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Synthesis of (−)-Piperitylmagnolol Featuring *ortho*-Selective Deiodination and Pd-Catalyzed Allylation

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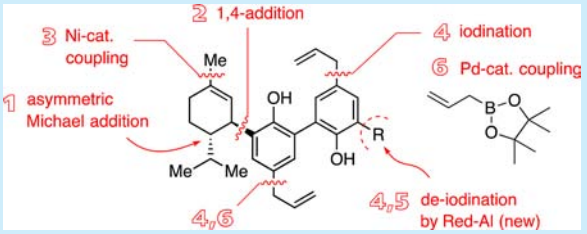
Supporting Information

ABSTRACT: A 1,4-addition strategy using an enone and a copper reagent was studied for the synthesis of (−)-piperitylmagnolol. A MOM-protected biphenol copper reagent was added to $BF_3{\cdot}OEt_2$-activated 4-isopropylcyclohexenone, whereas 1,4-addition of protected monophenol reagents possessing an allyl group was found to be unsuccessful. The allyl group was later attached to the *p*-,*p*′-diiodo-biphenol ring by Pd-catalyzed coupling with allylborate. The aforementioned iodide was synthesized using a new method for *ortho*-selective deiodination of *o*-,*p*-diiodophenols.



The medicinal plant *Magnolia officinalis* produces piperitylmagnolol (**1**)[1] (Figure 1), which exhibits inhibitory activity against Epstein−Barr virus antigen activation,[1a] antibacterial activity against vancomycin-resistant enterococci (VRE) and methicillin-resistant *Staphylococcus aureus* (MRSA),[2a] and moderate cytotoxic activity against several cancer cell lines.[2b] These properties are highly attractive from a pharmaceutical perspective. To the best of our knowledge, there has been only one report on the total synthesis of **1**.[3] However, this synthesis would be insufficient for primary biological studies, such as investigating the structure−activity relationships of **1** using structurally related compounds, because analogues to be synthesized would be limited to those based on camphor, which was a starting compound.

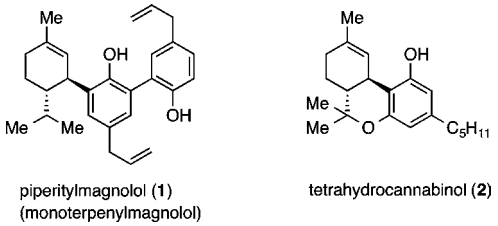
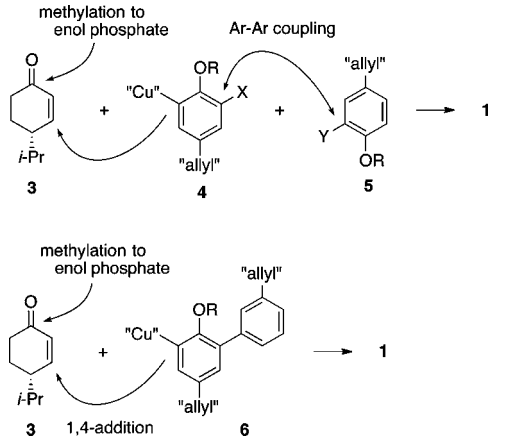


Figure 1. Piperitylmagnolol and tetrahydrocannabinol.

Although the 1,4-addition of sterically bulky copper reagents to $BF_3{\cdot}OEt_2$-activated enones produces only marginally reactive boron enolates, we recently developed a method to activate such enolates using MeLi, which allows phosphorylation to furnish enol phosphates.[4] This method was successfully utilized for the synthesis of tetrahydrocannabinol (**2**), which has analgesic effects. Owing to the structural similarities between **1** and **2**, we envisioned the synthesis of **1** from an enol phosphate derived from enone **3** and an arylcopper reagent of the monoaryl type **4** or bis-aryl type **6** (Scheme 1), though a step to

Scheme 1. 1,4-Addition Strategy Using Mono- or Bis-Aryl Copper Reagents



install the allyl group was uncertain because the acidic CH_2 in the allyl group restricted the catalogue of compatible reactions. Herein, synthesis of **1** along this line is presented, featuring (1) the formation of an iodine-containing biphenol intermediate; (2) the *ortho*-selective deiodination of an *o*-,*p*-diiodophenol derivative; and (3) Pd-catalyzed allylation of the resulting *p*-,*p*′-diiodophenol derivative.

First, we examined monoaryl copper reagents **8a** and **8b** possessing an allyl group and an allyl equivalent, respectively (Figure 2). The attempted preparation of copper reagent **8a** via the Br−Li exchange of bromide **7a** with *t*-BuLi was unsuccessful, and the corresponding monobromide was not isolated after aqueous quenching (Scheme 2, eq 1), indicating decomposition of the bromide before formation of the copper

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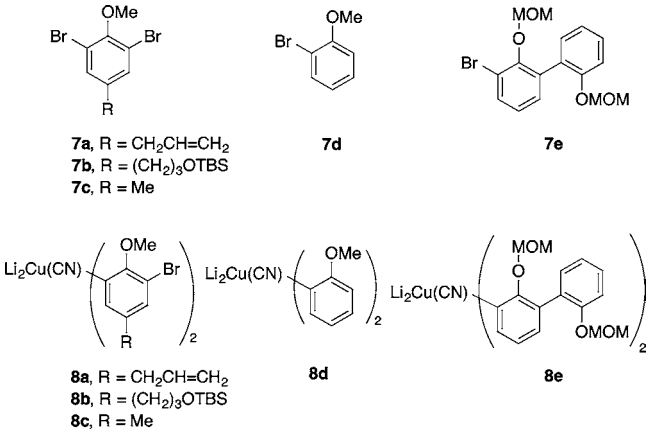


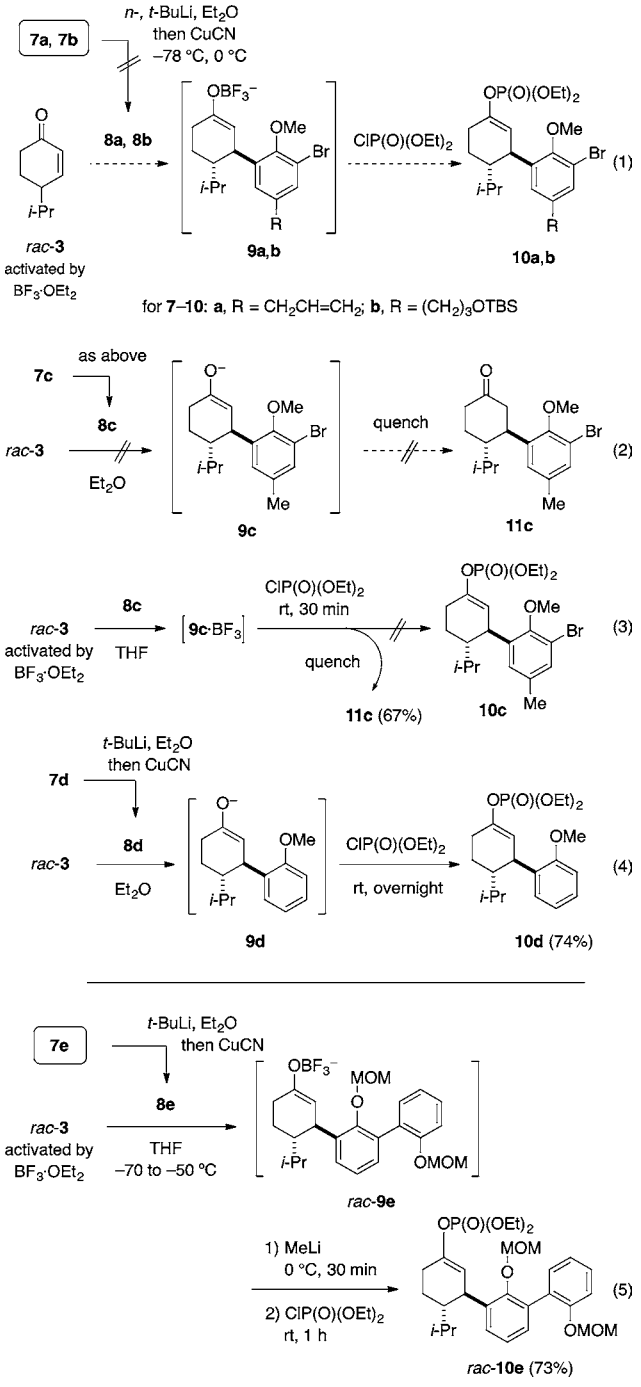
Figure 2. Copper reagents and their bromide precursors.

reagent with CuCN.[5] In contrast, Br−Li exchange of **7d** with *t*-BuLi and subsequent reaction with CuCN afforded copper reagent **8d**, which underwent 1,4-addition to racemic enone *rac*-**3**. Subsequent phosphorylation of the resulting enolate with $ClP(O)(OEt)_2$ produced enol phosphate **10d** in 74% yield (eq 4). The reaction of bromide **7b**, containing a masked allyl group, gave a mixture of unidentifiable products (eq 1), whereas model bromide **7c** was successfully converted to copper reagent **8c**. However, the subsequent 1,4-addition of **8c** to enone *rac*-**3** did not take place (eq 2). In contrast, the 1,4-addition to $BF_3{\cdot}OEt_2$-activated *rac*-**3** proceeded well, although the resulting boron enolate **9c** was almost unreactive toward $ClP(O)(OEt)_2$. As a result, instead of **10c**, ketone **11c** was obtained in 67% yield after aqueous quenching (eq 3). The Br atom was likely directing the Me group on the MeO substituent to occupy the space near the Cu atom in **8c**, thus increasing the steric bulk around the 1,4-addition center. Overall, the 1,4-addition strategy using monoaryl copper reagents possessing the allyl group or its equivalent, $(CH_2)_3OR$, was unsuccessful. Hence, we turned our attention to the alternative strategy using bis-aryl copper reagent (**6**), knowing that it would be feasible to install the allyl group at a later stage in the synthesis.

Bromide **7e**, which contains no allyl groups, was synthesized from 2,2′-biphenol by MOM protection and monobromination as described in the Supporting Information. Copper reagent **8e**, prepared by Br−Li exchange of **7e** with *t*-BuLi and subsequent reaction with CuCN, underwent a 1,4-addition to $BF_3{\cdot}OEt_2$-activated enone *rac*-**3**. The resulting boron enolate *rac*-**9e** was treated with MeLi before phosphorylation with $ClP(O)(OEt)_2$ to furnish enol phosphate *rac*-**10e** in 70% isolated yield (eq 5).[6] The stereochemistry was tentatively assigned as trans based on previous examples of 1,4-addition[4] and later confirmed by ^1H NMR spectroscopy of the final compound.

With the synthesis of enol phosphate *rac*-**10e** in hand, we continued the synthesis of (−)-**1** using **3** with 81−89% ee, favoring the (*S*)-configuration. Enone **3** was prepared via the previously reported asymmetric Michael reaction of methyl vinyl ketone with isovaleraldehyde.[7] The enantiomeric purity was increased at a later stage in the synthesis. As shown in Scheme 3, the 1,4-addition of **8e** to **3** (84% ee), followed by phosphorylation, gave **10e** in a comparable yield (73%) to that of *rac*-**3**. Nickel-catalyzed methylation of **10e** with MeMgCl afforded **12** in 91% yield.[8,9] Recrystallization of the solid mass of **12** followed by concentration of the mother liquor afforded 95% ee of **12** with 77% recovery (70% yield from **10e**). Attempted iodinations of **12** resulted in a complex mixture (I_2 and AcOAg) or starting material recovery (KI, *m*-CPBA, 18-crown-6).[10] Alternatively, **12** was hydrolyzed to biphenol derivative **13** in good yield. Iodination of **13** using NaI and oxidants (NaOCl, *m*-CPBA/18-crown-6) gave an unidentifiable mixture of products or the starting compound, whereas NIS unexpectedly produced tetraiodofuran **14** in 74% yield from **12**.[11] Attempted deiodination of **14** at the ortho position using aqueous amines such as pyridine and *N*-Me-morpholine according to the literature[12] gave unidentifiable mixtures of products. In contrast, the reaction of **14** with BBr_3, Bu_4NI, and pyridine successfully afforded triiodide **15** in good yield. In comparison to the reported conversion of 1-iodo-2-alkoxides to

Scheme 2. 1,4-Addition of Copper Reagents



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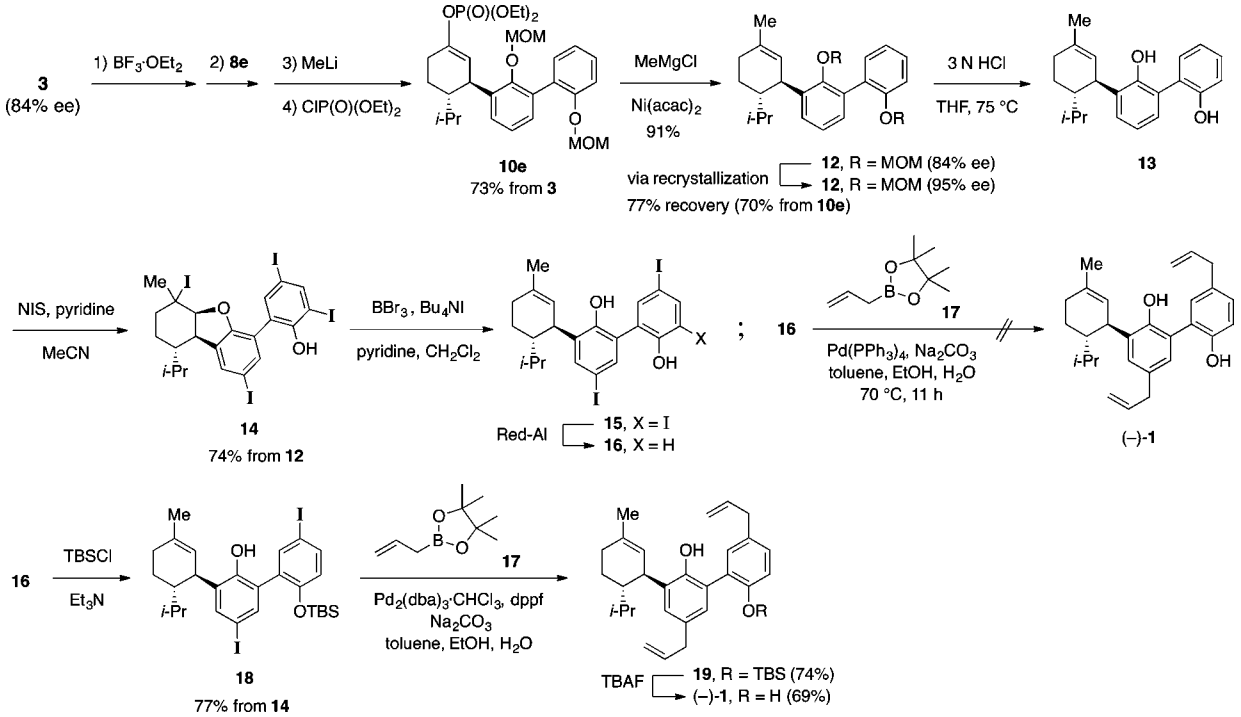
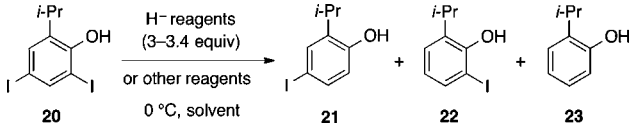
Scheme 3. Synthesis of (−)-1



1-olefins using Me_2BBr and Bu_4NI,[13] the present method was advantageous because of the ready availability of BBr_3.[14]

With triiodide **15** in hand, we envisioned *ortho*-selective deiodination of **15** through an intramolecular hydride attack, which was inspired by the $LiAlH_4$ reduction of iodobenzene to benzene.[15] However, the $LiAlH_4$ reduction of model iodide **20** at 0 °C proceeded slowly and showed low regioselectivity (**21** > **22**, **23**) (Table 1, entry 1). Hydride reduction was then

Table 1. Deiodination of Model Diiodide

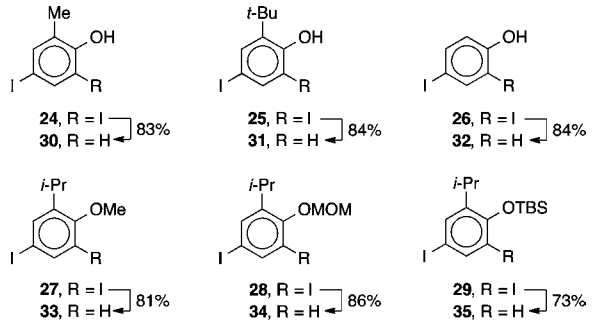


entry	reagent[a]	solvent	time, h	21:22:23:20[b]	yield, %[c]
1	$LiAlH_4$	Et_2O	0.5	30:18:8:44	nd[d]
2	DIBAL	Et_2O	0.5	0:0:0:100	–
3	Red-Al	Et_2O	0.5	96:0:4:0	79
4	Red-Al	CH_2Cl_2	0.5	97:0:0:3	89
5	Red-Al	CH_2Cl_2	3	96:0:3:1	nd[d]

[a]0 °C for 30 min with 3–3.4 equiv of reagents. [b]Determined by calculating signals in NMR spectra. [c]Isolated yield of **21**. [d]Not determined.

investigated using various hydride reagents to identify conditions for selective synthesis of **21** (see Table S1 in the Supporting Information for metalation of **20** with *n*-, *s*-, *t*-BuLi, and *i*-PrMgCl·LiCl followed by aqueous quenching and metal-catalyzed deiodination). Briefly, DIBAL was not productive (entry 2), whereas Red-Al gave **21** selectively (entries 3 and 4), with CH_2Cl_2 giving better product selectivity and isolated yield than Et_2O. Further deiodination of **21** in the para position was hardly observed even after reaction times of more than 30 min. The scope of this reaction was briefly investigated with results shown in Scheme 4. The presence of an alkyl group at the

Scheme 4. Regioselective Deiodination



ortho position did not affect the deiodination of **24**–**26**, affording **30**–**32** in good yields. Protected phenols **27**–**29** were also good substrates for *ortho*-selective deiodination, affording **33**–**35**. In general, the iodination of phenols affords *o*-,*p*-diiodophenols and/or *p*-iodophenols depending on the reaction conditions.[10,12,16] The present Red-Al deiodination would be useful in cases where the iodination of phenols results in polyiodination.

The above deiodination was successfully applied to triiodide **15** to afford diiodide **16**. Next, Pd-catalyzed allylation toward the final product was attempted using allylborate **17**, according to a literature procedure.[17] However, this allylation afforded an unidentifiable mixture of products. We proposed that the Pd catalyst activity was reduced by **16** chelating with the Pd atom as a bidentate ligand. Hence, **16** was silylated to give monosilyl ether **18** in 77% yield from **14**. The site of the TBS group was assigned tentatively on the basis of steric effects. The allylation of **18** with borane **17** was performed using $Pd(PPh_3)_4$ or $Pd(PPh_3)_4$/dppf as catalyst. TLC analysis indicated a somewhat clean coupling using the latter, affording **19** in 74% yield. Finally, desilylation of **19** furnished (−)-**1** in 69% yield. The ^1H and ^{13}C NMR spectra and the specific rotation were

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comparable with the literature data.[1a,b,2b,3] Furthermore, the ^{13}C–APT (attached proton test) NMR spectrum clearly differentiated all the aromatic carbons including the signals of the quaternary carbon (δ 131.0 ppm) and others nearby at δ 130.9 and 131.2 ppm as shown in the Supporting Information.

In summary, the synthesis of (−)-piperitylmagnolol (**1**) is presented, featuring (1) activation of the boron enolate, product of the 1,4-addition of MOM-protected biphenol copper reagent **8e** to the $BF_3{\cdot}OEt_2$-activated enone **3**, to afford the enol phosphate **10e**; (2) the subsequent intriguing transformation to triiodophenol **15**; and (3) the new finding of the *ortho*-selective deiodination of **15** using Red-Al. A total yield including synthesis of **3** from isovaleraldehyde was 5.3% over 11 steps, whereas that from (+)-camphor[3] was 1.6% over 11 steps. The scope of this deiodination was also briefly explored.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00706.

Experimental procedures and analytical data (PDF)

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Notes

The authors declare no competing financial interest.

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(5) A copper reagent $Li_2Cu(CN)(4\text{-}BrC_6H_4)_2$ could be prepared from 1,4-dibromobenzene (*t*-BuLi then CuCN) and used for 1,4-addition to the $BF_3{\cdot}OEt_2$-activated enone *rac*-**3**. The resulting boron enolate was activated by MeLi and transformed to the enol phosphate in 54% yield with $ClP(O)(OEt)_2$.

(6) 1,4-Addition of **8e** to inactivated *rac*-**3** (without $BF_3{\cdot}OEt_2$) followed by phosphorylation gave only 7% yield of *rac*-**10e**.

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(9) This product was also synthesized through 1,4-addition of a monoaryl copper reagent to *rac*-**3**: (a) *rac*-**3** with $Li_2Cu(CN)(2\text{-}MOMOC_6H_4)_2$ then $ClP(O)(OEt)_2$, 82%; (b) MeMgCl, $Ni(acac)_2$ (cat.), 89%; (c) *t*-BuLi, $ZnCl_2$ then $Pd(PPh_3)_2Cl_2$ (cat.)/DIBAL, 2-I-C_6H_4OMOM, 42% (three steps, 31%; cf. Scheme 2, two steps via **10a**, 66%).

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