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# Design of Chiral Auxiliaries for the Allene Ether Nazarov Cyclization

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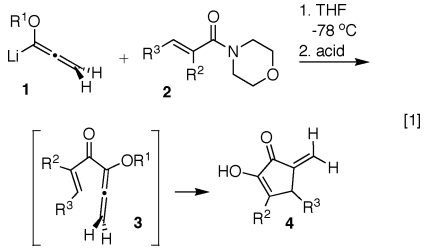
The allene ether version[1] of the Nazarov cyclization[2,3] takes place under very mild conditions and is distinguished by being highly suitable for asymmetric synthesis.[4] For example, lithioallene **1** (eq 1), prepared by deprotonating the hydrocarbon with *n*-butyllithium, adds to morpholino enamide **2**. Mild acidic workup presumably leads to allenyl vinyl ketone **3** that undergoes spontaneous cyclization to α-hydroxycyclopentenone **4** with loss of $R^1$ as a stable cation. High levels of asymmetry (er up to 96.5/3.5) can be induced in products **4** through choice of chiral auxiliary $R^1$.[5] Since the auxiliary is lost during the cyclization and no added step is needed for its cleavage, it is traceless.

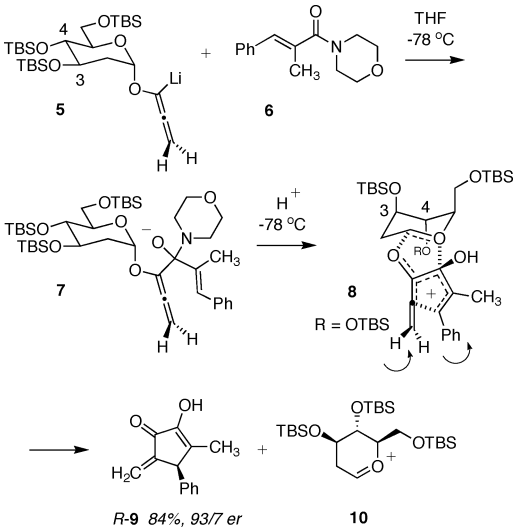



[1]

We recently described our results with 2-deoxy-D-glucose derived lithioallene **5** (Scheme 1), which is an excellent reagent for the allene ether Nazarov reaction.[5] Cyclic products from **5** were formed with er's of 92.5/7.5 to 96.5/3.5. We were puzzled by the fact that the tri-OTBS (TBS = *tert*-butyldimethylsilyl) reagent **5** led to products of much higher optical purity than the corresponding trimethoxy lithioallene, or the lithioallene that is derived from permethylated α-D-glucose. We rationalized this by postulating a change in conformation for the pyranose derived chiral auxiliary during the stereochemistry-determining step.[6] In this communication, we provide additional evidence to support our hypothesis and have designed greatly improved chiral auxiliaries for the allene ether Nazarov cyclization on this basis.

Woerpel has demonstrated that the groups at C-3 and C-4 exert a large influence on the conformational preferences of tetrahydropyran oxocarbenium ions relative to their uncharged precursors.[6,7] Specifically, C-3 and C-4 alkoxy groups have a *pseudoaxial* preference in the oxocarbenium ion. In the case of the Nazarov cyclization that is outlined in Scheme 1, nucleophilic addition of **5** to **6** probably gives intermediate **7** that leads to transition state **8** during workup with acid. The developing positive charge at C-1 causes inversion of the pyranose ring to occur, resulting in axial placement of the C-4 OTBS group. Steric shielding of the back face of the pentadienyl cation by the group at C-4 forces conrotation to take place in the counterclockwise direction as shown in Scheme 1, leading to (*R*)-**9** in an er of 93/7 with loss of the chiral auxiliary as pyrylium species **10**. According to this model, the pyranyl oxygen atom plays a pivotal role in the transmission of stereochemical

***Scheme 1***




information from auxiliary to product through electron pair donation to the developing pentadienyl cation.[4a,8] This has the effect of limiting the conformational mobility of the cation and enforcing proximity between the auxiliary and the developing five-membered ring. The pyran oxygen atom plays a critical role since the cyclohexyl version of **11** leads to (*R*)-**9** in low yield in ca. 55.5/44.5 er. For this model to be valid, the 3,4,5-triaxial conformation of the pyran ring in **7** must be energetically accessible,[9] and one must assume a late transition state for the cyclization.

If this model is valid, then one can make the following predictions. The *trans* equatorial group at C-3 in **7** will not exert much of an effect on the optical purity of product **9**, whereas the OTBS group at C-4 will. Furthermore, locking the C-4 substituent in the equatorial position of the pyran ring will lead to erosion of the optical purity of the product by preventing its close approach to the pentadienyl cation from taking place. All three predictions are borne out. To test the first prediction, lithioallene **11**, lacking a C-3 OTBS group, was allowed to react with **6** to produce (*R*)-**9** in 94/6 er, within experimental error the same result that was obtained with **5**. It is therefore clear that the silyloxy group at C-3 does not influence the stereochemical outcome of the cyclization. The same cannot be said for the group at C-4 since the reaction of 2,4-dideoxy compound **12** with **6** led to marked attenuation of the optical purity of (*R*)-**9** (86.5/13.5 er). Therefore, the equatorial C-4 group must be important, and preventing its close approach to the pentadienyl cation in the stereochemistry-determining transition state (see **8**) by conformationally locking the pyran ring also leads to erosion of the optical purity of **9**: Lithioallene **13** led to (*R*)-**9** in 86.5/13.5 er.

These results instill some confidence in the validity of the model. Since the model requires a 1,3-*cis* axial interaction in the transition state to influence the stereochemical outcome of the cyclization,

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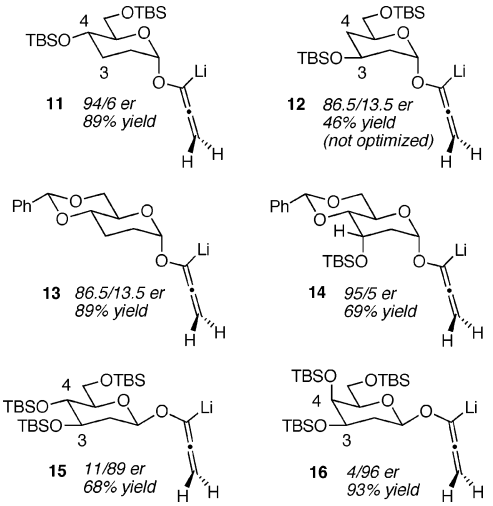
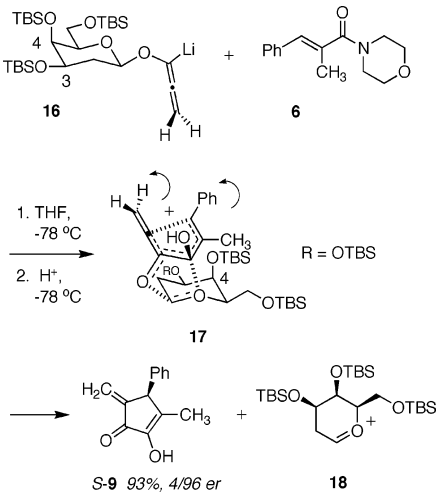
one can go a step further and predict that conformationally locked lithioallene **14**, which incorporates an axial C-3 OTBS group, should be an effective reagent. This also proved to be the case, and the reaction of **14** with **6** led to (*R*)-**9** in 95/5 er.




The absolute stereochemistry of the Nazarov cyclization product can be inverted by simply changing stereochemistry at the anomeric carbon atom.[4c] This allows both enantiomeric series of cyclopentenones to be derived from D sugars. We therefore set out to design $\beta$-pyranose derived chiral auxiliaries based on the model that has been described above. Lithioallene **15**, derived from $\beta$-2-deoxy-D-glucose, and lithioallene **16**, derived from $\beta$-2-deoxy-D-galactose, would present *cis* axial groups at both C-3 and at C-5 if conformational inversion were to take place in the stereochemistry-determining step. Both axial groups would be expected to influence the absolute stereochemistry of product in the same way. In fact, the reaction of **15** with **6** led to (*S*)-**9** in only 11/89 er, whereas lithioallene **16** led to (*S*)-**9** in 4/96 er. The results from **15** and **16** suggest that inversion of the pyran ring does *not* take place in these $\beta$-pyrans, or they would have given product of similar optical purity. The reason for the apparent difference in conformational behavior of α- and $\beta$-pyrans is not obvious but may be due to the absence of destabilizing 1,3-diaxial interactions involving the large C-1 substituent in the $\beta$ series. The absolute stereochemistry of product from **16** can be predicted according to the transition state **17** (Scheme 2). Electron pair donation by the pyran oxygen atom to the developing pentadienyl cation restricts its conformational mobility and brings it close to the axial C-4 OTBS group. The buttressing effect of this group forces the conrotation in **17** to take place in the counterclockwise direction, as shown in Scheme 2, leading to cyclopentenone (*S*)-**9** with loss of pyrylium ion **18**. These results appear to be congruent with Woerpel's conformational analysis of pyranose derived pyrylium ions.[10]

Lithioallene **5** had been screened against morpholino enamide **6** and eight other 2,3-disubstituted morpholino enamides, leading to products in er's ranging from 92.5/7.5 to 96.5/3.5. Enamide **6** was by no means the best substrate for **5**, and it is unlikely that it will prove to be the optimum substrate for lithioallenes **14** and **16**. A

***Scheme 2***




thorough screen of **14** and **16** against a collection of enamides to determine the scope of their cyclization chemistry is planned for future work.

The analysis presented above is overly simple, as it attributes the stereochemical outcome of the Nazarov cyclization to a single steric interaction, to the exclusion of all other contributory factors. Nevertheless, the results strongly suggest that the dominant stereochemical factor has been identified and that it can be used in the design of even more effective chiral auxiliaries for the Nazarov cyclization.

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**Supporting Information Available:** Complete experimental procedures for the preparation of **11**−**16** and **9**, analytical data, and $^1$H and $^{13}$C NMR spectra for **11**−**16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) Our observations can also be rationalized by invoking a charge-dipole interaction between cation and pyranyl oxygen atom and the *exo* anomeric effect. We thank Professor William R. Roush for suggesting this.
(9) Evidence suggests that this is the case. See: (a) Tius, M. A.; Busch-Petersen, J. *Tetrahedron Lett.* **1994**, *35*, 5181−5184. (b) Yamada, H.; Tanigakiuchi, K.; Nagao, K.; Okajima, K.; Mukae, T. *Tetrahedron Lett.* **2004**, *45*, 5615−5618.
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