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COMMUNICATION

Formal Total Syntheses of (+)- and (–)-*ar*-Macrocarpene *via* Rh(I)-BINAP Catalyzed Conjugate Addition

Arindam Khatua,[a] Souvik Pal,[a] and Vishnumaya Bisai*[a,b,c§]

Abstract: Catalytic asymmetric formal total syntheses of both antipodes of sesquiterpene, (+)-*ar*-macrocarpene (**1**) and (–)-*ar*-macrocarpene (*ent*-**1**) has been achieved from 5,5-dimethyl-(3-*p*-tolyl)cyclohexanone **12**. Enantioenriched compound **12** was accessed in 96% ee with excellent yield from catalytic enantioselective *p*-tolylboronic acid addition onto 5,5-dimethyl cyclohexen-2-one **13** using Rh(I)-(*S*)-BINAP (**L7**). Further, *ent*-**12** was achieved in 96% ee by using Rh(I)-(*R*)-BINAP (*ent*-**L7**).

Introduction

Recently, there is global interest in the synthesis of sesquiterpenoids owing to their volatile and combustible properties which make them ideal candidate for terpene-based renewable biofuels.[1] *ar*-Macrocarpene (**1**) and (*Z*)-γ-macrocarpene (**2**) are belonging to one such group of naturally occurring irregular aromatic sesquiterpenes (Figure 1), which were identified in foliage of *Cupressus macrocarpa* by Cool in 2005 in widely varying amounts.[2]

In spite of 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. *N*-Hexane extract of this species contains *ar*-macrocarpene **1** as a minor component (Figure 1).[2] Other structurally correlated sesquiterpenoids, include *ar*-tenuifolene (**4a**),[3] laurokamurene B (**4b**),[4] isolaurene (**5a**),[5] isolauraldehyde (**5b**),[5c] 12-hydroxy isolaurene (**5c**),[5c] cuparane (**6a**),[6] cuparenic acid (**6b**),[6] aplysin (**7a**),[7] and debromoaplysin (**7b**).[7] Biogenetically, these sesquiterpenoids are structural isomers with rearranged structural scaffolds as shown in Figure 1. In addition brominated sesquiterpenoid, majapolene B (**3**),[8] was originally isolated from *Laurencia majuscula.*

Structurally, macrocarpene (**1**) shares a common 3,3,4'-trimethyl-1,1'-(bicyclohexyl) skeleton,[2] whereas, the three methyl groups are situated on the 1-arylcyclopentane ring in 2,2,3-fashion in laurokamurenes (**4b**) (Figure 1).[4] There are sesquiterepenoids, where three methyl groups are situated in 1,2,3-fashion, such as isolaurene (**6**),[5] isolauraldehyde (**5b**),[5c] and 12-hydroxy isolaurene (**5c**).[5c] The same is true for other tricyclic sesquiterpenoids, such as aplysin (**7a**),[7] and debromoaplysin (**7b**).[7] Further, three methyl groups are found in 1,2,2-fashion in case of cuparane (**6a**),[6] and cuparenic acid (**6b**).[6] With regard to its biogenetic connection, *ar*-macrocarpene **1** seems to be possibly originated from bisabolyl cation (**10c**) via the intermediacy of congener *Z*-γ-macrocarpene (**2**) and other hypothetical intermediates **10d** and **10e** (Scheme 1).

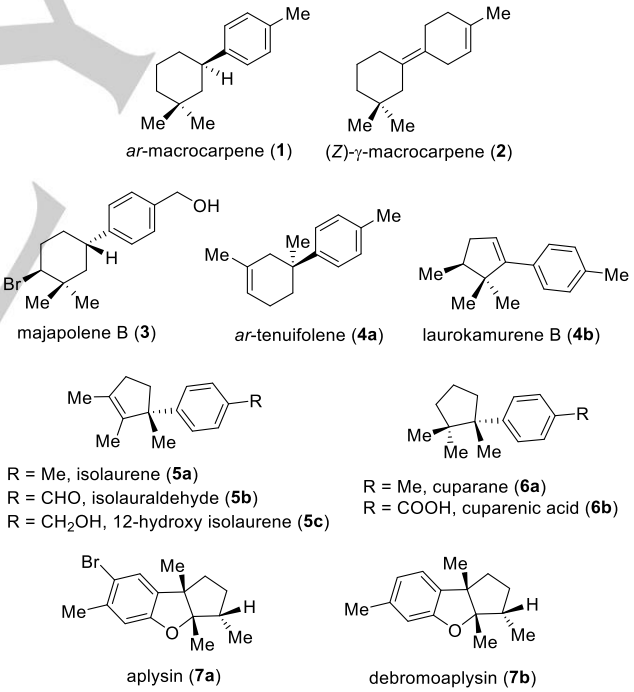

Figure 1: *ar*-Macrocarpene (**1**) and structurally related naturally occurring sesquiterpenes.

A plausible biogenetic connection between naturally occurring sesquiterpenes is shown in Scheme 1. Biosynthetically, bisabolyl cation (**10c**) can be obtained from a farnesyl pyrophosphate (FPP) **10a** with a C-15 unit *via* its isomeric rearranged scaffold nerolidyl pyrophosphate **10b** having C-15 unit (Scheme 1).[9] Whereas, other sesquiterpenes having a cyclopentane frame-work are supposed to be synthesized

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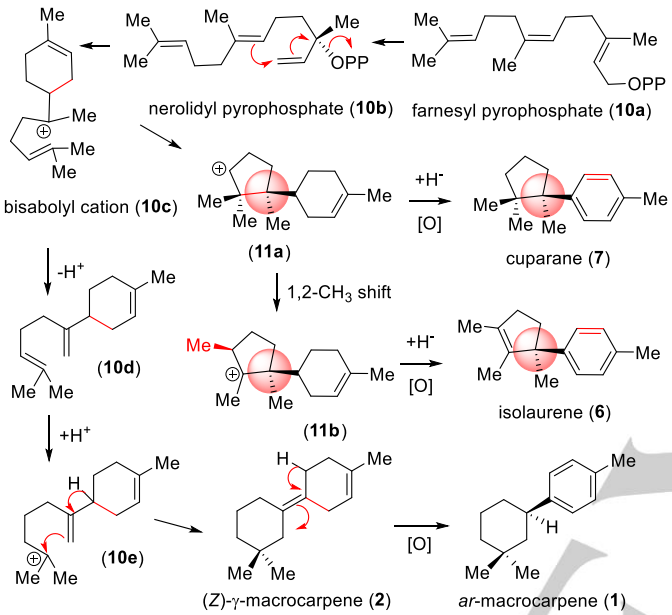
§This work is dedicated to Professor Subrata Ghosh, IACS Kolkata on the occasion of his 70th birthday.

from intermediate secondary carbocation **11a** (Scheme 1) *via* the rearrangement of methyl group (1,2-shift of methyl group) to establish a 3˚ carbocation intermediates such as **11b** (for isolaurene **6**). It is obvious to think that, the cyclopentane based 2˚ carbocation **11a** could be generated from a bisabolyl cation intermediate (**10c**) via a C-C bond forming reaction (Scheme 1). On the other hand, the hypothetical triene intermediate **10d** could have arisen from an elimination of 3˚ carbocation intermediate **10c**. Further, it has been hypothesized that 3˚ carbocation intermediate **10e** possibly responsible for the synthesis of *ar*-Macrocarpene (**1**) via naturally occurring (*Z*)-γ-Macrocarpene (**1**).

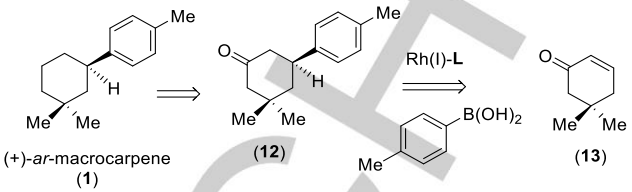


Scheme 1: A plausible biogenetic connections between different sesquiterpenes.

A number of reports has been directed toward the synthesis of natural sesquiterpenoids. In fact, soon after the isolation of *ar*-macrocarpene (**1**) in 2005, the first synthesis (racemic approach) of this secondary metabolite was featured by Srikrishna and co-workers in 2007.[11] However, there was no report of asymmetric total synthesis *ar*-macrocarpene (**1**) until very recently our report on the catalytic asymmetric synthesis via a key late-stage allylic diazene rearrangement (ADR) strategy (7 steps from commercially available 5,5-dimethylcyclohexane 1,3-dione),[12a] catalytic asymmetric enone reduction using Corey-Bakshi-Shibata catalyst as key steps (6 steps from commercially available 4,4-dimethylcyclohex-2-enone),[12b] and Pd(II)-catalyzed asymmetric conjugate addition of arylboronic acid onto (4 steps from commercially available dimidone).[12c] In spite of these approaches, there is still an urgent need for concise asymmetric synthesis of *ar*-macrocarpene **1** (Figure 1). Herein, we report a formal catalytic enantioselective total synthesis of (+)-*ar*-macrocarpene (**1**) via a key enantioselective Rh(I)-catalyzed arylboronic acid addition onto 5,5-dimethyl 2-cyclohexenone.[13]

Results and Discussion

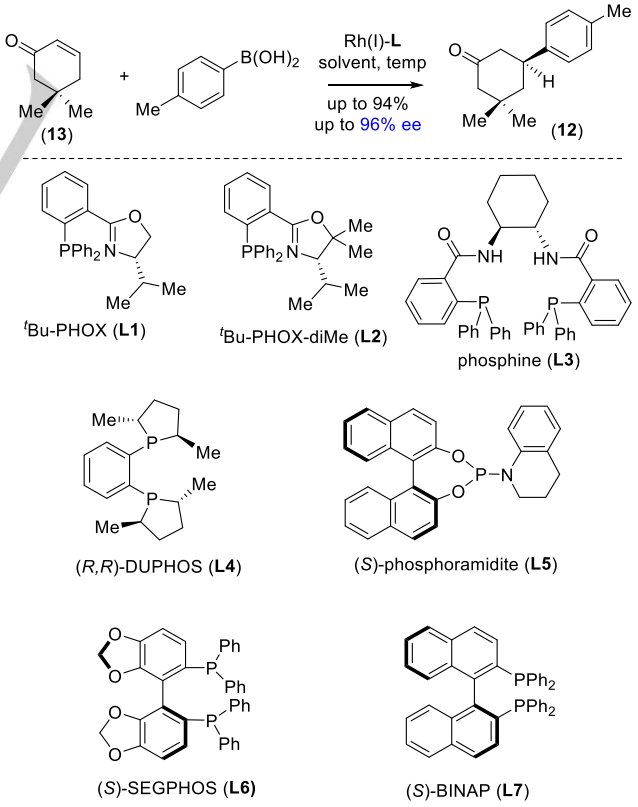
Retrosynthetically, we imagined that enantioenriched 3-arylcyclohexanone **12** may serve as an advanced intermediate for asymmetric synthesis (+)-*ar*-macrocarpene (**1**) via a Wolf-Kishner reduction,[12,14] which in turn could be accessed from a catalytic enantioselective (*p*-tolyl)boronic acid addition onto 5,5-dimethyl cyclohexen-2-one **13** (Scheme 2).[13]



Scheme 2: Retrosynthetic analysis of (+)-*ar*-macrocarpene (**1**).

For our synthesis, precursor 5,5-dimethyl cyclohexen-2-one **13** was synthesized from a well known Stork-Danheiser sequence of vinylogous ester.[12a, 12c] Initially, we carried out the optimization reaction using 1 equivalent of **13**[12c] with 2 equivalent of *p*-tolylboronic acid in the presence of 5 mol% $[Rh(COD)_2]BF_4$ in combination with 10 mol% of (*S*)-^{t}Bu-PHOX **L1** in tetrahydrofuran and water (10:1 mixture).[13] This reaction led to the formation of the expected product **12** in 90% isolated yield, however, with only 6% ee (entry 1). Therefore, we tested a number of phosphine based ligands such as ^{t}Bu-PHOX (**L2**), Trost's DACH ligand **L3**, and (*R,R*)-DUPHOS (**L4**), phosphoramidite **L5** to enrich enantioselectivity in product (Table 1). However, these reactions afforded only up to 34% ee with good yields (entries 1-5, table 1).

Table 1. Optimization of conjugate addition of 5,5-dimethyl cyclohexen-2-one **13**.



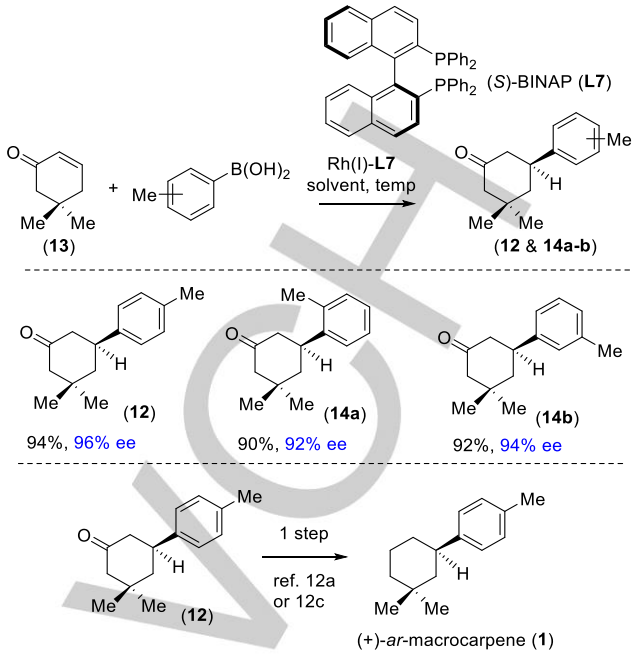
S. No.	Rh(I)-cat.	solvent	temp.	Time	yield[b]	ee[c]

1.	5 mol% Rh(I) & 10 mol% **L1**	THF:H_2O (10:1)	70 ºC	29 h	90%	12%[d]
2.	5 mol% Rh(I) & 10 mol% **L2**	THF:H_2O (10:1)	70 ºC	27 h	87%	21%[d]
3.	5 mol% Rh(I) & 10 mol% **L3**	(THF:H_2O (10:1)	70 ºC	30 h	85%	33%[d]
4.	5 mol% Rh(I) & 10 mol% **L4**	THF:H_2O (10:1)	100 ºC	29 h	79%	-21%[d]
5.	5 mol% Rh(I) & 10 mol% **L5**	THF:H_2O (10:1)	70 ºC	24 h	93%	34%[d]
6.	5 mol% Rh(I) & 6 mol% **L6**	THF:H_2O (10:1)	70 ºC	24 h	91%	89%[e]
7.	5 mol% Rh(I) & 10 mol% **L7**	THF:H_2O (10:1)	70 ºC	24 h	95%	90%[d]
8.	5 mol% Rh(I) & 10 mol% **L6**	dioxane:H_2O (10:1)	100 ºC	24 h	90%	91%[d]
9.	5 mol% Rh(I) & 10 mol% **L7**	dioxane:H_2O (10:1)	100 ºC	24 h	89%	93%[d]
10.	3 mol% Rh(I) & 6 mol% **L6**	dioxane:H_2O (10:1)	100 ºC	24 h	92%	93%[e]
11.	3 mol% Rh(I) & 6 mol% **L7**	dioxane:H_2O (10:1)	100 ºC	24 h	94%	96%[e]

[a]Reactions were carried out on a 1 mmol of **13** with 2 mmol of (*p*-tolyl)boronic acid in organic solvent and water (10:1 ratio). [b]Isolated yields after column chromatography. [c]ee's were determined by using chiralpak OD-H column. [d]substrate to catalyst ratio = 20:1. [e]substrate to catalyst ratio = 33:1.

Next, we carried out exhaustive optimization studies using axially chiral C2-symmetric bisphone ligands such as (*S*)-SEGPHOS (**L6**), and (*S*)-BINAP (**L7**). To our delight, it was found that corresponding product 3-(*p*-tolyl)-5,5-dimethyl cyclohexanone **12** was obtained in 91% yield with 89% ee, in dioxane:H_2O (10:1) at 70 °C in the presence of 5 mol% $[Rh(COD)_2]BF_4$ and 6 mol% of (*S*)-SEGPHOS (**L6**) ligand (entry 6, Table 1). Under similar conditions (*S*)-BINAP (**L7**) afforded cyclohexanone **12** in 90% ee (entry 7, Table 1).

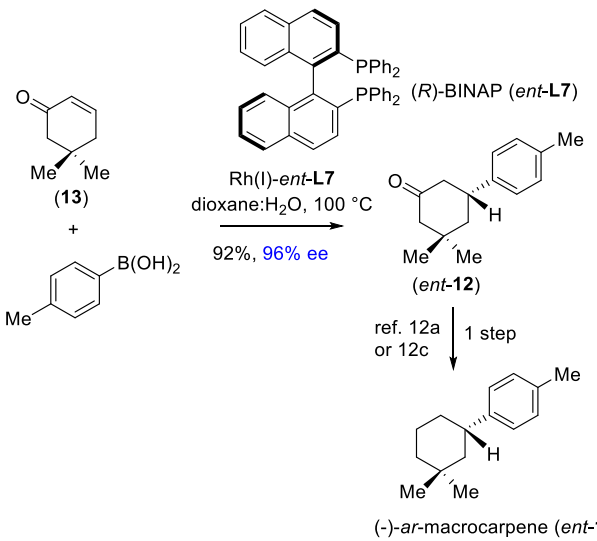
Further, by changing the solvent to dioxane and water (10:1), 6 mol% of (*S*)-SEGPHOS (**L6**) and (*S*)-BINAP (**L7**) furnished product **12** in 91% ee (entry 8) and 93% ee (entry 9), respectively. Noteworthy to observe was that a reaction in the presence of 3 mol% $[Rh(COD)_2]BF_4$ and 6 mol% of (*S*)-SEGPHOS (**L6**), compound **12** was obtained in 92% yield and 93% ee (entry 10). Delightfully, 3 mol% $[Rh(COD)_2]BF_4$ in combination with 6 mol% of **L7** afforded required 3-(*p*-tolyl)-5,5-dimethyl cyclohexanone **12** in 94% yield with 96% ee (entry 11).



[a]Reactions were carried out on a 1 mmol of **13** with 2 mmol of arylboronic acid in dioxane and water (10:1 ratio) in the presence of 3 mol% of $[Rh(COD)_2]BF_4$ in combination with 6 mol% (*S*)-BINAP. [b]ee's were determined by using chiralpak OD-H column. [c]Isolated yields after column chromatography.

Scheme 3. Substrate scope of arylboronic acid addition onto 5,5-dimethyl cyclohexen-2-one **13**.

Further, the optimized condition in hand, two aryl boronic acids sharing tolyl group were tested and the results are summarized in Scheme 4. As can be seen, 5,5-dimethyl-3-(tolyl)cyclohexanones (**14a-b**) could be synthesized in good yield (90-95% and excellent enantioselectivities (92-96% ee) in the presence of 3 mol% $[Rh(COD)_2]BF_4$ in combination with 6 mol% of (*S*)-BINAP (**L7**) (Scheme 3).



[a]Reactions were carried out on a 1 mmol of **13** with 2 mmol of arylboronic acid in dioxane and water (10:1 ratio) in the presence of 3 mol% of $[Rh(COD)_2]BF_4$ in combination with 6 mol% (*S*)-BINAP. [b]ee's were determined by using chiralpak OD-H column. [c]Isolated yields after column chromatography.

Scheme 4. Catalytic asymmetric (*p*-tolyl)boronic acid addition using Rh(I)-(*R*)-BINAP ligand (*ent*-**L7**).

Further in search for the asymmetric synthesis of naturally occurring sesquiterpenoid, (+)-*ar*-macrocarpene **1**, we have carried out the asymmetric (*p*-tolyl)boronic acid addition onto 5,5-dimethyl cyclohexen-2-one **11** using enantiomeric (*S*)-BINAP ligand (**L7**). Importantly, (*p*-tolyl)boronic acid addition onto **11** using 3 mol% of $[Rh(COD)_2]BF_4$ in combination with 6 mol% of **L7** furnished *ent*-**12** in 91% yield with 96% ee (Scheme 4).

Since, the total syntheses of (+)-**1** and (–)-*ent*-**1** are known from **12** (Scheme 3) and *ent*-**12** (Scheme 4), our effort culminated in formal total syntheses of (+)-*ar*-macrocarpene (**1**) and (–)-*ar*-macrocarpene (*ent*-**1**).

Conclusion

In conclusion, a formal total synthesis of naturally occurring sesquiterpenoid, (+)-*ar*-macrocarpene (**1**) has been developed from 5,5-dimethylcyclohex-2-enone **13**. The key step of this synthesis is the Rh(I)-catalyzed asymmetric conjugate addition of *p*-tolylboronic acid onto **13** in the presence of (*S*)-BINAP (up to 96% ee). Further asymmetric formal total synthesis of unnatural (–)-*ar*-macrocarpene (*ent*-**1**) has also been achieved with similar efficiency using Rh(I)-(*R*)-BINAP (96% ee). Further research to access other naturally occurring sesquiterpenoids is currently under active investigation in our laboratory.

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Keywords: Conjugate addition, (*p*-tolyl)boronic acid, Rh(I)-Catalyzed, Sesquiterpenoid, *ar*-Macrocarpene

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