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Asymmetric Induction in 8π Electrocyclizations. Design of a Removable Chiral Auxiliary

Keunsoo Kim, Joseph W. Lauher, and Kathlyn A. Parker*

Department of Chemistry, Stony Brook University, Stony Brook, New York 11733, United States

kparker@notes.cc.sunysb.edu

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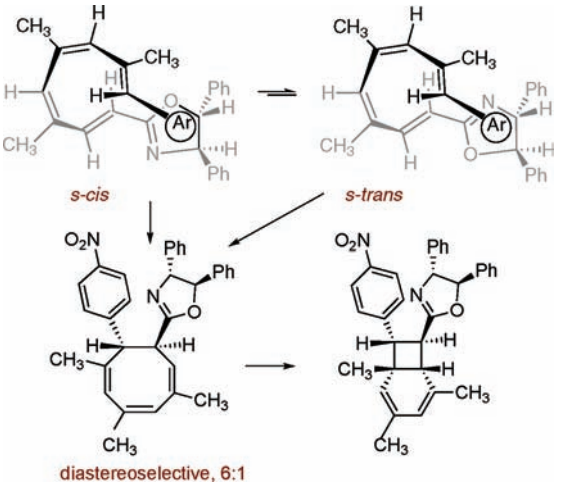
ABSTRACT

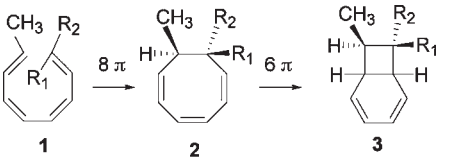


The pseudo C_2 symmetric *trans* diphenyl oxazoline group acts as an effective chiral auxiliary in the 8π, 6π tandem electrocyclization of a substituted tetraene 1-carboxylic acid. Assignment of absolute stereochemistry to the [4.2.0] bicyclooctadiene product supports a model in which both *s-cis* and *s-trans* conformations favor the transition states with the same helical twist. This assignment prefaces the development of analogs of SNF4435 C and D. These natural products demonstrate activity as androgen receptor antagonists and as multidrug resistance (mdr) reversal agents.

1,3,5,7-Octatetraenes in which the two internal olefins have the *Z*-configuration are thermally unstable with respect to the 8π, 6π electrocyclization cascade. Thus, their preparation leads directly to compounds that contain the [4.2.0] bicyclooctadiene ring system.

This chemistry was studied in the 1960s, most notably by Marvel and by Huisgen, who demonstrated in simple substituted systems (Scheme 1) that it followed the newly revealed Woodward–Hoffmann rules.[1] More recently, it has moved center stage because the bicyclooctadiene is a key structural component of a number of interesting natural products. In fact, the 8π, 6π electrocyclization

Scheme 1. Prototypical 8π, 6π Tandem Cyclizations



a $R_1 = CH_3$, $R_2 = H$
b $R_1 = H$, $R_2 = CH_3$

(1) (a) Marvell, E. N.; Seubert, J. *J. Am. Chem. Soc.* **1967**, *89*, 3377. (b) Marvell, E. N.; Caple, G.; Schatz, B. *Tetrahedron Lett.* **1965**, 385. (c) Huisgen, R.; Dahmen, A.; Huber, H. *J. Am. Chem. Soc.* **1967**, *89*, 7130. (d) Huisgen, R.; Dahmen, A.; Huber, H. *Tetrahedron Lett.* **1969**, 1461. See also:(e) Vogel, E.; Grimme, W.; Dinne, E. *Tetrahedron Lett.* **1965**, 391.

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sequence is thought to be one of the transformations in the biosynthetic schemes leading to these compounds and it has served as the conceptual basis of the chemical synthesis of the endiandric acids,[2] SNF4435 C and D (**4** and **5**, Figure 1),[3] elysiapyrones A and B,[4] ocellapyrones A and B,[5] shimalactones A and B,[6] and "pre-kingianin A," the presumed biosynthetic precursor of kingianin A.[7]

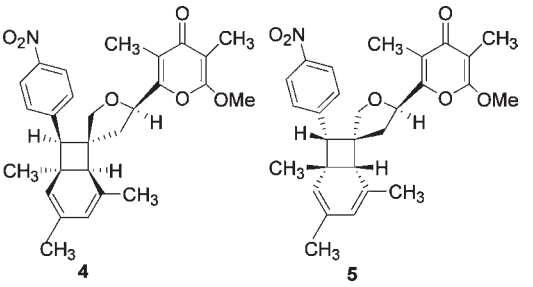


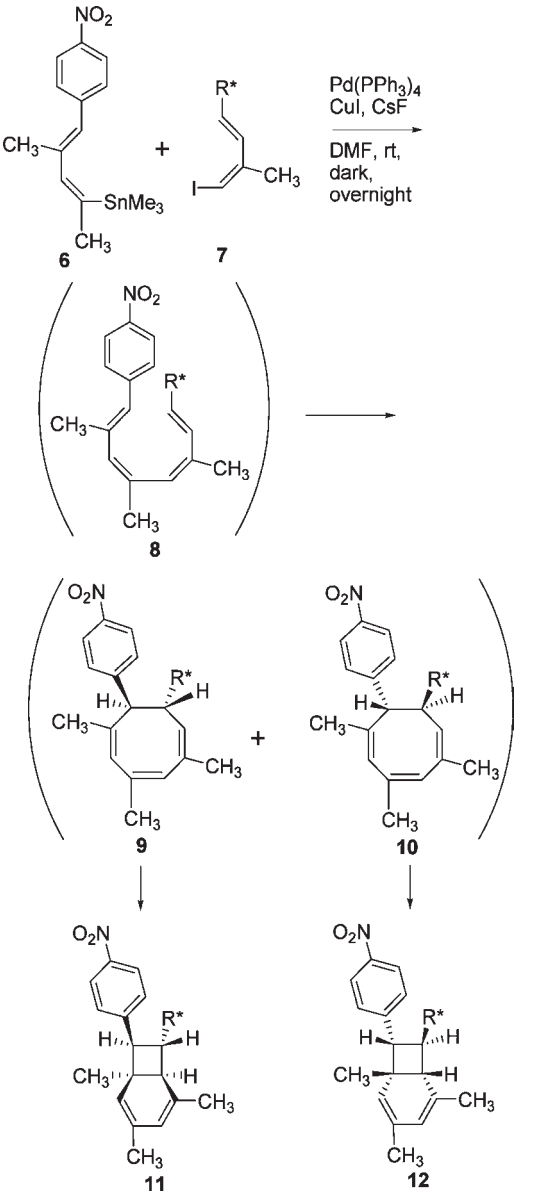
Figure 1. SNF4435 C and SNF4435 D.

Although the well-defined relative stereochemistry that results from the thermal 8π, 6π cascade has been understood for more than 40 years, the possibility of asymmetric induction in this conversion by means of a removable auxiliary was not investigated until recently. In a test of this refinement, we prepared a series of chiral auxiliary-bearing tetraene carboxylic acid esters and observed the ratios of diastereomeric 8π, 6π products.[8] Although none of the substrates gave a large excess of one of the diastereomers, our work in the series provided context for further experiments.

High asymmetric induction in electrocyclizations is an intellectual challenge and a practical problem.[9] Herein, we describe the rational design and effective use of oxazoline auxiliaries that impose a significant bias for one of the two helical arrangements that lead to 8π electrocyclization.

Because of our particular interest in the preparation of medicinally active analogs of the SNF compounds, we have tested candidate auxiliaries in the 9-(*p*-nitrophenyl)-4,6,8-trimethyl-2,4,6,8-tetraenoic acid (**8**, R* = CO_2H) system (Scheme 2).

Scheme 2. Synthesis of the [4.2.0] Bicyclo System of SNF Analogs



This tetraene system, prepared by coupling the stannane **6**[3c] with an iododiene **7**, offers the advantage of providing exclusively the endo products **11a/12a**[10] in the second electrocyclic step (i.e., the 6π electrocyclization). Consequently, in this system, analysis of the asymmetric induction is simpler than in cases in which both endo and exo products are formed.

(2) Nicolaou, K. C.; Petasis, N. A.; Uenishi, J.; Zipkin, R. E. *J. Am. Chem. Soc.* **1982**, *104*, 5557.

(3) (a) Parker, K. A.; Lim, Y.-H. *J. Am. Chem. Soc.* **2004**, *126*, 15968. (b) Jacobsen, M. F.; Moses, J. E.; Adlington, R. M.; Baldwin, J. E. *Org. Lett.* **2005**, *7*, 2473. (c) Beaudry, C. M.; Trauner, D. *Org. Lett.* **2005**, *7*, 4475. See also:(d) Kawamura, T.; Fujimaki, T.; Hamanaka, N.; Torii, K.; Kobayashi, H.; Takahashi, Y.; Igarashi, M.; Kinoshita, N.; Nishimura, Y.; Tashiro, E.; Imoto, M. *J. Antibiot.* **2010**, *63*, 601.

(4) Barbarow, J. E.; Miller, A. K.; Trauner, D. *Org. Lett.* **2005** *7*, 2901.

(5) Miller, A. K.; Trauner, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4602.

(6) (a) Sofiyev, V.; Navarro, G.; Trauner, D. *Org. Lett.* **2008**, *10*, 149. (b) Wei, H.; Itoh, T.; Kinoshita, M.; Kotoku, N.; Aoki, S.; Kobayashi, M. *Tetrahedron* **2005**, *6*, 8054. (c) Wei, H.; Itoh, T.; Kotoku, N.; Kobayashi, M. *Heterocycles* **2006**, *68*, 111.

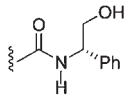
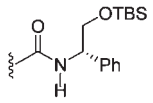
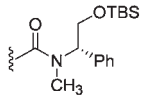
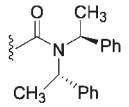
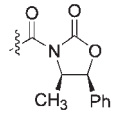
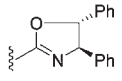
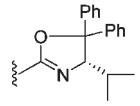
(7) Sharma, P.; Ritson, D. J.; Burnley, J.; Moses, J. E. *Chem. Commun.* **2011**, *47*, 10605.

(8) (a) Parker, K. A.; Wang, Z. *Org. Lett.* **2006**, *8*, 3553. (b) For examples of modest levels of chiral induction in a related sequence, the 8π electrocyclization/transannular aldol cascade, see: Paquette, L. A.; Tae, J. *J. Org. Chem.* **1998**, *63*, 2022.

(9) Thompson, S.; Coyne, A. G.; Knipe, P. C.; Smith, M. D. *Chem. Soc. Rev.* **2011**, *40*, 4217.

(10) Although the ratio of diastereomers was evident from the NMR spectrum of the product mixture in each case, the relative stereochemistry between the bicyclooctadiene and the chiral auxiliary for the two diastereomers was assigned only for the product pairs **11a/12a** (from crystallography) and **11f/12f** (by comparison with **11a** and **12a**).

Table 1. Preparation of Diastereomers **11** + **12**

entry	R	yield(%)	dr[10]
a		39	1:2
b		51	1:1
c		44	1:1
d		45	2:3
e		36	1:1
f		42	1:6
g		33	1:3

Initial experiments with substrates in which the carbonyl group was functionalized as an amide derived from readily accessible phenylglycinol (entries a and b in Table 1; see Supporting Information for synthesis of substrates) were unimpressive; the diastereomeric ratio (dr) in the product mixture hovered around 1:1. It is probable that the *s-cis,syn* and *s-trans,syn* transition states for closure of these primary amide substrates, like those of the ester substrates,[8a] are nearly isoenergetic.

Thinking that we might favor one helicity over the other by introducing a second substituent on the nitrogen, we tested the secondary amide system (entry c); again there was no preference for either diastereomer. Similarly, the substrate that contained the bis[(*S*)-1-phenethyl]-amine auxiliary (entry d) provided almost equal amounts of two diastereomeric products.

Next, we reasoned that introduction of dipole interactions would favor one of the four possible transition states over the others and we examined the acyl oxazolidinone system (entry e). Again the ring closure proved to be stereorandom.

We therefore returned to our analysis of the transition states for the 8π closure of the tetraene esters.[8a] We recognized that a cyclic chiral auxiliary would be more effective if the ring included the carbonyl carbon and the carbonyl oxygen of the parent carboxylic acid. Furthermore, rational design would become more feasible if we could reduce the number of possible transition state candidates from a minimum of four (as is the case for esters and amides) to two (as would be the case if R* were a C_2 symmetric or pseudo C_2 symmetric functional group). Consequently, we considered the effect of a *trans*-4,5-disubstituted oxazoline, a moiety that has a pseudo C_2 axis (Figure 2), on the helical transition state conformations available for 8π closure.

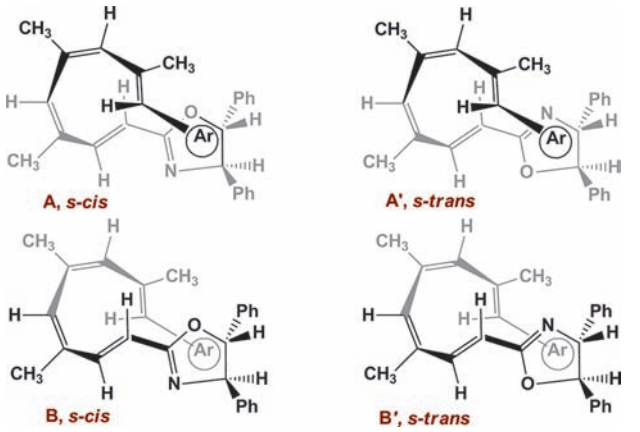


Figure 2. Four possible helical transition states.

Focusing now on the interactions between the nitrophenyl group (Ar) and the oxazoline substituents (Ar′) in the helical transition states A, A′, B, and B′, we found a convincing steric preference for the A, A′ pair. This model predicts that the major product from the coupling/8π, 6π cascade is bicyclooctadiene **12f** rather than its diastereomer **11f**.

The diphenyl oxazoline substrate **7f** was prepared in seven steps from commercially available materials (see Supporting Information) and subjected to the coupling cascade (Scheme 2). A 6:1 ratio of two diastereomers rewarded the rational design effort.[11]

Reasoning that an additional substituent on the oxazoline would, to a first approximation, leave the helicity preference unaltered, we examined substrate **7g**, derived from the inexpensive (*S*)-(−)-2-amino-3-methyl-1,1-diphenylbutan-1-ol. The presence of the additional substituent on the oxazoline ring should disfavor the transition state corresponding to **A** but not disfavor any of the other transition states. In the event, the substrate prepared to test this premise (entry g) provided a modest preference for one diastereomer.

Confirmation of our model for chiral induction in 8π electrocyclizations required correlation of one of the products with material of known absolute stereochemistry.

(11) In the terminology for the SNF compounds introduced by us, the endo product is the isomer in which the aryl substituent is cis to the cyclohexadiene ring; see: Parker, K. A.; Lim, Y. -H. *Org. Lett.* **2004**, *6*, 161.

For this purpose, we exploited the crystallinity of one of the isomers of **11a/12a**. These two compounds are easily separable on silica gel chromatography with 1:1 EtOAc/hex.[12] The slower moving isomer was recrystallized from $CHCl_3$/hex. Then slow evaporation of a solution in MeOH/Et_2O gave needles that were suitable for X-ray analysis. The relative stereochemistry of the slower moving isomer, determined by the crystallographic experiment, is as shown in Figure 3; this corresponds to isomer **11a**.

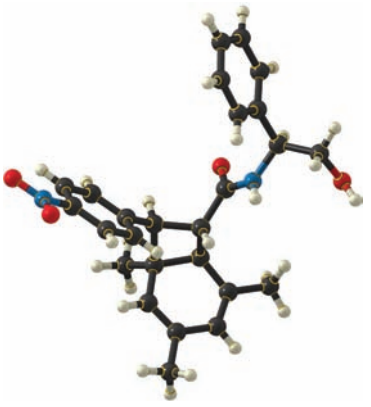
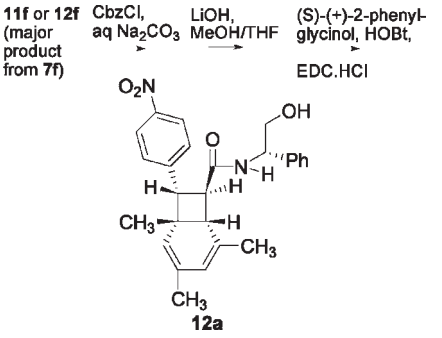


Figure 3. X-ray crystal structure of **11a**.

It remained for us to determine whether the chirality of the bicyclooctadiene moiety of our major product from substrate **7f** corresponds to that of amide **11a** or to amide **12a**. For this purpose, we converted the major product from oxazoline **7f** to the corresponding (*S*)-(+)-2-phenylglycinol amide. This was accomplished in three steps (Scheme 3; see the Supporting Information for details). The tlc behavior of the (*S*)-(+)-2-phenylglycinol amide derived from the major component of the mixture from **7f** was inconsistent with that of authentic **11a** and consistent with that of authentic **12a**. In this way, we were able to assign the stereochemistry of the major electrocyclization product from substrate **7f** as oxazoline **12f**.

Scheme 3. Relationship of Major Product from **7f** with more Rapidly Moving Stereoisomer from the **11a/12a** Pair



To our knowledge, the coupling/8π, 6π electrocyclization cascade of substrate **7f** is the first example of the exploitation of the pseudo C-2 axis of *trans*-4,5-disubstituted oxazolines for asymmetric induction. The underlying design principle allows a simple analysis of the energies of the transition states that lead to diastereomeric products. We anticipate the use of these oxazoline auxiliaries for providing asymmetric induction in other reactions of unsaturated carboxylic acid systems. Enantiomeric carboxylic acids **11** (R = CO_2H) and **12** (R = CO_2H) are key intermediates for elaboration to stereochemically homogeneous analogs of SNF4435 C and D.

Acknowledgment. This work was supported by the National Institutes of Health (GM 74776) and the National Science Foundation (CHE-0131146, NMR instrumentation and CHE-0840483, diffractometer).

Supporting Information Available. Schemes for the synthesis of substrates **7a**–**g** and authentic **11f/12f**, experimental procedures with analytical data for all new compounds, and crystallographic cif file for structure **11a**. This material is available free of charge via the Internet at http://pubs.acs.org.

(12) An authentic 1:1 mixture of oxazolines **11f** and **12f** was prepared in three steps from racemic carboxylic acid **11/12** (R = CO_2H) and (*S*),(*S*)-diphenylglycinol. For the scheme and experimental details, see the Supporting Information.

(13) A large separation factor for another pair of diastereomeric phenylglycinol amides was noted by Baek, D. J.; Daniels, S. B.; Reed, P. E.; Katzenellenbogen, J. A. *J. Org. Chem.* **1989**, *54*, 3962.