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Synthesis and Rearrangement of 3′-α-Diethylphosphono-3′-β-*O*-methanesulfonyluridines

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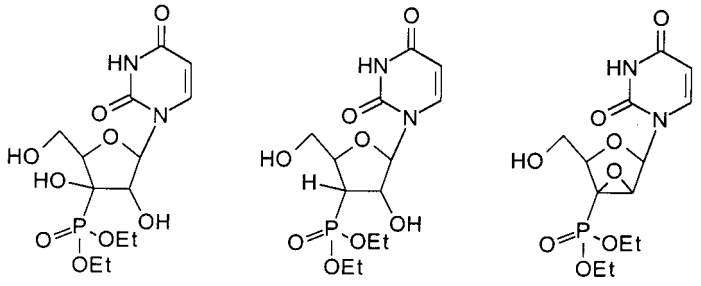
Abstract—Preparation of a uridine derivative bearing both diethylphosphono and methanesulfonate substituents at the 3′-position has been accomplished by reaction of the corresponding α-hydroxy phosphonate with methanesulfinyl chloride and subsequent oxidation. While this methanesulfonate did not undergo elimination under standard reaction conditions, treatment with TBAF results in a novel rearrangement leading to the corresponding 2′-phosphate.

In recent years, a number of nucleoside analogues have been found to display significant anti-viral activity and several have become medically useful.[1] Even though these drugs have shown significant clinical value, first when used alone and now as used in combination therapies, their use can be haunted by undesired side effects and complex dosing schemes that risk non-compliance.[2] To aid the search for new biologically active compounds with reduced toxicity and simpler dosing schemes, we have reported methods for preparation of several types of modified nucleosides, including geminal hydroxy phosphonates (such as the uridine derivative **1**)[3] and their deoxygenated (**2**)[4] and epoxide (**3**)[5] derivatives (Scheme 1). In this report, we describe first the synthesis of a nucleoside bearing both diethylphosphono and methanesulfonate substituents at the 3′-position, a highly functionalized compound that might serve as an intermediate for preparation of other modified nucleosides, as well as a new phosphonate–phosphate rearrangement found in this system.

Efforts to prepare the desired methanesulfonate **6** (Scheme 2) through direct reaction of the α-hydroxy phosphonate **4** with methanesulfonyl chloride in the presence of triethylamine or 4-dimethylaminopyridine (DMAP), or after treatment with potassium hydride and 18-crown-6, went unrewarded. This was not entirely surprising, given that our earlier efforts to conduct a Barton deoxygenation on this substrate had suggested that this hydroxyl group is sterically hindered.[4] Fortunately a method for preparation of the methanesulfonate of tertiary α-hydroxy phosphonates through reaction with methanesulfinyl chloride and subsequent oxidation has been reported by Creary et al.[6] based on their adaptation of an earlier tosylation procedure developed by Coates and Chen.[7] Following Creary's procedure,



Scheme 1.

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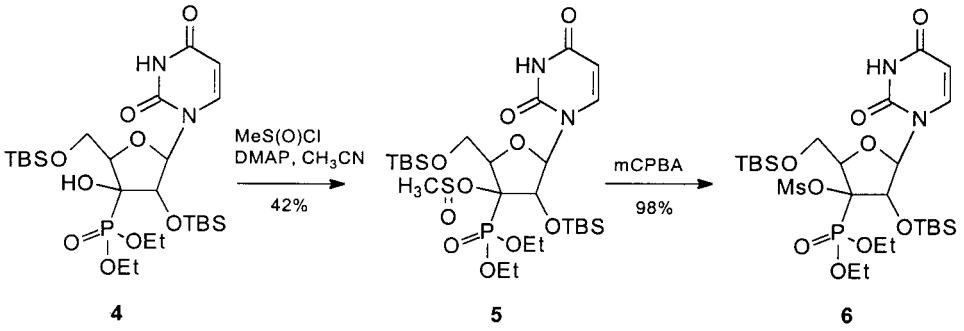


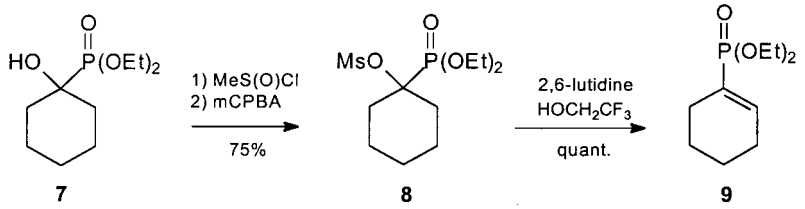
Scheme 2.

compound **4** was treated with freshly prepared methanesulfinyl chloride[8] and triethylamine in methylene chloride, but only trace amounts of the product **5** were detected. When the reaction was attempted with 3 equiv. of both the sulfinyl chloride and DMAP in acetonitrile, a significant amount of the sulfinyl ester **5** was formed. Unexpectedly, purification of this reaction mixture by radial chromatography resulted in significant hydrolysis of the sulfinate ester but compound **5** still was obtained in 42% yield along with ~48% of recovered starting material. The isolated sulfinate was oxidized to sulfonate **6** in 98% yield when treated with 5 equiv. of *m*-chloroperoxybenzoic acid (*m*CPBA). Despite the near-quantitative yield for last step, attempted *m*CPBA oxidation without purification of the reaction mixture resulted in decomposition. Furthermore, because of the relative instability of sulfinate **5**, it was necessary to oxidize the compound immediately after isolation to avoid decomposition.

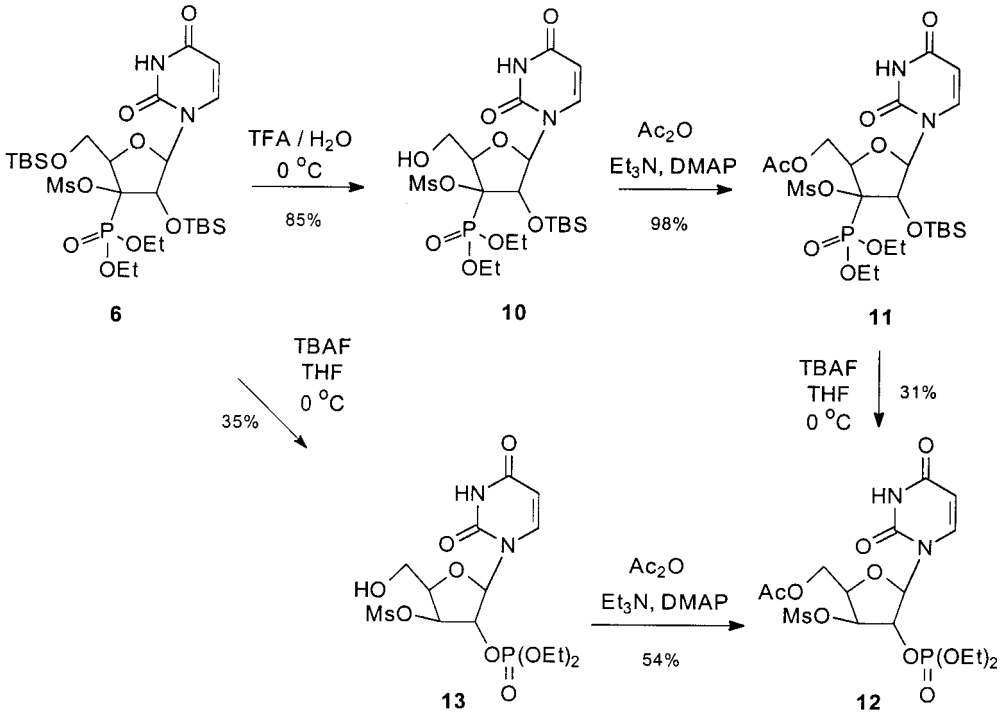
During their studies of methanesulfonyl phosphonates, Creary and coworkers[6] prepared the methanesulfonate **8** from the α-hydroxy phosphonate **7**, and then found that treatment with 2,6-lutidine resulted in smooth elimination to the vinyl phosphonate **9** (Scheme 3). Once the methanesulfonate **6** was in hand, similar strategies for base-induced elimination were investigated with this substrate. Elimination of the methanesulfonate was not achieved by treatment with a variety of bases including 2,6-lutidine, 1,8-diazabicyclo[4.3.0]undec-7-ene, potassium hydride, and sodium methoxide. Based on the assumption that the steric demand of the 5′-*tert*-butyldimethylsilyl (TBS) group may have restricted elimination,[4] a less sterically demanding protecting group for the 5′-position was examined. The 5′-TBS group could be removed selectively in 85% yield upon treatment of compound **6** with aqueous trifluoroacetic acid (Scheme 4). Subsequent acylation of alcohol **10** with acetic anhydride provided compound **11** in nearly quantitative yield. However, attempted elimination of this methanesulfonate failed to produce a vinyl phosphonate.

Because several investigators have employed fluoride ion to induce methanesulfonate elimination,[9] compound **11** was treated with tetrabutylammonium fluoride (TBAF) at 0°C (Scheme 4). In this case a novel phosphonate–phosphate rearrangement was observed instead of the desired elimination, providing compound **12** in 31% yield after purification by radial chromatography. In a parallel experiment, compound **6** was treated with excess TBAF to remove both the 5′- and the 2′-silyl groups. This reaction also resulted in a phosphonate–phosphate rearrangement providing compound **13** in 35% yield. To verify that the latter rearrangement gave a product analogous to the former, compound **13** was treated with acetic anhydride. Based on comparison of the ^{31}P and ^{1}H NMR spectra, this acetylation produced compound **12**.

Given the unexpected nature of this rearrangement, compound **12** was extensively characterized by spectroscopic data. The formation of a phosphate ester was made apparent by a ^{31}P NMR resonance at −1.8 ppm compared to the typical phosphonate resonance of compound **11** (16.4 ppm). An extended spin system observed in the ^{1}H NMR spectrum included resonances at δ 6.03 (d, H1′), 4.99 (ddd, H2′), 5.28 (dd, H3′), and 4.62 (ddd, H4′), and required one hydrogen on each carbon of the carbohydrate ring. Homonuclear decoupling experiments confirmed the connectivity shown while a heteronuclear decoupling experiment revealed a ^{31}P coupling to H2′ of 8.1 Hz and confirmed the regiochemistry of the phosphate attachment. The stereochemistry assigned to the rearrangement products also was supported by the magnitude of the coupling constants, particularly the $J_{1',2'}$ of 1.5 Hz which is consistent with the *trans* substituents, but deductions based on couplings on a 5-membered ring can be ambiguous.[10] A



Scheme 3.[6]



Scheme 4.

ROESY[11] experiment revealed strong through-space interactions between H1′ and H3′ as well as between H1′ and H4′, which further support the assigned stereochemistry. Nevertheless, a definitive determination of this stereochemistry may require crystallographic analysis, and appropriate crystals have not yet been obtained.

The mechanism responsible for rearrangement of phosphonate **11** to phosphate **12** is not completely clear. There are a number of precedents for phosphonate–phosphate rearrangements based on anion intermediates, and reaction of the silyl ether with TBAF might afford an alkoxide at C2′. In most[12] but not all[13] of the previous cases, transfer of the phosphoryl group generates a resonance-stabilized anion. However, in the rearrangement of compounds **11** and **6**, transfer of the phosphoryl group would leave a relatively unstabilized anion at C3′ and it may be unlikely that protonation of such an anion would result in the β methanesulfonate. In some respects it would be easier to envision a rearrangement based on radical intermediates. Crich and coworkers have reported a number of phosphate–phosphate rearrangements best explained by formation of radical intermediates adjacent to a phosphate ester.[14] In the case described here, if an alkoxy radical were formed at C2′ transfer of the phosphoryl group could be driven by formation of a phosphorus–oxygen bond at the expense of a phosphorus–carbon bond. Phosphoryl transfer would afford a C3′ radical that ultimately might be quenched by abstraction of a hydrogen atom from the solvent, and that process could take place from the less hindered α face of the carbohydrate to afford the observed β methanesulfonate. While such a mechanism would avoid formation of an unstabilized C3′ anion, there is no apparent precedent for formation of radical intermediates under these reaction conditions.

In conclusion, these studies have established a procedure for introduction of a methanesulfonate substituent at a highly hindered site on the carbohydrate ring of a nucleoside derivative. Even though this methanesulfonate did not undergo elimination reactions under typical reaction conditions, it did allow discovery of an intriguing phosphonate–phosphate rearrangement. Further studies to probe the mechanism of this rearrangement and to establish its generality will be reported in due course.

Experimental

Tetrahydrofuran (THF) and diethyl ether was distilled from sodium/benzophenone immediately prior to use, and CH_2Cl_2, Et_3N and CH_3CN were distilled from CaH. All nonaqueous reactions were conducted in oven-dried or flame-dried glassware, under an atmosphere of argon or nitrogen, with magnetic stirring. Radial chromatography was performed with a Chromatotron apparatus and Merck PF254 silica gel with $CaSO_4 \cdot H_2O$. Standard NMR spectra were recorded at 300 MHz for ^1H with $CDCl_3$ as solvent and $(CH_3)_4Si$ (^1H) or $CDCl_3$ (^{13}C, 77.0 ppm) as internal standards unless otherwise noted. The ROSEY NMR data were recorded at 500 MHz. ^{31}P NMR chemical shifts are reported in ppm relative to 85% H_3PO_4 (external standard). Low resolution (70 eV), high resolution and FAB mass spectra were obtained at the University of Iowa Mass Spectrometry Facility.

3′-α-Diethylphosphono-3′-*O*-methanesulfinyl-2′,5′-bis-*O*-*tert*-butyldimethylsilyluridine (5). Methanesulfinyl chloride (100 mg, 1.02 mmol) was added dropwise to a solution of compound **4** (200 mg, 0.329 mmol) and

DMAP (125 mg, 1.02 mmol) in 4.5 mL acetonitrile at 0°C. The reaction was allowed to warm to rt over 1 h and was then quenched by addition of H_2O. The aqueous phase was extracted with CH_2Cl_2, and the combined organic layer was washed with H_2O and brine, and then dried over $MgSO_4$. After concentration of the solution under reduced pressure, the product **5** (93 mg, 42%) and the starting material **4** (84 mg, 48%) were isolated by radial chromatography (95:5 $CHCl_3$/MeOH) as white foams: ^{1}H NMR δ 8.43 (br s, 1H), 7.65 (d, J=8.1 Hz, 1H), 5.72 (dd, J=8.1, 2.1 Hz, 1H), 5.69 (d, J=1.2 Hz, 1H), 5.09 (dd, J=2.4, 1.2 Hz, 1H), 4.76 (m, 1H), 4.26–4.09 (m, 4H), 4.08 (dd, J=12.0, 3.3 Hz, 1H), 3.92 (dd, J=11.7, 6.9 Hz, 1H), 2.67 (s, 3H), 1.40–1.34 (m, 6H), 0.93 (s, 18H), 0.25 (s, 3H), 0.22 (s, 3H), 0.13 (s, 6H); ^{13}C NMR δ 164.0, 150.5, 140.1, 100.8, 91.42 (d, J_{CP}=10.5 Hz), 87.8 (d, J_{CP}=170.3 Hz), 85.5 (d, J_{CP}=12.0 Hz), 80.2 (d, J_{CP}=2.0 Hz), 62.9 (d, J_{CP}=7.5 Hz), 62.6 (d, J_{CP}=7.5 Hz), 61.2, 45.1, 25.8 (3C), 25.6 (3C), 18.3, 17.9, 16.3 (d, J_{CP}=6.0 Hz), 16.2 (d, J_{CP}=6.8 Hz), −4.0, −5.4, −5.5, −5.9; ^{31}P NMR δ +17.86; HRFABMS calcd for $C_{26}H_{51}N_2O_{10}PSSi_2$ $(M+Na)^+$ 693.2438, found 693.2452.

3′-α-Diethylphosphono-3′-*O*-methanesulfonyl-2′,5′-bis-*O*-*tert*-butyldimethylsilyluridine (6). Solid *m*CPBA (186 mg, 1.08 mmol) was added in one portion to a solution of compound **5** (145 mg, 0.216 mmol) in 3 mL CH_2Cl_2 at rt. After 14 h, a solution of NaOH (1 M, 6 mL) was added to the reaction mixture, and the organic phase was washed with an aqueous solution of sodium iodide, sodium thiosulfate, NaOH, and brine, and then dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by radial chromatography (95:5 $CHCl_3$/MeOH) to afford compound **6** (145 mg, 98%) as a white foam: ^{1}H NMR δ 8.75 (br s, 1H), 7.68 (d, J=8.1 Hz, 1H), 5.73–5.69 (m, 2H), 5.24 (dd, J=3.3, 1.5 Hz, 1H), 4.88–4.84 (m, 1H), 4.40–4.09 (m, 5H), 3.96 (dd, J=11.7, 6.6 Hz, 1H), 3.27 (s, 3H), 1.39–1.34 (m, 6H), 0.94 (s, 9H), 0.93 (s, 9H), 0.24 (s, 3H), 0.21 (m, 3H), 0.13 (s, 6H); ^{13}C NMR δ 163.8, 150.6, 139.6, 101.8, 91.8 (d, J_{CP}=172.5 Hz), 91.5 (d, J_{CP}=9.8 Hz), 86.0 (d, J_{CP}=9.8 Hz), 80.5 (d, J_{CP}=2.3 Hz), 64.8 (d, J_{CP}=6.8 Hz), 62.4 (d, J_{CP}=6.8 Hz), 61.6, 40.3, 25.9 (3C), 25.8 (3C), 18.3, 17.9, 16.4 (d, J_{CP}=5.3 Hz), 16.1 (d, J_{CP}=7.5 Hz), −3.9, −5.3, −5.4, −5.8; ^{31}P NMR δ +16.79; HRFABMS calcd for $C_{26}H_{51}N_2O_{11}PSSi_2$ $(M+H)^+$ 687.2568, found 687.2564.

3′-α-Diethylphosphono-3′-*O*-methanesulfonyl-2′-*O*-*tert*-butyldimethylsilyluridine (10). Compound **6** (196 mg, 0.285 mmol) as a solid was treated with an ice cold solution of TFA/H_2O (9:1, 14 mL). After the reaction was allowed to stir for 45 min at 0°C, EtOH was added, and the solution was concentrated under reduced pressure. Purification of the residue by radial chromatography (5–10% MeOH in $CHCl_3$) yielded compound **10** (150 mg, 92%): ^{1}H NMR δ 7.65 (d, J=8.1 Hz, 1H), 5.72 (d, J=8.1 Hz, 1H), 5.68 (s, 1H), 5.30 (dd, J=3.3, 1.5 Hz, 1H), 4.95–4.90 (m, 1H), 4.38–4.14 (m, 4H), 4.10 (dd, J=12.3, 5.1 Hz, 1H), 4.00 (dd, J=12.3, 5.7 Hz, 1H), 3.27 (s, 3H), 1.38 (t, J=7.2 Hz, 6H), 0.93 (s, 9H), 0.24 (s, 3H), 0.21 (s, 3H); ^{13}C NMR δ 164.1, 150.6, 139.6, 101.7, 91.5 (d, J_{CP}=10.5 Hz), 91.4 (d, J_{CP}=173.3 Hz), 85.4 (d, J_{CP}=10.5 Hz), 80.4, 64.8 (d, J_{CP}=7.5 Hz), 63.1 (d, J_{CP}=7.5 Hz), 59.6, 40.3, 25.7 (3C), 17.9, 16.3 (d, J_{CP}=6.0 Hz), 16.1 (d, J_{CP}=6.8 Hz), −4.0, −5.9; ^{31}P NMR δ +17.27; HRFABMS calcd for $C_{20}H_{37}N_2O_{11}PSSi$ $(M+Na)^+$ 595.1523, found 595.1539.

5′-*O*-Acetyl-3′-α-diethylphosphono-3′-*O*-methanesulfonyl-2′-*O*-*tert*-butyldimethylsilyluridine (11). Acetic anhydride (25 μl, 0.258 mmol) was added to a solution of compound **10** (123 mg, 0.215 mmol), DMAP (5 mg, 0.043 mmol), and triethylamine (36 μl, 0.258 mmol) in acetonitrile (2.5 mL) at rt. After 3 h, EtOH (2 mL) was added, and the solution was concentrated in vacuo. The resulting residue was purified by radial chromatography (2–5% MeOH in $CHCl_3$) to give compound **11** (129 mg, 98%) as a white foam: ^{1}H NMR δ 9.58 (br s, 1H), 7.62 (d, J=8.4 Hz, 1H), 5.74 (d, J=8.1 Hz, 1H), 5.60 (br s 1H), 5.30 (br s, 1H), 5.04 (ddd, J=7.5, 3.6 Hz, J_{HP}=2.1 Hz, 1H), 4.55 (dd, J=12.3, 3.6 Hz, 1H), 4.49 (dd, J=12.3, 7.5 Hz, 1H), 4.44–4.07 (m, 4H), 3.28 (s, 3H), 2.15 (s, 3H), 1.37 (m, 6H), 0.93 (s, 9H), 0.28 (s, 3H), 0.23 (s, 3H); ^{13}C NMR δ 170.3, 164.0, 150.6, 139.1, 101.8, 92.4 (d, J_{CP}=10.6 Hz), 90.9 (d, J_{CP}=175.2 Hz), 83.4 (d, J_{CP}=10.6 Hz), 80.2 (d, J_{CP}=1.5 Hz), 65.1 (d, J_{CP}=6.8 Hz), 62.4 (d, J_{CP}=1.5 Hz), 61.0, 40.2, 25.7 (3C), 20.7, 17.8, 16.3 (d, J_{CP}=5.3 Hz), 15.9 (d, J_{CP}=7.6 Hz), −3.9, −6.1; ^{31}P NMR δ +16.4; HRFABMS calcd for $C_{22}H_{39}N_2O_{12}PSSi$ $(M+Na)^+$ 637.1638, found 637.1613.

5′-*O*-Acetyl-2′-α-*O*-diethoxyphosphonyl-3′-β-*O*-methanesulfonyluridine (12). To a solution of compound **11** (47 mg, 0.760 mmol) in THF (1 mL) was added TBAF (92 μl, 1 M) dropwise at 0°C. After 35 min, the mixture was quenched by addition of a saturated solution of NH_4Cl (3 mL) and diluted with CH_2Cl_2 (4 mL). After separation of the layers, the aqueous phase was extracted with CH_2Cl_2 (2×10 mL), and the combined organic layer was washed with H_2O and brine, dried ($MgSO_4$), and concentrated in vacuo. The resulting residue was purified by radial chromatography (2–10% MeOH in $CHCl_3$) to yield compound **12** (12 mg, 31%) as a colorless solid: ^{1}H NMR δ 7.47 (d, J=8.1 Hz, 1H), 6.03 (d, J=1.5 Hz, 1H), 5.79 (d, J=8.1 Hz, 1H), 5.28 (dd, J=3.6, 1.2 Hz, 1H), 4.99 (ddd, J_{HP}=8.1 Hz, J=1.5, 1.2 Hz, 1H), 4.62 (ddd, J=5.4, 3.6, 3.3 Hz, 1H), 4.48 (dd, J=5.4, 3.3 Hz, 2H), 4.27–4.16 (m, 4H), 3.17 (s, 3H), 2.13 (s, 3H), 1.38 (td, J=7.2 Hz, J_{HP}=1.2 Hz, 3H), 1.37 (td, J=7.2 Hz, J_{HP}=1.2 Hz, 3H); ^{13}C NMR δ 170.3, 162.4, 149.8, 138.8, 102.8, 89.6 (d, J_{CP}=9.8 Hz), 82.4 (d, J_{CP}=5.3 Hz), 79.9 (d, J_{CP}=3.0 Hz), 78.9, 65.2 (d, J_{CP}=6.0 Hz), 65.1 (d, J_{CP}=6.0 Hz), 60.5, 38.5, 20.7, 16.1 (d, J_{CP}=4.5 Hz), 16.0 (d, J_{CP}=3.8 Hz); ^{31}P NMR δ −1.8. HRFABMS calcd for $C_{16}H_{25}N_2O_{12}PS$ $(M+H)^+$ 501.0944, found 501.0936.

2′-α-*O*-Diethoxyphosphonyl-3′-β-*O*-methanesulfonyluridine (13). To a solution of compound **6** (160 mg, 0.233 mmol) in THF (4 mL) was added TBAF (0.51 mL, 1 M) dropwise at 0°C. After 30 min, the solution was quenched by addition of EtOAc and then concentrated in vacuo. The resulting residue was purified by radial chromatography (5–10% MeOH in $CHCl_3$) to yield compound **13** (36 mg, 35%) as a clear solid: ^{1}H NMR δ 7.62 (d, J=8.1 Hz, 1H), 6.05 (d, J=3.0 Hz, 1H), 5.78 (d, J=8.1 Hz, 1H), 5.31 (dd, J=4.2, 2.7 Hz, 1H), 5.05 (ddd, J_{CP}=8.1 Hz, J=3.0, 2.7 Hz, 1H), 4.51–4.46 (m, 1H), 4.24–4.05 (m, 4H), 4.03–3.99 (m, 2H), 3.22 (s, 3H), 1.39–1.31 (m, 6H) ^{31}P NMR δ −1.6.

Acetylation of compound 13

Acetic anhydride (20 μL, 0.190 mmol) was added to a solution of compound **13** (36 mg, 0.079 mmol), DMAP (4 mg, 0.032 mmol), and triethylamine (26 μL, 0.190 mmol) in acetonitrile (2 mL) at rt. After 1.5 h, EtOH (4 mL) was added, and the solution was concentrated in vacuo. The resulting residue was purified by radial chromatography (95:5 $CHCl_3$/MeOH) to afford compound **12** (21 mg, 54%) as a colorless solid based on comparison of ^1H and ^{31}P NMR data with that of the previously prepared compound **12**.

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