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Total Synthesis of (−)-Daphenylline

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Abstract: *Total synthesis of (−)-daphenylline, a hexacyclic Daphniphyllum alkaloid, was achieved. Construction of the tricyclic DEF ring system was initiated by asymmetric Negishi coupling followed by an intramolecular Friedel–Crafts reaction. Installation of a side chain onto the tricyclic core was carried out through Sonogashira coupling, stereocontrolled Claisen rearrangement by taking advantage of the characteristic conformation of the tricyclic DEF core, and the stereoselective alkylation of a lactone. After the introduction of a glycine unit, the ABC ring system was stereoselectively constructed through intramolecular cycloaddition of the cyclic azomethine ylide.*

More than 250 alkaloids have been isolated from plants of the genus *Daphniphyllum*.[1] These *Daphniphyllum* alkaloids show structural diversity and are classified into 14 structural types based on their characteristic ring systems. Daphenylline (**1**), isolated from the fruit of *D. longeracemosum* by Hao and co-workers in 2009, is the first member of the *Daphniphyllum* alkaloids that contains a benzene ring in the core structure (Figure 1).[2] Daphenylline includes a rearranged 22-nor-

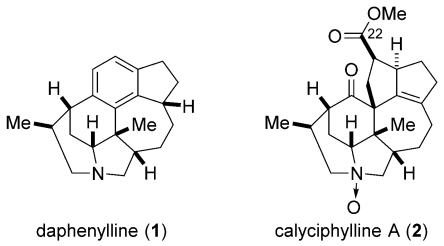
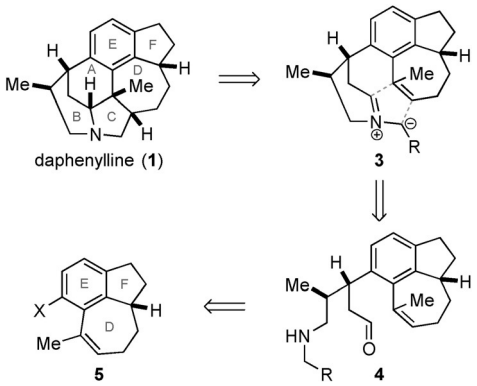


Figure 1. Structures of daphenylline and calyciphylline A.

calyciphylline A type skeleton,[3] the highly fused hexacyclic system of which has attracted significant attention in the chemical community. While several synthetic studies have been reported to date,[4,5] Li and co-workers recently accomplished the first total synthesis of (−)-daphenylline.[6] Herein, we disclose a novel total synthesis of daphenylline that takes advantage of the characteristic conformations of the tricyclic intermediates.

Our retrosynthetic analysis is illustrated in Scheme 1. The ABC ring system of daphenylline (**1**) would be constructed



Scheme 1. Retrosynthetic analysis of daphenylline.

via cycloaddition of cyclic azomethine ylide **3**,[7,8] which could be derived from aminoaldehyde **4**. Extensive conformational analysis of the tricyclic DEF core in **5** led to the conclusion that the olefin unit and the benzene ring in **5** would be expected to avoid coplanarity owing to steric repulsion between the methyl group on the olefin unit and the substituent *ortho* to the olefin unit (Figure 2). DFT calcu-

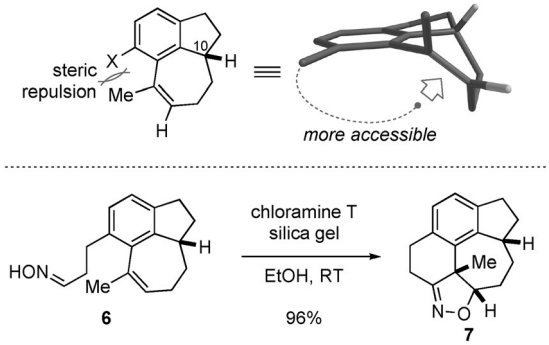


Figure 2. Conformation of the tricyclic core.

lations of the possible conformers of **5** suggested that the methyl group on the olefin unit and the hydrogen atom at C10 are situated on the same side of the tricyclic core.[9] Hence, the α face of the olefin unit is exposed to the substituent on the benzene ring, thereby assuring the desired stereoselectivity of the cycloaddition of the azomethine ylide. In fact, an attempted cycloaddition reaction of the nitrile oxide, derived from oxime **6**, proceeded stereoselectively to give **7** in 96%

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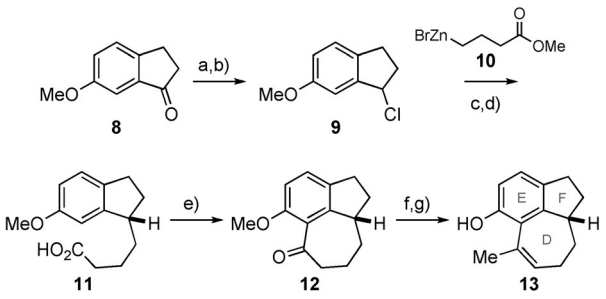
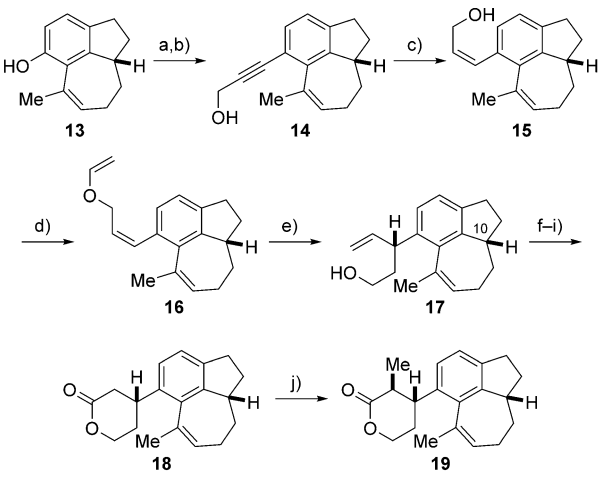
yield as the sole isomer. In addition, use of the steric bias in the tricyclic core should permit the stereoselective construction of the side chain in **4**. We thus began our synthesis by constructing the tricyclic DEF core.

We employed the asymmetric Negishi coupling reaction reported by Arp and Fu (Scheme 2).[10] Reduction of the commercially available 6-methoxyindan-1-one (**8**) with $NaBH_4$ followed by treatment with PCl_3 afforded chloroindane **9**. Reaction of **9** with zinc reagent **10** in the presence of $NiBr_2$/Pybox as a catalyst gave carboxylic acid **11** with e.r. 97:3 after hydrolysis of the resulting ester. The optical purity could be improved by recrystallization of the corresponding salt with (*R*)-1-phenylethylamine from cyclohexane (e.r. > 99:1). An intramolecular Friedel–Crafts reaction of **11** was effected by treatment with TFAA and TFA to furnish cyclic ketone **12**. After cleavage of the methyl ether with BBr_3,[11] addition of methylmagnesium bromide followed by dehydration afforded the tricyclic DEF core **13**.



Scheme 2. Preparation of the tricyclic core. a) $NaBH_4$, CH_2Cl_2, MeOH, RT, 99%; b) PCl_3, pyridine, CH_2Cl_2, −10°C; c) **10**, $NiBr_2$·diglyme, (*S*)-*i*Pr-Pybox, DMA, 0°C; d) aq. NaOH, EtOH, RT, 45% (3 steps); e) TFAA, TFA, CH_2Cl_2, RT; aq. Na_2CO_3, MeOH, RT, 81%; f) BBr_3, CH_2Cl_2, 0°C, quant.; g) MeMgBr, THF, 0°C; $MgBr_2$, TsOH·H_2O, THF, 50°C, 68%. DMA = *N*,*N*-dimethylacetamide, TFA = trifluoroacetic acid, TFAA = trifluoroacetic anhydride.

We next focused on installing the side chain with good control of the stereogenic centers (Scheme 3). After triflation of the hydroxy group in **13**, Sonogashira coupling with propargyl alcohol was carried out, giving **14** in good yield. Partial reduction of the alkyne moiety in **14** afforded *cis*-allyl alcohol **15**, onto which a vinyl group was introduced. Upon treatment of **16** with *i*Bu_3Al in hexane at 10°C, Al-mediated Claisen rearrangement[12] proceeded stereoselectively (d.r. 5.9:1) to give olefinic alcohol **17** as the major isomer.[13] The stereochemistry of the Claisen rearrangement was remotely controlled by the stereogenic center at C10. This could be rationalized as follows. Owing to the *cis* geometry of the allyl vinyl ether moiety, it is expected to be inclined to the plane of the benzene ring. Moreover, the allyl vinyl ether moiety should be positioned to avoid steric repulsion with the methyl group, which is oriented obliquely with respect to the plane of the tricyclic core (Figure 3).[14,15] In this conformation, the methyl group covers one face of the double bond. As a result, the vinyl group reacted on the other face, leading to **17** as the major isomer. After separation of the diastereomers, **17** was converted into lactone **18** through a four-step sequence



Scheme 3. Stereoselective installation of the side chain. a) Tf_2O, pyridine, CH_2Cl_2, 0°C, 73%; b) propargyl alcohol, $PdCl_2(dppf)$·CH_2Cl_2, pyrrolidine, TBAI, DMF, 60°C, 86%; c) H_2, Lindlar catalyst, quinoline, EtOAc, RT, 98%; d) *n*-butyl vinyl ether, $Hg(OAc)_2$, 60°C, 74%; e) *i*Bu_3Al, hexane, 10°C, 90%, d.r. 5.9:1; f) TBSCl, imidazole, DMF, RT, 96%; g) 9-BBN, THF, 0°C; aq. H_2O_2, aq. NaOH, 0°C to RT, quant.; h) AZADOL, $PhI(OAc)_2$, phosphate buffer (pH 6.8), MeCN, RT; i) TFA, CH_2Cl_2, RT, 63% (2 steps); j) LDA, THF, −78°C; MeI, HMPA, 0°C, 67%. AZADOL = 2-hydroxy-2-azaadamantane, 9-BBN = 9-borabicyclo-[3.3.1]nonane, dppf = 1,1′-bis(diphenylphosphino)ferrocene, DMF = *N*,*N*-dimethylformamide, HMPA = hexamethylphosphoric triamide, LDA = lithium diisopropylamide, TBAI = tetra-*n*-butylammonium iodide, TBS = *tert*-butyldimethylsilyl.

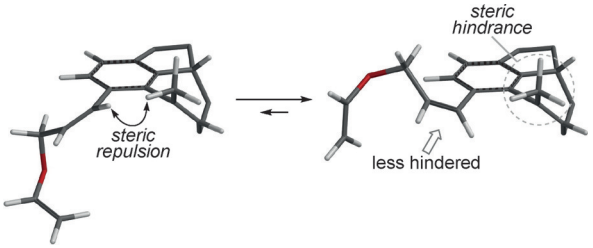
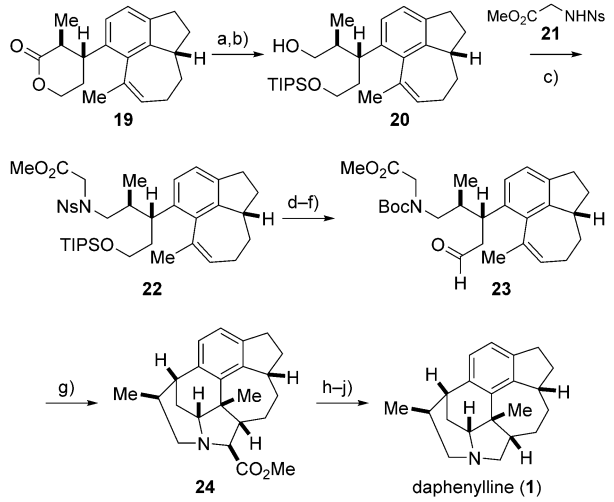


Figure 3. Conformation of allyl vinyl ether **16**.

involving protection of the alcohol, hydroboration, AZADO oxidation,[16] and lactonization under acidic conditions. Methylation at the α-position of the lactone occurred stereoselectively upon successive treatment with LDA and iodomethane to furnish **19** in 67% yield.

Having succeeded in the stereocontrolled installation of the side chain, we turned our attention to cycloaddition of the cyclic azomethine ylide to construct the ABC ring system (Scheme 4). Reduction of the lactone moiety in **19** with $LiAlH_4$ afforded a diol. After protection of the less hindered hydroxy group with a TIPS group, a glycine unit was introduced through a Mitsunobu reaction with *N*-Ns glycinate **21**.[17,18] Removal of the Ns and TIPS groups in **22** was followed by protection of the secondary amine with a Boc group. The resulting primary alcohol was oxidized with Dess–Martin periodinane to furnish aldehyde **23**. Cleavage of the Boc group by heating in toluene at 200°C with microwave irradiation triggered the formation of a cyclic azomethine



Scheme 4. Intramolecular cycloaddition of the cyclic azomethine ylide and completion of the synthesis. a) $LiAlH_4$, THF, 0 °C, 99%; b) TIPSCl, imidazole, DMF, RT, 64%; c) **21**, DEAD, Ph_3P, toluene, 70 °C, 85%; d) PhSH, K_2CO_3, DMF, 50 °C, 92%; e) TBAF, THF, RT; Boc_2O, aq. $NaHCO_3$, CH_2Cl_2, RT, 83%; f) Dess–Martin periodinane, CH_2Cl_2, RT, 93%; g) NaOAc, BHT, MS4A, toluene, microwave, 200 °C, 53%; h) NH_3, MeOH, 70 °C, 79%; i) Burgess reagent, CH_2Cl_2, RT, 94%; j) $NaBH_4$, MeOH, reflux, 36%. BHT = 3,5-di-*tert*-butyl-4-hydroxytoluene, Boc = *tert*-butyloxycarbonyl, DEAD = diethyl azodicarboxylate, Ns = 2-nitrobenzenesulfonyl, TBAF = tetra-*n*-butylammonium fluoride, TIPS = triisopropylsilyl.

ylide, which underwent intramolecular cycloaddition to give hexacyclic compound **24** in 53% yield as the sole isomer. Finally, the methyl ester **24** was converted into an aminonitrile, which was reduced with $NaBH_4$ to furnish (−)-daphenylline (**1**).

In conclusion, we have achieved the total synthesis of (−)-daphenylline (**1**). The characteristic conformation of the tricyclic DEF core was fully utilized to construct the stereogenic centers by means of a remote stereocontrolled Claisen rearrangement and intramolecular cycloaddition of a cyclic azomethine ylide.

Acknowledgements

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[8] Construction of the AC ring system by means of cycloaddition of a 2-azaallyl anion based on the Pearson's protocol has been reported. Subsequent *N*-alkylation formed the B ring (see Ref. [4a]).

[9] An exhaustive conformational search of **5a** (X = Me) using the Conflex program and DFT calculations of each conformer strongly suggested that the aforementioned conformation was energetically favorable. For details, see the Supporting Information.

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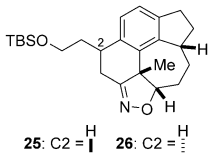

[13] The stereochemistries of the diastereomers were determined by NOESY experiments after conversion into the isoxazolines **25** or **26**. For details, see the Supporting Information.

[14] Claisen rearrangement of the *trans*-allyl vinyl ether proceeded with a lower stereoselectivity (d.r. = 2:1).

[15] A conformational search of **5b** (X = (*Z*)-1-propenyl) and DFT calculations also suggested that the aforementioned conformation was favorable. For details, see the Supporting Information.

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[18] Introduction of the glycine unit through reductive amination of the corresponding aldehyde did not provide the desired product.

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