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

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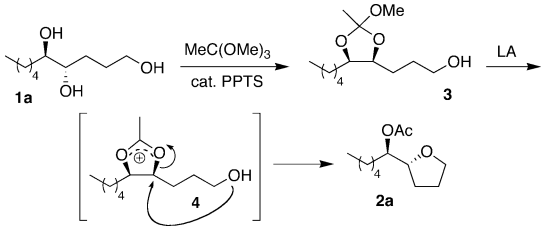
Substituted tetrahydrofurans and tetrahydropyrans represent versatile synthetic building blocks in a variety of natural products, such as polyether antibiotics and annonaceous acetogenins.[1,2] The Lewis acid-catalyzed intramolecular ring-opening of epoxides by alcohols is one of the most popular methods 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 epoxidation[5] and the Jacobsen−Katsuki[6] 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 $BF_3{\cdot}Et_2O$, 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 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.

***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 | $BF_3{\cdot}Et_2O$ | 0.1 | 1 h | 0 °C | 99 |

[a] Yields are based on GC analysis.

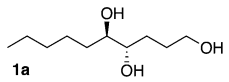
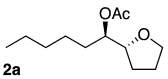
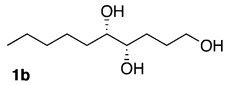
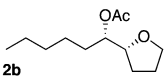
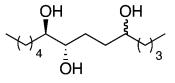
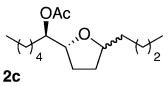
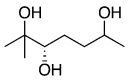
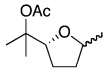
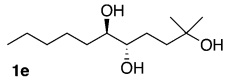
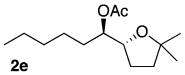
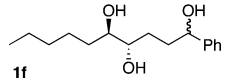
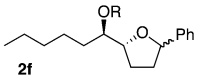
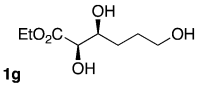
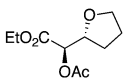
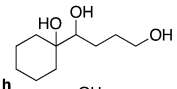
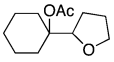
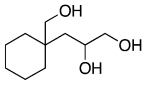
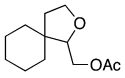
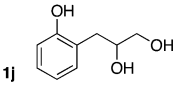
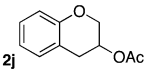
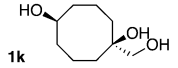
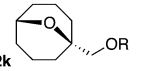
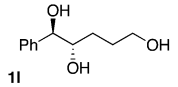
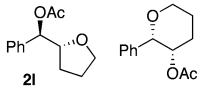
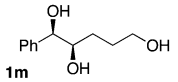
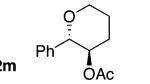
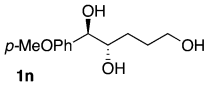
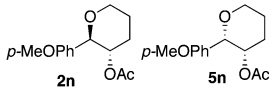
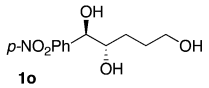
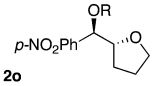
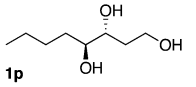
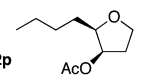
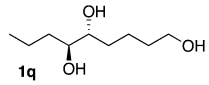
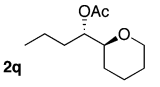
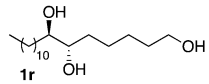
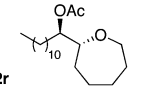
The aromatic substituted 1,2,5-triol **1l** gave mixtures of the tetrahydrofuran **2l** and tetrahydropyran **5l** products. Presumably, the stability of the intermediate carbocation allows nucleophilic attack at the benzylic position (forming a six-member ring) to compete with the expected 5-exo process leading to the five-member ring product. Evidence for this supposition was obtained via the one-pot cyclization of triols **1n** and **1o**, 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 **1o**, which yielded only tetrahydrofuran **2o**. 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 $BF_3{\cdot}Et_2O$ 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 **1l** 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



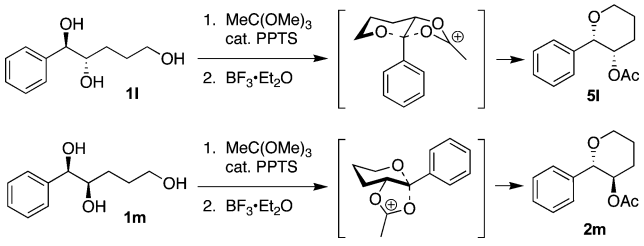
10.1021/ja043002i CCC: $30.25 

***Table 2.*** Cyclization of 1,2,*n*-Triols[a]

| entry | starting triol | product | yield |
|---|---|---|---|
| 1 |  **1a** |  **2a** | 81(98) |
| 2 |  **1b** |  **2b** | 74(94) |
| 3 |  **1c** |  **2c** | 82 |
| 4 |  **1d** |  **2d** | 52 |
| 5 |  **1e** |  **2e** | 80 |
| 6 |  **1f** |  **2f** | 55 (R=Ac)<br>36 (R=H) |
| 7 |  **1g** |  **2g** | 62 |
| 8 |  **1h** |  **2h** | 50 |
| 9 |  **1i** |  **2i** | 89 |
| 10 |  **1j** |  **2j** | 84 |
| 11 |  **1k** |  **2k** | 33 (R=Ac)<br>18 (R=H) |
| 12 |  **1l** |  **2l** **5l** | 48 (**2l**)<br>24 (**5l**) |
| 13 |  **1m** |  **2m** | 83 |
| 14 |  **1n** |  **2n** **5n** | 73 (**2n**)<br>20 (**5n**) |
| 15 |  **1o** |  **2o** | 60 (R=Ac)<br>8 (R=H) |
| 16 |  **1p** |  **2p** | 71 |
| 17 |  **1q** |  **2q** | 78(88) |
| 18 |  **1r** |  **2r** | 47[b] |

[a] Yields are based on isolation of product. Yields reported in parentheses refer to the one-step cyclization methodology, utilizing $BF_3{\cdot}Et_2O$ 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 $BF_3{\cdot}Et_2O$ 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 $BF_3{\cdot}Et_2O$ 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 (4*S*,5*S*)-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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**Note Added in Proof.** We are grateful to Professor David Williams (Indiana University) for making us aware of a seminal paper (ref 16) in this area.

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

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