Communication

Total Synthesis of Hybridaphniphylline B

Wenhao Zhang, Ming Ding, Jian Li, Zhicong Guo, Ming Lu, Yu Chen, Lianchao Liu, Yun-Heng Shen, and Ang Li

J. Am. Chem. Soc., **Just Accepted Manuscript** • DOI: 10.1021/jacs.8b01681 • Publication Date (Web): 01 Mar 2018

Total Synthesis of Hybridaphniphylline B

Wenhao Zhang,[†,§] Ming Ding,[†,§] Jian Li,[†,§] Zhicong Guo,[†] Ming Lu,[†] Yu Chen,[†] Lianchao Liu,[†] Yun-Heng Shen,[‡] and Ang Li*[,†]

[†]State Key Laboratory of Bioorganic and Natural Products Chemistry, Center for Excellence in Molecular Synthesis, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, China

[‡]Department of Phytochemistry, School of Pharmacy, Second Military Medical University, 325 Guohe Road, Shanghai 200433, China

Supporting Information Placeholder

ABSTRACT: Hybridaphniphylline B (**1**) is a *Daphniphyllum* alkaloid possessing 11 rings and 19 stereocenters. Here we report the first total synthesis of **1** featuring a late-stage intermolecular Diels−Alder reaction of a fully elaborated cyclopentadiene and asperuloside tetraacetate. The diene was prepared on the basis of a scalable route to daphnilongeranin B (**4**). Claisen rearrangement of an allyl dienol ether was exploited as a key step; the subtle variation of the substrate and use of protic solvents suppressed the undesired Cope rearrangement. Daphniyunnine E (**6**) and dehydrodaphnilongeranin B (**7**), two congeners of **4**, were also synthesized. The dienophile arose from (+)-genipin through glycosylation and lactonization. A one-pot protocol was developed for the diene formation and Diels−Alder reaction; one of the cycloadducts was converted into **1** through reductive desulfurization and global deacetylation.

The *Daphniphyllum* alkaloid family comprise more than 320 members with fascinating molecular architectures and diverse biological activities.[1] Synthetic chemists have been intrigued by the challenges posed by these molecules.[1–3] The groups of Heathcock,[4] Carreira,[5] Smith,[6] Fukuyama,[7] Zhai,[8] and Dixon[9] accomplished elegant syntheses of a dozen of *Daphniphyllum* alkaloids. Our endeavors in this area also resulted in the syntheses of several members of this family.[10] During the studies, we developed strategies such as 6π electrocyclization/aromatization for constructing multisubstituted benzenes[10a] and alkyne cyclization for assembling azabicyclo[3.3.1]nonanes,[10a,b] which found further use in the syntheses of other natural products.[11,12] Hybridaphniphylline B (**1**, Figure 1) is a complex *Daphniphyllum* alkaloids containing 11 rings and 19 stereogenic centers, which was isolated by Liu and co-workers from *Daphniphyllum longeracemosum*.[13,14] Biogenetically, **1** may result from an intermolecular Diels−Alder reaction of naturally occurring deacetylasperuloside (**2**) and a putative cyclopentadiene **3**.[13,14] This diene shares a 6-6-5-7-5-5-hexacyclic skeleton with the calyciphylline A type *Daphniphyllum* alkaloids, such as daphnilongeranin B[15] (**4**), daphniynnine C (longeracinphyllin A)[16] (**5**), daphniyunnine E[16a] (**6**), and dehydrodaphnilongeranin B[17] (**7**). Our experience with bioinspired Diels−Alder cycloaddtion[18] and *Daphniphyllum* alkaloid synthesis[10] suggested an opportunity for an expedient route to the undecacyclic scaffold of **1**. Here we report the first total synthesis of **1** as well as the syntheses of **4**, **6**, and **7**.

We first undertook a retrosynthetic analysis of **1** (Figure 1). Inspired by the biosynthetic hypothesis, **1** was disassembled to give the Diels−Alder substrates **2** and **3**. The latter may arise from **4** via a sequence of 1,2-reduction of the α,β-unsaturated enone and dehydration of the resultant allylic alcohol. Notably, [1,5]-H shift of the cyclopentadiene could occur under thermal conditions,[19] which suggested that the starting positions of the two C=C bonds should be inconsequential; therefore, **5**[10b] might serve as an

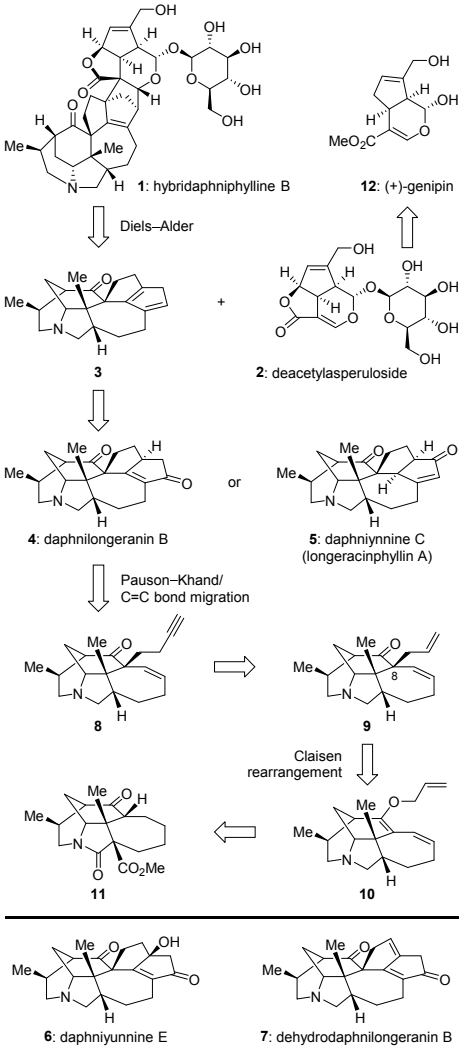


Figure 1. The structure and retrosynthetic analysis of hybridaphniphylline B (**1**).

Scheme 1. Total Syntheses of Daphnilongeranin B (4), Daphniyunnine E (6), and Dehydrodaphnilongeranin B (7)

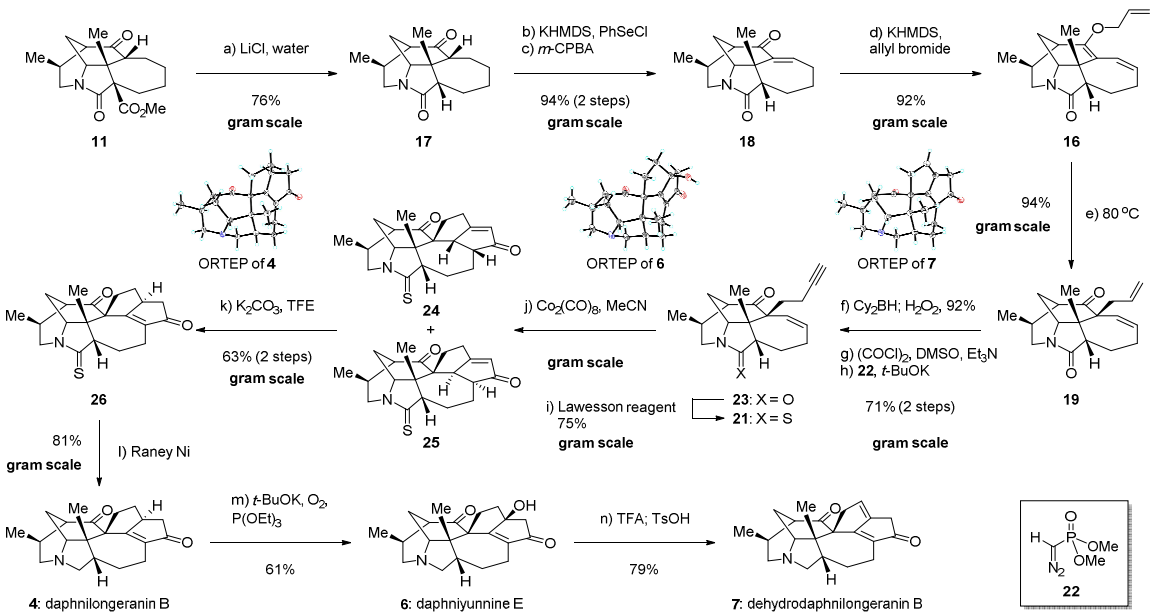
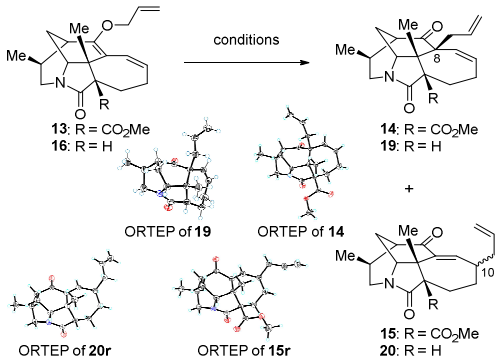


Table 1. Studies of the Claisen rearrangement of the allyl dienol ethers



entry	S	conditions	products (yield [%])	
1[a,b]	**13**	*o*-DCB, 140 °C, 3 h	**14** (<2)	**15**[c] (31)
2[d]	**13**	$TiCl_4$, $AlMe_3$, 0 °C	**14** (<5)	**15**[e] (47)
3[a,f]	**16**	*o*-DCB, 120 °C, 12 h	**19** (48)	**20**[e] (5)
4[a,g]	**16**	*o*-DCB, 120 °C, 24 h	**19** (46)	**20**[h] (27)
5[i]	**16**	aq. NaOH/MeOH, 80 °C, 3 d	**19** (94)	**20** (0)

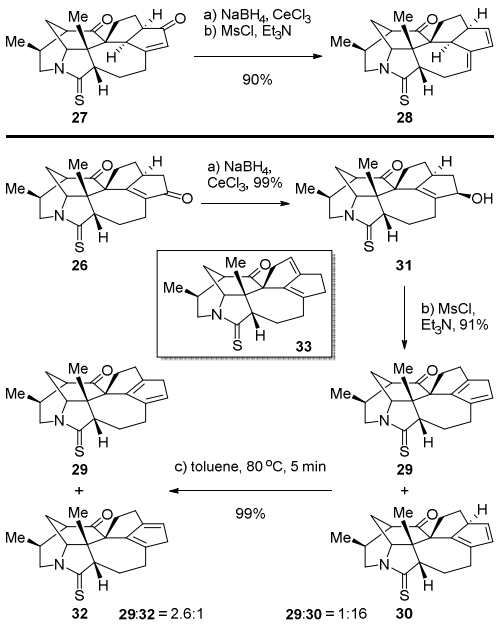
[a]47 mol% *i*-Pr_2NEt. [b]53% recovery of **13**. [c]10*R*:10*S* = 1.7:1. [d]3.2 equiv [Ti], 3.2 equiv [Al], 100 wt% 4 Å MS, CH_2Cl_2. [e]10*R* only. [f]38% recovery of **16**. [g]9% recovery of **16**. [h]10*R*:10*S* = 20:1. [i]v [aq. NaOH (0.010 M)]:v (MeOH) = 5:2.

alternative precursor of the diene. A robust route to **4** was required for the study of the Diels–Alder reaction. We could also exploit **4** as a versatile intermediate for the preparation of other calyciphylline A type *Daphniphyllum* alkaloids, such as **6** and **7**. The bicyclo[3.3.0]octenone motif of **4** indicated a Pauson–Khand/C=C bond migration[20] strategy, leading to 1,6-enyne **8** as a suitable precursor. Truncation of the side chain gave 1,5-diene **9**, the quaternary C8 of which could result from Claisen rearrangement of allyl dienol ether **10**. The challenge was to suppress the Cope rearrangement of **9** under the Claisen conditions. Notably, the direct alkylation strategy to prepare **9** type intermediates was unsuccessful because the O and γ-C of the dienolate precursor turned out to be more nucleophilic than the α-C. **10** was traced back to tetracycle **11**, which had been prepared by us on a large scale.[10b] It is noteworthy that Dixon and co-workers contributed greatly to the development of the Claisen[21] and Pauson–Khand/C=C bond migration[22] strategies toward the synthesis of calyciphylline A type alkaloids. We confirmed the stereochemical outcome of the Claisen rearrangement using an elaborated tetracyclic substrate in a previous study.[23] The dienophile **2** may arise from comerically available (+)-genipin (**12**).

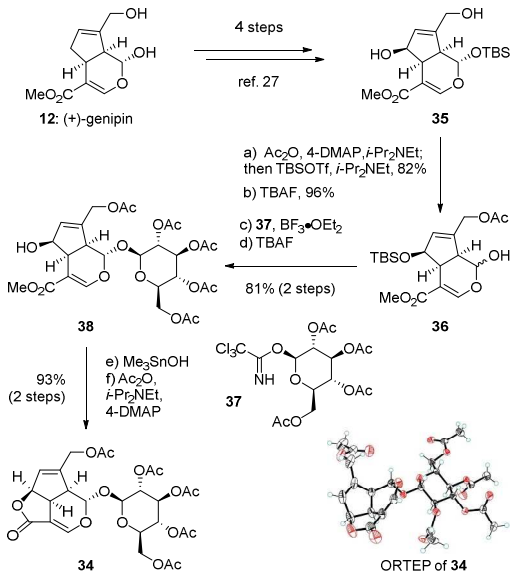
We first investigated the Claisen rearrangement for the construction of the quaternary C8 (Table 1). Dienol ether **13** (see the SI for preparation) was initially used as a substrate (entries 1 and 2). Under the thermal conditions (entry 1), a trace amount of Claisen product **14** (a single C8 diastereomer) was detected. Compound **15** resulting from a Claisen/Cope cascade turned out to be predominant; we observed the epimerization at C10 presumably through tautomerization at elevated temperature. Boeckman and co-workers exploited the combination of $TiCl_4$ and $AlMe_3$ to solely accelerate the Claisen rearrangement of an allyl dienol ether.[24] Under these conditions (entry 2), we still obtained **15** (a single C10 diastereomer; specified as **15r**) as a major product, along with a small amount of **14**. An alternative substrate **16** was then prepared (Scheme 1). **11** was subjected to Krapcho demethoxycarbonylation to afford compound **17**, which underwent α-selenation followed by oxidative elimination to give α,β-unsaturated enone **18**. Treatment with KHMDS and allyl bromide furnished the dienol ether, which was subjected to the conventional thermal conditions (entry 3). Claisen product **19** and Claisen/Cope product **20** (specified as **20r**) were isolated as single diastereomers in 48% and 5% yields, respectively, and 38% of **16** was recovered. However, an attempt to improve the conversion of **16** by prolonging the reaction times resulted in production of a significant amount of **20** (entry 4). To our delight, the Claisen rearrangement proceeded smoothly in basic MeOH/water[25] at 80 °C to provide **19** in 94% yield (entry 5); the Cope rearrangement did not ensue. The reaction was performed on 5 gram scale.

The completion of the syntheses of **4**, **6**, and **7** was depicted in Scheme 1. 1,5-Diene **19** was elaborated into a Pauson–Khand substrate **21**. Selective hydroboration of the terminal C=C bond with Cy_2BH followed by oxidation afforded a primary alcohol, which underwent Swern oxidation and Seyferth–Gilbert homologation with **22** to give alkyne **23**. Exposure of this compound to Lawesson reagent furnished **21**. A survey of Pauson–Khand conditions identified MeCN[26] as an effective promoter for the transformation from the the alkyne dicobalt complex [generated from

Scheme 2. Preparation of the Diene



Scheme 3. Preparation of the Dienophile



21 and $Co_2(CO)_8$] to the desired products; **24** and **25** were obatined in 73% yield in a ratio of ca. 2.4:1. This mixture was subjected to K_2CO_3/trifluoroethanol for the C=C bond migration, leading to more substituted enone **26** (63% overall yield from **21**). Raney Ni reduction of this thioamide rendered **4**. The syntheses of racemic and enantioenriched **4** were both achieved through the described route, and the former synthesis was carried out on a gram scale. Exposure of **4** to *t*-BuOK and O_2 in the presence of $P(OEt)_3$ gave **6** in 61% yield as a single detectable diastereomer. Treatment of the TFA salt of **6** with TsOH effected the dehydration smoothly, providing **7** in 79% yield.

Having developed a robust route to **4**, we moved forward to prepare the diene segment (Scheme 2). Luche reduction of enone **27**, a late intermediate in our recent synthesis of **5**,[10b] followed by mesylation and elimination, gave conjugated diene **28** which, unfortunately, was not a suitable substrate for Diels–Alder reaction. Interestingly, enone **26**, the immediate precursor of **4**, underwent a similar sequence to afford an inseparable mixture of **29** and **30** in a ratio of ca 1:16, via the intermediary of allylic alcohol **31**. At ambient temperature, the amount of **30** in the mixture gradually decreased, while that of **29** increased. Meanwhile, another cyclopentadiene isomer, which was postulated to be **32**, emerged. These observations may be attributable to [1,5]-H shift processes.[19] Upon heating at 80 °C for 5 min, the original mixture turned into another inseparable mixture of **29** and **32** (ca. 2.6:1, Scheme 2). Prolonged reaction times at this temperature resulted in the generation of a fifth diene isomer **33**, and the ratio of **29**:**32**:**33** reached ca. 2.6:1:2.1 after 4 h. We isolated **33** in a pure form. This compound turned back into a mixture of **29**, **32**, and **33** (ca. 2.6:1:2.1) at 80 °C in 4 h, which indicated that the formation of **33** should have essentially no bearing on the efficiency of the Diels–Alder reaction under thermal conditions.

Subsequently, we prepared asperuloside tetraacetate (**34**) as the dienophile (Scheme 3). Known compound[27] **35** arising from (+)-genipin (**12**) was subjected to a sequence of acetylation, silylation, and selective deprotection of the less hindered silyl ether, to give lactol **36** as a mixture of two anomers in a ca. 1:1 ratio. "Dynamic kinetic" glycosylation of **36** with trichloroacetimidate **37** followed by desilylation provided compound **38** as a single stereoisomer. Exposure of **38** to Me_3SnOH furnished the lactone moiety[28] despite partial deacetylation; re-acetylation of the resultant mixture afforded **34** smoothly.

With the diene and dienophile in hand, we focused our attention to the intermolecular Diels–Alder reaction for completing the synthesis of **1** (Scheme 4). A convenient protocol was developed for the in situ preparation of the dienes from their precursor **31**: $MgSO_4$ was exploited as a mild yet efficient dehydrating reagent at elevated temperature. In the presence of $MgSO_4$ and BHT at 160 °C, cyclopentadiene **29** was generated in situ from **31** and then reacted with **34** to give cycloadducts **35**–**37**. A small amount of cycloadduct **38** corresponding to diene **32** was also detected. The yield of the four products reached ca. 79%, and the ratio was determined to be ca. 3.9:1.7:2.7:1 by ^1H NMR. When the mixture of **29** and **32** (Scheme 2) were used, the cycloaddition efficiency decreased (ca. 58% yield), while the ratio of the four products remained unchanged. After HPLC purification, **35**–**38** was obtained in 24%, 12%, 17%, and 8% overall yields from **31**, respectively. The structures of **35** and **36** were confirmed by X-ray crystallographic analysis (Scheme 4), and those of **37** and **38** were elucidated through extensive NMR studies.[29] We then examined a variety of Lewis acids as promoters for the Diels–Alder reaction. However, both substrates were labile under strongly acidic conditions. Acetal tolerating $Eu(fod)_3$[30] (DCE, 80 °C) led to a mixture of cycloadducts in ca. 30% yield; the predominant component **36** was isolated in 21% yield. Finally, reduction of **35** with Raney Ni followed by global deacetylation[31] rendered **1** smoothly. Over 100 mg of **1** were prepared in total. The spectra and physical properties of synthetic **1**, **4**, **6**, and **7** were identical to those reported for their naturally occurring counterparts, respectively. The structures of synthetic natural products **4**, **6**, and **7** and intermediates **14**, **15r**, **17**, **19**, **20r**, **24**, **25**, **26**, **28**, **31**, and **34** were verified by X-ray crystallographic analysis.

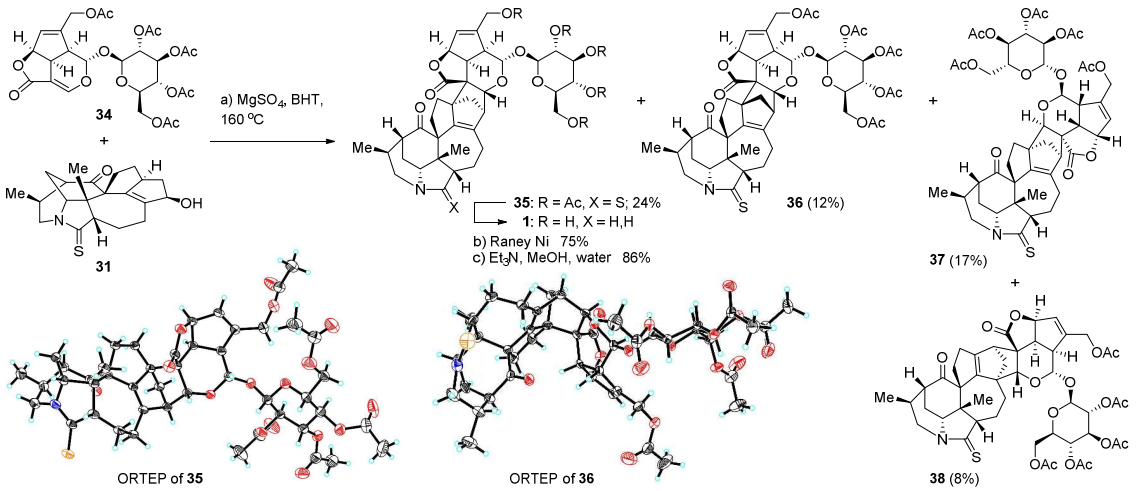
In summary, we have accomplished the first total synthesis of **1** exploiting an bioinspired Diels–Alder strategy. To prepare the diene, we developed a scalable route to **4** and achieved the first syntheses of **6** and **7**. The late stage cycloaddition of dienophile **34** and the in situ generated diene forged the highly congested norbornene domain of **1**.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Scheme 4. Completion of the Synthesis of Hybridaphniphylline B through an Intermolecular Diels−Alder Reaction



AUTHOR INFORMATION

Corresponding Author

*ali@sioc.ac.cn

Author Contributions

§W.Z., M.D., and J.L. contributed equally.

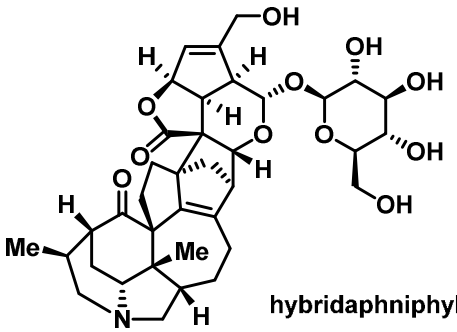
ACKNOWLEDGMENT

We thank Profs. Jian-Min Yue and Dean Tantillo and Dr. David Edmonds for discussions. Financial support was provided by the National Natural Science Foundation of China (21525209, 21621002, 21772225, and 21761142003), the Chinese Academy of Sciences (Strategic Priority Research Program XDB20000000 and Key Research Program of Frontier Sciences QYZDB-SSW-SLH040), Shanghai Science and Technology Commission (15JC1400400 and 17XD1404600), and the K. C. Wong Education Foundation.

REFERENCES

(1) (a) Kobayashi, J.; Kubota, T. *Nat. Prod. Rep.* **2009**, *26*, 936. (b) Chattopadhyay, A. K.; Hanessian, S. *Chem. Rev.* **2017**, *117*, 4104. (c) Kang, B.; Jakubec, P.; Dixon, D. J. *Nat. Prod. Rep.* **2014**, *31*, 550. (d) Yang, S.-P.; Yue, J.-M. *Acta Pharmacol. Sin.* **2012**, *33*, 1147.
(2) For a synthesis of isodaphlongamine H, a presumed *Daphniphyllum* alkaloid yet to be isolated from nature, see: Chattopadhyay, A. K.; Ly, V. L.; Jakkepally, S.; Berger, G.; Hanessian, S. *Angew. Chem., Int. Ed.* **2016**, *55*, 2577.
(3) For synthetic studies published after ref. 1b, see: (a) Coussanes, G.; Bonjoch, J. *Org. Lett.* **2017**, *19*, 878. (b) Shao, H.; Bao, W.; Jing, Z.-R.; Wang, Y.-P.; Zhang, F.-M.; Wang, S.-H.; Tu, Y.-Q. *Org. Lett.* **2017**, *19*, 4648.
(4) (a) Heathcock, C. H.; Davidsen, S. K.; Mills, S.; Sanner, M. A. *J. Am. Chem. Soc.* **1986**, *108*, 5650. (b) Ruggeri, R. B.; Hansen, M. M.; Heathcock, C. H. *J. Am. Chem. Soc.* **1988**, *110*, 8734. (c) Ruggeri, R. B.; McClure, K. F.; Heathcock, C. H. *J. Am. Chem. Soc.* **1989**, *111*, 1530. (d) Ruggeri, R. B.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 3714. (e) Stafford, J. A.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 5433. (f) Heathcock, C. H.; Stafford, J. A.; Clark, D. L. *J. Org. Chem.* **1992**, *57*, 2575. (g) Heathcock, C. H.; Kath, J. C.; Ruggeri, R. B. *J. Org. Chem.* **1995**, *60*, 1120. (h) Piettre, S.; Heathcock, C. H. *Science* **1990**, *248*, 1532.
(5) Weiss, M. E.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 11501.
(6) (a) Shvartsbart, A.; Smith, A. B. III, *J. Am. Chem. Soc.* **2014**, *136*, 870. (b) Shvartsbart, A.; Smith, A. B. III, *J. Am. Chem. Soc.* **2015**, *137*, 3510.
(7) Yamada, R.; Adachi, Y.; Yokoshima, S.; Fukuyama, T. *Angew. Chem., Int. Ed.* **2016**, *55*, 6067.
(8) Chen, X.; Zhang, H.-J.; Yang, X.; Lv, H.; Shao, X.; Tao, C.; Wang, H.; Cheng, B.; Li, Y.; Guo, J.; Zhang, J.; Zhai, H. *Angew. Chem., Int. Ed.* **2018**, *57*, 947. In this paper, a synthesis of daphnilongeranin B (**4**) was reported for the first time.
(9) Shi, H.; Michaelides, I. N.; Darses, B.; Jakubec, P.; Nguyen, Q. N. N.; Paton, R. S.; Dixon, D. J. *J. Am. Chem. Soc.* **2017**, *139*, 17755.
(10) (a) Lu, Z.; Li, Y.; Deng, J.; Li, A. *Nat. Chem.* **2013**, *5*, 679. (b) Li, J.; Zhang, W.; Zhang, F.; Chen, Y.; Li, A. *J. Am. Chem. Soc.* **2017**, *139*, 14893. (c) Chen, Y.; Zhang, W.; Ren, L.; Li, J.; Li, A. *Angew. Chem., Int. Ed.* **2018**, *57*, 952.
(11) (a) Li, J.; Yang, P.; Yao, M.; Deng, J.; Li, A. *J. Am. Chem. Soc.* **2014**, *136*, 16477. (b) Meng, Z.; Yu, H.; Li, L.; Tao, W.; Chen, H.; Wan, M.; Yang, P.; Edmonds, D. J.; Zhong, J.; Li, A. *Nat. Commun.* **2015**, *6*, 6096. (c) Yang, M.; Li, J.; Li, A. *Nat. Commun.* **2015**, *6*, 6445. (d) Yang, M.; Yang, X.; Sun, H.; Li, A. *Angew. Chem., Int. Ed.* **2016**, *55*, 2851. (e) Yang, P.; Yao, M.; Li, J.; Li, Y.; Li, A. *Angew. Chem., Int. Ed.* **2016**, *55*, 6964. (f) Li, H.; Chen, Q.; Lu, Z.; Li, A. *J. Am. Chem. Soc.* **2016**, *138*, 15555.
(12) Li, Y.; Zhu, S.; Li, J.; Li, A. *J. Am. Chem. Soc.* **2016**, *138*, 3982.
(13) Wang, F.; Mao, M.-F.; Wei, G.-Z.; Gao, Y.; Ren, F.-C.; Liu, J.-K. *Phytochemistry* **2013**, *95*, 428.
(14) For isolation of structurally related alkaloids, see: Di, Y.-T.; Wee, C.-S.; Li, C.-S.; Kong, N.-C.; Wang, J.-S.; Fang, X.; Zhu, H.-J.; Wu, Y.-D.; Hao, X.-J. *Tetrahedron* **2014**, *70*, 4017.
(15) Yang, S.-P.; Zhang, H.; Zhang, C.-R.; Cheng, H.-D.; Yue, J.-M. *J. Nat. Prod.* **2006**, *69*, 79.
(16) (a) Zhang, H.; Yang, S.-P.; Fan, C.-Q.; Ding, J.; Yue, J.-M. *J. Nat. Prod.* **2006**, *69*, 553. (b) Di, Y.-T.; He, H.-P.; Lu, Y.; Yi, P.; Li, L.; Wu, L.; Hao, X.-J. *J. Nat. Prod.* **2006**, *69*, 1074.
(17) Zhang, H.; Zhang, D.-D.; Li, J.-Y.; Shyaula, S. L.; Li, J.; Yue, J.-M. *RSC Adv.* **2016**, *6*, 44402.
(18) (a) Deng, J.; Zhou, S.; Zhang, W.; Li, J.; Li, R.; Li, A. *J. Am. Chem. Soc.* **2014**, *136*, 8185. (b) Deng, J.; Zhu, B.; Lu, Z.; Yu, H.; Li, A. *J. Am. Chem. Soc.* **2012**, *134*, 920.
(19) Spangler, C. W. *Chem. Rev.* **1976**, *76*, 187.
(20) Sisido, K.; Kurozumi, S.; Utimoto, K. *J. Org. Chem.* **1969**, *34*, 2661.
(21) Sladojevich, F.; Michaelides, I. N.; Darses, B.; Ward, J. W.; Dixon, D. J. *Org. Lett.* **2011**, *13*, 5132.
(22) Darses, B.; Michaelides, I. N.; Sladojevich, F.; Ward, J. W.; Rzepa, P. R.; Dixon, D. J. *Org. Lett.* **2012**, *14*, 1684.
(23) Xiong, X.; Li, Y.; Lu, Z.; Wan, M.; Deng, J.; Wu, S.; Shao, H.; Li, A. *Chem. Commun.* **2014**, *50*, 5294.
(24) Boeckman, R. K. Jr.; Rico Ferreira, M. d. R.; Mitchell, L. H.; Shao, P. *J. Am. Chem. Soc.* **2002**, *124*, 190.
(25) Grieco, P. A.; Brandes, E. B.; McCann, S.; Clark, J. D. *J. Org. Chem.* **1989**, *54*, 5849.
(26) Chung, Y. K.; Lee, B. Y.; Jeong, N.; Hudecek, M.; Pauson, P. L. *Organometallics* **1993**, *12*, 220.
(27) Nakatani, K.; Shimano, K.; Hiraishi, A.; Han, Q.; Isoe, S. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 2646.
(28) Nicolaou, K. C.; Estrada, A. A.; Zak, M.; Lee, S. H.; Safina, B. S. *Angew. Chem., Int. Ed.* **2005**, *44*, 1378.
(29) The facial bias of the dienophile presumably determined the *cis* ring junction of the furopyran system of the cycloadducts.
(30) Xiong, X.; Zhang, D.; Li, J.; Sun, Y.; Zhou, S.; Yang, M.; Shao, H.; Li, A. *Chem. Asian J.* **2015**, *10*, 869.
(31) Mangion, I. K.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 3696.

TOC



hybridaphniphylline B