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A Unified Approach to Sesquiterpenes Sharing Trimethyl(*p*-tolyl) Cyclopentanes: Formal Total Synthesis of (±)-Laurokamurene B

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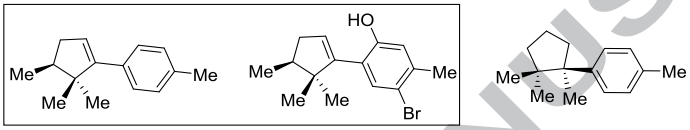

laurokamurene B (**1a**) laurokamurene A (**1b**) cuparene (**2a**)

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A Unified Approach to Sesquiterpenes Sharing Trimethyl(*p*-tolyl) Cyclopentanes: Formal Total Synthesis of (±)-Laurokamurene B

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ABSTRACT

A unified approach to the sesquiterpenoids sharing common trimethyl(*p*-tolyl) cyclopentane skeleton has been disclosed *via* a key Stork-Danheiser sequence on a cyclopentane based vinylogous ester with aryl Grignard reagent followed by α-methylation strategy. The strategy is eventually applied to the concise formal total synthesis of (±)-laurokamurene B (**1b**) in only 5 steps with 45.4% overall yield.

Red algae of the genus *Laurencia Lamouroux* are well-known for their ability to biosynthesize a large variety of structurally unusual secondary metabolites having brominated and non-brominated sesquiterpenes.[1] The genus *Laurencia* is particularly distributed widely in tropical and subtropical areas.[1] More than 1100 different metabolites with sesquiterepene (C-15 unit), diterpenes (C-20 unit), and triperpenes (30 unit) have been characterized from approximately 80 species of this genus till date.

During their investigations on the isolation of biologically active compounds from Chinese marine organisms, Mao and Guo isolated two new aromatic sesquiterpenes laurokamurenes A and B (**1a-b**) from genus *Laurencia* in 2006.[2a] Recently, in 2014, Mao and co-workers have isolated laurokamurenes C and D (**1c-d**) from the red alga *Laurencia okamurai Yamada*, together with six other known sesquiterpenes.[2b] The structures of these secondary metabolites, including relative configuration, were elucidated by detailed analysis of spectroscopic data (2D NMR experiments), and by comparison with data for related known compounds. Although, elaborate study of the biological profile of majority of these sesquiterpenes are yet to be undertaken, preliminary findings revealed that laurokamurene B (**1b**) displays antifungal and cytotoxic activities.[2b-d]

Structurally, laurokamurenes (**1a-d**) are closely related to other sesquiterpenoids, such as cuparenes (**2a-b**), deconins (**3a-c**)[3], and aplysins (**4-5**) with same total numbers of carbons present in them in a rearranged structural scaffold (Figure 1). Particularly, in laurokamurenes (**1a-d**), three methyl groups are situated at 2,2,3-fashion in 1-arylcyclopentane ring. In contrast, cuparanes (**2a-b**) share three methyl groups at 1,2,2-fashion, whereas in lauranes (**1a-d**) they follow 1,2,3-fashion.[4a] Among various sesquiterpenes isolated till date, laurokamurenes (**1a-b**) are the first members with three methyl groups in the aliphatic ring arranged in a 2,2,3 fashion.

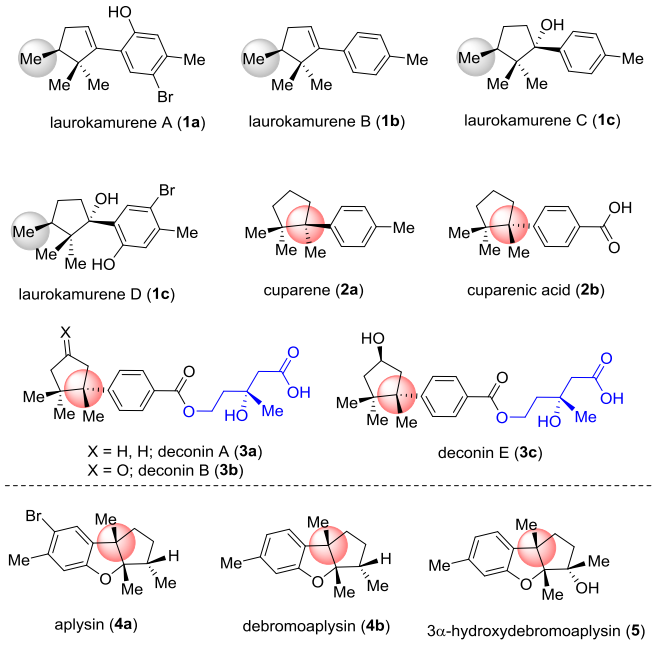
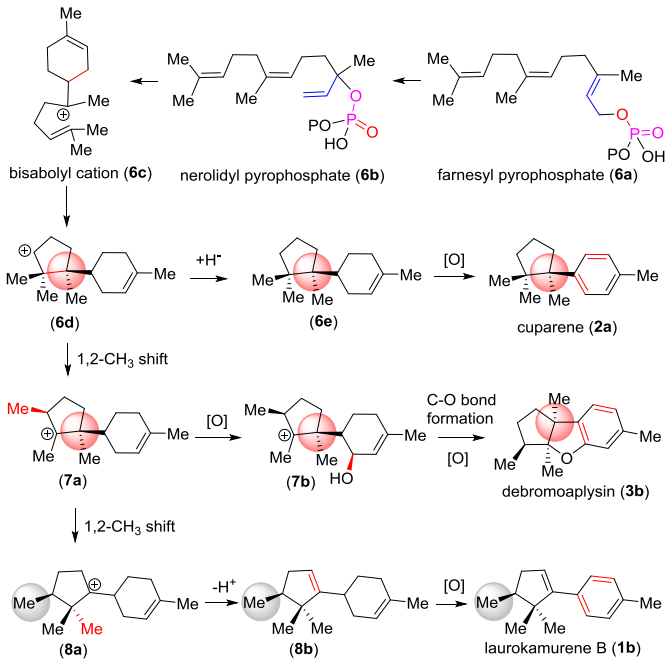


Figure 1: Selected sesquiterpene based secondary metabolites, laurokamurenes A-D (**1a-d**), cuparenes (**2a-b**), deconins (**3a-c**) and aplysins (**4-5**).

Biogenetically, they are synthesized from intermediate carbocation **6d** (Scheme 1) via the rearrangement of methyl group (1,2-shift of methyl group) to establish a 3° carbocation intermediates such as **7a** (for lauranes e.g. debromoaplysin **4b**) and **8a** (e.g. laurokamurenes

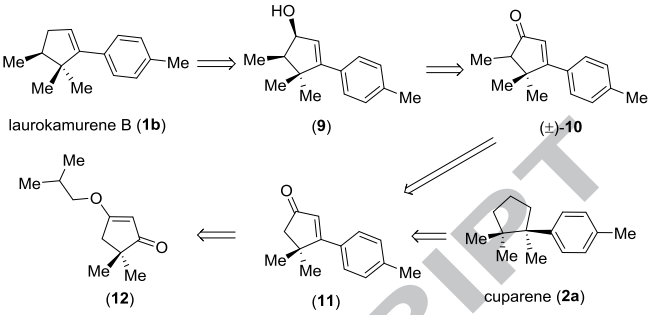
1a-d). Cyclopentane based 2˚ carbocation **6d** can be generated from a bisabolyl cation intermediate (**6c**) *via* a C-C bond formation, which in turn can be obtained from a farnesyl pyrophosphate **6a** (C-15 unit) via a nerolidyl pyurophosphate **6b** (C-15 unit) (Scheme 1).



Scheme 1: Biogenetic connections between laurokamurenes (**1b**), cuparene (**2-3**), and laurane (**4-5**).

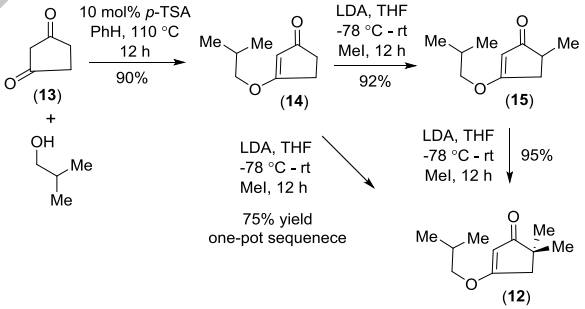
Owing to their diverse biological profiles and uncommon structural features, cuparane (**2a-b**) and laurane (**3-5**) based sesquiterpenoids have gained extensive attention from the synthetic community all over the world leading to numerous efficient synthetic approaches.[1a] Although laurokamurenes were isolated more than a decade, only a few synthesis of laurokamurene B **1a** are reported till date. In 2007,[5a] Srikrishna and co-workers have reported the first total synthesis of (±)-laurokamurene B **1a** from isobutyric acid employing a combination of an Ireland–Claisen rearrangement and RCM reactions establishing the structure of the marine natural product (22% overall yields over 11 steps). In 2008,[6] the same group has reported first asymmetric synthesis of (+)-laurokamurene B **1a** from commercially available α-campholenaldehyde[7] in 31.2% overall yields over 7 steps (this strategy is essentially a semisynthesis starting from a naturally occurring secondary metabolite). Subsequently, in 2009, Lecornué and co-workers have disclosed a total synthesis of (±)-laurokamurene B **1a** from 2-methylcyclopentenone (39.7% overall yields over 7 steps).[5b] Recently, in 2017, Echavarren and co-workers have reported total synthesis of (±)-laurokamurene B **1a** via an elegant Au(I)-catalyzed [3+2]-cycloaddition reaction between an allene and styrylcycloheptatriene.[5c]

Despite these reports, there is urgency for a straightforward and efficient unified approach for sesquiterpene natural products sharing a common arylcyclopentane skeleton (shown in Figure 1). Herein, we report a concise total synthesis of (±)-laurokamurene B **1a** via a key Stork-Danheiser sequence of vinylogous ester **9** with arylmagnesium halide followed by α-alkylation strategy. Retrosynthetically, it was envisioned that, 4,4-dimethyl 3-aryl cyclopenten-2-one (such as **11** in Scheme 2) could serve as a potential intermediate for unified synthesis of laurokamurene B (**1a**) and cuparene (**2a**) sesquiterpenoids (Scheme 2). α-Methylation of cyclopenten-2-one **11** with methyl iodide would afford (±)-**10**.[8] Deoxygenation of compound **9** could afford laurokamurene B **1b**. On the other hand, a methylcuprate addition onto 3-aryl cyclopenten-2-one (**11**) followed by the reduction of carbonyl group would provide cuparene **2a**. Compound **11** could be accessed from a Stork-Danheiser sequence[9] of vinylogous ester **12** with *p*-tolyllithium/*p*-tolylmagnesium halide.



Scheme 2: Unified retrosynthetic analysis of laurokamurenes B (**1a**) and cuparene (**2**a).

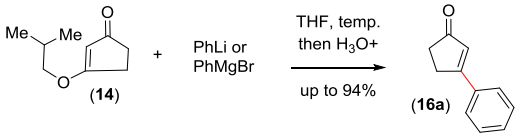
Assuming above hypothesis, we have carried out reaction of cyclopentane 1,3-dione **13** with *iso*-butylalcohol in the presence of catalytic *p*-toluenesulphonic acid to form vinylogous ester **14** (90% yield). α-Methylation of vinylogous ester **14** was carried out in the presence of LDA with methyl iodide at -78 ºC (Scheme 3). It was observed that a sequential α-methylation of **14** afforded *gem*-dimethyl vinylogous ester **12** in 75% yield. However, a two-step protocol of α-methylation of **14** following monomethylated intermediate **15** afforded **12** in 87% overall yield over 2 steps (Scheme 3).



Scheme 3. Synthesis of vinylogous ester **12**.

With *gem*-dimethyl vinylogous ester **12** in hand, our effort was thereafter to establish the reaction condition for the Stork-Danheiser sequence on the vinylogous ester **14** with arylmetal reagent (Table 1). Initially, we began our studies by carrying out a Stork-Danheiser sequence on the vinylogous ester **14** by subjecting it with phenylmagnesium bromide in THF at different temperature followed by treatment of dilute HCl. Following exhaustive optimization, it was found that phenylmagnesium bromide (entries 5-8) was a good nucleophile as compared to phenyllithium (entries 1-4) in terms of chemical yields (Table 1).

Table 1. Optimization of Stork-Danheiser sequence of **11**.

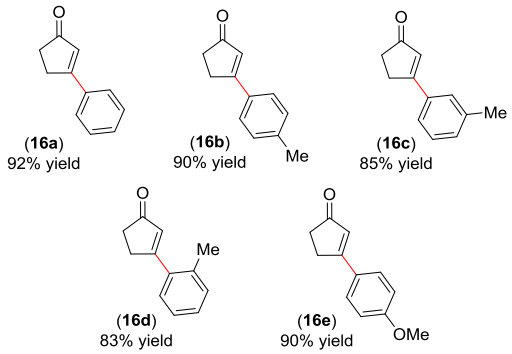


S. No.	nucleophile	temp. (1st step)	Time (1st step)	temp. (2nd step)	Time (2nd step)	yield
1.	PhLi	-78 ºC	4 h	0 ºC - rt	8 h	63%
2.	PhLi	-40 ºC	2 h	0 ºC - rt	9 h	69%
3.	PhLi	-20 ºC	2 h	0 ºC - rt	9 h	68%
4.	PhLi	0 ºC	2 h	0 ºC - rt	9 h	74%
5.	PhMgBr	-78 ºC	4 h	0 ºC - rt	8 h	90%
6.	PhMgBr	-40 ºC	2 h	0 ºC - rt	9 h	94%

7.	PhMgBr	-20 ºC	2 h	0 ºC - rt	9 h	92%
8.	PhMgBr	0 ºC	2 h	0 ºC - rt	9 h	92%

[a]Reactions were carried out on a 1 mmol of **14** under argon atmosphere. [b]Isolated yields after column chromatography. [c]12-23% of starting material **14** was recovered in case to case due to incomplete reaction.

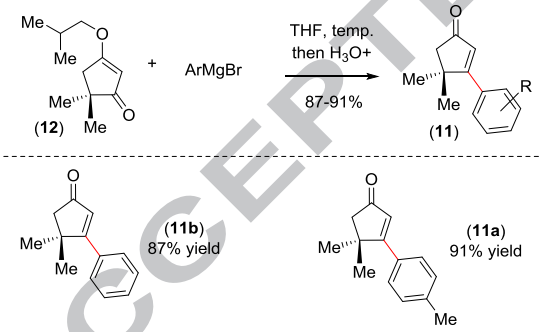
Later, a variety of aryl magnesium bromides were used under standard condition in THF at 0 ºC followed by treatment of dilute HCl. This resulted in a smooth reaction of Stork-Danheiser sequence on the vinylogous ester **14** to provide a variety of 3-aryl-cyclopenten-2-ones **16a-d** in 83-92% yields (Figure 2).



[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 **14**.

Since, laurokamurenes (**1a-d**) and cuparene (**2a-b**) sesquiterpenoids possess a *gem*-dimethyl group in their cyclopentane motifs, the Stork-Danheiser sequence of vinylogous ester **12** was further elaborated to furnish products 4,4-dimethyl 3-aryl-cyclopenten-2-ones **17a-d** in 87-91% yields (Scheme 4). Importantly, Stork-Danheiser sequence on compound **12** with *p*-tolylmagnesium bromide was performed in 5g scale to provide **11a** in 91% yields.

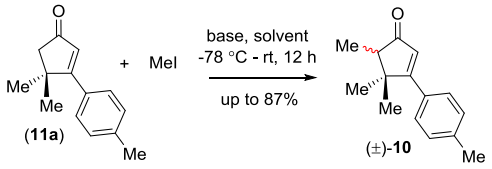


[a]Reactions were carried out on a 1 mmol of **12** under argon atmosphere. [b]Isolated yields after column chromatography.

Scheme 4. Stork-Danheiser sequence of **12**.

Next, with 4,4-dimethyl 3-(*p*-toyl)-cyclopenten-2-one **11a** in hand, it was α-methylated with methyl iodide (Table 2). It was observed that α-methylation at -40 ˚C afforded desired enone compound **10** in 56-75% yields (entries 1-3). Following optimization, it was found that LiHMDS at -78 ºC afforded α-methylated compound (±)-**10** in 87% yield (Table 2).

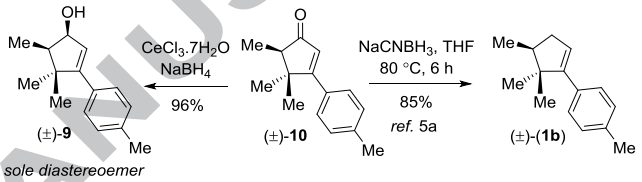
Table 2. α-Alkylation of enone **11a**.



S. No.	Base (solvent)	temp.	time	Yield (**10**)
1.	LDA (THF)	-40 ºC	8 h	63%
2.	LiHMDS (THF)	-40 ºC	9 h	75%
3.	KHMDS (THF)	-40 ºC	6 h	56%
4.	LiHMDS (THF)	-78 ºC	9 h	87%

[a]Reactions were carried out on a 0.5 mmol of **11a** with 0.6 mmol of MeI at -78 ˚C under argon atmosphere. [b]Isolated yields after column chromatography.

With enone (±)-**10**, we then investigated Luche reduction[10] at 0 ˚C, which afforded allylalcohol (±)-**9** in 96% yield as a sole diastereoemer.[11] Later, a concise total synthesis of (±)-laurokamurene B (**1a**) was achieved from enone (±)-**10** via a known $NaCNBH_3$ reduction[4a] in the presence of $BF_3.OEt_2$.



Scheme 5. Formal total synthesis of (±)-laurokamurene B (**1b**).

In conclusion, concise total synthesis of (±)-laurokamurene B (**1b**) has been achieved in 5 steps (45.4% overall yields) from cyclopentane 1,3-dione following a key Stork-Danheiser sequence followed by α-alkylation strategy. We believed that a catalytic enantioselective under a dynamic kinetic resolution (DKR) would afford allylalcohol **9** as enantiopure compound. Further investigation towards this direction as well as application of this strategy for the synthesis of cuparene (**2a**) is currently under active investigation.

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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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8. Reduction of (±)-**10** under the Dynamic Kinetic Resolution (DKR) could led to the formation of enantioenriched core **9**. For some of the important reviews, see: (a) Noyori, R.; Tokunaga, M.; Kitamura, M. *Bull. Chem. Soc. Jpn*. **1995**, *68*, 36-55. (c) Perllissier, H. *Tetrahedron* **2003**, *59*, 8291-8327.

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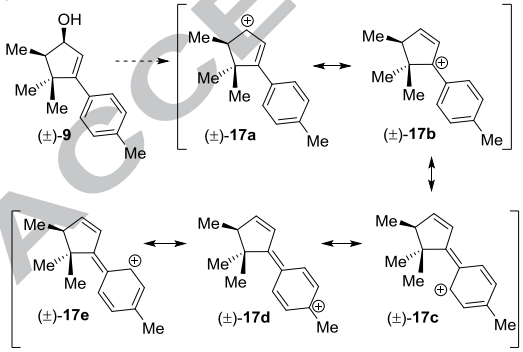
11. Compound **9** was found to be unstable and decomposes at room temperature. This is probably because of the sbalization of the allylic carbocation **17a-e** followed by polymerization via a Friedel-Crafts type alkylations.



14th May, 2019

Prof. Vinod K. Singh
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Highlights for the publication in *Tetrahedron Lett.*

Manuscript Title: A Unified Approach to Sesquiterpenes Sharing Trimethyl(*p*-tolyl) Cyclopentanes: Formal Total Synthesis of (±)-Laurokamurene B

Authors: Mrinal K. Das, Bidyut K. Dinda, and Vishnumaya Bisai*

Dear Professor Singh,
Please see following highlights for this manuscript:

(a) Approach to sesquiterpenoids with trimethyl(*p*-tolyl)cyclopentanes is reported.
(b) Stork-Danheiser sequence on vinylogous ester yileds 3-arylcyclopetenone **11a**.
(c) α-Methylation of enone **11a** sets all carbon present in Laurokamurene B (**1b**).
(d) (±)-Laurokamurene B (**1b**) is synthesized in 5 steps with 45.4% overall yield.

With best regards,

(Vishnumaya Bisai)