ARTICLE

OBC
www.rsc.org/obc

Stereoselective synthesis of several azido/amino- and diazido/diamino-*myo*-inositols and their phosphates from *p*-benzoquinone

Michael A. L. Podeschwa, Oliver Plettenburg and Hans-Josef Altenbach *
Institut für Organische Chemie, Bergische Universität Wuppertal, Gaussstrasse 20, 42097 Wuppertal, Germany. E-mail: orgchem@uni-wuppertal.de; Fax: +49 (0)202 439 2648

Received 10th March 2003, Accepted 10th April 2003
First published as an Advance Article on the web 30th April 2003

A practical route is described for the preparation of azido-*myo*-inositols, amino-*myo*-inositols and azido-conduritol B derivatives. Starting from *p*-benzoquinone, optically pure compounds in both forms can be prepared *via* enzymatic resolution of a derived diacetoxy conduritol B derivative. Selective introduction of nitrogen-containing functional groups in four of the six possible positions in the cyclitol moiety is followed by further functionalization to yield the target compounds.

Introduction

The *myo*-inositol pathway is an attractive target for intervention in the control of cellular growth and proliferation.[1,2] After the discovery in 1983[3,4] that D-*myo*-inositol 1,4,5-trisphosphate is involved in the signal transduction as a Ca^{2+}-mobilizing second messenger, there has been an increased interest in the synthesis of analogues. Legler showed that free and conjugated amino-derivatives of *myo*-inositol are capable of inhibiting glycosidases and play an active role in antibiotic action.[5] Azido *myo*-inositols have direct antiproliferative activity on tumor cells (derived from fibroblasts).[6] It was shown that 3-substituted azido- and amino-*myo*-inositol derivatives were taken up by cells and in the absence of *myo*-inositol selectively inhibited the cell growth.[7] These effects were attributed to interference of the examined azido- and amino-inositols with phosphatidylinositol 3′-kinase and interaction with the signalling cascade. Kozikowski showed that tritiated 3-azido-*myo*-inositol was incorporated into cellular phosphatidylinositols of v-sis NIH 3T3 cells.[6a] This suggests that certain azido- and amino-*myo*-inositol derivatives might be useful as therapeutic agents for cancer and other diseases in which cellular-growth regulation is disturbed.[7]

However, there are only a few syntheses of amino- or azido-*myo*-inositols reported in the literature to date. This might be attributed in part to the fact that starting from chiral materials like D-quebrachitol[8] offers access to only a very limited number of stereoisomers. The use of *myo*-inositol as the most inexpensive starting material requires introduction of the nitrogen-containing moiety either under retention or double-inversion of a specific stereocenter.[9] Alternatively, two separate inversions of a *cis* diol unit have been used to reconstitute the *myo*-conformation.[10] Furthermore, the non-chiral starting material has to be converted to an enantiomerically differentiated form. This problem, which can cause synthetic difficulties, can be circumvented by a *de-novo* approach.

A synthesis of 5-azido- and 6-azido-derivatives was previously reported by Sanfilippo and co-workers in a synthetic scheme requiring six steps from racemic conduritol E.[11]

Here we describe a novel route to azido-*myo*-inositols starting from *p*-benzoquinone and subsequent enzymatic resolution of the derived diacetate **1**. As intermediates in our synthesis of azido-*myo*-inositol derivatives the enantiopure azido-conduritol B derivatives were synthesized. These intermediates have themselves pharmacological potential. Lehmann and co-workers have shown that racemic diamino-conduritols, after β-D-galactosylation to pseudo-disaccharides, are stable toward enzymatic cleavage and competitively inhibit β-D-galactosidase from *Escherichia coli* (the NH_2 group competing for the activating proton).[12] Furthermore, azido-conduritol derivatives are potential precursors for the synthesis of compounds which may be useful to elucidate the biosynthesis of aminoglycosides like butirosin,[13,14] minosaminomycin[15] and streptomycin.[16]

In this report we show that in addition to the above mentioned monoazido-route the synthesis of enantiopure diazido-conduritol B can be carried out in a one-pot reaction starting from diacetate **1**.

Finally, amino- and azido-*myo*-inositol phosphates were synthesized. We were attracted to the synthesis of derivatives of *myo*-inositol phosphates as part of our ongoing study of the regiospecificity of phosphohydrolases.[17] Such compounds should prove valuable tools to explain substrate–structure relationships for dephosphorylation by phytases and other phosphohydrolases and can also serve as affinity-material ligands for the isolation of inositol pentakis- and hexakis-phosphate binding enzymes.

Results and discussion

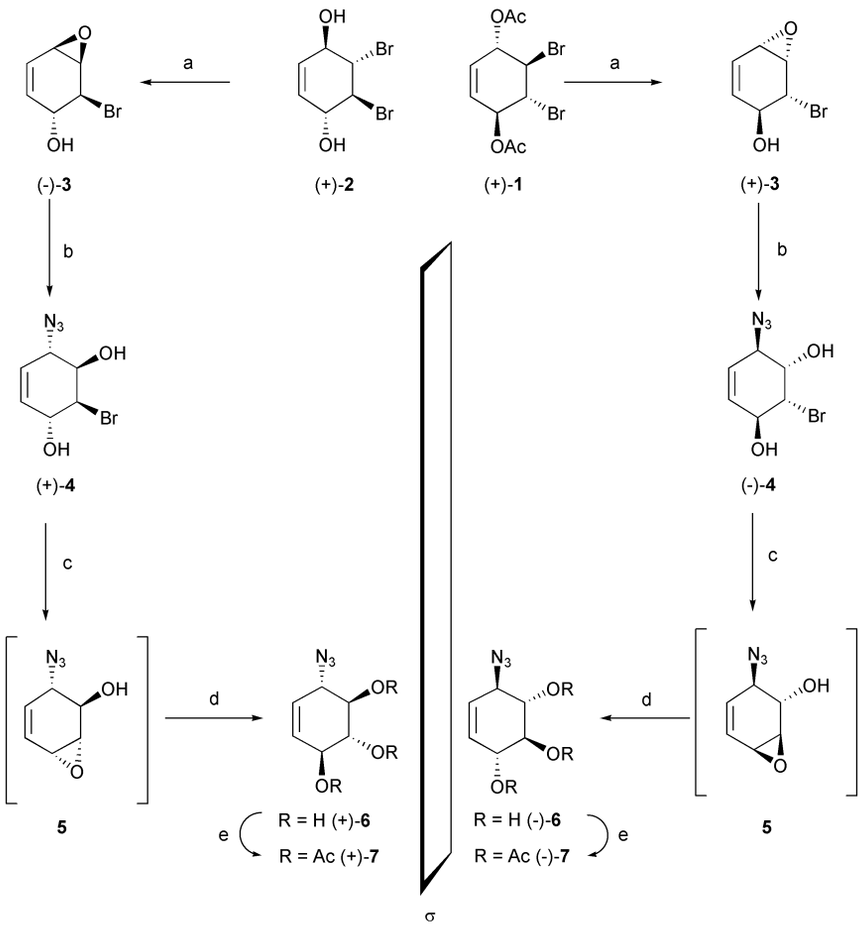
The known diacetoxy-dibromocyclohex-5-ene (+)-**1** and (−)-**1** (or the corresponding diols (−)- and (+)-**2**) are used as enantiomeric building blocks[18,19] for the synthesis of all the azido-/amino-*myo*-inositol derivatives. They can easily be prepared from *p*-benzoquinone in three steps and 70% overall yield. Enantiopure compounds are obtained by hydrolysis of racemic diacetate **1** with *PPL* in Et_2O–phosphate buffer at pH 7.0. The hydrolysis stopped after 50% conversion and proceeded with excellent enantioselectivity (>99% ee) for both the remaining diacetate (+)-**1** and the resulting diol (+)-**2**.[18,19] The products can easily be separated on a 100 g scale by their different solubility in dichloromethane.

Preparation of mono-azido/amino-*myo*-inositols

Epoxide (−)-**3** can be prepared in high yield (>90%) from diol (+)-**2** by use of lithium hydroxide as base. The diacetate (+)-**1** could be converted in the same way to give the enantiomer (+)-**3**. The azido moiety is introduced by selective opening of the epoxide in the allylic position.[20,18]

Reaction of the azide (+)-**4** under the above-mentioned mildly basic conditions resulted in the formation of an epoxide intermediate **5**. The direct hydrolysis of the intermediate in water with catalytic amounts of *p*-toluenesulfonic acid yielded a

DOI: 10.1039/b302622a



Scheme 1 *Reagents and conditions*: (a) LiOH, Et_2O–MeOH (99%). (b) NaN_3, DME, H_2O, EtOH, NH_4Cl (90%). (c) LiOH, Et_2O–MeOH. (d) *p*-TsOH, H_2O [overall yield (a–d): 41%]. (e) Ac_2O, pyridine (96%).

mixture which contained, besides the desired (+)-**6**, byproducts resulting from S_N'-reactions. However, simple recrystallization from ethyl acetate gave pure azido-conduritol B (+)-**6** (41% over four steps, starting from diol (+)-**2**). The details of this efficient reaction sequence are summarized in Scheme 1. The conduritol B derivative (+)-**6** was synthesized from diol (+)-**2** without need for purification of the intermediates. Only in the last step of this sequence is a recrystallization necessary. Because of this simple reaction sequence it is easy to scale up the synthesis of azido-conduritol B (+)-**6**.

Acetylation, followed by *cis*-dihydroxylation of the conduritol B derivative (+)-**7** with ruthenium trichloride and sodium metaperiodate, gave (+)-**9** and (−)-**8** in high yields. To minimize protection group migration, acetonitrile as a solvent proved to be superior to ethyl acetate. *cis*-Dihydroxylation of conduritol-B-derivatives led only to the *myo*-configuration of the resulting inositol, but in the case of non-symmetrical starting materials attack of the hydroxylating agent leads to two diastereomers in a 6 : 4 ratio (Scheme 2). The two products, however, show remarkably different solubility in chloroform; while 4,5,6-tri-*O*-acetyl-3-azido-*myo*-inositol (+)-**9** remained insoluble as a white solid (purity >99%), 3,4,5-tri-*O*-acetyl-6-azido-*myo*-inositol (−)-**8** (purity >90–95%) dissolves readily. If a higher purity of the 6-azido/6-amino-*myo*-inositol derivative is desired, the pentaacetate (+)-**10** can be recrystallised from EtOH. From triacetate **7**, 3-azido-pentaacetate **11** and 6-azido-pentaacetate **10** can be obtained in two steps in 50% and 35% yield, respectively.

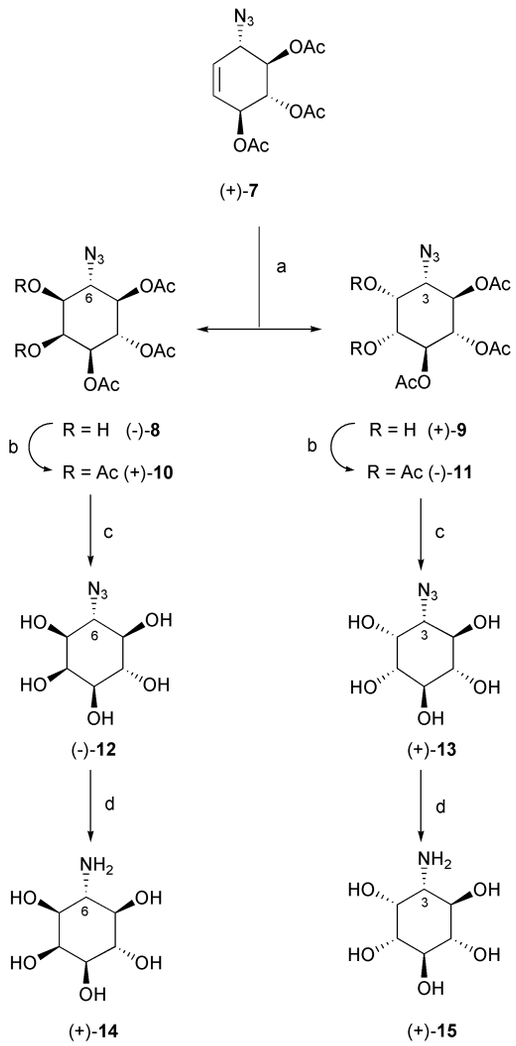
Deprotection of the 6-azido-tri- or pentaacetate and 3-azido-tri- or pentaacetate with sodium methoxide in anhydrous methanol gave 6-azido-*myo*-inositol (−)-**12** or 3-azido-*myo*-inositol (+)-**13**, respectively, in quantitative yield. Pd/C-catalyzed reduction of the azide with hydrogen led to 6-amino-*myo*-inositol (+)-**14** and 3-amino-*myo*-inositol (+)-**15** in quantitative yield. 3-Amino-*myo*-inositol (+)-**15** and 6-amino-*myo*-inositol (+)-**14** can be obtained in an overall yield of about 19% and 14%, respectively, from **2** in eight steps.

Since this route can start from either of two building blocks, as depicted in Scheme 3, azido and amino groups can easily be introduced in the 1-, 3-, 4- and 6-position of the cyclitol ring, depending on choice of starting material. For a deeper insight into *myo*-inositol nomenclature see refs. 1 and 2.

Starting from the diol (+)-**2** leads to the diastereomeric pair (+)-**13** and (−)-**12**, bearing nitrogen substituents in the 3- and 6-position. On the other hand, starting from the corresponding diacetate (+)-**1** leads to the diastereomeric pair (−)-**13** and (+)-**12**, containing an azido group in the 1- and 4-position, respectively (Scheme 3).

The derived inositol derivatives were used to synthesize inositol phosphate analogues.

The introduction of five phosphate functionalities was achieved by treatment of 6-azido-*myo*-inositol (−)-**12** or 3-azido-*myo*-inositol (+)-**13** with (1,5-dihydro-2,4,3-benzodioxaphosphepin-3-yl)diethylamine in the presence of 1*H*-tetrazole in acetonitrile (Scheme 4). After 4 h the resulting pentaphosphite was oxidized with *m*-CPBA and purified by flash chromatography to give the protected pentakisphosphate in 50% yield. The phosphorylation requires carefully chosen reaction conditions. An excess of the phosphorylation reagent or prolonged reaction times can lead to by-products probably by Staudinger reduction of the azido moiety. Since solubility of the free azido-inositol is low and the problems mentioned above interfere, a complete conversion can be difficult to achieve. However, bearing in mind the problems described above and considering that this reaction is a functionalization of five hydroxy groups, the yield of 51% seems acceptable, equalling an average yield of 87% per OH group. It proved to be possible to



Scheme 2 *Reagents and conditions*: (a) $RuCl_3$, $NaIO_4$, CH_3CN (91%). (b) Ac_2O, pyridine (98%). (c) NaOMe, MeOH (99%). (d) Pd/C, H_2, ethanol–water (99%).

phosphorylate diastereomeric mixtures of 3-azido-*myo*-inositol (+)-**13** and 6-azido-*myo*-inositol (−)-**12**, alternatively. Both phosphorylated products can easily be separated by flash chromatography.

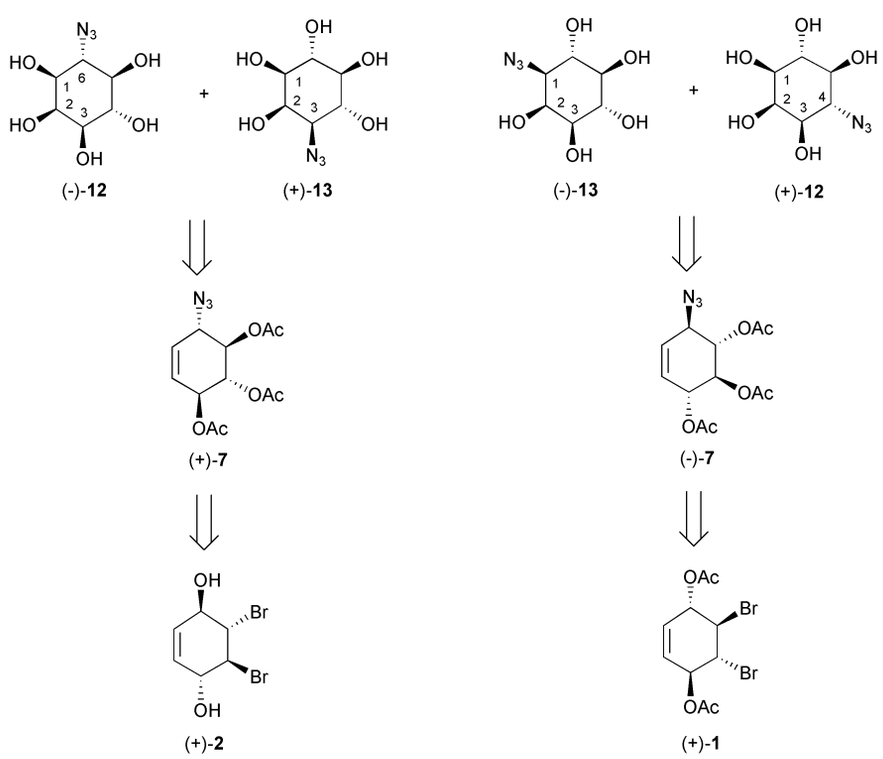
The subsequent Pd/C-catalyzed deprotection–hydrogenolysis gave 3-amino-*myo*-Ins(1,2,4,5,6)P_5 (−)-**16** or 6-amino-*myo*-Ins(1,2,3,4,5)P_5 (−)-**17**, respectively, already pure as detected by NMR (Fig. 1). Purification of the resulting amino-inositol pentakisphosphates by HPLC ensures isomeric purity suitable for biological experiments. Under the chosen chromatographic purification conditions, the two isomers differ in retention time by 5 min.

The two amino-substituted CH groups can be recognized easily as they do not change multiplicity upon phosphorus decoupling. They show characteristic coupling patterns, the 3-amino-isomer showing up as a doublet (with the small $^3J(H_2,H_3)$-*cis*-coupling not being resolved), while the 6-isomer is characterized by a triplet signal, resulting from two almost equivalent ^3J(H,H)-*trans*-couplings. Further positional assignment of hydrogen, phosphorus and carbon signals was carried out with two-dimensional NMR spectra.

The *N*-acetyl moiety was introduced by hydrogenolysis of (−)-**11** and (+)-**10** and further acetylation in pyridine–acetic anhydride. The acetamides obtained by this procedure were phosphorylated in an analogous manner to **17** to yield (−)-**18** and (+)-**19**, respectively.

Although chromatographic separation of phosphorylated derivatives is feasible and useful for the synthesis of pentakisphosphates, recrystallization at an earlier stage should prove to be extremely useful for preparation of more highly differentiated inositol analogues. This will enable the synthesis of more differentiated, orthogonally protected derivatives, which in turn should allow access to several analogues of biologically relevant molecules. It should be noted that this concept is not limited to the differentiation of the hydroxy groups introduced by dihydroxylation and the acetylated ones from the conduritol. We were delighted to see that isopropylidene protection of the triol **6** leads to exclusive formation of **21** (Scheme 5).

The course of this reaction can be rationalized by molecular modelling. The derivative protected in the 3- and 4-position is clearly energetically disfavoured. A similar outcome was



Scheme 3 Retrosynthetic scheme.

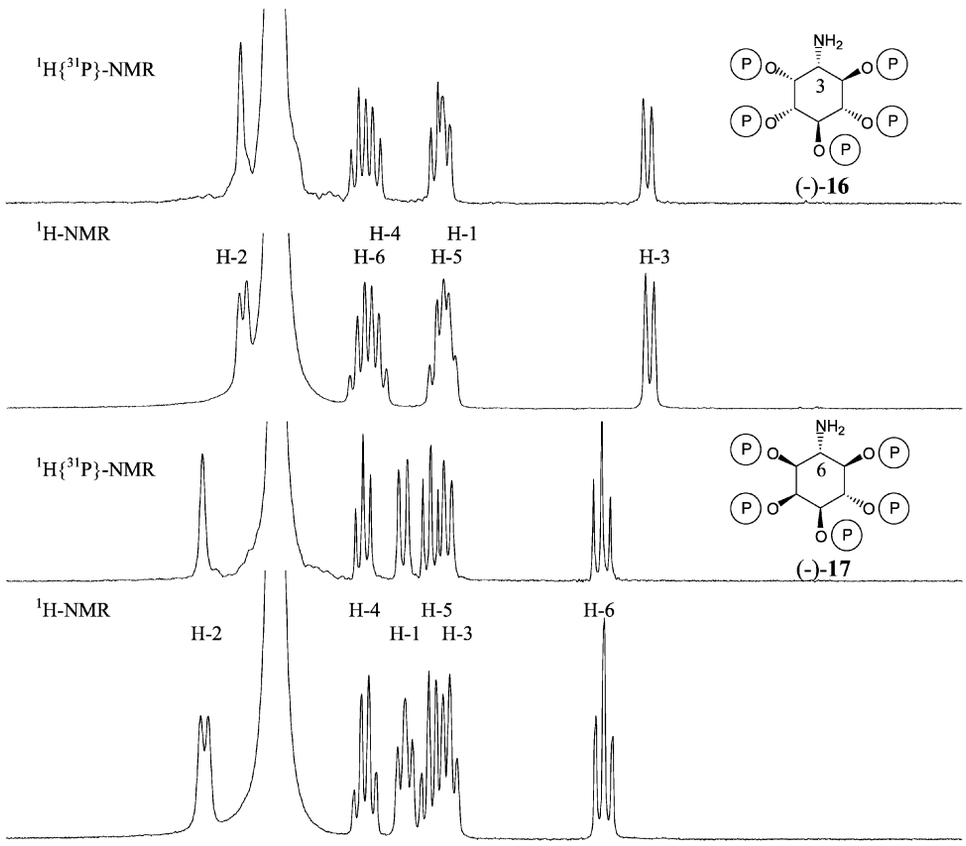
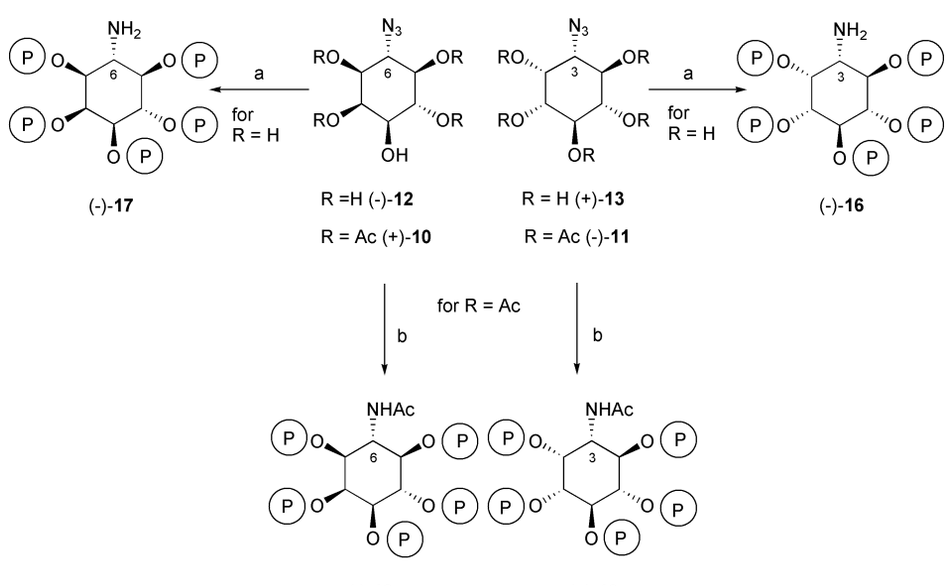
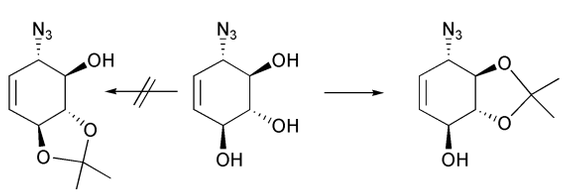


Fig. 1 ^{1}H{^{31}P}- and ^{1}H-NMR of 4-/6-amino-*myo*-inositolpentakisphosphate **17** and 1-/3-amino-*myo*-inositolpentakisphosphate **16**.



Scheme 4 *Reagents and conditions*: (a) 1, (1,5-dihydro-2,4,3-benzodioxaphosphepin-3-yl)diethylamine, 1*H*-tetrazole, CH_3CN, then *m*-CPBA (51%). 2, Pd/C, H_2 ethanol–water (90%). (b) 1, Pd/C, H_2, methanol (80%). 2, Ac_2O, pyridine (99%). 3, NaOMe, MeOH (80%). 4, (1,5-dihydro-2,4,3-benzodioxaphosphepin-3-yl)diethylamine, 1*H*-tetrazole, CH_3CN, then *m*-CPBA (43%). 5, Pd/C, H_2 ethanol–water (80%).



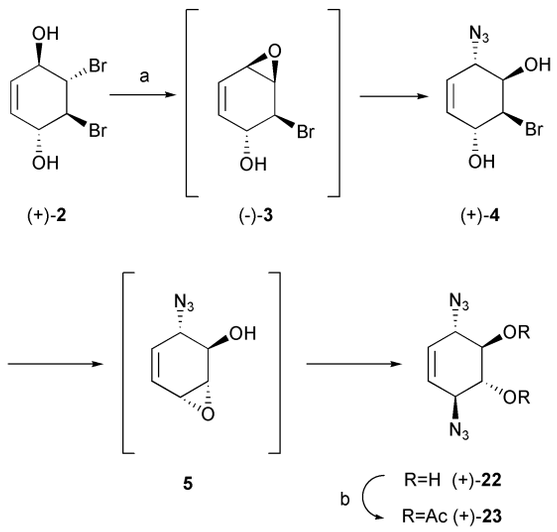
Scheme 5 *Reagents and conditions*: 1, 2,2-DMP, acetone, cat. PPTSA. 2, acetone, PTSA (73%).

observed by Trost[21] and coworkers for a different conduritol derivative.

Preparation of diazido/diamino-*myo*-inositols

Substituted 3,6-diazido-*myo*-inositol was prepared from the same precursor (+)-diol **2**. Synthesis of racemic diazido-conduritol B **22** has been reported from (±)-diol **2** in a two-step approach, *via anti*-benzene dioxide.[12] By use of enantiomerically pure *anti*-benzene dioxide, prepared accord-

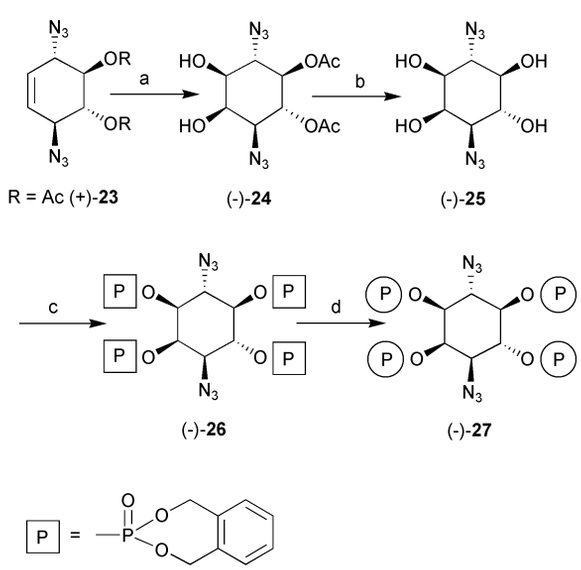
ing to a procedure reported previously by our group,[19] the diazido-conduritol B derivative (+)-**22** should be available enantiomerically pure. However, we were able to facilitate the synthesis by a one-pot approach, starting from **2**. We chose the same conditions as reported for the conversion of **3**, but instead of workup, we added sodium azide to the reaction. The epoxides generated *in situ* are directly opened in allylic position, delivering the desired product in 50% yield (Scheme 6).



Scheme 6 *Reagents and conditions*: (a) Et_2O–MeOH (2 : 1), LiOH, NaN_3, 40 °C for 1 day and then 2 days at room temperature (51%). (b) Ac_2O, pyridine (99%).

After acetylation, *cis*-dihydroxylation with ruthenium trichloride and sodium metaperiodate gave the protected diazido *myo*-inositol (−)-**24**. Because of the inherent C_2-symmetry of the acetylated diazido-conduritol B (+)-**23**, *cis*-dihydroxylation gives only one product. Cleavage of the acetate groups under basic conditions leads to free diazido-inositol (−)-**25**. Hydrogenation of (−)-**25** gives diamino-inositol (+)-**28** (structure not shown).

To test the potential of this approach, diazido-*myo*-Ins-(1,2,4,5)P_4 **27** was synthesized (Scheme 7). Phosphorylation of the diazido-tetrol **25** by reaction with (1,5-dihydro-2,4,3-benzodioxaphosphepin-3-yl)diethylamine in the presence of 1*H*-tetrazole followed by oxidation with *m*-CPBA gave the protected diazido-tetrakisphosphate (−)-**26**. To maintain the azido moiety of the required product, complete deprotection was achieved in one step with trimethylsilyl bromide to yield 3,6-diazido-*myo*-inositol tetrakisphosphate (−)-**27** in quantitative yield.



Scheme 7 *Reagents and conditions*: (a) $RuCl_3$, $NaIO_4$, CH_3CN (99%). (b) NaOMe, MeOH (99%). (c) (1,5-dihydro-2,4,3-benzodioxaphosphepin-3-yl)diethylamine, 1*H*-tetrazole, CH_3CN, then *m*-CPBA (45%). (d) CH_2Cl_2, TMSBr (90%).

This molecule may serve as a tool in elucidating further aspects in intracellular signalling. It has been shown that *myo*-Ins(1,2,4,5)P_4, a non-physiological inositol phosphate, binds to the 1,4,5-IP_3 receptor and promotes calcium release with potencies nearly comparable to that of *myo*-Ins(1,4,5)P_3.[22–24] Furthermore it has been demonstrated that racemic *myo*-Ins(1,2,4,5)P_4 competitively inhibits the dephosphorylation of tritiated *myo*-Ins(1,4,5)P_3 by a human erythrocyte membrane associated Ins(1,4,5)P_3 *5-phosphatase* with a K_i-value of 15.9 μM.[25]

Conclusion

The present work further emphasizes the potential of (+)- and (−)-**1** as a versatile building block in the construction of non-racemic inositol phosphate derivatives. The azido-conduritols obtained were transformed into several azido-inositols on a multigram scale without the need for chromatographic separation. The described efficient, high-yielding routes allowed the introduction of nitrogen-containing functional groups in the 1-, 3-, 4- and 6-position of the cyclitol ring system to give several pure azido- and amino-*myo*-inositols in both enantiomeric forms. The synthesis comprises ten steps, starting from *p*-benzoquinone.

Experimental

General

All NMR spectra were recorded on a Bruker ARX 400 (400 MHz) spectrometer. Besides ^1H, ^{13}C and ^{31}P experiments, 2D COSY (^1H–^1H, ^1H–^{13}C as well as ^1H–^{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 downfield of TMS, although the solvents actually served as internal standard. The multiplicity is given by the following symbols: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), ψt (pseudotriplet for unresolved dd) and br (broad). The coupling constant *J* is given in Hz. Melting points are uncorrected. 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 over $MgSO_4$, filtered and concentrated with a rotary evaporator under reduced pressure. Only distilled solvents were used. $[a]_D$ Values are given in units of 10^{-1} deg cm^2 g^{-1}.

Purification and analysis of inositol phosphates

Inositol phosphates were purified and analyzed by the HPLC-MDD method described previously.[26] The compounds were separated by anion-exchange chromatography on a Mono Q HR 10/10 column (Pharmacia). A linear gradient was applied to elute the inositol phosphates (0 min, 0.2 mM HCl; 70 min, 0.5 M HCl; flow rate 1.5 mL min^{-1}). In analytical runs, photometric detection at 546 nm was achieved with a modified 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^{-1}). Purification steps, where on-line detection was impossible, an analogous experiment could be carried out on microplate. In brief, a 0.2–10 μL portion of a sample (depending on the $InsP_x$ concentration) was mixed with 100 μL of metal–dye reagent, and the absorbance was measured at 540 nm.

(1*R*,2*S*,3*R*,6*R*)-2-Bromo-7-oxabicyclo[4.1.0]hept-4-en-3-ol (−)-3

2,3-Dibromocyclohex-5-ene-1,4-diol (+)-**2** (27.2 g, 0.1 mol) was dissolved in Et_2O (600 mL) and MeOH (300 mL). At 0 °C LiOH (5.4 g, 0.225 mol, 98%) was added and the mixture was stirred at this temperature for 2 h. After the reaction was completed, water (400 mL) and Et_2O were added, and the aqueous layer was extracted with Et_2O (4 × 250 mL). The combined organic layer was washed twice with brine and concentrated under reduced pressure to yield a colourless solid (19.2 g, 99%). For an analytical sample recrystallization from $CHCl_3$–hexane 1 : 1 yielded pure (−)-**3** as white needles. R_f: 0.37 (cyclohexane–EtOAc 1 : 1). $[a]_D^{20}$ = −170 (*c* = 0.4, $CHCl_3$); Lit:[18] $[a]_D^{20}$ = −172 (*c* = 0.36, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): δ 2.65 (d, 1 H, *J* 4.6 Hz, OH), 3.51 (dψt, 1 H, *J* 3–4 and 2 Hz, H-6), 3.75 (dd, 1 H, *J* 0.7 and 4.1 Hz, H-1), 4.05 (dd, 1 H, *J* 1.0 and 8.7 Hz, H-2), 4.49 (m, 1 H, H-3), 5.92 (dψt, 1 H, *J* 9.7 and 2.0–1.5 Hz, H-5), 6.06 (dψt, 1 H, *J* 9.7 and 3.1–3.6 Hz, H-4). ^{13}C-NMR ($CDCl_3$): δ 51.5 (C-6), 55.3 (C-1), 55.5 (C-2), 71.2 (C-3), 123.5 (C-4), 134.8 (C-5); MS (EI, 70 eV, *m*/*z* (%)): 163 (3), 161 (3), 111 (95), 81 (100). IR (KBr): 3300 (s), 3070 (w), 3040 (w), 2920 (m), 1650 (w), 1080 (s), 845 (s), 650 (s). Anal. Calcd. for $C_6H_7BrO_2$: C, 37.73; H, 3.69. Found: C, 38.00; H, 3.71%.

(1*S*,2*R*,3*S*,6*S*)-2-Bromo-7-oxabicyclo[4.1.0]hept-4-en-3-ol (+)-3

(+)-**1** was converted under the same conditions as described for the preparation of (−)-**3** to give (+)-**3**. $[a]_D^{20}$ = +171 (*c* = 0.7, $CHCl_3$). Analytical data were identical to data obtained for (−)-**3**.

(1*R*,2*S*,3*R*,6*S*)-6-Azido-2-bromocyclohex-4-ene-1,3-diol (+)-4

To a vigorously stirred ice-cooled solution of (−)-**3** (18.8 g, 98 mmol) in 1,2-dimethoxyethane (200 mL), water (130 mL) and ethanol (130 mL) was added NaN_3 (26 g, 0.4 mol) and NH_4Cl (21.1 g, 0.4 mol) and the mixture was stirred for 3 h at 0 °C. The solution was concentrated under reduced pressure, and the resulting aqueous layer was washed four times with EtOAc. The combined organic layer was evaporated to yield 21 g (90%) of a yellow oil. For an analytical sample, the oil was purified by flash-chromatography (cyclohexane–EtOAc 3 : 2) to yield pure (+)-**4** as a colourless solid. R_f: 0.37 (cyclohexane–EtOAc 1:1). $[a]_D^{20}$ = +220 (*c* = 0.66, $CHCl_3$); $[a]_D^{20}$ = +144 (*c* = 1.4, acetone); Lit:[18] $[a]_D^{20}$ = −146 (*c* = 1.1, acetone, for other enantiomer). ^{1}H-NMR ($CDCl_3$): δ 3.97 (m, 1 H, H-1), 4.07 (m, 1 H, *J* 7.1 Hz, H-6), 4.24 (ψt, 1H, *J* 3.1 Hz, H-2), 4.44 (m, 1 H, *J* 4.1 and 9.1 Hz, H-3), 5.03 (d, 1 H, *J* 6.1 Hz, OH-3), 5.07 (d, 1 H, *J* 5.6 Hz, OH-1), 5.67 (dd, 1 H, *J* 2.5 and 10.2 Hz, H-5), 5.85 (dddd, 1 H, *J* 10.2, 3.9, 1.7, and 1.0 Hz, H-4). ^{13}C-NMR ($CDCl_3$): δ 60.1 (C-2), 63.8 (C-6), 71.0 (C-1), 71.5 (C-3), 127.4 (C-5), 131.3 (C-4). IR (KBr): 3311 (s), 2886 (m), 2108 (s), 1393 (m), 1358 (m), 1282 (m), 1258 (m), 1094 (m), 1008 (m). Anal. Calcd. for $C_6H_8BrN_3O_2$: C, 30.79; H, 3.45; N, 17.95. Found: C, 30.75; H, 3.53; N, 18.10%.

(1*S*,2*R*,3*S*,6*R*)-6-Azido-2-bromocyclohex-4-ene-1,3-diol (−)-4

(+)-**3** was converted under the same conditions as described for the preparation of (+)-**4** to give (−)-**4**. $[a]_D^{20}$ = −212 (*c* = 0.5, $CHCl_3$). Analytical data were identical to those of obtained for (+)-**4**.

(1*S*,2*R*,3*R*,4*S*)-1-Azidoconduritol B (+)-6

To a vigorously stirred solution of (+)-**4** (20 g, 85 mmol) in Et_2O (430 mL) and MeOH (210 mL) was added at 0 °C LiOH (4.3 g, 180 mmol). The solution was stirred for 2 h at 10 °C. After the reaction was completed, water (250 mL) was added and the aqueous layer was extracted with Et_2O. The organic solution was washed twice with brine and concentrated under reduced pressure. To remove all LiOH, the residue was taken up in EtOAc and the organic solution washed again two times with brine. Evaporation of the solvent yielded 12.1 g of a yellow oil.

The resulting monoepoxide (11 g, 85 mmol) was dissolved in water (130 mL); a trace of *p*-toluenesulfonic acid was added, and the solution was stirred for 2 d at room temperature. The water was removed by lyophilisation. Recrystallization from EtOAc (30 mL) yielded (+)-**6** (7 g, 47%) as a colourless solid. R_f: 0.51 (CH_2Cl_2–MeOH 80 : 20). $[a]_D^{20}$ = +239 (*c* = 0.85, H_2O). mp 128 °C. ^{1}H-NMR (D_2O): δ 3.49 (Ψt, 1H, *J* 9.4 Hz, H-3), 3.58 (Ψt, 1H, *J* 9.4 Hz, H-2), 4.06 (Ψd, 1H, *J* 8.2 Hz, H-1), 4.16 (m, 1 H, H-4), 4.66 (s, 3 H, OH), 5.61 (d, 1H, *J* 10.2 Hz, H-5), 5.71 (d, *J* 10.7 Hz, H-6). ^{13}C-NMR (D_2O): δ 66.3 (C-1), 73.9 (C-4), 76.1 (C-2), 77.7 (C-3), 127.1 (C-5), 133.4 (C-6). IR (KBr): 3383 (s, br), 2890 (w), 2103 (s), 1358 (w), 1286 (w), 1245 (m), 1119 (w), 1021 (m). Anal. Calcd. for $C_6H_9O_3N_3$: C, 42.11; H, 5.30; N, 24.55. Found: C, 41.91; H, 5.24; N, 24.47%. HR-MS (ESI-pos., TOF): *m*/*z*: 194.0553 $[M + Na]^+$ calcd. for $C_6H_9O_3N_3Na$: 194.050416.

(1*R*,2*S*,3*S*,4*R*)-1-Azidoconduritol B (−)-6

A solution of (−)-**4** was allowed to react under the same conditions as described for the preparation of (+)-**6** to give (−)-**6**. $[a]_D^{20}$ = −238 (*c* = 0.36, H_2O). Analytical data were identical to the data obtained for (+)-**6**.

(1*S*,2*R*,3*R*,4*S*)-2,3,4-Tri-*O*-acetyl-1-azidoconduritol B (+)-7

(+)-**6** (4 g, 23 mmol) was dissolved in a cooled mixture of pyridine (20 mL) and acetic anhydride (12 mL). The mixture was stirred for 12 h at room temperature. Evaporation of the solvent and recrystallization from EtOH yielded pure **7** (6.7 g, 96 %) as a white solid. $[a]_D^{20}$ = +240 (*c* = 0.72, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): δ 2.03, 2.04, 2.09 (s, 9 H, CH_3), 4.20 (dd, 1H, *J* 7.7 and 2.5 Hz, H-1), 5.25 (Ψt, 1 H, *J* 10.7 Hz, H-2), 5.29 (Ψt, 1 H, *J* 10.8 Hz, H-3), 5.55 (dd, 1H, *J* 7.1 and 2.6 Hz, H-4), 5.72 (s, 2 H, H-5, H-6). ^{13}C-NMR ($CDCl_3$): δ 20.5 (2 × CH_3), 20.7 (CH_3), 61.1 (C-1), 71.3 (C-2), 71.4 (C-4), 71.8 (C-3), 126.7, 127.9 (C-5, C-6), 169.5, 169.9, 170.0 (C=O). MS (EI, 70 ev, *m*/*z* (%)): 297 $[M^+]$, 255 (4), 226 (2), 195 (2), 138 (83), 43 (100), IR (KBr): 2850 (w), 2097 (s), 1755 (s), 1375 (w), 1224 (s), 1057 (w), 1002 (m). Anal. Calcd. for $C_{12}H_{15}O_6N_3$: C, 48.49; H, 5.09; N, 14.14. Found: C, 48.46; H, 4.80; N, 13.96%.

(1*R*,2*S*,3*S*,4*R*)-2,3,4-Tri-*O*-acetyl-1-azidoconduritol B (−)-7

(−)-**6** was converted under the same conditions as described for the preparation of (+)-**7** to give (−)-**7**. $[a]_D^{20}$ = −233 (*c* = 1.25, $CHCl_3$). Analytical data were identical to the data obtained for (+)-**7**.

3,4,5-Tri-*O*-acetyl-6-azido-*myo*-inositol (−)-8 and 4,5,6-tri-*O*-acetyl-3-azido-*myo*-inositol (+)-9

To a vigorously stirred ice cooled solution of (+)-**7** (4.5 g, 15.2 mmol) in acetonitrile (220 mL, HPLC grade) was added a solution of sodium metaperiodate (4.7 g, 22 mmol, 1.5 eq.) and ruthenium trichloride trihydrate (290 mg, 1.1 mmol) in 33 mL water. The stirring was continued until TLC showed absence of starting material (approx. 8 min). The reaction was quenched by addition of aqueous $Na_2S_2O_3$ (300 mL, 20%). The aqueous layer was separated and extracted four times with EtOAc (4 × 200 mL). The combined organic layer, washed twice with brine and concentrated under reduced pressure, yielded the diastereomeric mixture as a colourless foam (4.6 g, 91%). The diastereomeric ratio of the two isomers (−)-**8** and (+)-**9** in the crude mixture was estimated by NMR to be 4 : 6.

The crude product was suspended in 25 mL $CHCl_3$. 4,5,6-tri-*O*-acetyl-3-azido-*myo*-inositol (+)-**9** remained insoluble as white solid (2.0 g, 40%) and was filtered off. The solvent was

evaporated to give 3,4,5-tri-*O*-acetyl-6-azido-*myo*-inositol (−)-**8** (2.5 g, 50%) as a colourless foam. Repeating the procedure with a smaller volume of $CHCl_3$ gave (−)-**8** (purity >90%).

Analytical data for 3,4,5-tri-*O*-acetyl-6-azido-*myo*-inositol (−)-**8**: R_f: 0.11 (EtOAc–cyclohexane 1 : 1). $[\alpha]_D^{20} = -20.1$ ($c = 1.27$, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): δ 2.00, 2.09, 2.10 (s, 9 H, CH_3), 3.14 (s, br, 2 H, OH), 3.65 (dd, 1 H, *J* 9.9 and 2.8 Hz, H-1), 3.91 (Ψt, 1 H, *J* 10.2 Hz, H-6), 4.27 (Ψt, 1 H, *J* 2.8 Hz, H-2), 4.90 (dd, 1 H, *J* 10.2 and 2.6 Hz, H-3), 5.00 (Ψt, 1 H, *J* 9.9 Hz, H-5), 5.50 (Ψt, 1 H, *J* 9.9 Hz, H-4). ^{13}C-NMR ($CDCl_3$): δ 20.51, 20.55, 20.67 (CH_3), 63.4 (C-6), 69.8 (C-4), 69.9 (C-2), 70.4 (C-1), 71.0 (C-3), 71.4 (C-5), 169.88, 170.02, 170.08 (C=O). IR (KBr): 3476 (s, br), 2925 (w), 2113 (s, $\nu[N_3]$), 1754 (s), 1371 (m), 1228 (s), 1062 (m), 1036 (m). Anal. Calcd. for $C_{12}H_{17}O_8N_3$: C, 43.51; H, 5.17; N, 12.68. Found: C, 43.20; H, 4.87; N, 12.01%. HR-MS (ESI): *m*/*z*: 330.0917 $[M - H]^+$ calcd. for $C_{12}H_{16}N_3O_8$: 330.0937.

Analytical data for 4,5,6-tri-*O*-acetyl-3-azido-*myo*-inositol (+)-**9**: R_f: 0.11 (EtOAc–cyclohexane 1 : 1). $[\alpha]_D^{20} = +21.8$ ($c = 0.83$, acetone). ^{1}H-NMR (d_6-DMSO): δ 1.88, 1.92, 1.98 (s, 9 H, CH_3), 3.62 (ddd, 1 H, *J* 10, 5.5 and 2.5 Hz, H-1), 3.64 (dd, 1 H, *J* 10.9 and 2.3 Hz, H-3), 3.95 (dΨt, 1 H, *J* 4.6 and 2.3 Hz, H-2), 5.01 (Ψt, 1 H, *J* 10.0 Hz, H-5), 5.11 (Ψt, 1 H, *J* 9.7 Hz, H-6), 5.25 (d, 1 H, *J* 5.2 Hz, C-1-OH), 5.27 (Ψt, 1 H, *J* 9.9 Hz, H-4), 5.77 (d, 1 H, *J* 4.8 Hz, C-2-OH). ^{13}C-NMR (d_6-DMSO): δ 20.2, 20.3, 20.6 (CH_3), 60.1 (C-3), 69.0 (C-1), 70.0 (C-4), 71.3 (C-2), 71.6 (C-5), 72.0 (C-6), 169.42, 169.45, 169.62 (C=O). IR (KBr): 3433 (s, br), 2971, 2958, 2938, 2914 (w), 2117 (s), 1749, 1725 (s), 1367 (m), 1232 (s), 1039 (s). Anal. Calcd. for $C_{12}H_{17}O_8N_3$: C, 43.51; H, 5.17; N, 12.68. Found C, 43.69; H, 5.53; N, 11.75%. HR-MS: *m*/*z*: 332.114 $[M + H]^+$ calcd. for $C_{12}H_{18}O_8N_3$: 332.1094.

1,5,6-Tri-*O*-acetyl-4-azido-*myo*-inositol (+)-8 and 4,5,6-tri-*O*-acetyl-1-azido-*myo*-inositol (−)-9

The (−)-enantiomer **7** was *cis*-dihydroxylated as described for (+)-**7** to yield 1,5,6-tri-*O*-acetyl-4-azido-*myo*-inositol (+)-**8** ($[\alpha]_D^{20} = +22.3$ ($c = 0.81$, $CHCl_3$)) and 4,5,6-tri-*O*-acetyl-1-azido-*myo*-inositol (−)-**9** ($[\alpha]_D^{20} = -22.2$ ($c = 0.77$, acetone)). Analytical data were identical to the data obtained for (−)-**8** and (+)-**9**, respectively.

1,2,3,4,5-Penta-*O*-acetyl-6-deoxy-6-azido-*myo*-inositol (+)-10

3,4,5-Tri-*O*-acetyl-6-azido-*myo*-inositol (−)-**8** (1 g, 3.0 mmol) was dissolved in a cooled mixture of pyridine (10 mL) and acetic anhydride (10 mL). The mixture was stirred for 12 h. Evaporation of the solvent and recrystallization from EtOH yielded pure **10** (1.22 g, 98%) as a white solid. R_f: 0.42 (EtOAc–cyclohexane 1 : 1). $[\alpha]_D^{20} = +16.5$ ($c = 0.47$, $CHCl_3$). Lit.[11] $[\alpha]_D^{20} = +14.3$ ($c = 0.4$, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): δ 1.97, 2.00, 2.07, 2.10, 2.19 (CH_3), 3.97 (Ψt, 1 H, *J* 10.7 Hz, H-6), 4.95 (dd, 1 H, *J* 10.9 and 2.8 Hz, H-1), 5.04 (Ψt, 1 H, *J* 9.9 Hz, H-5), 5.07 (dd, 1 H, *J* 10.4 and 2.8 Hz, H-3), 5.41 (Ψt, 1 H, *J* 10.2 Hz, H-4), 5.58 (Ψt, 1 H, *J* 2.8 Hz, H-2). ^{13}C-NMR ($CDCl_3$): δ 20.33, 20.41, 20.43, 20.45, 20.60 (CH_3), 60.9 (C-6), 68.25 (C-3), 68.32 (C-2), 69.1 (C-1), 69.7 (C-4), 71.0 (C-5), 169.06, 169.21, 169.30, 169.49, 169.86 (C=O). Anal. Calcd. for $C_{16}H_{21}O_{10}N_3$: C, 46.27; H, 5.10; N, 10.12. Found: C, 46.22; H, 5.64; N, 9.22%. HR-MS (ESI): *m*/*z*: 416.1355 $[M + H]^+$ calcd. for $C_{16}H_{22}N_3O_{10}$: 416.1305.

1,2,3,5,6-Penta-*O*-acetyl-4-deoxy-4-azido-*myo*-inositol (−)-10

The (+)-enantiomer **8** was acetylated as described for (+)-**10** to yield (−)-**10**. $[\alpha]_D^{20} = -16$ ($c = 0.45$, $CHCl_3$). Analytical data were identical to the data obtained for (+)-**10**.

1,2,4,5,6-Penta-*O*-acetyl-3-deoxy-3-azido-*myo*-inositol (−)-11

4,5,6-Tri-*O*-acetyl-3-azido-*myo*-inositol (+)-**9** (1 g, 3.0 mmol) was dissolved in a cooled mixture of 10 mL pyridine and 10 mL of acetic anhydride. The mixture was stirred for 12 h. Evaporation of the solvent and recrystallization from EtOH yielded pure **11** (1.24 g, 99%) as a white solid. R_f: 0.42 (EtOAc–cyclohexane 1 : 1). $[\alpha]_D^{20} = -2.0$ ($c = 1.09$, $CHCl_3$). Lit.[27] $[\alpha]_D^{20} = -3.5$ ($c = 2.9$, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): δ 1.99, 2.00, 2.01, 2.09, 2.19 (s, 15 H, CH_3), 3.68 (dd, 1 H, *J* 10.7 and 2.5 Hz, H-3), 4.97 (dd, 1 H, *J* 10.7 and 2.8 Hz, H-1), 5.16 (Ψt, 1 H, *J* 9.9 Hz, H-5), 5.44 (Ψt, 1 H, *J* 10.4 Hz, H-4), 5.45 (Ψt, 1 H, *J* 10.2 Hz, H-6), 5.64 (Ψt, 1 H, *J* 2.6 Hz, H-2); ^{13}C-NMR ($CDCl_3$): δ 20.37 (2 × CH_3), 20.47, 20.50, 20.60 (CH_3), 59.2 (C-3), 68.5 (C-2), 69.0 (C-6), 69.4 (C-1), 70.5 (C-4), 71.5 (C-5), 169.4, 169.46, 169.51 (C=O), 169.7 (2 × C=O). MS (EI, 70 ev, *m*/*z* (%)): 310 (1), 226 (15), 184 (25), 157 (15), 142 (44), 115 (27), 43 (100). IR (KBr): 2920 + 2850 (m), 2100 (m), 1750 (s). Anal. Calcd. for $C_{16}H_{21}O_{10}N_3$: C, 46.27; H, 5.10; N, 10.12. Found: C, 46.43; H, 5.75; N, 9.34. HR-MS (ESI): *m*/*z*: 416.1365 $[M + H]^+$ calcd. for $C_{16}H_{22}N_3O_{10}$: 416.1305.

2,3,4,5,6-Penta-*O*-acetyl-1-deoxy-1-azido-*myo*-inositol (+)-11

The (−)-enantiomer **9** was acetylated as described for (−)-**11** to yield (+)-**11**. $[\alpha]_D^{20} = +1.2$ ($c = 2.81$, $CHCl_3$). Analytical data were identical to the data obtained for (−)-**11**.

6-Deoxy-6-azido-*myo*-inositol (−)-12

3,4,5-Tri-*O*-acetyl-6-azido-*myo*-inositol (−)-**8** (760 mg, 2.3 mmol) was suspended in anhydrous methanol (15 mL) under argon and cooled to 4 °C. A 5.5 M sodium methanolate solution (80 μL, 0.4 mmol) was added. The solution was allowed to warm to room temperature and stirred for 12 h. The solution was neutralized by addition of ion exchanger (H^+-form, Dowex 50-X), filtered and the resin was washed with water. The filtrate was first reduced in volume under high vacuum and then lyophilized to yield (−)-**12** (470 mg, 100%) as a colourless foam. $[\alpha]_D^{20} = -14.8$ ($c = 0.25$, H_2O). ^{1}H-NMR (D_2O): δ 3.27 (Ψt, 1 H, *J* 9.4 Hz, H-5), 3.45 (dd, 1 H, *J* 10.2 and 3.0 Hz, H-3), 3.52–3.56 (m, 2 H, H-6, H-1), 3.62 (Ψt, 1 H, *J* 9.7 Hz, H-4), 4.02 (Ψt, 1 H, *J* 2.3 Hz, H-2). ^{13}C-NMR (D_2O): δ 65.9 (C-6), 70.3 (C-1), 71.0 (C-3), 72.3 (C-2), 72.7 (C-4), 73.4 (C-5). IR (KBr): 3350 (s, br), 2920 (w), 2110 (s). HR-MS (ESI): *m*/*z*: 204.0574 $[M - H]^+$ calcd. for $C_6H_{10}N_3O_5$: 204.062.

4-Deoxy-4-azido-*myo*-inositol (+)-12

The (+)-enantiomer **8** was deacetylated as described for (−)-**12** to yield (+)-**12**. $[\alpha]_D^{20} = +17.2$ ($c = 0.33$, H_2O). Analytical data were identical to the data obtained for (−)-**12**.

3-Deoxy-3-azido-*myo*-inositol (+)-13

The deprotection of 4,5,6-tri-*O*-acetyl-3-azido-*myo*-inositol (+)-**9** was carried out as described for (−)-**8**, yielding 3-deoxy-3-azido-*myo*-inositol (+)-**13** as a colourless solid. $[\alpha]_D^{20} = +9.2$ ($c = 0.71$, H_2O). ^{1}H-NMR (D_2O): δ 3.29 (Ψt, 1 H, *J* 9.2 Hz, H-5), 3.38 (dd, 1 H, *J* 10.4 and 2.3 Hz, H-3), 3.49 (dd, 1 H, *J* 10.2 and 2.5 Hz, H-1), 3.56 (Ψt, 1 H, *J* 9.7 Hz, H-6), 3.70 (Ψt, 1 H, *J* 9.9 Hz, H-4), 4.11 (Ψt, 1 H, *J* 2.4 Hz, H-2). ^{13}C-NMR (D_2O): δ 63.50 (C-3), 71.1 (C-2), 71.52 (C-4), 71.62 (C-1), 72.33 (C-6), 75.00 (C-5); IR (KBr): 3405 (s, br), 2969, 2917 (m), 2111 (s), 1376 (m), 1247 (m), 1091 (m), 1030 (m). Anal. Calcd. for $C_6H_{11}N_3O_5$: C, 35.12; H, 5.40; N, 20.48. Found: C, 34.71; H, 5.49; N, 19.99%. HR-MS (ESI): *m*/*z*: 204.0587 $[M - H]^+$ calcd. for $C_6H_{10}N_3O_5$: 204.062.

1-Deoxy-1-azido-*myo*-inositol (−)-13

The (−)-enantiomer **9** was deacetylated as described for (+)-**13** to yield (−)-**13**. $[\alpha]_D^{20} = -8.0$ ($c = 0.5$, H_2O). Analytical data were identical to the data obtained for (+)-**13**.

6-Deoxy-6-amino-*myo*-inositol (+)-14

Pd/C (12 mg) was added to a suspension of 6-deoxy (−)-**12** (50 mg, 0.24 mmol) in methanol (30 mL). The mixture was stirred at room temperature under H_2 overnight. The catalyst was filtered off and washed with water, and the filtrate was reduced in volume and lyophilized to give a colourless foam (42 mg, 99%). $[\alpha]_D^{20}$ = +7.1 (*c* = 0.17, H_2O). ^{1}H-NMR (D_2O): δ 2.94 (Ψt, 1 H, *J* 10.2 Hz, H-6), 3.15 (Ψt, 1 H, *J* 9.5 Hz, H-5), 3.41 (dd, 1 H, *J* 10.1 and 2.1 Hz, H-1), 3.47 (dd, 1 H, *J* 10.1 and 2.1 Hz, H-3), 3.56 (Ψt, 1 H, *J* 9.4 Hz, H-4), 3.99 (Ψt, 1 H, *J* 2.2 Hz, H-2). ^{13}C-NMR (D_2O): δ 55.7 (C-6), 73.1 (C-1), 73.4 (C-3), 74.6 (C-2), 75.1 (C-4), 76.1 (C-5). IR (KBr): 3339 (s, br), 2920, 2881 (w), 1596 (m), 1384 (m), 1091 (m), 1048 (s); HR-MS (ESI): *m*/*z*: 180.0853 $[M + H]^+$ calcd. for $C_6H_{14}NO_5$: 180.0872.

4-Deoxy-4-amino-*myo*-inositol (−)-14

The (+)-enantiomer **12** was hydrogenated as described for (+)-**14** to yield (−)-**14**. $[\alpha]_D^{20}$ = −9.4 (*c* = 0.14, H_2O). Analytical data were identical to the data obtained for (+)-**14**.

3-Deoxy-3-amino-*myo*-inositol (+)-15

The diastereomer (+)-**13** was deprotected as described for (−)-**12**. Work-up as before gave (+)-**15** as a colourless foam (99%). $[\alpha]_D^{20}$ = +9.4 (*c* = 0.35, H_2O). Lit.[28] $[\alpha]_D^{20}$ = +9.2 (H_2O). ^{1}H-NMR (D_2O): δ 2.49 (dd, 1 H, *J* 10.2 and 2.1 Hz, H-3), 3.11 (Ψt, 1 H, *J* 9.4 Hz, H-5), 3.26 (Ψt, 1 H, *J* 9.9 Hz, H-4), 3.36 (dd, 1 H, *J* 9.9 and 2.8 Hz, H-1), 3.43 (Ψt, 1 H, *J* 9.4 Hz, H-6), 3.82 (Ψt, 1 H, *J* 2.4 Hz, H-2). ^{13}C-NMR (D_2O): δ 55.4 (C-3), 73.9 (C-2), 74.3 (C-1), 74.6 (C-6), 75.3 (C-4), 77.3 (C-5). IR (KBr): 3363 (s, br), 2917 (w), 1591 (m), 1384 (m), 1115 (m), 1049 (m), 1002 (m). HR-MS (ESI): *m*/*z*: 180.0884 $[M + H]^+$ calcd. for $C_6H_{14}NO_5$: 180.0872.

1-Deoxy-1-amino-*myo*-inositol (−)-15

The (−)-enantiomer **13** was hydrogenated as described for (+)-**15** to yield (−)-**15**. $[\alpha]_D^{20}$ = −10 (*c* = 0.4, H_2O); Lit.[29] $[\alpha]_D^{20}$ = −4.2 (*c* = 2.7, H_2O). Analytical data were identical to the data obtained for (+)-**15**.

3-Deoxy-3-amino-*myo*-inositol 1,2,4,5,6-pentakisphosphate (−)-16

To a solution of 3-deoxy-3-azido-*myo*-inositol (+)-**13** (215 mg, 1.05 mmol) and 1*H*-tetrazole (700 mg, 10 mmol) in anhydrous acetonitrile (30 mL) under argon was added (1,5-dihydro-2,4,3-benzodioxaphosphepin-3-yl)diethylamine (1.4 g, 6 mmol), and the solution was stirred at room temperature for 4 h. The mixture was cooled to −20 °C, and an anhydrous solution of *m*-CPBA (4.3 g, 17.5 mmol) in dichloromethane (20 mL) [dried over $NaSO_4$] was added. The solution was allowed to warm to room temperature, and 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 $NaHCO_3$ and brine. After evaporation of dichloromethane the product was purified by flash chromatography (R_f = 0.20 (CH_2Cl_2–MeOH 95 : 5)) to yield the protected pentakisphosphate (570 mg, 51%) as a colourless foam.

Diastereomeric mixtures of 3-deoxy-3-azido-*myo*-inositol (+)-**13** and 6-deoxy-6-azido-*myo*-inositol (−)-**12** were also phosphorylated as mentioned above. The two protected products were easily separated by flash chromatography [R_f: 0.12 (CH_2Cl_2–MeOH 95 : 5) for 6-deoxy-6-azido-1,2,3,4,5-penta-*O*-(3-oxo-1,5-dihydro-3λ^5-2,4,3-benzodioxaphosphepin-3-yl)-*myo*-inositol].

Deprotection: to a suspension of 300 mg (0.27 mmol) 3-deoxy-3-azido-1,2,4,5,6-penta-*O*-(3-oxo-1,5-dihydro-3λ^5-2,4,3-benzodioxaphosphepin-3-yl)-*myo*-inositol in 30 mL ethanol–water (1 : 1) was added Pd/C (170 mg). The mixture was stirred at room temperature under H_2 overnight. The catalyst was filtered off, and the filtrate was reduced in volume and lyophilized to give (−)-**16** as a colourless, hygroscopic foam (149 mg, 99%). Preparative HPLC assured purity >99%. $[\alpha]_D^{20}$ = −10.8 (*c* = 6.3, H_2O). ^{1}H-NMR (D_2O, pH adjusted to 6 (ND_4OD)): δ 3.48 (d, 1 H, *J* 10.2 Hz, H-3), 4.11 (Ψt, 1 H, *J* 7.9 Hz, H-1), 4.14 (Ψq, 1 H, *J* 8.1 Hz, H-5), 4.34 (Ψq, 1 H, *J* 9.2 Hz, H-4), 4.39 (Ψq, 1 H, *J* 8.8 Hz, H-6), 4.76 (d, 1H, *J* 8.1 Hz, H-2). ^{13}C-NMR (D_2O, pH adjusted to 6 (ND_4OD)): δ 55.7 (s, C-3), 73.1 (d, *J* 5.1 Hz, C-2), 74.9 (m, C-4), 75.8 (m, C-1), 78.0 (m, C-6), 79.9 (m, C-5). ^{31}P-NMR{^{1}H} (D_2O, pH adjusted to 6 (ND_4OD)): δ 1.91 (PC-6), 2.14, 2.26 (PC-1, PC-5), 4.43 (PC-4), 4.67 (PC-2); HR-MS (MALDI-FTMS): *m*/*z*: 577.9013 $[M - H]^+$ calcd. for $C_6H_{17}NO_{20}P_5$: 577.9038.

1-Deoxy-1-amino-*myo*-inositol-2,3,4,5,6-pentakisphosphate (+)-16

The (−)-enantiomer **13** was phosphitylated as described for (−)-**16**. Oxidation, deprotection and purification as before gave (+)-**16**. $[\alpha]_D^{20}$ = +9 (*c* = 8.0, H_2O). Analytical data were identical to the data obtained for (−)-**16**.

6-Deoxy-6-amino-*myo*-inositol-1,2,3,4,5-pentakisphosphate (−)-17

Phosphorylation of 6-deoxy-6-azido-*myo*-inositol (−)-**12** and further deprotection were carried out as described for (+)-**13** (see synthesis of 3-deoxy-3-azido-*myo*-inositol-1,2,4,5,6-pentakisphosphate (−)-**16**), yielding 6-deoxy-6-amino-*myo*-inositol-1,2,3,4,5-pentakisphosphate (−)-**17** in 50% yield. $[\alpha]_D^{20}$ = −1.7 (*c* = 8.67, H_2O). ^{1}H-NMR (D_2O, pH adjusted to 6 (ND_4OD)): δ 3.62 (Ψt, 1 H, *J* 10.7 Hz, H-6), 4.11 (Ψt, 1 H, *J* 8.9 Hz, H-3), 4.16 (Ψq, 1 H, *J* 9.3 Hz, H-5), 4.25 (Ψt, 1 H, *J* 9.4 Hz, H-1), 4.37 (Ψq, 1 H, *J* 9.3 Hz, H-4), 4.88 (d, 1 H, *J* 9.7 Hz, H-2). ^{13}C-NMR (D_2O, pH adjusted to 6 (ND_4OD)): δ 56.3 (d, *J* 5.1 Hz, C-6), 72.6 (m, C-1), 75.5 (C-3, C-5), 76.3 (d, *J* 5.1 Hz, C-2), 78.6 (m, C-4). ^{31}P-NMR{^{1}H} (D_2O, pH adjusted to 6 (ND_4OD)): δ 1.82 (PC-2), 1.92 (PC-3), 2.33 (PC-4), 2.91 (PC-1), 4.15 (PC-5). HR-MS (MALDI-FTMS): *m*/*z*: 577.9031 $[M - H]^+$ calcd. for $C_6H_{17}NO_{20}P_5$: 577.9038.

4-Deoxy-4-amino-*myo*-inositol-1,2,3,5,6-pentakisphosphate (+)-17

The (+)-enantiomer **12** was phosphitylated as described for (−)-**17**. Oxidation, deprotection and purification as before gave (+)-**17**. $[\alpha]_D^{20}$ = +1.6 (*c* = 7.7, H_2O). Analytical data were identical to the data obtained for (−)-**17**.

6-Deoxy-6-acetamido-*myo*-inositol-1,2,3,4,5-pentakisphosphate (−)-18

Pd/C (40 mg Degussa RW 10, preactivated in 10 mL MeOH) was added to a solution of (+)-**10** (500 mg, 1.2 mmol) in MeOH (10 mL). The mixture was stirred under H_2 at room temperature until TLC showed absence of starting material (approx. 2 h). The catalyst was filtered off, and the residue was washed with EtOAc. The solvent was removed under reduced pressure, and the residue was dried under high vacuum.

The residue was dissolved in pyridine (5 mL) and acetic anhydride (3 mL). The mixture was stirred for 12 h, and the solvent was removed under high vacuum to yield 1,2,3,4,5-penta-*O*-acetyl-6-deoxy-6-acetamido-*myo*-inositol (400 mg, 0.95 mmol, 80%) as a colourless foam.

This crude product (350 mg, 0.8 mmol) was suspended in anhydrous MeOH (5 mL) under argon, and cooled to 4 °C. A 5.5 M sodium methanolate solution (80 μL, 0.4 mmol) was added dropwise. The solution was allowed to warm to room temperature and stirred for 4 h. The solution was neutralized by ion exchanger (H^+, Dowex 50-X), filtered off and washed with

water. The filtrate was reduced in volume and then lyophilized to give the pentol (140 mg, 80%) as a colourless solid.

The solid (140 mg, 0.63 mmol) and 1*H*-tetrazole (440 mg, 6.3 mmol) were suspended in anhydrous dichloromethane (30 mL) under argon, and (1,5-dihydro-2,4,3-benzodioxaphosphepin-3-yl)diethylamine (860 mg, 3.8 mmol) was added. The mixture was stirred at room temperature for 4 h. The product was worked up as described [2.7 g *m*-CPBA (70%), 11 mmol in 15 mL CH_2Cl_2; dried over $NaSO_4$] for **16**. Purification by flash chromatography yielded a colourless solid (300 mg, 43%, $R_f = 0.13$ (CH_2Cl_2–MeOH 95 : 5)).

To a suspension of 6-deoxy-6-acetamido-1,2,3,4,5-penta-*O*-(3-oxo-1,5-dihydro-3λ^5-2,4,3-benzodioxaphosphepin-3-yl)-*myo*-inositol (140 mg, 0.13 mmol) in ethanol–water (1 : 1, 30 mL) was added Pd/C (100 mg). 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 colourless, hygroscopic foam (76 mg, 99%). Further purification by HPLC assured purity >99%. $[a]_D^{20} = -4.4$ ($c = 5.2$, H_2O). ^{1}H-NMR (D_2O, pH adjusted to 6 (ND_4OD)): δ 2.01 (s, CH_3), 4.01 (Ψq, 1 H, *J* 9.7 Hz, H-5), 4.04 (Ψt, 1 H, *J* 8.4 Hz, H-3), 4.06 (Ψt, 1 H, *J* 7.9 Hz, H-1), 4.24 (Ψt, 1 H, *J* 10.4 Hz, H-6), 4.38 (Ψq, 1 H, *J* 9.5 Hz, H-4), 4.85 (d, 1 H, *J* 10.2 Hz, H-2). ^{13}C-NMR (D_2O, pH adjusted to 6 (ND_4OD)): δ 24.85 (CH_3), 54.1 (m, C-6), 74.5 (m, C-3), 75.7 (m, C-1), 76.8 (d, *J* 6.1 Hz, C-2), 77.8 (m, C-5), 78.6 (m, C-4), 177.5 (C=O). ^{31}P-NMR{^{1}H} (D_2O, pH adjusted to 6 (ND_4OD)): δ 1.30 (PC-3), 1.38 (PC-5), 2.16 (PC-2, PC-1), 3.13 (PC-4).). HR-MS (ESI-neg, phosphoric acid 0.002%, H_2O–acetonitrile 1 : 1, Q-TOF): *m*/*z*: 619.9150 $[M - H]^-$ calcd. for $C_8H_{19}NO_{21}P_5$: 619.9138.

4-Deoxy-4-acetamido-*myo*-inositol-1,2,3,5,6-pentakisphosphate (+)-18

A solution of (−)-**10** was allowed to react under the same conditions as described for the preparation of (−)-**18** to give (+)-**18**. $[a]_D^{20} = +4.6$ ($c = 6.0$, H_2O). Analytical data were identical to those obtained for (−)-**18**.

3-Deoxy-3-acetamido-*myo*-inositol-1,2,4,5,6-pentakisphosphate (+)-19

The diastereomer was synthesized as described for 6-deoxy-6-acetamido-*myo*-inositol-1,2,4,5,6-pentakisphosphate (−)-**18** (1,2,4,5,6-penta-*O*-acetyl-3-deoxy-3-azido-*myo*-inositol (−)-**11** was taken as starting material). Workup as before gave (+)-**19** as a colourless foam. $[a]_D^{20} = +4.9$ ($c = 1.6$, H_2O). ^{1}H-NMR (D_2O, pH adjusted to 6 (ND_4OD)): δ 2.01 (s, CH_3), 3.99 (d, 1 H, *J* 10.7 Hz, H-3), 4.16 (Ψt, 1 H, *J* 8.9 Hz, H-1), 4.17 (Ψq, 1 H, *J* 8.8 Hz, H-5), 4.28 (Ψq, 1 H, *J* 9.7 Hz, H-4), 4.37 (Ψq, 1 H, *J* 9.3 Hz, H-6), 4.66 (d, under HDO, H-2). ^{13}C-NMR (D_2O, pH adjusted to 6 (ND_4OD)): δ 24.7 (CH_3), 53.8 (m, C-3), 76.4 (m, C-1, C-2), 76.8 (m, C-4), 78.5 (m, C-6), 80.4 (m, C-5), 176.5 (C=O). ^{31}P-NMR{^{1}H} (D_2O, pH adjusted to 6 (ND_4OD)): δ 1.72 (PC-4), 1.80 (PC-1), 2.16 (PC-2), 2.33 (PC-6), 3.10 (PC-5). HR-MS (ESI-neg, phosphoric acid 0.002%, H_2O–acetonitrile 1 : 1, Q-TOF): *m*/*z*: 619.9121 $[M - H]^-$ calcd. for $C_8H_{19}NO_{21}P_5$: 619.9138.

1-Deoxy-1-acetamido-*myo*-inositol-2,3,4,5,6-pentakisphosphate (−)-19

A solution of (+)-**11** was allowed to react under the same conditions as described for the preparation of (+)-**19** to give (−)-**19**. $[a]_D^{20} = -5.6$ ($c = 2.1$, H_2O). Analytical data were identical to the data obtained for (+)-**19**.

(1*S*,2*R*,3*R*,4*S*)-1-Azido-2,3-*O*-isopropylconduritol B (+)-21

(1*S*,2*R*,3*R*,4*S*)-1-Azidoconduritol B (+)-**6** (1 g, 5.8 mmol) was dissolved in 2,2-dimethoxypropane (20 mL) and anhydrous acetone (10 mL). Pyridinium *p*-toluenesulfonic acid [PPTSA] (40 mg) was added, and the solution was stirred for 24 h. 10% aqueous NaOH (2 mL), brine (1 mL) and EtOAc (20 mL) were added, and the solution stirred for a further 5 min. The layers were separated, and the organic layer, washed with brine, was concentrated under reduced pressure.

The crude product contained mainly 1-azido-2,3-*O*-isopropylconduritol B and as by-product 1-azido-2,3-*O*-isopropyl-4-mono-*O*-(2-methoxy)isopropylconduritol B.

This crude product was dissolved in anhydrous acetone (15 mL), and a trace of *p*-toluenesulfonic acid (PTSA) was added. The solution was stirred until TLC showed absence of the by-product (30 minutes). The organic layer was washed with aqueous $NaHCO_3$ and with brine. Evaporation of the solvent gave **21** (900 mg, 73%) as an oil. R_f: 0.35 (EtOAc–cyclohexane 1 : 1). $[a]_D^{20} = +97$ ($c = 1.7$, acetone). ^{1}H-NMR ($CDCl_3$): δ 1.47 (s, 6 H, 2 × CH_3), 2.95 (s, br, 1 H, OH), 3.55 (m, 2 H, H-2, H-3), 4.17 (dd, 1H, *J* 4.8 and 2.3 Hz, H-1), 4.47 (d, 1 H, *J* 4.5 Hz, H-4), 5.61 (dΨt, 1 H, *J* 10.2 and 2.0 Hz, H-5), 5.77 (dΨt, 1 H, *J* 10.2 and 2.0 Hz, H-6).^{13}C-NMR ($CDCl_3$): δ 26.8 (CH_3), 26.9 (CH_3), 61.4 (C-1), 70.4 (C-4), 78.0, 81.0 (C-2, C-3), 111.7 ($C(CH_3)_2$), 125.8 (C-5), 132.7 (C-6). MS (EI, 70 ev, *m*/*z* (%)): 196 (15) $[M^+ - CH_3]$, 168 (3) $[M^+ - N_3]$, 111 (29), 59 (88) $[C_3H_7O^+]$, 43 (100) $[C_3H_7^+]$. IR (KBr): 3430 (s, br), 3030 (w), 2970 + 2860 (m), 2090 (s), 1630 (w). Anal. Calcd. for $C_9H_{13}O_3N_3$: C, 51.18; H, 6.20; N, 19.89. Found C, 51.30; H, 6.00; N, 20.10%.

(1*S*,2*R*,3*R*,4*S*)-1,4-Diazidoconduritol B (+)-22

A solution of diol (+)-**2** (6.8 g, 25 mmol), Et_2O–MeOH (2 : 1, 225 mL) and LiOH (3.0 g, 0.13 mol) was stirred for 2 h at 10 °C, and then a solution of NaN_3 (16.1 g, 0.25 mol) in water (30 mL) was added. The mixture was stirred at 40 °C for 1 day and then 2 days at room temperature. The solvent was removed under vacuum, and the residue was taken up with water (50 mL) and Et_2O. The aqueous layer was extracted four times with Et_2O, and the combined organic layer was washed with brine. Drying and evaporation of the solvent gave 4 g of a crude product. Purifying by flash chromatography (CH_2Cl_2–methanol 95 : 5) yielded (+)-**22** in 51% (2.5 g) as a colourless solid. R_f: 0.22 (CH_2Cl_2–MeOH 95 : 5). $[a]_D^{20} = +341$ ($c = 0.55$, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): δ 3.70 (dd, 2 H, *J* 2.3 and 5.85 Hz, H-2, H-3), 3.84 (s, 2 H, O*H*), 4.06 (dd, 2 H, *J* 2.3 and 5.85 Hz, H-1, H-4), 5.71 (s, H-5, H-6). ^{13}C-NMR ($CDCl_3$): δ 63.3 (C-1, C-4), 74.4 (C-2, C-3), 127.1 (C-5, C-6); MS (EI, 70 eV, *m*/*z* (%)): 153 (8), 136 (18), 124 (7), 96 (17), 81 (29), 53 (100). IR (KBr): 3300 (m), 2850 (m), 2080 (m, br), 1632 (m), 1347 (m), 1247 (s), 1106 (s), 1049 (m). Anal. Calcd. for $C_6H_8O_2N_6$: C, 36.74; H, 4.11; N, 42.84. Found C, 36.80; H, 4.12; N, 43.10%.

(1*R*,2*S*,3*S*,4*R*)-1,4-Diazidoconduritol B (−)-22

A solution of (+)-**1** was allowed to react under the same conditions as described for the preparation of (+)-**22** to give (−)-**22**. $[a]_D^{20} = -320$ ($c = 0.6$, $CHCl_3$). Analytical data were identical to the data obtained for (+)-**22**.

(1*S*,2*R*,3*R*,4*S*)-2,3-Di-*O*-acetyl-1,4-diazidoconduritol B (+)-23

(+)-**22** (1 g, 5.1 mmol) was dissolved in a cooled mixture of pyridine (10 mL) and acetic anhydride (5 mL). The mixture was stirred for 12 h. Evaporation of the solvent under high vacuum gave (+)-**23** (1.4 g, 100%) as a colourless solid. R_f: 0.63 (EtOAc–cyclohexane 1 : 1). $[a]_D^{20} = +324$ ($c = 0.29$, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): δ 2.10 (s, 6 H, CH_3), 4.20 (dd, 2 H, *J* 2.5 and 5.6 Hz, H-1, H-4), 5.21 (dd, 2 H, *J* 2.5 and 5.6 Hz, H-2, H-3), 5.78 (s, 2 H, H-5, H-6). ^{13}C-NMR ($CDCl_3$): δ 20.5 (CH_3), 60.9 (C-1, C-4), 71.8 (C-2, C-3), 127.2 (C-5, C-6), 169.7 (C=O). MS (EI, 70 eV, *m*/*z* (%)): 238 (2), 153 (4), 136 (5), 122 (8), 111 (8), 95 (14),

81 (76), 43 (100). Anal. Calcd. for $C_{10}H_{12}O_4N_6$: C, 42.86; H, 4.32; N, 29.99. Found: C, 42.77; H, 4.34; N, 29.90%.

(1*R*,2*S*,3*S*,4*R*)-2,3-Di-*O*-acetyl-1,4-diazidoconduritol B (−)-23

A solution of (−)-**22** was allowed to react under the same conditions as described for the preparation of (+)-**23** to give (−)-**23**. $[\alpha]_D^{20} = -323$ (c = 0.53, $CHCl_3$). Analytical data were identical to the data obtained for (+)-**23**.

4,5-Di-*O*-acetyl-3,6-dideoxy-3,6-diazido-*myo*-inositol (−)-24

To a vigorously stirred ice-cooled solution of (+)-**23** (1.0 g, 3.6 mmol) in acetonitrile (55 mL) was added a solution of sodium metaperiodate (1.1 g, 5.2 mmol, 1.5 eq.) and ruthenium trichloride trihydrate (70 mg, 0.23 mmol) in water (7 mL). The stirring was continued until TLC showed absence of starting material (approx. 8 min). The reaction was quenched by addition of aqueous $Na_2S_2O_3$ (20%, 50 mL). The aqueous layer was separated and extracted four times with EtOAc (4 × 100 mL). The combined organic layer was washed twice with brine and concentrated under reduced pressure to yield pure (−)-**24** as a colourless foam (1.1 g, 100%). R_f: 0.31 (EtOAc–cyclohexane 1 : 1). $[\alpha]_D^{20} = -48.3$ (c = 0.4, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): δ 2.09, 2.11 (s, 2 × 3 H, CH_3), 3.05 (s, br, 2 H, OH), 3.50 (dd, 1 H, J 2.5 and 10.2 Hz, H-3), 3.56 (dd, 1 H, J 2.5 and 10.2 Hz, H-1), 3.90 (Ψt, 1 H, J 10.2 Hz, H-6), 4.25 (Ψt, 1 H, J 2.5 Hz, H-2), 4.97 (Ψt, 1 H, J 9.9 Hz, H-5), 5.47 (Ψt, 1 H, J 10.2 Hz, H-4). ^{13}C-NMR ($CDCl_3$): δ 20.54, 20.57 (CH_3), 61.4 (C-3), 63.4 (C-6), 70.9 (C-2), 71.0 (C-4), 71.0 (C-1), 72.0 (C-5), 170.0 (2 × C=O). Anal. Calcd. for $C_{10}H_{14}O_6N_6$: H 4.49, C 38.22, N 26.74; found: H 4.73, C 38.01, N 27.00%.

5,6-Di-*O*-acetyl-1,4-dideoxy-1,4-diazido-*myo*-inositol (+)-24

(−)-**23** was allowed to react under the same conditions as described for the preparation of (−)-**24** to give (+)-**24**. $[\alpha]_D^{20} = +52$ (c = 0.4, $CHCl_3$). Analytical data were identical to the data obtained for (−)-**24**.

3,6-Dideoxy-3,6-diazido-*myo*-inositol (−)-25

(−)-**24** (500 mg, 1.6 mmol) was suspended in anhydrous methanol (10 mL) under argon and cooled to 4 °C. A 5.5 M sodium methanolate solution (100 µL, 0.55 mmol) was added dropwise over 10 min. The solution was allowed to warm to room temperature and stirred for 12 h. The solution was neutralized by ion exchanger (H^+, Dowex 50-X), activated carbon was added, then filtered off, and the residue was washed with MeOH. The filtrate was reduced in volume under high vacuum. recrystallization from methanol yielded (−)-**25** (400 mg, 99%) as colourless solid. $[\alpha]_D^{20} = -48.8$ (c = 0.24, MeOH). ^{1}H-NMR (d_4-MeOH): δ 3.12 (dd, 1 H, J 2.5 and 10.2 Hz, H-3), 3.18 (Ψt, 1 H, J 9.4 Hz, H-5), 3.36 (dd, 1 H, J 2.5 and 10.2 Hz, H-1), 3.50 (Ψt, 1 H, J 10.2 Hz, H-6), 3.78 (dd, 1 H, J 9.2 and 10.7 Hz, H-4), 3.97 (Ψt, 1 H, J 2.5 Hz, H-2). ^{13}C-NMR (d_4-MeOH): δ 64.9 (C-3), 67.7 (C-6), 72.5 (C-1), 72.9 (C-4), 73.0 (C-2), 75.8 (C-5); MS (70 eV, m/z (%)): 230 (2) [M^+], 173 (1), 98 (16), 88 (16), 73 (47), 60 (100), 42 (64). IR (KBr): 3384 (s, br), 2921 (w), 2110 (s), 1632 (w), 1259 (m), 1136 (m), 1104 (m), 1010 (m). Anal. Calcd. for $C_6H_{10}O_4N_6$: C, 31.31; H, 4.38; N, 36.51. Found: C, 31.12; H, 4.60; N, 36.82%.

1,4-Dideoxy-1,4-diazido-*myo*-inositol (+)-25

(+)-**24** was allowed to react under the same conditions as described for the preparation of (−)-**25** to give (+)-**25**. $[\alpha]_D^{20} = +44$ (c = 0.31, MeOH). Analytical data were identical to the data obtained for (−)-**25**.

3,6-Dideoxy-3,6-diamino-*myo*-inositol (+)-28

To a suspension of (−)-**25** (40 mg, 0.17 mmol) in methanol–water (1 : 3, 40 mL) was added Pd/C (20 mg). The mixture was stirred at room temperature under H_2 for 5 h. The catalyst was filtered off, and the filtrate was reduced in volume and lyophilized to give a colourless, hygroscopic foam (40 mg, 100%). $[\alpha]_D^{20} = +5.9$ (c = 0.34, H_2O). ^{1}H-NMR (D_2O): δ 2.72 (dd, 1 H, J 1.8 and 10.4 Hz, H-3), 2.97 (Ψt, 1 H, J 10.2 Hz, H-6), 3.20 (Ψt, 1 H, J 9.7 Hz, H-5), 3.44 (Ψt, 1 H, J 9.9 Hz, H-4), 3.48 (dd, 1 H, J 2.0 and 9.7 Hz, H-1), 3.97 (Ψs, 1 H, H-2). ^{13}C-NMR (D_2O): δ 55.6 (C-3), 55.9 (C-6), 73.59 (C-2), 73.65 (C-1), 75.1 (C-4), 76.4 (C-5). HR-MS (ESI-pos., TOF): m/z: 179.1024 $[M + H]^+$ calcd. for $C_6H_{15}N_2O_4$: 179.1032.

1,4-Dideoxy-1,4-diamino-*myo*-inositol (−)-28

A solution of (+)-**25** was allowed to react under the same conditions as described for the preparation of (+)-**28** to give (−)-**28**. $[\alpha]_D^{20} = -5.1$ (c = 0.3, H_2O); Analytical data were identical to the data obtained for (+)-**28**.

3,6-Dideoxy-3,6-diazido-1,2,4,5-tetra-*O*-(3-oxo-1,5-dihydro-3λ^5–2,4,3-benzodioxaphosphepin-3-yl)-*myo*-inositol (−)-26

To a solution of (−)-**25** (200 mg, 0.86 mmol) and 1*H*-tetrazole (480 mg, 6.8 mmol) in anhydrous dichloromethane (20 mL) under argon was added (1,5-dihydro-2,4,3-benzodioxaphosphepin-3-yl)diethylamine (980 mg, 4.1 mmol), and the mixture was stirred at room temperature for at most 4 h. The mixture was cooled to −40 °C, and an anhydrous solution of *m*-CPBA (3.5 g, 14.4 mmol) in dichloromethane (20 mL, dried over 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 $NaHCO_3$ and brine. After evaporation of dichloromethane the crude product was purified by flash chromatography (CH_2Cl_2–MeOH 95 : 5) to yield (−)-**26** (350 mg, 45%) as a colourless foam. R_f: 0.22 (CH_2Cl_2–MeOH 95 : 5). $[\alpha]_D^{20} = -34.4$ (c = 0.215, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): δ 3.80 (Ψt, 1 H, J 9.9 Hz, H-6), 4.23 (dd, 1 H, J 2.0 and 8.1 Hz, H-3), 4.95–5.70 (m, 20 H, 4 × $(CH_2)_2C_6H_4$, H-1, H-2, H-4, H-5), 7.18–7.38 (m, 16 H, Ph-H). ^{13}C-NMR ($CDCl_3$): δ = 60.9 (C-3), 63.5 (C-6), 68.71–69.43 (m, 4 × $(CH_2)_2C_6H_4$), 74.2 (m), 77.0 (m), 77.4 (m), 77.7 (Ψt, J 4.8 Hz) (C-1, C-2, C-4, C-5), 128–129.5 ($C_{arom.}$), 134.65, 134.74, 134.99, 135.15, 135.33, 135.49, 135.55 (C_{ipso}). ^{31}P{^{1}H}-NMR ($CDCl_3$): δ −1.90, −1.85, −1.20, −1.12 (PC-1, PC-2, PC-4, PC-5). HR-MS (ESI-pos., TOF): m/z: 959.1376 $[M + H]^+$ calcd. for $C_{38}H_{39}N_6O_{16}P_4$: 959.1373.

3,6-Dideoxy-3,6-diazido-1,2,4,5-*myo*-inositol tetrakisphosphate (−)-27

(−)-**26** (130 mg, 0.13 mmol) was dissolved in anhydrous CH_2Cl_2 (15 mL) under argon. At 0 °C trimethylsilyl bromide (530 µL, 4 mmol) was slowly added, and the solution was stirred for 3 h at 0 °C. The reaction was quenched by addition of 0.4 mL water, and the solvent was removed under vacuum. The residue was diluted with water and extracted with Et_2O. The aqueous layer was lyophilized to yield (−)-**27** (63 mg, 90%) as a colourless, hygroscopic foam. $[\alpha]_D^{20} = -13.0$ (c = 1.0, H_2O); ^{1}H-NMR (D_2O, pH 1): δ 3.76 (d, 1 H, J 10.2 Hz, H-3), 3.88 (Ψt, 1 H, J 10.2 Hz, H-6), 4.08 (Ψq, 1 H, J 9.5 Hz, H-5), 4.14 (Ψt, 1 H, J 10.9 Hz, H-1), 4.35 (Ψq, 1 H, J 9.8 Hz, H-4), 4.83 (d, 1 H, J 9.7 Hz, H-2). ^{13}C-NMR (D_2O, pH 1): δ 61.1 (Ψt, J 2.9 Hz, C-3), 63.1 (m, C-6), 73.7 (m, C-1), 75.3 (d, J 6.4 Hz, C-2), 76.1 (m, C-4), 77.0 (m, C-5). ^{31}P{^{1}H}-NMR (D_2O, pH 1): δ −0.25 (PC-2), +0.11 (PC-1), +0.58 (PC-5), +0.82 (PC-4). IR (KBr): 3423 (s, br), 2921 (m), 2121 (m), 1718, 1012 (s). HR-MS (ESI-neg, phosphoric acid 0.002%, H_2O–acetonitrile 1 : 1, Q-TOF): m/z: 548.9365 $[M - H]^-$ calcd. for $C_6H_{13}N_6O_{16}P_6$: 548.9339.

Acknowledgements

We thank Dr. W. V. Turner for critical reading of the manuscript. We are grateful to the Bayer AG Company for supporting this project in many aspects, especially for preparing the HR-MS spectra. We also thank in particular Dr. W. Schrader and Mrs. Blumenthal (Max-Planck Institut für Kohlenforschung) for mass spectra analysis. We thank Dr S. Adelt and G. Dallmann for purification of the inositol phosphates.

References

1 B. V. L. Potter and D. Lampe, *Angew. Chem.*, 1995, **107**, 2085–2125 (*Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 1933–1972).
2 R. F. Irvine and M. J. Schell, *Nature Rev.*, 2001, **2**, 327–338.
3 H. Streb, F. R. Irvine, M. J. Berridge and I. Schulz, *Nature*, 1983, **306**, 67–69.
4 H. Streb, R. F. Irvine, M. J. Berridge and I. Schulz, *Nature*, 1983, **312**, 375–376.
5 G. Legler, *Adv. Carbohydr. Chem. Biochem.*, 1990, **48**, 319–389.
6 (*a*) G. Brunn, A. H. Fauq, S. Chow, A. P. Kozikowski, A. Gallegos and G. Powis, *Cancer Chemother. Pharmacol.*, 1994, **35**, 71–79; (*b*) G. Powis, I. A. Aksoy, C. D. Melder, S. Aksoy, H. Eichinger, A. H. Fauq and A. P. Kozikowski, *Cancer Chemother. Pharmacol.*, 1991, **29**, 95–104; (*c*) A. P. Kozikowski, A. H. Fauq, G. Powis, P. Kurian and F. T. Crews, *J. Chem. Soc., Chem. Commun.*, 1992, 362.
7 A. P. Kozikowski, H. Fauq and G. Powis, *Curr. Med. Chem.*, 1994, **1**, 1–12.
8 (*a*) H. Paulsen and W. Roeben, *Liebigs Ann. Chem.*, 1985, 974–994; (*b*) H. Paulsen and F. R. Heiker, *Liebigs Ann. Chem.*, 1981, 2180–2203; (*c*) S. C. Johnson, J. Dahl, T. L. Shih and D. J. A. Schedler, *J. Med. Chem.*, 1993, **36**, 3628–35.
9 S. Ballereau, P. Guédat, S. N. Poirier, G. Guillemette, B. Spiess and G. Schlewer, *J. Med. Chem*, 1999, **42**, 4824–4835.
10 T. Suzuki, S. T. Suzuki, I. Yamada, Y. Koashi, K. Yamada and N. Chida, *J. Org. Chem.*, 2002, **67**, 2874–2880.
11 C. Sanfilippo, A. Patti and G. Nicolosi, *Tetrahedron: Asymmetry*, 1998, **9**, 2809–2817.
12 J. Lehmann and B. Rob, *Carbohydr. Res.*, 1995, **276**, 199–208 and references cited therein.
13 T. Furumai, K. Takeda, A. Kinumaki, Y. Ito and T. Okuda, *J. Antibiot.*, 1979, **32**, 891–899.
14 H. Tamegai, E. Nango, M. Kuwahara, H. Yamamoto, Y. Ota, H. Kuriki, T. Eguchi and K. Kakinuma, *J. Antibiot.*, 2002, **55**, 707–714.
15 I. Katsuharu, K. Shinichi, M. Kenji and U. Hamao, *Bull. Chem. Soc. Jpn.*, 1977, **50**, 1850–1854.
16 J. Ahlert, J. Distler, K. Mansouri and W. Piepersberg, *Arch. Microbiol.*, 1997, **168**, 102–113.
17 (*a*) S. Adelt, O. Plettenburg, G. Dallmann, F. P. Ritter, S. Shears, H.-J. Altenbach and G. Vogel, *Bioorg. Med. Chem. Lett.*, 2001, **11**, 2705–2708; (*b*) O. Plettenburg and S. Adelt, *Tetrahedron: Asymmetry*, 2000, **11**, 1057–1061; (*c*) see ref. 19.
18 O. Block, G. Klein and H.-J. Altenbach, *J. Org. Chem.*, 2000, **65**, 716–721.
19 S. Adelt, O. Plettenburg, R. Stricker, G. Reiser, H.-J. Altenbach and G. Vogel, *J. Med. Chem.*, 1999, **42**, 1262–1273.
20 B. Zipperer, D. Hunkler, H. Fritz, G. Rihs and H. Prinzbach, *Angew. Chem.*, 1984, **96**, 296–297.
21 B. M. Trost, D. E. Patterson and E. J. Hembre, *Chem. Eur. J.*, 2001, **7**, 3768–3775.
22 A. P. Kozikowski, A. H. Fauq, R. A. Wilcox and S. R. Nahorski, *Bioorg. Med. Chem. Lett.*, 1995, **5**, 1295–1300.
23 S.-K. Chung, B.-G. Shin, Y.-T. Chang, B.-C. Suh and K.-T. Kim, *Bioorg. Med. Chem. Lett.*, 1998, **8**, 659–662.
24 S. J. Mills and B. V. L. Potter, *J. Chem. Soc., Perkin Trans. 1*, 1997, **9**, 1279–1286.
25 S. J. Mills, T. S. Safrany, R. A. Wilcox, S. R. Nahorski and B. V. L. Potter, *Bioorg. Med. Chem. Lett.*, 1993, **3**, 1505.
26 G. Mayr, W. Mass, Determination of Inositol Phosphates by High Performance Liquid Chromatography with Postcolumn Complexometry (Metal-Dye Detection) in, *Methods in Inositide Research*, ed. R. F. Irvine, Raven Press, New York, 1990, p. 83–108.
27 H. Paulsen and W. Roeben, *Liebigs Ann. Chem.*, 1985, **5**, 974–994.
28 A. Olesker, D. Mercier, S. Gero, C. J. Pearce and J. E. Barnett, *J. Antibiot.*, 1975, **28**, 490.
29 K. Iinuma, S. Kondo, K. Maeda and H. Umezawa, *Bull. Chem. Soc. Jpn.*, 1977, **50**, 1850–1854.