

Glycoconjugate Coupling Strategy: Synthesis of a *L-chiro*-Inositol-*gala*-Quercitol Conjugate and the Synthesis of (+)-*proto*-Quercitol

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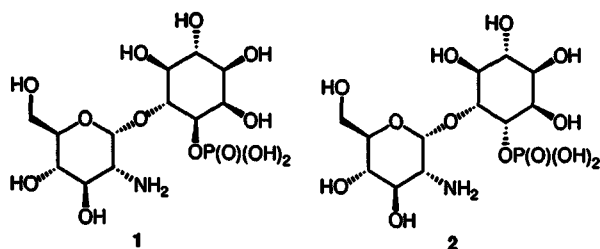
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Dedicated to Professor Charles W. Jefford on occasion of his 65 birthday and in recognition of his contribution to synthetic organic chemistry.

Abstract: The efficient syntheses of (+)-*proto*-quercitol and a conjugate consisting of *gala*-quercitol and *L-chiro*-inositol are described *via* methodology that provides a basis for a general method of producing cyclitol conjugates.

Efficient access to polyoxygenated sugar analogs continues to attract interest in synthesis.¹ In particular, there has recently been considerable effort in the preparation and biological evaluation of putative insulin mimics.² For example, disaccharides **1** and **2** have been prepared by Ley³ and Falck⁴ respectively, and the latter has been shown to display modest insulin agonist activity.

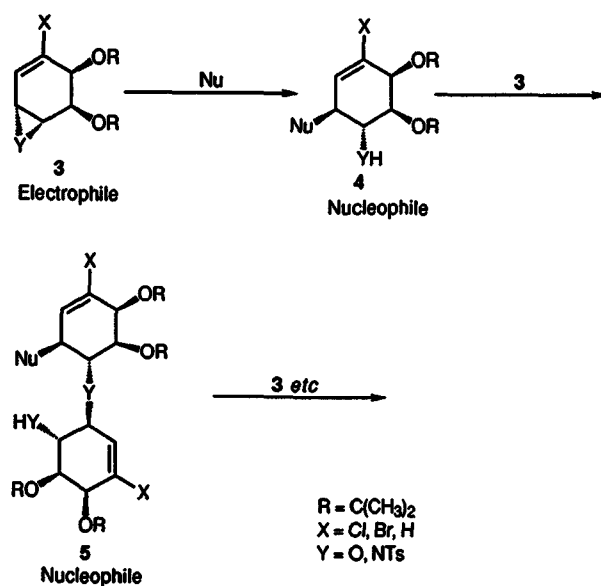


In both of these approaches standard glycosidation techniques were employed to couple the inositol and glycosyl amine progenitors. While this approach is eminently suitable for the synthesis of inositol-glycoside conjugates this method is unsatisfactory for producing, for example, inositol-inositol conjugates or their carba analogs, compounds that may also possess activity as putative insulin mediators.

As part of an ongoing program aimed at preparing carbocyclic and semi-carbocyclic analogs of conventional disaccharides, we required an efficient method of producing such compounds *via* the coupling of two oxygenated intermediates in a stereo- and regio-controlled fashion. Such a coupling method must be highly selective because of the immense number of possible conjugates (990 isomers of fully hydroxylated dimers of inositols).

The basic premise of this strategy (Scheme 1) involves the Lewis acid-mediated opening of vinyl epoxides or vinyl aziridines such as **3** with a nucleophile to produce a cyclitol derivative such as **4**. In this fashion the synthon **3** acts as an electrophilic partner in the initial condensation

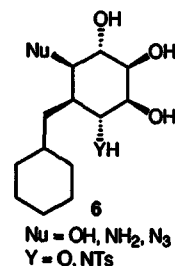
and is converted to **4** in which a single nucleophilic functionality is unraveled for the next coupling with another electrophilic partner.



Scheme 1. General Coupling Strategy

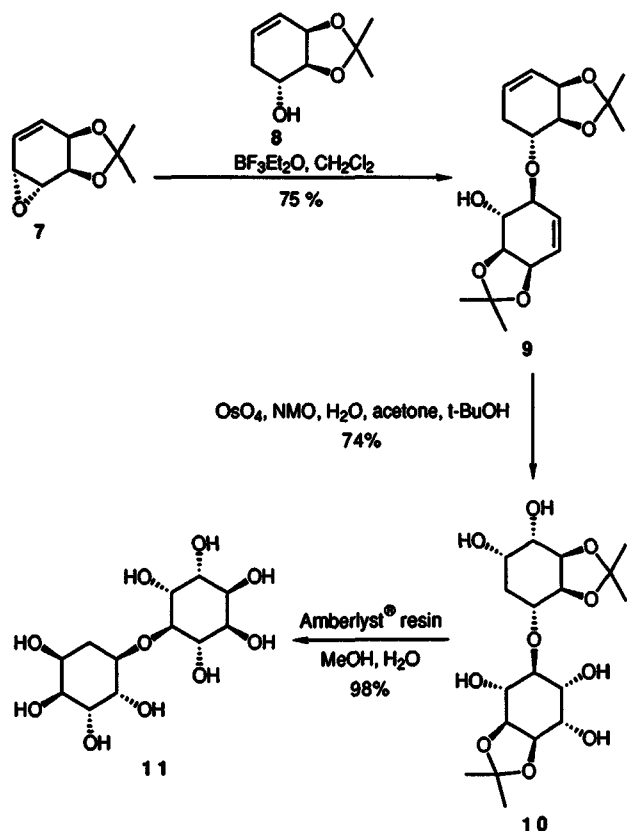
The identity of X in dimer **5** will allow for stepwise and diverse functionalization of the olefins through electronic differentiation of the two functionalities (i.e., disubstituted olefin vs. vinyl halide).

In related studies we have found that the methylcyclohexyl moiety can be effectively added to both epoxides and aziridines to provide models for C-saccharide conjugates of type **6**.⁵ We now wish to demonstrate this concept with the synthesis of the *gala*-quercitol-*L-chiro*-inositol conjugate **11** starting from aromatic precursors.



Reaction between the epoxide **7**⁶ and the secondary alcohol **8**,^{7,8} both readily accessible from halobenzenes *via* microbial oxidation,⁹ gave, in the presence of boron trifluoride, the coupled adduct **9**¹⁰ in 75% yield

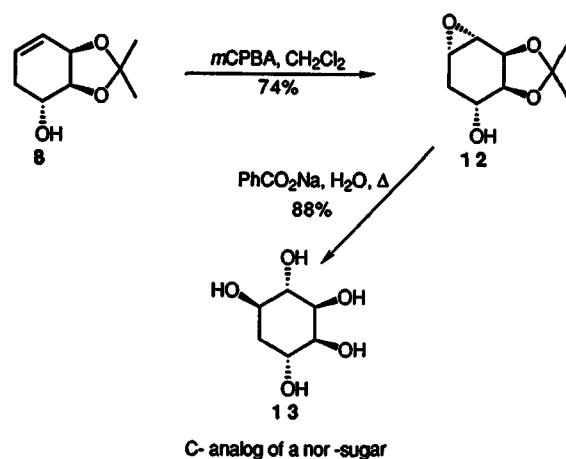
(Scheme 2). Predominant reaction of the vinyl epoxide **7** at the allylic position follows observation in our laboratories^{5,11} that nucleophiles preferentially attack the allylic position of substrates such as **7** *syn* to the isopropylidene group. Treatment of the di-alkene **9** with osmium tetroxide, continuously recycled by 4-methyl morpholine *N*-oxide, gave in 74% yield the *bis*-hydroxylated species **10** which was subsequently converted to the polyoxygenated conjugate **11**¹² under acidic catalysis.



Scheme 2

Alcohol **8** also served as an intermediate to the naturally occurring penta-alcohol (+)-*proto*-quercitol¹³ **13** (Scheme 3). Standard epoxidation of the alkene **8** with *m*CPBA gave the α -epoxide **12** which was subsequently hydrolyzed,¹⁴ with *trans*-diaxial opening expected for substrates of this type,^{7,14,15} to give (+)-*proto*-quercitol **13** in high yield. Thus one could expect either *cis* or the *trans* configuration of 1,6-diols to become available at the site of differentiated olefins in dimers of type **5**. The spectral and physical data of the penta-alcohol **13** were consistent with those reported in the literature.¹⁶

The method described above opens up possibilities of producing conjugates of saccharides and their carbocyclic analogs and will be fully exploited as a general method of synthesis. It further expands the potential of biocatalytically produced cyclohexadiene-*cis*-diols¹⁷ in the preparation of medicinally important compounds. The synthesis of



Scheme 3

other conjugates and their carbocyclic disaccharide analogs are currently being pursued and will be reported in the near future along with the results of their biological activities.

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References and Notes

- a) Liu, K. K.-C.; Danishefsky, S. J. *J. Am. Chem. Soc.*, **1993**, *115*, 4933. b) Ichikawa, Y.; Lin, Y.-C.; Dumas, D. P.; Shen, G.-W.; Garcia-Junceda, E.; Williams, M. A.; Bayer, R.; Ketcham, C.; Walker, L. E.; Paulson, J. C.; Wong, C.-H. *J. Am. Chem. Soc.*, **1992**, *114*, 9283.
- For examples see, a) Berlin, W. K.; Zhang, W.-S.; Shen, T. Y. *Tetrahedron*, **1991**, *47*, 1. b) Berlin, W. K.; Wang, S.-N.; Shen, T. Y.; *Tetrahedron Lett.*, **1990**, *31*, 1109. c) Plourde, R.; d'Alarcao, M. *Tetrahedron Lett.*, **1990**, *31*, 2693. d) Cobb, J. E.; Johnson, M. R. *Tetrahedron*, **1991**, *47*, 21. e) Plourde, R.; d'Alarcao, M.; Saltiel, A. R. *J. Org. Chem.*, **1992**, *57*, 2606.
- Ley, S. V.; Yeung, L. L. *Synlett*, **1992**, 997.
- Reddy, K. K.; Falck, J. R.; Capdevila, J. *Tetrahedron Lett.*, **1993**, *34*, 7869.
- Hudlicky, T.; Fan, R. unpublished results.
- Carless, H. A. *J. Tetrahedron Lett.*, **1992**, *33*, 6379.
- Hudlicky, T.; Luna, H.; Olivo, H. H.; Anderson, C.; Nugent, T.; Price, J. D. *J. Chem. Soc. Perkin Trans. 1*, **1991**, 2907.

8. Hudlicky, T.; Mandel, M.; Rouden, J.; Lee, R. S.; Bachmann, B.; Dudding, T.; Yost, K. J.; Merola, J. S. *J. Chem. Soc. Perkin Trans. 1*, **1994**, 1553.
9. a) Gibson, D. T.; Koch, G. R.; Kallio, R. E. *Biochemistry*, **1968**, *7*, 2653. b) Gibson, D. T.; Hensley, M.; Yoshioka, H.; Mabry, J. J. *Biochemistry*, **1970**, *9*, 1626.
10. Boron trifluoride diethyl etherate (5.5 μL , 4.5×10^{-5} mol) in dichloromethane (1 mL) was added to a stirred solution of the alcohol **8** (153 mg, 8.98×10^{-4} mol) and the epoxide **7** (181.3 mg, 1.078×10^{-3} mol) in dichloromethane (5 mL) at -10°C . After 25 minutes several drops of a saturated aqueous solution of sodium bicarbonate were added to the reaction followed by water (10 mL). The organic and aqueous layers were separated and the aqueous layer extracted with ether (3 X 10 mL). The combined organic extracts were dried (MgSO_4) and concentrated under reduced pressure. Flash chromatography (4% methanol in dichloromethane) gave the conjugate **9** (227.6 mg, 75%) as an oil: $[\alpha]_{\text{D}} -62.6^\circ$ (c 0.5, CHCl_3); IR (neat) 3460, 2992, 2920, 1648, 1209, 1165, 1050, 855, 738; ^1H NMR (270 MHz; CDCl_3) 5.85 (4H, m), 4.64 (2H, m), 4.38 (1H, s. Removable with D_2O), 4.15 (2H, dd, J 8.84 and 6.76), 3.85 (1H, d, J 8.41), 3.64 (2H, m), 2.40 (1H, m), 2.09 (1H, dd, J 16.04 and 10.58), 1.55 (3H, s), 1.54 (3H, s), 1.41 (3H, s), 1.38 (3H, s); ^{13}C NMR (67.9 MHz; CDCl_3), 133.22 (CH), 128.57 (CH), 124.62 (CH), 123.96 (CH), 110.40 (C), 109.28 (C), 81.24 (CH), 80.36 (CH), 78.3 (CH), 77.35 (CH), 74.71 (CH), 72.97 (CH), 72.34 (CH) 30.59 (CH_2), 28.03 (CH_3), 27.76 (CH_3), 25.68 (CH_3), 25.35 (CH_3); MS (CI) m/z (relative intensity) 323 (M-15, 40), 262 (38), 111 (75), 95 (78); HRMS calcd for $\text{C}_{18}\text{H}_{27}\text{O}_6$ 339.1807, found 339.1807.
11. a) Hudlicky, T.; Konigsberger, K.; Xinrong, T. *J. Org. Chem.* **1994**, *59*, 4037. b) Hudlicky, T.; Rouden, J.; Luna, H.; Allen, S. *J. Am. Chem. Soc.*, **1994**, *116*, 5099.
12. mp $104\text{--}106^\circ\text{C}$; $[\alpha]_{\text{D}} -29.1^\circ$ (c 1, H_2O); IR (KBr) 3030, 2592, 1620, 1402, 1065, 843, 651; ^1H NMR (270 MHz; D_2O) 3.86 (4H, m), 3.74 (3H, m), 3.58 (3H, m), 3.42 (1H, m), 2.04 (1H, m), 1.61 (1H, m); ^{13}C NMR (67.9 MHz; $(\text{CD}_3)_2\text{SO}$), 83.68 (CH), 79.13 (CH), 72.90 (CH), 72.71 (CH), 72.29 (CH), 71.95 (CH), 71.86 (CH), 70.80 (CH), 70.11 (CH), 66.00 (CH) 33.71 (CH_2); MS (CI) m/z (relative intensity) 327 (M+1, 25), 291 (22), 127 (37); HRMS calcd for $\text{C}_{12}\text{H}_{23}\text{O}_{10}$ 327.1291, found 327.1291.
13. For isolation of *proto-quercitol* see, Braconnot, H. *Ann. Chim. Phys.* **1849**, *27*, 392. Plouvier, V. *Compt. Rend.*, **1961**, *253*, 3047. For syntheses see, a) McCasland, G. E.; Naumann, M. O.; Durham, L. J. *Carbohydr. Res.*, **1967**, *4*, 516. b) Suami, T.; Ogawa, S.; Oki, T.; Ohashi, K. *Bull. Chem. Soc. Jpn.*, **1972**, *45*, 2597. c) Suami, T.; Ogawa, S.; Ueda, T.; Uchino, H. *Bull. Chem. Soc. Jpn.*, **1972**, *45*, 3226. d) Cambie, R. C.; Renner, N. D.; Rutledge, P. S.; Woodgate, P. D. *Aust. J. Chem.*, **1990**, *43*, 1597. e) Secen, H.; Salanci, E.; Sutbeyaz, Y.; Balci, M. *Synlett*, **1993**, 609.
14. Mandel, M.; Hudlicky, T.; Kwart, L. D.; Whited, G. M. *J. Org. Chem.*, **1993**, *58*, 2331.
15. Hudlicky, T.; Price, J. D.; Fan, R.; Tsunoda, T. *J. Am. Chem. Soc.*, **1990**, *112*, 9439.
16. McCasland, G. E.; Naumann, M. O.; Durham, L. J. *J. Org. Chem.*, **1968**, *33*, 4220.
17. For recent reviews see, a) Brown, S. M.; Hudlicky, T. In *Organic Synthesis: Theory and Practice*; Hudlicky, T., Ed.; JAI Press: Greenwich, CT, 1992; vol. 2, p 113. b) Widdowson, D. A.; Ribbons, D. A.; Thomas, S. D. *Janssen Chimica Acta*, **1990**, *8*, 3. c) Carless, H. A. J.; *Tetrahedron: Asymm.*, **1992**, 795.