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NOTE

Enantioselective total synthesis of (−)-cyathin B_2

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Ayer and Lee[1] isolated (−)-cyathin B_2 (**1**) (Scheme 1) as a component of various congeners, from *Cyathus earlei* Lloyd, which is a tropical or subtropical species of bird's nest fungus (family Nidulariaceae) found in Cuba, Puerto Rico, Mexico and Hawaii. It is a cyathane diterpenoid with a cyathane core as the common scaffold, which features a five–six–seven tricyclic ring system with a *trans*-[6–7] ring fusion and two all-carbon quaternary stereogenic centers at the ring junctions.

Although **1** shows moderate antibiotic activity against *Staphylococcus aureus*, certain cyathane diterpenoids and congeners show interesting biological activities. For example, (−)-erinacine E and (−)-scabronine A are the potent stimulators of nerve growth factor synthesis; moreover, (−)-erinacine E is a selective agonist of the κ-opioid receptor and a promising substitute for morphine.[2]

The therapeutic relevance and synthetic challenges of cyathane diterpenoids have attracted great attention over the past decade, and numerous synthetic studies as well as total syntheses of cyathane diterpenoids and congeners have been reported,[2–19] and review articles have been published.[20]

Although the structure of **1** is relatively simple and its biological activity is moderate, the total synthesis of **1** involves a basic problem that needs to be solved, that is, the efficient construction of the cyathane core that would enable the total syntheses of other cyathane diterpenoids with potent biological activities. Moreover, although the total synthesis of racemic **1** has been reported,[12] the enantioselective total synthesis of **1** has not yet been reported.

Thus far, we have accomplished the enantioselective total synthesis of (+)-allocyathin B_2,[8] (−)-erinacine B,[12] (−)-erinacine E,[14] (−)-scabronines G and A,[2] and (−)-episcabronine A.[2] Currently, we are involved in the study of the second-generation total synthesis of cyathane diterpenoids to elucidate their structure–activity relationships. Herein, we report the first and efficient enantioselective total synthesis of **1**.

Recently, we reported the enantioselective total synthesis of (−)-scabronines G and A, and (−)-episcabronine A via a common synthetic intermediate **2** in 16 steps and with 35% overall yield starting from a known compound **8** (Scheme 1).[2] The synthesis of **2** features a complete chirality transfer reaction of alkyne **7** to allene **6** with an organocopper reagent, the highly stereoselective oxidative dearomatization/intramolecular inverse-electron demand Diels-Alder reaction cascade from **6** to **5**, 1,2-diol cleavage of **4** with $PhI(OAc)_2$ to afford **3**, and the ring-closing metathesis of **3** providing **2**.

The efficient transformations of **2** to **1** would provide a foundation for the total synthesis of other cyathane diterpenoids. Therefore, further studies toward the efficient enantioselective total synthesis of **1** were pursued.

One of the problems in the transformation of **2** to **1** was the removal of the oxygen atom at the C17 position. To achieve it efficiently, the ketone in the seven-membered ring should remain intact, that is, the selective reduction of the aldehyde group was necessary to accomplish the transformation. The direct and selective reduction of the aldehyde group to the methyl group was complicated by the fact that the reduction of the keto group would also occur simultaneously.

The two carbonyl groups (aldehyde and keto) in **2** are attached to the all-carbon quaternary centers, that is, both the carbonyl groups are located at similar positions. The selective reaction of the more reactive aldehyde was expected to be possible by a suitable reaction. Therefore, we focused on finding a reaction that would be selective for the reduction of the aldehyde group.

We were unable to accomplish the direct and selective reduction of the aldehyde group in **2** to a methyl group. After extensive studies, the reduction of compound **2** with zinc borohydride in tetrahydrofuran (THF) at −5 °C for 1 h successfully afforded compound **9** in 99% yield (Scheme 2). The keto group in the seven-membered ring remained intact under these reaction conditions. In order to remove the resultant primary hydroxy group by the Barton–McCombie deoxygenation method, alcohol **9** was first converted to phenyl thiocarbonate; the subsequent reduction with tributyltin hydride in the presence of a catalytic amount of azobisisobutyronitrile (AIBN) in toluene at 100 °C successfully afforded compound **10**.

The *tert*-butyldiphenylsilyl (TBDPS) group in **10** was removed by TBAF; the oxidation of the resultant primary alcohol group

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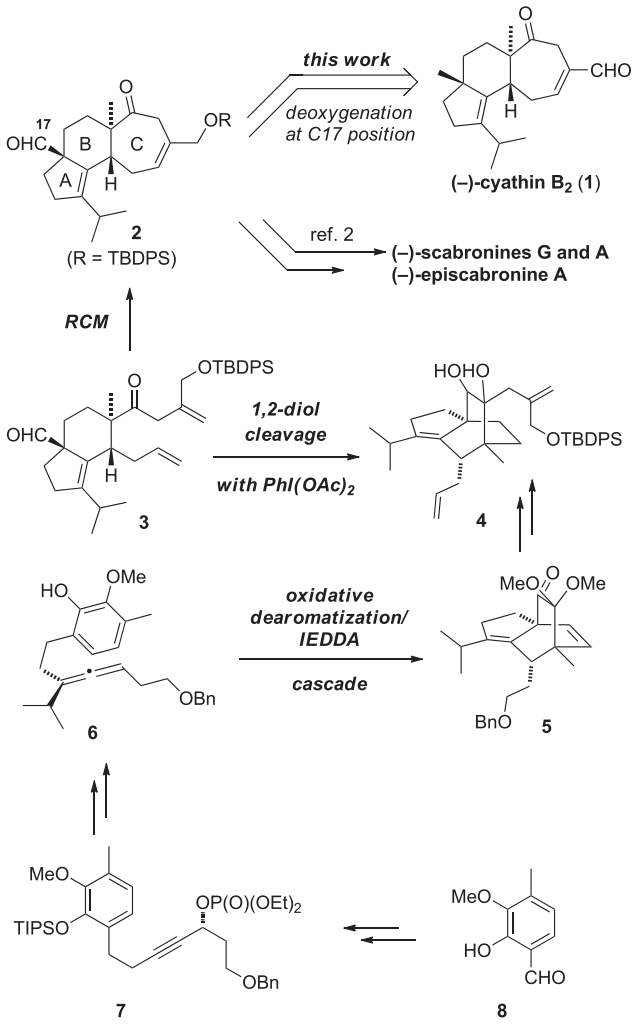
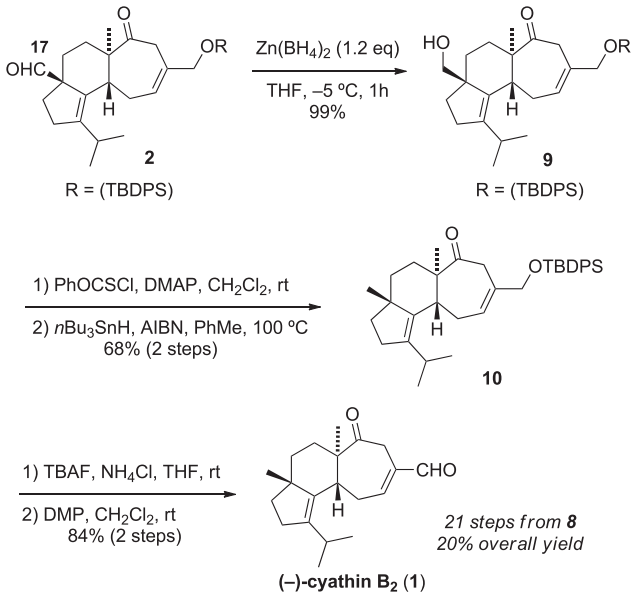


Scheme 1 Structure of the key intermediate **2** for total syntheses of (−)-cyathin B_2 (**1**), (−)-scabronines G and A, and (−)-episcabronine A.

with Dess–Martin periodinane reagent afforded the final product, **1**. The ^{1}H NMR, ^{13}C NMR, IR and HRMS spectral data of **1** completely matched with those reported by Ayer and Lee[1] and Kim and Cha,[16] thus confirming the formation of **1**. They did not report the $[\alpha]_D$ and melting point of **1** because Cha and co-workers reported the total synthesis of racemic cyathin B_2; therefore, herein we report the $[\alpha]_D$ and melting point of **1** for the first time.

In summary, we accomplished the first enantioselective total synthesis of (−)-cyathin B_2 (**1**) via the key intermediate **2** in 21 steps with 20% overall yield, starting from a known compound **8**. The total synthesis features the chemoselective reduction of the aldehyde group in the presence of a keto group, and the deoxygenation of the resultant primary hydroxy group at the C17 position by the Barton–McCombie protocol. We reported the $[\alpha]_D$ and melting point values of **1** for the first time. The relatively less number of steps and the overall high yield in the total synthesis of **1** may pave the way for the enantioselective synthesis of other cyathanes, their congeners and derivatives, and contribute to the research on their structure–activity relationships. Further studies are now in progress, and will be reported in due course.



Scheme 2 First enantioselective total synthesis of (−)-cyathin B_2 (**1**).

EXPERIMENTAL PROCEDURE

(−)-(3a*S*,5a*R*,8*E*,10a*R*)-8-(*tert*-butyldiphenylsilyloxymethyl)-2,3,3a,4,5,5a,6,7,10,10a-decahydro-3a-hydroxymethyl-1-isopropyl-5a-methyl-6-oxocyclohepta[*e*]indene (9)

To a stirred solution of **2** (88.1 mg, 0.159 mmol) in THF (5.0 ml) was added $Zn(BH_4)_2$ (0.5 M in THF, 0.38 ml, 0.191 mmol, 1.2 equiv) dropwise at −20 °C, and the reaction mixture was stirred at −5 °C for 30 min. After the reaction was completed, the reaction was quenched by adding saturated aqueous NH_4Cl solution (5 ml). The aqueous layer was extracted with EtOAc (20 ml × 2). The combined organic layer was washed with water (20 ml), brine (20 ml), dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 5/1) to afford **9** (87.1 mg, 99%) as a colorless oil:

R_f = 0.67 (hexane/ethyl acetate = 2/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72–7.61 (4H, m), 7.47–7.33 (6H, m), 5.72–5.65 (1H, m), 4.07 (1H, d, J = 13.3 Hz), 4.03 (1H, d, J = 13.3 Hz), 3.84 (1H, d, J = 10.4 Hz), 3.78 (1H, d, J = 13.6 Hz), 3.44 (1H, d, J = 10.4 Hz), 3.15 (1H, d, J = 13.6 Hz), 3.07 (1H, sept, J = 6.8 Hz), 2.70–2.53 (3H, m), 2.45-2.32 (2H, m), 2.06 (1H, ddd, J = 14.2, 8.2, 5.5 Hz), 1.86 (1H, dt, J = 13.7, 4.6 Hz), 1.71 (1H, ddd, J = 13.7, 4.6, 2.3 Hz), 1.62–1.42 (2H, m), 1.28–1.21 (2H, m), 1.08 (3H, s), 1.07 (9H, s), 1.03 (3H, d, J = 6.8 Hz), 1.03 (3H, d, J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.4, 146.1, 135.5, 135.5, 133.4, 131.1, 130.7, 129.7, 127.7, 123.8, 68.3, 66.3, 55.1, 54.2, 40.6, 39.1, 33.5, 32.9, 31.8, 30.0, 29.5, 27.2, 26.8, 22.2, 21.6, 19.3, 13.1; IR (ATR) ν_{max} 3445(br), 2930, 2856, 1698, 1427, 1111, 894, 612 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calcd for $C_{36}H_{48}NaO_3Si$: 579.3265, found: 579.3265; $[\alpha]_D^9$ −74.9 (c 0.29, $CHCl_3$).

(−)-(3a*R*,5a*R*,8*E*,10a*R*)-8-(*tert*-butyldiphenylsilyloxymethyl)-2,3,3a,4,5,5a,6,7,10,10a-decahydro-3a,5a-dimethyl-1-isopropyl-6-oxocyclohepta[*e*]indene (10)

To a stirred solution of **9** (85.9 mg, 0.154 mmol) in CH_2Cl_2 (3.0 ml) was added DMAP (37.7 mg, 0.309 mmol, 2.0 equiv) and PhOCSCl (3.1×10^{-1} ml, 0.231 mmol, 1.5 equiv) dropwise at room temperature, and the reaction mixture was stirred at room temperature for 2 h. After the reaction was completed, the reaction was quenched by adding saturated aqueous NH_4Cl solution (5 ml). The aqueous layer was extracted with EtOAc (10 ml × 2). The combined organic layer was washed with water (10 ml), brine (10 ml), dried over Na_2SO_4, and evaporated. The residue was filtered through a short plug of silica gel to afford crude product, which was used for the next step without further purification.

To a stirred solution of the above crude product in toluene (5.0 ml) were added AIBN (10.1 mg, 6.16×10^{-1} mmol, 0.4 equiv) and $^{n}Bu_3SnH$ (0.20 ml, 0.770 mmol, 5.0 equiv) at room temperature, and the reaction mixture was stirred at 100 °C for 30 min. The reaction mixture was evaporated and the residue was purified by flash chromatography (hexane/ethyl acetate = 50/1 to 20/1) to afford **10** (56.1 mg, 67% (2 steps)) as a colorless oil:

$R_f = 0.81$ (hexane/ethyl acetate = 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72–7.61 (4H, m), 7.46–7.34 (6H, m), 5.73–5.68 (1H, m), 4.09 (1H, d, $J = 13.3$ Hz), 4.04 (1H, d, $J = 13.3$ Hz), 3.86 (1H, d, $J = 13.3$ Hz), 3.24 (1H, d, $J = 10.5$ Hz), 2.97 (1H, sept, $J = 6.9$ Hz), 2.64 (1H, d, $J = 13.3$ Hz), 2.64–2.53 (2H, m), 2.38–2.63 (2H, m), 1.90 (1H, dt, $J = 12.8$, 5.5 Hz), 1.70–1.48 (4H, m), 1.23 (1H, ddd, $J = 13.3$, 4.1, 2.8 Hz), 1.14 (3H, s), 1.08 (9H, s), 1.08 (3H, s), 1.06 (3H, d, $J = 6.9$ Hz), 1.00 (3H, d, $J = 6.9$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.1, 140.4, 135.7, 135.5, 135.5, 133.4, 130.9, 129.7, 127.6, 124.3, 68.5, 54.5, 49.2, 40.3, 39.3, 38.2, 36.2, 33.0, 30.0, 28.5, 26.9, 26.8, 24.3, 21.8, 21.7, 19.3, 13.0; IR (ATR) ν_{max} 2928, 2855, 1703, 1427, 1251, 1111, 612 cm^{-1}; HRMS (ESI) $[M + Na]^+$ calcd for $C_{36}H_{48}NaO_2Si$: 563.3316, found: 563.3315; $[\alpha]_D^{19}$ −63.0 (c 1.00, $CHCl_3$).

(−)-cyathin B_2 (1)

To a stirred solution of **10** (10.9 mg, 2.02×10^{-2} mmol) and NH_4Cl (5.4 mg, 0.101 mmol, 5 equiv) in THF (2.0 ml) was added TBAF (1.0 M in THF, 0.72 ml, 0.717 mmol, 3.0 equiv) at 0 °C, and the reaction mixture was stirred at room temperature for 4 h. The reaction was quenched by adding saturated aqueous NH_4Cl solution (5 ml), and the aqueous layer was extracted with EtOAc (5 ml × 3). The combined organic layer was washed with brine (5 ml), dried over Na_2SO_4, and evaporated. The residue was filtered through a short plug of silica gel to afford crude alcohol, which was used for the next step without further purification.

To a stirred solution of the above crude alcohol in CH_2Cl_2 (2.0 ml) was added DMP (17.1 mg, 4.04×10^{-2} mmol, 2.0 equiv) at 0 °C, and the reaction mixture was stirred at room temperature for 2 h. After the reaction was completed, the reaction mixture was diluted with hexane (2.0 ml), and the resulting mixture was directly submitted to flash chromatography (hexane/ethyl acetate = 4/1) to afford (−)-cyathin B_2 (**1**) (5.1 mg, 84% (2 steps)) as a colorless solid:

$R_f = 0.85$ (hexane/ethyl acetate = 2/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.38 (1H, s), 6.76–6.71 (1H, m), 3.76 (1H, dd, $J = 13.7$, 2.8 Hz), 3.49 (1H, d, $J = 14.2$ Hz), 3.30 (1H, dd, $J = 12.4$, 1.8 Hz), 3.01–2.78 (3H, m), 2.37–2.28 (2H, m), 1.95 (1H, dt, $J = 13.3$, 5.5 Hz), 1.71–1.50 (3H, m), 1.27 (1H, ddd, $J = 13.3$, 4.1, 2.8 Hz), 1.12 (3H, s), 1.05 (3H, s), 1.02 (3H, d, $J = 6.9$ Hz), 1.01 (3H, d, $J = 6.9$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.8, 192.3, 153.5, 141.1, 135.9, 134.7, 55.1, 49.3, 39.5, 38.0, 35.9, 34.1, 32.9, 31.7, 28.6, 27.1, 24.2, 21.9, 21.6, 12.7; IR (ATR) ν_{max} 2957, 2927, 1690, 1680, 1440, 1251, 1077, 1053 cm^{-1}; HRMS (ESI) $[M + Na]^+$ calcd for $C_{20}H_{28}NaO_2$: 323.1982, found: 323.1982; $[\alpha]_D^{19}$ −57.7 (c 0.22, $CHCl_3$); mp 57.8–59.1 °C.

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