Tetrahedron 67 (2011) 2355–2389

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Tetrahedron report number 934

Recent advances in inositol chemistry: synthesis and applications

Benan Kılbaş [a], Metin Balci [b,*]

[a] Department of Chemistry, Faculty of Sciences, Düzce University, 81620 Düzce, Turkey
[b] Department of Chemistry, Middle East Technical University, 06531 Ankara, Turkey

ARTICLE INFO

Article history:
Received 13 December 2010
Available online 13 January 2011

Contents

1. Introduction

Cyclitols, described as polyhydroxy-substituted cycloalkanes with at least three hydroxy groups, each attached to a different ring carbon atom, have for the past decades attracted interest due to their significant biological properties and diverse synthetic intermediates.[1] Among the cyclitols, chemists have extensively studied inositols due to their remarkable, comprehensive, and important biological functions[2] including glycosidase inhibitors, intercellular communication, protein anchoring, phosphate storage etc. In recent years, inositol phosphates, which are important players in diverse cellular functions, such as cell growth, apoptosis, cell migration, endocytosis, and cell differentiation, have been particularly studied and new derivatives have been discovered, which possess vital biological and physiological functions in cellular signaling events. For instance, D-*myo*-inositol-1,4,5-trisphosphate [Ins(1,3,5,)P_4], a second messenger molecule, is used in intracellular transduction events, such as controlling the intracellular Ca^{+2} concentration.[3]

Abbreviations: AIBN, azobis(isobutyronitrile); BOMl, benzyloxymethyl; CSA, camphorsulfonic acid; DABCO, 1,4-diazabicyclo[2.2.2]octane; DABP, diethylamino-2,3,4-benzodioxaphosphepane; DBH, 1,3-dibromo-5,5-dimethylhydantoin; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; DCC, dicyclohexyl carbodiimide; DDQ, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; DEAD, diethyl azodicarboxylate; DIBAL, diisobutylaluminum hydride; DMA, dimethylacetamide; DMAD, dimethyl acetylenedicarboxylate; DMAP, 4-dimethylaminopyridine; DME, 1,2-dimethoxyethane; DMP, 2,2-dimethoxypropane; DMS, dimethyl sulfide; DPCP, diphenyl chlorophosphate; *m*-CPBA, *meta*-chloroperbenzoic acid; MOMCl, methyl chloromethyl ether; MPM, 4-OMe−PhCH(OMe)$_2$; NMI, *N*-methylimidazole; NBS, *N*-bromosuccinimide; NMO, NMMO, *N*-methylmorpholine-*N*-oxide; PCC, pyridinium chlorochromate; PMBCl, *p*-methoxybenzyl chloride; PMB, 4-*p*-methoxybenzyl; PTS, pyridinium *p*-toluenesulfonate; PTSA, *p*-toluenesulfonic acid; TBA, tetra-*n*-butylammonium; TBSCl, *tert*-butyldimethylsilylchloride; TBDMSCl, *tert*-butyldimethylsilylchloride; TBDMS, *tert*-butyldimethylsilyl; TBDPSCl, *tert*-butyldiphenylsilylchloride; TBME, *tert*-butyl methyl ether; TIPDSCl$_2$, 1,3-dichloro-1,1,3,3,-tetraisopropyldisiloxane; TEA, triethylamine; TFA, trifloroacetic acid; TIPS, triisopropylsilyl; TMSOTf, trimethylsilyl trifluoromethanesulfonate; TPP, *meso*-tetraphenylporphyrin; TrocCl, 2,2,2-trichloroethyl chloroformate.

* Corresponding author. Tel.: +90 312 210 5140; fax: +90 312 210 3200; e-mail address: mbalci@metu.redu.tr (M. Balci).

0040-4020/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2011.01.012

Inositols (cyclohexanehexols) are a class of cyclitols that possess nine possible isomers (**1**–**9**). Five are known as naturally occurring inositols namely *myo*-, *chiro*-, *scyllo*-, *muco*-, and neo-inositols and the unnaturally occurring isomers are *cis*-, *epi*-, and *allo*-inositols (Fig. 1).

Among the possible isomers, *myo*-inositol is the most abundant that is found in eukaryotic cells, including inositol phosphates,

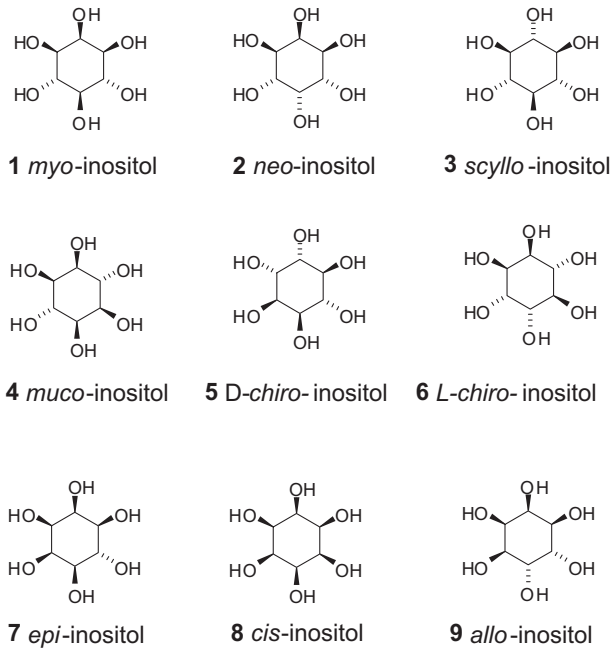


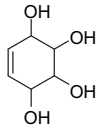
Fig. 1. Structures of isomeric inositols.

phosphatidylinositol (PI), and phosphatidylinositol phosphate (PIP) lipids as secondary messengers.[3h] In plants, the hexaphosphate of inositol is found as phytic acid. *myo*-Inositol (**1**) has a *meso* configurational structure and, therefore, it possesses a symmetry plane with five equatorial and one axial hydroxy group. The other inositol derivatives can be obtained by epimerization of one or two hydroxy groups of *myo*-inositol.[3b,4]

Numerous synthetic approaches for inositol derivatives have been developed including the use of naturally occurring inositols,[5] sugars,[6] aromatic compounds,[7] chiral acids,[8] tetrahydrobenzoquinone,[9] cyclohexene and its derivatives,[10] and norbornene.[11] This report is intended to provide an overview of new synthetic methodologies for inositols and their derivatives, primarily covering the literature published in the last decade. Furthermore, the report is not intended to be comprehensive, but rather to highlight those advances that are of most interest to synthetic chemists.

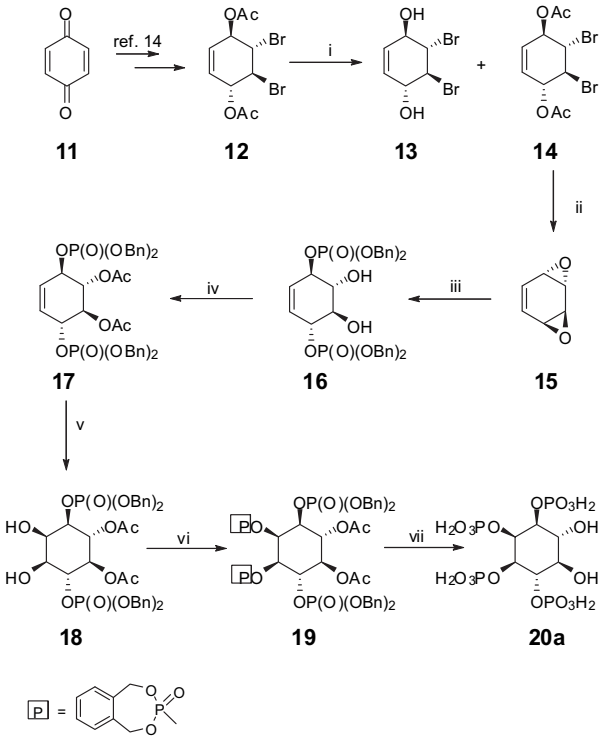
2. Synthesis of inositols via conduritols from benzoquinone

Conduritols have remarkable biological properties, namely they act as glycosidase inhibitors like inositols.[1d] They have one more remarkable biological property namely that they are t is particularly useful as glycosidase inhibitors like inositols.[1d]



Recently, conduritols have been used as precursors of the corresponding inositol derivatives. This is because of the presence of four hydroxy group and a C=C double bond in **10**. Hydroxylation of the double bond provides the synthesis of diverse inositols. Altenbach et al.[12] developed a new synthetic approach to *myo*-inositol tetrakisphosphate derivatives, such as Ins(1,2,3,4)P_4 **20a** and Ins(1,2,3,6)P_4 **20b** (the enantiomer of **20a**) starting from *p*-benzoquinone.

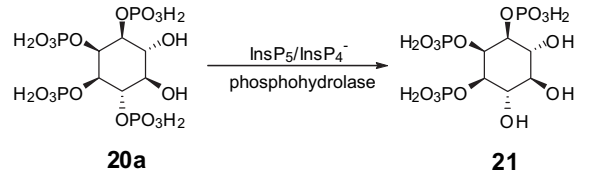
Racemic dibromodiacetate **12** obtained from *p*-benzoquinone (**11**) in three steps was subjected to enzymatic resolution with pig pancreas lipase to afford enantiomerically pure dibromo compounds **13** and **14**.[13] The reaction of **14** with base in methanol in turn yielded the diepoxide **15** followed by a ring-opening reaction with dibenzyl phosphate, which afforded diphosphoconduritol-B **16** (Scheme 1). Because conduritol-B has C_2-symmetry, it can easily be converted into *myo*-inositol derivatives. Acetylation of **16** to form **17** followed by cis-dihydroxylation led to protected *myo*-inositol derivative **18**. Phosphorylation of **18**, which was followed by oxidation with *m*-CPBA, gave **19**. Hydrogenation and subsequent cleavage of the acetate groups in aqueous NaOH afforded the corresponding compound **20a**. Synthesis of the enantiomer **20b** was also achieved.



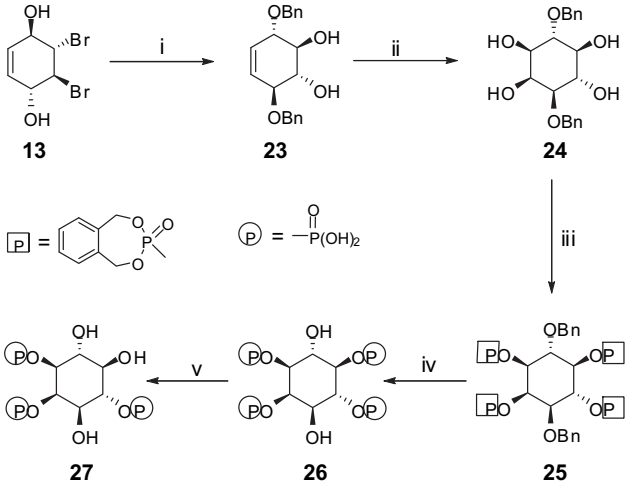
Scheme 1. Reagents: (i) Pig pancreas lipase; (ii) KOH, THF, 80%; (iii) dibenzyl phosphate, 55%; (iv) Ac_2O, pyridine, quant; (v) $RuCl_3$, $NaIO_4$, 86%; (vi) DABP, 1*H*-tetrazole then *m*-CPBA, 80%; (vii) Pd/C, H_2 then 0.25 M NaOH, quant.

After isolation, **20a** and **20b** were exposed to enzymatic dephoshorylation reactions with the appropriate phytases to furnish inositol triphosphates **21** and **22**, as shown in Scheme 2.

For the synthesis of isomeric phosphorylated *myo*-inositol derivatives, enantiomerically pure dibromodiol **13** was easily converted into conduritol-B derivative **23** with sodium benzylate in benzyl alcohol (Scheme 3) followed by cis-dihydroxylation to give **24**. The phosphorylation of **24** and subsequent oxidation with *m*-CPBA provided **25**. The deprotection of the Ins(1,2,4,5)P_4 derivative **25** was achieved in one step by Pd-catalyzed hydrogenation to give **26**. The triphosphate Ins(1,2,4)P_3 **27** was achieved by the dephosphorylation of **26**.[14] Furthermore, Altenbach et al.[15] succeeded in achieving the selective functionalization of axial and equatorial



Scheme 2.



Scheme 3. Reagents: (i) NaOBn, BnOH, 47%; (ii) $RuCl_3$, $NaIO_4$, 82%; (iii) DABP, 1*H*-tetrazole, then *m*-CPBA, 78%; (iv) H_2, Pd/C; (v) 5-phosphatase, quant.

hydroxy groups in conduritol-B and synthesized symmetric inositol phosphates as well as unsymmetrical, enantiomerically pure inositol phosphates.

Azido-*myo*-inositols **28** and **29** (Fig. 2), amino-*myo*-inositols, and their phosphorylated derivatives were prepared starting from conduritol-B. First, nitrogen-containing functional groups were introduced selectively into the desired positions followed by further functionalization to yield the target compounds.[16]

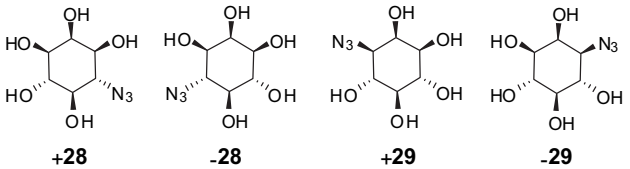
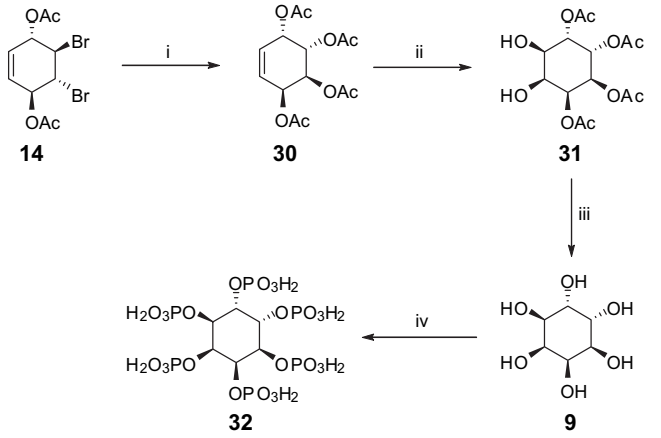


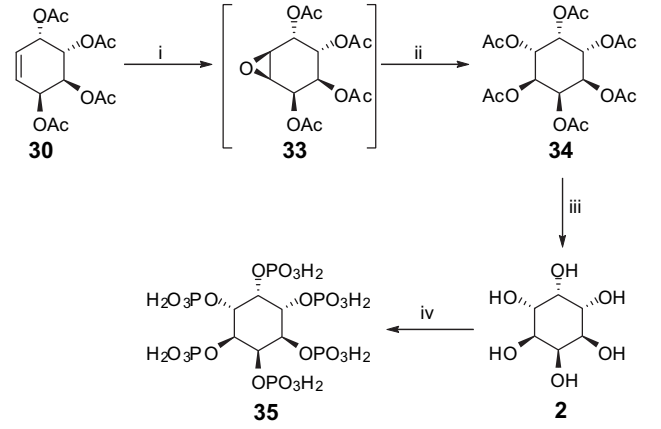
Fig. 2. Structures of azido-*myo*-inositols.

myo-Inositol synthesis from the conduritol-B derivatives attracted the synthesis of stereoisomeric inositols that differ from *myo*-inositol. Altenbach et al.[17] described new chiral inositols from key intermediates, conduritol-B, -C, -E, and, -F. Dibromodiacetate **14** was directly epimerized to conduritol-E[18] derivative **30** in the presence of aqueous acetic acid and sodium acetate, by heating for 10 days, followed by cis-hydroxylation with $RuCl_3$ and $NaIO_4$ provided (via **31**) *allo*-inositol **9**, which was transformed into the corresponding hexaphosphate derivative **32** (Scheme 4).



Scheme 4. Reagents: (i) 1. NaOAc, AcOH (95%), 10 days, Δ; 2. Ac_2O, CH_2Cl_2; (ii) $RuCl_3$, $NaIO_4$; (iii) NaOMe, MeOH; (iv) 1. (1,5-dihydro-2,4,3-benzodioxaphosphepin-3-yl)diethylamine, 1*H*-tetrazole then *m*-CPBA; 2. H_2, Pd/C, ethanol/water.

The neo-inositol (**2**) and its hexaphosphate **35** were synthesized by the epoxidation of **33** to conduritol-E **30** with trifluoroperacetic acid to give **33** followed by a subsequent ring-opening reaction (Scheme 5). The hydrolysis of **34** with NaOMe in MeOH provided the neo-inositol **2**, which was converted into the corresponding hexaphosphate **35**.[17]

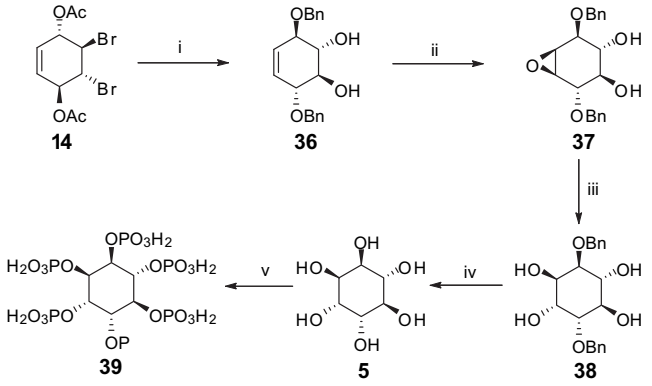


Scheme 5. (i) $(CF_3CO)_2$, H_2O_2, CH_2Cl_2, $NaHCO_3$; (ii) Ac_2O, pyridine; (iii) NaOMe, MeOH, then H_2O/NaOH; (iv) 1. (1,5-dihydro-2,4,3-benzodioxaphosphepin-3-yl)diethylamine, 1*H*-tetrazole then *m*-CPBA; 2. H_2, Pd/C, ethanol/water.

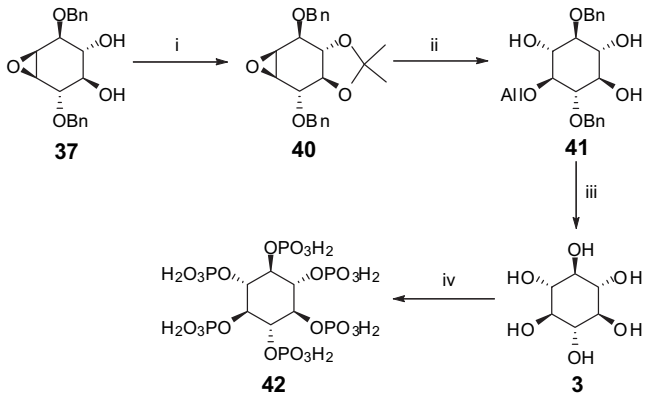
For the synthesis of *chiro*-inositol **5**, diacetate **14** was used. The reaction was carried out by heating **14** with an excess of sodium benzylate in anhydrous THF. The intermediate epoxide was opened with benzylate anion at the allylic position in order to give the conduritol-B derivative **36** in over 80% yield (Scheme 6). Direct epoxidation of **36** followed by ring opening by treatment with sulfuric acid in dioxane/water gave the *chiro*-inositol derivative **5** via **38** in high yield, which was converted into the hexaphosphate **39**.[17]

The regioselective epoxide opening of **37** was performed by the protection of the hydroxyl groups in the 5 and 6 positions with 2,2-dimethoxypropane as a cyclic isopropylidene group (Scheme 7). Treatment of the ketal **40** with allyl alcohol followed by deprotection with HCl provided **41** with a *scyllo*-inositol configuration.[17] The removal of the benzyl groups in **41** formed the pure isomer **3**, which was transformed into **42** in high yield.

Conduritol-C **45**,[18,19] a flexible precursor, was used as the key compound for the synthesis of *epi*-inositol **7**. The reaction of dibromodiacetate **14** with $RuCl_3$ and $NaIO_4$ gave **43**, which was acetylated to give **44**. Bromine elimination in **44** in the presence of zinc and acetic acid resulted in the formation of **45**.[17] Further oxidation of **45**



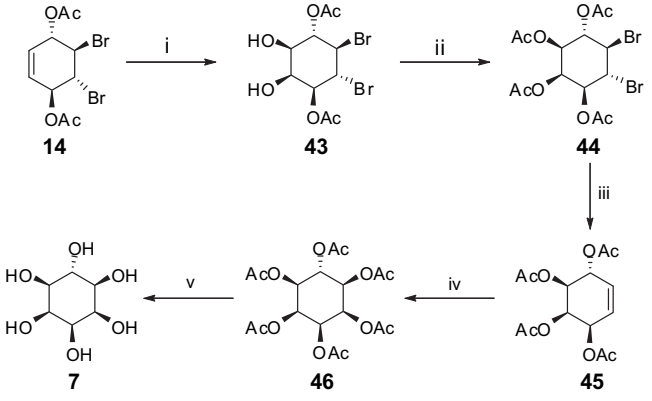
Scheme 6. Reagents: (i) NaOBn, BnOH/THF; (ii) $(CF_3CO)_2$, H_2O_2, CH_2Cl_2, Na_2CO_3; (iii) H_2SO_4, dioxane, H_2O; (iv) H_2, Pd/C, ethanol/water; (v) 1. (1,5-Dihydro-2,4,3-benzodioxaphosphepin-3-yl)diethylamine, 1*H*-tetrazole then *m*-CPBA; 2. H_2, Pd/C, ethanol/water.



Scheme 7. (i) 2,2-Dimethoxypropane, acetone, PTS; (ii) 1. NaOAll, AllOH, reflux; 2. HCl; (iii) 1. Pd/C, MeOH; 2. HCl; 3. Pd/C, H_2; (iv) 1. (1,5-Dihydro-2,4,3-benzodioxahosphepin-3-yl)diethylamine, 1*H*-tetrazole then *m*-CPBA; 2. H_2, Pd/C, ethanol/water.

with $RuCl_3$ and $NaIO_4$ followed by acetylation gave **46**, which was hydrolyzed to *epi*-inositol **7** in quantitative yield (Scheme 8).

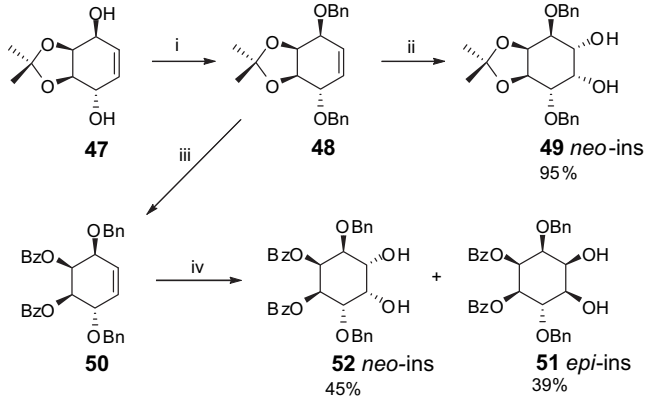
Chung et al.[20] reported the synthesis of all the possible diastereomers of conduritol in high enantiopurity starting from *myo*-



Scheme 8. (i) $RuCl_3$, $NaIO_4$, MeCN; (ii) Ac_2O, pyridine; (iii) Zn, Et_2O, AcOH; (iv) 1. $RuCl_3$, $NaIO_4$, MeCN; 2. Ac_2O, pyridine; (v) NaOMe, MeOH.

inositol. The formed conduritol derivatives were then converted into various inositol derivatives by an oxidation–reduction or Mitsunobu reaction, and cis-hydroxylation in a stereo- and regioselective manner.

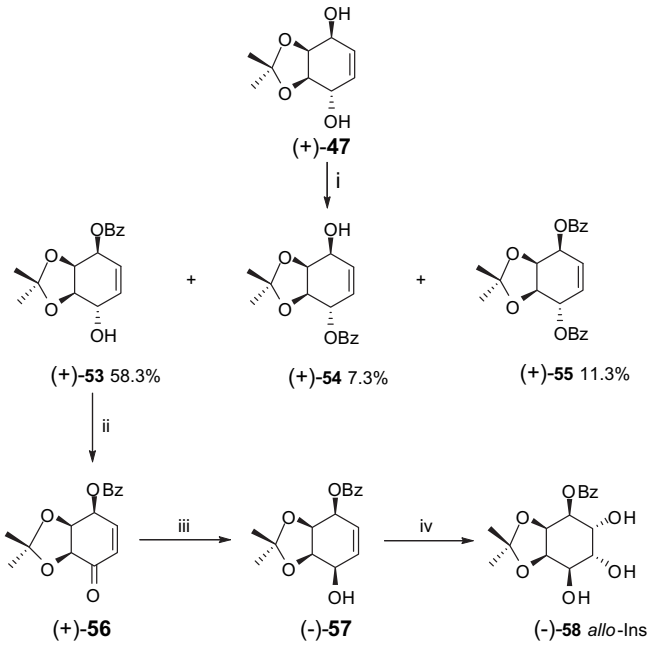
Conduritol-C derivative **47** was synthesized from *myo*-inositol under Samuelsson conditions.[20,21] The conduritol-C derivative **47** was transformed into dibenzyl derivative **48** (Scheme 9). The cis-hydroxylation of (+)-**48** with OsO_4 and NMMO in aqueous acetone gave the neo-inositol derivative **49** as expected due to steric reasons. On the other hand, the replacement of the acetonide group of **48** with benzoyl protecting groups afforded **50** followed by cis-hydroxylation, which resulted in the formation of neo-inositol **52** as well as *epi*-inositol **51** in 45 and 39% yields, respectively.



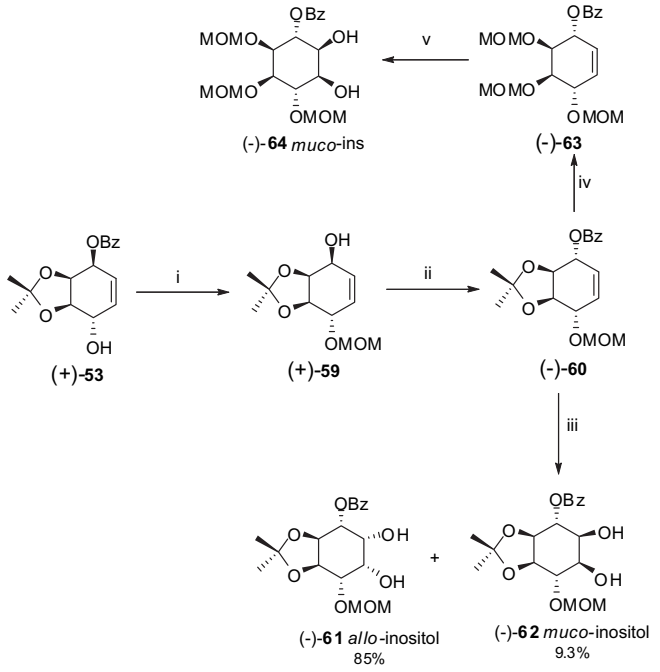
Scheme 9. (i) BnBr, NaH, DMF, 98.6%; (ii) OsO_4, NMO, aq acetone; (iii) 1. 80% aq AcOH, 100 °C; 2. BzCl, pyridine, 96%.

Selective protection of enantiomeric diol (+)-**47** with benzoyl chloride gave three separable isomers **53**–**55**. The major product **53** was oxidized to **56** by SO_3/pyridine complex and TEA in DMSO followed by reduction with $NaBH_4$, which led stereoselectively to conduritol derivative-D **57** (Scheme 10). cis-Dihydroxylation of **57** in the presence of OsO_4 and NMMO gave an *allo*-inositol derivative **58** in quantitative yield. The observed facial stereoselectivity arises from the acetonide group, which hinders the cis-addition to the olefinic group.

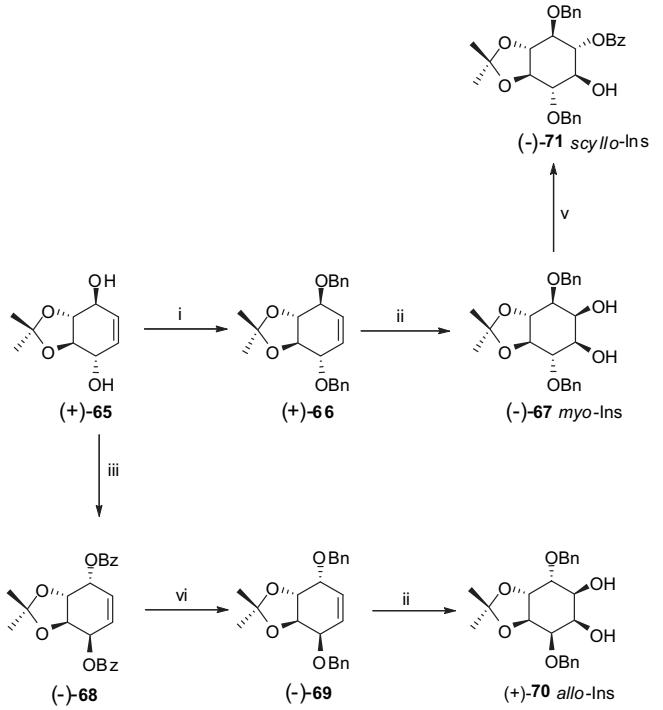
For the synthesis of *allo*- and *muco*-inositol derivatives, the hydroxyl group in **53** was protected using methyl chloromethyl ether (MOMCl) followed by deprotection of the benzoyl group that afforded **59** (Scheme 11). The stereochemistry of the hydroxyl group in **59** was inverted by treatment with BzOH, Ph_3P, and DEAD



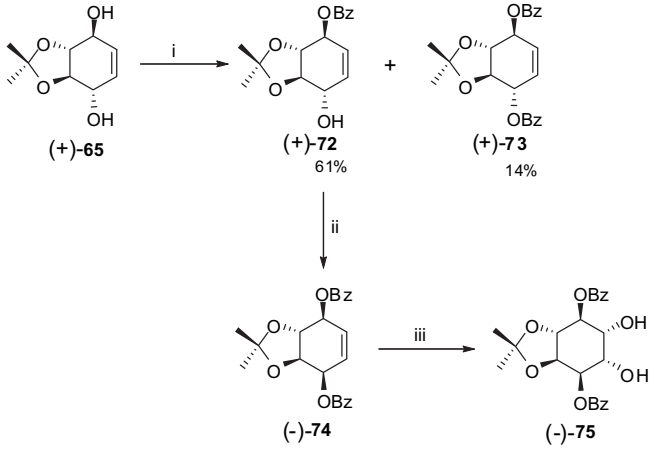
Scheme 10. (i) BzCl, pyridine; (ii) SO_3/pyridine complex, TEA, DMSO; (iii) $NaBH_4$, MeOH/CH_2Cl_2; (iv) OsO_4, NMMO, aq acetone, 88%.



Scheme 11. (i) 1. MOMCl, $(^{i}Pr)_2NEt$; 2. NaOMe, MeOH, 97.1% (ii) BzOH, Ph_3P, DEAD, toluene, rt, 97.1%; (iii) 1. OsO_4, NMMO, aq acetone; 2. BzCl, pyridine; (iv) 1. 80% aq AcOH, 70 °C; 2. MOMCl, $(^{i}Pr)_2NEt$; 2. NaOMe, MeOH, 97.1%; (v) OsO_4, NMMO, aq acetone.



Scheme 12. (i) BnBr, NaH, DMF, 96%; (ii) OsO_4, NMMO, aq acetone; (iii) BzOH, Ph_3P, DEAD, toluene, rt, 90% (iv) NaOMe, MeOH; 2. BnBr, NaH, DMF, 92%; (v) BzOH, Ph_3P, DEAD, toluene, 80 °C, 79%.



Scheme 13. (i) BzCl, pyridine; (ii) BzOH, Ph_3P, DEAD, toluene, rt, 98%; (iii) OsO_4, NMMO, aq acetone, 97.4%.

to give the conduritol-A derivative **60**. cis-Dihydroxylation of **60** led to *allo*-inositol **61** as well as *muco*-inositol **62**. The acetonide group hinders the cis approach to the double bond. The removal of the acetonide group in **60** followed by treatment with MOMCl (to give **63**) and cis-hydroxylation afforded stereoselectively the *muco*-inositol derivative **64**.

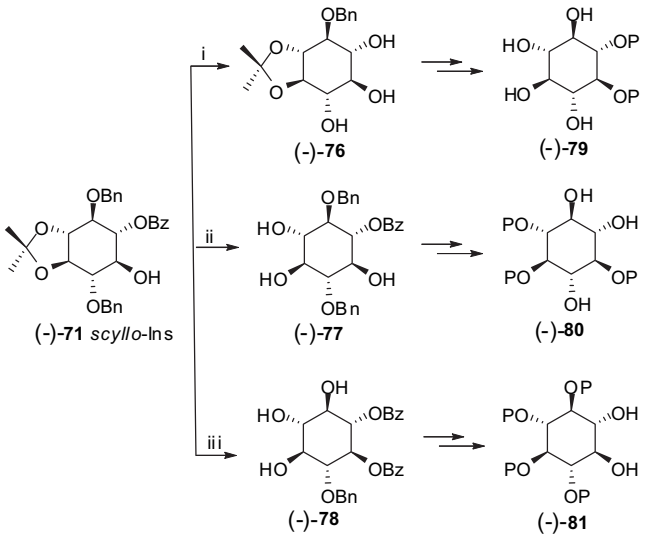
Enantiomerically pure conduritol-B derivative **66** synthesized by benzylation of **65** with NaH in DMF followed by cis-hydroxylation led to the *myo*-inositol derivative **67**. The double inversion of the hydroxyl groups in **65** was achieved by the treatment of **65** with BzOH, PPh_3, and DEAD in 90% yield to give the conduritol-E derivative **68**. Replacing the protecting groups by benzyl groups to give **69** followed by cis-hydroxylation provided the *allo*-inositol derivative **70**. Enantiomerically enriched *scyllo*-inositol derivative **71** was prepared by the Mitsunobu reaction of *myo*-inositol diol (−)-**67**, as shown in Scheme 12.[22]

Conduritol-F derivative **74** was prepared by the inversion of one of the hydroxyl groups in **65**. One of the hydroxyl groups was protected by reacting diol **65** with BzCl in pyridine to give **72** and **73** as the minor products. The inversion of configuration of the unprotected hydroxyl group in **72** was achieved by a Mitsunobu reaction to give the conduritol-F derivative **74**, which was subjected to cis-dihydroxylation to afford L-*chiro*-inositol **75** (Scheme 13).

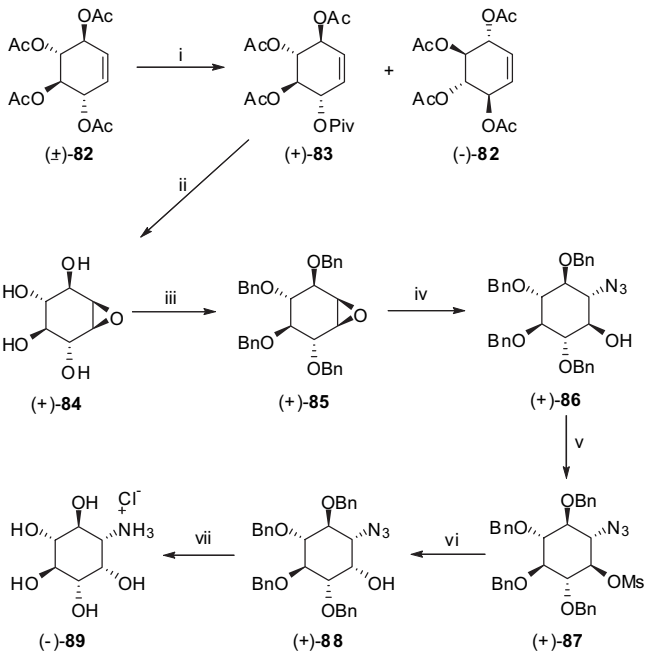
The inositol derivative **71** is a suitable protected intermediate for the synthesis of chiral phosphorylated *scyllo*-inositol derivatives (Scheme 14). Removal of the benzoate group from **71** with a catalytic amount of NaOH formed the vicinal diol **76**.[22] On the other hand, the acid-catalyzed hydrolysis of **71** provided the triol **77**. The vicinal dibenzoate **78** was prepared by the benzoylation of the free hydroxyl group in **71** followed by hydrogenolysis in the presence of a small amount of AcOH. The obtained precursors **76**–**78** were later converted into the phosphorylated compounds **79**–**81** by successive treatment with phosphoramidite and 1*H*-tetrazole, and then with *m*-CPBA.

Inosamines are inositols in which one of the hydroxyl groups is exchanged with an amino functional group. They show interesting roles in the cellular metabolism of animals, plants, and microorganisms.[23] Conduritols are not only important precursors for the synthesis of inositols, but are also important backbones for the synthesis of inosamine derivatives. Recently, Llebaria et al. have successfully synthesized an inosamine derivative with a *myo*-inositol configuration (Scheme 15).[24]

The starting material, racemic conduritol-B **82**, was resolved by Pd-catalyzed kinetic resolution using a chiral diphosphine developed by Trost and Hembre.[25] Hydrolysis of **83** followed by epoxidation to give **84** and then protection with benzyl chloride furnished **85** in 65% yield.[26] *trans*-Epoxide opening of **85** was accomplished with NaN_3 in the presence of $LiClO_4$ to give **86**. The critical point was the inversion of configuration of the free hydroxyl group after transformation into the mesylate **87**. The conversion of **87** into **88** was carried out in a sealed tube at 140 °C in DMF. Reduction of the azide functionality followed by deprotection of the



Scheme 14. (i) NaOMe, MeOH, reflux, 96%; (ii) 80% aq AcOH, 100 °C, quant; (iii) 1. BzCl, pyridine, 99%; 2. H_2 (50 psi), $Pd(OH)_2$/C, AcOH, EtOAc/MeOH, 96%.



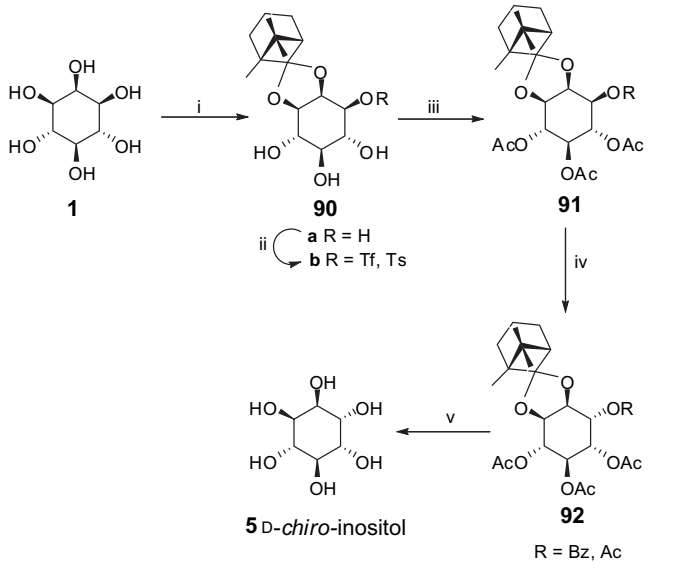
Scheme 15. (i) Diphosphine (*S,S*), $[\eta^3\text{-}C_3H_5PdCl]_2$, *n*-$Bu_4NBr$, $^tC_4H_9CO_2H$, NaOH, H_2O, CH_2Cl_2; (ii) 1. NaOMe/MeOH, 2. *m*-CBPA, MeOH; (iii) NaH, BnBr, DMF; (iv) $LiClO_4/NaN_3$, MeCN; (v) $MeSO_2Cl$, THF/TEA; (vi) DMF, 140 °C; (vii) 1. $LiAlH_4$, THF, 2. Pd/C, H_2, 3. $THF/_{aq}HCl$.

benzyl groups resulted in the formation of (−)-**89** in a *myo*-inositol configuration.

3. Synthesis of inositols via naturally abundant cyclitols and their derivatives

As mentioned previously, among the possible diastereoisomers of inositols, *myo*-inositol is inexpensive and is generally the most abundant in nature. Due to its commercially availability and having one more stereogenic center, it is a convenient starting material for the synthesis of inositol derivatives.

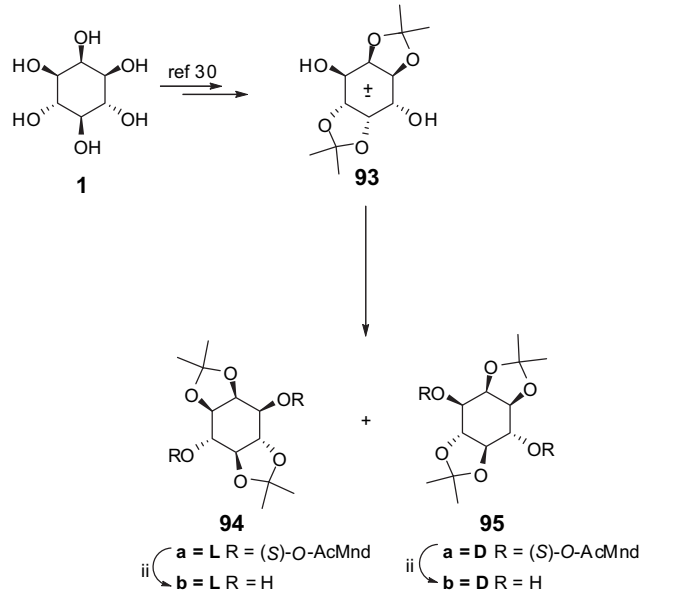
Miyake et al.[27] reported a short and practical method for *chiro*-inositol synthesis starting from the optically inactive *myo*-inositol **1** in four steps. First, *myo*-inositol was reacted with enantiomerically pure camphor dimethyl acetal to afford the ketal **90a** (Scheme 16).



Scheme 16. (i) 1. (1*R*)-(+)-Camphor dimethyl acetal, H_2SO_4, DMSO, 70 °C, 3 h, 2. MeONa, 3. *p*-TsOH, $CHCl_3$/MeOH/H_2O, 17 h, 63%; (ii) Tf_2O (or TsCl), Py/CH_2Cl_2, −20 °C, 2 h (or 20 h), 76% (or 85%); (iii) Ac_2O, Py/CH_2Cl_2; (iv) BzOLi, DMF, 80 °C, 2 h; (v) 1. MeONa, MeOH, 1 h, 2. 50% AcOH/H_2O, 80 °C, 0.5 h, 88–93%.

In order to introduce a leaving group at the C-1 carbon atom, the ketal **90a** was reacted with Tf_2O or TsCl to give the corresponding 1-triflate or 1-tosylate **90b**. The remaining hydroxyl groups were protected by conversion into the triacetate **91**. The critical point was the configuration isomerization at the C-1 carbon atom. The highest yield was obtained by the reaction of **91** with BzOLi in DMF at 80 °C to give **92**. The subsequent hydrolysis of **92** afforded D-*chiro*-inositol **5** in a quantitave yield (Scheme 16).

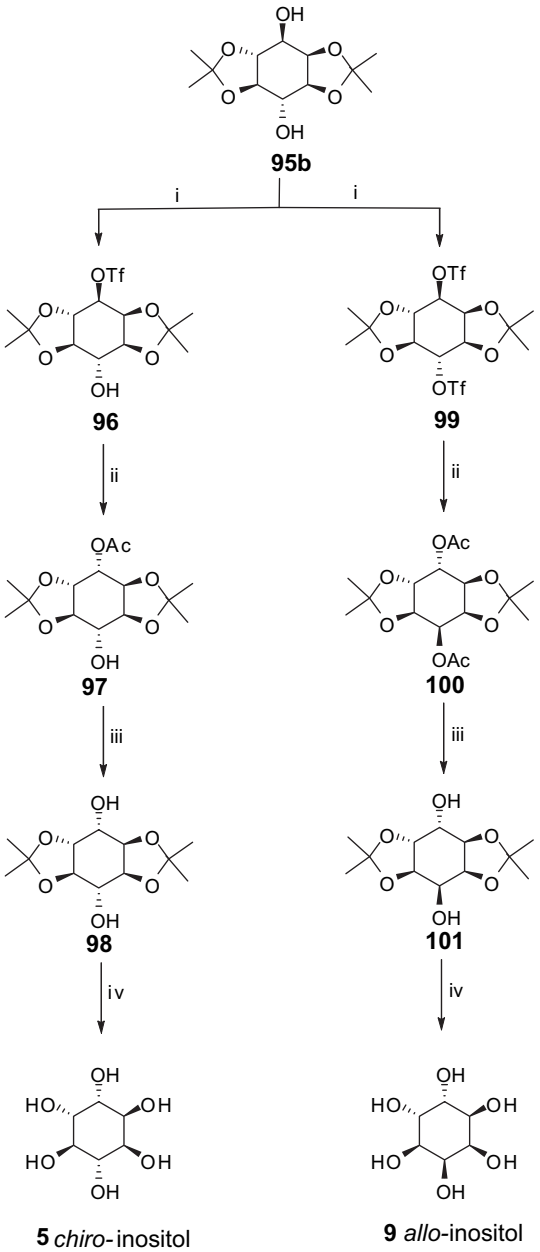
Another practical and more economical route for the synthesis of *chiro*- and *allo*-inositols starting from *myo*-inositol was reported by Watanabe and Sureshan.[28] First, 1,2:4,5-di-*O*-isopropylidene-*myo*-inositol **93**, which was used as a key intermediate, was synthesized by the reaction of *myo*-inositol with 2,2-dimethoxypropane in the presence of an acid, as reported by Gigg et al.[29] The free hydroxy groups in **93** were subjected to esterification by (*S*)-*O*-acetylmandeloyl chloride in the presence of pyridine (Scheme 17).



Scheme 17. (i) (*S*)-*O*-Acetylmandeloyl chloride, pyridine, 0 °C; (ii) isobutylamine, MeOH, reflux.

The resulting diastereoisomers **94a** and D-**95a** were separated by crystallization in a suitable solvent system followed by aminolysis with isobutylamine in methanol at reflux to give the enantiomerically pure key compounds **94b** and **95b**.

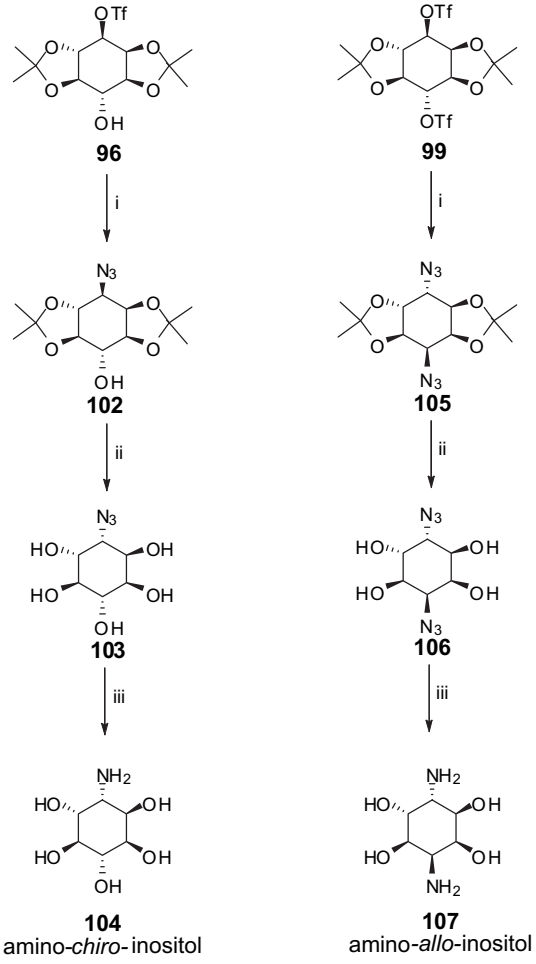
One of the free hydroxy groups of **95b** was converted into the monotriflate **96** by regioselective protection with triflic anhydride (Scheme 18).[28] The configuration isomerization of the monotriflate **96** was achieved by KOAc in DMA to give **97** as the L-chiro-inositol derivative. Methanolysis of the acetate functionality followed by acid hydrolysis of the diketal **99** provided L-*chiro*-inositol **5**.



Scheme 18. (i) Tf_2O, pyridine, CH_2Cl_2, −20 °C; (ii) KOAc, DMA, 70 °C; (iii) MeOH, Et_3N, reflux; (iv) TFA/H_2O (4:1), rt; (v) Tf_2O (2.2 equiv), pyridine, CH_2Cl_2, −20 °C; (vi) NaOMe, MeOH, reflux.

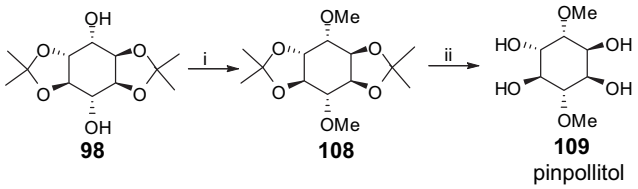
On the other hand, the sulfonylation of both free hydroxy groups with 2.2 equiv of triflic anhydride in pyridine gave the triflate **99**. Treatment of **99** again with KOAc provided *allo*-inositol derivative **100** in quantitative yield. Free *allo*-inositol **9** was obtained by the hydrolysis of the functional groups in **101** as described above (Scheme 18).

Mono and ditriflates **96** and **99** were suitable starting materials for the synthesis of amino-inositols. For the isomerization of the configuration of the triflate groups, **96** and **99** were reacted with NaN_3 in DMF to give **102** and **105** followed by the hydrolysis of the ketal groups to form **103** and **106** and hydrogenolysis of the azide functionalities to give **104** and **107** with *chiro*- and *allo*-inositol configurations, respectively (Scheme 19).[30]



Scheme 19. (i) NaN_3, DMF, 70 °C; (ii) TFA/H_2O (4:1), rt; (iii) H_2, Pd/C, MeOH, rt; (v) Tf_2O (2.2 equiv), Py, CH_2Cl_2, −20 °C.

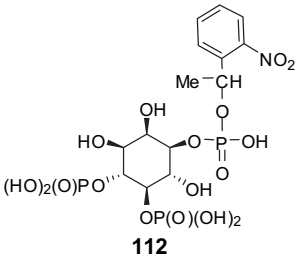
1,2:4,5-Di-*O*-isopropylidene-*myo*-inositol monotriflate **96** is also a reliable precursor for the synthesis of pinpollitol, di-*O*-methyl-(+)-*chiro*-inositol **109**. (+) Pinpollitol was isolated from the pollen and needles of the plant *Pinus radiata*.[31] The D-*chiro*-inositol structure of pinpollitol was established by a demethylation reaction, although the exact position of the methoxy groups was not assigned. The absolute structure of pinpollitol was determined by its total synthesis, as described in Scheme 20. First, **96** was converted into the *chiro*-inositol derivative **98**, as described in Scheme 18. The formed diol **98** was methylated to give **108** followed by acid



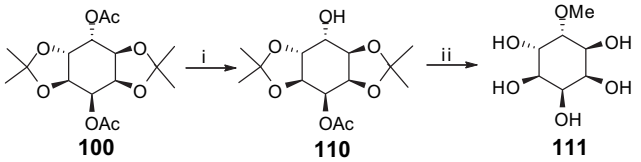
Scheme 20. (i) MeI, NaH, DMF, rt; (ii) TFA/H_2O, rt.

hydrolysis to provide the racemic 1,4-di-*O*-methyl-*chiro*-inositol **109** (Scheme 20).[32]

Brahol, a methylinositol **111**[33] isolated from the folklore medicinal plant *Stocksia brahuica*, was synthesized starting from the diacetate **100** (Scheme 21). Aminolysis of **100** with *iso*butylamine gave the monoacetate **110** in quantitative yield (Scheme 21).[34] The methylation of the free hydroxyl group with methyl iodide followed by acidic hydrolysis of the ketal groups provided the natural product, brahol **111**, in high yield.



112

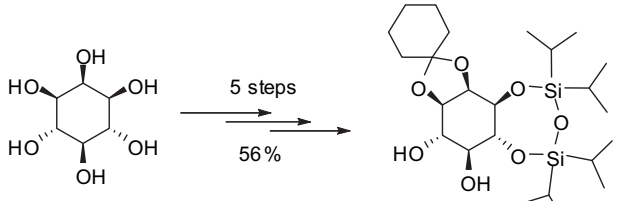


100 **110** **111** brahol

Scheme 21. (i) MeOH, Et_3N, reflux or MeOH, *iso*butylamine, 60 °C; (ii) 1. MeI, NaH, DMF, rt, 2. TFA/H_2O, rt.

Photolabile compounds that are biologically inactive, such as the 2-nitrobenzyl ester of *myo*-inositol 1,4,5-triphosphate **112**,[35] which can release the active compound *myo*-inositol (**1**) upon illumination with UV light, are called *caged* compounds.[36] Recently, Dinkel and Schultz reported the synthesis of a new enantiomerically pure Ins(1,3,4,5)P_4 derivative that has a photosensitive nitroveratryl group.[37]

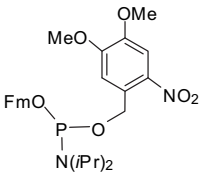
The starting material was the protected *myo*-inositol derivative **113**, which was prepared by regioselective protection of *myo*-inositol (**1**) with cyclohexanone in the presence of an acid catalyst followed by reaction with 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane (Scheme 22).[38]



1 **113**

Scheme 22.

The diol **113** was phosphorylated with bis(fluorenylmethyl) *N*,*N*-di-isopropylphosphor-amidite, followed by oxidation with ^{t}BuOOH (Scheme 23).[37] Removal of the ketal group gave the diol **114**. The regioselective esterification of the axial hydroxyl group was achieved by treatment with trimethyl orthobutyrate to give **115**. The equatorial hydroxyl group in **115** was reacted with **120** to introduce the photolabile part of the caged compound.



120 Fm = 9-fluorenylmethyl

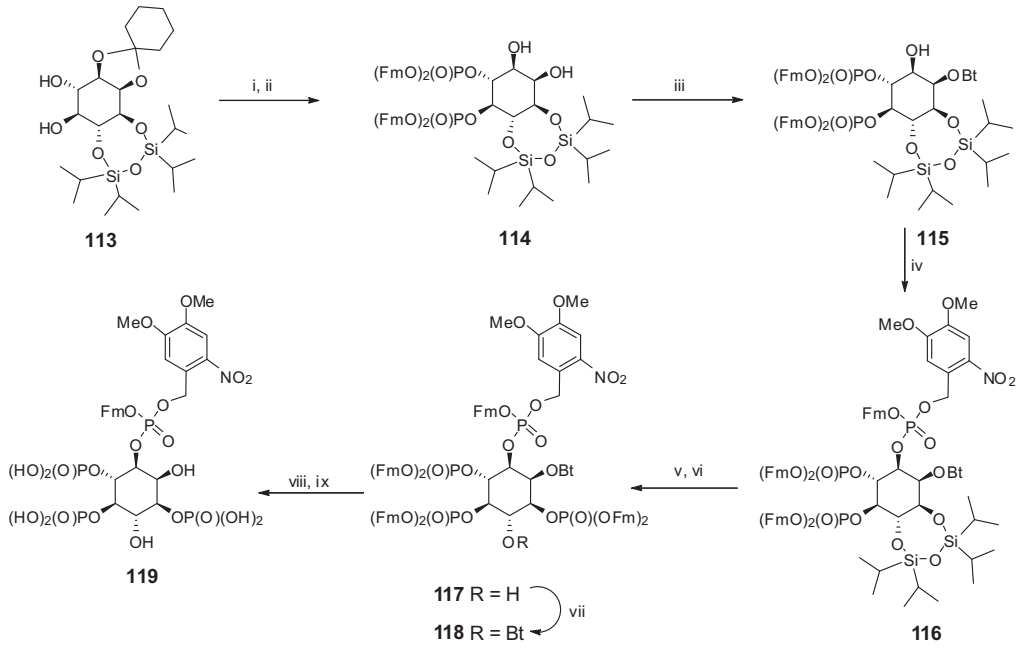
Subsequent oxidation of **116** provided the fully protected *myo*-inositol derivative **118**, via **117**. Final phosphorylation and removal of the protecting groups resulted in the formation of the target compound **119**.

Chemically resolved and protected *myo*-inositol derivative **113** was used to access the naturally occurring *myo*-inositol phosphates, which are important molecules for cell biology, particularly in intracellular signal transduction, exocytosis, and the regulation of membrane trafficking. The diol **113** was exposed to esterification followed by a known phosphorylation method to give **122** via **121** (Scheme 24).[39] Cleavage of the silyl protecting group in **122** with TBAF·3H_2O and AcOH in THF afforded **123**. Regioselective additional phosphorylation at the 3-OH position gave **124**, then subsequent deketalization resulted exclusively in the formation of **125**. The more reactive hydroxy group at the 1-O position was subjected to phosphorylation with the dipalmitoylglycerol phosphite **129** to afford **126**, which was easily transformed into **127**. The reactivity of the −OH groups was dramatically affected by the solvent system. The ratio of pyridine/dichloromethane was very important to reach the target molecule. The desired compound **128** was obtained as a single product by removal of the benzyl groups. Similar reactions were also carried out with the other enantiomer of **113**.

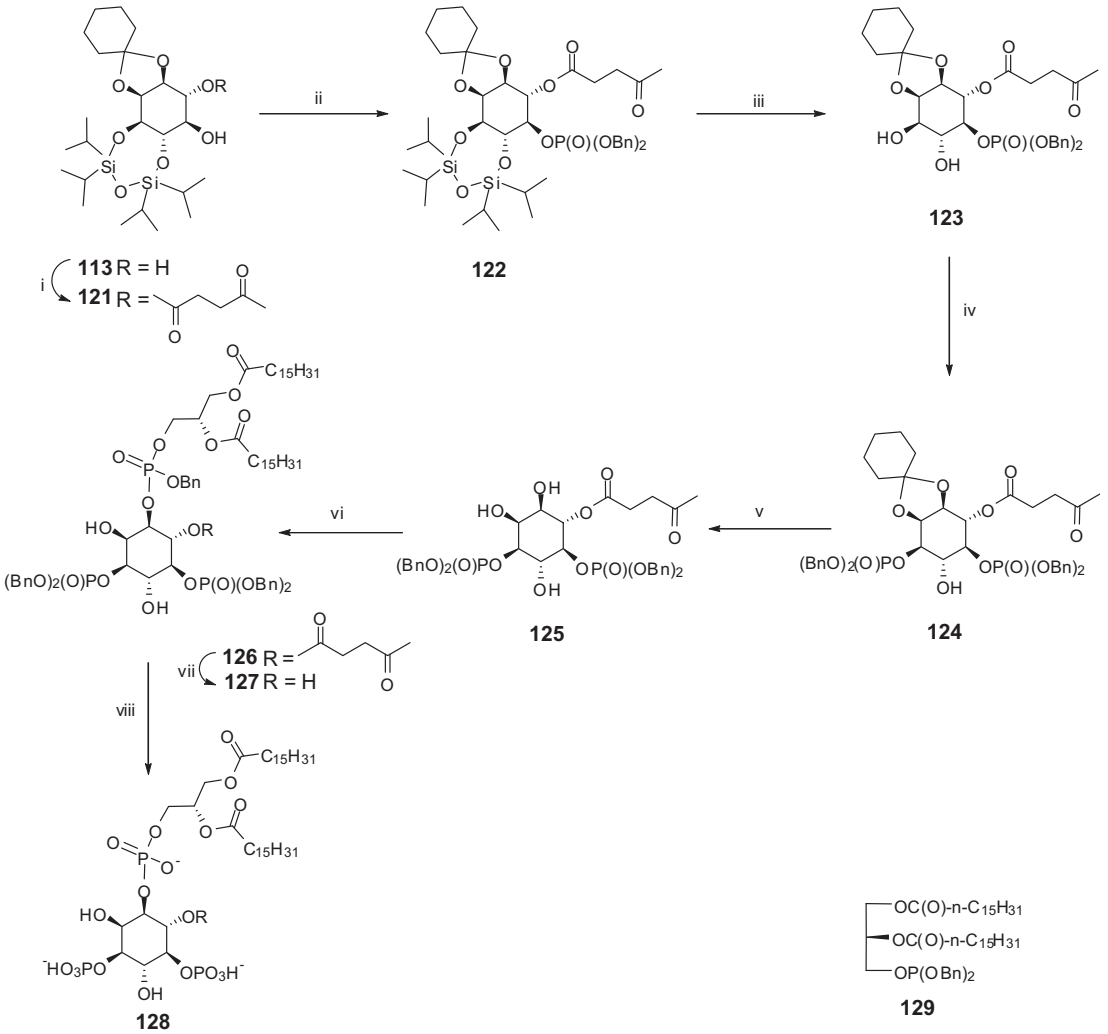
The racemic tetraol **130**,[29] obtained by the ketalization of *myo*-inositol, was used as a precursor for the synthesis of 6-deoxy-*myo*-inositol 1,3,4,5-tetrakisphosphate **139**, which is a structural analogue of *myo*-inositol 1,3,4,5-tetrakisphosphate. This compound may be used in the elucidation of the mechanism of action within the Ins(1,3,4,5)P_4 moiety. Monoketal **130** was converted into *rac*-**131** and *rac*-**132** with *p*-methoxybenzyl chloride in the presence of dibutyltin oxide and tetrabutylammonium iodide (Scheme 25).[40] All hydroxy groups except those located at the C-6 position were regioselectively protected. Radical deoxygenation of the free hydroxy group in **131** by the Barton–McCombie reaction to give **133**[41] followed by deketalization under acidic conditions afforded **134**. Subsequent regioselective protection of **134** gave *rac*-**135** quantitatively. The remaining −OH group was easily protected by benzyl bromide to form **136**. Selectively removing the *p*-methoxybenzyl groups with TFA in CH_2Cl_2 led to the formation of **137**. Successive phosphorylation of **137** followed by hydrogenation produced *rac*-**139** via **138**. Recently, Potter et al.[42] used DL-1,2-*O*-isopropylidene-*myo*-inositol as a precursor to synthesize the first derivatives modified at positions 2 and 3.

Recently Schoffers et al.[43] reported an efficient route to obtain *scyllo*-inosamine **144** starting from *myo*-inositol (**1**). Diol **140** was synthesized in three steps according to known procedures. Acetonide protection of the *cis*-diol,[29] and subsequent benzylation[44] followed by removal of the acetonide functionality gave the protected diol **140**. Dibutyltin oxide was then used for the regioselective benzylation to yield **141** followed by a nucleophilic substitution reaction to afford the azide **142**. Reduction of the azide **142** to its amine **143** with triphenylphosphine and subsequent deprotection of all benzoyl groups led to *scyllo*-inosamine derivative **144** (Scheme 26).

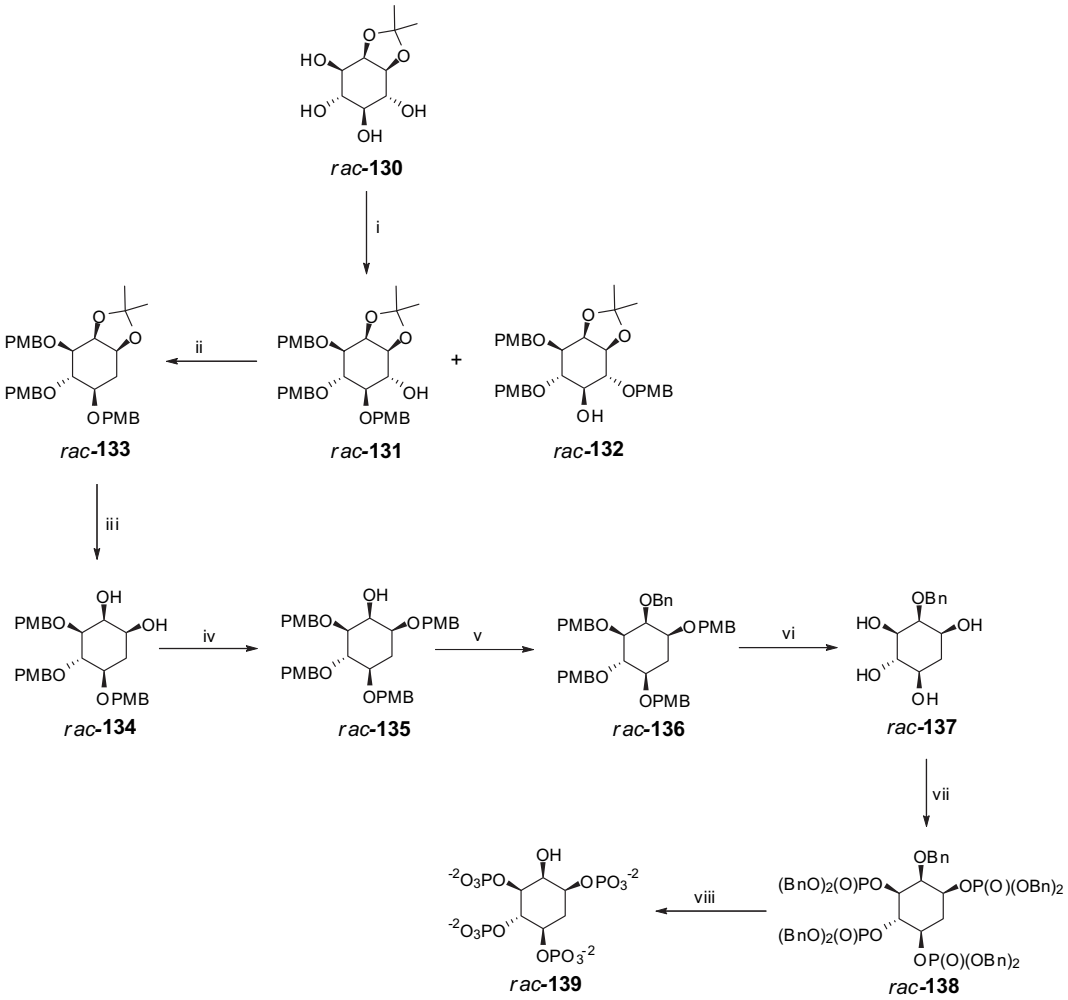
An efficient route to optically active inositol derivatives via the resolution of *myo*-inositol 1,3,5-orthoformate was recently developed by Watanabe and Sureshan[45] First, *myo*-inositol (**1**) was



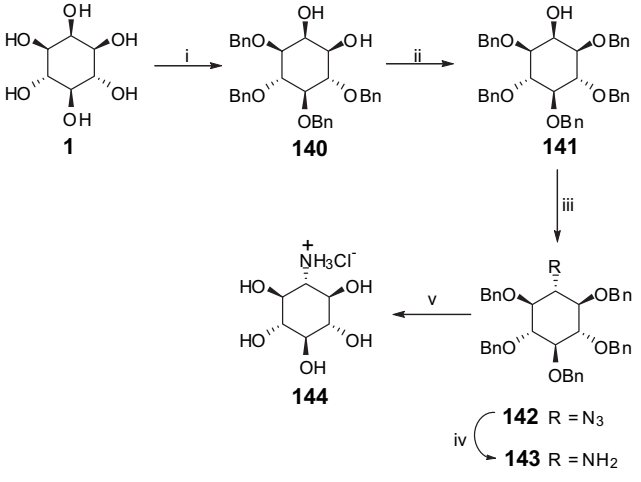
Scheme 23. (i) Bis(fluorenylmethyl) *N*,*N*-di-isopropylphosphoramidite, tetrazole, MeCN, rt, 5 h, then ^{t}BuOOH, rt, 30 min; (ii) TFA, MeOH (wet), 0 °C, 5 min; (iii) $(MeO)_3CCH_2CH_2Me$, CSA, toluene, rt, 30 min, then MeOH (wet), rt, 2 h; (iv) **120**, tetrazole, MeCN, rt, then ^{t}BuOOH, rt, 30 min; (v) HF (50% in water)/MeCN (1:10, v/v), rt, 4 h; (vi) 1 equiv bis(fluorenylmethyl) *N*,*N*-di-isopropylphosphoramidite, tetrazole, MeCN, rt, 5 h, then ^{t}BuOOH, rt, 30 min; (vii) butyric acid anhydride, DIC, tetrazole, DMAP, rt, 5 h; (viii) pyrrolidine, DCM, rt, 5 min; (ix) KOH (aq), pH 13, rt, 6 h.



Scheme 24. (i) $MeCO(CH_2)_2COOH$, DCC, DMAP, CH_2Cl_2, rt, 89%; (ii) $(BnO)_2PN(^{i}Pr)_2$, 1*H*-tetrazole, CH_2Cl_2, rt, then *m*-CPBA, −78 °C to rt, 96%; (iii) TBAF·$3H_2O$, AcOH, THF, −15 to −10 °C, 92%; (iv) $(BnO)_3P$, pyridinium tribromide, 2,6-lutidine, CH_2Cl_2, −42 to 0 °C, 91%; (v) Py(HF)*x*, ethylene glycol, CH_2Cl_2, 0 °C to rt, 84%; (vi) **129**, pyridinium tribromide, 2,6-lutidine, pyridine/CH_2Cl_2 (v/v 1.1:1), 22 °C to rt, 68%; (vii) hydrazine monohydrate, pyridine/AcOH (v/v 4:1), 0 °C to rt, 89%; (viii) 5% Pd/C, H_2, EtOAc/MeOH (v/v 1:1), rt, quant.



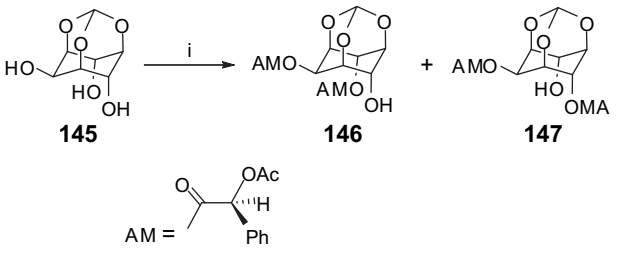
Scheme 25. (i) PMBCl, TBAI, Bu_2SnO, toluene, 120 °C, 16 h (*rac*-**131**, 32%; *rac*-**132**, 41%); (ii) 1. NaH, CS_2, THF, 1 h, then MeI, 1 h, 2. Bu_3SnH, AIBN, toluene, 120 °C, 1 h (83%); (iii) 80% AcOH, 100 °C, 1 h (77%); (iv) PMBCl, TBAI, Bu_2SnO, toluene, 120 °C, 16 h (76%); (v) BnBr, NaH, DMF, rt, 4 h (84%); (vi) 10% TFA (CH_2Cl_2), rt, 30 min (71%); (vii) dibenzyl diisopropylphosphoroamidate, 1*H*-tetrazole, CH_2Cl_2, rt, 1 h; then *m*-CPBA, −78 °C, 1 h (79%); (viii) Pd/C (10%), MeOH/H_2O 9:1, H_2, 80 psi, 16 h, and purification by Q-Sepharose Fast Flow ion-exchange chromatography (87%).



Scheme 26. (i) 1. DMP, *p*-TsOH, DMSO, NEt_3, 74%, 2. BnBr, NaOH, 95%, 3. HCl, MeOH, 89%; (ii) Bu_2SnO, TBAI, BnBr, MeCN, 83%; (iii) 1. Tf_2O, Py, CH_2Cl_2, 93%, 2. NaN_3, DMF, 81%; (iv) Ph_3P, THF, H_2O, 96%; (v) H_2/Pd, MeOH/CH_2Cl_2/H_2O, HCl, 56 psi, 82%.

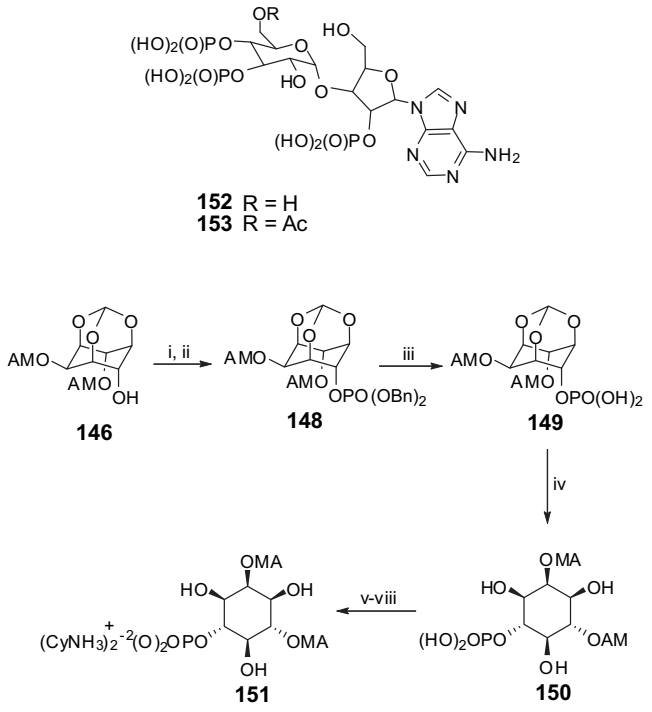
converted into an adamantane-like orthoester **146**[46] obtained from the protection of O-1, O-3, O-5 of *myo*-inositol. The orthoester cage provides a restricted *myo*-inositol conformation and makes it easier to differentiate the other three hydroxyl groups.

Acylation of triol **145** with (*S*)-*O*-acetyl-mandeloyl chloride in pyridine gave two diastereoisomers **146** and **147**, which were separated by column chromatography (Scheme 27). After determining the absolute configuration of the diastereoisomers, the free hydroxyl group in **146** was phosphorylated with dibenzyl *N*,*N*-diisopropylphosphoramidite using Fraser-Reid's method[47] followed by *m*-CPBA oxidation to give **148**. After removal of all of the protecting groups in **149**, D-*myo*-inositol-4-phosphate derivative **150** was isolated as its bis-cyclohexylammonium salt (Scheme 28).



Scheme 27. (i) (*S*)-(+)-*O*-Acetyl-mandelic acid chloride (2.1 equiv), Py, 0 °C, 2 h.

Adenophostins A and B (**152** and **153**) are 10–100-fold more potent as agonists of than the endogenous product and they contain the important functions of Ins(1,4,5)P_3.[48]



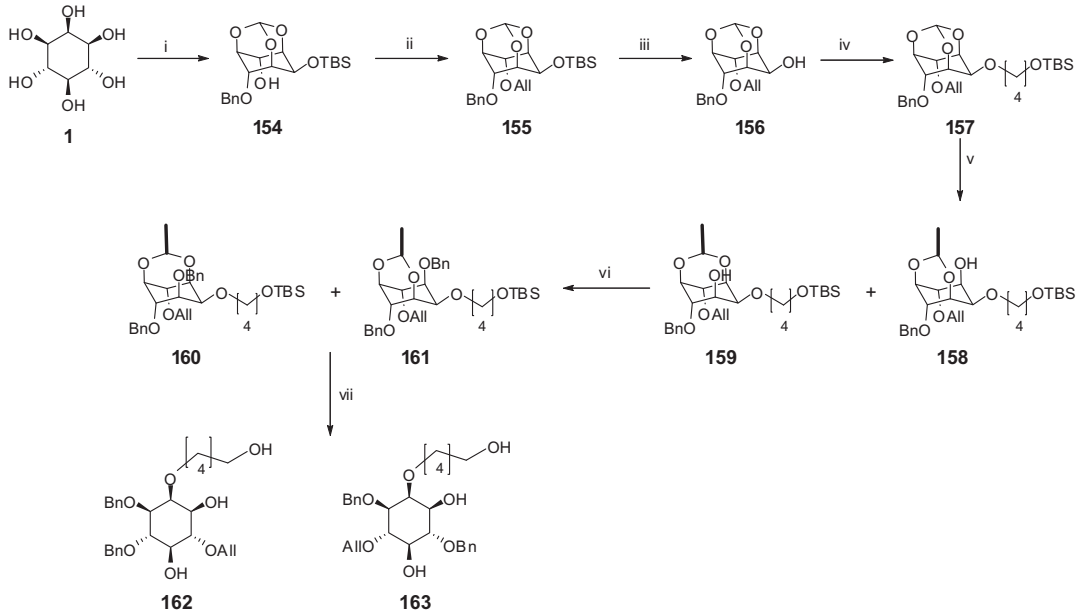
Scheme 28. (i) $(BnO)_2PN(^iPr)_2$, tetrazole, CH_2Cl_2, −42 °C; (ii) *m*-CPBA, −78 °C, 90%; (iii) H_2, 5% Pd/C, EtOAc; (iv) TFA/H_2O, rt, 12 h; (v) 1 M LiOH, THF, rt, 12 h; (vi) H^+, extract with CH_2Cl_2; (vii) DIAION SK1BH (H^+ form) resin; (viii) $CyNH_2$, rt, 10 min.

Schlewer et al.[49] have synthesized an adenophostin mimic based on the Ins(1,4,5)P_3 backbone starting from *myo*-inositol. Again, the orthoester **145** derived from *myo*-inositol (**1**) served as the starting material. The remaining hydroxyl groups were protected by means of *tert*-butylsilyl chloride, benzyl chloride, and allyl chloride to give **155** via **154**. After removal of the silyl group, the free hydroxyl group in **156** was alkylated with 1-*O*-tosyl-4-*O*-TBS-butane-1,4-diol to give **157**. Cleavage of the orthoester was performed using trimethylaluminium to give **158** and **159**.

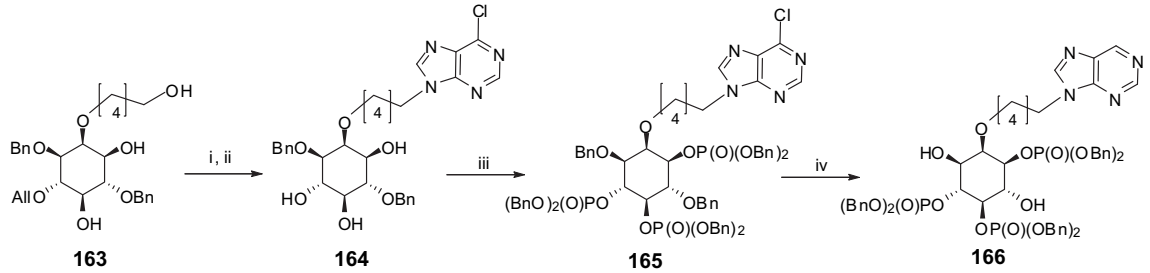
Alcohol functionalities were protected with benzyl bromide to give the fully protected *myo*-inositol derivatives **160** and **161**, which were hydrolyzed to the triols **162** and **163**, respectively (Scheme 29).

The allyl protective group in **163** was removed giving the triol **164**. The chloropurine group was introduced by a selective Mitsunobu reaction to give two isomers differing in the position of chlorine atom. After separation of the isomers, **164** was phosphorylated to give the protected compound **165**. The other protective groups and chlorine were removed in the presence of palladium dihydroxide in a microwave oven to furnish the target compound **166** (Scheme 30). Activity tests showed that **166** is a full agonist of with the same order of potency as D-*myo*-inositol 1,4,5-tris(phosphate).

myo-Inositol orthobenzoate **167** synthesized from *myo*-inositol (**1**) was used as a key intermediate to obtain the anticancer agent, Ins(1,3,4,5,6)P_5 **171**, in gram quantities.[50] The orthobenzoate ester **167** was used instead of the commonly used orthoformate in this work, and was synthesized by the reaction of *myo*-inositol with trimethyl orthobenzoate in the presence of an acid catalyst

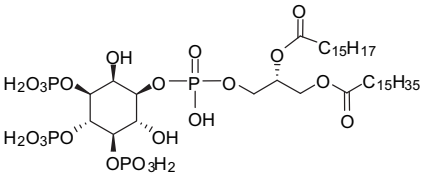


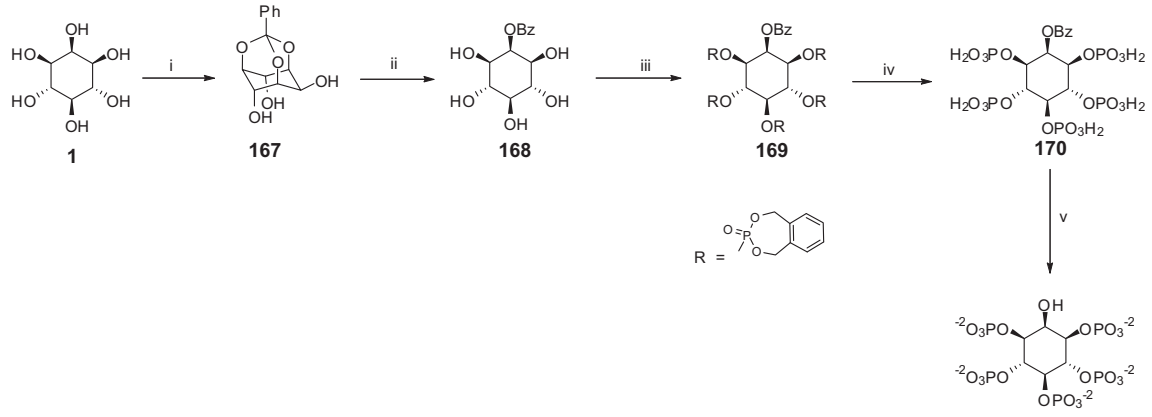
Scheme 29. (i) 1. $HC(OEt)_3$, DMF, *p*-TsOH, Ar, 70%, 2. TBSCl, imidazole, DMF, Ar, 62%, 3. NaH, BnBr, DMF, Ar, 90%; (ii) NaH, AllBr, DMF, Ar, 97%; (iii) TBAF, THF, 99%; (iv) NaH, 1-*O*-tosyl-4-*O*-TBS-butane-1,4-diol; (v) $AlMe_3$, CH_2Cl_2, 0 °C, 70%; (vi) NaH, BnBr, DMF; (vii) MeOH, *p*-TsOH, reflux, 45%.



Scheme 30. (i) $Rh(PPh_3)_3Cl$, DABCO, EtOH/H_2O 9:1, reflux, 62%; (ii) DEAD, PPH_3, 6-chloropurine, THF, Ar, 22 40%, 23%; (iii) NaH, tetrabenzyl pyrophosphate, THF, Ar, 39%; (iv) MeOH, cyclohexene, $Pd(OH)_2$, μW, 120 °C, 5 min, $CyNH_2$.

(Scheme 31). The advantage of using **167** is that it forms the stable benzoate after hydrolysis. The hydrolysis was carried out with TFA/H_2O. All free hydroxyl groups in **168** were exposed to a phosphitylation reaction by using *N*,*N*-diethyl-1,5-dihydro-2,4,3-benzodioxaphosphepin-3-amine in the presence of 5-phenyltetrazole to give **169**, followed by oxidation with *m*-CPBA to afford **170** quantitatively. Protected pentakisphosphate **170** was hydrogenated by Pd$(OH)_2$ on carbon. The reduction of the benzoyl group on the ring gave **171** in a yield of 86%.



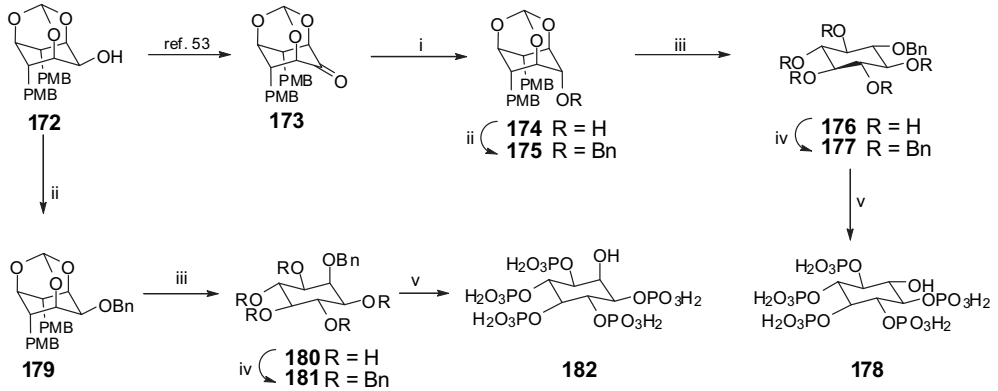


Scheme 31. (i) $(MeO)_3CPh$, CSA, DMSO, 80 °C, 30–40 mbar, 3 h, 90%; (ii) TFA/H_2O, 10:1, rt, quant; (iii) *N*,*N*,-diethyl-1,5-dihydro-2,4,3-benzodioxaphosphepin-3-amine, CH_2Cl_2, 5-phenyltetrazole, rt; *m*-CPBA, 0 °C to rt, 96%; (iv) H_2, $Pd(OH)_2$/C, MeOH/H_2O, quant; (v) concd aq NH_3, 60 °C, 12 h, quant.

scyllo-Inositol 1,3,4,5,6-pentakisphosphate **178** inhibits angiogenesis and blocks the growth of tumor cells, as mentioned previously. Recently, Potter et al.[51] synthesized *scyllo*-inositol pentakisphosphate **178** as an analogue of *myo*-inositol. Oxidation of the free hydroxy group of *myo*-inositol 1,3,5-orthobenzoate derivative **172**, followed by a stereoselective reduction of the ketone **173**, afforded an axial alcohol having a *scyllo*-inositol configuration as the sole product **174** (Scheme 32).[52] Cleavage of an orthoformate

Among the various phosphatidylinositol derivatives, 3,4,5-triphosphate **183** has also attracted much attention due to its various biological activities.[53]

For the synthesis of the target compound **183**, the orthobenzoate **167** was used as the starting material. Desymmetrization of the orthoester **167** with (1*S*)-(−)-camphanoyl chloride provided the chiral precursor **184**, which was converted into the dibenzyl ether **185** (Scheme 33).[54] Acidic hydrolysis of **185** gave the regioi-

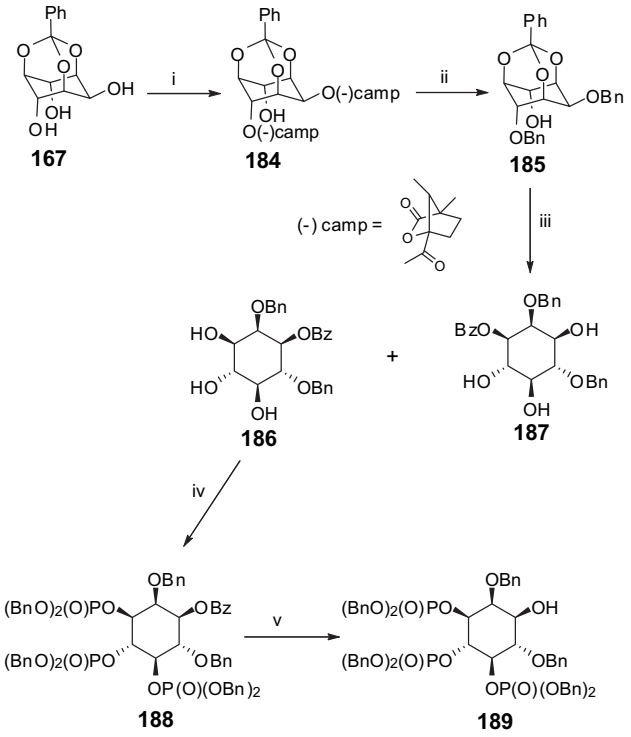


Scheme 32. (i) $NaBH_4$, THF, MeOH; (ii) BnBr, NaH, DMF; (iii) 1.0 M HCl/EtOH (1:2), reflux; (iv) 1. $(BnO)_2PN^iPr_2$, 1*H*-tetrazole, MeCN; 2. *m*-CPBA, CH_2Cl_2, −78 °C to rt; (v) Pd/C, MeOH, H_2O, H_2, 3.5 bar.

ester in **175** with HCl in refluxing EtOH gave 1-*O*-benzyl-*scyllo*-inositol **176** followed by a phosphorylation reaction, which resulted in the formation of *scyllo*-inositol pentakisphosphate **178** via **177**. Protection of the free hydroxyl group of **172** without any oxidation reaction followed by similar reaction sequences to those just mentioned gave exclusively the *myo* analogue **182** through **179**–**181**.

someric triols **186** and **187**. After separation, the isomer **186** was phosphorylated to give **188** followed by removal of the benzoate group with EtMgCl to form the monoalcohol **189**.

The free hydroxyl group in **189** was phosphitylated with phosphoramidite **190** in the presence of tetrazole to furnish **191**. The ketal group was removed by TFA to give the diol **192**, which was



Scheme 33. (i) (1*S*)-(−)-Camphanoyl chloride, Et_3N, DMAP, CH_2Cl_2, 0 °C to rt, 66%; (ii) 1. 2-methoxypropene, PTSA, THF, 0 °C to rt; 2. LiOH·H_2O, THF, MeOH, H_2O; 3. NaH, BnBr, DMF; 4. TFA, wet CH_2Cl_2 (85% for four steps); (iii) 1 M HCl, EtOH (1:2), reflux, 5 h, 11 (41%), 12 (48%); (iv) (1) $(BnO)_2PN(^iPr)_2$, 1*H*-tetrazole, CH_2Cl_2, rt, 45 min; (2) *m*-CPBA, −78 °C to rt, 1 h, 94%; (v) EtMgCl, THF, −42 °C, 30 min, 96%.

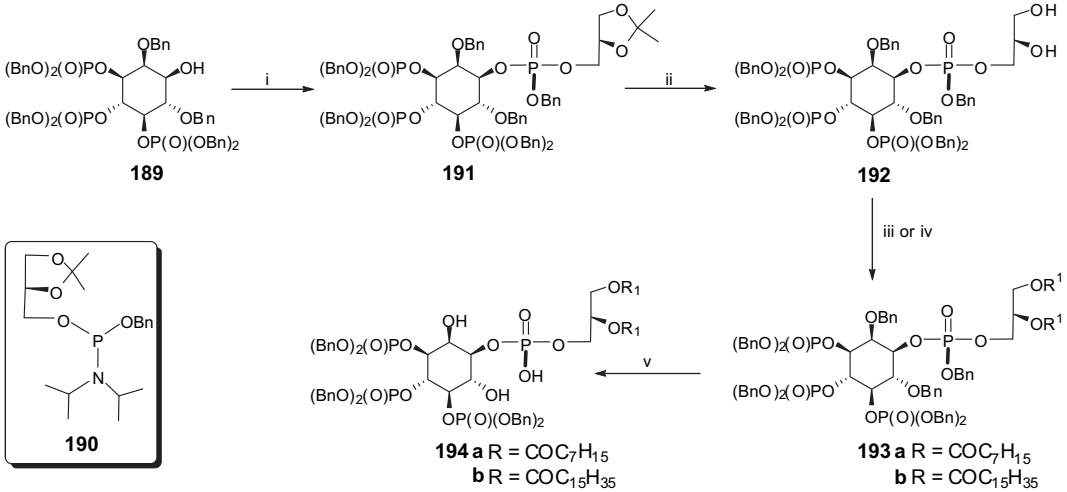
a key compound for the synthesis of various phosphatidylinositol derivatives (Scheme 34).[54] Esterification of the diol with octanoic or stearic acid to give **193a** and **193b** followed by removal of the benzyl protecting groups by hydrogenolysis gave PtdIns(3,4,5)P_3 analogues **194a** and **194b** in high yields.

following the acid hydrolysis of **195** provided separable isomers **196** and **197**. The reaction of diastereomers **196** and **197** with excess *O*,*O*-dibenzyl-*N*,*N*-di-isopropylphosphoramidite and peracid oxidation generated the corresponding bisphosphate triesters. Subsequent cleavage of the camphor ketal with trifluoroacetic acid gave the diol **198**, which was converted into **199**. Removal of the benzyl groups provided the target compound **200**. By the application of this methodology, other isomeric phosphatidyl-*myo*-inositol bisphosphates were also synthesized successfully.[57]

Inositol orthoesters have proved to be an important class of compounds for the synthesis of *myo*-inositol 1,4,5-tri- and *myo*-inositol 1,3,4,5-tetraphosphate. Full or partial cleavage of the orthoester cage can be carried out by either acidic hydrolysis or reduction. Most recently, Gaffney et al.[58] have demonstrated that a reduction of *myo*-inositol orthobenzoates **202a**–**d** with excess DIBAL-H exclusively gave the diastereoisomers **203a**–**d**. The full reduction of **202a**–**d** with 3.5 equiv DIBAL-H generates both **204a**–**d** and **205a**–**d** derivatives, which were subjected to subsequent deprotection and phosphorylation processes to complete the synthesis of **206a** and **206b** (Scheme 36).

The key steps in the synthesis of the inositol derivatives are the regioselective protection of the free hydroxyl groups and deprotection. The most protection is from the simultaneous protection of three hydroxyl groups (C-1, C-3, and C-5 in *myo*-inositol) as the orthoformate (Schemes 28–33).[4b,49,59] The cleavage of benzyl ethers and acetals using a palladium-based catalyst is a short and efficient route to obtain diverse cyclitols. Recently, Shashidhar et al.[60] demonstrated that, by varying the conditions of the hydrogenation reaction and the amount of $Pd(OH)_2$/C, methoxymethyl ethers as well as the orthobenzoate functions can be cleaved.

Reaction of **207** with $Pd(OH)_2$/C in ethyl acetate in the presence of H_2 only cleaved the benzyl group and formed **208** (Scheme 37). On the other hand, when the reaction was carried out in methanol in the absence of H_2, **208** was also formed after a prolonged period of time. When the reaction was carried out in methanol in the presence of H_2 and $Pd(OH)_2$/C, **209** was formed as the sole product.

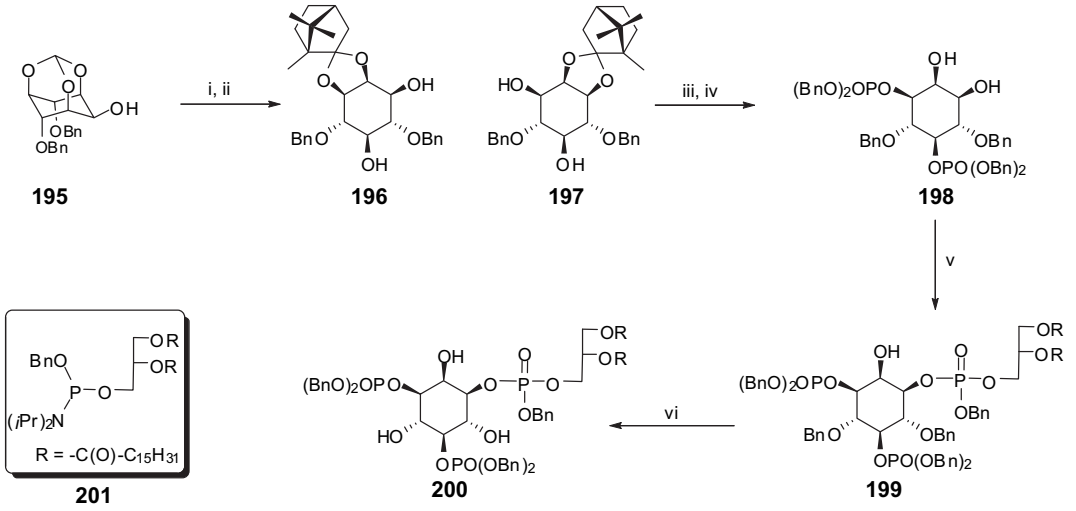


Scheme 34. (i) (1) **190**, 1*H*-tetrazole, DCM, rt, 1 h; (2) *m*-CPBA, −78 °C; (ii) $CHCl_3$, TFA, MeOH (1:1:1, v/v/v), 0 °C, 20 min; (iii) $C_7H_{15}COOH$, DCC, DMAP, DCM, rt, 12 h, 85%; (iv) $C_{17}H_{35}COOH$, DCC, DMAP, DCM, rt, 12 h, 100%; (v) H_2 (60 psi), $Pd(OH)_2$/C, ^{t}BuOH, H_2O (5:1, v/v), 12 h, **194a** (97%), **194b** (88%).

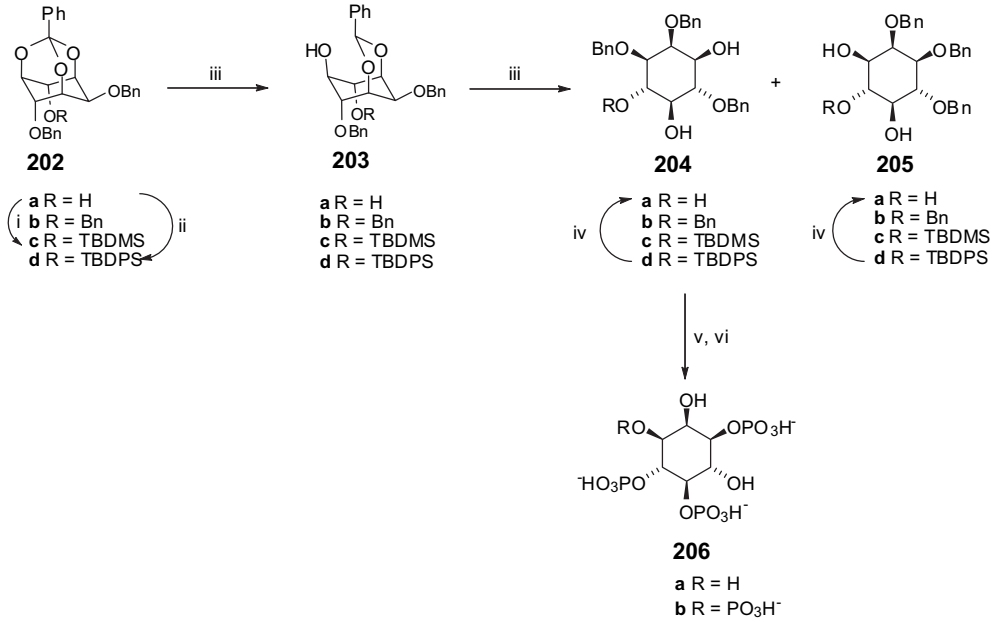
Investigations have revealed that L-α-phosphatidyl-D-*myo*-inositol 5-phosphate (5-PIP) and L-α-phosphatidyl-D-*myo*-inositol 3,5-bisphosphate (**200**, 3,5-PIP2) are potential new members of the PI cascade.[55] Falck et al.[56] reported the synthesis of some phosphatidyl-D-*myo*-inositol derivatives starting from orthoformate **195** (Scheme 35). Ketalization of **195** with (+)-camphor dimethyl ketal

When the reaction was carried out in the presence of excess $Pd(OH)_2$/C, however, all the protected groups were removed to give **1**, which was isolated as **210**.

Orthoesters are very important key molecules in the synthesis of phosphoinositols. The protection of the free hydroxyl groups of the adamantane-like orthoester cage is also a crucial point. Generally,

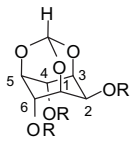


Scheme 35. (i) MeOH/10 N HCl (12.5:1), 65 °C, 0.45 h (87%); (ii) (+)-camphor dimethyl ketal (3 equiv), PTSA (2 mol %), CH_2Cl_2, 23 °C, 4 h (82%); (iii) $(^iPr)_2NP(OBn)_2$ (2.5 equiv), 1*H*-tetrazole, CH_2Cl_2, 23 °C, 2 h; *m*-CPBA, 40 °C, 1 h (88%); (iv) CF_3CO_2H/CH_2Cl_2/MeOH (1.5:3:0.5), 0 °C, 0.5 h (77%); (v) phosphite **201** (2 equiv), Py·HBr_3 (2.25 equiv), CH_2Cl_2/Py/Et_3N (5:1:0.1), 20 to 0 °C, 0.5 h (63%); (vi) Pd (black), H_2 (52 psi), $NaHCO_3$ (5 equiv), EtOH/H_2O (6:1), 23 °C, 6 h (79%).



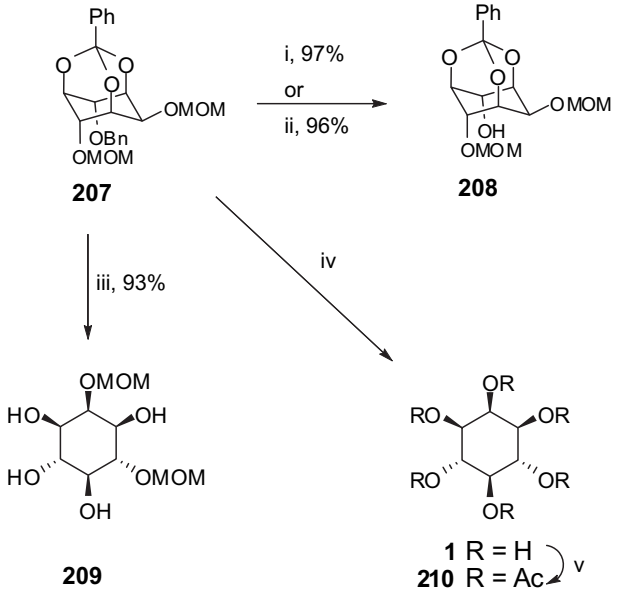
Scheme 36. (i) TBDMSCl, imidazole, Et_3N, DMF, 100 °C; (ii) TBDPSCl, imidazole, Et_3N, DMF, 100 °C; (iii) DIBAL-H, DCM, −78 °C to rt; (iv) TBAF, THF; (v) $(BnO)_2PN^iPr_2$, tetrazole then *m*-CPBA; (vi) Pd (black), H_2.

these hydroxyl groups have been protected by acylation, benzylation, silylation etc. A sulfonyl group is generally not preferable for protection, since it has a great tendency to undergo substitution and elimination reactions owing to it being a good leaving group. Furthermore, their deprotection is difficult. However, Shashidhar et al.[4b,61] have, however, explored a convenient method for regioselective and regiospecific sulfonylation of free hydroxyl groups in orthoesters depending on the reaction conditions and the nature of the base. Moreover, no inversion of configuration was observed during the cleavage of the sulfonylated orthoester.

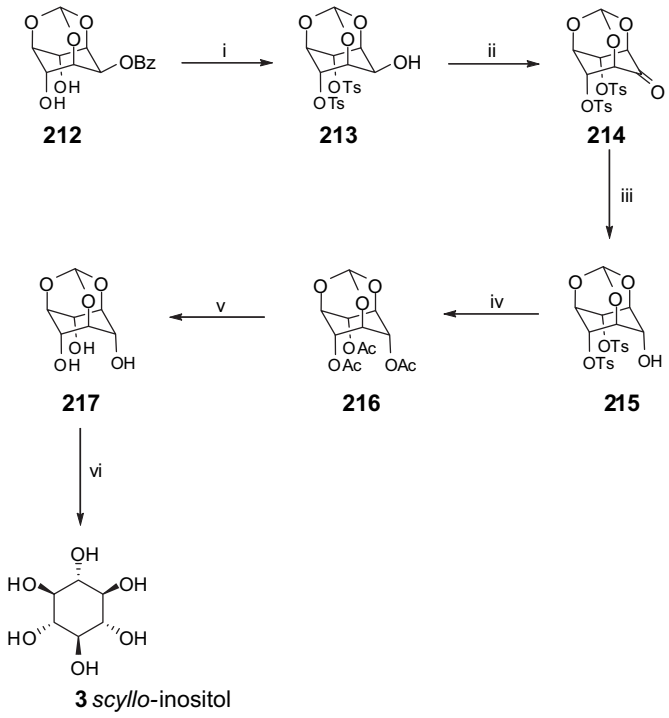


As an example, 1 equiv of sodium hydride or triethylamine resulted in the monosulfonylation of the orthoester at the C-4 position in **211**. Sulfonylation occurred at the C-2 position, however, if pyridine was used as a base. Excess sodium hydride provided sulfonylation at the C-4 and C-6 positions. Excess pyridine or triethylamine afforded regiospecific sulfonylation at the C-2 and C-4 positions. All of these regiospecific protection reactions provided a means for the synthesis of 2,4-di-*O*-benzyl-*myo*-inositol and 2-*O*-benzyl-*myo*-inositol, which are important precursors for phosphoinositol derivatives.

Tosylate protection has been successfully applied to the synthesis of *scyllo*-inositol (**3**). *myo*-Inositol 1,3,5-orthoformate was first benzoylated followed by tosylation of the remaining hydroxyl group to give **212** (Scheme 38).[61c] After removal of the benzoyl group by aminolysis, the alcohol **213** was subjected to a Swern oxidation reaction to give **214**. The reduction of the carbonyl group with sodium borohydride gave **215**, then methanolysis of the



Scheme 37. (i) H_2, $Pd(OH)_2$/C, EtOAc, 2 h, 97%; (ii) $Pd(OH)_2$/C, MeOH, rt, 7 days or reflux, 32 h, 96%; (iii) H_2, $Pd(OH)_2$/C, MeOH, 13 h, 93%; (iv) H_2, excess $Pd(OH)_2$/C, MeOH, 13 h; (v) Ac_2O, Py, rt, 40 h, 96%.



Scheme 38. (i) 1. *p*-TsCl, pyridine, 80–100 °C; 2. *iso*butylamine, MeOH, reflux; (ii) $(COCl)_2$, Me_2SO, DCM, −78 °C then Et_3N, rt; (iii) $NaBH_4$, MeOH/THF, rt; (iv) NaOMe, MeOH, reflux; (v) Ac_2O, pyridine, rt; (vi) TFA/H_2O (4:1).

tosylates yielded *scyllo*-inositol 1,3,5-orthoformate **217** (isolated as the triacetate **216**). The subsequent cleavage of the orthoformate resulted in the formation of *scyllo*-inositol (**3**) in a yield of 64%.

Recently, Watanabe et al.[32] reported the synthesis of an isomeric pinpollitol (**109**) derivative **222**, starting from *myo*-inositol (**1**). The free hydroxyl groups of *myo*-inositol 1,3,5-orthoformate were converted into the fully protected tribenzyl ether **218** (Scheme 39). Hydrolysis of the orthoformate group followed by regioselective benzylation of **219** provided the tetrabenzyl ether **220**. The more reactive hydroxyl group in **220** was sulfonylated with triflic anhydride to give the triflate **221a**. For characterization, the free hydroxyl group in **221a** was transformed into the corresponding acetate **221b**. Nucleophilic substitution at the C-3 position by acetylation led to the *chiro*-inositol derivative **222a**, which was successfully transformed into **222b** and **222c**. After hydrolysis of the acetyl group followed by methylation with MeI in the presence of NaH, subsequent deprotection of the benzoyl group successfully gave the racemic dimethyl ether *chiro*-inositol **223a** (isolated as the triacetate **223b**).

MosA is an enzyme that has been proposed to catalyze the conversion of *scyllo*-inosamine into 3-*O*-methyl-*scyllo*-inosamine. Palmer et al.[62] recently synthesized *scyllo*-inosamine **227** as well as a methyl derivative **228** starting from *myo*-inositol orthoformate **218**. The removal of the orthoformate with DOWEX (H^+) ion-exchange resin in methanol followed by benzylation of the tribenzyl-inositol provided hexabenzyl inositol **224** (Scheme 40). The regioselective deprotection of the axial benzyl group with $SnCl_4$ gave **225**. The mesylation of the hydroxyl group followed by substitution with NaN_3 (with configurational isomerization) provided the azide **226** with a *scyllo*-inositol configuration. The reduction of the azide functionality and the deprotection of the benzyl groups furnished *scyllo*-aminoinositol **227**. The corresponding methyl derivative **228** was synthesized by similar routes.[62] Finally, the interaction of MosA enzyme with **227** and **228** did not show any methyl transfer.

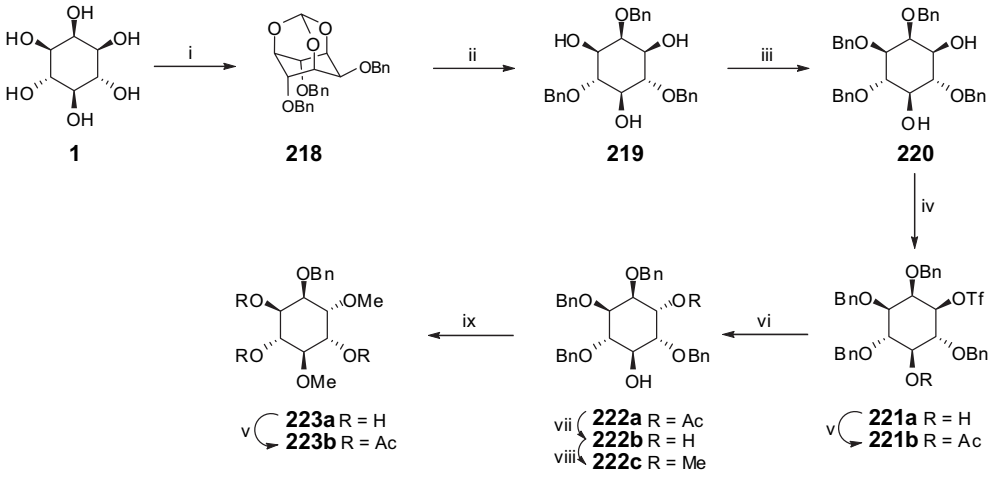
It has been demonstrated that *scyllo*-inositol (**3**) has shown promise as a potential therapeutic agent for Alzheimer's disease by inhibition of the Aβ42 peptide.[63] Nitz et al.[64] have synthesized a series of *scyllo*-inositol derivatives that contain fluoro, chloro, and methoxy substituents in order to study the inositol-Aβ42 peptide interaction. The reaction of vicinal diequatorial diols in m*yo*-inositol (**1**) with 2,2,3,3-tetramethoxybutane gave **229**,[65] which was exposed to a regioselective benzoylation reaction (Scheme 41). Direct chlorination or fluorination of the monoalcohol **230** was achieved with phosphorus pentachloride or diethylaminosulfur trifluoride to give **231a** and **231b**. The debenzoylation of the halo-substituted inositol with sodium methoxide in methanol and the subsequent cleavage of the acetal protecting group in the presence of an acid afforded the target molecules **232a**,**b** exclusively. An assay revealed that the 1-fluoro-*scyllo*-inositol **232a** significantly inhibits the formation of Aβ42 fiber.

Crown ethers, known as metal-complexing agents, have for the past decades attracted much interest. There have been many studies on the modification of crown ethers depending on the selectivity and ability of the metal binding. Recently, inositol-derived crown ethers have been designed from inositol derivatives. It was interesting to see whether the incorporation of an inositol unit into the crown ethers would affect the binding or complexation ability of the crown ethers with metal ions. *myo*-Inositol-derived crown ethers have been synthesized where the relative orientations of the oxygen atoms (such as 1,3-diaxial, 1,2-diequatorial, and 1,2-axial-equatorial) were varied.[66]

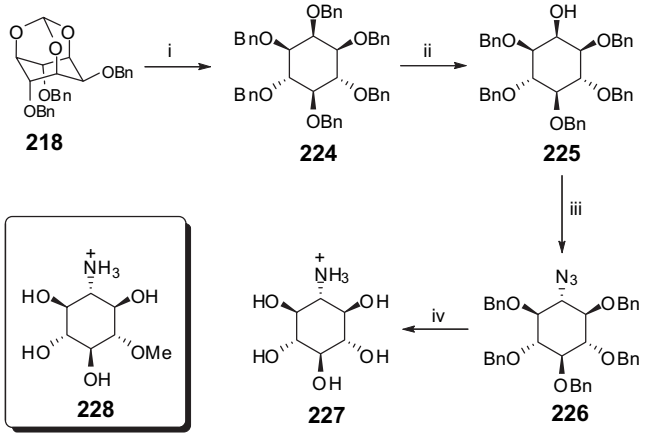
myo-Inositol derivatives **234**, **236**, and **238** were synthesized by the reaction of the properly protected diols **233**, **235**, and **237** with an oligo(ethylene glycol) ditosylate, in the presence of NaH (Scheme 42). These *myo*-inositol-derived crown ethers showed a strong binding ability toward silver and potassium picrate.

Further studies on *myo*-inositol- and *scyllo*-inositol-derived crown ethers have revealed that the binding efficiency to silver and potassium ions could be enhanced by the incorporation of benzyl ethers in the inositol ring.[67]

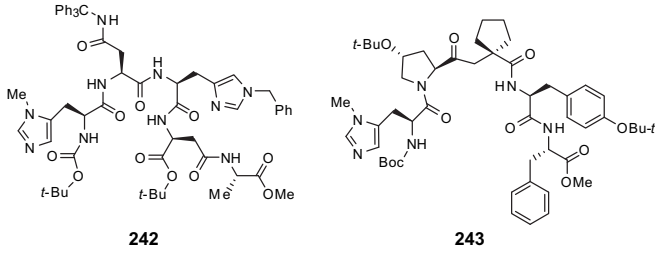
The enantioselective phosphorylation of inositol isomers is as important as the regioselective phosphorylation. Sculimbrene and Miller[68] have shown that some low-molecular-weight, peptide-based catalysts can be used in the asymmetric phosphorylation reactions. This methodology was successfully applied to the synthesis of D-*myo*-inositol-1-phosphate **241** via **240** (Scheme 43).



Scheme 39. (i) BnBr, NaH, DMF, 100 °C, 2 h; (ii) 1 M HCl, MeOH, reflux, 1 h; (iii) BnBr, NaH, DMF, rt, 10 min; (iv) Tf_2O, pyridine, 0 °C; (v) Ac_2O, pyridine, 0 °C; (vi) KOAc, DMA, 70 °C; (vii) Et_3N, MeOH, reflux, 1 h; (viii) MeI, NaH, DMF, 0 °C; (ix) Pd/C, H_2, MeOH, EtOAc, rt.

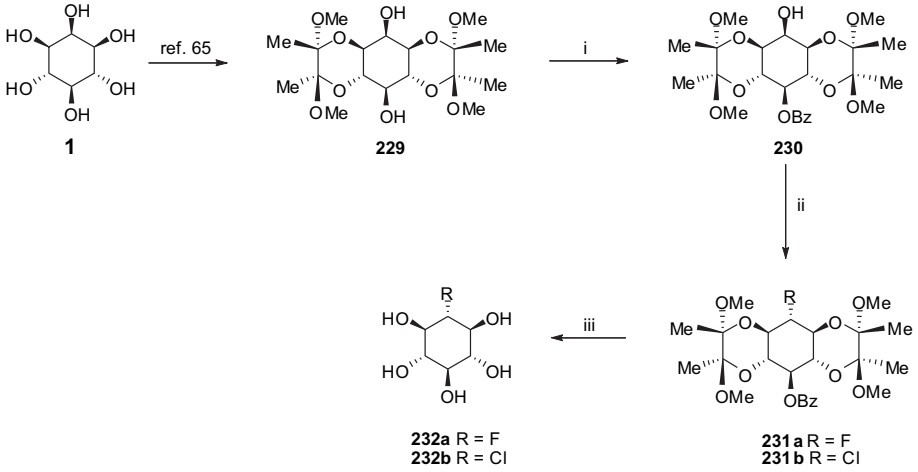


Scheme 40. (i) 1. Dowex (H^+) MeOH, 2. NaH, BnBr, DMF, 94%; (ii) $SnCl_4$, CH_2Cl_2, 58%; (iii) 1. MsCl, pyridine, 2. NaN_3, DMF, 80 °C, 63%; (iv) 1. $^tBoc_2O$, H_2, 10% Pd/C, 2. Dowex (H^+), 74%.



On the other hand, the other enantiomer, D-I-3P (−)-**241**, was synthesized by using the peptide **243** as a catalyst at 70% conversion in turn affording the product in 94% ee.

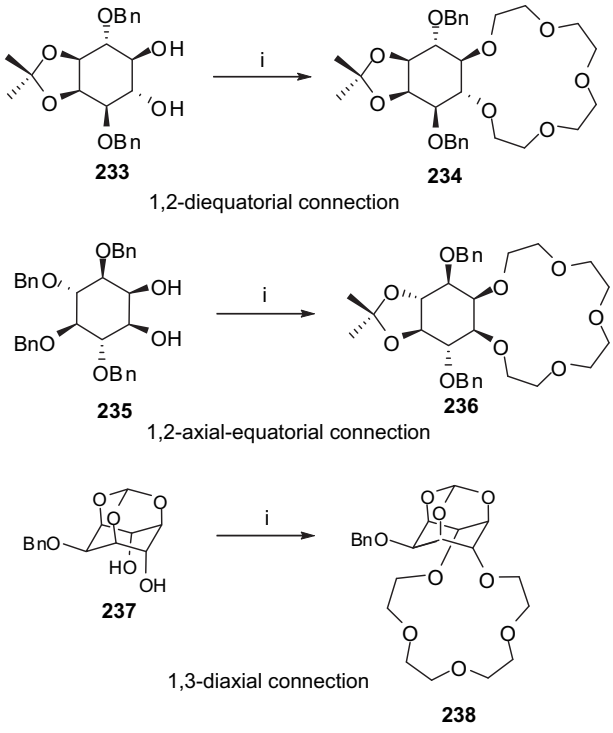
The enantioselective synthetic methodology described for the synthesis of (+)-**241** and (−)-**241** has successfully been applied to the synthesis of many of the inositol polyphosphates, such as **244**–**247** (Scheme 44).[70]



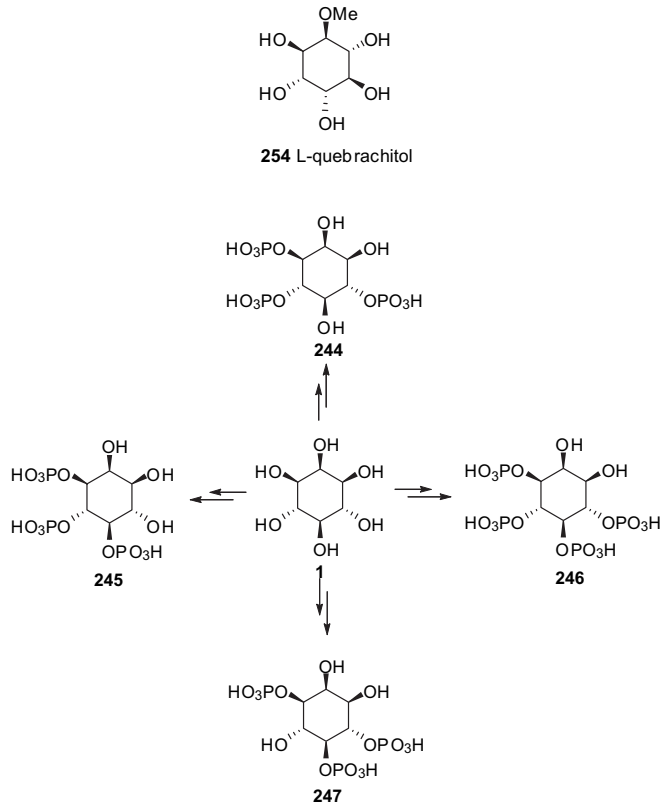
Scheme 41. (i) BzCl, Py/CH_2Cl_2, 64%; (ii) 1. Et_2NSF_3, toluene, **231a**, 62%; or 2. PCl_5, Py, 0 °C, **231b**, 31%; (iii) trifluoroacetic acid, CH_2Cl_2, MeOH 0 °C.

myo-Inositol (**1**) was first converted into the protected tribenzyl derivative **239**, which was then reacted with $ClP(O)(OPh)_2$ in the presence of pentapeptide **242** to furnish the monophosphate (+)-**241** as a single enantiomer with high enantioselectivity (>98% ee).[69]

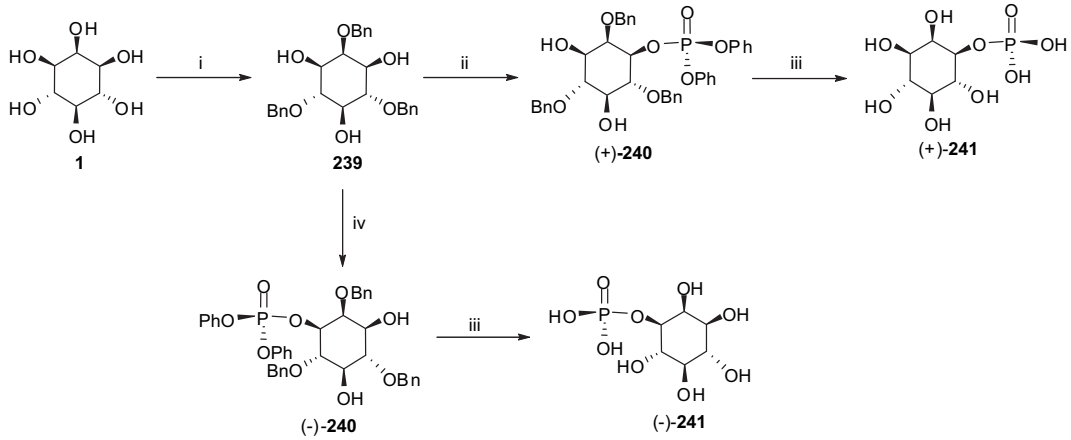
The protected inositol derivative **248**, synthesized from *myo*-inositol (**1**) in four steps served as the starting material for the enantioselective synthesis of **253**. The asymmetric phosphorylation of **248** was achieved using the peptide **243**. The 1- and 5-hydroxyl



Scheme 42. (i) THF, NaH, $TsOCH_2(CH_2OCH_2)_2CH_2OTs$.



Scheme 44.



Scheme 43. (i) 1. $HC(OEt)_3$, TsOH, 100 °C. 2. NaH, BnBr, DMF, 100 °C. 3. HCl, MeOH, reflux; (ii) $PO(OPh)_2Cl$, 2.5 mol % **242**, Et_3N, toluene, 0 °C, >98% ee; (iii) Li, NH_3, THF, 96%; (iv) $PO(OPh)_2Cl$, 2.5 mol % **243**, Et_3N, toluene, 0 °C, >98% ee.

groups in **249** were protected as the benzyloxymethyl ether followed by transesterification of the phosphate group to give **250**. Protection of the PMB ether groups was achieved with DDQ. The phosphorylation of the free hydroxyl groups in **251** to give **252** followed by hydrogenolysis provided the target compound **253**, which was isolated as the sodium salt (Scheme 45).

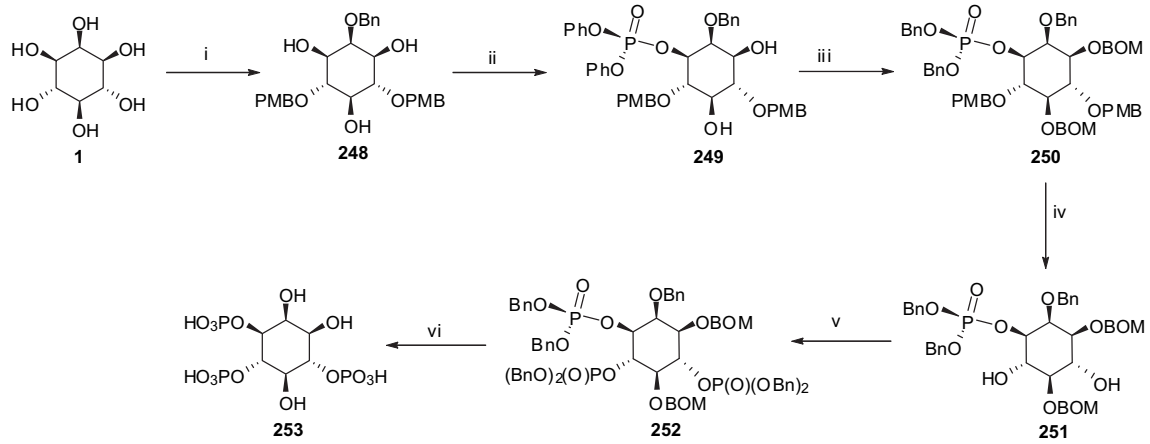
4. Synthesis of inositols and derivatives from quebrachitol and pinitol

L-Quebrachitol (**254**) is a methylated *chiro*-inositol derivative obtained from the exudate of rubber trees. Although naturally occurring quebrachitol is less abundant, compared to *myo*-inositol (**1**), it is a convenient precursor for the synthesis of different inositol derivatives. Since naturally occurring quebrachitol is optically active, it has also been used as a chiral auxiliary in the asymmetric reaction.

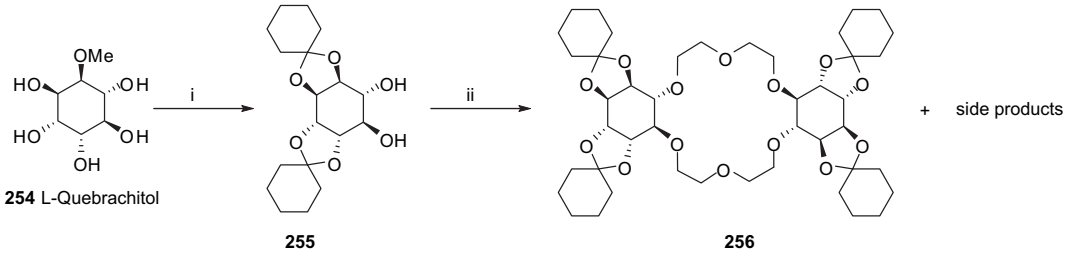
Akiyama et al.[71] have recently synthesized new crown ethers where inositols are incorporated into the crown ether units, starting from the L-quebrachitol. The protected diol **255**[72] was synthesized starting from quebrachitol **254** in three steps, followed by the reaction with diethylene glycol di-*O*-tosylate in the presence of NaH in DMF to give the crown ether **256** in 67% yield (Scheme 46).

This crown ether was used as a catalyst in the Michael addition reaction of glycine imine with several Michael acceptors. The applied Michael reactions in the presence of the new crown ether proceeded in high yield and high enantioselectivities.

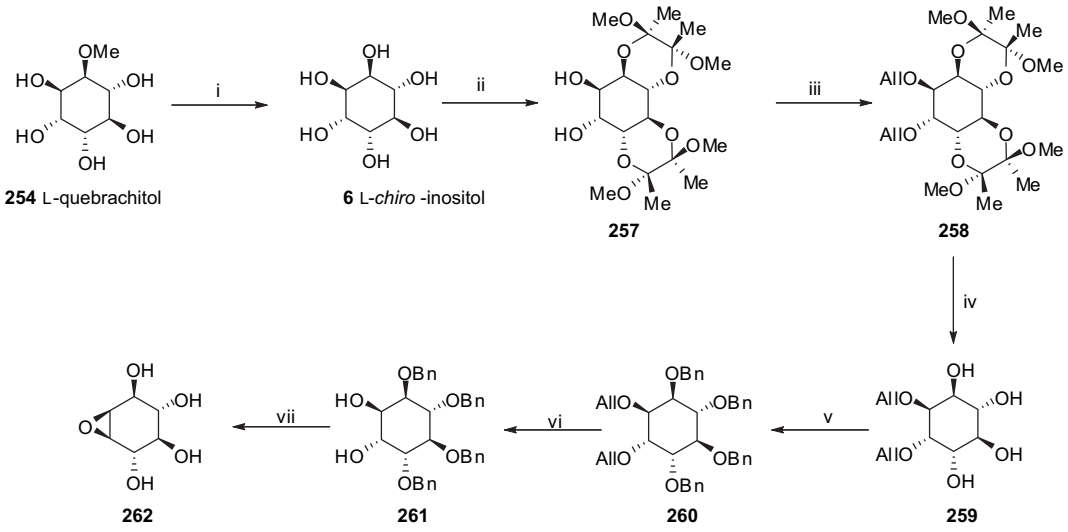
1,2-Anhydro-*myo*-inositol (conduritol-B epoxide) **262** has played an important role as an irreversible inhibitor of various β-glucosidases and can be exclusively obtained from L-quebrachitol.[73] First, L-*chiro*-inositol **6** was synthesized by the demethylation of L-quebrachitol **254** in the presence of an acid (Scheme 47). Diketalization of the vicinal diequatorial diol with



Scheme 45. (i) 1. $HC(OEt)_3$, TsOH, 76%. 2. NaH, PMBCl, 3. NaH, BnBr, 4. HCl, MeOH (23%); (ii) peptide **243**, DPCP, NEt_3, CH_2Cl_2, 53%, 98% ee; (iii) 1. BOMCl, Hunig's base, DMF, 2. NaH, BnOH; (iv) DDQ, CH_2Cl_2, 80%; (v) $(^iPr)_2NP(OBn)_2$, dicyanoimidazole, H_2O_2, 78%; (vi) $Pd(OH)_2/C$, H_2, 88%.



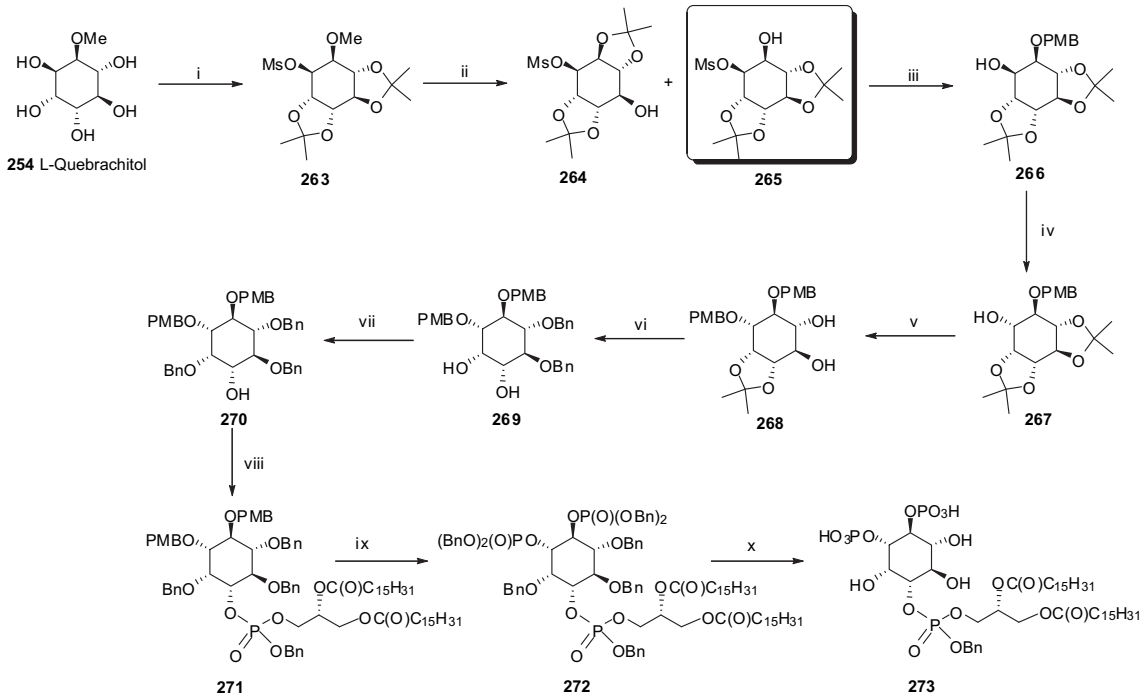
Scheme 46. (i) 1. aq HI, 2. cyclohexanone, H_3O^+, 3. CF_3COOH, MeOH; (ii) diethylene glycol di-*O*-tosylate, NaH, THF, 120 °C.



Scheme 47. (i) 1. 57% HI; (ii) cat. CSA, 2,3-butadienone, $CH(OCH)_3$; (iii) AllBr, NaH, DMF; (iv) TFA, water, MeOH, DCM; (v) BnBr, NaH, DMF; (vi) cat. PTSA, Pd/C, water, MeOH; (vii) 1. PPh_3, DEAD, toluene. 2. 10% Pd/C, H_2, 1:5 EtOAc, MeOH.

2,3-butadienone in the presence of camphorsulfonic acid to form **257** and subsequent protection reaction of the remaining free hydroxy group with allyl bromide provided **258**. Cleavage of the bis-diacetal groups to provide **259** followed by protection of the four hydroxyl groups with benzyl bromide again gave the fully protected *chiro*-inositol **260**. Deprotection of the allyl groups followed by epoxide formation successfully afforded conduritol-B epoxide **262** via **261**.

Kozikowski et al.[74] described a novel synthesis of phosphatidylinositol polyphosphates from L-(−)-quebrachitol. Four of the hydroxyl groups in L-(−)-quebrachitol **254** were protected as the acetonide **263**. Mesylation of the remaining hydroxyl group followed by demethylation and concurrent deprotection of the acetonide groups gave the monomesylate, which was submitted to reprotection to furnish two easily separable regioisomers **264** and **265**. The protection of regioisomer **265** with *p*-methoxybenzyl chloride gave **266**. The inversion of the stereochemistry of the mesylate was accomplished through an oxidation–reduction sequence (**266**/**267**) after the reduction of the mesylate group with $LiAlH_4$. Sequential protection/deprotection of the hydroxyl groups, as shown in Scheme 48, afforded the key intermediate **270** via **269**. Phosphorylation of the free hydroxyl group in **270** followed by removal of the protected groups furnished the target compound **273** through the intermediates **271** and **272**.

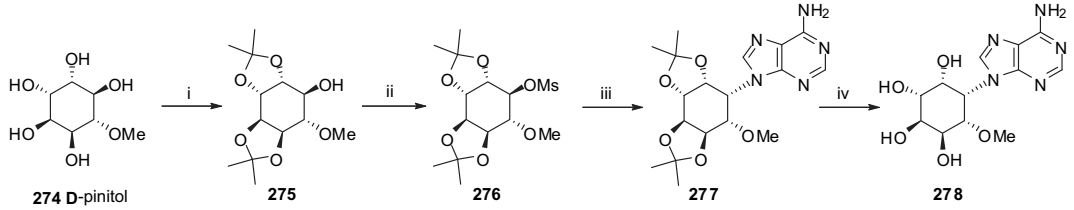


Scheme 48. (i) 1. 2-Methoxypropene, CSA, DMF, 60 °C, 4 h, 2. MsCl, Et_3N, DCM, 91%; (ii) 1. BBr_3, DCM, 0 °C, 8 h, 2. 2-Methoxypropene, CSA, DMF, 60 °C, 65%; (iii) 1. NaH, PMBCl, DMF, 2. $LiAlH_4$, THF, 63%; (iv) 1. Swern oxidn, 2. $NaBH_4$, MeOH, 86%; (v) 1. NaH/PMBCl, DMF, 2. AcCl (cat.), MeOH/CH_2Cl_2; (vi) 1. BnBr, NaH, DMF, 2. concd HCl (cat.), MeOH; (vii) 1. Bu_2SnO, toluene, reflux, 2. allyl bromide, CsF, DMF, 18 h, rt, 3. BnBr, NaH, DMF, 4. $RhCl(PPh_3)_3$ (cat.), DABCO, EtOH, reflux, 5. Acetone/1 N HCl (v/v 9/1), reflux; (viii) 1. $BnOP(N^iPr)_2$, *i*-Pr_2NH/tetrazole, 2. diacylglycerol, tetrazole, 3. ^{t}BuOOH; (ix) 1. DDQ, CH_2Cl_2/H_2O, 2. $BnOP(N^iPr)_2$, tetrazole, 3. BnBr, NaH, DMF; (x) 20% $Pd(OH)_2$/C, ^{t}BuOH.

Six-membered carbocyclic nucleosides have been shown to possess potent antiviral activities.[75] In order to study their structure–activity relationships, Lou et al.[76] have synthesized some six-membered carbocyclic nucleosides, starting from D-pinitol (**274**), a diasteroisomer of L-quebrachitol (**254**), found in nature. The key intermediate, diacetonide **275**, was synthesized in quantitative yield from D-pinitol **274**. Mesylation of the free hydroxyl group afforded the fully protected *chiro*-inositol derivative **276** (Scheme 49). The mesyl group was replaced by adenine with configuration isomerization to give **277**. Deketalization afforded the 4/5-deoxy-4/5-nucleobase derivative **278**. Some derivatives of **278** showed a mild inhibitory effect against human cancer cells.

protected tetrakisphosphate **282**. The benzyl groups were removed upon treatment with H_2 over palladium on carbon to give the tetrakisphosphate **283**. The tetrakisphosphate enantiomer *ent*-**283** was also synthesized starting from L-quebrachitol by application of the same synthetic methods (Scheme 50).

Larner et al.[77] have recently isolated a putative insulin mediator **287** from beef liver. A structural analysis has revealed that it has a pseudo-disaccharide Mn^{2+} chelate complex containing pinitol (**274**) and galactosoamine **285** structures. The structure of **287** was established by chemical synthesis. Glycosyl donor **284** derived from galactosamine was reacted with acetonide **275** synthesized from pinitol, by the assistance of trimethylsilyl triflate to give the key

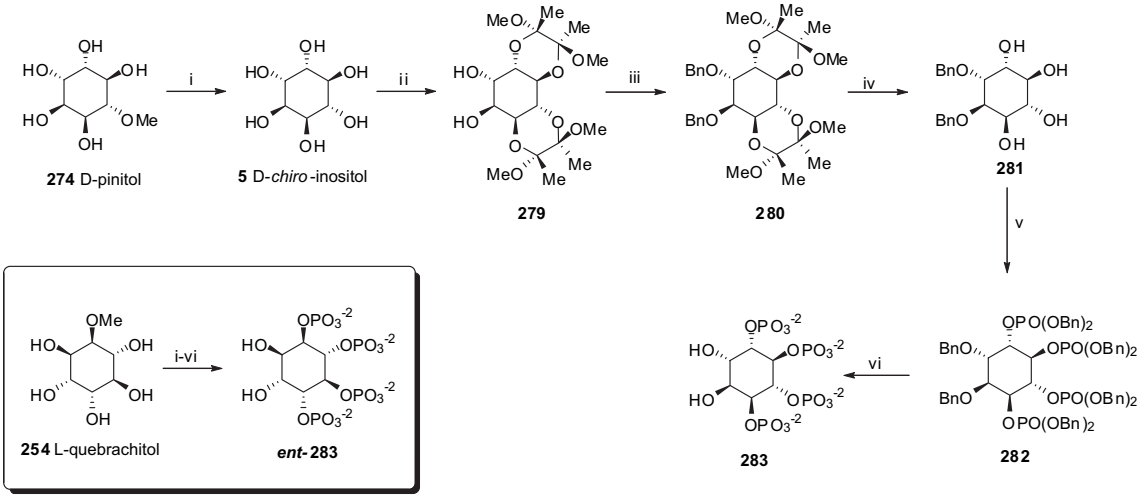


Scheme 49. (i) DMP, acetone, TsOH, rt, 16 h; (ii) MsCl, Et_3N, CH_2Cl_2, 0 °C, 24 h; (iii) adenine anion, K_2CO_3, 18-crown-6, DMF, 80 °C, 24 h; (iv) 80% aq AcOH, 80 °C, 5 h.

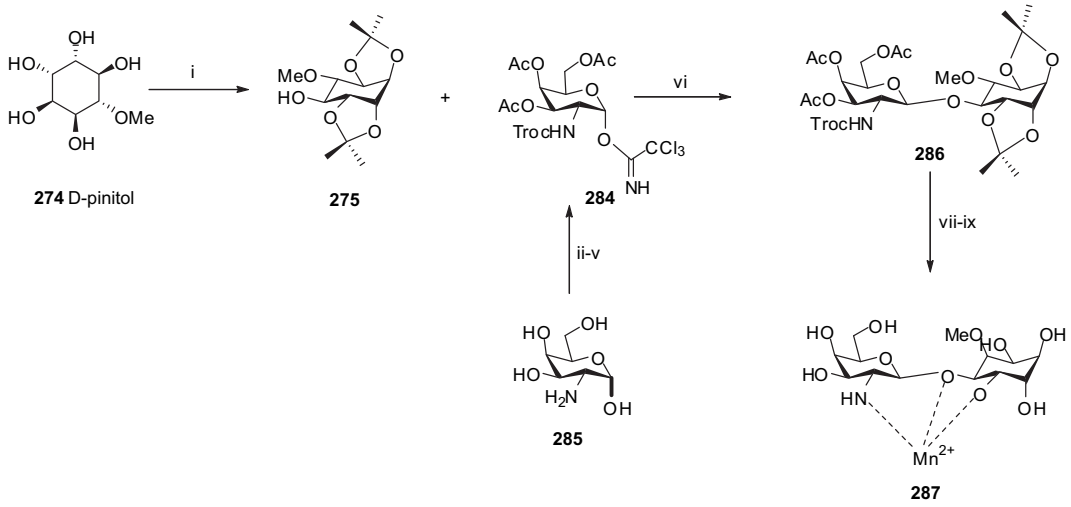
In order to avoid the tedious resolution of the intermediates involved in the synthesis of inositol phosphates, the optically active natural products, pinitol (**274**) and quebrachitol (**254**), were used as starting materials by Potter et al.[5h] D-Pinitol (**274**) was treated with hydroiodic acid to furnish D-*chiro*-inositol (**5**) followed by regioselective protection with 2,3-butanedione that afforded the diol **279**, which was converted into the fully protected inositol derivative **280** (Scheme 50). Removal of butane-2,3-diacetal by trifluoroacetic acid to form **281** followed by a phosphitylation reaction gave the fully

compound **286**. Deprotection procedures and reaction with $MnCl_2$ of **286** afforded the target compound **287** (Scheme 51).

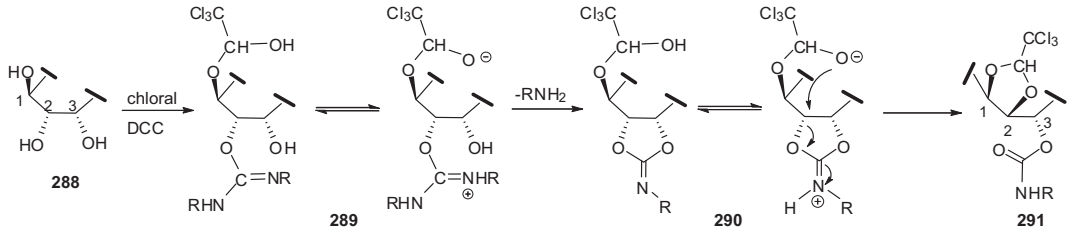
Recently, Miethchen et al.[78] reported a one-pot procedure for the selective epimerization of cyclitols having a *cis–trans* sequence of three neighboring hydroxyl groups. The mechanism of the reaction is given in Scheme 52. The configuration at the C-2 carbon atom was inverted by the treatment of the triol **288** with the reagent combination, chloral and dicyclohexyl carbodiimide (DCC) through the intermediates **289**–**291** (Scheme 52). The application



Scheme 50. (i) 47% HI, reflux; (ii) 2,3-butanedione, trimethyl orthoformate, $Et_2O{\cdot}BF_3$, MeOH, 97%; (iii) BnBr, NaH, DMF, 96%; (iv) TFA, H_2O, 84%; (v) 1. $^{i}Pr_2NP(OBn)_2$, 1*H*-tetrazole, CH_2Cl_2, 2. *m*-CPBA 84%; (vi) Pd/C, H_2, MeOH, H_2O, 81%.



Scheme 51. (i) DMP, acetone, *p*-TsOH; (ii) TrocCl, $NaHCO_3$, H_2O; (iii) Ac_2O, Py (1:1); (iv) $H_2NNH_2{\cdot}HOAc$, DMF; (v) Cl_3CCN, DBU, CH_2Cl_2; (vi) 4 Å molecular sieves, TMSOTf, CH_2Cl_2; (vii) 80% aq AcOH; (viii) Amberlite 420 (OH form), 2-propanol/H_2O (1:5); (ix) pH 6.8, $MnCl_2$ (aq).

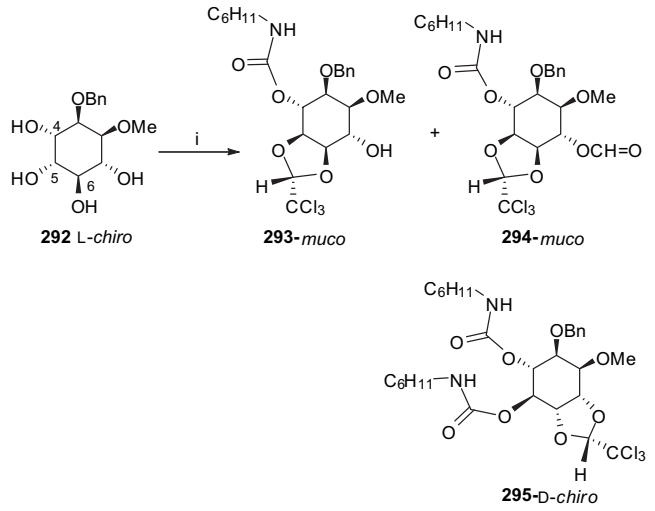


Scheme 52.

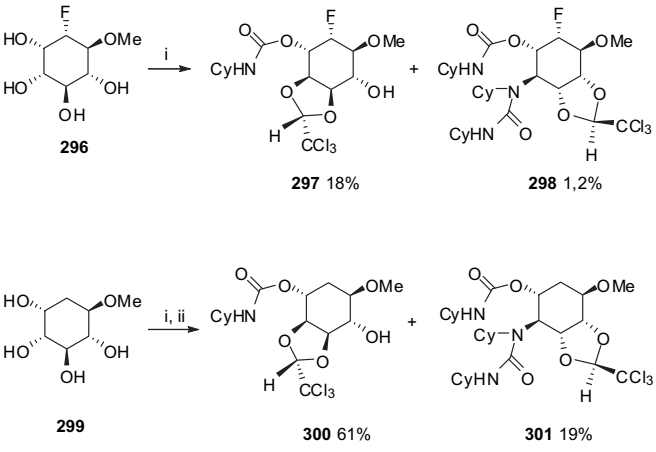
of this method to inositols, such as *myo*-inositol and L-quercitol failed, although substituted L-quebrachitol and pinitol derivatives were successfully epimerized.

The starting material **292**[72a,79] was synthesized from L-quebrachitol. The refluxing of **292** with chloral and DCC formed three products: *muco*-inositol derivatives **293** and **294** and the *chiro*-inositol derivative **295** (Scheme 53).[80] As shown in Scheme 52, only the middle carbon atom C-5 of the triol unit was inverted. It was interesting to note that the D-*chiro*-inositol derivative **295** was formed from the L-*chiro*-inositol derivative **292** where the configuration at C-4 as well as at C-5 was inverted.

Later, two competitive regio- and stereoselective epimerization reactions were investigated in cyclitols having four contiguous OH groups and two substituents **296** and **299**.[81] It has been noted that the substituents have an important effect on the product distribution; the lower the electron-withdrawing effect of the substituents, the higher the percentage of the doubly inverted product. In the case of **296**, the doubly inverted product **298** was isolated in 1.2% yield. When the fluorine atom was replaced by H (**299**), however, the amount of the doubly inverted product **301** was increased up to 19%. In all cases, however, the singly inverted products **297** and **300** were always formed as the major products (Scheme 54).



Scheme 53. (i) $Cl_3CCH{=}O/DCC/CH_2Cl_2$, reflux.



Scheme 54. (i) $Cl_3CCH{=}O/DCC/(CH_2Cl)_2$, reflux; (ii) MeOH, Et_3N, reflux.

5. Synthesis of inositols from aromatic compounds

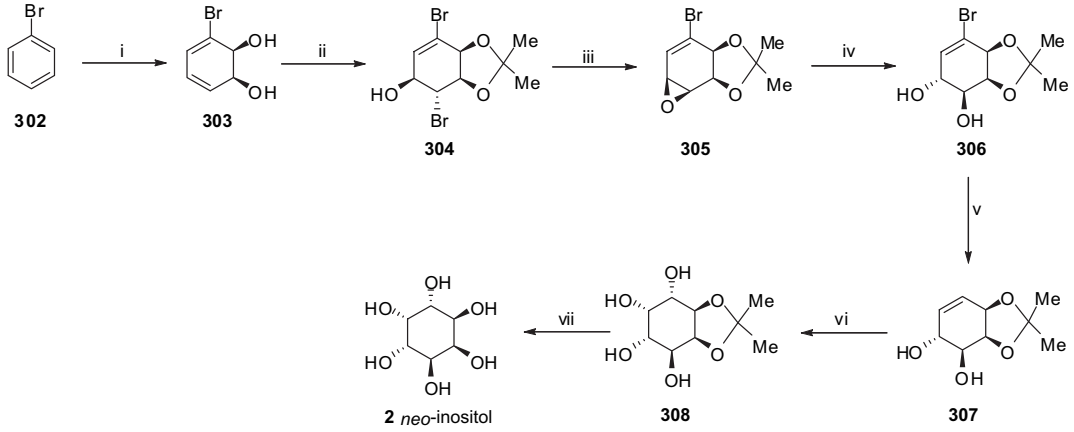
The development of synthetic routes, even to the most abundant inositols initiated the discovery of additional synthetic methodologies, in turn leading to various inositol derivatives. A reliable and efficient route for the synthesis of inositol analogues is the chemoenzymatic biooxidation of aromatic compounds. Recently, Hudlicky et al.[82] succeeded in the synthesis of various inositol derivatives.

Neo-inositol (**2**) was synthesized by the enzymatic oxidation of bromobenzene **302** in seven steps (Scheme 55). Toluene dioxygenase was used for this conversion to obtain the chiral material **303**. The formed diol was protected as the acetonide followed by the reaction with 1,3-dibromo-5,5-dimethylhydantoin in acetone/water to give **304**. The treatment of **304** with KOH formed the epoxide **305**, which underwent a ring-opening reaction at elevated temperatures to form **306**. Debromination of **306** and subsequent hydroxylation provided the protected neo-inositol skeleton **308** via **307**. The cleavage of the acetonide in the presence of an acid exclusively afforded neo-inositol (**2**).

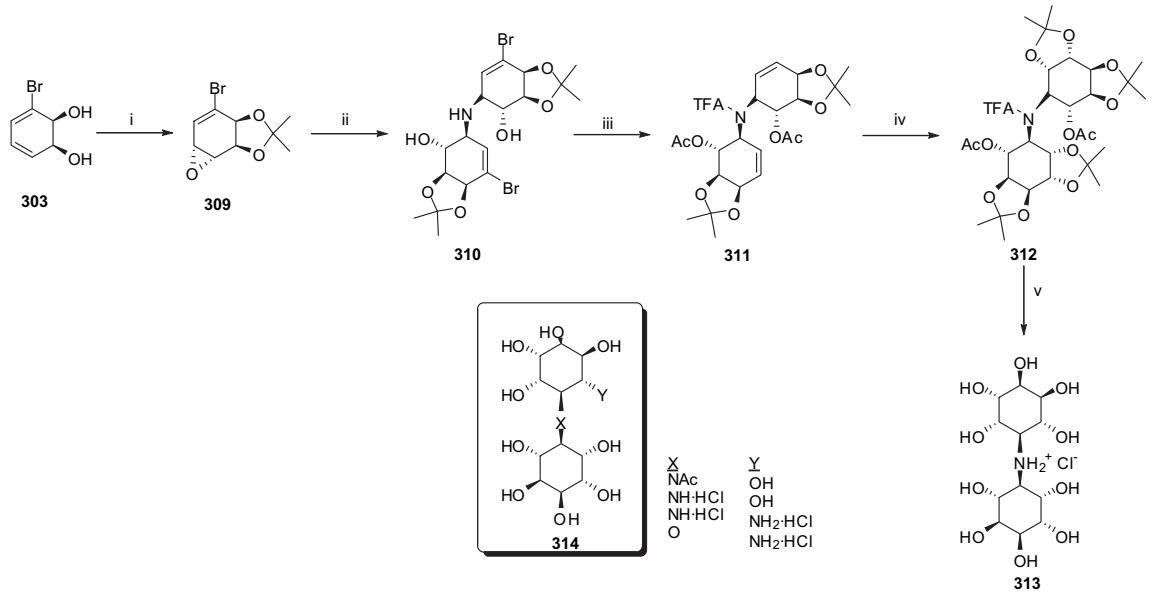
Novel O- and N-linked inositol oligomers described as a class of unnatural saccharide mimics are used as heparin analogs, insulin mediators, or inhibitors of natural glycosidase enzymes.[83] Hudlicky et al. synthesized some new inositol oligomers by a chemoenzymatic approach, starting from bromobenzene **302**.[7e,84a] Bromocyclohexadiene-*cis*-diol **303**, prepared by the biooxidation of bromobenzene, was easily converted into the acetonide vinyloxirane **309** by dimethoxypropane with an acid and followed by *m*-CPBA (Scheme 56). The reaction of vinyloxirane **309** with ammonia in the presence of $Yb(OTf)_3$ resulted in the rapid cleavage of epoxide to give the *trans*-amine, which was subjected to a coupling reaction of the vinyloxirane to yield the oligomer **310**. The radical debromination of **310** followed by acetylation of the free hydroxyl groups resulted in the formation of **311**, which was transformed into **312**. Cleavage of the acetonide ring successfully gave the dimer oligomer **313**. The O-linked oligomer **314** (X=O) was also synthesized by application of the same methodology.

epi-Inositol (**7**) has recently been evaluated as a potential antidepressant drug, which interacts with lithium and *myo*-inositol.[85] *epi*-Inositol (**7**) was synthesized by the chemoenzymatic route.[85] The treatment of bromocyclohexadiene-*cis*-diol **303** with OsO_4 and NMO followed by ketalization to give **315** and subsequent epoxidation led to **316** (Scheme 57). Epoxide **317** obtained by a radical debromination procedure was boiled in water containing either an acidic or basic resin to exclusively afford *epi*-inositol (**7**).

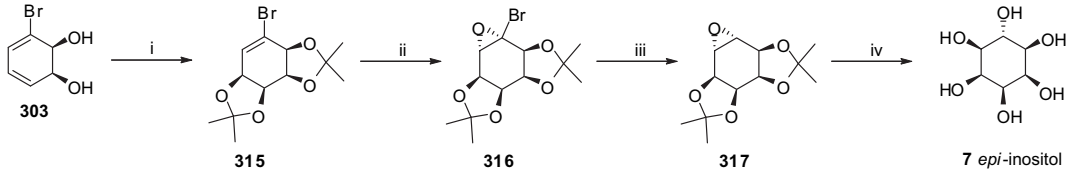
More recently, Gonzalez et al. reported the synthesis of unnatural cyclitol derivatives containing an −SCN group, starting from the epoxide **309** synthesized from bromobenzene.[86] Nucleophilic attack of thiocyanate on the oxirane **318** obtained by the radical debromination of **309** gave thiocyanohydrin **319** (Scheme 58). cis-Dihydroxylation of **319** gave the triol **320** and the subsequent removal of



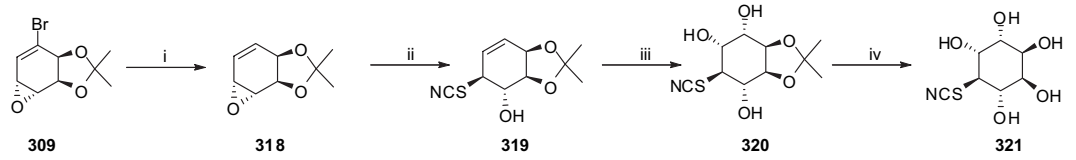
Scheme 55. (i) Toluene dioxygenase; (ii) DMP, PTSA, acetone, then DBH, H_2O, acetone; (iii) 10% aq KOH, DME, 5 h, rt; (iv) rt, reflux; (v) Bu_3SnH, AIBN, benzene, reflux, 18 h; (vi) OsO_4, NMO, ^{t}BuOH, acetone/water; (vii) concd HCl, MeOH, 48 h.



Scheme 56. (i) 1. DMP, H^+, 2. *m*-CPBA or PhINTs; (ii) $Yb(OTf)_3$, NH_3, dioxane; (iii) 1. Bu_3SnH, AIBN, 2. Ac_2O, pyridine, DMAP, 3. $(CF_3CO)_2O$, DMAP, Δ; (iv) 1. OsO_4, H_2O, acetone, 2. DMP, H^+; (v) 1. MeOH, NaOMe, 2. Na, NH_3, HCl, MeOH.



Scheme 57. (i) 1. OsO_4, NMO, CH_2Cl_2, rt, 2. DMP, TsOH, rt, 70%; (ii) *m*-CPBA, $CH_2Cl_2/CHCl_3$, 50 °C, 70%; (iii) $HSnBu_3$, $(PhCO_2)_2$, THF, 67 °C, 85%; (iv) DOWEX 1X8-200 H^+ cation, H_2O, 100 °C, 90%.



Scheme 58. (i) $HSnBu_3$, AIBN, THF, reflux, 70%; (ii) NH_4SCN, MeCN, 1 h, 85%; (iii) $RuCl_3/NaIO_4$, $AcOEt/CH_3CN/H_2O$, 15 min, 82%; (iv) Dowex 50 (H^+), $MeOH/H_2O$, rt, 1 h, 93%.

the ketal group successfully yielded 6-thiocyanodeoxy L-*chiro*-inositol **321**. Biological activity tests of **321** proved it to be a potential leader for the development of insect deterrents of high selectivity.

Since the inositols belong to an important class of biologically active compounds, synthetic analogues of inositols have also attracted much interest. Mehta et al.[87] introduced a new term, 'bicyclic inositols' **324** (inosito-inositols), as new structural motifs that might show unusual biological activities as well as metal-binding character. Furthermore, they have synthesized annulated inositols **322**/**323** and conjoined inositols **325** (Fig. 3). These new classes of compounds are principally derived from naphthalene, anthracene, and indene.

The *trans*-fused bicyclic inositols, such as **322** and **323**, are rigid and can be locked into a high-energy conformation. The presence of two chemodifferentiated tertiary hydroxyl groups may facilitate the generation of functional-group diversity. Furthermore, these kinds of compounds would have different activities. The syntheses of *trans*-fused bicyclic inositols **322** and **323** have been accomplished, starting from the readily available aromatic compounds, tetralin and indane.

Regioselective epoxidation of **326** followed by ring opening of the epoxide **327** and the subsequent acetylation of the resulting diol

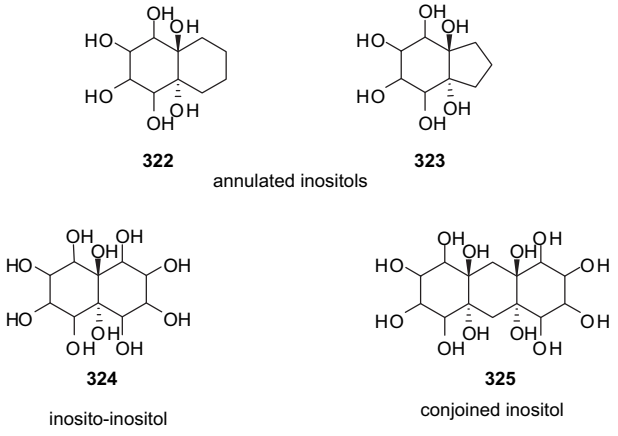
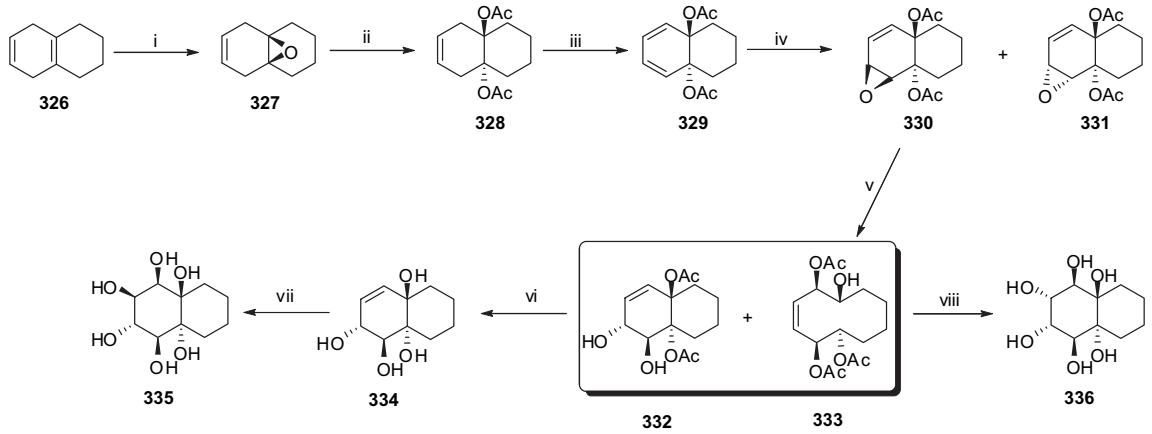


Fig. 3. Structures of some bicyclic inositol derivatives.

afforded the *trans*-diacetate **328**. The key compound, diene **329**, was formed by allylic bromination and subsequent elimination of hydrogen bromine. Diene **329** was treated with *m*-CPBA to yield two oxirane isomers, **330** and **331**, where the former was obtained as the

major product. The oxirane **330**, when treated with 10% AcOH in THF, gave **332** as well as the unexpected product **333** arising from the neighboring acetate-mediated opening of the epoxide ring followed by an S_N2' displacement. These products were exposed to cis-dihydroxylation separately, followed by hydrolysis, to give the cyclohexa-annulated *chiro*-inositol **336** and cyclohexa-annulated *myo*-inositol **335** via **334**, respectively (Scheme 59).

The regioselective epoxidation of the major product **342** afforded the diastereoisomeric epoxides **343** and **344**, which were exposed to a ring-opening reaction by an acid to give **345**. The resulting diol was acetylated followed by allylic bromination and subsequent elimination of 2 mol hydrogen bromide to furnish the diene **346**. Two sequential cis-dihydroxylations followed by hydrolysis successfully afforded the annulated *chiro*-inositol **348** via **347**.



Scheme 59. (i) a) *m*-CPBA, CH_2Cl_2, −5 °C, 5 min, 85%; (ii) 1. 10% AcOH, rt, 2 h, 90%, 2. Ac_2O, BF_3/Et_2O, rt, 2 h, 88%; (iii) 1. NBS, AIBN, CCl_4, reflux, 4 h, 2. DBU, DMSO, rt, 52% (two steps); (iv) *m*-CPBA, CH_2Cl_2, 10 °C, 5–6 h, 73% (based on recovered starting material); (v) 10% AcOH, THF, 50 °C, 16 h, 80%; (vi) K_2CO_3, MeOH, rt, 1 h, 95%; (vii) OsO_4 (cat.), NMMO, acetone/water 4:1, rt, 6 h, 80%; (viii) 1. OsO_4 (cat.), NMMO, acetone/water 4:1, rt, 2 h, 88%. 2. K_2CO_3, MeOH, rt, 2 h, 96%.

The synthesis of cyclopenta-annulated inositols **338** and **339** were also accomplished by the implementation of the same protocol to the diacetate **337** (Fig. 4) synthesized starting from indane.

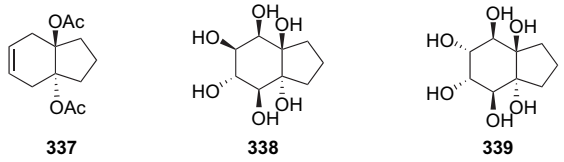
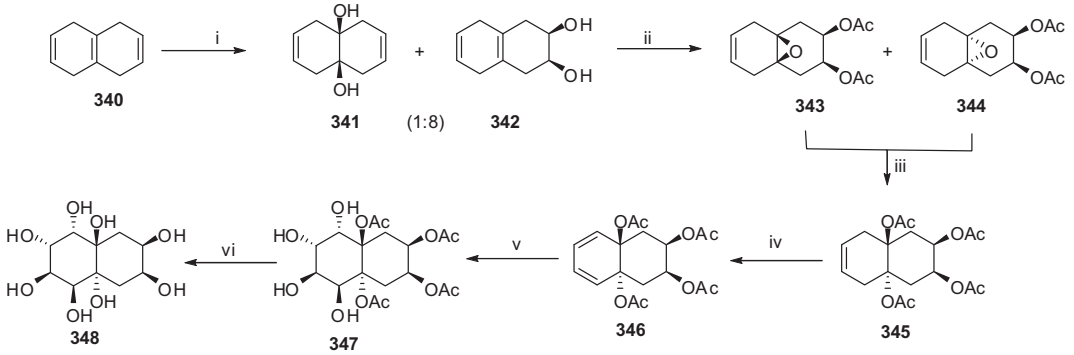


Fig. 4. Cyclopenta-annulated inositols.

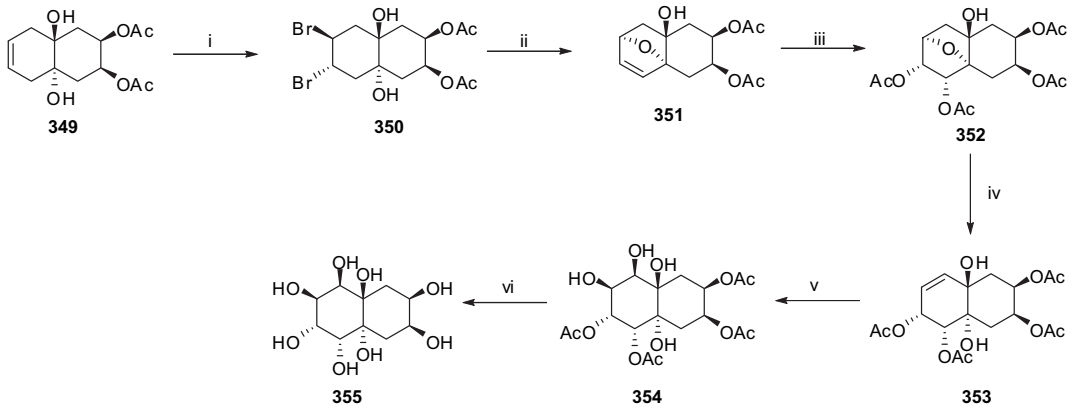
Inoso–inositols were successfully synthesized by Mehta and Ramesh, starting from naphthalene.[88] Isotetralin **340**, obtained by the Birch reduction of naphthalene, was subjected to a cis-dihydroxylation reaction to give the isomers **341** and **342**, where the latter was formed as the major product in a ratio of 8:1 (Scheme 60).

Cyclohexa-annulated neo-inositol derivative **355** was synthesized starting from the *trans*-diol–*cis*-diacetate **349**, which was obtained by the treatment of a mixture of **343** and **344** with mild acid.[88] Bromination of the double bond in **349** to give **350** followed by treatment with potassium *tert*-butoxide furnished the cyclic ether **351**, which was subjected to a cis-dihydroxylation reaction to give **352** (Scheme 61). Tetrabutylammonium iodide in the presence of BF_3-etherate cleaved the ether linkage and formed **353**. Again, the cis-dihydroxylation of the double bond on the opposite face to the acetate groups furnished **354**. Finally, the hydrolysis of the acetate groups with potassium carbonate gave the bicyclic inositol derivative **355** having the neo-inositol configuration.

More recently, Mehta and Sen[89] reported the synthesis of the conjoined inositol (**325**) precursors **357** and **359** from the commercially available aromatic precursor, anthracene (**356**) (Fig. 5). Hexahydroanthracene synthesized from the Birch reduction of anthracene was treated with *m*-CPBA to give the epoxide followed by cleavage of epoxide that afforded the diol. Similar procedures to those described in Scheme 61, were applied to afford conjoined precursors **357** and **358** having more stereogenic centers.



Scheme 60. (i) OsO_4 (1 mol %), NMMO, acetone/water (4:1), 10 °C, 60%; (ii) 1. *m*-CPBA, CH_2Cl_2, −5 to 0 °C, 2. Ac_2O, pyridine; (iii) 1. 10% AcOH, 1 h, 85%, 2. Ac_2O, $BF_3{\cdot}O(Et)_2$, 3 h, 88%; (iv) 1. NBS, AIBN, CCl_4, reflux, 1 h, 2. DBU, DMSO, 3 h, 56% (two steps); (v) OsO_4, NMMO, acetone/water (4:1), 2 days, 52%; (vi) K_2CO_3, MeOH, 1 h, 95%.



Scheme 61. (i) $Py^{+}HBr_3^{-}$, CH_2Cl_2, 3 h, 77%; (ii) KO^{t}Bu, ^{t}BuOH/dioxane (1:2), rt, 1 h–60 °C 3 h, 45%; (iii) 1. OsO_4 (1 mol %), NMMO, acetone/water (4:1), 2 h, 2. Ac_2O, DMAP, CH_2Cl_2, 30 min, 75% (two steps); (iv) 1. TBAI, $BF_3{\cdot}O(Et)_2$, $CHCl_3$, reflux, 4 h, 73%, 2. KO^{t}Bu, ^{t}BuOH/dioxane (1:2), 60 °C, 2 h, 63%; (v) OsO_4 (1 mol %), NMMO, acetone/water (4:1), 3–4 h, 60%; (vi) K_2CO_3, MeOH, rt, 1 h, 67%.

The ring-closing metathesis (RCM) method was also used in the asymmetric synthesis of *myo*-inositols starting from tartrates.[90] Bis-Weinreb amide of D-tatrate **360**[91] was reacted with vinylmagnesium bromide followed by a subsequent Luche reduction that produced the 1,7-diene **361**. Conduritol derivative **362** was formed by the RCM reaction. The protection of hydroxyl groups followed by cis-dihydroxylation gave **363**. Subsequent protection series (**364**, **365a**,**b**) afforded the *myo*-inositol analog **366a**,**b**, which were used for glycosylphosphatidylinositol (GPI) anchor synthesis (Scheme 62).

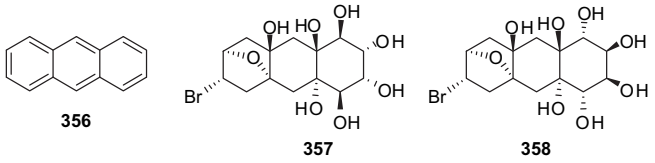


Fig. 5. Precursors for conjoined inositols.

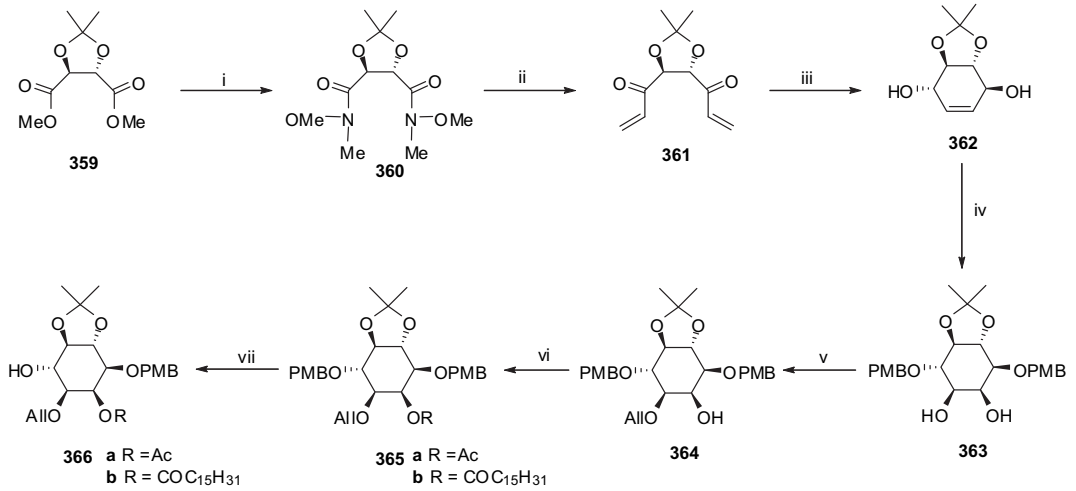
Recently, Roush et al.[92] described a novel asymmetric inositol synthesis, starting from the diene **369**, which was synthesised by the stereoselective γ-allylboration of aldehyde **367** with chiral γ-silylallylborane **368** (Scheme 63). Subsequent ring-closing metathesis gave the cyclohexenylsilane **370**. The cis-hydroxylation of **370** with OsO_4 furnished trihydroxysilane derivative **371** in quantitative yield. Hydroxysilane **371** was exposed to Fleming–Tamao oxidation to give **372**, followed by debenzylation to give D-(+)-*chiro*-inositol (**5**). Neo-inositol was also successfully synthesized using similar methodologies.

6. Synthesis of inositols from carbohydrates

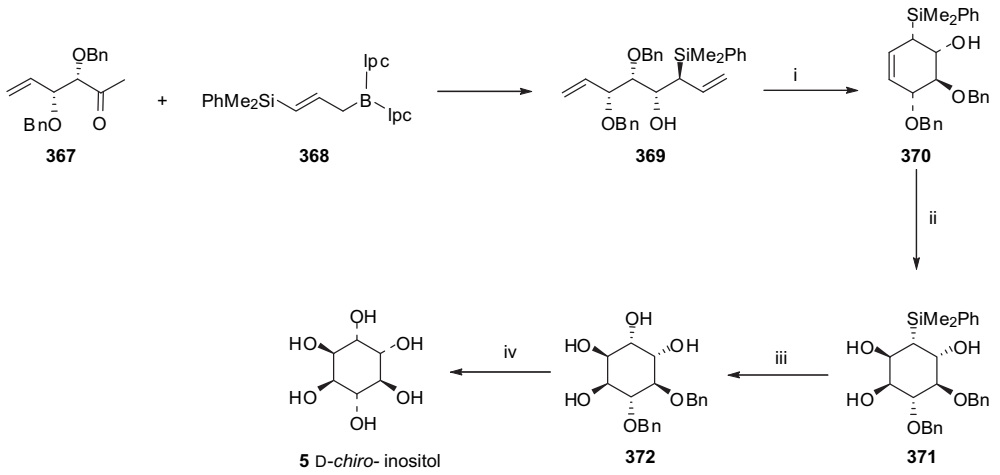
Carbohydrates are also versatile and convenient synthetic precursors for inositol derivatives, since they have more stereogenic centers and they are readily available. Among the synthetic approaches to inositol, Ferrier rearrangement,[93] ring-closing metathesis (RCM),[94] and pinacol coupling[95] have predominated.

The Ferrier-II reaction is an efficient one-step conversion of 5,6-unsaturated hexapyranose derivatives into cyclohexanone derivatives useful for the preparation of enantiomerically pure inositols or their amino and deoxy derivatives. The hydroxymercuration of **373** with mercury chloride gave the hemiacetal **374** from which aldehydoketone **375** and, hence, the hydroxyketone **376** were formed spontaneously (Scheme 64).[93a]

In a Ferrier-II reaction, palladium and mercury are the essential metals that are used for conversion of carbohydrates into inositols. Ikegami et al.[96] preferred palladium instead of mercury for the conversion of 6-deoxyhex-5-enopyranosides into the corresponding



Scheme 62. (i) $Me_3NHOMe{\cdot}HCl$, $AlMe_3$, CH_2Cl_2, −10 °C, 84%; (ii) 1. vinylmagnesium bromide, THF, from −78 to −5 °C, 2. $CeCl_3{\cdot}7H_2O$, $NaBH_4$, MeOH, −78 °C, 73%; (iii) $RuCl_2CHPh/PCy_3IMesH_2$ (2 mol %), CH_2Cl_2, reflux, 89%; (iv) 1. PMBCl, $BnEt_3N^{+}Cl^{-}$, 50% KOH/H_2O, toluene, 50 °C, 90%, 2. K_2OsO_4, K_2CO_3, $K_3Fe(CN)_6$, methanesulfonamide, quinuclidine, ^{t}BuOH, H_2O, 23 °C, 88%; (v) 1. Bu_2SnO, toluene, reflux, 2. Allyl bromide, TBAI, 60 °C, toluene, 91%; (vi) Ac_2O, DMAP, $^i Pr_2NEt$, CH_2Cl_2, 23 °C, 96% (gives **365a**) or palmitic acid, DCC, DMAP, THF, 23 °C, 89% (gives **365b**); (vii) DDQ, CH_2Cl_2, 0 °C, 70% yield of **366a**, 60% yield of **366b**.



Scheme 63. (i) $RuCl_2CHPh/PCy_3IMesH_2$, 80 °C, toluene, 2 h; (ii) OsO_4, NMO, acetone, 0 °C, pH 7 buffer; (iii) $Hg(OAc)_2$, AcOOH, AcOH, 23 °C, 1 h; (iv) H_2, Pd(C), EtOH.

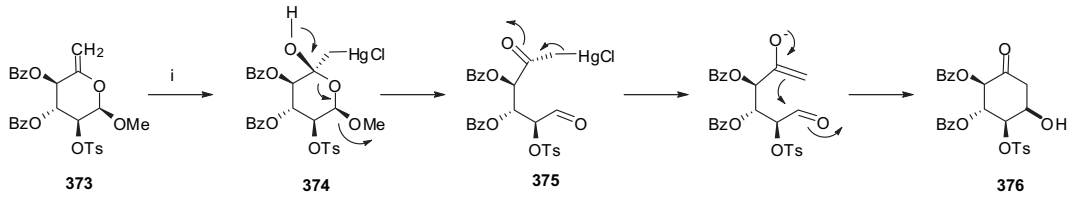
substituted cyclohexanones, which are the precursors of inositol diastereoisomers.

Ikegami et al.[96] first synthesized isomeric acetyl aldehydes, starting from protected methyl 2,3,4-tri-*O*-benzylglycosides. The oxidation of these compounds **377**–**379** followed by acetylation provided easily separable *Z*- and *E*-isomers **380**–**382**, which were then exposed to a Pd(II)-mediated Ferrier-II reaction to afford chiral penta-oxygenated cyclohexanones **383**–**385** (Scheme 65). Stereoselective reduction of the β-hydroxy ketones with $NaBH_4$ or $Me_4NB(OAc)_3$ provided the precursors of inositol diastereoisomers in good yields.

Although palladium was used as a catalyst in the Ferrier-II reaction and provides diverse inositol diasetereoisomers, it may cause inseparable isomeric products, depending on the nature of the precursors. More recently, Conway et al.[97] reported the Hg(II)-mediated Ferrier rearrangement-assisted D-*myo*-inositol 1,4,5-triphosphate synthesis, starting from methyl α-D-*myo*-inositol.

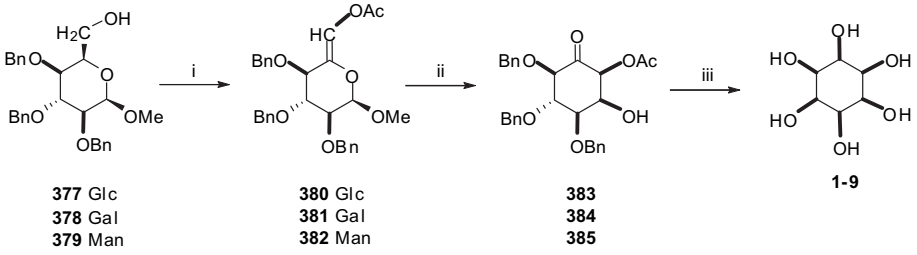
Anisylidene acetal **387** obtained from methyl α-D-glucopyranose **386** in three steps was reacted with DIBAL-H to cleave the anisylidene acetal group to give **388** (Scheme 66). Dess–Martin periodinane oxidation of the hydroxyl group furnished aldehyde **389**, which was converted into the enol acetate **390** by the reaction of the corresponding aldehyde with potassium carbonate and acetic anhydride as precursor for Ferrier reaction. The treatment of enol acetate **390** with mercury(II) acetate afforded the cyclohexanone derivative **391**, which was reduced to the protected inositol derivative **392**. Suitable protection, deprotection, and phosphorylation afforded the unnatural inositol phosphate derivative **394** via **393**.

Ring-closing metathesis (RCM)[94] is also a facile and practical method for inositol formation from carbohydrates. Shirai et al.[98] achieved the synthesis of L-α-phosphatidyl-D-*myo*-inositol (PI) and its phosphates (PIPn), showing biological activities in intracellular signal transduction as second messengers, from D-glucose by utilizing ring-closing metathesis.[99]

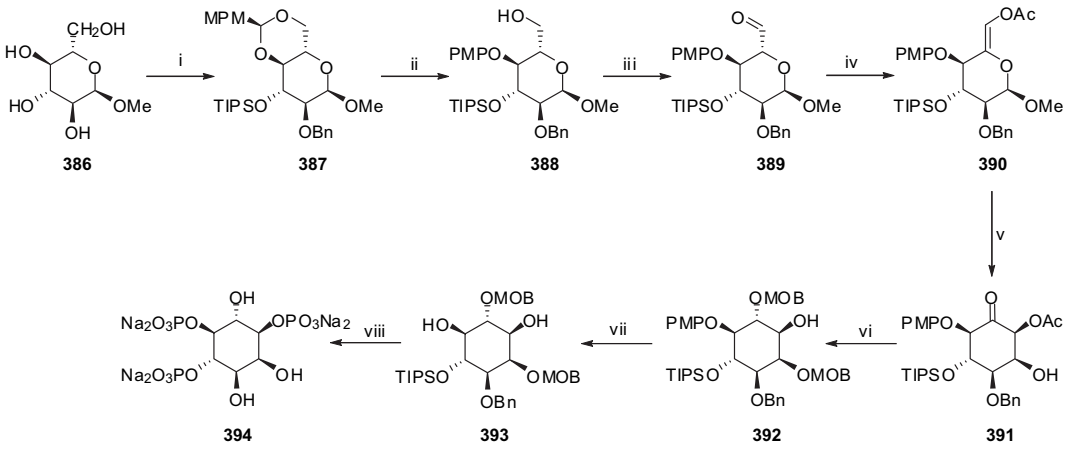


Scheme 64. (i) $HgCl_2$, Me_2CO, H_2O, reflux, 4.5 h, 83%.

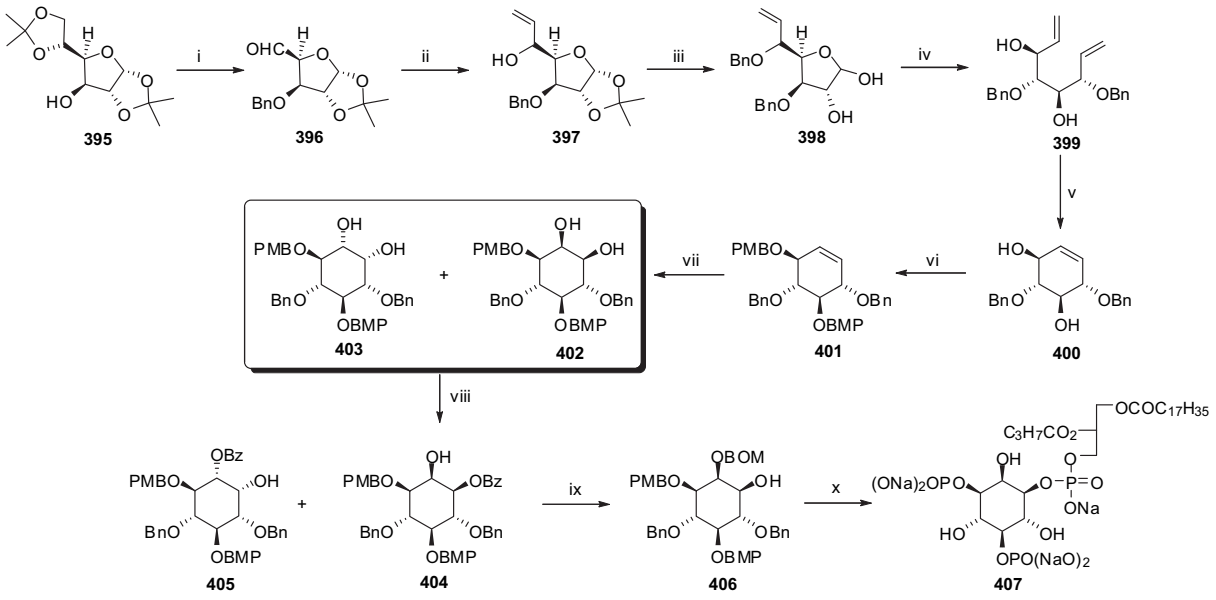
The aldehyde **396** prepared from 1,2,5,6-diisopropylidene-D-glucose **395** was reacted with organocopper reagent to afford the allyl alcohol **397** (Scheme 67). After benzylation of the hydroxyl group in **397**, the isopropylidene acetal group was removed and the formed hemiacetal **398** was subjected to Wittig olefination to give the 1,7-diene **399**, which is the desired compound for the ring-



Scheme 65. (i) 1. DCC, DMSO, pyridine, TFA, benzene, rt, 12 h, 2. Ac_2O, Et_3N, DMAP, $ClCH_2CH_2Cl$, 100 °C, 2 h; (ii) $PdCl_2 \cdot H_2O$, dioxane/water, 60 °C, 3 h; (iii) $Me_4NBH(OAc)_3$ (5.0 equiv), MeCN/AcOH or $NaBH_4$ (1.5 equiv), MeOH.



Scheme 66. (i) 1. 4-OMe/PhCH(OMe)$_2$, Amberlyst-15, DMF, 200 mbar, 80 °C, 58%, 2. *n*Bu$_2$SnO, TBABr, BnBr, MeCN, reflux, 54%, 3. Et$_3$N, TIPSOTf, CH$_2$Cl$_2$, rt, 92%; (ii) DIBAL-H, CH$_2$Cl$_2$, rt, 88%; (iii) Dess–Martin Periodinane, CH$_2$Cl$_2$, rt, 82%; (iv) K$_2$CO$_3$, Ac$_2$O, DMAP, MeCN, reflux, 65%; (v) 1. Hg(OAc)$_2$, acetone/H$_2$O (3:2), 2. NaCl (aq), 35%; (vi) 1. Me$_4$NBH(OAc)$_3$, AcOH, MeCN, 89%, 2. BOMCl, Hünig's base, 85 °C, 82%, 3. LiOH, MeOH, THF, 97%; (vii) DDQ, CH$_2$Cl$_2$/H$_2$O (18:1), rt, 95%; (viii) 1. TBAF in THF, CH$_2$Cl$_2$, rt, 90%, 2. (BnO)$_2$PN(*i*Pr)$_2$, 1*H*-tetrazole (0.43 M in MeCN), CH$_2$Cl$_2$, rt, 3. 3-chloroperbenzoic acid, 78 °C→rt, 93%, 4. H$_2$, *t*BuOH, H$_2$O, Pd (black), NaHCO$_3$, 95%.



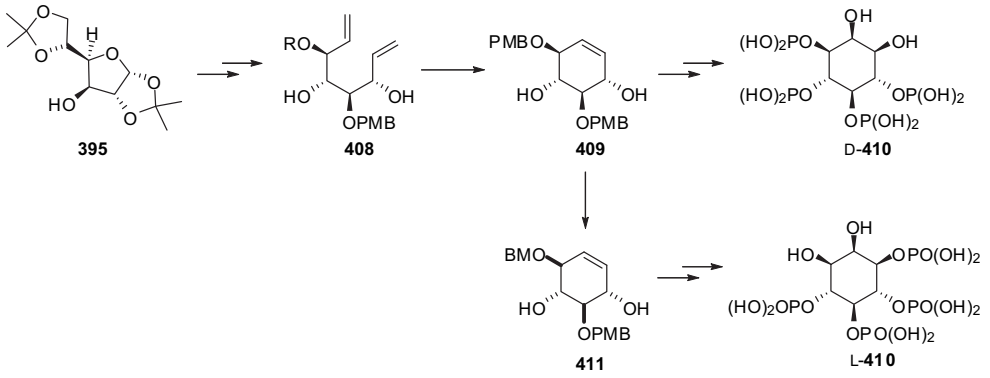
Scheme 67. (i) 1. NaH, BnBr, DMF, 89%, 2. 60% aq AcOH, rt, 95%, 3. NaIO$_4$, aq NaHCO$_3$, CH$_2$Cl$_2$, rt, 2 h, 73%; (ii) vinylmagnesium bromide (3.0 equiv), CuBr/Me$_2$S (3.4 equiv), THF/Me$_2$S, −40 °C→rt, 2 h, 59%; (iii) 1. NaH, BnBr, DMF, 95%, 2. 80% AcOH, 70 °C, 2 days, 92%; (iv) MePPh$_3$Br, *n*-BuLi, ether, rt, overnight, 68%; (v) Cl$_2$(PCy$_3$)$_2$Ru=CHPh (10 mol %), CH$_2$Cl$_2$, rt, 1 h, 85%; (vi) NaH, PMBCl, DMF, 92%; (vii) OsO$_4$ (5 mol %), quinuclidine (5 mol %), NMO, CH$_2$Cl$_2$, rt, overnight, 98% (1:1) mixture of diastereoisomers); (viii) BzCl (1.2 equiv), pyridine, DMAP, 67% (+dibenzoates, 27%); (ix) 1. BOMCl, diisopropylethylamine, TBABr, CH$_2$Cl$_2$, 70 °C, 2 days, 30% (recovered **403**, 68%); 2. K$_2$CO$_3$, MeOH, rt, 4 h, quant; (x) 1. phosphoramidite, 1*H*-tetrazole (8.0 equiv), CH$_2$Cl$_2$, rt, 2.5 h, then *m*-CPBA (4.2 equiv), −78 °C→rt, 45 min, quant, 2. DDQ (3.0 equiv), wet CH$_2$Cl$_2$, rt, 2.5 h, 52%, 3. (BnO)$_2$PNEt$_2$ (5.7 equiv), 1*H*-tetrazole (6.0 equiv), CH$_2$Cl$_2$, rt, 2.5 h, then *m*-CPBA (8.0 equiv), −78 °C→rt, 30 min, 82%, 4. H$_2$ (4.3 kgf/cm^2), Pd (black), NaHCO$_3$, *t*BuOH/H$_2$O, quant.

closing metathesis reaction. The diene was reacted with Grubbs' catalyst[100] to give conduritol derivative **400**. The protection of the free −OH groups followed by cis-dihydroxylation of the double bond resulted in the formation of diastereoisomeric *cis*-diols **402** and **403**, which were separated by column chromatography after regioselective benzylation and transformed into **404** and **405**, respectively. The coupling reaction of phosphoramidite with **406** followed by hydrolysis and following phosphorylation gave PI 3.5P2 **407**, exclusively.

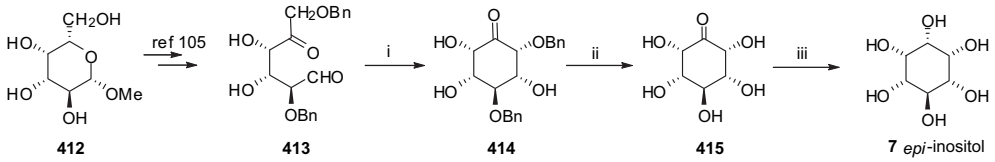
D- and L-*myo*-inositol 3,4,5,6-tetrakisphosphates, D-**410** and L-**410**, are bioactive molecules and play important roles in cellular signaling.[101] Conduritol-B derivative **409** was used as the key compound, which was synthesized by a ring-closing metathesis reaction of **408**, obtained from the protected D-glucose **395** (Scheme 68).[102] OsO$_4$-catalyzed cis-dihydroxylation of conduritol-B derivative **409** followed by protection to give **411**, hydrolysis, and phosphorylation provided D- and L-*myo*-inositol 3,4,5,6-tetrakisphosphates **410**, successfully.

Aldol-type intramolecular cyclization is another key step to afford inositols from carbohydrates. The treatment of 2,6-di-*O*-benzyl-L-*arabinose*-aldohexos-5-ulose **413**[103] derived from methyl β-D-galactopyranoside **412** with DBU in toluene led to *meso*-inosose **414** by intramolecular aldol cyclization (Scheme 69). Debenzylation of **414** by catalytic hydrogenation followed by reduction of the carbonyl group in **415** with NaBH$_4$ or Raney-Ni furnished *epi*-inositol **7** in quantitative yield.[104]

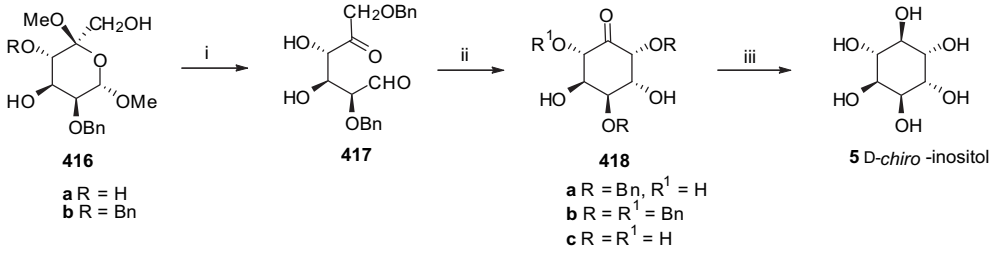
D-*chiro*-Inositol (**5**) was also synthesized by intramolecular aldol cyclization of hexos-5-uloses, starting from bis-glycosides **416a**,**b** (Scheme 70).[105] Bis-glycosides were reacted with trifloroacetic acid in MeCN to furnish hexos-5-uloses **417**. The treatment of **417** with



Scheme 68.



Scheme 69. (i) DBU, toluene; (ii) H_2/Pd(C), MeOH; (iii) Ni-Raney/H_2 or $NaBH_4$, −78 °C.



Scheme 70. (i) TFA/H_2O/MeCN; (ii) DBU/toluene/CH_2Cl_2; (iii) 1. $NaBH(OAc)_3$/AcOH/MeCN, 2. H_2/Pd(C)/MeOH.

DBU to give **418a**–**c** and subsequent reduction of the carbonyl group and debenzylation reactions successfully afforded chiro-inositol (**5**).

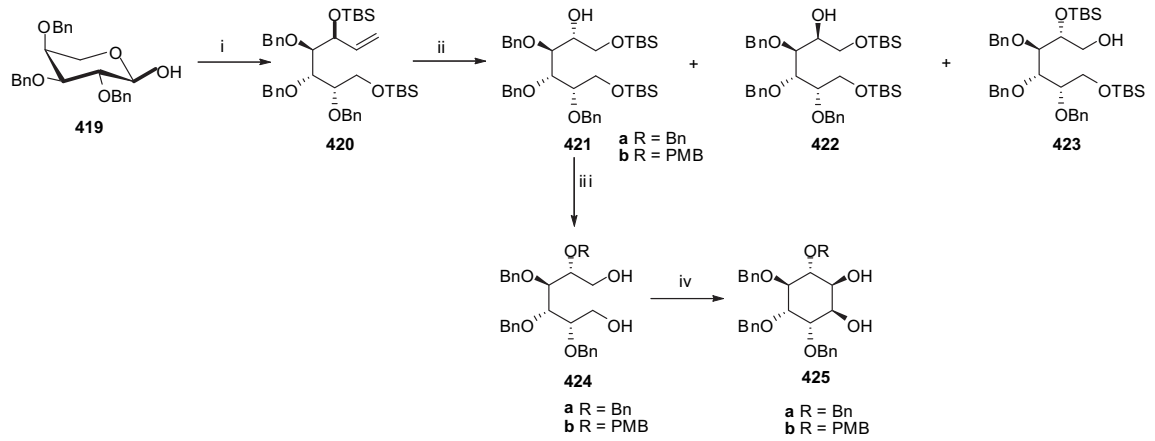
Recently, d'Alarcao and Marnera[106] demonstrated the synthesis of D-*chiro*-inositol derivative **425** obtained by the SmI_2-promoted pinacol coupling of an appropriately protected dialdehyde. The reaction of **419** with excess vinylmagnesium bromide led to the formation of isomeric alcohols. The protection of diols with TBDMSCl afforded a fully protected isomeric mixture **420** (Scheme 71). The reaction of **420** with ozone and subsequent reduction with $NaBH_4$ gave **421a**,**b**, **422**, and **423**. The protection of the hydroxyl groups in **421** and **423** was followed by the regioselective deprotection of TBS groups, providing diol **424a**,**b**. Swern oxidation of **424** followed by SmI_2-mediated pinacol coupling formed the *chiro*-inositol derivatives **425a**,**b**, exclusively. Interestingly, the cis-configuration of hydroxyl groups, which are trans aligned with respect to the alkoxy substituents, from intramolecular pinacol cyclization is well known as SmI_2-assisted selectivity.[107] The resulting *chiro*-inositol derivatives **425** were subjected to further glycosylation to form galactosaminyl D-*chiro*-inositols.

7. Synthesis of inositols from norbornene

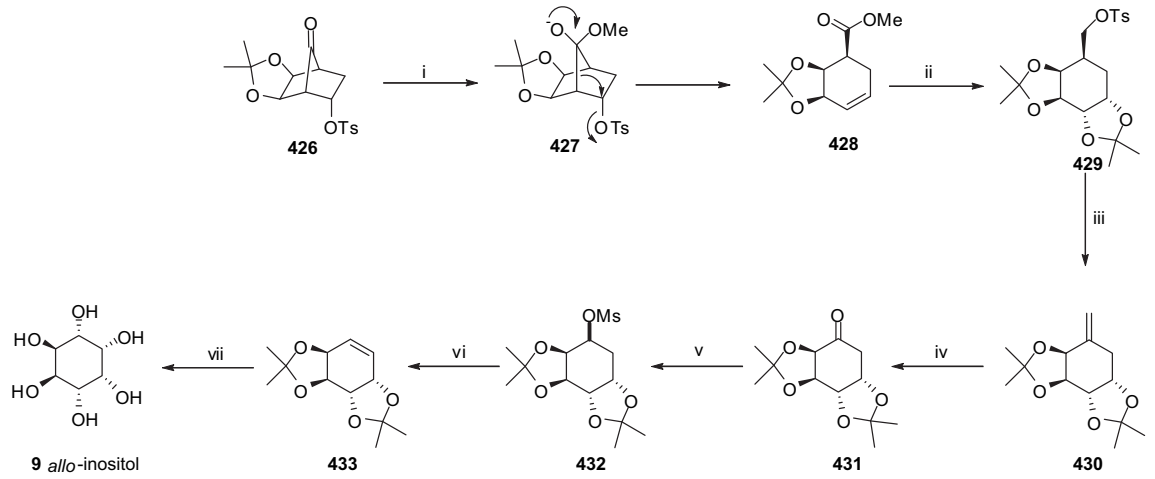
The synthesis of inositol derivatives is an active area of research. A great deal of effort has been devoted to the development of new synthetic methodologies for inositols and their derivatives. Mehta and Laksminath[108] have used the norbornane skeleton and applied a Grob-like 'top-to-bottom' fragmentation sequence to generate polyoxygenated cyclohexenoids, which were used as the intermediates in the synthesis of cyclitols.

The known starting material **426**, synthesized from 1,2,3,4-cyclopentadiene and vinyl acetate in a few steps, was reacted with NaOMe to give the fragmentation product **428** through the intermediate **427** as a single product (Scheme 72). The ester **428** was transformed into the tosylate **429**,[109] which was submitted to an ozonolysis reaction following an iodide-assisted elimination reaction to afford **431** via **430**. The reduction of the ketone followed by mesylation gave **432**, subsequent base-mediated elimination afforded the protected conduritol-E derivative **433**. The cis-dihydroxylation of bis-acetonoid **433** and deprotection gave *allo*-inositol (**9**) in high yield.

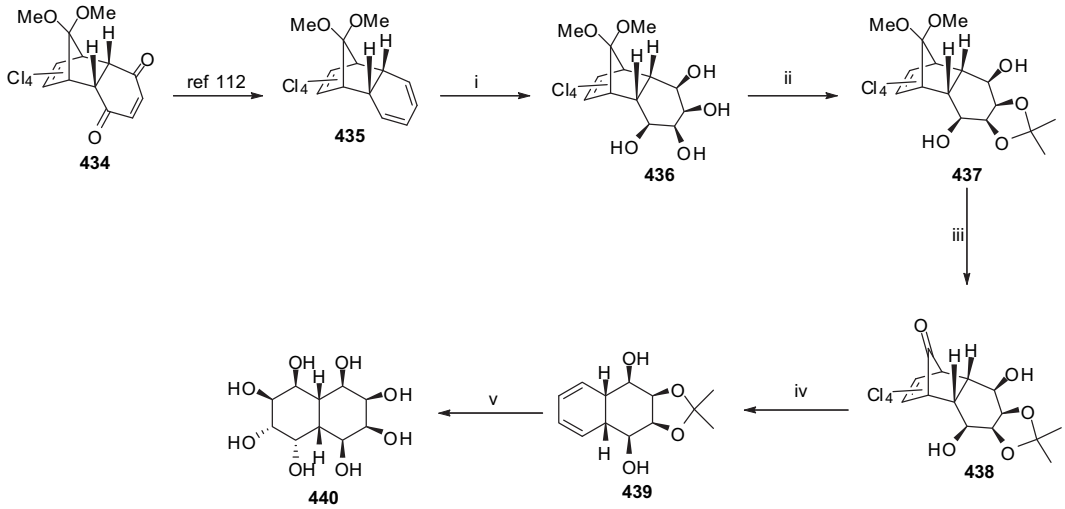
The cycloaddition product **434**, obtained from the reaction of 5,5-dimethoxy-1,2,3,4-tetrachlorocyclopentadiene and *p*-benzoquinone, was transformed into the tricyclic diene **435**,[110] which was exposed to a cis-hydroxylation reaction with OsO_4 to afford tetrol **436** (Scheme 73). Selective protection of the diol followed by reductive elimination of chlorine atoms gave the acetonide **437**, which was carefully hydrolyzed to the ketone **438**. The cyclohexadiene moiety in **439** was produced by thermally induced



Scheme 71. (i) 1. Vinylmagnesium bromide (10 equiv), THF, 0 °C to rt, 12 h, 91%, 2. TBDMSCl, imidazole, DMF, 12 h, 86%; (ii) O_3, 3:1 MeOH/CH_2Cl_2, Py (2 equiv), −78 °C; $NaBH_4$, −78 °C to rt; (iii) 1. NaH, BnBr, THF, TBAI, 12 h, for **421a**, 2. NaH, PMBCl, THF, 2 days, TBAI for **421b**; (iii) TBAF, THF, 2 h; (iv) 1. $(COCl)_2$, DMSO, THF, −78 °C, 30 min; 2-Pr_2NEt, −78 °C to rt; 2. SmI_2 (6 equiv), THF, ^{t}BuOH (3 equiv), −78 °C, 3 h.



Scheme 72. (i) NaOMe, MeOH, rt, 3 h; (ii) 1. OsO_4, NMMO, 30 h, 95%. 2. Me_2CO, Amberlyst-15, 1 h, 85%. 3. TosCl, Py, DCM, rt, 94%; (iii) 1. NaI, Me_2CO, Δ, 30 h, 92%, 2. ^{t}BuO$^-$K$^+$, ^{t}BuOH, Δ, 20 h, 70%; (iv) O_3, $NaHCO_3$, DCM, −78 °C, 5 min, DMS, 90%; (v) 1. $NaBH_4$, MeOH, 0 °C, 30 min, 89%, 2. MsCl, Et_3N, DCM, −10 °C, 30 min, 90%; (vi) ^{t}BuO$^-$K$^+$, DMSO, rt, 2 h, 75%; (vii) Amberlyst-15, aq MeOH, rt, 20 h, 93%.



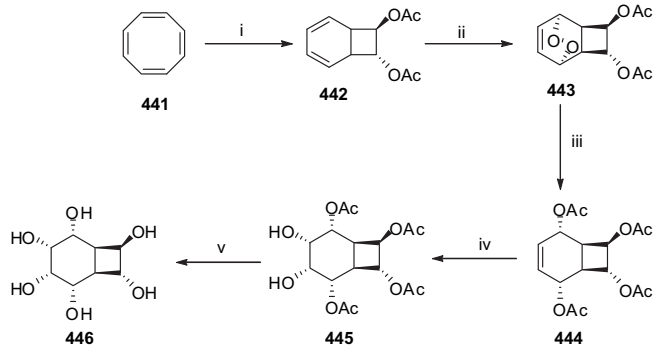
Scheme 73. (i) OsO_4, NMMO, Me_2CO/^{t}BuOH (5:2), 2 days, 66%; (ii) 1. Amberlyst-15, acetone, molecular sieves 4 Å, 75%, 2. Na, liq. NH_3, THF, EtOH, 49%; (iii) Amberlyst-15, acetone, 98%; (iv) $PhNO_2$, 160 °C, 62%; (v) 1. OsO_4, NMMO, Me_2CO/H_2O/^{t}BuOH (5:5:2), 85%, 2. 30% TFA, 95%.

decarbonylation. Double cis-dihydroxylation followed by deprotection successfully resulted in the bicyclic polyalcohol **440**.[111]

8. Bishomo-inositols

Balci and Kara[112] described a new class of inositols, bishomo-inositols from the commercially available cyclooctatetraene.

Cyclooctatetraene **441** was easily converted into diacetoxydiene **442**[113] by mercury(II) acetate, which was subjected to a TPP-sensitized photooxygenation reaction to furnish the *endo* peroxide **443** (Scheme 74). Selective reduction of the peroxide linkage in **443** with thiourea followed by acetylation of the hydroxyl groups



Scheme 74. (i) $Hg(OAc)_2$, AcOH, rt, 84%; (ii) 1. O_2, TPP, *hν*, CCl_4, rt, 70%; (iii) 1. thiourea, 2. Ac_2O, pyridine, 73%; (iv) $KMnO_4$, $MgSO_4$, EtOH, H_2O, 30%; (v) NH_3, MeOH, rt, 98%.

resulted in the formation of tetraacetate **444**. cis-Dihydroxylation of **444** with $KMnO_4$ in EtOH gave *cis*-diol **445**. Deacetylation of the diol exclusively yielded the bishomo-inositol **446** (Scheme 74).

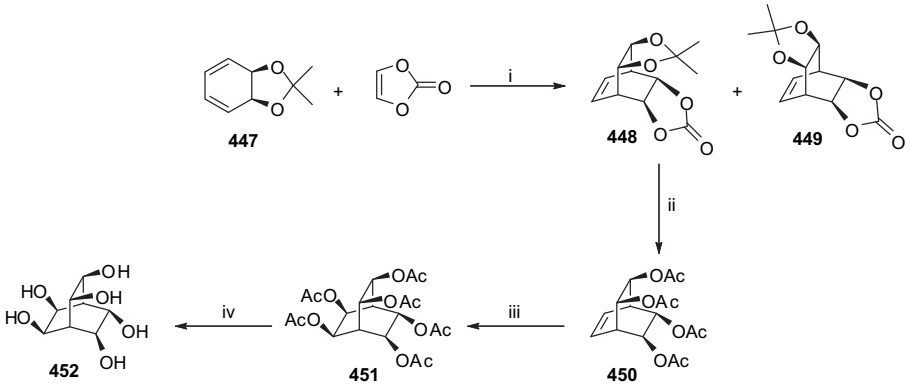
More recently, bishomo-inositol derivatives with a rigid bicyclo[2.2.2]octane geometry have been synthesized by Balci et al.[114] For the construction of the bicyclo[2.2.2]octane skeleton, diene **447** was reacted with vinylene carbonate to give the isomeric cycloaddition products **448** and **449** (Scheme 75). Hydrolysis of the ketal ring and opening of the carbonate functionality provided two separable isomeric bicyclic tetraacetates. The tetraacetate **450** was subjected to a cis-dihydroxylation reaction followed by acetolysis to give the highly symmetrical hexaacetate **451**. The removal of the acetate groups furnished symmetrical hexol **452**.

For the synthesis of other isomeric bishomo-inositols with a bicyclo[2.2.2]octane skeleton, the tetraacetate **450** was epoxidized to give only one isomer **453** with an *exo*-configuration. The reaction of the epoxide **453** with acidified acetic anhydride gave a mixture of hexaacetates **454a** and **455a**. The formation of the expected product **454a** can easily be explained by trans ring opening of the oxirane. Interestingly, during the formation of the other isomer **455a**, the configuration of one acetate group in **453** was changed, due to the neighboring group participation. The removal of the acetate functionalities with ammonia gave the expected hexols **454b** and **455b**. The hexol **454b** exhibited enzyme-specific inhibition against α-glycosidase (Scheme 76).

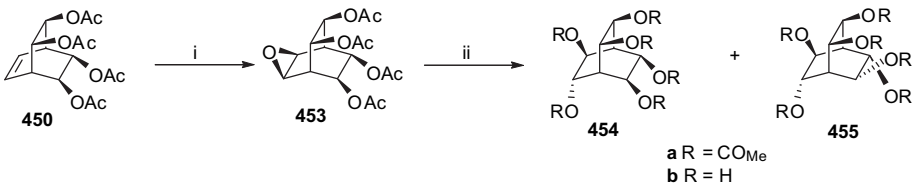
For the synthesis of various inositol analogues, Baran and Balci[115] have used a 1,3-diene **457**[116] as the starting material. The synthesis of **457** was accomplished in four steps, starting from the anhydride **456** obtained by the addition of maleic anhydride to in situ generated butadiene. Photooxygenation of the diene **457** followed by selective cleavage of the peroxide linkage in **458** and subsequent acetylation furnished the diacetate **459**, which was subjected to cis-dihydroxylation to give **460** and the subsequent deprotection and further hydrolysis afforded bishomo-*allo*-inositol **461** in high yield (Scheme 77).

For the synthesis of other isomeric bishomo-inositol derivatives, the diacetate **459** was reacted with *m*-chloroperbenzoic acid to give **462a** as the sole isomer (Scheme 78). Epoxydiacetate **462b** was subjected to a sulfamic acid-catalyzed ring-opening reaction in acetic acid and acetic anhydride to give the hexaacetate **463** with a bishomo-*chiro*-inositol configuration. The deacetylation of **463** with ammonia gave bishomo-inositol **464** in 94% yield.[115]

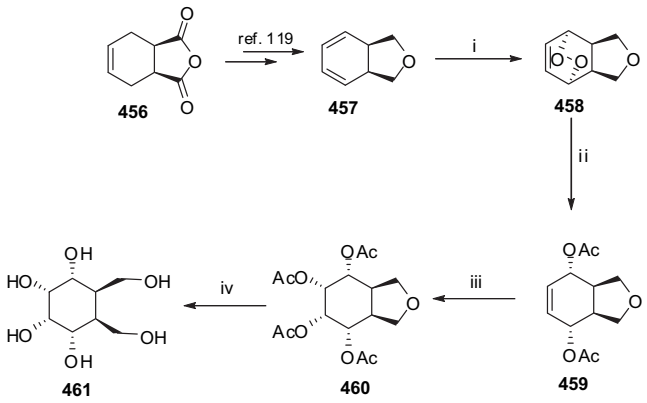
For the synthesis of bishomo-*allo*-inositol **469**, one of the double bonds in **457** was exposed to cis-dihydroxylation with OsO_4/NMO oxidation followed by acetylation to only furnish a single isomer **465**. The subsequent epoxidation of the diacetate **465** resulted in



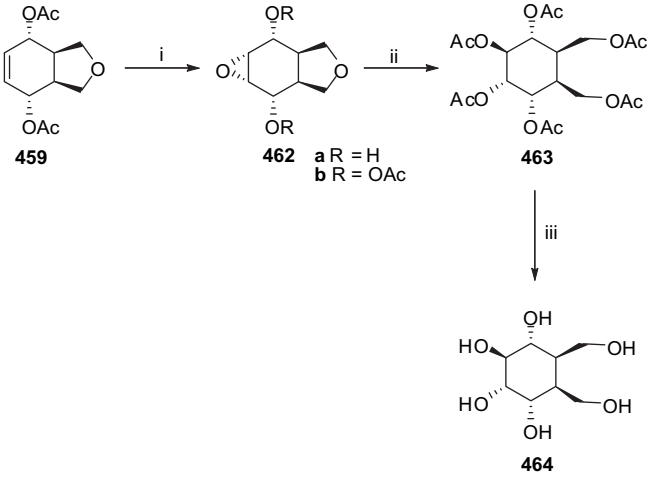
Scheme 75. (i) 123 °C, sealed tube, 12 h, 61%; (ii) 1. $HCl_{(g)}$, MeOH, 2. K_2CO_3, MeOH, 3. Ac_2O, pyridine, 89%; (iii) 1. OsO_4, NMO, 2. Ac_2O, pyridine, 64%; (iv) NH_3, MeOH, rt, 98%.



Scheme 76. (i) *m*-CPBA, $CHCl_3$, reflux, 21 days, 86%; (ii) 1. Ac_2O, H_2SO_4, CH_2Cl_2, 24 h, 2. NH_3, MeOH, rt.



Scheme 77. (i) 1. O_2, TPP, *hν*, CCl_4, 85%; (ii) 1. thiourea, MeOH, rt, 2. Ac_2O, pyridine, rt, 87%; (iii) 1. OsO_4, NMO, acetone/H_2O, 2. Ac_2O, pyridine, 73%; (iv) 1. NH_2SO_3H, Ac_2O, AcOH, 2. NH_3, MeOH, rt, 91%.



Scheme 78. (i) *m*-CPBA, $CH_2Cl_2/CHCl_3$, 85%; (ii) NH_2SO_3H, Ac_2O, AcOH, 24 h, 89%; (iii) NH_3, MeOH, rt, 93%.

the formation of two separable isomeric oxiranes **466** and **467**. The cleavage of epoxide and the tetrahydrofuran ring followed by hydrolysis of the formed tetraacetate **468** gave bishomo-*myo*-inositol **469** (Scheme 79).

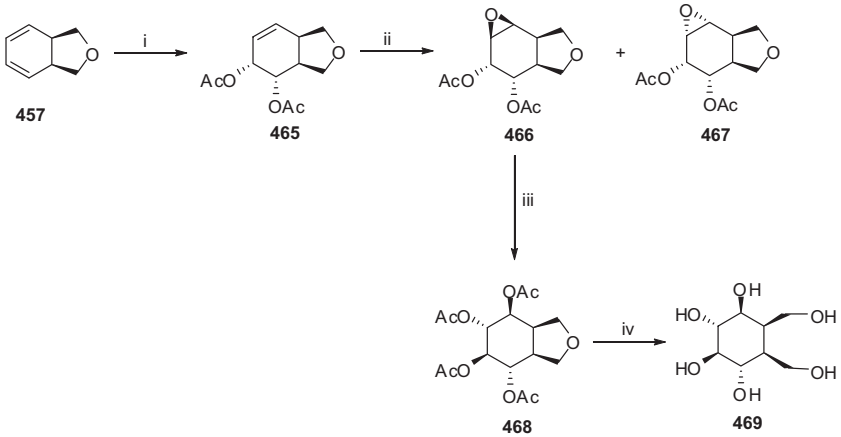
material. (*S*,*S*)-Hydrobenzoin (**471**) and (*S*)-mandelic acid served as the source of an oxygen atom and the chirality in the stereoselective cis-dihydroxylation reaction and enantiopure D-*chiro*- and *allo*-inositols were synthesized successfully.

The reaction of 3-bromocyclohexene (**470**) with (*S*,*S*)-hydrobenzoin (**471**) in the presence of NaH in DMF gave two diastereoisomeric allylic ethers **472** and **473**, which were directly subjected to intramolecular oxyselenation with PhSeOTf to provide **474** as the sole product (Scheme 80).[117] The treatment of selenide **474** with $NaIO_4$ followed by elimination afforded **475** in high yield. Epoxide **476** synthesized by the reaction of **475** with dimethyldioxirane was reacted with in situ-generated benzeneselenoate to give the ring-opening product **477**, which was again subjected to oxidation with hydrogen peroxide and the subsequent elimination reaction resulted in the formation of **478**. The protection of the allylic −OH group followed by the epoxidation of the double bond in **479** afforded the epoxide **480**. The regiospecific ring opening of epoxide with PhSeSePh led to the formation of hydroxyselenide **481**. Subsequent elimination to provide **482** followed by cis-dihydroxylation gave the tetrol **483**, which was reduced to *chiro*-inositol (**5**) exclusively.

Oxidation of the allylic alcohol **478** with PCC followed by the reduction of the resulting ketone **484** with $NaBH_4$ afforded the allylic alcohol **485** with inverted geometry. The treatment of the alkoxide generated by the reaction of **485** with BuLi, and then benzyl chloroformate gave the ester **486**. Cyclic carbonate **487** was synthesized by a selenium(II)-mediated cyclization reaction. The application of similar methodologies to the carbonate **487**, as described in Scheme 80, afforded the *allo*-configured inositol (**9**) exclusively (Scheme 81).

Glycosylphosphatidylinositols are glycolipids, which have biological functions to anchor various extracellular molecules onto cell membranes.[2k] They are composed of a phosphatidylinositol group linked through a carbohydrate-containing linker. Recently, Martín-Lomas et al. reported a new synthesis approach to **499**.[118] For the synthesis of the inositol part, D-*chiro*-inositol (**5**) was used as the starting material (Scheme 82).

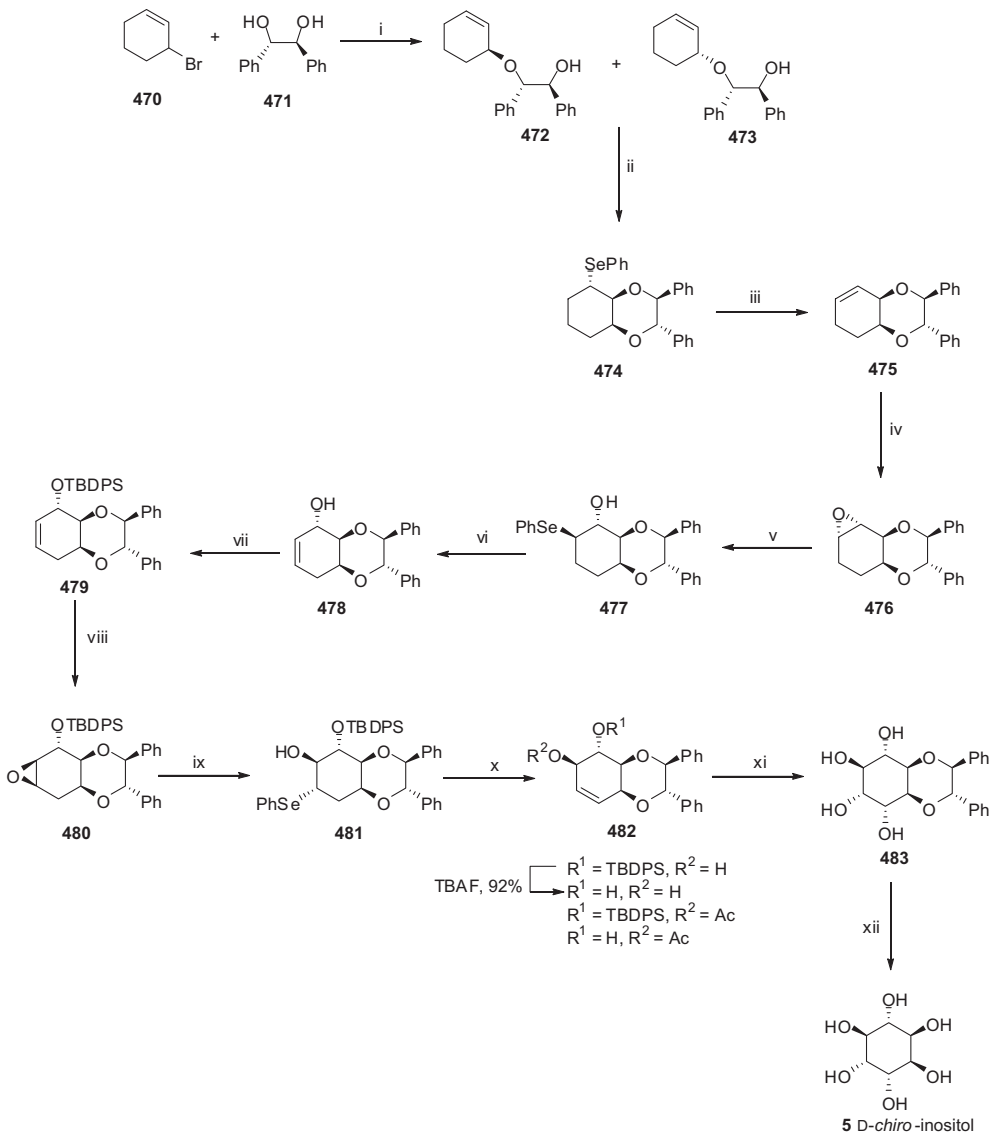
D-*chiro*-Inositol (**5**) was treated with 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane ($TIPDSCl_2$) in dimethylformamide in the presence of imidazole to give the protected diol **488**. This diol was converted to the epoxide **489** by the reaction of triphenylphosphine and diethyl azodicarboxylate. The opening of epoxide with the aid



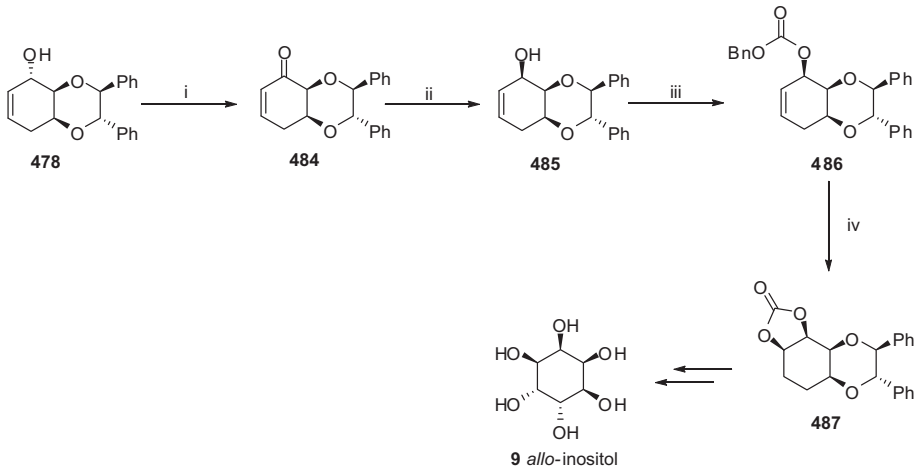
Scheme 79. (i) 1. OsO_4, NMO, acetone/H_2O, 2. Ac_2O, pyridine, 70%; (ii) 1. *m*-CPBA, $CHCl_3$, 21 days, 2. Ac_2O, pyridine; (iii) NH_2SO_3H, Ac_2O, AcOH, 24 h, 76%; (iv) NH_3, MeOH, rt, 95%.

9. Miscellaneous

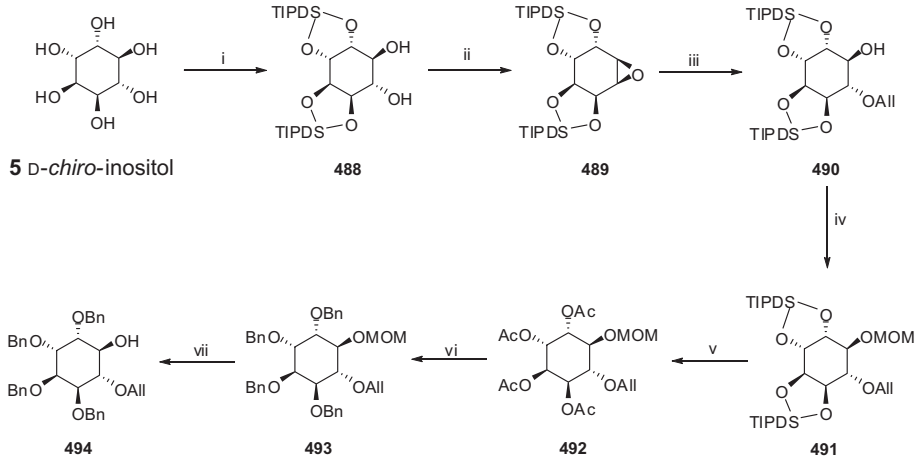
Among the numerous synthetic approaches toward inositol derivatives, (±)-3-bromocyclohexene (**470**) was used as the starting of a Lewis acid in the presence of allyl alcohol to give **490** followed by the protection of the remaining free hydroxyl with methoxymethyl chloride (MOMCl) gave the fully protected *chiro*-inositol derivative **491**. Desilylation–acetylation followed by deacetylation



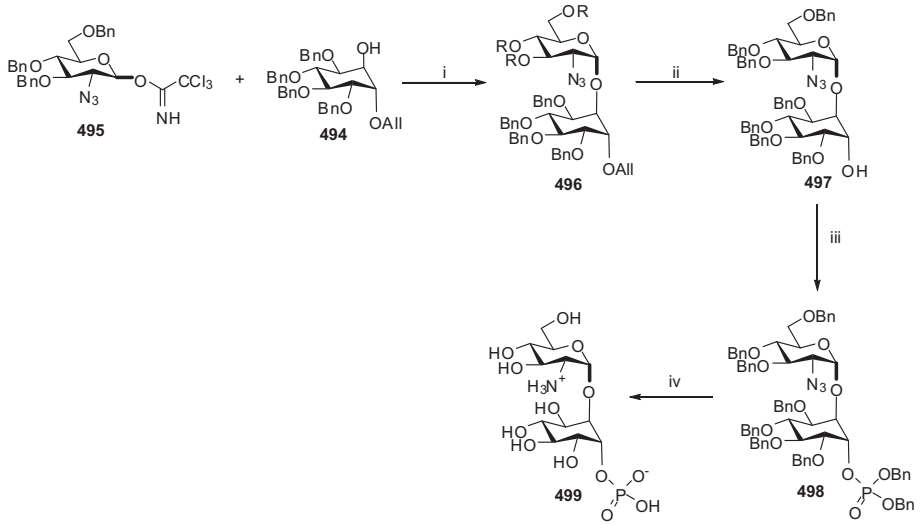
Scheme 80. (i) NaH, DMF, 55%; (ii) PhSeOTf, CH_2Cl_2, −78 °C, 33%; (iii) $NaIO_4$, $NaHCO_3$, MeOH/H_2O, rt to 90 °C, 90%; (iv) 3,3-dimethyldioxirane, acetone, 0 °C, 89%; (v) PhSeSePh, $NaBH_4$, EtOH, reflux; (vi) 30% H_2O_2, THF/EtOH, rt to reflux, 89%; (vii) TBDPSCl, imidazole, DMF, 80 °C, 87%; (viii) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, reflux, 51%; (ix) PhSeSePh, $NaBH_4$, *n*BuOH, reflux, 83%; (x) $NaIO_4$, $NaHCO_3$, MeOH/H_2O, rt to 90 °C, 90%; (xi) $K_2OsO_4 \cdot 2H_2O$, NMO, reflux, 87%; (xii) H_2, $Pd(OH)_2$/C, concd HCl.



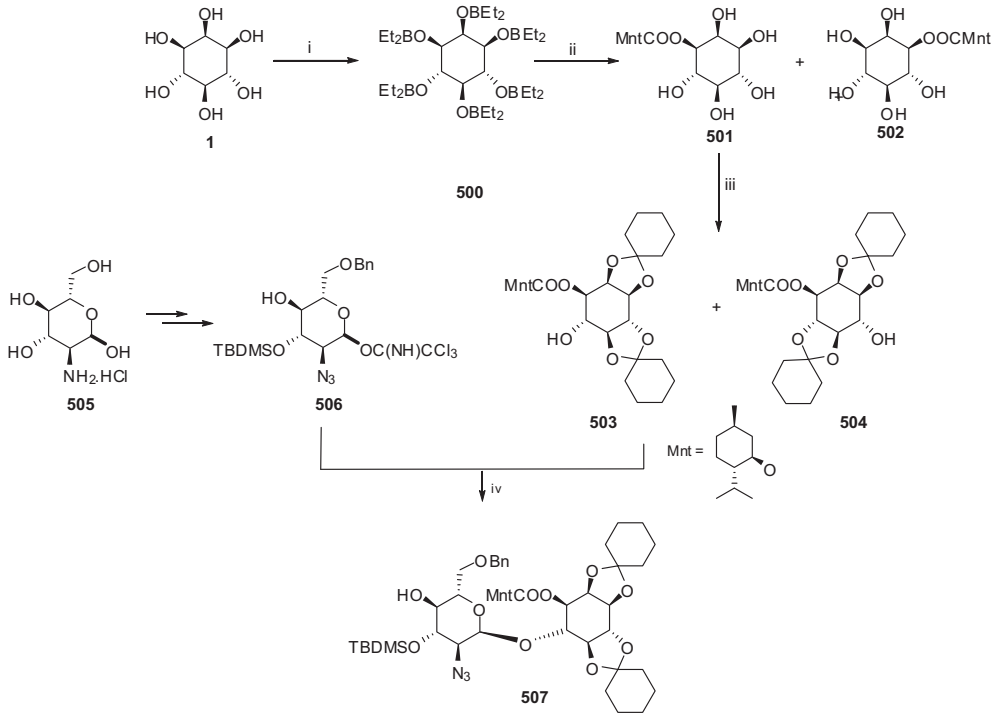
Scheme 81. (i) PCC, CH_2Cl_2, rt, 84%; (ii) $CeCl_3 \cdot 7H_2O$, $NaBH_4$, MeOH, 0 °C, 94%; (iii) 1. *n*-BuLi, THF, −78 °C, 2. CbzCl, 95%; (iv) PhSeOTf, CH_2Cl_2/THF, −78 °C to rt.



Scheme 82. (i) $TIPSCl_2$, DMF, imidazole, DAMP, rt, 76%; (ii) PPh_3, DEAD, THF, rt, 80%; (iii) AllOH, $BF_3{\cdot}OEt_2$, CH_2Cl_2, rt, 77%; (iv) NaI, MOMCl, $^iPr_2EtN$, dioxane, 85 °C, 90%; (v) 1. TBAF, THF, 2. Py, Ac_2O; (vi) 1. MeONa, MeOH, 2. NaH, BnBr, DMF, 89%; (vii) PhSH, $BF_3{\cdot}OEt_2$, CH_2Cl_2, rt, 86%.



Scheme 83. (i) TMSOTf, CH_2Cl_2, −25 °C; (ii) $PdCl_2$, AcOH, H_2O, 74%; (iii) $^iPr_2NP(OBn)_2$, tetrazole, MeCN, CH_2Cl_2, $RuCl_3{\cdot}3H_2O$, $NaIO_4$, 91%; (iv) Pd/C, MeOH, AcONa, AcOH, 73%.



Scheme 84. (i) $Et_3/^tBuCO_2BEt_2$, hexane, rt; (ii) 1. $Bu_2Sn(acac)_2$, toluene, rt, 2. (−)-MntCOCl, NMI, −30 °C to rt, 3. MeOH; (iii) 1-ethoxycyclohexene, *p*-TsOH, rt, cyclohexanone; (iv) TMSOTf, rt, Et_2O, 4 Å molecular sieves.

and benzylation afforded **493** via **492**. The removal of the MOM group using thiophenol with the aid of a Lewis acid led to the key compound **494** in quantitative yield.

The trichloroacetimidate method[119] using 2-azido-2-deoxy-glucose as a glycosyl donor is a reliable method for the glycolysation of the less reactive axial –OH group in inositol **494**. Trichloroacetimidate **495a** was condensed with inositol derivative **494** where TMSOTf was used as a promoter. The formed disaccharide **496** was reacted with palladium chloride to remove the allyl group. The phosphorylation of the hydroxyl group in **497**, followed by hydrogenolysis, furnished the target compound **499** via **498** (Scheme 83).

Martín-Lomas et al.[120] have also synthesized a pseudohexasaccharide precursor **503** (**504** was also formed as the side product) starting fully protected inositol derivative **500**, which were first converted into **501** and **502**. To reach the target molecule, the reaction of *myo*-inositol derivative **503** and D-glucosamine **506**, synthesized from **505**, using the trichloroacetimidate methodology was the key step. *myo*-Inositol was first converted into the key compound **503** in four steps.[121] The glycosylation of **503** with glycosyl donor using **506** with TMSOTf in ether afforded the key unit **507** of the pseudohexasaccharide precursor (Scheme 84).

Acknowledgements

The authors are indebted to TUBITAK (Scientific and Technological Research Council of Turkey), the Department of Chemistry at Middle East Technical University, and TUBA (Turkish Academy of Sciences) for their financial support of this work.

References and notes

1. (a) Posternak, T. *The Cyclitols*; Holden-Day: San Fransisco, 1965; (b) Pigman, W.; Horton, D. *The Carbohydrates Chemistry and Biochemistry*; Academic: New York, NY, 1972, pp 519–579; (c) Billington, D. C. *Chem. Soc. Rev.* **1989**, *18*, 83–122; (d) Legler, G. *Adv. Carbohydr. Chem. Biochem.* **1990**, *48*, 319–384; (e) Balci, M.; Sutbeyaz, Y.; Secen, H. *Tetrahedron* **1990**, *46*, 3715–3742; (f) Hudlicky, T.; Entwistle, D. A.; Pitzer, K. K.; Thorpe, A. J. *Chem. Rev.* **1996**, *96*, 1195–1220; (g) Balci, M. *Pure Appl. Chem.* **1997**, *69*, 97–104; (h) Rudolf, M. T.; Li, W. H.; Wolfson, N.; Traynor-Kaplan, A. E.; Schultz, C. *J. Med. Chem.* **1998**, *41*, 3635–3644; (i) Gultekin, M. S.; Celik, M.; Balci, M. *Curr. Org. Chem.* **2004**, *13*, 1159–1186; (j) Busscher, G. F.; Rutjes, F. P. J. T.; van Delft, F. L. *Chem. Rev.* **2005**, *105*, 775–791; (k) Arjona, O.; Gomez, A. M.; Lopez, J. C.; Plumet, J. *Chem. Rev.* **2007**, *107*, 1919–2036.
2. (a) Ferguson, M. A. J.; Williams, A. F. *Annu. Rev. Biochem.* **1988**, *57*, 285–320; (b) Thomas, J. R.; Dwek, R. A.; Rademacher, T. W. *Biochemistry* **1990**, *29*, 5413–5422; (c) Varki, A. *Glycobiology* **1993**, *3*, 97–130; (d) Dwek, A. *Chem. Rev.* **1996**, *96*, 683–720; (e) Hinchliffe, K.; Irvine, R. *Nature* **1997**, *390*, 123–124; (f) Ogawa, S. In *Carbohydrate Mimics: Concept and Methods*; Chapleur, Y., Ed.; Wiley-VCH: Weinheim, Germany, 1998; p 87; (g) Schultz, C.; Rudolf, M. T.; Gillandt, H. H.; Traynor-Kaplan, A. E. In *Phosphoinositides: Chemistry, Biochemistry and Biomedical Applications*; Bruzik, K. S., Ed.; Am. Chem. Soc. Symp. Ser.; 1999; Vol. 718, pp 232–243; (h) Heightman, T. D.; Vasella, A. T. *Angew. Chem., Int. Ed.* **1999**, *38*, 750–770; (i) Asano, N. *Glycobiology* **2003**, *13*, 93R–104R; (j) Irvine, R. F. *Nat. Rev. Mol. Cell Biol.* **2003**, *4*, 586–590; (k) Guo, Z.; Bishop, L. *Eur. J. Org. Chem.* **2004**, 3585–3596; (l) Michell, R. H. *Biochem. Soc. Symp.* **2007**, *74*, 223–246; (m) York, J. D.; Lew, D. J. *Nat. Chem. Biol.* **2008**, *4*, 16–17; (n) Chenette, E. J. *Nat. Rev. Mol. Cell Biol.* **2009**, *10*, 238–239.
3. (a) Streb, H.; Irvine, R. F.; Berridge, M. J.; Schulz, I. *Nature* **1983**, *306*, 67–69; (b) Potter, B. V. L.; Lampe, D. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1933–1972; (c) Chung, S. K.; Shin, B. G.; Chang, Y. T.; Suh, B. C.; Kim, K. T. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 659–662; (d) Hanck, T.; Stricker, R.; Krishna, U. M.; Falck, J. R.; Chang, Y. T.; Chung, S. K.; Reiser, G. *Eur. J. Biochem.* **1999**, *261*, 577–584; (e) Yang, J.; McBride, S.; Mak, D.-O. D.; Vardi, N.; Palczewski, K.; Haeseler, F.; Foskett, J. K. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 7711–7716; (f) Irvine, R. F. *J. Physiol.* **2005**, *566*, 295–300; (g) Bennett, M.; Onnebo, S. M.; Azevedo, C.; Saiardi, A. *Cell. Mol. Life Sci.* **2006**, *63*, 552–564; (h) Michell, R. H. *Nat. Rev. Mol. Cell Biol.* **2008**, *9*, 151–161; (i) Berridge, M. J. *Biochem. Soc. Symp.* **2007**, *7*, 1–7; (j) Barker, C. J.; Illies, C.; Gaboardi, G. C.; Berggren, P. O. *Cell. Mol. Life Sci.* **2009**, *66*, 3851–3871.
4. (a) Hipps, P. P.; Sehgal, R. K.; Holland, W. H.; Sherman, W. R. *Biochemistry* **1973**, *12*, 4705–4712; (b) Sureshan, K. M.; Shashidhar, M. S.; Praveen, T.; Das, T. *Chem. Rev.* **2003**, *103*, 4477–4503.
5. (a) Estevez, V. A.; Prestwich, G. D. *J. Am. Chem. Soc.* **1991**, *113*, 9885–9887; (b) Kozikowski, A. P.; Powis, G.; Gallegos, A.; Tückmantel, W. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 1323–1326; (c) Martin-Lomas, M. *Tetrahedron Lett.* **1994**, *35*, 2969–2972; (d) Kiddle, J. J. *Chem. Rev.* **1995**, *95*, 2189–2202; (e) Gigg, J.; Gigg, R. *Carbohydr. Res.* **1997**, *299*, 77–83; (f) Riley, A. M.; Jenkins, D. J.; Potter, B. V. L. *Carbohydr. Res.* **1998**, *314*, 277–281; (g) Husson, C.; Odier, L.; Vottéro, P. J. A. *Carbohydr. Res.* **1998**, *307*, 163–165; (h) Liu, C.; Riley, A. M.; Yang, X.; Shears, S. B.; Potter, B. V. L. *J. Med. Chem.* **2001**, *44*, 2984–2989; (i) Kubiak, R. J.; Bruzik, K. S. *J. Org. Chem.* **2003**, *68*, 960–968; (j) Bello, D.; Aslam, T.; Bultynck, G.; Slawin, A. M. Z.; Roderick, H. L.; Bootman, M. D.; Conway, S. J. *J. Org. Chem.* **2007**, *72*, 5647–5659; (k) Murali, C.; Gurale, B. P.; Shashidhar, M. S. *Eur. J. Org. Chem.* **2010**, 755–764.
6. (a) Guidot, J. P.; Le Gall, T.; Mioskowski, C. *Tetrahedron Lett.* **1994**, *35*, 6671–6672; (b) Jenkin, D. J.; Potter, B. V. L. *J. Chem. Soc., Perkin Trans. 1* **1998**, 41–50; (c) Chen, J.; Feng, L.; Prestwich, G. D. *J. Org. Chem.* **1998**, *63*, 6511–6522; (d) Clive, D. L. J.; He, X.; Poslema, M. H. D.; Mashimbye, M. J. *J. Org. Chem.* **1999**, *64*, 4397–4410; (e) Suzuki, T.; Suzuki, S. T.; Yamada, I.; Koashi, Y.; Yamada, K.; Chida, N. *J. Org. Chem.* **2002**, *67*, 2874–2880.
7. (a) Hudlicky, T. *Chem. Rev.* **1996**, *96*, 3–30; (b) Desjardins, M.; Brammer, L. E., Jr.; Hudlicky, T. *Carbohydr. Res.* **1997**, *304*, 39–42; (c) Jung, P. M. J.; Motherwell, W. B.; Williams, A. S. *Chem. Commun.* **1997**, 1283–1284; (d) Nguyen, B. V.; York, C.; Hudlicky, T. *Tetrahedron* **1997**, *53*, 8807–8814; (e) Paul, B. J.; Willis, J.; Martinot, T. A.; Ghiviriga, I.; Abboud, K. A.; Hudlicky, T. *J. Am. Chem. Soc.* **2002**, *124*, 10416–10426; (f) Freeman, S.; Hudlicky, T. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1209–1212.
8. (a) Sawada, T.; Shirai, R.; Iwasaki, S. *Tetrahedron Lett.* **1996**, *37*, 885–886; (b) Reddy, K. K.; Ye, J.; Falck, J. R.; Capdevila, J. H. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2115–2116; (c) Colobert, F.; Tito, A.; Khiar, N.; Denni, D.; Medina, M. A.; Martín-Lomas, M.; Ruano, J.-L. G.; Solladie, G. *J. Org. Chem.* **1998**, *63*, 8918–8921.
9. Angyal, S. J.; Odier, L.; Tate, M. E. *Carbohydr. Res.* **1995**, *266*, 143–146.
10. Kim, K. S.; Park, J. I.; Moon, H. K.; Yi, H. *Chem. Commun.* **1998**, 1945–1946.
11. (a) Mehta, G.; Ramesh, S. S. *Tetrahedron Lett.* **2001**, *42*, 1987–1990; (b) Mehta, G.; Pujar, S. R.; Ramesh, S. S.; Islam, K. *Tetrahedron Lett.* **2005**, *46*, 3373–3376.
12. Plettenburg, O.; Adelt, S.; Vogel, G.; Altenbach, H.-J. *Tetrahedron: Asymmetry* **2000**, *11*, 1057–1061.
13. Adelt, S.; Plettenburg, O.; Stricker, R.; Reiser, G.; Altenbach, H.-J.; Vogel, G. *J. Med. Chem.* **1999**, *42*, 1262–1273.
14. Adelt, S.; Plettenburg, O.; Dallmann, G.; Ritter, F. P.; Shears, S. B.; Altenbach, H.-J.; Vogel, G. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2705–2708.
15. (a) Podeschwa, M.; Plettenburg, O.; Altenbach, H.-J. *Eur. J. Org. Chem.* **2005**, 3101–3115; (b) Podeschwa, M.; Plettenburg, O.; Altenbach, H.-J. *Eur. J. Org. Chem.* **2005**, 3116–3127.
16. Podeschwa, M. A. L.; Plettenburg, O.; Altenbach, H.-J. *Org. Biomol. Chem.* **2003**, *1*, 1919–1929.
17. Podeschwa, M.; Plettenburg, O.; vom Brocke, J.; Block, O.; Adelt, S.; Altenbach, H.-J. *Eur. J. Org. Chem.* **2003**, 1958–1972.
18. Secen, H.; Maras, A.; Sütbeyaz, Y.; Balci, M. *Synth. Commun.* **1992**, *22*, 2613–2619.
19. (a) Johnson, C. R.; Ple, P. A.; Adams, J. P. *J. Chem. Soc., Chem. Commun.* **1991**, 1006–1007; (b) Ledrian, C.; Vieira, E.; Vogel, P. *Helv. Chim. Acta* **1989**, *72*, 338–347; (c) Land, G. E.; Reeves, J. M. *J. Am. Chem. Soc.* **1955**, *77*, 1812–1814.
20. Kwon, Y.-U.; Lee, C.; Chung, S.-K. *J. Org. Chem.* **2002**, *67*, 3327–3338.
21. Chung, S. K.; Kwon, Y. U. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2135–2140.
22. Kwon, Y.-U.; Im, J.; Choi, G.; Kim, Y.-S.; Choi, K. Y.; Chung, S.-K. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2981–2984.
23. Loewus, F. A.; Murthy, P. P. N. *Plant Sci.* **2000**, *150*, 1–19.
24. Gonzalez-Bulnes, P.; Casas, J.; Delgado, A.; Llebaria, A. *Carbohydr. Res.* **2007**, *342*, 1947–1952.
25. Trost, B. M.; Hembre, E. J. *Tetrahedron Lett.* **1999**, *40*, 219–222.
26. Serrano, P.; Llebaria, A.; Delgado, A. *J. Org. Chem.* **2005**, *70*, 7829–7840.
27. Takahashi, Y.; Nakayama, H.; Katagiri, K.; Ichikawa, K.; Ito, N.; Takita, T.; Takeuchi, T.; Miyake, T. *Tetrahedron Lett.* **2001**, *42*, 1053–1056.
28. Sureshan, K. M.; Watanabe, Y. *Synlett* **2004**, *3*, 493–496.
29. Gigg, L.; Gigg, R.; Payne, S.; Conant, R. *Carbohydr. Res.* **1985**, *142*, 132–134.
30. Sureshan, K. M.; Ikeda, K.; Asano, N.; Watanabe, Y. *Tetrahedron Lett.* **2004**, *45*, 8367–8370.
31. Sureshan, K. M.; Ikeda, K.; Asano, N.; Watanabe, Y. *Tetrahedron* **2008**, *64*, 4072–4080.
32. Sureshan, K. M.; Murakami, T.; Watanabe, Y. *Synlett* **2005**, *5*, 769–772.
33. Ahmad, V. U.; Ali, Z.; Ali, M. S.; Zahid, M.; Tareen, R. B. *Nat. Prod. Sci.* **1998**, *4*, 170–173.
34. Sureshan, K. M.; Murakami, T.; Watanabe, Y. *Tetrahedron* **2009**, *65*, 3998–4006.
35. Walker, J. M.; Feeney, J.; Trentham, D. R. *Biochemistry* **1989**, *28*, 1157–1159.
36. (a) Walker, J. M.; Somylo, A. V.; Goldman, Y. E.; Somylo, A. P.; Trentham, D. R. *Nature* **1987**, *327*, 249–252; (b) Li, W. H.; Llopis, J.; Whitney, M.; Zlokarnik, G.; Tsien, R. Y. *Nature* **1989**, *392*, 936–941.
37. Dinkel, C.; Schultz, C. *Tetrahedron Lett.* **2003**, *44*, 1157–1159.
38. Dinkel, C.; Moody, M.; Kaplan, A. T.; Schultz, C. *Angew. Chem., Int. Ed.* **2001**, *40*, 3004–3008.
39. Han, F.; Hayashi, M.; Watanabe, Y. *Eur. J. Org. Chem.* **2004**, 558–566.
40. Horne, G.; Potter, B. V. L. *Chem.—Eur. J.* **2001**, *7*, 80–87.
41. Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc. Perkin 1* **1975**, 1574–1585.
42. Horne, G.; Mills, S. J.; Potter, B. V. L. *Carbohydr. Res.* **2004**, *339*, 51–65.
43. Schoffers, E.; Gurung, S. R.; Kohler, P. R. A.; Rossbach, S. *Bioorg. Med. Chem.* **2008**, *16*, 7838–7842.
44. Gigg, R.; Warren, C. D. *J. Chem. Soc. C* **1969**, 2367–2371.
45. Sureshan, K. M.; Watanabe, Y. *Tetrahedron: Asymmetry* **2004**, *15*, 1193–1198.

46. Praveen, T.; Shashidhar, M. S. *Carbohydr. Res.* **2001**, *330*, 409–411.
47. Yu, K.-L.; Fraser-Reid, B. *Tetrahedron Lett.* **1988**, *29*, 979–982.
48. Takahashi, M.; Kagasaki, T.; Hosoya, T.; Takahashi, S. *J. Antibiot. (Tokyo)* **1993**, *46*, 1643–1647.
49. Moris, M. A.; Caron, A. Z.; Guillemette, G.; Rognan, D.; Schmidtt, M.; Schlewer, G. *J. Med. Chem.* **2005**, *48*, 1251–1255.
50. Godage, H. Y.; Riley, A. M.; Timothy, J. W.; Potter, B. V. L. *Chem. Commun.* **2006**, 2989–2991.
51. Riley, A. M.; Trusselle, M.; Kuad, P.; Borkovec, M.; Cho, J.; Choi, J. H.; Qian, X.; Shears, S. B.; Spiess, B.; Potter, B. V. L. *ChemBioChem* **2006**, *7*, 1114–1122.
52. Riley, A. M.; Guedat, P.; Schlewer, G.; Spiess, B.; Potter, B. V. L. *J. Org. Chem.* **1998**, *63*, 295–305.
53. Hinchliffe, K. A. *Curr. Biol.* **2001**, *11*, R371–R373.
54. (a) Sureshan, K. M.; Riley, A. M.; Potter, B. V. L. *Tetrahedron Lett.* **2007**, *48*, 1923–1926; (b) Riley, A. M.; Godage, H. Y.; Mahon, M. F.; Potter, B. V. L. *Tetrahedron: Asymmetry* **2006**, *17*, 171–174.
55. (a) Auger, K. R.; Serunian, L. A.; Soltoff, S. P.; Libby, P.; Cantley, L. C. *Cell* **1989**, *57*, 167–175; (b) Dove, S. K.; Cooke, F. T.; Douglas, M. R.; Sayers, L. G.; Parker, P. J.; Michell, R. H. *Nature* **1997**, *390*, 187–192; (c) Jones, D. R.; Gonzalez-Garcia, A.; Diez, E.; Martinez-, A. C.; Carrera, A. C.; Merida, I. *J. Biol. Chem.* **1999**, *274*, 18407–18413.
56. Falck, J. R.; Krishna, U. M.; Katipally, K. R.; Capdevila, J. H.; Ulug, E. T. *Tetrahedron Lett.* **2000**, *41*, 4271–4275.
57. Falck, J. R.; Krishna, U. M.; Capdevila, J. H. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1711–1713.
58. Swarbrick, J. M.; Cooper, S.; Bultynck, G.; Gaffney, P. R. J. *Org. Biomol. Chem.* **2009**, *7*, 1709–1715.
59. Lee, H. W.; Kishi, Y. *J. Org. Chem.* **1985**, *50*, 4402–4404.
60. Murali, C.; Shashidhar, S. M.; Gopinath, C. S. *Tetrahedron* **2007**, *63*, 4149–4155.
61. (a) Sureshan, K. M.; Shashidhar, M. S.; Praveen, T.; Gonnade, R. G.; Bhadbhade, M. M. *Carbohydr. Res.* **2002**, *337*, 2399–2410; (b) Sureshan, K. M.; Das, T.; Shashidhar, M. S.; Gonnade, R. G.; Bhadbhade, M. M. *Eur. J. Org. Chem.* **2003**, 1035–1041; (c) Sarmah, M. P.; Shashidhar, M. S. *Carbohydr. Res.* **2003**, *338*, 999–1001; (d) Sarmah, M. P.; Shashidhar, M. S.; Sureshan, K. M.; Gonnade, R. G.; Bhadbhade, M. M. *Tetrahedron* **2005**, *61*, 4437–4446.
62. Phenix, C. P.; Nienaber, K.; Tam, P. H.; Delbaere, L. T. J.; Palmer, D. R. J. *ChemBioChem* **2008**, *9*, 1591–1602.
63. Nitz, M.; Fenili, D.; Darabie, A. A.; Wu, L.; Cousins, J. E.; Mclaurin, J. *FEBS J.* **2008**, *275*, 1663–1674.
64. Sun, Y.; Zhang, G.; Hawkes, C. A.; Shaw, J. E.; McLaurin, J.; Nitz, M. *Bioorg. Med. Chem.* **2008**, *16*, 7177–7184.
65. (a) Hense, A.; Ley, S. V.; Osborn, H. M. I.; Owen, D. R.; Poisson, J. F.; Warriner, S. L.; Wesson, K. E. J. *Chem. Soc. Perkin. Trans. 1* **1997**, 2023–2031; (b) Montchamp, J. L.; Tian, F.; Hart, M. E.; Frost, J. W. *J. Org. Chem.* **1996**, *61*, 3897–3899.
66. Sureshan, K. M.; Shashidhar, M. S.; Varma, A. J. *J. Org. Chem.* **2002**, *67*, 6884–6888.
67. Dixit, S. S.; Shashidhar, M. S. *Tetrahedron* **2008**, *64*, 2160–2171.
68. Sculimbrene, B. R.; Miller, S. J. *J. Am. Chem. Soc.* **2001**, *123*, 10125–10126.
69. (a) Sculimbrene, B. R.; Morgan, A. J.; Miller, S. J. *J. Am. Chem. Soc.* **2002**, *124*, 11653–11656; (b) Davie, E. A. C.; Mennen, S. M.; Xu, Y.; Miller, S. J. *Chem. Rev.* **2007**, *107*, 5759–5812.
70. Morgan, A. J.; Komiya, S.; Xu, Y.; Miller, S. J. *J. Org. Chem.* **2006**, *71*, 6923–6931.
71. Akiyama, T.; Hara, M.; Fuchibe, K.; Sakamoto, S.; Yamaguchi, K. *Chem. Commun.* **2003**, 1734–1735.
72. (a) Angyal, S. J.; Irving, G. C.; Rutheford, D.; Tate, M. E. *J. Chem. Soc.* **1965**, 6662–6664; (b) Akiyama, T.; Nishinoto, H.; Kuwata, T.; Ozaki, S. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 180–188.
73. Falshaw, A.; Hart, J. B.; Tyler, P. C. *Carbohydr. Res.* **2000**, *329*, 301–308.
74. Qiao, L.; Hu, Y.; Nan, F.; Powis, G.; Kozikowski, A. P. *Org. Lett.* **2000**, *2*, 115–117.
75. Maurinsh, Y.; Schraml, J.; Blaton, N.; Peeters, O.; Lescrinier, E.; Rozenski, J.; Van Aerschot, A.; De Clercq, E.; Busson, R.; Herdewijn, P. *J. Org. Chem.* **1997**, *62*, 2861–2871.
76. Zhan, T. R.; Ma, Y. D.; Fan, P. H.; Ji, M.; Lou, H. X. *Chem. Biodiversity* **2006**, *3*, 1126–1137.
77. Larner, J.; Price, J. D.; Heimark, D.; Smith, L.; Rule, G.; Piccariello, T.; Fonteles, M. C.; Pontes, C.; Vale, D.; Huang, L. *J. Med. Chem.* **2003**, *46*, 3283–3291.
78. Frank, M.; Miethchen, R.; Reinke, H. *Eur. J. Org. Chem.* **1999**, 1259–1263.
79. Gero, S. D. *Tetrahedron Lett.* **1966**, *6*, 591–595.
80. Miethchen, R.; Sowa, C.; Frank, M.; Michalik, M.; Reinke, H. *Carbohydr. Res.* **2002**, *337*, 1–9.
81. Miethchen, R.; Neitzel, K.; Weise, K.; Michalik, M.; Reinke, H.; Faltin, F. *Eur. J. Org. Chem.* **2004**, 2010–2018.
82. Hudlicky, T.; Restrepo-Sànchez, N.; Kary, P. D.; Jaramillo-Gómez, L. M. *Carbohydr. Res.* **2000**, *324*, 200–203.
83. (a) Sears, P.; Wong, C.-H. *Angew. Chem., Int. Ed.* **1999**, *38*, 2301–2324; (b) Hudlicky, T.; Abboud, K. A.; Entwstle, D. A.; Fan, R.; Maurya, R.; Thorpe, A. J.; Bolonick, J.; Myers, B. *Synthesis* **1996**, 897–911.
84. (a) Paul, B. J.; Martinot, T. A.; Willis, J.; Hudlicky, T. *Synthesis* **2001**, *6*, 952–956.
85. Vitelio, C.; Bellomo, A.; Brovetto, M.; Seoane, G.; Gonzalez, D. *Carbohydr. Res.* **2004**, *339*, 1773–1778.
86. Bellomo, A.; Camarano, S.; Rossini, C.; Gonzalez, D. *Carbohydr. Res.* **2009**, *344*, 44–51.
87. Mehta, G.; Senaiar, R. S.; Bera, M. K. *Chem.—Eur. J.* **2003**, *9*, 2264–2272.
88. Mehta, G.; Ramesh, S. S. *Tetrahedron Lett.* **2003**, *44*, 3105–3108.
89. Mehta, G.; Sen, S. *Tetrahedron Lett.* **2010**, *51*, 503–507.
90. Conrad, R. M.; Grogan, M. J.; Bertozzi, C. R. *Org. Lett.* **2002**, *4*, 1359–1361.
91. Nugiel, D. A.; Jacobs, K.; Worley, T.; Patel, M.; Kaltenbach, R. F.; Meyer, D. T.; Jadhav, P. K.; De Lucca, G. V.; Smyser, T. E.; Klabe, R. M.; Bacheler, L. T.; Rayner, M. M.; Seitz, S. P. *J. Med. Chem.* **1996**, *39*, 2156–2169.
92. Heo, J.-N.; Holson, E. B.; Roush, W. R. *Org. Lett.* **2003**, *5*, 1697–1700.
93. (a) Ferrier, R. J. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1455–1458; (b) Ferrier, R. J.; Middleton, S. *Chem. Rev.* **1993**, *93*, 2779–2831; (c) Ferrier, R. J. *Top. Curr. Chem.* **2001**, *215*, 277–291.
94. Kornienko, A.; d'Alarcao, M. *Tetrahedron: Asymmetry* **1999**, *10*, 827–829.
95. (a) Watanabe, Y.; Mitani, M.; Ozaki, S. *Chem. Lett.* **1987**, 123–126; (b) Kornienko, A.; d'Alarcao, M. *Tetrahedron Lett.* **1997**, *38*, 6497–6500.
96. Takahashi, H.; Kittaka, H.; Ikegami, S. *J. Org. Chem.* **2001**, *66*, 2705–2716.
97. Keddie, N. S.; Bultynck, G.; Luyten, T.; Slawin, A. M. Z.; Conway, S. J. *Tetrahedron: Asymmetry* **2009**, 857–866.
98. Nishikawa, A.; Saito, S.; Hashimoto, Y.; Koga, K.; Shirai, R. *Tetrahedron Lett.* **2001**, *42*, 9195–9198.
99. Rameh, L. E.; Cantley, L. C. *Biol. Chem.* **1999**, *274*, 8347–8350.
100. Kirkland, T. A.; Grubbs, R. H. *J. Org. Chem.* **1997**, *62*, 7310–7318.
101. (a) Zonia, L.; Cordeiro, S.; Tupy, J.; Feijo, J. A. *Plant Cell* **2002**, *14*, 2233–2249; (b) Michell, R. H. *Curr. Biol.* **2002**, *12*, R313–R315.
102. Saito, S.; Shimazawa, R.; Shirai, R. *Chem. Pharm. Bull.* **2004**, *52*, 727–732.
103. Barili, P. L.; Berti, G.; Catelani, G.; D'Andrea, F. *Gazz. Chim. Ital.* **1992**, *122*, 135–142.
104. Pistarà, V.; Barili, P. L.; Catelani, G.; Corsaro, A.; D'Andrea, F.; Fisichella, S. *Tetrahedron Lett.* **2000**, *41*, 3253–3256.
105. Catelani, G.; Corsaro, A.; D'Andrea, F.; Mariani, M.; Pistarà, V. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3313–3315.
106. Marnera, G.; d'Alarcao, M. *Carbohydr. Res.* **2006**, *341*, 1105–1116.
107. Chiara, J. L.; Cabri, W.; Hanessian, S. *Tetrahedron Lett.* **1992**, *32*, 1125–1128.
108. Mehta, G.; Laksminath, S. *Tetrahedron Lett.* **2000**, *41*, 3509–3512.
109. Mehta, G.; Mohal, N.; Lakshminath, S. *Tetrahedron Lett.* **2000**, *41*, 3505–3508.
110. Forman, M. A.; Dailey, W. P. *J. Org. Chem.* **1993**, *58*, 1501–1507.
111. Mehta, G.; Ramesh, S. S. *Chem. Commun.* **2000**, 2429–2430.
112. Kara, Y.; Balci, M. *Tetrahedron* **2003**, *59*, 2063–2066.
113. Coppe, A. C.; Nelson, N. A.; Smith, D. S. *J. Am. Chem. Soc.* **1954**, *76*, 1100–1106.
114. Baran, A.; Günel, A.; Balci, M. *J. Org. Chem.* **2008**, *73*, 4371–4375.
115. Baran, A.; Balci, M. *J. Org. Chem.* **2009**, *74*, 88–95.
116. Goodridge, R. J.; Hambley, T. W.; Ridley, D. D. *Aust. J. Chem.* **1986**, *39*, 591–604.
117. Lee, Y. J.; Lee, K.; Jung, S.; Jeon, H. B.; Kim, K. S. *Tetrahedron* **2005**, *61*, 1987–2001.
118. Martín-Lomas, M.; Flores-Mosquera, M.; Khiar, N. *Eur. J. Org. Chem.* **2000**, 1539–1545.
119. Schmidt, R. R.; Kinzy, W. *Adv. Carbohydr. Chem. Biochem.* **1994**, *50*, 21–123.
120. Martín-Lomas, M.; Flores-Mosquera, M.; Chiara, J. L. *Eur. J. Org. Chem.* **2000**, 1547–1562.
121. (a) Potter, B. V. L.; Lampe, D. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1933–1979; (b) Zapata, A.; Fernàndez de la Pradilla, F. R.; Martín-Lomas, M.; Penadés, S. *J. Org. Chem.* **1991**, *56*, 444–447.

Biographical sketch

Metin Balci was born in Erzurum, Turkey in 1948 and studied chemistry at the University of Cologne in Germany followed by Ph.D. under the supervision of Prof Dr. Emanuel Vogel in 1976. He did postdoctoral work with Professors Harald Günther (University of Siegen, Germany), Waldemar Adam (University of Puerto Rico), and W.M. Jones (University of Florida). In 1980 he joined the Chemistry Department at the Atatürk University (Erzurum, Turkey) and he has been a full professor there since 1987. He spent 1 year in 1986 at the University of Cologne and one year 1996–1997 at the Auburn University in USA as guest professor. In 1997 he moved to the Middle East Technical University in Ankara upon reputation. He received many prices: Junior Research Prize (1983) and Scientific Prize from the Scientific and Technological Research Council of Turkey (1989), Scientific Prize from Scientific and Technology Foundation and Ministry of Public. He is member of Turkish Academy of Sciences. His main research interest include synthesis of cyclitols, endoperoxides, cyclic strained compounds, bromine chemistry, and heterocycles: he is the author of 234 scientific papers and two books 'Basic ^{1}H and ^{13}C NMR Spectroscopy' (Elsevier, 2005) and Reaction Mechanism in Organic Chemistry (TUBA, 2008, Turkish).

Benan Kilbas is an assistant professor at the Duzce University in Turkey. He was born in Erzurum, Turkey in 1980. He received his B.Sc. degree (2003) from Fatih University and Ph.D. (2009) from the Middle East Technical University, Turkey, under supervision of Dr. Metin Balci. His research interests include bicyclic strained allenes, carbenes, and natural product synthesis.