Cyclic Ethers

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Stereoselective Synthesis of 2,4,6-Trisubstituted Tetrahydropyrans by the Use of Cyclopropanols as Homoenols**

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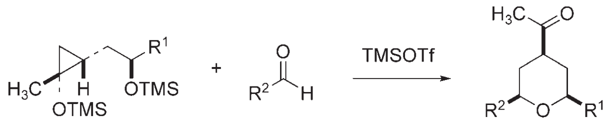
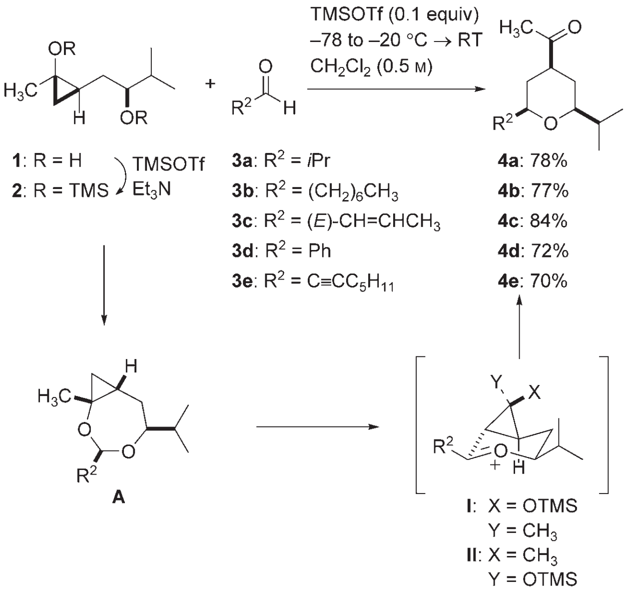
Dedicated to Professor Yoshito Kishi on the occasion of his 70th birthday

Functionalized tetrahydropyrans constitute key structural motifs of a large number of biologically active natural products.[1] The conspicuous prevalence of 2,4,6-trisubstituted tetrahydropyrans in these natural products spurred the development of many elegant methods for the enantio- and stereoselective synthesis of appropriately substituted tetrahydropyrans. Several useful synthetic methods are based on the efficient trapping of an oxocarbenium ion by a pendant nucleophile.[2] The ring opening of a cyclopropanol or its silyl ether and addition to a tethered oxocarbenium ion was recently documented by the Minbiole research group and by us.[3,4] We report herein an expedient synthesis of all-*cis* 2,4,6-trisubstituted tetrahydropyrans by the intramolecular addition of a cyclopropanol moiety to an oxocarbenium ion, which is generated conveniently by adaptation of the Noyori–Markó protocol (Scheme 1).



Scheme 1. Preparation of all-*cis* 2,4,6-trisubstituted tetrahydropyrans. Tf = trifluoromethanesulfonyl, TMS = trimethylsilyl.



Scheme 2. Synthesis of all-*cis* 2,4,6-trisubstituted tetrahydropyrans.

In connection with the synthetic applications of cyclopropanols as homoenol or homoenolate equivalents, we were attracted to the method developed by the research groups of Noyori and Markó for generating an oxocarbenium ion in situ as an electrophilic reaction partner.[5] We chose the *trans*-dialkyl cyclopropanol **1** with a 2-hydroxyalkyl side chain for our initial study (Scheme 2). The *syn* arrangement of the 1,4-diol relative to the cyclopropane ring in **1** was expected to promote formation of the 7-membered acetal **A** upon treatment with an aldehyde under the conditions described by Noyori and co-workers, and this intermediate might rearrange to form a tetrahydropyran **4**. Compounds of type **1** are readily available through the titanium-mediated hydroxycyclopropanation of homoallylic alcohols.[6,7] The treatment of the bis(trimethylsilyl) ether **2** with isobutyraldehyde (**3a**) or octanal (**3b**) in the presence of TMSOTf in CH_2Cl_2 indeed afforded **4a** and **4b**, respectively, as single isomers in good yields. Thin layer chromatographic analysis of the reaction mixture indicated that the acetal **A** formed rapidly after the addition of TMSOTf to the reactants at −78 °C and was then converted slowly into **4a** or **4b** upon warming.[8] This straightforward procedure was also applicable to a wide range of aldehydes, such as α,β-unsaturated aldehydes, aromatic aldehydes, and alkynals. Thus, **4c**–**e** were formed in comparable yields and with high selectivities (> 20:1). The observed all-*cis* relative configuration can be rationalized by the cyclization of an *E* oxocarbenium ion in a chairlike conformation **I**.

The preformation of bis(trimethylsilyl) ethers was subsequently found to be unnecessary; the direct treatment of **1** with an aldehyde in the presence of TMSOTf (2.5 equiv) also afforded the corresponding tetrahydropyrans. For example, **4b** and **4c** were obtained from **1** and **3b** or **3c** in 68 and 70 % (unoptimized) yield, respectively.

As a preliminary study toward natural product synthesis, we next examined the cognate coupling of two oxygenated

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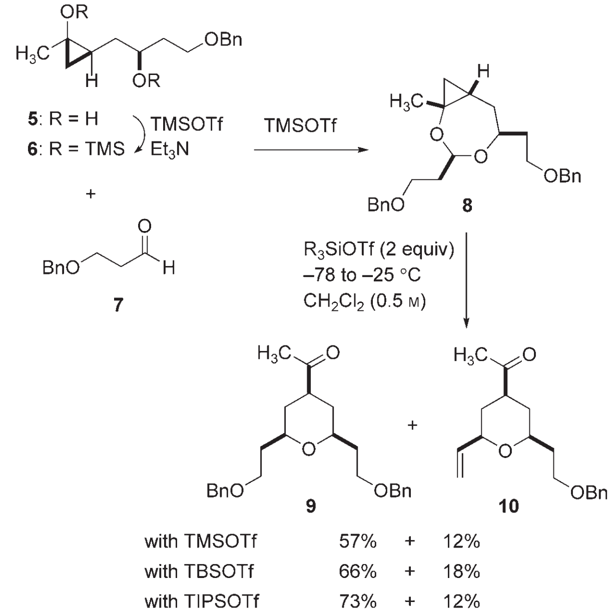
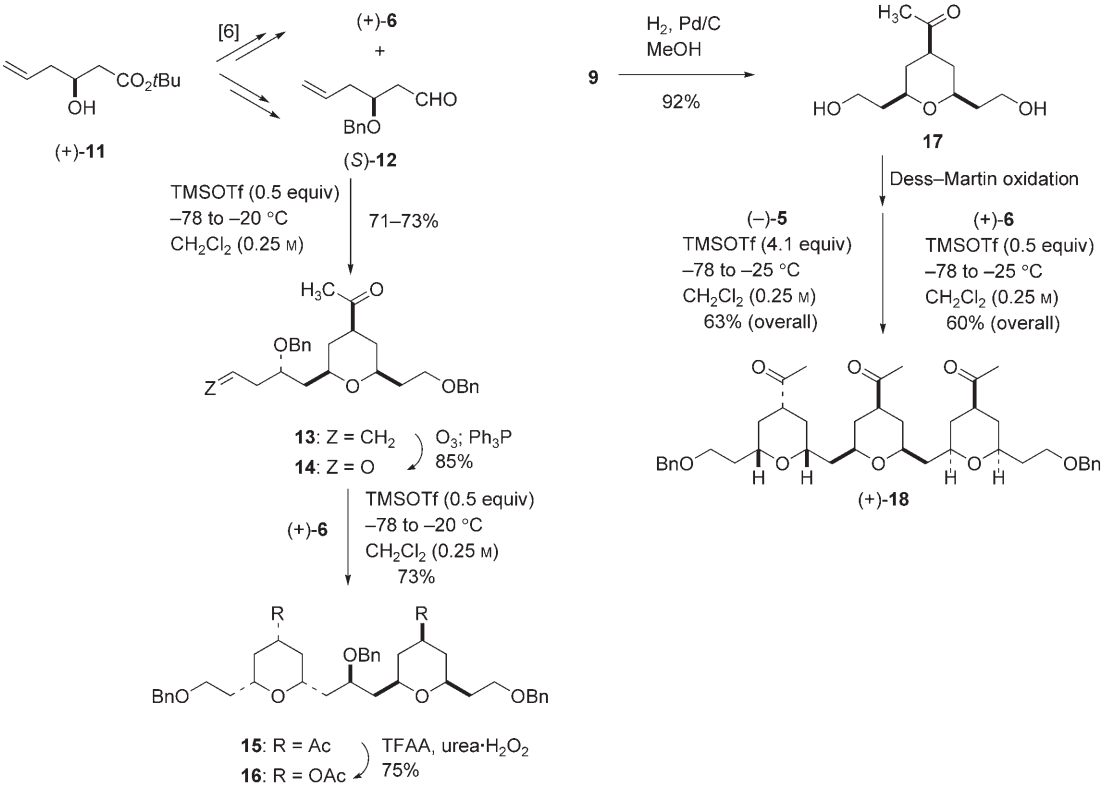
segments, **6**, and 3-benzyloxypropanal (**7**), so as to prepare the all-*cis* 2,4,6-trisubstituted tetrahydropyran **9** with skipped-polyol side chains (Scheme 3). Surprisingly, besides **9** (40 %), **10** was isolated in 22 % yield under the above-mentioned conditions (with 0.1 equivalents of TMSOTf). Optimization studies, in which the cyclic acetal intermediate was formed initially and treated subsequently with a silyl triflate (2 equiv), were undertaken to minimize the unwanted elimination: An acceptable result was obtained by treating the preformed acetal **8** with triisopropylsilyl triflate (TIPSOTf).[9]

The aforementioned investigations were performed with racemic substrates; however, this methodology provides straightforward access to enantiomerically pure tetrahydropyrans if readily available, nonracemic homoallylic alcohols[10] are used as precursors to the cyclopropanol substrates. Furthermore, through the convenient coupling of two large segments that contain multiple stereogenic centers, a new tetrahydropyran ring can be assembled with a well-defined stereochemical outcome. Examples of segment coupling[2c] are shown in Scheme 4. No elimination product was observed with aldehydes with a secondary alkoxy group at the β position (for example, **12** and **14**). A Baeyer–Villiger reaction of **15** with pertrifluoroacetic acid gave the corresponding diacetate **16** in 75 % yield. A particularly good illustration of the efficiency of this approach is the rapid assembly of (+)-**18** by using either **5** or **6** as the starting cyclopropanol for each of the three tetrahydropyran rings.

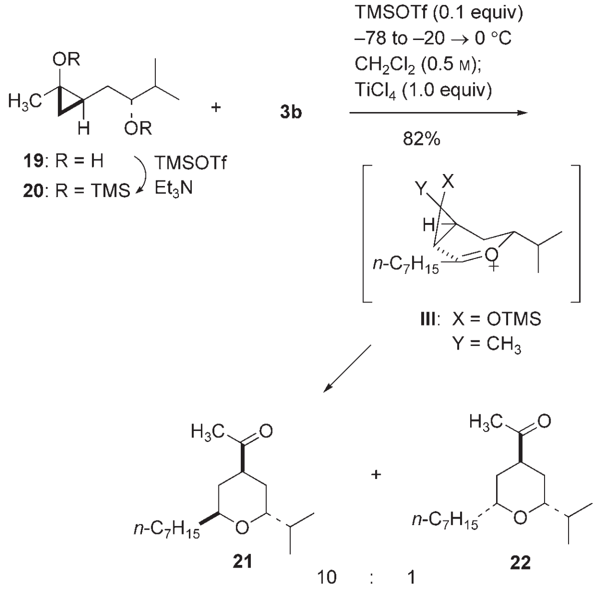
We next examined the stereochemical outcome of the annulation with the cyclopropanediol **19**, which is epimeric with **1** (Scheme 5).[11] The sequential treatment of the corresponding bis(trimethylsilyl) ether **20** and octanal (**3b**) with TMSOTf and $TiCl_4$ gave a 10:1 mixture of **21** and **22** in 82 % yield. The configuration of the major isomer **21** was gleaned easily from key coupling constants and is consistent with the adoption of the boatlike transition state **III** by an intermediate *E* oxocarbenium ion. This approach provides



Scheme 3. Coupling of **6** and 3-benzyloxypropanal (**7**). Bn = benzyl, TBS = *tert*-butyldimethylsilyl.



Scheme 4. Additional examples of the synthesis of all-*cis* 2,4,6-trisubstituted tetrahydropyrans. TFAA = trifluoroacetic anhydride.



Scheme 5. Preparation of a 2,6-*trans* tetrahydropyran isomer with **3b**.

ready entry to the more challenging *trans*-2,6-disubstituted structures. Thus, both 2,6-*cis* and 2,6-*trans* stereoisomers of 2,4,6-trisubstituted tetrahydropyrans can be prepared from epimeric *trans*-dialkyl cyclopropanols (for example, **2** and **20**).[12]

In summary, a new method has been developed for preparing all-*cis* 2,4,6-trisubstituted tetrahydropyrans from readily available cyclopropanols with a hydroxyalkyl side chain and aldehydes by making use of the titanium-mediated diastereoselective cyclopropanation of homoallylic alcohols. A useful route to synthetically challenging 2,6-*trans* isomers was also delineated through stereochemical investigations. The unique flexibility of having ready access to both 2,6-*cis* and 2,6-*trans* stereoisomers is a particularly valuable feature of this method, which seems to be suitable for the coupling of two large subunits to generate structural complexity rapidly in a highly convergent manner.

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[8] For example, the acetal derived from **2** and **3b** was isolated in excellent yield and characterized fully, as was acetal **8**. However, the intermediacy of a cyclic acetal **A** is not obligatory: The coupling reactions of the *cis*-dialkyl cyclopropanol that is epimeric with **2** also proceeded cleanly (via **II**; see Scheme 2) to provide **4a–e** in excellent yields.

[9] These results with different trialkylsilyl triflates, in combination with the finding that tetrahydropyran formation is completely shut down upon the addition of a base (for example, 2,6-di-*tert*-butyl-4-methylpyridine) or molecular sieves, suggest that triflic acid is the actual catalyst. Indeed, triflic acid can be employed in place of a silyl triflate to furnish tetrahydropyran products in comparable yields.

[10] The enantiomerically enriched starting material **11** (>95% *ee*) was prepared by adaptation of the following literature procedures: a) J. S. Panek, P. Liu, *J. Am. Chem. Soc.* **2000**, *122*, 11090; b) M. Tokunaga, J. F. Larrow, F. Kakiuchi, E. N. Jacobsen, *Science* **1997**, *277*, 936; c) J. W. A. Kinnaird, P. Y. Ng, K. Kubota, X. Wang, J. L. Leighton, *J. Am. Chem. Soc.* **2002**, *124*, 7920; for previous syntheses of nonracemic **12**, see also: d) D. Díez-Martin, N. R. Kotecha, S. V. Ley, S. Mantegani, J. C. Menéndez, H. M. Organ, A. D. White, *Tetrahedron* **1992**, *48*, 7899; e) J. A. Marshall, J. J. Sabatini, *Org. Lett.* **2005**, *7*, 4819; f) I. Paterson, M. J. Coster, D. Y.-K. Chen, R. M. Oballa, D. J. Wallace, R. D. Norcross, *Org. Biomol. Chem.* **2005**, *3*, 2399.

[11] Swern oxidation of **1**, followed by $NaBH_4$ reduction of the resulting lactol, gave a 1:1, but readily separable, mixture of **1** and **19**.

[12] Additional examples of the stereoselective preparation of 2,6-*trans* isomers and the corresponding starting cyclopropanols (for example, **19** from **1**) will be reported in a full paper. The coupling reactions of **20** with **3c–e** afforded tetrahydrofurans as the major isomers. The more-substituted C−C bond of the three-membered ring apparently reacts with the oxocarbenium ion in the presence of a carbenium-ion-stabilizing group.