Novel Strategy for Oligosaccharide Synthesis Featuring Reiterative Alkynol Cycloisomerization

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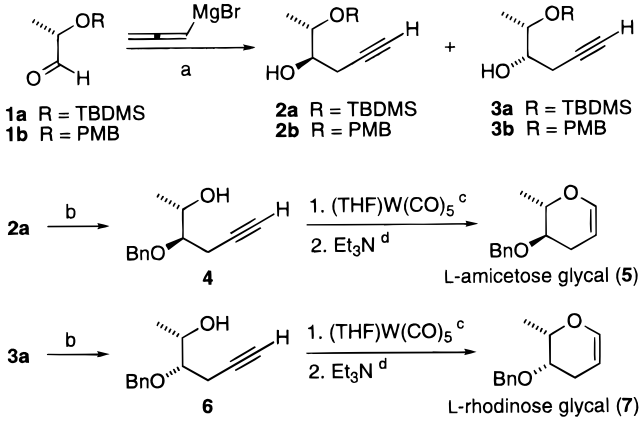
In recent years many significant advances have been made in the synthesis of oligosaccharides. Virtually all of these approaches link two or more cyclic monosaccharide components via glycoside bond formation.[1] Several classes of biologically active natural products possess polysaccharide domains composed of highly deoxygenated sugars. The most common patterns feature deoxygenation at the 2- and 6-positions and occasionally at the 3-position, and both D and L enantiomeric forms are known for many of these deoxy sugars.[2] Herein we describe a novel strategy for the preparation of oligosaccharides of 2,3,6-trideoxyhexoses, in which glycosylation with an acyclic alkynyl alcohol glycosyl acceptor is followed by transition-metal-promoted alkynol cycloisomerization to the glycal,[3] forming a polysaccharide in which the reducing terminus is activated as a glycosyl donor for subsequent glycosylation.

The absolute chirality for the deoxycarbohydrate target arose from the stereochemistry of the lactate precursor to aldehydes **1a,b** (Scheme 1).[4] Although addition of allenylmagnesium bromide to **1a,b** was not stereoselective, the 1:1 mixture of diastereomeric products could be chromatographically separated.[5] Compounds **2a**[6] and **3a** were separately converted into **4** and **6**, which each underwent tungsten-induced cyclization followed by triethylamine treatment to afford the pyranoid 1,2-glycals of L-amicetose (**5**)[7] and L-rhodinose (**7**), respectively.[8]

Scheme 1. Preparation and Cycloisomerization of Alkynols[a]



[a] Reagents: (a) (i) $H_2C{=}C{=}CHMgBr$, Et_2O (73−84%). For series **a**: (ii) silica gel chromatographic separation. For series **b**: (ii) Ac_2O, py, cat. DMAP, CH_2Cl_2. (iii) Silica gel chromatographic separation. (iv) K_2CO_3, CH_3OH/H_2O. (b) (i) NaH, $PhCH_2Br$, THF. (ii) Bu_4NF, THF (87−92%). (c) $(THF)W(CO)_5$, THF. (d) Et_3N, Et_2O/THF (28−32%, two steps).

Our first demonstration of the reiterative application of alkynol cycloisomerization to oligosaccharide synthesis began with stereoselective *N*-iodosuccinimide-promoted glycosylation of glycal **5** with the acyclic alkynol **3a** (R = TBDMS), followed by triphenylstannane-promoted dehalogenation[9] to afford the alkynyl glycoside **8** (Scheme 2).[10−12] Desilylation and tungsten-promoted cycloisomerization of the alkynol **9** provided the disaccharide glycal **10**. Although iodoglycosylation of **10** with **3a** proceeded in low yield, the direct acid-catalyzed glycosylation[11] of **10** with compound **3a** gave glycoside **11**[12] as a single diastereomer, due to the large L-amicetose substituent attached to C-4 of the glycal **10**. Desilylation and cycloisomerization steps as before furnished the L-amicetose-α-L-rhodinose-α-L-rhodinose trisaccharide glycal (**13**) in a straightforward manner.

To test this new strategy in a more challenging system, we engaged in syntheses of the disaccharide and trisaccharide glycals **17** and **20** (Scheme 3), which are reasonable synthetic precursors to the aquayamycin class of platelet aggregation inhibitor natural products exemplified by PI-080 (Figure 1).[2d,13,14]

The base-sensitive L-aculose donor **14**[15] could be stereoselectively glycosylated by $ZnCl_2$-catalyzed reaction[16] with alkynol **3a**. Desilylation of glycoside **15**[12] was accomplished under mildly

(1) Recent reviews: (a) Toshima, K.; Tatsuta, K. *Chem. Rev.* **1993**, *93*, 1503. (b) Halcomb, R. L.; Wong, C.-H. *Curr. Opin. Struct. Biol.* **1993**, *3*, 694. (c) Boons, G. J. *Tetrahedron* **1996**, *52*, 1095. (d) Danishefsky, S. J.; Bilodeau, M. T. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1380.

(2) For representative lead references, see the following. (a) Vineomycins: Imamura, N.; Kakinuma, K.; Ikekawa, N.; Tanaka, H.; Omura, S. *J. Antibiot.* **1981**, *34*, 1517. Ohta, K.; Mizuta, E.; Okazaki, H.; Kishi, T. *Chem. Pharm. Bull.* **1984**, *32*, 4350. (b) Digitoxin: Wiesner, K.; Tsai, T. Y. R.; Jin, H. *Helv. Chim. Acta* **1985**, *68*, 300. (c) Saquayamycins: Uchida, T.; Imoto, M.; Watanabe, Y.; Miura, K.; Dobashi, T.; Matsuda, T.; Naganawa, H.; Hamada, M.; Takiuchi, T.; Umezawa, H. *J. Antibiot.* **1985**, *38*, 1171. (d) PI-080: Kawashima, A.; Kishimura, Y.; Tamai, M.; Hanada, K. *Chem. Pharm. Bull.* **1989**, *37*, 3429. (e) Landomycin: Weber, S.; Zolke, C.; Rohr, J.; Beale, J. M. *J. Org. Chem.* **1994**, *59*, 4211. (f) Amicenomycin A: Kamamura, N.; Sawa, R.; Takahashi, Y.; Sawa, T.; Kinoshita, N.; Naganawa, H.; Hamada, M.; Takeuchi, T. *J. Antibiot.* **1995**, *48*, 1521. (g) Reviews: Rohr, J.; Thiericke, R. *Nat. Prod. Rep.* **1992**, *9*, 103. Kirschning, A.; Bechthold, A. F.-W.; Rohr, J. *Top. Curr. Chem.* **1997**, *188*, 1.

(3) (a) McDonald, F. E.; Gleason, M. M. *J. Am. Chem. Soc.* **1996**, *118*, 6648. (b) McDonald, F. E.; Bowman, J. L. *Tetrahedron Lett.* **1996**, *37*, 4675. (c) McDonald, F. E.; Zhu, H. Y. H. *Tetrahedron* **1997**, *53*, 11061.

(4) (a) Massad, S. K.; Hawkins, L. D.; Baker, D. C. *J. Org. Chem.* **1983**, *48*, 5180. (b) Ito, Y.; Kobayashi, Y.; Kawabata, T.; Takase, M.; Terashima, S. *Tetrahedron* **1989**, *45*, 5767. (c) Kobayashi, Y.; Takase, M.; Ito, Y.; Terashima, S. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 3038.

(5) Attempts to induce chelate-controlled addition to MEM-protected analogues of **1** also proceeded with low stereoselectivity.

(6) Compound **2a** exhibited a proton NMR spectrum identical to that of its enantiomer, prepared by addition of lithium acetylide to the TBDMS-ether of (2*S*,3*R*)-3-hydroxy-1,2-epoxybutane: (a) White, J. D.; Kang, M.-C.; Sheldon, B. G. *Tetrahedron Lett.* **1983**, *24*, 4539. (b) Kang, M.-C. Ph.D. Dissertation, Oregon State University, 1984. We thank Prof. White for providing a detailed procedure for preparation of (2*S*,3*R*)-3-hydroxy-1,2-epoxybutane.

(7) Glycal **5** is identical to the product obtained from the published three-step synthesis from 3,4-diacetoxy-L-rhamnal: (a) Martin, A.; Pais, M.; Monneret, C. *Carbohydr. Res.* **1983**, *113*, 21. (b) Suzuki, K.; Sulikowski, G. A.; Friesen, R. W.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1990**, *112*, 8895.

(8) For recent syntheses of rhodinose and amicetose, see: (a) Dondoni, A.; Fantin, G.; Fugagnolo, M.; Pedrini, P. *Tetrahedron* **1989**, *45*, 5141. (b) Sobti, A.; Sulikowski, G. A. *Tetrahedron Lett.* **1995**, *36*, 4193. (c) Itoh, T.; Yoshinaka, A.; Sato, T.; Fujisawa, T. *Chem. Lett.* **1985**, 1679.

(9) (a) Thiem, J.; Karl, H.; Schwentner, J. *Synthesis* **1978**, 696. (b) Thiem, J.; Klaffke, W. *Top. Curr. Chem.* **1990**, *154*, 285. (c) Köpper, S.; Thiem, J. *Carbohydr. Res.* **1994**, *260*, 219. (d) Suzuki, K.; Sulikowski, G. A.; Friesen, R. W.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1990**, *112*, 8895.

(10) Toluenesulfonic acid-catalyzed glycosylation (ref 11) of glycal **5** with alkynol **3a** gave compound **8** as the major diastereomer of a 3:1 anomeric mixture in 57% combined yield.

(11) (a) Daniels, P. J. L.; Mallams, A. K.; Wright, J. J. *J. Chem. Soc., Chem. Commun.* **1973**, 675. (b) Arcamone, F.; Bargiotti, A.; Cassinelli, G.; Redaelli, S.; Hanessian, S.; DiMarco, A.; Casazza, A. M.; Dasdia, T.; Necco, A.; Reggiani, P.; Supino, R. *J. Med. Chem.* **1976**, *19*, 733. (c) Tu, C. J.; Lednicer, D. *J. Org. Chem.* **1987**, *52*, 5624. (d) Wakamatsu, T.; Nakamura, H.; Naka, E.; Ban, Y. *Tetrahedron Lett.* **1986**, *27*, 3895. (e) Bolitt, V.; Mioskowski, C.; Lee, S.-G.; Falck, J. R. *J. Org. Chem.* **1990**, *55*, 5812.

(12) Coupling constants for anomeric hydrogens are consistent with formation of axial glycosides: **8** (4.86 ppm, doublet, $J = 3.1$ Hz); **11** (4.74 ppm, apparent single; 4.56 ppm, doublet, $J = 3.2$ Hz); **15** (5.35 ppm, doublet, $J = 3.6$ Hz); **19** (5.25 ppm, doublet, $J = 3.5$ Hz; 4.97 ppm, apparent singlet).

(13) The L-aculose-α-L-rhodinose-α-L-rhodinose trisaccharide of PI-080 has been synthesized: Sobti, A.; Kim, K.; Sulikowski, G. A. *J. Org. Chem.* **1996**, *61*, 6.

(14) The L-aculose-α-L-rhodinose disaccharide is also present in vineomycin and saquayamycin-type natural products (refs 2a and 2c).

(15) Prepared in 95% ee by the published procedure: Kusakabe, M.; Kitano, Y.; Kobayashi, Y.; Sato, F. *J. Org. Chem.* **1989**, *54*, 2085.

(16) (a) Mucha, B.; Hoffmann, H. M. R. *Tetrahedron Lett.* **1989**, *30*, 4489. (b) Kolb, H. C.; Hoffmann, H. M. R. *Tetrahedron* **1990**, *46*, 5127.

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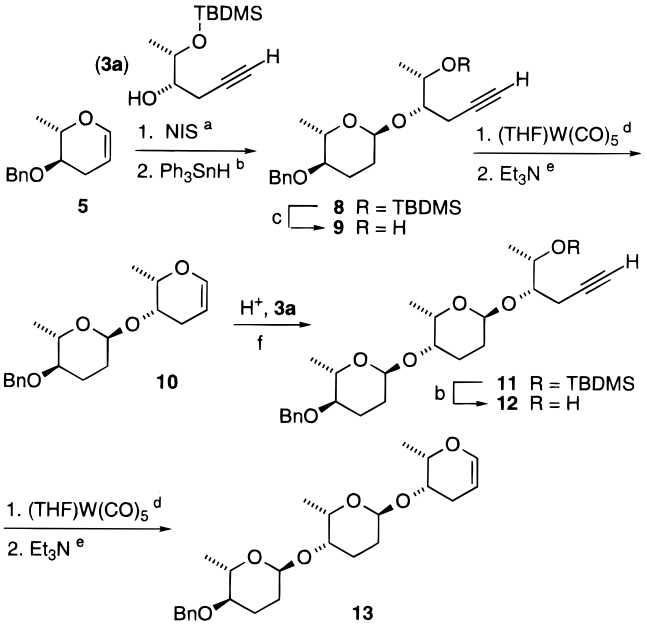
Scheme 2. Synthesis of Trisaccharide **13** via Alkynol Cycloisomerizations[a]



[a] Reagents: (a) NIS, CH_3CN, 3 Å molecular sieves, 0 °C. (b) Ph_3SnH, cat. AIBN, C_6H_6, 80 °C (58%, two steps). (c) Bu_4NF, THF (94−97%). (d) (THF)$W(CO)_5$, THF. (e) Et_3N, Et_2O/THF (45−47%, two steps). (f) cat. *p*-TsOH−H_2O, C_6H_6 (90%).

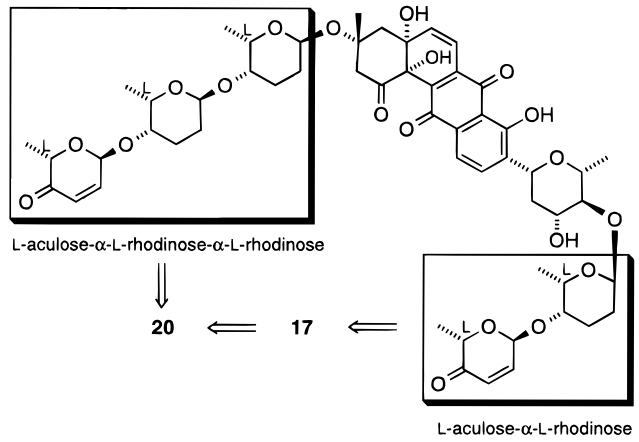
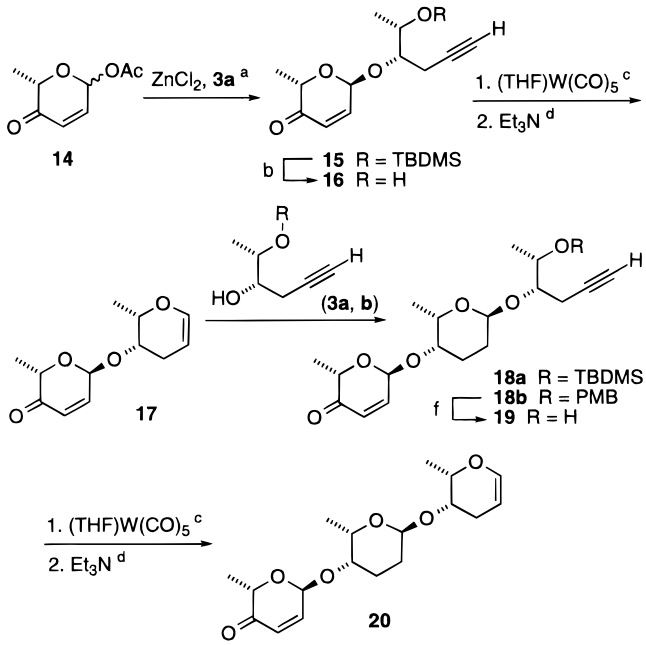


Figure 1. Structure of PI-080.

acidic conditions to afford **16**, which underwent tungsten-promoted cycloisomerization to the L-aculose-α-L-rhodinose disaccharide glycal **17** *in the presence of the sensitive aculose sugar*. The electron-rich enol ether of **17** could also be stereoselectively glycosylated with silyl ether−alkynol **3a** under acidic catalysis to afford the axial glycoside **18a**, but at this stage, we could not remove the silyl ether protective group without hydrolysis of the newly formed glycosidic bond. However, the *p*-methoxybenzyl-protected glycoside **18b** (from alkynol **3b** and glycal **17**) was

Scheme 3. Short Synthesis of Oligosaccharide Glycals **17** and **20**[a]



[a] Reagents: (a) cat. $ZnCl_2$−OEt_2, CH_2Cl_2/$ClCH_2CH_2Cl$ (80%). (b) HOAc, THF, H_2O (70%). (c) (THF)$W(CO)_5$, THF. (d) Et_3N, Et_2O/THF (for **17**, 34%; for **20**, 23% yield). (e) cat. *p*-TsOH−H_2O, C_6H_6. (f) DDQ, H_2O/CH_2Cl_2 (49%, two steps).

deprotected under oxidative conditions to yield the disaccharide-substituted alkynol **19**,[12] and cycloisomerization provided the glycal **20** corresponding to the L-aculose-α-L-rhodinose-α-L-rhodinose trisaccharide of PI-080.

The principal advantage of our strategy for oligosaccharide synthesis is the relatively inert nature of alkynes to the polar reaction conditions required for glycosylation and the minimal protective group manipulations, particularly the absence of anomeric deprotection and activation steps generally required with traditional glycosylation strategies. Note also that the affinity of the transition-metal-promoted transformation for the π-system of the alkyne readily accommodates acid-sensitive glycoside linkages as well as base- and nucleophile-sensitive aculose sugar. Although the challenge of yield optimization still remains, this novel strategy provides significant step savings toward the efficient synthesis of oligosaccharides of deoxygenated carbohydrates.

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Supporting Information Available: Preparation and characterization data for compounds **2**−**20** (19 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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