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An Unexpectedly Facile Cyclization of Polyhydric Alcohols

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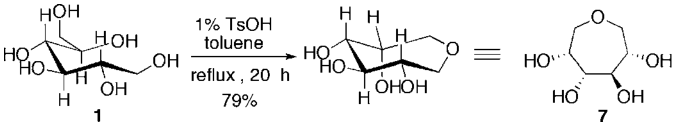
ABSTRACT



Contrary to previous reports in the literature, the reaction of polyhydric alcohols such as sorbitol or mannitol gives good yields of the tetrahydroxyoxepane derivative in the presence of an acid catalyst, in refluxing toluene, with complete retention of stereochemistry.

Of the methods that are available for the preparation of cyclic ethers, the intramolecular Williamson ether synthesis[1] and cyclodehydration of alcohols or diols are probably the most prevalent.[2] Formation of larger ring ethers is more difficult by this method, but the formation of five- and six-membered ring ethers from alcohols, using $Pb(OAc)_4$, HgO, or AgOAc, has been reported.[3a] Some examples have been reported for the preparation of the seven-membered ring ethers known as oxepanes.[3b−d] Seven- and eight-membered ring ethers have been identified as important structural motifs for several natural products, including cyclic ethers derived from *Laurencia*[4] and marine polycyclic ethers.[5] Yields of the larger ring ethers formed via cyclodehydration of diols tend to be rather poor. In one report done in supercritical fluids, 1,7-hexanediol was converted to the oxepane in only 8% yield along with 3% of 2-ethyltetrahydrofuran,[6] and mixtures of products are common. Other methodology has been used, such as the Lewis acid catalyzed cyclization of ω-alkenyl acetals,[7] which can generate good yields of substituted oxepanes. Good yields of substituted oxepanes were obtained by the *N*-iodocollidine salt mediated cyclization of ω-alkenyl alcohols and dienyl alcohols.[8] Other methods include an intramolecular Horner−Wadsworth−Emmons cyclization[9] and a ring-closing metathesis strategy from dienyl ethers.[10] The synthesis of polycyclic ether natural products has been accomplished using acid-catalyzed cyclization of intermediates that have multiple epoxide units. This approach generates seven- and eight-membered ring ethers that are highly substituted and with stereocontrol of the ring closure.[11]

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(1) Smith, M. B.; March, J. *March's Advanced Organic Chemistry*, 6th ed.; Wiley Interscience, New York, 2007, section 10-8, p 529. See: Kim, K. M.; Jeon, D. J.; Ryu, E. K. *Synthesis* **1998**, 835 for cyclization to an alkene in the presence of a catalytic amount of iodine.

(2) (a) For a list of reagents used to convert alcohols and phenols to ethers, see: Larock, R. C. *Comprehensive Organic Transformations*, 2nd ed.; Wiley-VCH, NY, 1999; pp 890−893. (b) Kotkar, D.; Ghosh, P. K. *J. Chem. Soc., Chem. Commun.* 1986, *650*; (c) Tagliavini, G.; Marton, D.; Furlani, D. *Tetrahedron* **1989**, *45*, 1187–1196. (d) Traynelis, V. J.; Hergenrother, W. L.; Hanson, H. T.; Valicenti, J. A. *J. Org. Chem.* **1964**, *29*, 123–129. (e) Costa, A.; Riego, J. M. *Synth. Commun.* **1987**, *17*, 1373–1376.

(3) (a) Smith, M. B.; March, J. *March's Advanced Organic Chemistry*, 6th ed.; Wiley: New York, 2007; pp 965−966. (b) Vowinkel, E. *Chem. Ber.* **1962**, *95*, 2997–3002. (c) Vowinkel, E. *Chem. Ber.* **1963**, *96*, 1702–1711. (d) Vowinkel, E. *Chem. Ber.* **1966**, *99*, 42–47.

(4) (a) Moore, R. E. In *Marine Natural Products*; Scheuer, P. J., Ed.; Academic: New York, 1978; Vol. 1, pp 43−121. (b) Erickson, K. In *Marine Natural Products*; Scheuer, P. J., Ed.; Academic: New York, 1983; Vol. 5, pp 131−257; (c) Faulkner, D. J. *Nat. Prod. Rep.* **1996**, *13*, 75–126.

(5) See Kadota, I.; Yamamoto, Y. *Acc. Chem. Res.* **2005**, *38*, 423–432.

(6) Gray, W. K.; Smail, F. R.; Hitzler, M. G.; Ross, S. K.; Poliakoff, M. *J. Am. Chem. Soc.* **1999**, *121*, 10711–10718.

(7) (a) Castaneda, A.; Kucera, D. J.; Overman, L. E. *J. Org. Chem.* **1989**, *54*, 5695–5707. (b) Blumenkopf, T. A.; Look, G. C.; Overman, L. E. *J. Am. Chem. Soc.* **1990**, *112*, 4399–4403. (c) Berger, D.; Overman, L. W.; Renhowe, P. A. *J. Am. Chem. Soc.* **1997**, *119*, 2446–2452.

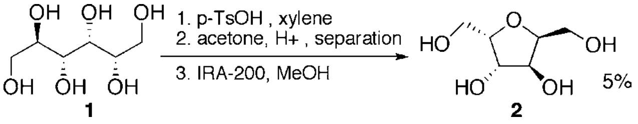
(8) Brunel, Y.; Rousseau, G. *J. Org. Chem.* **1996**, *61*, 5793–5800.

(9) See Taillier, C.; Bellostra, V.; Cossy, J. *Org. Lett.* **2004**, *6*, 2149–2151.

(10) See: Crimmins, M. T.; DeBaillie, A. C. *Org. Lett.* **2004**, *5*, 3009–3011, and ref 13 therein.

10.1021/ol9013427 CCC: $40.75

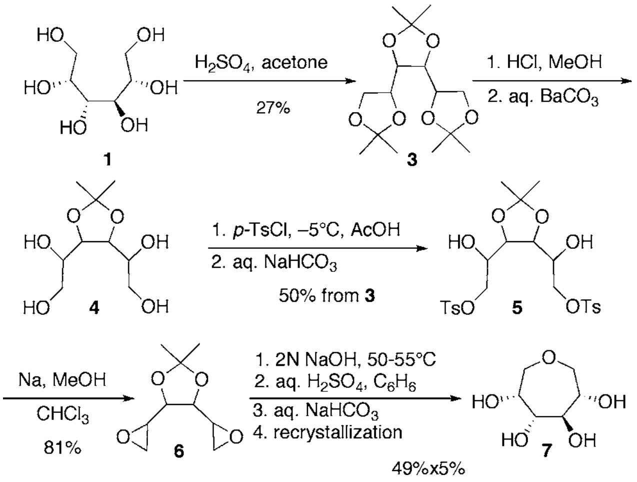
Scheme 1. Reported Acid-Catalyzed Cyclization of Sorbitol



Recent work in our laboratory includes an investigation into the role of alcohol additives with conducting polymers, and their ability to significantly enhance conductivity. As part of that investigation, we examined the reaction of sorbitol and other polyhydric alcohols with acid. Sorbitol is an important additive to conducting polymers, and the literature is clear in terms of the acid-catalyzed cyclization reactions. In a synthesis of C_2-symmetric diphosphinite ligands derived from carbohydrates by Diaz, Castillón, and co-workers, heating sorbitol (**1**, also known as D-glucitol) with tosic acid in xylene led to a mixture of products. Subsequent treatment with acetone and acid, separation and purification, and then passage through an ion exchange column led to 2,5-anhydro-L-iditol (**2**) in a low 5% yield.[12] An identical experiment was reported in a synthesis of linear, branched, and cyclic oligoglycerol derivatives, and when sorbitol was heated with methanesulfonic acid with isolation procedures similar to those reported by Diaz and Castillón, a 3% yield of **2** was obtained and it was suggested that 1,5-anhydrohexitrol and 1,4-anhydrohexitol (sorbitan) were produced as minor products.[13] The presence of these latter products was inferred from previous work without further proof. In these and other studies, the only reported products were five- and six-membered ring ethers, with no mention of oxepane derivatives.

Although direct cyclization of sorbitol to an oxepane has not been reported in the literature, there is a multistep synthesis of tetrahydroxyoxepanes from either sorbitol or mannitol. Starting with sorbitol (**1**), the fully protected triisopropylidene **3** was prepared and then reacted with HCl in MeOH to yield **4**. This 3,4-isopropylidene product was formed in only 27% yield as a mixture of the different isomers, presumably separated by recrystallization. The primary alcohol moieties were converted to the tosylates, resulting in **5**. The yield was about 50% and the product decomposed quickly, requiring that it be used immediately. Compound **5** reacted with sodium methoxide in $CHCl_3$ to yield the bis(epoxide) product **6** in a yield of 81%. Finally reaction with NaOH at approximately 55 °C for 10 h was followed by saturation with carbon dioxide to a pH of 8 and purification by slow recrystallization for several days to give the targeted tetrahydroxyoxepane, **7** (1,6-anhydrosorbitol), in very poor yield.[14] Stereochemistry is shown only for **1** and **7**, but the sequence produced enantiopure **7**.[14]

Scheme 2. Literature Synthesis of Tetrahydroxyoxepanes



Given the literature precedent, we were surprised to find that the reaction of sorbitol with 1% triflic acid in toluene at reflux gave a single isolated product in high yield. Initially, we anticipated that five- or six-membered ring anhydro sugars were formed.[15] Initial attempts to derivatize the unknown product by formation of the corresponding acetonide, by reaction with acetone and acid or with dimethoxypropane and acid, failed to give an isolable product. We therefore prepared a derivative using an excess of 3-fluorobenzoyl chloride to properly identify the product.[16] Proton NMR showed that the derivative was too symmetrical relative to products reported in the literature. The derivative did not have a hydroxymethyl unit, clearly indicating that our initial expectation was incorrect.[15b] Careful NMR analysis of the anhydro sugar product showed it to be a tetra(3-fluorobenzoate) derivative of an oxepane, 1,6-anhydrosorbitol (**7**).[17] Once the product was identified, determination of a yield was possible, and the conversion of **1** to **7** proceeded in 86% yield. This assignment resolved structural issues for the acid-catalyzed reaction. We next examined the reaction of D-mannitol (**8**) with triflic acid in refluxing toluene and obtained a product in 89% yield that was clearly different than the reaction with sorbitol and proved to be tetrahydroxyoxepane **9** (1,6-anhydromannitol).

In our acid-catalyzed reactions of **1** and **8**, the stereochemistry of the hydroxyl units in **7** and **9** were apparently retained. To confirm this, we prepared a synthetic standard

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(11) See for example, McDonald, F. E.; Wang, X.; Do, N.; Hardcastle, K. I. *Org. Lett.* **2000**, *2*, 2917–2919.

(12) Aghmiz, M.; Aghmiz, A.; Díaz, Y.; Masdeu-Bultó, A.; Claver, C.; Castillón, S. *J. Org. Chem.* **2004**, *69*, 7502–7510. Also see: Giacometti, J.; Milin, C.; Wolf, N.; Giacometti, F. *J. Agric. Food Chem.* **1996**, *44*, 3950–3954.

(13) Cassel, S.; Debaig, C.; Benvegnu, T.; Chaimbault, P.; Lafosse, M.; Plusquellec, D.; Rollin, P. *Eur. J. Org. Chem.* **2001**, *87*, 5–896.

(14) (a) Vargha, L.; Kasztreiner, E. *Chem. Ber.* **1960**, *93*, 1608–1616. (b) Vargha, L.; Kasztreiner, E. *Chem. Ber.* **1959**, *92*, 2506–2515.

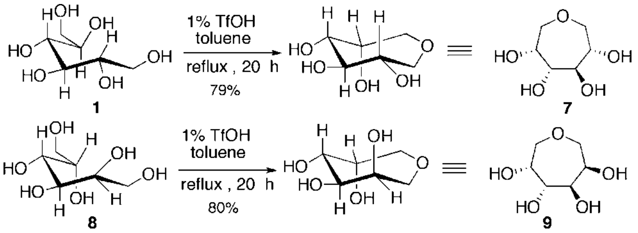
(15) (a) ORGN 101, Chemical Reactivity of Poly(ethylenedioxy)-thiophene (PEDOT), Smith, M. B.; Sotzing, G. A.; Onorato, A.; Kumar, A.; Delude, C. 232nd ACS National Meeting, San Francisco, CA, September 10, 2006. 234th ACS National Meeting, Boston, MA, August 20, 2007. (b) ORGN 359, The Chemical Reactivity Of Sorbitol With PEDOT; Onorato, A.; Navarathne, D.; Smith, M. B.; Sotzing, G. A.

(16) Yang, J.; Morton, M. D.; Hill, D. W.; Grant, D. F. *Chem. Phys. Lipids* **2006**, *140*, 75–87.

(17) (a) Sohár, P.; Vargha, L.; Kasztreiner, E. *Tetrahedron* **1964**, *20*, 647–653. (b) Vargha, L.; Kasztreiner, E. *Chem. Ber.* **1960**, *93*, 1608–1616.

(18) (a) Cohen, N.; Banner, B. L.; Laurenzano, A. J.; Carozza, L. *Org. Synth. Coll. Vol. 7* **1990**, 297–302. (b) Inoue, T.; Kitagawa, O.; Oda, Y.; Taguchi, T. *J. Org. Chem.* **1996**, *61*, 8256–8263.

Scheme 3. Acid-Catalyzed Cyclodehydration of Sorbitol and Mannitol



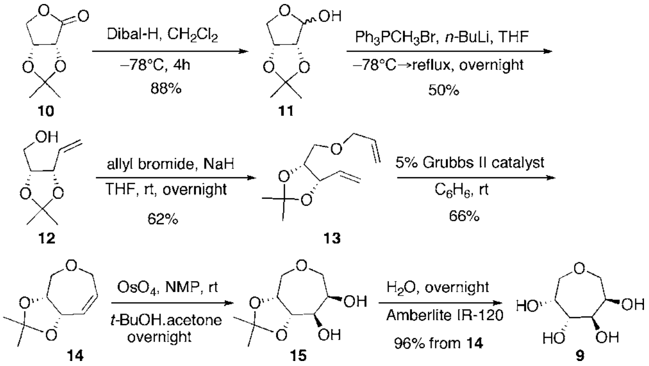
of the symmetrical mannitol derivative **9** by a six-step sequence starting with 2,3-*O*-isopropylidene-D-erythronolactone, **10**,[18] based on an approach reported by Sturino and co-workers.[19] Reduction with diisobutyl-aluminum hydride gave lactol **11** in 88% yield, and a Wittig reaction gave alkene-alcohol **12** in 50% yield. Subsequent treatment with base and then allyl bromide gave allylic ether **13** in 62% yield. Ring-closing metathesis with the Grubbs' II ruthenium catalyst led to **14** in 66% yield. Dihydroxylation with osmium tetroxide gave **1,** which was deprotected without further purification, to give tetrahydroxyoxepane **9** in 96% yield. Synthetic **9** was identical in all respects with that obtained by the reaction of **8** with *p*-TsOH or triflic acid in a single step. With this synthesis, we have demonstrated that D-mannitol (**8**) reacts with an acid catalyst to give tetrahydroxyoxepane, **9**, with complete retention of the stereochemical centers. Given the stereoselective nature of the mannitol reaction and the NMR identification of the sorbitol product, we are confident in the structural integrity of **7** as the sorbitol product.

Confirmation that polyols are converted to the cyclic ether under mild conditions and in good yield prompted us to examine the reaction of other commercially available polyhydric alcohols with *p*-TsOH as well as triflic acid. We observed that these polyols undergo cyclodehydration with high stereoselectivity, both with a catalytic amount of acid or with 1 molar equiv of the acid. With 1% *p*-TsOH, 1% triflic acid or with 1 full equiv of *p*-TsOH, sorbitol (**1**) is converted to **7** and D-mannitol (**8**) is converted to **9**. These results are shown in Table 1. In addition, we have shown that *meso*-erythritol (**16**) reacts with either *p*-TsOH or triflic acid to form 2,3-dihydroxytetrahydrofuran **17**. In addition, the acid-catalyzed reaction of threitol (**18**) leads to **19**. In future work, these reactions may be extended to more highly functionalized polyols and even sugars.

Table 1. Cyclodehydration of Polyhydric Alcohols

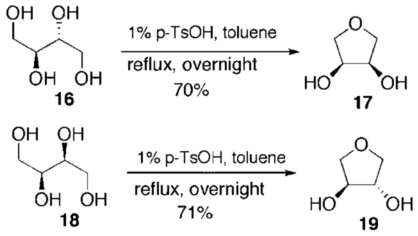
	cyclic ether		
polyol	1% TsOH	1 equiv TsOH	1% TfOH
1	**7** (79%)	**7** (84%)	**7** (86%)
8	**9** (80%)	**9** (76%)	**9** (89%)
16	**17** (70%)		**17** (75%)
18	**19** (71%)		**19** (73%)

Scheme 4. Multistep Synthesis of the 1,6-Anhydromannitol Synthetic Standard



An important question remains. Why have previous experiments failed to observe this transformation? The answer may never be known, but previous experiments used more vigorous conditions in some cases and derivatized the products prior to isolation. Our control experiments have shown that oxepane **7** decomposes when heated with sulfuric acid, although it is stable to heating with *p*-TsOH. Perhaps more relevant is our observation that **7** did not react with acetone and an acid catalyst or with dimethoxypropane and an acid catalyst under standard conditions. It is possible that previous work selectively derivatized the reported products, and it is important to note that the isolated yields reported in the literature were rather low.

Scheme 5. Acid-Catalyzed Conversion of Erythritol and Threitol to Dihydroxytetrahydrofurans



Despite previous reports, polyols are cleanly converted to the cyclic ethers under our conditions.[20] The relevance of polyol cyclodehydration to our ongoing work with conducting polymer additives is under investigation. More pertinent to this discussion

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(19) Wong, J. C. Y.; Lacombe, P.; Sturino, C. F. *Tetrahedron Lett.* **1999**, *40*, 8751–8754.

(20) A catalytic amount of toluenesulfonic acid (1% mmol in 5 mL of toluene) was added to a solution of D-sorbitol (0.18 g, 1 mmol) in 60 mL of toluene via syringe, under a positive pressure of nitrogen. The solution was heated to reflux overnight and cooled, and the solution was treated with 10 mg of $NaHCO_3$. The particulate matter was subsequently removed by filtration and washed with diethyl ether (10 mL). The toluene filtrate was concentrated in vacuo without heat to give 1,6-anhydrosorbitol **7** as a pale red waxy solid (129 mg, 0.786 mmol, 79%). Mp, 29−30°C. ^1H NMR (CD_3OD): δ 4.54 (t, $J = 4.7$ Hz, 1H), 4.38 (d, $J = 3.7$ Hz, 1H), 4.28 (dt, $J = 5.4, 6.9$ Hz, 1H), 4.2 (s, 1H), 3.9−3.8 (m, 3H), 3.45 (dt, $J = 7.5, 8.3$ Hz, 1H). ^{13}C NMR (CD_3OD): δ 88.3, 81.9, 76.2, 75.2, 72.2, 71.4. MS (EI) m/z 164, 147, 129, 111 102, 87, 69.

is the observation that polyols are converted to cyclic ethers in good yield and with retention of stereochemistry. These transformations may have value in the synthesis of natural products that bear these structural motifs.

Acknowledgment. We thank Dr. Srikanth Rapole, who obtained the exact mass determination of the sorbitol tetra(3-fluorobenzoate) derivative.

Supporting Information Available: Full experimental details for all cyclodehydration experiments, details of the synthesis of **9** from **10**, and spectral data for the tetra(3-fluorobenzoate derivative of **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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