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Asymmetric total syntheses of (−)-*ar*-turmerone, (−)-dihydro-*ar*-turmerone, (−)-*ar*-dehydrocurcumene, and (−)-*ar*-himachalene via a key allylic oxidative rearrangement

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This work is dedicated respectfully to Professor Sukh Dev on the occasion of his 98th birthday.

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ABSTRACT

A Nature inspired strategy to oxidized aromatic bisabolanes has been envision from naturally occurring 2-methyl-6-(4′-methylphenyl)-3-hepten-2-ol (**2a**). The key methodology utilized in this synthesis is the allylic oxidative rearrangement following a [3,3]-sigmatropic rearrangement (Dauben oxidation) of tertiary allylic alcohol of natural product **2a**. The enantioselectivity of **2a** has been introduced via a Rh(I)-(S)-BINAP catalyzed *p*-tolylboronic acid addition onto *E*-ethylcrotonate. Thus, the total syntheses of (−)-*ar*-turmerone (**1a**), (-)-dihydro-*ar*-turmerone (**1b**) and (-)-*ar*-himachalene (**3**) has been achieved only in 6–7 steps.

Aromatic bisabolanes are a large class of naturally occurring sesquiterpenoids those are widespread in nature and most of them are having a stereogenic center at the pseudobenzylic position [1]. In this regard, bisabolanes having an oxidized skeleton in their aliphatic side chain drew interests because of their important biological profiles. As for example, the rhizomes of Curcuma longa L. (*Zingiberaceae*) [2a] of turmeric is the source of many oxidized bisabolanes e.g. (+)-*ar*-turmerone (**1a**), (+)-dihydro-*ar*-turmerone (**1b**) etc. (Fig. 1) that are considered to be the anticancer constituents [2b]. It is interesting to note that both enantiomers of few bisabolane sesquiterpenes have been isolated from different species and both are having important biological activities. As for example, (−)-curcuphenol (**1c**) is produced by terrestrial plants and soft corals [3a] whereas (+)-curcuphenol (*ent*-**1c**) is isolated from marine sponges [3b–c]. Interestingly, (−)-curcuphenol (**1c**) has antibiotic activity [3b], while (+)-curcuphenol (*ent*-**1c**) exhibits cytotoxicity against murine and human tumors and inhibits HK-ATPase [3c]. (−)-Curcuphenol (**1c**) differs from (−)-curcumene (**1d**) only in the oxidation pattern in the aromatic ring (Fig. 1) [4a–c]. (+)-Dehydrocurcumene (**1e**) features a *S-trans* 1,3-butadiene motif in the aliphatic side chain [4d].

In 2003, a novel highly oxygenated bisabolene, 6-hydroxy-2-methyl-5-(5′-hydroxy-1′(*R*),5′-dimethyl-hex-3′-enyl)-phenol (**2b**) has been isolated from the resins of *Commiphora kuaa* (*Burseraceae*) (Fig. 2) [5a]. Fukuda and co-workers have isolated 2-methyl-6-(4′-methylphenyl)-3-hepten-2-ol (**2a**) from *Baccharis dracunculifolia* (Fig. 2) [5b,c]. The bicyclic aromatic sesquiterpene such as *ar*-himachalene (**3**) [6] are considered to be the cyclized derivatives of (+)-*ar*-turmerone (**1a**) (Fig. 2).

Although, (*E*)-tertiary allyl alcohol of types **2a** or **2b** are isolated, however, corresponding (*Z*)-tertiary allyl alcohol of type **2c** are not reported till date. Compound **2c** could be potential substrate to generate a tertiary allylic carbocation intermediate (LUMO) to react with arene (HOMO) to generate bicyclic structure like *ar*-himachalene (**3**) [6]. Because of their important biological profiles, a number of asymmetric total syntheses of oxidized bisabolanes are reported [7].

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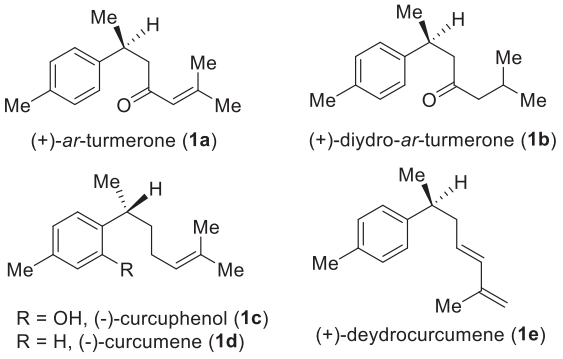


Fig. 1. Naturally occurring aromatic bisabolane sesquiterpenoids.

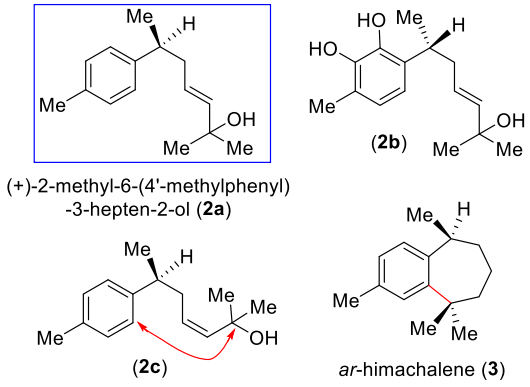
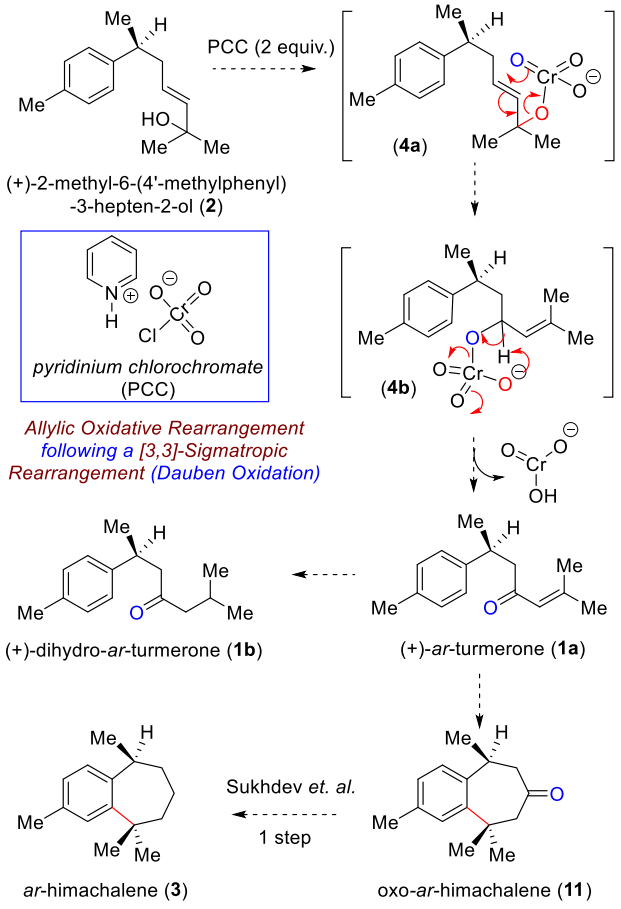


Fig. 2. Naturally occurring sesquiterpenes with benzylic stereocenter.

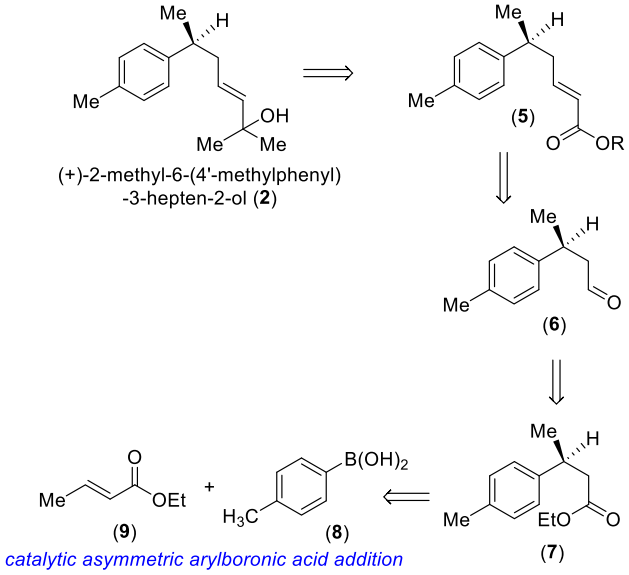
There is no report on the synthesis of secondary metabolites **2a** or **2b** *to the best of our knowledge* (Fig. 2). We envisioned that 2-methyl-6-(4′-methylphenyl)-3-hepten-2-ol (**2a**) could serve as an advanced intermediate for the total syntheses of several members of aromatic bisabolanes sharing an oxidized side chain via allylic oxidative rearrangement (Dauben oxidation) of tertiary allylic alcohol [8]. Our rationale of the conversion of **2a** to *ar*-turmerone (**1a**) and related sesquiterpenes such as dihydro-*ar*-turmerone (**1b**), *ar*-dehydrocurcumene (**3**) and *ar*-himachalene (**3**) via a key oxidative allylic rearrangement following [3,3]-sigmatropic rearrangement is shown in Scheme 1.

Therefore, our initial target was to ensure the total synthesis of naturally occurring 2-methyl-6-(4′-methylphenyl)-3-hepten-2-ol (**2a**). Our retrosynthetic analysis in this regard is shown in Scheme 2. We argued that **2a** could be synthesized from α,β-unsaturated ethyl ester **5** via methyl lithium addition. Ester **5** could be accessed from aldehyde **6** by a reaction with a stabilized Wittig reagent, which in turn could be accessed from a DIBAL-H reduction of ethyl ester **7** (Scheme 2).

Recently, our group has reported an expeditious synthesis of ethyl ester **7** via *p*-tolylboronic acid addition onto *E*-crotonate [9] to access product with benzylic stereogenic center (Scheme 3) [10]. We have shown a concise total syntheses of aromatic bisabolanes, (-)-dihydrocurcumene, (-)-nuciferol and (-)-nuciferal [9]. We have seen that a Rh(I)-(*S*)-BINAP (**L**) could efficiently catalyze *p*-tolylboronic acid addition onto *E*-crotonate in the presence of $NaHCO_3$ as an additive (Scheme 3). Upon completion of the reaction the crude product was purified via usual column chromatography and converted to corresponding primary alcohol **10** using lithium aluminum hydride reduction of **7** in THF at 25 °C. The HPLC analysis of primary alcohol **10** confirmed > 99% enantiopurity of product (Scheme 3).

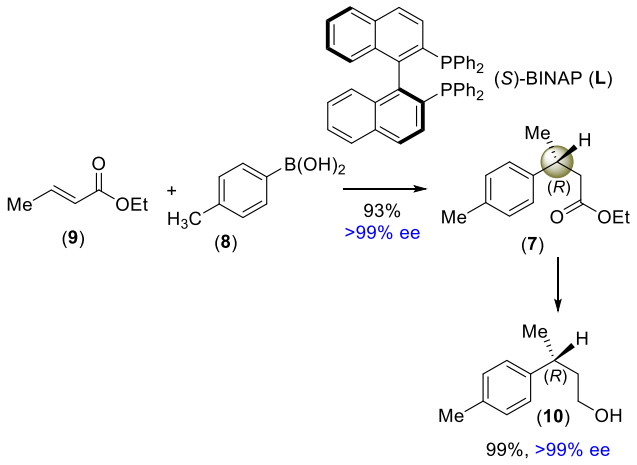


Scheme 1. Our hypothesis of *ar*-turmerone (**1a**) via oxidative transposition of allylic alcohol.

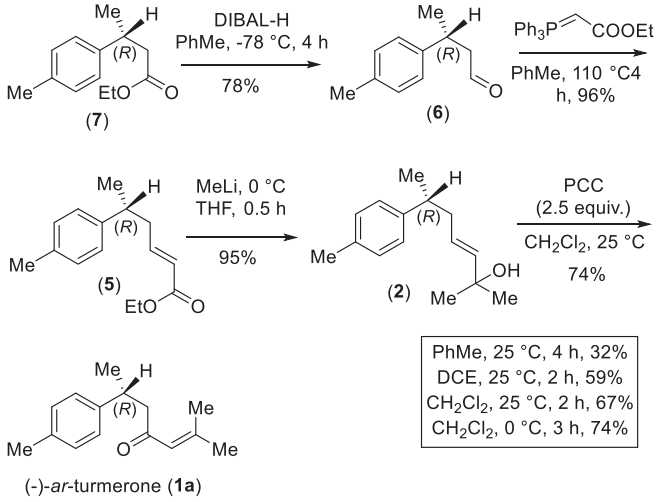


Scheme 2. Retrosynthetic analysis of *ar*-turmerone (**1a**).

Thus, we started our synthesis of **2a** from ethyl ester **7** (Scheme 4). DIBAL-H reduction of ester **7** furnished aldehyde 6 in 78% yield, which was reacted with a stabilized Wittig to obtain α, β -unsaturated ethyl ester **5** in 96% yield. The later was then



Scheme 3. Catalytic asymmetric *p*-tolyl boronic acid addition onto ethyl crotonate (**9**).

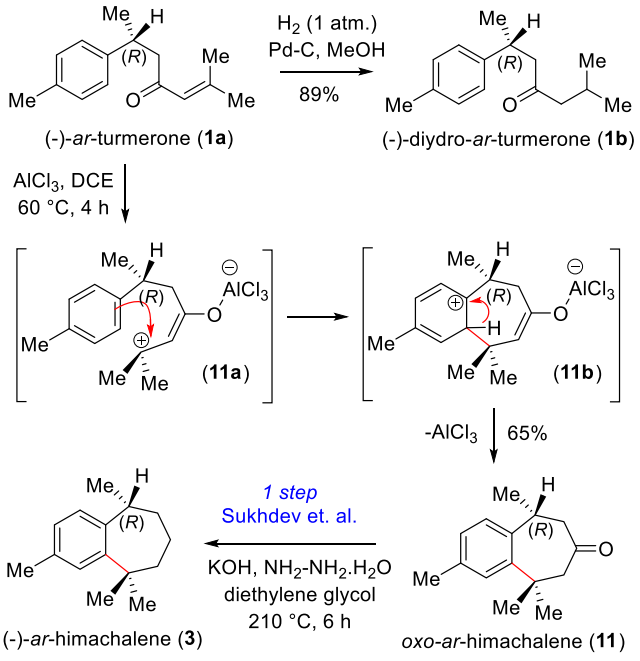


Scheme 4. Total syntheses of (-)-*ar*-turmerone (**8a**).

reacted with MeLi to afford tertiary allylic alcohol **2** (Scheme 4). Next, as per our hypotheses, oxidative transposition of allylic alcohol was conducted with 2.5 equivalent of pyridinium chlorochromate (PCC) (Scheme 4). A quick optimization of this reaction revealed that dichloromethane is a good solvent to furnish *ar*-turmerone (**1a**) in 74% yield at 0 °C to room temperature. Other oxidants such as SeO_2 and $PhI(OAc)_2$ were found to be inferiors as compared to PCC for the oxidative transposition of allylic alcohol **2**.

With the total synthesis of (-)-*ar*-turmerone (**1a**) secure, we have carried out hydrogenation with catalytic Pd-C under 1 atm. pressure of hydrogen, which completed the total synthesis of (-)-dihydro-*ar*-turmerone (**1b**) in 99% yield (Scheme 5). Next, we have attempted the synthesis of (-)-*ar*-himachalene (**3**) (Scheme 5).

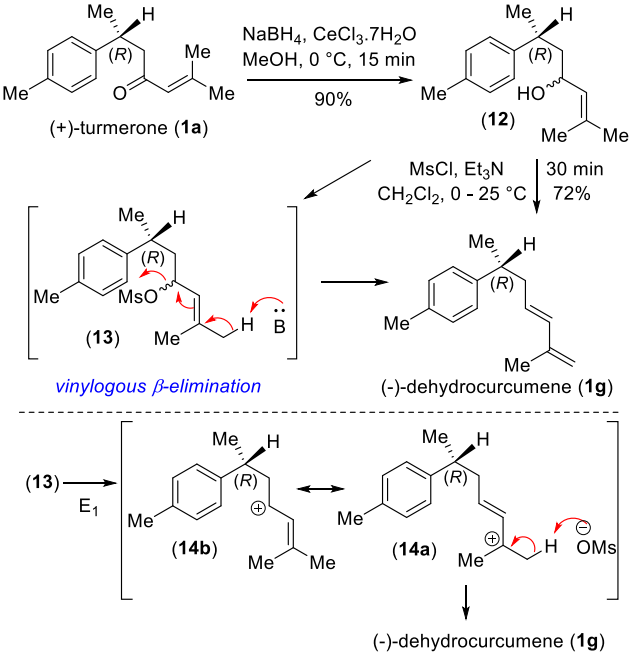
Towards this, we have carried out electrophilic Michael addition of aromatic ring under $AlCl_3$-catalyzed Friedel-Crafts condition. It is worthwhile to mention that Sukhdev et. al. [11] had reported the synthesis of (-)-oxo-*ar*-himachalene (**11**) in carbondisulfide (CS_2) as solvent, which afforded poor yields (40%) under tedious reaction condition. We have adopted an alternate reaction condition in dichloroethane to afford product in improved yield (65% yield, Scheme 5) with relatively simple work up procedure. Since, oxo-*ar*-himachalene (**11**) is already known to be the



Scheme 5. Asymmetric approach to (-)-dihydro-*ar*-turmerone (**1b**) and (-)-*ar*-himachalene (**3**).

precursor of (-)-*ar*-himachalene (**3**) in one step, our effort culminated in the formal total synthesis of this sesquiterpene.

Further synthetic exploration of (-)-*ar*-turmerone (**1a**) was carried out for the total synthesis of (-)-dehydrocurcumene (*ent*-**1g**). In this regard, Luche reduction [12] of **1a** afforded allylic alcohol **12** (Scheme 6). Interestingly, when compound **12** was reacted with methane sulfonyl chloride in Et_3N at 0 °C to room temperature for 30 min, it directly afforded (-)-dehydro-*ar*-curcumene (**1g**) with *S*-trans structure in 72% yield (Scheme 6).



Scheme 6. Total synthesis of (-)-dehydro-*ar*-curcumene (*ent*-**1 g**) via vinylogous β -eliminaion.

The mechanism of this reaction via a vinylogous β -elimination of mesylate **13** is proposed. However, an alternate mechanisn via the formation of secondary allylic carbocation **14b** and tertiary allylic carbocation **14a** can't be ruled out because of the plausible stabilization of **14a** via 6 hyperconjugation structures (Scheme 6).

In conclusion, a Nature inspired strategy for the total syntheses of bisabolanes having an oxidized skeleton in their aliphatic side chain has been shown from naturally occurring 2-methyl-6-(4′-methylphenyl)-3-hepten-2-ol (**2a**). The key methodology utilized in this synthesis is the allylic oxidative rearrangement (Dauben oxidation) of tertiary allylic alcohol of natural product **2a**. This strategy afforded (-)-*ar*-turmerone (**1a**), (-)-dihydro-*ar*-turmerone (**1b**) and (-)-*ar*-himachalene (**3**) only in 6–7 steps in good yields. Further application of this strategy for asymmetric syntheses of other secondary metabolites of this class [13] 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.2021.153105.

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