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Effective synthesis of negatively charged cyclodextrins. Selective access to phosphate cyclodextrins

Óscar López [a,*], Mikael Bols [b,*]

[a] Departamento de Química Orgánica, Facultad de Química, Universidad de Sevilla, Apartado 1203, E-41071 Seville, Spain
[b] Department of Chemistry, University of Copenhagen, Universitetsparken 5, 2100 Kbh. Ø, Denmark

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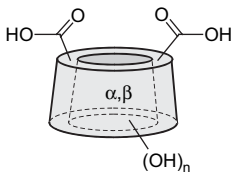
ABSTRACT

We report the selective preparation of α- and β-cyclodextrins bearing one and two phosphate moieties on the primary rim. These compounds were prepared by selective O-debenzylation of fully protected derivatives, followed by phosphorylation and deprotection. The synthesis of an α-cyclodextrin with both, a carboxylic group and a phosphate moiety on primary positions is also described. Title compounds are examples of negatively charged cyclodextrins that might be of interest in studying the complexation of cationic guests.

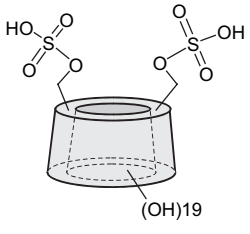
1. Introduction

Supramolecular chemistry is emerging as a challenging area in organic chemistry; the study of derivatives capable of establishing spontaneous non-covalent interactions is of great interest and has found many practical applications such as additives for food preservation,[1] drug delivery,[2,3] catalysis,[4,5] biomimetic recognition[6] and chiral separations.[7] In this context, cyclodextrins, cyclic oligosaccharides of six, seven or eight α-D-glucopyranose units are among the most important molecular hosts considered in supramolecular chemistry.[8] Numerous chemical[9–11] and enzymatic synthesis[8] of cyclodextrin derivatives have been reported so far; nevertheless, chemical modification of cyclodextrins is not a simple task due to the high number of hydroxyl groups present in these structures.

In this context, we have recently reported[12] the preparation of cyclodextrin-derived $6^A,6^D$-diacids **1** and **2**, as well as $6^A,6^D$-di-*O*-sulfate **3** as novel artificial enzymes, which accelerated the hydrolysis of aryl glycosides in a phosphate buffered medium up to 989 times.



1 n=16
2 n=19



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Reaction was shown to proceed faster when increasing the phosphate buffer concentration, and the proposed mechanism involves the cyclodextrin-mediated stabilization of the incipient positive charge in the transition state, followed by nucleophilic displacement of the aglycon by a phosphate molecule of the buffer.[12] This observation prompted us to prepare cyclodextrin derivatives bearing phosphate moieties in their structure, with the aim of studying the same hydrolysis reaction and to compare with isosteric carboxylic acid and sulfate derivatives **1**–**3** in order to determine whether the phosphate moiety can participate in the catalytic process. Thus, phosphorylated cyclodextrins might mimic the behaviour of phosphorylases, which catalyze the hydrolysis and/or transfer of glycosides through a phosphate group attached to pyridoxal.[13–16]

Furthermore, cyclodextrins incorporating ionizable groups represent an interesting family of maltooligosaccharides for complexing charged guests in aqueous media through attractive Coulombic interactions.[17] For instance, the use of a monophosphate cyclodextrin has been used by Cho et al.[18] for binding antineoplastic drugs and subsequent release of the guest upon phoshatase-mediated hydrolysis. Anionic cyclodextrins such as phosphates, carboxylates, sulfates or succinylates have been studied as additives for plant growth acceleration and for the release of essential nutrients.[19] Charged cyclodextrins also allow an improvement of the isolation of plant metabolites; in this context, strong non-covalent complexes between cyclodextrins and anticarcinogenic taxol and other taxanes have been reported, what led to higher amounts of the isolated product.[19]

2. Results and discussion

Ubiquitous organophosphorous derivatives are extremely important derivatives in biological systems and exhibit practical

* Corresponding authors.
E-mail addresses: osc-lopez@us.es (Ó. López), bols@kemi.ku.dk (M. Bols).

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applications such as chiral discriminators or membrane carriers;[20,21] however, reports on their use in supramolecular chemistry is relatively scarce. Breslow's group accomplished[22] the synthesis of the ammonium salt of β-cyclodextrin monophosphate by treatment of unprotected cyclodextrin with diphenylchlorophosphate; the corresponding phosphate ester was purified by a tedious series of crystallizations and hydrogenated under pressure to afford final compound in moderate yield. The same derivative was later re-studied[18] and partially characterized by Eliseev's group. Tarelli and co-workers described[23] treatment of α- and β-cyclodextrin with inorganic metaphosphate to afford a mixture of isomeric monophosphates on positions 2, 3 and 6, which were partially resolved by anion-exchange chromatography. Branched cyclodextrin triphosphates were prepared using either *cyclo*-mono-μ-imidotriphosphate (*c*-MITP)[24] or *cyclo*-triphosphate (P3m).[25] Liu et al. reported[26] the use of phosphoryl-tethered β-cyclodextrins as an enhancement of the chiral recognition ability of maltooligosaccharides. The use of cyclodextrin monophosphate esters for complexing aminoacids[27] and organic dyes[28] has also been reported.

We have synthesized cyclodextrins bearing two phosphate groups on primary positions starting from α- and β-cyclodextrins (Scheme 1); the starting materials are partially debenzylated cyclodextrins, which are accessed using a straightforward procedure, originally introduced by Sinaÿ's group for the selective and mild deprotection of benzylated[29] or methylated[30] derivatives. This procedure involves treatment of fully protected derivatives with DIBAL-H in anhydrous toluene; the original synthetic conditions were later optimized,[12,31–33] mainly by Sinaÿ's group in subsequent technical improvements. Selectively debenzylated cyclodextrins have been widely used in our group for the preparation of artificial enzymes based on cyclodextrins for catalyzing glycoside hydrolysis of amine oxidation.[12,34–43]

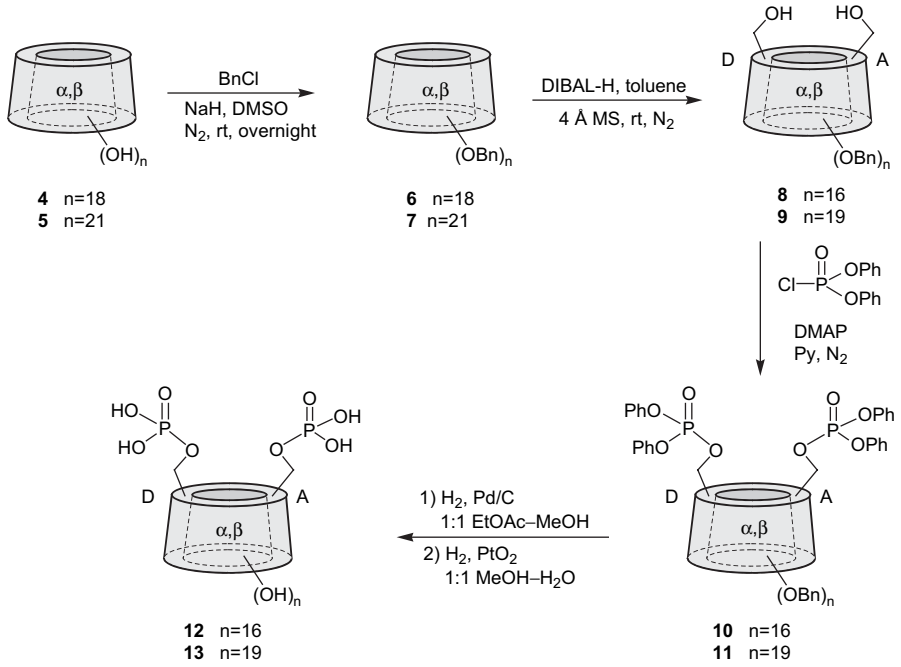
Initial attempts to transform diols **8** and **9** into the corresponding diphosphates using classical phosphate syntheses were unsuccessful; thus, reaction of α-cyclodextrin diol **8** with dibenzyl *N*,*N*-diisopropylamino phosphoramidate[44] in the presence of tetrazole, followed by oxidation with iodide resulted in decomposition to a mixture of more polar derivatives.

Nevertheless, DMAP-promoted phosphorylation of diols **8** and **9** with commercial chlorodiphenylphosphate in pyridine afforded diphosphorylated derivatives **10** and **11**, in 87% and 86% yields, respectively, after chromatography. The presence of the phosphate moiety was supported by NMR spectroscopy; ^{13}C NMR spectra of compounds **10** and **11** showed coupling between phosphorus and *ipso* carbons on aromatic phosphate ester residues with a $^{2}J_{P,C}$ of 4.0–6.5 Hz. ^{31}P NMR spectrum of α-cyclodextrin diphosphate **10** showed a singlet signal at −10.8 ppm; on the other hand, ^{31}P NMR spectrum of compound **11** showed two non-equivalent phosphate groups at −10.7 and −10.8 ppm.

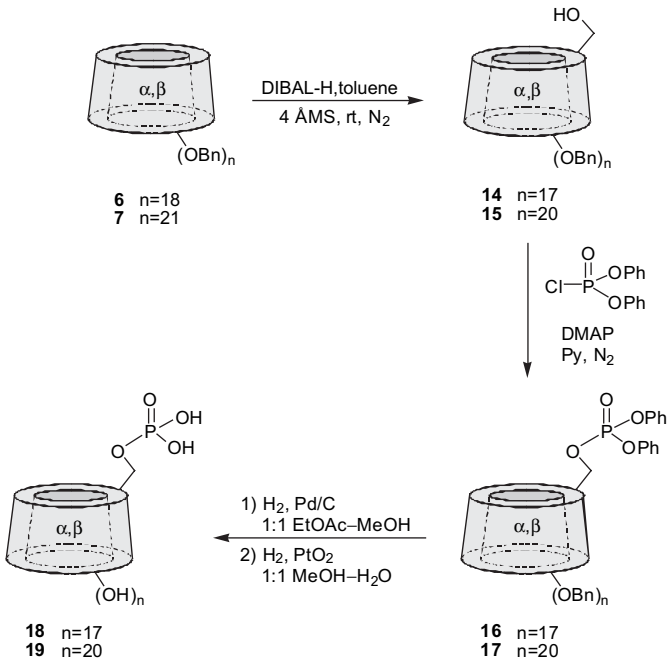
Phosphate esters could neither be deprotected under standard hydrogenation conditions nor basic hydrolysis. Fully unprotected derivatives **12** and **13** were achieved by first removal of the benzyl ether groups by Pd-catalyzed hydrogenation, followed by Pt-catalyzed hydrogenation at moderate pressure (20 atm). Filtration and removal of the solvents afforded pure **12** and **13** in 60% and 83% yields, respectively. ^{31}P NMR spectra of these cyclodextrin diphosphates showed a singlet signal at 1.7 and 1.3 ppm, respectively, in accordance with reported primary phosphate groups on carbohydrates.[18,45]

Following a similar procedure, we have also prepared cyclodextrin-derived monophosphates starting from α- and β-cyclodextrin (Scheme 2). Treatment of per-*O*-benzylated cyclodextrins **6** and **7** with fewer equivalents of DIBAL-H, and shorter reaction times afforded monodeprotected derivatives **14** and **15** that furnished protected monophosphates **16** and **17** upon reaction with chlorodiphenylphosphate, using the same conditions as indicated above. These compounds showed coupling between *ipso* aromatic carbons and phosphorous ($^{2}J_{P,C}$=6.5 Hz) and resonance at −10.7 ppm in ^{31}P NMR spectra. Standard hydrogenation, followed with Pt-catalyzed hydrogenation at 20 atm afforded fully unprotected derivatives **18** and **19** in 79% and 71% yields, respectively.

We also describe the preparation of an α-cyclodextrin derivative bearing a phosphate and a carboxylic acid moiety in the same molecule (Scheme 3). The key step for this synthesis is the monoprotection of α-cyclodextrin diol **8** with allyl bromide in the presence of ^{t}BuOK.[46] Derivative **20** was phosphorylated using the same conditions as indicated in Schemes 1 and 2; removal of



Scheme 1.

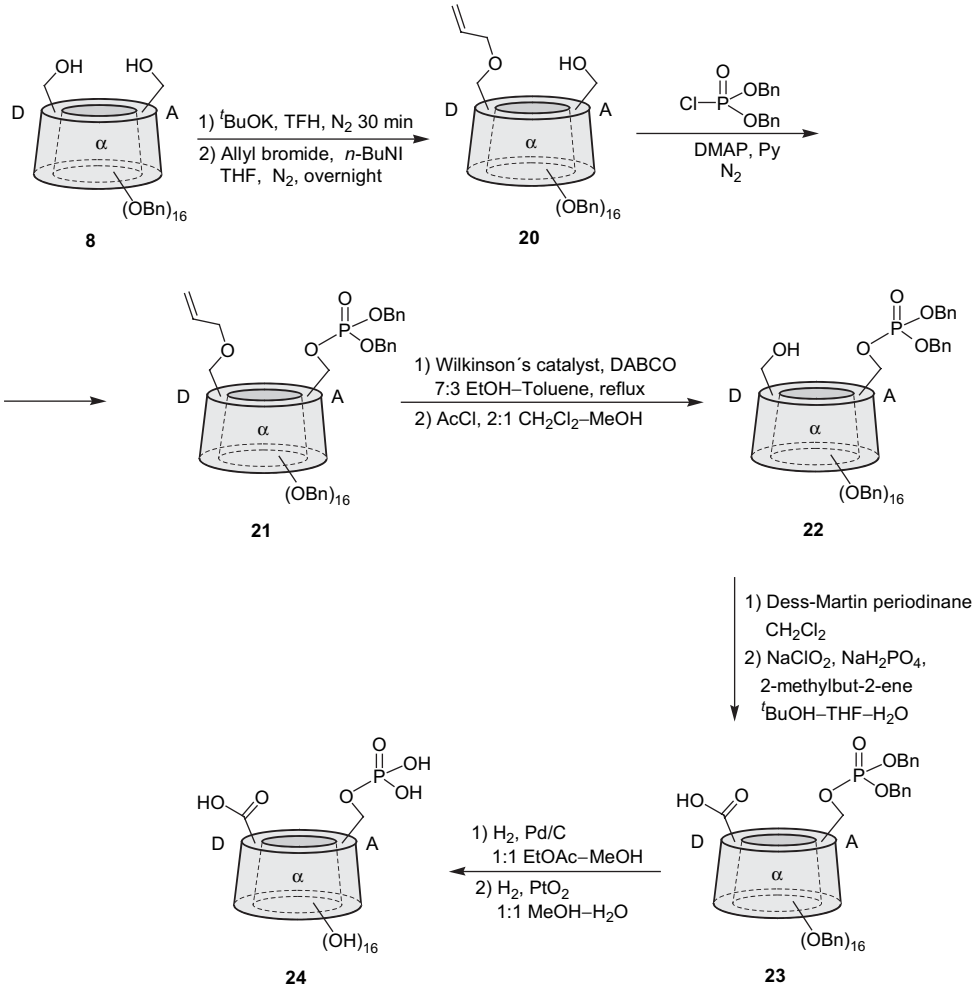


Scheme 2.

the allyl group of **21** was achieved by first isomerization with Wilkinson's catalyst, followed by in situ generated acid treatment to afford **22**.

The free hydroxyl group on **22** was first oxidized to the corresponding aldehyde by using Dess–Martin periodinane, followed by further oxidation to the carboxylic acid moiety with $NaClO_2$[47] in a buffered medium to afford protected derivative **23**. Final deprotection of **23** using the same conditions as for mono- and diphosphate derivatives (Schemes 1 and 2) afforded **24**, a novel cyclodextrin derivative bearing two different acidic moieties on primary positions (Scheme 3).

Fully unprotected derivatives **12**, **13**, **18**, **19** and **24** were tested for catalysis in hydrolysis reactions of aryl glycosides and of aryl phosphates at different pH values and temperatures. Surprisingly, title compounds did not show appreciable catalysis. A possible explanation is the different solvation properties exhibited by carboxylates, sulfates and phosphates. Calculated[12] pK_a values for diacids **1** and **2** turned out to be 3.5 and 3.2, respectively. On the other hand, the reported[48] pK_a's values for glucose-6-phosphate are 0.94 and 6.11. These data suggest that phosphate derivatives bear a larger negative charge than carboxylates and sulfates. Furthermore, thermodynamics data[49] for solvation of lithium and sodium salts of carboxylates, sulfates and phosphates indicate a significant stabilization of the latter in aqueous medium. This might lead to a prominent decrease of the stabilization of the incipient positive charge in the aryl glycoside hydrolysis transition state exerted by the cyclodextrin. Furthermore, a more solvated derivative might



Scheme 3.

also involve a more crowded system for complexing the aromatic residue of the glycoside, and thus, a reduced capacity of the cyclodextrin for establishing inclusion complexes.

In conclusion, we have developed a versatile methodology for the successful preparation of phosphate-containing cyclodextrins, compounds of high practical and biological interest. For this purpose, we have combined the practical and selective de-O-benzylation of fully benzylated cyclodextrins and phosphorylation with diphenylphosphoryl chloride. Although the final derivatives did not show appreciable catalysis in the aryl glycosides hydrolysis, they comprise a family of valuable chiral tools for the complexation of positively charged guests. These negatively charged cyclodextrins are obtained in a selective fashion that avoids mixtures of phosphate regioisomers as described in other procedures in the literature, and subsequent difficult purifications.

3. Experimental section

3.1. General

Solvents were distilled under anhydrous conditions. All reagents were used as purchased without further purification. Evaporation was carried out in a rotatory evaporator. Glassware used for water-free reactions was dried for 2 h at 130 °C before use. Columns were packed with silica gel 60 (230–400 mesh) as the stationary phase. TLC plates (Merck 60 F_{254}) were visualized by spraying with cerium sulfate (1%) and molybdic acid (1.5%) in 10% H_2SO_4 and heating until coloured spots appeared. ^1H, ^{13}C NMR and COSY experiments were carried out with a Varian Mercury 400 instrument. Monoisotopic mass spectra (MALDI-TOF MS) were obtained on a Bruker Daltonics mass spectrometer using an α-cyanohydroxycinnamic acid (α-CHCA) matrix. Spectra were calibrated using a peptide calibration standard solution.

3.2. $6^A,6^D$-Di-*O*-(diphenylphosphate)-hexadeca-*O*-benzyl-α-cyclodextrin (10)

To a solution of diol **8** (1.00 g, 0.41 mmol) and DMAP (15 mg, 0.12 mmol) in Py (10 mL) was added diphenylphosphoryl chloride (1.03 mL, 4.97 mmol) at 0 °C under N_2. The corresponding solution was kept stirring overnight and after that it was poured over water–ice. Dichloromethane was added (100 mL) and the organic phase was washed with 1 M HCl (3×50 mL), satd aq $NaHCO_3$ (1×50 mL), H_2O (1×50 mL), dried over Na_2SO_4, filtered and concentrated to dryness. The residue was purified by column chromatography (pentane → 1:3 EtOAc–pentane) to afford title compound (988 mg, 87%).

$[\alpha]_D^{23}$ +36 (*c* 1.4, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): δ 7.31–7.12 (m, 100H, Ar–H), 5.32 (d, 2H, $J_{H,H}$=10.8 Hz, CH), 5.25 (d, 2H, $J_{1,2}$=3.2 Hz, H-1), 5.15–5.12 (m, 5H, $J_{1,2}$=3.2 Hz, $J_{H,H}$=10.0 Hz, H-1, CH), 5.00 (d, 2H, $J_{1,2}$=3.1 Hz, H-1), 4.94–4.86 (m, 8H, CH), 4.56 (d, 1H, $J_{H,H}$=12.4 Hz, CH), 4.49–4.42 (m, 17H), 4.37–4.32 (m, 5H), 4.20–4.02 (m, 13H), 3.98–3.96 (m, 10H), 3.63 (m, 2H), 3.54–3.47 (m, 5H), 3.34 (dd, 2H, *J*=3.6, 9.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.7 (d, $J_{C,P}$=6.5 Hz, C_{ipso} phosphate), 150.6 (d, $J_{C,P}$=7.0 Hz, C_{ipso} phosphate), 139.4, 138.4, 138.3, 138.2, 138.1 (C_{ipso}), 129.8, 128.4, 128.3, 128.1, 128.0, 127.7, 127.6, 127.5, 127.3, 127.2, 127.1 (CH_{Ar}), 125.4, 125.3, 120.3, 120.2, 120.1 (CH_{Ar}–phosphate), 99.0, 98.7, 98.6 (C-1), 81.2, 80.7, 80.5, 80.4, 79.6, 79.3, 79.2, 78.4, 78.1, 76.0, 75.7, 75.3, 73.6, 73.5, 73.0, 72.7, 72.1, 71.6, 70.9, 70.8, 69.2, 69.0, 68.5, 60.6; ^{31}P NMR (161.9 MHz, $CDCl_3$): δ −10.8; MS: calcd for $C_{172}H_{174}NaO_{36}P_2$: 2900.1158; found: 2899.3690.

3.3. $6^A,6^D$-Di-*O*-(diphenylphosphate)-nonadeca-*O*-benzyl-β-cyclodextrin (11)

To a solution of diol **9** (1.50 g, 0.53 mmol) and DMAP (64 mg, 0.53 mmol) in Py (15 mL) was added diphenylphosphoryl chloride (1.54 mL, 7.38 mmol) at 0 °C under N_2. The corresponding solution was kept stirring overnight and after that it was poured over water–ice. Dichloromethane was added (120 mL) and the organic phase was washed with 1 M HCl (3×70 mL), satd aq $NaHCO_3$ (1×70 mL), H_2O (1×70 mL), dried over Na_2SO_4, filtered and concentrated to dryness. The residue was purified by column chromatography (pentane → 1:2 EtOAc–pentane) to afford title compound (1.51 g, 86%).

$[\alpha]_D^{23}$ +45 (*c* 0.4, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): δ 7.21–6.98 (m, 115H, Ar–H), 5.30 (d, 1H, $J_{1,2}$=3.6 Hz, H-1), 5.18 (d, 1H, $J_{1,2}$=3.6 Hz, H-1), 5.14 (d, 1H, $J_{1,2}$=3.6 Hz, H-1), 5.11 (d, 1H, $J_{1,2}$=3.2 Hz, H-1), 5.09 (d, 1H, $J_{1,2}$=3.5 Hz, H-1), 5.11–5.05 (m, 4H), 5.02 (d, 1H, $J_{1,2}$=4.00 Hz, H-1), 4.93–4.88 (m, 3H, $J_{H,H}$=10.0 Hz, CH), 4.76–4.69 (m, 7H), 4.55–4.23 (m, 22H), 4.01–3.91 (m, 24H), 3.84 (d, 1H, $J_{H,H}$=8.8 Hz), 3.82 (d, 1H, $J_{H,H}$=11.2 Hz), 3.79 (d, 1H, $J_{H,H}$=10.8 Hz), 3.77 (d, 1H, $J_{H,H}$=9.2 Hz), 3.69 (d, 1H, $J_{H,H}$=10.8 Hz), 3.62 (d, 1H, $J_{H,H}$=10.4 Hz), 3.51–3.41 (m, 9H), 3.27 (dd, 3H, $J_{2,3}$=9.6 Hz, H-2), 3.23 (dd, 3H, $J_{2,3}$=9.6 Hz, H-2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.7 (d, $J_{C,P}$=4.0 Hz, C_{ipso} phosphate), 150.6 (d, $J_{C,P}$=5.0 Hz, C_{ipso} phosphate), 150.5 (d, $J_{C,P}$=7.0 Hz, C_{ipso} phosphate), 139.4, 139.2, 138.5, 138.4, 138.3, 138.2 (C_{ipso}), 129.9, 129.7, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.6, 127.5, 127.4, 127.3, 127.1 (CH_{Ar}), 125.3, 120.2, 120.1, 120.0 (CH_{Ar}–phosphate), 98.9, 98.8, 98.5, 98.4, 98.3 (C-1), 81.0, 80.8, 80.7, 80.4, 79.3, 79.2, 79.1, 78.8, 78.6, 77.7, 75.8, 75.7, 75.5, 75.4, 75.1, 73.6, 73.4, 73.2, 72.9, 72.7, 72.6, 72.0, 71.6, 71.5, 70.8, 70.7, 70.6, 70.4, 69.4, 68.5, 68.1, 60.5; ^{31}P NMR (161.9 MHz, $CDCl_3$): δ −10.7, −10.8; MS: calcd for $C_{199}H_{202}NaO_{41}P_2$: 3332.3094; found: 3332.2608.

3.4. $6^A,6^D$-Di-*O*-phosphate-α-cyclodextrin (12)

Compound **10** (0.80 g, 0.29 mmol) was dissolved in 1:1 MeOH–EtOAc (20 mL). Then, Pd–C (320 mg) and TFA (cat.) were added and the mixture was kept stirring under hydrogen atmosphere for 3 days. Filtration and removal of the solvents afforded intermediate $6^A,6^D$-di-*O*-(diphenylphosphate)-α-cyclodextrin. This compound was dissolved in 1:1 MeOH−H_2O (20 mL), and to the solution was added PtO_2 (232 mg); the corresponding mixture was vigorously stirred under hydrogen atmosphere (20 atm) for 3 days. Filtration and removal of the solvents furnished title compound (194 mg, 60%).

$[\alpha]_D^{23}$ +101 (*c* 0.4, H_2O); ^1H NMR (400 MHz, D_2O): δ 5.05–5.01 (m, 6H, H-1), 4.12 (m, 2H), 3.94–3.92 (m, 10H), 3.81 (m, 9H), 3.59–3.54 (m, 17H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 102.3, 101.6, 101.2 (C-1), 83.3, 82.7, 82.5, 73.9, 73.4, 73.2, 73.1, 72.5, 72.3, 72.1, 72.0, 70.7, 65.2, 60.4; ^{31}P NMR (161.9 MHz, D_2O): δ 1.7; MS: calcd for $C_{36}H_{60}Na_3O_{36}P_2$: 1199.2033; found: 1198.3985.

3.5. $6^A,6^D$-Di-*O*-phosphate-β-cyclodextrin (13)

Compound **11** (1.50 g, 0.45 mmol) was dissolved in 1:1 MeOH−EtOAc (20 mL). Then, $Pd(OH)_2$ (356 mg) and TFA (cat.) were added and the mixture was kept stirring under hydrogen atmosphere for 2 days. Filtration and removal of the solvents afforded intermediate $6^A,6^D$-di-*O*-(diphenylphosphate)-β-cyclodextrin. This compound was dissolved in 1:1 MeOH–H_2O (40 mL), and to the solution was added PtO_2 (291 mg); the corresponding mixture was vigorously stirred under hydrogen atmosphere (20 atm) for 3 days. Filtration and removal of the solvents furnished title compound (482 mg, 83%).

$[\alpha]_D^{23}$ +104 (*c* 0.4, H_2O); ^1H NMR (400 MHz, D_2O): δ 5.13–5.10 (m, 7H, H-1), 4.19 (m, 2H), 4.01–3.91 (m, 23H), 3.69–3.61 (m, 17H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 103.5, 103.4, 103.3, 103.2 (C-1), 83.0, 82.9, 82.8, 82.7, 82.6, 82.5, 82.4, 74.6, 73.4, 72.5, 72.4, 65.4, 65.3, 61.7, 61.6; ^{31}P NMR (161.9 MHz, D_2O): δ 1.3; MS: calcd for $C_{42}H_{70}Na_3O_{41}P_2$: 1361.2561; found: 1360.3671.

3.6. 6^A-*O*-(Diphenylphosphate)-heptadeca-*O*-benzyl-α-cyclodextrin (16)

To a solution of derivative **14** (0.71 g, 0.29 mmol) and DMAP (20 mg, 0.16 mmol) in Py (7 mL) was added diphenylphosphoryl chloride (0.60 mL, 2.88 mmol) at 0 °C under N_2. The corresponding solution was kept stirring overnight and after that it was poured over water–ice. Dichloromethane was added (125 mL) and the organic phase was washed with 1 M HCl (2×50 mL), satd aq $NaHCO_3$ (1×50 mL), H_2O (1×50 mL), dried over Na_2SO_4, filtered and concentrated to dryness. The residue was purified by column chromatography (pentane→1:3 EtOAc-pentane) to afford title compound (731 mg, 91%).

$[\alpha]_D^{23}$ +38 (*c* 0.5, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27–7.09 (m, 95H, Ar–H), 5.26 (d, 1H, $J_{H,H}$=10.0 Hz, CH), 5.24 (d, 1H, $J_{H,H}$=11.2 Hz, CH), 5.22 (d, 1H, $J_{H,H}$=10.8 Hz, CH), 5.17–5.12 (m, 6H), 5.09 (d, 1H, $J_{1,2}$=3.6 Hz, H-1), 5.05 (d, 1H, $J_{1,2}$=3.6 Hz, H-1), 5.01 (d, 1H, $J_{1,2}$=3.2 Hz, H-1), 4.89–4.84 (m, 7H), 4.54–4.40 (m, 17H), 4.40 (d, 1H, $J_{H,H}$=11.6 Hz, CH), 4.37 (d, 1H, $J_{H,H}$=11.6 Hz, CH), 4.36 (d, 1H, $J_{H,H}$=12.0 Hz, CH), 4.32 (d, 1H, $J_{H,H}$=11.6 Hz, CH), 4.30 (d, 1H, $J_{H,H}$=13.2 Hz, CH), 4.27 (d, 1H, $J_{H,H}$=12.0 Hz, CH), 4.06–3.88 (m, 22H), 3.62 (d, 2H, $J_{H,H}$=10.8 Hz), 3.54–3.44 (m, 8H), 3.27 (dd, 2H, $J_{1,2}$=3.2 Hz, $J_{2,3}$=10.0 Hz, H-2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.7 (d, $J_{C,P}$=6.5 Hz, C_{ipso} phosphate), 150.7 (d, $J_{C,P}$=6.5 Hz, C_{ipso} phosphate), 139.5, 139.4, 138.5, 138.4, 138.3, 138.2 (C_{ipso}), 129.9, 129.8, 128.4, 128.3, 128.1, 127.8, 127.7, 127.5, 127.4, 127.1 (CH_{Ar}), 125.4 125.3 (CH_{Ar}–phosphate), 99.0, 98.9, 98.8, 98.7, 98.6 (C-1), 81.2, 81.1, 80.8, 80.6, 79.8, 79.7, 79.5, 79.3, 79.2, 79.1, 78.8, 78.6, 75.8, 75.6, 75.5, 73.6, 72.8, 72.1, 71.7, 71.6, 70.7, 69.3, 69.1, 68.3; ^{31}P NMR (161.9 MHz, $CDCl_3$): δ −10.7; MS: calcd for $C_{167}H_{171}NaO_{33}P_2$: 2758.1338; found: 2758.7788.

3.7. 6^A-*O*-(Diphenylphosphate)-eicosa-*O*-benzyl-β-cyclodextrin (17)

To a solution of derivative **15** (0.70 g, 0.24 mmol) and DMAP (23 mg, 0.19 mmol) in Py (7 mL) was added diphenylphosphoryl chloride (0.50 mL, 2.38 mmol) at 0 °C under N_2. The corresponding solution was kept stirring overnight and after that it was poured over water–ice. Dichloromethane was added (125 mL) and the organic phase was washed with 1 M HCl (2×50 mL), satd aq $NaHCO_3$ (1×50 mL), H_2O (1×50 mL), dried over Na_2SO_4, filtered and concentrated to dryness. The residue was purified by column chromatography (pentane→1:3 EtOAc–pentane) to afford title compound (620 mg, 82%).

$[\alpha]_D^{23}$ +46 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30–7.06 (m, 110H, Ar–H), 5.30–5.23 (m, 3H), 5.31 (d, 1H, $J_{1,2}$=3.2 Hz, H-1), 5.30 (d, 1H, $J_{1,2}$=4.0 Hz, H-1), 5.24 (d, 1H, $J_{1,2}$=4.0 Hz, H-1), 5.18–5.09 (m, 7H), 4.97–4.93 (m, 1H), 4.85–4.80 (m, 6H), 4.65–4.38 (m, 25H), 4.12–4.01 (m, 24H), 3.90 (t, 1H, $J_{H,H}$=8.8 Hz), 3.75 (d, 1H, $J_{H,H}$=9.6 Hz), 3.67–3.54 (m, 16H), 3.35 (dd, 2H, $J_{1,2}$=3.2 Hz, $J_{2,3}$=9.6 Hz, H-2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.7 (d, $J_{C,P}$=6.0 Hz, C_{ipso} phosphate), 150.6 (d, $J_{C,P}$=6.5 Hz, C_{ipso} phosphate), 139.4, 139.3, 139.2, 138.4, 138.3, 138.2 (C_{ipso}), 129.8, 129.7, 128.2, 127.9, 127.8, 127.7, 127.6, 127.5, 127.4, 127.0 (CH_{Ar}), 125.3, 120.2, 120.1 (CH_{Ar}–phosphate), 98.8, 98.7, 98.6, 98.5, 98.4 (C-1), 81.0, 80.8, 80.7, 80.4, 78.9, 78.7, 78.5, 75.6, 75.4, 73.4, 73.2, 72.7, 72.6, 71.9, 71.7, 71.5, 70.5, 69.3, 68.2; ^{31}P NMR (161.9 MHz, $CDCl_3$): δ −10.7; MS: calcd for $C_{194}H_{199}NaO_{38}P$: 3190.3275; found: 3190.1707.

3.8. 6^A-*O*-Phosphate-α-cyclodextrin (18)

Compound **16** (0.66 g, 0.24 mmol) was dissolved in 1:1 MeOH–EtOAc (30 mL). Then, $Pd(OH)_2$ (360 mg) and TFA (cat.) were added and the mixture was kept stirring under hydrogen atmosphere for 2 days. Filtration and removal of the solvents afforded intermediate 6^A-*O*-(diphenylphosphate)-α-cyclodextrin. This compound was dissolved in 1:1 MeOH–H_2O (30 mL), and to the solution was added PtO_2 (192 mg); the corresponding mixture was vigorously stirred under hydrogen atmosphere (20 atm) for 3 days. Filtration and removal of the solvents furnished title compound (196 mg, 79%).

$[\alpha]_D^{23}$ +103 (*c* 0.4, H_2O); ^{1}H NMR (400 MHz, D_2O): δ 5.06–5.02 (m, 6H, H-1), 4.13 (m, 2H), 3.97–3.80 (m, 20H), 3.61–3.55 (m, 14H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 102.1 (×2) 102.0, 101.9 (C-1), 82.6, 82.5, 82.4, 82.3, 82.1 73.6, 73.3, 73.2, 72.3, 72.2, 72.1, 71.8, 60.1; ^{31}P NMR (161.9 MHz, D_2O): δ 2.3; MS: calcd for $C_{36}H_{60}Na_2O_{33}P$: 1097.2550; found: 1096.5359.

3.9. 6^A-*O*-Phosphate-β-cyclodextrin (19)

Compound **17** (0.53 g, 0.17 mmol) was dissolved in 1:1 MeOH–EtOAc (20 mL). Then, $Pd(OH)_2$ (298 mg) and TFA (cat.) were added and the mixture was kept stirring under hydrogen atmosphere for 2 days. Filtration and removal of the solvents afforded intermediate 6^A-*O*-(diphenylphosphate)-β-cyclodextrin. This compound was dissolved in 1:1 MeOH–H_2O (20 mL), and to the solution was added PtO_2 (120 mg); the corresponding mixture was vigorously stirred under hydrogen atmosphere (20 atm) for 3 days. Filtration and removal of the solvents furnished title compound (146 mg, 71%).

$[\alpha]_D^{23}$ +115 (*c* 0.3, H_2O); ^{1}H NMR (400 MHz, D_2O): δ 5.14–5.10 (m, 7H, H-1), 4.15 (m, 2H), 4.02–3.88 (m, 25H), 3.72–3.59 (m, 14H) (lit.[18]); ^{13}C NMR (100 MHz, DMSO-d_6): δ 101.8, 101.5, 101.4, 101.3, 82.6, 82.0, 81.3, 81.0, 72.6, 71.9, 71.5, 71.4, 60.4, 59.9, 59.4, 59.3; ^{31}P NMR (161.9 MHz, DMSO-d_6): δ 0.16; MS: calcd for $C_{42}H_{70}Na_2O_{38}P$: 1259.3078; found: 1258.5734.

3.10. 6^A-*O*-allyl-6^D-*O*-(Diphenylphosphate)-hexadeca-*O*-benzyl-α-cyclodextrin (21)

To a solution of 6^A-*O*-allyl-hexadeca-*O*-benzyl-α-cyclodextrin **20** (0.59 g, 0.24 mmol) and DMAP (31 mg, 0.25 mmol) in Py (5 mL) was added diphenylphosphoryl chloride (0.35 mL, 1.69 mmol) at 0 °C under N_2. The corresponding solution was kept stirring overnight and after that it was poured over water–ice. Dichloromethane was added (150 mL) and the organic phase was washed with 1 M HCl (2×50) mL, satd aq $NaHCO_3$ (1×50 mL), H_2O (1×50 mL), dried over Na_2SO_4, filtered and concentrated to dryness. The residue was purified by column chromatography (pentane→1:3.5 EtOAc–pentane) to afford title compound (574 mg, 88%).

$[\alpha]_D^{23}$ +37 (*c* 1.2, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35–7.15 (m, 90H, Ar–), 5.89 (ddt, 1H, $J_{H,H}$=10.8 Hz, $J_{H,H}$=10.8 Hz, $J_{H.CH2}$=5.6 Hz, *CH*=CH_2), 5.35 (d, 1H, $J_{H,H}$=10.8 Hz, CH), 5.33 (d, 1H, $J_{H,H}$=10.8 Hz, CH), 5.30–5.20 (m, 9H), 5.18 (d, 1H, $J_{1,2}$=3.6 Hz, H-1), 5.15 (d, 1H, $J_{1,2}$=2.8 Hz, H-1), 5.13 (d, 1H, $J_{1,2}$=2.8 Hz, H-1), 4.99 (d, 3H, $J_{H,H}$=10.0 Hz, CH), 4.96 (d, 3H, $J_{H,H}$=9.2 Hz, CH), 4.62 (dd, 1H, $J_{5,6a}$=4.0 Hz, $J_{6a,6b}$=12.4 Hz, H-6a), 4.64–4.49 (m, 16H), 4.43 (dd, 3H, $J_{5,6a}$=3.2 Hz, $J_{6a,6b}$=11.6 Hz, H-6a), 4.28–3.96 (m, 24H), 3.73 (br d, 2H, $J_{H,H}$=11.6 Hz, CH), 3.69 (br d, 2H, $J_{H,H}$=11.2 Hz, CH), 3.64 (br d, 2H, $J_{H,H}$=10.8 Hz, CH), 3.74–3.56 (m, 6H), 3.38 (dd, 2H, $J_{H,H}$=3.2, 10.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.7 (d, $J_{C,P}$=6.3 Hz, C_{ipso} phosphate), 150.6 (d, $J_{C,P}$=6.7 Hz, C_{ipso} phosphate), 139.5, 139.4, 138.5, 138.4, 138.3, 138.2, 138.1 (C_{ipso}), 134.9 (*C*H=), 129.8, 129.7, 128.4, 128.3, 128.2, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 127.4, 127.3, 127.2, 127.0 (CH_{Ar}), 125.4, 125.3, 120.2, 120.1 (CH_{Ar}–phosphate), 117.0 (H_2C=), 98.9, 98.8, 98.7, 98.6 (C-1), 81.1, 81.0, 80.7, 80.5, 80.0, 79.7, 79.5, 79.3, 79.2, 79.1, 78.9, 78.8, 78.7, 78.5, 75.8, 75.7, 75.6, 75.5, 75.4, 73.5, 72.9, 72.8, 72.7, 72.4, 72.1, 71.6, 71.5, 70.7, 70.6, 69.2, 69.1, 68.3; ^{31}P NMR (161.9 MHz, $CDCl_3$): δ −10.6; MS: calcd for $C_{163}H_{169}NaO_{33}P$: 2708.1181; found: 2708.0223.

3.11. 6^A-*O*-(Diphenylphosphate)-hexadeca-*O*-benzyl-α-cyclodextrin (22)

To a solution of 6^A-*O*-allyl-6^D-*O*-(diphenylphosphate)-hexadeca-*O*-benzyl-α-cyclodextrin (**21**) (0.44 mg, 0.16 mmol) in 2:1 abs EtOH–toluene (20 mL) was added DABCO (11 mg, 0.10 mmol) and Wilkinson's catalyst (77 mg, 0.083 mmol), and the corresponding mixture was refluxed for 3 h. After cooling down to rt, the solution was concentrated to dryness and the residue was dissolved in EtOAc (80 mL) and washed with H_2O (2×50 mL); the organic layer was dried over $MgSO_4$, filtered and the filtrate was concentrated to dryness. The crude residue was dissolved in a 5:3 CH_2Cl_2–MeOH mixture (16 mL) and AcCl (0.18 mL, 2.53 mmol) was added at 0 °C (pH 1–2); reaction was kept at rt for 3 h. After that it was quenched by the addition of Et_3N (0.7 mL) and the solution was concentrated to dryness; the residue was dissolved in CH_2Cl_2 (80 mL) and washed with 10% $KHSO_4$ (50 mL) and H_2O (50 mL). The organic layer was dried over $MgSO_4$, filtered and the filtrate was concentrated to dryness and purified by column chromatography (pentane→1:3 EtOAc–pentane) to afford title compound (317 mg, 75%).

$[\alpha]_D^{23}$ +40 (*c* 0.6, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30–7.00 (m, 90H, Ar–H), 5.48 (d, 1H, $J_{1,2}$=4.0 Hz, H-1), 5.47 (d, 1H, $J_{1,2}$=3.6 Hz, H-1), 5.36 (d, 1H, $J_{H,H}$=11.2 Hz, CH), 5.34 (d, 1H, $J_{H,H}$=11.2 Hz, CH), 5.20 (d, 1H, $J_{H,H}$=10.8 Hz, CH), 5.15 (d, 1H, $J_{H,H}$=10.8 Hz, CH), 4.98–4.93 (m, 3H), 4.92–4.83 (m, 6H), 4.81 (d, 3H, $J_{H,H}$=11.2 Hz, CH), 4.70–4.63 (m, 4H), 4.57–4.38 (m, 13H), 4.54 (dd, 1H, $J_{5,6a}$=2.8 Hz, $J_{6a,6b}$=12.0 Hz, H6a), 4.36 (d, 1H, $J_{H,H}$=12.4 Hz, CH), 4.29 (d, 1H, $J_{H,H}$=12.4 Hz, CH), 4.24–3.85 (m, 20H), 3.80–3.66 (m, 6H), 3.59–3.52 (m, 3H), 3.47–3.43 (m, 3H), 3.36 (dd, 2H, $J_{2,3}$=9.6 Hz, H-2), 3.20 (dd, 2H, $J_{2,3}$=10.0 Hz, H-2), 2.14 (br s, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.7 (d, $J_{C,P}$=7.2 Hz, C_{ipso} phosphate), 150.6 (d, $J_{C,P}$=7.8 Hz, C_{ipso} phosphate), 139.4, 139.3, 138.6, 138.5, 138.4, 138.3, 138.2 (C_{ipso}), 129.9, 129.7, 128.5, 128.4, 128.1, 128.0, 127.9, 127.7, 127.6, 127.5, 127.1, 127.0, 126.8 (CH_{Ar}), 125.4, 125.3, 120.1 (CH_{Ar}–phosphate), 98.8, 98.6, 98.3, 98.2, 98.1, 97.9 (C-1), 81.4, 81.1, 80.9, 80.8, 80.3, 80.2, 79.9, 79.5, 79.4, 79.2, 79.0, 78.4, 78.2, 76.7, 76.3, 76.2, 75.9, 74.7, 73.5, 73.4, 73.2, 73.0, 72.4, 72.3, 72.0, 71.8, 70.1, 70.0, 69.5, 69.3, 69.2, 68.3, 68.2, 62.4 (C-6); ^{31}P NMR (161.9 MHz, $CDCl_3$): δ −10.6; MS: calcd for $C_{160}H_{165}NaO_{33}P$: 2668.0868; found: 2668.6484.

3.12. 6^A-Carboxylic acid-6^D*O*-phosphate-α-cyclodextrin (24)

A solution of 6^A-*O*-(diphenylphosphate)-hexadeca-*O*-benzyl-α-cyclodextrin **22** (0.36 g, 0.13 mmol) and Dess–Martin periodinane reagent (171 mg, 0.40 mmol) in CH_2Cl_2 (10 mL) was kept at room temperature overnight and then quenched by addition of Et_2O (25 mL) and satd aq $NaHCO_3$ containing 5% of $Na_2S_2O_3$ (25 mL). Then, the organic layer was separated, dried over $MgSO_4$ and concentrated to dryness. To a solution of the residue in 2-methyl-but-2-ene (4 mL), ^{t}BuOH (10 mL) and THF (4 mL) was added a solution of $NaClO_2$ (0.32 g, 3.54 mmol) and NaH_2PO_4 (0.29 g, 2.42 mmol) in water (2 mL) and the corresponding mixture was kept stirring at room temperature overnight. The reaction was quenched by addition of 1 M HCl (50 mL) and the product was extracted with EtOAc (3×30 mL). The organic phase was dried over $MgSO_4$, filtered and the filtrate was concentrated to dryness and purified by flash chromatography (1:3 EtOAc–pentane→1:2 EtOAc–pentane containing 1% HCOOH) to give 6^A-carboxylic acid-6^D-*O*-(diphenylphosphate)-hexadeca-*O*-benzyl-α-cyclodextrin **23** (190 mg, 53%, two steps).

Compound **23** (0.19 g, 0.17 mmol) was dissolved in 1:1 MeOH–EtOAc (10 mL). Then, $Pd(OH)_2$ (151 mg) and TFA (cat.) were added and the mixture was kept stirring under hydrogen atmosphere for 2 days. Filtration and removal of the solvents afforded intermediate 6^A-carboxylic acid-6^D-*O*-(diphenylphosphate)-α-cyclodextrin. This compound was dissolved in 1:1 MeOH–H_2O (20 mL), and to the solution was added PtO_2 (120 mg); the corresponding mixture was vigorously stirred under hydrogen atmosphere (15 atm) for 2 days. The solid was filtered off and the solvent was removed in vacuo; the residue was dissolved in water (20 mL) and washed with CH_2Cl_2 (2×15 mL). Removal of water furnished title compound (47 mg, 65%).

$[\alpha]_D^{23}$ +56 (*c* 0.5, H_2O); ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.01 (d, 1H, $J_{1,2}$=3.2 Hz, H-1), 5.0–4.92 (m, 5H, H-1), 4.66 (br s), 4.14–4.04, 3.90–3.72, 3.70–3.52 (4m, 50H, H2–H6, –OH); ^{13}C NMR (100 MHz, D_2O): δ 172.2 (CO), 102.0, 101.9, 101.8, 101.6, 101.4, 101.0 (C-1), 81.7, 81.6, 81.3, 81.0, 80.0, 73.3, 73.1, 72.9, 72.2, 71.9, 71.6, 71.4, 71.1, 71.0, 70.0, 64.3, 60.4, 60.3, 59.8; ^{31}P NMR (161.9 MHz, D_2O): δ 1.4; MS: calcd for $C_{36}H_{58}Na_2O_{34}P$: 1111.2342; found: 1110.3525.

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