

Rapid Construction of [5–6–7] Tricyclic Ring Skeleton of *Calyciphylline* Alkaloid Daphnilongeranin B

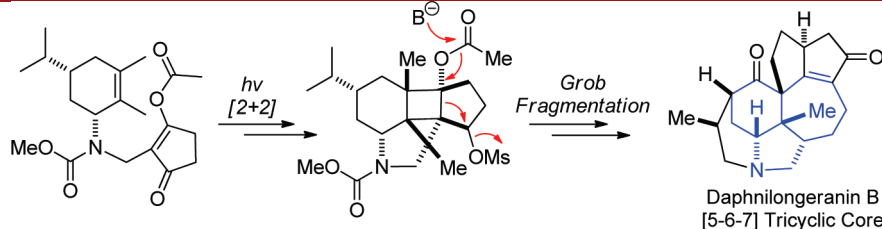
Chen Xu,[†] Zheng Liu,[†] Huifei Wang,[†] Bo Zhang,[†] Zheng Xiang,^{†,§} Xiaojiang Hao,^{*,‡} and David Zhigang Wang^{*,†}

Laboratory of Chemical Genomics, School of Chemical Biology and Biotechnology, Shenzhen Graduate School of Peking University, Shenzhen University Town, Nanshan District, Shenzhen, China 518055, and Kunming Institute of Botany, Chinese Academy of Sciences, Kunming, China 650204

dzw@szpku.edu.cn haoxj@mail.kib.ac.cn

Received February 3, 2011

ABSTRACT



A concise photochemical [2 + 2] cycloaddition–Grob fragmentation sequence sets the common tricyclic ring skeletons of the *Calyciphylline* A-type alkaloids, particularly those in daphnilongeranins, daphniyunnines, and daphniglaucins.

Of the many fascinating natural products uncovered in recent years, the *Daphniphyllum* class of alkaloids stood out for their highly impressive structural diversities, stereochemical complexities, and skeletal novelties. More than 200 members have been isolated from 13 species of the genus *Daphniphyllum*.¹ The biological functions and pharmacological activities of these compounds have been poorly studied so far due to their extremely limited natural supply. These, however, would invite further investigations since the relevant plant species themselves have long been used in acclaimed traditional herbal medical formulations, and several members had already been shown to have

meaningful cytotoxic² and antioxidation³ properties and enhancement effects on neurotrophic factor biosynthesis.⁴

Attracted by the synthetic challenges posed by these structures, particularly those of the *Daphniphyllum* subclass *Calyciphylline*-type alkaloids⁵ including calyciphylline A, daphniglaucins, daphnilongeranins, and daphniyunnines (Figure 1), we initiated a program aiming at total syntheses of some members of this series of compounds. Within this context, remarkably, as visualized by the

[†] Shenzhen Graduate School of Peking University.

[‡] Kunming Institute of Botany.

[§] Current address: The Jack H. Skirball Center for Chemistry & Proteomics, the Salk Institute for Biological Studies, 10010 N. Torrey Pines Road, La Jolla, CA 92037-1099.

(1) For a comprehensive overview, see: Kobayashi, J.; Kubota, T. *Nat. Prod. Rep.* **2009**, *26*, 936–962.

(2) (a) Morita, H.; Kobayashi, J. *Tetrahedron* **2002**, *58*, 6637–6641. (b) Kobayashi, J.; Ueno, S.; Morita, H. *J. Org. Chem.* **2002**, *67*, 6546–6549. (c) Zhang, Y.; He, H. P.; Di, Y. T.; Mu, S. Z.; Wang, Y. H.; Wang, J. S.; Li, C. S.; Kong, N. C.; Gao, S.; Hao, X. J. *Tetrahedron Lett.* **2007**, *48*, 9104–9107.

(3) Yamamura, S.; Hirata, Y. *Tetrahedron Lett.* **1974**, *15*, 2849–2852.

(4) (a) Saito, S.; Yahata, H.; Kubota, T.; Obara, Y.; Nakahata, N.; Kobayashi, J. *Tetrahedron* **2008**, *64*, 1901–1908. (b) Roll, D. M.; Biskupiak, J. E.; Mayne, C. L.; Ireland, C. M. *J. Am. Chem. Soc.* **1986**, *108*, 6680–6682.

(5) (a) Di, Y. T.; He, H. P.; Ping, Y. L.; Li, Y. L.; Wu, L.; Hao, X. J. *J. Nat. Prod.* **2006**, *69*, 1074–1076. (b) Mu, S. Z.; Li, C. S.; He, H. P.; Di, Y. T.; Wang, Y.; Wang, Y. H.; Zhang, Z.; Lü, Y.; Zhang, L.; Hao, X. J. *J. Nat. Prod.* **2007**, *70*, 1628–1631. (c) Chen, X.; Zhan, Z. J.; Yue, J. M. *Helv. Chim. Acta* **2005**, *88*, 854–860. (d) Yang, S. P.; Zhang, H.; Zhang, C. R.; Cheng, H. D.; Yue, J. M. *J. Nat. Prod.* **2006**, *69*, 79–82. (e) Zhang, H.; Yang, S. P.; Fan, C. Q.; Ding, J.; Yue, J. M. *J. Nat. Prod.* **2006**, *69*, 553–557. (f) Zhang, C. R.; Liu, H. B.; Dong, S. H.; Zhu, J. Y.; Wu, Y.; Yue, J. M. *Org. Lett.* **2009**, *11*, 4692–2695. (g) Morita, H.; Kobayashi, J. *Org. Lett.* **2003**, *5*, 2895–2898. (h) Takatsu, H.; Morita, H.; Shen, Y. C.; Kobayashi, J. *Tetrahedron* **2004**, *60*, 6279–6284. (i) Yahata, H.; Kubota, T.; Kobayashi, J. *J. Nat. Prod.* **2009**, *72*, 148–151. (j) Luo, D. Q.; Zhu, W. L.; Yang, X. L.; Liang, S. J.; Cao, Z. R. *Helv. Chim. Acta* **2010**, *93*, 1209–1215.

structural inner connections highlighted in Figure 1, the three types of alkaloids share the same [5–6–7] tricyclic core skeleton **1**. The importance of exploring a general and efficient approach toward the rapid assembly of **1** is

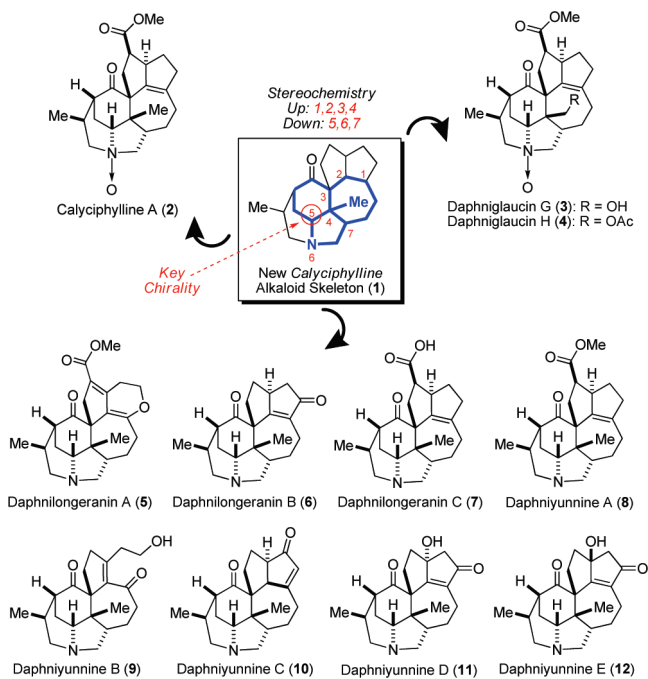


Figure 1. Structural diversities of *Calyciphylline* alkaloids.

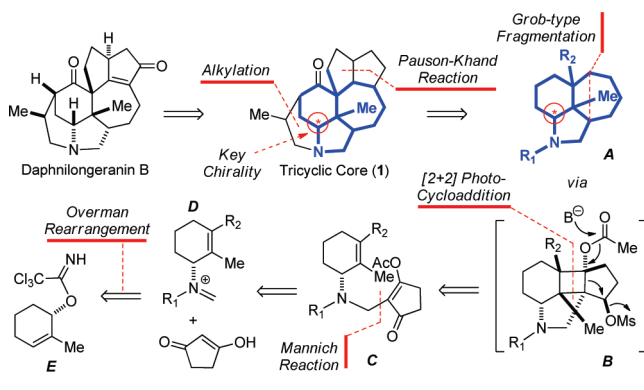
therefore immediately recognizable, as this motif potentially may constitute the central platform on which the structure and functionality complexities of these alkaloids might have evolved. Up to this point, no total synthesis of any member of these new alkaloid structures has been reported.⁶

Of several stereogenic centers present in these molecules, up to seven (six carbon atom-centered, i.e., 1–2–3–4–5–7, and one nitrogen atom-centered, i.e., 6) were found to be densely and contiguously distributed on the bowl-shaped framework of **1**. Further inspection on **1**'s stereochemical architecture revealed two interesting features: one, the ring junctions within the tricyclic skeleton adopt *cis*-geometry; and two, relative to the tricyclic plane, these stereogenic centers were well differentiated into two contiguous “up” and “down” sets (Figure 1) where such orientations flip at the key C-5 chirality. These observations in turn inspired a photochemical cycloaddition event⁷ as a key stereochemically

controlling strategy in the facile construction of the tricyclic core structure **1**.

With daphnilongeranin **B** as a specific target, our synthetic plan is briefly outlined in Scheme 1. We envisioned that the southwestern piperidine ring could be constructed through a relatively routine carbonyl-directed α -alkylation protocol, and the northeastern [5–5] bicyclic cyclopentenone unit could be installed with a tandem Pauson–Khand annulation–double bond shift sequence. These steps would efficiently degrade the target into the neatly tricyclic intermediate **A**. With the C-5 chirality (star-labeled below) as a critical stereochemical control element, the seven-membered ring in **A** could be accessed with a [2 + 2] photochemical cycloaddition event on allylic amine **C**, followed by a ring-strain-driven Grob-type fragmentation⁸ collapsed through a trajectory illustrated in **B**. **C** itself would be prepared by a Mannich-type⁹ condensation between an appropriately functionalized iminium ion **D** and cyclopentanedione. Finally, the required 1,3-transposition of amine

Scheme 1. Retrosynthetic Disconnections



and alcohol functions could be achieved by an Overman rearrangement¹⁰ on the carboximidate precursor **E**.

To examine the feasibility of the above strategies, a synthesis in the forward direction was then pursued with (*S*)-(+)-carvone as an appropriate starting point. We report herein our success in implementing these reaction sequences for the construction of *Calyciphylline* [5–6–7] tricyclic core structure **24** and its close analog **31** with two vicinally positioned angular methyl groups (*vide infra*).

As summarized in Scheme 2, (*S*)-(+)-carvone was converted into allylic alcohol **13** with a known PtO_2/H_2 alkene hydrogenation– LiAlH_4 carbonyl reduction procedure.¹¹

(6) For recent studies directed toward the total synthesis of new *Daphniphyllum* alkaloids, see: (a) Ikeda, S.; Shibuya, M.; Kanoh, N.; Iwabuchi, Y. *Org. Lett.* **2009**, *11*, 1833–1836. (b) Dunn, T. B.; Ellis, J. M.; Kofink, C. C.; Manning, J. R.; Overman, L. E. *Org. Lett.* **2009**, *11*, 5658–5661. (c) Solé, D.; Urbaneja, X.; Bonjoch, J. *Org. Lett.* **2006**, *7*, 5461–5464. (d) Coldham, I.; Burrell, A. J. M.; Guerrand, H. D. S.; Oram, N. *Org. Lett.* 2011, ASAP (DOI: 10.1021/ol102961x).

(7) (a) Hoffmann, N. *Chem. Rev.* **2008**, *108*, 1052–1103. (b) Winkler, J. D.; Bowen, C. M.; Liotta, F. *Chem. Rev.* **1995**, *95*, 2002–2020. (c) Oppolzer, W. *Acc. Chem. Res.* **1982**, *15*, 135–141. (d) Crimmins, M. T. *Chem. Rev.* **1988**, *88*, 1453–1473.

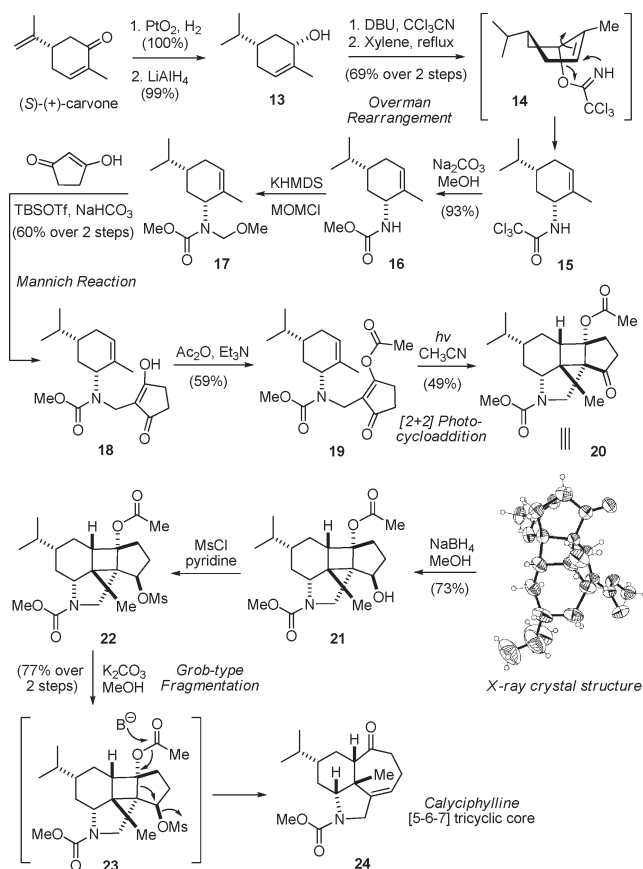
(8) (a) Prantz, K.; Mulzer, J. *Chem. Rev.* **2010**, *110*, 3741–3766. (b) Weyerstahl, P.; Marschall, H. *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 6, pp 1044–1065.

(9) For a review on Mannich reactions, see: Arend, M.; Westermann, B.; Risch, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 1045–1070.

(10) (a) Overman, L. E. *J. Am. Chem. Soc.* **1976**, *98*, 2901–2910. (b) Overman, L. E. *Acc. Chem. Res.* **1980**, *13*, 218–224. (c) Overman, L. E. *Angew. Chem., Int. Ed.* **1984**, *23*, 579–586.

(11) (a) Sorensen, E. J.; Shipe, W. D. *J. Am. Chem. Soc.* **2006**, *128*, 7025–7035. (b) Bourque, L. E.; Cleary, P. A.; Woerpel, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 12602–12603.

Scheme 2. Synthesis of [5–6–7] Tricyclic Core **24**

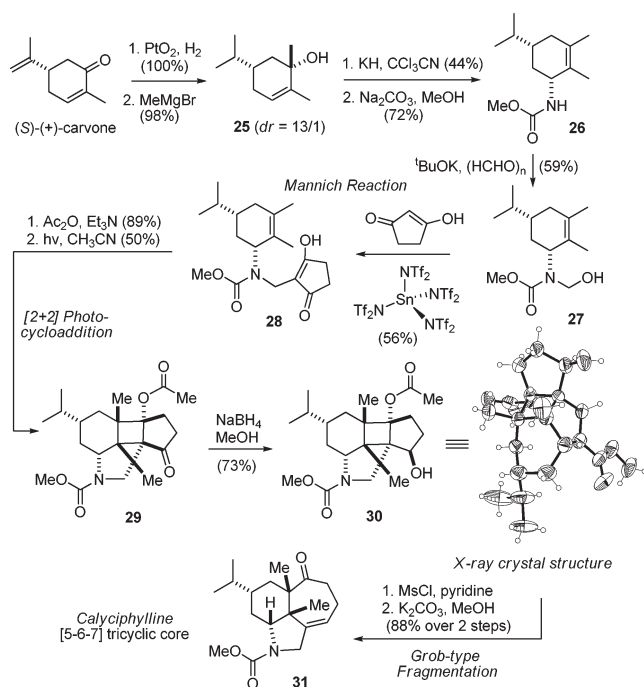


13 Reacted with CCl_3CN to yield an imidate which upon heating in xylene rearranged to **16** after methanolysis of the resultant allylic trichloroacetamide **15**¹² intermediate, with a total yield of 64% over the three-step sequence. **16** was next transformed to **17** with MOMCl, which, under the action of TBSOTf, underwent direct Mannich condensation with cyclopentanedione to give enone **18**.¹³ It merits a note here that the choice of TBSOTf is critical, as a range of other Lewis acid promoters screened, such as TMSOTf, TIPSOTf, TiCl_4 , BF_3 , all lead to significantly lower yields or complicated mixtures. Direct photochemical irradiation of **18** failed to give the desired cycloaddition product but cleanly yielded the de Mayo-type diketone structure, so its hydroxyl group was acylated first; the resultant **19** was then subjected to photochemical irradiation with light of a primary 254 nm (via medium-pressure Hg lamp) wavelength in CH_3CN to yield the expected [2 + 2] cycloaddition product **20** in 49% yield. **20** Possesses a highly congested [6–4–5–5] tetracyclic skeleton, and its absolute stereochemistry was unambiguously established through

(12) For an important improvement on Overman rearrangement, see: (a) Nishikawa, T.; Asai, M.; Ohya, N.; Isobe, M. *J. Org. Chem.* **1998**, *63*, 188–192. (b) Nishikawa, T.; Urabe, D.; Tomita, M.; Tsujimoto, T.; Iwabuchi, T.; Isobe, M. *Org. Lett.* **2006**, *8*, 3263–3266.

(13) Othman, R. B.; Bousquet, T.; Fousse, A.; Othman, M.; Dalla, V. *Org. Lett.* **2005**, *7*, 2825–2828.

Scheme 3. Synthesis of [5–6–7] Tricyclic Core **31**



single crystal X-ray analysis. Just as anticipated, the allylic chirality in **19** (i.e., the C-5 chirality in **1**) was capable of directing an intramolecular [2 + 2] cycloaddition through a highly organized *exo*-alkene-ene transition state assembly, thereby leading to **20** with essentially complete stereochemical control over the four contiguous chiral centers on its cyclobutane ring. It should be emphasized that the success of this photochemical cycloaddition seemed to depend sensitively on the electronic property of the *N*-protecting group; MeOC(O) was found to be optimal in a variety of substituents examined. The ketone carbonyl in **20** was reduced with NaBH_4 to generate alcohol **21**. **21** was subsequently mesylated with MsCl/pyridine and subjected to K_2CO_3 -promoted Grob fragmentation (structured as **23**); the tetracyclic rings collapsed rapidly to give the desired tricyclic [5–6–7] core **24** in 77% yield over these two steps.

Execution of these reaction sequences in pursuit of analogous structure **31** with the vicinally positioned angular methyl groups, however, had proven to be nontrivial (Scheme 3). Although (*S*)-(+)-carvone can be converted to allylic carbamate **26** smoothly with the aid of a room-temperature (i.e., no xylene refluxing was required herein) Overman rearrangement driven presumably by the release of quaternary steric congestion in the corresponding imidate intermediate, **26** failed completely to react in a similar manner as that defined in procedures from **16–18** of Scheme 2. It was only after extensive screening had we eventually been able to identify $\text{Sn}(\text{NTf}_2)_4$ as a viable Lewis acid¹⁴ that promoted the desired Mannich

(14) Othman, R. B.; Affani, R.; Tranchant, M. J.; Antonioti, S.; Dalla, V.; Duñach, E. *Angew. Chem., Int. Ed.* **2010**, *49*, 776–780.

condensation between an iminium ion generated from hydroxymethylated **26** (i.e., structure **27**) and cyclopentanedione, leading to enone **28** in 56% isolated yield. **28** was next photocyclized to give tetracyclic ketone **29** with comparable efficiency and stereoselectivity found previously in the transformation of **19** to **20**. Upon ketone reduction in **29**, the stereostructure of **30** was again determined by single crystal X-ray analysis. Finally, Grob fragmentation on mesylated **30** was triggered by K_2CO_3 in methanol to yield tricyclic [5–6–7] core **31** in 88% overall yield.

In summary, with Overman rearrangement, Mannich reaction, [2 + 2] photochemical cycloaddition, and Grob fragmentation as key steps, we have defined a concise and highly stereoselective synthetic approach for the construction of [5–6–7] tricyclic core skeletons commonly found in a range of the *Daphniphyllum* subclass *Calyciphylline* A-type alkaloids, particularly those in calyciphylline A, daphnihlaucins, daphnilongeranins, and daphniyunnines. Central to the success reported here is the recognition that

C-5 allylic chirality plays a pivotal role in directing the entire stereochemical course involved in the outlined sequences, thus significantly facilitating chirality control in a highly congested polycyclic setting. Continued efforts toward a total synthesis of daphnilongeranin B are currently underway.

Acknowledgment. We thank the National Science Foundation of China (Grants 20872004 and 20972008 to D.Z.W. and 20672120 to X.J.H.), the National “973 Project” from the State Ministry of Science and Technology, the Shenzhen Bureau of Science, Technology and Information, and the Shenzhen “*Shuang Bai Project*” for generous financial support.

Supporting Information Available. Experimental details and procedures, compound characterization data, copies of 1H , ^{13}C , and 2D-NMR spectra for new compounds, and X-ray crystallographic data. This material is available free of charge via the Internet at <http://pubs.acs.org>.