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Short Synthesis of 3-(Hydroxymethyl)xylitol and Structure Revision of the Anti-diabetic Natural Product from *Casearia esculenta*

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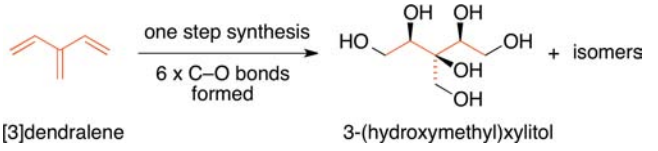
ABSTRACT



3-(Hydroxymethyl)xylitol, a compound reportedly isolated from the root of *Casearia esculenta* (Roxb.), along with its three possible stereoisomers, has been synthesized for the first time by way of a triple dihydroxylation reaction performed upon the simplest cross-conjugated hydrocarbon, [3]dendralene. The data for the natural product do not match any of the isomeric 3-(hydroxymethyl)pentitols. The structure of the natural product from the root of *Casearia esculenta* (Roxb.) has been corrected by reanalysis of the published data.

Unbranched carbohydrates are the most abundant organic compounds.[1] Their branched-chain congeners are surprisingly common in nature, and many have important biological activities.[2] A branched chain pentitol, 3-(hydroxymethyl)-xylitol (**1**, Scheme 1), was recently reported as a natural product isolated from the root of *Casearia esculenta* (Roxb.), a plant traditionally used in India to treat diabetes.[3,4] As described in a series of five publications from the Pugalendi group, the compound exhibits the following beneficial effects on streptozotocin-induced diabetic rats: (a) anti-hyperglycemic effects;[3] (b) antioxidant properties;[5] (c) favorable influences on hepatic and renal functional markers;[6] (d) anti-hyperlipidemic activity;[7] and (e) a significant beneficial effect on glycoprotein components.[8] These biological activities have led the Pugalendi group to patent their discovery.[9] The compound attracted our attention primarily because it appeared to be the ideal vehicle for a total synthesis utilizing the readily available, π-bond-rich hydrocarbon [3]dendralene (**2**).

Specifically, we identified a triple dihydroxylation reaction of [3]dendralene (**2**)[10] as an approach that would be

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(1) (a) *The Organic Chemistry of Sugars*; Levy, D. E., Fügedi, P., Eds.; CRC Press: Boca Raton, 2006. (b) *Carbohydrates: The Essential Molecules of Life*, 2nd ed.; Stick, R. V., Williams, S. J., Eds.; Elsevier: Amsterdam, 2009. (c) *Carbohydrates – Tools for Stereoselective Synthesis*; Boysen, M. M. K., Ed.; Wiley-VCH: Weinheim, 2013. (d) Sinnott, M. L. *Carbohydrate Chemistry and Biochemistry: Structure and Mechanism*, 2nd ed.; Royal Scoiety of Chemistry: Cambridge, U.K., 2013.

(2) For reviews, see: (a) Beck, E.; Hopf, H. In *Carbohydrates*; Dey, P. M., Ed.; Methods in Plant Biochemistry, Vol. 2; Academic Press: San Diego, 1990; pp 235–289. (b) Ferrier, R. J. In *Carbohydrate Chemistry*; Specialist Periodical Reports, Vol. 34; Royal Society of Chemistry: Cambridge, U.K., 2003; pp 175–187. This review comprehensively surveys the literature published in 2000 and cites 60 papers.

(3) Chandramohan, G.; Ignacimuthu, S.; Pugalendi, K. V. *Eur. J. Pharmacol.* **2008**, *590*, 437–443.

(4) For a recent review of plant-derived antidiabetic agents, see: (a) Hung, H.-Y.; Qian, K.; Morris-Natschke, S. L.; Hsu, C.-S.; Lee, K.-H. *Nat. Prod. Rep.* **2012**, *29*, 580–606. For a recent total synthesis of a family of plant-derived antidiabetic agents, see: (b) Xiao, Q.; Jackson, J. J.; Basak, A.; Bowler, J. M.; Miller, B. G.; Zakarian, A. *Nat. Chem.* **2013**, *5*, 410–416.

(5) Chandramohan, G.; Al-Numair, K. S.; Pugalendi, K. V. *Int. J. Integr. Biol.* **2009**, *5*, 176–181.

(6) Chandramohan, G.; Al-Numair, K. S.; Pugalendi, K. V. *African J. Biochem. Res.* **2009**, *3*, 198–204.

(7) Chandramohan, G.; Al-Numair, K. S.; Sridevi, M.; Pugalendi, K. V. *J. Biochem. Mol. Toxicol.* **2010**, *24*, 95–101.

(8) Chandramohan, G.; Al-Numair, K. S.; Alsaif, M. A.; Pugalendi, K. V. *J. Asian Nat. Prod. Res.* **2011**, *13*, 700–706.

(9) Chandramohan, G.; Ignacimuthu, S.; Pugalendi, K. V. Process for Preparation of a Novel Compound 3-Hydroxymethyl Xylitol with Antidiabetic Activity. Ind. Patent Appl. 268/CHE/2007 A, 2007 via the Indian Patent Office Journal, 2007 archive (accessed Sept 13, 2013): http://ipindia.nic.in/ipr/patent/journal_archieve/journal_2007/pat_arch_022007/official_journal_23022007.pdf.

(10) To our knowledge, dihydroxylation reactions have not previously been carried out on dendralenes. For a recent review of dendralenes, see: Hopf, H.; Sherburn, M. S. *Angew. Chem., Int. Ed.* **2012**, *51*, 2298–2338.

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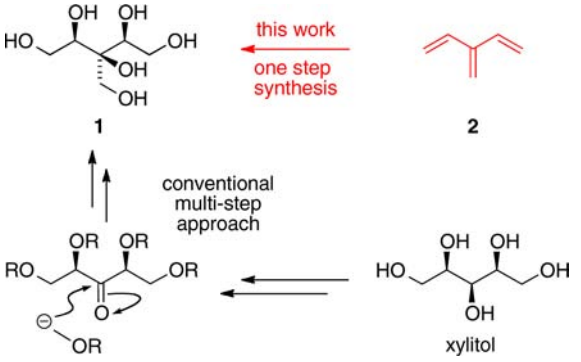
difficult to surpass, at least in terms of step economy.[11] The power of this approach is best demonstrated by consideration of the alternative, more traditional synthetic approaches to 3-(hydroxymethyl)xylitol **1** from a five-carbon sugar such as xylitol, which would involve, in the very least, selective protection of four of the five alcohol groups, oxidation of the unprotected secondary alcohol, stereoselective addition of a hydroxymethylene nucleophile equivalent, and deprotection (Scheme 1).

Scheme 1. Synthetic Approaches to 3-(Hydroxymethyl)xylitol (**1**)



Since the characterization data reported for the natural product did not, in our opinion, unequivocally establish its stereochemistry, we felt that an initial synthetic approach that allowed access to all possible stereoisomeric 3-(hydroxymethyl)-pentitol structures was the most prudent course of action. This would be followed by a subsequent optimization involving asymmetric dihydroxylation to target the specific stereoisomeric structure of the natural product. As will become apparent, this optimization was not necessary.

There are four possible stereoisomeric pentitols, namely xylitol, ribitol, arabitol, and *ent*-arabitol (Figure 1). The former two are *meso*-compounds, which differ in the configuration at the achirotopic but stereogenic central carbon.[12] Conversely, arabitol bears a chiral structure whose central carbon is, therefore, chirotopic. The symmetry of the chiral structure, however, results in this central carbon being nonstereogenic. The 3-hydroxymethyl analogues of these compounds have the same stereochemical attributes.

A review of the literature identified a relatively small number of papers describing the successful double

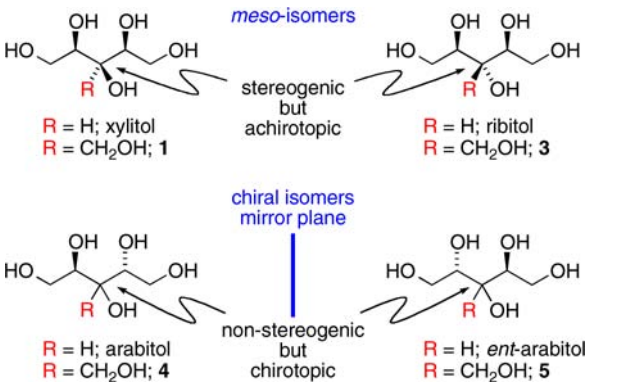
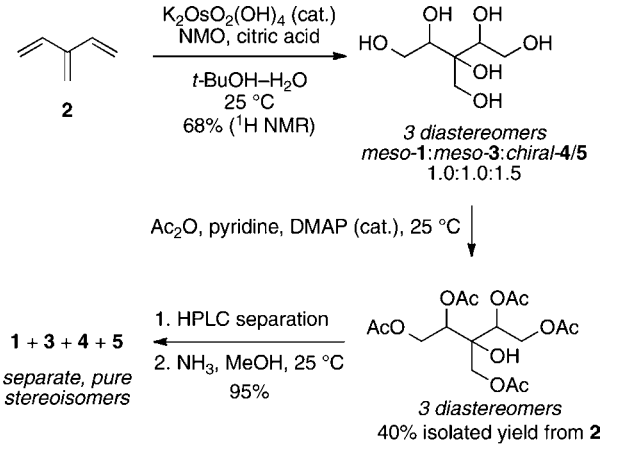


Figure 1. Four possible stereoisomeric pentitols and their 3-hydroxymethyl-substituted analogues.

dihydroxylation of conjugated dienes.[13] From these papers, we gleaned that Upjohn conditions[14] would be the method of choice to deliver the products of exhaustive dihydroxylation. In the event, 3-fold catalytic dihydroxylation of readily available[15] [3]dendralene (**2**) gave a ca. 1.0 (*meso*):1.0 (*meso*):1.5 (*chiral*) mixture of the three diastereomeric hexa-alcohols (Scheme 2). A little less of the chiral diastereomer is formed in this mixture than would be anticipated from a purely statistical outcome.[16] These stereoisomers are most conveniently separated by HPLC after conversion into their penta-acetate derivatives. The penta-acetate of 3-(hydroxymethyl)arabitol and its enantiomer were separated by chiral HPLC, and the four separated stereoisomers were subjected to deacetylation to deliver the free hexa-alcohols.

Scheme 2. Exhaustive Dihydroxylation of [3]Dendralene (**2**)



(11) (a) Wender, P. A.; Croatt, M. P.; Witulski, B. *Tetrahedron* **2006**, *62*, 7505–7511. (b) Wender, P. A.; Miller, B. L. *Nature* **2009**, *460*, 197–201.

(12) Mislow, K.; Siegel, J. *J. Am. Chem. Soc.* **1984**, *106*, 3319–3328.

(13) (a) Park, C. Y.; Kim, B. M.; Sharpless, K. B. *Tetrahedron Lett.* **1991**, *32*, 1003–1006. (This reference also includes an example of a triple dihydroxylation of a linear conjugated triene.) (b) Narkunan, K.; Nagarajan, M. *J. Chem. Soc., Chem. Commun.* **1994**, 1705–1706. (c) Armstrong, R. W.; Sutherlin, D. P. *Tetrahedron Lett.* **1994**, *35*, 7743–7746. (d) Armstrong, A.; Barsanti, P. A.; Jones, L. H.; Ahmed, G. *J. Org. Chem.* **2000**, *65*, 7020–7032. (e) Ahmed, M. M.; Berry, B. P.; Hunter, T. J.; Tomcik, D. J.; O'Doherty, G. A. *Org. Lett.* **2005**, *7*, 745–748. (f) Français, A.; Bedel, O.; Haudrechy, A. *Tetrahedron* **2008**, *64*, 2495–2524. (g) Caravano, A.; Field, R. A.; Percy, J. M.; Rinaudo, G.; Roig, R.; Singh, K. *Org. Biomol. Chem.* **2009**, *7*, 996–1008.

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(15) Bradford, T. A.; Payne, A. D.; Willis, A. C.; Paddon-Row, M. N.; Sherburn, M. S. *J. Org. Chem.* **2010**, *75*, 491–494.

(16) A 1.3 (*meso*):1.0 (*meso*):2.2 (*chiral*) ratio of diastereomers was obtained through Sharpless asymmetric dihydroxylation of [3]dendralene (**2**) with AD-mix-β.

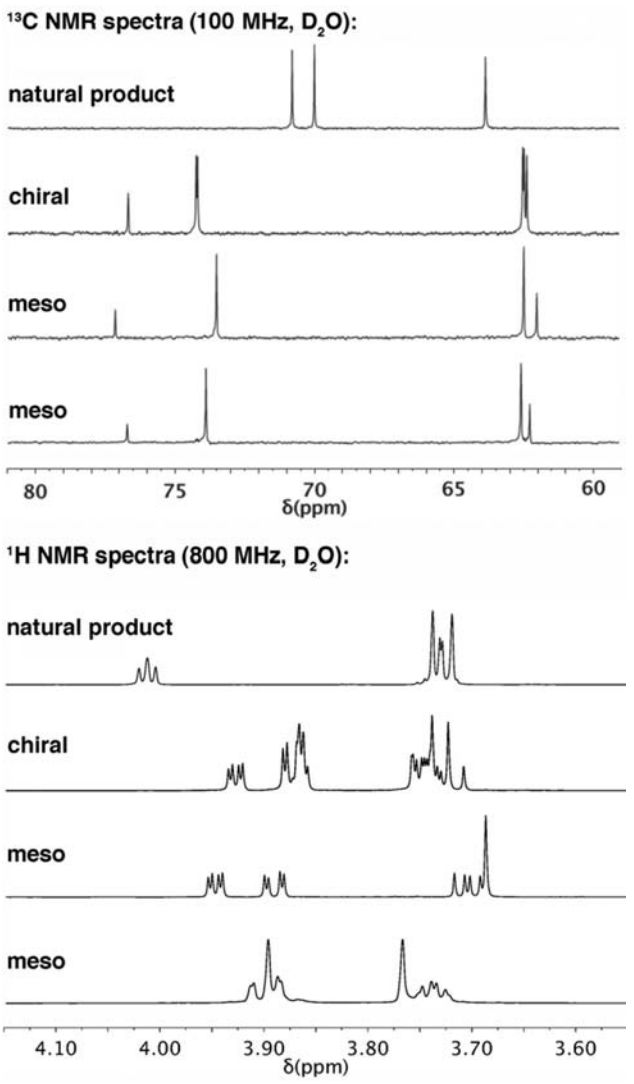
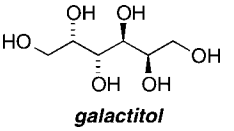


Figure 2. NMR spectra of the natural product from *Casearia esculenta* root and the three diastereomeric 3-(hydroxymethyl)-pentitols.

Broad band decoupled ^{13}C NMR spectra and ^{1}H NMR spectra of the three diastereomeric hexa-alcohols **1**, **3** and **4/5**,[17] along with that of the compound[18] isolated from the root of *Casearia esculenta* (Roxb.), are reproduced in Figure 2. None of the diastereomeric 3-(hydroxymethyl)pentitol spectra correlate with that of the natural product. Evidently, the structure assigned to the natural product is erroneous; it is neither 3-(hydroxymethyl)xylitol (**1**) nor a stereoisomer of 3-(hydroxymethyl)xylitol (i.e., **3**, **4**, or **5**).

(17) While the identities of the compounds have been unequivocally established, we have not been able to assign the structures of the two *meso* compounds.

(18) An analysis of ^{1}H and ^{13}C NMR spectra is provided in the Supporting Information. Spectra of galactitol are reproduced in Figure 2 for clarity.



galactitol

Figure 3. Corrected structure of the natural product from the root of *Casearia esculenta* (Roxb.).

The isolation chemists identified a molecular ion of m/z = 182 for the compound, which formulates for the correct molecular formula of $C_6H_{14}O_6$. The compound isolated from the root of *Casearia esculenta* (Roxb.) by Pugalendi and co-workers is, therefore, a constitutional isomer of 3-(hydroxymethyl)xylitol (**1**). During a database search,[19] we discovered that the spectroscopic data for the natural product are a match for galactitol (dulcitol, Figure 3), the reduced form of the second most abundant six-carbon sugar.

In summary, we have devised the shortest possible synthetic route to a structure erroneously identified as that of a branched chain sugar natural product. The approach employs a 3-fold dihydroxylation of the π-bond-rich hydrocarbon, [3]dendralene (**2**). The uncommonly rapid synthesis of all four possible 3-hydroxypentitol stereoisomers has allowed for a structural correction of the natural product in very short order.

The true value of modern day target-driven synthesis lies in its ability to promote a critical analysis of possible approaches and lead to better chemical syntheses. It is unfortunate that the structure assignment of 3-(hydroxymethyl)xylitol to the natural product was incorrect. Nevertheless, this structure inspired an unprecedented, one-step, six C–O bond-forming synthesis. The potency of this new approach for branched-chain sugar synthesis has thus been unequivocally established.

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Supporting Information Available. Experimental procedures and characterization data; ^{1}H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(19) We used the Spectral Database for Organic Compounds, SDBS, National Institute of Advanced Industrial Science and Technology (AIST), Japan: http://sdbs.riodb.aist.go.jp/sdbs/cgi-bin/cre_index.cgi (accessed Sept 13, 2013).

The authors declare no competing financial interest.