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Stereoselective Synthesis of the A,E-Ring Bicyclic Core of Calyciphylline B-Type Alkaloids

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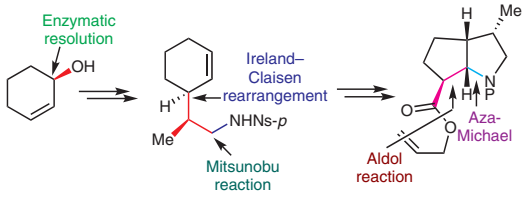

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Abstract A stereoselective synthesis of the bicyclic unit constituting the A and E rings of calyciphylline B-type alkaloids is disclosed. The propionate ester of (1*R*)-cyclohex-2-en-1-ol, obtained by enzymatic resolution, is subjected to an Ireland–Claisen rearrangement. Subsequent reduction of the acid, Mitsunobu reaction to introduce a nitrogen functionality, oxidative cleavage to a dialdehyde, and intramolecular aldol and aza-Michael reactions afford the bicyclic subunit.

Key words asymmetric synthesis, alkaloids, chiral resolution, electrocyclic reaction, Michael addition, Mitsunobu reaction

Calyciphylline B-type alkaloids constitute a subclass of calyciphylline alkaloids that belong to the large family of *Daphniphyllum* alkaloids. Calyciphylline B (**1**; Figure 1) was isolated from the leaves of *Daphniphyllum calycinum* by Morita and Kobayashi in 2003.[1] Subsequently, deoxycalyciphylline B (**2**) and deoxyisocalyciphylline B (**3**) were isolated from the stems of *D. subverticillatum*.[2] Hao and co-workers elucidated the structure of daphlongamine H (**4**).[3]

Calyciphylline B-type alkaloids contain a penta- or hexacyclic framework with eight or nine stereogenic centers, including one quaternary center, and a tertiary nitrogen. Alkaloids of this class possess a wide range of biological activities including cytotoxicity against murine lymphoma L1210 cells[1] and inhibition of platelet aggregation induced by platelet-activating factor.[4]

The first synthesis of isodaphlongamine H (**5**), possessing *cis*-fused B,C rings, was disclosed by Hanessian and coworkers.[5] Recently, Sarpong's group reported total syntheses of daphlongamine H and isodaphlongamine H.[6] The synthesis of the ABE core of these alkaloids was reported by Belanger in 2017.[7] We envisaged the synthesis of deoxycalyciphylline B by following the retrosynthetic strategy de-

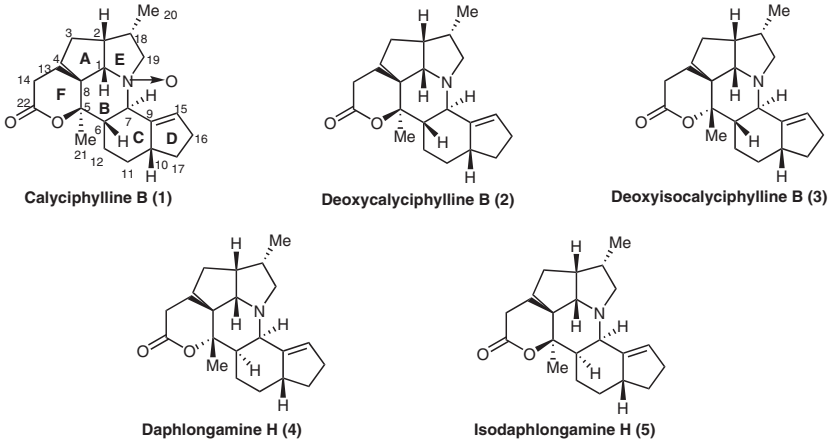

Figure 1 Representative calyciphylline B-type alkaloids

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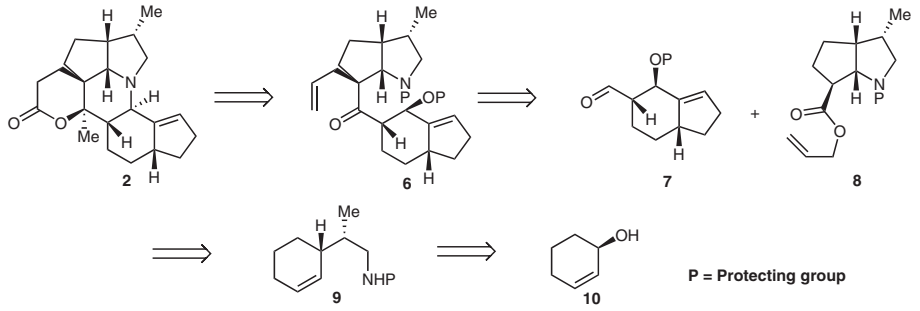
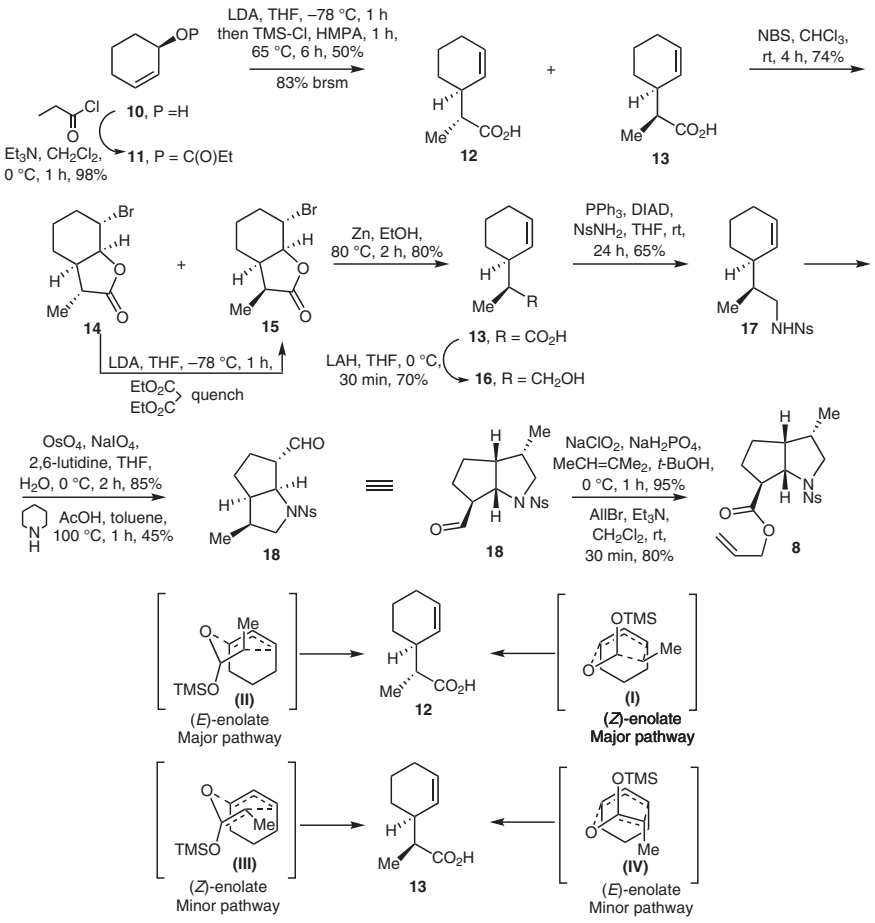


Scheme 1 Retrosynthetic disconnection of deoxycalyciphylline B

picted in Scheme 1. The target compound **2** might be obtained from ketone **6** by elaboration of the lactone ring, followed by C–N bond formation by means of the Appel reaction. We surmised that ketone **6** might be obtained by combining aldehyde **7** and ester **8**, followed by oxidation of the resulting alcohol to a β-keto ester and the creation of the quaternary center by means of the Stolz allylation protocol. We proposed to synthesize aldehyde **7** by organocatalysis and to prepare ester **8** from the cyclohexene derivative **9**, which, in turn, might be obtained from the cyclohexenol **10**.

Here, we report the synthesis of the A,E bicyclic core **8**, which is common to all calyciphylline B-type alkaloids. The synthesis commenced from (1*R*)-cyclohex-2-en-1-ol (**10**), obtained by enzymatic resolution following a reported procedure.[8] Esterification with propanoyl chloride furnished ester **11** (Scheme 2). The trimethylsilyl ketene acetal obtained from ester **11** on warming underwent Ireland–



Scheme 2 Synthesis of the bicyclic subunit **8**; brsm = based on recovered starting material Ns = (4-nitrobenzene)sulfonyl.

Claisen rearrangement to yield a 5:1 mixture of acids **12** and **13**, respectively.[9,10] The formation of acid **12** can be rationalized by invoking boat-like (**I**) and chair-like transition states (**II**) in the Claisen rearrangement of the (*Z*)- and (*E*)-silyl ketene acetal, respectively. The acids, on bromolactonization, furnished a separable mixture of bromolactones **14** and **15**. The lactone **14** was isomerized by enolization followed by quenching with diethyl malonate to furnish lactone **15**.[11] Reductive cleavage of lactone **15** by treatment with Zn/EtOH afforded the acid **13**, which was reduced to alcohol **16**.

The sulfonamide **17** was prepared in a straightforward manner by following a Mitsunobu protocol.[12,13] Subjecting the cyclohexene group of **17** to oxidative cleavage by means of Jin's protocol[14] afforded a dialdehyde that, without further purification, was treated with piperidinium acetate to furnish aldehyde **18**. Aldehyde **18** is probably formed by an intramolecular aldol reaction followed by an aza-Michael reaction or, alternatively, by a Mannich reaction. Pinnick oxidation[15] of aldehyde **18** afforded the corresponding acid that, on reaction with allyl bromide in the presence of triethylamine, gave the bicyclic compound **8** corresponding to the A and E rings of calyciphylline B-type alkaloids.[16]

In summary a short stereoselective synthesis of the bicyclic subunit of calyciphylline B-type alkaloids is disclosed. Enzymatic resolution, Ireland–Claisen rearrangement, Mitsunobu reaction, and an intramolecular aldol reaction followed by an aza-Michael reaction are the key steps in this synthetic protocol.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1690721.

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(10) The structure assigned to acids **12** and **13** is based on their conversion into lactones **14** and **15**, respectively, and a comparison of their spectra with known iodolactones; see: Bartlett, P. A.; Pizzo, C. F. *J. Org. Chem.* **1981**, *46*, 3896.
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(13) ***N*-[(1*S*)-1-Cyclohex-2-en-1-ylpropyl]-4-nitrobenzenesulfonamide** (**17**)
To a solution of alcohol **16** (1.4 g, 10 mmol) in anhyd THF (200 mL) were added Ph_3P (5.24 g, 20 mmol), (4-nitrobenzene)sulfonamide (4.04 g, 20 mmol), and DIAD (3.16 mL, 20 mmol) at 0 °C, and the mixture was stirred for 12 h at rt. H_2O (100 mL) was added and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 20 mL), and the combined organic extracts were washed with brine (20 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude product was purified by column chromatography [silica gel (100–200 mesh), 10% EtOAc–hexane] to give a colorless solid; yield: 2.21 g (6.5 mmol, 65%); mp 98–100 °C; $[\alpha]_D^{20}$ –15.3 (*c* 0.31, $CHCl_3$); R_f = 0.2 (15% EtOAc–hexane).
IR (neat): 3282, 2926, 2850, 1608, 1530, 1351, 1156, 753, 611 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.37 (d, *J* = 8.8 Hz, 2 H), 8.05 (d, *J* = 8.9 Hz, 2 H), 5.74 (ddd, *J* = 9.7, 6.5, 2.9 Hz, 1 H), 5.43 (d, *J* = 10.2 Hz, 1 H), 4.65 (t, *J* = 6.1 Hz, 1 H), 3.07–2.98 (m, 1 H), 2.92–2.83 (m, 1 H), 2.18–2.07 (m, 1 H), 2.00–1.89 (m, 2 H), 1.77–1.68 (m, 1 H), 1.67–1.59 (m, 2 H), 1.53–1.41 (m, 1 H), 1.31–1.13 (m, 1 H), 0.88 (d, *J* = 6.9, Hz, 3 H).$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 150.1, 146.0, 129.2, 128.6, 128.31, 124.4, 46.8, 38.1, 37.6, 25.7, 25.2, 22.1, 14.8. MS (ESI–TOF): *m/z* = 325 [M + H]$^+$; HRMS (ESI–TOF): *m/z* [M + H]$^+$ calcd for $C_{15}H_{21}N_2O_4S$: 325.1222; found: 325.1227..
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(16) **Allyl Ester 8**
Et_3N (80 μL, 0.56 mmol) and allyl bromide (25 μL, 0.28 mmol) were added to a solution of acid **19** (50 mg, 0.14 mmol) in anhyd CH_2Cl_2 (1.5 mL) cooled to 0 °C. The mixture was stirred for 30 min at rt then concentrated in vacuo and extracted with EtOAc (3 × 5 mL). The combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude product was purified by column chromatography [silica gel (100–200 mesh), 10% EtOAc–hexanes] to give a colorless solid; yield: 44 mg (0.11 mmol, 80%); mp 124–126 °C; $[\alpha]_D^{20}$ +2.6 (*c* 1.3, $CHCl_3$); R_f = 0.6 (20% EtOAc–hexane).

IR (KBr): 3096, 2927, 2860, 1727, 1531, 1351, 1167, 1115, 1026, 613 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.42 (d, *J* = 8.8 Hz, 2 H), 8.07 (d, *J* = 8.8 Hz, 2 H), 5.99 (ddd, *J* = 17.2, 10.7, 5.7 Hz, 1 H), 5.40 (dd, *J* = 17.2, 1.5 Hz, 1 H), 5.31 (dd, *J* = 10.4, 1.2 Hz, 1 H), 4.70–4.66 (m, 2 H), 4.12 (dd, *J* = 9.0, 3.8 Hz, 1 H), 3.73 (dd, *J* = 9.3, 6.3 Hz, 1 H), 3.25–3.21 (m, 1 H), 2.57 (t, *J* = 9.3 Hz, 1 H), 2.21–2.11 (m, 2 H), 1.99–1.90 (m, 2 H), 1.83–1.75 (m, 1 H), 1.55–1.50 (m, 1 H), 0.86 (d, *J* = 6.6 Hz, 3 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 174.0, 150.3, 141.4, 132.2, 129.3, 124.3, 118.4, 67.0, 65.5, 57.5, 51.7, 38.0, 30.4, 30.0, 16.5. MS (ESI–TOF): *m/z* = 395 [M + H]$^+$. HRMS (ESI–TOF): *m/z* [M + H]$^+$ calcd for $C_{18}H_{23}N_2O_6S$: 395.1277; found: 395.1275.