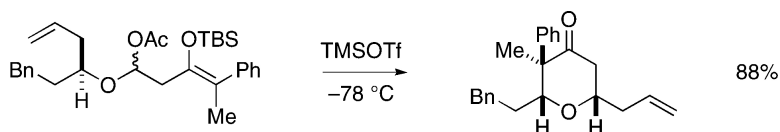Communication

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Oxonia-Cope Prins Cyclizations: A Facile Method for the Synthesis of Tetrahydropyranones Bearing Quaternary Centers

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Investigations from this lab and others have demonstrated the prevalence of 2-oxonia Cope rearrangements in Prins cyclization reactions.[1,2] In most cases, the 2-oxonia Cope rearrangement[3] takes place in the background and is not directly observable by product analysis.[4] In a few cases, the rearrangement leads to unwanted side reactions.[1a–c] Herein, we report a new oxocarbenium ion cascade reaction[5,6] and cyclization where the 2-oxonia Cope rearrangement is an integral step in the cascade. This oxonia-Cope Prins (OCP) process is efficient and allows for the preparation of tetrahydropyrans with quaternary carbon centers, synthetic targets that are normally not accessible by Prins cyclization strategies.[7]

The strategy for the oxonia-Cope Prins cyclization is outlined in Figure 1. The α-acetoxy ether **1** is a typical substrate for a segment-coupling Prins cyclization except that it contains a silyl enol ether. Treatment with a Lewis acid would generate the oxocarbenium ion **2**, the normal intermediate for a Prins cyclization. As we have shown previously,[1c] the 2-oxonia Cope rearrangement is fast, and oxocarbenium ions **2** and **3** should be in rapid equilibrium. Now the enol ether comes into play. As the best nucleophile in the system it would cyclize on the oxocarbenium ion via conformer **4** to produce the tetrahydropyranone **5**.[8] If a chair conformation dominates in the cyclization transition state, then the configuration of the product should be predictable from the geometry of the enol ether. Note that there is an apparent inversion at the secondary ether center in **1** en route to the C2 position in **5** that arises from the rearrangement and cyclization cascade. The successful realization of this strategy is described below.
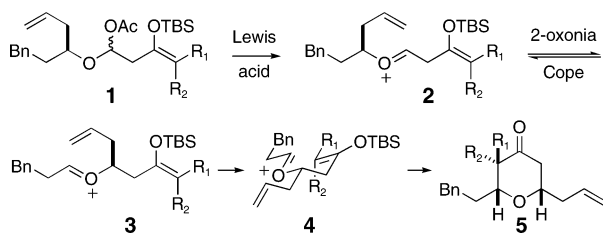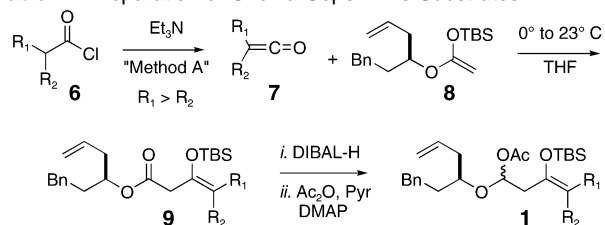

Figure 1. 2-Oxonia-Cope rearrangement of the oxocarbenium ion **2** sets up the intramolecular cyclization reaction of **4**.

The proposed cascade reaction is only practical if the substrates are synthetically accessible. Preparation of the silyl enol ether substrates is presented in Table 1. Rathke's strategy was employed to assemble the targets from ketenes **7** and the silyl enol ether **8**.[9] In Rathke's procedure, the ketenes were prepared by elimination of acid chlorides (method A). Method A worked well with unsubstituted and monosubstituted ketenes (entries 1–3) but led to moderate yields with some disubstituted ketenes (entries 5 and 8). Zinc reduction of the α-bromo acid bromides was used to produce disubstituted ketenes (method B).[10] One or the other method worked well and with all of the substrates investigated. The asymmetric ketenes in entries 2, 3, and 7 led to the (Z)-silyl enol ethers selectively, as would be expected by addition to the less

Table 1. Preparation of Oxonia-Cope Prins Substrates

Entry	R₁	R₂	Method[a]	Yield (%) step 1	Product	Yield (%) step 2
1	H	H	A	77	**10**	98
2	Et	H	A	86	**11**	98
3[b]	CH₂=CH	H	A	80	**12**	92
4	Me	Me	B	72	**13**	92
5	Me	Me	A	30	**13**	–
6	(CH₂)₅		B	68	**14**	93
7	Ph	Me	A	92	**15**	99
8[c]	CH₂O-TBDPS	Me	A	56	**16**	92

[a] Method A: Acid chloride and Et₃N were combined with silyl ketene acetal in THF from 0 to 23 °C. Method B: the α-bromo acetyl bromide was treated with zinc dust in THF at 0 °C for 30 min, and the ketene solution was decanted before use. [b] (E)-Crotonyl chloride was used to generate the ketene. [c] Enol ether produced as a 1.5:1 mixture of Z/E isomers.

hindered face of the ketene. The asymmetric ketene in entry 8 only produces a 1.5:1 mixture of silyl enol ethers. Presumably, the facial bias of the ketene was insufficient to ensure good selectivity. The second step was a reductive acetylation with DIBAL-H followed by acetic anhydride treatment that proceeded in uniformly good yields.[11] The OCP cyclization substrates were prepared in two steps from the silyl ketene acetal **8**.

Cyclization of the substrates is illustrated in Table 2. The cascade cyclization works remarkably well. We found that TMSOTf was a
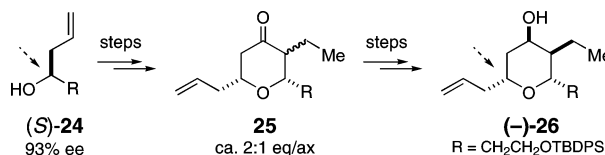
Table 2. Oxonia-Cope Prins Cyclization of Silyl Enol Ether Substrates

Entry	R₁	R₂	Lewis acid (product ratio)	Product	Yield (%)
1	H	H	TMSOTf	**17**	99
2	Et	H	TMSOTf (1.6:1 eq/ax)	**18**	99
3ᵃ	CH₂=CH	H	TMSOTf (2.1:1 eq/ax)	**19**	84
4	Me	Me	TMSOTf	**20**	92
5	(CH₂)₅		TMSOTf	**21**	93
6	Ph	Me	TMSOTf	**22**	88
7ᵇ	CH₂O-TBDPS	Me	TMSOTf (1.2:1)	**23**	77

ᵃ Chromatography on Et₃N-deactivated silica gel led to conjugation of the alkene to produce only the (E)-ethylidene isomer. ᵇ The 1.5:1 Z/E mixture of enol ether isomers led to a 1.2:1 mixture of stereoisomers with the major isomer shown.

Scheme 1. Oxonia-Cope Prins Cascade Leads to an Inversion of Configuration at the C2 Center in the Cyclization

(S)-**24** 93% ee → **25** ca. 2:1 eq/ax → (−)-**26** R = CH₂CH₂OTBDPS

The cyclizations described so far used racemic starting material. The use of optically pure starting material **24** in Scheme 1 produced optically pure tetrahydropyranone **25**. Compound **25** was reduced to alcohol **26**,[13] and its configuration was determined by Mosher's analysis.[15] As predicted by the proposed mechanism in Figure 1, the stereogenic center in (S)-**24** was transformed to the inverted C2 center in compound (−)-**26**. The oxonia-Cope Prins sequence is stereospecific.

We describe a new method for the synthesis of tetrahydropyranone rings based on an oxonia-Cope rearrangement and Prins cyclization. The reactions proceed in high yield and are stereoselective with some substrates. This new method will be useful in the synthesis of the many natural products that incorporate tetrahydropyran rings.

Supporting Information Available: Experimental details for the reactions described (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

very efficient promoter of the reaction, perhaps because triflate is not a good nucleophile and does not favor the competing Prins cyclization of oxocarbenium ion **2**. The TMSOTf catalyst produces two diastereomers in the cyclization of the trisubstituted enol ethers (entries 2 and 3.) The moderate diastereoselectivity could arise from enol ether E/Z isomerization,[12] competing chair−boat cyclizations, or epimerization of the product under the reaction conditions. The latter possibility was discounted by monitoring the reaction in entry 3 by NMR spectroscopy: the reaction was essentially complete after 5 min at −78 °C, and the diastereomeric ratio did not change.[13] The E/Z isomerization of the silyl enol ether could not be demonstrated, but the result was ambiguous.[14] Modest selectivity between the chair and boat transition states was the likely origin of the stereoisomeric products, and there is precedent for competing stereochemical pathways with similar cyclizations.[8c]

The tetrasubstituted enol ethers cyclized efficiently to give tetrahydropyranones with quaternary centers at the 3-position (entries 4−7). The phenyl-methyl substrate (entry 6) led to the diastereomer with an axial methyl group, as one would expect from a chair transition state in the cyclization. The mixture of enol ethers in entry 7 predictably led to a mixture of stereoisomeric products **23**. Unlike the case with trisubstituted enol ethers, the tetrasubstituted enol ethers appear to rearrange stereoselectively. All of the enol ethers cyclized to tetrahydropyranones in good yields.

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