nature chemistry

ARTICLES

PUBLISHED ONLINE: 30 JUNE 2013 | DOI: 10.1038/NCHEM.1694

Total synthesis of the *Daphniphyllum* alkaloid daphenylline

Zhaoyong Lu†, Yong Li†, Jun Deng and Ang Li*

The *Daphniphyllum* alkaloids are a large class of natural products isolated from a genus of evergreen plants widely used in Chinese herbal medicine. They display a remarkable range of biological activities, including anticancer, antioxidant, and vasorelaxation properties as well as elevation of nerve growth factor. Daphenylline is a structurally unique member among the predominately aliphatic *Daphniphyllum* alkaloids, and contains a tetrasubstituted arene moiety mounted on a sterically compact hexacyclic scaffold. Herein, we describe the first total synthesis of daphenylline. A gold-catalysed 6-*exo*-dig cyclization reaction and a subsequent intramolecular Michael addition reaction, inspired by Dixon's seminal work, were exploited to construct the bridged 6,6,5-tricyclic motif of the natural product at an early stage, and the aromatic moiety was forged through a photoinduced olefin isomerization/6π-electrocyclization cascade followed by an oxidative aromatization process.

Plant natural products have played an important role in chemistry, biology and medical science for centuries[1], and chemical synthesis continues to serve as a powerful tool to understand the functions of these compounds[2–5]. *Daphniphyllum* is a genus of dioecious evergreen plants native to Asia, the leaves and roots of which are used widely in Chinese herbal medicine[6]. About 250 *Daphniphyllum* alkaloids have been isolated from this genus to date[7]. From a structural perspective, these naturally occurring molecules usually possess a bridged and fused hexa- or pentacyclic scaffold that contains continuous stereogenic centres; based on their connectivity modes, they can be further classified into more than 20 subfamilies. Shown in Fig. 1 are the molecular architectures that represent several major subfamilies of *Daphniphyllum* alkaloids. Intrigued by these fascinating structures, a series of biosynthetic hypotheses were suggested[7], led by Heathcock's elegant proposal for the biosynthesis of methyl homosecodaphniphyllate (**1**; Fig. 1) from a squalene derivative[8,9]. Although some isotopic labelling experiments were carried out[7], identifying the biosynthetic network that connects all the subfamilies of *Daphniphyllum* alkaloids at the biochemical level remains a formidable challenge. These structurally diverse and complex natural products display a remarkable range of biological activities[7], such as anticancer[10], antioxidation[11], elevation of nerve growth factor[12] and vasorelaxation[13]. However, the systematic biological profiling of the *Daphniphyllum* alkaloids and their derivatives is hampered by the scarce supply of these compounds from natural sources.

The formidable challenge posed by their intricate structures resulted in intensive efforts to achieve the total synthesis of *Daphniphyllum* alkaloids[7,8,14–33], which would also provide a great opportunity to accelerate biological and biosynthetic studies of them. Heathcock and co-workers accomplished a landmark synthesis of methyl homosecodaphniphyllate (**1**) guided by their biosynthetic hypothesis[8,14], which formed the basis for their successful syntheses of methyl homodaphniphyllate[16], daphnilactone A[17] and bukittinggine[18] (**2**–**4**; Fig. 1), as well as secodaphniphylline[19] and codaphniphyllin[20] (side-chain analogues of **1** and **2**, respectively). Recently, Carreira and co-workers disclosed the total synthesis of daphmanidin E (**5**; Fig. 1) from a non-methyl homodaphniphyllate-type subfamily[21], which represents the first breakthrough in *Daphniphyllum* alkaloid synthesis in nearly two decades. To date, however, the remaining members of this large natural product family, including those from the calyciphylline A (**6**) and daphnicyclidin (**7**) subfamilies[7], which feature a 6,*n*,5-briged tricyclic moiety (Fig. 1, total number up to about 50), have not been synthesized successfully. Notably, Dixon and co-workers developed an elegant synthesis of the tricyclic core of calyciphylline A-type *Daphniphyllum* alkaloids (Fig. 2)[26], which sets an important basis for the collective synthesis of the above-mentioned subfamily members. The highly diastereoselective intramolecular Michael addition reaction used for their construction of the 5,6-bicyclic system[26,27] is particularly inspiring to this work (*vide infra*). A structurally unique calyciphylline A family member, isolated by Hao and co-workers from the fruits of *D. longeracemosum* in 2009, namely daphenylline (Fig. 1; **8**)[34], attracted our, as well as others', attention[30,31]. Daphenylline is the only *Daphniphyllum* alkaloid to incorporate an arene motif, in contrast to the other members of this aliphatic natural product family. Herein, we report the first total synthesis of daphenylline (**8**).

Results and discussion

The structural features of the bridged 6,*n*,5-tricyclic ($n = 6$ or 7) motif (Fig. 1, bottom right) of daphenylline (**8**) and its congeners (for example, **6** and **7**), as well as Dixon's seminal work[26] described above (Fig. 2), inspired us to envision a common intermediate such as **9** (Fig. 3), potentially useful for the divergent synthesis of a number of structurally related *Daphniphyllum* alkaloids. In the case of daphenylline, the most significant synthetic challenge (the assembly of the sterically encumbered tetrasubstituted arene set in a sterically demanding environment) could be achieved by a 6π-electrocyclization/aromatization sequence, similar to that used during our total synthesis of tubingensin A[35]. With this strategy in mind, we undertook a retrosynthetic analysis, as shown in Fig. 3. Hexacyclic ketolactam **10** was considered to be a direct precursor of daphenylline (**8**), the seven-membered ring of which could be disassembled to afford a pentacyclic iodide **11** as the substrate for a 7-*exo*-trig radical cyclization. Based on the 6π-electrocyclization/

State Key Laboratory of Bioorganic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, China, †These authors contributed equally to this work. *e-mail: ali@sioc.ac.cn

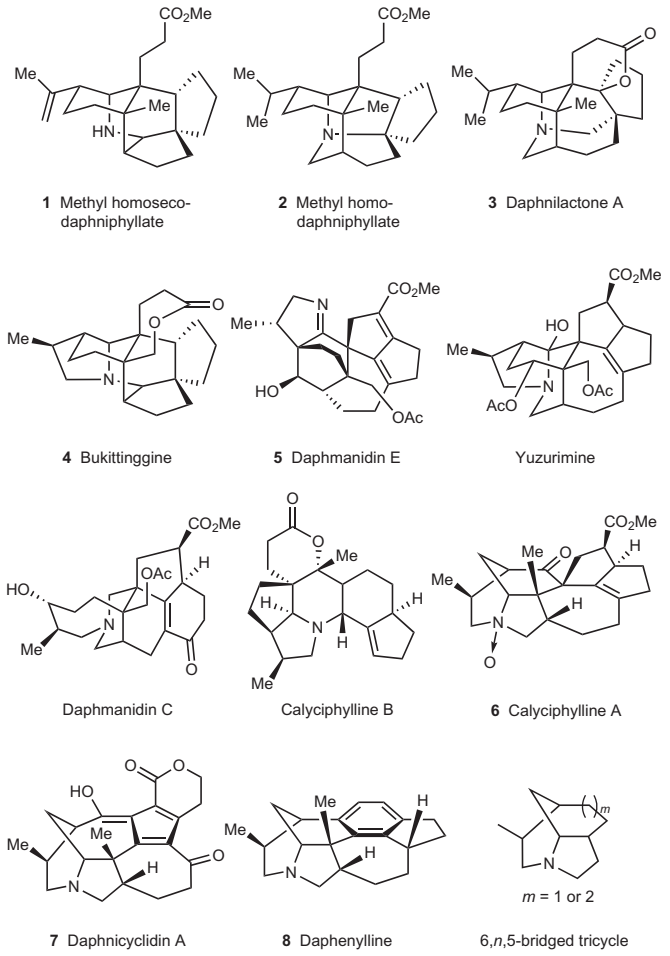

Figure 1 | Selected natural products that represent major subfamilies of *Daphniphyllum* alkaloids. The 6,*n*,5-bridged tricycle (bottom right) indicates a common structural motif shared by **6**, **7** and **8**, as well as the related *Daphniphyllum* subfamily members (up to about 50). A versatile intermediate for the divergent synthesis of these *Daphniphyllum* alkaloids could be devised based on this structural motif.

aromatization strategy, deconstruction of the benzene ring of **11** would give a *cis*-triene **12**, which could be further disconnected at the C1–C13 bond to give the devised bridged tricyclic intermediate **9** and a suitable side-chain coupling partner. Compound **9** was traced back to bridged-bicyclic amine **13** and carboxylic acid **14**. The recombination of these two fragments could be achieved through an amide-bond formation followed by an intramolecular 1,4-addition; both reactions are well-precedented in Dixon's synthesis of the calyciphylline A-type skeleton (Fig. 2)[26,27]. A gold-catalysed alkyne-cyclization process (Toste–Conia-ene reaction)[36] could be exploited to construct **13** from the silyl enol ether generated from ketone **15**. This precursor should be readily accessible from the known hydroxy enone **16** and sulfonamide **17** through a Mitsunobu reaction. Notably, the C18 stereochemistry of **8** could be established by facial selective hydrogenation of the corresponding methylene substrate at a suitable stage.

Based on the above analysis, we started our adventure with the initial aim to reach the bridged tricycle **9**, as shown in Fig. 4. Coupling of the enantioenriched hydroxy enone **16** (six steps from *m*-methylanisole, 98% enantiomeric excess (e.e.))[37] and sulfonamide **17** under Mitsunobu conditions provided compound **15** in 86% yield, which retained high enantiopurity (97% e.e.). Not surprisingly, the following gold-catalysed 6-*exo*-dig cyclization[36,38] to construct the bridged [3.3.1]bicyclic system turned out to be more difficult than that of the well-precedented 5-*exo*-dig cases[36,39]. Attempts to form the silyl enol ether **18** in the presence of triisopropylsilyl trifluoromethanesulfonate (TIPSOTf) and triethylamine (Et_3N) or diisopropylethylamine[36] led to a mixture of **18** and **19** (Fig. 4) in favour of the latter. To avoid the undesired γ-deprotonated product **19**, the less basic 2,6-lutidine was employed in the above reaction to give **18** almost exclusively. Compound **18** was subjected to standard cationic gold cyclization conditions (chloro(triphenylphosphine)gold(I) ($Au(PPh_3)Cl$, 0.2 equiv.), $AgSbF_6$ (0.3 equiv.) and MeOH), which rapidly generated the desired bridged bicycle **20** (28%), and a significant amount of the direct desilylated product **15** was recovered. From a mechanistic point of view, the formation of **20** involved protonolysis of the corresponding alkenyl gold species under strongly acidic conditions, which may also lead to rapid desilylation. Thus, we examined the effect of different silyl groups in tuning the ratio of cyclization/desilylation products. As we expected, the *tert*-butyldimethylsilyl (TBS) enol ether gave a poorer ratio (14% of **20**, 74% of **15**), and the *tert*-butyldiphenylsilyl enol ether improved the reaction output (60% of **20**, 20% of **15**). As the counterion of the gold complex (initially from the corresponding silver salt) may have a subtle influence on the reactivity of the active gold species[40] as well as on the Brönsted acidity of the reaction environment, various silver salts ($AgBF_4$, $AgSbF_6$, silver trifluoromethanesulfonate (AgOTf), $AgOCOCF_3$ and others) were also tested. To our delight, AgOTf proved to be the most effective additive and rendered **20** in 72% yield from **15** (with 11% of **15** recovered). Replacing MeOH with other protic solvents, such as isopropyl alcohol, did not improve the efficiency, and decreasing the catalyst loading to 0.1 equiv. led to 70% yield of **20** with 29% of **15** recovered. With **20** in hand, desulfonation with *p*-thiocresol in the presence of K_2CO_3, followed by condensation with carboxylic acid **14** under 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC·HCl)/1-hydroxybenzotriazole (HOBt) conditions afforded amide **21** in 72% overall yield. Compound **21** underwent intramolecular Michael addition[26,27] promoted by K_2CO_3 in CH_3CN at 100 °C to give **9** in 86% yield, together with 9% of the chromatographically separable C6 diastereomer. Interestingly, treatment of **21** with potassium hexamethyldisilazide (KHMDS)

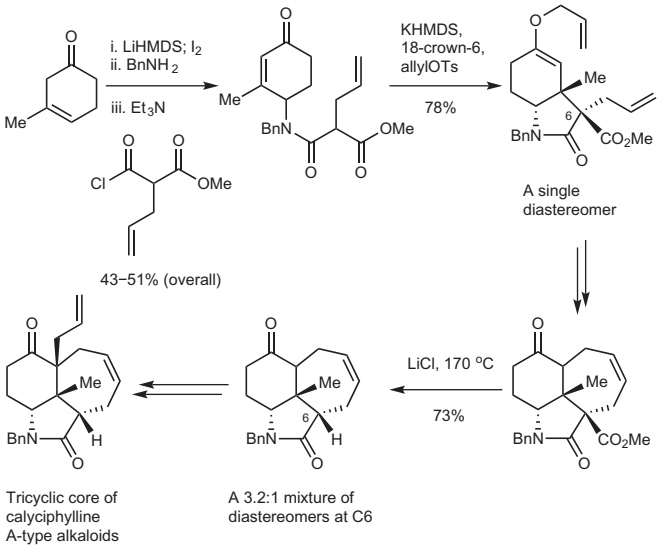

Figure 2 | An inspiring synthesis of the tricyclic core of calyciphylline A-type alkaloids by Dixon and co-workers[26]. A highly diastereoselective intramolecular Michael addition reaction was developed for the construction of the 5,6-bicyclic system. LiHMDS, lithium hexamethyldisilazide; Ts, *p*-toluenesulfonyl.

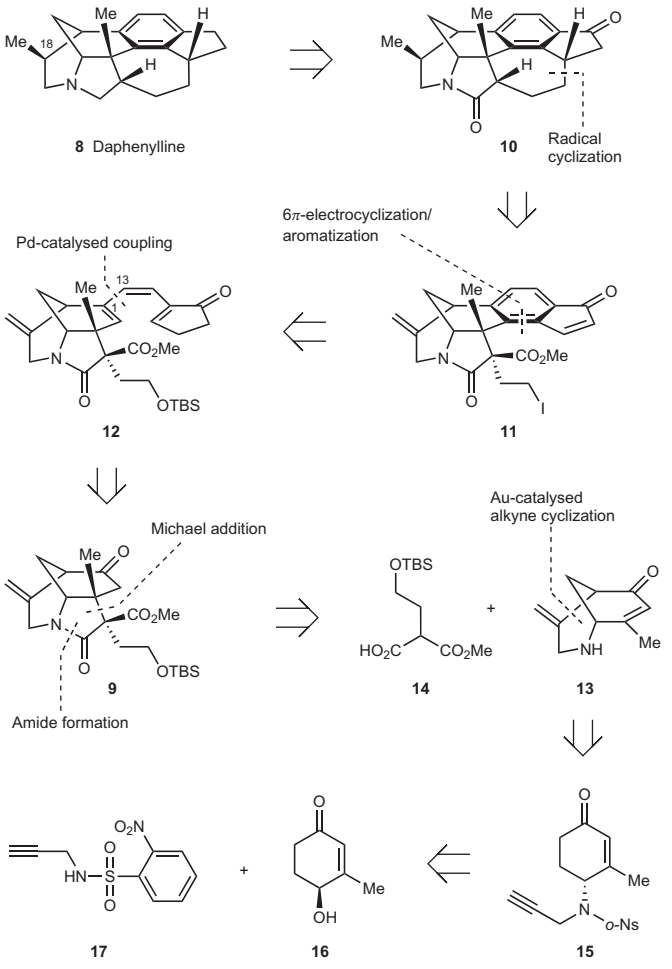

Figure 3 | Retrosynthetic analysis of daphenylline. The key strategies include (1) a radical cyclization for the assembly of the seven-membered ring, (2) a sequence of 6π-electrocyclization/aromatization for the construction of the tetrasubstituted arene, (3) an intramolecular Michael addition to form the pyrrolidine ring with the desired stereochemistry and (4) a gold(I)-catalysed 6-*exo*-dig cyclization to prepare the bridged 6,6-bicyclic building block (**13**). Inspired by Dixon's work[26], intermediate **9** is devised on the basis of the common structural motif of daphenylline-related *Daphniphyllum* alkaloids. The 6π-electrocyclization/aromatization strategy, which was applied to our previous synthesis of tubingensin A, plays a determining role in the entire daphenylline plan. *o*-Ns, 2-nitrobenzenesulfonyl.

in tetrahydrofuran (THF) at −78 °C afforded the undesired C6 epimer as the major product (~3:1 diastereomeric ratio (d.r.)). In contrast, Dixon and co-workers observed the desired stereochemistry at C6 when synthesizing the 5,6-bicyclic system through an intramolecular Michael addition under KHMDS conditions (Fig. 2)[26]. The structure of **9** was confirmed by X-ray crystallographic analysis of its desilylated derivative (Fig. 4; T_m 144–147 °C, ethyl acetate (EtOAc)/*n*-hexane 1:1). All the above transformations were performed readily on a multigram scale with consistent efficiency.

With the tricyclic intermediate **9** in hand, we focused our attention on the construction of the challenging tetrasubstituted arene motif, as shown in Fig. 5a. *cis*-Triene **12** was considered a suitable precursor to explore the feasibility of the 6π-electrocyclization/aromatization strategy. However, well-recognized approaches, such as partial hydrogenation[41] of the corresponding ynediene, proved to be unsatisfactory because of the poor positional selectivity; attempts to prepare seemingly simple *cis*-boronate/stannane reagents were also fruitless. To our delight, however, photoisomerization of the *trans*-triene afforded the desired *cis*-isomer. Indeed, treatment of ketone **9** with KHMDS and *N*-phenylbis(trifluoromethanesulfonimide) ($PhNTf_2$) furnished the corresponding triflate, which further underwent Suzuki coupling with *trans*-boronate **22** to render triene **23** with good overall efficiency. Irradiation of **23** with a 125 W Hg lamp for five minutes provided **12** readily[42]. Surprisingly, this *cis*-triene was found to be reluctant to enter the 6π-electrocyclization pathway under thermal conditions[43]; elevating the reaction temperature merely led to skeletal decomposition. Inspired by Trauner's seminal work[44,45], we examined 6π-electrocyclization promoted by a Lewis acid to take advantage of the carbonyl functionality conjugated to the triene system of **12**. Unfortunately, a variety of Lewis acids, such as diethylaluminium chloride, boron trifluoride diethyl etherate, $SnCl_4$ and copper(I) trifluoromethanesulfonate[35], failed to effect the desired cyclization, and desilylation followed by decomposition gradually occurred under these conditions. The failure of these efforts may be attributable to the formidable steric hindrance generated in the disrotatory cyclization process. The conrotatory pathway is expected to develop less steric congestion and, encouragingly, we occasionally detected a trace amount of cyclization product under photoirradiation conditions in the process of triene isomerization. Under optimized conditions (500 W Hg lamp, 15 minutes), *trans*-triene **23** converted cleanly into pentacyclic compound **24** (as a single diastereomer in 71% yield) through a photoinduced isomerization/electrocyclization cascade with the intermediacy of *cis*-

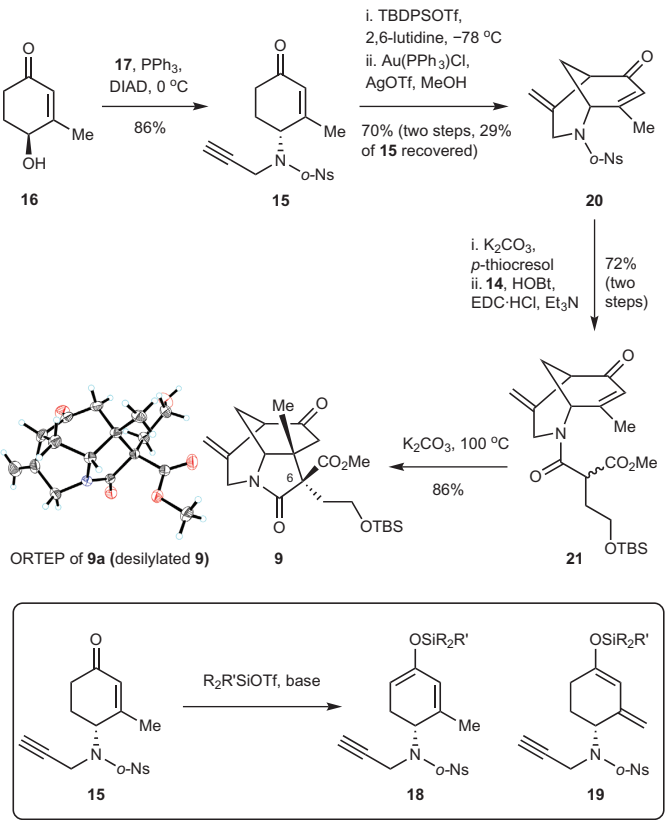

Figure 4 | Construction of the bridged tricycle 9. A gold(I)-catalysed alkyne cyclization was exploited to construct the bridged 6,6-bicycle **20**. Silyl enol ether **18**, the substrate for this reaction, was prepared from enone **15** (inset); 2,6-lutidine as a base was found to suppress the formation of the undesired regioisomeric silyl enol ether **19**. An intramolecular Michael addition assembled **9** in a diastereoselective manner. DIAD, diisopropyl azodicarboxylate; TBDPSOTf, *tert*-butyldiphenylsilyl trifluoromethanesulfonate.

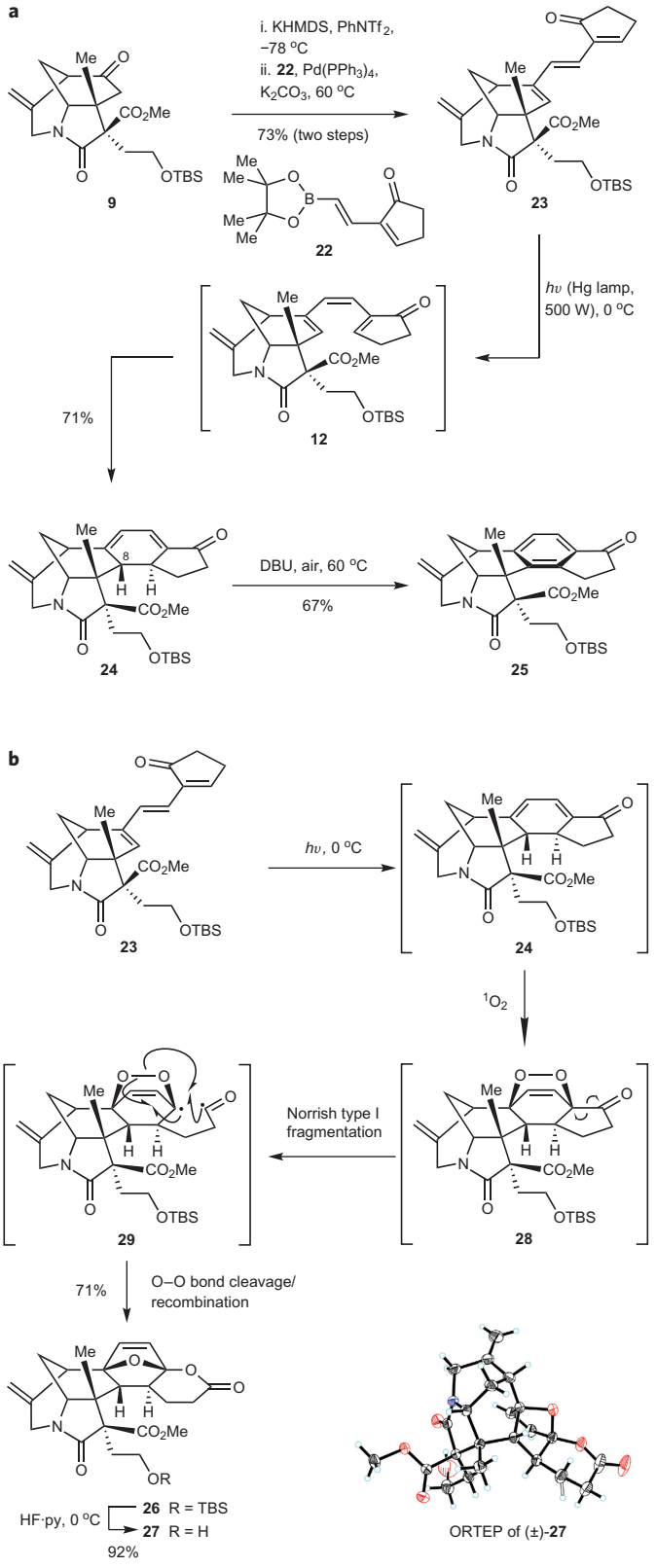

Figure 5 | Assembly of the pentacyclic intermediate 25. a, *Trans*-triene **23** underwent a photoinduced C=C bond isomerization/6π-electrocyclization cascade reaction to afford the compact pentacyclic product **24**, which further aromatized to **25** under oxidative conditions. **b**, An unexpected photoinduced cascade reaction occurred when **23** was photoirradiated in the presence of air. A postulated mechanism involved a Norrish type I fragmentation followed by O–O bond homolysis and radical recombination. HF·py, hydrogen fluoride pyridine.

triene **12**[46–48]. In a stepwise experiment, purified **12** was subjected to the same conditions to give **24** (~50% overall yield from **23**). The yield of **24** significantly decreased when O_2 was not strictly excluded (*vide infra*). This cyclohexadiene displayed unexpected reactivity in the subsequent aromatization process; treatment with various oxidants or dehydrogenation reagents, such as 2,3-dichloro-5,6-dicyano-*p*-benzoquinone, 2-iodoxybenzoic acid, MnO_2, I_2/MeOH, Pd/C and $Pd(OCOCF_3)_2$, failed to aromatize it, but resulted in skeletal decomposition on prolonged reaction times. Finally, in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)/air at elevated temperature[49], **24** was converted into arene **25** in 67% yield, taking advantage of the C8 proton acidity induced by the carbonyl group conjugated to the cyclohexadiene system. Compound **25** retained high enantiopurity (96% e.e., measured by high-performance liquid chromatography using synthetic (±)-**25** as a reference).

Interestingly, a clean, but unexpected, transformation occurred to furnish hexacyclic lactone **26** when **23** was photoirradiated in the presence of air, as shown in Fig. 5b. Desilylation of **26** gave alcohol **27**, the structure of which was determined by X-ray crystallographic analysis of single crystals of (±)-**27** (T_m 136–138 °C, EtOAc/*n*-hexane 1:1). We postulate that cyclohexadiene **24** reacted with singlet O_2 to provide the Diels–Alder adduct **28**, which may further undergo Norrish type I fragmentation to generate the diradical species **29**. The O–O bond could cleave homolytically and recombine with the diradical to render **26**. Thus, the stereochemical outcome of the conrotatory 6π-electrocyclization was verified indirectly by the structural elucidation of **27**.

Having forged the pentacyclic scaffold of the natural product, we entered the final stage of the total synthesis, as shown in Fig. 6. According to our retrosynthetic analysis, a suitable precursor for the 7-*exo*-trig cyclization needed to be prepared. Thus, ketone **25** was converted into enone **30**, in 81% overall yield, through a sequence of silyl enol ether formation and Saegusa–Ito oxidation[50]. Desilylation followed by iodination furnished compound **11**, which set the stage for the intramolecular 1,4-addition. The radical cyclization reaction was initiated by 2,2′-azobisisobutyronitrile (AIBN) at 75 °C; tris(trimethylsilyl)silane ($(TMS)_3SiH$) was found to be superior to tributyltin hydride as a hydride source. It was crucial to add CH_2Cl_2 as cosolvent to obtain an excellent and consistent yield, presumably because of the poor solubility of **11** in toluene. Under the above conditions, the primary radical attacked the enone moiety to afford compound **31** (98%) as a single diastereomer. The excellent facial selectivity is attributable to the strong stereochemical bias of the substrate. With the hexacyclic core of daphenylline in hand, a series of reductions was performed. Hydrogenation of the exocyclic C=C bond with Crabtree's catalyst provided the desired C18 diastereomer predominantly (>30:1 d.r.), but reduction with Pd/C led to the opposite stereochemical output. This product was subjected to Krapcho demethoxycarbonylation conditions ($LiCl{\cdot}H_2O$, dimethyl sulfoxide, 160 °C) employed by Dixon and co-workers in their synthesis of the tricyclic core of calyciphylline A-type alkaloids (Fig. 2)[26], in this case to give compound **10** as a single detectable diastereomer. The structure of **10** was unambiguously verified by X-ray crystallographic analysis (Fig. 6, T_m 165–167 °C, EtOAc/*n*-hexane 1:1), which ensured the connectivity of the hexacyclic scaffold and stereochemical output of the radical cyclization, hydrogenation and decarboxylation reactions. Finally, deoxygenation promoted by Pd/C under a H_2 atmosphere, followed by $LiAlH_4$ reduction of the lactam moiety, rendered synthetic daphenylline (**8**) in 66% yield over two steps. The daphenylline purified with silica gel displayed identical spectral and physical properties to those of an authentic sample provided by Hao and co-workers[34].

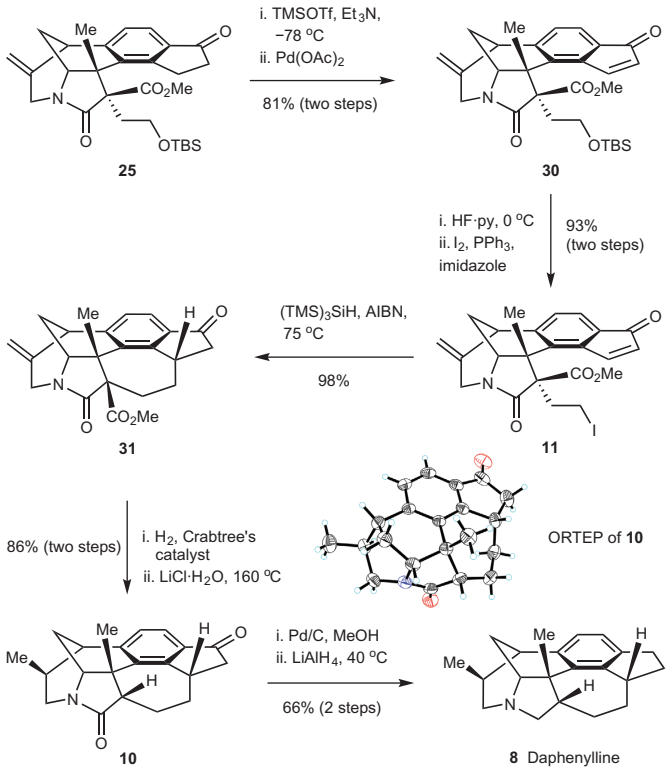

Figure 6 | Completion of the total synthesis of daphenylline. The last ring of the natural product was forged by a 7-*exo*-trig radical cyclization. Facial selective hydrogenation followed by Krapcho demethoxycarbonylation gave an advanced intermediate **10**, which converted readily into daphenylline through two reductions. TMSOTf, trimethylsilyl trifluoromethanesulfonate.

Conclusion

We accomplished the total synthesis of the *Daphniphyllum* alkaloid daphenylline. The synthesis features a gold-catalysed 6-*exo*-dig cyclization reaction for the construction of a bridged bicyclic motif, and a photoinduced olefin isomerization/6π-electrocyclization/aromatization sequence to forge the sterically compact arene. The chemistry developed may find use in the synthesis of other polycyclic natural products and pharmaceutically interesting molecules. The above endeavour represents the first example of a chemical synthesis of a member of the *Daphniphyllum* alkaloid subfamilies that share a bridged 6,*n*,5-tricyclic motif. Taking advantage of the versatility of the tricyclic intermediate **9**, studies towards the total synthesis of related *Daphniphyllum* alkaloids are currently underway, which, together with this work, should accelerate further biological and biosynthetic investigations of these fascinating natural products.

Received 31 December 2012; accepted 3 May 2013; published online 30 June 2013

References

1. Balunas, M. J. & Kinghorn, A. D. Drug discovery from medicinal plants. *Life Sci.* **78,** 431–441 (2005).
2. Keasling, J. D., Mendoza, A. & Baran, P. S. Synthesis: a constructive debate. *Nature* **492,** 188–189 (2012).
3. Tarselli, M. A. *et al.* Synthesis of conolidine, a potent non-opioid analgesic for tonic and persistent pain. *Nature Chem.* **3,** 449–453 (2011).
4. Wender, P. A. *et al.* Gateway synthesis of daphnane congeners and their protein kinase C affinities and cell-growth activities. *Nature Chem.* **3,** 615–619 (2011).
5. Mendoza, A., Ishihara, Y. & Baran, P. S. Scalable enantioselective total synthesis of taxanes. *Nature Chem.* **4,** 21–25 (2012).
6. Editorial Committee of the Administration Bureau of Traditional Chinese Medicine in *Chinese Materia Medica* (*Zhonghua Bencao*), Vol. 4, 865–867 (Shanghai Science & Technology Press, 1999).
7. Kobayashi, J. & Kubota, T. The *Daphniphyllum* alkaloids. *Nat. Prod. Rep.* **26,** 936–962 (2009).
8. Piettre, S. & Heathcock, C. H. Biomimetic total synthesis of *proto*-daphniphylline. *Science* **248,** 1532–1534 (1990).
9. Heathcock, C. H. The enchanting alkaloids of yuzuriha. *Angew. Chem. Int. Ed.* **31,** 665–681 (1992).
10. Kobayashi, J., Inaba, Y., Shiro, M., Yoshida, N. & Morita, H. Daphnicyclidins A–H, novel hexa- or pentacyclic alkaloids from two species of *Daphniphyllum*. *J. Am. Chem. Soc.* **123,** 11402–11408 (2001).
11. Mu, S-Z. *et al.* Secophnane-type alkaloids from *Daphniphyllum oldhami*. *Chem. Biodivers.* **4,** 129–138 (2007).
12. Morita, H. *et al.* Daphmanidins C and D, novel pentacyclic alkaloids from *Daphniphyllum teijsmanii*. *Org. Lett.* **7,** 459–462 (2005).
13. Matsuno, Y. *et al.* Pordamacrines A and B, alkaloids from *Daphniphyllum macropodum*. *J. Nat. Prod.* **70,** 1516–1518 (2007).
14. Ruggeri, R. B., Hansen, M. M. & Heathcock, C. H. Total synthesis of (±)-methyl homosecodaphniphyllate: a remarkable new tetracyclization reaction. *J. Am. Chem. Soc.* **110,** 8734–8736 (1988).
15. Heathcock, C. H., Davidsen, S. K., Mills, S. & Sanner, M. A. Total synthesis of (+)-methyl homodaphniphyllate. *J. Am. Chem. Soc.* **108,** 5650–5651 (1986).
16. Ruggeri, R. B. & Heathcock, C. H. Biomimetic total synthesis of (±)-methyl homodaphniphyllate. *J. Org. Chem.* **55,** 3714–3715 (1990).
17. Heathcock, C. H., Ruggeri, R. B. & McClure, K. F. *Daphniphyllum* alkaloids. 15. Total syntheses of (±)-methyl homodaphniphyllate and (±)-daphnilactone A. *J. Org. Chem.* **57,** 2585–2594 (1992).
18. Heathcock, C. H., Stafford, J. A. & Clark, D. L. *Daphniphyllum* alkaloids. 14. Total synthesis of (±)-bukittinggine. *J. Org. Chem.* **57,** 2575–2585 (1992).
19. Stafford, J. A. & Heathcock, C. H. Asymmetric total synthesis of (−)-secodaphniphylline. *J. Org. Chem.* **55,** 5433–5434 (1990).
20. Heathcock, C. H., Kath, J. C. & Ruggeri, R. B. *Daphniphyllum* alkaloids. 16. Total synthesis of (+)-codaphniphylline. *J. Org. Chem.* **60,** 1120–1130 (1995).
21. Weiss, M. E. & Carreira, E. M. Total synthesis of (+)-daphmanidin E. *Angew. Chem. Int. Ed.* **50,** 11501–11505 (2011).
22. Ikeda, S., Shibuya, M., Kanoh, N. & Iwabuchi, Y. Synthetic studies on daphnicyclidin A: enantiocontrolled construction of the BCD ring system. *Org. Lett.* **11,** 1833–1836 (2009).
23. Dunn, T. B., Ellis, J. M., Kofink, C. C., Manning, J. R. & Overman, L. E. Asymmetric construction of rings A–D of daphnicyclidin-type alkaloids. *Org. Lett.* **11,** 5658–5661 (2009).
24. Bélanger, G., Boudreault, J. & Lévesque, F. Synthesis of the tetracyclic core of daphnilactone B-type and yuzurimine-type alkaloids. *Org. Lett.* **13,** 6204–6207 (2011).
25. Coldham, I., Watson, L., Adams, H. & Martin, N. G. Synthesis of the core ring system of the yuzurimine-type *Daphniphyllum* alkaloids by cascade condensation, cyclization, cycloaddition chemistry. *J. Org. Chem.* **76,** 2360–2366 (2011).
26. Sladojevich, F., Michaelides, I. N., Darses, B., Ward, J. W. & Dixon, D. J. Expedient route to the functionalized calyciphylline A-type skeleton via a Michael addition–RCM strategy. *Org. Lett.* **13,** 5132–5135 (2011).
27. Kourra, C., Klotter, F., Sladojevich, F. & Dixon, D. J. Alkali base-initiated Michael addition/alkyne carbocyclization cascades. *Org. Lett.* **14,** 1016–1019 (2012).
28. Darses, B. *et al.* Expedient construction of the [7–5–5] all-carbon tricyclic core of the *Daphniphyllum* alkaloids daphnilongeranin B and daphniyunnine D. *Org. Lett.* **14,** 1684–1687 (2012).
29. Xu, C., Wang, L., Hao, X. & Wang, D. Z. Tackling reactivity and selectivity within a strained architecture: construction of the [6−6−5−7] tetracyclic core of *calyciphylline* alkaloids. *J. Org. Chem.* **77,** 6307–6313 (2012).
30. Li, H. *et al.* Rapid construction of the [6−6−6−5] tetracyclic skeleton of the *Daphniphyllum* alkaloid daphenylline. *Chem. Asian J.* **7,** 2519–2522 (2012).
31. Fang, B. *et al.* Synthesis of the tetracyclic core (ABCE rings) of daphenylline. *J. Org. Chem.* **77,** 8367–8373 (2012).
32. Yang, M. *et al.* Tandem semipinacol-type 1,2-carbon migration/aldol reaction toward the construction of [5–6–7] all-carbon tricyclic core of calyciphylline A-type alkaloids. *Org. Lett.* **14,** 5114–5117 (2012).
33. Yao, Y. & Liang, G. Rapid construction of the ABC ring system in the *Daphniphyllum* alkaloid daphniyunnine C. *Org. Lett.* **14,** 5499–5501 (2012).
34. Zhang, Q. *et al.* Daphenylline, a new alkaloid with an unusual skeleton, from *Daphniphyllum longeracemosum*. *Org. Lett.* **11,** 2357–2359 (2009).
35. Bian, M. *et al.* Total syntheses of anominine and tubingensin A. *J. Am. Chem. Soc.* **134,** 8078–8081 (2012).
36. Staben, S. T. *et al.* Gold(I)-catalyzed cyclizations of silyl enol ethers: application to the synthesis of (+)-lycopladine A. *Angew. Chem. Int. Ed.* **45,** 5991–5994 (2006).
37. Piers, E. & Oballa, R. M. Concise total syntheses of the sesquiterpenoids (−)-homalomenol A and (−)-homalomenol B. *J. Org. Chem.* **61,** 8439–8447 (1996).

38. Huwyler, N. & Carreira, E. M. Total synthesis and stereochemical revision of the chlorinated sesquiterpene (±)-gomerone C. *Angew. Chem. Int. Ed.* **51,** 13066–13069 (2012).
39. Nicolaou, K. C., Tria, G. S., Edmonds, D. J. & Kar, M. Total syntheses of (±)-platencin and (−)-platencin. *J. Am. Chem. Soc.* **131,** 15909–15917 (2009).
40. Phipps, R. J., Hamilton, G. L. & Toste, F. D. The progression of chiral anions from concepts to applications in asymmetric catalysis. *Nature Chem.* **4,** 603–614 (2012).
41. Nicolaou, K. C., Petasis, N. A., Zipkin, R. E. & Uenishi, J. The endiandric acid cascade. Electrocyclizations in organic synthesis. 1. Stepwise, stereocontrolled total synthesis of endiandric acids A and B. *J. Am. Chem. Soc.* **104,** 5555–5557 (1982).
42. Jung, M. E. & Duclos, B. A. Synthetic approach to analogues of betulinic acid. *Tetrahedron* **62,** 9321–9334 (2006).
43. Trost, B. M., Pfrengle, W., Urabe, H. & Dumas, J. Palladium-catalyzed alkylative cyclization of 1,6- and 1,7-enynes. *J. Am. Chem. Soc.* **114,** 1923–1924 (1992).
44. Bishop, L. M., Barbarow, J. E., Bergman, R. G. & Trauner, D. Catalysis of 6π electrocyclizations. *Angew. Chem. Int. Ed.* **47,** 8100–8103 (2008).
45. Beaudry, C. M., Malerich, J. P. & Trauner, D. Biosynthetic and biomimetic electrocyclizations. *Chem. Rev.* **105,** 4757–4778 (2005).
46. Brückner, S., Baldwin, J. E., Moses, J., Adlington, R. M. & Cowley, A. R. Mechanistic evidence supporting the biosynthesis of photodeoxytridachione. *Tetrahedron Lett.* **44,** 7471–7473 (2003).
47. Jacobsen, M. F., Moses, J. E., Adlington, R. M. & Baldwin, J. E. The total synthesis of spectinabilin and its biomimetic conversion to SNF4435C and SNF4435D. *Org. Lett.* **7,** 2473–2476 (2005).
48. Miller, A. K. & Trauner, D. Mining the tetraene manifold: total synthesis of complex pyrones from *Placobranchus ocellatus*. *Angew. Chem. Int. Ed.* **44,** 4602–4606 (2005).
49. Ikeda, S., Mori, N. & Sato, Y. Regioselective cyclic cotrimerization of α,β-enones and alkynes by a nickel-aluminum catalyst system. *J. Am. Chem. Soc.* **119,** 4779–4780 (1997).
50. Ito, Y., Hirao, T. & Saegusa, T. Synthesis of α,β-unsaturated carbonyl compounds by palladium(II)-catalyzed dehydrosilylation of silyl enol ethers. *J. Org. Chem.* **43,** 1011–1013 (1978).

Acknowledgements

This paper is dedicated to Dawei Ma for his contributions to China's natural product synthesis on the occasion of his 50th birthday. We thank X-J. Hao for providing an authentic sample of daphenylline, Z-J. Yao for assistance with the cryoprobe NMR facility and D. J. Edmonds and R. Denton for helpful discussions. Financial support was provided by the Ministry of Science & Technology (2013CB836900) and the National Natural Science Foundation of China (21290180, 21172235 and 21222202).

Author contributions

Z.L. and Y.L. contributed equally to this work. A.L., Z.L. and Y.L. conceived the synthetic route and analysed the results. Z.L., Y.L. and J.D. conducted the experimental work. A.L. directed the project and wrote the manuscript.

Additional information

Supplementary information and chemical compound information are available in the online version of the paper. Reprints and permissions information is available online at www.nature.com/reprints. Correspondence and requests for materials should be addressed to A.L.

Competing financial interests

The authors declare no competing financial interests.