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Stereoselective syntheses of 2-methyl-1,3-diol acetals *via* Re-catalyzed [1,3]-allylic alcohol transposition†

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Rhenium-catalyzed stereoselective transposition of allylic alcohols is reported. In the presence of 1 mol% of Re_2O_7 , (*E*- or *Z*-) δ -hydroxymethyl-*anti*-homoallylic alcohols were converted into the acetals of 2-methyl-1,3-*syn*-diols with excellent diastereoselectivities. 1,3-*syn*-Diol acetals can also be synthesized from (*E*-) δ -hydroxymethyl-*syn*-homoallylic alcohols.

Introduction

Polyhydroxylated natural products, oxo polyene macrolide antibiotics for instance, have played an important role in modern drug discovery.^{1,2} Driven by a myriad of the biological activities, these natural products have garnered significant attention from the organic synthesis and chemical biology communities. One indispensable structural motif of these polyhydroxylated natural products is the stereodefined 2-methyl-1,3-diol (Fig. 1).³ Traditionally, these 2-methyl-1,3-diols are often assembled *via* a reiterative carbonyl crotylation approach⁴ or an aldol-reduction reaction sequence.⁵ These methods have been widely adopted in the total syntheses of polyhydroxylated natural products. Despite these advances, the development of catalytic methods that permit stereoselective syntheses of these 2-methyl-1,3-diol entities still remains an important objective in organic chemistry.

Pioneered by the Osborn group, rhenium catalysts, such as $\text{O}_3\text{ReOSiPh}_3$, Re_2O_7 , have been shown to promote [1,3]-allylic alcohol transposition.^{6,7} However, the regiochemical control of these reactions is generally poor, resulting in a thermodynamic mixture of allylic alcohols (*e.g.*, A and B, Scheme 1). More recently, several strategies have been developed to address this limitation. For instance, the reaction can be rendered regioselective through capitalizing on alkene conjugation or steric effect.⁸ High regio-control can also be accomplished through capturing the alcohol group with a trapping agent, thereby shifting the equilibrium toward the desired direction.⁹

In the context of our program on asymmetric synthesis,^{10,11} we recently reported enantio- and stereoselective syntheses of δ -hydroxymethyl homoallylic alcohols 1, 2 and 3.¹² As one venue to explore the synthetic utilities of these molecules, we were intrigued whether the allylic alcohol moiety in 1–3 can undergo

[1,3]-allylic transposition to generate stereodefined 2-methyl-1,3-diols (*e.g.*, 4, 5). Taking the inspiration from prior studies,^{8,9} we report herein Re-catalyzed highly stereoselective allylic transposition of alcohols 1–3 (Scheme 1). With 1 mol% Re_2O_7 as the catalyst, the operationally simple protocol permits stereoselective syntheses of 2-methyl-1,3-*syn*-diol acetals 4 (*anti, anti*) and 5 (*syn, syn*) in high yields from alcohols 1–3.¹³

Results and discussion

In initial experiments, alcohol 1a was treated with 1 mol% of Re_2O_7 and 2,2-dimethoxypropane in CH_2Cl_2 . The reaction

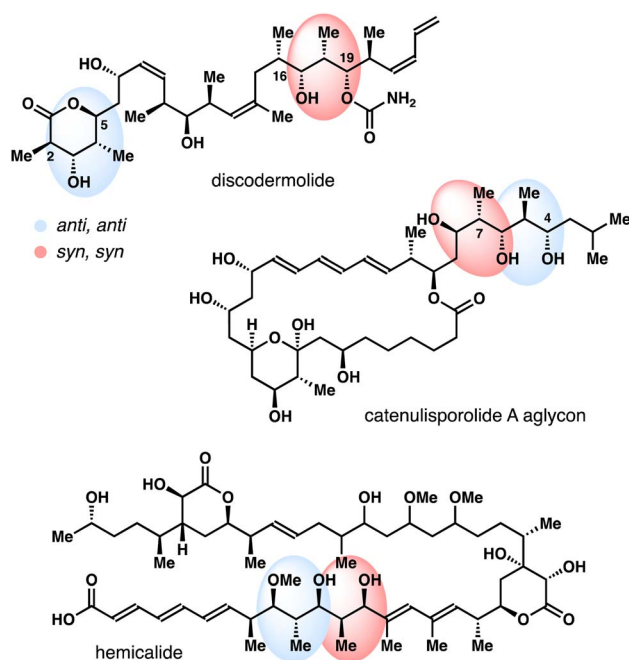
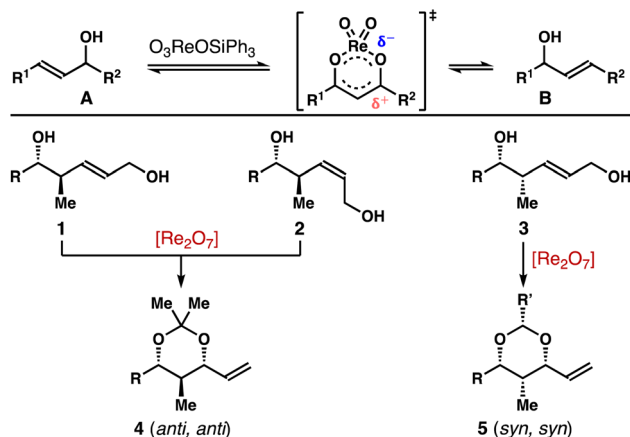


Fig. 1 Selected natural products with 2-methyl-1,3-diols.

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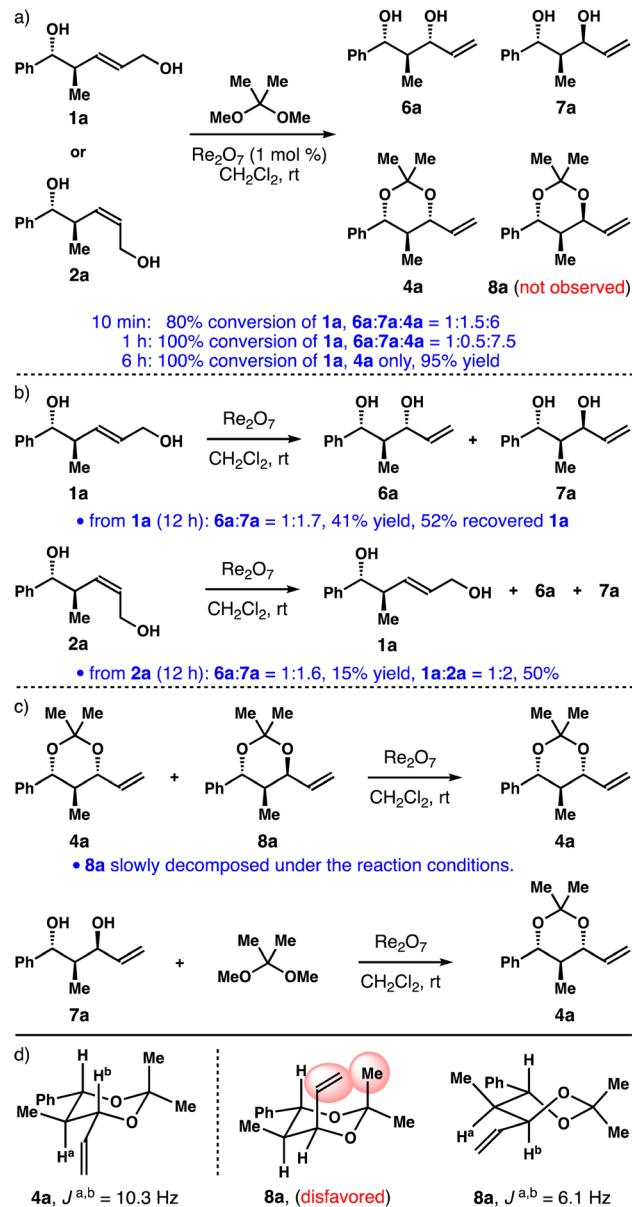




Scheme 1 Transposition of allylic alcohols.

progress was monitored by the ^1H NMR spectroscopy. We discovered that, within 10 minutes, about 80% of alcohol **1a** was converted into a 1 : 1.5 : 6 mixture of diols **6a**, **7a** and acetal **4a**. Formation of acetal **8a** was not detected (panel a, Scheme 2). Full conversion of **1a** was achieved in 1 h, affording a 1 : 0.5 : 7.5 mixture of **6a**, **7a** and **4a**. After 6 h at ambient temperature, acetal **4a** was isolated as the only product in 95% yield. Similar results were obtained when *Z*-isomer **2a** was used. Next, we treated alcohol **1a** with 1 mol% of Re_2O_7 in the absence of 2,2-dimethoxypropane (panel b, Scheme 2). After 12 h at ambient temperature, a 1 : 1.7 mixture of diols **6a** and **7a** was obtained in 41% yield, and 52% of alcohol **1a** was recovered. In the case of alcohol **2a**, a 1 : 1.6 mixture of **6a**, **7a** was isolated in 15% yield, and a 1 : 2 mixture of diols **1a**, **2a** was also obtained in 50% yield after 12 h, together with some unidentifiable by-products. We also treated a mixture of acetals **4a** and **8a** with Re_2O_7 catalyst (panel c, Scheme 2). After 6 h at ambient temperature, acetal **8a** completely decomposed and **4a** remained unchanged under the reaction conditions. Finally, when single isomer 1,3-*anti*-diol **7a** was exposed to the reaction conditions, it was fully converted into 1,3-*syn*-acetal **4a**. We did not observe the formation of 1,3-*anti*-acetal **8a**. The structures of acetals **4a** and **8a** were assigned based on the coupling constant analyses and nOe studies. While 1,3-*syn*-acetal **4a** adopts a chair conformation, 1,3-*anti*-isomer **8a** prefers a twist-boat conformation, as the corresponding chair conformation is disfavoured due to the 1,3-diaxial interactions (shown in red in **8a**). On the basis of these data, it is apparent that, for alcohol **1a**, the equilibrium among **1a** and diols **6a**, **7a** was established under the catalytic conditions (panel b, Scheme 2). And 1,3-*syn*-diol **6a** reacted irreversibly with 2,2-dimethoxypropane to give acetal **4a**. 1,3-*anti*-Diol **7a** did not react to form acetonide **8a** under the conditions, presumably owing to the higher energy of a twist-boat-like transition state. Diol **7a** was funnelled into **6a** via **1a** through the reversible Re-catalyzed [1,3]-allylic transposition, eventually affording acetal **4a** as the sole product.

The operationally simple protocol was extended to a variety of diols **1** and the results are summarized in Table 1. Except diols with an electron-donating group at the *para*-position of the

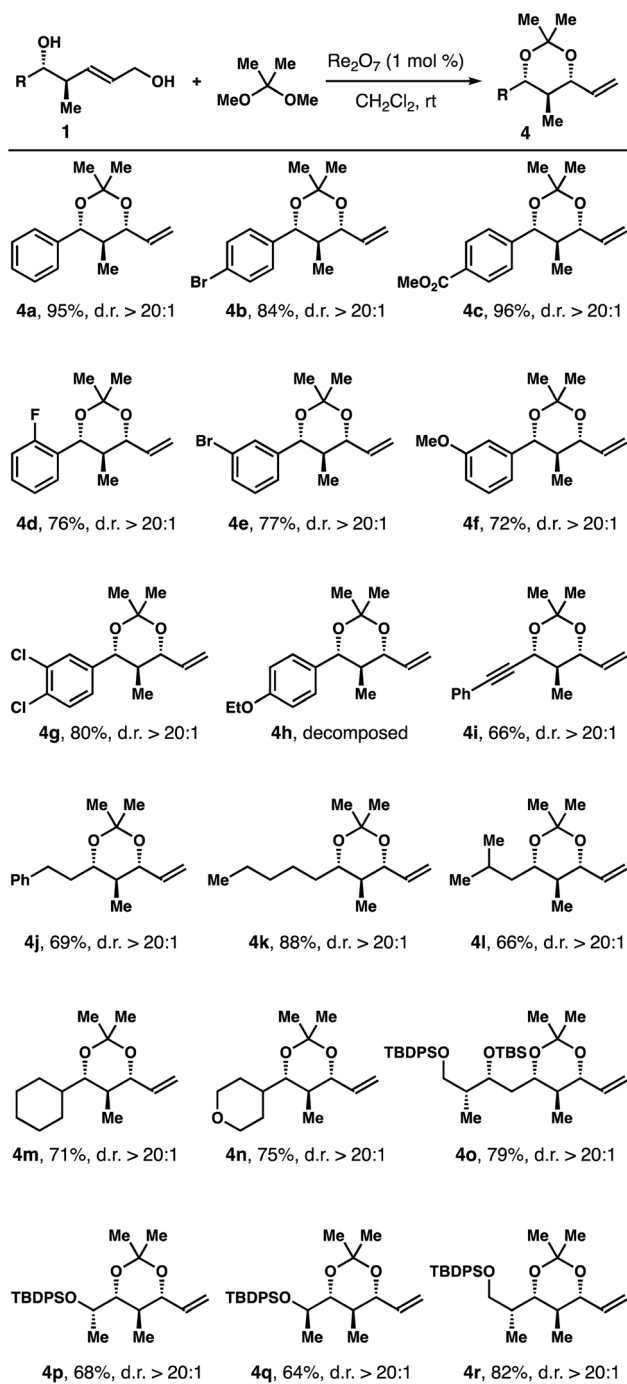


Scheme 2 Initial studies on allylic alcohol transposition.

arene, **1h** for example, the reaction worked quite well with other diols regardless the substitution patterns and steric environments on the arenes. And acetals **4a-g** were obtained in 72–96% yields with excellent 1,3-*syn*-selectivities. The reaction tolerates an alkyne group, and acetal **4i** was isolated in 66% yield with >20 : 1 diastereoselectivity. Diols with an aliphatic side chain also reacted under the reaction conditions to give **4j-n** in 66–88% yield with >20 : 1 1,3-*syn*-selectivities. Encouraged by these results, we tested the protocol with structurally more elaborated diol substrates. Gratifyingly, the reactions proceeded smoothly to give acetals **4o-r** in 64–82% yields with excellent diastereoselectivities.

Table 2 summarizes the results of reactions with a few (*Z*)-alcohols **2** under the same conditions. As anticipated, 1,3-*syn*-

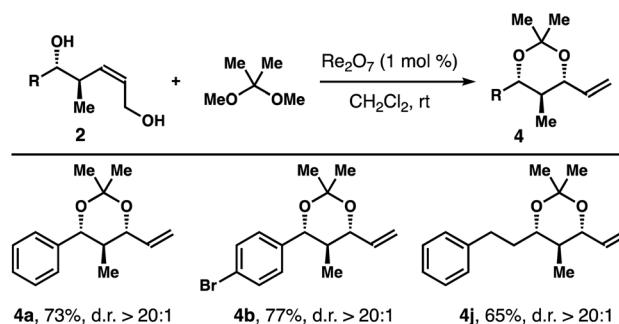


Table 1 Scope of diols **1** for rhenium-catalyzed stereoselective allylic alcohol transposition^{a,b,c}

^a Reaction conditions: diol **1** (0.1 mmol, 1.0 equiv.), acetal (0.2 mmol, 2.0 equiv.), Re₂O₇ (1 mol%), CH₂Cl₂, rt. ^b Diastereoselectivities were determined by ¹H NMR analysis of the crude reaction products. ^c Yields of isolated products are listed.

isomers **4a**, **4b**, and **4j** were obtained in 65–77% yields with >20:1 diastereoselectivities.

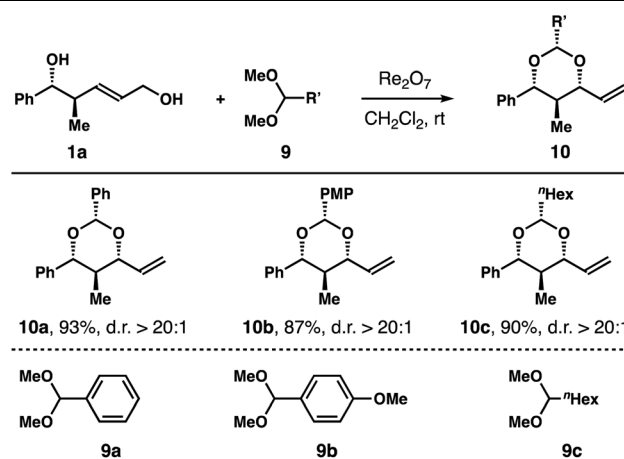
In addition to 2,2-dimethoxypropane, we also conducted reactions of diol **1a** with dimethyl acetals **9a–c**. As shown in

Table 2 Rhenium-catalyzed stereoselective allylic alcohol transposition with diols **2**^{a,b,c}

^a Reaction conditions: diol **2** (0.1 mmol, 1.0 equiv.), acetal (0.2 mmol, 2.0 equiv.), Re₂O₇ (1 mol%), CH₂Cl₂, rt. ^b Diastereoselectivities were determined by ¹H NMR analysis of the crude reaction products. ^c Yields of isolated products are listed.

Table 3, the reactions afforded products **10a–c** in 87–93% yields with excellent 1,3-*syn*-selectivities.

Next, we considered the reactions with (*E*)-*syn*-homoallylic alcohols **3** under the standard reaction conditions. Intriguingly, when R is a phenyl group in **3**, the reaction mostly led to the decomposition of the starting diol, only a small amount of acetal product was obtained (~20%). For substrate **3a** bearing an aliphatic side chain (R = PhCH₂CH₂), 70% of starting diol **3a** was consumed in 1.5 h. And a 1:1 mixture of diols **11a** and **12a** was obtained in 18% yield, together with a 9:1 mixture of acetals **13a** and **14a** in 45% isolated yield (panel a, Scheme 3). When the reaction was conducted at ambient temperature for 12 h, **3a** was fully consumed, and acetal **13a** was isolated in 73% yield with 15:1 *syn*-selectivity (panel b, Scheme 3). When diol **3a**

Table 3 Rhenium-catalyzed transposition of allylic alcohol **1a** using other acetals^{a,b,c}

^a Reaction conditions: diol **1a** (0.1 mmol, 1.0 equiv.), acetal **9** (0.2 mmol, 2.0 equiv.), Re₂O₇ (1 mol%), CH₂Cl₂, rt. ^b Diastereoselectivities were determined by ¹H NMR analysis of the crude reaction products. ^c Yields of isolated products are listed.



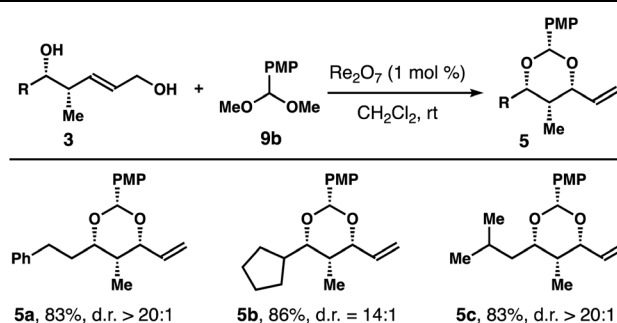
was subjected to the reaction conditions in the absence of 2,2-dimethoxypropane for 12 h, a 1 : 1 mixture of **11a** and **12a** was obtained in 45% yield, and remaining **3a** was recovered in 50% yield (panel c, Scheme 3). On the basis of these data, we conclude that an analogous reaction pathway to *anti*-diols **1** is operational for the *syn* counterpart **3a**. Similar to the cases of **4a** and **8a** in Scheme 2, 1,3-*syn*-isomer **13a** adopts a chair conformation and 1,3-*anti*-isomer **14a** prefers a twist-boat conformation (panel d, Scheme 3).

Table 4 summarizes the results of reactions with several alcohols **3** with an aliphatic side chain. In these experiments, acetal **9b** was utilized to minimize the volatility of the reaction products. Under the standard reaction conditions, acetals **5a–c** were isolated in 83–86% yields with high 1,3-*syn*-selectivities.

A few structurally more complex diols **15a–c** were subjected to the reaction conditions in the presence of **9b** (Scheme 4). The reaction with **15a** produced acetal **16** in 72% yield with >20 : 1 diastereoselectivity. For substrate **15b**, the product was inseparable from the aldehyde by-product derived from **9b**. After treating the reaction mixture with TBAF, alcohol **17** was obtained in 62% yield with 18 : 1 dr. For substrate **15c**, partial deprotection of the silyl ether was observed during the course of the reaction. After prolonged reaction time (24 h) with 3 equiv. of **9b**, bis-acetal **18** was isolated in 70% yield with >20 : 1 diastereoselectivity.

The results from stereochemically rich diol substrates in Table 1 (**40–r**) and Scheme 4 are worth noting, as the products could be utilized as valuable intermediates for the synthesis of

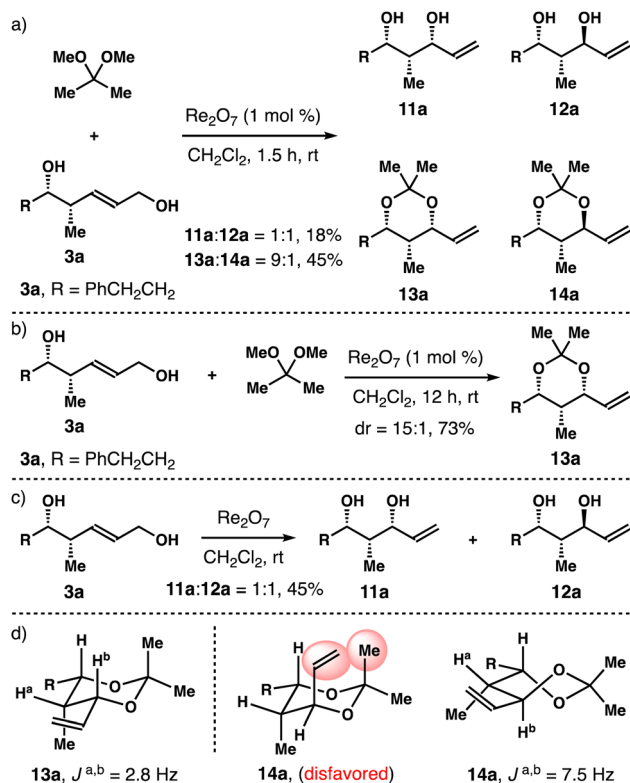
Table 4 Rhenium-catalyzed stereoselective allylic alcohol transposition with diols **3**^{a,b,c}



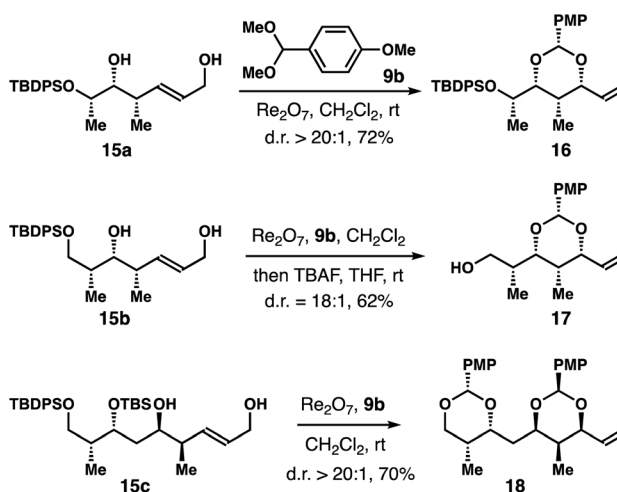
^a Reaction conditions: diol **3** (0.1 mmol, 1.0 equiv.), acetal **9b** (0.2 mmol, 2.0 equiv.), Re_2O_7 (1 mol%), CH_2Cl_2 , rt. ^b Diastereoselectivities were determined by ^1H NMR analysis of the crude reaction products. ^c Yields of isolated products are listed.

polyhydroxylated natural products. For example, the relative configuration of the four contiguous stereocenters in acetal **4r** nicely matches the C2–C5 fragment of discodermolide and the C4–C7 fragment of catenulisporolide A aglycon (Fig. 1). The relative configuration of the four contiguous stereocenters in acetal *ent*-**17** matches the C16–C19 fragment of discodermolide and the C2–C5 fragment of erythronolide B.

Further product derivatization studies are summarized in Scheme 5. Acetal **4a** underwent an alkene metathesis reaction with acrylate **19** to furnish α,β -unsaturated ester **20** in 72% yield with >20 : 1 *E*-selectivity. Hydroboration–oxidation of the alkene group of **4a** gave primary alcohol **21** in 71% yield. Dess–Martin oxidation of alcohol **21** afforded aldehyde **22** in 68% yield.¹⁴ Aldehyde **22** could participate in a variety of transformations. For instance, Wittig olefination of aldehyde **22** with reagent **23** delivered α,β -unsaturated ester **24** in 89% yield with >20 : 1 *E*-selectivity.

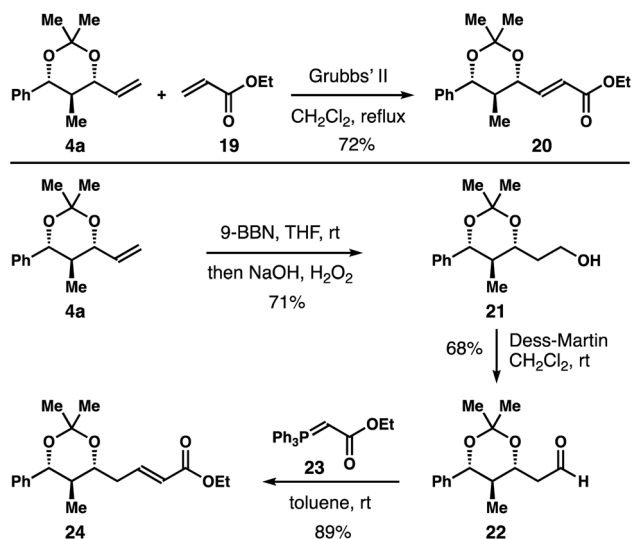


Scheme 3 Rhenium-catalyzed stereoselective allylic alcohol transposition studies with diol **3a**.



Scheme 4 Rhenium-catalyzed stereoselective allylic alcohol transposition with structurally complex diols **15**.





Scheme 5 Product derivatization.

Conclusions

In summary, we developed a Re-catalyzed allylic alcohol transposition protocol to convert diols 1–3 into the acetals of 2-methyl-1,3-*syn*-diols with excellent diastereoselectivities. In addition to 2,2-dimethoxypropane, several other acetals can also be utilized in the reactions. Importantly, reactions with a variety of structurally complex allylic alcohols worked well under the standard conditions, affording acetal intermediates that are synthetically valuable for the construction of poly-hydroxylated natural products.

Data availability

All the data have been included in the ESI.†

Author contributions

The concept of the manuscript is conceived by Ming Chen, and Jiaming Liu conducted all the experiments.

Conflicts of interest

There are no conflicts to declare.

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