Total synthesis of cyrneines A–B and glaucopine C

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The cyrneine diterpenoids represent a structurally intriguing subfamily of cyathane diterpenoids and could significantly induce neurite outgrowth. Therefore, the efficient synthesis of these natural products is of great importance. Herein, we present a route for the collective synthesis of cyrneines A, B, and glaucopine C. As the key precursor, the 5-6-6-tricyclic scaffold is efficiently constructed by employing a mild Suzuki coupling of heavily substituted nonactivated cyclopentenyl triflate and a chelation-controlled regiospecific Friedel-Crafts cyclization as key transformations. The stereoselective installation of the all-carbon quaternary center at C6 ring junction of the tricycle is achieved via Birch reductive methylation. Subsequently, a carbenoid-mediated ring expansion furnishes the essential 5-6-7-tricyclic core. Finally, manipulation of this core by several appropriately orchestrated conversions accomplishes a more step-economic synthesis of cyrneine A (20 steps), and the first synthesis of cyrneine B (24 steps) and glaucopine C (23 steps).

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The cyathane diterpenoids compose a large family of natural products with greater than 100 members\textsuperscript{1–3}. These molecules feature a common 5-6-7 fused tricarbocyclic core with most of which possessing two all-carbon quaternary stereocenters at the ring junctions with anti-orientation. The unique structural framework coupled with the diverse oxidation and unsaturation states around the ring periphery gives rise to the structural complexity and diversity. Biological evaluation revealed that cyathane diterpenoids exhibit a rich variety of biological activities such as antibiotics, antimicrobial, antitumor, anti-inflammatory, and most significantly, nerve growth factor (NGF)-regulating properties. Over the roughly 20 years, considerable total synthesis efforts have been conducted, and a number of molecules within the subclasses of allocyathin, erinacine, sarcodonin, cyathin, scabronine, and cyanthiwigin have been synthesized by Gademann and co-workers\textsuperscript{20} with an elegant sequence of 24 steps from (-)-(R)-carvone (Fig. 1b). The key transformations involved a reductive Knoevenagel condensation, a Heck cyclization, and a Yamamoto ring expansion. On the other hand, biological evaluations showed the activity of this subfamily was markedly influenced by the minor structural differences. Among the molecules evaluated, cyrneines A (1) and B (2) could induce significantly the neurite outgrowth in PC12 cells and the expression of NGF in 1321N1 cells in a concentration-dependent manner. Thus, driven by the structural complexity, biological potential, and the interest for an in-depth SAR elucidation, it is of great importance to develop a strategically new route that could be used for efficient and versatile synthesis of these natural products and potential analogues. Herein, we report such a route as demonstrated by a more step-economic synthesis of cyrneine A (1), and the first synthesis of cyrneine B (2) and glaucopine C (3).

**Results**

**Retrosynthetic analysis.** We envisioned that the 5-6-7 tricyclic core A could serve as an advanced intermediate for our divergent synthesis (Fig. 2). The key challenge for accessing cyrneine A (1) and the intermediate B would be the β-selective reduction of carbonyl at C\textsubscript{14} in A. The glaucopine C (3) and cyrneine B (2)
were planned to be synthesized from C by means of 1,3-proto-
tropic shift and γ-oxidation at C9, albeit numerous concerns such
as stereo- as well as regio- and chemoselectivity are appreciably
involved in these late-stage manipulations arising from the con-
jugation effect of multiple olefinic functionalities in the 5- and 7-
membered ring, and the acidity of proton at C2 and C18. The

intermediate A was proposed to be derived from the 5-6-6 tri-
cyclic D by ring expansion. For the installation of the all-carbon
quaternary stereocenter at the angular C6, we conceived of Birch
reductive methylation from tricyclic ketone E. To our knowledge,
such transformation has never been explored in the synthesis of
cyathane-type natural products presumably due to the concerns
of annular strain, steric hindrance, and stereoselectivity.1,3
However, the great potential to streamline the synthesis of cy-
thane compounds prompted us to investigate it. The construc-
tion of the crucial tricyclic system F might be achieved through an
intramolecular Friedel-Crafts reaction of aldehyde G whose
synthesis would be implemented through the Suzuki-Miyaura
cross-coupling of a heavily substituted nonactivated vinyl trflate
H. Simplification of H revealed the five-membered cyclic ketone
I, which was to be prepared through an enantioselective desym-
metric reduction of 2,2-disubstituted 1,3-cyclopentanedione J.

Synthesis of cyrneine A. The synthesis commenced with asym-
metric synthesis of the cyclopentenyl trflate 15a (Fig. 3). Accord-
ingly, allylation of the readily available 2-methyl 1,3-
cyclopentanedione 7 with allylic bromide 8 or 9 afforded 2,2-
disubstituted cyclopentanedione 10 and 11 in high yields, re-
spectively. Desymmetric enantioselective reduction of 10 and
11 was carried out by CBS reduction21,22. However, the result was
less satisfactory in terms of enantio- and diastereoselectivity, and
scalability. We then inspected the enzyme-catalyzed reduction
with baker’s yeast23,24. Excellent enantioselectivity of up to 99%
and moderate diastereoselectivity of ca. 8–9:1 were observed
for 10. The imperfect diastereoselectivity prompted us to inves-
tigate the sterically more hindered 11. Delightedly, the d.r. ratio
could be improved to ca. 25:1. Thus, a comparison of the results
obtained from different ways showed that the enzyme-catalyzed
reduction of prenyl substituted 11 afforded the best outcome. The
reaction could be uneventfully performed on decagram scales to
give α-hydroxyketone 12 in 65–68% yield with 99% ee and 25:1
d.r. (see Supplementary Fig. 36). Configuration inversion of the

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Table 1 Suzuki-Miyaura cross-coupling of 15a and 16a

| Entry | Catalyst (5 mol%) | Base (equiv) | Solvent | T (°C) | Yield (%) |
|-------|-------------------|--------------|---------|--------|----------|
| 1     | PdCl₂(dpp)        | K₂CO₃        | DMSO    | 85     | 21       |
| 2     | Pd(PPh₃)₃        | K₂CO₃        | dioxane | 85     | 34       |
| 3     | Pd(PPh₃)₃        | K₂CO₃        | dioxane | 85     | 44       |
| 4     | Pd(OAc)₂/dpp     | K₂CO₃        | dioxane | 85     | 33       |
| 5     | Pd(OAc)₂/dpp     | K₂CO₃        | dioxane | 85     | 41       |
| 6     | PdCl₂(dpp)       | K₂CO₃        | dioxane | 85     | 22       |
| 7     | Pd(OAc)₂/dpp     | K₂CO₃        | dioxane | 85     | 61       |
| 8     | 18                | K₂CO₃        | DMF/EtOH(v/v = 1:1) | rt | >99c |
| 9     | 18                | K₂CO₃        | DMF/EtOH(v/v = 1:1) | rt | 95d |

*aReaction conditions: 15a (47.0 mg, 0.1 mmol), 16a (27.6 mg, 0.2 mmol), catalyst (5 mol%), and base (3.0 equiv), in 1 mL solvent under nitrogen atmosphere for 12 h
*bIsolated yield
*The reaction was run at rt for 5 h
*The reaction was performed with 6.6 g of 15a and was quenched until 15a had disappeared as monitored by TLC.
Table 2 Scope of substrates^a

| Entry | Substrate | Yield (%) |
|-------|-----------|-----------|
| 17a   | Boc-p-OMe | 92%       |
| 17b   | Boc-p-Bu   | 92%^b     |
| 17c   | Boc-p-Cl   | 94%^b     |
| 17d   | Boc-p-CH3  | 75%       |
| 17e   | Boc-p-F    | 83%       |
| 17f   | Boc-p-OMe  | 81%       |
| 17g   | Boc-p-F    | 83%       |
| 17h   | Boc-p-OMe  | 83%       |
| 17i   | Boc-p-F    | 71%       |
| 17j   | Boc-p-OMe  | 83%       |
| 17k   | Boc-p-Cl   | 70%       |
| 17l   | Boc-p-OMe  | 81%       |
| 17m   | Boc-p-Cl   | 55%       |

^aConditions: Enol triflate 15 (0.2 mmol), boronic acid 16 (0.4 mmol), K_2PO_4 (3.0 equiv) in a mixed EtOH/DMF (v/v = 1:1) solvent (2.0 mL) at room temperature under nitrogen. Isolated yield. The use of K_2PO_4 instead of K_2CO_3 was more effective for the coupling of boronic acids without free phenol group.
^bThe yield was determined based on the 1H NMR spectroscopy because of the contamination of a small amount of inseparable homocoupled product of boronic acid.
^cThe methyl ester group of the product was partially exchanged to ethyl ester.

α-hydroxy group in 12 was carried out smoothly under Mitsunobu conditions to give the desired α-hydroxy intermediate 13. Protection of the α-hydroxy in 13 with TBS followed by a base-mediated isopropylation with ipPrI provided ketone 14 in 80% yield over two steps (94% brsm). A literature survey showed that the α-alkylation of ketone with secondary alkyl iodide was relatively difficult.25,26 We examined the isopropylation under the effect of LDA, MHMDS (M = Li, Na, K), and NaH, respectively. The results showed that NaH was a more efficient base. Treatment of 14 with LiHMDS and PhNTf2 afforded the enol triflate 15a.

The Suzuki-Miyaura cross-coupling involving sterically congested nonactivated enolate substrates was relatively rare. Initial scouting of the conditions for coupling triflate 15a with 16a was carried out by examining an array of conditions reported in literature27–31 (Table 1). Unfortunately, most of the reactions were less effective, affording the coupled product 17a in low yields (entries 1–6). While a combination of Pd(OAc)_2 and dppb ligand could afford the product in moderate yield (entry 7), a large scale synthesis was problematic owing to an elongated reaction time, leading to partial hydrolysis of 15a. To compare with the prior literature27–31, the low coupling efficiency is probably due to the excessively congested structure of 15a with the additional presence of a bulky OTBS. To overcome this obstacle, we turned to examine the catalytic efficiency of phospinamide-derived palladacycle 18, which was developed in our previous studies toward synthesizing P-stereogenic 18-phosphinamide-derived palladacycle – where we exhibited excellent catalytic activity for Suzuki cross-coupling of aryl (pseudo)halides under mild conditions.34 To our delight, we found that the palladacycle 18 did display high catalytic activity for such a heavily substituted nonactivated triflate 15a. The coupled product 17a could be obtained in almost quantitative yield at room temperature (entry 8). Most significantly, the reaction could be reliably scaled up to multigram scales (6.6 g of 15a) without compromising the yield (entry 9).

To further expand the potential utility of the new precatalyst for mild and effective coupling of sterically hindered nonactivated enolate derivatives, we examined the substrate scope by varying the structures of both reaction partners. Effective cross-coupling was observed for an extensive combination of an array of heavily substituted nonactivated enol triflates and aryl boronic acids. As shown in Table 2, both the five-membered (17b–17n) and six-membered (17o–17r) cyclic enol triflates reacted smoothly with a rich range of aryl boronic acids whose structure was modified by electron-donating OMe, tBu, and Me, as well as electron-withdrawing F, 3,4,5-trifluoro, CF_3, and CO_2Me groups. In addition, a [2.2.1]-bridged bicycle (17s–17w) also exhibited good...
The completion of the synthesis of cyrneine A. Reagents and conditions: (a) Liq. NH₃, BuOH (1.0 equiv), K (2.5 equiv), Et₂O, −78 °C, 10 min; then LiBr (2.5 equiv), Mel (5.0 equiv), and THF were charged in situ, −78 °C, 1 h, then warmed to rt over a period of 1 h (72%); (b) 25 (5.0 equiv), NaOAc (5.0 equiv), EtOH, 35 °C, 3 h; (c) KO’Am (5.0 equiv), degassed xylene, 140 °C, 1.8 h (36% for 26, 18% for 27); (d) TBSCl, imidazole (1.2 equiv), DMF, rt, overnight (93%); (e) 5% aq. HCl, THF, 15 to 20 °C, 40 min (89%); (f) LiHMDS (1 M in THF, 3.5 equiv), CNCO₂Me (3.0 equiv), THF, −78 °C, 1 h; (g) ZnEt₂ (1.0 M in hexane, 6.0 equiv), CH₂Cl₂, rt, 2 h; I₂ (7.0 equiv), rt; then saturated aq. Na₂S₂O₃ (excess), rt; then DBU (20.0 equiv), rt, 10 min (73% for 2 steps); (h) TMSOTf (5.0 equiv), CH₂Cl₂, −25 °C, 15 min; (i) LiAlH₄ (6.0 equiv), Et₂O, 10 min at −78 °C, then warmed to rt; (j) MnO₂ (50 equiv), CH₂Cl₂, rt, overnight (58% in 3 steps); tAm = tert-amyl; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; TMSOTf = trimethylsilyl trifluoromethanesulfonate.

compatibility. Notably, the reaction was viable for 2-furyl and benzo-2-furyl boronic acids (17 f, 17 j, 17 n, 17 t, and 17 w). These results would be appealing because coupling of 2-heteroaryl boronic acids is a considerable challenge resulting from the detrimental pyrolysis under conventional heating conditions 35, especially with the nonactivated enol trillates as seen from the sporadic examples explored in the synthesis of relevant natural products 36.

Having established the robust conditions for large scale synthesis of 17 a in this way, we then shifted our focus to construct the 5-6-6 tricyclobicyclic system 23 (Fig. 4). Oxidation of the double bond in 17 a delivered the aldehyde 19. For the Friedel-Crafts cyclization of 19, we first examined the acid-mediated protocols as investigated in Trost’s 28 and Jiang’s 27 synthesis of hamigeran B. However, similar to their outcome, the reaction proved to be futile owing to multiple difficulties associated with the poor regioselectivity of para vs. ortho to phenolic OH, the lability of OTBS group, and the ease of further dehydration of the cyclized product. After a careful deliberation, we devised a chelation-controlled strategy and found that EtMgBr was a suitable reagent. Namely, treatment of 19 with EtMgBr produced a magnesium phenolate salt. The Mg(II) ion may be acting to serve as a Lewis acid to coordinate with the aldehyde group, and thereby forming intermediate 20 through chelation control. Consequently, the Friedel-Crafts reaction proceeded exclusively at the position ortho to phenolic OH to afford the tricyclic product 21. Upon in situ selective methylation of phenolic OH, the tricyclic alcohol 22 could be obtained as a single regioisomer in 64–72% yield on multigram scales. Oxidation of 22 gave the corresponding ketone 23 smoothly.

Next, our task was moved forward to complete the synthesis of cyrneine A (1) (Fig. 5). Attempted installation of methyl group at C₆ in 23 was carried out by executing the Birch reductive methylation. However, initial trials showed that the reaction was considerably challenging. Only a complex mixture was afforded under a broad array of conditions. Based on the NMR analysis of the crude products, the reaction was mainly complicated by the competitive reduction of C₃ over C₄ double bond, aryl ring, and carbonyl group without observation of the methylated product. After an exhaustive screening and optimization of conditions, we could successfully install the angular methyl group based on the methods reported early by Narisada 38 and Gibbard 39. It was found that addition of scrupulously dried LiBr was crucial. The desired product 24 could be obtained in 72–75% yield as a single diastereoisomer over gram scale. The exceptionally high stereo-selectivity is presumably attributed to the steric hindrance of methyl group at C₉, which compels the nucleophilic attack of MeI to take place from the less hindered -face.

Concerning the reduction of the carbonyl functionality in the central ring of 24, many unexpected obstacles were encountered.
First, we examined the Barton-McCombie\(^{40}\) radical reduction involving reduction of the carbonyl group (NaBH\(_4\), MeOH), thiacarbonation of hydroxyl (NaH, CS\(_2\), MeI), and radical induced deoxygenation. However, the product 26 was obtained in lower than 20% yield under a free combination of various radical initiators (e.g., AIBN, ABCN, Et\(_3\)B) and reductants (e.g., Bu\(_3\)SnH, TMSH, TTMS, and Ph\(_2\)SiH\(_2\)). Although no rigorous proof, it seemed that the cleavage of C\(_6\)–C\(_7\) bond occurred facilely under radical conditions. Alternatively, the Wolff–Kishner–Huang type reduction was also proved to be ineffective under an array of routine conditions\(^{41-48}\). Extensive decomposition of substrate was observed. Fortunately, a patient investigation revealed that the reaction of 24 with semicarbazide 25\(^{49,50}\) followed by treatment of the resulting semicarbazide with KOrAm in degassed xylene afforded 26 in ca. 36% yield accompanied by ca. 18% of desilylated 27, which could be resilylated to give 26. As a result, 26 could be obtained in 53% yield in a synthetically useful level. Hydrolysis of the vinyl ether in 26 gave ketone 28, which was immediately subjected to the ring expansion reaction without careful purification since 28 was somewhat easily oxidized under ambient atmosphere. For ring expansion, Nakada in the synthesis of allocyathin B\(^2\) employed a four-step sequence involving acylation, iodomethylation, Sm\(_3\)-promoted ring expansion, and LDA/I\(_2\)-mediated elimination. Inspired by a protocol of Zercher\(^{31}\), we accomplished the conversions through a two-step operation involving acylation followed by a one-pot Zn carbene-modified ring expansion and I\(_2\)-promoted elimination. Compound 29 was thus obtained efficiently in 73% yield over two steps. Finally, elaboration of 29 by removal of TBS, simultaneous reduction of ketone and ester, and selective oxidation of allylic primary alcohol furnished the total synthesis of cyrneine A (1) in 58% yield over three steps. Notably, the reduction proceeded highly stereoselectively at C\(_3\) to afford \(\beta\)-OH product. The structure of 1 was unambiguously confirmed by \(^1\)H- and \(^1^3\)C-NMR, HRMS, and single crystal X-ray (CCDC 1830226) analysis. The data and dextrorotary property of the final product matched well with those of the reported natural sample\(^{16}\) (See Supplementary Table 1 and 2, and Supplementary Fig. 26).

**Synthesis of cyrneine B and glaucopine C.** Having successfully synthesized cyrneine A, we entered the final stage toward synthesizing cyrneine B (2) and glaucopine C (3) (Fig. 6). Based on our retrosynthetic design, the advanced intermediate 29 was converted into \(\beta\),\(\gamma\)-ene 30 through four routine transformations. After an optimization of reaction sequence and conditions, we found that the 1,3-prototropic shift and concomitant deprotection of acetyl in 30 proceeded smoothly under the effect of NaOMe to deliver the thermodynamically preferred enone 31 as a single C\(_4\) \(\beta\)-H steriosomer. The stereochemistry was determined by NOESY correlation (see Supplementary Fig. 29). The exceptionally good stereoselectivity is presumably resulted from the differential steric hindrance between re-face and si-face of TS-2. As a result, the enolate anion prefers to approach the electrophiles from the less congested si-face rather than the hindered re-face (i.e., mode III vs. IV). Subsequently, selective oxidation of the allylic primary alcohol completed the synthesis of glaucopine C (3). Encouraged by the highly stereo- and regioselective prototropic shift, the installation of C\(_4\) \(\beta\)-hydroxy toward synthesizing cyrneine B (2) was carried out through a base-mediated prototropic shift and aerobic \(\gamma\)-CH oxidation cascade from 30. While a complex mixture with high polarity was obtained in initial scouting of the conditions under the effect of weak bases and heating presumably due to over oxidation of olefins and acidic CH at C\(_2\) and C\(_{19}\), treatment of 30 with LiHMDS by lowering the temperature to \(\sim 78\) \(^\circ\)C under O\(_2\) atmosphere afforded 32 in 58% yield. Finally, removal of acetyl followed by selective oxidation of the allylic alcohol delivered cyrneine B (2). The structures of cyrneine B and glaucopine C were confirmed by various spectroscopic analyses and by comparison of the analytical data of the synthetic samples with those reported for natural products\(^{16,19}\) (see Supplementary Table 3–6, and Supplementary Fig. 30–35).

**Discussion**

In summary, we have developed an efficient route that allowed for a more step-economic total synthesis of cyrneine A (20 steps), and the first total synthesis of cyrneine B (24 steps) and glaucopine C (23 steps) from readily available commercial materials. The synthesis features the use of a mild and efficient Suzuki-coupling of heavily substituted nonactivated vinyl triflate, a Mg(II)-mediated chelation-controlled Friedel–Crafts cyclization, a Birch reductive methylation, and a zinc carbene-mediated ring expansion. These key transformations enable an efficient and rapid construction of the 5-6-7 tricyclic core. Finally, the divergent synthesis of the three natural products from this core is achieved through several carefully orchestrated manipulations involving a stereoselective reduction of C\(_{14}\) carbonyl, a stereo- and chemo- selective 1,3-protoprototic shift, and a stereo- and chemoselective prototropic shift/\(\gamma\)-CH oxidation cascade at C\(_4\). The utility of the new strategy and methods for efficient and flexible synthesis of other structurally relevant products is currently underway.
Methods
Procedures for the synthesis of cyrneines A–B and glaucopine C. The detailed experimental procedures for the synthesis of cyrneines A, B, and glaucopine C were provided in Supplementary Information.

General procedure for the cross-coupling reaction of enol triflates. To a solution of vinyl triflate 15 (0.2 mmol) in a mixed solvent of DMF (1.0 mL) and EtOH (1.0 mL) was added arylboronic acid 16 (0.4 mmol, 2.0 equiv), palladacycle 17 (5.6 mg, 5 mmol%), and K3PO4 [127 mg, 0.6 mmol, 3.0 equiv (K2CO3 was used for the coupling of 15a with 16a)] at room temperature under nitrogen atmosphere. The resulting mixture was stirred at the same temperature until the vinyl triflate had disappeared as monitored by TLC. The reaction mixture was then poured into water and extracted with ethyl acetate (3 × 25 mL). The organic layer was combined, washed with brine, dried over Na2SO4, and concentrated under vacuum. The residue was purified by silica gel column chromatography to afford the desired cross-coupling product 17.

Data availability. Chemical compound information including NMR and HRMS data, copies of 1H- and 13C-NMR of all new compounds, 2D NMR of compounds 24, 31, cyrneine B (2), and glaucopine (3), HPLC charts for compound 12, and single X-ray crystal data of cyrneine A (1). This material is provided in Supplementary Information. The X-ray crystallographic coordinates for cyrneine A (1) reported in this study have also been deposited at the Cambridge Crystallographic Data Centre (CCDC), under deposition number 1830226. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request.cif. Other supporting data related to this work are available from the corresponding author upon reasonable request.

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Author contributions
F.S.H. conceived the synthetic strategy, directed the project, and wrote the manuscript. F.S.H. and G.J.W. analyzed the experiment results. G.J.W., Y.H.Z. and D.X.T. conducted the experimental work.

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