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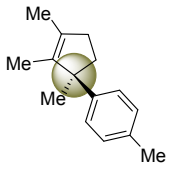
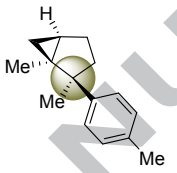


isolaurene (**1a**)



cyclolaurene (**2a**)

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Unified Approach to the Sesquiterpenoids, Lauranes and Cyclcolauranes: Total Synthesis of (±)-Isolaurene

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

[a]*Department of Chemistry, Indian Institute of Science Education and Research Bhopal, Bhauri, Bhopal - 462 066, Madhya Pradesh, India*
[b]*Department of Chemistry, Indian Institute of Science Education and Research Berhampur, Berhampur - 462 066, Odisha, India*
Contact: +91-755-6692374, Fax: +91-755-6692392. Address for correspondence: vishnumayabisai@gmail.com

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ABSTRACT

A general approach to the total synthesis of sesquiterpene, isolaurene (**1a**) and cyclolaurene (**2a**) is featured from commercially available 3-methyl cyclopenten-2-one. The strategy includes a Stork-Danheiser sequence concomitant with a Ni(II)-catalyzed conjugate addition of methyl group onto 3-aryl 2-methyl cyclopenten-2-one to afford the advanced intermediate **11**. A methyllithium addition onto compound **11** with an eventual dehydration completed the total synthesis of isolaurene (**1a**) in 5 steps (58.3% overall yields).

Bioactive secondary metabolites originated from marine organisms display wide range of effects on many diseases in contrast to their terrestrial counterparts. Efficient synthetic ventures towards these molecules may lead to the discovery of newer bioactive metabolites with different modes of action.[1] Laurene-type sesquiterpenes (**1a-c**; Figure 1) include one such class having substituted aryl cyclopentanes with three methyl groups in 1, 2 and 3 fashion and cyclolauranes **2a-d** (Figure 1) having two methyl groups in 1 and 2 position with a cyclopropane ring caught our attention. Other sesquiterpenes like laurokamurenes (**4a-b**) [1, 1, 2 fashion], cuparenes (**5a-b**), herbertenes (**6a-b**) differ from lauranes only in the methylation pattern *viz*. 1, 2, 2 for **4a-b** and 2, 2, 3 for **5a-b** and **6a-b**, respectively (Figure 1).

Masamune and co-workers have isolated laurene and isolaurene (**1a**) from *Laurencia glandulifera*.[2a-b] Later, in 2012, Alarif and co-workers have isolated three laurene-type sesquiterpenes, isolaurene (**1a**), isolauraldehyde (**1b**), and 12-hydroxy isolaurene (**1c**) from the organic extract of the red alga *Laurencia obtusa*.[2c] The newly isolated compounds were tested for their bioactivity profile and found that natural products **1b-c** exhibited potent activity against the Gram-positive *Bacillus subtilis* and *Staphylococcus aureus*, where **1b** proved to be the most active (MIC 35 and 27 μg/mL, respectively). Compound **1b** exhibited a significant activity against *Candida albicans* (MIC of 70 μg/mL).[2]

Importantly, several metabolites of *Laurencia* showed noticeable antibacterial,[3] insecticidal,[4a] antifungal,[4b] antiviral activity,[5a] tyrosine inhibitor[5b] and apoptosis inducing or suppressing activity.[6] Although, detailed biological profiles of most of the laurenes are yet to be investigated, other similar class of sesquiterpenoids, such as cuparenes (**5a-b**) and herbertenes (**6a-b**) are found to be potent antifungal, antibiotic, neurotrophic and antilipidperoxidation agents.[7, 8, 9a-b]

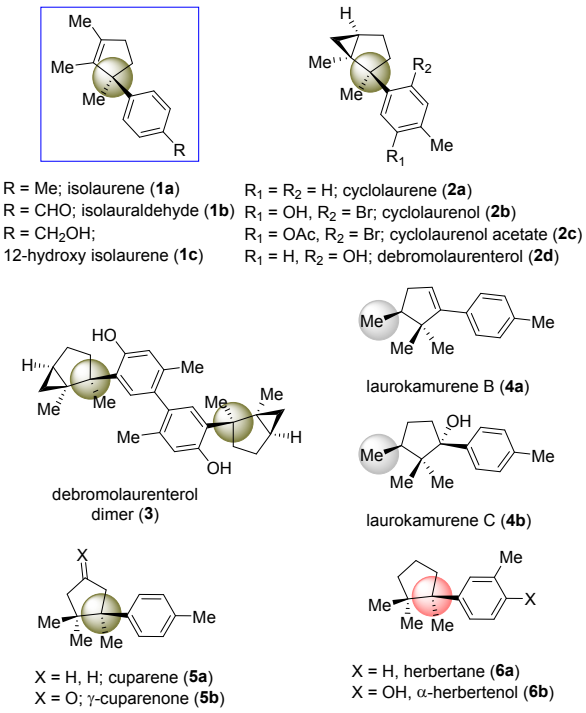
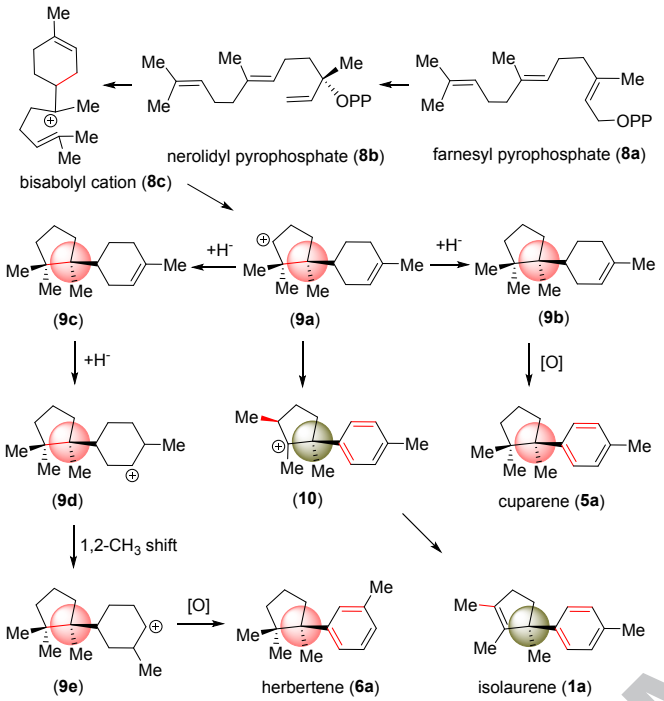


Figure 1: Sesquiterpenes, isolaurenes (**1a-c**), cyclolaurenes (**2a-d**, **3**), laurokamurenes (**4a-d**), cuparenes (**5a-b**), and herbertanes (**6a**).[10]

A rare cuparane sesquiterpene, cyclolaurene **2a**, was also isolated together with brominated analogs cyclolaurenol **2b** and cyclolaurenol acetate **2c** from the sea hare A. *dactylomela* in Kohama Island (Okinawa, Japan).[9c] Also, debromolaurenterol dimer **3** was later identified from the same source which is also found in the red alga *Laurencia tristicha*.[9d]

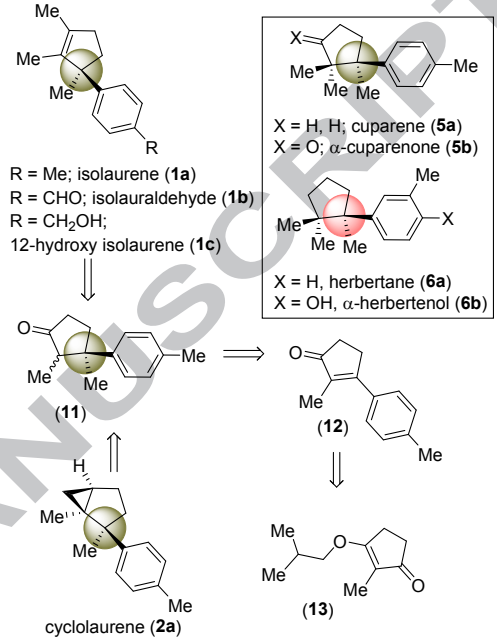


Scheme 1: Biogenetic connections between isolaurene (**1a**), cuparane (**5a**), and herbertane (**6a**).

A closure view of the biogenetic connection of these sesquiterpenoids[9b] brings them back to bisabolyl cation (**8c**) generating from farnesyl pyrophosphate (**8a**) via the intermediacy of nerolidyl pyrophosphate (**8b**). Intermediate **8c** might be responsible for the syntheses of cuparane **5a**, herbertene **6a** and isolaurane **1a** involving rearrangement of methyl groups (1,2-shift of methyl group) and carbocation intermediates (Scheme 1). This cation intermediate (**8c**) may generate cyclopentane based 2˚ carbocation **9a**, from where oxidation-reduction events lead to the formation of cuparanes **5a-b** and related secondary metabolites. Whereas, 2˚ carbocation **9a** after a 1,2-migration of methyl group generates another 2˚ carbocation **9e** enroute to herbertanes **6a-b** and related natural products following a series of oxidation-reduction processes. Isolaurane **1a** seems to be originated from intermediate **10** following similar processes (Scheme 1).

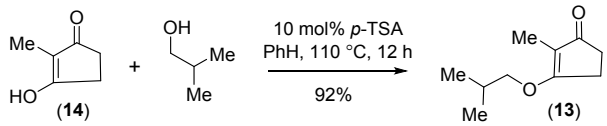
Although, there are a number of elegant total synthesis approaches for cuparanes (**5a-b**),[11] herbertanes (**6a-b**)[12] and isolaurene (**1a**),[13] there is an urgency for a flexible approach to 1-methyl 1'-(*p*-tolyl)cyclopentane based sesquiterepenes. Herein, we report a unified and concise route to isolaurenes and cyclolaurenes following a Stork-Danheiser sequence concomitant with a Ni(II)-catalyzed conjugate addition[14] of methyl group onto 3-aryl 2-methyl cyclopenten-2-one (see **11**) and a 4 steps total syntheses of (±)-isolaurene (**1a**) starting from vinylogous ester **13** (Scheme 3).

Retrosynthetically, it was envisioned that, 2-methyl 3-(*p*-tolyl)-3-methyl cyclopentanone (compound **11**) may serve as potential advanced intermediate for unified synthesis of (±)-isolaurene (**1a**) and (±)-cyclolaurene (**2a**) (Scheme 2). Methyllithium addition onto cyclopentanone **11** followed by elimination/dehydration could afford (±)-isolaurene (**1a**). On the other hand, $NaBH_4$-reduction of 2-methyl 3-(*p*-tolyl)-3-methyl cyclopentanone **11** followed by elimination and subsequent cyclopropanation would provide straight access to cyclolaurene (±)-**2a** (Scheme 2). Advanced intermediate **11** may be procured through a 1,4-addition of a methyl group[14] onto enone **12**, which in turn could be synthesized from a Stork-Danheiser sequence[15] on vinylogous ester **13** with *p*-tolyllithium/*p*-tolylmagnesium halide (Scheme 2).



Scheme 2: Retrosynthetic analysis of isolaurene (**1a**) and cyclolaurene (**3a**).

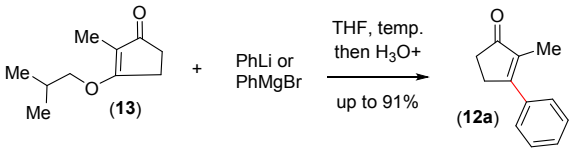
To realize the proposed hypothesis, we set forth to carry out the reaction of 2-methyl cyclopentane 1,3-dione **14** with *iso*-butylalcohol in the presence of catalytic *p*-toluenesulphonic acid to fetch vinylogous ester **13** (92% yield) (Scheme 3).



Scheme 3. Synthesis of vinylogous ester **13**.

Our next effort thereafter was to establish the reaction conditions for Stork-Danheiser sequence on vinylogous ester **13** with arylmetal reagent (Table 1).

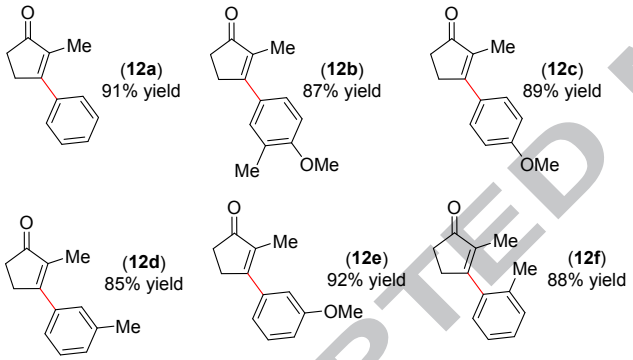
Table 1. Optimization of Stork-Danheiser sequence of vinylogous ester **13**.



S. No.	nucleophile	temp. (1st step)	Time (1st step)	temp. (2nd step)	Time (2nd step)	yield
1.	PhLi	-78 ºC	6 h	0 ºC - rt	3 h	71%
2.	PhLi	-40 ºC	5 h	0 ºC - rt	4 h	75%
3.	PhLi	-20 ºC	4 h	0 ºC - rt	3 h	73%
4.	PhLi	0 ºC	4 h	0 ºC - rt	3 h	70%
5.	PhMgBr	-78 ºC	6 h	0 ºC - rt	3 h	87%
6.	PhMgBr	-40 ºC	5 h	0 ºC - rt	3 h	86%
7.	PhMgBr	-20 ºC	5 h	0 ºC - rt	4 h	89%
8.	PhMgBr	0 ºC	6 h	0 ºC - rt	3 h	93%

[a]Reactions were carried out on a 1 mmol of **13** under argon atmosphere. [b]Isolated yields after column chromatography. [c]12-23% of starting material **13** as recovered in case to case due to incomplete reaction.

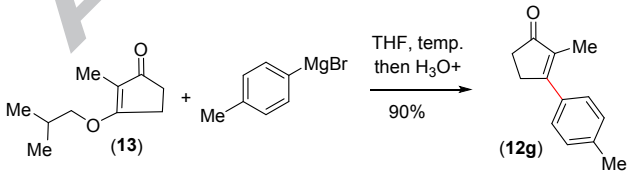
We began our studies by carrying out the Stork-Danheiser sequence on the vinylogous ester **13** by subjecting it with penyllithium and /or phenylmagnesium bromide in THF at different temperature followed by treatment of dilute HCl. A quick optimization showed that phenylmagnesium bromide (entries 5-8) was a good nucleophile as compared to phenyllithium (entries 1-4) in terms of chemical yields (Table 1). Later, a variety of aryl magnesium bromides were used under standard condition in THF at 0 ºC followed by treatment of dilute HCl. A smooth Stork-Danheiser sequence on vinylogous ester **13** led to the synthesis of a variety of 3-aryl-cyclopenten-2-ones **12a-f** in 85-92% yields (Figure 2).



[a]Reactions were carried out on a 1 mmol of **13** under argon atmosphere. [b]Isolated yields after column chromatography.

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

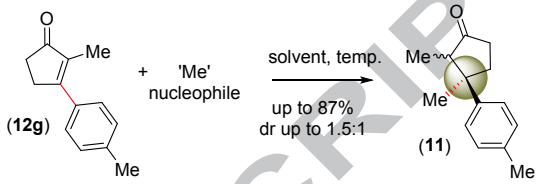
Particularly, the Stork-Danheiser sequence on vinylogous ester **13** with *p*-tolylmagnesium bromide was performed in 2g scale to provide enone **12g** in 90% yields, which is required for the synthesis of isolaurene (**1a**) and cyclolaurene (**3a**) (Scheme 4).



Scheme 4. Stork-Danheiser sequence of **13** using (*p*-tolphenyl)-magnesium bromide.

Next very important target was to install the all carbon quaternary center present in sesquiterpenes **1a** and **2a** (Figure 1) at the pseudobenzylic position. We thought that conjugate addition of a methyl group onto 2-methyl 3-(*p*-tolyl) cyclopentanone **12g** might be the straightforward way to achieve this. For this, we chose to explore a transition-metal catalyzed process utilizing few organometallic sources of methyl group in tetrahydrofuran at 0 °C – 25 °C and the results are summarized in Table 2. Unfortunately, it was observed that a well-known 1,4-addition using Me_2CuLi [prepared *in-situ* from organometallic reagents and Cu(I)I] were unsuccessful (entries 1-3), clearly depicting the formation of quaternary center needs special attention. We, therefore, thought of adopting Ni(II)-catalyzed conjugate addition of methyl group with various methyl nucleophiles (entries 4-8).

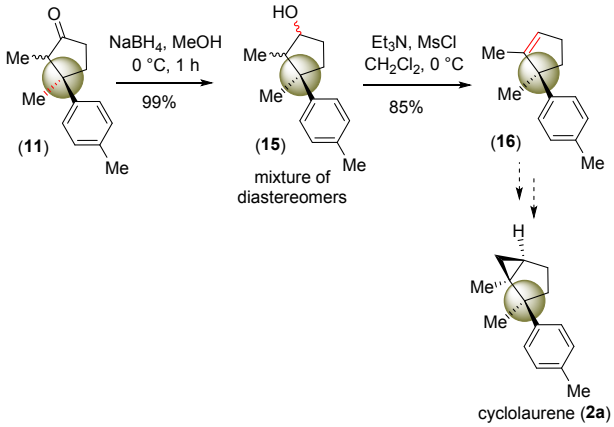
Table 2. Optimization of conjugate addition of 2-methyl 3-(*p*-tolyl) cyclopentanone **1g**.



S. No.	reagent	T-M catalyst	solvent	temp.	Time	yield
1.	MeLi	Cu(I)I	THF	0 ºC - 25 ºC	12 h	ND
2.	MeMgBr	Cu(I)I	THF	0 ºC - 25 ºC	14 h	ND
3.	Me_3Al	Cu(I)I	THF	0 ºC - 25 ºC	12 h	ND
4.	MeLi	$Ni(acac)_2$	THF	0 ºC - 25 ºC	12 h	12%
5.	MeMgBr	$Ni(acac)_2$	THF	0 ºC - 25 ºC	11 h	16%
6.	Me_3Al	$Ni(acac)_2$	THF	0 ºC - 25 ºC	20 h	87%
7.	Me_3Al	$Ni(acac)_2$	Et_2O	0 ºC - 25 ºC	12 h	50%
8.	Me_3Al	$Ni(acac)_2$	THF	0 ºC - 70 ºC	12 h	71%

[a]Reactions were carried out on a 0.2 mmol of **12g** with 0.4 mmol of organometallic reagent in the presence of 10 mol% of Cu(I)I or $Ni(acac)_2Cl_2$ under argon atmosphere. [b]Isolated yields after column chromatography.

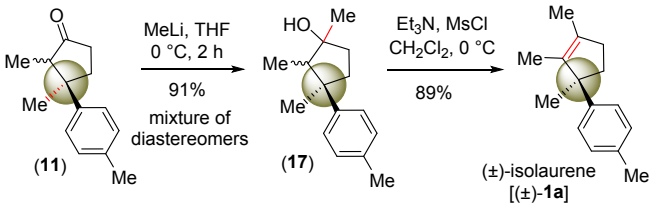
It was observed that, when methyllithium, and methyl magnesium bromide, were used in the presence of 10 mol% of $Ni(acac)_2$, product **11** was observed only in trace amount (entries 4-5). Interestingly, a reaction of trimethyl aluminum in the presence of 10 mol% of $Ni(acac)_2$ afforded the product in 50% yield in diethylether (entry 7). Delightfully, the reaction of trimethyl aluminum in the presence of 10 mol% of $Ni(acac)_2$ in refluxing tetrahydrofuran, as used by Cossy[14] for their synthesis of β-cuparenone, afforded 2-methyl 3-(*p*-tolyl)-3-methyl cyclopentanone (**11**) in 87% yield with approx. 1.5:1 diastereomeric ratio (entries 6 and 8).



Scheme 5. Synthetic approach to cyclolaurene (**2a**).

Next, for a concise approach to (±)-cyclolaurene (**2a**), we carried out sodium borohydride reduction of 2-methyl 3-(*p*-tolyl)-cyclopenten-2-ones **11** to form secondary alcohol **15** in a mixture of diastereomers (Scheme 5). Further, a subsequent elimination of hydroxyl group by converting it to mesylate furnished cyclopentene **16** in 84% yields over 2 steps (Scheme 5). Since the

cyclopropanation of similar type intermediate is well-known,[16] our approach can be utilized for a concise route to the (±)-cyclolaurene (**2a**) (Figure 1).



Scheme 6. Total synthesis of (±)-isolaurene (**1a**).

Later, following our proposed strategy, MeLi addition onto 2-methyl 3-(*p*-tolyl)-cyclopenten-2-ones **11** furnished tertiary alcohol **17** in the form of mixture of diastereomers (Scheme 6). A similar dehydration/elimination of tertiary alcohol **17** as shown in Scheme 5 was carried out under mesylation condition to complete the total synthesis of (±)-isolaurene (**1a**) in 89% yield.

To conclude, a concise total synthesis of (±)-isolaurene (**1a**) has been achieved in 5 steps (58.3% overall yields) starting from 2-methyl cyclopentane 1,3-dione following a Stork-Danheiser sequence and a Ni(II)-catalyzed conjugate addition as key synthetic transformations. It is believed that a catalytic enantioselective version of this strategy can be envisioned if the advanced intermediate 2-methyl 3-(*p*-tolyl)-3-methyl cyclopentanone (**11**) is synthesized in enantioenriched form.[17] Further investigation towards this direction as well as application of this strategy for the synthesis of complex dimeric cyclolaurenes (such as **3**) is currently under active investigation.

Acknowledgments

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Supplementary data

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

§Current Address:
The AB Research Group, Department of Chemistry, Indian Institute of Science Education and Research Bhopal, Bhopal Bypass Road, Bhopal - 462 066, India.

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(a) Unified approach to the isolaurene and cyclolaurene sesquiterpenoids has been disclosed.
(b) Stork-Danheiser sequence on cyclopentane based vinylogous ester is explored.
(c) Ni(II)-catalyzed conjugate addition of methyl group sets the all carbon Quaternary center.
(d) Sesquiterpene, (±)-isolaurene (**1a**) is synthesized in only 5 steps with 58.3% overall yield.