Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 1945–1949

The anomeric Pudovik rearrangement

Spencer Knapp* and Kehinde Ajayi

Department of Chemistry and Chemical Biology, Rutgers—The State University of New Jersey, 610 Taylor Road, Piscataway, NJ 08854-8087, USA

Received 19 December 2006; revised 15 January 2007; accepted 16 January 2007
Available online 20 January 2007

Abstract—The *O*,*O*-dibenzyl-*S*-glycosyl phosphothioite derived from 3,4,6-tri-*O*-acetyl-2-acetamido-2-deoxy-1-thio-α-D-glucopyranose rearranges under the influence of triethylborane and air to provide the corresponding 1-*C*-pyranosyl-*O*,*O*-dibenzylphosphonothioate, a new type of carbohydrate derivative. The isomeric beta phosphothioite is compared, and evidence of a radical chain mechanism for the Pudovik rearrangement is presented.

O-GlcNAc transferase (OGT) is a biologically ubiquitous enzyme that promotes the 2-acetamido-2-deoxy-β-D-glucosylation of serine and threonine residues of a wide variety of nuclear and cytoplasmic proteins (Fig. 1).[1] Despite the importance of OGT in myriad biological processes and disease states, there is a dearth of OGT inhibitors for use as probes of its action and effects. As a component of our search for OGT inhibitors, we examined the phosphorylation of 3,4,6-tri-*O*-acetyl-2-acetamido-2-deoxy-1-thio-α-D-glucopyranose (**1**), and have uncovered a new, anomeric, version of the Pudovik rearrangement of phosphothioites to phosphonothioates.

The reactions of **1** with *O*,*O*-dialkyl(*N*,*N*-diisopropyl)-phosphoramidites under acidic activation with tetrazole (Table 1), followed by oxidation with *tert*-butylhydroperoxide,[2–5] gave good to poor yields of the desired *O*,*O*-dialkyl-*S*-glycosylphosphothioates **2a**–**c**, as a function of the *O*-alkyl substituent (allyl, methyl, or benzyl, respectively). These products were characterized by their mass, ^{1}H NMR ($J_{H\text{-}1/H\text{-}2} \sim 5$ Hz), ^{13}C NMR, and ^{31}P NMR (diagnostic signal near 24 ppm) spectra. In addition, **2** was accompanied by varying amounts of the rearranged *O*,*O*-dialkyl-*P*-glycosyl-phosphonothioates **3a**–**c** (Table 1, entries 1–3). These products were characterized by their mass, ^{1}H NMR, ^{13}C NMR, and ^{31}P NMR (diagnostic signal near 88 ppm) spectra. The alpha configurations of **3** were indicated by their large trans-diaxial H-2/P couplings (e.g., 31 Hz for **3c**, whereas the beta isomer should show ~10 Hz).[6] Products **3a**–**c** reflect a Pudovik rearrangement (Scheme 1), wherein the phosphothioite S-substituent (here, glucopyranosyl) has migrated to phosphorus. This reaction, which may be viewed as a version of the Arbuzov rearrangement, has been previously studied by Pudovik and Pudovik and their co-workers,[7–14] as well as by others.[15–18] The Arbuzov rearrangement[19] itself encompasses a broad family of phosphite to phosphonate transformations initiated variously by alkylation, heat, light, or radicals.

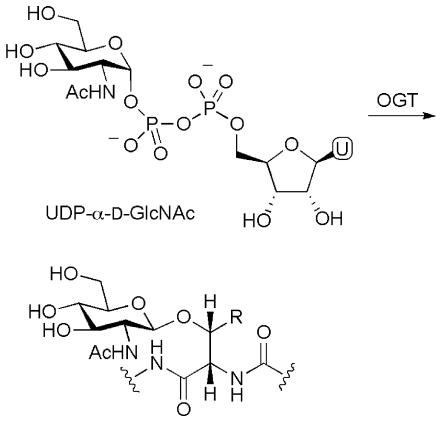


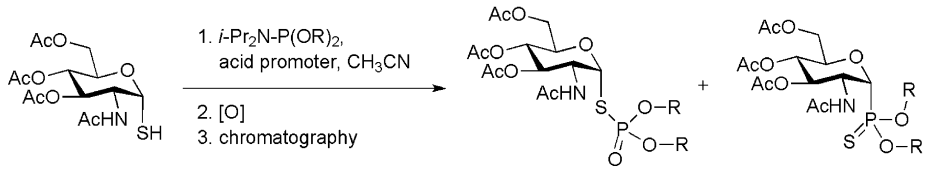
Figure 1. Glycosyl transfer to serine/threonine catalyzed by *O*-GlcNAc transferase (OGT).

Most prior examples of the Pudovik rearrangement occur upon exposure of the phosphothioite to oxygen or air, and are postulated to be radical processes.[13] Accordingly, the reaction of **1** with *O*,*O*-dibenzyl(*N*,

* Corresponding author. Tel.: +1 732 445 2627; fax: +1 732 445 5312; e-mail: knapp@rutchem.rutgers.edu

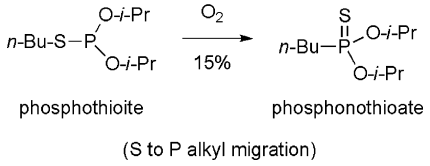
0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.01.081

Table 1. *S*-Phosphorylations with *O*,*O*-dialkyl *N*,*N*-diisopropylphosphoramidites



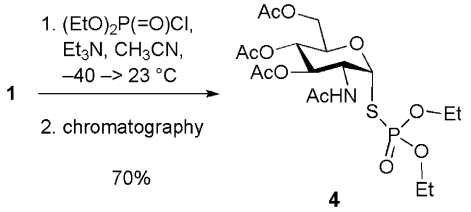
1 **2a**: R = allyl **2b**: R = Me **2c**: R = Bn **3a**: R = allyl **3b**: R = Me **3c**: R = Bn

Entry	R	Acid promoter	[O]	Yield of **2**	Yield of **3**
1	Allyl	Tetrazole	*t*-BuOOH	62% (**2a**)	—
2	Methyl	Tetrazole	*t*-BuOOH	5% (**2b**)	45% (**3b**)
3	Benzyl	Tetrazole	*t*-BuOOH	—	48% (**3c**)
4	Benzyl	Tetrazole + BHT	*t*-BuOOH	41% (**2c**)	13% (**3c**)
5	Benzyl	Tetrazole, 0 °C	Et_3B, air	<1%	79% (**3c**)
6	Benzyl	NMB·HOTf	*m*-CPBA	72% (**2c**)	—



Scheme 1. A prototypal Pudovik rearrangement.

N-diisopropyl)phosphoamidite was repeated, but with the radical inhibitor 2,6-di-*tert*-butyl-4-methylphenol (BHT) added during the oxidation step. The result (entry 4) was an increase in the percentage of phosphothioate **2c**, and less rearrangement to **3c**. Very likely the *O*-allyl substituents in entry 1 also inhibit radical propagation, accounting for the preferred formation of **2a**. In contrast, the Pudovik rearrangement product **3c** was formed almost exclusively when the oxidation was promoted by the radical initiator combination[20] of triethylborane and air (entry 5). Modifications in the promoter[21] and the oxidation conditions allowed the isolation of the phosphorylation product **2c** in good yield to the exclusion of the rearrangement (entry 6, NMB = *N*-methylbenzimidazole). The oxidant *m*-chloroperbenzoic acid probably operates by a polar mechanism, minimizing the formation of **3c**. Alternatively, the *S*-glycosylphosphothioate product **4** was prepared without oxidation by treating **1** directly with base and diethyl chlorophosphate (Scheme 2). The latter reaction failed in the *O*,*O*-dibenzyl version; instead, benzyl 3,4,6-tri-*O*-acetyl-2-acetamido-2-deoxy-1-thio-α-D-glucopyranoside was formed in 27% yield as the result of thiolate S-benzylation.

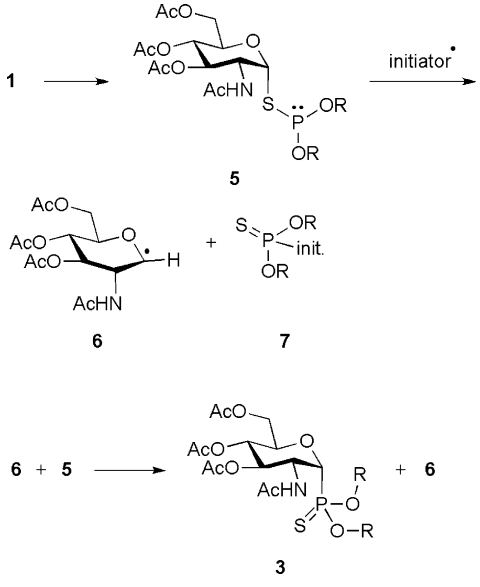


4

Scheme 2. Direct phosphorylation of mercaptan **1**.

The formation of phosphonothioates **3** can be accommodated by the radical chain process shown in Scheme 3. Initial S-phosphitylation of **1** to give the intermediate phosphothioite **5** is followed, upon addition of initiator, by a radical initiation step consisting of the removal of the phosphothiyl fragment **7** and formation of the 3,4,5-*O*-triacetyl-2-acetamido-2-deoxy-D-glucopyranosyl anomeric radical **6**.[22] Subsequent and analogous reaction of **6** with **5** in a propagation step provides product **3** and regenerates **6**. The alpha anomeric stereochemistry of **3** reflects the tendency (with ample precedent) of D-glucopyranosyl anomeric radicals such as **6** to react with almost exclusive alpha stereoselectivity.[23]

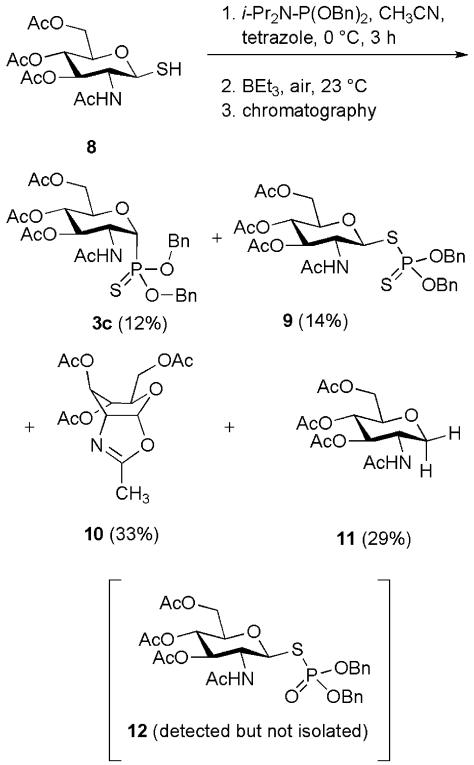
A radical fragmentation/recombination mechanism has been advanced for the Pudovik rearrangement;[13] to our knowledge the stereochemical consequences at the migrating carbon have not previously been investigated. Application of the reaction conditions of entry 5 to the



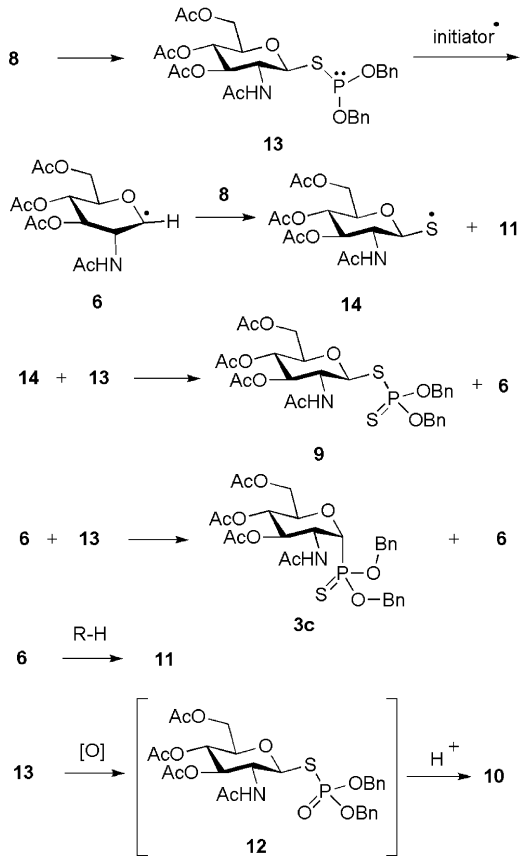
Scheme 3. Radical chain mechanism for the Pudovik rearrangement of **5**.

phosphitylation/oxidation of the corresponding beta anomeric mercaptan **8** led, after chromatography, to the array of products shown in Scheme 4. The alpha phosphothioate **3c** matched the compound obtained from **1**. The corresponding beta phosphonothioate, which if formed should have eluted near **3c**, was neither isolated nor detected by ^{31}P or ^{1}H NMR analysis of the crude reaction mixture or chromatography fractions. The beta phosphodithioate **9** was characterized by its ^{1}H (with COSY analysis), ^{13}C, ^{31}P, and mass spectra.[24] Its beta configuration was established by the large H-1/H-2 coupling (10 Hz). The oxazoline **10** and 3,4,5-tri-*O*-acetyl-2-acetamido-1,5-anhydro-2-deoxy-D-glucitol **11** were identified by spectroscopic comparison with the known compounds.

Scheme 5 shows pathways that rationalize the formation of **3c**, **9**, **10**, and **11** from **8**. Following phosphitylation of **8** analogous to that of **1**, the phosphothioite **13** reacts with the radical initiator to produce the same 3,4,5-*O*-triacetyl-2-acetamido-2-deoxy-D-glucopyranosyl anomeric radical **6**. The analogous chain propagation step involving **6** and **13** likewise produces the alpha phosphonothioate **3c** (the Pudovik rearrangement product). To the extent that starting mercaptan **8** remains, reaction of **6** with **8** gives thiyl radical **14** by hydrogen atom transfer, and a chain propagation step involving **14** and **13** leads to the phosphodithioate **9**. Dithio products analogous to **9** have been isolated previously from the Pudovik rearrangement reaction mixtures, particularly when excess mercaptan is present.[4,11] The other (reduced) product from the latter process has not been reported, but in this case can be isolated in the form of tri-*O*-acetyl-2-acetamido-1,5-anhydro-2-deoxy-D-glucitol **11**. While **9** can come from unreacted **8**, an additional reductive pathway (e.g., **6** → **11**) is likely present to account for the fact that there is formed more **11** than **9**.



Scheme 4. Phosphitylation/oxidation/rearrangement of the beta mercaptan **8**.



Scheme 5. Proposed pathways for the beta mercaptan phosphitylation/oxidation.

Some of the (P-oxidized) phosphothioate **12** probably formed in competition with **3c**, as has been noted in other systems,[4,11,18] and in the entries in Table 1. Circumstantial evidence for **12** was found in the crude reaction mixture: ^{31}P NMR analysis showed a phosphothioate peak at 25.1 ppm (compare **2c** at 24.4), and the mass spectrum featured a prominent signal at *m*/*z* 646, which corresponds to $[M+Na]^{+}$ for **12**. Instead of **12**, however, oxazoline **10** was isolated in significant amounts, even though it was not present in the crude product mixture (e.g., no H-4 of **10** at or near 4.81 ppm). Oxazoline **10** could be formed by acid-promoted cyclization of **12** during chromatography.

The formation of **3c**, independent of the stereochemistry of the precursor phosphothioite (**5** or **13**) and to the apparent exclusion of the beta stereoisomer, provides strong evidence that the same anomeric radical (**6**) is the intermediate in both reactions. Formation of the reduction product **11** is also rationalized by invoking **6** as the intermediate.

The differences in the phosphitylation/oxidation reactions of **1** and **8** merit comment. Although the reaction

conditions are very similar, the relative rates of initial phosphitylation differ, with alpha mercaptan **1** being qualitatively more reactive according to TLC analysis. The relative rates of conversion of the phosphothioites **5** and **13** to the anomeric radical **6** may also differ, although the related 2,3,4,6-tetra-*O*-acetyl-D-glucopyranosyl anomeric radical is formed from both the alpha and beta anomeric chloride precursors at about the same rate (Cl abstraction by tributyltin radical).[25] Finally, autooxidation at phosphorus[26] of **5** and **13** to the respective phosphothioates **2c** and **12** (competing with formation of **6**) may occur at different rates. A faster rate of oxidation of **13** would account for the formation of more oxidized product **12** (and hence **10**) compared with **2c** under these conditions.[27]

Acknowledgments

We are grateful to NIH (AI055760) for financial support. K.A. thanks the GAANN program for a graduate fellowship.

References and notes

1. Love, D. L.; Hanover, J. A. *Sci. STKE* **2005**, *312*, 1–13; Zachara, N. E.; Hart, G. W. *Chem. Rev.* **2002**, *102*, 431–438.
2. Knapp, S.; Myers, D. S. *J. Org. Chem.* **2001**, *66*, 3636–3638.
3. Knapp, S.; Myers, D. S. *J. Org. Chem.* **2002**, *67*, 2995–2999.
4. Kulesza, A.; Frank, C. G.; Aebi, M.; Vasella, A. *Helv. Chim. Acta* **2004**, *87*, 3106–3117.
5. Cohen, S. B.; Halcomb, R. L. *J. Org. Chem.* **2000**, *65*, 6145–6152.
6. Briner, K.; Vasella, A. *Helv. Chim. Acta* **1987**, *70*, 1341–1356.
7. Pudovik, A. N.; Faizullin, E. M. *J. Gen. Chem. USSR, Engl. Transl.* **1968**, *38*, 1857.
8. Ustaniva, L. N.; Burilov, A. R.; Belyalov, R. U.; Gazizov, T. K.; Pudovik, M. A.; Pudovik, A. N. *J. Gen. Chem. USSR, Engl. Transl.* **1987**, *57*, 1278.
9. Alfonsov, V. A.; Pudovik, D. A.; Batyeva, E. S.; Pudovik, A. N. *J. Gen. Chem. USSR, Engl. Transl.* **1988**, *58*, 1554–1557.
10. Burilov, A. R.; Gazizov, T. K.; Usmanova, L. N.; Pudovik, M. A.; Drozdova, Y. A.; Pudovik, A. N. *J. Gen. Chem. USSR, Engl. Transl.* **1989**, *59*, 1494–1495.
11. Burilov, A. R.; Drozdova, Y. A.; Pudovik, M. A.; Pudovik, A. N. *Bull. Russ. Acad. Sci. USSR, Div. Chem. Sci.* **1991**, 1885–1890.
12. Burilov, A. R.; Drozdova, Y. A.; Pudovik, M. A.; Pudovik, A. N. *Bull. Russ. Acad. Sci. USSR, Div. Chem. Sci.* **1991**, 2491–2492.
13. Burilov, A. R.; Cherepashkin, D. V.; Pudovik, M. A. *Russ. J. Gen. Chem.* **1994**, *64*, 1573–1576.
14. Burilov, A. R.; Cherepachkin, D. V.; Nikolaeva, I. L.; Pudovik, M. A. *Russ. Chem. Bull.* **1995**, *44*, 345–349.
15. Pastushkov, V. N.; Kondratev, Y. A.; Ivin, S. Z.; Vdovina, E. S.; Vasilev, A. S. *J. Gen. Chem. USSR, Engl. Transl.* **1968**, *38*, 1361.
16. Danchenko, M. N.; Sinitsa, A. D. *J. Gen. Chem. USSR, Engl. Transl.* **1986**, *56*, 1567–1570.
17. Despax, C.; Navech, J. *Phosphorus Sulfur Silicon* **1991**, *56*, 105–115.
18. Brill, W. K.-D.; Nielsen, J.; Caruthers, M. H. *J. Am. Chem. Soc.* **1991**, *113*, 3972–3980.
19. Bhattacharya, A. K.; Thyagarajan, G. *Chem. Rev.* **1981**, *81*, 415–430.
20. Ollivier, C.; Renaud, P. *Chem. Rev.* **2001**, *101*, 3415–3434.
21. Hyodo, M.; Ando, H.; Nishitani, H.; Hattori, A.; Hayakawa, H.; Kataoka, M.; Hayakawa, Y. *Eur. J. Org. Chem.* **2005**, 5216–5223.
22. Glucopyranosyl radicals similar to **6** are thought to exist in a boat conformation: Sustmann, R.; Korth, H.-G. *J. Chem. Soc., Faraday Trans. 1* **1987**, *83*, 95–105.
23. Grant, L.; Liu, Y.; Walsh, K. E.; Walter, D. S.; Gallagher, T. *Org. Lett.* **2002**, *4*, 4623–4625; Kahne, D.; Yang, D.; Lim, J. J.; Miller, R.; Pasguaga, E. *J. Am. Chem. Soc.* **1988**, *110*, 8716–8717.
24. The formation of a related dithiophosphate has been inferred by ^{31}P NMR analysis: Kudelska, W.; Michalska, M. *Synthesis* **1995**, 1539–1544.
25. Giese, B.; Dupuis, J. *Tetrahedron Lett.* **1984**, *25*, 1349–1352.
26. Hwang, W.-S.; Yoke, J. T. *J. Org. Chem.* **1980**, *45*, 2088–2091.
27. *Experimental procedures and spectral data*. Compound **3c**: Dibenzyl *N*,*N*-diisopropylphosphoramidite (0.09 mmol, 30.1 mg) was added to a solution of **1** (0.05 mmol, 18.6 mg) and tetrazole (0.15 mmol, 10.8 mg) in acetonitrile (0.80 mL) at 0 °C. After 2 h at 23 °C, triethylborane (1 M in hexanes, 0.052 mmol, 5.2 mg) was added, and a slow stream of compressed air was bubbled through the reaction for 15 min. Concentration and then chromatography with 2:3 ethyl acetate/hexanes as the eluant provided 24 mg of **3c**: R_f 0.27 (1:1 ethyl acetate/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) (all δ in ppm, then multiplicity, *J* in Hz, integral or assignments based on COSY analysis) 7.31–7.35 (m, Ph–H's), 5.96 (d, 8.4, –N*H*Ac), 5.82 (dd, 8.4, 10.4, H-3), 5.12 (dd, 11.6, 13.2, –C*H*Ph), 5.07 (app t, 11.2, –C*H*Ph), 5.03 (app t, 11.6 –C*H*Ph), 5.03 (t, 9.6, H-4), 4.93 (dd, 9.2, 11.2, –C*H*Ph), 4.69 (dd, 6.8, 9.2, H-1), 4.55 (dddd, 6.8, 8.4, 10.0, 31.2, H-2), 4.34 (dddd, 2.4, 5.2, 8.4, 9.6, H-5), 4.12 (dd, 5.2, 12.4, H-6), 3.98 (dd, 2.4, 12.4, H-6′), 2.02 (s, 2 –COCH_3). 2.01 (s, –COCH_3), 1.57 (s, –COCH_3); ^{13}C NMR (100 MHz) 171.2, 170.6, 170.2, 169.2, 135.5 (d, 6.1), 135.4 (d, 6.1), 128.8, 128.74 (3C's), 128.68 (2C's), 128.6 (2C's), 128.4 (2C's), 75.1 (d, 120.6), 72.8 (d, 2.3), 70.1, 69.2 (d, 7.6), 67.9, 67.7 (d, 7.6), 61.8, 50.3 (d, 2.3), 22.7, 20.7, 20.64, 20.62; ^{31}P NMR (121 MHz) 88.24; ESI-MS *m*/*z* 630 MNa^+. Compound **2c**: A solution of **1** (1.42 mmol, 514 mg) in dichloromethane (3.14 mL) was added via a cannula to a solution of dibenzyl *N*,*N*-diisopropylphosphoramidite (5.94 mmol, 2.05 g), 1-methylbenzimidazolium triflate (5.66 mmol, 1.60 g) and powdered, activated 4-Å molecular sieves in 1:1 dichloromethane/acetonitrile (6.29 mL), held at −52 °C during addition. After 5 h at −25 °C, the reaction was cooled to −50 °C and *m*-CPBA (7.08 mmol, 1.22 g) was added. The reaction was stirred for 1 h while warming to 23 °C. The mixture was filtered through Celite, diluted with dichloromethane, washed sequentially with 20% aq Na_2SO_3, 1 N aq HCl, and water, dried over $MgSO_4$, and then concentrated. Chromatography with 1:4 ethyl acetate/dichloromethane as the eluant afforded 640 mg (72%) of **2c** as a sticky solid: R_f 0.36 (1:1 ethyl acetate/dichloromethane); ^{1}H NMR 7.36–7.34 (m, 10H), 6.01 (dd, 5.0, 11.6, H-1), 5.73 (d, 8.4, –N*H*Ac), 5.16 (t, 9.6, H-4), 5.14–5.09 (m, 4 –C*H*Ph), 5.03 (dd, 10.8, 9.6, H-3), 4.56

(ddd, 10.8, 8.4, 4.8, H-2), 4.16 (dd, 13.6, 3.8, H-6), 4.19–4.13 (m, H-5), 3.91 (dd, 13.6, 3.8, H-6), 2.04, 2.03. 1.98, 1.83 (s, 3H each, –COCH_3); ^{13}C NMR (assignments based on HMQC analysis) 171.6, 170.5, 169.9, 169.1, 135.0, 134.8, 128.9 (2C's), 128.7 (4C's), 128.3 (2C's), 128.2 (2C's), 85.7 (d, 3.0, C-1), 70.9 (C-3), 70.6 (C-5), 69.7 (d, 6.7, –CH_2Ph), 69.5 (d, 6.7, –CH_2Ph), 67.4 (C-4), 61.4 (C-6), 52.6 (d, 6.6, C-2), 23.0, 20.7, 20.6 (2C's);^{31}P NMR 24.44; ESI-MS *m*/*z* 646 MNa^+. Compound **4**: Triethylamine (0.55 mmol, 55.6 mg) was added to a solution of **1** (0.46 mmol, 166.1 mg) and diethyl chlorophosphate (0.55 mmol, 94.7 mg) in acetonitrile (9.1 mL), held at −40 °C during addition. After 4 h at 23 °C, the reaction was diluted with ethyl acetate, washed with 10% aq $NaHCO_3$, dried, concentrated, and then chromatographed with 7:3 ethyl acetate/dichloromethane as the eluant to afford 161 mg (70%) of **4** as a white solid, mp 108–111 °C: R_f 0.25 (1:19 methanol/dichloromethane); ^{1}H NMR 5.89 (dd, 4.8, 12.0, 1H), 5.87 (d, 8.4, 1H), 5.15 (t, 9.6, 1H), 5.01 (dd, 10.8, 9.6, 1H), 4.53 (ddd, 11.1, 8.7, 5.1, 1H), 4.28–4.08 (m, 7H), 2.06 (s, 3H), 2.04 (s, 6H), 1.94 (s, 3H), 1.35 (ddd, 6.6, 3.3, 0.6, 6H); ^{13}C NMR 171.7, 170.6, 170.0, 169.2, 85.7 (d, 3.4), 71.2, 70.8, 67.8, 64.6 (d, 6.3), 64.5 (d, 6.3), 61.9, 52.3 (d, 6.5), 23.5, 21.0 (2C's), 20.9, 16.5 (d, 2.3), 16.4 (d, 2.3); ^{31}P NMR 23.25; ESI-MS *m*/*z* 522 MNa^+. ***Phosphitylation of* 8**: A solution of **8** (0.12 mmol, 42.1 mg) in degassed acetonitrile (0.6 mL) was added to a solution of tetrazole (0.42 mmol, 29.3 mg) and dibenzyl *N*,*N*-diisopropylphosphoramidite (0.20 mmol, 68.0 mg) in degassed acetonitrile (0.6 mL) at 0 °C. After 3 h at 23 °C, triethylborane (1 M in hexanes, 0.12 mmol, 11.4 mg) was added, and a slow stream of compressed air was bubbled through the reaction for 20 min. The reaction was stirred overnight, and then diluted with ethyl acetate, washed with 5% aq $NaHCO_3$, concentrated, and then chromatographed with 2:3 ethyl acetate/hexanes, then ethyl acetate, as the eluant, to give the following products in order of elution. Compound **3c**, 8.2 mg. Compound **9**, 10.4 mg, R_f 0.22 (1:1 ethyl acetate/hexanes); ^{1}H NMR 7.37–7.32 (m, Ph–H), 5.50 (d, 9.5, –N*H*Ac), 5.16 (dd, 11.5, 10.0, –C*H*Ph), 5.14–5.11 (m, 2 –C*H*Ph), 5.09 (t, 10.0, H-4), 5.09 (dd, 11.5, 10.0, –C*H*Ph), 5.06 (dd, 10.0, 9.5, H-3), 4.97 (dd, 14.0, 10.5, H-1), 4.35 (q, 10.0, H-2), 4.12 (dd, 12.5, 5.0, H-6), 4.04 (dd, 12.5, 2.0, H-6′), 3.69 (ddd, 10.0, 5.0, 2.0, H-5), 2.03 (s, 2 –COCH_3), 1.97 (s, –COCH_3), 1.89 (s, –COCH_3); ^{13}C NMR 171.1, 170.6, 170.0, 169.2, 135.4 (d, 9.3), 135.1 (d, 8.8), 128.7, 128.64, 128.61 (2C's) 128.60 (2C's), 128.2 (2C's), 128.1 (2C's), 87.4 (d, 3.3), 73.81, 73.80, 69.74 (d, 6.5), 69.69 (d, 6.4), 67.8, 61.9, 53.2 (d, 10.6), 23.1, 20.6 (3C's); ^{31}P NMR 94.99; ESI-MS *m*/*z* 662 MNa^+. Compound **10**, 12.5 mg, R_f 0.30 (ethyl acetate). Compound **11**, 11.2 mg, R_f 0.23 (ethyl acetate).