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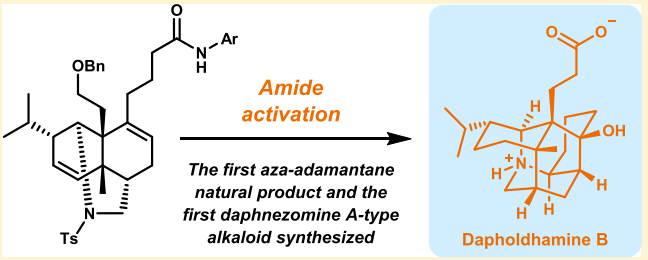
Total Synthesis of Dapholdhamine B and Dapholdhamine B Lactone

Lian-Dong Guo, Jieping Hou,[†] Wentong Tu,[†] Yan Zhang,[†] Yue Zhang, Louxi Chen, and Jing Xu*

Department of Chemistry and Shenzhen Grubbs Institute, Southern University of Science and Technology, Shenzhen, China

Supporting Information

ABSTRACT: The intriguing structural complexity and bioactivities of the *Daphniphyllum* alkaloids have long attracted much attention. Herein, we report the first and enantioselective total synthesis of *Daphniphyllum* alkaloid dapholdhamine B and its lactone derivative. The chemical structure of dapholdhamine B contains a unique aza-adamantane core skeleton and eight contiguous stereocenters, including three contiguous fully substituted stereocenters, which present a formidable synthetic challenge. This concise approach used to achieve the first synthesis of an aza-adamantane natural product features a vinylogous Mannich reaction, an optimized α-bromo-α,β-unsaturated ketone synthesis, a substrate-dependent intramolecular aza-Michael addition, a key annulation via amide activation, an S_N2'-type lactonization, and a facile Horner−Wadsworth−Emmons reaction that converts the hemiacetal moiety to the corresponding homologated carboxylic acid.



INTRODUCTION

The genus *Daphniphyllum* comprises evergreen trees and shrubs native to the Asia-Pacific region, which have long been used in traditional Chinese medicine.[1a] Various *Daphniphyllum* alkaloids have exhibited diverse bioactivities, such as antitubulin polymerization, anticarcinogenic, anti-HIV, vasorelaxant, and cytotoxic activities.[1,2] More than 330 *Daphniphyllum* alkaloids have been isolated from the genus *Daphniphyllum* to date, comprising a structurally fascinating and diverse natural product family.[1] From a chemical structure perspective, these alkaloids can be categorized into over a dozen subfamilies on the basis of their distinct structural backbones.[1] Highly challenging and congested polycyclic ring systems, along with promising bioactivities, make these alkaloids intriguing synthetic targets.[1b−d,3] Since Heathcock's pioneering syntheses of methyl homodaphniphyllate[4a,b] and codaphniphylline[4c] (daphniphylline-type), methyl homosecodaphniphyllate[4d] and secodaphniphylline[4e] (secodaphniphylline-type), bukittinggine[4f] (bukittinggine-type), and daphnilactone A[4g] (daphnilactone A-type), many impressive total syntheses of various *Daphniphyllum* alkaloids have been reported by the groups of Carreira[5] (daphmanidin E; daphmanidin A-type), Smith[6] (calyciphylline N; daphmanidin A-type), Li[7] (daphenylline,[7a,b] daphnilongeranin B,[7c] daphnipaxianine A,[7b] daphniyunnine E,[7c] dehydrodaphnilongeranin B,[7c] hybridaphniphylline B,[7c] himalenine D,[7b] and longeracinphyllin A;[7d] calyciphylline A-type), Hanessian[8] (isodaphlongamine H; a putative member of calyciphylline B-type alkaloids), Fukuyama[9] (daphenylline; calyciphylline A-type), Zhai[10] (daphenylline and daphnilongeranin B; calyciphylline A-type), Dixon[11] (himalensine A; calyciphylline A-type), Qiu[12] (daphenylline; calyciphylline A-type), ourselves[13] (himalensine A; calyciphylline A-type), Gao[14] (himalensine A; calyciphylline A-type), and Sarpong[15] (daphlongamine H and isodaphlongamine H; calyciphylline B-type) (Figure 1).

Dapholdhamine B (**1**, Figures 1 and 2) belongs to the unexplored daphnezomine A-type subfamily and was isolated

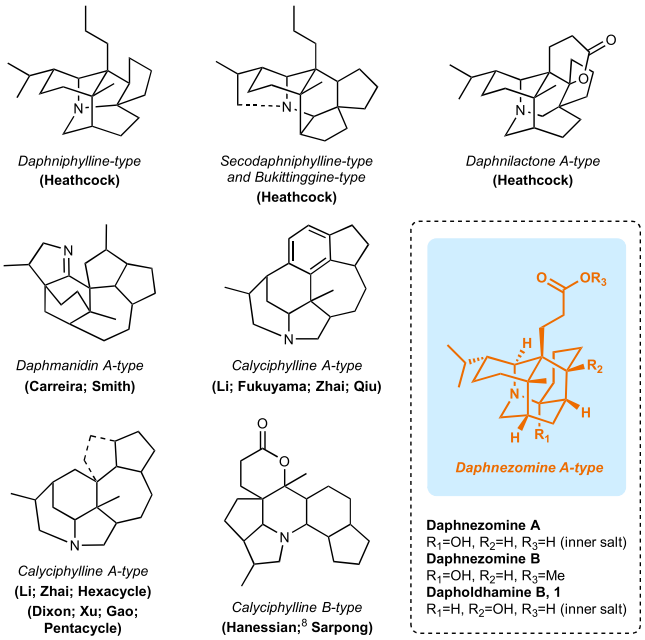


Figure 1. Common skeletons of previously synthesized *Daphniphyllum* alkaloids, along with daphnezomine A-type alkaloids.

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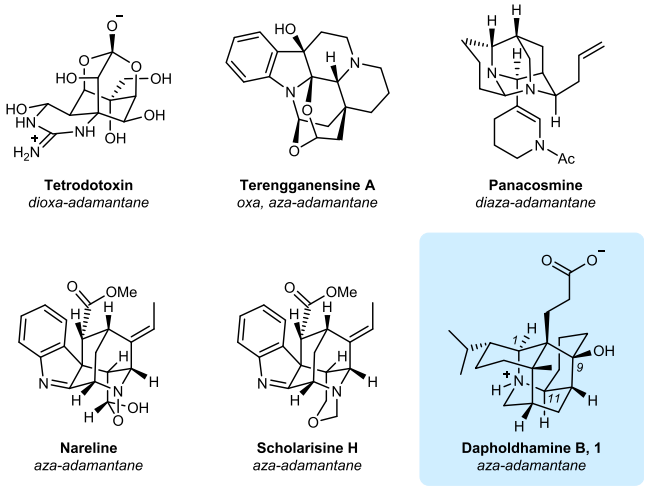


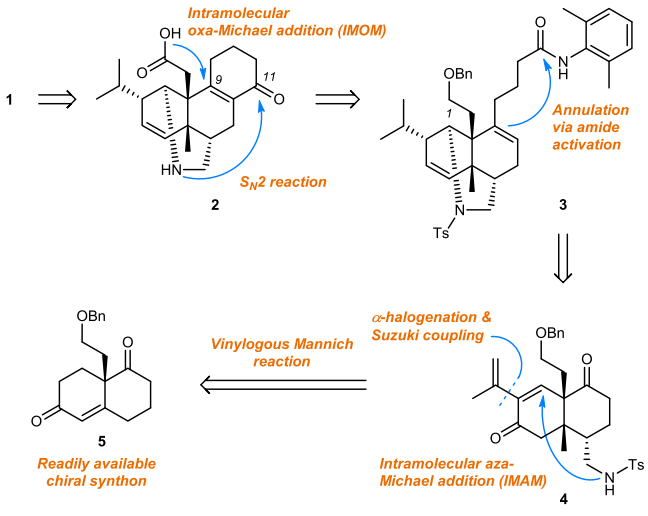
Figure 2. Adamantane-type natural products.

and structurally assigned in 2009 by Hao et al.[16] The chemical structure of dapholdhamine B contains a rare aza-adamantane core skeleton and eight contiguous stereocenters, including three contiguous fully substituted stereocenters, which present a daunting synthetic challenge. To our knowledge, dapholdhamine B and its congeners daphnezomines A and B (Figure 1),[17] acosmine-type diaza-adamantanes (such as panacosmine),[18] and the indole alkaloids nareline[19a] and scholarisine H[19b] (Figure 2) are among the only known aza-adamantane natural products. Representative oxa- and oxa, aza-adamantane natural products, such as tetrodotoxin[20] and terengganensine A,[21] have been synthesized previously. Herein, we report the first and asymmetric total synthesis of **1**, which is also the first synthesis of an aza-adamantane natural product.

RESULTS AND DISCUSSION

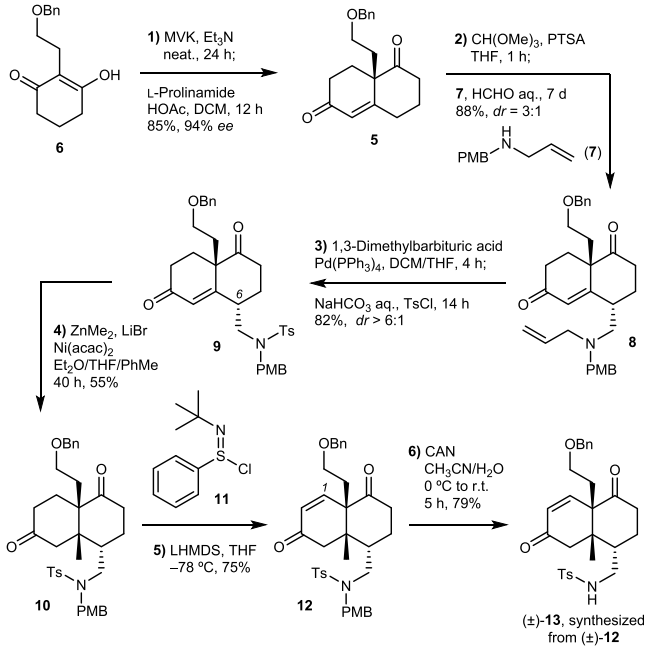
As shown in Scheme 1, our retrosynthetic analysis of **1** indicated that the key C-9 tertiary hydroxyl group could be introduced via an intramolecular oxa-Michael (IMOM) reaction. The equally crucial C_{11}–N bond could be formed through an S_N2-type reaction, and formation of the cyclohexenone motif in enone **2** was envisaged to be accessible from amide **3** using Huang's amide-activation–annulation reaction.[22] The C_1–N bond can be formed by an intramolecular aza-Michael addition (IMAM) of sulfonylamide **4**. Finally, the aminomethylene group in **4** can be introduced using a vinylogous Mannich reaction of readily available chiral diketone **5**.

Scheme 1. Retrosynthetic Analysis of Dapholdhamine B



Our synthesis began with an L-prolinamide-catalyzed asymmetric Robinson annulation of known compound **6**[23] to afford diketone **5** (Scheme 2; 85%, 94% ee).[24] Selective methyl enol ether formation followed by a vinylogous Mannich reaction[25] produced tertiary amine **8**, which was then deallylated and tosylated to give sulfonylamide **9**. Notably, diastereomeric enrichment was observed during the purification process. Subjecting this sulfonylamide to conjugate addition under Luche's conditions[26] formed the critical quaternary center to afford diketone **10** as a single diastereomer. It was postulated that the C-6 epimer of **9** could not undergo the conjugate addition. Subsequently, treating **10** with lithium bis(trimethylsilyl)amide (LHMDS) selectively generated the corresponding lithium enolate, which was then treated with sulfinimidoyl chloride **11** to trigger a Mukaiyama dehydrogenation,[27] affording desired enone **12** in 75% yield. Subsequent oxidative cleavage of the PMB group afforded sulfonylamide **13**.

Scheme 2. Synthesis of IMAM Precursor 13



With IMAM precursor **13** in hand, triggering the IMAM reaction and introducing the isopropyl group into the skeleton of compound **13** in the same step would be preferred (Table 1). These transformations would have ideally been achieved through an IMAM/alkylation or IMAM/aldol cascade reaction using sulfonylamide **13** and appropriate electrophiles, such as 2-iodopropane or acetaldehyde, under basic conditions. However, these attempts, based on racemic model substrate (±)-**13**, were all unsuccessful. In particular, extensive investigation of the IMAM/aldol cascade reaction using various bases and additives led only to the formation of IMAM product **15**. No trace of desired IMAM/aldol product **14** was detected by NMR or LC–MS. Subsequent traditional aldol or Mukaiyama aldol reactions using **15** led only to a

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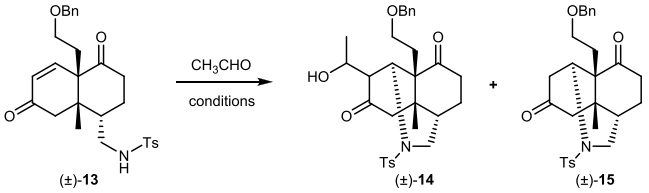
Table 1. Study of the IMAM Reaction



entry[a]	conditions	14 (%)	15[c] (%)
1	NaH (1.5 equiv), 0 °C to r.t.	ND[b]	80
2	NaH (1.5 equiv), $ZnCl_2$ (3 equiv), 0 °C to r.t.	ND	85
3	DBU (2 equiv), r.t.	ND	96
4	DBU (2 equiv), $ZnCl_2$ (3 equiv), r.t.	ND	92
5	LDA (1.1 equiv), −78 °C to r.t.	ND	80[d]
6	LDA (1.1 equiv), $ZnCl_2$ (2 equiv), −78 °C to r.t.	ND	85[e]
7	KHMDS (1.1 equiv), −78 °C to r.t.	ND	75[d]
8	KHMDS (1.1 equiv), $ZnCl_2$ (2 equiv), −78 °C to r.t.	ND	85[e]

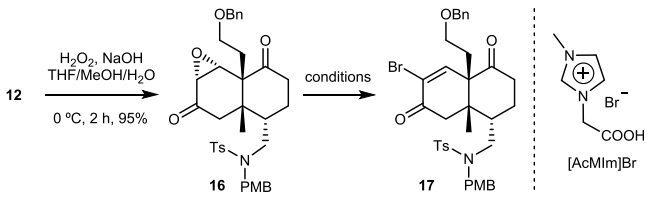
[a]0.2 mmol; THF, 0.1 M. [b]Not detected. [c]Isolated yield. [d]Base, −78 °C, 1 h, then acetaldehyde added dropwise. [e]Base, −78 °C, 1 h, then $ZnCl_2$, 30 min, then acetaldehyde added dropwise.

retro-IMAM reaction product in about 20% yield, with a large amount of **15** recovered. Substrate **15** was postulated to strongly favor the retro-aldol reaction in the corresponding reaction equilibrium. The unsuccessful alkylation might be attributed to steric hindrance by our substrate and the bulky electrophile, 2-iodopropane.

Owing to the unsuccessful IMAM/alkylation and IMAM/aldol attempts, we decided to first introduce the isopropyl group into the core skeleton, envisaging that a subsequent IMAM reaction should also work well. However, the desired α-halogenation of α,β-unsaturated ketone **12** proved to be extremely difficult, with all traditional methods resulting in failure,[28] possibly due to severe steric hindrance at the C-1 position. Fortunately, an optimized α-bromination method was developed on the basis of a reported example[29] using epoxide **16**,[30] which was produced from enone **12** via an epoxidation reaction (Table 2). Various bromine sources, including TBAB,[31] LiBr, [AcMIm]Br,[32] and HBr·Py, were screened with substrate **16**. LiBr was found to be the only effective bromine source, while the other bromine sources gave very poor results (no reaction, decomposition, or only trace amounts of **17**). Although LiBr/TFA conditions (Table 2, entries 2 and 3) gave poor results, neutral conditions using anhydrous acetonitrile were found to give the best results in this bromination step (Table 2, entry 7). Furthermore, microwave conditions improved the reaction yield from 30 to 52% (Table 2, entry 9, 0.2 mmol scale) or 46% (Table 2, entry 10, 2 mmol scale), producing a sufficient amount of vinyl bromide **17** for further investigation.

Subsequently, a Suzuki coupling reaction between vinyl bromide **17** and boronate **18** furnished diene **19** in 90% yield using XPhos Pd G2 as catalyst.[33] Other ligands, such as PPh_3 or $AsPh_3$, gave lower or irreproducible yields (Scheme 3). After oxidative removal of the PMB group, sulfonylamide **4** was produced in 76% yield from **19**. Alternatively, partial hydrogenation of diene **19** was attempted, followed by oxidative cleavage of the PMB group, to afford sulfonylamide **20** (in racemic form, synthesized from racemic **19**). Interestingly, the seemingly trivial structural difference between IMAM precursors **4** and **20** resulted in completely

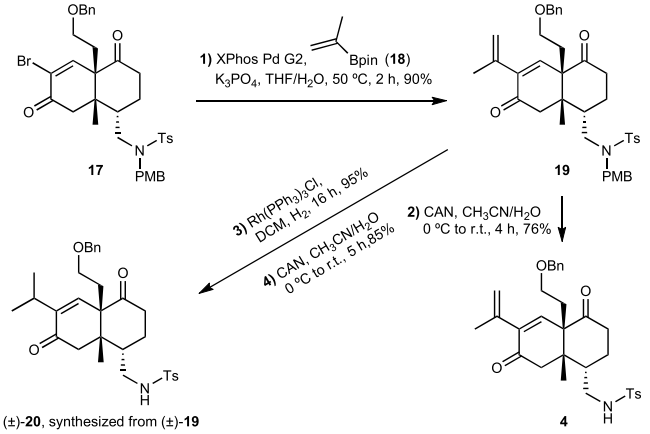
Table 2. Study of Vinyl Bromide Synthesis



entry[a]	conditions[b]	17[c] (%)
1	TBAB, BF_3·Et_2O, DCM, r.t., 0.5 h	decomp.
2	LiBr, TFA, THF, r.t., 0.5 h	NR
3	LiBr, TFA, THF, 60 °C, 2 h	decomp.
4	LiBr, DMF, 150 °C, 12 h	trace[e]
5	[AcMIm]Br, 65 °C, 2 h	NR
6	LiBr, CH_3CN, reflux, 12 h	20
7	LiBr, CH_3CN, 120 °C (sealed tube), 12 h	30
8	LiBr, CH_3CN, MW, 100 °C, 0.5 h	41
9	LiBr, CH_3CN, MW, 120 °C, 10 min	52
10[d]	LiBr, CH_3CN, MW, 120 °C, 12 min	46
11	LiBr, CH_3CN/H_2O (2/1), MW, 120 °C, 1 h	NR
12	LiBr, HOAc, CH_3CN, MW, 120 °C, 12 min	<10[f]
13	LiBr, DMF, MW, 120 °C, 12 min	NR
14	HBr·Py, CH_3CN, MW, 120 °C, 12 min	trace[e]

[a]0.2 mmol. [b]Bromine source, 10 equiv; Lewis acid or protonic acid, 2 equiv; solvent, 0.1 M. [c]Isolated yield. [d]2.0 mmol. [e]Most of the starting material was recovered. [f]Most of the starting material was decomposed.

Scheme 3. Synthesis of IMAM Precursors 4 and 20



different outcomes from the IMAM trials. Treating substrate **20** under different acidic or basic conditions did not produce even trace amounts of IMAM product **21** (Table 3). Furthermore, when MeOH or EtOH was used as solvent, a vinylogous retro-Dieckmann reaction of substrate **20** occurred, followed by an IMAM reaction to give product **22** or **23**, respectively. Substrate **20** was assumed to strongly favor the retro-IMAM reaction in the corresponding reaction equilibrium.

The presence of an isopropenyl group was also postulated to provide better stabilization of the resulting enolate anion. Pleasingly, the desired IMAM reaction was successfully triggered when sulfonylamide **4** was treated with potassium bis(trimethylsilyl)amide (KHMDS) and TBSCl (Scheme 4). To further improve the overall synthetic efficiency, the silyl enol ether from the aforementioned IMAM reaction mixture was treated with excess KHMDS and $PhNTf_2$ to give enol

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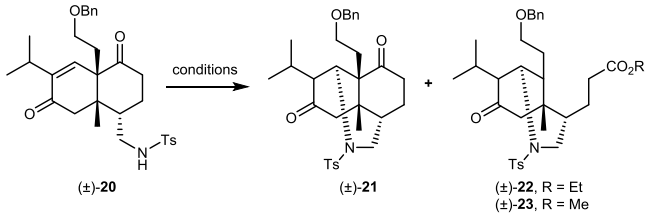
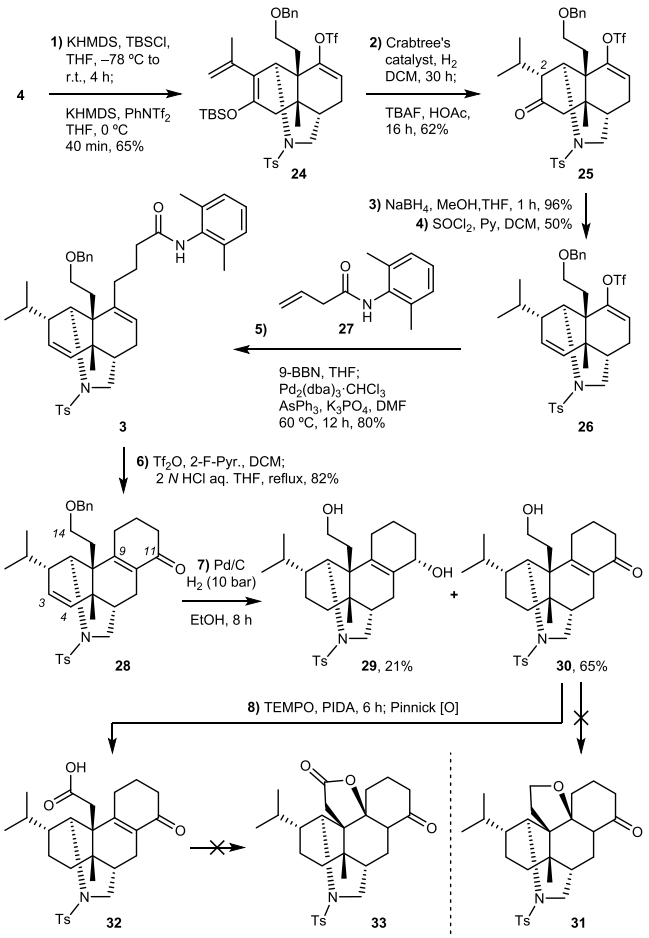
Table 3. Study of the IMAM Reaction of 20



entry[a]	conditions	yield of **21**
1	PTSA (2 equiv), DCM, r.t., 12 h	NR
2	PTSA (2 equiv), PhMe, 80 °C, 12 h	decomp.
3	DBU (2 equiv), PhMe, reflux, 3 h	NR
4	DBU (2 equiv), CH_3CN, reflux, 3 h	NR
5	DBU (2 equiv), $ZnCl_2$ (3 equiv), CH_3CN, MW, 120 °C, 1 h	NR
6	DBU (2 equiv), EtOH, 75 °C, 12 h	ND[b]
7	NaOMe (5 equiv), MeOH, 60 °C, 1.5 h	ND[c]
8	LDA (2 equiv), $ZnCl_2$ (2 equiv), THF, −78 °C to r.t., 3 h	NR
9	NaH (2 equiv), DCM, r.t., 12 h	NR
10	KHMDS (1.1 equiv), THF, −78 °C to r.t.	NR

[a]0.1 mmol; solvent, 0.05 M. [b]Ethyl ester **22** isolated in 60% yield as a single isomer. [c]Methyl ester **23** isolated in 75% yield as a single isomer.

Scheme 4. Key Annulation via Amide Activation Reaction and Unsuccessful IMOM Attempts



triflate **24**. Homogeneous hydrogenation of **24** using Crabtree's catalyst,[34] followed by treatment with TBAF/AcOH in the same pot, produced desired ketone **25** in 62% yield. The C-2 stereochemistry was clearly assigned later by single crystal X-ray diffraction of compound **29**. At this stage, we hoped that an efficient and high-yielding annulation would proceed to construct the additional cyclohexenone ring motif. To this end, the carbonyl group in **25** was reduced and eliminated to give compound **26**. A Suzuki coupling reaction between enol triflate **26** and the borane obtained from treating amide **27** with 9-BBN produced key amide intermediate **3**. Subjecting compound **3** to Huang's amide-activation−annulation reaction under Tf_2O/2-fluoropyridine conditions,[22] with subsequent acid hydrolysis of the corresponding imine intermediate, afforded desired tetracycle **28** bearing the cyclohexanone moiety in 82% yield.

On the basis of our original synthetic design, it was envisaged that the key C-9 hydroxyl group could be introduced into the skeleton via an IMOM reaction (Scheme 4). To this end, compound **28** was partially hydrogenated to give enone **30** in 65% yield, along with a small amount of allylic alcohol **29** (21%). Furthermore, primary alcohol **30** was oxidized to its carboxylic acid derivative **32**. However, neither primary alcohol **30** nor carboxylic acid **32** underwent the planned IMOM reaction under various basic or acidic conditions (NaOAc, DBU, NaOMe, NaH, pyrrolidine, PTSA, HCl aq., or PPTS), failing to give desired tetrahydrofuran **31** or lactone **33**, respectively.

In the amide-activation−annulation step, we were pleased to observe the generation of tetrahydrofuran **34** in approximately 10% yield, along with desired enone **28** (82%, Scheme 5). As enone **28** could not be further converted into **34** under the same acidic workup conditions as those used in the annulation step, the plausibility of the debenzylation/IMOM pathway could be ruled out. Therefore, we propose that the formation of the tetrahydrofuran moiety occurs through the formation of cationic intermediate **35**, followed by oxygen trapping and debenzylation.

Inspired by the aforementioned critical observation, we proposed that compound **29** or its carboxylic acid derivative (Scheme 6) would undergo an S_N2'-type reaction under acidic conditions via a similar cationic intermediate. Pleasingly, this pivotal S_N2'-type reaction finally paved the way for the total synthesis of dapholdhamine B. One-pot global hydrogenation/hydrogenolysis of the C_3-C_4 double bond, C-11 ketone, and

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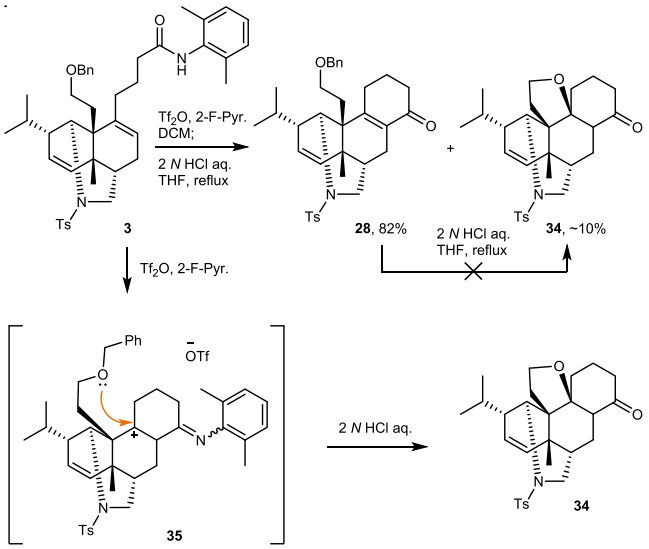
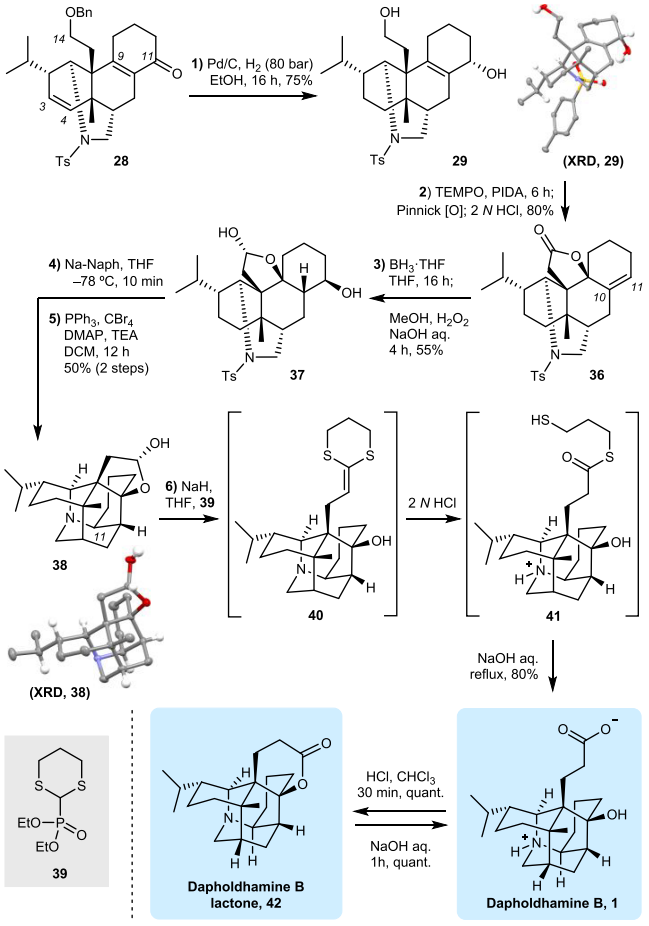
Scheme 5. Formation of Compound 34 and the Proposed Mechanism That Inspired the Key S_N2' Reaction



Scheme 6. Total Synthesis of Dapholdhamine B and Dapholdhamine B Lactone



C-14 *O*-benzyl group using a high pressure of hydrogen (80 bar) efficiently converted compound **28** into tetracyclic diol **29**. The absolute stereochemistry of **29** was unambiguously assigned by single crystal X-ray diffraction.[35] A one-pot selective oxidation (TEMPO/PIDA, then Pinnick oxidation) of the C-14 primary alcohol followed by acid workup triggered the formation of lactone **36** via the proposed pivotal S_N2'-type reaction. Hydroboration of the C_{10}–C_{11} double bond followed by oxidation produced compound **37**. The lactone moiety of **36** was simultaneously reduced to the corresponding lactol moiety in the hydroboration reaction. To our surprise, this lactol motif was highly stable, with all attempts at reduction or homologation proving unsuccessful. Consequently, we decided to construct the remaining C_{11}–N bond first, with the aim to change the reactivity of the lactol. Removal of the N-tosyl group using sodium naphthalenide followed by an S_N2-type reaction[36] successfully afforded **38**, which possessed the pivotal aza-adamantane core skeleton. The structure of **38** was unambiguously confirmed by single crystal X-ray diffraction.[37] As compound **38** contains all of the stereogenic centers of **1**, all stereoconfigurations in **1** were confirmed. After extensive investigation, the critical homologation of lactol **38** was achieved using a Horner–Wadsworth–Emmons reaction[38] with sodium hydride and phosphonate **39** to give intermediate **40**, which then underwent one-pot acid hydrolysis to give thioester **41**. Compounds **40** and **41** did not need to be isolated, as basic hydrolysis of the thioester motif in the same pot successfully produced dapholdhamine B (**1**, 80%). As an authentic sample of natural **1** was not available, comparing the ^1H and ^{13}C NMR data of the natural product with our synthetic sample was difficult because the NMR chemical shifts of our synthetic amino acid were extremely pH-sensitive (see the Supporting Information). Consequently, a small amount of synthetic **1** was treated with HCl to quantitatively give dapholdhamine B lactone (**42**). Furthermore, basic hydrolysis of **42** also produced **1** quantitatively. Through extensive NMR analysis (see the Supporting Information), we clearly assigned the chemical structure of **42**, which, along with the unambiguous structural assignment of the last intermediate **38**, allowed the identity of synthetic **1** to be confirmed beyond a doubt.

CONCLUSIONS

In summary, we have accomplished the first and asymmetric total synthesis of *Daphniphyllum* alkaloid dapholdhamine B in 21 steps. This is also the first synthesis of an aza-adamantane natural product. Our concise approach features the following: (i) a vinylogous Mannich reaction to introduce the key C-6 aminomethyl group; (ii) an optimized α-bromo-α,β-unsaturated ketone synthesis, because all other known methods failed; (iii) a substrate-dependent IMAM reaction to construct the critical C_1–N bond; (iv) a key annulation strategy via an amide activation reaction that formed the cyclohexanone moiety in a highly efficient manner; (v) introduction of a critical C-9 hydroxyl group via an S_N2'-type reaction inspired by the observation of a side product from the amide-activation–annulation step; and (vi) a facile Horner–Wadsworth–Emmons reaction that converted the hemiacetal to the corresponding homologated carboxylic acid. Efforts toward the synthesis of other daphnezomine A-type alkaloids, as well as other aza-adamantane alkaloids, are currently ongoing in our laboratory.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.9b05641.

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Experimental procedures and spectral data for all new compounds (PDF)
Crystallographic Information File for compound **16** (CIF)
Crystallographic Information File for compound **29** (CIF)
Crystallographic Information File for compound **38** (CIF)

AUTHOR INFORMATION

Corresponding Author

*xuj@sustech.edu.cn

ORCID

Jing Xu: 0000-0002-5304-7350

Author Contributions

†J.H., W.T., Y.Z.: These authors contributed equally.

Notes

The authors declare no competing financial interest.

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