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Dioxolane-to-Bridged Acetal-to-Spiroketal via Ring-Closing Metathesis and Rearrangement: A Novel Route to 1,7-Dioxaspiro[5.5]undecanes

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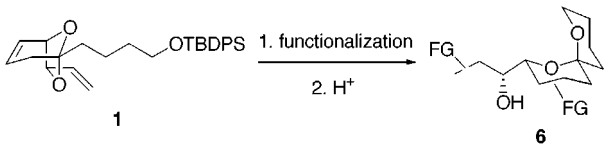
ABSTRACT



Several examples of 1,7-dioxaspiro[5.5]undecane spiroketal systems have been synthesized from the common bicyclic intermediate 1 via acid-catalyzed rearrangement. Intermolecular ketalization of C_2 symmetric diene diol 3 with ketone 9 and then desymmetrization by ring-closing metathesis rapidly constructs bicyclic acetal 1. The locked conformation and steric bias of 1 allow stereoselective functionalization of one or both double bonds before spiroketalization.

Spiroketals occur widely among natural products of biological and pharmaceutical interest, including marine toxins, insect pheromones, antibiotics, and anticancer agents.[1] Recent synthetic and therapeutic interest in spiroketal-containing natural products such as the halichondrins[2] and the spongistatins[3] underscores the need for efficient, versatile, and stereoselective methods of spiroketal synthesis.

Traditional routes to spiroketals typically involve construction of an acyclic keto-diol via intermolecular C−C bond formation followed by an intramolecular dehydrative ketalization. An appealing alternative is illustrated in this paper that employs an intermolecular ketalization to converge subunits, followed by an intramolecular C−C bond formation/desymmetrization through ring-closing metathesis (RCM).[4]

Bicyclic acetal formation via this ketalization/RCM sequence has been developed for the synthesis of (+)-*exo*- and *endo*-brevicomin[5a] and the sialic acids KDN and Neu5Ac.[5b,c] The rigid 6,8-dioxabicyclo[3.2.1]octanes formed in these routes allow stereoselective functionalization of the six membered ring as a result of the locked conformation and

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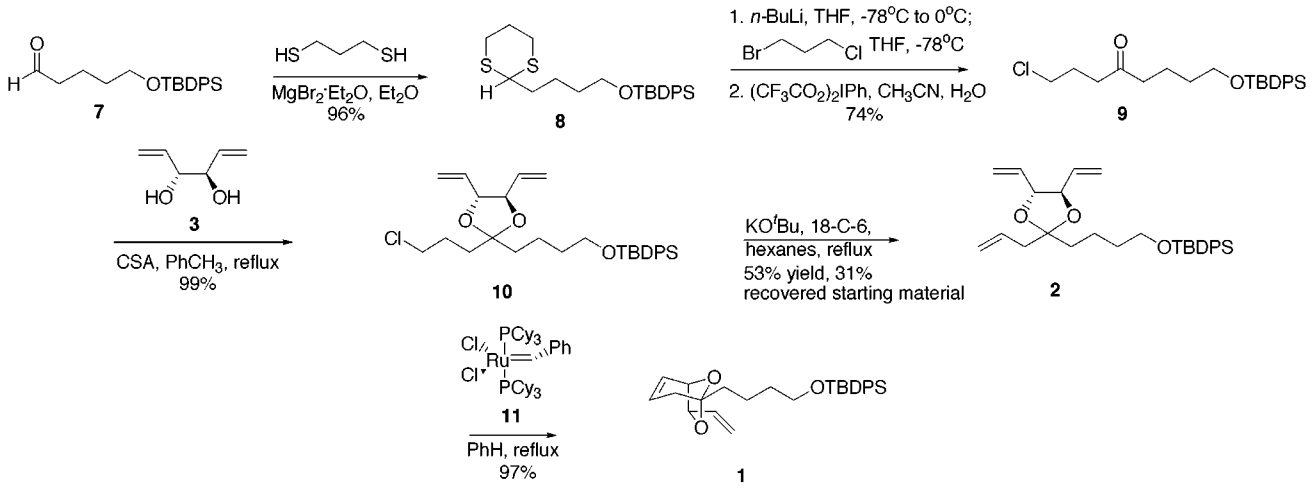
Scheme 1. Synthesis of Bicyclic Acetal **1**



steric bias of the bicyclic acetal. We envisioned bicyclic acetal **1** as a common intermediate in the strategy to obtain 1,7-dioxaspiro[5.5]undecanes **6** as illustrated in Figure 1.

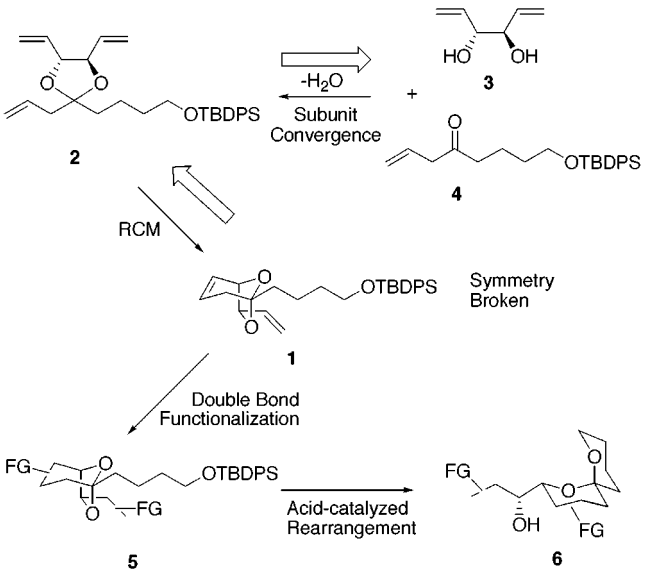


Figure 1. Desymmetrization/spiroketalization strategy.

Bicyclic acetal **1** was synthesized in six steps from known aldehyde **7**[6] (Scheme 1). This aldehyde was subjected to Lewis acid promoted thioketalization with 1,3-propanedithiol to produce **8** in a quick and mild transformation.[7] Dithiane **8** was alkylated with 1-bromo-3-chloropropane and deprotected with the hypervalent iodine species $(CF_3CO_2)_2IPh$[8] to provide ketone **9**, one partner for the intermolecular ketalization. This ketalization was accomplished by combining C_2 symmetric diene diol **3**,[9] CSA, and **9** in refluxing toluene with azeotropic removal of water to produce **10** in excellent yield. Subjection of **10** to elimination with KO^{t}Bu/18-crown-6[5a] in hexane gave triene **2** in modest yield, which could be increased to 71% upon one recycle of the recovered starting material. Intramolecular C−C bond formation/desymmetrization of pseudo-C_2-symmetric triene **2** via RCM with Grubbs' catalyst **11** afforded the 6,8-dioxabicyclo[3.2.1]-octane **1** in excellent yield.

Several olefin functionalizations were performed that exploited the rigid conformation of **1** (Scheme 2). Only one

Scheme 2. Functionalization of **1**

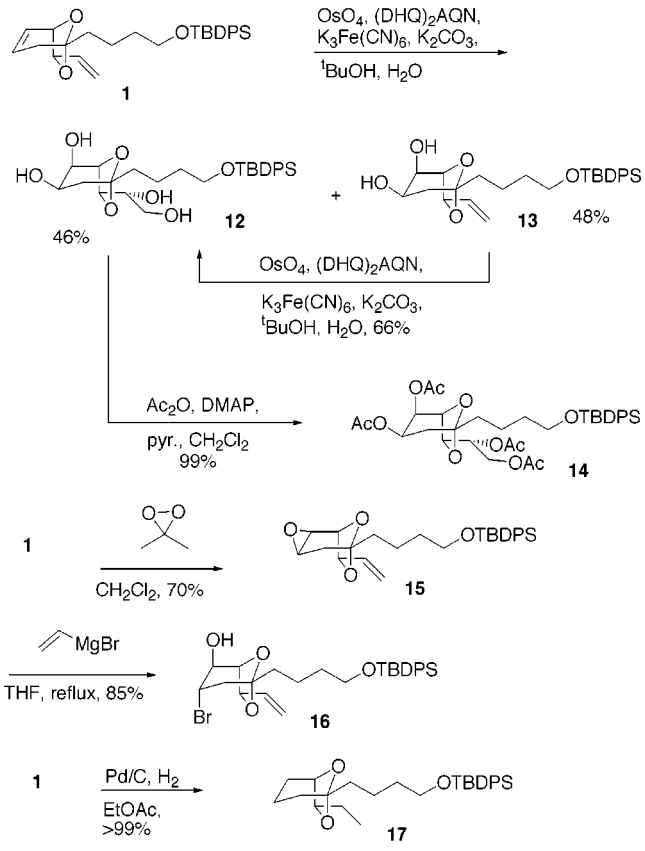
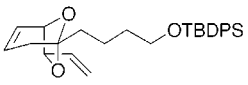
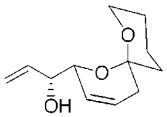
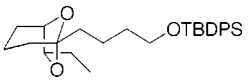
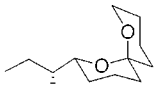
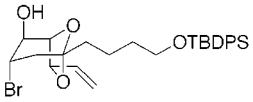
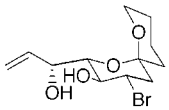
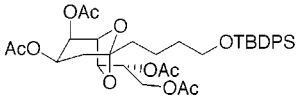
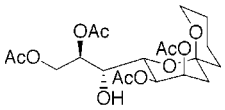


Table 1. Spiroketalization Data

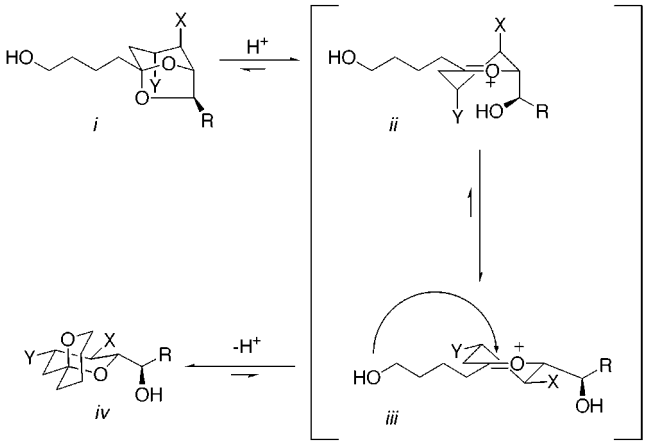
substrate	spiroketal	HF / CH_3CN[a] yield, time	HCl / MeOH[b] yield, time
 **1**	 **18**	71%, 30 min	97%, 6 hr
 **17**	 **19**	89%, 14 hr	75%, 5 d
 **16**	 **20**	83%, 4 hr	87%, 1 d
 **14**	 **21**	72%, 1 d	c

[a] 3 M HF in CH_3CN. [b] 3% v/v HCl in MeOH. [c] Complex mixture of **21** and other uncharacterized products due to competitive deacetylation.

side of the ring olefin was accessible to Sharpless asymmetric dihydroxylation while the $(DHQ)_2AQN$[10] ligand was employed to control the stereochemistry of dihydroxylation on the terminal double bond. The reaction was rather sluggish and took 2 days to convert 46% to the tetraol **12** and 48% to the diol **13**. Resubmission of **13** to the reaction conditions resulted in 66% conversion to **12**. Acetylation of **12** proceeded nearly quantitatively to yield the tetraacetate **14**. Epoxidation of **1** with dimethyldioxirane (DMDO)[11] occurred regio- and stereoselectively to give **15**. This epoxide was resistant to opening with vinyl Grignard, vinyl cuprate, and hydride (Red-Al) nucleophiles. The sole product from the attempted opening of epoxide **15** with vinyl Grignard was the unexpected bromohydrin **16**. This transformation was also performed with $MgBr_2 \cdot Et_2O$, but only 47% of the bromohydrin **16** was isolated. Catalytic hydrogenation of **1** gave the saturated bicyclic acetal **17**.

Acid-catalyzed spiroketalization of the functionalized 6,8-dioxabicyclo[3.2.1]octanes was envisioned to occur via deprotection of the primary alcohol to give intermediate *i* (Scheme 3). Protonation promotes ring opening to the

Scheme 3. Spiroketalization



oxacarbenium ion *ii*, which has all three substituents in pseudoaxial positions; a ring flip to *iii* places the substituents in pseudoequatorial positions. Axial attack of the primary alcohol on the oxacarbenium ion occurs in structure *iii*, leading to a chair-chair conformation for spiroketal *iv*. In this structure both ring oxygens are in axial positions, fully maximizing the anomeric effect.[1]

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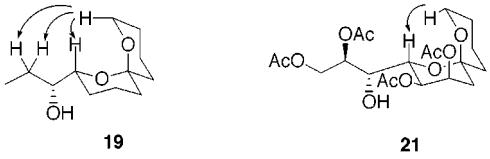
(11) Prepared as described in: Adam, W.; Bialas, J.; Hadjiarapoglou, L. *Chem. Ber.* **1991**, *124*, 2377.

Functionalized dioxabicyclo[3.2.1]octanes **14** and **16**, fully saturated **17**, and the original bridged bicyclic acetal **1** were subjected to both HF and HCl conditions for deprotection/spiroketalization (Table 1). Reaction times were faster with HF than HCl, a result of the TBDPS protecting group being more labile under the former conditions. Spiroketalization of the four substrates proceeded without complications except for **14** where an inseparable mixture of **21** and other unidentified products was obtained upon treatment with HCl in methanol. Deacetylation is competitive with silyl deprotection under these conditions, revealing the secondary alcohols, which can trap the oxacarbenium ion.

^{1}H NMR and crystallographic data for spiroketals **19**−**21** confirm their stereochemistry as that depicted in *iv* (Scheme 3). NOE studies of spiroketals **19**[12] and **21** showed the enhancements illustrated in Figure 2. A crystal structure of



19 **21**

Figure 2. NOE enhancements.

bromohydrin spiroketal **20** (Figure 3) confirms this stereochemical outcome, with both ring oxygens in axial positions.

In conclusion, we have shown that **1** can be used as a general substrate that can be selectively functionalized to produce a variety of spiroketal precursors. Acid-catalyzed ketal isomerization proceeds well with these substrates, resulting in only one spiroketal diastereomer. Applications

(12) Unsaturated spiroketal **18** was subjected to catalytic hydrogenation and the spectra of the resulting product were identical to those of **19**, confirming its structure.

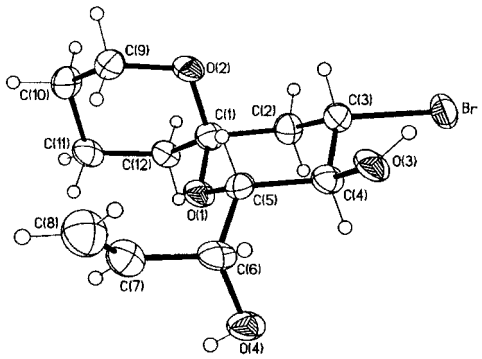


Figure 3. Crystal structure of **20**.

of this new route to spiroketals in target- and diversity-oriented synthesis[13] are underway.

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Supporting Information Available: Experimental procedures and spectral data for compounds **1**, **2**, **7**−**10**, and **12**−**21** and crystallographic data for compound **20**. This material is available free of charge via the Internet at http://pubs.acs.org.

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