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A mercury-catalyzed transetherification cyclization leading to fused cyclic polyethers[†,‡]

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Abstract

Dihydropyran **6** serves as a key intermediate in a route to fused cyclic polyethers. The dihydropyran was first converted to 2-hydroxy-1-γ-methoxyallyltetrahydropyrans, **10**. Mercury trifluoroacetate-catalyzed transetherification cyclization generated new bicyclic dihydropyrans, **12**, ready for additional rounds of synthesis. Attempted cyclization under stoichiometric conditions resulted in isolation of α-mercurial acetal intermediates, **11**, that could also be converted to the dihydropyran by treatment with ethyl vinyl ether. © 2000 Published by Elsevier Science Ltd.

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Target-oriented syntheses of members of the fused cyclic polyether class of natural products have received much attention due to the biological potency and structural complexity of these molecules.[1] Their signature structural element, a series of fused cyclic ethers having regular *trans-syn-trans* stereochemistry, has stimulated numerous iterative routes to these molecules.[2–5]

As a central discovery element in chemical genetic research[6] we have been using diversity-oriented syntheses of small molecules for use in both phenotypic and protein-binding screens.[7–9] Polycyclic compounds are attractive in diversity-oriented synthesis because they provide a rigid three-dimensional structure for the display of diverse building blocks. An efficient and iterative route to fused cyclic polyethers would allow this class of molecules to be featured in diversity-oriented synthesis, particularly if the reaction pathway were amenable to branching, where different skeletal arrays of polyethers would be generated in a single synthesis.[7]

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† Dedicated to Professor Harry H. Wasserman, whose research, teaching and humanity continue to inspire many generations of chemists. We feel fortunate to be among this group.

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Target-oriented synthesis of the polycyclic natural products in this class has generally depended upon convergent approaches, however, structures with only two to four rings would be attractive for a diversity-oriented synthesis, making a linear, iterative approach feasible. Diversity could arise from both the number and size of the rings, the coupling of structurally diverse building blocks to the rings using diverse coupling reactions, and, notably, the systematic alteration of stereochemistry at the ring junctions.

With these considerations in mind, we developed the general route shown in Fig. 1. The common intermediate is a dihydropyran, **1**. Dihydropyrans have served as key intermediates in iterative routes reported by Rainer and Allwein,[2,3] and Bowman and McDonald.[5b] This type of starting material could undergo stereoselective epoxidation at either face of the olefin to provide either stereoisomer at C2. If desired, stereochemistry at C1 could be inverted with the appropriate nucleophile, followed by introduction of the C1 sidechain. In addition to allowing various ring sizes, substituents might be included or introduced on the sidechain to increase structural diversity further. The presence of appropriate functionality on the C1 sidechain should allow cyclization directly to a new dihydropyran that could undergo additional cycles of synthesis. The presence of an olefin in the C1 sidechain might allow even non-cyclized products to undergo further rounds of synthesis. Thus, the ideal route would require only three to four steps per cycle, with the potential to introduce diversity at every step.

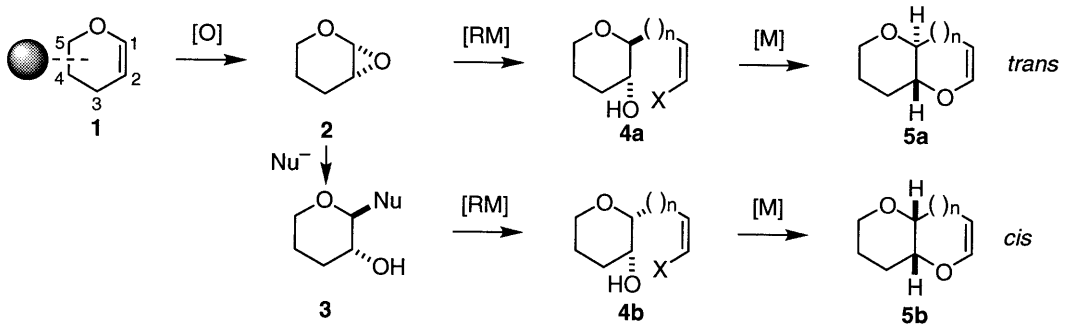

Figure 1. Dihydropyran-based general strategy for iterative synthesis of fused cyclic polyethers

An efficient and related route has been reported by Rainer and Allwein, involving transacetalization–elimination at the cyclization step.[3] With a view towards diversity-oriented synthesis, we elected to develop a new cyclization reaction that proceeds under mild, neutral conditions tolerant of a wide range of functional groups. Mercury(II)-mediated transetherification (X = OMe) seemed an attractive candidate.[10]

A first generation synthesis of cyclization precursors **10a–c** followed substantial literature precedent (Fig. 2). The C6 hydroxyl of D-glucal was protected with a triisopropylsilyl group[11] as a mimic for the alkyldiisopropylsilyl solid support linker in use at the Harvard Institute of Chemistry and Cell Biology.[12] Benzylation at both C3 and C4 provided protected dihydropyran **6**.[11] Epoxidation with dimethyldioxirane proceeded with the expected β-stereoselectivity.[13] Allylation at C1 provided **8a**, along with a limited amount of the C1 epimer **8b**, which was carried along separately.[2,14] Oxidation of **8a**, followed by reduction with L-Selectride, provided mannose-type intermediate **8c**. Ozonolysis and Wittig olefination with methoxymethyltriphenylphosphorane provided the desired cyclization substrates **10a–c**.[4]

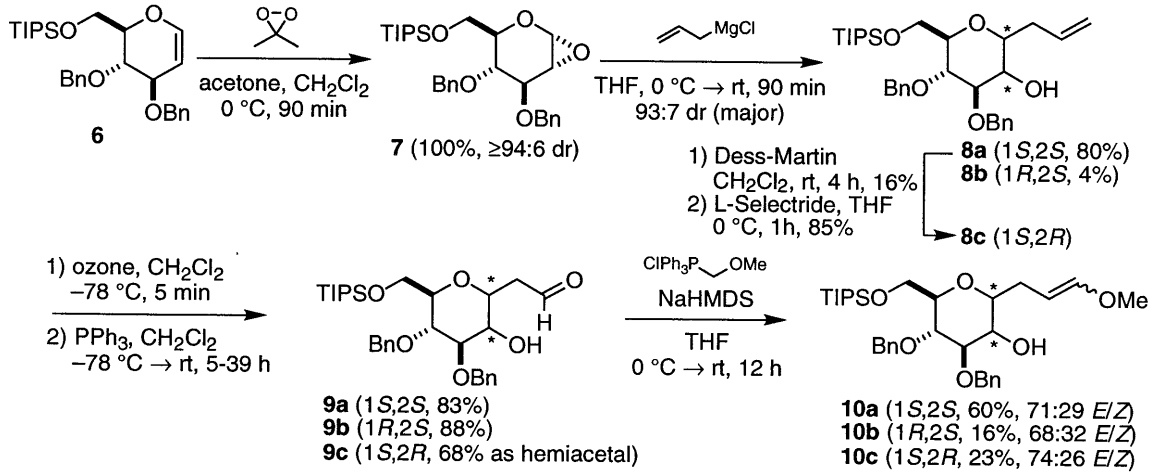

Figure 2. Synthesis of γ-methoxyallyl cyclization precursors **10a–c** from protected D-glucal

Initial attempts at cyclization of **10a** were carried out with a stoichiometric amount of mercuric acetate. However, only the α-mercurial acetal, **11a**, was isolated from the reaction mixture (Fig. 3). Use of mercuric trifluoroacetate led to the corresponding α-mercurial acetal **11b**. In intermolecular mercury-catalyzed transetherifications, ethyl or butyl vinyl ether is used as the solvent (Fig. 4). Presumably, this is required not only to drive the overall equilibrium toward the desired vinyl ether product, but also to promote elimination of the stable α-mercurial acetal intermediate.

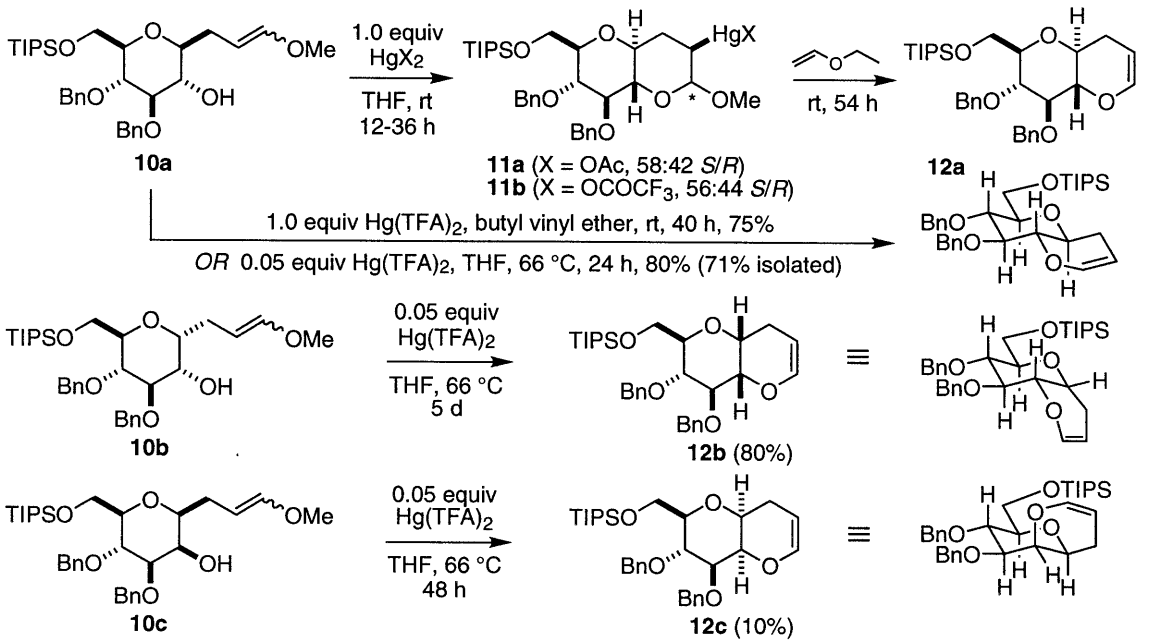

Figure 3. Cyclization of γ-methoxyallyl substrates with stoichiometric and catalytic mercury(II)

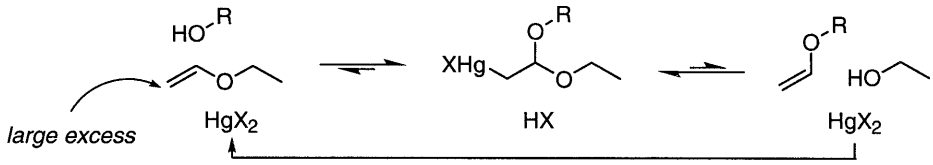

Figure 4. Elimination of the α-mercury acetal intermediate is equilibrium controlled

Thus, we were gratified to find that treatment of α-mercurial acetal intermediate **11b** with an excess of ethyl vinyl ether led to the desired bicyclic dihydropyran **12a**. This two step process could also be carried out in a single step using butyl vinyl ether as the reaction solvent. Ultimately, by performing the reaction with 5 mol% mercuric trifluoroacetate in refluxing THF, we were able to isolate **12a** directly in good yield. Two methyl acetal side products were each isolated in 5% yield, presumably arising from reaction of **12a** with the liberated methanol, catalyzed by uncomplexed trifluoroacetic acid present during the reaction. As expected, a trace of the α-mercurial acetal was also observed in the crude product. Cyclization of the *cis* glucose-type substrate **10b** under these optimized conditions provided bicycle **12b** with similar high efficiency. However, cyclization of the *cis* mannose-type substrate **10c** yielded only 10% of the desired dihydropyran bicycle **12c** with the major products being the corresponding bicyclic methyl acetals. Future versions of this reaction might eliminate these side products by neutralization of either the methanol or free trifluoroacetic acid present in the reaction.

We have demonstrated an intramolecular mercury-catalyzed transetherification cyclization as part of a potential diversity-oriented synthesis of fused cyclic polyethers. To our knowledge, this is the first example of an intramolecular mercury-catalyzed transetherification cyclization. The cyclization reaction of *cis* and *trans* glucose-type substrates is efficient and mild and should tolerate a wide range of functional groups in diversity-oriented synthesis. Further development of the complete synthetic route and adaptation to solid phase synthesis remain to be explored.

Supplementary material. Complete experimental procedures and analytical data for all compounds (PDF, 18 pages) are available on the Internet at 'http://www-schreiber.chem.harvard.edu/home/research_results.html' and 'http://preprint.chemweb.com/orgchem/0009004'.

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