Asymmetric Total Syntheses of Di- and Sesqui-Terpenoids via Catalytic C–C Activation of Cyclopentanones

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Abstract

To show the synthetic utility of the catalytic C–C activation of less strained substrates, here we describe collective and concise syntheses of natural products (−)-microthecaline A, (−)-leubehanol, (+)-pseudopteroxazole, (+)-*seco*-pseudopteroxazole, pseudopterosin A-F and G-J aglycones, and (+)-heritonin. The key step in these syntheses involve a Rh-catalyzed C–C/C–H activation cascade of 3-arylcyclopentanones, which provides a rapid and enantioselective route to access the polysubstituted tetrahydronaphthalene cores presented in these natural products. Other important features include (i) the direct C–H amination of the tetralone substrate in the synthesis of (−)-microthecaline A, (ii) the use of phosphoric acids to enhance efficiency and regioselectivity for problematic cyclopentanone substrates in the C–C activation reactions, and (iii) the direct conversion of serrulatane to amphilectane diterpenes via an allylic cyclodehydrogenation coupling.

Graphical Abstract
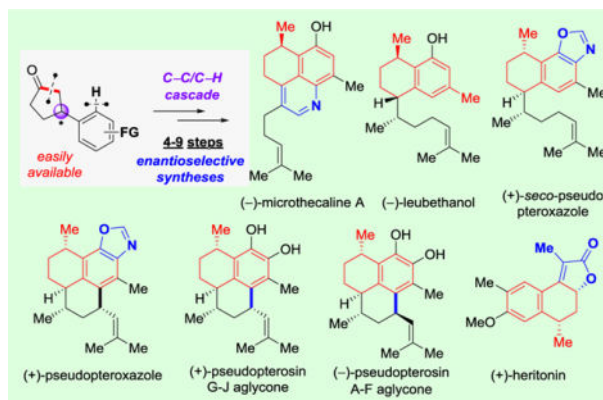
To show the synthetic utility of the Rh-catalyzed C–C/C–H activation cascade of 3-arylcyclopentanones, here we describe collective concise asymmetric syntheses of terpenoids (−)-microthecaline A, (−)-leubehanol, (+)-pseudopteroxazole, (+)-*seco*-pseudopteroxazole, pseudopterosin A-F and G-J aglycones, and (+)-heritonin (see scheme) in 4–9 steps.

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Keywords

C–C activation; Total synthesis; Terpenoid; Asymmetric synthesis; C–H activation

Introduction

Reactions involving cleavage of carbon–carbon (C–C) σ bonds, such as Baeyer-Villiger oxidation, Grob fragmentation and various rearrangement reactions (Schmidt, Cope, Wolff, Pinacol-type, Wagner–Meerwein, etc.), have found broad utilities in synthesis of complex and biologically active compounds.[1] Besides classical approaches, the transition metal-catalyzed C–C bond activation enables conversion of a relatively inert C–C bond to a more reactive C–metal bond under redox and near pH-neutral conditions.[2] therefore offering unique opportunities for unusual bond disconnections to access complex scaffolds from simpler substrates. To date, activation of highly strained three or four-membered rings has been employed as key steps in several total syntheses;[3,4] however, utility of methods that activate less strained 5-, 6-membered rings or linear substrates in constructing complex target molecules remain elusive,[5] as these methods often either are non-constructive (e.g. decarbonylation or fragmentation of the substrate) or need permanent directing groups (DGs).[6] Recently, through merging catalytic C–C and C–H activation, an initial approach was realized to transform 3-arylcyclopentanones and cyclohexanones into functionalized α-tetralones and α-indanones (Scheme 1).[7] In this full article, we describe our detailed efforts towards collective asymmetric syntheses of seven natural products in the serrulatane/amphilectane diterpene and cadinane sesquiterpene families, where catalytic C–C activation of cyclopentanones is employed as the key step to streamline construction of the tetrahydronaphthalene cores in these natural products.

α-Tetralones have been found in numerous bioactive compounds, and frequently serve as versatile building blocks in syntheses of complex natural products and pharmaceutical intermediates.[8,9] While a number of methods for preparing α-tetralones are available,[10] it remains challenging to introduce a stereocenter at the C4 position with controlled absolute stereochemistry.[11] Given that 3-arylcyclopentanones can be easily prepared in high enantioselectivity *via* asymmetric 1,4-addition,[12] the catalytic C–C/C–H cascade reaction therefore provides a rapid approach to access various C4-substiutted α-tetralones in a high enantiopurity (Scheme 1). To demonstrate the efficiency of this strategy, serrulatane diterpenes, such as (−)-microthecaline A, (−)-leubehanol and (+)-*seco*-pseudopteroxazole, amphilectane diterpenes, such as (+)-pseudopteroxazole, pseudopterosin A-F and G-J aglycones, and cadinane sesquiterpene (+)-heritonin have been chosen as the synthetic targets (Scheme 1).

Results and Discussion

Microthecaline A.

(−)-Microthecaline A (**1**) is a unique nitrogen-containing serrulatane-type natural product (Figure 1), isolated recently by the Davis group in 2018 from the roots of a Australian desert plant *Eremophila microtheca*.[13] It contains a penta-substituted quinoline scaffold and

exhibits antimalarial activity against *Plasmodium falciparum* (IC_{50} = 7.7 μM). Compared to a typical serrulatane diterpene, distinct features of microthecaline A include a nitrogen substituent at the C5 position and a higher oxidation at the C18 terminal carbon. To date, there is only one racemic synthesis of microthecaline A reported in 15 steps with a 5% overall yield.[14]

One key question to synthesize (–)-microthecaline A is how to efficiently introduce the C1 stereocenter and the C5 nitrogen moiety. We envisioned that the penta-substituted quinoline core in **1** could be constructed using the Friedländer Condensation between aldehyde **8** and amine-substituted α-tetralone **9** (Scheme 2). Aniline **9** could be possibly prepared via C–H amination of intermediate **10** in a straightforward manner. α-Tetralone **10** is expected to be synthesized through the catalytic C–C activation of 3-arylcyclopentanone **11** that can be conveniently accessed from 2-cyclopentenone and commercially available 1-bromo-2-methoxy-4-methylbenzene.

Our synthesis started with the asymmetric conjugation to prepare cyclopentanone **11** (Scheme 3). Lithiation of 1-bromo-2-methoxy-4-methylbenzene followed by *in situ* treatment with $B(OMe)_3$ generated the corresponding arylborate salt, which can directly participate in the Rh-catalyzed 1,4-addition of 2-cyclopentenone in the same reaction vessel. [15] Using $[Rh(COD)Cl]_2$ as the catalyst, the desired racemic cyclopentanone (**11**) was isolated in 98% yield. Moderate enantioselectivity was obtained with the $Rh(C_2H_4)_2(acac)/$ (*S*)-BINAP catalyst system;[15] switching to the $[Rh(C_2H_4)_2Cl]_2/(S,S)$-Ph-bod combination, 3-arylcyclopentanone **11** was isolated in a high yield with excellent optical purity (95% ee). [16] The key C–C activation reaction was investigated next. To our delight, under the previously reported conditions,[7a] the desired α-tetralone **10** was isolated in a 76% yield uneventfully with retention of high enantiopurity (92% ee), which is the major product through cleavage of the proximal C1–C2 bond; the undesired 1-indanone product (**10–1**) was generated in a 14% yield via cleavage of the distal C1–C5 bond and can be separated from the main product. Attempts to combine these two Rh-catalyzed steps were unfruitful, as different ligands were required for each step.

With α-tetralone **10** in hand, the next question was how to install an amino group at the C5 position (Scheme 4). Gratifyingly, bromination of the arene was found to occur selectively at the C5 instead of the C7 position; subsequent Buchwald-Hartwig amination followed by Boc-deprotection afforded the desired aniline **9** in a 63% yield over three steps. Given the high site-selectivity observed in the electrophilic bromination step, an intriguing question is whether direct electrophilic amination could be realized for α-tetralone **10**. To the best of our knowledge, the direct C–H (NH_2)-amination of arenes that contain a ketone substituent (like substrate **10**) has not been reported yet.[17] The challenge is *three-fold*: 1) as a strong electron-withdrawing group, the ketone moiety would deactivate the arene for electrophilic substitution; 2) the amine reagent or product could condense with the ketone to give imine side-products; and 3) amination at the enolizable ketone α position could be a side reaction pathway. Towards the end, a number of arene amination conditions have been evaluated (Table 1). Under the Ritter's condition with $MsONH_2$ as the electrophile and $FeSO_4$ as the catalyst,[17e] aniline **9** was not observed and substrate **10** was fully decomposed likely due to the elevated reaction temperature (entry 1, Table 1). Switching solvent to $MeCN/H_2O$ (2:1)

and running the reaction at room temperature (Morandi's condition),[17c] the desired aniline product (**9**) was isolated in 52% yield along with oxime **9–1** in 6% yield (entry 2, Table 1). Further tuning the reaction conditions, e.g. the reagent and catalyst loading and solvent, improved the yield to 68% without amination at other positions (entries 3–5, Table 1). Meanwhile, the Kurti/Falck's rhodium-catalyzed amination was also found to be efficient (entries 6–9, Table 1).[17b] Finally, after some modification of the reaction conditions, aniline **9** was isolated in 79% yield along with a separable minor isomer **9–2** in 14% yield (entry 9, Table 1).

The stage was now set for the Friedländer condensation[18] between aniline **9** and known aldehyde **8** (prepared in three steps from inexpensive dihydropyran)[19] to form the quinoline ring (Scheme 5). A number of conditions have been examined: while sulfuric acid, acetic acid and tosylic acid failed to promote this reaction, use of diphenylphosphoric acid in toluene afforded the desired quinoline **12** in 94% yield. Finally, removal of the methyl group by NaSEt gave (–)-microthecaline A (**1**) in 91% yield, which displays identical spectral and physical properties to those of natural sample.[13] Overall, the asymmetric total synthesis of (–)-microthecaline A (**1**) was completed in only *5 steps* in the longest linear sequence (LLS) with a 43% overall yield.

Serrulatane and Amphilectane Diterpenes.

Serrulatane and amphilectane diterpenes exhibit a broad spectrum of promising biological activities including anti-malarial, anti-inflammatory, analgesic, anti-tuberculosis and antibacterial, etc. (Figure 2).[20] Consequently, intensive efforts have been continuously devoted in the last three decades to the asymmetric syntheses of these natural products.[20a,b] Despite the seemingly uncomplex structures, significant challenges have been found for 1) controlling the relative and absolute stereochemistry for constructing these non-polar stereogenic centers and 2) synthesizing penta- and hexa-substituted benzene rings in most of these natural products. After seminar works by Broka[24a] and Corey[24b], a number of elegant and innovative synthetic approaches have been devised.[21–24] However, there is still room to develop a unified and concise route (with less than 10 steps) to access diverse serrulatane and amphilectane diterpenes.

A proposed general retrosynthetic strategy is described in Scheme 6. Compared to serrulatanes, amphilectane diterpenes contain an additional six-membered ring through bond forming at the C5 and C13 positions. Thus, a straightforward approach to access amphilectanes would be to directly oxidize the corresponding serrulatane at the allylic C13 position to forge C–C bond formation with the aromatic ring. Serrulatane diterpenes are expected to be assembled through coupling a tetrahydronaphthalene fragment (e.g. **13**) and an alkyl fragment (e.g. **14**). While a number of asymmetric sp^3-sp^3 cross coupling methods have been established,[25] we feel that Aggarwal's lithiation-borylation approach could be most suitable in this scenario to construct the C4-C11 bond with excellent control of the diastereoselectivity.[25b,26] The carbamate fragment **13** could be prepared from α-tetralone **15**, which would again be synthesized via the asymmetric conjugate addition and C–C/C–H cascade approach.[7a]

To examine the proposed strategy, (–)-leubethanol (**2**) was chosen as the first target, which is a serrulatane diterpene isolated from the roots of *Leucophyllum frutescens* by Waksman in 2011[22a] with a promising level of *anti*-tuberculosis activity (MIC 6.25–12.50 μg/mL). In a forward manner, α-tetralone **10** (prepared in the prior section) was first converted to the secondary alcohol (**17**) in an excellent yield and 7:1 dr under the Noyori asymmetric reduction[27] conditions (Scheme 7). Note that enantio-enrichment (92% ee→ 99% ee) was observed in this situation, as the minor enantiomer of **10** became the minor diastereomer of **17**.[28] Carbamoylation with *N*,*N*-diisopropylcarbamoyl chloride (CbCl) delivered carbamate **18**, which can then be used to couple with the chiral organoborane fragment (*S*-**14**, prepared in three steps from 5-bromo-2-methyl-2-pentene) using Aggarwal's lithiation-borylation reaction.[9d] The treatment of TBAF gave primarily retention of the stereochemistry at the C4 position;[26b] the major desired diastereomer (**19**) can be isolated in its pure form. Upon removal of the methyl group in a good yield, synthesis of (–)-leubethanol (**2**) was furnished in *6 LLS steps* and a 29% overall yield.

The syntheses of structurally related terpenoids **3**-**6** were pursued next. Compared with (–)-leubethanol (**2**), these terpenoids exhibit opposite stereochemistry at the C1 and C4 positions, as well as an additional substituent at the C7 position (Figure 2).

The synthesis started with preparing boronic acid **20** on a decagram scale via *ortho* lithiation of commercially available 2,3-dimethoxytoluene followed by quenching with trimethylborate (Scheme 8).[29] The Rh-catalyzed asymmetric 1,4-addition proceeded efficiently to deliver cyclopentanone **21** in 98% yield with 98% ee using (*R*,*R*)-Ph-bod as the chiral ligand.[30] Under the standard conditions for the C−C activation of 3-arylcyclopentanones,[7a] however, only moderate conversions for the desired α-tetralone product (**22**) were observed (entry 1, Table 1). This is likely due to the presence of the OMe group *para* to the aryl C−H bond to be activated (*vide infra*, Table 3), as the resulting electron-rich aryl group could destabilize the aryl–Rh intermediate (or transition state) during the C−H activation step.[7a] A solution was ultimately found: by changing the acid co-catalyst from TsOH to $(PhO)_2PO_2H$ (10 mol%), both the conversion and selectivity were notably enhanced. It is possible that $(PhO)_2PO_2H$ promoted the C−H arene metalation step to some extent,[31] though the exact reason remains to be disclosed. Eventually, α-tetralone **22** was isolated in *77% yield and 94% ee* (entry 3, Table 2). Increasing the loading of 2-aminopyridine (**C1**) decreased the tetralone/indanone selectivity (entry 4, Table 2). In addition, changing aminopyridine from simple **C1** to a more electron-rich **C2** only gave a moderate yield with 83% ee, though the tetralone/indanone selectivity was improved. Subsequent Noyori asymmetric reduction of the ketone moiety and carbamate formation, followed by Aggarwal's lithiation-borylation reaction (*vide supra*, Scheme 8), afforded the key serrulatane intermediate **24** with the desired stereochemistry at the C1, C4 and C11 positions (different from leubethanol).

To access amphilectane diterpenes, the remaining challenge was to form the C5–C13 bond (Scheme 9). Conversion of olefin **24** to allylic alcohol **25** was realized though oxyselenation and oxidative elimination.[32,33] The expected cyclization was found to be effectively promoted by $MeSO_3H$ or $BF_3 \cdot Et_2O$ to deliver amphilectane-type compounds **26** and **27**, and it appears that these two acids showed somewhat opposite diastereoselectivity. It is

interesting to observe that tricyclic compounds **26** and **27** were formed simultaneously in a high yield from a $CDCl_3$ solution in NMR tube after 4 days, likely due to a trace amount of acid in the NMR solvent.[28] While this two-step protocol is efficient, it would be more attractive to realize a direct *cross-dehydrogenative-coupling* (CDC)[34] at the C5/C13 positions, which, to our knowledge, has not been reported in the syntheses of these types of natural products. If an allyl cation or an allyl radical could be generated at the C13 position, such a species would in principle be trapped by the arene to form the C5–C13 bond. However, the challenge of this CDC strategy is also obvious: substrate **24** contains a number of weak C–H bonds; therefore, besides the *three allylic* positions, oxidation at the tertiary and benzylic C1 and C4 positions could be a significant concern. In addition, the arene moiety in substrate **24** is highly electron-rich, thus selective allylic oxidation instead of arene oxidation would also be difficult. After examining numerous allylic oxidation conditions,[35] including the use of transition-metal catalysts, e.g. $Pd(OAc)_2$/BQ, $Pd(TFA)_2$, and $[RhCp*Cl_2]_2$,[36] finally the treatment with *o*-chloranil in MeCN at room temperature was found to be most effective.[37] DDQ also afforded the desired products albeit in a lower yield (30%).[28] Diastereomeric compounds **26** and **27** can be readily separated by reverse phase HPLC.

With compounds **26** and **27** in hand, removal of the methyl protecting groups afforded (+)-pseudopterosin G-J aglycone (**5**) and (–)-pseudopterosin A-F aglycone (**6**), respectively (Scheme 9); the deprotection of compounds **24** and **26** followed by a one-pot oxidative oxazole formation furnished the total syntheses of (+)-*seco*-pseudopteroxazole (**3**) and (+)-pseudopteroxazole (**4**) in 8 and 9 LLS steps, respectively. [23e,38]

(+)-Heritonin.

The application of the catalytic C–C activation of cyclopentanones could also be demonstrated in the enantioselective synthesis of (+)-heritonin (**7**), which was isolated from the mangrove plant *Heritiera littoralis* in 1989 by Miles and belongs to the family of cadinane sesquiterpenes.[39] this nnatural product exhibits potent piscicidal activity and has been used by local fishermen to kill invasive fishes. To date, a number of synthetic routes have been reported to access heritonin;[40] however, only two of them are asymmetric, which require 9–15 steps.[11a,40h] We proposed that the α-tetralone intermediate (**28**) (Scheme 10) in Chavan's synthesis[11a] could be accessed by the C–C/C–H cascade approach in a convenient manner, which would lead to a streamlined preparation of **7**.

Following the same procedure of preparing compound **11**, compound **29** was obtained in 95% yield and 99% ee with the $[Rh(C_2H_4)_2Cl]_2$/(*R*, *R*)-Ph-bod catalyst system (Scheme 10). As expected, the presence of the *meta* OMe group (*vide supra*, Table 2) in cyclopentenone **29** posted substantial difficulty for the key C–C activation reaction. Using the original C–C activation conditions,[7a] the desired α-tetralone **28** was only obtained in 19% yield with 77% ee (entry 1, Table 3). After examining various acid co-catalysts, the desired tetralone **28** was ultimately isolated in 68% yield (83% ee) by switching TsOH to the binol-derived phosphoric acid (*rac*-**acid 1**)[41] with 20 mol% aminopyridine **C1** (entry 2, Table 3). After recrystallization, 91% ee was obtained, which can be used in the next step. Use of $(PhO)_2PO_2H$, the best acid for substrate **21**, gave a high conversion but somewhat a lower

yield and selectivity (entry 3, Table 3). Increasing the loading of 2-aminopyridine **C1** reduced the tetralone/indanone selectivity (entry 4, Table 4). Interestingly, use of the more electron-rich aminopyridine (**C2**) instead gave the desired product **28** in a high yield and excellent selectivity, albeit with a low optical purity (entry 5, Table 4). Further enhancing the reaction temperature only led to a diminished yield (entry 6, Table 4).

At this stage, formal synthesis of heritonin was accomplished; however, a different end-game from Chavan's synthesis[11a] was pursued via merging merits of other routes. Stereoselective α-hydroxylation of tetralone **28** gave compound **30** with a 7:1 dr.[40h] After further recrystallization, 96% ee and >20:1 dr could be obtained. Finally, the tandem acylation/Wittig olefination[40f] afforded (+)-heritonin (**7**) in a good yield.

Conclusion

In summary, the use of catalytic C–C activation of cyclopentanones as a key step has been illustrated in the enantioselective total syntheses of a range of di- and sesqui-terpenoids **1**-**7** in 4–9 steps. This strategy can accelerate asymmetric construction of the polysubstituted tetrahydronaphthalene cores, therefore significantly simplifying the overall syntheses. In addition, some other features, such as (i) the direct C–H amination of the tetralone substrate in the synthesis of (–)-microthecaline A, (ii) the use of phosphoric acids to enhance efficiency and selectivity for problematic substrates in the C–C activation reactions and (iii) the *direct* conversion of serrulatane to amphilectane diterpenes via an allylic cyclodehydrogenation, should have implications beyond this work.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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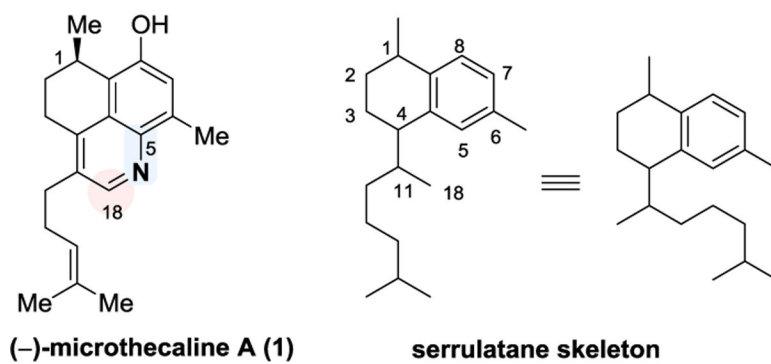[41]. Optically pure (*R*) or (*S*)-**acid 1** gave almost the same results as *rac*-**acid 1** in this reaction.

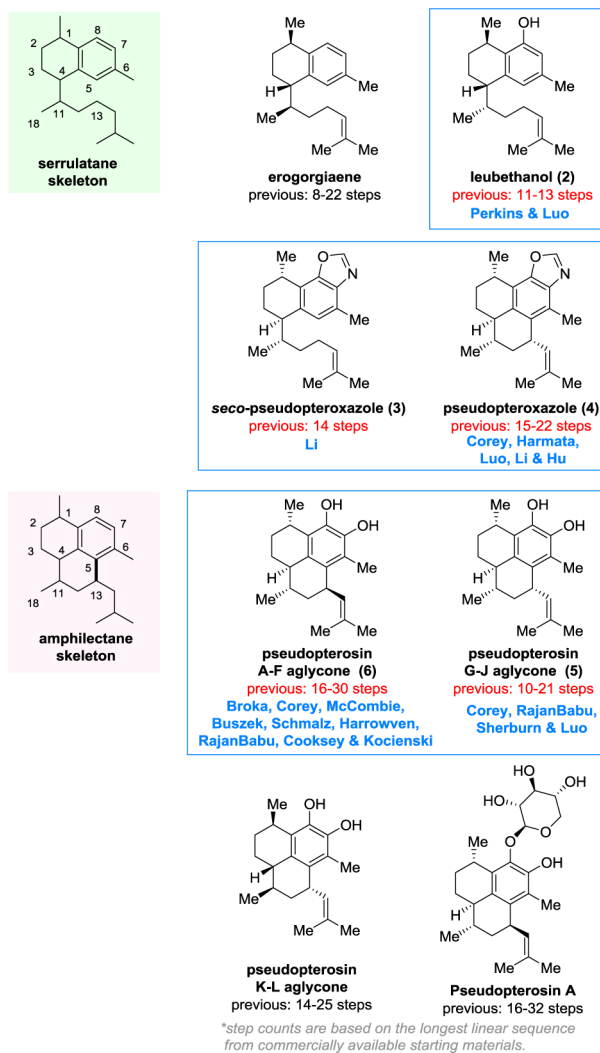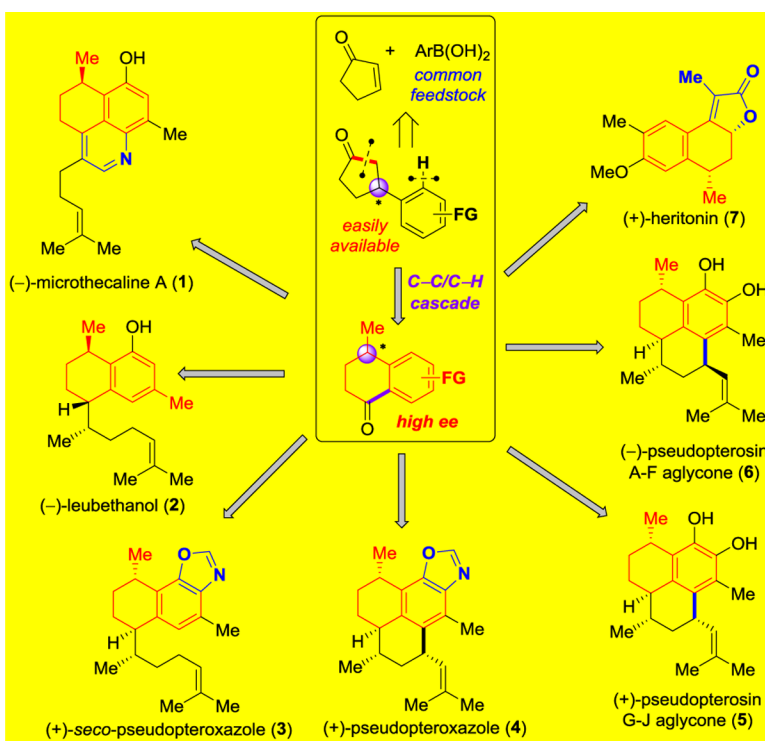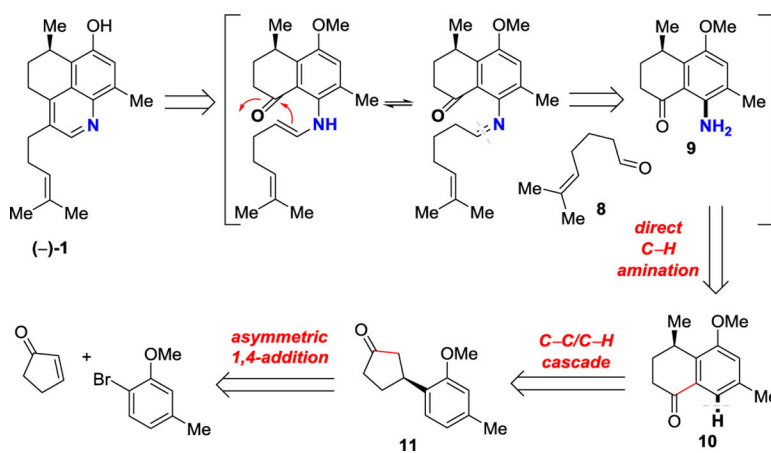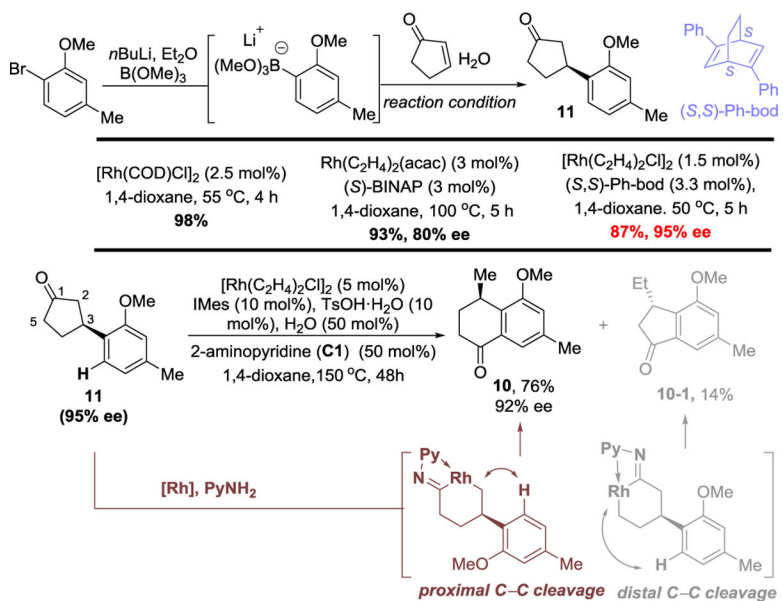**Figure 1.**
Structure of (–)-Microthecaline A (1).

Figure 2.
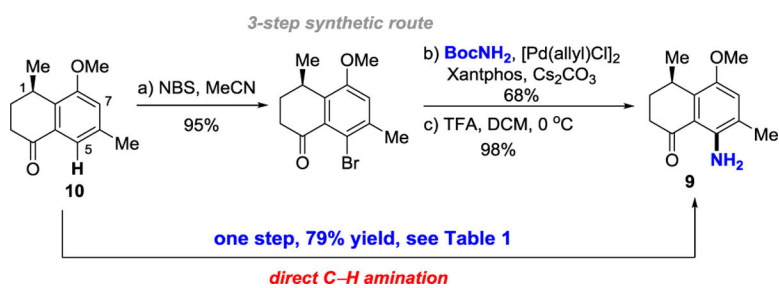Examples of Serrulatane and Amphilectane Diterpenoids.

Scheme 1.
Collective Asymmetric Syntheses of Serrulatane/Amphilectane Diterpene and Cadinane Sesquiterpene Nature Products via Catalytic Activation of C–C bonds in 3-Arylcyclopentanones.

Scheme 2.
Retrosynthetic Analysis of (–)-Microthecaline A (1).

Scheme 3.
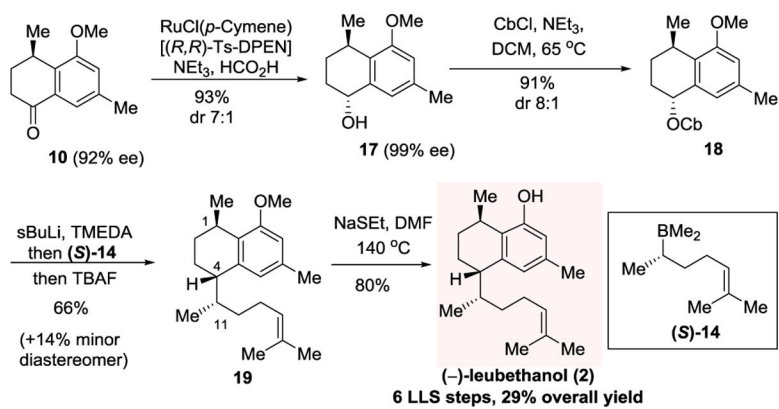
Synthesis of α-Tetralone **10**.

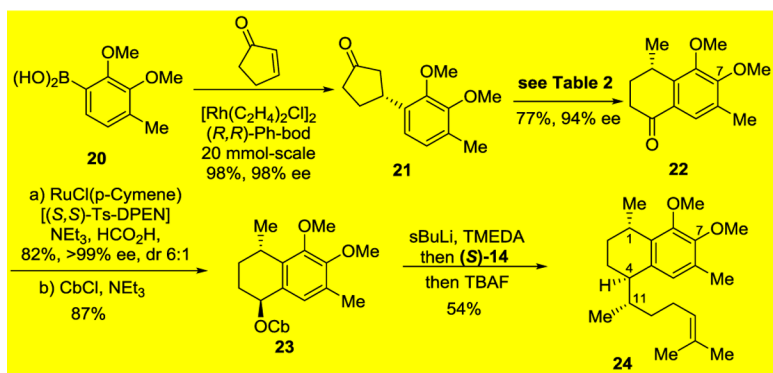**Scheme 4.**
Synthesis of Aniline **9**.
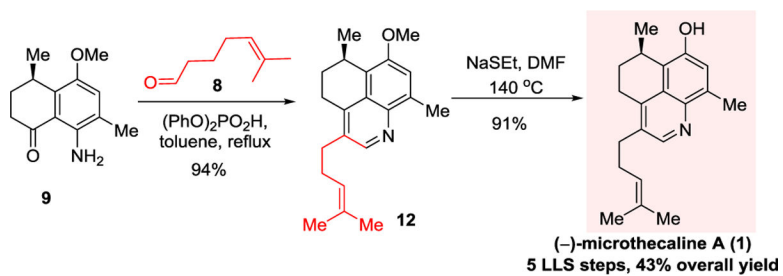
Scheme 5.
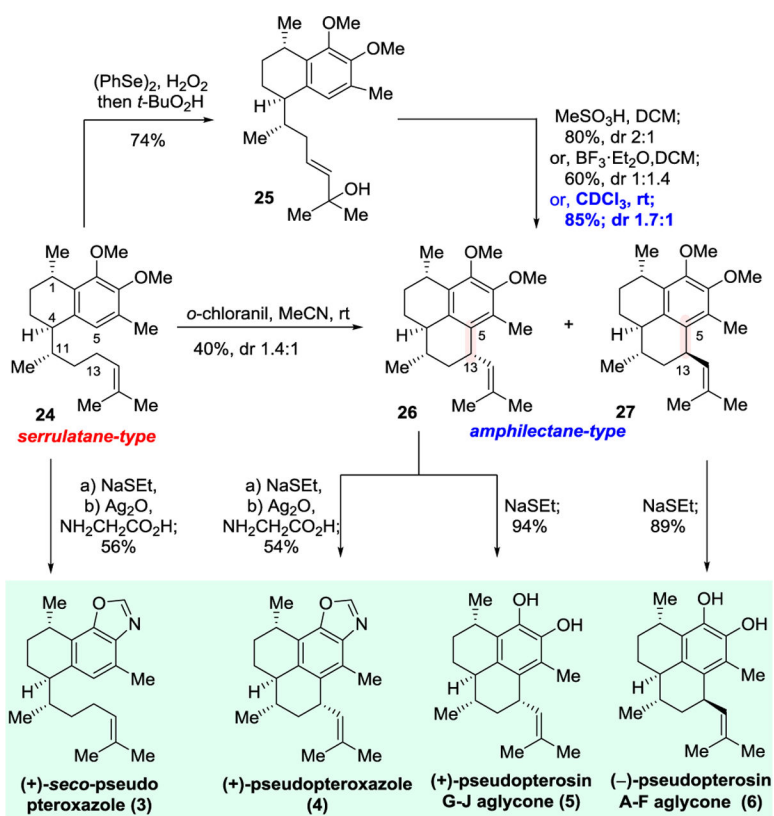Completion of the Total Synthesis of (–)-Microthecaline A (**1**).
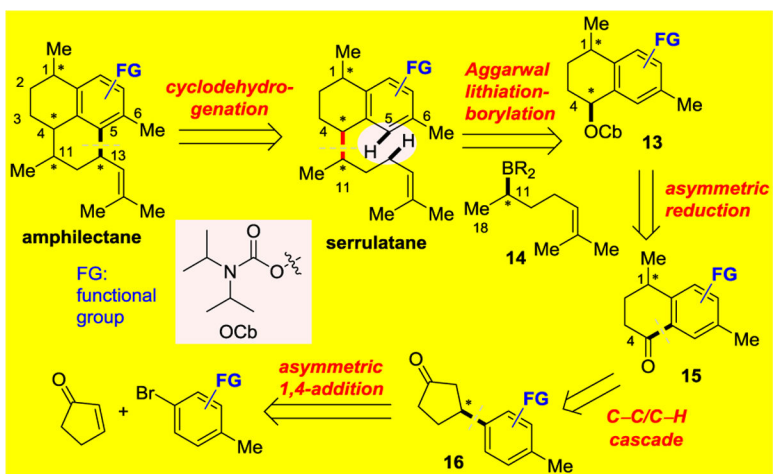
Scheme 6.
A General Streamlined Strategy for Preparing Serrulatane and Amphilectane Diterpenoids.
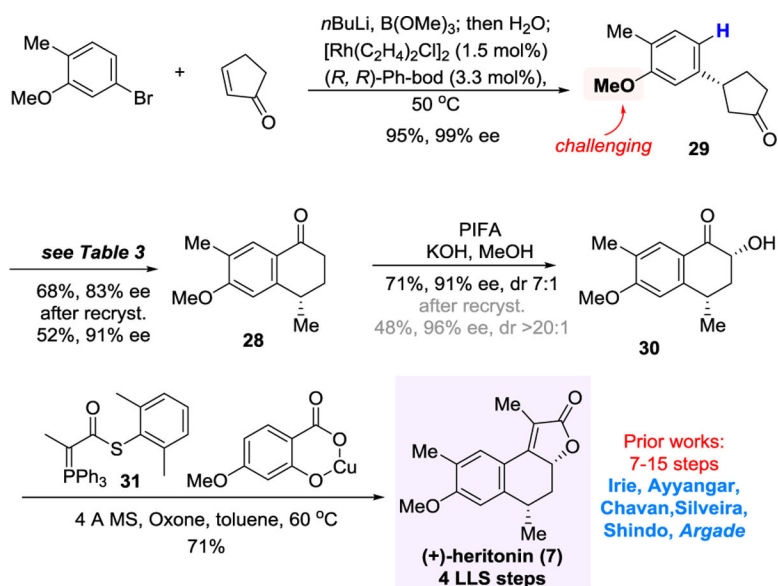
Scheme 7.
Total Synthesis of (−)-Leubethanol (**2**).
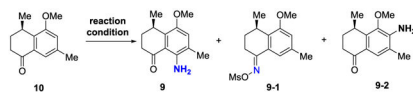
Scheme 8.
Synthesis of Key Intermediate **24**.

Scheme 9.
Conversion of Serrulatane to Amphilectane-type Diterpenes and Total Syntheses of **3**-**6**.

Scheme 10.
Total Synthesis of (+)-Heritonin (**7**).

Table 1.

Optimization of the Direct C–H Arene Amination.

entry	reaction condition[a]	yield[b]			
		9	**9–1**	**9–2**	**10**
1	MsONH$_2$ HOTf (2 equiv.),FeSO$_4$-7H$_2$O (1 mol%), HFIP, 60 °C, 24h	n.d.[c]	n.d.	n.d.	n.d.
2	MsONH$_2$ HOTf (2 equiv.), FeSO$_4$ 7H$_2$O (5 mol%), MeCN/H$_2$O (2:1, 0.1 M), rt, 24h	52%	6%	n.d.	20%
3	MsONH$_2$ HOTf (4 equiv.), FeSO$_4$-7H$_2$O (5 mol%), MeCN/H$_2$O (2:1, 0.1 M), rt, 24 h	38%	< 2%	n.d.	< 2%
4	MsONH$_2$ HOTf (3.5 equiv.), FeSO$_4$-7H$_2$O (10 mol%), TFE/H$_2$O (2:1, 0.1 M), rt, 12h	61%	n.d.	n.d.	n.d
5[d]	MsONH$_2$ HOTf (4.5 equiv.), FeSO$_4$ 7H$_2$O (5 mol%), MeCN/H$_2$O (2:1, 0.1M), rt, 48 h	68%	< 5%	n.d.	n.d.
6	MesONHBoc (1.5 equiv.), Rh$_2$(esp)$_2$ (2 mol%), TFA (2 equiv.), HFIP (0.1 M), rt, 40h	6%	n.d.	6%	48%
7	TsONHBoc (1.5 equiv.), Rh$_2$(esp)$_2$ (2 mol%), TFA (2 equiv.), HFIP (0.1 M), rt, 40h	64%	n.d.	13%	n.d.
8	TsONHBoc (1.5 equiv.), Rh$_2$(esp)$_2$ (2 mol%), TFA (2 equiv.), TFE (0.1 M), rt, 40h	73%	n.d.	13%	n.d.
9	TsONHBoc (1.3 equiv.), Rh$_2$(esp)$_2$ (2 mol%), TFA (1.5 equiv.), TFE (0.1 M), rt, 24h	**79%**	n.d.	14%	n.d.

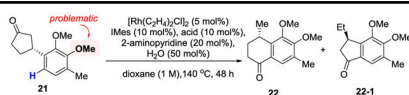[a] The reaction was run on a 0.1 mmol scale.
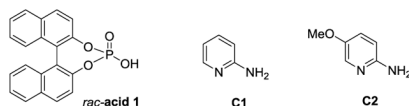
[b] Isolated yield.

[c] Not detected.

[d] MsONH$_2$·HOTf was added portion-wise to the reaction mixture in 3 times.

Table 2.

Optimization of the C−C Activation of Cyclopentenone **21**.[a]

entry	acid	2-aminopyridine	conversion %[b]	22			22–1	rr[d]
				yield/%[b]	ee/%[c]		yield/%[b]	
1	TsOH	**C1**	50	33	94		10	3.1:1
2	*rac*-**acld 1**	**C1**	77	55	96		9	6.2:1
3	(PhO)$_2$PO$_2$H	**C1**	>95	**81 (77)**[e]	**94**		13	6.2:1
4[f]	(PhO)$_2$PO$_2$H	**C1**	>95	73	95		17	4.2:1
5	(PhO)$_2$PO$_2$H	**C2**	77	48	83		8	7.8:1

[a] The reaction was run on a 0.2 mmol scale.

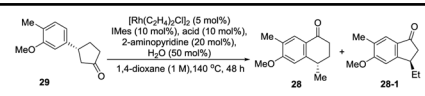[b] NMR yields using dibromomethane as the internal standard.

[c] Determined by chiral HPLC.

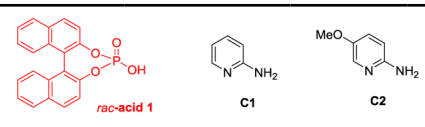[d] Ratio between **22** and **22–1**.

[e] Numbers in parentheses are isolated yields.

[f] The loading of **C1** was 25 mol%.

Table 3.

Optimization of the C−C Activation of Cyclopentenone **29**[a]

entry	acid	2-aminopyridine	conversion %[b]	28 yield/%[b]	ee/%[c]	28–1 yield/%[b]	rr[d]
1	TsOH	**C1**	60	19	77	5	4:1
2	*rac*-**acid 1**	**C1**	89	75 (68)[e]	83	10	7.5:1
3	(PhO)₂PO₂H	**C1**	93	61	70	7	5.7:1
4[f]	*rac*-**acid 1**	**C1**	87	63	79	22	2.9:1
5	*rac*-**acid 1**	**C2**	>95	84 (76)[e]	47	5	16:1
6[g]	*rac*-**acid 1**	**C1**	93	57 (52)[e]	79	7	8.3:1

[a]The reaction was run on a 0.2 mmol scale.

[b]NMR yields using dibromomethane as the internal standard.

[c]Determined by chiral HPLC.

[d]Ratio between **28** and **28–1**.

[e]Numbers in parentheses are isolated yields.

[f]The loading of **C1** was 25 mol%.

[g]The reaction temperature was 150 °C