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Stereoselective Synthesis of L-Oliose Trisaccharide via Iterative Alkynol Cycloisomerization and Acid-Catalyzed Glycosylation†

Frank E. McDonald* and Minglang Wu

Department of Chemistry, Emory University, 1515 Pierce Drive, Atlanta, Georgia 30322

fmcdona@emory.edu

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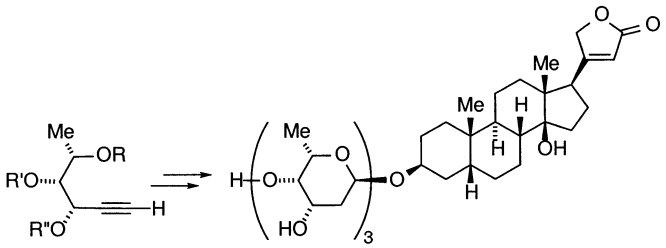
ABSTRACT



The synthesis of an all-α L-oliose diastereomer of digitoxin provides valuable insights into the generality and protective-group dependence of acid-catalyzed glycosylations of glycals to 2-deoxycarbohydrates.

The synthesis of oligosaccharides has become an important area of synthetic organic chemistry due in part to the biological activity associated with many oligosaccharides and carbohydrate-containing conjugates.[1] However, the synthetic carbohydrate chemist continues to face challenging issues of stereoselectivity and regioselectivity in forming many desired oligosaccharide structural patterns, but experience has shown that each stereoisomer requires specific solutions to glycoside synthesis. Furthermore, many suitable methods for monosaccharide synthesis prove to be more difficult to apply to oligosaccharide components.

We recently developed a novel strategy for synthesis of oligosaccharides composed of 2-deoxysugars, featuring iterative application of tungsten-catalyzed alkynol cycloisomerization and stereoselective acid-catalyzed glycosylation, which was applied to the stereoselective synthesis of the D-digitoxose trisaccharide of digitoxin.[2] In this communication, we describe a synthesis of the L-oliose[3] trisaccharide diastereomer of digitoxin. In the course of this work, we have discovered some similarities as well as differences in reactivity of the oliose vs digitoxose stereoisomers in the course of iterative acid-catalyzed glycosylation chemistry.

The synthesis began with the fully protected alkynyl triol **1**,[2a] which upon deprotection to alkynyl alcohol **2** and tungsten-catalyzed cycloisomerization afforded L-oliose (lyxo) glycal **5**.[2a] Acid-catalyzed glycosylation of the monosilyl alkynyl alcohol **4** with glycal **5** provided α-glycoside **6** with virtually complete stereoselectivity.[4] Deprotection of the *para*-nitrobenzoate ester and tungsten-catalyzed cycloisomer-

† Dedicated to our colleague, Prof. Albert Padwa, on the occasion of his 65th birthday.

(1) Reviews: (a) Toshima, K.; Tatsuta, K. *Chem. Rev.* **1993**, *93*, 1503. (b) Boons, G. J. *Contemp. Org. Synth.* **1996**, *3*, 173. (c) Danishefsky, S. J.; Bilodeau, M. T. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1380. (d) Davis, B. G. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2137. (e) Kirschning, A.; Jesberger, M.; Schoning, K. U. *Synthesis* **2001**, 507.

(2) (a) McDonald, F. E.; Reddy, K. S.; Díaz, Y. *J. Am. Chem. Soc.* **2000**, *122*, 4304. (b) McDonald, F. E.; Reddy, K. S. *Angew. Chem., Int. Ed.* **2001**, *40*, 3653.

(3) (a) Also known as 2-deoxy-L-fucose or 2,6-dideoxy-L-galactose. (b) A similar L-lyxo trisaccharide is present in the pregnane natural product brevine: Oberai, K.; Khare, M. P.; Khare, A. *Phytochemistry* **1985**, *24*, 3011.

(4) Diastereomeric α-glycoside (1−2%) is isolated from this glycosylation transformation. We tentatively assigned this diastereomer as arising from minor amounts of enantiomers from **4** and/or **5**, which were prepared with approximately 98% ee.

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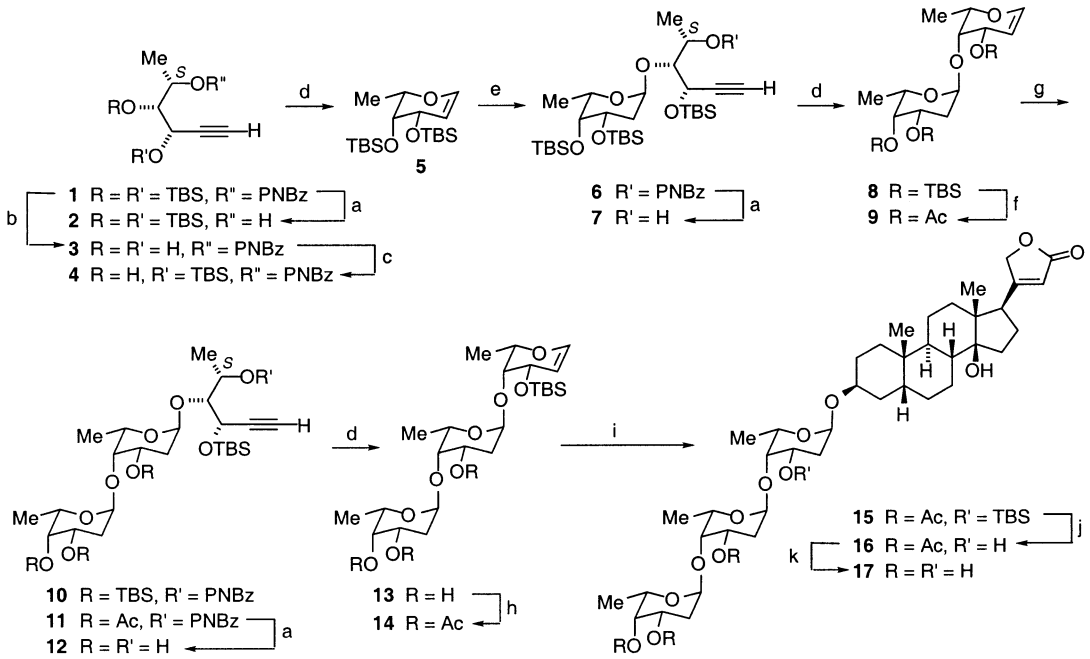
Scheme 1. Stereoselective Synthesis of L-Oliose Trisaccharide Analog of Digitoxin[a]



[a] Reagents and Conditions: (a) DIBAL, CH_2Cl_2, −78 °C (**2**, 95% yield; **7**, 83% yield; **12**, 82% yield). (b) HF-pyridine, THF, 0 °C. (c) TBSCl (1.1 equiv), imidazole, CH_2Cl_2 (72% yield, two steps). (d) $W(CO)_6$ (25 mol %), Et_3N, THF, *hν* (350 nm), 65 °C (**5**, 92% yield; **8**, 87% yield; **13**, 59% yield). (e) **4**, camphorsulfonic acid (2 mol %), toluene (95% yield). (f) Bu_4NF (5 equiv), THF, from 0 to 20 °C; then Ac_2O, DMAP, Et_3N, THF (46% yield). (g) **4** (9 equiv), Ph_3P−HBr (10 mol %), CH_2Cl_2 (**11**, 61% yield + 94% recovery of excess **4**). (h) Ac_2O, DMAP, Et_3N, THF (73% yield). (i) Digitoxigenin, camphorsulfonic acid (2 mol %), toluene/CH_2Cl_2 (75% yield). (j) HF−pyridine, THF, 0 °C (63% yield). (k) K_2CO_3, MeOH/H_2O (82% yield).

ization of alkynyl alcohol **7** gave the disaccharide glycal **8**. Initial glycosylation studies on trisilyl ether glycal **8** with the alkynyl alcohol **4** provided a 64% yield of a mixture of compounds that was determined to be an inseparable 4:3 mixture of glycoside **10** accompanied by **6**, which arose from competitive glycoside hydrolysis. On the basis of earlier observations that electron-withdrawing acetate substituents on the nonreducing sugar of disaccharide glycals provided a "protective" effect on glycoside linkages in acid-catalyzed glycosylations of glycals,[5] we elected to change the protective group pattern to triacetate glycal **9**. Glycosylation of triacetate **9** proceeded slowly and required an excess of alkynyl alcohol reactant **4** in order to obtain complete conversion of limiting reactant **9**, but glycoside **11** was produced in good yield and complete stereoselectivity as well as with efficient recovery of unreacted alkynyl alcohol **4**. Removal of all ester protective groups and tungsten-catalyzed cycloisomerization of alkynyl tetraol substrate **12** afforded trisaccharide glycal **13**, with acylation of the unreacted alcohols to **14**. The choice of silyl group on the glycal of **14** favored glycosylation with commercially available digitoxigenin under mild conditions, whereas the acetate esters on the remaining sugars stabilized preexisting glycosidic linkages, to give the protected digitoxin stereoisomer **15**. Removal of the single silyl group from the relatively unhindered equatorial position could be accomplished in good yield with HF-pyridine, and removal of acetate protective groups from **16** afforded the all-α-linked L-oliose digitoxin stereoisomer **17**.

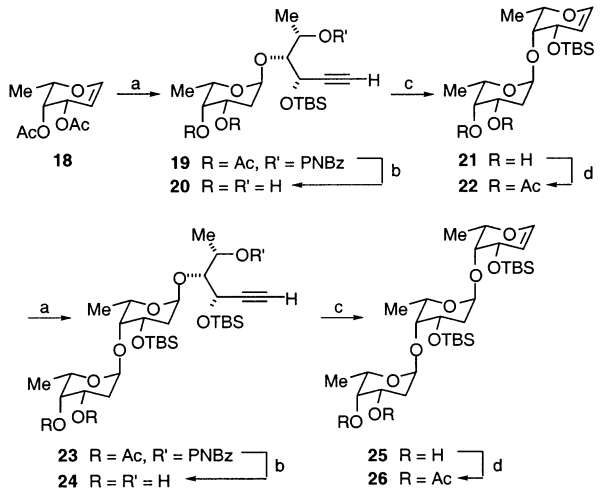
Two other strategies were explored in order to facilitate the formation of the glycosidic bond between the second and third sugars. In the first alternative approach (Scheme 2), glycosylation of diacetyl-L-fucal (**18**)[6,7] with the alkynyl alcohol **4** proceeded slowly but provided a good yield of axial glycoside **19**, again as a single stereoisomer. Conversion to alkynyl triol **20**, tungsten-catalyzed cycloisomerization and acylation of the unreacted hydroxyl groups of **21** afforded disaccharide glycal **22** bearing a silyl ether protective group at the allylic oxygen of the glycal sugar. With this protective group combination, disaccharide glycal **22** was considerably more reactive to acid-catalyzed glycosylation, so only 1 equiv of alcohol **4** was required in order to provide a satisfactory yield of glycoside **23**. This product was converted into trisaccharide glycal **26** by a route similar to that shown in Scheme 1. Unfortunately, attempts to glycosylate bissilyl ether-protected trisaccharide **26** with digitoxigenin resulted only in degradation of the previously formed glycosidic bond

(5) (a) Kunz, H.; Unverzagt, C. *Angew. Chem., Int. Ed.* **1988**, *27*, 1697. (b) Unverzagt, C.; Kunz, H. *Bioorg. Med. Chem.* **1994**, *2*, 1189. (c) McDonald, F. E.; Danishefsky, S. J. *J. Org. Chem.* **1992**, *57*, 7001.

(6) Iselin, B.; Reichstein, T. *Helv. Chim. Acta* **1944**, *27*, 1200.

(7) For other acid-catalyzed glycosylations of fucose glycal derivatives, see: (a) Wakamatsu, T.; Nakamura, H.; Naka, E.; Ban, Y. *Tetrahedron Lett.* **1986**, *27*, 3895. (b) Toshima, K.; Tatsuta, K.; Kinoshita, M. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 2369. (c) Kolar, C.; Kneissl, G.; Wolf, H.; Kämpchen, T. *Carbohydr. Res.* **1990**, *208*, 111. (d) Sabesan, S.; Neira, S. *J. Org. Chem.* **1991**, *56*, 5468. (e) Kaila, N.; Yu, H.-A.; Xiang, Y. *Tetrahedron Lett.* **1995**, *36*, 5503.

Scheme 2. Alternate Protective Group Scheme for the Synthesis of L-Oliose Trisaccharide Glycal[a]



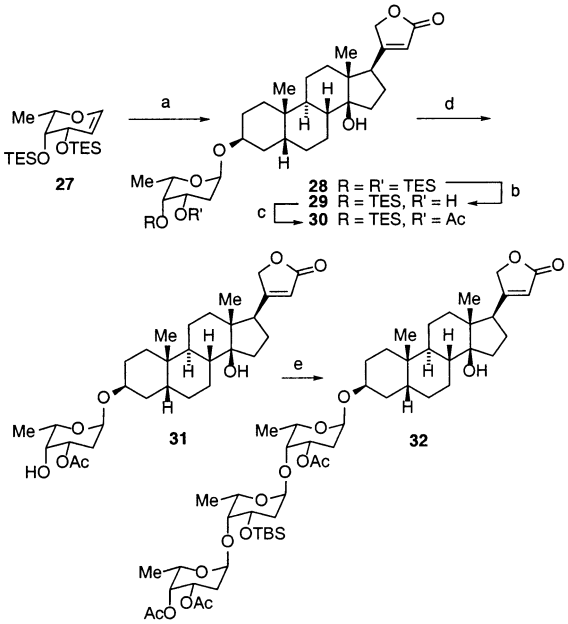
[a] Reagents and Conditions: (a) **4**, camphorsulfonic acid (2 mol %), toluene (**19**, 86% yield; **23**, 65% yield). (b) DIBAL, CH_2Cl_2, −78 °C (**20**, 88% yield; **24**, 100% yield). (c) $W(CO)_6$ (33 mol %), Et_3N, THF, *hν* (350 nm), 65 °C. (d) Ac_2O, Et_3N, DMAP (50 mol %), THF (**22**, 65% yield, two steps; **26**, 41% yield, two steps).

between the two silyl-protected sugars. This behavior is attributed to the higher reactivity of axial anomers of 2-deoxyglycosides to acid-catalyzed glycoside cleavage.[8]

The other alternative explored was formation of the oligosaccharide by reaction of a monosaccharide digitoxigenin conjugate **31** with disaccharide glycal **22** (Scheme 3). Glycosylation of silylated monosaccharide glycal **27** with digitoxigenin gave glycoside **28** in good yield as the α-anomer. At this stage, the triethylsilyl ether at the equatorial and less hindered O-3 was selectively removed to provide the hydroxyl group of **29**, which was acylated to give **30**. Removal of the remaining silyl ether was accomplished with HF-pyridine to provide **31**. However, glycosylation of **31** with disaccharide glycal **22** proceeded in moderately low yield, and a mixture of anomers was observed.

In summary, we have shown that acid-catalyzed glycosylations of oligosaccharides bearing L-fucose glycal at the reducing termini are generally stereoselective favoring

Scheme 3. Alternate Glycosylation Strategy for Digitoxigenin Oligosaccharide[a]



[a] Reagents and Conditions: (a) digitoxigenin, camphorsulfonic acid (2 mol %), CH_2Cl_2/toluene (84% yield). (b) $(NH_4)HF_2$, *N*-methylpyrrolidinone, DMF (73% yield). (c) Ac_2O, Et_3N, cat. DMAP, THF (94% yield). (d) HF−pyridine, THF, 0 °C (93% yield). (e) **22**, Ph_3P−HBr (10 mol %), CH_2Cl_2 (38% yield, 2:1 α:*β*).

formation of the axial (α) anomeric 2-deoxyglycosides, as previously demonstrated for L-fucose glycal *monosaccharides*.[7,9] For the fucose (lyxo) stereoisomers, acid-catalyzed glycosylation occurs without elimination with both trialkylsilyl ether and acetate ester protective groups at the allylic center when camphorsulfonic acid[7a,b] or triphenylphosphine−hydrogen bromide[9] are used as glycosylation catalysts.[10]

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Supporting Information Available: Experimental details and procedures for compounds **2**, **4**−**9**, **11**−**17**, **19**−**26**, **28**, and **30**−**32**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) Overend, W. G.; Rees, C. W.; Sequeira, J. S. *J. Chem. Soc.* **1962**, 3429.

(9) In addition to refs 7c−e, see acid-catalyzed glycosylations of rhamnose (arabino) glycals bearing equatorial allylic acetates: (a) Bolitt, V.; Mioskowski, C.; Lee, S.-G.; Falck, J. R. *J. Org. Chem.* **1990**, *55*, 5812. (b) Kaila, N.; Blumenstein, M.; Bielawska, H.; Franck, R. W. *J. Org. Chem.* **1992**, *57*, 4576. (c) France, C. J.; McFarlane, I. M.; Newton, C. G.; Pitchen, P.; Webster, M. *Tetrahedron Lett.* **1993**, *34*, 1635.

(10) In contrast, Lewis acids such as BF_3−OEt_2 or $SnCl_4$ generally promote glycosylation with elimination of the allylic substituent. (a) Ferrier, R. J.; Prasad, N. *J. Chem. Soc. C* **1969**, 570. (b) Ferrier, R. J. *Top. Curr. Chem.* **2001**, *215*, 153.