Inositols

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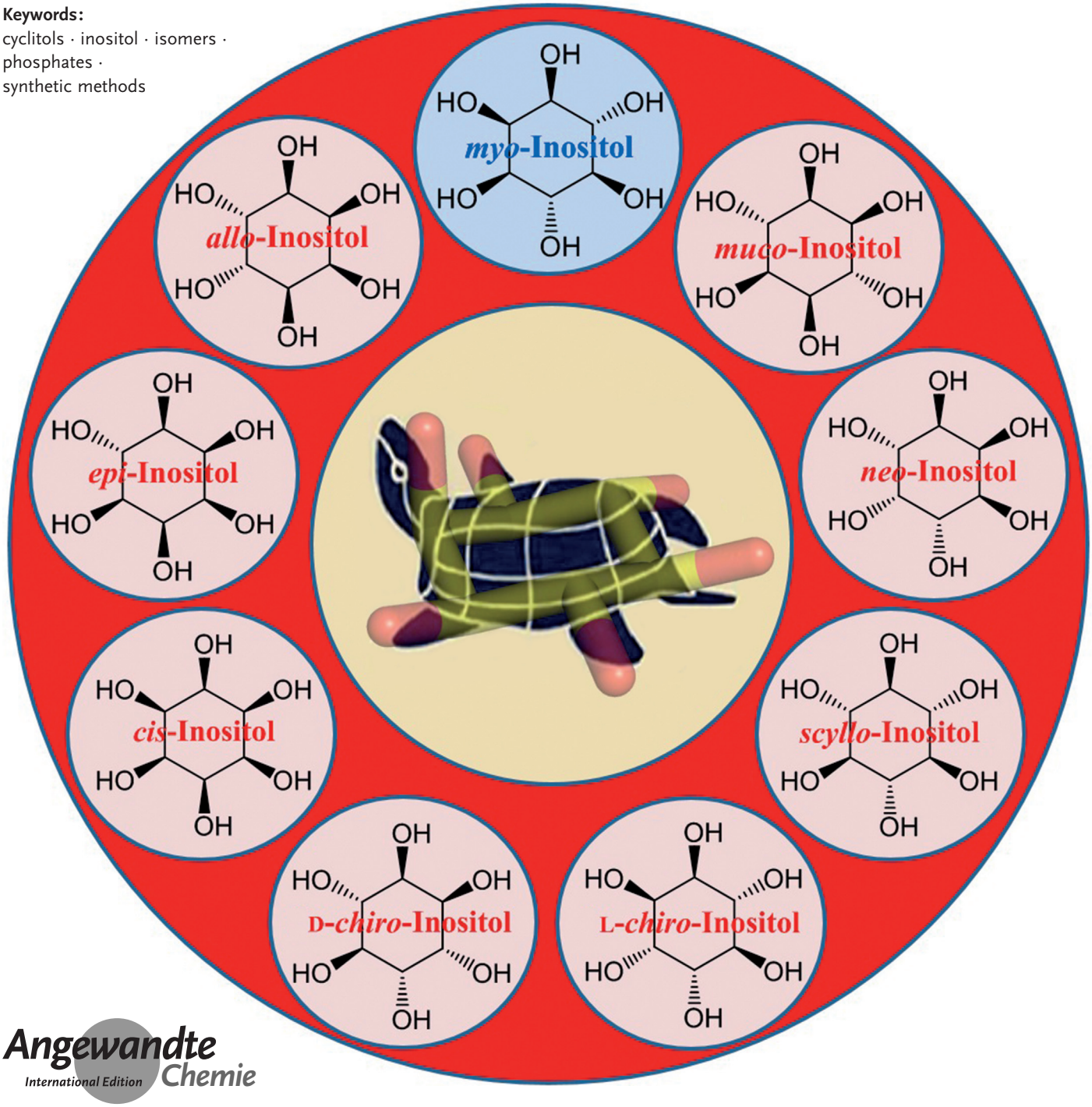
The "Other" Inositols and Their Phosphates: Synthesis, Biology, and Medicine (with Recent Advances in *myo*-Inositol Chemistry)

*Mark P. Thomas, Stephen J. Mills, and Barry V. L. Potter**

Keywords:
cyclitols · inositol · isomers · phosphates · synthetic methods



Cell signaling via inositol phosphates, in particular via the second messenger myo*-inositol 1,4,5-trisphosphate, and phosphoinositides comprises a huge field of biology. Of the nine 1,2,3,4,5,6-cyclohexanehexol isomers,* myo*-inositol is pre-eminent, with "other" inositols (*cis*-, epi-, allo-, muco-, neo-, L-chiro-, D-chiro-, *and* scyllo*-) and derivatives rarer or thought not to exist in nature. However,* neo*- and* D*-*chiro*-inositol hexakisphosphates were recently revealed in both terrestrial and aquatic ecosystems, thus highlighting the paucity of knowledge of the origins and potential biological functions of such stereoisomers, a prevalent group of environmental organic phosphates, and their parent inositols. Some "other" inositols are medically relevant, for example,* scyllo*-inositol (neurodegenerative diseases) and* D*-*chiro*-inositol (diabetes). It is timely to consider exploration of the roles and applications of the "other" isomers and their derivatives, likely by exploiting techniques now well developed for the* myo *series.*

From the Contents

1. Introduction

myo-Inositol (**1**; *cis*-1,2,3,5-*trans*-4,6-cyclohexanehexol) and its derivatives, particularly its phosphates, are common in biology. These compounds have a multitude of functions across the various taxa,[1] including roles in regulating ion-channel permeability,[2] phosphate levels,[3] metabolic flux,[4] transcription, mRNA export and translation,[5] insulin signaling, embryonic development,[6] and the stress response.[7] *myo*-Inositol is also a component of membrane-incorporated phosphatidylinositols.[8] Reviews of the various roles of *myo*-inositol and its derivatives continue to be published.[9]

However, *myo*-inositol is only one of nine possible structural isomers of inositol (1,2,3,4,5,6-cyclohexanehexol; Figure 1). As illustrated in the center of the frontispiece, a commonly used structural mnemonic to aid biochemists in particular is "Agranoff's turtle",[*] as explained in a recent review.[10] The "other" inositols include seven that are naturally occurring [*scyllo*- (**2**), *muco*- (**3**), *epi*- (**4**), *neo*- (**5**), *allo*- (**6**), and both the D-*chiro*- (**7**) and L-*chiro*-inositols (**8**)], and one that is not known to occur naturally, *cis*-inositol (**9**). It is these compounds that are the focus of this Review, which looks at the synthesis and the biological and medicinal roles of each of them in turn. *myo*-Inositol and its derivatives have been much studied—a search of PubMed using "*myo*-inositol" as the search term returns more than 40 000 references. In comparison, a search for each of the other inositols in turn returns a total of fewer than 400 references.

A stimulus to compile this Review was provided by results from our recent report, where we used ^{31}P NMR spectroscopy to reveal the presence of *neo*- and D-*chiro*-inositol hexakisphosphates in both terrestrial and aquatic ecosystems.[11] This report and a related commentary highlighted the paucity of our knowledge on the origins and biological functions of the inositol hexakisphosphate stereoisomers, despite the fact that they constitute one of the most prevalent groups of organic phosphates in the environment.[12] By implication also, this lack of knowledge extends to the parent inositol stereoisomers and any polyphosphate or other derivative thereof.

In the past few years, the inositols and their derivatives have been the subject of several books,[13] although these concentrate on *myo*-inositol and its derivatives. An older text mentions what little was known about the other inositols and their phosphates but, again, is predominantly about *myo*-inositol.[14] We are unaware of any recent publication that tries to summarize concisely the accumulated knowledge on the "other" inositols, and this Review is an attempt to fill the gap in the literature. After brief general sections covering the synthesis and biology of the inositols and their phosphates, each inositol is considered in more detail, looking at the chemical synthesis and roles in biology and medicine. Advances in *myo*-inositol chemistry since 2010 are then

[*] Prof. Dr. B. V. L. Potter
Department of Pharmacology, University of Oxford
Mansfield Road, Oxford OX1 3QT (UK)
E-mail: barry.potter@pharm.ox.ac.uk
Dr. M. P. Thomas, Dr. S. J. Mills
Department of Pharmacy & Pharmacology, University of Bath
Claverton Down, Bath BA2 7AY (UK)

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[*] Turtle motif adapted with permission from *Inositol Phosphates and Derivatives*, ACS Symposium Series 463 (1991), cover, Allen B. Reitz (Ed.). Copyright (1991) American Chemical Society.

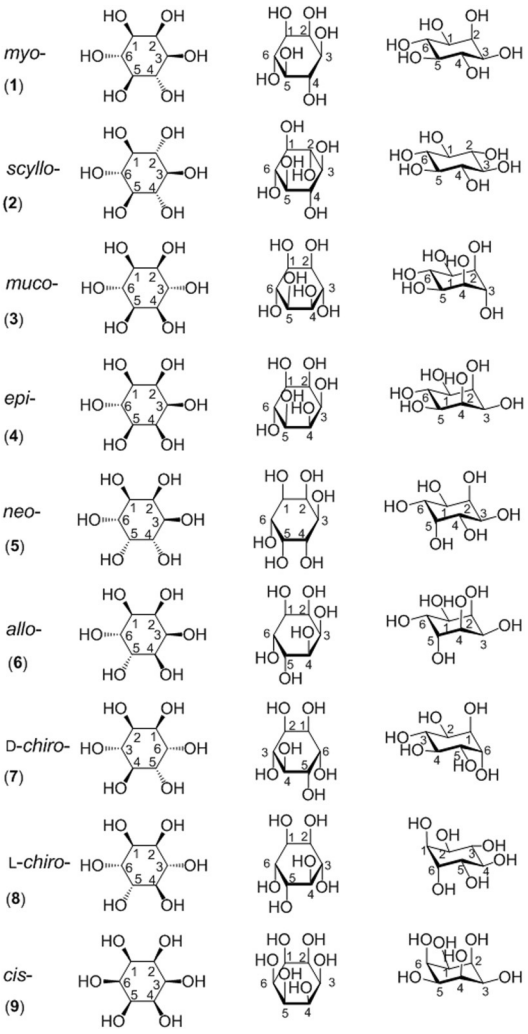


Figure 1. The structures of the inositol isomers. Three projections of each of the inositols are shown. The first column is a Mills projection, the second column is a Haworth projection, and the third column shows a more realistic three-dimensional structure (not necessarily the most stable structure) for each of the inositols. The numbering of the carbon atoms in the ring is shown.

discussed to illustrate novel chemical approaches that may be applied to the chemistry of the "other" inositols. A concluding section highlights possible directions for further study. Space constraints preclude a discussion of the nomenclature of the inositols and their phosphates, but this is discussed in detail in the accompanying Supporting Information (SI_1). For the same reason, the discussion in this Review of the biology and medicine is largely limited to that pertaining to mammals: the roles of the "other" inositols in non-mammalian species (and in the environment) are also detailed in the accompanying Supporting Information (SI_2).

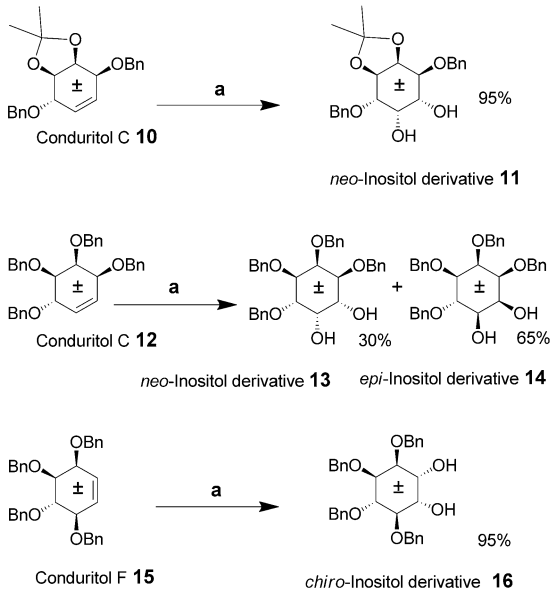
2. General Synthetic Routes to the "Other" Inositols

The following subjects have previously been reviewed: the regioselective protection and deprotection of inositol hydroxy groups;[15] the chemical and chemoenzymatic synthesis of deoxyfluoroinositols;[16] the chemoenzymatic synthesis of inositols and their analogues;[17] and a general overview of recent advances in inositol chemistry.[18]

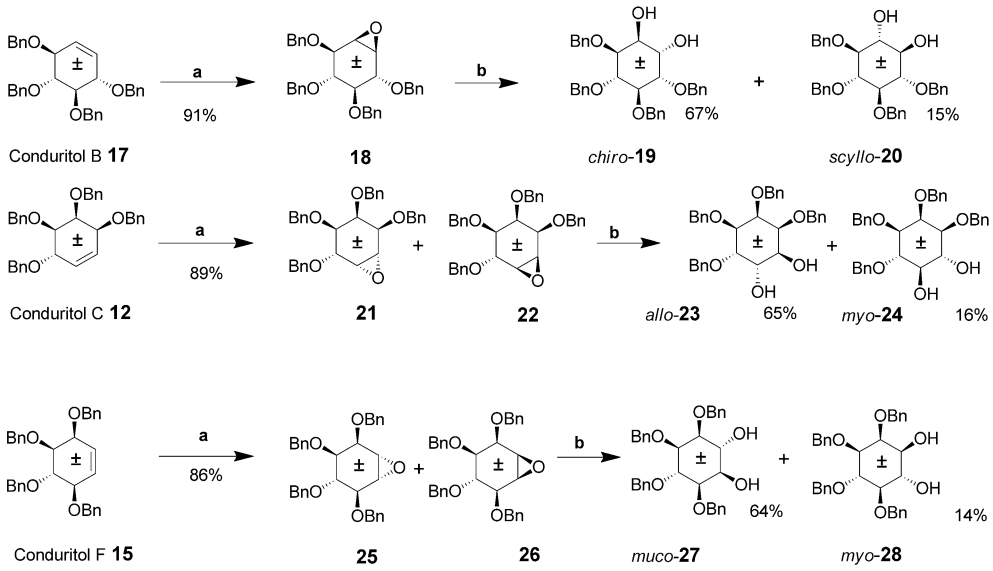
Synthetic routes to each of the inositols are described in this section. First, some general approaches are discussed to illustrate the versatility of a given route for the synthesis of a number of inositols from several intermediates. In principle, all the isomers may be derived from *myo*-inositol by inversion of the configuration at either one or two of the carbon atoms. A chemical synthesis for six of the *meso*-inositol isomers, (*neo*-, *epi*-, *scyllo*-, *allo*-, *myo*-, and *muco*-) and a synthesis of racemic *chiro*-inositol derivatives from *myo*-inositol via conduritol intermediates has been described.[19] The route makes this a quick and attractive pathway for accessing inositol derivatives on a multigram scale from intermediates derived from a one-pot reaction. A *cis*-inositol derivative was also synthesized by a different route, but using simple readily available starting materials. Conduritol C, F, and B derivatives (Schemes 1 and 2), **10**, **12**, **15**, and **17** were prepared from known racemic benzoylated inositol derivatives. Initially, the benzoylated conduritol precursors (not shown) were used to effect the transformation into inositol derivatives. However, the resulting products were insoluble in many cases, and benzyl groups replaced the intermediate benzoyl protecting groups. The conduritol C and F derivatives were then transformed into benzylated inositol compounds, which could be hydrogenated to give the corresponding inositols. The conduritol C derivative **10** was dihydroxylated to give a *cis*-diol and the *neo*-inositol derivative **11** in 95% yield. The *epi*-inositol derivative **14** together with a *neo*-inositol derivative

Barry Potter is Professor of Biological and Medicinal Chemistry at Oxford University and Wellcome Trust Senior Investigator, with interests in signal transduction and anti-cancer drug discovery. He studied Chemistry at Oxford, also earning a DPhil and a DSc. After postdoctoral research in Oxford and at the Max-Planck-Institut für experimentelle Medizin in Göttingen, he was Lecturer at Leicester University, then moved to the University of Bath as Full Professor, and in 2015 returned to Oxford. He cofounded Sterix Ltd. and was elected to the UK Academy of Medical Sciences and Academia Europaea.

Mark Thomas has a BSc (biochemistry, 1989, Wales), a PhD (protein chemistry and enzymology, 1992, London), and an MSc (computer science, 2000, Bristol). He has academic experience in protein chemistry, enzymology, crystallization, and crystallography, as well as both academic and industrial experience in computational drug discovery, design, and development.



Scheme 1. Reaction conditions: a) OsO_4, NMO, acetone (aq).



Scheme 2. Reaction conditions: a) I_2, Ag_2O, dioxane (aq), 90 °C, b) CF_3COOH (aq), THF, 50 °C.

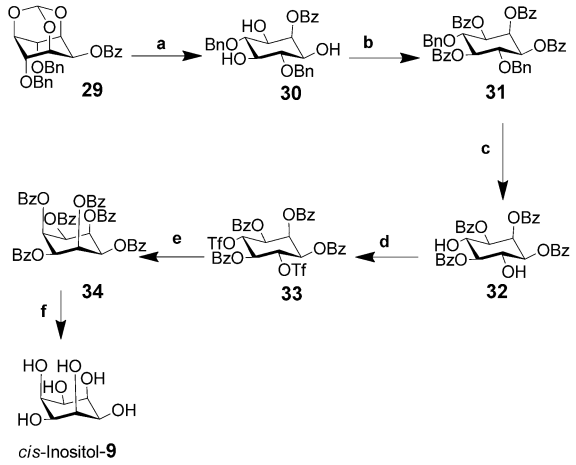
13 was provided by dihydroxylation of the conduritol C derivative **12** under the same conditions. In a similar fashion, the dihydroxylation of conduritol F derivative **15** gave the racemic tetrabenzylated *chiro*-inositol derivate **16** in good yield.

The benzylated derivatives of conduritol B (**17**), C (**12**), and F (**15**) were epoxidized in the presence of iodine and silver(I) oxide (Scheme 2). Conduritol B derivative **17** gave epoxide **18** in high yield. The epoxide was opened in the presence of acid to give racemic 1,4,5,6-tetra-*O*-benzyl-*chiro*-inositol (**19**) and racemic 1,2,3,4-tetra-*O*-benzyl-*scyllo*-inositol (**20**). However, epoxidation of the C derivative **12** gave a mixture of epoxides **21** and **22**, while the F derivative **15** gave a mixture of epoxides **25** and **26**. The epoxide derivatives **21** and **22** were subjected to acidic hydrolysis to provide racemic 1,2,3,6-tetra-*O*-benzyl-*allo*-inositol (**23**) and racemic 1,2,3,4-tetra-*O*-benzyl-*myo*-inositol (**24**). Ring opening of epoxides **25** and **26** under acidic conditions gave racemic 1,2,5,6-tetra-*O*-benzyl-*muco*-inositol (**27**) and racemic 2,3,4,5-tetra-*O*-benzyl-*myo*-inositol (**28**). Further deprotection of these derivatives was not discussed; however, simple hydrogenation in the presence of a palladium on carbon catalyst will give the respective inositols in high yield.

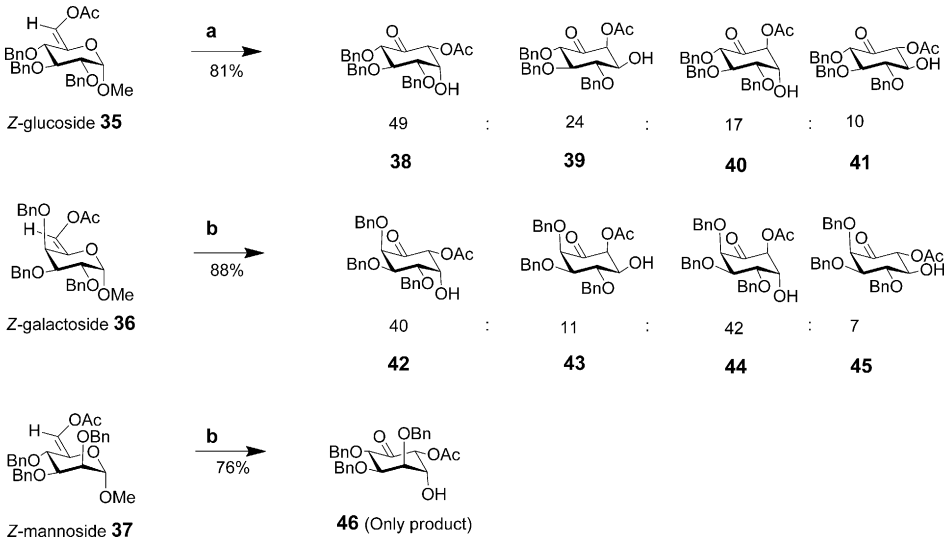
cis-Inositol hexabenzoate (**34**) was prepared in five steps from 2-*O*-benzoyl-4,6-di-*O*-benzyl-*myo*-inositol orthoformate (**29**) and was not accessible by the conduritol route (Scheme 3). The orthoester was hydrolyzed under acidic conditions to give 2-*O*-benzoyl-4,6-di-*O*-benzyl-*myo*-inositol (**30**), which was further benzoylated to give 1,2,3,5-tetra-*O*-benzoyl-4,6-di-*O*-benzyl-*myo*-inositol (**31**). Hydrogenolysis of the benzyl groups to expose the hydroxy groups gave compound **32**, which was triflated to provide **33**. This intermediate was then heated with potassium benzoate in DMSO to give the *cis*-inositol derivative **34**. The protecting groups on this derivative can then be cleaved with base to give *cis*-inositol.[19]

All nine inositol diastereoisomers were synthesized using three different pyranosides (glucose, galactose, and mannose) as the starting materials (Schemes 4 and 5).[20] The cost of the raw materials and the inherent chirality of the starting materials make the synthesis of inositol derivatives particularly attractive, especially for D- and L-*chiro*-inositols. Functional-group manipulation of the intermediates should give suitably protected compounds and provide any inositol or its phosphorylated derivative. These sugars were used to prepare the 6-*O*-acetyl-5-enopyranoside intermediates **35**–**37**, which

Stephen Mills obtained an MPhil at the University of Leicester in 1991 and a PhD at the University of Bath in 1994 with Professor Barry V. L. Potter. After a short break, Stephen returned to continue scientific research in 2000. His research interests include the synthesis of new types of compound that modulate the inositol 1,4,5-trisphosphate receptor and the inhibition and characterization of the inositol 5-phosphatase enzyme family.



Scheme 3. Reaction conditions: a) PTSA, MeOH, reflux; b) BzCl, pyr., 91%; c) $Pd(OH)_2/C$, MeOH, (50 psi) H_2, 96%; d) Tf_2O, CH_2Cl_2, pyridine, −42°C→RT, 89%; e) KOBz, DMSO, 100°C 32%; f) base (step not shown in original literature). Note that some axial bonds are exaggerated to lessen clashing with other substituents).



Scheme 4. Reaction conditions: a) 5% mol $PdCl_2$, dioxane/H_2O, 4:1, 81%; b) 5% mol $PdCl_2$, dioxane/H_2O, 2:1.

were transformed into chiral-substituted cyclohexanones in a Ferrier carbocyclization mediated by $PdCl_2$. For the glucoside derivative, the *Z* isomer **35** was treated with $PdCl_2$ in aqueous dioxane to effect the transformation to the cyclohexanones in 81% yield and a ratio of 49:24:17:10 for **38**, **39**, **40**, and **41**. The *E* isomer did not give any product under these conditions. Similarly, the galactoside *Z* isomer under similar conditions as described for the glucoside (dioxane/water 2:1) gave a mixture of cyclohexanone derivatives in a ratio of 40:11:42:7 for **42**, **43**, **44**, and **45** in 88% overall yield. The *E* isomer (not shown) of the galactoside also gave a similar ratio, but in poor yield. The mannoside *Z* isomer provided a single product **46** in 76% yield. The *E* isomer of the mannoside (not shown) also gave the single product **46**, but in lower yield.

Eight of the nine inositols were prepared by the stereoselective reduction of the carbonyl group to either an axial or equatorial alcohol followed by alkaline hydrolysis and hydrogenation of the benzyl groups. *cis*-Inositol (**9**) could not be synthesized directly in three steps from any of the intermediates, so was synthesized in six steps from intermediate **38**.

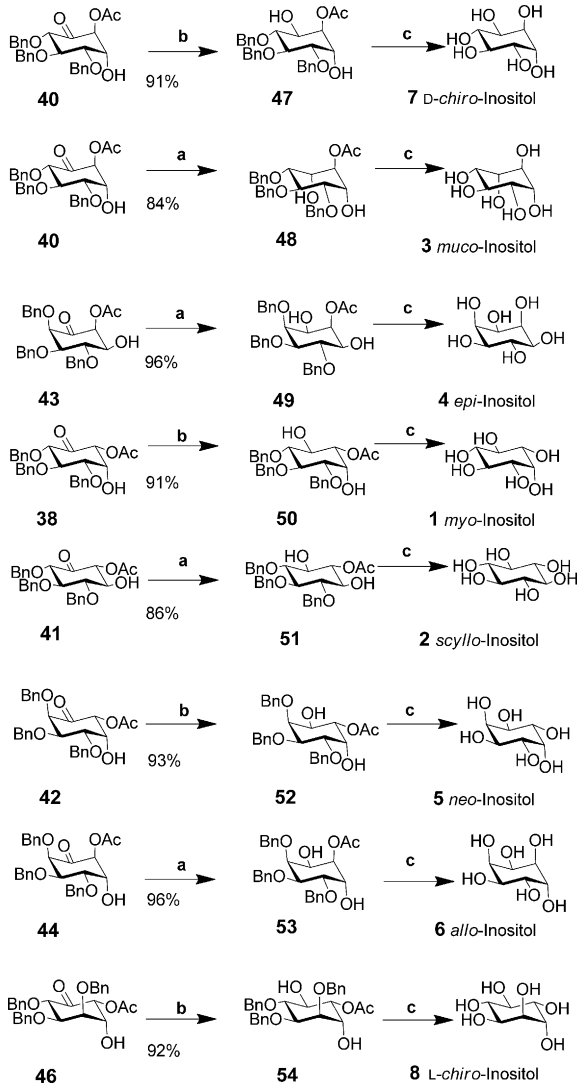
Intermediate **38** (Scheme 6) was reduced using sodium borohydride in methanol to give the axial alcohol and the *epi*-inositol derivative **55**. Hydrogenolysis, as described for other intermediates (Scheme 5), provided the acetate **56**, which was protected with isopropylidene groups to give intermediate **57**. Triflation of the free hydroxy group gave **58**. A subsequent inversion of an equatorial position to give an axial derivative followed by hydrolysis of the trifluoroacetate provided the *cis*-inositol derivative **59**, which was hydrolyzed under acidic conditions to give *cis*-inositol (**9**).

The transformation of *p*-benzoquinone (**60**; Scheme 7) into seven of the nine inositols (*cis*-inositol (**9**) and *muco*-inositol (**3**) were not made) was described more than ten years ago.[21] Although this paper reports that the *meso*-inositols can be synthesized from racemic precursors (that are crystalline and easier to handle), the intermediates were resolved and then eventually the protecting groups cleaved to give *meso* compounds. This may appear a waste of chiral precursor to synthesise *meso*-inositols, but the ultimate goal was to produce chiral inositol phosphates for biological evaluation from the same precursor, and it was easier to use the same common chiral intermediate. The chiral derivatives were also used to prepare the only two chiral inositols D- and L-*chiro*-inositol (**7** and **8**, respectively).

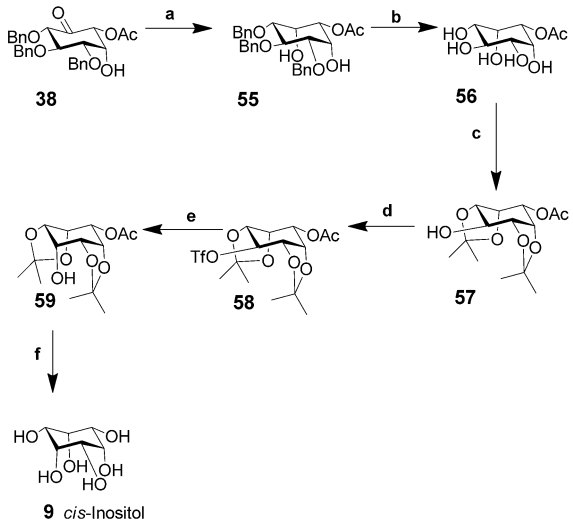
Benzoquinone (**60**) was brominated and the two carbonyl groups of the quinone were reduced to alcohols and then acetylated to give diacetate **61**. This product was resolved in the presence of porcine pancreatic lipase (PPL) suspended in phosphate buffer to provide the fully deacetylated product **62** and the chiral diacetate **63** (Scheme 7).

Compound **63** (Scheme 8) was central to the synthesis of further inositol derivatives, including *neo*-inositol, D- and L-*chiro*-inositol, and *allo*-inositol. For the synthesis of *allo*-inositol (**6**), compound **63** was heated with sodium acetate in acetic acid for 10 days to give conduritol E derivative **64**, which was then dihydroxylated to give **65**. A catalytic deacetylation using sodium methoxide led to *allo*-inositol (**6**) on a multigram scale (Scheme 8).

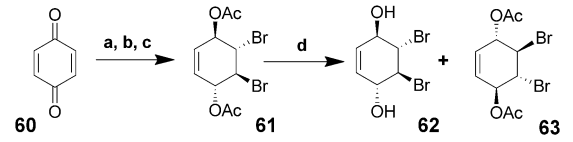
neo-Inositol (**5**) was prepared from conduritol E tetraacetate (**64**), which was epoxidized to give **66** and then ring opened to give 2,3,4,5-tetra-*O*-acetyl-*neo*-inositol. Further acetylation gave *neo*-inositol hexaacetate (**67**). Catalytic



Scheme 5. Reaction conditions: a) $NaBH_4$, MeOH, 0 °C, 30 min; up to 99:1 of desired product; b) $Me_4NBH(OAc)_3$, 5.0 equiv, MeCN, AcOH, 0 °C, 3 h, up to 99:1 of desired product; c) NaOH, MeOH, 0 °C, then $Pd(OH)_2$, H_2, MeOH.



Scheme 6. Reaction conditions: a) $NaBH_4$, MeOH, 0 °C, 30 min., 97%; b) $Pd(OH)_2/C$, H_2, MeOH, 12 h, quantitative yield; c) H_2SO_4 (conc.), $Me_2C{=}O$, 0 °C, 1 h, 83%; d) Tf_2O, pyridine, CH_2Cl_2, RT, 1 h, 89%; e) CF_3CO_2Cs, 18-crown-6, toluene, DMF, 80 °C, 1.5 h, then saturated $NaHCO_3$, RT, 1 h, 78% from **57**; f) TFA, MeOH, 60 °C, 3 h. Note that some of the bonds are exaggerated to lessen clashes with other functional groups.



Scheme 7. Reaction conditions: a) Br_2, $CHCl_3$, 0 °C, (98%); b) $NaBH_4$, Et_2O, −20 °C→RT (88%); c) pyridine, acetic anhydride, overnight, (68%); d) PPL phosphate buffer (pH 7), 4 days (38% of each compound). PPL = porcine pancreatic lipase.

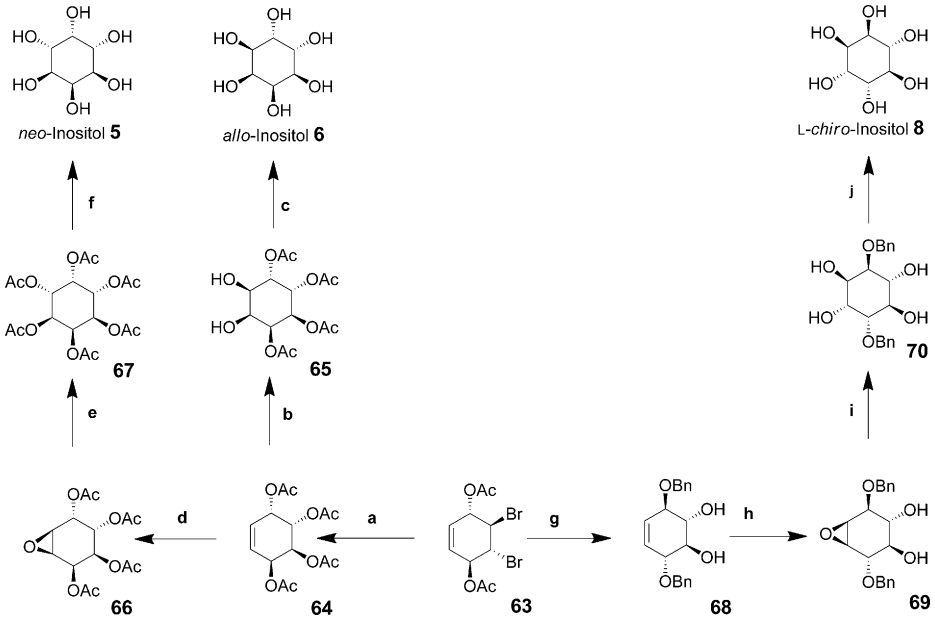
deacetylation then provided *neo*-inositol in near quantitative yield (Scheme 8).

L-*chiro*-Inositol (**8**; Scheme 8) was prepared from intermediate **63** through the formation of an epoxide that was ring opened at the allylic position when treated with sodium benzylate below 0 °C. Warming the mixture to room temperature gave the chiral 1,4-di-*O*-benzylconduritol B derivative **68** in good yield. Epoxidation of **68** and ring opening under acidic conditions gave 2,5-di-*O*-benzyl-L-*chiro*-inositol (**70**) in good yield. Hydrogenolysis in the presence of palladium on carbon gave L-*chiro*-inositol in near quantitative yield. D-*chiro*-Inositol (**7**) was synthesized from the enantiomer of compound **63** and the same chemical transformations (not shown).

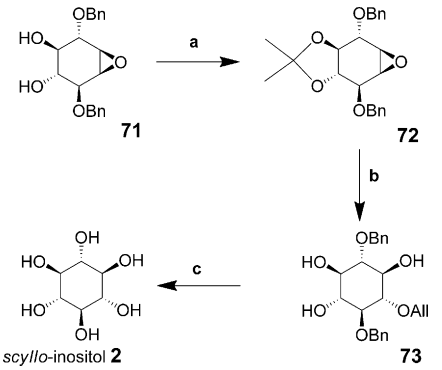
scyllo-Inositol (**2**; Scheme 9) was synthesized when the diol **71** was protected with an isopropylidene acetal to give fully protected epoxide **72**, which was opened with the sodium salt of allyl alcohol to give the *scyllo*-inositol derivative **73** in good yield. The allyl group was then isomerized and the resulting enol ether cleaved under acidic conditions. Hydrogenolysis of the remaining benzyl groups using palladium on carbon as a catalyst provided *scyllo*-inositol (**2**).

epi-Inositol (**4**; Scheme 10) was derived from the important intermediate **63**, which was *cis*-dihydroxylated in the presence of ruthenium trichloride and sodium periodate to give diol **74** and then acetylated to provide **75**. Reductive removal of bromine using zinc produced the conduritol C tetraacetate derivative **76**. *cis*-Dihydroxylation and further acetylation gave **77**, the treatment of which with sodium methoxide followed by sodium hydroxide solution and neutralization led to complete deacetylation to give *epi*-inositol (**4**) in near quantitative yield.

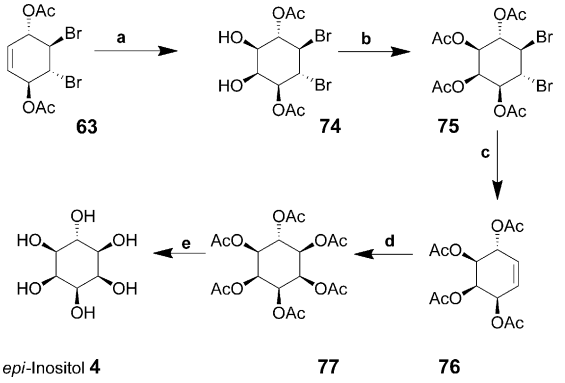
L-*chiro*-Inositol and D-*myo*-inositol derivatives were prepared from 2,3,4-tri-*O*-benzyl-D-xylose (**78**; Scheme 11), which was transformed into *myo*- and L-*chiro*-inositol intermediates.[22–24] Compound **78** was transformed into **79** by a Wittig reaction followed by oxidation of the primary alcohol to an aldehyde.[25] In the presence of vinylmagnesium bromide, the *anti*-alcohol is mainly formed (**80**/**81** 1:8) as two inseparable dienes. Ring closure of the mixture of



Scheme 8. Reaction conditions: a) NaOAc, AcOH (95%), 10 days, 125°C; Ac_2O, CH_2Cl_2, DMAP; b) $RuCl_3$, $NaIO_4$, MeCN; c) NaOMe, MeOH; d) $(CF_3CO)_2O$, H_2O_2, CH_2Cl_2, $NaHCO_3$; e) Ac_2O, pyridine; f) NaOMe, MeOH, then water/NaOH; g) NaOBn, BnOH/THF (1:6:2.1), 13–14 h; h) $(CF_3CO)_2O$, H_2O_2, CH_2Cl_2, Na_2CO_3; i) H_2SO_4, dioxane, H_2O; j) Pd/C, H_2, ethanol/water (1:1).

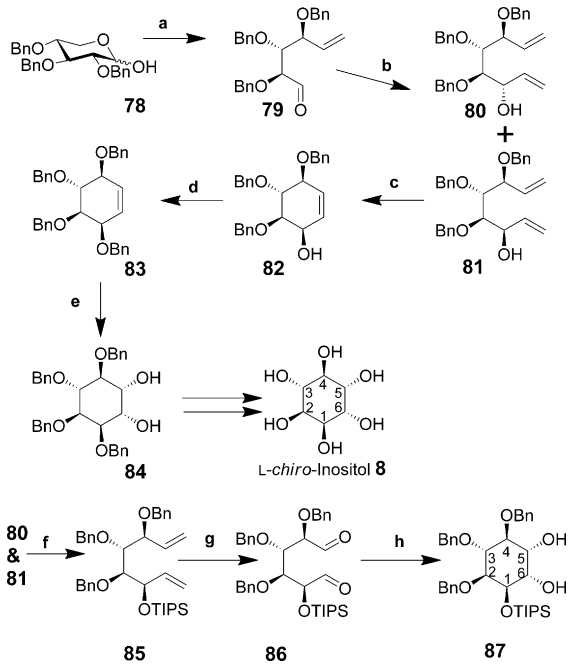


Scheme 9. Reaction conditions: a) 2,2-dimethoxypropane, acetone, PPTS, b) 1. NaOAll, 90°C, 2. HCl; c) 1. Pd/C, MeOH; 2. HCl, 3. Pd/C, H_2.



Scheme 10. Reaction conditions: a) $RuCl_3$, $NaIO_4$, acetonitrile; b) Ac_2O, pyridine; c) Zn, Et_2O, AcOH; d) 1. $RuCl_3$, $NaIO_4$, acetonitrile; 2. Ac_2O, pyridine; e) NaOMe, MeOH.

compounds (**80** and **81**) using the Grubbs' catalyst provided conduritols B (not shown) and F (**82**, major product). Benzylation of **82** provided **83** and a subsequent dihydroxylation gave 1,2,3,4-tetra-*O*-benzyl-L-*chiro*-inositol **84**.[23] Alternatively, when the dienes (**80** and **81**) were silylated, the required compound **85** could be separated from the mixture by chromatography. Subsequent ozonolysis gave the dialdehyde **86**, which was used immediately and subjected to a pinacol coupling reaction in the presence of samarium iodide to provide L-*chiro*-inositol derivative **87**.[24] If **87** is subjected to desilylation and hydrogenolysis, L-*chiro*-inositol should be produced in good yield. Both enantiomers of **78** are available and the L-xylose derivative should provide a route to D-*chiro*-inositol intermediates, thus making it suitable for the synthesis of several inositol compounds.



Scheme 11. Reaction conditions: a) $CH_2{=}PPh_3$, THF, 45°C, 10 h; then $COCl_2$, Me_2SO, CH_2Cl_2, −78°C, 20 min, Et_3N, −78°C→RT; b) vinyl magnesium bromide, $MgBr_2{\cdot}OEt_2$, −78°C, CH_2Cl_2, 3 h; c) $[(Cy_3P)_2RuCl_2(CHPh)]$ (CHPh = benzylidene; Cy_3P = tricyclohexylphosphine), 10 mol%, CH_2Cl_2, 15 min, 99%; d) BnBr, DMF, NaH, 94%; e) OsO_4, NMO, $Me_2C{=}O/H_2O$ (9:1), 93%; f) TIPS-Cl, DMF, $AgNO_3$, separate compounds, (yield not given for this step, but 54% over 3 preceding steps); g) O_3, CH_2Cl_2, pyridine, then Me_2S, h) SmI_2, *tert*-BuOH, THF, −78°C, 3 h, then 20°C, overnight.

2.1. Summary

A number of general synthetic methods are described in Section 2 for the synthesis of several or all of the inositols. One procedure[19] was used in an earlier study, where all the compounds in the crude mixture were isolated and used.[26] These compounds include three main benzoylated isopropylidene and di-*O*-isopropylidene-protected compounds that were used to provide an inexpensive route to racemic conduritol B, C, and F derivatives, thus making it a good method to synthesize all the nonchiral inositols. The benzoyl groups were changed to benzyl groups because of the formation of insoluble benzoylated intermediates. From an economic standpoint, the synthesis made use of the organic-solvent-soluble benzoylated derivatives, which usually go into the waste solvent. The highly insoluble 3,6-di-*O*-benzoyl-1,2:4,5-di-*O*-isopropylidene-*myo*-inositol derivative was a precursor to conduritol C. *cis*-Inositol cannot be obtained from conduritol derivatives and needed a separate starting material for its synthesis. This is an economical method to synthesize some of the *meso*-inositols from the benzoylated isopropylidene intermediates once the derivatives are isolated from the crude mixture.

All nine inositol isomers can be synthesized in relatively few steps using the Ferrier II carbocyclization of a pyranoside enol acetate derived from glucose, galactose, and mannose.[20] The synthesis of *cis*-inositol requires six extra chemical transformations after the carbocyclization. This method is the most complete for synthesizing any inositol and uses palladium(II) chloride for ring closure, thereby making the reaction less toxic than that with the original mercury(II) chloride catalyst. However, seven of the nine inositols are achiral, and the synthesis uses chiral material to produce achiral inositols. The overall purpose of the synthesis is to produce chiral inositol phosphate derivatives that do not need to be resolved via diastereoisomeric derivatives. If temporary protecting groups (for example *p*-methoxybenzyl) can be used to provide intermediates that give a specific protection pattern and that can then be removed without affecting the remaining benzyl groups, the remaining hydroxy groups could be phosphorylated. Global deprotection will then lead to the desired phosphorylated inositol derivative. On balance, the synthesis of inositols from carbohydrate precursors appears to be the most complete general method to give all the inositols and is worth considering if chemists and biologists require some of the rare inositols.

Another general method for the synthesis of inositols has been described.[21] The important intermediate was the enantiomerically pure **63**, which was used to prepare all the inositol derivatives apart from *cis*- and *muco*-inositols. *p*-Benzoquinone is inexpensive and the only starting material needed to prepare seven of the nine inositols in multigram quantities, thus making this a diverse synthesis from one starting material. The intermediates were resolved using the racemic derivative of **63** (by enzymatic resolution), thereby providing a pathway to both D and L enantiomers for other inositol derivatives. However, some reactions were slow, such as the conversion of **63** into **64**, taking 10 days to complete. The time course could potentially be shortened by using a different salt form, such as cesium acetate. The overall purpose of the synthesis was to prepare chiral inositol phosphates with a *myo* and *epi* configuration from simple starting materials as well as the synthesis of *chiro*-, *neo*-, *scyllo*-, and *allo*-inositol hexakisphosphates in reasonable quantities required for biological investigation. Furthermore, the synthesis of each of the inositols has been achieved in fewer than ten steps (including resolution) by using *p*-benzoquinone as the starting material.

2,3,4-Tri-*O*-benzyl-D-xylose (**78**) is the starting material used to make D-*myo*-inositol and L-*chiro*-inositol derivatives, but the synthetic approach used could be applicable to the synthesis of further inositol derivatives.[23,24] It is a noteworthy synthesis, since the diene derived from xylose intermediate **81** can be ring closed using a Grubbs' catalyst to give **82**, which provides the chiral derivative **83** after benzylation. Introduction of hydroxy groups from the upper face of the cyclohexene ring would provide an *epi*-inositol derivative. Similarly, a different method of ring closure, such as a samarium iodide pinacol-type reaction, produces a single L-*chiro*-inositol derivative (**87**).[24] If 2,3,5-tri-*O*-benzyl-L-xylose is used, the corresponding D-*chiro*-inositol derivative could be made, thereby giving access to more inositols. *epi*- And *allo*-inositol derivatives could be made using dialdehydes **130** (see Section 7.1) and **147** (see Section 10.1), respectively. The Ferrier II carbocyclization provides the best method for preparing all the inositol derivatives. The benzoquinone route comes a close second, only because seven of the nine inositols were synthesized. The most economical route to the *meso*-inositols is derived from the benzoylated isopropylidene derivatives, but the use of a Grubbs' catalyst or a samarium iodide ring closure requires a greater knowledge of chemistry.

3. Biology Overview

As stated in the Introduction, *cis*-inositol is not known to occur naturally, but the other eight inositols, or derivatives of them, have been observed in nature. *myo*-Inositol is both widespread and much studied, but the others are rarer and relatively little studied. This section provides a very brief overview of the biology of the "other" inositols and is unreferenced: for details and references see the sections on the individual inositol isomers in both this Review and the Supporting Information (SI_2).

3.1. Occurrence

Apart from *cis*-inositol, all the inositol isomers, or derivatives of them, have been found in plants. *scyllo*-Inositol has been observed, also, in mammals, non-mammalian animals, and bacteria. D-*chiro*-Inositol has been detected in mammals, protozoa, and bacteria, and *neo*-inositol in insects and protozoa. Phosphatidylinositol-containing *scyllo*-inositol has been found in plants and protozoa, but not in mammals. *neo*-Inositol phosphates have been detected in protozoa. Pinitol, the 3-*O*-methyl derivative of D-*chiro*-inositol, has been detected in insects.

3.2. Metabolism

Not much is known about the metabolism of the inositol isomers. An enzyme in a calf brain extract that converts D-glucose 6-phosphate into D-*myo*-inositol 3-phosphate has also been shown to convert D-mannose 6-phosphate into L-*neo*-inositol 1-phosphate. Similarly, mammalian L-*myo*-inositol-1-phosphate synthase is able to catalyze the conversion of galactose 6-phosphate into *muco*-inositol 1-phosphate. Epimerases have been shown to convert *myo*-inositol into *scyllo*-, D-*chiro*-, and *neo*-inositols. Both *scyll*o- and D-*chiro*-inositols enter mammalian cells through active and passive transport processes. The hexakisphosphates of both *scyllo*- and D-*chiro*-inositols are degraded by soil bacteria.

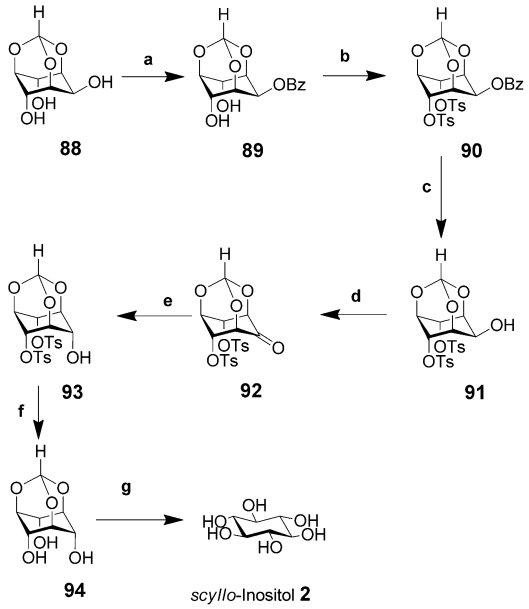
3.3. Medicine

Both *scyllo*- and D-*chiro*-inositols have potential roles in medicine. *scyllo*-Inositol has been found to interact with the amyloid-β peptide: it helps prevent the formation of insoluble amyloid fibers that are a feature of Alzheimer's disease, thereby alleviating memory deficits, decreasing disease symptoms, and improving cognitive function. ^{1}H NMR spectroscopy has been used to detect *scyllo*-inositol in the brain and in cancers. D-*chiro*-Inositol can act as an insulin mimetic by restoring insulin sensitivity and reducing hyperglycaemia. It also aids recovery of normal ovulation in those suffering from polycystic ovary syndrome.

4. scyllo-*Inositol*

4.1. Chemical Synthesis

scyllo-Inositol (**2**) has been isolated from a mixture of inositol isomers formed during the hydrogenation of benzenehexol under high pressure when using Raney nickel as a catalyst.[27] The synthesis of *scyllo*-inositol from *myo*-inositol via the orthoformate has been described (Scheme 12).[28] This synthesis illustrated that a large amount of *scyllo*-inositol could be produced from inexpensive starting materials. *myo*-Inositol orthoformate (**88**) was prepared without any chromatographic purification, then selectively benzoylated at the 2-hydroxy group to give **89**. Tosylation of the 4- and 6-hydroxy groups gave **90** and selective debenzoylation gave the 2-hydroxy derivative **91**. Swern oxidation gave the ketone **92**, which was reduced with sodium borohydride to provide the *scyllo*-inositol derivative **93** in excellent yield. Further cleavage of the tosyl groups under basic conditions led to **94**, hydrolysis of which under acidic conditions gave *scyllo*-inositol (**2**).



Scheme 12. Reaction conditions: a) NaH, BzCl, DMF, RT; b) tosyl chloride, pyridine, 80–100 °C; c) isobutylamine, MeOH, reflux; d) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, then Et_3N, RT; e) $NaBH_4$, MeOH/THF (4:1), RT; f) NaOMe, MeOH, reflux; g) TFA/water 4:1.

4.2. Overview of scyllo-Inositol Derivatives

A range of fluorinated, C-methyl, and deoxy-*scyllo*-inositols have been prepared and evaluated for their ability to inhibit amyloid-β aggregation.[29] The synthesis and purification of all 12 possible regioisomers of *scyllo*-inositol bis-, tris-, and tetrakisphosphates in *meso* or racemic forms has been described.[30] *scyllo*-Inositol was generated from *myo*-inositol by stereoinversion of the vicinal *cis*-diol under Mitsunobu conditions. The phosphorylated products were obtained from *scyllo*-inositol benzoate intermediates. The same research group went on to synthesize and purify all three enantiomeric pairs of *scyllo*-inositol phosphates (*scyllo*-inositol 1,2-bisphosphate, *scyllo*-inositol 1,2,4-trisphosphate, and *scyllo*-inositol 1,2,3,4-tetrakisphosphate) from enzymatically resolved conduritol B derivatives.[31] The syntheses of *myo*-inositol 1,3,4,5,6-pentakisphosphate and its C2 epimer *scyllo*-inositol pentakisphosphate starting from *myo*-inositol orthoformate have been described.[32]

4.3. Biology and Medicine

The non-mammalian biology and the role of *scyllo*-inositol in the environment are discussed in the Supporting Information (SI_2). The detection of *scyllo*-inositol in mammals was first reported in the 1950s, when it was found in urine.[33] The finding of *scyllo*-inositol in whole rat homogenates and in rat tissues was accompanied by evidence that it can be generated from *myo*-inositol via a *myo*-inosose-2 (**95**) intermediate (Figure 2).[34] After oral ingestion by women of reproductive age, *myo*-inositol rapidly entered the bloodstream, with a small amount being converted into *scyllo*-inositol.[35]

A *scyllo*-inositol-containing sialyloligosaccharide has been detected in human urine.[36] *scyllo*-Inositol is not incorporated into phospholipids in mammals.[37] The analogue

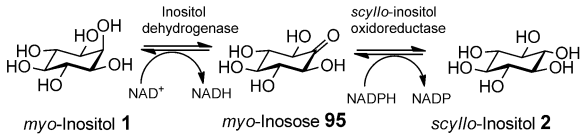


Figure 2. The conversion of *myo*-inositol into *scyllo*-inositol via *myo*-inosose.

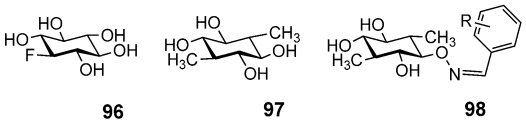


Figure 3. 1-Deoxy-1-fluoro-*scyllo*-inositol (**96**); 1,4-dideoxy-1,4-dimethyl-*scyllo*-inositol (**97**); oxime derivatives of *scyllo*-inositol (**98**). R = H or up to three hydroxy substituents on the ring.

1-deoxy-1-fluoro-*scyllo*-inositol (**96**; Figure 3) inhibits the incorporation of *myo*-inositol into phosphatidylinositols.[38] *scyllo*-Inositol inhibits the incorporation of *myo*-inositol into lipid-soluble phosphoinositides and water-soluble inositol phosphates in the developing rat conceptus (causing dysmorphogenesis) and also impairs the hydrolysis of phosphoinositides.[39] *scyllo*-Inositol is a more potent inhibitor of mycobacterial phosphatidylinositol synthase than of the mammalian equivalents.[40]

The transport of *scyllo*-inositol into cells in rat kidney slices is an active process that is inhibited by *myo*-inositol, thus suggesting that both are imported into cells by the same transporter.[41] The uptake of *myo*-inositol by L1210 leukaemia cells is only partially inhibited by *scyllo*-inositol, which suggests that *myo*-inositol may be taken up using two different routes, only one of which is inhibited by *scyllo*-inositol.[42] This is supported by the finding that in rats the transport of *myo*-inositol through the blood–brain barrier occurs by both simple diffusion and through a specific, saturable transport system that can also transport *scyllo*-inositol but not other inositol isomers.[43] *scyllo*-Inositol can also be transported, in competition with *myo*-inositol, into bovine cardiac cells through a Mg^{2+}-dependent Na^+ co-transport process that is both electrogenic and specific: D-*chiro*-inositol and *epi*-inositol are weaker competitors of *myo*-inositol transport.[44] The concentration of *myo*- and *scyllo*-inositol in the brain is about 100-fold greater than in the surrounding tissues, which suggests that the transport of both into the brain is an active process.[45] Two sodium/*myo*-inositol transporters, SMIT1 and SMIT2, capable of transporting both *myo*- and *scyllo*-inositol into the brain have been identified.[46] The asymmetric distribution of *scyllo*-inositol (and other metabolites) throughout the vitreous humor implies that the vitreous humor has different roles in different parts of the eye, and that it is not just "the clear jelly that fills the eyeball".[47]

At a high (1 mM) concentration, *scyllo*-inositol induces the translocation of the GLUT4 glucose transporter to the plasma membrane in an in vitro model system using rat L6 myotubes.[48] The transport of GLUT4 to the plasma membrane of skeletal muscle cells was also observed following the oral administration of *scyllo*-inositol to mice.[49]

4.4. scyllo*-Inositol and Neurological Disorders*

Alzheimer's disease is a common form of dementia for which there is no cure. It is neuropathologically characterized by selective neuronal loss, neurofibrillary tangles, and amyloid deposits (insoluble amyloid fibers). The major component of amyloid deposits is amyloid-β (Aβ), a peptide of 39–43 residues, the most amyloidogenic of which has 42 residues (Aβ42). The role of Aβ in the pathogenesis of Alzheimer's disease has been reviewed and critiqued.[50] The role of *scyllo*-inositol in Alzheimer's disease has been the subject of a recent comprehensive review, so this aspect of *scyllo*-inositol science is not reviewed in detail herein.[51] *scyllo*-Inositol is able to stabilize soluble oligomers of Aβ, the structure of which has been recently described,[52] and prevent the formation of insoluble amyloid fibers.[53] Aβ aggregation is inhibited by *scyllo*-inositol derivatives with single hydroxy conservative substitutions (1-deoxy-1-fluoro-*scyllo*-inositol, **96**), but not single chloro or methoxy substitutions. However, the disubstituted 1,4-dimethyl derivative **97** is effective.[54] Oxime derivatives such as **98** are also effective at promoting the formation of soluble oligomers and preventing the formation of insoluble fibers.[55] The cited references mention *scyllo*-inositol binding to Aβ, but the results of in vitro measurements in another report suggest that it does not bind to Aβ42.[56] However, a modeling study suggests that *scyllo*-inositol can bind to the surface of β-sheet aggregates in a manner that disrupts their lateral stacking into amyloid fibrils.[57] Shorter versions of Aβ containing 25–35 residues transition from isotropic to β-sheet oligomers by the time five molecules are present: *scyllo*-inositol binds weakly to these oligomers with no adverse effect on the conversion from isotropic into fibrillar conformations.[58] The mechanism of action of *scyllo*-inositol is unclear.[59] *scyllo*-Inositol, when dosed in a murine model of Aβ production in combination with R-flurbiprofen (an agent that lowers Aβ production), is not as effective in treating the mice as *scyllo*-inositol alone.[60]

Another feature of Alzheimer's disease is the neuronal accumulation of autophagic vacuoles, which suggests that the degradative pathway is dysfunctional in these cells.[61] The accumulation of Aβ and the enzymes responsible for Aβ production in autophagic vacuoles suggests that Aβ may be responsible for the impaired clearance of autophagic vacuoles.[62] In a transgenic mouse model of Alzheimer's disease, treatment with *scyllo*-inositol caused a decrease in both the size and number of autophagic vacuoles.[63]

In the same mouse model, *scyllo*-inositol inhibited the aggregation of Aβ when administered orally, and reduced the severity of several of the symptoms of Alzheimer's disease, including impaired cognition, altered synaptic physiology, cerebral Aβ pathology, and accelerated mortality.[64] These effects were observed whether the *scyllo*-inositol was administered before symptoms first appeared or several months after their first appearance. The administration of *scyllo*-inositol also rescues hippocampal function and restores memory function in animals with pre-existing Aβ oligomers.[65] Some of the symptoms of Alzheimer's disease can be attributed to the obstruction of blood vessels by amyloid

plaques: the administration of *scyllo*-inositol to model transgenic mice eased both the structural and functional impairment of the cortical microvasculature.[66] The expression levels of the sodium/*myo*-inositol transporters do not differ between healthy individuals and those with Alzheimer's disease.[67] A phase 2 clinical trial of *scyllo*-inositol established a twice daily dose of 250 mg as being safe, but the sample size was too small to establish efficacy.[68]

scyllo-Inositol inhibits the aggregation of Aβ in Alzheimer's disease and also inhibits the neuronal aggregation of α-synuclein, a pathological hallmark of Parkinson's disease.[69] Likewise, *scyllo*-inositol reduces the number of neuronal aggregates and inclusions containing polyglutamine-expanded huntingtin protein in Huntington disease, and does this by reducing the amount of mutant protein produced.[70] Amyloid deposits can also form in the islets of Langerhans and may contribute to the development of diabetes: *scyllo*-, *myo*-, and *epi*-inositols are ineffective in preventing the formation of these amyloid deposits.[71]

In rats, seizures induced by pentylenetetrazole were reduced in severity following the administration of *scyllo*-inositol. This finding suggests that it may have a role to play in antiepileptic therapy.[72]

4.5. scyllo-*Inositol and Diagnostics*

Several techniques have been used to measure the amount of *scyllo*-inositol in both healthy and diseased tissue. Differences in these values may have applications in disease diagnosis. ^{1}H NMR spectroscopy has been used to measure the in vivo, ex vivo, or in vitro concentrations of many metabolites, particularly in the brain.[73] Many publications have reported the use of ^{1}H NMR spectroscopy to measure the concentration of *scyllo*-inositol in healthy people (and animals) and those with a variety of diseases. Space constraints preclude herein a detailed discussion of this topic, but the papers that have used this technique are listed and briefly summarized in the Supporting Information (SI_2).

Positron emission tomography has been used to establish that [^{18}F]-1-deoxy-1-fluoro-*scyllo*-inositol does not penetrate the brain of rats or mice following injection into a tail vein, but is taken up by human breast cancer xenografts in mice.[74] However, cancer cells injected into the cranium are able to take up [^{18}F]-1-deoxy-1-fluoro-*scyllo*-inositol to a fivefold greater extent than the surrounding brain tissue.[75] In a human breast cancer model, [^{18}F]-1-deoxy-1-fluoro-*scyllo*-inositol is taken up to a lesser extent than [^{18}F]-2-deoxy-2-fluoro-*myo*-inositol.[76] These results show that radiotracers may be useful in monitoring inositol uptake in tumors and that inositol transport into cells is not specific for one inositol isomer.

Gas chromatography has been used to establish that the *scyllo*-inositol content of the sciatic nerve in spontaneous-onset diabetic Chinese hamsters is reduced at five months of age and onwards, when compared with healthy equivalents.[77] *scyllo*-Inositol levels in the frontal or occipital cortex of unipolar, bipolar, and schizophrenic patients, suicide victims, and normal controls do not differ.[78] Intracellular *scyllo*-inositol levels in rat brain extracts have been analyzed by micellar electrokinetic chromatography.[79]

4.6. scyllo-*Inositol Phosphates*

scyllo-Inositol is not incorporated into phospholipids in mammals,[37] but *scyllo*-inositol-containing phosphatidylinositol has been detected in non-mammalian species. See the Supporting Information (SI_2) for details.

In studies of structure–activity relationships, chemically synthesized *scyllo*-inositol phosphates have been investigated for their ability to compete with *myo*-inositol phosphates for binding to various receptors and enzymes (Figure 4). DL-

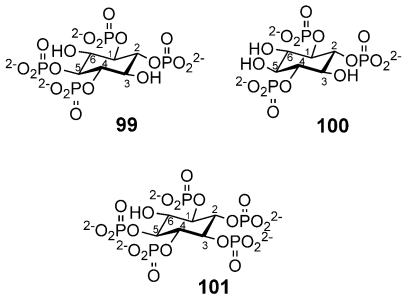


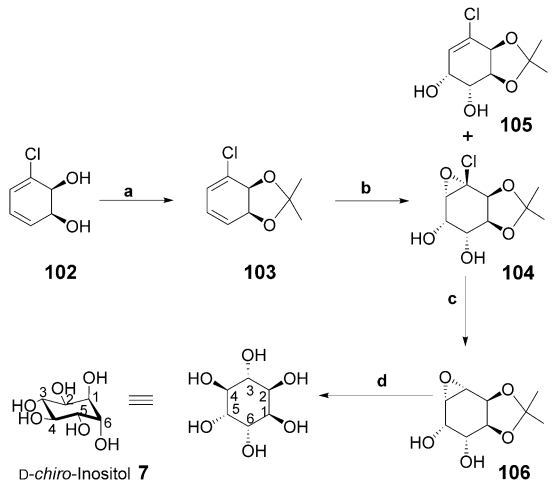
Figure 4. *scyllo*-Inositol-1,2,4,5-tetrakisphosphate (**99**); L-*scyllo*-inositol-1,2,4-trisphosphate (**100**); *scyllo*-inositol-1,2,3,4,5-pentakisphosphate (**101**).

scyllo-Inositol 1,2,4-trisphosphate and *scyllo*-inositol 1,2,4,5-tetrakisphosphate (**99**) were full agonists at the Ca^{2+}-mobilizing inositol 1,4,5-trisphosphate receptor of SH-SY5Y cells, and displaced *myo*-inositol 1,4,5-trisphosphate from its receptor in bovine adrenal cells.[80] The tetrakisphosphate was also readily metabolized by enzymes with 3-kinase and 5-phosphatase activities. L-*scyllo*-Inositol 1,2,4-trisphosphate (**100**) was evaluated for binding to rat type 1, 2, and 3 inositol trisphosphate receptors: it has binding affinities similar to those of Ins(1,4,5)P_3 in all three receptor subtypes.[81] *scyllo*-Inositol 1,2,3,4,5-pentakisphosphate (**101**) is hydrolyzed by multiple inositol polyphosphate phosphatase, but is not dephosphorylated by PTEN (PTEN = phosphatase and tensin homologue on chromosome 10; the protein encoded by this gene is a phosphatidylinositol 3,4,5-trisphosphate 3-phosphatase) or phosphorylated at the 6-position (the equivalent of the *myo*-inositol 2-position) by pentakisphosphate 2-kinases.[32]

5. D-chiro-*Inositol*

5.1. Chemical Synthesis

D-*chiro*-Inositol (**7**) has been synthesized from the chiral chlorodiol **102**, which was produced by dihydroxylation of chlorobenzene in the presence of *Pseudomonas putidia* strain 39/D (Scheme 13).[82] Since the introduction of the diol was



Scheme 13. Reaction conditions: a) 2,2-dimethoxypropane, PTSA; b) $KMnO_4$, $MgSO_4$, aqueous acetone, **104**/**105** 8:1, 60%; c) AIBN, tris(trimethylsilyl)silane, toluene, 42%; d) H_2O, sodium benzoate, 77% yield, >95% purity.

stereoselective, it is a suitable method for the preparation of chiral derivatives such as D-*chiro*-inositol. Diol **102**, as its acetonide **103**, was treated with $KMnO_4$ to give an unexpected derivative **104** together with alkene **105** in a reasonable yield. Compound **104** was dehalogenated in the presence of AIBN and tris(trimethylsilyl)silane to give **106**. After trying a number of different reaction conditions, the opening of epoxide **106** was achieved at reflux temperature in water with a catalytic amount of sodium benzoate to provide D-*chiro*-inositol (**7**).

5.2. Overview of D-chiro-Inositol Derivatives

D-*chiro*-Inositol-1,3,4,6-tetrakisphosphate (**107**; Figure 5) has been synthesized from D-pinitol (the 3-*O*-methyl derivative of D-*chiro*-inositol) via the 2,5-di-*O*-benzyl-protected intermediate then phosphorylation of the hydroxy groups followed by deprotection.[83] Starting from D-pinitol and proceeding via the 1,6-di-*O*-benzyl-protected intermediate, the synthesis of D-*chiro*-inositol 2,3,4,5-tetrakisphosphate (**108**; Figure 5) has also been described via the intermediate D-1,6-di-*O*-benzyl-*chiro*-inositol,[84] and D-*chiro*-inositol-1,3,4-trisphosphate (**109**) has been synthesized from D-1,2,5-tri-*O*-benzoyl-3,4-di-*O*-benzyl-*chiro*-inositol.[85]

The syntheses of fagopyritols A1 and B1 (galactopyranosyl derivatives of D-*chiro*-inositol), the biological role of which are discussed in the Supporting Information (SI_2), have been described.[86] Starting from the appropriate penta-*O*-benzyl-D-*chiro*-inositol, all six isomeric D-galactosaminopyranosyl-D-*chiro*-inositols have been prepared.[87]

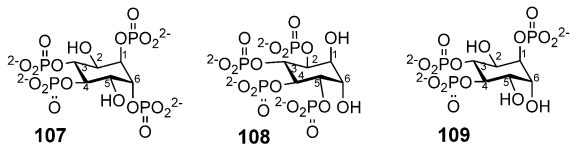


Figure 5. D-*chiro*-Inositol-1,3,4,6-tetrakisphosphate (**107**); D-*chiro*-inositol-2,3,4,5-tetrakisphosphate (**108**); D-*chiro*-inositol-1,3,4-trisphosphate (**109**).

5.3. Biology and Medicine

After *myo*-inositol, and along with *scyllo*-inositol, D-*chiro*-inositol (and its 3-*O*-methyl derivative, pinitol) is the most studied of the inositols. Pinitol is considered separately below. The non-mammalian biology of D-*chiro*-inositol and pinitol is discussed in the Supporting Information (SI 2).

The uptake of *myo*-inositol by a Mg^{2+}-dependent, Na^+-inositol co-transport process in cardiac sarcolemmal cells is inhibited by D-*chiro*-inositol, but to a lesser extent than by *scyllo*-inositol.[44] In HepG2 liver cells, there is a stereospecific *myo*-inositol/D-*chiro*-inositol transporter: L-*chiro*-inositol is not transported.[88] The *myo*-inositol transporter SMIT2, but not SMIT1, is able to transport D-*chiro*-inositol into cells:[89] the rat protein does so with high affinity.[90]

Rats absorb D-*chiro*-inositol from the diet, but it is neither synthesized endogenously nor produced from *myo*-inositol.[91] This contradicts earlier work which found that *myo*-inositol is converted into D-*chiro*-inositol in a range of rat tissues with little or no conversion in the opposite direction.[92] The first committed step in *myo*-inositol catabolism is the ring opening catalyzed by *myo*-inositol oxygenase. This enzyme, isolated from pig kidneys, also catabolizes D-*chiro*-inositol, although at a slower rate than *myo*-inositol.[93]

Mice genetically engineered to develop folate-resistant neural-tube defects in utero can be more effectively treated with D-*chiro*-inositol than with *myo*-inositol.[94] D-*chiro*-Inositol is able to prevent and reverse endothelial dysfunction in rat and rabbit blood vessels.[95]

Some bone-related diseases are caused by excessive bone resorption by osteoclasts, which are multinucleated giant cells formed by cell–cell fusion. D-*chiro*-Inositol has been shown to inhibit cell–cell fusion and the expression of several osteoclastogenic genes by down-regulating the nuclear factor of activated T cells c1.[96]

The insecticide DDT, when fed to rats, causes increases in liver weight and hepatic lipids. The coadministration of L-*chiro*- or D-*chiro*-inositol with DDT promotes this effect.[97]

5.4. D-chiro-Inositol in Diabetes, Pregnancy, and Polycystic Ovary Syndrome

D-*chiro*-Inositol is a component, along with galactosamine, of an uncharacterized modulator of insulin function: it stimulates pyruvate dehydrogenase phosphatase[98] and allosterically activates protein phosphatase 2C.[99] A three-day fast causes a 20% drop in the amount of D-*chiro*-inositol in muscle, which may contribute to the insulin resistance that occurs after short-term starvation.[100] The fruit from *Cucurbita ficifolia*, a member of the squash family, is used in Asia as an antihyperglycaemic agent. The effectiveness of this treatment is due to the high D-*chiro*-inositol content.[101] Extracts

of both *C. ficifolia* and synthetic D-*chiro*-inositol reduced oxidative stress, as measured by changes in the ratio of oxidized to reduced glutathione in murine adipocytes: D-*chiro*-inositol, but not the plant extract, demonstrated insulin mimetic action.[102] Pumpkin seeds contain several molecules, including D-*chiro*-inositol, reported to have antiglycemic effects, and the seeds help maintain glycemic control.[103] Insulin prevents damage caused by the synaptic accumulation of amyloid β oligomers and this effect is enhanced by the presence of D-*chiro*-inositol.[104] D-*chiro*-Inositol phosphoglycans move from the foetus to the placenta during pregnancy, but diabetic women have lower concentrations of these compounds in the placenta.[105] Insulin resistance is a prominent feature of pre-eclampsia and D-*chiro*-inositol levels are increased in this condition and may contribute to insulin resistance.[106]

The urinary excretion of D-*chiro*-inositol has been measured at 2.1 μmol day^{-1} in nondiabetics, but increases sixfold in non-insulin-dependent diabetics and another thirtysixfold in insulin-dependent diabetics.[107] In a rat model of type 1 diabetes and a mouse model of type 2 diabetes, the urinary excretion of D-*chiro*-inositol was much greater than in healthy rats and mice.[108] These studies contradict earlier work that shows a lower urinary excretion (and lower muscle content) of D-*chiro*-inositol in non-insulin-dependent diabetics than in nondiabetics.[109] The transport of D-*chiro*-inositol into cells by SMIT2 is up-regulated by insulin, so the increased urinary excretion of D-*chiro*-inositol in diabetics may be due to the lack of activity of SMIT2 consequent upon a shortage of insulin.[110] In older nondiabetic adults, resistive (strength) training does not influence the urinary excretion of inositols.[111] However, in these older nondiabetic adults, higher D-*chiro*-inositol excretion is linked to a lower activation of skeletal muscle insulin receptor signaling.[112] Low urinary clearance of D-*chiro*-inositol in men with a wide range of insulin sensitivity is closely related to hyperinsulinemia.[113] Compared with the kidneys from nondiabetic rats, those from diabetic rats had a fourfold greater excretion of D-*chiro*-inositol under normoglycemic conditions, with higher excretion under hyperglycemic conditions.[114] Increases in *myo*-inositol excretion also occurred but were not as great, despite increased renal expression of both SMIT1 and SMIT2.

Rats suffering from streptozotocin-induced diabetes and diabetic mice have reduced plasma glucose levels when D-*chiro*-inositol or a buckwheat concentrate containing high concentrations of D-*chiro*-inositol is administered;[115] the role of D-*chiro*-inositol from the buckwheat concentrate in the biological response of hepatomas has, however, been questioned.[116] Similarly, insulin-resistant hyperinsulinemic Rhesus monkeys had lower plasma glucose concentrations (and slightly lower insulin concentrations) after being fed a meal with D-*chiro*-inositol than a meal without D-*chiro*-inositol.[117] Male Wistar rats suffering from insulin resistance induced by recombinant human growth hormone were treated with D-*chiro*-inositol, which offset the peripheral insulin resistance but not the hepatic insulin resistance.[118] Glucosamine induces peripheral and hepatic insulin resistance in rats, but pretreatment with D-*chiro*-inositol prevented the induced peripheral insulin resistance.[119] In mice suffering from streptozotocin-induced diabetes, chronic treatment with D-*chiro*-inositol prevents autonomic and somatic neuropathy.[120] When infused into streptozotocin-induced diabetic rats, a D-*chiro*-inositol glycan mediator of insulin action normalizes plasma glucose at a dose equivalent to insulin without inducing hypoglycaemia.[121] D-*chiro*-Inositol has been found to inhibit hepatic glucose output, thus suggesting that this may be the mechanism by which D-*chiro*-inositol exerts its antidiabetic effect.[122]

The uptake of insulin by rat L6 myotubes is stimulated by D-*chiro*-, L-*chiro*-, *epi*-, and *muco*-inositol and may be associated with the translocation of the glucose transporter 4 protein to the plasma membrane: *allo*- and *scyllo*-inositols are less-potent stimulants.[48]

Intra-uterine growth restriction in piglets results in low weight at birth. These low-weight piglets have significantly higher plasma concentrations of *myo*-inositol and D-*chiro*-inositol than their larger siblings. Since both *myo*-inositol and D-*chiro*-inositol have been associated with glucose intolerance and insulin resistance in adults, it has been suggested that impaired glucose metabolism during foetal development may be a contributing factor to the development of type 2 diabetes in adulthood.[123]

The administration of D-*chiro*-inositol in combination with *myo*-inositol, folic acid, and manganese to women during the second trimester of pregnancy results, after thirty days, in significantly lower cholesterol, low density lipoprotein, triglyceride, and glycemia compared with controls.[124]

Polycystic ovary syndrome (PCOS) afflicts 5–10% of women of reproductive age, thus making it the most common gynecological disorder. It is characterized by hyperandrogenism, chronic anovulation (irregular menstrual cycles), and polycystic ovaries. Common complications of PCOS include obesity, glucose intolerance and insulin resistance. The general features of PCOS (definition, prevalence, aetiology, pathophysiology, clinical features, adverse health consequences, assessment, and management) have been recently reviewed.[125]

The deficiency of a putative D-*chiro*-inositol-containing phosphoglycan that mediates insulin action has been tested by the administration of D-*chiro*-inositol in the hope that this would replenish the mediator stores and improve insulin sensitivity in PCOS sufferers.[126] It was found that the action of insulin was increased, with consequent improved ovulatory function, and lowered serum androgen concentrations, blood pressure, and plasma triglyceride concentrations. However, dietary supplementation with a combination of *myo*-inositol and D-*chiro*-inositol resulted in improved oocyte and embryo quality as well as better pregnancy rates in PCOS sufferers undergoing in vitro fertilization (IVF) treatment than in those PCOS sufferers whose diet was supplemented with just D-*chiro*-inositol.[127] This supports the finding that increasing the D-*chiro*-inositol dosage progressively worsens oocyte quality and the ovarian response,[128] and that *myo*-inositol is better able to improve oocyte quality in intracytoplasmic sperm injection cycles than D-*chiro*-inositol.[129] It has been hypothesized that the activity of the epimerase that converts *myo*-inositol into D-*chiro*-inositol is enhanced in the ovaries of PCOS sufferers and that the consequent deficiency of *myo*-

inositol is responsible for the poor oocyte quality.[130] PCOS sufferers taking *myo*-inositol and D-*chiro*-inositol in a physiological ratio have an improved metabolic (i.e. lipid) profile, thus reducing the risk of cardiovascular disease.[131] Both *myo*-inositol and D-*chiro*-inositol are effective in improving ovarian function and metabolism in PCOS sufferers, but *myo*-inositol has a greater effect on the metabolic profile while D-*chiro*-inositol is better able to reduce hyperandrogenism.[132] The treatment of 48 patients affected by PCOS and menstrual irregularities with D-*chiro*-inositol and folic acid resulted in statistically significant improvements in several measures of ovarian function and metabolic function.[133] In PCOS sufferers, metformin increases the insulin-stimulated release of the putative D-*chiro*-inositol-containing phosphoglycan that mediates insulin action:[134] there is a selective impairment in PCOS sufferers of the interdependence between insulin action and the release of the mediator.[135] PCOS has been associated with a degree of oxidative stress: the administration of D-*chiro*-inositol to PCOS sufferers prevents the oxidation of protein thiol groups in the follicular fluid.[136] The administration of D-*chiro*-inositol to obese hyperinsulinemic PCOS sufferers improves insulin sensitivity and hormonal parameters.[137]

In the previous paragraph there are a couple of references to a "putative D-*chiro*-inositol-containing phosphoglycan". The structure of this compound is currently unknown: we have been unable to find any evidence that it even contains a phosphate moiety, the presence of which is implied by it being called a phosphoglycan. The fact that the assay for this compound is based on its ability to activate pyruvate dehydrogenase phosphatase suggests that it may be the modulator of insulin function mentioned above that contains D-*chiro*-inositol and galactosamine.[98]

PCOS sufferers have higher D-*chiro*-inositol urinary clearance rates than nonsufferers: urinary clearance is inversely correlated with insulin sensitivity and is a good independent predictor of insulin resistance and compensatory hyperinsulinemia.[138] The number of PCOS sufferers reporting irregular menstrual cycles decreases with increasing duration of D-*chiro*-inositol treatment.[139]

The use of D-*chiro*-inositol (and other insulin-sensitizing agents) in PCOS has been the subject of several reviews.[140]

5.5. D-chiro-*Inositol Phosphates*

Glycosylphosphatidylinositols (GPIs) containing D-*chiro*-inositol have been reported to exist in electric rays (*Torpedo* species),[141] bovine liver,[142] and *Entamoeba histolytica* trophozoites.[143] Furthermore, D-*chiro*-inositol-containing phosphoglycan derivatives that are mediators of insulin action have been reported to be derived from D-*chiro*-inositol-containing GPI anchors.[144] However, these reports may reflect the method of isolating the GPI and D-*chiro*-inositol: the isomerization of *myo*-inositol in GPIs to D-*chiro*-inositol occurs upon acidic hydrolysis of GPI-anchored proteins.[145] Recent reviews of GPIs state that they contain *myo*-inositol and make no mention of D-*chiro*-inositol.[146] Chemically synthesized GPIs containing D-*chiro*-inositol are cleaved by GPI-specific phospholipase D but not by phosphatidylinositol-specific phospholipase C.[147]

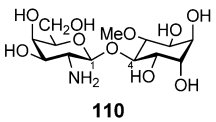
D-*chiro*-Inositol 1,3,4,6-tetrakisphosphate (**107**) is a full agonist of the inositol trisphosphate receptor in two cell lines, but the enantiomer is inactive.[83] With an IC_{50} value of 1.5 μM, D-*chiro*-inositol 2,3,4,5-tetrakisphosphate (**108**) is a potent inhibitor of Ins(3,4,5,6)P_4 1-kinase/Ins(1,3,4)P_3 5/6 kinase but its enantiomer is more than 20-fold less active.[84] The release of calcium from saponin-permeabilized rat basophilic leukaemia cells is inhibited by D-*chiro*-inositol 1,3,4-trisphosphate (**109**) with $EC_{50} = 4.2$ μM, while the enantiomer has $EC_{50} = 120$ μM.[85]

5.6. Pinitol

Pinitol is the 3-*O*-methyl derivative of D-*chiro*-inositol. The insulin-like effects of D-*chiro*-inositol described above are mimicked by pinitol in streptozotocin-induced diabetic mice, thus causing decreases in hyperglycaemia and plasma glucose concentrations.[148] Another study with streptozotocin-induced diabetic rats found that after treatment with pinitol, the levels of blood glucose, total cholesterol, triglycerides, free fatty acids, and both low-density lipoprotein and very low-density lipoprotein cholesterol were all significantly reduced, but that levels of high-density lipoprotein cholesterol increased.[149]

The oral administration of pinitol to obese humans with diet-treated type 2 diabetes or glucose intolerance resulted in no change to glucose production, insulin-mediated glucose disposal, or the rate of appearance in the plasma of free fatty acids or glycerol, but did increase the amount of pinitol in the plasma.[150] However, another study has reported that postprandial blood glucose is reduced in patients with type 2 diabetes when given pinitol 60 min prior to a meal.[151] Patients with type 2 diabetes that was poorly controlled by hypoglycaemic drugs were treated with pinitol at a dosage of 20 mg kg^{-1} day^{-1} for twelve weeks, after which they had decreased fasting and postprandial glucose levels but unchanged lipid profiles and adipocytokine levels.[152] A 6 g dose of pinitol, when coadministered with glucose, reduced serum glucose and insulin at 45 and 60 min compared with controls.[153] The administration of pinitol to nondiabetic humans one hour prior to an oral glucose tolerance test did not alter glucose or insulin levels, nor did it alter the activation of the skeletal muscle insulin receptor.[154]

A pinitol galactoside (pinitol β-1,4-galatosamine, INS-2, **110**, Figure 6) isolated from beef liver has insulin mimetic properties, as shown by its ability to decrease elevated blood glucose in streptozotocin-induced diabetic rats and the stimulation of glucose incorporation into glycogen in hepatoma cells in the presence of insulin.[155] INS-2 stimulates insulin secretion in MIN6 β cells, and potentiates glucose-stimulated insulin secretion in isolated mouse islets.[156] It does this through a mechanism that involves the stimulation of the



110

Figure 6. INS-2, pinitol β-1,4-galatosamine.

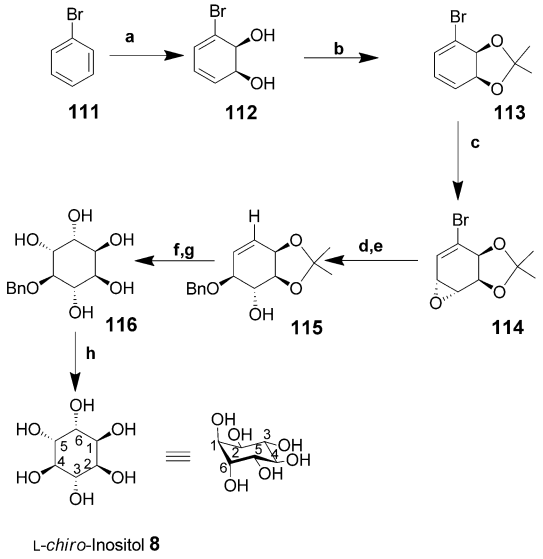
protein phosphatase 2C mediated inhibition of ATP-sensitive potassium channels.

Pinitol slightly inhibits the formation of foam cells (lipid-laden macrophages) and significantly reduces the release of tumor necrosis factor α, monocyte chemoattractant protein-1, interleukin-1β, and interleukin-8.[157] It also suppresses inflammation- and carcinogen-induced activation of NF-κB, thereby leading to the reduced expression of a number of genes involved in proliferation, apoptosis, invasion, and angiogenesis.[158] Pinitol reduces osteoclastogenesis by inhibiting the receptor activator of NF-κB ligand (RANKL).[159] Pinitol inhibits prostate cancer metastasis by reducing the cell-surface expression of αvβ3 integrin and inhibiting focal adhesion kinase phosphorylation, c-Src kinase activity, and NF-κB activation.[160] In rats, pinitol has a protective effect against chemically induced liver damage.[161]

6. L-chiro-*Inositol*

6.1. Chemical Synthesis

The synthesis of L-*chiro*-inositol (**8**) by the microbial oxidation of bromobenzene has been described (Scheme 14).[162] Bromobenzene (**111**) was oxidized in the presence of toluene dioxygenase from *E. coli* to give diol **112**.



Scheme 14. Reaction conditions: a) toluene dioxygenase; b) 2,2-dimethoxypropane, TsOH, RT; c) MCPBA, CH_2Cl_2, 96%; d) $PhCH_2OH$, $BF_3{:}Et_2O$, −10°C, 85%; e) nBu_3SnH, AIBN, THF, 78%; f) OsO_4, acetone, H_2O, NMO, 75%; g) HCl, EtOH, 79%; h) 10% Pd/C, H_2, H_2O, 81%, (30% overall yield from **114**).

The enantioselective dihydroxylation and subsequent easy steps make this route to chiral L-*chiro*-inositol (**8**) particularly attractive. Protection of diol **112** as an acetonide **113** and epoxidation provided the required intermediate **114**. The epoxide ring was opened with benzyl alcohol in the presence of a Lewis acid to give compound **115**. *cis*-Dihydroxylation and acid hydrolysis of the acetonide provided 4-*O*-benzyl-L-*chiro*-inositol (**116**) and deprotection (over a palladium catalyst) gave L-*chiro*-inositol (**8**).

6.2. Biology

Lithium ions potentiate the epileptogenic effects of cholinergic agents, for example, pilocarpine. This effect of lithium can be reversed by the coadministration of *myo*-inositol but not L-*chiro*-inositol.[163]

At a concentration of 0.1 mM, L-*chiro*-inositol is as efficient as 100 nM insulin in promoting GLUT4-dependent glucose uptake by rat L6 myotubes.[48] There was little difference in the urinary excretion of L-*chiro*-inositol between nondiabetics and non-insulin-dependent diabetics, but excretion increased just over threefold, to 0.51 μmol day^{-1}, in insulin-dependent diabetics.[107]

The non-mammalian biology of L-*chiro*-inositol is discussed in the Supporting Information (SI_2).

6.3. L-chiro-*Inositol Phosphates*

L-*chiro*-Inositol-2,3,5-trisphosphate (**117**; Figure 7)[164] and L-*chiro*-inositol-2,3,5-trisphosphorothioate (**118**) have been synthesized from quebrachitol, the 2-*O*-methyl derivative of L-*chiro*-inositol.[165] L-*chiro*-Inositol-1,4,6-trisphosphate (**119**)

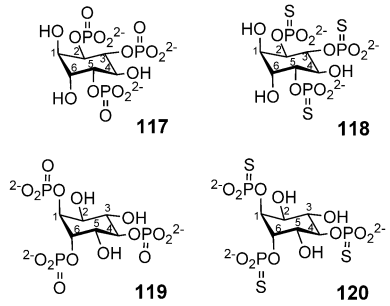


Figure 7. L-*chiro*-Inositol-2,3,5-trisphosphate (**117**); L-*chiro*-inositol-2,3,5-trisphosphorothioate (**118**); L-*chiro*-inositol-1,4,6-trisphosphate (**119**); L-*chiro*-inositol-1,4,6-trisphosphorothioate (**120**).

and the trisphosphorothioate (**120**) have also been synthesized, as have L-*chiro*-inositol-1,3,4,6-tetrakisphosphate (**121**; Figure 8),[83] L-*chiro*-inositol-2,3,4,5-tetrakisphosphate (**122**),[84] and L-*chiro*-inositol-1,3,4-trisphosphate (**123**).[85]

L-*chiro*-Inositol-2,3,5-trisphosphate (**117**)[164] binds to the inositol trisphosphate receptor, inhibits inositol 1,4,5-trisphosphate 5-phosphatase and inositol 1,4,5-trisphosphate 3-kinase, and is a full agonist at the Ca^{2+}-mobilizing receptor in SH-SY5Y cells.[166] L-*chiro*-Inositol-2,3,5-trisphosphorothioate (**118**) is a partial agonist for the release of intracellular calcium from saponin-permeabilized platelets,[167] and is a potent inhibitor of inositol 1,4,5-trisphosphate 5-phosphatase and inositol 1,4,5-trisphosphate 3-kinase.[168] Both compounds inhibit phosphatidylinositol 3-kinase noncompetitively.[169]

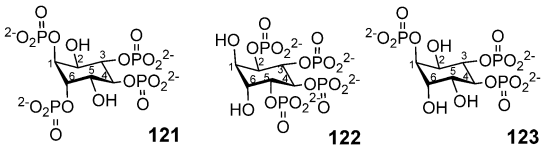


Figure 8. L-*chiro*-Inositol-1,3,4,6-tetrakisphosphate (**121**); L-*chiro*-inositol-2,3,4,5-tetrakisphosphate (**122**); L-*chiro*-inositol-1,3,4-trisphosphate (**123**).

The inhibition of inositol $(1,4,5)P_3$/$(1,3,4,5)P_4$-polyphosphate 5-phosphatase by L-*chiro*-inositol-1,4,6-trisphosphate (**119** in Figure 7) and its trisphosphorothioate analogue (**120**) has been described.[170] These same two compounds also have a significant effect on the kinetics of a small chloride channel in the sarcoplasmic reticulum from skeletal muscle.[171]

121,[83] **122**,[84] and **123**,[85] when compared with their D-*chiro*-inositol equivalents, are less-potent inhibitors/agonists of the inositol trisphosphate receptor, Ins(3,4,5,6)P_4 1-kinase/Ins(1,3,4)P_3 5/6 kinase, and the release of calcium from saponin-permeabilized rat basophilic leukaemia (RBL) cells, respectively. The synthesis of L-*chiro*-Ins(1,2,3,4,5,6)P_6 and its subsequent degradation to other L-*chiro*-inositol phosphates by phytases has been described.[172]

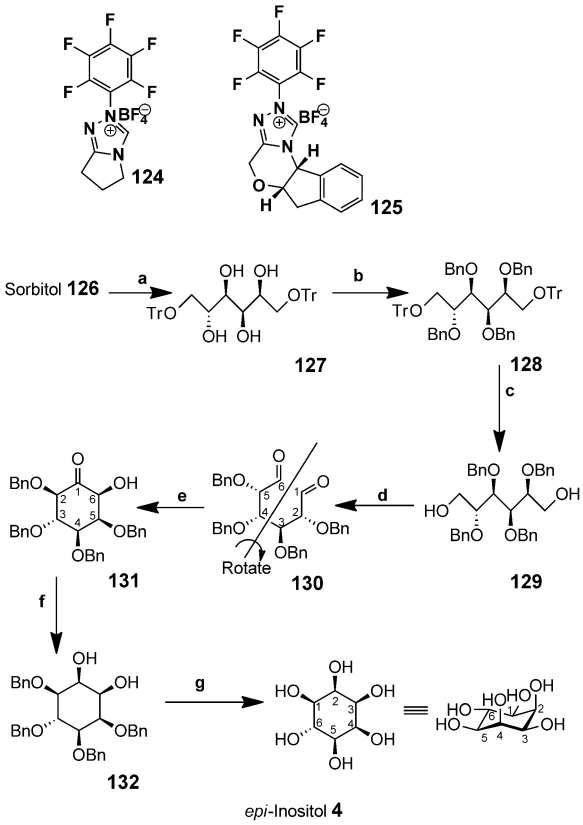
6.4. Quebrachitol

The 2-*O*-methyl derivative of L-*chiro*-inositol is known as quebrachitol. As discussed in the Supporting Information (SI_2), it is naturally occurring in some plants and apicomplexan parasites. Quebrachitol has a mildly sweet taste, but is not a substitute for glucose in reducing diabetic hypoglycaemia: in doses large enough to taste as sweet as cane sugar it causes colic and diarrhea.[173] Quebrachitol inhibits platelet activating factor receptor binding to rabbit platelets (IC_{50} = 42.2 μM).[174] Quebrachitol has a role to play in protecting cells as a result of it having antioxidant and free-radical scavenging properties.[175] Acute gastric lesions can be caused by ethanol and indomethacin. Quebrachitol protects against the effects of these drugs, although there is an inverse dose response: the smaller the dosage of quebrachitol the larger the protective effect,[176] although one explanation may be that the larger doses are themselves causing gastrointestinal upset. The protective effect of quebrachitol is due to mechanisms that involve nitric oxide release and/or the activation of K^+-ATP channels.

7. epi-*Inositol*

7.1. Chemical Synthesis

Recently, *allo*- and *epi*-inositols have been synthesized from carbohydrate dialdehyde intermediates (Scheme 15).[177] In the presence of N-heterocyclic carbene catalysts, such as **124** and **125**, the dialdehyde derivatives gave cyclic acyloin products. The cyclization of the dialdehyde intermediates synthesized from readily available starting materials is, therefore, worth highlighting, because the limits of the chemical cyclization using these catalysts have not been widely explored. *epi*-Inositol was synthesized from sorbitol (**126**) by a protection/deprotection strategy of tritylation to give **127**, benzylation to form **128**, and detritylation to generate **129**. Swern oxidation of the diol gave the dialdehyde **130**. Since dialdehyde **130** is not symmetrical, treatment with catalysts **124** or **125** led to the formation of two products, with **131** being the desired precursor to *epi*-inositol (**4**). The other isomer (not shown) was problematic to purify and most likely decomposed on silica. Compound **131** was then reduced with sodium borohydride to give **132** and the benzyl groups removed by hydrogenolysis to give *epi*-inositol (**4**) in 78% yield from ketone **131**.



Scheme 15. Reaction conditions: *epi*-inositol synthesis: a) TrCl, pyridine, reflux, 1.5 h, 93%; b) BnBr, NaH, $Bu_4N^+I^-$, THF, 25 °C, 6 h, reflux 19 h, 85%; c) CH_2Cl_2/MeOH 2:1, TFA, 18 h, 79%; d) 1. $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, 25 min; 2. Et_3N, −78 °C to 25 °C, 1.5 h, 88%; e) catalyst **124** or **125**, Et_3N, 14%; f) EtOH, $NaBH_4$, 1 h, reflux; g) $PdCl_2$, EtOH, H_2, 78% for steps (f) and (g).

7.2. Biology and Medicine

Lithium ions probably modulates the in vivo response to serotonergic and cholinergic stimulants through a common phosphoinositide signal transduction pathway.[178] Seizures induced by serotonergic (2,5-dimethoxy-4-iodoprenyl-2-aminopropane) and cholinergic (pilocarpine) receptor agonists in rats with either acutely or chronically high levels of lithium

ions were largely blocked by *epi*-inositol, but with less effect than *myo*-inositol.[178] These results for pilocarpine have been confirmed with the finding that *epi*-inositol is less potent, but as effective as *myo*-inositol in reversing the effects of lithium; *scyllo*- and L-*chiro*-inositol were less effective or inactive.[179] Pilocarpine is toxic to retinal ganglion cells in a dose-dependent fashion, with the toxicity being potentiated by lithium but blocked by *epi*- and *myo*-inositols.[180] The lithium-induced suppression of neuronal firing in the hypothalamic suprachiasmatic nucleus can be reversed by *myo*-inositol but not *epi*-inositol.[181] *myo*-Inositol, but not *epi*-inositol, reverses the effect of lithium by increasing the rate of spreading of neuronal growth cones.[182] Lithium is a classical inhibitor of the phosphoinositide pathway and is teratogenic. The teratogenicity can be overcome by equimolar *myo*-inositol but not *epi*-inositol.[183]

In yeast, *epi*-inositol has no effect on inositol monophosphatase but does inhibit the expression of the *INO1* gene (which encodes inositol-1-phosphate synthase), thereby resulting in lower conversion of glucose-6-phosphate into D-*myo*-inositol 3-phosphate than might otherwise be the case.[184] *epi*-Inositol thus reverses the lithium-induced increase in *INO1* expression. The daily intraperitoneal injection of *epi*-inositol into rats reduced anxiety levels compared to a control group and was more effective than *myo*-inositol.[185]

In cardiac sarcolemmal vesicles, the transport of *myo*-inositol into cells is through a Mg^{2+}-dependent, Na^{+}-inositol co-transport process that is inhibited by *epi*-inositol.[44] *epi*- and *scyllo*-inositols have been shown to be more potent inhibitors of mycobacterial phosphatidylinositol synthase than of mammalian analogues.[40] 0.1 mM *epi*-Inositol is as efficient as 100 nM insulin in promoting GLUT4-dependent glucose uptake by rat L6 myotubes.[48] *epi*-Inositol has an initial impact on the aggregation of amyloid-β associated with Alzheimer's disease, but is unable to maintain that impact over time.[64]

The non-mammalian biology of *epi*-inositol is discussed in the Supporting Information (SI_2).

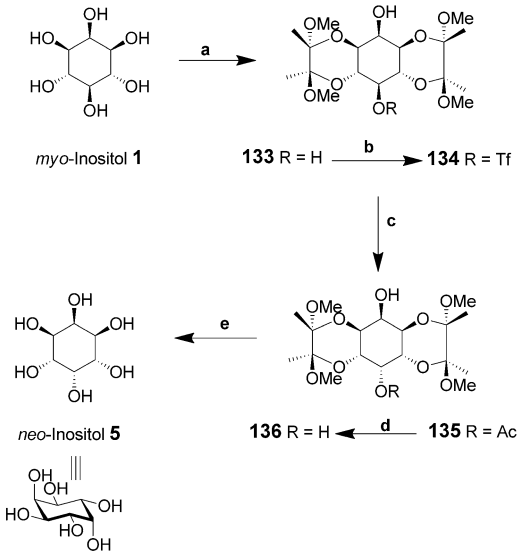
7.3. epi-*Inositol Phosphates*

The synthesis of *epi*-inositol 1,4,5-trisphosphate has been described; the compound shows poor affinity for the inositol 1,4,5-trisphosphate receptor.[186]

8. neo-*Inositol*

8.1. Chemical Synthesis

A multigram high-yielding simple synthesis of *neo*-inositol from *myo*-inositol in five steps has been reported (Scheme 16).[187] The synthesis relies on the selective protection of two pairs of *trans*-1,2-diols at the 1-/6-positions and the 3-/4-positions of *myo*-inositol by using butane-2,3-diacetal (BDA) protecting groups. The hydroxy groups at positions 2 and 5 of diol **133** are axial and equatorial, respectively. The



Scheme 16. Reagents and conditions: a) butanedione, MeOH, $CH(OMe)_3$, (±)-10-camphorsulfonic acid, reflux; b) trifluoromethanesulfonic anhydride, pyridine, CH_2Cl_2, −78 °C→RT; c) dimethylacetamide/water 50:1, 50 °C; d) NaOMe, MeOH, reflux; e) AcOH/water 4:1, reflux.

more reactive C-5-OH group allowed selective triflation of the 5-hydroxy group in good yield at low temperature to give **134**. Clean inversion of configuration at C-5 was only accomplished in wet dimethylacetamide (DMA) at an elevated temperature to give **135**; mixed products were observed when cesium acetate was used in the presence of dimethylformamide (DMF). Deacylation of **135** was accomplished using a catalytic amount of sodium methoxide, and the resulting diol **136** precipitated from the solution. The BDA protecting groups were removed using refluxing aqueous acetic acid and the product recrystallized from boiling water to provide pure *neo*-inositol (**5**) in a good overall yield from compound **1**.

neo-Inositol is the least water-soluble of the inositol isomers due to its unusually stable crystal structure.[188]

8.2. Biology

An enzyme in a calf brain extract that converts D-glucose 6-phosphate into D-*myo*-inositol 3-phosphate is also capable, although at a much slower rate, of converting D-mannose 6-phosphate into L-*neo*-inositol 1-phosphate.[189] *neo*-Inositol has also been found to be formed by the action of an epimerase isolated from bovine brain.[190]

The non-mammalian biology of *neo*-inositol is discussed in the Supporting Information (SI_2).

8.3. neo-*Inositol Phosphates*

Although originally identified as *myo*-inositol phosphates,[191] a subsequent reassessment of the data revealed that trophozoites in *Entamoeba histolytica* contain *neo*-

inositol hexakisphosphate (**137** in Figure 9), 2-diphospho-*neo*-inositol 1,3,4,5,6-pentakisphosphate (**138**), and 2,5-bisdiphospho-*neo*-inositol 1,3,4,6-tetrakisphosphate (**139**).[192] The synthesis of *neo*-Ins(1,2,3,4,5,6)P_6 (**137**) and subsequent degradation to other *neo*-inositol phosphates by phytases has been described.[172]

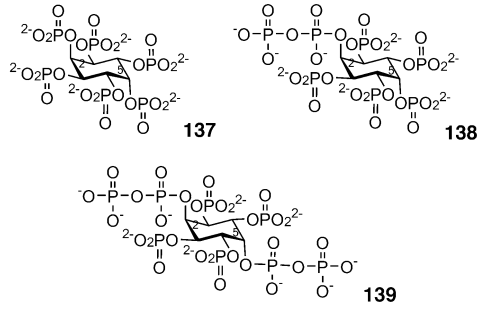


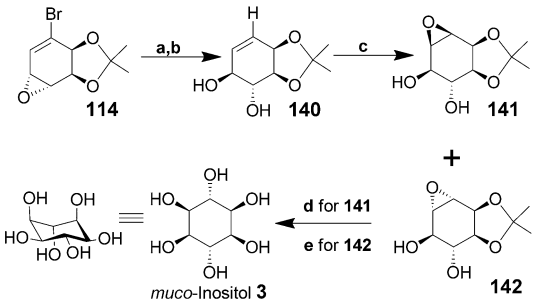
Figure 9. *neo*-Inositol hexakisphosphate (**137**); 2-diphospho-*neo*-inositol 1,3,4,5,6-pentakisphosphate (**138**); 2,5-bisdiphospho-*neo*-inositol 1,3,4,6-tetrakisphosphate (**139**).

9. muco-*Inositol*

9.1. Chemical Synthesis

muco-Inositol was first synthesized in the 1930s[193] and the fascinating historical background describing why the publication of the experimental parts of the paper was delayed is also explained.[194] More recently, *muco*-inositol has been chemoenzymatically synthesized starting from bromobenzene (Scheme 17).[162] Bromobenzene (**111**) was converted into the bromo epoxide **114**, as described for L-*chiro*-inositol. Ring opening of epoxide **114** furnished the required configuration of the two hydroxy groups and was accomplished in excellent yield using dilute potassium hydroxide. Radical dehalogenation gave the *trans*-diol **140** and epoxidation of the double bond gave compounds **141** and **142** in a ratio of 1.8:1 and in good yield. Different conditions for acid hydrolysis of compounds **141** and **142** using (d) and (e), respectively, afforded *muco*-inositol (**3**) in high yield.

L-*chiro*-Inositol has been selectively epimerized to *muco*-inositol derivatives.[195] *muco*-Inositol oligomers have been synthesized starting from 1-bromo-2,3-dihydroxycyclohexa-4,6-diene.[196] Derivatives of *muco*-inositol have been used as the starting point for the synthesis of derivatives of *epi*- and *cis*-inositols.[197]



Scheme 17. Reaction conditions: a) 10% aqueous KOH, H_2O, DME, 87%; b) nBu_3SnH, AIBN, THF, 90%; c) MCPBA, CH_2Cl_2, 71%; d) 10% H_2SO_4 (aq), 78%; e) Amberlyst A-27, H_2O, 89%.

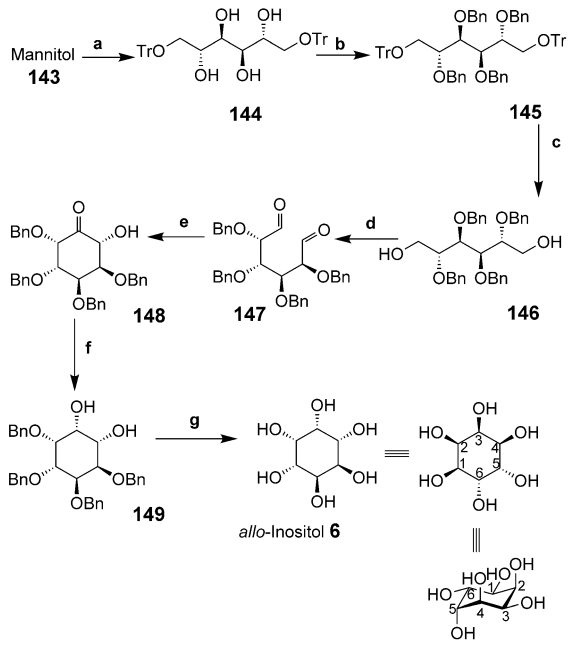
9.2. Biology

0.1 mM *muco*-inositol is as efficient as 100 nM insulin in promoting GLUT4-dependent glucose uptake by rat L6 myotubes.[48] L-*myo*-Inositol-1-phosphate synthase isolated from human fetal brain and adult rat brain is able to catalyze the conversion of galactose 6-phosphate into *muco*-inositol 1-phosphate.[198] Whether this reaction occurs in vivo is unknown. The non-mammalian biology of *muco*-inositol is discussed in the Supporting Information (SI_2).

10. allo-*Inositol*

10.1. Chemical Synthesis

allo-Inositol has been synthesized using carbohydrate dialdehyde intermediates in a similar manner to *epi*-inositol (Scheme 18).[177] This route is attractive for reasons similar to those discussed for *epi*-inositol. Mannitol (**143**) was tritylated at the 1- and 6-positions to provide **144**, then benzylation of the remaining hydroxy groups gave the fully protected intermediate **145**. Acid hydrolysis of the trityl groups gave **146** and a subsequent oxidation of the diol gave dialdehyde



Scheme 18. Reagents and conditions: *allo*-inositol synthesis: a) TrCl, pyridine reflux, 1.5 h, 97%; b) BnBr, NaH, $Bu_4N^+I^-$, THF, 25 °C, 6 h, reflux 19 h, 90%; c) CH_2Cl_2/MeOH 2:1, TFA, 18 h, 86%; d) 1. $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, 25 min; 2. Et_3N, −78 °C→25 °C, 1.5 h, 99%; e) catalyst **124** or **125**, Et_3N, 54%; f) EtOH, $NaBH_4$, 1 h, reflux; g) $PdCl_2$, EtOH, H_2, 81% for both steps (f) and (g).

147, the ^{1}H NMR spectrum of which showed its characteristic symmetry. Compound **147** was then treated with catalyst **124** or **125** over a 24 h period in the presence of triethylamine to provide the ring-closed product **148**. Hydroxyketone **148** was reduced to give a single product **149**, and the benzyl groups were removed by hydrogenolysis (in the presence of a palladium catalyst) in high yield to give *allo*-inositol (**6**).

allo-Inositol is unique among the inositols in that, although the Mills projection appears to show a plane of symmetry, when the ring inverts the conformational isomers are also enantiomers (Figure 10):[199] *allo*-inositol does not have a plane of symmetry. As interconversion between conformational isomers (**6a** and **6b**) is rapid, *allo*-inositol exists as an optically inactive racemic mixture despite being chiral. Therefore, it is likely impossible, at least at room temperature, to observe or separate the two enantiomers[200] and optical rotations have also not been formally assigned. It is possible, however, to synthesize *allo*-inositol derivatives from suitably protected *myo*-inositol derivatives and characterize protected or partially protected derivatives of the two enantiomers that are conformationally stable or fixed.[201] Such compounds or their phosphorylated derivatives might possess interesting biological activities.

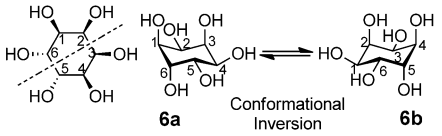


Figure 10. The black dashed line indicates an apparent plane of symmetry that does not really exist: the hydroxy group on one side of the line is equatorial, while the equivalent hydroxy group on the other side of the line is axial. The lack of any plane of symmetry in *allo*-inositol means that the conformational isomers are also enantiomers.

10.2. Biology

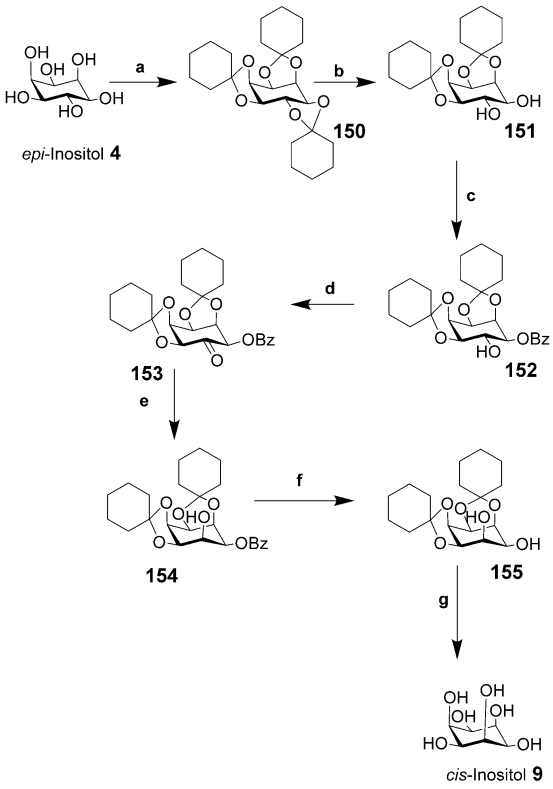
allo-Inositol has been found to be an inhibitor of amyloid-β aggregation,[202] and at 1 mM it is as efficient as 100 nM insulin in promoting GLUT4-dependent glucose uptake by rat L6 myotubes, but has little effect at 0.1 mM.[48] It is not known, for either of these activities, if one particular conformational isomer evokes these effects.

The non-mammalian biology of *allo*-inositol is discussed in the Supporting Information (SI_2).

11. cis-*Inositol*

11.1. Chemical Synthesis

cis-Inositol is available by a one-step hydrogenation of tetrahydroxyquinone, but with complex chromatography required.[203] *cis*-Inositol has also been synthesised from *epi*-inositol in a seven step process with a 25% yield (Scheme 19).[204] The good yield of the seven transformations from *epi*-inositol makes it a suitable starting point for the synthesis of this rare inositol. *epi*-Inositol (**4**) was fully



Scheme 19. Reaction conditions: a) cyclohexanone, benzene, reflux, PTSA, 59%; b) light petroleum, benzene, PTSA/EtOH, 71%; c) pyridine, benzoyl chloride, 70–75 °C, 5 h, 51%; d) benzene, DMSO, Ac_2O 17 h, 62%; e) chloroform/methanol (1:1), $NaBH_4$, 2 h, 96%; f) sodium, dry MeOH, 99%; g) 80% acetic acid, heat, 76%.

protected as the tricyclohexylidene derivative (**150**). Acid-catalyzed hydrolysis of the 5,6-*trans*-cyclohexylidene derivative **150** exposed the 5,6-diol to give **151**, and benzoylation of **151** gave a mixture of products from which **152** was isolated after recrystallization. Swern oxidation of the 6-OH group of **152** gave **153**. Interestingly, other oxidation procedures failed. The ketone was reduced stereoselectively and in near quantitative yield using sodium borohydride to provide **154**. Debenzoylation in near quantitative yield to give **155** followed by acidic hydrolysis of the cyclohexylidene protecting groups gave *cis*-inositol (**9**). From a historical perspective, this synthesis still holds today, although some of the yields could be improved by using new methods. Others have inverted the orientation of one or two hydroxy groups of a suitably protected inositol by conversion into a triflate, or oxidized a hydroxy group to give a ketone and then inverted the configuration at the carbon center, as described in Schemes 3 and 6.[205]

11.2. Biology

As far as we have been able to determine, *cis*-inositol is not known to occur naturally and we have been unable to find any literature describing biological roles for it.

12. myo-*Inositol*

Although this Review is focused primarily upon the inositol isomers other than *myo*, we felt it of interest to mention a few of the more recent papers in the *myo*-inositol area, especially where they feature chemistry that might be applied more widely. A number of reviews up to 2010 have covered the preparation of biologically important *myo*-inositol derivatives.[9,206] This section briefly reviews what we consider to be the most active areas since 2010 and does not attempt to deal, with two exceptions, with reports of any studies on *myo*-inositol-based phospholipids, but we briefly describe the biological activity of other *myo*-inositol derivatives.

12.1. myo-*Inositol 1,4,5,6-Tetrakisphosphate*

Much recent interest has centered upon the higher inositol polyphosphates, and new developments have revealed that higher *myo*-inositol phosphates play cellular roles in previously unexplored areas. In one recent highlight of note, a link was found with the histone deacetylase (HDAC) enzyme family that catalyzes the acetylation and deacetylation of lysine residues in histones which are involved in regulating gene expression. Thus, the assembly of a deacetylase activation domain (DAD)-HDAC3-(SMRT/NCOR2) (nuclear receptor co-repressor 2) complex is regulated by D-*myo*-inositol 1,4,5,6-tetrakisphosphate (Ins(1,4,5,6)P_4, **156**; Figure 11) during assembly of a complex with Ins(1,4,5,6)P_4 binding in a specific deep basically charged cleft.[207] Although studies on the precise structure–activity relationship in terms of specificity are as yet unavailable, it has since been shown that this is a more general mode of regulating HDACs, since the NuRD (nucleosome remodeling and deacetylase) complex, which contains HDAC1, also requires inositol phosphates for activity.[208] Phosphorylated *myo*-inositol derivatives containing four to six phosphate groups have been reviewed.[209]

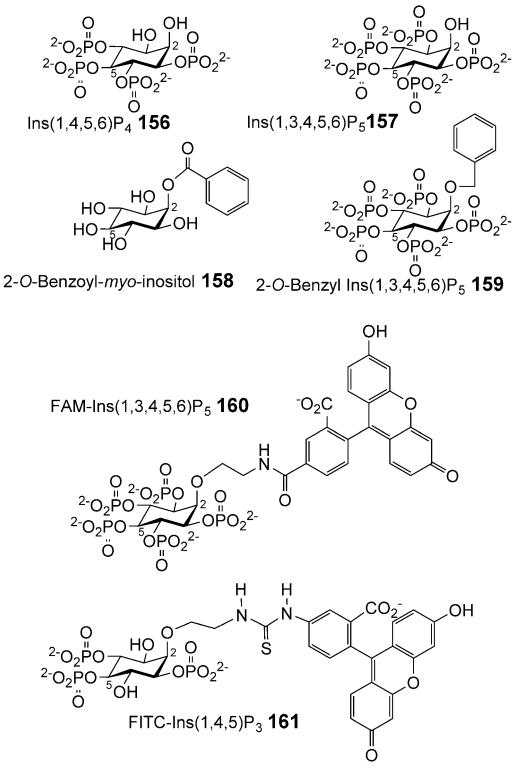


Figure 11. Some *myo*-inositol derivatives and fluorescently tagged polyphosphates.

12.2. myo-*Inositol Pentakisphosphate and Hexakisphosphate Derivatives*

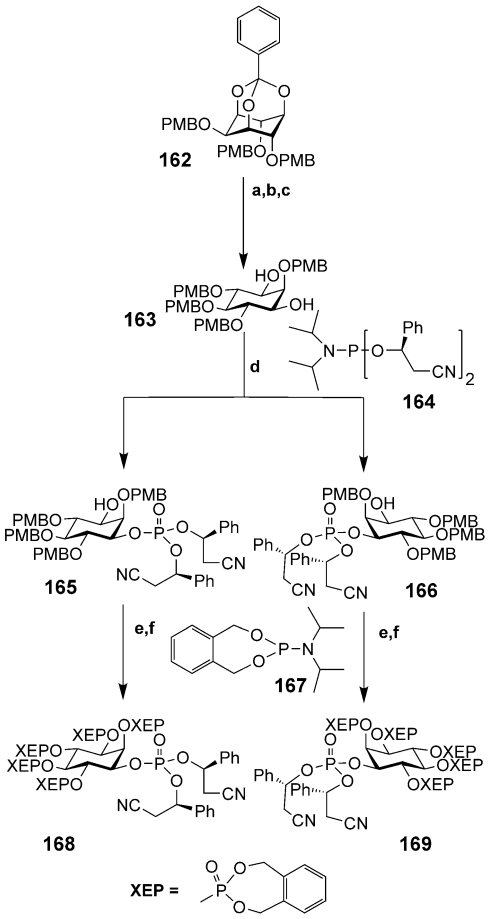
The higher phosphorylated *myo*-inositol derivatives include isomers of *myo*-inositol pentakisphosphate, for example, *myo*-inositol 1,3,4,5,6-pentakisphosphate (**157**), the metal ion coordination properties of which have recently been explored.[210] Ins(1,3,4,5,6)P_5 (**157**) and related derivatives were recently synthesized by using a route from *myo*-inositol 1,3,5-orthobenzoate that led regioselectively to the precursor 2-*O*-benzoyl-*myo*-inositol (**158**) via a 1,2-bridged 2′-phenyl-1′,3′-dioxolan-2′-ylium ion.[211] Substituted pentakisphosphate derivatives are of interest, and 2-*O*-benzyl-*myo*-inositol 1,3,4,5,6-pentakisphosphate (2-*O*-Bn-Ins(1,3,4,5,6)P_5, **159**) showed anticancer activity in xenograft studies and is also a nanomolar inhibitor of 3-phosphoinositide-dependent protein kinase 1 (PDK1).[212] 2-*O*-Bn-Ins(1,3,4,5,6)P_5 is more potent than Ins(1,3,4,5,6)P_5 and also inhibits the mammalian target of rapamycin (mTOR) in vitro. Compounds such as Ins(1,3,4,5,6)P_5[213] and Ins(1,2,3,4,5,6)P_6[214] were already known to possess anticancer properties. How Ins(1,3,4,5,6)P_5 and 2-*O*-Bn-Ins(1,3,4,5,6)P_5 apparently enter cells is a matter of some debate, but visualization of fluorescent derivatives has provided some clues.[215] Thus, Ins(1,3,4,5,6)P_5 was modified at the 2-position to provide 2-aminoethyl-*myo*-inositol 1,3,4,5,6-pentakisphosphate, which was then conjugated to a fluorescein derivative to give the fluorescent FAM-Ins(1,3,4,5,6)P_5 (**160**). This ligand enabled direct visualization of the compound, which was taken up apparently through nonspecific endocytosis by H1229 tumor cells, thus supporting previous data that Ins(1,3,4,5,6)P_5 can be taken up by some cell types.[216] Another fluorescent multiply phosphorylated *myo*-inositol derivative was synthesized by conjugating 2-aminoethyl-Ins(1,4,5)P_3 with fluorescein isothiocyanate to give FITC-Ins(1,4,5)P_3 (**161**). This was used to develop a high-throughput fluorescence polarization (FP) assay and to uncover the thermodynamics of Ins(1,4,5)P_3 binding to the Ins(1,4,5)P_3-binding core and N-terminal domain.[217] FITC-Ins(1,4,5)P_3 is a high-affinity weak partial agonist, possibly because of the large hydrophobic FITC moiety that may block interaction between the Ins(1,4,5)P_3 binding domain and the N-terminal domain.

12.3. *Synthesis of Diphosphoinositol Phosphate Derivatives*

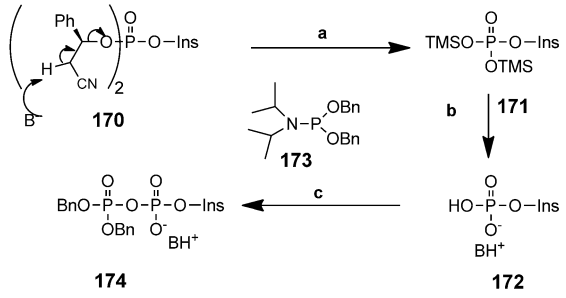
Perhaps the current most topical *myo*-inositol-derived chemical targets are diphosphoinositol phosphates, which

have numerous functions including the regulation of insulin sensitivity and weight gain,[218] the control of telomere length,[219] apoptosis,[220] and vesicle trafficking.[221] Diphosphoinositol phosphates were identified independently in 1993 by two separate groups[222] and the first synthesis was published shortly thereafter.[223] These compounds are difficult to isolate from cells because of their high negative charge density, tiny quantities, and the lack of a UV-active chromophore. New and improved methods are necessary to synthesize the pyrophosphate linkage regiospecifically in the presence of other phosphate groups and to address initial approaches to the design and exploitation of the first useful analogues. The biochemistry of these naturally occurring diphosphoinositol phosphates has been the subject of a number of reviews[224] and will not be discussed here.

Ten-step syntheses of 1D-diphosphoinositol 2,3,4,5,6-pentakisphosphate (**177**, 1PP-InsP_5) and 3D-diphosphoinositol 1,2,4,5,6-pentakisphosphate (**178**, 3PP-InsP_5) have been reported.[225] The synthesis had a number of new chemical transformations or modifications of existing reactions that had not previously been used in inositol chemistry. *myo*-Inositol was transformed into the fully blocked orthobenzoate intermediate in two steps from *myo*-inositol. Partial reduction of the orthoester **162** with DIBAL-H exposed the 5-hydroxy group, which was then *p*-methoxybenzylated. Careful acidic hydrolysis produced the *meso*-derivative 2,4,5,6-tetra-*O*-*p*-methoxybenzyl *myo*-inositol (**163**). These transformations allowed the desymmetrization of the 1,3-diol with a chiral reagent and separation into the required 1D and 3D derivatives (Scheme 20). Interestingly, the chirality is derived from the protecting groups on the P^{III} reagent **164** used to monophosphitylate the diol. The products were then oxidized to give both 1- and 3-phosphorylated derivatives **165** and **166**. Both derivatives were isolated from the mixture, **166** by crystallization and **165** by chromatography with high diastereoselectivity. All the *p*-methoxybenzyl groups were cleaved under different acidic conditions than previously used, to provide the pentahydroxy compounds (not shown). Phosphitylation of the remaining five hydroxy groups using reagent **167** followed by oxidation gave the *myo*-inositol hexakisphosphate derivatives **168** and **169**.



Scheme 20. Reaction conditions: a) DIBAL-H (2.7 equiv), CH_2Cl_2, −78 °C; b) PMB-Cl, NaH, DMF; c) PTSA (cat.), MeOH/CH_2Cl_2 (5:2), 5 min, reflux; d) **163** (3 equiv), mix with reagent **164**, 5-(4-fluorophenyl)-1*H*-tetrazole, CH_3CN, then, 0 °C, mCPBA; **165**/**166** 1:1, separated by chromatography or recrystallization, with yield based upon consumption of P^{III} reagent (**164**). e) TFA (2.5 %) in $CHCl_3$; f) P^{III} reagent **167** (10 equiv), 4,5-dicyanoimidazole (15 equiv), 0 °C, CH_3CN, then MCPBA (10 equiv).

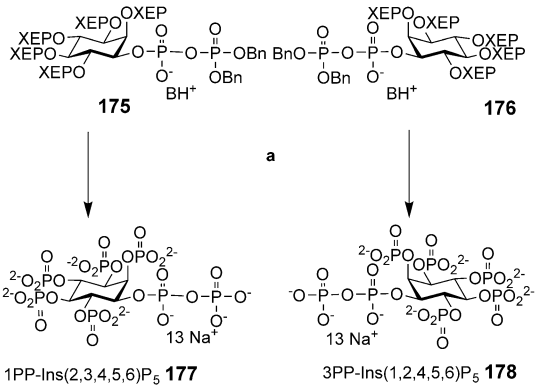


Scheme 21. Reaction conditions: pyrophosphate formation: a) DBU, then BSTFA in CH_3CN to give intermediate **171**; b) TFA in methanol then remove solvent; c) P^{III} reagent **173**, 0.45 M 1*H*-tetrazole in CH_3CN, then MCPBA. B = DBU.

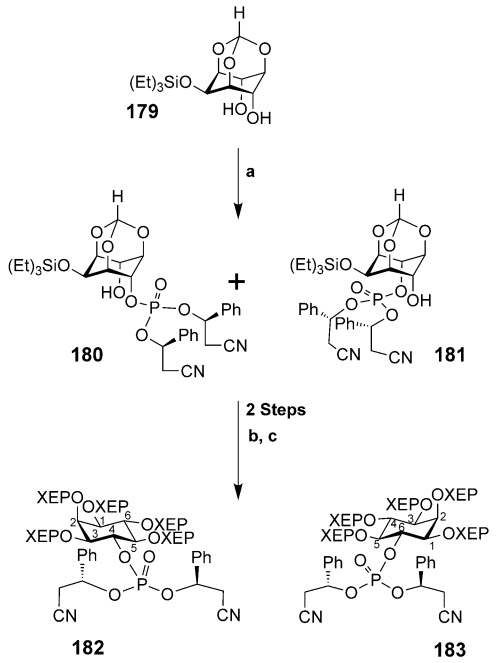
The pyrophosphate motif was prepared by base-induced elimination of one base-labile protecting group of the chiral phosphate triester **170** to eliminate cinnamonitrile, thereby exposing a negative charge, and masked using a trimethylsilyl (TMS) equivalent derived from *N*,*O*-bis(trimethylsilyl)trifluoroacetamide (BSTFA). A second elimination of cinnamonitrile followed by remasking as above gave **171** (Scheme 21). Intermediates such as **171** can also be generated from the elimination of other protecting groups followed by TMS masking in a similar manner. **171** Can be used for the synthesis of the pyrophosphate motif via other suitable derivatives. Methanolysis of the TMS group of **171** provided the monophosphate as the DBU salt **172**, and the phosphate monoester was phosphitylated using reagent **173** to give a P^{III}-P^{V} intermediate, which was oxidized to give **174** (general intermediate) and specifically provide crystalline products **175** and **176** from **168** and **169**, respectively. This is the first time a P^{III}-P^{V} inositol pyrophosphate derivative has been reported, and the P^{III}-P^{V} bond is discussed in detail in a publication from the nucleoside field.[226] The benzyl and *o*-xylylene groups of **175** and **176** were cleaved by hydro-

genolysis to unveil the phosphorylated derivatives 1D-diphosphoinositol 2,3,4,5,6-pentakisphosphate (**177**, 1PP-InsP_5) and 3D-diphosphoinositol 1,2,4,5,6-pentakisphosphate (**178**, 3PP-InsP_5) after crystallization (Scheme 22).

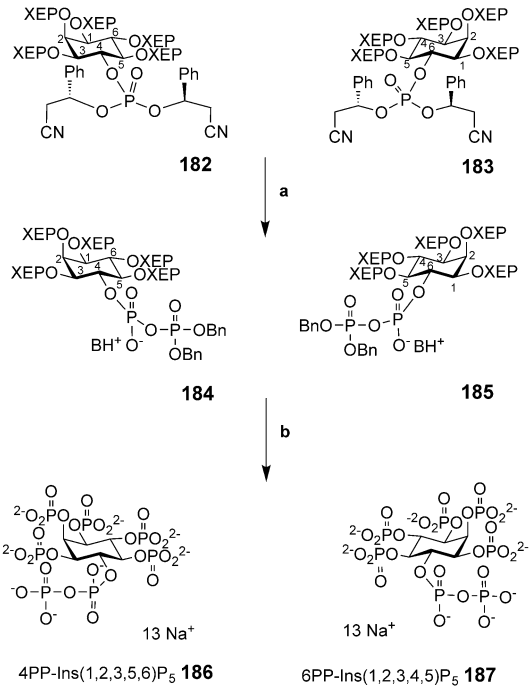
Similar methods were used to synthesize 4-PP-InsP_5 and 6-PP-InsP_5 (Schemes 23 and 24). The *meso*-silylated orthoester **179** was prepared in two steps from *myo*-inositol.[225] The 4- and 6-hydroxy groups were monophosphorylated (using the phosphitylating reagent **164**) and then oxidized to afford the chiral monophosphates at the 4- and 6-positions, **180** and **181**, respectively. The two diastereoisomers were then separated by chromatography and identified



Scheme 22. Reaction conditions: a) H_2, palladium black or PtO_2, 80 bar, *tert*-BuOH/H_2O 4:1→1:1, $NaHCO_3$, 3 h, recrystallization.



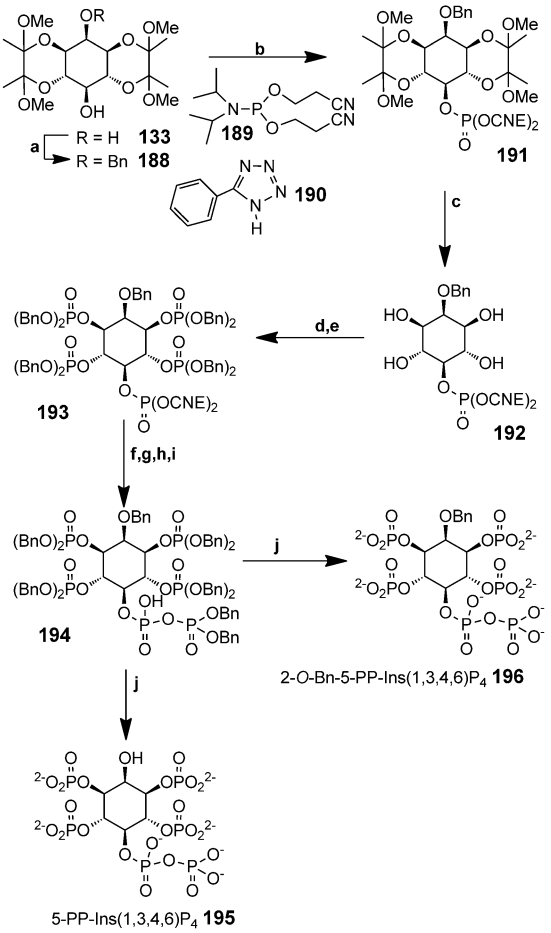
Scheme 23. Reaction conditions: a) Reagent **164**, (1 equiv), **179** (3 equiv), DCI CH_3CN, 0 °C, *tert*-BuOOH (5.5 M in nonane), 45% for **180**, 36% for **181**, and resolved by chromatography and recrystallization (high purity), yield based upon consumption of reagent **164**; b) PTSA (cat.), MeOH, 8 h, recrystallization; c) reagent **167**, DCI, 0 °C, CH_3CN, 0 °C, MCPBA, recrystallization.



Scheme 24. Reaction conditions: a) see Scheme 21; b) H_2, palladium black or PtO_2, 80 bar, *tert*-BuOH/H_2O 4:1→1:1, $NaHCO_3$, 3 h, recrystallization.

using X-ray diffraction. Acidic hydrolysis first removed the silicon protecting group and then the orthoformate, thus exposing the remaining five hydroxy groups, which were phosphitylated using reagent **167**. The intermediate was then oxidized to give the fully protected hexakisphosphates **182** and **183**. The pyrophosphate linkage was achieved as described in Scheme 21 and the benzyl and *o*-xylylene groups of compounds **184** and **185** were cleaved and the product subjected to anion-exchange chromatography to provide the final compounds **186** and **187** after seven steps.

A different chemical strategy was used to synthesize 5PP-InsP_4 (Scheme 25).[227] The suitably protected compound **133**, made in one step, was selectively benzylated at the 2-hydroxy position to give **188**. Phosphitylation with the P^{III} reagent **189** in the presence of **190** and oxidation gave the fully protected derivative **191**. Careful cleavage of the di-BDA acetal-protecting groups provided the tetrol **192**, which was phosphitylated with reagent **173**. Oxidation of the product gave **193**. Two compounds, 5PP-Ins(1,3,4,6)P_4 (**195**) and 2-*O*-Bn-5PP-Ins(1,3,4,6)P_4 (**196**), were provided from this single *meso* intermediate **194**. Compounds **195** and **196** were made by removing both cyanoethyl groups in the presence of DBU (in a similar method to that presented in Scheme 21) followed by temporary protection with a TMS group (by using a BSTFA protection strategy). A subsequent methanolysis and acidification provided the phosphate monoester. Phosphitylation of the phosphate monoester at the 5-position using reagent **173** gave a P^V-P^{III} phosphate-phosphite intermediate, oxidation of which then provided the pyrophosphate intermediate **194**, which was deprotected by hydrogenolysis to give 5PP-Ins-(1,3,4,6)P_4 (**195**). 2-*O*-Bn-5PP-Ins(1,3,4,6)P_4 (**196**) was prepared from crude **194** containing DBU, which inhibited the

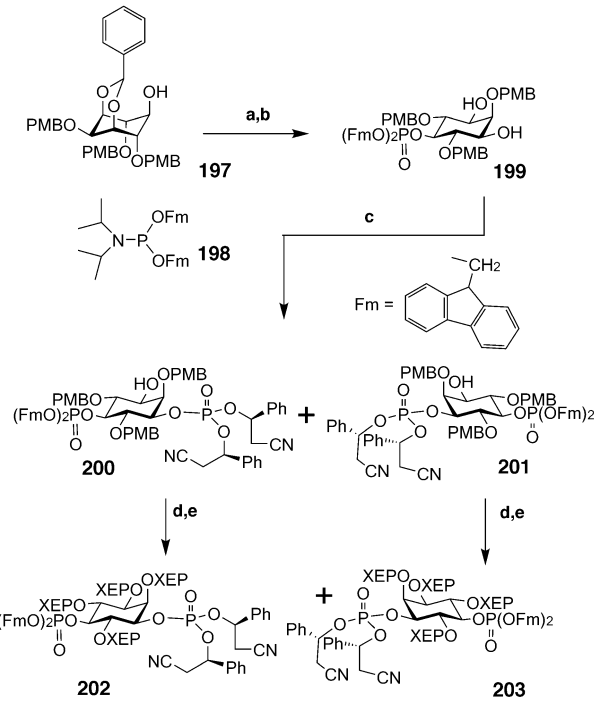


Scheme 25. Reaction conditions: a) BnBr, NaH, DMF; b) reagent **189**, 5-Ph-1*H*-tetrazole **190**, CH_2Cl_2, then MCPBA, −40 °C→RT; c) 90% TFA (aq), CH_2Cl_2 (1:1); d) reagent **173**, CH_2Cl_2, 5-Ph-1*H*-tetrazole; e) MCPBA, −40 °C→RT; f) DBU then BSTFA; g) TFA, MeOH; h) reagent **173**, CH_2Cl_2, 5-Ph-1*H*-tetrazole **190**; i) MCPBA, −40 °C→RT; j) $Pd(OH)_2$, H_2, *tert*-BuOH, H_2O (**196** was prepared in the presence of DBU to inhibit *O*-benzyl cleavage).

hydrogenolysis of the 2-*O*-benzyl group. All final compounds were purified by ion-exchange chromatography.

12.4. The First Synthesis of D-1,5- and D-3,5-Diphosphoinositol 1,2,4,6-Tetrakisphosphate, $InsP_8$

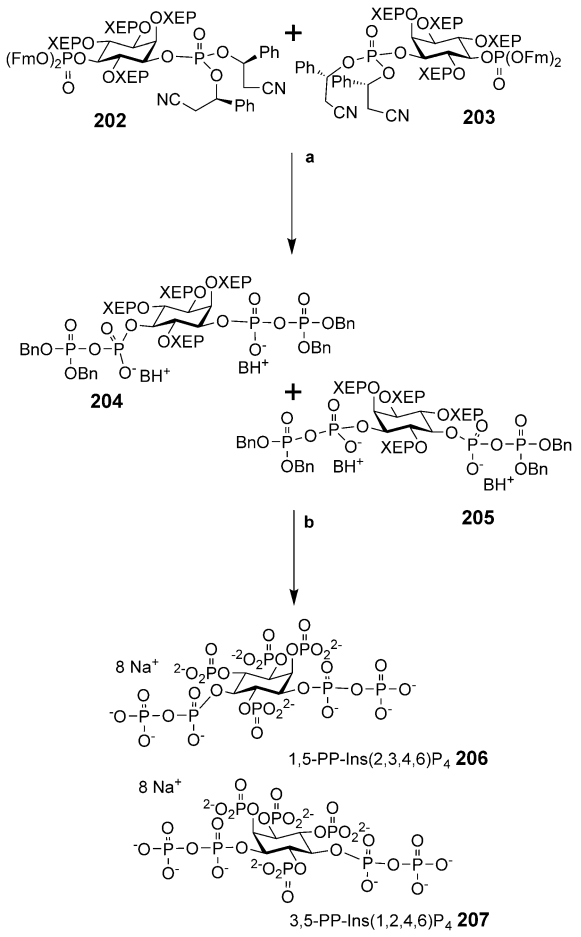
The benzylidene derivative (Scheme 26, **197**) was prepared in three steps from *myo*-inositol. The 5-hydroxy group (shown in an axial orientation) was phosphitylated with the bis(fluorenylmethyl) phosphoamidite (**198**) and the intermediate was oxidized. The benzylidene acetal was cleaved under acidic conditions, thereby resulting in a *meso*-1,3-diol **199** that was desymmetrized with the C_2-symmetric P^{III} reagent **164**. A subsequent oxidation gave a mixture of 1- and 3- phosphorylated derivatives **200** and **201**, which were isolated in high diastereoisomeric purity. Acidic hydrolysis of the *p*-methoxybenzyl groups gave the corresponding tetraols, which were phosphitylated with reagent **167** and oxidized to provide the fully protected hexakisphosphates **202** and **203**.



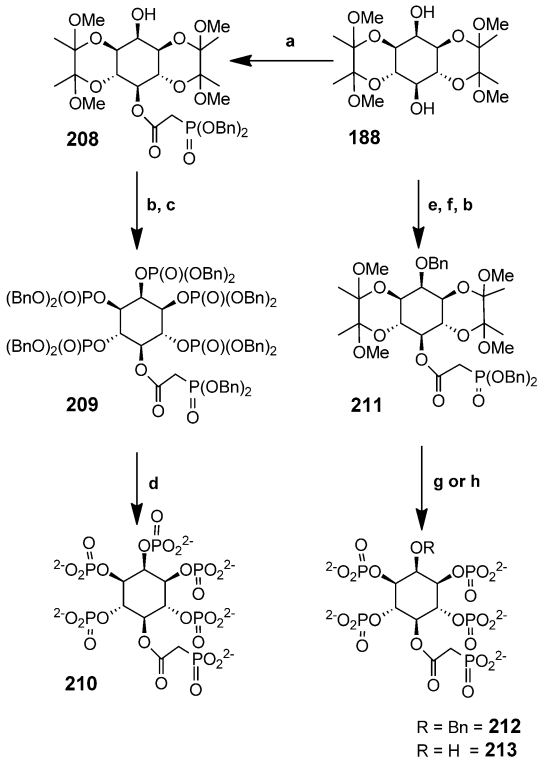
Scheme 26. Reaction conditions: a) reagent **198**, *tert*-BuOOH, 1 h, b) PTSA, CH_2Cl_2, MeOH, Δ, 10 min; c) reagent **164**, 1*H*-tetrazole, CH_3CN, then MCPBA; d) 5% TFA, $CHCl_3$, 4 h, recrystallization; e) reagent **167**, DCI, CH_3CN, then MCPBA.

The absolute configuration was not established at this stage, but the diastereoisomeric purity of these compounds was high. The bis(fluorenylmethyl) and bis(chiral) auxiliary phosphate protecting groups were removed under different basic conditions and replaced with TMS groups, as previously described in Scheme 21. Methanolysis cleaved the TMS groups and monoprotonation of the phosphate monoesters gave suitable phosphitylation precursors to form the bis(diphospho) derivative at the 1- and 5-positions. Thus, phosphitylation of the bis(1,5-phosphate monoesters) with reagent **173** and oxidation afforded the 1,5- and 3,5-bis(diphosphates) **204** and **205** (Scheme 27). Hydrogenolysis provided the enantiomeric compounds **206** and **207** (although configurationally unassigned) containing a 10% impurity of $InsP_7$.[228] The synthesis of compounds **206** and **207** was the second method for the formation of a bis(pyrophosphate). Previously, the synthesis of *myo*-inositol 2,5-PP-1,3,4,6-tetrakisphosphate had been described.[229] However, there was no indication of the purity of the final compound, critical for establishing the usefulness of the method for the synthesis of other inositol pyrophosphate derivatives. Furthermore, *myo*-inositol 2,5-PP-1,3,4,6-tetrakisphosphate was only used as a standard to analyze other higher phosphorylated molecules and seemed impure by HPLC with metal dye detection.

In the first practical synthesis of an $InsP_8$ (Schemes 26 and 27), a pair of diphosphorylated *myo*-inositol enantiomers, namely diphosphoinositol tetrakisphosphates 1,5-PP-Ins-(2,3,4,6)P_4 (natural enantiomer) and 3,5-PP-Ins(1,2,4,6)P_4 (unnatural enantiomer), was synthesized.[228] The absolute configuration was proven by X-ray crystallography of the



Scheme 27. Reaction conditions: a) see Scheme 21 for reaction conditions; b) Pd/C, H_2 (180 bar), *tert*BuOH, H_2O, $NaHCO_3$.



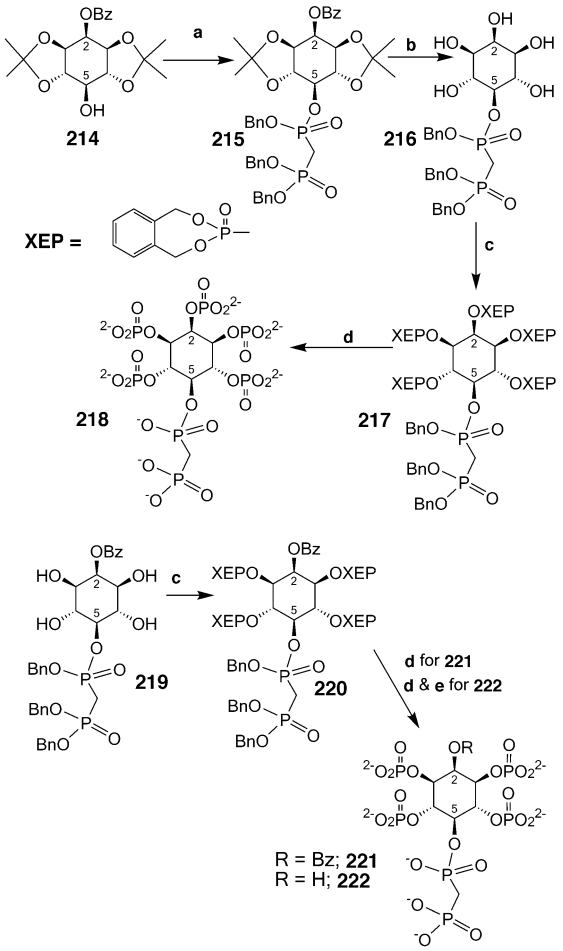
Scheme 28. Reaction conditions: a) $(BnO)_2P(O)CH_2CO_2H$, DCC, CH_2Cl_2, 73%; b) TFA, H_2O, 5 min, up to 62%; c) reagent **173**, 5-Ph-1*H*-tetrazole **190**, CH_2Cl_2, then 3-chloroperoxybenzoic acid, CH_2Cl_2, up to 93%; d) H_2, palladium hydroxide/carbon, MeOH, H_2O, 50 psi, 92%; e) BnBr, NaH, DMF, 55%; f) $(BnO)_2P(O)CH_2CO_2H$, EDAC, DMAP, CH_2Cl_2, 95%; g) H_2, palladium hydroxide/carbon, MeOH, TEAB (aq), 79%; h) H_2, $Pd(OH)_2$/C, MeOH, H_2O, 50 psi, 79%.

kinase domain of human diphosphoinositol pentakisphosphate kinase 2 (PPIP5K2), with each enantiomer separately soaked in the protein.

12.5. Synthesis of Diphosphoinositol Analogues

The first diphosphoinositol analogues to be designed had a phosphonoacetate group instead of the diphosphoinositol linkage at position 5, with the other hydroxy positions decorated with phosphate monoesters.[230] Two other analogues were synthesized, either benzylated at position 2 or left unmodified, both with a phosphonoacetate at the 5-position. Diol **133** was easily prepared from *myo*-inositol in large amounts, and regioselective acylation at the 5-position gave the protected phosphonoacetate derivative **208** (Scheme 28). The butane diacetal (BDA) groups were then removed under acidic conditions and the hydroxy groups phosphitylated with reagent **173**. Oxidation of the products gave the fully protected compound **209**. All benzyl groups were removed in one step to give the target compound 5-PA-$InsP_5$ (**210**) in excellent yield. Diol **133** was a key starting intermediate for the synthesis of two further analogues. Selective benzylation of the axial 2-hydroxy group and esterification of the hydroxy group at the 5-position then gave phosphonoacetate **211**. Acidic hydrolysis for a short period of time exposed the remaining hydroxy groups, which were then phosphorylated to provide the fully protected compound (not shown). Hydrogenolysis for a short period, importantly in the presence of triethylammonium bicarbonate (TEAB), removed the benzyl phosphate protecting groups to give compound **212**. Longer hydrogenolysis under pressure in the absence of TEAB removed the benzyl group at position 2 to provide compound **213**. These compounds have fewer charges than the pyrophosphates and are nonhydrolyzable, even though they possess an ester group between the inositol ring and the phosphonate group and were good surrogates for the natural product. Indeed, they were successfully cocrystallized with the kinase PPIP5K2. The binding of 5-PP-$InsP_5$ to the kinase domain of PPIP5K2 is mimicked by 5-PA-$InsP_5$, and analogues were phosphorylated by the enzyme. PA-InsPs are thus promising candidates for further studies into the biology of PP-InsPs[230] and are already finding biological application.[231]

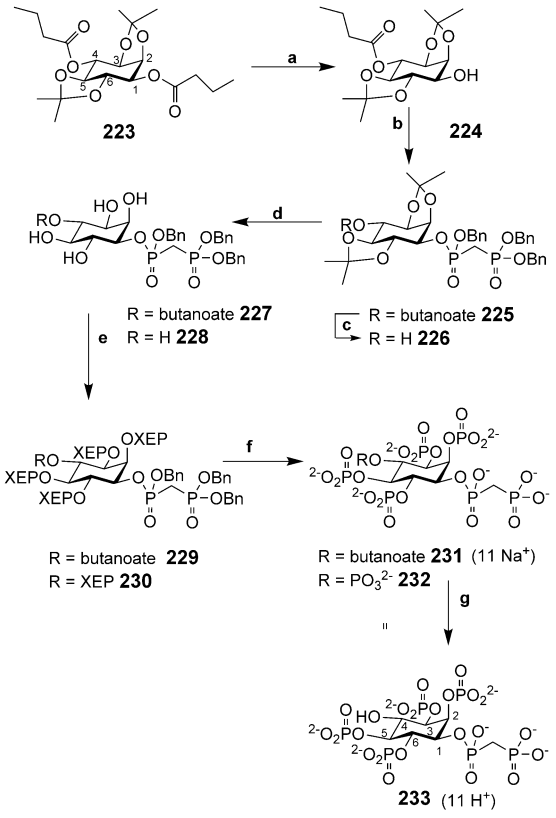
A second type of diphosphoinositol analogue, a derivative with a methylene bisphosphonate derivative at the 5-position and the remaining five hydroxy groups substituted with phosphate monoesters, was synthesized from an isopropylidene derivative (**214**, Scheme 29).[232]



Scheme 29. Reaction conditions: a) benzyl{[bis(benzyloxy)phosphoryl]methyl}phosphonochloridate, KHMDS, THF, −78 °C→RT, overnight; b) sodium methoxide, MeOH, RT, overnight, then *p*-toluenesulfonic acid, H_2O, $(CH_3)_2CO$, overnight; c) reagent **167**, MeCN, 1*H*-tetrazole, 0 °C→RT, 1.5 days, then 3-chloroperoxybenzoic acid, MeCN, 0 °C→RT, 3 h; d) H_2, palladium black, $NaHCO_3$, *t*BuOH/H_2O, RT, overnight; e) NH_3 (aq) conc, 4 days, then H^+-Dowex.

The 5-hydroxy group of the isopropylidene derivative **214** was pyrophosphonylated to give **215**, and the remaining hydroxy groups were unveiled by debenzoylation. Acidic hydrolysis of the two *trans*-isopropylidene groups then gave **216**. Phosphitylation of the pentahydroxy derivative with reagent **167** was followed by oxidation to the pentakisphosphate **217**. Cleavage of all the benzyl groups by hydrogenolysis gave the desired derivative **218** in good yield. Compound **215** was subjected to acidic hydrolysis to give **219**, which was subjected to phosphitylation using reagent **167** followed by oxidation to give **220**. Hydrogenolysis removed all the benzyl and *o*-xylylene groups, and the target compounds **221** and **222** were obtained after deprotection. The synthesis of analogues of 5PP-Ins(1,2,3,4,6)P_5, such as compound **218**, is an important step in elucidating the mechanism of its natural parent pyrophosphate, which is associated with cellular functions such as repair of damaged DNA.[233] Critically, **218** exhibited only slightly different pK_a values to 5PP-Ins(1,2,3,4,6)P_5 and, importantly, was resistant to hydrolysis.[232] 5PP-Ins(1,2,3,4,6)P_5 binds the PH domain of Akt or protein kinase Bα (PKBα) and stabilizes the complex, thereby preventing its phosphorylation at threonine 308 by 3-phosphoinositide-dependent protein kinase (PDK1), as monitored by a phosphospecific antibody. Potent inhibition of PKB phosphorylation was demonstrated.[232] If the 2-phosphate group was removed (**221** and **222**), there was improved inhibition of PKBα, and the presence of the aromatic moiety in **221** increased inhibition significantly. The methylenephosphonate moiety provides a suitable substitute for the parent pyrophosphate derivative.[232] **218** was also used to compare the relative affinities of $InsP_6$ and 5PP-$InsP_5$ for CK2 (casein kinase II) phosphorylation.[234]

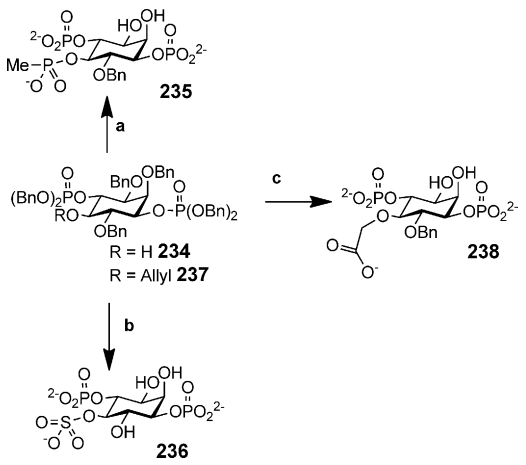
Several analogues possessing a methylene bisphosphonate at the 1D-position with phosphate groups at the 2-, 3-, 5-, and 6-positions and a variety of substituents at the 4-position have been reported (Scheme 30).[235] The 1D-butanoate ester of enantiomerically pure **223** (commercially available) was carefully removed to unveil the 1-hydroxy group (**224**), phosphonylation of which gave the methylene bisphosphonate **225**.[232] After phosphonylation, the butanoate ester at position 4 either remained intact or was removed using base to give **226**. The isopropylidene acetals of compounds **225** and **226** were hydrolyzed under acidic conditions to give tetraol



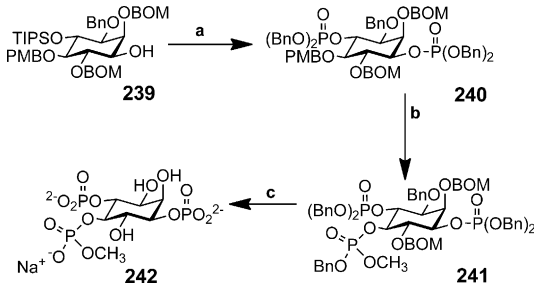
Scheme 30. Reagents and conditions: a) DIPE, MeOH, 14 h 36 °C; b) bis[benzyloxyphosphoryloxy)methyl]phosphoryl chloride, DBU, 1*H*-tetrazole, CH_2Cl_2, 0 °C→RT, overnight; c) DIBAL-H, CH_2Cl_2, −78 °C, 6 min; d) TFA/MeOH/CH_2Cl_2 (3:1:6), 0 °C, 3 h; e) reagent **167**, 5-Ph-1*H*-tetrazole **190**, CH_2Cl_2, 0 °C→RT, 18 h, then MCPBA oxidation, −78 °C→RT, 3 h; f) H_2, palladium black, $NaHCO_3$, H_2O-*t*BuOH (7:40), RT, overnight; g) NH_3 (aq) conc., RT, 4 days, then Dowex-H^+.

227 and pentaol **228**, which were phosphorylated using reagent **167**, as described previously, to give **229** and **230**, respectively. Deprotection by hydrogenolysis gave **231** and **232** and further deprotection of the butanoate ester of **231** with base gave the target methylene bisphosphonate tetrakisphosphate **233**.

Similarly to 5PCP-InsP_5 (**218**), 1PCP-InsP_5 was also evaluated for PKBα inhibition.[235] **233** is a potent inhibitor of the phosphorylation of PKBα by PDK1 and, similarly, **220** and **221** are around threefold less potent. **218**, **221**, and **222** were also tested against the PP-InsP-metabolizing enzyme, human diphosphoinositol polyphosphate phosphohydrolase-1 (hDIPP1).[236] Using Ap_5A (diadenosine pentakisphosphate) as a substrate in the presence of hDIPP1, **218** and 5PP-InsP_5 showed similar competitive inhibition. However, **232** has a 136-fold lower K_i value but that of **218** is approximately twofold lower compared to its natural parent 1PP-InsP_5 (**177**) and in line with the substrate preference for 1PP-InsP_5.[237] Removing the 4-phosphate to give **233** provides a further fourfold enhancement of inhibition compared to **232**, thus demonstrating that removal of a negative charge increases the inhibition of hDIPP1. **231** has similar inhibition properties to **233** in the low nanomolar region and may be a useful candidate to produce a lipophilic analogue for in vivo studies, in a similar way as **253**.



Scheme 31. Reagents and conditions: a) bis[6-trifluoromethyl)benzotriazol-1-yl)]methyl phosphonate, pyridine, then BnOH, deprotection using palladium black, H_2, H_2O, $NaHCO_3$; b) SO_3, pyridine; then *tert*-butanol, H_2O, $NaHCO_3$; c) $RuCl_3.H_2O$, CCl_4, $NaIO_4$, MeCN, H_2O; deprotection for (b) and (c) as for (a).



Scheme 32. Reagents and conditions: a) TBAF in THF; then reagent **173**, CH_2Cl_2, 1*H*-tetrazole, then MCPBA; b) ceric ammonium nitrate, MeCN, H_2O; then (MeO)(BnO)P*N*iPr_2, CH_2Cl_2, 1*H*-tetrazole; then MCPBA; c) palladium black, H_2, *tert*-butanol, H_2O, $NaHCO_3$.

12.6. Replacement of the 5-Phosphate Group of Ins(1,4,5)P_3 with Bioisosteres

Animal cells generally express mixtures of the three subtypes of inositol 1,4,5-trisphosphate receptor. Recent data have provided the first structure–activity analyses of key Ins(1,4,5)P_3 analogues by using homogeneous populations of each mammalian Ins(1,4,5)P_3R subtype.[238] Other *myo*-inositol phosphate analogues have been synthesized that may provide new mechanistic insights and structure–activity relationship information for the inositol trisphosphate receptor. Inositol 1,4,5-trisphosphate analogues in which the 5-phosphate group was replaced with less-acidic bioisosteres have been synthesized.[239] The chiral protected 1,4-bisphosphate **234** (Scheme 31) was prepared by using a nine-step procedure that exposes the 5-hydroxy group for the introduction of a bioisostere to replace the 5-phosphate. Two compounds were prepared from the versatile 1,4-bisphosphate intermediate **234**: one having a methylphosphonate and one a sulfate group at the 5-position. The methylphosphonate group was incorporated at the 5-position of the inositol ring by using bis[6-(trifluoromethyl)benzotriazol-1-yl]methylphosphonate. Hydrogenolysis in the presence of a catalyst then removed all the benzyl groups in excellent yield to give **235**. The sulfate group was introduced at the 5-hydroxy position by using sulfur trioxide in pyridine. Hydrogenolysis removed all the benzyl groups to give the 5-modified sulfate product **236**. The 5-carboxylate group was generated by oxidative cleavage of the 5-*O*-allyl derivative **237** and the remaining benzyl groups were deprotected by hydrogenolysis to give **238**. For the final modified compound, a slightly different intermediate (**239** in Scheme 32) was used. Desilylation, then phosphitylation and oxidation provided 1,4-bisphosphorylated derivative **240**. Oxidative removal of the *p*-methoxybenzyl group followed by phosphitylation and oxidation provided fully protected derivative **241**. The protected 5-phosphate group contains one OBn and one OMe protecting group, and the benzyl groups were cleaved by hydrogenolysis to yield **242**. Compounds **235** and **242** were found to be weak Ins(1,4,5)P_3 receptor antagonists in the low millimolar range.

12.7. Inositol Phosphate Ligands that Uncovered the Capture Site of PPIP5K2

In addition to the substrate analogues designed for the kinase PPIP5K2,[230] a number of inositol phosphate analogues (Figure 12) modified with aromatic substituents at position 2 of InsP_5, such as **159**, were found to stimulate significantly the ATPase activity of the kinase PPIP5K2, although 2-aminoethyl-Ins(1,3,4,5,6)P_5 (**243**) had no effect and the 2-*O*-butanoate derivative (**244**) was weak.[227] Surprisingly, however, compounds modified at both the 2- and 5-

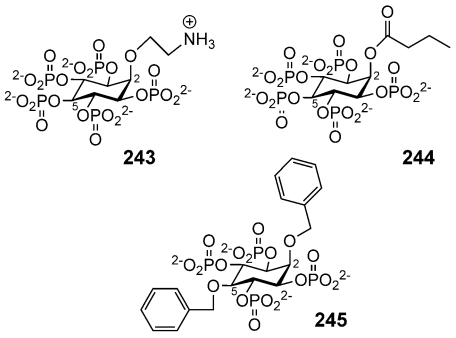
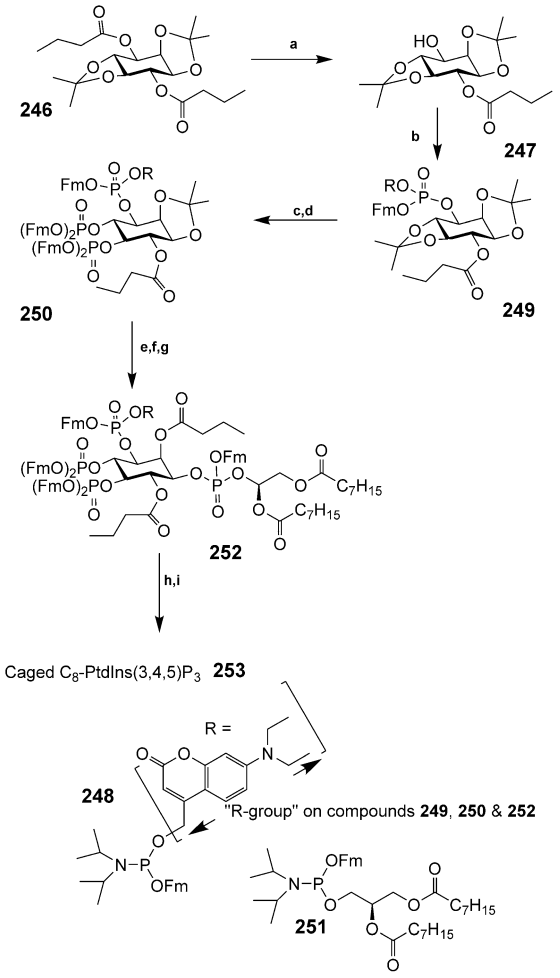


Figure 12. Inositol phosphate ligands evaluated at PPIP5K2; **245** is the most potent ligand.

positions showed significantly enhanced activity, and it was particularly unexpected that 2-*O*-Bn-5-PA-InsP_4 (**212**) should be a more effective activator of ATPase activity than the two natural substrates InsP_6 and the pyrophosphate PP-InsP_5. 2,5-Di-*O*-benzyl-*myo*-inositol 1,3,4,6-tetrakisphosphate (**245**) was even more effective.

Earlier studies on the phosphonoacetate derivative 5-PA-InsP_5 (**210**) soaked with PPIP5K2 indicated unresolved structural information. When crystals were resoaked at a higher concentration, a second ligand binding site was detected, located near to the entrance of the catalytic pocket and only one of the two sites could be occupied at any time. Soaking PPIP5K2 in the presence of 2-*O*-Bn-5-PA-InsP_4 (**212**) or 2,5-di-*O*-Bn-*myo*-inositol-1,3,4,6-tetrakisphosphate (**245**) resulted in both compounds being exclusively located in the second ligand-binding site (named the substrate capture site). The aromatic nature of the functional group, especially at position 2, was critical in revealing the second site. This second site facilitates substrate capture prior to transfer into the catalytic pocket and reveals a so-called "catch and pass" reaction mechanism, the first to be observed in a small molecule kinase. This second binding site offers new opportunities for targeted drug design and **245**, particularly with its reduced phosphate quotient, offers an interesting initial lead for further optimization.



Scheme 33. Reagents and conditions: a) Et*i*Pr$_2$N/MeOH 1:4, 36 °C, 11 h, 91%; b) reagent **248**, 4,5-dicyanoimidazole, CH_2Cl_2, 0 °C→RT, 20 min, then AcOOH, −18 °C→RT, 1 h, 70%; c) formic acid/CH_2Cl_2 7:3, RT, 3.5 h; d) reagent **198**, 4,5-dicyanoimidazole, CH_2Cl_2/MeCN 4:1, RT, 1 h, then AcOOH, −18 °C→RT, 1.5 h, 48% (over 2 steps); e) formic acid/CH_2Cl_2 95:5, 4.5 h; f) 1,1,1-trimethoxybutane, CH_2Cl_2, jandajel pyridinium trifluoroacetate, RT, 23 h, Dowex 50WX8, H^+, H^+-Dowex 50WX8, 1 h; g) reagent **251** 4,5-dicyanoimidazole, CH_2Cl_2, RT, 30 min, then AcOOH, −18 °C→RT, 30 min, 46% (over 3 steps); h) CH_2Cl_2, piperidine, RT, 1 h; i) bromomethyl acetate, Et*i*Pr$_2$N, MeCN, RT, 10 h, 16% (over 2 steps).

12.8. Photoactivated myo*-Inositol Lipid Derivatives*

Although Section 12 primarily focuses on soluble *myo*-inositol phosphates, a few examples of recent studies on *myo*-inositol lipid derivatives are noteworthy. A photoactivatable and membrane-permeable phospholipid derivative of phosphatidylinositol 3,4,5-trisphosphate PtdIns(3,4,5)P_3 (**253**) has been designed.[240] The C_8 lipid derivative **253** contains a photolabile 7-diethylamino-4-methylenehydroxycoumarin moiety attached at the 3-phosphate of C_8-PtdIns(3,4,5)P_3. Butanoate esters are located on the 2- and 6-hydroxy groups, and acetoxymethyl groups block the remaining negatively charged phosphate groups. The synthesis of **253** (Scheme 33) is a useful addition to the biological armoury, since it is the first membrane-permeable caged fluorescent phosphoinositol lipid. The monobutanoate **247** was prepared as described previously from **246**.[235] Phosphitylation using **248** followed by oxidation gave **249**; selective removal of the *trans*-isopropylidene under mild acidic conditions and further phosphitylation and oxidation with reagent **198** gave derivative **250**. Acidic hydrolysis of the *cis*-isopropylidene exposed the 1,2-diol, which was then reprotected as an orthoester; partial hydrolysis then provided the 2-butanoate derivative. Phosphitylation at the 1-position with reagent **251** followed by oxidation provided the fully protected precursor **252**, which could be made into the target lipophilic analogue. Selective removal of the 9*H*-fluorenylmethyl groups in the presence of piperidine exposed the phosphate monoesters, which were then reprotected as acetoxymethyl esters to give **253** albeit in low yield.

The lipophilic compound crosses the cell membrane, thus allowing enzyme hydrolysis of the esters whilst the molecule is unmasked to reveal its hydroxy groups and phosphate units (Figure 13). The resulting product **254** remains unmetabolized. The uncaging of **254** by photolysis reveals di-C_8-PtdIns-(3,4,5)P_3, with which cellular events such as PH-domain translocation and the induction of membrane ruffling can be observed under a suitable microscope.

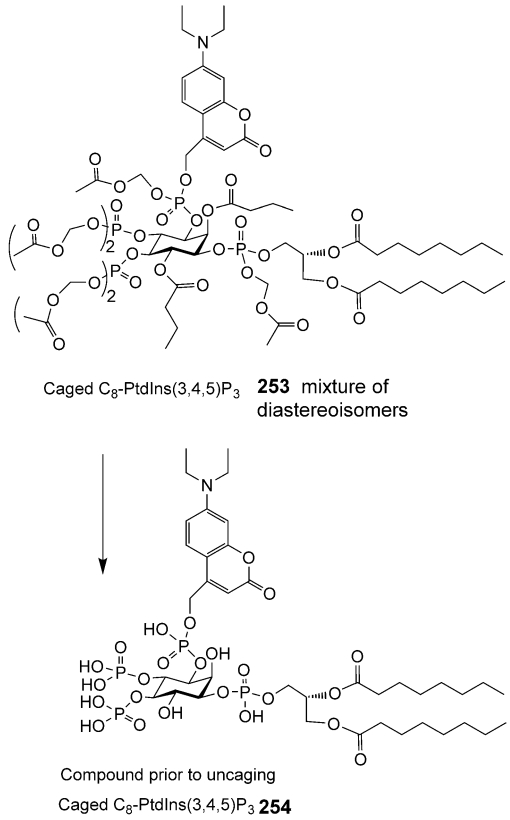
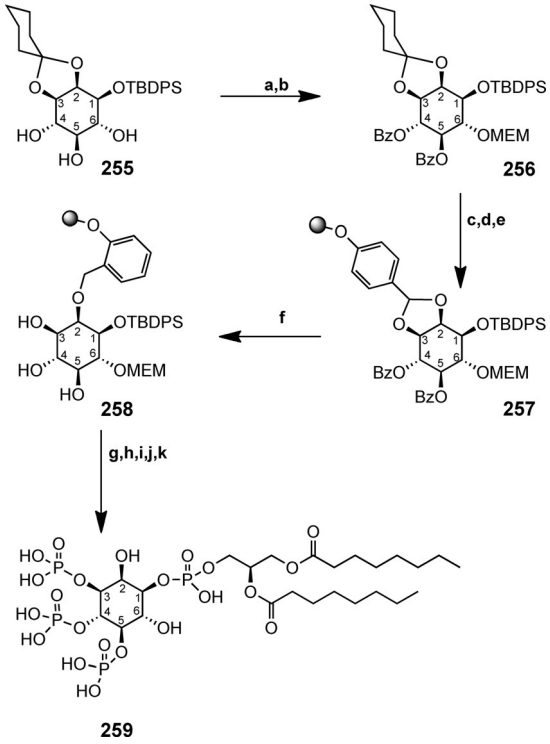


Figure 13. Caged C_8-PtdIns(3,4,5)P_3 (**253**) protected with acetoxymethyl groups that are enzymatically hydrolyzed to give a photolabile derivative (**254**) prior to uncaging.

12.9. Solid-Phase Synthesis of myo*-Inositol C_8-Phospholipids*

A new solid-phase synthesis strategy for the production of inositol phospholipid analogues has been developed over the last few years.[241] This had not previously been achieved. A suitable linker was found to be the benzylidene acetal derivative (using the Wang alcohol resin),[242] which is easily introduced and removed from the inositol ring and cleaved from the solid support, thereby avoiding tedious purification steps. A suitable inositol precursor such as **255** was also sought to be resolved and blocked with protective groups that could be introduced and removed as required in a strategy loosely based upon the protecting groups previously employed elsewhere.[243] The protecting groups employed were the acetal at the 2,3-positions (**256**; cyclohexylidene was then replaced with a benzylidene derivative **257** on the Wang resin) and TBDPS (*tert*-butyldiphenylsilyl) was located at the 1-position. The less-toxic MEM (methoxyethoxymethyl) and benzoyl protecting groups were also used at positions 4, 5, and 6 in **257** to synthesize phosphatidylinositol analogues containing a short C_8 chain or an aminopropyl derivative that made them water soluble. Furthermore, regioselective ring opening of the benzylidene using DIBAL-H exposes the 3-hydroxy group of **258** in readiness for phosphorylation at this position. The synthesis of the C_8 phospholipid **259** (Scheme 34) is discussed to illustrate the use of solid-support methods for the synthesis of inositol lipids. These methods can also be adapted for the synthesis of water-soluble inositol phosphates and other derivatives.



Scheme 34. Reagents and conditions: a) BzCl in $CHCl_3$, Pyr. −40 °C, 1 h; b) MEM-Cl, Hünigs base, $CHCl_3$, Δ, 48 h; c) 65 % HCOOH, in MeOH, RT, 48 h; d) 4-(dimethoxymethyl)phenol, CH_2Cl_2, PPTS, RT, 24 h, then 40 °C for 4 h; e) Wang alcohol resin, DIAD, triphenylphosphine, THF, RT, 48 h; f) DIBAL-H, CH_2Cl_2, −78 °C→−30 °C, 3 h; g) reagent **173**, DCI, CH_2Cl_2, CH_3CN, 24 h, then peracetic acid, −30 °C→RT, 1 h; h) TASF in DMF, 32 h; i) glycerol diester phosphoramidite, DCI, CH_2Cl_2, MeCN, 24 h, then peracetic acid −30 °C→RT, 1 h; j) DDQ, CH_2Cl_2, H_2O; k) TMSBr, RT, 1 h.

The chiral derivative **255** (Scheme 34) was used as a starting material to deliver the required intermediate, with the TBDMS group located at the 1-position and the cyclohexylidene at positions 2 and 3 of the D-enantiomer. Selective benzoylation followed by MEM protection then provided **256**. The cyclohexylidene acetal was removed and replaced with a benzylidene acetal attached to the Wang resin in a three-step process to provide compound **257**. Cleavage of the benzylidene derivatives and benzoyl groups with DIBAL-H gave the 2-*O*-benzyl intermediate **258** and exposed the 3-hydroxy group for further phosphorylation. Phosphorylation

of the hydroxy groups at the 3-, 4-, and 5-positions, and deprotection of the silicon protecting group allowed the introduction of the lipid derivative at the 1-hydroxy group. The 2-benzylated compounds were removed from the resin using DDQ to provide the pure derivatives. Full deprotection of the individual compounds using TMSBr provided the final compound **259** in quantitative yield (Scheme 34). This strategy has the advantage of preparing a number of water-soluble di-C_8-phospholipid derivatives in relatively few steps without the need for tedious purification, which can be the most time-consuming process in a synthesis. The intermediates are also stable when stored, and further compounds can be synthesized by producing large amounts of intermediate on a solid phase, thus making these methods versatile and time-saving.

12.10. Plasmanylinositols

There are few molecular analyses of the composition of inositol phospholipids across species. Mammalian inositol phospholipids (**260** in Figure 14) mainly consist of the inositol

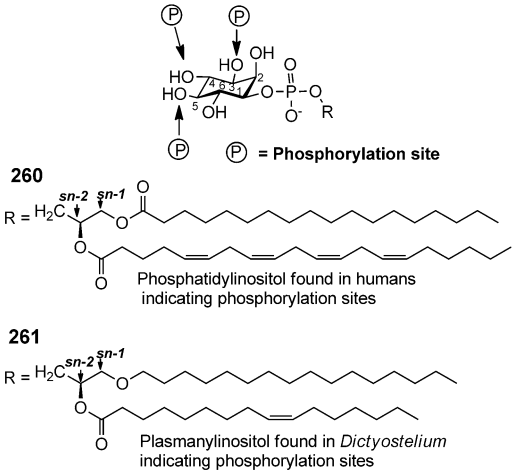


Figure 14. The structure of a mammalian phospholipid (**260**) compared to the newly discovered plasmanylinositol (**261**) found in *Dictyostelium*.

ring and a phosphodiester motif with a diacylglycerol backbone for phosphatidylinositol. Phosphatidylinositol can be further decorated with up to three phosphate groups located at the 3-, 4-, and 5-positions. The phosphodiester linkage located at position 1 of inositol, is bonded to a molecule of glycerol containing a C_{18} octadecanoyl ester at the *sn*-1 position on glycerol and a $C_{20:4}$ arachidonic ester at the *sn*-2 position on the glycerol backbone. Unusual *myo*-inositol lipids such as **261** have recently been identified in the slime mold *Dictyostelium discoideum*.[244] They contain an ether linkage at the *sn*-1 position and an unsaturated ester (11-*Z*-octadecenoyl ester) at the *sn*-2 position of the glycerol phosphodiester structure, and are designated "plasmanylinositols". These compounds respond to cell stimuli through chemoattractants and their levels are controlled by kinases and phosphatases such as PI-3-kinase and PTEN. Establishing their functions and potential wider distribution will be a future challenge.

12.11. Biphenyl Phosphate Derivatives

myo-Inositol 1,4,5-trisphosphate (Ins(1,4,5)P_3) stimulates Ca^{2+} release from intracellular stores via the Ins(1,4,5)P_3 receptor. This can also be achieved by various regioisomeric inositol polyphosphates and their analogues, including those based on structures without a *myo*-inositol core that bind in a variety of modes. Recent data have provided structure–activity analyses of homologous populations of all mammalian receptor subtypes.[238] Additionally, there has been much interest in synthetic glyconucleotides based upon the naturally occurring adenophostins, where the pharmacophore presented to the receptor is comprised of a combination of a phosphorylated carbohydrate and a pendant group that can be a nucleotide or other motif.[245] Recent data have also focussed upon receptor subtypes in concert with adenophostin analogues.[246]

Designing simple synthetic modulators of the Ins(1,4,5)P_3 receptor not based upon inositol that would mimic a *myo*-inositol polyphosphate has always been a challenge. Since the publication of the first antagonist lead, biphenyl 2,3′,4,5′,6-pentakisphosphate BiPh(2,3′,4,5′,6)P_5, (**262**; Figure 15),[247] which also exhibits other biological activities,[248] similar compounds have been reported that explore the growing potential of benzene polyphosphates in cell-signaling applications. Thus, a noncarbohydrate/inositol phosphate Ins(1,4,5)P_3 receptor agonist, based upon a biphenyl structure and decorated with phosphate groups—biphenyl 3,3′,4,4′,5,5′-hexakisphosphate (BiPh(3,3′,4,4′,5,5′)P_6, **263**)—has been syn-

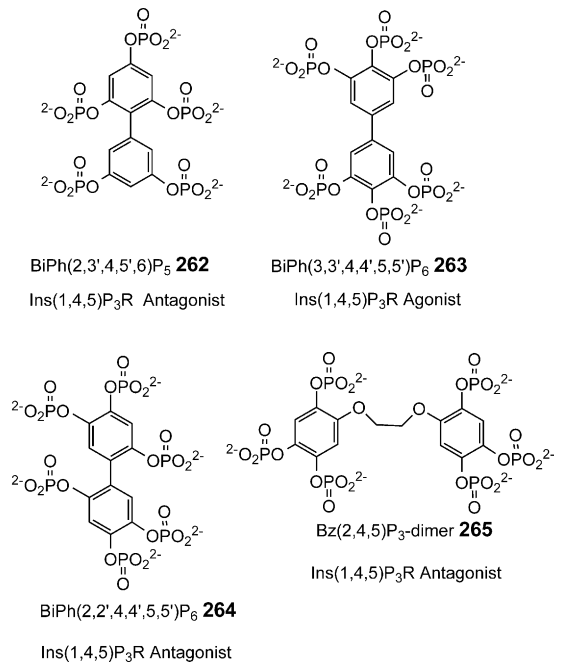


Figure 15. The structures of benzene polyphosphates showing agonist behavior and antagonist behavior at the Ins(1,4,5)P_3 receptor.

thesized that surprisingly stimulates the release of Ca^{2+} ions.[249] Interestingly, by relocating a phosphate group at the 3- and 3′-positions on each ring back one carbon atom, the resulting compound BiPh(2,2′,4,4′,5,5′)P_6 (**264**) then acts as a full antagonist. Increasing the length of the connection between the two polyphosphorylated head groups of **264** by two carbon and two oxygen atoms to give **265** results in retention of the antagonist effect, but with a slightly less potency than **264**.[249] Although such compounds are clearly not membrane permeant, and are thus limited as investigative cellular tools, they do offer a radically new structural model and, with such surprising activities, may offer, through optimization, a new and simple approach to explore the design of badly needed selective receptor modulators. More understanding of their mode of action is required.

Additionally, such benzene polyphosphates have been shown to be good mimics at *myo*-inositol phospholipid headgroup binding sites. Moving on from the initial report,[250] a recent cocrystal structure reported with the lipid phosphatase SHIP2 may offer clues for drug design at lipid phosphatases of potential therapeutic interest.[251]

13. Summary and Outlook

The field of signal transduction, one of the most active in biology, provides rich opportunities for interrogation through chemistry. *myo*-Ins(1,4,5)P_3 has enjoyed pre-eminent status in Ca^{2+} signaling for many years and signals in virtually all mammalian cells through the Ins(1,4,5)P_3R ion channel. This ubiquitous system regulates processes ranging from transcription and cell division to memory and learning. There are now also the emerging complementary nucleotide messengers nicotinic acid adenine dinucleotide 2′-phosphate (NAADP), cyclic adenosine 5′-diphosphate ribose (cADPR), and adenosine 5′-diphosphate ribose (ADPR). Together, they regulate the majority of cellular functions, often with spatial and temporal coordination. Although Ins(1,4,5)P_3, cADPR, and NAADP act through mobilization of intracellular Ca^{2+} ions, many fundamental aspects of the newer signaling pathways are still unknown.

The pathways based upon *myo*-inositol, including phospholipids and soluble inositol polyphosphates, have now enjoyed more than 30 years of interrogation and development. Ins(1,4,5)P_3 and other inositol phosphates and phosphoinositides are regulated by specific kinases and phosphatases; several signaling pathways are dysregulated in disease, thus placing some of these enzymes, for example PI-3 kinase (PI3K), at the forefront of drug discovery. However, even many years after the discovery of Ins(1,4,5)P_3, the fundamental question of exactly how IP_3 binding leads to Ca^{2+} release remains essentially unanswered[259] and there are still no truly effective and selective Ins(1,4,5)P_3R antagonists—a continuing challenge for medicinal chemistry. Further surprises in this area are clearly still in store. Recently, an Ins(1,4,5,6)P_4 stereoisomer emerged as a co-regulator of histone deacetylases.[207,208] Acetylation and deacetylation of histones is an epigenetic mechanism that regulates chromatin organization and gene expression. Furthermore, deacetylase inhibitors are promising clinical cancer drugs. Targeting the inositol polyphosphate binding site, for example, might offer exciting new therapeutic approaches. Higher inositol polyphosphates (IP_5–IP_8) have been a developing theme over recent years and also offer rich potential. Ins(1,3,4,5,6)P_5 has anticancer properties and IP_6 is linked to chromatin remodeling, RNA editing, mRNA export, and DNA repair. Ubiquitous in eukaryotic cells, but not found in bacteria, IP_6 is also a cofactor in the activation of bacterial toxins (e.g. from *Clostridium difficile)*, a mechanism that would be pertinent to target synthetically. IP_5 and IP_6 are phosphorylated to the still higher diphosphoinositol phosphates IP_7 and IP_8, which have been linked to vesicular trafficking, apoptosis, DNA repair, telomere maintenance, stress responses, neurological function, and immune responses. IP_7 and IP_8, which represent the most crowded 3D arrays of phosphates in nature, are at the cutting-edge of current biological interest, with few available tools and few real targets understood. However, progress is being made in the design of both parent molecules and their nonhydrolyzable analogues,[225–228,230,232,235] with early promise from the application of the latter.[231] Recent work in this area has also illustrated how, for the kinase PPIP5K2, identification of a second binding site might allow chemical modulation of the active site and identified a simple substituted inositol polyphosphate lead.[227] Another very recent and cutting-edge advance has been the identification of the inositol hexakisphosphate kinase IP6K2, as a mediator of cancer cell migration and metastasis, by IP_7 synthesis, thus suggesting that IP6K2 could be a novel cancer drug target.[252] These are just some examples as to how the biological range based exclusively upon the *myo*-inositol isomer has expanded and continues to develop since the initial discovery of Ins(1,4,5)P_3 in 1983. Given this and the comparative paucity of information about the distribution and possible roles of many of the other eight inositol isomers and their numerous potential polyphosphates, as discussed here, further and wider research in the inositol field is warranted. Although the field based upon the *myo* isomer is not slowing down, one aim of this Review is to stimulate a greater interest in the other eight isomers and, importantly given the vast literature now available on *myo*-inositol, in the large armamentarium of chemical techniques and tools now available that could be applied elsewhere. The time is now ripe for a concerted excursion beyond the *myo* isomer. A recent stimulus has been provided.[11]

As stated in the Introduction, the studies cited describe effects across a very wide area of biology and biochemistry. As such, it is difficult to draw any general conclusions about the roles of the "other" inositols beyond saying that they are very diverse, and too few of these roles are yet known to support the drawing of any wide conclusions. Unsurprisingly, the different isomers have different effects (relative to each other) in different systems. Large amounts of these isomers are readily available through the numerous chemical syntheses described herein. We have tried to concentrate on highly practical routes for synthesis, mindful that this is a prime feature for biological investigations and indeed early attempts have been made to explore medical applications (as for *scyllo* and D-*chiro*-inositols), but have not neglected the routes of

interest and elegance. Many of the papers cited compare the effects of one or more of the less-common inositol isomers with *myo*-inositol in some particular role, but none compares all nine isomers in the same situation. The phosphorylated forms of most of the inositol isomers are widespread in the environment, where they form a large but poorly understood pool of environmental phosphate that is derived mainly from plants.[11] Some of these phosphorylated inositol isomers have been chemically synthesized and tested in assays against various enzymes and receptors to find possible biological roles.[32,80,84,164] Clearly, such derivatives with different stereochemistry or regiochemistry of substitution can merely just act on systems controlled by *myo*-inositol derivatives, but the hope would be to find unique activities. The field of higher inositol polyphosphates is an emerging area of likely seminal importance in signaling, largely unexplored structurally, and PP-InsP binding sites could be attractive new drug targets. One has to point to these emerging *myo*-inositol pyrophosphates and their complexity as an area of great current chemical and biological activity and potential, but also note that *neo*-inositol IP_7 and IP_8 pyrophosphates are already known from protozoa, but are still of unknown function.[192] There are, thus, tantalizing hints of wider activity already in evidence.

Although work on lipids is not really described here, there is a vast amount of literature available based around the design of druglike compounds to block PI3K. Disappointing PI3K inhibitor selectivity, however, underlies the search for alternative targets, for example, amongst promising inositol phospholipid phosphatases. SHIP enzymes, for example, are linked to human diseases, particularly diabetes, cancer, and obesity. The recent structure of a SHIP2:head group surrogate complex with a simple inositol polyphosphate surrogate identified an active site loop for targeting inhibition and specificity,[251] and earlier studies had demonstrated that a simple benzene tetrakisphosphate could be crystallized with the Akt-PKB PH domain.[250] The structure of the Akt PH domain in complex with Ins(1,3,4,5)P_4 was used to design more druglike compounds, moving away from the phospholipid head group by using computational virtual screening techniques.[253] To illustrate how this has also developed for other related potential drug targets based upon second messengers mobilizing Ca^{2+}, but which is substantially beyond the scope of this Review, one can point to the discovery of druglike inhibitors, for example, SAN 2589 and 4825 that block cardiac ADP-ribosyl cyclase,[254] which produces cADPR from NAD; also to the considerable success of the NED-19 class of compounds where, by using computational virtual screening techniques, an organic molecule of real biological application that mimics NAADP was discovered to modulate the activity of NAADP.[255] Indeed, the simple NAADP derivative BZ194 has also shown activity in T cells[256] as well as in vivo in autoimmune disease[257] and in the heart.[258] These are promising advances for the idea of pharmacological intervention in second messenger signaling and it should be clear that all of these techniques and ideas that move away from parent polyphosphate structures to more simple and druglike compounds are in principle applicable to *myo*-inositol polyphosphates and their various targets, and, naturally, perhaps more widely in the inositol series. Still of more interest from this general area is the observation that non-inositol-based polyphosphates (for example, benzene polyphosphates) can act as both agonists and antagonists at Ins(1,4,5)P_3R. How this functions still remains to be properly understood, but the potential is clear. This is a general area of considerable promise, and chemistry in concert with structural biology has huge potential contributions to make here.

Exploration will be greatly assisted by the development of new and/or efficient methods for synthesizing the inositols, their analogues, and derivatives, providing that they are practical routes. These areas benefit enormously from the large amount of work that has been carried out on designed derivatives and tools to investigate *myo*-inositol phosphates, in particular, for example, fluorescently tagged and caged derivatives. Such techniques, which have now been refined substantially since the mid-1980s, will make it much easier to access the tools required to explore the biology of other inositol isomers and their phosphate derivatives.

14. Glossary

Aβ	amyloid-β
ADPR	adenosine 5′-diphosphate ribose
cADPR	cyclic adenosine 5′-diphosphate ribose
AcOH	acetic acid
AIBN	azobisisobutyronitrile
BDA	butane-2,3-diacetal
Bn	benzyl
BOM	benzyloxymethyl
BSTFA	*N*,*O*-bis(trimethylsilyl)trifluoroacetamide
BzCl	benzoyl chloride
CK2	casein kinase II
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene.
DCC	*N*,*N*-dicyclohexylcarbodiimide
DCI	4,5-dicyanoimidazole
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIAD	diisopropyl azodicarboxylate
DIBAL-H	diisobutylaluminum hydride
DIPE	*N*,*N*-diisopropylethylamine
DMAP	*N*,*N*-dimethylaminopyridine
DME	dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
EDAC	1-ethyl-3-(3-dimethlaminopropyl)carbodiimide
Fm	fluorenylmethyl
GLUT4	glucose transporter type 4
GPI	glycosylphosphatidylinositol
HDAC	histone deacetylase
hDIPP1	human diphosphoinositol polyphosphate phosphohydrolase 1
IP6K2	inisotol hexakisphosphate kinase 2
KHDMS	potassium bis(trimethylsilyl)amide
KOBz	potassium benzoate
MCPBA	3-chloroperoxybenzoic acid
MeCN	acetonitrile

MEM-Cl	methoxyethoxymethyl chloride
MeOH	methanol
NAADP	nicotinic acid adenine dinucleotide 2′-phosphate
NCOR2	nuclear receptor co-repressor 2
NF-κB	nuclear factor kappa-light-chain-enhancer of activated B cells
NMO	*N*-methylmorpholine-*N*-oxide
NuRD	nucleosome remodeling and deacetylase
PDK1	3-phosphoinositide-dependent protein kinase
PMB-Cl	*p*-methoxybenzyl chloride
PI3K	phosphoinositide 3-kinase
PKBα	protein kinase B α
PPL	porcine pancreatic lipase
PPTS	pyridinium *p*-toluenesulfonate
PTEN	phosphatase and tensin homologue on chromosome 10; the protein encoded by this gene is a phosphatidylinositol 3,4,5-trisphosphate 3-phosphatase
PTSA	*p*-toluenesulfonic acid
RANKL	receptor activator of nuclear factor kappa-B ligand
SHIP2	SH-2 domain containing inositol 5-phosphatase 2
TASF	tris(dimethylamino)sulfonium difluorotrimethyl silicate
TBAF	tetrabutylammonium fluoride
TEAB	triethylammonium bicarbonate
TFA	trifluoroacetic acid
Tf	trifluoromethanesulfonyl
Tf_2O	trifluoromethanesulfonic anhydride
THF	tetrahydrofuran
TIPS-Cl	triisopropylsilyl chloride
TMS	trimethylsilyl
TMSBr	bromotrimethylsilane
TFSA	trifluoromethylsulfonic acid
TrCl	trityl chloride
UV	ultraviolet
XEP	*o*-xylyene

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[259] Note added in proof: A seminal paper reporting the structure of the full-length Ins(1,4,5)P_3 receptor by electron cryomicroscopy has recently been published; see: G. Fan, M. L. Baker, Z. Wang, M. R. Baker, P. A. Sinyagovskiy, W. Chiu, S. J. Ludtke, I. I. Serysheva, *Nature* **2015**, DOI: 10.1038/nature15249.

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