Stereoselective Synthesis of *myo*-, *neo*-, L-*chiro*, D-*chiro*, *allo*-, *scyllo*-, and *epi*-Inositol Systems via Conduritols Prepared from *p*-Benzoquinone

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Keywords: Natural products / Asymmetric synthesis / Chiral resolution / HPIC-IPAD

A practical route is described for the flexible preparation of a wide variety of inositol stereoisomers and their polyphosphates. The potential of this approach is demonstrated by the synthesis of *myo*-, L-*chiro*-, D-*chiro*-, *epi*-, *scyllo*-, *allo*-, and *neo*-inositol systems. Optically pure compounds in either enantiomeric form can be prepared from *p*-benzoquinone via enzymatic resolution of a derived conduritol B key intermediate. High-performance anion-exchange chromatography with pulsed amperometric detection permits inositol stereoisomers to be resolved and detected with high sensitivity.

Introduction

Inositols (hexahydroxycyclohexanes) and their derivatives are widespread in nature and have various biological functions.[1,2,3] *myo*-Inositol phosphates in particular represent a large family of naturally occurring compounds which have been intensively studied during the last two decades because of their considerable role in cell signaling and homeostasis.[4,5,6] Since cellular concentrations of *myo*-inositol phosphates are low and a fast metabolic interconversion occurs, practical synthetic approaches to inositol phosphates are a prerequisite to further elucidation of their biological activity.

One important way to gain a better understanding of the metabolism and to study structure−activity relationships is the examination of specific stereoisomeric inositols (see Figure 1). For this reason there is an increasing demand for practical and efficient synthetic methods for preparing not only naturally occurring inositols but also diastereomers and their analogues. Although *myo*-inositol systems are by far the most abundant in living nature, several other inositol isomers have been detected; in most cases, however, their function remains unknown. We were attracted to the synthesis of stereoisomers of *myo*-inositol because of our ongoing study of the regiospecificity of phosphohydrolases.[7] Hexaphosphorylated inositol stereoisomers can serve as tools for exploring the structural requirements for dephosphorylation of phytases and other phosphohydrolases, enzymes which possess remarkable features for chemoenzymatic preparation of defined inositol phosphate isomers. A summary of the occurrence and possible functions of inositol stereoisomers is given in the following paragraphs.

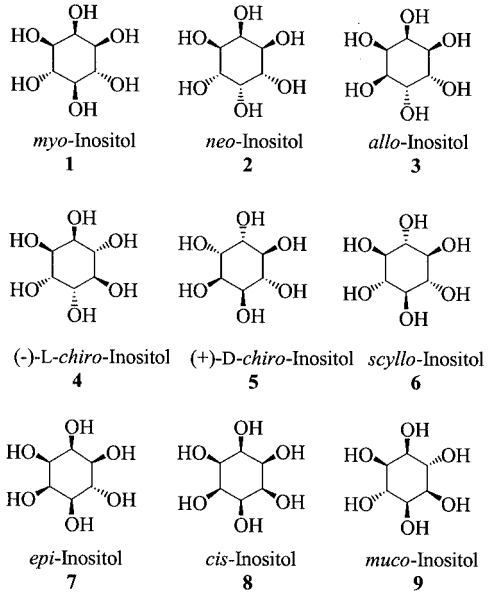

Figure 1. Stereoisomeric inositols

neo-Inositol **2**: This was first isolated as a by-product of the synthesis of L-*chiro*-inositol from 1,2:5,6-di-*O*-isopropylidine-L-*chiro*-inositol.[8] *neo*-Inositol hexakis(phosphate) has been recognized as a constituent of soil, in which it is often accompanied by larger amounts of *myo*- and *scyllo*-inositol hexakis(phosphates).[9] It has been shown that *Entamoeba histolytica*, a human intestinal parasite that causes

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  DOI: 10.1002/ejoc.200200572

amebiasis, contains high levels of several *neo*-inositol polyphosphates.[10] L-*neo*-Inositol-1-phosphate has been found in micromolar concentrations in the brain, heart, testes, and spleen of rat.[11] The most recent stereoselective synthesis of *neo*-inositol has been described by Hudlicky et al.[12] in a synthetic route requiring seven steps.

D-*chiro* **5** and L-*chiro*-Inositol **4**: Derivatives of *chiro*-inositol have recently been shown to mediate many important biological processes. For example, D-pinitol (3-*O*-methyl-D-*chiro*-inositol), an active component of the traditional antidiabetic plant *Bougainvillea spectabilis*, is claimed to possess insulin-like properties.[13] The phosphoinositolglycans generated in rat liver in response to insulin stimulation were reported to contain exclusively or predominantly *chiro*-inositol.[14] D-*chiro*-Inositol itself has been observed in reduced urinary excretion of rhesus monkeys and humans with impaired glucose tolerance, insulin resistance and type 2 diabetes mellitus.[15]

allo-Inositol **3**: This has not yet been found in nature; it was first synthesized in 1939 by Dangschat and Fischer.[16] Other syntheses have since been reported.[17]

epi-Inositol **7**: Shaldubina and co-workers showed that *epi*-inositol, another "non-natural" isomer, has the ability to modify the expression of the yeast *INO1* gene encoding the *myo*-inositol-3-phosphate synthase.[18] *epi*-Inositol is thus biologically active in its ability to affect the regulation of the *myo*-inositol biosynthetic pathway. *myo*-Inositol phosphates, especially *myo*-inositol 1,4,5-trisphosphate [*myo*-Ins(1,4,5)P_3], act as intracellular second messengers.[19] Binding of *myo*-Ins(1,4,5)P_3 to its endoplasmic reticulum receptor (ERR) induces the release of calcium from intracellular stores. Its closely related structure suggests that *epi*-Ins(1,4,5)P_3 **49** may also have a high affinity for this receptor.

scyllo-Inositol **6**: This has been found in animals and plants,[20] and it has been suggested that certain human diseases are associated with *scyllo*-inositol depletion.[21]

Many syntheses of inositol isomers either start from enantiomerically pure natural substances, particularly carbohydrates,[22] or involve resolution and stereospecific processes starting from inexpensive *myo*-inositol.[23] Some *de novo* concepts have also been described, for instance based on microbial oxidation of bromobenzene[12] or on generation of the cyclohexene ring by ring-closing metathesis and further functionalization of the derived conduritol (5-cyclohexene-1,2,3,4-tetrol, see Figure 2) systems.[24] Such strategies, however, often allow access to only one enantiomeric series and also require tedious multistep sequences.

In this paper we present easy and flexible syntheses of different inositols, with the potential to produce both enantiomers in the case of chiral systems. The key intermediates of our concept are conduritol B, E, and C derivatives (see Figure 2). Conduritols and their derivatives have themselves remarkable biological properties, as they can act as inhibitors of glycosidases.[25] Besides their pharmacological potential, they are useful precursors for the syntheses of inositols by stereoselective functionalization of the double bond. Because of their C_2-symmetry, conduritol B or E are especially valuable precursors, as the *cis*-dihydroxylation or epoxidation of the double bond leads to a single diastereomer.

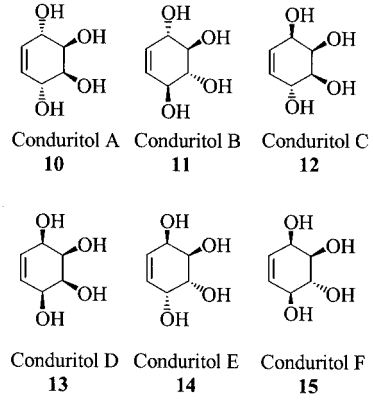


Figure 2. Stereoisomeric conduritols

Results and Discussion

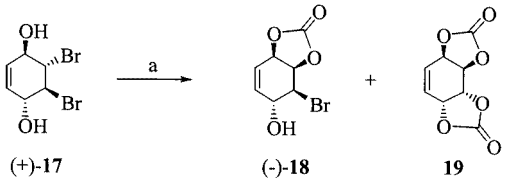
We have chosen a synthetic strategy for the synthesis of all chiral inositols in enantiomerically pure forms because the biological activities of these compounds and their phosphate derivatives, especially their role in signal transduction, can only be studied with enantiomerically pure phosphate derivatives.

Previous work led us to believe that the known enantiomerically pure diacetoxy-dibromocyclohex-5-ene (+)-**16** and (−)-**16** [or the corresponding diols (−)- and (+)-**17**], which can easily be obtained from *p*-benzoquinone in four steps on multigram scale, would be appropriate starting materials for the preparation of various conduritols.[26] Our synthetic concept is based on the stereospecific conversion of the building blocks (+)-**16** and (−)-**16** into suitably protected enantiomerically pure conduritol derivatives, which can subsequently be transformed to inositol isomers by simple functionalization of the double bond. Thus a single established enzymatic resolution can be used for the preparation of a wide variety of conduritol and inositol isomers. In this paper we describe a new synthetic methodology leading to conduritol E, conduritol C, conduritol F and conduritol B derivatives from enantiopure diacetate **16**.

To avoid confusion we should mention that, for the synthesis of *meso*-compounds (**1**, **2**, **3**, **6**, and **7**) all routes can likewise be carried out employing racemic **16** and **17**, respectively. As well as the benefits of a shortened synthetic route, this facilitates purification by recrystallization, since the racemic intermediates show an increased tendency to crystallize. We performed the synthetic sequences with enantiomerically pure starting material to provide the maximum analytical data and to use the full potential of the strategy for the enantiospecific synthesis of chiral derivatives. The intermediates presented can be used as valuable inositol building blocks, as their hydroxy groups are protected in an orthogonal way. Besides the examples shown in

this article, we have used the methodology to derive other *neo*- and *myo*-inositol phosphates, synthetic details are discussed in ref.[27] and in ref.[7] However, this concept is certainly not limited to the given examples and should prove valuable for the preparation of further compounds.

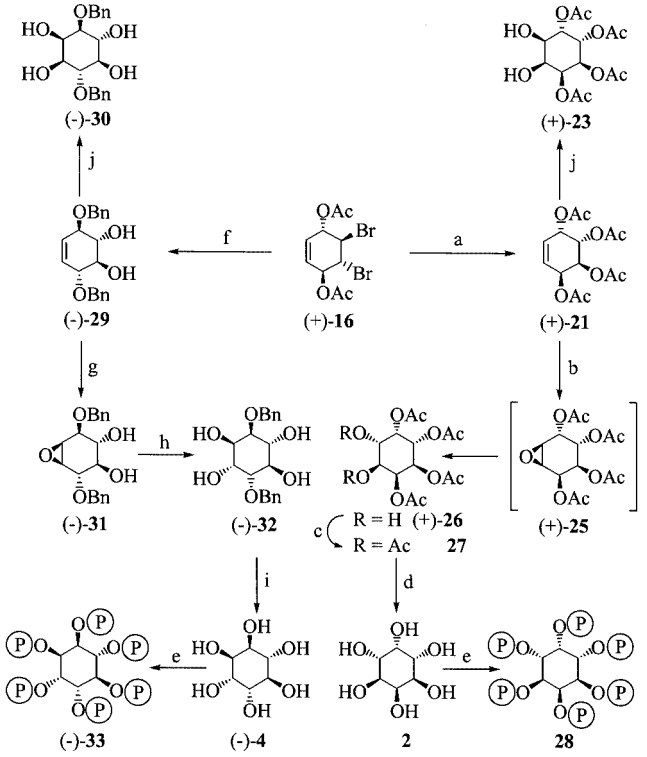
Synthesis of conduritol E systems: Retrosynthetic considerations showed that conduritol E derivatives should be suitable precursors for the synthesis of *neo*-inositol. Treatment of the diol (+)-**17** with DBU and CO_2 (see Scheme 1) afforded conduritol E bis-carbonate **19** in 30% yield along with the monocarbonate (−)-**18**.



Scheme 1. Preparation of the monocarbonate (−)-**18**; reagents and conditions: DBU, THF, CO_2, −50 °C, stirring for 2 h (−)-**18**: 92%, **19**: 0%; stirring for 12 h (−)-**18**: 60%, **19**: 30%

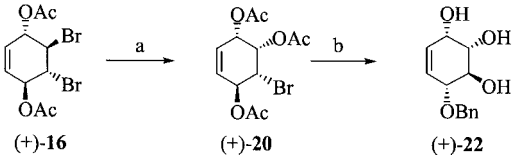
The low yield, purification problems, difficulties in scaling the reaction up and the extremely low solubility of **19** made it necessary to change the protection groups to acetates. We therefore tried to find a direct conversion of the diacetate (+)-**16** into the conduritol E (+)-**21**, as no easy and inexpensive large-scale conversion of (+)-**16** into (+)-**21** has been reported yet. The first synthesis of racemic conduritol E from *p*-benzoquinone was described by Balci et al.[28] in 1992 and involves five steps from **17**. Haines and co-workers[29] tried to generate **21** directly from **16** by heating it in aqueous acetic acid and potassium acetate for 24 h, but only 1,2,4-triacetoxy-3-bromocyclohex-5-ene **20** was isolated. The key intermediate in this reaction is an acetoxonium species. We thought that under appropriate conditions this intermediate should lead to conduritol E derivatives; namely, if the reaction were carried out in the presence of a sufficient amount of water, the diacetoxonium intermediate should direct the reaction towards the Woodward product.[30,31] We first tried this reaction under more forcing conditions by heating in aqueous acetic acid in the presence of silver acetate for 72 h. After acetylation under these conditions only (+)-**21** could be be detected by NMR spectroscopy. The low yield [less than 30%, which is presumably due to oxidation of allyl alcohol by silver(I)] and also the high price of silver acetate, which made this reaction unattractive for large-scale synthesis, made us look for alternatives. We were delighted to find that conduritol E could be obtained from (+)-**16** in aqueous acetic acid and sodium acetate simply by longer heating (10 days).

After acetylation and purification, (+)-**21** was obtained in 70% yield as the only isomer detected by NMR spectroscopy. The enantiomeric purity of this conduritol E tetraacetate was checked by chiral HPLC and found to be > 99% (see Scheme 2).



Scheme 2. Preparation of *neo*- **2** and L-*chiro*-inositol **4**; reagents and conditions: (a) 1. NaOAc, AcOH (95%), 10 days, 125 °C; 2. Ac_2O, CH_2Cl_2, DMAP (cat.). (b) $(CF_3CO)_2O$, H_2O_2, CH_2Cl_2, $NaHCO_3$. (c) Ac_2O, pyridine. (d) NaOMe, MeOH, then water/NaOH. (e) 1. (1,5-dihydro-2,4,3-benzodioxaphosphepin-3-yl)diethylamine, 1*H*-tetrazole, acetonitrile, then *m*-CPBA; 2. Pd/C, H_2, ethanol/water. (f) NaOBn, BnOH/THF. (g) $(CF_3CO)_2O$, H_2O_2, CH_2Cl_2, Na_2CO_3. (h) H_2SO_4, dioxane, H_2O. (i) Pd/C, H_2, ethanol/water. (j) $RuCl_3$, $NaIO_4$, acetonitrile

Enantiopure 1,2,4-triacetoxy-3-bromocyclohex-5-ene (+)-**20** was found to be an intermediate in this reaction and could easily be isolated in 85% yield if the reaction was stopped after three days (see Scheme 3).

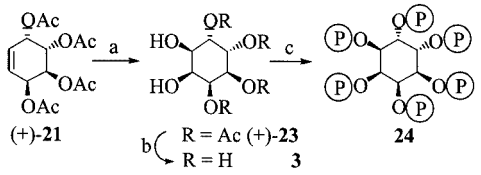


Scheme 3. Preparation of conduritol F derivative (+)-**22**; reagents and conditions: (a) 1. NaOAc, AcOH (95%), 3 days, 110 °C; 2. Ac_2O, CH_2Cl_2, DMAP (cat.); (b) NaOBn, BnOH

Synthesis of conduritol F systems: Synthesis of the conduritol F derivative **22** could be effected by treatment of (+)-**20** with an excess of sodium benzylate at room temperature by base-induced epoxide formation and subsequent ring opening at the allylic position (see Scheme 3). Chromatography of the crude reaction mixture on silica gel gave (+)-**22** as a colorless solid in 66% yield. Since *cis*-dihydroxylation of **22** would lead predominantly to *chiro*-inositol derivatives, which are also available by the route de-

scribed in Scheme 2, we did not carry out this reaction. However, this sequence allows access to *chiro*-inositol derivatives bearing a different protection group pattern. This may be of interest if the synthesis of specific derivatives is desired.

Synthesis of *allo*-inositol systems: The inherent C_2-symmetry of the conduritol E (+)-**21** makes it an ideal precursor for chiral *allo*-inositol systems (see Scheme 4). *cis*-Dihydroxylation leads only to the *allo*-configuration, regardless of the direction of attack by the hydroxylating reagent, and is carried out by reaction of conduritol E (+)-**21** with ruthenium trichloride and $NaIO_4$ in acetonitrile. Deprotection of (+)-**23** by treatment with a catalytic amount of sodium methoxide in methanol leads to pure *allo*-inositol **3** in 83% yield on multigram scale.



Scheme 4. Preparation of *allo*-InsP_6 **24**; Reagents and conditions: (a) $RuCl_3$, $NaIO_4$, acetonitrile. (b) NaOMe, MeOH. (c) 1. (1,5-dihydro-2,4,3-benzodioxaphosphepin-3-yl)diethylamine, 1*H*-tetrazole, dichloromethane then *m*-CPBA; 2. Pd/C, H_2, ethanol/water

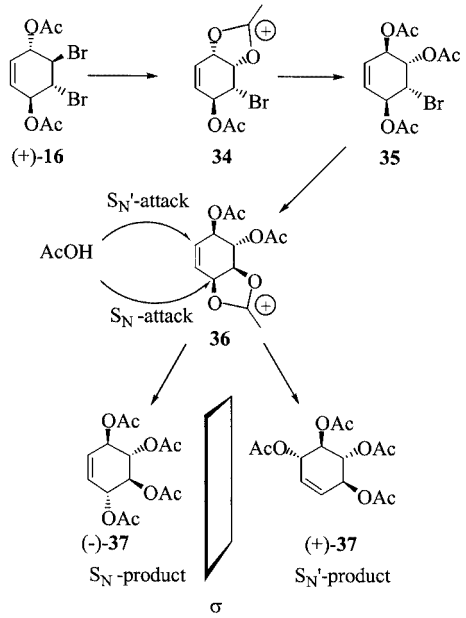
Synthesis of *neo*-inositol systems (see Scheme 2): Oxidation of (+)-**21** with trifluoroperacetic acid gave conduritol E epoxide (+)-**25**, which could be isolated for analytical purposes in 24% yield, besides epoxide-opening products. More forcing conditions effected complete in situ hydrolysis, the *neo*-inositol isomer being the only product detected. Hydrolysis of (+)-**26** or **27** with a catalytic amount of sodium methoxide in methanol was unsatisfactory because **2** precipitated along with some unsaponified material. Full deprotection was accomplished by refluxing the resulting precipitate in aqueous NaOH. Even in boiling water the solubility of **2** is very low.[32] Thus *neo*-inositol can easily be purified by recrystallization from water.

Synthesis of conduritol B systems: It is well known that diacetate (+)-**16** can be used for the preparation of conduritol B derivative (−)-**29** (see Scheme 2).[7] The reaction is carried out by heating (+)-**16** with an excess of sodium benzylate in anhydrous THF. The intermediate epoxides are opened with benzylate anion at the allylic position and form the conduritol B derivative (−)-**29** in over 80% yield.

Synthesis of *myo*-inositol systems: Compound (−)-**29** has served as a valuable precursor for the synthesis of *myo*-inositol derivatives. A fast *cis*-dihydroxylation of (−)-**29** with $RuCl_3/NaIO_4$ gives compound (−)-**30** with *myo*-inositol stereochemistry. The potential of C_2-symmetric intermediates in *myo*-inositol phosphate synthesis has been exploited several times.[7]

Synthesis of *chiro*-inositol systems: Because of the C_2-symmetry, epoxidation of the conduritol B derivative (−)-**29** gives only one product, (−)-**31** (see Scheme 2). In accordance with the "Fuerst−Plattner rule"[33] the oxirane ring under acidic conditions opens selectively to form only the *trans*-diaxial product, the *chiro*-isomer (−)-**32**. Hydrogenation of the dibenzyl *chiro*-inositol (−)-**32** gives the free *chiro*-inositol (−)-**4** as a colorless solid.

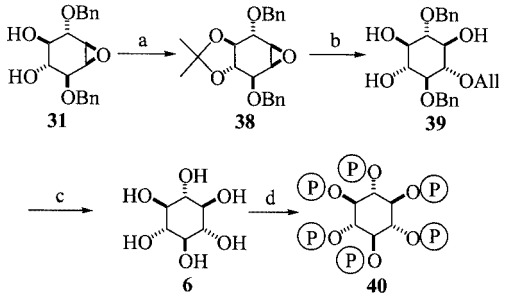
Considering the newly developed successful synthetic route to conduritol E **21**, it should be possible by means of an analogous method in the absence of water to synthesize conduritol B tetraacetate **37** in one step. We used a method reported by Stegelmeier, in which racemic diacetate **16** was converted into conduritol B **37** by heating under reflux in acetic acid/acetic anhydride in the presence of silver acetate.[34] In this reaction the acetoxonium intermediate undergoes ring opening by attack of acetate anions exclusively at the allylic centers to form the Prévost[35] product. Carrying out the reaction with enantiomerically pure (+)-**16** led to the conduritol B tetraacetate **37** as the only product (Scheme 5). The NMR spectroscopic data showed a pure product; however, the observed optical rotation was suspect with $[\alpha]_D^{20} = -54.1$ (c = 1.2, $CHCl_3$). Trost[36] and Ley[37] have reported substantially higher values for (−)-**32** {$[\alpha]_D^{20} = -172.8$ (c = 1.28, $CHCl_3$) and $[\alpha]_D^{20} = -70$ (c = 0.85, $CHCl_3$)}. The isolated product was analyzed by chiral HPLC (chiracell ODH, heptane/2-propanol, 95:5) and in accordance with the measured low optical rotation it indicated an enantiomeric excess for (−)-**37** of only 24%. The reason for this result may be that besides S_N2-attack (opening in the allylic position) there is some S_N'-attack (1,4-attack) which occurs for steric reason from the back side to form the opposite enantiomer (+)-**37** and leads to partial racemization.



Scheme 5. Preparation of the Prévost product **37** from diacetate (+)-**16**; reagents and conditions: (a) AgOAc, absolute AcOH/Ac_2O, 1 day, 125 °C

Synthesis of *scyllo*-inositol systems: We were pleased to see that the regioselectivity of the epoxide opening of **31** could be controlled by careful choice of reaction conditions

and protection groups. We observed that derivative **38** bearing a cyclic isopropylidene group in the 5 and 6 position showed inverted regioselectivity on epoxide opening, leading mainly to the *scyllo* isomer **39** (see Scheme 6). Upon opening with several *O*-nucleophiles, for instance allyl alcohol or methanol, we were able to isolate the corresponding inositols in good yield. After epoxide opening with allyl alcohol followed by deprotection with acid we obtained the pure *scyllo* isomer **39** in 60% yield after recrystallization. In the case of methanol as the nucleophile, the *scyllo*/*chiro* ratio was determined to be 95:5 (by GC, products detected as acetates).



Scheme 6. Synthesis of *scyllo*-inositol; Reagents and conditions: (a) 2,2-dimethoxypropane, acetone, PPTS. (b) 1. NaOAll, AllOH, 90 °C. 2. HCl. (c) 1. Pd/C, MeOH; 2. HCl, 3. Pd/C, H_2. (d) 1. (1,5-dihydro-2,4,3-benzodioxaphosphepin-3-yl)diethylamine, 1*H*-tetrazole, dichloromethane, then *m*-CPBA; 2. Pd/C, H_2, ethanol/water

The regioselectivity of the epoxide opening of **38** seems to be in contrast to the "Fuerst–Plattner Rule", which applies for a cyclohexene epoxide in chair conformation.[33] It is likely that the strain of the cyclic isoproylidene ring favors reaction via a twist intermediate (see Figure 3), which is the preferred conformation of **38** according to molecular modeling with HyperChem. 5.01 (TM of Hypercube Inc; the calculation was performed with a semiempirical AM1 method as algorithm).

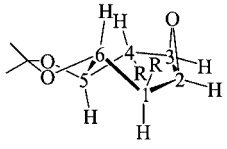
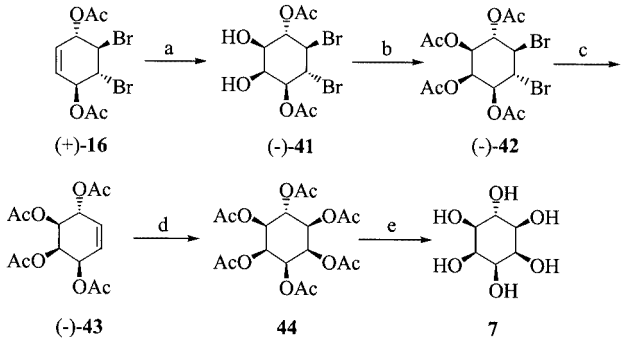


Figure 3. Model of isopropylidene-protected epoxide **38** in a twist conformation; for better view the OBn groups are replaced with R

Acidic workup of the epoxide-opening reaction left the allylic group intact. Therefore, isomerization of the double bond was induced by palladium on charcoal, followed by acidic cleavage of the resulting enol ether. Finally, hydrogenation led to the desired *scyllo*-inositol **6** in 85% overall yield from **39**.

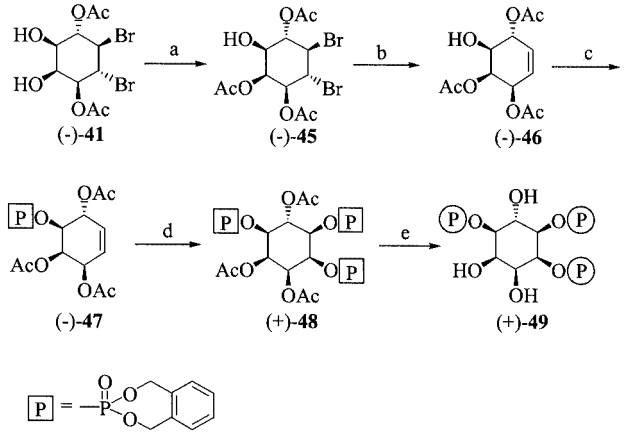
Synthesis of *epi*-inositol systems: A key compound for the preparation of *epi*-inositol might be a conduritol C derivative. An easy preparation of this conduritol derivative by the route depicted in Scheme 7 has already been devised.[38]



Scheme 7. Preparation of *epi*-inositol; Reagents and 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

Interestingly, *cis*-dihydroxylation of conduritol C tetraacetate (−)-**43** with $RuCl_3/NaIO_4$ resulted predominantly in *epi*-inositol stereochemistry. The observed high diastereoselectivity (80% *de*) may be caused by the axial acetate group, which might be a Lewis donor for the ruthenium complex. To avoid protecting-group movement, the product was converted directly into the hexaacetate **44**, whose diastereomeric ratio was determined. Recrystallization from ethanol led to pure **44**, which was deprotected under standard conditions.

As an example of the opportunities provided by this concept for the synthesis of enantiomerically pure *epi*-inositol derivatives, we describe the synthesis of *epi*-Ins(1,4,5)P_3 (+)-**49** (see Scheme 8).



Scheme 8. Preparation of *epi*-Ins(1,4,5)P_3 (+)-**49**; Reagents and conditions: (a) 1. $CH_3C(OEt)_3$, THF, *p*TsOH; 2. AcOH (80%). (b) Zn, Et_2O, AcOH, I_2. (c) (1,5-dihydro-2,4,3-benzodioxaphosphepin-3-yl)diethylamine, 1*H*-tetrazole, CH_2Cl_2 then *m*-CPBA. (d) 1. $RuCl_3$, $NaIO_4$, acetonitrile; 2. (1,5-dihydro-2,4,3-benzodioxaphosphepin-3-yl)diethylamine, 1*H*-tetrazole, CH_2Cl_2 then *m*-CPBA. (e) 1. Pd/C, H_2, ethanol/water; 2. 0.25 M NaOH

The first step in the synthesis of *epi*-Ins(1,4,5)P_3 was the monofunctionalization of the axial hydroxy group of (−)-**41**. Reaction of diol (−)-**41** under acidic conditions (*p*-toluenesulfonic acid) with triethyl orthoacetate in anhydrous

THF resulted in the formation of an intermediate orthoester, which was directly converted with acetic acid into the axial acetate (−)-**45**.[39] Regioselectivity in this reaction can be traced back to stereoelectronic effects.[40] This step was followed by debromination under mild conditions to give (−)-**46**. The introduction of the phosphate functionality was realized by treatment with (1,5-dihydro-2,4,3-benzodioxaphosphepin-3-yl)diethylamine in the presence of 1*H*-tetrazole and subsequent oxidation of the resulting phosphite with *m*-CPBA to give (−)-**47**. Flash *cis*-dihydroxylation with $RuCl_3/NaIO_4$ again furnished predominantly the *epi*-configured product (99% yield, 80% *de*), which was phosphorylated under the conditions described above to give (+)-**48** in 50% yield. Hydrogenation followed by cleavage of the acetate groups in aqueous NaOH delivered the target compound (+)-**49** quantitatively.

It has been reported previously that *epi*-Ins(1,3,6)P_3 [it was incorrectly named *epi*-Ins(1,4,5)P_3 in this article] has a poor affinity for the endoplasmic reticulum receptor (ERR).[41] The dramatically lower affinity to ERR found for *epi*-Ins(1,3,6)P_3 is the result of the modification of the essential 6-hydroxy group (see Figure 4).[42] Thus *epi*-Ins(1,4,5)P_3 may have a higher activity than other analogues. With authentic *epi*-Ins(1,4,5)P_3 (+)-**49** in hand this hypothesis will be tested in due course.

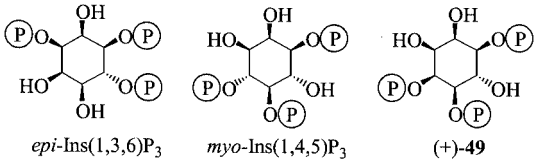


Figure 4. Structures of *epi*-Ins(1,4,5)P_3 (+)-**49** analogues

Syntheses of inositol hexakis(phosphates): The introduction of six phosphate groups was achieved by treatment of *chiro*-**4**, *neo*-**2**, *scyllo*-**6**, and *allo*-**3** inositol with (1,5-dihydro-2,4,3-benzodioxaphosphepin-3-yl)diethylamine in the presence of 1*H*-tetrazole in dichloromethane/acetonitrile. After 12 h to 36 h the resulting phosphites were oxidized with *m*-CPBA and purified by flash chromatography to give the protected hexakis(phosphates) in 50% yield at most. Because of the low solubility of free inositol, especially *neo*-inositol, the phosphorylation is quite difficult, so that complete conversion is a problem. Changing the conditions by varying the solvents or extending the reaction times did not increase the yield. The subsequent Pd/C-catalyzed deprotection/hydrogenolysis gave the free inositol hexakis(phosphates). Alternatively, *neo*-inositol **2** was phosphorylated in polyphosphoric acid to give **28** in better yield. This direct method, however, is only of minor value because of the tedious purification necessitated by the great excess of polyphosphoric acid. Purification of the resulting inositol hexakis(phosphates) (−)-**33**, (+)-**33**, **28**, **40**, and **24** by preparative HPLC ensures purities suitable for biological experiments.[27]

High-performance anion-exchange chromatography of inositols: In the course of our investigations we looked for an easy chromatographic method to determine the purity of inositols. Inositols are weak acids that ionize at pH 13 to 14. At these pH levels near their pK_a values, they can be separated by anion-exchange mechanisms. We employed a linear gradient up to 250 mM NaOH and a high-capacity column (CarboPac MA1) to resolve a mixture of the stereoisomers *neo*-, *myo*-, *scyllo*-, *epi*-, *chiro*-, and *allo*-inositol by HPIC-IPAD (high-performance ion chromatography with integrated pulsed amperometric detection) (see Figure 5). Most of these compounds are epimers of *myo*-inositol, differing structurally only in the orientation of one hydroxy group. Pulsed amperometric detection (PAD) is a powerful detection technique for inositols (more generally carbohydrates) that requires, in contrast to gas chromatography, no sample derivatization. At high pH, the compounds are electrocatalytically oxidized at the surface of a gold electrode by application of a positive potential, and the current generated is proportional to their concentration. We applied a waveform recommended by the manufacturer (DIONEX®) with integration of the recorded signal over the time period of the detection potential (see Experimental Section). This variation of the PAD technique is called IPAD. The detection limit achieved for the inositol isomers is about 50 nM (corresponding to 5 pmol per substance in analytical runs). As mentioned in the introduction, recent reports indicate that, besides the major isomer *myo*-inositol, other isomers can be found in many different organisms. Their function, however, is not yet clear. The powerful analytical method described might be very useful for the direct detection and quantification of inositol isomers and could provide information about their distribution in different species and habitats. It should therefore be of general interest, as methods for the direct detection of free inositols have been rarely described in the literature.[43]

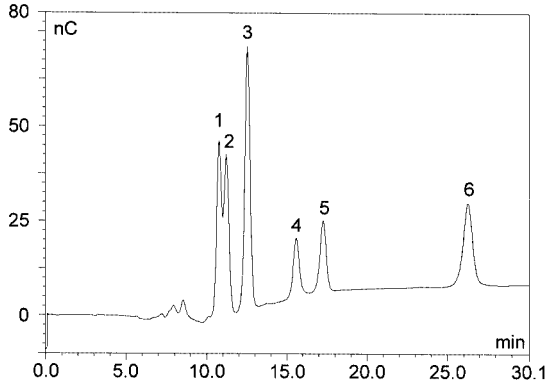


Figure 5. HPIC-IPAD analysis of inositol stereoisomers; 1: *neo*-, 2: *myo*-, 3: *scyllo*-, 4: *epi*-, 5: *chiro*-, 6: *allo*-inositol

Conclusion

We have extended the synthetic potential of the versatile building block (+)- and (−)-**16** to the synthesis of enantiomerically pure conduritol systems, namely conduritol B,

C, E, and F. With these conduritols as flexible precursors, efficient and high-yielding stereoselective routes to *myo*-, *neo*-, L-*chiro*, D-*chiro*, *allo*-, *scyllo*-, and *epi*-inositol derivatives could be established. For further biological investigation, several inositol hexakis(phosphates) and *epi*-Ins(1,4,5)P_3 have been synthesized.[27] If required, all reactions can be carried out on a multigram scale for both enantiomers of different chiral inositol systems.

Experimental Section

General: All NMR spectra were recorded on a Bruker ARX 400 (400 MHz) spectrometer. Besides ^{1}H, ^{13}C, and ^{31}P experiments, 2D COSY- (^{1}H-^{1}H, ^{1}H-^{13}C, and ^{1}H-^{31}P) and DEPT spectra for the unequivocal correlation of the hydrogen, carbon, and phosphorus atoms were recorded. The chemical shifts are given in ppm, relative to the solvents as internal standard. The multiplicity is given by the following symbols: s (singlet), d (doublet), t (triplet), q (quadruplet), m (multiplet), ψt (pseudotriplet for unresolved dd) and br (broad). Melting points were recorded on a Büchi 510 heating block (not corrected). IR spectra were obtained in KBr, and only noteworthy absorptions (cm^{-1}) are listed. Flash-column chromatography was performed on Merck silica gel (40−63 μm). All organic extracts were dried with $MgSO_4$, filtered, and concentrated on a rotary evaporator. Only distilled solvents were used.

HPIC-IPAD of Inositol Stereoisomers: Inositol analysis was performed with a DX-500 ion chromatography system (DIONEX®) consisting of a gradient pump (GP50), a chromatography oven (LC30) with an internal valve bearing a 100 μL sample loop, a tunable absorbance detector (AD25), and an electrochemical detector (ED50) connected to a gold cell equipped with a pH-Ag/AgCl reference electrode. At a constant temperature of 30 °C a CarboPac MA1 (4 × 50 mm, DIONEX®) precolumn and a CarboPac MA1 (4 × 250 mm, DIONEX®) analytical column were used for the separation presented. A linear gradient of NaOH was applied to elute the inositol isomers (0 min, 0 mM NaOH; 10 min, 250 mM NaOH; 30 min, 250 mM NaOH; flow rate: 0.4 mL/min). The waveform had the following characteristics: 0 s, 0.05 V; 0.2 s, 0.05 V (Start Integration); 0.4 s, 0.05 V (Stop Integration); 0.41 s, 0.75 V; 0.6 s, 0.75 V; 0.61 s, −0.15 V; 1 s, −0.15 V. The Chromeleon 6.2 software (DIONEX®) was used for data processing: The inositol stereoisomers had the following retention times: 1: *neo*- (11.07 min), 2: *myo*- (11.48 min), 3: *scyllo*- (12.83 min), 4: *epi*- (15.93 min), 5: *chiro*- (17.48), and 6: *allo*-inositol (26.37 min).

Deionized water for HPIC was purified by a Millipore system to a specific resistance of 18 MΩ·cm or greater. NaOH of the highest purity was purchased from Sigma. All eluents were sparged with and pressurized under helium.

Purification and Analysis of Inositol Phosphates (HPLC-MDD): Inositol phosphates were purified and analyzed by the HPLC-MDD method described previously.[44,26] The compounds were separated by anion-exchange chromatography on a MonoQ HR10/10 column (Pharmacia). To purify inositol phosphates a linear gradient of HCl was applied (0 min 0.2 mM HCl; 70 min 0.5 M HCl; flow rate 1.5 mL/min). In analytical runs photometric detection at 546 nm was achieved with a metal-dye reagent [2 M Tris/HCl (pH, 9.1), 200 μM 4-(2-pyridylazo)resorcinol (PAR), 30 μM YCl_3, 10% (v/v) MeOH; flow rate 0.75 mL/min]. In purification steps, where on-line detection was impossible, an analogous experiment was carried out on a microplate. In brief, a 0.2−2-μL portion of the collected fraction was mixed with 100 μL of metal-dye reagent, and the absorbance at 540 nm was measured.

The building blocks (+)-**17**, (−)-**17**, (−)-**16**, and (+)-**16** and their precursors were prepared according to literature methods.[26]

(3a*R*,4*S*,5*R*,7a*R*)-4-Bromo-5-hydroxy-3a,4,5,7a-tetrahydro-1,3-benzdioxol-2-one [(−)-18] [(1*R*,2*R*,3*S*,4*R*)-3-Bromoconduritol-1,2-carbonate C]: A portion of Na_2SO_4 was added to a vigorously stirred solution of (1*R*,2*S*,3*S*,4*R*)-2,3-dibromocyclohex-5-ene-1,4-diol (+)-**17** (20.0 g, 73.8 mmol) in anhydrous THF (350 mL). At −45 to −65 °C carbon dioxide (dried with concentrated sulfuric acid) was continuously bubbled into the reaction mixture for 1 h. With a syringe, diazabicycloundecene (DBU, 32 mL, 0.2 mol) was added slowly, and the solution was stirred under continuous carbon dioxide addition for another 2 h at −50 °C. The reaction mixture was allowed to warm up to 0 °C and worked up by addition of 5% aqueous HCl (400 mL) and extraction of the aqueous layer with ethyl acetate. The organic layer was washed twice with aqueous HCl (5%, 200 mL), then with saturated $NaHCO_3$, and finally with brine. The solvent was removed under vacuum to yield 16.0 g (0.70 mmol, 92%) of a colorless solid. $[\alpha]_D^{20} = -155$ (c = 1.47, MeOH). ^{1}H NMR (DMSO): δ = 4.22 (m, 1 H, 5-H), 4.28 (dd, J = 8.65, J = 2.5 Hz, 1 H, 4-H), 5.24−5.31 (m, 2 H, 3a-H, 7a-H), 5.77 (dψt, J = 10.2, J = 3.3 Hz, 1 H, 7-H), 5.87 (d, J = 6.6 Hz, 1 H, OH), 6.06 (dd, J = 10.2, J = 2.1 Hz, 1 H, 6-H) ppm. ^{13}C NMR (DMSO): δ = 52.07 (C-4), 65.95 (C-5), 73.16, 77.92 (C-3a, C-7a), 121.65 (C-7), 137.39 (C-6), 153.16 (C=O) ppm. IR (KBr): $\tilde{\nu}$ = 3400 (m), 3040, 3020 (w), 2880 (m), 1770 (s), 1150, 1130 (s), 885 (s) cm^{-1}. $C_7H_7BrO_4$ (235.0): calcd. C 35.77, H 3.00; found C 35.49, H 3.02.

1,2,3,4-Tetra-*O*-acetylconduritol E [(+)-21]: (1*S*,2*R*,3*R*,4*S*)-1,4-Diacetoxy-2,3-dibromocyclohex-5-ene (10 g, 28 mmol) (+)-**16** was added to a hot solution of potassium acetate or sodium acetate (10 g) in acetic acid (100 mL) and water (5 mL). The mixture was stirred for 10 days at 125 °C. The solvent was removed under reduced pressure and the residue was dried under high vacuum. The residue was suspended in anhydrous dichloromethane, then acetic anhydride (30 mL) and DMAP (200 mg) were added. The mixture was stirred overnight. For workup the mixture was added slowly to a vigorously stirred aqueous solution of $NaHCO_3$ (16 g, 0.19 mol, 100 mL water). The aqueous phase was extracted several times with dichloromethane. The combined organic phase was washed with saturated aqueous $NaHCO_3$ and then with brine. After evaporation of the solvent, the raw product (10 g, oil) was purified by flash chromatography (cyclohexane/ethyl acetate, 3:2) to yield (+)-**21** (6.5 g, 70%) as a colorless oil which crystallized after 1 day. Racemic **21** was purified without flash chromatography simply by recrystallization from EtOH to yield pure **21** (6 g, 67%) as a colorless solid. R_f = 0.35 (cyclohexane/ethyl acetate, 3:2). $[\alpha]_D^{20} = +243$ (c = 1.27, $CHCl_3$). Ref.[45] $[\alpha]_D^{20} = +244$ (c = 1.6, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 2.04 (s, 6 H, CH_3), 2.07 (s, 6 H, CH_3), 5.44 (m, 2 H, 2-H, 3-H), 5.68 (m, 2 H, 1-H, 4-H), 5.91 (dd, J = 2.8, J = 1.2 Hz, 2 H, 5-H, 6-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 20.46 (2 × CH_3), 20.76 (2 × CH_3), 66.07 (C-2, C-3), 66.57 (C-1, C-4), 128.14 (C-5, C-6), 169.90, 170.18 (C=O) ppm. MS [EI, 70 eV, *m*/*z* (%)]: 288 (2.0), 228 (9), 210 (5), 168 (38), 43 (100), 41 (10). IR (KBr): $\tilde{\nu}$ = 2960, 2900 (m), 1740 (s, br.), 1440, 1370 (s), 1210 (s) cm^{-1}. $C_{14}H_{18}O_8$ (314.10): calcd. C 53.50, H 5.77; found C 53.65, H 6.00.

1,2,3,4-Tetra-*O*-acetylconduritol E [(−)-21]: A solution of (−)-**16** was allowed to react under the same conditions as described for the preparation of (+)-**21** to give (−)-**21**. $[\alpha]_D^{20} = -246$ (c = 1.1, $CHCl_3$). Identical R_f, ^{1}H NMR and ^{13}C NMR spectroscopic data to those of (+)-**21**.

(1*S*,2*S*,3*R*,4*S*)-1,2,4-Triacetoxy-3-bromocyclohex-5-ene [(+)-20]: Diacetate (+)-**16** (10 g, 28 mmol) was added to a hot solution of potassium acetate or sodium acetate (10 g) in acetic acid (100 mL) and water (5 mL). The mixture was stirred for 3 days at 110 °C. The product was worked up as described for (+)-**21**. Purification by flash chromatography (cyclohexane/ethyl acetate, 3:2) yielded pure (+)-**20** (8.0 g, 85%) as a colorless oil that crystallized after some days to give an oily solid. R_f = 0.50 (cyclohexane/ethyl acetate, 3:2). $[\alpha]_D^{20}$ = +104 (*c* = 1.2, $CHCl_3$). ^1H NMR ($CDCl_3$,): δ = 2.01 (s, 3 H, CH_3), 2.12 (s, 3 H, CH_3), 2.14 (s, 3 H, CH_3), 4.22 (dd, *J* = 9.2, *J* = 2.03 Hz, 2 H, 3-H), 5.61 (m, 1 H, 1-H), 5.64 (dd, *J* = 10.2, *J* = 2.0 Hz, 1 H, 6-H), 5.71 (dd, *J* = 8.9, *J* = 2.3 Hz, 1 H, 4-H), 5.75 (ψt, *J* = 1.8 Hz, 1 H, 2-H), 5.80 (dψt, *J* = 10.2, *J* = 2.3 Hz, 1 H, 5-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 20.47 (CH_3), 20.55 (CH_3), 20.77 (CH_3), 47.29 (C-3), 67.72 (C-1), 72.16, 72.21 (C-2, C-4), 126.70 (C-6), 128.36 (C-5), 169.73, 169.94, 170.04 (C=O) ppm. MS (EI, 70 eV, *m*/*z* (%)): 277, 275 (2), 195 (77), 153 (67), 110 (30), 43 (100). IR (KBr): $\tilde{\nu}$ = 3043 (w, ν[=CH]), 2998, 2949, 2938 (w), 1750 (s), 1370 (m), 1224 (br. s,), 1144 (m), 1041 (s) cm^{-1}. $C_{12}H_{15}BrO_6$ (334.01): calcd. C 43.01, H 4.51; found C 43.05, H 4.58.

(1*R*,2*R*,3*S*,4*R*)-1,2,4-Triacetoxy-3-bromocyclohex-5-ene [(−)-20]: A solution of (−)-**16** was allowed to react under the same conditions as described for the preparation of (+)-**20** to give (−)-**20**. $[\alpha]_D^{20}$ = −96 (*c* = 0.9, $CHCl_3$). Identical R_f, ^1H NMR and ^{13}C NMR spectroscopic data to those of (+)-**20**.

(1*R*,2*S*,3*S*,4*S*)-1-*O*-Benzylconduritol F [(+)-22]: Sodium (70 mg, 3 mmol) was added to anhydrous benzyl alcohol (5 mL). The mixture was stirred until the sodium dissolved (3 h). This solution was added to a solution of 1,2,4-triacetate (+)-**20** (500 mg, 1.5 mmol) in anhydrous benzyl alcohol/THF (1:2). After being stirred for 12 h at room temperature, the solution was neutralized by addition of ion exchanger (H^+, Dowex 50-X), which was filtered off and washed with dichloromethane/methanol. The filtrate was evaporated, and the remaining benzyl alcohol was removed by distillation. The resulting oil (350 mg) was purified by flash chromatography (CH_2Cl_2/methanol 90:10) to yield (+)-**22** (250 mg, 66%) as a colorless solid. R_f = 0.57 (CH_2Cl_2/methanol, 90:10). $[\alpha]_D^{20}$ = +3.8 (*c* = 3.15, MeOH). ^1H NMR ([D$_4$]MeOH): δ = 3.41 (dd, *J* = 10.2, *J* = 4.2 Hz, 3-H), 3.78 (dd, 1 H, *J* = 10.2, *J* ≈ 7.6 Hz, 2-H), 3.87 (dψt, *J* = 7.6, *J* ≈ 1.8 Hz, 1 H, 1-H), 3.98 (br. s, 3 H, OH), 4.14 (ψt, *J* = 4.6 Hz, 1 H, 4-H), 4.65, 470 (AB, *J* = 10.2 Hz, 2 H, Ph-CH_2), 5.77 (m, 2 H, 5-H, 6-H), 7.2−7.4 (m, 5 H, Ph-H) ppm. ^{13}C NMR ([D$_4$]MeOH): δ = 62.36 (C-4), 67.40, 67.44 (C-3, C-4), 67.97 (Ph-*C*H$_2$), 75.95 (C-1), 123.60, 126.39 (C-5, C-6), 123.77, 123.94, 124.39 ($C_{arom.}$), 138.45 (C_{ipso}) ppm. MS [EI, 70 eV, *m*/*z* (%)]: 236 (1.0) [M^+], 176 (10.9), 112 (28.11), 91 (100) [Bn^+]. HR-MS [CI, (DE), *iso*-butane]: *m*/*z*: 237.112794 [M + H]$^+$ calcd. for $C_{13}H_{17}O_4$: 237.11268.

(1*S*,2*R*,3*R*,4*R*)-1-*O*-Benzyl-conduritol F [(−)-22]: A solution of (−)-**20** was allowed to react under the same conditions as described for the preparation of (+)-**22** to give (−)-**22**. $[\alpha]_D^{20}$ = −4.9 (*c* = 2.0, MeOH). Identical R_f, ^1H NMR and ^{13}C NMR spectroscopic data to those of (+)-**22**.

2,3,4,5-Tetra-*O*-acetyl-*neo*-inositol [(+)-26]: A solution of trifluoroperacetic acid[23] was prepared by slow addition of hydrogen peroxide (1.4 mL, 85%, 42 mmol) to an ice-cooled solution of trifluoroacetic anhydride (7 mL, 50 mmol) in dichloromethane (20 mL). The solution was stirred for 1 h at room temperature. This solution, freshly prepared, was added dropwise at 0 °C over 15 min to a suspension of conduritol E (+)-**21** (1.2 g, 3.8 mmol) and $NaHCO_3$ (1.4 g, 16 mmol) in dichloromethane (35 mL). Then the mixture was refluxed for 2 h and stirred for another 12 h at room temperature. The reaction mixture was added slowly to a cooled and stirred solution of saturated aqueous $NaHCO_3$ (30 mL), $NaHCO_3$ (8.4 g) in brine (100 mL), and dichloromethane (200 mL). After addition of 20% aqueous $Na_2S_2O_3$ solution (50 mL,) the mixture was extracted four times with dichloromethane or ethyl acetate (4 × 100 mL). The combined organic layer was washed with brine and then dried with $MgSO_4$. Evaporation of the solvent gave a yellow foam (1.2 g). The crude product was purified by fractionated silica-gel filtration (first cyclohexane/ethyl acetate 8:2 until starting material/epoxide could not be detected by TLC, then ethyl acetate). The ethyl acetate fraction was evaporated to yield (+)-**26** (900 mg, 2.7 mmol, 71%) as a colorless foam. R_f = 0.03 (cyclohexane/ethyl acetate, 1:1). $[\alpha]_D^{20}$ = +12.7 (*c* = 1.1, $CHCl_3$). ^1H NMR ($CDCl_3$): δ = 1.99 (s, 6 H, 2 × CH_3), 2.13 (s, 6 H, 2 × CH_3), 3.27 (br., 2 H, OH), 4.01 (s, 2 H, 1-H, 6-H), 5.20 (s, 2 H, 3-H, 4-H), 5.62 (s, 2 H, 2-H, 5-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 20.58 (2 × CH_3), 20.70 (2 × CH_3), 68.33, 68.57, 70.19 (C-1/C-6, C-2/C-5, C-3/C-4), 170.17 (2 × C=O), 170.66 (2 × C=O) ppm. MS [EI, 70 eV, *m*/*z* (%)]: 271 (2), 228 (1), 210 (5), 168 (16), 157 (9), 126 (27), 115(16), 60 (18), 43 (100). $C_{14}H_{20}O_{10}$ (348.11): calcd. C 48.28, H 5.79; found C 48.18, H 6.00.

1,2,5,6-Tetra-*O*-acetyl-*neo*-inositol [(−)-26]: A solution of (−)-**21** was allowed to react under the same conditions as described for the preparation of (+)-**26** to give (−)-**26**. $[\alpha]_D^{20}$ = −12.0 (*c* = 0.95, $CHCl_3$). Identical ^1H NMR and ^{13}C NMR spectroscopic data to those of (+)-**26**.

(1*R*,2*R*,3*R*,4*R*,5*R*,6*S*)-1,6-Epoxy-2,3,4,5-tetra-*O*-acetyl-7-oxabicyclo[4.1.0]heptane [(+)-25] [(+)-Conduritol E epoxide]: A freshly prepared solution of trifluoroperacetic acid[23] [see synthesis of (+)-**26**] was added dropwise at 0 °C to a suspension of conduritol E (+)-**21** (1.2 g, 3.8 mmol) and sodium carbonate (2 g, 19 mmol) in dichloromethane (35 mL) over the course of 15 min. The mixture was stirred for 4 h at room temperature. The product was worked up as described for (+)-**26**. Purification by flash chromatography (cyclohexane/ethyl acetate, 3:2) yielded pure epoxide (300 mg, 24%) as a colorless oil. R_f = 0.31 (cyclohexane/ethyl acetate, 1:1). $[\alpha]_D^{20}$ = +109 (*c* = 1.4, $CHCl_3$). ^1H NMR ($CDCl_3$): δ = 2.03 (s, 3 H, CH_3), 2.04 (s, 3 H, CH_3), 2.14 (s, 6 H, 2 × CH_3), 3.32 (dd, *J* = 3.3, *J* = 2.3 Hz, 1 H, 1-H), 3.47 (ψt, *J* = 3.8 Hz, 1 H, 6-H), 5.28 (dd, *J* = 9.9, *J* = 5.3 Hz, 1 H, 4-H), 5.33 (dd, *J* = 9.9, *J* = 3.3 Hz, 1 H, 3-H), 5.57 (ψt, *J* = 4.6 Hz, 1 H, 5-H), 5.70 (ψt, *J* = 2.3 Hz, 1 H, 2-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 20.52 (2 × CH_3), 20.55 (CH_3), 20.64 (CH_3), 50.99 (C-6), 53.27 (C-1), 65.29 (C-3), 65.77 (C-4), 65.84 (C-5), 66.59 (C-2), 169.35, 169.61, 169.81, 170.19 (C=O) ppm. MS [EI, 70 eV, *m*/*z* (%)]: 255 (19), 212 (43), 152 (100), 43 (84), 41 (8). IR (KBr): $\tilde{\nu}$ = 2960, 2900 (w), 1740 (s), 1460, 1370 (s), 1200 (s), 1060 (s) cm^{-1}.

Hexa-*O*-acetyl-*neo*-inositol (27): (+)-**26** (1 g, 2.9 mmol) was dissolved in a cooled mixture of pyridine (7 mL) and acetic anhydride (5 mL). The mixture was stirred for 12 h. Evaporation of the solvent and recrystallization from ethyl acetate (7 mL) yielded pure **27** (1.0 g, 83%) as a white solid. ^1H NMR ($CDCl_3$): δ = 1.99 (s, 12 H, 4 × CH_3), 2.16 (s, 6 H, 2 × CH_3), 5.34 (s, 4 H, 1-H, 3-H, 4-H, 6-H), 5.66 (s, 2 H, 2-H, 5-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 20.46 (4 × CH_3), 20.62 (2 × CH_3), 67.45 (C-1, C-3, C-4, C-6), 67.99, (C-2, C-5), 169.5 (4 × C=O), 169.8 (2 × C=O) ppm. MS [EI, 70 eV, *m*/*z* (%)]: 373 (1), 330 (1), 270 (8), 210 (63), 168 (94), 157 (28), 126 (40), 115 (31), 43(100). IR (KBr): $\tilde{\nu}$ = 2984, 2962 (w), 1758 (s), 1369 (m), 1226 (s, br.), 1117 (m), 1090 (m), 1047 (m) cm^{-1}. $C_{18}H_{24}O_{12}$: (432.13): calcd. C 50.00, H 5.59; found C 50.11, H 5.72.

***neo*-Inositol (2):** Compound **27** (2.4 g, 5.4 mmol) was suspended in anhydrous methanol (50 mL) under argon and cooled to 4 °C. Sodium methoxide solution (500 μL of a 5.5 M solution, 2.25 mmol) was added dropwise over 10 min. The solution was allowed to warm to room temperature and stirred for 12 h. The solvent was removed, and for complete turnover the residue was dissolved in aqueous NaOH (20 mL of a 0.25 M solution) and refluxed for 2 h. The hot solution was neutralized by addition of ion exchanger (H^+, Dowex 50-X) and filtered, and the Dowex material was washed with boiling water. The filtrate was first concentrated under high vacuum and then lyophilized. Recrystallization from water (50 mL) yielded **2** (1 g, 99%) as a colorless solid. ^{1}H NMR ($CDCl_3$): δ = 3.74 (s, 4 H, 1-H, 3-H, 4-H, 6-H), 4.03 (s, 2 H, 2-H, 5-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 69.75 (C-1, C-3, C-4, C-6), 71.99, (C-2, C-5) ppm. MS [EI, 70 eV, *m*/*z* (%)]: 144 (9), 102 (39), 73 (100). IR (KBr): $\tilde{\nu}$ = 3422, 3342, 3197 (s, br.), 2970, 2948, 2921 (w), 1687 (w), 1632(w), 1423 (w), 1384 (w), 1281 (w), 1130 (s), 1092 (m), 1036 (s) cm^{-1}. $C_6H_{12}O_6$: calcd. C 40.00; H 6.71; found C 39.75; H 6.61. HR-MS: *m*/*z*: 179.0526 $[M - H]^+$ calcd. for $C_6H_{11}O_6$: 179.0556.

***neo*-Inositol Hexakis(phosphate) (28):** (1,5-Dihydro-2,4,3-benzodioxaphosphepin-3-yl)diethylamine (514 mg, 2.26 mmol) was added to a suspension of *neo*-inositol **2** (50 mg, 0.27 mmol) and 1*H*-tetrazole (315 mg, 4.5 mmol) in anhydrous dichloromethane/acetonitrile (1:1, 20 mL), and the solution was stirred at 40 °C for 3 days. For workup the solution was cooled to −40 °C, and an anhydrous solution of *m*-CPBA (1.5 g, 6 mmol) in dichloromethane (15 mL, dried with Na_2SO_4) was added. The solution was allowed to warm to room temperature, and the stirring was continued for another hour. The reaction mixture was diluted with dichloromethane (150 mL) and washed consecutively with aqueous sodium bisulfite (20%, 2 × 100 mL), saturated $NaHCO_3$ (3 × 100 mL), and then with brine. After evaporation of the solvent the resulting colorless foam was purified by flash chromatography with silica gel (R_f = 0.22 (CH_2Cl_2/MeOH, 95:5) to yield hexa-*O*-(3-oxo-1,5-dihydro-3λ^5-2,4,3-benzodioxaphosphepin-3-yl)-*neo*-inositol (75 mg, 21%) as a colorless foam. ^{1}H NMR ($CDCl_3$): δ = 5.15 (m, 4 H, 1-H, 3-H, 4-H, 6-H), 5.58 (m, 2 H, 2-H, 5-H), 5.00 −5.82 [m, 24 H, 6 × $(CH_2)_2C_6H_4$], 7.26−7.43 (m, 24 H, Ph-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 69.19 −69.63 [m, 6 × $(CH_2)_2C_6H_4$], 72.86 (m, C-1, C-3, C-4, C-6), 77.06 (C-2, C-5), 128.94 −129.48 ($C_{arom.}$), 134.54, 135.63, 135.77 (C_{ipso}) ppm. ^{31}P{^{1}H} NMR ($CDCl_3$): δ = −1.48 (PC-2, PC-5), −2.39 (PC-1, PC-3, PC-4, PC-6) ppm.

Pd/C (50 mg, Degussa RW 10) was added to a suspension of hexa-*O*-(3-oxo-1,5-dihydro-3λ^5-2,4,3-benzodioxaphosphepin-3-yl)-*neo*-inositol (50 mg, 39 μmol) in ethanol/water (1:2, 30 mL). The mixture was stirred at room temperature under H_2 overnight. The catalyst was filtered off, and the filtrate was concentrated under high vacuum and then lyophylized to give **28** (24 mg, 99%) as a colorless, strongly hygroscopic foam. Purification by HPLC assured purity > 99%. ^{1}H NMR [D_2O, pH adjusted to 6 (ND_4OD)]: δ = 4.37 (d, *J* = 4.6 Hz, 4 H, 1-H, 3-H, 4-H, 6-H), 4.89 (d, *J* = 9.2 Hz, 2 H, 2-H, 5-H) ppm. ^{13}C NMR [D_2O, pH adjusted to 6 (ND_4OD)]: δ = 74.24 (C-1, C-3, C-4, C-6), 76.57 (C-2, C-5) ppm. ^{31}P{^{1}H} NMR [D_2O, pH adjusted to 6 (ND_4OD)]: δ = 1.89 (PC-2, PC-5), 2.07 (PC-1, PC-3, PC-4, PC-6) ppm. HR-MS (MALDI-FTMS): *m*/*z*: 658.8541 $[M - H]^+$ calcd. for $C_6H_{17}O_{24}P_6$: 658.8527.

Alternative Preparation: *neo*-Inositol **2** (70 mg, 0.38 mmol) was dissolved in phosphoric acid (0.22 mL) at 60 °C. Polyphosphoric acid (4 mL) was added, and the mixture was heated to 150 °C under vacuum for 12 h. The mixture was diluted with water and purified on an ion exchange column (Cl^--form, DEAE sepharose) with a linear gradient of hydrochloric acid (0−1 N HCl). Purification by HPLC yielded 80 mg (31%) of *neo*-$InsP_6$ **28**.

3,4,5,6-Tetra-*O*-acetyl-*allo*-inositol [(+)-23]: A solution of sodium metaperiodate (1.2 g, 5.5 mmol, 1.5 equiv.) and ruthenium trichloride trihydrate (100 mg, 0.4 mmol) in water (14 mL) was added to a vigorously stirred, ice-cooled solution of conduritol E (+)-**21** (1 g, 3.2 mmol) in acetonitrile (60 mL). The stirring was continued until TLC showed absence of the starting material (approx. 10 min). The reaction was quenched by addition of 20% aqueous $Na_2S_2O_3$ (130 mL). The aqueous layer was separated and extracted with ethyl acetate (4 × 100 mL). The combined organic layer was washed twice with brine and concentrated under reduced pressure to yield pure (+)-**23** as a colorless solid (1 g, 90%). $[\alpha]_D^{20}$ = +3.0 (*c* = 0.78, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 2.01 (s, 6 H, 2 × CH_3), 2.06 (s, 3 H, CH_3), 2.10 (s, 3 H, CH_3), 2.94 (br. s, 2 H, OH), 3.95 (dd, *J* = 5.1, *J* = 3.9 Hz, 1 H, 1-H or 2-H), 4.11 (ψs, 1 H, 1-H or 2-H), 5.23 (dd, *J* = 7.3, *J* = 3.3 Hz, 1 H), 5.41 (m, 3 H) (3-H, 4-H, 5-H, 6-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 20.91 (CH_3), 20.93 (CH_3), 21.05 (2 × CH_3), 67.13 (CH), 68.45 (CH), 70.23 (m, 4 × CH), 170.14, 170.21, 170.42, 170.81 (C=O) ppm. IR (KBr): $\tilde{\nu}$ = 3467 (s, br.), 2979, 2936 (m), 1747 (s), 1375 (m), 1252 (s), 1075, 1051 (m), 933 (m) cm^{-1}. MS (EI, 70 eV, *m*/*z* (%)): 228 (9), 210 (4), 168 (48), 157 (28), 126 (81), 115 (58), 43 (100). $C_{14}H_{20}O_{10}$ (348.11): calcd. C 48.28, H 5.79; found C 48.14, H 5.95.

1,2,5,6-Tetra-*O*-acetyl-*allo*-inositol [(−)-23]: A solution of (−)-**21** was allowed to react under the same conditions as described for the preparation of (+)-**23** to give (−)-**23**. $[\alpha]_D^{20}$ = −2.7 (*c* = 1.0, $CHCl_3$). Identical R_f, ^{1}H NMR, and ^{13}C NMR spectroscopic data to those of (+)-**23**.

***allo*-Inositol (3):** (+)-23 (800 mg, 2.3 mmol) was suspended in anhydrous methanol (20 mL) under argon and cooled to 4 °C. Sodium methoxide solution (150 μL of a 5.5 M solution, 0.8 mmol) was added dropwise over 10 min. The solution was allowed to warm to room temperature and stirred for 12 h. It was then neutralized by ion exchanger (H^+, Dowex 50-X), which was filtered off and washed with water. The filtrate was first reduced in volume under high vacuum, then lyophilized. Recrystallization from ethanol (50 mL) yielded **3** (350 mg, 83%) as a colorless solid. ^{1}H NMR (D_2O): δ = 3.85 (s, 2 H), 3.98 (m, 4 H) ppm. ^{13}C NMR (D_2O): δ = 72.70, 73.90, 74.00 ppm. MS [EI, 70 eV, m/z (%)]: 144 (1), 102 (8), 73 (100). $C_6H_{12}O_{16}$ (340.2): calcd. C 40.00, H 6.71; found C 39.82, H 6.85. HR-MS: m/z: 179.0515 $[M - H]^+$ calcd. for $C_6H_{11}O_6$: 179.0556.

***allo*-Inositol-hexakis(phosphate) (24):** (1,5-Dihydro-2,4,3-benzodioxaphosphepin-3-yl)diethylamine (610 mg, 2.7 mmol) was added to a suspension of *allo*-inositol **3** (66 mg, 0.37 mmol) and 1*H*-tetrazole (270 mg, 3.9 mmol) in anhydrous dichloromethane (30 mL), and the solution was stirred at 40 °C for 1 day. The solution was then cooled to −40 °C, and an anhydrous solution of *m*-CPBA (2.3 g, 10 mmol) in dichloromethane (15 mL, dried with Na_2SO_4) was added. The solution was allowed to warm to room temperature, and the stirring was continued for another hour. The reaction mixture was diluted with dichloromethane (150 mL) and washed consecutively with aqueous sodium bisulfite (20%, 2 × 100 mL), saturated $NaHCO_3$ (3 × 100 mL), and then with brine. After evaporation of the solvent the resulting colorless foam was purified by flash chromatography [R_f = 0.15 (CH_2Cl_2/MeOH, 95:5)] to yield hexa-*O*-(3-oxo-1,5-dihydro-3λ^5-2,4,3-benzodioxaphosphepin-3-yl)-*allo*-inositol (100 mg, 30%) as a colorless foam.

Pd/C (50 mg, Degussa RW 10) was added to a suspension of hexa-*O*-(3-oxo-1,5-dihydro-3λ^5-2,4,3-benzodioxaphosphepin-3-yl)-*allo*-

inositol (80 mg, 39 μmol) in ethanol/water (1:2, 30 mL). The mixture was stirred at room temperature under H_2 overnight. The catalyst was filtered off, and the filtrate was reduced in volume under high vacuum and then lyophylized to give **24** (40 mg, 99%) as a colorless, highly hygroscopic foam. Separation by HPLC assured purity > 99% for the subsequent reactions. ^{1}H NMR [D_2O, pH adjusted to 6 (ND_4OD)]: δ = 4.42 (ψs, 2 H), 4.66 (m, 2 H, under HDO), 4.89 (ψs, 2 H) ppm. ^{13}C NMR [D_2O, pH adjusted to 6 (ND_4OD)]: δ = 71.13 (m), 72.30 (m), 75.40 (m) ppm. ^{31}P{^{1}H} NMR [D_2O, pH adjusted to 6 (ND_4OD)]: δ = 1.54 (2 × P), 2.02 (4 × P) ppm. HR-MS (ESI-neg, phosphoric acid 0.002%, H_2O/acetonitrile 1:1, Q-TOF): *m/z*: 658.8502 [M − H]$^-$ calcd. for $C_6H_{17}O_{24}P_6$: 658.8536.

1,4-Di-*O*-benzylconduritol B [(−)-29]: Sodium (23 g, 1 mol) was added to freshly distilled, ice-cooled benzyl alcohol (705 mL) with the temperature not exceeding 40 °C. The mixture was stirred at room temperature until all the sodium was dissolved (3 h). This solution was cooled to −20 °C, and a solution of 1,4-diacetoxy-2,3-dibromocyclohex-5-ene (+)-**16** (73.1 g, 0.2 mol) in absolute THF (210 mL) was added slowly (over 40 min). The solution was stirred for 1 h at 0 °C and stirring was continued for 12 h at room temperature to provide complete conversion. The cooled solution was diluted with hydrochloric acid (1 M) and later with ethyl acetate (700 mL). The aqueous layer was separated and extracted with ethyl acetate (3 × 330 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ and brine. The organic solution was concentrated under reduced pressure, and the remaining benzyl alcohol was removed by distillation. The resulting oil (85 g) was crystallized from cyclohexane to yield (−)-**29** (52 g, 80%) as a colorless solid. R_f = 0.55 (ethyl acetate/cyclohexane, 5:1). $[\alpha]_D^{20}$ = −134 (*c* = 1.60, acetone). ^{1}H NMR ($CDCl_3$): δ = 3.20 (s, 2 H, OH), 3.78 (s, 2 H, AA′XX′), 4.08 (s, 2 H, AA′XX′), 4.72 (s, 4 H, Ph-CH_2), 5.74 (s, 2 H, 1-H, 2-H), 7.35 (m, 10 H, Ph-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 71.9 (Ph-CH_2), 74.7 (C-4, C-5), 79.2 (C-3, C-6), 126.9, 127.7, 127.8 ($C_{arom.}$), 128.4 (C-1, C-2), 138.2 (2 × C_{ipso}) ppm. MS [EI, 70 eV, *m/z* (%)]: 326 (3.78) [M$^+$], 266 (36.38), 235 (3.76), 189 (25.21), 176 (21.64), 112 (45.15), 91 (100). IR (KBr): ṽ = 3440 (s, br.), 3180, 3145, 3110 (m), 2940 (m), 1630 (w), 1470 (m), 1400 (m), 1225 (m), 1075 (s) cm^{-1}. $C_{20}H_{22}O_4$ (326.4): calcd. C 73.60, H 6.79; found C 73.37, H 6.65.

1,4-Di-*O*-benzyl-conduritol B [(+)-29]: A solution of (−)-**16** (or alternatively (+)-**17**] was allowed to react under the same conditions as described for the preparation of (−)-**29** to give (+)-**29**. $[\alpha]_D^{20}$ = +130 (*c* = 1.6, acetone). Identical R_f, ^{1}H NMR and ^{13}C NMR spectroscopic data to those of (−)-**29**.

2,3-Anhydro-1,4-di-*O*-benzyl-*myo*-inositol [(−)-31]: A freshly prepared solution of trifluoroperacetic acid[23] [from trifluoroacetic anhydride (10.6 mL, 75 mmol) and H_2O_2 (2 mL, 85%, 70 mmol) in dichloromethane (30 mL), see synthesis of (+)-**26**] was added dropwise at 0 °C over 30 min to a suspension of dibenzylconduritol B (−)-**29** (5 g, 15.3 mmol) and Na_2CO_3 (4.75 g, 45 mmol) in dichloromethane (60 mL). After the reaction mixture had been stirred for 3 h at room temperature, aqueous saturated $NaHCO_3$ (50 mL) and water (20 mL) were added slowly. After addition of $Na_2S_2O_3$ (11 g, 44 mmol), the mixture was extracted four times with dichloromethane (4 × 100 mL). The combined organic layer was washed with brine and then dried. Evaporation of the solvent gave a white solid (4.6 g). Recrystallization from cyclohexane/ethyl acetate (3:2) yielded pure (−)-**31** (3.7 g, 71%) of a colorless solid. $[\alpha]_D^{20}$ = −72 (*c* = 0.25, $CHCl_3$), ^{1}H NMR ($CDCl_3$): δ = 3.21 (d, *J* = 3.6 Hz, 1 H, 2-H), 3.35 (m, 1 H, 3-H), 3.51(dd, *J* = 10.2, *J* = 8.1 Hz, 1 H, 6-H), 3.61(dd, *J* = 10.2, *J* = 8.1 Hz, 1 H, 5-H), 3.74 (d, *J* = 8.2 Hz, 1 H, 1-H), 3.77 (dd, *J* = 8.2, *J* = 1.6 Hz, 1 H, 4-H), 4.80−4.88 (m, 4 H, AB, CH_2), 7.33−7.56 (m, 10 H, Ph-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 54.01 (C-2), 54.1 (C-3), 69.76 (C-5), 72.16 (CH_2Ph), 73.01 (CH_2Ph), 74.61 (C-6), 78.14 (C-1), 78.75 (C-4), 127.92, 127.98, 128.02, 128.55 ($C_{arom.}$), 137.62, 137.97 (C_{ipso}) ppm. MS [EI, 70 eV, *m/z* (%)]: 342 (2), 251 (18), 107 (27), 91 (100). IR (KBr): ṽ = 3300 (s, br.), 3070 −3010 (w), 2910 −2880 (w), 1470(w, br.), 1100 (s) cm^{-1}. $C_{20}H_{22}O_5$ (342.4): calcd. C 70.16, H 6.48; found C 69.86, H 6.52.

1,2-Anhydro-3,6-di-*O*-benzyl-*myo*-inositol [(+)-31]: A solution of (+)-**29** was allowed to react under the same conditions as described for the preparation of (−)-**31** to give (+)-**31**. $[\alpha]_D^{20}$ = +65 (*c* = 0.4, $CHCl_3$). Identical R_f, ^{1}H NMR and ^{13}C NMR spectroscopic data to those of (−)-**31**.

2,5-Di-*O*-benzyl-L-*chiro*-inositol [(−)-32]: 2,3-Anhydro-*myo*-inositol (−)-**31** (700 mg, 2.0 mmol) was added to a solution of dioxane (14 mL), water (2 mL) and sulfuric acid (2.1 mL, 15%), and the mixture was stirred at 80 °C for 24 h. The solution was neutralized with $NaHCO_3$ (ca. 1 g) and diluted with ethyl acetate (200 mL). The organic layer was washed with brine and after evaporation of the solvent yielded (−)-**32** (570 mg, 80%) as a colorless solid. $[\alpha]_D^{20}$ = −53.5 (*c* = 0.39, MeOH); ref.[46] $[\alpha]_D^{20}$ = −35.9 (*c* = 0.4, EtOH). ^{1}H NMR ([D_6]DMSO/H_2O): δ = 3.40 (AA′, 2 H, 2-H, 5-H), 3.50 (MM′, 2 H, 3-H, 4-H), 3.93 (XX′, 2 H, 1-H, 6-H), 4.52−4.61 (m, 2 H, CH_2), 7.21−7.37 (m, 10 H, Ph-H) ppm. ^{13}C NMR ([D_6]DMSO/H_2O): δ = 68.9 (C-1/C-6), 71.3 (CH_2Ph), 72.8 (C-3/C-4), 79.1 (C-2/C-5), 127.4, 127.8, 128.3 ($C_{arom.}$), 139.6 (C_{ipso}) ppm. MS [EI, 70 eV, *m/z* (%)]: 360 (2), 269 (52), 107 (58), 91 (100). IR (KBr): ṽ = 3403 (br. s, ν[OH]), 3028 (w, ν[$CH_{olef.}$]), 2932 (w, ν[$CH_{ali.}$]), 1740 (w), 1453 (w), 1216 (w), 1099 (s), 1049 (br. s, ν[C−O]), 918 (w), 753 (w), 701 (m) cm^{-1}. $C_{20}H_{24}O_6$: calcd. C 66.65, H 6.71; found C 66.39, H 6.52. HR-MS (EI, (DE)): *m/z*: 360.15701 [M]$^+$ calcd. for $C_{20}H_{24}O_6$: 360.15728.

2,5-Di-*O*-benzyl-D-*chiro*-inositol [(+)-32]: A solution of (+)-**31** was allowed to react under the same conditions as described for the preparation of (−)-**32** to give (+)-**32**. $[\alpha]_D^{20}$ = +50 (*c* = 0.26, $CHCl_3$). Identical ^{1}H NMR and ^{13}C NMR spectroscopic data to those of (−)-**32**.

L-*chiro*-Inositol [(−)-4]: Pd/C (40 mg) was added to a suspension of (−)-**32** (250 mg, 0.7 mmol) in ethanol/water (1:1, 20 mL). The mixture was stirred at room temperature under H_2 overnight. The catalyst was filtered off, and the filtrate was reduced in volume under high vacuum and then lyophilized to give a voluminous foam (120 mg, 99%). Crystallization from ethanol yielded pure (−)-**4** (125 mg, 99%) as a white solid. $[\alpha]_D^{20}$ = −70 (*c* = 0.55, H_2O). ^{1}H NMR (D_2O): δ = 3.30 (s, *scyllo*-inositol), 3.53 (AA′, 2 H, 3-H, 4-H), 3.70 (MM′, 2 H, 2-H, 5-H), 3.97 (XX′, 2 H, 1-H, 6-H) ppm. ^{13}C NMR (D_2O): δ = 70.6 (C-2/C-5), 71.8 (C-1/C-6), 72.9 (C-3, C-4) ppm. MS [EI, 70 eV, *m/z* (%)]: 154 (4), 144 (4), 102 (22), 86 (28), 73 (100), 60 (54). IR (KBr): ṽ = 3388 (br. s, ν[OH]), 2930 (w, ν[$CH_{ali.}$]), 1681 (s), 1433 (m), 1205 (s), 1136 (s), 1065 (s), 1023 (s), 901 (w), 837 (m), 802 (m), 724 (m), 668 (m) cm^{-1}. HR-MS (ESI-neg., TOF): *m/z*: 179.0515 [M − H]$^-$ calcd. for $C_6H_{11}O_6$: 179.0556.

D-*chiro*-Inositol [(+)-5]: A solution of (+)-**32** was allowed to react under the same conditions as described for the preparation of (−)-**4** to give (+)-**5**. $[\alpha]_D^{20}$ = +57.6 (*c* = 0.9, H_2O). Identical R_f, ^{1}H NMR, and ^{13}C NMR spectroscopic data to those of (−)-**4**.

L-*chiro*−Inositol Hexakis(phosphate) [(−)-33]: (1,5-Dihydro-2,4,3-benzodioxaphosphepin-3-yl)diethylamine (470 mg, 2.0 mmol) was added to a suspension of L-*chiro*-inositol (−)-**4** (50 mg, 0.27 mmol)

and 1*H*-tetrazole (226 mg, 3.2 mmol) in anhydrous dichloromethane (20 mL) and the solution was stirred at room temperature overnight. The product was worked up as described for **28**. Purification by flash chromatography on silica gel yielded hexa-*O*-(3-oxo-1,5-dihydro-3λ^5−2,4,3-benzodioxaphosphepin-3-yl)-L-*chiro*-inositol (200 mg, 60%) as a colorless foam with a purity >80%. ^{13}C NMR ($CDCl_3$): δ = 69.03−69.74 [m, 6 × $(CH_2)_2C_6H_4$], 73.51 (m, CH), 73.81 (m, CH), 76.28 (m, CH), 128.4 −129.4 ($C_{arom.}$), 134.41, 134.51, 135.33, 135.47, 135.52, 136.88 (C_{ipso}) ppm. ^{31}P{^{1}H} NMR ($CDCl_3$): δ = −1.30, −2.05, −2.74 ppm.

Hydrogenolysis of hexa-*O*-(3-oxo-1,5-dihydro-3λ^5−2,4,3-benzodioxaphosphepin-3-yl)-L-*chiro*-inositol was carried out as described for **28**. Separation by HPLC assured a purity > 99%. $[\alpha]_D^{20}$ = −24.4 (*c* = 1.17, H_2O). ^{1}H NMR [D_2O, pH adjusted to 6 (ND_4OD)]: δ = 4.30 (AA′, 2 H, 3-H, 4-H), 4.36 (MM′, 2 H, 2-H, 5-H), under HDO (4.65) (XX′, 2 H, 1-H, 6-H) ppm. ^{13}C NMR [D_2O, pH adjusted to 6 (ND_4OD)]: δ = 72.9 (m, C-1/C-6), 73.3 (m, C-2/C-5), 76.5 (m, C-3, C-4) ppm. ^{31}P{^{1}H} NMR [D_2O, pH adjusted to 6 (ND_4OD)]: δ = 1.63 (PC-1, PC-6), 1.91 (PC-2, PC-5), 2.66 (PC-3, PC-4) ppm. HR-MS (ESI-neg, phosphoric acid 0.002%, H_2O/acetonitrile 1:1, Q-TOF): *m*/*z*: 658.8516 [M − H]$^-$ calcd. for $C_6H_{17}O_{24}P_6$: 658.8536.

D-*chiro*−Inositol Hexakis(phosphate) [(+)-33]: The (+)-enantiomer **5** was phosphitylated as described for (−)-**4**. Oxidation, deprotection and purification as before gave (+)-**33**. $[\alpha]_D^{20}$ = +22 (*c* = 0.8, H_2O). Identical ^{1}H NMR, ^{13}C NMR and ^{31}P NMR spectroscopic data to those of (−)-**33**.

1,4-Di-*O*-benzyl-*myo*-inositol [(−)-30]: A solution of sodium metaperiodate (2.0 g, 9.5 mmol, 1.5 equiv.) and ruthenium trichloride trihydrate (164 mg, 0.6 mmol) in water (20 mL) was added to a vigorously stirred, ice-cooled solution of (−)-**29** (2.1 g, 6.4 mmol) in acetonitrile (80 mL). The stirring was continued until TLC showed absence of starting material (ca. 7 min). The reaction was quenched by addition of 20% aqueous $Na_2S_2O_3$ (150 mL). The aqueous layer was separated and extracted five times with ethyl acetate (5 × 200 mL). The combined organic layer was washed twice with brine and dried with $MgSO_4$. Concentration under reduced pressure gave a white solid (1.9 g, 82%). m.p. 170 °C (ref.[47] 172 °C). R_f = 0.25 (ethyl acetate/cyclohexane, 1:1). $[\alpha]_D^{20}$ = −18.3 (*c* = 2, MeOH). ^{1}H NMR ($CDCl_3$/[D_4]MeOH, 6:1): δ = 3.16 (dd, *J* = 9.7, *J* = 2.0 Hz, 1 H, 3-H or 1-H), 3.31 (ψt, 1 H, *J* = 9.4 Hz, 4-H or 6-H), 3.38 (dd, *J* = 9.7, *J* = 2.5 Hz, 1 H, 1-H or 3-H), 3.58 (ψt, 1 H, *J* = 9.4 Hz, 5-H), 3.78 (ψt, 1 H, *J* = 9.4 Hz, 4-H or 6-H), 4.07 (ψt, 1 H, *J* = 2.0 Hz, 2-H), 4.61 (ψq, 2 H, AB, Ph-CH_2), 4.79 (ψdd, 2 H, AB, Ph-CH_2), 7.16−7.38 (m, 10 H, Ph-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 65.51 (C-2), 67.92 (C-1 or C-3), 68.30 (Ph-CH_2), 68.49 (C-5), 70.79 (C-4 or C-6), 71.13 (Ph-CH_2), 75.46 (C-1 or C-3), 77.46 (C-4 or C-6), 127.76, 127.93, 128.01, 128.13, 128.42, 128.48 ($C_{arom.}$), 137.90, 138.73 (C_{ipso}). Further analytical data is in accordance with the literature.[47]

4,5-Didesoxy-4,5-dibromo-3,6-di-*O*-acetyl-D-*myo*-inositol [(−)-41]: A solution of sodium metaperiodate (4.74 g, 22 mmol, 1.5 equiv.) and ruthenium trichloride trihydrate (200 mg, 0.8 mmol) in water (30 mL) was added to a vigorously stirred, ice-cooled solution of (1*S*,2*R*,3*R*,4*S*)-1,4-diacetoxy-2,3-dibromocyclohex-5-ene (+)-**16** (5.0 g, 14.2 mmol) in acetonitrile (140 mL, HPLC-grade). The stirring was continued until TLC showed absence of starting material (ca. 10 min). The reaction was quenched by addition of 20% aqueous $Na_2S_2O_3$ (100 mL). The aqueous layer was separated and extracted four times with dichloromethane (4 × 100 mL). The combined organic layer was washed twice with brine and dried with $MgSO_4$. Concentration under reduced pressure gave a white solid (4.5 g, 81%). R_f = 0.13 (ethyl acetate/cyclohexane, 1:1). $[\alpha]_D^{20}$ = −87 (*c* = 0.23, $CHCl_3$). $[\alpha]_D^{20}$ = −76 (*c* = 0.82, acetone). ^{1}H NMR ($CDCl_3$/[D_4]MeOH, 6:1): δ = 2.09 (s, 3 H, CH_3), 2.10 (s, 3 H, CH_3), 3.53 (dd, *J* = 2.8, *J* = 9.9 Hz, 1 H, 1-H), 3.94 (ψt, 1 H, *J* = 11.1 Hz, 5-H), 4.04 (ψt, 1 H, *J* = 2.5 Hz, 2-H), 4.40 (ψt, 1 H, *J* = 10.9 Hz, 4-H), 4.89 (dd, *J* = 2.5, *J* = 10.7 Hz, 1 H, 3-H), 5.37 (ψt, 1 H, *J* = 10.2 Hz, 6-H) ppm. ^{13}C NMR ($CDCl_3$/[D_4]MeOH, 6:1): δ = 20.74 (CH_3), 20.90 (CH_3), 52.78 (C-4), 53.59 (C-5), 70.52 (C-2), 71.23 (C-1), 74.69 (C-3), 74.77 (C-6), 170.50, 170.99 (C=O) ppm. MS [EI, 70 eV, *m*/*z* (%)]: 293, 291 (2, 2), 251, 249 (8, 8), 191, 189 (24, 23), 109 (18), 43 (100). IR (KBr): $\tilde{\nu}$ = 3475 (m, br.), 2975, 2925 (w), 1744, 1722 (s), 1372 (m), 1225 (s), 1036 (m) cm^{-1}. $C_{10}H_{14}O_6Br_2$: (387.92): calcd. C 30.80, H 3.62; found C 30.45, H 3.42.

5,6-Didesoxy-5,6-dibromo-1,4-di-*O*-acetyl-D-*myo*-inositol [(+)-41]: The (−)-enantiomer **16** was *cis*-dihydroxylated as described for (+)-**16**. $[\alpha]_D^{20}$ = +80 (*c* = 0.22, $CHCl_3$). Identical ^{1}H NMR and ^{13}C NMR spectroscopic data to those of (−)-**41**.

4,5-Didesoxy-4,5-dibromo-2,3,6-tri-*O*-acetyl-D-*myo*-inositol [(−)-45]: *p*-Toluenesulfonic acid monohydrate (150 mg, 0.8 mmol) and triethyl orthoacetate (11.3 mL, 79 mmol) were added to a solution of (−)-**41** (4.9 g, 12.6 mmol) in anhydrous tetrahydrofuran (140 mL) under argon. The mixture was stirred vigorously for 12 h. The solvent was removed under reduced pressure, and the residue was dried under high vacuum. The residue was dissolved in aqueous acetic acid (80 mL, 80%) and stirred for 1 h at room temperature. The organic phase was evaporated, and the residue was dissolved in ethyl acetate (100 mL). The organic phase was washed with saturated aqueous $NaHCO_3$ (2 × 50 mL) and then with brine (50 mL). Evaporation of the ethyl acetate gave a colorless, voluminous foam (5.0 g, 93%). For an analytical sample the resulting foam was purified by flash chromatography (cyclohexane/ethyl acetate, 1:1) to yield pure (−)-**45**. R_f = 0.37 (ethyl acetate/cyclohexane, 1:1). $[\alpha]_D^{20}$ = −85 (*c* = 0.17, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 2.08 (s, 3 H, CH_3), 2.19 (s, 3 H, CH_3), 2.21 (s, 3 H, CH_3), 3.81 (dd, *J* = 3.0, *J* = 9.7 Hz, 1 H, 1-H), 4.02 (ψt, 1 H, *J* = 10.9 Hz, 5-H), 4.28 (ψt, 1 H, *J* = 10.9 Hz, 4-H), 5.04 (dd, *J* = 2.8, *J* = 10.9 Hz, 1 H, 3-H), 5.37 (ψt, 1 H, *J* = 10.2 Hz, 6-H), 5.55 (ψt, 1 H, *J* = 2.8 Hz, 2-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 20.49 (CH_3), 20.77 (CH_3), 20.83 (CH_3), 51.44 (C-4), 52.44 (C-5), 69.87 (C-1), 70.87 (C-2), 72.08 (C-3), 74.49 (C-6), 169.48, 170.13, 170.72 (C=O) ppm. MS [EI, 70 eV, *m*/*z* (%)]: 353, 351 (3, 4), 293, 291 (48, 40), 233, 231 (13, 11), 191, 189 (18, 19), 169 (19), 109 (49), 43 (100). IR (KBr): $\tilde{\nu}$ = 3480 (m, br.), 2992, 2965, 2934 (w), 1747 (s), 1428 (m), 1377 (m), 1229 (s), 1107 (m), 1054 (m) cm^{-1}. HR-MS (CI, (DE), *iso*-butane): *m*/*z*: 430.93377 [M + H]$^+$ calcd. for $C_{12}H_{17}Br_2O_7$: 430.93412.

(1*R*,2*R*,3*S*,4*R*)-1,2,4-Tri-*O*-acetylconduritol C [(−)-46]: Zinc dust (6.1 g, 93 mmol) and a trace of iodine were added to a solution of (−)-**45** (2.9 g, 6.7 mmol) in anhydrous diethyl ether (150 mL) and acetic acid (6.1 mL, 99%). The mixture was refluxed for 4 h and stirred further for 12 h at room temperature. It was then filtered and the residue washed with diethyl ether. The organic phase was washed once with saturated aqueous $NaHCO_3$ and then with brine. Evaporation of the solvent gave a colorless, pasty oil. Separation by flash chromatography (cyclohexane/ethyl acetate, 1:1) yielded pure (−)-**46** (1.8 g, 82%) as a colorless solid. R_f = 0.25 (ethyl acetate/cyclohexane, 1:1). $[\alpha]_D^{20}$ = −177 (*c* = 0.71, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 2.04 (s, 3 H, CH_3), 2.12 (s, 3 H, CH_3), 2.13 (s, 3 H, CH_3), 2.65 (br. s, 1 H, OH), 3.99 (dd, *J* = 2.0, *J* = 7.6 Hz, 1 H, 3-H), 5.52 (dd, *J* = 2.0, *J* = 7.6 Hz, 1 H, 4-H), 5.58 (m, 2 H, 1-H, 2-H), 5.65 (dψq, 1 H, *J* = 2.0, *J* = 10.3 Hz, 6-H), 5.79 (dψt, 1 H,

J = 2.3, J = 10.2 Hz, 5-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 20.70 (CH_3), 20.74 (CH_3), 21.02 (CH_3), 67.92 (C-2), 70.56 (C-3), 71.98 (C-1), 72.84 (C-4), 126.94 (C-6), 127.64 (C-5), 170.00, 170.84, 171.49 (C=O) ppm. MS [EI, 70 eV, *m*/*z* (%)]: 212 (2), 183 (3), 170 (5), 152 (5), 141 (7), 128 (11), 110 (45), 99 (11), 43 (100). IR (KBr): $\tilde{\nu}$ = 3459 (m, br.), 2985, 2955 (w), 1743 (s), 1372 (s), 1258 (s), 1231 (s), 1032 (m) cm^{-1}. HR-MS (CI, (DE), *iso*-butane): *m*/*z*: 273.09760 $[M + H]^+$ calcd. for $C_{12}H_{17}O_7$: 273.09742.

(1*R*,2*R*,3*S*,4*R*)-1,2,4-Tri-*O*-acetyl-3-*O*-(3-oxo-1,5-dihydro-3λ^5-2,4,3-benzodioxaphosphepin-3-yl)conduritol C [(−)-47]: (1,5-Dihydro-2,4,3-benzodioxaphosphepin-3-yl)diethylamine (0.6 g, 2.5 mmol) was added to a solution of 1,2,4-tri-*O*-acetylconduritol C (−)-**46** (600 mg, 2.2 mmol) and 1*H*-tetrazole (380 mg, 5.4 mmol) in anhydrous dichloromethane (20 mL), and the solution was stirred at room temperature for 4 h. The mixture was cooled to −40 °C, and an anhydrous solution of *m*-CPBA (1.6 g, 6.5 mmol) in dichloromethane (20 mL, dried with Na_2SO_4) was added. The solution was allowed to warm to room temperature and stirred for another hour. The reaction mixture was diluted with dichloromethane (50 mL) and washed consecutively with 20% aqueous sodium bisulfite (2 × 60 mL), saturated $NaHCO_3$ (3 × 70 mL), and then with brine (70 mL). After evaporation of the dichloromethane the resulting colorless foam was purified by flash chromatography (cyclohexane/ethyl acetate, 2:3) to yield (−)-**47** (700 mg, 70%) as a colorless foam. R_f = 0.20 (ethyl acetate/cyclohexane, 3:2). $[\alpha]_D^{20}$ = −102 (*c* = 0.56, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 2.03 (s, 3 H, CH_3), 2.13 (s, 3 H, CH_3), 2.16 (s, 3 H, CH_3), 4.88 (dψt, 1 H, J = 2.2, J = 8.3 Hz, 3-H), 5.07 −5.23 [m, 4 H, $(CH_2)_2C_6H_4$), 5.61 −5.68 (m, 2 H, 1-H, 5-H or 6-H), 5.74 −5.84 (m, 3 H, 2-H, 4-H, 5-H or 6-H), 7.24−7.40 (m, 4 H, Ph-H). ^{13}C NMR ($CDCl_3$): δ = 20.60 (CH_3), 20.72 (CH_3), 20.99 (CH_3), 67.67 (C-1), 68.51 [d, J = 6.1 Hz, $(CH_2)_2C_6H_4$], 68.71 [d, J = 6.1 Hz, $(CH_2)_2C_6H_4$], 69.96 (d, J = 4.1 Hz), 70.56 (d, J = 4.1 Hz) (C-2, C-4), 75.34 (d, J = 5.1 Hz, C-3), 126.86, 127.28 (C-5, C-6), 128.74, 128.80, 129.09, 129.17 ($C_{arom.}$), 134.83, 135.00 (C_{ipso}), 169.60, 170.02, 170.61 (C=O) ppm. ^{31}P{^{1}H} NMR ($CDCl_3$): δ = −0.1 (PC-3) ppm. MS [EI, 70 eV, *m*/*z* (%)]: 454 (1) [M^+], 395 (2), 335 (4), 201 (100), 43 (100). HR-MS [EI, (DE)]: *m*/*z*: 454.10295 $[M]^+$ calcd. for $C_{20}H_{23}O_{10}P$: 454.10289.

2,3,6-Tri-*O*-acetyl-1,4,5-tri-*O*-(3-oxo-1,5-dihydro-3λ^5-2,4,3-benzodioxaphosphepin-3-yl)-D-*epi*-inositol [(+)-48]: A solution of sodium metaperiodate (450 mg, 2.1 mmol, 1.5 equiv.) and ruthenium trichloride trihydrate (20 mg, 0.08 mmol) in water (3 mL) was added to a vigorously stirred, ice-cooled solution of (−)-**47** (600 mg, 1.3 mmol) in acetonitrile (30 mL, HPLC-grade). The stirring was continued until TLC showed absence of starting material (ca. 5 min). The reaction was quenched by addition of 20% aqueous $Na_2S_2O_3$ (30 mL). The aqueous layer was separated and extracted four times with ethyl acetate (4 × 40 mL). The combined organic layer was washed twice with brine and dried with $MgSO_4$. Concentration under reduced pressure gave a white solid (660 mg, 99%, 80% *de*). Further purification was rendered counterproductive by protecting-group movement. NMR spectroscopic data for 2,3,6-tri-*O*-acetyl-1-*O*-(3-oxo-1,5-dihydro-3λ^5-2,4,3-benzodioxaphosphepin-3-yl)-D-*epi*-inositol. ^{1}H NMR ($CDCl_3$): δ = 2.07 (s, 3 H, CH_3), 2.13 (s, 3 H, CH_3), 2.18 (s, 3 H, CH_3), 3.68 (dd, J = 3.1, J = 9.7 Hz, 1 H, 5-H), 4.21 (ψs, 1 H, 4-H), 4.72 (dψt, 1 H, J = 3.4, J = 9.7 Hz, 1-H), 4.97 (ψt, 1 H, J = 3.3 Hz, 3-H), 5.05−5.17 [m, 4 H, $(CH_2)_2C_6H_4$], 5.57 (ψt, 1 H, J = 9.9 Hz, 6-H), 5.74 (ψt, 1 H, J = 2.8 Hz, 2-H), 7.21 −7.38 (m, 4 H, Ph-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 20.54 (CH_3), 20.73 (CH_3), 20.93 (CH_3), 67.68 (s, C-3), 68.44 [d, J = 7.1 Hz, $(CH_2)_2C_6H_4$], 68.71 (d, J = 7.1 Hz, $(CH_2)_2C_6H_4$), 70.13 (s, C-5), 70.35 (d, J = 3.1 Hz, C-2), 70.79 (m, C-4, C-6), 74.03 (d, J = 5.1 Hz, C-1), 126.86, 127.28 128.71, 128.79, 129.10, 129.18 ($C_{arom.}$), 134.65, 134.84 (C_{ipso}), 169.53, 169.78, 171.26 (C=O) ppm. ^{31}P{^{1}H} NMR ($CDCl_3$): δ = −0.29 (PC-1) ppm.

(1,5-Dihydro-2,4,3-benzodioxaphosphepin-3-yl)diethylamine (0.7 g, 2.9 mmol) was added to a solution of the crude product thus obtained (575 mg, 1.2 mmol) and 1*H*-tetrazole (350 mg, 5 mmol) in anhydrous dichloromethane (30 mL) under argon, and the mixture was stirred at room temperature for 12 h. The product was worked up as described for (−)-**47**. Separation by flash chromatography (ethyl acetate) yielded pure (+)-**48** (420 mg, 50%) as a colorless foam. R_f = 0.10 (ethyl acetate). $[\alpha]_D^{20}$ = +5.8 (*c* = 0.28, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 2.03 (s, 3 H, CH_3), 2.08 (s, 3 H, CH_3), 2.23 (s, 3 H, CH_3), 4.85 (m, 2 H, C-1, C-5), 5.04 −5.49 [m, 14 H, C-3, C-4, 3 × $(CH_2)_2C_6H_4$], 5.80 (ψt, 1 H, J = 2.8 Hz, 2-H), 5.83 (ψt, 1 H, J = 10.2 Hz, 6-H), 7.16−7.38 (m, 12 H, Ph-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 20.37 (CH_3), 20.60 (CH_3), 20.99 (CH_3), 65.66 (s, C-4), 68.11 (m, C-6), 68.32−68.95 [m, $(CH_2)_2C_6H_4$], 69.14 (m, C-2), 73.22 (d, J = 4.8 Hz), 73.63 (m, C-1, C-5), 75.73 (m, C-3), 128.49−129.13 ($C_{arom.}$), 134.64, 134.73, 134.85, 134.93, 135.01, 135.33 (C_{ipso}), 169.16, 169.66, 170.71 (C=O) ppm. ^{31}P{^{1}H} NMR ($CDCl_3$): δ = 0.27, −0.10, −1.25 ppm. HR-MS [EI, (DE)]: *m*/*z*: 852.13485 $[M]^+$ calcd. for $C_{36}H_{39}O_{18}P_3$: 852.13491.

D-*epi*-Inositol-1,4,5-trisphosphate [(+)-49]: Pd/C (150 mg) was added to a suspension of (+)-**48** (100 mg, 0.11 mmol) in ethanol/water (1:1, 20 mL). The mixture was stirred at room temperature under H_2 overnight. The catalyst was filtered off, and the filtrate was concentrated under high vacuum. The residue was dissolved in ice-cooled 0.25 M aqueous NaOH (10 mL) and stirred for 4 h. The solution was neutralized by ion exchanger (H^+, Dowex 50-X) and filtered, and then activated carbon was added. The solution was filtered again, and the filtrate was lyophilized to give 50 mg (99%) of a colorless foam. $[\alpha]_D^{20}$ = +7.7 (*c* = 2.85, H_2O). ^{1}H NMR [D_2O, pH adjusted to 6 (ND_4OD)]: δ = 3.75 (ψs, 1 H, 3-H), 3.85 −4.04 (m, 3 H, 1-H, 5-H, 6-H), 4.13 (ψs, 1 H, 2-H), 4.70 (d, under HDO, J = 10.7 Hz, 4-H) ppm. ^{31}P{^{1}H} NMR [D_2O, pH adjusted to 6 (ND_4OD)]: δ = 1.84, 3.05, 4.58 ppm. HR-MS (ESI-neg, phosphoric acid 0.002%, H_2O/acetonitrile, 1:1, Q-TOF): *m*/*z*: 418.9525 $[M - H]^-$ calcd. for $C_6H_{14}O_{15}P_3$: 418.9546.

4,5-Didesoxy-4,5-dibromo-1,2,3,6-tetra-*O*-acetyl-D-*myo*-inositol [(−)-42]: 4,5-Didesoxy-4,5-dibromo-3,6-di-*O*-acetyl-D-*myo*-inositol (−)-**41** (5.3 g, 13 mmol) was dissolved in a cooled mixture of pyridine (20 mL) and acetic anhydride (15 mL). The mixture was stirred for 12 h. Evaporation of the solvent gave (−)-**42** (5.9 g, 99%) as a white solid. For an analytical sample, recrystallization from ethanol yielded pure (−)-**42** as a white solid. R_f = 0.56 (ethyl acetate/cyclohexane, 2:3). $[\alpha]_D^{20}$ = −49.5 (*c* = 0.76, $CHCl_3$). $[\alpha]_D^{20}$ = −69.4 (*c* = 1.57, CH_2Cl_2). m.p. 161.5 °C. ^{1}H NMR ($CDCl_3$): δ = 1.99, 2.08, 2.10, 2.20 (4 × s, 4 × 3 H, CH_3), 4.05 (ψt, 1 H, J = 10.9 Hz), 4.33 (ψt, 1 H, J = 11.3 Hz) (4-H, 5-H), 5.05 (dd, J = 2.8, J = 10.4 Hz, 1 H), 5.16 (dd, J = 2.8, J = 10.9 Hz, 1 H) (1-H, 3-H), 5.56 (ψt, 1 H, J = 2.8 Hz, 2-H), 5.57 (ψt, 1 H, J = 10.2 Hz, 6-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 20.38 (CH_3), 20.43 (CH_3), 20.59 (CH_3), 20.66 (CH_3), 51.26, 52.31 (C-4, C-5), 68.61, 69.36, 71.32, 71.37 (C-1, C-2, C-3, C-6), 168.93, 169.14, 169.27, 169.72 (C=O) ppm. MS [EI, 70 eV, *m*/*z* (%)]: 395, 393 (1.3, 1.6), 333, 335 (6.7, 6.0), 293, 291 (6.6, 6.3), 233, 231 (6.5, 7.4), 169 (8.0), 109 (25.4), 43 (100). IR (KBr): $\tilde{\nu}$ = 2981, 2964 (w), 1765, 1749 (s), 1368 (m), 1241 (s), 1213 (s), 1056 (m) cm^{-1}. $C_{14}H_{18}O_8Br_2$ (471.93): calcd. C 35.47, H 3.83; found C 35.60, H 3.77. HR-MS (CI, (DE), *iso*-butane): *m*/*z*: 472.94498 $[M + H]^+$ calcd. for $C_{14}H_{19}Br_2O_8$: 472.94468.

5,6-Didesoxy-5,6-dibromo-1,2,3,4-tetra-*O*-acetyl-D-*myo*-inositol [(+)-42]: The (+)-enantiomer **41** was acetylated as described for (−)-**42** to give (+)-**42**. $[\alpha]_D^{20} = +52$ ($c = 0.65$, $CHCl_3$). Identical ^1H NMR and ^{13}C NMR spectroscopic data to those of (−)-**42**.

(1*R*,2*R*,3*S*,4*R*)-1,2,3,4-Tetra-*O*-acetylconduritol C [(−)-43]: Acetic acid (10 mL) and zinc dust (10 g, 150 mmol) were added to a solution of 4,5-didesoxy-4,5-dibromo-1,2,3,6-tetra-*O*-acetyl-D-*myo*-inositol (−)-**42** (4 g, 8.3 mmol) in anhydrous diethyl ether (200 mL). The mixture was refluxed for 12 h and then filtered, and the residue was washed with diethyl ether. The organic phase was washed once with saturated aqueous $NaHCO_3$ and then with brine. Evaporation of the solvent gave a colorless oil. Crystallization from ethanol removed most of the starting material. The filtrate was concentrated under vacuum and the resulting residue purified by flash chromatography on silica gel (cyclohexane/ethyl acetate, 7:3) to yield pure (−)-**43** (1.8 g, 68%). $R_f = 0.24$ (ethyl acetate/cyclohexane, 3:7). $[\alpha]_D^{20} = -192$ ($c = 0.28$, $CHCl_3$). ref.[48] $[\alpha]_D^{20} = -194$ ($c = 3.0$, $CHCl_3$). ^1H NMR ($CDCl_3$): δ = 2.03, 2.04, 2.07, 2.13 (4 × s, 4 × 3 H, CH_3), 5.20 (dd, $J = 1.5$, $J = 8.3$ Hz, 1 H, 3-H), 5.62 −5.72 (m, 4 H, 1-H, 2-H, 4-H, $H_{olef.}$), 5.80 (dψt, 1 H, $J = 1.6$, $J = 10.8$ Hz, $H_{olef.}$) ppm. ^{13}C NMR ($CDCl_3$): δ = 20.65 (CH_3), 20.70 (2 × CH_3), 20.90 (CH_3), 67.60, 69.48, 69.78 (C-1, C-2, C-4), 70.56 (C-3), 127.07, 127.51 (C-5, C-6), 169.68, 169.87, 170.23, 170.42 (C=O) ppm. MS [EI, 70 eV, *m/z* (%)]: 212 (4), 152 (51.1), 110 (100),43 (69). IR (KBr): $\tilde{\nu}$ = 3087, 3013 (w), 2956 (w), 1758 (s), 1372 (m), 1230 (s), 1044 (m) cm^{-1}. $C_{14}H_{18}O_8$ (314.10): calcd. C 53.50, H 5.77; found C 53.65, H 5.69.

(1*S*,2*S*,3*R*,4*S*)-1,2,3,4-Tetra-*O*-acetylconduritol C [(+)-43]: The (+)-enantiomer **42** was debrominated as described for (−)-**43** to give (+)-**43**. $[\alpha]_D^{20} = +188$ ($c = 0.6$, $CHCl_3$). Identical ^1H NMR and ^{13}C NMR spectroscopic data to those of (−)-**43**.

Hexa-*O*-acetyl-*epi*-inositol (44): A solution of sodium metaperiodate (1.1 g, 5.2 mmol, 1.5 equiv.) and ruthenium trichloride trihydrate (100 mg, 0.4 mmol) in water (12 mL) was added to a vigorously stirred, ice-cooled solution of (1*R*,2*R*,3*S*,4*R*)-1,2,3,4-tetra-*O*-acetylconduritol C (−)-**43** (1.1 g, 3.4 mmol) in acetonitrile (60 mL). The stirring was continued until TLC showed absence of starting material (ca. 10 min). The reaction was quenched by addition of 20% aqueous $Na_2S_2O_3$ (50 mL). The aqueous layer was separated and extracted with ethyl acetate (4 × 100 mL). The combined organic layer was washed twice with brine and concentrated under reduced pressure. The residue was dissolved in a cooled mixture of pyridine (20 mL) and acetic anhydride (10 mL). The mixture was stirred for 12 h. Evaporation of the solvent under high vacuum and recrystallization from ethanol yielded pure **44** as a white solid (1.1 g, 74%). ^1H NMR ($CDCl_3$): δ = 1.98 (s, 3 H, CH_3), 1.99 (s, 2 × 3 H, CH_3), 2.02(s, 3 H, CH_3), 2.15 (s, 2 × 3 H, CH_3), 5.07 (dd, $J = 3.3$, $J = 10.4$ Hz, 2 H, 1-H, 5-H), 5.11 (ψt, 1 H, $J = 3.3$ Hz, 3-H), 5.59 (ψt, 2 H, $J = 3.5$ Hz, 2-H, 4-H), 5.69 (ψt, 1 H, $J = 10.7$ Hz, 6-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 20.31(CH_3), 20.35 (2 × CH_3), 20.54 (CH_3), 20.64 (2 × CH_3), 65.74 (C-3), 67.26 (C-6), 68.49 (C-2, C-4), 68.79 (C-1, C-5), 169.05 (C=O), 169.39 (2 × C=O), 169.69 (C=O), 169.93 (2 × C=O) ppm. MS [EI, 70 eV, *m/z* (%)]: 390 (2), 373 (2), 330 (2), 270 (9), 210 (80), 168 (100), 126 (50), 43 (79). IR (KBr): $\tilde{\nu}$ = 2992, 2965 (w), 1751 (s, br.), 1433 (m), 1370 (s), 1225 (s, br.), 1087 (m), 1050 (s) cm^{-1}. $C_{18}H_{14}O_{12}$ (432.126777): calcd. C 50.00, H 5.59; found C 49.89, H 5.53. HR-MS [CI (DE), *iso*-butane]: *m/z*: 433.13490 $[M + H]^+$ calcd. for $C_{18}H_{25}O_{12}$: 433.13460.

***epi*-Inositol (7):** Hexa-*O*-acetyl-*epi*-inositol **44** (400 mg, 0.9 mmol) was suspended in anhydrous methanol under argon and cooled to 4 °C. Sodium methoxide solution (200 μL of a 5.5 M solution, 1.1 mmol) was added dropwise over 10 min. The reaction mixture was allowed to warm to room temperature and stirred for 12 h. The solvent was removed, and the residue was dissolved in 0.25 M aqueous NaOH (10 mL) and refluxed for 2 h. The solution was neutralized by ion exchanger (H^+, Dowex 50-X) and filtered, and the Dowex material was washed with water. The filtrate was first concentrated under high vacuum and then lyophilized to give **7** (170 mg, 99%) as a colorless solid. ^1H NMR ($CDCl_3$): δ = 3.44 (dd, $J = 2.1$, $J = 9.7$ Hz, 2 H, 1-H, 5-H), 3.69 (ψt, 1 H, $J = 2.5$ Hz, 3-H), 3.80 (ψt, 1 H, $J = 9.9$ Hz, 6-H), 4.03 (ψt, 2 H, $J = 2.5$ Hz, 2-H, 4-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 69.07 (C-3), 72.29 (C-6), 73.99 (C-1, C-5), 76.70 (C-2, C-4) ppm. MS [EI, 70 eV, *m/z* (%)]: 144 (2), 102 (4), 73 (100), 60 (26). IR (KBr): $\tilde{\nu}$ = 3406 (s, br.), 2920 (w), 1634 (w), 1418 (w), 1132 (w), 1064 (w), 1048 (m) cm^{-1}. $C_6H_{12}O_6$ (180.16): calcd. C 40.00, H 6.71; found C 39.84, H 6.86.

1,2-Anhydro-3,6-di-*O*-benzyl-4,5-di-*O*-isopropyl-*myo*-inositol (38): 2,2-Dimethoxypropane (40 mL) and pyridinium *p*-toluenesulfonate (150 mg, 0.6 mmol) were added to a solution of **31** (3.0 g, 8.76 mmol) in dry acetone (12 mL). The reaction mixture was stirred for 16 h at room temperature.To the white suspension diethyl ether, 2 M sodium hydroxide (8 mL) and brine (8 mL) were added subsequently. The stirring was continued for another 30 min. The layers were separated, and the organic layer was washed with brine, dried with sodium sulfate, and the solvents evaporated to dryness to yield 3.2 g (96%) of **38** as a colorless solid, which was used for further conversions without purification. m.p. 104 °C. ^1H NMR ($CDCl_3$): δ = 1.48 (s, 3 H, CH_3), 1.51 (s, 3 H, CH_3), 3.25 (d, $J = 3.4$ Hz, 1 H, 1-H), 3.39 (m, 1 H, 2-H), 3.55 (dd, $J = 9.9$, $J = 8.8$ Hz, 1 H, 5-H), 3.78 (dd, $J = 8.6$, $J = 9.9$ Hz, 1 H, 4-H), 3.98 (d, $J = 8.8$ Hz, 1 H, 6-H), 3.98 (dd, $J = 2.0$, $J = 8.6$ Hz, 1 H, 3-H), 4.75 −4.98 (m, 4 H, Ph-CH_2), 7.33 −7.49 (m, 10 H, Ph-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 27.4 (CH_3), 27.6 (CH_3), 56.8 (C-2), 56.9 (C-1), 72.3 (Ph-CH_2), 72.6 Ph-CH_2), 75.6 (C-4), 76.4 (C-6), 76.6 (C-3), 80.6 (C-5), 112.0 [$C(CH_3)_2$], 128.2 −129.0 (C_{arom}), 138.2, 138.6 (C_{ipso}) ppm. IR (KBr): 3080−3010 (w), 3000−2850 (m), 1490−1450 (m), 1080 (s, br.), MS [EI, 70 eV, *m/z* (%)]: 382 (5) $[M^+]$, 107 (22), 91 (100) cm^{-1}. $C_{23}H_{26}O_5$ (382.5): calcd. C 72.23, H 6.85; found C 72.29, H 6.88.

1-*O*-Allyl-2,5-di-*O*-benzyl-*scyllo*-inositol (39): Sodium (450 mg, 20 mmol) was dissolved in allylic alcohol (5 mL). **38** (150 mg, 0.4 mmol) was added to the solution and the reaction mixture was heated for 24 h at 90 °C. After the reaction was complete, the mixture was diluted with THF and adjusted to pH 0 by addition of 4 M HCl. After stirring at room temperature, solid $NaHCO_3$ was added, and the aqueous layer was extracted several times with ethyl acetate (5 × 50 mL). The combined organic layer was dried and the solvents evaporated. Recrystallization of the crude product from hexane/ethyl acetate delivered **39** as the pure *scyllo* isomer (96 mg, 60%). m.p. 179 °C. ^1H NMR ([D$_6$]DMSO): δ = 3.07 −3.39 (m, 6 H); 4.17 −4.34 (m, 2 H, O-CH_2), 4.69 −4.87 (m, 4 H, Ph-CH_2), 4.90 (d, $J = 4.0$ Hz, 1 H, -OH), 4.96 (d, $J = 4.0$ Hz, 1 H, -OH), 5.03 −5.22 (m, 3 H, -OH and CH=CH_2), 5.88 −5.94 (m, 1 H, CH=CH_2), 7.22−7.44 (m, 10 H, Ph-H) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 73.8, 74.3, 74.4, 74.6, 74.8, 83.0 (2 C), 83.4, 116.1 (CH=CH_2), 127.6−128.6 (C_{arom}), 136.9 (CH=CH_2), 140.0, 140.3 (C_{ipso}) ppm. MS [EI, 70 eV *m/z* (%)]: 400 (2), $[M^+]$, 359 (3), 309 (100), 107 (45), 91 (100).

***scyllo*-Inositol (6): 39** (96 mg, 0.24 mmol) was dissolved in methanol (10 mL). Palladium on charcoal (10%, 20 mg) was added and the mixture was heated under reflux for 6 h. The charcoal was filtered off and washed thoroughly with methanol, and the organic layer

was taken to dryness. The residue was taken up in 2 M HCl and heated to 80 °C. The reaction mixture was allowed to cool to room temperature, neutralized by addition of sodium hydroxide solution (10 M) and extracted several times with ethyl acetate (5 × 50 mL). The combined organic layer was dried and the solvents evaporated and the crude product was taken up in methanol/water (1:1; 5 mL). Palladium on charcoal (10%, 20 mg) was suspended in methanol/water (10 mL) and stirred under an atmosphere of H_2 for 15 min. The solution of the crude product in methanol was added via a syringe, and stirring under H_2 was continued for 12 h. The reaction mixture was filtered, and the residue was washed thoroughly with water. The filtrate was taken to dryness, and the precipitate was recrystallized from water/methanol to yield **6** as a colorless solid (37 mg, 85%). ^{1}H NMR (D_2O): δ = 3.30 (s, 6 H, 1-H − 6-H) ppm. ^{13}C NMR (D_2O): δ = 75.84 (C-1 − C-6) ppm. MS (EI, 70 eV, *m*/*z* (%)]: 144 (3), 102 (35), 73 (78), 60 (100). $C_6H_{12}O_6$ (180.16): calcd. C 40.00, H 6.71; found C 39.95, H 6.71.

***scyllo*-Inositol Hexakis(phosphate) (40):** (1,5-Dihydro-2,4,3-benzodioxaphosphepin-3-yl)diethylamine (470 mg, 2.0 mmol) was added to a suspension of *scyllo*-inositol **6** (50 mg, 0.27 mmol) and 1*H*-tetrazole (226 mg, 3.2 mmol) in anhydrous dichloromethane (20 mL), and the solution was stirred at room temperature overnight. The product was worked up as described for **28**. Purification by flash chromatography on silica gel yielded hexa-*O*-(3-oxo-1,5-dihydro-3λ^5-2,4,3-benzodioxaphosphepin-3-yl)-*scyllo*-inositol (133 mg, 40%) as a colorless foam. ^{1}H{^{31}P} NMR ($CDCl_3$/[D_4]MeOH, 9:1): δ = 5.09 [AB, 12 H, *J* = 13.7 Hz, $(CH_2)_2C_6H_4$], 5.19 (s, 6 H, 1-H − 6-H), 5.50 [AB, 12 H, *J* = 13.7 Hz, $(CH_2)_2C_6H_4$], 7.13−7.39 (m, 24 H, Ph-H). ^{13}C NMR ($CDCl_3$/[D_4]MeOH, 9:1): δ = 69.75, 69.83 [$(CH_2)_2C_6H_4$], 78.3 (C-1 − C-6), 129.5, 129.7 ($C_{arom.}$), 129.4, 135.8 (C_{ipso}) ppm. ^{31}P{^{1}H} NMR ($CDCl_3$/[D_4]MeOH, 9:1): δ = −3.30 (PC-1 − PC6).

Hydrogenolysis of hexa-*O*-(3-oxo-1,5-dihydro-3λ^5-2,4,3-benzodioxaphosphepin-3-yl)-*scyllo*-inositol was carried out as described for **28**. ^{1}H NMR [D_2O, pH adjusted to 6 (ND_4OD)]: δ = 4.35 (d, *J* = 3.6 Hz, 6 H, 1-H − 6-H) ppm. ^{13}C NMR [D_2O, pH adjusted to 6 (ND_4OD)]: δ = 78.6 (C-1 − C-6) ppm. ^{31}P{^{1}H} NMR [D_2O, pH adjusted to 6 (ND_4OD)]: δ = 1.2 (PC-1 − PC-6) ppm. HR-MS (ESI-neg, phosphoric acid 0.002%, H_2O/acetonitrile, 1:1, Q-TOF): *m*/*z*: 658.8511 [M − H]$^-$ calcd. for $C_6H_{17}O_{24}P_6$: 658.8536.

Acknowledgments

We thank Dr. W. V. Turner for critical reading of the manuscript. This work was supported by the Deutsche Forschungsgemeinschaft (Grant VO 348/3-1) and the Fonds der Chemischen Industrie. We are grateful to the Bayer AG Company for supporting many aspects of this project, especially for preparing the HR-MS spectra. We also thank the Max-Planck Institut für Kohlenforschung, in particular Dr. W. Schrader and Mrs. M. Blumenthal, and Mr. M. Constapel for further HR-MS spectra.

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Received October 15, 2002

