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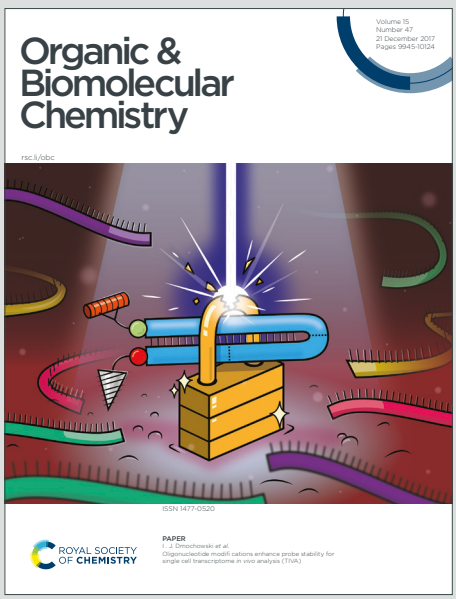

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Total Synthesis of (+)-*ar*-Macrocarpene†

Arindam Khatua,[a] Sovan Niyogi,[a] and Vishnumaya Bisai*[a,b,c]

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This report features first catalytic asymmetric total synthesis of sesquiterpene, (+)-*ar*-macrocarpene (**1**) in 7 steps in 42.1% overall yields from commercially available inexpensive 5,5-dimethylcyclohexane 1,3-dione. The strategy relies on a key [3,3]-sigmatropic rearrangement effecting reductive transposition through allylic diazene rearrangement (ADR) in a single step from intermediate allylic alcohol (+)-**12** under Mitsunobu reaction condition with *o*-nitrobenzenesulfonyl hydrazide (*o*-NBSH). Enantioselective reduction of α-bromo vinylogous ester **16** under Corey-Bakshi-Shibata reduction condition forges the required stereocenter in the allylic alcohol (+)-**12** in highly enantioenriched manner (95% ee).

Introduction

Owing to their wide-ranging bioactivity profiles and many uncommon structural features, total synthesis endeavors toward sesquiterpenoids holds considerable synthetic challenge. Towards this, we found Macrocarpenes (**1-3**) are naturally occurring irregular sesquiterpenes possessing a 3,3,4'-trimethyl-1,1'-(bicyclohexyl) skeleton to be compelling synthetic targets (Figure 1). From structural perspective, macrocarpenes bear only three terminal carbons and the presence of the fourth terminal carbon might be incorporated during the biogenesis of the dimethylcyclohexane ring. These sesquiterpenoids were identified in foliage of *Cupressus macrocarpa* by Cool in 2005 in widely varying amount.[1]

Despite its limited natural range (only on Point Lobos and Cypress Point, Monterey Co., California), *Cupressus macrocarpa* Hartw. ex Gord. (Monterey cypress) is one of the most widely planted conifers in the state. The minor component of *N*-hexane extract of this species contains *ar*-macrocarpene **1** (Figure 1). The absolute configuration of *ar*-macrocarpene **1** has been assigned tentatively, on the basis of the optical rotation and correlation with the related natural products in the literature. Other structurally correlated sesquiterpenoids, include laurokamurene B (**6**),[2] cuparane (**7**), cuparenic acid (**8**)[3], aplysin (**9**) and debromoaplysin (**10**) having same total numbers of carbons *i.e* they are structural isomers with rearranged structural scaffolds (Figure 1). Apart from this, majapolene B (**4**),[4] a brominated sesquiterpene, was originally isolated from *Laurencia majuscula.* Reisolation of majapolene B (**4**) from *Laurencia* sp. (Teluk Juara, Malaysia), along with the isolation of the previously unreported acetylmajapolene B (**5**), led to the determination of the absolute configuration of both compounds by vibrational circular dichroism (VCD).

Results and Discussion

Structurally, macrocarpenes (**1-3**) share a common 3,3,4'-trimethyl-1,1'-(bicyclohexyl) skeleton. However, the three methyl groups are situated on the 1-arylcyclopentane ring in 2,2,3-fashion,[5] 1,2,2-fashion,[6] and 1,2,3-fashion.[7] in laurokamurene B (**6**), cuparanes (**7-8**) and lauranes [such as aplysin (**9**) and debromoaplysin (**10**)] respectively. Among various sesquiterpenes isolated till date, *ar*-macrocarpene **1** is the first member having arylcyclohexane skeleton (Figure 1).

[a]Department of Chemistry, IISER Bhopal, Bhopal Bypass Road, Bhauri, Bhopal - 462 066, Madhya Pradesh, INDIA.
[b]Department of Chemistry, IISER Berhampur, Transit Campus (Govt. ITI Building), Engg. School Junction, Berhampur, Odisha – 760 010, INDIA.
[b]Department of Chemistry, IISER Tirupati, Rami Reddy Nagar, Karkambadi Road, Mangalam, Tirupati – 517 507, INDIA.

Corresponding author: *vishnumayabisai@gmail.com*
§both authors contributed equally to this work.

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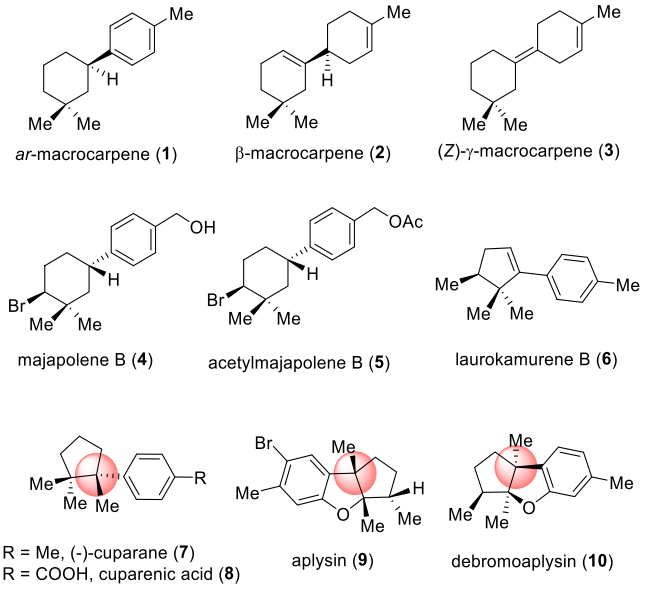
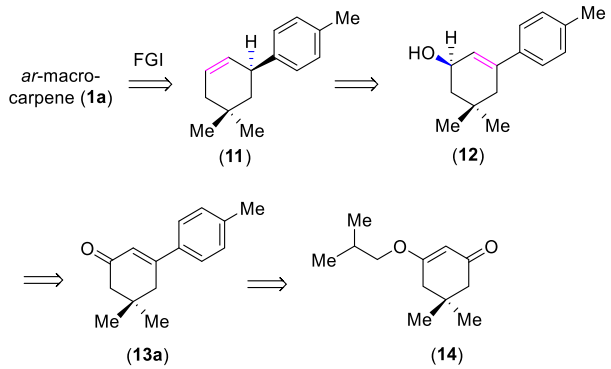


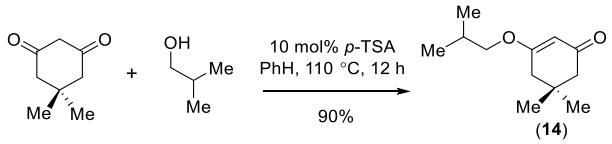
Figure 1: Selected naturally occurring sesquiterpenes, macrocarpenes (**1-3**), majapolene B (**4-5**), laurokamurene B (**6**), cuparanes (**7-8**), and aplysins (**9-10**).

Since its isolation more than a decade, till date just a single racemic approach of *ar*-macrocarpene **1** is featured in the literature by Srikrishna and co-workers in 2007.[8] The report demonstrates the first total synthesis of (±)-*ar*-macrocarpene **1a** starting from 3-methylcyclohexenone in four steps. Therefore, there is an urgent need for asymmetric synthesis of *ar*-macrocarpene **1a** sharing 3,3-dimethyl 1-arylcyclohexane (Figure 1). Herein, we report the details of first total syntheses of naturally occurring (+)-*ar*-macrocarpene **1a** via catalytic asymmetric enone reduction of ketone functionality under CBS reduction[9] followed by a key reductive transposition of enantioenriched allylic alcohol under Myers condition.[10]



Scheme 1: Retrosynthetic analysis of (+)-*ar*-macrocarpene (**1a**).

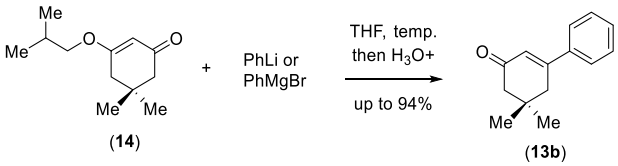
In devising a retrosynthetic strategy for accessing the *ar*-macrocarpene **1**, we simplified our target to enantioenriched 5,5-dimethyl 3-arylcyclohexene **11**, which could serve as a platform to the asymmetric synthesis of *ar*-macrocarpene **1a** via late stage hydrogenation (Scheme 1). We envisioned the conversion of allylic alcohol **12** to compound **11** via a key [3,3]-sigmatropic rearrangement effecting reductive transposition of double bond in a single step. This sequence involves a Mitsunobu reaction with *o*-nitrobenzenesulfonyl hydrazide (*o*-NBSH) as described by Myers and co-workers.[10] Allylic alcohol **12** could be generated through catalytic asymmetric reduction of carbonyl functionality in 5,5-Dimethyl 3-aryl 2-cyclohexenone **13a** under CBS reduction condition.[9] Compound **13a** could be easily accessed from a Stork-Danheiser sequence[11] of vinylogous ester **14** with *p*-tolyllithium/*p*-tolylmagnesium halide.



Scheme 2. Synthesis of vinylogous ester **14**.

With above hypothesis, we have carried out reaction of 5,5-dimethylcyclohexane 1,3-dione with *iso*-butylalcohol in the presence of catalytic *p*-toluenesulphonic acid to form vinylogous ester **14** (Scheme 2). We then established the reaction condition for Stork-Danheiser sequence on vinylogous ester with various arylmetal reagents (Table 1). Following a quick optimization, it was found that enone **13b** could be accessed in 94% yield, when phenylmagnesium bromide (entries 5-8) was used as a nucleophile. In fact, phenylmagnesium bromide is a good nucleophile as compared to phenyllithium (entries 1-4) in terms of efficiency of the process (Table 1).

Table 1. Optimization of Stork-Danheiser sequence of **14**.



S. No.	nucleophile	temp. (1st step)	Time (1st step)	temp. (2nd step)	Time (2nd step)	yield
1.	PhLi	-78 °C	7 h	0 °C - rt	2 h	76%
2.	PhLi	-40 °C	6 h	0 °C - rt	2 h	62%
3.	PhLi	-20 °C	6 h	0 °C - rt	2 h	69%
4.	PhLi	0 °C	4 h	0 °C - rt	1 h	72%
5.	PhMgBr	-78 °C	8 h	0 °C - rt	2 h	83%
6.	PhMgBr	-40 °C	5 h	0 °C - rt	2 h	85%
7.	PhMgBr	-20 °C	5 h	0 °C - rt	1 h	82%
8.	PhMgBr	0 °C	5 h	0 °C - rt	1 h	90%

[a]Reactions were carried out on a 1 mmol of **14** under argon atmosphere.
[b]Isolated yields after column chromatography.

A variety of aryl magnesium bromide nucleophiles were the subjected to the Stork-Danheiser sequence on the vinylogous ester **14** in THF at 0 °C followed by treatment of dilute HCl. This resulted in the synthesis of wide range of 3-aryl-cyclopenten-2-ones **13a-i** in 86-92% yields without event (Figure 2).[11c]

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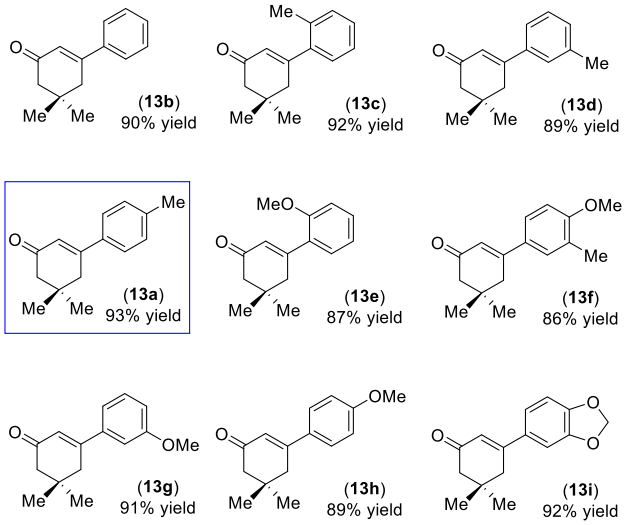
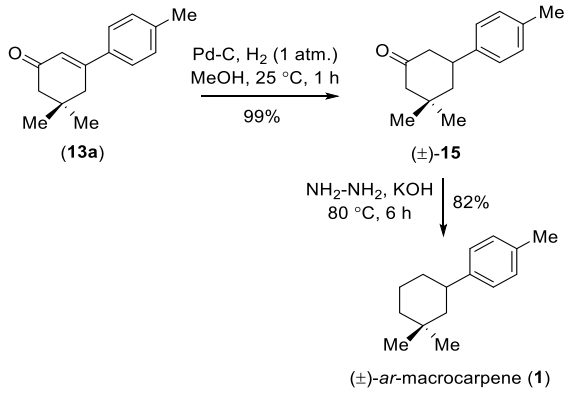


[a]Reactions were carried out on a 1 mmol of **14** under argon atmosphere. [b]Isolated yields after column chromatography.

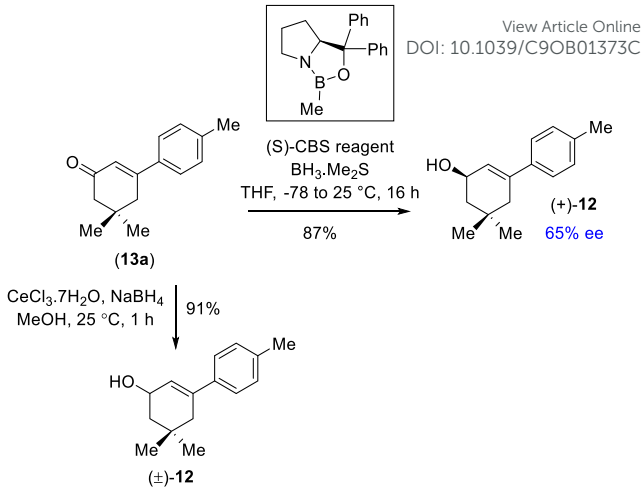
Figure 2. Substrate scope of Stork-Danheiser sequence of **13**.

With 5,5-Dimethyl 3-(*p*-tolyl)-2-cyclohexenone **13a** in significant quantity, next step was its hydrogenation to form 3-arylketone **15** in quantitative yield (Scheme 3). In fact, a concise total synthesis of racemic (±)-*ar*-macrocarpene (**1a**) was achieved from ketone **15** via a modified Wolff-Kishner reduction in 82% yield (67.9% yield over 4 steps from commercially available 5,5-dimethylcyclohexane 1,3-dione).[12] Further synthetic elaboration of 5,5-Dimethyl 3-aryl 2-cyclohexenone **13a** was done under Luche condition,[13] which afforded allylic alcohol (±)-**12** in 91% yield (Scheme 4).



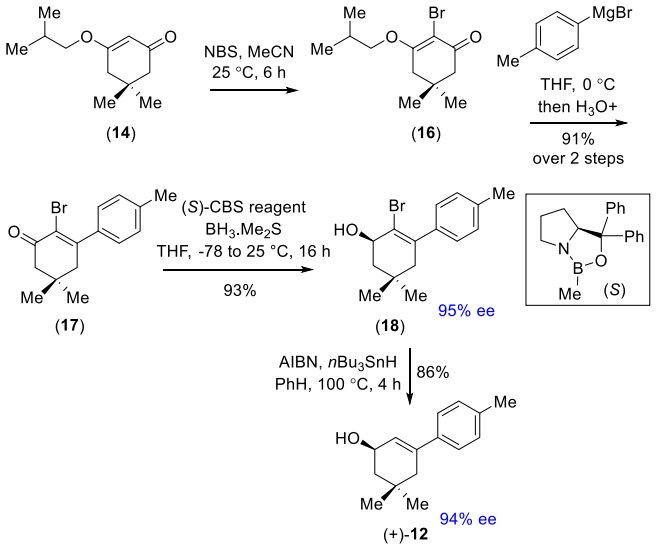
Scheme 3. Total synthesis of (±)-*ar*-macrocarpene (**1**).

Next, we turned our attention for asymmetric total synthesis of (+)-**1**. Towards this direction, unfortunately, Corey-Bakshi-Shibata reduction of enone **13a** with borane using 10 mol% (*S*)-CBS reagent at -78 °C for 16 h furnished the product only in 65% ee in favor of (*R*)-**12** (Scheme 4), thus implying the presence of sterics at the α-position of carbonyl might be essential to achieve excellent enantioselectivity.[14] Thus, we thought of installing an easily removable bromo group at the α-position of enone **13a** i.e. **17** (Scheme 5) to test if that helps in securing enantioenriched allylic alcohol.



Scheme 4. Catalytic enantioselective reduction of enone **13a**.

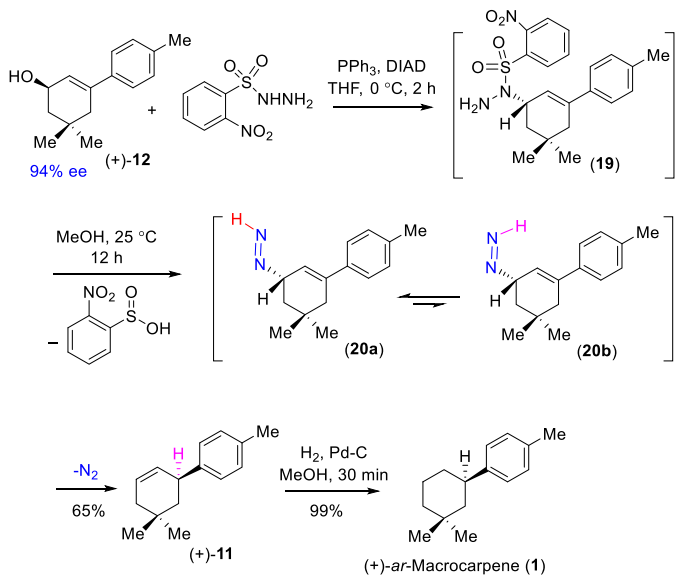
Starting from vinylogous ester **16,** compound **17** was synthesized in 91% yield following a Stork-Danheiser sequence. Fortuitously, as per our expectation, a catalytic enantioselective reduction of 5,5-Dimethyl 3-(*p*-tolyl)-2-bromo cyclohexenone **17** with CBS reagent, afforded the allylic alcohol (+)-**18** in 93% yield with excellent enantioselectivity i.e. 95% ee (Scheme 5). Further allylic alcohol (*R*)-**12** was synthesized via a reductive cleavage of bromo group in the presence of *n*-tributyltin hydride and 10 mol% azo-*bis*-isobutyronitrile (AIBN) as radical initiator, without compromising enantiopurity (94% ee).



Scheme 5. Catalytic enantioselective reduction of sterically crowded 2-bromoenone **16**.

Next, we sought to demonstrate the feasibility of reductive transposition through allyllylic diazene rearrangement (ADR) on compound (*R*)-**12** (94% ee) under Mitsunobu condition using *o*-nitrophenylsulfonyl hydrazide (Myer's protocol).[13] The procedure involves first formation of corresponding stereo inverted sulfonylhydrazine **19** which on gentle extrusion of *O*-nitrobenzenesulfinic acid in the presence of methanol leads to concomitant formation of a diazene intermediates **20a-20b**.

Intermediate **20b** slowly loses N_2 gas (through spontaneous *retro*-ene reaction) to furnish the deoxygenated product cyclohexene (+)-**11** in 65% yield *via* a reductive transposition following a [3,3]-sigmatropic rearrangement (Scheme 6). Finally, hydrogenation of cyclohexene (+)-**11** completed the synthesis of (+)-*ar*-macrocarpene (**1**) in quantitative yield.



Scheme 6. Total synthesis of (+)-*ar*-macrocarpene (**1**).

Conclusions

In conclusion, a concise total synthesis of (+)-*ar*-macrocarpene (**1**) has been achieved (42.1% overall yields over 7 steps) from commercially available inexpensive 5,5-dimethylcyclohexane 1,3-dione. A key reductive transposition on enantioenriched allylic alcohol (+)-**12** is achieved in single step using Myers protocol to afford advanced intermediate cyclohexene (+)-**11**. Enantioenriched (95% ee) allylic alcohol (+)-**12** was prepared via a catalytic enantioselective CBS reduction of 5,5-Dimethyl 3-(*p*-tolyl)-2-bromo cyclohexenone **17**. Further application of this strategy for the synthesis of other sesquiterpenoids is currently under active investigation in our laboratory.

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