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A SIMPLE ACCESS TO CARBOCYCLIC ANALOGS OF 2-DEOXY-D-RIBOSE HAVING THE 3-HYDROXYMETHYLENE MOIETY REPLACED BY HETEROATOMS

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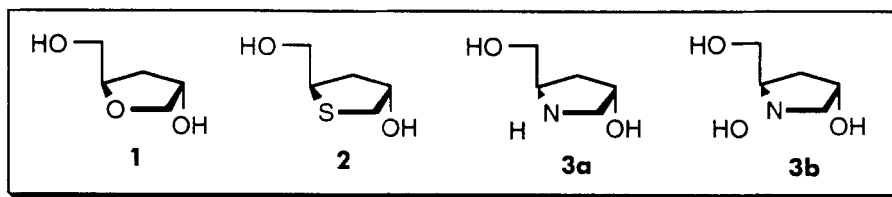
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ABSTRACT

(2*S*,4*S*)-1-*O*-Benzyl-2,5-di-*O*-mesyl-4-*O*-methoxymethylpentan-1,2,4,5-tetrol, a versatile precursor for subsequent cyclisations with bivalent nucleophiles, was obtained in five steps from the easily accessible (3*S*,5*S*)-3-hydroxy-5-hydroxymethyl-dihydrofuran-2(3*H*)-one. Using disodium phosphide in DMSO or disodium selenide in acetone-water, (2*R*,4*S*)-2-benzyloxymethyl-4-*O*-methoxymethylphospholane and (2*R*,4*S*)-2-benzyloxymethyl-4-*O*-methoxymethylselenolane were prepared. The phospholane was oxidized by oxygen (hydrogen peroxide) to give the analogous cyclic phospholane oxide (phosphinic acid) which was then transformed with benzyl bromide and alkali carbonate into the 1-benzyl phospholane oxide (phosphinic acid benzyl ester). All heterocyclic compounds synthesized, formally resemble *carba*-2,3-dideoxy-D-glycero-pentofuranose, the carbocyclic analog of 2-deoxy- α -D-ribofuranose.

INTRODUCTION

A number of five membered heterocyclic sugar analogs, serving as glycomimetics or subunits of antivirally active modified nucleosides,¹ have been recently prepared.² Among representative examples reported are structural analogs of carbocyclic 2'-deoxyribosides bearing oxygen (iso-ddA) **1**,³ sulfur **2**,⁴ NH **3a**,⁵ or N-OH **3b**⁵ in place of the 3'-hydroxymethylene moiety.

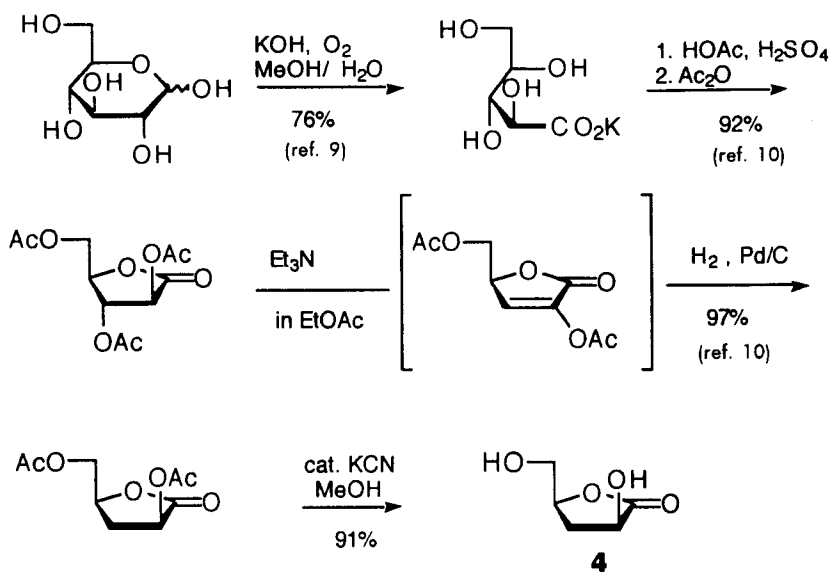


In this contribution a general, very simple and short synthetic route to this class of heterocyclic ribose analogs is demonstrated by representative syntheses of novel homologs having either *selenium* or *phosphorus* inserted in the 3' position. Besides the interest in their syntheses, carbohydrate analogs with phosphorus in the ring such as sugar-derived cyclic phosphine oxides,⁶ cyclic phosphinic acid derivatives⁶ or carbohydrate phosphones⁷ are currently being evaluated as potential glycomimetics.⁸

RESULTS AND DISCUSSION

(3*S*,5*S*)-3-hydroxy-5-hydroxymethyldihydrofuran-2(3*H*)-one **4**, readily prepared from glucose on a 20-mmol scale (scheme 1),^{9,10} served as starting material for the planned synthesis. However, a slight modification concerning the final deacetylation step was applied to the original protocol.¹⁰ Instead of an equivalent of KOH in ethanol, a catalytic amount of potassium cyanide dissolved in methanol served as a mild agent for the simultaneous removal of both acetates.¹¹

The primary alcohol function was protected as the benzyl ether **5** (BnBr, NaH in DMF) before the secondary alcohol was converted into the

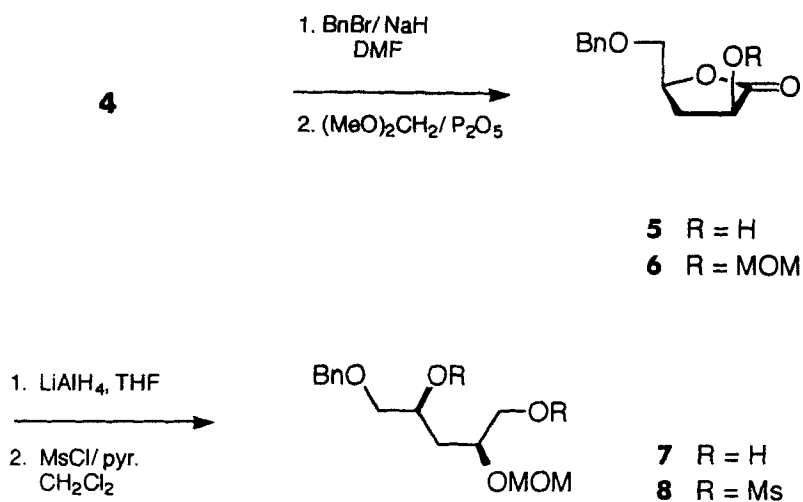


Scheme 1: Synthesis of (3*S*,5*S*)-3-hydroxy-5-hydroxymethylidihydrofuran-2(3*H*)-one (**4**) from D-glucose (according to refs. 9,10)

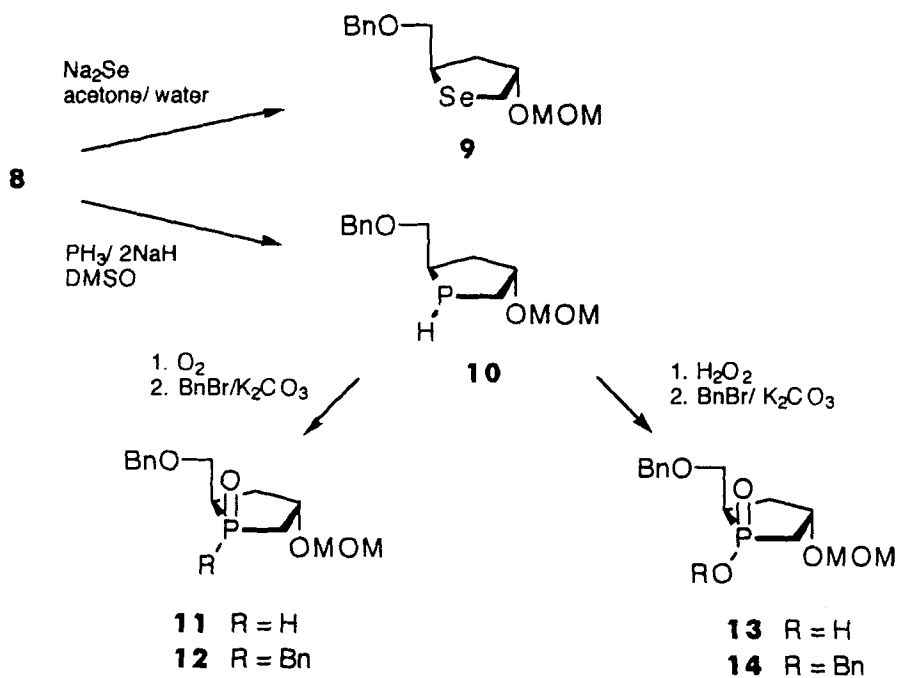
MOM-acetal **6** (dimethoxymethane/phosphorus pentoxide¹²). Complete reduction of the lactone by use of lithium aluminum hydride in THF afforded the 1,4-diol **7** whose transformation into the corresponding bis-mesylate **8** (2 eq MsCl/2 eq pyridine, CH₂Cl₂, 0 °C) provided the pivotal intermediate for the synthesis (scheme 2).

Reaction with bivalent nucleophiles in appropriate solvents should result in cyclisation by intramolecular substitution thus forming the optically pure C-branched heterocycles.

In a first experiment (scheme 3), sodium selenide,¹³ suspended in oxygen free acetone/water (4:1), reacted with **8** at a temperature between 40- 50 °C to give the selenolane **9** in almost quantitative yield. When kept at ambient temperature and with exclusion of air, light and strong acid, no decomposition of the cyclic selenide **9** was detected. The ¹³C-resonances assigned to the α-carbons C-2 and C-5 of **9** confirmed the influence of the oxygen atoms bound to C-4 and C-6 exerting downfield shifts of approximately 20 ppm relative to the unsubstituted selenolane. Complementarily, the elemental analysis for **9** supported a selenide structure in favor of a selenoxide.



Scheme 2



Scheme 3

In another sequence (scheme 3), the intermediate phospholane derivative **10** was synthesized by alkylation of deprotonated phosphine with the bis-mesylate **8** in DMSO. The phosphide solution was previously prepared from phosphine dispersed into an oxygen-free DMSO solution which had been deprotonated by sodium hydride (2 eq referring to **8**).¹⁴ The predominant formation of phospholane **10**, besides small amounts of acyclic phosphines and oxidized products (totally less than 15 %), was concluded from ³¹P and ¹³C NMR spectra. Due to the rapid exchange of the P-H protons caused by traces of H⁺, only one ³¹P resonance signal was found at -67 ppm.

Oxygen dispersed into a dichloromethane solution of the impure phospholane **10** provided the secondary phosphine oxide **11** which was eventually transformed into the corresponding trialkylphosphine oxide **12** by use of potassium carbonate and benzyl bromide in dry DMF. The separation of the (11:1)-mixture of the two stereoisomers of **12** succeeded by HPLC [silica gel, ethyl acetate/ethanol mixtures (12:1 and 4:1 v/v)] which resulted in a severe reduction in yield.

Establishing the stereochemistry at the phosphorus simply from ³¹P NMR data (δ_P : 62.4 and 62.8 ppm) still is restricted to special cases.¹⁵⁻²¹ Analysis of the ¹H and ¹³C NMR spectra however, especially the comparison to the ¹H NMR data from thoroughly analyzed related compounds¹⁹⁻²¹ provided arguments supporting the (1 *R*)-configuration at the phosphorus center of the major isomer (1 *R*)-**12**.

For instance, the orientation of the P=O bond could be determined from the characteristic downfield shifts exerted on H-2. The δ_{H-2} -value of the minor (1 *S*)-isomer (2.47 ppm in contrast to 2.27 ppm) hinted to the *cis* relationship between H-2 and the P=O group. Additional evidence was extracted from the lower $J_{2,P}$ value of (1 *R*)-**12** which was 14.7 Hz in contrast to 22.6 Hz with the (1 *S*)-isomer.

The corresponding phosphinic acid **13** was obtained by stirring hydrogen peroxide into the dichloromethane solution of the phospholane **10** (1 h, 0 °C). In order to facilitate purification, the phosphinic acid **13** was transformed into the benzyl ester derivative **14** [benzyl bromide/potassium hydrogen carbonate/DMF, yield 34% from **10**]. The ratio (7:1) of stereoisomers determined from the ³¹P NMR spectrum (δ_P : 73.0 and 73.7 ppm) proved the stereoselectivity of the reaction. Arguments as presented above, e. g. the ¹H-downfield shift of H-2 of the minor isomer

(2.13 ppm vs. 2.22 ppm), strongly suggested the (1 *R*)- configuration of the major isomer as depicted in scheme 3.

CONCLUSIONS

An efficient synthesis of the optically pure acyclic (2*S*,4*S*)-1-*O*-benzyl-2,5-di-*O*-mesyl-4-*O*-methoxymethylpentan-1,2,4,5-tetrol **8**, representing a universal precursor to various derivatives of carbocyclic 2-deoxyribose having the 3-hydroxymethylene replaced by heteroatoms was developed. Similar to the known sulfolane compound,⁴ the novel phospholane and selenolane homologs were easily accessible by cyclisation on bis-alkylation of the respective bivalent nucleophiles.

So far, little is known about the biological properties and the toxicity of compounds **9-14**. Syntheses of the corresponding nucleosides remain to be investigated in subsequent studies.

Safety remarks: In the literature, there are no reports on the toxicity or any dangers caused by substances related to compounds **11-14**.^{6,19-21} However, since phosphine oxides and phosphinic acid derivatives are found among the most effective neurotoxins, the appropriate laboratory safety rules should be observed strictly. This applies even more importantly when working with phosphanes and phospholanes which generally are very toxic.

With respect to compound **9**, it should be worth mentioning that organo-selenium compounds are considered highly toxic. Interestingly, a surprising range of selenium containing biomolecules was found during the last two decades.²²

EXPERIMENTAL

General methods. Melting points are uncorrected and were determined on a Büchi SMP-20 apparatus. Microanalyses were obtained from a Perkin Elmer 240 B analyzer and are reported within ± 0.5 % of calculated values. TLC was performed on aluminium sheets coated with silica gel F 254 (Merck) with analysis by either 254 nm UV or by spraying

with a sulfuric acid/ethanol mixture (1: 4) before heating. The respective v/v-ratios given below, mixtures of ethyl acetate/hexane or ethyl acetate/ethanol served as eluants for TLC and for preparative chromatography which was run on silica gel 60 (Merck, 70- 230 mesh). Merck silica gel columns were used for analytical HPLC of the phosphorous compounds and ethyl acetate/ ethanol mixtures (12:1 and 4:1 v/v) served as mobile phase. ¹H NMR spectra were recorded with a Bruker WM 250 instrument. ¹³Carbon resonances were registered under broad range proton decoupling. Chemical shifts are given in ppm, external references: Me₄Si and 85% H₃PO₄. Optical rotation angles were measured at 20 °C using a Perkin Elmer PE 141 polarimeter.

(3*S*,5*S*)-5-Benzyloxymethyl-3-hydroxydihydrofuran-2(3*H*)-one (5).

Sodium hydride (2.33 g, 1.1 eq) was added within 1 h to an ice-cooled and well stirred solution of dry (3*S*,5*S*)-5-hydroxymethyl-3-hydroxydihydrofuran-2(3*H*)-one **4** (11.67 g, 88.4 mmol) and benzyl bromide (11.5 mL, 1.1 eq) in dry DMF (120 mL). The mixture was stirred overnight while the ice (about 300 g) was allowed to melt. The solvent was evaporated under vacuum at 30 °C and the residue was resuspended in dichloromethane (200 mL) and washed with water (50 mL). After evaporation of the solvent and careful drying of the remainder under high vacuum (10⁻⁴ mmHg), the pure title product was obtained by crystallization from ethyl ether. Recrystallization from EtOAc/hexane furnished white needles (16.9 g, 86%). R_f [silica gel, EtOAc/hexane (2:3)] 0.23; mp 81 °C ; [α]_D²⁰ -39.7° (c 1.55, THF); δ_H (CDCl₃) 7.35 (*m*, 5H, H-ar), 4.91 (*d*, 1H, 11.8 Hz, CH₂Ph), 4.72 (*d*, 1H, 11.8 Hz, CH₂Ph), 4.43 (*m*, 1H, H-4), 4.30 (*dd*, 1H, 9.8 and 8.5 Hz, H-2), 3.83 (*m*, 1H, 12.6 Hz, H-5), 3.60 (*m*, 1H, 12.6 Hz, H-5), 3.10 (*s*, 1H, OH), 2.46 (*m*, 1H, 12.6Hz, H-3b), 2.12 (*ddd*, 1H, 9.8, 9.8 and 12.6 Hz, H3a); δ_C (CDCl₃) 174.88 C-1, 136.64, 128.35, and 127.95 (5C-ar), 76.39 CH₂Ph, 73.28 C-2, 72.11 C-5, 63.22 C-4, 30.32 C-3.

Anal. Calcd for C₁₂H₁₄O₄ (222.243): C, 64.85; H, 6.35. Found: C, 64.64; H, 6.42

(3*S*,5*S*)-5-Benzyloxymethyl-3-*O*-methoxymethyldihydrofuran-2(3*H*)-one (6). Benzyl ether **5** (6 g, 27 mmol) was dissolved in dimethoxymethane (200 mL) and phosphorus pentoxide¹² (3 g) was added under vigorous stirring in small portions until the TLC indicated that the alcohol had been completely converted into the MOM-acetal **6**. After

dilution with diethyl ether (250 mL), the liquid was poured into a saturated sodium hydrogen carbonate solution (80 mL) and stirred for 3 min. Then the organic phase was separated, dried and concentrated under reduced pressure leaving the pure oil (7g, 97 %). Rf [silica gel; EtOAc/hexane (1:1)] 0.61; $[\alpha]^{20}_{\text{D}}$: -33.9 ° (c 0.51, THF); δ_{H} (CDCl₃) 7.39-7.32 (m, 5H, H-ar), 4.95 (d, 1H, 11.8 Hz, CH₂Ph), 4.73 (d, 1H, 11.8 Hz, CH₂Ph), 4.64 (s, 2H, O-CH₂-O), 4.51 (m, 1H, H-4), 4.27 (dd, 1H, 8.4 and 9.7 Hz, H-2), 3.70 (m, 2H, H-5), 3.35 (s, 3H, OMe), 2.49 (m, 1H, H-3b), 2.14 (ddd, 1H, 9.6, 9.6, and 12.8 Hz, H-3a).

Anal. Calcd for C₁₄H₁₈O₅ (266.115): C, 63.13; H, 6.82. Found: C, 63.55; H, 7.17.

(2S,4S)-1-O-Benzyl-4-O-methoxymethyl-*n*-pentan-1,2,4,5-tetrol (7).

The lactone **6** (5 g, 18.8 mmol), dissolved in dry THF (90 mL), was added within 0.5 h to an ice-cooled and well-stirred suspension of lithium aluminium hydride (910 mg, 1.3 eq) in THF and the reaction mixture was kept under the above conditions for an additional hour. Then water (1 mL), 15% NaOH (1 mL) and again water (3 mL) were added to the reaction mixture. After filtration, the solution was dried and concentrated leaving the diol **7** as a colorless oil (4.6 g, 89 %). $[\alpha]^{20}_{\text{D}}$ -23.3 ° (c 1.2, THF); δ_{H} (CDCl₃) 7.37-7.30 (m, 5H, H-ar), 4.65 (s, 2H, O-CH₂-O), 4.65 (dd, 2H, O-CH₂-Ph, 11 and 10 Hz), 4.00 (m, 1H, H-2), 3.80 (m, 2H, H-5), 3.59 (m, 2H, H-1), 3.43 (dd, 1H, H-4, 10.2 and 7.3 Hz), 3.39 (s, 3H, OMe), 3.0-2.0 (2 br.s, 2H, 2 OH), 1.77 (m, 1H, H-3), 1.63 (ddd, 1H, H-3, 13.8, 9.6 and 4.2 Hz); δ_{C} (CDCl₃) 138.75, 128.89, 128.24, and 125.88 (5C-ar), 97.42 (O-CH₂-O), 77.45 (C-4), 73.68 (C-1), 72.55 (Ph-CH₂-O), 68.33, 64.81 (C-2/5), 55.78 (OMe), 35.74 (C-3).

(2S,4S)-1-O-Benzyl-2,5-di-O-mesyl-4-O-methoxymethylpentan-1,2,4,5-tetrol (8). The diol **7** (4.4 g, 16.30 mmol), dissolved in dry dichloromethane (20 mL) was slowly added to an ice-cooled and well-stirred solution of pyridine (6.6 mL, 5 eq) and mesyl chloride (3.1 mL, 2.5 eq) in dichloromethane (30 mL). After 1 h, water (0.6 mL, 2 eq) was added and 30 min later, the organic phase was extracted with water (2 x 25 mL), dried and concentrated leaving the crude product. Removal of residual pyridinium salts succeeded by redissolving the product in a large amount of diethyl ether (1000 mL) and washing with water (50 mL) from which the sufficiently pure title compound was obtained as a slightly red-coloured oil (6.8 g, 98 %); $[\alpha]^{20}_{\text{D}}$ -15.9 ° (c 1.7, THF); δ_{H} (CDCl₃) 7.41-

7.35 (m, 5H, H-ar), 5.12 (1H, *dq*, 6.6, 3.5, 3.5, and 3.5 Hz, H-2), 4.65 (2H, *d*, 3.2 Hz, CH₂Ph), 4.62 (2H, *s*, O-CH₂-O), 4.44 (1H, *dd*, 11 and 3.8 Hz, H-5), 4.16 (1H, *dd*, 11 and 3.8 Hz, H-5), 3.94 (1H, *dddd*, 9, 6, 3.8, and 3.8 Hz, H-4), 3.65 (2H, *m*, H-1), 3.33 (3H, *s*, Me), 3.08 (3H, *s*, Me), 2.98 (3H, *s*, Me), 1.88 (1H, *dd*, 9 and 3.5 Hz, H-3), 1.88 (1H, *t*, 6 and 6.6 Hz, H-3).

Anal. Calcd for C₁₆H₂₆O₉S₂ (426.50): C, 45.06; H, 6.15. Found: C, 45.50; H, 6.64

(2*R*,4*S*)-2-Benzyloxymethyl-4-*O*-methoxymethylselenolane (9). Bis-mesylate **8** (3.75 g, 8.7 mmol) was added to an oxygen-free suspension of sodium selenide (1.1 g, 8.8 mmol) in a mixture of acetone (40 mL) and water (12 mL). After reaction at 50 °C for 2 h, the acetone was evaporated and the aqueous phase washed with dichloromethane (100 mL). The usual work up (drying, solvent evaporation) provided the NMR-pure title compound in almost quantitative yield (2.68 g, 97%). It was purified by chromatography with ethyl acetate/hexane [1:2], but crystallization, however, failed. $[\alpha]_D^{20}$ -62.5 ° (*c* 1.4, THF); δ_H (CDCl₃) 7.36-7.30 (5H, *m*, H-ar), 4.64 (2H, *s*, OCH₂-O), 4.56 (2H, *d*, PhCH₂-O, 4.4 Hz), 4.36 (1H, *dddd*, H-4, 5.5, 4.1, 4.1, and 4.0 Hz), 3.93 (1H, *dddd*, H-2, 7.5, 7.5, 7.5, and 5.5 Hz), 3.85 (1H, *dd*, H-6, 9.6 and 7.5 Hz), 3.66 (1H, *dd*, H-6, 9.6 and 7.5 Hz), 3.38 (3H, *s*, OMe), 3.08 (2H, *dd*, H-5, 4.1 and 0.5 Hz), 2.38 (1H, *ddd*, H-3, 12.5, 5.5 and 5.5 Hz), 1.77 (1H, *ddd*, H-3, 12.5, 7.5 and 4 Hz); δ_C (CDCl₃) 138.02, 128.09, 128.07, 127.3, and 127.2 (5C-ar), 96.04 (OCH₂-O), 81.82 (C-6), 72.64 (Ph-CH₂-O) and 72.05 (C-4), 54.99 (OMe), 39.82 and 39.08 (C-2/5), 28.34 (C-3).

Anal. Calcd for C₁₄H₂₀O₃Se (315.27): C, 53.34; H, 6.39. Found: C, 52.87; H, 6.44

(2*R*,4*S*)-2-Benzyloxymethyl-4-*O*-methoxymethylphospholane (10). A well stirred suspension of sodium hydride (1 g, 41.6 mmol) in dry and oxygen-free DMSO (60 mL) was heated to 70 °C until the formation of hydrogen ceased and a clear solution resulted. After cooling to 45 - 50 °C, the solution was saturated with phosphine before the bis-mesylate **8** (7.9 g, 18.5 mmol), dissolved in dry, oxygen-free DMSO (20 mL), was slowly added from a dropping funnel while monitoring the pressure and compensating for uptake of phosphine. After 1 h, the mixture was allowed to cool to room temperature. Ice-cooled and oxygen-free water (200 mL) was slowly added before addition of oxygen-free diethyl ether (600 mL). The organic phase was separated, washed with oxygen-free water (100 mL)

then dried and concentrated to leave the crude phospholane **10**. (3.47 g, 66%) δ_C (CDCl₃) 137.1, 129.1, 128.9, 128.4, 128.2, 127.0 (C-ar), 96.2 (O-CH₂-O), 76.4 (*d*, 10 Hz, C-6), 74.2 (*d*, 3.5 Hz, C-4), 71.9 (C-ar), 55.5 (OMe), 30.2 (*d*, 4 Hz, C-3), 24 (*d*, 6 Hz, C-5), 20.3 (*d*, 9 Hz, C-2); δ_P (CDCl₃) - 67.7 ppm

(1*R*,2*R*,4*S*)-2-Benzoyloxymethyl-4-*O*-methoxymethylphospholane-1-oxide (**11**). The crude phospholane **10** (2.3 g, 8.1 mmol) was redissolved in ice-cooled dichloromethane and oxygen was gently dispersed into the stirred solution for at least 1 day. The crude phosphine oxide (1*R*)-**11** was left after evaporation of all solvent and brief lyophilisation (2.41 g, 99 %). δ_H (CDCl₃) 7.35-7.28 (5H, *m*, H-ar), 4.65 (2H, *s*, O-CH₂-O); 4.61-4.58 (2H, *m*, H-6); 4.48 (1H, *ddd*, H-4, 14.8, 6.7, and 0.8 Hz); 4.44 (1H, *m*, H-2); 4.02 (1H, *td*, H-5, 15.5, 14.8, and 2 Hz); 2.13-2.03 (2H, *m*, H-3). δ_C (CDCl₃) 138.3, 129.6, 128.8, and 128.3 (C-ar), 96.9 (O-CH₂-O), 77.6 (*d*, 8 Hz, C-6) 34.5 (*d*, C-5, 45 Hz), 70.8 (Ph-CH₂), 39.6 (*d*, Ph-CH₂-P, 60 Hz), 56.4 (OMe), 30.0 (*d*, C-2, 50.3 Hz), 75.8 (*d*, C-4, 9 Hz), 26.2 (*d*, C-3, 36.5 Hz). δ_P (CDCl₃) 1*R*: 47.6 ppm (96%) and 1*S*: 44.1 ppm (4%).

(2*R*,4*S*)-1-Benzyl-2-benzyloxymethyl-4-*O*-methoxymethylphospholane-1-oxide (**12**). The crude phosphine oxide **11** (0.97 g, 3.24 mmol) was redissolved in dry DMF (8 mL), then potassium carbonate (1.34 g, 3 eq) and benzyl bromide (1.93 mL, 5eq) were added and the mixture was stirred at 35 °C overnight. After removal of the solvent under high vacuum, the residue was redissolved in chloroform (10 mL) and extracted with water (5 mL). The organic phase was separated, dried and concentrated to leave the crude mixture of the phosphine oxide **12**. Column chromatography using ethyl acetate/ethanol (12:1) as eluant served to isolate the pure title compound: yield 0.29 g 24 %. Data of (1*R*)-**12**: mp 112 °C; $[\alpha]^{20}_D$ -37.8 ° (*c* 0.8, THF); δ_H (CDCl₃) 7.24-7.20 (10 H, H-ar), 4.56 (2 H, O-CH₂-O), 4.45 (2 H, *d*, 12 Hz, Ph-CH₂-O), 3.97 (1 H, *m*, 20, 4.5, 3, 3 Hz, H-4), 3.73 (2 H, *m*, 12, 12, 8, 5 Hz, H-6), 3.29 (3 H, *s*, Me), 3.27 (2 H, *m*, 42 Hz, Ph-CH₂-P), 2.89 (1 H, *ddd*, 14.5, 7, 5 Hz, H-5a), 2.78 (1 H, *dddd*, 14.5, 12, 4, 3, H-5e), 2.27 (1 H, 14.7, 9, 5, 4 Hz, H-2), 1.83 (1 H, *ddd*, 10, 5, 4.5 Hz, H-3a), 1.59 (1 H, *dt*, 10, 4, 3 Hz, H-3e); δ_C (CDCl₃) 138.17, 132.32 (2C-ar), 130.16, 129.22, 129.20, 128.77, 128.07, 127.98, 127.43, 127.41 (C-ar), 96.99 (O-CH₂-O), 77.75 (*d*, 6 Hz, C-6) 74.60 (*d*, C-4, 8.2 Hz), 70.66 (Ph-CH₂ ether), 39.6 (*d*, Ph-CH₂-P, 60 Hz), 55.01 (OMe), 36.4 (*d*, C-2, 55 Hz), 34.5 (*d*, C-3, 11 Hz), 32.0 (*d*, C-5, 66.1 Hz); δ_P [CDCl₃ (H₃PO₄)]: 62.4 ppm.

Anal. Calcd for $C_{21}H_{27}O_4P$ (374.42): C, 67.37; H, 7.27. Found: C, 68.96; H, 7.04

(1*R*,2*R*,4*S*)-1-*O*-Benzyl-2-benzyloxymethyl-4-*O*-methoxymethylphospholane-1-oxide (**14**). The crude phospholane **10** (1 g, 3.5 mmol) was redissolved in a mixture of ice-cooled dichloromethane (10 mL) and 30% hydrogen peroxide (1 mL) which was stirred for 1 h. The residue mainly consisting of the phosphinic acid **13** (δ_P (CDCl₃) 30.2 ppm) was dried under high vacuum after removal of all liquid.

The crude phosphinic acid **13** (1.04 g, 3.3 mmol) was redissolved in dry DMF (80 mL), then potassium carbonate (13.44 g, 3 eq) and benzyl bromide (19.3 mL, 5eq) were added and the mixture was stirred at 30 °C overnight. After removal of the solvent under vacuum, the remainder was redissolved in chloroform (100 mL) and extracted twice with water (2 x 30 mL). The organic phase was separated, dried and concentrated to leave the crude phosphinic acid ester **14** which consisted of a 7:1-mixture of stereoisomers according to ³¹P NMR (δ_P 73.0 and 73.7 ppm). Repeated column chromatography (3 runs) using ethyl acetate/ethanol (12:1) as eluant was necessary to isolate the major (1*R*)-isomer. The TLC-pure title compound appeared as a honey-like mixture of crystals suspended in an viscous oil (454 mg, 34 %). δ_H (CDCl₃) 7.42-7.30 (10 H, *m*, H-ar), 5.16 (2 H, *ddd*, 16.5, 12, 4 Hz, Ph-CH₂-O-P), 4.61 (2 H, *s*, O-CH₂-O), 4.49 (2 H, *t*, 12, 12 Hz, H-6), 4.15 (1 H, *m*, H-4), 3.80 (2 H, *ddd*, 16, 8, 6 Hz, H-6), 3.35 (3 H, *s*, Me), 2.75 (1 H, *ddd*, 14, 9, 6 Hz, H-5a) 2.42 (1 H, *ddd*, 14, 10, 4 Hz, H-5e), 2.13 (1 H, *m*, H-2), 1.90 (1 H, *dt*, 13, 13, 4 Hz, H-3a), 1.78 (1 H, *dt*, 13, 13, 2 Hz, H-3e); δ_C (CDCl₃) 137.03, 137.08 (2 C, C-ar), 129.02, 128.94, 128.85, 128.74, 128.54, 128.38, 128.32, 128.18, 127.98 (8 C, C-ar), 96.83 (O-CH₂-O), 77.74 (*d*, 8 Hz, C-6), 74.0 (*d*, 6Hz, C-4), 70.8 (Ph-C, ether), 66.8 (*d*, 41 Hz, Ph-C,ester), 55.76 (OMe), 36.6 (*d*, 86 Hz, C-2), 34.4 (*d*, 13 Hz, C-3), 32.6 (*d*, 84 Hz, C-5); δ_P (CDCl₃) 73.0 ppm.

Anal. Calcd for $C_{21}H_{27}O_5P$ (390.42): C, 64.61; H, 6.97. Found: C, 64.32; H, 7.18.

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