Medium-Sized Rings

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A Migratory Ether Formation Route to Medium-Sized Sugar Mimetics

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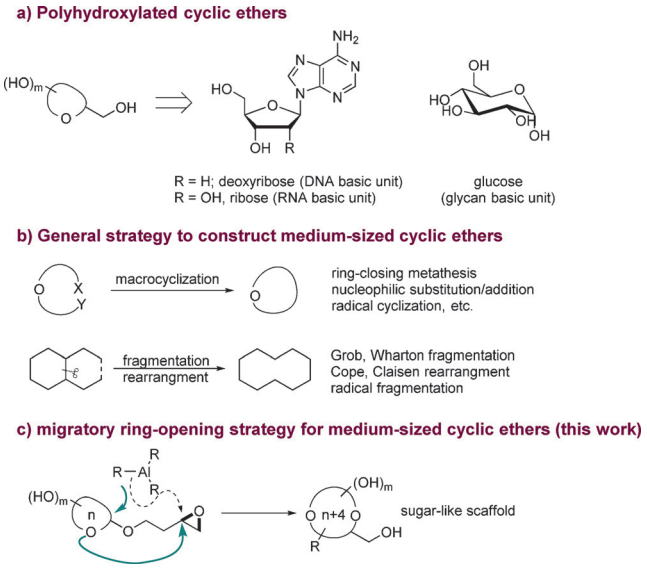
Abstract: *Polyol-substituted cyclic ethers are fundamental building blocks of biomolecules. The position and stereochemistry of multiple hydroxy substituents of cyclic ethers play a central role in their biological function. Current methods for the synthesis of such structures are limited to "naked" ring products with no or few substituents. Here we describe a general route to medium-sized polyol cyclic ethers using a migratory ether formation strategy. In contrast to the common pathway of direct opening of epoxides, Me_3Al was found to promote an unprecedented ether addition reaction, opening a neighboring epoxide. The resulting oxonium intermediate triggers a 1,3-methyl shift to yield 2-deoxyribital products. When the hemiacetal auxiliary is a monosaccharide, the sugar ring is expanded by four atoms to give the corresponding 9- to 11-membered analogues. This method provides an entry into the untapped chemical space of medium-sized sugar mimetics.*

Polyol-substituted cyclic ethers are fundamental structural motifs for biomolecules, natural products and pharmaceutical agents.[1] Five- and six-membered polyol cyclic ethers, pentoses and hexoses for example, are basic building blocks of the backbones of DNA, RNA and glycans (Scheme 1a).[2] The structural and functional diversity of these biomolecules originates from their numerous isomers with differently substituted hydroxy groups.[3] As a consequence, considerable effort has been devoted to the synthesis of polyol cyclic ethers.[4] Many syntheses of five- and six-membered monosaccharides have been reported but synthetic and biological studies of larger ring analogues are very few.[5] In general, 7- to 11-membered cyclic scaffolds, often referred to as medium-sized rings, are the most difficult of all ring systems to construct. Kinetically, large entropic penalties significantly reduce the probability of the appropriate cyclization reaction. Thermodynamically, transannular orbital interactions in medium-sized rings create extra ring strain in both the transition states and the products. Among medium sized cyclic systems, 9- to 11-membered rings are most challenging from a synthetic point of view. There are two general approaches to this problem: macrocyclization[4,6] and ring expansion[7] (Scheme 1b), but the applicability of these methods quickly diminishes as the number of substituents, especially hydroxy groups, increases. These OH groups complicate the critical ring closure process by creating extra bond opposition forces (Pitzer strain) and unintended hydrogen bonds. So far, no synthesis is available for medium-sized polyol cyclic ethers, a class of molecules that might possess sugar-like properties. Here, we report a migratory ether formation strategy to synthesize 9- to 11-membered cyclic ethers (Scheme 1c). This unprecedented transformation features a relay ring-opening process that expands the ring size of the starting material by 4 atoms. In view of the readily accessible 5-, 6-, and 7-membered cyclic ethers, this protocol is particularly attractive for the construction of 9- to 11-membered medium-sized rings. Importantly, this method allows convenient stereospecific introduction of multiple hydroxy substituents using starting materials derived from sugars.



Scheme 1. Polyol cyclic ethers.

This novel transformation (Scheme 1c) emerged from our investigation of a nucleophilic epoxide-opening reaction.[8] Epoxy methanols, readily available in optically enriched forms via the Sharpless epoxidation reaction,[9] are popular synthons for a number of highly sought-after chiral scaffolds.[10] Epoxy alcohols are particularly susceptible to various nucleophilic addition reactions in the presence of a Lewis acid.[11] With tight chelation control, these reactions generally occur with exclusive regio- and stereochemical control. Ring-opening of epoxy alcohols using an alkylaluminum reagent for example, is a classical method for the preparation of useful chiral diols with an adjacent carbon stereogenic center.[12]

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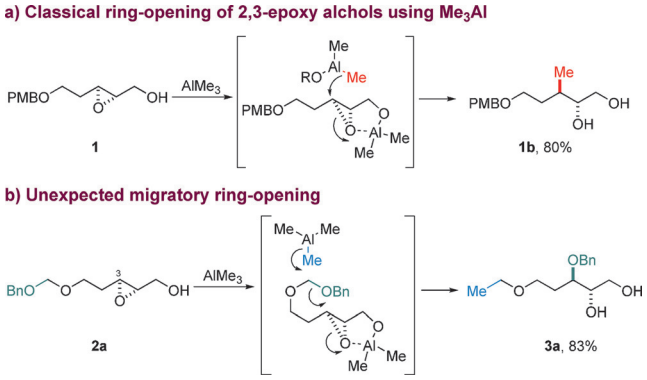
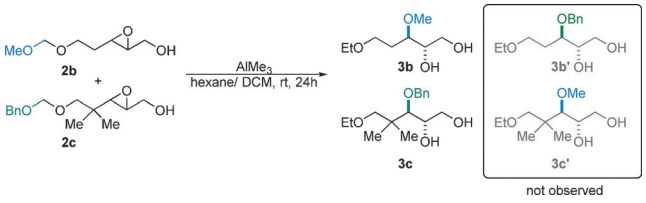
When we treated Me_3Al with a substrate (**1**) bearing a *p*-methoxybenzyloxy (PMBO) group two carbons away, the expected 3-methylpentanediol derivative **1b** was obtained in high yield as the sole product (Scheme 2a).[13] In contrast, we found that the epoxide-opening pathway was completely avoided when the PMBO group was replaced by benzyloxymethoxy (BOMO) group. Instead of opening the epoxide directly, Me_3Al attacked the hemiacetal carbon, causing the benzyloxy residue to open the epoxide. As a result, the protected 2-deoxyribital (**3a**) was isolated in 83% yield (Scheme 2b).



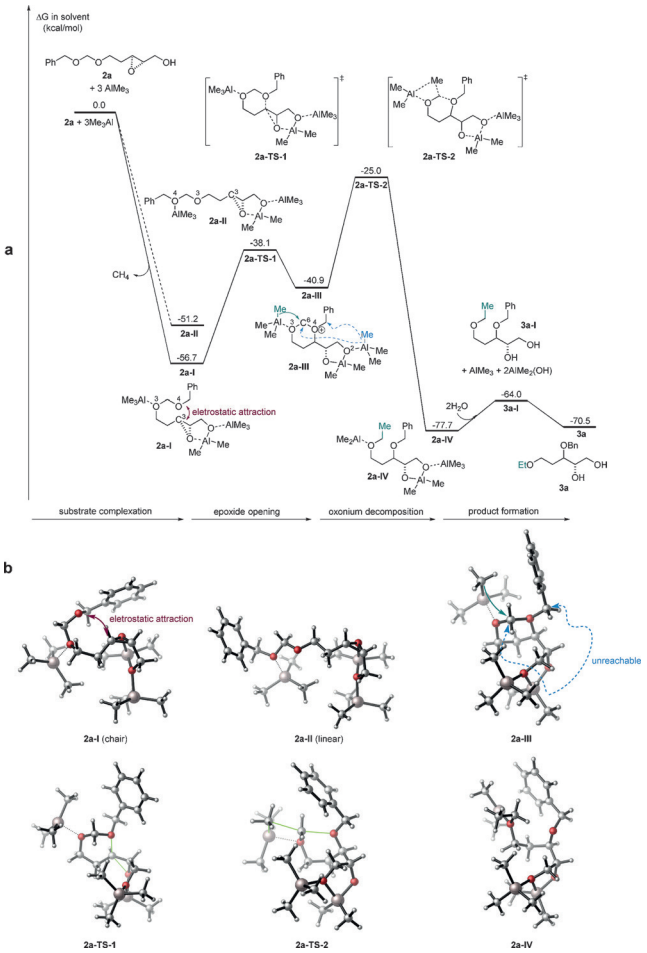
Scheme 2. Ring-opening reactions of 2,3-epoxy alcohols using trimethylaluminum.

Migration of the alkoxy group could be either intra- or intermolecular. For intramolecular transfer, epoxide-opening would occur either before the attack of Me_3Al or in concert with it. In the intermolecular pathway, Me_3Al would react well before the opening of the epoxide. In order to distinguish these two possibilities, a cross-over experiment was carried out. A pair of substrates with different hemiacetal groups was subjected together to reaction with Me_3Al. In order to distinguish the intra- and intermolecular products, extra methyl groups were introduced to one substrate. High resolution mass spectrometry (HRMS) clearly showed the existence of only the intramolecular products (Scheme 3).



Scheme 3. Crossover experiments.

The reaction is sensitive to the amount of Me_3Al used. The reaction employing 1.0 equivalent of Me_3Al led to a complex mixture with very little 2-deoxyribital product. In the presence of 2.0 equivalents of Me_3Al, the product (**3a**) was isolated in 22% yield. Complete conversion was achieved with 3.0 equivalents of the aluminum reagent. These data suggest that three Me_3Al molecules are involved in this reaction. A density functional theory (DFT) study was conducted for the reaction using epoxymethanol (**2a**) and Me_3Al (Scheme 4). Substrate **2a** has two stable conformations and the folded, chair-like conformer is 3.0 kcal mol^{-1} more stable than the linear conformer. Upon mixing Me_3Al with **2a**, gas bubbles were immediately observed and the reaction became highly exothermic. Calculations suggested two molecules of Me_3Al bound to the epoxy alcohol oxygens, releasing one molecule of methane. The third Me_3Al coordinates to either O3 or O4 of the hemiacetal. Computer minimization yielded two distinct complex conformers **2a-I** (O3-bonded) and **2a-II** (O4-bonded), which adopt chair and linear conformations, respectively. Due to the electrostatic attraction between O4 and C3, **2a-I** is more stable than **2a-II** by 5.5 kcal mol^{-1}. This interaction facilitates epoxide opening by O4 to generate the oxonium intermediate **2a-III**, in which the hemiacetal carbon C6 is exposed to the O3-bound Me_3Al. Subsequent 1,3-methyl migration gives the desired product **3a**. Based on the minimized structure of **2a-III**, the O2-bound Me_3Al is too distant to react with either C6 or the benzylic carbon.



Scheme 4. Energy profiles and optimized structures for complex formation, epoxide-opening and methylation steps.

In addition to Me_3Al, Et_3Al and Et_2Zn were also tested in this migratory ether formation reaction. Comparable yields

were obtained for higher order alkylaluminum reagents but Et_2Zn alone failed to react with substrate **2a**. However, addition of 3.0 equivalents of $ZnCl_2$ or trifluoroacetic acid led to smooth conversion to the desired 2-deoxyribitol products. Various 2,3-epoxy pentanol analogues were prepared and examined (Figure 1). The reaction conditions showed gener-

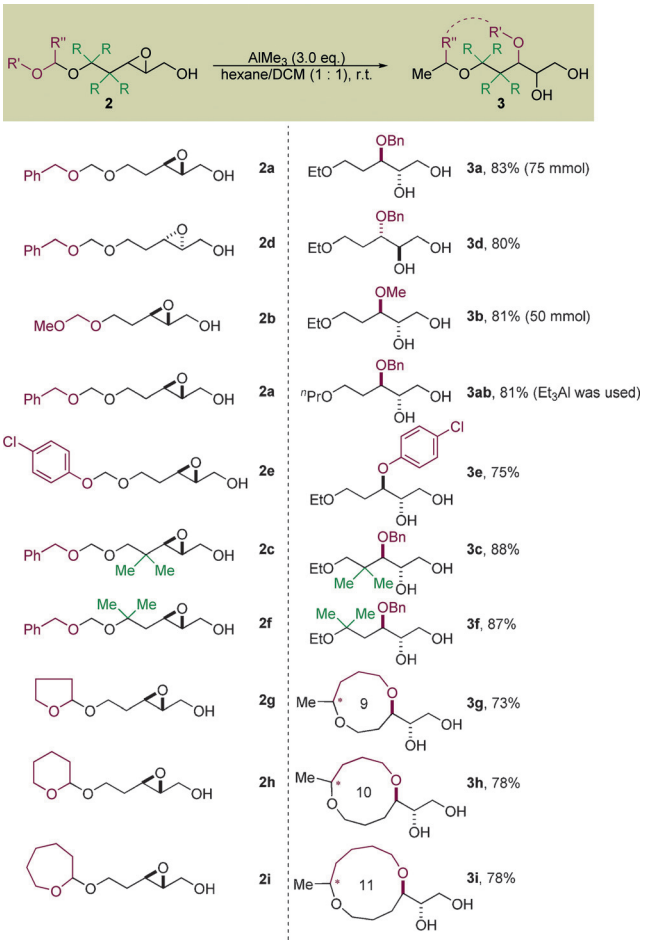
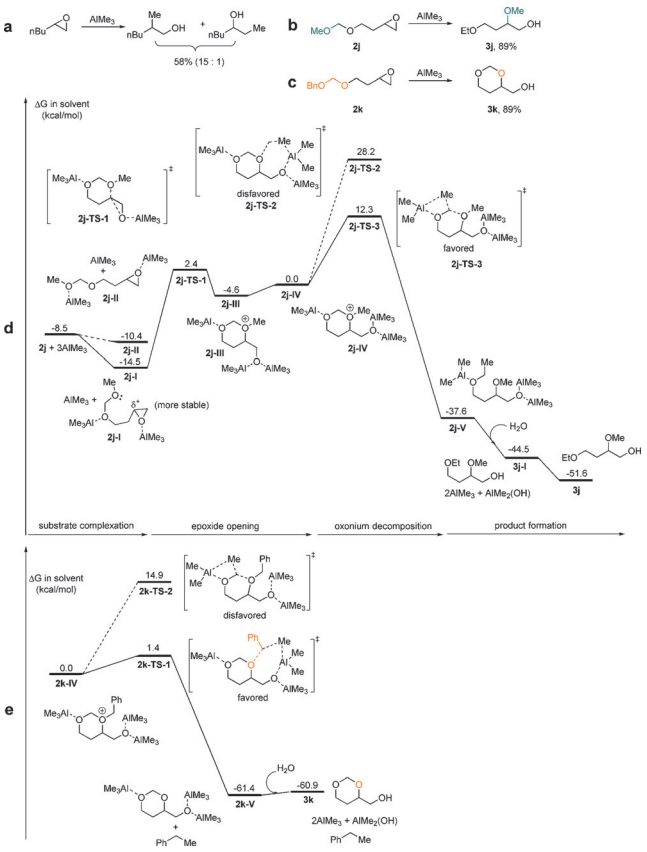


Figure 1. $AlMe_3$-mediated migratory epoxide-opening reaction. The reactions were carried out at room temperature for 24 h, except for products **3c** and **3f**. Complete conversions to these two products were accomplished in 4–6 h.

ality towards hemiacetal, trialkylaluminum and substituents at C4 and C5. Good yields were uniformly observed after 24 h. Interestingly, gem-dialkyl substituted substrates reacted noticeably more rapidly. The reactions reached completion after 4 to 6 h, the beneficial Thorpe–Ingold effect of these substituents apparently overriding the steric hindrance. When a phenol-derived hemiacetal was used, the phenoxy group migrated with similar efficiency despite its reduced nucleophilicity. Encouraged by these results, we examined cyclic hemiacetal analogues and found that 5-, 6-, and 7-membered cyclic hemiacetals all participate in this migratory ring expansion reaction leading, respectively to 9-, 10, and 11-membered cyclic ethers which were formed with good yields. Due to lack of communication between the epoxyalcohol and hemiacetal functionalities, no steric bias was observed when cyclic hemiacetal contains a racemic stereogenic center. The reaction could be conveniently scaled up to 75 mmol without compromising the yields.

We next examined whether the terminal alcohol is required for the reaction.[14] Schneider and Brauner reported that a normal ring opening reaction occurs for simple terminal epoxides with Me_3Al (Scheme 5a).[15] We found that the migratory ether formation proceeds smoothly for a substrate



Scheme 5. Results and calculations for substrates lacking a terminal hydroxy group.

bearing a methoxymethoxy (MOMO) group (Scheme 5b). Interestingly, when the hemiacetal was replaced by a benzyloxymethoxy (BOMO) group, the expected benzyloxy migration failed to occur. Instead, the reaction proceeded with debenzylation to give a 1,3-dioxanylmethanol product (**3k**), which was isolated in high yield (Scheme 5c). Energy profiles were mapped for the formation of **3j** and **3k**. In the absence of the free hydroxy functionality, the oxonium intermediate (**2j-IV**) has two decomposition pathways: **2j-TS1** and **2j-TS2**. For the MOMO substrate (**2j**), the four-membered migratory transition state **2j-TS2** is more stable by 15.9 kcal mol^{-1} (Scheme 5d) but in sharp contrast, the six-membered debenzylation pathway through **2k-TS1** leading to **3k** and ethylbenzene as a by-product (Scheme 5e) is more favorable by 13.5 kcal mol^{-1}.

In order to access polyol-substituted medium-sized cyclic ethers, we examined sugar-substituted epoxy alcohol substrates.[16] Despite multiple oxygen atoms on the sugar

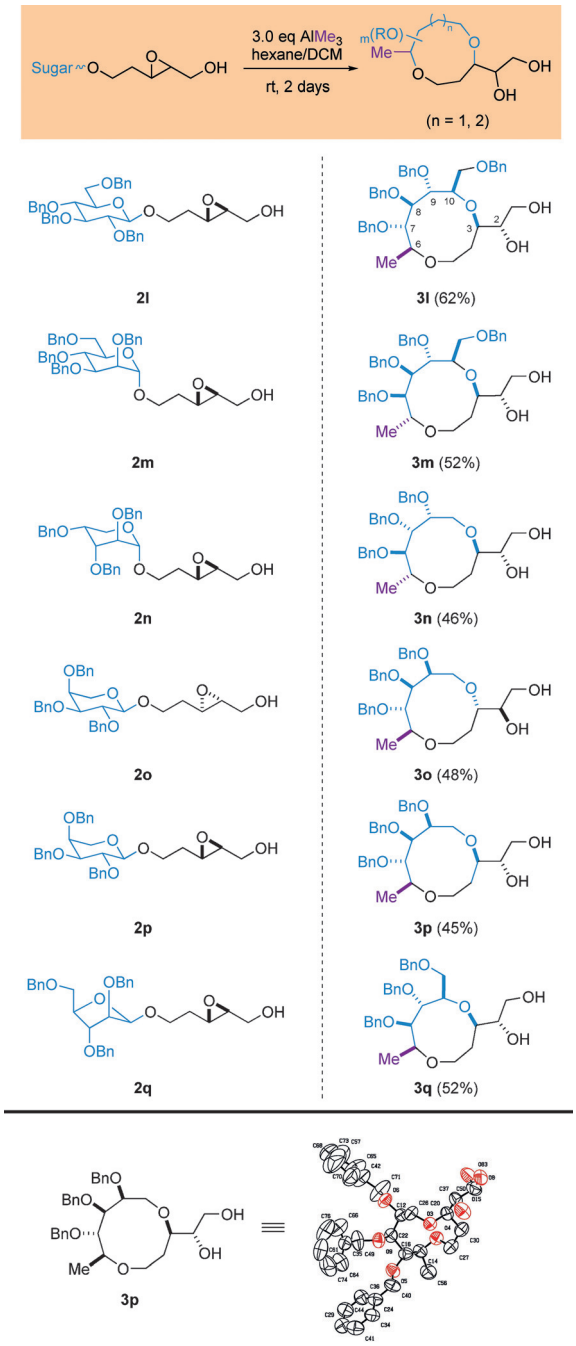


Figure 2. Synthesis of polyol substituted medium-sized cyclic ethers with defined stereochemistry.

sidechain that could coordinate with aluminum, various types of monosaccharides were well tolerated in the migratory open-ring reactions using 3.0 equivalents of Me_3Al (Figure 2). The reactions normally required 2 days to reach maximum conversion and the desired products were isolated in moderate yield. The stereochemistry of the multiple chiral centers on the products is dictated by the chirality of the sugar and epoxide. The sugar anomeric carbon controls the configuration of carbon 6. α-Glycosides lead to *S* isomers at the methylated carbon and β-glycosides lead to *R* isomers. No epimerization of the glycosidic bond was observed. The absolute stereochemistry for C7–C10 is determined by the type of sugar used and the stereochemistry at C2 and C3 is determined by the configuration of the epoxide. The relative stereochemistry for product **3p** was confirmed by X-ray crystallography.[17] Both D- and L-sugars reacted with similar efficiency, suggesting little steric interference from the chiral epoxide. Both pyranoses and furanoses are compatible, leading to 9- and 10-membered cyclic products. To date, there are no alternative synthetic methods for these medium-sized sugar mimetics.

In conclusion, we have discovered a novel, trialkylaluminum-mediated, migratory ether formation reaction using epoxyalcohols bearing a hemiacetal terminal. Instead of directly opening the epoxide, the Lewis acid aluminum reagent promotes an intramolecular oxy-addition to the epoxide, and this triggers a migratory alkylation reaction. 2-Deoxyribitals can be prepared in good yield by this reaction. Computational studies suggest that a chair-like conformation of a trialuminum bonded complex is responsible for the facile addition of the ether to the epoxide. Significantly, reactions using sugar-tagged substrates lead to the first general synthesis of a family of novel medium-sized sugar mimetics. We expect these new chemical syntheses will find wide applications in glycan chemistry and medicinal chemistry.

Acknowledgements

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[17] X-ray crystallographic data: CCDC 1448136 (**3p**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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