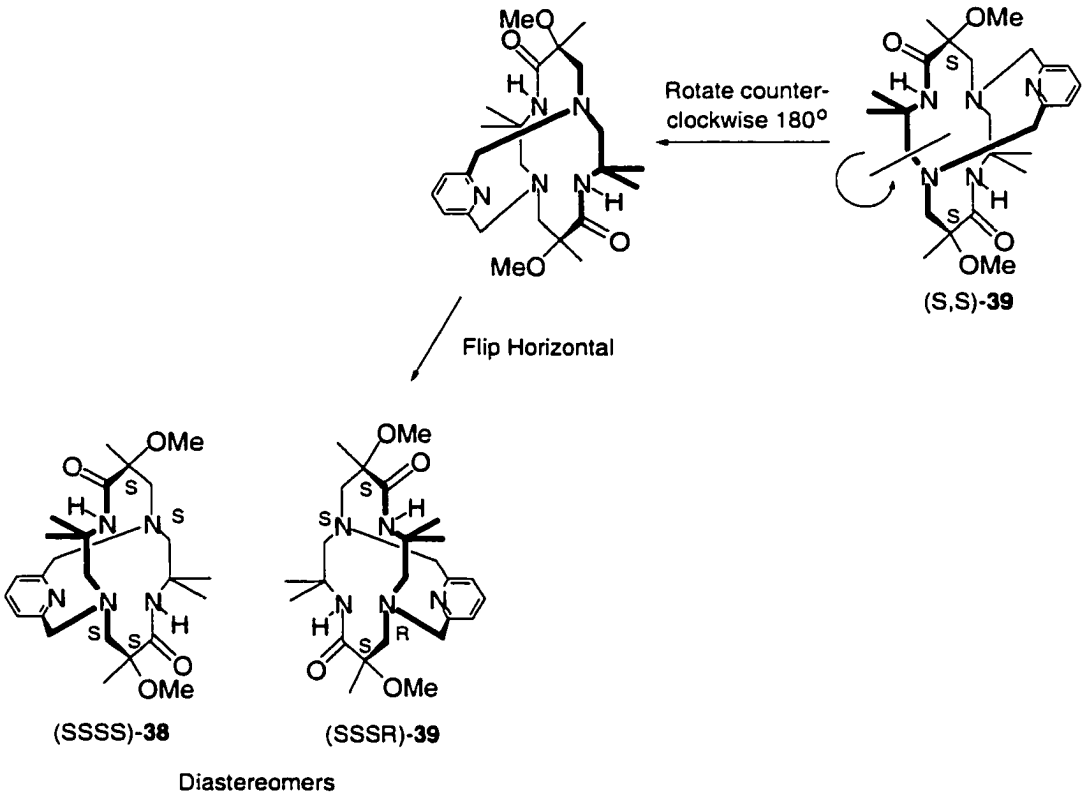
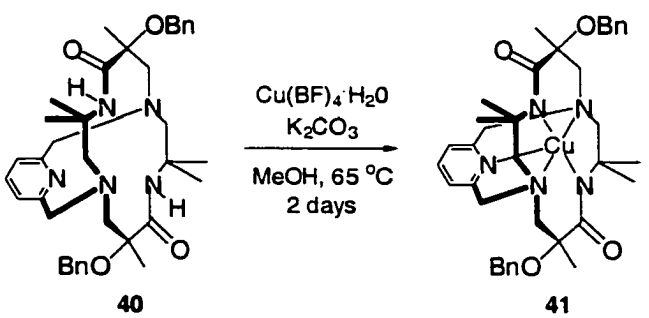


Figure 3.4

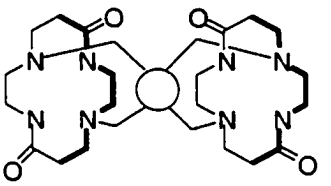
Hegedus also synthesized copper complexes of the capped dioxocyclam systems.[12] Treatment of capped dioxocyclam **40** with copper tetrafluoroborate and potassium carbonate in methanol at reflux gave **41** in 75% yield (Scheme 3.12). In the X-ray crystal structure, the copper is clearly five-coordinate, with an



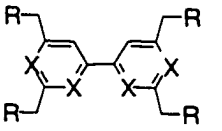
Scheme 3.12

average bond length of 2.13 Å for the pyridine nitrogen-copper bond.

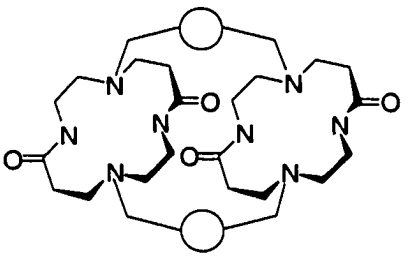
Nitrogen substitution of dioxocyclams can also be performed to give complex macrocycles such as bridged bis-dioxocyclams (**42**) or bis-bridged bis-dioxocyclams (**44**), as seen in Figure 3.5. Methods to synthesize these macrocycles use poly-electrophilic aromatic or aliphatic groups as the "bridging arms" which can be a variety of compounds (such as **43** and **45**). Suitable bridging arms can participate in metal coordination or could facilitate communication between the two metals. These complicated macrocycles could be used in catalysis, small molecule encapsulation and activation, electron transfer studies, and nonlinear optics.



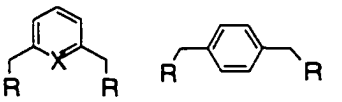
Bridged Bis-dioxocyclam **42**



Tetradentate Bridging Arms **43**



Bis-bridged Bis-dioxocyclam **44**

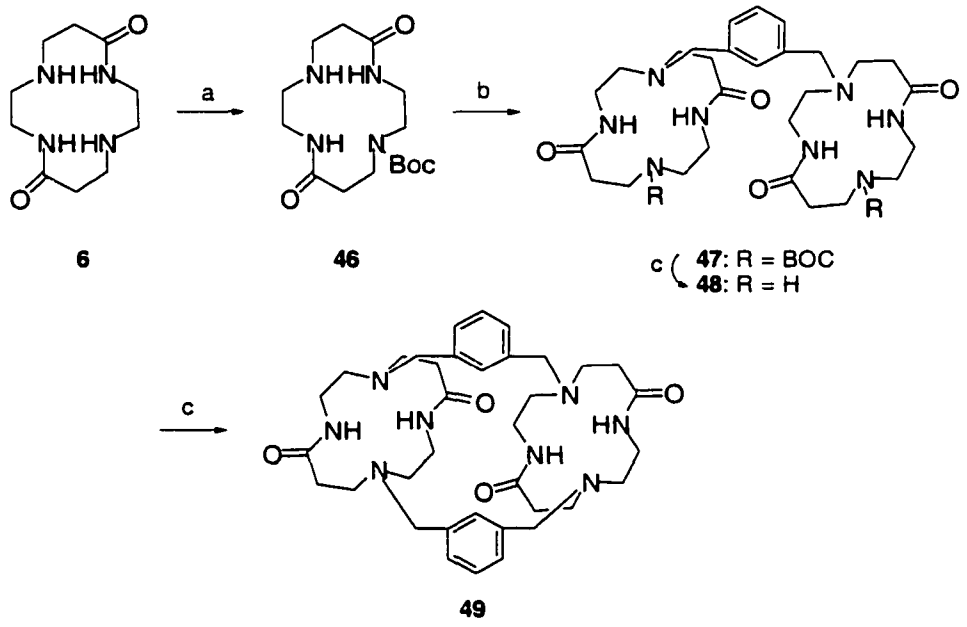


Bidentate Bridging Arms **45**

Figure 3.5 X = CH, N; R = Br, Cl, OTs, OMs, etc.

Guilard used unfunctionalized dioxocyclam **6** to synthesize bridged bis-dioxocyclam **49**. Monoprotection of **6** with *t*-butyloxycarbonyl (Boc) anhydride gave protected dioxocyclam **46** in 48% yield (Scheme 13). Treatment of **46** with α,α′-dibromo-*m*-xylene and sodium carbonate gave monobridged bis-dioxocyclam **47** in 84% yield. Removal of the protecting group with acid,

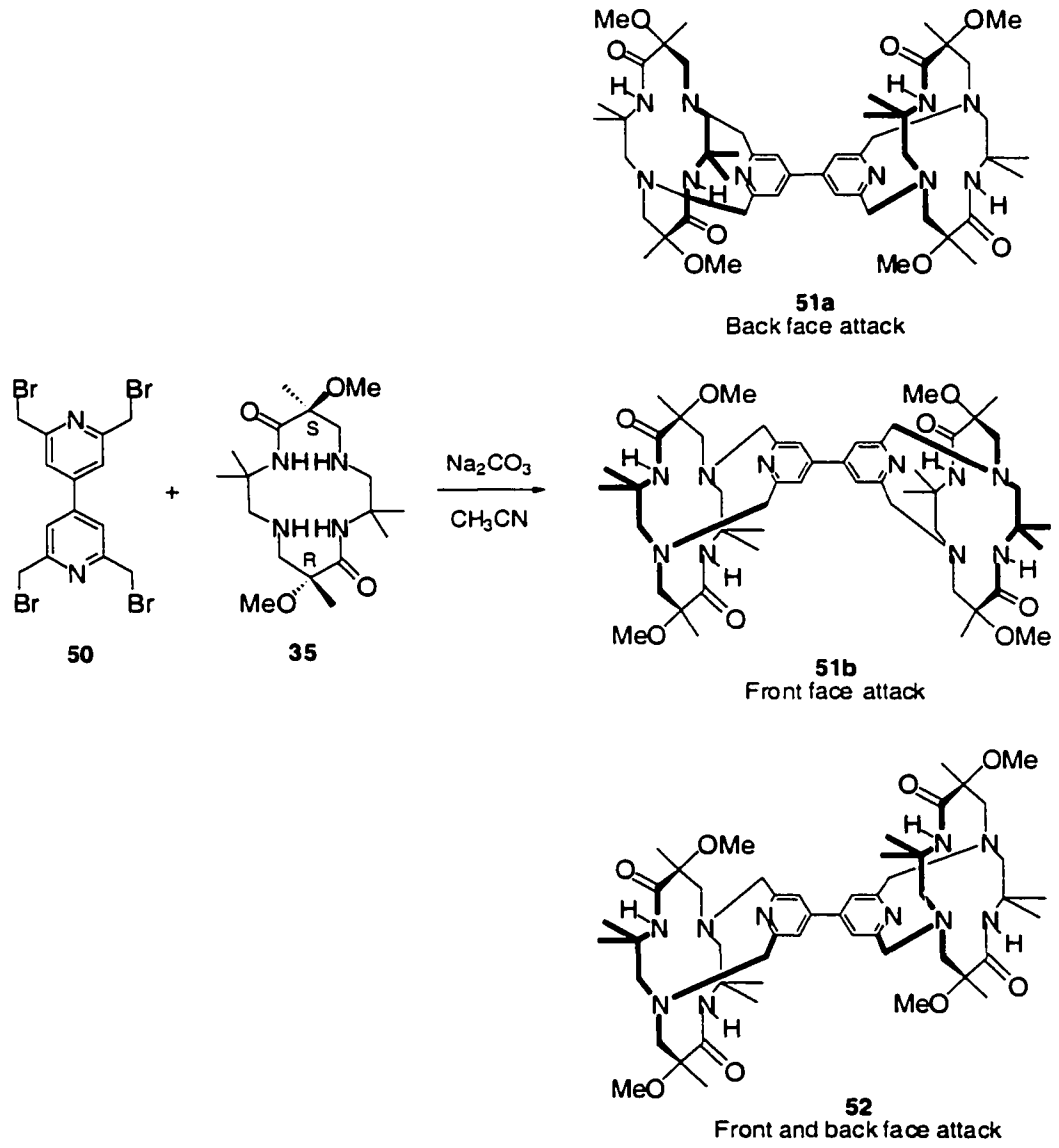
followed by treatment with sodium carbonate and an additional equivalent of α,α′-dibromo-*m*-xylene gave bridged **49** in 66% yield over two steps. Unfortunately, metal complexation of **49** has not been reported.



6 **46** **49**

Scheme 3.13 (a) Boc_2O; (b) α.α′-dibromo-*m*-xylene, Na_2CO_3; (c) HCl; (d) α.α′-dibromo-*m*-xylene, Na_2CO_3.

Hegedus has researched the synthesis of functionalized bridged bis-dioxocyclams. Treatment of 2 eq. of *trans*-dioxocyclam **35** with 1 eq. of tetrakis(bromomethyl)bipyridine **50** gave bipyridine-bridged bis-dioxocyclams (±)-**51** and **52** in 26% yield, as a racemic mixture of diastereomers (Scheme 3.14).[14] Substitution can occur on either face of the *trans*-dioxocyclam **35**, giving (±)-**51a** (back face attack), (±)-**51b** (front face attack), or **52** (front and back face attack).



Scheme 3.14 Bipyridine-bridged Bis-dioxocyclams. The pyridine bridge is not drawn in the same plane as the cyclam to emphasize which face was alkylated.

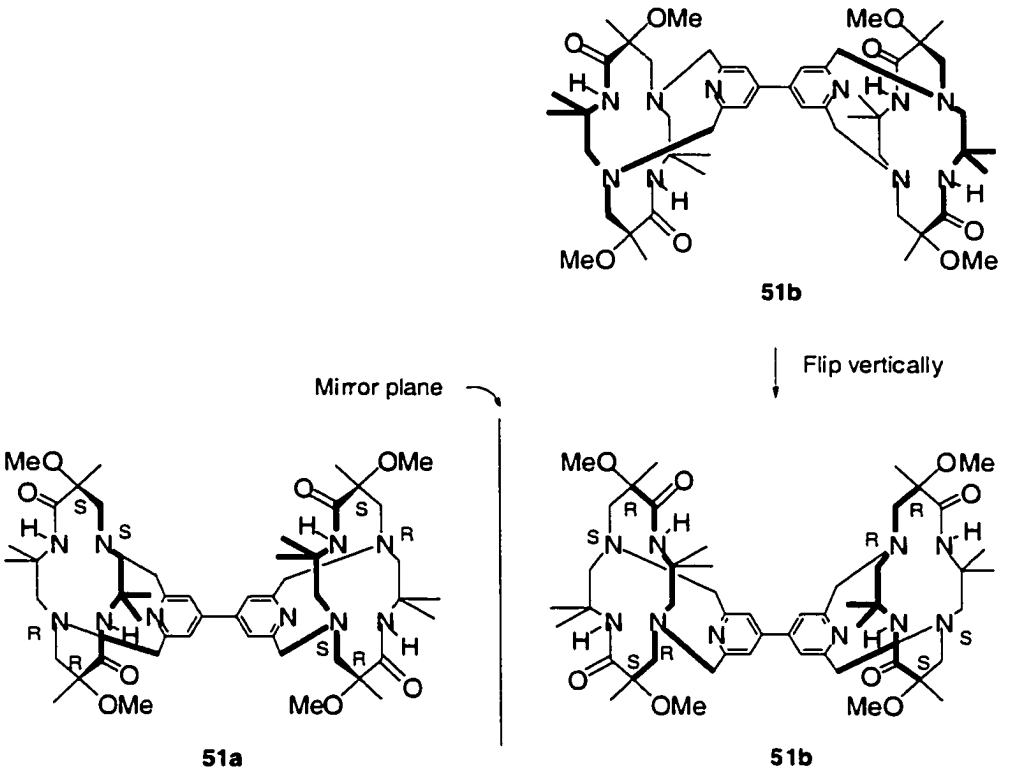


Figure 3.6

The mirror image relationship that makes **51a** and **51b** enantiomers is shown in Figure 3.6. Bipyridine-bridged bis-dioxocyclam **52** is achiral, as shown in Figure 3.7.

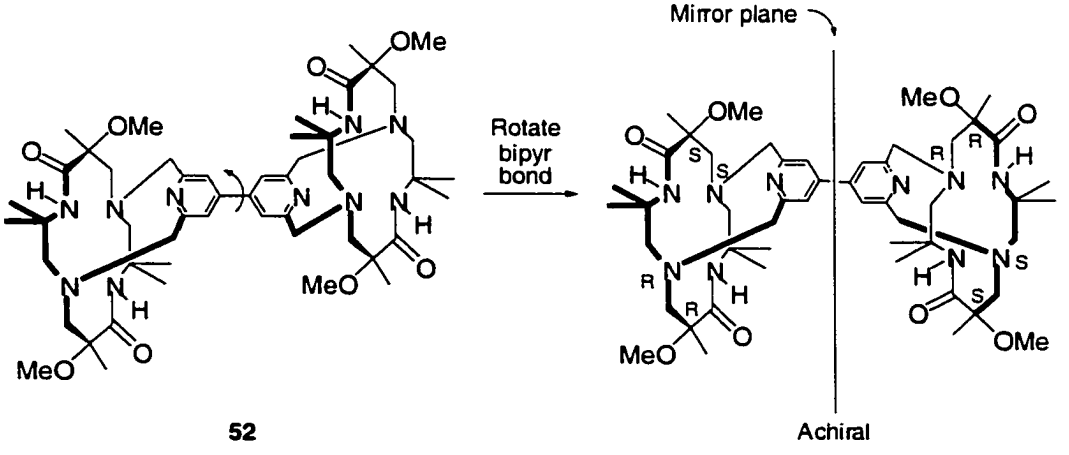
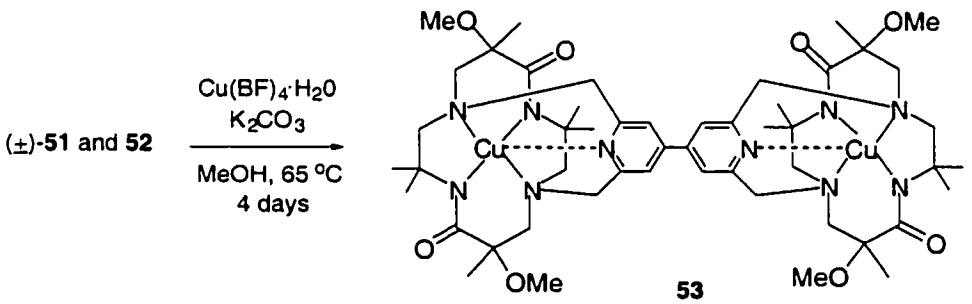


Figure 3.7

Hegedus has also synthesized the copper complex of pyridine-bridged bis-dioxocyclams (±)-**51** and **52** to give **53** in 78% yield (Scheme 3.15).[14] X-ray crystal data were obtained for the copper complex of (±)-**51** and it showed that the nitrogens on the pyridine bridge could be coordinated to the copper because the average pyridine nitrogen-copper distance was 2.13 Å. In addition, the σ bond between the two pyridine rings was slightly shorter than that of the free ligand (1.52 Å average and 1.57 Å respectively) and the dihedral angle was 23° (average) compared to 63° in the free ligand, results which may indicate that the two copper centers are in communication across the bipyridine bridge.

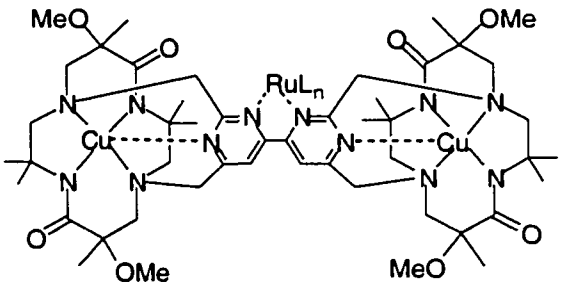


Scheme 3.15 Stereochemistry not shown for clarity.

II. Rationale

There is possible rotation around the bipyridine bond in bis-dioxocyclam **53** and this could disrupt the potential communication between the two copper ions. Therefore, it is of interest to synthesize the bipyrimidine-bridged system **54**, which is "lockable" through coordination of a ruthenium ion to the pyrimidine nitrogens (Figure 3.8). This system is also interesting because the ruthenium may be in electronic communication with the copper ions. This

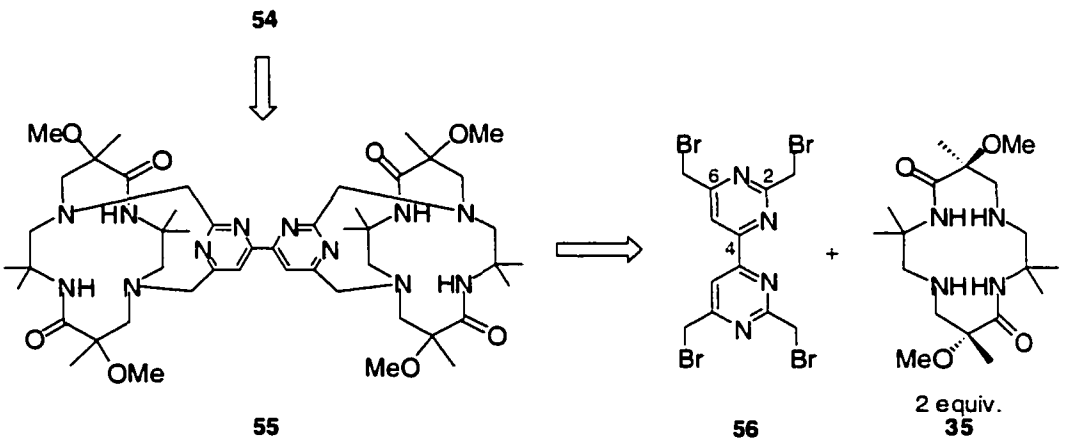
system may be used for a range of applications. However, at present the foremost challenge lies in the synthesis and characterization of the compound.



54

Figure 3.8

Bipyrimidine-bridged bis-dioxocyclam **55** was envisioned to be synthesized by coupling two *trans*-dioxocyclams **35** to tetrakis(bromomethyl)-bipyrimidine **56** (Scheme 3.16). With **55** in hand, complexation by copper into the cyclam cavity and ruthenium to the pyrimidine nitrogens would complete the synthesis of **54**.



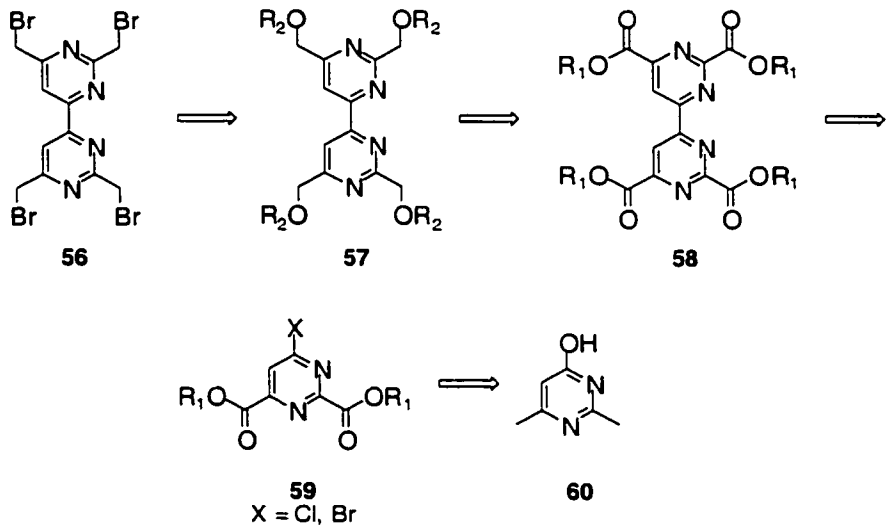
55 **56** **35**

Scheme 3.16 Retrosynthesis of Bipyrimidine-bridged Bis-dioxocyclam. Stereochemistry not shown for clarity.

The synthesis of bipyrimidine **56** seems trivial but the available literature on compounds of this type is sparse. One reason the synthesis of **56** is difficult is that the same substituent needs to be placed on the chemically inequivalent C-2

and C-6 positions, while different substituents need to be placed on the chemically equivalent C-4 and C-6 positions.

It was envisioned that tetrakis(bromomethyl)bipyrimidine **56** could be synthesized from bipyrimidine **57** (Scheme 3.17). Bipyrimidine **57** could be available from reduction of 2,2′,6,6′-dicarboxylic ester-bipyrimidine **58**, which could be synthesized by homocoupling ester **59**. The synthesis of ester **59** was envisioned from commercially available 2,6-dimethyl-4-hydroxypyrimidine (**60**).

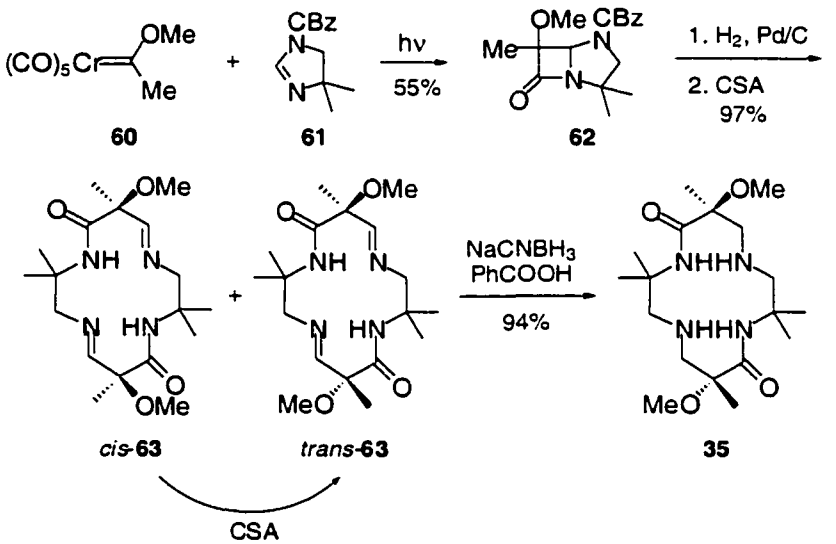


Scheme 3.17 Retrosynthesis of Bipyrimidine Bridge. R_1 = Bu, Me, etc. R_2 = Ts, Ms, etc.

III. Results and Discussion

(Methyl)(methoxy)cyclam **33** was synthesized following protocol previously established in the Hegedus group. (Methyl)(methoxy)chromium carbene complex **60** was photolyzed in the presence of imidazoline **61** to give the protected azapenam **62** in an unoptimized 55% yield (Scheme 3.18). Removal of the CBz protecting group with Pd/C at 1 atmosphere hydrogen followed by treatment with CSA gave imines **63** in 97% yield as a 1:1 mixture of *cis*- and *trans*-

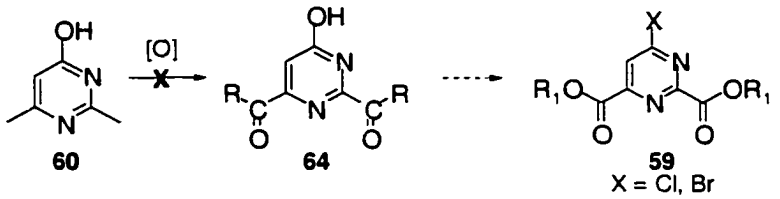
isomers which were separable by recrystallization. Since the ring opening/dimerization reaction is reversible, treatment of pure *cis*-imine **63** with CSA gave a 1:1 mixture of *cis*- and *trans*-imines. Therefore, *cis*-imine **63** can be completely converted to *trans*-imine **63** by successive recrystallizations, separations, and treatments with acid. *trans*-Imine **63** can be reduced with sodium cyanoborohydride in the presence of benzoic acid, a deviation from published procedures,[12] to give *trans*-dioxocyclam **35** in 94% yield.

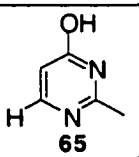
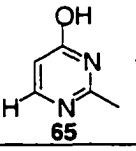


Scheme 3.18 *trans*-(Methyl)(methoxy)dioxocyclam Synthesis.

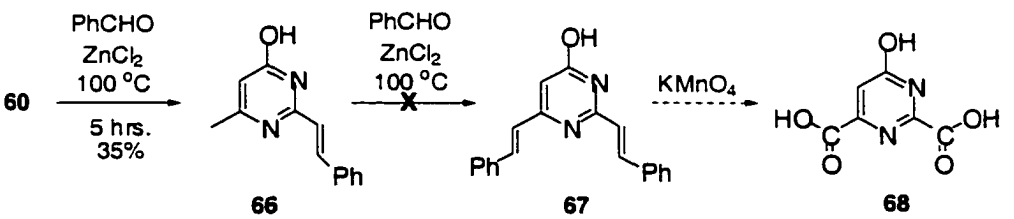
For synthesis of bipyrimidine bridge **56**, the first approach to ester **59** involved a variety of methods to oxidize 2,6-dimethyl-4-hydroxy pyrimidine (**60**). Unfortunately, all attempts to oxidize both methyl groups failed (Table 3.1). Treatment of dimethyl **60** with selenium dioxide in pyridine[15] or potassium dichromate[16] gave demethylated pyrimidine **65** from oxidation of the 6-methyl group and subsequent decarboxylation. Oxidation of dimethyl **60** with potassium permanganate gave recovered starting material and a trace amount of aldehyde.

Table 3.1 Oxidations of **60**.



Reagent	Desired Product	Result
SeO_2, dioxane	R = OH	 + SM + Decomp.
$K_2Cr_2O_7$, CH_3CO_2H	R = OH	 + SM
$KMnO_4$, KOH, nBuNHSO$_4$	R = H	SM + Trace aldehyde

Oxidation of dimethyl **60** might be accomplished by formation of its styrene derivative **67** and subsequent conversion to dicarboxylic acid **68**. Therefore, pyrimidine **60** was treated with benzaldehyde and zinc dichloride.[17] However, 6-methyl-2-styryl-pyrimidin-4-ol (**66**) was obtained in a crude 35% yield (Scheme 3.19). Further treatment of **66** with benzaldehyde and zinc chloride to give **67** was unsuccessful, with only starting material recovered.

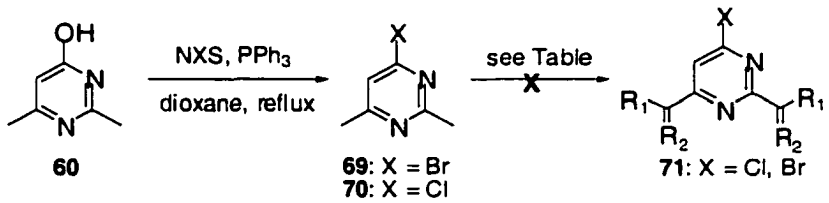


Scheme 3.19

The oxidation of 4-bromo- and 4-chloro-2,6-dimethylpyrimidine (**69** and **70**) was also investigated. Bromination of **60** with NBS and PPh_3[18] was tedious and gave bromide **69** in 30 - 57% yield. The yield is low and variable because the product formed an azeotrope with the reaction solvent. Chlorination of **60** under

the same reaction conditions was straightforward giving **70** in 72% yield. Unfortunately, oxidation of bromide **69** and chloride **70** was unsuccessful, as shown in Table 3.2.

Table 3.2 Oxidation of Halopyrimidines **69** and **70**.



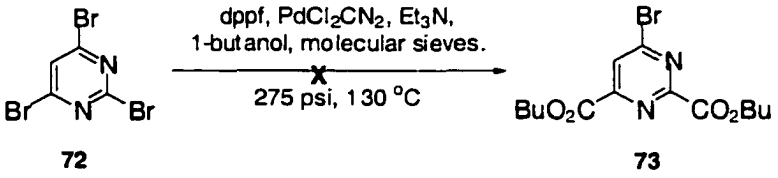
60 **69**: X = Br **70**: X = Cl **71**: X = Cl, Br

SM	Oxidant	Desired Product	Result
69	SeO_2, pyr, $SOCl_2$/MeOH	R_1 = OMe R_2 = O	Decomp.
69	PhCHO, $ZnCl_2$	R_1 = H R_2 = CHPh	Decomp.
70	SeO_2, pyr	R_1 = H R_2 = O	No C=O peaks by IR spectroscopy

The failure of "standard" oxidations of hydroxide **60**, bromide **69** and chloride **70** led to the investigation of palladium catalyzed carbonylation reactions with 2,4,6-tribromopyrimidine (**72**).[19] The chemical behavior of pyrimidines is comparable to that of 1,3-dinitrobenzene or 3-nitropyridine and the C-4 or C-6 position is generally more reactive than the C-2 position for nucleophilic displacement or oxidative addition to Pd(0). However, there is literature precedent in which the 2-position is more reactive than the 4-postion.[20]

It was reported that palladium catalyzed carbonylation reactions at 100 °C and 100 psi were unsuccessful with 2-chloropyrimidine, while 5-chloropyrimidine reacted to give 5-ethoxycarbonylpyrimidine in 100% yield.[21] Therefore, high temperature and pressures were used in the carbonylation reaction of tribromide **72**. Tribromide **72** was treated with dppf, $PdCl_2CN_2$,

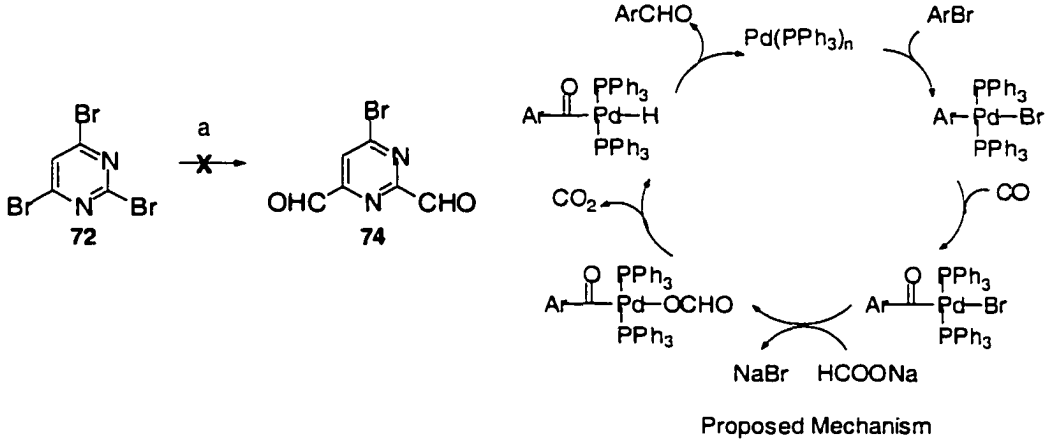
triethylamine, and 1-butanol at 130 °C and 275 psi CO.[22] However, only decomposition was seen instead of ester **73** (Scheme 3.20).



72 **73**

Scheme 3.20

Formylation of aryl bromides is known to be catalyzed by palladium (0),[23] therefore, **72** was treated with sodium formate and $PdCl_2(PPh_3)_2$ in the presence of carbon monoxide to synthesize dialdehyde **74** (Scheme 3.21). Unfortunately only recovered starting material and decomposition were seen.

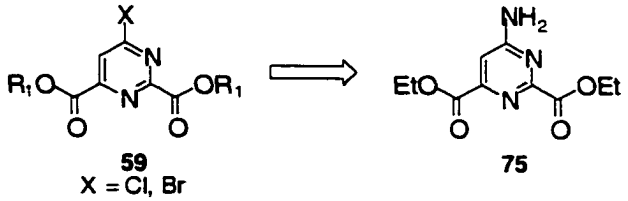


72 **74**

Proposed Mechanism

Scheme 3.21 (a) NaOOCH, $PdCl_2(PPh_3)_2$, CO.

A new approach to **59**, using Boger's method to synthesize 6-amino-2,4-(dicarboxylic diethyl ester)pyrimidine (**75**), was attempted (Scheme 3.22).[24]

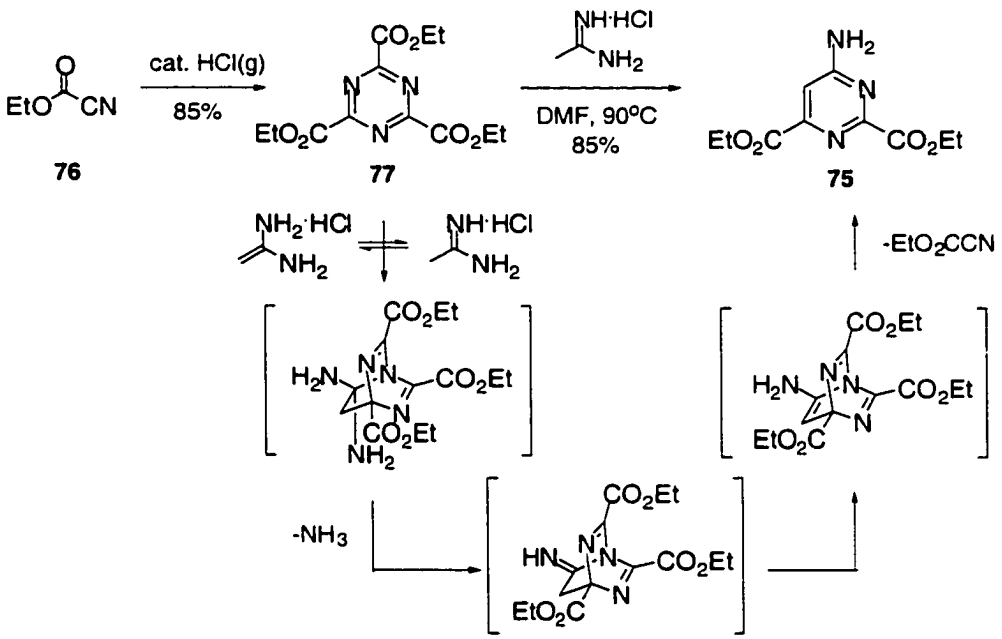


59
X = Cl, Br

75

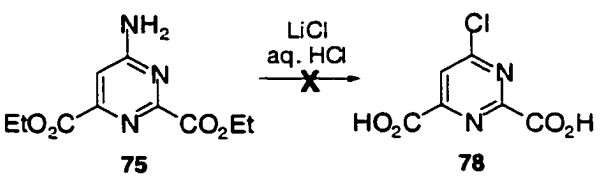
Scheme 3.22

Using published procedures, ethyl cyanoformate (**76**) was allowed to react with gaseous HCl (anhydrous) to give triazine **77**. Treatment of triazine **77** with acetamidine hydrochloride gave pyrimidine **75** via a Diels-Alder/retro-Diels-Alder reaction (Scheme 3.23).[24]



Scheme 3.23

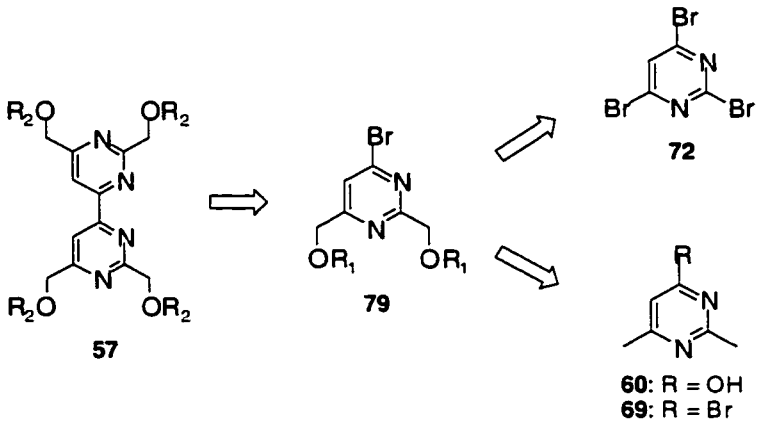
Literature precedent exists for the conversion of 2-aminopyrimidine to 2-chloropyrimidine in 50% yield.[25] Unfortunately, treatment of **75** with lithium chloride in aqueous HCl only gave recovered starting material (Scheme 3.24).



Scheme 3.24

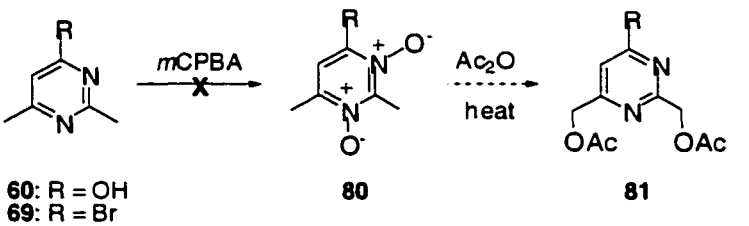
Since the synthesis of intermediate **59** failed, a new synthetic route to bipyrimidine **57** was needed. 2,6-(Protected hydroxyl methyl)-4-bromopyrimidine **79** would be a more straightforward intermediate to

bipyrimidine **57**, which might be synthesized from hydroxide **60**, bromide **69**, or tribromide **72** (Scheme 3.25).



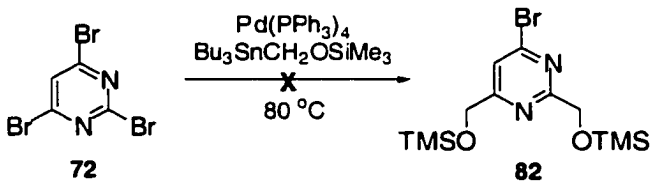
Scheme 3.25 Second Retrosynthesis.

It was envisioned that N-oxide **80** would give diacetate **81** upon rearrangement[26] and once in hand further treatment may be needed to give intermediate **79**. However, when dimethyl **60** or bromide **69** was treated with *m*-CPBA only decomposition was seen (Scheme 3.26).



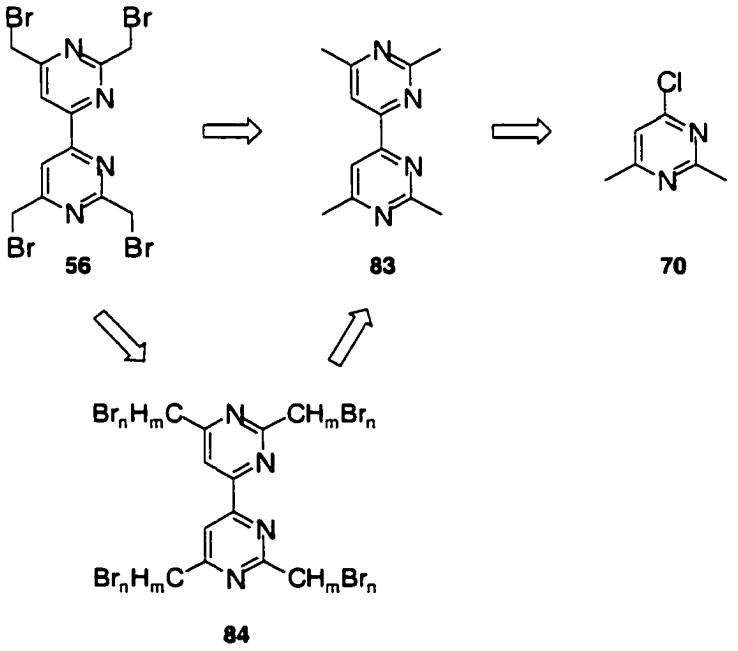
Scheme 3.26

It was also anticipated that TMS protected hydroxymethyl pyrimidine **82** could be synthesized from tribromopyrimidine **72**.[27] Unfortunately, treatment of **72** with $Pd(PPh_3)_4$ and $Bu_3SnCH_2OSiMe_3$[27,28] only gave decomposition (Scheme 3.27).



Scheme 3.27

The most straightforward approach to tetrakis(bromomethyl)bipyrimidine **56** would be monobromination of each methyl group on bipyrimidine **83** (Scheme 3.28). However, bromination reactions are hard to control. A variety of polybrominated products is usually obtained, reducing the yield and making purification very difficult. Therefore, selective monobromination of each of the four methyl groups of **83** seemed extremely unlikely. However, there is



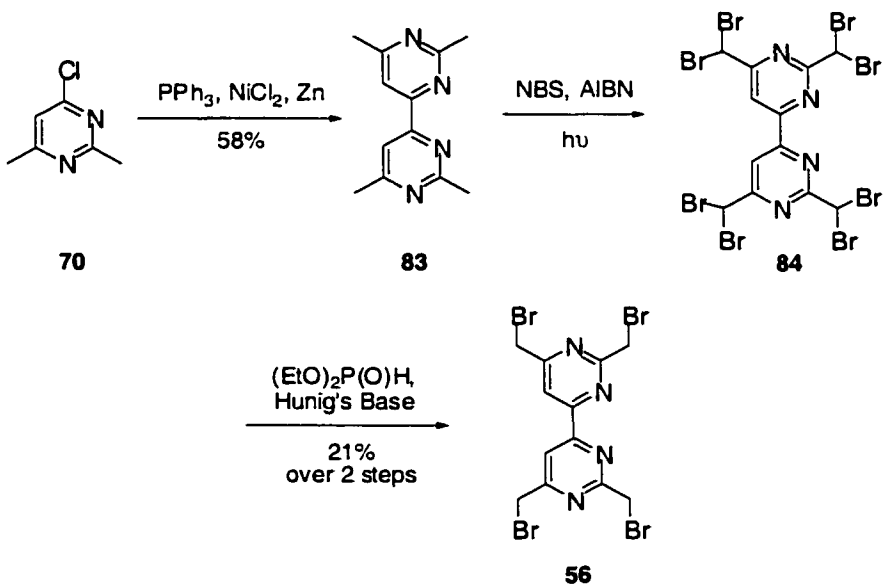
Scheme 3.28 The New Retrosynthesis.

literature precedent in which polybrominated products are reduced with diethylphosphite and Hunig's Base[29] to give the desired bromomethylene substituent. Therefore, it was anticipated that tetrakis(bromomethyl)pyrimidine

might be synthesized by this method (polybrominated **84** → tetrakis(bromomethyl)pyrimidine **56**).

The synthesis of tetramethylbipyrimidine **83** was accomplished by homocoupling of chloropyrimidine **70** using Ni(0), formed *in situ* from $NiCl_2 6H_2O$, zinc metal, and triphenylphosphine.[30] As shown in Scheme 3.29, tetramethylbipyrimidine **83** was obtained in 58% yield.

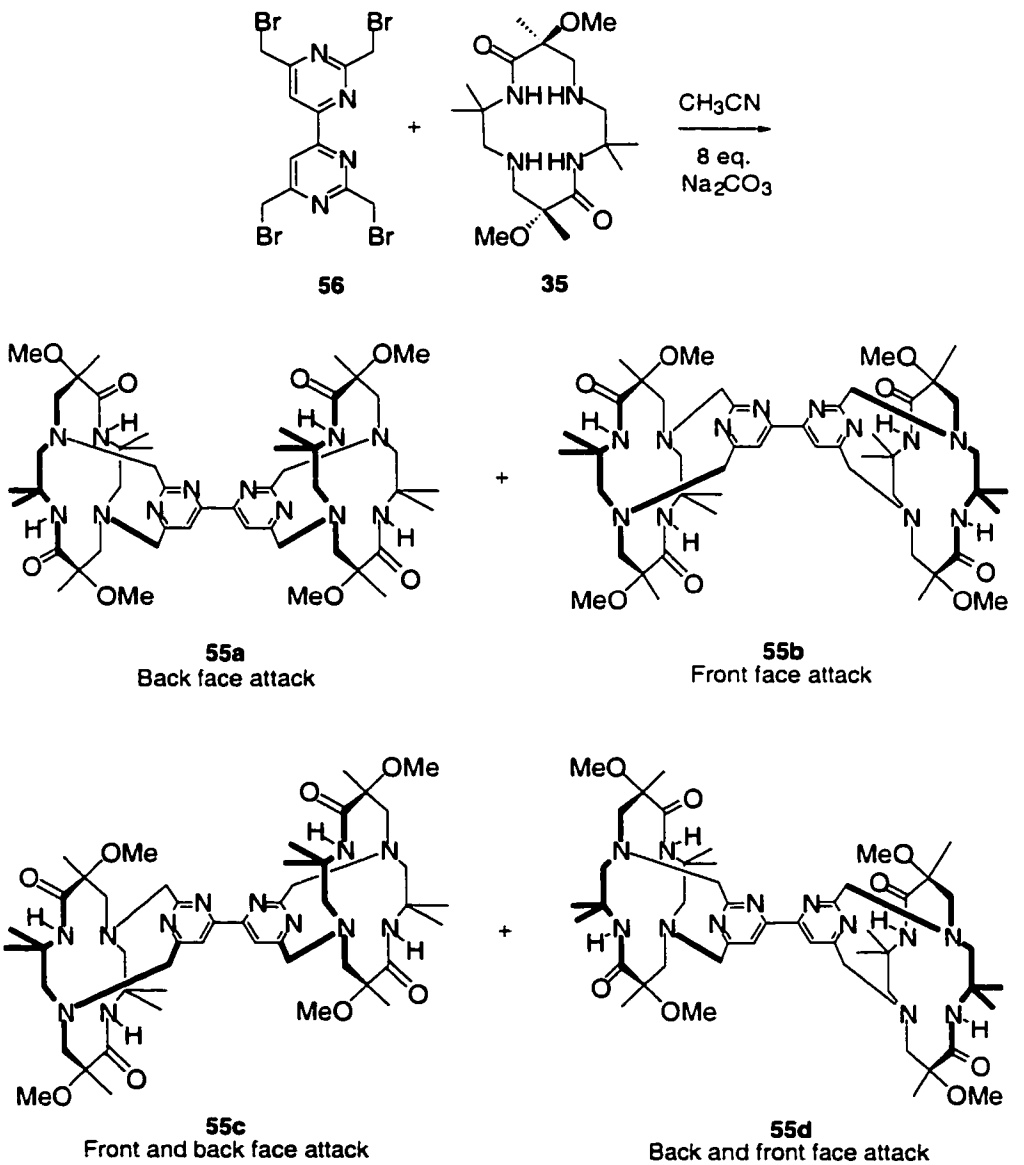
Tetramethylbipyrimidine **83** was irradiated in the presence of 10 eq. NBS and a catalytic amount of AIBN, as shown in Scheme 3.29. After 24 hours, another 5.0 eq. NBS was added and after 48 hours the starting material was almost completely converted to tetrakis-(dibromomethyl)pyrimidine **84**. The crude material was reduced with diethylphosphite and Hunig's base to give tetrakis(bromomethyl)pyrimidine **56** in 21% yield over two steps. The phosphite reduction is highly dependent on the purity of the polybrominated product. Therefore, if the bromination step produces a variety of polybrominated products, the reduction also gives multiple products.



70 **83** **84** **56**

Scheme 3.29 Synthesis of **56**.

With bipyrimidine **56** in hand, attention was then turned to the synthesis of bipyrimidine-bridged bis-dioxocyclam **55**. Based on the work of the bipyridine system (Scheme 3.14), it was believed that only facial selectivity needed to be addressed for the determination of the number of possible isomers of **55**.[B] Using this analysis, each cyclam can be alkylated from the front or back



Scheme 3.30 Bipyrimidine-bridged Bis-dioxocyclams.

[B] See Appendix II for a more indepth analysis of the stereochemistry.

face to give a mixture of diastereomers, (±)-**55a,b** and (±)-**55c,d** (Scheme 3.30). Bipyrimidine-bridged bis-dioxocyclams **55a** (front face attack) and **55b** (back face attack) are enantiomers, as shown in Figure 3.9. Unlike the bipyridine system,

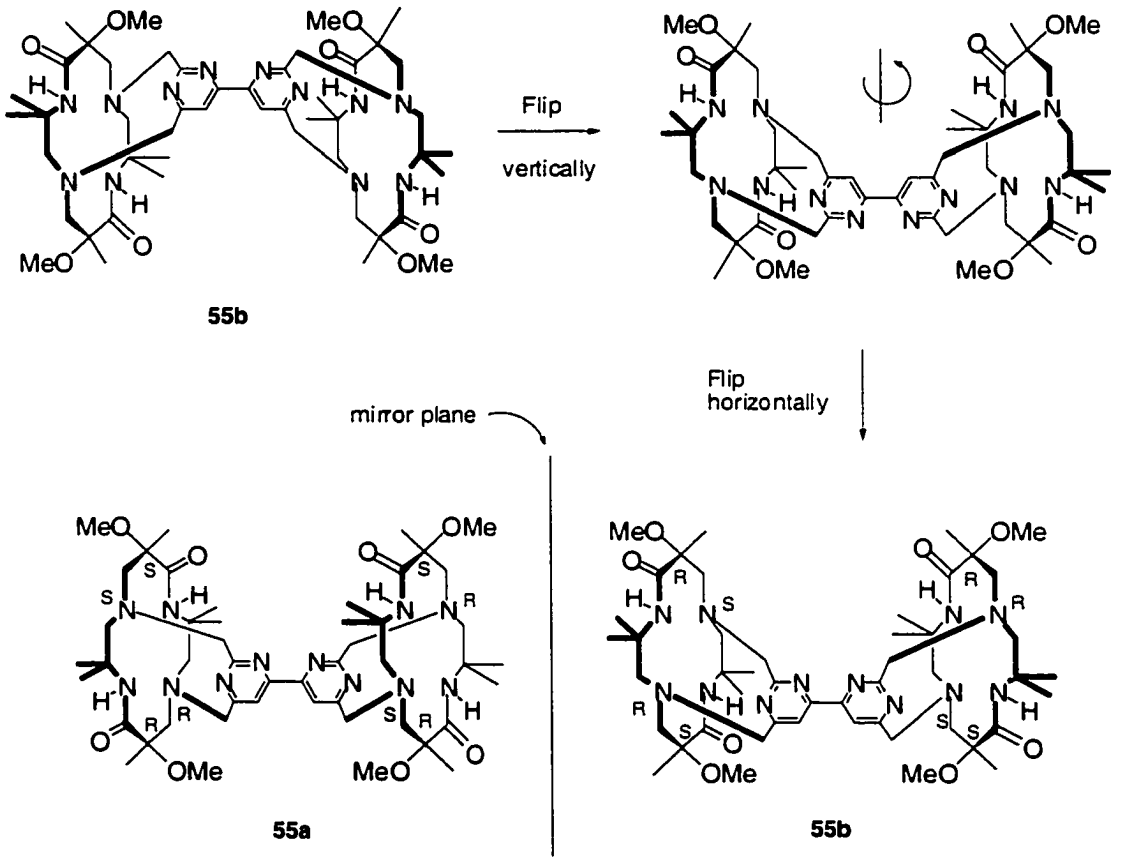


Figure 3.9

both diastereomers are obtained as racemates. The mirror plane (compared to **52** in the pyridine system, Figure 3.7) within **55c** that would make it achiral is destroyed because of the pyrimidine nitrogens (Figure 3.10). Therefore,

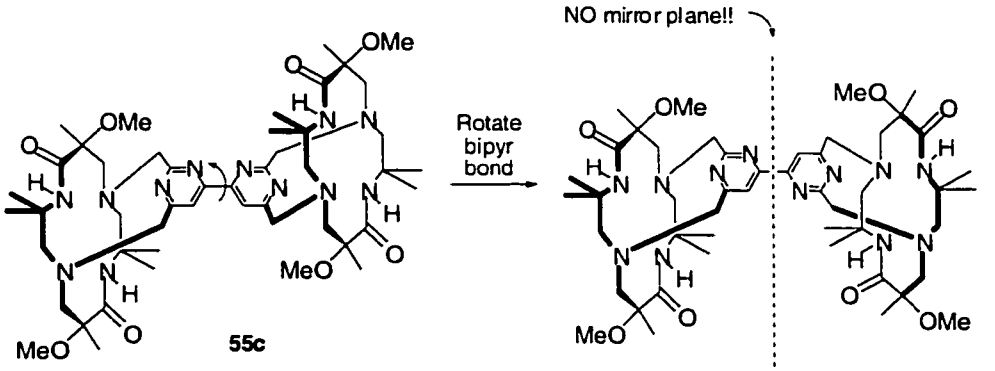


Figure 3.10

it is formed along with its enantiomer **55d** (Figure 3.11).

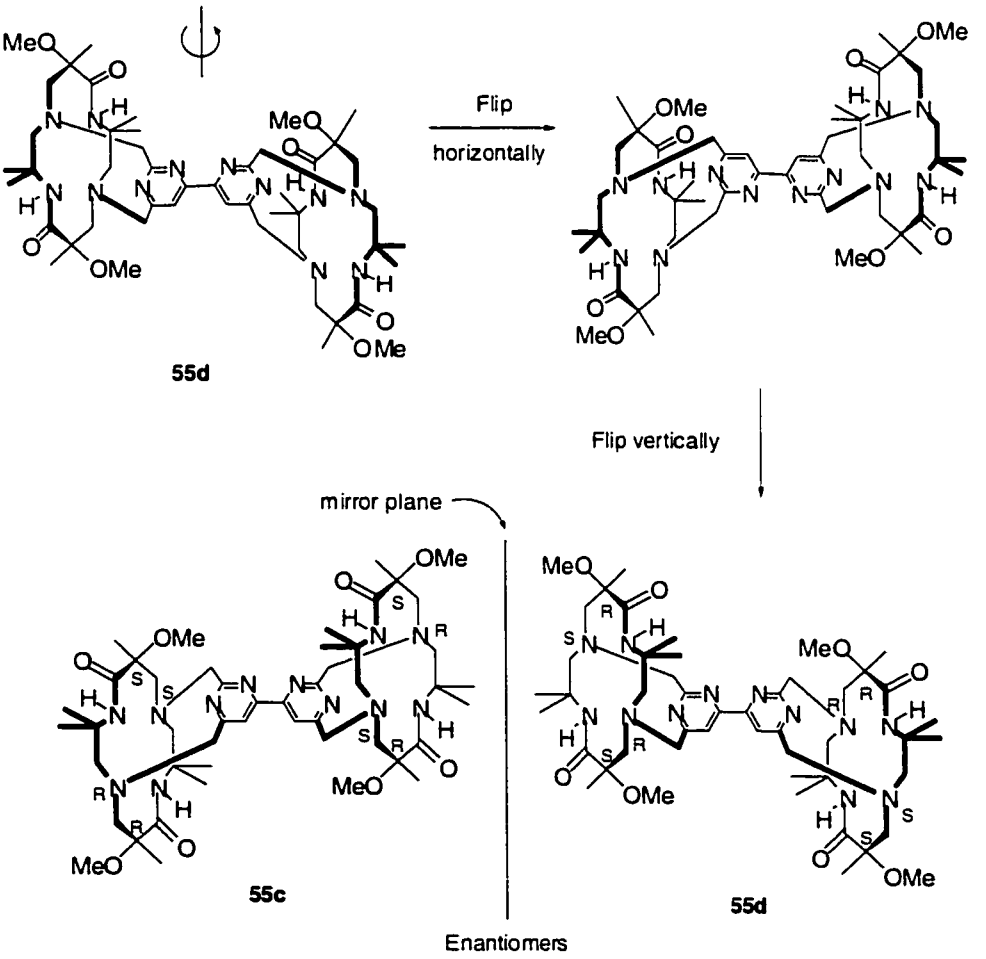
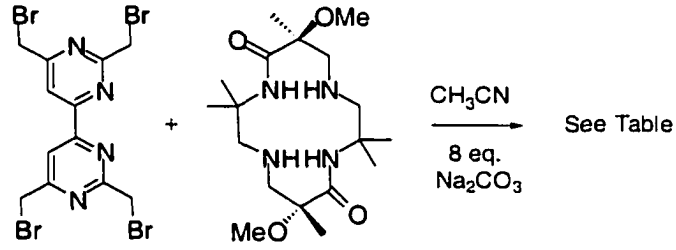


Figure 3.11 Enantiomers **55c** and **55d**.

Standard conditions used to synthesize the pyridine system (±)-**51** and **52** (8 eq. crushed Na_2CO_3, 1 eq. bridge, and 2 eq. *trans*-dioxocyclam in distilled acetonitrile) were used in the synthesis of **55**. As seen in Table 3.3, the

Table 3.3



56 **35**

Entry	Molarity	Temp.	Time	Additives	Purification	Result
1	0.01M	80 °C	1 day	-	Recry. crude mixture	Recry. unsuccessful
2	0.018M	90 °C	1 day	-	FCC	26% yield both diastereomers (B)*
3	0.018M	90 °C	1.5 days	-	Radial Chromatography	2% yield of one diastereomer (D)* & 11% yield mixture of diastereomers
4	0.025M	80 °C	1 day	-	PTLC	32% yield of both diastereomers with contamination caused by PTLC plates
5	0.025M	90 °C	1 day	-	FCC, then recry.	6% yield of one diastereomer (C)*
6	0.035M	50 °C or 80 °C	1 day or 6 hrs. respectively	-	1. Washed crude with 5% aq. NaOH to eliminate potential salts 2. FCC	Same as entry 2
7	0.025M	60 °C	3 days	0.2 eq. Bu_4NI	FCC basified solvents	23% yield both diastereomers
8	0.025M	microwave power 20 - 50	30 sec - 1 min. intervals	-	-	Recovered all of **56** and **35**
9	0.0025M	60 °C	3 days	-	-	Same as entry 2

All reactions were carried out with 1 eq. bipyrimidine **56** and 1.95 – 2.2 eq. **35**.
* refers to Material A, B, and C in Figure 3.12 and 3.13

temperature, molarity, and purification methods were varied to probe the reaction. When product was obtained the crude material had a good mass balance and seemed to be mainly desired product. However, good yields of purified material could not be obtained. TLC analysis the crude material (silica gel, 10% MeOH in EtOAc) showed three spots with R_f's of 0.27, 0.23, and baseline. No obvious by-products were detectable in the crude material by NMR spectroscopy (material A, Figure 3.12) with the spectrum very similar to

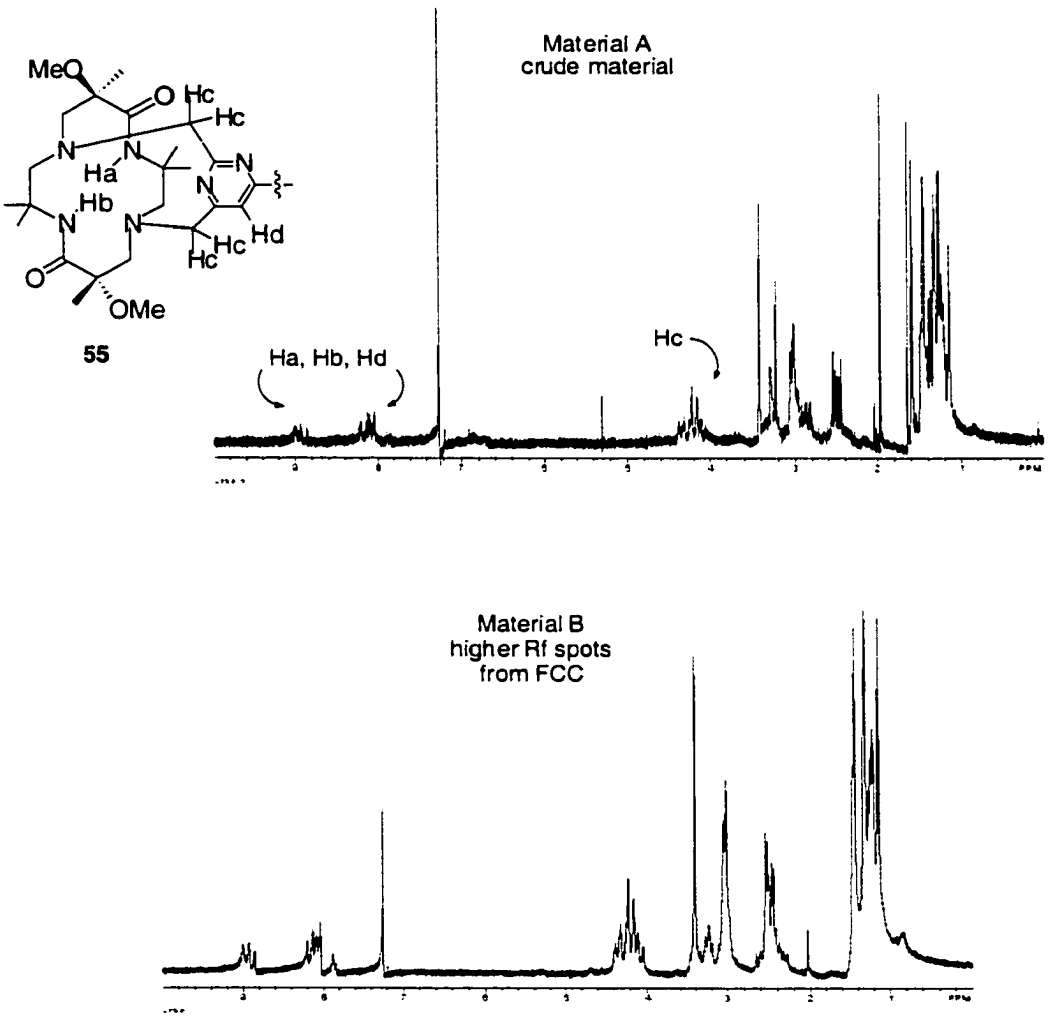


Figure 3.12 ^{1}H NMR Spectra of Material A and B.

bipyridine-bridged bis-dioxocyclam **51** and **52**.[31] High temperature NMR was performed on the crude material in DMSO up to 80 °C to see if rotamers were present. The signals around 8 ppm moved but did not coalesce.

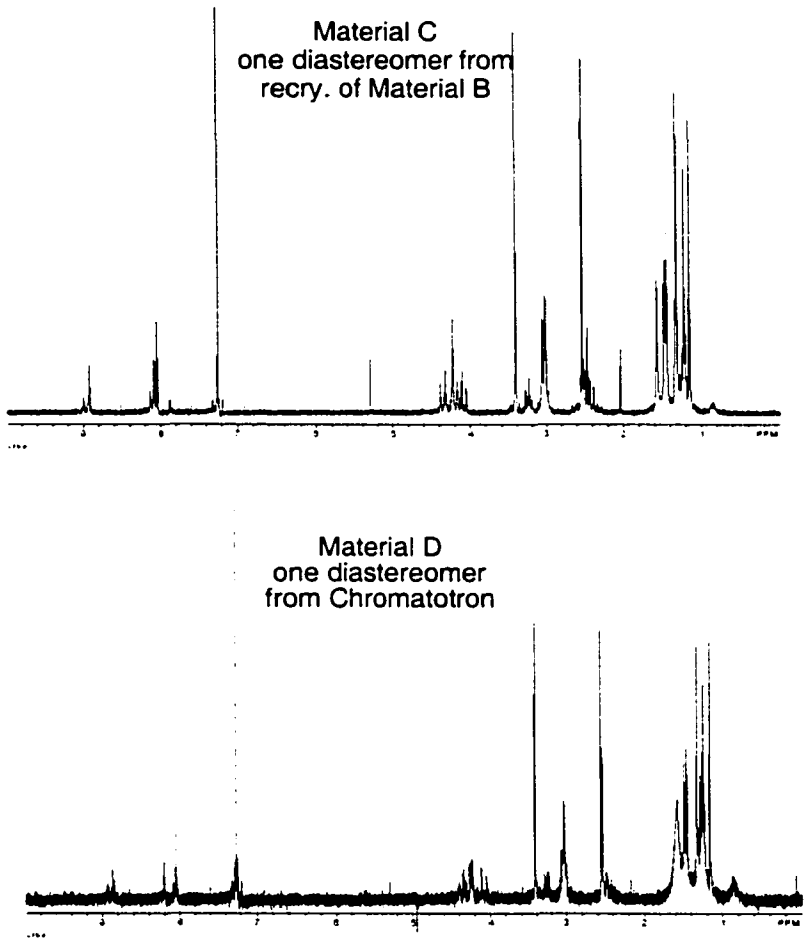


Figure 3.13 ^{1}H NMR Spectra of Material C and D.

The two high R_f spots on TLC can be separated from the baseline material using flash column chromatography to give material B (Figure 3.12). Material B is believed to be a mixture of diastereomers (±)-**55a,b** and (±)-**55c,d**. Recrystallization of material B gave a 6% yield of what is believed to be one diastereomer (material C, Figure 3.13). Unfortunately, X-ray quality crystals could not be obtained because the crystals were too small. Purification of the

crude material by radial chromatography gave a 2% yield of what is believed to be the other diastereomer (material D, Figure 3.13).

The constitution of the baseline material is still in question. The ^{1}H NMR spectrum of the baseline material (material E, Figure 3.14) is similar to the ^{1}H NMR spectra of the other materials (A-D). Material E could be an oligomer but FABS mass spectrometry of the crude material does not show any mass above 951.2 g/mol, the mass of bipyrimidine-bridged bis-dioxocyclam **55**. However, this alone cannot rule out the formation of oligomers in the reaction. It was envisioned that the baseline material was an N-H isomer of **55**, therefore, material E was subjected to basic conditions (5% aq. NaOH) to test this theory. However, the material did not convert to another compound by TLC.

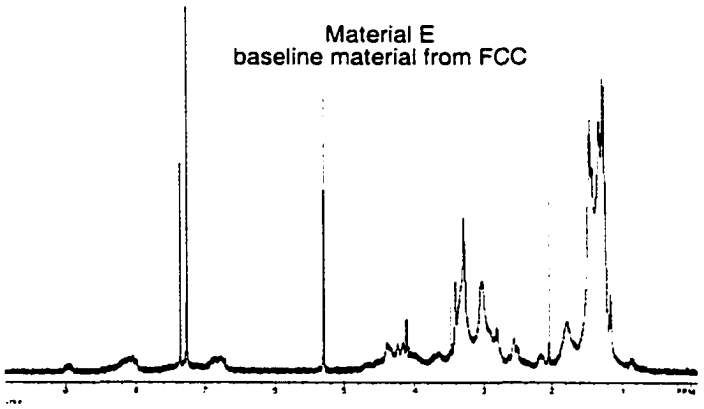
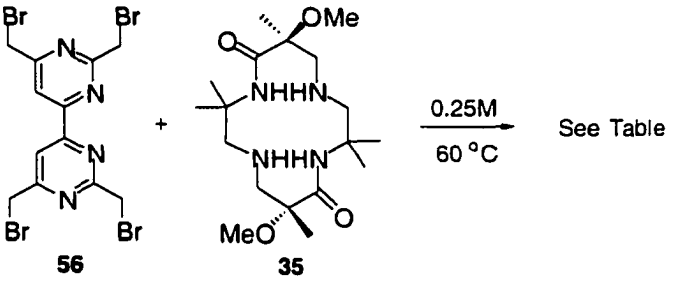


Figure 3.14 NMR Spectrum of Material E.

Unfortunately, changing the temperature or molarity of the reaction, as shown in Table 3.3, did not improve the yield of either diastereomer or control the formation of baseline material. Therefore, the reaction was run in different solvents (Table 3.4). Unfortunately, no reaction occurred in DMSO or DMF. When Finkelstein conditions were employed to boost the reactivity of the bipyrimidine bridge **56**, only trace amounts of product were seen.

Table 3.4



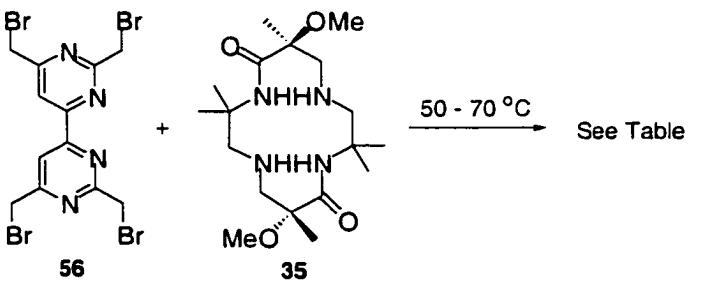
56 **35**

Solvent	Time	Additive	Result
DMF	2 days	-	No product
DMF	1 days	0.2 eq. Bu_4NI	Trace product & recovered **35**
DMSO	2 days	-	recovered **35**
DMSO	1 days	0.2 eq. Bu_4NI	recovered **35**

All reactions were performed at 0.025 M and 60 °C with 1 eq. **56** and 1.99 eq. dioxocyclam **35**.

Another modification to the reaction was the use of a soluble base. Bipyrimidine **56** and dioxocyclam **35** were treated with Hunig's base, instead of sodium carbonate, however no improvement to the yield was seen (Table 3.5).

Table 3.5



56 **35**

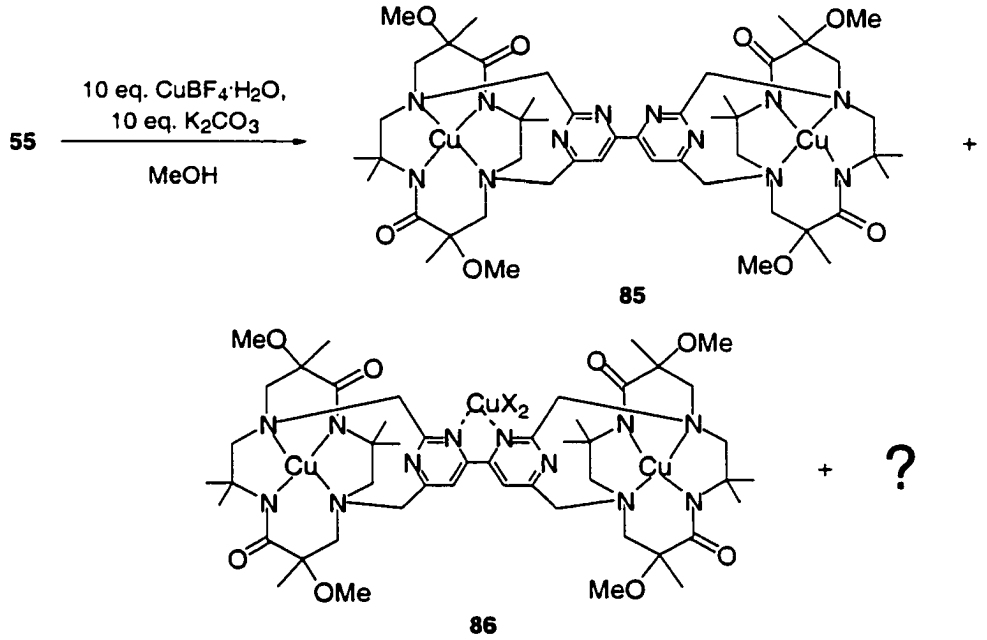
Base	Solvent	Time	Molarity	Result
4.5 eq. Hunig's	CH_3CN	4 days	0.007M	Linker decomp. **35** recovered
4.5 eq. Hunig's	CH_3CN	overnight	0.035M	Crude same as with Na_2CO_3
20 eq. Hunig's	CH_3CN	overnight	0.05M	Linker decomp. **35** recovered
5 eq. Hunig's	THF	4 days	0.008M	Linker decomp. **35** recovered

All reactions were performed with 1 eq. **56** and 1.95 eq. **35**.

Copper complexation of the crude material and material B was investigated. When copper tetrafluoroborate hydrate was added to material B, the solution turned light purple within 30 minutes at 65 °C. Further heating caused the solution to turn dark red-brown. After 24 hours, IR spectroscopy showed the presence of starting material (1666 cm^{-1}) and a new carbonyl stretch (1575 cm^{-1}), which is characteristic of copper cyclam complexes. When the reaction was heated for 3 days, all the starting material had converted to the material with an IR carbonyl stretch of 1575 cm^{-1}. Mass spectrometry was inconclusive for this material and all recrystallization attempts were unsuccessful.

Copper complexation of the crude material gave mixed results. Treatment of the crude material with copper tetrafluoroborate hydrate turned the solution light purple and then red-brown after 3 days. IR spectrometry indicated copper

complexed material (1585 cm^{-1}) and no starting material. Unfortunately, mass spectrometry revealed a mixture of products (Scheme 3.31). The identifiable masses were of copper complexed **85** and the mass of **85** plus another copper (from a compound such as **86**). All attempts to recrystallize this material were unsuccessful.



Scheme 3.31

In an attempt to suppress complexation of copper to the bipyrimidine bridge (**86**), coordination of nickel to the pyrimidine nitrogens of **55** was investigated. Material B was subjected to $NiCl_2 \cdot 6H_2O$ in CH_3NO_2 and was heated to reflux.[32] Surprisingly, only decomposition was seen. When the baseline material (material E) was treated under the same conditions, decomposition was also seen. Nickel chloride should not be able to decompose bipyrimidine-bridged bis-dioxocyclam **55**. Therefore, it is believed that these materials contain an impurity that is causing the decomposition.

IV. Conclusion

A bipyrimidine bridge, tetrakis(bromomethyl)pyrimidine **56**, was synthesized by formation of tetrakis(dibromomethyl)pyrimidine **84** and subsequent reduction. Studies were performed on the alkyation of two *trans*-dioxocyclams with this bipyrimidine bridge. A wide variety of reaction conditions was performed; however, only low yields of pure bipyrimidine-bridged bis-dioxocyclam **55** could be obtained.[c] In addition, copper complexation of the crude or semipure material was unsuccessful.

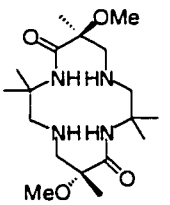
V. Experimental

Materials. The following compounds were synthesized according to literature procedures: 4-chloro-2,6-dimethylpyrimidine **70**[18] and imine **63**.[12] Their purity was confirmed by NMR spectroscopy.

General Methods. The general methods described for Chapter One were followed with the exceptions that dioxane and acetonitrile were distilled from CaH_2. Microwave reactions were carried out in a Sharp 700 W microwave oven (model R-220BW) in pressure tubes purchased from Ace Glass (Ace catalog No. 8648-23) and fitted with Teflon plugs (Ace catalog No. 5846-48) and Teflon encapsulated O-rings (Ace catalog No. 7855-818). Extreme caution should be taken when heating a sealed tube in a microwave oven. High pressure and

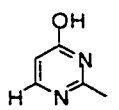
[c] See Appendix II for further discussion.

temperatures are generated which have led to explosions. In the event of such explosions, glass shreds may penetrate the walls of the oven. Therefore, all reactions should be run in a fume hood with a blast shield in place.



$C_{18}H_{36}N_4O_4$ **35**
Exact Mass: 372.27
Mol. Wt.: 372.50
C, 58.04; H, 9.74; N, 15.04; O, 17.18

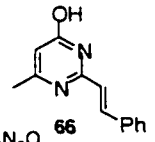
***trans*-Dioxocyclam 35.** *trans*-Imine **63** (175.5 mg, 0.4762 mmol) was dissolved in 6 mL EtOH and 11 mL CH_2Cl_2. Benzoic acid (113 mg, 1.05 mmol) was added and the solution was cooled to 0 °C. $Na(CN)BH_3$ (95%, 63 mg, 0.95 mmol) was dissolved in 1.4 mL EtOH and added dropwise via syringe. A precipitate formed immediately. After 5 minutes, the reaction was transferred to a separatory funnel. The solution was basified with 0.5M NaOH until pH 9-10. The organic layer was washed with DI H2O (X2), dried and stripped to give *trans*-dioxocyclam **35** (166 mg, 0.446 mmol, 94%). Recrystallization can be performed (CH_2Cl_2/hexane) to give analytically pure material. The ^{1}H NMR spectrum of this compound was identical to previously reported material.[12]



65
$C_5H_6N_2O$
Exact Mass: 110.05
Mol. Wt.: 110.11
C, 54.54; H, 5.49; N, 25.44; O, 14.53

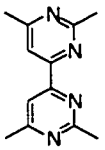
4-Hydroxyl-2-methylpyrimidine (65). 2,6-Dimethyl-4-hydroxypyrimidine **60** (0.110 g, 0.883 mmol) and selenium dioxide (0.294 g, 2.65 mmol) were dissolved in dioxane. The light yellow, cloudy solution was heated to reflux for 12 hours. The solution turned brown with black precipitate and was cooled to room temperature, filtered, and stripped. A small portion of the crude material was purified by preparative TLC to give demethylated pyrimidine **65**. The ^{1}H NMR

spectrum of this compound in DMSO was identical to that of previously reported material.[33,34]



66
$C_{13}H_{12}N_2O$
Exact Mass: 212.09
Mol. Wt.: 212.25
C, 73.56; H, 5.70; N, 13.20; O, 7.54

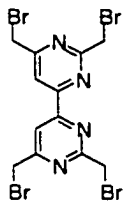
6-Methyl-2-styryl-pyrimidin-4-ol (66). A flask containing pyrimidine **60** (0.50 g, 4.0 mmol), $ZnCl_2$ (0.27 g, 2.0 mmol), and benzylaldehyde (0.8 mL, 8.06 mmol) was heated to 100 °C. After 3 hours, there was a noticeable precipitate in the yellow solution. After 5 hours, the solution was so thick the stir bar could not stir. At this time, the reaction was cooled to room temperature, diluted with 1% NH_4OH in DI H_2O and $CHCl_3$. The aqueous layer was extracted with $CHCl_3$, washed with sat. aq. K_2CO_3, dried, and stripped. 6-Methyl-2-styryl-pyrimidin-4-ol (**66**) was obtained in a crude 35% yield: ^{1}H NMR δ 13.45 (bs, 1H), 8.03 (d, *J*=16.5 Hz, 1H), 7.62 (m, 2H), 7.40 (m, 3H), 6.87 (d, *J*=16.2 Hz, 1H), 6.26 (s, 1H), 2.37 (s, 3H).



83
$C_{12}H_{14}N_4$
Exact Mass: 214.12
Mol. Wt.: 214.27
C, 67.27; H, 6.59; N, 26.15

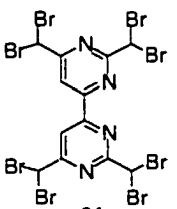
2,6,2',6'-Tetramethyl-[4,4']bipyrimidine (83). A flask containing PPh_3 (8.8 g, 34 mmol), $NiCl_2 6H_2O$ (2.4 g, 10 mmol) and 300 mL DMF was flushed with argon. The blue solution was heated to 50 °C and zinc powder (0.66 g, 10 mmol) was added. After the solution turned dark red (~15 minutes), chloropyrimidine **70** (1.2 g, 8.4 mmol) was added via pipette and the reaction was flushed with argon. The reaction was stirred at 50 °C for 12 hours and then cooled to room temperature. A solution of 120 mL NH_4OH in 300 mL DI H_2O was added and the brown solution was stirred for 12 hours. Ethylenediamine was then added and the clear purple solution was extracted with CH_2Cl_2 (X3). The organic layer was washed with DI H_2O, dried, and stripped. The crude material was purified

by flash column chromatography (1:1 hexane/EtOAc) to yield bipyrimidine **83** as a white solid (0.525 g, 2.45 mmol, 58%). The ^{1}H NMR spectrum of this compound was identical to those previously reported.[35,36]



$C_{12}H_{10}Br_4N_4$ **56**
Exact Mass: 525.76
Mol. Wt.: 529.85
C, 27.20; H, 1.90; Br, 60.32; N, 10.57

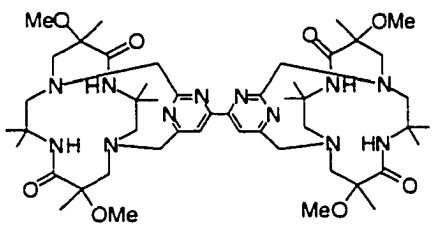
Tetrakis(bromomethyl)bipyrimidine 56. Bipyrimidine **83** (0.37 g, 1.73 mmol), freshly recrystallized NBS (3.07 g, 17.3 mmol) and AIBN (74 mg, 0.45 mmol) were placed in a pressure tube. 19 mL of benzene were added and the solution was flushed with argon. The pressure tube was sealed and irradiated for 24 hours during which the solution gently heated to reflux. After 24 hours, TLC (silica gel, 3:1 hexane/EtOAc) showed a variety of spots, therefore another 5 eq. of NBS was added. The reaction was irradiated for another 24 hours and TLC showed mainly one spot. The solution was cooled to room temperature, filtered over Celite, washed with sat. aq. $NaHCO_3$ (X2) and DI H_2O, dried and stripped to give crude **84**: ^{1}H NMR δ 8.79 (s, 1H), 6.81 (s, 1H), 6.67 (s, 1H); FAB-HRMS calcd for $C_{12}H_7N_4Br_4$ (M+H): 846.4056, found 846.4062.



84
$C_{12}H_6Br_8N_4$
Exact Mass: 837.41
Mol. Wt.: 845.44
C, 17.05; H, 0.72; Br, 75.61; N, 6.63

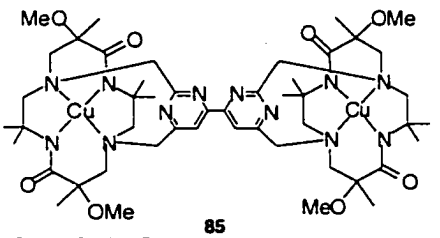
Polybromide **84** was dissolved in 17 mL THF, flushed with argon, and cooled to 0 °C. Hunig's base (1.3 mL, 6.9 mmol, equivalents were determined by the theoretical yield of **84** from the NBS reaction) and then diethyl phosphite (0.83 mL, 6.9 mmol) were added via syringe. The reaction was monitored by TLC (silica gel, 3:1 hexane/EtOAc) until the major spot was the desired product (~1 hour). The reaction was quenched with ice water and concentrated. The brown film was dissolved in Et_2O and DI H_2O. The solution

was filtered, extracted with Et_2O (X3), washed with DI H_2O and brine, and concentrated. The crude material was purified by flash column chromatography (6:1 hexane/EtOAc) to give tetrakis(bromomethyl)bipyrimidine **56** (110 mg, 0.208 mmol, 21% yield). Bipyrimidine **56** can also be recrystallized after the column by layering CH_2Cl_2 over hexane to get pure material: ^1H NMR δ 8.48 (s, 1H), 4.70 (s, 2H), 4.57 (s, 2H); ^{13}C NMR δ 168.0, 166.7, 162.2, 115.7, 33.2, 31.4; IR (thin film) 1567, 1527 cm^{-1}; FAB-HRMS calcd for $C_{12}H_{11}N_4Br_4$ (M+H): 530.7676, found 530.7668; m.p. decomposed 160 – 163 °C.



$C_{48}H_{78}N_{12}O_8$ (±)-**55a,b** and (±)-**55c,d**
Exact Mass: 950.61
Mol. Wt.: 951.21
C, 60.61; H, 8.27; N, 17.67; O, 13.46

General Procedure for Bipyrimidine-bridged Bis-dioxocyclam (±)-55a,b and (±)-55c,d. A small vial was charged with tetrakis-(bromomethyl)bipyrimidine **56**, freshly crushed Na_2CO_3, and *trans*-dioxocyclam **35**. The mixture was flushed with argon (X3) and heated to 65 °C in an oil bath. The reaction was monitored by TLC (10% MeOH/EtOAc) until no starting materials were present and then cooled to room temperature, filtered through Celite, and concentrated. The brown film was dissolved in CH_2Cl_2, filtered through Celite, and concentrated to give the crude material: IR (thin film) 3253, 1660, 1540 cm^{-1}. Material B: ^{13}C NMR δ 173.8, 173.1, 172.9, 172.7, 172.4, 170.3, 169.6, 161.4, 112.7, 112.5, 82.7, 82.6, 79.4, 79.4, 74.7, 74.2, 74.0, 73.6, 73.5, 73.3, 70.5, 68.7, 68.4, 67.2, 66.8, 66.6, 65.4, 65.5, 65.1, 55.7, 54.6, 54.6, 54.4, 51.7, 51.7, 50.5, 50.4, 50.1, 29.7, 26.0, 25.5. 23.3, 22.9, 19.1, 18.9; FAB-HRMS calcd for $C_{48}H_{79}N_{12}O_8$ (M+H): 951.6144, found 951.6130.



85

$C_{48}H_{74}Cu_2N_{12}O_8$
Exact Mass: 1072.45
Mol. Wt.: 1074.27
C, 53.67; H, 6.94; Cu, 11.83; N, 15.65; O, 11.91

General Procedure for Copper Complexation. A small pressure tube was charged with $CuBF_4$ hydrate (10 eq.) dissolved in MeOH, K_2CO_3 (10eq.), and bipyrimidine-bridged bis-dioxocyclam (±)-**55** . The solution was flushed with argon and heated (60 °C-90 °C) for 4 days. The solution was cooled to room temperature, filtered through Celite, and concentrated. The residue was then dissolved in CH_2Cl_2, filtered through Celite, and concentrated to give the crude material.

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(31) Bipyridine-bridged bis-dioxocyclam's ^{1}H NMR spectrum: 9.03 (s, 2H), 7.15 (m, 4H), 4.1 (m, 8H), 3.42 (s, 6H), 3.21 (d, J=14.0 Hz, 2H), 2.98 (m, 6H), 2.90 (d, J=14.0 Hz, 2H), 2.58 (d, J=14.0 Hz, 2H), 2.49 (s, 6H), 2.33 (d, J=14.0 Hz, 2H), 1.46 (s, 6H), 1.43 (s, 6H), 1.36 (s, 6H), 1.32 (s, 6H), 1.19 (s, 6H), 1.13 (s, 6H).
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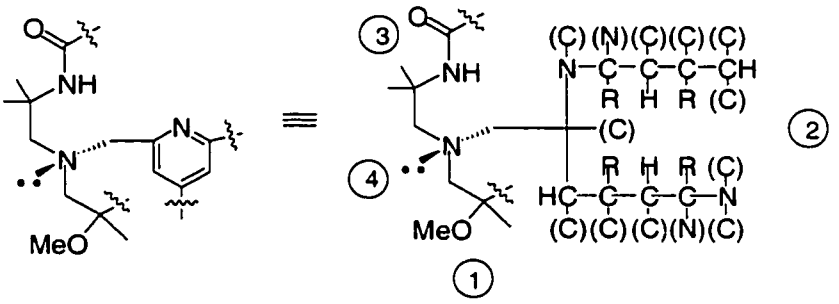
APPENDIX I

PRIORITIES FOR R/S ASSIGNMENT OF THE CHIRAL AMINES OF ALKYLATED 5,12-DIOXOCYCLAMS

1st Kekule structure of the pyridine ring.



Prioritizing 2 and 3:

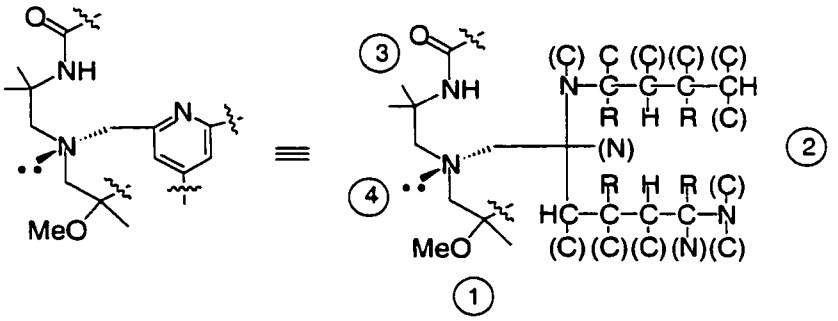
amide's sphere 1: C-HH
pyridine's sphere 1: C-HH

amide's sphere 2: C-CCN
pyridine's sphere 2: C-C(C)N
These are the same priority because the phantom carbon is treated as a real carbon because further exploration is not through it.

Follow the path of highest precedence for the next sphere.
amide's sphere 3: N-CCH
pyridine's sphere 3: N-CC(C)

The pyridyl group is higher priority.

2nd Kekule structure of the pyridine ring.



Prioritizing 2 and 3:

amide's sphere 1: C-HH
pyridine's sphere 1: C-HH

amide's sphere 2: C-CCN
pyridine's sphere 2: C-C(N)N

The pyridyl group is higher priority.

APPENDIX II

A MORE INDEPTH ANALYSIS OF THE POSSIBLE ISOMERS OF BIPYRIMIDINE-BRIDGED BIS-DIOXOCYCLAM **55**

In the original analysis, the isomerism induced by the bipyrimidine linker was not consider leading to only four isomers being proposed (compounds **55a**, **55b**, **55c**, **55d** in Scheme 3.30). However, a more indepth analysis considering the symmetry of the bipyrimidine bridge showed that there are a total of sixteen possible isomers (see Figures A.1 - A.4 below). It is likely that the reason pure product **55** could not be obtained was due to the formation of several of these isomers which made purification very difficult.

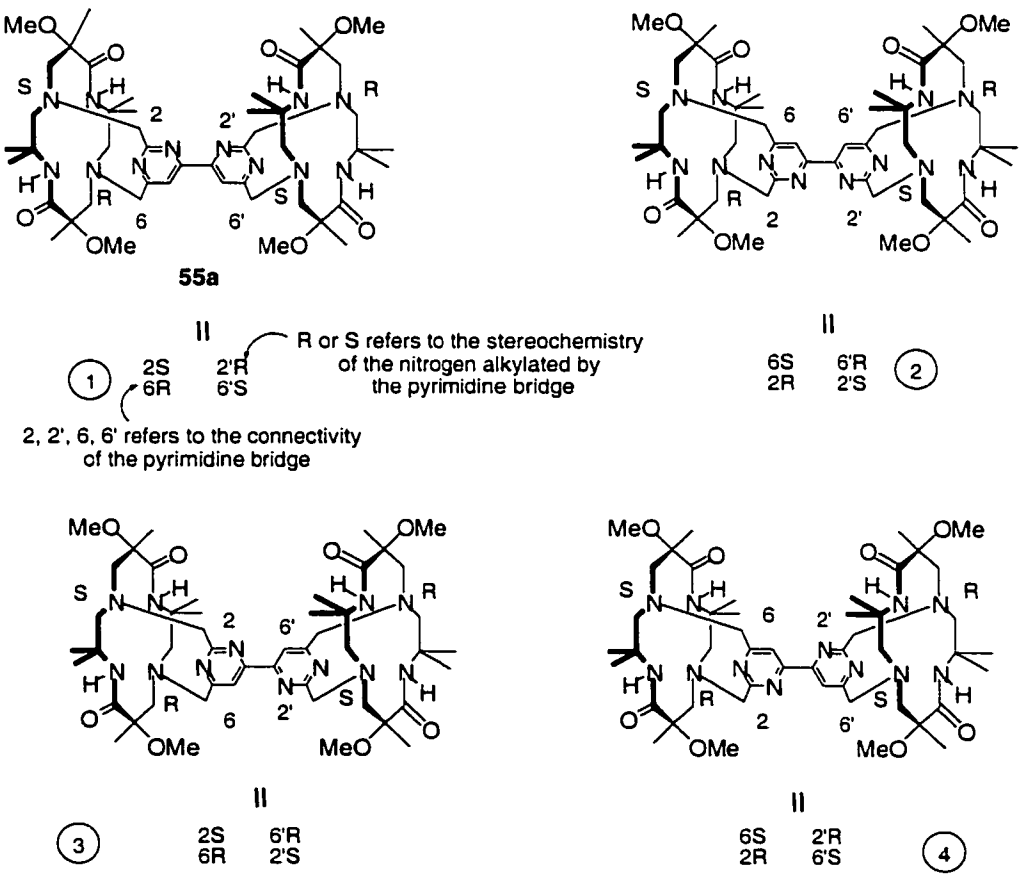
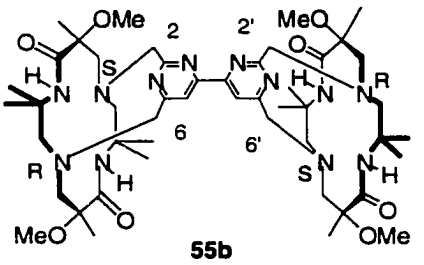
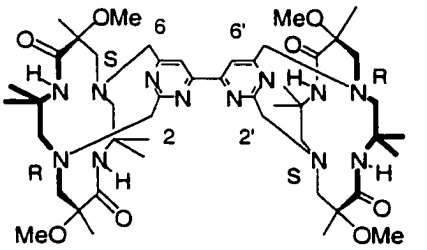


Figure A.1 Isomers of **55a**.



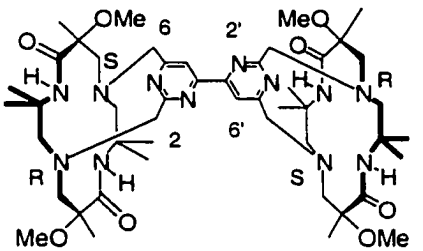
II

① 2S 2'R
6R 6'S



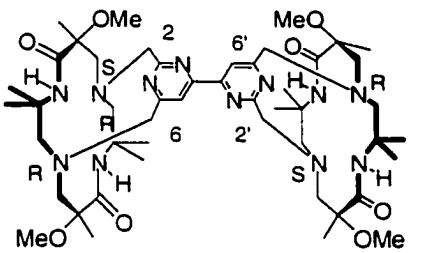
II

6S 6'R
2R 2'S ②



II

③ 6S 2'R
2R 6'S

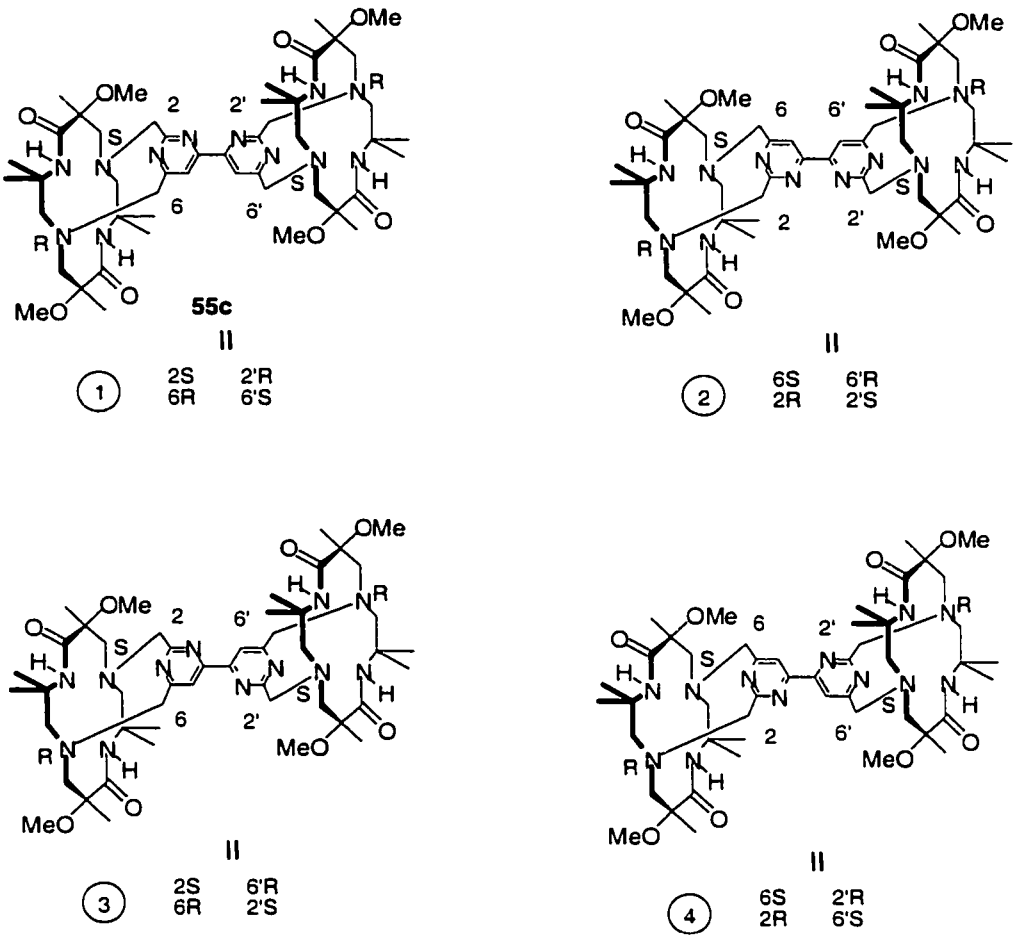


II

2S 6'R
6R 2'S ④

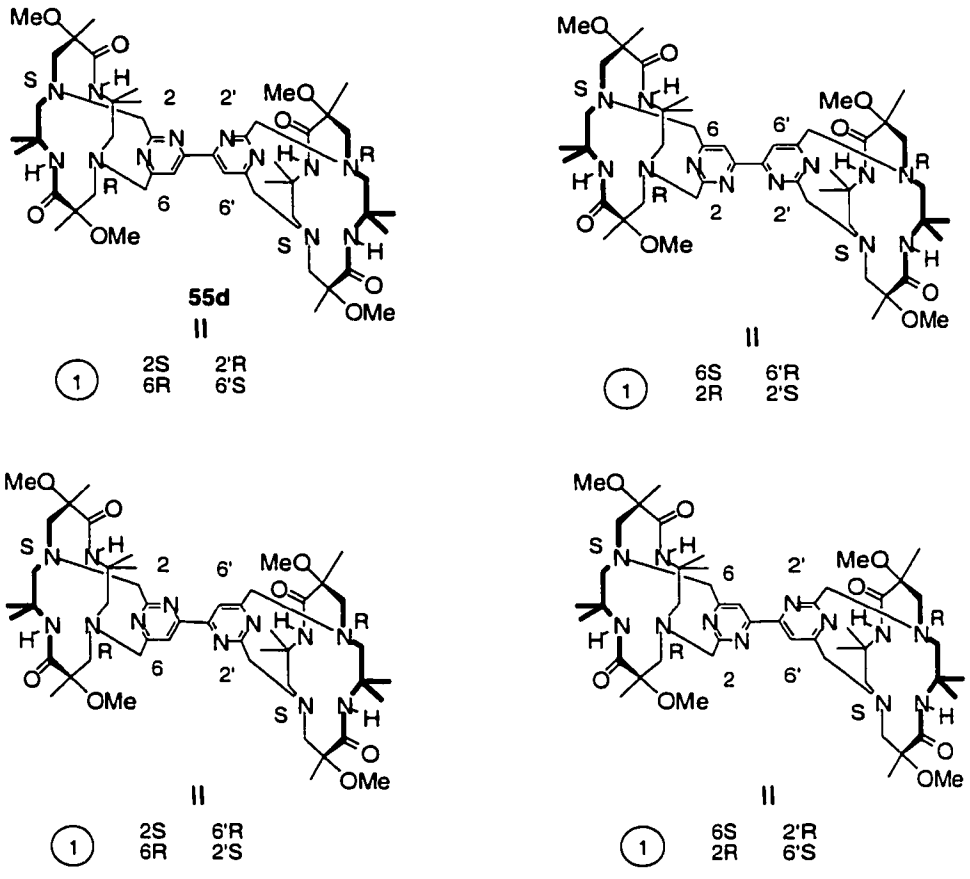
4 possible isomers for 55b!

Figure A.2 Isomers of **55b**.



4 possible isomers for 55c!

Figure A.3 Isomers of **55c**.



4 possible isomers for 55d!

Figure A.4 Isomers of **55d**.