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Deoxygenation of Unhindered Alcohols via Reductive Dealkylation of Derived Phosphate Esters

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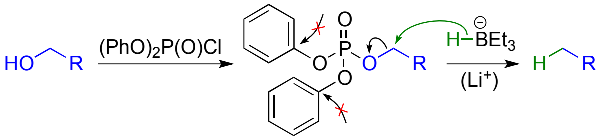
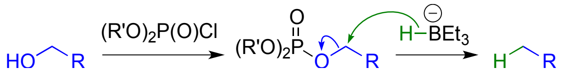


Abstract: Primary alcohols can be deoxygenated cleanly and in yields of 60-95% by reduction of derived diphenyl phosphate esters with lithium triethylborohydride in tetrahydrofuran at room temperature. Selective deoxygenation of a primary alcohol in the presence of a secondary alcohol was demonstrated. The two-step process can be performed in one pot, making it simple and convenient.

Deoxygenation of alcohols is a common and valuable synthetic procedure.[1–4] The most widely used methods for accomplishing this transformation fall into two categories, radical and nucleophilic, with largely complementary applications. Radical deoxygenations are typified by the Barton-McCombie reaction,[5] which involves free-radical chain reduction of a thiocarbonyl derivative of the alcohol. The process is mild, efficient and compatible with a wide array of functional groups. As such, it has found many applications, and numerous modifications of the basic approach have been reported over the years.[1–4,3–9] It is most suited to secondary alcohols but has also found application to tertiary[10,11] and primary[12–14] alcohols. The latter typically require elevated temperatures, and clever alternatives have been introduced in which the intermediate primary radical is generated at ambient or lower temperature through decomposition of monoalkyl diazenes,[15] or more recently, by photochemical reduction of alkyl bromides,[16] iodides[17] or 3,5-bis(trifluoromethyl)benzoates[18] using precious metal catalysts.

Nucleophilic deoxygenations typically employ a first- or second-row metal hydride reagent, such as lithium aluminum hydride or lithium triethylborohydride, to reduce an activated derivative of the alcohol (halide or sulfonate ester).[19-21] These reactions are complementary to radical methods in that they are most efficient for unhindered primary alcohols, and their main limitation is incompatibility with reducible functional groups. Hydrosilanes, in combination with Brønsted or Lewis acids, have proven to be effective nucleophiles for the deoxygenation of alcohols.[22–24] Hydrosilane reductions typically proceed through the S_N1 mechanism and are hence effective only for tertiary, secondary or benzylic alcohols. The introduction of tris(pentafluorophenyl)borane as a catalyst extended the scope of the reaction to primary alcohols and ethers, which are presumed to react by an S_N2-like mechanism,[25,26] and a copper catalyst has proven effective for reduction of triflates and iodides derived from primary or secondary alcohols.[27]

Scheme 1. Deoxygenation of alcohols via reduction of derived phosphate esters



Our exploration of a new method ensued from our fortuitous discovery that lithium trialkylborohydrides (triethyl or tri-*s*-butyl) rapidly dealkylate phosphonic diesters through reduction at carbon via a presumed S_N2 mechanism, with no indication of reaction at phosphorus.[28] Exclusively mono-dealkylated products were obtained, and over reduction was not observed even after addition of excess hydride reagent and prolonged stirring. This observation immediately suggests the possibility of using phosphonates as intermediates for the deoxygenation of alcohols, and we expected that phosphate esters might prove more reactive due to the weaker basicity of the leaving group (Scheme 1). For this study we chose the triethyl reagent because of its less hindered steric environment and exceptional nucleophilicity.[20]

Phosphate triesters are easily obtained through derivatization of alcohols. Implementation of our scheme required that the groups introduced through phosphorylation be refractory to S_N2 sustitution, such that regioselective dealkylation could be effected at the desired site. Two candidates were initially considered, diphenyl phosphates (**1**) and pinacol phosphates (**2**) (Figure 1). Of these, the former were judged preferable due to their stability and ease of synthesis from inexpensive, readily available diphenyl chlorophosphate (**3**).

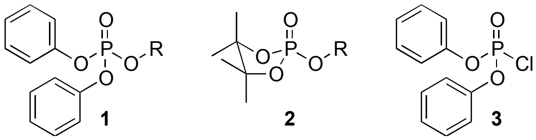


Figure 1. Phosphate esters amenable for deoxygenation (**1** and **2**) and an inexpensive phosphorylating reagent (**3**).

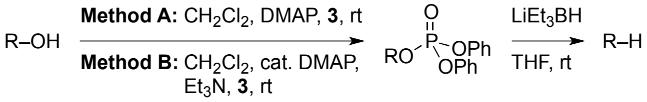
Phosphorus derivatives have been used to activate alcohols for subsequent deoxygenation by radical and single-electron transfer processes. For example, phosphites can undergo Barton-McCombie deoxygenation[29] and diphenyl phosphinates can be electrochemically deoxygenated through an analogous pathway.[30] Phosphate esters and related species have been used to activate phenols, enols and alcohols for subsequent reduction using alkalai metals.[31–34] Less work has been done in the area of nucleophilic processes. Diethyl alkylphosphonates can be deethylated by Et_3SiH in conjunction with $B(C_6F_5)_3$ as catalyst,[35] presumably with liberation of ethane, and this reaction could potentially be applied for deoxygenation in analogy to the approach described herein. Hendrickson employed a phosphonium anhydride reagent, $(Ph_3P^+)_2O{\bullet}2(CF_3SO_3^-)$, to convert alcohols into highly reactive triphenylphosphonium derivatives that could be reduced *in situ* with sodium borohydride.[36] Earlier, Haley et al.[37] had activated neryl and geranyl alcohols as their diphenylphosphate esters and found that these substrates could be reduced to the corresponding alkadienes with sodium borohydride in a hot mixture of aqueous sodium hydroxide and diglyme. The main products were consistent with S_N2 substitution, but small amounts of allylically rearranged and cyclized hydrocarbons formed, likely the result of carbocation formation in the reaction medium. This promising observation was not further explored as a general approach to deoxygenation.

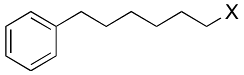
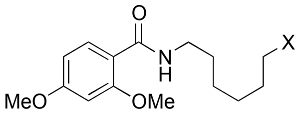
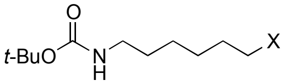
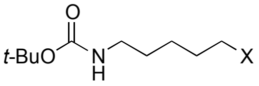
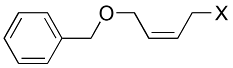
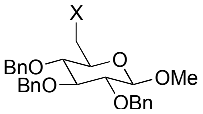
We found that the phosphorylation–reduction sequence using $LiBHEt_3$ proceeds smoothly at room temperature in THF, can be effected in one pot, gives high yields of deoxygenated primary alcohols, and can selectively dealkylate primary over secondary alcohols. As such, the diphenyl phosphate derivative provides a convenient general alternative to halides and sulfonate esters for nucleophilic deoxygenation.

Our first model substrate was 6-phenylhexanol (**4**). Treatment of this alcohol with diphenyl chlorophosphate and DMAP in dichloromethane generated the desired phosphotriester, which after isolation was treated with 1.7 equiv of $LiBHEt_3$ in THF. To our gratification, the reduction proceeded to completion within five hours at room temperature, affording hexylbenzene in 82% isolated yield over two steps (based on alcohol **4**). Given this initial success, we undertook a broader study of the reaction's scope and sought to streamline the experimental procedures. Our study included a set of primary alcohols (Table 1) with different steric and chemical environments, secondary alcohols, and a steroidal diol containing both primary and secondary hydroxyl groups.

We first examined compatibility of the process with primary amides and urethanes. The *N*-Boc and *N*-2,4-dimethoxybenzoyl derivatives of 6-aminohexan-1-ol (**6** and **8**, respectively) were deoxygenated cleanly. In these cases, >2 equiv. of hydride were required to cause complete reduction due to an acid–base reaction with the amide. The rapid deprotonation of primary amides by $LiHBEt_3$ is well-known, as is the consequent sluggishness of nucleophilic attack at the amide carbonyl.[38] Although the amidate ion could hypothetically initiate side reactions, such as nucleophilic attack at phosphorus or carbon (e.g, cyclization of **10** to *N*-Boc-piperidine), no evidence of such processes was observed.

Table 1. Deoxygenation of representative primary alcohols



Entry	Substrate (X=OH)	Product (X=H)	Method	Yield		
				Phosphorylation	Reduction	Overall
	**4**	**5**	B			82
	**6**	**7**	A	86[b]	~100	86
	**8**	**9**	A	95[b]	~100	95
	**10**	**11**	B			72
	**12**	**13**	B			59 (64)[a]
	**14**	**15**	A	87	70	61

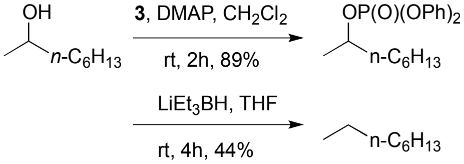
[a] based on recovered substrate

Having successfully employed the deoxygenation protocol on several unhindered primary alcohols, we next examined reduction of a model allylic alcohol, the monobenzyl ether of *cis*-butene-1,4-diol,[39] to assess whether S_N2' substitution was competitive with S_N2. Application of the phosphorylation–reduction protocol to this substrate afforded the S_N2 product **13**. Though the yield was modest (59%; 64% based on recovered starting **12**), no evidence of S_N2' reduction or elimination products was detected.

A β-branched alcohol, glucopyranoside **14**, was next examined to test the applicability of this method on a sterically crowded primary alcohol. The substrate **14** was first converted to corresponding phosphate, and the resultant phosphate was treated with $LiHBEt_3$ at room temperature. Gratifyingly, the desired 6-deoxy sugar **15** was obtained in 70% yield. This example illustrates that reaction is effective with sterically hindered primary alcohols and provides access to 6-deoxy sugars.

We proceeded to investigate the effectiveness of the procedure on secondary alcohols. 2-Octanol was converted in high yield to the corresponding diphenylphosphate. Reaction of this compound with $LiHBEt_3$ for 4 h at room temperature produced *n*-octane as the major product, but conversion was poor (44% by GC using *n*-decane as an internal standard, Scheme 2).

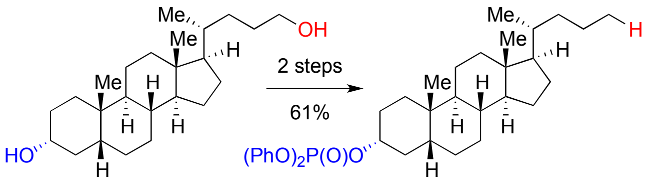
Scheme 2. Deoxygenation of 2-octanol.



Two cyclic secondary alcohols, *exo*-norborneol and (1*S*,2*R*,5*S*)-menthol, were likewise converted to diphenyl phosphate derivatives. After treatment with $LiHBEt_3$ in THF, no deoxygenated products could be detected, and unreacted starting materials were recovered. A third secondary alcohol, diacetone glucose (1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose), was likewise readily phosphorylated with **3** but produced an intractable mixture upon reduction. We subsequently attempted to make the pinacol phosphate of diacetone glucose using either pinacolyl chlorophosphate or pinacolyl chlorophosphite. However, the products proved too unstable to isolate and purify, consistent with the known lability of pinacol phosphates.[40] Thus, deoxygenation of secondary alcohols via derived diphenyl phosphates may proceed with limited success for unhindered substrates, but is likely to fail completely for hindered ones.

Having found as expected that the reduction is sluggish with hindered secondary systems, we sought to determine whether it was possible to deoxygenate a primary alcohol selectively in the presence of a secondary alcohol. We chose lithocholanyl alcohol **19**, formed by reduction of lithocholic acid with $LiAlH_4$, as a test substrate. Compound **19** was first bisphosphorylated with diphenyl chlorophosphate, and after isolation, the crude bis-phosphate was subjected to treatment with $LiHBEt_3$. In accordance with expectation, only the primary phosphate was reduced under the reaction conditions. The secondary phosphate remained intact, affording monophosphorylated compound **20** as the only product (Scheme 3).

Scheme 3. Selective reduction of a primary phosphate ester.[a]

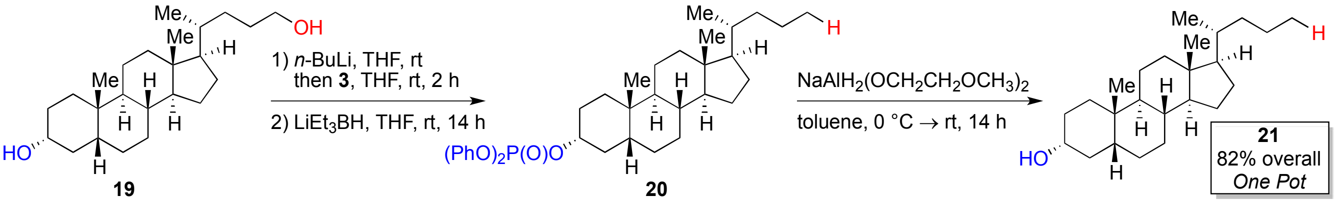


19 **20**

[a]Conditions: 1) **3**, DMAP, CH_2Cl_2, rt, 3h; 2) $LiHBEt_3$, THF, rt, 4.5 h.

In order to simplify the two-step phosphorylation–deoxygenation process, we explored development a one-pot protocol (Scheme 4). Success was realized with a switch to THF as solvent with *n*-BuLi as base for the phosphorylation reaction. Thus, a solution of diol **19** in THF was treated with 2.1 equiv. of *n*-BuLi, followed by 2.1 equiv. of diphenylphosphoryl chloride to effect bis-phosphorylation. After 2 hours, $LiHBEt_3$ (1.3 equiv.) was added, and the reaction was stirred at room temperature for 14 h to effect selective reduction of the primary phosphate. The crude product was treated with sodium bis(2-methoxyethoxy)aluminum hydride (1.2 equiv) to cleave the secondary phosphate group, liberating the secondary alcohol **21** in 82% overall yield for the three steps. This last sequence of reactions (**21**→**22**) illustrates the clear dichotomy between boron hydrides, which reduce carbon (**19**→**20**), and aluminum hydrides, which reduce phosphorus (**20**→**21**). It further illustrates how the phosphate ester can be used as a protecting group for alcohols.

Scheme 4. Selective deoxygenation of a primary alcohol employing one-pot phosphorylation–reduction procedure.

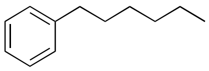


Conclusions

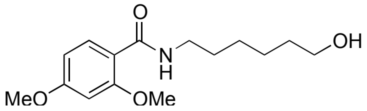
Primary alcohols can be deoxygenated cleanly and in high-yield by reduction of their diphenyl phosphate esters with $LiBHEt_3$ in THF at room temperature. The two-step procedure can be effected in a one-pot process that is environmentally friendly in that no halogenated solvents are required for the reaction or workup, and in that no heating or cooling is required. The process works less well with simple secondary alcohols and fails with hindered ones. Selective deoxygenation of a primary alcohol in the presence of a secondary one was readily effected. Overall, diphenyl phosphate esters are a readily accessible and useful alternative to sulfonate esters and halides for deoxygenation of primary alcohols.

Experimental Section

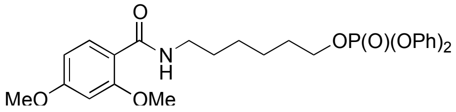
General Methods. All reactions were run in glassware sealed with rubber septa and stirred magnetically under nitrogen unless otherwise specified. Tetrahydrofuran (THF) and methylene chloride (DCM) were dried by use of a sorbent-based purification system. Other commercial reagents and solvents were used without purification. Flash chromatography was performed using silica gel 60 (40-63 µm particle size), and TLC was performed on silica gel 60 F254 plates (glass-backed, 0.25 mm layer thickness). TLC chromatograms were visualized with iodine vapor or $KMnO_4$. NMR spectra were recorded at the indicated frequencies and were calibrated using internal tetramethylsilane or solvent peaks ($C\underline{H}Cl_3$ = δ 7.27, $\underline{C}DCl_3$ = δ 77.23). High-resolution mass spectra were obtained using electrospray ionization (ESI) with either a quadrupole–time-of-flight (QTOF) or a Fourier transform ion cyclotron resonance (FTICR) mass spectrometer.



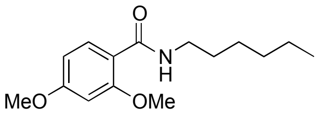
*1-Phenylhexane (**5**).* To a stirred solution of 6-phenylhexan-1-ol (**4**, 0.1095 g, 0.6142 mmol) and DMAP (22 mol%, 0.1359 mmol, 0.1665 g) in 4 mL of THF under nitrogen was added triethylamine (1.2 equiv, 0.5609 mmol, 0.08 mL) followed by diphenyl phosphoryl chloride (1.2 equiv, 0.7370 mmol, 0.15 mL) at room temperature. After completion of the reaction (3 h), the reaction mixture was concentrated. The residue was taken up in ethyl acetate and washed with water, 1N $NaHCO_3$ and brine. The organic layer was dried with Na_2SO_4 and concentrated in vacuo to give phosphoric acid (6-phenyl hexyl) diphenyl ester. The crude product was dissolved in THF (4 mL) and $LiHBEt_3$ (1.0 M in THF; 1.7 equiv, 1.0441 mmol, 1.0 mL). The reaction was monitored by TLC, and upon consumption of the starting material, the reaction was quenched with water and extracted with EtOAc (5×). The combined organic layer was dried with Na_2SO_4, and the solvent was evaporated under reduced pressure to afford the crude product. Purification by flash chromatography using hexanes:ethyl acetate (6:1) afforded 0.0819 g (0.505 mmol, 82%) of the product: R_f 0.89 (hexanes:EtOAc 1:1); ^{1}H NMR (400 MHz, $CDCl_3$, δ) 7.22–7.19 (m, 2H), 7.12–7.08 (m, 3H), 2.53 (t, J = 7.8 Hz, 2H), 1.57–1.48 (m, 2H), 1.35–1.20 (m, 6H), 0.81 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 143.2, 128.6, 128.4, 125.7, 36.2, 31.9, 31.7, 29.9, 29.2, 22.8, 14.3. NMR data are consistent with those reported in the Spectral Database for Organic Compounds (SDBS).[41]



N-*(6-hydroxyhexyl)-2,4-dimethoxybenzamide (**6**).* To a stirred solution of 6-aminohexanol (0.1168 g, 0.9969 mmol) and triethylamine (1.0 equiv, 0.14 mL) in DCM (4 mL) was added dropwise over 1 h a solution of 2,4-dimethoxybenzoyl chloride (1.0 equiv, 0.2 g, 0.9969 mmol) in 2 mL of DCM at 0 °C under nitrogen. After 3h, the reaction was quenched with water, and the organic layer was evaporated off. The aqueous layer was extracted with ethyl acetate (3×), and the combined organic layer was then dried with anhydrous Na_2SO_4 and filtered. Evaporation of the solvent afforded the crude product, which upon purification by flash chromatography using DCM:methanol (93:7) as eluent afforded 0.2366 g (0.8409 mmol, 84%) of the product as white solid: R_f 0.43 (DCM:methanol 95:5); ^{1}H NMR (500 MHz, $CDCl_3$, δ) 8.15 (d, J = 8.7 Hz, 1H), 7.77 (br t, $J \approx$ 6 Hz, 1H), 6.58 (dd, J = 8.8, 2.3 Hz, 1H), 6.46 (d, J = 2.3 Hz, 1H), 3.92 (s, 3H), 3.83 (s, 3H), 3.62 (t, J = 6.5 Hz, 2H), 3.43 (q, J = 5.8 Hz, 2H), 2.13 (br s, 1H), 1.64–1.52 (4H, m), 1.46–1.35 (4H, m); ^{13}C NMR (125 MHz, $CDCl_3$, δ) 165.3, 163.4, 158.9, 134.0, 114.8, 105.4, 98.7, 62.7, 56.1, 55.7, 39.5, 32.8, 29.8, 26.8, 25.4; HRMS (ESI–QTOF) calcd for $C_{15}H_{23}NO_4Na$ [M+Na] 304.1525, found 304.1523.

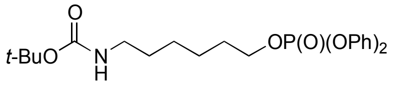


*Phosphoric acid, 6-(2,4-dimethoxybenzamido)hexyl diphenyl ester (diphenyl phosphate of **6**).* To a stirred solution of *N*-(6-hydroxyhexyl)-2,4-dimethoxybenzamide (**6**, 0.1196 g, 0.4251 mmol) and DMAP (2.0 equiv, 0.1039 g, 0.8502 mmol) in DCM (7.5 mL) was added diphenylphosphoryl chloride (2.0 equiv, 0.8502 mmol, 0.18 ml), and the reaction mixture was stirred under nitrogen at room temperature. After 2 h, the solvent was evaporated. Ethyl acetate and water were added, and the organic layer was separated. The aqueous layer was washed with ethyl acetate (2×), and the combined organic layer was washed with water, saturated $NaHCO_3$ and brine, then dried with Na_2SO_4 and concentrated under reduced pressure. Purification of the crude product by flash chromatography (DCM:methanol, 9:1) afforded 0.1878 g (86%) of the product as colorless oil: IR (neat) 3412, 3070, 2937, 2857, 1652, 1605, 1533, 1489, 1463, 1284, 1264, 1209, 1190, 1165, 1010, 951, 768 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, δ) 8.18 (d, J = 8.8 Hz, 1H), 7.75 (br t, $J \approx$ 6 Hz, 1H), 7.35 (t, J = 8.3 Hz, 4H), 7.23–7.16 (m, 6H), 6.59 (dd, J = 6.5, 2.3 Hz, 1H), 6.47 (d, J = 2.3 Hz, 1H), 4.25 (q, J = 7.4 Hz, 2H), 3.91 (s, 3H), 3.83 (s, 3H), 3.41 (q, J = 5.9 Hz, 2H), 1.72 (p, J = 6.8 Hz, 2H), 1.57 (p, J = 6.9 Hz, 2H), 1.41–1.23 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 165.2, 163.3, 158.8, 150.7 (d, J = 6.8 Hz), 134.0, 129.9, 125.4 (d, J = 5.2 Hz), 120.2 (d, J = 5 Hz), 114.8, 105.3, 98.7, 69.4 (d, J = 6.5 Hz), 56.0, 55.6, 39.6, 30.2 (d, J = 6.7 Hz) 29.7, 26.6, 25.2; HRMS (ESI–QTOF) calcd for $C_{27}H_{32}NO_7PNa$ [M+Na] 536.1814, found 536.1828.

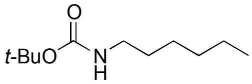


N-*hexyl-2,4-dimethoxybenzamide (7).* To a stirred solution of phosphoric acid 6-(2,4-dimethoxybenzamido)hexyl diphenyl ester (diphenyl phosphate of **6**) (0.0951 g, 0.1852 mmol) in THF (1.3 mL) was added $LiEt_3BH$ (1.0 M solution in THF; 1.3 equiv, 0.2410 mmol, 0.24 mL) at room under nitrogen. After 1 h, TLC showed a trace of the starting material. Another 0.24 mL of $LiEt_3BH$ solution was added, and the reaction was stirred at room temperature. After 1.5 h the reaction was judged complete by TLC, and it was quenched by addition of water. The mixture was acidified so that the aqueous layer was at pH 1 and extracted with EtOAc (3×). The combined EtOAc layer was dried with Na_2SO_4 and evaporated under reduced pressure.

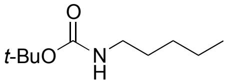
Purification of the residue by flash chromatography (DCM:MeOH, 9:1) afforded 0.0491 g (~100%) of the product as colorless oil: IR (neat) 3413, 2953, 2928, 2855, 1727, 1650, 1606, 1536, 1498, 1438, 1309, 1264, 1209, 1169, 1104, 835 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, δ) 8.20 (d, *J* = 8.7 Hz, 1H), 7.76 (br s, 1H), 6.59 (dd, *J* = 8.8, 2.3 Hz, 1H), 6.48 (d, *J* = 2.3 Hz, 1H), 3.93 (s, 3H), 3.84 (s, 3H), 3.44 (td, *J* = 5.6, 1.3 Hz, 2H), 1.60 (p, *J* = 7.3 Hz, 2H), 1.44–1.28 (m, 6H), 0.90 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 165.2, 163.3, 158.9, 134.0, 114.9, 105.3, 98.7, 56.0, 55.7, 39.8, 31.7, 29.8, 27.0, 22.8, 14.2.



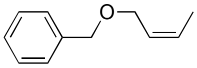
*Phosphoric acid 6-(tert-butoxycarboxamido)hexyl diphenyl ester (diphenyl phosphate of **8**).* To a stirred solution of 6-(*tert*-butoxycarboxamido)hexanol (**8**, 0.3805 g, 1.7509 mmol) and DMAP (2.0 equiv, 3.5018 mmol, 0.4277 g) in DCM (30 mL) was added diphenyl phosphoryl chloride (2.0 equiv, 3.5018 mmol, 0.73 mL) at room temperature under nitrogen. The reaction went to completion within 1h, after which it was concentrated and the residue was taken up in ethyl acetate (40 mL) and water (15 mL). The ethyl acetate layer was separated, and the aqueous layer was extracted with ethyl acetate (15mL). The combined ethyl acetate layer was washed sequentially with water, 1N $NaHCO_3$ and brine, then dried with Na_2SO_4 and evaporated to dryness to afford the target compound as a white solid (0.7507 g, 1.6701 mmol, 95%): R_f 0.2 hexanes:EtOAc 2:1); ^{1}H NMR (400 MHz, $CDCl_3$, δ) 7.37–7.28 (m, 4H), 7.24–7.11 (m, 6H), 4.63 (br s, 1H), 4.22 (q, *J* = 6.6 Hz, 2H), 3.05 (br q, *J* = 6.3 Hz, 2H), 1.67 (p, *J* = 6.9 Hz, 2H), 1.43 (s, 9H) 1.48–1.36 (m, 2H), 1.36–1.18 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 156.1, 150.6 (d, *J* = 7.3 Hz), 129.8, 125.4, 120.1 (d, *J* = 4.8 Hz), 79.0, 69.3 (d, *J* = 6.7 Hz), 40.4, 30.1 (d, *J* = 6.7 Hz), 30.0, 28.5, 26.2, 25.1; HRMS (ESI–FTICR) calcd for $C_{23}H_{33}NO_6P$ $[M+H]^+$ 450.20455, found 450.20352.



*6-(*tert-*Butoxycarboxamido)hexane (**9**).* A solution of phosphoric acid 6-(*tert*-butoxycarboxamido)hexyl diphenyl ester (diphenylphosphate of **8**) (0.0540 g, 0.1201 mmol) in THF (0.8 mL) was treated with $LiHBEt_3$ (1.0 M solution in THF; 1.2 equiv, 0.14 mmol, 0.14 mL) at room temperature. The progress of the reaction slowed after 1h. After 2 h, an additional 0.14 mL of $LiHBEt_3$ solution was added. When the remaining starting material had been consumed (3h), the reaction was cooled to 0 °C and quenched by addition of water. The aqueous layer was extracted with hexanes (2 × 1 mL), and the combined organic layer was dried with Na_2SO_4 then concentrated under reduced pressure. The crude product was purified by flash chromatography using hexanes:ethyl acetate (6:1) as mobile phase to afford 0.0242 g (~100%) of the desired product **9** as clear oil: R_f 0.70 (hexanes:EtOAc 2:1); ^{1}H NMR (400 MHz, $CDCl_3$, δ) 4.51 (br s, 1H), 3.11 (br q, J = 6.6 Hz, 2H), 1.55–1.38 (m, 2H), 1.44 (s, 9H), 1.32–1.21 (m, 6H), 0.88 (t, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 156.0, 79.0, 40.6, 31.5, 30.0, 28.4, 26.5, 22.6, 14.0. NMR data are consistent with those reported previously.[42]

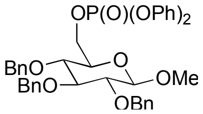


*5-(*tert-*butoxycarboxamido)pentane (**11**).* A solution of 5-(*tert*-butoxycarboxamido)pentyl alcohol (**10**, 0.0976 g, 0.480 mmol) and DMAP (2.1 equiv, 1.0106 mmol, 0.1234 g) in 5 mL of DCM was treated with diphenyl phosphoryl chloride (2.0 equiv, 0.9839 mmol, 0.20 mL) at room temperature. After 2 h, the reaction was evaporated under reduced pressure, and the residue was dissolved in ethyl acetate. The solution was washed with water, 1N $NaHCO_3$ and brine. After drying with Na_2SO_4, the organic layer was evaporated *in vacuo*. The crude phosphoric acid 5-(*tert*-butoxycarboxamido)pentyl diphenyl ester was dissolved in THF (3 mL). To the stirred solution was added $LiHBEt_3$ (1.0 M in THF, 1.7 equiv., 0.8362 mmol, 0.84 mL) at room temperature. After 5h, TLC showed the presence of some unreacted starting material, so an additional 0.14 mL of $LiHBEt_3$ solution was added. When the remaining starting material had been consumed (14h), the reaction was cooled to 0 °C and quenched by addition of water. The aqueous layer was extracted with hexanes, and the combined organic layer was dried with Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography using hexanes:ethyl acetate (4:1) to afford 0.0648 g (0.3460 mmol, 72%) of the desired product **11** as a clear oil: R_f 0.75 (hexanes/ EtOAc 2/1); ^{1}H NMR (400 MHz, $CDCl_3$, δ) 4.55 (br s, 1H), 3.09 (br q, J = 6.6 Hz, 2H), 1.50–1.38 (m, 2H), 1.43 (s, 9H), 1.36–1.20 (m, 4H), 0.88 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 156.2, 79.2, 40.8, 29.9, 29.2, 28.6, 22.5, 14.2. NMR data are consistent with those reported previously.[43]



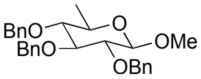
*(Z)-1-benzyloxy-2-butene (**13**).* To a round-bottom flask containing a stir bar, (*Z*)-4-benzyloxybut-2-en-1-ol (**12**, 0.1590 g, 0.8928 mmol; prepared as described[39]) and DMAP (20 mol%, 0.1785 mmol, 0.0218 g) was added 10 mL of DCM followed by triethylamine (1.1 equiv., 0.9821 mmol, 0.14 mL) and diphenyl phosphoryl chloride (1.2 equiv, 1.0714 mmol, 0.22 mL). The reaction was stirred at room temperature for 2 h, after which the solvent was removed under reduced pressure. Ethyl acetate was added, and the organic layer was sequentially washed with water, 1N $NaHCO_3$ and brine. The organic layer was dried with Na_2SO_4, and the solvent was evaporated under reduced pressure. The crude material was dissolved in 6 mL of THF, treated with $LiHBEt_3$ (1.0 M in THF, 1.7 equiv., 1.5178 mmol, 1.5 mL) and stirred at room temperature. After 6 h the reaction was quenched by addition of water, and the mixture was extracted with EtOAc (5×). The combined organic layer was dried with Na_2SO_4, and the solvent was removed

under reduced pressure. Purification by flash chromatography using hexanes:EtOAc gave unreacted starting material (0.0132 g, 0.0740 mmol) along with pure but-2-enyloxymethyl-benzene (0.0856g, 0.5276 mmol) as clear oil in 59% yield (64% based on recovered starting material): R_f 0.42 (hexanes:EtOAc 8:1); ^{1}H NMR (400 MHz, $CDCl_3$, δ) 7.39–7.27 (m, 5H), 5.75–5.60 (m, 2H), 4.53 (s, 2H), 4.10 (dp, *J* = 6.3, 1.0 Hz, 1H), 1.66 (br d, *J* = 7.5 6.0Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 138.6, 128.6, 128.3, 128.0, 127.8, 127.0, 72.3, 65.6, 13.4. NMR data are consistent with those reported previously.[44]

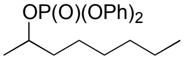


*Methyl 2,3,4-tri-*O*-(benzyl)-β-d-glucopyranoside, diphenyl phosphate (diphenyl phosphate of* ***14****).* To a round-bottom flask containing a stir bar, methyl 2,3,4-tri-*O*-(benzyl)-β-D-glucopyranoside (0.0427 g, 0.0919 mmol) and DMAP (2.0 equiv, 0.1838 mmol, 0.224 g) was added DCM (1.0 mL) at room temperature under nitrogen. Diphenyl phosphoryl chloride (2.0 equiv, 0.1838 mmol, 0.4 mL) was added, and the reaction mixture was stirred at room temperature. After completion of the reaction (2h) the solvent was evaporated under reduced pressure. The residue was dissolved in ethyl acetate and washed with water. The water layer was extracted with ethyl acetate (3×), and the combined organic layer was washed with 1N $NaHCO_3$, water and brine, then dried over Na_2SO_4. Evaporation of the solvent under reduced pressure gave the crude product, which was purified by flash chromatography using hexanes:ethyl acetate (3:1) to afford 0.0555 g (0.0797 mmol, 87%) of the desired compound: ^{1}H NMR (400 MHz, $CDCl_3$, δ) 7.37–7.12 (m, 25H), 4.92 (dd, *J* = 11.0, 6.9 Hz, 2H), 4.78 (dd, *J* = 10.8, 4.3 Hz, 2H), 4.70 (d, *J* = 11.0 Hz, 1H), 4.53 (ddd, *J* = 10.0, 6.4, 1.0 Hz, 1H), 4.47 (d, 1H, *J* = 10.8 Hz), 4.40–4.33 (m, 1H), 4.31 (d, 1H, *J* = 7.8 Hz), 3.65 (t, 1H, *J* = 3.4 Hz), 3.51 (s, 3H), 3.55–3.46 (m, 2H), 3.40 (dd, *J* =

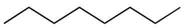
7.9, 0.9 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$, δ) 150.65 (d, J = 7.4 Hz), 150.58 (d, J = 7.2 Hz), 138.53, 138.49, 137.8, 129.91, 129.87, 128.6, 128.53, 128.51, 128.22, 128.17, 128.08, 127.95, 127.83, 127.80, 125.55 (d, J = 4.8 Hz), 125.50 (d, J = 4.8 Hz), 120.32 (d, J = 5.0 Hz), 120.25 (d, J = 4.8 Hz), 104.6, 84.5, 82.3, 77.1, 75.8, 75.2, 74.9, 73.5 (d, J = 7.9 Hz), 67.7 (d, J = 5.5 Hz), 57.1; HRMS (ESI–FTICR) calcd for $C_{40}H_{41}O_9PNa$ $[M+Na]^+$ 719.23859, found 719.23795.



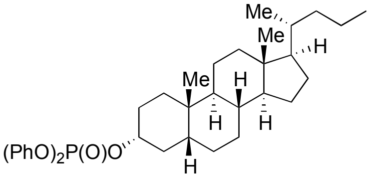
*Methyl 6-deoxy-3,4,5-tri-*O*-benzyl-β-d-glucopyranoside (**15**).* To a stirred solution of methyl 2,3,4-tri-O-(benzyl)-β-D-glucopyranoside, diphenyl phosphate (diphenylphosphate of **14**, 0.0383 g, 0.0550 mmol) in THF (0.38 mL) and *o*-xylene (0.1 mL) was added LiEt$_3$BH (1.0 M solution in THF; 1.8 equiv, 0.1 mmol, 0.1 mL) at room under nitrogen. After 1 h, TLC showed unreacted starting material, so another 0.15 mL of LiEt$_3$BH solution was added. After 4 h, the reaction was complete, as evidenced by TLC, and it was quenched by addition of water, then extracted with ethyl acetate (3×). The combined organic layer was dried with Na$_2$SO$_4$, and the solvent was evaporated under reduced pressure. Purification of the residue by flash chromatography using hexanes:ethyl acetate (8:1) afforded 0.0173 g (0.0386 mmol, 70%) of the product as colorless oil: R_f 0.28 hexanes:EtOAc 8:1); ^{1}H NMR (400 MHz, CDCl$_3$, δ) 7.37–7.28 (m, 15H), 4.94 (d, J = 10.7 Hz, 1H), 4.93 (d, J = 11.0 Hz, 1H), 4.89 (d, J = 10.9 Hz, 1H), 4.81 (d, J = 10.8 Hz, 1H), 4.72 (d, J = 11.0 Hz, 1H), 4.64 (d, J = 10.8, 1H), 4.30 (d, J = 7.8 Hz, 1H), 3.62 (t, J = 9.2 Hz, 1H), 3.58 (s, 3H), 3.45–3.37 (m, 2H), 3.21 (t, J = 9.2 Hz, 1H), 1.33 (d, J = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$, δ) 138.8, 138.3, 128.7, 128.6, 128.31, 128.27, 128.1, 128.06, 127.9, 104.8, 84.6, 83.6, 82.8, 75.9, 75.6, 74.9, 71.3, 57.3, 18.1. NMR data are consistent with those reported previously.[45]



Phosphoric acid 1-methylheptyl diphenyl ester. To a round-bottom flask containing a stir bar, (±)-2-octanol (0.3 g, 2.304 mmol) and DMAP (2 equiv, 4.608 mmol, 0.5630 g) was added DCM (38 mL) under nitrogen. Diphenyl chlorophosphate (2.0 equiv, 5.630 g, 0.95 mL) was added at room temperature to the stirred solution After 1.5 h, the reaction mixture was concentrated under reduced pressure. The residue was taken up in EtOAc, washed with water, 1N $NaHCO_3$, and brine, then dried with Na_2SO_4. Removal of the solvent under reduced pressure afforded the crude product, which was purified by flash chromatography using hexanes:ethyl acetate (4:1) to give the desired compound as colorless oil (0.7515 g, 2.0736 mmol) in 89% yield: R_f 0.74 hexanes:EtOAc 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (br t, J = 7.6 Hz, 4H), 7.23 (br d, J = 8.1 Hz, 4H), 7.17 (br t, J = 7.3 Hz, 2H), 4.73 (sep, J = 6.5 Hz, 1H), 1.73–1.62 (m, 1H), 1.56–1.48 (m, 1H), 1.34 (d, J = 6.2 Hz, 3H), 1.32–1.14 (m, 8H), 0.86 (t, 3H, J = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.88 (d, J = 7.2 Hz), 150.86 (d, J = 7.2 Hz), 129.8, 125.3, 120.29 (d, J = 5.1 Hz), 120.26 (d, J = 5.0 Hz), 78.7 (d, J = 6.7 Hz), 37.5 (d, J = 6.4 Hz), 31.8, 29.1, 25.1, 22.7, 21.7 (d, J = 3.3 Hz), 14.2; HRMS (ESI–QTOF) calcd for $C_{20}H_{27}NaO_4P$ [M+Na] 385.1545, found 385.1545.

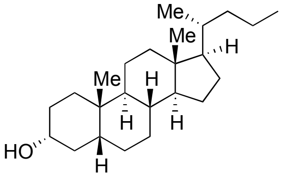


Octane. To a stirred solution of phosphoric acid 1-methylheptyl diphenyl ester (0.0334 g, 0.0922 mmol) in THF (0.6 mL) was added dropwise at room temperature $LiEt_3BH$ (1.0M in THF, 2.2 equiv, 0.2027 mmol, 0.20 mL). Upon completion of the reaction in 4h, the reaction was quenched with saturated aqueous NH_4Cl, and the aqueous layer was extracted with DCM (3×). The combined organic layer (the total volume 4.5 mL) was dried with Na_2SO_4. An aliquot of 38 μL was diluted with DCM to 2 mL, and the solution was subjected to GC analysis using decane as internal standard. Octane was produced in 44% yield.



*(3α,5β)-Cholan-3-ol, diphenyl phosphate (**20**).* To a stirred solution of (3α,5β)-cholane-3,24-diol (**19**, 0.1000 g, 0.2655 mmol) and DMAP (1.0 equiv, 0.2655 mmol, 0.0324g) in DCM (7.5 mL) was added triethylamine (2.2 equiv, 0.5841 mmol, 0.08 mL) and diphenyl phosphoryl chloride (2.4 equiv., 0.6372 mmol, 0.13 mL) at room temperature. Upon completion of the reaction (3h), the solvent was removed under reduced pressure. The residue taken up in ethyl acetate, then washed with water, 1N $NaHCO_3$ and brine. After drying with Na_2SO_4, the solvent was removed *in vacuo*. The crude bis-phosphate was dissolved in 1.6 mL of THF and treated with $LiEt_3BH$ (1.0 M solution in THF; 1.7 equiv, 0.4513 mmol, 0.45 mL) at room temperature under nitrogen. After 3 h, TLC showed a trace of the starting material, so another 0.20 mL of $LiEt_3BH$ solution was added. After an additional 1.5 h, the reaction was quenched by addition of water and extracted with ethyl acetate (5×). The combined organic layer was washed with brine and dried with Na_2SO_4 before the solvent was removed under reduced pressure. The residue was repeatedly dissolved in methanol and evaporated under reduced pressure to remove residual borate. Purification by flash chromatography (hexanes:ethyl acetate, 5:1) afforded 0.0966 g (61%) of the product as colorless oil: R_f 0.82 hexanes:EtOAc 5:1); IR 3067, 2937, 2865, 1591, 1489, 1193, 1015, 951, 689 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, δ) 7.36–7.32 (m, 4H), 7.25–7.16 (m, 6 H), 4.50–4.63 (m, 1H), 2.06–1.94 (m, 2H), 1.90–1.78 (m, 4H), 1.71–1.62 (m, 1H), 1.61–1.52 (m, 2H), 1.46–1.32 (m, 8H), 1.31–0.95 (m, 11H), 0.92 (s, 3H), 0.91 (d, J = 6.6 Hz, 3H),

0.88 (t, J = 7.0 Hz, 3H), 0.65 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 150.8 (d, J = 7.2 Hz), 129.9, 125.3, 120.30 (d, J = 5.0 Hz), 120.27 (d, J = 5.0 Hz), 81.3 (d, J = 6.6 Hz), 56.5, 56.5, 42.8, 42.2, 40.6, 40.3, 38.5, 35.9, 35.7, 35.1, 34.6, 34.1 (d, J = 4.4 Hz), 28.6 (d, J = 4.4 Hz), 28.5, 27.1 26.4, 24.4, 23.4, 21.0, 19.4, 18.8, 14.8, 12.2; HRMS (ESI–QTOF) calcd for $C_{36}H_{51}NaO_4P$ [M+Na] 601.3423, found 601.3444.



*(3α,5β)-Cholan-3-ol (**21**).* To a solution of (3α,5β)-cholane-3,24-diol (0.0550 g, 0.1517 mmol) in 1.5 mL of THF was added dropwise at room temperature *n*-BuLi (2.5M in hexanes, 2.1 equiv, 0.3212 mmol, 0.13 mL). The reaction mixture was stirred for 30 min at room temperature. Some white precipitate formed, and additional THF (0.5 mL) was added. After 30 min, the reaction mixture was treated with diphenyl chlorophosphate (2.1 equiv, 0.3212 mmol, 0.067 mL) at room temperature, which led to dissolution of the precipitate. After 2 h at room temperature, $LiEt_3BH$ (1.0 M in THF, 1.32 equiv, 0.2 mmol, 0.2 mL) was added, and the mixture was left to stir overnight. The reaction was quenched with saturated aqueous NH_4Cl and extracted with ethyl acetate (7×). After drying with Na_2SO_4, the solvent was removed *in vacuo*. The crude phosphate was dissolved in 1.5 mL of dry toluene, cooled to 0 °C and treated with sodium bis(2-methoxyethoxy)aluminum hydride (65 wt. % solution in toluene, 0.28 mL), and the mixture was gradually warmed to room temperature. The reaction was quenched with water, followed by slow addition of 10% HCl at 0 °C until all solids dissloved. The organic layer was separated, and the aqueous layer was extracted with DCM (3×). After drying with Na_2SO_4, the combined organic layer was concentrated *in vacuo* to afford cholanol **21** as colorless solid 0.0448 g (0.1242

mmol, 82%): ^{1}H NMR (400 MHz, $CDCl_3$, δ) 3.68–3.58 (m, 1H), 1.98 (dt, J = 12.0, 3.0, 1H), 1.92–1.71 (m, 4H), 1.70–0.94 (m, 24H), 0.93 (s, 3H), 0.90 (d, J = 6.6 Hz, 3H), 0.87 (t, J = 7.0 Hz, 3H), 0.65 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 72.1, 56.7, 56.6, 42.9, 42.3, 40.7, 40.4, 38.5, 36.7, 36.1, 35.8, 35.6, 34.8, 30.8, 28.5, 27.4, 26.6, 24.5, 23.6, 21.0, 19.4, 18.8, 14.8, 12.2. NMR data are consistent with those reported previously.[15]

Acknowledgements

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Supporting Information. ^{1}H and ^{13}C spectra in a PDF file for the following (includes all novel componds): **5**, **6**, **7**, **9**, **11**, **13**, **15**, **20**, **21** and the diphenyl phosphates of **6**, **8**, **14** and 2-octanol.

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