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Synthesis of the 6,6,5,7-tetracyclic core of daphnilongeranin B†

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An efficient approach toward the synthesis of the 6,6,5,7-tetracyclic core of the daphnilongeranin B, a *Daphniphyllum* alkaloid, is reported. The bridged 6,6-bicyclic system was constructed using a gold(I) catalysed Conia-ene reaction, while the 5- and 7-membered rings were assembled by two diastereoselective Michael addition reactions, respectively.

Daphniphyllum alkaloids, isolated from the evergreen plant genus *Daphniphyllum*, comprise a large (>250 members) and rapidly growing family of polycyclic natural products.[1] Consistent with the fact the plant species has long been used in Chinese herbal medicine,[2] these compounds exhibit a variety of biological activities.[3] From a chemical synthesis perspective, this collection of molecules has attracted remarkable attention in the past decades.[1a,4–6] Notably, Heathcock and co-workers reported an exceptionally elegant synthesis of a *Daphniphyllum* alkaloid called methyl homosecodaphniphyllate,[5c] which not only convincingly supports their basic hypothesis for *Daphniphyllum* alkaloid biosynthesis,[4] but also sets a landmark example for an "ideal synthesis".[7]

Among the *Daphniphyllum* alkaloids, the calyciphylline A-subfamily members (*e.g.* **1–5**, Fig. 1) containing a common 6,6,5,7-tetracyclic motif (Fig. 1) have been of increasing interest from a synthesis perspective in recent years;[6f–m] daphnilongeranin B (**2**), isolated by Yue *et al.* from *Daphniphyllum longeracemosum*,[8] has been a representative target molecule. Wang and co-workers reported a creative strategy leading to the syntheses of the 6,5,7-tricyclic[6f] and 6,6,5,7-tetracyclic[6j] cores of **2**. This work took advantage of a [2+2] photocycloaddition followed by a Grob fragmentation for the 7-membered ring formation. Dixon and co-workers disclosed a concise synthesis of the 6,5,7-tricyclic system, featuring a ring closing metathesis to construct the functionalized cycloheptene moiety and a Claisen rearrangement to establish the stereochemistry of the quaternary C8.[6g] Liang and Yao exploited the functionalities and chirality of (*S*)-carvone to assemble the 6,6,5-tricyclic moiety efficiently.[6m] Most recently, we accomplished the first total synthesis of daphenylline (**5**) with a unique arene-containing structure.[5j] On the basis of our work on **5**, we report here the synthesis of the 6,6,5,7-tetracyclic core of daphnilongeranin B (**2**).

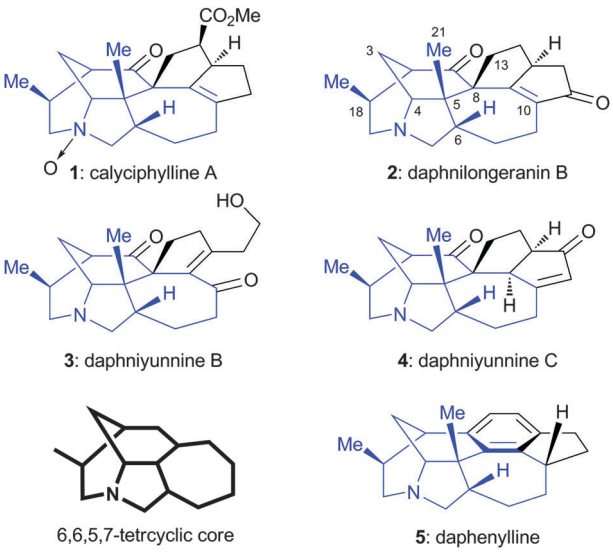

Fig. 1 Structures of daphnilongeranin B and other representative molecules of calyciphylline A-type *Daphniphyllum* alkaloids.

We began our synthesis (Scheme 1) with readily available building block (±)-**6**.[9] Enone sulfonamide **7** was obtained through Mitsunobu reaction of **6** and *o*-nosylamine **8**.[5j] **7** was then activated by forming the corresponding silyl enol ether **9**, which served as the substrate for the devised Conia-ene reaction. After a series of optimizations, we were delighted to find that the stable and commercially available $[Au(PPh_3)]NTf_2$ displayed better catalytic properties than the *in situ* mixture of $[Au(PPh_3)]Cl$ and AgOTf used previously.[10] 10 mol% of this catalyst effected the cyclization at 22 °C, to afford the desired product **10** in 76% yield. This result

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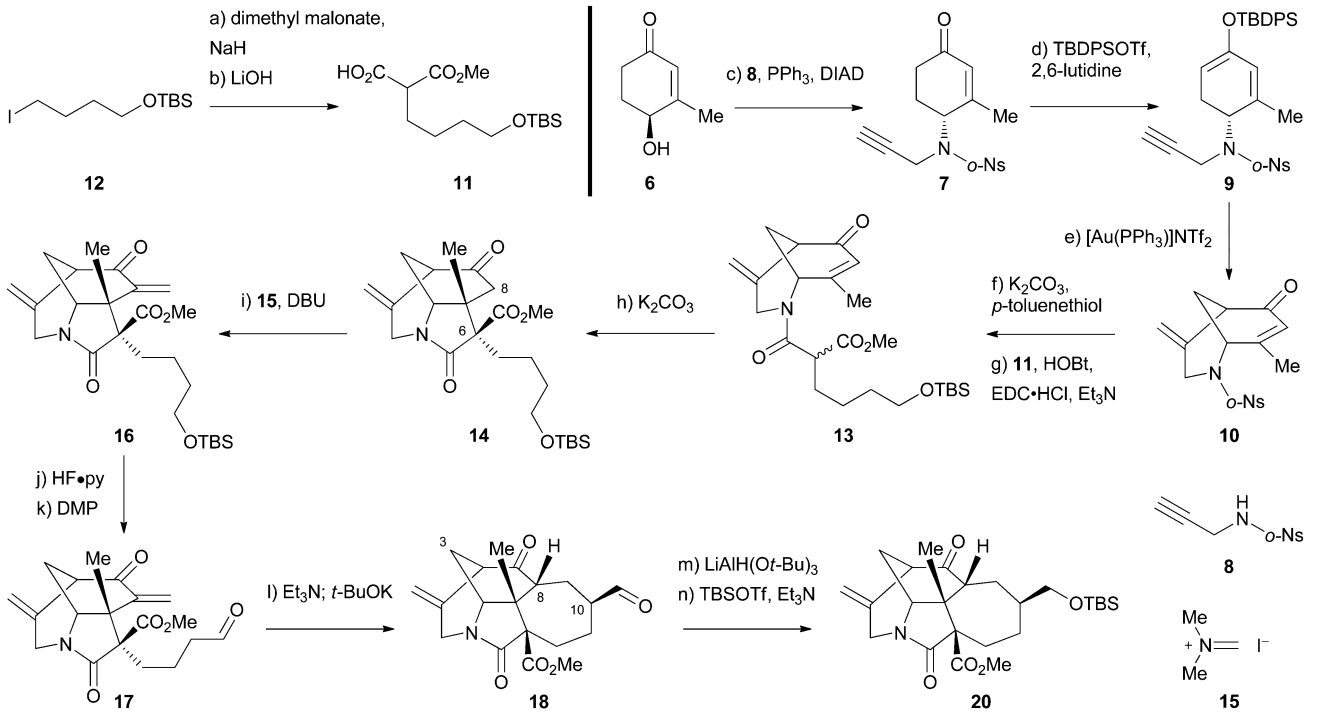


Scheme 1 Synthesis of the 6,6,5,5-tetracyclic core of daphnilongeranin B. *Reagents and conditions*: (a) dimethyl malonate (1.2 eq.), NaH (1.2 eq.), THF, 60 °C, 4 h; (b) aq. LiOH (1.1 eq., 1.0 M), MeOH, 22 °C, 12 h, 42% (2 steps); (c) **8** (1.1 eq.), PPh_3 (1.1 eq.), DIAD (1.1 eq.), THF, 0 °C, 10 min, 84%; (d) TBDPSOTf (1.1 eq.), 2,6-lutidine (1.2 eq.), CH_2Cl_2, −78 °C, 10 min; (e) $Au(PPh_3)NTf_2$ (0.1 eq.), toluene–MeOH (10 : 1), 22 °C, 76% (2 steps); (f) *p*-toluenethiol (1.5 eq.), K_2CO_3 (2.0 eq.), DMF, 1 h, 22 °C; (g) **11** (1.2 eq.), HOBt (2.0 eq.), EDC·HCl (2.0 eq.), Et_3N (3.0 eq.), CH_2Cl_2, 22 °C, 12 h, 78% (2 steps); (h) K_2CO_3 (5.0 eq.), MeCN, 100 °C, 3 h, 82%; (i) **15** (2.0 eq.), DBU (5.0 eq.), CH_2Cl_2, 55 °C, 6 h, 64%; (j) HF·py–THF (1 : 5), 0 °C, 10 min; (k) DMP (1.5 eq.), CH_2Cl_2, 22 °C, 10 min, 81% (2 steps); (l) Et_3N (10.0 eq.), CH_2Cl_2, 5 h, 60 °C; then *t*-BuOK (2.0 eq.), *t*-BuOH, 0 °C, 10 min, 45%; (m) $LiAlH(Ot\text{-}Bu)_3$ (1.5 eq.), CH_2Cl_2, −40 °C, 15 min; (n) TBSOTf (2.0 eq.), Et_3N (5.0 eq.), CH_2Cl_2, −78 °C, 5 min, 67% (2 steps).

excludes the involvement of Ag(I) in the Conia-ene reaction. Nosyl deprotection of **10** with *p*-toluenethiol/K_2CO_3 furnished the corresponding secondary amine, which, without purification, underwent an amide coupling with carboxylic acid **11** under standard EDC·HCl–HOBt conditions. It should be noted that **11** was prepared from known iodide **12**[11] through a sequence of malonate alkylation and partial hydrolysis (Scheme 1). The resulting amide **13** was subjected to basic conditions (K_2CO_3 in MeCN) at elevated temperature for an intramolecular Michael addition,[5j,6g,h] furnishing a *ca.* 8 : 1 C6 diastereomeric mixture in favor of compound **14** (82% isolated yield).

The next 7-membered ring closure proved to be the most challenging transformation in the whole route. **14** was first converted to the corresponding aldehydes and halides *via* the intermediacy of the primary alcohol. However, the seemingly straightforward intramolecular aldol or alkylation reaction failed to give any desired cyclization product, presumably due to the steric and kinetic reasons. Thus, we decided to close the ring in a sterically more friendly manner. An exo-cyclic methylene was then introduced at C8 of **14** by treating with a powerful electrophile, Eschenmoser's salt **15**, in the presence of DBU at 55 °C. Desilylation of the resulting compound **16** followed by oxidation with Dess–Martin periodinane provided aldehyde **17**. The 1,3-dipolar cycloaddition reactions were examined with the nitrone and nitrile oxide substrates prepared from **17** but turned to be fruitless, which may be attributable to the severe strain of the desired fused ring system. Finally, a second Michael addition reaction solved the ring closure problem to an acceptable extent, as shown in Scheme 1. Strong bases such as *t*-BuOK and LDA resulted in severe decomposition of the substrate. Fortunately, heating **17** in the presence of a large excess of Et_3N (essentially as a co-solvent) proved to be optimal to render tetracyclic compound **18**, together with a small portion of its C10 epimer, which was readily converted back to **18** by treating with *t*-BuOK for short reaction times. Thus, **18** was obtained in 45% overall yield from **17**. We then derived **18** into the corresponding diacetate **19** [$LiAlH(Ot\text{-}Bu)_3$ reduction followed by acetylation with Ac_2O at 40 °C] for X-ray crystallographic analysis (Fig. 2),[12] which secured the connectivity of **18**, as well as all its relative stereochemistry except for C8. In addition, the NOE studies on **18** indicated a strong correlation between H-8 and H-3b.

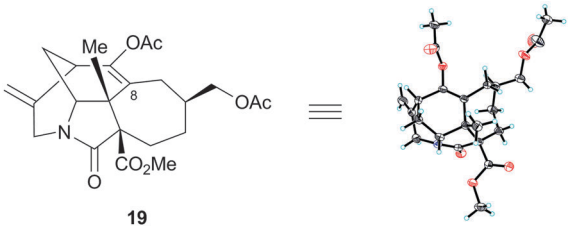
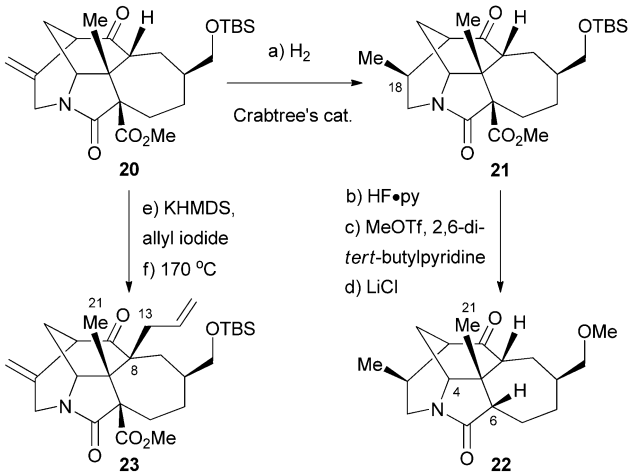


Fig. 2 X-ray derived ORTEP of compound **19**.



Scheme 2 Functionalization of the tetracyclic core of daphnilongeranin B. *Reagents and conditions*: (a) Crabtree's cat. (0.2 eq.), H_2 (balloon), CH_2Cl_2, 22 °C, 20 min, 82%; (b) HF·py–THF (1 : 4), 0 °C, 5 min; (c) MeOTf (10.0 eq.), 2,6-di-*tert*-butylpyridine (20.0 eq.), 22 °C, 20 min; (d) LiCl·H_2O (20.0 equiv.), DMSO, 170 °C, 5 h, 42% (3 steps); (e) allyl iodide (3.0 eq.), KHMDS (2.0 eq.), HMPA–THF (1 : 10), −78 °C → 0 °C, 10 min; (f) mesitylene, 170 °C, 4 h, 64% (2 steps).

Reduction of **18** with $LiAlH(Ot\text{-}Bu)_3$ followed by silylation furnished compound **20**.

We then functionalized this tetracyclic intermediate **20**, as shown in Scheme 2. Hydrogenation with Crabtree's catalyst gave the desired stereochemistry at C18, while Pd/C led to the opposite epimer exclusively. These results were verified by NOE studies and consistent with our observations in the daphenylline synthesis.[5j] Compound **21** and its desilylated analogue were found to be incompatible with the Krapcho decarboxylation conditions and underwent skeletal decomposition. Thus, the *O*-protecting group was switched to methyl, and the subsequent demethoxycarbonylation occurred smoothly at 170 °C to furnish compound **22** in 42% yield for the three steps.[5j,6g] The stereochemistry of C6 was confirmed by NOE studies (H6 and H4, H6 and H21, respectively). Because ketone and olefin functionalities are considerably stable under the Krapcho conditions as Dixon *et al.*[6g] and we found,[5j] the removal of the methoxycarbonyl group should be planned at the very end of the daphnilongeranin B synthesis, to avoid the incompatibility problem of the protecting groups. Inspired by Dixon's work,[6g] we also installed the quaternary C8 using a Claisen rearrangement strategy. Treatment of **20** with KHMDS and allyl iodide gave the corresponding *O*-allylated compound as the single detectable product, presumably due to the steric hindrance of the ketone enolate. This allyl ether underwent a thermal Claisen rearrangement to afford the *C*-allylated compound **23** in 64% yield for the two steps. The relative stereochemistry of the quaternary C8 was determined by NOE studies (H13 and H21), which is consistent with Dixon's observations.[6g]

In summary, we have developed an efficient synthesis of the 6,6,5,7-tetracyclic system of daphnilongeranin B, a *Daphniphyllum* alkaloid. A gold(I) catalysed Conia-ene reaction and two diastereoselective Michael addition reactions played the key roles in the construction of the carbon skeleton. Functionalization studies on compound **20** provide considerable information for the late stage manipulation of the natural product. On the basis of these endeavors, the total synthesis of daphnilongeranin B, as well as the related calyciphylline A-subfamily members, is currently underway in our laboratories.

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