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Synthesis of Some Biologically Relevant β-*C*-Glycoconjugates

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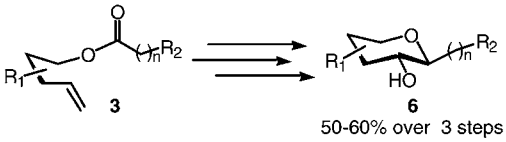
ABSTRACT



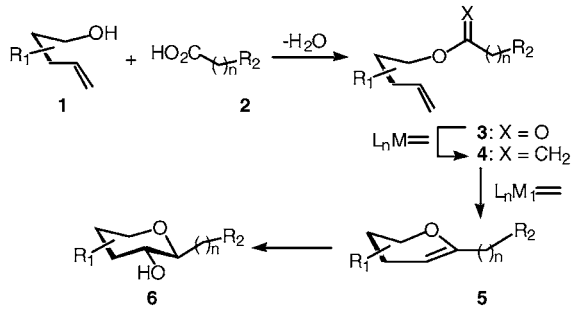
An esterification–RCM approach to a variety of biologically relevant β-*C*-glycoconjugates is reported herein. A range of carboxylic acids were coupled with several different olefin alcohols 1 to provide esters 3. The esters were then converted to the final ring-closed product 6 in three steps in 49–60% overall yield. The formed compounds are biologically relevant and serve as stable carbohydrate mimics of the corresponding *O*-glycosides.

The replacement of the interglycosidic oxygen atom in *O*-glycosides leads to stable *C*-glycoside analogues that exhibit increased stability toward hydrolysis.[1] There have been a wealth of synthetic approaches[2] toward this class of carbohydrate mimics,[3] and in recent years, biological data on these compounds have started to appear. Recently, several *C*-glycoside derivatives have been found to possess binding constants and biological properties very similar to those of their oxygen counterparts.[4]

Our laboratory has been involved in the synthesis of a variety of *C*-saccharide[5] mimics via a ring-closing metathesis-based[6] (RCM) approach,[7] and in this letter, we communicate our results toward the synthesis of a variety of β-*C*-glycoconjugates.[8]

Our generic approach to *C*-glycosides is outlined in Scheme 1 and shows the esterification−RCM protocol to furnish *C*-glycoside **6**. Implied within is the fact that a large number of β-*C*-glycosides are readily accessible by simply employing the appropriate carboxylic acid in the esterification step.

Scheme 1. RCM Approach to β-*C*-Glycosides



(1) (a) Postema, M. H. D. *C-Glycoside Synthesis*; CRC Press: Boca Raton, 1995, p 379. (b) Levy, D. E.; Tang, C. *The Chemistry of C-Glycosides;* Elsevier Science: Oxford, 1995; Vol. 13, 290p.

(2) For reviews on *C*-glycoside synthesis, see: (a) Postema, M. H. D.; Calimente, D. In *Glycochemistry*: *Principles*, *Synthesis and Applications*; Wang, P. G., Bertozzi, C., Eds.; Marcel Dekker: New York, 2000; Chapter 4, pp 77−131. (b) Du, Y.; Lindhardt, R. J. *Tetrahedron* **1998**, *54*, 9913−9959. (c) Beau, J.-M.; Gallagher, T. *Top. Curr. Chem.* **1997**, *187*, 1−54. (d) Nicotra, F. *Top. Curr. Chem.* **1997**, *187*, 55−83. (e) Togo, H.; He, W.; Waki, Y.; Yokoyama, M. *Synlett* **1998**, 700−717. (f) Jaramillo, C.; Knapp, S. *Synthesis* **1994**, 1−20. (g) Herscovici, J.; Antonakis, K. In *Studies in Natural Product Chemistry*, *Stereoselective Synthesis*; Rahman, A., Ed.; Elsevier: Amsterdam, 1992; Vol. 10, Part F, pp 337−403.

(3) For some recent approaches to *C*-glycosides, see: (a) Chiara, J. L.; Sesmilo, E. *Angew. Chem., Int. Ed.* **2002**, *41*, 3242−3246. (b) Liu, H.; Smoliakova, I. P.; Koikov, L. N. *Org. Lett.* **2002**, *4*, 3895−3898. (c) Larrosa, I.; Romea, P.; Urpi, F.; Balsells, D.; Vilarrasa, J.; Font-Bardia, M.; Solans, X. *Org. Lett.* **2002**, *4*, 4651−4654. (d) Paterson, D. E.; Griffin, F. K.; Alcaraz, M. L.; Taylor, R. J. K. *Eur. J. Org. Chem.* **2002**, 1323−1336. (e) Cheng, X. H.; Khan, N.; Mootoo, D. R. *J. Org. Chem.* **2000**, *65*, 2544−2547.

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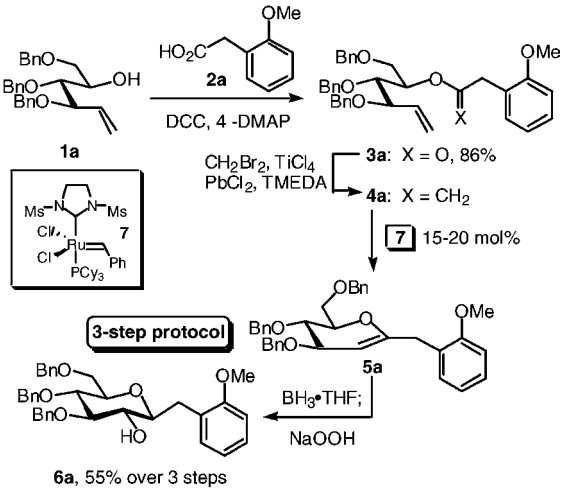
Accordingly, known olefin alcohol **1a**[9] was coupled with acid **2a**[10] to give ester **3a** in good yield.[11] Takai methylenation[12] of ester **3a** to acyclic enol ether **4a** was followed by exposure of crude **4a** to 20 mol % of the second generation Grubbs catalyst **7**[13] in hot toluene to give an intermediate glycal **5a** that was not isolated but regioselectively hydroborated[14] with an excess of BH_3·THF. Oxidative quench (H_2O_2, NaOH) of the intermediate borane then afforded the target *β*-*C*-glycoside **6a** in 55% yield[15] over three steps, Scheme 2. The stereochemistry of hydroboration was verified by

Scheme 2. Synthesis of a Benzylic *β*-*C*-Glycoside

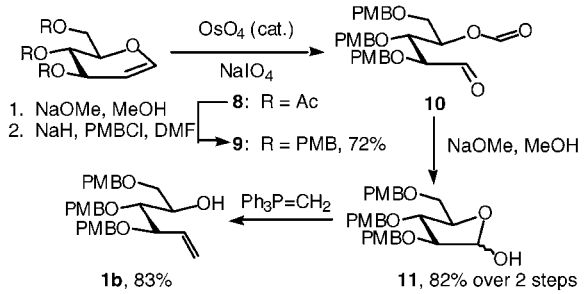


acetylation of **6a** and examination of proton NMR data ($J_{1,2} = J_{2,3} = 8.9$ Hz).

This three-step protocol efficiently provided the target *C*-glycoside **6a**, a carbon mimic of an *O*-phenyl glycoside,[16] in good overall yield.

To explore the use of different protecting groups on the olefin alcohol fragment, compound **1b** was targeted for synthesis. Deacetylation of tri-*O*-acetyl-D-glucal (**8**) was followed by *p*-methoxybenzylation to deliver **9**. Oxidative cleavage of the olefin[17] then gave aldehydo-formate ester **10** that was isolable but instable and, therefore, directly converted to lactol **11** by exposure to basic methanol. Wittig reaction of the lactol with an excess of $Ph_3P{=}CH_2$ then provided olefin alcohol **1b**, Scheme 3.

Scheme 3. Synthesis of Olefin Alcohol **1b**



A variety of diverse *C*-glycoconjugates (**6a**−**i**) were then prepared as outlined in Table 1. The esterifications (**1** + **2** → **3**), mediated by DCC and 4-DMAP, proceeded in excellent yield, and application of the three-step protocol to the formed esters **3a**−**i** served to deliver the target *β*-*C*-glycosides **6a**−**i**, respectively, in 49−60% overall yield for the three steps. Entry 2 represents a *C*-glycoside that carries a very lipophilic group at the anomeric center.

Entries 3 and 4 are stable mimics of sterol glycosides, while compounds **6e** and **6f** are *C*-glycoside analogues of O-linked amino acid glycosides based on serine and tyrosine.[18]

In these latter two examples, the Boc group on the nitrogen was found to be compatible with the methylenation chemistry

(4) (a) Wei, A.; Boy, K. M.; Kishi, Y. *J. Am. Chem. Soc.* **1995**, *117*, 9432−9436. (b) Wang, J.; Kóvac, P.; Sinay, P.; Glaudemans, C. P. J. *Carbohydr. Res.* **1998**, *308*, 191−193. (c) Tsuruta, O.; Yuasa, H.; Kurono, S.; Hashimoto, H. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 807−810. (d) Yang, G.; Franck, R. W.; Bittman, R.; Samadder, P.; Arthur, G. *Org. Lett.* **2001**, *3*, 197−200. (e) Cheng, X. H.; Khan, N.; Mootoo, D. R. *J. Org. Chem.* **2000**, *65*, 2544−2547.

(5) For a comprehensive review on the synthesis of *C*-saccharides, see: Liu, L.; McKee, M.; Postema, M. H. D. *Curr. Org. Chem.* **2001**, *5*, 1133−1167.

(6) For reviews on olefin metathesis chemistry, see: (a) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18−29. (b) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012−3043. (c) Wright, D. L. *Curr. Org. Chem.* **1999**, *3*, 211−240. (d) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413−4450. (e) Ivin, K. J. *J. Mol. Catal. A.: Chem.* **1998**, *133*, 1−16. (f) Randall, M. L.; Snapper, M. L. *J. Mol. Catal. A: Chem.* **1998**, *133*, 29−40. (g) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371−388. (h) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2036−2056. (i) Fürstner, A. *Top. Catal.* **1997**, *4*, 285−299. (j) Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28*, 446−452. (k) Schmalz, H.-G. *Angew. Chem., Int. Ed.* **1995**, *34*, 1833−1836.

(7) (a) Postema, M. H. D.; Calimente, D. *J. Org. Chem.* **1999**, *64*, 1770−1771. (b) Postema, M. H. D.; Calimente, D.; Liu, L.; Behrmann, T. L. *J. Org. Chem.* **2000**, *65*, 6061−6068. (c) Liu, L.; Postema, M. H. D. *J. Am. Chem. Soc.* **2001**, *123*, 8602−8603. (d) Postema, M. H. D.; Piper, J. L.; Liu, L.; Shen, J.; Faust M.; Andreana, P. R. *J. Org. Chem.* **2003**, in press.

(8) For a review on the use of olefin metathesis in carbohydrate chemistry, see: Jörgensen, M.; Hadwiger, P.; Madsen, R.; Stutz, A. E.; Wrodnigg, T. M. *Curr. Org. Chem.* **2000**, *4*, 565−588.

(9) Maryanoff, B. E.; Nortey, S. O.; Inners, R. R.; Campbell, S. A.; Reitz, A. B. Liotta, D. *Carbohydr. Res.* **1987**, *171*, 259−278.

(10) See Supporting Information.

(11) All new compounds were fully characterized by extensive one- and two-dimensional NMR techniques, IR and high-resolution mass spectrometry, and optical rotation.

(12) Takai, K.; Kakiuchi, T.; Kataoka, Y.; Utimoto, K. *J. Org. Chem.* **1994**, *59*, 2668−2670.

(13) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953−956.

(14) (a) Hanessian, S.; Martin, M.; Desai, R. C. *J. Chem. Soc., Chem. Commun.* **1986**, 926−927. (b) Schmidt, R. R.; Preuss, R.; Betz, R. *Tetrahedron Lett.* **1987**, *28*, 6591−6594.

(15) Yields refer to chromatographically and spectroscopically homogeneous materials.

(16) There are a large number of natural products that contain this type of linkage, e.g., vancomycin.

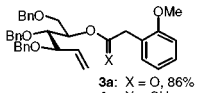
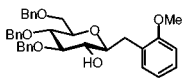
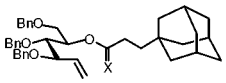
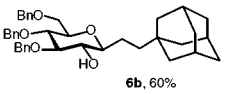
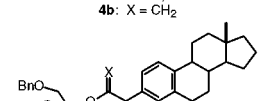
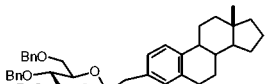
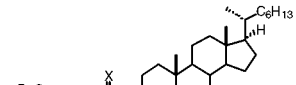
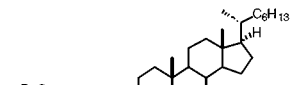
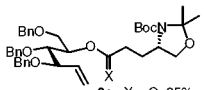
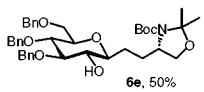
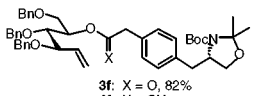
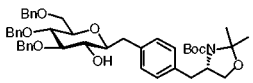
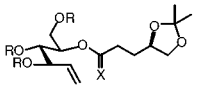
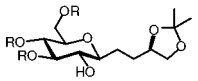
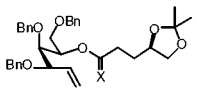
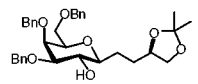
(17) Darrow, J. W.; Drueckhammer, D. G. *J. Org. Chem.* **1994**, *59*, 2976−2985.

(18) For a review on carbon-linked amino acids, see: Dondoni, A.; Marra, A. *Chem Rev.* **2000**, *100*, 4395−4422.

(19) Nagatsu, A.; Watanabe, M.; Ikemoto, K.; Hashimoto, M.; Murakami, N.; Sakakibara, J.; Tokuda, H.; Nishino, H.; Iwashima, A.; Yazawa, K. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1619−1622.

(20) See, for example: (a) Cipolla, L.; Nicotra, F.; Vismara, E.; Guerrini, M. *Tetrahedron* **1997**, *53*, 6163−6170. (b) Gujar, M. K.; Reddy, R. *Carbohydr. Lett.* **1997**, *2*, 293−298. (c) Dodoni, A.; Perrone, D.; Turturici, E. *J. Org. Chem.* **1999**, *64*, 5557−5564. (d) Yang, G.; Franck, R. W.; Byun, H.-S.; Bittman, R.; Samadder, P.; Arthur, G. *Org. Lett.* **1999**, *1*, 2149−2151.

Table 1. Synthesis of β-*C*-Glycoconjugates[a]

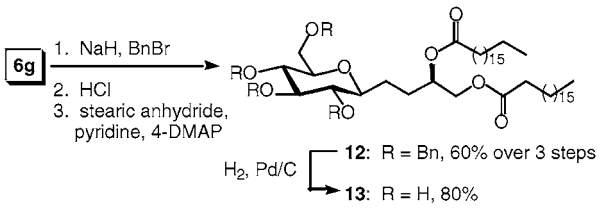
entry	ester **3** / enol ether **4**	*C*-glycoside **6**[b,c]
1	 **3a**: X = O, 86% **4a**: X = CH_2	 **6a**, 55%
2	 **3b**: X = O, 93% **4b**: X = CH_2	 **6b**, 60%
3	 **3c**: X = O, 82% **4c**: X = CH_2	 **6c**, 52%
4	 **3d**: X = O, 91% **4d**: X = CH_2	 **6d**, 50%
5	 **3e**: X = O, 85% **4e**: X = CH_2	 **6e**, 50%
6	 **3f**: X = O, 82% **4f**: X = CH_2	 **6f**, 59%
7	 **3g**: R = Bn, X = O, 94% **4g**: R = Bn, X= CH_2	 **6g**: R = Bn, 57%
8	**3h**: R = PMB, X = O, 87% **4h**: R = PMB, X= CH_2	**6h**: R = PMB, 50%
9	 **3i**: X = O, 97% **4i**: X= CH_2	 **6i**: R = Bn, 57%

[a] All compounds have been fully characterized by standard spectral methods. [b] Formed by RCM with 20 mol % **7** followed by hydroboration (BH_3·THF) and oxidative quench (NaOH, H_2O_2). [c] Yields are over three steps (methylenation, RCM, and hydroboration and oxidative quench).

even in the presence of an excess of the Takai reagent. Compounds **6g**−**i** are precursors to *C*-glycoside analogues of *O*-glycoglycerolipids. Certain *O*-glycoglycerolipids have been found to possess antitumor activity,[19] and the corresponding *C*-glycoside analogues[4d,20] would provide stable mimics of these compounds.

Scheme 4 shows the conversion of **6g** to a representative *C*-glucoglycerolipid **13**. Benzylation of O-2 on **6g** was

Scheme 4. Synthesis of β-*C*-Glucoglycerolipid



followed by removal of the acetonide protecting group and acylation with stearic anhydride of the resulting diol yielding **12** in 60% overall yield. Hydrogenolysis of the benzyl groups then completed the sequence to produce the *C*-glucoglycerolipid **13**. The use of *p*-methoxybenzyl groups, as in **6h**, should allow for the introduction of double bonds in the long-chain fatty acid.

We have shown that our convergent RCM-based approach to β-*C*-glycosides is flexible and allows for the synthesis of a variety of functionalized β-*C*-glycoconjugates such as *C*-glucoglycerolipids, *C*-glycosyl amino acids, and *C*-glycosyl steroids in good overall yield.

Acknowledgment. We thank Mr. Anuj Prasher for preliminary technical assistance, Professor Christopher Hadad (The Ohio State University) for HRMS spectra, and Dr. M. K. Ksebati (Wayne State University) for assistance with NMR data. Acknowledgment is gratefully made to the NSF (CHE-0132770) for support of this research.

Supporting Information Available: Representative procedures for the preparation of **3a**, **6a**, **11**, **1b**, **3g**, **6g**, **12**, and **13** along with spectral data listings and copies of NMR spectra for **3a**, **6a**, **11**, **1b**, **3g**, **6g**, **12**, and **13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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