

Enantioselective Pathway for the
Synthesis of Laurenditerpenol

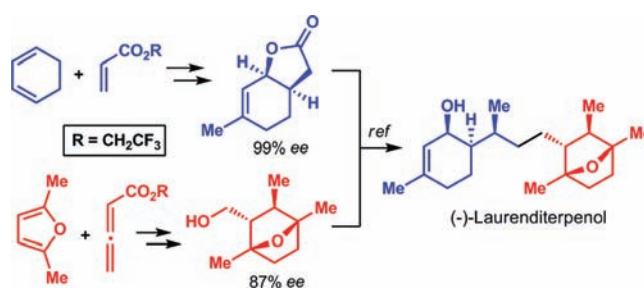
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ABSTRACT



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 (IC₅₀ 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*),

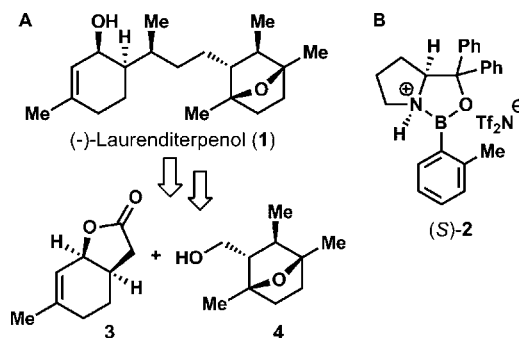
(1) Mohammed, K. A.; Hossain, C. F.; Zhang, L.; Bruick, R. K.; Zhou, Y.-D.; Nagle, D. G. *J. Nat. Prod.* **2004**, *67*, 2002–2007.

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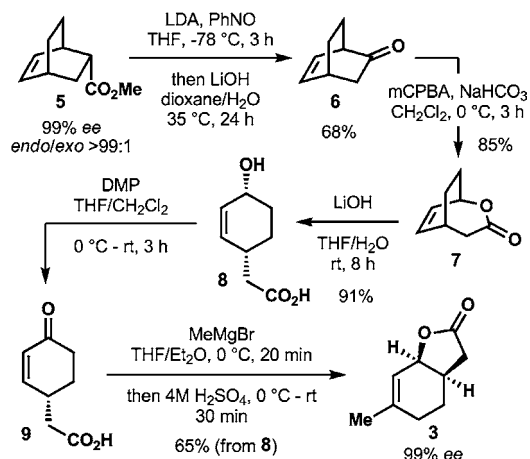
(4) For a recent review, see: Corey, E. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 2100–2117.

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



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 cleavage⁶ 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 2. Enantioselective Synthesis of the Key Intermediate 3



Villiger oxidation⁷ 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 CH₃ of crotonaldehyde and one of the CH₃ 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 reports⁹ 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 alle-

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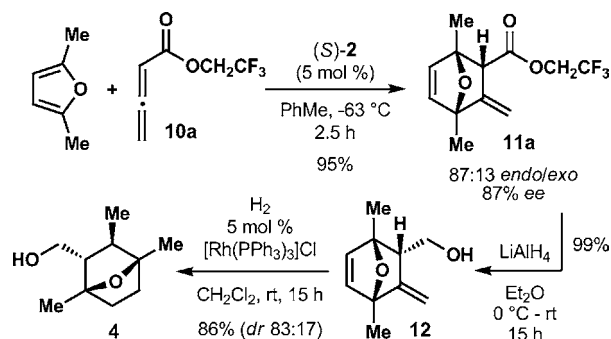
(7) The Baeyer–Villiger oxidation must be conducted at 0 °C. Even though the reaction at rt was found to be complete within 45 min, a substantial amount of epoxide formation from the starting ketone was observed together with other byproducts (see the Supporting Information).

(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.

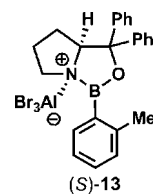
noate **10a** in the presence of 10 mol % of the catalyst (*S*)-**2** (Scheme 3). The desired *endo*-product **11a** was

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 hydrogenation¹⁰ using Wilkinson's catalyst provided the desired diastereomer **4** with good diastereoselectivity (*dr* 83:17) without any optimization.

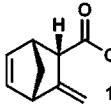
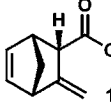
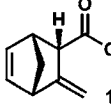
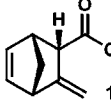
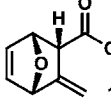
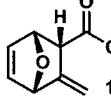
The catalytic asymmetric Diels–Alder reaction exemplified with allenic ester **10a** in Scheme 3 has been found to be quite general. Several other examples are summarized in Table 1. The corresponding AlBr₃-activated catalyst **13** (see below) was found to be superior to catalyst **2** in most cases. Diels–Alder adducts were obtained in high yields with excellent levels of diastereoselectivity and enantioselectivity.



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.

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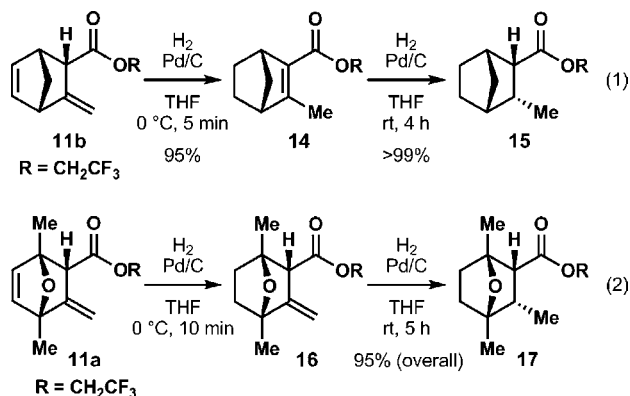
Table 1. Catalytic Enantioselective Diels–Alder Reactions of Allenic Esters

entry	product	catalyst (mol %)	solvent	temp (°C)	time (h)	yield (%) ^a	ee (%) ^b (<i>endo/exo</i>)
1		13 (5)	CH ₂ Cl ₂ / PhMe (1:1)	-100	3	94	>99 (>99:1)
2		13 (20)	CH ₂ Cl ₂	-90	4	90	92 (91:9)
3		13 (10)	CH ₂ Cl ₂	-78	2.5	99	89 (>99:1)
4		13 (10)	CH ₂ Cl ₂	-90	3.5	99	88 (>99:1)
5		2 (10)	CH ₂ Cl ₂	-78	1.5	87	>99 (86:14)
6		13 (20)	CH ₂ Cl ₂	-78	20	60	94 (>99:1)

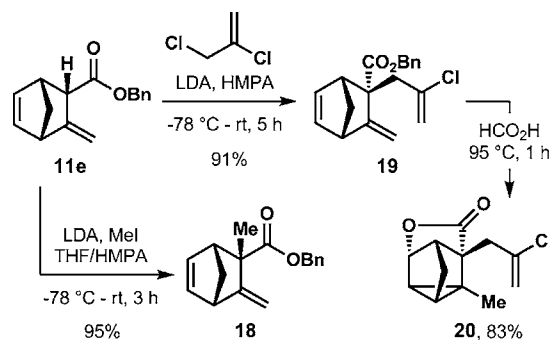
^a The yields correspond to the amount of product obtained after column chromatography. ^b Enantiomeric excess was determined by GC analysis using a chiral column (see the Supporting Information). Diastereomeric ratios were determined by ¹H NMR analysis of the total product mixture.

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 assign-

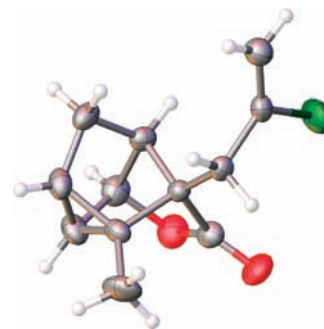


Figure 1. X-ray structure of the tetracyclic lactone **20**.

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>.

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