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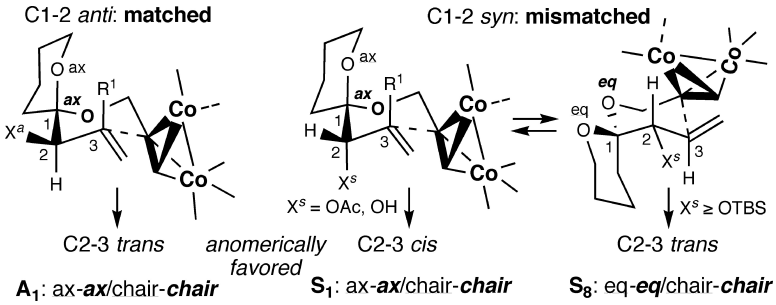

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An Anomeric Control on Remote Stereochemistry in the Synthesis of Spiroketals

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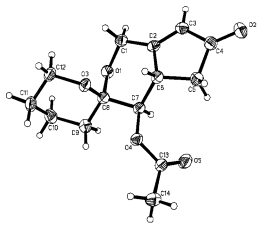
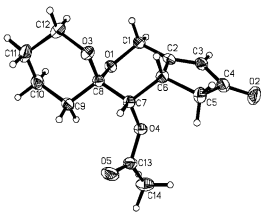
Spiroketals are prevalent structural motifs in natural products.[1] Their syntheses have predominantly relied on the classical internal ketalization from ketodiols with the stereochemical outcome of the spirocenter being dictated thermodynamically by the existing stereocenters in the ketodiol (**2** → **1** in Figure 1).[1] Seldom has it been in the opposite direction using a cyclic ketal as a tether-like template to control the reactivity and stereochemical issues away from the pending spirocenter (**3** → **1**). The lack of activities is likely because ketals have been mostly used as protecting groups such as those shown in **4** and **5**, although this approach can take advantage of conformational control via the well-known anomeric effect (1.5 kcal mol^{-1}).[1a,2−4] Our recent efforts in ketal-tethered reactions such as IMDA[5] and RCM[6] have identified some unique reactivity related to conformational control as a result of anomeric effect when employing cyclic ketals **3**. Our continued efforts on ketal-tethered reactivities uncovered a unique anomeric control on the stereoselectivity of a remote center. We report here evidence for such an anomeric effect.

It all began with our simple interest in exploring a ketal-tethered Pauson−Khand cycloaddition,[7,8] which led to the isolation of spiroketals **8** and **9**,[9] respectively, from ketal **7a** (C1−2 *anti*) and **7s** (C1−2 *syn*) using the standard $Co_2(CO)_8$ conditions (Scheme 1). However, we found a third product, which was initially thought to be a simple diastereomer. However, because it was found from reactions of both **7a** and **7s**, it was vigorously assigned. It turned to be dienone **10**, an elimination product, which can be derived from both **8** and **9**.



Spiroketal **8**



Spiroketal **9**

X-ray structures of spiroketals **8** and **9** provided an explanation as to why dienone **10** was found more abundantly from the reaction of **7s**. The C3−H and C2−OAc groups are perfectly anti in alignment in **9** for a facile E_2 elimination given its cis relative stereochemistry at C2−3, whereas it is trans at C2−3 in **8** with C3−H and C2−OAc being syn. We then became very intrigued with this reaction stereochemically since the results in Scheme 1 imply that the stereochemistry at C2 did not impact the outcome at C3 but the ketal center at C1 did.

A general transition state (TS) structure (see the left box in Scheme 2) is illustrated with the *existing* and ***pending*** pyran rings both in chair conformations and their respective oxygen substituent holding the axial position with respect to one another to account for two anomeric effects (∼3.0 kcal mol^{-1}).[1a,2−4] This overview

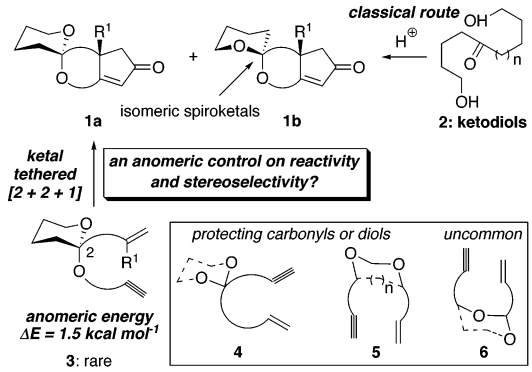
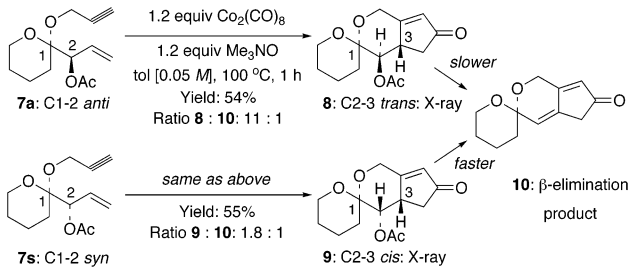
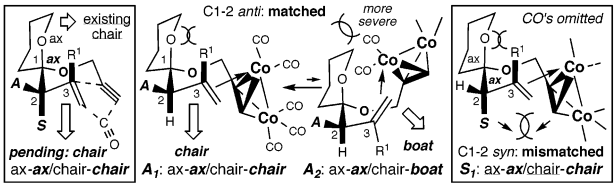


Figure 1. Ketal-Tether Approach to Spiroketal Synthesis.

Scheme 1. Preliminary Contrast



Scheme 2. Proposed Mechanistic Model



points to a matched or mismatched possibility depending upon the nature of the ***A*** or ***S*** group at C2 and that the stereochemistry at C2 appeared irrelevant to the outcome at C3.

When ***A*** = OAc and ***S*** = H (*anti*-ketals), it is perfectly matched. In this case, TS-$\boldsymbol{A_1}$ is likely the most favored conformation (versus TS-$\boldsymbol{A_2}$ and six additional conformations not shown[10]) for it possesses, in addition to the two anomerically favored mutually axial oxygen substituents, a chair TS conformation for the ***pending*** pyran ring with the ***A*** group in the pseudoequatorial position with no significant 1,3-diaxial interactions between R^1 and the *existing* pyran ring, thereby leading to spiroketals with C2−3 being exclusively trans. This selectivity is indifferent to the size of the ***A*** group (see Table 1). While the size of the terminal substituent (R) exerts no impact on the trans selectivity (entries 1−4),[11] the ***A*** group can be OH or as large as OTBDPS (entries 5−8 and 13), and the selectivity continues to favor C2−3 being trans.

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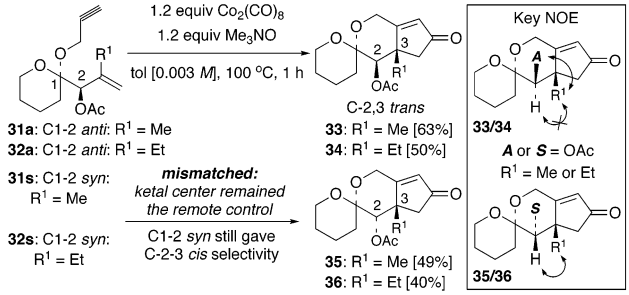
Table 1. Matched and Mismatched

entry	ketals[a]	R	P	spiroketals	yield[b] [cis:trans]
1	C1-2 *anti*	**7a** H	-		**8** 91%[c] [≤ 5 : 95][e]
2		**11a** Me	-		**14** 95 [≤ 5 : 95]
3		**12a** Ph	-		**15** 90 [≤ 5 : 95]
4		**13a** *n*-pent	-		**16** 95 [≤ 5 : 95]
5		**17a** -	H		**21** 64[d] [≤ 5 : 95]
6		**18a** -	TES		**22** 78 [≤ 5 : 95]
7		**19a** -	TBS		**23** 67 [≤ 5 : 95]
8		**20a** -	TBDPS		**24** 63 [≤ 5 : 95]
9	C1-2 *syn*	**7s** H	-		**9** 90% [≥ 95 : 5]
10		**11s** Me	-		**25** 88 [≥ 95 : 5]
11		**12s** Ph	-		**26** 86 [≥ 95 : 5]
12		**13s** *n*-pent	-		**27** 96 [≥ 95 : 5]
13		**28a**: C1-2 *anti*			**29** 78 [≤ 5 : 95]
14		**28s**: C1-2 *syn*			**30** 75 [≥ 95 : 5]

[a] Reactions were run in tol [0.003 M] at 100 °C to 1 h, and 1.2 equiv of $Co_2(CO)_8$ and 1.2 equiv of Me_3NO were used. [b] Isolated yields. [c] 0.008 M. [d] 0.005 M. [e] C2−3 cis to trans ratios were determined using ^{1}H NMR.

Scheme 3. Stereoselective Constructing Quaternary Centers

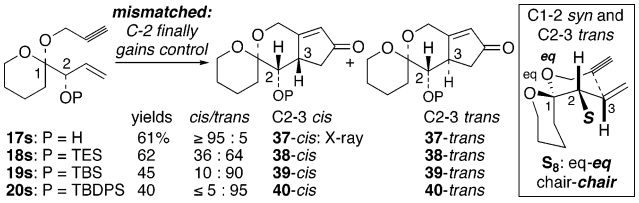


When ***A*** = H and ***S*** = OAc (*syn*-ketals), it should be mismatched, for there is a more severe 1,3-diaxial interaction between the pseudoaxial ***S*** *group* with the Co complex if both oxygen substituents are allowed to remain in the axial position (see TS-$\boldsymbol{S_1}$ in the right box in Scheme 2). However, in this case, given the observed stereochemical outcome in **9** as well as those in Table 1 (entries 9−12 and 14) the anomeric effect in controlling the conformation appears to be the dominant factor in the stereochemical control of C3, a remote center, and provides spiroketals with C2−3 being cis at the expense of the ***S*** group being pseudoaxial. We should caution that the penalty paid for the ***S*** group being pseudoaxial may be less than what it would appear to be since there are documented cases in which one or more oxygen substituents at homo-anomeric position(s) could actually prefer to be axial.[2,12] The question that remains is what is the limit of this anomeric control on the conformation and the impending stereoselectivity?[13]

Toward this goal, we prepared ketals **31a/32a** and **31s/32s** (Scheme 3) in which the R^1 group is now Me and Et, respectively, in an attempt to enhance the 1,3-diaxial interactions between R^1 and the *existing* pyran ring and to disrupt the anomeric control shown in both TS-$\boldsymbol{A_1}$ and TS-$\boldsymbol{S_1}$. To our surprise, the relative stereochemistry at C2−3 remained the same for the respective major diastereomers **33/34** and **35/36**, although there is a noticeable erosion in the yields in the mismatched case. The level of tolerance in the anomerically favored conformation TS-$\boldsymbol{A_1}$ or TS-$\boldsymbol{S_1}$ appears to be impressive, allowing stereoselective constructions of a remote quaternary stereocenter at C3.

Recognizing that an enhanced 1,3-diaxial interaction between the pseudoaxial ***S*** group with the Co complex could eventually disrupt the stronghold on the conformation TS-$\boldsymbol{S_1}$ exerted by the anomeric effect, we varied the ***S*** group for the C1−2 *syn*-ketals. It appears that we have found the threshold (***S*** = OTES or OTBS) in which the anomeric control is being overcome (Scheme 4). When ***S*** = OTBDPS, only **40**-*trans* was found, thereby suggesting that the C2 stereocenter has finally gained control to favor a reactive conformation as shown in TS-$\boldsymbol{S_8}$, in which both oxygen substituents have lost their axial orientation, leading to the trans relative configuration at C2−3 that we had expected.

Scheme 4. Thresholds of Anomeric Control



This study demonstrates a remarkable anomeric control on remote stereochemical control in a stereoselective synthesis of spiroketals from cyclic ketals. Application of this method in the natural product synthesis is currently underway.

Acknowledgment. We thank PRF-AC for support and Dr. Victor Young and Mr. Ben Kucera for X-ray analysis.

Supporting Information Available: Experimental procedures, NMR spectra and characterizations for all new compounds, and X-ray data (CIF, PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) See Supporting Information for details of characterizations.
(10) The other six possible conformations would lose either one of the two or both anomerically favored axial oxygen substituents, although some of them can still lead to the observed relative stereochemistry at C2−3.
(11) It is noteworthy that the elimination product dienone **10** was not found when reactions are run at lower concentrations. This helped providing a more distinct cis:trans ratio. However, dienone **10** is only a real minor product even at concentrations higher than 0.05 M.
(12) For reference, see: Yamada, H.; Tanigakiuchi, K.; Nagao, K.; Okajima, K.; Mukae, T. *Tetrahedron Lett.* **2004**, *45*, 5615 and references therein.
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