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Recent Developments in the Synthesis of *myo*-Inositol Phosphates

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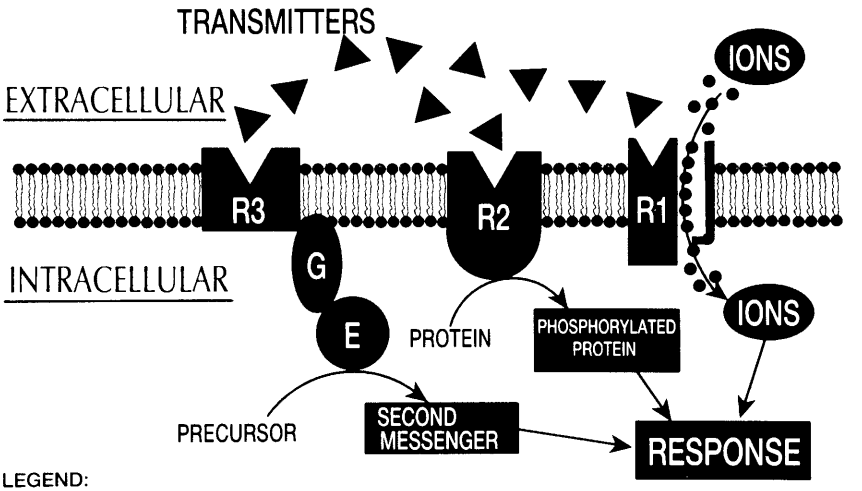
1 Introduction

This review aims to present the current state of the art in inositol phosphate synthesis. A brief introduction to cell signalling is provided and the importance of the inositol phosphates in this area is outlined. This is followed by an introduction to the stereochemical properties of *myo*-inositol and a description of the problems posed by the synthesis of the inositol phosphates. An outline of the methods developed recently to overcome these problems is then followed by the bulk of the review which is concerned with the synthesis of the individual inositol phosphates, arranged according to their degree of phosphorylation.

A. Intercellular Signalling.—Communication between cells is essential for the maintenance of life processes in complex organisms. Nature uses a wide variety of chemical signals to pass information from one cell to another, and these signals may be classified according to their function as neurotransmitters, hormones, growth factors, *etc.* These chemical messengers are received by specific receptors located on the surface of the receiving cells and the incoming signal is then converted into a response inside the target cell by a number of different mechanisms.[1]

One class of receptors either contains or is closely linked to an ion channel which spans the plasma membrane, Figure 1. Stimulation of the receptor leads to alterations in the ability of the ion channel to allow the ions for which it is specific to pass across the cell membrane. A second class of receptors are membrane-spanning enzymes called tyrosine kinases. Binding of the extracellular messenger to the receptor leads to activation of the enzyme which then phosphorylates specific tyrosine residues in target proteins inside the cell. This system is used by many growth factors and hormones such as insulin. A third class of cell surface receptor exists which have no intrinsic activity as either ion channel control systems or as enzymes. These receptors are 'coupled' *via* a class of proteins known as 'G proteins'[2] to the enzymes or ion channels through which they evoke their responses. Activation of the receptor causes its associated G protein to release guanosine diphosphate (GDP) and bind guanosine triphosphate (GTP). In this form the G protein regulates the activity of the ion channel or enzyme

[1] 'Molecular Mechanisms of Transmembrane Signalling', ed. P. Cohen and M. D. Houslay, Elsevier, Oxford, 1985.
[2] R. L. Rawls, *Chem. Eng. News*, 1987, 26.



LEGEND:
R1 is an ion channel linked Receptor.
R2 is a membrane spanning tyrosine kinase.
R3 is a receptor linked via a G protein[G] to an enzyme[E] which produces second messengers.

Figure 1

which forms the next link in the chain. In the case of receptors which are coupled to enzymes, these enzymes act to change the intracellular levels of 'second messenger' species. The classical example of this type of receptor system produces the second messenger cyclic adenosine monophosphate (cAMP) from adenosine triphosphate (ATP) *via* the G protein regulated enzyme adenylate cyclase. The alteration in intracellular levels of cAMP produced on stimulation of this type of receptor causes the observed overall cellular response. In recent years overwhelming evidence has been obtained for a new widely distributed second messenger system involving the hydrolysis of inositol* phospholipids. A detailed description of this complex system, which is still under intensive investigation, is far outside the scope of this review. Only a very brief overview of current ideas is given here in order to place the synthesis of the inositol phosphates in context, and the interested reader is directed to the many recent reviews available on the biochemistry of the PI cycle.[3–12]

* Throughout this review 'inositol' refers to the *myo* stereochemistry unless otherwise indicated.

[3] N. N. Osbourne, A. B. Tobin, and H. Ghazi, *Neurochem. Res.*, 1988, **13**, 177.
[4] J. Altman, *Nature*, 1988, **331**, 119.
[5] J. L. Marx, *Science*, 1987, **235**, 974.
[6] C. W. Taylor, *Trends Pharmacol. Sci.*, 1987, **8**, 79; A. H. Drummond, *ibid.*, 1987, **8**, 129.
[7] M. D. Houslay, *Trends Biochem. Sci.*, 1987, **12**, 133.
[8] R. H. Michell, *Nature*, 1986, **324**, 613.
[9] C. P. Downes, *Trends Neurochem. Sci.*, 1986, 394.
[10] P. W. Majerus, T. M. Connolly, H. Deckmyn, T. S. Ross, T. E. Bross, H. Ishii, V. S. Bansal, and D. B. Wilson, *Science*, 1986, **234**, 1519.
[11] R. H. Michell, *Nature*, 1986, **319**, 176.
[12] C. W. Taylor and J. E. Merritt, *Trends Pharmacol. Sci.*, 1986, **7**, 238; S. R. Nahorski and I. Batty, *ibid.*, 1986, **7**, 83.

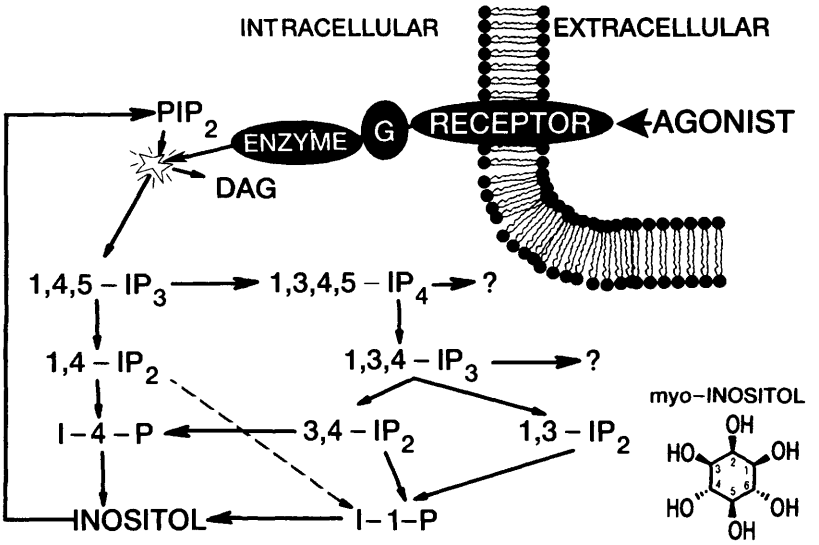


Figure 2

B. Inositol Phosphates as Second Messengers.—In 1975 Michell[13] suggested that the receptor-controlled hydrolysis of inositol phospholipids could be directly linked to changes in calcium levels within cells. It is now known that receptor-stimulated hydrolysis of the phospholipid phosphatidylinositol 4,5-bisphosphate (PIP_2) occurs *via* a G protein-controlled enzyme, phospholipase C (PLC), releasing two second messengers, diacylglycerol (DAG) and D-inositol 1,4,5-trisphosphate (1,4,5-IP_3), Figure 2.[3–6] Diacylglycerol acts as a second messenger by binding to and activating protein kinase C, and also serves as a precursor to the metabolites of the arachidonic acid cascade. 1,4,5-IP_3 binds to specific receptors on the endoplasmic reticulum and stimulates the release of calcium from intracellular storage sites. The complex metabolic cycle that converts 1,4,5-IP_3 into free inositol, which is used for the resynthesis of PIP_2, has been an area of intense biochemical interest during the past five years. It is now clear that two pathways exist for the metabolism of 1,4,5-IP_3, Figure 2. The first pathway begins with a specific dephosphorylation giving inositol 1,4-bisphosphate (1,4-IP_2). This bisphosphate is subsequently sequentially dephosphorylated, mainly *via* inositol 4-phosphate (I-4-P) to free inositol. This pathway probably serves only to terminate the 1,4,5-IP_3 signal. The second, recently discovered, pathway begins with a specific phosphorylation of 1,4,5-IP_3 giving inositol 1,3,4,5-tetrakisphosphate (1,3,4,5-IP_4). Recent experiments have suggested that this 1,3,4,5-IP_4 may have a messenger role of its own, affecting the influx of calcium into the cell from the external medium. The tetrakisphosphate is then metabolized *via* a

[13] R. H. Michell. *Biochim. Biophys. Acta*, 1975, **415**, 81.

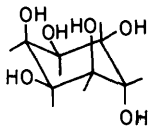
second trisphosphate, inositol 1,3,4-trisphosphate (1,3,4-IP_3), and two further bisphosphates, inositol 1,3- and 3,4-bisphosphates (1,3- and 3,4-IP_2) to inositol monophosphates. These monophosphates are then converted into free inositol as before. Enzymic pathways also exist which convert 1,3,4-IP_3 into a second tetrakisphosphate, 1,3,4,6-IP_4, which is believed to be sequentially dephosphorylated once more to give free inositol. The relative importance of these latter pathways remains to be established. Inositol polyphosphates also exist in other systems, for example avian red blood cells contain 1,4,5,6-IP_4 and 1,3,4,5,6-IP_5, whose function and metabolism are not clear at the present time.

The rapidly expanding complexity of the metabolic cycle, coupled with the fact that only minute amounts of these metabolites were available from natural sources, stimulated intense worldwide interest in the chemical synthesis of the inositol polyphosphates during the mid-1980s. Many laboratories have subsequently contributed methodology and techniques such that most of the naturally occurring metabolites have now been synthesized and are available in quantities sufficient to allow the isolation of the individual enzymes of the PI cycle. The availability of these substrates will prove crucial to the next generation of biological studies of this fascinating fundamental cell-signalling system.

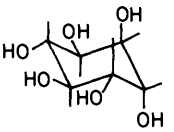
C. *myo*-Inositol.—An optically inactive cyclohexanehexol was first isolated in 1850[14] and given the name 'inosit' by Scherer. This became a generic term for cyclohexanehexols with the suffix *ol* added in English usage. There are nine isomeric inositols: *allo*, (+)-*chiro*, (−)-*chiro*, *cis*, *epi*, *muco*, *myo*, *neo*, and *scyllo*, Figure 3. The naming and numbering of the inositols and their derivatives pose many complex problems for which several different solutions have been advocated and used. IUPAC have published the '1967 IUPAC/IUB tentative rules for cyclitols'.[15] For a basic guide to nomenclature, and a concise coverage of inositol phosphate chemistry up to 1980 the reader should consult the excellent book by Cosgrove.[16a] A recent review on nomenclature and stereochemistry is also available.[16b]

Fortunately the only isomer of inositol which we are concerned with in the context of receptor signalling is *myo*-inositol, Figure 3. *myo*-Inositol has a single axial hydroxyl at C-2, and a plane of symmetry between C-2 and C-5, Figure 4. To emphasize this, the two-dimensional representation in Figure 4 will be used throughout this review and the inositol carbon atoms will be numbered anticlockwise, with C-1 at 2 o'clock. Incorporation of a substituent at C-2 or C-5 leads to an optically inactive compound (plane of symmetry retained), whereas substitution at C-1 (enantiotopic to C-3) and/or C-4 (enantiotopic to C-6) leads to a pair of enantiomers (plane of symmetry lost). Thus inositol 2-phosphate, 5-phosphate, and 1,3-bisphosphate are achiral, whereas inositol 1-phosphate, 4-phosphate, and 1,4-bisphosphate all exist as pairs of enantiomers, Figure 5. The

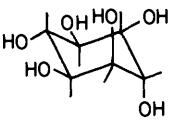
[14] J. Scherer, *Ann.*, 1850, **73**, 322.
[15] IUPAC Information Bulletin, 1968, **32**, 51.
[16] (*a*) 'Inositol Phosphates, their Chemistry, Biochemistry and Physiology', D. J. Cosgrove, Elsevier, Oxford, 1980; (*b*) R. Parthasarathy and F. Eisenberg, *Biochem. J.*, 1986, **235**, 313.



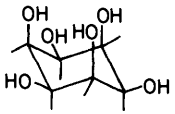
allo



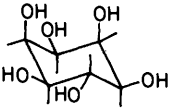
(+)-chiro



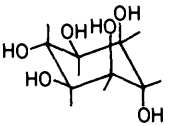
(-)-chiro



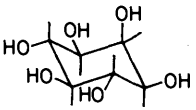
cis



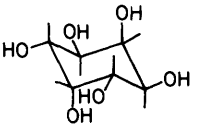
epi



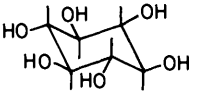
muco



myo

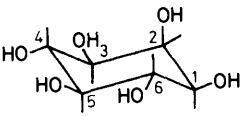


neo



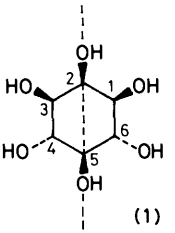
scyllo

Figure 3



myo - Inositol (1)

≡



(1)

= Symmetry plane

Figure 4

enantiomers of inositol 1-phosphate shown in Figure 5 exemplify the fact that it is equally correct to number the inositol carbon atoms clockwise, with C-1 at 10 o'clock. The normal convention is to choose the alternative which leads to the lowest overall number count. As outlined above a C-1 at 2 o'clock anticlockwise

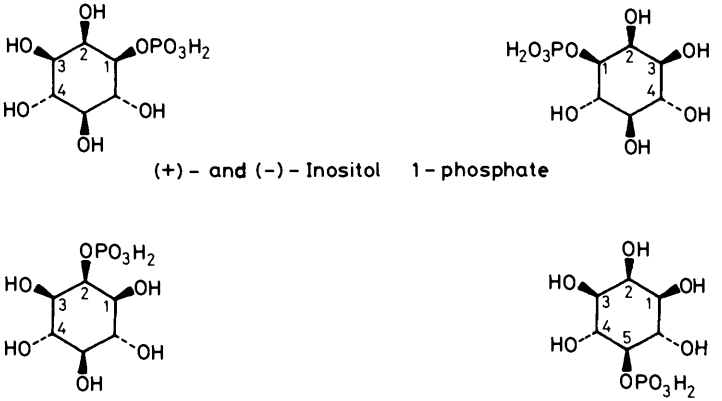


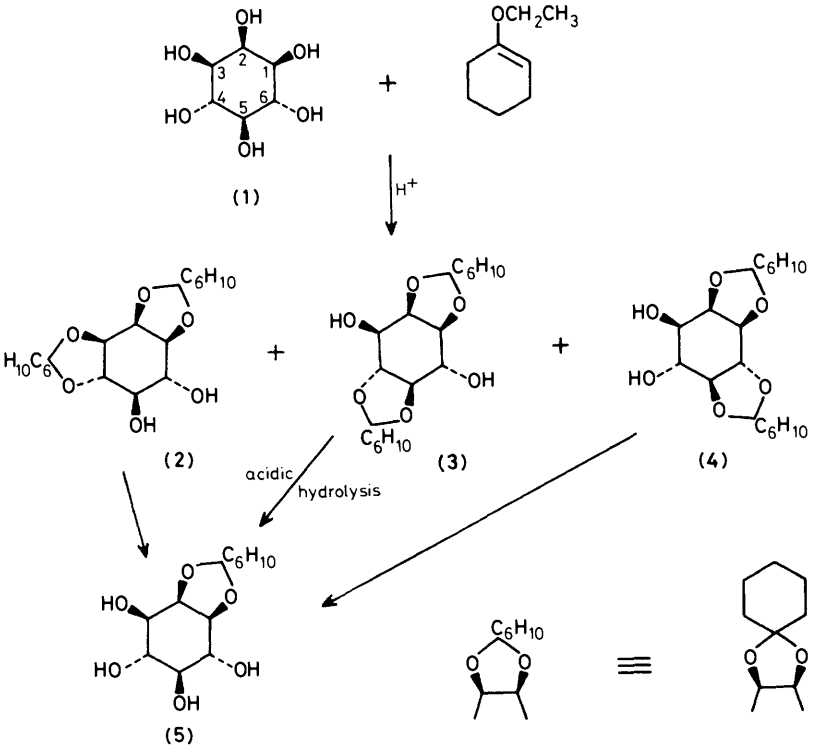
Figure 5

system will be followed in this review, and any examples which require the opposite numbering system to generate the correct chemical name will be indicated in the schemes by numbering of the ring atoms. The symmetry properties of *myo*-inositol have been exploited in a number of synthetic strategies.

D. Synthesis of Inositol Phosphates.—The synthesis of the inositol phosphates poses three main problems: (i) the synthesis of a suitable selectively protected inositol derivative; (ii) phosphorylation in an efficient manner with a reagent bearing suitable phosphate-protecting groups (this is a particularly serious problem for polyphosphates containing vicinal diols where cyclic phosphate formation is a major side reaction) and (iii) deprotection without migration of phosphate substituents to adjacent free hydroxyl functions. Although considerable methodology was available for the synthesis of selectively protected inositols, it was not until the mid-1980s that the problems of efficient polyphosphorylation, and deprotection without migration were solved. An additional requirement is for efficient procedures for the resolution of suitable synthetic intermediates, allowing the preparation of optically pure inositol phosphates.

(i) *Synthesis of Protected Inositols.* Due to the ready availability of pure *myo*-inositol, most syntheses begin with the parent cyclitol. Reaction of inositol (1) with cyclohexanone,[17] or more efficiently with a cyclohexanone precursor such as 1-ethoxycyclohexene,[18,19] in the presence of an acid catalyst gives a mixture of three bisacetals [(2)—(4)] which may be separated by crystallization and chromatography, Scheme 1. Each of these bisacetals gives the monoacetal (5) on mild hydrolysis of the less stable transacetal.[18,19] Due to the conformational constraints imposed on the inositol ring by the bisacetal groups, each of the free

[17] S. J. Angyal, M. E. Tate, and S. D. Gero, *J. Chem. Soc.*, 1961, 4116.
[18] R. Gigg and C. D. Warren, *J. Chem. Soc.* (*C*), 1969, 2367.
[19] D. E. Kiely, G. J. Abruscato, and V. Baburao, *Carbohydr. Res.*, 1974, **34**, 307.



Scheme 1

hydroxyl groups in (2), (3), and (4) may be selectively manipulated under suitable conditions,[20] providing access to a series of inositol derivatives having five hydroxyl groups differentially protected. The selective hydrolysis of the *trans* acetal, coupled with the possibility of selective reactions at specific hydroxyl groups in (2), (3), and (4)[20] *before* hydrolysis of the less stable acetal has led to the widespread use of (2), (3), and (4) in synthesis. Other acetals such as the isopropylidene and cyclopentylidene derivatives have also been used.[21]

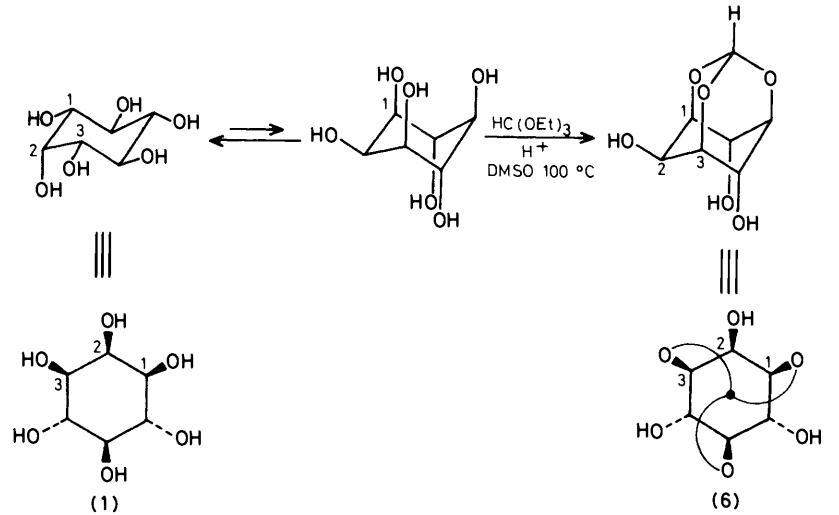
Recently the mono orthoformate of inositol (6) has been isolated and characterized,[22] Scheme 2. The orthoformate (6) provides a derivative in which positions 1, 3, and 5 are simultaneously protected. In addition, the normal axial/equatorial relationship of the remaining free hydroxyls is reversed, Scheme 2. The spatial juxtaposition of the axial hydroxyls in (6) allows highly selective alkylations to be performed at these positions,[23] Scheme 3.

(ii) *Phosphorylation Methodology*. Two successful general strategies have been

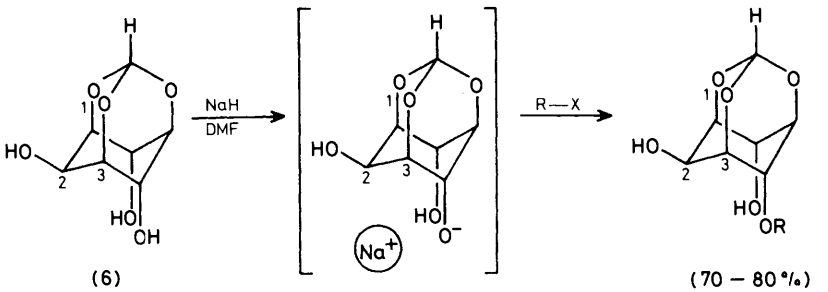
[20] P. J. Garegg, T. Iversen, R. Johansson, and B. Lindberg, *Carbohydr. Res.*, 1984, **130**, 322 and references therein.

[21] J. Gigg, R. Gigg, S. Payne, and R. Conant, *Carbohydr. Res.*, 1985, **142**, 132; *ibid.*, 1985, **140**, c1—c3.

[22] H. W. Lee and Y. Kishi, *J. Org. Chem.*, 1985, **50**, 4402.



Scheme 2

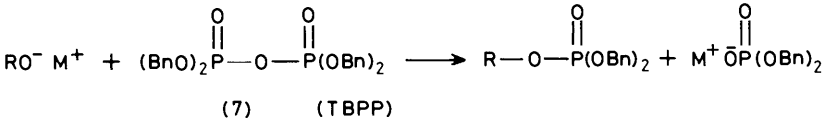


R = benzyl , allyl , *etc.*

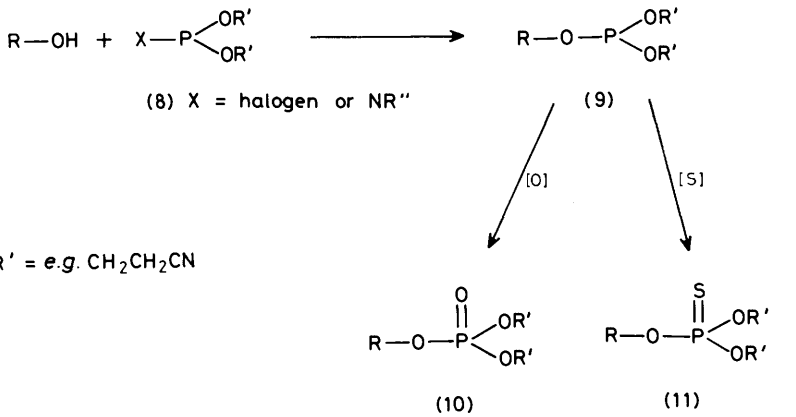
Scheme 3

developed for the phosphorylation of polyhydroxy-inositol derivatives. The first involves reaction of alkoxide anions with the readily available, crystalline reagent tetrabenzylpyrophosphate (7) (TBPP),[23,24] Scheme 4. This method gives good results for polyhydroxy compounds incorporating up to four phosphate esters in a single reaction and in high yield. Vicinal diols are efficiently phosphorylated, and the benzyl protecting groups are readily removed by hydrogenolysis, without phosphate migration.[23,25]

[23] D. C. Billington and R. Baker, *J. Chem. Soc., Chem. Commun.*, 1987, 1011.
[24] Y. Watanabe, H. Nakahira, M. Bunya, and S. Ozaki, *Tetrahedron Lett.*, 1987, **28**, 4179.
[25] D. C. Billington, R. Baker, J. J. Kulagowski, and I. M. Mawer, *J. Chem. Soc., Chem. Commun.*, 1987, 314.



Scheme 4

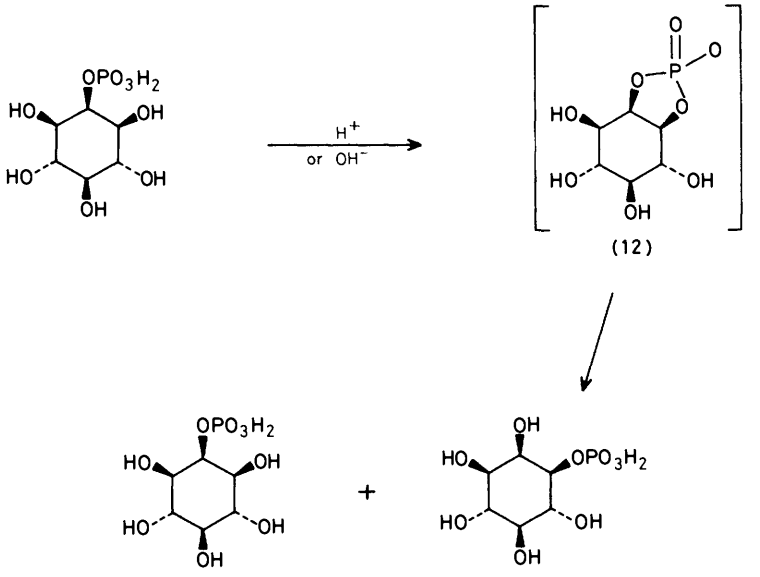


Scheme 5

The second phosphorylation strategy has developed from the use of P^{III} species for the synthesis of polynucleotides. Reaction of the polyol with a P^{III} reagent (8) with displacement of either NR_2 or halogen gives an intermediate phosphite (9).[26–28] This phosphite may then be oxidized (*e.g.* using mCPBA) to the protected phosphate[26] (10) or to the thiophosphate (S_8 in pyridine) (11), Scheme 5.[29] Numerous variations on this theme have been used for the synthesis of inositol polyphosphates, with varying degrees of success, and these are discussed in full below.

(iii) *Deprotection.* Migration of phosphate groups *via* cyclic intermediates [*e.g.* (12)] means that strongly acidic or basic conditions need to be avoided, Scheme 6. In addition, methods which lead to free ring hydroxyls adjacent to protected phosphate esters can also lead to migration. These problems are avoided by using benzyl esters as protecting groups for phosphate, in conjunction with benzyl ethers for protection of the ring hydroxyls. Hydrogenolysis rapidly cleaves the phosphate esters giving free phosphates which are not prone to migration during the slower hydrogenolysis of the benzyl ether on the ring.[23,25] Cyanoethyl groups are also suitable as phosphate protecting groups in conjunction with benzyl ethers of the ring hydroxyls, as they may be deprotected without

[26] K.-L. Yu and B. Fraser-Reid, *Tetrahedron Lett.*, 1988, **29**, 979.
[27] A. M. Cooke, B. V. L. Potter, and R. Gigg, *Tetrahedron Lett.*, 1987, **28**, 2305.
[28] A. M. Cooke, R. Gigg, and B. V. L. Potter, *Biochem. Soc. Trans.*, 1987, **15**, 904.
[29] A. M. Cooke, R. Gigg, and B. V. L. Potter, *J. Chem. Soc., Chem. Commun.*, 1987, 1525.



mixture of isomers

Scheme 6

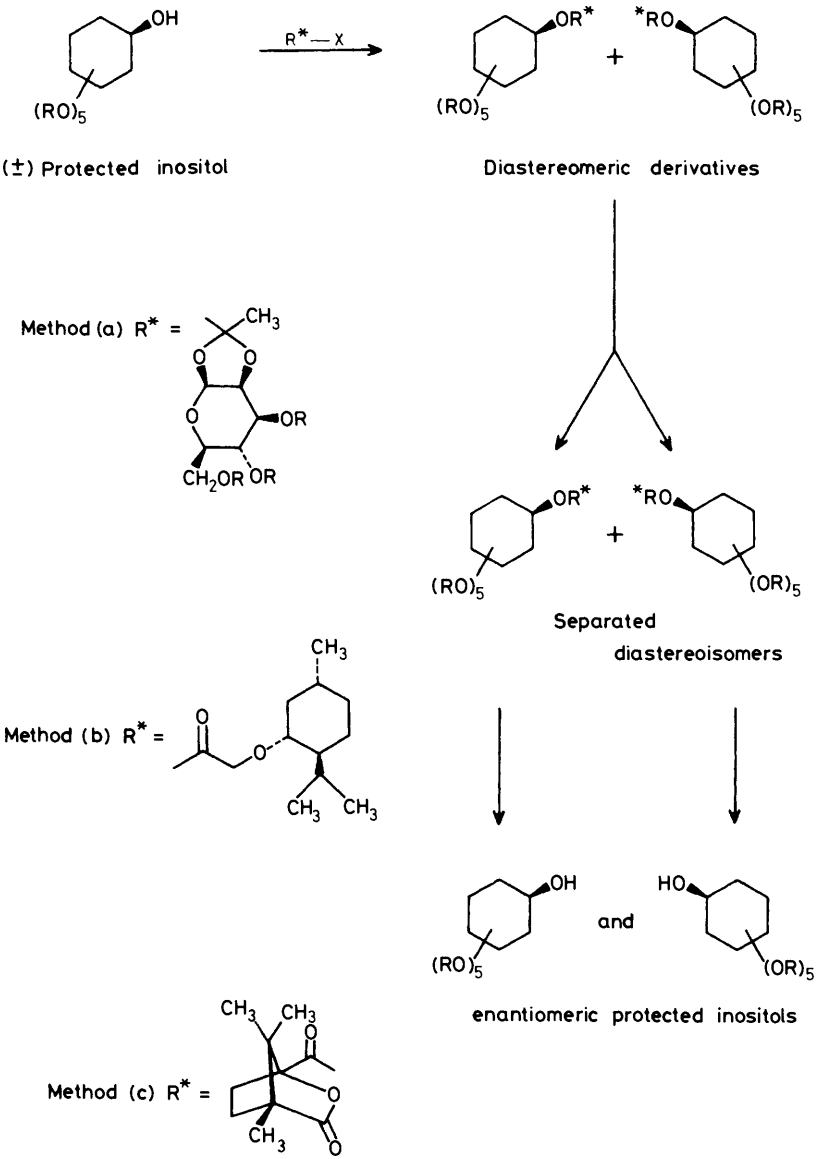
migration using alkali metals in liquid ammonia, with concomittant deprotection of the benzyl ethers.[28,29]

A number of other successful strategies have been developed, which will be apparent from the individual syntheses described below.

(iv) *Resolution of Protected Inositols.* Three resolution methods having general applicability have been reported for protected inositol derivatives. All of these methods rely on conversion of the racemic inositol derivative into a pair of diastereomeric esters, followed by separation of the diastereomers and regeneration of the separate enantiomers of the protected inositol, Scheme 7. While each of these methods (formation of orthoesters of D-mannose, formation of menthoxyacetates, and formation of camphanate esters) is successful in certain cases, the most generally useful method available at the present time appears to be that involving the formation and separation of camphanate esters,[25,30] Scheme 7(c). The camphanate route appears the most attractive for the following reasons:

(a) It uses (−)-camphanic acid chloride, a stable crystalline reagent, readily available in high optical purity from a number of commercial sources.

[30] (*a*) J. Gigg, R. Gigg, S. Payne, and R. Conant, *J. Chem. Soc., Perkin Trans. 1*, 1987, 1757; (*b*) T. Desai, J. Gigg, R. Gigg, and S. Payne, 'Studies directed towards the synthesis of inositol phosphates of biological interest', (Plenary Lecture) Glycolipids in molecular recognition and membrane organization, University of Sheffield, September 12th, 1988.



Scheme 7

(b) The camphanate esters formed are normally readily separated by chromatography on silica gel, or by recrystallization.

(c) HPLC analysis may be used to determine the diastereomeric purity of

the intermediate esters, and thus the enantiomeric purity of the final products.

(d) The camphanate esters are often highly crystalline and suitable for *X*-ray analysis,[25] thus allowing the absolute configuration of the individual enantiomers to be established.

(e) The route has been successfully used for a wide variety of inositol derivatives,[30] many of which have not as yet been converted into inositol phosphates, and are thus outside the scope of this review.

2 Synthesis of Inositol Monophosphates

There are four possible inositol monophosphates. Inositol 1-phosphate and inositol 4-phosphate exist as pairs of enantiomers, while inositol 2-phosphate and inositol 5-phosphate are meso compounds with a plane of symmetry through C-2 and C-5. Both of the optically active monophosphates have been synthesized as pure enantiomers, in addition to racemic syntheses.

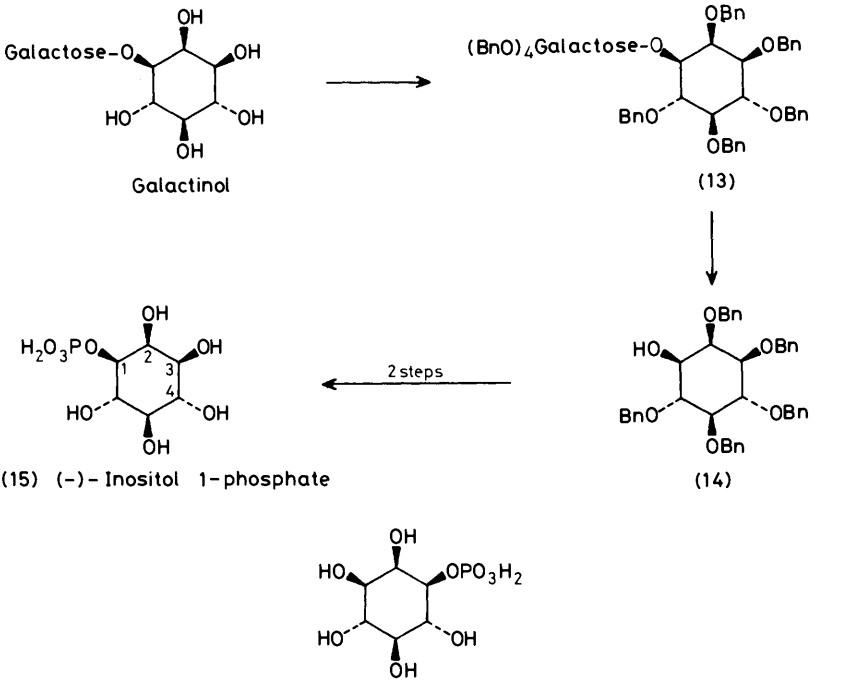
A. Inositol 1-Phosphate.—The dextrorotatory *myo*-inositol monophosphate, isolated by alkaline hydrolysis of phospholipids, was shown to be D-(+)-*myo*-inositol 1-phosphate by Pizer and Ballou.[31] This was followed by a number of syntheses of both the racemic compound and of its individual enantiomers. The absolute configurations of (+)- and (−)-inositol 1-phosphate were established by synthesis of the (−) form from galactinol which was known to have the absolute configuration shown, Scheme 8. Galactinol was perbenzylated to the nonabenzyl derivative (13) which on hydrolysis gave the pentabenzyl inositol (14). Phosphorylation and deprotection then gave the laevorotatory inositol 1-phosphate (15). The naturally occurring dextrorotatory isomer is therefore the enantiomer of this material. *i.e.* (16). The isolation of (16) from natural lipids on a useful scale has been described, but it is not possible to isolate useful quantities of the enantiomer (15) from natural sources.[31,32]

(i) *Syntheses of Racemic Material* (±)-(19). Diacetyl-1,2-anhydroconduritol (17), Scheme 9, may be converted into the protected phosphate (18) by epoxide opening using dibenzylphosphate followed by acetylation of the free hydroxyl group.[33] Permanganate oxidation of (18) followed by deprotection gives a mixture of inositol 1-phosphate (19) and inositol 4-phosphate (20). These isomeric materials may be separated by crystallization to give pure (±)-(19) in very low yield. Benzylation of the monoacetal (5), see Scheme 1, followed by acidic hydrolysis gives 3,4,5,6-tetra-*O*-benzyl inositol (21), Scheme 10. Direct phosphorylation of (21) with $POCl_3$ gives a mixture of protected inositol 2-phosphate (22) and inositol 1-phosphate (23).[19] These isomeric phosphates may be separated by careful crystallization and (±)-(19) is obtained by deprotection of (23).

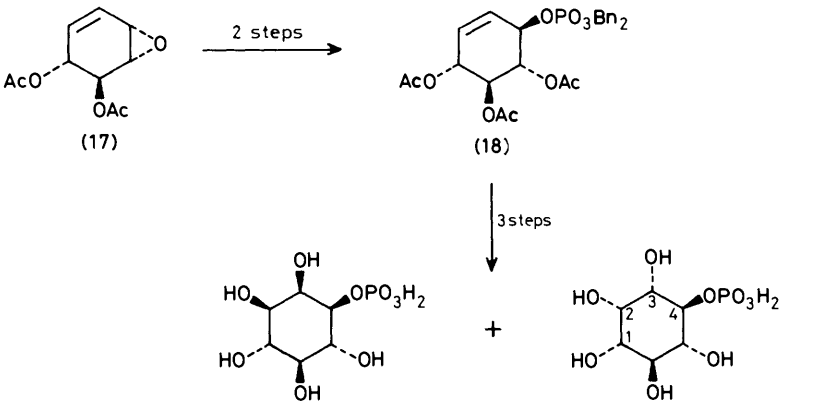
[31] F. L. Pizer and C. E. Ballou, *J. Am. Chem. Soc.*, 1959, **81**, 915; C. E. Ballou and L. I. Pizer, *J. Am. Chem. Soc.*, 1960, **82**, 3333.

[32] C. E. Ballou, *Biochem. Prep.*, 1962, **9**, 99.

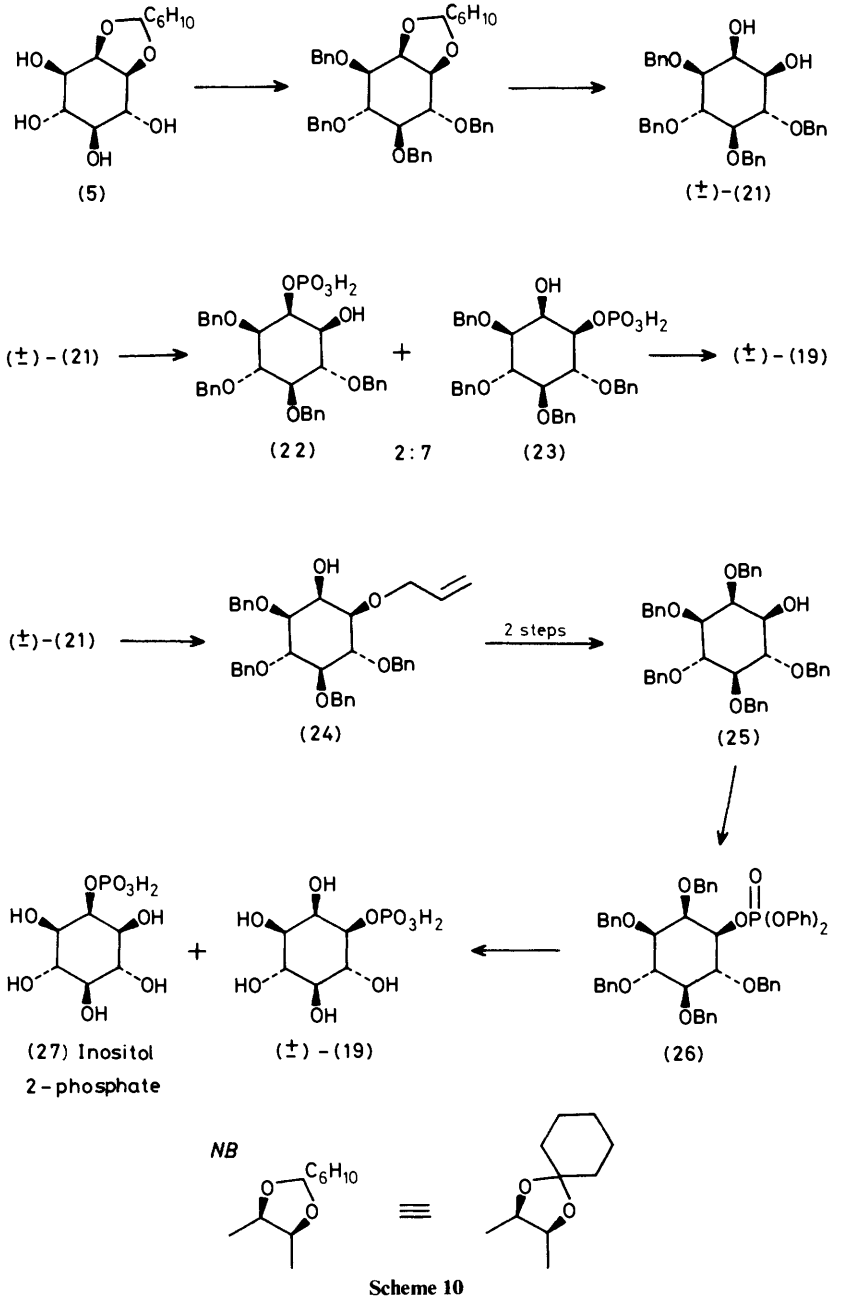
[33] N. Kurihara, H. Shibata, H. Saeki, and M. Nakajima, *Liebigs Ann. Chem.*, 1967, **701**, 225.



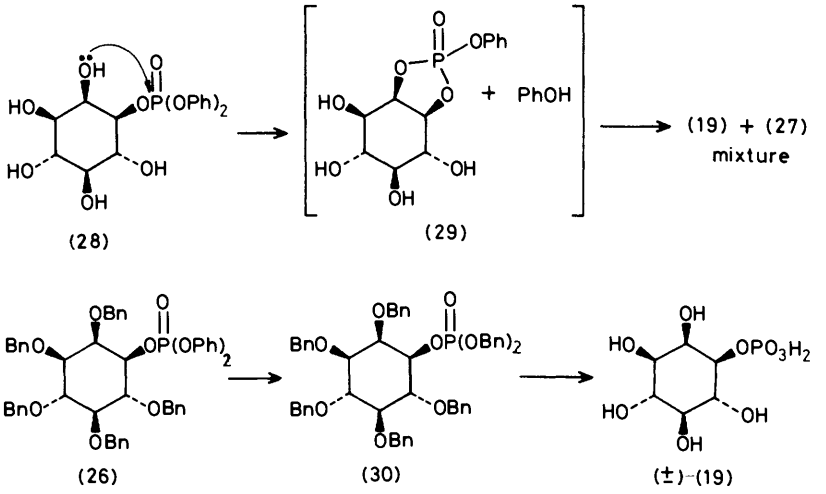
Scheme 8



Scheme 9


(5)
(±)-(21)
(±)-(21)
(22)
2 : 7
(23)
(±)-(19)
(±)-(21)
(24)
2 steps
(25)
(26)
(27) Inositol 2-phosphate
(±)-(19)
NB

Scheme 10



Scheme 11

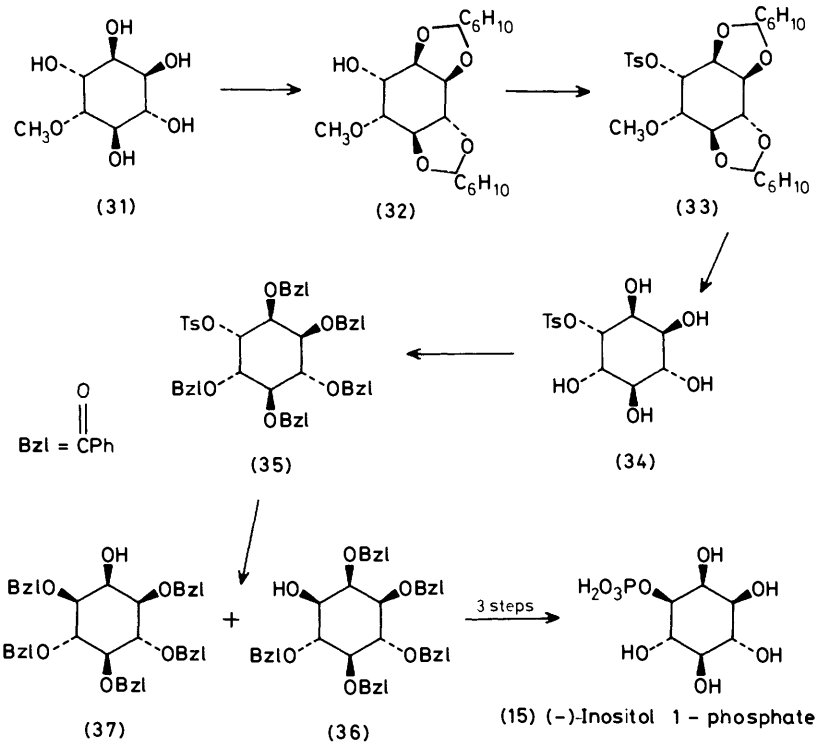
A more selective approach is to exploit the higher reactivity of the equatorial alcohol in (21), for example by reaction with allyl bromide giving mainly (24).[18] Benzylation of the remaining free hydroxyl group followed by removal of the allyl group gives (25), which may be phosphorylated using diphenylchlorophosphate to give the pentabenzyl diphenylphosphate (26). Hydrogenolysis of (26) using palladium to remove the benzyl ethers, followed by platinum to remove the phenyl phosphate esters, gives (19) contaminated with 2.5% of the isomeric 2-phosphate (27).[25]

The isomeric product (27) presumably arises *via* formation of a cyclic phenylphosphate ester (29) from the intermediate diphenylphosphate (28) formed in the two-step deprotection procedure, Scheme 11. This problem may be overcome by transesterification of the fully protected compound (26) using the anion of benzyl alcohol to give the dibenzyl phosphate (30).[25] This dibenzyl ester may be deprotected without phosphate migration [25] using a single hydrogenolysis over palladium, as the benzylphosphate esters are cleaved much faster than the benzyl ethers, to give a free phosphate which is not prone to migration under these conditions, Scheme 11.

(ii) (−)-*Inositol* 1-*phosphate* (15) *and* (+)-*inositol* 1-*phosphate* (16). The synthesis of (15) from galactinol has been described above,[31] Scheme 8. The optically active natural product quebrachitol (31) has also been used as a starting material in the synthesis of (15), Scheme 12. Treatment of (31) with cyclohexanone gives the bisacetal (32) which may be converted into tosylate (33).[34,35] Boron trichloride removes both the acetal and methyl protecting groups, giving (34). Benzoylation of (34) gives (35) which on treatment with NaF in *N'N'*-dimethyl-

[34] S. D. Gero, D. Mercier, and J. E. G. Barnett, *Methods Carbohydr. Chem.*, 1972, **6**, 403.

[35] D. Mercier, J. E. G. Barnett, and S. D. Gero, *Tetrahedron*, 1969, **25**, 5681; S. D. Gero, *Tetrahedron Lett.*, 1966, 591; D. Mercier and S. D. Gero, *ibid.*, 1968, 3459.

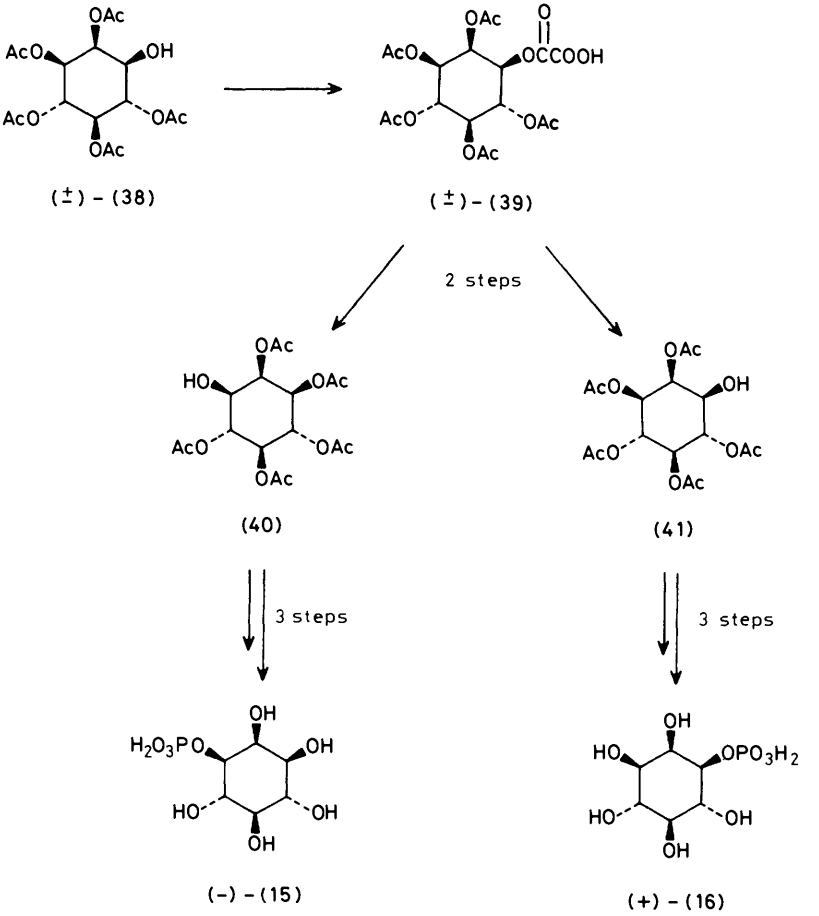


Scheme 12

formamide undergoes intramolecular benzoyloxy displacement of the tosyl ester giving a mixture of the desired optically active 2,3,4,5,6-pentabenzoyl inositol (36) and the isomeric 1,3,4,5,6-meso material (37). Recrystallization affords pure (36) which on phosphorylation with diphenylchlorophosphate, followed by deprotection by hydrogenolysis of the phenylphosphate esters and subsequent basic hydrolysis of the benzoyl esters yields pure (−)-inositol 1-phosphate (15).

A number of approaches have succeeded in resolving protected inositol derivatives, allowing the synthesis of the individual enantiomers of inositol 1-phosphate. Conversion of the racemic pentaacetate (38) into its acid oxalate gives (39), Scheme 13, which is amenable to resolution using salt formation with chiral bases.[36,37] Unfortunately to obtain good yields of the resolved materials, salt formation with quinidine is required to obtain one enantiomer and with (−)-α-phenylethylamine to obtain the other enantiomer. Multiple recrystallization of the diastereomeric salts is also necessary. The enantiomeric pentaacetates (40) and (41) obtained on hydrolysis may then be converted into the enantiomers of

[36] J. G. Molotkovsky and L. D. Bergelson, *Tetrahedron Lett.*, 1971, 4791.
[37] J. G. Molotkovsky and L. D. Bergelson, *Chem. Phys. Lipids*, 1973, 135.

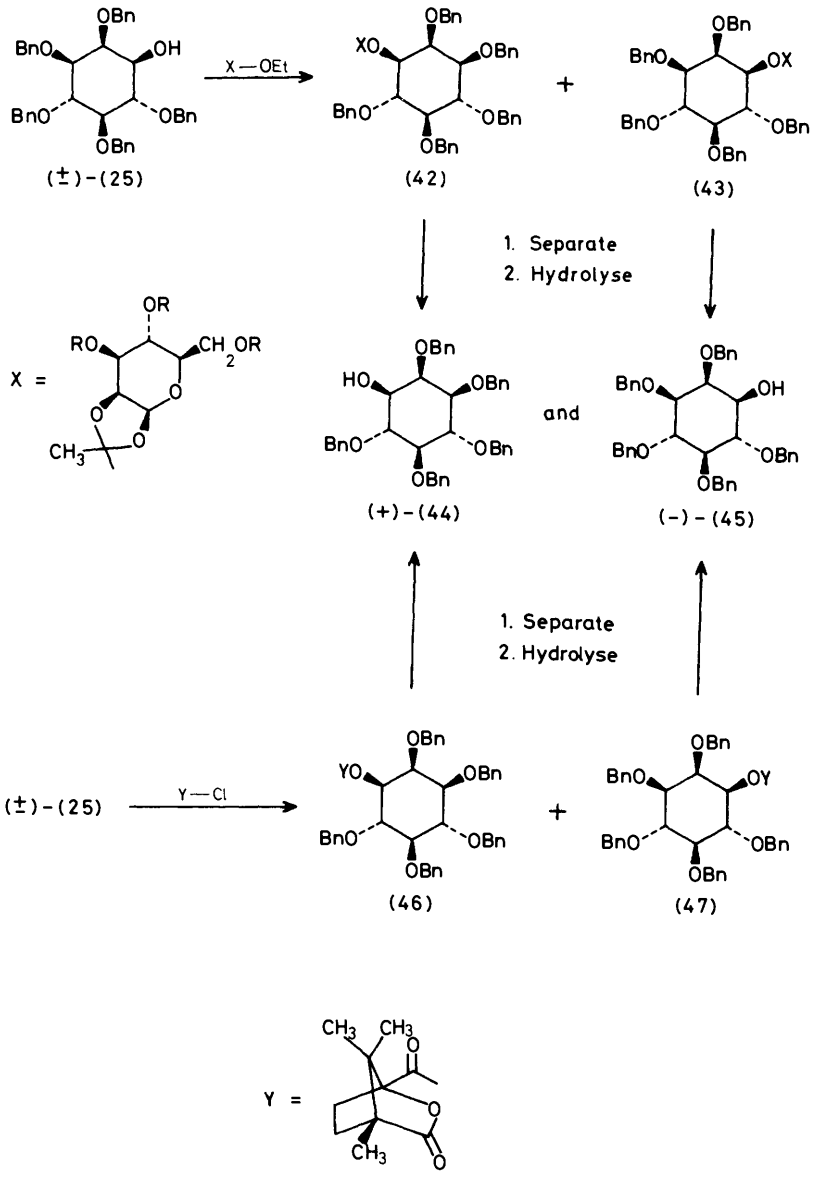


Scheme 13

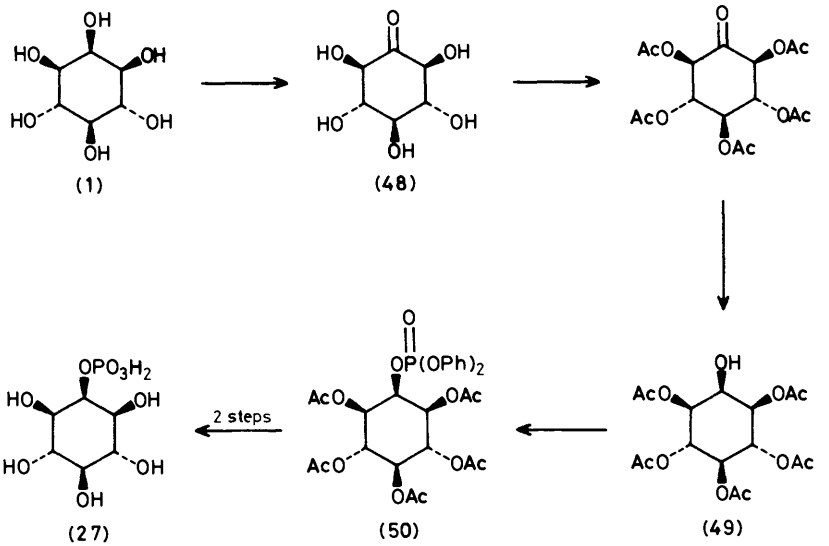
inositol 1-phosphate (15) and (16) by standard methods. Conversion of racemic protected inositols into diastereomeric mixed orthoesters using mannose derivatives has been used to resolve a number of useful intermediates.[38,39] Treatment of the racemic pentabenzyl derivative (25) with the orthoester of D-mannose gives the diastereomeric mixed orthoesters (42) and (43) (Scheme 14), which may be separated by a mixture of chromatography on alumina and

[38] V. I. Shvets, B. A. Klyashchitskii, A. E. Stepanov, and R. P. Evstigneeve, *Tetrahedron*, 1973, **29**, 331.

[39] A. E. Stepanov, O. O. Tutorskaya, B. A. Klyashchitskii, V. I. Shvets, and R. P. Eustigneeva, *Zh. Obs. Khim.*, 1972, **42**, 709; S. P. Kozlova, I. S. Pekarskaya, B. A. Klyashchitskii, V. I. Shvets, and R. P. Eustigneev, *ibid.*, 702; B. A. Klyashchitskii, V. V. Pimenova, A. I. Bashkatova, E. G. Zhelvakova, S. D. Sokolov, V. I. Shvets, R. P. Evstigneeva, and N. A. Preobrazhenskii, *ibid.*, 1970, **40**, 2482.


OBn
BnO
OH
OBn
OBn
(±)-(25)
X—OEt
XO
(42)
+
OX
(43)
1. Separate
2. Hydrolyse
X =
OR
RO
CH2OR
CH3
HO
(+)-(44)
and
(-)-(45)
1. Separate
2. Hydrolyse
(±)-(25)
Y—Cl
YO
(46)
OY
(47)
Y =
CH3
O

Scheme 14



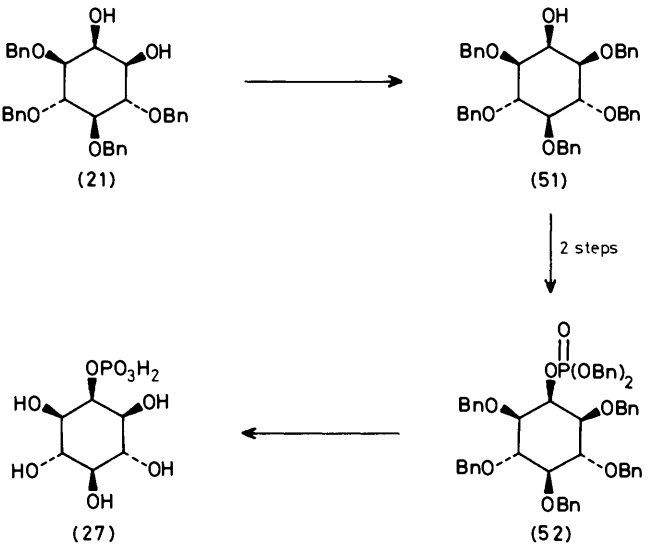
Scheme 15

recrystallization.[39] Mild acidic hydrolysis regenerates the pure enantiomers (44) and (45). The racemic alcohol (25) has also been resolved *via* conversion into the diastereomeric camphanate esters (46) and (47), Scheme 14, *via* treatment with commercially available (−)-camphanic acid chloride.[25] The camphanates were separated by chromatography, and their diastereomeric purity confirmed by HPLC. Single crystal *X*-ray structure analysis of one of these esters allowed the absolute configuration of the camphanates, and thus of the inositol 1-phosphates derived from them to be assigned. This confirmed the original assignment of structure (16) to the dextrorotatory isomer of inositol 1-phosphate. Phosphorylation of (44) and (45) with diphenylchlorophosphate, followed by transesterification with the anion of benzyl alcohol and deprotection by hydrogenolysis give the pure enantiomers of inositol 1-phosphate (15) and (16).[25]

B. Inositol 2-Phosphate.—An optically inactive inositol monophosphate was isolated from the acidic hydrolysis of wheat bran in 1912 and subsequently assigned the structure (27).[40,41] It is now clear the penultimate product of the acidic, alkaline, or enzymic hydrolysis of inositol hexakisphosphate (phytic acid) is inositol 2-phosphate (27).

Acetobacter suboxydans selectively oxidizes *myo*-inositol at the 2-position giving *scyllo*-inose (48)[40] and this intermediate has been used to prepare (27), Scheme 15.[41] Acetylation of (48) followed by hydrogenation of the carbonyl group gives

[40] T. Posternak, *Helv. Chim. Acta*, 1941, **24**, 1045.
[41] B. M. Iselin, *J. Am. Chem. Soc.*, 1949, **71**, 3822.



Scheme 16

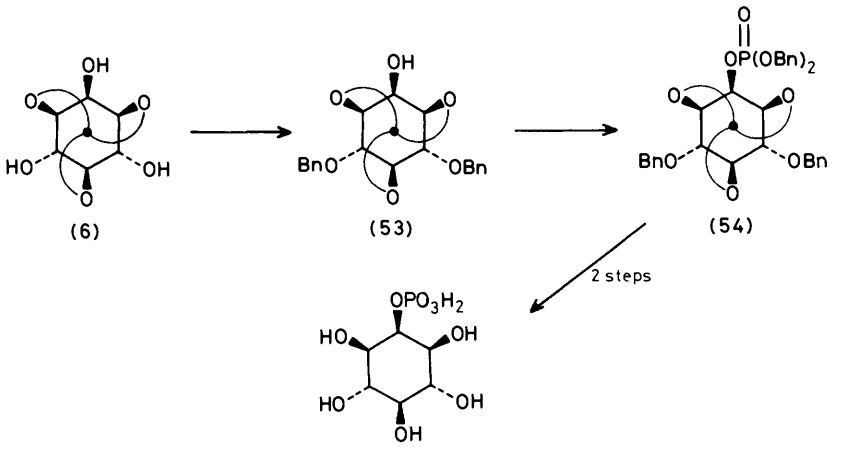
the pentaacetate (49). Phosphorylation with diphenyl chlorophosphate then gives (50) and subsequent deprotection gives inositol 2-phosphate (27).[41]

A more conventional approach[42] uses the previously described selective alkylation of the tetrabenzyl diol (21), Scheme 16. Benzylation of (21) gives predominantly the pentabenzyl alcohol (51). Phosphorylation using diphenylchlorophosphate under vigorous conditions, followed by transesterification then gives the fully protected compound (52). A single hydrogenolysis then removes all of the protecting groups, giving pure inositol 2-phosphate (27).

The previously described orthoformate (6) may be selectively dibenzylated at the 4- and 6-positions by taking advantage of the chelation-controlled reactions of mono anions of (6).[43] Thus, sequential treatment of (6) with 1 eq. of sodium hydride and 1 eq. of benzyl bromide, followed, after alkylation is complete, by a second treatment with 1 eq. of base and alkylating agent, gives (53) in good yield. Phosphorylation of (53) with sodium hydride/tetrabenzylpyrophosphate gives (54) which on deprotection gives inositol 2-phosphate (27), Scheme 17.

C. Inositol 4-Phosphate.—Alkaline hydrolysis of brain phospholipids gives a second optically active inositol monophosphate,[44] in addition to the dextrorotatory 1-phosphate, in minor quantities, and this is therefore one enantiomer of inositol 4-phosphate (20).

[42] J. J. Kulagowski and D. C. Billington, unpublished observations.
[43] D. C. Billington, R. Baker, J. J. Kulagowski, I. M. Mawer, J. P. Vacca, S. J. de Solms, and J. R. Huff, *J. Chem. Soc., Perkin Trans. 1*, in the press.
[44] C. Grado and C. E. Ballou, *J. Biol. Chem.*, 1961, **236**, 54.

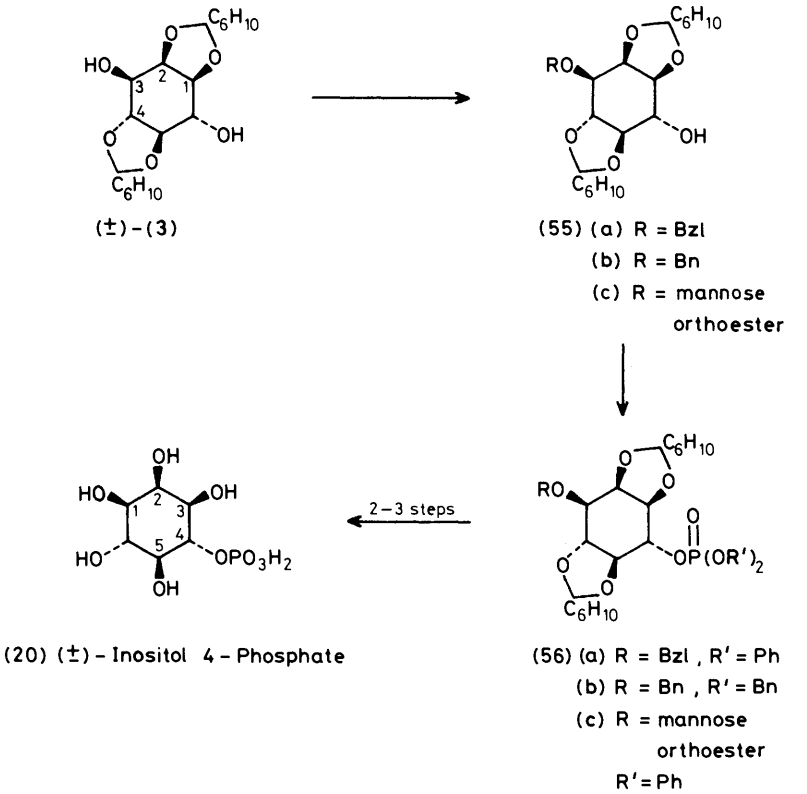


Scheme 17

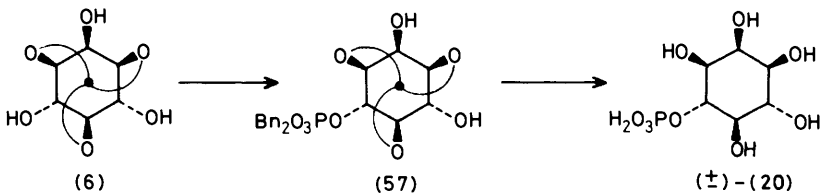
(i) *Racemic Material* (±)-(20). The majority of the racemic syntheses reported use the biscyclohexylidene acetal (3), Scheme 1 as starting material. Selective protection of the more reactive 3-hydroxyl group in (3) is possible, and the mono benzoate ester (55a),[45] mannose orthoester (55c),[39] and benzyl ether (55b)[25] have all been prepared and used as intermediates, Scheme 18. Phosphorylation of the selectively protected intermediate (55) at the free 6-hydroxyl gives the corresponding fully protected phosphate (56a—c). As C-4 and C-6 of *myo*-inositol are enantiotopic, the deprotection of these intermediates (56a—c) using standard methods gives (±)-inositol 4-phosphate, exploiting the symmetry inherent in the parent inositol. A more recent synthesis uses the chelation-controlled phosphorylation of the monoanion of orthoformate (6) to generate the protected phosphate (57), Scheme 19, in a single step.[23,43] Deprotection by hydrogenolysis of the dibenzylphosphate esters followed by acidic hydrolysis of the orthoformate group, gives (±)-inositol 4-phosphate (20) in excellent yield.

(ii) (+) *and* (−) *Inositol* 4-*phosphate* (60 *and* 61). Attempts to separate the diastereomeric D-mannose orthoesters formed from (±)-(3) [i.e. the diastereomers of (55c), Scheme 18] have not succeeded to date.[39] In contrast, treatment of the alcohol (55b) with commercial (−)-camphanic acid chloride gives a mixture of diastereomeric camphanate esters (58) and (59), Scheme 20, which are readily separable by crystallization and chromatography.[25] Hydrolysis of the camphanate esters gives the free enantiomers of (55b), which may then be converted into the enantiomers of inositol 4-phosphate (60) and (61) by the same methods used for the racemic series.[25] The absolute configurations of these enantiomers have not been confirmed by physical means to date.

[45] S. J. Angyal and M. E. Tate, *J. Chem. Soc.*, 1961, 4122.



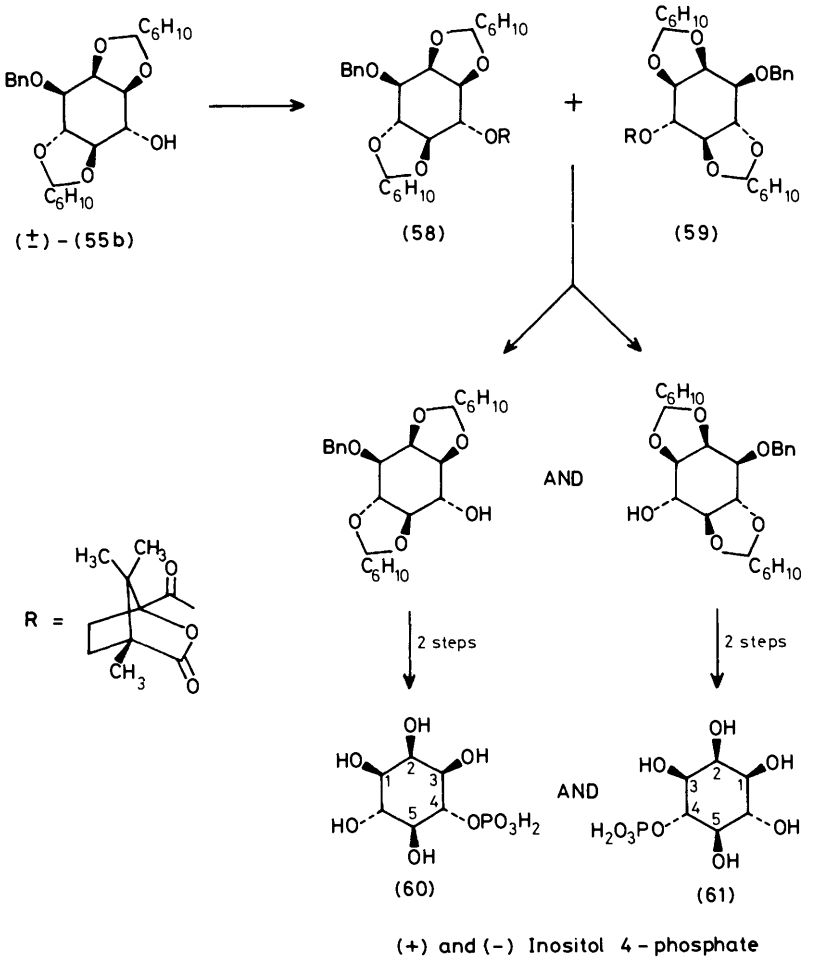
Scheme 18



Scheme 19

D. Inositol 5-Phosphate.—A single synthesis of inositol 5-phosphate (65) has been reported,[45] starting from the rather inaccessible 2-amino-2-deoxy-*neo*-inositol (62),[46,47] Scheme 21. The amino inositol (62) (obtained either by synthesis,[46] or by hydrolysis of the antibiotic hygromycin A[47]), protected as its pentaacetate

[46] G. R. Allen, *J. Am. Chem. Soc.*, 1956, **78**, 5691.
[47] J. B. Patrick, R. P. Williams, C. W. Waller, and B. L. Hutchings, *J. Am. Chem. Soc.*, 1956, **78**, 2652; R. L. Mann and D. O. Woolf, *ibid.*, 1957, **79**, 120.

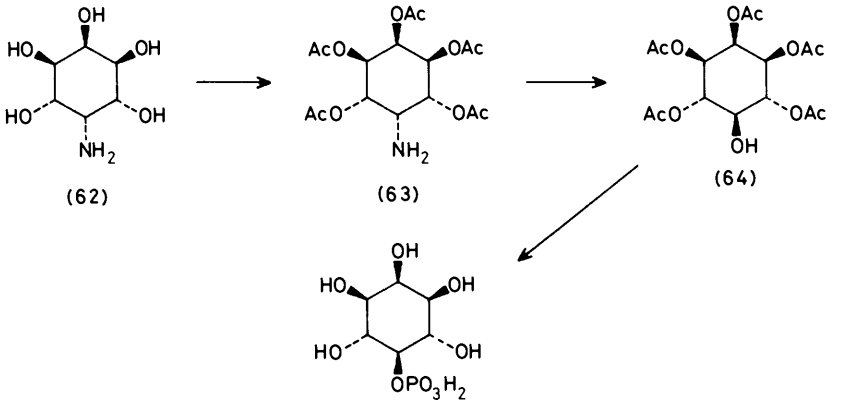


Scheme 20

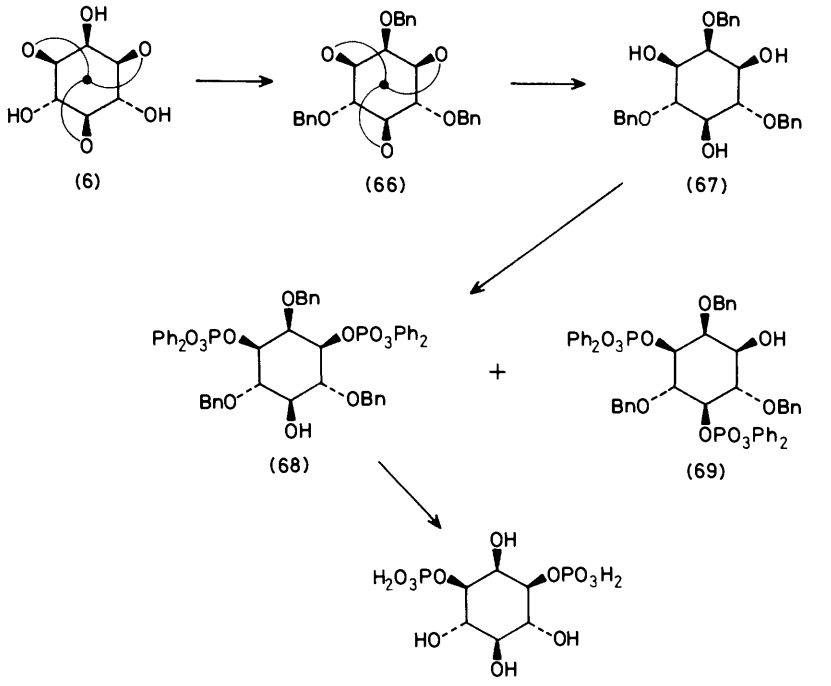
(63), gives the protected inositol (64) on treatment with nitrous acid. This conversion of NH_2 into OH proceeds exclusively with inversion of stereochemistry. Phosphorylation of (64) with diphenylchlorophosphate, followed by deprotection using standard methods gave inositol 5-phosphate (65).[45]

3 Synthesis of Inositol Bisphosphates

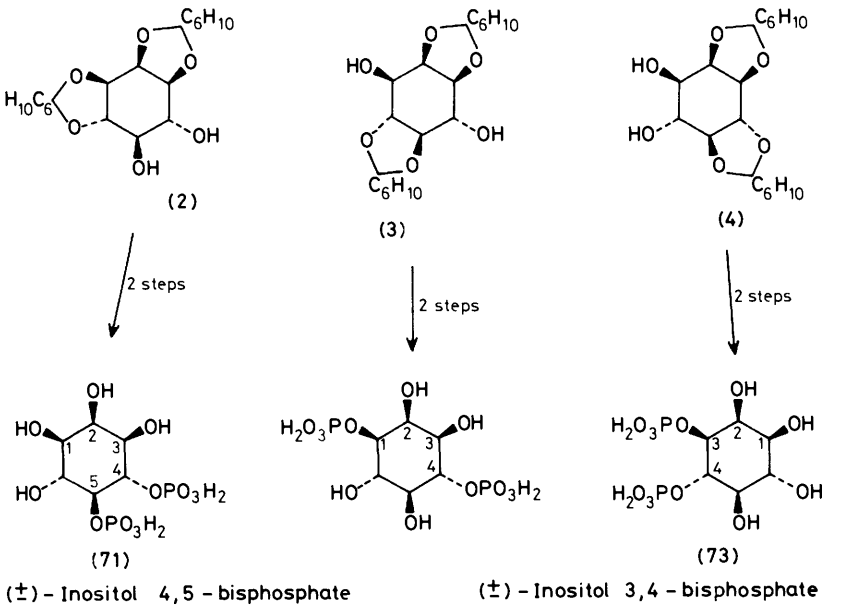
A. Inositol 1,3-Bisphosphate.—The symmetric nature of the orthoformate (6) has been exploited in the synthesis of inositol 1,3-bisphosphate.[23] Exhaustive benzylation of (6) gives the fully protected intermediate (66), Scheme 22, which on acidic



Scheme 21



Scheme 22

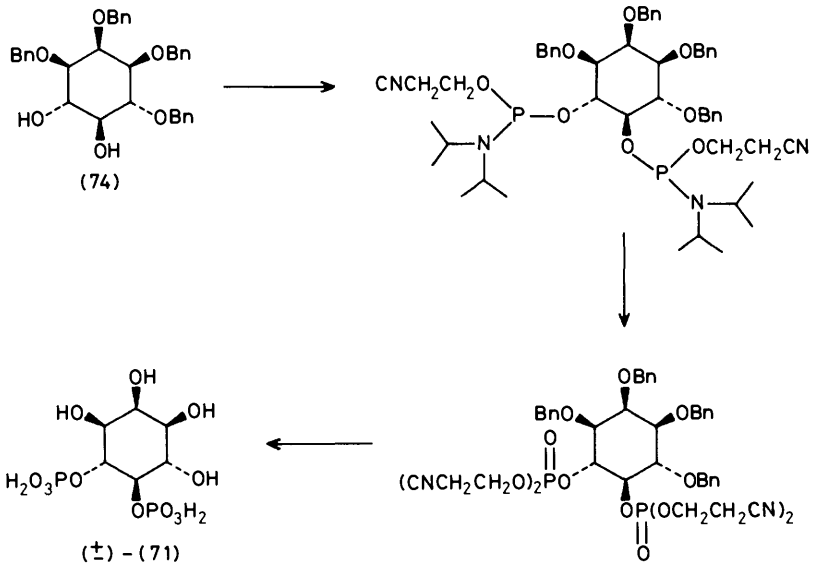


Scheme 23

hydrolysis gives 2,4,6-tri-*O*-benzyl inositol (67). As the 1- and 3-hydroxyl groups in (67) are less sterically hindered than the 5-hydroxyl, phosphorylation with diphenylchlorophosphate gives an 8:2 mixture of the 1,3-(68) and 1,5-(69) bisphosphorylated products. The desired 1,3-isomer (68) may be isolated by crystallization, and deprotection using lithium in liquid ammonia at −78 °C gives inositol 1,3-bisphosphate (70).[23,43]

B. Inositol 1,4-, 3,4-, and 4,5-Bisphosphates.—(i) *Racemic Syntheses.* Phosphorylation of the 3-biscyclohexylidine acetals (2), (3), and (4) of *myo*-inositol, Scheme 1, leads to syntheses of inositol 4,5-, 1,4-, and 3,4-bisphosphates (71), (72), and (73) respectively.[45] Scheme 23. The original method used employed diphenylchlorophosphate as a phosphorylating agent.[45] However, the use of a phosphite reagent, followed by oxidation to the phosphate, and deprotection has been reported recently, and is probably more efficient.[48] The phosphite method also allows the synthesis of phosphorothioates by oxidation of the intermediate P^{III} species with S_8 in pyridine in place of mCPBA, and has been applied to tetrabenzyl inositols [e.g. (74)] in addition to inositol bisacetals.[49,50] Scheme 24.

[48] M. R. Hamblin, J. S. Flora, and B. V. L. Potter, *Biochem. J.*, 1987, **246**, 771.
[49] M. R Hamblin, B. V. L. Potter, and R. Gigg, *J. Chem. Soc., Chem. Commun.*, 1987, 626.
[50] M. R. Hamblin, B. V. L. Potter, and R. Gigg, *Biochem. Soc. Trans.*, 1987, **15**, 415.



Scheme 24

Note the need to number compounds (71) and (72) clockwise in order to obtain the lowest number count (*i.e.* 4,5- and 1,4-bisphosphates, *not* 5,6- and 3,6-bisphosphates).

(ii) *Individual Enantiomers.* The individual enantiomers of all three of the above bisphosphates have been prepared from the resolved antipodes of the three bisacetals.[51] The acetals were resolved using the orthoesters of D-mannose as seen previously for the enantiomers of inositol 1-phosphate, Scheme 14.[38,39] The optically active bisacetals were then phosphorylated as before using diphenylchlorophosphate.

A more recent approach,[52] uses the conversion of the bisacetal (3) into its diastereomeric biscamphanate esters by treatment with 2 equivalents of (−)-camphanic acid chloride. These diesters may then be separated chromatographically and basic hydrolysis gives the enantiomeric bisacetals (*cf.* Scheme 20). Phosphorylation and deprotection gave the enantiomers of inositol 1,4-bisphosphate.

4 Synthesis of Inositol Trisphosphates

As previously outlined D-inositol 1,4,5-trisphosphate is now well established as a fundamental intracellular second messenger, directly involved in the mobilization of calcium from cellular stores. The problems inherent in the synthesis of this

[51] V. N. Krylova, N. I. Kobel'kova, G. F. Oleinik, and V. I. Shvets, *Zh. Org. Khim.*, 1980, **16**, 62.

[52] J. P. Vacca, S. J. de Solms, J. R. Huff, D. C. Billington, R. Baker, J. J. Kulagowski, and I. M. Mawer, manuscript in preparation.

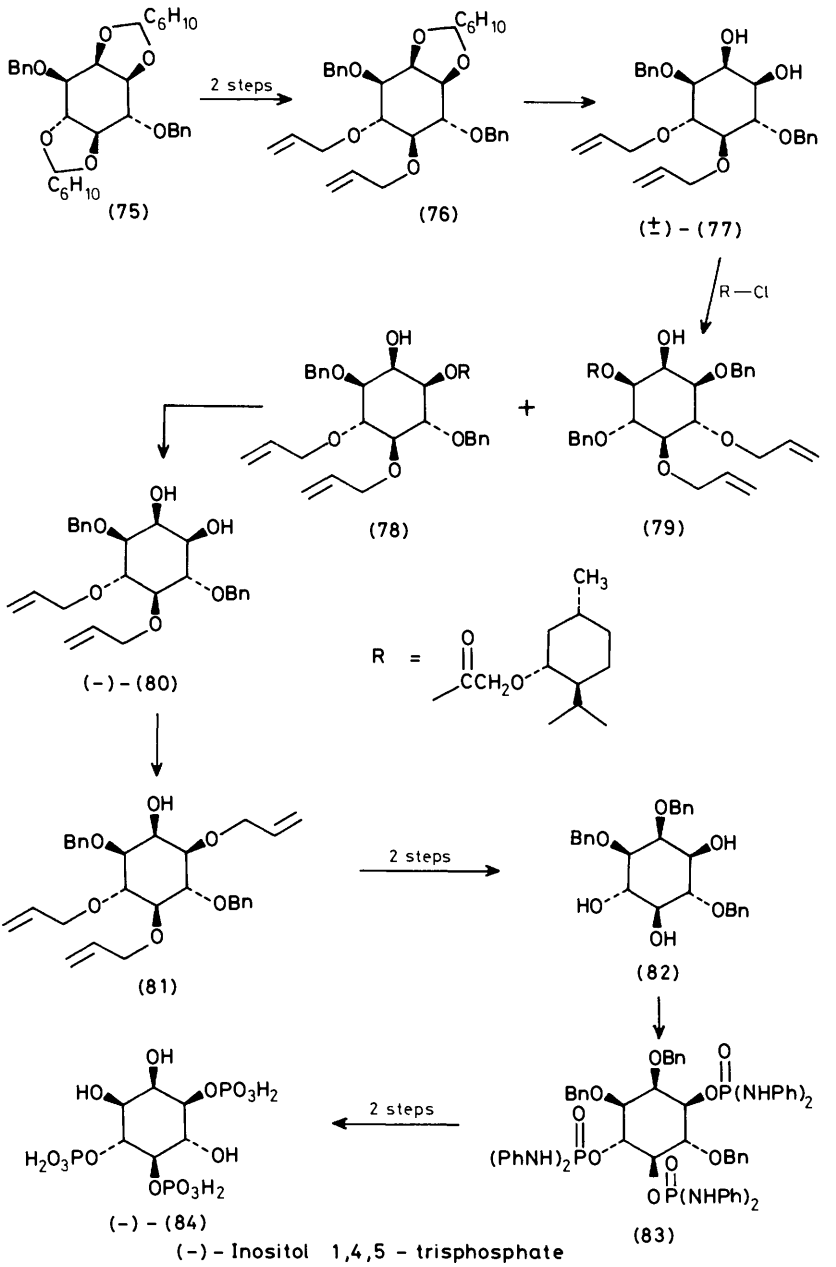
type of polyphosphate are highlighted by the fact that the first synthesis of 1,4,5-IP_3 was not reported until late 1986. A number of more efficient synthetic approaches have been published following this first disclosure, and isomeric trisphosphates including the 1,3,4-trisphosphate and 2,4,5-trisphosphate have also been prepared.

A. Inositol 1,4,5-Trisphosphate.—The first reported synthesis was of the D-(−)-isomer, (−)-(84). Benzylation of the bisacetal (3) gives the fully protected inositol (75), Scheme 25.[53] Selective hydrolysis of the less stable *trans* acetal, followed by allylation of the free hydroxyl groups generated gives (76), which on acidic hydrolysis gives (77). Racemic (77) may be resolved by conversion into its diastereomeric monomenthoxyacetyl derivatives (78) and (79) (reaction occurring only at the less hindered equatorial OH group), which are separable by crystallization and chromatography. Hydrolysis of the desired isomer (78) then gives the optically active diol (80). Selective allylation of the more reactive equatorial OH group in (80) [*cf.* Scheme 10, (21)—(24)] gives (81), which on benzylation and cleavage of the allyl protecting groups gives the triol (+)-(82). Phosphorylation of (+)-(82) with dianilidochlorophosphate gives the fully protected inositol 1,4,5-trisphosphate (83) which was sequentially deprotected to (−)-inositol 1,4,5-trisphosphate (84). The phosphorylation/deprotection strategy used gave only low yields of the desired product D-(−)-(84).

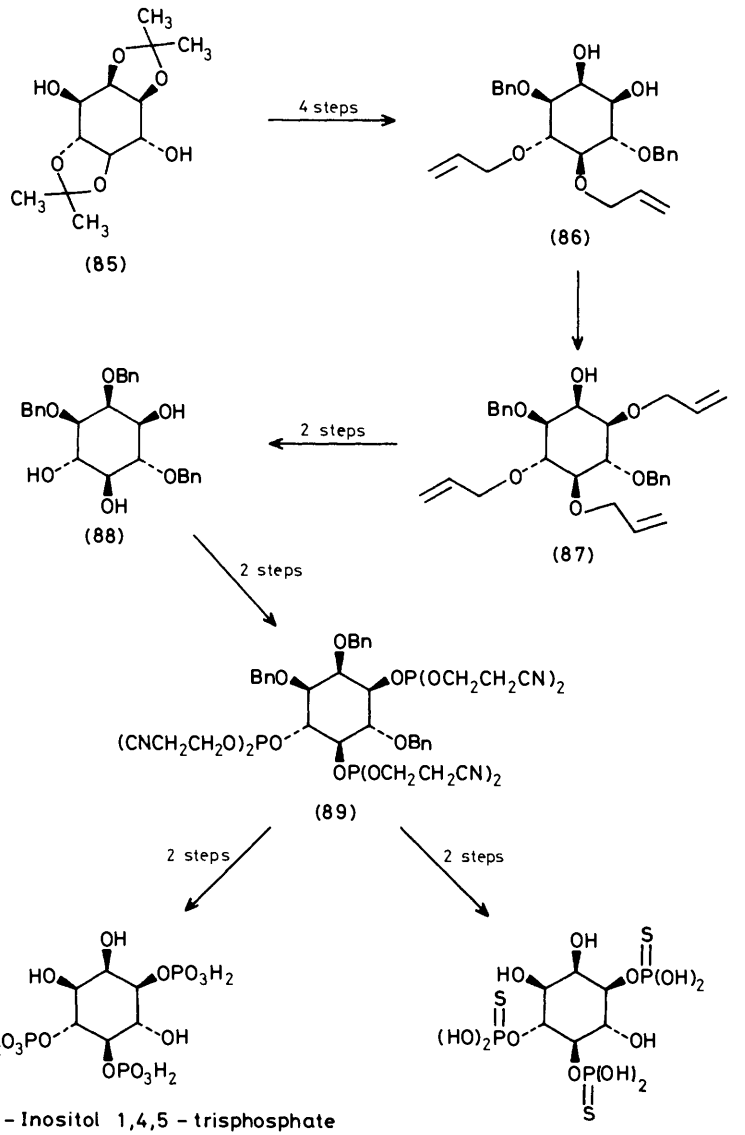
A more efficient synthesis of (−)-(84) would be possible by using one of the more recently reported phosphorylation/deprotection strategies, *e.g.* phosphorylation of the alkoxide with tetrabenzylpyrophosphate,[23,24] or reaction of the triol with *N,N*-diisopropyl dibenzylphosphoramidite, followed by oxidation and deprotection.[26] Both of these strategies have been shown to be generally applicable.

The selective allylation approach used above is based on the original work of Gigg *et al.*[18] who subsequently reported a modified route to the racemic form of (±)-(84), starting from the bis-isopropylidene acetal (85),[54] Scheme 26. Benzylation of (85), followed by acidic hydrolysis of the less stable *trans* acetal, allylation of the resulting diol, and a second acidic hydrolysis cleaving the *cis* acetal, gives the diol (86), as before. Treatment of the diol (86) with tributyltin oxide gave the cyclic dibutylstannylene derivative,[55] which on treatment with allyl bromide gave a high yield of the desired tri-*O*-allyl derivative (87). Benzylation of the free hydroxyl group in (87), followed by cleavage of the allyl groups then gives the racemic triol (±)-(88).[54] Reaction of (88) with $ClP(OCH_2CH_2CN)N(CHMe_2)_2$ followed by displacement of the diisopropyl amine with cyanoethanol gave the phosphite (89) (*cf.* Scheme 24 for the use of these reagents). Oxidation of phosphite (89) to the protected trisphosphate with t-butylhydroperoxide, followed by deprotection gave (±)-inositol 1,4,5-trisphosphate (±)-(90).[27,28] Alternatively

[53] S. Ozaki, Y. Watanabe, T. Ogasawara, Y. Kondo, N. Shiotani, H. Nishii, and T. Matsuki, *Tetrahedron Lett.*, 1986, **27**, 3157.
[54] J. Gigg, R. Gigg, S. Payne, and R. Conant, *J. Chem. Soc., Perkin Trans. 1*, 1987, 423.
[55] S. David and S. Hanessian, *Tetrahedron*, 1985, **41**, 643.


(75)
2 steps
(76)
(±) - (77)
R—Cl
(78)
(79)
(-) - (80)
R =
(81)
2 steps
(82)
2 steps
(-) - (84)
(83)
(-) - Inositol 1,4,5 - trisphosphate

Scheme 25


4 steps
(85)
(86)
(87)
2 steps
(88)
2 steps
(89)
2 steps
2 steps
(90) (±) - Inositol 1,4,5 - trisphosphate
(91) (±) - Inositol 1,4,5 - trisphosphorothioate

Scheme 26

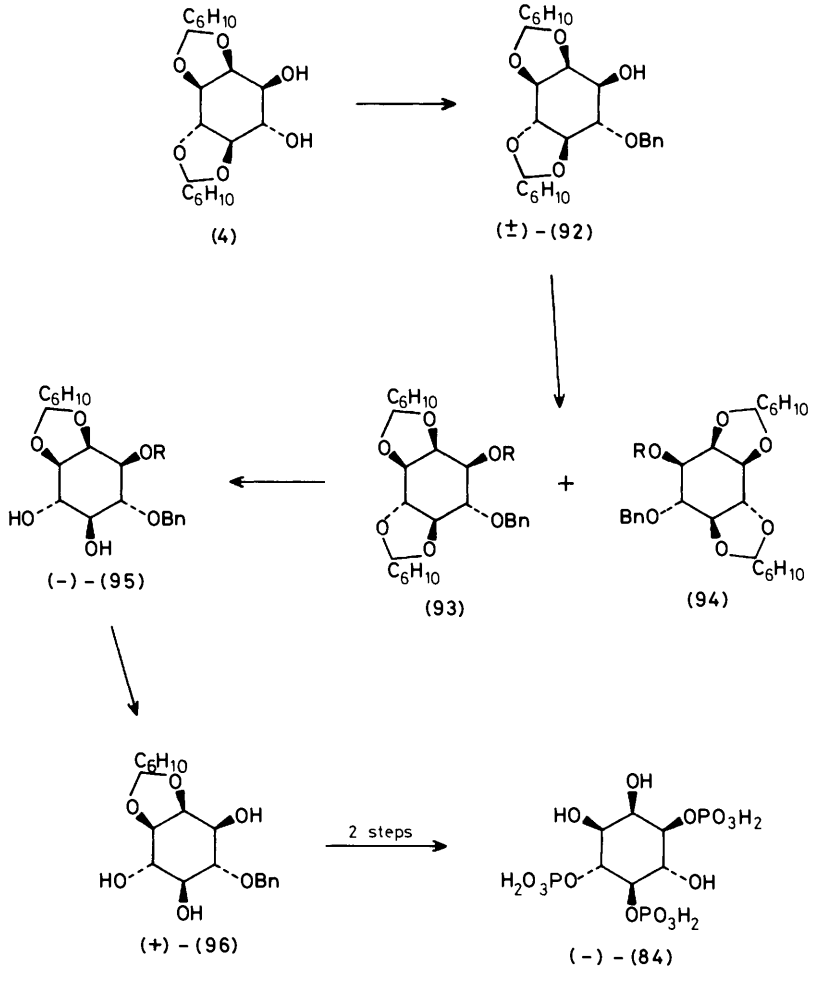
treatment of (89) with S_8 in pyridine followed by deprotection gave the trisphosphorothioate (±)-(91).[29]

In a related approach, Scheme 27, selective protection of the more reactive hydroxyl group in bisacetal (4) as the benzyl ether gives alcohol (92).[56] Conversion of this alcohol into its diastereomeric camphanate esters with (−)-camphanic acid chloride, followed by separation of the diastereomers [(93) + (94)] and hydrolysis of the less stable *trans* acetal in the desired isomer, gives the optically active diol (−)-(95). Basic hydrolysis of the ester group then provides the optically active triol (+)-(96). This triol may be efficiently phosphorylated using KH/THF/tetrabenzyl pyrophosphate, and deprotection by hydrogenolysis, and acidic hydrolysis of the remaining acetal gives (−)-inositol 1,4,5-trisphosphate, (−)-(84). The value of tetrabenzyl pyrophosphate as a phosphorylating agent is underlined by the *ca.* 60% overall yield of (−)-(84) from the triol (96).

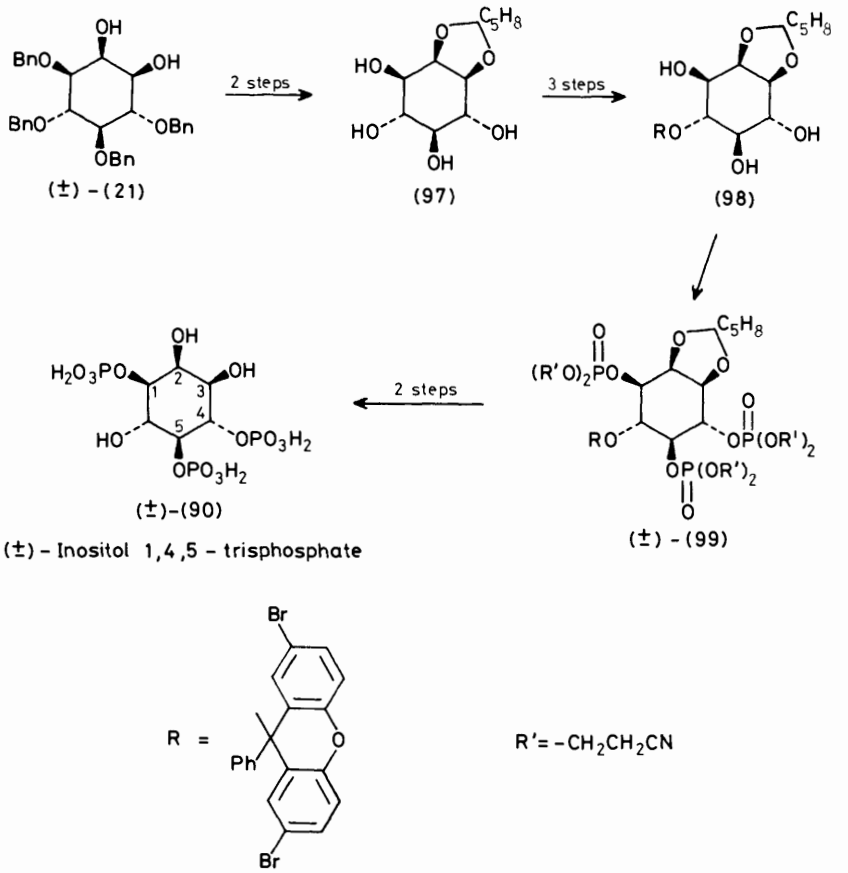
A less conventional approach[57] uses the cyclopentylidene acetal (97). Scheme 28, obtained from the previously described diol (21) (see Scheme 10) by acetalization and removal of the benzyl ethers using Na/NH_3. In a three-step sequence triol (98) is obtained by silylation of (97) with t-butyldimethylsilyl chloride, reaction of the crude product with 9-chloro-2,7-dibromo-9-phenylxanthene, and subsequent desilylation, in some 30—40% yield. Phosphitylation of (98) and oxidation to the phosphate gives the fully protected trisphosphate (99). Deprotection of (99) then gives racemic inositol 1,4,5-trisphosphate, (±)-(90). Repetition of the synthesis using enantiomerically pure diol (21) (obtained from the racemic diol by the method of Stepanov[58]) gave the optically active inositol 1,4,5-trisphosphate (−)-(84). An interesting and very short synthesis of the racemic trisphosphate (±)-(90) has recently been reported.[59] Phosphitylation of the tetrol (100) [obtained by benzoylation of bisacetal (3) and subsequent hydrolysis of both acetals], with 3.3 eq. of dimethyl chlorophosphate, followed by acylation of the crude product and oxidation of the phosphite products to phosphates with H_2O_2 gave the protected trisphosphate (101) in *ca.* 94% yield and 95% purity, Scheme 29. This selective phosphitylation of the equatorial hydroxyl groups thus avoids the need for a selective protection strategy. Deprotection with HBr in acetic acid and ester hydrolysis gave (±)-inositol 1,4,5-trisphosphate (±)-(90) of *ca.* 95% purity.

B. Inositol 1,3,4-Trisphosphate.—The racemic triol (104) required for the synthesis of inositol 1,3,4-trisphosphate (105) has been prepared by essentially the same strategy as seen for the 1,4,5-trisphosphate intermediates, Scheme 26, and has formed the basis of several synthetic approaches. Bis-allylation of acetal (3), followed by selective hydrolysis of the less stable *trans* acetal and benzylation of the resulting diol gives (102), Scheme 30. Hydrolysis of the *cis* acetal in (102) followed by regioselective allylation of the more reactive equatorial hydroxyl

[56] J. P. Vacca, S. J. de Solms, and J. R. Huff, *J. Am. Chem. Soc.*, 1987, **109**, 3478.
[57] C. B. Reese and J. G. Ward, *Tetrahedron Lett.*, 1987, **28**, 2309.
[58] A. E. Stepanov, B. A. Klyashchitskii, V. I. Shvets, and R. P. Evstigneeva, *Bioorg. Khim.*, 1976, **2**, 1627.
[59] J. L. Meek, F. Davidson, and F. W. Hobbs, *J. Am. Chem. Soc.*, 1988, **110**, 2317.



Scheme 27

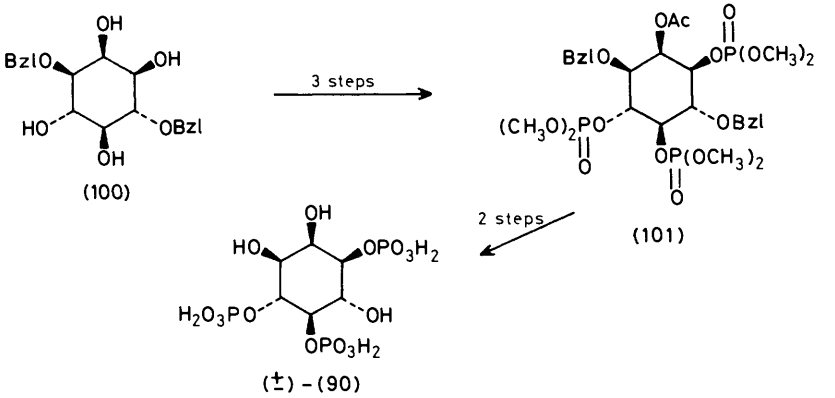


Scheme 28

group gives alcohol (103). Benzylation of (103) followed by cleavage of the allyl groups gives triol (104). This route has been followed with both the biscyclohexylidine acetal (3)[60] and the analogous bisisopropylidine acetal.[54] Phosphorylation of the alkoxide of (104) with tetrabenzylpyrophosphate (TBPP) gave the fully benzylated trisphosphate[61] which was cleanly deprotected to (±)-inositol 1,3,4-trisphosphate (±)-(105). Alternatively[60] phosphitylation with $ClP(OCH_2CH_2CN)_2$ followed by oxidation of the trisphosphite to the protected trisphosphate, and subsequent deprotection also gave pure (±)-(105).

A second approach involves the use of the bisacetals (2) and (4),[62] Scheme 31.

[60] C. E. Dreef, G. A. van der Marel, and J. H. van Boom, *J. R. Neth. Chem. Soc.*, 1987, **106**, 161.
[61] S. J. de Solms, J. P. Vacca, and J. R. Huff, *Tetrahedron Lett.*, 1987, **28**, 4503.
[62] S. Ozaki, M. Kohno, H. Nakahira, M. Bunya, and Y. Watanabe, *Chem. Lett.*, 1988, 77.



Scheme 29

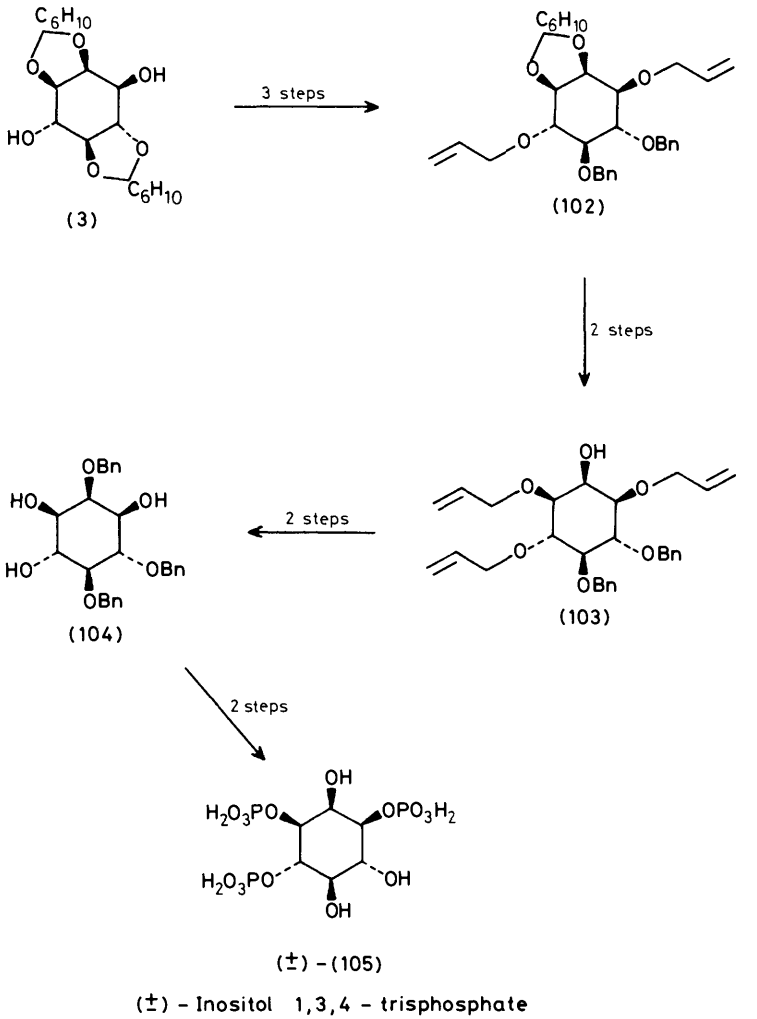
By reversing the order of incorporation of the benzyl and *p*-methoxybenzyl protecting groups, both (2) and (4) may be converted into the racemic diol (107), *via* selective hydrolysis of the *trans* acetals in (106a) and (106b) and subsequent protection of the diols. Cleavage of the remaining acetal gives diol (108) which may be resolved *via* its monomenthyloxyacetyl derivative (*cf.* resolution of (77) in Scheme 25] to give the required enantiomer of (108). Selective incorporation of a methoxymethyl group at the equatorial 1-position followed by benzylation gives the fully protected enantiomerically pure intermediate (109) which on removal of the PMB and MOM groups gives the optically active triol (110). Phosphorylation using TBPP as before then gives D-inositol 1,3,4-trisphosphate (111). A similar strategy using allyl ethers as temporary protecting groups has been used to obtain racemic triol (104) from ketal (2).[26]

C. Inositol 2,4,5-Trisphosphate.—Diol (112) has been prepared from the isopropylidene acetal corresponding to acetal (3), Scheme 32, by benzylation, hydrolysis of the less stable *trans* acetal, allylation of the resulting diol, and hydrolysis of the remaining acetal [*cf.* preparation of (86) from (85), Scheme 26].[54] Selective benzylation of the equatorial hydroxyl group in (112) and cleavage of the allyl groups gives (113) which, on phosphorylation with NaH/TBPP, followed by hydrogenolysis to remove the benzyl ethers and esters, gives (±)-inositol 2,4,5-trisphosphate (114).[61]

A formal synthesis of D-inositol 2,4,5-trisphosphate has also been reported[63] in which an intermediate diol corresponding to (112) was resolved *via* its monomenthoxy acetate derivatives as outlined previously, Scheme 25. This synthesis has not been successfully concluded to date due to problems with phosphorylation technology.

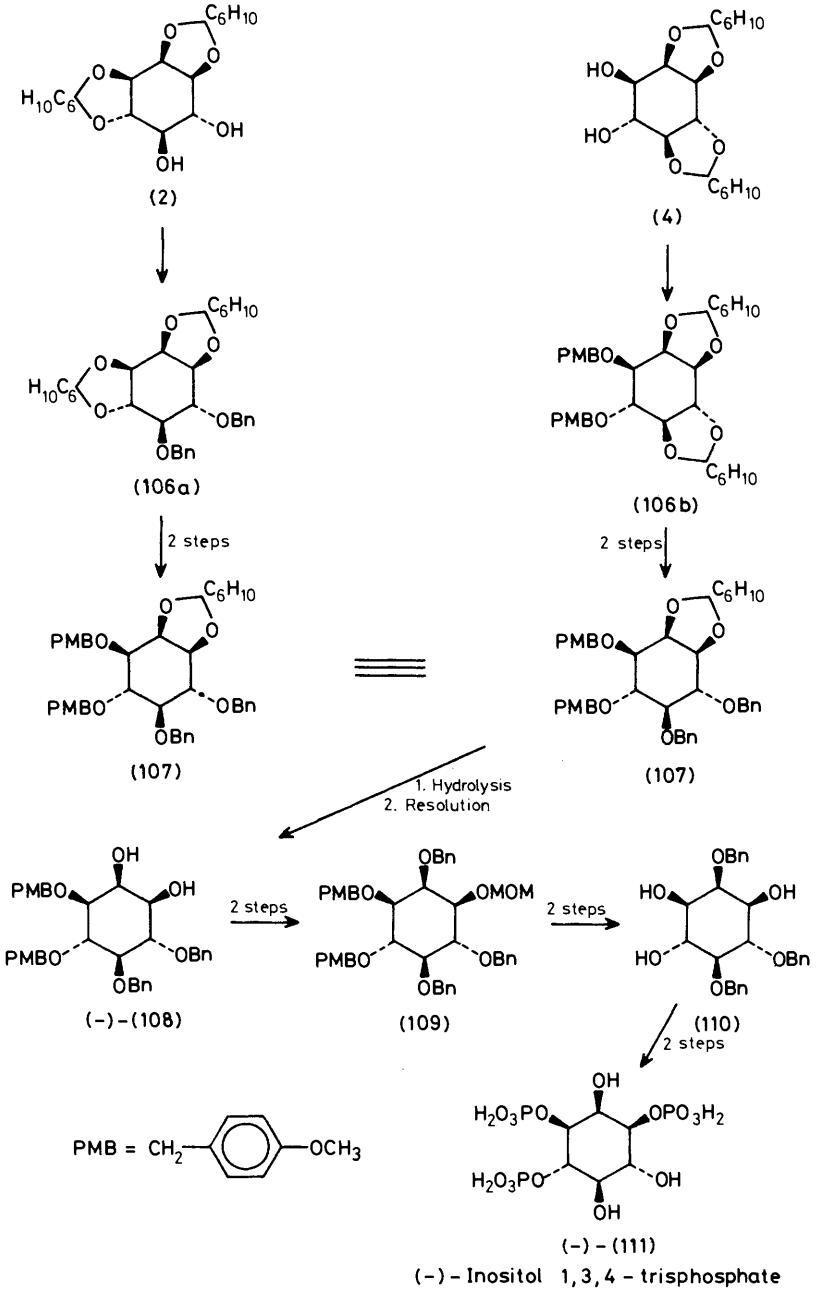
5 Synthesis of Inositol Tetrakisphosphates. The first reported synthesis of inositol 1,3,4,5-tetrakisphosphate[23] takes advantage of the highly specific chelation-con

[63] Y. Watanabe, T. Ogasawara, N. Shiotani, and S. Ozaki, *Tetrahedron Lett.*, 1987, **28**, 2607.

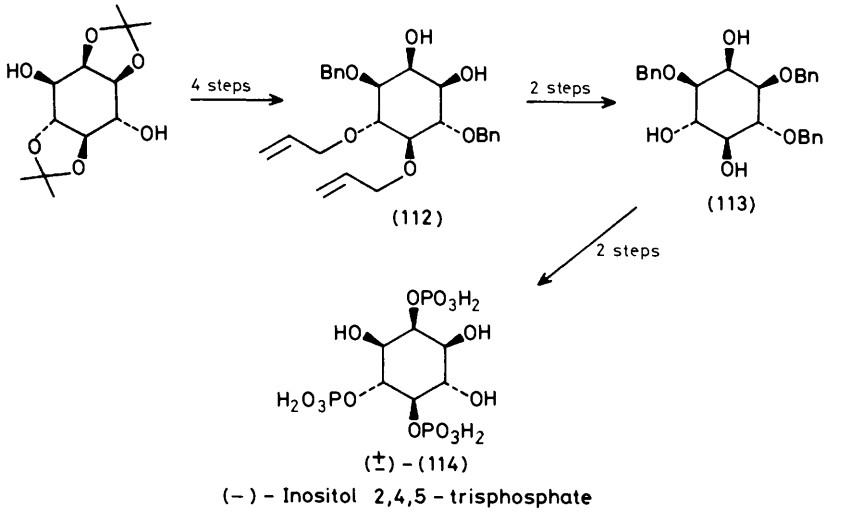


Scheme 30

trolled alkylation reactions of orthoformate (6), Scheme 33 (described previously Scheme 2, Scheme 17, and Scheme 19). Selective mono-allylation of (6) gives (115), which on benzylation gives (116). Isomerization of the allyl group to the enol ether followed by acid hydrolysis of the enol ether and orthoformate groups gives tetrol (117). Phosphorylation of (117) with TBPP/NaH/imidazole, gave the decabenzyl tetraphosphate (118) in high yield, which on hydrogenolysis gave (±)-inositol 1,3,4,5-tetrakisphosphate (119). An essentially identical synthesis


(2)
(4)
(106a)
(106b)
2 steps
2 steps
(107)
(107)
1. Hydrolysis
2. Resolution
(-)-(108)
2 steps
(109)
2 steps
(110)
2 steps
PMB = CH2 OCH3
(-)-(111)
(-)-Inositol 1,3,4-trisphosphate

Scheme 31



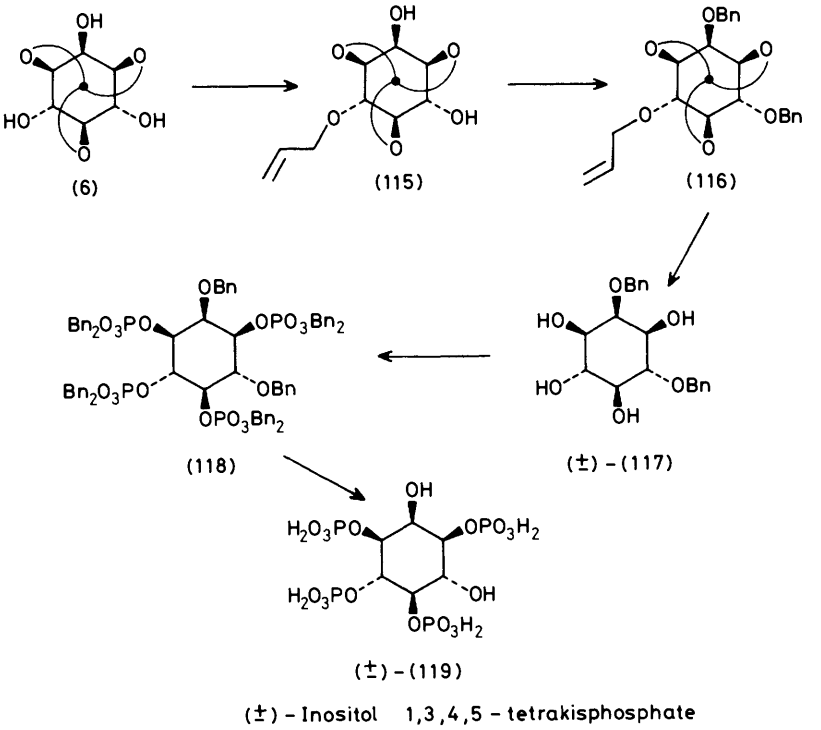
Scheme 32

using a benzyloxymethyl ether in place of the allyl group for temporary protection was completed concurrently and has subsequently appeared.[61] Phosphitylation of (117) with *N,N*-diisopropyl dibenzyl phosphoramidite, followed by oxidation of the tetrakisphosphite to the tetrakisphosphate and subsequent deprotection also gives (119) in high yield.[26] In a more conventional approach, Scheme 34,[64] acetal (3) was selectively benzoylated (*cf.* Scheme 18) using benzoyl imidazole/CsF giving (55a). Benzylation of the free hydroxyl in (55a) using benzyltrichloroacetimidate and a catalyst, followed by selective hydrolysis of the less stable *trans* acetal, benzoylation of the resulting diol, and subsequent hydrolysis of the remaining *cis* acetal gave diol (120). Conversion of diol (120) into its diastereomeric monomenthoxy acetates followed by separation of the diastereomers (121) and (122) gave optically pure intermediates. The desired diastereomer (121) was then benzylated to give the fully protected inositol (123), which on hydrolysis of the four ester groups gave the optically pure tetrol (124). Phosphorylation using TBPP followed by hydrogenolysis gave D-inositol 1,3,4,5-tetrakisphosphate (125).

Recently the enantiomers of tetrol (117) [*i.e.* (124) and (130)] have been reported,[65] prepared from the monosilyl orthoformate (126). Monobenzylation of (126) gives the alcohol (±)-(127), which may be resolved *via* conversion into the diastereomeric carbamates (128) and (129), Scheme 35.

Separation of the diastereomers is possible only after desilylation, and then benzylation of the free hydroxyl group, followed by hydrolysis of the carbamate and orthoformate groups gives the enantiomeric tetrols (124) and (130). An

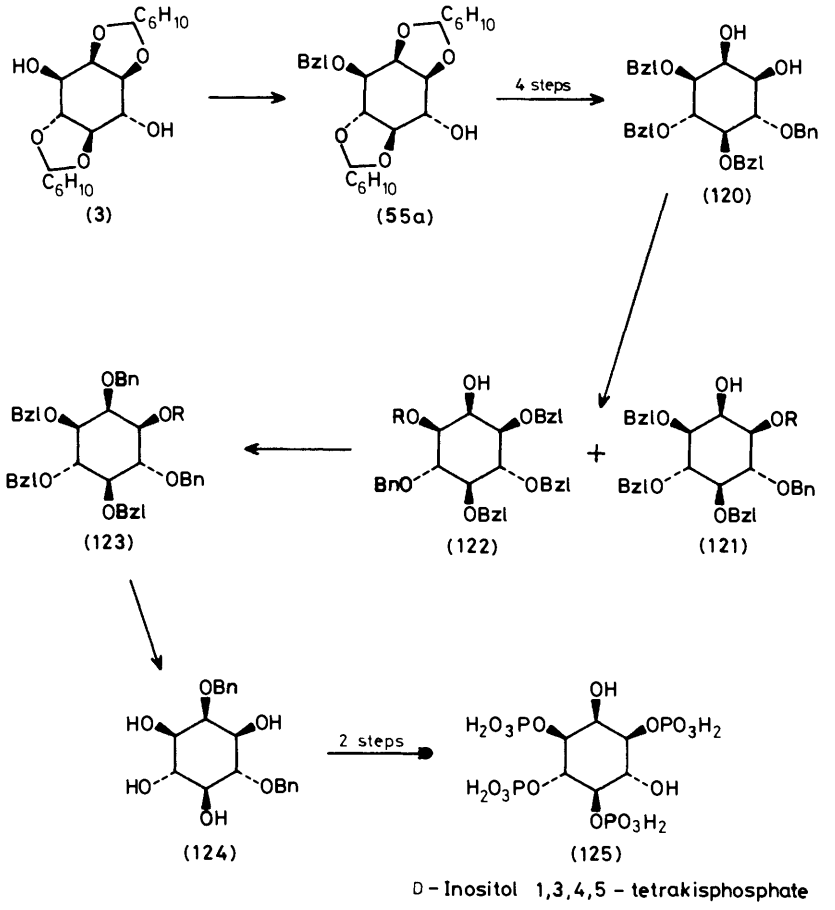
[64] S. Ozaki, Y. Kondo, H. Nakahira, S. Yamaoka, and Y. Watanabe, *Tetrahedron Lett.*, 1987, **28**, 4691.
[65] G. Baudin, B. I. Glanzer, K. S. Swaminathan, and A. Vasella, *Helv. Chim. Acta*, 1988, **71**, 1367.



Scheme 33

alternative approach[65] involves diesterification of (126) and subsequent desilylation to (131). Treatment of (131) with pig liver esterase gives a high yield of the optically active ester (−)-(132) in 95% e.e. Dibenzylation of (−)-(132), followed by ester and orthoformate hydrolysis then gives tetrol (130). Taking advantage of the symmetry properties of *myo*-inositol, (−)-(132) may also be converted into the enantiomeric tetrol (124). Protection of (−)-(132) as its bistetrahydropyranyl (THP) ether, ester cleavage, and benzylation of the resulting free hydroxyl group gives (133). Hydrolysis of the THP ethers followed by selective benzylation at the less hindered equatorial hydroxyl group gives (134), which on orthoformate cleavage gives (124). Phosphitylation, oxidation[65,26] and deprotection of these enantiomeric tetrols then gives (+)- and (−)-inositol 1,3,4,5-tetrakisphosphate.

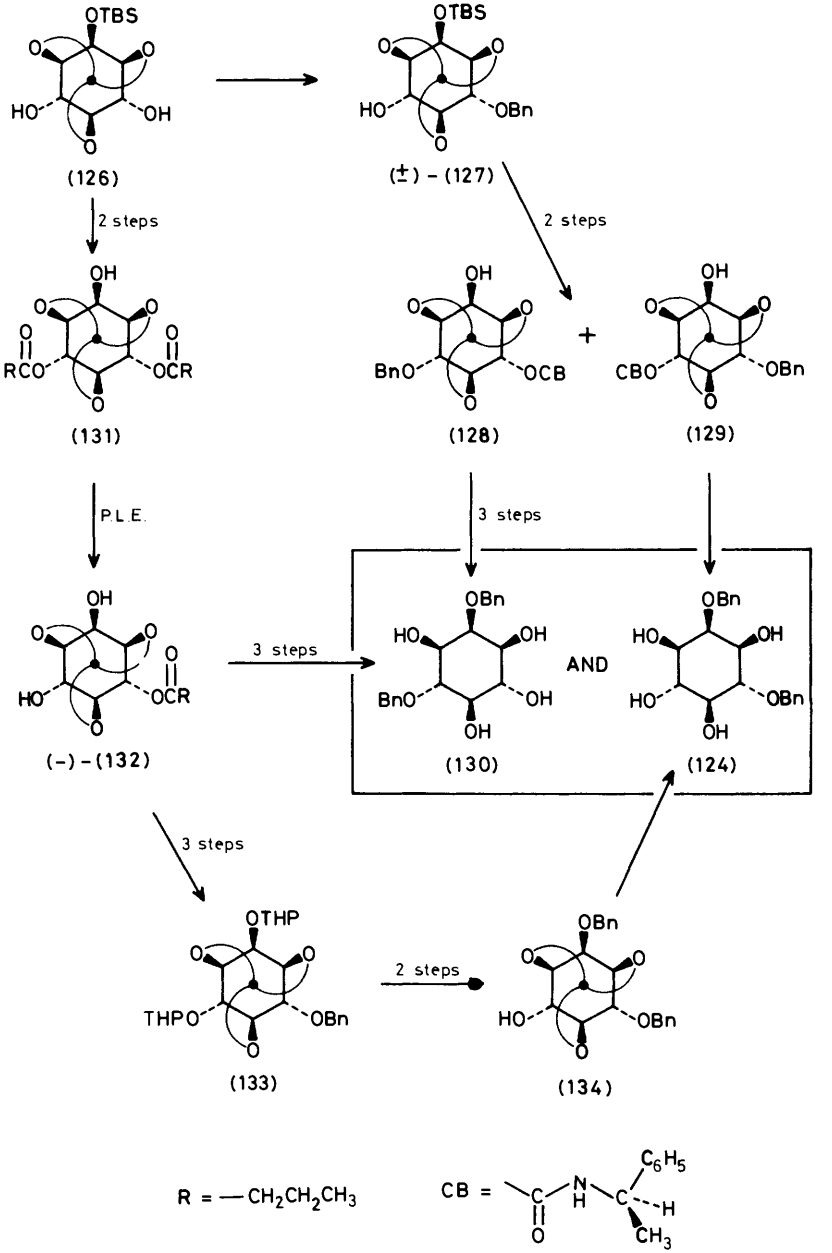
An alternative approach uses the migration of a benzoyl group from the equatorial position in (100) to the neighbouring axial position to obtain tetrol (135) in modest yield,[59] Scheme 36. Phosphitylation of (135) with $ClP(OMe)_2$, followed by oxidation gives the protected tetrakisphosphate (136). Acidic hydrolysis of the phosphate esters, followed by basic hydrolysis of the benzoate esters then gives racemic inositol 1,3,4,5-tetrakisphosphate (119).



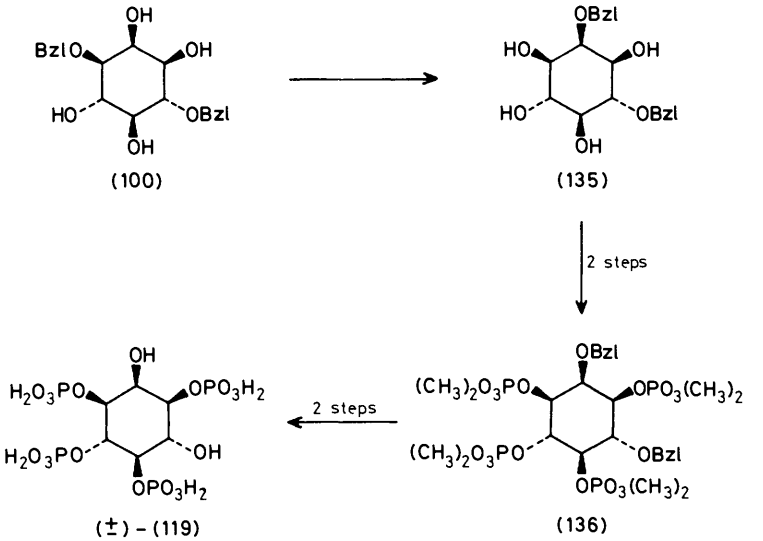
Scheme 34

6 Conclusions

From the above account it is clear that the major problems posed by the synthesis of inositol polyphosphates have been solved. Efficient protection


OTBS
HO
OH
(126)
2 steps
OH
RCO
OCR
(131)
P.L.E.
OH
HO
OCR
(-)-(132)
3 steps
OTBS
HO
OBn
(±)-(127)
2 steps
OH
BnO
OCB
(128)
+
OH
CBO
OBn
(129)
3 steps
OBn
HO
OH
BnO
OH
OH
(130)
AND
OBn
HO
OH
HO
OBn
OH
(124)
3 steps
OTHP
THPO
OBn
(133)
2 steps
OBn
HO
OBn
(134)
R = —CH2CH2CH3
CB =
C6H5
N
H
C
H
CH3
O

Scheme 35



Scheme 36

strategies, phosphorylation methods and deprotection techniques all exist. The next challenge to chemists in this area will be to design and synthesize molecular mimics with selective actions on specific enzymes in the PI cycle. These compounds hold the promise of establishing the details of this fundamental process, and may lead to improved therapies for a number of disease states.