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Synthesis of the 4-Azatricyclo[5.2.2.0^{4,8}]undecan-10-one Core of *Daphniphyllum* Alkaloid Calyciphylline A Using a Pd-Catalyzed Enolate Alkenylation

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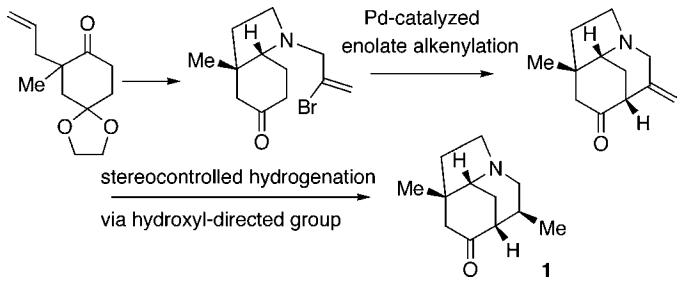
ABSTRACT



The ABC ring system of the natural product calyciphylline A has been synthesized. The key steps were a palladium-catalyzed intramolecular coupling of an amino-tethered vinyl bromide with a ketone using potassium phenoxide as the base to generate the C-ring and a hydroxyl-directed hydrogenation of an exocyclic double bond to give the azatricyclic ketone 1.

The *Daphniphyllum* alkaloids are a unique group of architecturally complex natural products derived from squalene.[1] Some years ago, Heathcock proposed a biogenetic pathway and developed biomimetic total syntheses of several members.[2] Recently, the Kobayashi group has renewed the interest in this classical group of natural products with the isolation of several novel types of *Daphniphyllum* alkaloids.[3] Among these, we have focused our attention on calyciphylline A[4,5] and daphniglaucins D−F[6] (Figure 1), which show an unprecedented hexacyclic ring framework containing a bridged ABC tricyclic subunit of 4-azatricyclo[5.2.2.0^{4,8}]-undecane.[7−9] Apart from the oxidation level of the nitrogen atom, they only differ in the substitution pattern at C-5 (biogenetic number), incorporating a methyl group in the

(1) Kobayashi, J.; Morita, H. *Alkaloids Chem. Biol.* **2003**, *60*, 165−205.
(2) (a) Heathcock, C. H. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 665−681. (b) Wallace, G. A.; Heathcock, C. H. *J. Org. Chem.* **2001**, *66*, 450−454 and references therein.
(3) More than 60 alkaloids of this family have been isolated so far, nearly half of them in the past 6 years; see inter alia: (a) Kobayashi, J.; Inaba, Y.; Shiro, M.; Yoshida, N.; Morita, H. *J. Am. Chem. Soc.* **2001**, *123*, 11402−11408. (b) Morita, H.; Ishioka, N.; Takatsu, H.; Shinzato, T.; Obara, Y.; Nakahata, N.; Kobayashi, J. *Org. Lett.* **2005**, *7*, 459−462 and references therein.
(4) Morita, H.; Kobayashi, J. *Org. Lett.* **2003**, *5*, 2895−2898.
(5) Calyciphylline A de-*N*-oxide is the aglycon of the daphcalycinosidine C, a recently isolated iridoid alkaloid: El Bitar, H.; Nguyen, V. H.; Gramain, A.; Sévenet, T.; Bodo, B. *J. Nat. Prod.* **2004**, *67*, 1094−1099.
(6) Takatsu, H.; Morita, H.; Shen, Y.-C.; Kobayashi, J. *Tetrahedron* **2004**, *60*, 6279−6284.
(7) In the context of the synthesis of *Strychnos* indole alkaloids, some procedures to achieve 4-azatricyclo[5.2.2.0^{4,8}]undecanes have been described, either from 2-azabicyclo[3.3.1]nonanes[8] or octahydroindoles,[9] but neither the pattern of the substitution nor the functionalization of the compounds described allows an elaboration to the *Daphniphyllum* alkaloids.
(8) (a) Bonjoch, J.; Casamitjana, N.; Quirante, J.; Rodríguez, M.; Bosch, J. *J. Org. Chem.* **1987**, *52*, 267−275. (b) Bonjoch, J.; Casamitjana, N.; Quirante, J.; Torrens, A.; Paniello, A.; Bosch, J. *Tetrahedron* **1987**, *43*, 377−381.

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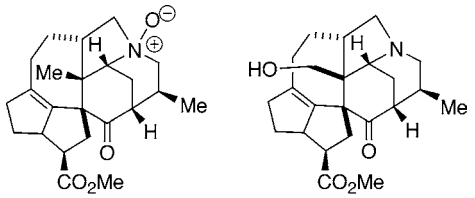
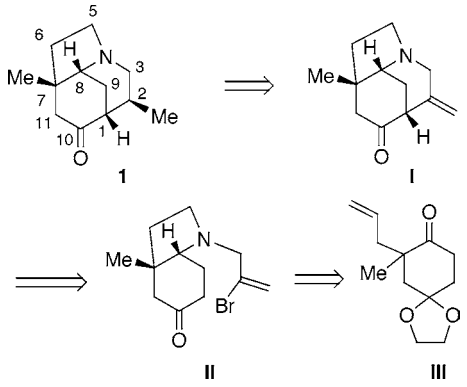


Figure 1. Structures of the hexacyclic alkaloids.

calyciphylline A and a hydroxymethyl substituent in daphniglaucins D−F.

In this work, we report our studies on the synthesis of the ABC tricyclic framework of calyciphylline A and daphniglaucins D−F, based on the palladium-catalyzed coupling of vinyl halides and ketone enolates,[10,11] which could allow the cyclization process **II** → **I** (Scheme 1). In turn, we

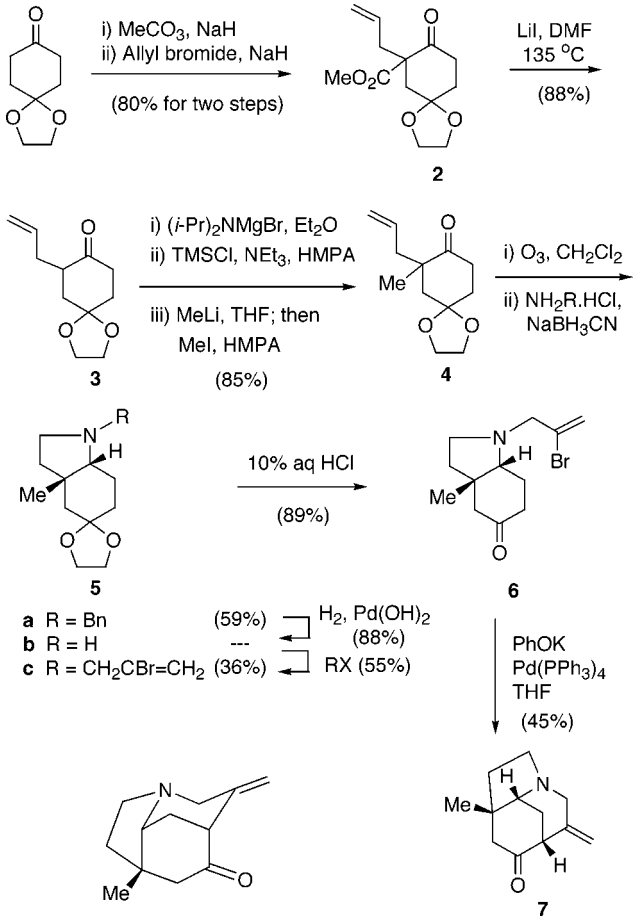
Scheme 1. Retrosynthetic Plan for Synthesis of the ABC Rings of Calyciphylline A



planned to obtain the required octahydroindole derivative **II** through a one-pot procedure of ozonolysis and double reductive amination of an appropriate α-allyl ketone, such as **III**.[12]

The starting material was the known α-allylcyclohexanedione **3**,[13] prepared in three steps from the monoethylene

Scheme 2. Synthesis of Azatricyclic Ketone **7**



acetal of the 1,4-cyclohexanedione (Scheme 2). Treating the ketone **3** with (*i*-Pr)$_2$NMgBr in Et$_2$O followed by entrapment of the enolate with TMSCl[14] smoothly furnished the more substituted TMS-enol ether (not shown), which upon treatment with methyllithium and reaction of the resulting enolate with methyl iodide gave rise to **4**[15] in 85% overall yield.[16]

The required azabicyclic compound **5c** was prepared from **4** either by a tandem process of ozonolysis and double reductive amination to elaborate the octahydroindole ring (36%) or via the *N*-benzyl derivative **5a**. The latter was transformed into **5c** through a sluggish debenzylation and alkylation with 2,3-dibromopropene of the resulting **5b**, thus avoiding the use of toxic 2-bromoallylamine[17] required for the direct synthesis of **5c**. The aminocyclization leading to both **5a** and **5c** was stereoselective, only the cis ring-fused octahydroindoles being isolated.[18] Hydrolysis of the acetal

(9) (a) Quesada, M. L.; Kim, D.; Ahn, S. K.; Jeong, N. S.; Hwang, Y.; Kim, M. Y.; Kim, J. W. *Heterocycles* **1987**, *25*, 283−286. (b) Angle, S. R.; Fevig, J. M.; Knight, S. D.; Marquis, R. W., Jr.; Overman, L. E. *J. Am. Chem. Soc.* **1993**, *115*, 3966−3976. (c) Bonjoch, J.; Solé, D.; García-Rubio, S.; Bosch, J. *J. Am. Chem. Soc.* **1997**, *119*, 7230−7240. (d) Solé, D.; Bonjoch, J.; García-Rubio, S.; Peidró, E.; Bosch, J. *Chem. Eur. J.* **2000**, *6*, 655−665.

(10) (a) Solé, D.; Peidró, E.; Bonjoch, J. *Org. Lett.* **2000**, *2*, 2225−2228. (b) Solé, D.; Diaba, J.; Bonjoch, J. *J. Org. Chem.* **2003**, *68*, 5746−5749. (c) Bonjoch, J.; Diaba, F.; Puigbó, G.; Peidró, E.; Solé, D. *Tetrahedron Lett.* **2003**, *44*, 8387−8390. (d) Solé, D.; Urbaneja, X.; Bonjoch, J. *Adv. Synth. Catal.* **2004**, *346*, 1646−1650.

(11) For other examples of intramolecular Pd-catalyzed vinylations, see: (a) Piers, E.; Oballa, R. M. *Tetrahedron Lett.* **1995**, *36*, 5857−5860 and references therein. (b) Yu, J.; Wang, T.; Liu, X.; Deschamps, J.; Flippen-Anderson, J.; Liao, X.; Cook, J. M. *J. Org. Chem.* **2003**, *68*, 7565−7581 and references therein.

(12) For the use of this methodology to arrive at 3a-substituted octahydroindol-4-ones, see: Solé, D.; Bosch, J.; Bonjoch, J. *Tetrahedron* **1996**, *52*, 4013−4028.

(13) Zhou, G.-C.; Zhu, D.-Y. *Synth. Commun.* **2002**, *32*, 37−44. See also: Montgomery, J.; Overman, L. E. *J. Org. Chem.* **1993**, *58*, 6476−6479.

(14) Krafft, M. E.; Holton, R. A. *Tetrahedron Lett.* **1983**, *24*, 1345−1348.

(15) The first enantioselective synthesis of **4** by a Tsuji allylation process has been recently described: Behenna, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2004**, *126*, 15044−15045.

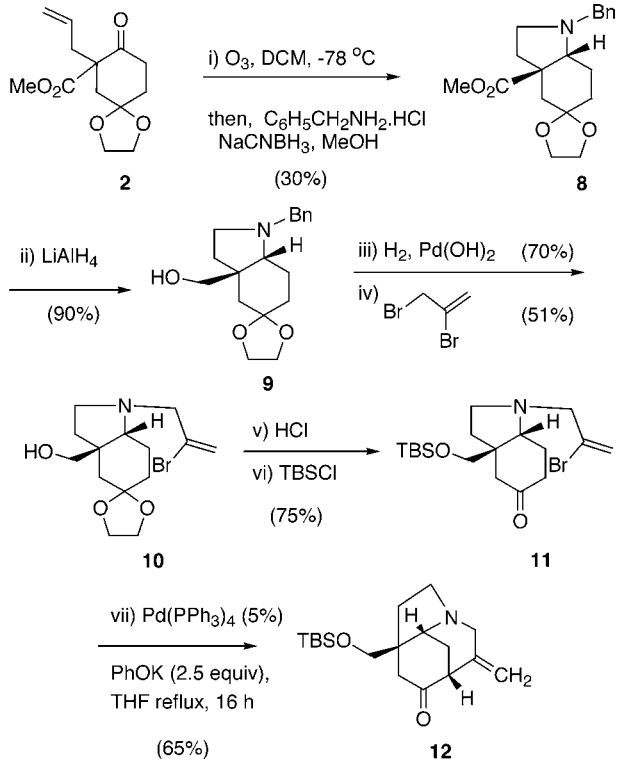
(16) Regioselective methylation of **3** to give α,α-disubstituted ketone **4** was also carried out in only one step (KO^{t}Bu, MeI), but in lower yield (65%).

(17) Bottini, A. T.; Dev, V. *J. Org. Chem.* **1962**, *27*, 968−973.

in **5c** provided the amino tethered vinyl halide **6**, which was submitted to the Pd-promoted cyclization in the presence of KOPh,[10d] in which a nucleophilic substitution takes place upon the vinylpalladium intermediate. This ring-forming reaction, involving the treatment of a THF solution of **6** with 5% of $Pd(PPh_3)_4$ and 3 equiv of PhOK at reflux temperature, led to the azatricyclic compound **7** in 45% yield and constitutes a novel approach to this heterocyclic system.

This promising result prompted us to begin the synthesis of compound **12**, which embodies the hydroxymethyl group present in daphniglaucins D−F (Scheme 3). Thus, we

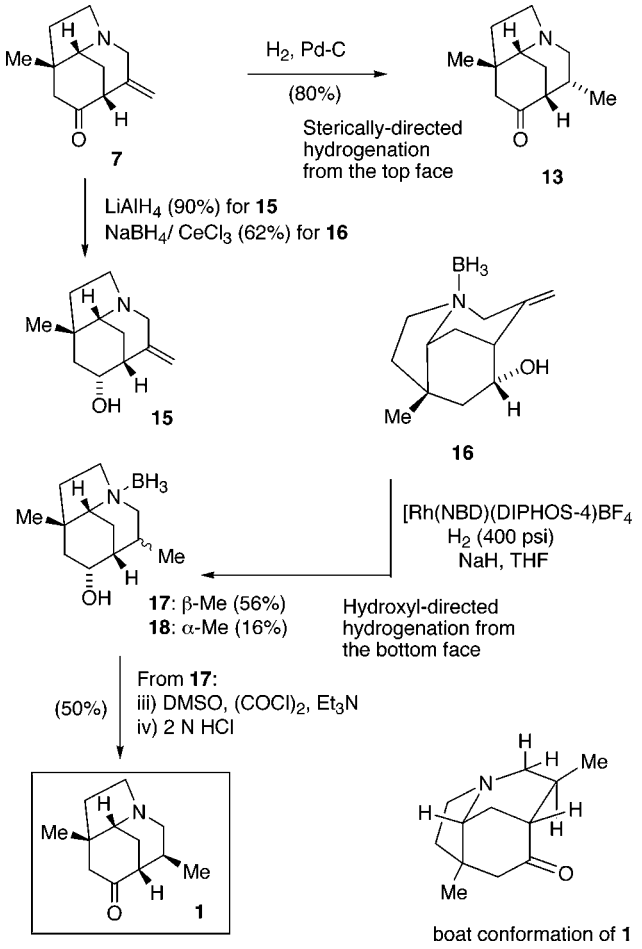
Scheme 3. Synthesis of Azatricyclic Ketone **12**



repeated the same sequence of reactions but starting from β-keto ester **2**. In this series, after the aminocyclization step, the ester group in **8** was reduced to the corresponding alcohol **9**, from which the *N*-benzyl group was exchanged to prepare octahydroindole **10**. After the acetal cleavage, the key Pd-promoted cyclization was carried out upon **11**, in which the hydroxymethyl group is protected as its TBS ether, to give azatricyclic compound **12** in 65% yield.

At this point, we explored the transformation **7** → **1**, in which the exocyclic double bond of **7** had to be hydrogenated in a stereoselective way into target **1** (Scheme 4). In fact, **7** would have to approach the catalyst surface via its more hindered face in order to obtain the required β-methyl on

Scheme 4. Synthesis of **1**



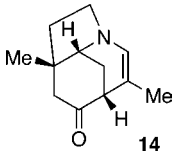
C(2), which of course is less likely than the opposite case. Indeed, when a catalytic hydrogenation using 10% palladium on carbon in methanol was performed, compound **13**, the epimeric derivative of target **1**, was obtained. To reverse the selectivity of the hydrogenation, we decided to explore a substrate-directed process[19] by submitting the exocyclic alkene **7** to a hydrogenation in the presence of Crabtree's reagent,[20] but enamine **14** was isolated.[21] Reduction of **14** in acetic acid medium and $NaCNBH_3$ gave the same tricyclic derivative **13** already isolated. Thus, we decided to prepare the homoallylic alcohol **15** because its hydroxyl group could direct the transfer of hydrogen from the bottom face by

(18) The *cis* stereochemistry of compounds **5a** and **5c** and their preferred conformation are apparent from the ^{1}H NMR data of the 7a-methine proton (t, J = 2.4 Hz at δ 2.23), which is consistent only with an equatorial disposition with respect to the cyclohexane ring. For detailed ^{13}C NMR data, see Supporting Information.

(19) For a classic review of substrate-directed chemical reactions, see: Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307−1370.

(20) Ir(cod)Py(PCy_3)py]PF_6 is known to participate in hydrogenations directed by oxygen-containing functional groups: Crabtree, R. H.; Davis, M. W. *J. Org. Chem.* **1986**, *51*, 2655−2661.

(21) A double-bond isomerization catalyzed by Crabtree's iridium(I) catalyst has also been observed recently: Krel, M.; Lallemand, J.−Y.; Guillou, C. *Synlett* **2005**, 2043−2046.



coordination when cationic iridium or rhodium catalysts were used. Reduction of ketone **7** with $LiAlH_4$ exclusively gave the equatorial alcohol **15**, but with $NaBH_4-CeCl_3$ a surprising faster-running compound on TLC was obtained, presumably the borane−amine complex (i.e., **16**) of alcohol **15**.[22] We thought that **16** could be useful for the control in the hydrogenation process, since there was now more steric crowding on the top face and the haptophilicity of the amine group[23] was blocked.[24] A hydroxyl-directed hydrogenation was thus possible, implying the reduction of the exocyclic methylene from the face opposite to that observed in ketone **7**. Gratifyingly, when this hypothesis was tested by treating the adduct **16** with 20% $[Rh(NBD)(DIPHOS\text{-}4)]BF_4$[25] the major product was the methyl derivative **17**, whose configuration at C-2 was opposite to that of **13**, the minor epimer **18** also being isolated.[26] Both epimers (**17** and **18** in separate runs) were subjected to Swern oxidation, and after treatment with 2 N HCl to cleave the aminoborane complex,[27] the target ketone **1** was obtained from **17** in 50% yield and ketone **13**, identical in all aspects to the product of direct hydrogenation of **7**, was isolated from the minor epimer **18**. The relevant NMR data for **1** were fully consistent with its assignment and comparable in value to those found in related natural products,[4−6] indicating that the piperidine ring in **1** also adopted a boat conformation. In summary, the syntheses of the ABC ring system of calyciphylline A and daphniglaucins D−F have been accomplished by elaboration of the bridged azatricyclic nucleus via an intramolecular palladium-catalyzed enolate-driven cross-coupling between vinyl bromides and ketones.

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Supporting Information Available: Experimental procedures, spectroscopic and analytical data, and copies of NMR spectra of the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(22) In fact, acid treatment of **16** renders **15**.

(23) Thompson, H. W.; Wong, J. K. *J. Org. Chem.* **1985**, *50*, 4270−4276 and references therein.

(24) For an example of a hydrogenation controlled process by formation of amine complexes, see: Rejzek, M.; Stockman, R. A.; Hughes, D. L. *Org. Biomol. Chem.* **2005**, *3*, 73−83.

(25) (a) Evans, D. A.; Morrissey, M. M. *J. Am. Chem. Soc.* **1984**, *106*, 3866−3868. DIPHOS-4 is 1,4-bis(diphenylphosphino)butane. (b) Peng, X.; Bondar, D.; Paquette, L. A. *Tetrahedron* **2004**, *60*, 9589−9598.

(26) The same compounds were obtained using Crabtree's catalyst but the reaction mixture gives some byproducts and the overall yield is lower than that obtained using the Rh catalyst.

(27) For the use of borane for blocking reactivity at the nitrogen atom in alkaloid chemistry, see: White, J. D.; Amedio, J. C.; Gut, S.; Ohira, S.; Jayasinghe, L. R. *J. Org. Chem.* **1992**, *57*, 2270−2284.