ORGANIC LETTERS

2010
Vol. 12, No. 8
1836−1838

Enantioselective Pathway for the Synthesis of Laurenditerpenol

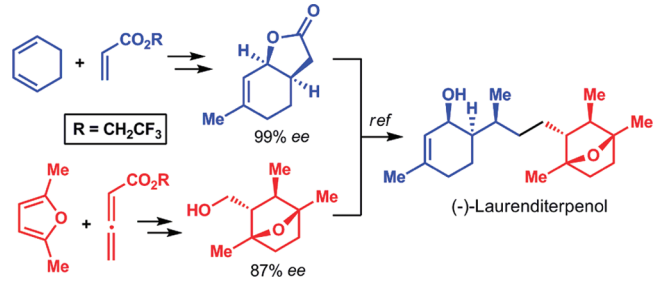
Santanu Mukherjee, Alex P. Scopton, and E. J. Corey*

Department of Chemistry and Chemical Biology, Harvard University, 12 Oxford Street, Cambridge, Massachusetts 02138

corey@chemistry.harvard.edu

Received February 25, 2010

ABSTRACT



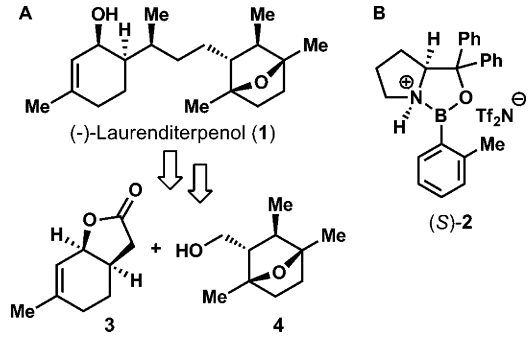
Simple enantioselective routes to the two key intermediates shown above (at center) for the synthesis of laurenditerpenol have been developed using a Diels−Alder step and the same catalyst system for each.

The diterpenoid laurenditerpenol (**1**, Scheme 1), isolated from the marine alga *Laurencia intricata*, is of special interest because it inhibits hypoxia-inducible factor-1 (HIF-1), a factor that promotes tumor growth.[1] A synthesis of **1** and diastereomers served to clarify the stereochemistry of this quite active HIF-1 inhibitor (IC_{50} 400 nM).[2] A synthesis of the racemate of **1** has also been recorded.[3]

We report herein a stereocontrolled pathway for the enantioselective synthesis of **1**. In this synthesis, both cyclic subunits of **1** were constructed using the enantioselective Diels−Alder reaction promoted by catalysis with a chiral oxazaborolidinium cation (**2**).[4] The subunits for the current route to **1** were the enantiomerically pure forms of the same two key intermediates, **3** and **4**, that were employed in the recent synthesis of (±)-**1** (Scheme 1).[3]

The route for the enantioselective synthesis of **3** (Scheme 2) started with the *endo*-adduct **5** (90% yield, 99% *ee*), obtained via Diels−Alder reaction of acrylate ester and 1,3-cyclohexadiene using the chiral oxazaborolidinium triflimide (*S*)-**2**, as described previously.[5] Nitrosobenzene-mediated oxidative C−C bond cleavage[6] of **5** afforded the bicyclic ketone **6** (in 68% yield), which was easily transformed into the hydroxy acid **8** following the sequence of Baeyer−

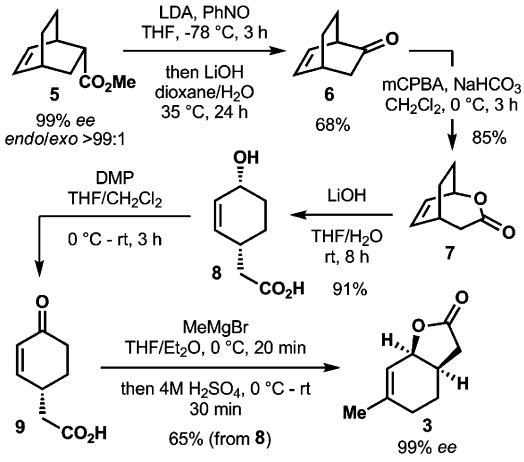
Scheme 1. (A) Intermediates for the Synthesis of Laurenditerpenol **1** and (B) Chiral Oxazaborolidinium Triflimide **2**



(1) Mohammed, K. A.; Hossain, C. F.; Zhang, L.; Bruick, R. K.; Zhou, Y.-D.; Nagle, D. G. *J. Nat. Prod.* **2004**, *67*, 2002–2007.
(2) Chittiboyina, A. G.; Kumar, G. M.; Carvalho, P. B.; Liu, Y.; Zhou, Y.-D.; Nagle, D. G.; Avery, M. A. *J. Med. Chem.* **2007**, *50*, 6299–6302.
(3) (a) Jung, M. E.; Im, G.-Y. J. *Tetrahedron Lett.* **2008**, *49*, 4962–4964. (b) Jung, M. E.; Im, G.-Y. J. *J. Org. Chem.* **2009**, *74*, 8739–8753.
(4) For a recent review, see: Corey, E. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 2100–2117.

10.1021/ol1004802
Published on Web 03/25/2010

Scheme 2. Enantioselective Synthesis of the Key Intermediate **3**



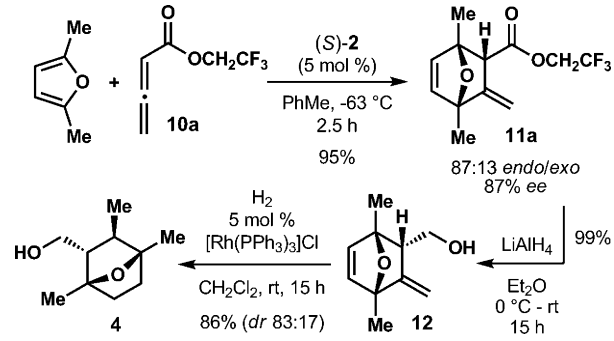
Villiger oxidation[7] and alkaline hydrolysis of the lactone **7**. Dess−Martin periodinane (DMP) oxidation of the allylic alcohol generated the enone **9**, which without any purification was treated with MeMgBr in THF at 0 °C. Simple aqueous acid treatment of the resulting tertiary alcohol produced the lactone **3** without any loss of enantiomeric purity.

Although the subunit **4** could in principle be constructed by an enantioselective Diels−Alder reaction of crotonaldehyde and 2,5-dimethylfuran followed by reduction of CHO and C═C, in practice, this approach was not operable because the required Diels−Alder step did not proceed, even at 0 °C. This failure is apparently due to strong steric repulsion between the CH_3 of crotonaldehyde and one of the CH_3 groups of 2,5-dimethylfuran in the transition state. That repulsion is especially consequential because the most advanced bonding in the transition state involves C(β) of the α,β-enal and C(α) of the furan component.[8]

This difficulty in the synthesis of the subunit **4** was overcome by use of an asymmetric Diels−Alder reaction employing an allenic ester as the dienophile (*vide infra*). Allenic esters are a class of highly reactive dienophiles, and the corresponding Diels−Alder adducts are of synthetic value. Despite the existence of a number of reports[9] on substrate-controlled *diastereoselective* Diels−Alder reactions of allenic esters, a *catalytic* enantioselective version of this reaction has remained elusive.

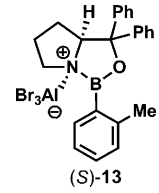
With the goal of an efficient approach to **4**, we studied the reaction of 2,5-dimethylfuran and trifluoroethyl allenoate **10a** in the presence of 10 mol % of the catalyst (*S*)-**2** (Scheme 3). The desired *endo*-product **11a** was

Scheme 3. Asymmetric Diels−Alder Reaction of Allenic Ester **10a** and Enantioselective Synthesis of Subunit **4**



obtained in 95% yield with 87:13 *dr* and 87% *ee*. Reduction of the ester group followed by directed hydrogenation[10] using Wilkinson's catalyst provided the desired diastereomer **4** with good diastereoselectivity (*dr* 83:17) without any optimization.

The catalytic asymmetric Diels−Alder reaction exemplified with allenic ester **10a** in Scheme 3 has been found to be quite general. Several other examples are summarized in Table 1. The corresponding $AlBr_3$-activated catalyst **13** (see below) was found to be superior to catalyst **2** in most cases. Diels−Alder adducts were obtained in high yields with excellent levels of diastereoselectivity and enantioselectivity.



(*S*)-**13**

The usefulness of these Diels−Alder adducts is illustrated in Scheme 4. Hydrogenation of cycloadduct **11b** under carefully controlled conditions leads to selective reduction of the endocyclic double bond with concomitant migration of the exocyclic double bond. The resulting α,β-unsaturated ester **14** can be reduced further to produce the fully saturated product **15** as a single diastereomer (Scheme 4, eq 1). In contrast, the corresponding 2,5-dimethylfuran adduct **11a** undergoes hydrogenation *without* migration of the exocyclic double bond (Scheme 4, eq 2), and further reduction produces **17** as a single diastereomer. The later result is noteworthy since hydrogenation of the corresponding alcohol **12** occurs at the opposite face of the exocyclic double bond, as shown in Scheme 3.

(5) (a) Ryu, D. H.; Corey, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 6388–6390. (b) Brown, M. K.; Corey, E. J. *Org. Lett.* **2010**, *12*, 172–175.

(6) (a) Payette, J. N.; Yamamoto, H. *J. Am. Chem. Soc.* **2008**, *130*, 12276–12278. (b) Li, P.; Payette, J. N.; Yamamoto, H. *J. Am. Chem. Soc.* **2007**, *129*, 9534–9535.

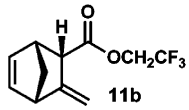
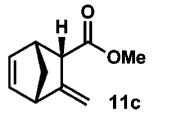
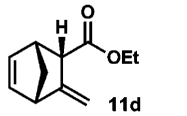
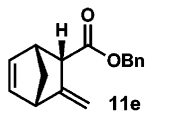
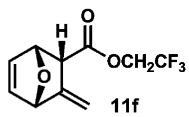
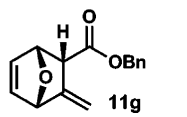
(7) The Baeyer−Villiger oxidation must be conducted at 0 °C. Even though the reaction at rt was found to be complete within 45 min, a substantial amount of epoxide formation from the starting ketone was observed together with other byproducts (see the Supporting Information).

(8) (a) Ryu, D. H.; Zhou, G.; Corey, E. J. *Org. Lett.* **2005**, *7*, 1633–1636. (b) Mukherjee, S.; Corey, E. J. *Org. Lett.* **2010**, *12*, 1024–1027.

(9) (a) Oppolzer, W.; Chapuis, C. *Tetrahedron Lett.* **1983**, *24*, 4665–4668. (b) Oppolzer, W.; Chapuis, C.; Dupuis, D.; Guo, M. *Helv. Chim. Acta* **1985**, *68*, 2100–2114. (c) Henderson, J. R.; Chesterman, J. P.; Parvez, M.; Keay, B. A. *J. Org. Chem.* **2010**, *75*, 988–991.

(10) (a) Thompson, H. W.; Mcpherson, E. *J. Am. Chem. Soc.* **1974**, *96*, 6232–6233. (b) Brown, J. M. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 190–203. For a review on substrate-directable reactions, see: (c) Hoveyda, A. H.; Fu, G. C.; Evans, D. A. *Chem. Rev.* **1993**, *93*, 1307–1370.

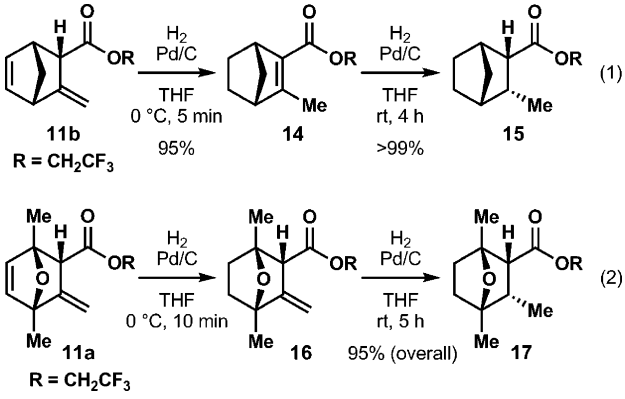
Table 1. Catalytic Enantioselective Diels−Alder Reactions of Allenic Esters

entry	product	catalyst (mol %)	solvent	temp (°C) time (h)	yield (%)[a]	*ee* (%) (*endo*/*exo*)[b]
1	 **11b**	**13** (5)	CH_2Cl_2/PhMe (1:1)	-100, 3	94	>99 (>99:1)
2	 **11c**	**13** (20)	CH_2Cl_2	-90, 4	90	92 (91:9)
3	 **11d**	**13** (10)	CH_2Cl_2	-78, 2.5	99	89 (>99:1)
4	 **11e**	**13** (10)	CH_2Cl_2	-90, 3.5	99	88 (>99:1)
5	 **11f**	**2** (10)	CH_2Cl_2	-78, 1.5	87	>99 (86:14)
6	 **11g**	**13** (20)	CH_2Cl_2	-78, 20	60	94 (>99:1)

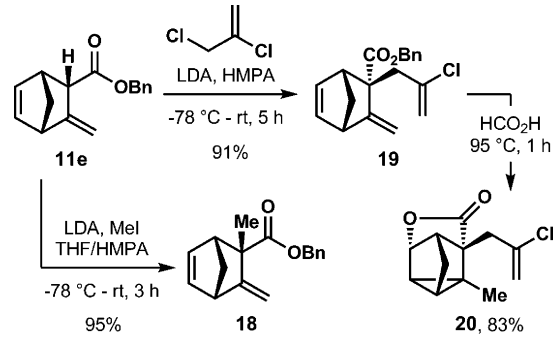
[a] The yields correspond to the amount of product obtained after column chromatography. [b] Enantiomeric excess was determined by GC analysis using a chiral column (see the Supporting Information). Diastereomeric ratios were determined by ^{1}H NMR analysis of the total product mixture.

The α-alkylation of the *β*,*γ*-unsaturated Diels−Alder adduct **11e** occurred exclusively from the *exo*-face[9a] as demonstrated for methylation and allylation (Scheme 5). The products were obtained in high yield and essentially as a single diastereomer (*dr* > 98:2). Interestingly, treatment of the allylated adduct **19** with formic acid at 95 °C causes

Scheme 4. Hydrogenation of the Allenic Ester Diels−Alder Adducts



Scheme 5. Alkylation of the Diels−Alder Adduct **11e**



rapid cyclization to the tetracyclic compound **20**. The crystalline lactone **20** was subjected to X-ray crystallographic analysis, which established the structure and absolute configuration shown (Figure 1). This result supports the assig-

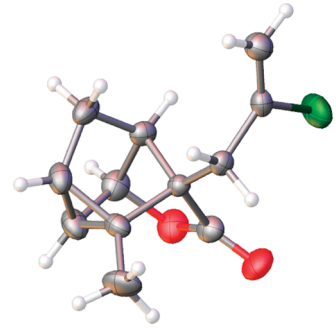


Figure 1. X-ray structure of the tetracyclic lactone **20**.

ments of absolute configuration of the Diels−Alder adducts shown in Table 1, which is as predicted by the previously proposed stereochemical model.[4]

In summary, a simple and efficient synthetic approach to the diterpenoid (−)-laurenditerpenol is reported using catalytic asymmetric Diels−Alder reactions to generate both key intermediates (**3** and **4**). The methodology used for generating **3** provides an interesting approach for the enantioselective synthesis of other chiral bicyclic *γ*-lactones.

Acknowledgment. We thank Dr. Douglas Ho and Dr. Shao-Liang Zheng of Harvard University for X-ray diffraction analysis. Dr. Nathan Wallock of Sigma Aldrich Co. is gratefully acknowledged for a gift of the oxazaborolidine precatalyst and triflimide.

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

OL1004802