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Concise asymmetric total syntheses of (−)-nuciferol, (−)-nuciferal, and (−)-dihydrocurcumene via Rh(I)-catalyzed boronic acid addition

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ABSTRACT

A general catalytic asymmetric total synthesis of aromatic bisabolane sesquiterpenes, (−)-nuciferol (*ent*-**1c**), (−)-nuciferal (*ent*-**1d**), and (−)-dihydrocurcumene (*ent*-**1h**) have been achieved in 5–6 steps in high chemical yields from commercially available (*E*)-ethylcrotonate. A key catalytic enantioselective boronic acid addition onto (*E*)-crotonate in the presence of Rh(I)-(*S*)-BINAP afforded enantioenriched product with benzylic stereogenic center in 93% yield with up to >99% ee.

Among various sesquiterpenoids, naturally occurring aromatic bisabolanes are components of many plant essential oils that possess a benzylic stereogenic centers. [1]. In particular, oxidized aromatic bisabolanes (Fig. 1) are attracting increasing attention because of their valuable biological activities [2]. As per a recent report, the volatile oil from *P. dasyrachis* containing oxidized bisabolanes such as (+)-*ar*-turmerone (**1e**) and (+)-dihydro-*ar*-turmerone (**1g**) exhibit inhibitory activities against acetylcholinesterase (AChE) [2]. Since the inhibition of AChE may be one of the most realistic approaches to the symptomatic treatment of Alzheimer's diseases (AD), therefore, these oxidized bisabolanes have garnered interests from the synthetic community [2]. On the other hand, oxidized aromatic bisabolanes isolated from the rhizomes of Curcuma longa L. (*Zingiberaceae*) are popular herbal medicines worldwide and are considered to be the anticancer constituents of turmeric [3]. (+)-Nuciferol (**1c**) [4] and (+)-nuciferal (**1d**) [1], possess side chains that are more highly oxidized than those present in (+)-α-curcumene (**1a**). Interestingly, both enantiomers of curcuphenol, namely (+)-curcuphenol (**1b**) [isolated from marine sponges *Didiscus flavus* and shows potent antifungal and antitumor activities] [5a] and (−)-curcuphenol (*ent*-**1b**) [isolated from gorgonian corals *Pseudopterogorgia rigida* and shows antibacterial activity] [5b] are isolated from Nature. In addition, aromatic bisabolane with a fully saturated carbon skeleton such as (+)-dihydrocurcumene (**1h**) has also been isolated from various sources [6].

Aromatic monocyclic bisabolenes with oxidized side chains could be the advanced intermediate for the synthesis of bicyclic sesquiterpenes with a *trans* double bond such as parvifoline (**2a**) [7a] and parvifoline isovalerate (**2b**) (Fig. 1) [7b]. In addition, isomerized parvifolines with a double bond at the benzylic position such as isoparvifoline (**3a**) [8a] and isoparvifolinone (**3b**) [8b] are also secondary metabolites that are isolated from various species (Fig. 1). From a structural viewpoint it could be hypothesized that these secondary metabolites **2**–**3** could be accessed from an intramolecular Friedel-Crafts alkylation of (*Z*)-isomer of nuciferol (**1d**). Therefore, asymmetric strategies to enantioenriched bisabolanes having oxidized side chain such as (+)-nuciferol (**1c**) and (+)-nuciferal (**1d**) would be an important problem to be tested. Although, there are many reports on racemic approaches to these congeners [9], however, a catalytic asymmetric approach would be very much welcome to these targets having oxidized side chains, given their interesting biological profiles [4,10].

We envisioned that (−)-nuciferol (*ent*-**1c**) and (−)-nuciferal (*ent*-**1d**) could be accessed from a reduction of α,β-unsaturated ester **4**, which in turn could be synthesized from aldehyde

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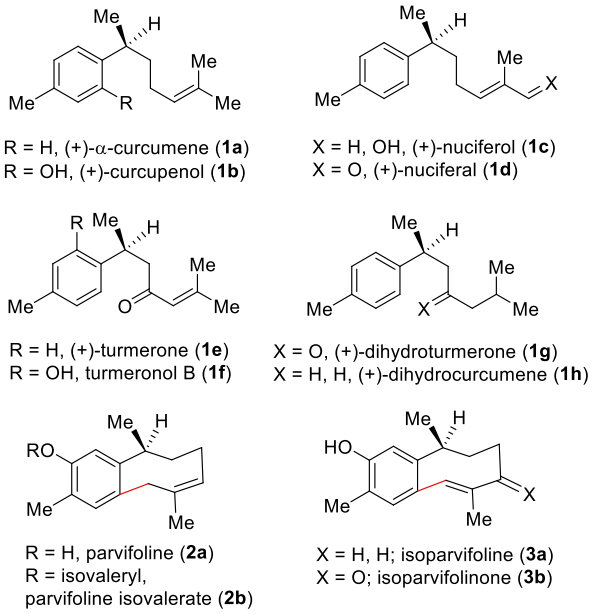
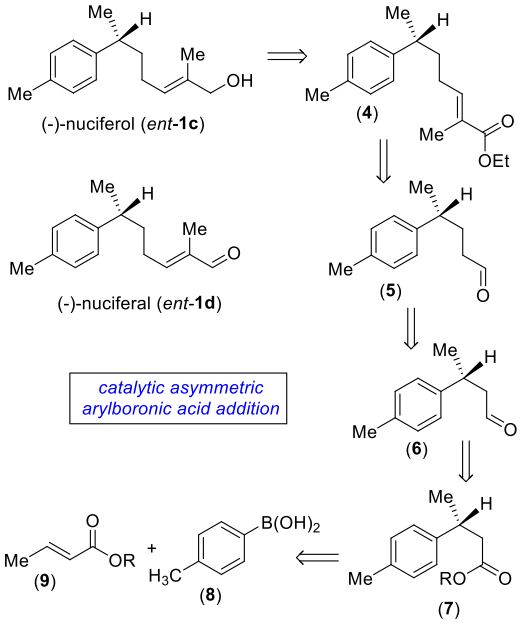


Fig. 1. Naturally occurring monocyclic bisabolene sesquiterpenes.



Scheme 1. Retrosynthetic analysis of (−)-nuciferol (*ent*-**1c**) and (−)-nuciferal (*ent*-**1d**).

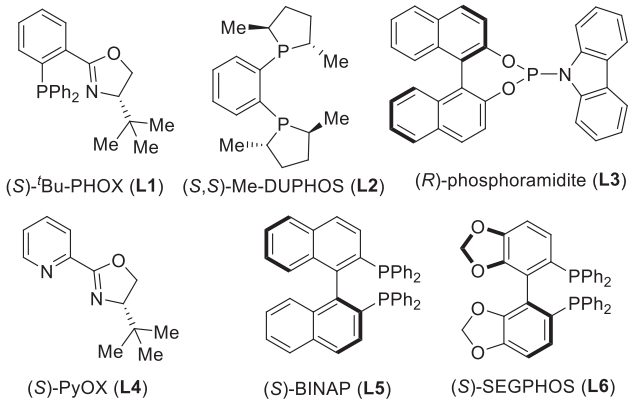


Fig. 2. Ligand screened in *p*-tolylboronic acid addition onto ethylcrotonate **9a**.

5 following an obvious approach (Scheme 1). Compound **5** could be prepared from aldehyde **6** via one carbon elongation via Wittig olefination. We thought of exploring *p*-tolylbenzene boronic acid addition onto (*E*)-crotonates to install benzylic stereocenter required for these natural products.

As per our hypothesis, we carried out Miyura's Rh(I)-catalyzed asymmetric arylboronic acid addition onto (*E*)-ethylcrotonate **9a** in refluxing dioxane and water mixture (dioxane: water = 10:1) in the presence of a number of ligands shown in Fig. 2. For our targets we have chosen *p*-tolylboronic acid for the synthesis of required aldehyde **6** (Scheme 1) [11].

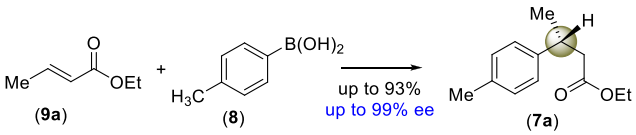
Initially, we tested Rh(I)-catalyzed *p*-tolylboronic acid addition in the presence of 2 mol% Rh(I) and 4 mol% of a number of phosphines (**L1-L3** and **L5-L6**) and oxazoline based ligands (**L4**). The best enantioselectivity was observed with 2 mol% Rh(I)-(*S*)-BINAP (**L5**) catalyst, which afforded product in 67% yield with 95% ee (entry 5). Under this condition, 2 mol% Rh(I)-(*S*)-SEGPHOS (**L6**) afforded **7a** in 91% ee (entry 6) (Table 1).

Since Rh(I)-(*S*)-BINAP (**L5**) catalyst was found to be superior over Rh(I)-(*S*)-SEGPHOS (**L6**) catalyst in terms of enantioselectivity, the metal complex of **L5** was utilized for further studies. In order to have optimum chemical yields, number of inorganic bases such as potassium carbonate, sodium bicarbonate, sodium carbonate, cesium carbonate were added as additives (entries 7–14) [12]. Further few other solvents were tested as well. Gratifyingly, the enantioselectivity of compound **7a** could be increased to >99% ee when 2 mol% Rh(I)-(*S*)-BINAP (**L5**) was employed in combination with 1 equivalent of sodium bicarbonate refluxing dioxane and water mixture (entry 8). It is worthwhile to mention that 1 mol% Rh(I) and 3 mol% of (*S*)-BINAP (**L5**) afforded product in 95% ee in 24 h (87% yield, entry 14). Further, *p*-tolylboronic acid addition onto (*E*)-benzylcrotonate **9b** afforded **7b** in 94% ee. Enantioselectivities of esters **7a** and **7b** were determined by converting these to corresponding primary alcohol **10** using lithium aluminum hydride reduction in tetrahydrofuran at room temperature (Scheme 2).

With a perfect enantioselectivity of ethyl ester **7a** in hand, this was further elaborated to the secondary metabolites, (+)-nuciferol (**1c**) and (+)-nuciferal (**1d**) (Scheme 3). In this regard, compound **7a** was reduced with DIBAL-H to furnish aldehyde **6** in 74% yield. The absolute configuration of the product from enantioselective *p*-tolylboronic acid addition onto (*E*)-crotonate was determined by comparing their specific rotation with the literature data [13]. However, this reaction was always associated with 15–20% yield of primary alcohol **10**. Alternatively, a 2-step protocol comprising lithium aluminum hydride reduction of **7a** followed oxidation by Dess-Martin Periodinane (DMP) produce aldehyde **6** in 89% yield over 2 steps. Next, homologation of aldehyde **6** was carried out with methoxymethyl Wittig reagent followed by hydrolysis of *in-situ* prepared methylvinyl ether **11**, which afforded aldehyde **5** in 68% yield (Scheme 3).

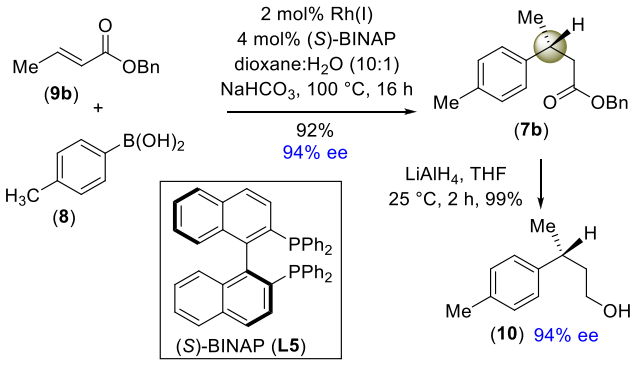
Next, aldehyde **5** was reacted with a stabilized Wittig reagent **12** in refluxing toluene to furnish α,β-unsaturated ester **4** in 96% yield (Scheme 3). Compound 4 is considered to be a common intermediate for the total syntheses of various members of bisabolane sesquiterpenoids. Later, a lithium aluminum hydride reduction of **4** in tetrahydrofuran at room temperature completed the total synthesis of unnatural (−)-nuciferol (*ent*-**1c**) in 91% yield. Allylic alcohol functionality of *ent*-**1c** was oxidized with pyridinium chlorochromate (PCC) to complete the total synthesis of unnatural (−)-nuciferal (*ent*-**1d**).

Table 1
Optimization of *p*-tolylboronic acid addition onto ethylcrotonate **9a**[a].



S. No.	Rh(I):**L** (ratio of mol%)	Additive	Solvent	Temp.	Time	Yield[b]	ee[c]
1.	2 mol% : 4 mol% **L1**	none	dioxane : H_2O (10:1)	100 °C	48 h	61%	32%
2.	2 mol% : 4 mol% **L2**	none	dioxane : H_2O (10:1)	100 °C	48 h	56%	47%
3.	2 mol% : 4 mol% **L3**	none	dioxane : H_2O (10:1)	100 °C	48 h	48%	36%
4.	2 mol% : 4 mol% **L4**	none	dioxane : H_2O (10:1)	100 °C	48 h	59%	16%
5.	2 mol% : 4 mol% **L5**	none	dioxane : H_2O (10:1)	100 °C	48 h	67%	95%
6.	2 mol% : 4 mol% **L6**	none	dioxane : H_2O (10:1)	100 °C	48 h	65%	91%
7.	2 mol% : 4 mol% **L5**	K_2CO_3	dioxane : H_2O (10:1)	100 °C	16 h	93%	96%
8.	2 mol% : 4 mol% **L5**	$NaHCO_3$	dioxane : H_2O (10:1)	100 °C	16 h	91%	99%
9.	2 mol% : 4 mol% **L5**	Na_2CO_3	dioxane : H_2O (10:1)	100 °C	16 h	90%	95%
10.	2 mol% : 4 mol% **L5**	Cs_2CO_3	dioxane : H_2O (10:1)	100 °C	16 h	89%	93%
11.	2 mol% : 4 mol% **L5**	$NaHCO_3$	THF : H_2O (10:1)	70 °C	28 h	57%	84%
12.	2 mol% : 4 mol% **L5**	$NaHCO_3$	DME : H_2O (10:1)	110 °C	20 h	68%	87%
13.	1 mol% : 2 mol% **L5**	$NaHCO_3$	dioxane : H_2O (10:1)	100 °C	24 h	85%	93%
14.	1 mol% : 3 mol% **L5**	$NaHCO_3$	dioxane : H_2O (10:1)	100 °C	24 h	87%	95%

[a] Reactions were carried out on a 1 mmol of **9a** with 2 mmol of arylboronic acid **8** in specified solvent.
[b] Isolated yields of **7a** after column chromatography.
[c] ee's were determined by HPLC using Chiralpak AD-H column.

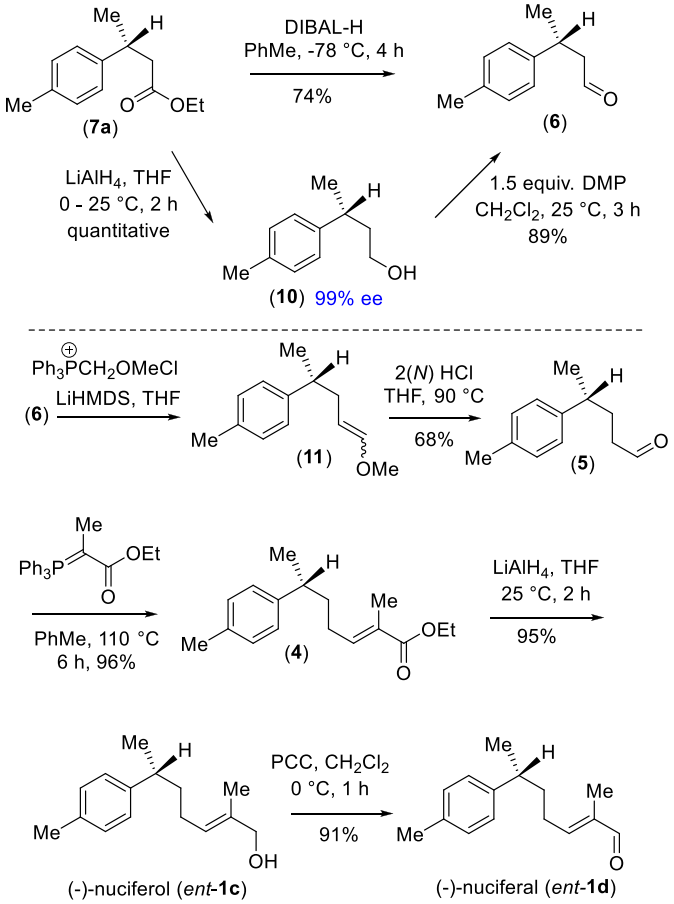


Scheme 2. *p*-Tolylboronic acid addition onto benzylcrotonate **9b**.

Further synthetic elaborations of homologated aldehyde **6** were carried out for the synthesis of (−)-curcumene (*ent*-**1a**) (Scheme 4). In this regard, four carbon installation on **6** was made via Grignard addition to access **12** in 90% yield. When reduction of secondary allyl alcohol functionality of **12** was carried out with triethylsilane in the presence of trifluoroacetic acid (TFA), it afforded disubstituted diene **13** as sole regioisomer in 74% yield (Scheme 4). There was no trace of trisubstituted olefin as present in (−)-curcumene (*ent*-**1a**). A probable mechanism to account this observation is shown in Scheme 4. Silane reduction takes place via a more stable 3° allyl alcohol (**14a**) than a 2° allyl alcohol (**14b**), thereby affording **13** as sole regioisomer (Scheme 4).

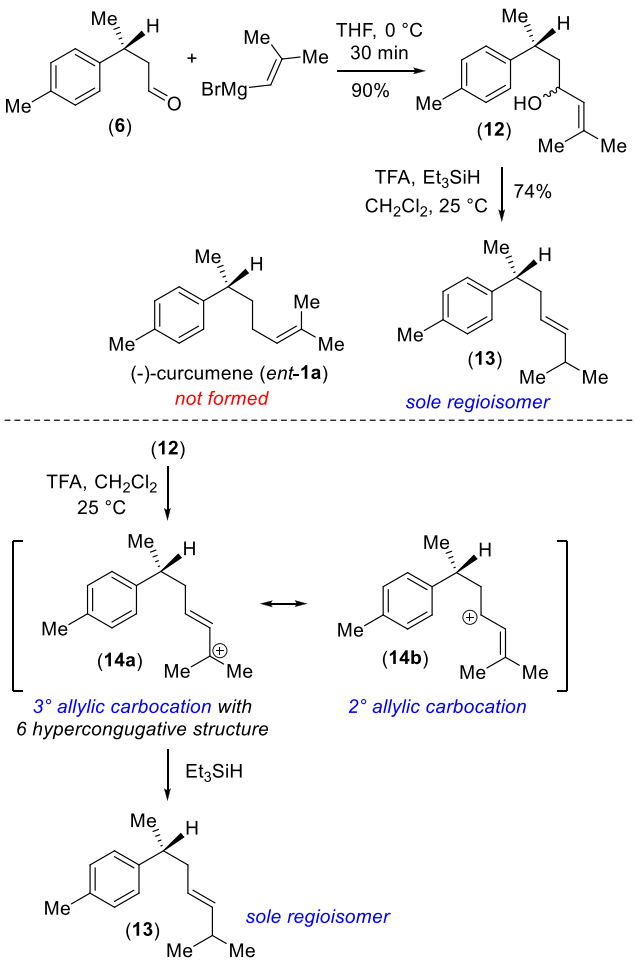
Later, olefin **13** in hand our effort was to complete the synthesis of aromatic bisabolane with a saturated side chain, (−)-dihydrocurcumene (*ent*-**1h**) (Scheme 5). Towards this, hydrogenation using catalytic Pd-C in the presence of 1 atm. pressure of hydrogen simply completed the total synthesis of (−)-dihydrocurcumene (*ent*-**1h**).

In conclusion, a unified total synthesis of bisabolane sesquiterpenoids has been shown only in 5–6 steps from commercially available (*E*)-crotonate. This synthesis nicely explored the catalytic enantioselective addition of *p*-tolylboronic acid onto (*E*)-crotonate catalyzed by Rh(I)-(*S*)-BINAP (**L5**). Further exploration of aldehyde

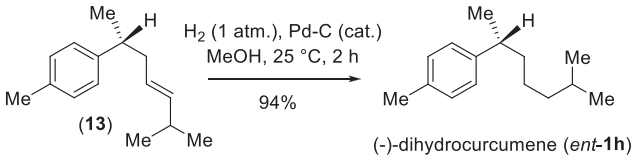


Scheme 3. Total syntheses of (−)-nuciferol (*ent*-**1c**) and (−)-nuciferal (*ent*-**1d**).

6 enabled the total synthesis of (−)-dihydrocurcumene (*ent*-**1h**). Since both enantiomers of BINAP is available, one can synthesize naturally occurring aromatic bisabolanes, (+)-nuciferol (**1c**) and



Scheme 4. Further synthetic elaboration of aldehyde **6**.



Scheme 5. Total synthesis of (−)-dihydrocurcumene (*ent*-**1h**).

(+)-nuciferal (**1d**) by using Rh(I)-(*R*)-BINAP (*ent*-**L5**) catalyst. Further exploration towards the rationale extension of this strategy for catalytic asymmetric syntheses of other congeners is currently under active investigation in our laboratory.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2020.152790.

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