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Cleavable Chiral Auxiliaries in 8π (8π, 6π) Electrocyclizations

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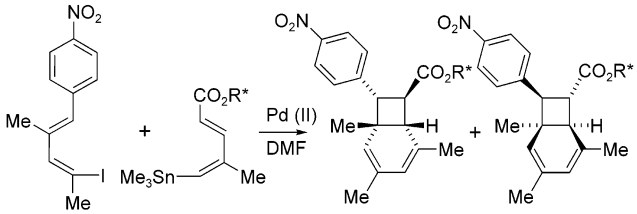
ABSTRACT



Low to moderate diastereoselectivity was observed in the 8π electrocyclization of a series of chiral auxiliary-bearing tetraenic esters. In the 8-arylmenthyl series, diastereomeric products were separated by chromatography.

A number of natural products that contain a bicyclo[4.2.0]-octane or -octadiene have been reported recently.[1−4] For example, in 2001, SNF4435 C and D (**1a** and **1b**, Figure 1), notable for their immunosuppressant and multidrug resistance reversal activity, were isolated from the soil organism *Streptomyces spectabilis*.[1]

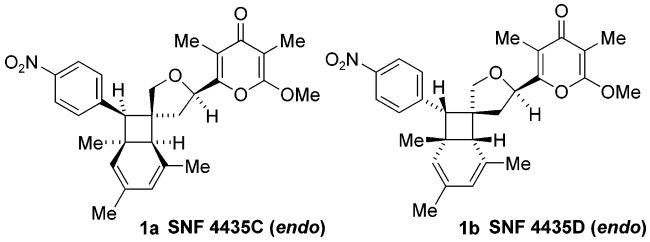


Figure 1. SNF compounds from *Streptomyces spectabilis*.

In 2005, the elysiapyrones A and B (**2a** and **2b**) were isolated from the Pacific Panamanian sea slug *Elysia diomedea*,[2] and the ocellapyrones (**3a** and **3b**) were isolated from the Indian Ocean mollusk *Placobranchus ocellatu*[3] (Figure 2).

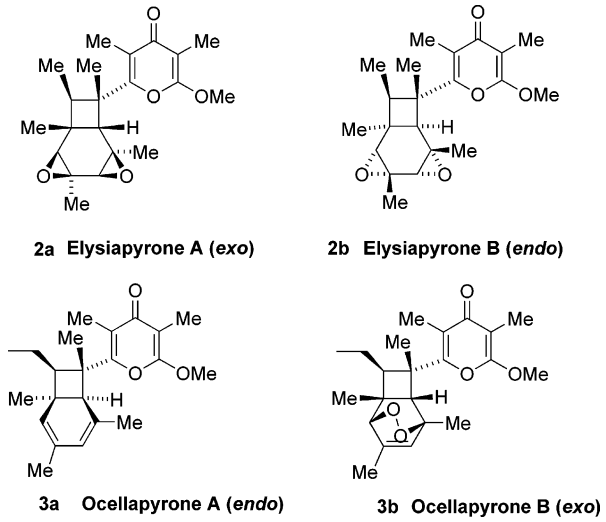


Figure 2. Bicyclooctadiene derivatives from mollusks.

(1) (a) Kurosawa, K.; Takahashi, K.; Tsuda, E. *J. Antibiot.* **2001**, *54*, 541. (b) Takahashi, K.; Tsuda, E.; Kurosawa, K. *J. Antibiot.* **2001**, *54*, 548.

(2) Cueto, M.; D'Croz, L.; Maté, J. L.; San-Martín, A.; Darias, J. *Org. Lett.* **2005**, *7*, 415.

(3) (a) Manzo, E.; Ciavatta, M. L.; Gavagnin, M.; Mollo, E.; Wahidulla, S.; Cimino, G. *Tetrahedron Lett.* **2005**, *46*, 465. (b) The structure of ocellapyrone A was reassigned by total synthesis of the racemic **3a**: see Miller, A. K.; Trauner. D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4602. Miller and Trauner also described the synthesis of racemic **3b**.

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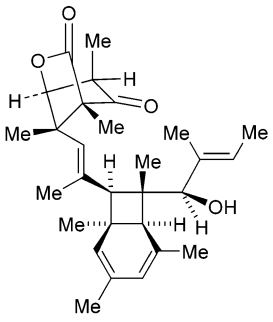
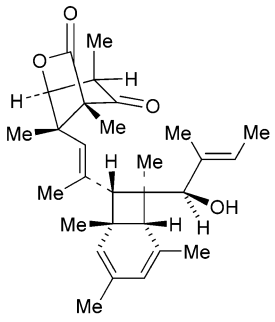


4a Shimalactone A (*endo*)

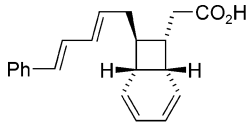


4b Shimalactone B (*endo*)

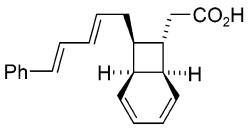
Figure 3. Shimalactones from the marine fungus *Emericella variecolor*.

Also in 2005, the marine fungus *Emericella variecolor GF10* yielded the structurally complex shimalactone A (**4a**) and its stereoisomer shimalactone B (**4b**) (Figure 3). The shimalactones are inducers of neuritogenesis.[4]

All of these polypropionates are believed to be produced from linear tetraenes by an 8π, 6π tandem electrocyclization pathway[5] as originally proposed by Black[6] for the well-known polyacetate-derived endiandric acids (e.g., **5a** and **5b**, Figure 4).[7]



5a Endiandric acid D (*exo*)

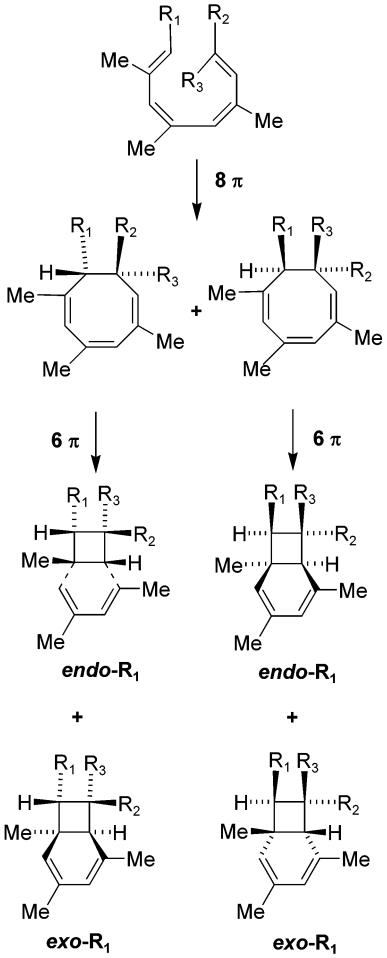


5b Endiandric acid E (*endo*)

Figure 4. Endiandric acids D and E from leaves of the Australian tree *Endiandra introrsa* (Lauraceae).

The 8π, 6π double closure can, in principle, produce four stereoisomers (Scheme 1). Neither the biosynthesis of the racemic endiandric acids[6] nor that of the diastereomeric SNF pair[5] requires an enzyme for control of relative or absolute stereochemistry. Both the endiandric acids[8] and the SNF diastereomers[9] were prepared by total synthesis without the aid of a removable chiral appendage. Likewise, the [4.2.0] ring system of the shimalactones presumably arises by a nonenzymatic biosynthetic process, and total synthesis of the pair might be achieved by nonenzymatic cyclization of an appropriate tetraene.

Scheme 1. Possible 8π, 6π Electrocyclization Products from a Polypropionate-Derived Tetraene



On the other hand, optical activities for the elysiapyrones and the ocellapyrones have been reported, and a role for an enzyme has been invoked.[2] Syntheses of the chiral elysiapyrones[10] or the ocellapyrones[3b] will require an external chirality source; these preparations and also those of chiral analogues of the SNF compounds and the shimalactones might be based on an approach in which the 8π electrocyclization step of the tandem closure was influenced by a chiral auxiliary.

Numerous chiral auxiliaries derived from chiral natural products and also from the resolution of synthetic materials have been shown to affect the diastereomeric excesses in additions to the olefinic bonds of substituted acrylates. For the first study of the effectiveness of chiral auxiliaries in this context, we chose the closure of esters of 4,6,8-

(4) (a) Wei, H.; Itoh, T.; Kotoku, N.; Kobayashi, M. *Heterocycles* **2006**, 68, 111. (b) Wei, H.; Itoh, T.; Kinoshita, M.; Kotoku, N.; Aoki, S.; Kobayashi, M. *Tetrahedron* **2005**, *61*, 8054.

(5) (a) Beaudry, C. M.; Trauner, D. *Org. Lett.* **2002**, *4*, 2221. (b) Moses, J. E.; Baldwin, J. E.; Marquez, R.; Adlington, R. M.; Cowley, A. R. *Org. Lett.* **2002**, *4*, 3731. (c) Parker, K. A.; Lim, Y.-H. *Org. Lett.* **2004**, *6*, 161.

(6) Banfield, J. E.; Black, D. St. C.; Johns, S. R.: Willing, R. I. *Aust. J. Chem.* **1982**, *35*, 2247 and references therein.

(7) For a recent review on electrocyclizations in biosynthesis and in biomimetic schemes, see: Beaudry, C. M.; Malerich, J. P.; Trauner, D. *Chem. Rev.* **2005**, *105*, 4757.

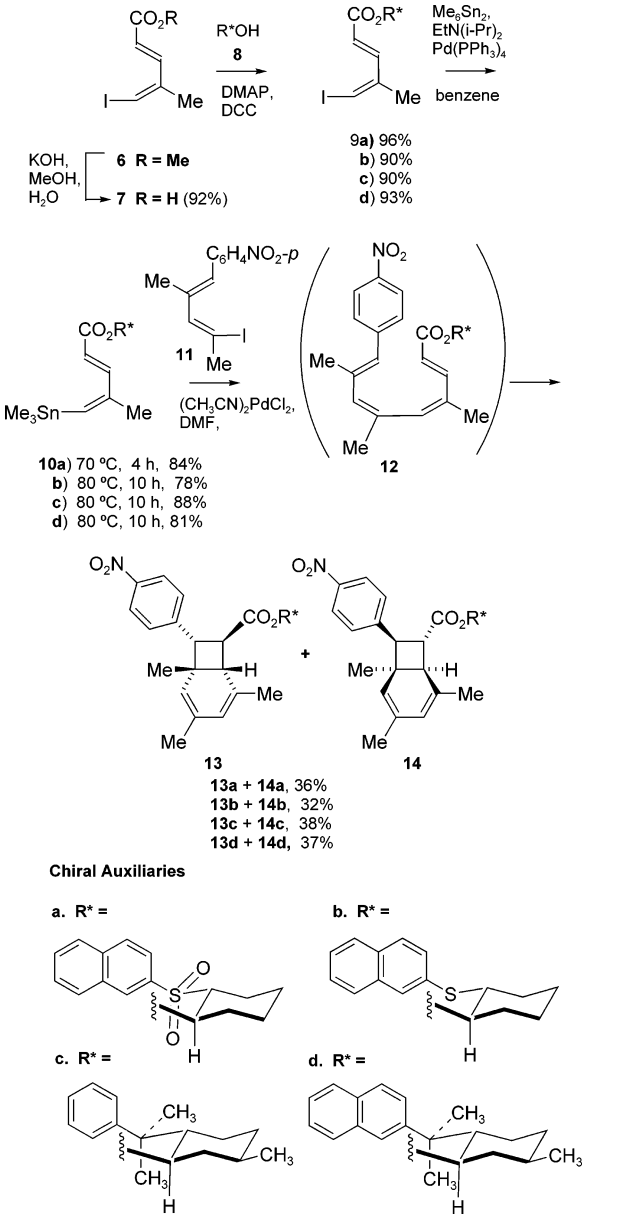
(8) For the biomimetic synthesis of the endiandric acids, see: Nicolaou, K. C.; Petasis, N. A.; Zipkin, R. E. *J. Am. Chem. Soc.* **1982**, *104*, 5560.

(9) (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.

(10) For the total synthesis of racemic elysiapyrones and racemic ocellapyrones, see: Barbarow, J. E.; Miller, A. K.; Trauner, D. *Org. Lett.* **2005**, *7*, 2901.

trimethyl-(2*E*,4*Z*,6*Z*,8*E*)-9-(4-nitrophenyl)nonatetraenic acid (see Scheme 2). This system has the important feature of being stereoselective for the "endo" product in the second step of the double closure.[5] Therefore, product analysis is simplified to the ratio of two endo diastereomers. An additional advantage for us was that precursors for the key building blocks of the tetraene substrate were available in our laboratory.

Scheme 2. Preparation of Diastereomeric SNF Analogues That Bear Cleavable Chiral Auxiliaries



Our plan was to couple the iodo acid **7** with a chiral alcohol auxiliary alcohol **8**, convert the iodo ester **9** to the vinyl stannane **10**, and then carry out a Stille coupling with the known iododiene **11**.[5a] The resulting tetraene **12** can then undergo the $8\pi/6\pi$ tandem closure to give a mixture of diastereomers **13** and **14**. The diastereomeric excess can be measured directly from the NMR spectrum of this mixture. We first examined the utility of the exceptionally convenient Corey−Sarakinos sulfone **8a**[11] in this sequence. Thus, acid **7**, from basic hydrolysis of the known **6**, underwent DCC coupling with alcohol **8a**, providing iododiene **9a** in 95% yield. However, standard stannylation conditions, intended to afford the auxiliary-bearing diene **10a**, were unsuccessful, leading to the product of elimination from the β-acyloxy sulfone (see the Supporting Information).

Because we had sulfide **8b**, an intermediate in the synthesis of sulfone **8a** in hand, we next prepared iodo ester **9b**. Stannylation provided ester **10b** which underwent the coupling/electrocyclization procedure with vinyl iodide **11** to give a mixture of ring-closed products **13b** and **14b**. The NMR spectrum of the mixture showed two diastereomers in a ratio of 1:1.5.

Convinced that the sulfone **12a**, if it could be prepared, would provide a larger bias toward a preferred transition state for the 8π closure,[12] we reexamined the stannylation of iodo ester **9a**. A combination of lower reaction temperature and shorter time allowed isolation of the desired vinyl stannane **10a** which was then submitted to the coupling/electrocyclization procedure with vinyl iodide **11**. An NMR analysis of the resulting mixture revealed two diastereomeric bicyclooctadienes **13a** and **14a** in a ratio of 4:1.

The effects of the 8-arylmenthyl chiral auxiliaries were examined next. Both the phenyl- and the naphthyl-substituted menthols (**8c** and **8d)** were prepared according to the literature procedures.[13,14] Esterification of acid **7** with alcohol **8c** followed by stannylation and Stille coupling gave a mixture of bicyclic esters **13c** and **14c**. The ratio of diastereomers was 1:2. Likewise, esterification of acid **7** with alcohol **8d**, stannylation of **9d**, and Stille coupling gave a mixture of esters **13d** and **14d**. Here the ratio of isomers was also 1:2.

Hoping to influence the ratio of diastereomers in the product mixture by the "additive effect" described by Tsutsumi, Kakiuchi, and co-workers,[15] we repeated our coupling/cyclization protocol in both arylmenthyl ester sequences (**9c** → **13c** + **14c**) and (**9d** → **13d** + **14d**) in the presence of 10 molar equiv of naphthalene. In the phenylmenthyl sequence, no change in ratio was observed. For the naphthylmenthyl series, the ratio shifted from 1:2 to 1:2.5. Diastereomeric excesses for all experiments are summarized in Table 1 in the Supporting Information.

(11) Sarakinos, G.; Corey, E. J. *Org. Lett.* **1999**, *1*, 1741. Because the product analysis was one of diastereomers, we worked with racemic **8a** and **8b**.

(12) Sarakinos and Corey (ref 11) had reported that the Lewis acid-catalyzed Diels Alder reactions of acrylates of the β-hydroxy sulfones were more stereoselective than those of the corresponding sulfides, noting that sulfide complexation might be involved. One might expect this result also on the basis of the buttressing effect of the sulfone oxygens.

(13) (a) Ort, O. *Org. Synth.* **1987**, *65*, 203. (b) Corey, E. J. Ensley, H. E. *J. Am. Chem. Soc.* **1995**, *97*, 6908.

(14) D'Angelo, J.; Maddaluno, J. *J. Am. Chem. Soc.* **1986**, *108*, 8112.

(15) Tsutsumi, Kakiuchi, and co-workers showed that aromatic cosolutes altered the ratio of diastereomers resulting from [2 + 2] additions to arylmenthyl esters of cyclohexenonecarboxylic acids; see: Tsutsumi, K.; Nakano, H.; Furutani, A.; Endou, K.; Merpuge, A.; Shintani, T.; Morimoto, T.; Kakiuchi, K *J. Org. Chem.* **2004**, *69*, 785.

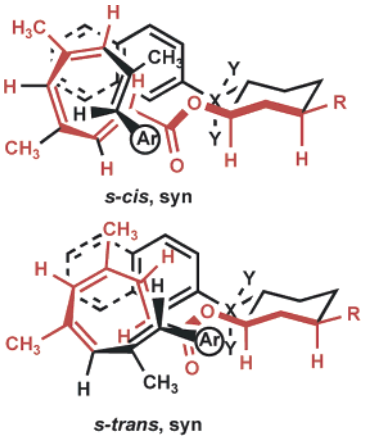


Figure 5. General structures for the reactive helical conformations for 8π electrocyclization of tetraene esters **12**. For **12a**, X = S, Y = O, aromatic system is β-naphthyl; for **12b**, X = S, Y = electron pair, aromatic system is β-naphthyl; for **12c**, X = C, Y = CH_3, aromatic system is phenyl; for **12d**, X = C, Y = CH_3, aromatic system is β-naphthyl.

Although cycloaddition reactions of related arylmenthyl and Corey−Sarakinos acrylates are often reported to give high diastereomeric excesses,[16] the protocols for these optimized reactions are based on Lewis acid catalysis. Studies by Houk[17] and also d'Angelo[18] suggest that Lewis acid coordination and possibly hydrogen-bonding solvents favor the *s-trans* conformation of unsaturated esters over the *s-cis* conformation; addition to the unshielded face of the π system then leads to the predominance of one diastereomeric product. In the absence of coordinating effects however, the cycloaddition transition states corresponding to the *s-cis,syn* and *s-trans,syn* conformations of acrylates are nearly isoenergetic.[19] The product distributions in our electrocyclic cascade show that the *s-cis,syn* and *s-trans,syn* helical transition states (Figure 5) are also of similar energies.

Thus, in the nitrophenyl-substituted *E,Z,Z,E*-tetraene series which was the subject of this initial study, none of the standard chiral auxiliaries influenced the 8π closure to provide a product with the high diastereomeric excess required for direct application in asymmetric synthesis. Indeed, the modest excesses obtained highlight the need for examining alternative auxiliaries and/or modifying one of those already tested to favor either the *s-cis,syn* or the *s-trans,syn* conformation. On the other hand, the diastereomeric products in the arylmenthyl series were easily separated on chromatography, providing compounds that offer access to chiral analogues of both SNF4435 C and D. Each of these esters is a prospective chiral intermediate for elaboration to designed drug candidates in the SNF series.

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Supporting Information Available: Detailed descriptions of the experimental procedures and complete analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) For a recent review on π-shielding that includes a number of examples of the use of the aryl menthyl auxiliaries, see: Jones, G. B. *Tetrahedron* **2001**, *57*, 7999.

(17) Loncharich, R. J.; Schwartz, T. R.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 14.

(18) Dumas, F.; Mezrhab, B.; d'Angelo, J.; Riche, C.; Chiaroni, A. *J. Org. Chem.* **1996**, *61*, 2293.

(19) Curran, D. P.; Kim, B. H.; Piyasena, H. P.; Loncharich, R. J.; Houk, K. N. *J. Org. Chem.* **1987**, *52*, 2137 and references therein.