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Article

Unprecedented Convergent Synthesis of Sugar-Functionalization of Phosphinic Acids under Metal-Free Conditions

Moaz M. Abdou,* Paul M. O'Neill, Eric Amigues, and Magdalini Matziari*

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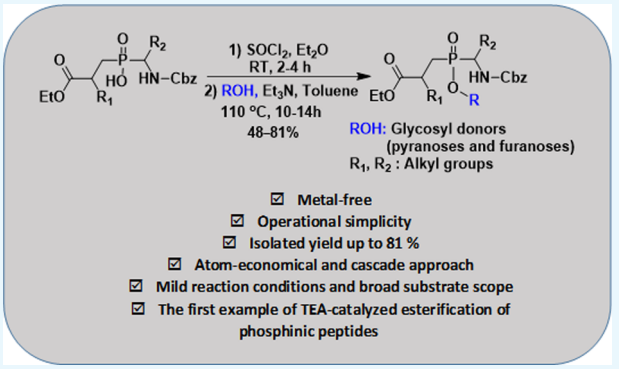
ABSTRACT: A novel TEA-catalyzed sugar-esterification of phosphinic acids was used as a general and efficient approach for the synthesis of a variety of phosphinates without any transition metal. The high efficiency of the current methodology and a convenient experimental procedure compensate for the moderate yields obtained. Another advantage is that the reaction tolerates different substituents attached to the phosphinic acids and the sugar moieties alongside the ease of isolation of the product.



1. INTRODUCTION

The *in vivo* administration of phosphinic acid as a drug is subject to some restrictions compared with peptides owing to the P−OH moiety.[1−3] They are negatively charged at physiological pH and, due to their polarity, are unable to permeate cell membranes. To solve this problem, esters can be utilized as prodrugs. These esters should meet several requirements, such as chemical stability/solubility of the prodrug in the gastrointestinal tract, good permeability across cell membranes, and finally, efficient release of the drug at the target.

Improved methods for phosphinate synthesis are still attracting a lot of interest since phosphinates show a multitude of distinct characteristics serving as prodrugs and drugs (Figure 1).[1−5] Given their widespread application as pharmacological agents and important synthetic intermediates, the construction of the P−OR bond remains to be investigated. One of the central problems in phosphinate chemistry is the protecting group manipulation. The phosphate itself is acidic and charged at neutral pH and, therefore, difficult to carry through and be purified by standard organic synthetic methods. Conventional reaction conditions are often inconvenient, requiring very long reaction times and resulting in a complex mixture of side products or a low overall yield.[6,7] Subsequently, to bypass the issues mentioned above, significant efforts have been directed toward the synthetic manipulation of phosphinic esters. However, surprisingly, no sugar-based esters as proposed here have yet been reported.

On the other hand, sugar-based moieties have been used as water-soluble derivatives with medicinal activities comprising antioxidant, anticancer, cardioprotective, neuroprotective, antidiabetic, and antiviral activities (Figure 2).[8−19] Therefore, the esterification strategy of phosphinic acid with suitable sugar derivatives would be beneficial to produce more soluble variants of phosphinate prodrug candidates. Moreover, the use of glycosyl−phosphinate prodrug conjugates with enhanced drug delivery properties to the brain could provide a new approach to more efficient prodrug candidates.

Herein, a transition-metal-free acylation of phosphinic acids via TEA-catalyzed esterification reaction of phosphinic acids and sugars is developed. Initially, the synthesis of pseudo-dipeptide synthons **9a−d** and sugar-protected derivatives **14**, **16**, and **19** as model coupling partners for esterification studies was undertaken. In this regard, the preparation of pseudo-dipeptide synthons **9a−d** and suitable sugar molecules **14**, **16**, and **19** was an absolute requirement for accomplishing this goal. Then, a detailed unveiling and tackling led to a standardized set of conditions, allowing the synthesis of functionalized phosphinates.

2. EXPERIMENTAL SECTION

2.1. Materials and Instrumentation. Reagents were purchased from Aladdin, TCI, and Acros Organics. Anhydrous

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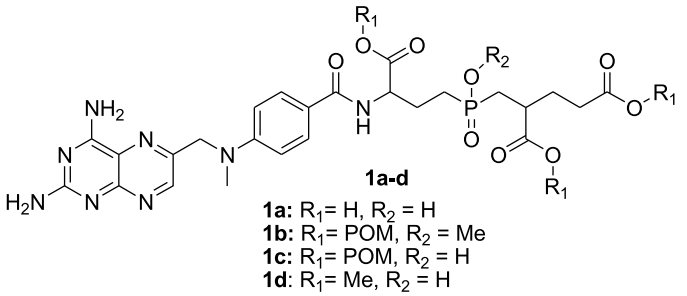
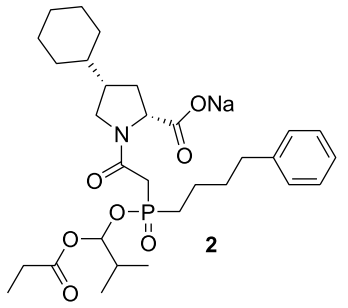
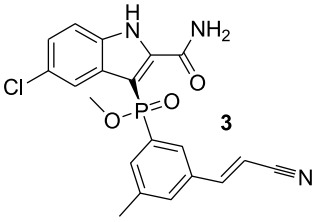


Folylpolyglutamate inhibitors: Anticancer prodrugs



Fosinopril: An ACE inhibitor prodrug



Fosdevirine: HIV disease drug

Figure 1. Structures of phosphinic acid prodrugs and drugs with promising clinical applicability.

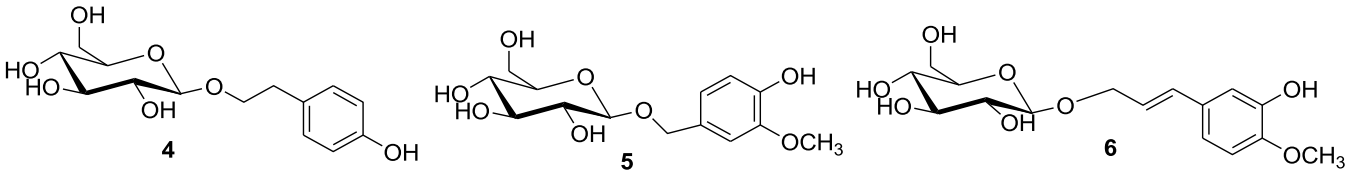
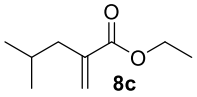


Figure 2. Structures of bioactive sugar derivatives: vanillyl β-D-glucose (**4**), salidroside (**5**), and isoconferin (**6**).

toluene and Et_2O were purchased from Aldrich, purged with argon, and passed through a solvent purification system (PureSolv, Innovative Technology-Amesbury, MA). Et_3N and iPr_2NEt were distilled from CaH_2. Organic layers were routinely dried with anhydrous $MgSO_4$ or Na_2SO_4 and concentrated using a Büchi rotary evaporator. Melting points were determined on an MPA100 OptiMelt (Stanford Research Systems, Sunnyvale) and are reported uncorrected (heating rate 5 °C/min).

^1H, ^{31}P, and ^{13}C NMR spectra were recorded on a Bruker Avance III 400. For mass spectrometry data acquisition, a micrOTOF-Q II electrospray time-of-flight (ESI-TOF) mass spectrometer (Bruker Daltonik GmbH, Bremen, Germany) was used; this was coupled to an Agilent 1260 LC system (Agilent Technologies, Waldbronn, Germany). Mass values are reported within the error limits of ±5 ppm mass units. Optical rotation was measured on AUTOPOL IV. Infrared spectra (IR) were measured using an Agilent Cary 660 FTIR spectrometer, and only the most representative frequencies (in cm^{-1}) are given.

2.2. Synthesis and Spectroscopic Characterization.



*2.2.1. Ethyl-2-isobutyl acrylate (**8c**).*[20] Under an Ar atmosphere (2 cycles of vacuum and Ar), a solution of *t*-BuOK (0.84 g, 7.5 mmol) in dry DMF (25 mL) was added, followed by triethyl phosphonoacetate **10** (1.12 g, 5 mmol) slowly, and the solution was kept on stirring for 10 min at 75 °C under Ar. Isobutyl bromide (0.81 mL, 7.5 mmol) was added slowly into the flask, and the reaction mixture was allowed to stir for 3 h at 75 °C under Ar. Then, K_2CO_3 (2.07 g, 15 mmol), dried by storage in a drying oven, and paraformaldehyde (0.45, 15 mmol) were added, and the mixture was maintained at reflux for 3 h. Upon completion, the reaction was quenched with 0.5 M HCl to pH ∼ 5, and the mixture was extracted twice with Et_2O. The organic phase was dried over $MgSO_4$, filtered, and then evaporated under reduced pressure. Flash column chromatography on silica gel (hexane/DCM, v/v, 2/1) provided **8c** as a colorless oil (67%). R_f = 0.32 (hexane/DCM, v/v, 2/1); IR (KBr) ν (cm^{-1}) 1635, 1725; ^1H NMR (400 MHz, $CDCl_3$) δ 0.89 (d, J = 7.20 Hz, 6H), 1.31 (t, J = 7.12 Hz, 3H), 1.80−1.70 (m, 1H), 2.18 (d, J = 7.99 Hz, 2H), 4.20 (q, J = 7.12 Hz, 2H), 5.49 (s, 1H), 6.17 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.20, 22.27, 27.20, 167.77, 41.04, 60.85, 125.38, 140.04. HRMS (ESI/QTOF) m/z: $[M + H]^+$ calcd for $C_9H_{16}O_2H$ 157.1229; found 157.1200.

*2.2.2. General Procedure for the Preparation of Synthons **9a−c**.*[4,20] A mixture of Cbz *N*-protected aminophosphinic acid **7** (319 mg, 1 mmol) and HMDS (1 mL, 5 mmol) was heated at 110 °C for 1 h under Ar. After cooling to 90 °C, the acrylate (1.3 mmol) was added dropwise over 30 min, and the reaction mixture was allowed to stir for an additional 3.5 h at 90 °C.

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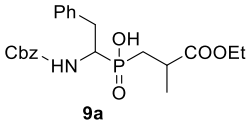
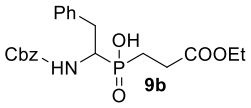
ACS Omega 2022, 7, 21444−21453

The resulting mixture was allowed to cool to 70 °C, and absolute EtOH (3 mL) was added dropwise. Stirring was continued for a further 15 min at this temperature. The solvent was removed, and the residue was purified by column chromatography ($CHCl_3$/MeOH/AcOH, v/v, 7/0.3/0.3).



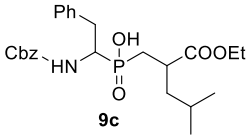
9a

*2.2.2.1. 2-Methyl-3-((1′-(N-benzyloxycarbonylamino)-2′-phenyl ethyl)-hydroxyphosphinyl)propanoic acid, ethyl ester (**9a**).*[20] White solid (76% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (t, J = 7.5 Hz, 6H), 1.69−1.89 (m, 1H), 2.22−2.37 (m, 1H), 2.81−2.96 (m, 2H), 3.29 (d, 1H), 4.14 (m, 3H), 4.98 (s, 2H), 7.08−7.30 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.97, 18.92, 29.44, 30.53, 33.91, 51.14, 61.07, 67.05, 126.77, 127.78, 128.01, 128.44, 129.20, 136.35, 136.62, 156.29, 175.66; ^{31}P NMR (162 MHz, $CDCl_3$) δ 53.08, 51.84, 51.48. HRMS (ESI/QTOF) m/z: $[M + H]^+$ calcd for $C_{22}H_{28}NO_6PH$ 434.1732; found 434.1701.



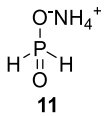
9b

*2.2.2.2. (R,S)-3-((1′-(N-Benzyloxycarbonylamino)-2′-phenyl ethyl)methyl oxy phosphinyl)propanoic acid, ethyl ester (**9b**).*[4] White solid (82% yield); IR (KBr) ν (cm^{-1}) 3640−3122 (br), 3018, 1725, 1669, 1549, 1489, 1456; ^{1}H NMR ($CDCl_3$) δ 1.19 (t, J = 7.4 Hz, 3H), 2.02−2.17 (m, 2H), 2.56−2.73 (m, 2H), 2.79−2.92 (m, 1H), 3.26−3.37 (m, 1H), 4.15 (q, J = 7.4 Hz, 2H), 4.24−4.37 (m, 1H), 4.87−5.07 (m, 2H), 5.35 (s, 1H), 7.02−7.40 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.30, 21.89, 26.44, 33.88, 50.58, 61.14, 67.06, 126.88, 127.79, 128.07, 128.56, 129.17, 136.17, 136.32, 136.44, 156.10, 172.32; ^{31}P NMR (162 MHz, $CDCl_3$) δ 52.14, 53.81. HRMS (ESI/QTOF) m/z: $[M + Na]^+$ calcd for $C_{21}H_{26}NO_6PNa$ 442.1395; found 442.1358.



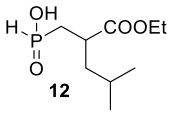
9c

*2.2.2.3. 2-Isobutyl-3-((1′-(N-benzyloxycarbonylamino)-2′-phenyl ethyl)-hydroxyphosphinyl)propanoic acid, ethyl ester (**9c**).*[20] White solid (71% yield); mp 144−145 °C (lit. 143−144), ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85−0.91 (m, 6H), 1.21−1.31 (m, 3H), 1.48−1.60 (m, 2H), 1.71−1.85 (m, 1H), 2.13−2.22 (m, 1H), 2.87 (s, 2H), 3.27 (d, J = 7.3 Hz, 1H), 4.06−4.21 (m, 2H), 4.95−5.03 (q, J = 7.3 Hz, 2H), 5.50 (s, 1H), 7.02−7.58 (m, 11H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.13, 21.96, 22.69, 25.78, 34.02, 37.33, 43.34, 51.31, 60.90, 66.91, 126.75, 127.72, 128.01, 128.50, 129.20, 136.38, 136.64, 156.32, 175.14; ^{31}P NMR (162 MHz, $CDCl_3$) δ 53.29, 52.77. HRMS (ESI/QTOF) m/z: $[M + H]^+$ calcd for $C_{25}H_{34}NO_6PH$ 476.5268; found 476.5265.



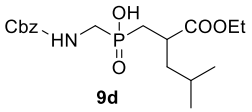
11

*2.2.3. Ammonium phosphinate (**11**).*[22] A total of 15.8 mL of 50% H_3PO_2 (d = 1.27 g/cm^3, 158 mmol) was mixed slowly to 13 mL of 26% NH_3(aq.) (d = 0.90 g/cm^3, 172 mmol) at 0 °C. The mixture was evaporated to give a white powder. It was dissolved in 15 mL of hot MeOH, and the solution was cooled before 30 mL of Et_2O was added while stirring. White crystalline precipitation was obtained after 5 h followed by filtering and washing with Et_2O and finally dried in a vacuum to give **11** (10.0 g, 77%). Mp 158−161 °C; IR (KBr) ν (cm^{-1}) 3489, 3228, 1169.



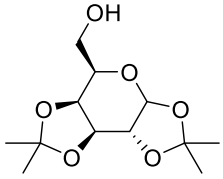
12

*2.2.4. 2-Hydroxyphosphinoylmethyl-4-methyl-pentanoic acid, ethyl ester (**12**).*[20,23] A mixture of dry ammonium phosphinate **11** (6.64 g, 0.08 mol) and HMDS (25.2 mL, 0.12 mol) was allowed to stir under Ar at 110 °C for 3 h. The reaction mixture was cooled to 0 °C, and **8c** (3.12 g, 0.02 mol) was added dropwise at that temperature. The mixture was allowed to stir at RT for 3 h. EtOH (30 mL) was carefully added dropwise upon cooling and vigorous stirring, and the formed mass was evaporated in a vacuum. The residue was dissolved in $CHCl_3$ and washed with 3 M HCl. The organic phase was dried over $MgSO_4$ and evaporated under reduced pressure to give **12** as a viscous colorless oil (3.64 g, 82%), R_f ($CHCl_3$/MeOH/AcOH, v/v, 7/2/1) = 0.67. The obtained spectral data were found identical to the literature data.[32]



9d

*2.2.5. P-(Benzyloxycarbonylaminomethyl)-P-(ethyl 2-isobutyl propionate-3-yl)phosphinic acid (**9d**).*[20,23] Phosphinic acid **12** (2.2 g, 10 mmol) was dissolved in 12 mL (AcCl/AcOH, v/v, 5/1), and Cbz-NH_2 (1.5 g, 10 mmol) was added. Paraformaldehyde (0.33 g, 11 mmol) was added at 0 °C, and the reaction mixture was allowed to stir at RT for 6 h. Evaporation of the solvents and purification by column chromatography, using ($CHCl_3$/*i*-PrOH/AcOH, v/v, 20/4/1) as the eluent system, afforded the pure product **9d** as a white solid (R_f = 0.30), after trituration with PE (40−60 °C); ^{1}H NMR (400 MHz, $CDCl_3$ + a drop of CF_3COOH) δ 0.90 (m, 6H), 1.25 (t, J = 7.2 Hz, 3H), 1.52−1.66 (m, 2H), 1.75−1.89 (m, 1H), 2.10−2.29 (m, 1H), 2.86 (m, 2H), 3.72 (d, J = 7.2 Hz, 2H), 5.13 (s, 2H), 5.76 (s, 1H) 7.23−7.44 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.39, 22.01, 22.77, 25.51, 29.09, 37.23, 43.15, 60.85, 67.41, 128.08, 128.17, 128.51, 136.36, 156.60, 175.37; ^{31}P NMR (162 MHz, $CDCl_3$) δ 49.81. HRMS (ESI/QTOF) m/z: $[M + H]^+$ calcd for $C_{18}H_{28}NO_6PH$ 386.1732; found 386.1699.



14

*2.2.6. 1,2:3,4-Di-O-isopropylidene-D-galactopyranose (**14**).*[24] In a round-bottomed flask containing a solution of D-galactose **13** (0.9 g, 0.5 mmol), acetone (20 mL), and anhydrous $ZnCl_2$ (1.7 g, 12.5 mmol) was added dropwise concentrated H_2SO_4 (0.1 mL) at room temperature. The mixture was allowed to stir at RT overnight and then neutralized with sat. aq. $NaHCO_3$. The resulting suspension

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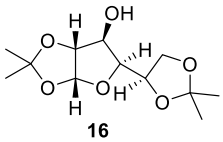
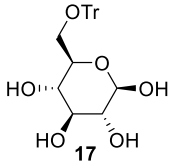
ACS Omega 2022, 7, 21444−21453

was filtrated through a pad of Celite; then, the Celite pad was washed with acetone. The filtrate was concentrated under a vacuum on a rotary evaporator to remove excess acetone and extracted AcOEt. The resulting oily residue was purified by silica gel flash column chromatography (hexane/AcOEt, v/v, 3/1) to afford the desired 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose **14** (0.97 g, 75%) as a colorless oil; R_f = 0.39 (hexane/AcOEt, v/v, 1/1); $[\alpha]_D^{24}$ = −0.55 (*c* = 1.0, acetone). IR (KBr) ν (cm^{-1}) 3710−3140, 1465, 1393; ^{1}H NMR (400 MHz, CD_3OD) δ 1.36 (s, 6H), 1.48 (s, 3H), 1.56 (s, 3H), 3.72−3.82 (m, 1H), 3.86−3.94 (m, 2H), 4.29 (dd, *J* = 7.9 Hz, *J* = 1.6 Hz, 1H), 4.36 (dd, *J* = 5.1 Hz, *J* = 2.4 Hz, 1H), 4.65 (dd, *J* = 7.4 Hz, *J* = 2.5 Hz, 1H), 5.59 (d, *J* = 5.2 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 24.31, 24.99, 25.93, 26.03, 62.37, 68.09, 70.59, 70.77, 71.63, 96.46, 108.69, 109.49.



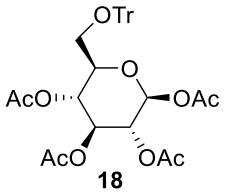
16

*2.2.7. 1,2:5,6-Di-O-isopropylidene-α-D-glucofuranose (**16**).*[25] To a mixture of D-glucose **15** (1.0 g, 5.56 mmol) in dry acetone (50 mL) was added $FeCl_3$ (540 mg). The reaction mixture was allowed to stir at RT for 30 h and quenched by addition of 10% K_2CO_3 solution (20 mL). After evaporation of the solvent, the solution was extracted with DCM and the organic phase was washed with H_2O and dried with anhydrous Na_2SO_4. Recrystallization from PE (40−60 °C)/AcOEt gave the product **16** as white crystals (0.84 g, 58%). Mp 110−112 °C; R_f = 0.28 (hexane/AcOEt, v/v, 2/1); $[\alpha]_D^{24}$ = −0.12 (*c* = 1.0, acetone). IR (KBr) ν (cm^{-1}) 3411, 2969, 2955, 2932, 2864, 1452, 1370, 1314, ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33 (s, 3H), 1.37 (s, 3H), 1.45 (s, 3H), 1.51 (s, 3H), 2.86 (d, *J* = 3.6 Hz, 1H), 4.00 (dd, *J* = 8.8 Hz, *J* = 5.5 Hz, 1H), 4.08 (dd, *J* =7.4 Hz, *J* = 2.6 Hz, 1H), 4.18 (t, *J* = 8.7 Hz, 1H), 4.33 (dd, *J* = 12.2 Hz, *J* = 5.8 Hz, 2H), 4.54 (d, *J* = 3.2 Hz, 1H), 5.94 (d, *J* = 3.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.14, 26.16, 26.76, 26.83, 67.62, 73.32, 75.05, 81.14, 85.08, 105.24, 109.63, 111.81.



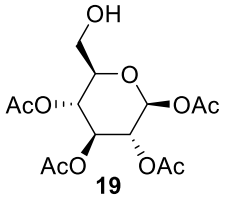
17

*2.2.8. 6-O-Trityl-D-glucopyranose (**17**).*[26] To a solution of D-glucose **15** (1 g, 5.55 mmol) in anhydrous pyridine (120 mL) was added TrCl (1.7 g, 6.1 mmol). The reaction mixture was then heated at 80 °C for 18 h and then allowed to cool to ambient temperature. Pyridine was removed under reduced pressure to afford a yellow gum. This residue was extracted with DCM, and the collected organic layer was concentrated under reduced pressure to give the crude 6-*O*-trityl-D-glucose. Purification by flash chromatography (DCM/EtOH, v/v, 95/0.5) afforded the pure compound **17** as a white foam (1.8 g, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.25−3.38 (m, 4H), 3.59 (t, *J* = 9.2 Hz, 1H), 3.94 (m, 1H), 5.13 (d, *J* = 3.7 Hz, 2H), 7.11−7.30 (m, 9H), 7.42 (d, *J* = 9.4 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 63.73, 69.35, 69.09, 70.04, 72.20, 73.97, 86.45, 92.3, 93.15, 98.16, 127.32, 127.44, 128.78, 144.28.



18

*2.2.9. 1,2,3,4-Tetra-O-acetyl-6-O-trityl-β-D-glucopyranose (**18**).*[27] The title compound was prepared from 6-*O*-trityl-D-glucopyranose **17** according to a general procedure.[27] The air-dried product was then introduced into Et_2O, and the less soluble β-isomer was isolated and recrystallized from hot EtOH. Upon cooling, white crystals of **18** were liberated. R_f = 0.74 (AcOEt/hexane, v/v, 1/1); mp 164−165 °C; $[\alpha]_D^{24}$ = 45 (*c* = 1.0, pyridine). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.14−1.73 (4s, 12H), 2.83 (dd, *J* = 10.3, 4.2 Hz, 1H), 3.16 (d, *J* = 10.3 Hz, 1H), 4.14 (m, 1H), 5.02 (t, *J* = 9.1 Hz, 1H), 5.18 (t, *J* = 10.2 Hz, 1H), 5.37 (t, *J* = 10.2 Hz, 1H), 5.97 (d, *J* = 8.1 Hz, 1H), 7.38−7.25 (m, 15H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 20.66, 20.78, 21.02, 61.62, 68.19, 70.63, 72.63, 73.10, 86.28, 91.62, 127.55, 128.37, 128.66, 143.79, 169.08, 169.29, 169.62, 170.02.



19

*2.2.10. 1,2,3,4-Tetra-O-acetyl-β-D-glucopyranose (**19**).*[28,29] The tritylated compound **18** (5 g, 8.0 mmol) was dissolved in AcOH (2.17 mL, 0.38 mmol) and heated at 90 °C in an oil bath under constant stirring for 30 min. When the solid fully dissolved, the solution was cooled to 10 °C before carefully adding 48% aq. HBr (1.95 mL, 80.0 mmol) in a dropwise manner for 10 min. The liberated trityl bromide was removed by filtration, and the filtrate was poured into ice H_2O to give a precipitate of a white solid. The produced glucose tetraacetate was extracted with DCM, and the collected organic layer was washed with H_2O to remove residual AcOH, dried over $MgSO_4$, and concentrated under a vacuum. Anhydrous Et_2O was introduced onto the viscous solution and agitated with a glass rod to effect crystallization. The solid obtained was filtered to afford β-D-glucose-1,2,3,4-tetraacetate **19** (1.11 g, 40%) as a white solid, R_f = 0.22 (AcOEt/hexane, v/v, 1/1); mp 131−132 °C; $[\alpha]_D^{24}$ = 11.63 (*c* = 1.0, $CHCl_3$). IR (KBr) ν (cm^{-1}) 3545, 2958, 1759; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.94 (s, 3H), 1.99 (s, 3H), 2.01 (s, 3H), 2.07 (s, 3H), 3.48−3.37 (m, 2H), 3.90 (m, 1H), 4.93 (m, 2H), 5.39 (t, *J* = 9.6 Hz, 1H), 5.91 (d, *J* = 8.3 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 20.73, 20.76; 20.91, 20.94, 59.99, 68.44, 70.63, 72.72, 74.84, 91.40, 169.25, 169.58, 169.65, 170.04.

*2.2.11. General Procedure for the Preparation of Compounds **21a−f**.* Freshly distilled thionyl chloride (0.3 mmol) was added dropwise to the stirred solution of phosphinic acid **9a−d** (0.12 mmol) in Et_2O (0.5 mL) followed by one drop of DMF under an argon atmosphere at 0 °C using a NaCl ice bath. The mixture was allowed to stir at RT for 2−3 h. The reaction progress was monitored by ^{31}P NMR. After completing the reaction, the turbid mixture was concentrated to give the acid chloride a yellow solid. This material (0.1 mmol) was used without further purification and dissolved in 0.3 mL of toluene, and the resulting solution was added

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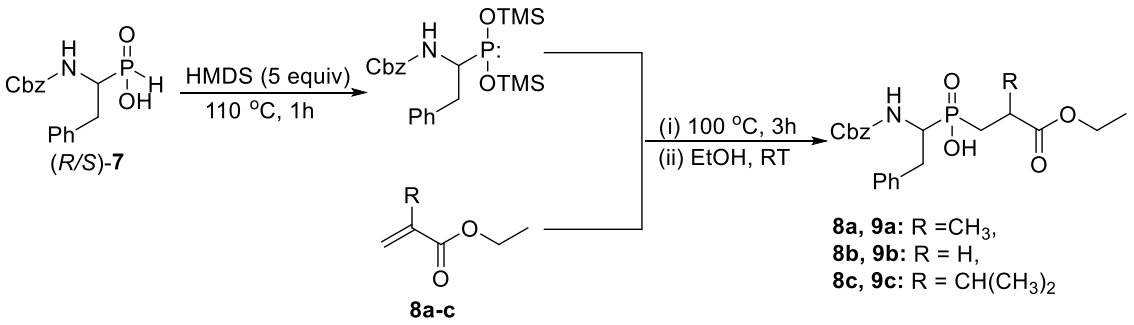
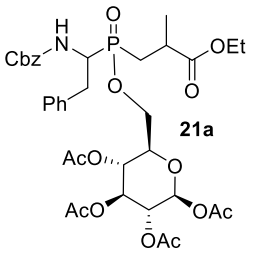
ACS Omega 2022, 7, 21444−21453

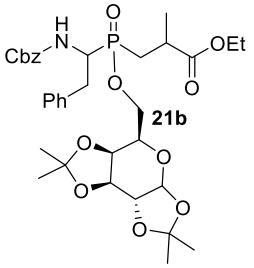
Scheme 1. General Scheme for the Syntheses of the Phosphinic Dipeptide Derivatives 9a−c



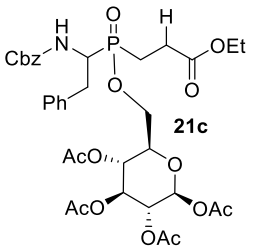
dropwise to the mixture of sugar **14**, **16**, and **19** (0.12 mmol) and TEA (0.2 mmol) in 0.3 mL of toluene at 0 °C. The reaction mixture was heated to 80 °C for 10−14 h (monitored with ^{31}P NMR), and then, the triethylammonium chloride was removed by filtration. The filtrate was condensed to dryness under reduced pressure. The residue was diluted with AcOEt and washed successively with a saturated solution of Na_2CO_3 and brine. The organic phase was dried over Na_2SO_4 and filtered. The filtrate was dried under a vacuum to dryness. The residue was treated with Et_2O/hexane (1/1) at 0 °C for 24 h to give the white crystalline precipitate of the corresponding phosphinates **21a−f**.



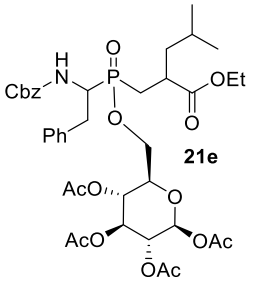
*2.2.11.1. (2S,3R,4S,5R,6R)-6-((((1-(((Benzyloxy)carbonyl)-amino)-2-phenyl ethyl)(3-ethoxy-2-methyl-3-oxopropyl)-phosphoryl)oxy)methyl)tetrahydro-2H-pyran-2,3,4,5-tetrayl tetraacetate (**21a**).* White solid (78%); ^{13}C NMR (100 MHz, DMSO-d_6) δ 12.88, 19.62, 20.71, 20.78, 20.85, 20.92, 30.11, 30.55, 33.80, 52.23, 61.62, 61.32, 67.88, 66.15, 71.13, 71.93, 75.04, 91.88, 126.65, 127.65, 128.53, 128.43, 129.50, 135.20, 135.54, 157.19, 169.21, 169.55, 169.69, 170.02, 175.21; ^{31}P NMR (162 MHz, DMSO-d_6) δ 56.21, 57.91. HRMS (ESI/QTOF) m/z: $[M + H]^+$ calcd for $C_{36}H_{46}NO_{15}P$ 763.2605; found 763.2609.



*2.2.11.2. Ethyl-3-((1-(((benzyloxy)carbonyl)amino)-2-phenyl ethyl)(((5R,5aS, 8aS,8bR)-2,2,7,7-tetramethyltetrahydro-5H-bis([1,3]dioxolo)[4,5-b:4′,5′-d]pyran-5-yl)methoxy)-phosphoryl)-2-methylpropanoate (**21b**).* White solid (69%); ^{13}C NMR (100 MHz, DMSO-d_6) δ 14.03, 18.42, 24.62, 25.01, 25.99, 26.21, 28.94, 30.61, 33.51, 52.19, 61.35, 62.55, 67.11, 68.23, 70.41, 70.89, 71.54, 97.11, 108.46, 109.52, 127.01, 127.88, 128.31, 128.21, 129.34, 136.12, 136.75, 157.11, 175.03; ^{31}P NMR (162 MHz, DMSO-d_6) δ 55.10, 56.51. HRMS (ESI/QTOF) m/z: $[M + H]^+$ calcd for $C_{34}H_{46}NO_{11}P$ 675.2808; found 675.2817.



*2.2.11.3. (2S,3R,4S,5R,6R)-6-((((1-(((Benzyloxy)carbonyl)-amino)-2-phenyl ethyl)(3-ethoxy-3-oxopropyl)phosphoryl)-oxy)methyl)tetrahydro-2H-pyran-2,3,4,5-tetrayl tetracetate (**21c**).* White solid (81%); ^{13}C NMR (100 MHz, DMSO-d_6) δ 13.99, 21.13, 21.80, 21.90, 21.99, 22.04, 60.03, 26.11, 33.38, 50.32, 62.10, 67.21, 68.32, 71.03, 72.10, 74.18, 91.43, 127.12, 127.84, 128.43, 128.89, 129.23, 137.23, 135.88, 136.13, 156.23, 169.41, 169.66, 169.72, 170.13, 173.41; ^{31}P NMR (162 MHz, DMSO-d_6) δ 56.66, 58.01. HRMS (ESI/QTOF) m/z: $[M + H]^+$ calcd for $C_{35}H_{44}NO_{15}P$ 749.2449; found 749.2443.



*2.2.11.4. (2S,3R,4S,5R,6R)-6-((((1-(((Benzyloxy)carbonyl)-amino)-2-phenyl ethyl)(2-(ethoxycarbonyl)-4-methylpentyl)phosphoryl)oxy)methyl)tetrahydro-2H-pyran-2,3,4,5-tetrayl tetraacetate (**21e**).* White solid (55%); ^{13}C NMR (100 MHz, DMSO-d_6) δ 13.45, 20.63, 20.77, 20.82, 20.99, 21.34, 22.51, 25.66, 33.97, 37.2′, 43.31, 52.01, 58.97, 61.02, 67.11, 68.49, 72.57, 72.11, 75.14, 92.58, 127.65, 127.77, 128.26, 128.45, 129.35, 136.27, 136.71, 157.32, 169.13, 169.34, 169.56, 171.21, 174.82; ^{31}P NMR (162 MHz, DMSO-d_6) δ 57.31, 58.12. HRMS (ESI/QTOF) m/z: $[M + H]^+$ calcd for $C_{39}H_{52}NO_{15}P$ 805.3075; found 805.3069.

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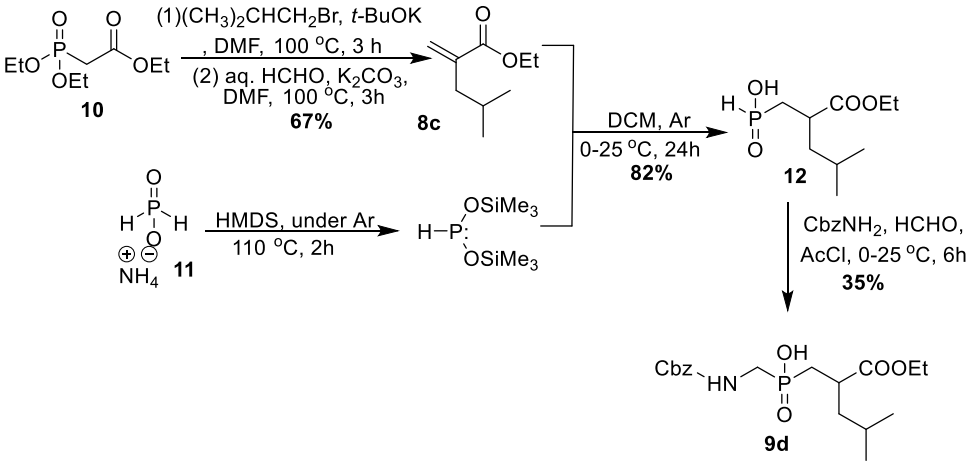
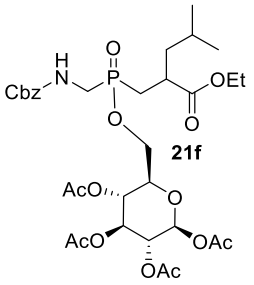
ACS Omega 2022, 7, 21444−21453

Scheme 2. Synthesis of Pseudo-Peptide 9d





*2.2.11.5. (2S,3R,4S,5R,6R)-6-((((1-(((Benzyloxy)carbonyl)-amino)methyl)(2-(ethoxycarbonyl)-4-methylpentyl)-phosphoryl)oxy)methyl)tetrahydro-2H-pyran-2,3,4,5-tetrayl tetraacetate (**21f**).* White solid (48%); ^{13}C NMR (100 MHz, DMSO-d_6) δ 14.39, 20.73, 20.76, 20.91, 20.94, 22.01, 22.77, 25.51, 29.09, 37.23, 43.15, 59.99, 60.85, 67.41, 68.44, 70.63, 72.72, 74.84, 91.40, 128.08, 128.17, 128.51, 136.36, 156.60, 169.25, 169.58, 169.65, 170.04, 175.37; ^{31}P NMR (162 MHz, DMSO-d_6) δ 57.10, 57.88. HRMS (ESI/QTOF) *m/z*: [M + H]$^+$ calcd for $C_{32}H_{46}NO_{15}P$ 715.2605; found 715.2612.

3. RESULTS AND DISCUSSIONS

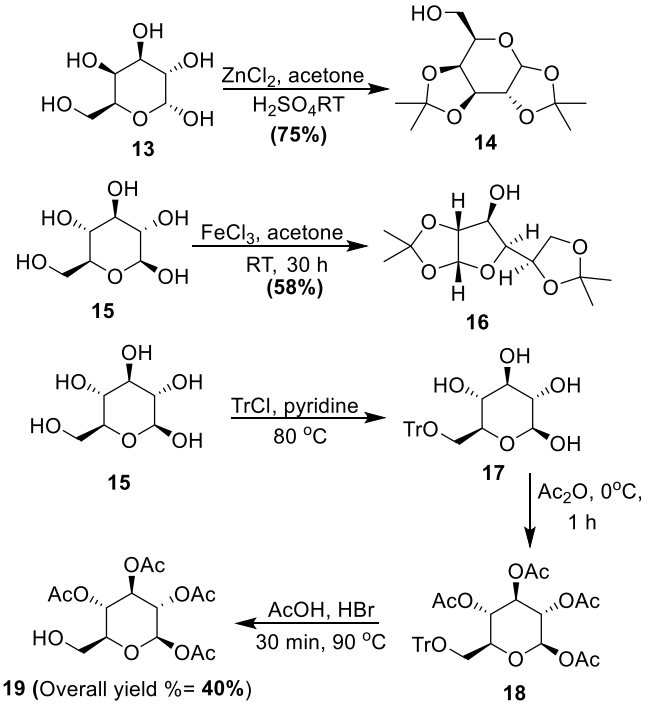
3.1. Preparation of Diversely Substituted Pseudo-Dipeptidic Synthons 9a−d. The primary step for the preparation of the phosphinate dipeptide building blocks **9a−d** is forming the P−C bond. Activating the P-moiety to its trivalent form is required and subsequent attack to acrylic acid esters (Scheme 1) or an imine (Scheme 2). In the first case, phosphinic pseudo-amino acids **9a−c** can be formed using a procedure involving the phospha-Michael addition of the protected aminomethyl phosphinic acid **7** to various acrylic acid esters **8a−c** using hexamethyldisilazane (HMDS) as the silylating agent (Scheme 1).[4,21,30] This reaction proceeds under mild conditions and is fully compatible with the protecting groups used, generating phosphinic dipeptide analogues **9a−c**.

Alternatively, the pseudo-peptide **9d** was synthesized through a three-component amidoalkylation reaction of benzyl carbamate, formaldehyde, and the LeuPO_2H_2 analogue **12** in acetyl chloride (Scheme 2).[20] The synthesis of the phosphinic analogue of leucine **12** can be achieved via the Michael addition of bis(trimethylsilyl)hypophosphite (generated in situ from the ammonium hypophosphite salt **11**) to ethyl 2-isobutyl acrylate **8d**,[21] which was synthesized by the alkylation of triethyl phosphonoacetate **10** followed by a Horner−Wadssworth−Emmons (HWE) condensation with formaldehyde (Scheme 2).[31] Using this modified procedure for the synthesis and isolation of the Leu-aminophosphinic analogue avoids a very cumbersome and low-yielding previously reported procedure.[32−34]

3.2. Synthesis of Sugar-Protected Derivatives. Another absolute requirement for accomplishing the synthesis of sugar phosphinates is the preparation of suitably protected sugar molecules. Various glycosyl donors such as **14**, **16**, and **19** derived from pyranoses and furanoses were prepared in good yields to achieve this. Starting from the readily available commercial sugars galactose and glucose, and in accordance with previously reported procedures in the literature, the protected derivatives were synthesized (Scheme 3).[35−39]

3.3. Study of the Esterification of 9a−d with Suitable Sugar Derivatives under Basic Conditions. The inves-

Scheme 3. Syntheses of Sugar-Protected Derivatives 14, 16, and 19



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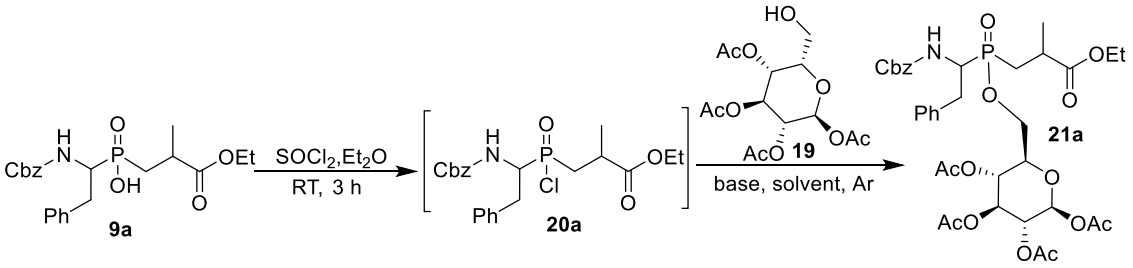
ACS Omega 2022, 7, 21444−21453

Table 1. Optimization of Reaction Conditions[a]



entry	solvent	base	yield[b]
1	acetonitrile	TEA	37%
2	DCM	TEA	38%
3	THF	TEA	43%
4	DMF	TEA	28%
5	DMSO	TEA	30%
6	toluene	TEA	78%
7	toluene	DBU	35%
8	toluene	Hünig's base	45%
9	toluene	DIEA	65%
10	toluene	NaOH	Nr[c,d]
11	toluene	*t*-BuOK	Nr[d]
12	toluene	TEA	73%[e]
13	toluene	TEA	40%[f]
14	toluene	TEA/4 Å MS	79%
15	toluene	TEA	Nr[d,g]
16	toluene	TEA	65%[c]

[a]Reaction was carried out using **20a** (0.05 mmol), base (0.1 mmol), and **19** (0.06 mmol) in a dry solvent (0.25 mL) under an Ar atmosphere at 80 °C for 12 h. [b]NMR conversion yields are determined by integrating all of the resonances in the crude ^{31}P NMR spectra. [c]110 °C. [d]No reaction. [e]TEA (0.2 mmol). [f]TEA (0.05 mmol). [g]40 °C.

tigation was commenced using the in situ-generated phosphinic acid chloride of Cbz-Phe-(P)-Gly-OEt **9a** and **19** as templates for this study employing triethylamine (2 equiv) as the base in dry toluene under an Ar atmosphere. Gratifyingly, the ester product **21a** was obtained with a 78% yield within 12 h under dry conditions (Table 1, entry 6). Inspired by the initial result and to corroborate this scenario, the reaction was performed under different conditions, varying solvents, bases, base/catalyst loadings, and temperatures to test the feasibility of this method, and the selected data are summarized in Table 1. The progress of the reaction was optimized and monitored using ^{31}P NMR.

At the outset, the effect of various solvents such as acetonitrile, DCM, THF, toluene, DMSO, and DMF was probed (Table 1, entries 1−6). The highest yield of the desired product was obtained in toluene (Table 1, entry 6), while the other solvents could not achieve comparable results as toluene (Table 1, entries 1−5 vs 6). Subsequently, numerous bases were evaluated, such as TEA, DBU, Hünig's base, and DIEA (Table 1, entries 6−9). Among the organic bases screened, TEA displayed an outstanding performance in delivering the desired product (Table 1, entry 6). DIEA (entry 9) appears to be a less active promoter of the reaction than TEA (entry 6).

Furthermore, other organic bases were not as effective for the reaction (Table 1, entries 7 and 8). Although not shown in Table 1, the reaction was carried out with different alkali metal carbonates (Li_2CO_3, Na_2CO_3, K_2CO_3, Cs_2CO_3), and cesium carbonate, which gave poor conversions with several by-products formed. Also, it was noticed that the reaction using NaOH and *t*-BuOK failed to provide the desired product as the hydrolysis cleavage of the ester is expected (Table 1, entries 10 and 11).[4] Thus, it appears that the stability of **21a** of the ester is greatly influenced by the nature of the base, suggesting that a requirement for success with this latter procedure is that the appropriate mild bases must not react destructively with the acid chloride and the expected formed ester. This high selectivity may be attributed to the unprecedented "triethylamine effect" of facilitating numerous esterifications efficiently.[5] Its popularity stems from availability and low cost, alongside a mid-range boiling point (88.8 °C), making it easier to remove through rotary evaporation. Also, the triethylammonium chloride is somewhat insoluble in organic solvents and can be removed by simple filtration. All of these factors made it the best choice as a promoter of this reaction.

Regarding the appropriate TEA loading, it was found that 2 equiv was the best option, affording the desired product in 78% yield (entry 6). However, a lower product yield was obtained by decreasing its loading (1 equiv) (Table 1, entry 13), but the reaction was not further improved by increasing the amount of TEA (4 equiv) (entries 12 vs 6). Additionally, TEA in the presence of activated molecular sieves was also found to be suitable. However, no significant increase in product yield was noticed (entry 14). Hence, it is noteworthy that great care should be taken when using acid chlorides because of their extreme sensitivity toward hydrolysis.

The influence of temperature on the reaction outcomes was evaluated. It is clear that temperature also played an essential role in this reaction; the reaction did not work well at 40 °C (entry 15). When the reaction was performed with mild heating to 80 °C, the yield of the desired product was improved to 78% yield (Table 1, entry 6), but lower yields were observed when the temperature was increased to 110 °C

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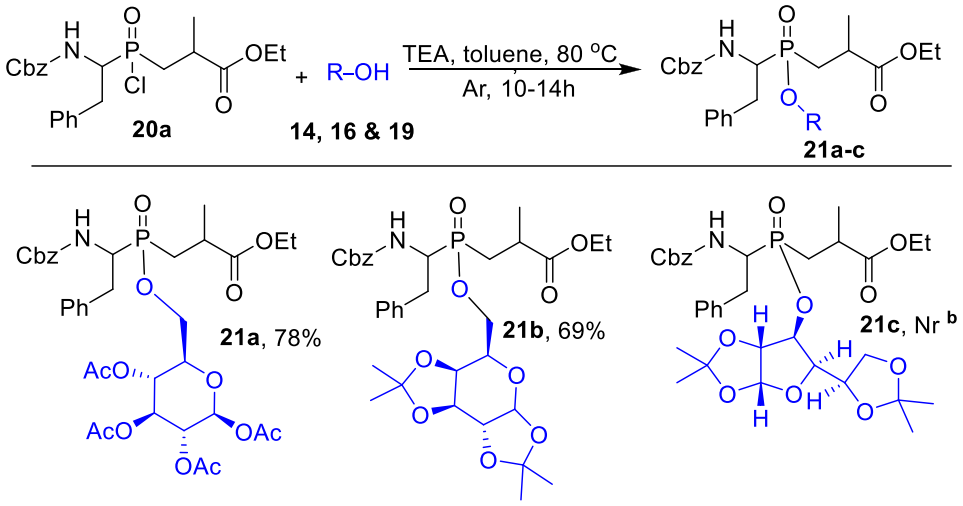
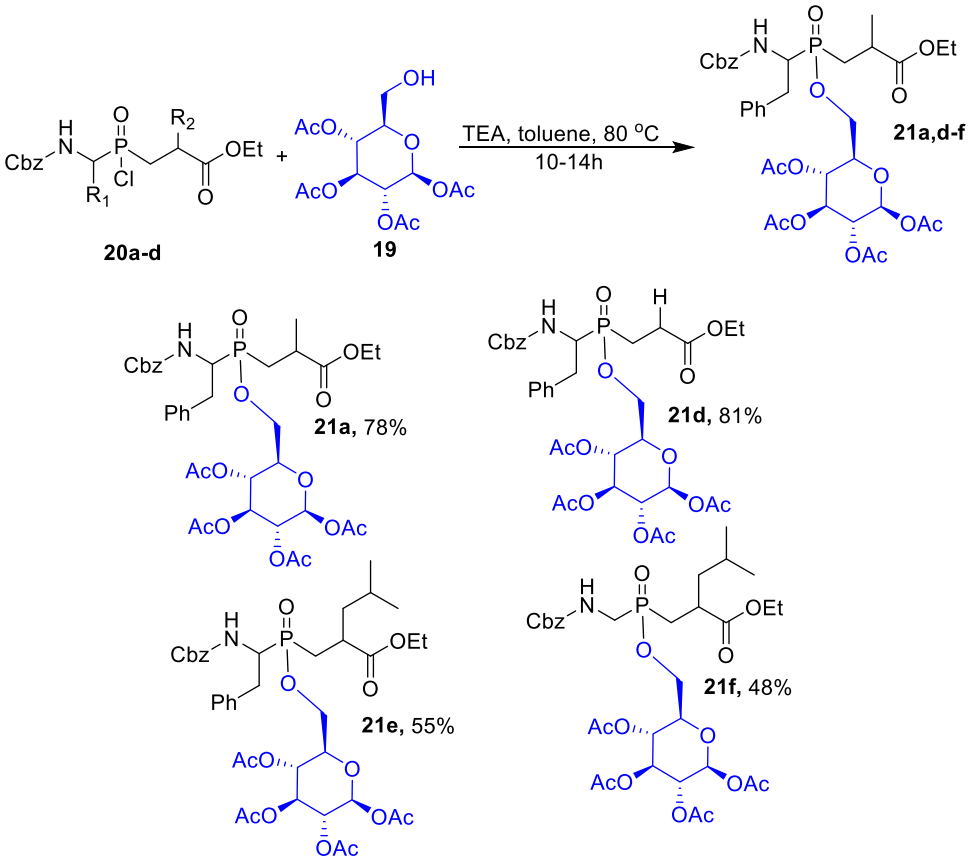
ACS Omega 2022, 7, 21444−21453

Scheme 4. Substrate Scope of Sugar Derivatives[a]



[a]The reaction was carried out using **20a** (0.1 mmol), TEA (0.2 mmol), and **14**, **16**, and **19** (0.12 mmol) in dry toluene (0.5 mL) at 80 °C for 12 h under an Ar atmosphere. [b]No reaction.

Scheme 5. Substrate Scope of Phosphinic Acids[a]



[a]The reaction was carried out using **20a−d** (0.1 mmol), TEA (0.2 mmol), and **19** (0.12 mmol) in dry toluene (0.5 mL) at 80 °C for 10−14 h under an Ar atmosphere.

(Table 1, entry 16). This may be due to the highly volatile nature of TEA (88.8 °C). Based on these results, the optimal condition for this multicomponent reaction was therefore established as follows: **9a** (0.05 mmol), TEA (0.1 mmol), and 19 (0.06 mmol) in dry toluene (0.25 mL) at 80 °C for 12 h under an Ar atmosphere (Table 1, entry 6).

With the optimal conditions in hand, the method's applicability was subsequently assessed with a set of both primary and secondary hydroxyl groups in either the pyranose or furanose ring configurations, including isopropylidene ketals (**14** and **16**) and acetate esters **19**. The examples in Scheme 4 reveal that the reaction is very smooth using the protecting

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ACS Omega 2022, 7, 21444−21453

groups of primary hydroxyl groups as substrates **14** and **19**. It was also observed that steric hindrance with isopropylidene ketal had a significant effect on the reaction course, as **21b** was obtained in 69% yield. Notably, the secondary hydroxyl substrate **16**, as expected, was resistant to esterification employing this procedure.

To widen the scope of this novel methodology, the studies were extended to optimize its robustness and generality to a panel of phosphinic acids bearing various substituents **20a−d**, which worked well and converted to the desired products in moderate to good yields of 48−81%, as summarized in Scheme 5. Initially, the influence of the substituents attached to the α-position of the phosphinic acids was evaluated. In terms of electronic effects, phosphinic acid with the benzyl group furnished the products **21a**, **d**, and **e** in higher chemical yields than the unsubstituted phosphinic acid (**21f**). Furthermore, the extension of the substituted alkyl chain on phosphinic acids **21a**, **d**, and **e** proved fruitful.

The significant benefits of this method are the operational simplicity and product isolation. The triethylamine hydrochloride byproduct is isolated from the reaction mixture simply by filtration followed by solvent concentration and extraction to remove unreacted starting materials, and thus, the process required no chromatographic purification step. With the successful synthesis of a library of novel phosphinic esters, the next objective is to use this method to synthesize a complex phosphinate prodrug analogue of biological importance.

4. CONCLUSIONS

We have revealed a powerful esterification protocol for the precise construction of P−OR bonds in the presence of TEA as a catalyst. The reaction proceeded under transition-metal-free conditions and tolerated different substituents attached to the phosphinic acids and sugar moieties. In addition to the novelty of the method (offering the first TEA-catalyzed esterification of phosphinic acids), it is general, selective, and operationally simple. We expect that this esterification strategy will enable the development of libraries of these pseudopeptides without restrictions on peptide size or the presence of functional groups at the side chains. Implementation of this attractive methodology to prepare biologically relevant phosphinate analogues is underway in our laboratory and will be reported in a separate publication.

AUTHOR INFORMATION

Corresponding Authors

Moaz M. Abdou − *Egyptian Petroleum Research Institute, Cairo 11727, Egypt*; orcid.org/0000-0003-0253-5714; Email: moaz.chem@gmail.com

Magdalini Matziari − *Department of Chemistry, Xi'an Jiaotong Liverpool University, Suzhou, Jiangsu 215123, P. R. China*; Email: Magdalini.Matziari@xjtlu.edu.cn

Authors

Paul M. O'Neill − *Department of Chemistry, University of Liverpool, Liverpool L69 7ZD, U.K.*

Eric Amigues − *Department of Chemistry, Xi'an Jiaotong Liverpool University, Suzhou, Jiangsu 215123, P. R. China*

Complete contact information is available at: https://pubs.acs.org/10.1021/acsomega.2c00712

Notes

The authors declare no competing financial interest.

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