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Total Syntheses of Enokipodins A and B Utilizing Palladium-Catalyzed Addition of An Arylboronic Acid to An Allene

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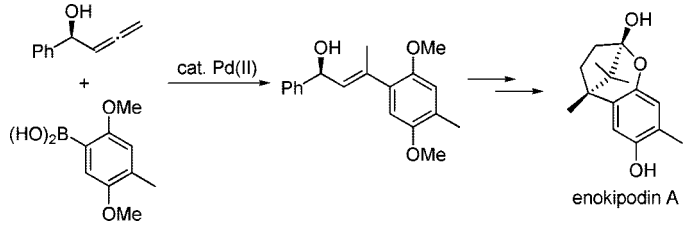
ABSTRACT



The enantioselective total syntheses of enokipodins A and B, α-cuparenone-type sesquiterpenoids with antimicrobial activity, have been achieved. The key step is the enantiospecific construction of the quaternary carbon center using a palladium-catalyzed addition of an arylboronic acid to an allene followed by an Eschenmoser−Claisen rearrangement.

The enokipodins A (**1**) and B (**2**), isolated by Takahashi et al. from a culture broth of an edible mushroom (*Flammulina velutipes*, "enokidake" in Japanese),[1,2] are highly oxidized α-cuparenone-type sesquiterpenoids that exhibit antimicrobial activity against *Cladosporium herbarum* and *Bacillus subtilis*.[1b] Owing to the sterically congested structures of these compounds (Figure 1), which possess a quaternary carbon stereocenter on the cyclopentane ring, they have attracted considerable synthetic interest.[3]

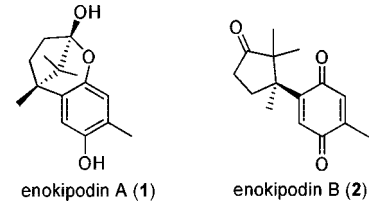


Figure 1. Structures for enokipodins A and B.

Recently, we have developed a regiocontrolled addition of arylboronic acids to allenic alcohols using a palladium or platinum catalyst.[4] The selectivity of the reaction can be altered by the choice of the metal reagent and the base, with the aryl-substituted allylic alcohol having an *endo* olefin being obtained regio- and stereoselectively when the hy-

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(2) For the total synthesis of the enokipodins A and B, see: (a) Srikrishna, A.; Rao, M. S. *Synlett* **2004**, 374–376. (b) Kuwahara, S.; Saito, M. *Tetrahedron Lett.* **2004**, *45*, 5047–5049. (c) Kuwahara, S.; Saito, M. *Biosci. Biotechnol. Biochem.* **2005**, *69*, 374–381.

(3) For selected examples, see: (a) Natarajan, A.; Ng, D.; Yang, Z.; Garcia-Garibay, M. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 6485–6487. (b) Spino, C.; Godbout, C.; Beaulieu, C.; Harter, M.; Mwene-Mbeja, T. M.; Boisvert, L. *J. Am. Chem. Soc.* **2004**, *126*, 13312–13319. (c) Acherar, S.; Audran, G.; Cecchin, F.; Monti, H. *Tetrahedron* **2004**, *60*, 5907–5912. (d) Satoh, T.; Yoshida, M.; Takahashi, Y.; Ota, H. *Tetrahedron: Asymmetry* **2003**, *14*, 281–288. (e) Nakashima, H.; Sato, M.; Taniguchi, T.; Ogasawara, K. *Tetrahedron Lett.* **2000**, *41*, 2639–2642. (f) Kosaka, T.; Bando, T.; Shishido, K. *Chem. Commun.* **1997**, 1167–1168.

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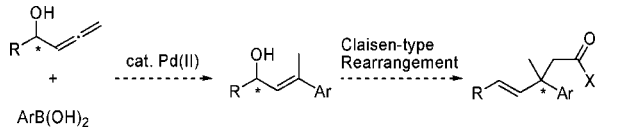
droxopalladium complex and Et_3N were used. Consequently, we expected that a quaternary carbon center could be stereoselectively created by a Claisen-type rearrangement[5] of this resulting allylic alcohol (Scheme 1), and thus we

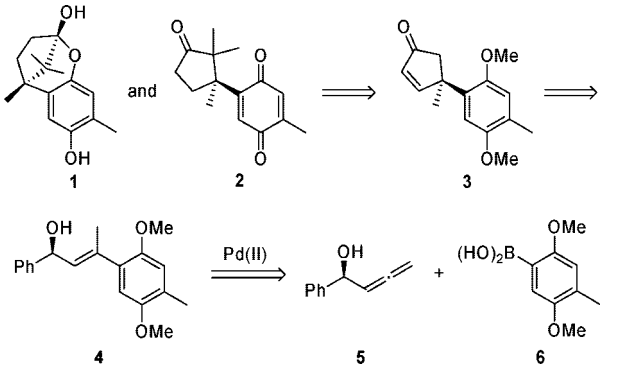
Scheme 1. Stereoselective Construction of a Quaternary Carbon Center



applied this methodology toward the synthesis of **1** and **2**. Herein, the enantioselective total syntheses of enokipodins A and B are described.

Our strategy for enokipodins A (**1**) and B (**2**) is shown in the retrosynthetic analysis in Scheme 2. We anticipated

Scheme 2. Strategy for **1** and **2**



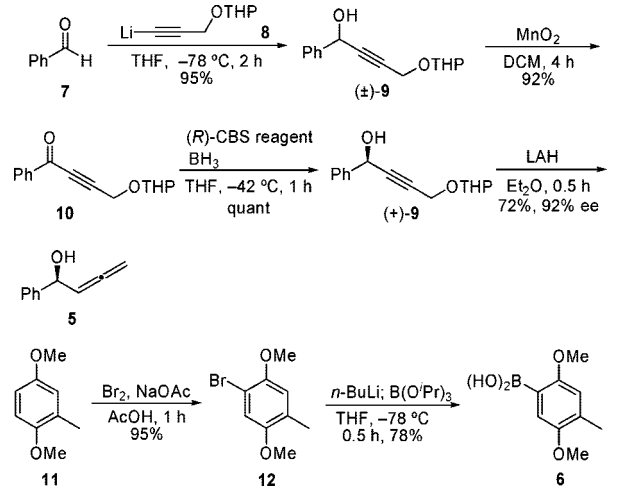
synthesizing enokipodins A (**1**) and B (**2**) from cyclopentenone **3**, according to Kuwahara's protocol.[2b,c] The cyclopentenone **3** could be obtained enantiospecifically via a Claisen-type rearrangement of the allylic alcohol **4**, which would be prepared by the palladium-catalyzed addition of the arylboronic acid **6** to the optically active allenic alcohol **5**.

The synthesis of the optically active allenic alcohol **5** and the arylboronic acid **6** was conducted as shown in Scheme 3. Addition of the lithium acetylide **8** to benzaldehyde (**7**) afforded the propargylic alcohol (±)-**9**, which was oxidized with MnO_2 to give the ketone **10**. Enantioselective reduction of **10** with the (*R*)-CBS reagent[6] and BH_3 and subsequent treatment of the resulting (+)-**9** with LAH furnished the optically active allenic alcohol **5** in 92% ee. The aryl bromide **12**, prepared by bromination of the arene **11**, was converted to the arylboronic acid **6** by reaction with *n*-BuLi and $B(O^iPr)_3$.

With the key substrates in hand, we next examined the palladium-catalyzed reaction of **5** with **6** (Table 1). When **5**

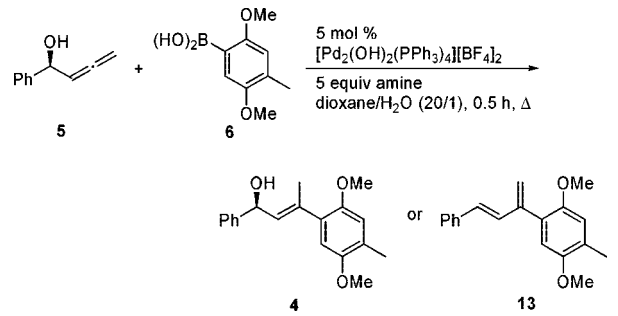
(6) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986–2012.

Scheme 3. Syntheses of **5** and **6**



was treated with 5 mol % of $[Pd_2(OH)_2(PPh_3)_4][BF_4]_2$ and 5 equiv of Et_3N in dioxane/H_2O (20/1) at 60 °C,[4] the desired

Table 1. Palladium-Catalyzed Reaction of **5** with **6**



entry	amine	temp (°C)	product	yield (%)
1	Et_3N	60	**4**	61
2	Et_3N	80	**4**	68
3	Et_3N	100	**4**	60
4	$^iPr_2NEt$	80	**4**	53
5	$^iPr_2NH$	80	**4**	47
6	pyridine	80	**13**	92
7	Et_3N^a	80	**4**	56
8	Et_3N^b	80	**4**	42

[a] 0.5 equiv of Et_3N was added. [b] 0.2 equiv of Et_3N was added.

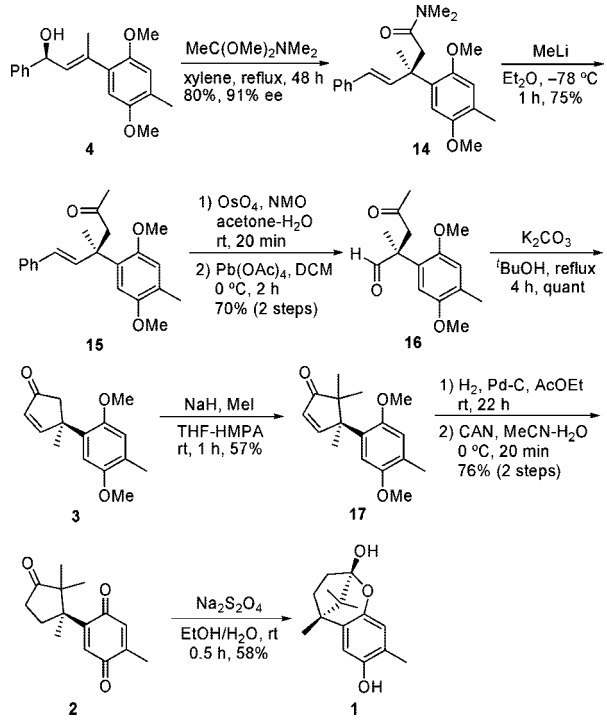
aryl-substituted allylic alcohol **4** was produced as the sole product in 61% yield (entry 1). With the yields of **4** being influenced by the reaction temperature (entries 2 and 3), the best result was obtained when the reaction was carried out at 80 °C (entry 2). Similar results were observed when other amines such as $^iPr_2NEt$ and $^iPr_2NH$ were used (entries 4 and 5). Interestingly, the dehydrated diene **13** was predominant

(7) Although the reason for the pyridine effect is not clear, similar reactivity to afford dienes has been observed in the presence of platinum catalysts. See ref 4.

in the presence of pyridine (entry 6).[7] Even with decreased amounts of Et_3N (0.5 equiv and 0.2 equiv), the reactions afforded the product **4** in moderate yields (entries 7 and 8). These results suggest that the role of the amine is the activation of the catalyst by coordination to the palladium metal.[4]

To construct the quaternary asymmetric center, we next attempted Claisen-type rearrangements of **4**. The Eschenmoser rearrangement[5,8] successfully provided the corresponding amide **14** in 80% yield, with an enantiomeric excess of 91% (Scheme 4), indicating that the [3,3]-sigmatropic

Scheme 4. Syntheses of **1** and **2**



rearrangement had proceeded in a highly enantiospecific manner. Conversion of the amide **14** to the methyl ketone **15** with MeLi followed by the oxidative cleavage of the double bond furnished the ketoaldehyde **16**. The cyclopentenone **3** was obtained quantitatively by the intramolecular aldol condensation of **16** with K_2CO_3. Since the cyclopentenone **3** has already been utilized as an intermediate in the Kuwahara total synthesis,[2b,c] we followed their procedure to complete our total synthesis. Thus, treatment of **3** with MeI and NaH in THF-HMPA provided the dimethylated product **17**, which was hydrogenated and oxidized with CAN to give enokipodin B (**2**) [mp 120−122 °C, $[\alpha]_D^{25}$ −52 (*c* 0.4, MeOH); lit.[1a] semisolid, $[\alpha]_D^{24}$ −63 (*c* 0.05, MeOH)]. Reduction of the benzoquinone moiety of **2** with $Na_2S_2O_4$ produced enokipodin A (**1**) [mp 140−142 °C, $[\alpha]_D^{26}$ +42 (*c* 0.6, MeOH); lit.[1a] 138.5−138.9 °C, $[\alpha]_D^{23}$ +48 (*c* 0.5, MeOH)]. The ^1H and ^{13}C NMR data of synthetic **1** and **2** were completely identical with those of the natural enokipodins A and B, respectively.

In conclusion, we have completed the enantioselective total synthesis of enokipodins A and B, in which the enantiospecific construction of the quaternary carbon center, using a palladium-catalyzed addition of an arylboronic acid to an allene followed by an Eschenmoser−Claisen rearrangement, has been successfully accomplished. As the stereoselective construction of molecules with quaternary carbon centers represents a challenging area in organic synthesis,[9] our methodology would provide a new synthetic protocol. Application of these results to the syntheses of other natural products is now in progress.

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Supporting Information Available: Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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