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An Efficient Route for the Synthesis of Glycosyl Phosphinic Acids

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An efficient method for the synthesis of glycosyl phosphinic acids (**21**) from the corresponding *C*-phosphonates is described. The route developed involves three steps: reduction of the glycosyl *C*-phosphonate to a primary phosphine, reaction of this product with an alkylating agent to afford a secondary phosphine, and finally oxidation to the phosphinic acid. Deprotection provides compounds suitable for testing as glycosyl phosphate analogues. Although the focus of this report is the synthesis of analogues of arabinofuranosyl-containing phosphate esters, the method should be readily applicable to other systems, carbohydrate or otherwise.

Introduction

Glycosyl phosphates and the corresponding phosphate diesters have important biological roles, serving for example as key intermediates in the biosynthesis of oligosaccharides.[1] Representative examples of these compounds are provided in Chart 1 and include glucose-1-phosphate (**1**) and dolichol phosphate mannose (**2**). The biological importance of these and other such compounds has, for many years, stimulated interest both in the synthesis of nonhydrolyzable glycosyl phosphate analogues and in their subsequent evaluation as inhibitors of the enzymes involved in glycosyl phosphate metabolism.[2−5]

Significant work has been done on the synthesis of glycosyl *C*-phosphonates (e.g., **3**). Routes commonly used for the preparation of such compounds include (1) a Michaelis−Arbuzov reaction between an alkyl halide and a trialkyl phosphite[4] and (2) a Horner−Emmons olefination of a protected reducing sugar with subsequent cyclization of the resulting vinyl phosphonate.[5] These methods are well developed, and glycosyl *C*-phosphonates are, in general, straightforwardly prepared. Syntheses of glycosyl *C*-phosphonate diesters (e.g., **4**) are less common, although there are routes available for their preparation.[5c,6]

In contrast, there have been few reported syntheses of glycosyl phosphinic acids, analogues of glycosyl phosphates in which two of the P−O bonds of the phosphate moiety have been replaced with P−C bonds (e.g., **5**). To date, the only reported phosphinic acid analogues of naturally occurring carbohydrate phosphates are **6**[7] and **7**,[8] as well as nucleotides derived from **7**. In the assembly of **6**, the carbon−phosphorus bonds were formed by the reaction of alkene **8** with hypophosphorus acid derivative **9**, followed by the coupling of this product with **10**.[7] The key step in the synthesis of **7** was the coupling of the phosphorus anion derived from **11** with **12**; subsequent functional group transformations afforded the target.[8] Related to these investigations are a series of papers that describe the synthesis of monosaccharide analogues in which the ring oxygen has been replaced with phosphorus.[9] Included among these “phosphosugars” are phosphinic acid derivatives such as **13**.

We previously described the synthesis of *C*-phosphonate analogues (**14**−**19**, Chart 2) of decaprenolphosphoarabinose (DPA, **20**).[10] DPA is the donor substrate used by the arabinosyltransferases that synthesize the arabinan portions of two polysaccharides that are the major structural components of the cell wall complex in mycobacteria, including the human pathogen *Mycobacterium tuberculosis*.[11] Nonhydrolyzable analogues of **20** are of interest not only as biochemical tools but also as lead compounds for new antituberculosis agents. Such species

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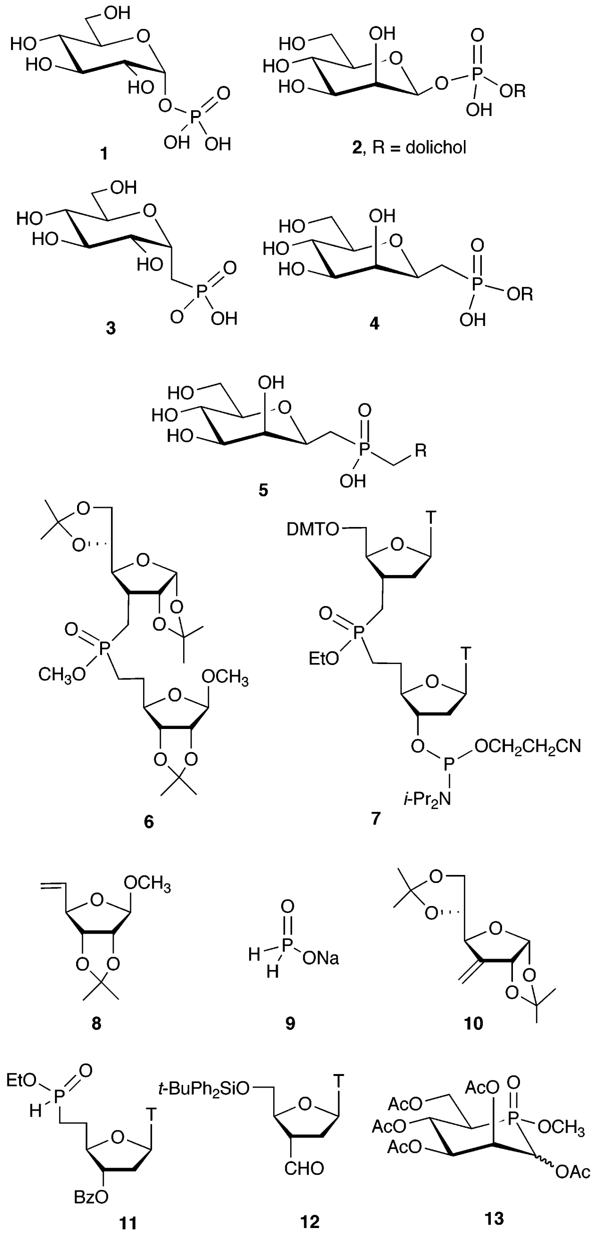
CHART 1



1

2, R = dolichol

3

4

5

6

7

8

9

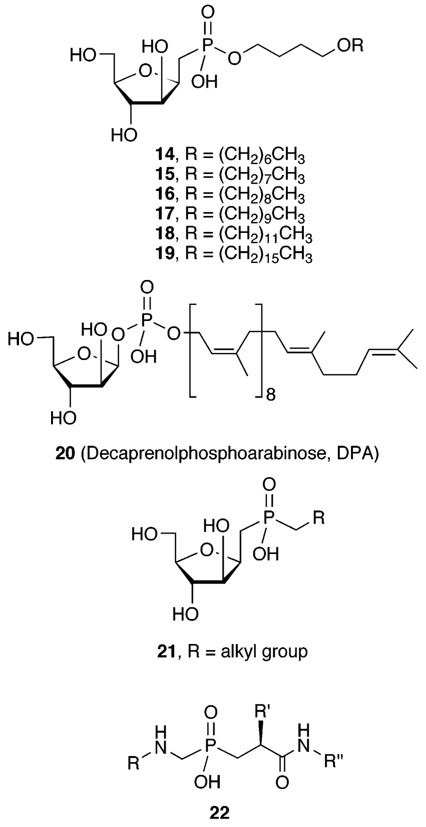
10

11

12

13

CHART 2



14, R = $(CH_2)_6CH_3$
15, R = $(CH_2)_7CH_3$
16, R = $(CH_2)_8CH_3$
17, R = $(CH_2)_9CH_3$
18, R = $(CH_2)_{11}CH_3$
19, R = $(CH_2)_{15}CH_3$

20 (Decaprenolphosphoarabinose, DPA)

21, R = alkyl group

22

are expected to arrest cell wall arabinan biosynthesis by competing with **20** for the active site of mycobacterial arabinosyltransferases. These enzymes have been validated as suitable targets for drug action in that one of the drugs used to treat tuberculosis, ethambutol, is an arabinosyltransferase inhibitor.[12] In our earlier investigation, we demonstrated that one of these *C*-phosphonate compounds, **19**, was active in vitro against *M. tuberculosis*, with an MIC value of 3.13 μg/mL.[10] This compound is currently being tested to determine its potency in vivo.

On the basis of these results, we endeavored to synthesize additional DPA analogues and turned our attention to phosphinic acids of the general type **21**. In designing routes for the synthesis of these compounds, we found previously reported methods for the synthesis of carbohydrate-containing phosphinic acids unattractive, given the number of steps involved. We also considered the routes that have been used to synthesize phosphinic acid containing peptides (e.g., **22**), which have been studied as protease inhibitors.[13] The approach most commonly used for the synthesis of the phosphinic acid moiety of these peptides is similar to the one used for the preparation of **6** and involves the radical addition of hypophosphorus acid derivatives to an alkene. We envisioned a more efficient route to the glycosyl phosphinic acids of interest to us. The retrosynthetic analysis of this approach is shown in Figure 1. We postulated that the targets could be obtained by oxidation of secondary phosphines of the general type **27**, which were to be prepared by monoalkylation of primary phosphine **26**. We hoped to access **26** via reduction of the easily prepared *C*-phosphonate **25**.

Results and Discussion

With this route in mind, *C*-phosphonate **25** was synthesized in three steps from the commercially available 2,3,5-tri-*O*-benzyl arabinofuranose, **23**, as shown in Scheme 1. Wittig olefination of **23** followed by cyclization of the resulting alkene with iodine[14] yielded **24**, which was then heated in refluxing triethyl phosphite to afford

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[12] (a) Mikusová, K.; Slayden, R. A.; Besra, G. S.; Brennan, P. J. *Antimicrob. Agents Chemother.* **1995**, *39*, 2484. (b) Deng, L.; Mikusová, K.; Robuck, K. G.; Scherman, M.; Brennan, P. J.; McNeil, M. R. *Antimicrob. Agents Chemother.* **1995**, *39*, 694. (c) Khoo, K.-H.; Douglas, E.; Azadi, P.; Inamine, J. M.; Besra, G. S.; Mikusová, K.; Brennan, P. J.; Chatterjee, D. *J. Biol. Chem.* **1996**, *271*, 28682.

[13] Representative examples: (a) Malachowski, W. P.; Coward, J. K. *J. Org. Chem.* **1994**, *59*, 7625. (b) Buchardt, J.; Ferreras, M.; Krog-Jensen, C.; Delaisse, J.-M.; Foged, N. T.; Meldal, M. *Chem. Eur. J.* **1999**, *5*, 2877. (c) Ellsworth, B. A.; Tom, N. J.; Bartlett, P. A. *Chem. Biol.* **1996**, *3*, 37.

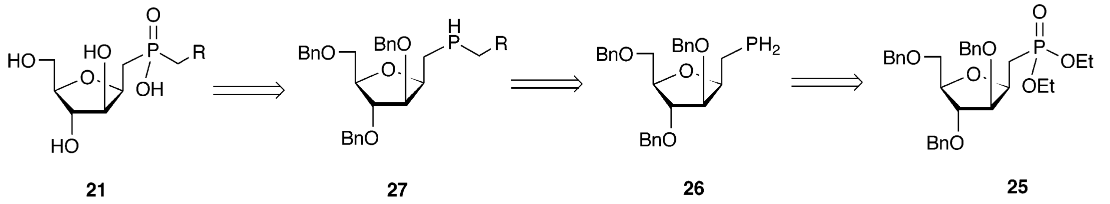
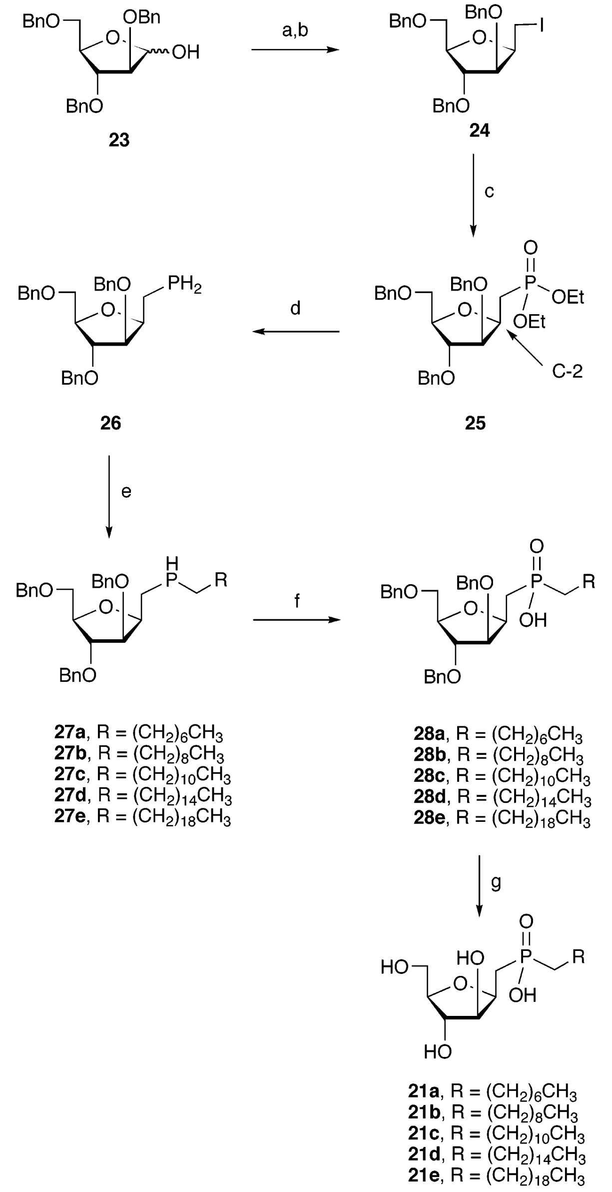


FIGURE 1. Retrosynthetic analysis of glycosyl phosphinic acid derivatives **21**.

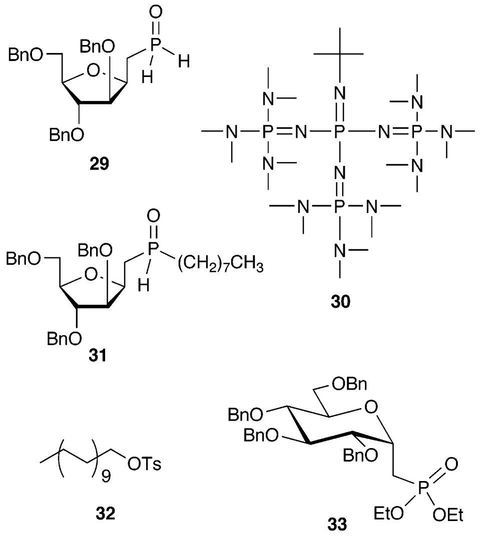
SCHEME 1. **Synthesis of 21a−21e**[a]



[a] (a) Ph_3PCH_3Br, *n*-BuLi, THF, rt, 77%. (b) I_2, Et_2O, $NaHCO_3$, rt, 95%. (c) $(EtO)_3P$, reflux, 85%. (d) $LiAlH_4$, Et_2O, rt, 69%. (e) **30**, R-I or **32**, diethyl ether, rt. (f) I_2, pyridine, H_2O, rt, 26−64% from **26**. (g) H_2, Pd/C, CH_3OH, rt 70−88%.

25. As was previously reported[15] for the synthesis of the C-2 epimer of **25**, when this Michaelis−Arbuzov reaction was attempted in refluxing trimethyl phosphite, iodide **24** was recovered unreacted.

CHART 3



The reduction of the phosphonate moiety in **25** was achieved upon treatment with lithium aluminum hydride in ether at room temperature.[16] The product phosphine, **26**, was prone to air oxidation, but it was nevertheless possible to purify the product by quickly passing the crude reaction mixture though a column of silica gel. Following this purification step, **26** was obtained in 69% yield. In addition to a signal for the desired compound, the mass spectrum indicated the formation of the corresponding oxidation byproduct, **29** (Chart 3), which is presumably produced in the ion source.[17] In the ^1H NMR spectrum of **26** (recorded in $CDCl_3$) the phosphine appeared as a broad singlet between 2.60 and 3.15 ppm and the ^1H-decoupled ^{31}P NMR spectrum showed a single peak at −150.6 ppm (relative to external phosphoric acid at 0.0 ppm).

We initially explored the alkylation of phosphine **26** using *n*-butyllithium and an alkyl halide in THF.[18] However, under these conditions no alkylation of **26** was observed; similar results were obtained when *t*-BuLi was used as the base. We then turned our attention to a previous report that described the monoalkylation of primary phosphines using a phosphazene (Schweshinger) base.[19] These alkylation reactions, which were carried out by treating a solution of phosphine **26** in diethyl ether with an alkylating agent and the P_4-Schweshinger base,

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(14) Freeman, F.; Robarge, K. D. *Carbohydr. Res.* **1987**, *171*, 1.

(15) McGurk, P.; Chang, G. X.; Lowary, T. L.; McNeil, M.; Field, R. A. *Tetrahedron Lett.* **2001**, *42*, 2231.

(16) Prabhu, K. R.; Pillarsetty, N.; Gali, H.; Katti, K. V. *J. Am. Chem. Soc.* **2000**, *122*, 1554.

(17) A signal at m/z = 489.1716 was observed, which corresponds to the Na^+ adduct of **29** ($M + Na^+$ = 489.1806). A resonance arising from **29** was not present in the ^{31}P NMR spectrum of **26**.

(18) Yan, Y.-Y.; RajanBabu, T. V. *Org. Lett.* **2000**, *2*, 4137.

(19) Uhlig, F.; Puschner, B.; Herrmann, E.; Zobel, B.; Bernhardt, H.; Uhlig, W. *Phosphorus Sulfur Silicon Relat. Elem.* **1993**, *81*, 155.

30 (Chart 3), were successful. For the synthesis of secondary phosphines **27a**−**27d**, commercially available alkyl iodides were used as the electrophile. The alkyl iodide required for the preparation of **27e** is not available, and we therefore used tosylate **32** (Chart 3), which was synthesized from 1-eicosanol. Like the primary phosphine **26**, the secondary phosphines produced in these reactions were also air-sensitive; however, their purification could be achieved by rapid chromatography on silica gel.[20]

Given their air sensitivity, these compounds were not further purified or characterized but were instead immediately dissolved in a solution of pyridine and water and then oxidized upon treatment with iodine.[21] After stirring for 3 days at room temperature, the reaction mixtures were purified by chromatography. Following chromatography, the products were typically contaminated with traces of pyridine, which were removed upon stirring in methanol with Amberlite IR-120 (H+) resin. The yields of the oxidized products **28a**−**28e** from secondary phosphine **26** ranged from 26% to 64%.

In an effort to improve the overall yields and efficiency of the process, we investigated oxidation of the crude secondary phosphines **27** immediately following the alkylation reaction. Unfortunately, although the oxidation proceeded without difficulty, we were unable to separate the phosphinic acid products **28** from other byproducts produced during these reactions. It appears, therefore, that despite the air-sensitivity of phosphines **27a**−**27e**, a rapid purification of these products prior to treatment with iodine provides the best overall results.

A disadvantage of the iodine/pyridine/water oxidation system employed here is that the method requires extended reaction times (3 days). We therefore explored the use of H_2O_2 or *m*-CPBA to carry out this reaction. With both of these reagents, however, the product obtained was only partially oxidized and was resistant to further oxidation. For example, reaction of **27a** with either H_2O_2 or *m*-CPBA yielded **31**. The structure of this product was confirmed by mass spectrometry and also by ^{1}H-coupled ^{31}P NMR spectroscopy, which showed the presence of two diastereomeric oxidation products (δ_P = 34.33 and 33.92 ppm, $CDCl_3$) with $^1J_{P,H}$ magnitudes of 462 and 476 Hz, as would be expected for compounds of this type.[22]

Our initial attempts to characterize **28a**−**28e** by NMR spectroscopy were complicated by the fact that in either $CDCl_3$ or CD_3OD the resonances in the ^{1}H and ^{13}C NMR spectra were significantly broadened. Further complicating the issue was that the spectra of the crude reaction mixtures following evaporation of the reaction solvent (the pyridinium salts of **28a**−**28e**) were well-resolved and showed the products to be of reasonable purity prior to purification. One explanation for these observations is that the compounds degrade upon silica gel chromatography, but we viewed this as unlikely. Instead, we hypothesized that the free phosphinic acids may be aggregating in both CD_3OD and $CDCl_3$, thus leading to the poor quality spectra. Given the relatively well-resolved spectra obtained for the crude pyridinium salts (above) we investigated the use of deuterated pyridine as the NMR solvent. Dissolution of **28a**−**28e** in pyridine-d_5 should lead to the immediate formation of the corresponding pyridinium salts. We were pleased to see that when these NMR spectra were recorded in pyridine-d_5, the resonances in the ^{1}H and ^{13}C NMR spectra sharpened substantially. In addition, the ^{1}H-decoupled ^{31}P NMR spectrum of each product showed a singlet at approximately 50 ppm (relative to external phosphoric acid at 0.0 ppm), which is consistent with the compounds being phosphinic acids.[22] Similarly, in the ^{13}C NMR spectra, the presence of the two C−P bonds was established by two resonances between 30 and 32 ppm, which appeared as doublets with $^1J_{C,P}$ magnitudes of approximately 90 Hz.

Having developed a successful method for the synthesis of the protected phosphinic acids **28a**−**28e**, we deprotected them without difficulty. Hydrogenation (H_2, Pd/C, CH_3OH) provided the targets **21a**−**21e** in yields of 70−88%.[23] As was true with the tribenzylated phosphinic acids, the best NMR data for **21a**−**21e** was obtained when pyridine-d_5 was used as the NMR solvent. In all cases, the ^{1}H-decoupled ^{31}P NMR spectra showed the characteristic phosphinic acid singlet around 50 ppm, and in the ^{13}C NMR spectra two doublets ($^1J_{C,P} \approx 90$ Hz) arising from the carbons directly bonded to the phosphorus atoms were present between 30 and 32 ppm.

In summary, we have developed an efficient method for the preparation of glycosyl phosphinic acid derivatives via a route that involves monalkylation of a primary glycosyl phosphine and subsequent oxidation of the resulting product. Although the focus of this paper has been on the synthesis of analogues of arabinofuranosyl-containing glycosyl phosphate esters, this method should be straightforwardly applied to other carbohydrate systems. In many cases, the required *C*-phosphonate starting materials (e.g., **33**, Chart 3) have already been reported.[3,4] The extension of this method to the synthesis of phosphinic acid analogues of non-carbohydrate phosphate esters should also be readily achieved. Testing of **21a**−**21e** as inhibitors of mycobacterial growth is in progress.

Experimental Section

General. General experimental procedures and analytical data for new compounds (^{1}H NMR, ^{13}C NMR, ^{13}P NMR, HRMS, $[\alpha]_D$) are provided in Supporting Information.

1-(Octyl)-2,5-anhydroglucityl Phosphinic Acid (21a). Phosphinic acid **28a** (90 mg, 0.15 mmol) was dissolved in CH_3OH (5 mL) and 10% Pd/C (30 mg) was added. The reaction mixture was stirred under H_2 overnight at atmospheric pressure before being filtered and concentrated. The resulting oil was purified by chromatography on Iatrobeads (1% pyridine in CH_2Cl_2 → 3:1 CH_2Cl_2/CH_3OH) providing a compound that was then redissolved in water and lyophilized to afford **21a** (40 mg, 81%) as an off-white solid.

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[20] We attempted to obtain mass spectrometric data for these phosphines; however, the only signal detected was for the corresponding oxidation product, the phosphinous acid derivative, e.g., **31** (Chart 3), which we propose is produced in the ion source. For example, the mass spectrum recorded with **27a** (M + Na$^+$ = 585.3104) showed only a signal at *m*/*z* = 601.3024, which arises from the sodium adduct of **31** (M + Na$^+$ = 601.3059).

[21] Lindh, I.; Stawinski, J. *J. Org. Chem.* **1989**, *54*, 1338.

[22] Gorenstein, D. G. *Prog. Nucl. Magn. Reson. Spectrosc.* **1983**, *16*, 1.

[23] Prior to the hydrogenation step, we converted the pyridinium salts of **28a**−**28e**, which were generated upon dissolving the protected phosphinic acids in pyridine-d_5, back to the free phosphinic acids. This was achieved by stirring these pyridinium salts with Amberlite IR-120 (H+) resin in methanol overnight at room temperature.

1-(Decyl)-2,5-anhydroglucityl Phosphinic Acid (21b). Phosphinic acid **28b** (140 mg, 0.23 mmol) was hydrogenated in CH_3OH (5 mL) using 10% Pd/C (50 mg) as described for the preparation of **21a**. Purification of the product was done as described for **21a** to provide **21b** (65 mg, 82%) as an off-white solid.

1-(Dodecyl)-2,5-anhydroglucityl Phosphinic Acid (21c). Phosphinic acid **28c** (98 mg, 0.15 mmol) was hydrogenated in CH_3OH (5 mL) using 10% Pd/C (40 mg) as described for the preparation of **21a**. Purification of the product was done as described for **21a** to provide **21c** (50 mg, 88%) as an off-white solid.

1-(Hexadecyl)-2,5-anhydroglucityl Phosphinic Acid (21d). Phosphinic acid **28d** (189 mg, 0.27 mmol) was hydrogenated in CH_3OH (5 mL) using 10% Pd/C (70 mg) as described for the preparation of **21a**. The compound was purified by crystallization from methanol to provide **21d** (81 mg, 70%) as an off-white solid.

1-(Eicosanyl)-2,5-anhydroglucityl Phosphinic Acid (21e). Phosphinic acid **28e** (29 mg, 0.038 mmol) was hydrogenated in CH_3OH (5 mL) using 10% Pd/C (15 mg) as described for the preparation of **21a**. The compound was purified by crystallization from methanol to provide **21e** (15 mg, 80%) as an off-white solid.

Diethyl 3,4,6-tri-*O*-benzyl-2,5-anhydroglucityl Phosphonate (25). Iodide **24**[14] (3.85 g, 7.08 mmol) was dissolved in triethyl phosphite (20 mL), and the reaction mixture was heated at reflux (156 °C) for 12 h. The excess triethyl phosphite was evaporated by heating under high vacuum, and the resulting oil was purified by chromatography (hexane/EtOAc 4:1 → EtOAc/hexane 2:1) to afford **25** (3.34 g, 85%) as a colorless oil.

3,4,6-Tri-*O*-benzyl-2,5-anhydroglucityl Phosphine (26). A solution of phosphonate **25** (235 mg, 0.42 mmol) in anhydrous Et_2O (5 mL) was added dropwise to a mixture of $LiAlH_4$ (40 mg, 1.10 mmol) in anhydrous Et_2O (5 mL) stirring at room temperature. After 20 min, EtOAc (1 mL) was added to the mixture, followed a few minutes later by H_2O (0.2 mL). After all gas evolution had subsided, the mixture was filtered though Celite and concentrated to give a clear oil. Purification of the product by rapid passage of the crude reaction mixture through a column of silica gel (6:1 hexane/EtOAc) afforded **26** (132 mg, 69%) as a colorless oil.

1-(Octyl)-3,4,6-tri-*O*-benzyl-2,5-anhydroglucityl Phosphinic Acid (28a). Phosphine **26** (245 mg, 0.54 mmol) was dissolved in Et_2O (10 mL) and stirred at room temperature before **30** (600 μL of a 1 M solution in hexane, 0.60 mmol) was added, followed by 1-iodooctane (100 μL, 0.60 mmol). After 30 min, the mixture was neutralized with AcOH, and the salts that precipitated were removed by filtration through a cotton plug, which was rinsed with Et_2O. The solvent was evaporated, and the residue was purified by rapid elution though a short column of silica gel (6:1 hexane/EtOAc) to afford **27a** as a colorless oil: R_f 0.36 (6:1 hexane/EtOAc). This oil was immediately dissolved in pyridine/H_2O (98:2, 5 mL), I_2 (189 mg, 0.751 mmol) added, and the reaction mixture stirred for 3 days at room temperature. The mixture was then diluted with CH_2Cl_2, washed with an aqueous 5% $NaHSO_3$, solution, and dried (Na_2SO_4). The solvent was then evaporated, and the residual oil was purified by chromatography (12:1 CH_2Cl_2/CH_3OH). The product following chromatography was contaminated with traces of pyridine, which were removed by redissolving the material in CH_3OH (5 mL) and then stirring the solution with Amberlite 120 (H+) resin (150 mg) overnight. Filtration of the resin and evaporation of the solvent afforded **28a** (111 mg, 34% from **26**) as a clear oil.

1-(Decyl)-3,4,6-tri-*O*-benzyl-2,5-anhydroglucityl Phosphinic Acid (28b). Alkylation of phosphine **26** (203 mg, 0.45 mmol) with 1-iododecane (100 μL, 0.50 mmol) was achieved as described for the preparation of **27a** using **30** (500 μL of a 1 M solution in hexane, 0.50 mmol) in Et_2O (10 mL). Phosphine **27b** (R_f 0.26, 9:1 hexane/EtOAc) was obtained following the purification process outlined above for **27a** using 9:1 hexane/EtOAc as the eluant. This product was immediately oxidized as described for the preparation of **28a** using I_2 (187 mg, 0.74 mmol) in pyridine/H_2O (98:2, 6 mL). Purification of the oxidized product was achieved via chromatography (12:1 CH_2Cl_2/CH_3OH) and subsequent treatment of the resulting residue with ion-exchange resin as described for **28a**. Phosphinic acid **28b** was isolated (158 mg, 57% from **26**) as a clear oil.

1-(Dodecyl)-3,4,6-tri-*O*-benzyl-2,5-anhydroglucityl Phosphinic Acid (28c). Alkylation of phosphine **26** (208 mg, 0.46 mmol) with 1-iodododecane (125 μL, 0.51 mmol) was achieved as described for the preparation of **27a** using **30** (490 μL of a 1 M solution in hexane, 0.49 mmol) in Et_2O (10 mL). Phosphine **27c** (R_f 0.30, 9:1 hexane/EtOAc) was obtained following the purification process outlined above for **27a** using 9:1 hexane/EtOAc as the eluant. This product was immediately oxidized as described for the preparation of **28a** using I_2 (143 mg, 0.57 mmol) in pyridine/H_2O (98:2, 6 mL). Purification of the oxidized product was achieved via chromatography (12:1 CH_2Cl_2/CH_3OH) and subsequent treatment of the resulting residue with ion-exchange resin as described for **28a**. Phosphinic acid **28c** was isolated (118 mg, 40% from **26**) as a clear oil.

1-(Hexadecyl)-3,4,6-tri-*O*-benzyl-2,5-anhydroglucityl Phosphinic Acid (28d). Alkylation of phosphine **26** (189 mg, 0.42 mmol) with 1-iodohexadecane (155 mg, 0.44 mmol) was achieved as described for the preparation of **27a** using **30** (440 μL of a 1 M solution in hexane, 0.44 mmol) in Et_2O (10 mL). Phosphine **27d** (R_f 0.33, 8:1 hexane/EtOAc was obtained following the purification process outlined above for **27a** using 9:1 hexane/EtOAc as the eluant. This product was immediately oxidized as described for the preparation of **28a** using I_2 (216 mg, 0.86 mmol) in pyridine/H_2O (98:2, 6 mL). Purification of the oxidized product was achieved via chromatography (12:1 CH_2Cl_2/CH_3OH) and subsequent treatment of the resulting residue with ion-exchange resin as described for **28a**. Phosphinic acid **28d** was isolated (189 mg, 64% from **26**) as a clear oil.

1-(Eicosanyl)-3,4,6-tri-*O*-benzyl-2,5-anhydroglucityl Phosphinic Acid (28e). Alkylation of phosphine **26** (79 mg, 0.18 mmol) with 1-*p*-toluenesulfonyloxy-eicosane (**32**, 130 mg, 0.29 mmol) was achieved as described for the preparation of **27a** using **30** (180 μL of a 1 M solution in hexane, 0.18 mmol) in Et_2O (5 mL). Phosphine **27e** (R_f 0.26, 12:1 hexane/EtOAc) was obtained following the purification process outlined above for **27a** using 12:1 hexane/EtOAc as the eluant. This product was immediately oxidized as described for the preparation of **28a** using I_2 (66 mg, 0.26 mmol) in pyridine/H_2O (98:2, 4 mL). Purification of the oxidized product was achieved via chromatography (12:1, CH_2Cl_2/CH_3OH,) and subsequent treatment of the resulting resin with ion-exchange residue as described for **28a**. Phosphinic acid **28e** was isolated (35 mg, 26% from **26**) as a clear oil.

1-*p*-Toluenesulfonyloxy-eicosane (32). 1-Eicosanol (500 mg, 1.67 mmol) was dissolved in THF (15 mL) and stirred at room temperature. *n*-Butyllithium (1.1 mL of a 1.6 M solution in hexanes, 1.84 mmol) was added, followed by *p*-toluenesulfonyl chloride (639 mg, 3.35 mmol) in THF (15 mL). After 3 h, the mixture was diluted with EtOAc (20 mL), washed with H_2O (25 mL) and brine (25 mL), and then dried over Na_2SO_4. The solvent was evaporated and the solid was purified by chromatography (hexane/EtOAc 10:1) to afford **32** (501 mg, 66%) as a white solid.

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Supporting Information Available: Analytical data and ^1H, ^{13}C, and ^{31}P NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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