Stereoselective Synthesis

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Hydride Shift Generated Oxonium Ions: Evidence for Mechanism and Intramolecular Trapping Experiments to Form *trans* THF Derivatives**

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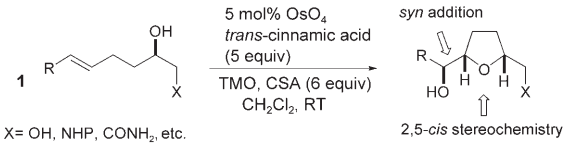
Given the large number and variety of tetrahydrofuran (THF) rings in natural products (many with interesting and useful biological activity), we are engaged in the development of new methods to prepare these heterocycles with control of all aspects of stereo- and regiochemistry.[1]

In this regard, we have recently reported a general method for the catalytic oxidative cyclization of vicinal alcohols, and derivatives thereof, onto proximal alkenes, thus forming *cis*-2,5-disubstituted THF rings (Scheme 1).[2] The reaction involves stereospecific *syn* addition of two heteroatoms across the double bond, meaning that the stereochemical outcome of the cyclization is controllable.

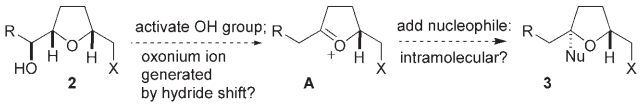


Scheme 1. Oxidative cyclization to form *cis* THF derivatives with control of relative and absolute stereochemistry. CSA = (±)-10-camphorsulfonic acid, NHP = protected amine, TMO = Me_3NO.

One of the restrictions of using such transition-metal-catalyzed oxidative cyclizations to form THF derivatives is the strong and inherent preference to form *cis* THF heterocycles.[3] The origins for this preference lie in the bidentate nature of coordination between the cyclization precursor and osmium, which places constraints upon the geometry of the transition structure and enforces *cis*-2,5-stereoselectivity. Recently, our attention turned to methods for preparing *trans*-2,5-disubstituted THF derivatives, because these motifs are commonly found in natural-product targets.

Attempts to modify the catalytic oxidative cyclization reaction to form *trans* THF rings directly have not been successful,[4] and instead we sought an indirect method of making these useful ring systems. The idea was to modify the products of oxidative cyclization to produce *trans* THF derivatives so that we could retain all of the benefits of the parent reaction (generation of single enantiomers, control of both exo- and endocyclic stereochemistry, etc.) and yet still access any stereochemical pattern at the C-2/5 positions.

Our work concentrated upon generation of an oxonium ion at the C-2 position in the THF ring and subsequent trapping of this species. We suspected that a range of nucleophiles could potentially be useful and that intra- versus intermolecular trapping would help to control the stereochemistry of the products (Scheme 2). In this regard we focused upon the removal of one of the exocyclic hydroxy groups (as a leaving group) that was introduced by the oxidative cyclization, with the hope that a 1,2-hydride shift would ensue and generate the desired oxonium ion **A** within the THF ring, ready for trapping. Our thoughts that such a process may take place derive from observations made by the groups of Nakata and others, who studied ring expansion reactions of related systems and discovered unwanted byproducts that appeared to have come from this process.[5]



Scheme 2. Formation of an oxonium ion by hydride shift.

Therefore, we prepared a series of THF derivatives with one of the two hydroxy groups activated to become a leaving group and the other bearing a silicon hydride group to act as an in situ nucleophile (Scheme 3). Early studies had shown that the stereochemistry between the ring junction and the stereogenic center bearing the OMs group was critical in promoting the rearrangement reaction;[6] therefore, this arrangement was kept constant, and optimal, throughout the series. Instead, the three compounds that were prepared allowed us to study the role of substitution and stereochemistry on the directing arm of the THF ring.

Pleasingly, when each of the compounds **5**, **8**, and **11** was subjected to reaction with zinc acetate in a polar protic solvent ($(CF_3)_2CHOH$, HFIPA), the desired reaction took place. Each compound was formed as a single diastereoisomer of the THF ring, and the 2,5-stereochemistry was shown to be *trans* in each case.

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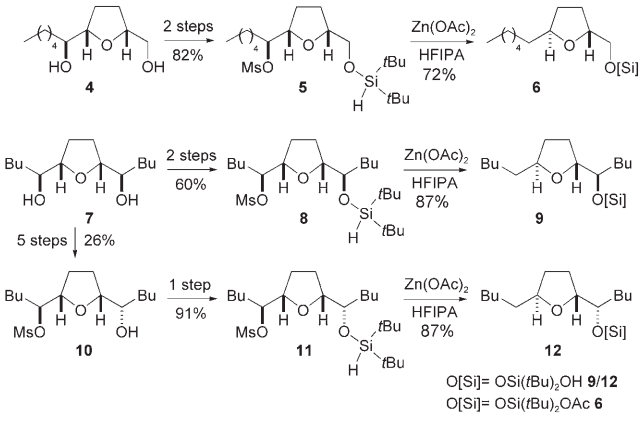
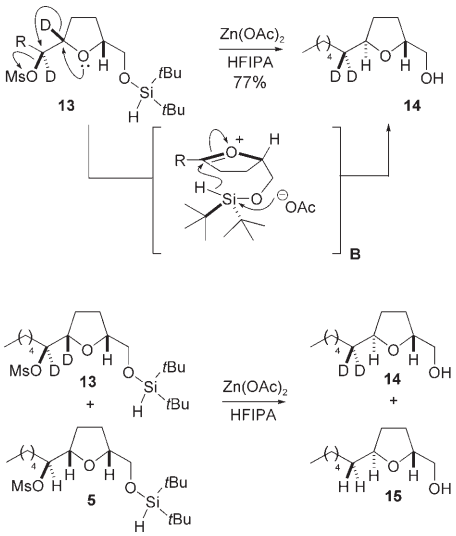


Scheme 3. Stereoselective formation of *trans* THF rings. Ms = methanesulfonyl, HFIPA = $(CF_3)_2CHOH$.

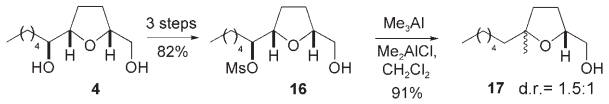
In studies designed to define the mechanism for this reaction, we prepared the doubly deuterated compound **13** from oxidative cyclization onto a *trans*-1,2-dideuterated alkene (Scheme 4).[7] When this compound was subjected to



Scheme 4. Evidence for the intramolecular nature of the hydride shift.

solvolysis conditions, the only product that could be detected (**14**) had the expected doubly deuterated substitution pattern. Repetition of this experiment in the presence of an excess of the protonated analogue **5** gave only products **14** and **15**, and no cross-over products containing one deuterium atom were detected by mass spectrometry.[8] In fact, compound **13** rearranged approximately two to three times more slowly than **5**, which is itself circumstantial evidence for a process that involves breaking of a C–H (or C–D) bond in the transition state. Note that during the accordingly extended time of reaction, the silyl group is deprotected in situ.

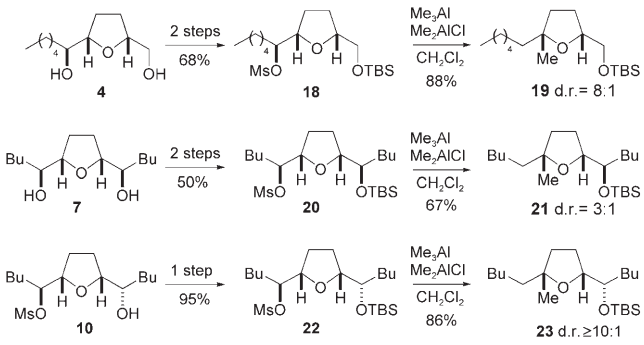
Next, we attempted to use a free hydroxy group to direct organometallic addition onto the transient oxonium ion and extend the range of groups that could be installed at the C-2 position. Thus, compound **16** was prepared and then ionized under aprotic conditions; trimethyl aluminum was envisaged as a complex that might coordinate to the hydroxy group and allow intramolecular addition of a methyl group (Scheme 5).[9] The reaction worked best when dimethylalu-



Scheme 5. Attempted hydroxy-delivered organometallic addition.

minum chloride was added; it probably functions as a separate Lewis acid to help ionize the OMs group. While we did find that these conditions allowed the ionization/hydride-shift/methyl trapping, we could not control the stereochemistry of product **17**. The highest ratio attained for *trans*/*cis* stereochemistry (which probably reflects intra-/intermolecular trapping of the oxonium ion) was 1.5:1.[10]

Therefore, our attention turned to the OTBS-protected mesylated compounds **18**, **20**, and **22** (Scheme 6). In these cases we hoped that intramolecular delivery of a methyl group



Scheme 6. Stereoselective organometallic addition. OTBS = OSi*t*-$BuMe_2$.

would be disfavored completely, thus allowing intermolecular (and stereoselective) addition to take place. This turned out to be the case, and each of the three compounds studied gave the *cis* diastereoisomer (**19**, **21**, **23**) as the major compound with good to excellent stereoselectivity. Although this process did not deliver the desired *trans* stereoisomer, it does greatly extend the variety of substituents that can be introduced stereoselectively at the C-2 position.

To conclude, we have shown that *cis* THF derivatives produced from oxidative cyclization can be transformed into *trans* heterocycles through a 1,2-hydride shift and intramolecular trapping with a hydride nucleophile. Moreover, organometallic compounds can be used to trap the oxonium ion generated in this way so that it is possible to introduce various groups at the C-2 position with control of stereochemistry.

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[6] The analogue of compound **5**, which is diastereomeric at the OMs center, returned starting material under the reaction conditions. This stereoelectronic effect can be considered to be further evidence for a concerted hydride shift/OMs displacement, because the reactive conformation (C–H and C–OMs antiperiplanar) suffers from undue steric hinderance between the sidechain and the THF ring: this strain is reduced with its diastereoisomer **5**.
[7] We do not assume concomitant attack of acetate anion and loss of hydride from the silicon. Removal of the silyl group that is generated by this mechanism, as shown in Scheme 3, is straightforward using tetra-*n*-butylammonium fluoride (TBAF). For related directed ionic hydrogenation reactions, see: a) S. Anwar, G. Bradley, A. P. Davis, *J. Chem. Soc. Perkin Trans. 1* **1991**, 1381; b) R. J. P. Corriu, G. F. Lanneau, Z. Yu, *Tetrahedron* **1993**, *49*, 9019; c) S. W. McCombie, C. Ortiz, B. Cox, A. K. Ganguly, *Synlett* **1993**, 541.
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[10] We know that intermolecular attack of nucleophiles (such as Et_3SiH) onto oxonium ions such as **A** gives predominantly the *cis* diastereoisomer, presumably for steric reasons; see also Scheme 6. For the influence that substituents within the THF ring can have on oxonium ion trapping, see: a) C. H. Larsen, B. H. Ridgway, J. T. Shaw, K. A. Woerpel, *J. Am. Chem. Soc.* **1999**, *121*, 12208; b) D. A. Evans, L. Kværnø, J. A. Mulder, B. Raymer, T. B. Dunn, A. Beauchemin, E. J. Olhava, M. Juhl, K. Kagechika, *Angew. Chem.* **2007**, *119*, 4777 – 4781; *Angew. Chem. Int. Ed.* **2007**, *46*, 4693 – 4697.

