EurJOC European Journal of Organic Chemistry

FULL PAPER

DOI: 10.1002/ejoc.201201426

Stereoselective Synthesis of Polyhydroxycycloheptanes and Their Phosphate Derivatives from 8-Oxabicyclo[3.2.1]octenes

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Keywords: Cyclitols / Carbasugars / Phosphorylation / Dihydroxylation / Inhibitors / Enantioselectivity

The first directed synthesis of seven-membered mono- and tris-phosphates is described. The key steps involve a DIBAL-H/DIBAL-Cl-mediated ring opening of 8-oxabicyclo-[3.2.1]octenes in the presence of [Ni(acac)$_2$] and stereoselective *syn*-dihydroxylation with NMO and OsO_4. An enantioselective approach to ring opening has been examined with chiral phosphane. The phosphorylation of mono- and triols followed by deprotection gave the corresponding phosphates in high yields with structures similar to those of known inhibitors of *myo*-inositol monophosphatase (IMPase) and *myo*-inositol tris-phosphate receptor ligands. The inhibitory activities of the monophosphates thus formed were evaluated against IMPase.

Introduction

In the last few decades, polyhydroxycarbocycles have gained importance as pharmacological tools for investigating cellular processes related to the inositol cycle[1] and also as potent glycosidase inhibitors.[2] Although a wide range of cyclopentane and -hexane derivatives are readily available, the stereoselective synthesis of polyhydroxycycloheptanes (homoinositols, seven-membered cyclitols) is considered a difficult task.[3] A variety of synthetic carbohydrate-based methods have been reported for the synthesis of seven-membered carbocyclic frameworks, including ring-closing metathesis,[4] 1,3-dipolar cycloaddition,[5] intramolecular nucleophilic attack,[6] and radical-mediated cyclization[7] among others.[3] Synthetic approaches starting from non-natural-product origin are less popular and the oxidation of tropone is the most common route.[8]

Owing to the high flexibility of the seven-membered ring (compared with five- and six-membered rings), cycloheptanes easily adopt the different conformations required to mimic the transition state in different processes along the minimum energy path, thus facilitating its binding to enzymes[9] (e.g., glycosidases). The effect of the high flexibility of polyhydroxycycloheptanes was clearly demonstrated by Sinaÿ[4c] and Le Merrer[6c] and their co-workers: Some seven-membered cyclitols inhibited α-D-glucosidase with lower K_i values than the six-membered structural analogues. Many examples of efficient glycosidase inhibition by seven-membered iminocyclitols (polyhydroxyazepanes) have also been reported.[10]

There are two main targets to affect the inositol cycle in the human body: *myo*-inositol monophosphatase (IMPase) and the *myo*-inositol tris-phosphate ($InsP_3$) receptor.[1b] IMPase is known to play different physiological roles: It is involved in the phosphatidylinositol (PI) signal transduction pathway and carbohydrate metabolism as well as exhibiting Zn^{2+}-dependent tyrosine phosphatase activity.[11] A number of active six-membered monophosphates have been synthesized (Figure 1) and studies of their inhibitory activity have shown encouraging results.[12] $InsP_3$ analogues (different six-membered tris-phosphates) interact with the $InsP_3$ receptor, thus influencing the release of Ca^{2+} inside

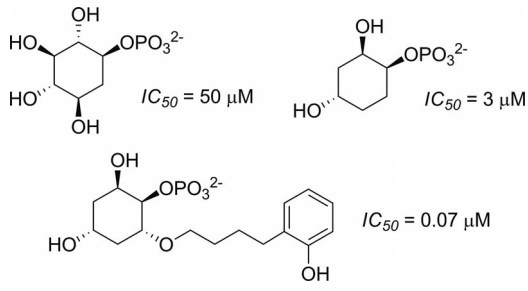

Figure 1. Examples of IMPase inhibitors.[12]

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201201426.

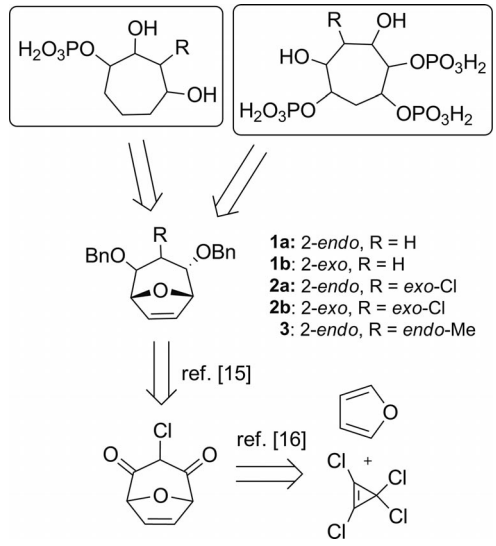
the cell. Other targets for them are $InsP_3$ 3-kinase and $InsP_3$ 5-phosphatase.[1b,13]

Thus, mono- and tris-phosphate derivatives of cyclitols are a focus of interest. Although glucosidase active sites revealed favorable binding towards seven-membered cyclitols, interactions of the corresponding phosphates with IMPase and the $InsP_3$ receptor have not been studied at all. Moreover, to the best of our knowledge, no attempts have been made to perform the directed synthesis of seven-membered mono- and tris-phosphates.

Results and Discussion

The assembly of the polyhydroxylated cycloheptane ring with high diastereoselectivity in a few steps starting from non-sugar materials is an intriguing challenge. In addition to the tropone approach,[8] the 8-oxabicyclo[3.2.1]octene-based protocol of Lautens et al.[14] seems to be convenient and limited only by the availability of oxa-bridged cycloheptenes. Thus, a number of 8-oxabicyclo[3.2.1]oct-6-ene-2,4-diols are necessary for the synthesis of 2,4-dihydroxy-1-phosphates as analogues of IMPase inhibitors (Figure 1). As a part of our ongoing research directed towards the design of new seven-membered cyclitols, we have recently reported[15] the stereoselective synthesis of the required 2,4-diols **1**–**3** (Scheme 1) based on the Diels–Alder reaction of furan and tetrachlorocyclopropene.[16] In this work we applied the ring-opening methodology to synthesize highly substituted cycloheptanes and used them for the synthesis of inositol mono- and tris-phosphate homoanalogues.

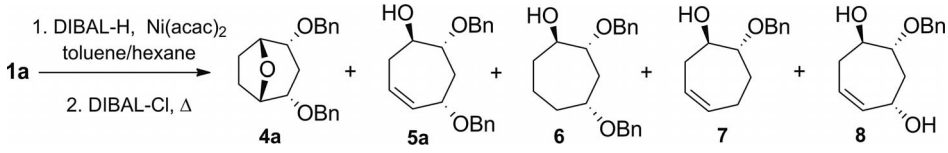
The mechanism of reductive ring opening was proposed by Lautens et al.[14] The nickel-catalyzed reaction of 8-oxabicyclo[3.2.1]octenes with DIBAL-H involves two steps. In the first, organometallic species are generated. In the second, they undergo β-elimination in the presence of Lewis acids to form ring-opened unsaturated compounds (e.g., DIBAL-Cl). In the presence of phosphanes at elevated temperatures, the reaction proceeds by a different pathway.



Scheme 1. Available 8-oxabicyclo[3.2.1]octenes and the retrosynthesis of seven-membered phosphates.

Because initial attempts to apply the ring-opening procedure to alkenes **1**–**3** showed low selectivity, the reaction conditions were optimized for alkene **1a**. The amount of DIBAL-H was found to be of most importance for the total yield and selectivity. Hence, 1.5–8 equiv. of DIBAL-H were tested in the temperature range of 60–85 °C (Table 1). $[Ni(cod)_2]$ and $[Ni(acac)_2]$ were investigated as catalysts (15–30 mol-%) but no significant difference was found. Hence, acetylacetonate was used in further reactions. The use of a large excess of DIBAL-H led to a dramatic decrease in both the yield and selectivity. Thus, for example, treatment with

Table 1. Optimization of ring-opening reaction of **1a**.



Entry	DIBAL-H [equiv.]	DIBAL-Cl [equiv.]	*T* [°C]	Heating time [h]	Total yield [%]	Ratio **4a/5a/6/7/8**[a]
1	1.5	5	70	5	84	41:54:0:5:0[b]
2	2.0	5	60	7	82	24:63:4:7:2
3	2.0	5	85	3	83	21:64:5:8:2
4	2.0	5	75	4	83	20:70:3:5:2[c]
5	2.0	5	65	5	78	22:66:3:7:2
6	2.0	7	75	4	77	20:61:5:10:4
7	2.0	7	65	5	75	18:53:5:18:6
8	3.0	5	75	4	73	18:51:8:16:7
9	3.0	5	65	5	72	17:47:10:18:8
10	4.0	5	75	4	70	16:44:11:20:9
11	4.0	5	65	5	68	15:43:12:21:9
12	8.0	5	65	5	62	13:40:15:22:10[d]

[a] Ratio determined by ^1H NMR spectroscopy. [b] 14% of alkene **1a** was also recovered. [c] Isolated yields: 17% of **4a** and 58% of **5a**. [d] Isolated yields: 8% of **4a**, 23% of **5a**, 9% of **6**, 12% of **7**, and 6% of **8**.

8 equiv. of DIBAL-H and 5 equiv. of DIBAL-Cl gave a complex mixture of products (at least seven substances according to TLC). Five of these products were isolated by column chromatography (entry 12). In addition to the saturated bicycle **4a** (8%) and the desired cycloheptenol **5a** (23%), over-reduced cycloheptanol **6** (9%) and two products containing only one benzyl group were obtained: Compound **7** (12%) lacks a benzyloxy group (BnOH was also detected among the reaction products) and compound **8** (6%) lacks a benzyl group.

Finally, treatment with 2 equiv. of DIBAL-H and 5 equiv. of DIBAL-Cl in toluene/hexane gave the best results: 58% of the desired cycloheptenol **5a** was isolated together with 17% of the saturated bicycle **4a** (entry 4). The process did not go to completion with a smaller amount of DIBAL-H (1.5 equiv.). Thus, some unreacted alkene **1a** was recovered even after 5 h (entry 1).

The effect of the addition of phosphane ligands to the nickel-catalyzed reductive ring-opening of alkene **1a** was next examined. In all cases, the optimized protocol with the use of 30 mol-% phosphane was detrimental to the reaction yield. Of the monodentate ligands tested [Ph_3P, Cy_3P (Cy = cyclohexyl), $(OiPr)_3P$], Ph_3P was found to give the best results (Table 2). The yield was increased by using a greater amount of the nickel catalyst (30 mol-%) and by slowly adding DIBAL-H and DIBAL-Cl (during 4 h). Finally, the desired cycloheptene **5a** was isolated in 64% yield (entry 5). The bidentate 1,4-bis(diphenylphosphanyl)butane (dppb) was not so efficient and gave 46% of the product under the same conditions (entry 6).

Table 2. Effect of phosphane ligands on the ring-opening of **1a**.

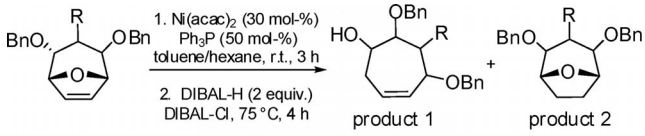
Entry	Phosphane (amount [mol-%])	$[Ni(acac)_2]$ [mol-%]	Isolated yield: of **5a** [%]	*ee* [%]
1	Cy_3P (30)	15	14	
2	$(OiPr)_3P$ (30)	15	26	
3	Ph_3P (30)	15	32	
4	Ph_3P (60)	30	52	
5[a]	Ph_3P (50)	30	64	
6[a]	dppb (50)	30	46	
7[a]	(*R*)-BINAP (50)	50	43	82
8[b]	(*R*)-BINAP (50)	50	28	95

[a] DIBAL-H (2 equiv.) and DIBAL-Cl (5 equiv.) were added over 4 h at 75 °C. [b] No DIBAL-Cl was added.

The enantioselective ring-opening approach was further explored. Chiral (*R*)-BINAP (50 mol-%) was used as the phosphane ligand in the protocol described above and the amount of $[Ni(acac)_2]$ was increased to 50 mol-%. Under these conditions, cycloheptene **5a** was isolated in 43% yield with 82% *ee* (Table 2, entry 7). The *ee* increased to 95% in the absence of DIBAL-Cl, but the yield decreased to 28% (entry 8). Other variations of the reaction parameters did not improve the yield.

We then applied the optimized Ph_3P-based protocol to the ring-opening of symmetrical 3-substituted ethers **2a** and **3**. In this case, similar main products were isolated (Table 3) with the desired cycloheptenols **9a** and **10** isolated in yields of 67 and 70%, respectively. Debenzylated products were detected by NMR spectroscopy, but in amounts too small for isolation. Other nonchiral phosphanes gave results similar to those observed for alkene **1a**.

Table 3. Ring-opening reaction of 8-oxabicyclo[3.2.1]octenes **1**–**3**.



Substrate	Product 1	Product 2
1b	**5b** + **5c** (1:1), 47%	**4b**, 13%
2a	**9a**, 67%	**11a**, 16%
2b	**9b** + **9c** (1:1), 49%	**11b**, 14%
3	**10**, 70%	**12**, 15%

We also examined the ring-opening protocol for asymmetrical benzyl ethers **1b** and **2b**. According to the reaction mechanism, a mixture of products can be obtained. In fact, no selectivity was observed and mixtures of cycloheptenol isomers **5b**+**5c** and **9b**+**9c** were produced in ratios of around 1:1 along with reduced bicycles **4b** and **11b** (Table 3). Their separation became possible only after repeated silica gel column chromatography. Pure diastereomers were isolated in yields of 13–15% (see the Exptl. Sect.). Note that the presence of other phosphanes did not improve the yields and selectivity of the ring opening of asymmetric products.

The stereochemistry of the benzyloxy groups was deduced from NMR data, including NOE measurements. As expected for cycloheptane systems,[4c] a strong NOE effect was detected between the *cis* protons (see Figure 2).

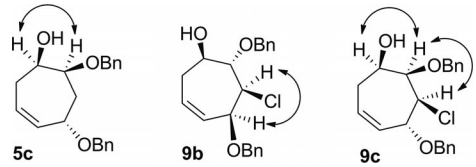
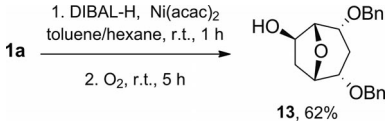


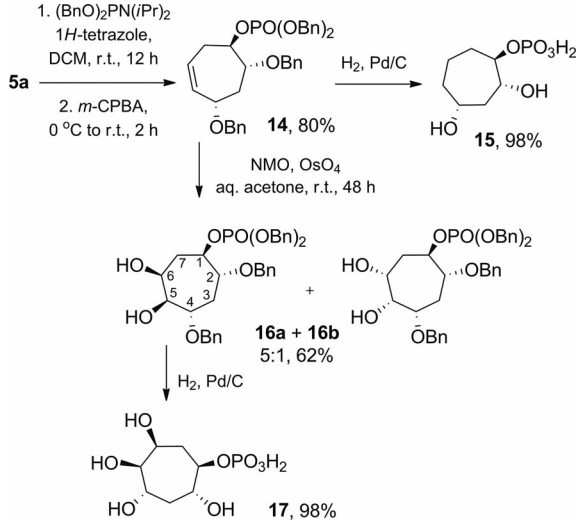
Figure 2. NOEs observed for cycloheptenes **5c**, **9b**, and **9c**.

In some cases another unsymmetrical bicyclic product was detected in the reaction mixtures after the ring-opening procedures. Although all the reactions were carried out under argon, the oxidation of organoalanes was suggested. To confirm this proposal for compound **1a**, the product of hydroalumination was placed under oxygen. The exposure of organoalane to air gave *exo*-alcohol **13** in 62% yield (Scheme 2).



Scheme 2. Oxidation of organoalane.

The cycloheptenol **5a** thus obtained can be used for the preparation of monophosphorylated derivatives structurally similar to the known inhibitors of IMPase (Figure 1) because it requires 1,2,4-substitution. It was found that the hydroxy groups at the 2- and 4-positions play a crucial role in the recognition of InsP by the enzyme and other OH groups can be removed. Moreover, it is usually necessary to promote the inhibition properties.[1b] To demonstrate the monophoshate synthesis, cycloheptene **5a** was phosphorylated. Dibenzyl *N*,*N*-diisopropylphosphoramidite[17] was the reagent of choice due to its relative stability and the ease of benzyl group removal. A weak acid (1*H*-tetrazole) was used as the catalyst and *m*-CPBA was employed as the oxidant, resulting in the formation of the desired protected phosphate **14** in high yield (Scheme 3).



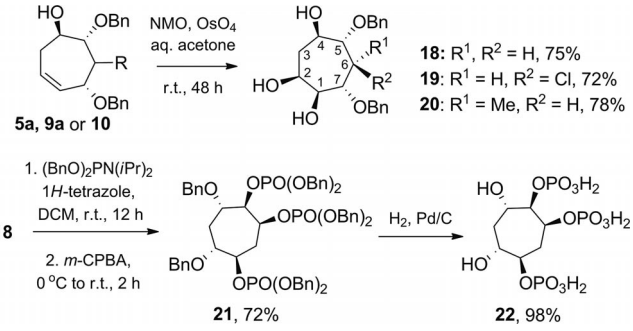
Scheme 3. Synthesis of monophosphates.

Cycloheptene **14** was hydroxylated with NMO and OsO_4 to obtain a diastereoisomeric mixture of **16a** and **16b** in a ratio of 5:1; the minor isomer **16b** was not isolated (Scheme 3). The stereochemistry of the major isomer **16a** was determined by NOE experiments. A strong interaction is observed between $PhCH_2$ at the 4-position and 5-H. The final phosphates **15** and **17** were obtained by catalytic hydrogenolysis of **14** and **16a**, respectively, using Pd on carbon without further purification. The biological assays performed with these compounds showed encouraging results; they exhibited stronger inhibition than the six-membered analogues (Table 4, compare with Figure 1) and both substances displayed a competitive mode of action.

Table 4. Inhibition of IMPase by phosphates **15** and **17**.

Phosphate	IC_{50} [μM]	Mode of action
15	0.8	Competitive
17	13	Competitive

On the other hand, the functionalization of the double bond in alkenes **5**, **9**, and **10** led to the corresponding triols that can be converted into tris-phosphates. The dihydroxylation seemed to be a straightforward approach. Hence, compounds **5a**, **9a**, and **10** were treated with NMO and OsO_4 in aqueous acetone/*tert*-butyl alcohol. As expected from the structures of the substrates, high diastereoselectivity was observed and the corresponding triols **18**–**20** were obtained in high yields (Scheme 4). Other isomers (<7%) were also detected in the reaction mixtures by NMR spectroscopy, but they were not isolated. The stereochemistry was deduced from NOE experiments; a strong interaction was observed between $PhCH_2$ at the 7-position and 1-H.



Scheme 4. Synthesis of tris-phosphate **22**.

Triol **18** was transformed into the corresponding tris-phosphate **22** by phosphorylation followed by deprotection (Scheme 4). This compound can be considered as the structural analogue of the known $InsP_3$ receptor ligands.

Conclusions

A versatile synthesis of polyhydroxylated cycloheptanes and their phosphate derivatives from 8-oxabicyclo[3.2.1]octene precursors has been developed. The stereoselectivity of the bicyclic approach is provided by reductive ring-opening and dihydroxylation procedures. The possibility of asymmetric synthesis was demonstrated by using (*R*)-BINAP as the ligand. The mono- and tris-phosphates thus formed can be considered as racemic homoanalogues of the inositol compounds involved in the signal transduction pathway. The inhibition of IMPase for two seven-membered monophosphates was found to be in the low micromolar range.

Experimental Section

General: All solvents were distilled prior to use. Dry solvents were prepared according to standard procedures. Reactions requiring an inert atmosphere were performed under argon. All reactions were monitored by TLC using Merck 60 F254 precoated silica gel plates (0.25 mm thickness). Flash and column chromatography were performed on silica gel 60. ^{1}H, ^{13}C, and^{31}P NMR spectra were recorded in $CDCl_3$ or [D$_6$]DMSO with a Bruker Avance 400 spectrometer (400 MHz for ^{1}H NMR, 100 MHz for ^{13}C NMR, 162 MHz for ^{31}P NMR). The ^{1}H NMR spectroscopic data are reported as chemical shift (δ [ppm]), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet), coupling constant (J [Hz]), and the number of protons. The ^{13}C NMR spectroscopic data are reported as chemical shifts (δ [ppm]). The chemical shifts were measured relative to the residual solvent as an internal standard. Elemental analyses were performed with a Vario MICRO cube analyzer.

General Method A. Nickel-Catalyzed Reductive Ring Opening (Phosphane-Based Protocol): Ph_3P (39.5 mg, 0.15 mmol) and 1.0 M DIBAL-H in hexane (0.15 mL, 0.15 mmol) were added to [Ni(acac)$_2$] (24.0 mg, 0.09 mmol) in a mixture of freshly distilled toluene (4 mL) and hexane (2 mL). The resulting yellow solution was stirred for 3 h by which time the color was a deep red. The alkene **1a** (0.30 mmol) was dissolved in toluene (1 mL) and transferred to the catalyst solution. The reaction mixture was placed in an oil bath preheated to 75 °C and 1.0 M DIBAL-H solution in hexane (0.45 mL, 0.45 mmol) was slowly added together with DIBAL-Cl (0.3 mL, 1.50 mmol) over 4 h through a syringe pump. The reaction mixture was cooled to room temp. and quenched by the addition of a saturated NH_4Cl aqueous solution (5 mL) and then enough 10% H_2SO_4 was added to make the aqueous layer transparent. The organic layer was separated and the aqueous layer was extracted with Et_2O and EtOAc. The combined organics were dried with Na_2SO_4. The removal of the solvent in vacuo yielded product mixtures that were subjected to silica gel column chromatography (gradient elution with 20–50% Et_2O in hexane).

(1*S*,5*R*,7*S*)-5,7-Bis(benzyloxy)cyclohept-3-enol (5a): The racemic product was afforded according to general method A from alkene **1a** in a yield of 64%. Enantioselective ring opening was also performed by using (*R*)-BINAP instead of Ph_3P and 50 mol-% of [Ni(acac)$_2$]. The substrate purity and solvent quality were found to be crucial for the success of the asymmetric reaction. In the presence of DIBAL-Cl, the compound was isolated in a yield of 43% (42 mg) and 82% *ee*; without DIBAL-Cl it was isolated in a yield of 28% (27 mg) and 95% *ee*. The *ee* was determined by using HPLC analysis on a chiral OD column [95:5 hexane/*i*PrOH, retention times of 15.7 and 16.4 min (major)]. Pale-yellow oil; R_f = 0.50 (Et_2O/hexanes = 1:1); $[\alpha]_D^{25}$ = 35.2 (c = 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 7.30–7.41 (m, 10 H, 2 Ph), 6.03 (dt, J = 2.3, 11.1 Hz, 1 H, 4-H), 5.71–5.78 (m, 1 H, 3-H), 4.75 (d, J = 11.1 Hz, 1 H, CH_2Ph), 4.64 (d, J = 11.6 Hz, 1 H, CH_2Ph), 4.53 (d, J = 11.6 Hz, 1 H, CH_2Ph), 4.51 (d, J = 11.1 Hz, 1 H, CH_2Ph), 4.09 (dd, J = 2.3, 11.1 Hz, 1 H, 5-H), 3.33–3.45 (m, 2 H, 1-H, 7-H), 3.03 (s, 1 H, OH), 2.40–2.47 (m, 2 H, 2-H), 2.06–2.14 (m, 1 H, 6-H), 1.65–1.74 (m, 1 H, 6-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 138.5, 138.2, 137.9, 128.7, 128.5, 128.0, 127.9, 127.8, 127.7, 124.6, 84.1, 74.1, 71.7, 71.2, 70.9, 36.3, 31.1 ppm. $C_{21}H_{24}O_3$ (324.42): calcd. C 77.75, H 7.46; found C 77.86, H 7.34.

(1*R,5*R**,7*R**)-5,7-Bis(benzyloxy)cyclohept-3-enol (5b):** Compound **5b** was afforded according to general method A from alkene **1b** as a 1:1 mixture with compound **5c** in a yield of 46 mg (47%). Isolated yield: 13 mg (14%) after repeated column chromatography; pale-yellow oil; R_f = 0.45 (Et_2O/hexanes = 1:1). ^{1}H NMR ($CDCl_3$): δ = 7.30–7.43 (m, 10 H, 2 Ph), 5.97–6.01 (m, 1 H, 4-H), 5.74–5.80 (m, 1 H, 3-H), 4.68 (d, J = 11.6 Hz, 1 H, CH_2Ph), 4.58 (d, J = 11.8 Hz, 1 H, CH_2Ph), 4.51 (d, J = 11.6 Hz, 1 H, CH_2Ph), 4.47 (d, J = 11.8 Hz, 1 H, CH_2Ph), 4.42 (br. d, J = 8.2 Hz, 1 H, 5-H), 3.72–3.79 (m, 2 H, 1-H, 7-H), 2.64–2.68 (m, 1 H), 2.27–2.33 (m, 1 H), 1.98–2.04 (m, 1 H), 1.84–1.90 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 138.4, 137.8, 133.5, 128.6, 128.5, 128.1, 127.9, 127.8, 127.7, 124.7, 83.4, 74.7, 72.3, 71.3, 70.9, 35.6, 31.0 ppm. $C_{21}H_{24}O_3$ (324.42): calcd. C 77.75, H 7.46; found C 77.72, H 7.34.

(1*S,5*R**,7*R**)-5,7-Bis(benzyloxy)cyclohept-3-enol (5c):** Compound **5c** was afforded according to general method A from alkene **1b** as a 1:1 mixture with compound **5b** in a yield of 46 mg (47%). Isolated yield: 12 mg (13%) after repeated column chromatography; pale-yellow oil; R_f = 0.43 (Et_2O/hexanes = 1:1). ^{1}H NMR ($CDCl_3$): δ = 7.29–7.40 (m, 10 H, 2 Ph), 5.94–5.97 (dt, J = 2.4, 11.0 Hz, 1 H, 4-H), 5.67–5.73 (m, 1 H, 3-H), 4.69 (d, J = 11.6 Hz, 1 H, CH_2Ph), 4.59 (d, J = 11.9 Hz, 1 H, CH_2Ph), 4.52 (d, J = 11.6 Hz, 1 H, CH_2Ph), 4.47 (d, J = 11.9 Hz, 1 H, CH_2Ph), 4.27 (dd, J = 3.1, 9.0 Hz, 1 H, 5-H), 3.64–3.76 (m, 2 H, 1-H, 7-H), 2.40–2.45 (m, 2 H), 2.28–2.33 (m, 1 H), 1.84–1.90 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 138.2, 137.4, 136.6, 128.6, 128.5, 128.1, 128.0, 127.8, 127.6, 124.7, 79.4, 74.0, 72.7, 71.3, 70.9, 37.1, 31.0 ppm. $C_{21}H_{24}O_3$ (324.42): calcd. C 77.75, H 7.46; found C 77.68, H 7.36.

(1*R,5*R**,6*S**,7*S**)-5,7-Bis(benzyloxy)-6-chlorocyclohept-3-enol (9a):** Compound **9a** was afforded from alkene **2a** according to general method A. Yield: 72 mg (67%); pale-yellow oil; R_f = 0.55 (Et_2O/hexanes = 3:2). ^{1}H NMR ($CDCl_3$): δ = 7.30–7.45 (m, 10 H, 2 Ph), 5.90–5.95 (m, 1 H, 4-H), 5.82–5.86 (m, 1 H, 3-H), 5.06 (d, J = 11.1 Hz, 1 H, CH_2Ph), 4.70 (d, J = 11.1 Hz, 1 H, CH_2Ph), 4.68 (s, 2 H, CH_2Ph), 4.25 (t, J = 6.8 Hz, 1 H, 6-H), 4.17 (dd, J = 4.6, 7.6 Hz, 1 H, 5-H), 3.89 (t, J = 9.9 Hz, 1 H, 1-H), 3.60–3.64 (m, 1 H, 7-H), 2.49–2.56 (m, 1 H, 2-H), 2.24–2.32 (m, 1 H, 2-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 137.8, 137.7, 130.8, 129.6, 128.7, 128.4, 128.2, 128.1, 127.9, 127.8, 89.9, 76.7, 75.3, 72.0, 70.7, 64.0, 32.1 ppm. $C_{21}H_{23}ClO_3$ (358.86): calcd. C 70.29, H 6.46; found C 70.32, H 6.45.

(1*R,5*S**,6*S**,7*S**)-5,7-Bis(benzyloxy)-6-chlorocyclohept-3-enol (9b):** Compound **9b** was afforded according to general method A from alkene **2b** as a 1:1 mixture with compound **9c** in a yield of 52 mg (49%). Isolated yield: 17 mg (15%) after repeated column chromatography; pale-yellow oil; R_f = 0.55 (Et_2O/hexanes = 1:1). ^{1}H NMR ($CDCl_3$): δ = 7.30–7.42 (m, 10 H, 2 Ph), 5.88 (dt, J = 5.1, 11.4 Hz, 1 H, 4-H), 5.79–5.83 (m, 1 H, 3-H), 4.82 (d, J = 11.1 Hz, 1 H, CH_2Ph), 4.72 (d, J = 11.9 Hz, 1 H, CH_2Ph), 4.66 (d, J = 11.1 Hz, 1 H, CH_2Ph), 4.62 (d, J = 11.9 Hz, 1 H, CH_2Ph), 4.47 (d, J = 5.1 Hz, 1 H, 5-H), 4.27 (dd, J = 1.0, 6.0 Hz, 1 H, 6-H), 3.96 (t, J = 6.0 Hz, 1 H, 7-H), 3.78–3.84 (m, 1 H, 1-H), 3.18 (s, 1 H, OH), 2.55–2.63 (m, 1 H, 2-H), 2.46 (dd, J = 5.3, 15.2 Hz, 1 H, 2-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 137.3, 137.2, 134.1, 129.7, 128.6, 128.5, 128.2, 128.1, 127.8, 127.7, 87.4, 81.3, 74.2, 70.9, 69.2, 61.4, 32.2 ppm. $C_{21}H_{23}ClO_3$ (358.86): calcd. C 70.29, H 6.46; found C 70.15, H 6.58.

(1*R,5*R**,6*S**,7*R**)-5,7-Bis(benzyloxy)-6-chlorocyclohept-3-enol (9c):** Compound **9c** was afforded according to general method A from alkene **2b** as a 1:1 mixture with compound **9b** in a yield of 52 mg (49%). Isolated yield: 16 mg (14%) after repeated column chromatography; pale-yellow oil; R_f = 0.50 (Et_2O/hexanes = 1:1). ^{1}H NMR ($CDCl_3$): δ = 7.30–7.41 (m, 10 H, 2 Ph), 5.82–5.87 (m, 1 H, 4-H), 5.74–5.81 (m, 1 H, 3-H), 5.09 (d, J = 11.5 Hz, 1 H, CH_2Ph), 4.82 (d, J = 11.5 Hz, 1 H, CH_2Ph), 4.68 (d, J = 11.6 Hz, 1 H, CH_2Ph), 4.64 (d, J = 11.6 Hz, 1 H, CH_2Ph), 4.48 (br. d, J =

9.6 Hz, 1 H, 5-H), 4.27 (s, 1 H, OH), 4.21 (dd, J = 1.3, 9.6 Hz, 1 H, 6-H), 3.64–3.79 (m, 2 H, 1-H, 7-H), 2.61–2.69 (m, 1 H, 2-H), 2.15 (dd, J = 7.3, 15.2 Hz, 1 H, 2-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 137.7, 137.6, 132.3, 131.2, 128.7, 128.4, 128.3, 128.2, 127.9, 127.8, 83.6, 77.4, 74.5, 70.7, 69.0, 62.4, 32.1 ppm. $C_{21}H_{23}ClO_3$ (358.86): calcd. C 70.29, H 6.46; found C 70.22, H 6.56.

(1*R,5*R**,6*R**,7*R**)-5,7-Bis(benzyloxy)-6-methylcyclohept-3-enol (10):** Compound **10** was afforded from alkene **3** according to general method A. Yield: 71 mg (70%); pale-yellow oil; R_f = 0.50 (Et_2O/hexanes = 3:2). ^{1}H NMR ($CDCl_3$): δ = 7.30–7.41 (m, 10 H, 2 Ph), 5.78–5.82 (m, 2 H, 3-H, 4-H), 4.73 (d, J = 11.2 Hz, 1 H, CH_2Ph), 4.63 (d, J = 12.0 Hz, 1 H, CH_2Ph), 4.52 (d, J = 12.0 Hz, 1 H, CH_2Ph), 4.44 (d, J = 11.2 Hz, 1 H, CH_2Ph), 4.19–4.22 (m, 1 H, 5-H), 3.55 (ddd, J = 2.8, 9.2, 11.5 Hz, 1 H, 1-H), 3.33 (dd, J = 4.4, 9.2 Hz, 1 H, 7-H), 2.63–2.70 (m, 1 H, 2-H), 2.38–2.44 (m, 1 H, 2-H), 2.02–2.10 (m, 1 H, 6-H), 1.00 (d, J = 7.1 Hz, 3 H, CH_3) ppm. ^{13}C NMR ($CDCl_3$): δ = 138.4, 137.9, 136.0, 128.6, 128.4, 128.0, 127.6, 127.5, 127.0, 124.6, 87.1, 77.8, 71.0, 70.9, 66.3, 36.9, 31.4, 7.7 ppm. $C_{22}H_{26}O_3$ (338.45): calcd. C 78.07, H 7.74; found C 78.15, H 7.78.

General Method B – Phosphorylation of Alcohols: 1*H*-Tetrazole (63 mg, 0.9 mmol, 2.0 mL of a 0.45 M solution in CH_3CN) and dibenzyl diisopropylphosphoramidite (200 μL, 0.6 mmol) were added to a solution of the corresponding alcohol (0.30 mmol) in CH_2Cl_2 (3.0 mL) at room temperature and the mixture was stirred for 12 h. The solution was cooled (0 °C) and NaH_2PO_4 (132 mg, 1.1 mmol) and *m*-CPBA (155 mg, 0.9 mmol) were added. The reaction mixture was then stirred at room temperature for 2 h and then diluted with CH_2Cl_2, quenched with saturated aqueous Na_2SO_3, and washed with saturated aqueous $NaHCO_3$ followed by 1 N HCl. The organic phase was neutralized with saturated aqueous $NaHCO_3$ and dried with Na_2SO_4. The solvent was evaporated and the residue was purified through a column of silica gel (gradient elution with 10–30% of EtOAc in CH_2Cl_2) to give protected phosphates as viscous oils.

Dibenzyl (1*R,5*S**,7*R**)-5,7-Bis(benzyloxy)cyclohept-3-enyl Phosphate (14):** Compound **14** was afforded from alcohol **5a** according to general method B. Yield: 140 mg (80%); pale-yellow oil; R_f = 0.40 (Et_2O/hexanes = 2:1). ^{1}H NMR ($CDCl_3$): δ = 7.26–7.39 (m, 20 H, 4 Ph), 6.02 (br. d, J = 11.1 Hz, 1 H, 4-H), 5.57–5.64 (m, 1 H, 3-H), 5.01–5.06 (m, 4 H, 2 CH_2Ph), 4.65 (s, 2 H, CH_2Ph), 4.57 (d, J = 11.9 Hz, 1 H, CH_2Ph), 4.50 (d, J = 11.9 Hz, 1 H, CH_2Ph), 4.30–4.37 (m, 1 H, 1-H), 4.07 (br. d, J = 10.7 Hz, 1 H, 5-H), 3.56–3.62 (m, 1 H, 7-H), 2.62–2.68 (m, 1 H), 2.27–2.38 (m, 2 H), 1.79–1.88 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 138.5, 138.2, 138.1, 136.1, 136.0, 128.6, 128.5, 128.4, 128.3, 128.2, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 127.4, 123.2, 81.0 (d, J_{CP} = 7.3 Hz), 79.0 (d, J_{CP} = 5.9 Hz), 73.4, 72.1, 70.7, 69.2 (d, J_{CP} = 11.7 Hz), 69.1, 37.5, 30.7 ppm. ^{31}P NMR ($CDCl_3$): δ = –1.9 ppm. $C_{35}H_{37}O_6P$ (584.65): calcd. C 71.90, H 6.38; found C 72.05, H 6.36.

Dibenzyl (1*R,2*S**,4*R**,5*R**,7*S**)-5,7-Bis(benzyloxy)cycloheptane-1,2,4-triyl Triphosphate (21):** Compound **21** was afforded from triol **18** according to general method B. Yield: 246 mg (72%); pale-yellow oil; R_f = 0.43 (Et_2O). ^{1}H NMR ($CDCl_3$): δ = 7.20–7.42 (m, 40 H, 8 Ph), 4.90–5.04 (m, 13 H, 6 CH_2Ph, 1-H), 4.76 (t, J = 7.7 Hz, 1 H, 4-H), 4.62–4.69 (m, 1 H, 2-H), 4.41–4.55 (m, 4 H, 2 CH_2Ph), 3.69–3.79 (m, 2 H, 5-H, 7-H), 2.40–2.48 (m, 1 H), 1.79–1.88 (m, 1 H), 1.65–1.75 (m, 1 H), 1.27–1.37 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 138.0, 137.9, 135.9, 135.8, 128.6, 128.5, 128.4, 128.3, 128.2, 128.0, 127.9, 127.8, 127.7, 127.6, 77.6 (dd, J_{CP} = 5.1, 9.5 Hz), 75.0 (t, J_{CP} = 8.0 Hz), 71.9 (d, J_{CP} = 8.8 Hz), 69.1–69.5 (m), 32.9, 28.7 (some signals in the aromatic region are not resolved) ppm. ^{31}P NMR ($CDCl_3$): δ = –1.4, –1.6, –1.7 ppm. $C_{63}H_{65}O_{14}P_3$ (1139.12): calcd. C 66.43, H 5.75; found C 66.38, H 5.79.

General Method C. *syn*-Dihydroxylation of Alkenes with NMO and OsO_4: An *O*-benzyl-protected alkene (0.30 mmol) was dissolved in acetone (5 mL) and water (2 mL), OsO_4 (0.01 mmol, 0.25 mL of a 2.5 wt.-% solution in *t*BuOH), and NMO (200 mg, 1.50 mmol) were added. The mixture was stirred at room temperature for 48 h and an aqueous solution of Na_2SO_3 (10 wt.-%, 10 mL) was added. Acetone was removed from the resulting mixture by evaporation under reduced pressure and the residue was extracted with EtOAc. The organic phase was washed with brine (10 mL), dried (Na_2SO_4), and concentrated. The *syn*-diols were purified by flash chromatography on silica gel (gradient elution with 10–50% EtOAc in CH_2Cl_2).

Dibenzyl (1*R,2*R**,4*S**,5*S**,6*S**)-2,4-Bis(benzyloxy)-5,6-dihydroxycycloheptyl Phosphate (16a):** Compound **16a** was afforded from alkene **14** according to general method C. Yield: 96 mg (52%); white viscous oil; R_f = 0.50 (Et_2O/acetone = 4:1). ^{1}H NMR ($CDCl_3$): δ = 7.21–7.38 (m, 20 H, 4 Ph), 4.98–5.05 (m, 4 H, 2 CH_2Ph), 4.60–4.67 (m, 1 H, 1-H), 4.53–4.60 (m, 3 H, CH_2Ph), 4.43 (d, J = 11.5 Hz, 1 H, CH_2Ph), 4.06 (br. d, J = 7.7 Hz, 1 H, 4-H), 3.71–3.78 (m, 1 H, 2-H), 3.62 (dd, J = 2.9, 7.7 Hz, 1 H, 5-H), 3.53–3.58 (m, 1 H, 6-H), 2.15 (br. d, J = 14.9 Hz, 1 H), 1.98 (dd, J = 4.2, 15.5 Hz, 1 H), 1.67 (ddd, J = 9.7, 14.9, 19.5 Hz, 1 H), 0.89–0.96 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 138.2, 138.0, 135.7, 135.6, 128.6, 128.5, 128.4, 128.3, 128.2, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 127.4, 80.4 (d, J_{CP} = 6.6 Hz), 79.8 (d, J_{CP} = 8.8 Hz), 78.3, 76.3, 72.3, 69.2 (d, J_{CP} = 8.7 Hz), 69.1, 68.2, 34.0, 30.3 ppm. ^{31}P NMR ($CDCl_3$): δ = –1.8 ppm. $C_{35}H_{39}O_8P$ (618.66): calcd. C 67.95, H 6.35; found C 67.86, H 6.30.

(1*S,2*S**,4*R**,5*R**,7*S**)-5,7-Bis(benzyloxy)cycloheptane-1,2,4-triol (18):** Compound **18** was afforded from alkene **5a** according to general method C. Yield: 81 mg (75%); pale-yellow oil; R_f = 0.45 (Et_2O/acetone = 5:1). ^{1}H NMR ($CDCl_3$): δ = 7.30–7.42 (m, 10 H, 2 Ph), 4.65 (d, J = 11.5 Hz, 1 H, CH_2Ph), 4.63 (d, J = 11.6 Hz, 1 H, CH_2Ph), 4.60 (d, J = 11.6 Hz, 1 H, CH_2Ph), 4.48 (d, J = 11.5 Hz, 1 H, CH_2Ph), 4.18 (d, J = 8.5 Hz, 1 H, 7-H), 3.84–3.91 (m, 1 H, 5-H), 3.54–3.62 (m, 3 H, 1-H, 2-H, 4-H), 3.33 (br. s, 1 H, OH), 3.17 (br. s, 1 H, OH), 3.09 (br. s, 1 H, OH), 2.24–2.29 (m, 1 H, 3-H), 2.15 (ddd, J = 6.1, 8.6, 14.8 Hz, 1 H, 3-H), 1.91–1.96 (m, 1 H, 6-H), 1.56–1.65 (m, 1 H, 6-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 138.3, 137.9, 128.7, 128.6, 128.1, 128.0, 127.9, 127.8, 82.1, 78.2, 77.1, 73.6, 71.8, 71.6, 69.3, 33.5, 31.7 ppm. $C_{21}H_{26}O_5$ (358.43): calcd. C 70.37, H 7.31; found C 70.44, H 7.38.

(1*S,2*S**,4*R**,5*S**,6*R**,7*R**)-5,7-Bis(benzyloxy)-6-chlorocycloheptane-1,2,4-triol (19):** Compound **19** was afforded from alkene **9a** according to general method C. Yield: 85 mg (72%), pale-yellow oil; R_f = 0.55 (Et_2O/acetone = 5:1). ^{1}H NMR ($CDCl_3$): δ = 7.31–7.42 (m, 10 H, 2 Ph), 5.00 (d, J = 10.9 Hz, 1 H, CH_2Ph), 4.92 (d, J = 11.0 Hz, 1 H, CH_2Ph), 4.62–4.65 (m, 2 H, CH_2Ph), 4.18–4.26 (m, 3 H, 5-H, 6-H, 7-H), 3.93–4.00 (m, 2 H, 1-H, 4-H), 3.78 (d, J = 6.5 Hz, 1 H, 2-H), 2.20 (ddd, J = 1.9, 4.9, 14.3 Hz, 1 H, 3-H), 2.01–2.08 (m, 1 H, 3-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 137.5, 137.3, 128.7, 128.6, 128.3, 128.2, 128.1, 128.0, 86.2, 80.3, 75.4, 74.7, 73.3, 69.2, 68.4, 65.7, 33.0 ppm. $C_{21}H_{25}ClO_5$ (392.88): calcd. C 64.20, H 6.41; found C 64.32, H 6.53.

(1*S,2*S**,4*R**,5*R**,6*S**,7*S**)-5,7-Bis(benzyloxy)-6-methylcycloheptane-1,2,4-triol (20):** Compound **20** was afforded from alkene **10** according to general method C. Yield: 95 mg (78%); pale-yellow oil; R_f = 0.50 (Et_2O/acetone = 5:1). ^{1}H NMR ($CDCl_3$): δ = 7.29–7.41 (m, 10 H, 2 Ph), 4.59–4.63 (m, 2 H, CH_2Ph), 4.56 (d, J = 11.5 Hz, 1 H, CH_2Ph), 4.44 (d, J = 11.5 Hz, 1 H, CH_2Ph), 4.17 (dt, J = 2.5,

8.1 Hz, 1 H, 7-H), 3.86 (ddd, J = 5.1, 8.1, 10.1 Hz, 1 H, 5-H), 3.56–3.66 (m, 3 H, 1-H, 2-H, 4-H), 2.54–2.61 (m, 1 H, 6-H), 2.00–2.15 (m, 2 H, 3-H), 1.00 (d, J = 7.3 Hz, 3 H, CH_3) ppm. ^{13}C NMR ($CDCl_3$): δ = 138.4, 138.0, 128.6, 128.6, 128.1, 127.9, 127.8, 127.7, 85.1, 81.1, 73.6, 72.2, 71.9, 70.7, 69.2, 34.9, 33.0, 7.7 ppm. $C_{22}H_{28}O_5$ (372.46): calcd. C 70.94, H 7.58; found C 70.84, H 7.65.

General Method D. Global Deprotection of the $InsP_1$ and $InsP_3$ Analogues: 20% Pd/C (25 mg) was added to a solution of the protected phosphate (0.15 mmol) in MeOH (3.0 mL) and H_2 was bubbled through the mixture for 14 h at room temperature. The solution was then filtered through a pad of Celite and the filtrate concentrated to give the deprotected phosphates as syrups.

(1*R,2*R**,4*R**)-2,4-Dihydroxycycloheptyl Dihydrogen Phosphate (15):** Compound **15** was afforded from phosphate **14** according to general procedure D. Yield: 33 mg (98%). ^{1}H NMR ([D$_6$]DMSO/D_2O, 3:1): δ = 4.42–4.50 (m, 1 H, 1-H), 3.76–3.84 (m, 1 H, 2-H), 3.43–3.51 (m, 1 H, 4-H), 1.90–2.01 (m, 2 H), 1.65–1.73 (m, 1 H), 1.22–1.38 (m, 4 H), 0.95–1.02 (m, 1 H) ppm. ^{13}C NMR ([D$_6$]-DMSO/D_2O, 3:1): δ = 75.8 (d, J_{CP} = 7.8 Hz), 67.3, 66.3 (d, J_{CP} = 6.1 Hz), 37.4, 34.0, 30.9 (d, J_{CP} = 3.9 Hz), 21.8 ppm. ^{31}P NMR ($CDCl_3$): δ = –2.3 ppm. $C_7H_{15}O_6P$ (226.17): calcd. C 37.17, H 6.69; found C 37.35, H 6.56.

(1*R,2*R**,4*S**,5*R**,6*S**)-2,4,5,6-Tetrahydroxycycloheptyl Dihydrogen Phosphate (17):** Compound **17** was afforded from phosphate **16** according to general procedure D. Yield: 38 mg (98%). ^{1}H NMR ([D$_6$]DMSO/D_2O, 2:1): δ = 4.87–4.94 (m, 1 H, 1-H), 3.99–4.07 (m, 1 H, 5-H), 3.41–3.58 (m, 3 H, 2-H, 4-H, 6-H), 1.81–1.94 (m, 2 H), 1.39–1.51 (m, 1 H), 1.11–1.20 (m, 1 H) ppm. ^{13}C NMR ([D$_6$]DMSO/D_2O, 2:1): δ = 79.8, 76.1 (d, J_{CP} = 7.4 Hz), 69.7, 67.6 (d, J_{CP} = 8.1 Hz), 66.1, 35.1, 31.3 ppm. ^{31}P NMR ($CDCl_3$): δ = –3.2 ppm. $C_7H_{15}O_8P$ (258.16): calcd. C 32.57, H 5.86; found C 32.42, H 6.02.

(1*R,2*S**,4*R**,5*R**,7*S**)-5,7-Dihydroxycycloheptane-1,2,4-triyl Tris(dihydrogen phosphate) (22):** Compound **22** was afforded from phosphate **21** according to general procedure D. Yield: 61 mg (98%). ^{1}H NMR ([D$_6$]DMSO/D_2O, 1:1): δ = 4.50–4.59 (m, 1 H, 4-H), 4.33–4.43 (m, 1 H, 1-H), 3.99–4.10 (m, 1 H, 3-H), 3.63–3.77 (m, 2 H, 5-H, 7-H), 1.75–1.88 (m, 1 H), 1.35–1.52 (m, 2 H), 1.11–1.21 (m, 1 H) ppm. ^{13}C NMR ([D$_6$]DMSO/D_2O, 1:1): δ = 77.4 (dd, J_{CP} = 5.2, 9.7 Hz), 75.1 (t, J_{CP} = 8.0 Hz), 71.9 (d, J_{CP} = 8.2 Hz), 70.1 (t, J_{CP} = 7.1 Hz), 69.1 (d, J_{CP} = 7.3 Hz), 32.8, 28.9 ppm. ^{31}P NMR ($CDCl_3$): δ = 0.2, 0.4, 0.7 ppm. $C_7H_{17}O_{14}P_3$ (418.12): calcd. C 20.11, H 4.10; found C 20.02, H 4.20.

Biological Assay: The colorimetric assay according to Itaya et al. was applied to test the phosphate compounds **15** and **17** as inhibitors of IMPase.[18] Inositol monophosphatase from Bovine brain was used. The rate determinations were performed at 37.8 °C in triplicate in assay buffer A containing KCl (300 mmol dm^{-3}), $MgCl_2$ (2 mmol dm^{-3}), and Tris·HCl (50 mmol dm^{-3}) at pH 7.8. The colorimetric assay reagent malachite green (1.5 g) was dissolved in hydrochloric acid (5 mol dm^{-3}; 25 cm^3) and diluted with water (750 cm^3). Ammonium molybdate (10.5 g) in hydrochloric acid (5 mol dm^{-3}; 225 cm^3) was added to this solution, which was stirred at room temperature for 10 min. The solution was filtered by gravity and stored in the dark. Incubation samples were composed of assay buffer A (210 mm^3), substrate ($InsP_1$) at various concentrations in assay buffer (30 mm^3), inhibitor at various concentrations in assay buffer [30 mm^3; in the absence of an inhibitor, this addition was substituted by assay buffer (30 mm^3)] and enzyme solution (30 mm^3). The assay solutions were incubated at 37.8 °C and the reaction was quenched by the addition of colorimetric assay reagent (2.0 cm^3) at the required time (relative to the addition of the enzyme solution). The color was allowed to develop over a period of 30 min and the absorbance at 660 nm was measured in a cuvette with a pathlength of 10 mm. Phosphate concentrations were determined by comparison of the absorbance value with a preconstructed standard curve prepared with known phosphate concentrations. IC_{50} values of 0.8 μM for compound **15** and 13 μM for compound **17** were obtained.

(1*S,2*S**,4*R**,5*R**,6*R**)-2,4-Bis(benzyloxy)-8-oxabicyclo[3.2.1]-octan-6-ol (13):** A 1.0 M DIBAL-H solution in hexane (0.26 mL, 0.26 mmol) was added to alkene **1a** (0.30 mmol) and [Ni(acac)$_2$] (4.3 mg, 0.024 mmol) in toluene (3.0 mL) at room temperature. After 15 min, when the starting material had been consumed, air was bubbled through the dark-brown solution for 5 h. The reaction mixture was worked up by adding an aqueous saturated NH_4Cl solution and then 10% H_2SO_4 was added to make the aqueous layer transparent. The aqueous layer was extracted with Et_2O (3 × 10 mL) and the combined organics were dried with Na_2SO_4. The volatiles were removed under reduced pressure and the residue purified by flash chromatography with 10–30% Et_2O in hexanes to afford alcohol **13** as a pale-yellow oil. Yield: 63 mg (62%); R_f = 0.45 (Et_2O/hexanes = 2:1). ^{1}H NMR ($CDCl_3$): δ = 7.29–7.40 (m, 10 H, 2 Ph), 4.60 (d, J = 11.9 Hz, 1 H, CH_2Ph), 4.57 (d, J = 11.9 Hz, 1 H, CH_2Ph), 4.54 (d, J = 11.6 Hz, 1 H, CH_2Ph), 4.51 (d, J = 11.6 Hz, 1 H, CH_2Ph), 4.46–4.50 (m, 2 H, 1-H, 5-H), 4.10 (d, J = 4.4 Hz, 1 H, 6-H), 3.50–3.56 (m, 2 H, 2-H, 4-H), 2.51 (dd, J = 7.8, 14.1 Hz, 1 H, 7-H), 2.35 (dd, J = 5.7, 11.6 Hz, 1 H, 3-H), 2.08 (br. s, 1 H, OH), 1.75–1.81 (m, 1 H, 7-H), 1.14–1.23 (m, 1 H, 3-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 138.3, 138.2, 128.5, 128.4, 127.9, 127.8, 127.7, 127.6, 83.6, 76.2, 73.1, 72.3, 71.4, 71.0, 70.8, 36.2, 30.9 ppm. $C_{21}H_{24}O_4$ (340.42): calcd. C 74.09, H 7.11; found C 73.94, H 7.20.

Supporting Information (see footnote on the first page of this article): ^{1}H, ^{13}C, and ^{31}P NMR spectra of all new compounds and experimental data for compounds **4a**, **4b**, **6**–**8**, **11a**, **11b**, and **12**.

Acknowledgments

We are grateful to the Russian Foundation for Basic Research (Project No. 11-03-00641/12) and the Council on Grants of the President of the Russian Federation (Program for State Support of Leading Scientific Schools of the Russian Federation, Grant 16.120.11.6464-NSH) for financial support.

[1] a) D. C. Billington, *The Inositol Phosphates: Chemical Synthesis and Biological Significance*, VCH Verlagsgesellschaft, Weinheim, Germany, **1993**; b) B. V. L. Potter, D. Lampe, *Angew. Chem.* **1995**, *107*, 2085; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1933–1972; c) R. F. Irvine, M. J. Schell, *Nature Rev. Mol. Cell Biol.* **2001**, *2*, 327–338; d) S. J. Conway, G. J. Miller, *Nat. Prod. Rep.* **2007**, *24*, 687–707; e) M. J. Berridge, *Biochim. Biophys. Acta Mol. Cell Res.* **2009**, *1793*, 933–940; f) J. Duchek, D. R. Adams, T. Hudlicky, *Chem. Rev.* **2011**, *111*, 4223–4258.

[2] a) Y. Chapleur (Ed.), *Carbohydrate Mimics: Concepts and Methods*, Wiley-VCH, Weinheim, Germany, **1998**; b) N. Asano, R. Nash, R. Molyneux, G. Fleet, *Tetrahedron: Asymmetry* **2000**, *11*, 1645–1680; c) E. J. Chenette, *Nat. Rev. Mol. Cell Biol.* **2009**, *10*, 238–239.

[3] O. Arjona, A. M. Gomez, J. C. Lopez, J. Plumet, *Chem. Rev.* **2007**, *107*, 1919–2036.

[4] a) J. Marco-Contelles, E. Opazo, *J. Org. Chem.* **2000**, *65*, 5416–5419; b) F. D. Boyer, I. Hanna, L. Ricard, *Org. Lett.* **2001**, *3*, 3095–3098; c) Y. Bleriot, A. Girault, J. M. Mallet, E. Rodriguez, P. Vogel, P. Sinay, *Tetrahedron: Asymmetry* **2002**, *13*, 2553–2566; d) J. Marco-Contelles, E. Opazo, *J. Org. Chem.* **2002**, *67*, 3705–3717; e) P. R. Skaanderup, R. J. Madsen, *J. Org. Chem.*

2003, *68*, 2115–2122; f) O. Andriuzzi, C. Gravier-Pelletier, P. Vogel, Y. Le Merrer, *Tetrahedron* **2005**, *61*, 7094–7104; g) C. Ramana, S. Chaudhuri, M. Gurjar, *Synthesis* **2007**, 523–528.

[5] a) R. Patra, N. Bar, A. Roy, B. Achari, N. Ghoshal, S. Mandal, *Tetrahedron* **1996**, *52*, 11265–11272; b) A. Roy, K. Chakrabarty, P. Dutta, N. Bar, N. Basu, B. Achari, S. Mandal, *J. Org. Chem.* **1999**, *64*, 2304–2309; c) J. Marco-Contelles, E. Opazo, *J. Carbohydr. Chem.* **2002**, *21*, 201–218; d) T. Shing, W. Wong, T. Ikeno, T. Yamada, *Org. Lett.* **2007**, *9*, 207–209; e) T. Shing, W. Wong, T. Ikeno, T. Yamada, *Chem. Eur. J.* **2009**, *15*, 2693–2707.

[6] a) I. Dyong, R. Bonn, *Chem. Ber.* **1973**, *106*, 944–955; b) K. Krohn, G. J. Boerner, *Org. Chem.* **1994**, *59*, 6063–6068; c) C. Gravier-Pelletier, W. Maton, T. Dintinger, C. Tellier, Y. Le Merrer, *Tetrahedron* **2003**, *59*, 8705–8720; d) Y. L. Chen, H. Redlich, K. Bergander, R. Frohlich, *Org. Biomol. Chem.* **2007**, *5*, 3330–3339.

[7] a) H. Redlich, W. Sudau, A. Szardenings, R. Vollerthun, *Carbohydr. Res.* **1992**, *226*, 57–78; b) L. Yet, *Tetrahedron* **1999**, *55*, 9349–9403; c) J. Marco-Contelles, E. Opazo, *Tetrahedron Lett.* **2000**, *41*, 5341–5346.

[8] a) C. Rucker, W. Seppelt, H. Fritz, H. Prinzbach, *Chem. Ber.* **1984**, *117*, 1801–1833; b) W. Seppelt, C. Rucker, C. Kaiser, H. Prinzbach, *Chem. Ber.* **1984**, *117*, 1834–1855; c) C. Johnson, A. Golebiowski, D. Steensma, *J. Am. Chem. Soc.* **1992**, *114*, 9414–9418; d) A. Pearson, K. Srinivasan, *J. Org. Chem.* **1992**, *57*, 3965–3973; e) J. Soulie, T. Faitg, J. Betzer, J. Lallemand, *Tetrahedron* **1996**, *52*, 15137–15146; f) M. Falk-Heppner, U. Hugger, M. Keller, C. Kaiser, R. Krieger, H. Fritz, H. Prinzbach, *Liebigs Ann./Recueil* **1997**, 1481–1498; g) A. Pearson, S. Katiyar, *Tetrahedron* **2000**, *56*, 2297–2304.

[9] a) H. Johnson, N. Thomas, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 237–241; b) S. Pino-Gonzalez, C. Assiego, N. Onas, *Targ. Heterocycl. Syst.* **2004**, *8*, 364–397; c) K. Martınez-Mayorga, J. L. Medina-Franco, S. Mari, F. J. Canada, E. Rodrıguez-Garcıa, P. Vogel, H. Li, Y. Bleriot, P. Sinay, J. Jimenez-Barbero, *Eur. J. Org. Chem.* **2004**, 4119–4129; d) F. Marcelo, Y. He, S. A. Yuzwa, L. Nieto, J. Jimenez-Barbero, M. Sollogoub, D. J. Vocadlo, G. D. Davies, Y. Bleriot, *J. Am. Chem. Soc.* **2009**, *131*, 5390–5392; e) J. Perez-Castells, M. Fontanella, A. Arda, F. J. Canada, M. Sollogoub, Y. Blériot, J. Jimenez-Barbero, *New J. Chem.* **2012**, *36*, 1008–1013.

[10] a) X. H. Qian, F. Moris-Varas, M. C. Fitzgerald, C. H. Wong, *Bioorg. Med. Chem.* **1996**, *4*, 2055–2069; b) Y. Le Merrer, L. Poitout, J. Depazy, I. Dosbaa, S. Geoffroy, M. Foglietti, *Bioorg. Med. Chem.* **1997**, *5*, 519–533; c) G. F. Painter, P. J. Eldridge, A. Falshaw, *Bioorg. Med. Chem.* **2004**, *12*, 225–232; d) H. Li, Y. Bleriot, C. Chantereau, J. M. Mallet, M. Sollogoub, Y. Zhang, E. Rodriguez-Garcia, P. Vogel, J. Jimenez-Barbero, P. Sinay, *Org. Biomol. Chem.* **2004**, *2*, 1492–1499; e) H. Li, C. Schutz, S. Favre, Y. Zhang, P. Vogel, P. Sinay, Y. Bleriot, *Org. Biomol. Chem.* **2006**, *4*, 1653–1662; f) H. Li, T. Liu, Y. Zhang, S. Favre, C. Bello, P. Vogel, T. Butters, N. Oikonomakos, J. Marrot, Y. Bleriot, *ChemBioChem* **2008**, *9*, 253–260; g) H. Li, F. Marcelo, C. Bello, P. Vogel, T. Butters, A. Rauter, Y. Zhang, M. Sollogoub, Y. Bleriot, *Bioorg. Med. Chem.* **2009**, *17*, 5598–5604; h) N. B. Kalamkar, V. M. Kasture, S. T. Chavan, S. G. Sabharwal, D. D. Dhavale, *Tetrahedron* **2010**, *66*, 8522–8526.

[11] a) C. Fauroux, M. Lee, P. M. Cullis, K. T. Douglas, M. G. Gore, S. Freeman, *J. Med. Chem.* **2002**, *45*, 1363–1373; b) D. J. Miller, R. K. Allemann, *Mini-Rev. Med. Chem.* **2007**, *7*, 107–113.

[12] a) R. Baker, J. J. Kulagowski, D. C. Billington, P. D. Leeson, I. C. Lennon, N. J. Liverton, *J. Chem. Soc. Perkin Trans. 1* **1989**, 1383–1385; b) R. Baker, P. D. Leeson, N. J. Liverton, J. J. Kulagowski, *J. Chem. Soc., Chem. Commun.* **1990**, 462–464; c) R. Baker, C. Carrick, P. D. Leeson, I. C. Lennon, N. I. Liverton, *J. Chem. Soc., Chem. Commun.* **1991**, 298–300; d) C. M. J. Faroux, S. Freeman, *J. Enzyme Inhib.* **1999**, *14*, 97.

[13] M. J. Berridge, M. D. Bootman, H. L. Roderick, *Nat. Rev. Mol. Cell Biol.* **2003**, *4*, 517.

[14] a) M. Lautens, P. Chiu, *J. Am. Chem. Soc.* **1997**, *119*, 6478–6487; b) M. Lautens, T. Rovis, *J. Am. Chem. Soc.* **1997**, *119*, 11090–11091; c) P. Chiu, M. Lautens, *Top. Curr. Chem.* **1997**, *190*, 1–85.

[15] D. A. Khlevin, S. E. Sosonyuk, M. V. Proskurnina, N. S. Zefirov, *Tetrahedron* **2012**, *68*, 5785–5792.

[16] D. C. F. Law, S. W. Tobey, *J. Am. Chem. Soc.* **1968**, *90*, 2376–2386.

[17] K. L. Yu, B. Fraser-Reid, *Tetrahedron Lett.* **1988**, *29*, 979–982.

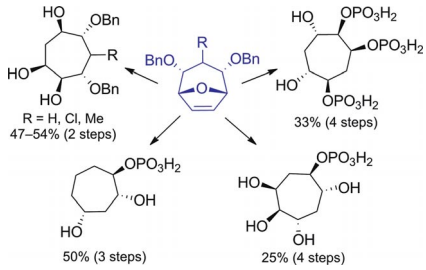
[18] K. Itaya, M. Ui, *Clin. Chim. Acta* **1966**, *14*, 361–366.

Received: October 26, 2012
Published Online: ■

EurJOC European Journal of Organic Chemistry

Oxabicyclic Carbasugars

New seven-membered cyclitols have been synthesized from 8-oxabicyclo[3.2.1]octenes by ring-opening followed by dihydroxylation. High enantioselectivity was observed with (*R*)-BINAP as ligand. The polyhydroxycycloheptanes thus prepared were phosphorylated to yield mono- and tris-phosphates, which can be considered as homoanalogues of inositol derivatives involved in the signal transduction pathway.



Keywords: Cyclitols / Carbasugars / Phosphorylation / Dihydroxylation / Inhibitors / Enantioselectivity

