ORGANIC LETTERS

2009
Vol. 11, No. 19
4322−4325

Synthesis of the Fully Glycosylated Cyclohexenone Core of Lomaiviticin A

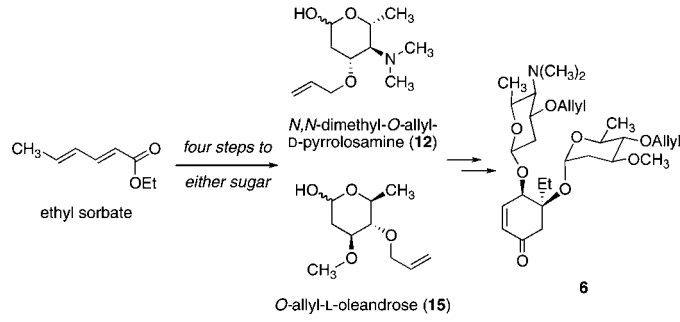
Shivajirao L. Gholap, Christina M. Woo, P. C. Ravikumar, and Seth B. Herzon*

Department of Chemistry, Yale University, New Haven, Connecticut 06520

seth.herzon@yale.edu

Received July 25, 2009

ABSTRACT



We describe two four-step sequences for conversion of the inexpensive reagent ethyl sorbate to either *O*-allyl-*N*,*N*-dimethyl-D-pyrrolosamine or *O*-allyl-L-oleandrose, protected forms of the 2,6-dideoxy sugar residues found in the complex bacterial metabolite lomaiviticin A. We also report a gram-scale synthesis of the highly-oxygenated cyclohexenone ring of this metabolite, and show this may be coupled with the aforementioned donors to form the bis(glycoside) 6. The longest linear sequence to 6 is nine steps.

In 2001, He and co-workers reported the isolation of the complex (fw = 1364 Da) dimeric metabolite lomaiviticin A (**1**) from a strain of *Micromonospora lomaivitiensis* (Figure 1).[1] Extensive NMR, MS, and IR analysis led to formulation of the structure shown, though the absolute stereochemistry (suggested as depicted) was not rigorously established. Lomaiviticin A (**1**) was reported to be a powerful antiproliferative agent, with IC_{50} values in the 0.01−100 nM range; it was also shown to inhibit the growth of Gram-positive bacteria at ng/mL concentrations.[1] Lomaiviticin A (**1**) bears some homology to the kinamycins (**2**−**5**), antiproliferative metabolites isolated in the 1970s by Omura and co-workers.[2] The structure of the kinamycins was initially proposed to contain an *N*-cyanocarbazole unit, but subsequent syntheses of a biosynthetic precursor[3] and re-evaluation of the spectral data of the isolates[4] prompted reconsideration of this proposal, eventually leading to incorporation of an unusual

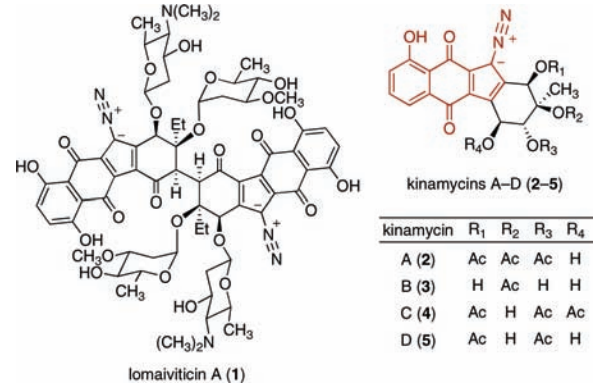


Figure 1. Structures of lomaiviticin A (**1**) and kinamycins A−D (**2**−**5**).

(1) He, H.; Ding, W. D.; Bernan, V. S.; Richardson, A. D.; Ireland, C. M.; Greenstein, M.; Ellestad, G. A.; Carter, G. T. *J. Am. Chem. Soc.* **2001**, *123*, 5362.

(2) Isolation: (a) Ito, S.; Matsuya, T.; Omura, S.; Otani, M.; Nakagawa, A. *J. Antibiot.* **1970**, *23*, 315. (b) Hata, T.; Omura, S.; Iwai, Y.; Nakagawa, A.; Otani, M. *J. Antibiot.* **1971**, *24*, 353. (c) Omura, S.; Nakagawa, A.; Yamada, H.; Hata, T.; Furusaki, A.; Watanabe, T. *Chem. Pharm. Bull.* **1971**, *19*, 2428. Syntheses: (d) Lei, X.; Porco, J. A. *J. Am. Chem. Soc.* **2006**, *128*, 14790. (e) Kumamoto, T.; Kitani, Y.; Tsuchiya, H.; Yamaguchi, K.; Seki, H.; Ishikawa, T. *Tetrahedron* **2007**, *63*, 5189. (f) Nicolaou, K. C.; Li, H.; Nold, A. L.; Pappo, D.; Lenzen, A. *J. Am. Chem. Soc.* **2007**, *129*, 10356.

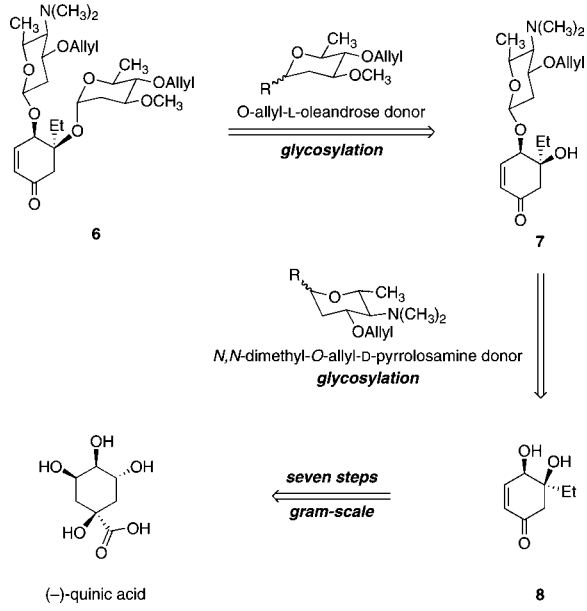
10.1021/ol901710b CCC: $40.75
Published on Web 08/31/2009

diazonapthoquinone function (diazofluorene, red in the kinamycin structure, Figure 1), which had not been seen before in natural products. Subsequently, this functional group was also shown to exist in the structure of lomaiviticin A (**1**).[1]

The unusual functionality, connectivity, and topology of lomaiviticin A (**1**) pose great challenges to synthesis. Central to preparation of this target is a method for the stereocontrolled construction of the oxygenated cyclohexenone ring and introduction of the appended *N*,*N*-dimethyl-β-D-pyrrolosamine and α-L-oleandrose glycoside residues. Although syntheses of the cyclohexenone core[5] and the monomeric aglycone[6] of lomaiviticin A (**1**) have been reported, the preparation and incorporation of the sugar residues into advanced intermediates has not yet been addressed.

We describe herein two exceedingly simple, four-step sequences that deliver the *N*,*N*-dimethyl-D-pyrrolosamine and L-oleandrose residues of lomaiviticin A (**1**) in protected form and high overall yield. We also report a gram-scale synthesis of the diol **8** and the coupling of these three intermediates to form the glycosylated core of lomaiviticin A (**1**). The overall synthetic route is exceptionally short, requiring only nine linear steps to obtain the bis(glycoside) **6** (Scheme 1).

Scheme 1. Retrosynthetic Analysis of Bis(glycoside) **6**



As detailed in Scheme 1, the bis(glycoside) **6** was prepared by sequential glycosylation reactions of the diol **8** with suitably protected *N*,*N*-dimethyl-D-pyrrolosamine and L-oleandrose sugar donors. Both D- and L-oleandrose are well-known, and several synthetic routes to each have been described.[7] The 2-deoxyaminosugar *N*,*N*-dimethyl-D-pyrrolosamine is less common among natural products,[8] and preparation of pyrrolosamine, bearing the fully alkylated tertiary amine function, has not yet been reported.[9,10]

Our synthetic approach to these sugars was guided by the recognition of the pseudoenantiomeric relationship between them, which suggested they might be accessible using parallel synthetic routes that began with enantiomerically pure material of opposite configurations (Figure 2). The additional

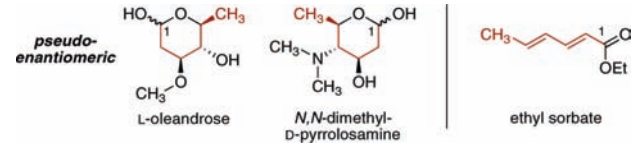


Figure 2. Illustration of the pseudoenantiomeric relationship between the L-oleandrose and *N*,*N*-dimethyl-D-pyrrolosamine sugars of lomaiviticin A (**1**).

realization that both carbon skeletons are readily transcribed onto the inexpensive commercial reagent ethyl sorbate led to the selection of this compound for initiation of our synthetic studies.

Synthesis of the protected *N*,*N*-dimethyl-D-pyrrolosamine residue began by heating solutions of the epoxide **9** (prepared in enantiomerically pure form by Shi epoxidation of ethyl sorbate)[11] in ethanol in the presence of dimethylamine at 45 °C for 2 days. Under these conditions, the aminoalcohol **10** was obtained in 51% yield, along with trace amounts of its (separable) regioisomer. The product of conjugate addition of dimethylamine to the unsaturated ester, without opening of the epoxide function, was also isolated separately (28%, not shown). The latter could be converted to the aminoalcohol **10** by heating in ethanol in a sealed vessel at 60 °C for 4 days (93%, see Supporting Information). Next, the ester

(3) (a) Echavarren, A. M.; Tamayo, N.; Paredes, M. C. *Tetrahedron Lett.* **1993**, *34*, 4713. (b) Hauser, F. M.; Zhou, M. *J. Org. Chem.* **1996**, *61*, 5722.

(4) (a) Gould, S. J.; Tamayo, N.; Melville, C. R.; Cone, M. C. *J. Am. Chem. Soc.* **1994**, *116*, 2207. (b) Mithani, S.; Weeratunga, G.; Taylor, N. J.; Dmitrienko, G. I. *J. Am. Chem. Soc.* **1994**, *116*, 2209. (c) Proteau, P. J.; Li, Y.; Chen, J.; Williamson, R. T.; Gould, S. J.; Laufer, R. S.; Dmitrienko, G. I. *J. Am. Chem. Soc.* **2000**, *122*, 8325. For a review of kinamycin biosynthesis, see: (d) Gould, S. J. *Chem. Rev.* **1997**, *97*, 2499.

(5) (a) Freed, J. D. Ph.D. Thesis, Harvard University, Cambridge, MA, 2005. (b) Nicolaou, K. C.; Denton, R. M.; Lenzen, A.; Edmonds, D. J.; Li, A.; Milburn, R. R.; Harrison, S. T. *Angew. Chem., Int. Ed.* **2006**, *45*, 2076. (c) Krygowski, E. S.; Murphy-Benenato, K.; Shair, M. D. *Angew. Chem., Int. Ed.* **2008**, *47*, 1680. (d) Zhang, W.; Baranczak, A.; Sulikowski, G. A. *Org. Lett.* **2008**, *10*, 1939.

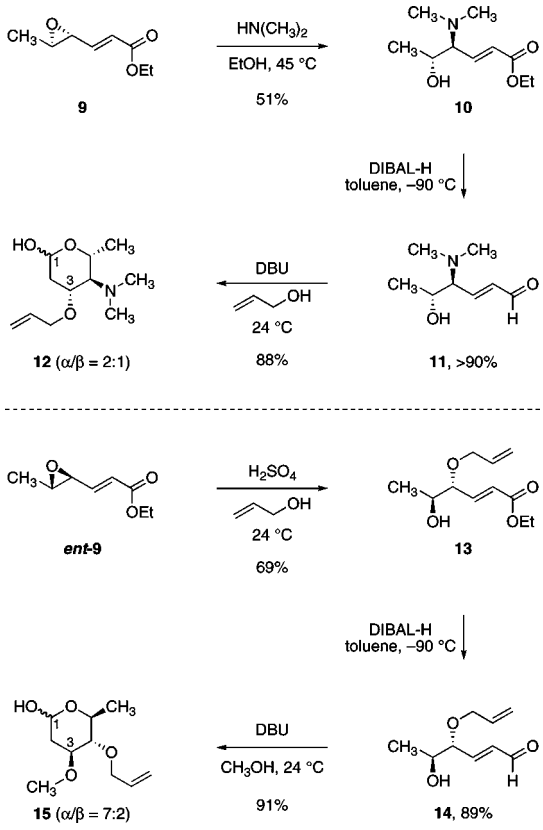
(6) Nicolaou, K. C.; Nold, A. L.; Li, H *Angew. Chem., Int. Ed.* **2009**, *48*, 5860.

(7) (a) Blindenbacher, F.; Reichstein, T. *Helv. Chim. Acta* **1948**, *31*, 2061. (b) Berti, G.; Catelani, G.; Colonna, F.; Monti, L. *Tetrahedron* **1982**, *38*, 3067. (c) Wuts, P. G. M.; Bigelow, S. S. *J. Org. Chem.* **1983**, *48*, 3489. (d) Ravi, D.; Kulkarni, V. R.; Mereyala, H. B. *Tetrahedron Lett.* **1989**, *30*, 4287. (e) Tolman, R. L.; Peterson, L. H. *Carbohydr. Res.* **1989**, *189*, 113. (f) Ford, M. J.; Ley, S. V. *Synlett* **1990**, 771. (g) Bredenkamp, M. W.; Holzapfel, C. W.; Toerien, F. *Synth. Commun.* **1992**, *22*, 2459. (h) Zhao, X. Y.; Ono, M.; Akita, H.; Chi, Y. M. *Chin. Chem. Lett.* **2006**, *17*, 730. (i) Brasholz, M.; Reissig, H.-U. *Eur. J. Org. Chem.* **2009**, 3595.

(8) *N*,*N*-Dimethylpyrrolosamine is present in two other known isolates, lomaiviticin B[1] and pyrrolosporin. Schroeder, D. R.; Colson, K. L.; Klohr, S. E.; Lee, M. S.; Matson, J. A.; Brinen, L. S.; Clardy, J. *J. Antibiot.* **1996**, *49*, 865.

(9) For synthesis of *N*-protected pyrrolosamine, see: Morris, W. J.; Shair, M. D. *Org. Lett.* **2008**, *11*, 9.

Scheme 2. Synthesis of *N*,*N*-Dimethyl-*O*-allyl-D-pyrrolosamine (**12**) and *O*-Allyl-L-oleandrose (**15**)

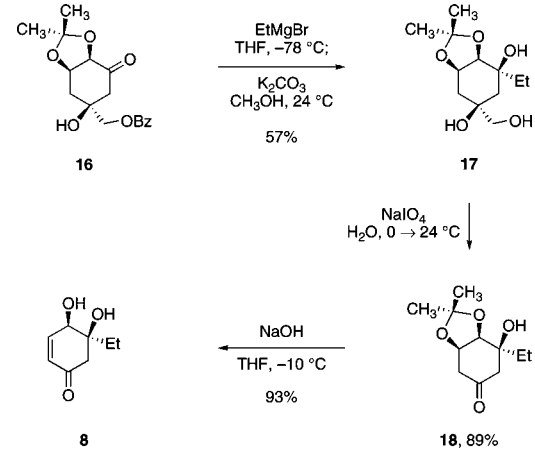


function of **10** was reduced by treatment with diisobutylaluminum hydride (DIBAL-H, 2 equiv), to furnish the aldehyde **11** in nearly quantitative yield. Stirring a solution of the aldehyde **11** and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 5 equiv) in allyl alcohol as solvent afforded the protected *N*,*N*-dimethyl-D-pyrrolosamine derivative **12** in 88% yield, as a 2:1 mixture of α and *β* anomers. The stereochemistry of the newly formed C-1 and C-3 stereocenters were established by 2D-NOESY experiments and analysis of ^{1}H−^{1}H coupling constants (see Supporting Information). The alternate C-3 diastereomer could not be detected in the unpurified reaction mixture (^{1}H NMR analysis).

Our synthesis of the protected L-oleandrose residue follows a parallel route. The epoxide ***ent*-9** was opened with allyl alcohol in the presence of sulphuric acid to form the hydroxy ether **13** (69%). The ester function of **13** was then reduced with DIBAL-H (2 equiv) to generate the unsaturated aldehyde **14** (89%). Stirring solutions of the unsaturated aldehyde **14** and DBU (5 equiv) in methanol[7f] at 24 °C smoothly formed the protected L-oleandrose intermediate **15** as well as its C-3 diastereomer (91%, 1:1 mixture of C-3 diastereomers). These were readily separable by flash column chromatography, and subjection of the undesired diastereomer to the reaction conditions re-established this mixture and served to increase material throughput.

With an efficient synthetic route to the sugar residues of lomaiviticin A (**1**) in hand, attention turned toward preparation of the key diol intermediate **8** (Scheme 3). The synthesis

Scheme 3. Synthesis of Diol **8**



of **8** began with the ketone **16**, prepared from (−)-quinic acid by an established sequence.[12] Addition of excess ethylmagnesium bromide (3 equiv) to the ketone **16** served to form the tertiary hydroxyl group of the diol **8** as a single detectable diastereomer (^{1}H NMR analysis); the benzoyl protecting group of **16** was then cleaved by exposure to potassium carbonate in methanol, to yield the triol **17**. Oxidative cleavage of the vicinal diol function of **17** (sodium periodate, 89%) generated the ketone **18**. Deprotection of the acetonide function of **18** via elimination of the *β*-oxygen substituent (2 mol % sodium hydroxide) smoothly formed the diol **8** (93%).[13] This short sequence was easily scalable, allowing preparation of **8** in gram quantities in a single pass.

Our efforts then focused on methods to introduce the protected *N*,*N*-dimethyl-D-pyrrolosamine and L-oleandrose

(10) For syntheses of the stereoisomeric sugar L-kedarosamine, see: (a) Vuljanic, T.; Kihlberg, J.; Somfai, P. *J. Org. Chem.* **1998**, *63*, 279. (b) Lear, M. J.; Hirama, M. *Tetrahedron Lett.* **1999**, *40*, 4897. (c) Priebe, W.; Skibicki, P.; Neamati, N.; Achmatowicz, O.; Grynkiewicz, G.; Szechner, B. *Pol. J. Chem.* **1999**, *73*, 1143. (d) Matsushima, Y.; Nakayama, T.; Tohyama, S.; Eguchi, T.; Kakinuma, K. *J. Chem. Soc., Perkin Trans. 1* **2001**, 569. (e) Ren, F.; Hogan, P. C.; Anderson, A. J.; Myers, A. G. *Org. Lett.* **2007**, *9*, 1923.

(11) (a) Wang, Z.-X.; Tu, Y.; Frohn, M.; Zhang, J.-R.; Shi, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11224. (b) Frohn, M.; Dalkiewicz, M.; Tu, Y.; Wang, Z.-X.; Shi, Y. *J. Org. Chem.* **1998**, *63*, 2948. (c) Shi, Y. In *Modern Oxidation Methods*; Wiley: New York, 2004; p 51.

(12) (a) Barros, M. T.; Maycock, C. D.; Ventura, M. R. *Tetrahedron* **1999**, *55*, 3233. (b) Trost, B. M.; Romero, A. G. *J. Org. Chem.* **2002**, *51*, 2332.

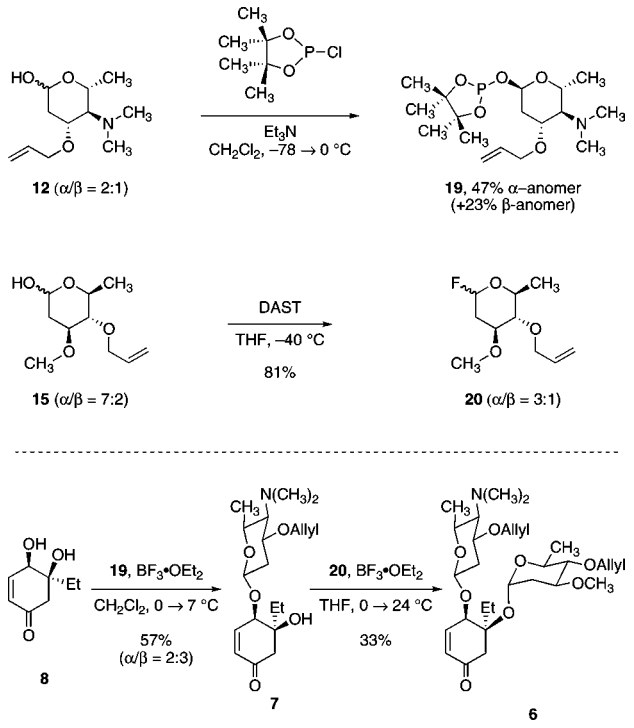
(13) The relative stereochemistry of the diol **8** was confirmed by NOE analysis of the corresponding acetonide (see Supporting Information).

(14) (a) Toshima, K.; Tatsuta, K. *Chem. Rev.* **1993**, *93*, 1503. (b) Marzabadi, C. H.; Franck, R. W. *Tetrahedron* **2000**, *56*, 8385. (c) Nicolaou, K. C.; Mitchell, H. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 1576. (d) Zhu, X.; Schmidt, R. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 1900.

(15) For example, treatment of the diol **8** with *p*-toluenesulfonic acid in acetone or *tert*-butyldimethylsilyl triflate−2,6-lutidine in dichloromethane resulted in rapid formation of 2-ethyl hydroquinone.

(16) (a) Hashimoto, S.-i.; Sano, A.; Sakamoto, H.; Hakajima, M.; Yanagiya, Y.; Ikegami, S. *Synlett* **1995**, 1271. (b) Guo, Y.; Sulikowski, G. A. *J. Am. Chem. Soc.* **1998**, *120*, 1392. (c) Pongdee, R.; Wu, B.; Sulikowski, G. A. *Org. Lett.* **2001**, *3*, 3523.

Scheme 4. Activation of *N*,*N*-Dimethyl-*O*-allyl-D-pyrrolosamine (**12**) and *O*-Allyl-L-oleandrose (**15**) Fragments and Coupling with **8** To Form Bis(glycoside) **6**



residues to the diol **8**. At the outset, we were aware that these would be challenging glycosylations, as both residues lack the C-2 substituents that often provide anchimeric assistance and stereocontrol for such transformations.[14] Additionally, the trialkylamino substituent of the *N*,*N*-dimethylpyrrolosamine residue **12** was envisioned to be reactive toward the strong Lewis acids typically used in synthetic glycosylations, and the acceptor **8** had been established as unstable toward strong protic or Lewis acids for prolonged periods of time.[15] We found that *N*,*N*-dimethyl-*O*-allyl-D-pyrrolosamine (**12**) was best activated as its corresponding glycosylphosphinate (**19**), achieved by treatment of **12** with 2-chloro-4,4,5,5-tetramethyl-1,3,2-dioxaphospholane and triethylamine at low temperature (Scheme 4).[16] The glycosylphosphinate **19** was obtained as a 2:1 mixture of α/β anomers, and these could be separated by flash column chromatography. Treatment of a mixture of the diol **8** and the diastereomerically pure α-glycosylphosphinate **19** with boron trifluoride diethyl etherate complex in tetrahydrofuran at 0 °C afforded the β-glycosylated product **7** in 35% yield, along with the undesired α-anomer (23%, not shown).[17] Extensive investigations of other donors (e.g., glycosyl fluoride, phenylthioglycoside, trichloroacetimidate) were less successful, primarily leading to lower β-selectivity and/or conversion. For installation of the second sugar residue, the glycosyl fluoride **20** was prepared by treatment of the *O*-allyl-L-oleandrose **9** with excess diethylaminosulfur trifluoride (DAST, 81%).[18] Treatment of a mixture of the mono(glycoside) **7** and the glycosyl fluoride **20** with boron trifluoride diethyl etherate complex then afforded the key bis(glycoside) **6**.

In summary, we have developed an efficient synthetic route to the bis(glycoside) **6** that was enabled by development of a concise synthesis of each of the protected sugar residues of lomaiviticin A (**1**), as well as a straightforward synthesis of the key diol intermediate **8**. We envision that the sugar syntheses described herein may find application in the preparation of other 2,6-dideoxyglycosides.

Acknowledgment. We thank Professors Miller, Micalizio, Wiberg, Spiegel, and Moore and their respective groups (Yale University) for generous donations of equipment and chemicals. Financial support from Yale University and Eli Lilly is gratefully acknowledged.

Supporting Information Available: Experimental procedures and spectral data (^{1}H and ^{13}C NMR, IR, and HRMS) for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL901710B

(17) Use of the β-anomer of **19** in the glycosylation reaction resulted in formation of the glycosylated product with nearly exclusive α-selectivity, suggesting the β-glycoside **7** arises from an S_N2-like displacement of the activated α-phosphinate.

(18) Posner, G. H.; Haines, S. R. *Tetrahedron Lett.* **1985**, *26*, 5.