

RELATIVE STEREOCONTROL IN AN INTRAMOLECULAR 4+3 CYCLOADDITION REACTION

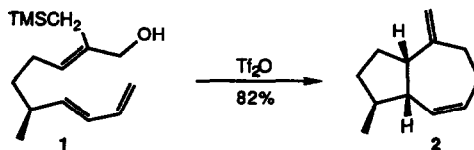
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Summary: The first complete study of relative stereocontrol in an intramolecular 4+3 cycloaddition has been performed. Thus, CH_2Cl_2 solutions of alkoxyallylic sulfones **5**, **7**, and **9** were treated with TiCl_4 at -78°C to give diastereomeric cycloadducts in fair yield. For **5** and **7** diastereoselectivity was low, but suggested that allylic cation geometry plays a small but definitive role in determining the diastereomer distribution in the cycloadducts. For the cycloaddition reaction of **9**, cation geometry is irrelevant and the cycloadduct is obtained in very high diastereomeric purity.

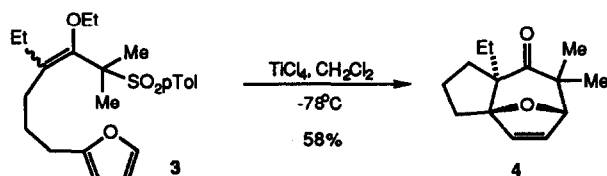
The intramolecular 4+3 cycloaddition reaction is potentially an important tool in the synthesis of complex carbocyclic molecules.¹ To date, however, relatively little work has been conducted either on synthetic development or fundamental aspects of this reaction.² In addressing the paucity of data available, several years ago we began a program to study the intramolecular 4+3 cycloaddition reaction in detail from both points of view.

As in the isoelectronic Diels-Alder reaction, up to four stereocenters may be formed upon reaction of an allylic cation with a diene in a 4+3 cycloaddition.³ An additional complication involves the effect of preexisting stereocenters, particularly in the tether joining the allylic cation and the diene for the intramolecular variant of the reaction. How such stereocenters affect the overall diastereoselectivity of the cycloaddition process is not well understood. Further, most examples to date exhibit poor relative stereocontrol.^{2j,k} An important exception is found in a report by Giguere and co-workers who showed that **1** undergoes intramolecular 4+3 cycloaddition to give **2** in 80% yield with greater than 90% stereochemical purity (Equation 1).^{2e}



Equation 1

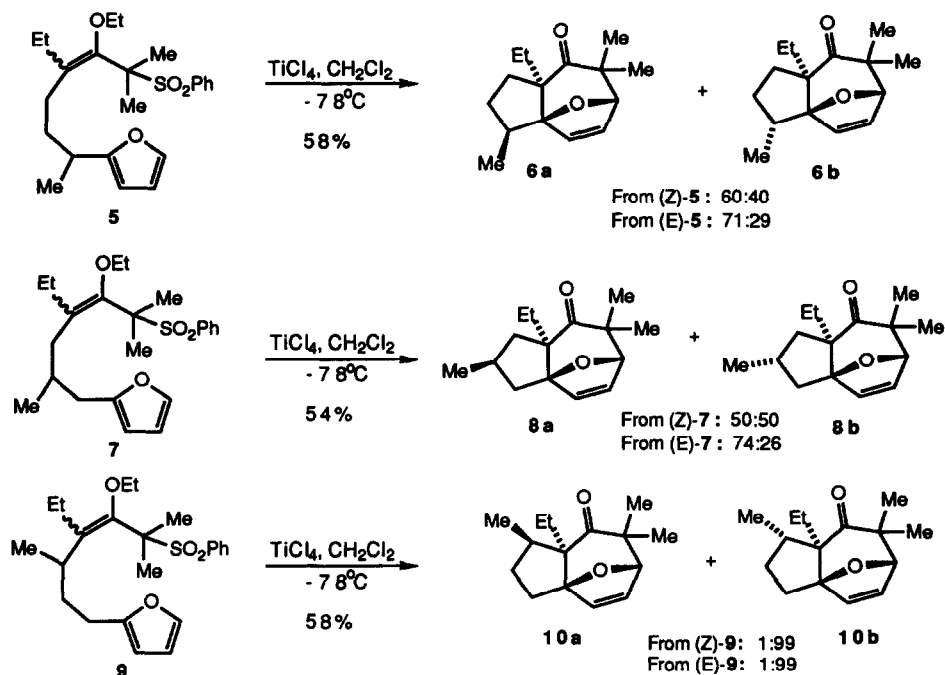
We recently reported that the intramolecular 4+3 cycloaddition of either (*E*)-**3** or (*Z*)-**3** proceeds in reasonable yield to give **4** as the sole product (Equation 2).^{2b} We wondered if the allylic cations generated from the stereoisomers of **3** interconverted before undergoing cycloaddition or if each intermediate remained



Equation 2

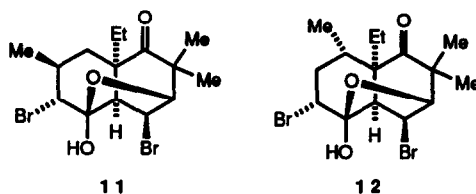
stereochemically unique and both simply reacted to give the same product. In an effort to probe this, we decided to conduct a complete study of relative asymmetric induction in this system.

To that end, sulfones **5**, **7**, and **9** were prepared and their cycloaddition chemistry studied.⁴ The cycloadditions were conducted according our standard procedure.^{2a} Treatment of a 0.1 M CH_2Cl_2 solution of the allylic sulfone with a slight excess of TiCl_4 at -78°C resulted in rapid cycloaddition. The stereochemistry of the products **6a** and **6b** was assigned using NOESY. A cross peak between the methyl signal and olefinic hydrogen of **6b** was observed while the corresponding cross peak in the spectrum of **6a** was absent. The assignments for **8a**, **8b** and **10b** were firmly established by X-ray analysis of **11** and **12**, obtained by treating **8a** and **10b** with excess bromine. The mechanism of the formation of these rearrangement products has been presented elsewhere.^{2b}



Scheme 1

Upon intramolecular cycloaddition of **5a** and **5b** it became immediately obvious that, at least to some degree, the allylic cations derived from the stereoisomeric starting material retained their identity and did not interconvert



faster than cycloaddition. To what extent "stereochemical leakage" may have occurred is not known.

Though these experiments were sufficient to give an answer to the question prompting this study, we also investigated **7** and **9**. The isomers of **7** again showed, in slightly more definitive terms, that the allylic cation intermediates in this reaction are stereochemically unique. Surprisingly, both isomers of **9** gave rise to the same single product **10a**. No other product could be detected. This is only the second example of an intramolecular 4+3 cycloaddition in which high relative stereocontrol has been observed and is the only example in which such stereocontrol seems complete.^{2c}

An inspection of CPK models suggests a basis for this high degree of stereoselectivity. Within the constraints of the relative angular stereochemistry demanded by this system,⁵ two reasonable transition structures are possible for each cation geometry. These are shown in Figure 1.

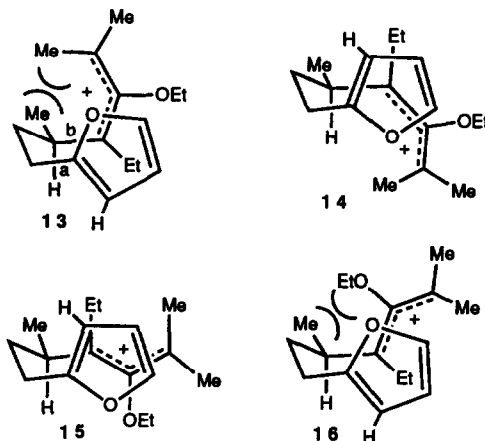


Figure 1

The cation from (*E*)-**9** can adopt two conformations leading to **10a**, **13** and **14**. Both possess a puckered, incipient 5-membered ring and a pseudoequatorially disposed methyl group. There apparently exists little conformation preference for the furan ring about bond "a" relative to the strong conformational preference about bond "b" arising from severe steric interaction between the methyl on the tether and the proximal methyl on the allylic cation, as shown. Transition structure **14** is thus favored. Similar steric arguments can be made for the interaction of the ethoxy and methyl groups in **16**, making **15** the preferred transition structure from (*Z*)-**9**. While **13** and **15** clearly possess several untoward steric interactions, these are less severe than those in **14** and **16**. Thus, a strong preference for a trans relative angular stereochemistry, coupled with steric effects which fortuitously operated in the same direction independent of cation stereochemistry, resulted in the formation of a single

cycloaddition product. Overlap considerations suggest that **14** should lead to product via a stepwise process while **15** could lead to cycloadduct in a concerted fashion. A more formal discussion of mechanistic possibilities will be presented in a full paper.

In summary, we have reported the first complete study of relative stereocontrol in an intramolecular 4+3 cycloaddition. In the system studied, allylic cation geometry played a small but definitive role in determining the diastereomer distribution in the cycloadducts. In one case, cation geometry was irrelevant and the cycloadduct was obtained in very high diastereomeric purity. Further work on many aspects of the intramolecular 4+3 cycloaddition reaction is in progress and will be reported in due course.⁶

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References and Notes

- For reviews of 4+3 cycloaddition, see: (a) Hoffmann, H.M.R. *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 1. (b) Mann, J. *Tetrahedron* **1986**, *42*, 4611. (c) Noyori, R.; Hayakawa, Y. *Org. React.* **1983**, *29*, 163.
- (a) Harmata, M.; Gamlath C.G. *J. Org. Chem.* **1988**, *53*, 6154. (b) Harmata, M.; Gamlath, C.G.; Barnes, C.L. *Tetrahedron Lett.* **1990**, 5981. (c) Harmata, M.; Fletcher, V.R.; Claassen II, R.J. *J. Am. Chem. Soc.* **1991**, *113*, 9861. (d) Giguere, R.J.; Duncan, S.M.; Bean, J.M.; Puruis, L. *Tetrahedron Lett.* **1988**, 6071. (e) Giguere, R.J.; Tassely, S.M.; Rose, M.I. *Tetrahedron Lett.* **1990**, 5981. (f) Schultz, A.G.; Macielag, M.; Plummer, M. *J. Org. Chem.* **1988**, *53*, 391. (g) Föhlich, B.; Gehrlach, E.; Herter, R. *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 137. (h) Föhlich, B.; Herter, R. *Chem. Ber.* **1984**, *117*, 2580. (i) Kaiser, R.; Föhlich, B. *Helv. Chim. Acta* **1990**, *73*, 1504. (j) Hoffmann, H.M.R. Renning, R. *Helv. Chim. Acta* **1983**, *66*, 828. (k) Hoffmann, H.M.R.; Eggert, U.; Gibbels, U.; Giesel, K.; Koch, O.; Lies, R.; Rabe, J. *Tetrahedron* **1988**, *44*, 3899. (l) Noyori, R.; Nishizawa, M.; Shimizu, F.; Hayakawa, Y.; Maruoka, K.; Hashimoto, S.; Yamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.* **1979**, *101*, 221.
- For a review of the intramolecular Diels-Alder reaction, see: Rousch, W.R. In *Advances in Cycloaddition*; Curran, D.P., Ed.; JAI: Greenwich, 1990; Vol 2, pp 91-146.
- Precursors to **5**, **7**, and **9** with no methyl groups adjacent to the sulfone were separated chromatographically into pure E and Z isomers. Conversion to **5**, **7**, and **9** was stereospecific. The stereochemistry of these precursors was established by comparison to the ¹H NMR and chromatographic behavior of the corresponding E and Z isomers of precursors to **3**, whose structures were rigorously established by NOESY.^{2b} All the E isomers of the precursors to **3**, **5**, **7**, and **9** were less polar than their corresponding Z isomers. Further, for the E isomers of precursors of **3**, **5**, **7**, and **9** the chemical shifts of the methylene adjacent to the sulfone were 3.92, 3.87, 3.92, and 3.94 ppm, respectively. For the corresponding Z isomers, 4.00, 4.00, 4.04, and 4.03 ppm, respectively. Other spectroscopic comparisons were also possible.
- This preference is well precedented and will be discussed in the full paper. See citation 2a and references therein.
- All new compounds exhibited acceptable ¹H and ¹³C NMR and IR spectral data as well as satisfactory combustion analysis or exact mass data.

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