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One-Pot Regio- and Stereoselective Cyclization of 1,2,*n*-Triols

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Substituted tetrahydrofurans and tetrahydropyrans represent versatile synthetic building blocks in a variety of natural products, such as polyether antibiotics and annonaceous acetogenins.^{1,2} The Lewis acid-catalyzed intramolecular ring-opening of epoxides by alcohols is one of the most popular methods to construct cyclic ethers in an efficient and stereocontrolled manner.^{3,4} Although the necessary epoxide substrates can be delivered with a variety of well-established methods, including the Sharpless asymmetric epoxidations⁵ and the Jacobsen–Katsuki⁶ and Shi epoxidations,⁷ the structural requirements of the parent olefin can limit synthetic strategy.

Compared to asymmetric epoxidations, the well-defined Sharpless asymmetric dihydroxylation is less limited in its choice of substrates. Since its inception,⁸ substantial progress has been attained in the development of ligands for the SAD that generate high levels of enantioselectivity from unfunctionalized olefins of various substitution patterns.⁹ However, to utilize the chirality induced by the Sharpless asymmetric dihydroxylation in intramolecular cyclizations to generate cyclic ethers, the diol often needs to be converted to an epoxide or reactive equivalent,^{10,11} such as a cyclic sulfate.¹²⁻¹⁴ Noteworthy is the method developed by Kolb and Sharpless in which vicinal diols are converted to their corresponding epoxides via the use of a cyclic ortho ester.¹⁵ However, these conversions are often multistep and/or intolerant of certain functional groups. We have effectively addressed these shortcomings by the development of a mild, convenient, one-pot method to access cyclic ethers directly from 1,2,*n*-triols via the intermediacy of a cyclic ortho ester.

As depicted in the scheme in Table 1, the overall strategy depends on the in situ generation of an ortho ester (3) via transortho esterification of trimethyl orthoacetate with a 1,2-diol (1a). The subsequent ionization of the intermediate ortho ester with a Lewis acid leads to a reactive acetoxonium species (4), which upon intramolecular displacement with the pendant hydroxyl yields the cyclized ether (2a). A short list of Lewis acids screened to effect the cyclization employing *trans*-decane-1,4,5-triol 1a is provided in Table 1. We were pleased to find that after treatment of 1a with 1.2 equiv of trimethyl orthoacetate and a catalytic amount of PPTS (0.1 equiv) in dichloromethane, followed by addition of 0.1 equiv of BF₃-Et₂O, the cyclization proceeded to deliver product 2a as a single diastereomer in excellent yield (entry 5). Other Lewis acids screened also delivered the desired 2a, albeit in lower yields (Table 1).

A variety of 1,2,*n*-triols were synthesized and subjected to the one-pot cyclization reaction (Table 2). The following details are noteworthy: (1) The substitution pattern of the nucleophilic hydroxyl did not affect the efficiency and stereoselectivity of the reaction. Substrates with a primary, secondary, or tertiary hydroxyl group all afforded good yields of the desired product (entries 1-7, Table 2). An exception was the use of a tertiary cyclic alcohol to generate a spiro compound, which was unsuccessful (data not shown). Moving the nucleophilic alcohol one carbon away from the *pro*spiro center (entry 9) again resulted in successful generation of the cyclic ether. (2) Comparable results were obtained for syn and anti vicinal diols (entries 1 and 2). (3) Bicyclic structures can be obtained (entries 8–11). It is noteworthy that triol **1j** yielded the six-member

Table 1. One-Pot Cyclization of trans-1,4,5-Decanetriol with Various Acid Promoters



entry	LA	equiv	time	temp	% yield ^a
1	AcCl	1.2	5 min	0 °C	0
2	AlMe ₃	1.0	12 h	rt	12
3	TMSCl	1.2	1 h	0 °C	72
4	TMSOTf	1.2	5 min	0 °C	91
5	BF ₃ •Et ₂ O	0.1	1 h	0 °C	99

^a Yields are based on GC analysis.

ring product 2j instead of the expected tetrahydrofuran. This is most likely due to the reversibility in the ring-opening of the anticipated five-member ring product afforded by the presence of the aryl group that eventually leads to the production of the more thermodynamically stable six-member ring. (4) Partially deacetylated products were observed along with the desired product in some cases (entries 6, 11, and 15), possibly as a result of transesterification of the acetate with the methanol generated during the course of the reaction.

The aromatic substituted 1,2,5-triol 11 gave mixtures of the tetrahydrofuran 21 and tetrahydropyran 51 products. Presumably, the stability of the intermediate carbocation allows nucleophilic attack at the benzylic position (forming a six-member ring) to compete with the expected 5-exo process leading to the five-member ring product. Evidence for this supposition was obtained via the onepot cyclization of triols 1n and 10, which contain electron-donating and electron-withdrawing aromatic groups, respectively. As anticipated, the *p*-methoxyaryl group in **1n** led to the formation of tetrahydropyran products 2n and 5n, exclusively, in contrast to the reaction of 10, which yielded only tetrahydrofuran 20. The formation of the epimeric 2n also points to the stable carbocationic nature of the intermediate; in fact, treatment of a pure sample of 2n or 5n with BF₃·Et₂O gave isomerization to a mixture of 2n and 5n in a similar ratio observed for cyclization of **1n**. Interestingly, cyclization of triol 1m (epimer of 1l) yielded the six-member ring product 2m, exclusively. A possible explanation is illustrated in Scheme 1. The phenyl group in the anti triol 11 is axially juxtaposed in the putative transition state. Presumably, the increased steric repulsion counterbalances the greater carbocation stability at the benzylic position and thus leads to two pathways yielding a mixture of five- and six-member ring products. On the other hand, the syn triol 1m would have its aryl group situated equatorially in the transition state, therefore, enjoying both steric relief and electronic stability, which results in the formation of only the six-member ring product.

Five- and six-member cyclic ethers were also produced from 1,2,4- and 1,2,6-triols in good yields using our one-pot process



^a Yields are based on isolation of product. Yields reported in parentheses refer to the one-step cyclization methodology, utilizing BF₃·Et₂O as the sole catalytic acid for both ortho ester formation and cyclization. ^b Toluene, 80 °C.

Scheme 1



(entries 16 and 17). Cyclization of 1p leads to the tetrahydrofuran 2p without any evidence for the formation of an oxetane; similarly, cyclization of 1q leading to 2q proceeds without the formation of an oxepane. Oxepanes could be formed from 1,2,7-triols as evidenced by the conversion of 1r to 2r by heating to 80 °C in toluene, albeit in modest yield. The major side products of this reaction were monoacetylations of the triol, presumably from hydrolysis of the acetoxonium intermediate.

The general reaction scheme could be further simplified with use of BF3·Et2O to promote both transortho esterification and the subsequent cyclization. As a demonstration, triols 1a, 1b, and 1q were converted to the corresponding cyclic ethers in high yields using only BF₃·Et₂O in an essentially one-step reaction (Table 2, yields given in parentheses).

Finally, to demonstrate the stereospecific nature of this reaction, an enantiomerically enriched triol was used as the starting material for the cyclization. Oxidation of trans-4-decenol with AD-mix- α gave (4S,5S)-decane-1,4,5-triol 1b in 91% ee. Gratifyingly, the tetrahydrofuran product was obtained with complete transfer of stereochemical fidelity (92% ee).

In conclusion, we report a general and practical cyclization to construct THF and THP structures from 1,2,n-triols based on the Lewis acid-mediated cyclization of cyclic ortho esters. In this manner 1,2-diols can be regarded as epoxide surrogates in reactivity, thus increasing the repertoire of transformations available from asymmetric dihydroxylations.

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Supporting Information Available: Experimental procedures and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

References

- (1) Dutton, C. J.; Banks, B. J.; Cooper, C. B. Nat. Prod. Rep. 1995, 12, 165-181
- (2) Zeng, L.; Ye, Q.; Oberlies, N. H.; Shi, G.; Gu, Z. M.; He, K.; McLaughlin, J. L. Nat. Prod. Rep. **1996**, 13, 275–306. Boivin, T. L. B. Tetrahedron **1987**, 43, 3309–3362. Koert, U. Synthesis **1995**, 115–132.

- (5)Johnson, R. A.; Sharpless, K. B. In Catalytic Asymmetric Synthesis; Ojima, I., Ed.; Wiley-VCH: New York, 1993; pp 101–158. (6) Jacobsen, E. N. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; Wiley-
- VCH: New York, 1993; pp 159–202. Frohn, M.; Shi, Y. *Synthesis* **2000**, 1979–2000. Jacobsen, E. N.; Marko, I.; Mungall, W. S.; Schroder, G.; Sharpless, K.
- B. J. Am. Chem. Soc. 1988, 110, 1968-1970. (9)Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. Chem. Rev. 1994,
- 94. 2483-2547 Fleming, P. R.; Sharpless, K. B. J. Org. Chem. 1991, 56, 2869–2875. Golding, B. T.; Hall, D. R.; Sakrikar, S. J. Chem. Soc., Perkin Trans. 1
- **1973**. 1214-1220
- (12) Kalantar, T. H.; Sharpless, K. B. Acta Chem. Scand. 1993, 47, 307-313. (13) Byun, H. S.; He, L. L.; Bittman, R. Tetrahedron 2000, 56, 7051-7091.
- (14) Beauchamp, T. J.; Powers, J. P.; Rychnovsky, S. D. J. Am. Chem. Soc. 1995, 117, 12873–12874.
- Kolb, H. C. Sharpless, K. B. Tetrahedron 1992, 10515-10519.
- Williams, D. R.; Ĥarigaya, Y.; Moore, J. L.; D'sa, A. J. Am. Chem. Soc. 1984, 106, 2641-2644

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