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RESEARCH ARTICLE

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Total Synthesis of Liangshanone

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Dedication ((optional))

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Abstract: The first total synthesis of a hexacyclic *ent*-kaurane diterpenoid alkaloid, liangshanone, has been completed. Its intricate cage-like framework was assembled through several key transformations including an oxidative dearomatization/Diels-Alder (OD/DA) cycloaddition sequence, a tandem alkene cleavage/Mannich cyclization, a Robinson-type annulation, and an intramolecular aldol reaction. Notably, an organocatalytic enantioselective α-hydroxymethylation process allowed the preparation of the enantioenriched tricycle **15a** that should enable asymmetric access to the target natural product.

The C_{20}-diterpenoid alkaloids represent a category of fascinating natural products that are biogenetically derived from two classes of diterpene precursors, namely, the *ent*-atisanes and *ent*-kauranes.[1] The major types of *pseudo*-alkaloids from the *ent*-atisane diterpenes (e.g., atisines, hetidines, hetisines, and denudatines; Figure 1A) structurally feature typical bicyclo-[2.2.2]octane C/D rings. In contrast, the alkaloidal compounds originating from the *ent*-kaurane class (e.g., veatchines, anopterines, napellines, and aconicarmisulfonines; Figure 1B) contain bicyclo[3.2.1]octane C/D fragments.[2] All the aforementioned diverse types of C_{20}-diterpenoid alkaloids possess highly complex and cage-like architectures. These features, combined with their intriguing bioactivities, rendered the C_{20}-diterpenoid alkaloids challenging targets for synthetic chemists.[3] While total synthesis of the *ent*-atisane diterpene-derived alkaloids has been the focus of research for decades that resulted in numerous creative synthetic approaches,[4–8] successful access to the *ent*-kaurenoid alkaloids remains limited.[9,10]

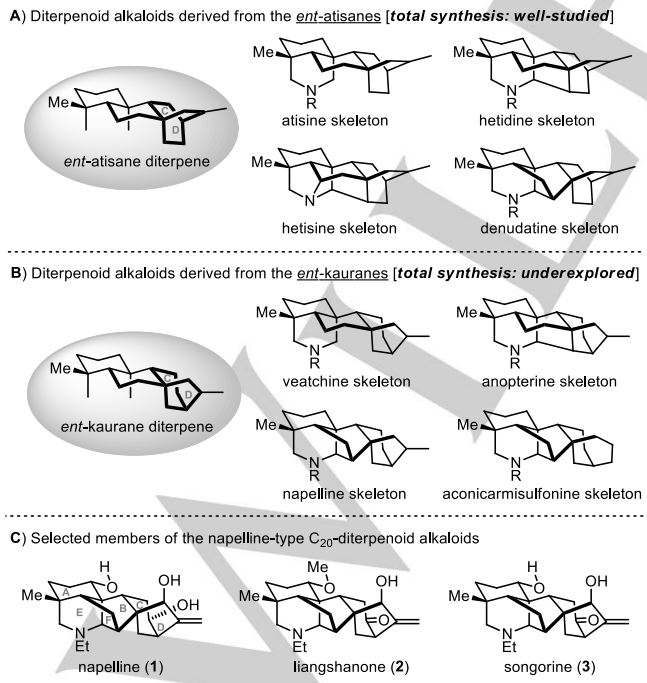
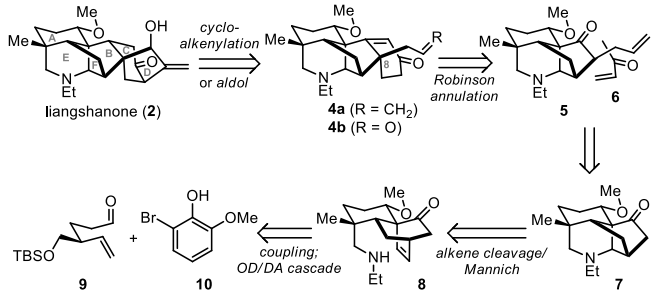


Figure 1. A) Diterpenoid alkaloids derived from the *ent*-atisanes; B) diterpenoid alkaloids derived from the *ent*-kauranes; C) selected members of the napelline-type C_{20}-diterpenoid alkaloids.

Among various types of the *ent*-kaurenoid alkaloids, the napellines (e.g., **1**–**3**,[11] Figure 1C) are structurally characterized by a compact hexacyclic framework bearing an azabicyclo[3.3.1]nonane (A/E rings), a bicyclo[2.2.1]heptane (B/F rings), and a bicyclo[3.2.1]octane (C/D rings) moieties. Such molecules display a wide spectrum of pharmacological effects involving antiarrhythmic, anti-inflammatory, anti-nociceptive, and anxiolytic activities.[12] To date, the only known total synthesis of a napelline-type alkaloid (i.e., **1**, racemic form) was achieved by Wiesner and colleagues with a longest linear sequence of over 45 steps.[10] As part of our continuous pursuit to synthesize architecturally intricate diterpenoid alkaloids,[3c,e,4j,8a,d] herein we report the first total synthesis of the napelline alkaloid liangshanone (**2**).

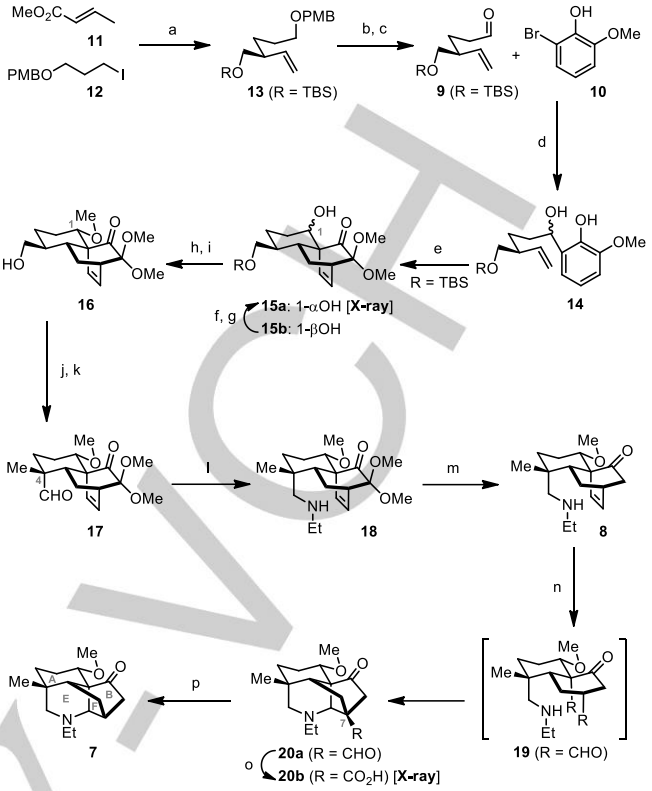
Illustrated in Scheme 1 is our retrosynthetic analysis of liangshanone (**2**). Disassembly of the bicyclo[3.2.1]octane moiety in the target natural product **2** led back to pentacyclic **4a** or **4b**. An intramolecular cycloalkenylation[13] of alkene **4a** or an aldol addition of aldehyde **4b** would establish the desired bridged C/D ring system. We envisioned that **4a**/**b** could be accessed from ketone **5** and methyl vinyl ketone (MVK, **6**) through a Robinson annulation. The crucial C8 stereocenter in **4a**/**b** could be secured by approach of MVK from the sterically less hindered convex face of the tetracyclic intermediate **5**. In turn, **5** could arise via α-alkylation of ketone **7**. At this stage, a key transformation in our synthetic design would be the assembly of tetracyclic core **7** from tricycle **8** through a tandem reaction sequence of oxidative cleavage of cycloalkene[14] and Mannich cyclization. Compound **8** could be obtained from aldehyde **9** and bromophenol **10** via the coupling of both fragments, followed by an oxidative dearomatization/Diels-Alder cycloaddition (OD/DA) cascade.[3e,15]



Scheme 1. Retrosynthetic analysis of liangshanone (**2**).

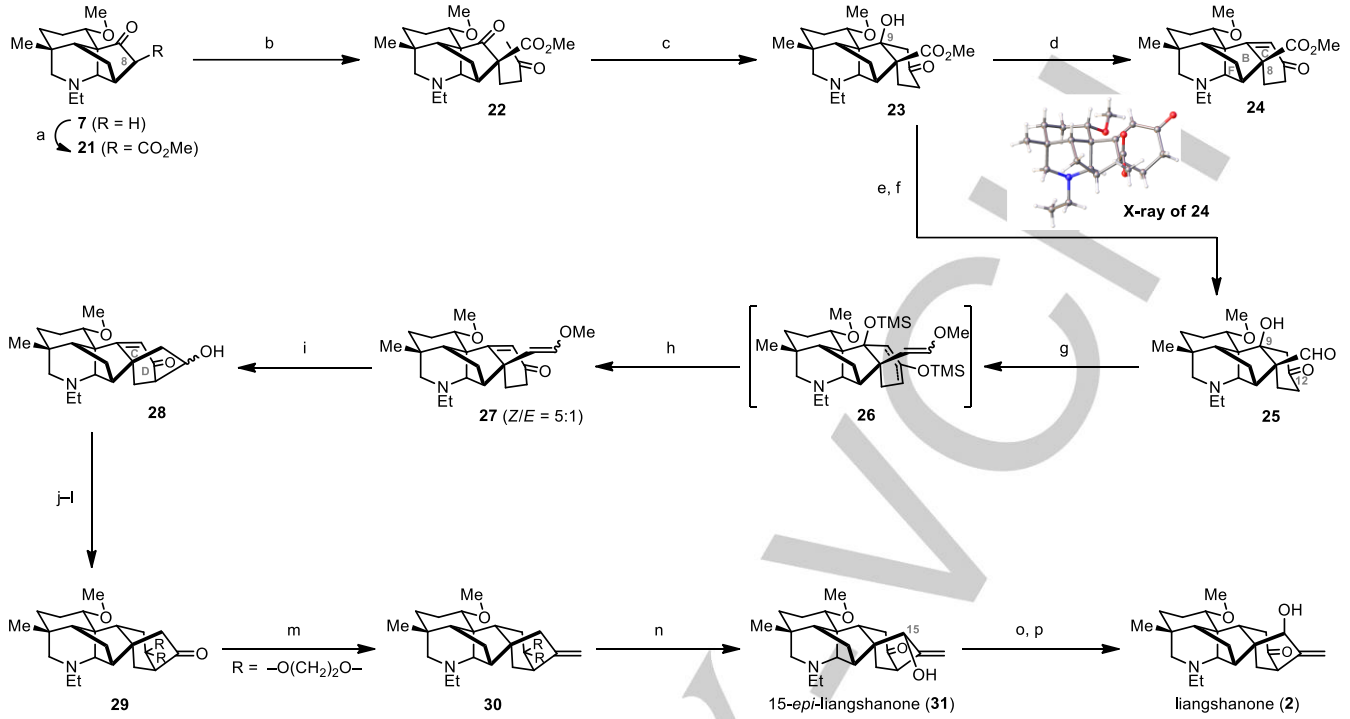
We commenced our synthesis with the preparation of aldehyde **9** (Scheme 2). Deconjugative alkylation of methyl crotonate (**11**) with known iodide **12**[16] in the presence of LDA/HMPA, followed by reduction of the carboxylic ester with $LiAlH_4$ and protection of the resultant primary hydroxyl group with TBSCl, generated alkene **13** in a one-pot manner with 60% overall yield. Note that conducting the above three-step transformation separately gave an inferior isolate yield of product **13** compared to that of the one-pot procedure. Exposure of **13** to DDQ effected removal of the PMB group; the resultant alcohol was then oxidized with DMP to efficiently afford the expected aldehyde **9**. After a lithium-bromine exchange of **10** in the presence of *n*BuLi at –78 ºC, addition of the generated lithium species to aldehyde **9** produced diol **14** as a pair of inseparable diastereomers (82% combined yield, 5:4 *d.r.*). Next, the OD/DA cascade reaction was investigated. As a result, treating phenol **14** with $PhI(OAc)_2$/MeOH facilely produced a dimerized cycloadduct mixture (structure not shown) after the dearomatization process, which, upon heating in mesitylene at 180 ºC, underwent tandem retro Diels-Alder/intramolecular Diels-Alder cycloaddition[4i,17] to deliver a pair of separable diastereomers **15a** (48% yield) and **15b** (39% yield) with exclusive *endo*-selectivity. The structure of the desired isomer **15a** with an α-oriented hydroxyl group at C1 was determined by X-ray crystallography,[18] and the undesired **15b** could be smoothly converted to **15a** via an oxidation and selective reduction sequence. After installation of the requisite C1 methoxy group in **15a**, the ensuing desilylation reaction took place with TBAF to provide alcohol **16** in 95% yield. Next, subjecting **16** to DMP oxidation followed by diastereoselective α-methylation of the resultant aldehyde secured the C4 quaternary stereocenter,[19] thereby delivering compound **17** in 72% yield over two steps. Reductive amination of aldehyde **17** occurred employing $EtNH_2$•HCl/$NaBH_3CN$ to give amine **18** (88% yield). Subsequent removal of the two methoxy groups in **18** with SmI_2 in THF/MeOH afforded **8**. The above approach easily supplied tricyclic **8** in multigram quantities.

We then focused on construction of the A/B/E/F tetracyclic core of liangshanone through a sequence of alkene oxidative cleavage, Mannich cyclization, and decarbonylation (Scheme 2). Initially, subjecting **8** to the standard ozonolysis conditions (O_3, –78 ºC; then PPh_3, 0 ºC), followed by successively treating the resultant mixture with Et_3N, allowed us to detect a trace amount of tetracyclic aldehyde **20a** via LC-MS. It is likely that the secondary amine group in **8** was labile under the above-mentioned oxidative conditions. Thus, an in situ formed TFA salt of amine **8** was employed in the following optimization studies. As anticipated, exposure of such a salt form to the same



Scheme 2. Construction of the A/B/E/F tetracycle **7**. Reagents and conditions: a) LDA, HMPA, **11**, –78 °C, THF; then **12**, –78 °C; then $LiAlH_4$, 0 °C; then TBSCl, imidazole, RT, 60%; b) DDQ, CH_2Cl_2/H_2O (10:1), RT, 95%; c) DMP, $NaHCO_3$, CH_2Cl_2, RT, 89%; d) *n*BuLi, THF, 0 to –78 °C, 82%, 5:4 *d.r.*; e) $PhI(OAc)_2$, $NaHCO_3$, MeOH, RT; then mesitylene, 180 °C, **15a** (48%), **15b** (39%); f) DMP, $NaHCO_3$, CH_2Cl_2, RT, 93%; g) $NaBH(OMe)_3$, THF, –78 °C, 73%, 7:1 *d.r.*; h) MeI, NaH, THF, 0 to 30 °C, 92%; i) TBAF, THF, RT to 60 °C, 95%; j) DMP, $NaHCO_3$, CH_2Cl_2, RT, 90%; k) MeI, *t*BuOK, THF, –10 °C, 80%; l) $EtNH_2$·HCl, Et_3N, HOAc, MeCN, RT; then $NaBH_3CN$, RT, 88%; m) SmI_2, MeOH, THF, 0 °C, 93%; n) TFA, O_3, –78 °C, CH_2Cl_2; then PPh_3, 0 °C; then *t*$BuNH_2$, RT, 80%; o) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*BuOH/H_2O (1:1), RT, 95%; p) NHPI, DIC, DMAP, CH_2Cl_2, RT; then Zn, $NiCl_2$·$6H_2O$/di-*t*Bubipy, $PhSiH_3$, DMF, THF, 50 °C, 53%. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, DMAP = *N,N*-4-dimethylaminopyridine, DMP = Dess-Martin periodinane, DIC = diisopropyl carbodiimide, di-*t*Bubipy = 4,4'-di-*tert*-butyl-2,2'-dipyridyl, HMPA = hexamethylphosphoric acid triamide, LDA = lithium diisopropylamide, NHPI = *N*-hydroxyphthalimide, PMB = *p*-methoxybenzyl, TBAF = tetra-*n*-butylammonium fluoride, TBS = *t*-butyldimethylsilyl, TFA = trifluoroacetic acid.

oxidative cleavage conditions resulted in an improved yield of **20a** (28% yield; see the SI) after sequential reaction with Et_3N. Presumably, the active dialdehyde intermediate **19** generated by ozonolysis of **8** was prone to undergo Mannich reaction in the presence of a base to furnish the desired **20a**. Accordingly, we further screened different bases and were delighted to find that an optimal 80% yield of **20a** was obtained by the use of *t*$BuNH_2$ (see the SI). Notably, cleavage of one carbon-carbon bond as well as formation of new carbon-carbon and carbon-nitrogen bonds were achieved in this one-pot protocol, efficiently converting the 6/6/6 tricyclic **8** into 6/5/5/6 tetracyclic **20a**. Furthermore, to reach the desired product **7**, removal of the extra carbon at C7 in **20a** was required. However, subjecting **20a** to various metal-mediated deformylation conditions[20] resulted in either no reaction or decomposition. Hence, we turned to a decarboxylation process to access **7**. To this end, aldehyde **20a** was first transformed into acid **20b** (95% yield)



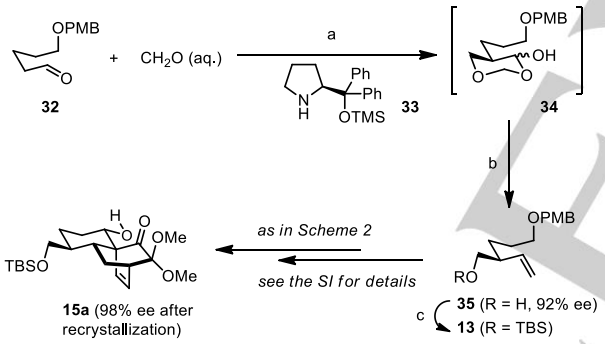
Scheme 3. Completion of the total synthesis of liangshanone (**2**). Reagents and conditions: a) LDA, $NCCO_2Me$, THF, –78 °C, 95%, 5:4 *d.r.*; b) Cs_2CO_3, MVK, THF, 0 °C to RT, 92%; c) LDA, THF, –78 °C, **23** (52%, 91% brsm); d) Et_3N, MsCl, PhMe, RT to 100 °C, 81%; e) $LiAlH_4$, Et_2O, 30 °C; f) AZADO, DMAP, bpy, CuCl, air (open), MeCN, 0 °C to RT, 78% (2 steps); g) TMSOTf, Et_3N, CH_2Cl_2, 0 °C; then Ph_3PCH_2OMeCl, *n*BuLi, THF, 0 to –78 °C; h) NaOH, MeOH, 60 °C, 56% (2 steps); i) TfOH, MeCN, 40 °C, 82%, 1:1.3 *d.r.*; j) Pd/C, HOAc, H_2, EtOH, RT; k) $CH(OEt)_3$, *p*TsOH, ethylene glycol, CH_2Cl_2, RT; l) DMP, TFA, CH_2Cl_2, 0 °C, 57% (3 steps); m) Petasis reagent, THF, 70 °C, 76%; n) SeO_2, TBHP, CH_2Cl_2, 0 °C to RT; then *p*TsOH, RT, 69%; o) DMP, TFA, CH_2Cl_2, 0 °C, 77%; p) $NaBH(OMe)_3$, THF, –78 °C, 91%. AZADO = 2-azaadamantane *N*-oxyl, bpy = 2,2'-bipyridyl, MVK = methyl vinyl ketone, Petasis reagent = dimethyltitanocene, TBHP = *tert*-butyl hydroperoxide, TMS = trimethylsilyl.

under the standard Pinnick oxidation conditions. The corresponding tetracyclic structure was verified by an X-ray crystallography of **20b**.[18] While decarboxylation of **20b** via Barton radical conditions proved to be inefficient, a superior result was obtained according to a method recently disclosed by the Baran group.[21] Specifically, coupling of acid **20b** with *N*-hydroxyphthalimide (NHPI) afforded the corresponding ester (structure not shown); this activated form smoothly underwent nickel-catalyzed decarboxylative fragmentation at 50 ºC, producing **7** with 53% yield in one pot.

To complete the total synthesis of liangshanone, the remaining task was to assemble the bicyclo[3.2.1]octane C/D ring system (Scheme 3).[22] To this end, we first sought to employ a cycloalkenylation strategy[13] of enone **4a** according to the retrosynthesis discussed in Scheme 1. Unfortunately, attempts to prepare **4a** from **7** by establishing the C8 all-carbon quaternary stereocenter through a variety of alkylation and Michael addition conditions were unsuccessful (see the SI). In this context, we introduced an α-methoxycarbonyl group in ketone **7** to enhance the reactivity of C8 for the ensuing Michael addition. Thus, treatment of **7** with LDA and Mander's reagent[23] efficiently delivered β-ketoester **21**. While direct one-pot Robinson annulation of **21** to the corresponding enone **24** was unfruitful, an alternative stepwise approach was adopted. Consequently, **21** was first converted into diketone **22** (92% yield) as a single diastereomer using Cs_2CO_3 and MVK. Afterwards, intramolecular aldol addition of diketone **22** proceeded with LDA to yield the pentacycle **23**; dehydration (Et_3N, MsCl) of the latter secured enone **24**. An X-ray crystallographic analysis of **24** unambiguously confirmed its pentacyclic structure including the correct configuration of the key C8 stereocenter.[18] However, subsequent homologation of the ester functionality in **24** was problematic, probably because it was in a congested concave face of the B/C/F ring motif. By contrast, we envisioned that the presence of a tertiary hydroxyl group at C9 in **23** might release the steric hindrance and benefit the ensuing synthesis. As expected, two steps of reduction ($LiAlH_4$) and oxidation (AZADO, DMAP, bpy., CuCl, air)[24] successfully transformed **23** into aldehyde **25** in 78% overall yield. In situ protection of the C9 hydroxyl and C12 carbonyl groups in **25** with TMSOTf/Et_3N, followed by adding the reaction mixture to the freshly prepared Wittig reagent Ph_3P=CHOMe, gave enol ether **26** (determined via LC-MS). Immediate treatment of the above crude product with NaOH effected desilylation and elimination to furnish **27** as a pair of inseparable geometric isomers (*Z*/*E* = 5:1). At this point, formation of the remaining D ring was explored. Gratifyingly, subjecting **27** to TfOH at 40 ºC promoted hydrolysis of the methyl enol ether and concomitant intramolecular aldol addition that completed the hexacyclic backbone of liangshanone, resulting in **28** as an inconsequential diastereomeric mixture (82% combined yield, 1:1.3 *d.r.*). Both isomers were transformed into ketone **29** through three-step functionality manipulations including reduction of the olefin double bond by catalytic hydrogenation,

ketalization, and oxidation of the secondary hydroxyl group. Further installation of the exocyclic alkene through Petasis olefination[25] converted **29** into **30** (76% yield). Since partial deketalization was observed during allylic oxidation of **30** with SeO_2 and *tert*-butyl hydroperoxide (TBHP), directly adding *p*TsOH to the reaction mixture after complete consumption of **30** allowed removal of the ketal protecting group in the same pot and produced **31**,[26] the C15-epimer of liangshanone. Finally, oxidation of the allylic alcohol with DMP and TFA, followed by regio- and diastereoselective reduction of the resultant ketone using $NaBH(OMe)_3$ at –78 ºC,[8d] ensured the natural product liangshanone (**2**). The spectral data of synthetic **2** were identical to those reported in the isolation paper.[11b]

Having established a synthetic approach to liangshanone (**2**) in racemic form, an enantioselective synthesis of the advanced tricyclic intermediate **15a** was carried out (Scheme 4). Specifically, asymmetric α-hydroxymethylation of aldehyde **32**[27] with formaldehyde proceeded using Jørgensen-Hayashi catalyst **33**[28] and generated cyclic lactol **34** according to Boeckman's protocol.[29] The crude lactol intermediate was directly subjected to the Wittig methylenation conditions, leading to the formation of homoallylic alcohol **35** with 92% ee (57% yield over two steps). After silylation (**35** to **13**), subsequent transformations based on the synthetic route shown in Scheme 2 converted **13** into the advanced tricycle **15a**. Recrystallization of the latter from hexane/dichloromethane yielded enantioenriched **15a**, which can be used to access optically pure liangshanone.



Scheme 4. Asymmetric synthesis of the advanced tricyclic intermediate **15a**. Reagents and conditions: a) **33** (10 mol %), pH 7 buffer, PhMe, RT; b) PPh_3CH_3Br, *n*BuLi, THF, –78 °C to RT, 57% (2 steps), 92% ee; c) TBSCl, imidazole, CH_2Cl_2, RT, 93%.

In summary, we have accomplished the first total synthesis of the three-dimensionally complex napelline-type C_{20}-diterpenoid alkaloid liangshanone (**2**). Key strategies of the synthesis involve the following: 1) a one-pot alkene cleavage/Mannich cyclization protocol that enabled conversion of the bicyclo[2.2.2]octane resulting from an OD/DA sequence into the bicyclo[2.2.1]heptane (B/F rings) as well as formation of the piperidine unit (E ring), and 2) a Robinson-type annulation and an intramolecular aldol addition that forged the characteristic [3.2.1] bicyclic system (C/D rings). The present study again highlighted the utility of the OD/DA strategy in the total synthesis of various diterpenoid alkaloids.[3e]

Acknowledgements

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Keywords: alkaloids • cycloaddition • *ent*-kaurane • terpenoids • total synthesis

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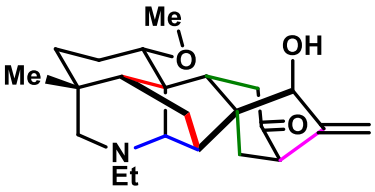

liangshanone

- *OD/DA sequence*
- *Alkene cleavage/Mannich*
- *Robinson-type annulation*
- *Aldol addition*

A synthetic approach to the napelline-type diterpenoid alkaloid liangshanone is presented. Key steps involve an oxidative dearomatization/Diels-Alder (OD/DA) cycloaddition, a domino alkene cleavage/Mannich cyclization, a Robinson-type annulation, and an intramolecular aldol addition.