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Synthesis of (*R*)-2-methyl-4-deoxy and (*R*)-2-methyl-4,5-dideoxy analogues of 6-phosphogluconate as potential inhibitors of 6-phosphogluconate dehydrogenase †

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The synthesis of (2*R*)-2-methyl-4,5-dideoxy and (2*R*)-2-methyl-4-deoxy analogues of 6-phosphogluconate is described. The synthetic strategy relies on the Evans aldol reaction for the installation of the chiral centres in the 2- and 3-positions. The selective phosphorylation at the primary alcohol function of (2*R*,3*S*)-3,6-dihydroxy-2-methylhexanoic acid benzyl ester (**5**) and (2*R*,3*S*,5*S*)-3,5,6-trihydroxy-2-methylhexanoic acid benzyl ester (**20**) was achieved with dibenzyl phosphochloridate and dibenzyl phosphoiodinate respectively, working at low temperature. (2*R*,3*S*)-3-Hydroxy-2-methyl-6-phosphonoxyhexanoic acid (**9**) was obtained in 25% overall yield from 4-benzyloxybutanol and (2*R*,3*S*,5*S*)-3,5-dihydroxy-2-methyl-6-phosphonoxyhexanoic acid (**28**) in 10% overall yield from L-malic acid.

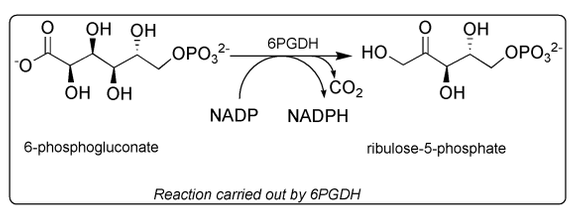
Introduction

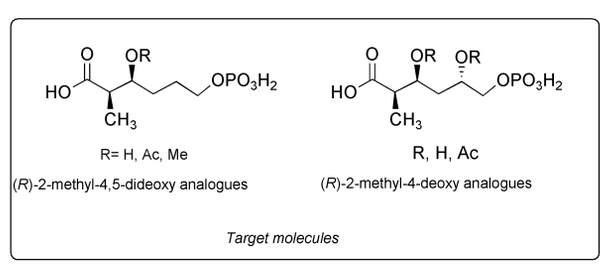
The parasitic infection Human African Trypanosomiasis (sleeping sickness) is a major health problem in sub-Saharan Africa causing an estimated 66 000 deaths per year.[1] The treatment of African Trypanosomiasis is unsatisfactory, with most of the drugs in use giving rise to serious side effects, increasing problems of resistance and, in some cases, poor blood-brain barrier permeability.[2] Thus, there is an urgent need for new drugs to treat sleeping sickness.

Bloodstream forms of *Trypanosoma brucei* (*T. brucei*), the causative organisms of sleeping sickness, exclusively produce energy (ATP) through glycolysis, making the inhibition of any of the glycolytic enzymes a potential therapeutic approach.[3] In our search for new anti-trypanosomal agents, we decided to target the enzyme 6-phosphogluconate dehydrogenase (6PGDH), the third enzyme of the pentose phosphate pathway (PPP).[4] The PPP is responsible for generation of NADPH (a biosynthetic intermediate used in protection against oxidative stress) and ribulose 5-phosphate (used in the biosynthesis of nucleotides) (Fig. 1).

A number of reasons suggest that 6PGDH could be a good target for chemotherapy[5] and inhibitors have been found that are selective for 6PGDH of *T. brucei.* In particular, 2-deoxy-6-phosphogluconate (Fig. 1) is a selective inhibitor of the *T. brucei* enzyme.[6]

Crystallographic studies of the sheep liver[7] as well as the *T. brucei*[8] enzyme have shown differences at the active site that it should be possible to exploit for selective drug design. A particular point of interest is a larger binding pocket for the trypanosome enzyme in the region of the 2-OH group of the substrate. Moreover, molecular modelling studies[9] on the interaction between 6PG and the *T. brucei* enzyme revealed a number of important functionalities involved in the interaction. In particular, the 4-OH group does not appear to have strong interactions with the enzyme and we wanted to probe the importance of the 5-OH in determining activity and selectivity. These findings were used to design a series of (2*R*)-2-methyl-4,5-dideoxy and (2*R*)-2-methyl-4-deoxy analogues of 6PG (Fig. 1) that will allow us to carry out Structure Activity Relationship studies to probe the active site of 6PGDH enzyme.





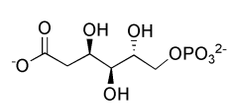


Fig. 1

Results and discussion

General synthetic approach

The synthetic strategy relies on the Evans aldol reaction for the installation of the chiral centres in the 2- and 3-positions. The use of boron *Z*-enolates of chiral oxazolidin-2-one derivatives allows high diastereoselectivity in the reaction and formation of almost exclusively the *syn* aldol product.[10] The second step is the exchange of the chiral auxiliary with a benzyl ester protecting group that can be removed in very mild conditions (*i.e.* catalytic hydrogenolysis). Finally, introduction of the phosphate moiety with protected phosphorus(V) reagents is achieved selectively at the primary alcohol working at low temperature.

† Electronic supplementary information (ESI) available: experimental procedure and spectroscopic data (^{1}H NMR, ^{13}C NMR, DEPT) for compounds **2**, **12**, **13**, **14**, **15** and **21b** and the previous synthetic approach tried for the synthesis of (2*R*)-2-methyl-4,5-dideoxy analogues. See http://www.rsc.org/suppdata/ob/b2/b210606j/

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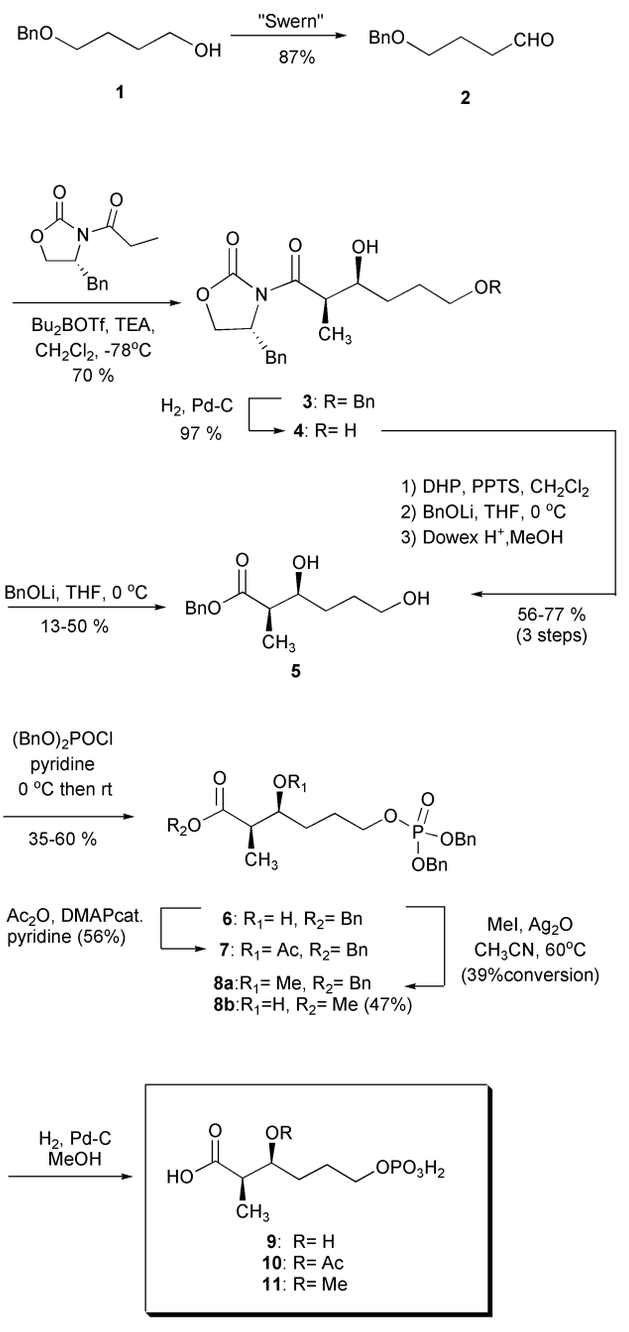
A previous approach[11] in which we tried to remove the chiral auxiliary at the end of the synthesis just before the deprotection of the phosphate turned out to be unsuccessful because of the sensitivity of the phosphate to the reaction conditions used ($LiOH–H_2O_2$). The phosphate group was cleaved using these reaction conditions and the main product obtained was a seven-member ring lactone that resulted from the intramolecular attack of the terminal 5-OH to the carbonyl at C1.

Synthesis of (2*R*)-2-methyl-4,5-dideoxy analogues (Scheme 1)

Swern oxidation[12] of 4-benzyloxybutanol **1** yielded 4-benzyloxybutyraldehyde[13] **2** in 87% yield. Aldehyde **2** was used in the boron aldol reaction[14] with (4*R*)-4-benzyl-3-propionyloxazolidin-2-one[15] and freshly prepared dibutylboron triflate‡[16] to afford the *syn* aldol product (2*R*,3*S*)-**3** in 70% yield.

Hydrogenolysis of the benzyl protecting group with 10% Pd–C followed by lithium benzyloxide transesterification[17] allowed isolation of the benzyl ester **5** in only low to moderate yield (13–50%). Since we thought that the presence of the free hydroxy groups could be in part responsible for the low to moderate yields, diol **4** was first protected as a THP ether and the crude THP-protected **4** reacted with three equivalents of lithium benzyloxide. In this reaction, excess benzyl alcohol, generated as a by-product, has the same R_f value as the THP-protected benzyl ester product, which makes the purification of the intermediate difficult. Hence, the crude reaction mixture was treated with Dowex acidic resin to remove the THP protecting groups, and **5** could be isolated by chromatography (overall yield for the three steps from **4**–**5** is 56–77%).



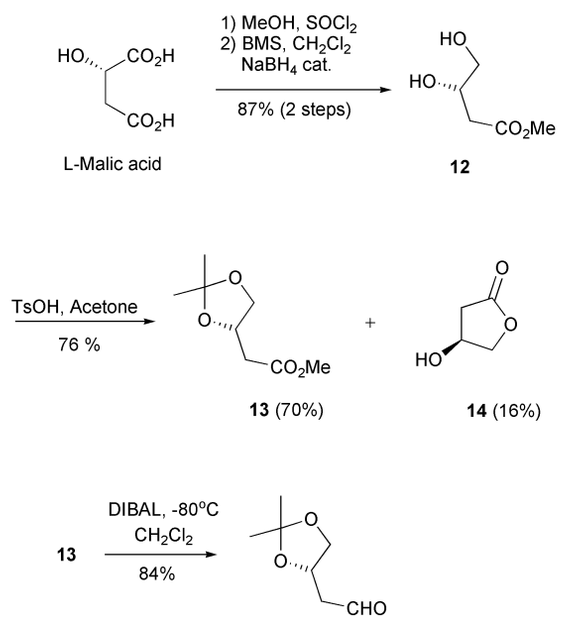
Scheme 1

Selective phosphorylation of **5** at the primary alcohol group was accomplished by adding 1.3 eq. of dibenzyl phosphochloridate (freshly prepared from dibenzyl phosphate and sulfuryl chloride in CCl_4)[18] at 0 °C to a solution of **5** in pyridine. That phosphorylation occurred on the primary alcohol was established by the diagnostic downfield ^{1}H NMR chemical shift of the CH_2 protons at C6 (4.06 ppm compared to 3.70 ppm for **5**) and the unaffected CH proton at C2 (3.9 ppm).

To probe the necessity of the 3-OH, the 3-hydroxy was derivatised as follows: phosphate **6** was acetylated with acetic anhydride and a catalytic amount of DMAP in pyridine to afford **7**. The methylated derivative **8** was obtained by reaction of **5** with silver(II) oxide and MeI in CH_3CN at 60 °C for 3 days. André *et al.*[19] reported that among the numerous procedures of alkylation of hydroxy groups described in the literature, it appeared that the one using MeI and Ag_2O was the most efficient for substrates possessing an ester or a lactone group.[20] However, the main products we obtained in this reaction were the transesterification product **8b** (47%) and recovered starting material **6** together with 20% of the expected **8a** (39% conversion). An attempt at methylation of **6** with MeI and NaH failed and no expected product was detected in the reaction mixture. Finally, the free phosphate derivatives **9**, **10** and **11** were obtained quantitatively by hydrogenolysis of the benzyl protecting groups.

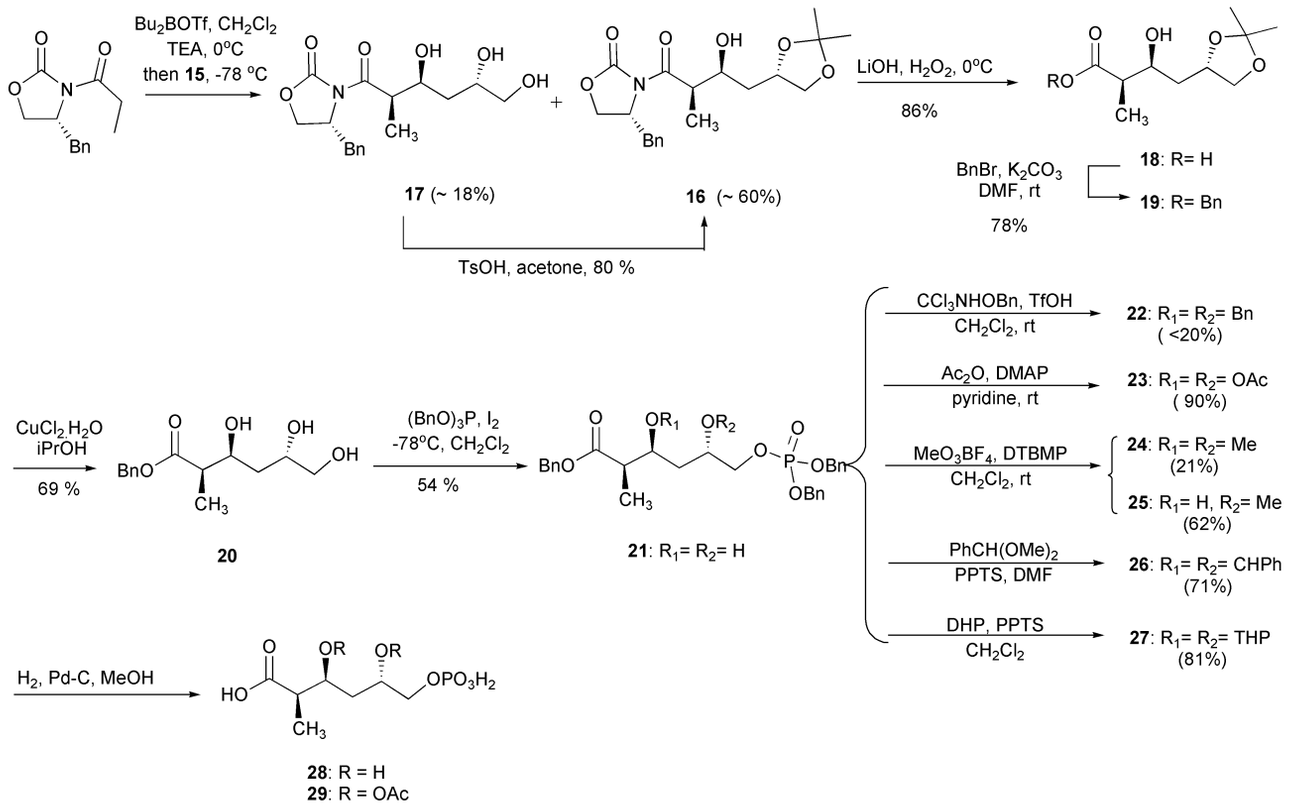
Synthesis of (2*R*)-2-methyl-4-deoxy analogues (see Scheme 3)

The strategy used for the preparation of the 4-deoxy analogues was similar to that used for the 4,5-dideoxy analogues, using the aldehyde (3*S*)-**15**[19,21] in the boron aldol reaction. Enantio-pure (3*S*)-**15** was prepared in four high-yielding steps from L-malic acid (Scheme 2).[22]



Scheme 2

‡ Triflate = trifluoromethanesulfonate.



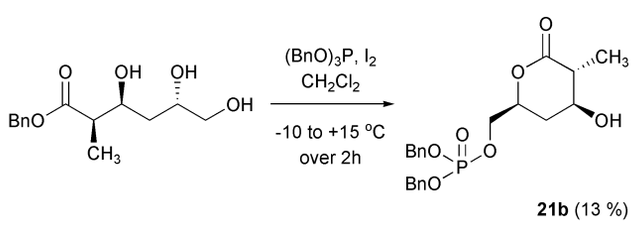
Scheme 3

Diastereoselective boron aldol reaction with aldehyde **15** and (*R*)-4-benzyl-3-propionyloxazolidin-2-one afforded a mixture of the expected (2*R*,3*S*)-acetonide **16** (60%) and the deprotected triol (2*R*,3*S*)-**17** (18%, Scheme 3). The latter could be protected again by reaction with acetone and catalytic toluene-*p*-sulfonic acid. Direct removal of the chiral auxiliary by BnOLi transesterification[17] gave a mixture of the expected benzyl ester **19** and a by-product arising from the opening of the oxazolidinone ring and an elimination process. Moreover, BnOH has the same R_f value as the desired product **19**, making its purification by chromatography rather difficult. Since the direct transesterification reaction did not give good results, the benzyl ester **19** was prepared in two steps: the chiral auxiliary was first removed with $LiOH–H_2O_2$,[17] affording the pure acid **18** in good yield (86%) by acid-base work-up. Acid **18** was subsequently esterified with benzyl bromide and K_2CO_3 in DMF affording **19** in 78% yield (67% for two steps).

Removal of the isopropylidene protective group is not as straightforward as it seems because of the presence of the benzyl ester functionality and therefore the risk of debenzylation during acid hydrolysis or transesterification when using alcohol as solvent. This behaviour was observed when Dowex 50WX2 in MeOH was used to hydrolyse the acetonide and the methyl ester derivative was obtained as a major by-product. Eventually, $CuCl_2{\cdot}2H_2O$ in ^{i}PrOH was used according to the procedure of Iwata *et al.*[23] to afford the triol **20** in good yield (69%).

Selective phosphorylation at the primary hydroxy group was first attempted with dibenzyl phosphochloridate giving only low yield (< 20%) of the phosphate **21**. The fact that starting material **20** was always recovered in these attempts prompted us to use the more reactive dibenzyl phosphoiodinate (prepared from $(BnO)_3P$ and I_2 in CH_2Cl_2)[24] as the phosphorylating agent. Working at −78 °C allowed the preparation of **21** in 54% yield. However, higher temperatures (*i.e.* −10 °C to +15 °C over 2 h) resulted in the lactonisation of the product to **21b** (Scheme 4).[25]

Furthermore, although two equivalents of dibenzyl phosphoiodinate are used to drive the reaction, the second equivalent should be added in small portions, controlling



Scheme 4

progression of the reaction to avoid bis-phosphorylation of the product (this behaviour was observed when 2 eq. of reagent were added at once).

Acetylation of **21** yielded **23** (90%) whereas methylation with MeO_3BF_4–2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) in CH_2Cl_2 afforded a mixture of the mono and bismethylated products **24** and **25** respectively. These two compounds were isolated by flash chromatography with 21% and 62% yield respectively. The last step of the synthesis, consisting of hydrogenolysis of the benzyl protective group with Pd–C, was successfully carried out with **23**. However, in the case of **21**, which contains two free hydroxy groups, hydrogenolysis led to a mixture of two phosphorus compounds, possibly due to the migration of the phosphate to the adjacent free hydroxy group. Phosphate migration during hydrogenolysis is a well-known phenomenon, in inositols for instance,[26] where migration of fully protected phosphate around the ring can occur. On the contrary, migration of phosphate in fully deprotected inositol 1-phosphate only occurs in strong acid or strong base. Moreover, cyclic phosphate formation is a potential side reaction where vicinal diols are present.[27] Some authors have successfully prepared some L-*glycero*-D-*manno*-heptoside phosphate derivatives by catalytic hydrogenolysis of their fully benzyl-protected precursors (no migration was observed in this case).[28] Those facts suggested that the protection of the 5-hydroxy of **21** as benzyl ether should reduce the tendency to phosphate migration during hydrogenolysis. Protection of **21** with benzyl trichloroacetimidate and catalytic triflic acid in CH_2Cl_2 was attempted, affording only a moderate yield of **22** (< 25%) in all

the attempts carried out. Thus, the 1,3-diol **21** was protected as its benzylidene acetal derivative with benzaldehyde dimethyl acetal and PPTS in DMF to afford **26** (71%).

Unfortunately, hydrogenolysis of either **22** or **26** led to a mixture of two phosphate regioisomers. To circumvent this problem, **21** was protected as a THP ether **27** in high yield (81%) and then subjected to hydrogenolysis[30] followed by mild acidic hydrolysis to remove the THP protecting groups, and afford the phosphate **28** (70%).

Conclusion

An efficient synthetic route to (2*R*)-2-methyl-4-deoxy and (2*R*)-2-methyl-4,5-dideoxy analogues of 6-phosphogluconate is reported, starting from 4-benzyloxybutanol **1** and L-malic acid respectively and using boron aldol methodology for the incorporation of the (2*S*,3*R*) chiral centres. This general approach is currently being used to prepare more 2-substituted-4-deoxy analogues of 6-phosphogluconate.[29]

Experimental section

Where applicable, all glassware was oven dried overnight and all reactions were carried out under nitrogen. All dry solvents were purchased from Aldrich or Fluka in sure seal bottles. All reactions were monitored by Thin Layer Chromatography (TLC) using silica gel 60 F_{254} plates (Merck). Column chromatography was performed on Uetikon silica gel C-560 Act (0.035–0.070 mm). The infrared spectroscopy (IR) of the compounds was recorded on a Perkin Elmer 1600 series FTIR spectrometer as films on sodium chloride discs (thin film). $[\alpha]_D$ values were measured on a ADP220 polarimeter (Bellingham & Stanley Ltd) and are given in 10^{-1} deg cm^2 g^{-1}. ^{1}H NMR, ^{13}C NMR and ^{31}P NMR spectra were recorded on a Bruker Avance DPX 300 MHz spectrometer at 300, 75 and 121 MHz respectively, using the solvent residual peak as internal reference. *J* values are given in Hz. Elemental analyses were determined on a Perkin-Elmer 240C elemental analyser. Low resolution mass spectra (MS) were recorded on a Fisons VG Platform II spectrometer using electrospray ionisation (ES) technique either in positive or negative ion modes. Mobile phases were acetonitrile–water 1 : 1 or methanol (ES). High-resolution mass spectra (HRMS) in chemical ionisation (CI) and fast atom bombardment (FAB) were determined by the EPSRC Mass Spectroscopy Centre, Swansea, UK.

(4*R*)-4-Benzyl-3-[(2*R*,3*S*)-6-benzyloxy-3-hydroxy-2-methyl-hexanoyl]oxazolidin-2-one (3)

Freshly prepared dibutylboron triflate[16] (2.35 cm^3, 9.3 mmol) was added to a solution of (3*R*)-3-propionyl-4-benzyloxazolidin-2-one (1.67 g, 7.2 mmol) in dry CH_2Cl_2 (15 cm^3) at 0 °C. Et_3N (1.3 cm^3, 9.3 mmol) was then added keeping the internal temperature below +3 °C. The resulting yellow solution was cooled to −78 °C and aldehyde **2** (1.53 g, 8.6 mmol) was added dropwise. The clear yellow solution was stirred for 1 h 15 min at 0 °C. The reaction was quenched with 7 cm^3 of phosphate buffer (pH 7.2) and 20 cm^3 of MeOH. Then, 10 cm^3 of a 2 : 1 solution of MeOH–H_2O_2 (30% in water) was added dropwise, keeping the internal temperature below +10 °C. This mixture was stirred for 1 h at 0 °C. The solvent was removed *in vacuo* and the resulting oil was partitioned between water and EtOAc. The aqueous phase was extracted with EtOAc (2 × 50 cm^3). Organic extracts were washed with $NaHCO_3$, brine, and dried ($MgSO_4$). Removal of the solvent afforded a yellow oil that was chromatographed (40% EtOAc–hexane) to give **3** as a colourless oil (2.06 g, 70%); R_f: 0.37 (50% EtOAc in hexane); $[\alpha]_D^{22}$ = −40 (*c* 0.1, CH_2Cl_2); υ_{max}(neat)/cm^{-1} 3442; 1777; 1696; δ_H ($CDCl_3$) 7.5–7.25 (10H, m); 4.75 (1H, m, C*H*N); 4.6 (2H, s, OCH_2Ph); 4.25 (2H, m, OCH_2CH); 4.1 (1H, m, C*H*OH); 3.85 (1H, m, C*H*Me); 3.55 (2H, m); 3.3 (1H, dd, *J* 3.3 and 13.5, CH_2Ph); 2.85 (1H, dd, *J* 9.5 and 13.5, CH_2Ph); 1.9–1.6 (5H, m); 1.3 (3H, d, *J* 7, CH_3); δ_C ($CDCl_3$) 177.6 (s); 153.5 (s); 138.7 (s); 135.5 (s); 129.9 (d); 129.4 (d); 128.8 (d); 128.2 (d); 128.14 (d); 128.1 (d); 128.0 (d); 127.9 (d); 73.4 (t); 71.9 (d); 70.6 (t); 66.6 (t); 55.6 (d); 42.8 (d); 38.2 (d); 31.5 (t); 26.8 (t); 11.1 (q); *m*/*z* (ES$^+$) 434 (M + Na); *m*/*z* (ES) 412.2117 (M + H.$C_{24}H_{30}NO_5$ requires: 412.2124).

(4*R*)-4-Benzyl-3-[(2*R*,3*S*)-3,6-dihydroxy-2-methylhexanoyl]-oxazolidin-2-one (4)

A solution of **3** (572 mg, 1.4 mmol) was dissolved in MeOH (50 cm^3) and hydrogenated for 2.5 h with 5% Pd–C (200 mg) and 30 Psi H_2 pressure. The catalyst was filtered off and the solvent evaporated to yield **4** as a yellowish oil (434 mg, 97%); R_f: 0.2 (25% hexane in EtOAc); $[\alpha]_D^{20}$ = −81.8 (*c* 0.11, MeOH); υ_{max}(neat)/cm^{-1} 3400; 1780; 1696; δ_H ($CDCl_3$) 7.5–7.2 (5H, m); 4.85 (1H, m, C*H*N); 4.35 (2H, m, OCH_2CH); 4.15 (1H, m, C*H*OH); 4.0–3.75 (3H, m); 3.4 (1H, dd, *J* 3.3 and 13.5, CH_2Ph); 2.9 (1H, dd, *J* 9.4 and 13.5, CH_2Ph); 2.6 (2H, br s, 2 × O*H*); 1.85 (2H, quint, $CH_2CH_2CH_2$); 1.75 (2H, m); 1.4 (3H, d, *J* 7, CH_3); δ_C ($CDCl_3$) 177.3 (s); 153.7 (s); 135.5 (s); 129.9 (d); 129.4 (t); 127.8 (t); 72.2 (d); 66.7 (t); 62.8 (t); 55.6 (d); 43.2 (d); 38.1 (t); 31.6 (t); 29.8 (t); 11.5 (q); *m*/*z* (ES$^+$) 344 (M + Na).

(2*R*,3*S*)-3,6-Dihydroxy-2-methylhexanoic acid benzyl ester (5)

A solution of **4** (453 mg, 1.41 mmol), 3,4-dihydro-2*H*-pyran (DHP) (0.77 cm^3, 8.5 mmol) and PPTS (38 mg, 0.14 mmol) in CH_2Cl_2 (6 cm^3) was stirred at rt for 16 h. The reaction was partitioned between CH_2Cl_2 and half-saturated brine. The organic phase was dried ($MgSO_4$) and concentrated to give a colourless oil (702 mg). The crude THP-protected diol **4** was dissolved in THF (8 cm^3) and treated at −5 °C with a BnOLi solution [prepared by addition at 0 °C of nBuLi (4.9 mmol) to a solution of benzyl alcohol (0.58 cm^3, 5.6 mmol) in THF (3 cm^3)]. After 2 h at 0 °C, the reaction was quenched with saturated NH_4Cl solution (2 cm^3). The mixture was partitioned between water and EtOAc and the aqueous phase was extracted with EtOAc (3 × 20 cm^3). Combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated to give a yellowish oil (1.23 g). This oil was dissolved in 50 cm^3 of MeOH and treated with wet Dowex 50X8 resin for 18 h. The resin was filtered off and rinsed with MeOH. The methanolic solution was concentrated *in vacuo* and the residue was partitioned between EtOAc and brine. The organic phase was dried ($MgSO_4$) and concentrated to give a crude yellow oil. Chromatography with EtOAc–hexane (3 : 1) afforded the pure ester **5** as a colourless oil (200 mg, typical yield: 56–77%); R_f: 0.22 (EtOAc–hexane: 3 : 1); $[\alpha]_D^{23}$ = −10 (*c* 0.1, MeOH); δ_H ($CDCl_3$) 7.45 (5H, m); 5.2 (2H, s, OCH_2Ph); 3.95 (1H, m, C*H*OH); 3.70 (2H, m, CH_2OH); 3.20 (1H, br, O*H*); 2.7 (1H, m, C*H*Me); 2.4 (1H, br, O*H*); 1.75 (2H, m); 1.6 (2H, m); 1.3 (3H, d, *J* 7, CH_3); δ_C ($CDCl_3$) 176.3 (s); 136.1 (s); 129.0 (d); 128.8 (d); 128.6 (d); 72.3 (d); 66.9 (t); 63.1 (t); 45.2 (d); 31.6 (t); 30.0 (t); 11.5 (q); *m*/*z* (ES$^+$) 275 (M + Na); *m*/*z* (ES) 253.1442 (M + H. $C_{14}H_{21}O_4$ requires: 253.1440).

(2*R*,3*S*)-6-(Bis(benzyloxy)phosphoryloxy)-3-hydroxy-2-methyl-hexanoic acid benzyl ester (6)

Sulfuryl chloride (0.12 cm^3,1.5 mmol) was added with a syringe to a flask containing a solution of dibenzyl phosphite (0.33 cm^3, 1.5 mmol) in CCl_4 (2 cm^3). After 1 h at rt, the volatiles were removed *in vacuo* and the product was used directly without purification. $(BnO)_2P(O)Cl$ (320 mg, 1.3 eq.) was added at 0 °C to the alcohol **5** dissolved in pyridine (2 cm^3) under a N_2 atmosphere. The reaction was stirred for 2 h at 0 °C and 1 h at rt. The solvent was removed *in vacuo* and the crude yellow oil was chromatographed with EtOAc–hexane (5 : 2) to give **6** (247 mg,

60%) as a colourless oil; R_f: 0.47 (EtOAc–hexane, 3 : 1); $[\alpha]_D^{23}$ = −4.3 (*c* 0.23, MeOH); δ_H ($CDCl_3$) 7.4 (15H, m); 5.2 (2H, s, OCH_2Ph); 5.1 (2H, d, *J* 3.3, POCH_2Ph); 5.08 (2H, d, *J* 3.3, POCH_2Ph); 4.06 (2H, m, CH_2CH_2OP); 3.9 (1H, m, C*H*OH); 2.86 (1H, d, *J* 4.9, O*H*); 2.58 (1H, qd, *J* 7.2 and 3.8, C*H*Me); 1.85 (1H, m); 1.7 (1H, m); 1.45 (2H, m); 1.23 (3H, d, *J* 7.2, CH_3); δ_C ($CDCl_3$) 176.2 (s); 136.3 (2 × s); 136.1 (s); 129.1 (d); 129.0 (2 × d); 128.8 (d); 128.6 (d); 128.4 (d); 71.7 (d); 69.6 (d, *J* 7.5, CH_2); 68.2 (d); 66.9 (t); 45.0 (d); 30.2 (t); 27.4 (d, *J* 7.5, CH_2); 11.3 (q); δ_P (CD_3OD) + 0.5; *m*/*z* (ES^+) 535 (M + Na); *m*/*z* (ES) 513.2047 (M + H. $C_{28}H_{34}O_7P$ requires: 513.2042).

(2*R*,3*S*)-3-Acetoxy-6-bis(benzyloxy)phosphoryloxy-2-methylhexanoic acid benzyl ester (7)

A solution of **6** (80 mg, 0.156 mmol), acetic anhydride (16 µl, 0.17 mmol) and DMAP (4 mg, 0.03 mmol) in pyridine (2 cm^3) was stirred for 18 h at rt. Pyridine was removed *in vacuo* and the crude oil was chromatographed with 50% EtOAc–hexane to afford **7** as a colourless oil (48 mg, 56%); R_f: 0.34 (50% EtOAc–hexane); $[\alpha]_D^{22}$ = −4 (*c* 0.25, MeOH); δ_H ($CDCl_3$) 7.4 (15H, m); 5.2 (1H, m, C*H*OAc); 5.13 (2H, s, OCH_2Ph); 5.1 (2H, m, POCH_2Ph); 5.05 (2H, m, POCH_2Ph); 4.0 (2H, m, CH_2CH_2OP); 2.75 (1H, m, C*H*Me); 2.0 (3H, s, CH_3CO); 1.65 (4H, m); 1.2 (3H, d, *J* 7.1, CHCH_3); δ_C ($CDCl_3$) 173.8 (s); 170.89 (s); 136.3 (s); 136.21 (s); 136.16 (s); 129.03 (d); 129.0 (d); 128.84 (d); 128.76 (d); 128.39 (d); 73.86 (d); 69.73 (t); 69.66 (t); 67.7 (*J* 5.9, CH_2); 67.03 (t); 43.48 (d); 28.35 (t); 26.8 (d, *J* 7.3, CH_2); 21.2 (q); 12.1 (q); δ_P ($CDCl_3$) + 0.32; *m*/*z* (FAB/3-nitrobenzyl alcohol (NOBA) matrix) 555 (M + H); *m*/*z* (FAB) 555.2143 (M + H. $C_{30}H_{36}O_8P$ requires: 555.2148).

(2*R*,3*S*)-6-Bis(benzyloxy)phosphoryloxy-3-methoxy-2-methylhexanoic acid benzyl ester (8a)

A solution of **6** (100 mg, 0.195 mmol), Ag_2O (68 mg, 0.29 mmol) and MeI (0.5 cm^3, 8 mmol) in CH_3CN (2.5 cm^3) was stirred for 1 day at rt and 3 days at 60–70 °C. The reaction mixture was diluted with CH_2Cl_2 and filtered on a path of Celite. Evaporation of the solvent gave an orange oil that was chromatographed with 50% EtOAc–hexane. The expected product **8a** (20 mg, 39% conversion) was eluted first, then the starting material **6** (50 mg, 50%) and finally the methyl ester by-product **8b** (40 mg, 47%). $[\alpha]_D^{21}$ = −2.5 (*c* 2, MeOH); δ_H ($CDCl_3$) 7.4 (15H, br s); 5.2 (2H, d, *J* 4.4, OCH_2Ph); 5.12 (2H, m, POCH_2Ph); 5.09 (2H, m, POCH_2Ph); 4.0 (2H, m, CH_2CH_2OP); 3.5 (1H, m, C*H*OH); 3.3 (3H, s, OCH_3); 2.65 (1H, m, C*H*Me); 1.9–1.5 (4H, m); 1.2 (3H, d, *J* 7.2, CHCH_3); δ_P ($CDCl_3$) + 0.45; *m*/*z* (ES^+) 549 (M + Na); *m*/*z* (ES) 527.2195 (M + H. $C_{29}H_{36}O_7P$ requires 527.2198).

(2*R*,3*S*)-6-Bis(benzyloxy)phosphoryloxy-3-hydroxy-2-methylhexanoic acid methyl ester (8b)

δ_H ($CDCl_3$) 7.4 (10H, br s); 5.1 (2H, m, POCH_2Ph); 5.05 (2H, m, POCH_2Ph); 4.1 (2H, m, CH_2CH_2OP); 3.9 (1H, m, C*H*OH); 3.75 (3H, s, COOCH_3); 2.72 (1H, br d, *J* 4.7, OH); 2.54 (1H, qd, *J* 3.5 and 7.2, C*H*Me); 1.9 (1H, m); 1.7 (1H, m); 1.5 (2H, m); 1.2 (3H, d, *J* 7.1, CHCH_3); δ_P ($CDCl_3$) + 0.5; *m*/*z* (ES^+) 459 (M + Na); *m*/*z* (ES^+) 437.1729 (M + H. $C_{22}H_{30}O_7P$ requires: 437.1729).

(2*R*,3*S*)-3-Hydroxy-2-methyl-6-phosphonoxyhexanoic acid (9)

A solution of **6** (54 mg, 0.1 mmol) in MeOH (2 cm^3) was hydrogenated for 5 h with 5% Pd–C (12 mg). The catalyst was filtered off and the solvent evaporated to yield a colourless oil (24 mg). Et_2O-mediated precipitation of the product dissolved in a little MeOH yielded **9** as a very hygroscopic colourless solid (24 mg, 94%). $[\alpha]_D^{22}$ = −8.3 (*c* 0.24, MeOH); δ_H (CD_3OD) 4.0 (2H, br m); 3.8 (1H, br m); 2.45 (1H, m); 1.9 (1H, br m); 1.8–1.4 (4H, br m); 1.2 (3H, d, *J* 7, CH_3); δ_C (CD_3OD) 179.3 (s); 73.5 (d); 68.0 (t); 47.4 (d); 32.6 (t); 28.65 (d, *J* 7.5, CH_2); 12.9 (q); δ_P (CD_3OD) +1.37; *m*/*z* (ES^-) 241 (M − H); *m*/*z* (ES^-) 241.0478 (M − H. $C_7H_{14}O_7P$ requires 241.0477).

(2*R*,3*S*)-3-Acetoxy-2-methyl-6-phosphonoxyhexanoic acid (10)

A suspension of **7** (25 mg, 0.045 mmol) and 5% Pd–C in MeOH (5 cm^3) was hydrogenated for 1 h to yield **10** as a colourless oil (16 mg, 100%); $[\alpha]_D^{24}$ = −6.2 (*c* 0.16, MeOH); δ_H (CD_3OD) 5.2 (1H, br m); 4.0 (2H, br); 2.7 (1H, m); 2.05 (3H, s, CH_3CO); 1.8–1.5 (4H, br m); 1.15 (3H, d, *J* 6.9, CHCH_3); δ_C (CD_3OD) 177.82 (s); 172.84 (s); 75.59 (d); 67.33 (t); 44.75 (d); 30.0 (t); 28.22 (t); 21.28 (q); 12.87 (q); δ_P (CD_3OD) +1.42; *m*/*z* (ES^-) 283 (M − H); *m*/*z* (ES^+) 307.0554 (M + Na. $C_9H_{17}NaO_8P$ requires 307.0559).

(2*R*,3*S*)-3-Methoxy-2-methyl-6-phosphonoxyhexanoic acid (11)

A suspension of **8a** (45 mg) and 5% Pd–C in MeOH (4 cm^3) was hydrogenated for 22 h at rt to yield **11** as a yellowish oil. δ_H (CD_3OD) 4.0 (2H, br); 3.7 (1H, br d); 3.55 (1H, br m); 3.4 (3H, s, OCH_3); 2.62 (1H, m); 1.9–1.6 (4H, m); 1.15 (3H, d, *J* 7.2, CHCH_3); δ_C (CD_3OD) 179 (s); 83.6 (d); 67.6 (t); 58.6 (q); 44.4 (d); 29.4 (t); 28.0 (t); 12.4 (q); δ_P (CD_3OD) +1.33; *m*/*z* (ES^-) 255 (M − H); *m*/*z* (ES^-) 255.0632 (M − H. $C_8H_{16}O_7P$ requires 255.0638).

(4*R*)-4-Benzyl-3-{(2*R*,3*S*)-4-[(1*S*)-2,2-dimethyl-[1,3]-dioxolan-4-yl]-3-hydroxy-2-methylbutyryl}oxazolidin-2-one (16)

Dibutylboron triflate (3.55 cm^3, 14 mmol) was added dropwise to a solution of (3*R*)-3-propionyl-4-benzyloxazolidin-2-one (2.995 g, 12.8 mmol) in dry CH_2Cl_2 (20 cm^3) at 0 °C, followed by Et_3N (2.1 cm^3, 15.4 mmol), keeping the internal temperature below +3 °C. The clear light yellow solution was then cooled to −65 °C and a solution of aldehyde **15** (2.4 g, 16.7 mmol) in CH_2Cl_2 (20 cm^3) was added dropwise. The solution was stirred for 40 min at −65 °C and 1 h at −5 °C. The reaction was quenched with pH 7.2 phosphate buffer (20 cm^3) and MeOH (40 cm^3). Then, 42 cm^3 of a 2 : 1 solution of MeOH–H_2O_2 (30% in water) was added dropwise, keeping the internal temperature below +10 °C. This mixture was stirred for 1 h at 0 °C. Solvent was removed *in vacuo* and the resulting oil was partitioned between water and EtOAc. The aqueous phase was extracted with EtOAc (2 × 70 cm^3). Organic extracts were washed with 5% $NaHCO_3$, brine, and dried ($MgSO_4$). Removal of the solvent afforded an oil that was chromatographed. The aldol product **16** (2.313 g, 60%) was eluted first (hexane–EtOAc, 50⟶100%) and then, the deprotected aldol product **17** (790 mg) was eluted with EtOAc–MeOH 10%. **16** is a colourless oil that solidified on standing. R_f: 0.4 (50% EtOAc in hexane); $[\alpha]_D^{23.7}$ = −10.7 (*c* 0.28, CH_2Cl_2); δ_H ($CDCl_3$) 7.45–7.2 (5H, m); 4.74 (1H, m, C*H*N); 4.39 (1H, m); 4.33–4.12 (4H, m, OCH_2CHN, CH_2CH(OH)CH_2(O) and CH(OH)CH_2OC); 3.86 (1H, qd, *J* 3 and 7, C*H*Me); 3.65 (1H, dd, *J* 7.4 and 8.0, CH(OH)CH_2OC); 3.3 (1H, dd, *J* 3.3 and 13.4,CH_2Ph); 3.24 (1H, br, O*H*); 2.85 (1H, dd, *J* 9.4 and 13.4, CH_2Ph); 1.9–1.65 (2H, m, CHCH_2CH); 1.47 (3H, s, CCH_3); 1.42 (3H, s, CCH_3); 1.33 (3H, d, *J* 7, CHCH_3); δ_C ($CDCl_3$) 177.6 (s); 153.5 (s); 135.4 (s); 129.9 (d); 129.4 (d); 127.9 (d); 109.2 (s); 73.9 (d); 70.4 (t); 69.1 (d); 66.6 (t); 55.5 (d); 42.9 (d); 38.2 (t); 38.0 (t); 27.4 (q); 26.1 (q); 11.3 (q); *m*/*z* (ES^+) 400 (M + Na); *m*/*z* (ES^+) 378.1910 (M + H. $C_{20}H_{28}NO_6$ requires 378.1916).

(4*R*)-4-Benzyl-3-[(2*R*,3*S*)-3,5,6-trihydroxy-2-methylhexanoyl]-oxazolidin-2-one (17)

White foam; Yield: 18%; R_f: 0.18 (EtOAc); $[\alpha]_D^{26}$ = −141.7 (*c* 0.24, MeOH); δ_H ($CDCl_3$) 7.45–7.2 (5H, m); 4.8 (1H, m, C*H*N); 4.4–4.2 (3H, m); 4.05 (1H, br m); 3.95–3.5 (4H, m); 3.3 (1H, dd, *J* 13.3 and 3.3, CH_2Ph); 2.85 (1H, dd, *J* 9.3 and 13.3, CH_2Ph); 2.48 (1H, br s); 1.8–1.4 (3H, m); 1.3 (3H, d, *J* 7,

$CHCH_3$); δ_C ($CDCl_3$) 176.9 (s); 154.0 (s); 135.5 (s); 129.8 (d); 129.3 (d); 127.8 (d); 69.48 (d); 68.88 (d); 66.94 (t); 66.79 (t); 55.7 (d); 43.7 (d); 38.0 (t); 37.7 (t); 12.0 (q); *m/z* (ES^+) 360 (M + Na).

Acetonide protection of 17

A solution of **17** (1.5 g, 4.45 mmol) and TsOH (40 mg, 0.21 mmol) in acetone (150 cm^3) was stirred for 2 h at rt. A few drops of Et_3N were added and the solvent removed *in vacuo*. The residue was partitioned between EtOAc and 5% $NaHCO_3$ and the aqueous phase was extracted with EtOAc. The organic extract was washed with brine, dried ($MgSO_4$) and concentrated to afford the pure acetonide **16** (1.34 g, 80%).

(2*R*,3*S*)-4-[(1*S*)-2,2-Dimethyl-[1,3]-dioxolan-4-yl]-3-hydroxy-2-methylbutyric acid (18)

A 0.05 M solution of the aldol product **16** (410 mg, 1.1 mmol) in 3 : 1 THF–H_2O (20 cm^3) was treated at 0 °C with H_2O_2 (30% in water, 0.5 cm^3) followed by lithium hydroxide monohydrate (53 mg, 2.2 mmol). The resulting mixture was stirred for 1 h at ice-bath temperature. Excess peroxide was quenched at 0 °C with 1.5 M Na_2SO_3 (5 cm^3) and buffered with 5% $NaHCO_3$ (2 cm^3). The chiral auxiliary was recovered by CH_2Cl_2 extraction (2 × 20 cm^3). The aqueous phase was acidified (pH ~ 2) with 1 M HCl and extracted with EtOAc (3 × 20 cm^3). Ethyl acetate extracts were dried ($MgSO_4$) and concentrated to give the acid **18** as a colourless oil (200 mg, 86%); R_f: 0.2 (EtOAc); $[\alpha]_D^{21} = -14.5$ (*c* 2, CH_2Cl_2); δ_H ($CDCl_3$) 7.5 (1H, br, CO_2H); 4.3 (1H, m, C*H*(OH)CH_2O); 4.2–4.0 (1H, m, C*H*OH); 4.05 (1H, dd, *J* 8.1 and 6.2, CH(OH)CH_2O); 3.5 (1H, dd, *J* 8.1 and 7.3, CH(OH)CH_2O); 2.55 (1H, m, C*H*Me); 2.0 (1H, d, O*H*); 1.6 (2H, m, CHCH_2CH); 1.35 (3H, s, CCH_3); 1.3 (3H, s, CCH_3); 1.15 (3H, d, *J* 7.2, CHCH_3); δ_C ($CDCl_3$) 180.2 (s); 109.4 (s); 73.2 (d); 69.8 (t); 69.4 (d); 45.0 (d); 37.8 (t); 27.3 (q); 26.0 (q); 11.4 (q); *m/z* (ES^+) 241 (M + Na); *m/z* (ES) 236.1500 (M + NH_4. $C_{10}H_{22}NO_5$ requires 236.1498).

(2*R*,3*S*)-4-[(1*S*)-2,2-Dimethyl-[1,3]-dioxolan-4-yl]-3-hydroxy-2-methylbutyric acid benzyl ester (19)

A mixture of the acid **18** (737 mg, 3.38 mmol), benzyl bromide (0.8 cm^3, 6.8 mmol) and K_2CO_3 (938 mg, 6.8 mmol) in DMF (15 cm^3) was stirred for 16 h at rt. The reaction was diluted with CH_2Cl_2 and inorganic insoluble salts were filtered off (Celite). The filter cake was rinsed with CH_2Cl_2 and the filtrate was concentrated *in vacuo*. Chromatography with hexane–EtOAc (4 : 1) afforded **19** as a colourless oil (810 mg, 78%) (Found: C, 65.74; H, 8.07. $C_{17}H_{24}O_5 \cdot 0.1\ H_2O$ requires C, 65.82; H, 7.80%); R_f: 0.36 (hexane–EtOAc, 2 : 1); $[\alpha]_D^{24} = -3.6$ (*c* 1.66, CH_2Cl_2); δ_H ($CDCl_3$) 7.4 (5H, br s); 5.2 (2H, s, OCH_2Ph); 4.34 (1H, m, C*H*(OH)CH_2O); 4.15 (1H, m, C*H*OH); 4.05 (1H, dd, *J* 8.1 and 6, CH(OH)CH_2O); 3.55 (1H, dd, *J* 8.1 and 7.5, CH(OH)-CH_2O); 3.1 (1H, d, *J* 4.6, O*H*); 2.65 (1H, m, C*H*Me); 1.8–1.6 (2H, m, CHCH_2CH); 1.48 (3H, s, CCH_3); 1.39 (3H, s, CCH_3); 1.28 (3H, d, *J* 7.2, CHCH_3); δ_C ($CDCl_3$) 175.9 (s); 136.1 (s); 129.0 (d); 128.8 (d); 128.7 (d); 109.2 (s); 73.9 (d); 70.0 (t); 69.6 (d); 66.8 (t); 45.3 (d); 37.9 (t); 27.4 (q); 26.1 (q); 11.9 (q); *m/z* (ES^+) 331 (M + Na).

(2*R*,3*S*,5*S*)-3,5,6-Trihydroxy-2-methylhexanoic acid benzyl ester (20)

A solution of **19** (524 mg, 1.7 mmol) and $CuCl_2 \cdot 2H_2O$ (1.45 g, 8.5 mmol, 5 eq.) in ^{i}PrOH (20 cm^3) was stirred for 2 h at rt. The reaction was quenched with 9.5 cm^3 Na_2CO_3 1 M. When CO_2 evolution had stopped, the reaction mixture was diluted with MeOH and filtered on a path of Celite. The solvent was removed *in vacuo* and the residue was partitioned between EtOAc and water. The aqueous phase was extracted with EtOAc (2 × 40 cm^3). Organic extracts were dried ($MgSO_4$) and concentrated. Chromatography on silica with EtOAc yielded **20** as a colourless oil that solidified on standing (315 mg, 69%) (Found: C, 62.10; H, 7.48. $C_{14}H_{20}O_5$ requires C, 62.67; H, 7.51%); R_f: 0.28 (EtOAc); $[\alpha]_D^{24} = -22.2$ (*c* 0.09, MeOH); δ_H ($CDCl_3$) 7.45 (5H, m); 5.25 (2H, s, OCH_2Ph); 4.3 (1H, m, CH_2C*H*(OH)CH_2); 4.1 (1H, m, CHC*H*OH); 3.7 (1H, m); 3.55 (1H, m); 3.5 (1H, br, O*H*); 3.3 (1H, br, O*H*); 2.8 (1H, br, O*H*); 2.72 (1H, m, C*H*Me); 1.75–1.5 (2H, m, CHCH_2CH); 1.35 (3H, d, *J* 7.1, CHCH_3); δ_C ($CDCl_3$) 176.0 (s); 138.0 (s); 129.0 (d); 128.6 (d); 69.5 (d); 69.0 (d); 67.3 (t); 66.9 (t); 45.8 (d); 37.4 (t); 12.2 (q); *m/z* (ES^+) 269 (M + Na); *m/z* (ES) 269.1388 (M + H. $C_{14}H_{21}O_5$ requires 269.1389).

(2*R*,3*S*,5*S*)-6-[Bis(benzyloxy)phosphoryloxy]-3,5-dihydroxy-2-methylhexanoic acid benzyl ester (21)

Iodine (575 mg, 2.26 mmol) was added at 0 °C to a solution of tribenzyl phosphite [24] (852 mg, 2.4 mmol) in CH_2Cl_2 (7.5 cm^3). After 15 min at 0 °C and 10 min at rt, 4 cm^3 of the clear solution was added at −78 °C to a solution of **20** (345 mg, 1.29 mmol) and pyridine (0.3 cm^3, 3.0 mmol) in CH_2Cl_2 (7 cm^3). The reaction was followed by TLC and the rest of the dibenzyl phosphoiodinate was added in 1 cm^3 portions (to avoid diphosphorylation) approximately every 30 min. After a total of 5 h at −78 °C, all the reagent (7.5 cm^3, 1.8 eq.) had been added and the reaction was diluted with CH_2Cl_2, filtered, washed with water, dried ($MgSO_4$) and concentrated *in vacuo*. The crude yellow oil was chromatographed (hexane–EtOAc, 25⟶100%) to give the phosphate **21** as a colourless oil (370 mg, 54%); R_f: 0.2 (EtOAc–hexane, 2 : 1); $[\alpha]_D^{22} = -12.5$ (*c* 0.4, MeOH); δ_H ($CDCl_3$) 7.4 (15H, br s); 5.18 (2H, s, OCH_2Ph); 5.12 (2H, m, POCH_2Ph); 5.08 (2H, m, POCH_2Ph); 4.3–3.85 (4H, m); 3.45 (1H, br, O*H*); 3.3 (1H, br d, *J* 4.2, O*H*); 2.65 (1H, m, C*H*Me); 1.7–1.4 (2H, m, CHCH_2CH); 1.25 (3H, d, *J* 7.2, CHCH_3); δ_C ($CDCl_3$) 176.0 (s); 136.1 (2 × s); 136.0 (s); 129.1 (2 × d); 128.8 (d); 128.6 (d); 128.5 (d); 72.45 (*C*H_2, *J* 7.5); 70.05 (*C*H_2, *J* 7.5); 68.9 (d); 68.05 (*C*H, *J* 7.5); 66.8 (t); 45.3 (d); 36.4 (t); 11.9 (q); δ_P ($CDCl_3$) +1.08; *m/z* (ES^+) 551 (M + Na); *m/z* (ES) 546.2269 (M + NH_4. $C_{28}H_{37}NO_8P$ requires 546.2257).

(2*R*,3*S*,5*S*)-3,5-Bis(benzyloxy)-6-bis(benzyloxy)phosphoryloxy)-2-methylhexanoic acid benzyl ester (22)

To a solution of diol **21** (104 mg, 0.2 mmol) and benzyl trichloroacetimidate (0.112 cm^3, 0.6 mmol) in CH_2Cl_2 (2.5 cm^3) was added 10 drops of an ethereal solution of TfOH (3 drops neat TfOH in 1 cm^3 Et_2O). The progress of the reaction was followed by TLC and more ethereal TfOH solution was added after 1 h (0.1 cm^3), 1 h 25 min (0.3 cm^3), 2 h (0.2 cm^3 + 1 drop of neat TfOH). After 5 h, 2 drops of neat TfOH and $CCl_3CNHOBn$ (0.02 cm^3, 0.1 mmol) were added to drive the reaction to completion. After an additional 2 h stirring, the reaction was quenched with 5% $NaHCO_3$ (2 cm^3) and partitioned between water and CH_2Cl_2. The aqueous phase was extracted with CH_2Cl_2 (2 × 15 cm^3) and the combined organic extracts washed with brine, dried ($MgSO_4$) and concentrated to a crude white solid. Chromatography (hexane–EtOAc, 25⟶50%) afforded a mixture of **22** and trichloroacetimidate (same R_f as **22**) as shown by ^{1}HNMR. This by-product was crystallised from $CHCl_3$ (white crystals) and removed by filtration. **22** was isolated as a colourless oil (60 mg, 43%). $[\alpha]_D^{21} = -22$ (*c* 1, CH_2Cl_2); δ_H ($CDCl_3$) 7.5 (25H, m); 5.17 (2H, s); 5.09 (2H, s); 5.06 (2H, s); 4.68 (1H, d, *J* 11.4); 4.52 (1H, d, *J* 11.2); 4.34 (2H, d, *J* 11.4); 4.18 (1H, d, *J* 11.2); 4.1–3.9 (3H, m); 3.81 (1H, m); 2.86 (1H, m); 1.76 (2H, m); 1.24 (3H, d, *J* 7, CH_3CH); δ_C ($CDCl_3$) 174.81 (s); 138.66 (s); 138.59 (s); 136.29 (s); 136.16 (s); 129.01 (d); 128.97 (2 × d); 128.83 (d); 128.74 (d); 128.65 (d); 128.38 (2 × d); 128.35 (d); 128.15 (d); 128.02 (d); 77.20 (d); 74.68 (d, *J* 7.5, *C*H); 72.37 (d, *J* 5.6, *C*H_2); 69.74 (d, *J* 5.5, *C*H_2); 69.52 (t); 69.44 (t); 66.81 (t); 43.34 (d); 35.56 (t); 12.14 (q); δ_P ($CDCl_3$) + 0.46; *m/z* (ES^+) 709 (M + H); *m/z* (ES) 709.2930 (M + H. $C_{42}H_{46}O_8P$ requires 709.2930).

(2*R*,3*S*,5*S*)-3,5-Diacetoxy-6-bis(benzyloxy)phosphoryloxy-2-methylhexanoic acid benzyl ester (23)

A solution of **21** (70 mg, 0.13 mmol), acetic anhydride (40 µl, 0.4 mmol) and DMAP (3 mg, 0.026 mmol) in pyridine (2 cm^3) was stirred for 2 h at rt. The solvent was removed *in vacuo* and the crude oil was partitioned between CH_2Cl_2 and water. The organic phase was dried ($MgSO_4$) and concentrated to give the pure **23** as an oil (73 mg, 90%); R_f: 0.53 (50% EtOAc–hexane); $[\alpha]_D^{23} = -20.3$ (*c* 0.59, CH_2Cl_2); δ_H ($CDCl_3$) 7.4 (15H, m); 5.25 (1H, m, C*H*OAc); 5.15 (2H, s, OCH_2Ph); 5.15–5.0 (5H, m, 2 × POCH_2Ph and C*H*OAc); 4.15 (1H, m, CHCH_2OP); 3.97 (1H, m, CHCH_2OP); 2.75 (1H, m, C*H*Me); 2.05 (3H, s, CH_3CO); 2.0 (3H, s, CH_3CO); 1.85 (2H, m, CHCH_2CH); 1.2 (3H, d, *J* 7.1, CH_3CH); δ_C ($CDCl_3$) 172.1 (s); 169.4 (s); 169.3 (s); 134.7 (s); 134.6 (s); 127.6 (d); 127.4 (d); 127.3 (d); 127.0 (d); 126.9 (d); 68.7 (d); 68.4 (2 × t); 67.15 (d, *J* 7.5, *C*H_2); 66.75 (d, *J* 7.5, *C*H); 65.6 (t); 42.2 (d); 31.0 (t); 19.8 (q); 19.7 (q); 11.1 (q); δ_P ($CDCl_3$) + 0.35; *m*/*z* (ES^+) 635 (M + Na); *m*/*z* (ES) 630.2476 (M + NH_4. $C_{32}H_{41}NO_{10}P$ requires 630.2568).

(2*R*,3*S*,5*S*)-6-Bis(benzyloxy)phosphoryloxy-3,5-dimethoxy-2-methylhexanoic acid benzyl ester (24)

A solution of diol **21** (50 mg, 0.095 mmol), MeO_3BF_4 (70 mg, 0.47 mmol) and DTBMP (117 mg, 0.57 mmol) in CH_2Cl_2 (3 cm^3) was stirred for 3 h at rt. The reaction was diluted with EtOAc and washed successively with 5% $NaHCO_3$ and brine. The organic phase was dried (Na_2SO_4) and concentrated. Chromatography (hexane–EtOAc, 33 ⟶ 66%) afforded 11 mg of **24** (21%, R_f: 0.66, hexane–EtOAc, 1 : 2) and 33 mg of **25** (62%, R_f: 0.43, hexane–EtOAc, 1 : 2). $[\alpha]_D^{23} = -5$ (*c* 0.2, CH_2Cl_2); δ_H ($CDCl_3$) 7.4 (15H, br s); 5.18 (2H, s, OCH_2Ph); 5.11 (2H, m, POCH_2Ph); 5.08 (2H, m, POCH_2Ph); 4.12 (1H, 1/2 ABX, CHCH_2OP); 3.94 (1H, 1/2 ABX, CHCH_2OP); 3.73 (1H, m, C*H*OMe); 3.53 (1H, m, C*H*OMe); 3.41 (3H, s, OCH_3); 3.36 (3H, s, OCH_3); 2.76 (1H, m, C*H*Me); 1.62 (2H, m, CHCH_2CH); 1.2 (3H, d, *J* 7.1, CH_3CH); δ_P ($CDCl_3$) + 0.46; m/z (ES^+) 579 (M + Na); *m*/*z* (ES) 557.2305 (M + H. $C_{30}H_{38}O_8P$ requires 557.2304).

(2*R*,3*S*,5*S*)-6-Bis(benzyloxy)phosphoryloxy-5-hydroxy-3-methoxy-2-methylhexanoic acid benzyl ester (25)

δ_H ($CDCl_3$) 7.4 (15H, br s); 5.19 (2H, s, OCH_2Ph); 5.12 (2H, m, POCH_2P); 5.09 (2H, m, POCH_2P); 4.14 (2H, m, CHCH_2OP and C*H*OH); 3.98 (1H, m, CHCH_2OP); 3.66 (1H, m, C*H*OMe); 3.43 (3H, s, OCH_3); 2.6 (1H, m, C*H*Me); 1.57 (2H, m, CHCH_2CH); 1.25 (3H, d, *J* 7.2, CH_3CH); δ_C ($CDCl_3$) 176.3 (s); 136.4 (s); 136.3 (s); 129.2 (2 × d); 129.1 (d); 129.0 (d); 128.9 (d); 128.4 (d); 69.9 (2 × t); 69.0 (t); 68.9 (d); 67.0 (t); 59.0 (d); 58.8 (q); 45.5 (d); 36.0 (t); 11.8 (q); δ_P ($CDCl_3$) + 0.57; *m*/*z* (ES^+) 565 (M + Na); *m*/*z* (ES) 543.2153 (M + H. $C_{29}H_{36}O_8P$ requires 543.2148).

(2*R*,3*S*,5*S*)-3,5-(Benzylidenedioxy)-6-bis(benzyloxy)phosphoryloxy-2-methylhexanoic acid benzyl ester (26)

A solution of **21** (90 mg, 0.17 mmol); PPTS (171 mg, 0.68 mmol) and benzaldehyde dimethyl acetal (0.25 cm^3, 0.68 mmol) in DMF (2 cm^3) was stirred for 24 h at rt. At this time, the reaction was not complete and was then heated at *ca*. 40 °C for 3 h. The reaction was diluted with EtOAc, washed successively with 5% $NaHCO_3$ and brine, then dried ($MgSO_4$) and concentrated. Flash chromatography (gradient 0⟶33% EtOAc–hexane) afforded **26** as a mixture of 2 diastereoisomers (colourless oil, 74 mg, 71%). R_f: 0.61 (50% EtOAc–hexane); δ_H ($CDCl_3$) d 7.55–7.3 (40H, m); 5.85 (1H, s, C*H*Ph); 5.65 (1H, s, C*H*Ph); 5.2 (4H, s, OCH_2Ph); 5.15–5.05 (8H, m, POCH_2Ph); 4.63 (1H, m); 4.5–4.3 (2H, m); 4.3–3.97 (5H, m); 3.38 (1H, m, C*H*Me); 2.71 (1H, quint, *J* 7, C*H*Me); 2.2–1.95 (2H, m); 1.6–1.4 (2H, m); 1.41 (3H, d, *J* 6.9, CH_3CH); 1.37 (3H, d, *J* 7, CH_3CH); δ_C ($CDCl_3$) 174.4 (s); 174.0 (s); 138.7 (s); 138.5 (s); 136.2 (s); 136.1 (s); 136.0 (s); 129.4 (d); 129.2 (2 × d); 129.1 (d); 129.0 (2 × d); 128.8 (2 × d); 128.6 (2 × d); 128.4 (4 × d); 126.6 (d); 126.5 (d); 95.8 (d); 95.0 (d); 74.0 (d); 73.6 (d); 71.4 (d, *J* 7.5, *C*H); 70.9 (d, *J* 7.5, *C*H); 70.0 (t); 69.93 (t); 69.85 (t); 69.79 (t); 69.75 (t); 69.72 (t); 67.0 (t); 66.8 (t); 66.0 (d, *J* 6, *C*H_2); 45.7 (d); 40.0 (d); 28.5 (t); 28.4 (t); 14.9 (q); 13.3 (q); δ_P ($CDCl_3$) + 0.71; + 0.23; *m*/*z* (ES^+) 634 (M + NH_4); *m*/*z* (ES) 634.2572 (M + NH_4. $C_{35}H_{41}NO_8P$ requires 634.2570).

(2*R*,3*S*,5*S*)-6-Bis(benzyloxy)phosphoryloxy-2-methyl-3,5-bis-(tetrahydropyran-2-yloxy)hexanoic acid benzyl ester (27)

A solution of **21** (85 mg, 0.16 mmol), PPTS (20 mg, 0.08 mmol) and 3,4-dihydro-2*H*-pyran (0.15 cm^3,1.6 mmol) in CH_2Cl_2 (2.5 cm^3) was stirred for 24 h at rt. Solvent was removed *in vacuo* and the residue was chromatographed (0⟶70% EtOAc–hexane) to afford **27** as a colourless oil (90 mg, 81%). δ_H (acetone-d_6) 7.4–7.2 (15H, m); 5.05–4.95 (6H, m); 4.75–4.2 (2H, m); 4.2–3.65 (6H, m); 3.4–3.15 (2H, m); 2.67 (1H, m); 1.8–1.2 (14H, m); 1.05 (3H, m); δ_P (acetone-d_6) +0.63; +0.53; +0.41; + 0.36; *m*/*z* (ES^+) 714 (M + NH_4); *m*/*z* (ES) 714.3401 (M + NH_4. $C_{38}H_{53}NO_{10}P$ requires 714.3407).

(2*R*,3*S*,5*S*)-3,5-Dihydroxy-2-methyl-6-phosphonoxyhexanoic acid (28)

A suspension of **27** (55 mg) and 5% Pd–C[30] (10 mg) in MeOH (5 cm^3) was hydrogenated for 30 min at rt. The catalyst was filtered off and the solvent was removed *in vacuo*. The crude residue was dissolved in THF (5 cm^3) and 2 M aqueous HCl (0.5 cm^3) was added. The reaction was stirred for 2 h at rt and the solvent was evaporated. The residue dissolved in MeOH was treated with Et_2O and the precipitate was allowed to settle down overnight in the fridge. The solvent was removed with a pasteur pipette and the oily residue dried *in vacuo* to afford **28** as a yellowish hygroscopic foam (14 mg, 70%); $[\alpha]_D^{24} = -14.28$ (*c* 0.28, MeOH); δ_H (CD_3OD) 4.1–3.7 (4H, m); 2.4 (1H, m, C*H*Me); 1.65–1.18 (2H, m, CHCH_2CH); 1.05 (3H, d, *J* 7.3, CH_3CH); δ_C (CD_3OD) 177.4 (s); 72.2 (t); 70.2 (d); 68.6 (d, d); 47.8 (d); 39.4 (t); 12.5 (q); δ_P (CD_3OD) + 1.5 (br); *m*/*z* (ES^-) 257 (M − H); *m*/*z* (ES) 281.0400 (M + Na. $C_7H_{15}O_8NaP$ requires: 281.0402).

(2*R*,3*S*,5*S*)-3,5-Diacetoxy-2-methyl-6-phosphonoxyhexanoic acid (29)

Hydrogenolysis of **23** (34 mg, 0.055 mmol) with 10% Pd–C (10 mg) for 16 h afforded **29** as a colourless oil. $[\alpha]_D^{20} = -16.7$ (*c* 0.24, MeOH); δ_H (CD_3OD) 5.25 (1H, br); 5.05 (1H, br); 4.0 (2H, br m); 2.65 (1H, br m, C*H*Me); 2.08 (3H, s, CH_3CO); 2.03 (3H, s, CH_3CO); 2.0 (2H, br, CHCH_2CH); 1.15 (3H, d, *J* 6.9, CH_3CH); δ_C (CD_3OD) 177.4 (s); 172.8 (s); 172.7 (s); 71.8 (d); 70.3 (d); 68.4 (t); 45.4 (d); 34.4 (t); 21.4 (q); 21.2 (q); 13.3 (q); δ_P (CD_3OD) + 1.76; *m*/*z* (ES^-) 341 (M − H); *m*/*z* (ES^-) 341.0642 (M − H. $C_{11}H_{18}O_{10}P$ requires: 341.0638).

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