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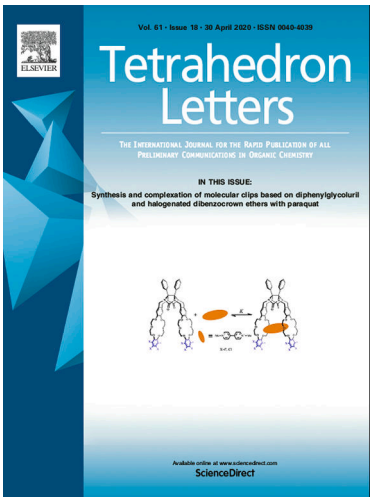

Catalytic Asymmetric Total Syntheses of (+)-α-Cuparenone, (+)-Cuparene and (+)-Herbertene

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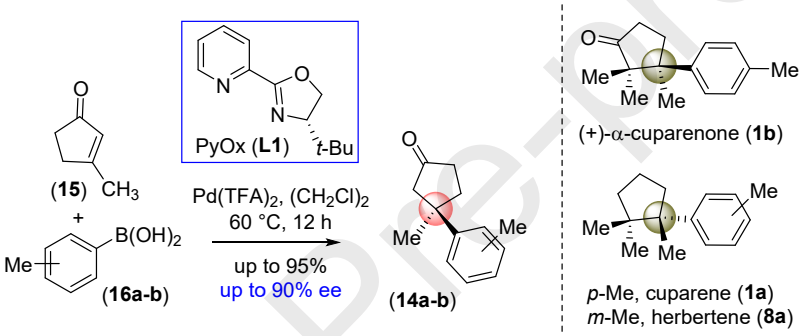

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Catalytic Asymmetric Total Syntheses of (+)-α-Cuparenone, (+)-Cuparene and (+)-Herbertene

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This work is dedicated to Professor Amit Basak, IIT Kharagpur

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ABSTRACT

A general catalytic asymmetric route to either enantiomers of sesquiterpenes, cuparenes (**1-2**) and herbertenes (**8-9**) is disclosed from commercially available 3-methyl cyclopenten-2-one. Following a catalytic enantioselective addition of arylboronic acids to enone **15**, compounds **14a-b** with all carbon quaternary stereocenters are synthesized in up to 90% ee in the presence of Pd(II)-PyOx (pyridine oxazoline). Compounds **14a-b** are used as precursors for the asymmetric total syntheses of (+)-cuparene (**1a**) (35% overall yield in 3 steps), α-(+)-cuparenone (**1b**) (56% overall yield in 2 steps), and (+)-herbertene (**8a**) (34% overall yield in 3 steps).

Naturally occurring secondary metabolites cuparenes (**1-7**) (Figures 1) and herbertenes (**8-11**) (Figure 2) are sesquiterpenes with a cyclopentanoid backbone.[1] They possess vicinal all-carbon quaternary centers, including at least one stereogenic quaternary center situated at the pseudobenzylic position.[2] Although no biological activities are reported for (*R*)-(+)-cuparene (**1a**), isolated in 1958 by Erdtman et. al., [1] secondary metabolites (*S*)-α-cuparenone (**1b**) and (*S*)-β-cuparenone (**1c**) from the essential oil of leaves from *Thujaorientallis* (commonly known as '*Morpankhi*' tree) are biologically significant. Isolated by Dev and Chetty in 1964,[3a] these compounds are used to treat fungal infections, cancer, coughs, hemorrhages, excessive menstruation, bronchitics, asthma, and arthritic pains.

Subsequently, the (*R*)-enantiomer of both α-cuparenone (***ent*-1b**) and β-cuparenone (***ent*-1c**) were also isolated from the liverworts *Mania fragrans* by Benesova et. al.[3b] Later, in 1997, two new cuparene-type sesquiterpenoids, aquaticenol (**5**) and 1,4-cuparenediol were isolated from the Japanese liverwort *Lejeuneaaquatica,* along with 2-cuparenol (**2a**), 1,2-cuparenediol (**2b**) and other congeners.[4] Further, in 2015, Stadler and co-workers reported the isolation of deconins A (**6**), and B (**7**) as conjugates of β-cuparenone (**1c**) or cuparenic acid (**3**) with mevalonic acid from cultures of a basidiomycete from Northern Thailand, which represents a new species of the genus *Deconica*.[4] The crude extracts from submerged cultures of Deconica sp. 471 showed antimicrobial activities against Gram-positive bacteria, i.e., *Bacillus subtilis* and *Staphylococcus aureus*.[5]

On the other hand, (*R*)-(+)-herbertene (**8a**) was isolated in 1981 by Matsuo and co-workers.[6] A number of dimeric herbertenes were isolated with biaryl structural scaffolds,[7] such as mastigophorenes A and B (**10-11**) from the liverwort *Mastigophora diclados*[8a] and aquaticenols (**5**) from the liverwort *Lejeunea aquatica*.[8b] These novel sesquiterpenoid biaryls, were co-isolated with their monomeric phenolic precursors, such as herbertenediol (**9b**) and 1,2-cuparenediol (**2b**). Importantly, mastigophorene A (**10**) exhibits nerve growth and network formation acceleration activities.[8a]

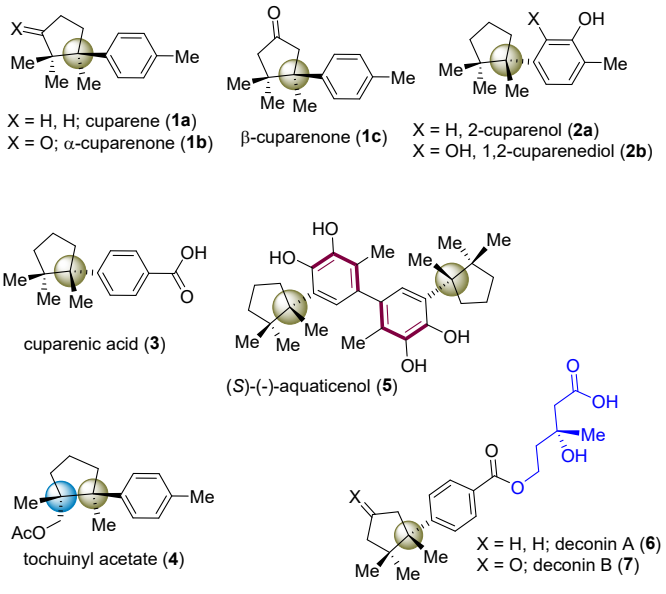


Figure 1: Cuparene (**1a**), α-cuparenone (**1b**), β-cuparenone (**1c**), 2-cuparenol (**2a**), 1,2-cuparene diol (**2b**), and cuparenic acid (**3**).

In spite of its compact size, the perimeter of these sesquiterpenes contains vicinal all-carbon quaternary centers those are part of a cyclopentane ring, thus posing a respectable synthetic challenge. Few congeners of this class of sesquiterpenoid, such as tochuinyl acetate (**4**, Figure 1) and herbertinolide (**12**, Figure 2) possess two contiguous all-carbon quaternary stereogenic centers.

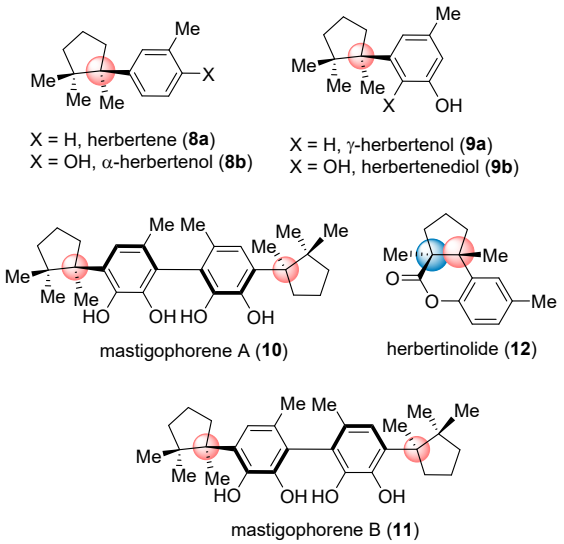
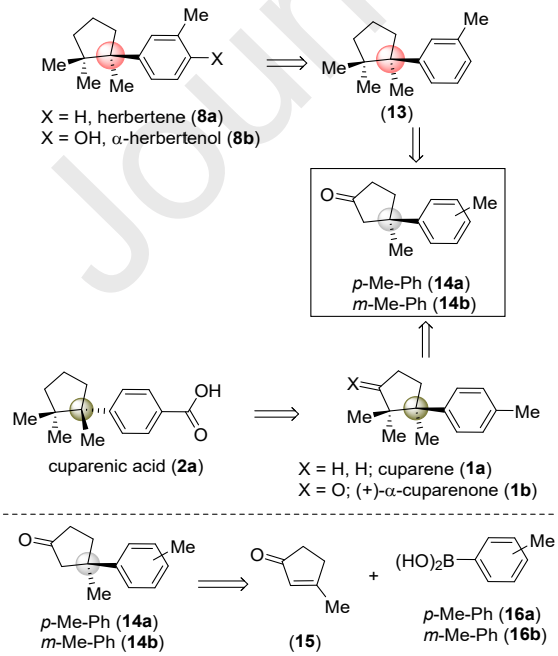


Figure 2: Herbertene (**8a**), α-herbetenol (**8b**) and γ-herbetenol (**9a**), herbertenediol (**9b**), mastigophorenes A (**10**) and B (**11**) and herbertinolide (**12**).

Although, there are a number of elegant total syntheses of racemic cuparene (**1a**)[9] and herbertene (**8a**)[10] reported in the literature, the catalytic enantioselective syntheses of these compounds are very limited.[11-12] In fact, the total syntheses of such sesquiterpenoids via catalytic asymmetric processes are scarcely reported.[11a] A unified catalytic asymmetric approach to both of these classes of sesquiterpenoids would eventually allow access of both their natural and unnatural synthetic analogues. Herein, we delineate our efforts towards a unified total synthesis of cuparene (**1a**), α-cuparenone (**1b**), and herbertene (**8a**) from appropriately functionalized common cyclopentenone intermediate **12**. Key to this synthetic strategy is Stoltz's elegant Pd(II)-PyOx catalyzed arylboronic acid addition onto 3-methylcyclopenten-2-one[13] to install all carbon quaternary stereocenter in enantioenriched fashion (Scheme 1).

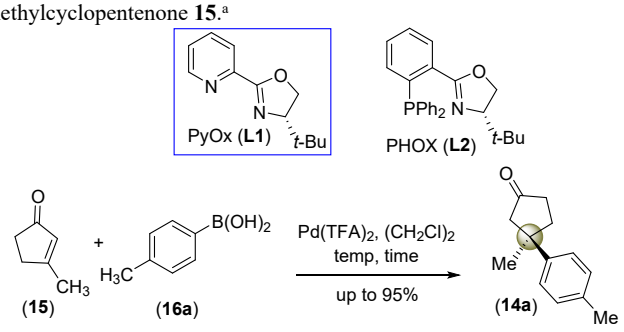


(**8a**).

Scheme 1 shows our retrosynthetic plan for cuparene (**1a**), α-cuparenone (**1b**), and herbertene (**8a**). We envisioned that 2,2-dimethyl 3-aryl-3-methylcyclopenten-5-ones (**13** and **1b**) having vicinal all-carbon quaternary centers could be advanced intermediates for a unified approach to sesquiterpenoids **1a-b** and **8a** via Wolff-Kishner reduction.[14] These compounds could be synthesized from 3-aryl-3-methylcyclopentanones **14a-b** by a highly regioselective *gem*-dimethylation. The latter could be achieved via a key Pd(II)-PyOx catalyzed arylboronic acid (**16**) addition onto 3-methylcyclopenten-2-one (**15**) (Scheme 1) following Stoltz's condition.[15] In this regard, it is worthwhile to mention that an elegant $PdCl_2$-Ph-BOX catalyzed aryl boronic acid addition onto 3-methyl cycloalkanone has been reported by Minnaard et. al. for the total synthesis of α-cuparenone (**1b**).[16a] This methodology has nicely been utilized for catalytic asymmetric total syntheses of several other congeners[16b] including an atropselective total synthesis of mastigophorene A (**10**).[16c]

Since, there were no reports for Pd(II)-PyOx catalyzed addition of *p*-tolylboronic acid (**16a**) onto 3-methylcyclopenten-2-one (**15**), which is relevant to our synthetic plan,[17] we carried out optimization studies using 3-methylcyclopenten-2-one (**15**) with boronic acid **16a** (Table 1). The optimization studies of asymmetric boronic acid addition onto **15** using **L1-L2** is shown in Table 1. It was observed that Pd(II)-PyOx (**L1**) is found to be superior over Pd(II)-PHOX (**L2**) (entries 1-3) and $Pd(OCOCF_3)_2$ is better choice as Pd-source than $Pd(OAc)_2$ (entries 1-4). Among various solvents, dichloroethane was found to be good choice than dichloromethane, toluene, and tetrahydrofuran (Table 1). Following exhaustive optimization, it was discovered that corresponding product 3-(*p*-tolyl)-3-methylcyclopentanone **14a** could be obtained in 95% yield with 85% ee, in dichloroethane at 60 °C in the presence of 5 mol% $Pd(TFA)_2$ and 8 mol% of (*S*)-PyOx (**L1**) ligand (entry 7, Table 1).

Table 1. Optimization of *p*-tolylboronic acid (**16a**) addition onto 3-methylcyclopentenone **15**.[a]

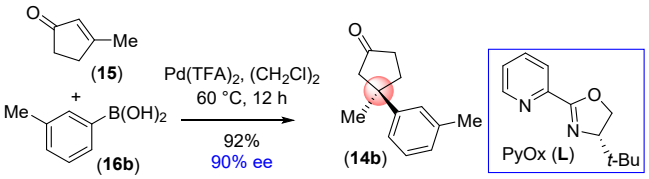


S. No.	Pd(II):**L**	solvent	temp.	time	yield[b]	ee[c]
1.	2.5 mol%: 6 mol% **L1**	$(CH_2Cl)_2$	40 ºC	28 h	60%	78%
2.	5 mol%: 6 mol% **L1**	$(CH_2Cl)_2$	40 ºC	24 h	72%	80%
3.	5 mol%: 6 mol% **L2**	$(CH_2Cl)_2$	40 ºC	24 h	67%	58%
4.	5 mol%: 6 mol% **L1**	$(CH_2Cl)_2$	40 ºC	30 h	55%	72%[d]
5.	5 mol%: 8 mol% **L1**	$(CH_2Cl)_2$	60ºC	18 h	94%	77%
6.	5 mol%: 6 mol% **L1**	CH_2Cl_2	40 ºC	25 h	65%	70%
7.	5 mol%: 8 mol% **L1**	$(CH_2Cl)_2$	60 ºC	14 h	95%	85%
8.	5 mol%: 12 mol% **L1**	$(CH_2Cl)_2$	60 ºC	18 h	94%	81%
9.	5 mol%: 16 mol% **L1**	$(CH_2Cl)_2$	60 ºC	18 h	90%	78%

10.	20 mol% **L1**					
11.	5 mol%: 8 mol% **L1**	PhMe	60 ºC	24 h	66%	69%
12.	5 mol%: 8 mol% **L1**	THF	60 ºC	24 h	20%	60%

[a]Reactions were carried out on a 1 mmol of **15** with 2 mmol of aryl boronic acid in dichloromethane or dichloroethane (DCE). [b]Isolated yields after column chromatography. [c]ee's were determined by HPLC using Chiralpak AD-H column. [d]$Pd(OAc)_2$ was used as catalyst.

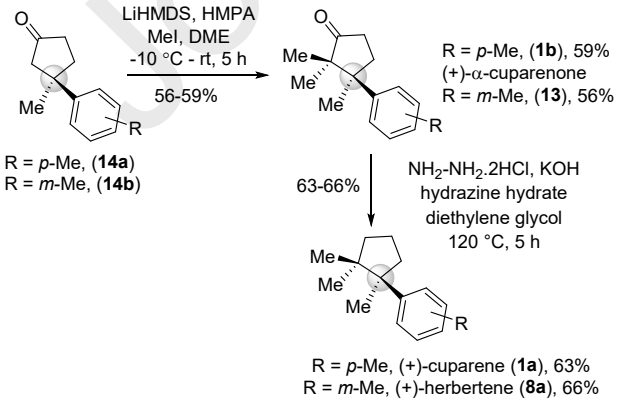
Under the standard condition, *m*-tolylboronic acid (**16b**) addition onto 3-methylcyclopenten-2-one (**15**) afforded 3-(*m*-tolyl)-3-methyl cyclopentane 2-one **14b** in 92% yield with 90% ee (Scheme 2).



Scheme 2. *m*-Tolylboronic acid addition onto 3-methylcyclopentenone **15**.

Thereafter, we sought to elaborate the enantioenriched 3-aryl-3-methylcyclopentanones **14a-b** to the natural products cuparene (**1a**) and herbertene (**8a**) (Scheme 3). Towards this, a highly regioselective *gem*-dimethylation of 3-(aryl)-3-methylcyclopentanones **14a-b** was explored using different bases such as LDA, LiHMDS, KHMDS, and NaHMDS in a solvent capable of stabilizing metal-enolate (as well as corresponding carbanion) complex such as dimethoxyethane (DME). The optimization of *gem*-dimethylation was carried out using 3 equivalents of base, 0.6 equivalent of hexamethyl phosphoramide (HMPA), and 6 equivalents of methyl iodide (Scheme 3). Following a quick optimization, we were pleased to find that a highly regioselective *gem*-dimethylated products **1b** and **13** were obtained in 59% and 56% yields, respectively, when sequential methylation was carried out using LiHMDS (3 equiv.), HMPA (0.6 equiv.) and methyl iodide (6 equiv.).[18, 16a]

The preference of *gem*-dimethylation at C-2 position of **14a-b** rather than at C-5 position clearly indicates that the corresponding lithiated carbanions **17a-b** and **20a-b** are probably stabilized by the favorable interactions shown in Figure 3. It is most likely that, in the presence of corresponding carbanion of Li-enolate of **14a-b**, Li^+ might interact with the arene substrate through a favorable Li^+ ion-p interactions to promote highly regioselective *gem*-dimethylation.[19]



Scheme 3. Total syntheses of (+)-α-cuparenone (**1b**), (+)-cuparene (**1a**) and (+)-herbertene (**8a**).

Another possibility might be the stabilizing interactions arising from the interaction between Li^+ with *ortho*-C-H bond of arenes as shown in **17a'-b'** and **20a'-b'**. However, since there is no trace of *ortho*-methylation of arenes were observed, the later possibility of interactions between Li^+ and *ortho*-C-H bond may be ruled out.

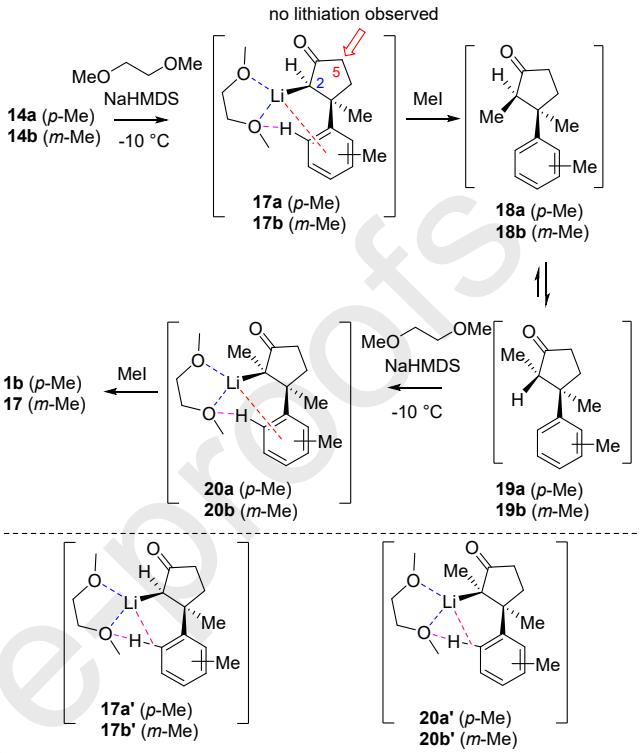
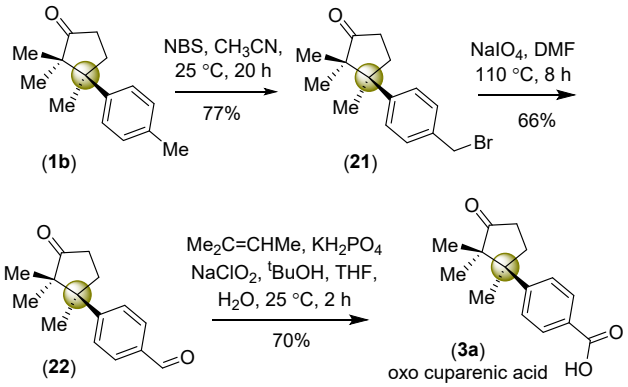


Figure 3: Plausible transition states **17a-b** and **20a-b**.

Thus, our effort culminated a 2 steps stereoselective total synthesis of α-cuparenone (**1b**) in 56% overall yield for the first time, *to the best of our knowledge* (Scheme 3). Later, Wolff-Kishner reductions[14] of (+)-α-cuparenone (**1b**) and compound **13** completed the total synthesis of (+)-cuparene (**1a**) (35% yields over 3 steps from enone **15**), and (+)-herbertene (**8a**) (34% yields over 3 steps from enone **15**), clearly indicating greater efficiencies of our approach.



Scheme 4. Synthesis of oxo cuparenic acid (**3a**).

Further synthetic elaboration was shown by synthesizing oxo cuparenic acid (**3a**) from (+)-α-cuparenone (**1b**), which is the advanced intermediate for cuparenic acid (**3**) and *ent*-deconin A (***ent*-6**) (Figure 1). Towards this end, benzylic bromination of **1b** using *N*-bromo succinimide (NBS) in acetonitrile at room temperature afforded benzyl bromide **21** in 77% yield (Scheme 4). Compound **21** upon treatment with $NaIO_4$ in *N*,*N*-

dim

benzaldehyde **22** in 66% yield. Next, Pinnick oxidation of benzaldehyde **22** with $NaClO_2$ in the presence of excess 2-methyl 2-butene at room temperature furnished oxo cuparenic acid (**3a**) in 70% yield.

In conclusion, a unified total synthesis of (+)-cuparene (**1a**), (+)-α-cuparenone (**1b**) and (+)-herbertene (**8a**) has been demonstrated in only 2-3 steps in high chemical yields from commercially available 3-methylcyclopenten-2-one (**15**). The Stoltz methodology of Pd(II)-PyOx (**L1**) catalyzed aryl boronic acids (**16a-b**) addition onto 3-methylcyclopenten-2-one (**15**) worked well for our synthetically relevant substrates. Further application of this strategy to asymmetric total syntheses of structurally complex sesquiterpenoids is currently under active investigation in our laboratory and will be reported in due course.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http:.....

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17. This is the first example of *p*-totylboronic acid addition onto 3-methylcyclopenten-2-one to get 85% ee.

18. *gem*-Dimethylation of cyclopentanone **14a** afforded 32% and 39% of product **1b** (along with 16-20% of recovery of **14a**), when reactions were carried out using NaHMDS and LDA as bases, respectively. Under the same condition, KHMDS furnished 52% yield of **1b**.

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