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Radical Cyclization Routes to α-Hydrazino Lactones, *C*-Glycosyl Amino Acids and (+)-Furanomycin, and Synthetic Studies on CP-225,917 and CP-263,114

by

Junhu Zhang ©

A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

DEPARTMENT OF CHEMISTRY

Edmonton, Alberta

Fall, 1999

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DEGREE: Doctor of Philosophy

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FACULTY OF GRADUATE STUDIES AND RESEARCH

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research for acceptance, a thesis entitled **Radical Cyclization Routes to α-Hydrazino Lactones, *C*-Glycosyl Amino Acids and (+)-Furanomycin, and Synthetic Studies on CP-225,917 and CP-263,114** submitted by **Junhu Zhang** in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

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Dr. J. W. Lown

Dr. S. H. Bergens

Dr. D. Hall

Dr. E. Knaus

Dr. R. Mitchell

(External Examiner)

To

the memory of my father

Liangyin Zhang

and to my mother, Guilan Fang,

and

my wife, Yunjiao Zheng

ABSTRACT

Glyoxylic acid diphenylhydrazone (**207**) and the corresponding *O*-benzyloxime (**208**) are easily esterified in high yield by β-bromo- or β-(phenylselenenyl)alcohols, and the resulting esters undergo radical cyclization to α-(2,2-diphenylhydrazino)- or α-(benzyloxyamino)-lactones in good yield on treatment with tributyltin hydride; the initial radical can be formed by homolysis of a carbon-selenium bond as well as a carbon-bromine bond and, when applied to appropriate alcohols, the esterification-radical closure sequence can also be used to make six- or seven-membered lactones. This general methodology has been applied to the preparation of *C*-glycosyl lactones. Such lactones can be elaborated into optically pure *C*-glycosyl α-amino acids. The usefulness of the methodology was further demonstrated by the synthesis of the natural antibiotic (+)-furanomycin from L-xylose, and utilizing the intermediate (**309**) with two sites of radical reactivity to accomplish deoxygenation and cyclization in a single operation.

In the second part of this thesis, an efficient and stereoselective route has been described to construct the advanced models **167** and **175** for the synthesis of the core structure of CP-225,917 (**1**) and CP-263,114 (**2**). Compounds **167** and **175** contain two very challenging structural elements (the quaternary center and bridgehead double bond) of **1** and **2**. The facile thermal siloxy-Cope rearrangement of **166** and

174 demonstrates that the strain in the bicyclic lactone systems facilitates the oxy-Cope process. Further elaboration of **175** towards the more advanced models relevant to the total synthesis of **1** and **2** is currently under way.

ACKNOWLEDGMENTS

I would like to express my gratitude to my supervisor Dr. D. L. J. Clive for his advice, encouragement, enthusiasm and training during the course of my graduate studies, and for his assistance in the preparation of this thesis.

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LIST OF ABBREVIATIONS

Ac.....acetyl

AIBN.....2,2'-azobisisobutyronitrile

Arndt-Eistert

reaction.....the reaction for homologated one more carbon to carboxylic acids

Bn.....benzyl

BOM.....benzyloxymethyl

t-Bu.....*t*-butyl

Bz.....benzoyl

CSA.....camphorsulfonic acid

cf. .....compare

DABCO.....1,4-diazabicyclo[2.2.2]octane

DBU.....1,8-diazabicyclo[5.4.0]undec-7-ene

DCC.....*N*,*N*-dicyclohexylcarbodiimide

DDQ.....2,3-dichloro-5,6-dicyano-1,4-benzoquinone

DEAD.....diethyl azodicarboxylate

Dess-Martin

reagent.....1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxo-3(1H)-one

DIBAL.....diisobutylaluminum hydride

DMAP.....4-(dimethylamino)pyridine

DMF.....dimethylformamide

DMSO.....dimethyl sulfoxide

FPTase.....farnesyl protein transferase

FTIs.....farnesyl protein transferase inhibitors

GDP.....guanosine diphosphate

GTP.....guanosine triphosphate

HMPA.....hexamethylphosphoric triamide

Jones' reagent...chromic acid solution (ca. 8 N)

KHMDS.....potassium hexamethyldisilazane

LDA.....lithium diisopropylamide

LHMDS.....lithium hexamethyldisilazane

MCPBA.....*m*-chloroperoxybenzoic acid

MOM.....methoxymethyl

MoOPH.....Oxodiperoxymolybdenum (pyridine)
(hexamethylphosphoric triamide)

NMO.....4-methylmorpholine *N*-oxide

PCC.....pyridinium chlorochromate

PDC.....pyridinium dichromate

Ph.....phenyl

PMB.....*p*-methoxybenzyl

PPTs.....pyridinium *p*-toluenesulfonate

Pr.....propyl

Py.....pyridine

SEM.....2-(trimethylsilyl)ethoxymethyl

TBAF.....tetra(*n*-butyl)ammonium fluoride

TBDPS.....*t*-butyldiphenylsilyl

TBS.....*t*-butyldimethylsilyl

TEMPO.....2,2,6,6-tetramethylpiperidinyl-1-oxy

TES.....triethylsilyl

TMS.....trimethylsilyl

Tf.....trifluoromethanesulfonyl

TFA.....trifluoroacetic acid

TFAA.....trifluoroacetic anhydride

THF.....tetrahydrofuran

THP.....tetrahydropyran

TIPS.....trisiopropylsilyl

TPAP.....tetra-*n*-propylammonium perruthenate

Tr.....triphenylmethyl

Ts.....*p*-toluenesulfonyl

Part 1

Radical Cyclization Routes to α-Hydrazino Lactones, *C*-Glycosyl Amino Acids and (+)-Furanomycin

I. Introduction

Though free radical reactions have been known for nearly a century, it is only in the last two decades that this knowledge has been widely used in synthetic organic chemistry.[1] Strategies involving radical reactions have become powerful tools in organic synthesis, in particular, free radical-mediated cyclization has developed as a preeminent method for preparing diverse cyclic compounds via carbon-carbon bond-forming processes. Due to the mild and neutral reaction conditions, and the compatibility with various functional groups, free radical reactions have increasingly attracted attention from synthetic chemists.[1] Several recent reviews[1] are available in this area. My survey of free radical reactions will cover only intramolecular cyclizations of carbon radicals onto carbon-nitrogen double bonds, with an emphasis on the most recent developments. Two other topics, recent synthetic approaches to *C*-glycosyl amino acids, and synthetic routes to (+)-furanomycin, are also included in the review section, as they are closely related to my research work.

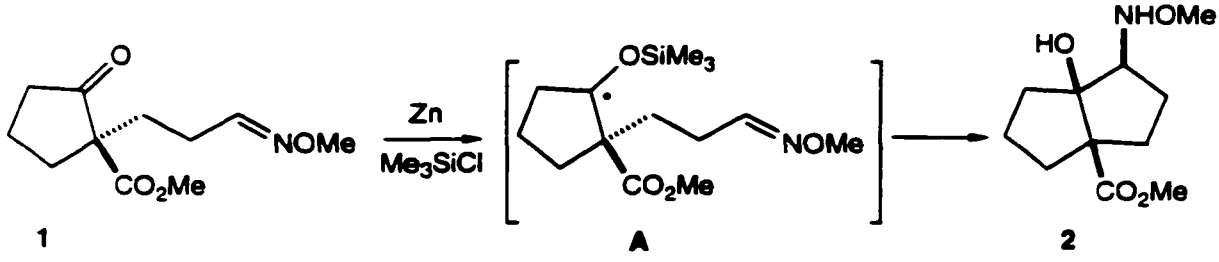
A. Addition of Carbon Radicals onto C=N Systems

Historically, oxime ethers were the first of the important unsaturated nitrogen functional groups to be employed for free radical cyclization. However, detailed examination of hydrazones and imines represent more recent

investigations.[1e] Since the products of addition of carbon radicals onto carbon-nitrogen double bond systems retain synthetically useful functionality for subsequent manipulation, the study and application[1e] of oxime ethers and related acceptors have expanded greatly in recent years.

1. Oxime Ether Acceptors

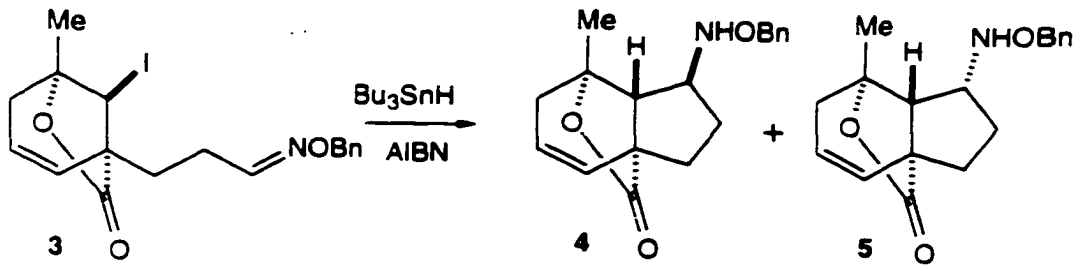
One of the first examples of the cyclization of a carbon-centered radical onto a C=N system was reported by Corey and Pyne[2] in 1983. The ketyl radical **A** (Scheme 1),



Scheme 1

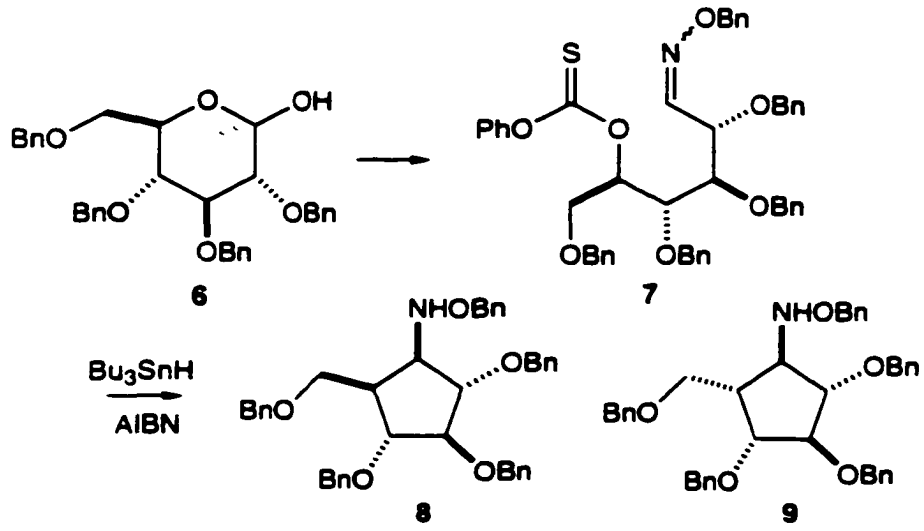
generated *in situ* by treatment of a suitable cyclopentanone, such as **1**, with Zn-Me_3SiCl afforded the amino alcohol **2** in 84% yield as a single diastereomer. Oxime ethers are thus efficient radical traps.

Hart and Seely[3] reported that the bicyclic iodolactone **3** cyclized in the presence of Bu_3SnH to afford a 1:1 diastereomeric mixture of **4** and **5** in 85% yield (Scheme 2).



Scheme 2

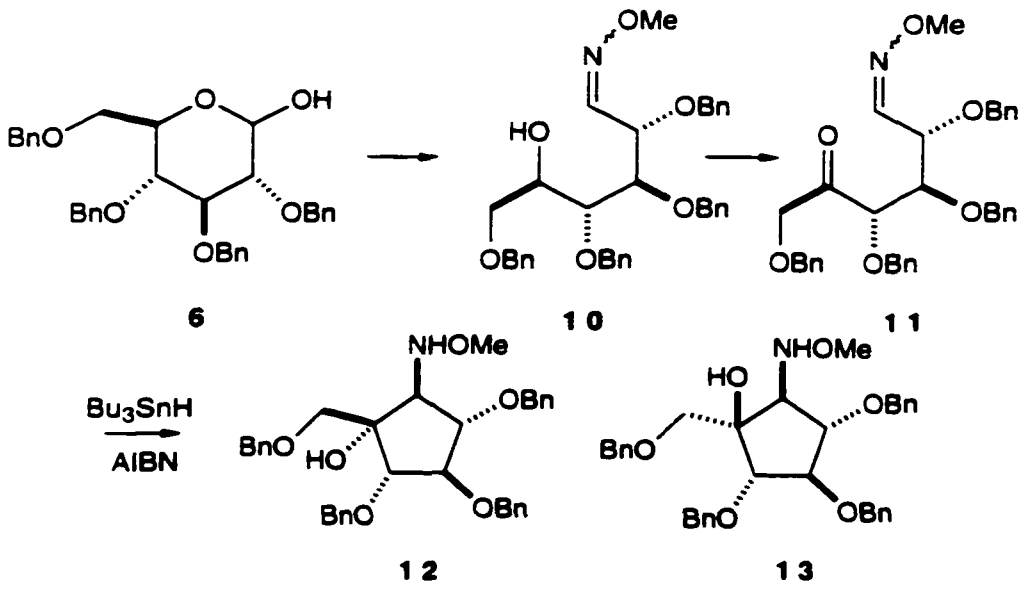
Bartlett and coworkers[4] described the synthesis of both cyclopentanes and cyclohexanes, using *O*-benzyloxime acceptors for the capture of radicals formed from bromide or phenyl thiocarbonate precursors. An interesting example involved the conversion of a carbohydrate into a carbocycle. The benzyl-protected D-glucose **6** (Scheme 3) was transformed into *O*-benzyloximes **7**, and then radical cyclization of **7** afforded a 62:38 ratio of **8** and **9** in 93% yield.



Scheme 3

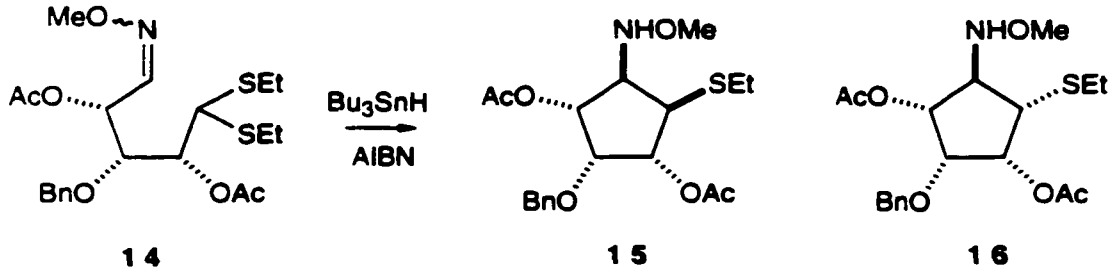
Naito's group[5] employed a ketyl radical, generated from

carbohydrate derivatives **11** (Scheme 4), to obtain **12** and **13** in 68% yield in a 57:43 ratio, respectively.



Scheme 4

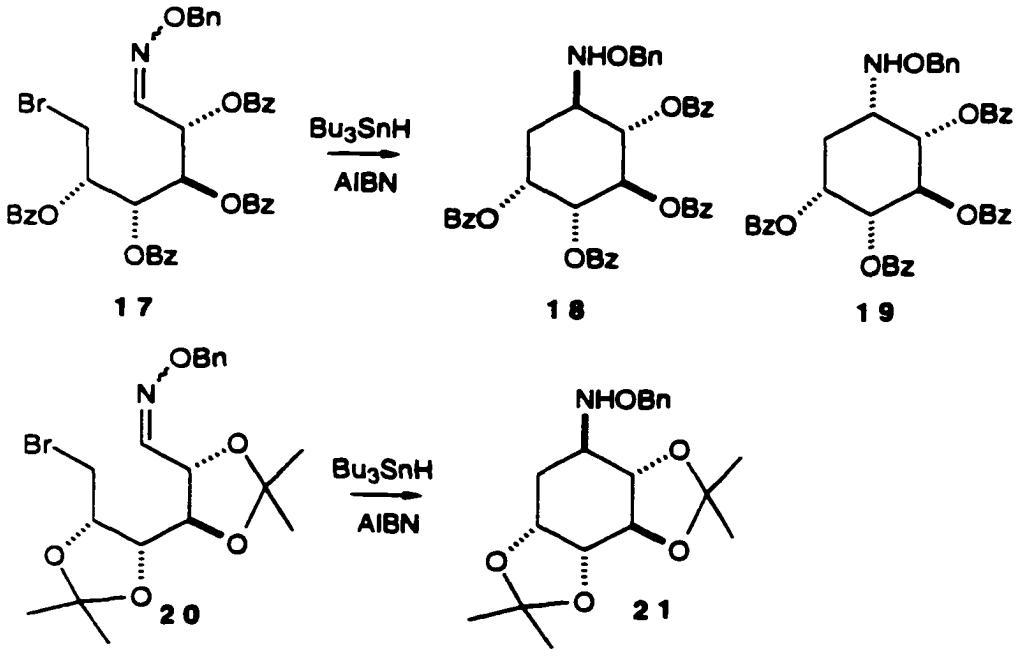
Moore and coworkers[6] reported that the radical derived from the sugar dithioacetal **14** (Scheme 5) could be cyclized to **15** and **16** in a 3:1 ratio (80%).



Scheme 5

Similar chemistry, developed by Marco-Contelles and coworkers,[7a] and based on D-ribose precursors, has been used

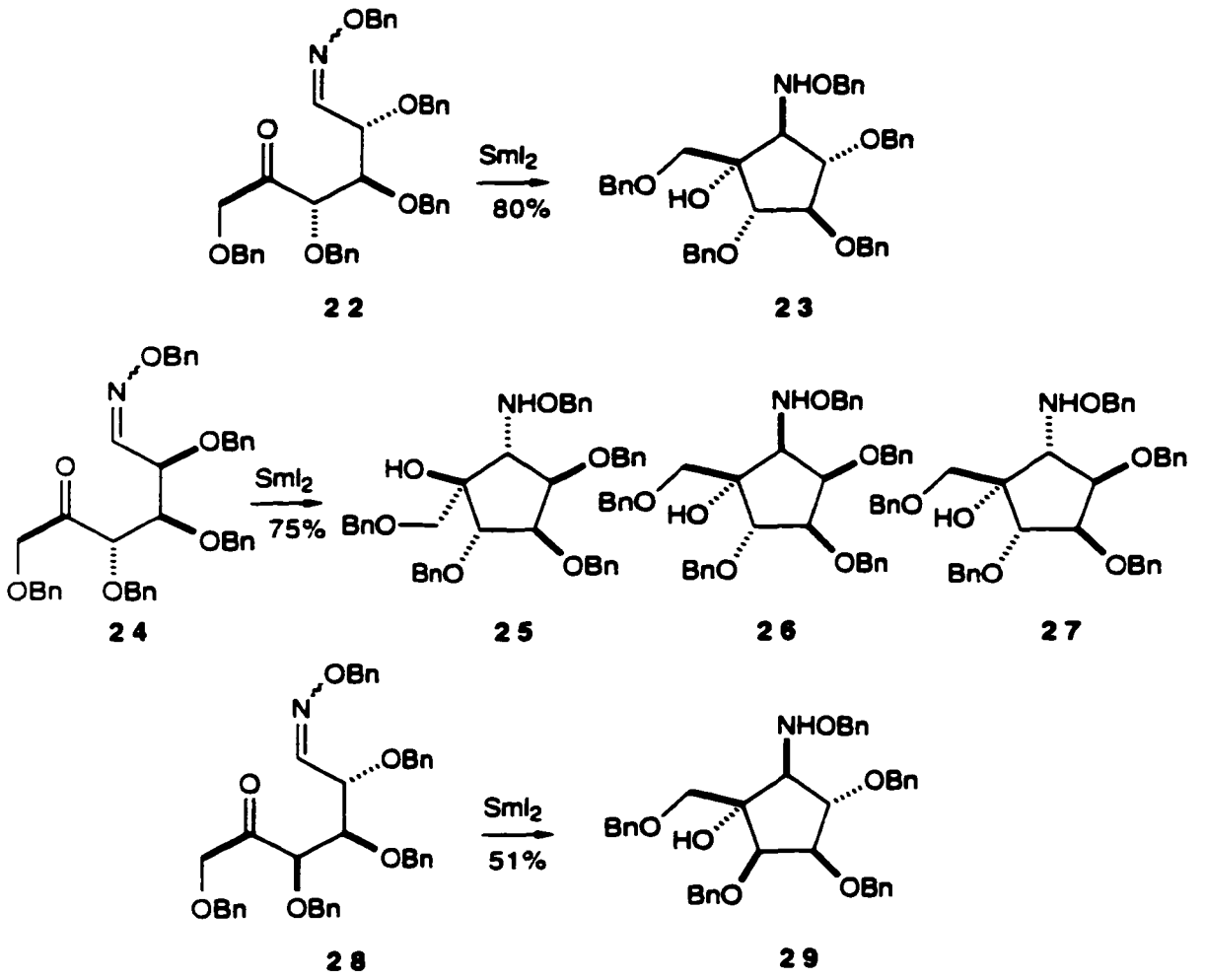
to make analogs of mannostatin A. The general approach of this research group is illustrated by their synthesis of cyclohexylamines by 6-*exo* cyclizations of the acyclic carbohydrate-derived *O*-benzyloximes **17**.[7b] Cyclization proceeded in 55% yield to provide a 75:25 mixture of **18** and **19** (Scheme 6). The stereoselectivity is improved significantly when the number of conformers is restricted by the presence of isopropylidene acetal groups. For example, the oxime ethers **20** in the *gluco* series cyclized in 75% yield to carbocycle **21** with a diastereomeric excess of 82%.



Scheme 6

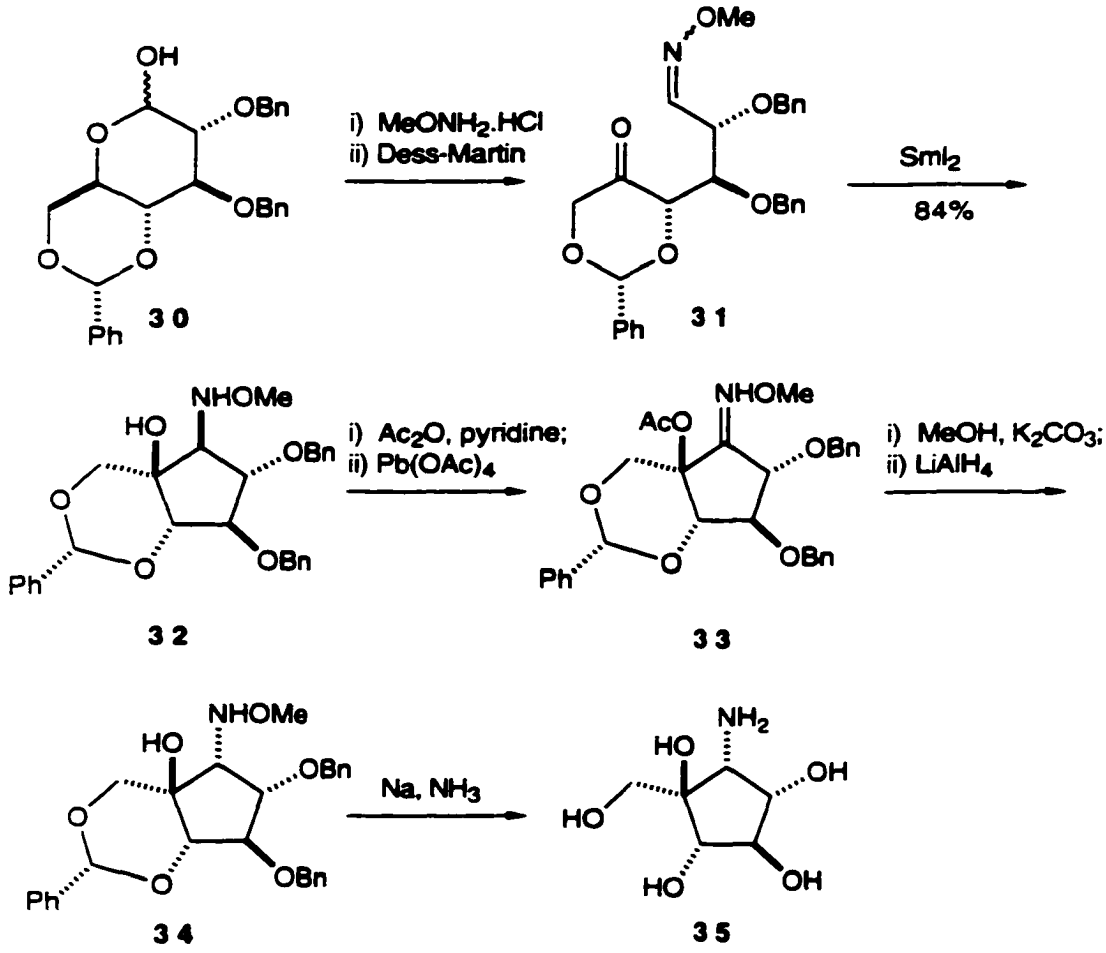
A systematic investigation of the SmI_2-promoted synthesis of aminocyclitols from carbohydrate-derived oximes was reported by Marco-Contelles and colleagues[8] (Scheme 7). The oximes **22** derived from D-glucose could be cyclized

smoothly to the branched aminocyclopentitol **23** in 80% yield as a single diastereomer; under the same conditions **24** (Scheme 7), derived from D-mannose, afforded a mixture of the three aminocyclopentitols **25**, **26**, **27** in a 15:3:1 ratio, and **28** (Scheme 7), derived from D-galactose, gave aminocyclopentitol **29** in 51% yield. It should be noted that compounds **23**, **25**, **26**, **27**, and **29** can be readily converted, by hydrogenolysis, into isomers of trehazolamine, the aglycon of the trehalase inhibitor trehazoline.[9]



Scheme 7

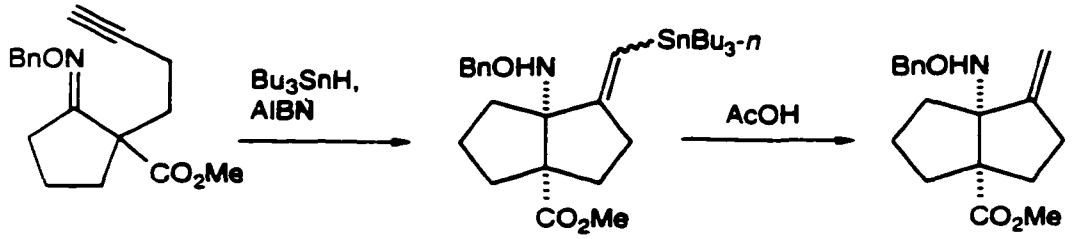
In the recent synthesis of trehazoline, Giese's group[10] used oximes **31** (Scheme 8), derived from D-glucose, to make the key intermediate trehazolamine **35**. Since the protected oximes **22** did not give the desired configurations at all the newly formed stereogenic carbons in **35**, the stereochemistry of the radical cyclization was inverted by connecting the oxygens at C(4) and C(6) as a six-membered cyclic acetal (**31**). Compound **31** can be made easily from **30** by conventional methods. Treatment of **31** with SmI_2 in THF at -78 °C gave exclusively diastereoisomer **32**, in 84% yield.



Scheme 8

Protection of the tertiary hydroxyl of **32**, followed by oxidation with $Pb(OAc)_4$, gave the oxime ethers **33**. After deprotection of the tertiary hydroxyl, the resulting *O*-methyloximes were reduced to **34** by $LiAlH_4$. Full deprotection of **34** with Na in liquid NH_3 afforded trehazolamine (**35**).

Vinyl radicals also add readily to oxime ethers in an intramolecular manner in both the 5-*exo* and 6-*exo* modes. Terminal alkynes undergo free radical hydrostannylation to generate a vinyl stannane radical that cyclizes readily onto an attached *O*-benzyloxime. Enholm and coworkers[11] reported that addition of the tributylstannyl radical to the triple bond of **36** (Scheme 9) was followed by cyclization to **37**, which contained a vinyl tin substituent and a protected amine. Subsequent protodestannylation with acetic acid afforded **38**.

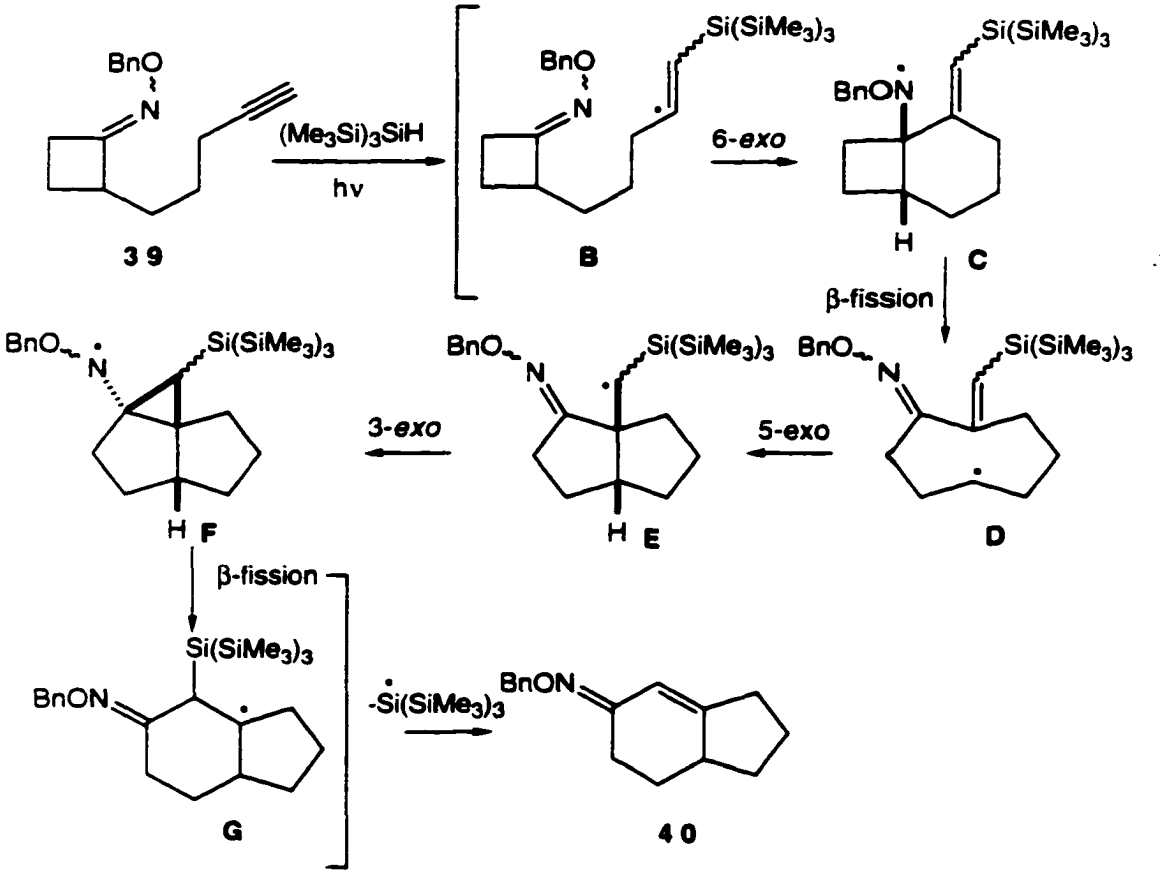


36 **37** **38**

Scheme 9

Pattenden and coworkers[12] have described an interesting cascade sequence for the synthesis of bi- and tricyclic ring systems in which an oxime ether plays a key role. This cascade commenced with the cyclobutanone oxime **39** (Scheme 10). The reaction was initiated by formation of the vinyl

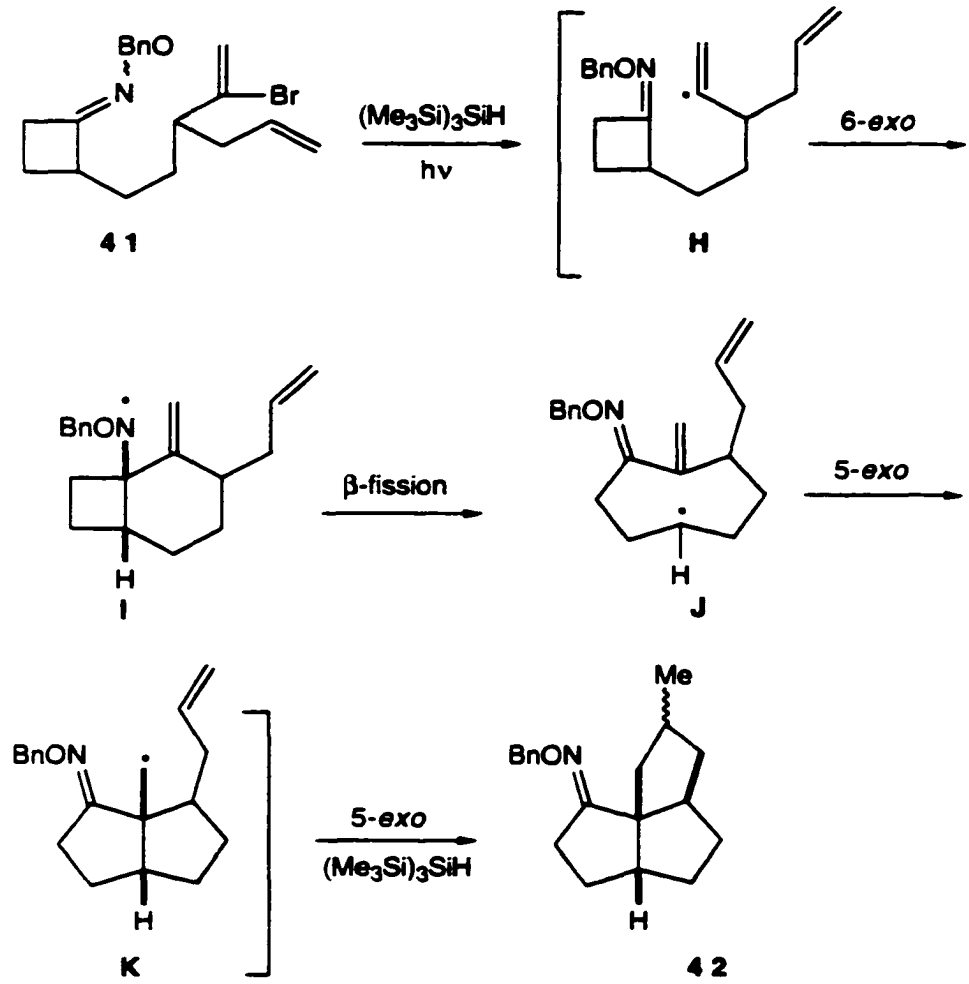
radical **B**. As indicated in Scheme 10, 6-*exo* cyclization onto the oxime ether afforded **C**. A β-fission led, in sequence, to the intermediate **D**, and then **E**, from a second cyclization. A third ring closure afforded the α-cyclopropylaminyl radical **F**. Regeneration of the oxime from a second β-fission to give **G**, was followed by the final elimination of the tris(trimethylsilyl)silyl radical to continue the chain.



Scheme 10

Thus the bicyclic product **40** of this novel "one pot" cascade arose via a double ring expansion-cyclization process involving aminyl radicals **C** and **F**. The oxime functionality

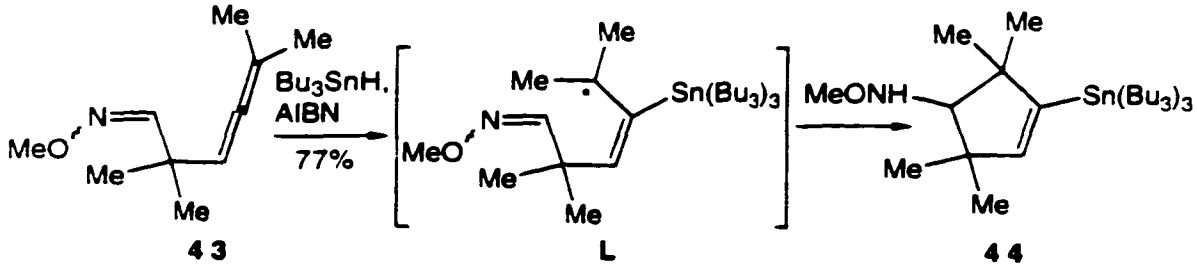
is thus preserved, and the corresponding enone could be generated by hydrolysis. In related studies, Pattenden's group[12b] reported that irradiation of **41** (Scheme 11) in the presence of tris(trimethylsilyl)silane afforded the triquinane **42** as a 1:1 mixture of α- and β-methyl diastereomers in 38% yield. The product resulted from a cascade radical sequence that utilized a 6-*exo* cyclization, (**H** → **I**), an aminyl radical fragmentation (**I** → **J**), a 5-*exo* radical transannulation (**J** → **K**), and finally a further 5-*exo*



Scheme 11

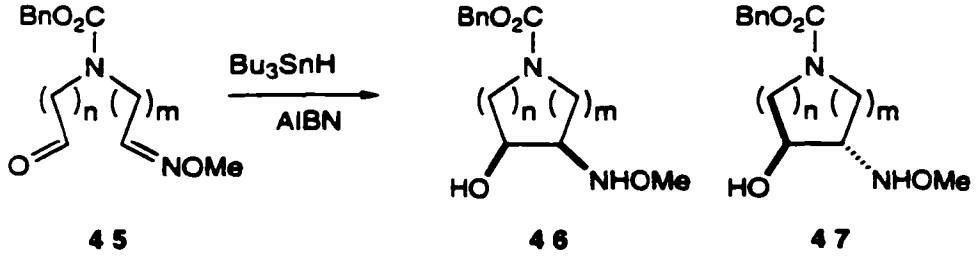
ring closure to generate the tricyclic compound **42**.

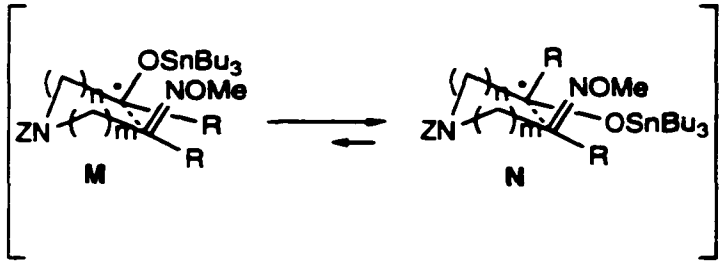
Hatem and coworkers[13] reported that allene derivatives **43** (Scheme 12) can be cyclized to **44** through a radical intermediate **L**.



Scheme 12

Naito's group[14] have described the synthesis of five-, six- and seven-membered nitrogen heterocycles. α-Amino cyclic alcohols **46** and **47** (Scheme 13) can be prepared from the ketyl radical generated upon treatment of the ketone or aldehyde oxime ethers represented by **45**, with Bu_3SnH in the

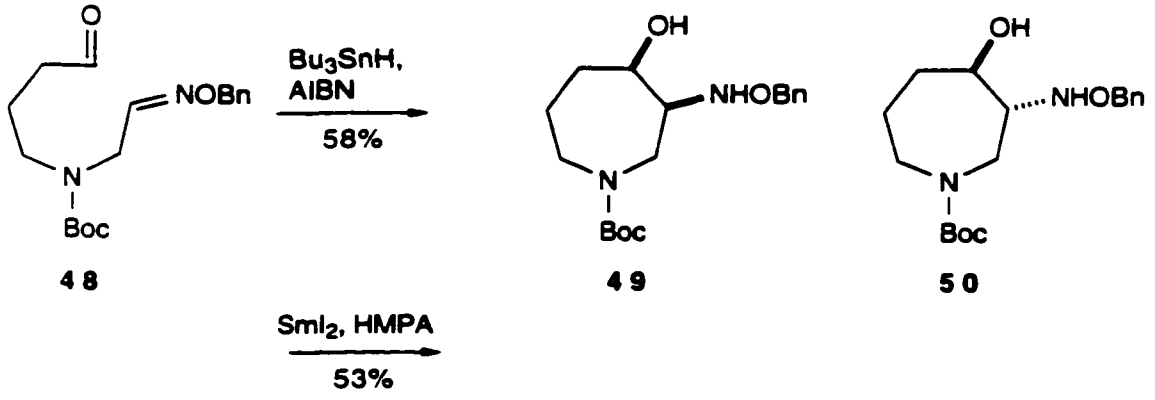




Scheme 13

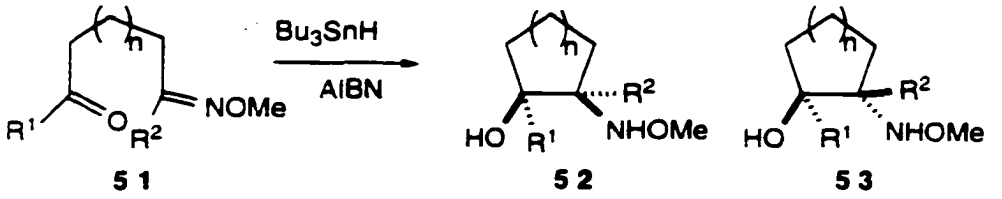
presence of AIBN. In all cases the *trans* isomer predominated. The best yield was 71% for n = 2, m = 1. The proposed transition state is shown in Scheme 13. Steric and electronic repulsions in **M** are larger than in **N**.

Naito's group[15a,b] also used the above strategy to synthesize the hexahydroazepine ring system in balanol,[16] which contains adjacent amino and alcohol groups in a trans relationship. The aldehyde oxime ethers **48** (Scheme 14) can be cyclized in the presence of Bu_3SnH and AIBN, to **49** and **50** in 58% yield as a 1:1.5 mixture. However, if cyclization is induced by SmI_2, then **49** and **50** are obtained in 53% yield as a 1:6.6 mixture. The major isomer **50** was resolved for conversion into (-)-balanol[15b].



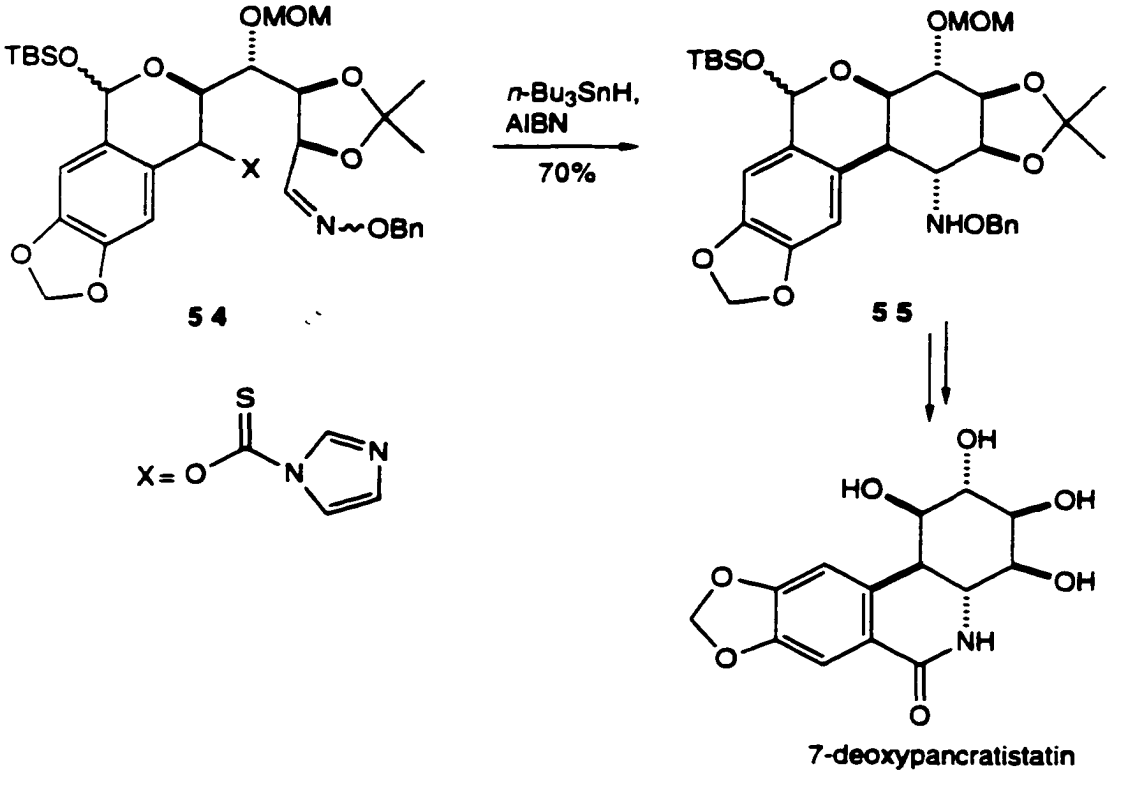
Scheme 14

Similar chemistry was extended recently by Fu's group.[16] They reported that the ketone or aldehyde oxime ethers **51** (Scheme 15) (n = 1-2, R^1, R^2 = H or Me), in the presence of Bu_3SnH and AIBN, gave β-amino alcohols **52** and **53**, with the *trans* isomer **53** predominating.



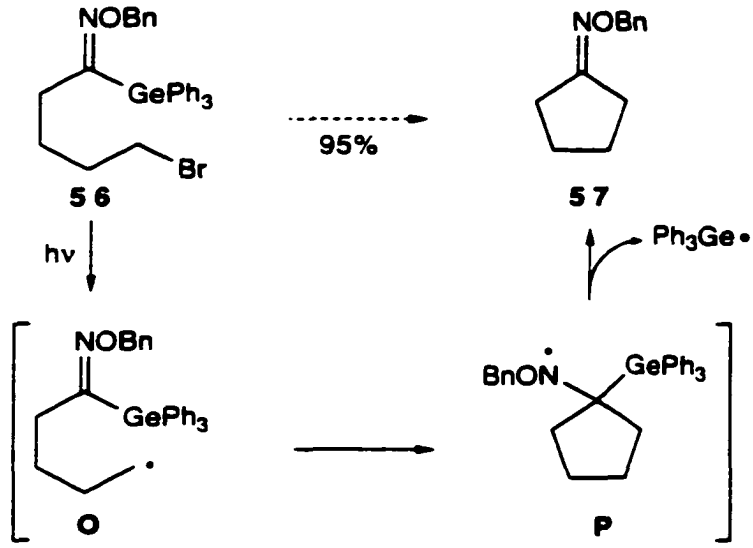
Scheme 15

Keck's group[17a] reported the total synthesis of the naturally occurring alkaloid 7-deoxypancratistatin[18] via an approach based on radical cyclization of the oxime ether **54** (Scheme 16). In the presence of Bu_3SnH and AIBN, **54** can be cyclized smoothly to **55** in 70% yield, and subsequent elaboration of **55** gave the natural product.



Scheme 16

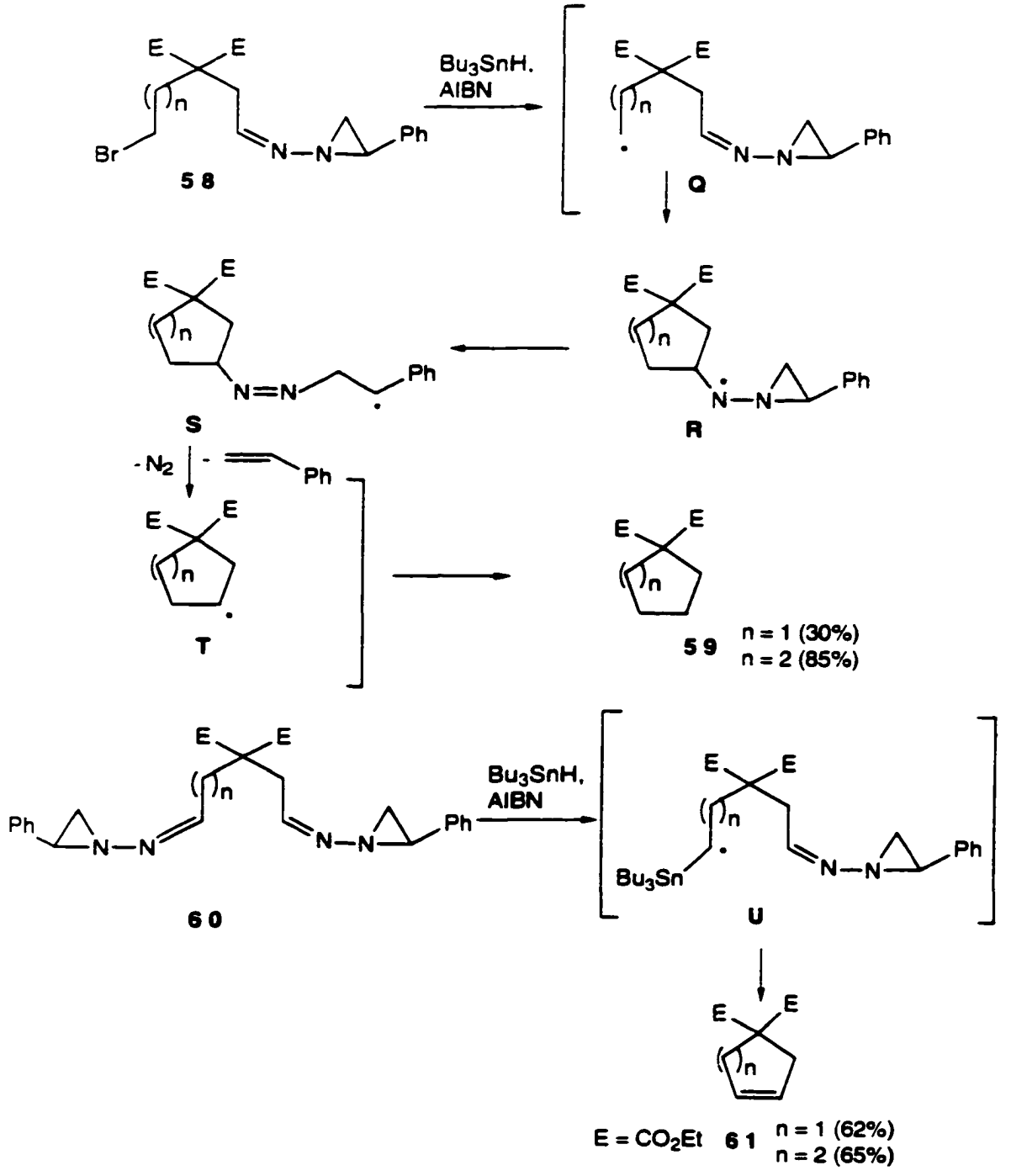
Very recently, Curran and his colleagues[19] described the synthesis of cyclic oxime ethers by radical closure of acylgermane oxime ethers. A representative example is shown in Scheme 17. Irradiation of **56** in benzene resulted in isolation of the oxime ether **57** in 95% yield. The proposed mechanism (Scheme 17) is as follows: upon irradiation, radical precursor **56** generates radical **O**, and then this alkyl radical adds to the acylgermane oxime in 5-*exo* fashion giving rise to aminyl radical **P**, which rapidly collapses to oxime ether **57**.



Scheme 17

2. Hydrazone Acceptors

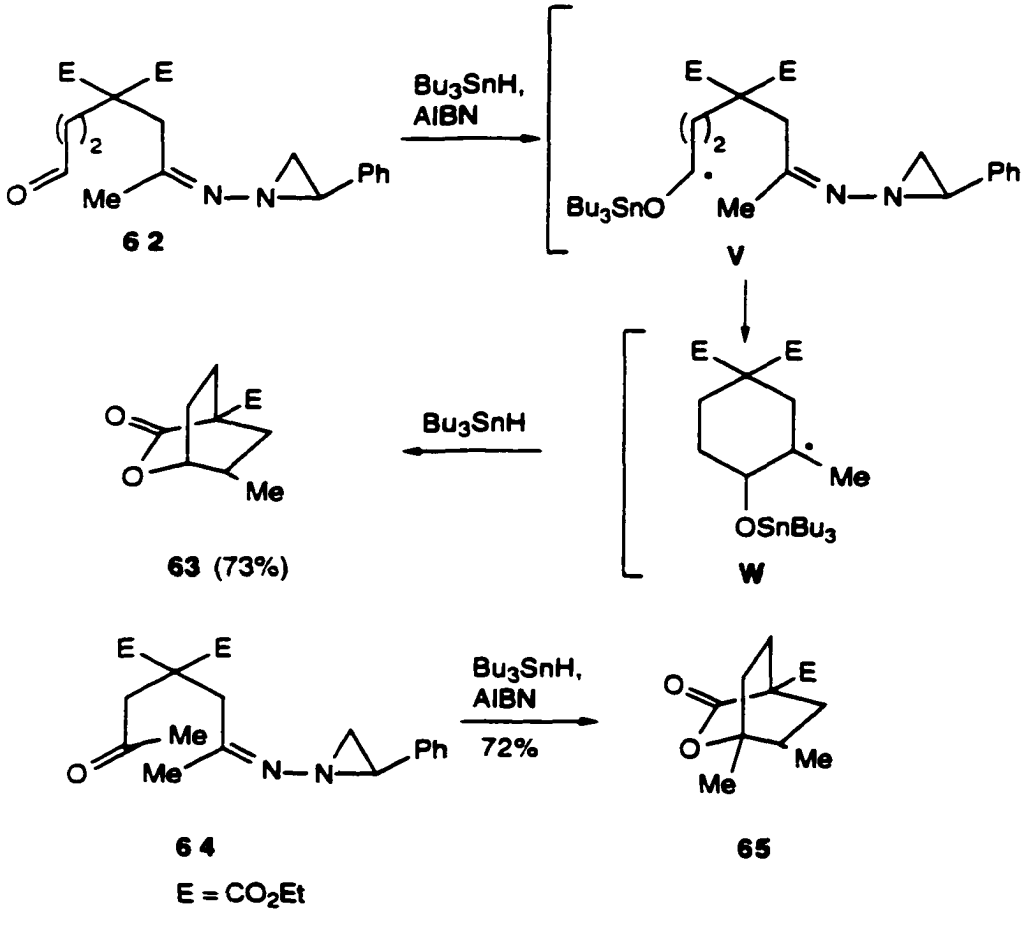
The first example of a radical cyclization onto a hydrazone was reported in 1991 by Kim's group.[20a] This interesting example employed a special hydrazone – a 2-phenyl-*N*-aziridinyl imine – as the radical acceptor. Upon



Scheme 18

treatment of bromide **58** (Scheme 18) with Bu_3SnH, the initial radical **Q** added to the imine double bond to generate an α-

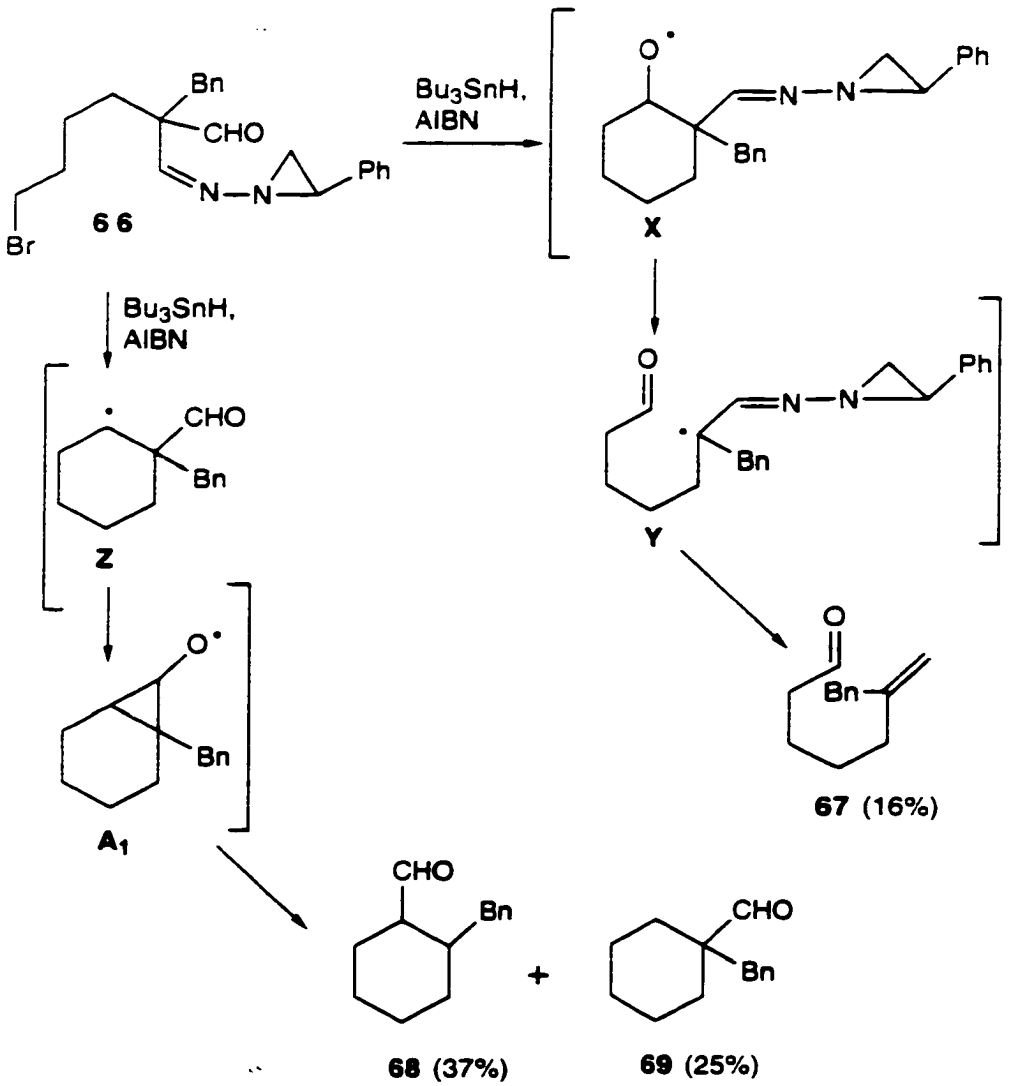
aziridinyl aminyl radical **R**. This underwent rapid ring opening to the benzyl radical **S**. Subsequent expulsion of styrene and nitrogen from **S** gave the carbocycle **59**, from quenching of **T** with the stannane. For the 5-*exo* cyclization (n = 1) the yield was modest (30%), but for the 6-*exo* process, the cyclohexane **59** (n = 2) was obtained in 85% yield. If desired, the intermediate cyclohexyl radical **T** (n = 2) may be trapped with methyl acrylate and acrylonitrile in yields of 87% and 86%, respectively. The reaction also proceeded smoothly with keto-hydrazones and with alternative



Scheme 19

radical precursors such as phenyl selenides and acetylenes. Exposure of the bisaziridinyl substrate **60** (Scheme 18) to 0.3 equivalent Bu_3SnH and AIBN afforded, via the α-stannyl radical **U**, the expected cyclopentene and cyclohexene **61** in yields of 62% and 65%, respectively. In order to expand the potential of the *N*-aziridinyl amino group as a radical acceptor, Kim and his colleagues[20b] examined the competition between carbonyl and hydrazone groups as radical acceptors. The preferred pathway for **62**, in the competition between a keto-hydrazone and an aldehyde carbonyl, involved initial attack at the aldehyde. The stannyloxy radical **V** generated from this addition cyclized onto the hydrazone to form the secondary radical **W**, after loss of nitrogen and styrene. Subsequent reaction afforded **63**. A similar preference was observed in the methyl ketone series, in which clean conversion of **64** (Scheme 19) into **65** was observed. This situation was reversed when the alkyl radical could add onto a formyl group or imine group. Thus **66** (Scheme 20) afforded 16% of the aldehyde **67** from initial attack of the stannane on the bromide, followed by addition to the aldehyde, to form **X**. This was followed by ring opening to **Y** and expulsion of the *N*-aziridinyl moiety. The competing pathway for addition to the hydrazone dominated and afforded 37% of **68** from rearrangement of $\mathbf{A_1}$, and 25% of **69** from the quenching of **Z**.

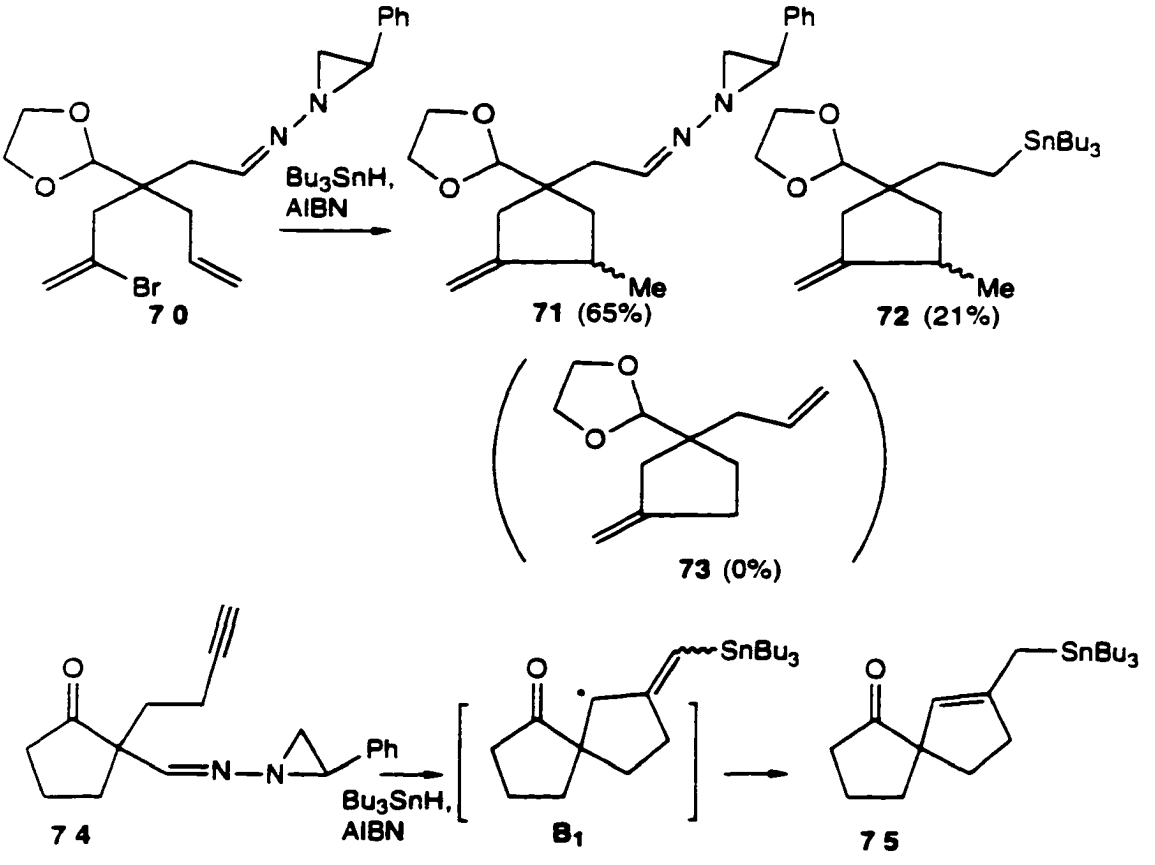
The competition between an alkenyl double and an imino group has also been investigated.[20b] In this case the alkene proved to be a better acceptor than the *N*-aziridinyl imino



Scheme 20

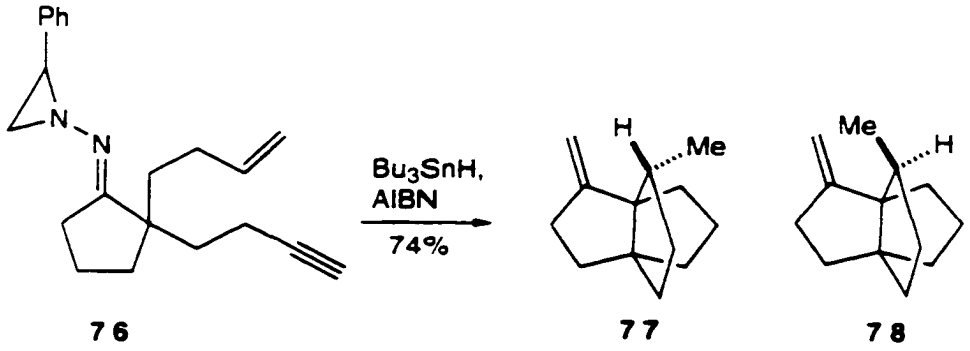
function. With 1.1 equivalents of Bu_3SnH a mixture of **71** and **72** (Scheme 21) was obtained in 65% and 21% yield, respectively, and there was no evidence that any of the diene **73** was produced. When the quantity of Bu_3SnH was increased to 2.2 equivalents, the stannane **72** was obtained in 80% yield as the only product; it arose by addition of Bu_3SnH to the imino group in **70**. The situation was altered again when the

competition was between a cyclopentanone and the imino group. The reactive vinyl radical derived from acetylene **74** added preferentially to the hydrazone to afforded the spiro diquinane **75** in 85% yield.



Scheme 21

In a formal total synthesis of *dl*-modhephene[20c], *N*-aziridinyl imine **76** (Scheme 22) has been used in a tandem radical cyclization to produce compounds **77** and **78**, containing the [3.3.3]propellane skeleton, in a 9:1 ratio (74%). Elaboration of **77** completed the formal synthesis of *dl*-modhephene.



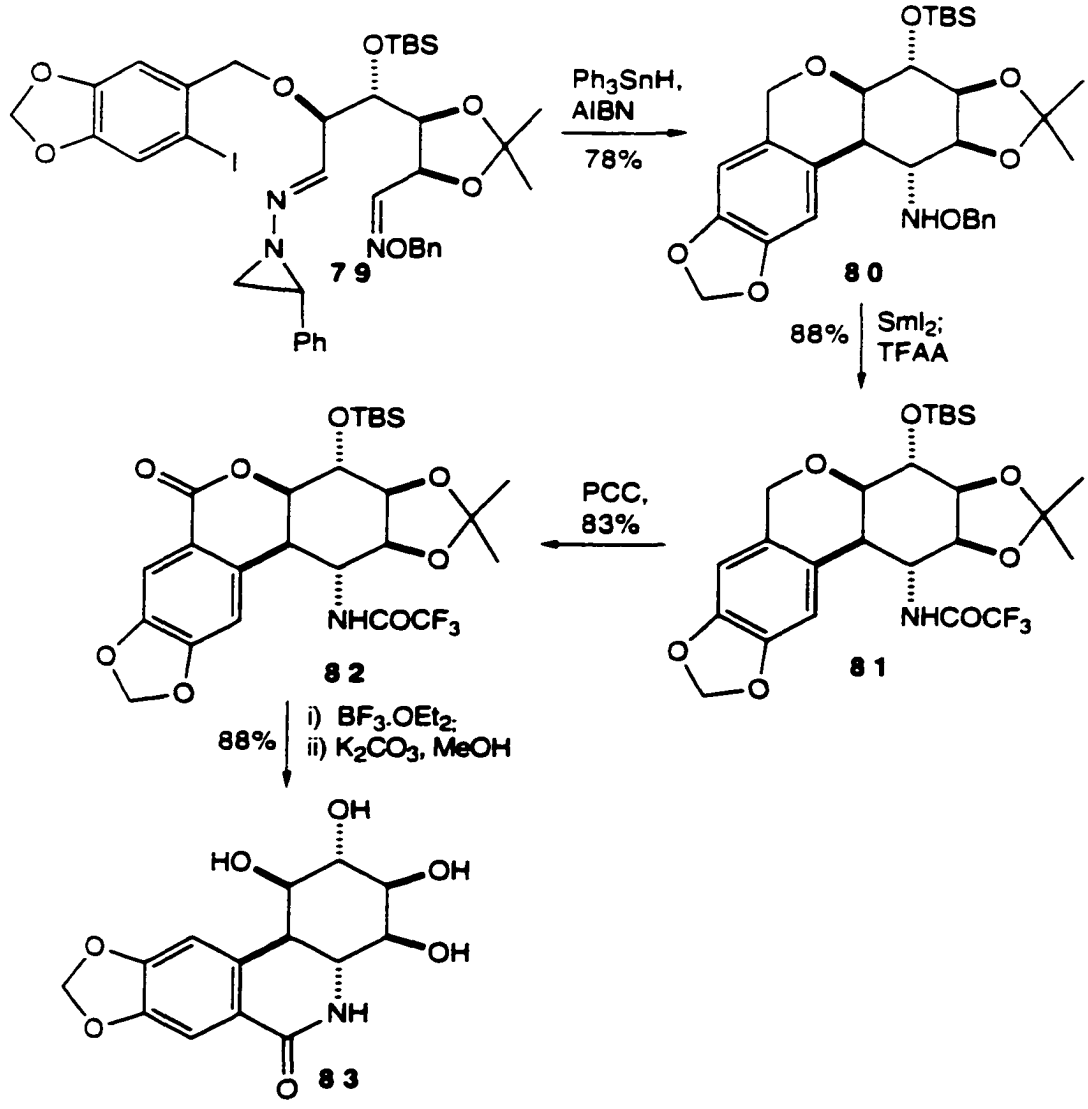
76 **77** **78**

Scheme 22

More recently, Keck's group[17b] have reported an elegant synthesis of (+)-7-deoxypancratistatin, based on a tandem radical cyclization of the hydrazone/oxime ether **79** (Scheme 23). Upon treatment of **79** with Ph_3SnH in the presence of AIBN, the desired cyclization product **80** was isolated in 78% yield as a single stereoisomer. Cleavage of the N-O bond, using SmI_2 in THF, and direct quenching with TFAA, gave the trifluoroacetamide **81** in 88% isolated yield. Installation of the carbonyl group was accomplished by PCC oxidation to **82**. Further deprotection and cyclization gave (+)-7-deoxypancratistatin (**83**).

The radical cyclizations of *N*-aziridinyl imines have provided a versatile new approach for making five- and six-membered rings. However, this strategy does not retain the nitrogen functionality, due to the expulsion of nitrogen. That can be an advantage as seen through all the examples above. Fallis' group[21a] established that *N,N*-diphenylhydrazones are excellent radical acceptors and can be used to obtain nitrogen-functionalized cyclopentanes and

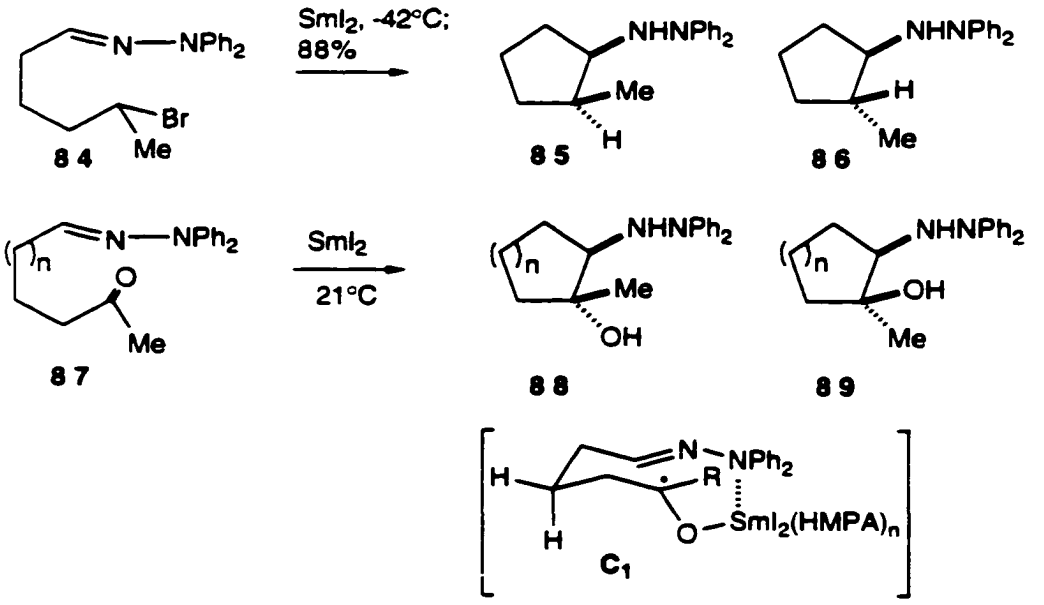
cyclohexanes. The reaction temperature significantly affected the *cis*:*trans*



Scheme 23

ratio of the cyclic products. Treatment of bromide ketone **84** (Scheme 24) with Bu_3SnH at 80 °C afforded **85** and **86** in 95% yield, in a 67:33 ratio. The same ratio was obtained with SmI_2 at 21 °C in 91%. However, with SmI_2, the diastereoselectivity increased as the temperature decreased. At -42

°C with SmI_2, **84** gave **85** and **86** (88%) in a ratio of 88:12. For keto hydrazones, the radical cyclization with SmI_2 was more stereoselective. For example, cyclization of **87** (n = 1) at 21 °C afforded **88** and **89** in 63% yield as a ratio of 99:1. For cyclization of **87** (n = 2), similar results were obtained, and **88** and **89** were isolated in 62% yield and in a ratio of 99:1. This high level of selectivity is believed to arise from a nine-membered ring chelate of type $\mathbf{C_1}$ (Scheme 24).

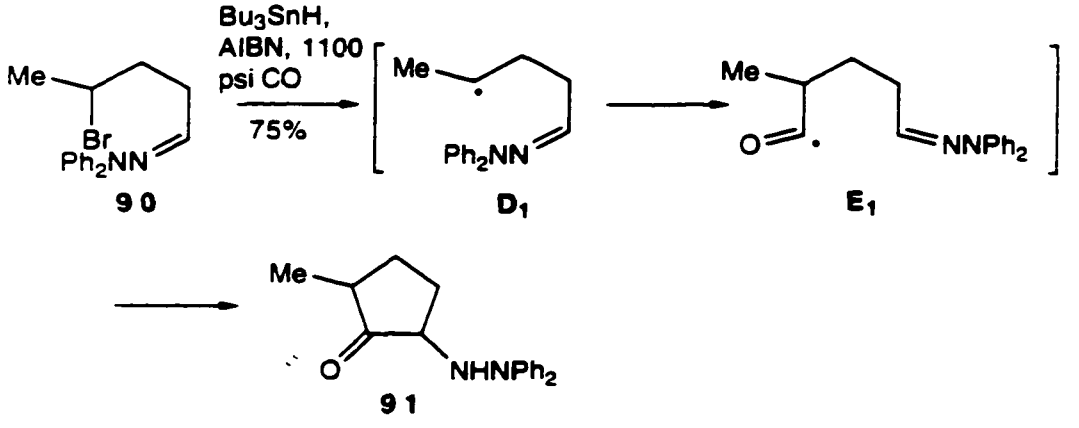


Scheme 24

Fallis' group[21b] also established the rate constants for the 5-*exo* and 6-*exo* cyclizations. The rate constant for 5-*exo* cyclization onto *N,N*-diphenylhydrazones is about 1 x 10^8 s^{-1} at 80 °C. The 6-exo cyclization rate constant is approximately 1 x 10^6 s^{-1} at the same temperature. The important conclusion is that 5-*exo* cyclization for addition

to these hydrazones was approximately 200 times faster than the corresponding cyclization for 5-*exo* closure onto alkenes, while for the 6-*exo* process, the rate of addition onto *N,N*-diphenylhydrazones is about 100 times faster than for the corresponding alkenes.

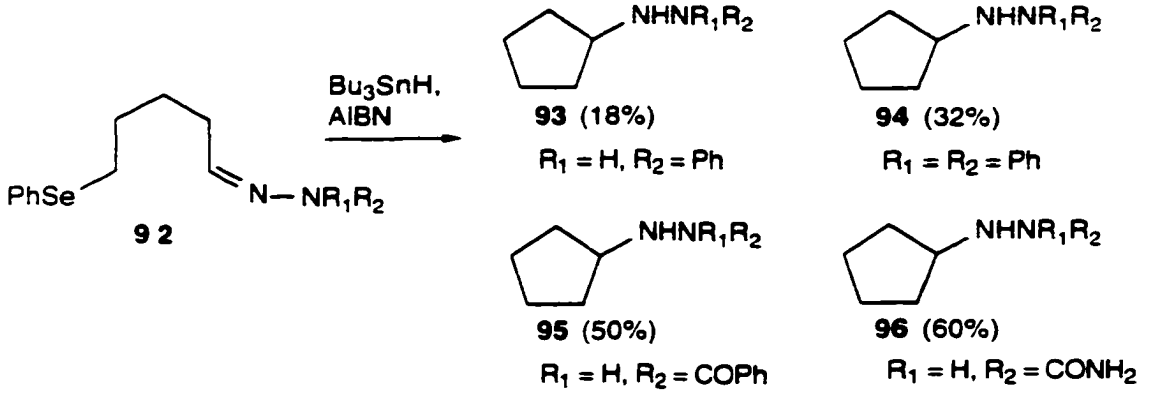
As an extension of this chemistry, Fallis' group[21c] reported that the initial radical **D_1**, generated from **90** (Scheme 25), could be captured with carbon monoxide under pressure (1100 psi) to form the acyl radical **E_1**. Cyclization gave the α-hydrazinocyclopentanone **91** in 75% yield as a 1:1 *cis/trans* mixture.



Scheme 25

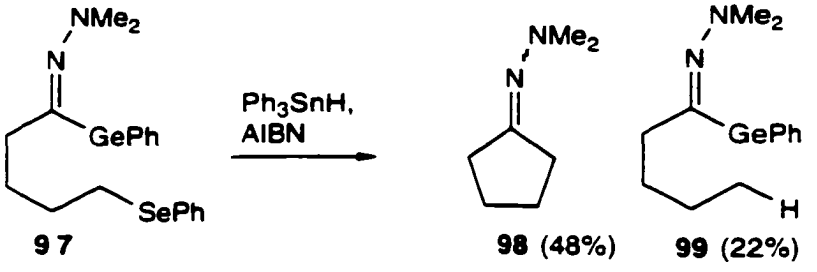
Bowman and coworkers[22] have examined the effect of different substituents on the hydrazone acceptors. The yield was increased as electron withdrawing groups were added to the singly bonded nitrogen, thus rendering the imine nitrogen more electropositive and raising the rate of closure. The *N*-phenylhydrazone **92** (R_1 = H, R_2 = Ph, Scheme 26) gave **93** in

18%, but this increased to 60% with the urea system (R_1 = H, R_2 = $CONH_2$), which gave **96**. The lower yield in the *N,N*-diphenylhydrazone cyclization (**92**, R_1 = R_2 = Ph, 32% vs 95%), compared to the process of Scheme 24, may reflect the slightly different reaction conditions, the use of a primary versus a secondary radical, and the nature of the radical precursor (here a selenide instead of a bromide).



Scheme 26

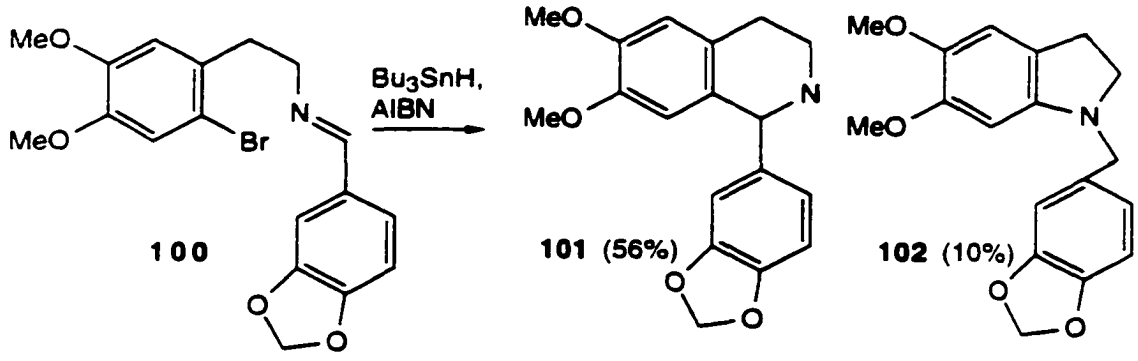
Recently, Curran's group[19] found that acylgermane hydrazone selenide **97** (Scheme 27) could be cyclized to hydrazone **98** in 48% yield, together with 22% reduction product **99**, in the presence of Ph_3SnH and AIBN.



Scheme 27

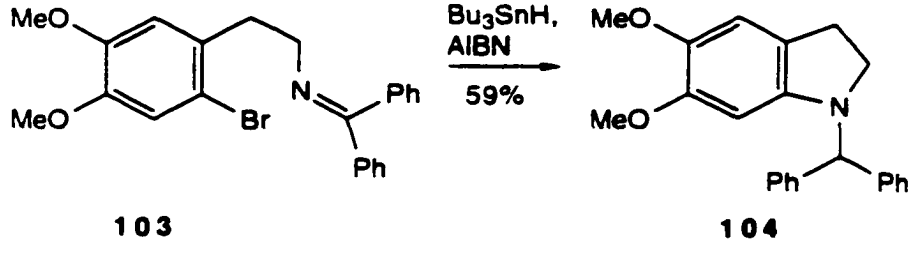
3. Imine Acceptors

An early example of an intramolecular radical addition onto an imine double bond was reported by Takano's group[23a] in 1990. Upon treatment of imine **100** (Scheme 28) with Bu_3SnH and AIBN, **101**, arising from 6-*endo* addition, was isolated in 56% yield together with the dihydroindole derivative **102** (10%) from 5-*exo* addition.



Scheme 28

Takano's group[23b] also discovered that with the ketimines derived from acetophenone and benzophenone, contrary to the above example, the carbon radical added

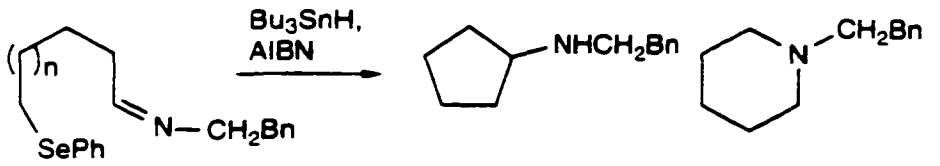


Scheme 29

exclusively to the nitrogen terminus of the azomethine bond

in a 5-*exo* fashion, and radical cyclization of **103** (Scheme 29) gave **104** exclusively in 59% yield.

Bowman's group[22a] also examined the cyclization of various primary radicals, generated from phenyl selenides, onto diverse imines. Representative examples include the cyclization (Scheme 30) of **105** (n = 1) to give the 5-*exo* product **106** (47%) and the 6-*endo* product **107** (5% yield). In the case of **105** (n = 2), the only product was **107** (43%), resulting from 6-*exo* cyclization; no seven-membered ring was found.



105 n = 1 **106** (47%) **107** (5%)

n = 2 **107** (43%)

Scheme 30

In summary, hydrazones and oximes are versatile radical acceptors for a variety of situations. Further advances and new insights into the basic reactions, and more sophisticated synthetic applications will undoubtedly be seen in the years to come.

B. Recent Synthetic Approaches to *C*-Glycosyl Amino Acids

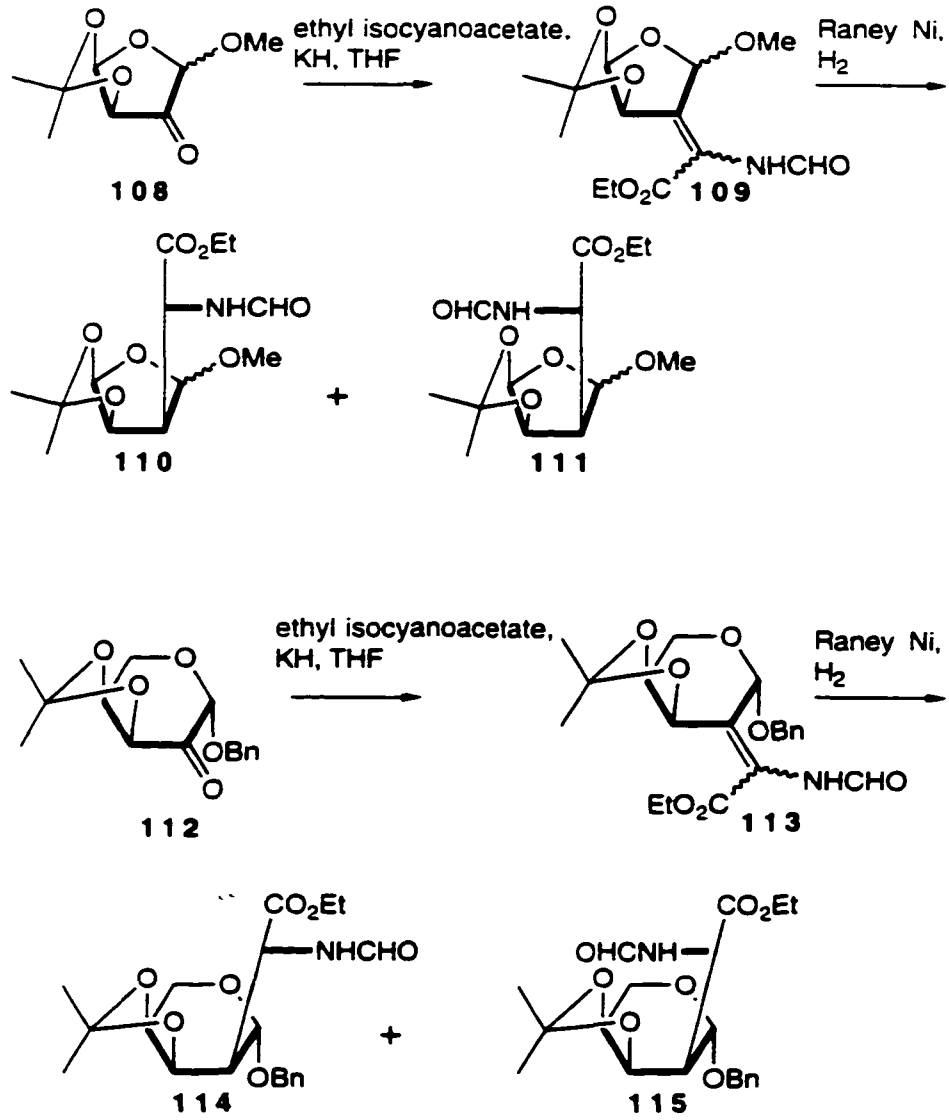
In recent years, glycopeptides have become the focus of considerable bioorganic/medicinal chemical research, due to

their involvement in various normal and pathological cellular processes.[24] A fundamental problem in using oxygen-linked glycopeptides-based therapeutic approaches to the treatment of disease is the inherent lack of *in vivo* stability of such compounds, since natural oxygen-linked glycopeptides are easily degraded in both acidic and basic media.[24] A solution to this problem lies in obtaining carbon-linked analogs of oxygen-linked glycopeptides. In addition, the nucleoside antibiotics amipurimycin,[25] miharamicyns,[26] polyoxins[27] and nikkomycins[28] belong to the class of *C*-glycosyl amino acids. Consequently, the synthesis of *C*-glycosyl amino acids and related *C*-glycopeptides has generated considerable interest from synthetic chemists.[29] Most of the syntheses were developed for preparation of a single target compound, and it is not possible to include all the syntheses in the following review section. Only syntheses of *C*-glycosyl α-amino acids, which are closely related to my research work will be discussed.

In 1977, Brink and coworkers[30] reported that the protected furanosuloside **108** (Scheme 31) and pyranosuloside **112** condensed smoothly with ethyl isocyanoacetate in the presence of KH to give **109** and **113**, respectively. After hydrogenation, protected *C*-glycosyl α-amino acids **110** and **111** (from **109**), and **114** and **115** (from **113**) were obtained.

In the total synthesis of polyoxin C, Barrett and Lebold[31] described a different method to obtain the sugar α-amino acid component **120** (Scheme 32). Condensation of

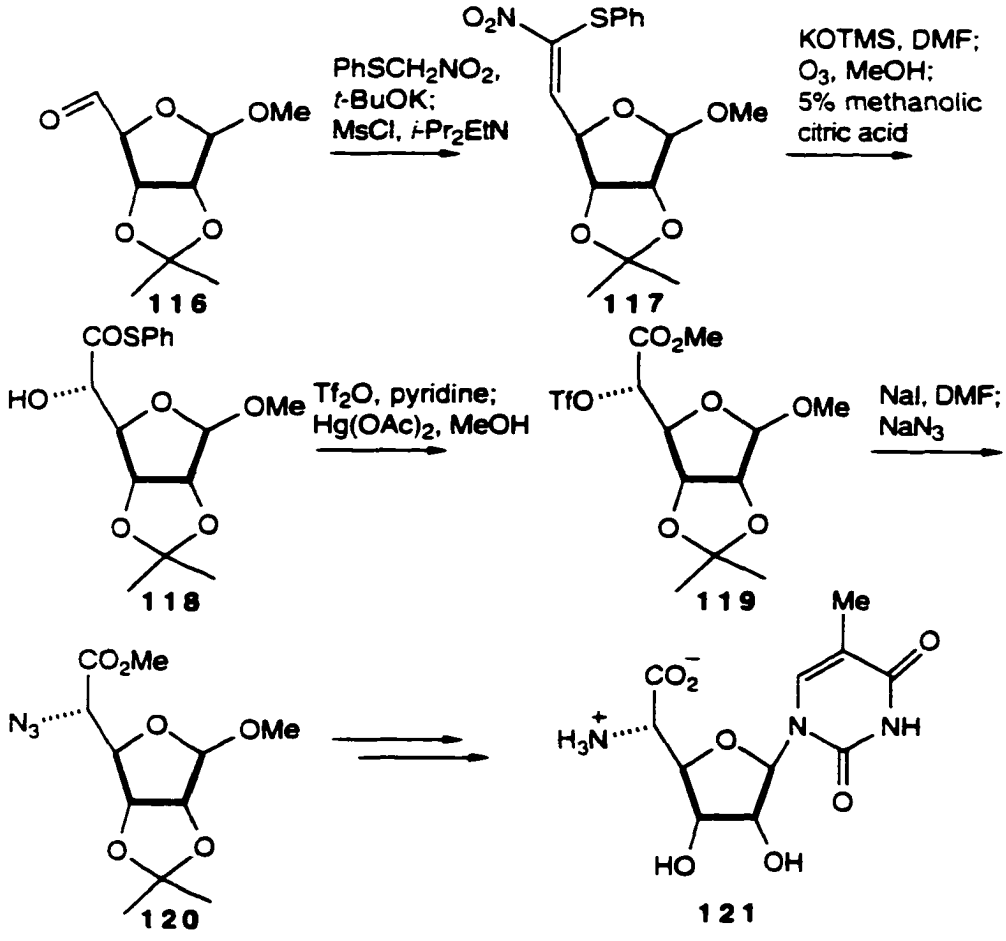
(phenylthio)nitromethane with 2,3-*O*-isopropylidene-β-D-*ribo*-pentodialdo-1,4-furanoside **116** gave the (*Z*)-nitro olefin



Scheme 31

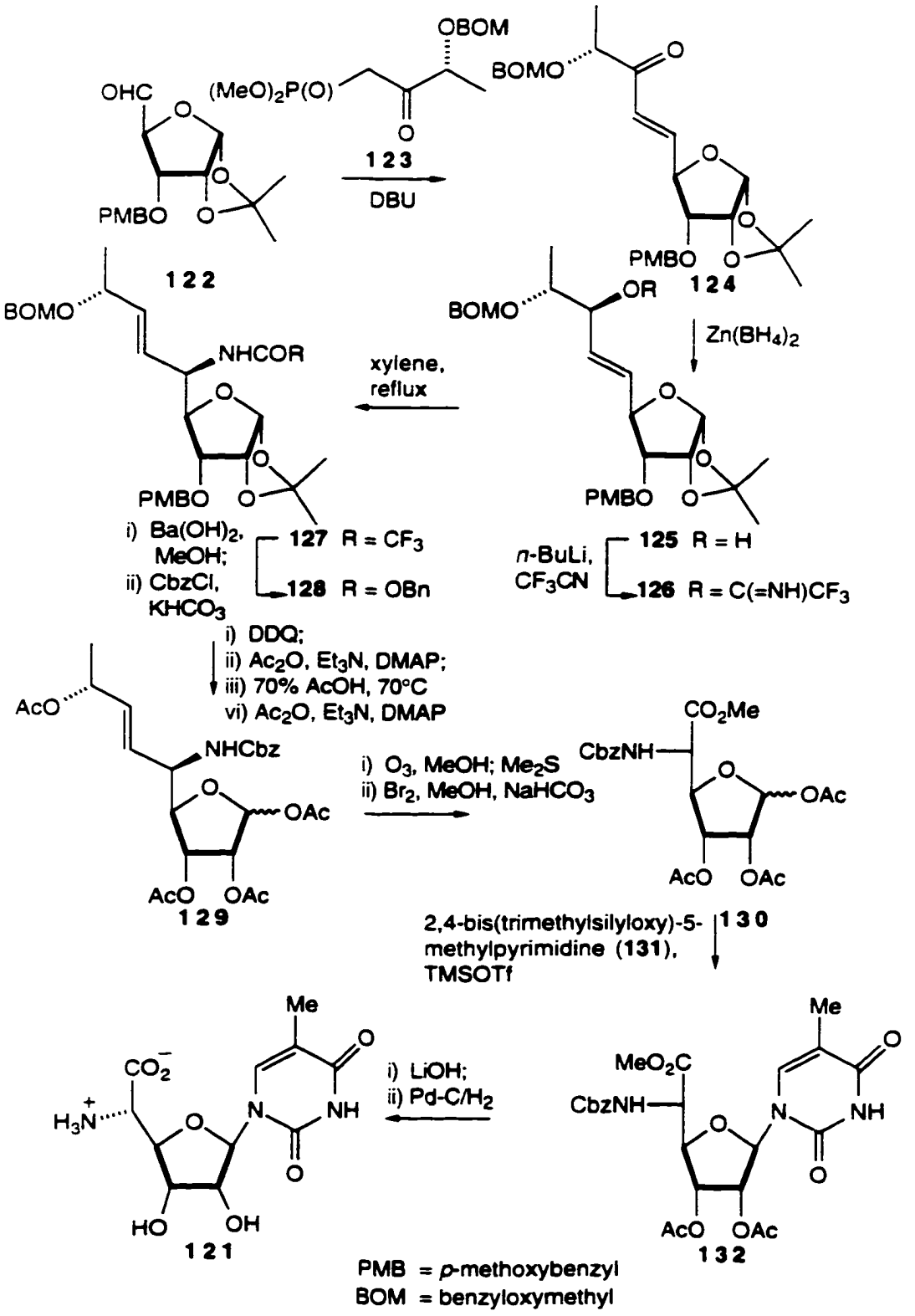
117. Addition of potassium trimethylsilanoate, and ozonolysis then gave the α-hydroxy thioester **118**, which was formed with excellent diastereoselectivity. Alcohol **118** was converted into its triflate (Tf_2O, pyridine, CH_2Cl_2, 0 °C),

and subsequent mild hydrolysis of the thioester gave **119**. The amine functionality was introduced by displacement of the triflate with NaI, followed by NaN_3, to yield azide **120**. Further elaboration of **120** furnished polyoxin C (**121**), with the desired sugar α-amino acid component.



Scheme 32

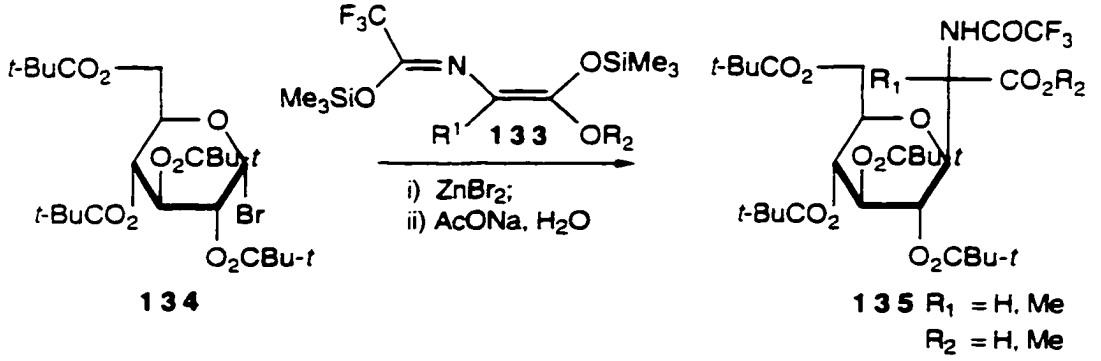
[3,3]-Rearrangement of an allylic trifluoroacetimidate was used by Thomas's group[29e] to make a *C*-glycosyl α-amino acid (**132**) for another synthesis of polyoxin C (Scheme 33). Diacetone D-glucose was converted into its C(3) epimer, which



Scheme 33

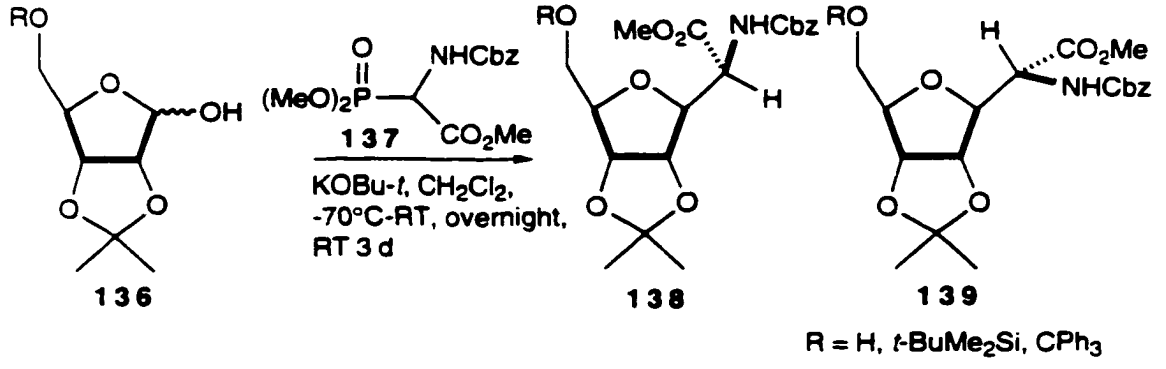
was protected as its *p*-methoxybenzyl ether and hydrolyzed. Oxidative cleavage then gave aldehyde **122**. Condensation of this aldehyde with the ketophosphonate **123** led to enone **124**, which was reduced with $Zn(BH_4)_2$, and treated with trifluoroacetonitrile. These operations gave the trifluoroacetimidate **126**. The latter rearranged cleanly on heating in xylene (8 h) to give the trifluoroacetamide **127**. After conversion of the trifluroacetamide into the carbamate **128**, oxidative removal of the PMB group, acetylation, hydrolysis of the acetonide (which was accompanied by loss of the BOM group), and acetylation gave the tetra-acetate **129**. Ozonolysis, using reductive (Me_2S) work-up, followed by oxidation of the crude aldehyde with Br_2 in MeOH, afforded the methyl ester **130**. This was taken on to the nucleoside **132**, using 2,4-bis(trimethylsilyloxy)-5-methylpyrimidine (**131**), under standard conditions. Finally, deprotection gave polyoxin C (**121**).

A short synthesis of *C*-glycosyl α-amino acid derivatives **135** (Scheme 34) was reported by Simchen and Purkner.[32] Upon treatment of ketene acetals **133** with the α-glycosyl bromide **134** in the presence of $ZnBr_2$, *C*-glycosyl α-amino acid derivatives **135** formed smoothly in 75-91% yield.



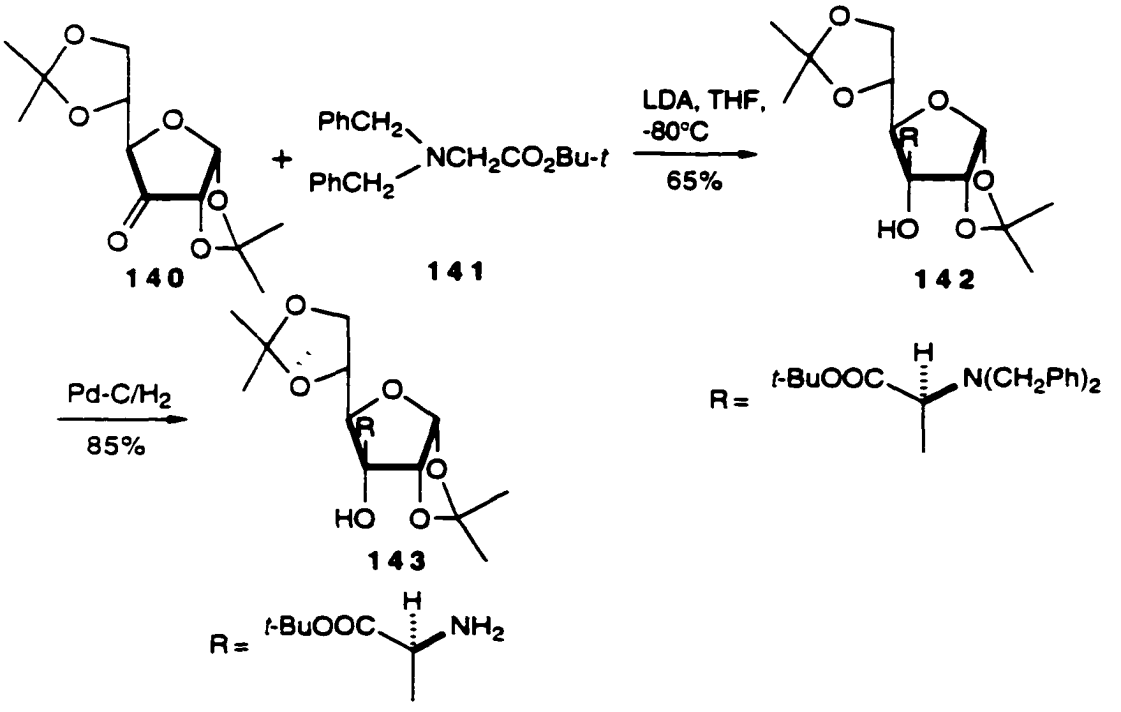
Scheme 34

Lieberknecht and colleagues[33] described a one-pot diastereoselective synthesis of ribofuranosyl glycines **138** (Scheme 35) by condensation of ribofuranoses **136** and phosphoryl glycine ester **137**. They conducted the condensation under different conditions with **136** (R = H, *t*-$BuMe_2Si$, CPh_3), and found that the best chemical yield (88-92%) and best diastereoselectivities (**138**/**139** ~ 85/15) were obtained with R = *t*-$BuMe_2Si$ or CPh_3, when **136** was treated with **137** (KOBu-*t*, CH_2Cl_2, -70 °C to room temperature overnight).



Scheme 35

Another one-step diastereoselective synthesis of *C*-glycosyl α-amino acids was reported by Lavergne's group.[29n] The approach involved the diastereoselective condensation of glycine enolates (generated by the action of LDA on various glycine esters) onto the carbonyl at C(3) of protected α-D-*ribo*hexofuranos-3-ulose **140**. A representative example is shown in Scheme 36. Condensation of the enolate obtained by the action of LDA on *t*-butyl *N,N*-dibenzyl amino acetate **141** on the carbonyl function of **140** led to a single product (**142**) in 65% yield. Removal of the benzyl group by hydrogenolysis gave **143** in 85% yield.

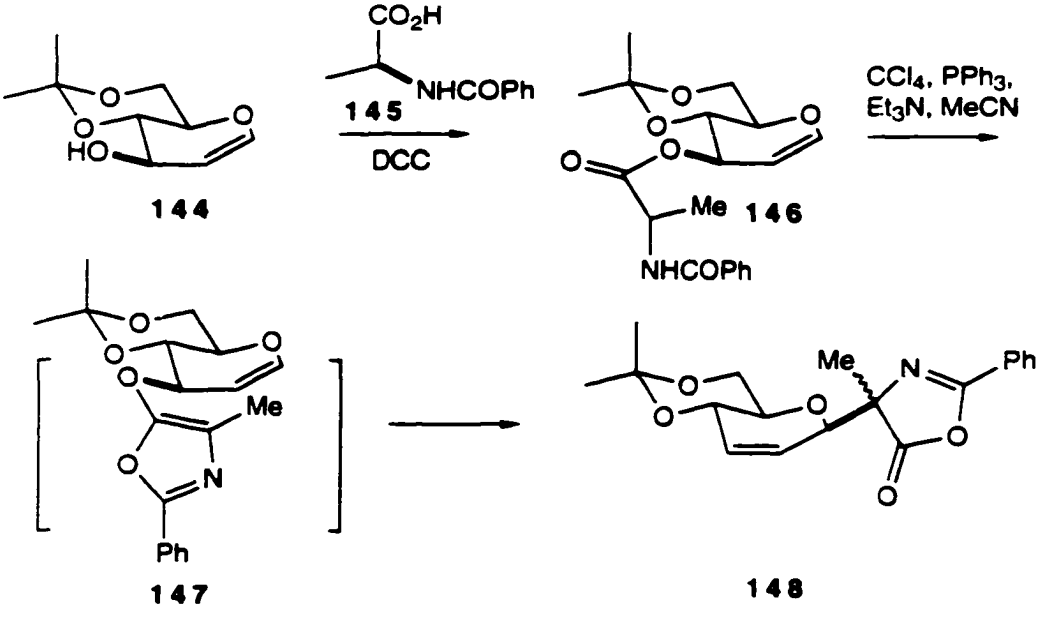


Scheme 36

Colombo and coworkers[34] reported a stereoselective synthesis of *C*-glycopyranosyl α-amino acids based on a

Claisen rearrangement. The synthesis started from glycal **144** (Scheme 37). Esterification of **144** with *N*-benzoylalanine (**145**) gave the allylic ester **146**, and treatment of the ester with $Ph_3P/CCl_4/Et_3N$ as a dehydrating agent afforded, directly, the oxazolone **148** as a mixture of two diastereoisomers in a 3:1 ratio. This process involved formation and rearrangement of an intermediate oxazole **147**.

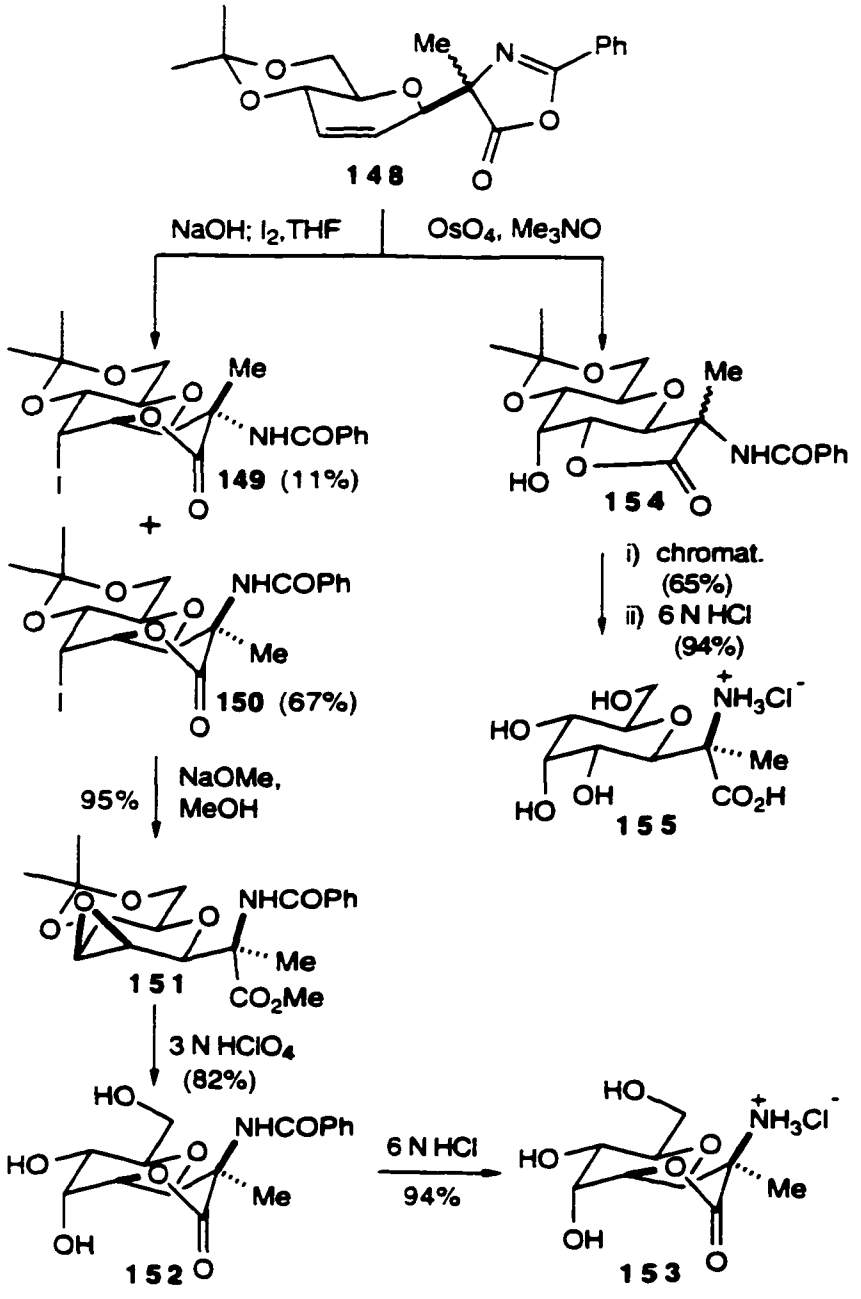
With intermediate **148** in hand, treatment with 1 N NaOH,



Scheme 37

and subsequent addition of I_2, to the resulting carboxylate gave two iodolactones **149** and **150** (Scheme 38). The major isomer (**150**) was converted into epoxy ester **151** by mild methanolysis with MeONa in MeOH. Stereoselective diaxial opening of epoxide **151** with acid afforded trihydroxy lactone **152**, and the final β-*C*-altrosyl-(*R*)-alanine lactone **153** was

obtained from **152** by hydrolysis with 6 N HCl. β-*C*-Allosyl-

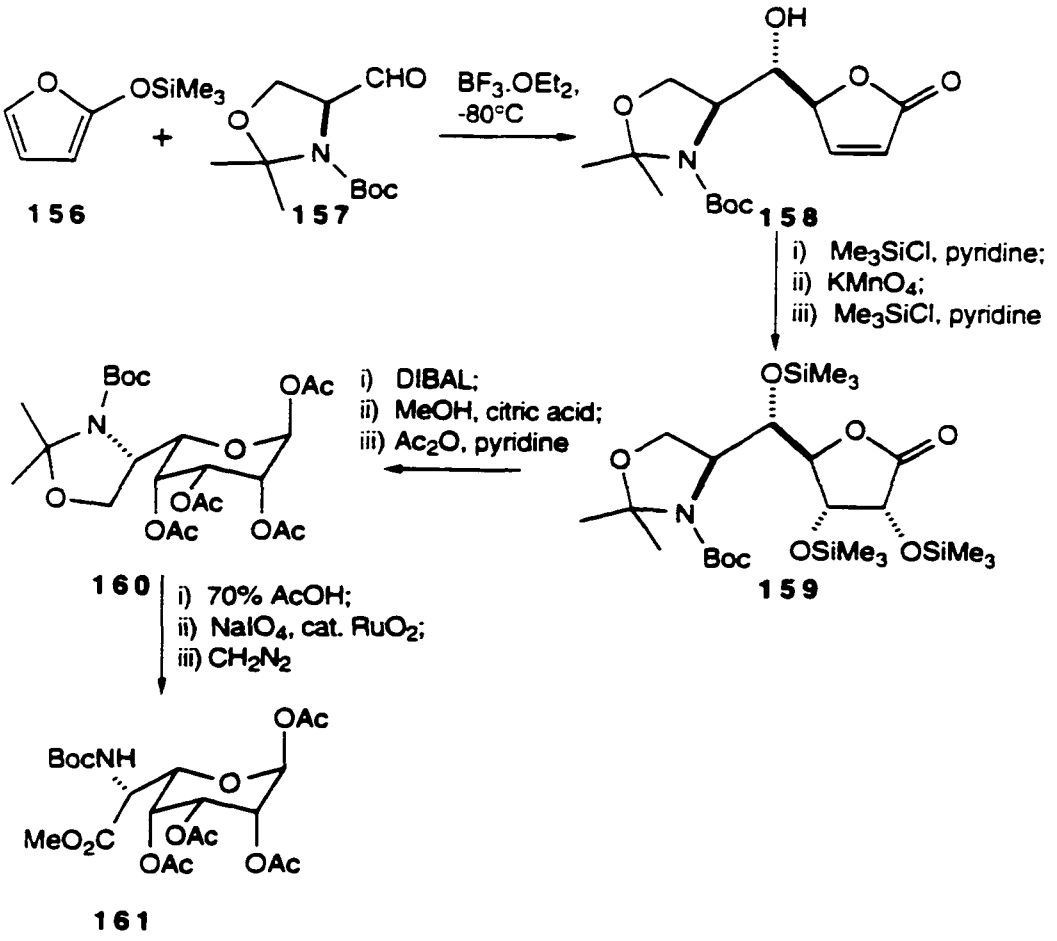


Scheme 38

(*R*)-alanine **155** was synthesized from **148** in two steps by a slightly different approach. Catalytic dihydroxylation with

OsO_4 gave **154** as a 3:1 mixture of diastereoisomers. Separation of the major isomer and subsequent hydrolysis furnished the desired sugar α-amino acid **155**.

Casiraghi and colleagues[35] described the synthesis of several terminal *C*-glycopyranosyl α-amino acids from non-sugar components. They employed enantiomerically pure butenolide intermediates made from the L- or D-serine-derived oxazolidine aldehyde (*cf.* **157** from L-serine in Scheme 39) and 2-(trimethylsiloxy)furan (**156**). The key synthetic steps involved sequential *anti*-selective *cis* dihydroxylation of the butenolide double bond in, for example, **158**, and the clean furanose-to-pyranose ring expansion to construct the sugar skeleton with the proper stereochemistry. The best-yielding example is illustrated in Scheme 39.

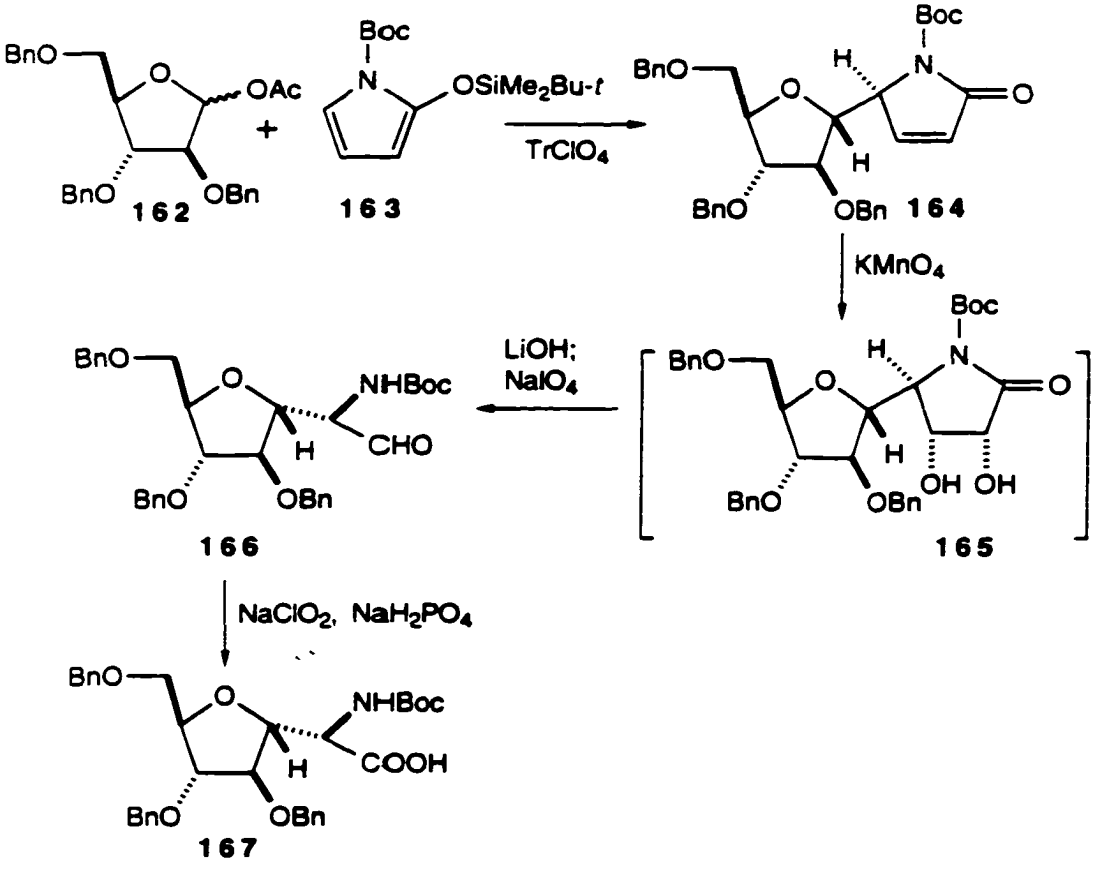


Scheme 39

Stereoselective condensation of **156** with **157** in the presence of $BF_3.Et_2O$ at -80 °C, gave **158** in 88% yield. Protection of the hydroxyl in **158** as a trimethylsilyl ether, *anti cis*-dihydroxylation of the butenolide double bond with $KMnO_4$, and silylation provided **159** in 60% yield over three steps. The ring expansion from **159** was accomplished by three further operations: DIBAL reduction generated a γ-lactol intermediate, and this was followed by citric acid-methanol treatment and subsequent acetylation to provide the desired ring expansion product **160**. Treatment of **160** with 70%

aqueous AcOH resulted in selective removal of the acetonide. The resulting crude primary alcohol was subjected to oxidation with $RuO_4/NaIO_4$ to the expected carboxylic acid, which was finally transformed into the target compound **161**.

Diastereoselective synthesis of *C*-arabinofuranosyl α-amino acid **167** (Scheme 40) was developed by Rassu and

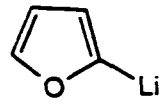


Scheme 40

coworkers.[29f] Trityl perchlorate-promoted addition of *N*-(*t*-butoxycarbonyl)-2-(*t*-butyldimethylsiloxy)pyrrole (TBSOP) **163** to the protected arabinose **162** proceeded with excellent diastereoselectivity to give **164** as the predominant adduct in

62% yield. Dihydroxylation of the double bond with $KMnO_4$, followed by opening of the lactam ring (LiOH, THF) and fission of the vicinal 2,3-diol ($NaIO_4$) gave the crude α-amino aldehyde **166**. Without purification, this material was oxidized to the desired protected amino acid **167** by $NaClO_2/NaH_2PO_4$ in 90% yield.

A recent synthesis of *C*-glycosyl α-amino acids was reported by Dondoni and coworkers.[29m] The approach involved stereoselective addition of 2-furyllithium (**168**) or 2-thiazolyllithium (**169**) (Figure 1) to various sugar nitrones.



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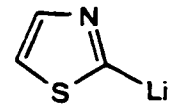


169

Figure 1 Structures of **168** and **169**

The reaction occurred with opposite diastereofacial selectivity depending on whether the free nitrone or the diethylaluminum chloride-precomplexed derivative[36] is employed. The resulting furyl or thiazolyl hydroxylamines are reduced to amines by the action of $TiCl_3$. From the resulting compounds the amino acids are released by oxidative cleavage of the furan or thiazole ring to carboxylic acids. Compounds have been prepared wherein the α-amino acid moiety is installed at C(4) and C(1) of furanoses (*ribo*, *manno*, *xylo*, and *lyxo*) and at C(5) and C(1) of a pyranose (*galacto*). The sugar nitrones that were examined are shown in Figure 2.

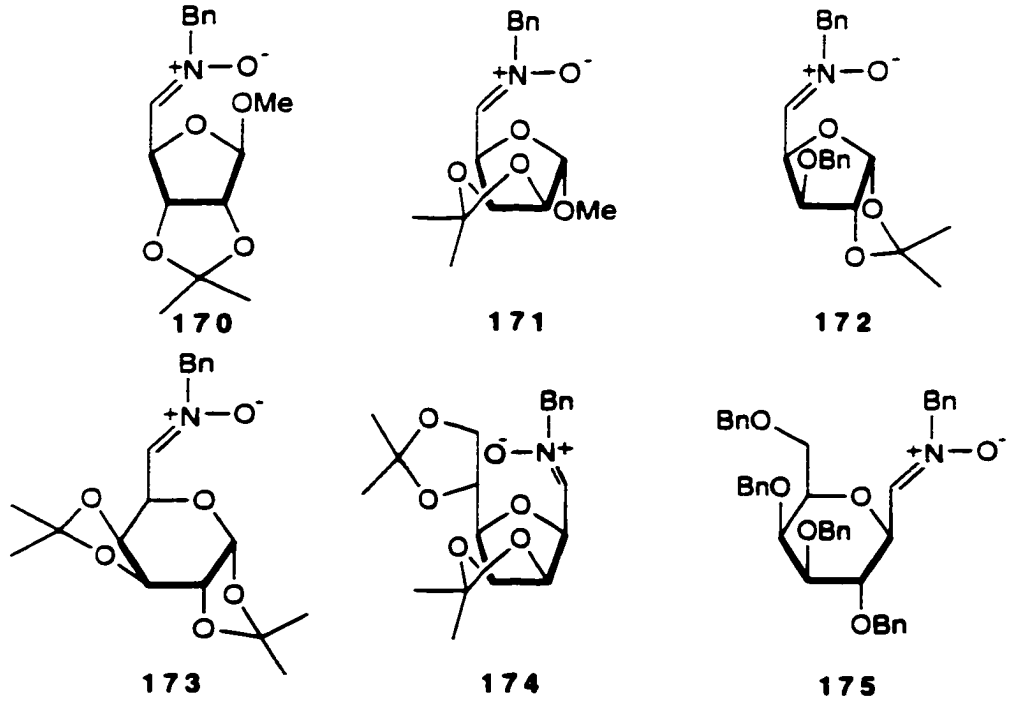
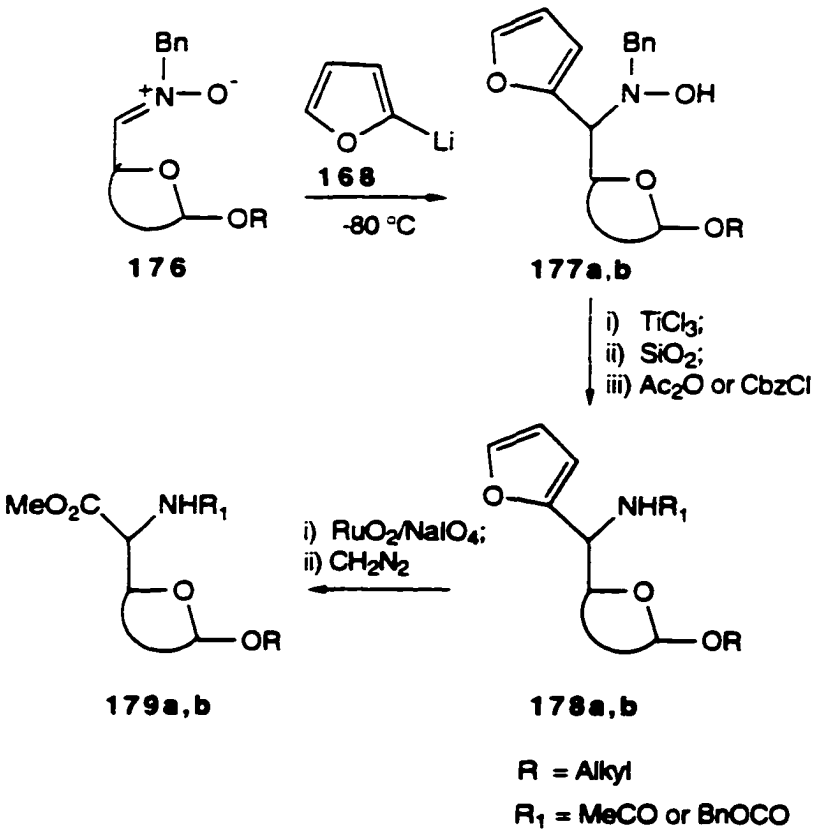


Figure 2 Structures of various nitrones

These nitrones all reacted with **168** or **169**. In the case of **168**, for example, they gave the hydroxylamines **177a** and **177b** as two diastereomers (Scheme 41). The ratio of **177a** and **177b** depends on whether the free nitrones or the diethylaluminum chloride-precomplexed derivatives are used.[36] The thiazole organometallic **169** reacted similarly. Treatment of **177a** or **177b** first with $TiCl_3$ and then with wet silica gel, followed by acylation with acetic anhydride or benzyl chloroformate, provided **178a** or **178b**. Oxidation of **178a** or



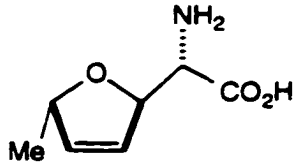
Scheme 41

178b with $RuO_2/NaIO_4$, and treatment of the resulting carboxylic acids with diazomethane afforded the desired sugar amino acid esters **179a** or **179b**.

In conclusion, though various routes have been developed for the preparation of *C*-glycosyl α-amino acids, new general, efficient and stereoselective methods are still needed. Since *C*-glycosyl α-amino acids are such important class of compounds, all the methodologies have their own advantages and disadvantages.

C. Synthetic Routes to (+)-Furanomycin

The bacterial metabolite furanomycin (**180**)[37,38] (Figure 3) is an antibiotic substance that is a competitive antagonist of L-isoleucine.[37] It also inhibits the growth of



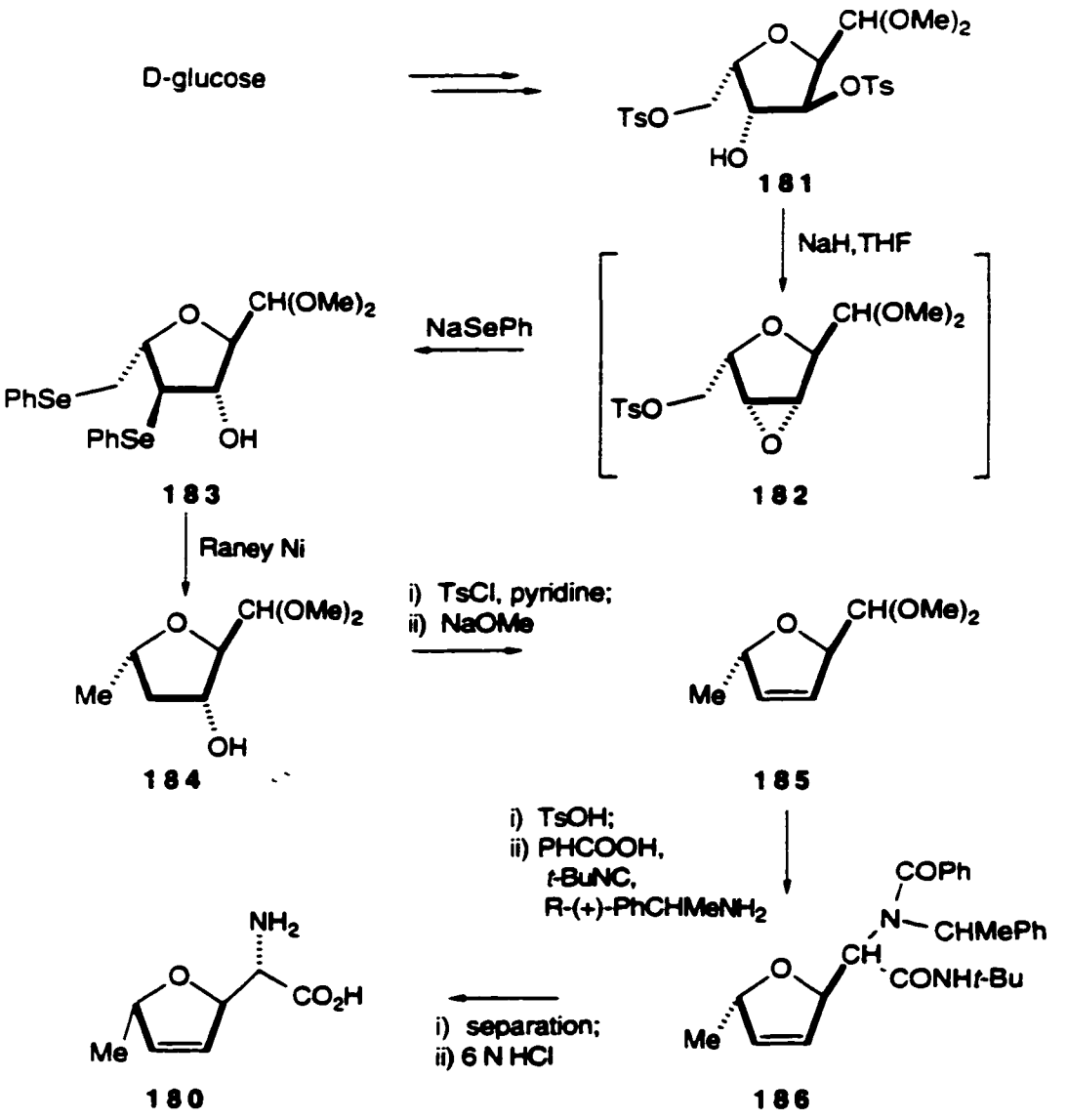
180

Figure 3 Structure of (+)-furanomycin (**180**)

T-even coliphage. The gross structure was established by degradative and spectroscopic studies,[37] but the stereochemical assignment was made on the basis of total synthesis,[39a,b] and later corroborated by X-ray analysis of the derived *N*-acetate.[40] Only two synthetic routes to (+)-furanomycin (**180**) had been published before we completed our own synthesis. Joullié and coworkers[39a,b] reported the first total synthesis of **180** (Scheme 42) by using the Ugi four-component condensation as a key reaction. The synthesis involved generating the functionalized tetrahydrofuran derivative **181** from D-glucose,[41] and this was then induced to undergo a series of deoxygenations and the incorporation of an amino acid unit.

The presence of the tosylate in **181** allowed the desired deoxygenation reaction via epoxide **182**. The bis(selenide) derivative **183** was obtained in quantitative yield from **182**. Removal of phenylseleno groups from **183** by Raney nickel,

followed by deoxygenation of the resulting alcohol **184**, via its tosylate, gave **185**. After introduction of unsaturation in this way, the sensitive aldehyde obtained from **185** by mild hydrolysis was subjected to the Ugi four-component reaction



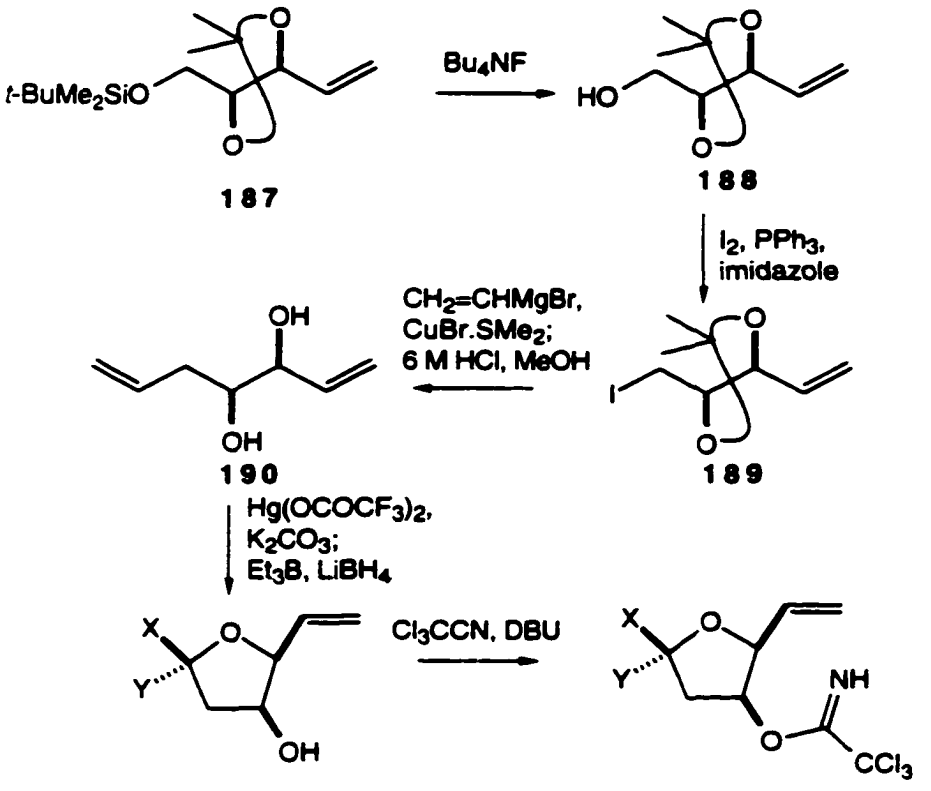
Scheme 42

to provide a 1:1 mixture of epimeric amino acid derivatives **186**. The desired isomer was separated and converted into

(+)-furanomycin (**180**) by deprotection.

The most recent enantioselective synthesis of (+)-furanomycin was reported by Kang and Lee.[42] The key steps involved the mercury cation-mediated cyclization of γ-hydroxy alkene **190** and, as described below, of the homoallylic trichloroacetimidate **193**, the last operation serving to generate the *trans*-2,5-disubstituted tetrahydrofuran and the (α*S*)-amino acid side chain.

The synthesis started from the known silyl ether **187** (Scheme 43), prepared from dimethyl L-tartrate,[43] was desilylated using Bu_4NF, and the resulting alcohol **188** was



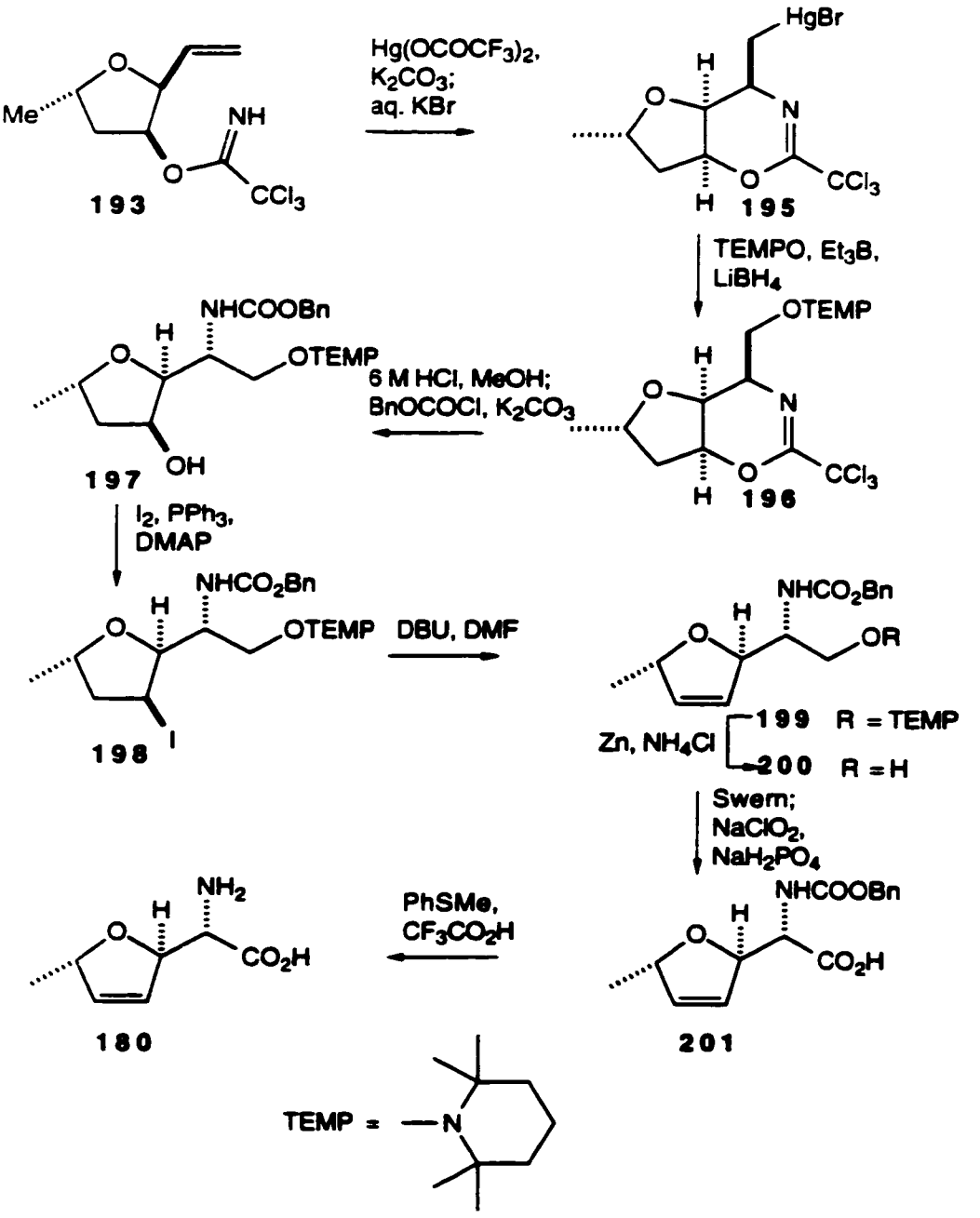
191 X = H, Y = Me
192 X = Me, Y = H
193 X = H, Y = Me
194 X = Me, Y = H

Scheme 43

treated with I_2, PPh_3 and imidazole to yield the corresponding iodide **189**. Treatment of **189** with vinylmagnesium bromide in the presence of $CuBr.SMe_2$ gave the expected diene acetonide, and hydrolysis of the acetonide with methanolic HCl provided diene diol **190**. This γ-hydroxy alkene was subjected to cyclization with $Hg(OCOCF_3)_2$ in the presence of K_2CO_3 in THF at -78 °C to afford a mixture of *trans*- and *cis*-2,5-disubstituted mercuric tetrahydrofuran derivatives. These were reduced *in situ* with Et_3B and $LiBH_4$ at -78 °C to produce an inseparable 9:1 mixture of **191** and **192**. This mixture was converted into the readily separable trichloroacetimidates **193** and **194**.

With **193** in hand, the second key mercury cation-mediated cyclization was performed (Scheme 44) with $Hg(OCOCF_3)_2$ in the presence of K_2CO_3 in THF at 0 °C. This experiment yielded only the desired organomercury bromide **195** in 95% yield after work-up with aqueous KBr. Exposure of **195** to TEMPO and $LiBH_4$ in the presence of Et_3B gave the oxidized product **196**. Compound **196** was then hydrolyzed with 6 M HCl and the unmasked amino alcohol was protected with benzyl chloroformate to afford carbamate **197**. Replacement of the hydroxyl in **197** by iodine, and elimination of HI from the resulting iodide (**198**) gave **199**. The TEMP group of **199** was reductively removed with Zn dust to yield the primary alcohol **200**. Swern oxidation, followed by treatment with $NaClO_2/NaH_2PO_4$, afforded the carboxylic acid **201**. Finally, removal of the BnOCO group with thioanisole in TFA furnished

(+)-furanomycin **180**.

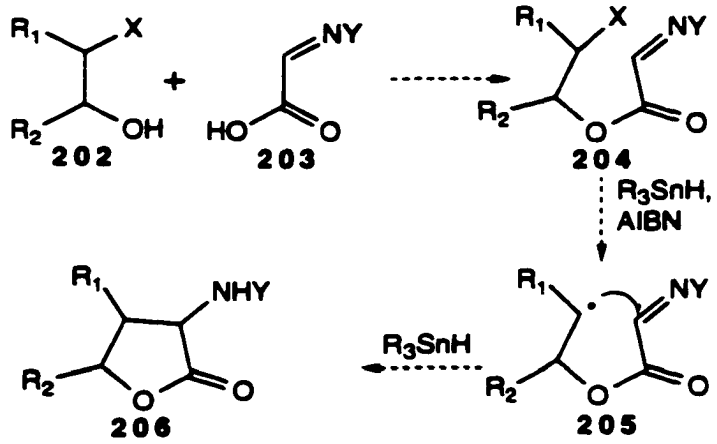


Scheme 44

II. Results and Discussion

A. Preparation of α-(2,2-Diphenylhydrazino)- and α-(Benzyloxyamino)-Lactones

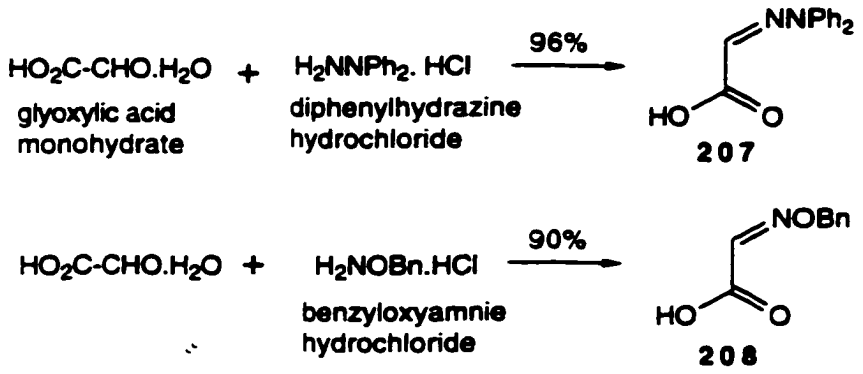
Formation of carbocycles by addition of a carbon radical onto a carbon-nitrogen double bond is a well-established process, as described in the previous section.[2-23] During exploratory studies to effect such additions intermolecularly, we decided to try an intramolecular version. It was convenient to attempt to make lactones with the α-position containing a nitrogen functionality. Such a process has not been reported. Lactones of the type we had in mind (see Scheme 45), should be convertible into natural



Scheme 45

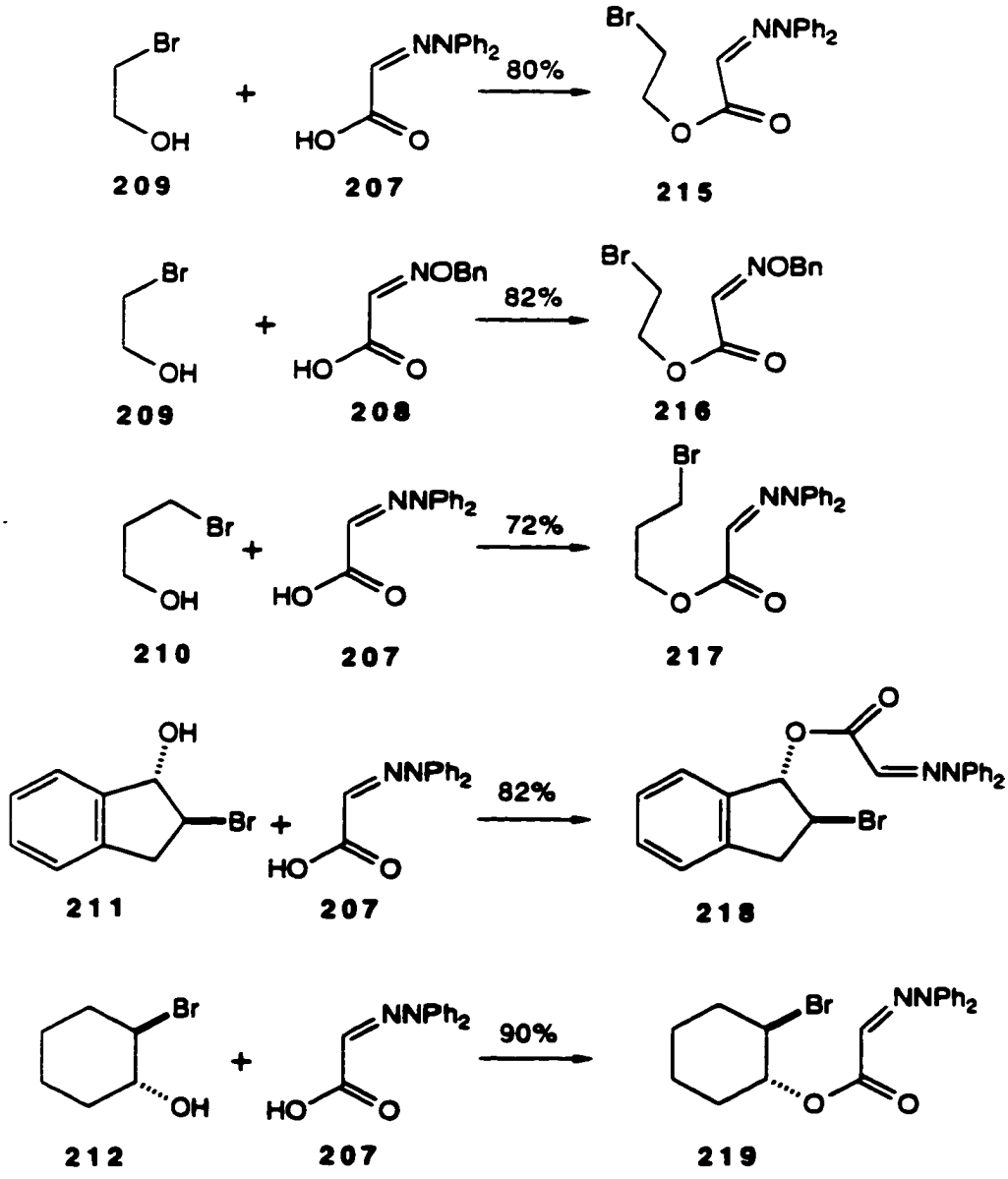
and unnatural amino acids, and a particularly useful possibility is that *C*-glycosyl α-amino acids might be

accessible if such lactones are fused onto carbohydrates. Our approach to the lactones is shown in Scheme 45. Addition of a carbon radical onto *O*-benzyloximes or diphenylhydrazones to make carbocycles had been studied previously.[4,7b,8,17,21] We considered that glyoxylic acid diphenylhydrazone and the corresponding *O*-benzyloxime may be a good choice for making lactones by the above route. Both compounds **207** and **208** can be prepared according to the literature procedure (Scheme 46).[44a] Luckily, glyoxylic acid diphenylhydrazone[44b](**207**) (Scheme 46) can also be made by a similar route to **208** in 96% yield. Both **207** and **208** are stable, crystalline reagents.



Scheme 46

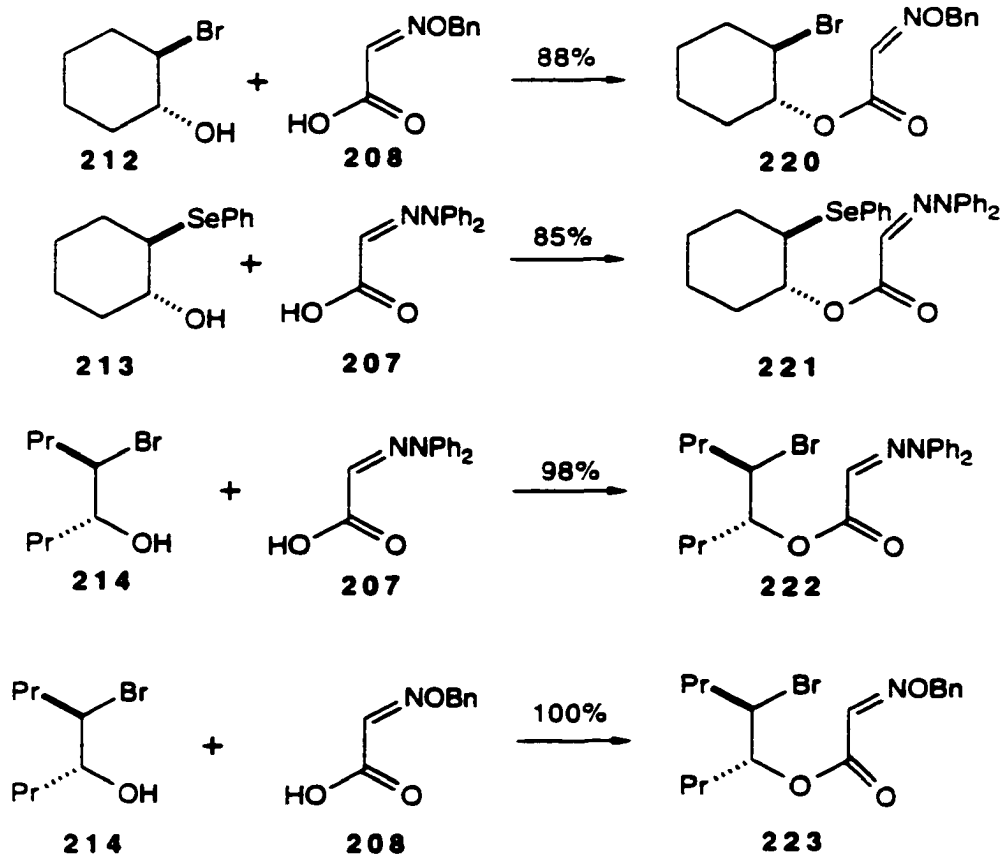
One of the other starting materials in our approach is a β-bromo or β-(phenylselenenyl) alcohol (**202**) (see Scheme 45). Several of these, such as $BrCH_2CH_2OH$ (**209**), $BrCH_2CH_2CH_2OH$ (**210**), and 2-bromoindanol (**211**) are commercially available (Scheme 47). *trans*-2-Bromocyclohexanol (**212**),[45] *trans*-2-(phenylselenenyl)cyclohexanol (**213**)[46] and 5-bromo-4-octanol (**214**)[47] (see Scheme 48) were made by the literature



Scheme 47

procedures. Each of these alcohols was converted into the corresponding radical precursor (see **204**, Scheme 45) by esterification. All the esterification experiments were done by addition of DCC (1.1 equiv) and DMAP (0.1 equiv) to a stirred solution of the alcohol (1.1 equiv) and reagent **207**

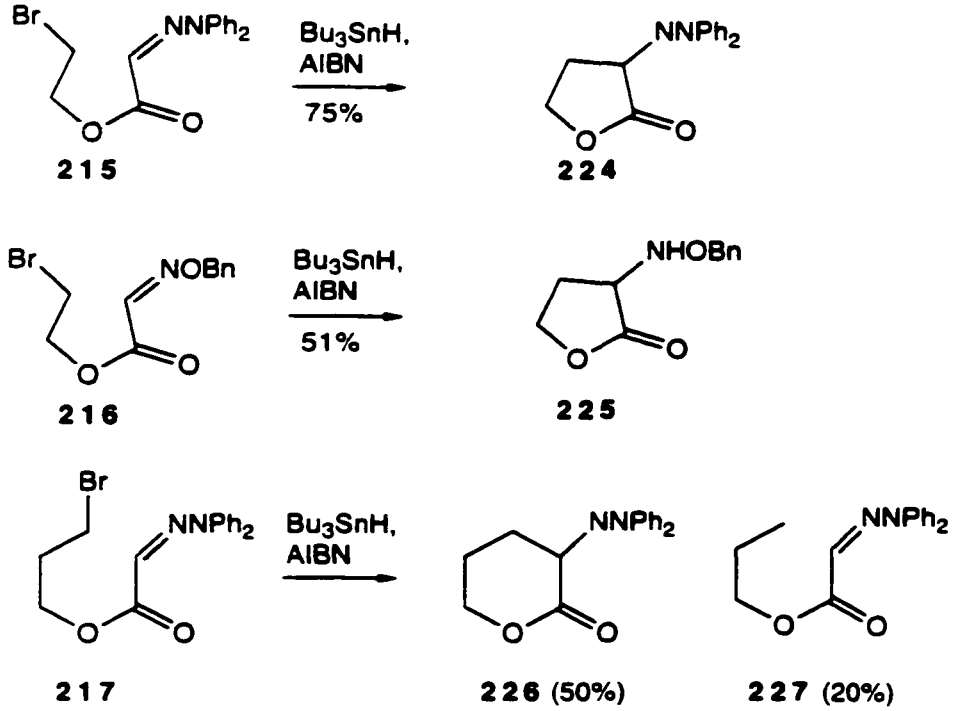
or **208** (1 equiv) in CH_2Cl_2. After 6-12 h at room temperature, the esters could be isolated in good yields shown in Schemes 47 and Scheme 48.



Scheme 48

The radical cyclization step shown for **205** (Scheme 45) requires the indicated proximity of the carbon radical and the carbon-nitrogen double bond; this conformation is adequately accessible because of the sufficiently low rotational barrier about an ester C(O)-O single bond.[48] As expected, when **215** and **216** (Scheme 49) were treated with Bu_3SnH and AIBN (slow addition) in refluxing benzene, the

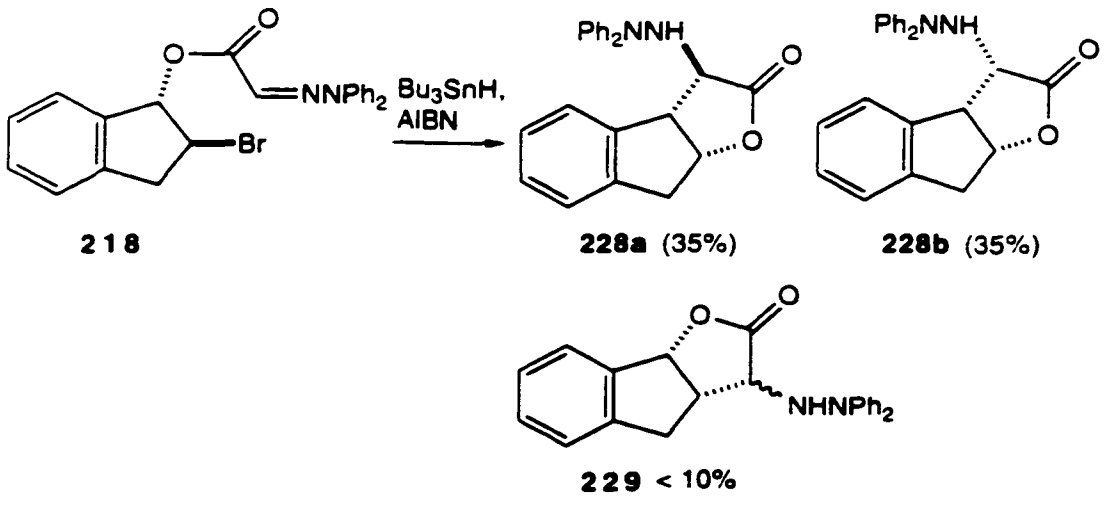
corresponding lactones **224** and **225** were formed by 5-*exo*-closure, the respective yields being 75% and 51%. However, radical cyclization of **217** by 6-*exo*-closure was less efficient, compared to **215**, and gave 50% cyclization product **226** plus 20% of the simple reduction product **227**.



Scheme 49

When **218** (Scheme 50) was submitted to the radical cyclization, we isolated compounds **228a** and **228b** in 70% yield, and a small amount of a mixture **229**. Spectral analysis of **228a** and **228b** revealed the structure of the compounds; they must have arisen from the intervention of a 1,2-acyl migration[49] which, in this case, must be especially fast because of the fact that it leads – via a readily accessible and favorable geometry – to a benzylic radical.

The stereochemistry of **228a** and **228b** was assigned by NOE measurements (see experimental section).



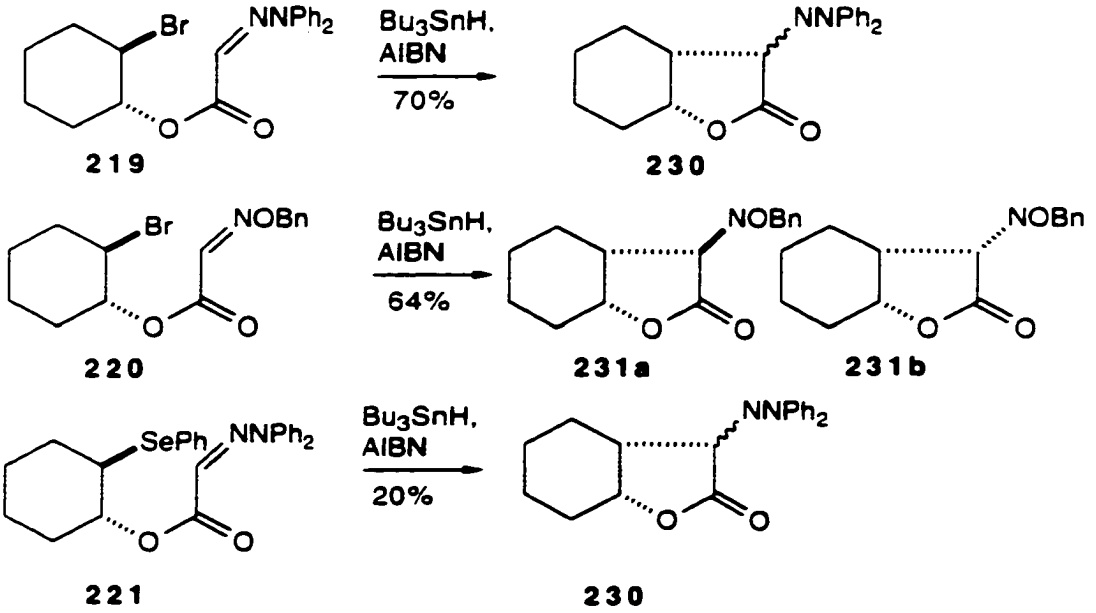
218 **228a** (35%) **228b** (35%)

229 < 10%

Scheme 50

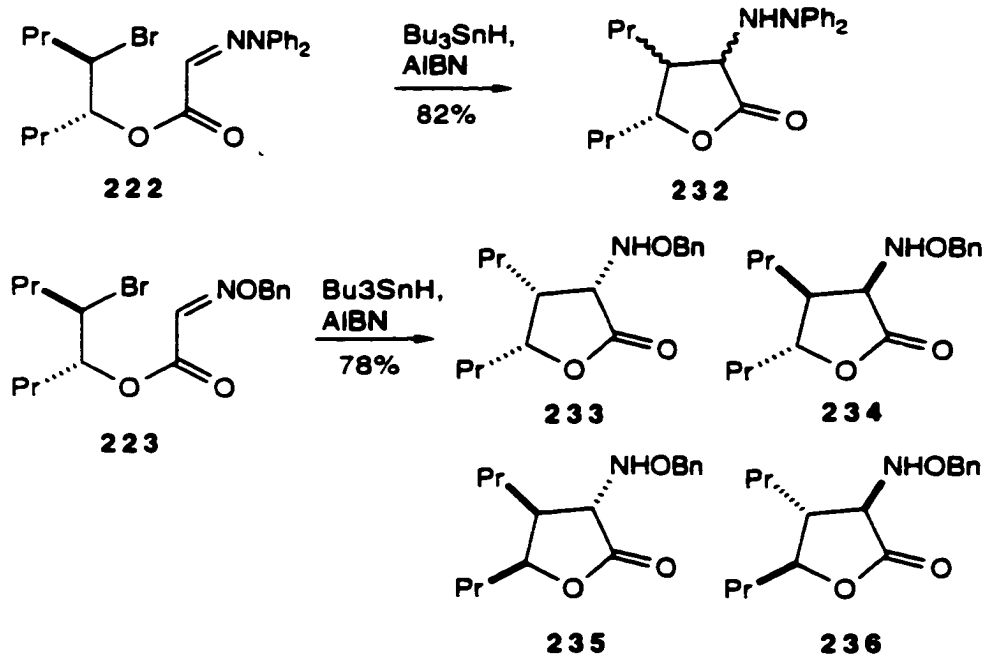
Radicals generated from six-membered rings were also examined. Scheme 51 shows that selenide **221** gave the cyclization product **230** in low yield. Bromides **219** and **220** cyclized in good yield. In the case of **219**, a 1:1 mixture (**230**) of two isomers was formed, and with **220** a 1:1 separable mixture of **231a** and **231b** was obtained. It is not clear why the selenide **221** gave a low yield.

The addition of the secondary open chain carbon radical generated from **222** (Scheme 52) and **223** onto C=N double bond systems was also included our investigation. The hydrazone **222** gave a 2:3:2:3 mixture (**232**) of four isomers. The *O*-



Scheme 51

benzyloxime ether **223** afforded **233**, **234**, **235**, **236** in a ratio of 1:3:1:2. The stereochemistry of **233-236** was

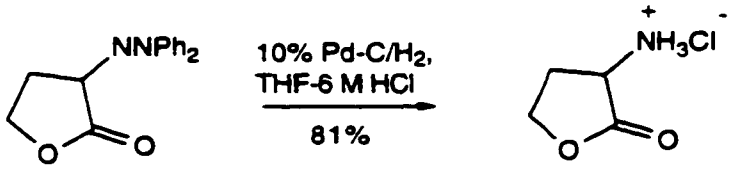


Scheme 52

assigned by NOE measurements (see experimental section).

The above experimental results demonstrated the generality of the methodology for preparation of α-(2,2-diphenylhydrazino)- and α-(benzyloxyamino)lactones by radical cyclization. Both the esterification (**202** + **203** → **204**) and the radical closure (**204** → **205** → **206**) generally proceeded in good yield. The reaction produced lactones bearing an α-nitrogen substituent. When the starting alcohol **202** is cyclic, the stereochemical outcome at the newly-created ring junction is determined by the stereochemistry of the original hydroxyl-bearing carbon in **202**, but for both cyclic and non-cyclic starting esters the degree of stereoselectivity α to the lactone carbonyl is low.

α-Hydrazino- and α-(hydroxyamino)-γ-lactones are not well-known; neither are the corresponding δ-lactones. In principle, these α-substituted lactones can be modified in various ways and, in the case of **224** (Scheme 53), for example, hydrogenolysis (10% Pd-C, THF-aqueous HCl 6 M) gave homoserine γ-lactone hydrochloride (**237**)[50] (81% after crystallization from acetone).



224 **237**

Scheme 53

B. Synthesis of *C*-Glycosyl Lactones and α-Amino Acids

Since the above general methodology had been established, we next wanted to extend our method to synthesis of carbohydrate-fused lactones, so as to provide an entry to *C*-glycosyl α-amino acids by further elaboration.

1. Preparation of Starting Materials

The starting materials for the synthesis of the sugar-based series were modified carbohydrates bearing a hydroxyl group. These were each esterified to the corresponding hydrazono esters with reagent **207** in the presence of DCC and DMAP. The carbohydrate-derived alcohols we prepared are shown in Figure 4, and the preparative routes are discussed below.

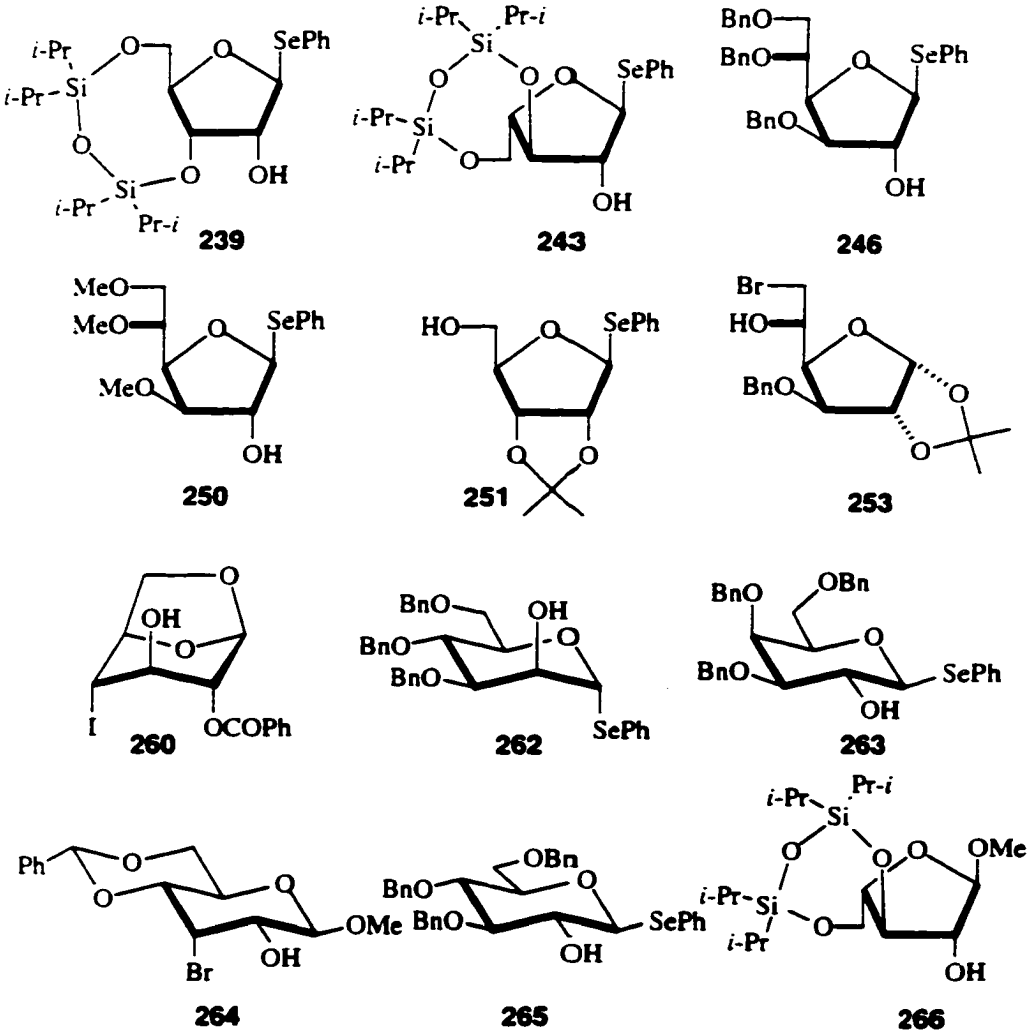
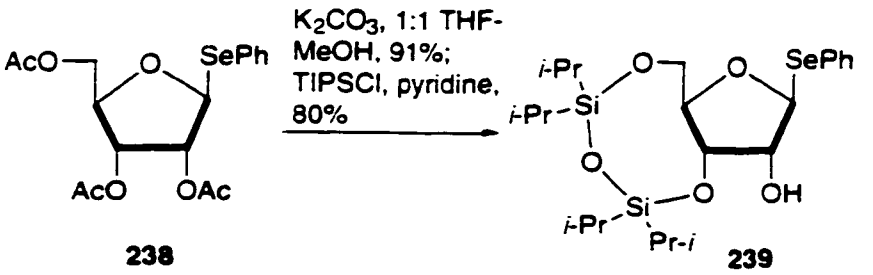


Figure 4 Structures of the carbohydrate-derived alcohols

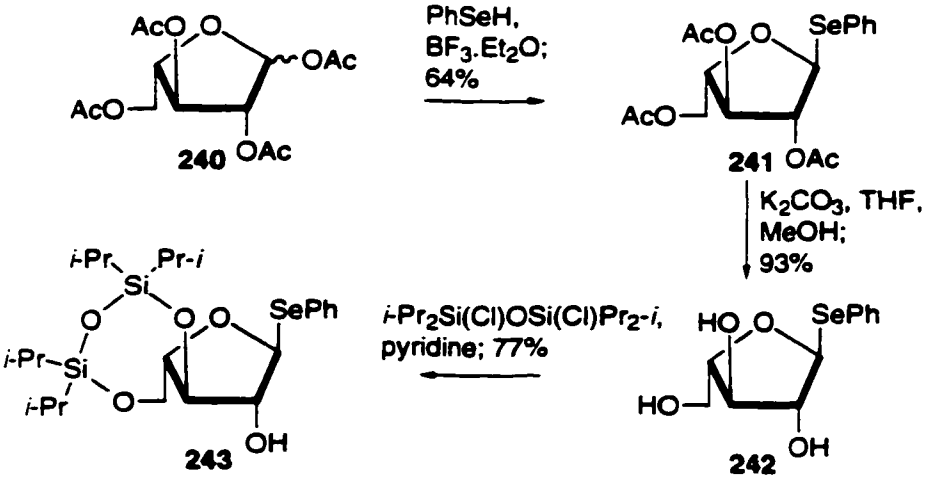
Treatment of commercial tetra-*O*-acetyl-β-D-ribofuranose with PhSeH in the presence of $BF_3 \cdot Et_2O$[51] gave (92%) the β-phenyl selenide **238**[52] (Scheme 54), from which **239** was formed by solvolysis (K_2CO_3, THF-MeOH; 91%) and silylation [*i*-$Pr_2Si(Cl)OSi(Cl)Pr_2$-*i*, pyridine; 80%].

L-Arabinose was converted by a known procedure[53] into its tetraacetate **240** (as a mixture of anomers) (Scheme 55) which, on treatment with PhSeH/$BF_3 \cdot Et_2O$ gave α-selenide **241** (64%).



Scheme 54

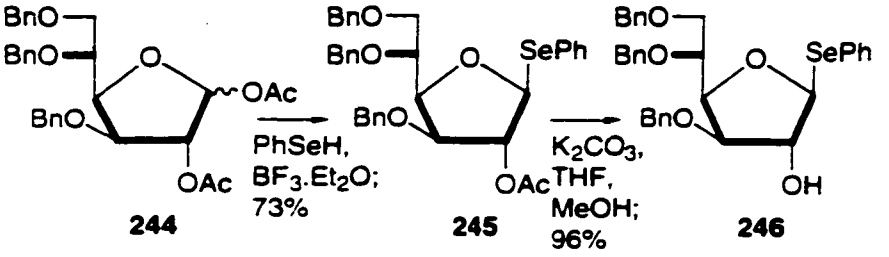
Solvolysis (**241** → **242**, K_2CO_3, THF-MeOH; 93%) and silylation [*i*-$Pr_2Si(Cl)OSi(Cl)Pr_2$-*i*, pyridine; 77%] afforded **243**.



Scheme 55

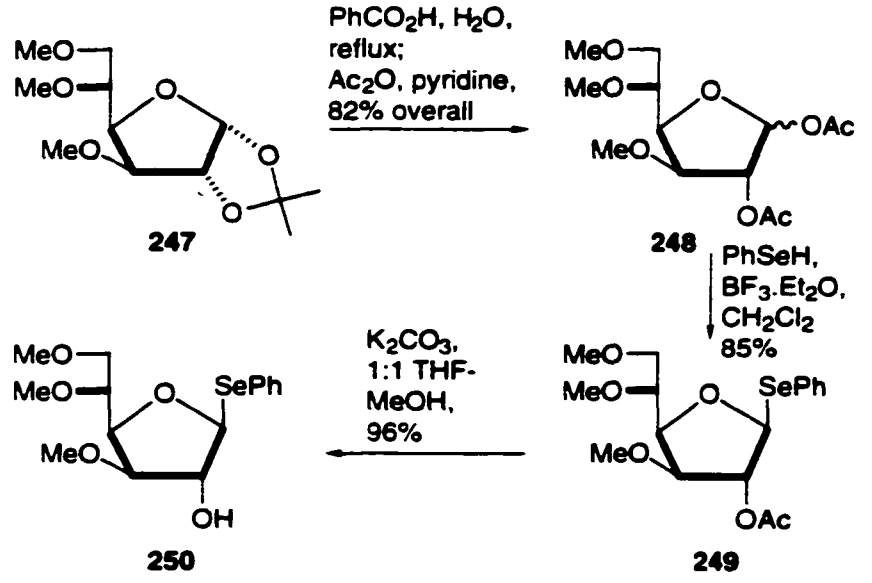
A mixture of the anomeric diacetates **244** (Scheme 56), made from diacetone glucose,[54] afforded the β-selenide **245** on treatment with $PhSeH/BF_3 \cdot Et_2O$ (73%), and alcohol **246** was then obtained by base hydrolysis (**245** → **246**, K_2CO_3, THF-MeOH; 96%).

Diacetone glucose was also used (Scheme 57) to synthesize **250**. Selective deprotection of diacetone glucose



Scheme 56

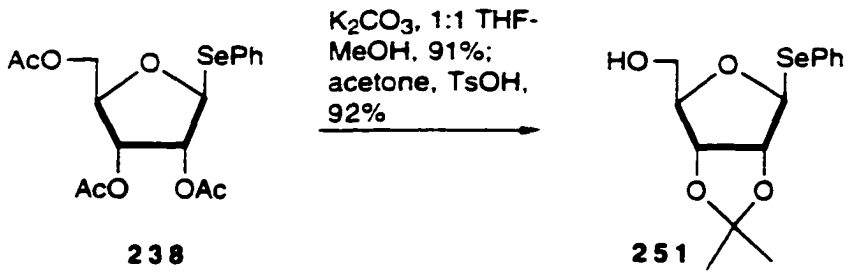
at C(5)-C(6) by acid hydrolysis,[55] and tris-methylation[56] (Me_2SO_4, DMSO, NaOH; 82% overall), gave **247** (Scheme 57).[57] Mild hydrolysis ($PhCO_2H$ in water at reflux), followed by acetylation took the route as far as **248** (82%). This was treated with $PhSeH/BF_3.Et_2O$ (**248** → **249**, 85%), and the required alcohol was again obtained by base hydrolysis (**249** → **250**, K_2CO_3, THF-MeOH; 96%).



Scheme 57

Alcohol **251** (Scheme 58) was made by hydrolysis (K_2CO_3,

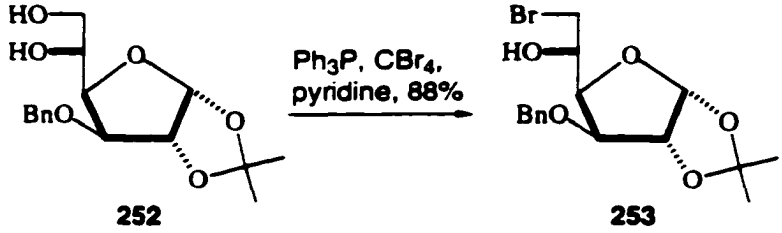
THF-MeOH; 92%) and ketalization (acetone, TsOH; 92%) of selenide **238**.



238 **251**

Scheme 58

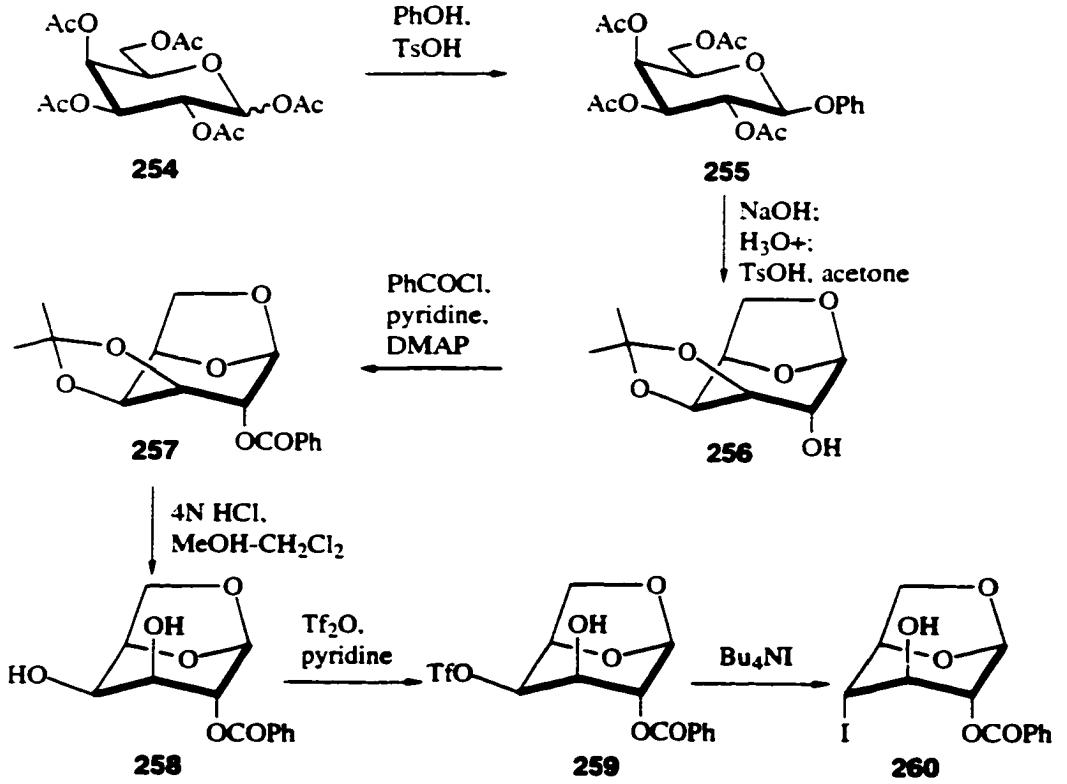
Diol **252** (Scheme 59) was prepared by the literature procedure[58] in two steps from diacetone glucose, and treatment with Ph_3P/CBr_4 served to convert it into **253** (88%).



252 **253**

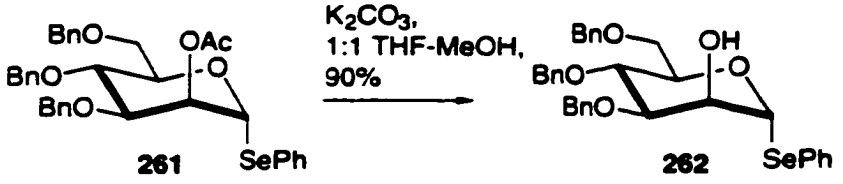
Scheme 59

β-D-Galactose pentaacetate **254** (Scheme 60) was converted into **260** by literature procedures.[59]



Scheme 60

The alcohol **262** (Scheme 61) was made from the known acetate **261**[60] by hydrolysis (K_2CO_3, THF-MeOH; 90%).

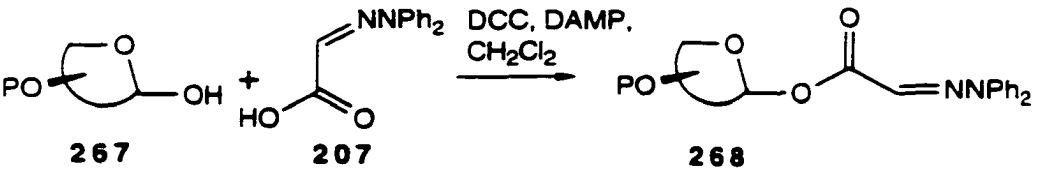


Scheme 61

The alcohols **263**,[61] **264**,[62] **265**,[63] **266**[64] (see Figure 4, page 56) were prepared by literature procedures.

The radical precursors used in my work were prepared directly from the carbohydrate alcohols (Scheme 62) by

esterification with reagent **207** in the presence of DCC and DMAP, except for **266**, in which case an indirect route was used, as described below.



267 **207** **268**

Scheme 62

The hydrazono esters made by the general Scheme 62 are shown in Figure 5.

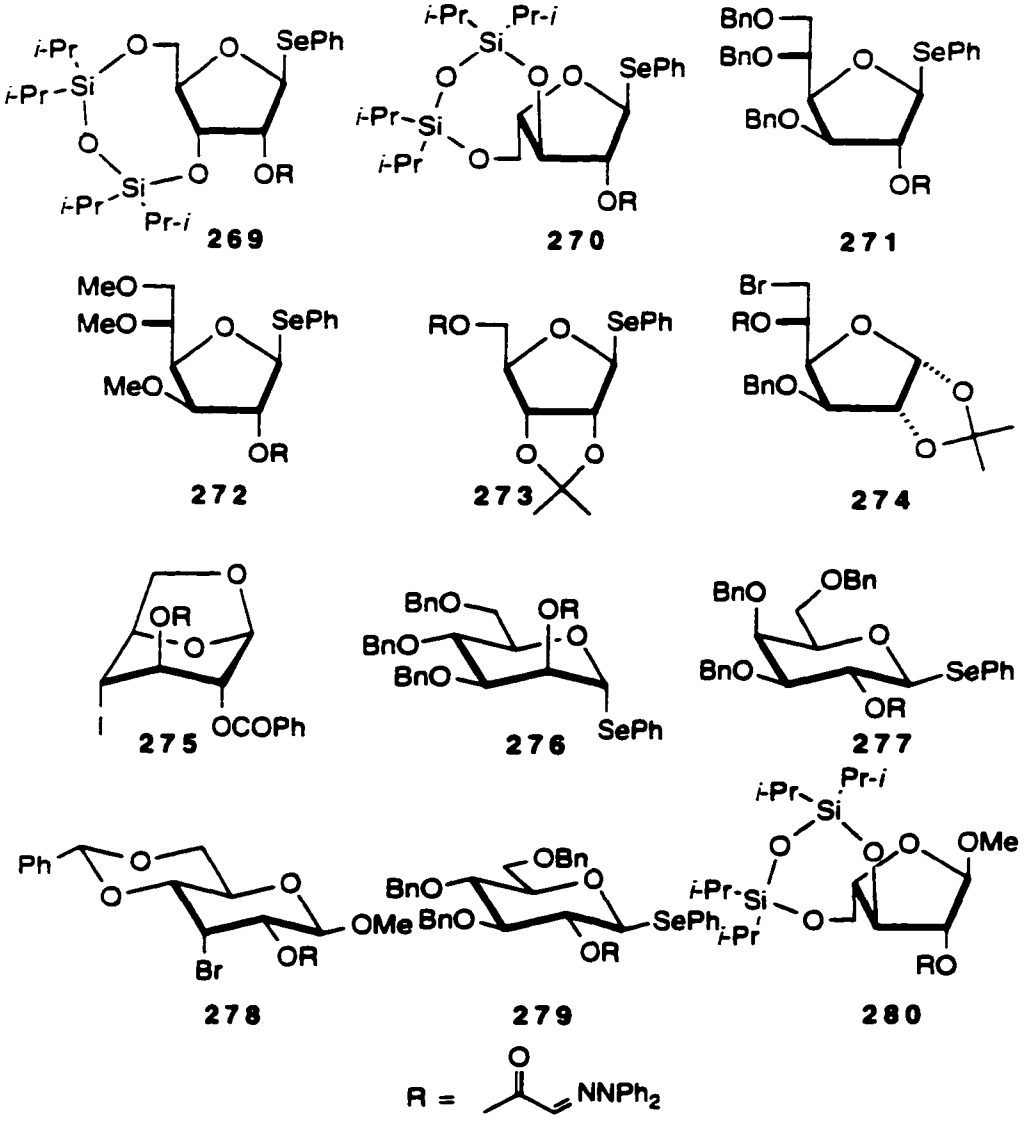


Figure 5 Structures of the hydrazono esters

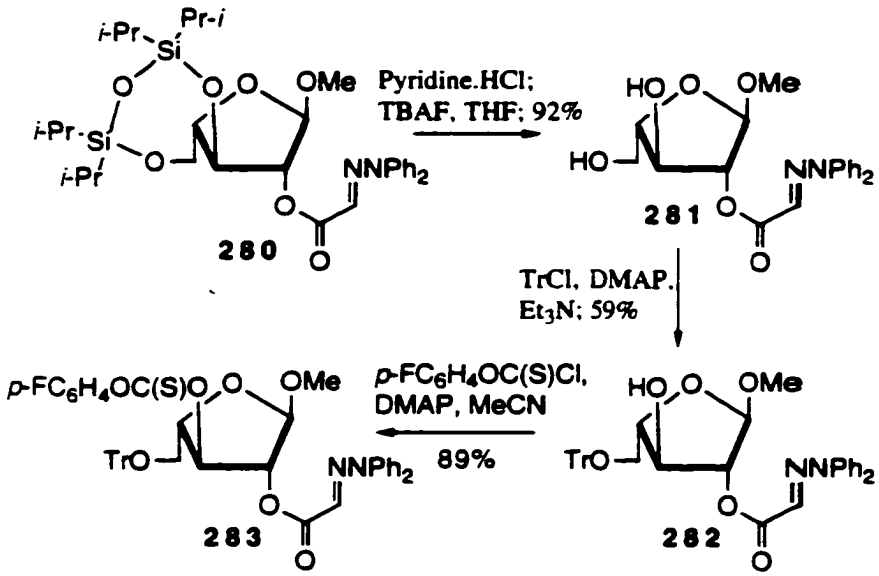
The yields are listed in Table 1. In every case the reaction was efficient, the yields always being at least 90%.

The hydrazono ester **280** had to be transformed into **283** (Scheme 63) before it could be used as a radical precursor.

Table 1 Synthesis of the hydrazono esters

alcohols	**239**	**243**	**246**	**250**	**251**	**253**	**260**	**262**	**263**	**264**	**265**	**266**
esters	**269**	**270**	**271**	**272**	**273**	**274**	**275**	**276**	**277**	**278**	**279**	**280**
yield(%)	94	90	97	93	92	96	91	92	90	91	94	90

Desilylation of **280** (Bu_4NF, 92%) in the presence[65] of pyridinium hydrochloride gave **281**. The proton source is necessary in order to suppress acyl migration, and the fluoride source must be added slowly. Selective tritylation (TrCl, Et_3N, DMAP; 59%) then gave **282**, from which **283** was obtained by acylation with *p*-$FC_6H_4OC(S)Cl$ (DMAP, MeCN; 89%).



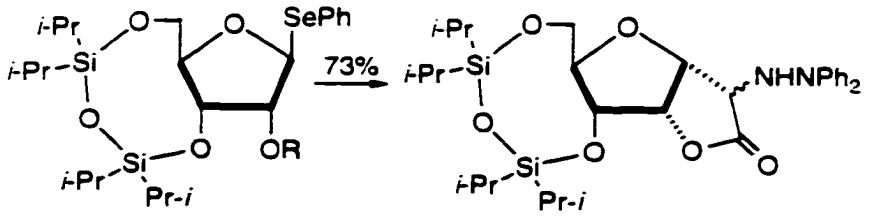
Scheme 63

2. Radical Cyclizations

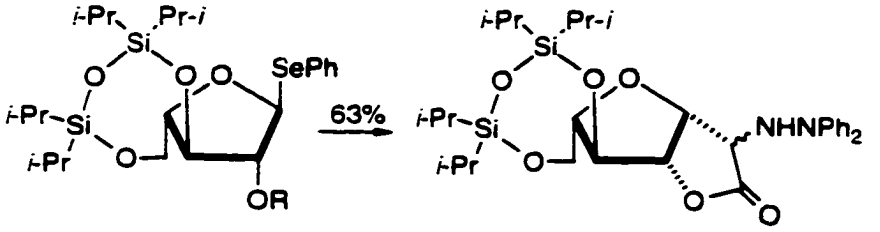
Our general procedure for radical cyclization involves slow addition (ca. 10 h) of individual solutions of Bu_3SnH

(0.06-0.2 M, 1.5-3.0 equiv) and AIBN (0.003-0.02 M, 0.2-0.4 equiv) in PhMe to a stirred and refluxing solution of the hydrazono ester (0.015 M) in the same solvent. The hydrazono esters **269-275** cyclized smoothly to lactones (for the general equation, see Scheme 45, page 47) **284a,b-289a,b** and **291a,b** in yields of 57-82% (Table 2). Even a seven-membered ring can be formed (**288a,b**; 64%). (The numbers in brackets in Table 2 are the ratios of isomers.) The results indicated that a mixture of isomers was always obtained, and in all but

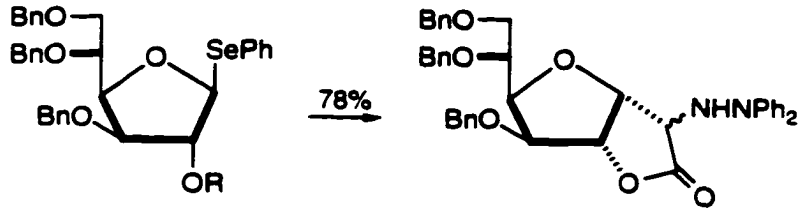
Table 2



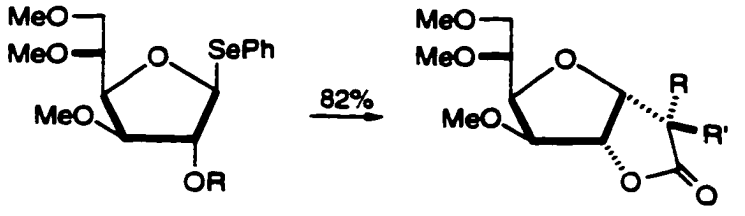
269 R = C(O)CH=NNPh$_2$ **284a,b** (46:27)



270 R = C(O)CH=NNPh$_2$ **285a,b** (1.5:1)

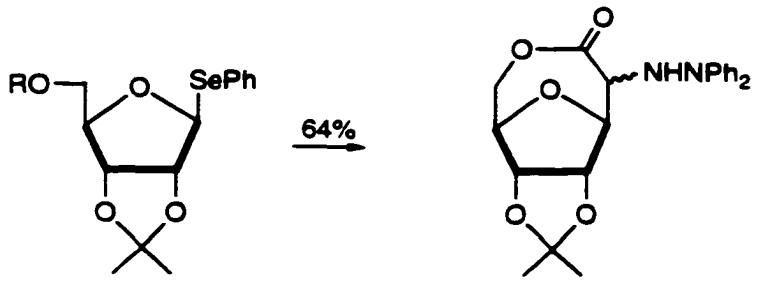


271 R = C(O)CH=NNPh$_2$ **286a,b** (40:38)



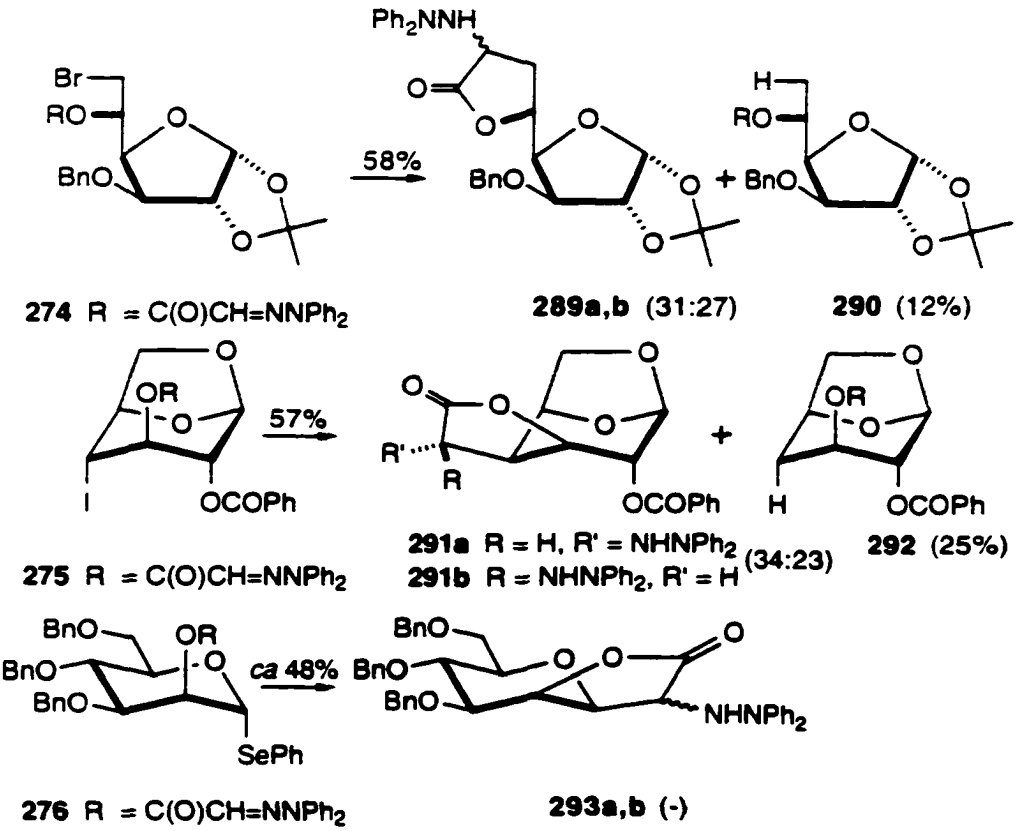
272 R = C(O)CH=NNPh$_2$

287a R = H, R' = NHNPh$_2$
287b R = NHNPh$_2$, R' = H
(42:40)



273 R = C(O)CH=NNPh$_2$ **288a,b** (1.5:1)

Table 2 continued

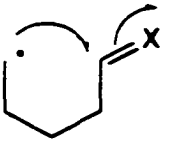


two cases (**285a,b** and **288a,b**) the isomers could be separated by flash chromatography. In a few cases the simple reduction product was also isolated [**290**, 12% (as judged by ^{1}H NMR measurements); **292**, 25%]. Sometimes trace amounts of Ph_2NH were detected in the reaction mixtures. With **276** cyclization gave **293a,b** only in 48% yield.

Compounds **277-279** (Figure 5) and **283** (Scheme 63), which are not listed in the Table 2, gave complex mixtures after the radical cyclization. Use of an excess of stannane (1.2-3.0 equiv, depending on the individual experiment) generally gave better results. The structures of the lactones in Table

2 were clear from their spectra, and NOE measurements allowed us to assign the stereochemistry at the position α to the lactone carbonyl for compounds **287a,b** and **291a,b**. In the former case, X-ray analysis of one of the isomers (**287b**) confirmed our assignment.

A notable feature of the radical closure in the carbohydrate series is the absence of acyl migration.[49,66,67] 5-*Exo*-cyclization of a radical onto a C=NNPh$_2$ group is extremely fast and, for an all-carbon chain, as in **294** (X = NNPh$_2$) (Figure 6), the rate constant at 80 °C is of the order



294

Figure 6 Structure of **294**

of 10^7-10^8 s^{-1}, while the corresponding value for closure onto a carbon-carbon double bond (**294**, X = CH_2) is only about 10^5 s^{-1}.[21b] 1,2-Acyl migrations have rate constants that span the range[66] (at 75 °C) ca. 10^2-10^6 s^{-1} and can sometimes be significantly faster than closure onto a hydrazono unit (see Scheme 50, page 52). The fact that acyl migration does not compete with the closures reported here shows that the rotational barrier about the ester C(O)-O single bond is sufficiently low[48] to permit easy access to a conformation (see Scheme 45, page 47) in which the radical center is close to the C=N double bond, and that closure onto an α-acyl

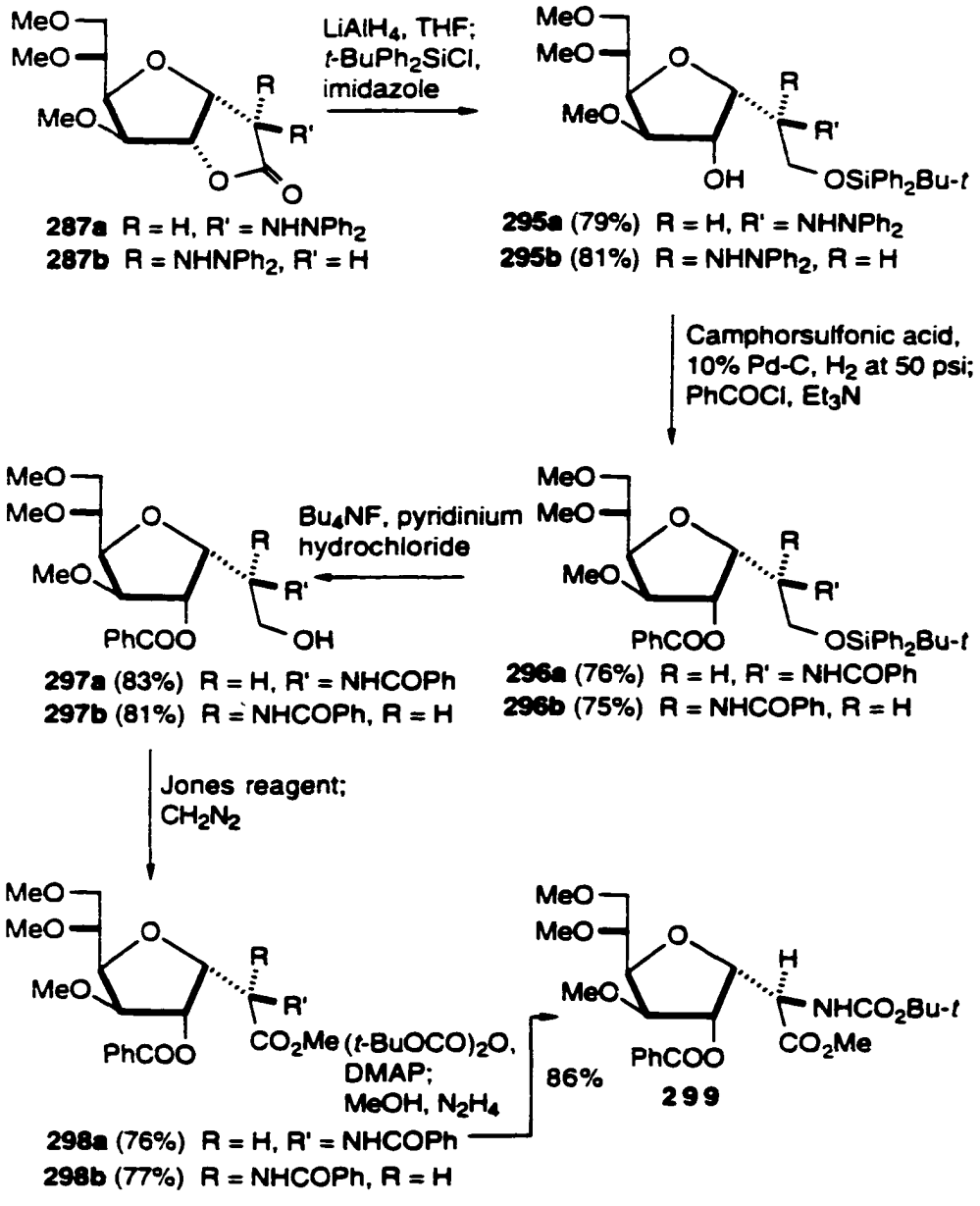
hydrazono unit is fast.

With hydrazono esters of six-membered sugars **277-279** (see Figure 5, page 62), and the furanose example **283** (see Scheme 63), the radical cyclization did not proceed well. But with **275** and **276** (Table 2) the desired lactones are formed in yields of 57% and 48%, respectively. We are not sure whether the axial nature of the hydrazono pendant in the anhydrosugar **275** and in the mannose derivative **276** contributes to the relative efficiency of closure, as compared with the galactose- (**277**) or glucose-derived examples (**278**, **279**), as efficient closures involving both axial and equatorial pendants have been observed experimentally.[68]

3. Modification of the Hydrazino Lactones and Formation of *C*-Glycosyl α-Amino Acids

In principle, opening of the lactone unit of the radical cyclization products and hydrogenolysis of the N-N single bond should afford a *C*-glycosyl amino acid, but in practice this overall transformation had to be effected indirectly. In our initial attempts, hydrogenolysis of 2,2-diphenylhydrazino lactones (10% Pd-C/H_2, camphorsulfonic acid, MeOH, at 50 psi) was unsuccessful, and lactone opening with various bases (LiOH, MeONa, $NH_3 \cdot H_2O$) resulted in expulsion of diphenylamine. Therefore, the formation of a *C*-glycosyl amino acid had to be accomplished in the following way.

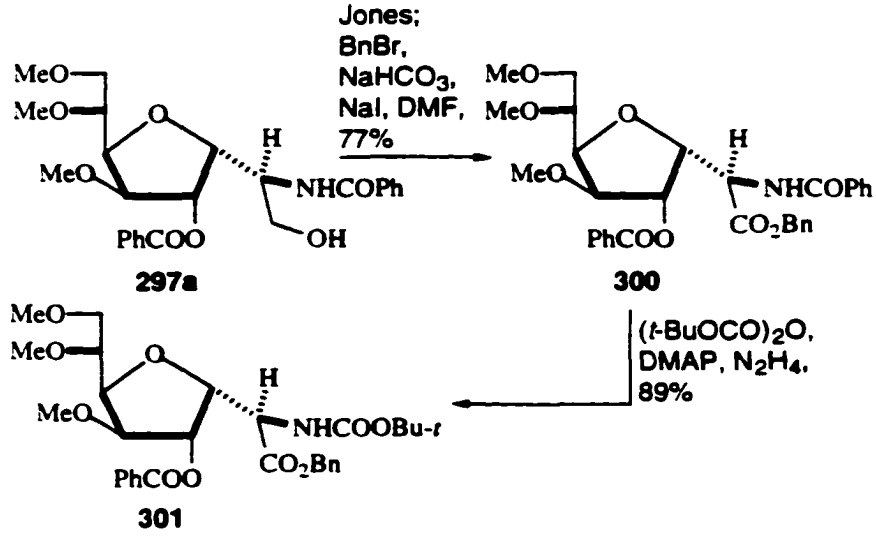
Hydride reduction ($LiAlH_4$) of **287a** (Scheme 64), selective silylation of the resulting primary hydroxyl (*t*-$BuPh_2SiCl$, imidazole; 79% overall) (**287a** → **295a**), hydrogenolysis (10% Pd-C/H_2, camphorsulfonic acid, EtOAc-MeOH), and benzoylation (PhCOCl, Et_3N, DMAP; 76% overall)



Scheme 64

gave **296a** (**295a** → **296a**). Desilylation, using Bu_4NF, is complicated by benzoyl migration, but this process could be suppressed by using Bu_4NF in the presence of 1.5 equiv of pyridinium hydrochloride,[65] and under these conditions the yield was 83%. The resulting primary alcohol was oxidized and esterified (**297a** → **298a**; 76%), and the *N*-benzoyl group was replaced directly by a *t*-butoxycarbonyl group [(*t*-BuOCO)$_2$O, DMAP, NH_2NH_2; 86%],[69] so as to afford the protected *C*-glycosyl amino acid **299**. The other isomeric hydrazone closure product (**287b**) was subjected to the same operations, except for the last step (Scheme 64), and provided the protected *C*-glycosyl amino acid **298b**.

In a slightly different set of reactions, alcohol **297a** (Scheme 65) was oxidized to the corresponding acid, and this



Scheme 65

was converted into its benzyl ester (**297a** → **300**; Jones

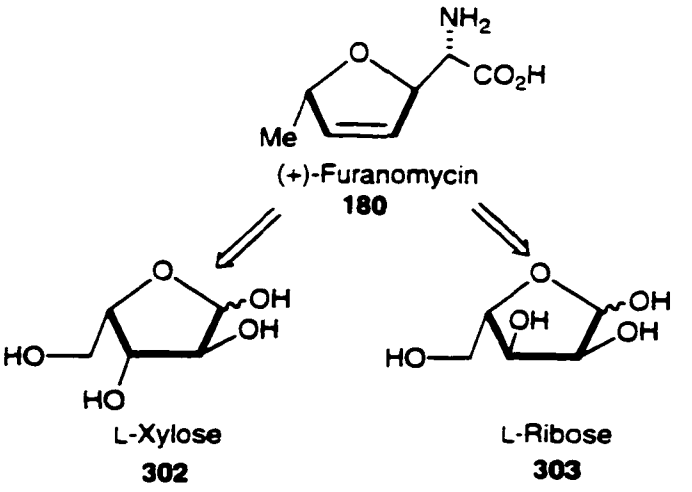
oxidation; BnBr, $NaHCO_3$, NaI; 77%). Finally, the *N*-benzoyl group was replaced directly by a *t*-butoxycarbonyl group [$(t\text{-BuOCO})_2O$, DMAP, NH_2NH_2; 89%; **300** → **301**].

The formation of compounds **298b**, **299**, and **301** shows that *C*-glycosyl α-amino acid derivatives are accessible by the radical cyclization approach described above. The stereochemistry α to the carbonyl is not controlled, but the epimers are often separable, and the α or β stereochemistry with respect to the carbohydrate subunit is determined by the stereochemistry of the hydroxyl that is initially acylated with reagent **207**.

C. Synthesis of (+)-Furanomycin

Although the antibiotic (+)-furanomycin **180** (Scheme 66) has a seemingly simple structure, to date there are only two other synthetic routes[39,42] available to this substance, in part due to the difficulties in assembling the *trans*-2,5-dihydrofuran and (*S*)-amino acid units. The successful application of our methodology to the synthesis of *C*-glycosyl α-amino acids promoted us to approach this natural antibiotic. Retrosynthetic analysis led to two commercial sugars, L-ribose and L-xylose (Scheme 66) as our starting materials. Since L-ribose is very expensive, we started from L-xylose.

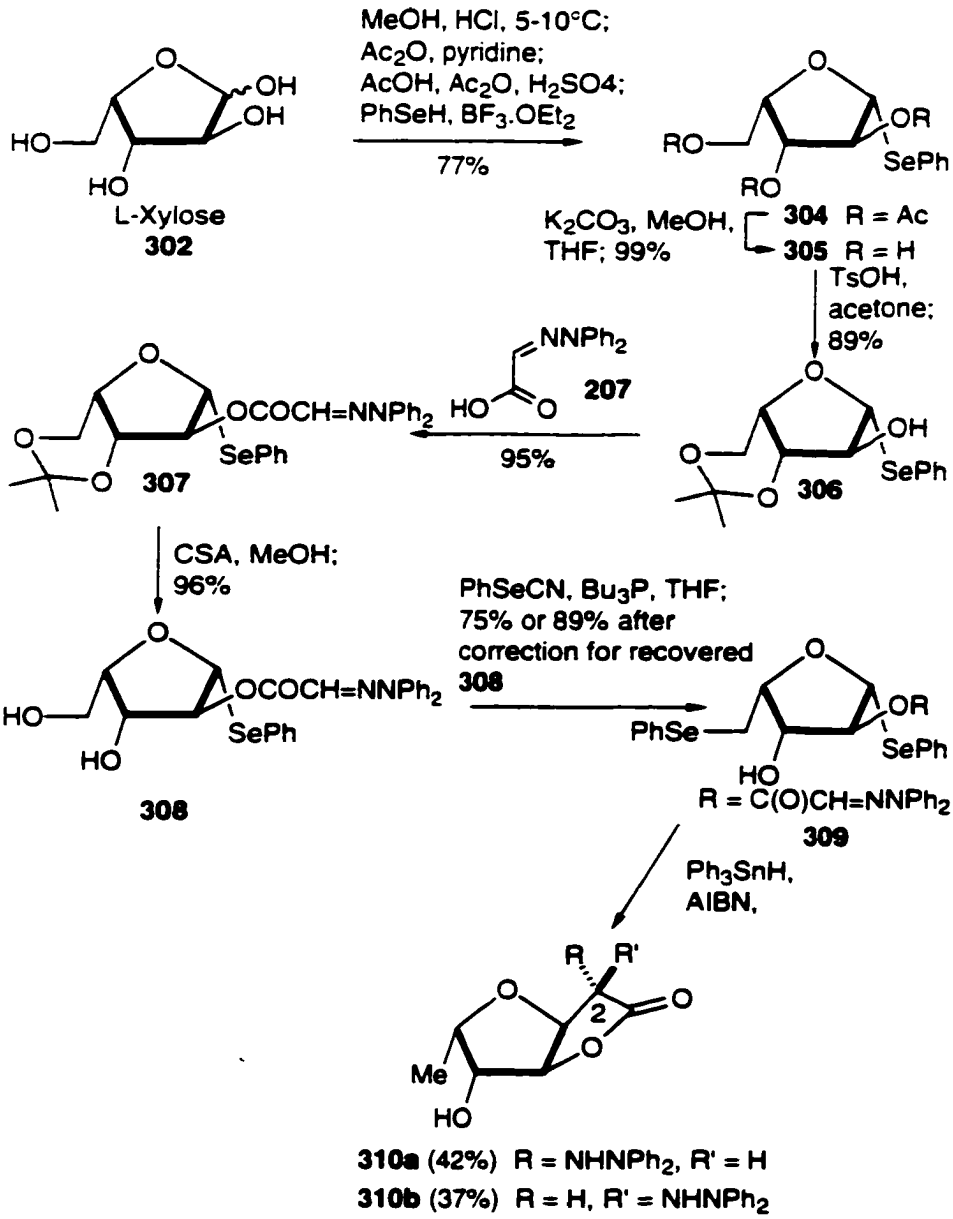
The key step in our synthesis is based on radical cyclization to form the crucial intermediate α-(2,2-diphenylhydrazino)lactone **310a** (Scheme 67). Scheme 67



Scheme 66

outlines how we approached this lactone. Commercial L-xylose (**302**) was converted into its methyl glycoside (MeOH, HCl), acetylated (Ac_2O, pyridine), subjected to acetolysis (AcOH, Ac_2O, H_2SO_4), and treated with $PhSeH/BF_3 \cdot Et_2O$, to afford triacetate **304**. These steps are best done without isolation of the intermediates, in which case the overall yield is 77%. Mild basic hydrolysis (K_2CO_3, MeOH-THF; 99%) then liberated the three hydroxyl groups (**304** → **305**), and those at C(3) and C(5) were protected as a ketal (**305** → **306**; TsOH, acetone; 89%, or 94% after correction for recovered **305**). DCC-mediated coupling with (2,2-diphenylhydrazono)acetic acid (**207**, Scheme 67) then gave the hydrazono ester **307** in excellent yield (95%).

Although the ester underwent radical cyclization (83%), it was better to delay this process, so that another radical reaction – deoxygenation at C(5) – could be accomplished at the same time as the required ring closure (see later, **309** →



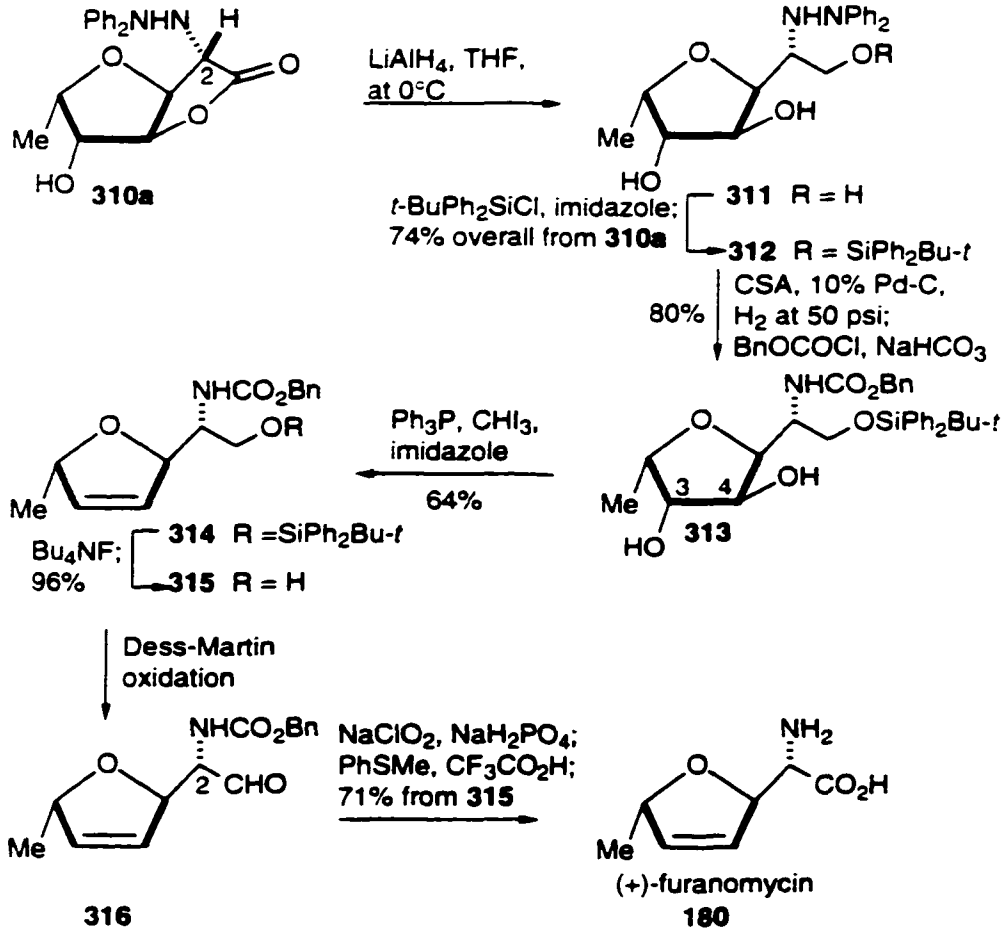
Scheme 67

310a,b). To this end, selenide ester **307** was deprotected (**307** → **308**; CSA, MeOH; 96%) in order to liberate the two hydroxyls. The primary hydroxyl was selectively replaced by a PhSe group (**308** → **309**; PhSeCN, Bu_3P; 75%, 89% after correction for recovered **308**), and then treatment with Ph_3SnH

under conditions previously established (slow addition of Ph_3SnH and AIBN, PhMe at reflux) served not only to induce radical cyclization but also to generate the required methyl group at C(5). That experiment afforded a 42:37 isomer mixture of chromatographically separable hydrazino lactones epimeric at C(2) (**309** → **310a,b**). These compounds were readily distinguished by NOE measurements. Compound **310a** has the desired stereochemistry at C(2).

We had now obtained the crucial intermediate **310a**, and the next task was to elaborate this intermediate to (+)-furanomycin. Since we had successfully converted such lactones into *C*-glycosyl α-amino acids (see Scheme 64), we wanted to apply a similar approach here. In practice, opening the lactone by reduction with $LiAlH_4$ worked well with **310a**, however, conversion of the primary hydroxyl into the corresponding carboxylic acid with Jones reagent did not work in this case. Therefore, the route summarized in Scheme 68 was followed to complete our synthesis. Reduction ($LiAlH_4$) of **310a** gave a triol (**310a** → **311**), and the primary hydroxyl was selectively protected as its *t*-butyldiphenylsilyl ether (**311** → **312**; *t*-$BuPh_2SiCl$, imidazole; 74% from **310a**). Hydrogenolysis in an acidic medium (CSA, MeOH-EtOAc, H_2, Pd-C), followed by acylation (BnOCOCl, $NaHCO_3$), then afforded benzyl carbamate **313** (80% from **312**).

At this point the two remaining hydroxyls had to be removed to introduce a C(3)-C(4) double bond. This transformation turned out to be problematical. Conversion of



Scheme 68

313 into the corresponding dimesylates was not successful, and direct deoxygenation by Ph_2PCl and I_2 or Ph_3P and I_2 in the presence of imidazole[70] did not give the C(3)-C(4) double bond compound. Attempts to convert **313** into a dixanthate[71] also failed. Eventually, we found that the two hydroxyl groups in **313** could be removed by treatment with Ph_3P and CHI_3 in the presence of imidazole;[72] this experiment generated the required C(3)-C(4) double bond (**313** → **314**). This step was accompanied by extensive bis-dehydration (to the corresponding furan), but under optimum conditions, gave **314**

in 64% yield. Desilylation with Bu_4NF, took the route as far as alcohol **315**, which had been reported recently in another synthesis[42] of furanomycin. The remaining steps required are oxidation of the hydroxyl, and deprotection of the amino group. The oxidation of the hydroxyl in **315** was troublesome. Jones reagent[73] did not work, neither did TPAP,[74] PDC[75] or TEMPO[76] oxidation. In our hands the hydroxyl was best oxidized by the Dess-Martin reagent (ca. 100%), since use of the Swern procedure led to significant amounts (in one experiment ca. 30%) of epimerization at C(2).[77] Further oxidation of the crude aldehyde (**316**), using buffered $NaClO_2$,[78] generated the required acid, and treatment with CF_3CO_2H in the presence of PhSMe[79] served to deprotect the amino group, and liberate furanomycin (**180**) of 98% purity (71% from **315**). A single crystallization on a small scale gave pure, crystalline **180** (52% from **315**).[39b]

The epimerization observed in oxidation of alcohol **315** under Swern conditions suggested that it might be possible to elaborate **310b** to the corresponding aldehyde and then effect epimerization; in this way, both products from the radical cyclization step would be convertible into furanomycin. In the event, however, the aldehyde from **310b** [i.e. the C(2) epimer of **316**] could not be epimerized under the conditions we examined: DBU (0.1 equiv) in CH_2Cl_2 at -78 °C; DBU (0.25 equiv) in CH_2Cl_2 at room temperature; Et_3N in CH_2Cl_2 at room temperature.

D. Conclusions

A general methodology for the preparation of α-(2,2-diphenylhydrazino)- and α-(benzyloxyamino)lactones by a radical cyclization process has been developed. Though the reaction produces lactones bearing an α-nitrogen substituent, the degree of stereoselectivity α to the lactone carbonyl is low. Our methodology has been applied to the preparation of *C*-glycosyl lactones. Such lactones can be successfully elaborated into optically pure *C*-glycosyl α-amino acids. The usefulness of the methodology was demonstrated by the synthesis of the natural antibiotic (+)-furanomycin.

III. Experimental Section

General Procedure.

Unless stated to the contrary, the following conditions apply: Reactions were carried out under a slight static pressure of Ar that had been purified by passage through a column (3.5 x 42 cm) of R-311 catalyst[80] and then through a similar column of Drierite. All solvents for reactions were dried, as described below. Glassware was dried in an oven for at least 3 h before use (120 °C) and either cooled in a desiccator over Drierite, or assembled quickly, sealed with rubber septa, and allowed to cool under a slight static pressure of Ar. Reaction mixtures were stirred by Teflon-coated magnetic stirring bars.

Hexane used for chromatography was distilled before use.

Products were isolated from solution by evaporation under water aspirator vacuum at room temperature, using a rotary evaporator.

Microliter syringes were washed with water and acetone, using a suction device to draw the solvents through. Then air was sucked through for 1 min. The solution to be dispensed was drawn up and expelled, and this operation was repeated several times before drawing up the sample to be used. Cannula transfers were always done under slight pressure (Ar), not by suction.

Commercial thin layer chromatography (TLC) plates (silica gel, Merck 60F-254) were used. Spots were detected

by spraying the plate with a solution of phosphomolybdic acid,[81] followed by charring on a hot plate, or by examination under UV light. Silica gel for flash chromatography was Merck type 60 (230-400 mesh).

Dry solvents were prepared under an inert atmosphere and transferred by dry syringes fitted with oven-dried needles, or by cannula. Dry THF, and PhMe were distilled from sodium benzophenone ketyl. Dry Et_3N, CH_2Cl_2, and pyridine were distilled from CaH_2. All other solvents were used as purchased.

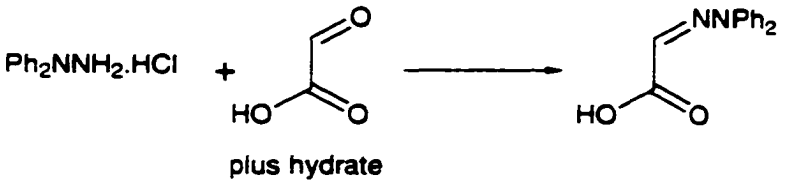
FT-IR measurements were recorded on a Nicolet 7000 FTIR instrument. Measurements were made as casts from the specified solvent using potassium bromide plates.

^1H nuclear magnetic resonance spectra were recorded with Bruker AM-300 (at 300 MHz), Varian INOVA-300 (at 300 MHz), Bruker AM-360 (at 360 MHz) or Bruker AM-400 (at 400 MHz) spectrometers in the specified deuterated solvent. ^{13}C spectra were recorded with Bruker AM-300 (at 75.5 MHz) or Varian UNITY-500 (at 125 MHz). The symbols s', d', t', and q' used for ^{13}C NMR signals indicate 0, 1, 2, or 3 attached hydrogens, respectively, which are assigned based on the APT experiment.

Mass spectra were recorded with AEI Models MS-12, MS-50 MS9 (modified), Kratos MS50 (modified) or Micromass ZabSpec Hybrid Sector-TOF mass spectrometers. For isotope peaks, high-resolution mass data were taken from the highest mass number peak shown in the spectrum.

X-Ray analysis was done in this Department. Isolated products were pure by TLC and, unless otherwise stated, also as judged by high field ^{1}H and ^{13}C NMR spectra.

(2,2-Diphenylhydrazono)acetic acid (207).



207

This procedure differs from that reported[44b] in the literature. Glyoxylic acid monohydrate (5.52 g, 60.0 mmol) was added to a stirred solution of commercial $Ph_2NNH_2.HCl$ (13.2 g, 60.0 mmol) in H_2O (720 mL). Stirring was continued for 2 h, and the precipitate was filtered off, washed with H_2O (5 x 30 mL), and dried under oil-pump vacuum to afford **207** (13.9 g, 96%) as a grey power: mp 201-203 °C (lit.[44b] 200-202 °C).

General Procedure for Coupling of Alcohols with Reagent 207 or Glyoxylic acid *O*-benzyloxime (208).

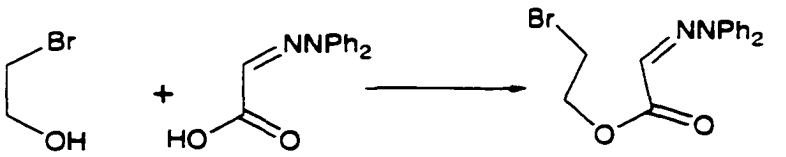
Glyoxylic acid diphenylhydrazone (**207**) or Glyoxylic acid *O*-benzyloxime (**208**) (1.2 equivalent) was added to a stirred mixture of the alcohol (1.0 equivalent), DCC (1.32 equivalent) and DMAP (0.12 equivalent) in dry CH_2Cl_2.

Stirring was continued for 12 h, and the mixture was then filtered. The insoluble material was washed with dry CH_2Cl_2 and the combined filtrates were evaporated to give a residue which was processed as described for the individual experiments.

General Procedure for Radical Cyclization.

The substrate was placed in a round-bottomed flask equipped with a Teflon-coated stirring bar and a reflux condenser sealed with a rubber septum. The system was flushed with argon for 5-10 min, and dry PhMe was injected into the flask. The flask was placed in an oil bath preheated to 110 °C, and solutions of Bu_3SnH and AIBN in PhMe were injected simultaneously by syringe pump over 10 h. Refluxing was continued for an arbitrary period of 1-4 h after the addition, except in the preparation of **291a,b**, where a longer period (7 h) was used. The reaction mixture was cooled, and the solvent was evaporated to give a residue which was processed as described for the individual experiments.

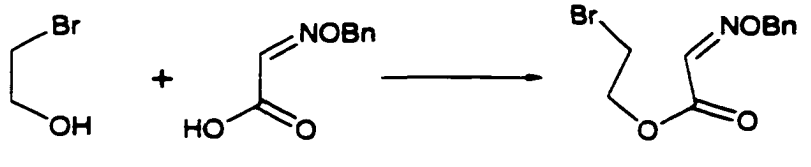
2-Bromoethyl (Diphenylhydrazono)acetate (215).



209 **207** **215**

The general procedure for coupling alcohols with reagent **207** was followed, using **207** (1.21 g, 5.00 mmol), alcohol **209** (0.685 g, 5.50 mmol), DCC (1.14 g, 5.50 mmol), and DMAP (61.0 mg, 0.50 mmol) in CH_2Cl_2 (25 mL). Flash chromatography of the residue over silica gel (3.0 x 30 cm), using 10% EtOAc-hexane, gave **215** (1.39 g, 80%) as a crystalline solid: mp 102-104 °C; FTIR (CH_2Cl_2 cast) 1730, 1705 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.57 (t, J = 6.3 Hz, 2 H), 4.52 (t, J = 6.3 Hz, 2 H), 6.50 (s, 1 H), 7.15-7.50 (m, 10 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 28.5 (t'), 63.8 (t'), 123.0 (d'), 126.2 (d'), 129.9 (d'), 141.9 (s'), 164.0 (s'); exact mass *m/z* calcd for $C_{16}H_{15}BrN_2O_2$ 346.0317, found 346.0326.

2-Bromoethyl [(Phenylmethoxy)imino]acetate (216).

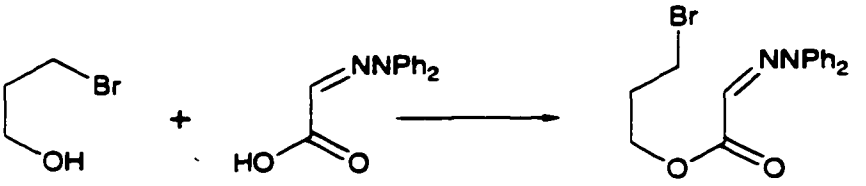


209 **208** **216**

The general procedure for coupling alcohols with reagent

208 was followed, using **208** (1.790 g, 10.00 mmol), alcohol **209** (1.370 g, 11.00 mmol), DCC (2.270 g, 11.00 mmol), and DMAP (122 mg, 1.00 mmol) in CH_2Cl_2 (50 mL). Flash chromatography of the residue over silica gel (4 x 30 cm), using 10% EtOAc-hexane, gave **216** (2.371 g, 83%) as a pale yellow oil: FTIR(CH_2Cl_2 cast) 1727, 1598, 1497 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.57 (t, J = 6.3 Hz, 2 H), 4.56 (t, J = 6.3 Hz, 2 H), 5.32 (s, 2 H), 7.32-7.40 (m, 5 H), 7.58 (s, 1 H); ^{13}C NMR (CD_2Cl_2, 50.3 MHz) δ 28.8 (t'), 64.9 (t'), 78.2 (t'), 128.4 (d'), 128.7 (d'), 128.8 (d'), 136.6 (s'), 141.1 (d'), 161.5 (s'); exact mass *m/z* calcd for $C_{11}H_{12}BrNO_3$ 286.9980, found 286.9976.

3-Bromopropyl (Diphenylhydrazono)acetate (217).

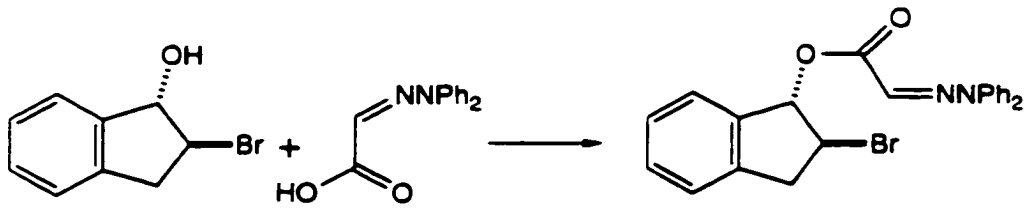


210 **207** **217**

The general procedure for coupling alcohols with reagent **207** was followed, using **207** (1.21 g, 5.00 mmol), alcohol **210** (497 µL, 5.50 mmol), DCC (1.14 g, 5.50 mmol), and DMAP (61 mg, 0.50 mmol) in CH_2Cl_2 (25 mL). Flash chromatography of the residue over silica gel (3.0 x 30 cm), using 10% EtOAc-hexane, gave **217** (1.30 g, 72%) as a pale yellow oil: FTIR (CH_2Cl_2 cast) 1729, 1703 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.26

(quintet, J = 6.3 Hz, 2 H), 3.52 (t, J = 6.6 Hz, 2 H), 4.36 (t, J = 6.0 Hz, 2 H), 6.47 (s, 1 H), 7.16-7.50 (m, 10 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 29.4 (t'), 31.5 (t'), 62.0 (t'), 122.1 (d'), 123.4 (d'), 125.9 (d'), 129.8 (d'), 141.8 (s'), 164.1 (s'); exact mass *m/z* calcd for $C_{17}H_{17}BrN_2O_2$ 360.0473, found 360.0475.

trans-2-Bromo-2,3-dihydro-1*H*-inden-1-yl (Diphenylhydrazono)acetate (218).

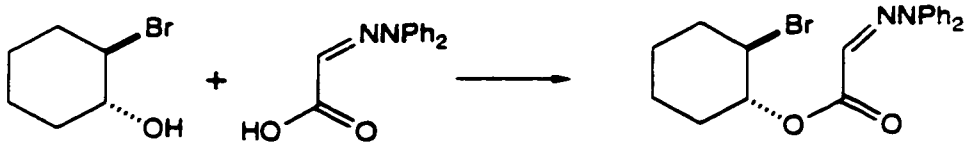


211 **207** **218**

The general procedure for coupling alcohols with reagent **207** was followed, using **207** (1.21 g, 5.00 mmol), alcohol **211** (1.17 g, 5.50 mmol), DCC (1.14 g, 5.50 mmol), and DMAP (61 mg, 0.50 mmol) in CH_2Cl_2 (25 mL). After evaporation of the solvent, MeOH (10 mL) was added to the residue. The resulting precipitate was filtered off and washed with MeOH (2 x 5 mL), to give **218** (1.80 g, 82%) as a crystalline solid: mp 159-161 °C; FTIR (CH_2Cl_2 cast) 1728, 1701 cm^{-1}; ^{1}H NMR (CD_2Cl_2, 360 MHz) δ 3.29 (dd, J = 17.1, 3.9 Hz, 1 H), 3.75 (dd, J = 17.1, 6.5 Hz, 1 H), 4.58-4.62 (m, 1 H), 6.43 (d, J = 3.2 Hz, 1 H), 6.48 (s, 1 H), 7.12-7.50 (m, 14 H); ^{13}C NMR (CD_2Cl_2, 50.3 MHz) δ 41.9 (t'), 50.8 (d'), 84.2 (d'), 122.8

(d'), 123.7 (d'), 125.3 (d'), 126.4 (d'), 126.6 (d'), 127.9 (d'), 130.1 (d'), 130.4 (d'), 138.8 (s'), 142.0 (s'), 164.0 (s'); exact mass *m/z* calcd for $C_{23}H_{19}BrN_2O_2$ 436.0609, found 436.0609.

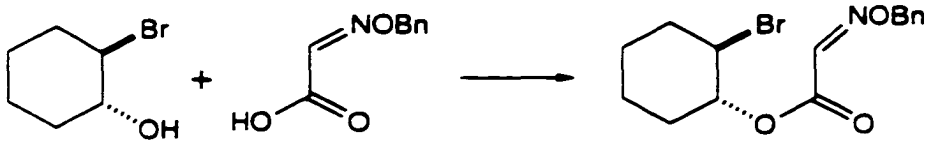
trans-2-Bromocyclohexyl (Diphenylhydrazono)acetate (219).



212 **207** **219**

The general procedure for coupling alcohols with reagent **207** was followed, using **207** (1.21 g, 5.00 mmol), alcohol **212** (0.895 g, 5.00 mmol), DCC (1.14 g, 5.50 mmol), and DMAP (61 mg, 0.50 mmol) in CH_2Cl_2 (25 mL). Flash chromatography of the residue over silica gel (1.6 x 30 cm), using 5% EtOAc-hexane, gave **219** (1.80 g, 90%) as a pale yellow oil: FTIR (CH_2Cl_2 cast) 1728, 1702 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.22-1.54 (m, 3 H), 1.67-2.00 (m, 3 H), 2.12-2.27 (m, 1 H), 2.30-2.42 (m, 1 H), 4.01-4.10 (m, 1 H), 5.00-5.10 (m, 1 H), 6.50 (s, 1 H), 7.14-7.50 (m, 10 H); ^{13}C NMR (CD_2Cl_2, 50.3 MHz) δ 23.7 (t'), 25.9 (t'), 31.6 (t'), 36.1 (t'), 53.6 (d'), 76.3 (d'), 122.7 (d'), 124.3 (d'), 126.5 (d'), 130.4 (d'), 142.6 (s'), 163.7 (s'); exact mass *m/z* calcd for $C_{20}H_{21}BrN_2O_2$ 400.0786, found 400.0786.

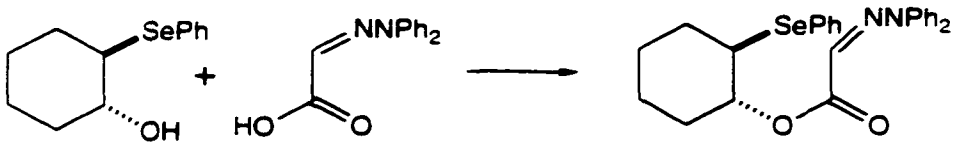
***trans*-2-Bromocyclohexyl [(Phenylmethoxy)imino]acetate (220).**



212 **208** **220**

The general procedure for coupling alcohols with reagent **208** was followed, using **208** (0.895 g, 5.00 mmol), alcohol **212** (0.970 g, 5.42 mmol), DCC (1.14 g, 5.50 mmol), and DMAP (61 mg, 0.50 mmol) in CH_2Cl_2 (25 mL). Flash chromatography of the residue over silica gel (1.6 x 30 cm), using 3% EtOAc-hexane, gave **220** (1.50 g, 88%) as a colorless oil: FTIR (CH_2Cl_2 cast) 1744, 1724 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.25-1.52 (m, 3 H), 1.70-1.95 (m, 3 H), 2.12-2.23 (m, 1 H), 2.33-2.41 (m, 1 H), 4.02-4.09 (m, 1 H), 5.03-5.10 (m, 1 H), 5.33 (s, 2 H), 7.33-7.45 (m, 5 H), 7.57 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 23.3 (t'), 25.5 (t'), 31.1 (t'), 35.6 (t'), 52.2 (d'), 77.1 (d'), 78.2 (t'), 128.5 (d'), 128.6 (d'), 128.7 (d'), 136.0 (s'), 141.0 (d'), 160.9 (s'); exact mass *m/z* calcd for $C_{15}H_{18}BrNO_3$ 341.0450, found 341.0453.

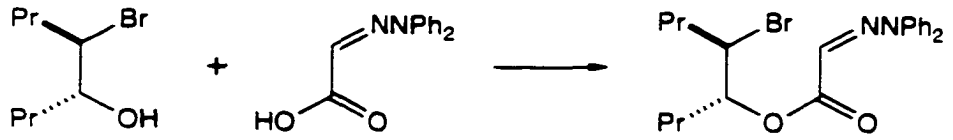
***trans*-2-(Phenylseleno)cyclohexyl (Diphenylhydrazono)-acetate (221).**



213 **207** **221**

The general procedure for coupling alcohols with reagent **207** was followed, using **207** (1.77 g, 7.37 mmol), alcohol **213** (2.06 g, 8.11 mmol), DCC (1.68 g, 8.11 mmol), and DMAP (89 mg, 0.74 mmol) in CH_2Cl_2 (40 mL). Flash chromatography of the residue over silica gel (4 x 30 cm), using 5% EtOAc-hexane, gave **221** (2.99 g, 85%) as a pale yellow, viscous oil: FTIR (CH_2Cl_2 cast) 1723, 1698 cm^{-1}; ^1H NMR (CD_2Cl_2, 360 MHz) δ 1.28-1.79 (m, 6 H), 2.07-2.24 (m, 2 H), 3.23-3.32 (m, 1 H), 4.93-5.01 (m, 1 H), 6.37 (s, 1 H), 7.16-7.60 (m, 15 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 24.0 (t'), 26.1 (t'), 32.1 (t'), 32.8 (t'), 46.8 (d'), 75.9 (d'), 124.7 (d'), 126.4 (d'), 127.8 (d'), 129.2 (d'), 129.4 (s'), 130.3 (d'), 135.2 (d'), 163.8 (s'); exact mass *m/z* calcd for $C_{26}H_{26}N_2O_2Se$ 478.1159, found 478.1161.

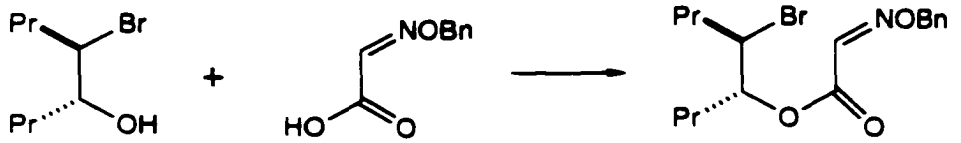
(*R,*R**)-2-Bromo-1-propylpentyl (Diphenylhydrazono)-acetate (222).**



207 **214** **222**

The general procedure for coupling alcohols with reagent **207** was followed, using **207** (1.60 g, 6.67 mmol), alcohol **214** (930 mg, 4,45 mmol), DCC (1.38 g, 6.67 mmol), and DMAP (81 mg, 0.67 mmol) in CH_2Cl_2 (25 mL). Flash chromatography of the residue over silica gel (3.0 x 22 cm), using 5% EtOAc-hexane, gave **222** (1.88 g, 98%) as a pale yellow oil: FTIR (CH_2Cl_2 cast) 1728, 1703 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 0.90-0.98 (m, 6 H), 1.35-1.85 (m, 8 H), 4.08-4.15 (m, 1 H), 5.13-5.20 (m, 1 H), 6.52 (s, 1 H), 7.10-7.46 (m, 10 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 13.2 (q'), 13.7 (q'), 18.5 (t'), 20.8 (t'), 34.1 (t'), 36.8 (t'), 57.3 (d'), 74.8 (d'), 123.0 (d') 126.0 (d'), 129.8 (d'), 141.9 (s'), 163.9 (s'); exact mass *m/z* calcd for $C_{22}H_{27}BrN_2O_2$ 432.1235, found 432.1237.

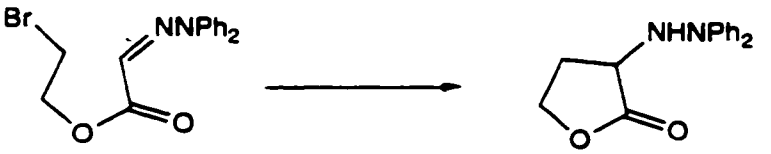
(*R,*R**)-2-Bromo-1-propylpentyl [(Phenylmethoxy)imino]-acetate (223).**



208 **214** **223**

The general procedure for coupling alcohols with reagent **208** was followed, using **208** (0.895 g, 5.00 mmol), alcohol **214** (1.15 g, 5.50 mmol), DCC (1.14 g, 5.50 mmol), and DMAP (61 mg, 0.50 mmol) in CH_2Cl_2 (25 mL). Flash chromatography of the residue over silica gel (3.0 x 30 cm), using 10% EtOAc-hexane, gave **223** (1.85 g, 100%) as a colorless oil: FTIR (CH_2Cl_2 cast) 1744, 1722 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.90-0.98 (m, 6 H), 1.30-1.50 (m, 3 H), 1.57-1.87 (m, 5 H), 4.05-4.11 (m, 1 H), 5.15-5.20 (m, 1 H), 5.33 (s, 2 H), 7.30-7.44 (m, 5 H), 7.60 (s, 1 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 13.3 (q'), 13.7 (q'), 18.6 (t'), 20.9 (t'), 34.0 (t'), 36.8 (t'), 56.5 (d'), 76.3 (d'), 78.2 (t'), 128.5 (d'), 128.7 (d'), 135.9 (s'), 140.7 (d'), 161.3 (s'); exact mass *m/z* calcd for $C_{17}H_{24}BrNO_3$ 371.0919, found 371.0917.

3-(2,2-Diphenylhydrazino)dihydro-2(3*H*)-furanone (224).

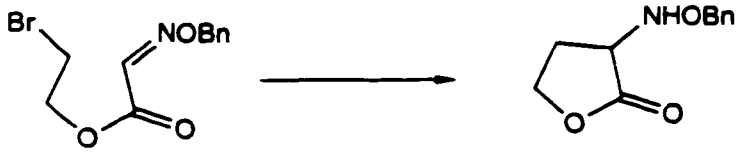


215 **224**

The general procedure for radical cyclization was followed, using **215** (0.400 g, 1.15 mmol) in PhMe (70 mL), Bu_3SnH (500 μL, 1.86 mmol) in PhMe (10 mL), and AIBN (20 mg, 0.12 mmol) in PhMe (10 mL). Flash chromatography of the residue over silica gel (1.6 x 30 cm), using first 5% EtOAc-hexane (500 mL), and then 10% EtOAc-hexane, gave **224** (234 mg,

75%) as a crystalline solid: mp 92-93 °C; FTIR (CH_2Cl_2 cast) 3281, 1774 cm^{-1}; ^1H NMR (CD_2Cl_2, 300 MHz) δ 2.30-2.53 (m, 2 H), 3.84-3.92 (m, 1 H), 4.14-4.24 (m, 1 H), 4.46 (td, *J* = 8.7, 3.2 Hz, 1 H), 4.70 (s, 1 H), 7.03-7.40 (m, 10 H), ^{13}C NMR (CD_2Cl_2, 75.5 MHz) δ 29.9 (t'), 55.8 (d'), 66.7 (t'), 120.7 (d'), 123.2 (d'), 129.6 (d'), 147.4 (s'), 175.9 (s'); exact mass *m/z* calcd for $C_{16}H_{16}N_2O_2$ 268.1212, found 268.1210.

Dihydro-3-[(phenylmethoxy)amino]-2(3*H*)-furanone (225).

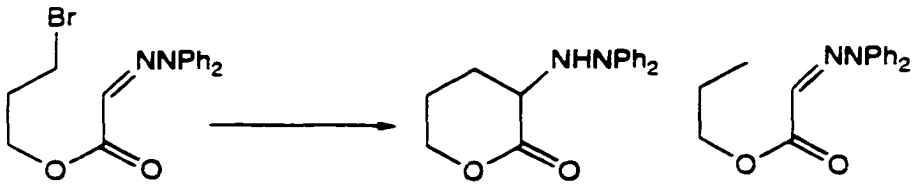


216 **225**

The general procedure for radical cyclization was followed, using **216** (0.315 g, 1.10 mmol) in PhMe (70 mL), Bu_3SnH (474 μL, 1.76 mmol) in PhMe (10 mL), and AIBN (30 mg, 0.18 mmol) in PhMe (10 mL). Flash chromatography of the residue over silica gel (1.6 x 30 cm), using first 10% EtOAc-hexane (700 mL), and then 30% EtOAc-hexane, gave **225** (118 mg, 51%) as a colorless oil: FTIR (CH_2Cl_2 cast) 1774 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 2.22-2.42 (m, 2 H), 3.79 (td, *J* = 8.9, 1.8 Hz, 1 H), 4.18-4.26 (m, 1 H), 4.38 (td, *J* = 8.9, 3.8 Hz, 1 H), 4.71 (d, *J* = 11.8 Hz, 1 H), 4.76 (d, *J* = 11.8 Hz), 6.12 (s, 1 H), 7.24-7.40 (m, 5 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 26.4 (t'), 59.1 (d'), 66.2 (t'), 77.1 (t'), 128.1 (d'), 128.5 (d'), 128.6 (d'), 137.2 (s'), 175.6 (s'); exact mass *m/z*

calcd for $C_{11}H_{13}NO_3$ 207.0895, found 207.0896.

3-(2,2-Diphenylhydrazino)tetrahydro-2*H*-pyran-2-one (226) and Propyl (Diphenylhydrazono)acetate (227).



217 **226** **227**

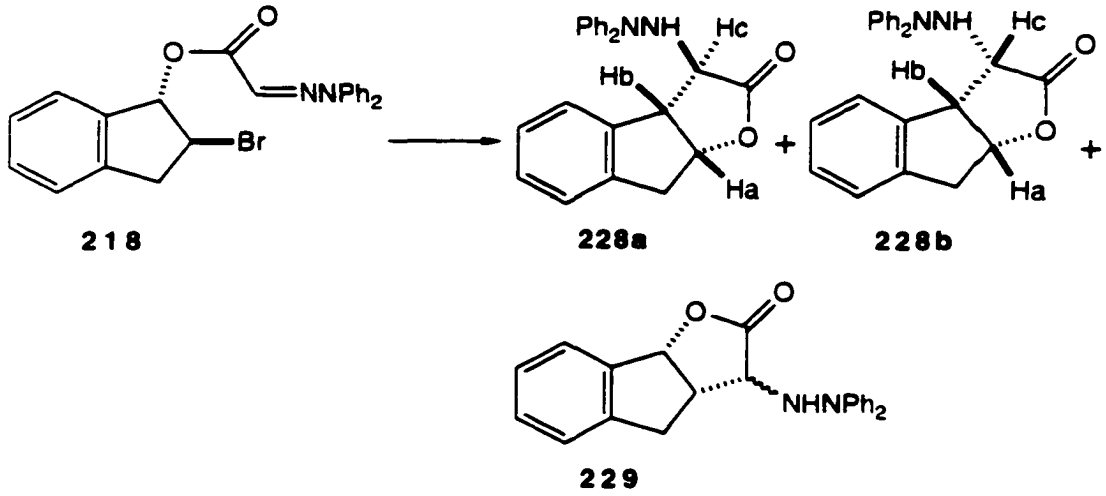
The general procedure for radical cyclization was followed, using **217** (0.415 g, 1.15 mmol) in PhMe (70 mL), Bu_3SnH (474 µL, 1.76 mmol) in PhMe (10 mL), and AIBN (30 mg, 0.18 mmol) in PhMe (10 mL). Flash chromatography of the residue over silica gel (1.6 x 30 cm), using 5% EtOAc-hexane, gave **227** (66 mg, 20%) as a crystalline solid, and **226** (163 mg, 50%) as a colorless oil.

Compound **227** had: mp 83-84 °C; FTIR (CH_2Cl_2 cast) 1728, 1702 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.00 (t, *J* = 7.4 Hz, 3 H), 1.73 (sextet, *J* = 7.1 Hz, 2 H), 4.20 (t, *J* = 6.8 Hz, 2 H), 6.52 (s, 1 H), 7.12-7.50 (m, 10 H); ^{13}C NMR ($CDCl_3$, 50,3 MHz) δ 10.4 (q'), 22.1 (t'), 66.3 (t'), 122.4 (d'), 124.3 (d'), 126.0 (d'), 130.0 (d'), 143.0 (s'), 164.8 (s'); exact mass *m/z* calcd for $C_{17}H_{18}N_2O_2$ 282.1368, found 282.1374.

Compound **226** had: FTIR (CH_2Cl_2 cast) 3292, 1732 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 1.80-2.01 (m, 3 H), 2.22-2.37 (m, 1 H), 3.64-3.73 (m, 1 H), 4.27-4.37 (m, 2 H), 5.06 (s, 1 H),

7.00-7.31 (m, 10 H); ^{13}C NMR (CD_2Cl_2, 50.3 MHz) δ 21.6 (t'), 25.3 (t'), 55.7 (d'), 69.8 (t'), 120.6 (d'), 122.9 (d'), 129.5 (d'), 147.6 (s'), 171.7 (s'); exact mass *m/z* calcd for $C_{17}H_{18}N_2O_2$ 282.1368, found 282.1366.

(3α,3aα,8aα)-3-(2,2-Diphenylhydrazino)-3,3a,8,8a-tetrahydro-2*H*-indeno[2,1-b]furan-2-one (228a), (3α,3aβ,8aβ)-3-(2,2-Diphenylhydrazino)-3,3a,8,8a-tetrahydro-2*H*-indeno[2,1-b]furan-2-one (228b) and (3a*R,8b*S**)-3-(2,2-Diphenylhydrazino)-3,3a,4,8b-tetrahydro-2*H*-indeno[1,2-b]furan-2-one (229).**



218 **228a** **228b**

229

The general procedure for radical cyclization was followed, using **218** (0.500 g, 1.15 mmol) in PhMe (70 mL), Bu_3SnH (474 μL, 1.76 mmol) in PhMe (10 mL), and AIBN (30 mg, 0.18 mmol) in PhMe (10 mL). The solvent was evaporated and the residue was covered with 40% EtOAc-hexane and let stand for 0.5 h. The precipitate was then filtered off and washed

with 40% EtOAc-hexane (2 x 3 mL) to give a first crop of **228b** (70.0 mg, 17%) as a crystalline solid. Evaporation of the filtrate and flash chromatography of the residue over silica gel (1.6 x 30 cm), using 5% EtOAc-hexane, gave a 1:1.2 mixture (67 mg) of **228a** and **229**, pure compound **228a** (100 mg, 24%) and pure compound **228b** (90 mg, 22%), each of the three fractions being a crystalline solid.

The fraction corresponding to **229** had: FTIR (CH_2Cl_2 cast) 1770 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 2.88-2.95 (m, 0.64 H), 3.20-3.50 (m, 2.35 H), 3.69 (dd, J = 6.0, 1.6 Hz, 0.29 H), 3.95 (t, J = 1.7 Hz, 0.47 H), 4.15 (d, J = 5.6 Hz, 0.49 H), 4.31 (dd, J = 7.9, 1.3 Hz, 0.33 H), 4.62 (d, J = 2.0 Hz, 0.49 H), 4.72-4.79 (m, 0.61 H), 5.56-5.63 (m , 0.77 H), 6.03 (d, J = 7.6 Hz, 0.25 H), 6.85-7.50 (m, 14 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 32.4 (t'), 36.2 (t'), 38.9 (t'), 44.1 (d'), 44.9 (d'), 51.3 (d'), 60.0 (d'), 63.0 (d'), 63.6 (d'), 84.8 (d'), 85.9 (d'), 86.6 (d'), 120.8 (d'), 120.9 (d'), 121.0 (d'), 123.3 (d'), 123.4 (d'), 123.5 (d'), 125.3 (d'), 125.6 (d'), 125.8 (d'), 126.2 (d'), 126.5 (d'), 127.4 (d'), 127.8 (d'), 128.7 (d'), 129.67 (d'), 129.70 (d'), 129.8 (d'), 130.3 (d'), 130.7 (d'), 138.5 (s'), 139.1 (s'), 140.2 (s'), 140.9 (s'), 142.7 (s'), 145.7 (s'), 147.3 (s'), 147.6 (s'), 147.7 (s'), 174.6 (s'), 174.9 (s'), 175.6 (s'); exact mass *m/z* calcd for $C_{23}H_{20}N_2O_2$ 356.1525, found 356.1522.

Compound **228a** had: mp 158-160 °C; FTIR (CH_2Cl_2 cast) 1771 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.33 (d, J = 3.3 Hz, 2 H), 3.97 (t, J = 1.5 Hz, 1 H), 4.17 (d, J = 5.8 Hz, 1 H),

4.56 (d, J = 1.8 Hz, 1 H), 5.59 (dt, J = 5.8, 3.4 Hz, 1 H), 6.82-7.40 (m, 14 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 38.6 (t'), 50.9 (d'), 63.4 (d'), 84.6 (d'), 120.5 (d'), 123.3 (d'), 125.0 (d'), 125.4 (d'), 127.6 (d'), 128.5 (d'), 129.6 (d'), 139.7 (s'), 140.3 (s'), 146.9 (s'); 174.9 (s'); exact mass *m/z* calcd for $C_{23}H_{20}N_2O_2$ 356.1525, found 356.1519.

Compound **228b** had: mp 183-185 °C; FTIR (CH_2Cl_2 cast) 1761 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.21-3.37 (m, 2 H), 4.20 (dd, J = 8.1, 4.7 Hz, 1 H), 4.34 (dd, J = 8.1, 1.5 Hz, 1 H), 4.55 (s, 1 H), 5.17 (t, J = 4.7 Hz, 1 H), 7.03-7.40 (m, 14 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 38.6 (t'), 49.6 (d'), 60.6 (d'), 82.0 (d'), 121.5 (d'), 123.7 (d'), 125.0 (d'), 126.9 (d'), 128.4 (d'), 128.9 (d'), 129.5 (d'), 137.1 (s'), 140.9 (s'), 148.0 (s'), 174.5 (s'); exact mass *m/z* calcd for $C_{23}H_{20}N_2O_2$ 356.1525, found 356.1518. Irradiation of the H_a ^{1}H NMR signal (for **228a**) caused an NOE of 6% in the signal for H_b, and 0% for the H_c signal; in the case of **228b**, the corresponding values were 6% and 3%, respectively.

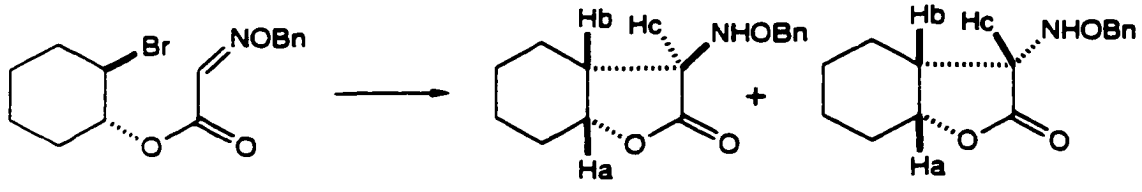
(3a*R,7a*R**)-3-(2,2-Diphenylhydrazino)hexahydro-2(3*H*)-benzofuranone (230).**

219 **230**

The general procedure for radical cyclization was

followed using **219** (0.450 g, 1.12 mmol) in PhMe (70 mL), Bu_3SnH (474 μL, 1.76 mmol) in PhMe (10 mL), and AIBN (50 mg, 0.31 mmol) in PhMe (10 mL). Flash chromatography of the residue over silica gel (1.6 x 30 cm), using 3% EtOAc-hexane, gave **230** (0.261 g, 72%) as a pale yellow oil which was a 1:1 mixture (^{1}H NMR measurements) of isomers: FTIR (CH_2Cl_2 cast) 1773 cm^{-1}; ^{1}H NMR (CD_2Cl_2, 400 MHz) δ 1.10-1.90 (m, 8 H), 2.15-2.25 (m, 0.49 (H), 2.48-2.68 (m, 0.69 H), 3.65 (dd, *J* = 6.2, 1.3 Hz, 0.41 H), 4.00 (dd, *J* = 6.2, 1.3 Hz, 0.42 H), 4.37-4.41 (m, 0.49 H), 4.48 (s, 0.91 H), 4.78 (dd, *J* = 12.2, 5.6 Hz, 0.34 H), 7.00-7.35 (m, 10 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 20.1 (t'), 21.4 (t'), 22.1 (t'), 23.1 (t'), 23.4 (t'), 25.3 (t'), 27.7 (t'), 29.0 (t'), 39.8 (d'), 41.1 (d'), 60.7 (d'), 63.3 (d'), 76.8 (d'), 78.2 (d'), 120.8 (d'), 121.1 (d'), 123.2 (d'), 123.4 (d'), 129.6 (d'), 129.7 (d'), 147.6 (s'), 147.9 (s'), 175.6 (s'), 176.2 (s'); exact mass *m/z* calcd for $C_{20}H_{22}N_2O_2$ 322.1681, found 322.1678.

(3α,3aα.7aα)-Hexahydro-3-[(phenylmethoxy)amino]-2(3*H*)-benzofuranone (231a) and (3α,3aβ.7aβ)-Hexahydro-3-[(phenylmethoxy)amino]-2(3*H*)-benzofuranone (231b).



220 **231a** **231b**

The general procedure for radical cyclization was followed, using **220** (0.202 g, 0.595 mmol) in PhMe (40 mL), Bu_3SnH (240 μL, 0.893 mmol) in PhMe (5 mL), AIBN (20 mg, 0.12 mmol) in PhMe (5 mL). Flash chromatography of the residue over silica gel (1.6 x 28 cm), using first 3% EtOAc-hexane (500 mL), and then 10% EtOAc-hexane, gave **231a** (51 mg, 33%) as a crystalline solid and **231b** (50 mg, 32%) as a colorless oil.

Compound **231a** had: FTIR (CH_2Cl_2 cast) 3254, 1775 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 1.22-1.75 (m, 7 H), 1.95-2.03 (m, 1 H), 2.59-2.67 (m, 1 H), 3.56 (dd, J = 9.4, 2.6 Hz, 1 H), 4.50-4.58 (m, 1 H), 4.68 (s, 2 H), 6.11 (d, J = 2.3 Hz, 1 H), 7.25-7.39 (m, 5 H); ^{13}C NMR (CD_2Cl_2, 50.3 MHz) δ 21.2 (t'), 22.0 (t'), 24.7 (t'), 29.7 (t'), 37.2 (d'), 62.9 (d'), 77.36 (d'), 77.44 (t'), 128.2 (d'), 128.6 (d'), 129.0 (d'), 137.8 (s'), 175.4 (s'); exact mass m/z calcd for $C_{15}H_{19}NO_3$ 261.1365, found 261.1361.

Compound **231b** had: mp 71.5-72.5 °C; FTIR (CH_2Cl_2 cast) 1774 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 0.93-0.40 (m, 3 H), 1.52-1.73 (m, 4 H), 2.13-2.26 (m, 1 H), 2.50-2.57 (m, 1 H), 4.11 (dd, J = 6.1, 4.0 Hz, 1 H), 4.41-4.45 (m, 1 H), 4.70 (s, 2 H), 5.91 (d, J = 3.5 Hz, 1 H), 7.30-7.40 (m, 5 H); ^{13}C NMR (CD_2Cl_2, 50.3 MHz) δ 20.1 (t'), 22.7 (t'), 23.3 (t'), 27.7 (t'), 39.3 (d'), 66.6 (d'), 76.80 (t'), 76.81 (d'), 128.3 (d'), 128.7 (d'), 128.8 (d'), 138.1 (s'), 174.8 (s'); exact mass m/z calcd for $C_{15}H_{19}NO_3$ 261.1365, found 261.1359. Irradiation of the H_a ^1H NMR signal (for **231a**) caused an NOE

of 8% in the signal for H_b, and 1% for the H_c signal; in the case of **231b**, the corresponding values were 12% and 11%, respectively.

(3a*R,7a*R**)-(2,2-Diphenylhydrazino)hexahydro-2(3*H*)-benzofuranone (230).**

221 **230**

The general procedure for radical cyclization was followed, using **221** (500 mg, 1.05 mmol) in PhMe (70 mL), Bu_3SnH (370 μL, 1.37 mmol) in PhMe (10 mL), and AIBN (69 mg, 0.42 mmol) in PhMe (10 mL). Flash chromatography of the residue over silica gel (1.6 x 28 cm), using 3% EtOAc-hexane, gave **230** (70 mg, 20%) as a pale yellow oil, which was a 1:1 mixture (^{1}H NMR) of isomers. The spectroscopic data were identical to those of **230** obtained previously.

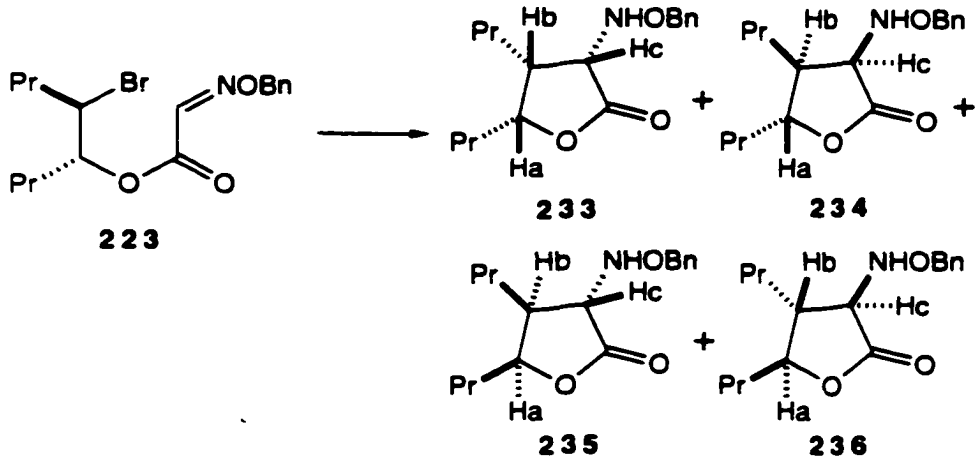
3-(2,2-Diphenylhydrazino)dihydro-4,5-dipropyl-2(3*H*)-furanone (232).

222 **232**

The general procedure for radical cyclization was followed, using **222** (0.494 g, 1.15 mmol) in PhMe (70 mL), Bu_3SnH (474 μL, 1.76 mmol) in PhMe (10 mL), and AIBN (30 mg, 0.18 mmol) in PhMe (10 mL). Flash chromatography of the residue over silica gel (1.6 x 28 cm), using 2% EtOAc-hexane, gave a crude fraction, which contained a small amount of tributyltin residues (^1H NMR, 400 MHz). Further purification by flash chromatography over silica gel (1.6 x 28 cm), using 3% EtOAc-hexane, gave **232** (330 mg, 82%) as a pale yellow oil, which was a 2:3:2:3 mixture (^1H NMR) of four chromatographically inseparable isomers: FTIR (CH_2Cl_2 cast) 1771 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 0.85-1.08 (m, 6 H), 1.25-1.95 (m, 8 H), 2.30-2.75 (m, 1 H), 3.65-3.75 (m, 0.42 H), 4.00-4.07 (m, 0.58 H), 4.09-4.15 (m, 0.22 H), 4.31-4.39 (m, 0.27 H), 4.40-4.45 (m, 0.33 H), 4.48 (s, 0.33 H), 4.63 (s, 0.27 H), 4.72 (s, 0.19 H), 4.74-4.80 (m, 0.18 H), 4.88 (s, 0.21 H), 7.05-7.40 (m, 10 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 13.94 (q'), 13.97 (q'), 14.05 (q'), 14.1 (q'), 14.2 (q'), 14.3 (q'), 14.4 (q'), 14.8 (q'), 19.5 (t'), 19.7 (t'), 19.9 (t'), 20.1 (t'), 20.2 (t'), 20.7 (t'), 21.0 (t'), 25.8 (t'), 29.5 (t'), 29.6 (t'), 32.4 (t'), 32.5 (t'), 33.5 (t'), 36.8 (d'), 37.4 (d'), 43.1 (d'), 43.9 (d'), 45.5 (d'), 48.4 (d'), 58.1 (d'), 60.8 (d'), 61.1 (d'), 61.8 (d'), 81.8 (d'), 82.1 (d'), 83.4 (d'), 83.7 (d'), 120.7 (d'), 121.0 (d'), 121.2 (d'), 123.1 (d'), 123.3 (d'), 123.4 (d'), 129.5 (d'), 129.57 (d'), 129.62 (d'), 147.58 (s'), 147.7 (s'), 147.9 (s'), 148.0 (s'), 175.36 (s'), 175.41 (s'), 175.7 (s'); exact mass *m/z*

calcd for $C_{22}H_{28}N_2O_2$ 352.2151, found 352.2146.

(3α,4α,5α)-Dihydro-3-[(phenylmethoxy)amino]-4,5-dipropyl-2(3*H*)-furanone (233), (3α,4α,5β)-Dihydro-3-[(phenyl-methoxy)amino]-4,5-dipropyl-2(3*H*)-furanone (234), (3α,4β,5β)-Dihydro-3-[(phenylmethoxy)amino]-4,5-dipropyl-2(3*H*)-furanone (235), and (3α,4β,5α)-Dihydro-3-[(phenyl-methoxy)amino]-4,5-dipropyl-2(3*H*)-furanone (236),



The general procedure for radical cyclization was followed, using **223** (0.407 g, 1.10 mmol) in PhMe (70 mL), Bu_3SnH (474 μL, 1.76 mmol) in PhMe (10 mL), and AIBN (30 mg, 0.18 mmol) in PhMe (10 mL). Flash chromatography of the residue over silica gel (1.6 x 30 cm), using 5% EtOAc-hexane, gave a crude fraction which contained a small amount of tributyltin residues (^1H NMR, 400 MHz). Further purification by flash chromatography over silica gel (1.6 x 24 cm), using

5% EtOAc-hexane, gave a 1:3:1:2 mixture (250 mg, 78% in all) of **233**, **234**, **235**, and **236** (as judged by ^{1}H NMR measurements). Flash chromatography of the mixture over silica gel (1.6 x 25 cm), using 3% EtOAc-hexane, gave four fractions, #1-#4. Each fraction was further purified by flash chromatography over silica gel (1.0 x 20 cm), using 2% EtOAc-hexane. Fractions #1, #2, #3, and #4 gave **233**, **234**, **235**, **236**, respectively, as colorless oils.

Compound **233** had: FTIR (CH_2Cl_2 cast) 3259, 1773 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.89-0.98 (m, 6 H), 1.29-1.61 (m, 7 H), 1.72-1.81 (m, 1 H), 2.52-2.60 (m, 1 H), 3.98 (dd, J = 7.6, 3.2 Hz, 1 H), 4.36-4.42 (m, 1 H), 4.72 (s, 2 H), 5.90 (s, 1 H), 7.27-7.37 (m, 5 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 13.9 (q'), 14.5 (q'), 19.4 (t'), 20.9 (t'), 25.7 (t'), 32.4 (t'), 41.9 (d'), 63.7 (d'), 82.3 (d'), 128.1 (d'), 128.5 (d'), 128.6 (d'), 137.2 (s'), 174.6 (s'); exact mass *m/z* calcd for $C_{17}H_{25}NO_3$ 291.1834, found 291.1833. Irradiation of the H_a ^{1}H NMR signal for **233** caused an NOE of 7.2% in the signal for H_b, and 3.5% for the H_c signal.

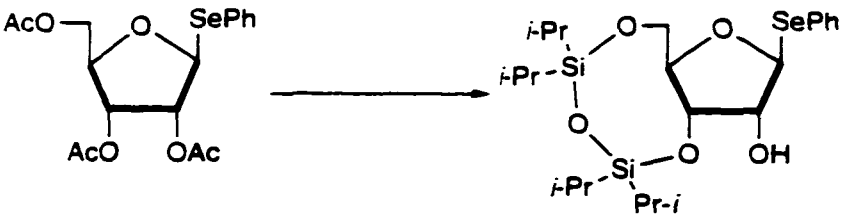
Compound **234** had: FTIR (CH_2Cl_2 cast) 3237, 1773 cm^{-1}; ^{1}H NMR (CD_2Cl_2, 400 MHz) δ 0.92-0.99 (m, 6 H), 1.25-1.73 (m, 8 H), 2.11-2.20 (m, 1 H), 3.75 (dd, J = 8.5, 2.9 Hz, 1 H), 4.21-4.28 (m, 1 H), 4.70 (d, J = 11.6 Hz, 1 H), 4.75 (d, J = 11.6 Hz, 1 H), 6.02 (d, J = 2.7 Hz, 1 H), 7.28-7.40 (m, 5 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 14.0 (q'), 14.4 (q'), 19.5 (t'), 21.3 (t'), 29.0 (t'), 37.0 (t'), 44.1 (d'), 62.2 (d'), 76.3 (t'), 85.4 (d'), 128.4 (d'), 128.8 (d'), 137.6 (s'), 175.8

(s'); exact mass *m/z* calcd for $C_{17}H_{25}NO_3$ 291.1834, found 291.1827. Irradiation of the H_a ^1H NMR signal for **234** caused a NOE of 5% in the signal for the H_b, and 0% for the H_c signal.

Compound **235** had: FTIR (CH_2Cl_2 cast) 3253, 1778 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 0.88-1.00 (m, 6 H), 1.25-1.65 (m, 8 H), 2.60-2.70 (m, 1 H), 3.36 (d, *J* = 10.5 Hz, 1 H), 4.49-4.56 (m, 1 H), 4.69 (d, *J* = 0.9 Hz, 2 H), 6.13 (s, 1 H), 7.28-7.40 (m, 5 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 14.0 (q'), 14.3 (q'), 19.5 (t'), 21.0 (t'), 30.3 (t'), 32.7 (t'), 40.6 (d'), 64.6 (d'), 77.4 (t'), 80.9 (d'), 128.3 (d'), 128.7 (d'), 129.1 (d'), 137.9 (s'), 175.4 (s'); exact mass *m/z* calcd for $C_{17}H_{25}NO_3$ 291.1834, found 291.1836. Irradiation of the H_a ^1H NMR signal for **235** caused a NOE of 13% in the signal for the H_b, and 0% for the H_c signal.

Compound **236** had: FTIR (CH_2Cl_2 cast) 1776 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.91-0.98 (m, 6 H), 1.30-1.72 (m, 8 H), 2.20-2.30 (m, 1 H), 3.41 (d, *J* = 9.9 Hz, 1 H), 4.02 (td, *J* = 8.5, 3.5 Hz, 1 H), 4.72 (d, *J* = 2.8 Hz, 2 H), 6.15 (s, 1 H), 7.27-7.38 (m, 5 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 13.9 (q'), 14.3 (q'), 18.9 (t'), 20.4 (t'), 34.2 (t'), 37.0 (t'), 42.7 (d'), 66.5 (d'), 76.9 (t'), 83.0 (d'), 128.0 (d'), 128.4 (d'), 128.7 (d'), 137.3 (s'), 175.1 (s'); exact mass *m/z* calcd for $C_{17}H_{25}NO_3$ 291.1834, found 192.1831. Irradiation of the H_a ^1H NMR signal for **236** caused a NOE of 4% in the signal for the H_b, and 5% for the H_c signal.

Phenyl 1-Seleno-3,5-*O*-(tetraisopropyldisiloxane-1,3-diyl)-β-D-ribofuranoside (239).



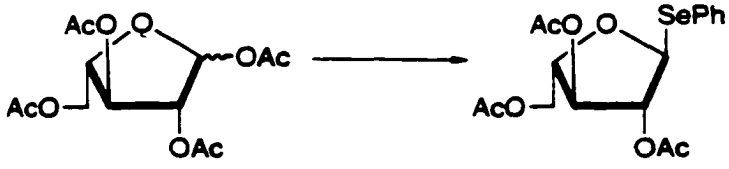
238 **239**

K_2CO_3 (123 mg, 0.891 mmol) was added to a stirred solution of **238**[52] (370 mg, 0.891 mmol) in 1:1 THF-MeOH (5 mL). Stirring was continued for 6 h, and the mixture was filtered through a pad (1 cm x 2 mm) of silica gel, and evaporated. Flash chromatography of the residue over silica gel (1.2 x 21 cm), using 2% MeOH-EtOAc, gave phenyl 1-seleno-β-D-ribofuranoside (236 mg, 91%) as a pale yellow oil: FTIR (MeOH cast) 3374 cm^{-1}; ^1H NMR (CD_3OD, 360 MHz) δ 3.54-3.66 (m, 2 H), 3.92-3.97 (m, 1 H), 4.03 (dd, J = 6.1, 5.0 Hz, 1 H), 4.13-4.15 (m, 1 H), 4.75-4.97 (br, 3 H), 5.48 (d, J = 3.3 Hz, 1 H), 7.25-7.36 (m, 3 H), 7.58-7.70 (m, 2 H); ^{13}C NMR (CD_3OD, 100.6 MHz) δ 63.7 (t'), 72.4 (d'), 77.6 (d'), 86.3 (d'), 88.2 (d'), 128.8 (d'), 130.1 (d'), 130.2 (s'), 135.6 (d'); exact mass *m/z* calcd for $C_{11}H_{14}O_4Se$ 290.0057, found 290.0062.

1.3-Dichloro-1,1,3,3-tetraisopropyldisiloxane (470 μL, 1.47 mmol) was added dropwise to a stirred and cooled (0 °C) solution of the above triol (424.2 mg, 1.468 mmol) in dry pyridine (14 mL). Stirring was continued for 30 min at 0 °C, and then for 6 h after removal of the ice bath. Pyridine was

evaporated under vacuum, and flash chromatography of the residue over silica gel (2.6 x 25 cm), using 5% EtOAc-hexane, gave **239** (624 mg, 80%) as a colorless oil: $[\alpha]_D$ = -112.3 (c 1.14, $CHCl_3$); ^1H NMR (CD_2Cl_2, 360 MHz) δ 0.93-1.17 (m, 28 H), 3.03 (d, *J* = 1.6 Hz, 1 H), 3.88-4.02 (m, 3 H), 4.27 (dt, *J* = 5.1, 1.4 Hz, 1 H), 4.37 (dd, *J* = 6.2, 5.2 Hz, 1 H), 5.59 (d, *J* = 1.2 Hz, 1 H), 7.26-7.35 (m, 3 H), 7.57-7.62 (m, 2 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 13.0 (d'), 13.2 (d'), 13.6 (d'), 13.6 (d'), 17.2 (q'), 17.2 (q'), 17.2 (q'), 17.4 (q'), 17.5 (q'), 17.6 (q'), 17.7 (q'), 64.4 (t'), 74.6 (d'), 77.9 (d'), 83.4 (d'), 86.1 (d'), 128.4 (d'), 128.8 (s'), 129.5 (d'), 135.3 (d'); exact mass (electrospray) *m/z* calcd for $C_{23}H_{40}NaO_5SeSi_2$ (M + Na) 555.1477, found 555.1485.

Phenyl 2,3,5-Tri-*O*-acetyl-1-seleno-α-L-arabinofuranoside (241).



240 **241**

$BF_3.Et_2O$ (232 μL, 1.88 mmol) was added dropwise to a stirred and cooled (0 °C) solution of **240**[53] (637 mg, 2.00 mmol) and PhSeH (314 μL, 2.96 mmol) in CH_2Cl_2 (20 mL). Stirring was continued for 28 h at 0 °C, and then saturated aqueous $NaHCO_3$ (5 mL) was added. The organic phase was

washed with water (3 x 5 mL) and brine (5 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.6 x 26 cm), using 20% EtOAc-hexane, gave **241** (533 mg, 64%) as a colorless oil: $[\alpha]_D$ = -161.4 (c 1.98, $CHCl_3$); FTIR (CH_2Cl_2 cast) 1747 cm^{-1}; ^1H NMR (CD_2Cl_2, 360 MHz) δ 2.06 (s, 3 H) 2.07 (s, 3 H), 2.12 (s, 3 H), 4.25 (dd, *J* = 12.0, 5.6 Hz, 1 H), 4.40 (dd, *J* = 12.0, 3.7 Hz, 1 H), 4.46-4.50 (m, 1 H), 5.03-5.05 (m, 1 H), 5.34-5.38 (m, 1 H), 5.80-5.82 (m, 1 H), 7.29-7.34 (m, 3 H), 7.60-7.66 (m, 2 H); ^{13}C NMR (CD_2Cl_2, 75.5 MHz) δ 20.8 (q'), 62.9 (t'), 77.6 (d'), 81.5 (d'), 82.5 (d'), 87.3 (d'), 128.3 (d'), 129.5 (d'), 129.6 (s'), 134.6 (d'), 169.8 (s'), 170.2 (s'), 170.6 (s'); exact mass *m/z* calcd for $C_{17}H_{20}O_7Se$ 416.0374, found 416.03774.

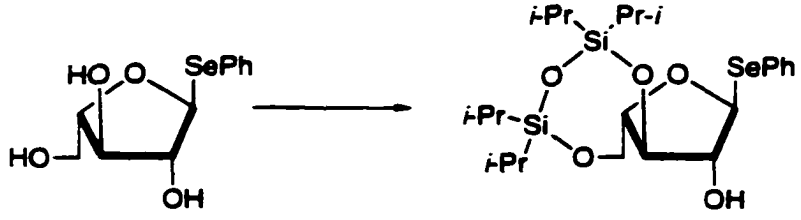
Phenyl 1-Seleno-α-L-arabinofuranoside (242).

241 **242**

K_2CO_3 (173 mg, 1.26 mmol) was added to a stirred solution of **241** (522 mg, 1.26 mmol) in 1:1 THF-MeOH (8 mL), and the mixture was stirred for 1 h, filtered through a pad (1 x 2 mm) of silica gel, and evaporated. Flash chromatography of the residue over silica gel (1.6 x 28 cm), using 2% MeOH-EtOAc, gave **242** (338 mg, 93%) as a pale yellow

oil: $[\alpha]_D$ = -267.9 (c 1.04, $CHCl_3$); FTIR (CH_2Cl_2 cast) 3373 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 3.71 (d, *J* = 11.5 Hz, 1 H), 3.79 (d, *J* = 11.5 Hz, 1 H), 4.11 (br s, 2 H), 4.20-4.59 (br m, 4 H), 5.69 (d, *J* = 2.6 Hz, 1 H), 7.22-7.30 (m, 3 H), 7.57-7.62 (m, 2 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 61.3 (t'), 77.2 (d'), 83.1 (d'), 84.6 (d'), 89.2 (d'), 128.1 (d'), 129.5 (d'), 130.1 (s'), 134.3 (d'); exact mass *m/z* calcd for $C_{11}H_{14}O_4Se$ 290.0057, found 290.0056.

Phenyl 1-Seleno-3,5-*O*-(tetraisopropyldisiloxane-1,3-diyl)-α-L-arabinofuranoside (243).

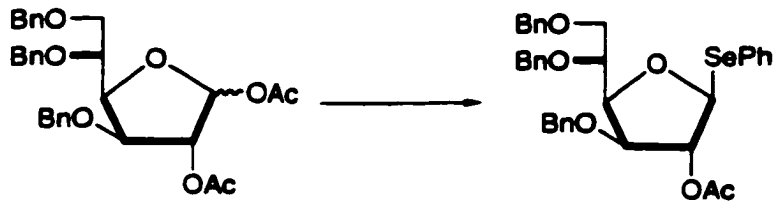


242 **243**

1,3-Dichloro-1,1,3,3-tetraisopropyldisiloxane (304 μL, 0.952 mmol) was added dropwise to a stirred and cooled (0 °C) solution of **242** (275 mg, 0.952 mmol) in dry pyridine (10 mL). Stirring was continued for 30 min at 0 °C, and then for 6 h after removal of the ice bath. Pyridine was evaporated under vacuum, and flash chromatography of the residue over silica gel (1.6 x 28 cm), using 5% EtOAc-hexane, gave **243** (390 mg, 77%) as a colorless oil: $[\alpha]_D$ = -141.2 (c 1.32, $CHCl_3$); ^1H NMR (CD_2Cl_2, 300 MHz) δ 0.96-1.15 (m, 28 H), 2.54 (d, *J* = 5.1 Hz, 1 H), 3.91-4.04 (m, 3 H), 4.16-4.26 (m, 1 H), 3.33 (dd, *J*

= 10.4, 5.0 Hz, 1 H), 5.62 (d, J = 4.6 Hz, 1 H) 7.27-7.33 (m, 3 H), 7.60-7.67 (m, 2 H); ^{13}C NMR (CD_2Cl_2, 75.5 MHz) δ 13.0 (d'), 13.3 (d'), 13.5 (d'), 13.9 (d'), 17.2 (q'), 17.2 (q'), 17.3 (q'), 17.5 (q'), 17.7 (q'), 61.9 (t'), 77.4 (d'), 82.0 (d'), 83.2 (d'), 88.5 (d'), 127.9 (d'), 129.4 (d'), 130.5 (s'), 134.0 (d'); exact mass (electrospray) *m/z* calcd for $C_{23}H_{40}NaO_5SeSi_2$ (M + Na) 555.1477, found 555.1477.

Phenyl 2-*O*-Acetyl-3,5,6-tri-*O*-benzyl-1-seleno-β-D-glucofuranoside (245).

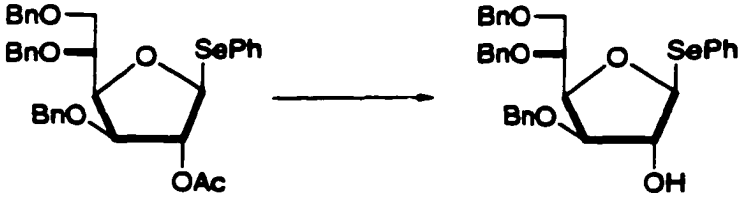


244 **245**

$BF_3.Et_2O$ (476 µL, 3.872 mmol) was added dropwise to a stirred and cooled (0 °C) solution of **244**[54] (2.20 g, 4.12 mmol) and PhSeH (648 µL, 6.09 mmol) in CH_2Cl_2 (40 mL). Stirring was continued for 2 h at 0 °C, and then saturated aqueous $NaHCO_3$ (5 mL) was added. The organic phase was washed with water (2 x 10 mL) and brine (10 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.6 x 28 cm), using 10% EtOAc-hexane, gave **245** (1.91 g, 73%) as a colorless oil: $[\alpha]_D$ = -117.8 (c 1.27, $CHCl_3$); FTIR (CH_2Cl_2 cast) 1747 cm^{-1}; ^1H NMR (CD_2Cl_2, 300 MHz) δ 2.12 (s, 3 H), 3.80 (dd, J = 10.8, 4.6 Hz, 1 H), 3.99 (dd,

J = 10.8, 2.0 Hz, 1 H), 4.21 (ddd, J = 9.4, 4.5, 1.9 Hz, 1 H), 4.26 (d, J = 4.0 Hz, 1 H), 4.44 (dd, J = 9.4, 4.0 Hz, 1 H), 4.52 (d, J = 11.3 Hz, 1 H), 4.61-4.65 (m, 3 H), 4.79 (d, J = 11.3 Hz, 1 H), 4.95 (d, J = 11.4 Hz, 1 H), 5.74 (s, 1 H), 7.29-7.51 (m, 18 H), 7.66-7.73 (m, 2 H); ^{13}C NMR (CD_2Cl_2, 75.5 MHz) δ 21.1 (q'), 70.5 (t'), 72.5 (t'), 72.6 (t'), 73.7 (t'), 76.3 (d'), 80.9 (d'), 81.1 (d'), 81.9 (d'), 87.5 (d'), 127.8 (d'), 127.8 (d'), 127.9 (d'), 128.1 (d'), 128.3 (d'), 128.5 (d'), 128.6 (d'), 128.7 (d'), 129.5 (d'), 131.9 (s'), 133.9 (d'), 137.9 (s'), 139.1 (s'), 139.3 (s'), 170.0 (s'); exact mass (electrospray) *m/z* calcd for $C_{35}H_{36}NaO_6Se$ (M + Na) 655.1575, found 655.1577.

Phenyl 3,5,6-Tri-*O*-benzyl-1-seleno-β-D-glucofuranoside (246).

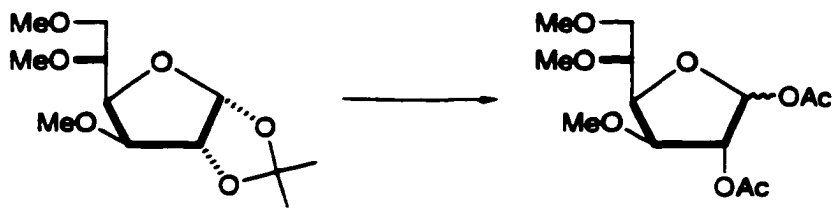


245 **246**

K_2CO_3 (177 mg, 1.28 mmol) was added to a stirred solution of **245** (812 mg, 1.28 mmol) in 1:1 THF-MeOH (10 mL), and the mixture was stirred vigorously for 15 min, filtered through a pad (2 cm x 1 mm) of silica gel, and evaporated. Flash chromatography of the residue over silica gel (1.6 x 28 cm), using 20% EtOAc-hexane, gave **246** (727 mg, 96%) as a

colorless oil: $[\alpha]_D$ = -143.7 (c 1.47, $CHCl_3$); FTIR (CH_2Cl_2 cast) 3415 cm^{-1}; ^1H NMR (CD_2Cl_2, 300 MHz) δ 2.38 (br, 1 H), 3.74 (dd, J = 10.8, 4.8 Hz, 1 H); 3.93 (dd, J = 10.8, 2.0 Hz, 1 H), 4.07 (d, J = 4.2 Hz, 1 H), 4.14 (ddd, J = 9.2, 4.8, 2.0 Hz, 1 H), 4.43 (dd, J = 9.2, 4.2 Hz, 1 H), 4.49 (dd, J = 11.4, 2.2 Hz, 1 H), 4.59 (s, 2 H), 4.67-4.77 (m, 3 H), 5.56 (br s, 1 H), 7.22-7.41 (m, 18 H), 7.58-7.65 (m, 2 H); ^{13}C NMR (CD_2Cl_2, 75.5 MHz) δ 70.8 (t'), 72.6 (t'), 72.7 (t'), 73.7 (t'), 76.6 (d'), 80.1 (d'), 81.6 (d'), 83.2 (d'), 90.4 (d'), 127.5 (d'), 127.7 (d'), 127.7 (d'), 127.9 (d'), 127.9 (d'), 128.1 (d'), 128.1 (d'), 128.5 (d'), 128.6 (d'), 128.7 (d'), 129.4 (d'), 132.2 (s'), 133.6 (d'), 138.1 (s'), 139.1 (s'), 139.3 (s'); exact mass (electrospray) *m/z* calcd for $C_{33}H_{34}NaO_5Se$ (M + Na) 613.1469, found 613.1480.

1,2-Di-*O*-acetyl-3,5,6-tri-*O*-methyl-α,β-D-glucofuranoses (248).



247 **248**

$PhCO_2H$ (170 mg, 1.39 mmol) was added to a stirred solution of **247**[57] (1.09 g, 4.18 mmol) in water (8.5 mL) and the mixture was refluxed for 6 h, cooled in an ice bath and filtered. The insoluble material was washed with cold H_2O (2 x 1 mL), and the combined filtrates were evaporated. Water

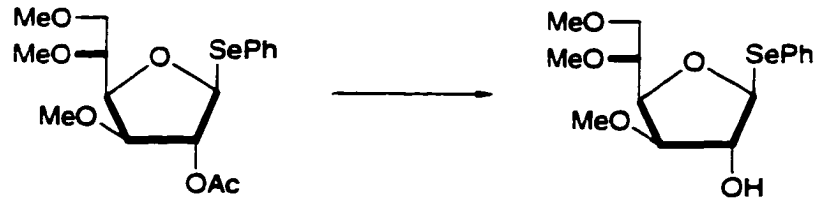
(6 mL) was added, and the solution was evaporated. The procedure was repeated with a further portion of water (6 mL), and water (25 mL) was added to the residue. The resulting solution was extracted with Et_2O (2 x 4 mL). Evaporation of the aqueous solution afforded a colorless syrup, which was dried under vacuum. Pyridine (9 mL) and Ac_2O (6 mL) were added to the dried residue, and the mixture was stirred for 14 h. Excess of pyridine and Ac_2O were evaporated under vacuum, and flash chromatography of the residue over silica gel (1.6 x 28 cm), using 30% EtOAc-hexane, gave **248** (1.05 g, 82%) as a 67:33 mixture of α and β anomers [^{1}H NMR (300 MHz)]: $[\alpha]_D$ = +8.7 (c 1.47, $CHCl_3$); FTIR (CH_2Cl_2 cast) 1751 cm^{-1}; ^{1}H NMR (CD_2Cl_2, 300 MHz) δ 2.03 (s, 2 H), 2.05 (s, 1 H), 2.07 (br s, 3 H), 3.34-3.47 (m, 10 H), 3.52-3.69 (m, 2 H), 3.76 (d, *J* = 4.5 Hz, 0.33 H), 3.91-3.93 (m, 0.67 H), 4.13-4.22 (m, 1 H), 5.14 (br s, 0.33 H), 5.19 (dd, *J* = 4.5, 2.6 Hz, 0.67 H), 6.02 (s, 0.33 H), 6.29 (d, *J* = 4.4 Hz, 0.67 H); ^{13}C NMR (CD_2Cl_2, 75.5 MHz) δ 20.6 (q'), 20.9 (q'), 21.0 (q'), 21.2 (q'), 58.0 (q'), 58.2 (q'), 59.3 (q'), 72.2 (t'), 75.7 (d'), 77.5 (d'), 77.5 (d'), 78.8 (d'), 78.9 (d'), 81.9 (d'), 82.3 (d'), 83.2 (d'), 95.0 (d'), 99.8 (d'), 169.6 (s'), 169.8 (s'), 169.9 (s'); exact mass (electrospray) *m/z* calcd for $C_{13}H_{22}NaO_8$ (M + Na) 329.1212, found 329.1211.

Phenyl 2-*O*-acetyl-3,5,6-tri-*O*-methyl-1-seleno-β-D-glucofuranoside (249).

248 **249**

$BF_3.Et_2O$ (404 μL, 3.28 mmol) was added dropwise to a stirred and cooled (0 °C) solution of **248** (1.07 g, 3.49 mmol) and PhSeH (557 μL, 5.24 mmol) in CH_2Cl_2 (35 mL). Stirring was continued for 1.5 h at 0 °C, and then saturated aqueous $NaHCO_3$ (5 mL) was added. The organic phase was washed with water (2 x 10 mL) and brine (10 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.6 x 28 cm), using 20% EtOAc-hexane, gave **249** (1.20 g, 85%) as a colorless oil: $[\alpha]_D$ = -147.7 (c 1.33, $CHCl_3$); FTIR (CH_2Cl_2 cast) 1748 cm^{-1}; ^1H NMR (CD_2Cl_2, 360 MHz) δ 2.04 (s, 3 H), 3.36 (s, 3 H), 3.42 (s, 3 H), 3.47-3.51 [m, including s (3 H) at δ 3.50, 4 H in all], 3.67-3.73 (m, 2 H), 3.83 (d, *J* = 4.0 Hz, 1 H), 4.12 (dd, *J* = 9.5, 4.0 Hz, 1 H), 5.50 (s, 1 H), 5.57 (s, 1 H), 7.27-7.32 (m, 3 H), 7.57-7.63 (m, 2 H); ^{13}C NMR (CD_2Cl_2, 75.5 MHz) δ 21.0 (q'), 58.0 (q'), 58.2 (q'), 59.4 (q'), 72.1 (t'), 77.4 (d'), 80.8 (d'), 81.6 (d'), 82.7 (d'), 87.3 (d'), 127.7 (d'), 129.4 (d'), 131.7 (s'), 133.9 (d'), 170.0 (s'); exact mass (electrospray) *m/z* calcd for $C_{17}H_{24}NaO_6Se$ (M + Na) 427.0636, found 427.0634.

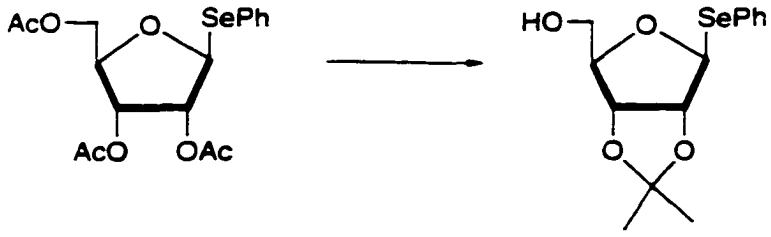
Phenyl 3,5,6-Tri-O-methyl-1-seleno-β-D-glucofuranoside (250).



249 **250**

K_2CO_3 (385 mg, 2.78 mmol) was added to a stirred solution of **249** (1.12 g, 2.78 mmol) in 1:1 THF-MeOH (20 mL) and the mixture was stirred vigorously for 15 min, filtered through a pad (1 cm x 2 mm) of silica gel, and evaporated. Flash chromatography of the residue over silica gel (1.6 x 28 cm), using 40% EtOAc-hexane, gave **250** (0.964 g, 96%) as a colorless oil: $[\alpha]_D$ = -196.0 (c 1.30, $CHCl_3$); FTIR (CH_2Cl_2 cast) 3410 cm^{-1}; ^1H NMR (CD_2Cl_2, 300 MHz) δ 2.88 (d, *J* = 4.2 Hz, 1 H), 3.35 (s, 3 H), 3.42 (s, 3 H), 3.44 (s, 3 H), 3.47-3.53 (m, 1 H), 3.68-3.77 (m, 3 H), 4.19 (dd, *J* = 9.2, 4.2 Hz, 1 H), 4.58-4.63 (m, 1 H), 5.50 (br s, 1 H), 7.25-7.32 (m, 3 H), 7.56-7.63 (m, 2 H); ^{13}C NMR (CD_2Cl_2, 75.5 MHz) δ 58.0 (q'), 58.0 (q'), 59.4 (q'), 72.3 (t'), 77.6 (d'), 79.7 (d'), 81.2 (d'), 84.9 (d'), 90.3 (d'), 127.5 (d'), 129.4 (d'), 132.0 (s'), 133.5 (d'); exact mass (electrospray) *m/z* calcd for $C_{15}H_{22}NaO_5Se$ (M + Na) 385.0530, found 385.0532.

Phenyl 2,3-*O*-Isopropylidene-1-seleno-β-D-ribofuranoside (251).



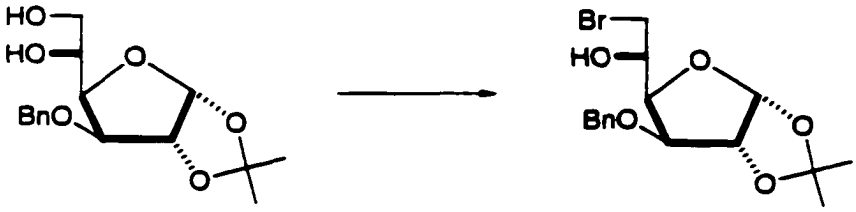
238 **251**

K_2CO_3 (123 mg, 0.891 mmol) was added to a stirred solution of **238**[52] (370 mg, 0.891 mmol) in 1:1 THF-MeOH (5 mL). Stirring was continued for 6 h, and the mixture was filtered through a pad (1 cm x 2 mm) of silica gel, and evaporated. Flash chromatography of the residue over silica gel (1.2 x 21 cm), using 2% MeOH-EtOAc, gave phenyl 1-seleno-β-D-ribofuranoside (235 mg, 91%) as a pale yellow oil.

p-$MeC_6H_4SO_3H.H_2O$ (9.2 mg, 0.048 mmol) was added to a stirred solution of phenyl 1-seleno-β-D-ribofuranoside (140.0 mg, 0.484 mmol) in acetone (5 mL). Stirring was continued for 5 h, $NaHCO_3$ (12.2 mg, 0.145 mmol) was then added. Stirring was continued for another 0.5 h, and the mixture was then evaporated. Flash chromatography of the residue over silica gel (1.0 x 20 cm), using 30% EtOAc-hexane, gave **251** (148 mg, 92%) as a colorless oil: FTIR (CH_2Cl_2 cast) 3462 cm^{-1}; ^1H NMR (CD_2Cl_2, 360 MHz) δ 1.32 (s, 3 H), 1.48 (s, 3 H), 2.10 (dd, *J* = 7.0, 6.3 Hz, 1 H), 3.69-3.81 (m, 2 H), 4.30-4.33 (m, 1 H), 4.76 (dd, *J* = 6.1, 1.8 Hz, 1 H), 4.88 (dd, *J* =

6.1, 2.1 Hz, 1 H), 5.82 (d, J = 2.1 Hz, 1 H), 7.28-7.40 (m, 3 H), 7.59-7.68 (m, 2 H); ^{13}C NMR (CD_2Cl_2, 75.5 MHz) δ 25.4 (q'), 27.0 (q'), 63.1 (t'), 82.1 (d'), 87.1 (d'), 88.8 (d'), 88.9 (d'), 113.7 (s'), 128.3 (d'), 129.3 (s'), 129.6 (d'), 134.4 (d'); exact mass *m/z* calcd for $C_{14}H_{18}O_4Se$ 330.0370, found 330.0364.

3-*O*-Benzyl-6-bromo-6-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose (253).



252 **253**

Ph_3P (642 mg, 2.44 mmol) was added to a stirred and cooled (0 °C) solution of **252**[58] (379 mg, 1.2 mmol) in pyridine (20 mL), and then CBr_4 (405 mg, 1.22 mmol) was added in several portions at 0 °C. After the addition, the mixture was heated to 60 °C for 10 min. MeOH (5 mL) was added to destroy any excess of reagents, and the mixture was evaporated. Flash chromatography of the residue over silica gel (1.6 x 28 cm), using 20% EtOAc-hexane, gave **253** (402 mg, 88%) as a colorless oil: $[\alpha]_D$ = -41.8 (c 1.25, $CHCl_3$); FTIR (CH_2Cl_2 cast) 3482 cm^{-1}; ^1H NMR (CD_2Cl_2, 300 MHz) δ 1.31 (br s, 3 H), 1.46 (br s, 3 H), 2.38 (d, J = 5.9, 1 H), 3.58 (dd, J = 10.5, 5.7 Hz, 1 H), 3.71 (dd, J = 10.5, 2.7 Hz, 1 H),

4.03-4.14 (m, 3 H), 4.58 (d, J = 11.7 Hz, 1 H), 4.64 (d, J = 3.7 Hz, 1 H), 4.72 (d, J = 10.7 Hz, 1 H), 5.89 (d, J = 3.7 Hz, 1 H), 7.32-7.40 (m, 5 H); ^{13}C NMR (CD_2Cl_2, 75.5 MHz) δ 26.4 (q'), 27.0 (q'), 38.8 (t'), 68.4 (d'), 72.5 (t'), 81.1 (d'), 81.9 (d'), 82.5 (d'), 105.6 (d'), 112.2 (s'), 128.2 (d'), 128.4 (d'), 128.9 (d'), 137.8 (s'); exact mass (electrospray) *m/z* calcd for $C_{16}H_{21}BrNaO_5$ (M + Na) 395.0470, found 395.0475.

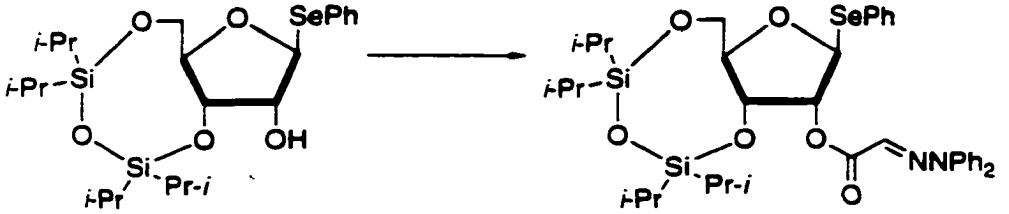
Phenyl 3,4,6-Tri-*O*-benzyl-1-seleno-α-D-mannopyranoside (262).

261 **262**

K_2CO_3 (153 mg, 1.10 mmol) was added to a stirred solution of **261**[60] (350 mg, 0.555 mmol) in 1:1 THF-MeOH (10 mL), and the mixture was stirred vigorously for 30 min, filtered through a pad (1 cm x 2 mm) of silica gel, and evaporated. Flash chromatography of the residue over silica gel (1.6 x 27 cm), using 20% EtOAc-hexane, gave **262** (326 mg, 90%) as a colorless oil: $[\alpha]_D$ = +158.6 (c 1.2, $CHCl_3$); FTIR (CH_2Cl_2 cast) 3428 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 2.87 (br, 1 H), 3.70 (dd, J = 10.8, 1.9 Hz, 1 H); 3.82 (dd, J = 10.8, 4.5 Hz, 1 H), 3.89 (dd, J = 9.1, 3.2 Hz, 1 H), 3.94-3.99 (m, 1 H), 4.19-4.23 (m, 1 H), 4.37 (dd, J = 3.0, 1.5 Hz, 1 H),

4.50 (d, J = 11.8, 1 H), 4.59-4.63 (m, 2 H), 4.73 (dd, J = 17.1, 11.5 Hz, 1 H), 4.89 (d, J = 10.9 Hz, 1 H), 5.90 (d, J = 1.3 Hz, 1 H), 7.25-7.45 (m, 18 H), 7.62-7.66 (m, 2 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 69.2 (t'), 70.6 (d'), 72.2 (t'), 73.6 (t'), 74.3 (d'), 74.7 (d'), 75.4 (t'), 80.9 (d'), 85.8 (d'), 127.9 (d'), 127.9 (d'), 128.1 (d'), 128.2 (d'), 128.3 (d'), 128.3 (d'), 128.6 (d'), 128.6 (d'), 128.8 (d'), 129.5 (d'), 129.6 (s'), 134.4 (d'), 138.2 (s'), 138.6 (s'), 138.9 (s'); exact mass (electrospray) *m/z* calcd for $C_{33}H_{34}NaO_5Se$ (M + Na) 613.1469, found 613.1477.

Phenyl 2-*O*-(Diphenylhydrazono)acetyl-1-seleno-3,5-*O*-(tetraisopropyldisiloxane-1,3-diyl)-β-D-ribofuranoside (269).

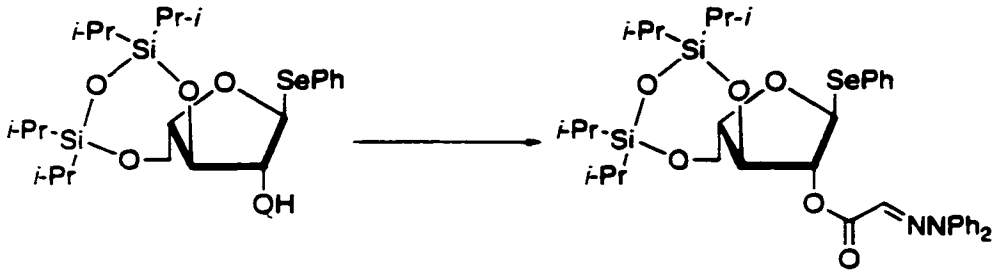


239 **269**

The general procedure for coupling alcohols with reagent **207** was followed, using **207** (341 mg, 1.42 mmol), **239** (630 mg, 1.18 mmol), DCC (322 mg, 1.56 mmol), and DMAP (20.0 mg, 0.164 mmol) in CH_2Cl_2 (10 mL). Flash chromatography of the residue over silica gel (1.6 x 28 cm), using 5% EtOAc-hexane, gave **269** (839 mg, 94%) as a pale yellow oil: $[\alpha]_D$ = -57.7 (c 1.05, $CHCl_3$); FTIR (CH_2Cl_2 cast) 1740, 1711 cm^{-1}; ^{1}H NMR

(CD_2Cl_2, 360 MHz) δ 0.84-1.19 (m, 28 H), 3.90-4.06 (m, 3 H), 4.42-4.49 (m, 1 H), 5.62-5.68 (m, 2 H), 6.51 (d, J = 2.2 Hz, 1 H), 7.14-7.69 (m, 15 H); ^{13}C NMR (CD_2Cl_2, 50.3 MHz) δ 13.1 (d'), 13.4 (d'), 13.6 (d'), 17.1 (q'), 17.2 (q'), 17.3 (q'), 17.4 (q'), 17.6 (q'), 63.3 (t'), 72.7 (d'), 79.1 (d'), 82.9 (d'), 83.6 (d'), 122.7 (d'), 123. (d'), 126.5 (d'), 128.5 (s'), 128.6 (d'), 129.5 (d'), 130.3 (d'), 135.5 (d'), 142.6 (s'), 163.4 (s'); exact mass (electrospray) *m/z* calcd for $C_{37}H_{50}N_2NaO_6SeSi_2$ (M + Na) 777.2270, found 777.2276.

Phenyl 2-*O*-(Diphenylhydrazono)acetyl-1-seleno-3,5-*O*-(tetraisopropyldisiloxane-1,3-diyl)-α-L-arabinofuranoside (270).

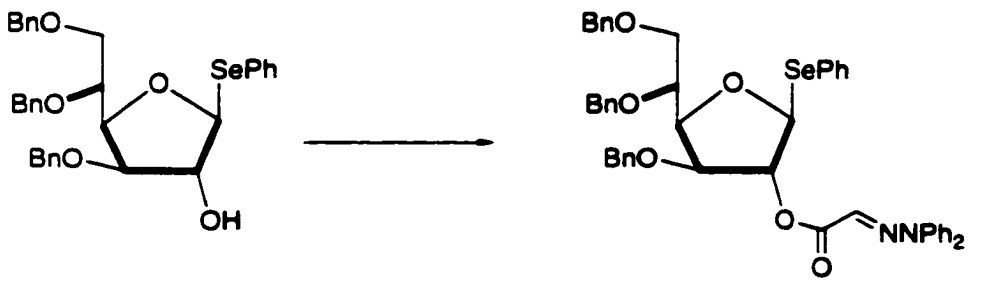


243 **270**

The general procedure for coupling alcohols with reagent **207** was followed, using **207** (162 mg, 0.677 mmol), **243** (240 mg, 0.452 mmol), DCC (153 mg, 0.745 mmol), and DMAP (10.0 mg, 0.082 mmol) in CH_2Cl_2 (4 mL). Flash chromatography of the residue over silica gel (1.6 x 300 cm), using 5% EtOAc-hexane, gave **270** (308 mg, 90%) as a pale yellow oil: $[\alpha]_D$ = -56.9 (c 1.27, $CHCl_3$); FTIR (CH_2Cl_2 cast) 1711 cm^{-1}; ^1H NMR

(CD_2Cl_2, 300 MHz) δ 0.98-1.17 (m, 28 H) 3.95 (dd, *J* = 12.4, 5.4 Hz, 1 H), 4.07 (dd, *J* = 12.4, 3.3 Hz, 1 H), 4.19-4.24 (m, 1 H), 4.46-4.50 (m, 1 H), 5.46-5.49 (m, 1 H), 5.72-5.76 (m, 1 H), 7.16-7.66 (m, 15 H); ^{13}C NMR (CD_2Cl_2, 75.5 MHz) δ 12.8 (d'), 13.3 (d'), 13.6 (d'), 13.8 (d'), 17.1 (q'), 17.2 (q'), 17.5 (q'), 17.7 (q'), 62.0 (t'), 76.3 (d'), 82.5 (d'), 84.0 (d'), 86.0 (d'), 123.3 (d'), 127.9 (d'), 129.3 (d'), 130.4 (d'), 130.5 (s'), 134.2 (d'), 163.9 (s'), exact mass (electrospray) *m/z* calcd for $C_{37}H_{50}N_2NaO_6SeSi_2$ (M + Na) 777.2270, found 777.2279.

Phenyl 3,5,6-Tri-*O*-benzyl-2-*O*-(diphenylhydrazono)acetyl-1-seleno-β-D-glucofuranoside (271).



246 **271**

The general procedure for coupling alcohols with reagent **207** was followed, using **207** (293 mg, 1.22 mmol), **246** (600 mg, 1.01 mmol), DCC (277 mg, 1.34 mmol), and DMAP (15.0 mg, 0.123 mmol) in CH_2Cl_2 (10 mL). Flash chromatography of the residue over silica gel (1.6 x 28 cm), using 10% EtOAc-hexane, gave **271** (804 mg, 97%) as a pale yellow oil: $[\alpha]_D$ = -81.7 (c 1.26, $CHCl_3$); FTIR (CH_2Cl_2 cast) 1731, 1704 cm^{-1}; ^1H

NMR (CD_2Cl_2, 300 MHz) δ 3.78 (dd, J = 10.8, 4.6 Hz, 1 H), 3.98 (dd, J = 10.8, 1.9 Hz, 1 H), 4.21 (ddd, J = 9.4, 4.6, 1.9 Hz, 1 H), 4.31 (d, J = 4.0 Hz, 1 H), 4.43 (dd, J = 9.3, 4.0 Hz, 1 H), 4.51 (d, J = 11.3 Hz, 1 H), 4.61-4.68 (m, 3 H), 4.77 (d, J = 11.3 Hz, 1 H), 4.99 (d, J = 11.4 Hz, 1 H), 5.78 (s, 1 H), 5.87 (s, 1 H), 6.51 (s, 1 H), 7.19-7.72 (m, 30 H); ^{13}C NMR (CD_2Cl_2, 50.3 MHz) δ 70.5 (t'), 72.5 (t'), 72.6 (t'), 73.6 (t'), 76.3 (d'), 80.9 (d'), 81.2 (d'), 82.0 (d'), 87.5 (d'), 123.3 (d'), 126.6 (d'), 127.7 (d'), 127.8 (d'), 127.9 (d'), 128.1 (d'), 128.3 (d'), 128.5 (d'), 128.6 (d'), 128.7 (d'), 129.4 (d'), 130.3 (d'), 131.8 (s'), 133.9 (d'), 137.9 (s'), 139.1 (s'), 139.2 (s'), 142.3 (s'), 163.5 (s'); exact mass (electrospray) *m/z* calcd for $C_{47}H_{44}N_2NaO_6Se$ (M + Na) 835.2262, found 835.2264.

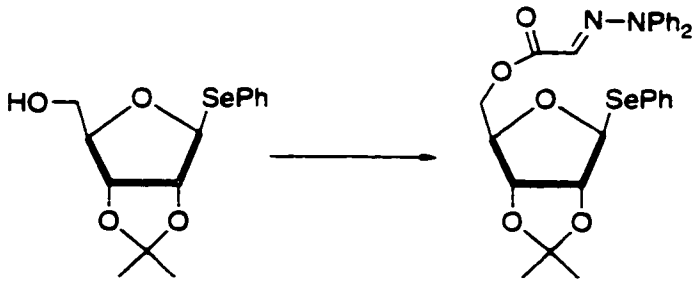
Phenyl 2-*O*-(Diphenylhydrazono)acetyl-3,5,6-tri-*O*-methyl-1-seleno-β-D-glucofuranoside (272).

250 **272**

The general procedure for coupling alcohols with reagent **207** was followed, using **207** (714 mg, 2.97 mmol), **250** (895 mg, 2.47 mmol), DCC (675 mg, 3.27 mmol), and DMAP (36.3 mg,

0.298 mmol) in CH_2Cl_2 (25 mL). Flash chromatography of the residue over silica gel (1.6 x 28 cm), using 30% EtOAc-hexane, gave **272** (1.50 g, *ca* 103%) as a partially crystalline light brown mass which contained a small amount [<10 mol% by ^1H NMR (400 MHz)] of chromatographically inseparable impurities. An analytical sample was prepared by swirling the material in 40% EtOAc-hexane (15 mL) and evaporating the clear supernatant. The resulting **272** had: $[\alpha]_D$ = -116.4 (c 1.12, $CHCl_3$); FTIR (CH_2Cl_2 cast) 1734, 1708 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 3.36 (s, 3 H), 3.42 (s, 3 H), 3.48-3.55 [m, including s (3 H) at δ 3.54, 4 H in all], 3.68-3.75 (m, 2 H), 3.90 (d, J = 4.0 Hz, 1 H) 4.14 (dd, J = 9.1, 4.0 Hz, 1 H), 5.62 (s, 1 H), 5.65 (s, 1 H), 6.43 (s, 1 H), 7.15-7.65 (m, 15 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 58.1 (q'), 58.2 (q'), 59.4 (q'), 72.2 (t'), 77.4 (d'), 81.0 (d'), 81.7 (d'), 82.8 (d'), 87.4 (d'), 123.3 (d'), 127.7 (d'), 129.4 (d'), 130.4 (d'), 131.7 (s'), 133.9 (d'), 163.4 (s'); exact mass (electrospray) *m/z* calcd for $C_{29}H_{32}N_2NaO_6Se$ (M + Na) 607.1323, found 607.1323.

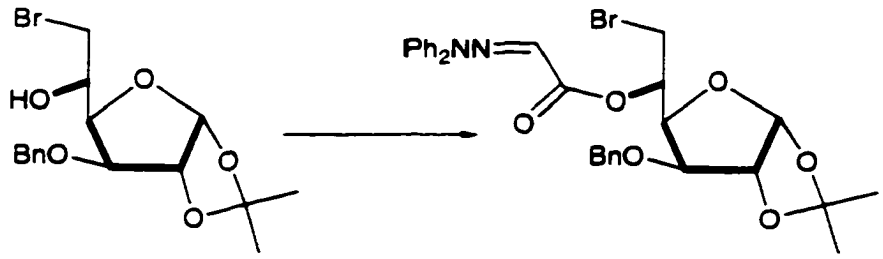
Phenyl 5-*O*-(Diphenylhydrazono)acetyl-2,3-*O*-isopropylidene-1-seleno-β-D-ribofuranoside (273).



251 **273**

The general procedure for coupling alcohols with reagent **207** was followed, using **207** (121 mg, 0.504 mmol), alcohol **10a** (148 mg, 0.449 mmol), DCC (114 mg, 0.550 mmol), and DMAP (6.1 mg, 0.05 mmol) in CH_2Cl_2 (2 mL). Flash chromatography of the residue over silica gel (1.0 x 20 cm), using 20% EtOAc-hexane, gave **273** (230 mg, 92%) as a pale yellow oil: FTIR (CH_2Cl_2 cast) 1731, 1706 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 1.37 (s, 3 H), 1.45 (s, 3 H), 4.39 (dd, *J* = 10.0, 4.7 Hz, 1 H), 4.46-4.54 (m, 2 H), 4.81 (dd, *J* = 6.0, 1.6 Hz, 1 H), 4.96 (dd, *J* = 6.0, 1.8 Hz, 1 H), 5.82 (d, *J* = 1.8 Hz, 1 H), 6.56 (s, 1 H), 7.20-7.64 (m, 15 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 25.5 (q'), 27.0 (q'), 63.9 (t'), 82.6 (d'), 85.4 (d'), 87.1 (d'), 88.3 (d'), 113.8 (s'), 123.9 (d'), 126.5 (d'), 128.1 (d'), 129.4 (d'), 129.5 (d'), 130.3 (d'), 134.6 (d'), 164.1 (s'); exact mass *m/z* calcd for $C_{28}H_{28}N_2O_5Se$ 552.1163, found 552.1157.

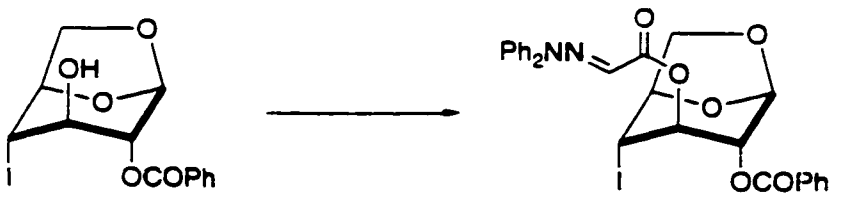
3-*O*-Benzyl-6-bromo-6-deoxy-5-*O*-(diphenylhydrazono)acetyl-1,2-*O*-isopropylidene-α-D-glucofuranose (274).



253 **274**

The general procedure for coupling alcohols with reagent **207** was followed, using **207** (303 mg, 1.26 mmol), **253** (392 mg, 1.05 mmol), DCC (286 mg, 1.39 mmol), and DMAP (20.0 mg, 0.164 mmol) in CH_2Cl_2 (10 mL). Flash chromatography of the residue over silica gel (1.6 x 28 cm), using 10% EtOAc-hexane, gave **274** (601 mg, 96%) as a pale yellow oil: $[\alpha]_D$ = -38.1 (c 2.0, $CHCl_3$); FTIR (CH_2Cl_2 cast) 1732, 1708 cm^{-1}; ^1H NMR (CD_2Cl_2, 360 MHz) δ 1.33 (s, 3 H), 1.50 (s, 3 H), 3.75 (dd, *J* = 11.5, 4.2 Hz, 1 H), 3.94 (dd, *J* = 11.5, 2.7 Hz, 1 H), 4.01 (d, *J* = 3.1 Hz, 1 H), 4.45-4.48 (m, 2 H), 4.60-4.66 (m, 2 H), 5.35-5.39 (m, 1 H), 5.90 (d, *J* = 3.6 Hz, 1 H), 6.43 (s, 1 H), 7.16-7.52 (m, 15 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 26.5 (q'), 27.0 (q'), 34.3 (t'), 69.2 (d'), 72.5 (t'), 79.3 (d'), 81.2 (d'), 82.3 (d'), 105.6 (d'), 112.5 (s'), 123.6 (d'), 128.3 (d), 128.4 (d'), 128.8 (d'), 130.4 (d'), 137.6 (s'), 163.3 (s'); exact mass *m/z* calcd for $C_{30}H_{31}N_2O_6Br$ 596.1345, found 596.1345.

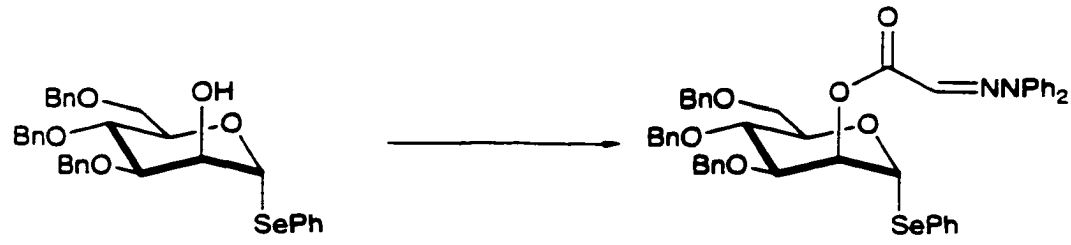
1,6-Anhydro-2-*O*-benzoyl-4-deoxy-3-*O*-(diphenyl-hydrazono)-acetyl-4-iodo-β-D-glucopyranose (275).



260 **275**

The general procedure for coupling alcohols with reagent **207** was followed, using **207** (674 mg, 2.81 mmol), **260**[59] (880 mg, 2.34 mmol), DCC (637 mg, 3.09 mmol), and DMAP (34.3 mg, 0.281 mmol) in CH_2Cl_2 (20 mL). Flash chromatography of the residue over silica gel (2.6 x 28 cm), using first 10% EtOAc-hexane (300 mL) and then 20% EtOAc-hexane, gave **275** (1.276 g, 91%) as a pale yellow oil: $[\alpha]_D$ = -25.2 (c 1.0, $CHCl_3$); FTIR (CH_2Cl_2 cast) 1722 cm^{-1}; ^1H NMR (CD_2Cl_2, 300 MHz) δ 3.74 (dd, J = 7.7, 5.6 Hz, 1 H), 4.29 (br s, 1 H), 4.33-4.36 (m, 1 H), 4.83 (d, J = 5.1 Hz, 1 H), 4.92-4.96 (m, 1 H), 5.40-5.44 (m, 1 H), 5.64 (br s, 1 H), 6.49 (s, 1 H), 7.19-7.67 (m, 13 H), 8.18-8.26 (m, 2 H); ^{13}C NMR (CD_2Cl_2, 75.5 MHz) δ 21.3 (d'), 67.6 (t'), 69.4 (d'), 73.6 (d'), 78.1 (d'), 99.5 (d'), 122.6 (d'), 128.8 (d'), 129.5 (s'), 130.4 (d'), 133.8 (d'), 162.9 (s'), 165.4 (s'); exact mass m/z calcd for $C_{27}H_{23}N_2O_6I$ 598.0601, found 598.0610.

Phenyl 3,4,6-Tri-*O*-benzyl-2-*O*-(diphenylhydrazono)acetyl-1-seleno-α-D-mannopyranoside (276).

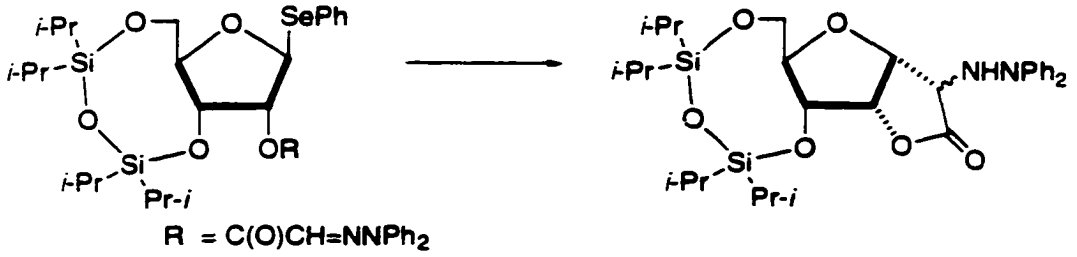


262 **276**

The general procedure for coupling alcohols with reagent **207** was followed, using **207** (156 mg, 0.652 mmol), alcohol **262** (310 mg, 0.526 mmol), DCC (148 mg, 0.717 mmol), and DMAP (15.0 mg, 0.123 mmol) in CH_2Cl_2 (10 mL). Flash chromatography of the residue over silica gel (1.6 x 28 cm), using 10% EtOAc-hexane, gave **276** (396 mg, 92%) as a pale yellow oil: $[\alpha]_D$ = +61.5 (c 0.96, $CHCl_3$); FTIR (CH_2Cl_2 cast) 1728, 1705 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 3.71 (dd, *J* = 10.9, 1.9 Hz, 1 H), 3.81 (dd, *J* = 10.9, 4.9 Hz, 1 H), 3.94-4.00 (m, 2 H), 4.18-4.26 (m, 1 H), 4.49 (d, *J* = 12.1 Hz, 1 H), 4.55-4.61 (m, 3 H), 4.77 (d, *J* = 11.3 Hz, 1 H), 4.89 (d, *J* = 10.9 Hz, 1 H), 5.8 (t, *J* = 2.0 Hz, 1 H), 5.84 (d, *J* = 1.3 Hz, 1 H), 6.56 (s, 1 H), 7.20-7.48 (m, 28 H), 7.61-7.65 (m, 2 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 69.3 (t'), 71.5 (d'), 72.1(t'), 73.5 (t'), 74.8 (d'), 75.0 (d'), 75.5 (t'), 79.2 (d'), 84.1 (d'), 123.4 (d'), 127.8 (d'), 127.9 (d'), 128.1 (d'), 128.1 (d'), 128.2 (d'), 128.6 (d'), 128.6 (d'), 128.7 (d'), 129.5 (d'),

129.6 (s'), 130.3 (d'), 134.4 (d'), 138.2 (s'), 138.7 (s'), 138.9 (s'), 163.8 (s'); exact mass (electrospray) *m/z* calcd for $C_{47}H_{44}N_2NaO_6Se$ (M + Na) 835.2262, found 835.2256.

3,6-Anhydro-2-deoxy-2-(2,2-diphenylhydrazino)-5,7-*O*-(tetraisopropyldisiloxane-1,3-diyl)-D-*glycero*-D-*manno*-heptono-1,4-lactone and 3,6-Anhydro-2-deoxy-2-(2,2-diphenylhydrazino)-5,7-*O*-(tetraisopropyldisiloxane-1,3-diyl)-D-*glycero*-D-*gluco*-heptono-1,4-lactone (284a,b).



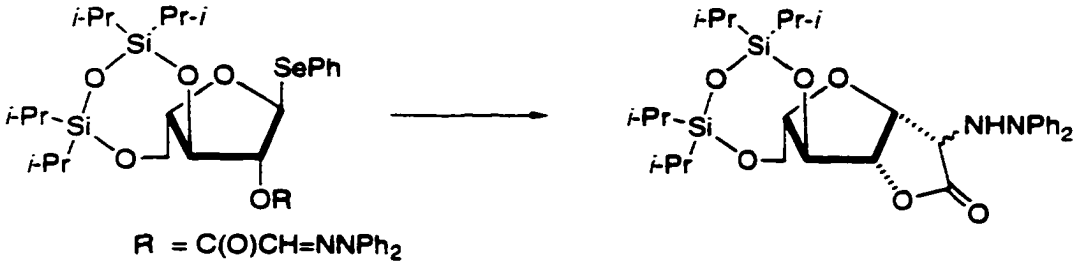
269 **284a,b**

The general procedure for radical cyclization was followed, using **269** (316 mg, 0.421 mmol) in PhMe (30 mL), Bu_3SnH (340 µL, 1.26 mmol) in PhMe (10 mL), and AIBN (30 mg, 0.183 mmol) in PhMe (10 mL). Flash chromatography of the residue over silica gel (1.6 x 29 cm), using 3% EtOAc-hexane, gave the chromatographically less polar product **284a** (or **284b**) (117 mg, 46%), and the more polar product **284b** (or **284a**) (69.7 mg, 27%) as colorless oils. The chromatographically less polar diastereomer had: $[\alpha]_D$ = +27.6 (c 1.09, $CHCl_3$); FTIR (CH_2Cl_2 cast) 1779 cm^{-1}; ^1H NMR

(CD_2Cl_2, 400 MHz) δ 1.01-1.17 (m, 28 H), 3.64 (dt, *J* = 9.2, 2.3 Hz, 1 H), 3.77-3.79 (m, 1 H), 3.89-4.01 (m, 2 H), 4.28-4.35 (m, 2 H), 4.80 (dd, *J* = 4.8, 0.6 Hz, 1 H), 5.13 (t, *J* = 4.6 Hz, 1 H), 7.06-7.38 (m, 10 H); ^{13}C NMR (CD_2Cl_2, 75.5 MHz) δ 12.9 (d'), 13.1 (d'), 13.3 (d'), 13.8 (d'), 17.0 (q'), 17.1 (q'), 17.2 (q'), 17.4 (q'), 17.4 (q'), 17.5 (q'), 60.0 (t'), 63.8 (d'), 71.7 (d'), 79.6 (d'), 79.7 (d'), 82.8 (d'), 121.2 (d'), 123.7 (d'), 129.8 (d'), 147.4 (s'), 174.8 (s'); exact mass (electrospray) *m/z* calcd for $C_{31}H_{46}N_2NaO_6Si_2$ (M + Na) 621.2792, found 621.2792.

The chromatographically more polar diastereomer had: $[\alpha]_D$ = +69.6 (c 1.09, $CHCl_3$); FTIR (CH_2Cl_2 cast) 1786 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 1.01-1.13 (m, 28 H), 3.76 (dt, *J* = 9.2, 2.4 Hz, 1 H), 3.79 (dd, *J* = 5.8, 3.5 Hz, 1 H), 3.94-4.10 (m, 2 H), 4.37 (dd, *J* = 9.2, 4.1 Hz, 1 H), 4.56 (dd, *J* = 5.8, 3.8 Hz, 1 H), 4.83 (t, *J* = 3.9 Hz, 1 H), 4.86 (d, *J* = 3.5 Hz, 1 H), 7.01-7.35 (m, 10 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 13.0 (d'), 13.2 (d'), 13.4 (d'), 13.8 (d'), 17.0 (q'), 17.1 (q'), 17.3 (q'), 17.4 (q'), 17.4 (q'), 17.4 (q'), 17.6 (q'), 60.4 (d'), 60.5 (t'), 72.5 (d'), 75.6 (d'), 80.2 (d'), 81.2 (d'), 121.0 (d'), 123.2 (d'), 129.5 (d'), 147.5 (s'), 174.7 (s'); exact mass (electrospray) *m/z* calcd for $C_{31}H_{46}N_2NaO_6Si_2$ (M + Na) 621.2792, found 621.2791.

3,6-Anhydro-2-deoxy-2-(2,2-diphenylhydrazino)-5,7-*O*-(tetraisopropyldisiloxane-1,3-diyl)-L-*glycero*-L-*gulo*-heptono-1,4-lactone and 3,6-Anhydro-2-deoxy-2-(2,2-diphenylhydrazino)-5,7-*O*-(tetraisopropyldisiloxane-1,3-diyl)-L-*glycero*-L-*ido*-heptono-1,4-lactone (285a,b).

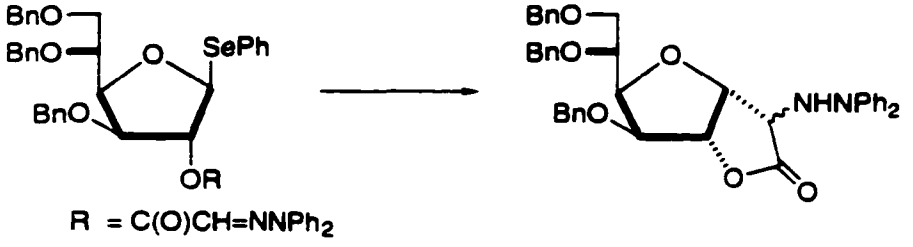


270 **285a,b**

The general procedure for radical cyclization was followed, using **270** (194 mg, 0.258 mmol) in PhMe (15 mL), Bu_3SnH (208 μL, 0.773 mmol) in PhMe (5 mL), and AIBN (20 mg, 0.12 mmol) in PhMe (5 mL). Flash chromatography of the residue over silica gel (1.6 x 28 cm), using 2% EtOAc-hexane, gave **285a,b** (97 mg, 63%) as a colorless oil which was a chromatographically inseparable mixture of two isomers in a 1.5:1 ratio (^1H NMR, 400 MHz): $[\alpha]_D$ = +70.5 (c 0.88, $CHCl_3$); FTIR (CH_2Cl_2 cast) 1791 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 1.02-1.17 (m, 28 H), 3.75-3.79 (m, 0.44 H), 3.84-4.03 (m, 2.54 H), 4.17 (dd, *J* = 10.8, 3.2 Hz, 0.61 H), 4.32 (d, *J* = 2.0 Hz, 0.40 H), 4.37 (dd, *J* = 7.5, 3.1 Hz, 0.37 H), 4.45-4.47 (m, 0.57 H), 4.53-4.55 (m, 0.58 H), 4.73 (dd, *J* = 3.6, 0.6 Hz, 0.58 H), 4.77 (dd, *J* = 5.9, 1.4 Hz, 0.39 H), 4.81 (d, *J* = 3.7

Hz, 0.56 H), 5.14 (dd, J = 5.9, 3.1 Hz, 0.36 H), 7.02-7.38 (m, 10 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 12.9 (d'), 13.2 (d'), 13.3 (d'), 13.5 (d'), 13.6 (d'), 13.7 (d'), 13.7 (d'), 17.0 (q'), 17.1 (q'), 17.1 (q'), 17.2 (q'), 17.3 (q'), 17.3 (q'), 17.5 (q'), 17.5 (q'), 17.6 (q'), 17.7 (q'), 61.3 (d'), 62.8 (t'), 63.2 (d'), 64.8 (t'), 77.4 (d'), 78.7 (d'), 80.4 (d'), 80.6 (d'), 84.8 (d'), 87.7 (d'), 88.6 (d'), 89.7 (d'), 120.9 (d'), 121.2 (d'), 123.2 (d'), 123.8 (d'), 129.5 (d'), 129.8 (d'), 147.4 (s'), 147.6 (s'), 173.4 (s'), 174.0 (s'); exact mass (electrospray) m/z calcd for $C_{31}H_{46}N_2NaO_6Si_2$ (M + Na) 621.2792, found, 621.2805.

3,6-Anhydro-5,7,8-tri-*O*-benzyl-2-deoxy-2-(2,2-diphenyl-hydrazino)-D-*erythro*-L-*gulo*-octono-1,4-lactone and 3,6-Anhydro-5,7,8-tri-*O*-benzyl-2-deoxy-2-(2,2-diphenyl-hydrazino)-D-*erythro*-L-*ido*-octono-1,4-lactone (286a,b).



276 **286a,b**

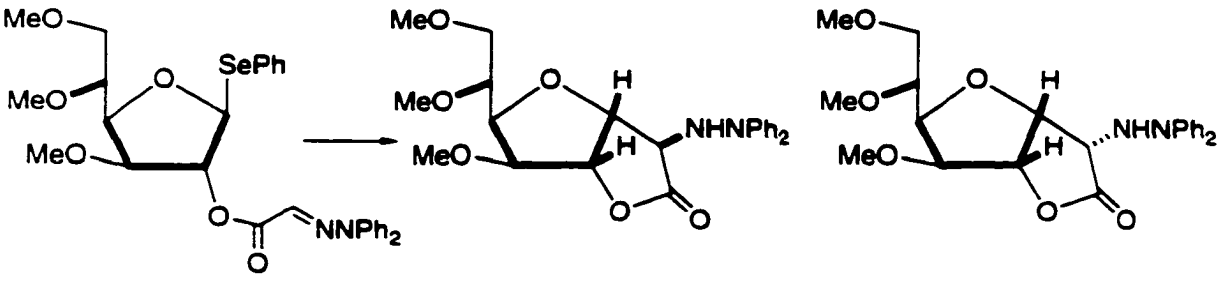
The general procedure for radical cyclization was followed, using **276** (335 mg, 0.413 mmol) in PhMe (30 mL), Bu_3SnH (334 µL, 1.23 mmol) in PhMe (10 mL), and AIBN (30 mg,

0.18 mmol) in PhMe (10 mL). Flash chromatography of the residue over silica gel (1.6 x 27 cm), using 10% EtOAc-hexane, gave the chromatographically less polar product **286a** (or **286b**) (108 mg, 40%), and the more polar product **286b** (or **286a**) (105 mg, 38%) as a colorless oil. The chromatographically less polar diastereomer had: $[\alpha]_D$ = +1.9 (c 1.13, $CHCl_3$); FTIR (CH_2Cl_2 cast) 3277, 1784 cm^{-1}; ^1H NMR (CD_2Cl_2, 300 MHz) δ 3.62 (dd, J = 10.7, 5.0 Hz, 1 H), 3.78-3.82 (m, 1 H), 3.88 (dd, J = 10.7, 2.0 Hz, 1 H), 3.99 (ddd, J = 8.6, 5.0, 2.0 Hz, 1 H), 4.09 (dd, J = 8.6, 33 Hz, 1 H), 4.32-4.38 (m, 2 H), 4.47-4.82 (m, 6 H), 4.93 (d, J = 4.9 Hz, 1 H), 5.18 (d, J = 4.9 Hz, 1 H), 7.07-7.40 (m, 25 H); ^{13}C NMR (CD_2Cl_2, 75.5 MHz) δ 62.9 (d'), 70.6 (t'), 72.5 (t'), 72.9 (t'), 73.6 (t'), 76.1 (d'), 80.1 (d'), 81.2 (d'), 81.3 (d'), 84.6 (d'), 121.1 (d'), 123.7 (d'), 127.7 (d'), 127.8 (d'), 127.9 (d'), 128.1 (d'), 128.3 (d'), 128.6 (d'), 128.8 (d'), 129.7 (d'), 137.7 (s'), 138.9 (s'), 139.1 (s'), 147.5 (s'), 174.2 (s'); exact mass (electrospray) *m/z* calcd for $C_{41}H_{40}N_2NaO_6$ (M + Na) 679.2784, found 679.2783.

The chromatographically more polar diastereomer had: $[\alpha]_D$ = +47 (c 1.19, $CHCl_3$); FTIR (CH_2Cl_2 cast) 3289, 1791 cm^{-1}; ^1H NMR (CD_2Cl_2, 300 MHz) δ 3.72 (dd, J = 10.6, 5.2 Hz, 1 H), 3.78-3.83 (m, 1 H), 3.93 (dd, J = 10.6, 1.8 Hz, 1 H), 3.98-4.03 (m, 1 H), 4.16 (dd, J = 9.0, 3.3 Hz, 1 H), 4.36 (d, J = 3.1 Hz, 1 H), 4.41-4.66 (m, 6 H), 4.78-4.86 (m, 3 H), 7.00-7.41 (m, 25 H); ^{13}C NMR (CD_2Cl_2, 75.5 MHz) δ 60.7 (d'), 70.9 (t'), 72.4 (t'), 73.2 (t'), 73.8 (t'), 76.0 (d'), 77.4

(d'), 80.5 (d'), 81.5 (d'), 82.1 (d'), 120.9 (d'), 123.0 (d'), 127.7 (d'), 127.9 (d'), 128.0 (d'), 128.1 (d'), 128.3 (d'), 128.5 (d'), 128.7 (d'), 128.8 (d'), 129.4 (d'), 137.7 (s'), 139.0 (s'), 139.2 (s'), 147.5 (s'), 173.9 (s'); exact mass (electrospray) *m/z* calcd for $C_{41}H_{40}N_2NaO_6$ (M + Na) 679.2784, found 679.2781.

3,6-Anhydro-2-deoxy-2-(2,2-diphenylhydrazino)-5,7,8-tri-*O*-methyl-D-*erythro*-L-*ido*-octono-1,4-lactone (287a) and 3,6-Anhydro-2-deoxy-2-(2,2-diphenylhydrazino)-5,7,8-tri-*O*-methyl-D-*erythro*-L-*gulo*-octono-1,4-lactone (287b).



272 **287a** **287b**

The general procedure for radical cyclization was followed, using **272** [containing 3% impurities (^{1}H NMR, 400 MHz)] (392 mg, 0.651 mmol) in PhMe (45 mL), Bu_3SnH (544 µL, 2.02 mmol) in PhMe (10 mL), and AIBN (30 mg, 0.18 mmol) in PhMe (10 mL). Flash chromatography of the residue over silica gel (1.6 x 30 cm), using 15% EtOAc-hexane, gave **287a** (117.2 mg, 42%) as a colorless oil, and further elution, using 30% EtOAc-hexane, gave **287b** (113.3 mg, 40%) as a

crystalline solid. Compound **287a** had: $[\alpha]_D$ = +14.7 (c 1.13, $CHCl_3$); FTIR (CH_2Cl_2 cast) 3265, 1783 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 3.31 (s, 3 H), 3.37-3.41 [m, including s (3 H) at δ 3.40, 4 H in all), 3.47 (s, 3 H), 3.49-3.55 (m, 1 H), 3.65 (dd, *J* = 10.7, 2.1 Hz, 1 H), 3.74-3.78 (m, 1 H), 3.85 (dd, *J* = 8.8, 3.4 Hz, 1 H), 3.98 (d, *J* = 3.4 Hz, 1 H), 4.29 (d, *J* = 2.0 Hz, 1 H), 4.84 (d, *J* = 4.9 Hz, 1 H), 5.12 (d, *J* = 4.9 Hz, 1 H), 7.05-7.37 (m, 10 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 58.1 (q'), 58.4 (q'), 59.4 (q'), 62.9 (d'), 72.3 (t'), 77.3 (d'), 79.7 (d'), 81.3 (d'), 83.0 (d'), 84.4 (d'), 121.2 (d'), 123.7 (d'), 129.7 (d'), 147.5 (s'), 174.3 (s'); exact mass *m/z* calcd for $C_{23}H_{28}N_2O_6$ 428.1947, found 428.1951. Compound **287b** had: mp 141-142 °C; $[\alpha]_D$ = +59.7 (c 1.16, $CHCl_3$); FTIR (CH_2Cl_2 cast) 1790 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 3.39 (s, 3 H), 3.41 (s, 3 H), 3.44-3.49 [m, including s (3 H) at δ 3.45, 4 H in all], 3.51-3.55 (m, 1 H), 3.70 (dd, *J* = 10.5, 1.8 Hz, 1 H), 3.80 (t, *J* = 4.9 Hz, 1 H), 3.92 (dd, *J* = 9.0, 3.4 Hz, 1 H), 4.01 (d, *J* = 3.4 Hz, 1 H), 4.52 (dd, *J* = 5.2, 3.8 Hz, 1 H), 4.80-4.83 (m, 1 H), 7.00-7.34 (m, 10 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 58.1 (q'), 58.7 (q'), 59.5 (q'), 60.7 (d'), 72.7 (t'), 77.2 (d'), 77.4 (d'), 80.3 (d'), 81.9 (d'), 83.2 (d'), 120.9 (d'), 123.1 (d'), 129.4 (d'). 147.6 (s'), 174.0 (s'); exact mass *m/z* calcd for $C_{23}H_{28}N_2O$ 428.1947, found 428.1947. Irradiation of the **H**CNHNPh$_2$ ^1H NMR signal (for **287b**) caused a NOE of 13.3% in the signal for the C(1)**H** of the furanose ring, and 4.4% for the C(2)**H**; in the case of **287a**, the corresponding values were 4.9% and 1.2%, respectively. On

this basis, we assigned the stereochemistries as shown, and our assignment was confirmed by an X-ray structure of **287b**. Crystal data: monoclinic space group $P2_1$ with a = 9.2836(5) Å, b = 8.5947(4) Å, c = 13.8264(6) Å, β = 91.089(5)° V = 1103.01(9) Å^3, Z = 2, d_{calcd} = 1.290 g cm^{-3}, μ (Cu Kα [λ = 1.54178 Å]) = 0.772 mm^{-1}; 3347 reflections measured (2913 unique; 2749 with $F_o^2 \geq 2\sigma(F_o^2)$); $R_1(F)$ = 0.0327 ($F_o^2 \geq 2\sigma(F_o^2)$), $wR_2(F^2)$ = 0.0868 (all data), GOF = 1.055 (all data).

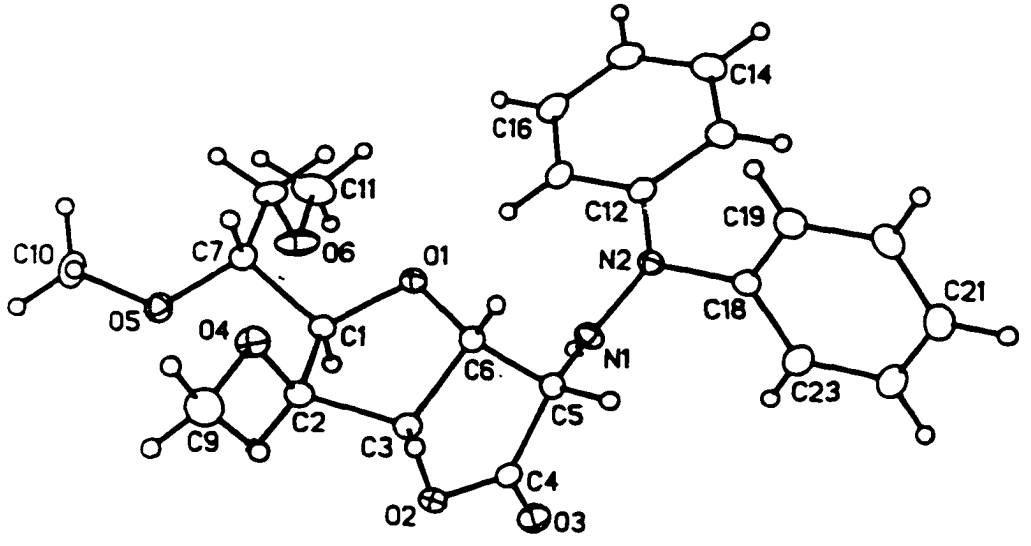
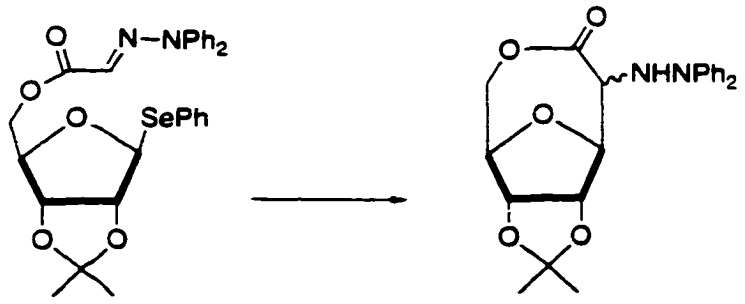


Figure 7 Structure of **287b** in the crystal

3,6-Anhydro-2-deoxy-2-(2,2-diphenylhydrazino)-4,5-*O*-isopropylidene-D-*glycero*-D-*allo*-heptono-1,7-lactone and 3,6-Anhydro-2-deoxy-2-(2,2-diphenylhydrazino)-4,5-*O*-isopropylidene-D-*glycero*-D-*altro*-heptono-1,7-lactone (288a,b).

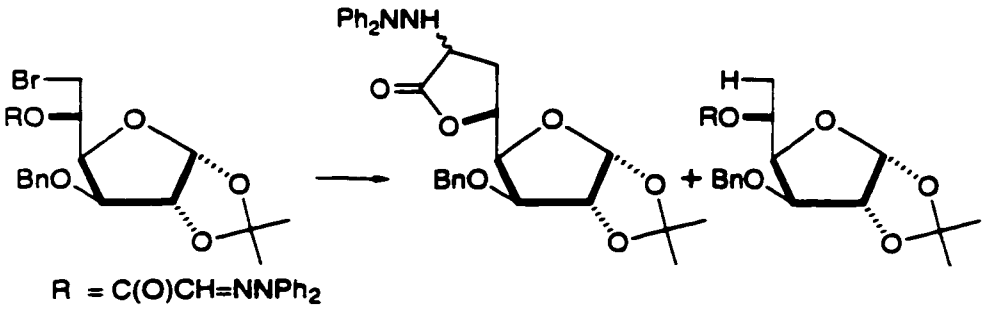


273 **288a,b**

The general procedure for radical cyclization was followed, using **273** (160 mg, 0.290 mmol) in PhMe (20 mL), Bu_3SnH (120 μL, 0.445 mmol) in PhMe (5 mL), and AIBN (10 mg, 0.06 mmol) in PhMe (5 mL). Flash chromatography of the residue over silica gel (1.0 x 20 cm), using 20% EtOAc-hexane, gave **288a,b** (73 mg, 64%) as a crystalline solid which was a chromatographically inseparable mixture of two isomers in a 1.5:1 ratio (^1H NMR, 400 MHz): FTIR (CH_2Cl_2 cast) 3292, 1736 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 1.29 (s, 1.2 H), 1.37 (s, 1.8 H), 1.46 (s, 1.2 H), 1.48 (s, 1.8 H), 3.86 (d, J = 2.4 Hz, 0.6 H), 3.98 (dd, J = 4.9, 2.2 Hz, 0.4 H), 4.15-4.46 (m, 3.6 H), 4.60 (d, J = 5.7 Hz, 0.4 H), 4.75-4.97 (m, 3 H), 7.03-7.37 (m, 10 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 24.4 (q'), 24.5 (q'), 26.0 (q'), 26.1 (q'), 64.2 (d'), 66.1

(d'), 70.6 (t'), 72.5 (t'), 80.7 (d'), 81.2 (d'), 81.5 (d'), 81.9 (d'), 82.6 (d'), 82.8 (d'), 83.4 (d'), 83.5 (d'), 112.7 (s'), 113.0 (s'), 121.0 (d'), 123.5 (d'), 129.7 (d'), 147.6 (s'), 170.8 (s'), 172.3 (s'); exact mass *m/z* calcd for $C_{22}H_{24}N_2O_5$ 396.1685, found 396.1686.

3-*O*-Benzyl-6,7-dideoxy-7-(2,2-diphenylhydrazino)-1,2-*O*-isopropylidene-L-*glycero*-α-D-glucofuranurono-8,5-lactone and 3-*O*-Benzyl-6,7-dideoxy-7-(2,2-diphenylhydrazino)-1,2-*O*-isopropylidene-D-*glycero*-α-D-glucofuranurono-8,5-lactone (289a,b), 3-*O*-Benzyl-6-deoxy-5-*O*-(diphenylhydrazono)-acetyl-1,2-*O*-isopropylidene-α-D-glucofuranose (290).



274 **289a,b** **290**

The general procedure for radical cyclization was followed, using **274** (303 mg, 0.509 mmol) in PhMe (30 mL), Bu_3SnH (274 μL, 1.01 mmol) in PhMe (10 mL), and AIBN (10 mg, 0.06 mmol) in PhMe (10 mL). Flash chromatography of the residue over silica gel (1.6 x 29 cm), using 10% EtOAc-hexane, gave fractions #1, #2, and #3, which all contained a

small amount of tributyltin residues (^{1}H NMR, 400 MHz). Each fraction was further purified by flash chromatography over silica gel (1.0 x 20 cm), using 10% EtOAc-hexane. Fraction #1 gave a 1:1.7 mixture (51 mg) of the starting material and the simple reduction product **290** (12% as judged by ^{1}H NMR measurements); fraction #2 gave the chromatographically less polar lactone **289a** (or **289b**) (71 mg, 27%) as a colorless oil; fraction #3 gave the chromatographically more polar lactone **289b** (or **289a**) (81 mg, 31%) as a colorless oil.

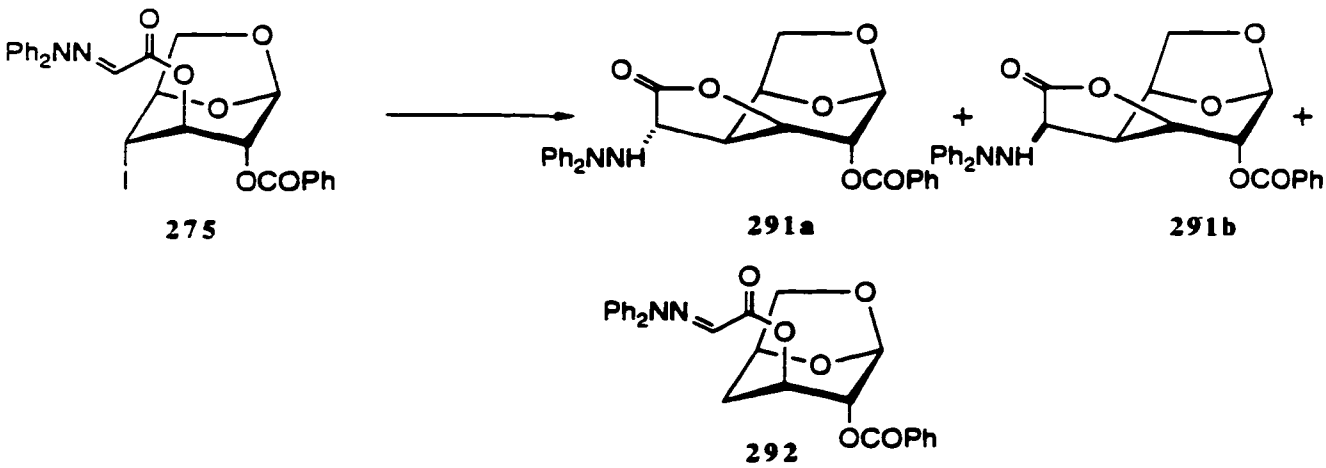
The fraction containing **290** had: FTIR (CH_2Cl_2 cast) 1730, 1704 cm^{-1}; ^{1}H NMR (CD_2Cl_2, 400 MHz) δ 1.29-1.34 (m, 3 H), 1.40 (d, J = 6.3 Hz, 2 H), 1.49 (s, 3 H), 3.72-3.76 (m, 0.40 H), 3.92-4.01 (m, 1.43 H), 4.18 (dd, J = 8.4, 3.2 Hz, 0.65 H), 4.43-4.47 (m, 1.42 H), 4.59-4.65 (m, 2.12 H), 5.24-5.38 (m, 1 H), 5.90-5.91 (m, 1 H), 6.42 (s, 0.65 H), 6.46 (s, 0.35 H), 7.15-7.52 (m, 15 H); ^{13}C NMR (CD_2Cl_2, 50.3 MHz) δ 17.9 (q'), 26.3 (q'), 26.5 (q'), 26.9 (q'), 27.0 (q'), 34.3 (t'), 68.2 (d'), 69.2 (d'), 72.3 (t'), 72.5 (t'), 79.3 (d'), 81.1 (d'), 81.3 (d'), 82.3 (d'), 82.4 (d'), 105.5 (d'), 105.6 (d'), 111.9 (s'), 112.5 (s'), 122.8 (d'), 123.5 (d'), 124.7 (d'), 126.4 (d'), 128.1 (d'), 128.3 (d'), 128.4 (d'), 128.4 (d'), 128.7 (d'), 130.3 (d'), 137.5 (s'), 137.8 (s'), 142.6 (s'), 163.2 (s'), 163.4 (s'); exact mass (electrospray) *m/z* calcd for $C_{30}H_{32}N_2NaO_6$ (M + Na) 539.2158, found 539.2153.

The chromatographically less polar lactone had: $[\alpha]_D$ = -27.3 (c 1.19, $CHCl_3$); FTIR (CH_2Cl_2 cast) 3278, 1782 cm^{-1}; ^{1}H NMR (CD_2Cl_2, 400 MHz) δ 1.34 (s, 3 H), 1.51 (s, 3 H), 2.32-

2.40 (m, 1 H), 2.65-2.71 (m, 1 H), 3.92-3.97 (m, 1 H), 4.11 (d, J = 3.2 Hz, 1 H), 4.32 (dd, J = 7.4, 3.2 Hz, 1 H), 4.56-4.73 (m, 5 H), 5.92 (d, J = 3.7 Hz, 1 H), 7.02-7.39 (m, 15 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 26.3 (q'), 27.0 (q'), 33.7 (t'), 56.5 (d'), 72.6 (t'), 74.5 (d'), 81.7 (d'), 82.0 (d'), 82.6 (d'), 105.6 (d'), 112.4 (s'), 120.8 (d'), 123.1 (d'), 128.1 (d'), 128.3 (d'), 128.8 (d'), 129.6 (d'), 137.8 (s'), 147.3 (s'), 175.0 (s'); exact mass (electrospray) *m/z* calcd for $C_{30}H_{32}N_2NaO_6$ (M + Na) 539.2158, found 539.2160.

The chromatographically more polar lactone had: $[\alpha]_D$ = -16.2 (c 1.25, $CHCl_3$); FTIR (CH_2Cl_2 cast) 3282, 1779 cm^{-1}; ^{1}H NMR (CD_2Cl_2, 400 MHz) δ 1.31 (s, 3 H), 1.45 (s, 3 H), 2.42-2.49 (m, 1 H), 2.59-2.65 (m, 1 H), 3.94-3.99 (m, 1 H), 4.05 (d, J = 3.5 Hz, 1 H), 4.27 (dd, J = 5.5, 3.4 Hz, 1 H), 4.53-4.56 (m, 2 H), 4.64-4.70 (m, 2 H), 4.93-4.99 (m, 1 H), 5.89 (d, J = 3.7 Hz, 1 H), 7.02-7.39 (m, 15 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 26.3 (q'), 26.9 (q'), 31.1 (t'), 55.9 (d'), 72.6 (t'), 76.5 (d'), 81.2 (d'), 82.2 (d'), 82.6 (d'), 105.7 (d'), 112.3 (s'), 120.8 (d'), 123.2 (d'), 128.1 (d'), 128.3 (d'), 128.8 (d'), 129.6 (d'), 137.7 (s'), 147.7 (s'), 175.4 (s'); exact mass (electrospray) *m/z* calcd for $C_{30}H_{32}N_2NaO_6$ (M + Na) 539.2158, found, 539.2153.

1,6-Anhydro-2-*O*-benzyl-4-deoxy-3-*O*-(diphenylhydrazono)-acetyl-β-D-*xylo*-hexopyranose (292). 1,6-Anhydro-2-*O*-benzoyl-4-deoxy-4-*C*-[(*R*)-(2,2-diphenylhydrazino)carboxy-methyl)]-β-D-galactopyranose 2',3-lactone (291b) and 1,6-Anhydro-2-*O*-benzoyl-4-deoxy-4-*C*-[(*S*)-α-(2,2-diphenyl-hydrazino)carboxymethyl)]-β-D-galactopyranose 2',3-lactone (291a).



The general procedure for radical cyclization was followed, using **275** (268.0 mg, 0.448 mmol) in PhMe (30 mL), Bu_3SnH (181 μL, 0.6723 mmol) in PhMe (10 mL), and AIBN (5 mg, 0.031 mmol) in PhMe (10 mL). Refluxing was continued for 7 h after the addition. Flash chromatography of the residue over silica gel (1.6 x 30 cm), using 10% EtOAc-hexane, gave fractions #1, #2, and #3, which all contained a small amount of tributyltin residues (^1H NMR). Fraction #1 was further purified by flash chromatography over silica gel (1.0 x 20

cm), using 10% EtOAc-hexane, and gave **291a** (73.6 mg, 34%) as a colorless oil. Fraction #2 was purified similarly, using 20% EtOAc-hexane, and gave **292** (53.2 mg, 25%) as a crystalline solid. Fraction #3 was purified similarly, using 20% EtOAc-hexane, and gave **291b** (48.6 mg, 23%) as a colorless oil.

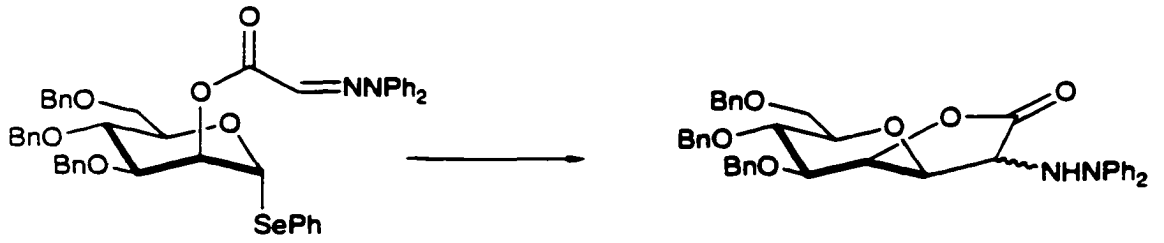
Compound **291a** had: $[\alpha]_D$ = +87.8 (c 1.0, $CHCl_3$); FTIR (CH_2Cl_2 cast) 1782, 1725 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 3.32-3.37 (m, 1 H), 3.84 (dd, *J* = 8.9, 5.4 Hz, 1 H), 4.01 (d, *J* = 8.9 Hz, 1 H), 4.11 (dd, *J* = 8.1, 1.4 Hz, 1 H), 4.42 (br s, 1 H), 4.47-4.49 (m, 1 H), 4.58 (t, *J* = 5.2 Hz, 1 H), 5.11-5.13 (m, 1 H), 5.56-5.58 (m, 1 H), 7.08-7.17 (m, 6 H), 7.32-7.66 (m, 7 H), 8.03-8.11 (m, 2 H); ^{13}C NMR (CD_2Cl_2, 75.5 MHz) δ 38.5 (d'), 57.8 (d'), 65.3 (t'), 67.5 (d'), 71.5 (d'), 75.0 (d'), 99.4 (d'), 121.2 (d'), 124.1 (d'), 128.9 (d'), 129.5 (s'), 129.9 (d'), 130.1 (d'), 134.0 (d'), 147.6 (s'), 165.3 (s'), 173.8 (s'); exact mass *m/z* calcd for $C_{27}H_{24}N_2O_6$ 472.1634, found 472.1629. Irradiation of the C**H**NHNPh_2 ^1H NMR signal caused an NOE of 7% in the pyranose C(3)**H** signal; the corresponding value for **291b** was 0%.

Compound **292** had: mp 169-171 °C; $[\alpha]_D$ = +126 (c 1.0, $CHCl_3$); FTIR (CH_2Cl_2 cast) 1722 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 1.85-1.89 (m, 1 H), 2.50-2.56 (m, 1 H), 3.79-3.82 (m, 1 H), 4.33 (d, *J* = 6.9 Hz, 1 H), 4.62-4.64 (m, 1 H), 4.88 (d, *J* = 1.2 Hz, 1 H), 5.15-5.17 (m, 1 H), 5.55 (br s, 1 H), 6.50 (s, 1 H), 7.18-7.64 (m, 13 H), 8.05-8.11 (m, 2 H); ^{13}C NMR (CD_2Cl_2, 50.3 MHz) δ 31.5 (t'), 67.63 (t'), 67.8 (d'), 69.8

(d'), 71.6 (d'), 99.3 (d'), 123.8 (d'), 126.5 (d'), 128.8 (d'), 130.1 (d'), 130.3 (d'), 133.7 (d'), 163.7 (s'), 165.3 (s'); exact mass (electrospray) *m/z* calcd for $C_{27}H_{24}N_2NaO_6$ (M - Na) 495.1532, found 495.1537.

Compound **291b** had: [α] = +42.1 (c 0.73, $CHCl_3$); FTIR (CH_2Cl_2 cast) 3280, 1783, 1725 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 3.23-3.26 (m, 1 H), 3.58 (d, *J* = 2.2 Hz, 1 H), 3.60-3.66 (m, 2 H), 4.38 (d, *J* = 2.2 Hz, 1 H), 4.47-4.49 (m, 1 H), 4.88-4.94 (m, 1 H), 5.17 (br s, 1 H), 5.58-5.59 (m, 1 H), 7.05-7.68 (m, 13 H), 8.02-8.08 (m, 2 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 38.9 (d'), 59.3 (d'), 64.8 (t'), 68.3 (d'), 71.9 (d'), 77.2 (d'), 99.5 (d'), 120.9 (d'), 123.8 (d'), 128.9 (d'), 129.0 (s'), 129.9 (d'), 130.1 (d'), 134.0 (d'), 147.3 (s'), 165.4 (s'), 172.7 (s'); exact mass *m/z* calcd for $C_{27}H_{24}N_2O_6$ 472.1634, found 472.1635.

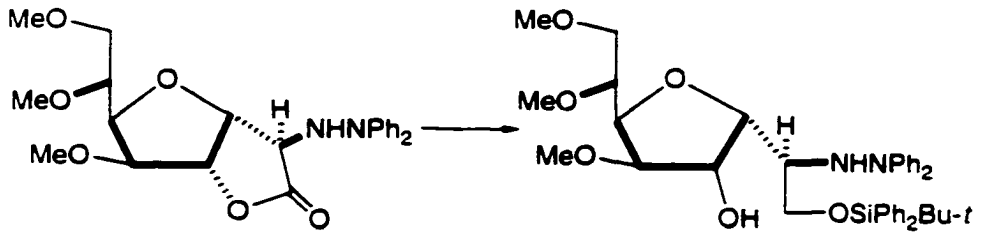
3,7-Anhydro-5,6,8-tri-*O*-benzyl-2-deoxy-2-(2,2-diphenyl hydrazino)-D-*erythro*-L-*manno*-octono-1,4-lactone and 3,7-Anhydro-5,6,8-tri-*O*-benzyl-2-deoxy-2-(2,2-diphenyl-hydrazino)-D-*erythro*-L-*gluco*-octono-1,4-lactone (293a,b).



276 **293a,b**

The general procedure for radical cyclization was followed, using **276** (391.1 mg, 0.482 mmol) in PhMe (35 mL), Bu_3SnH (195μL, 0.7234 mmol) in PhMe (5 mL), and AIBN (30 mg, 0.183 mmol) in PhMe (5 mL). Flash chromatography of the residue over silica gel (1.6 x 27 cm), using 10% EtOAc-hexane, gave **293a,b** (151.8 mg, *ca* 48%), which contained a small amount of chromatographically inseparable impurities (^1H NMR, 300 MHz). The structural assignment was made on the basis of the following characteristic spectroscopic properties: FTIR (CH_2Cl_2 cast) 1788 cm^{-1} (γ-lactone); ^1H NMR (CD_2Cl_2, 300 MHz) δ 3.35-3.93 (m, 6.1 H), 4.21-5.13 (m, 8.5 H), 7.06-7.50 (m, 25.5 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 69.3 (t'), 69.6 (t'), 72.1 (t'), 72.5 (t'), 73.7 (t'), 73.9 (t'), 74.4 (d'), 74.6 (d'), 75.1 (t'), 75.5 (t'), 75.6 (d'), 76.5 (d'), 78.3 (d'), 78.4 (d'), 78.5 (d'), 79.4 (d'), 80.0 (d'), 147.5 (s', NPh_2 quaternary carbon), 147.75 (s', NPh_2 quaternary carbon), 173.33 (s', γ-lactone carbonyl), 173.50 (s', γ-lactone carbonyl); exact mass *m/z* calcd for $C_{41}H_{40}N_2O_6$ 656.2886, found 656.2887.

3,6-Anhydro-1-*O*-[(1,1-dimethylethyl)diphenylsilyl]-2-deoxy-2-(2,2-diphenylhydrazino)-5,7,8-tri-*O*-methyl-D-*erythro*-L-*ido*-octitol (295a).



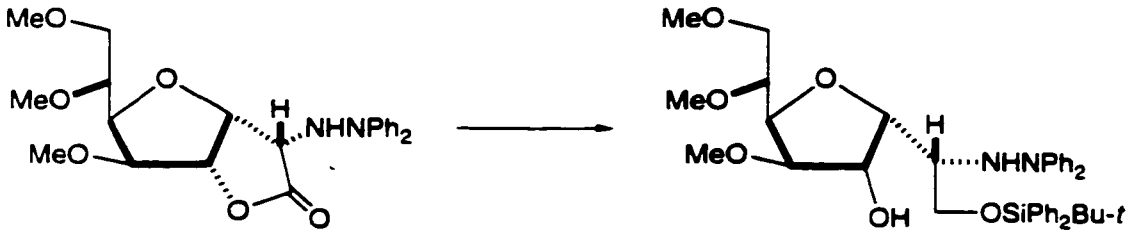
287a **295a**

A solution of **287a** (124 mg, 0.291 mmol) in THF (0.5 mL, plus 2 x 0.5 mL as a rinse) was added to a stirred and cooled (0 °C) suspension of $LiAlH_4$ (24.3 mg, 0.639 mmol) in THF (1.5 mL). Stirring was continued for 30 min at 0 °C, and then for 1 h after removal of the ice bath. MeOH (0.2 mL) was added carefully to quench the reaction, followed by saturated $NaHCO_3$ (0.1 mL). The mixture was stirred for 15 min, filtered through a pad (1 cm x 2 mm) of Celite, using EtOAc, and evaporated, to give the expected diol.

t-$BuPh_2SiCl$ (77 μL, 0.29 mmol) was added dropwise to a stirred solution of the above diol and imidazole (37.0 mg, 0.543 mmol) in CH_2Cl_2 (3 mL). Stirring was continued for 3.5 h, and the solvent was evaporated. Flash chromatography of the residue over silica gel (1.6 x 28 cm), using 20% EtOAc-hexane, gave **295a** (154 mg, 79%) as a colorless oil: $[\alpha]_D$ = +3.5 (c 1.18, $CHCl_3$); FTIR (CH_2Cl_2 cast) 3444 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 1.08 (s, 9 H), 3.43 (s, 3 H), 3.45 (s, 3

H), 3.48 (s, 3 H), 3.52-3.67 (m, 5 H), 3.75-3.85 (m, 2 H), 3.94-3.98 (m, 2 H), 4.12 (dd, J = 9.1, 3.3 Hz, 1 H), 4.44 (br s, 1 H), 4.79 (s, 1 H), 6.95-7.05 (m, 6 H), 7.21-7.66 (m, 14 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 19.2 (s'), 26.9 (q'), 58.1 (q'), 58.2 (q'), 59.5 (q'), 59.7 (d'), 64.2 (t'), 73.1 (t'), 74.1 (d'), 77.5 (d'), 79.2 (d'), 83.7 (d'), 86.0 (d'), 120.4 (d'), 122.5 (d'), 128.2 (d'), 129.2 (d'), 130.4 (d'), 130.4 (d'), 132.4 (s'), 132.6 (s'), 135.8 (d'), 135.9 (d'), 148.2 (s'); exact mass *m/z* calcd for $C_{39}H_{50}N_2O_6Si$ 670.3438, found 670.3434.

3,6-Anhydro-1-*O*-[(1,1-dimethylethyl)diphenylsilyl]-2-deoxy-2-(2,2-diphenylhydrazino)-5,7,8-tri-*O*-methyl-D-*erythro*-L-*gulo*-octitol (295b).



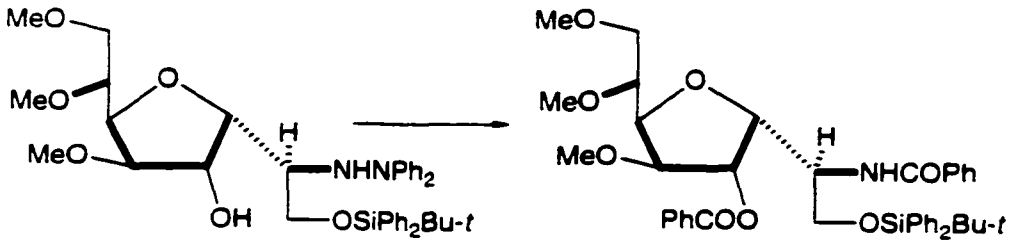
287b **295b**

A solution of **287b** (121 mg, 0.283 mmol) in THF (0.5 mL, plus 2 x 0.5 mL as a rinse) was added to a stirred and cooled (0 °C) suspension of $LiAlH_4$ (23.6 mg, 0.623 mmol) in THF (1.5 mL). Stirring was continued for 30 min at 0 °C, and then for 1 h after removal of the ice bath. MeOH (0.2 mL) was added carefully to quench the reaction, followed by saturated

aqueous $NaHCO_3$ (0.1 mL). The mixture was stirred for 15 min, filtered through a pad (1 cm x 2 mm) of Celite, using EtOAc, and evaporated, to give the expected diol.

t-$BuPh_2SiCl$ (75 μL, 0.28 mmol) was added dropwise to a stirred solution of the above diol and imidazole (36.0 mg, 0.530 mmol) in CH_2Cl_2 (3 mL). Stirring was continued for 3.5 h, and the solvent was evaporated. Flash chromatography of the residue over silica gel (1.6 x 28 cm), using 20% EtOAc-hexane, gave **295b** (153 mg, 81%) as a pure (^1H NMR, 400 MHz), colorless oil: $[\alpha]_D$ = +27.1° (c 1.0, $CHCl_3$); FTIR (CH_2Cl_2 cast) 3405, 1589, 1496, 741, 701 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 1.04 (s, 9 H), 3.33 (s, 3 H), 3.38-3.41 [m, including s (3 H) at δ 3.39, 4 H in all], 3.43 (s, 3 H), 3.50 (ddd, *J* = 9.3, 5.5, 1.8 Hz, 1 H), 3.60-3.67 (m, 2 H), 3.73 (d, *J* = 3.4 Hz, 1 H), 3.79 (dd, *J* = 10.6, 6.7 Hz, 1 H), 4.02-4.08 (m, 3 H), 4.16 (br s, 1 H), 4.35 (br s, 1 H), 4.74 (br s, 1 H), 7.06-7.49 (m, 16 H), 7.60-7.66 (m, 4 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 19.4 (s'), 27.0 (q'), 58.0 (q'), 58.1 (q'), 59.2 (d'), 59.3 (q'), 63.6 (t'), 73.5 (t'), 74.6 (d'), 77.6 (d'), 79.3 (d'), 81.9 (d'), 85.9 (d'), 121.5 (d'), 123.9 (d'), 128.1 (d'), 128.1 (d'), 129.6 (d'), 130.1 (d'), 133.3 (s'), 133.5 (s'), 135.9 (d'), 136.0 (d'), 148.9 (s'); exact mass *m/z* calcd for $C_{39}H_{50}N_2O_6Si$ 670.3438, found 670.3437.

3,6-Anhydro-2-benzamido-4-*O*-benzoyl-1-*O*-[(1,1-dimethyl-ethyl)diphenylsilyl]-2-deoxy-5,7,8-tri-*O*-methyl-D-*erythro*-L-*ido*-octitol (296a).

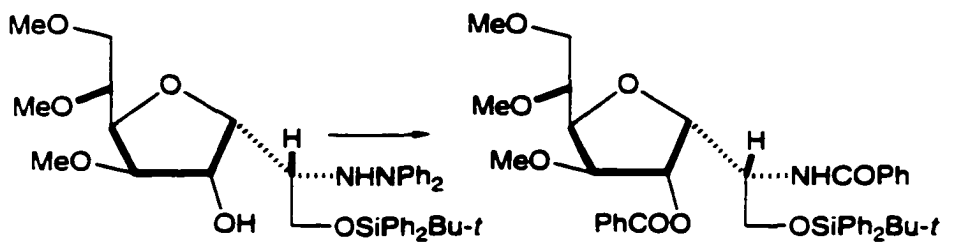


295a **296a**

Camphorsulfonic acid (72.4 mg, 0.312 mmol) and then 10% Pd-C (30.0 mg) were added to a solution of **295a** (95.0 mg, 0.142 mmol) in a mixture of EtOAc (2.4 mL) and MeOH (0.6 mL). The mixture was shaken under H_2 (50 psi) for 2 h (Parr shaker), and then filtered through a pad of Celite. The pad was washed with EtOAc (3 x 5 mL, and the combined filtrates were evaporated, and stored under oil-pump vacuum for 4 h. Then CH_2Cl_2 (5 mL), Et_3N (197 µL, 1.41 mmol), PhCOCl (131 µL, 1.133 mmol), and DMAP (15.0 mg, 0.123 mmol) were added in that order to a stirred solution of the resulting yellow foam. Stirring was continued for 24 h, and the solvent was evaporated. Flash chromatography of the residue over silica gel (1.6 x 28 cm), using 30% EtOAc-hexane, gave **296a** (77 mg, 76%) as a pale yellow oil: $[\alpha]_D$ = -7.5 (c 1.06, $CHCl_3$); FTIR (CH_2Cl_2 cast) 3438, 1723, 1667 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 1.07 (s, 9 H), 3.39 (s, 3 H), 3.43 (s, 3 H), 3.56 (dd, *J* = 10.5, 4.4 Hz, 1 H), 3.59 (s, 3 H), 3.63 (ddd, *J* = 9.3, 4.4,

1.8 Hz, 1 H), 3.74-3.79 (m, 3 H), 3.93 (d, J = 3.4 Hz, 1 H), 4.19 (dd, J = 9.3, 3.4 Hz, 1 H), 4.52-4.60 (m, 1 H), 4.79-4.82 (m, 1 H), 5.64 (dd, J = 4.0, 0.6 Hz, 1 H), 6.81 (d, J = 8.3 Hz, 1 H), 7.15-7.54 (m, 12 H), 7.62-7.84 (m, 8 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 19.5 (s'), 26.9 (q'), 50.2 (d'), 58.1 (q'), 58.3 (q'), 59.5 (q'), 64.6 (t'), 72.4 (t'), 77.0 (d'), 77.4 (d'), 77.4 (d'), 79.8 (d'), 84.3 (d'), 127.2 (d'), 128.0 (d'), 128.1 (d'), 128.5 (d'), 128.8 (d'), 129.7 (s'), 129.9 (d'), 130.0 (d'), 130.1 (d'), 131.6 (d'), 133.5 (d'), 133.6 (s'), 134.8 (s'), 135.9 (d'), 165.9 (s'), 166.0 (s'); exact mass (electrospray) *m/z* calcd for $C_{41}H_{49}NNaO_8Si$ (M + Na) 734.3125, found 734.3130.

3,6-Anhydro-2-benzamido-4-*O*-benzoyl-1-*O*-[(1,1-dimethyl-ethyl)diphenylsilyl]-2-deoxy-5,7,8-tri-*O*-methyl-D-*erythro*-L-*gulo*-octitol (296b).



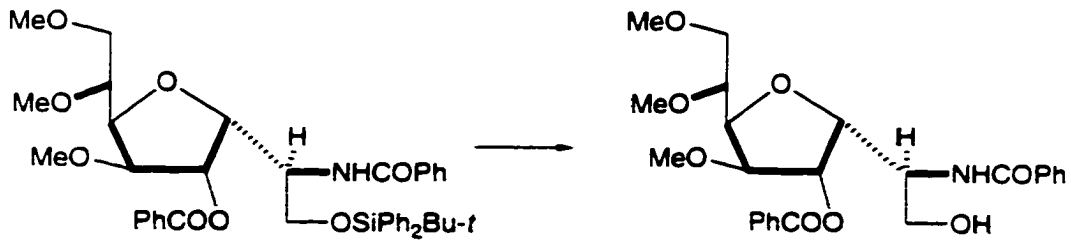
295b **296b**

Camphorsulfonic acid (102 mg, 0.443 mmol) and then 10% Pd-C (35.0 mg) were added to a solution of **295b** (135 mg, 0.201 mmol) in a mixture of EtOAc (3.2 mL) and MeOH (0.8 mL). The mixture was shaken under H_2 (50 psi) for 2 h (Parr

shaker), and then filtered through a pad of Celite. The pad was washed with EtOAc (3 x 6 mL), and the combined filtrates were evaporated and stored under oil-pump vacuum for 4 h. CH_2Cl_2 (5 mL), Et_3N (280 μL, 2.01 mmol), PhCOCl (187 μL, 1.61 mmol), and DMAP (10.0 mg, 0.082 mmol) were added in that order to a stirred solution of the resulting yellow foam. Stirring was continued for 24 h, and the solvent was evaporated. Flash chromatography of the residue over silica gel (1.6 x 28 cm), using 30% EtOAc-hexane, gave **296b** (107 mg, 75%) as a pure (^1H NMR, 300 MHz), pale yellow viscous oil which recrystallized after the NMR solvent (CD_2Cl_2) evaporated, to give a white solid: mp 186-188 °C; $[\alpha]_D$ = -47.9° (c 1.11, $CHCl_3$); FTIR (CH_2Cl_2 cast) 1720, 1671 cm^{-1}; ^1H NMR (CD_2Cl_2, 300 MHz) δ 1.09 (s, 9 H), 3.35 (s, 3 H), 3.44-3.50 [m, including s (3 H) at δ 3.44, 4 H in all], 3.57 (s, 3 H), 3.64 (ddd, *J* = 9.3, 5.3, 1.8 Hz, 1 H), 3.76 (dd, *J* = 10.5, 1.8 Hz, 1 H), 3.88 (dd, *J* = 10.0, 1.5 Hz, 1 H), 3.93 (d, *J* = 3.8 Hz, 1 H), 4.13-4.20 (m, 2 H), 4.61-4.66 (m, 2 H), 5.62 (br s, 1 H), 6.51-6.54 (br m, 1 H), 7.30-7.71 (m, 18 H), 8.02-8.07 (m, 2 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 19.6 (s'), 27.0 (q'), 49.4 (d'), 58.3 (q'), 58.5 (q'), 59.4 (q'), 64.0 (t'), 73.1 (t'), 75.4 (d'), 77.6 (d'), 78.2 (d'), 79.9 (d'), 84.6 (d'), 127.1 (d'), 128.1 (d'), 128.6 (d'), 128.7 (d'), 128.8 (d'), 130.1 (d'), 130.2 (d'), 130.2 (d'), 130.5 (s'), 131.7 (d'), 133.4 (d'), 133.5 (s'), 133.6 (s'), 135.2 (s'), 135.8 (d'), 135.9 (d'), 165.8 (s'), 166.5 (s'); exact mass (electrospray) *m/z* calcd for $C_{41}H_{49}NNaO_8Si$ (M + Na) 734.3125,

found 734.3122.

3,6-Anhydro-2-benzamido-4-*O*-benzoyl-2-deoxy-5,7,8-tri-*O*-methyl-D-*erythro*-L-*ido*-octitol (297a).

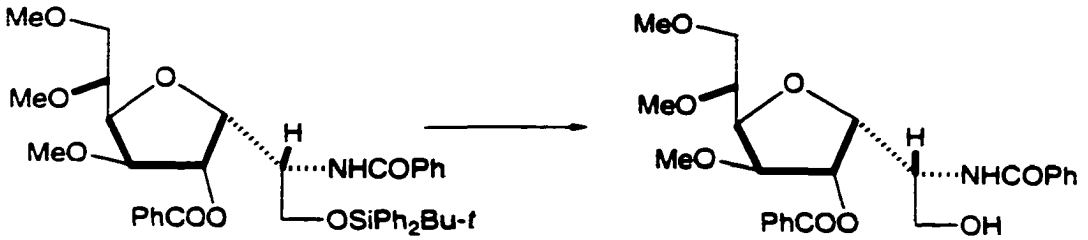


296a **297a**

Bu_4NF (1.0 M solution in THF, 388 μL, 0.388 mmol) was added dropwise to a stirred solution of **296a** (92.0 mg, 0.129 mmol) and anhydrous pyridinium hydrochloride (22.4 mg, 0.194 mmol) in THF (1 mL). Stirring was continued for 12 h, and the mixture was then evaporated. Flash chromatography of the residue over silica gel (1.6 x 27 cm), using 80% EtOAc-hexane, gave **297a** (51 mg, 83%) as a pale yellow oil: $[\alpha]_D$ = -12.3 (c 1.4, $CHCl_3$); FTIR (CH_2Cl_2 cast) 3427, 1722, 1651 cm^{-1}; ^1H NMR (CD_2Cl_2, 300 MHz) δ 3.25-3.35 (br, 1 H), 3.41 (br s, 6 H), 3.55-3.79 [m, including s (3 H) at δ 3.56, 8 H in all], 3.93 (dd, J = 3.4, 0.8 Hz, 1 H), 4.22 (dd, J = 9.2, 3.4 Hz, 1 H), 4.38-4.47 (m, 1 H), 4.59 (t, J = 3.9 Hz, 1 H), 5.64 (dd, J = 3.9, 0.8 Hz, 1 H), 6.97 (d, J = 7.5 Hz, 1 H), 7.15-7.55 (m, 6 H), 7.68-7.87 (m, 4 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 51.6 (d'), 58.0 (q'), 58.3 (q'), 59.5 (q'), 64.5 (t'), 72.2 (t'), 76.8 (d'), 77.2 (d'), 77.6 (d'), 79.9 (d'), 84.3 (d'),

127.2 (d'), 128.6 (d'), 128.8 (d'), 129.6 (s'), 129.9 (d'), 131.8 (d'), 133.6 (d'), 134.4 (s'), 165.9 (s'), 167.4 (s'); exact mass (electrospray) *m/z* calcd for $C_{25}H_{31}NNaO_8$ (M + Na) 496.1947, found 496.1933.

3,6-Anhydro-2-benzamido-4-*O*-benzoyl-2-deoxy-5,7,8-tri-*O*-methyl-D-*erythro*-L-*gulo*-octitol (297b).

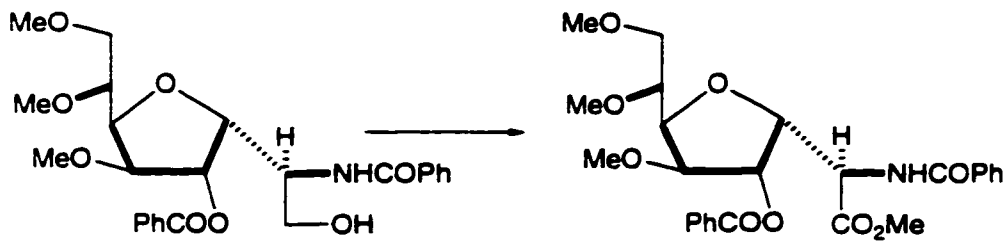


296b **297b**

Bu_4NF (10 M solution in THF, 397 µL, 0.397 mmol) was added dropwise to a stirred solution of **296b** (94.0 mg, 0.132 mmol) and dry pyridinium hydrochloride (19.0 mg, 0.164 mmol) in THF (1 mL). Stirring was continued for 17 h, and the mixture was then evaporated. Flash chromatography of the residue over silica gel (1.6 x 28 cm), using 80% EtOAc-hexane, gave **297b** (51 mg, 81%) as a pure (^{1}H NMR, 360 MHz), pale yellow oil: $[\alpha]_D$ = -80.2° (c 1.07, $CHCl_3$); FTIR (CH_2Cl_2 cast) 3331, 1721, 1643 cm^{-1}; ^{1}H NMR (CD_2Cl_2, 360 MHz) δ 2.75-3.14 (br, 1 H), 3.38 (s, 3 H), 3.40 (s, 3 H), 3.50-3.56 [m, including s (3 H) at δ 3.55, 4 H in all], 3.59 (ddd, *J* = 9.3, 4.6, 2.0 Hz, 1 H), 3.73 (dd, *J* = 10.5, 2.0 Hz, 1 H), 3.81 (dd, *J* = 11.3, 3.5 Hz, 1 H), 3.92 (d, *J* = 3.6 Hz, 1 H), 4.04

(dd, J = 11.3, 3.2 Hz, 1 H), 4.19 (dd, J = 9.2, 3.7 Hz, 1 H), 4.41-5.53 (m, 2 H), 5.63 (d, J = 4.1 Hz, 1 H), 6.77 (d, J = 8.2 Hz, 1 H), 7.36-7.70 (m, 8 H), 7.99-8.06 (m, 2 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 50.5 (d'), 58.1 (q'), 58.4 (q'), 59.4 (q'), 63.3 (t'), 72.7 (t'), 75.9 (d'), 77.2 (d'), 79.7 (d'), 80.1 (d'), 84.1 (d'), 127.3 (d'), 128.8 (d'), 130.0 (d'), 131.7 (d'), 133.7 (d'), 134.9 (s'), 165.8 (s'), 167.4 (s'); exact mass (electrospray) *m/z* calcd for $C_{25}H_{31}NNaO_8$ (M + Na) 496.1947, found 496.1934.

Methyl 3,6-Anhydro-2-benzamido-4-*O*-benzoyl-2-deoxy-5,7,8-tri-*O*-methyl-D-*erythro*-L-*ido*-octonate (298a).

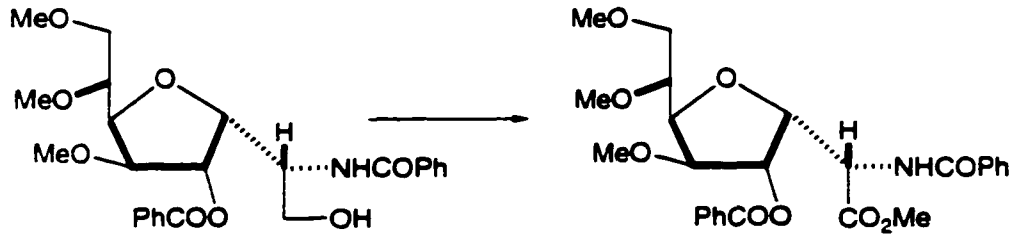


297a **298a**

Jones reagent (125 µL, 8 N) was added dropwise to a stirred and cooled (0 °C) solution of **297a** (53.0 mg, 0.112 mmol) in acetone (0.8 mL). Stirring was continued for 1.5 h before the excess of Jones reagent was quenched with *i*-PrOH (70 µL). Stirring was continued for 2 h, the mixture was filtered, and the green precipitate was washed with Et_2O (3 x 4 mL). The combined filtrates were evaporated, dissolved in a little Et_2O, and treated with an ethereal solution of CH_2N_2

until a slight yellow color persisted. The excess of CH_2N_2 was destroyed with a few drops of AcOH, and the solvent was evaporated. Flash chromatography of the residue over silica gel (1.6 x 27 cm), using 40% EtOAc-hexane, gave **298a** (43 mg, 76%) as a white foam: $[\alpha]_D$ = -11.2 (c 0.86, $CHCl_3$); FTIR (CH_2Cl_2 cast) 3344, 1725, 1667 cm^{-1}; ^1H NMR (CD_2Cl_2, 300 MHz) δ 3.41 (br s, 6 H), 3.52-3.62 (m, 5 H), 3.70 (s, 3 H), 3.71-3.77 (m, 1 H), 3.92 (d, *J* = 3.4 Hz, 1 H), 4.24 (dd, *J* = 9.0, 3.4 Hz, 1 H), 4.79 (t, *J* = 3.9 Hz, 1 H), 5.02 (dd, *J* = 8.1, 3.6 Hz, 1 H), 5.71 (d, *J* = 4.2 Hz, 1 H), 6.96 (d, *J* = 8.1 Hz, 1 H), 7.19-7.57 (m, 6 H), 7.70-7.88 (m, 4 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 52.2 (d') or (q'), 52.9 (d') or (q'), 58.0 (q'), 58.4 (q'), 59.5 (q'), 72.2 (t'), 76.5 (d'), 77.2 (d'), 78.5 (d'), 80.3 (d'), 84.2 (d'), 127.4 (d'), 128.6 (d'), 128.8 (d'), 129.5 (s'), 130.0 (d'), 132.0 (d'), 133.6 (d'), 134.1 (s'), 165.8 (s'), 166.7 (s'), 171.1 (s'); exact mass (electrospray) *m/z* calcd for $C_{26}H_{31}NNaO_9$ (M + Na) 524.1896, found 524.1900.

Methyl 3,6-Anhydro-2-benzamido-4-*O*-benzoyl-2-deoxy-5,7,8-tri-*O*-methyl-D-*erythro*-L-*gulo*-octonate (298b).

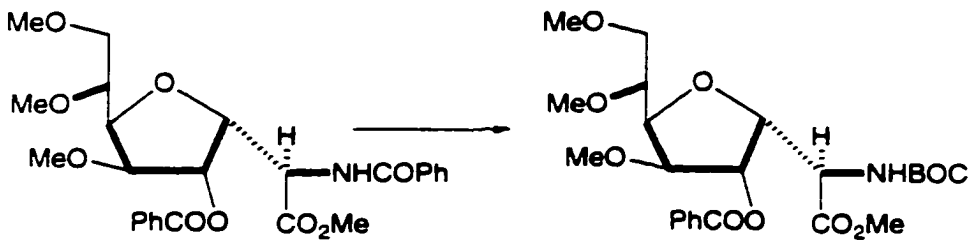


297b **298b**

Jones reagent (104 μL, 8 N) was added dropwise to a stirred and cooled (0 °C) solution of **297b** (44.0 mg, 0.093 mmol) in acetone (0.8 mL). Stirring was continued for 1.5 h before the excess of Jones reagent was quenched with *i*-PrOH (60 μL). Stirring was continued for 2 h, the mixture was filtered, and the green precipitate was washed with Et_2O (3 x 3 mL). The combined filtrates were evaporated, dissolved in a little Et_2O, and treated with an ethereal solution of CH_2N_2 until a slight yellow color persisted. The excess of CH_2N_2 was destroyed with a few drops of AcOH, and the solvent was evaporated. Flash chromatography of the residue over silica gel (1.6 x 25 cm), using 40% EtOAc-hexane, gave **298b** (36 mg, 77%) as a pure (^{1}H NMR, 300 MHz), white foam: $[\alpha]_D$ = +16.1° (c 1.05, $CHCl_3$); FTIR (CH_2Cl_2 cast) 3321, 1745, 1723, 1646 cm^{-1}; ^{1}H NMR (CD_2Cl_2, 300 MHz) δ 3.27 (s, 3 H), 3.39 (s, 3 H), 3.40-3.44 (m, 1 H), 3.52-3.59 [m, including s (3 H) at δ 3.56, 4 H in all], 3.70 (dd, *J* = 10.6, 2.0 Hz, 1 H), 3.73 (s, 3 H), 3.92 (d, *J* = 3.4 Hz, 1 H), 4.17 (dd, *J* = 9.3, 3.4 Hz, 1 H), 4.70 (dd, *J* = 7.7, 4.1 Hz, 1 H), 5.27 (dd, *J* = 8.7, 7.9 Hz, 1 H), 5.69 (d, *J* = 4.1 Hz, 1 H), 6.77 (d, *J* = 8.9 Hz, 1 H), 7.38-7.72 (m, 8 H), 7.99-8.05 (m, 2 H); ^{13}C NMR (CD_2Cl_2, 50.3 MHz) δ 52.3 (d') or (q'), 52.7 (d') or (q'), 58.0 (q'), 58.4 (q'), 59.3 (q'), 72.2 (t'), 76.1 (d'), 77.2 (d'), 79.4 (s'), 80.3 (d'), 84.1 (d'), 127.3 (d'), 128.8 (d'), 128. (d'), 129.8 (s'), 129.9 (d'), 132.0 (d'), 133.8 (d'), 134.3 (s'), 165.6 (s'), 167.1 (s'), 171.0 (s'); exact mass (electrospray) *m/z* calcd for $C_{26}H_{31}NNaO_9$ (M + Na) 524.1896,

found 524.1882.

Methyl 3,6-Anhydro-4-*O*-benzoyl-2-[[(1,1-dimethylethoxy)-carbonyl]amino]-2-deoxy-5,7,8-tri-*O*-methyl-D-*erythro*-L-*ido*-octonate (299).

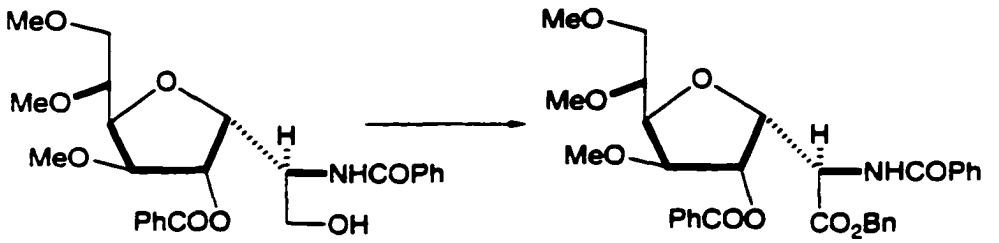


298a **299**

(t-BuOCO)$_2$O (56.0 mg, 0.257 mmol) was added to a stirred solution of **298a** (35.0 mg, 0.070 mmol) and DMAP (2.1 mg, 0.017 mmol) in THF (1 mL), and the mixture was refluxed for 4 h. The solution was cooled to room temperature, MeOH (1 mL) and N_2H_4 (13 μL, 0.419 mmol) were added, and the mixture was stirred for 4 h (TLC indicated complete reaction), and evaporated. Flash chromatography of the residue over silica gel (1.6 x 24 cm), using first 30% EtOAc-hexane (200 mL) and then 40% EtOAc-hexane, gave **299** (30 mg, 86%) as a colorless oil: $[\alpha]_D$ = -5.6 (c 1.02, $CHCl_3$); FTIR (CH_2Cl_2 cast) 3365, 1723, 1601, 1585 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 1.30 (s, 9 H), 3.38 (s, 3 H), 3.40 (s, 3 H), 3.45-3.49 (m, 1 H), 3.52-3.58 [m, including s (3 H) at δ 3.54, 4 H in all], 3.66 (s, 3 H), 3.71 (dd, J = 10.5, 1.9 Hz, 1 H), 3.91 (dd, J = 3.6, 0.8 Hz, 1 H), 4.13 (dd, J = 9.2, 3.6 Hz, 1 H), 4.48-4.58 (m, 2

H), 5.26 (d, J = 8.3 Hz, 1 H), 5.60 (d, J = 3.4 Hz, 1 H), 7.42-7.62 (m, 3 H), 8.00-8.05 (m, 2 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 28.2 (q'), 52.7 (d') or (q'), 53.6 (d') or (q'), 58.3 (q'), 58.4 (q'), 59.4 (q'), 72.9 (t'), 76.3 (d'), 77.4 (d'), 78.5 (d'), 79.9 (s'), 80.1 (d'), 84.3 (d'), 128.8 (d'), 129.8 (s'), 130.1 (d'), 133.7 (d'), 155.5 (s'), 165.8 (s'), 171.4 (s'); exact mass (electrospray) *m/z* calcd for $C_{24}H_{35}NNaO_{10}$ (M + Na) 520.2159, found 520.2167.

Benzyl 3,6-Anhydro-2-benzamido-4-*O*-benzoyl-2-deoxy-5,7,8-tri-*O*-methyl-D-*erythro*-L-*ido*-octonate (300).

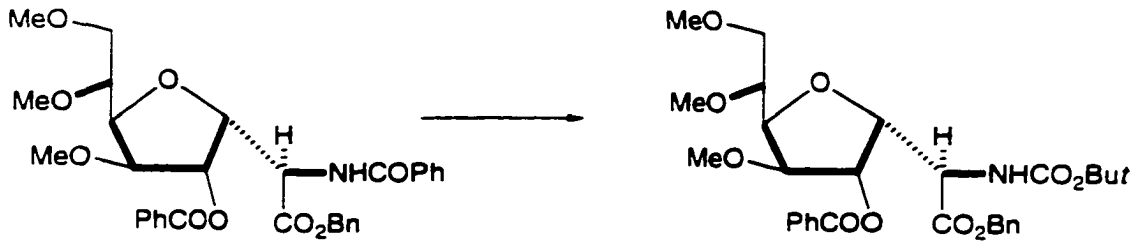


297a **300**

Jones reagent (121 μL, 8 N) was added dropwise to a stirred and cooled (0 °C) solution of **297a** (51.0 mg, 0.108 mmol) in acetone (0.9 mL). Stirring was continued for 1.5 h before the excess of Jones reagent was quenched with *i*-PrOH (70 μL). Stirring was continued for 2 h, the mixture was filtered, and the green precipitate was washed with Et_2O (3 x 5 mL). The combined filtrates were washed with brine (2 x 2 mL), dried ($MgSO_4$), and evaporated. DMF (1 mL), $NaHCO_3$ (27.2 mg, 0.323 mmol), BnBr (64 μL, 0.53 mmol), and NaI (1.0 mg,

0.007 mmol) were added to the resulting residue, and the mixture was stirred for 22 h (TLC indicated complete reaction). The DMF was evaporated under oil-pump vacuum. Flash chromatography of the residue over silica gel (1.6 x 27 cm), using 40% EtOAc-hexane, gave **300** (48 mg, 77%) as a colorless oil: $[\alpha]_D$ = -19.7 (c 0.98, $CHCl_3$); FTIR (CH_2Cl_2 cast) 3350, 1725, 1668 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 3.39 (s, 3 H), 3.41 (s, 3 H), 3.52 (dd, *J* = 10.6, 4.3 Hz, 1 H), 3.55 (s, 3 H), 3.59 (ddd, *J* = 9.2, 4.3, 1.8 Hz, 1 H), 3.73 (dd, *J* = 10.6, 1.8 Hz, 1 H), 3.94 (dd, *J* = 3.4, 0.6 Hz, 1 H), 4.24 (dd, *J* = 9.2, 3.4 Hz, 1 H), 4.82 (t, *J* = 3.9 Hz, 1 H), 5.09 (dd, *J* = 8.2, 3.7 Hz, 1 H), 5.14 (d, *J* = 12.4 Hz, 1 H), 5.20 (d, *J* = 12.4 Hz, 1 H), 5.69 (dd, *J* = 4.1, 0.7 Hz, 1 H), 7.00 (d, *J* = 8.2 Hz, 1 H), 7.19-7.56 (m, 11 H), 7.70-7.87 (m, 4 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 52.5 (d'), 58.1 (q'), 58.4 (q'), 59.5 (q'), 67.6 (t'), 72.3 (t'), 76.5 (d'), 77.2 (d'), 78.5 (d'), 80.3 (d'), 84.2 (d'), 127.4 (d'), 128.3 (d'), 128.6 (d'), 128.8 (d'), 129.5 (s'), 130.0 (d'), 132.0 (d'), 133.6 (d'), 134.1 (s'), 135.8 (s'), 165.8 (s'), 166.8 (s'), 170.5 (s'); exact mass (electrospray) *m/z* calcd for $C_{32}H_{35}NNaO_9$ (M + Na) 600.2209, found 600.2218.

Benzyl 3,6-Anhydro-4-*O*-benzoyl-2-[[(1,1-dimethylethoxy)-carbonyl]amino]-2-deoxy-5,7,8-tri-*O*-methyl-D-*erythro*-L-*ido*-octonate (301).



300 **301**

(t-BuOCO)$_2$O (56.0 mg, 0.257 mmol) was added to a stirred solution of **300** (41.0 mg, 0.071 mmol) and DMAP (2.2 mg, 0.018 mmol) in THF (1 mL), and the mixture was refluxed for 4 h. The solution was cooled to room temperature, MeOH (1 mL) and N_2H_4 (16 μL, 0.50 mmol) were added, and the mixture was stirred for 6 h (TLC indicated complete reaction), and evaporated. Flash chromatography of the residue over silica gel (1.6 x 25 cm), using 40% EtOAc-hexane, gave **301** (36 mg, 89%) as a colorless oil: $[\alpha]_D$ = -2.7 (c 1.12, $CHCl_3$); FTIR (CH_2Cl_2 cast) 3367, 1723, 1601, 1585 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 1.29 (s, 9 H), 3.37 (s, 3 H), 3.40 (s, 3 H), 3.41-3.48 (m, 1 H), 3.51-3.58 [m, including s (3 H) at δ 3.52, 4 H in all], 3.68 (dd, J = 10.6, 1.9 Hz, 1 H), 3.92 (d, J = 3.5 Hz, 1 H), 4.13 (dd, J = 9.2, 3.7 Hz, 1 H), 4.55-4.63 (m, 2 H), 5.12 (s, 2 H), 5.30 (d, J = 8.1 Hz, 1 H), 5.58 (d, J = 3.3 Hz, 1 H), 7.25-7.62 (m, 8 H), 7.97-8.02 (m, 2 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 28.2 (q'), 53.8 (d'), 58.3 (q'), 58.4

(q'), 59.4 (q'), 67.4 (t'), 72.9 (t'), 76.4 (d'), 77.3 (d'), 78.4 (d'), 79.9 (s'), 80.0 (d'), 84.2 (d'), 128.3 (d'), 128.5 (d'), 128.8 (d'), 129.7 (s'), 130.1 (d'), 133.7 (d'), 135.8 (s'), 155.5 (s'), 165.7 (s'), 170.8 (s'); exact mass (electrospray) *m/z* calcd for $C_{30}H_{39}NNaO_{10}$ (M + Na) 596.2472, found 596.2473.

Phenyl 2,3,5-Tri-*O*-acetyl-1-seleno-β-L-xylofuranoside (304).

302 **304**

Methanolic hydrogen chloride [1.06 M, prepared by addition of AcCl (235 μL) to stirred and cooled (0 °C) dry MeOH (3.15 mL)], was added to a stirred mixture of anhydrous L-xylose (**302**) (0.500 g, 3.33 mmol) and dry MeOH (10 mL). Stirring at 5-10 °C was continued overnight. Pyridine (2 mL) was then added to neutralize the acid, and the mixture was evaporated at room temperature, the pyridine being removed under high vacuum. The residue was dissolved in pyridine (4 mL), and Ac_2O (1.5 mL) was added with ice-bath cooling. The cold bath was left in place and the solution was stirred for 24 h. Evaporation of the solvents under high vacuum gave a syrupy product which was dissolved in a mixture of AcOH (5 mL) and Ac_2O (1.25 mL). Concentrated H_2SO_4 (0.25 mL) was

added at 0 °C. The solution was left overnight at room temperature, and then poured onto crushed ice (7.5 g). The mixture was stirred for 1.5 h, and extracted with $CHCl_3$ (3 x 25 mL). The combined extracts were washed with water (5 mL) and saturated aqueous $NaHCO_3$ (4 x 5 mL), dried (Na_2SO_4), and evaporated. The residue was kept under high vacuum for 4 h, and then dissolved in dry CH_2Cl_2 (35 mL). PhSeH (600 μL, 5.649 mmol) was added, and the mixture was stirred and cooled (0 °C). $BF_3.Et_2O$ (387 μL, 3.1446 mmol) was added dropwise over 0.5 h. Stirring was continued for 36 h at 0 °C, and then saturated aqueous $NaHCO_3$ (2 mL) was added. The organic phase was washed with water (2 x 5 mL) and brine (5 mL), dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1.6 x 28 cm), using first 10% EtOAc-hexane (200 mL), and then 20% EtOAc-hexane, gave **304** (1.067 g, 77%) as a colorless oil: $[\alpha]_D$ = 107.2 (c 1.18, $CHCl_3$); FTIR (CH_2Cl_2 cast) 1748 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 2.06 (s, 3 H), 2.07 (s, 3 H), 2.10 (s, 3 H), 4.26 (dd, *J* = 11.7, 6.9 Hz, 1 H), 4.34 (dd, *J* = 11.7, 5.1 Hz, 1 H), 4.50 (dt, *J* = 6.8, 4.9 Hz, 1 H), 5.33 (dd, *J* = 4.6, 1.5 Hz, 1 H), 5.41 (t, *J* = 1.7 Hz, 1 H), 5.55 (d, *J* = 1.8 Hz, 1 H), 7.29-7.34 (m, 3 H), 7.62-7.66 (m, 2 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 20.7 (q'), 20.8 (q'), 20.9 (q'), 62.2 (t'), 75.1 (d'), 79.7 (d'), 81.8 (d'), 86.2 (d'), 128.2 (d'), 129.4 (d'), 129.9 (s'), 134.6 (d'), 169.5 (s'), 169.6 (s'), 170.6 (s'); exact mass (electrospray) *m/z* calcd for $C_{17}H_{20}NaO_7Se$ (M + Na) 439.0272, found 439.0279.

Phenyl 1-Seleno-β-L-xylofuranoside (305).

304 **305**

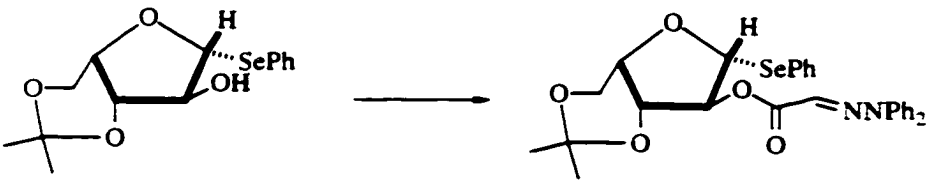
K_2CO_3 (345 mg, 2.50 mmol) was added to a stirred solution of **304** (1.03 g, 2.50 mmol) in 1:1 THF-MeOH (20 mL), and the mixture was stirred vigorously for 20 min, filtered through a pad (2 mm x 1 cm) of flash chromatography silica gel, and evaporated. Flash chromatography of the residue over silica gel (1.6 x 28 cm), using 2% MeOH-EtOAc, gave **305** (0.715 g, 99%) as a pale yellow oil: $[\alpha]_D$ = 189.2 (c 1.0, MeOH); FTIR (CH_2Cl_2 cast) 3407 cm^{-1}; ^1H NMR (CD_2Cl_2), 400 MHz) δ 2.31-2.35 (m, 2 H), 3.74 (d, J = 5.5 Hz, 1 H), 3.88-3.94 (m, 1 H), 3.97-4.02 (m, 1 H), 4.24-4.30 (m, 2 H), 4.39-4.41 (m, 1 H), 5.56 (d, J = 2.4 Hz, 1 H), 7.29-7.35 (m, 3 H), 7.60-7.66 (m, 2 H); ^{13}C NMR (CD_3OD, 100.6 MHz) δ 61.9 (t'), 77.1 (d'), 84.3 (d'), 84.8 (d'), 90.5 (d'), 128.1 (d'), 130.0 (d'), 132.9 (s'), 134.3 (d'); exact mass *m/z* calcd for $C_{11}H_{14}NaO_4Se$ 312.9955, found 312.9944.

Phenyl 3,5-*O*-Isopropylidene-1-seleno-β-L-xylofuranoside (306).

305 **306**

p-$MeC_6H_4SO_3H.H_2O$ (6.0 mg, 0.03 mmol) was added to a stirred solution of **305** (506 mg, 1.75 mmol) in dry acetone (10 mL). Stirring was continued for 1.5 h, $NaHCO_3$ (20 mg) was added, stirring was continued for 0.5 h, and the mixture was filtered through a pad (2 mm x 1 cm) of flash chromatography silica gel. Evaporation of the filtrate and flash chromatography of the residue over silica gel (1.6 x 27 cm), using 30% EtOAc-hexane, gave **306** [510 mg, 89% or 94% after correction for recovered starting material (28 mg)] as a white powder: mp 130-131 °C; $[\alpha]_D$ = 178.6 (c 1.1, $CHCl_3$); FTIR (CH_2Cl_2 cast) 3419 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 1.43 (s, 6 H), 2.26 (d, *J* = 4.1 Hz, 1 H), 4.00-4.11 (m, 3 H), 4.23 (dd, *J* = 3.0, 1.0 Hz, 1 H), 4.60 (d, *J* = 4.0 Hz, 1 H), 5.54 (s, 1 H), 7.23-7.32 (m, 3 H), 7.59-7.65 (m, 2 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 19.6 (q'), 28.4 (q'), 60.5 (t'), 74.5 (d'), 75.2 (d'), 83.1 (d'), 91.5 (d'), 97.9 (s'), 127.3 (d'), 129.4 (d'), 132.8 (s'), 133.2 (d'); exact mass (electrospray) *m/z* calcd for $C_{14}H_{18}NaO_4Se$ (M + Na) 353.0268, found 353.0269.

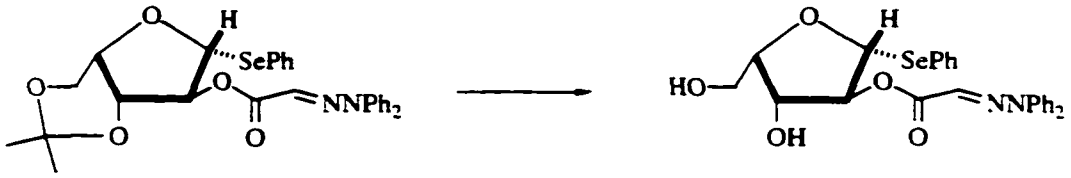
Phenyl 2-*O*-(Diphenylhydrazono)acetyl-3,5-*O*-isopropylidene-1-seleno-β-L-xylofuranoside (307).



306 **307**

(2,2-Diphenylhydrazono)acetic acid (**207**) (225 mg, 0.941 mmol) was added to a stirred mixture of **306** (258 mg, 0.784 mmol), DCC (213 mg, 1.03 mmol) and DMAP (11.5 mg, 0.094 mmol) in dry CH_2Cl_2 (15 mL). Stirring was continued for 12 h, and the mixture was then filtered. The insoluble material was washed with dry CH_2Cl_2 and the combined filtrates were evaporated. Flash chromatography of the residue over silica gel (1.6 x 26 cm), using 10% EtOAc-hexane, gave **307** (409 mg, 95%) as a white powder: mp 158-160 °C; $[\alpha]_D$ = 160.9 (c 1.17, $CHCl_3$); FTIR (CH_2Cl_2 cast) 1733, 1706 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 1.45 (s, 3 H), 1.47 (s, 3 H), 4.02-4.14 (m, 3 H), 4.38-4.42 (m, 1 H), 5.57 (s, 1 H), 5.65 (s, 1 H), 6.43 (s, 1 H), 7.13-7.49 (m, 13 H), 7.62-7.68 (m, 2 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 19.7 (q'), 28.3 (q'), 60.4 (t'), 72.6 (d'), 75.5 (d'), 84.3 (d'), 89.1 (d'), 98.1 (s'), 123.0 (d'), 127.5 (d'), 129.3 (d'), 130.3 (d'), 132.6 (s'), 133.6 (d'), 163.1 (s'); exact mass (electrospray) *m/z* calcd for $C_{28}H_{28}N_2NaO_5Se$ (M + Na) 575.1061, found 575.1067.

Phenyl 2-*O*-(Diphenylhydrazono)acetyl-1-seleno-β-L-xylofuranoside (308).



307 **308**

Camphorsulfonic acid (158 mg, 0.684 mmol) was added to a stirred solution of **307** (377 mg, 0.684 mmol) in MeOH (225 mL). Stirring was continued for 3.5 h, $NaHCO_3$ (57.5 mg, 0.684 mmol) was added, and stirring was continued for 0.5 h. The mixture was then evaporated. Flash chromatography of the residue over silica gel (1.6 x 28 cm), using 50% EtOAc-hexane, gave **308** (336 mg, 96%) as a pale yellow foam: $[\alpha]_D$ = 132.7 (c 1.12, $CHCl_3$), FTIR (CH_2Cl_2 cast) 3427, 1706 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 2.60 (br s, 1 H), 3.92-4.06 (m, 2 H), 4.15-4.22 (m, 1 H), 4.28 (dd, *J* = 8.1, 4.3 Hz, 1 H), 4.43-4.46 (m, 1 H), 5.42 (d, *J* = 1.6 Hz, 1 H), 5.71 (d, *J* = 2.0 Hz, 1 H), 6.45 (s, 1 H), 7.15-7.51 (m, 13 H), 7.62-7.70 (m, 2 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 61.4 (t'), 76.4 (d'), 82.7 (d'), 85.0 (d'), 86.1 (d'), 123.0 (d'), 128.1 (d'), 129.5 (d'), 130.3 (d'), 130.5 (s'), 134.2 (d'), 164.0 (s'); exact mass (electrospray) *m/z* calcd for $C_{25}H_{24}N_2NaO_5Se$ (M + Na) 535.0748, found 535.0746.

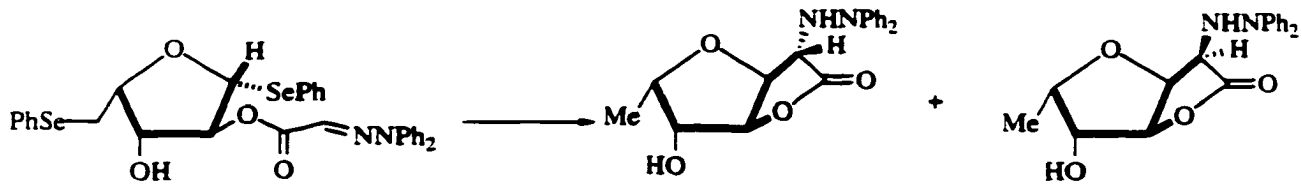
Phenyl 5-Deoxy-2-*O*-(Diphenylhydrazono)acetyl-5-phenylseleno-1-seleno-β-L-xylofuranoside (309).

308 **309**

Freshly prepared PhSeCN[82] (107 mg, 0.592 mmol) in THF (2 mL) was added over 6 h by syringe pump to a stirred solution of **308** (275 mg, 0.538 mmol) and Bu_3P (161 μL, 0.645 mmol) in THF (2 mL). Stirring was continued for 1.5 h, and the mixture was then evaporated. Flash chromatography of the residue over silica gel (1.6 x 26 cm), using first 10% EtOAc-hexane (100 mL), and then 30% EtOAc-hexane, gave **309** [349 mg, 75% or 89% after correction for recovered starting material (44 mg)] as a pale yellow oil: $[\alpha]_D$ = 135.1 (c 1.04, $CHCl_3$); FTIR (CH_2Cl_2 cast) 3419, 1705 cm^{-1}; ^1H NMR (CD_2Cl_2, 300 MHz) δ 2.84 (d, *J* = 6.1 Hz, 1 H), 3.23-3.35 (m, 2 H), 4.36-4.45 (m, 2 H), 5.43-5.44 (m, 1 H), 5.64 (d, *J* = 1.8 Hz, 1 H), 6.44 (s, 1 H), 7.14-7.50 (m, 16 H), 7.53-7.69 (m, 4 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 26.1 (t'), 75.0 (d'), 83.7 (d'), 84.9 (d'), 85.3 (d'), 123.1 (d'), 127.4 (d'), 128.2 (d'), 129.5 (d'), 130.4 (d'), 132.9 (d'), 134.6 (d'), 163.9 (s'); exact mass (electrospray) *m/z* calcd for $C_{31}H_{28}N_2NaO_4Se_2$ (M + Na) 675.0277, found 675.0264.

3,6-Anhydro-2,7-dideoxy-2-(2,2-diphenylhydrazino)-L-

***glycero*-D-*ido*-heptono-1,4-lactone (310a) and 3,6-Anhydro-2,7-dideoxy-2-(2,2-diphenylhydrazino)-L-*glycero*-D-*gulo*-heptono-1,4-lactone (310b).**



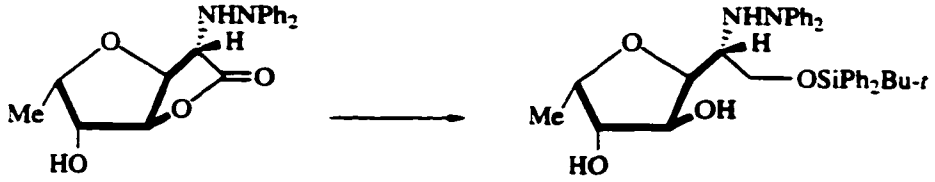
309 **310a** **310b**

This experiment was carried out in a 200 mL round-bottomed flask equipped with a Teflon-coated stirring bar and a reflux condenser sealed with a rubber septum. The flask was charged with **309** (858 mg, 1.32 mmol), and the system was flushed with argon for 5-10 min. Dry PhMe (80 mL) was injected , and the flask was placed in an oil bath preheated to 110 °C. Solutions of Ph_3SnH (2.54 g, 7.26 mmol) in PhMe (10 mL) and of AIBN (130 mg, 0.792 mmol) in PhMe (10 mL) were injected simultaneously by syringe pump over 10 h. Refluxing was continued for 2 h after the addition. The mixture was cooled, and the solvent was evaporated. Flash chromatography of the residue over silica gel (2.5 x 29 cm), using first 20% EtOAc-hexane (300 mL), and then 30% EtOAc-hexane, gave two fractions which all contained a small amount of triphenyltin residues (^1H NMR). Each fraction was further purified by flash chromatography over silica gel (1.6 x 28 cm), using 30% EtOAc-hexane, to give **310a** (187 mg, 42%), and **310b** (166.1 mg, 37%), both as colorless oils.

Compound **310a** had: $[\alpha]_D$ = -23.1 (c 1.19, $CHCl_3$); FTIR (CH_2Cl_2 cast) 3452, 1779 cm^{-1}; ^1H NMR (CD_2Cl_2, 300 MHz) δ 1.23 (d, *J* = 6.4 Hz, 3 H), 1.95 (d, *J* = 6.1 Hz, 1 H), 3.76 (t, *J* = 1.0 Hz, 1 H), 4.02 (qd, *J* = 6.3, 2.8 Hz, 1 H), 4.22 (dd, *J* = 5.8, 2.8 Hz, 1 H), 4.31 (d, *J* = 2.0 Hz, 1 H), 4.86 (d, *J* = 4.9 Hz, 1 H), 5.08 (d, *J* = 4.9 Hz, 1 H), 7.05-7.18 (m, 6 H), 7.30-7.38 (m, 4 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 13.1 (q'), 62.9 (d'), 75.3 (d'), 77.2 (d'), 80.2 (d'), 88.2 (d'), 121.1 (d'), 123.7 (d'), 129.7 (d'), 147.4 (s'), 174.7 (s'); exact mass *m/z* calcd for $C_{19}H_{20}N_2O_4$ 340.1423, found 340.1422.

Compound **310b** had: $[\alpha]_D$ = -48.7 (c 0.94, $CHCl_3$); FTIR (CH_2Cl_2 cast) 3455, 1781 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 1.28 (d, *J* = 6.4 Hz, 3 H), 2.02 (d, *J* = 4.3 Hz, 1 H), 3.75 (d, *J* = 5.7 Hz, 1 H), 4.08-4.15 (m, 1 H), 4.20-4.24 (m, 1 H), 4.60 (dd, *J* = 5.7, 4.0 Hz, 1 H), 4.77 (d, *J* = 4.0 Hz, 1 H), 4.89 (s, 1 H), 7.00-7.05 (m, 2 H), 7.25-7.34 (m, 8 H); ^{13}C NMR.(CD_2Cl_2, 100.6 MHz) δ 13.3 (q'), 60.1 (d'), 75.6 (d'), 76.4 (d'), 77.8 (d'), 85.7 (d'), 120.9 (d'), 123.0 (d'), 129.4 (d'), 147.4 (s'), 174.9 (s'); exact mass *m/z* calcd for $C_{19}H_{20}N_2O_4$ 340.1423, found 340.1422.

2,5-Anhydro-1,6-dideoxy-7-*O*-[(1,1-dimethylethyl)diphenyl-silyl]-6-(2,2-diphenylhydrazino)-D-*glycero*-L-*ido*-heptitol (312).



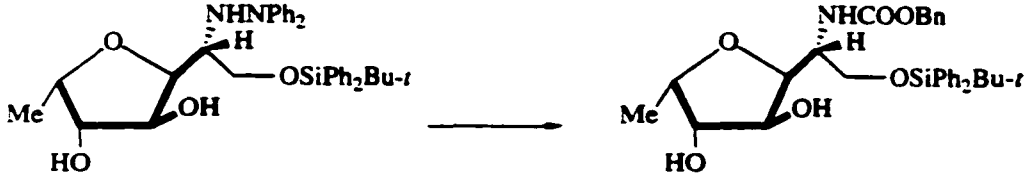
310a **312**

A solution of **310a** (186 mg, 0.547 mmol) in THF (1 mL, plus 2 x 1 mL as a rinse) was added to a stirred and cooled (0 °C) suspension of $LiAlH_4$ (68.5 mg, 1.81 mmol) in THF (2 mL). Stirring was continued for 0.5 h at 0 °C, and then for 1.5 h after removal of the ice bath. MeOH (0.3 mL) was added carefully to quench the reaction, followed by saturated aqueous $NaHCO_3$ (0.3 mL). The mixture was stirred for 15 min, diluted with THF (5 mL), and filtered through a pad (2 mm x 1 cm) of Celite, using THF (40 mL). Evaporation of the filtrate gave the expected triol (**311**), which was used directly in the next step.

t-$BuPh_2SiCl$ (151 µL, 0.581 mmol) was added dropwise to a stirred solution of the triol (all the material from the above experiment) and imidazole (69.6 mg, 1.02 mmol) in THF (4 mL). Stirring was continued for 6 h, and the solvent was evaporated. Flash chromatography of the residue over silica gel (1.6 x 28 cm), using 30% EtOAc-hexane, gave **312** (236 mg, 74%) as a colorless oil: $[\alpha]_D$ = -42.1 (c 1.19, $CHCl_3$); FTIR

(CH_2Cl_2 cast) 3439 cm^{-1}; ^1H NMR (CD_2Cl_2, 300 MHz) δ 1.01 (s, 9 H), 1.25 (d, J = 6.5 Hz, 3 H), 1.71 (d, J = 5.0 Hz, 1 H), 3.51 (td, J = 9.0, 2.4 Hz, 1 H), 3.58-3.65 (m, 1 H), 3.79 (d, J = 2.1 Hz, 1 H), 3.94 (dd, J = 10.1, 2.5 Hz, 1 H), 4.00-4.05 (m, 2 H), 4.27-4.38 (m, 2 H), 4.78 (s, 1 H), 6.91-7.00 (m, 6 H), 7.17-7.63 (m, 14 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 13.8 (q'), 19.1 (s'), 26.9 (q'), 59.4 (d'), 64.2 (t'), 76.6 (d'), 78.5 (d'), 78.6 (d'), 82.8 (d'), 120.6 (d'), 122.5 (d'), 128.2 (d'), 129.2 (d'), 130.4 (d'), 130.4 (d'), 132.4 (s'), 132.5 (s'), 135.8 (d'), 135.9 (d'), 148.2 (s'); exact mass (electrospray) *m/z* calcd for $C_{35}H_{43}N_2O_4Si$ (M + H) 583.2992, found 583.2994.

2,5-Anhydro-7-*O*-[(1,1-dimethylethyl)diphenylsilyl]-6-[[(phenylmethoxy)carbonyl]amino]-1,6-dideoxy-D-*glycero*-L-*iodo*-heptitol (313).

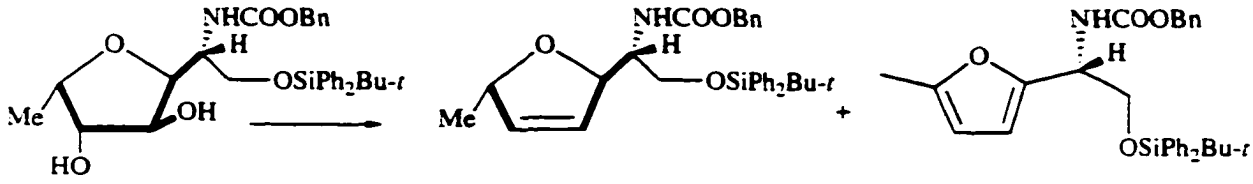


312 **313**

Camphorsulfonic acid (199 mg, 0.858 mmol) and then 10% Pd-C (90.0 mg) were added to a solution of **312** (227 mg, 0.390 mmol) in a mixture of EtOAc (5.6 mL) and MeOH (1.4 mL). The mixture was shaken under H_2 (50 psi) for 2 h (Parr shaker), and then filtered through a pad of Celite. The pad was

washed with EtOAc (3 x 12 mL), and the combined filtrates were evaporated. THF (7.5 mL), water (2.5 mL), and $NaHCO_3$ (170 mg, 2.02 mmol) were added to the resulting yellow foam. The mixture was stirred and cooled (0 °C), and BnOCOCl (84 μL, 0.58 mmol) was added dropwise. Stirring was continued for 0.5 h at 0 °C, and then for 0.5 h after removing the cold bath. The mixture was extracted with CH_2Cl_2 (50 mL), and the organic extract was washed with brine (10 mL), dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (1.6 x 28 cm), using 40% EtOAc-hexane, gave **313** (171 mg, 80%) as a colorless oil: $[\alpha]_D$ = -4.8 (c 1.04, $CHCl_3$); FTIR (CH_2Cl_2 cast) 3434, 1700 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 1.06 (s, 9 H), 1.19 (d, *J* = 6.5 Hz, 3 H), 2.05 (s, 1 H), 3.34 (s, 1 H), 3.62-3.69 (m, 1 H), 3.78 (dd, *J* = 10.2, 4.4 Hz, 1 H), 3.95-4.02 (m, 1 H), 4.03-4.12 (m, 1 H), 4.15-4.22 (m, 2 H), 4.27 (qd, *J* = 6.5, 3.5 Hz, 1 H), 5.06 (s, 2 H), 5.20 (br d, *J* = 6.3 Hz, 1 H), 7.28-7.48 (m, 11 H), 7.63-7.72 (m, 4 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 14.1 (q'), 19.4 (s'), 26.9 (q'), 52.6 (d'), 64.9 (t'), 67.1 (t'), 76.5 (d'), 78.6 (d'), 78.9 (d'), 79.2 (d'),128.2 (d'), 128.3 (d'), 128.8 (d'), 130.3 (d'), 133.0 (s'), 135.9 (d'), 137.0 (s'), 156.8 (s'); exact mass (electrospray) *m/z* calcd for $C_{31}H_{40}NO_6Si$ (M + H) 550.2625, found 550.2641.

2,5-Anhydro-1,3,4,6-tetradeoxy-7-*O*-[(1,1-dimethylethyl)-diphenylsilyl]-6-[[(phenylmethoxy)carbonyl]amino]-D-*xylo*-hept-3-enitol (314).



313 **314**

Ph_3P (324 mg, 1.23 mmol), CHI_3 (243 mg, 0.619 mmol) and imidazole (42.2 mg, 0.619 mmol) were added to a stirred solution of diol **313** (170 mg, 0.310 mmol) in dry PhMe (5 mL). The mixture was refluxed for 22 h, cooled to room temperature, and extracted with PhMe (50 mL). The organic extract was washed with saturated aqueous $NaHCO_3$ (10 mL), saturated aqueous $Na_2S_2O_3$ (5 mL) and brine (10 mL), dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (1.6 x 28 cm), using 10% EtOAc-hexane, gave **314** (102 mg, 64%) and phenylmethyl (*R*)-[[2-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-1-(5-methylfuran-2-yl)]ethyl]carbamate (33 mg, 21%).

Compound **314** had: mp 111-112 °C; $[\alpha]_D$ = 80.6 (c 1.08, $CHCl_3$); FTIR (CH_2Cl_2 cast) 3321, 1715, 1693 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 1.05 (s, 9 H), 1.21 (d, *J* = 6.4 Hz, 3 H), 3.71 (d, *J* = 6.4 Hz, 2 H), 3.85-3.95 (m, 1 H), 4.80-4.95 (m, 2 H), 5.03 (s, 2 H), 5.13-5.18 (m, 1 H), 5.72 (br d, *J* = 5.3

Hz, 1 H), 5.83-5.89 (m, 1 H), 7.26-7.46 (m, 11 H), 7.64-7.72 (m, 4 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 19.4 (s'), 21.9 (q'), 26.9 (q'), 55.8 (d'), 64.1 (t'), 66.7 (t'), 83.0 (d'), 84.2 (d'), 127.1 (d'), 128.0 (d'), 128.1 (d'), 128.2 (d'), 128.7 (d'), 130.0 (d'), 130.1 (d'), 133.5 (d'), 133.8 (s'), 135.9 (d'), 137.4 (s'), 156.6 (s'); exact mass (electrospray) *m/z* calcd for $C_{31}H_{38}NO_4Si$ (M + H) 516.2570, found 516.2582.

Phenylmethyl (*R*)-[[2-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-1-(5-methylfuran-2-yl)]ethyl]carbamate had: $[\alpha]_D$ = 15.3 (c 1.05, $CHCl_3$); FTIR (CH_2Cl_2 cast) 3445, 3332, 1725 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 1.01 (s, 9 H), 2.25 (s, 3 H), 3.91 (d, *J* = 4.7 Hz, 2 H), 4.83-4.93 (m, 1 H), 5.10 (d, *J* = 1.2 Hz, 2 H), 5.35-5.45 (m, 1 H), 5.91-5.97 (m, 1 H), 6.13 (d, *J* = 3.0 Hz, 1 H), 7.28-7.75 (m, 15 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 13.6 (q'), 19.4 (s'), 26.8 (q'), 51.5 (d'), 65.5 (t'), 67.0 (t'), 106.4 (d'), 107.9 (d'), 128.0 (d'), 128.3 (d'), 128.3 (d'), 128.8 (d'), 129.9 (d'), 130.1 (d'), 133.5 (s'), 133.6 (s'), 135.1 (d'), 135.9 (d'), 137.2 (s'), 151.3 (s'), 151.9 (s'), 156.0 (s'); exact mass *m/z* calcd for $C_{31}H_{35}NO_4Si$ 513.2335, found 513.2335.

2,5-Anhydro-1,3,4,6-tetradeoxy-6-[[(phenylmethoxy)-carbonyl]amino]-D-*xylo*-hept-3-enitol (315).

314 **315**

Bu_4NF (1.0 M solution in THF, 335 μL, 0.334 mmol) was added dropwise to a stirred solution of **314** (114 mg, 0.223 mmol) in THF (3.6 mL). Stirring was continued for 0.5 h, and the mixture was then evaporated. Flash chromatography of the residue over silica gel (1.6 x 28 cm), using first 40% EtOAc-hexane (100 mL), and then 60% EtOAc-hexane, gave **315** (59 mg, 96%) as a white solid: mp 69.5-71.5 °C; $[\alpha]_D$ = 196 (c 1.0, $CHCl_3$) [lit.[42] $[\alpha]_D^{28}$ = 195.8 (c 0.99, $CHCl_3$)]; FTIR (CH_2Cl_2 cast) 3425, 3327, 1702 cm^{-1}; ^1H NMR (CD_2Cl_2, 360 MHz) δ 1.21 (d, *J* = 6.3 Hz, 3 H), 2.60-2.68 (br, 1 H), 3.64-3.88 (m, 3 H), 4.93-5.01 (m, 1 H), 5.03-5.10 (m, 3 H), 5.23 (br d, *J* = 6.6 Hz, 1 H), 5.73 (d, *J* = 6.0 Hz, 1 H), 5.86 (ddd, *J* = 6.2, 2.1, 1.5 Hz, 1 H), 7.28-7.39 (m, 5 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 21.9 (q'), 55.1 (d'), 64.9 (t'), 66.8 (t'), 83.4 (d'), 87.1 (d'), 126.9 (d'), 128.1 (d'), 128.3 (d'), 128.7 (d'), 133.4 (d'), 137.2 (s'), 157.0 (s'); exact mass *m/z* calcd for $C_{15}H_{19}NO_4$ 277.1314, found 277.1308.

2-Amino-3,6-anhydro-2,4,5,7-tetradeoxy-L-*xylo*-hept-4-enonic acid (furanomycin) (180).

315 **180**

A solution of **315** (44.0 mg, 0.159 mmol) in CH_2Cl_2 (1 mL, plus 2 x 0.5 mL as a rinse) was added dropwise to a stirred solution of Dess-Martin reagent (87.6 mg, 0.207 mmol) in CH_2Cl_2 (0.8 mL). Stirring was continued for 0.5 h, and Et_2O (5 mL) was added, followed by saturated aqueous $NaHCO_3$ (1.7 mL) containing $Na_2S_2O_3$ (409 mg). The mixture was stirred for 5 min, and Et_2O (10 mL) was added. The organic phase was washed with saturated aqueous $NaHCO_3$ (2 mL) and brine (2 mL), dried (Na_2SO_4), and evaporated. The residue (aldehyde **316**) was dissolved in *t*-BuOH (3.2 mL) and 2-methyl-2-butene (1.6 mL), and a solution of $NaClO_2$ (53.9 mg, 80%, 0.476 mmol) and NaH_2PO_4 (65.7 mg, 0.476 mmol) in water (657 µL) were added over 5 min. The pale yellow reaction mixture was stirred at room temperature for 10 h. Volatile components were evaporated under water pump vacuum, and the residue was dissolved in water (5 mL), and extracted with hexane (2 x 2 mL). The aqueous layer was acidified to pH 3 with 3% HCl and extracted with Et_2O (3 x 15 mL). The combined organic extracts were washed with brine (5 mL), dried (Na_2SO_4), and evaporated.

TFA (5 mL), followed by PhSMe[79] (136 μL, 1.15 mmol) was added to the resulting pale yellow oil (crude furanomycin benzyl ester), and stirring was continued for 12 h at room temperature. The solvents were then evaporated under oil-pump vacuum. The resulting residue was dissolved in water (10 mL), and passed through an ion-exchange column (AG 50W-X8, 1.4 x 9 cm), the column being washed slowly with water (100 mL), and then eluted with NH_4OH (0.5 N). Ninhydrin positive fractions were collected and evaporated to give **180** (18 mg, 71%) as a white powder of at least 98% purity (^1H NMR, 300 MHz). Recrystallization from an acetone-water mixture gave crystalline material (13 mg, 52%) (we suspect that a better yield could be obtained if the crystallization is practiced, and done on a larger scale; we tried the crystallization once): mp 221-223 °C (dec.) [lit.[39b] mp 222.5-224.5 (dec.)]; $[\alpha]_D^{25}$ = 142.6 (c 0.53, H_2O) [lit.[39b] $[\alpha]_D$ = 140 (c 1, H_2O)]; the ^1H NMR spectrum (360 MHz, D_2O was identical to that reported previously.[39b]

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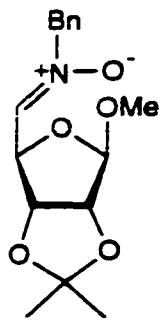
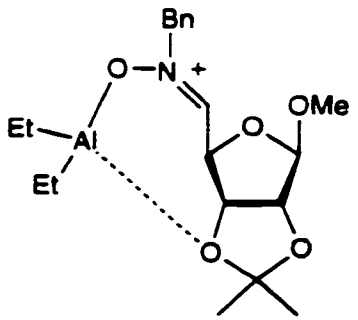
and precomplexed sugar nitrones adopt different conformations, as shown below for nitrone **170**. This difference explains the opposite diastereofacial selectivity of the free nitrone and precomplexed nitrone.



170



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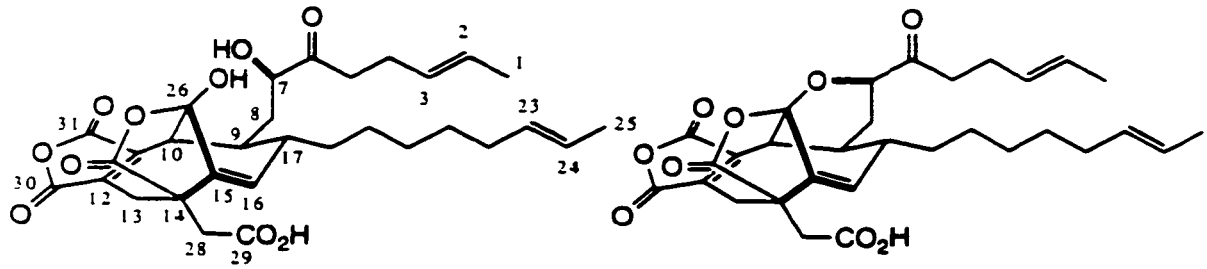
Part 2

Synthetic Studies on CP-225,917 and CP-263,114

I. Introduction

CP-225,917 (**1**) and CP-263,114 (**2**) were isolated recently from an unidentified fungus by Pfizer scientists.[1] Both have been shown to inhibit Ras farnesyl protein transferase.[2] Inhibition of this transferase is particularly important



CP-225,917 **1** CP-263,114 **2**

Figure 1 Structure of the fungal metabolites **1** and **2**

because farnesylated mutagenic Ras is implicated in many types of human cancers.[3] This fact suggests that these compounds may serve as leads in the design of anticancer drugs.[4] Structurally, the compounds have a unique polycyclic skeleton, which consists of a bridgehead double bond, γ-lactone acetal or hemiacetal, and a maleic anhydride moiety.[1] The proposed biosynthetic origin[1,2] of both compounds suggests that they are related to the nonadride family of natural products[5] in that they contain a nine-membered ring fused to a maleic anhydride moiety. Because of the unique skeletal complexity and interesting biological activities, these compounds have attracted considerable interest from synthetic chemists. Several early and interesting model studies

directed at the synthesis of **1** and **2** have been reported by the groups of Nicolaou,[6] Davies,[7] Clive,[8] Armstrong,[9] Danishefsky,[10] Fukuyama,[11] Shair,[12] and Leighton.[13]

Two topics are relevant in the review section for my work aimed at the synthesis of **1** and **2**: the biological basis of the importance of the compounds, and recent synthetic studies related to **1** and **2**.

A. Biological Activity of CP-225,917 and CP-263,114

The fungal metabolites **1** and **2** are inhibitors of Ras farnesyl protein transferase, a medicinal target of great current interest.[14] They serve as lead structures for the design of other inhibitors. The development of such inhibitors holds great promise for the discovery of a new commercial anticancer drug, and the following paragraphs will describe the role of Ras farnesyl transferase, as well as how chemical intervention in the action of the transferase can be used in the search for a cure for cancer.

Cell growth is a carefully regulated process but, occasionally, the mechanisms that control cell proliferation fail. The proteins responsible for control of cell growth are encoded by four classes of proto-oncogenes: growth factors (Class I proto-oncogenes), growth factor receptors (Class II proto-oncogenes), intracellular signal transducers (Class III proto-oncogenes), and nuclear transcription factors (Class IV proto-oncogenes).[15] Of all classes of

proto-oncogenes, intracellular signal transducers (Class III) is the largest,[15] and comprises the ras genes [Harrey (Ha), Kirsten (Ki), and N-ras].[3a] The ras gene products, a family of 21-kDa proteins called p21 or Ras,[3a,16] play key roles in cell growth and are closely associated with 30% of all human cancers.[3b]

Optimal division and differentiation in many cells requires the synthesis of normal Ras.[3a,16] Ras is synthesized as a biologically inactive precursor protein and is found in the soluble fraction (cytoplasm) of cells.[14b] Several post-translational modifications are required at the carboxy-terminal of Ras before it becomes a biologically active protein that is then localized in the plasma membrane.[4]

The lipophilic farnesyl group, a C_{15}-isoprenoid unit, covalently attached to Ras, is responsible for membrane localization of Ras, by interacting with the lipids that constitute the inner side of the cell membrane.[4]

Farnesylation (attachment of a farnesyl group to Ras) is essential to Ras function[17] and is performed by an enzyme – a farnesyl transferase (FTase) – able to recognize certain amino acid sequences of the protein, the so-called Caax motifs.[4] This short sequence is composed of a cysteine residue (C), followed in general by two aliphatic (a) amino acids and one carboxy-terminal amino acid (X).

In malignant cells, some of the common mutations are alterations of the Harrey (Ha-), Kirsten (Ki-) and N-ras genes.[3b] These alterations have been found in many different

tumors, including carcinomas of the colon, pancreas, lung, and in various leukemias.[3]

The transformation of the normal ras proto-oncogene into a ras oncogene can be triggered by carcinogens or oncogenic viruses; the ras oncogene then codes for the synthesis of a mutant oncogenic Ras protein.[16] Normally, bioactive Ras protein binds GTP and GDP and serves as a molecular switch.[3a] When Ras is stimulated by receptor activation to bind GTP, it promotes cell proliferation. Normal farnesylated ras has GTPase activity, and this then turns off the biological event.[3a] The most common mutation of ras genes in human cancer cells produces Ras protein that lacks GTPase activity, and so Ras remains bound to GTP and continuously stimulates cell growth[3a] (i.e., the switch is stuck in the "on" position). Consequently, the membrane-bound mutant Ras protein is permanently activated and continuously generates uncontrolled proliferation signals,[3a] thus leading to cancer.

Based on the above summary, it is clear that one way of halting the unregulated cell growth mechanism is to prevent membrane attachment of mutant Ras protein (and hence the dispatch of proliferation signals). This can be achieved by inhibiting the post-translational farnesylation step, because such action would stop the mutant protein from becoming anchored to the cell membrane and would therefore prevent the triggering of proliferation signals.

Recent research in the area of farnesyl transferase inhibition supports the above idea.[18,19] It has been shown

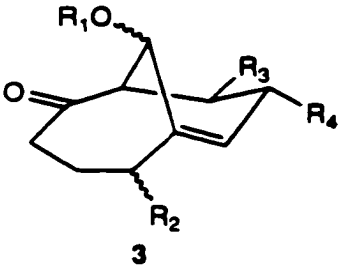
that the growth of malignant cells can be inhibited by FTase inhibitors (FTIs) *in vitro*,[20] and experiments *in vivo*[21] have also shown that certain tumors can completely regress. Surprisingly, the growth of normal cells was not affected.[21b] The above facts indicate that the development of FTIs is a very promising lead to new chemotherapeutic agents for treatment of cancers.

CP-225,917 (**1**) and CP-263,114 (**2**) belong to an emerging group of natural products[22] that are FTase inhibitors. Compounds **1** and **2** inhibit FTase activity with IC_{50} values of 6 μM and 20 μM,[2] respectively. Although the mode of inhibition and what features confer inhibitory properties are unknown, one might speculate that the anhydride substructure serves as a prodrug that is converted into a dicarboxylic acid on hydrolysis. In this respect it is noteworthy that chaetomellic acids[22b,c] (which are alkyl derivatives of maleic acid) are also inhibitors of farnesyl transferase. The hydrocarbon appendages may mimic the farnesyl unit that becomes attached to the Ras protein, and this suggests that the hydrocarbon chains of **1** and **2** may be important, although those present in the natural product may not be the best ones for high activity.

No synthetic route to **1** and **2** is presently available, but current synthetic work, which is described in the following section, may provide the tools necessary for the design of novel anticancer drugs, based on the properties and features of the natural products **1** and **2**.

B. Synthetic Approaches to CP-225,917 and CP-263,142

Although no synthetic route to CP-225,917 (**1**) and CP-263,142 (**2**) has been reported, synthetic chemists have made considerable efforts towards the total synthesis. Inspection of the structures of **1** and **2** reveals that the basic carbon skeleton can be simplified to the model system **3** (Figure 2), which contains the key – and challenging – bicyclic core, as well as anchoring groups for elaborating the remaining functionalities and side chains.



3

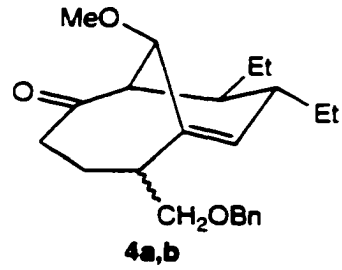
Figure 2 Structure of **3**

The key reactions that have been used to construct the model system **3** can be classified as follows: intramolecular Diels-Alder reaction, Cope and oxy-Cope or related rearrangements, intramolecular aldol condensation, or a combination of aldol condensation and Heck reaction.

1. Intramolecular Diels-Alder Reaction

Nicolaou and his colleagues[6a] used a Diels-Alder

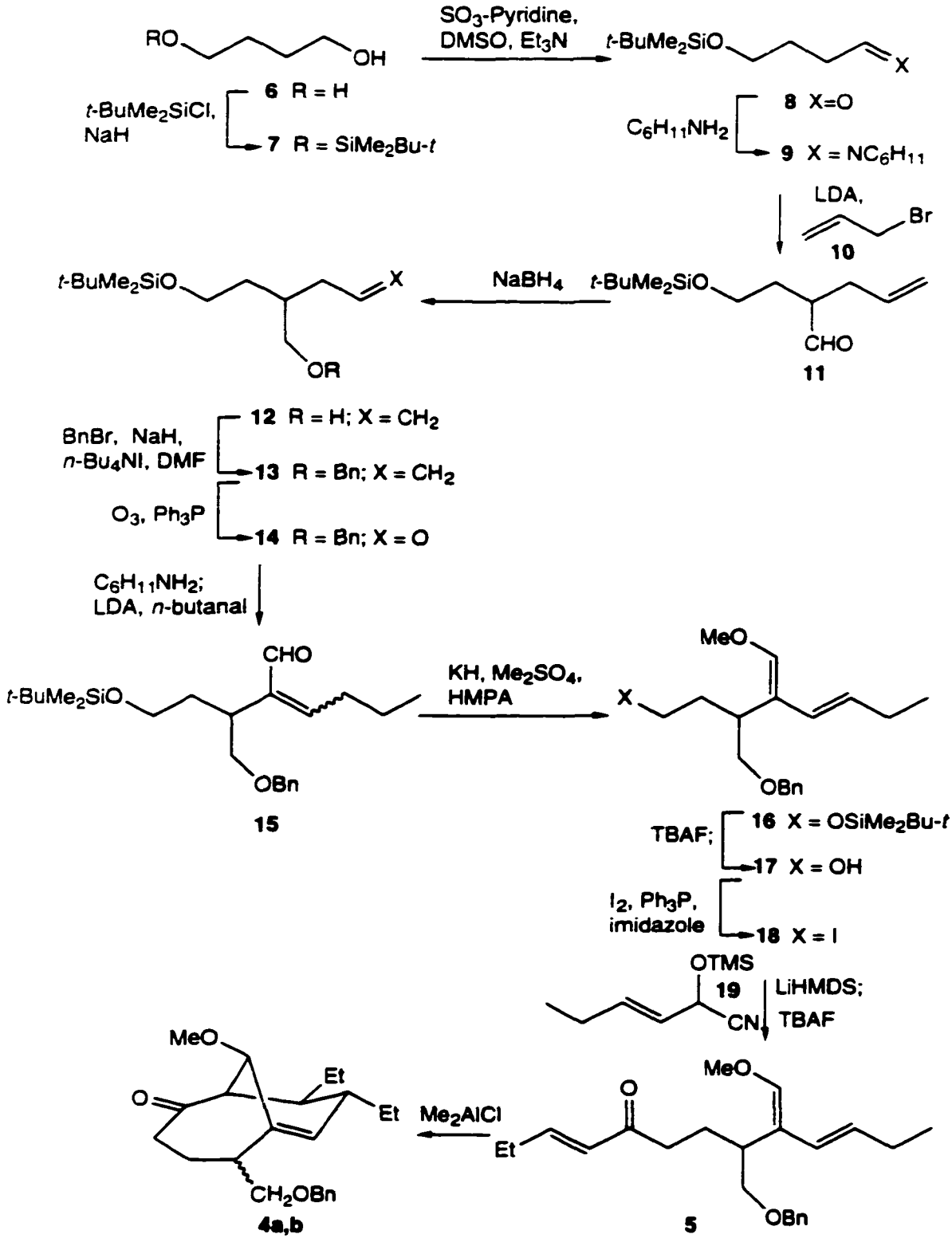
reaction to prepare the model systems **4a,b** (Figure 3). Applying a [4 + 2] retroanalysis to **4a,b** leads to the



4a,b

Figure 3 Structure of **4a,b**

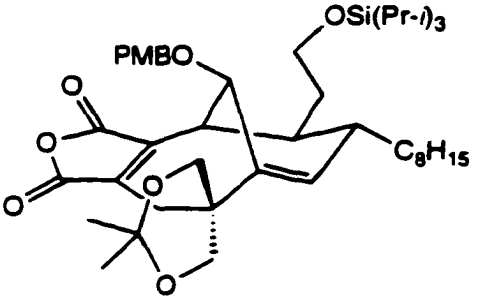
open-chain triene **5** (Scheme 1) as a potential precursor. Scheme 1 summarizes the synthesis of **5** from 1,4-butanediol (**6**). Monosilylation of **6**, followed by oxidization of the resulting alcohol **7**, gave aldehyde **8**. Alkylation of **8**, via its *N*-cyclohexylimine derivative **9**, with LDA and allyl bromide (**10**) furnished **11**, which was reduced with $NaBH_4$ in methanol to afford alcohol **12**. After benzylation of **12**, the resulting terminal olefin **13** was cleaved by ozonolysis to give aldehyde **14**. Formation of the imine of **14**, followed by anion generation, and condensation with *n*-butanal afforded aldehyde **15** as a mixture of isomers (*E*:*Z* ca. 1:1). *O*-Methylation of **15** with Me_2SO_4 in the presence of KH and HMPA proceeded to afford diene **16** as a single geometrical isomer. Desilylation of **16**, and replacement of the resulting hydroxyl by iodine, gave iodide **18**. Finally reaction of **18** with the lithio derivative of the trimethylsilyl-protected cyanohydrin **19**, followed by exposure to Bu_4NF in aqueous THF, led to the key triene **5**.



Scheme 1

This triene smoothly underwent intramolecular Diels-Alder reaction in the presence of Me_2AlCl in CH_2Cl_2 at -10 °C to give **4a,b** (stereochemistry unassigned) in 66% and 20% yield, respectively.

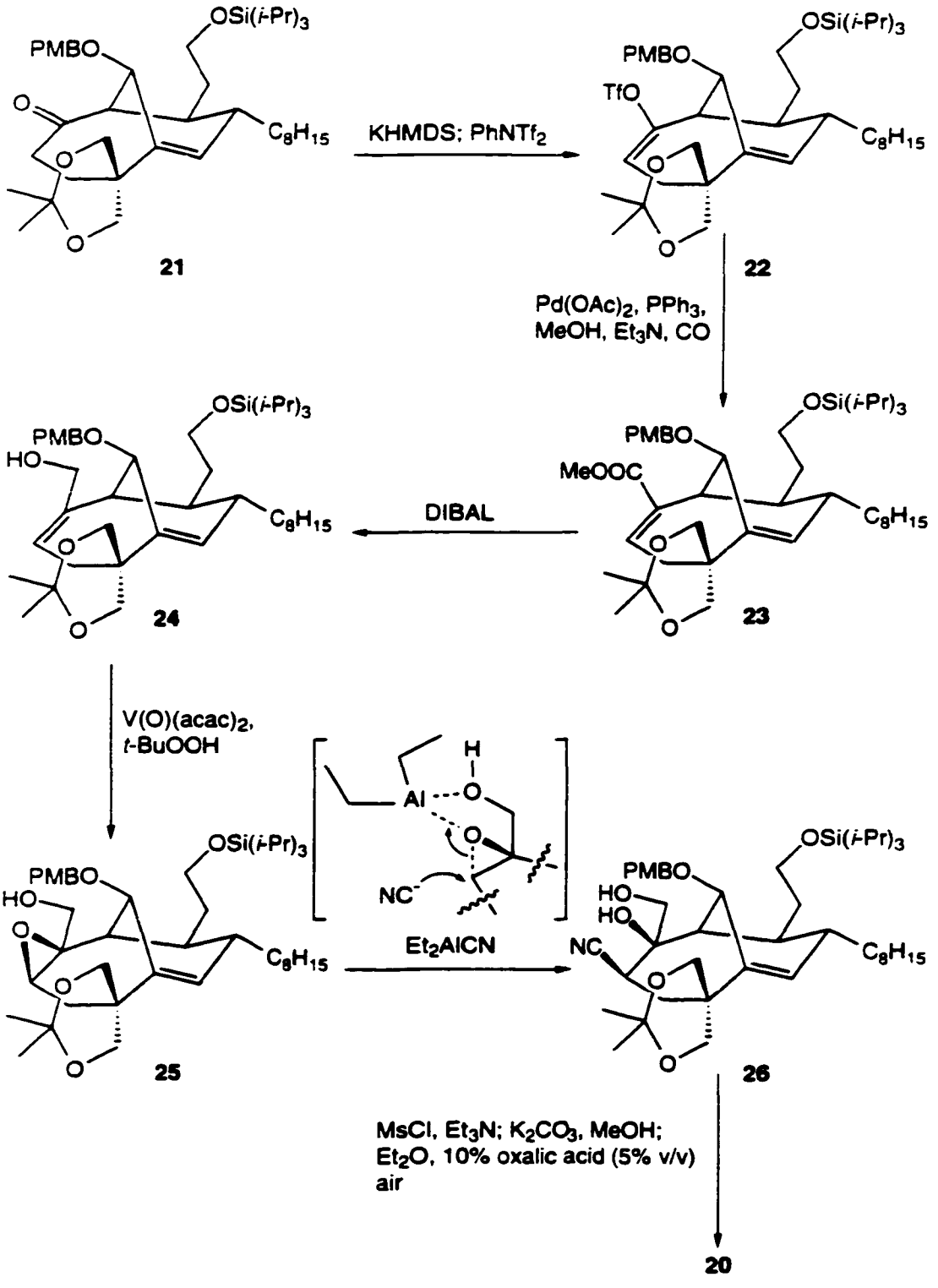
Very recently, Nicolaou's group[6c] have reported the synthesis of the more advanced model **20** (Figure 4), with a maleic anhydride moiety, by a novel route from compound **21** (Scheme 2). The latter was probably synthesized by a similar approach[23] to **4a,b**, but details have not yet been published.



20

Figure 4 Structure of **20**

Ketone **21** (Scheme 2) was first converted into the corresponding enol triflate **22**, and then palladium-catalyzed carboxymethylation provided the α,β-unsaturated ester **23** in 76% yield from **22**. DIBAL reduction of **23**, followed by directed epoxidation of the resulting allylic alcohol **24**, furnished epoxide **25** (85% yield, 3.7:1 in favor of epoxide **25**). Diethylaluminium cyanide-mediated epoxide opening resulted in the formation of the cyano diol **26**, which had the



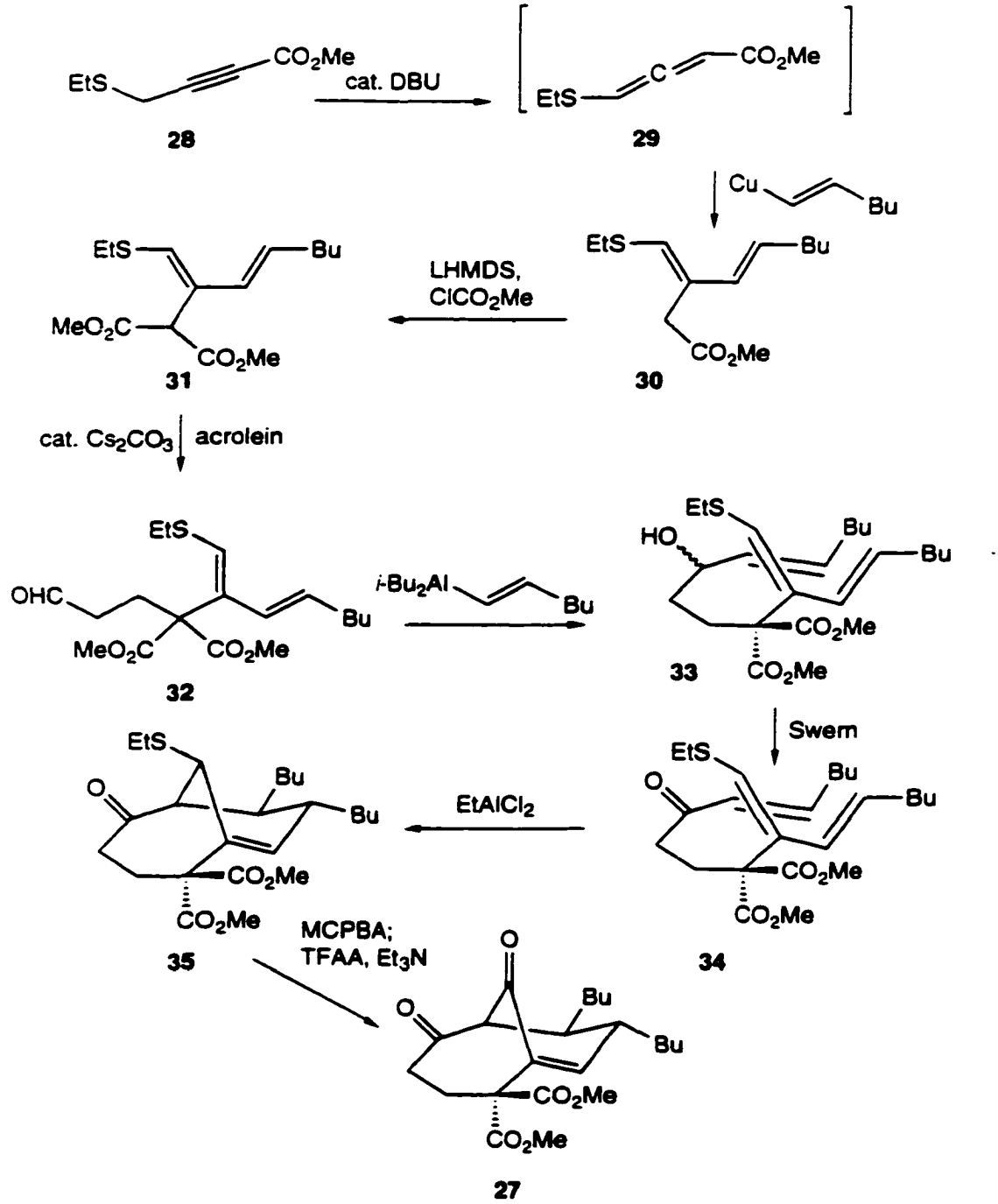
Scheme 2

correct geometrical arrangement for the ensuing reactions. Diol **26** was then transformed into maleic anhydride **20** in 60% yield, without isolation of intermediates. Thus, **26** was submitted to mesylation, followed by treatment of the crude mesylate with potassium carbonate in methanol, evaporation of the solvent, dissolution of the residue in diethyl ether, and addition of a 10% aqueous oxalic acid. This sequence of operations resulted in the maleic anhydride **20**. Evidently, the sequence involves (a) selective mesylation, (b) epoxide formation, (c) epoxide opening by β-elimination, (d) 5-*exo*-digonal cyclization, (e) oxidation, and (f) nitrogen/oxygen exchange. The synthesis of **20** represents a promising strategy for the total synthesis of **1** and **2**.

Fukuyama's group[11] also used an intramolecular Diels-Alder reaction to construct their bicyclic model **27** (Scheme 3).

The synthesis (Scheme 3) started from methyl 4-ethylthio-2-butynoate **28**. Upon treatment with a catalytic amount of DBU in THF, **28** underwent smooth isomerization to allene **29**. The addition of *E*-1-hexenylcopper to **29** gave (*E,E*)-diene **30** with high stereoselectivity. A second methoxycarbonyl group was then introduced by acylation of **30** under conventional conditions to give malonate **31**. This was subjected to Michael addition to acrolein so as to obtain aldehyde **32**. After reaction of an alkenylaluminum reagent with **32**, and Swern oxidation of the resulting allylic alcohols **33**, enone **34** was formed. This compound is the key

substrate for the intramolecular Diels-Alder reaction.



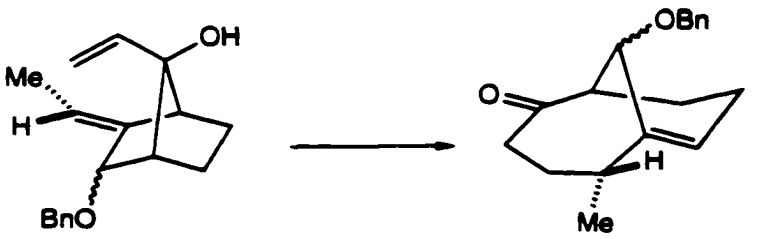
Scheme 3

Upon treatment of **34** with $EtAlCl_2$ at 0 °C, the critical

intramolecular Diels-Alder reaction proceeded to give the desired bicyclic product **35**. Oxidation of **35** with MCPBA, followed by Pummerer rearrangement, then gave the desired diketone **27**.

2. Cope and Oxy-Cope or Related Rearrangements

Clive's group[8] was the first to use an oxy-Cope rearrangement to approach the core structure of **1** and **2**. The strategy was based on the idea that anionic oxy-Cope rearrangement of **36a,b** (Scheme 4) should provide ketones

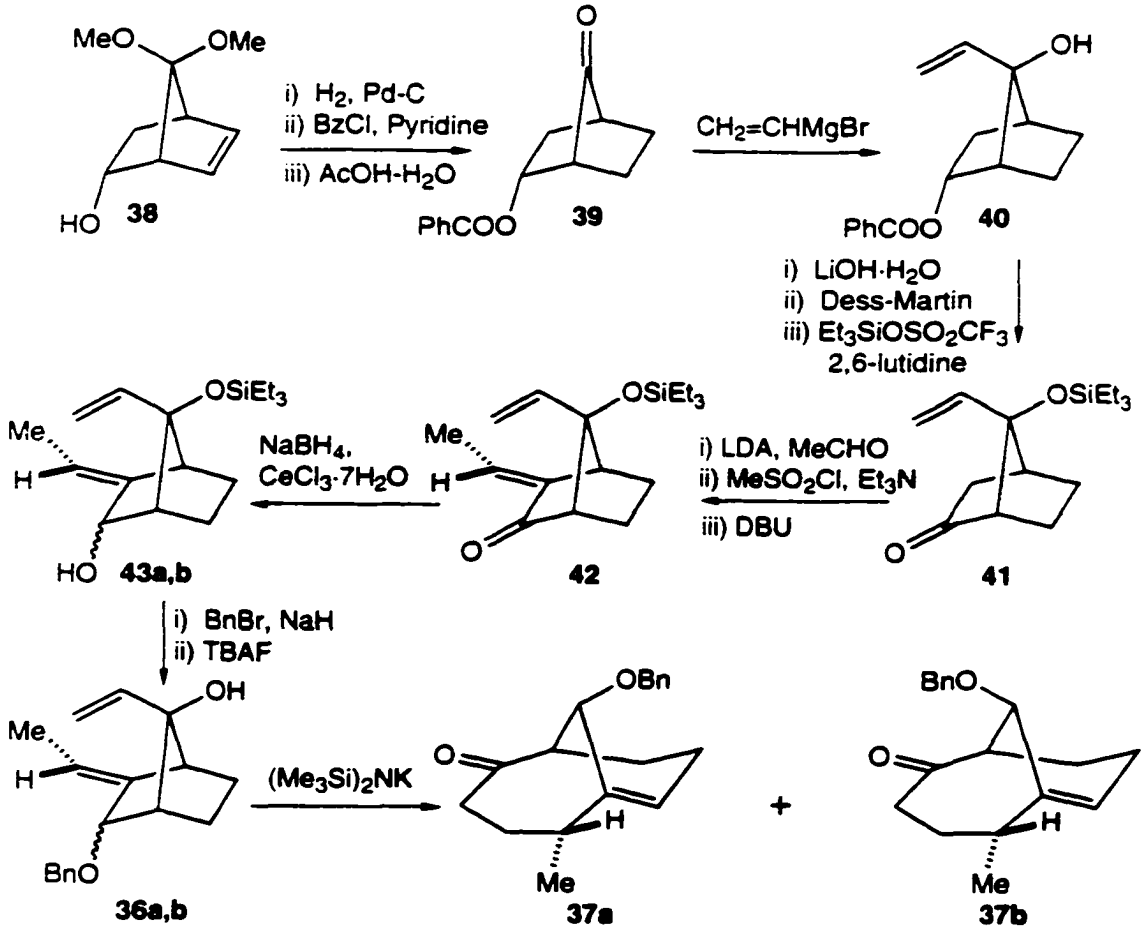


36a,b **37a,b**

Scheme 4

37a,b, which resemble the core skeleton of **1** and **2**.

The synthesis of **36a** and **36b** started from the known norbornene **38**[24] (Scheme 5). Hydrogenation of **38**, followed by benzoylation and acetal hydrolysis gave ketone **39**. Treatment of **39** with vinylmagnesium bromide afforded a mixture of tertiary alcohols, with contained largely the desired isomer **40**. Hydrolysis of the benzoyl group, followed by Dess-Martin oxidation and protection of the tertiary



Scheme 5

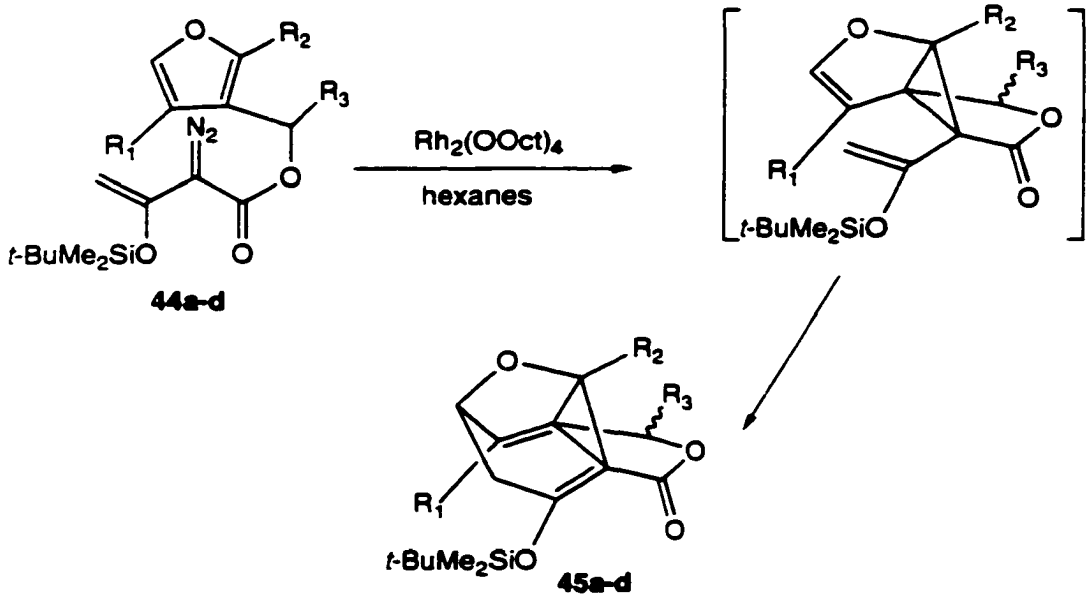
hydroxyl, gave ketone **41**. Aldol condensation, mesylation and base-induced elimination then produced **42** as a major isomer. Reduction of **42** gave a 1:1 mixture of *endo*- and *exo*-alcohols (**43a,b**). Benzylation of **43a** and **43b**, followed by desilylation with Bu_4NF, took the sequence as far as **36a** and **36b**.

When **36a** and **36b** were individually submitted to anionic oxy-Cope rearrangement [$(Me_3Si)_2NK$, PhMe, 100 °C, ca. 20 h], reaction proceeded smoothly to give **37a** and **37b**, thus showing that the anionic oxy-Cope route could be used to make

models that represent the core system of the target natural products.

Davies[7] employed a tandem cyclopropanation/Cope rearrangement to generate appropriate substrates to construct [4.3.1]-bicyclic compounds which might be useful for the synthesis of **1** and **2**.

Rhodium(II) octanoate-catalyzed decomposition of **44a** (Scheme 6) (for values of a-d, see Table 1) led to the tricyclic product **45a** in 83% yield. Extended investigations



44a-d **45a-d**

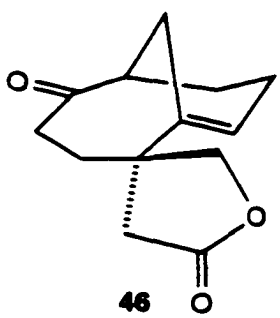
Scheme 6

were carried out on more elaborate furan systems, and the results are listed in Table 1.

Table 1 Synthesis of [4.3.1]-bicyclic compounds

	R_1	R_2	R_3	yield %
a	H	H	H	83
b	H	Me	H	29
c	CH_2Bn	H	H	66
d	H	H	Et	48

In their preliminary studies, Nicolaou's group also tried to apply a divinylcyclopropane rearrangement to construct compound **46** as a model (see Figure 5). However, they finally got **57** (Scheme 8) which has the opposite stereochemistry at the quaternary center.

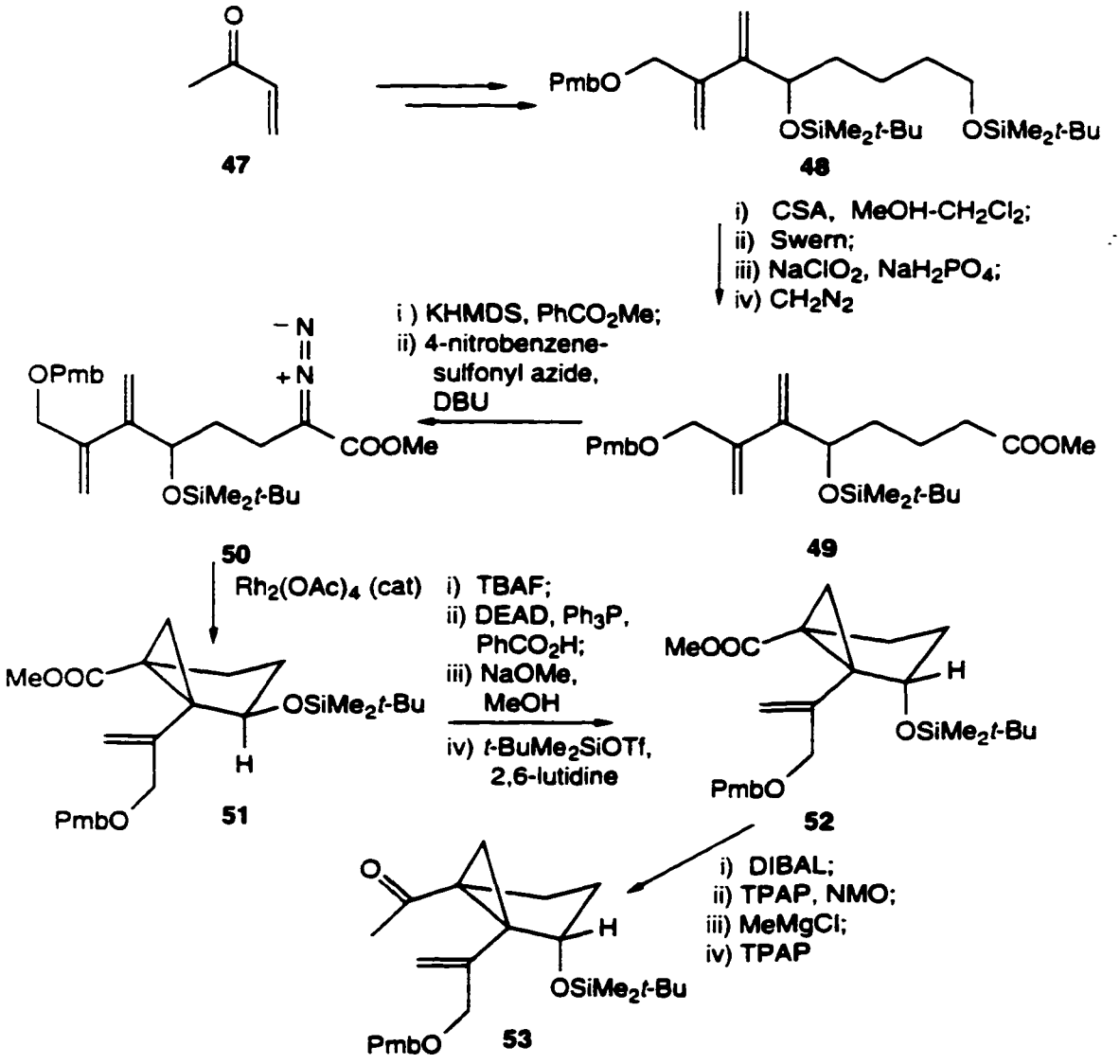


46

Figure 5 Structure of **46**

The synthesis of **46** required the intermediate ketocyclopropane **53**, which was prepared by the route shown in Scheme 7.[6b] Methyl vinyl ketone (**47**) was converted into bis(silyl)ether **48** in several steps.[25] Sequential deprotection, Swern and $NaClO_2/NaH_2PO_4$ oxidations, followed by

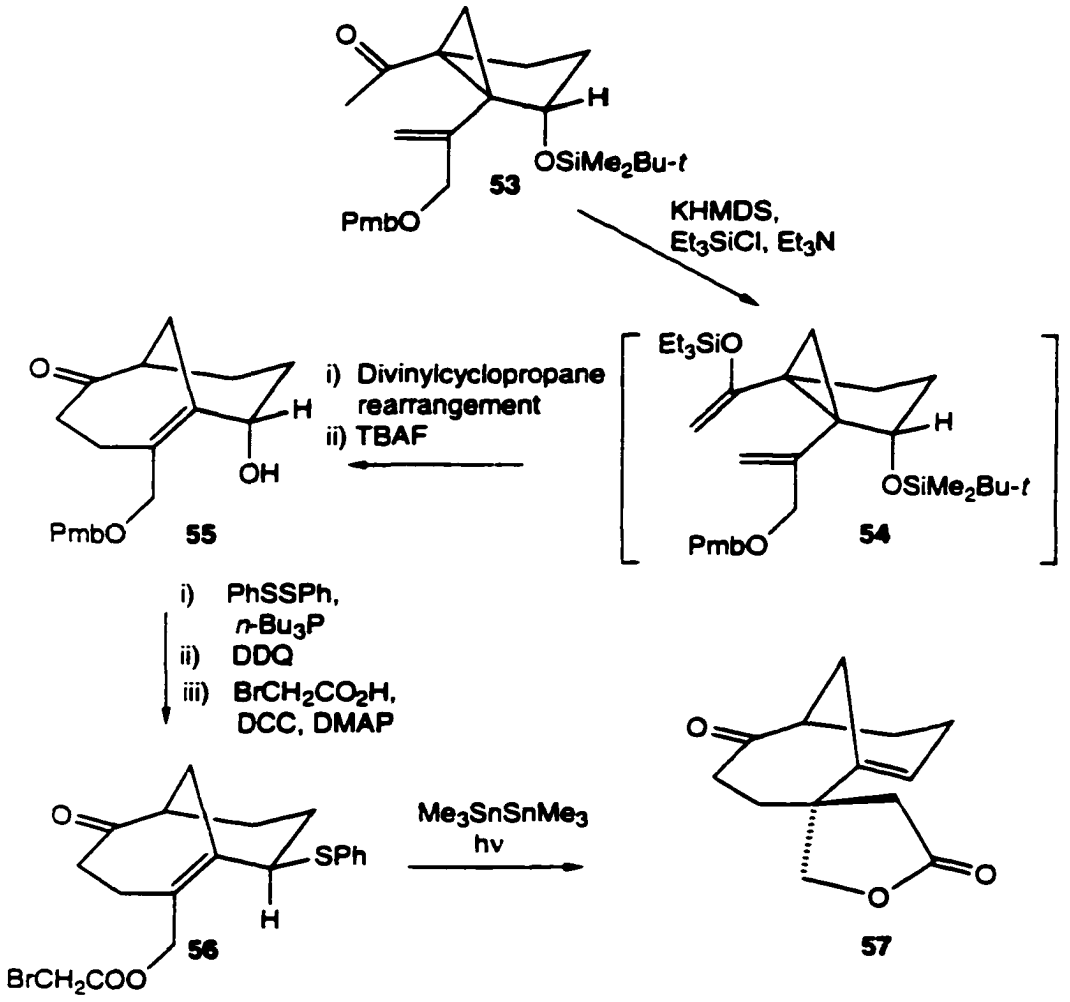
exposure of the resulting carboxylic acids to diazomethane, led to methyl ester **49**. The diazo ester **50** was synthesized from **49** by a modified Taber procedure.[26] Treatment of **50** with a catalytic amount of $Rh_2(OAc)_4$ gave predominantly vinylcyclopropane **51**, together with some diastereoisomer **52**. The configuration of **51** was inverted to **52** by desilylation, Mitsunobu inversion, removal of the resulting benzoate group,



Scheme 7

and silylation. Finally, the desired ketocyclopropane **53** was reached from **52** by the following sequence: DIBAL reduction, NMO/TPAP oxidation, MeMgCl addition, and a second NMO/TPAP oxidation.

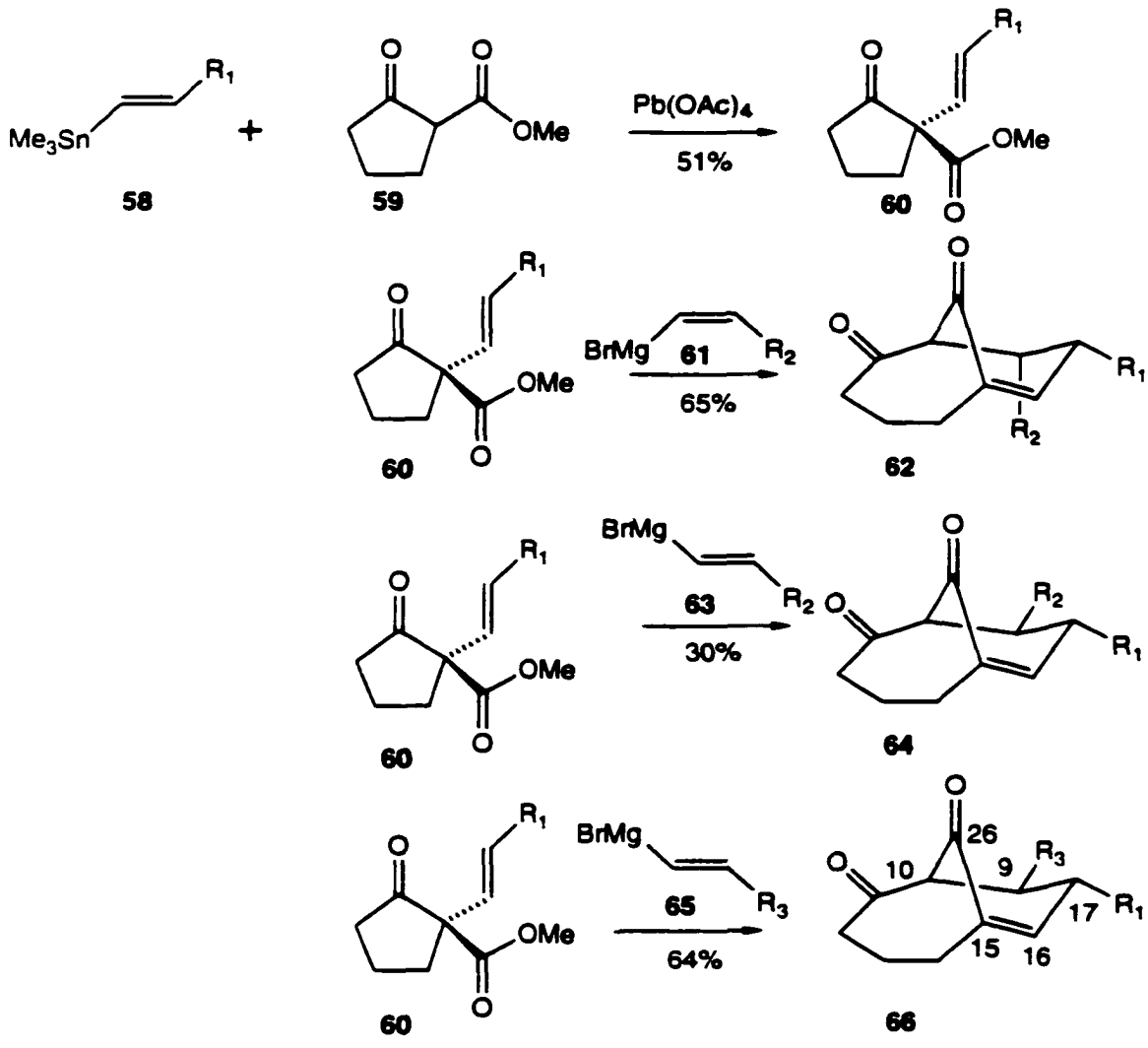
Treatment of **53** (Scheme 8) with KHMDS and Et_3N/Et_3SiCl gave the intermediate silyl enol ether **54**, which underwent divinylcyclopropane rearrangement to give, after removal of both silyl groups, alcohol **55**. This alcohol was then



Scheme 8

converted into a phenyl sulfide with inversion, the PMB group was removed, and protection of the liberated hydroxyl as an α-bromoacetate, furnished compound **56**.

Exposure of **56** to $Me_3SnSnMe_3$ and irradiation (hv) led to lactone **57** by means of radical intermediates and ring closure with concomitant expulsion of sulfenyl radical. This last operation served to generate simultaneously the required



$R_1 = C_6H_{13}$; $R_2 = CH_3$; $R_3 = CH_2CH_2OSiPh_2Bu\text{-}t$

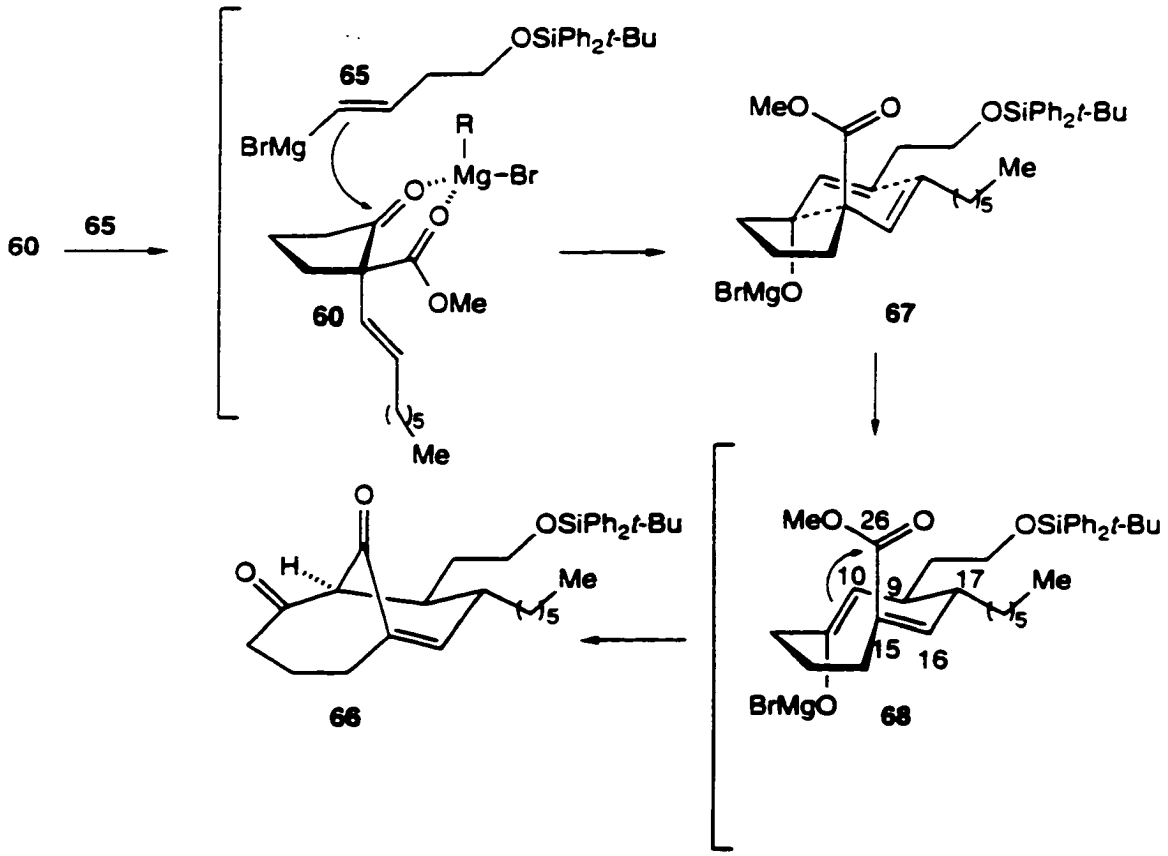
Scheme 9

quaternary center (albeit with the opposite stereochemistry to that of **46**) and the bridgehead olefin, which are two of the challenging structural elements in **1** and **2**.

Recently, Shair and his colleagues[12] reported a rapid and stereospecific synthesis of the core structure of **1** and **2**. The method is based on tandem oxy-Cope rearrangement/transannular bond formation between C(10) and C(26) to generate the core skeleton. The synthesis (Scheme 9) was started by treatment of vinylstannane **58** with $Pb(OAc)_4$, followed by exposure of the intermediate vinylated reagent to β-ketoester **59**, to obtain ketone **60**. Treatment of **60** with (*Z*)-1-propenylmagnesium bromide **61** gave compound **62** (65% yield), which represents the desired bicyclic ring system.

The stereoselectivity of the bicyclization reaction was examined by exposure of ketone **60** to (*E*)-1-propenylmagnesium bromide (**63**) and the (*E*)-vinyl Grignard reagent **65**. The major products, **64** and **66**, show a *trans* relationship between C(9) and C(17), corresponding to the stereochemistry of the side chains of **1** and **2**.

A mechanistic and stereochemical interpretation of this process is provided in Scheme 10. It is assumed that *anti* addition of a vinyl Grignard reagent to chelated intermediate **60** generates magnesium alkoxide **67**. An anionic oxy-Cope rearrangement of **67** though a chair transition state would afford the *Z,Z*-1,5-cyclononadiene intermediate **68**, as a bromomagnesium enolate. The chair transition state (Scheme



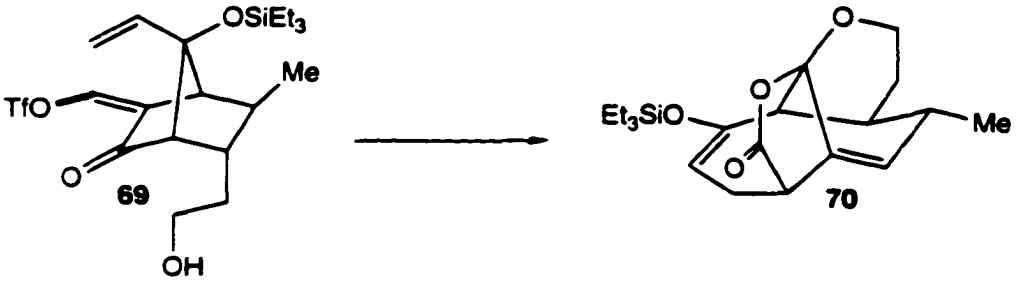
Scheme 10

10) would explain the stereochemical outcome observed with vinyl Grignard reagents **61**, **63** and **65**. The presence of the methyl ester in **67** may explain the facility of the rearrangement of **67** (0 °C, magnesium alkoxide), since Evans and coworkers have reported[27] that anion-accelerated oxy-Cope rearrangements are further accelerated by appropriately-positioned carbanion-stabilizing groups that promote C-C bond ionization. Following the rearrangement, the bromomagnesium enolate **68** underwent transannular acylation between C(10) and C(26) to furnish **66**, the core structure of **1** and **2**.

In the above process, four stereochemical or structural

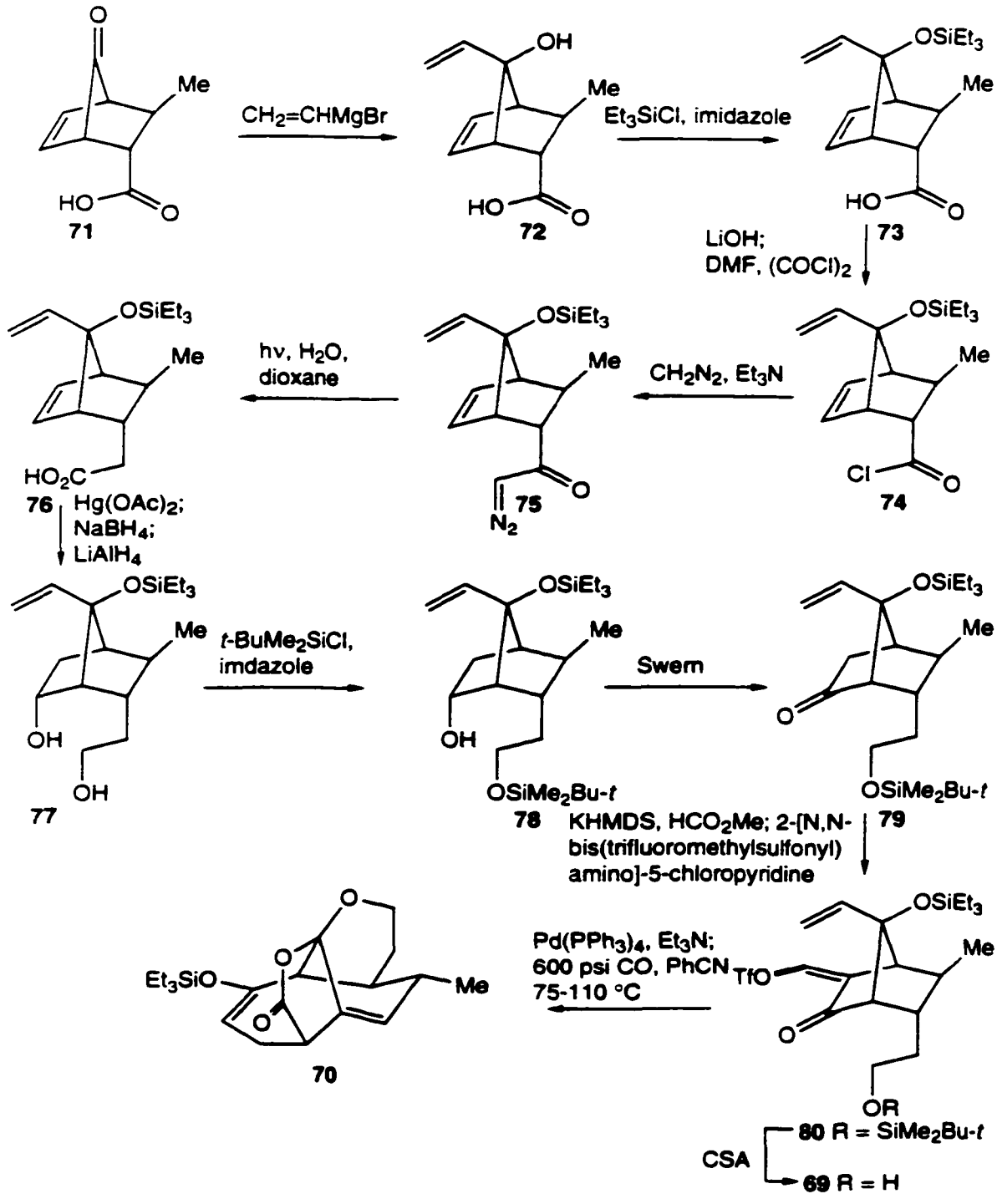
problems [see C(9), C(10), and C(17), and the C(15)-C(16) trisubstituted bridgehead double bond in Scheme 10] have been effectively dealt with in a single transformation, while assembling the core system of **1** and **2**. The reactions described above also demonstrate the feasibility of a C(10)-C(26) transannular cyclization that has been proposed for the biosynthesis of **1** and **2**.[1]

More recently, Bio and Leighton[13] described a mild version of an oxy-Cope process similar to Clive's for making the advanced model **70** (Scheme 11) that resembles the core skeleton of **1** and, especially, **2**.



Scheme 11

Their synthesis commenced with ketone **71** (Scheme 12). Treatment with an excess of vinylmagnesium bromide gave allylic alcohol **72** with very high diastereoselectivity, and the alcohol was then protected as its triethylsilyl ether **73**. A straightforward transformation of **73** into **76** was effected by the Arndt-Eistert sequence. Chemo- and regioselective functionalization of the endocyclic double bond in **76** was accomplished by treatment of acid **76** with $Hg(OAc)_2$, followed by treatment first with $NaBH_4$ to reduce the alkylmercury, and



Scheme 12

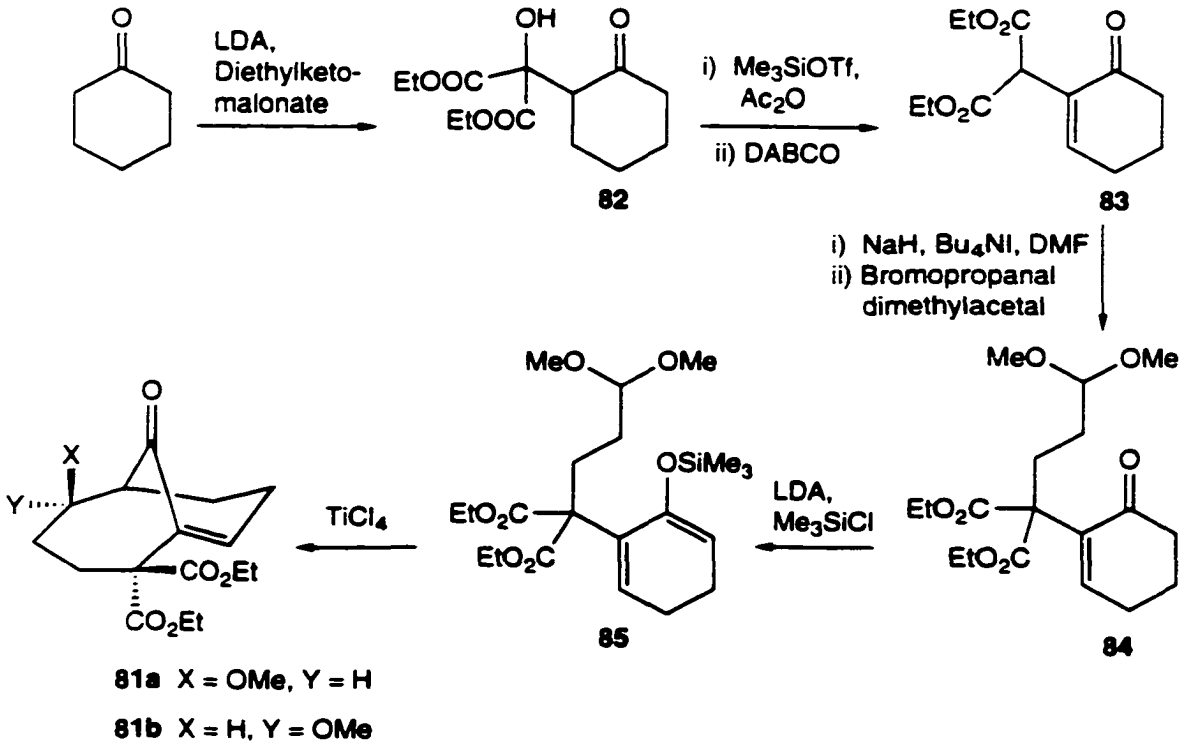
then with $LiAlH_4$ to reduce the lactone. This sequence

afforded the desired diol **77**. Selective protection of the primary alcohol as its *t*-butyldimethylsilyl (TBDMS) ether **78**, was followed by Swern oxidation of the secondary alcohol to obtain **79**. Ketone **79** was subjected to a Claisen condensation with methyl formate and the product was trapped *in situ* with 2-[*N*,*N*-bis(trifluoromethanesulfonyl)amino]-5-chloropyridine.[28] This procedure provide vinyl triflate **80** in 48% yield, as a > 10:1 *Z*:*E* mixture of olefin isomers, along with 41% recovered **79**. Selective methanolysis of the *t*-butyldimethylsilyl group then gave the required hydroxy enol triflate **69** in 74% yield. Treatment of **69** with $Pd(PPh_3)_4$ and Et_3N under 600 psi CO in benzonitrile at 75°C, and then simply raising the temperature of the reaction mixture to 110°C, led to the isolation of **70** with the required γ-lactone acetal unit in 46% yield. This route illustrates mild oxy-Cope conditions to construct the functionalized core skeleton of **1** and **2**.

3. Intramolecular aldol condensation, or a combination of aldol condensation and Heck reaction

Intramolecular Mukaiyama aldol condensation has been used by Armstrong's group[9] to synthesize the bicyclo[4.3.1]decenones **81a** and **81b** from cyclohexanone (Scheme 13). Reaction of the lithium enolate of cyclohexanone with diethyl ketomalonate gave **82**. Conversion of **82** into **83** was achieved using a two step procedure: acetylation (Ac_2O, cat. Me_3SiOTf, 93%) followed by treatment

with DABCO to effect acetate elimination and alkene isomerization (75%). Regioselective alkylation with 3-bromopropanal dimethyl acetal then afforded **84**. At that



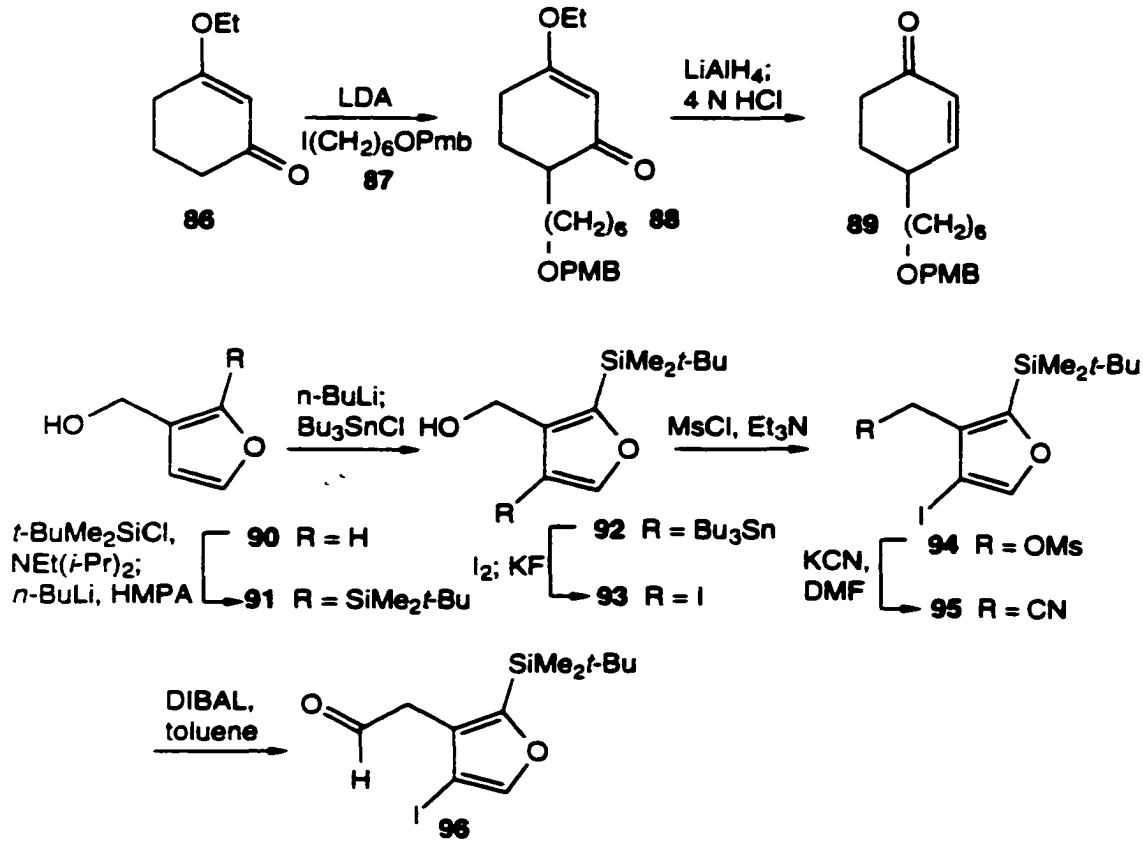
Scheme 13

point, conversion of **84** into the trimethylsilyl enol ether **85**, set the stage for the key ring closure step. Treatment of **85** with $TiCl_4$ in CH_2Cl_2, resulted in an intramolecular Mukaiyama aldol reaction, and provided the desired bicyclic products **81a** and **81b**.

All the above approaches dealt directly with the introduction of the C(15)-C(16) bridgehead double bond, which is present in both compounds **1** and **2**; however a route explored by Danishefsky's group reflected a different view of

the problem.[10] His group applied a combination of aldol condensation and intramolecular Heck reaction to construct the main framework of **1** and **2** with a 15,16-dihydro ring system.

Two starting components, enone **89** and 2,3,4-trisubstituted furan **96**, for aldol condensation were made by the route shown in Scheme 14.[10a] Alkylation of **86** with **87** afforded **88** in 78% yield, and reduction of **88** and acidic hydrolysis led to enone **89**. The synthesis of 2,3,4-

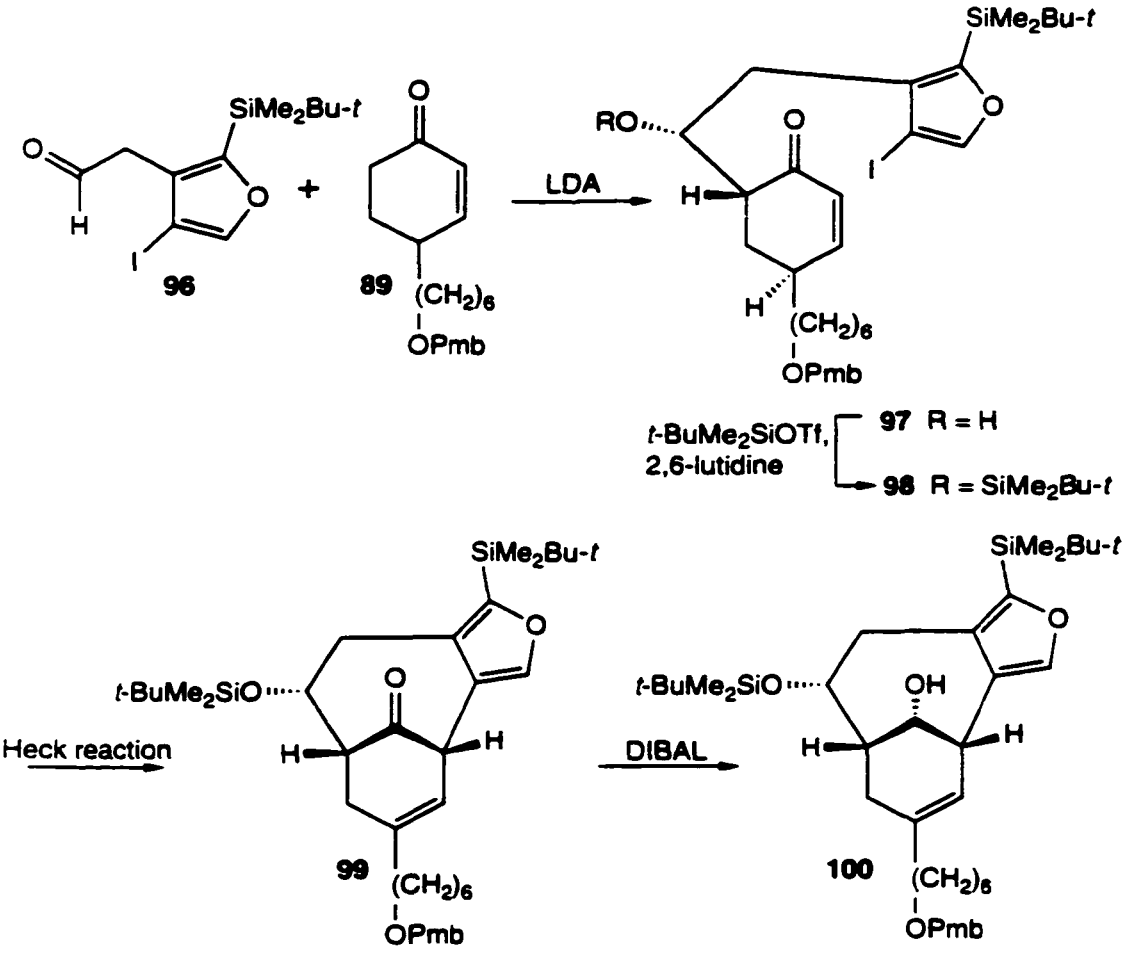


Scheme 14

trisubstituted furan **96** started from the commercially

available **90**. Compound **90** was first silylated with *t*-$BuMe_2SiCl$ (TBSCl), followed by treatment with *n*-BuLi in HMPA to furnish **91**. Hydroxyl-directed metalation at C(3) of **91** afforded **92**. Destannylative iodination provided **93**, which was homologated (via mesylate **94**) into the furanylacetonitrile derivative **95**. Reduction of **95** with DIBAL gave the required 2,3,4-trisubstituted furan **96**.

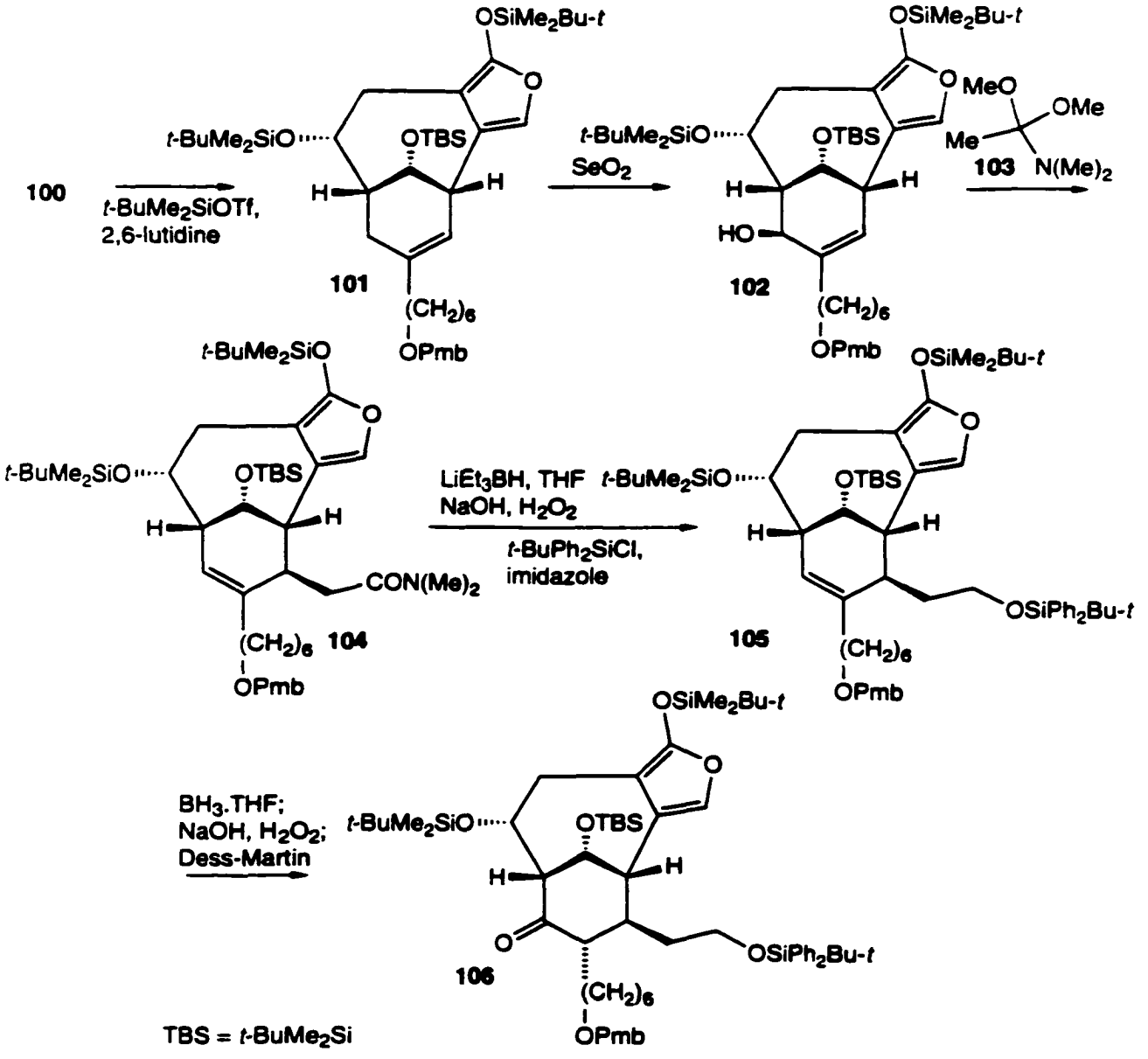
Aldol condensation of the α'-enolate derived from **89** (Scheme 15) with aldehyde **96** proceeded with high stereoselectivity, and afforded **97** in 91% yield. After



Scheme 15

silylation of **97**, the critical intramolecular Heck reaction of **98** resulted in formation of **99**. Reduction gave alcohol **100**, which appears to be correctly constituted for further functional group elaboration, so as to introduce all the features required to reach **1** and **2**.

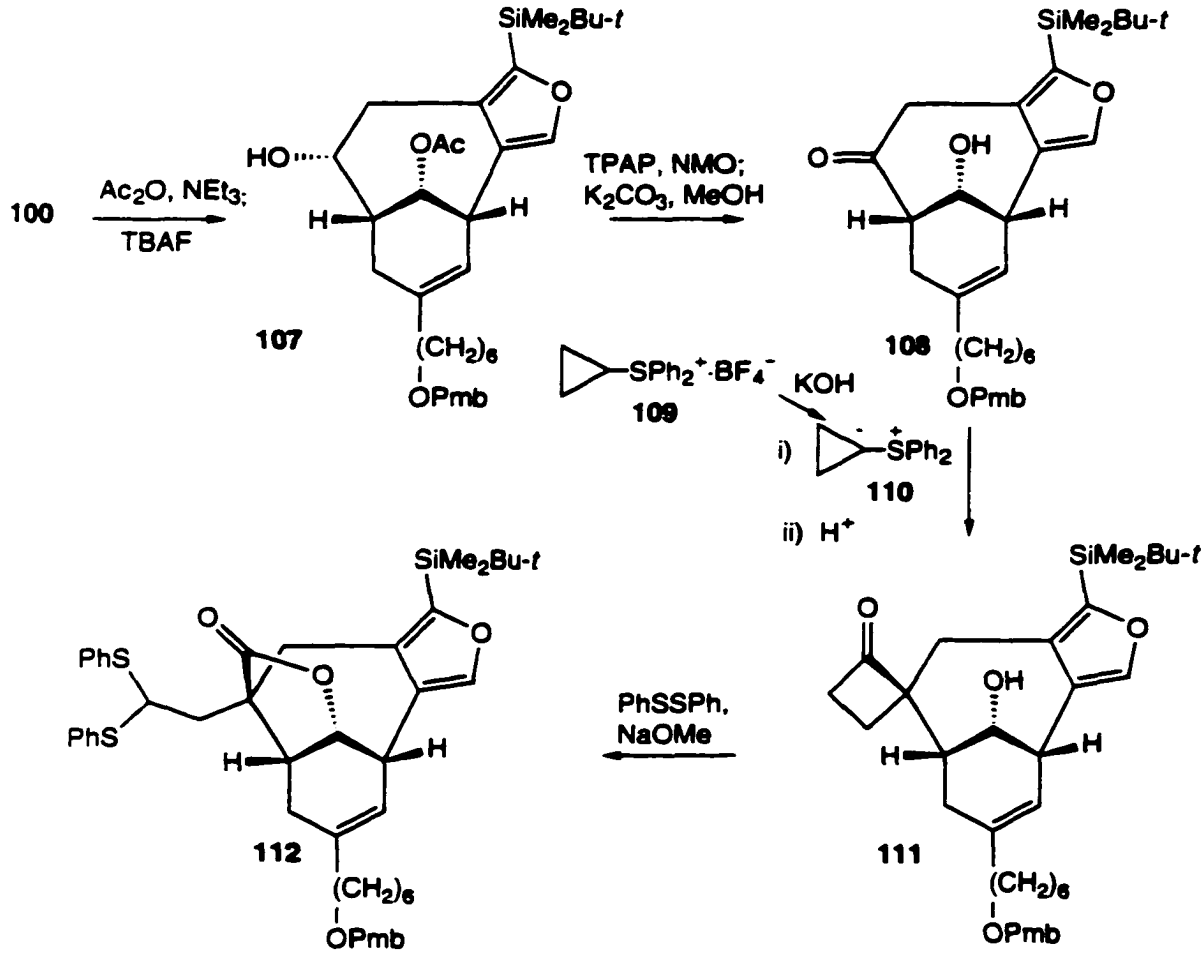
Installation of the side chain at C(9) (see Figure 1)



Scheme 16

was achieved in the following way. Silylation of **100** (Scheme 16)[10a] gave **101**, and oxidation with SeO_2 furnished **102**. Reaction of **102** with **103** gave, upon [3,3]-sigmatropic rearrangement, the γ,δ-unsaturated amide **104**. Reduction of the amide linkage and protection of the resulting primary alcohol then led to **105** which, on hydroboration and oxidation, provided **106** with the desired side chain. Introduction of the required quaternary center at C(14)[10b] was practiced by carrying out the following transformations.

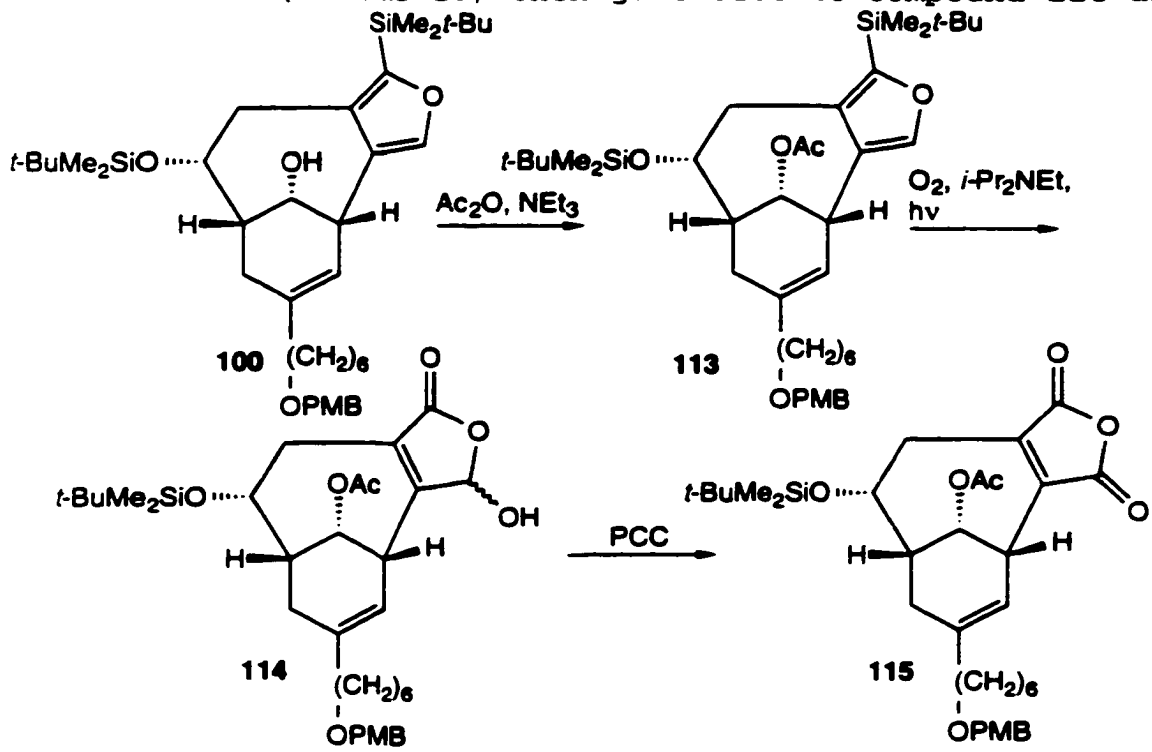
Acetylation of **100** (Scheme 17), followed by desilylation



Scheme 17

of the resulting acetates, gave **107**. Oxidation and then deacetylation, afforded **108**. Reaction of **108** with reagent **110**, a relatively non-basic ylide derived from the Trost sulfonium salt **109**,[29] occurred in a highly stereo-selective fashion to provide, after acidic treatment, the spirocyclobutanones **111**. Under Trost's conditions[29] for bis-sulfenylative fragmentation, the cyclobutanone **111** afforded lactone **112**. This sequence therefore establishes a method for introducing the required quaternary center at C(14) in **1** and **2**.

The maleic anhydride moiety[10b] was also assembled in these model studies. Acetylation of **100** provided **113**, and photooxidation (Scheme 18) then gave rise to compound **114** as



Scheme 18

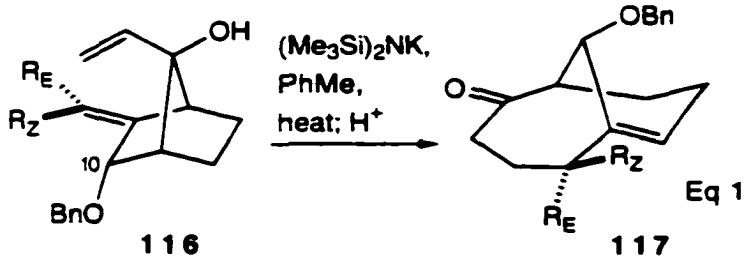
a mixture of diastereomers. Further oxidation with PCC afforded the desired anhydride **115**.

In summary, the challenging structure of **1** and **2** provides many opportunities for synthetic organic chemists to develop and apply new strategies. Although it is not clear how the compounds will eventually be reached by total synthesis, it is apparent that **1** and **2** represent attractive and important targets.

II. Results and Discussion

Background Information

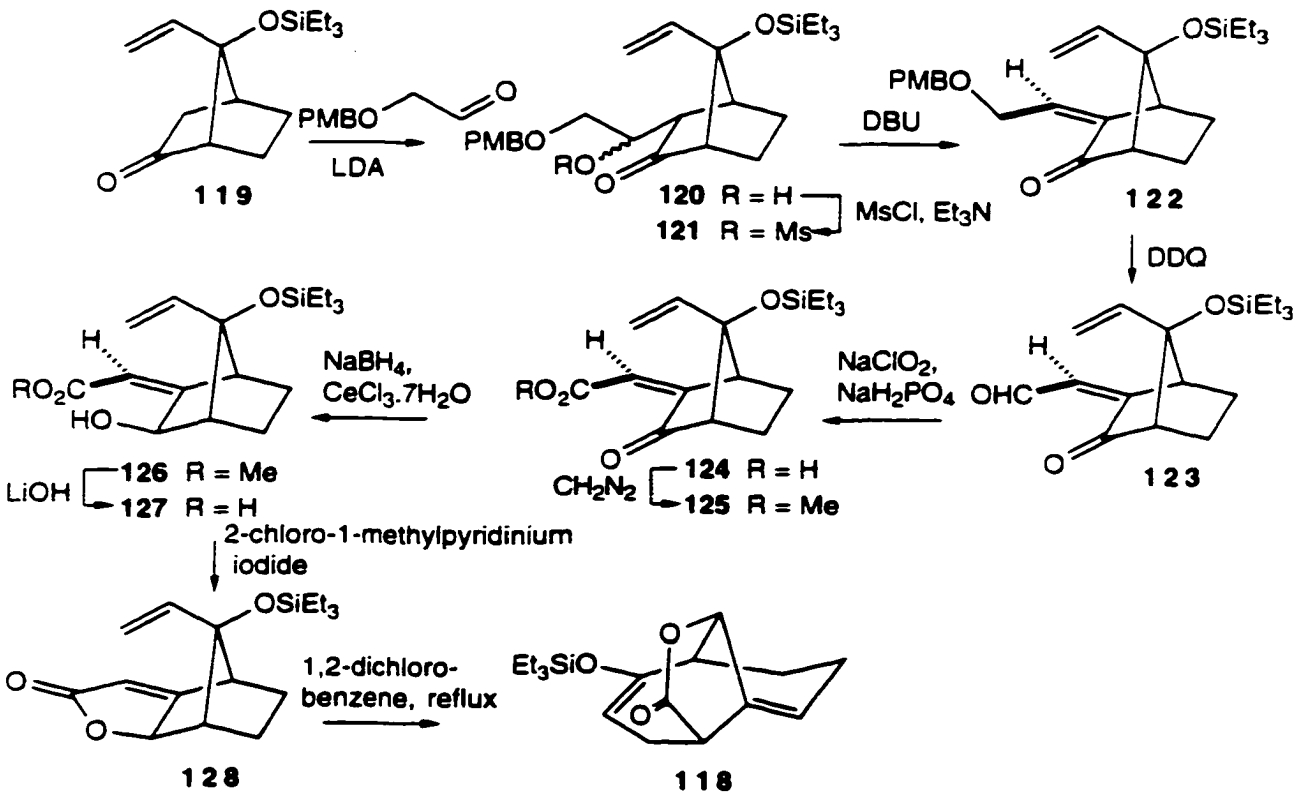
Anionic oxy-Cope rearrangement (Scheme 19) (R_E = Me, R_Z = H) represented an initial approach developed[8] earlier in this laboratory in work aimed at the total synthesis of both natural products **1** and **2**. When I started my own work, the



116 **117** Eq 1

Scheme 19

following two additional findings had been made: (i) The anionic rearrangement did not proceed[30] if the ethylidene unit is modified by increase in chain length (**116**, R_E = CH_2CH_2OPMB or CH_2OBn, R_Z = H; R_E = R_E = CH_2OBn). (ii) The thermal oxy-Cope rearrangement, to afford **118**, does proceed smoothly with the bicyclic strained lactone **128**, made by the route[31] shown in Scheme 20. Aldol condensation of the readily available ketone **119** with 2-[(4-methoxyphenyl)methoxy]acetaldehyde, mesylation, and treatment with DBU gave *Z*-olefin **122** (58%), as well as the corresponding *E*-isomer (30%). Removal of the (4-methoxyphenyl)methyl group was done in such a way as to lead directly to an aldehyde (**122** → **123**, DDQ, 2.3 equiv, CH_2Cl_2, 12 h; 94%) so that a single further oxidation provided

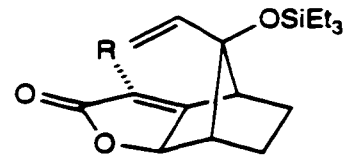


Scheme 20

acid **124**, which was then esterified to give **125**. At this point, reduction with $NaBH_4$ and $CeCl_3.7H_2O$ gave largely (65%) the desired exo-alcohol **126**. Ester hydrolysis liberated hydroxy acid **127**, and this could be cyclized to lactone **128** by treatment with 2-chloro-1-methylpyridinium iodide (Et_3N, CH_2Cl_2, reflux, 34 h; 81%). When **128** was heated in refluxing 1,2-dichlorobenzene for 40 min, it was converted into **118** in 79% yield.

In order to establish the applicability of the above findings for the construction of more advanced [4,3,1]-decadienones, especially for the introduction of differentiable substituents at C(14), which is a quaternary

center and is a significant structural feature in **1** and **2**, we proposed to make compounds **129** (Figure 6), having a modifiable substituent R, as such substrates would give the



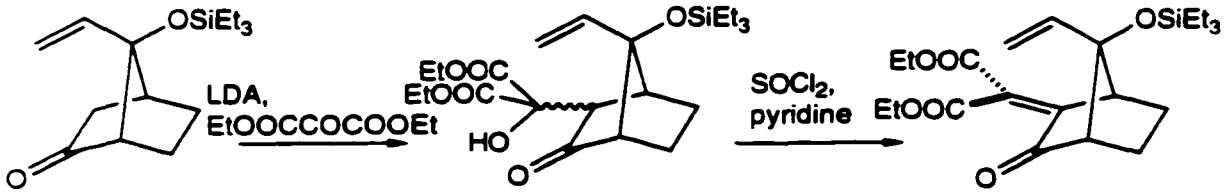
129

Figure 6 Structure of **129**

required quaternary center in **1** and **2** after thermal oxy-Cope rearrangement.

Preparation of the Strained Lactones

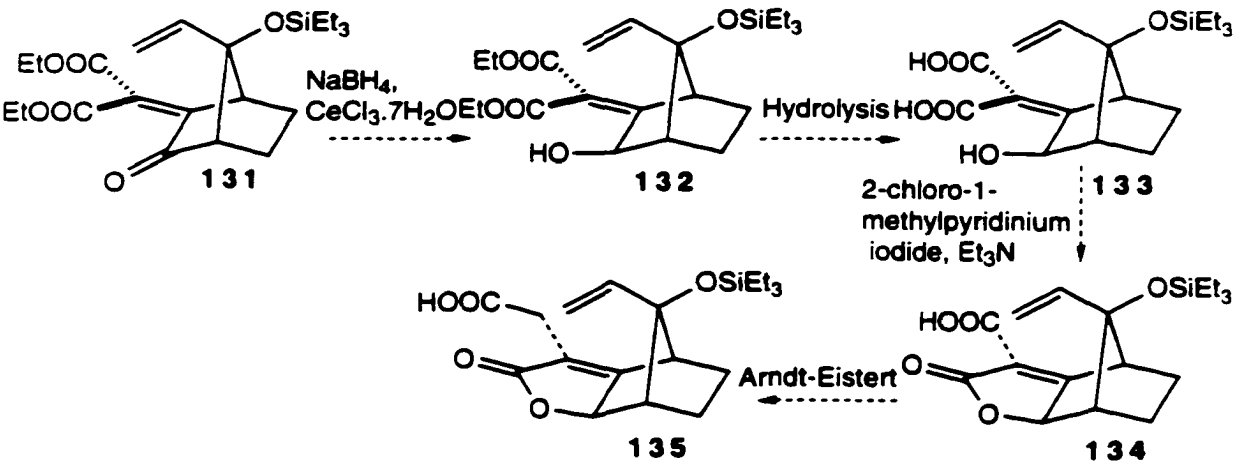
Retrosynthetic analysis suggested that the first task in making **129** was to carry out an aldol condensation of **119**[8] with a ketone so as to attach the required side chain for further modification. Since it had been found[32] in this laboratory that aldol reactions of ketone **119** did not occur with ordinary ketones, it was clear that the ketone used had to be extremely reactive, and we thought that diethyl ketomalonate might be a suitable choice. Fortunately, when



119 **130a** 52% **130b** 43% **131** 91% from **130a** 76% from **130b**

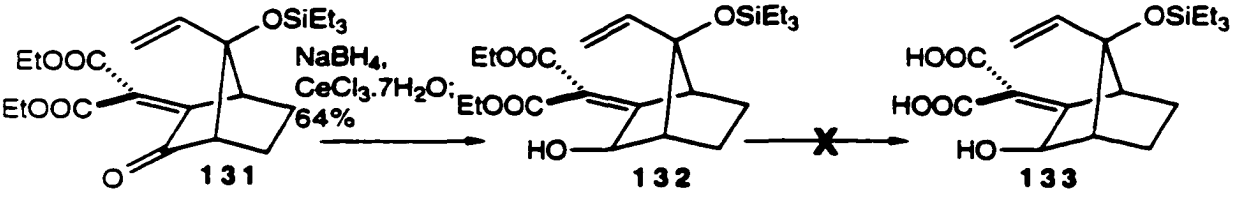
Scheme 21

ketone **119** was subjected to aldol condensation with diethyl ketomalonate (Scheme 21), the reaction proceeded smoothly to give two separable aldol adducts **130a** and **130b** in 95% combined yield. Both aldol adducts could be dehydrated[33] to afford compound **131** with a doubly substituted ethylidene unit. This encouraging result promoted us to attempt the synthesis of the strained lactone **135** by the route shown in



Scheme 22

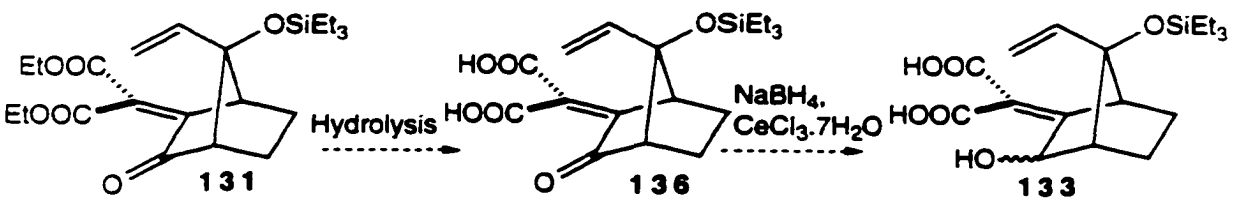
Scheme 22. Accordingly, **131** (Scheme 23) was reduced to give largely the desired *exo*-alcohol **132** (64%). However, many attempts to effect hydrolysis of **132** were unsuccessful, and



Scheme 23

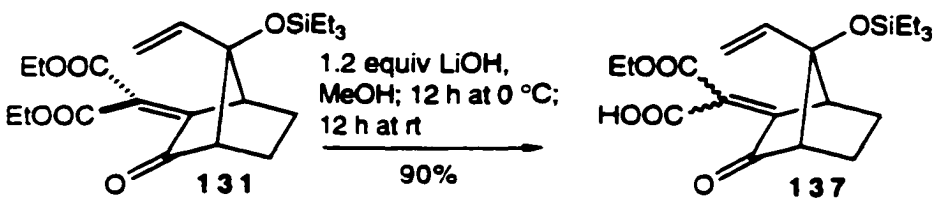
we had to modify the procedure. [In these exploratory

experiments, not all the compounds were fully characterized, since some of the routes could not be carried on to the end, but all compounds that are part of the final routes were characterized.] Ketone **131** (Scheme 24) was first hydrolyzed to keto diacid **136**, followed by reduction of the ketonic carbonyl to give the required **133**. When we first tried this modified route, we found that hydrolysis of the two ester



Scheme 24

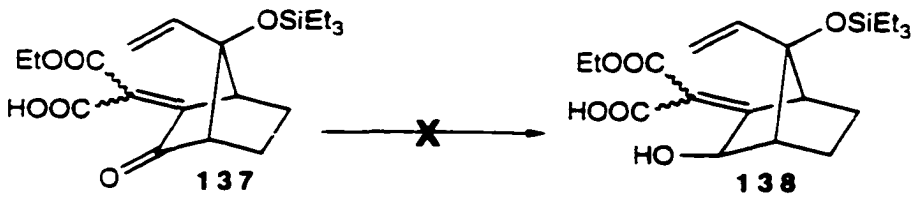
groups was troublesome. However, after many attempts, we eventually found conditions (see Scheme 25) to hydrolyze **131** to the monoester **137** in 90% yield. The stereochemistry of **137** was not assigned; we intended, of course, to assign it



Scheme 25

later by chemical transformations. Although the keto monoester **137** was not what we had wanted originally, it does carry two differentiable substituents on the ethylidene unit, and it offers several possibilities for further elaboration.

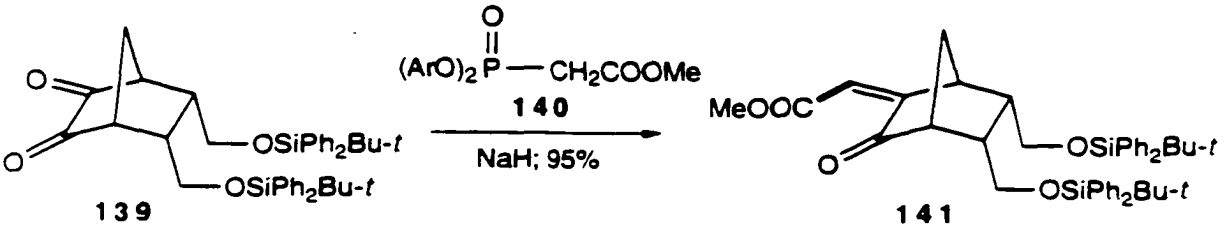
First, we planned to reduce **137** (Scheme 26) to alcohol **138**.



Scheme 26

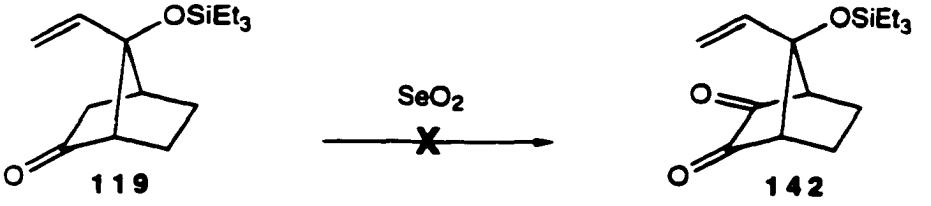
We expected the *exo*-alcohol to be the major isomer, and we would then be able to effect lactonization of **138**. If lactonization of **138** occurred to give a lactone ester, the carboxylic acid group of **138** would, of necessity, be *syn* to the ketonic carbonyl group, and so the stereochemistry of **137** would thereby be established. However, reduction of **137** could not be effected with $NaBH_4$ and $CeCl_3.7H_2O$, and only the starting material was recovered. Attempts to reduce **137** with $LiBH_4$ and $CeCl_3.7H_2O$, or with DIBAL gave complex mixtures. We also tried to convert the carboxylic acid group in **137** to an acid chloride [$(COCl)_2$, CH_2Cl_2, cat. DMF] or to an *N*-acyl imidazole[34] (carbonyldiimidazole, THF, 1 h at room temperature) in the hope that we would then be able to effect the reduction by $NaBH_4$ or $LiBH_4$.[35] Unfortunately, experiments along such lines were fruitless, and we decided to abandon this route.

It has been reported[36] that Horner-Wadsworth-Emmons (HWE) reaction between the α-diketone **139** (Scheme 27) and **140** proceeds stereoselectively and in excellent yield. We envisaged that if we could oxidize the siloxy ketone **119** to



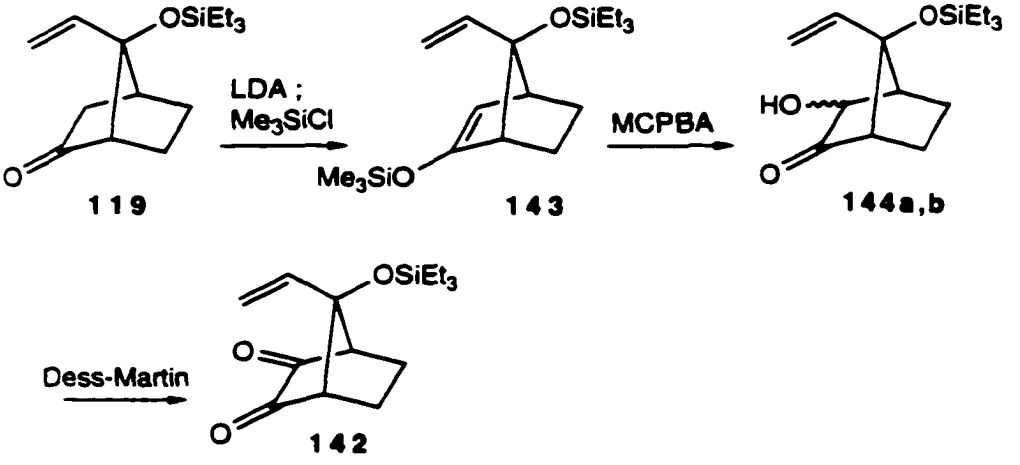
Scheme 27

the α-diketone **142**, similar HWE reaction might also be stereoselective. With this plan in mind, we first tried to oxidize **119** (Scheme 28) with SeO_2, but it failed to give the



Scheme 28

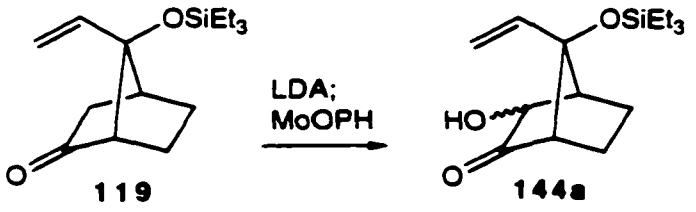
desired diketone. We turned next to another approach (Scheme 29). Ketone **119** was first converted into its silyl enol



Scheme 29

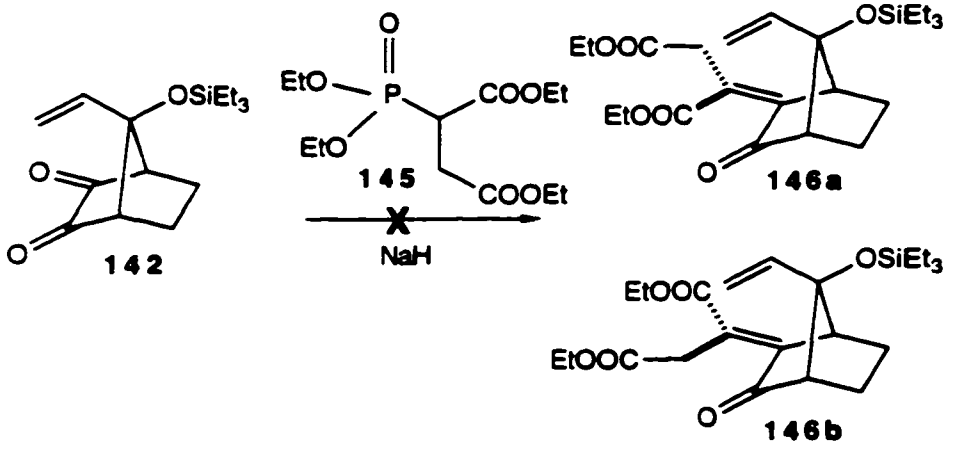
ether **143**. Oxidation of **143** with MCPBA gave **144a,b** as a mixture of *exo*- and *endo*-alcohol isomers in 20% yield. Dess-Martin oxidation of **144a,b** afforded diketone **142** in almost quantitative yield.

We could not improve the yield of the MCPBA oxidation step (**143** → **144a,b**), although the reaction was tried under various conditions (oxidation of **143** with 1.2 equiv, 1.5 equiv, 2.0 equiv MCPBA in CH_2Cl_2 or EtOAc), and so we decided to try Vedejs[37] oxidation. Luckily,



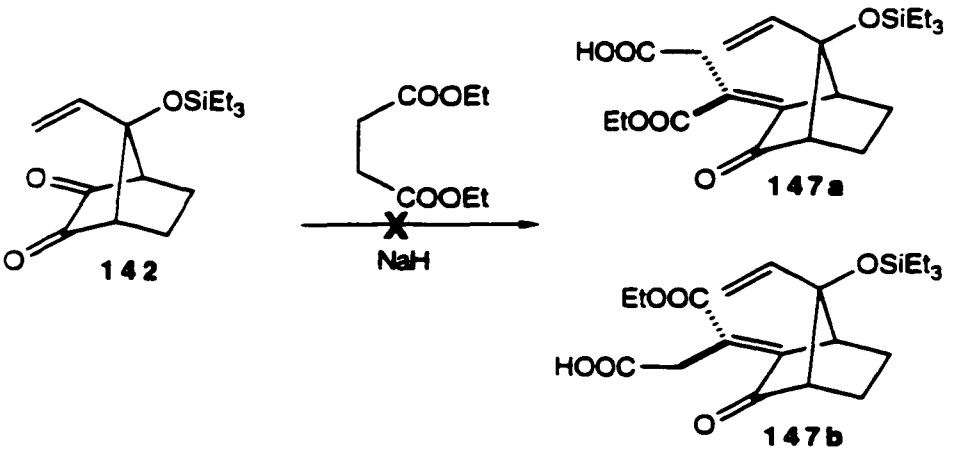
Scheme 30

oxidation of ketone **119** (Scheme 30) with Vedejs' reagent (MoO_5·py·HMPA) (LDA, THF, 1 h at -78 °C; add MoO_5·py·HMPA at -23 °C, 0.5 h)



Scheme 31

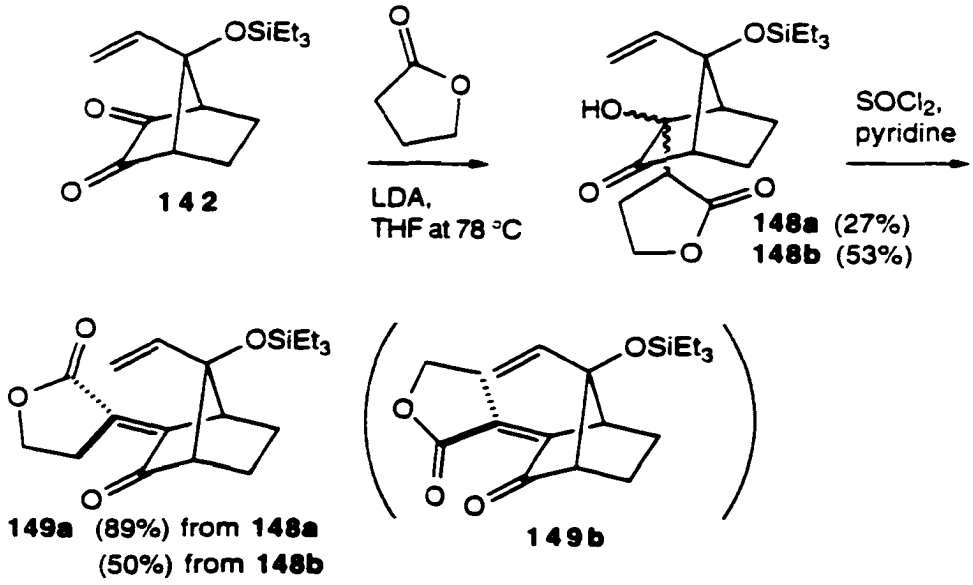
gave hydroxy ketone **144a** as a single isomer (stereochemistry unassigned) in 85% yield (91% corrected for recovered **119**). The next step was to effect the HWE reaction with **142**. The HWE reagent **145** with the desired four carbon unit was made according to the literature procedure;[38] however, the HWE reaction (Scheme 31) did not proceed under the conditions we tried (NaH, THF at room temperature and refluxing). A literature search indicated that a Stobbe[39] condensation (Scheme 32) might be an alternative for the desired HWE reaction. However, on treatment of **142** with diethyl succinate and NaH, a complex mixture was obtained.



Scheme 32

We next decided to find out if α-diketone **142** would react with the enolate of an ester. For this purpose, γ-butyrolactone was chosen, since it contained the desired four-carbon unit. In the event, we were pleased to observe that the enolate of the γ-lactone, generated by the action of LDA at -78 °C, reacted smoothly with diketone **142** (Scheme 33)

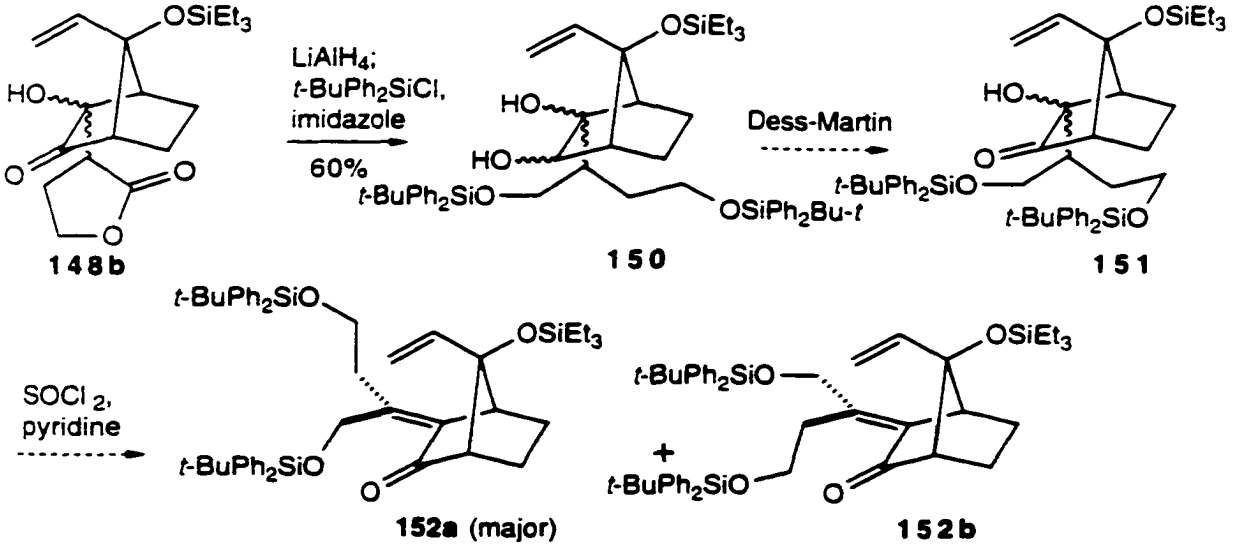
to give two isomers **148a** and **148b** (stereochemistry unassigned) in 80% yield.



Scheme 33

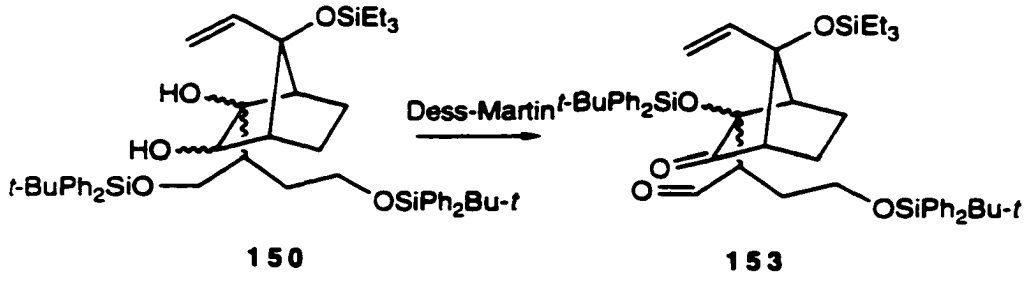
Dehydration of both isomers led to the formation of **149a** as a single isomer. The stereochemistry was assigned, based on the chemical shift of the bridgehead hydrogen[40] adjacent to the newly formed double bond and, on this basis, it was clear that **149a** was not the desired isomer. It is not clear why dehydration of both **148a** and **148b** give the same isomer **149a**. In order to obtain the compound with the desired stereochemistry, **148b** was reduced with $LiAlH_4$ (Scheme 34). The resulting two primary hydroxyls were then protected, to give **150** as a single isomer (stereochemistry unassigned). We expected Dess-Martin oxidation of **150** to give the desired ketone **151** (Scheme 34). Finally, dehydration of **151** should

give **152a** and **152b**. It would, of course, be understandable,



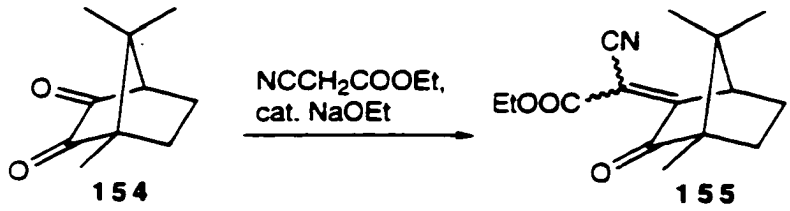
Scheme 34

if compound **152a** turned out to be the major isomer because it is less sterically crowded than **152b**. However, Dess-Martin oxidation of **150** gave the undesired product **153**[41] in 65% yield (Scheme 35), and so we were obliged to stop this approach.



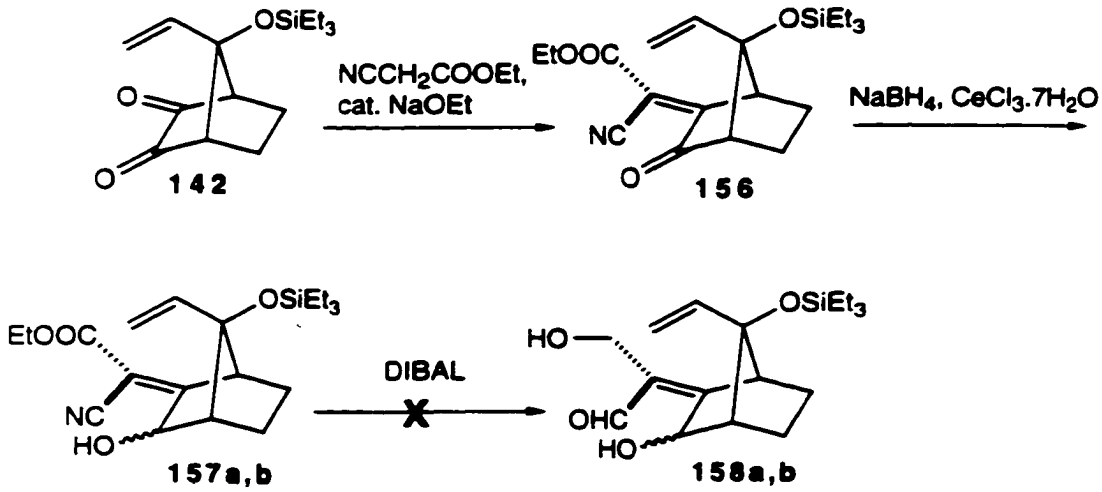
Scheme 35

It has been known for a long time that camphorquinone **154** (Scheme 36) condenses[42] with $NCCH_2COOEt$ in the presence of a catalytic amount of EtONa to give **155** in high yield.



Scheme 36

Since the structure of our α-diketone **142** resembles camphorquinone, a similar reaction might also be expected in our case. Indeed, upon treatment of **142** (Scheme 37) with $NCCH_2COOEt$ in the presence of a catalytic amount of EtONa, reaction proceeded readily to give **156** as a single stereoisomer in 80% yield. We were pleased with this

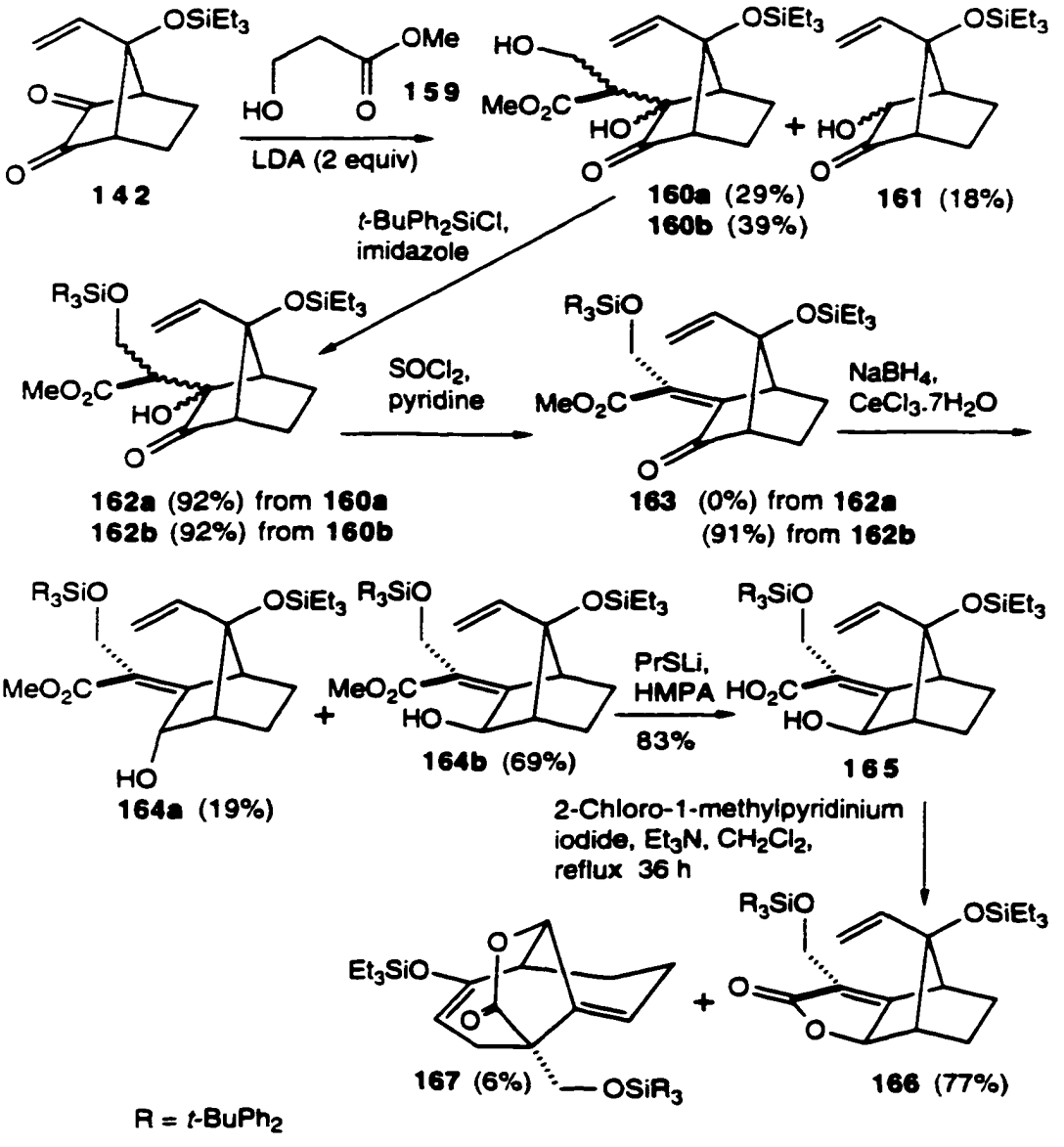


Scheme 37

transformation since the differentiable two substituents on the ethylidene unit in **156** might allow us to elaborate this substrate regioselectively to the desired lactone. Thus, **156** (Scheme 37) was reduced to **157a,b** by $NaBH_4$ and $CeCl_3.7H_2O$,

but several attempts (using different amounts of reagent, different solvents, and different temperatures) to reduce **157a,b** to **158a,b** with DIBAL were unsuccessful, and direct reduction of **156** with DIBAL also failed to give **158a,b**.

Because of the reduction problem in the above approach, we next wanted to choose a substrate that might avoid the



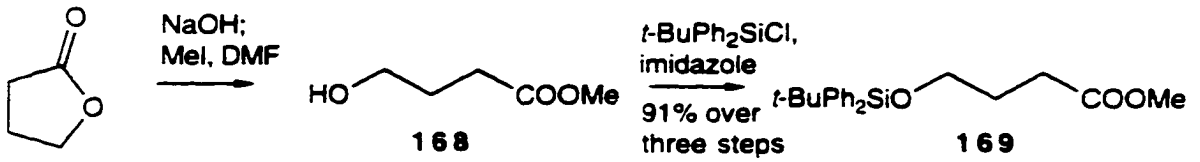
Scheme 38

troublesome reduction step, and therefore, the following route (Scheme 38) was explored: Diketone **142** was condensed with the dianion derived from methyl 3-hydroxypropanoate **159** by treatment with 2 equivalents of LDA. Two separable diastereoisomers **160a** (29%) and **160b** (39%), whose stereochemistry was not established, plus **161**[43] (18%) were isolated. Silylation of both isomers **160a** and **160b** (*t*-$BuPh_2SiCl$, imidazole) gave **162a** and **162b** in 92% yield in each case; however, on attempted dehydration ($SOCl_2$, pyridine), only the major isomer **162b** afforded the desired *Z*-olefin **163** (91% yield). The minor isomer gave back the starting material under the same conditions.

Reduction of **163** ($NaBH_4$, $CeCl_3.7H_2O$, MeOH) gave the desired *exo*-alcohol **164b** (69%) as well as the *endo*-alcohol **164a** (19%). Initial demethylation of **164b** was troublesome, but we later found that demethylation with *n*-PrSLi[44] in HMPA proceeded smoothly to deliver hydroxy acid **165** in 83% yield. Refluxing of a solution of **165**, 2-chloro-1-methylpyridinium iodide,[45] and Et_3N in CH_2Cl_2 gave the strained lactone **166** in 77% yield, as well as a small amount of the oxy-Cope rearrangement product **167** (6%). We were delighted with this exploratory experiment. Next, **166** was subjected to oxy-Cope rearrangement which we will discuss in the next section.

The yield in the condensation step (**142** → **160a,b**) in the above approach was not good; moreover, isomer **162a** could not be dehydrated to **163**. In addition, the final product **167** from the oxy-Cope rearrangement (see next section) would

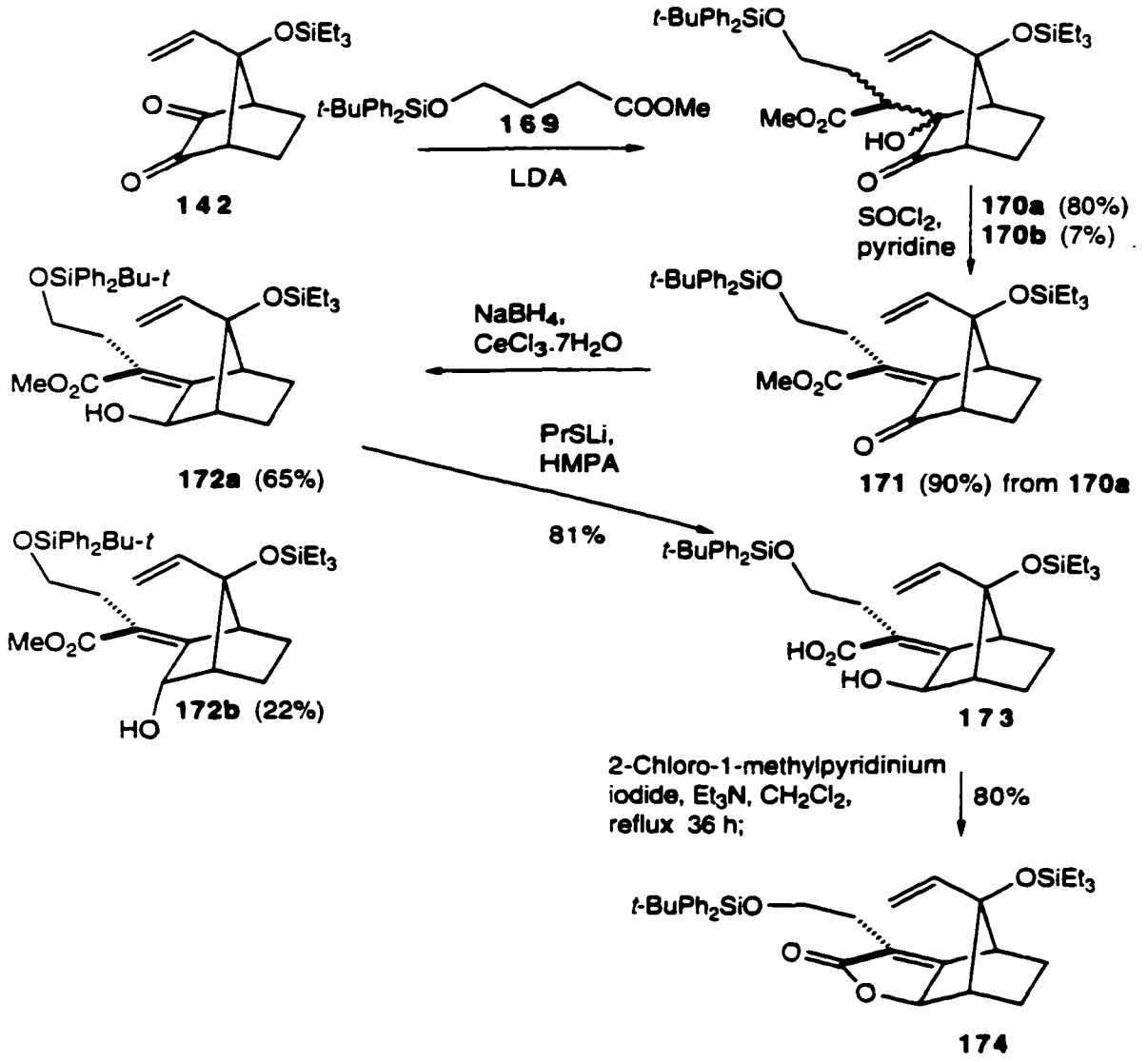
have to be modified in order to add one more carbon unit of the side chain containing the *t*-butyldiphenylsilyl (TBDPS) group. For these reasons we wondered if we could use **169** (Scheme 39) for condensation with diketone **142**. Ester **169** had not been reported in the literature, but it was easily made by the route shown in Scheme 39.



Scheme 39

Opening of γ-butyrolactone with NaOH,[46] followed by treatment with MeI in DMF,[47] afford **168**, and silylation with *t*-$BuPh_2SiCl$ then gave **169** in 91% yield over the three steps. With **169** in hand, the route shown in Scheme 40 was tested, and found, in the event, to be much better than that of Scheme 38, in terms of stereoselectivity, as well as the fact that it gives a side arm of desired length, so that subsequent homologation is not required. Condensation of diketone **142** with the anion derived (LDA, THF) from **169** gave two diastereoisomers, **170a** (80%) and **170b** (7%), whose stereochemistry was not assigned. Dehydration of the major isomer **170a** by the action of $SOCl_2$ in the presence of pyridine afforded the desired olefin **171** in 90% yield. (The stereochemistry of this substance follows from its subsequent conversion into lactone **174**. We were unable to make the

assignment on the basis of the ^1H NMR spectrum.) Reduction of **171** with $NaBH_4$ and $CeCl_3.7H_2O$ afforded the desired *exo*-alcohol **172a** (65%) together with the *endo*-alcohol **172b** (22%). Demethylation of **172a** with *n*-PrSLi in HMPA liberated the carboxylic acid **173** in 81% yield. Finally, lactonization of **173** was readily achieved with 2-chloro-1-methylpyridinium iodide to give **174** in 80% yield. At this point, a facile and

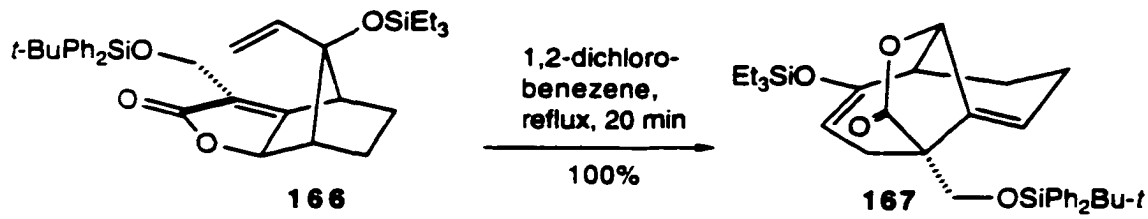


Scheme 40

reliable method to construct the strained lactone had been established. The *endo*-alcohol **172b** can be recycled by Dess-Martin oxidation and reduction.

Thermal siloxy-Cope rearrangement

The idea of preparing the strained lactone **174** is based on the expectation that the release of strain would facilitate oxy-Cope rearrangement. It had, in fact, been found in this laboratory that the siloxy-Cope rearrangement proceeds readily with the strained lactone **128**.[31] We had found that strained lactone **166** (see above) also rearranged smoothly (Scheme 41) when heated in 1,2-dichlorobenzene.

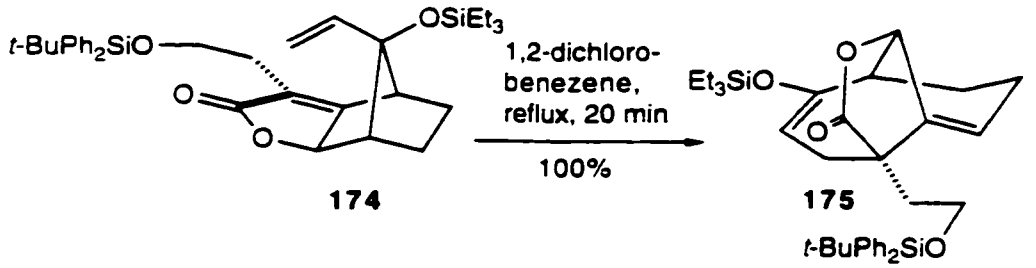


166 **167**

Scheme 41

It appeared (TLC control) to rearrange completely within 10 min and, after a further 10 min, evaporation of the 1,2-dichlorobenzene afforded **167** in 100% yield. The ^{1}H and ^{13}C NMR spectra indicated that **167** was pure. This compound represents the first example of a substance made by oxy-Cope rearrangement with the required modifiable substituent at quaternary center C(14) and the bridgehead double bond. We next heated **166** in toluene. Under these conditions it rearranged to **167** within 1.5 h (TLC control) in almost

quantitative yield. When the strained lactone **174** (Scheme 42) was submitted to oxy-Cope rearrangement in 1,2-dichlor-



174 **175**

Scheme 42

benzene, it gave the same exciting result as **166**, the desired product **175** being isolated in 100% yield.

Conclusions

In summary, an efficient and stereoselective route has been developed to construct the advanced models **167** and **175** which contain two very challenging structural elements (quaternary center and bridgehead double bond) of **1** and **2**. The facile thermal siloxy-Cope rearrangement of **166** and **174** demonstrated that the strain in the bicyclic lactone systems facilitates the oxy-Cope process. Compound **175** represents the first example to date[48] which has the required quaternary center with a side chain of correct length, and a bridgehead double bond. Further elaboration of **175** towards more advanced models relevant to the total synthesis of **1** and **2** is currently under way in our laboratory.

III. Experimental Section

General Procedures. Unless stated to the contrary, the following conditions apply: Reactions were carried out under a slight static pressure of Ar that had been purified by passage through a column (3.5 x 42 cm) of R-311 catalyst[49] and then through a similar column of Drierite. All solvents for reactions were dried, as described below. Glassware was dried in an oven for at least 3 h before use (120 °C) and either cooled in a desiccator over Drierite, or assembled quickly, sealed with rubber septa, and allowed to cool under a slight static pressure of Ar. Reaction mixtures were stirred by Teflon-coated magnetic stirring bars.

Hexane used for chromatography was distilled before use.

Products were isolated from solution by evaporation under water aspirator vacuum at room temperature, using a rotary evaporator.

Microliter syringes were washed with water and acetone, using a suction device to draw the solvents through. Then air was sucked through for 1 min. The solution to be dispensed was drawn up and expelled, and this operation was repeated several times before drawing up the sample to be used. Cannula transfers were always done under slight pressure (Ar), not by suction.

Commercial thin layer chromatography (TLC) plates (silica gel, Merck 60F-254) were used. Spots were detected by spraying the plate with a solution of phosphomolybdic

acid,[49] followed by charring on a hot plate, or by examination under UV light. Silica gel for flash chromatography was Merck type 60 (230-400 mesh).

Dry solvents were prepared under an inert atmosphere and transferred by dry syringes fitted with oven-dried needles, or by cannula. Dry THF was distilled from sodium benzophenone ketyl. Dry Et_3N, *i*-Pr_2NH, CH_2Cl_2, and pyridine were distilled from CaH_2. HMPA was distilled from CaH_2 under reduced pressure (oil pump), and kept under Ar atmosphere over molecular sieves. All other solvents were used as purchased. Commercial (Aldrich) solutions of *n*-BuLi (in hexanes) were assumed to have the stated molarity.

FT-IR measurements were recorded on a Nicolet 7000 FTIR instrument. Measurements were made as casts from the specified solvent using potassium bromide plates.

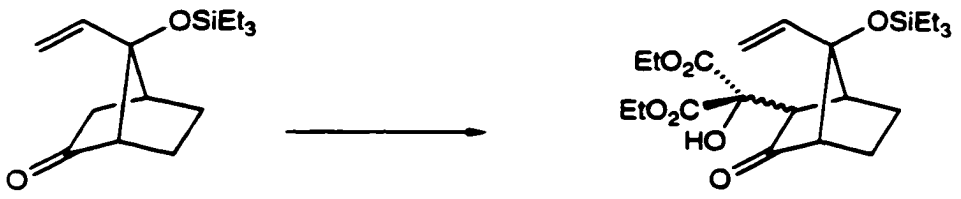
^1H nuclear magnetic resonance spectra were recorded with Bruker AM-300 (at 300 MHz), Varian INOVA-300 (at 300 MHz), Bruker AM-360 (at 360 MHz) or Bruker AM-400 (at 400 MHz) spectrometers in the specified deuterated solvent. ^{13}C spectra were recorded with Bruker AM-300 (at 75.5 MHz) or Varian UNITY-500 (at 125 MHz). The symbols s', d', t', and q' used for ^{13}C NMR signals indicate 0, 1, 2, or 3 attached hydrogens, respectively, which are assigned based on the APT experiment.

Mass spectra were recorded with AEI Models MS-12, MS-50 MS9 (modified), Kratos MS50 (modified) or Micromass ZabSpec Hybrid Sector-TOF mass spectrometers. For isotope peaks,

high-resolution mass data were taken from the highest mass number peak shown in the spectrum.

Compounds isolated by flash chromatography were pure by TLC and, unless otherwise stated, also as judged by high field ^{1}H and ^{13}C NMR spectra.

Diethyl (*exo,anti*)- and (*endo,anti*)-2-Hydroxy-2-[7-ethenyl-2-oxo-7-[(triethylsilyl)oxy]bicyclo[2.2.1]heptan-3-yl]propanedioate (130a and 130b).



119 **130a, 130b**

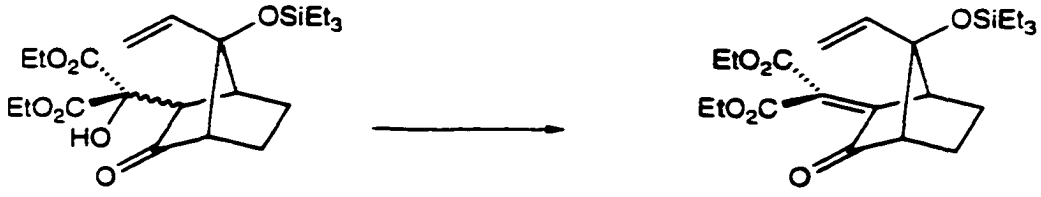
Ketone **119** (102 mg, 0.383 mmol) in THF (1 mL, plus 2 x 0.2 mL as a rinse) was added dropwise to a stirred and cooled (-78 °C) solution of LDA [prepared by addition of *n*-BuLi (2.5 M in hexane, 176 µL, 0.441 mmol) to a stirred and cooled (0 °C) solution of $(i\text{-Pr})_2NH$ (69 µL, 0.52 mmol) in THF (2 mL), followed by stirring at 0 °C for 15 min]. The mixture was stirred at -78°C for 1 h, and then diethyl ketomalonate (117 µL, 0.767 mmol) was added dropwise. Stirring at -78°C was continued for 1 h, and the mixture was quenched with saturated aqueous NH_4Cl (1.5 mL) and allowed to warm to room temperature over ca. 15 min. Water (0.5 mL) was added and

the mixture was extracted with EtOAc (25 mL). The organic extract was washed with water (3 mL) and brine (5 mL), dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (1.6 x 29 cm), using 10% EtOAc-hexane, gave **130a** (88 mg, 52%) and **130b** (72 mg, 43%) as colorless oils. Compound **130a** had: FTIR (CH_2Cl_2 cast) 3489, 1743 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 0.54-0.61 (m, 6 H), 0.92 (t, J = 7.9 Hz, 9 H), 1.25 (t, J = 7.1 Hz, 6 H), 1.62-1.70 (m, 2 H), 2.10-2.20 (m, 1 H), 2.37-2.46 (m, 2 H), 2.59-2.63 (m, 1 H), 3.16 (s, 1 H), 3.45 (s, 1 H), 4.12-4.33 (m, 4 H), 5.10 (dd, J = 17.8, 0.8 Hz, 1 H), 5.19 (dd, J = 10.8, 0.8 Hz, 1 H), 6.17 (dd, J = 17.8, 10.8 Hz, 1 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 6.6 (t'), 7.0 (q'), 14.0 (q'), 14.1 (q'), 22.3 (t'), 30.5 (t'), 47.9 (d'), 56.1 (d'), 58.6 (d'), 62.9 (t'), 63.4 (t'), 77.7 (s'), 84.7 (s'), 118.0 (t'), 139.7 (d'), 169.4 (s'), 170.5 (s'), 211.2 (s'); exact mass *m/z* calcd for $C_{22}H_{36}O_7Si$ 440.2230, found 440.2222.

Compound **130b** had: FTIR (CH_2Cl_2 cast) 3480, 1751 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 0.55-0.63 (m, 6 H), 0.94 (t, J = 7.9 Hz, 9 H), 1.21-1.28 (m, 6 H), 1.48-1.58 (m, 1 H), 1.94-2.03 (m, 1 H), 2.08-2.21 (m, 2 H), 2.47 (t, J = 4.0 Hz, 1 H), 2.58 (d, J = 4.7 Hz, 1 H), 3.44 (d, J = 4.0 Hz, 1 H), 3.98 (d, J = 0.7 Hz, 1 H), 4.18-4.32 (m, 4 H), 5.23-5.32 (m, 2 H), 6.16 (dd, J = 17.8, 10.8 Hz, 1 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 6.6 (t'), 7.1 (q'), 14.1 (q'), 14.2 (q'), 21.7 (t'), 23.8 (t'), 48.0 (d'), 55.4 (d'), 57.6 (d'), 63.0 (t'), 63.6 (t'), 78.7 (s'), 85.1 (s'), 119.0 (t'), 138.5 (d'), 169.2 (s'),

170.5 (s'), 211.5 (s'); exact mass *m/z* calcd for $C_{22}H_{36}O_7Si$ 440.2230, found 440.2228.

Diethyl (1α,4α,7R*)-2-[7-Ethenyl-2-oxo-7-[(triethylsilyl)oxy]bicyclo[2.2.1]heptan-2-ylidene]propanedioate (131).

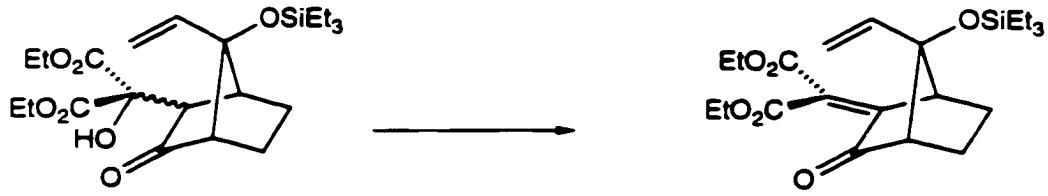


130a **131**

$SOCl_2$ (306 μL, 4.195 mmol) was added dropwise to a stirred solution of **130a** (336 mg, 0.764 mmol) in pyridine (2.5 mL), and stirring was continued for 8 h. The mixture was cooled (0 °C), water (2 mL) was added dropwise, and the mixture was extracted with EtOAc (60 mL). The organic extract was washed with 5% hydrochloric acid (10 mL), saturated aqueous $NaHCO_3$ (10 mL), water (10 mL) and brine (10 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1.6 x 28 cm), using 5% EtOAc-hexane, gave **131** (293 mg, 91%) as a pale yellow oil: FTIR (CH_2Cl_2 cast) 1745, 1724 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 0.58-0.66 (m, 6 H), 0.96 (t, *J* = 7.9 Hz, 9 H), 1.23-1.32 (m, 6 H), 1.54-1.63 (m, 2 H), 2.20-2.32 (m, 1 H), 2.36-2.46 (m, 1 H), 2.70 (dd, *J* = 4.8, 1.7 Hz, 1 H), 3.85 (dd, *J* = 4.8, 1.6 Hz, 1 H), 4.18-4.29 (m, 4 H), 5.19-5.28 (m, 2 H), 6.05 (dd, *J*

= 17.7, 10.8 Hz, 1 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 6.6 (t'), 7.0 (q'), 14.0 (q'), 14.1 (q'), 23.4 (t'), 26.5 (t'), 50.9 (d';), 57.1 (d'), 62.0 (t'), 62.3 (t'), 84.2 (s'), 119.6 (t'), 124.6 (s') 138.3 (d'), 151.0 (s'), 163.6 (s'), 165.2 (s'), 201.6 (s'); exact mass *m/z* calcd for $C_{22}H_{34}O_6Si$ 422.2125, found 422.2113.

Diethyl (1α,4α,7*R)-2-[7-Ethenyl-2-oxo-7-[(triethylsilyl)oxy]bicyclo[2.2.1]heptan-2-ylidene]propanedioate (131).**

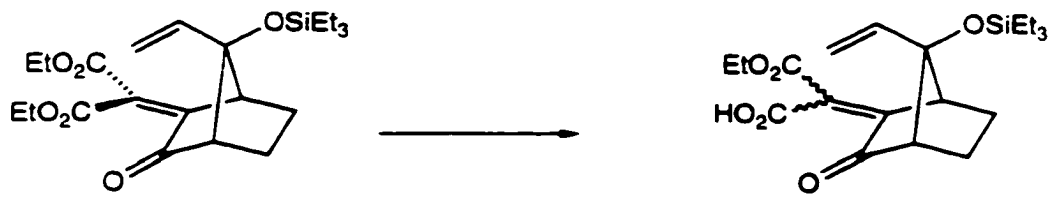


130b **131**

$SOCl_2$ (139 μL, 1.91 mmol) was added dropwise to a stirred solution of **130b** (84.0 mg, 0.191 mmol) in pyridine (0.6 mL), and stirring was continued for 5 days. The mixture was cooled (0°C), water (1 mL) was added dropwise, and the mixture was extracted with EtOAc (25 mL). The organic extract was washed with 5% hydrochloric acid (5 mL), saturated aqueous $NaHCO_3$ (5 mL), water (5 mL) and brine (5 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1.6 x 23 cm), using first 5% EtOAc-hexane (200 mL) and then 15% EtOAc-hexane, gave **131** [47 mg, 59% or 76% after correction for recovered starting

material (19 mg)]. The material was spectroscopically identical to that obtained in the previous experiment.

Ethyl Hydrogen (1α,3*E*,4α,7*R)- or (1α,3*Z*,4α,7*R**)-2-[7-Ethenyl-2-oxo-7-[(triethylsilyl)oxy]bicyclo[2.2.1]heptan-2-ylidene]propanedioate (137).**



131 **137**

LiOH (1.0 N, 938 μL, 0.938 mmol) was added dropwise to a stirred and cooled (0 °C) solution of **131** (330 mg, 0.782 mmol) in MeOH (10 mL). After 12 h, the cold bath was removed, and stirring was continued 12 h. The solvent was evaporated, and the residue was acidified to pH 1 with 10% hydrochloric acid and extracted with Et_2O (100 mL). The organic extract was washed with brine (10 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1.6 x 28 cm), using 10:16:24 MeOH-EtOAc-hexane, gave **137** (278 mg, 90%) as a pale yellow oil, which was a single compound, of unassigned stereochemistry: FTIR (CH_2Cl_2 cast) 2750-3600 (br), 1786 1740 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 0.64 (q, *J* = 7.9 Hz, 6 H), 0.93 (t, *J* = 7.9 Hz, 9 H), 1.26 (t, *J* = 6.9 Hz, 3 H), 1.52-1.63 (m, 2 H), 2.19-2.45 (m, 2 H),

2.66-2.73 (m, 1 H), 3.83-3.91 (m, 1 H), 4.22 (q, J = 6.9 Hz, 2 H), 5.19-5.27 (m, 2 H), 6.04, J = 17.7, 10.8 Hz, 1 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 6.6 (t'), 7.0 (q'), 13.8 (q'), 23.4 (t'), 26.5 (t'), 51.1 (d'), 57.0 (d'), 62.5 (t'), 84.2 (s'), 119.5 (t'), 125.4 (s'), 138.4 (d'), 151.4 (s'), 167.2 (s'), 168.7 (s'), 201.9 (s'); exact mass (electrospray) m/z calcd for $C_{20}H_{30}NaO_6Si$ (M + Na) 417.1709, found 417.1711.

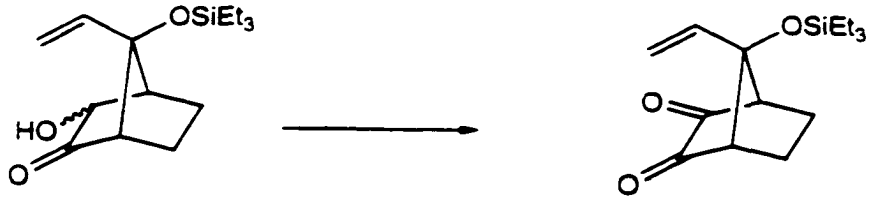
(1α,2α,4α,7*R)- and (1α,2β,4α,7*R**)-7-Ethenyl-3-hydroxy-7-[(triethylsilyl)oxy]bicyclo[2.2.1]heptan-2-one (144a).**

119 **144a**

A solution of ketone **119** (500 mg, 1.88 mmol) in THF (10 mL, plus 2 x 0.6 mL as a rinse) was added dropwise to a stirred and cooled (-78 °C) solution of LDA [prepared by addition of *n*-BuLi (2.5 M in hexane, 1.0 mL, 2.500 mmol) to a stirred and cooled (0 °C) solution of $(i\text{-Pr})_2NH$ (330 μL, 2.52 mmol) in THF (5 mL), followed by stirring at 0 °C for 15 min]. The mixture was stirred at -78 °C for 1 h and then transferred to a dry ice/CCl_4 bath at -23 °C. Freshly prepared solid MoO_5•py•HMPA (1.46 g, 3.37 mmol) was added in one portion with vigorous stirring. Stirring at -23 °C was

continued for 0.5 h, and the mixture was quenched with saturated aqueous Na_2SO_3 solution (10 mL), allowed to warm to room temperature over ca. 10 min, diluted with brine (20 mL), and extracted with Et_2O (2 x 50 mL). The combined organic extracts were washed with aqueous 5% HCl (10 mL) and brine (10 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1.6 x 28 cm), using 10% EtOAc-hexane, gave **144a** [453 mg, 85% or 91% after correction for recovered starting material (35 mg)] as a colorless oil: FTIR (CH_2Cl_2 cast) 3428, 1758 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 0.58-0.65 (m, 6H), 0.95 (t, J = 7.9 Hz, 9 H), 1.43-1.51 (m, 1H), 1.89-2.02 (m, 2 H), 2.22-2.32 (m, 1 H), 2.42-2.48 (m, 1 H), 2.66 (d, J = 5.1 Hz, 1 H), 3.23 (br s, 1 H), 4.00 (dd, J = 4.8, 0.9 Hz, 1 H), 5.20 (dd, J = 17.7, 0.5 Hz, 1 H), 5.24 (dd, J = 10.7, 0.5 Hz, 1 H), 6.14 (dd, J = 17.7, 10.7 Hz, 1 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 6.7 (t'), 7.0 (q'), 18.6 (t'), 25.8 (t'), 50.1 (d'), 56.8 (d'), 75.4 (d'), 82.5 (s'), 118.7 (t'), 138.6 (d'); exact mass (electrospray) m/z calcd for $C_{15}H_{26}NaO_3Si$ (M + Na) 305.1549, found 305.1543.

(*Anti*)-7-Ethenyl-7-[(triethylsilyl)oxy]bicyclo[2.2.1]heptan-2,3-dione (142).

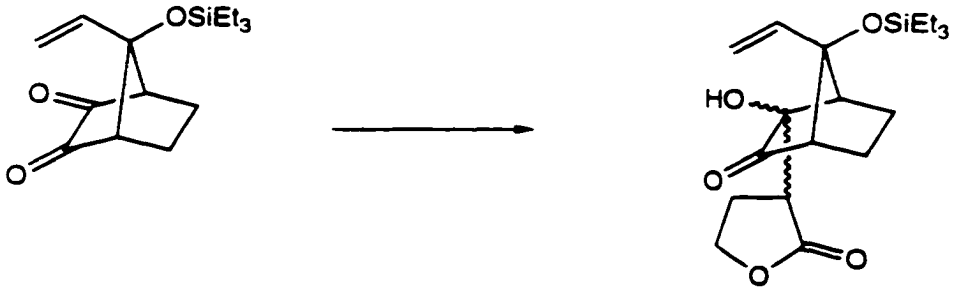


144a **142**

A solution of **144a** (360 mg, 1.28 mmol) in CH_2Cl_2 (7 mL, plus 3 x 0.5 mL as a rinse) was added dropwise to a stirred solution of Dess-Martin reagent (700 mg, 1.66 mmol) in CH_2Cl_2 (8 mL). Stirring was continued for 0.5 h, and Et_2O (40 mL) was added, followed by saturated aqueous $NaHCO_3$ (20 mL) containing $Na_2S_2O_3$ (2.52 g). The mixture was stirred for 5 min, and extracted with Et_2O (100 mL). The organic extract was washed with saturated aqueous $NaHCO_3$ (10 mL), water (10 mL) and brine (10 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1.6 x 26 cm), using 5% EtOAc-hexane, gave **142** (339 mg, 95%) as a yellow solid: mp 38-41 °C; FTIR (CH_2Cl_2 cast) 1782, 1758 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 0.60-0.67 (m, 6 H), 0.96 (t, J = 7.9 Hz, 9 H), 1.68-1.75 (m, 2 H), 2.35-2.44 (m, 2 H), 3.01 (dd, J = 3.2, 2.5 Hz, 2 H), 5.24 (d, J = 17.7 Hz, 1 H), 5.32 (d, J = 10.8 Hz, 1 H), 6.13 (dd, J = 17.7, 10.8 Hz, 1 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 6.6 (t'), 7.0 (q'), 23.5 (t'), 58.7 (d'), 81.3 (s'), 120.7 (t'), 138.4 (d'), 200.6 (s'); exact

mass (electrospray) m/z calcd for $C_{15}H_{24}NaO_3Si$ (M + Na) 303.1392, found 303.1397.

(*Exo,anti*)- and (*Endo,anti*)-3-[7-Ethenyl-3-hydroxy-2-oxo-7-[(triethylsilyl)oxy]bicyclo[2.2.1]heptan-3-yl]dihydro-2(3*H*)-furanone (148a and 148b).



142 **148a, 148b**

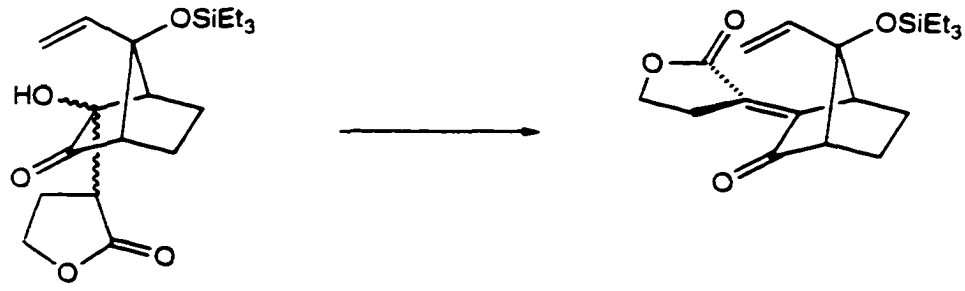
γ-Butyrolactone (34 μL, 0.44 mmol) in THF (0.2 mL, plus 2 x 0.2 mL as a rinse) was added dropwise to a stirred and cooled (-78 °C) solution of LDA [prepared by addition of *n*-BuLi (2.5 M in hexane, 160 μL, 0.400 mmol) to a stirred and cooled (0 °C) solution of $(i\text{-Pr})_2NH$ (60 μL, 0.45 mmol) in THF (0.5 mL), followed by stirring at 0 °C for 15 min]. Stirring at -78 °C was continued for 30 min, and then diketone **142** (103 mg, 0.368 mmol) in THF (0.2 mL, plus 2 x 0.2 mL as a rinse) was added dropwise. Stirring at -78°C was continued for 30 min, and the mixture was quenched with saturated aqueous NH_4Cl (0.3 mL) and allowed to warm to room temperature over ca. 15 min. Water (0.3 mL) was added and the mixture was extracted with Et_2O (30 mL). The organic

extract was washed with brine (5 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1.6 x 25 mL), using 30% EtOAc-hexane, gave **148a** (36 mg, 27%) and **148b** (72 mg, 53%) as crystalline solids whose stereochemistry was not established.

Compound **148a** had: mp 124-127°C; FTIR (CH_2Cl_2 cast) 3466, 1751 cm^{-1}; ^1H NMR (CD_2Cl_2 400 MHz) δ 0.55-0.66 (m, 6 H), 0.95 (t, *J* = 7.9 Hz, 9 H), 1.46-1.56 (m, 1 H), 1.75-1.85 (m, 1 H), 2.14-2.29 (m, 2 H), 2.36-2.49 (m, 2 H), 2.72-2.88 (m, 4 H), 4.11-4.18 (m, 1 H), 4.25-4.34 (m, 1 H), 5.34-5.42 (m, 2 H), 6.41 (dd, *J* = 18.0, 10.8 Hz, 1 H); 6.6 (t'), 7.0 (q'), 22.5 (t'), 23.4 (t'), 23.6 (t'), 42.9 (d'), 56.2 (d'), 56.7 (d'), 67.8 (t'), 79.2 (s'), 84.2 (s'), 120.0 (t'), 140.9 (d'), 176.1 (s'), 214.7 (s'); exact mass *m/z* calcd for $C_{19}H_{30}O_5Si$ 366.1863, found 366.1867.

Compound **148b** had: mp 125-126.5°C; FTIR (CH_2Cl_2 cast) 3460, 1770 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 0.56-0.64 (m, 6 H), 0.94 (t, *J* = 7.9 Hz, 9 H), 1.48-1.55 (m, 1 H), 1.59-1.67 (m, 1 H), 2.14-2.22(m, 1 H), 2.25-2.45 (m, 4 H), 2.65 (s, 1 H), 2.74 (t, *J* = 8.6 Hz, 1 H), 2.82 (dd, *J* = 5.0, 1.7 Hz, 1 H), 4.15-4.22 (m, 1 H), 4.26-4.33 (m, 1 H), 5.28 (dd, *J* = 10.8, 0.5 Hz, 1 H), 5.32 (dd, *J* = 18.0, 0.5 Hz, 1 H), 6.32 (dd, *J* = 18.0, 10.8 Hz, 1 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 6.6 (t'), 7.0 (q'), 22.3 (t'), 22.9 (t'), 26.4 (t'), 44.8 (d'), 56.0 (d'), 57.2 (d'), 67.2 (t'), 79.7 (s'), 83.7 (s'), 118.9 (t'), 140.0 (d'), 175.3 (s'), 211.9 (s'); exact mass *m/z* calcd for $C_{19}H_{30}O_5Si$ 366.1863, found 366.1864.

(1α,3*E*,4α,7*R)-3-[7-Ethenyl-2-oxo-7-[(triethylsilyl)oxy]bicyclo[2.2.1]heptan-3-ylidene]dihydro-2(3*H*)-furanone (149a).**

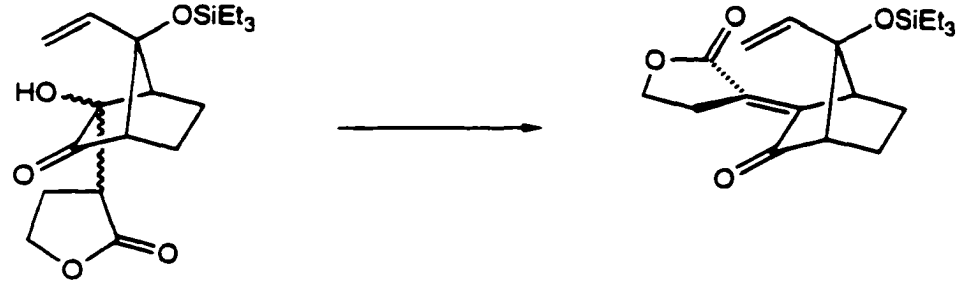


148a **149b**

$SOCl_2$ (334 μL, 0.453 mmol) was added dropwise to a stirred solution of **148a** (33.0 mg, 0.092 mmol) in pyridine (0.4 mL), and stirring was continued for 12 h. The mixture was cooled (0 °C), water (0.5 mL) was added dropwise, and the mixture was extracted with EtOAc (30 mL). The organic extract was washed with 5% hydrochloric acid (5 mL), saturated aqueous $NaHCO_3$ (5 mL), water (5 mL) and brine (5 mL), dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (1.6 x 23 cm), using 10% EtOAc-hexane, gave **149a** (28 mg, 89%) as a pale yellow oil: FTIR (CH_2Cl_2 cast) 1759, 1732 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz δ 0.58-0.65 (m, 6 H), 0.95 (t, *J* = 7.9 Hz, 9 H), 1.42-1.56 (m, 2 H), 2.21-2.31 (m, 1 H), 2.35-2.45 (m, 1 H), 2.71 (dd, *J* = 4.8, 1.7 Hz, 1 H), 3.16-3.22 (m, 2 H), 4.07 (dd, *J* = 4.3, 1.4 Hz, 1 H), 4.32-4.38 (m, 2 H), 5.18 (dd, *J* = 10.7, 0.9 Hz, 1 H), 5.20 (dd, *J* = 17.7, 0.9 Hz, 1 H), 6.02 (dd, *J* = 17.7, 10.8

Hz, 1 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 6.6 (t'), 7.0 (q'), 23.3 (t'), 26.8 (t'), 28.3 (t'), 49.1 (d'), 57.7 (d'), 66.7 (t'), 84.6 (s'), 119.2 (t'), 125.1 (s'), 138.6 (d'), 146.8 (s'), 171.3 (s'), 205.1 (s'); exact mass *m/z* calcd for $C_{19}H_{28}O_4Si$ 348.1757, found 348.1764.

(1α,3*E*,4α,7*R)-3-[7-Ethenyl-2-oxo-7-[(triethylsilyl)oxy]bicyclo[2.2.1]heptan-3-ylidene]dihydro-2(3*H*)-furanone (149a).**

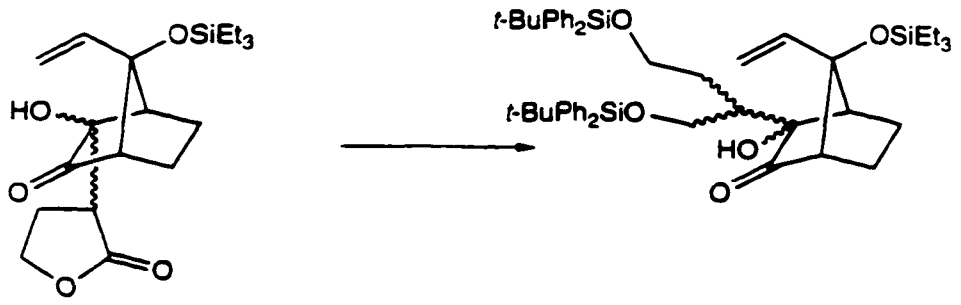


148b **149a**

$SOCl_2$ (55 μL, 0.75 mmol) was added dropwise to a stirred solution of **148b** (27.6 mg, 0.075 mmol) in pyridine (0.4 mL), and stirring was continued for 30 h. The mixture was cooled (0 °C), water (0.5 mL) was added dropwise, and the mixture was extracted with EtOAc (30 mL). The organic extract was washed with 5% hydrochloric acid (5 mL), saturated aqueous $NaHCO_3$ (5 mL), water (5 mL) and brine (5 mL), dried (Na_2SO_4), and evaporated. Flash chromatography of the reside over silica gel (1.6 x 23 cm), using 10% EtOAc-hexane, gave **149a** [10 mg, 40% or 50% after correction for the recovered

starting material (5.5 mg)].

(*Anti*)-7-Ethenyl-3-[3-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-1-[[[(1,1-dimethylethyl)diphenylsilyl]oxy]methyl]propyl]-3-hydroxy-7-[(triethylsilyl)oxy]bicyclo[2.2.1]heptan-2-one (150).



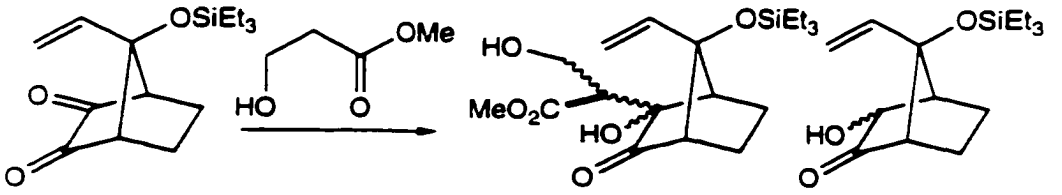
148b **150**

A solution of **148b** (58.0 mg, 0.158 mmol) in THF (0.3 mL, plus 2 x 0.1 mL as a rinse) was added dropwise to a stirred and cooled (0°C) suspension of $LiAlH_4$ (30.1 mg, 0.792 mmol) in THF (0.8 mL). Stirring was continued for 30 min, the ice bath was removed, and stirring was continued for 1 h. The mixture was quenched by careful addition of MeOH (0.2 mL), followed by saturated aqueous $NaHCO_3$ (0.2 mL). The mixture was stirred for 5 min, filtered through a pad (1 cm x 2 mm) of Celite, using EtOAc, and evaporated, to give the expected alcohol.

t-$BuPh_2SiCl$ (79 µL, 0.30 mmol) was added dropwise to a stirred solution of the above alcohol and imidazole (38.0 mg,

0.557 mmol) in CH_2Cl_2 (1.5 mL). Stirring was continued for 3 h, and the solvent was evaporated. Flash chromatography of the residue over silica gel (1.6 x 28 cm), using 5% EtOAc-hexane, gave **150** (83 mg, 62%) as a colorless oil, which was a single compound of unassigned stereochemistry: FTIR (CH_2Cl_2 cast) 3519, 3425 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 0.55-0.62 (m, 6 H), 0.94 (t, J = 7.9 Hz, 1 H), 0.97 (s, 9 H), 0.99 (s, 9 H), 1.31-1.39 (m, 1 H), 1.60-1.66 (m, 1 H), 1.70-1.96 (m, 4 H), 2.01-2.05 (m, 1 H), 2.19-2.22 (m, 1 H), 2.92 (d, J = 10.0 Hz, 1 H), 3.25-3.33 (m, 2 H), 3.55 (dd, J = 10.9, 3.4 Hz, 1 H), 3.58-3.65 (m, 1 H), 3.96 (dd, J = 11.0, 2.1 Hz, 1 H), 4.43 (s, 1 H), 5.19 (dd, J = 10.8, 1.6 Hz, 1 H), 5.40 (dd, J = 17.8, 1.6 Hz, 1 H), 6.52 (dd, J = 17.8, 10.8 Hz, 1 H), 7.24-7.65 (m, 20 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 7.0 (t'), 7.2 (q'), 19.3 (s'), 19.4 (s'), 21.1 (t'), 25.9 (t'), 27.0 (q'), 28.4 (t'), 41.6 (d'), 49.4 (d'), 54.6 (d'), 61.3 (t'), 63.0 (t'), 80.7 (d'), 82.7 (s'), 87.9 (s'), 116.0 (t'), 128.0 (d'), 128.1 (d'), 128.2 (d'), 130.0 (d'), 130.3 (d'), 130.4 (d'), 132.6 (s'), 132.7 (s'), 134.11 (s'), 134.14 (s'), 135.90 (d'), 135.92 (d'), 136.09 (d'), 136.12 (d'), 142.2 (d'); exact mass (electrospray) *m/z* calcd for $C_{51}H_{72}NaO_5Si_3$ (M + Na) 871.4585, found 871.4592.

Methyl (*anti*)-2-[7-Ethenyl-3-hydroxy-2-oxo-7-[(triethylsilyl)oxy]bicyclo[2.2.1]hept-2-yl]-3-hydroxypropanoate (160a and 160b) and (1α,2α,4α,7*R)- and (1α,2β,4α,7*R**)-7-Ethenyl-3-hydroxy-7-[(triethylsilyl)oxy]bicyclo[2.2.1]heptan-2-one (161).**



142 **159** **160a, 160b** **161**

A solution of **159** (61.3 mg, 0.589 mmol) in THF (0.2 mL, plus 2 x 0.1 mL as a rinse) was added dropwise to a stirred and cooled (-78 °C) solution of LDA [prepared by addition of *n*-BuLi (2.5 M in hexane, 471 μL, 1.18 mmol) to a stirred and cooled (0 °C) solution of $(i\text{-Pr})_2NH$ (155 μL, 1.18 mmol) in THF (0.6 mL), followed by stirring at 0 °C for 15 min]. Stirring at -78 °C was continued for 40 min, and then diketone **142** (110 mg, 0.393 mmol) in THF (0.2 mL, plus 2 x 0.1 mL as a rinse) was added dropwise. Stirring at -78 °C was continued for 10 min, and the mixture was quenched with saturated aqueous NH_4Cl (0.5 mL) and allowed to warm to room temperature over ca. 15 min. Water (0.3 mL) was added and the mixture was extracted with EtOAc (50 mL). The organic extract was washed with brine (5 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1.6 x 27 cm), using 20% EtOAc-hexane, gave **161** (20 mg,

18%; a mixture of two isomers), **160a** (44 mg, 29%; a mixture of three isomers) and **160b** (59 mg, 39%; a mixture of two isomers) as colorless oils.

Fraction **161** had: FTIR (CH_2Cl_2 cast) 3425, 1757 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 0.56-0.65 (m, 6 H), 0.94 (t, *J* = 7.9 Hz, 5.0 H), 0.95 (t, *J* = 7.9 Hz, 4.0 H), 1.36-1.54 (m, 2 H), 1.89-2.03 (m, 1.5 H), 2.09-2.19 (m, 0.70 H), 2.23-2.33 (m, 1.2 H), 2.34-2.40 (m, 0.88 H), 2.43-2.48 (m, 0.40 H), 2.67 (d, *J* = 4.9 Hz, 0.84 H), 3.62 (d, *J* = 7.2 Hz, 0.46 H), 4.00 (br s, 0.39 H), 5.17-5.28 (m, 0.88 H), 5.31 (s, 0.50 H), 5.35 (d, *J* = 7.2 Hz, 0.50 H), 6.14 (dd, *J* = 17.7, 10.8 Hz, 0.39 H), 6.28 (dd, *J* = 17.8, 10.8 Hz, 0.50 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 6.6 (t'), 6.7 (t'), 7.0 (q'), 18.5 (t'), 21.9 (t'), 25.4 (t'), 25.9 (t'), 50.0 (d'), 52.5 (d'), 56.2 (d'), 56.7 (d'), 75.5 (d'), 78.5 (d'), 82.5 (s'), 85.1 (s'), 118.7 (t'), 119.7 (t'), 138.6 (d'), 140.0 (d'); exact mass (electrospray) m/z calcd for $C_{15}H_{26}NaO_3Si$ (M + Na) 305.1549, found 305.1552.

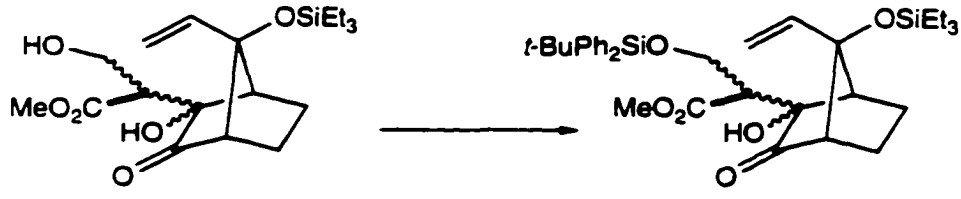
Fraction **160a** had: FTIR (CH_2Cl_2 cast) 3450, 1744 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 0.53-0.63 (m, 6 H), 0.88-0.97 (m, 9 H), 1.43-1.55 (m, 1.0 H), 1.60-1.86 (m, 2.0 H), 2.22-2.46 (m, 2.0 H), 2.75-2.81 (m, 0.33 H), 2.89-2.95 (m, 0.14 H), 3.21 (s, 0.71 H), 3.38-3.47 (m, 0.88 H), 3.54 (s, 0.71 H), 3.60-3.75 (m, 2.94 H), 3.78-3.95 (m, 0.29 H), 3.96-4.05 (m, 0.71 H), 4.09-4.18 (m, 1.0 H), 5.21-5.52 (m, 2.0 H), 6.23-6.37 (m, 0.29 H), 6.60 (dd, *J* = 17.9, 10.9 Hz, 0.71 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 6.7 (t'), 6.8 (t'), 6.9 (t'), 7.01 (q'),

7.07 (q'), 7.1 (q'), 20.4 (t'), 21.0 (t'), 21.2 (t'), 22.5 (t'), 22.7 (t'), 23.7 (t'), 49.6 (d') or (q'), 50.1 (d') or (q'), 52.0 (d') or (q'), 52.2 (d') or (q'), 52.4 (d') or (q'), 53.0 (d') or (q'), 54.1 (d') or (q'), 54.6 (d') or (q'), 54.6 (d') or (q'), 57.1 (d') or (q'), 57.4 (d') or (q'), 60.8 (t'), 66.2 (t'), 68.9 (t'), 80.6 (s'), 81.7 (s'), 84.0 (s'), 86.1 (s'), 89.6 (s'), 108.6 (s'), 110.2 (s'), 118.1 (t'), 118.4 (t'), 118.6 (t'), 139.8 (d'), 140.3 (d'), 141.7 (d'), 171.2 (s'), 171.7 (s'), 172.8 (s'), 214.2 (s'); exact mass (electrospray) m/z calcd for $C_{19}H_{32}NaO_6Si$ (M + Na) 407.1866, found 407.1868.

Fraction **160b** had: FTIR (CH_2Cl_2 cast) 3455, 1757, 1720 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 0.52-0.65 (m, 6 H), 0.88-0.94 (m, 9 H), 1.18-1.26 (m, 0.37 H), 1.47-1.58 (m, 1.20 H), 1.62-1.69 (m, 0.37 H), 1.77-1.86 (m, 0.37 H), 1.93-2.04 (m, 0.37 H), 2.12-2.32 (m, 2.86 H), 2.46 (dd, J = 5.0, 1.8 Hz, 0.37 H), 2.71 (dd, J = 9.0, 4.7 Hz, 0.63 H), 2.75 (dd, J = 5.1, 1.3 Hz, 0.63 H), 3.08 (s, 0.37 H), 3.19 (t, J = 10.5 Hz, 0.37 H), 3.44 (s, 0.37 H), 3.73 (s, 3 H), 3.82 (dd, J = 10.8, 4.6 Hz, 0.63 H), 3.92 (dd, J = 10.8, 9.4 Hz, 0.37 H), 3.95-4.02 (m, 0.63 H), 4.26 (t, J = 9.8 Hz, 0.37 H), 4.40 (s, 0.63 H), 5.11-5.18 (m, 1.26 H), 5.42 (dd, J = 10.9, 1.4 Hz, 0.37 H), 5.60 (dd, J = 18.1, 1.3 Hz, 0.37 H), 6.28 (dd, J = 17.7, 10.8 Hz, 0.63 H), 6.66 (dd, J = 18.1, 10.9 Hz, 0.37 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 6.7 (t'), 6.8 (t'), 7.0 (q'), 21.3 (t'), 22.0 (t'), 22.6 (t'), 23.0 (t'), 49.3 (d') or (q'), 52.2 (d') or (q'), 52.6 (d') or (q'), 53.3 (d') or (q'), 54.68 (d') or

(q'), 54.73 (d' or q'), 55.3 (d' or q') 56.1 (d') or (q'), 79.5 (s'), 84.8 (s'), 85.3 (s'), 88.4 (s'), 111.0 (s'), 116.9 (t'), 120.0 (t'), 140.1 (d'), 141.6 (d'), 171.5 (s'), 175.3 (s'), 213.9 (s'); exact mass (electrospray) m/z calcd for $C_{19}H_{32}NaO_6Si$ (M + Na) 407.1866, found 407.1866.

Methyl (*anti*)-3-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-2-[7-ethenyl-3-hydroxy-2-oxo-7-[(triethylsilyl)oxy]bicyclo[2.2.1]hept-2-yl]propanoate (162b).

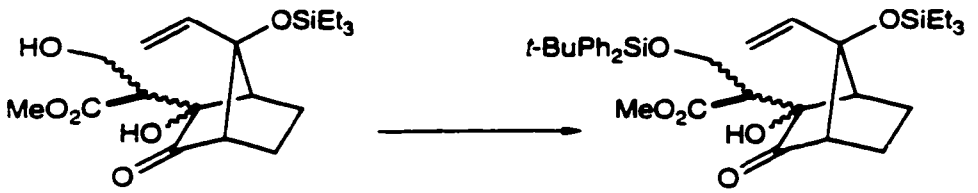


160b **162b**

t-$BuPh_2SiCl$ (47 μL, 0.18 mmol) was added dropwise to a stirred solution of **160b** (a mixture of two isomers, 58.0 mg, 0.151 mmol) and imidazole (22.6 mg, 0.333 mmol) in CH_2Cl_2 (1.5 mL). Stirring was continued for 1 h, and the solvent was evaporated. Flash chromatography of the residue over silica gel (1.6 x 28 cm), using 5% EtOAc-hexane, gave **162b** (86 mg, 92%) as a colorless oil, which was a single isomer of unassigned stereochemistry: FTIR (CH_2Cl_2 cast) 3451, 1757, 1719 cm^{-1}; ^1H NMR (CD_2Cl_2, 300 MHz) δ 0.51-0.61 (m, 6 H), 0.91 (t, *J* = 7.8 Hz, 9 H), 1.02 (s, 9 H), 1.34-1.44 (m, 1 H),

1.92-2.16 (m, 3 H), 2.70 (dd, J = 10.4, 5.3 Hz, 1 H), 3.74-3.81 [m, including s (3 H) at δ 3.78. 4 H in all], 4.12 (t, J = 10.3 Hz, 1 H), 4.45 (s, 1 H), 5.07-5.10 (m, 1 H), 5.14 (dd, J = 8.5, 0.7 Hz, 1 H), 6.22 (dd, J = 17.7, 10.7 Hz, 1 H), 7.38-7.50 (m, 6 H), 7.63-7.72 (m, 4 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 6.7 (t'), 7.0 (q'), 19.3 (s'), 21.7 (t'), 23.1 (t'), 26.8 (q'), 49.6 (d') or (q'), 52.5 (d') or (q'), 54.5 (d') or (q'), 56.0 (d') or (q'), 62.2 (t'), 79.0 (s'), 84.9 (s'), 116.8 (t'), 128.2 (d'), 130.2 (d'), 130.3 (d'), 133.3 (s'), 133.6 (s'), 135.9 (d'), 136.0 (d'), 140.1 (d'), 175.7 (s'), 214.2 (s'); exact mass (electrospray) m/z calcd for $C_{35}H_{50}NaO_6Si_2$ (M + Na) 645.3044, found 645.3041.

Methyl (*anti*)-3-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-2-[7-ethenyl-3-hydroxy-2-oxo-7-[(triethylsilyl)oxy]bicyclo[2.2.1]hept-2-yl]propanoate (162a).

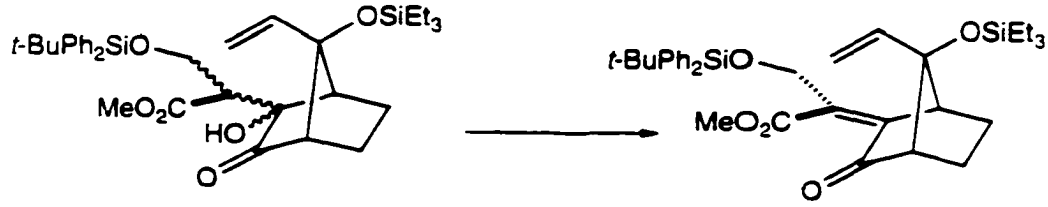


160a **162a**

t-$BuPh_2SiCl$ (34 μL, 0.13 mmol) was added dropwise to a stirred solution of **160a** (a mixture of three isomers, 44.0 mg, 0.115 mmol) and imidazole (17.2 mg, 0.252 mmol) in CH_2Cl_2

(1.2 mL). Stirring was continued for 2 h, and the solvent was evaporated. Flash chromatography of the residue over silica gel (1.6 x 26 cm), using 3% EtOAc-hexane, gave **162a** (65 mg, 92%) as a colorless oil. The material was a single isomer and was only slightly contaminated by *t*-$BuPh_2SiOH$ (^1H NMR): FTIR (CH_2Cl_2 cast) 3479, 1755 cm^{-1}; ^1H NMR (CD_2Cl_2, 300 MHz) δ 0.53-0.63 (m, 6 H), 0.93 (t, *J* = 7.9 Hz, 9 H), 1.02 (s, 9 H), 1.27-1.40 (m, 1 H), 1.62-1.72 (m, 1 H), 2.01-2.28 (m, 3 H), 2.67 (dd, *J* = 4.9, 1.4 Hz, 1 H), 2.78 (dd, *J* = 8.6, 4.6 Hz, 1 H), 3.45 (s, 1 H), 3.75 (s, 3 H), 4.21-4.37 (m, 2 H), 5.11-5.20 (m, 2 H), 6.28 (dd, *J* = 17.9, 10.7 Hz, 1 H), 7.35-7.48 (m, 6 H), 7.61-7.68 (m, 4 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 6.7 (t'), 7.0 (q'), 19.3 (s'), 22.3 (t'), 22.6 (t'), 26.9 (q'), 50.9 (d') or (q'), 52.2 (d') or (q'), 57.0 (d') or (q'), 57.3 (d') or (q'), 62.3 (t'), 79.8 (s'), 84.2 (s'), 117.6 (t'), 128.0 (d'), 130.1 (d'), 130.2 (d'), 133.5 (s'), 133.7 (s'), 135.95 (d'), 136.00 (d'), 140.2 (d'), 173.8 (s'), 212.3 (s'); exact mass (electrospray) m/z calcd for $C_{35}H_{50}NaO_6Si_2$ (M + Na) 645.3044, found 645.3041.

Methyl (1α,3*Z*,4α,7*R)-3-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-2-[7-ethenyl-2-oxo-7-[(triethylsilyl)oxy]bicyclo[2.2.1]heptan-2-ylidene]propanoate (163).**

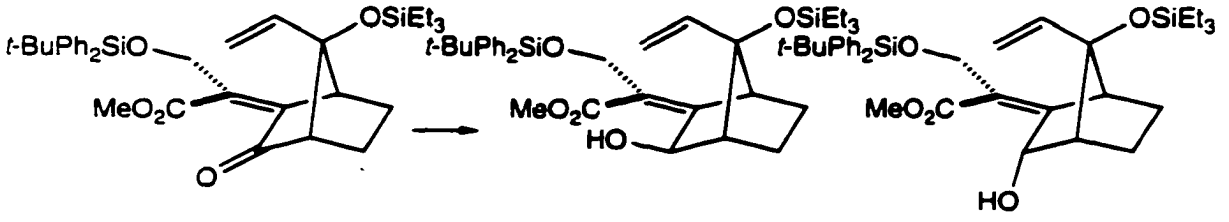


162b **163**

$SOCl_2$ (50 μL, 0.69 mmol) was added dropwise to a stirred solution of **162b** (86.0 mg, 0.138 mmol) in pyridine (1 mL). Stirring was continued for 8 h. The mixture was cooled (0 °C), water (0.5 mL) was added dropwise, and the mixture was extracted with EtOAc (30 mL). The organic extract was washed with 5% HCl (5 mL), saturated aqueous $NaHCO_3$ (5 mL), water (5 mL) and brine (5 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1.6 x 28 cm), using 10% EtOAc-hexane, gave **163** (76 mg, 91%) as a colorless oil: FTIR (CH_2Cl_2 cast) 1738 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 0.58 (q, J = 7.8 Hz, 6 H), 0.92 (t, J = 7.8 Hz, 9 H), 1.03 (s, 9 H), 1.34-1.41 (m, 1 H), 1.46-1.54 (m, 1 H), 2.12-2.23 (m, 2 H), 2.63 (d, J = 3.2 Hz, 1 H), 2.77-2.80 (m, 1 H), 3.77 (s, 3 H), 4.42 (d, J = 1.9 Hz, 2 H), 5.17-5.28 (m, 2 H), 5.95 (dd, J = 17.7, 10.8 Hz, 1 H), 7.40-7.49 (m, 6 H), 7.65-7.71 (m, 4 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 6.6 (t'), 7.0 (q'), 19.4 (s'), 23.2 (t'), 26.6 (t'), 26.7 (q'), 49.2 (d') or

(q'), 52.3 (d') or (q'), 57.4 (d') or (q'), 62.5 (t'), 84.6 (s'), 119.3 (t'), 128.2 (d'), 130.3 (d'), 133.1 (s'), 134.3 (s'), 135.9 (d'), 138.1 (d'), 139.1 (s'), 168.4 (s'), 201.2 (s'); exact mass (electrospray) m/z calcd for $C_{35}H_{48}NaO_5Si_2$ (M + Na) 627.2938, found 627.2942.

Methyl (1α,2β,3*Z*,4α,7*S)-3-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-2-[7-ethenyl-2-hydroxy-7-[(triethylsilyl)oxy]bicyclo[2.2.1]heptan-2-ylidene]propanoate (164b) and Methyl (1α,2α,3*Z*,4α,7*R**)-3-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-2-[7-ethenyl-2-hydroxy-7-[(triethylsilyl)oxy]bicyclo[2.2.1]heptan-2-ylidene]propanoate (164a).**



163 **164b** **164a**

$NaBH_4$ (14.3 mg, 0.378 mmol) was added in three portions to a stirred and cooled (0 °C) mixture of **163** (76.0 mg, 0.126 mmol) and $CeCl_3 \cdot 7H_2O$ (70.3 mg, 0.189 mmol) in dry MeOH (2 mL). Stirring at 0 °C was continued for 0.5 h, the cold bath was removed, and stirring was continued for 1.5 h. The mixture was then diluted with EtOAc (5 mL) and water (1 mL), and extracted with EtOAc (30 mL). The organic extract was washed

with brine (5 mL), dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (1.6 x 26 cm), using 5% EtOAc-hexane, gave **164a** (14 mg, 19%) and **164b** (52.7 mg, 69%) as colorless oils. Compound **164a** had: FTIR (CH_2Cl_2 cast) 3474, 1696 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 0.58-0.65 (m, 6 H), 0.96 (t, J = 7.9 Hz, 9 H), 1.04 (s, 9 H), 1.34-1.41 (m, 1 H), 1.84-1.94 (m, 1 H), 1.97-2.05 (m, 1 H), 2.17-2.30 (m, 2 H), 3.07 (d, J = 4.7 Hz, 1 H), 3.58 (s, 3 H), 4.36 (s, 2 H), 4.60 (br s, 1 H), 4.92 (d, J = 2.5 Hz, 1 H), 5.16 (dd, J = 10.8, 1.1 Hz, 1 H), 5.38 (dd, J = 17.7, 1.1 Hz, 1 H), 5.99 (dd, J = 17.7, 10.8 Hz, 1 H), 7.37-7.48 (m, 6 H), 7.66-7.72 (m, 4 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 6.8 (t'), 7.1 (q'), 19.3 (t'), 19.5 (s'), 26.9 (q'), 27.8 (t'), 49.8 (d') or (q'), 51.9 (d') or (q'), 52.0 (d') or (q'), 61.2 (t'), 70.9 (d'), 84.5 (s'), 118.7 (t'), 122.5 (s'), 127.9 (d'), 128.0 (d'), 130.0 (d'), 130.1 (d'), 133.9 (s'), 136.05 (d'), 136.09 (d'), 138.2 (d'), 169.1 (s'), 171.7 (s'); exact mass (electrospray) m/z calcd for $C_{35}H_{50}NaO_5Si_2$ (M + Na) 629.3095, found 629.3096.

Compound **164b** had: FTIR (CH_2Cl_2 cast) 3485, 1698 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 0.59-0.65 (m, 6 H), 0.96 (t, J = 7.9 Hz, 9 H), 1.04 (s, 9 H), 1.18-1.28 (m, 2 H), 2.03-2.20 (m, 3 H), 3.12 (d, J = 3.2 Hz, 1 H), 3.61 (s, 3 H), 4.31 (d, J = 2.9 Hz, 1 H), 4.35-4.44 (m, 3 H), 5.12 (dd, J = 10.8, 1.1 Hz, 1 H), 5.29 (dd, J = 17.7, 1.1 Hz, 1 H), 6.27 (dd, J = 17.7, 10.8 Hz, 1 H), 7.35-7.48 (m, 6 H), 7.68-7.75 (m, 4 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 6.8 (t'), 7.2 (q'), 19.4 (s'),

25.0 (t'), 26.9 (q'), 27.0 (t'), 50.2 (d') or (q'), 52.0 (d') or (q'), 52.1 (d') or (q'), 61.3 (t'), 75.6 (d'), 87.2 (s'), 116.8 (t'), 123.9 (s'), 127.98 (d'), 128.00 (d'), 130.1 (d'), 133.9 (s'), 136.0 (d'), 140.4 (d'), 168.9 (s'), 170.0 (s'); exact mass (electrospray) m/z calcd for $C_{35}H_{50}NaO_5Si_2$ (M + Na) 629.3095, found 629.3085.

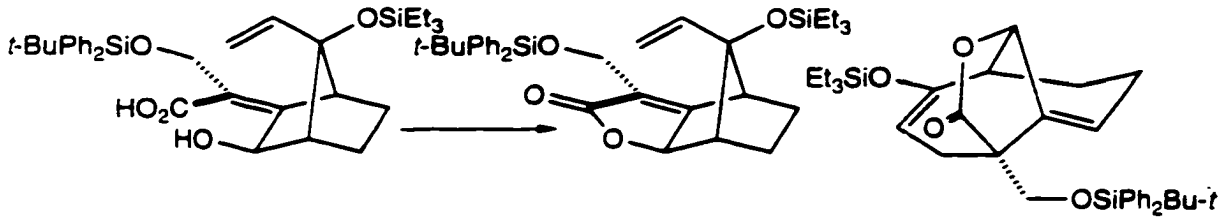
(1α,2β,3*Z*,4α,7*S)-3-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-2-[7-ethenyl-2-hydroxy-7-[(triethylsilyl)oxy]bicyclo[2.2.1]heptan-2-ylidene]propanoic acid (165).**

164b **165**

n-PrSLi[44] (2.5 M in HMPA, 209 μL, 0.522 mmol) was added dropwise to a stirred solution of **164b** (45.0 mg, 0.074 mmol) in degassed (by passage of a stream of Ar for 0.5 h) HMPA (3 mL). Stirring was continued for 2 h (TLC indicated complete reaction), the mixture was poured into ice water (50 mL) containing 10% HCl (2 mL), and extracted with Et_2O (4 x 35 mL). The combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (1.6 x 28 cm), using 50% EtOAc-hexane, gave **165** (37 mg, 83%) as a colorless oil: FTIR

(CH_2Cl_2 cast) 2750-3400 (br), 1688, 1640 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 0.54-0.62 (m, 6 H), 0.94 (t, J = 7.9 Hz, 9 H), 1.06 (s, 9 H), 1.11-1.24 (m, 1 H), 2.03-2.14 (m, 2 H), 2.19 (d, J = 2.5 Hz, 1 H), 2.97 (d, J = 2.4 Hz, 1 H), 4.31 (s, 1 H), 4.40 (d, J = 11.4 Hz, 1 H), 4.51 (d, J = 11.4 Hz, 1 H), 5.20 (dd, J = 10.8, 1.1 Hz, 1 H), 5.29 (dd, J = 17.7, 1.1 Hz, 1 H), 6.28 (dd, J = 17.7, 10.8 Hz, 1 H), 7.38-7.50 (m, 6 H), 7.67-7.75 (m, 4 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 6.8 (t'), 7.1 (q'), 19.4 (s'), 24.9 (t'), 26.8 (t'), 26.9 (q'), 62.3 (t'), 75.6 (d'), 86.9 (s'), 118.2 (t'), 124.0 (s'), 128.19 (d'), 128.22 (d'), 130.4 (d'), 132.9 (s'), 133.0 (s'), 136.0 (d'), 136.1 (d'), 140.6 (d'), 167.1 (s'), 169.1 (s'); exact mass (electrospray) m/z calcd for $C_{34}H_{48}NaO_5Si_2$ (M + Na) 615.2938, found 615.2944.

(4α,7α,7aβ,8R*)-3-[[[(1,1-Dimethylethyl)diphenylsilyl]oxy]methyl]-8-ethenyl-5,6,7,7a-tetrahydro-4,7-methano-8-[(triethylsilyl)oxy]benzofuran-2(4*H*)-one (166) and (3*R,7*S**,8*S**)-3,7,8-[3]Buten[1]yl[4]ylidene-3-[[[(1,1-dimethylethyl)diphenylsilyl]oxy]methyl]-3,4,7,8-tetrahydro-6-[(triethylsilyl)oxy]-2*H*-oxocin-2-one (167).**



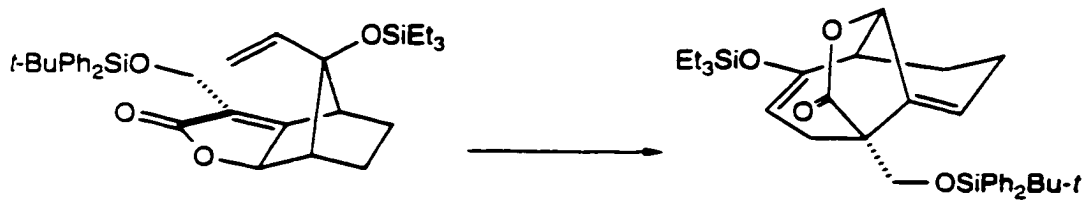
165 **166** **167**

A solution of **165** (27.3 mg, 0.046 mmol) and Et_3N (52 μL, 0.37 mmol) in CH_2Cl_2 (0.6 mL, plus 2 x 0.2 mL as a rinse), was added dropwise to a stirred solution of 2-chloro-1-methypyridinium iodide (48.6 mg (97%), 0.185 mmol) in CH_2Cl_2 (2 mL). The mixture was refluxed for 36 h, cooled to room temperature, diluted with Et_2O (5 mL), and filtered through a pad (1 cm x 2 mm) of silica gel with Et_2O. Evaporation of the filtrate and flash chromatography of the residue over silica gel (1.3 x 23 cm), using 5% EtOAc-hexane, gave **167** (1.6 mg, 6%) and **166** (20 mg, 77%) as colorless oils. Compound **167** had: 1786, 1643 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 0.59-0.67 (m, 6 H), 0.95 (t, *J* = 7.9 Hz, 9 H), 1.01 (s, 9 H),

1.56-1.65 (m, 1 H), 1.95-2.23 (m, 3 H), 2.25-2.41 (m, 2 H), 2.94-2.99 (m, 1 H), 3.84 (d, J = 10.0 Hz, 1 H), 4.02 (d, J = 10.0 Hz, 1 H), 4.53 (dd, J = 5.6, 3.0 Hz, 1 H), 4.74-4.77 (m, 1 H), 5.75-5.80 (m, 1 H), 7.37-7.47 (m, 6 H), 7.64-7.70 (m, 4 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 5.4 (t'), 6.8 (q'), 19.5 (s'), 21.9 (t'), 23.8 (t'), 26.9 (q'), 38.4 (t'), 45.9 (d'), 53.4 (s), 64.5 (t'), 79.1 (d'), 102.1 (d'), 119.1 (d'), 128.1 (d'), 130.1 (d'), 133.46 (s'), 133.54 (s'), 136.1 (d'), 141.3 (s'), 151.5 (s'), 179.5 (s'); exact mass (electrospray) m/z calcd for $C_{34}H_{47}O_4Si_2$ (M + H) 575.3013, found 575.3012.

Compound **166** had: FTIR (CH_2Cl_2 cast) 1762, 1686 cm^{-1}; ^{1}H NMR (CD_2Cl_2, 400 MHz) δ 0.58 (q', J = 7.9 Hz, 6 H), 0.92 (t, J = 7.9 Hz, 9 H), 1.09 (s, 9 H), 1.41-1.49 (m, 1 H), 1.70-1.78 (m, 1 H), 2.08-2.18 (m, 1 H), 2.28-2.37 (m, 1 H), 2.76 (d, J = 4.4 Hz, 1 H), 3.29 (d, J = 4.4 Hz, 1 H), 4.38 (t, J = 2.4 Hz, 2 H), 4.54 (t, J = 2.1 Hz, 1 H), 5.13 (dd, J = 10.8, 0.9 Hz, 1 H), 5.18 (dd, J = 17.7, 0.9 Hz, 1 H), 5.92 (dd, J = 17.7, 10.8 Hz, 1 H), 7.38-7.48 (m, 6 H), 7.65-7.72 (m, 4 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 6.7 (t'), 7.0 (q'), 19.4 (s'), 22.8 (t'), 27.0 (q'), 28.1 (t'), 47.2 (d'), 51.9 (d'), 59.5 (t'), 86.9 (d'), 89.5 (s'), 118.9 (t'), 126.7 (s'), 128.2 (d') 130.3 (d'), 133.3 (s'), 135.9 (d'), 136.0 (d'), 137.5 (d'), 171.0 (s'), 172.7 (s'); exact mass (electrospray) m/z calcd for $C_{34}H_{46}NaO_4Si_2$ (M + Na) 597.2832, found 597.2832.

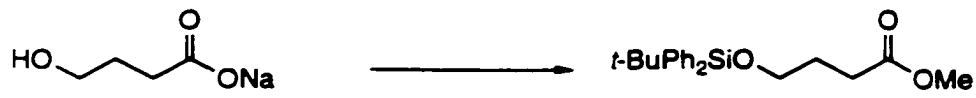
(3*R,7*S**,8*S**)-3,7,8-[3]Buten[1]yl[4]ylidene-3-[[[(1,1-dimethylethyl)diphenylsilyl]oxy]methyl]-3,4,7,8-tetrahydro-6-[(triethylsilyl)oxy]-2*H*-oxocin-2-one (167).**



166 **167**

A solution of **166** (17.0 mg, 0.030 mmol) in degassed (by bubbling Ar for 0.5 h) 1,2-dichlorobenzene (10 mL) was refluxed for 20 min. The solution was cooled and evaporated, and the residue was kept under oil-pump vacuum for 4 h, to give **167** (17 mg, 100%) as a pure (^{1}H NMR, 400 MHz), pale yellow oil, spectroscopically identical to **167** obtained from the above experiment.

Methyl 4-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]butanoate (169).

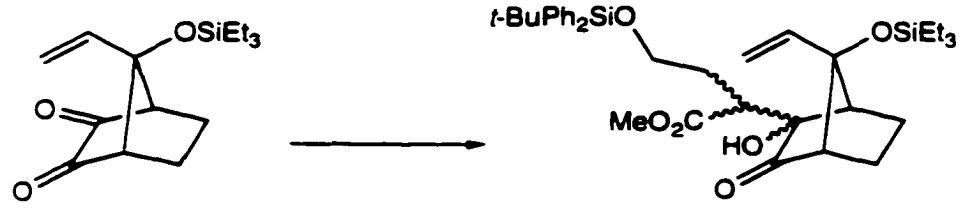


169

MeI (3.3 mL, 52 mmol) in dry DMF (6 mL) was added to a stirred solution of sodium 4-hydroxy-butanoate (1.01 g, 8.01 mmol) in DMF (22 mL). Stirring was continued for 24 h, and

then imidazole (1.20 g, 17.6 mmol) was added, followed by *t*-$BuPh_2SiCl$ (2.5 mL, 9.6 mmol). Stirring was continued for 12 h, and the mixture was diluted with EtOAc (70 mL), washed with water (5 x 35 mL), and brine (10 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (3.2 x 28 cm), using 5% EtOAc-hexane, gave **169** (2.60 g, 91%) as a colorless oil: FTIR (CH_2Cl_2 cast) 1740 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 1.06 (s, 9 H), 1.85-1.93 (m, 2 H), 2.47 (t, *J* = 7.4 Hz, 2 H), 3.64 (s, 3 H), 3.71 (t, *J* = 6.1 Hz, 2 H), 7.37-7.47 (m, 6 H), 7.65-7.70 (m, 4 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 19.6 (s'), 27.2 (q'), 28.3 (t'), 30.9 (t'), 51.7 (q'), 63.4 (t'), 128.2 (d'), 130.1 (d'), 134.3 (s'), 136.0 (d'), 174.1 (s'); exact mass (electrospray) *m/z* calcd for $C_{21}H_{28}NaO_3Si$ (M + Na) 379.1705, found 379.1702.

Methyl (1α,4α,7*R)-4-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-2-[7-ethenyl-3-hydroxy-2-oxo-7-[(triethylsilyl)oxy]bicyclo[2.2.1]hept-3-yl]butanoate (170a and 170b).**



142 **170a, 170b**

A solution of **169** (158 mg, 0.444 mmol) in THF (0.2 mL,

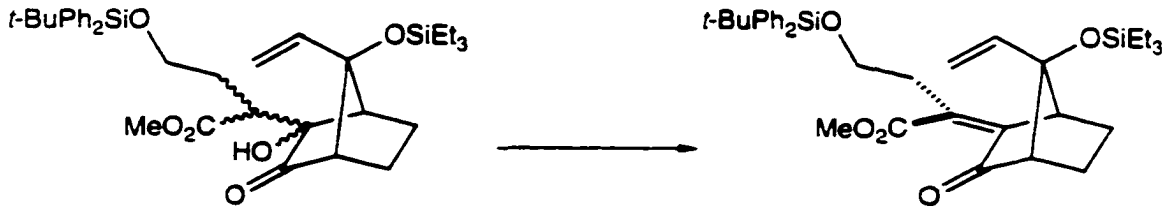
plus 2 x 0.1 mL as a rinse) was added dropwise to a stirred and cooled (-78 °C) solution of LDA in THF (0.5 mL) [prepared by addition of *n*-BuLi (2.5 M in hexane, 178 μL, 0.445 mmol) to a stirred and cooled (0 °C) solution of $(i\text{-Pr})_2NH$ (58 μL, 0.44 mmol) in THF (0.5 mL), followed by stirring at 0 °C for 15 min]. Stirring at -78°C was continued for 1 h, and then diketone **142** (113 mg, 0.404 mmol) in THF (0.4 mL, plus 2 x 0.2 mL as a rinse) was added dropwise. Stirring at -78°C was continued for 15 min, the mixture was quenched with saturated aqueous NH_4Cl (0.5 mL) and allowed to warm to room temperature over ca. 15 min. Water (0.5 mL) was added and the mixture was extracted with Et_2O (40 mL). The organic extract was washed with water (5 mL) and brine (5 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1.6 x 28 cm), using 5% EtOAc-hexane, gave **170a** (207 mg, 80%) and **170b** (20.0 mg, 8%) as colorless oils.

Compound **170a** had: FTIR (CH_2Cl_2 cast) 3458, 1756, 1716 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 0.59-0.66 (m, 6 H), 0.96 (t, J = 7.9 Hz, 9 H), 1.06 (s, 9 H), 1.48-1.71 (m, 2 H), 1.80-1.88 (m, 1 H), 1.92-2.02 (m, 1 H), 2.15-2.34 (m, 3 H), 2.74-2.78 (m, 1 H), 2.86 (dd, J = 11.5, 2.8 Hz, 1 H), 3.50 (td, J = 10.2, 3.9 Hz, 1 H), 3.66 (s, 3 H), 3.70-3.76 (m, 1 H), 4.35 (s, 1 H), 5.16 (dd, J = 10.7, 0.7 Hz, 1 H), 5.18 (dd, J = 17.7, 0.7 Hz, 1 H), 6.33 (dd, J = 17.7, 10.7 Hz, 1 H), 7.37-7.48 (m, 6 H), 7.64-7.69 (m, 4 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 6.8 (t'), 7.1 (q'), 19.4 (s'), 21.6 (t'), 23.3 (t'), 27.0 (q'), 31.3 (t'), 43.9 (d'), 52.3 (d') or (q'), 54.6 (d') or

(q'), 56.7 (d') or (q'), 61.6 (t'), 80.4 (s'), 84.7 (s'), 116.9 (t'), 128.1 (d'), 130.1 (d'), 133.8 (s'), 133.9 (s'), 135.9 (d'), 136.0 (d'), 140.2 (d'), 176.9 (s'), 214.9 (s'); exact mass (electrospray) *m/z* calcd for $C_{36}H_{52}NaO_6Si_2$ (M + Na) 659.3200, found 659.3189.

Compound **170b** had: FTIR (CH_2Cl_2 cast) 3495, 1755 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 0.56-0.63 (m, 6 H), 0.94 (t, *J* = 7.9 Hz, 9 H), 1.02 (s, 9 H), 1.48-1.56 (m, 1 H), 1.80-1.95 (m, 2 H), 2.08-2.28 (m, 3 H), 2.57-2.65 (m, 1 H), 2.73-2.77 (m, 1 H), 3.01-3.07 (m, 2 H), 3.52-3.60 (m, 1 H), 3.63 (s, 3 H), 3.66-3.72 (m, 1 H), 5.20-5.26 (m, 2 H), 6.31 (dd, *J* = 17.7, 10.8 Hz, 1 H), 7.35-7.45 (m, 6 H), 7.61-7.67 (m, 4 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 6.7 (t'), 7.0 (q'), 19.4 (s'), 22.5 (t'), 22.6 (t'), 26.9 (q'), 29.6 (t'), 45.7 (d'), 52.1 (d') or (q'), 57.3 (d') or (q') 57.5 (d') or (q'), 62.2 (t'), 79.6 (s'), 84.2 (s'), 117.8 (t'), 128.0 (d'), 130.0 (d'), 134.08 (s'), 134.12 (s'), 135.9 (d'), 140.3 (d'), 174.9 (s'), 212.5 (s'); exact mass (electrospray) *m/z* calcd for $C_{36}H_{52}NaO_6Si_2$ (M + Na) 659.3200, found 659.3209.

Methyl (1α,3*Z*,4α,7*R)-4-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-2-[7-ethenyl-2-oxo-7-[(triethylsilyl)oxy]bicyclo[2.2.1]hept-3-ylidene]butanoate (171).**

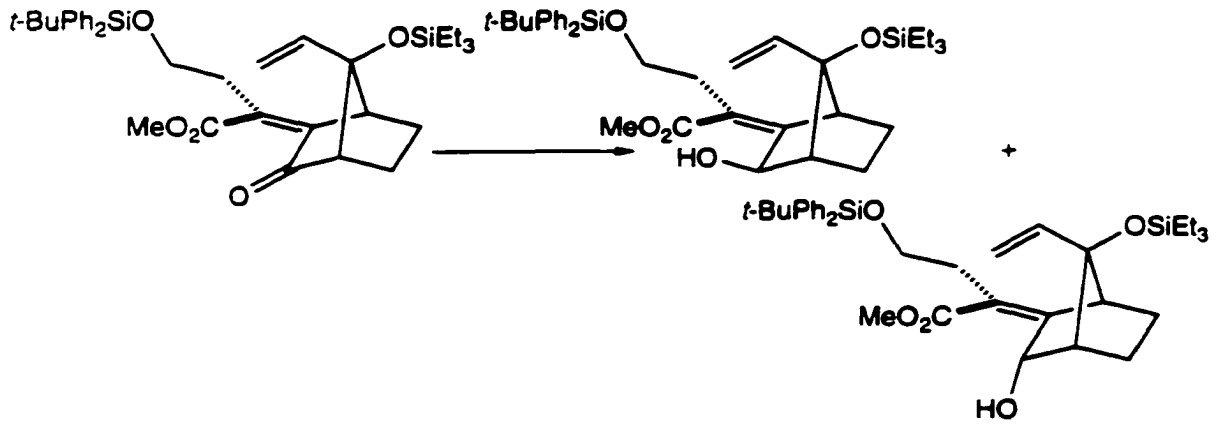


170a **171**

$SOCl_2$ (118 μL, 1.62 mmol) was added dropwise to a stirred solution of **170a** (206 mg, 0.324 mmol) in pyridine (2 mL). Stirring was continued for 3 h. The mixture was cooled (0 °C), water (1 mL) was added dropwise, and the mixture was extracted with Et_2O (100 mL). The organic extract was washed with 5% hydrochloric acid (10 mL), saturated aqueous $NaHCO_3$ (10 mL), water (5 mL) and brine (10 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1.6 x 27 cm), using 5% EtOAc-hexane, gave **171** (180 mg, 90%) as a colorless oil: FTIR (CH_2Cl_2 cast) 1736, 1658 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 0.57-0.65 (m, 6 H), 0.96 (t, J = 7.9 Hz, 9 H), 1.05 (s, 9 H), 1.36-1.52 (m, 2 H), 2.11-2.28 (m, 2 H), 2.45-2.58 (m, 2 H), 2.61 (dd, J = 4.5, 1.3 Hz, 1 H), 2.77-2.78 (m, 1 H), 3.66 (s 3 H), 3.72 (t, J = 7.1 Hz, 2 H), 5.14-5.20 (m, 2 H), 5.93 (dd, J = 17.8, 10.7 Hz, 1 H), 7.38-7.48 (m, 6 H) 7.64-7.69 (m, 4 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 6.7 (t'), 7.1 (q'), 19.4 (s'), 23.2 (t'), 27.00 (q'),

27.04 (t'), 35.3 (t'), 49.3 (d') or (q'), 52.4 (d') or (q'), 57.7 (d') or (q'), 62.0 (t'), 84.5 (s'), 119.1 (t'), 128.1 (d'), 130.2 (d'), 132.6 (s'), 133.9 (s'), 136.0 (d'), 138.3 (d'), 141.8 (s'), 170.0 (s'), 200.8 (s'); exact mass *m/z* calcd for $C_{36}H_{50}O_5Si_2$ 618.3197, found 618.3190.

Methyl (1α,2α,3*Z*,4α,7*S)-4-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-2-[7-ethenyl-2-hydroxy-7-[(triethylsilyl)oxy]bicyclo[2.2.1]hept-3-ylidene]butanoate (172a) and Methyl (1α,2β,3*Z*,4α,7*S**)-4-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-2-[7-ethenyl-2-hydroxy-7-[(triethylsilyl)oxy]bicyclo[2.2.1]hept-3-ylidene]butanoate (172b).**



171 **172a** **172b**

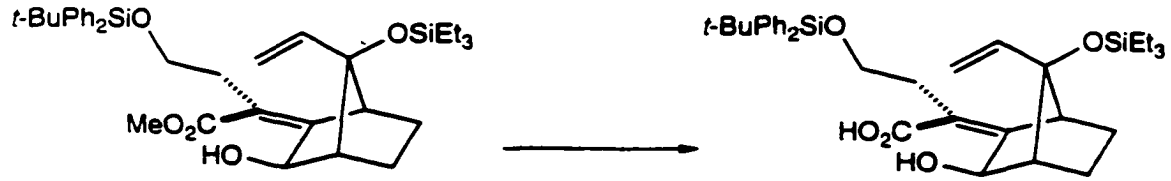
$NaBH_4$ (14.8 mg, 0.391 mmol) was added in three portions to a stirred and cooled (0 °C) mixture of **171** (80.0 mg, 0.130 mmol) and $CeCl_3 \cdot 7H_2O$ (72.8 mg, 0.195 mmol) in dry MeOH (2 mL). Stirring was continued for 0.5 h, the cooling bath was

removed, and stirring was continued for 1.5 h. The mixture was diluted with EtOAc (5 mL) and water (1 mL), and extracted with EtOAc (30 mL). The organic extract was washed with brine (5 mL), dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (1.6 x 28 cm), using 5% EtOAc-hexane, gave **172b** (18 mg, 22%) and **172a** (52 mg, 65%) as colorless oils. Compound **172b** had: FTIR (CH_2Cl_2 cast) 3472, 1694, 1634 cm^{-1}; ^1H NMR (CD_2Cl_2, 360 MHz) δ 0.56-0.64 (m, 6 H), 0.95 (t, *J* = 7.8 Hz, 9 H), 1.05 (s, 9 H), 1.19-1.28 (m, 1 H), 1.76-1.86 (m, 1 H), 1.95-2.03 (m, 1 H), 2.06-2.16 (m, 1 H), 2.28 (t, *J* = 3.9 Hz, 1 H), 2.56-2.72 (m, 3 H), 3.63-3.71 [m, including s (3 H) at δ 3.64, 5 H in all], 4.50 (br s, 1 H), 4.92 (d, *J* = 2.4 Hz, 1 H), 5.07 (dd, *J* = 10.8, 1.2 Hz, 1 H), 5.09 (dd, *J* = 17.7, 1.2 Hz, 1 H), 5.89 (dd, *J* = 17.7, 10.8 Hz, 1 H), 7.37-7.47 (m, 6 H), 7.65-7.71 (m, 4 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 6.8 (t'), 7.1 (q'), 19.3 (t'), 19.4 (s'), 27.0 (q'), 27.7 (t'), 33.5 (t'), 49.5 (d') or (q'), 52.2 (d') or (q'), 52.6 (d') or (q'), 63.6 (t'), 70.8 (d'), 84.3 (s'), 118.2 (t'), 120.5 (s'), 128.0 (d'), 130.0 (d'), 134.2 (s'), 135.9 (d'), 138.2 (d'), 167.7 (s'), 169.6 (s'); exact mass (electrospray) *m/z* calcd for $C_{36}H_{52}NaO_5Si_2$ (M + Na) 643.3251, found 643.3255.

Compound **172a** had: FTIR (CH_2Cl_2 cast) 3489, 1696, 1637 cm^{-1}; ^1H NMR (CD_2Cl_2, 360 MHz) δ 0.58-0.65 (m, 6 H), 0.96 (t, *J* = 7.9 Hz, 9 H), 1.00-1.18 [m, including s (9 H) at δ 1.06, 11 H in all], 1.96-2.13 (m, 3 H), 2.58-2.72 (m, 2 H), 2.75-2.79 (m, 1 H), 3.63-3.75 [m, including s (3 H) at δ 3.65, 5 H

in all], 4.24 (d, J = 3.0 Hz, 1 H), 4.28 (d, J = 3.0 Hz, 1 H), 5.01 (dd, J = 10.8, 1.4 Hz, 1 H), 5.07 (dd, J = 17.6, 1.4 Hz, 1 H), 6.30 (dd, J = 17.6, 10.8 Hz, 1 H), 7.37-7.48 (m, 6 H), 7.67-7.71 (m, 4 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 6.9 (t'), 7.2 (q'), 19.4 (s'), 25.0 (t'), 27.0 (q'), 27.2 (t'), 33.7 (t'), 50.8 (d') or (q'), 51.8 (d') or (q'), 52.2 (d') or (q'), 63.3 (t'), 75.8 (d'), 86.9 (s'), 116.3 (t'), 121.5 (s'), 128.1 (d'), 130.1 (d'), 134.18 (s'), 134.22 (s'), 135.9 (d'), 140.7 (d'), 167.2 (s'), 169.4 (s'); exact mass (electrospray) *m/z* calcd for $C_{36}H_{52}NaO_5Si_2$ (M + Na) 643.3251, found 643.3252.

(1α,1α,3*Z*,4α,7*SR)-4-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-2-[7-ethenyl-2-hydroxy-7-[(triethylsilyl)oxy]bicyclo[2.2.1]hept-3-ylidene]butanoic acid (173).**

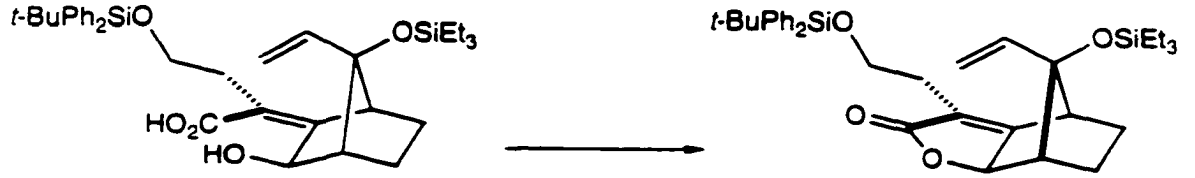


172a **173**

n-PrSLi[44] (2.5 M in HMPA, 226 μL, 0.565 mmol) was added dropwise to a stirred solution of **172a** (50.0 mg, 0.081 mmol) in degassed (by passage of a stream of Ar for 0.5 H) HMPA (3 mL). Stirring was continued for 2 h (TLC indicated complete reaction), the mixture was poured into ice water (50 mL)

containing 10% hydrochloric acid (2 mL), and extracted the with Et_2O (4 x 30 mL). The combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (1.6 x 28 cm), using 40% EtOAc-hexane, gave **173** (39 mg, 81%) as a colorless oil: FTIR (CH_2Cl_2 cast) 2750-3400 (br), 1684, 1637 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 0.60 (q, J = 7.9 Hz, 6 H), 0.94 (t, J = 7.9 Hz, 9 H), 0.98-1.22 [m, including s (9 H) at δ 1.06, 11 H in all], 1.88-2.09 (m, 2 H), 2.14-2.18 (m, 1 H), 2.58-2.72 (m, 2 H), 2.78 (d, J = 2.3 Hz, 1 H), 3.69-3.78 (m, 2 H), 4.26 (s, 1 H), 5.04-5.14 (m, 2 H), 6.29 (dd, J = 17.7, 10.8 Hz, 1 H), 7.35-7.47 (m, 6 H), 7.63-7.69 (m, 4 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 6.8 (t'), 7.1 (q'), 19.3 (s'), 24.8 (t'), 27.0 (q'), 27.1 (t'), 33.9 (t'), 50.4 (d'), 51.8 (d'), 63.7 (t'), 75.6 (d'), 86.8 (s'), 117.3 (t'), 123.2 (s'), 128.14 (d'), 130.2 (d'), 133.4 (s'), 133.5 (s'), 135.9 (d'), 140.6 (d'), 165.8 (s'), 171.1 (s'); exact mass (electrospray) m/z calcd for $C_{35}H_{50}NaO_5Si_2$ (M + Na) 629.3095, found 629.3105.

(4α,7α,7aβ,8R*)-3-[2-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]-8-ethenyl-5,6,7,7a-tetrahydro-4,7-methano-8-[(triethylsilyl)oxy]benzofuran-2(4H)-one (174).

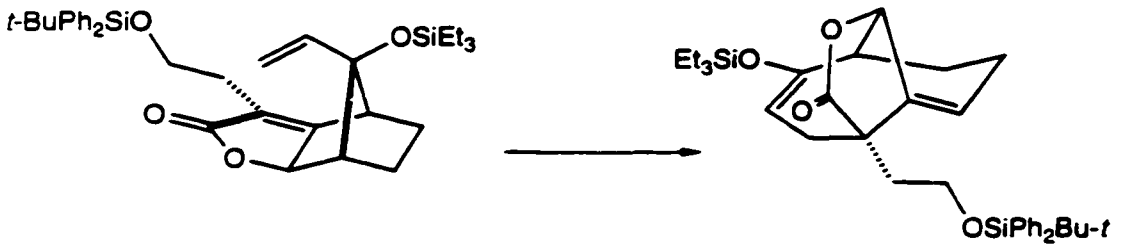


173 **174**

A solution of **173** (21.0 mg, 0.035 mmol) and Et_3N (39 μL, 0.277 mmol) in CH_2Cl_2 (0.4 mL, plus 2 x 0.2 mL as a rinse), was added dropwise to a stirred solution of 2-chloro-1-methylpyridinium iodide (36.5 mg (97%), 0.139 mmol) in CH_2Cl_2 (1.5 mL). The mixture was refluxed for 36 h, cooled to room temperature, diluted with Et_2O (5 mL), and filtered through a pad (1 cm x 2 mm) of silica gel with Et_2O. Evaporation of the filtrate, and flash chromatography of the residue over silica gel (1.3 x 24 cm), using 5% EtOAc-hexane, gave **174** (16 mg, 80%) as a colorless oil: FTIR (CH_2Cl_2 cast) 1783, 1759 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 0.56 (q, J = 7.9 Hz, 6 H), 0.92 (t, J = 7.9 Hz, 9 H), 1.05 (s, 9 H), 1.38-1.45 (m, 1 H), 1.61-1.69 (m, 1 H), 2.05-2.15 (m, 1 H), 2.23-2.52 (m, 3 H), 2.71 (d, J = 4.5 Hz, 1 H), 2.85 (d, J = 4.5 Hz, 1 H), 3.73-3.86 (m, 2 H), 4.48 (s, 1 H), 5.05 (dd, J = 10.8, 0.9 Hz, 1 H), 5.12 (dd, J = 17.7, 0.9 Hz, 1 H), 5.73 (dd, J = 17.7, 10.8 Hz, 1 H), 7.36-7.46 (m, 6 H), 7.62-7.68 (m, 4 H); ^{13}C NMR

(CD_2Cl_2, 100.6 MHz) δ 6.6 (t'), 7.0 (q'), 19.4 (s'), 22.9 (t'), 27.0 (q'), 28.2 (t'), 28.8 (t'), 46.9 (d'), 51.8 (d'), 62.2 (t'), 86.5 (d'), 89.4 (s'), 118.9 (t'), 124.4 (s'), 128.0 (d'), 130.0 (d'), 134.1 (s'), 135.9 (d'), 137.2 (d'), 170.5 (s'), 174.4 (s'); exact mass (electrospray) calcd for $C_{35}H_{48}NaO_4Si_2$ (M + Na) 611.2989, found 611.2980.

(3*R,7*S**,8*S**)-3,7,8-[3]Buten[1]yl[4]ylidene-3-[2-[[(1,1-dimethylethyl)diphenylsilyl]oxy]ethyl]-3,4,7,8-tetrahydro-6-[(triethylsilyl)oxy]-2*H*-oxocin-2-one (175).**



174 **175**

A solution of **174** (12.7 mg, 0.022 mmol) in degassed (by bubbling Ar for 0.5 h) 1,2-dichlorobenzene (7 mL) was refluxed for 20 min. The solution was cooled and evaporated, and the residue was kept under oil-pump vacuum for 4 h, to gave **175** (13 mg, 100%) as a pale yellow oil: FTIR (CH_2Cl_2 cast) 1784 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 0.60-0.68 (m, 6 H), 0.95 (t, J = 7.9 Hz 9 H), 0.99 (s, 9 H), 1.55-1.63 (m, 1 H), 1.82-1.89 (m, 1 H), 1.92-2.13 (m, 2 H), 2.15-2.22 (m, 1 H), 2.29-2.41 (m, 3 H), 2.91-2.98 (m, 1 H), 3.61-3.68 (m, 1

H), 3.70-3.78 (m, 1 H), 4.53 (q, t = 2.9 Hz, 1 H), 4.65-4.70 (m, 1 H), 5.60-5.65 (m, 1 H), 7.34-7.45 (m, 6 H), 7.60-7.68 (m, 4 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 5.4 (t'), 6.8 (q'), 19.2 (s'), 21.8 (t'), 23.6 (t'), 26.7 (q'), 35.3 (t'), 44.2 (t'), 45.6 (d'), 49.0 (s'), 60.6 (t'), 78.6 (d'), 102.5 (d'), 117.7 (d'), 128.0 (d'), 129.9 (d'), 130.0 (d'), 133.8 (s'), 134.0 (s'), 135.9 (d'), 136.0 (d'), 142.1 (s'), 151.7 (s'), 180.8 (s'); exact mass (electrospray) calcd for $C_{35}H_{48}NaO_4Si_2$ (M + Na) 611.2989, found 611.2987.

IV. References and Footnotes

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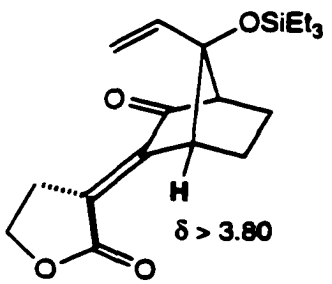

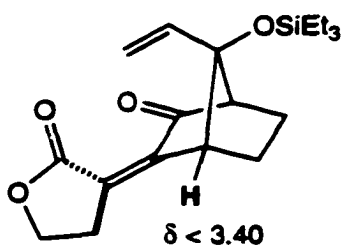

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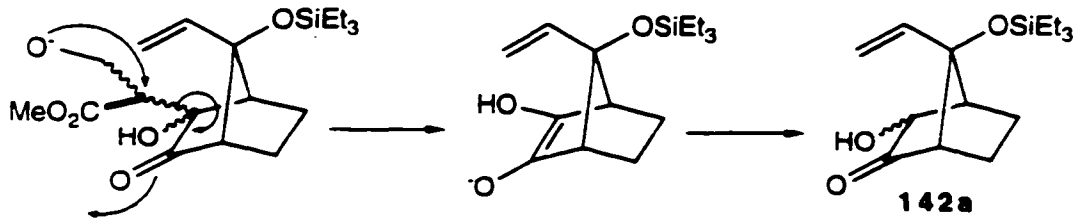

142a

Alternaively, residual excess of LDA may reduce some of the diketone.

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