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Tandem organochromium-coupling and epoxide ring opening: a direct approach for the synthesis of cyclic ethers

Isabel C. González and Craig J. Forsyth*

Department of Chemistry, University of Minnesota, Minneapolis, MN 55455, USA

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Abstract

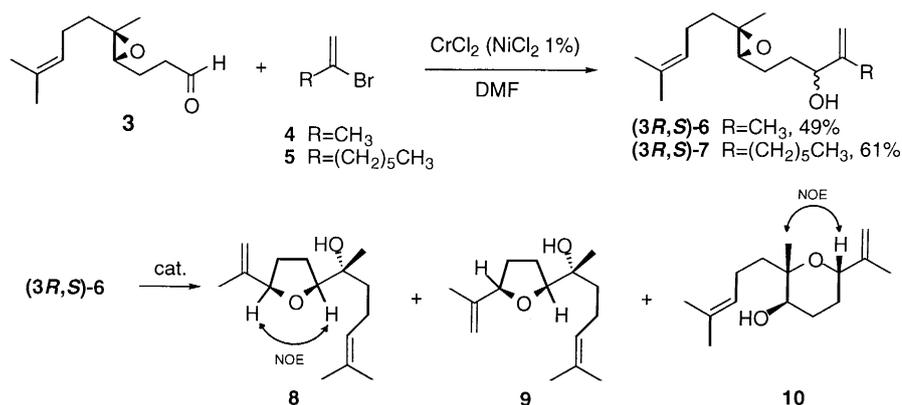
A two-step protocol for the convergent formation of cyclic ethers has been demonstrated. This involves the chemoselective 1,2-addition of vinylchromium species to a 4,5-epoxy aldehyde to generate γ,δ -epoxy alcohols followed by acid-induced transesterification to generate substituted tetrahydrofuran and pyran products. © 2000 Elsevier Science Ltd. All rights reserved.

The efficient and stereocontrolled syntheses of substituted ethers occupies a central role in the assembly of complex polyether natural products.¹ Reported here is the direct formation of tetrahydrofuran and tetrahydropyran rings via a convergent two-step protocol that involves the chemoselective addition of vinylchromium² reagents to 4,5-epoxy aldehydes followed by acid-catalyzed intramolecular epoxide opening.

The addition of an organometallic nucleophile chemoselectively to a 4,5-epoxy aldehyde was examined with **3**, synthesized in a four-step sequence³ from (2*R*,3*R*)-epoxy geraniol.⁴ Preliminary attempts to join **3** with 2-bromo-1-propene (**4**) using CrCl₂–NiCl₂ (0.1% wt/wt) in THF or DMSO failed to provide the desired allylic alcohol. However, **3** was successfully coupled with **4** and 2-bromo-1-octene (**5**)⁵ using CrCl₂–NiCl₂ (1% wt/wt) in DMF, to obtain **6** and **7**, respectively, as chromatographically homogeneous mixtures of (3*R*,*S*)-hydroxy epoxides (1.1–1.3:1,⁶ Scheme 1). Cyclic ethers derived from spontaneous epoxide ring openings were minor side products in the synthesis of **6** (9%) and **7** (5%). The use of a modified work-up (1 M aq. potassium serinate, pH 8)⁷ for **7** reduced the amount of cyclic byproducts. It is noteworthy that the epoxide withstands the conditions of the organochromium coupling, although its presence had little or no effect on the stereoselectivity of the 1,2-addition.⁸ In contrast, use of the vinylmagnesium or vinyl lithium species yielded products of decomposition of epoxide **3**.

A variety of acid-catalyzed conditions examined for the transesterification of hydroxy epoxides (3*R*,*S*)-**6** produced almost invariable mixtures of **8**, **9** and **10** (ca. 87–96% combined yield, Scheme 1 and Table 1). Modest levels of regio- and diastereoselectivity were observed in the transesterification reactions. The

* Corresponding author.



Scheme 1.

relative configurations of the cyclic products were determined by NOE studies, which revealed that (3*R*)-**6** yielded exclusively the tetrahydrofuran **8**,⁹ whereas (3*S*)-**6** modestly favored tetrahydropyran **10**. The formation of the six-membered ring from (3*R*)-**6** was disfavored, presumably because of steric repulsion (1,3-diaxial interactions) in the transition state.

Table 1
Selectivity of acid-induced transesterification of (3*R,S*)-**6**

Entry	Conditions	Product ratios: 8:9:10 *
1	CSA (10% mol), CH ₂ Cl ₂ (0.05 M), -40 °C	52:15:33
2	CSA (10% mol), CH ₃ CN (0.05 M), -40 °C	52:17:31
3	CSA (10% mol), DMF (0.01 M), -40 °C	48:23:29
4	Ti(O ^{<i>i</i>} Pr) ₄ (20% mol), CH ₂ Cl ₂ (0.01 M), 0 °C	49:18:33
5	TFA (10% mol), CH ₂ Cl ₂ (0.05 M), 0 °C	45:18:37

*Ratios determined by gas chromatography using a HP-1 (12 m x 0.2 mm x 0.33 μm film thickness) column.

This study demonstrates that the chemoselective addition of organochromium nucleophiles to a 4,5-epoxy aldehyde may be paired with the well-established acid-catalyzed transesterification of hydroxy epoxides to provide a tandem process for the convergent formation of substituted tetrahydrofurans and pyrans. Although the epoxide in **3** was largely stable to the organochromium conditions, it does not appear to appreciably affect the diastereoselectivity of the carbon–carbon bond-forming step. This present deficiency may be compensated for by the ability to join a variety of nucleophiles and epoxy aldehydes to provide facile entry to a wide range of cyclic ethers.

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