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Highly α-Selective Hydrolysis of α,β-Epoxyalcohols using Tetrabutylammonium Fluoride

Purba Mukerjee,[†] Mohammed Abid, and Frank C. Schroeder*

Boyce Thompson Institute and Department of Chemistry and Chemical Biology, Cornell University, Ithaca, New York 14853

schroeder@cornell.edu

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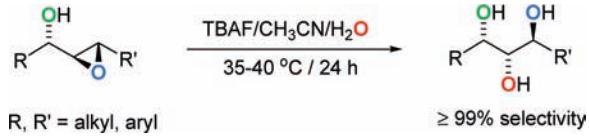
ABSTRACT



We report a simple method for the highly regio- and stereoselective hydrolysis of α,β-epoxyalcohols. Treatment of enantiopure epoxyalcohols derived from Sharpless epoxidation with TBAF/H_2O resulted in exclusive ring opening at the normally disfavored α-position, providing access to *arabino*- or *lyxo*-configured triols with full preservation of stereochemical purity. The method was applied in syntheses of 5-deoxy-L-arabinose (26) and a family of bicyclic acetals based on the insect pheromone hydroxybrevicomin (4).

Arrays of three or more consecutive hydroxylated chiral centers are a common structural feature of natural products from diverse sources, including polyketides (e.g., aspicilin (**1**),[1] erythromycin A (**2**),[2] or FK506 (**3**)[3]), products of fatty acid metabolism (e.g., hydroxybrevicomin (**4**)[4]), and carbohydrate derivatives. A variety of approaches are available for the synthesis of these polyol moieties, for example, asymmetric dihydroxylation,[5] carbohydrate-based methods,[6] or the hydrolysis of chiral epoxides.[7] However, with the exception of carbohydrate-based approaches, the diastereomeric purity of the resulting triols is often relatively low. Because α,β-epoxyalcohols can be obtained in very high stereoselectivity *via* Sharpless epoxidation/kinetic resolution,[8] their use for the preparation of polyol motifs is particularly attractive, and methods of varying selectivity have been

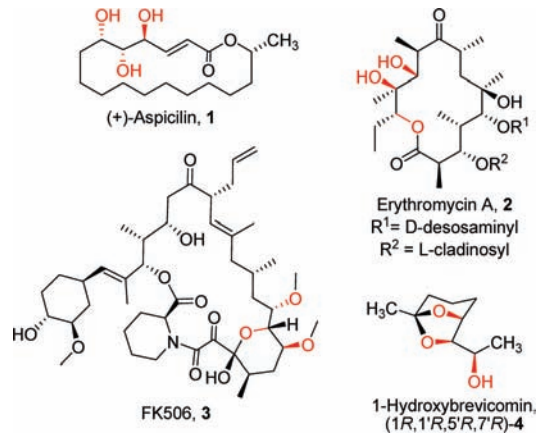


Figure 1. Natural products including or derived from D- or L-*arabino*-configured triols.

[†] Current address: University of Wisconsin.

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described for epoxide ring opening at the β-position.[7,9] Here we report a simple method for the highly selective hydrolysis of α,β-epoxyalcohols at the usually disfavored α-position, providing direct access to *arabino*- or *lyxo*-configured triols of very high diastereomeric purity.

We started investigating methods for the stereoselective preparation of triols as part of our efforts toward synthesis of a library of bicyclic acetals representing cryptic ketodiols and -triols, which play important roles as pheromones in insects and mammals.[10]

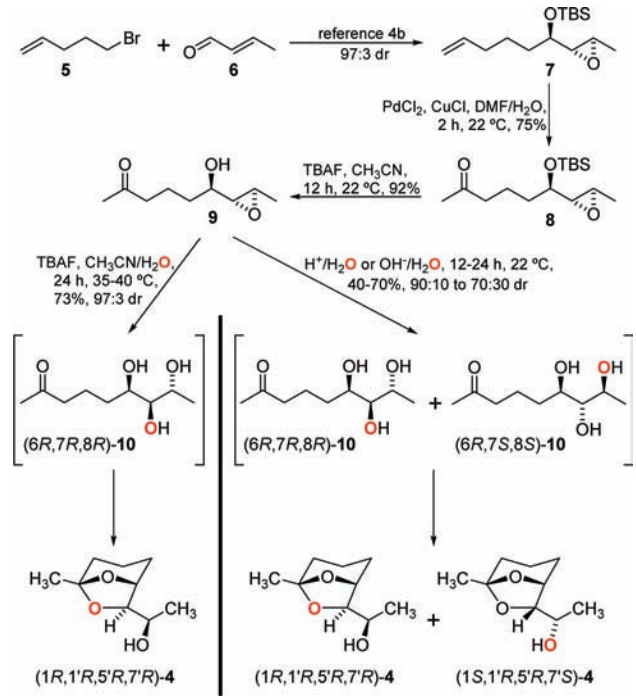
Previous syntheses of the bicyclic acetal hydroxybrevicomin (**4**) relied on preparation of the corresponding triol *via* hydrolysis of chiral epoxyalcohols.[4b,11] Francke et al. based their approach on Sharpless epoxidation and harnessed its powerful kinetic resolution for generating the required epoxyalcohols in up to 99.5% de.[4b] However, subsequent hydrolysis of the epoxide led to considerable loss of stereochemical purity. Using a similar approach, we investigated a variety of conditions to improve regioselectivity of the hydrolysis of chiral epoxyalcohols such as **9**, which was prepared as described previously (Scheme 1).[4b]

Consistent with previous examples,[7,9] treatment of epoxyalcohol **9** with acids or bases in a variety of solvents resulted in mixtures of the corresponding (6,7-*syn*,6,8-*anti*)- and (6,7-*anti*,6,8-*syn*)-triols **10** (Scheme 1). For example, treatment of **9** with KOH in water, HF in CH_3CN, or HCl, H_2SO_4, or TsOH in water resulted in formation of (6*R*,7*R*,8*R*)-**10** and (6*R*,7*S*,8*S*)-**10** in ratios of about 70:30 to 90:10. Upon isolation, these mixtures of ketotriols rapidly cyclized to yield mixtures of two stereoisomers of the bicyclic acetal **4** (Scheme 1). Relative configurations were determined using NOESY spectra.

Serendipitously, it was noted that deprotection of the TBS-ether in **8** using TBAF in acetonitrile occasionally produced small amounts of an unexpectedly nonpolar byproduct. Upon isolation, this byproduct was identified as (1*R*,1′*R*,5′*R*,7′*R*)-**4** of very high diastereomeric purity. This observation suggested that the desilylation conditions induced slow but highly regioselective α-hydrolysis of the desilylated epoxyalcohol **9**.

Therefore, we investigated whether TBAF could be used to convert epoxyalcohols into the corresponding triols without loss of diastereomeric purity. Screening of a variety

Scheme 1. Synthesis of Hydroxybrevicomin **4** via Stereoselective Hydrolysis of Epoxyalcohol **9**



of solvent, temperature, and reagent combinations revealed that treatment of the epoxyalcohols **8** or **9** with 3 equiv of TBAF in the presence of small amounts of acetonitrile and water at 35−40 °C produced optimal results. Under these conditions, reaction of silylated epoxyalcohol **8** or unsilylated **9** directly yielded bicyclic acetal (1*R*,1′*R*,5′*R*,7′*R*)-**4** (derived from cyclization of initially formed ketotriol (6*R*,7*R*,8*R*)-**10**) without any detectable loss of diastereomeric purity (Figure 2). The *in situ* formation of bicyclic acetals **4** from the initially produced ketotriols **10** enabled fast and unambiguous assessment of the regioselectivity of the epoxide hydrolysis process, because the bicyclic acetals' configuration could be assigned easily via analysis of NOESY NMR spectra.

Using THF, ether, dichloromethane, or chloroform instead of acetonitrile or increasing the amount of water in the reaction mixture starkly increased reaction times and reduced stereoselectivity. Additionally, a high concentration of TBAF (~60% by weight) in the reaction mixture was necessary to maintain high stereoselectivity.

To demonstrate general utility of the method, we applied these conditions to a variety of diastereomerically pure epoxyalcohols. Representative examples are shown in Scheme 2, all of which were prepared *via* Sharpless kinetic resolution followed by Sharpless epoxidation. In order to investigate whether anchimeric assistance of the carbonyl in **9** played a role for the stereoselectivity of epoxide opening, we also included epoxyalcohols **20**, **22**, and **24**, which lack additional oxygenation. In all cases, TBAF-promoted hydrolysis selectively produced the corresponding *arabino*- or *lyxo*-configured triols, of which those featuring 4-oxopentyl or

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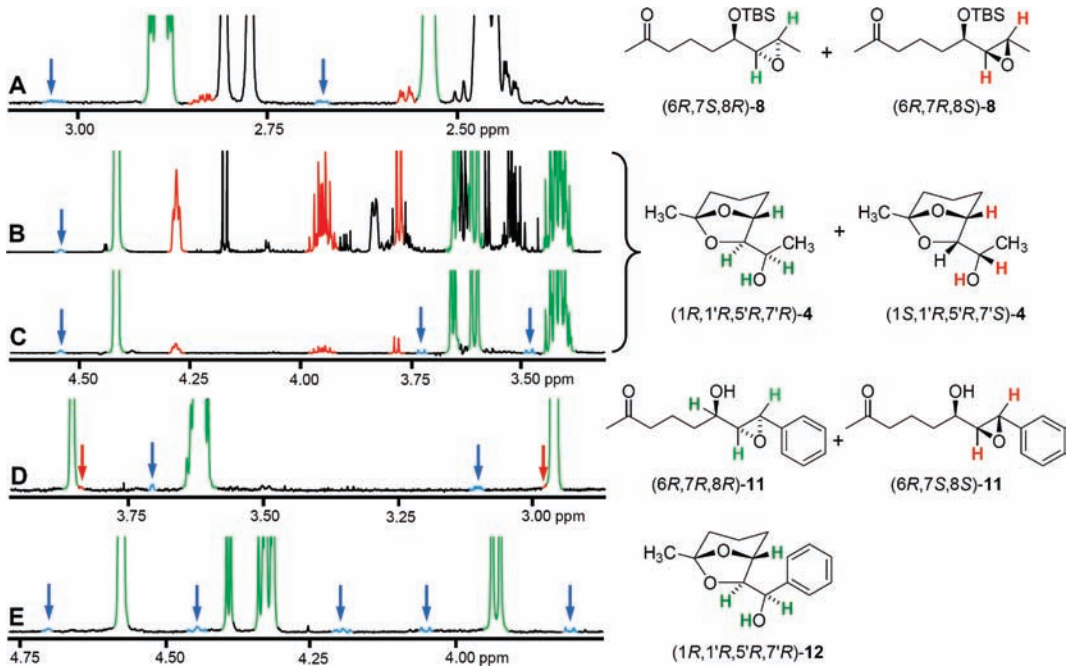
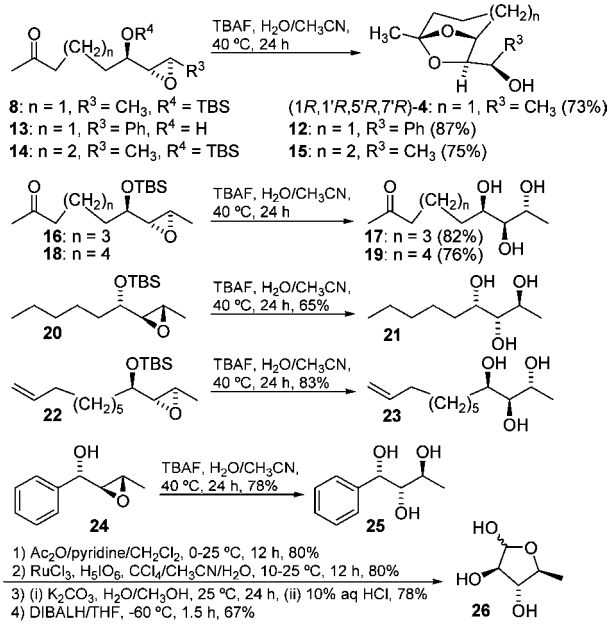


Figure 2. NMR spectroscopic analysis of TBAF-promoted epoxyalcohol hydrolysis (600 MHz, acetone-d_6). (A) ^{1}H NMR spectrum of epoxyalcohol (6*R*,7*S*,8*R*)-**8** (green signals), containing about 3% of the (6*R*,7*R*,8*S*)-diastereomer (red signals). To illustrate sample purity, ^{13}C-satellites (intensity 0.5% of the parent signals) are marked blue. (B) ^{1}H NMR spectrum of a 4:1 mixture of (1*R*,1′*R*,5′*R*,7′*R*)-4 (green) and its (1*S*,1′*R*,5′*R*,7′*S*)-diastereomer (red signals), along with smaller amounts of other cyclization products, obtained from (6*R*,7*S*,8*R*)-**8** via treatment with H_2SO_4. (C) ^{1}H NMR spectrum of a 97:3 mixture of 6,8-dioxabicyclo[3.2.1]octanes obtained from (6*R*,7*S*,8*R*)-**8** via treatment with TBAF. (D) ^{1}H NMR spectrum of (6*R*,7*R*,8*R*)-**11** (green signals), containing 0.5% or less of the (6*R*,7*S*,8*S*)-diastereomer (red signals). (E) ^{1}H NMR spectrum of (1*R*,1′*R*,5′*R*,7′*R*)-**12** (green signals) derived from treatment of (6*R*,7*R*,8*R*)-**11**. ^{13}C-satellites (blue arrows, intensity 0.5% of parent signal) are clearly visible, whereas signals of other diastereomers are too small to be discerned.

Scheme 2. TBAF-Promoted Hydrolysis of a Variety of Epoxyalcohols and Synthesis of 5-Deoxy-L-arabinose

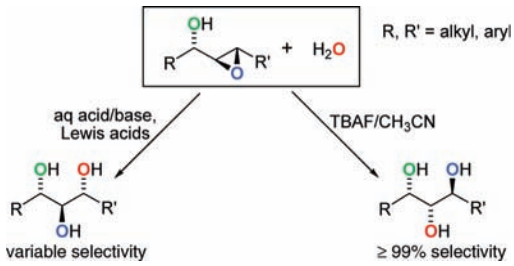


5-oxohexyl substituents quickly cyclized forming bicyclic acetals. NMR spectroscopic analysis of the reaction products confirmed full preservation of diastereomeric purity of the employed epoxyalcohols. Isolated yields varied between 65% and 87%, in addition to 0−20% of recovered starting materials.

These results show that TBAF-promoted hydrolysis of epoxyalcohols is effective for a wide range of substrates, for example, tolerating the presence of unprotected carbonyl groups. The applicability toward double bond or phenyl-substituted epoxyalcohols such as **13** or **24** allows introduction of additional oxygenation proximal to the triol, providing access to uncommon carbohydrate derivatives. A simple example is 5-deoxy-L-arabinose (**26**), an intermediate in several published syntheses of biopterin derivatives.[12] As shown in Scheme 2, TBAF-promoted hydrolysis of epoxyalcohol **24** allowed preparation of 5-deoxy-L-arabinose of high diastereomeric purity (>99% de for the mixture of anomers) in five straightforward steps.

In conclusion, our method enables preparation of *arabino*- or *lyxo*-configured consecutive triols of very high diastereomeric purity *via* diastereoselective α-hydrolysis of the appropriate epoxyalcohols. The method's simplicity and mild

Scheme 3. Ring Opening of α,β-Epoxyalcohols Using TBAF Compared to Other Methods[7,9]



conditions suggest broad applicability, and it effectively complements methods that facilitate ring opening in the β-position of epoxyalcohols (Scheme 3).[7,9]

Given that for α,β-epoxyalcohols nucleophilic attack at the β-position is generally much preferred,[7,9] the selectivity for α-attack in the presence of TBAF is striking. Interestingly, this unusual reactivity seems to be specific to the fluoride salt, as attempts to substitute TBAF with the similarly basic tetrabutylammonium hydroxide were not successful. Treatment of epoxyalcohols with tetrabutylammonium hydroxide in acetonitrile at 40 °C produced only small amounts of triol (<20% conversion after 24 h), which was found to be of low diastereomeric purity. As could be expected, treatment of epoxyalcohols with the much less basic tetrabutylammonium chloride or perchlorate did not effect any epoxide opening. On the basis of other recent examples for solvent-dependent changes in regioselectivity of epoxide opening,[13] it seems possible that specific hydrogen-bonding interactions facilitate α-attack in water-limited TBAF/CH_3CN/H_2O mixtures. We are currently exploring the utility of this method for opening epoxides with nucleophiles other than hydroxyl or water.

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Supporting Information Available: Complete experimental details along with spectroscopic data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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