

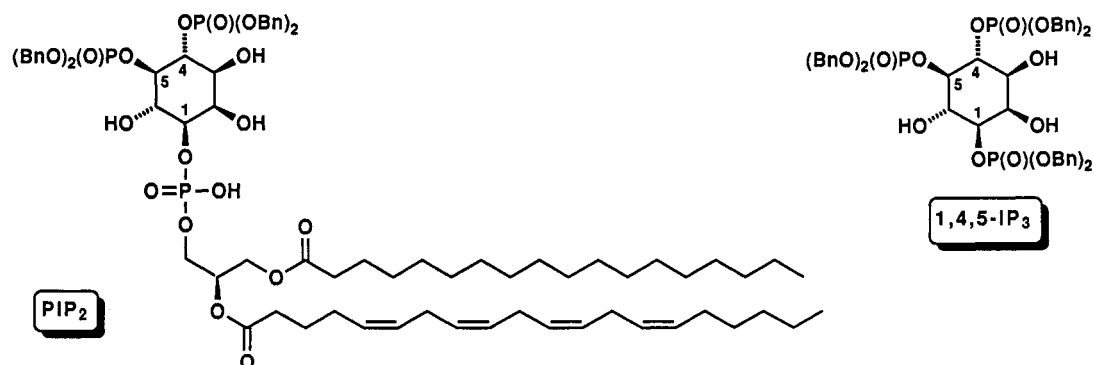
Stereoselective synthesis of inositol phosphates

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Abstract: *Pseudomonas putida* oxidation of benzene affords *cis*-3,5-cyclohexadiene-1,2-diol (**1**) which serves as a novel precursor for the syntheses of several natural products including (+)-pinitol, (+)-conduritol F, D-(-)-*myo*-inositol 1,4,5-trisphosphate and D-*myo*-inositol 1-phosphate. The versatility of this approach is further demonstrated by the preparation of other functionalised cyclitol derivatives, in particular 6-deoxy, 6-deoxy-6-fluoro, 6-deoxy-6-methyl and 6-methyl inositol 1,4,5-trisphosphates.

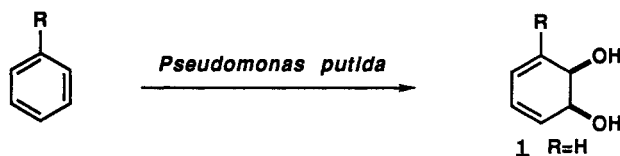
Following the discovery and characterisation of phospholipids from the brain by Ballou in 1961 (ref. 1), the hypothesis by Michell in 1975 (ref. 2) that the turnover of phosphoinositides coupled receptors to cellular calcium mobilisation, and the observation by Berridge in 1984 (ref. 3) that inositol 1,4,5-trisphosphate (IP₃) was the missing second messenger, a fundamental cell-signal transduction mechanism has been elucidated (ref. 4). This has led to a dramatic increase in interest in the inositol phosphates (refs. 5,6), in particular IP₃ which acts as a second messenger by binding to specific receptors on the endoplasmic reticulum thus stimulating the release of calcium ions from intracellular stores. The second messengers generated in the phosphatidylinositol (PI) cycle, by receptor controlled hydrolysis of phosphatidylinositol 4,5-bisphosphate (PIP₂), are known to regulate a large array of cellular processes including secretion, metabolism, contraction and proliferation.



Although knowledge of this phosphoinositide cell signalling system continues to grow rapidly (ref. 7), many factors remain unclear. For this reason there is an increased demand for supplies of the natural products and particularly of novel analogues to probe these mechanisms in more detail. The role of the synthetic chemist is therefore crucial to these studies.

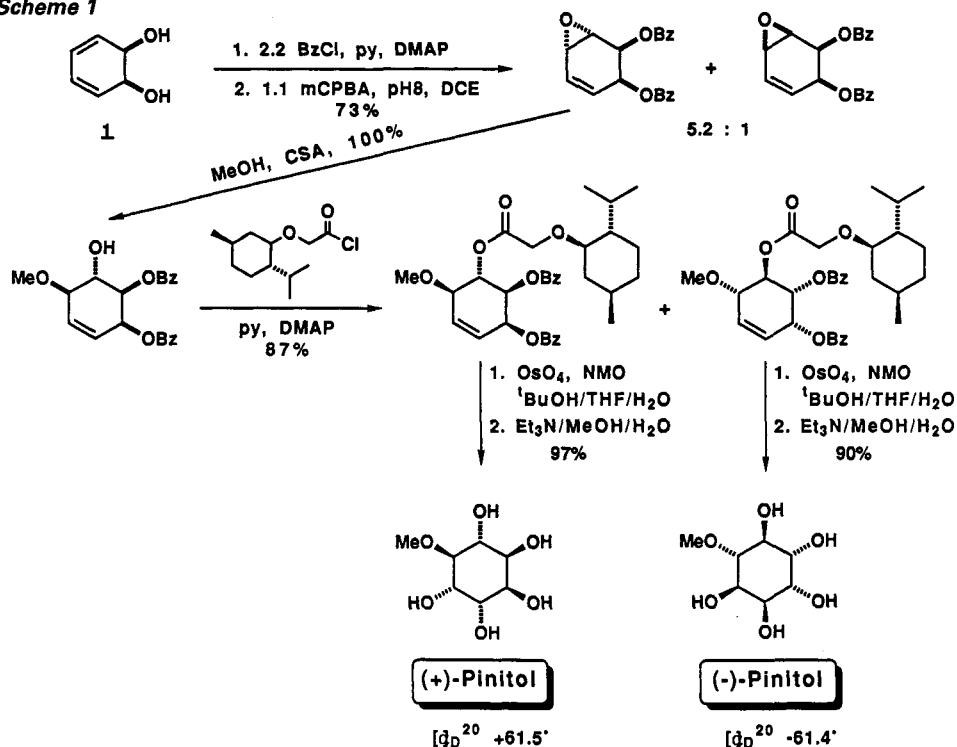
Furthermore, other cyclitol natural products (refs. 8,9), commonly found in plants, are emerging as important molecules for study owing to their involvement in regulatory processes, host recognition and perception by feeding insects, and many secondary biological processes. Biological screening has identified compounds which act as glycosidase inhibitors and hypoglycemic agents. Clearly opportunities exist for labelling experiments and for chemical modifications to enhance or alter the biological profile of these molecules.

Many of these compounds have already been synthesised (refs. 5,8,9), however, we chose to adopt a conceptually different approach which introduces the required stereogenic centres in a sequential fashion starting from an aromatic precursor. Conversion of the arene, such as benzene, to the corresponding *cis*-cyclohexadienediol (refs. 10–12), a superb cyclitol precursor, is achieved by the strategically important *Pseudomonas putida* microbial oxidation. The significance of this biotransformation stems from the fact that it converts an aromatic compound directly into an oxidised intermediate not presently accessible by a single conventional chemical reaction (ref. 13).



Moreover by using substituted arenes optically active derivatives can be obtained (refs. 10,14,15), and these diols serve as excellent novel building blocks for organic synthesis. Here we discuss some of our studies which have led to the preparation of several cyclitol natural products, and also show how the route may be adapted to yield a number of novel analogues for biological evaluation. Our studies have concentrated on the uses of commercially available *cis*-3,5-cyclohexadiene-1,2-diol (**1**), derived from benzene by microbial oxidation, although other diols have been investigated (refs. 10,14,15).

Scheme 1

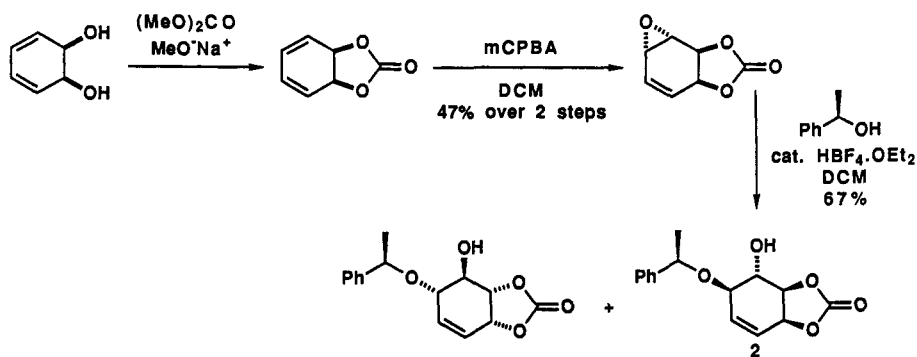


Our initial results showed how the diol (**1**) could be readily transformed in just five steps and excellent overall yield into the cyclitol natural product (+)-pinitol (ref. 10) (scheme 1). (+)-Pinitol has been shown to be a feeding stimulant for the larvae of the yellow butterfly *Eurema hecabe mandarina* and also a larval growth inhibitor of *Heliothis zea* on soybeans. More interestingly, however, this diol has recently been shown to have significant hypoglycemic and antidiabetic activity in normal and alloxan-induced diabetic albino mice and appears to be free from acute toxicity.

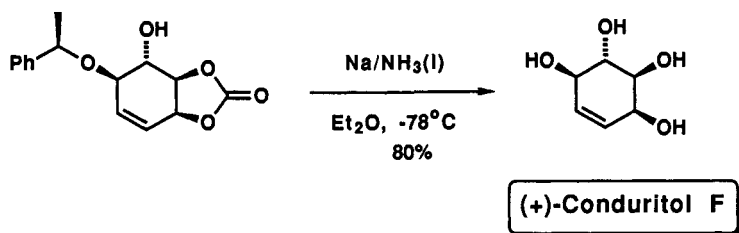
During this work the unnatural antipode (-)-pinitol was also obtained which was useful for comparative biological studies.

Our main effort however, has been directed towards the use of diol (**1**) as a precursor for the syntheses of inositol 1,4,5-trisphosphate (IP₃) and related derivatives. Here we have developed routes to racemic as well as optically pure compounds together with many novel analogues (refs. 11,12). Since space here does not permit a full discussion of this work the reader is referred to the cited references for further details. As an example of these investigations the preparation of (D)-(-)-1,4,5-IP₃ (ref. 12) is shown in scheme 3. Diol (**1**) is converted into the required racemic cyclic epoxy-carbonate by treatment with dimethyl carbonate followed by stereoselective epoxidation with *m*-chloroperbenzoic acid. The epoxide was then regioselectively opened with (R)-(+)-*sec*-phenethyl alcohol to give the readily separable diastereoisomeric alcohols (scheme 2).

Scheme 2



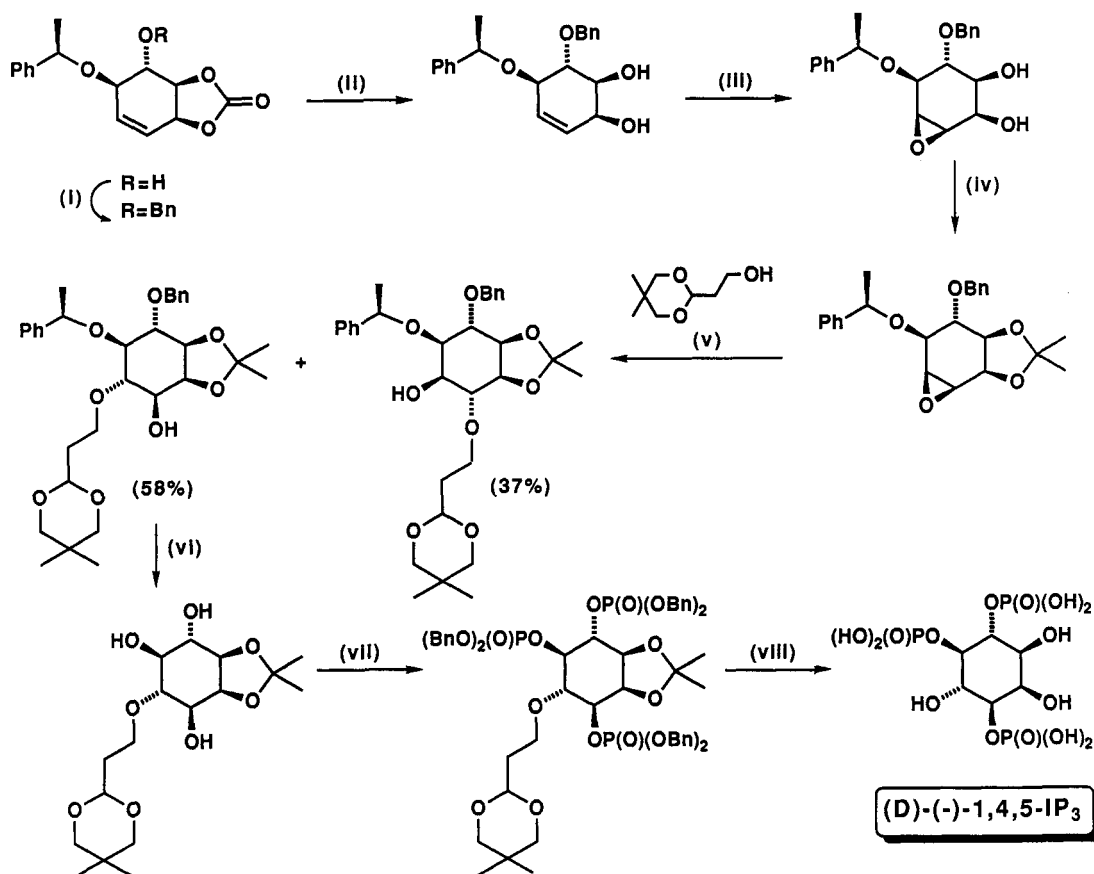
These key building blocks also pave the way to other natural products for example (+)-conduiritol F (ref. 18). This cyclohexenetetrol, found in most green plants, is obtained by simple reduction of alcohol (2) with sodium in liquid ammonia.



Overall this constitutes a synthesis of natural (+)-conduiritol F, with its four asymmetric carbon atoms, in only five steps from benzene. Another feature of scheme 3 which deserves comment is the use of the anion derived from 5,5-dimethyl-1,3-dioxane-2-ethanol as a new hydroxide equivalent. The unmasking of this group *via* hydrolysis of the acetal and subsequent β -elimination is achieved with the same reagent combination which simultaneously deprotects the 2,3-acetonide, thus providing three hydroxyl substituents at C-2,3 and 6 in one step. Also as the synthesis proceeds functional groups are introduced sequentially with a great deal of selectivity, thus providing considerable opportunity for interception of intermediates to yield novel compounds and phosphorylation patterns not easily obtainable by derivation of inositol itself. The use of the chiral benzyl substituent controls preparation of the homochiral materials and simultaneously affords hydroxyl group protection. The synthesis proceeds to optically pure products from an achiral precursor without the need for additional synthetic steps over the racemic route (ref. 12).

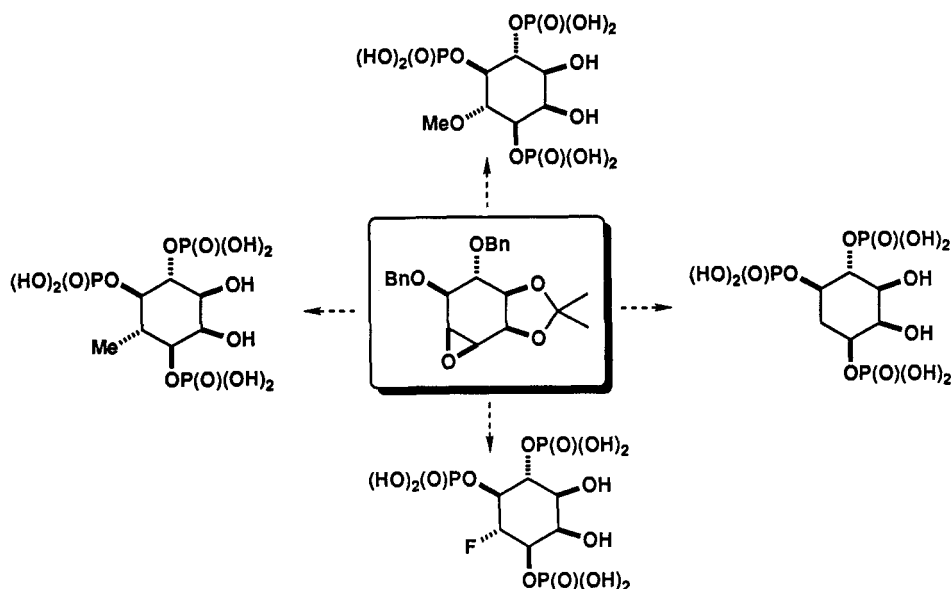
Regioselective ring opening of the epoxide in scheme 3 to set up the C-6 substituent is also important. Opening with other nucleophiles would give alternative C-6 derivatives which could be used to probe the various enzyme

Scheme 3

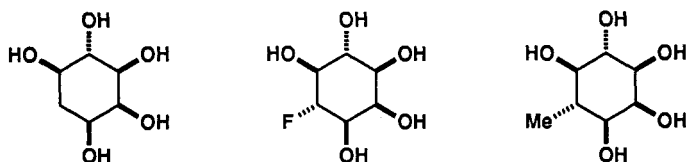


- (i) BnBr, Ag₂O, DMF, 3 days, 100%; (ii) Et₃N/MeOH/H₂O, 3 days, 99%; (iii) mCPBA, DCM, 87%;
 (iv) 2,2-Dimethoxypropane, CSA, DCM, 89%; (v) NaH, TMEDA, 110°C, 3 days, 95% combined yield;
 (vi) H₂, 10% Pd-C, EtOH, 16 h, 100%; (vii) ⁿBuLi, ⁱPr₂NH, THF, tetrabenzylpyrophosphate, -30°C-RT, 67%;
 (viii) a. H₂, 10% Pd-C, EtOH, 48 h; b. 80% aq. TFA, 4h, 88% overall.

mechanisms in the PI cycle. These would include binding and hydrolysis of the phosphate groups. We have therefore studied nucleophilic ring opening with methoxide, hydride, fluoride and methyl cuprates to provide these novel triphosphate analogues (refs. 11,12).



During these syntheses precursors for related parent cyclitols were also obtained giving a range a products, some of which are shown below (ref. 12).



Obviously, by appropriate modification of the route a vast number of other products and substitution patterns would be available in a concise and efficient manner. Moreover, by manipulation of the intermediate cyclohexene derivatives by cycloaddition reactions or ring cleavage processes an even greater range of useful synthetic materials becomes available. This novel approach for the conversion of arene to polyol derivatives harnessing, as it does, biotechnology and organic synthesis is a powerful strategy for future development. This is especially true when the biotechnological reaction cannot be readily achieved by conventional synthetic methods. Indeed it would be profitable to seek out these unique combinations and apply them to other situations.

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