Quebrachitol: A Versatile Building Block in the Construction of Naturally Occurring Bioactive Materials

James J. Kiddle

Department of Chemistry, The University of North Carolina at Wilmington, 601 South College Road, Wilmington, North Carolina 28403-3297

Received March 22, 1995 (Revised Manuscript Received June 12, 1995)

Contents

James J. Kiddle was born in Illinois in 1963. He received his B.A. in chemistry and biology from Drake University in Iowa. His M.S. in chemistry was completed at the University of Illinois at Chicago under the direction of Robert M. Moriarty. He received his doctorate in chemistry from Loyola University of Chicago in 1993 under the supervision of James H. Babler and Charles M. Thompson. His dissertation dealt with the novel syntheses of organophosphorus compounds and the total synthesis of indolizidine alkaloids. From 1993 to 1994 he held a postdoctoral position under the auspices of Alan P. Kozikowski in the area of medicinal chemistry. He has also held a postdoctoral research position with John R. Cashman at Seattle Biomedical Research Institute, working in the field of biocatalysis and catalytic antibodies. At present he is an assistant professor in the department of chemistry at the University of North Carolina at Wilmington. His research interests are in the areas of organophosphorus, medicinal, and bioorganic chemistry.

I. Introduction

Advances in the elucidation of biological processes has generated a demand for the efficacious synthesis of biologically active compounds in enantiomerically pure form. Isolation from natural sources usually does not provide sufficient amounts of material to complete biological studies. In addition, structural modification of a natural substrate often provides valuable information about a system not afforded by the parent molecule. Because of these needs, a major focus of synthetic organic chemistry has been the enantiomeric synthesis of molecules and their analogues for the study of the expanding number of biological pathways that continue to be investigated. Due to the broad number of biological systems and the diverse molecular structure of their components, a number of strategies have been developed for the asymmetric synthesis of biologically active materials.

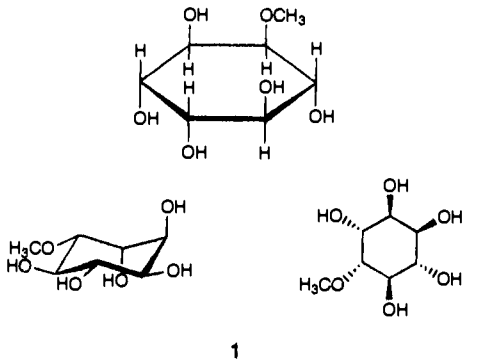
Traditionally two approaches have been paramount in providing access to asymmetric centers in the construction of biological molecules. Stereoselective and stereospecific reactions have been extensively employed to establish asymmetric centers in compounds of interest via a continually expanding arsenal of synthetic methodologies. A second tactic has been to employ starting materials with established asymmetric centers and elaborate these structures to the target compound. Molecules used for these purposes are said to come from the "chiral pool".

The use of molecules from the "chiral pool" has greatly extended the synthesis of biologically interesting compounds.[1] Amino acids and carbohydrates represent the two most frequently encountered chiral building blocks in asymmetric organic synthesis. These classes of starting materials offer the advantage of being available in pure enantiomeric form at relatively low cost. Due to the vast number of isolated and synthetic biologically active compounds, as well as their structural diversity, the continued identification of new members of the "chiral pool" is warranted.

L-Quebrachitol (1-L-(−)-2-*O*-methyl-*chiro*-inositol, **1**; Figure 1), an optically active cyclitol has only recently emerged as a new chiral building block, even though it has been known in the literature for over a century.[2] L-Quebrachitol offers an alternative molecular architecture for the construction of polyhydroxylated natural products. The structure of **1** allows chemical transformations to be effected via established methods in carbohydrate chemistry, like those for furanoses and pyranoses currently utilized in asymmetric synthesis. The distinct advantage offered by **1** is that there are no synthetic limitations imposed by the presence of an hemiacetal/ketal functionality. L-Quebrachitol has currently been used as a starting material for the synthesis of a wide variety of bioactive materials, most notably the inositols.[3]

This review covers the literature through December of 1994 and the scope is an overview of the total syntheses where L-quebrachitol was converted to a

0009-2665/95/0795-2189$15.50/0



1

Figure 1. Representations of L-quebrachitol.

naturally occurring bioactive material. The focus will be to present a unique perspective of the chemistry of L-quebrachitol in asymmetric synthesis, which may be underestimated due to the ample literature coverage of the use of L-quebrachitol in the synthesis of inositol analogues. Because of this, construction of analogues of the inositols, which has been extensively reviewed, has been omitted.[4] In addition, material representing protection/deprotection and functional group manipulations, which also has been previously reviewed, is excluded.[5] Also, the use of L-quebrachitol as a chiral auxiliary[6] has been omitted, this material will only be included if pertinent to a synthetic strategy.

II. Isolation of L-Quebrachitol

L-Quebrachitol was first isolated in 1889 from the quebracho bark of *Aspidosperma quebracho* by Tanret.[2] L-Quebrachitol occurs naturally in 11 families of dicotyledons and because it is seldom found with its isomer D-pinitol (one example where they occur together is in mistletoe) in the same plant family, isolation from a biological source provides an excellent means of obtaining pure material.[7]

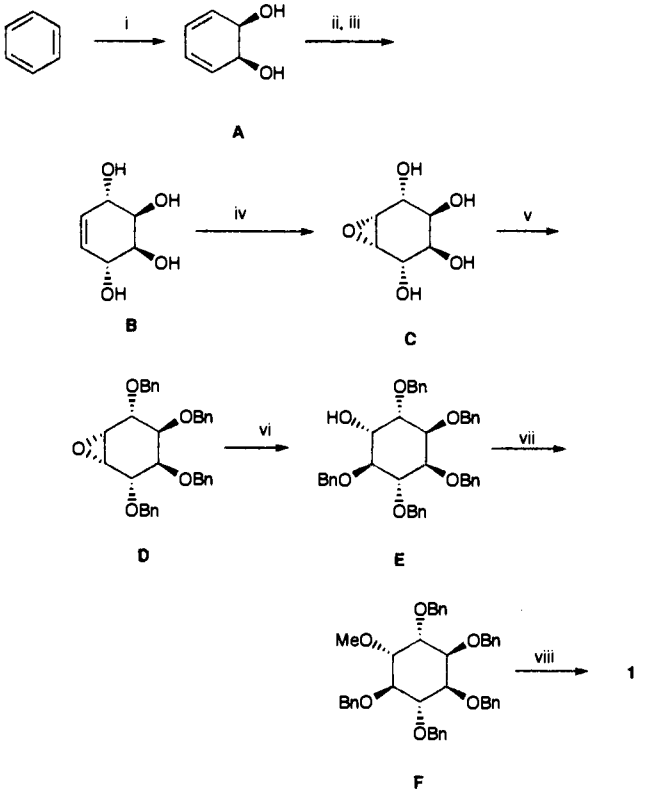
The use of L-quebrachitol as a chiral building block is further augmented by its availability in high concentrations from one particular plant species. L-Quebrachitol is isolated as a byproduct of the rubber industry. The rubber tree *Heava brasiliensis* provides L-quebrachitol, which is reported to constitute 1.5% of the aqueous phase (serum) of the latex.[5] The first reported practical method of laboratory isolation of L-quebrachitol was by van Alphen in 1951,[8] although prior to the publication of the procedure, a number of companies held patents on methods for extracting L-quebrachitol. It is surprising that such an accessible chiral building block would not be used to synthesize bioactive materials for another three decades.

III. Synthesis of L-Quebrachitol

Because of the accessibility of L-quebrachitol there has been only one reported total synthesis of this cyclitol. Carless and co-workers[9] used the *cis*-cyclohexa-3,5-diene-1,2-diol (**A**), obtained from microbial oxidation of benzene by *Pseudomonas putida*, as a pivotal intermediate for the synthesis of (±)-quebrachitol, as well as four inositol isomers (Scheme 1).

The epoxide **C** was obtained by singlet oxygen reaction of the cyclohexadiene **A** followed by peracid

Scheme 1[a]



[a] Reagents: (i) *Pseudomonas putida*; (ii) $^1O_2$, −70 °C, (iii) thiourea, MeOH; (iv) *m*-CPBA, CH_2Cl_2/MeOH (3:1 v/v); (v) NaH, excess BnBr, DMF; (vi) excess BnOH, NaH, DMF, 130 °C; (vii) NaH, MeI; (viii) Pd/C, H_2, EtOH/AcOH (19:1 v/v).

epoxidation (Scheme 1). Epoxide **C** was then fully benzylated, and the symmetrical epoxide was opened with benzyl alcohol to provide compound **E**. Subsequent methyl ether formation and hydrogenation of the benzyl groups provided the (±)-quebrachitol.

Although it is elegant and extends the scope of microbial oxidations of benzene, the synthesis has little practical use as the optically active L-quebrachitol can be easily obtained in enantiomeric form by isolation from a natural source. This is most likely why this is the only synthesis of L-quebrachitol that has appeared in the literature to date.

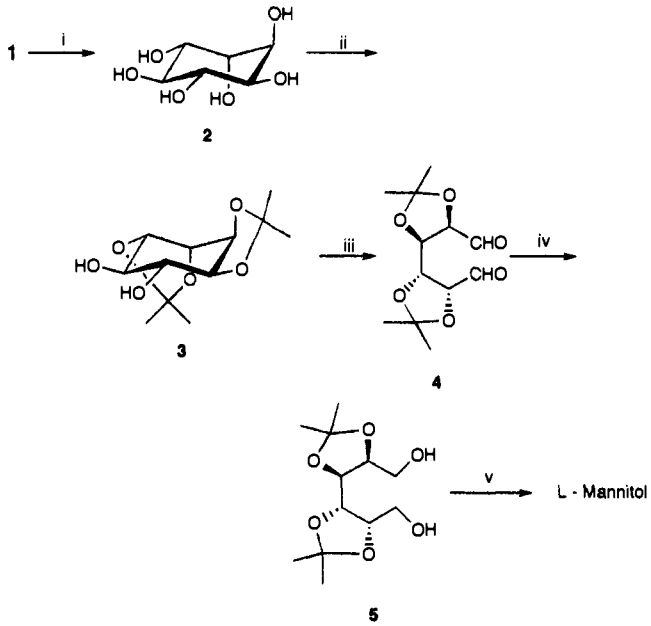
IV. Asymmetric Syntheses Utilizing L-Quebrachitol

Ogawa has extensively studied the synthetic utility of L-quebrachitol in the construction of biofunctional molecules. The work has focused on the chemical transformation of L-quebrachitol to natural products other than the inositols. Along with work by Ozaki, the conversion of L-quebrachitol to a diverse number of bioactive materials has been realized.

A. Carbohydrates

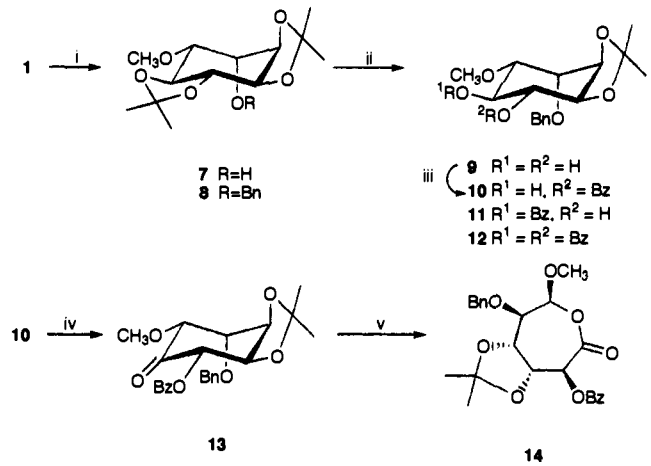
The first reported synthesis of a natural product from L-quebrachitol was of L-mannitol by Angyal and Hoskinson in 1963.[10] The short synthesis of L-mannitol (Scheme 2) provided a practical method for obtaining this sugar which had not been found in nature at that time.

Scheme 2[a]



[a] Reagents: (i) HI; (ii) $ZnCl_2$, acetone; (iii) $NaIO_4$; (iv) $NaBH_4$; (v) HCl.

Scheme 3[a]



[a] Reagents: (i) 2,2-Dimethoxypropane, *p*-TsOH, DMF; (ii) *p*-TsOH, MeOH; (iii) pyridine, BzCl; (iv) PCC, molecular sieves, CH_2Cl_2; (v) *m*-CPBA, $KHCO_3$.

The methyl ether of L-quebrachitol was cleaved using hydroiodic acid to L-*chiro*-inositol which was then protected as the diacetonide to furnish the *trans*-diol **3**. Sodium periodate oxidative opening of the diacetonide, sodium borohydride reduction, and hydrolysis of the diacetonide provided L-mannitol in good yield and in five steps from L-quebrachitol.

Ogawa and Chida have reported the synthesis of a number of D and L sugars from L-quebrachitol. The synthesis of D- and L-galactose has been accomplished from a common intermediate 7-membered acetal-lactone which was obtained by regioselective Baeyer–Villiger oxidation of inososе.[11]

Inosose (**13**) was prepared from L-quebrachitol in four steps by traditional carbohydrate protection methodology (Scheme 3). The crucial conversion of **13** to the pivotal intermediate **14** was proposed to occur in the desired regioselective manner because the C-2 position possessed an electron-rich methoxy group compared to the electron-withdrawing benzoyloxy group at C-6. Oxidation of **13** with *m*-CPBA in the presence of potassium hydrogen carbonate proceeded to give the regioselectively expected product of Baeyer–Villiger oxidation (**14**).

The synthesis of methyl D-galactoside **18b** was completed by cyclization of intermediate **14** to the anomeric isomers **15a** and **15b** (Scheme 4), which were reduced using lithium aluminum hydride (LAH) to give the anomeric pair **16a** and **16b**, respectively, which could be separated on silica gel. The desired product **18b** was obtained by deprotection of **16b** and acetylation of the β-anomer, followed by chromatographic separation. L-Galactose was obtained by sodium borohydride reduction of hemiacetal lactone **14** to give L-galacturonate **19**. Acid treatment of **19** and diisobutylaluminum hydride (DiBAL-H) reduction gave the α- and β-anomers (**21a** and **b**) of the methyl L-galactoside as an inseparable mixture. Removal of the protecting groups, followed by careful chromatographic separation and acetylation of the product provided the desired methyl L-galactoside **22b**. The ^1H NMR spectrum of **18b** was superimposable on that of **22b** confirming its structure. The results of this synthetic strategy showed that L-quebrachitol could be transformed asymmetrically to molecules other than cyclitols.

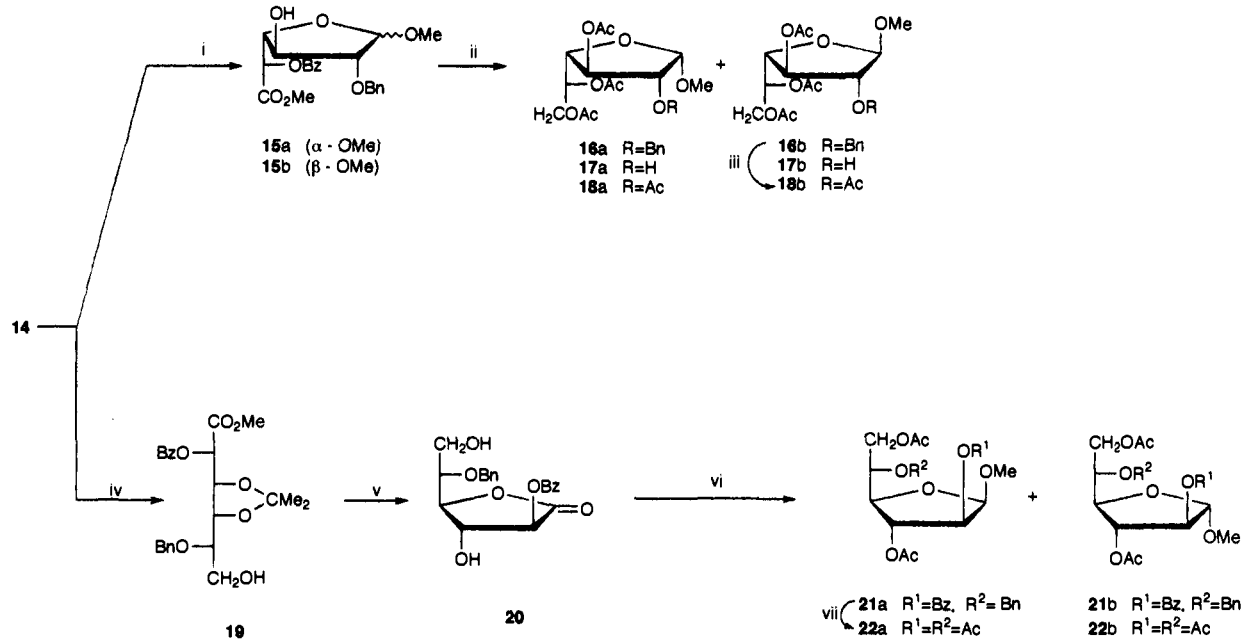
Ogawa and Chida have also completed the facile synthesis of several other L sugars using L-quebrachitol as a chiral building block. The synthesis of L-mannofuranose, L-talofuranose, and a methyl L-guluronate derivative have been reported.[12] The starting material for the synthesis of the three sugars was the known mono- and diacetonide of L-quebrachitol **23** and **7**, respectively (Scheme 5).

Sodium periodate oxidation of the monoacetonide **23** followed by sodium borohydride reduction gave the protected 5-*O*-methyl-L-mannofuranose solely as the α-anomer. Acid hydrolysis and acetylation gave a mixture of anomers (**26a** and **b**), which were separated by column chromatography to give the α-anomer (**26a**) as the major product. The product showed satisfactory NMR data and the structure was further confirmed by conversion of **26a** to the known L-mannopyranoside **28**, which demonstrated identical ^1H NMR spectral properties and an equal but opposite specific rotation to an authentic sample of D-mannopyranoside (Scheme 6).

On the other hand, oxidation of the diacetonide **7** with RuO_4 affords the ketone **29**. Reduction with sodium borohydride provided the inverted alcohol **30**. Selective deprotection of the *trans*-isopropylidene using *p*-toluenesulfonic acid (*p*-TsOH) gave the triol **31** suitably protected for the conversion to the furanose. Sodium periodate oxidative cyclohexane ring opening, reduction, acidic hydrolysis, and acetylation gave the L-talofuranose as a 9:1 mixture of α- and β-anomers (**34a** and **b**, respectively). Subsequent chromatographic separation furnished the β-L-talofuranose in 24% yield (Scheme 7).

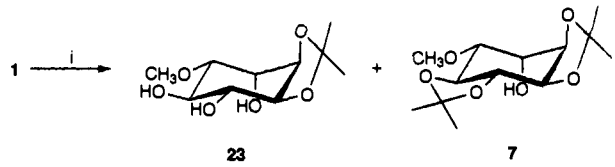
Transformation of the diacetonide **7** to the guluronate derivative **38** was accomplished by first converting the C-3 hydroxy to the mesylate **35**, followed by treatment of **35** with DBU to afford the vinyl ether **36** properly set up for oxidative cyclohexane ring

Scheme 4[a]



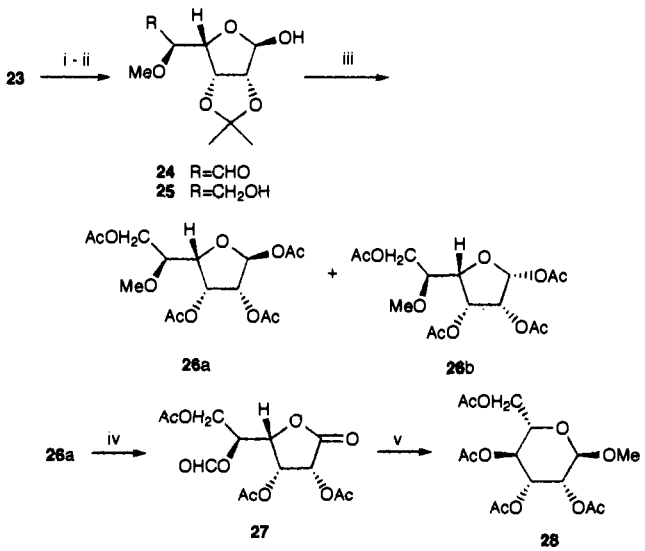
[a] Reagents: (i) *p*-TsOH, $(CH_3O)_3CH$, MeOH; (ii) LAH, THF; (iii) a, $Pd(OH)_2/C$, H_2, EtOH; b, Ac_2O, pyridine; (iv) $NaBH_4$, MeOH; (v) *p*-TsOH, MeOH; (vi) a, DIBAL-H, THF; b, *p*-TsOH, $(CH_3O)_3CH$, MeOH; (vii) a, $Pd(OH)_2/C$, H_2, MeOH; b, CH_3ONa, MeOH; c, Ac_2O, pyridine.

Scheme 5[a]



[a] Reagents: (i) 2,2-Dimethoxypropane, *p*-TsOH, DMF.

Scheme 6[a]



[a] Reagents: (i) $NaIO_4$, acetone/H_2O; (ii) $NaBH_4$; (iii) a, 1 M H_2SO_4, THF; b, Ac_2O, pyridine; (iv) CrO_3, HOAc; (v) a, DIBAL-H, THF; b, HCl/MeOH, reflux.

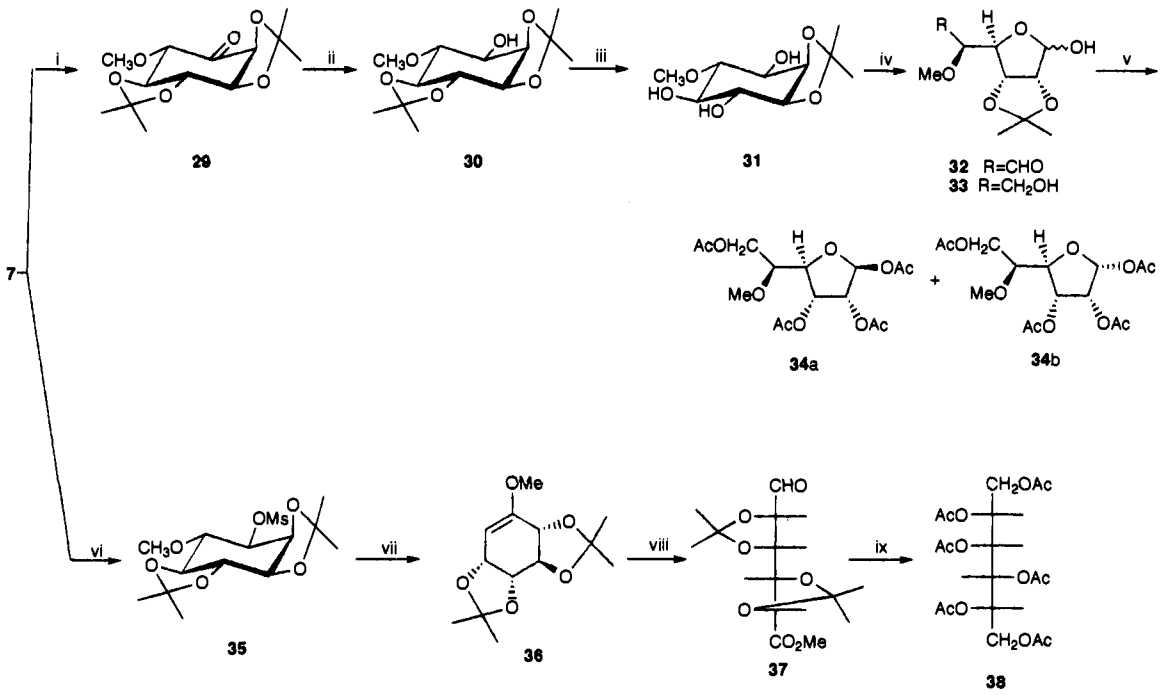
opening. Ozonolysis of **36** gave the rare open-chain aldehydo uronic acid derivative **37**. Reduction of **37** provides the D-glucitol derivative **38** in good yield (Scheme 7).

The construction of pseudo-α-D-galactopyranose and pseudo-β-D-mannopyranose has also been accomplished by Paulsen and co-workers[13] using L-quebrachitol as a chiral starting material.

The pseudo-α-anomer was synthesized (Scheme 8) by converting the known L-*chiro*-inositol to its triisopropylidene derivative **39** with 2,2-dimethoxypropane and *p*-toluenesulfonic acid. Selective deprotection of the *trans*-isopropylidene, benzylation, and separation of the benzylated regioisomers provides intermediate **41**. Swern oxidation (**42**) and subsequent Wittig reaction of the ketone gives the *exo*-methylene compound **43**. Hydroboration of the alkene under anti-Markovnikov conditions gave the primary alcohol **44**. Intermediate **44** could be converted to the acetate **45** to confirm the structure. Protection of the primary alcohol of **44** as the MEM ether, hydrogenation of the benzyl ether protecting group, and dithiocarbonate formation provided intermediate **48** appropriately set up for deoxygenation. Reaction of **48** with tributyltin hydride yielded the deoxy compound **49**, which can be deprotected to afford the desired pseudo-α-D-galactopyranose **51**.

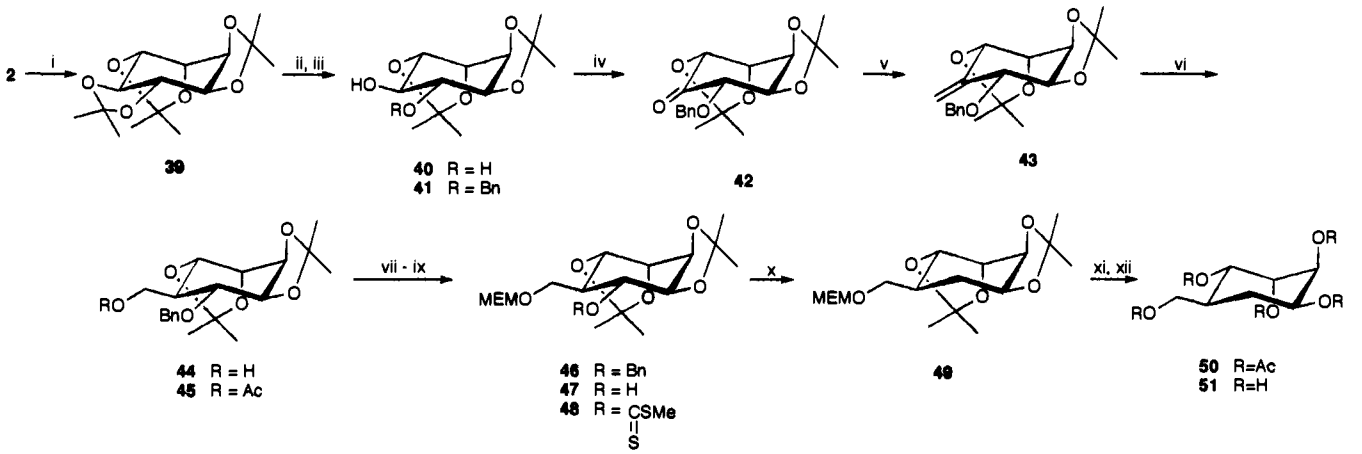
The synthesis of the pseudo-β-D-mannopyranose was accomplished from intermediate **41** by first, converting the alcohol to the iodide **52** (Scheme 9). The iodide is eliminated with LAH to yield two olefin products (only the desired product is shown). The product not shown results from elimination of the benzyl ether while product **53** results from opening of the isopropylidene group and ensuing elimination. No mechanistic explanation is offered for the formation of **53**, but spectroscopic evidence of the acetate derivative was in support of the structure described. Oxidation of **53** and conjugate addition of the formyl anion equivalent, 1,3-dithiane-2-carboxylate furnishes intermediate **55**. Subsequent reduction of the ketone **55** with LAH gave the secondary alcohol **56**. Conversion of the fully protected pseudo-β-D-mannopyranose to the final product was accomplished via the intermediate aldehyde **57**. Sequential deprotection of the formyl anion equivalent, sodium borohydride reduction of the aldehyde, and acetylation to form **58**, followed by deprotection of the remaining

Scheme 7[a]



[a] Reagents: (i) RuO_4; (ii) $NaBH_4$, MeOH; (iii) *p*-TsOH, MeOH; (iv) a, $NaIO_4$, acetone/water; b, $NaBH_4$, MeOH; (v) a, 1 M H_2SO_4, THF; b, Ac_2O, pyridine; (vi) pyridine, MsCl; (vii) DBU, toluene, reflux; (viii) O_3, CH_2Cl_2, $(CH_3)_2S$; (ix) a, LAH, Et_2O; b, *p*-TsOH, MeOH; c, Ac_2O, pyridine.

Scheme 8[a]



[a] Reagents: (i) 2,2-DMP, *p*-TsOH, DMF; (ii) HCl/MeOH; (iii) $(Et)_4NI$, BnBr, 20% NaOH, CH_2Cl_2; (iv) oxalyl chloride, CH_2Cl_2, DMSO; (v) $Ph_3PCH_3{}^+Br^-$, BuLi, THF; (vi) BH_3THF, methyl-2-butene, H_2O_2, THF; (vii) MEMCl, $(i\text{-}Pr)_2NEt$, CH_2Cl_2; (viii) 10% Pd/C, MeOH; (ix) imidazole, NaH, CS_2, MeI, THF; (x) *n*-Bu_3SnH, toluene, reflux; (xi) a, HCl/MeOH; b, NaOMe, Ac_2O, pyridine; (xii) NaOMe, MeOH.

hydroxy groups gave the pseudo-β-D-mannopyranose **59**.

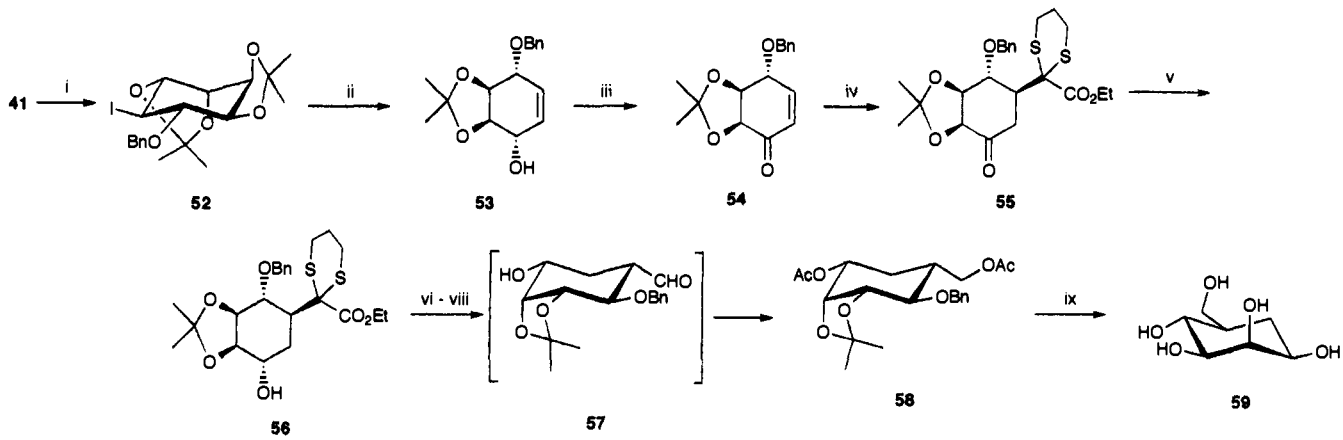
The synthesis of the carbohydrates by Ogawa and Paulsen shows the diverse chiral molecules which can be easily constructed from L-quebrachitol. The products then could serve as useful vehicles for the synthesis of many other natural products.

B. Antibiotics and Enzyme Inhibitors

Synthetic strategies for the preparation of a number of antibiotics and enzyme inhibitors in optically active form have also been achieved from L-quebrachitol. Paulsen and Heiker have constructed the aminocyclitol valienamine from L-quebrachitol.[14,15] Valienamine is a structural component of the aminoglycoside antibiotics of the validamycin class. In addition, it is a key structural feature of the antidiabetic drug acarbose.

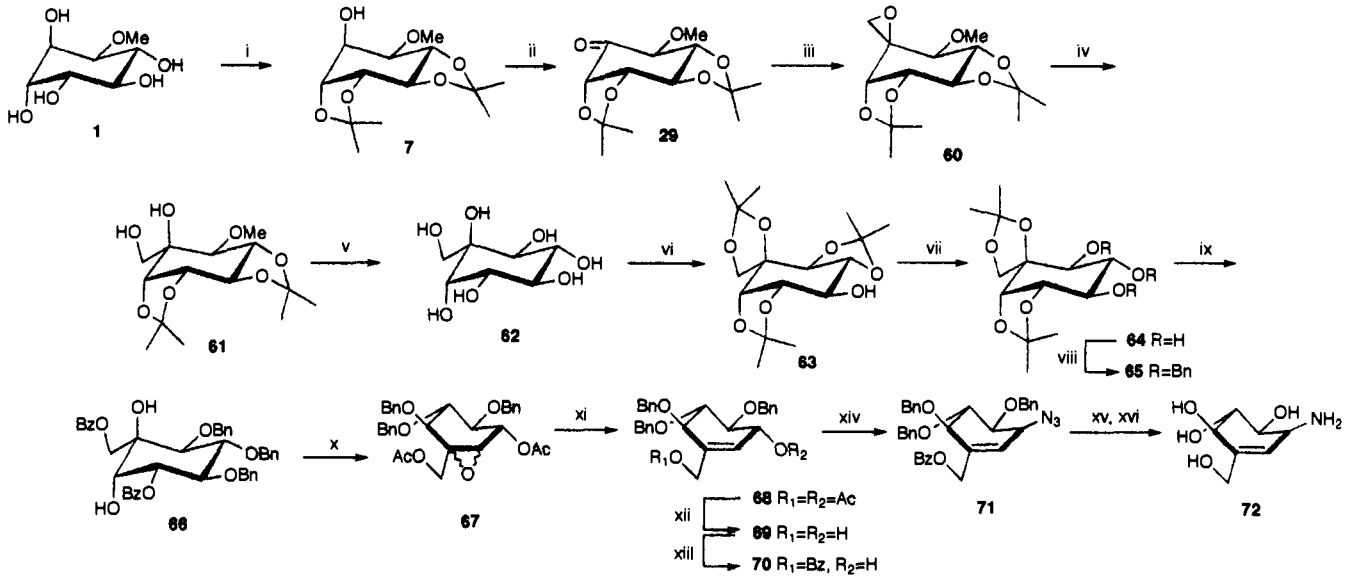
The initial synthetic sequence follows that previously described in this review for the fabrication of the protected ketone **29** (Scheme 10). The epoxide **60** was stereoselectively formed by reaction of the ketone **29** with dimethyloxosulfonium methylide, followed by hydrolysis with potassium hydroxide to yield the diol **61**. Deprotection with boron tribromide gave the polyhydroxyl compound **62**. Subsequent protection of **62** with 2,2-dimethoxypropane gave the secondary alcohol **63**. Selective deprotection of the more reactive *trans*-isopropylidene followed by benzyl ether protection of the resulting triol affords the fully protected intermediate **65**. Acid hydrolysis of the remaining isopropylidene groups and benzoyl ester

Scheme 9[a]



[a] Reagents: (i) Ph_3P, imidazole, I_2, toluene; (ii) LAH; (iii) Swern oxidation; (iv) LDA, ethyl 1,3-dithiane-2-carboxylate, THF; (v) LAH, THF; (vi) HgO, $HgCl_2$, CH_3CN; (vii) $NaBH_4$, CH_2Cl_2; (viii) a, $NaOCH_3$, MeOH; b, $NaIO_4$, cat. Bn_4NBr; c, $NaBH_4$, CH_2Cl_2; d, Ac_2O; (ix) a, cat. TFA, 10% Pd/C; b, pyridine.

Scheme 10[a]



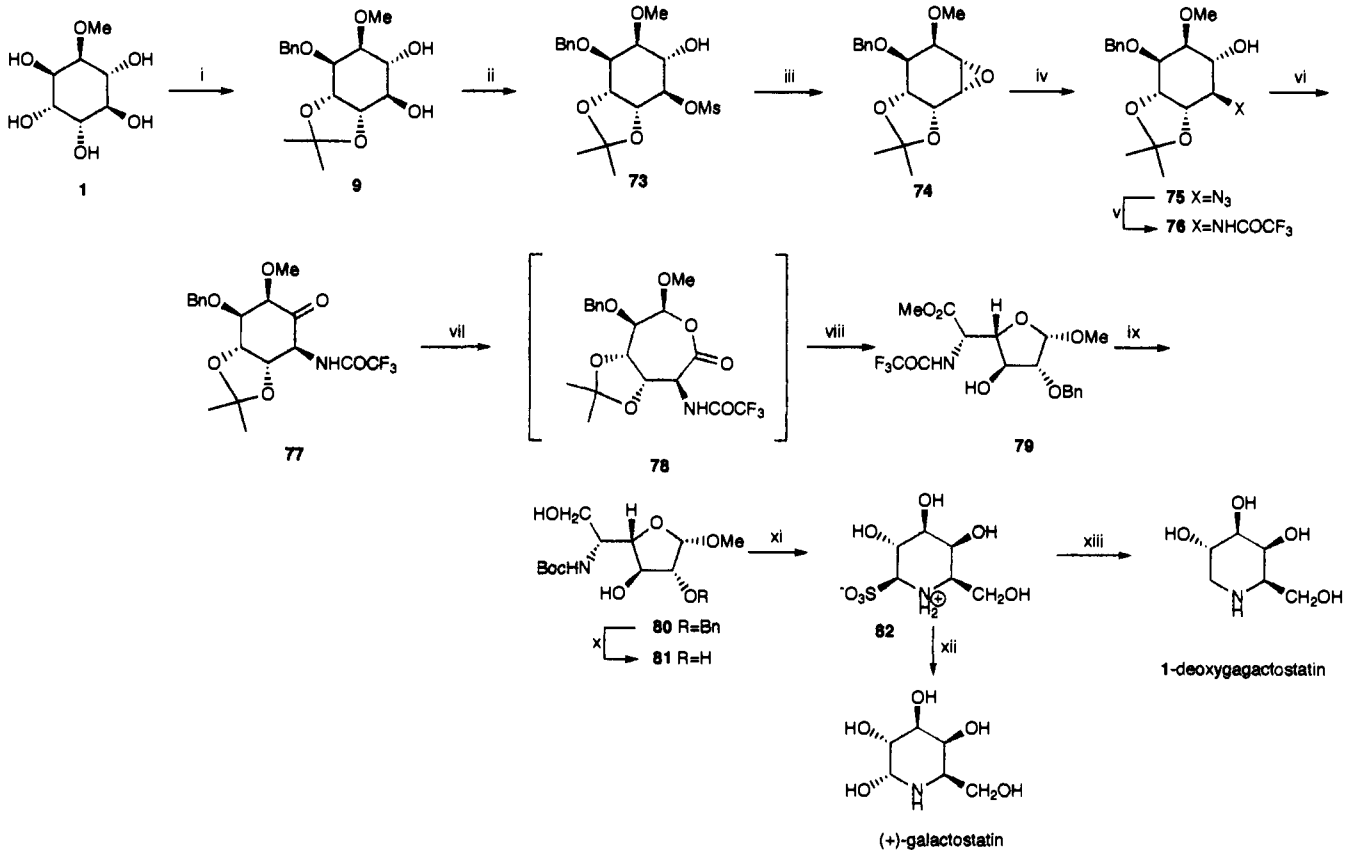
[a] Reagents: (i) 2,2-dimethoxypropane, *p*-TsOH; (ii) RuO_4, $NaIO_4$; (iii) dimethyloxosulfonium methylide; (iv) KOH, H_2O; (v) BBr_3, CH_2Cl_2; (vi) 2,2-dimethoxypropane, *p*-TsOH; (vii) HCl, MeOH; (viii) NaH, BnBr; (ix) a, HCl, MeOH; b, BzCl, K_2CO_3; (x) a, MsCl; b, NaOEt, EtOH; (xi) a, NaI; b, $P(O)Cl_3$; (xii) HCl, MeOH; (xiii) BzCl, K_2CO_3; (xiv) HN_3, Ph_3P, DEAD; (xv) a, Ph_3P, H_2O; (xvi) Na, NH_3.

formation furnishes the dibenzoate **66**. The formation of the resulting dibenzoate over other products is governed by the lower reactivity of the axial hydroxy groups, compared with that of the equatorial or primary hydroxy groups arising from the removal of the isopropylidene moieties. Treatment of the diol with mesyl chloride followed by sodium ethoxide affords intermediate **67** as a mixture of two epoxides, which could be isolated as their acetate derivatives. Reaction of **67** with sodium iodide and phosphorus oxychloride leads cleanly to the olefin **68**. Hydrolysis of **68** to **69** and selective benzoylation gave **70**, which was suitably protected for the introduction of the amino group. The allylic alcohol is converted to the azido group by reaction with hydrazoic acid, triphenylphosphine, and diethyl azodicarboxylate (DEAD). The azido group is then transformed to the amino functionality via a phosphinimide by reaction with triphenylphosphine and ensuing hydrolysis. Final deprotection with sodium in liquid ammonia gave the desired valienamine (**72**).

In an extension of their work on carbohydrates Ogawa and Chida have applied the regioselective Baeyer–Villiger ring expansion/ring hydrolysis methodology to the synthesis of two azahexoses. Galactostatin and 1-deoxygalactostatin, which are potent α- and β-galactosidase inhibitors, were synthesized from L-quebrachitol via a common intermediate late in the synthetic strategy (Scheme 11).[16]

The known diol **9** could be synthesized in three steps by the methodology previously described in this review and was the starting point for this synthesis (see Scheme 3). Reaction of **9** with bis(tributyltin) oxide followed by mesyl chloride provides the mesylate **73**. Treatment of **73** with sodium methoxide gave epoxide **74**, which can undergo regioselective opening of the epoxide with sodium azide to give the azide intermediate **75**. The azido group is converted to the trifluoroacetamido group (**76**), which was selected because the electron-withdrawing trifluoroacetamido group would direct the regioselectivity of the key Baeyer–Villiger reaction. Oxidation of **76**

Scheme 11[a]



[a] Reagents: (i) see Scheme 3; (ii) $(Bu_3Sn)_2O$, toluene, reflux, then MsCl, toluene, room temperature; (iii) MeONa, MeOH, room temperature; (iv) NaN_3, NH_4Cl, $MeOCH_2CH_2OH-H_2O$ (4:1), reflux; (v) H_2, Raney-Ni(W4), EtOH, then CF_3CO_2Et, Et_3N, MeOH, room temperature; (vi) TEMPO (5 mol %), $NaBrO_2$, CH_2Cl_2–5% aq $NaHCO_3$ (1:2), room temperature; (vii) *m*-CPBA, $KHCO_3$, CH_2Cl_2, room temperature (viii) TsOH (40 mol %), $CH(OMe)_3$, MeOH, 60 °C, then MeI–$NaHCO_3$, DMF, room temperature; (ix) $NaBH_4$, MeOH, 0 °C, then $(Boc)_2O$, MeOH, room temperature; (x) H_2, Pd–C, EtOH; (xi) SO_2 gas, H_2O, 50 °C, 3 days; (xii) Dowex X8 resin (HO^- form), H_2O or $Ba(OH)_2$, H_2O; (xiii) H_2, Raney-Ni (W4), $Ba(OH)_2$, H_2O.

to ketone **77** provides the appropriately functionalized cyclohexane ring for the Baeyer–Villiger reaction. The pivotal Baeyer–Villiger reaction is accomplished by *m*-CPBA oxidation and proceeds smoothly to the regioselectively desired product **78**. Subsequent hydrolysis and methyl ester formation affords the α-anomer of furanose **79** as the major product. Reaction of **79** with sodium borohydride in ethanol effects deprotection of the trifluoroacetamido group and reduction of the ester moiety to provide **80**, which was isolated as its *tert*-butyl carbamate. Removal of the benzyl group to give **81**, followed by reaction of an aqueous suspension of the intermediate with sulfur dioxide, cleaves off the remaining protecting groups and affords the galactostatin hydrogen sulfite **82**. Conversion of **82** to (+)-galactostatin is concluded by reaction with either a basic ion exchange resin or barium hydroxide in water. On the other hand, hydrogenolysis of **82** with Raney-Ni in the presence of barium hydroxide yields the 1-deoxygalactostatin.

Simmondsin (Figure 2) a cyanoglucoside isolated from the seeds of the jojoba plant has been the target molecule in another synthesis from L-quebrachitol.

Simmondsin consists of a D-glucose unit and a substituted cyclohexane molecule containing an α,β-unsaturated nitrile functional group. The aglycon structural component has been synthesized by Ogawa and Chida in their continued work on L-quebrachitol

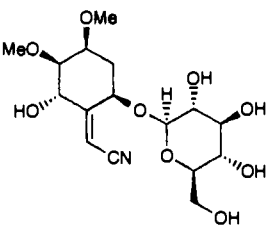
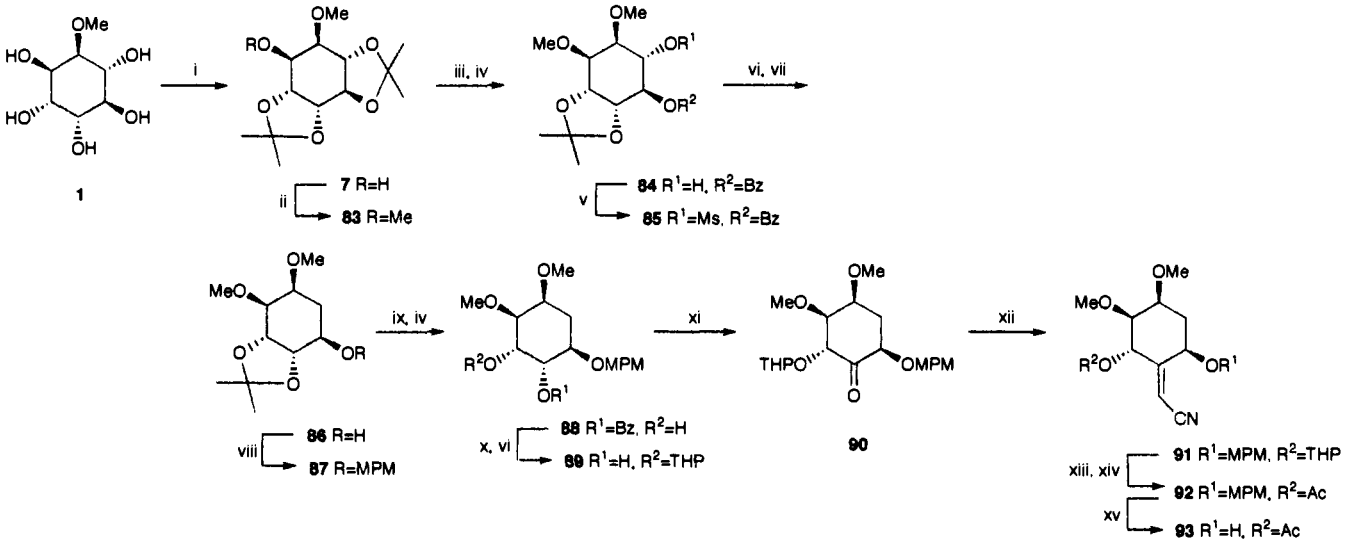


Figure 2. Structure of simmondsin.

as a template for construction of bioactive materials (Scheme 12).[17]

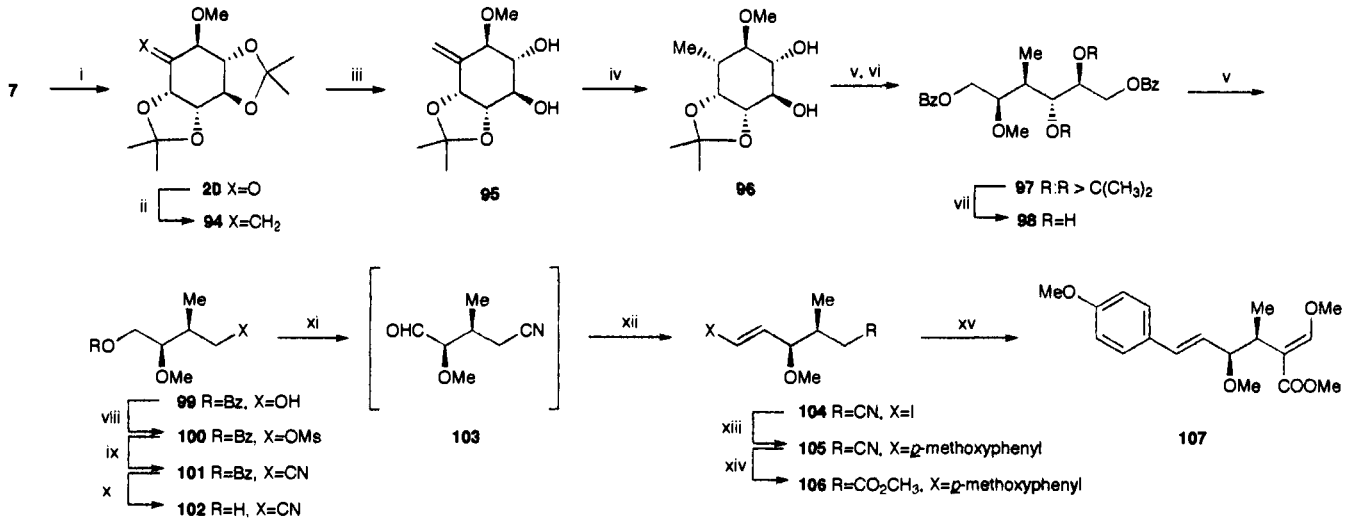
The starting point of the synthesis was the known isopropylidene derivative of L-quebrachitol **7**. The free hydroxy was converted to its methyl ether **83** and the *trans*-isopropylidene selectively cleaved. Reaction with an equal molar amount of benzoyl chloride afforded primarily **84**, which was then converted to the mesylate **85**. Reaction of **85** with base to form the epoxide, followed by reduction of the epoxide with LAH, results in the formation of secondary alcohol **86**. The alcohol was protected as its *p*-methoxybenzyl ether (**87**), and the remaining acetonide was hydrolyzed to give an intermediate diol. The equatorial hydroxy was selectively benzoylated to form **88**, and the remaining alcohol was then converted to its tetrahydropyranyl ether (THP). The benzoyl group was subsequently removed to yield the secondary alcohol **89**. Oxidation of the alcohol with PCC gave the protected ketone **90**. Horner–Emmons

Scheme 12[a]



[a] Reagents: (i) 2,2-Dimethoxypropane, *p*-TsOH; (ii) NaH, MeI, *N*,*N*-dimethylformamide (DMF), room temperature; (iii) *p*-TsOH, MeOH, 0 °C; (iv) BzCl, pyridine; (v) MsCl, pyridine, 50 °C; (vi) MeONa, MeOH; (vii) $LiAlH_4$,THF, room temperature; (viii) NaH, MPMCl, DMF, room temperature; (ix) *p*-TsOH, MeOH, room temperature; (x) dihydropyran, *p*-TsOH, CH_2Cl_2; (xi) PCC, CH_2Cl_2; (xii) $NCCH_2P(O)(Et)_2$, *t*-BuOK, toluene; (xiii) PPTS, EtOH; (xiv) Ac_2O, pyridine; (xv) DDQ, $CH_2Cl_2-H_2O$ (10:1), room temperature.

Scheme 13[a]



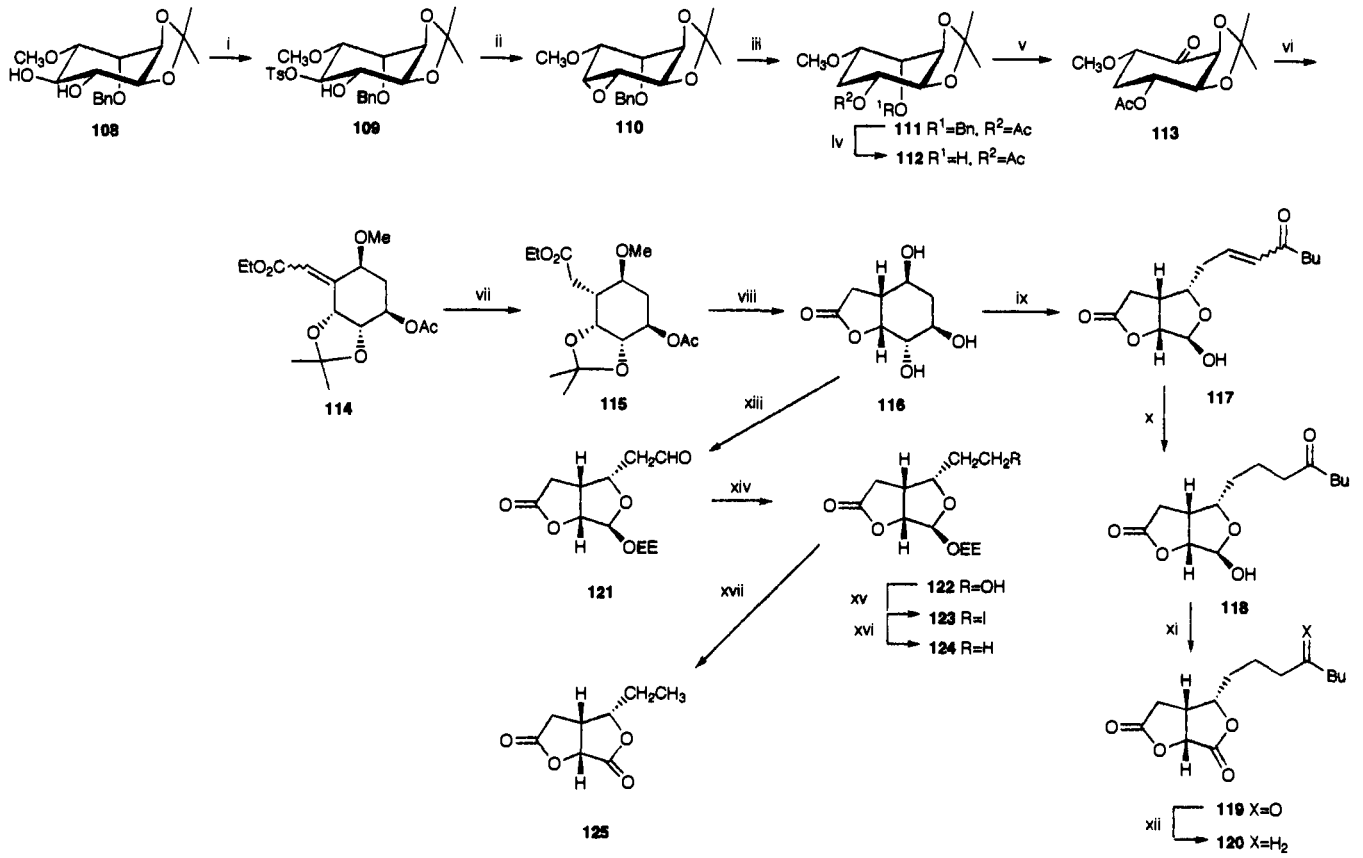
[a] Reagents: (i) RuO_4, $NaIO_4$; (ii) Me_3SiCH_2MgCl, THF, room temperature, then KH, THF, room temperature; (iii) *p*-TsOH (1 mol %), MeOH, 0 °C; (iv) H_2, Raney-Ni, EtOH; (v) $NaIO_4$, $NaHCO_3$, acetone–H_2O, 0 °C, then $NaBH_4$, MeOH, 0 °C; (vi) BzCl, pyridine 0 °C; (vii) 80% AcOH, 70 °C; (viii) MsCl, pyridine; (ix) NaCN, DMF, 50 °C, 6 h; (x) NaOMe, MeOH; (xi) PCC, CH_2Cl_2; (xii) CHI_3, $CrCl_2$, DMF–THF, room temperature; (xiii) (*p*-OMe)C_6H_4MgBr, $Pd(PPh_3)_4$ (5 mol %), benzene, room temperature; (xiv) a, DIBAL-H, CH_2Cl_2, 0 °C, 2 h then acidic (aq H_2SO_4) workup; b, $NaClO_2$, NH_2SO_3H, NaH_2PO_4, *t*-BuOH–H_2O, room temperature; c, CH_2N_2, ether–CH_2Cl_2; (xv) a, $(Me_3Si)_2NLi$, THF, −78 to −40 °C, 1 h, then HCOOMe, −78 to 0 °C; b, $(MeO)_2SO_2$, K_2CO_3, acetone, room temperature.

reaction of **90** with the anion of diethyl (cyanomethyl)phosphonate gave a mixture of the *E*- and *Z*- α,β-unsaturated nitriles, of which the desired *E*-isomer **91** was carried through the remaining synthetic manipulations. Cleavage of the O-THP ether with pyridinium *p*- toluenesulfonate (PPTS) in ethanol and acetylation of the alcohol gave the precusor to simmondsin **92**. Deprotection of the MPM ether with wet DDQ furnished the required cyclohexane, which could be coupled with a suitably protected D-glucose unit, to give, after deprotection, the target molecule simmondsin (Figure 2).

In an innovative synthesis, the rigid structure of L-quebrachitol has been utilized as a platform to construct the acyclic oxygenated portion of the antibiotic (−)-oudemansin X.[18]

Synthesis of the previously described ketone **20** from the diacetonide was accomplished from L-quebrachitol in two steps (Scheme 13). Peterson olefination of ketone **20** affords the *exo*-methylene intermediate **94** in good yield. Treatment of **94** with mild acid provides selective removal of the *trans*-isopropylidene protecting group to give **95**. Hydrogenation of **95** with Raney-Ni yields the methyl derivative **96**, which upon treatment with sodium periodate yields the product of oxidative ring opening. This was then immediately reduced with sodium borohydride and the resulting primary alcohols protected as their benzoyl esters (**97**). Removal of the remaining isopropylidene moiety (**98**) and a second periodate cleavage of the glycol furnishes the desired four-carbon fragment **99** for the synthesis of the

Scheme 14[a]



[a] Reagents: (i) *p*-TsCl, pyridine; (ii) NaOMe; (iii) a, LAH; b, Ac_2O; (iv) 20% $Pd(OH)_2/C$, H_2; (v) PCC; (vi) Ph_3PCHCO_2Et, toluene; (vii) Raney-Ni, EtOH; (viii) BBr_3, CH_2Cl_2; (ix) a, $NaIO_4$/acetone:H_2O; b, $Ph_3PCHC(O)Bu$, CH_3CN; (x) 20% $Pd(OH)_2/C$, H_2, EtOH; (xi) PCC, molecular sieves, CH_2Cl_2; (xii) HCl, Zn, ether; (xiii) a, $NaIO_4$/acetone:H_2O; b, ethyl vinyl ether, pyridinium, toluene–*p*-sulfonate; (xiv) $NaBH_4$, MeOH; (xv) Ph_3P, DEAD, MeI, THF; (xvi) Raney-Ni; (xvii) Jones reagent.

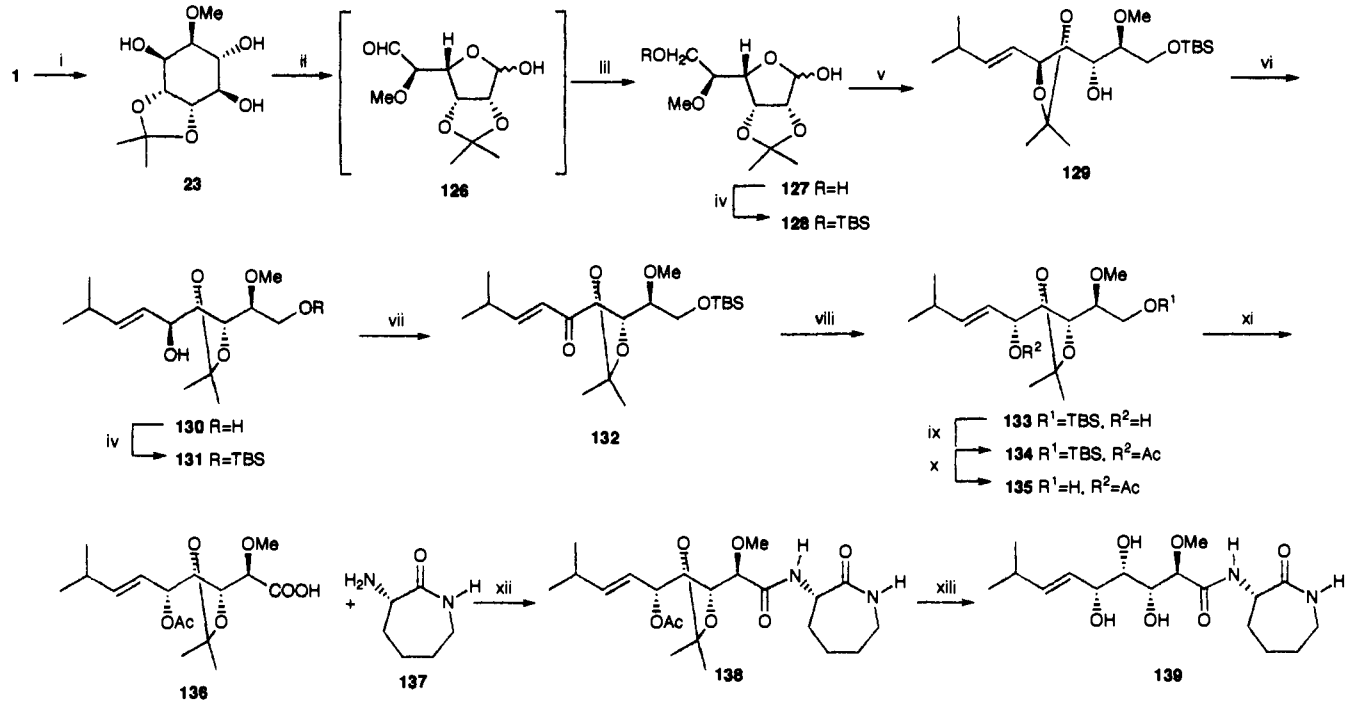
target structure. Through a series of standard manipulations the free alcohol is converted first to the mesylate (**100**), displaced with cyanide (**101**), and the benzoyl protecting group was removed to give the primary alcohol **102**. Oxidation of **102** with PCC gives intermediate **103** which is converted to the vinyl iodide via the Takai reaction. Palladium-catalyzed cross-coupling of **103** with (*p*-methoxyphenyl)magnesium bromide produces the nitrile **105**. The remaining critical conversion of the nitrile (**105**) to the target methoxymethylene compound was accomplished by DiBAL-H reduction of the nitrile, acidic hydrolysis of the resulting imine, oxidation to the carboxylic acid, and esterification to give the methyl ester **106.** The synthesis was concluded by the trapping of the ester enolate with methyl formate, followed by *O*-methylation with dimethyl sulfate to give (−)-oudemansin X (**107**), which was spectroscopically identical to an authentic sample.

The bislactones (−)-isoavenaciolide and (−)-ethisolide, mold metabolites reported to have antifungal and antibiotic activities, have been the subject of a formal total synthesis via a common intermediate from L-quebrachitol (Scheme 14).[19]

Synthesis of the common intermediate begins with the protected diol **108** constructed from L-quebrachitol in three steps. The diol was reacted with tosyl chloride to furnish a mixture of monotosylates, which are separated to provide the desired regioisomer **109**. Epoxide formation to yield **110**, reduction of the epoxide with LAH, followed by acetylation gave acetate **111** as the sole product. Catalytic hydrogenation of **111** gave the secondary alcohol **112**, which was oxidized with PCC to yield the ketone **113**. Wittig reaction of the ketone **113** with (ethoxycarbonylmethylene)triphenylphosphorane furnishes the *E*- and *Z*-olefins **114**. Reduction of the carbon−carbon double bond with Raney-Ni gave stereoselectively the pivotal intermediate **115** and its epimer in a ratio of 35:1. Synthesis of the intermediate for divergence to the two target molecules was effected by boron tribromide deprotection of the methyl ether, acetyl groups and isopropylidene, with simultaneous lactonization to provide the γ-lactone **116**.

The formal synthesis of (−)-isoavenaciolide is completed by first subjecting intermediate **116** to periodate oxidation to yield an unstable hemiacetal aldehyde which was directly treated with the Wittig reagent (valerylmethylene)triphenylphosphorane to generate the α,β-unsaturated ketone **117**. Hydrogenation of the *E*- and *Z*-alkene mixture (**117**) to afford intermediate **118**, with ensuing oxidation gave the bis-lactone **119**. The (−)-isoavenaciolide precursor was obtained by Clemmensen reduction of the ketone **119** to furnish **120**. Achievement of the formal synthesis of (−)-ethisolide was accomplished by reaction of pivotal intermediate **116** with periodate to again give the unstable hemiacetal aldehyde, which was trapped with ethyl vinyl ether to provide the acetal aldehyde **121**. Subsequent reduction of the acetal aldehyde affords the primary alcohol **122**. Iodination of **122** with methyl iodide, triphenylphos-

Scheme 15[a]



[a] Reagents: (i) see Scheme 5; (ii) $NaIO_4$, acetone–H_2O (5:1), 0 °C, 2.5 h; (iii) $NaBH_4$, MeOH, 0 °C, 1 h; (iv) TBSCl, Et_3N, 4-(dimethylamino)pyridine, CH_2Cl_2, room temperature, 20 h; (v) $Me_2CHCH_2P^+Ph_3Br^-$, *n*-BuLi, benzene, room temperature, 4 h; (vi) *p*-TsOH, CH_3CN, 0 °C, 8 h; (vii) MnO_2, CH_2Cl_2, room temperature, 16 h; (viii) $Zn(BH_4)_2$, ether–toluene (1:1), −78 to 0 °C, 1 h; (ix) Ac_2O, pyridine, room temperature, 15 h; (x) *n*-Bu_4NF, AcOH, THF, 0 °C to room temperature, 12 h; (xi) Jones reagent, acetone, 0 °C, 2 h; (xii) $(EtO)_2P(O)CN$, Et_3N, DMF; (xiii) a, MeONa; b, TFA, THF, H_2O.

phine, and DEAD gave the iodide **123**. Hydrogenolysis of **123** yielding **124**, followed by Jones oxidation, concluded the formal synthesis of (−)-ethisolide **125**.

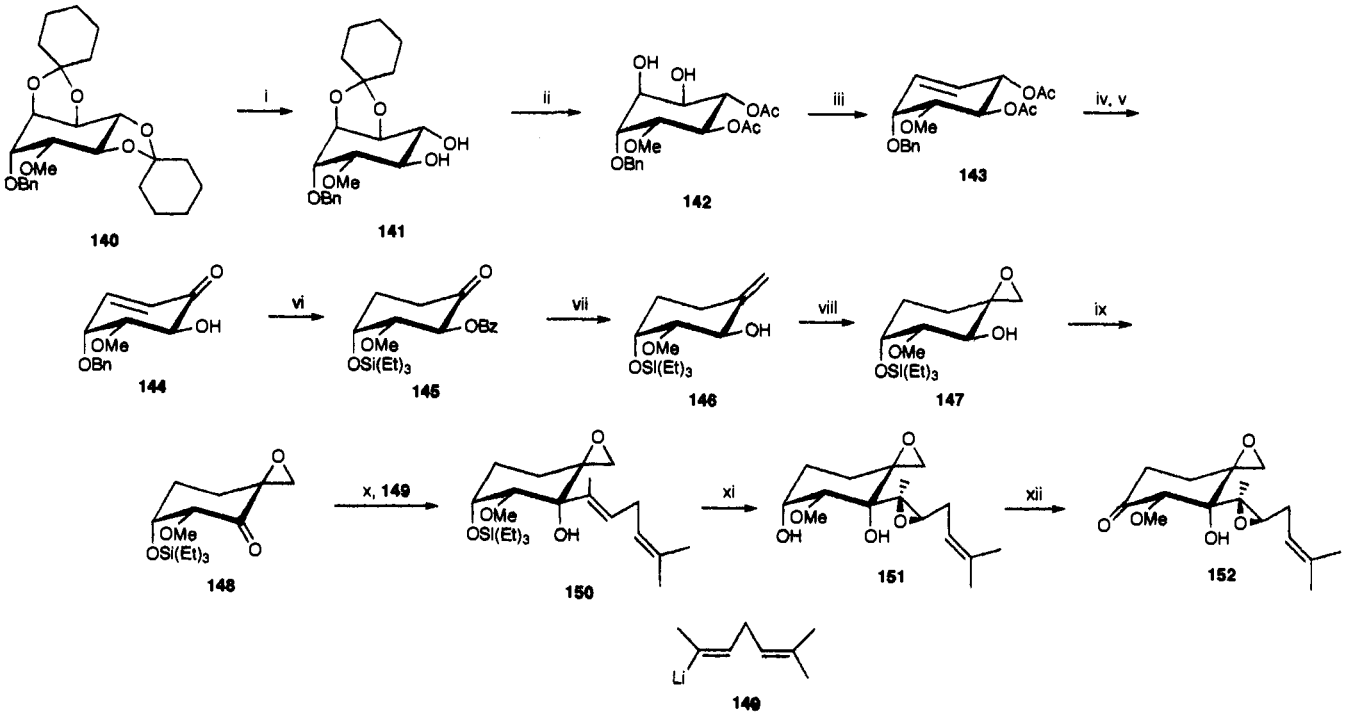
Ogawa and Chida have utilized the monoacetonide of L-quebrachitol **23** as a starting material for the construction of bengamide E.[20] The bengamides contain a cyclo-L-lysine unit and a side chain possessing four adjacent hydroxyls, where one is a methyl ether. This arrangement of functional groups makes L-quebrachitol an excellent choice as a chiral building block for the side chain segment.

The monoacetonide **23** synthesized from L-quebrachitol (see Scheme 5) was oxidized with sodium periodate to furnish the intermediate furanose **126**, which was immediately reduced to generate the primary alcohol **127** (Scheme 15). Protection of the primary alcohol as its *tert*-butyldimethylsilyl ether (TBS) afforded the mannofuranose **128**. Wittig reaction of **128** with isobutyltriphenylphosphorane effects ring opening of the furanose to generate the acyclic derivative **129**. It was found in this reaction the best yields were obtained with *n*-BuLi as base and benzene as the solvent. Treatment of **129** with *p*-TsOH in acetonitrile induced acetonide migration and, in addition, partial cleavage of the TBS protecting group (**130**). The mixture of protected and free alcohol was then reacted with TBSCl again to furnish the protected intermediate **131**. Oxidation of the free alcohol to provide the enone **132** was accomplished using fresh manganese dioxide in methylene chloride. Reduction of the ketone affords the inverted alcohol **133** which was acetylated (**134**) and the TBS protecting group removed to produce the primary alcohol **135**. Oxidation of the primary alcohol **135** with Jones reagent leads to the carboxylic acid intermediate **136**. Coupling of the side-chain fragment **136** with the cyclo-L-lysine **137** using Shioiri's protocol [$(EtO)_2P(O)CN$, TEA, DMF, 0 °C] gave the protected bengamide E **138**. Final deprotection of **138** first with sodium methoxide and second with TFA provided the desired bengamide E **139**. The synthesis of bengamide E again exhibits the application of L-quebrachitol as a template for the formation of acyclic bioactive materials of interest.

The first reported chiral synthesis of (−)-ovalicine from L-quebrachitol has recently been published.[21] (−)-Ovalicine is a secondary metabolite with antibiotic, antitumor and immunosuppresive properties. The structure is related to the known antibiotic and antitumor agent fumagillin.

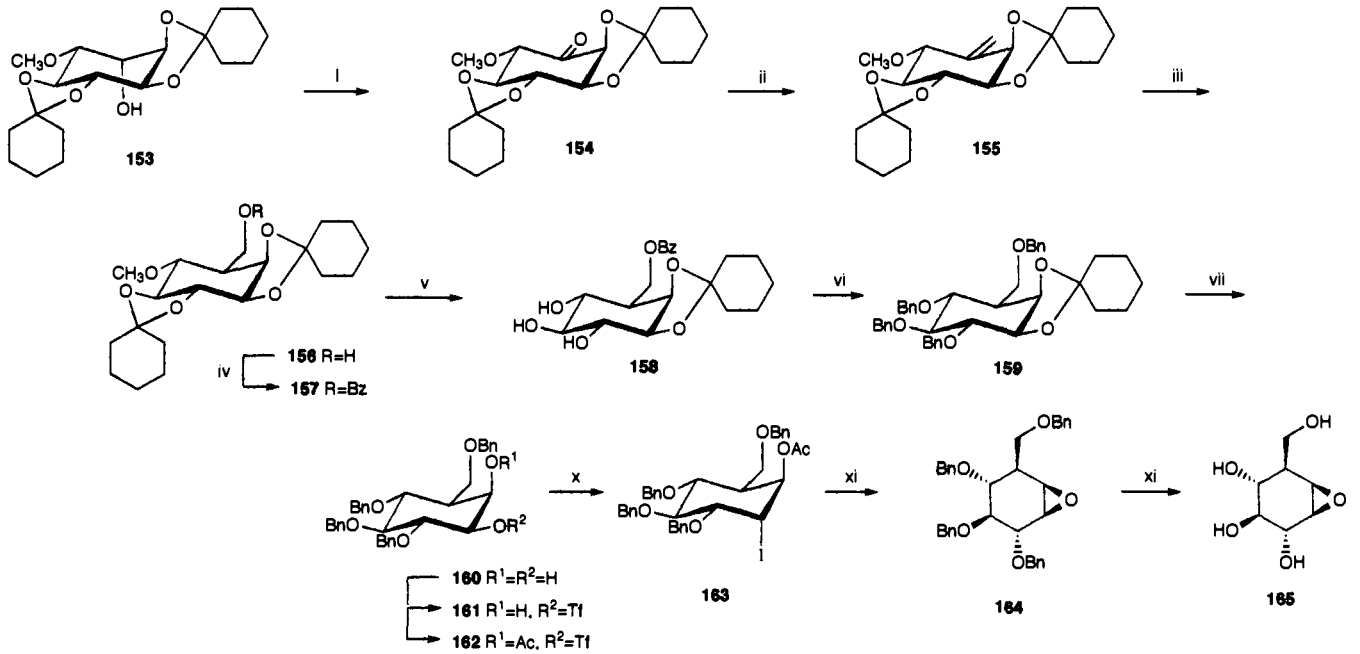
The synthesis begins with the known fully protected L-quebrachitol derivative **140**, obtained from **1** in two steps (Scheme 16). Selective hydrolysis of the *trans*-acetonide to yield **141**, followed by acetylation of the alcohols with subsequent cleavage of the *cis*-acetonide provides the *cis*-diol **142**. Corey–Winter *cis*-deoxygenation of **142** with thiophosgene and DMAP in methylene chloride afforded the alkene **143**. The acetate esters were cleaved with ammonia in methanol and the allylic alcohol is selectively oxidized with manganese dioxide to furnish the α,β-unsaturated ketone **144**. Catalytic hydrogenation of **144** provides reduction of the olefin and cleavage of the benzyl ether. Subsequent benzoylation of the more reactive equatorial hydroxy and silylation of the axial hydroxy furnishes the protected ketone **145**. The exocyclic olefin (**146**) was introduced using methyltriphenylphosphorane, followed by *m*-CPBA epoxidation of the alkene which gave the spirocyclic epoxide **147**. Swern oxidation of **147** to the ketone

Scheme 16[a]



[a] Reagents: (i) $HOCH_2CH_2OH$, *p*-TSA, CH_2Cl_2; (ii) a, $(CH_3CO)_2O$, pyridine; b, CF_3COOH, THF–H_2O; (iii) a, $CSCl_2$, DMAP, CH_2Cl_2; b, $(CH_3O)_3P$; (iv) NH_3, MeOH; (v) MnO_2, CH_2Cl_2; (vi) a, Pd/C 10%, EtOH, Et_3N; b, PhCOCl, pyridine; c, $(Et)_3SiCl$, imidazole, DMF; (vii) $Ph_3P{=}CH_2$, THF; (viii) *m*-CPBA, CH_2Cl_2; (ix) DMSO, $(CF_3CO)_2O$, CH_2Cl_2; (x) **149**, THF–toluene −78 °C; (xi) a, $(acacO)_2VO$, *t*-BuOOH, PhH; b, TBAF, THF; (xii) PDC, CH_2Cl_2.

Scheme 17[a]



[a] Reagents: (i) Ac_2O, DMSO, CH_2Cl_2; (ii) a, $(CH_3)_3SiCH_2MgCl$; b, KH; (iii) a, BH_3THF; b, H_2O_2, NaOH; (iv) Bz_2O, pyridine; (v) $AlCl_3$, *n*-Bu_4NI, CH_3CN; (vi) BnBr, NaH, $NaOCH_3$, DMF; (vii) TFA, MeOH; (viii) Tf_2O, pyridine (ix) Ac_2O, room temperature; (x) *n*-Bu_4NI, reflux, benzene; (xi) $NaOCH_3$, THF/MeOH; (xii) Pd/C, H_2.

148, and subsequent Shapiro reaction with the *in situ* generated vinyllithium **149** forms the product of addition (**150**). Sharpless asymmetric epoxidation of **150** generated a mixture of the bisepoxides (**151**), which could only be separated following removal of the silyl protecting group. The final elaboration, conversion of the secondary alcohol to the ketone, was accomplished with PDC to give the target (−)-ovalicine **152**.

The β-glucosidase inhibitor cyclophellitol isolated from a mushroom shows potent activity against infection from HIV and has also been synthesized from L-quebrachitol (Scheme 17).[22,23] Ozaki and coworkers have synthesized cyclophellitol via the chemoselective cleavage of the methyl ether[24] of a suitably protected L-quebrachitol intermediate.

The synthesis of cyclophellitol begins with the dicyclohexylidene derivative **153**, obtained by react-

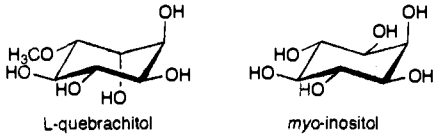


Figure 3. Comparison of the structure of L-quebrachitol and *myo*-inositol.

ing L-quebrachitol with cyclohexanone and *p*-TsOH in benzene. Swern oxidation of **153** provides the ketone **154**, which was converted to the *exo*-methylene compound (**155**) by Peterson olefination. The primary alcohol **156** was obtained by hydroboration of **155** under anti-Markovnikov conditions. Subsequent benzoyl ester formation gave the fully protected molecule **157**. The chemoselective methyl ether cleavage was accomplished with aluminum chloride–tetrabutylammonium iodide in acetonitrile to yield the triol **158**. The reaction has been postulated to occur by initial cleavage of the *trans*-cyclohexylidene group in **157** providing a hydroxy vicinal to the methyl ether, which appears to be essential in directing the chemoselectivity via aluminum coordination. The triol **158** was reacted with benzyl bromide, sodium hydride, and sodium methoxide to effect benzoyl ester cleavage with successive benzylation to provide **159**. The crucial epoxide of the target molecule was introduced via a series of standard manipulations. Cleavage of the remaining cyclohexylidene group gave diol **160**, which was reacted with trifluoromethanesulfonyl anhydride forming the trifluoromethanesulfonyl derivative at the more reactive equatorial hydroxy (**161**). Acetylation of the secondary alcohol (**162**) and displacement of the trifluoromethanesulfonyl group with tetrabutylammonium iodide gave the iodo intermediate **163** appropriately set up for epoxide formation. Treatment of **163** with sodium methoxide in methanol smoothly converts the iodide to the desired epoxide **164**. Final deprotection of the benzyl ethers completes the synthesis of cyclophellitol (**165**).

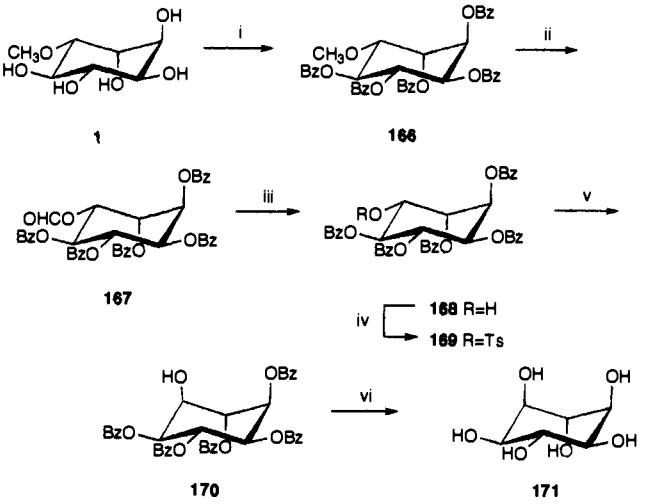
In summary, the syntheses of the antibiotics and enzyme inhibitors presented have shown that L-quebrachitol is a valuable resource for the construction of natural products. L-Quebrachitol has been effectively converted to a variety of highly oxygenated, structurally diverse molecules, through stereoselective conversions.

C. Inositols

The inositols, inositol phosphates, and phosphatidylinositols are a diverse group of molecules intimately involved in intracellular signaling.[25] *myo*-Inositol the parent cyclitol of this biological cascade is structurally related to L-quebrachitol (Figure 3). Inversion of the hydroxy at C-1 and methyl ether cleavage at C-2 of L-quebrachitol provides *myo*-inositol.

Because L-quebrachitol is accessible in optically active form and can be easily manipulated to the inositol structure it is a logical starting material for the synthesis of the naturally occurring inositol phosphates. While very few naturally occurring inositols have been synthesized from L-quebrachitol, the diversity of the inositol analogues synthesized

Scheme 18[a]



[a] Reagents: (i) BzCl, pyridine; (ii) CrO_3, HOAc; (iii) methanolic HCl, reflux; (iv) *p*-TsCl, pyridine; (v) DMF/H_2O, reflux; (vi) $NaOCH_3$, MeOH.

utilizing L-quebrachitol as a chiral building block appearing in the literature is worth noting. The presentation of the construction of unnatural inositol analogues from L-quebrachitol, although not within the scope of this review, deserves reference as an excellent source of fundamental cyclitol chemistry.[4,26] The analogues synthesized from L-quebrachitol range from inositol phosphates derived from isomers of *myo*-inositol,[27] inositol thiophosphates,[28] 3-deoxy-3-substituted analogues,[29] and 3-deoxy-3-substituted phosphatidylinositol analogues.[30]

1. Stereoisomers of the Inositols

Only one reported synthesis of an inositol isomer has appeared in the literature to date. The synthesis of the rare cyclitol *muco*-inositol has been achieved in a short synthesis from L-quebrachitol.[31]

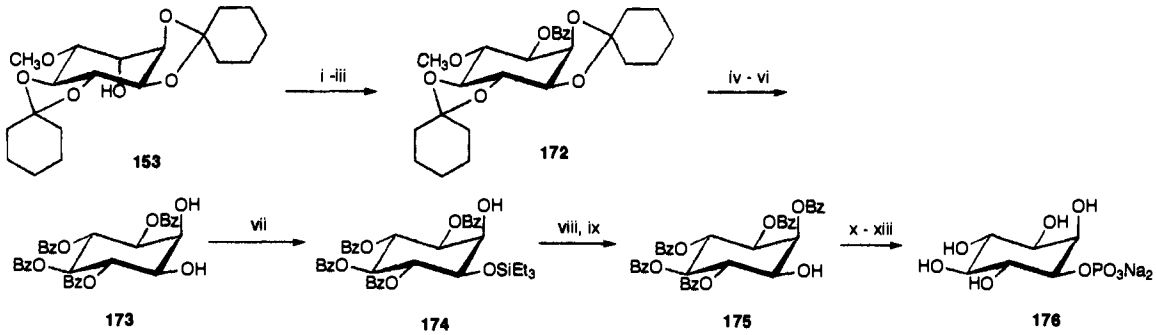
Treatment of L-quebrachitol with benzoyl chloride in pyridine affords the fully protected intermediate **166** (Scheme 18). Chromium trioxide oxidation of **166** converts the methyl group to the formyl derivative **167**. Removal of the formyl group with methanolic hydrochloric acid provides the secondary alcohol **168**. Tosylation of **168** to yield the tosylate **169** followed by solvolysis gave the protected *muco*-inositol precursor **170** which, surprisingly, proved to be optically active. Debenzoylation of **170** provides the *muco*-inositol **171** in good yield.

2. Inositol Phosphates

Ozaki and co-workers have described one of the two syntheses of the naturally occurring D-*myo*-inositol 1-phosphate.[32,33] Modulation of the metabolism of D-*myo*-inositol 1-phosphate *in vivo* has been shown to play a role in the pharmaceutical profile of the neurological activity of lithium carbonate.[34]

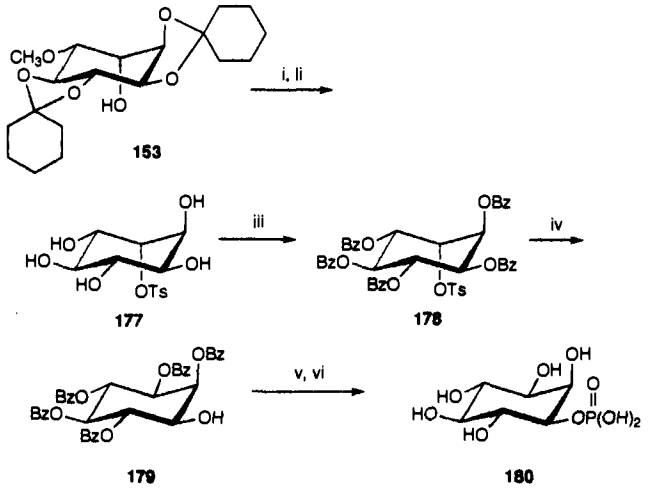
The synthesis of the D-*myo*-inositol 1-phosphate begins with the previously described cyclohexylidene derivative of L-quebrachitol **153**. Swern oxidation of the secondary alcohol to the ketone and stereoselective reduction with lithium borohydride provides intermediate **172**, following protection of the alcohol as its benzoyl ester (Scheme 19). Selective cleavage

Scheme 19[a]



[a] Reagents: (i) Ac_2O, DMSO, CH_2Cl_2, reflux, 8 h; (ii) $LiBH_4$, THF, −78 °C, 20 min; (iii) PhCOCl, NEt_3, DMAP, CH_2Cl_2, 0 °C; (iv) $AlCl_3$–NaI, CH_3CN, room temperature overnight; (v) PhCOCl, NEt_3, DMAP, CH_2Cl_2; (vi) CF_3COOH, MeOH, room temperature; (vii) Et_3SiCl, py, 0 °C; (viii) PhCOCl, NEt_3, DMAP, CH_2Cl_2; (ix) *p*-TsOH, 80% AcOH; (x) a, *H*-Tetrazole, 3-(dimethylamino)-1,5-dihydro-2,4,3-benzodioxaphosphepine, CH_2Cl_2; b, H_2O; (xi) *m*-CPBA; (xii) 10% Pd/C, H_2, MeOH, room temperature.

Scheme 20[a]



[a] Reagents: (i) *p*-TsCl, pyridine; (ii) BCl_3; (iii) BzCl, pyridine; (iv) NaF, DMF; (v) $(PhO)_2P(O)Cl$, pyridine; (vi) PtO_2, H_2, EtOAc.

of the *trans*-cyclohexylidene, with subsequent benzoylation of the resulting diol and removal of the *cis*-cyclohexylidene group gave the *cis*-diol **173**. Exclusive formation of the monosilyl derivative **174**, due to the increased reactivity of the equatorial hydroxy provides a suitable precursor for the introduction of the 1-phosphate. Benzoylation of the alcohol and desilylation provide the desired intermediate for phosphorylation bearing an alcohol at the putative 1-position of *myo*-inositol. Introduction of the phosphorus with 3-(diethylamino)-1,5-dihydro-2,3,4-benzodioxaphosphepine, followed by oxidation with *m*-CPBA provided the protected target molecule which was subsequently deprotected and converted to the sodium salt to complete the synthesis of D-*myo*-inositol 1-phosphate (**176**).

The second synthesis of D-*myo*-inositol 1-phosphate was also the second reported construction of a naturally occurring bioactive material from L-quebrachitol. Barnett and co-workers synthesized the D-*myo*-inositol 1-phosphate in six steps from L-quebrachitol via the previously depicted dicyclohexylidene **153** (Scheme 20).[35]

Tosylation of the protected L-quebrachitol **153** and boron trichloride deprotection of the cycloalkylidenes affords the monotosylate **177**. Benzoylation of the alcohols yielding **178**, and solvolysis of the tosylate with sodium fluoride in DMF provides the inverted secondary alcohol **179**. Phosphorylation of the alcohol in **179** and deprotection gave the desired D-*myo*-inositol 1-phosphate (**180**).

While *myo*-inositol is one of the meso isomers of the inositols, its presence in nature occurs extensively in optically active structures. Thus, the ready availability of L-quebrachitol and the ease of manipulation to *myo*-inositol, as well as, inositol isomers makes it an invaluable source in the synthesis of optically active cyclitols.

V. Conclusions

The synthetic approaches previously described have revealed that L-quebrachitol has proven to be a useful addition to the existing "chiral pool" of molecules for the construction of bioactive materials. Despite the fact that L-quebrachitol is quite abundant, easily isolated, and obtainable in optically active form, it has received considerably less attention than other carbohydrates like the aldohexoses and pentoses. One reason may be the relatively few syntheses using L-quebrachitol to construct biologically diverse molecules other than the inositols. In addition, the clear relation between target and starting material for the fabrication of an inositol from L-quebrachitol may have caused researchers to overlook its utility in other asymmetric syntheses.

It is the focus and hope of this review to present the divergence of molecular structures that can be achieved from L-quebrachitol. The cyclic structure offers a precursor platform for the construction of acyclic molecules, as well as, an assortment of ring structures through expansion/contraction of the parent 6-membered ring. Also important is the ease and variety of protection/deprotection methods of the polyhydroxyl groups allowing for a diversity of functional group manipulations. It is the ambition of this review to foster development of other syntheses employing L-quebrachitol as a chiral building block and to encourage progress in the area of cyclitol chemistry.

VI. Acknowledgments

I would like to thank Dr. Alan P. Kozikowski for the opportunity to work in his laboratory and to learn about L-quebrachitol. In addition, thanks is due to him for the opportunity to write this review. I would

also like to thank Christina Baldinger for assistance in the preparation of the schemes.

VII. References

(1) Scott, J. W. In *Asymmetric Synthesis*; Morrison, J. D., Scott, J. W., Eds.; Academic Press: Florida, 1984; Vol. IV, p 1.
(2) Tanret, C. *C. R. Hebd. Seances Acad. Sci.* **1889**, *109*, 908.
(3) Balci, M.; Sütbeyaz, Y.; Secen, H. *Tetrahedron* **1990**, *46*, 3715.
(4) Billington, D. C. *Chem. Soc. Rev.* **1989**, *18*, 83. Reitz, A. B., Ed. *Inositol Phosphates and Derivatives: Synthesis, Biochemistry, and Therapeutic Potential*; American Chemical Society: Washington D.C., 1991. Billington, D. C. *The Inositol Phosphates—Chemical Synthesis and Biological Significance*; VCH: Weinheim; New York, 1993. Potter, B. V. L. *Nat. Prod. Rep.* **1990**, *7*, 1.
(5) Anderson, L. *The Carbohydrates; Chemistry and Biochemistry*; Pigman, W., Horton, D., Eds.; Academic Press: New York, 1972; Vol. Ia, pp 519–579.
(6) Akiyama, T.; Nishimoto, H.; Ozaki, S. *Tetrahedron Lett.* **1991**, *32*, 1335. Akiyama, T.; Takechi, N.; Shima, H.; Ozaki, S. *Chem. Lett.* **1990**, 1881. Akiyama, T.; Nishimoto, H.; Kuwata, T.; Ozaki, S. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 180.
(7) Plouvier, V. *Bull. Soc. Chim. Biol.* **1963**, *45*, 1079.
(8) van Alphen, J. *J. Ind. Eng. Chem.* **1951**, *43*, 141.
(9) Carless, H. A. J.; Oak, K. B. O. Z. *Synlett* **1993**, 672.
(10) Angyal, S. J.; Hoskinson, R. M. *Methods Carbohydr. Chem.* **1963**, *2*, 87.
(11) Chida, N.; Yamada, K.; Suzuki, M.; Ogawa, S. *J. Carbohydr. Chem.* **1989**, *8*, 319.
(12) Chida, N.; Yamada, K.; Suzuki, M.; Ogawa, S. *J. Carbohydr. Chem.* **1992**, *11*, 137.
(13) Paulsen, H.; van Deyn, W.; Röben, W. *Liebigs Ann. Chem.* **1984**, 433.
(14) Paulsen, H.; Heiker, F. R. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 904.
(15) Paulsen, H.; Heiker, F. R. *Liebigs Ann. Chem.* **1981**, 2180.
(16) Chida, N.; Tanikawa, T.; Tobe, T.; Ogawa, S. *J. Chem. Soc., Chem. Commun.* **1994**, 1247.
(17) Chida, N.; Yamada, K.; Ogawa, S. *J. Chem. Soc., Chem. Commun.* **1991**, 588.
(18) Chida, N.; Yamada, K.; Ogawa, S. *Chem. Lett.* **1992**, 687.
(19) Chida, N.; Tobe, T.; Suwama, M.; Ohtsuka, M.; Ogawa, S. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2667. Chida, N.; Tobe, T.; Suwama, M.; Ohtsuka, M.; Ogawa, S. *J. Chem. Soc., Chem. Commun.* **1990**, 994
(20) Chida, N.; Tobe, T.; Ogawa, S. *Tetrahedron Lett.* **1991**, *32*, 1063.
(21) Bath, S.; Billington, D. C.; Gero, S. D.; Quiclet-Sire, B.; Samadi, M. *J. Chem. Soc., Chem. Commun.* **1994**, 1495.
(22) Akiyama, T.; Shima, H.; Ohnari, M.; Okazaki, T.; Ozaki, S. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 3760.
(23) Akiyama, T.; Shima, H.; Ozaki, S. *Synlett* **1991**, 831.
(24) Akiyama,T.; Takechi, N.; Shima, H.; Ozaki, S. *Chem. Lett.* **1990**, 1881.
(25) Berridge, M. J.; Irvine, R. F. *Nature* **1989**, *341*, 197.
(26) For reviews see: Kozikowski, A. P.; Fauq, A. H.; Malaska, M. J.; Tückmantel, W.; Ognyanov, V. I.; Powis, G. *Curr. Med. Chem.* **1994**, *1*, 1. Potter, B. V. L. In *Drug Design for Neuroscience*; Kozikowski, A. P., Ed.; Raven Press Ltd.: New York, 1993.
(27) Liu, C.; Nahorski, S. R.; Potter, B. V. L. *J. Chem. Soc., Chem. Commun.* **1991**, 1014. Liu, C.; Nahorski, S. R.; Potter, B. V. L. *Carbohydr. Res.* **1992**, *234*, 107.
(28) Lampe, D.; Liu, C.; Potter, B. V. L. *J. Med. Chem.* **1994**, *37*, 907. Liu, C.; Nahorski, S. R.; Safrany, S. T.; Potter, B. V. L. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 1523. Liu, C.; Al-Hafidh, J.; Westwick, J.; Potter, B. V. L. *Bioorg. Med. Chem.* **1994**, *2*, 253. Kozikowski, A. P.; Fauq, A. H.; Wilcox, R. A.; Nahorski, S. R. *J. Org. Chem.* **1994**, *59*, 2279.
(29) For reviews see: Kozikowski, A. P.; Fauq, A. H.; Powis, G.; Medler, D. C. *Med. Chem. Res.* **1991**, *1*, 277. Kozikowski, A. P.; Fauq, A. H.; Malaska, M. J.; Tückmantel, W.; Ognyanov, V. I.; Powis, G. *Curr. Med. Chem.* **1994**, *1*, 1. Fauq, A. H.; Kozikowski, A. P.; Ognyanov, V. I.; Wilcox, R. A.; Nahorski, S. R. *J. Chem. Soc., Chem. Commun.* **1994**, 1301. 3-Fluoro,chloro analogues: Kozikowski, A. P.; Xia, Y.; Rusnak, J. M. *J. Chem. Soc., Chem. Commun.* **1988**, 1301. Kozikowski, A. P.; Fauq, A. H.; Rusnak, J. M. *Tetrahedron Lett.* **1989**, *30*, 3365. Kozikowski, A. P.; Fauq, A. H. *J. Am. Chem. Soc.* **1990**, *112*, 7403. Kozikowski, A. P.; Fauq, A. H.; Powis, G.; Melder, D. C. *J. Am. Chem. Soc.* **1990**, *112*, 4528. 3-Azido,amino analogues: Kozikowski. A. P.; Fauq, A. H.; Powis, G.; Kurian, P.; Crews, F. T. *J. Chem. Soc., Chem. Commun.* **1992**, 362. Kozikowski, A. P.; Fauq, A. H.; Wilcox, R. A.; Challiss, J.; Nahorski, S. R. *J. Med. Chem.* **1994**, *37*, 868. 3-Deoxy analogues: Seewald, M. J.; Aksoy, I. A.; Powis, G.; Fauq, A. H.; Kozikowski, A. P. *J. Chem. Soc., Chem. Commun.* **1990**, 1638. Kozikowski, A. P.; Ognyanov, V. I.; Fauq, A. H.; Nahorski, S. R.; Wilcox, R. A. *J. Am. Chem. Soc.* **1993**, *115*, 4429. 3-Trifluormethyl analogue: Kozikowski, A. P.; Ognyanov, V. I.; Fauq, A. H.; Wilcox, R. A.; Nahorski, S. R. *J. Chem. Soc., Chem. Commun.* **1994**, 599. 3-Phosphonate analogue: Kozikowski, A. P.; Powis, G.; Gallegos, A.; Tückmantel, W. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 1323.
(30) Kozikowski, A. P.; Tückmantel, W.; Powis, G. *Angew. Chem., Int. Ed. Engl.* **1992**, *32*, 1379. Fauq, A. H.; Kozikowski, A. P.; Gallegos, A.; Powis, G. *Med. Chem. Res.* **1993**, *3*, 17. Kozikowski, A. P.; Powis, G.; Fauq, A. H.; Tückmantel, W.; Gallegos, A. *J. Org. Chem.* **1994**, *59*, 963. Kozikowski, A. P.; Kiddle, J. J.; Frew, T.; Berggren, M; Powis, G. *J. Med. Chem.* **1995**, *38*, 1053.
(31) Angyal, S. J.; Odier, L. *Carbohydr. Res.* **1980**, *80*, 203.
(32) Akiyama, T.; Takechi, N.; Ozaki, S. *Tetrahedron Lett.* **1990**, *31*, 1433.
(33) Akiyama, T.; Takechi, N.; Ozaki, S.; Shiota, K. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 366.
(34) Jope, R. S.; Williams, M. B. *Biochem. Pharmacol.* **1994**, *47*, 429.
(35) Mercier, D.; Barnett, J. E. D.; Gero, S. D. *Tetrahedron* **1969**, *25*, 5681.

CR941114U