

Asymmetric Synthesis of Seven-Membered Carbocyclic Rings via a Sequential Oxyanionic 5-Exo-Dig Cyclization/Claisen Rearrangement Process. Total Synthesis of (–)-Frondosin B

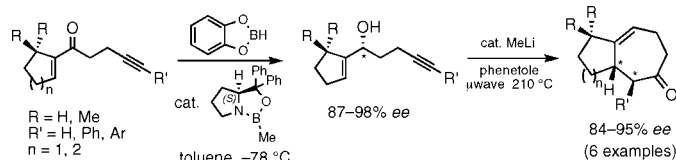
Timo V. Ovaska,* Jonathan A. Sullivan, Sami I. Ovaska, Jacob B. Winegrad, and Justin D. Fair†

Department of Chemistry, Connecticut College, 270 Mohegan Avenue,
New London, Connecticut 06320

tvova@conncoll.edu

Received May 1, 2009

ABSTRACT



Appropriately substituted nonracemic allyl alcohols, readily prepared from the corresponding enones by application of the CBS methodology, were converted to optically active cycloheptenone derivatives with almost complete transfer of chirality via an efficient “one-pot”, cycloisomerization/Claisen rearrangement process. This methodology was directly applied to the expedient total synthesis of (–)-frondosin B.

Carbocyclic seven-membered rings are ubiquitous in nature and constitute the central structural unit in a number of polycyclic natural products, including phorbol esters,¹ guanacastepenes,² guianolides,³ and the frondosins.⁴ Despite their prevalence and considerable medicinal relevance, the construction of cycloheptanoid systems through chemical synthesis remains challenging and is generally limited to processes other than direct intramolecular cyclization reactions. Among the most important of these are various cycloaddition strategies, such as the [5 + 2] and [4 + 3] reactions, which have proven useful for the synthesis of a number of seven-membered ring-containing natural products.⁵

We have recently demonstrated that a variety of cycloheptanoid fused ring systems may be conveniently accessed through a microwave-assisted tandem process that involves an oxyanionic 5-exo-dig cycloisomerization reaction,⁶ followed by in situ Claisen rearrangement of the resulting 2-alkyldenetetrahydrofuran intermediate.⁷ Herein, we wish to report a new asymmetric variant of this strategy, which allows an efficient and practical construction of a number of optically active cycloheptenone derivatives. To highlight the synthetic potential of this methodology, an expedient total synthesis of (–)-frondosin B is also described.

The Claisen rearrangement reaction⁸ has been widely exploited for the generation of optically active products, e.g., through the use of a stereodirecting element built either

† Present address: Department of Chemistry, University of Connecticut, Storrs, CT 06269-3060.

(1) Evans, F. J., Ed. *Naturally Occurring Phorbol Esters*; CRC: Boca Raton, 1986.

(2) Bondi, S. M.; Clardy, J. *J. Am. Chem. Soc.* **2001**, *123*, 9900–9901.

(3) Wong, H.-F.; Brown, G. D. *J. Nat. Prod.* **2002**, *65*, 481–486.

(4) Patil, A. D.; Freyer, A. J.; Killmer, L.; Offen, P.; Carte, B.; Jurewicz, A. J.; Johnson, R. K. *Tetrahedron* **1997**, *53*, 5047–5060.

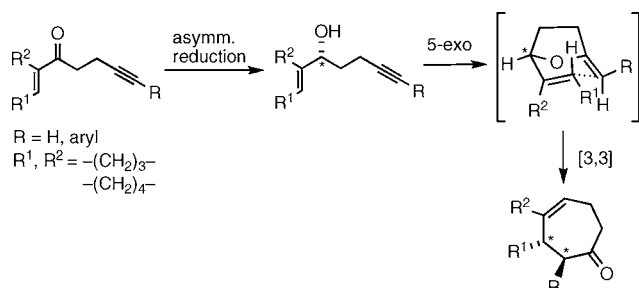
(5) For a recent review, see: Battiste, M. A.; Pelphrey, P. M.; Wright, D. L. *Chem.-Eur. J.* **2006**, *12*, 3438–3447.

(6) For an early example of this process, see: Marvell, E. N.; Titterton, D. *Tetrahedron Lett.* **1980**, 2123–2134.

within the allyl⁹ or the vinyl¹⁰ portion of the allyl vinyl ether moiety. Most of these processes involve enolate variants of the Claisen rearrangement, often operating under metal-promoted chelate control.¹¹ In addition, Lewis acid-promoted Claisen rearrangements, conducted in the presence of chiral ligands such as quinine and quinidine, have been employed to generate nonracemic products with varying degrees of asymmetric induction.¹² However, none of these strategies have been applied to the asymmetric synthesis of substituted cycloheptenone derivatives.

Our approach to nonracemic cycloheptenones relies on the ability of a single stereogenic center installed within the allylic alcohol starting material to transfer stereochemical information to the final carbocyclic product with up to two new stereocenters through an all intramolecular tandem cycloisomerization/Claisen rearrangement sequence. Undoubtedly, the observed diastereocontrol in these reactions evolves through a preferred chairlike six-membered transition state, where the two prochiral centers of the 2-alkylidene tetrahydrofuran intermediate occupy a pseudo-diequatorial relationship (Scheme 1).^{7h}

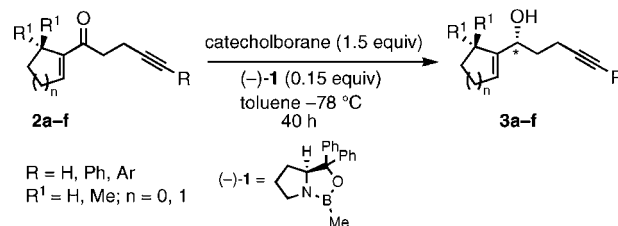
Scheme 1. Synthesis of Optically Active Cycloheptenone Derivatives



The prochiral enones employed for this investigation were prepared from the corresponding allylic alcohols^{7h} by Swern oxidation¹³ or using the Bobbitt reagent.¹⁴ The enone products were then converted to the desired nonracemic homopropargylic allylic alcohols according to the Corey–Bakshi–Shibata¹⁵ (CBS) protocol employing stoichiometric catechol borane in the presence of a chiral oxazaborolidine catalyst ((-)-**1**, Table 1).

In the series examined, the degree of enantioselectivity generally increased on going from cyclopentenyl to cyclohexenyl systems and was notably higher when additional substituents were placed near the reaction site (Table 1, entry 6). Thus, the more highly substituted enone **2f** bearing a *gem*-dimethyl moiety on the cyclohexenyl ring at C6 exhibited the highest level of enantioselectivity upon CBS reduction, providing alcohol **3f** in 98% ee (Table 1, entry 6). Although the absolute stereochemistry of the stereogenic center in **3f** or in the other allylic alcohols prepared was not unequivocally established, ample literature precedent¹⁵ involving analogous systems and examination of the relevant transition state structures for the reduction are consistent with the formation of the *R* isomer as the major product in each case.

Table 1. Preparation of Optically Active Homopropargylic Allyl Alcohols via CBS Reduction






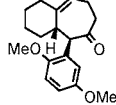

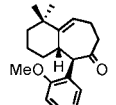
entry	enone (2)	allyl alcohol (3)	yield (%) ^a	ee (%) ^b
1			86	87
2			66	89
3			95	91
4			81	91
5			52	89
6			68 ^d	98

^a Yields of chromatographically purified products. ^b Enantiomer ratios were determined either by chiral GC or chiral HPLC. ^c Ar = 2,6-dimethoxyphenyl. ^d Reaction was quenched after 72 h.

Gratifyingly, almost complete transfer of chirality was observed when each nonracemic allylic alcohol was subjected to catalytic MeLi and heat under microwave irradiation in phenetole. The expected 5–7 and 6–7 fused bicyclic ketones were produced in yields ranging from 62% to 82% and in ee's as high as 95% (Table 2). Compounds **4c–f** represent examples where a single stereogenic center in the starting alcohol—ultimately lost in the course of the cyclization/rearrangement sequence—controls the absolute stereochemistry of two new adjacent stereocenters in the bicyclic cycloheptanoid product. It should be noted that the observed diastereomer ratios could be improved further through simple isomerization under basic conditions. For example, the initial 83:17 ratio of diastereomers in the case of **4f** (Table 2, entry 6) was further enriched to a final ratio of 91:9 after stirring in a solution of MeONa/MeOH at room temperature for 24 h.

Ketone **4f** was selected as a suitable precursor for elaboration into optically active frondosin B, which is one

Table 2. Synthesis of Optically Active Bicyclic Cycloheptenone Derivatives via Tandem 5-Exo-Cyclization/Claisen Rearrangement

$\text{3a-f} \xrightarrow[\text{phenetole, } \mu\text{wave } 210^\circ\text{C, 60 min}]{\text{cat. MeLi (0.15 equiv)}} \text{4a-f}$					
entry	allyl alcohol (3)	bicyclic ketone (4)	yield (%) ^a	dr	ee (%) ^b
1	3a		62		85
		4a			
2	3b		77		87
		4b			
3	3c		78	92:8	85
		4c			
4	3d		82	77:23	89
		4d			
5	3e		76	92:8	84
		4e			
6	3f		79	83:17 (91:9) ^c	95
		4f			

^a Combined yield of both diastereomers. ^b Enantiomeric excess of the major diastereomer was determined either by chiral GC or chiral HPLC. ^c After 24 h of stirring in MeONa/MeOH at 25 °C.

of five structurally related natural products first isolated in 1997 from the Micronesian marine sponge *Dysidea frondosa* (Figure 1).⁴ The unique structural features coupled with the therapeutic potential of this class of natural products as novel anti-inflammatory,⁴ antitumor,¹⁶ and anti-HIV¹⁷ agents has sparked considerable interest in their total synthesis by several research groups,¹⁸ including our own.^{7f,g,19,20}

Thus far, the total syntheses of the naturally occurring (+)-frondosin B and its (–)-enantiomer have been achieved by the groups of Danishefsky^{18b} and Trauner,^{18c,d} respectively. Although elegant in many ways, both of these approaches are somewhat lengthy, requiring multistep sequences at the early stages to prepare the requisite nonracemic starting materials. Danishefsky initially concluded that the sole stereogenic center in (+)-frondosin B is *R* configured; however, Trauner later challenged this assignment.^{18d} Trauner suggested that a key nonracemic material in the Danishefsky process had undergone an inadvertent inversion of configuration early on in the synthesis, ultimately resulting

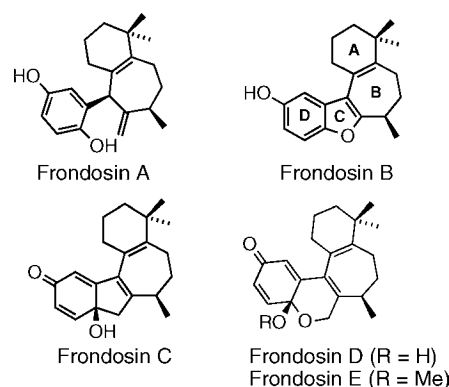
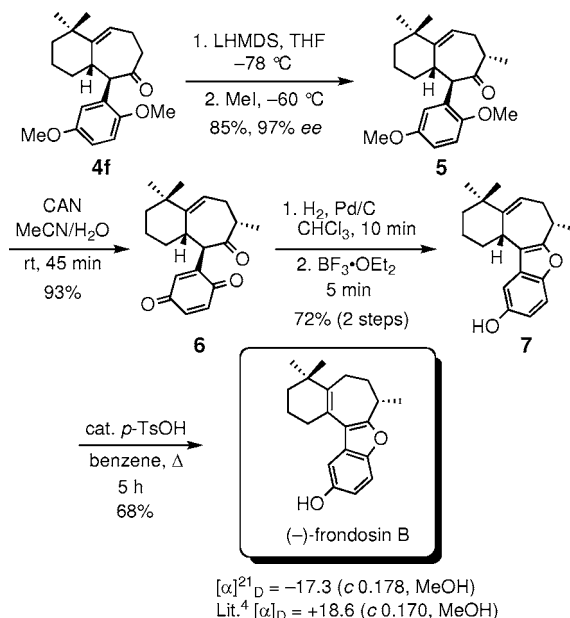


Figure 1. Frondosins A–E.

in misassignment of absolute stereochemistry at C8 of the natural product.^{18d}

Overall, our approach to (–)-frondosin B involves only two additional steps compared to that already reported for its racemic analogue (Scheme 2).²⁰ Thus, optically active

Scheme 2. Total Synthesis of (–)-Frondosin B



4f (prepared from enone 2f in two steps) was methylated regio- and stereospecifically at C8, providing ketone 5 in 85% yield and 97% ee after purification. Ceric ammonium nitrate (CAN)-promoted oxidative demethylation of 5 gave the benzoquinone derivative 6, which was subsequently reduced under catalytic hydrogenation conditions. The resulting hydroquinone intermediate was directly exposed to BF₃·OEt₂, smoothly affording tetracycle 7, a close structural analogue of frondosin B. On treatment with catalytic *p*-TsOH

in refluxing benzene, **7** was converted to (–)-frondosin B in 68% isolated yield ($[\alpha]_D^{21} = -17.3$, c 0.178, MeOH).²¹

It is worth emphasizing that the absolute configuration of the final product is ultimately derived from **3f** where the *R* stereogenic center controls the stereochemical course of the tandem cyclization/Claisen rearrangement process, providing **4f** as the 10*R*,11*S* stereoisomer (major diastereomer). The C10 aryl substituent, in turn, directs the subsequent methylation reaction at C8, affording ketone **5**. The observed *trans* relationship between the C10 aryl and C8 methyl substituents has been previously confirmed by X-ray crystallography involving a racemic analogue of **4f**.²⁰ Since it is unlikely that the configuration at C8 would change in the course of the remaining four steps of the reaction sequence, it is concluded that (–)-frondosin B must be *S* configured at C8. This result is in agreement with Danishefsky's original

assignment according to which the naturally occurring (+)-frondosin B has an *R* stereogenic center at C8.^{18b}

In summary, an asymmetric variant of the oxyanionic 5-exo-dig cyclization/Claisen rearrangement has been developed, allowing a straightforward synthesis of a number of optically active cycloheptanoid ring systems, including (–)-frondosin B. Further studies employing this methodology to the asymmetric synthesis of the remaining members of the frondosin family as well as other cycloheptanoid natural product targets are currently underway in our laboratories. The results from these studies will be reported in due course.

Acknowledgment. This research was supported by a grant from the National Institutes of Health (NIGMS). T.V.O also gratefully acknowledges support from the Hans and Ella McCollum-Vahlteich '21 endowment.

Supporting Information Available: Full experimental details, characterization data, and copies of ¹H and ¹³C NMR spectra for all new compounds are provided. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL900967J

(7) (a) Ovaska, T. V.; Roark, J. L.; Shoemaker, C. M. *Tetrahedron Lett.* **1998**, 39, 5705–5708. (b) Ovaska, T. V.; Roses, J. B. *Org. Lett.* **2000**, 2, 2361–2364. (c) Ovaska, T. V.; Reisman, S. E.; Flynn, M. A. *Org. Lett.* **2001**, 3, 115–117. (d) Ovaska, T. V.; Ravi Kumar, J. S.; Hulford, C. A.; O'Sullivan, M. F.; Reisman, S. E. *Tetrahedron Lett.* **2002**, 43, 1939–1941. (e) McIntosh, C. E.; Martinez, I.; Ovaska, T. V. *Synlett* **2004**, 2579–2581. (f) Martinez, I.; Alford, P. E.; Ovaska, T. V. *Org. Lett.* **2005**, 7, 1133–1135. (g) Li, X.; Kyne, R. E.; Ovaska, T. V. *Org. Lett.* **2006**, 8, 5153–5156. (h) Li, X.; Kyne, R. E.; Ovaska, T. V. *J. Org. Chem.* **2007**, 72, 6624–6627.

(8) For reviews on the Claisen rearrangement, see: (a) Wipf, P. *The Claisen Rearrangement*. In *Comprehensive Organic Synthesis*; Wiley: New York, 1991; Vol. 5, pp 827–873. (b) Castro, A. M. M. *Chem. Rev.* **2004**, 104, 2939–3002.

(9) For representative examples, see: (a) Katzmaier, U.; Schneider, C. *Tetrahedron Lett.* **1998**, 39, 817–818. (b) Looper, R. E.; Williams, R. M. *Tetrahedron Lett.* **2001**, 42, 769–771. (c) Samy, R.; Kim, H. Y.; Stein, K.; Toogood, P. L. *J. Org. Chem.* **1999**, 64, 2711–2728. (d) Fernandez de la Pradilla, R.; Montero, C.; Tortosa, M. *Org. Lett.* **2002**, 4, 2373–2376.

(10) For representative examples, see: (a) Kallmerten, J.; Gould, T. J. *J. Org. Chem.* **1986**, 51, 1152–1155. (b) Kazmaier, U.; Maier, S. *J. Org. Chem.* **1999**, 64, 4574–4575. (c) Kazmaier, U.; Maier, S. *Org. Lett.* **1999**, 1, 1763–1966.

(11) Kazmaier, U.; Mues, H.; Krebs, A. *Chem.–Eur. J.* **2002**, 8, 1850–1855.

(12) For representative examples, see: (a) Maruoka, K.; Banno, H.; Yamamoto, H. *J. Am. Chem. Soc.* **1990**, 112, 7791–7793. (b) Maruoka, K.; Saito, S.; Yamamoto, H. *J. Am. Chem. Soc.* **1995**, 117, 1165–1166. (c) Kazmaier, U.; Krebs, A. *Angew. Chem., Int. Ed.* **1995**, 34, 2012–2013. (d) Corey, E. J.; Lee, D.-H. *J. Am. Chem. Soc.* **1991**, 113, 4026–4028. (e) Hiersemann, M.; Abraham, L. *Eur. J. Org. Chem.* **2002**, 146, 1–1471.

(13) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165–185.

(14) Bobbitt, J. M. *J. Org. Chem.* **1998**, 63, 9367–9374.

(15) For reviews, see: (a) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, 37, 1986–2012. (b) Byung, T. C. *Tetrahedron* **2006**, 62, 7621–7643.

(16) (a) Brat, D. J.; Bellail, A. C.; Van Meir, E. G. *Neuro-oncol.* **2005**, 7, 122–133. (b) Zhu, Y. M.; Webster, S. J.; Flower, D.; Woll, P. J. *Br. J. Cancer* **2004**, 91, 1970–1976. (c) Yuan, A.; Chen, J. J.; Yao, P. L.; Yang, P. C. *Front. Biosci.* **2005**, 853–865.

(17) Hallock, Y. F.; Cardellina, J. H., II; Boyd, M. R. *Nat. Prod. Lett.* **1998**, 11, 153–160.

(18) (a) Inoue, M.; Frontier, A. J.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2000**, 39, 761–764. (b) Inoue, M.; Carson, M. W.; Frontier, A. J.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2001**, 123, 1878–1889. (c) Hughes, C. C.; Trauner, D. *Angew. Chem., Int. Ed.* **2002**, 41, 1569–1573. (d) Hughes, C. C.; Trauner, D. *Tetrahedron* **2004**, 60, 9675–9686. (e) Kerr, D. J.; Willis, A. C.; Flynn, B. L. *Org. Lett.* **2004**, 6, 457–460. (f) Trost, B. M.; Hu, Y.; Horne, D. B. *J. Am. Chem. Soc.* **2007**, 129, 11781–11790. (g) Olson, P.; Davies, H. M. L. *Org. Lett.* **2008**, 10, 573–576. (h) Masters, K.-S.; Flynn, B. L. *J. Org. Chem.* **2008**, 73, 8081–8084. (i) Mehta, G.; Likhite, N. S. *Tetrahedron Lett.* **2008**, 49, 7113–7116.

(19) Li, X.; Kyne, R. E.; Ovaska, T. V. *Tetrahedron* **2007**, 63, 1899–1906.

(20) Li, X.; Ovaska, T. V. *Org. Lett.* **2007**, 9, 3837–3840.

(21) The balance of the reaction consisted mostly of isomeric impurities, which were separated from (–)-frondosin B by column chromatography.