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Expedient Route to the Functionalized Calyciphylline A-Type Skeleton via a Michael Addition–RCM Strategy

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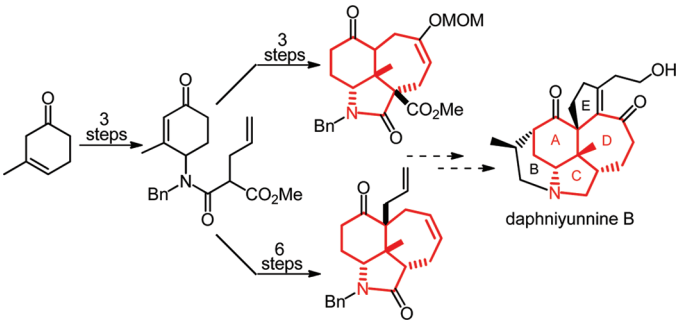
ABSTRACT



An efficient, robust, and scalable strategy to access the functionalized core of calyciphylline A-type alkaloids has been developed starting from commercially available 3-methylanisole. Key features of this approach are an intramolecular Michael addition/allylation sequence and a ring-closing metathesis step.

Daphniphyllum alkaloids are a structurally diverse group of natural products found in the genus *Daphniphyllum* (Daphniphyllaceae).[1] The structural complexity and biological significance of the members of this family has led to significant interest from the synthetic community.[2] Among the vast family of *Daphniphyllum* alkaloids, we were particularly intrigued by the calyciphylline A-type alkaloids, given their unique structural features and the fact that there are no reports of total syntheses of any member of this subgroup.

Following the discovery of calyciphylline A,[3] 19 calyciphylline A-type alkaloids have been isolated: daphniglaucins D–H (leaves of *D. glaucescens*),[4] longistylumphylline A (leaves of *D. longistylum*),[5] daphnilongeranins A–C (stems and leaves of *D. longeracemosum*),[6] daphniyunnines A–E (stems and leaves of *D. yunnanense*),[7] longeracinphyllins

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(1) For a review on *Daphniphyllum* alkaloids, see: Kobayashi, J.; Kubota, T. *Nat. Prod. Rep.* **2009**, *26*, 936–962.

(2) For some recent synthetic approaches to *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.* **2005**, *7*, 5461–5464. (d) Coldham, I.; Burrell, A. J. M.; Guerrand, H. D. S.; Oram, N. *Org. Lett.* **2011**, *13*, 1267–1269. (e) Xu, C.; Liu, Z.; Wang, H.; Zhang, B.; Xiang, Z.; Hao, X.; Wang, D. Z. *Org. Lett.* **2011**, *13*, 1812–1815.

(3) Morita, H.; Kobayashi, J. *Org. Lett.* **2003**, *5*, 2895–2898.

(4) Takatsu, H.; Morita, H.; Shen, Y.-C.; Kobayashi, J. *Tetrahedron* **2004**, *60*, 6279–6284.

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(6) Yang, S.-P.; Zhang, H.; Zhang, C.-R.; Cheng, H.-D.; Yue, J.-M. *J. Nat. Prod.* **2006**, *69*, 79–82.

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(8) Di, Y.-T.; He, H.-P.; Lu, Y.; Yi, P.; Li, L.; Wu, L.; Hao, X.-J. *J. Nat. Prod.* **2006**, *69*, 1074–1076.

(9) 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.

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A and B (leaves of *D. longeracemosum*),[8] and daphnipaxianines A–C (leaves and fruits of *D. paxianum*).[9] Some representative structures are illustrated in Figure 1.

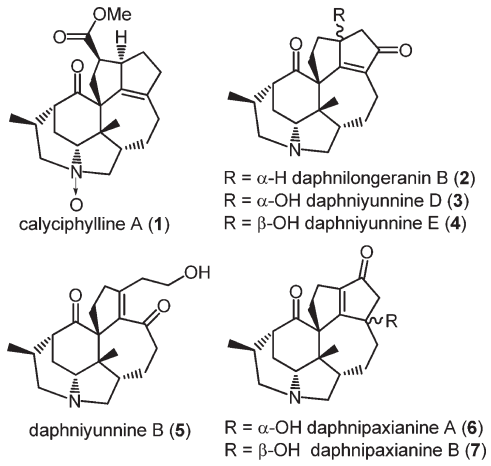
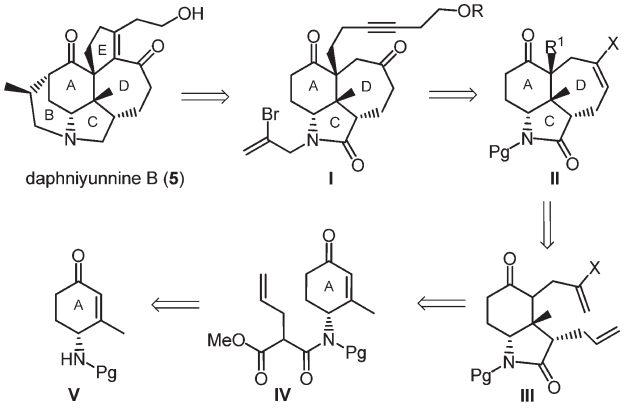


Figure 1. Representative calyciphylline A-type alkaloids.

All 19 compounds present a characteristic core structure based on four 6–6–5–7-fused rings (ABCD rings in Scheme 1). As part of a long-term synthetic program to develop a general strategy for the synthesis of various calyciphylline A-type alkaloids, we decided to center our attention on the total synthesis of daphniyunnine B (**5**).[7] Herein we present our efforts toward the synthesis of the functionalized ADC core (structure **II**, Scheme 1) of this structurally complex natural product.

Our retrosynthetic analysis identified the tricyclic structure of type **II** (Scheme 1) as a potentially flexible precursor, bearing four of the six stereocenters present in the target molecule, including the two contiguous quaternary stereocenters.

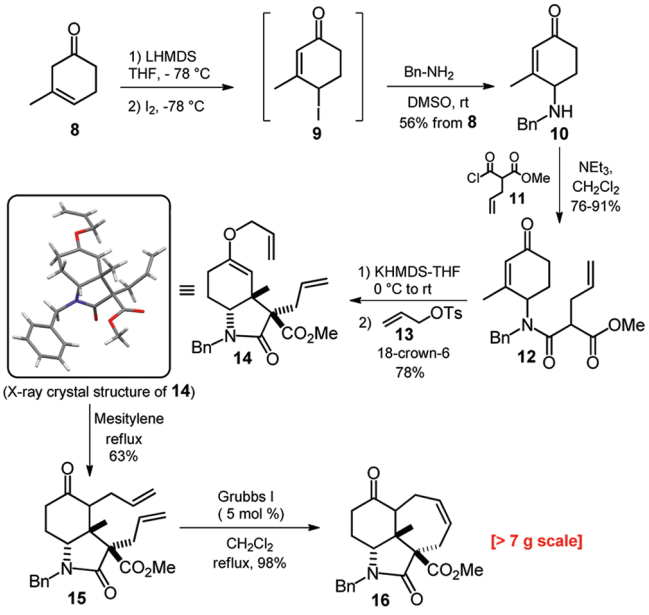
Scheme 1. Retrosynthetic Analysis of Daphniyunnine B



We envisaged that structure **II** could be converted to the advanced precursor **I** using relatively straightforward transformations. Construction of ring B from intermediate **I** could be achieved via Pd-catalyzed enolate alkenylation using the chemistry previously developed by Bonjoch[2c] and ring E could be formed via alkyne carbocyclization using methodologies previously developed within our[10] or other research groups.[11] In our plans, ring D would be installed through intramolecular ring closing metathesis (RCM) from precursor **III** and the five-membered ring C through intramolecular Michael addition of a precursor bearing structural similarities to compound **IV**.

Our route toward the synthesis of the ACD core is presented in Scheme 2. Amine **10** was prepared starting from the known ketone **8**[12] via enolate formation and subsequent γ-iodination to give intermediate **9**.[13] Intermediate **9** has limited stability[14] and was therefore directly used without any purification for the alkylation of benzylamine, yielding **10** in a satisfactory 56% yield from ketone **8**. For the success of the alkylation step, the use of DMSO and a short reaction time was found to be crucial in order to avoid the formation of aromatic side products. Amine **10** smoothly reacted with acid chloride **11** to provide amide **12** as a mixture of two inseparable diastereoisomers in 76–91% yield.

Scheme 2. Synthesis of Tricyclic Compound **16**



(10) Yang, T.; Ferrali, A.; Sladojevich, F.; Campbell, L.; Dixon, D. J. *J. Am. Chem. Soc.* **2009**, *131*, 9140–9141. For other examples of cyclizations involving unactivated alkynes from our group, see: (a) Yang, T.; Ferrali, A.; Sladojevich, F.; Dixon, D. J. *J. Am. Chem. Soc.* **2009**, *131*, 9140–9141. (b) Wang, H.-F.; Yang, T.; Xu, P.-F.; Dixon, D. J. *Chem. Commun.* **2009**, 3916–3918. (c) Li, M.; Yang, T.; Dixon, D. J. *Chem. Commun.* **2010**, *46*, 2191–2193. (d) Barber, D. M.; Sanganee, H.; Dixon, D. J. *Chem. Commun.* **2011**, *47*, 4379–4381.

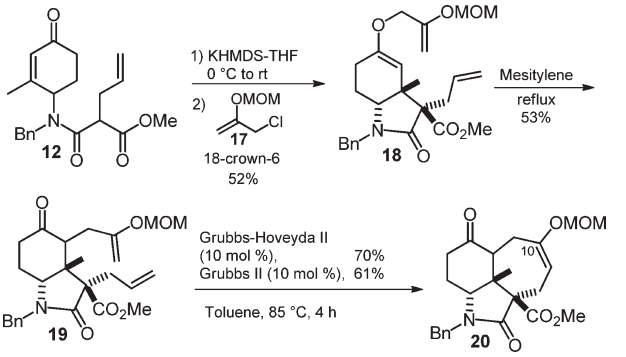
(11) (a) For a comprehensive review on addition of metal enolates to unactivated carbon–carbon multiple bonds, see: Dénès, F.; Pérez-Luna, A.; Chemla, F. *Chem. Rev.* **2010**, *110*, 2366–2447. For other examples of carbocyclizations involving unactivated alkynes, see: (b) Binder, J. T.; Crone, B.; Haug, T. T.; Menz, H.; Kirsch, S. F. *Org. Lett.* **2008**, *10*, 1025–1028 and references cited therein. (c) Davies, P. W.; Detty-Mambo, C. *Org. Biomol. Chem.* **2010**, *8*, 2918–2922.

When amide **12** was treated with KHMDS in THF, it was cleanly converted to the expected Michael addition product with complete stereocontrol, yielding the expected cis-fused adduct. We found it convenient to combine the Michael addition step, with a tandem enolate allylation reaction through sequential addition of KHMDS followed by tosylate **13** and catalytic 18-crown-6. This protocol allowed the isolation of enol ether **14** in 78% yield, as a single diastereomer, starting from precursor **12**. The relative stereochemistry of the Michael adduct was unequivocally established by single-crystal X-ray crystallographic analysis on compound **14**.[15] Heating enol ether **14** in refluxing mesitylene yielded the Claisen product **15** as a diastereomeric mixture (6:1 dr by ^{1}H NMR) in 63% yield. Compound **15** was found to be perfectly poised for the subsequent RCM step. Refluxing **15** in dry CH_2Cl_2 with 5 mol % of first-generation Grubbs catalyst furnished the tricyclic core **16** in almost quantitative yield. The diastereomeric excess was not affected by the RCM step, and **16** was isolated as a 6:1 mixture of two separable diastereoisomers. Once a robust protocol was established for the preparation of tricyclic ACD core, we turned our attention to the possibility of using the RCM step for directly installing a ketone on the C-10 of the seven-membered ring. We therefore decided to perform the Michael addition/allylation cascade in the presence of enol ether **17**.

Although proceeding with a lower yield in comparison with the formation of **14**, we were pleased to observe that the Michael addition/allylation sequence took place with the desired stereo- and regiocontrol and allowed us to isolate intermediate **18** in 52% yield.

Heating a freshly prepared batch of intermediate **18** in refluxing mesitylene furnished the desired rearranged product **19** with the expected regioselectivity in 53% yield (Scheme 3). In this case, the required reaction time was longer than in the case of enol ether **14**, as expected for allyl enol ethers with similar substitution patterns.[16] The subsequent RCM step did not proceed in the presence of Grubbs I catalyst (no product was observed in refluxing CH_2Cl_2 or in toluene at 85 °C). Pleasingly, the desired

Scheme 3. Synthesis of Tricyclic Compound **20** via Enol Ether Ring-Closing Metathesis



product was isolated in 70% yield as a separable mixture of two diastereomeric products when Grubbs–Hoveyda II was used in toluene at 85 °C. The use of Grubbs II under similar reaction conditions was also effective, but proceeded in a slightly lower yield (61%). To the best of our knowledge, this is one of the rare examples of enol ether RCM being used for the construction of a 7-membered ring.[17]

Finally, we considered the possibility of installing the two stereocenters at C-6 and C-8 (Scheme 4). The problem was addressed using tricyclic structure **16**, easily available on a multigram scale using the protocol previously described in Scheme 2. Stereo- and regioselective alkylation of **16** on C-8 proved to be troublesome. Standard Michael acceptors such as methyl vinyl ketone (MVK) or methyl acrylate did not react under a variety of conditions. Furthermore, ketone **16** was surprisingly unreactive toward a variety of common alkylating reagents. We finally identified that the combination of allyltosylate **13** and catalytic 18-crown-6 furnished the O-alkylated product **21** in almost quantitative yield and with complete regioselectivity. Subsequent Claisen rearrangement afforded the carbon allylated product in good yield and in 2.6:1 dr in favor of **22**. Unfortunately, the two diastereoisomers at C-8 proved to be very difficult to separate via standard flash column chromatography. Nevertheless, compound **22** could be isolated in 60% yield. Subsequent Krapcho dealkoxycarbonylation also proved to be problematic with a screen of different conditions typically affording the desired product **25** as the minor diastereoisomer.

(12) See the Supporting Information for references regarding the preparation of compound **8**.

(13) Parker, K. A.; Fokas, D. *J. Org. Chem.* **1994**, *59*, 3933–3938.

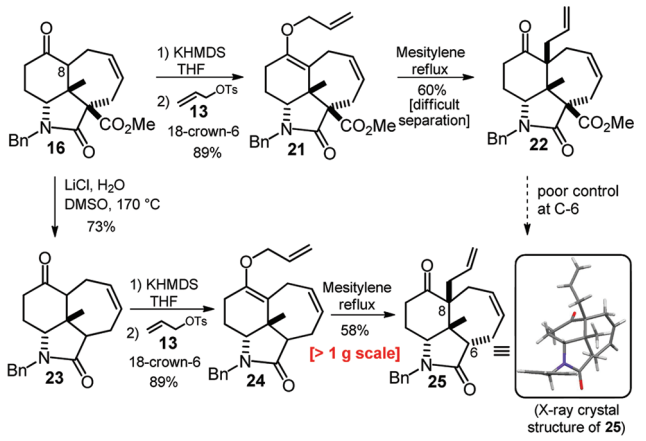
(14) Intermediate **9** was always used within 1–2 h from its preparation, without any purification, and was stored in the dark.

(15) Data were collected at low temperature [Cosier, J.; Glazer, A. M. *J. Appl. Crystallogr.* **1986**, *19*, 105] using an Enraf-Nonius KCCD diffractometer [Otwinowski, Z.; Minor, W. *Processing of X-ray Diffraction Data Collected in Oscillation Mode Methods Enzymol*; Carter, C. W., Sweet, R. M., Eds.; Academic Press: New York, 1997; p 276]. The crystal structures of 14 and 25 were solved using SIR92 [Altomare, A.; Cascarano, G.; Giacovazzo, C.; Guagliardi, A.; Burla, M. C.; Polidori, G. Camalli, M. *J. Appl. Crystallogr.* **1994**, *27*, 435] and refined using the CRYSTALS software suite [Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, K.; Watkin, D. J. *J. Appl. Crystallogr.* **2003**, *36*, 1487], and H atoms were treated in the usual manner [Cooper, R. I.; Thompson, A. L.; Watkin, D. J. *J. Appl. Crystallogr.* **2010**, *43*, 1100] as per the Supporting Information (CIF). Crystallographic data (excluding structure factors) for **14** and **25** have been deposited with the Cambridge Crystallographic Data Centre (CCDC 838995 and 838996), and copies of these data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif.

(16) Martín Castro, A. M. *Chem. Rev.* **2004**, *104*, 2939–3002 and references cited therein.

(17) For an example of enol ether RCM in natural product total synthesis, see: Oliver, S. F.; Högenauer, K.; Simic, O.; Antonello, A.; Smith, M. D.; Ley, S. V. *Angew. Chem., Int. Ed.* **2003**, *42*, 5996–6000. For representative examples of cyclic enol ether synthesis through olefin metathesis reactions, see: (a) Fujimura, O.; Fu, G. C.; Grubbs, R. H. *J. Org. Chem.* **1994**, *59*, 4029–4031. (b) Sturino, C. F.; Wong, J. C. Y. *Tetrahedron Lett.* **1998**, *39*, 9623–9626. (c) Clark, J. S.; Kettle, J. G. *Tetrahedron* **1999**, *55*, 8231–8248. (d) Rainier, J. D.; Allwein, S. P.; Cox, J. M. *J. Org. Chem.* **2001**, *66*, 1380–1386. (e) Liu, L.; Postema, M. H. D. *J. Am. Chem. Soc.* **2001**, *123*, 8602–8603. (f) Sutton, A. E.; Seigal, B. A.; Finnegan, D. F.; Snapper, M. L. *J. Am. Chem. Soc.* **2002**, *124*, 13390–13391. (g) Hekking, K. F. W.; van Delft, F. L.; Rutjes, F. P. J. T. *Tetrahedron* **2003**, *59*, 6751–6758. (h) Lee, A.-L.; Malcolmson, S. J.; Puglisi, A.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2006**, *128*, 5153–5157.

Scheme 4. Synthesis of Tricyclic Compound **25**



Given the difficulties in the two steps required for converting **16** to **25**, we decided to invert the order of the Claisen and Krapcho steps. This approach proved successful and amenable to scale up (conversion of **24** to **25** was carried out on a greater than 1 g scale). Dealkoxycarbonylation of **16** with wet DMSO–LiCl afforded **23** as a diastereomeric mixture at C-6 and C-8. The inseparable mixture was treated with allyl tosylate/18-crown-6 and allylated with complete regiocontrol to give **24** as 3.2:1 diastereomeric mixture at C-6. Subsequent Claisen rearrangement of **24** afforded a mixture of three diastereoisomers out of which **25** was the main component and was easily isolated via chromatography in 58% yield. Final confirmation of the stereochemistry of **25** was obtained via single-crystal X-ray analysis of a crystalline sample (Scheme 4).[15]

In summary, we have developed a practical and scalable route to the tricyclic [5–6–7] skeleton of calyciphylline A-type alkaloids. Our strategy is based on an intramolecular Michael addition, a ring-closing metathesis, and a Claisen rearrangement as pivotal steps and allows for the efficient and rapid construction of four stereocenters, including the two contiguous quaternary stereocenters at C-5 and C-8. One of the rare examples of enol ether RCM for the construction of a 7-membered ring has been reported and allows the straightforward installation of the ketone present on the 7-membered ring of daphniyunnine B. Further studies toward the total synthesis of daphniyunnine B and other members of the calyciphylline A-type alkaloids are currently under investigation in our laboratories and will be reported in due course.

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Supporting Information Available. Experimental procedures and spectral data for compounds **10**–**12**, **14**–**16**, and **18**–**25** and CIF files for compounds **14** and **25**. This material is available free of charge via the Internet at http://pubs.acs.org.