



Synthesis of fused tetrahydropyrans by hydroalkoxylation of δ -hydroxy allenes



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ABSTRACT

Fused tetrahydropyrans were synthesized by silver(I)- and mercury(II)-mediated intramolecular hydroalkoxylation of δ -hydroxy allenes installed on a tetrahydropyran template. Cyclization of simple allenes was promoted by silver perchlorate to afford vinyl-substituted *trans*-fused bis-tetrahydropyrans, whereas cyclization of methyl-substituted allenes at the internal allenic carbon atom was achieved more effectively with a catalytic amount of mercuric triflate rather than with silver salts.

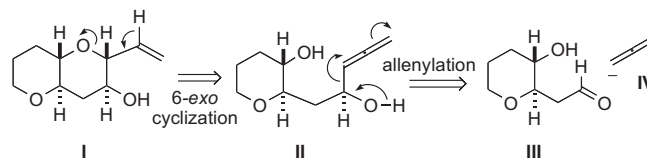
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1. Introduction

Highly substituted tetrahydropyran rings are common structural units encountered in a number of biologically active natural products such as acetogenins,¹ polyether antibiotics,² and ladder-like marine polycyclic ethers.³ Their complex architecture has attracted the attention of synthetic chemists, and a great deal of effort has been devoted to the development of new methodologies for tetrahydropyran synthesis.^{4,5} Among the many different approaches, intramolecular hydroalkoxylation of allenes with alcohols represents an attractive alternative in which a new carbon–oxygen bond is formed by activation of an allenic double bond by a metal cation such as silver, palladium, or gold followed by nucleophilic attack by a hydroxy group. The metal-mediated hydroalkoxylation of α -, β -, and γ -hydroxy allenes has been well studied and allows access to five- and six-membered oxygen heterocycles in a straightforward manner.^{6,7} However, hydroalkoxylation of δ -hydroxy allenes has rarely been studied. The few reported examples are restricted to simple acyclic δ -hydroxy allenes,⁸ and their application to the synthesis of fused polycyclic ether ring systems remains unexplored.

In the course of our synthetic study on polycyclic ethers,⁹ we have become interested in the hydroalkoxylation reaction of δ -hydroxy allene **II** to tetrahydropyran **I** (Scheme 1). Structural units

such as **I** have usually been prepared using the π -orbital assisted 6-*endo* hydroxy epoxide opening method¹⁰ and a palladium-catalyzed cyclization of hydroxy allylic alcohols.¹¹ The cyclization precursor **II** could be readily prepared by the nucleophilic addition of allenyl anion **IV** to aldehyde **III**. This retrosynthetic analysis enables a short route to the vinyl-substituted tetrahydropyran **I**. Herein, we report the reactivities and stereoselectivities of silver(I)- and mercury(II)-mediated hydroalkoxylation of δ -hydroxy allenes templated on a tetrahydropyran ring.

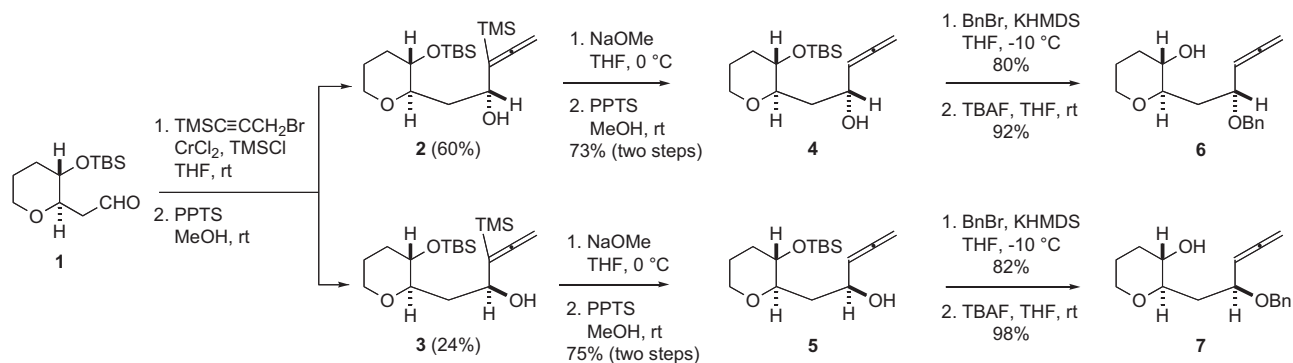


Scheme 1. Retrosynthetic analysis of **I**.

2. Results and discussion

The requisite δ -hydroxy allenes were prepared by allenylation of the optically active aldehyde **1**¹² (Scheme 2). Regioselective addition of commercially available 1-trimethylsilyl-3-bromopropyne with **1** in the presence of CrCl_2 and trimethylchlorosilane¹³ afforded allenic alcohols **2** and **3** in 60% and 24% yields, respectively. Selective desilylation of the C-TMS group in the presence of the *O*-

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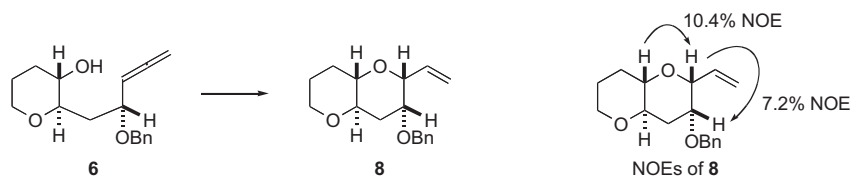
Scheme 2. Synthesis of δ -hydroxy allenes **6** and **7**.

TBS group was carried out under the [1,3]-Brook rearrangement reaction conditions.¹⁴ Thus, treatment of **2** and **3** with sodium methoxide in THF at 0 °C yielded α -trimethylsilyloxy allenes, whose *O*-TMS groups were selectively removed by treatment with PPTS in methanol to give alcohols **4** and **5** in good yields. In order to verify the stereochemistry of **5**, we attempted a reaction in which the reagent control can be simply extended to **1**, Corey's asymmetric allenylation of aldehyde **1** with (4*R*,5*R*)-2-bromo-1,3-bis(*p*-toluenesulfonyl)-4,5-diphenyl-1,3,2-diazaborolidine.¹⁵ The sample prepared by asymmetric allenylation was identical to **5**, confirming the (*S*)-configuration of the hydroxy group. Benzoylation of **4** and **5** followed by cleavage of the TBS ether with TBAF afforded α -benzyloxy δ -hydroxy allenes **6** and **7** in 74% and 80% yields, respectively, after the two steps.

First, intramolecular hydroalkoxylation of **6** with silver salts was studied (Table 1). The cyclization reaction of δ -hydroxy allene **6** with AgNO_3 under Gore's standard conditions^{8a} did not proceed at ambient temperature. However, the cyclization was driven at elevated temperatures over a longer reaction time (80 °C, 40 h) with 4 equiv of AgNO_3 in dioxane/ H_2O to afford bis-tetrahydropyran **8** in 40% yield as a single isomer (entry 1). Treatment with 1.2 equiv of AgClO_4 in 1,2-dichloroethane (DCE) at

level (0.3 equiv) resulted in the incomplete consumption of **6** after prolonged time (data not shown). A higher temperature shortened the reaction time but lowered the yield (entry 3). The reactions with AgBF_4 and AgOTf were also effective in affording the product in moderate yields (entries 4 and 5). It has been reported that $\text{Hg}(\text{OCOCF}_3)_2$ can promote hydroalkoxylation of γ -hydroxy allenes under stoichiometric conditions,¹⁶ and, more recently, Nishizawa reported that $\text{Hg}(\text{OTf})_2$ has a higher affinity for alkenes and alkynes and promotes intramolecular heterocyclization under very mild reaction conditions with high catalytic turnover.¹⁷ However, the reaction for hydroxy allenes has not been explored yet. We therefore attempted to examine the use of $\text{Hg}(\text{OTf})_2$ for the hydroalkoxylation of **6**. The reaction caused significant decomposition of the reaction mixture, even with a catalytic amount (10 mol %) of $\text{Hg}(\text{OTf})_2$ at a lower temperature (0 °C), and led to a poor yield (entry 6).

Hydroalkoxylation of the diastereomeric δ -hydroxy allene **7** was examined next. The cyclization was promoted by silver salts, but the yields were generally low, and a mixture of diastereoisomers was formed (Table 2). Treatment of **7** with AgClO_4 or AgBF_4 led to inseparable 8:1 mixtures of isomers **9** and **10** in 42% or 32% combined yields, respectively (entries 2 and 3). The

Table 1
Hydroalkoxylation of **6**

Entry	Reagent	equiv	Solvent	Temp (°C)	Time (h)	Yield ^a (%)
1	AgNO_3	4.0	Dioxane/ H_2O	80	40	40
2	AgClO_4	1.2	DCE	50	20	88
3	AgClO_4	1.5	DCE	80	10	59
4	AgBF_4	1.5	DCE	50	20	62
5	AgOTf	1.5	DCE	50	15	53
6	$\text{Hg}(\text{OTf})_2$	0.1	CH_2Cl_2	0	5	20

^a Isolated yield.

50 °C for 20 h afforded product **8** in 88% yield (entry 2). ¹H NMR analysis of the isolated product showed the exclusive formation of **8**, whose stereochemistry was unambiguously determined according to the nuclear Overhauser effect (NOE) enhancements, as shown. Decreasing the amount of the silver salt to a catalytic

diastereomeric ratio (dr) increased to 49:1 when AgOTf was employed (entry 4). In contrast to the silver(I)-mediated reactions, the mercury(II)-catalyzed hydroalkoxylation showed the opposite diastereoselectivity to afford a 1:2 mixture of products in 59% yield (entry 5).

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