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FEATURE ARTICLE

Synthesis of acyclic and heterocyclic natural products utilizing cyclitols as novel chiral building blocks

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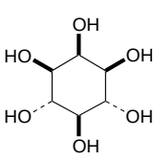
The synthesis of biologically important natural products which contain acyclic or heterocyclic structures, starting from cyclitols, is described. Stereoselective functionalization and subsequent regioselective ring cleavage of cyclitol derivatives provides precursors for the synthesis of a wide variety of natural products. The successful synthesis of acyclic and heterocyclic natural products reveals the usefulness and importance of cyclitols as novel chiral building blocks.

Introduction

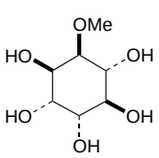
The synthesis of natural products possessing biological activity and interesting structures in an enantiomerically pure form is a highly important area of modern organic and medicinal chemistry. To construct the asymmetric centres in the target molecule, compounds with established asymmetric centres, such as naturally occurring amino acids,[1] terpenes[2] and carbohydrates, are frequently employed as the starting material (chiral building block).[3] Among them, carbohydrates, especially aldohexoses such as d-glucose, have been widely used due to their ready availability and versatility.[4] Cyclitols (polyhydroxycycloalkanes), which are classified as a type of carbohydrate, occur widely in nature.[5] *myo*-Inositol **1**, known as a constituent of a secondary messenger in cells which stimulates the release of calcium from storage sites, is easily obtained from corn-steep liquors and commercially available at relatively low price.‡ While *myo*-inositol is a meso compound, l-quebrachitol [1l-(−)-2-*O*-methyl-*chiro*-inositol] **2**, isolated in large quantities from the serum of the rubber tree,[6]§ is an optically active cyclitol possessing a methyl ether function. In spite of their abundance in nature and ready availability, cyclitols have not been utilized widely as starting materials for the synthesis of natural products other than cyclitol derivatives. Given that regioselective cleavage of their cyclohexane ring is possible, cyclitols are expected to be versatile starting materials for the synthesis of acyclic or heterocyclic natural products. In this article, the synthesis of several acyclic and heterocyclic natural products starting from cyclitols (*myo*-inositol and l-quebrachitol), based on tactics involving stereoselective functionalization followed by regioselective ring cleavage of the cyclitol ring, are described.

Regioselective ring cleavage of the cyclohexane ring in cyclitols

A major advantage in using cyclitol as a starting material compared with aldohexoses is that there are no synthetic limitations imposed by the presence of a hemiacetal functionality. The cyclic structure as well as the established protection-deprotection methods of polyhydroxy groups[5] in cyclitols allowed us to introduce many kinds of functional groups stereoselectively on the cyclohexane ring. If one could cleave the cyclohexane ring in functionalized cyclitol derivatives at any chosen position, the array of chiral centres from the cyclitol derivatives, which are sometimes difficult to obtain from convensional sugars such as d-glucose, d-galactose, d-mannitol and so on, could be transferred to the target molecule. To cleave the cyclohexane ring in cyclitols, oxidative glycol cleavage would be anticipated to be an effective and reliable method. However, difficulty is sometimes encountered in distinguishing between the two newly formed formyl carbons. On the other hand, Baeyer–Villiger reaction of polyhydroxycyclohexanone derivatives possessing oxygen and other functionalities at the α-carbons is an attractive method to cleave the cyclohexane ring, since the terminal carbons of the product usually have different oxidative states. Early studies on the Baeyer–Villiger reaction of polyhydroxycyclohexanones derived from *myo*-inositol by Fukami *et al.*[7] revealed that the reaction proceeded in a highly regioselective manner, and suggested that the substituent on the α-carbon should be an important factor for influencing the regioselectivity. To clarify the governing factor controlling the regioselectivity, a series of unsymmetrical polyhydroxycyclohexanone derivatives were synthesized from *myo*-inositol and l-quebrachitol, and subjected to Baeyer–Villiger reaction.[8] Some results are shown in Scheme 1. This study showed that the migratory ability of substituted carbons adjacent to the carbonyl in the polyhydroxycyclohexanone system are strongly affected by the nature of substituents on the α-carbon; the migratory aptitudes are: a carbon possessing benzyloxy > methoxy > cyclic ketaloxy ≫ acyloxy ≈ methyl > hydrogen. These results suggested that n-electron density on the oxygen atom attached to the adjacent carbon to the carbonyl is of significance, implying that an n–σ*≠ interaction (Cieplak postulate[9]) might account for the observed regioselectivity. Thus it should now be possible to design polyhydroxycyclohexanone derivatives which undergo regioselective Baeyer–Villiger reaction.



myo-inositol **1**



L-quebrachitol **2**

Synthesis of natural products starting from *myo*-inositol

Iduronic acid derivative and nojirimycin

Since *myo*-inositol **1** is a *meso* compound, chemical transformation usually provides *meso* or racemic products. Therefore it is necessary to perform an asymmetric reaction[10] or optical resolution[11] to prepare optically pure *myo*-inositol derivatives. Cyclic ketal formation of **1** gave racemic **3**[12] in high yield (Scheme 2). After *O*-benzylation, diol **4** was obtained by acidic hydrolysis. When diol **4** was reacted with an equimolar amount of (*S*)-(+)-α-(acetoxy)phenylacetic acid in the presence of 1,3-dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) at −15 °C, formation of a pair of diastereoisomers (**5D** and **5L**) was observed. These compounds are easily separated by silica gel chromatography or recrystallization to

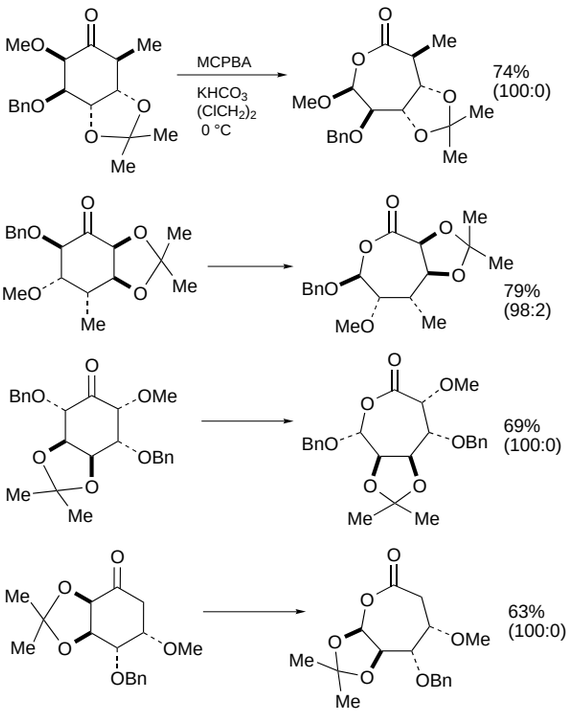
provide **5D** and **5L** in 36 and 35% isolated yields, respectively. Removal of the (*S*)-(+)-α-(acetoxy)phenylacetyl group from **5D** afforded **4D**, and from **5L** gave **4L**, both in quantitative yield. The absolute configurations of **4D** and **4L** were confirmed by comparison of their $[\alpha]_D$ values with literature ones,[11a] and the optical purities of **4D** and **4L** were estimated to be > 98% ee, respectively, by HPLC analyses using a chiral column (chiralcel OD).

Oxidation of **5L** afforded ketone **6**, whose Baeyer–Villiger reaction with MCPBA proceeded in a highly regioselective manner and provided the 7-membered acetal lactone **7**. Treatment of **7** with MeOH and $HC(OMe)_3$ in the presence of toluene-*p*-sulfonic acid (TsOH) caused the lactone ring to open, providing acyclic product **8** after methyl ester formation. This compound was transformed into l-iduronic acid derivative **9L**.[13] Similar treatment of **5D** provided the enantiomer **9D**.[13]

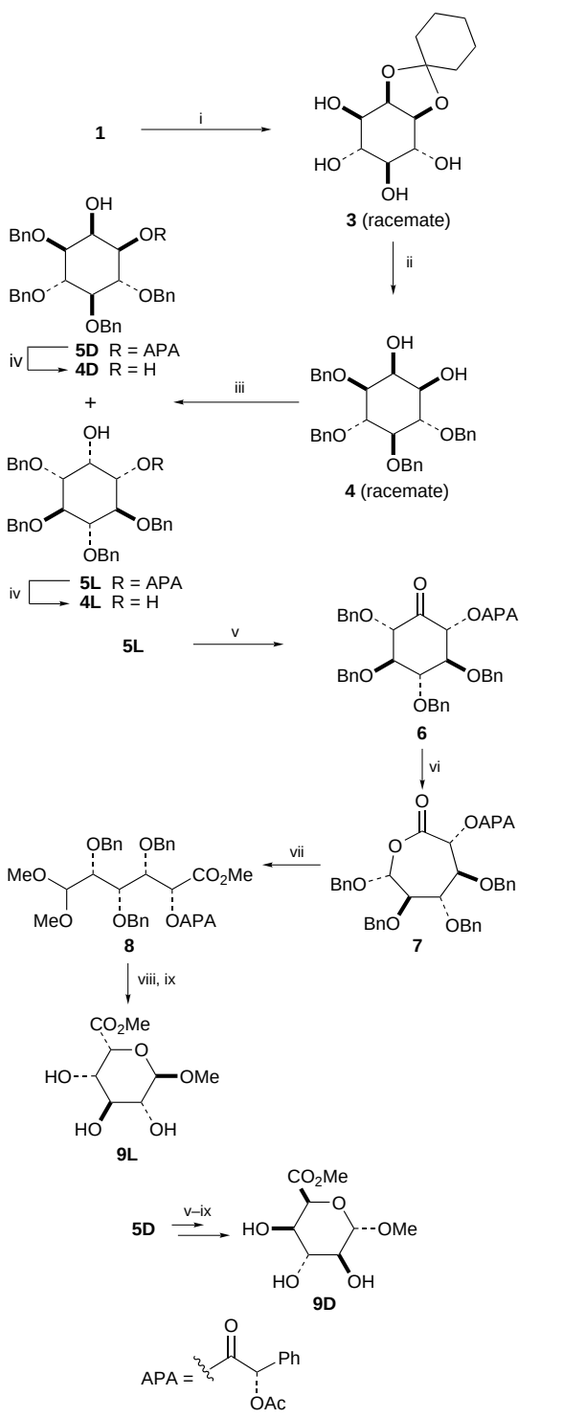
The acyclic sugar derivative **8** is a versatile intermediate for the synthesis of natural products possessing polyhydroxy functionality. DIBAL-H reduction of **8** gave diol **10** (Scheme 3), whose primary hydroxy group was selectively protected to afford **11**. Introduction of an amino functionality by Mitsunobu reaction provided **12**. Compound **12** was effectively converted into (+)-nojirimycin bisulfite adduct **13**.[14] (+)-Nojirimycin **14**[14] and (+)-1-deoxynojirimycin **15**[14b] were easily obtained from the adduct **13**.

Sphingofungin D

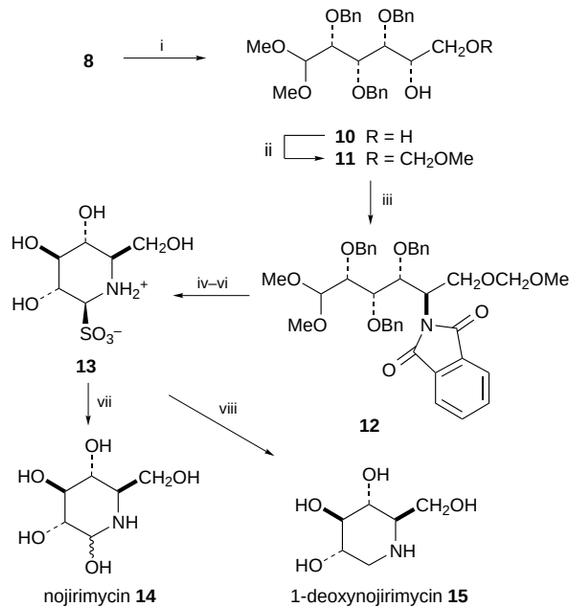
Compound **8** was also employed for the total synthesis of the novel antifungal agent sphingofungin D (*N*-acetyl asperfungin) (Scheme 4).[15] Acidic hydrolysis of the dimethyl acetal group in **8** afforded the corresponding acyclic *aldehydo*-sugar, whose Wittig reaction with $Ph_3P{=}CHCO_2Et$ provided *E*-alkene **16**. This was transformed into allyl bromide **18** in three steps. Reaction of **18** with sulfone **19**, which was synthesized from the coupling product of commercially available (*R*)-epoxyoctane and 4-[(tetrahydropyran-2-yl)oxy]butylmagnesium chloride in four steps, followed by desulfonization afforded the C_{20} backbone **21** of sphingofungins. Removal of the acetonide group provided diol **22**. Although introduction of an amino functionality at the C-2 position in **22** by intermolecular S_N2 reaction was difficult, it was found that intramolecular nitrogen delivery worked well for this substrate. Thus, Mitsunobu reaction of **22** afforded epoxide **23**, which was transformed into primary azide **24**. Treatment of **24** with Ph_3P followed by reaction with ZCl generated inverted aziridine **26**, whose



Scheme 1 Partial decomposition of the products during silica gel chromatography was observed. The ratios of the major product and its regioisomer were determined by 270 MHz ^1H NMR analysis of the products before isolation.



Scheme 2 *Reagents and conditions*: i, cyclohexanone, TsOH, C_6H_6; ii, NaH, BnCl, DMF; iii, (*S*)-(+)-(AcO)CHPhCO_2H, DCC, DMAP, CH_2Cl_2, −15 °C; iv, MeONa, MeOH; v, CrO_3 in dil. H_2SO_4, Me_2CO, 0 °C; vi, MCPBA, $KHCO_3$, $(ClCH_2)_2$, 0 °C; vii, TsOH, $HC(OMe)_3$, MeOH, 80 °C, then CH_2N_2, CH_2Cl_2; viii, 3% methanolic HCl, reflux; ix, H_2, 20% $Pd(OH)_2$ on carbon, EtOH.

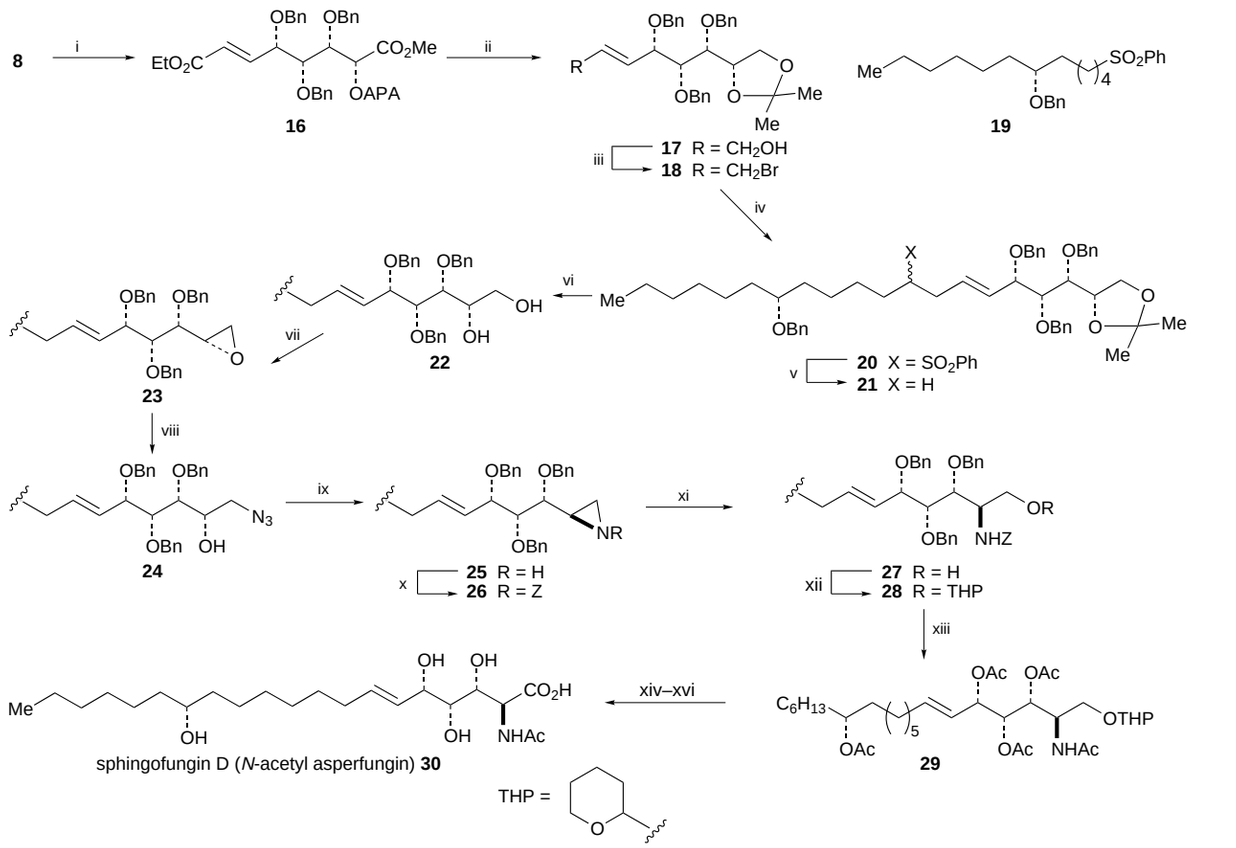


Scheme 3 *Reagents and conditions*: i, $LiAlH_4$, THF, 0 °C; ii, $MeOCH_2Cl$, Pr^i_2NEt, CH_2Cl_2, 0 °C; iii, phthalimide, Ph_3P, diethyl azodicarboxylate (DEAD), THF, room temp.; iv, $H_2NNH_2{\cdot}H_2O$, MeOH, reflux, then Boc_2O, Et_3N, CH_2Cl_2; v, H_2, 20% $Pd(OH)_2$ on carbon, EtOH; vi, SO_2(gas), H_2O, 40 °C; vii, Dowex 1 X2 resin (OH^- form), H_2O; viii, H_2, Raney-Ni (W-4), $Ba(OH)_2$, H_2O.

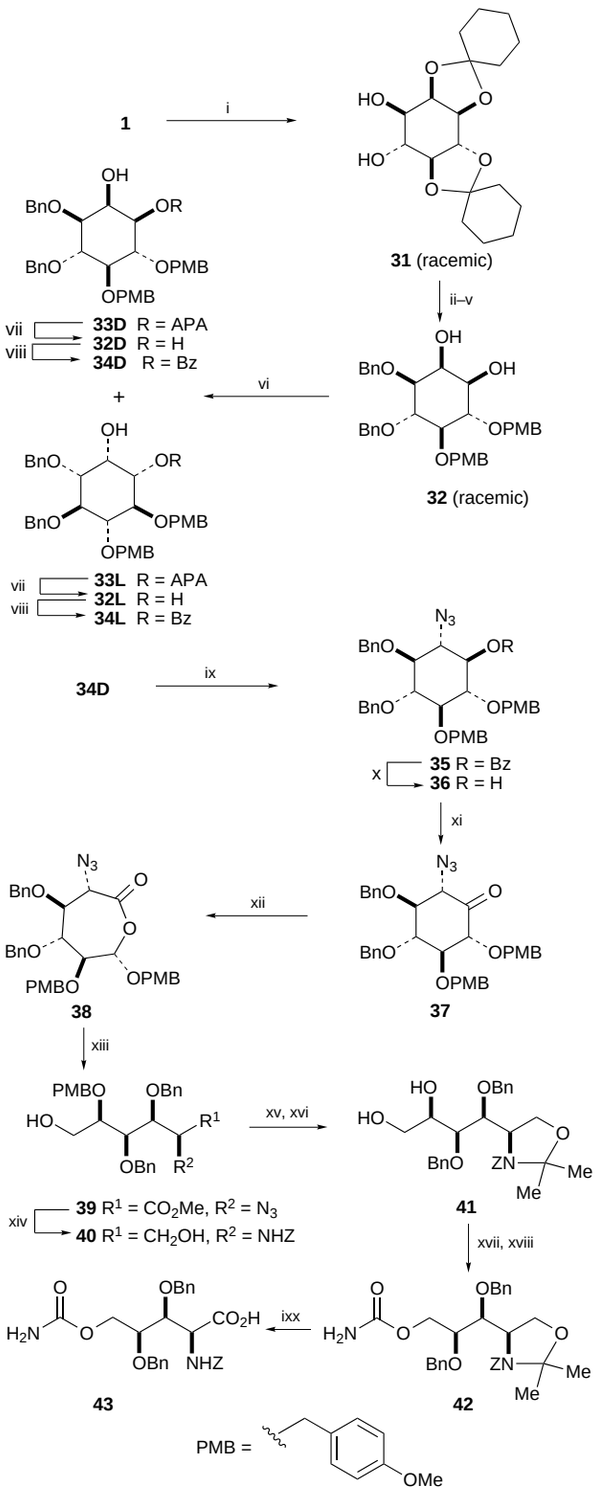
aziridine ring was cleaved with KOAc to provide **27** after hydrolysis of the *O*-acetyl function. The primary hydroxy group was protected as a tetrahydropyran-2-yl (THP) ether to afford **28**. Treatment of **28** with Li–NH_3 gave **29** after *N*,*O*-acetylation. Removal of the *O*-THP group and subsequent oxidation, followed by de-*O*-acetylation afforded sphingofungin D **30**. This total synthesis confirmed the proposed C-2–C-5 stereochemistry, and assigned the undetermined absolute configuration at C-14 in sphigofungins to be *R*.[15]

Polyoxin J

The antifungal antibiotic polyoxin J **55** consists of two fragments, amino acid portion **43** and nucleic acid portion **53**. These two key fragments were synthesized from a pair of optically resolved *myo*-inositol derivatives (**32D** and **32L**), respectively.[16] The known racemic diol **31**,[12] prepared from **1** in one step was converted into another racemic diol **32** (Scheme 5). Optical resolution of **32** using (*S*)-(+)-α-(acetoxy)phenylacetic acid afforded **33D** and **33L**, which are easily separated by silica gel chromatography. Basic methanolysis of **33D** and **33L** provided optically active diols **32D** and **32L**, respectively. Synthesis of the amino acid moiety in polyoxin J employed **32D**, which was converted into **34D**. After introduction of an azide group in an S_N2 fashion, ketone **37** was subjected to Baeyer–Villiger reaction to provide lactone **38** as the sole product. Basic opening of the lactone ring followed by reduction gave acyclic product **39**. Further reduction of the ester and azide functions and subsequent protection of the amino group afforded diol **40**. *N*,*O*-Acetalization and removal of the *para*-methoxybenzyl (PMB) group gave **41**, and subsequent



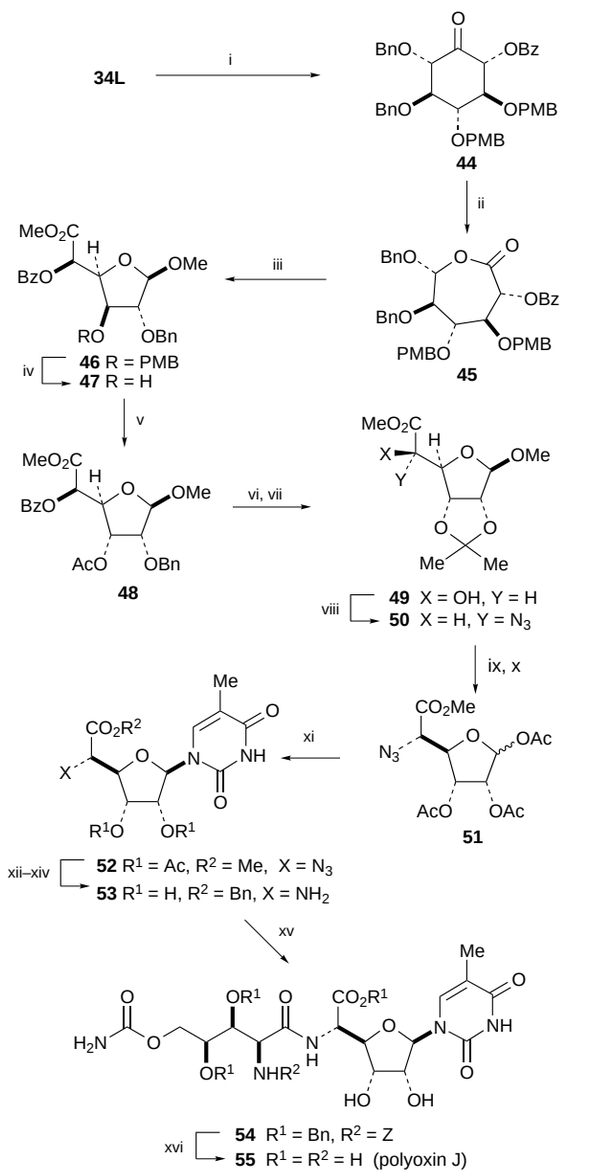
Scheme 4 *Reagents and conditions*: i, AcOH–H_2O (4:1), 80 °C, then $Ph_3P{=}CHCO_2Et$, CH_2Cl_2, room temp.; ii, DIBAL-H, CH_2Cl_2, 0 °C, then Me_2CO, camphorsulfonic acid (CSA), 0 °C; iii, Ph_3P, CBr_4, CH_2Cl_2, room temp.; iv, BuLi, **19**, THF–HMPA (10 : 1), −78 °C; v, Na–Hg (6%), Na_2HPO_4, THF–MeOH (1 : 1), room temp.; vi, CSA, MeOH, room temp.; vii, Ph_3P, DEAD, PhMe, reflux; viii, NaN_3, DMF–H_2O (9 : 1), 100 °C; ix, Ph_3P, toluene, 50 °C, 30 min, then reflux; x, ZCl, Et_3N, CH_2Cl_2; xi, AcONa, 15-crown-5, DMF, 100 °C, then K_2CO_3, MeOH, room temp.; xii, 3,4-dihydro-2*H*-pyran, pyridinium toluene-*p*-sulfonate (PPTS), CH_2Cl_2, room temp.; xiii, Na, THF–liq. NH_3 (1 : 1), −78 °C, then Ac_2O, pyridine, room temp.; xiv, PPTS, EtOH, 50 °C; xv, CrO_3 in dil. H_2SO_4, acetone, 0 °C; xvi, LiOH, THF–H_2O (2 : 1), room temp.



Scheme 5 *Reagents and conditions*: i, 1,1-dimethoxycyclohexane, TsOH, DMF; ii, NaH, BnBr, DMF; iii, TsOH, EtOH, room temp.; iv, NaH, 4-$MeOC_6H_4CH_2Cl$, DMF; v, AcOH–H_2O (4 : 1), 80 °C; vi, (*S*)-(+)-(AcO)CHPhCO_2H, DCC, DMAP, CH_2Cl_2, −15 °C; vii, MeONa, MeOH, 0 °C; viii, BzCl, DMAP, pyridine, room temp.; ix, $MeSO_2Cl$, pyridine, 50 °C, then NaN_3, DMF, 80 °C; x, MeONa, MeOH; xi, dimethyl sulfoxide, DCC, CF_3CO_2H, pyridine, C_6H_6, room temp.; xii, MCPBA, $KHCO_3$, $(ClCH_2)_2$, 0 °C; xiii, $NaBH_4$, MeONa, MeOH, 0 °C; xiv, $LiAlH_4$, Et_2O, then ZCl, $NaHCO_3$, THF–H_2O; xv, 2,2-dimethoxypropane, TsOH, DMF, then Ac_2O, pyridine; xvi, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), CH_2Cl_2–H_2O, then MeONa, MeOH; xvii, $Pb(OAc)_4$, C_6H_6, room temp., then $NaBH_4$, MeOH; xviii, 4-nitrophenyl chloroformate, then NH_3–MeOH, CH_2Cl_2; ixx, TsOH, MeOH, room temp., then CrO_3 in dil. H_2SO_4, Me_2CO, 0 °C.

glycol cleavage followed by carbamoylation gave **42**. This was transformed into amino acid moiety **43**.

On the other hand, preparation of the nucleoside portion started from the enantiomeric diol **32L** (Scheme 6). Baeyer–Villiger reaction of the ketone **44** derived from **32L** in two steps afforded the acetal lactone **45** as the sole product. Acidic methanolysis of **45** followed by methyl ester formation provided furanoside **46** as the major product. Interestingly, the PMB group at C-3 in **45** was removed under the acidic reaction conditions. Inversion of the C-3 hydroxy group in **46** and subsequent exchange of the protecting groups gave **49**, into



Scheme 6 *Reagents and conditions*: i, pyridinium dichromate, molecular sieves 4A, CH_2Cl_2; ii, MCPBA, $KHCO_3$, $(ClCH_2)_2$, 0 °C; iii, TsOH, $HC(OMe)_3$, MeOH, room temp., then MeI, $NaHCO_3$, DMF; iv, DDQ, CH_2Cl_2–H_2O; v, $(CF_3SO_2)_2O$, pyridine, CH_2Cl_2, 0 °C, then AcOK, DMF, 5 °C; vi, MeONa, MeOH then H_2, $Pd(OH)_2$, EtOH; vii, 2,2-dimethoxypropane, TsOH, DMF, room temp.; viii, $(CF_3SO_2)_2O$, pyridine, CH_2Cl_2 then NaN_3, DMF, room temp.; ix, Dowex 50W X8 (H^+ form), MeOH, room temp., then Ac_2O, pyridine; x, Ac_2O, H_2SO_4, CH_2Cl_2–AcOH; xi, 5-methyl-2,4-bis(trimethylsilyloxy)pyrimidine, $Me_3SiOSO_2CF_3$, CH_2Cl_2, room temp.; xii, H_2, 5% Pd–$BaSO_4$, dioxane–H_2O, then $Ba(OH)_2$, dioxane–H_2O, room temp.; xiii, Boc_2O, K_2CO_3, dioxane–H_2O, then BnBr, $NaHCO_3$, DMF, room temp.; xiv, CF_3CO_2H, EtOAc, 0 °C; xv, **43**, $(EtO)_2P(O)CN$, Et_3N, DMF, room temp.; xvi, H_2, 10% Pd–C, MeOH–H_2O.

which was introduced an azide function with inversion of configuration to provide **50**. Acetolysis of **50** gave **51**, which was condensed with 5-methyl-2,4-bis(trimethylsilyloxy)pyrimidine under Vorbruggen conditions to afford **52**. This was transformed into the benzyl ester of the nucleoside portion **53** of polyoxin J in four steps. Coupling of **43** with **53** using the Shioiri procedure gave **54**, deprotection of which provided polyoxin J **55**.[16]

Synthesis of natural products starting from l-quebrachitol

Bengamide A, B and E

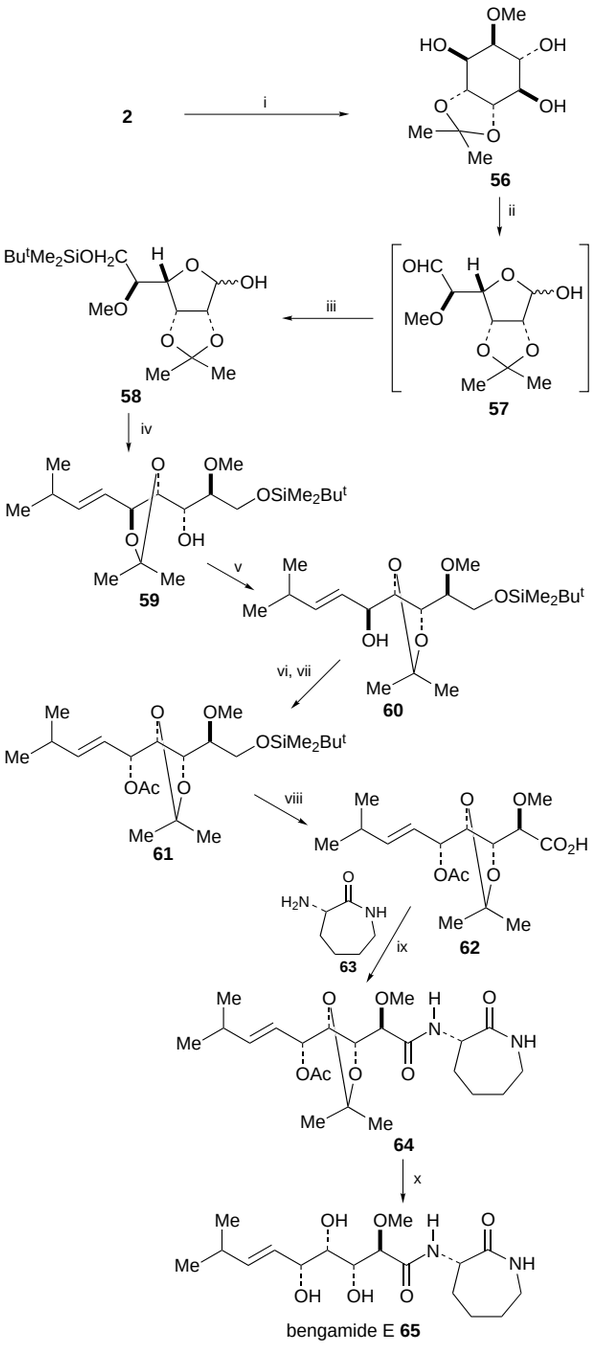
l-Quebrachitol **2** is optically active and has a convenient configuration for the selective protection of hydroxy groups. Compounds derived from **2** by cleavage of the cyclohexane ring are expected to be versatile and useful chiral building blocks for the synthesis of a variety of natural products. A short synthesis of l-mannitol from **2** reported by Angyal and Hoskinson[17] in 1963 revealed the effectiveness of this approach. We applied this approach to the total synthesis of the bengamides,[18,19] which are novel amino acid derivatives with anti-infectious disease activity isolated from marine organisms.

Periodate oxidation of mono-*O*-isopropylidene derivative **56**[20] of l-quebrachitol gave dialdofuranose derivative **57** (Scheme 7). Spontaneous furanose ring formation allowed us to distinguish the two formyl carbons generated by the oxidation. Treatment of **57** with $NaBH_4$ followed by silyl ether formation provided furanose **58**, which was subjected to Wittig olefination to give *E*-alkene **59** as the major product. In this reaction, the combination of base (BuLi) and solvent (benzene) was found to be essential for the selective formation of the *E*-alkene. Mild acid treatment of **59** caused the migration of acetonide group and the partial removal of the $SiMe_2Bu^t$ group. After resilylation, the C-5 hydroxy group in **60** was inverted by an oxidation-reduction procedure followed by *O*-acetylation to give **61**. Oxidation of the primary hydroxy group gave carboxylic acid **62**, which was condensed with cyclo-l-lysine **63** under the conditions of Shioiri to afford **64**. Deprotection of **64** provided bengamide E **65**. This first total synthesis fully confirmed the proposed structure of bengamide E.[18]

The novel hydroxylated caprolactams **68** and **69** found in bengamide A and B, respectively, were initially synthesized from l-glutamic acid[19*a*] in non-stereoselective manner, and later from l-quebrachitol stereoselectively using Pd-catalysed regio- and stereo-selective azidation of conduritol derivative **66** as the key reaction[19*b*] (Scheme 8). Similar condensation of the caprolactams **68** and **69** with **62** gave **70** and **71**, respectively. Selective acylation of **70** and **71** with myristic acid, (tetradecanoic acid), followed by deprotection, furnished the total synthesis of bengamide A **72**[19*a*] and B **73**.[19*b*]

Oudemansin X

If one can introduce carbon substituents into cyclitol rings stereoselectively, the usefulness of cyclitols as chiral building blocks would be further extended. We pursued this idea, which culminated in the total synthesis of the novel antifungal antibiotic oudemansin X **86** (Scheme 9).[21] Peterson olefination of ketone **74**[20] derived from **2** in two steps, gave *exo*-alkene **75**. Removal of the *trans*-*O*-isopropylidene group gave **76**, whose hydrogenation afforded **77** exclusively. The bicyclic structure in **76** completely controlled the reaction face. Periodate oxidation of **77**, followed by reduction and benzoylation, provided **78**, which was converted into another diol **79**. Glycol cleavage of **79** followed by $NaBH_4$ treatment gave four-carbon unit **80**. After one-carbon homologation by introduction of a cyano group, the benzoyl group was deprotected and the resulting alcohol was oxidized to give aldehyde **83**. Wittig olefination and subsequent isomerization of the double bond, or Takai reaction (formation of *E*-vinyl iodide) followed by Pd-catalysed cross-coupling reaction of **83**, provided the β-styryl compound **84**. The nitrile group in **84** was converted into a methoxycarbonyl group to give **85**, whose lithium ester enolate was trapped with methyl formate; *O*-methylation with dimethyl sulfate completed the first total synthesis of oudemansin X **85**.[21]



Scheme 7 *Reagents and conditions*: i, 2,2-dimethoxypropane, TsOH, DMF; ii, $NaIO_4$, Me_2CO–H_2O (5:1), 0 °C; iii, $NaBH_4$, MeOH, 0 °C, then Bu^tMe_2SiCl, Et_3N, DMAP, CH_2Cl_2, room temp.; iv, $Me_2CHCH_2P^+Ph_3Br^-$, BuLi, C_6H_6, room temp.; v, TsOH (5 mol%), MeCN, 0 °C then Bu^tMe_2SiCl, Et_3N, DMAP, CH_2Cl_2; vi, MnO_2, CH_2Cl_2, room temp., then $Zn(BH)_4$, Et_2O–PhMe, −78–0 °C; vii, Ac_2O, pyridine, room temp.; viii, Bu_4NF, AcOH, THF, then CrO_3 in dil. H_2SO_4, Me_2CO, 0 °C; ix, **63**, $(EtO)_2P(O)CN$, Et_3N, DMF; x, MeONa, MeOH, then CF_3CO_2H–THF–H_2O.

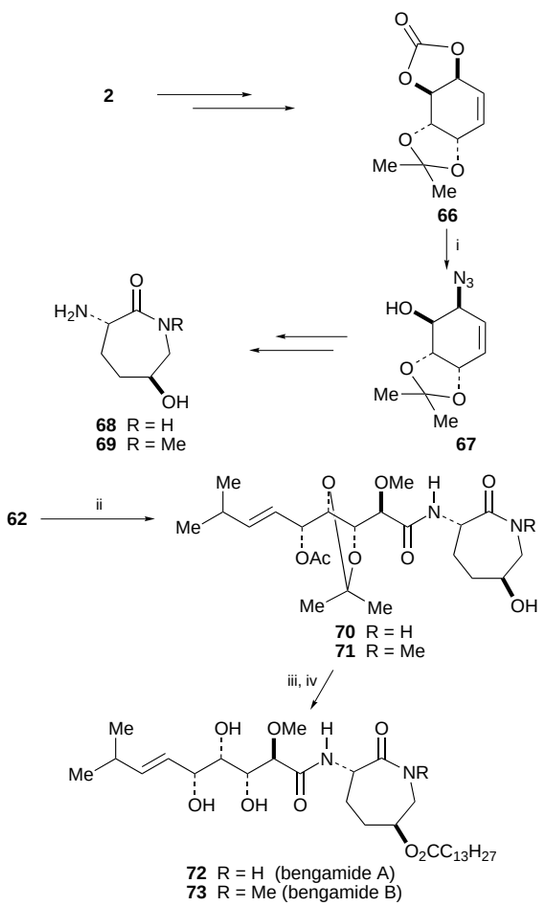
Other related work

As discussed above, cyclitols, by their regioselective ring cleavage, have now become useful chiral building blocks for the preparation of acyclic and heterocyclic natural products. Successful implementation of this strategy by our group has given: d- and l-galactose derivatives,[6b] l-mannose, l-talo and l-guluronate derivatives,[22] (−)-isoavenaciolide,[23] (−)-ethisolide,[23b] (+)-galactostatin,[24] (+)-1-deoxygalactostatin,[24] restricticin[25] (from l-quebrachitol) and lincosamine[26] (from *myo*-inositol).

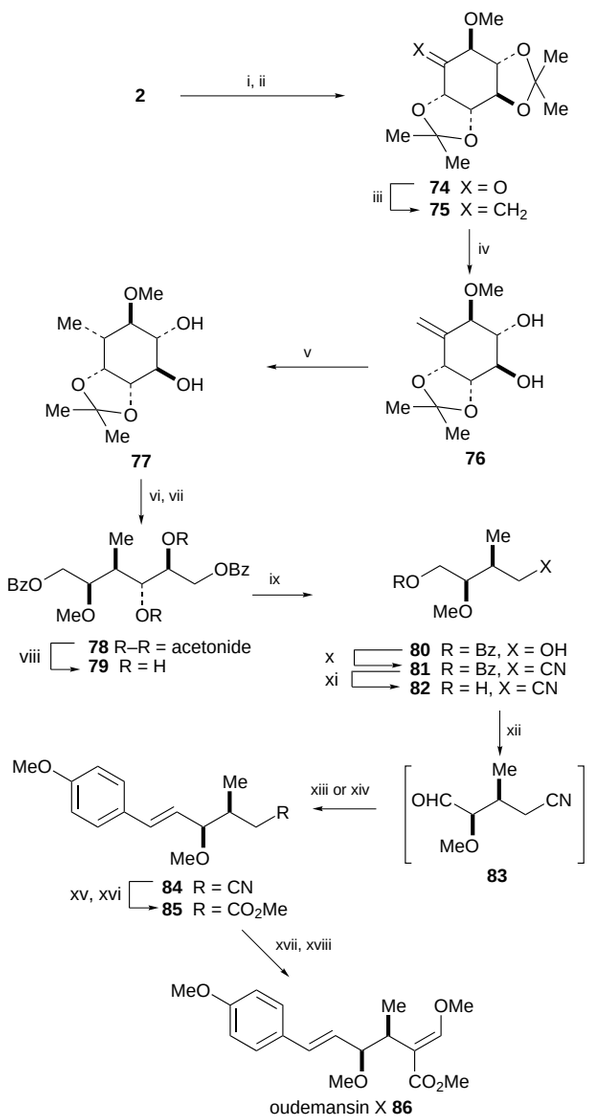
Since l-quebrachitol is an optically active polyhydroxy cyclohexane derivative, transformation of l-quebrachitol into natural or unnatural products having polyfunctional cyclohexane structures is also important work. Such approaches include syntheses of: aminocyclitols by Ogawa and co-workers,[27] carba-sugar derivatives by Paulsen *et al.*[28] (−)-ovalicine by Bath *et al.*[29] cyclophellitol by Akiyama and co-workers,[30] inositol phosphate derivatives by Kozikowski and co-workers,[31] Akiyama and co-workers[32] and Potter and co-workers,[33] and simmondsin by Chida and co-workers.[34] Utilization of l-quebrachitol as a chiral auxiliary in asymmetric synthesis is reported by Akiyama and co-workers.[35] Other applications of l-quebrachitol in the preparation of bioactive compounds are found in the recent excellent review by Kiddle.[36]

Conclusions

We have shown that cyclitols are versatile chiral building blocks in natural product synthesis. The cyclic structure of cyclitols allowed us to introduce a variety of functionalities regio- and stereo-selectively on the cyclohexane ring. By subsequent cleavage of the cyclohexane ring at a chosen position, cyclitols serve as useful precursors for acyclic and heterocyclic natural products. The regioselective Baeyer–Villiger reaction can be used for the successful implementation of such approaches. As *myo*-inositol and l-quebrachitol are readily available in large quantities from plants, they are expected to be used widely as a chiral building block for the synthesis of structurally complex natural or non-natural products, and are also expected to be employed as raw materials for the preparation of non-carbohydrate products in the chemical industry.



Scheme 8 *Reagents and conditions*: i, NaN_3, $Pd(PPh_3)_4$ (3 mol%), THF–H_2O (5 : 1), room temp.; ii, **68** or **69**, $(EtO)_2P(O)CN$, Et_3N, DMF; iii, MeONa, MeOH, then $C_{13}H_{27}CO_2H$, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, DMAP, CH_2Cl_2–THF, −50 to −15 °C; iv, MeONa, MeOH, then CF_3CO_2H–THF–H_2O.



Scheme 9 *Reagents and conditions*: i, 2,2-dimethoxypropane, TsOH, DMF; ii, RuO_2, $NaIO_4$, $CHCl_3$, room temp.; iii, Me_3SiCH_2MgCl, THF, then KH, THF, room temp.; iv, TsOH, MeOH, 0 °C; v, H_2, Raney-Ni (W-4), EtOH, room temp.; vi, $NaIO_4$, $NaHCO_3$, Me_2CO–H_2O, 0 °C, then $NaBH_4$, MeOH, 0 °C; vii, BzCl, pyridine, viii, AcOH–H_2O (4 : 1), 70 °C; ix, $NaIO_4$, $NaHCO_3$, Me_2CO–H_2O, 0 °C then $NaBH_4$, MeOH, 0 °C; x, $MeSO_2Cl$, pyridine, then NaCN, DMF, 50 °C; xi, MeONa, MeOH, 0 °C; xii, pyridinium chlorochromate, CH_2Cl_2; xiii, $Ph_3P^+CH_2C_6H_4$(*p*-OMe)Cl^-, BuLi, THF, 0 °C then PhSH, AlBN, C_6H_6, reflux; xiv, CHI_3, $CrCl_2$, DMF–THF, room temp., then (*p*-OMe)C_6H_4MgBr, $Pd(PPh_3)_4$ (5 mol%), C_6H_6, room temp.; xv, DIBAL-H, CH_2Cl_2, acidic (aq. H_2SO_4) work up; xvi, $NaClO_2$, NH_2SO_3H, NaH_2PO_4, Bu^{t}OH–H_2O, room temp., then CH_2N_2, Et_2O–CH_2Cl_2; xvii, $(Me_3Si)_2NLi$, THF, −78 to −40 °C, then HCO_2Me; xviii, $(MeO)_2SO_2$, K_2CO_3, Me_2CO, room temp.

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Footnotes

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‡ *myo*-Inositol is produced in large quantities as a food ingredient and can be purchased (*ca*. $100 per 1 kg) from most reagent suppliers.

§ l-Quebrachitol is now commercially available from MYFEC SDN, BHD, 76100 Durian Tunggal, Melaka, Malaysia.

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