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Synthetic Studies on Enantioselective Total Synthesis of Cyathane Diterpenoids: Cyrneines A and B, Glaucopine C, and (+)-Allocyathin B_2

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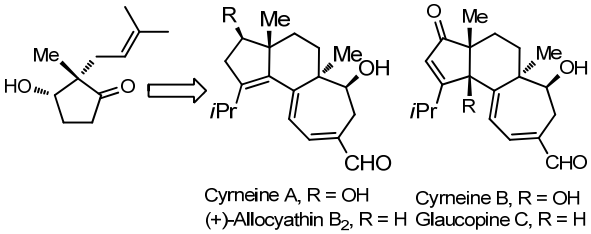


A collective synthesis of cyathane diterpenoids

Abstract: The details for the synthetic studies on enantioselective total synthesis of cyathane diterpenoids cyrneine A (**1**) and B (**2**), glaucopine C (**3**), and (+)-allocyathin B_2 are presented. We established a mild Suzuki coupling for heavily substituted nonactivated cyclopentenyl triflates using a phosphinamide-derived palladacycle as precatalyst and a chelation-controlled highly regioselective Friedel-Crafts cyclization. The utilization of these two key reactions enabled a rapid construction of the 5-6-6-tricyclic skeleton. In the middle-stage of the synthesis, a Birch reductive methylation, a modified Wolff-Kishner-Huang reduction, and a carbenoid-mediated ring expansion were employed as the key reactions to furnish the 5-6-7-tricyclic core bearing two anti-orientated all-carbon quaternary stereocenters at the C_6 and C_9 ring junctions. By applying these key transformations, a more efficient total synthesis of cyrneine A and allocyathin B_2, and the first total synthesis of cyrneine B and glaucopine C were accomplished through a collective manner. The late-stage conversions involving a base-mediated double bond migration and a double bond migration/aerobic γ-CH oxidation cascade for the stereoselective synthesis of

cyrneine B and glaucopine C were interesting.

INTRODUCTION

Since the first isolation and structural elucidation of cyathane diterpene natural products by Ayer and co-workers in 1972,[1] a rich variety of cyathane diterpenoids of more than 100 members have been isolated and categorized different subclasses,[2] such as cyathins,[1,3] erinacines,[4] sarcodonins,[1d,e,5] scabronine,[6] glaucopines,[7] cyrneines,[7c,8] cyanthiwigins,[9] and striatoids,[10] *et al*. With only a few exceptions, the majority of cyathane natural products possesses a common 5-6-7 tricyclic carbon core and bears two *anti*-orientated all-carbon quaternary stereogenic centers at the C_6 and C_9 ring junctions. The unique 5-6-7 tricyclic skeleton coupled with the existence of different degree of oxidation states and various unsaturated double bonds around the ring periphery gives rise to the structural complexity and diversity of cyathane diterpenoids. In addition to the intriguing structural features, it is also attractive that almost all of the cyathane diterpenoids exhibit a wide variety of mild to moderate biological properties such as antibiotics, antimicrobial, antitumor, antitumor, and anti-inflammatory activities. Most interestingly, some of the molecules display strong activity for *anti*-neuroinflammatory[3g,h] or for stimulating the synthesis of Nerve Growth Factor (NGF).[4a,c,6b,7c,8a,10] The unique and complex structural feature as well as the wide biological properties of cyathane natural products has attracted the great interests of synthetic organic community. Over the past 20 years, numerous syntheses have been reported such as the leading contributions from the groups of Nakada,[11] Ward,[12] Trost,[13] Danishefsky,[14] Stoltz,[15] Phillips,[16] Reddy,[17] Snider,[18] Cha,[19] and others.[20]

While immense achievements have been accomplished in the synthesis of cyathane diterpenoids, the development of new methods and synthetic strategies toward more practical synthesis is still interesting. On the other hand, despite of the great advances, there remains a large number of molecules belonging to the subclasses of neocyathins,[3g] glaucopines,[7] cyrneines,[7c,8] and striatoids,[10] continue to challenge the synthetic chemists. As shown by some representative structures in Fig. 1A (**1**–**6**), the key structural features of these subfamilies that unique to others are the presence of extra oxidation at C_1 to C_4 carbons in the five-membered ring periphery. The increased oxidation states associated with the generation of additional stereocenters increase the structural complexity of the molecules. As a result, such intricate polycyclic architecture provides

a good proving ground for the development of new synthetic methods and strategies. In a 2012 report,[21] Gademann and co-workers furnished an elegant total synthesis of cyrneine A (**1**) through a sequence of 24 steps from (-)-(*R*)-carvone (Fig. 1B) by employing a reductive Knoevenagel condensation, a Heck cyclization, and a Yamamoto ring expansion as the key transformations. To our knowledge, this represents the only molecule that has been synthesized among the compounds of aforementioned subclasses.

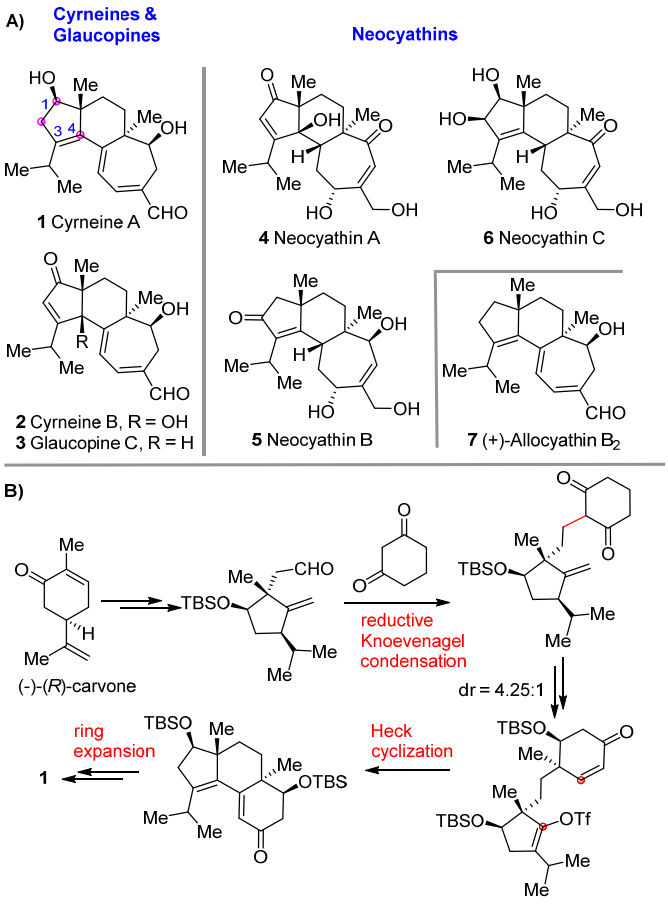


Fig. 1. **A**) Representative structures of cyrneines (**1** and **2**), glaucopines (**3**), neocyathins (**4**–**6**), and (+)-allocyathin B_2 (**7**), and **B**) the key transformations in Gademann's synthesis of cyrneine A (**1**)

In addition to the intriguing structures, many molecules within these subclasses exhibit appealing biological properties. Notably, a number of molecules within the neocyathins, cyrneines, and striatoids possess significant *anti*-inflammatory activities,[3g,h] and pronounced neurite outgrowth-promoting activities.[7c,8a,10] Therefore, it is anticipated that these bioactive compounds might be used as leading molecules for the development of new agents against Alzheimer disease (AD) and related neurodegenerative disorder. Driven by the complex structures, the potential

biological properties, and an in-depth SAR elucidations, we initiated an investigation toward establishing a strategically new route that is capable of flexibly synthesizing the natural products as well as potential analogues with structural diversity.

Very recently, we successfully developed a route that could be used for a collective total synthesis of cyrneines A (**1**) and B (**2**), and glaucopine C (**3**).[22] As illustrated in Fig. 2, the pivotal transformations involved in our synthetic route were: (i) an enzyme-catalyzed desymmetric enantioselective reduction of the readily available diketone **8** for preparing the chiral starting material **9** in excellent enantioselectivity (99% ee) and diastereoselectivity (*ca.* 25:1); (ii) a highly efficient Suzuki-Miyaura cross-coupling of the heavily substituted nonactivated enol triflate **10** catalysed by a phosphinamide-derived palladacyclic catalyst to synthesize the congested cyclopentene **11**; (iii) a chelation-controlled intramolecular cyclization for highly regioselective construction of 5-6-6 tricyclic carbon scaffold **12**; (iv) a Birch reductive methylation for stereoselective installation of C_6 quaternary carbon of **13**; (v) a one-pot Zn carbenoid-mediated ring expansion for construction the 5-6-7 tricyclic core **14**; (vi) a stereoselective reduction of the carbonyl group at C_{14} for the synthesis of advanced intermediate **15**; (vii) a base-promoted double bond migration, and (viii) a stereo- and chemoselective double bond migrration/γ-CH oxidation cascade. By adopting these key transformations, three polyoxygenated diterpenoids **1**−**3** were achieved from **15** through a divergent manner.

On the journey of our synthetic study, we also designed and investigated several other strategies in addition to the successful one. Although these efforts failed to access our targeted molecules, some chemistries established in the study would be interesting for practical applications or, at least, would find important appeal within a wider synthetic community. In addition, to further exemplify the generality and high efficiency of our synthetic route, we recently carried out a synthetic study of (+)-allocyathin B_2 (**7**)[23] which has been previously synthesized by Trost,[13] and Nakada.[24] The details of these results will be presented herein.

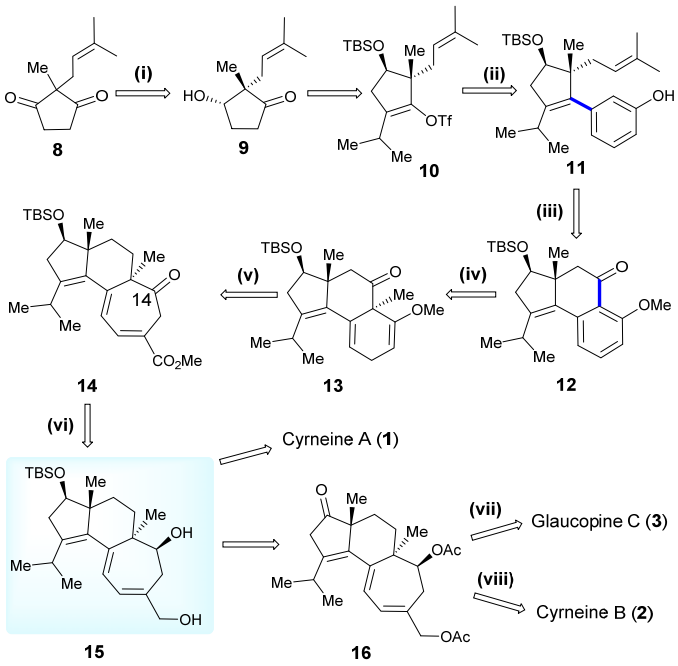
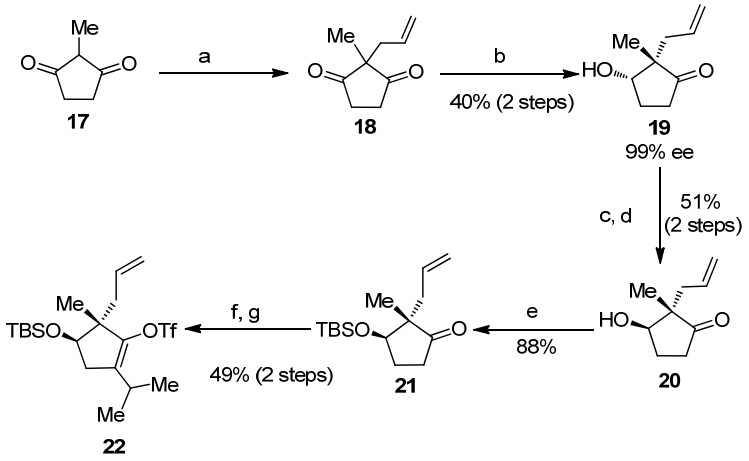


Fig. 2. Key transformations for the synthesis of cyrneines A and B (**1** and **2**), and glaucopine C (**3**) developed by our group.[22]

RESULTS AND DISCUSSION

Starting from the commercially readily available 2-methyl 1,3-cyclopentanedione **17** (Scheme 1), alkylation of **17** with allyl bromide gave the 2,2-disubstituted cyclopentanedione **18**.[25] Desymmetric enantioselective reduction of **18** was firstly carried out by using CBS reduction according to the reported literatures.[26] While good enantioselectivity of higher than 90% ee was observed, the diastereoselectivity was modest (d.r. = *ca.* 5−6:1). In addition, although the CBS catalyst derived from *L*-threonine by Shimizu[26a] could afford directly the 3-β-hydroxy ketone **20** with desired chirality, a stoichiometric amount of catalyst has to be used to gain good enantioselectivity. As a result, the issues raised from the modest diastereoselectivity and the use of large amount catalyst made the CBS reduction problematic for large scale preparation of **20**. Alternatively, we examined the baker's yeast-catalyzed reduction.[27] To compare with CBS reduction, the enzyme-catalyzed reduction afforded 3-α-hydroxy ketone **19** with excellent enantioselectivity of up to 99% ee and a slightly increased diastereoselectivity of up to *ca.* 7.7:1. Another added advantage is that the reaction could be more easily performed on multigram scales albeit the yield was still not sufficiently high (*ca.* 40% yield over two steps from **17**). This was mainly resulted from the somewhat tedious purification process to remove the diastereoisomers of

19 by column chromatography for getting pure **19**. By employing Mitsunobu conditions,[28] the 3-α-hydroxy group in **19** was inverted to give the desired 3-β-hydroxy ketone **20** in 51% yield over two steps without a careful optimization of the reaction conditions. Transformation of **20** to enol triflate **22** was carried out smoothly following a three-step procedure involving silylation, isopropylation, and enolation.

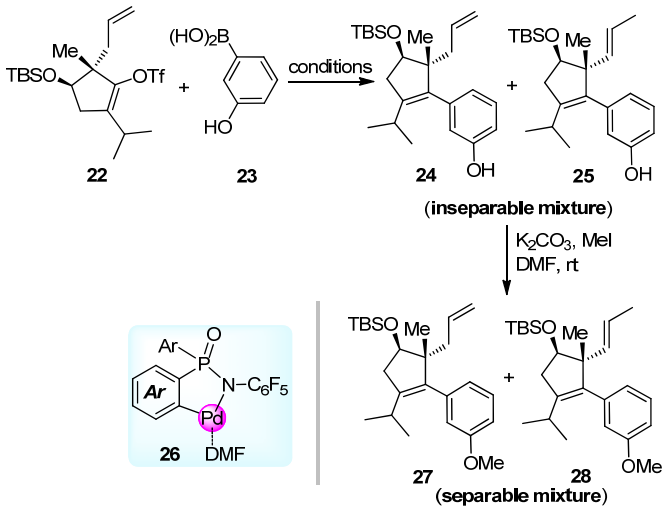


Scheme 1. Synthesis of enol triflate **22**. Reagents and conditions: (a) allyl bromide (2.0 equiv), TBAI (1 mol%), 2 *N* NaOH, H_2O, 50 °C, 8 h. (b) yeast extract (50 wt%), *D*-glucose (1756 wt%), dry active baker's yeast (1181 wt%), H_2O, 35 °C, 48 h (40% for 2 steps). (c) *p*-NO_2-$C_6H_4CO_2H$ (2.0 equiv), PPh_3 (2.0 equiv), DEAD (2.0 equiv), THF, 0 to 50 °C, overnight. (d) K_2CO_3 (2.0 equiv), MeOH/THF (v/v = 1:2), 0 °C, 30 min (51% for 2 steps). (e) TBSCl (1.2 equiv), imidazole (1.2 equiv), DMF, rt, overnight (88%). (f) NaH (5.0 equiv), *i*PrI (10.0 equiv), THF, reflux, overnight; then *aq.* HCl (2 M), rt, 1.5 h. (g) LiHMDS (1.3 equiv, 1.0 M in THF), $PhNTf_2$ (1.3 equiv), THF, -78 °C to rt, 3 h (56% for 2 steps). TBAI = tetra-*n*-butylammonium iodide; DEAD = diethyl azodicarboxylate; TBSCl = *t*-butyldimethylsilyl chloride; LiHMDS = lithium hexamethyldisilazide; THF = tetrahydrofuran; DMF = *N*,*N*-dimethylformamide.

The Suzuki-Miyaura cross-coupling reaction of the densely substituted enol triflate **22** with boronic acid **23** was initially carried out by referring to some reported methods relevant to sterically hindered substrates.[29] Representative data for optimization of reaction conditions were shown in Table 1. Among an array of conditions being examined, $Pd(PPh_3)_4$ (entry 2) and the combination of $Pd(OAc)_2$ with dppb (entry 7) gave the coupled product **24** in moderately high yields. However, these conditions were problematic for large scale synthesis due to partial hydrolysis of triflate **22** arising from an elongated reaction time. We then inspected the catalytic efficiency of a palladacycle **26** derived from diaryl phosphinamide in our previous study[30] which displayed high activity for Suzuki-Miyaura coupling of aryl (*pseudo*)halides.[30c] Delightedly, after a brief screening of conditions, we found that this catalyst was highly active for the sterically

hindered enol triflate **22**. Rapid and complete conversion was observed at room temperature to give the product **24** in almost quantitative yield using K_2CO_3 as base (entry 8). NMR analysis showed that the product was contaminated by a small amount of inseparable by-product. A further optimization revealed that K_3PO_4 was also a suitable base, the side reaction could be partially suppressed although the yield was somewhat decreased (entry 9). Disappointedly, when the reaction was performed on large scale, the quantity of the by-product was apparently increased with the presence of either K_2CO_3 or K_3PO_4 base.

Table 1 Suzuki-Miyaura Cross-Coupling of Enol Triflate **22**.[a]

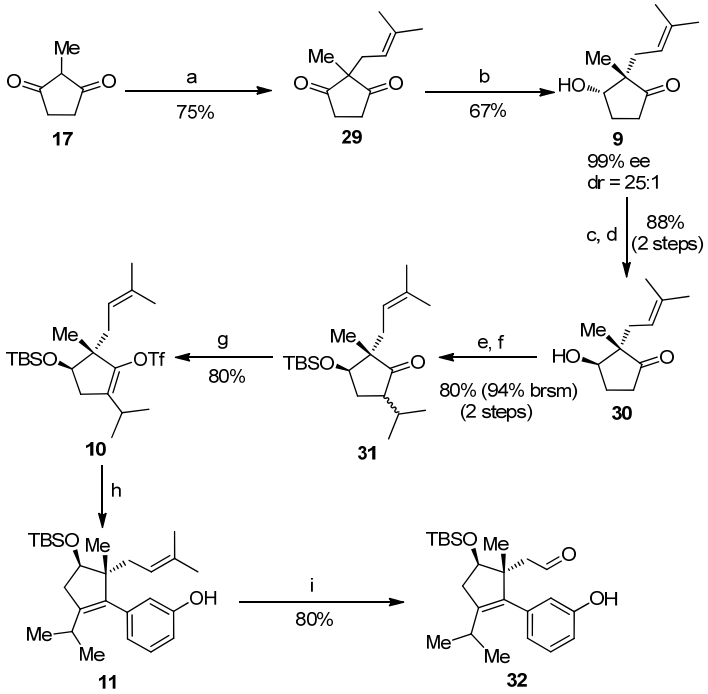


Entry	Catalyst (5 mol%)	Base	Solvent	*T* (°C)	T (h)	Yield of **24** (%)[b]
1	$PdCl_2(dppf)$	K_2CO_3	DMSO	85	10	22
2	$Pd(PPh_3)_4$	K_2CO_3	dioxane	85	4	66
3	$PdCl_2$/dppe	K_2CO_3	dioxane	85	10	trace
4	$PdCl_2$/dppb	K_2CO_3	dioxane	85	10	44
5	$Pd(OAc)_2$/dppe	K_2CO_3	dioxane	85	10	trace
6	$Pd(OAc)_2$/dppp	K_2CO_3	dioxane	85	10	48
7	$Pd(OAc)_2$/dppb	K_2CO_3	dioxane	85	10	67
8	**26**	K_2CO_3	DMF/EtOH (v/v = 1:1)	rt	2.5	98[c]
9	**26**	K_3PO_4	DMF/EtOH (v/v = 1:1)	rt	2.5	82

[a] Reaction conditions: **22** (0.1 mmol), **23** (0.2 mmol), catalyst (5 mol%), and base (3.0 equiv) in 1 mL solvent under nitrogen atmosphere. [b] Isolated yield. [c] Containing a small amount of inseparable by-product **25**.

To clarify the details of the by-product, the mixture of the cross-coupled products was methylated to give a pair of separable compounds whose structures were determined to be **27** and **28**, respectively. Thus, the by-product formed during the cross-coupling reaction was assigned as **25** resulting from the migration of double bond. While the detailed reasons for the migration await

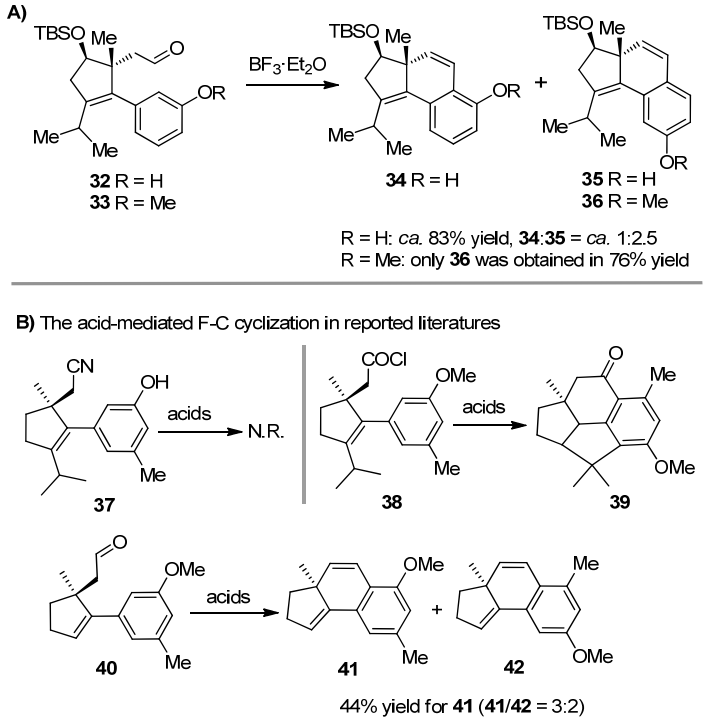
further investigation, based on the results of various control experiments, it seemed that the migration reaction was mainly influenced by the electronic nature and position of the substituents in boronic acids. For instance, when *para*-methoxylphenyl boronic acid instead of meta-methoxyphenyl or *meta*-hydroxyphenyl boronic acids was coupled with **22**, only negligible amount of migrated by-product was detected. In addition, the migration was also affected by other parameters such as base, reaction time, and solvent. Thus, although extensive efforts aiming at improving the efficiency of the coupling reaction were attempted, we were unable to establish a set of reliable conditions to perform the reaction on large scales at current stage.



Scheme 2. Synthesis of intermediate **32**.[22] (a) prenyl bromide (2.0 equiv), K_2CO_3 (1.5 equiv), acetone, rt, overnight (75%). (b) yeast extract (50 wt%), *D*-glucose (1500 wt%), dry active baker's yeast (1333 wt%), H_2O, rt, 36 h (67%). (c) *p*-NO_2-$C_6H_4CO_2H$ (2.0 equiv), PPh_3 (2.0 equiv), DEAD (2.0 equiv), THF, 0 to 50 °C, overnight (90%). (d) K_2CO_3 (2.0 equiv), MeOH/THF (v/v = 1:2), 0 °C, 30 min (98%). (e) TBSCl (1.2 equiv), imidazole (1.2 equiv), DMF, rt, overnight (91%). (f) NaH (5.0 equiv), *i*PrI (10.0 equiv), THF, reflux, overnight; then aq. HCl (2 M), rt, 1.5 h (88%). (g) LiHMDS (1.3 equiv, 1.0 M in THF), $PhNTf_2$ (1.3 equiv), THF, -78 °C to rt, 3 h (80%). (h) Boronic acid **23** (2.0 equiv), cat. **26** (5 mol%), K_2CO_3 (3.0 equiv), DMF/EtOH (v/v = 1:1), rt (93–98%). (i) OsO_4 (4 mol%), $NaIO_4$ (5.0 equiv), pyridine (3.0 equiv), dioxane/H_2O (v/v = 5:1), 80 °C (80%).

Owing to the relatively low efficiency for large scale synthesis of **19** resulting from the modest diastereoselectivity for desymmetric reduction of **18** and the problematic Suzuki-Miyaura cross-coupling of **22**, we had to renew our synthetic route. Accordingly, 1,3-cyclopentanedione **29** bearing a bulkier prenyl group was prepared (Scheme 2). We assumed that by replacing the allyl group in **18** with a sterically more hindered prenyl group, the diastereoselectivity of desymmetric

reduction might be improved and the migration might be suppressed. As expected, the enzyme-catalyzed desymmetrization of **29** afforded the 3-α-hydroxy ketone **9** with up to 99% ee and *ca.* 25:1 diastereoselectivity. Subsequently, **9** was smoothly converted into the enol triflate **10** in five steps by implementing the similar procedure for the synthesis of **22**. More importantly, the coupling reaction of **10** with boronic acid **23** catalyzed by the palladacycle **26** proceeded uneventfully to give the desired product **11** in excellent yield on decagram level without the observation of any migrated by-product. Notably, as shown in our previous report,[22] the palladacycle **26** exhibited a broad compatibility to a rich range of heavily substituted enol triflates. Oxidative cleavage of the trisubstituted alkene in **11** proceeded selectively to afforded the aldehyde **32**. Since all the transformations from **17** to **32** could be reliably performed on multigram scales, the modified route provided a practical way for supplying sufficient intermediate **32** for late-stage synthetic study.

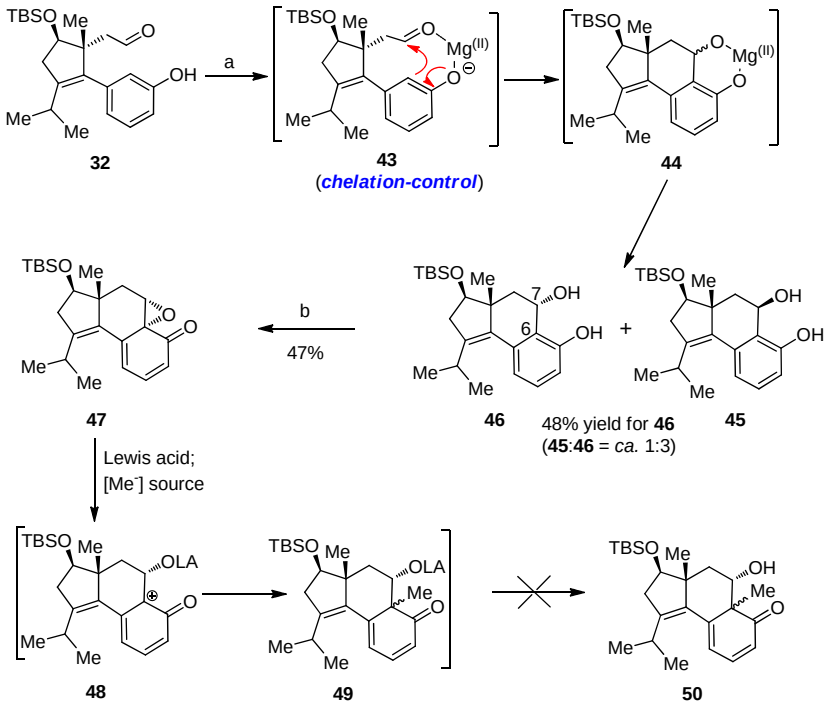


Scheme 3. Unsuccessful Friedel-Crafts cyclization mediated by acids: **A**) the results using our substrates; and **B**) the reported results in literature (ref 29b and 31)

For the Friedel-Crafts cyclization of **32**, we first examined the acid-mediated reactions (Scheme 3A). Among an array of Lewis and Brønsted acids being screened, $BF_3 \cdot Et_2O$ could promote the cyclization of **32**. However, the desired product was not obtained due to the poor

regioselectivity of *ortho* vs. *para* to phenolic OH and the subsequent dehydration of the central six-membered ring. As a result, a *ca.* 1:2.5 mixture of dehydrated regioisomers **34** and **35** was afforded in *ca.* 83% yield. Under the same conditions, the methyl protected substrate **33** gave the dehydrated product **36** with exclusive *para* selectivity in 76% yield. In fact, similar results concerning the acid-mediated cyclization have been reported in prior literature in the synthesis of hamigeran B (Scheme 3B). For instances, Trost and co-workers[29b] demonstrated that in the presence of various acids, the cyclization of the nitrile compound **37** was ineffective; alternatively, the acyl chloride **38** afforded only the tetracyclic by-product **39** with *para* selectivity to MeO group. Recently, Jiang and co-workers[31] showed that with the presence of $BF_3 \cdot Et_2O$, the cyclization of aldehyde **40** could proceed to produce the dehydrated products. However, a poor regioselectivity of **41**:**42** = *ca.* 3:2 was observed.

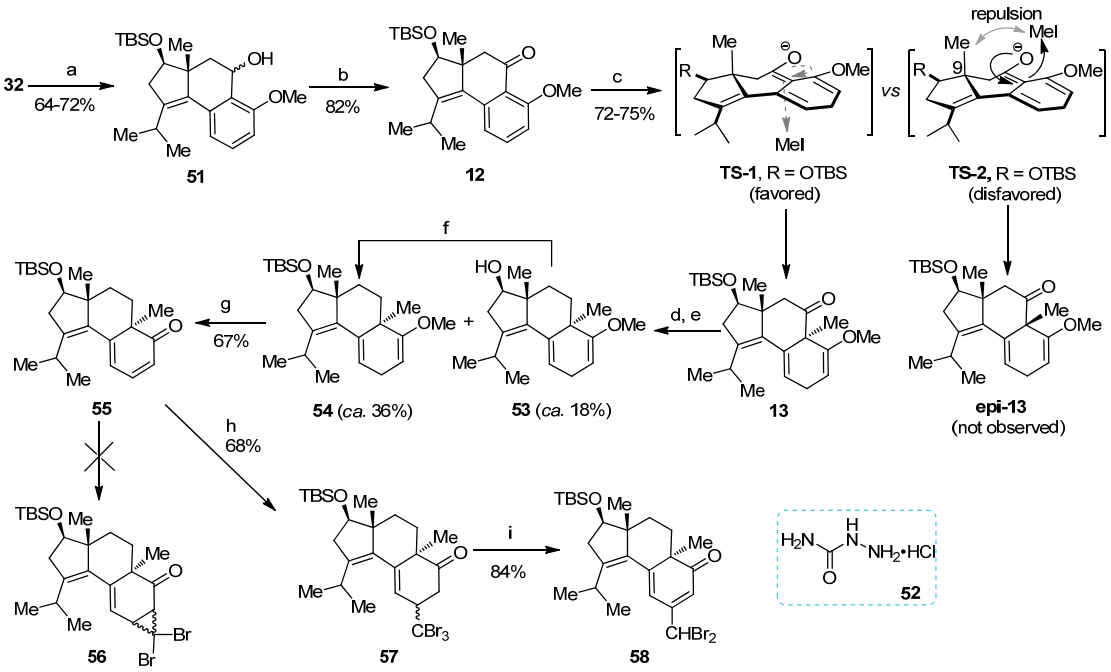
The unsuccessful efforts on acid-promoted cyclization encouraged us to redesign and develop an alternative strategy. After extensive exploration, we established a chelation-controlled protocol that could achieve the cyclization reaction in high regioselectivity at the position *ortho* to phenolic OH. As illustrated in Scheme 4, treatment of **32** with EtMgBr generated a magnesium phenolate. The Mg(II) salt thus generated may serve as a weak Lewis acid which may coordinate with the aldehyde functionality,[32] forming a closed transition state **43**. Due to the fixed transition state, the followed Friedel-Crafts reaction proceeds exclusively at the *ortho* position to phenolic OH, and ultimately delivering the cyclized magnesium salt **44**. As a result, a couple of C_7 epimers **45** and **46** with *ca.* 1:3 ratio were formed. The major isomer **46** could be isolated in 48% yield. For the introduction of C_6 methyl group, we initially examined a ring-opening/methylation cascade of epoxide.[33] Accordingly, oxidative cyclization[34] of **46** afforded the epoxide **47** in 47% yield. Unfortunately, attempted ring-opening/methylation toward synthesizing **50** by means of capturing the possible species **48** with an appropriate Me^- source was proved to be futile. A complex mixture was obtained under various conditions.



Scheme 4. Successful cyclization and attempted introduction of C_6 methyl group through the ring-opening/methylation cascade of epoxide. (a) EtMgBr (1.1 eqiuv, 1.0 M in THF), -78 to 40 °C, overnight (64% total). (b) $NaIO_4$ (2.0 equiv), MeCN/H_2O (v/v =3:1), 0 °C to rt, 2 h (47%).

We then inspected the Birch reductive alkylation although a literature survey showed that such transformation has been rarely investigated in a fused-ring system presumably due to the concerns of annular strain, steric hindrance, and stereoselectivity. Accordingly, treatment of **32** with EtMgBr followed by *in situ* selective methylation of the phenolic OH furnished the construction of the tricyclic compound **51** in 64−72% yield (Scheme 5). PCC oxidation of the alcohol in **51** gave ketone **12**. After an exhaustive optimization of reaction conditions, we could successfully introduce the C_6 angular methyl by means of Birch reductive methylation,[22] affording **13** with exclusive α-stereoselectivity in 72−75% yield without the detection of epi-**13**. The stereochemistry was determined by NOESY spectroscopic analysis and was further demonstrated by the single X-ray crystallographic analysis of cyrneine A (**1**) after completion of its total synthesis (See Scheme 6). The exclusively high stereoselectivity is presumably due to the sterical repulsion between the C_9 methyl and MeI electrophile. As a result, the nucleophilic attack of carbon anion form the *si*-face via **TS-1** rather than the *re*-face via **TS-2** is preferred. Notably, these transformations could be reliably implemented on gram scale. Deoxygenation of carbonyl in the central ring of **13** was carried out by employing the Wolff-Kishner-Huang reaction. Our extensive experiments showed that the use of semicarbazide **52** to form a semicarbazone and the use of

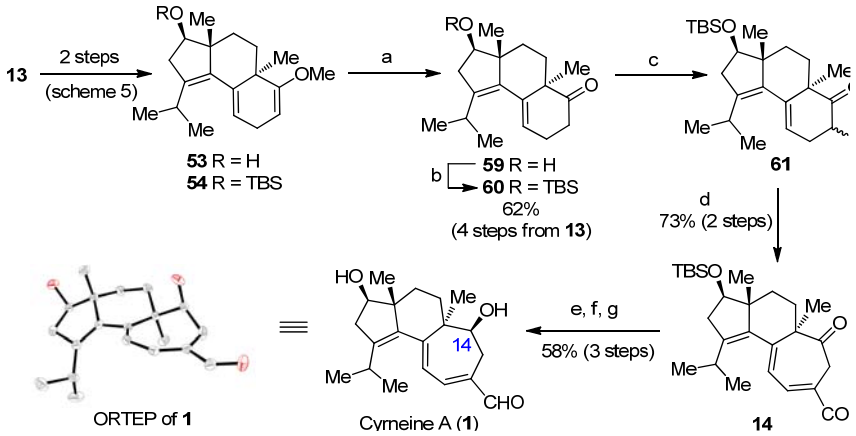
KO*t*Am in degassed xylene for the following reduction of semicarbazone was crucial. Under the optimized conditions, the desired **54** was obtained in *ca.* 36% yield accompanied by the formation of a small amount of desilylated **53**, which could be resilylated to give **54**. Consequently, **54** was afforded in *ca.* 53% total yield. Next, our attention was shifted to the construction of the seven-membered ring. Thus, **54** was converted into dienone **55** by means of selective bromination of electron-riched double bond of enol ether with NBS followed by base-mediated elimination.[35] Attempted cyclopropanation of **55** with bromoform aimed at synthesizing the dibromocyclopropane **56** was carried out under various conditions according to the reported literature.[29e,36] However, the desired cyclopropanation did not proceed. The reaction was terminated at the 1,4-addition stage to give the Michael addition product **57** as the sole product. The structure of **57** was deduced from the structural proof of compound **58** since the structure of **57** cannot be definitely assigned by NMR and MS analyses due to the complexity of the product raising from the formation of a pair of epimeric **57** and the easy of debromination.



Scheme 5. Successful introduction of C_6 methyl group by Birch reductive methylation and attempted ring expansion reaction. (a) EtMgBr (1.1 eqiuv, 1.0 M in THF), -78 to 40 °C, overnight, then K_2CO_3 (2.0 equiv), MeI (5.0 equiv), and DMF were charged in situ, 55 °C, 10 h (64–72%). (b) PCC (4.0 equiv), NaOAc (4.0 equiv), celite (*ca.* 130 wt%), rt, 6 h (82%). (c) Liq. NH_3, *t*BuOH (1.0 equiv), K (2.5 equiv), Et_2O, -78 °C, 10 min; then LiBr (2.5 equiv), MeI (5.0 equiv), and THF were charged in situ, -78 °C, 1 h, then warmed to rt over a period of 1 h (72%). (d) **52** (5.0 equiv), NaOAc (5.0 equiv), EtOH, 35 °C, 3 h. (e) KO*t*Am (5.0 equiv), degassed xylene, 140 °C, 1.8 h (36% for **54**; 18% for **53**). (f) TBSCl (1.2 equiv), imidazole (1.2 equiv), DMF, rt, overnight (93%). (g) NBS (1.1

equiv), H_2O (2.0 equiv), THF, 0 °C to rt, 15 min; then DBU (2.0 equiv), 45 °C, 3.5 h (67%). (h) LiHMDS (1.0 M in THF, 1.5 equiv), $CHBr_3$ ((5.0 equiv), Et2O, -78 °C, 2 h (68%). (i) DBU (2.0 equiv), THF, rt, 15 min (84%). PCC = pyridinium chlorochromate; *t*Am = *tert*-amyl; NBS = *N*-bromosuccinimide; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

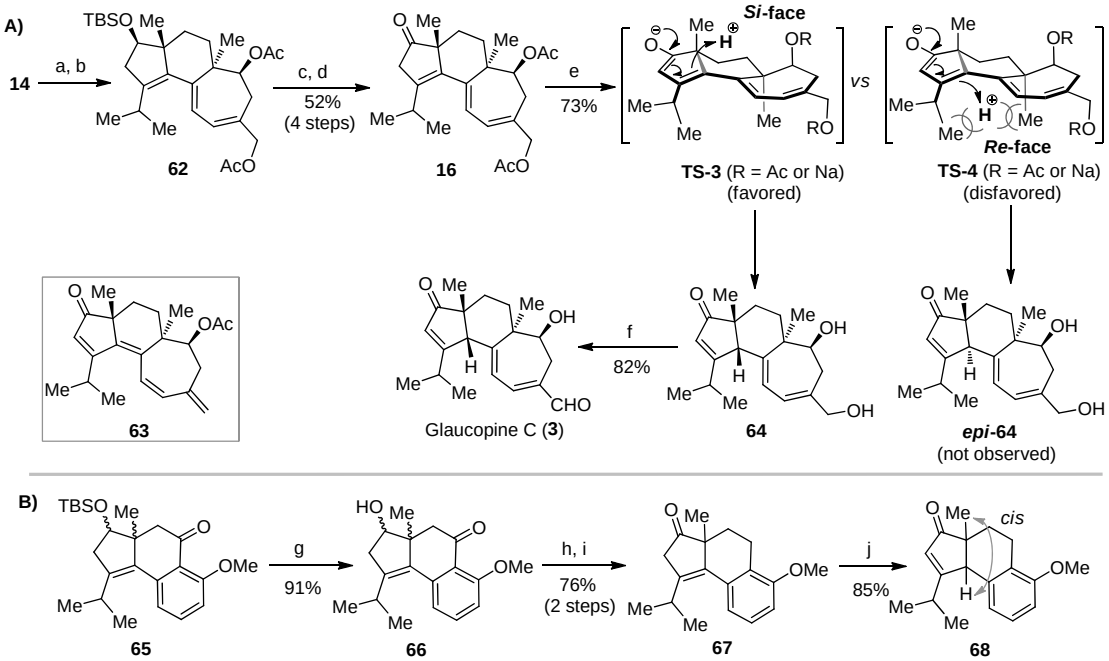
We then tried the Zn carbenoid-mediated ring expansion based on a protocol reported by Zercher[37] (Scheme 6). Accordingly, Wolff-Kishner-Huang reduction of **13** afforded a mixture of **53** and **54**. Without purification, the mixture was hydrolysed under acid conditions to give a mixture of ketone **59** and **60**. The mixture was subjected to resilylation to convert **59** into **60**. As a result, **60** could be efficiently synthesized in 62% overall yield through a four-step sequence from **13**. The α-acylation of **60** afforded a mixture of **61** and its enol tautomer, which was smoothly transformed to the 5-6-7-tricyclic compound **14** by a one-pot Zn carbenoid-mediated ring expansion following a iodination and DBU-promoted elimination. Finally, removal of TBS with TMSOTf, reduction of ketone and ester groups with $LiAlH_4$,[24] and selective oxidation of the allylic primary alcohol to aldehyde with MnO_2 accomplished the total synthesis of cyrneine A (**1**) in 20 linear steps from commercially available 2-methyl 1,3-cyclopentanedione **17**. The structure of **1** was unambiguously confirmed by a combination of multiple analyses including ^{1}H- and ^{13}C-NMR, HRMS, specific rotation, and single crystal X-ray diffraction (CCDC 1830226).[38]



Scheme 6. Successful construction of the seven-membered ring and the completion of the synthesis of cyrneine A. (a) 5% *aq.* HCl, THF, 15 to 20 °C, 40 min (89%). (b) TBSCl (1.2 equiv), imidazole (1.2 equiv), DMF, rt, overnight (62%, 4 steps from **13**). (c) LiHMDS (1.0 M in THF, 3.5 equiv), $CNCO_2Me$ (3.0 equiv), THF, -78 °C, 1 h. (d) $ZnEt_2$ (1.0 M in hexane, 6.0 equiv), CH_2I_2 (6.0 equiv), CH_2Cl_2, rt, 2 h; then I_2 (7.0 equiv), rt; then saturated aq. $Na_2S_2O_3$ (excess), rt; then DBU (20.0 equiv), rt, 10 min (73% for 2 steps). (e) TMSOTf (5.0 equiv), CH_2Cl_2, -25 °C, 15 min. (f) $LiAlH_4$ (6.0 equiv), Et_2O, 10 min at -78 °C, then warmed to rt. (g) MnO_2 (50 equiv), CH_2Cl_2, rt, overnight (58%, 3 steps from **14**). TMSOTf = trimethylsilyl trifluoromethanesulfonate.

Having successfully accomplished the synthesis of cyrneine A (**1**), we then moved forward to

the total synthesis of cyrneine B (**2**) and glaucopine C (**3**). To the end, compound **14** was converted into diacetate **62** through reduction and acylation (Scheme 7A). Subsequently, removal of TBS in **62** followed by Dess-Martin oxidation of the hydroxyl group gave ketone **16**. To establish a method for regio- and stereoselective introduction of C_4 β-H by means of double bond migration, we investigated the reaction conditions using the more readily available racemic **67** as the model compound which could be derived from **65** within three steps (Scheme 7B). It was found that the double bond migration of **67** could proceed smoothly in the presence of an array of bases under heating to give the thermodynamically preferred **68** with exclusive *cis*-selectivity. Typically, the isomerization proceeded cleanly to give **68** in 85% yield under the effect of DBU in refluxed benzene. The relative stereochemistry of **68** was confirmed by NOESY correlation.

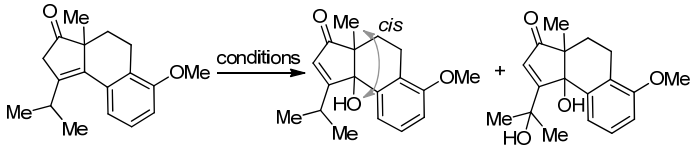


Scheme 7. The completion of the synthesis of glaucopine C. (a) $LiAlH_4$ (6.0 equiv), Et_2O, 20 min at -78 °C, then warmed to rt. (b) Ac_2O (15.0 equiv), DMAP (20 mol%), pyridine, 30 min, rt. (c) HF•Py (excess), THF, rt, 2 h. (d) DMP (1.6 equiv), CH_2Cl_2, 30 min, rt (52% for 4 steps). (e) NaOMe, MeOH, 35 °C, 4 h (73%). (f) MnO_2 (15 equiv), CH_2Cl_2, rt, 3 h (82%). (g) TMSOTf (6.0 equiv), CH_2Cl_2, 0 °C, 1.5 h (91%). (h) Et_3SiH (10.0 equiv), TFA (15.0 equiv), CH_2Cl_2, 0 °C to rt, 2 h (92%). (i) DMP (1.3 equiv), CH_2Cl_2, rt, 30 min (82%). (j) DBU (5.0 equiv), PhH, 80 °C, 2 h (85%). DMAP = 4-(dimethylamino)pyridine; Py = pyridine; DMP = Dess-Martin periodinane.

Unfortunately, when the reaction conditions were applied to the substrate **16**, the desired 1,3-proton shifted product was not obtained. The tetraene **63** was most likely formed as a result of elimination of HOAc. We reasoned that this should attribute to the good leaving property of OAc group. To overcome this problem, the hydrolysis of ester group was carried out prior to proton

shift. After a further optimization of the reaction conditions, we found that treatment of **16** with NaOMe in MeOH resulted in a simultaneous deprotection of Ac group and proton shift, affording the diol **64** in 73% yield as a single C_4 β-H diastereoisomer. The stereochemistry of the product was confirmed by NOESY correlation.[22] The high stereoselectivity may be resulted from the sterically less hindered *si*-face of **TS-3** as compared to the more hindered *re*-face of **TS-4.** In addition, the thermodynamically favorite *cis*-selectivity cannot be ignored. Finally, selective oxidation of the allylic primary alcohol in **64** to aldehyde gave glaucopine C (**3**).[38]

Table 2 Optimization of the conditions for double bond migration and γ-CH oxidation cascade reactions.[a]



67 69 70

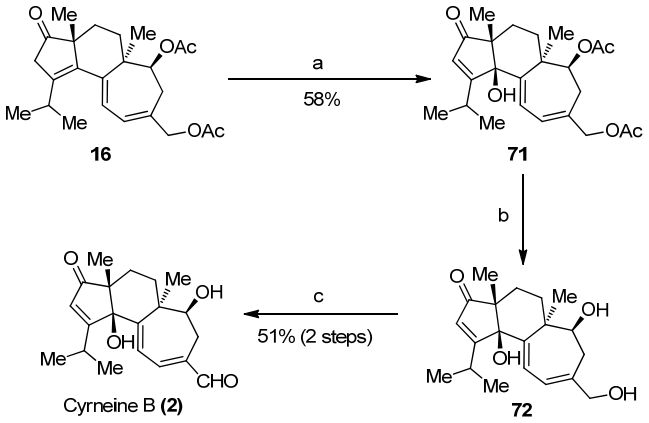
Entry	Conditions	Yield of **69** (%)[b]
1	DBU (5 equiv), O_2 (balloon), DMSO, 80 °C	25
2	DBU (5 equiv), O_2 (balloon), DMSO, 50 °C	41
3	DBU (5 equiv), O_2 (balloon), DMSO, 40 °C	37
4	TMG (5 equiv), O_2 (balloon), DMSO, 50 °C	44
5	TMG (5 equiv), O_2 (balloon), $P(OMe)_3$ (2 equiv) DMSO, 50 °C	37
6	LiHMDS (2 equiv), THF, N_2, -78 °C, 15 min; then $P(OMe)_3$ (2 equiv), O_2 (balloon), -78 °C	65

[a] Reaction conditions: 15 mg (0.056 mmol) of **67** in 0.6 mL solvent. [b] Isolated yield. TMG = 1,1,3,3-tetramethylguanidine.

Encouraged by the base-mediated smooth double bond migration reaction of **16**, we planned to introduce the β-OH at C_4 toward synthesizing cyrneine B (**2**) by implementing a base-mediated double bond migration and γ-CH oxidation cascade reaction. The optimization of the reaction conditions was carried out employing **67** as a model compound based on some methods reported in literature.[39] As shown in Table 2, while the desired C_4 β-hydroxylation could proceed to give the *tertiary* alcohol **69** under an array of conditions (entries 1−5), the yield was low to moderate. In many cases, a by-product which was tentatively assigned as the dihydroxylated **70** was formed due presumably to the relatively harsh reaction conditions. In considering of this, **67** was treated with a strong base such as LiHMDS at a lowered temperature followed by trapping the anion with molecular oxygen. With this alteration, the yield of **69** could be substantially improved to 65%

with exclusive *cis*-selectivity. The relative stereochemistry of **69** was confirmed by NOESY correlation.

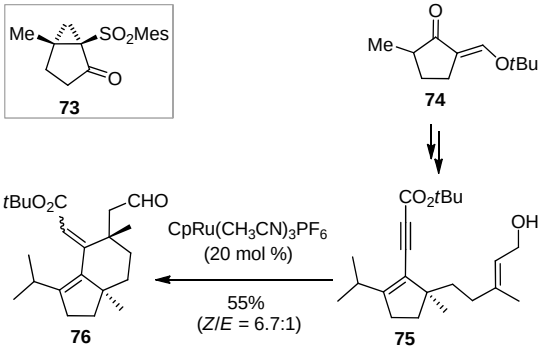
With the suitable conditions for C_4 β-hydroxylation being established through the model reaction, we entered the final stage toward the completion of the synthesis of cyrneine B (**2**) (Scheme 8). Thus, treatment of **16** under the optimized conditions for model reaction afforded the C_4 β-hydroxylated product **71** in 58% yield whose stereochemistry was also verified by NOESY correlation.[22] Here, the high stereoselectivity for the oxidative hydroxylation should be arisen from the same reasons as the stereoselective prototropic shift (*vide supra*). Hydrolysis of the two ester groups in **71** followed by selective oxidation of the primary allylic alcohol in **72** accomplished the total synthesis of cyrneine B (**2**) in 51% yield over two steps.[38]



Scheme 8. The completion of the synthesis of cyrneine B. (a) LiHMDS (1.0 M in THF, 2.0 equiv), THF, -78 °C, 15 min, then $P(OMe)_3$ (4.0 equiv), O_2, 2 h (58%). (b) K_2CO_3 (excess), MeOH, 35 °C, 4 h. (c) MnO_2 (15 equiv), CH_2Cl_2, rt, 3 h (51% for 2 steps).

Finally, to further demonstrate the flexible applicability and efficiency of our new synthetic strategy developed herein, we carried out the total synthesis of (+)-allocyathin B_2. Two enantioselective syntheses for this compound have been reported. The first total synthesis was accomplished by Nakada and co-workers[24] in 2004 within a longest linear step of 23 steps (total 28 steps) from the known cyclopentanone derivative **73** (Scheme 9). In 2005, Trost and co-workers[13] reported a more efficient synthesis through a longest linear sequence of 17 steps (total 19 steps) from the cyclopentanone derivative **74**. In the whole synthetic route, only the Ru-catalyzed cycloisomerization of **75** for constructing **76** was somewhat less effective due to the moderate yield and *Z*/*E* selectivity, and high catalyst loading. Since it was found in a very recent

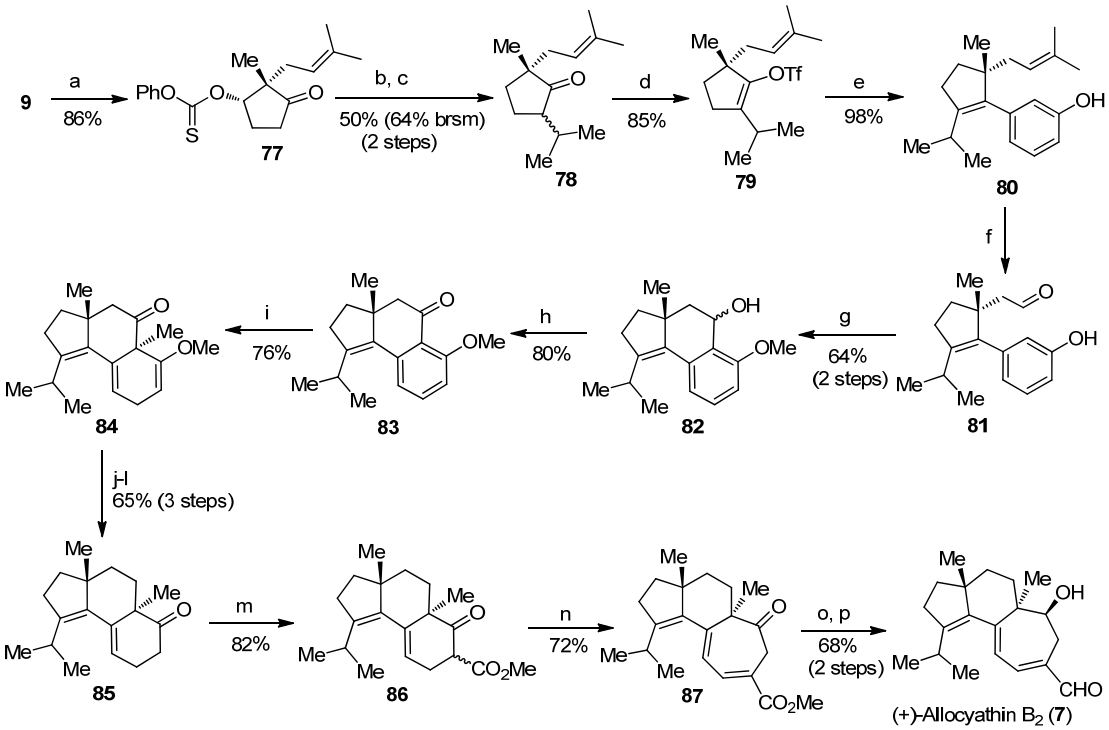
research by Gao[3h] that (+)-allocyathin B_2 displayed promising biological property for inhibition of nitric oxide (NO) production with an IC_{50} value of 19.8 μM, the development of a new route toward more practical synthesis of this molecule as well as its potential analogues would be much appealing for an in-depth SAR evaluation and the discovery of new *anti*-neuroinflammatory compounds.



Scheme 9. Starting materials used in Nakada's and Trost's synthesis, and one of the key reactions in Trost's synthetic route

Our synthesis commenced with enantiomerically pure **9** (Scheme 10). Activation of the hydroxy group in **9** with carbonochloridothioate afforded the carbonothioate **77**. Barton-McCombie radical deoxygenation[40] followed by isopropylation of the deoxygenated cyclopentanone gave **78** in 50% yield over two steps (64% brsm). Conversion of **78** into enol triflate **79** and cross-coupling of **79** with boronic acid **23** catalyzed by palladacycle **26** provided the arylated cyclopentene **80**. Selective oxidation of the less hindered olefin outside the cycle followed by a one-pot cyclization/methylation via aldehyde **81** produced the 5-6-6-tricyclic intermediate **82**. PCC oxidation of **82** afforded ketone **83**. Birch reductive methylation of **83** led to a regio- and stereoselective construction of C_6 chiral quaternary carbon center in **84**. Subsequently, Wolff-Kishner-Huang reduction of the carbonyl group in the central ring and acid-promoted hydrolysis of vinyl methyl ether gave ketone **85**. Then α-acylation of **85** afforded uneventfully a mixture of β-ketone ester **86** and its enol tautomer. Finally, by implementing a carbenoid-meidated one-pot ring-expansion reaction, a reduction of carbonyl and ester groups, and a selective oxidation of primary alcohol furnished the total synthesis of (+)-allocyathin B_2 with a 16-step linear sequence from the known compound **9** (total 18 steps from the commercially available **17**). It should be mentioned that most of the reactions in the synthetic route (from **17** to **85**) could be

uneventfully performed on gram scale. While we did not examine the scalability of the last four steps from **85** to (+)-allocyathin B_2 on large scale, they could be reliably peformed on about 40–100 mg scale. These results demonstrated that the synthetic route presented herein would be useful for supplying (+)-allocyathin B_2 and its analogues on a level of dozens of milligrams.



Scheme 10. The completion of the synthesis of (+)-allocyathin B_2. (a) PhOC(S)Cl (1.5 equiv), pyridine (2.0 equiv), DMAP (0.1 equiv), CH_2Cl_2, rt, 4 h (86%). (b) AIBN (1 mol%), Bu_3SnH (2.0 equiv), toluene, 100 ^oC, 1 h. (c) NaH (5.0 equiv), *i*PrI (10.0 equiv), THF, reflux, overnight; then aq. HCl (2 M), rt, 3 h (50% for 2 steps). (d) LiHMDS (1.3 equiv, 1.0 M in THF), $PhNTf_2$ (1.3 equiv), THF, -78 ^oC to rt, 3 h (80%). (e) Boronic acid **23** (2.0 equiv), cat. **26** (5 mol%), K_2CO_3 (2.0 equiv), DMF/EtOH (v/v = 1:1), rt (98%). (f) OsO_4 (4 mol%), $NaIO_4$ (5.0 equiv), pyridine (3.0 equiv), dioxane/H_2O (v/v = 5:1), rt. (g) EtMgBr (1.0 eqiuv, 1.0 M in THF), -78 ^oC to rt, 4 h, then K_2CO_3 (2.0 equiv), MeI (5.0 equiv), and DMF were charged in situ, 45 ^oC, 6 h (64% for 2 steps). (h) PCC (4.0 equiv), NaOAc (4.0 equiv), celite (*ca.* 100 wt%), rt, 3 h (80%). (i) Liq. NH_3, *t*BuOH (1.0 equiv), K (2.5 equiv), THF, -78 ^oC, 20 min; then LiBr (2.2 equiv), MeI (5.0 equiv), and THF were charged in situ, -78 ^oC, 1 h, then warmed to rt over a period of 1 h (76%). (j) **52** (5.0 equiv), NaOAc (5.0 equiv), EtOH, rt, 2 h. (k) KO*t*Am (10.0 equiv), degassed xylene, 140 ^oC, 2.5 h. (l) 2 *N* HCl (5.0 equiv), THF, rt, 20 min (65% for 3 steps). (m) LiHMDS ((1.0 M in THF, 2.0 equiv), THF, -78 ^oC, 30 min, then $CNCO_2Me$ (2.0 equiv), 2 h (82%). (n) $ZnEt_2$ (1.0 M in hexane, 6.0 equiv), CH_2I_2 (6.0 equiv), CH_2Cl_2, 0 ^oC to rt, 1 h; then I_2 (6.0 equiv), rt, 10 min; then saturated aq. $Na_2S_2O_3$ (excess), rt; then DBU (10.0 equiv), rt, 1 h (72%). (o) $LiAlH_4$ (5.0 equiv), Et_2O, -78 ^oC, 30 min. (p) MnO_2 (20 equiv), CH_2Cl_2, rt, 1 h (63%, for 2 steps). AIBN = 2,2'-azobisisobutyronitrile.

CONCLUSION

In conclusion, through an extensive investigation of different strategies and methodologies,

we have successfully established an efficient route for a collective synthesis of various cyathane-type diterpenoids from the very cheap 2-methyl 1,3-cyclopentanedione **17**. Namely, cyrneine A and (+)-allocyathin B_2 could be accomplished more efficiently through a longest linear sequence of 20 and 18 steps, respectively. The cyrneine B and glaucopine C were conquered for the first time consisting of the longest linear sequence of 24 and 23 steps, respectively. Notably, most of the transformations involved in the route could be reliably performed on multigram scales, making the current route potentially useful for large scale synthesis of natural products and their potential analogues. Additional highlights are that by employing the mild Suzuki coupling and the chelation-controlled Friedel-Crafts cyclization as the key reactions, a concise synthesis of (−)-hamigeran B and (−)-4-bromohamigeran B could also be achieved in a 13-step procedure.[41] These results demonstrated that the new synthetic strategy as well as some of the key transformations established herein could find extensive applications for efficient and flexible synthesis of various types of terpenoid natural prodcuts. Further application of the synthetic strategy and methodologies toward synthesizing more challenging targets is underway.

EXPERIMENTAL SECTION

General Informations: Unless otherwise stated, all oxygen or moisture sensitive reactions were conducted in flame-dried glassware under an atmosphere of nitrogen or argon. All solvents were purified and dried according to standard methods prior to use. Reagents purchased from commercial sources were used without further purification. Analytical thin layer chromatography (TLC) was performed on 0.2 mm thick silica gel 60-F254 plates (Merck) and visualized by exposure to ultraviolet light, or an ethanolic solution of phosphomolybdic acid. Chromatographic purification of products was accomplished using forced-flow chromatography on 230-400 mesh silica gel. The ^{1}H-NMR spectra were recorded on Bruker AV at 300, 400, or 600 MHz and ^{13}C-NMR spectra were recorded at 75, 101, 126, or 151 MHz. Chemical shifts are given relative to TMS or the appropriate solvent peak. High resolution mass spectra (HRMS) were obtained on an IonSpec Ultima 7.0 T FT-ICR-MS (IonSpec, USA) using ESI as ionization method. HPLC analysis was performed on Shimadzu LC solution (CTO-10AS, LC-20AD, RID-10A). X-ray crystallographic analysis was performed on a Bruker D8 ADVANCE diffractometer with Cu-Kα radiation (λ = 1.54178 Å).

2-Allyl-2-methylcyclopentane-1,3-dione (18):[25] To a solution of 2-Methyl cyclopentane-1,3-dione **17** (10.0 g, 89.2 mmol) and TBAI (330 mg, 0.89 mmol) in H_2O (100 mL) was added 2 *N* NaOH (45 ml) dropwise at 0 °C. The mixture was allowed to warm to room temperature and stirred for 10 min. To this mixture was added allyl bromide (15.0 mL, 178 mmol), the resulting solution was stirred at 50 °C for 8 h. The reaction mixture was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed successively with H_2O (2 × 50 mL) and brine (50 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude reaction mixture was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 20:1) to provide the 2-allyl-2-methyl-1,3-cyclopentanedione **18** (12.3 g, 91% yield) as a colorless oil (R_f = 0.5, petroleum ether/ethyl acetate = 4:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 5.53–5.53 (m, 1H), 5.10–5.03 (m, 2H), 2.81–2.66 (m, 4H), 2.36 (d, *J* = 7.5 Hz, 2H), 1.12 (s, 3H).

(2*S*,3*S*)-2-Allyl-3-hydroxy-2-methylcyclopentan-1-one (19):[27] To a solution of *D*-glucose (65.0 g) in H_2O (430 mL) was added dry active baker's yeast (43.7 g) and yeast extract (1.85 g) at room temperature. 2-Allyl-2-methyl-1,3-cyclopentanedione **18** (3.7 g, 24.5 mmol) was added dropwise, and the resulting mixture was vigorously stirred at room temperature for 48 h. The reaction mixture was extracted with dichloromethane (3 × 150 mL). The combined organic layers were washed with H_2O (2 × 30 mL) and brine (30 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 10:1→9:1→8:1→ 7:1) to provide the enantiomerically pure hydroxy ketone **19** (1.4 g, 40% yield for two steps) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 5.97–5.80 (m, 1H), 5.21–5.09 (m, 2H), 4.16–4.09 (m, 1H), 2.55 (m, 5H), 2.03–1.91 (m, 1H), 1.79 (bs, 1H), 1.00 (s, 3H).

(2*S*,3*R*)-2-Allyl-3-hydroxy-2-methylcyclopentan-1-one (20): To a stirred solution of **19** (2.63 g, 17.09 mmol), triphenylphophine (8.97 g, 34.2 mmol, 2.0 equiv), and *p*-nitrobenzoic acid (5.71 g, 34.2 mmol, 2.0 equiv) in THF (70 mL) was added DEAD (5.38 mL, 34.2 mmol, 2.0 equiv) dropwise over a 10 min period at 0 ^{o}C under argon. The solution was then stirred at 50 ^{o}C overnight. The solvent was removed under reduced pressure to leave an oil, which was purified by column chromatography on silica gel (petroleum ether/EtOAc = 15/1→10/1) to give the corresponding *p*-nitrobenzoate (2.72 g, 52% yield) as a white solid.

To a solution of *p*-nitrobenzoate (2.72 g, 8.97 mmol) in the mixed solvents of THF (30 mL) and MeOH (15 mL) was added K_2CO_3 (2.48 g, 17.9 mmol). The reaction mixture was stirred at 0 ^oC for 30 min. The solvent was removed under reduced pressure and the residue was partitioned between water (60 mL) and CH_2Cl_2 (60 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, concentrated, and purified by column chromatography on silica gel (petroleum ether/EtOAc = 5/1→5/2) to afford **20** (1.35 g, 97% yield) as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 5.83–5.66 (m, 1H), 5.14–5.05 (m, 2H), 4.21 (t, *J* = 6.3 Hz, 1H), 2.52 (m, 1H), 2.31–2.09 (m, 4H), 1.92–1.79 (m, 2H), 1.00 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ (ppm) 220.2, 133.6, 118.9, 75.5, 53.1, 39.9, 35.0, 27.6, 15.1.

(2*S*,3*R*)-2-Allyl-3-((tert-butyldimethylsilyl)oxy)-2-methylcyclopentan-1-one (21): To a solution of compound **20** (2.59 g, 16.78 mmol) in DMF (30 mL) was added imidazole (1.37 g, 20.1 mmol, 1.2 equiv) and TBSCl (3.04 g, 20.1 mmol, 1.2 equiv). The solution was stirred overnight at room temperature. The reaction mixture was poured into aqueous sodium bicarbonate solution (50 mL) and extracted with ethyl acetate (3 × 60 mL). The combined organic layers were washed with brine (5 × 20 mL), dried over Na_2SO_4, filtered, concentrated, and purified by column chromatography on silica gel (petroleum ether/EtOAc = 30/1) to afford **21** (3.96 g, 88% yield) as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 5.73–5.59 (m, 1H), 5.10–4.99 (m, 2H), 4.18–4.11 (m, 1H), 2.50–2.02 (m, 5H), 1.88–1.75 (m, 1H), 0.96 (s, 3H), 0.89 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H); $^{13}C(^1H)$ NMR (75 MHz, $CDCl_3$) δ (ppm) 220.6, 133.7, 118.3, 75.2, 53.7, 39.6, 35.2, 28.5, 25.8, 18.1, 16.2, -4.2, -4.8.

(4*R*,5*S*)-5-Allyl-4-((tert-butyldimethylsilyl)oxy)-2-isopropyl-5-methylcyclopent-1-en-1-yl trifluoromethanesulfonate (22): To a stirred suspension of NaH (60% dispersion in mineral oil, 2.88 g, 72.0 mmol, 5.0 equiv) in THF (35 mL) was added dropwise a solution of **21** (3.86 g, 14.4 mmol) in THF (20 mL) at 0 ^oC. Then 2-iodopropane (14.4 mL, 144 mmol, 10.0 equiv) was added. The reaction mixture was refluxed overnight. The resulting mixture was quenched at 0 °C by H_2O. Then 2 *N* HCl (36 mL) was added, and the mixture was stirred at room temperature for 3 h. Then brine was added to the solution to form a biphasic solution. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 × 60 mL). The combined organic layers were

washed with brine (30 mL), dried over Na_2SO_4, concentrated, and purified by column chromatography on silica gel (petroleum ether/CH_2Cl_2 = 3/1) to afford the TBS protected isopropylated product (2.81 g, 63% yield) as a colorless oil.

The isopropylated product (2.81 g, 9.06 mmol) was dissolved in dry THF (20 mL) and the solution was cooled to -78 °C. LiHMDS (1.0 M in THF, 11.8 mL, 11.8 mmol, 1.3 equiv) was added and the solution was stirred at the same temperature for 1 h. Then a solution of $PhNTf_2$ (4.21 g, 11.8 mmol, 1.3 equiv) in dry THF (20 mL) was added slowly. The reaction mixture was allowed to warm to room temperature and stirred for 7 h. Brine (50 mL) was added to the reaction mixture. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, concentrated, and purified by column chromatography on silica gel (petroleum ether/CH_2Cl_2 = 50/1) to give **22** (3.09 g, 77% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 5.76–5.60 (m, 1H), 5.11–5.02 (m, 2H), 4.12 (t, *J* = 6.9 Hz, 1H), 2.83 (m, *J* = 6.9 Hz, 1H), 2.46 (dd, *J* = 15.3, 7.2 Hz, 1H), 2.27–2.05 (m, 3H), 1.06 (s, 3H), 1.01 (d, *J* = 6.9 Hz, 3H), 1.01 (s, *J* = 6.9 Hz, 3H), 0.91 (s, 9H), 0.07 (s, 3H), 0.07 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ (ppm) 143.3, 135.5, 134.3, 118.8 (d, *J* = 317 Hz), 118.3, 73.1, 49.9, 40.9, 34.4, 25.9, 25.6, 20.6, 20.1, 18.1, 17.6, -4.1, -4.7.

3-((4*R*,5*R*)-5-Allyl-4-((*tert*-butyldimethylsilyl)oxy)-2-isopropyl-5-methylcyclopent-1-en-1-yl)phenol (24): To a solution of **22** (44.3 mg, 0.10 mmol) in a mixed solvent of DMF (1.0 mL) and EtOH (1.0 mL) was added arylboronic acid **23** (27.4 mg, 0.20 mmol, 2.0 equiv), palladacycle **26** (2.8 mg, 5 mmol%), and K_2CO_3 (41.4 mg, 0.3 mmol, 3.0 equiv) at room temperature under nitrogen. The resulting mixture was stirred at the same temperature for 2.5 h. The reaction mixture was then poured into water and extracted with ethyl acetate (3 × 15 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by silica gel column chromatography to afford the desired **24** (37.9 mg, 98% yield, containing a small inseparably **25**). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.18 (d, *J* = 7.8 Hz, 1H), 6.77–6.56 (m, 3H), 5.74–5.57 (m, 1H), 5.07 (bs, 1H), 4.98–4.87 (m, 2H), 4.14 (t, *J* = 6.9 Hz, 1H), 2.50 (dd, *J* = 15.6, 7.2 Hz, 1H), 2.41 (m, *J* = 6.9 Hz, 1H), 2.18 (dd, *J* = 15.3, 6.9 Hz, 1H), 2.09–1.94 (m, 2H), 1.03 (s, 3H), 0.96 (d, *J* = 6.9 Hz, 3H), 0.93 (s, 9H), 0.87 (d, *J* = 6.9 Hz, 3H), 0.09 (s, 3H), 0.08 (s, 3H).

(((1*R*,2*R*)-2-Allyl-4-isopropyl-3-(3-methoxyphenyl)-2-methylcyclopent-3-en-1-yl)oxy)(*tert*-but

yl)dimethylsilane (27) and *tert*-butyl(((1*R*,2*R*)-4-isopropyl-3-(3-methoxyphenyl)-2-methyl-2-((*E*)-prop-1-en-1-yl)cyclopent-3-en-1-yl)oxy)dimethylsilane (28): To a solution of a mixture **24** and **25** (85 mg, 0.22 mmol, the ratio of **24**:**25** was varied depending on the variation of reaction conditions) in DMF (1.0 mL) was added K_2CO_3 (61 mg, 0.44 mmol, 2.0 equiv) and MeI (27 μL, 0.44 mmol, 2.0 equiv). The mixture was stirred overnight at room temperature. The reaction mixture was poured into water and extracted with ethyl acetate (3 × 15 mL). The combined organic layers were washed with brine (5 × 10 mL), dried over Na_2SO_4, filtered, and evaporated to dryness. The residue was purified by column chromatography on silica gel (petroleum ether/CH_2Cl_2 = 40/1→30/1→25/1) to afford **27** and **28** as colorless oil, respectively, in quantitative overall yield. Compound **27**: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.22 (t, *J* = 7.8 Hz, 1H), 6.83–6.76 (m, 1H), 6.71–6.61 (m, 2H), 5.73–5.56 (m, 1H), 4.96–4.85 (m, 2H), 4.14 (t, *J* = 6.9 Hz, 1H), 3.80 (s, 3H), 2.49 (dd, *J* = 15.3, 7.5 Hz, 1H), 2.40 (m, *J* = 6.9 Hz, 1H), 2.17 (dd, *J* = 15.3, 6.9 Hz, 1H), 2.09–1.92 (m, 2H), 1.03 (s, 3H), 0.95 (d, *J* = 6.9 Hz, 3H), 0.91 (s, 9H), 0.87 (d, *J* = 6.9 Hz, 3H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C(^{1}H) NMR (151 MHz, $CDCl_3$) δ (ppm) 159.2, 142.1, 140.7, 139.7, 136.3, 128.8, 122.2, 116.5, 115.6, 111.6, 76.4, 55.3, 53.6, 42.8, 37.1, 27.6, 26.0, 21.7, 21.3, 19.3, 18.2, -3.9, -4.7; compound **28**: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.18 (t, *J* = 7.8 Hz, 1H), 6.79–6.73 (m, 1H), 6.69–6.59 (m, 2H), 5.39–5.23 (m, 2H), 4.02 (t, *J* = 6.0 Hz, 1H), 3.78 (s, 3H), 2.58–2.45 (m, 2H), 2.19 (dd, *J* = 15.6, 5.7 Hz, 1H), 1.62 (d, *J* = 5.1 Hz, 3H), 1.03 (s, 3H), 0.95 (d, *J* = 6.9 Hz, 3H), 0.93 (d, *J* = 6.9 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 3H), 0.02 (s, 3H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ (ppm) 159.0, 142.1, 140.2, 140.0, 137.9, 128.5, 123.2, 122.1, 115.3, 111.6, 79.4, 56.6, 55.2, 37.0, 27.6, 26.0, 21.6, 21.4, 18.3, 18.2, 17.1, -4.4, -4.5.

For the detailed synthetic procedures, characterization data, and copies of spectra for the compounds **9**–**11** and **29**–**32** in Scheme 2, see the Supplementary Information (SI) of ref 22.

Acid-mediated cyclization of 32: To a solution of **32** (159 mg, 0.41 mmol) in freshly distilled ethyl ether (40.0 mL) was added BF_3•OEt_2 (0.26 mL, 2.06 mmol, 5.0 equiv) at 0 °C over a period of 15 min. The mixture was stirred for 1 h at 0 ^{o}C. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with ethyl ether (2 × 25 mL). The combined organic layers were dried over Na_2SO_4, filtered, concentrated, and purified by column chromatography on

silica gel (petroleum ether/EtOAc = 100/1→80/1→50/1) to afford **34** (36 mg, 24% yield) and **35** (89 mg, 59% yield). Compound **34**: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.09–6.97 (m, 2H), 6.68–6.61 (m, 2H), 6.02 (d, *J* = 9.6 Hz, 1H), 4.76 (bs, 1H), 4.14 (dd, *J* = 9.0, 7.8 Hz, 1H), 3.19 (m, *J* = 6.9 Hz, 1H), 2.49 (dd, *J* = 15.0, 7.5 Hz, 1H), 2.21 (dd, *J* = 15.0, 9.0 Hz, 1H), 1.17 (d, *J* = 6.9 Hz, 3H), 0.98 (d, *J* = 6.9 Hz, 3H), 0.94 (s, 9H), 0.86 (s, 3H), 0.13 (s, 3H), 0.11 (s, 3H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ (ppm) 151.2, 143.2, 137.4, 133.7, 132.6, 127.2, 120.9, 120.1, 117.1, 114.1, 79.1, 50.3, 35.5, 27.0, 26.0, 21.9, 21.2, 18.3, 16.5, -4.2, -4.6. Compound **35**: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 6.98 (d, *J* = 8.1 Hz, 1H), 6.91 (d, *J* = 2.7 Hz, 1H), 6.66 (dd, *J* = 8.1, 2.7 Hz, 1H), 6.25 (d, *J* = 9.6 Hz, 1H), 5.88 (d, *J* = 9.6 Hz, 1H), 5.04 (bs, 1H), 4.12 (dd, *J* = 9.0, 7.5 Hz, 1H), 3.19 (m, *J* = 6.9 Hz, 1H), 2.48 (dd, *J* = 15.0, 7.5 Hz, 1H), 2.21 (dd, *J* = 15.0, 9.3 Hz, 1H), 1.17 (d, *J* = 6.9 Hz, 3H), 0.98 (d, *J* = 6.9 Hz, 3H), 0.94 (s, 9H), 0.86 (s, 3H), 0.12 (s, 3H), 0.11 (s, 3H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ (ppm) 154.3, 143.3, 135.4, 133.8, 132.6, 128.1, 127.5, 123.9, 114.1, 113.7, 79.1, 50.4, 35.5, 26.9, 26.0, 21.9, 21.1, 18.2, 16.7, -4.2, -4.6.

Acid-mediated cyclization of 33: To a solution of **33** (24 mg, 0.06 mmol) in freshly distilled ethyl ether (6.0 mL) was added BF_3•OEt_2 (76 μL, 0.60 mmol, 10.0 equiv) at 0 °C over a period of 15 min. The mixture was stirred for 1 h at 0 °C and then at room temperature for an additional 6 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with ethyl ether (2 × 15 mL). The combined organic layers were dried over Na_2SO_4, filtered, concentrated, and purified by column chromatography on silica gel (petroleum ether/Et_2O = 50/1→30/1) to give **36** (17.5 mg, 76% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.04 (d, *J* = 8.4 Hz, 1H), 6.96 (d, *J* = 2.4 Hz, 1H), 6.73 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.26 (d, *J* = 9.3 Hz, 1H), 5.88 (d, *J* = 9.3 Hz, 1H), 4.13 (dd, *J* = 9.0, 7.5 Hz, 1H), 3.83 (s, 3H), 3.21 (m, *J* = 6.9 Hz, 1H), 2.48 (dd, *J* = 15.0, 7.5 Hz, 1H), 2.21 (dd, *J* = 15.0, 9.0 Hz, 1H), 1.19 (d, *J* = 6.9 Hz, 3H), 0.99 (d, *J* = 6.9 Hz, 3H), 0.94 (s, 9H), 0.85 (s, 3H), 0.12 (s, 3H), 0.10 (s, 3H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ (ppm) 158.4, 143.0, 135.5, 134.1, 132.3, 127.9, 127.4, 123.9, 113.5, 111.5, 79.1, 55.4, 50.5, 35.5, 27.0, 26.0, 21.9, 21.2, 18.3, 16.7, -4.2, -4.6.

(3*R*,3a*R*,5*S*)-3-((tert-Butyldimethylsilyl)oxy)-1-isopropyl-3a-methyl-3,3a,4,5-tetrahydro-2H-cyclopenta[*a*]naphthalene-5,6-diol (46): To a solution of **32** (0.804 g, 2.07 mmol) in THF (20 mL) was added EtMgBr (1.0 M in THF, 2.3 mL, 2.3 mmol, 1.1 equiv) slowly over a period of 20 min at -78 °C under argon atmosphere. The mixture was then warmed up slowly to 40 °C, and stirred

at the same temperature overnight. The reaction mixture was poured into water and extracted with ethyl acetate (3 × 40 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by silica gel column chromatography (petroleum ether/Et_2O = 25/1→15/1→10/1) to afford **46** (0.386 g, 48% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.44 (s, 1H), 7.16 (t, *J* = 8.0 Hz, 1H), 7.07 (d, *J* = 8.0 Hz, 1H), 6.78 (d, *J* = 8.0 Hz, 1H), 5.25–5.16 (m, 1H), 3.97 (t, *J* = 8.4 Hz, 1H), 3.28 (m, *J* = 6.8 Hz, 1H), 2.56 (dd, *J* = 15.2, 8.0 Hz, 1H), 2.45 (dd, *J* = 11.6, 6.4 Hz, 1H), 2.37 (dd, *J* = 15.6, 9.2 Hz, 1H), 2.10 (d, *J* = 8.8 Hz, 1H), 1.57 (t, *J* = 11.2 Hz, 1H), 1.14 (d, *J* = 6.8 Hz, 3H), 1.04 (d, *J* = 6.8 Hz, 3H), 0.93 (s, 9H), 0.91 (s, 3H), 0.10 (s, 3H), 0.09 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ (ppm) 157.3, 140.2, 133.4, 133.0, 129.1, 122.2, 119.9, 115.3, 79.8, 69.3, 50.5, 46.8, 37.7, 27.4, 26.0, 21.7, 20.7, 18.2, 16.0, -4.2, -4.6.

(4a*R*,5a*S*,6a*R*,7*R*)-7-((tert-Butyldimethylsilyl)oxy)-9-isopropyl-6a-methyl-6,6a,7,8-tetrahydro cyclopenta[3,4]naphtho[1,8*a*-*b*]oxiren-4(5a*H*)-one (47): To a solution of **46** (43 mg, 0.11 mmol) in MeCN (1.5 mL) at 0 ^{o}C was added a solution of $NaIO_4$ (47 mg, 0.22 mmol, 2.0 equiv) in H_2O (0.5 mL) over a period of 15 min. The reaction mixture was stirred at room temperature for an additional 2 h and was extracted with ethyl acetate (3 × 15 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, concentrated, and purified by column chromatography on silica gel (petroleum ether/CH_2Cl_2/Et_2O = 100/10/1→50/5/1→20/2/1) to give **47** (20 mg, 47% yield) as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.22 (dd, *J* = 9.9, 6.3 Hz, 1H), 6.32 (d, *J* = 6.0 Hz, 1H), 6.19–6.13 (m, 1H), 4.07 (t, *J* = 8.2 Hz, 1H), 3.86 (d, *J* = 3.6 Hz, 1H), 2.86 (m, *J* = 6.9 Hz, 1H), 2.48 (dd, *J* = 15.6, 7.5 Hz, 1H), 2.20 (d, *J* = 15.6 Hz, 1H), 2.12 (dd, *J* = 15.9, 8.7 Hz, 1H), 2.03 (dd, *J* = 15.6, 3.6 Hz, 1H), 1.02 (d, *J* = 6.9 Hz, 3H), 0.98 (d, *J* = 6.9 Hz, 3H), 0.91–0.87 (m, 12H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ (ppm) 195.4, 145.6, 144.0, 142.5, 134.2, 124.7, 123.2, 82.0, 70.6, 59.1, 52.3, 38.6, 37.2, 26.9, 25.9, 21.5, 21.5, 21.2, 18.2, -4.2, -4.6; HRMS (ESI) m/z calcd for $C_{23}H_{35}O_3Si$ $[M+H]^+$: 387.2350, found 387.2346.

For the detailed synthetic procedures, characterization data, and copies of spectra for the compounds **12**, **13**, **51**, and **54** in Scheme 5, see the Supplementary Information (SI) of ref 22.

(3*R*,3a*R*,5a*R*)-3-((*tert*-Butyldimethylsilyl)oxy)-1-isopropyl-3a,5a-dimethyl-2,3,3a,4,5,5a-hexah

ydro-6*H*-cyclopenta[*a*]naphthalen-6-one (55): To a stirred solution of NBS (102 mg, 0.57 mmol, 1.1 equiv) in THF (3.0 mL) was added H_2O (19 μL, 1.04 mmol, 2.0 equiv) and a solution of **54** (210 mg, 0.52 mmol) in THF (4.0 mL) at 0 °C. The reaction mixture was stirred at room temperature for 10 min. Then a solution of DBU (158 mg, 1.04 mmol, 2.0 equiv) in THF (1.0 mL) was added and the mixture was stirred at 45 °C for 3.5 h. Then brine (15 mL) was added and the resulting mixture was extracted with ethyl acetate (3 × 15 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, concentrated, and purified by column chromatography on silica gel (petroleum ether/Et_2O = 20/1) to afford **55** (135 mg, 67% yield) as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.06 (dd, *J* = 9.6, 6.0 Hz, 1H), 6.04–5.98 (m, 2H), 4.04–3.95 (m, 1H), 2.89 (m, *J* = 6.9 Hz, 1H), 2.48 (dd, *J* = 15.3, 7.8 Hz, 1H), 2.23 (dd, *J* = 15.3, 9.0 Hz, 1H), 2.07–1.98 (m, 1H), 1.79–1.59 (m, 3H), 2.13 (s, 3H), 1.03 (d, *J* = 6.9 Hz, 3H), 0.95 (d, *J* = 6.9 Hz, 3H), 0.90 (s, 9H), 0.83 (s, 3H), 0.07 (s, 3H), 0.07 (s, 3H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ (ppm) 206.6, 154.0, 142.4, 142.1, 136.7, 123.5, 117.2, 82.2, 51.8, 50.7, 37.5, 34.7, 31.8, 26.8, 26.0, 24.0, 21.6, 21.3, 18.2, 16.9, -4.3, -4.6; HRMS (ESI) m/z calcd for $C_{24}H_{39}O_2Si$ $[M+H]^+$: 387.2714, found 387.2705.

(3*R*,3a*R*,5a*R*)-3-((*tert*-Butyldimethylsilyl)oxy)-8-(dibromomethyl)-1-isopropyl-3a,5a-dimethyl -2,3,3a,4,5,5a-hexahydro-6*H*-cyclopenta[*a*]naphthalen-6-one (58): To a stirred solution of **55** (30 mg, 0.078 mmol) and $CHBr_3$ (34 μL, 0.38 mmol, 5.0 equiv) in Et_2O (1.0 mL) was added LiHMDS (1.0 M in THF, 87 μL, 0.087 mmol, 1.5 equiv) at -78 °C under argon atmosphere. The reaction mixture was stirred at the same temperature for 2 h and then quenched with H_2O. The reaction mixture was extracted with ethyl acetate (3 × 15 mL). The combined organic layers were dried over Na_2SO_4, filtered, concentrated, and purified by column chromatography on silica gel (petroleum ether/CH_2Cl_2 = 50/1) to afford **57** (34 mg, 68% yield).

To a solution of **57** (34 mg, 0.053 mmol) in THF (1.0 mL) was added DBU (16 mg, 0.106 mmol, 2.0 equiv) at room temperature. The reaction mixture was stirred at the same temperature for 15 min and quenched with H_2O. The reaction mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, concentrated, and purified by column chromatography on silica gel (petroleum ether/Et_2O = 20/1) to afford **58** (25 mg, 84% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 6.27 (s, 1H), 6.26 (d, *J* = 1.8 Hz, 1H), 5.94 (d, *J* = 1.8

Hz, 1H), 4.05–3.97 (m, 1H), 2.97 (m, *J* = 6.9 Hz, 1H), 2.51 (dd, *J* = 15.3, 7.8 Hz, 1H), 2.27 (dd, *J* = 15.3, 9.3 Hz, 1H), 2.07–1.99 (m, 1H), 1.82–1.61 (m, 3H), 1.13 (s, 3H), 1.11 (d, *J* = 6.9 Hz, 3H), 0.99 (d, *J* = 6.9 Hz, 3H), 0.91 (s, 9H), 0.86 (s, 3H), 0.08 (s, 3H), 0.08 (s, 3H); $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$) δ (ppm) 205.9, 154.2, 152.3, 143.9, 136.4, 116.4, 116.2, 82.2, 51.5, 50.2, 40.8, 37.6, 34.7, 31.4, 27.1, 26.0, 24.1, 21.7, 21.3, 18.2, 16.9, -4.3, -4.6; HRMS (ESI) m/z calcd for $C_{25}H_{39}Br_2O_2Si$ $[M+H]^+$: 557.1081; found 557.1078.

For the detailed synthetic procedures, characterization data, and copies of spectra for the compounds **14**, **60**, **61**, and cyrneine A in Scheme 6, see the Supplementary Information (SI) of ref 22.

For the detailed synthetic procedures, characterization data, and copies of spectra for the compounds **16**, **62**, **64**, and glaucopine C in Scheme 7A, see the Supplementary Information (SI) of ref 22.

1-Isopropyl-6-methoxy-3a-methyl-2,3a,4,5-tetrahydro-3*H*-cyclopenta[*a*]naphthalen-3-one (67): To a solution of **65** (108 mg, 0.27 mmol, prepared according to the procedure for the synthesis of chiral compound **12**) in dry CH_2Cl_2 (4.0 mL) was added TMSOTf (0.29 mL, 1.62 mmol, 6.0 equiv) at 0 ^{o}C. The clear solution was stirred at the same temperature for 1.5 h and quenched by saturated aqueous $NaHCO_3$. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, concentrated, and purified by column chromatography on silica gel (petroleum ether/EtOAc = 5/1→3/1) to give compound **66** (70 mg, 91% yield).

To a solution of **66** (120 mg, 0.42 mmol) and Et_3SiH (0.67 mL, 4.20 mmol, 10 equiv) in dry CH_2Cl_2 (5.0 mL) was added TFA (0.49 mL, 6.30 mmol, 15 equiv) at 0 ^{o}C. The clear solution was stirred at room temperature for 2 h and quenched by saturated aqueous $NaHCO_3$. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, concentrated, and purified by column chromatography on silica gel (petroleum ether/EtOAc = 15/1→10/1) to give the decarbonylated product (105 mg, 92% yield).

To a solution of the decarbonylated product (105 mg, 0.39 mmol) in CH_2Cl_2 (5.0 mL) was

added DMP (213 mg, 0.50 mmol, 1.3 equiv) at room temperature. The reaction mixture was stirred for 30 min. The reaction mixture was quenched by saturated aqueous Na_2SO_3 and $NaHCO_3$. The organic phase was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, concentrated, and purified by column chromatography on silica gel (petroleum ether/Et_2O = 20/1) to give **67** (85 mg, 82% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.21 (t, *J* = 7.8 Hz, 1H), 7.06 (d, *J* = 7.8 Hz, 1H), 6.78 (d, *J* = 7.8 Hz, 1H), 3.84 (s, 3H), 3.34 (m, *J* = 6.9 Hz, 1H), 3.21 (d, *J* = 23.4 Hz, 1H), 3.01 (d, *J* = 23.4 Hz, 1H), 2.96–2.83 (m, 1H), 2.82–2.66 (m, 1H), 2.03–1.92 (m, 1H), 1.77–1.64 (m, 1H), 1.25 (d, *J* = 6.9 Hz, 3H), 1.04 (s, 3H), 1.00 (d, *J* = 6.9 Hz, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ (ppm) 220.9, 157.4, 137.0, 136.2, 133.1, 126.3, 124.9, 120.1, 108.5, 55.4, 51.7, 40.7, 30.1, 27.0, 21.6, 21.2, 20.8, 18.7; HRMS (ESI) m/z calcd for $C_{18}H_{22}NaO_2$ $[M+Na]^+$: 293.1512; found 293.1524.

1-Isopropyl-6-methoxy-3a-methyl-3a,4,5,9b-tetrahydro-3*H*-cyclopenta[*a*]naphthalen-3-one (68): To a solution of **67** (10 mg, 0.04 mmol) in PhH (1.0 mL) was added a solution of DBU (28 mg, 0.19 mmol, 5.0 equiv) in PhH (0.2 mL). The reaction mixture was stirred at 80 °C for 2 h. Then H_2O was added and the reaction mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, concentrated, and purified by column chromatography on silica gel (petroleum ether/Et_2O = 10/1→5/1) to afford **68** (8.5 mg, 85% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 7.18 (t, *J* = 7.8 Hz, 1H), 6.90 (d, *J* = 7.8 Hz, 1H), 6.76 (d, *J* = 7.8 Hz, 1H), 5.99–5.97 (m, 1H), 3.79 (s, 3H), 3.75 (d, *J* = 1.8 Hz, 1H), 2.93 (dt, *J* = 16.2, 3.6 Hz, 1H), 2.39 (m, *J* = 6.6 Hz, 1H), 2.25 (dt, *J* = 13.2, 3.6 Hz, 1H), 1.81 (td, *J* =15.0, 3.6 Hz, 1H), 1.25 (td, *J* = 13.2, 3.6 Hz, 1H), 1.23 (d, *J* = 6.6 Hz, 3H), 1.21 (s, 3H), 0.89 (d, *J* = 6.6 Hz, 3H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ (ppm) 214.5, 187.7, 156.5, 136.3, 128.7, 126.6, 126.2, 122.0, 108.8, 56.3, 55.6, 49.6, 35.5, 29.1, 25.2, 22.0, 21.2, 19.5; HRMS (ESI) m/z calcd for $C_{18}H_{23}O_2$ $[M+H]^+$: 271.1693; found 271.1680.

9b-Hydroxy-1-isopropyl-6-methoxy-3a-methyl-3a,4,5,9b-tetrahydro-3*H*-cyclopenta[*a*]naphthalen-3-one (69): To a solution of **67** (15 mg, 0.06 mmol) in dry THF (0.6 mL) was added LiHMDS (1 M in THF, 0.112 mL, 0.11 mmol, 2.0 equiv) at –78 °C under argon atmosphere. The resulting solution was stirred for 15 min. $P(OMe)_3$ (26 μL, 0.22 mmol, 4.0 equiv) was added and the argon balloon was replaced with O_2 balloon. After being stirred for an additional 2 h, the

reaction mixture was quenched by water. The reaction mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, concentrated, and purified by column chromatography on silica gel (petroleum ether/EtOAc = 10/1→5/1) to give **69** (10.5 mg, 65% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 7.49 (d, *J* = 7.8 Hz, 1H), 7.25 (d, *J* = 7.8 Hz, 1H), 6.89 (d, *J* = 7.8 Hz, 1H), 6.02 (s, 1H), 5.72 (s, 1H), 3.73 (s, 3H), 2.83 (dt, *J* = 16.2, 3.6 Hz, 1H), 2.68 (m, *J* = 6.9 Hz, 1H), 2.00 (dt, *J* = 12.6, 3.6 Hz, 1H), 1.61 (td, *J* = 15.0, 3.6 Hz, 1H), 1.22–1.09 (m, 4H), 1.05 (s, 3H), 0.45 (d, *J* = 6.9 Hz, 3H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ (ppm) 212.2, 187.8, 156.0, 138.7, 127.6, 126.8, 126.6, 118.9, 109.6, 82.0, 55.7, 53.9, 33.9, 27.0, 23.7, 23.5, 20.9, 19.5; HRMS (ESI) m/z calcd for $C_{18}H_{22}NaO_3$ $[M+Na]^+$: 309.1461; found 309.1458.

For the detailed synthetic procedures, characterization data, and copies of spectra for the compounds **71**, **72**, and cyrneine B in Scheme 8, see the Supplementary Information (SI) of ref 22.

***O*-((1*S*,2*S*)-2-Methyl-2-(3-methylbut-2-en-1-yl)-3-oxocyclopentyl) *O*-phenyl carbonothioate (77)**: To a solution of compound **9** (5.40 g, 29.6 mmol) and DMAP (0.36 g, 2.96 mmol, 0.1 equiv) in DCM (70 mL) was added pyridine (4.8 mL, 59.3 mmol, 2.0 equiv) and PhOC(S)Cl (7.68 g, 44.5 mmol, 1.5 equiv). The reaction mixture was stirred for 4 h at room temperature. The solution was quenched by H_2O (50 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine (2 × 30 mL), dried over Na_2SO_4, filtered, and evaporated to dryness. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc = 30/1) to afford the compound **77** (8.13 g, 86% yield) as a yellow oil. $[\alpha]_D^{25}$ = + 693.2 (*c* = 1.0 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.44 (t, *J* = 7.5 Hz, 2H), 7.31 (t, *J* = 7.5 Hz, 1H), 7.10 (d, *J* = 7.5 Hz, 2H), 5.60 (t, *J* = 3.6 Hz, 1H), 5.09 (t, *J* = 7.5 Hz, 1H), 2.52–2.42 (m, 2H), 2.40–2.26 (m, 4H), 1.75 (s, 3H), 1.67 (s, 3H), 1.11 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ (ppm) 218.9, 194.2, 153.3, 135.3, 129.7, 126.8, 121.9, 118.5, 89.2, 53.3, 34.1, 29.6, 26.3, 25.1, 20.0, 18.1; HRMS (ESI) m/z calcd for $C_{18}H_{22}NaO_3S$ $[M+Na]^+$: 341.1182; found 341.1186.

(2*R*)-5-Isopropyl-2-methyl-2-(3-methylbut-2-en-1-yl)cyclopentan-1-one (78): To a solution of compound **77** (7.6 g, 23.8 mmol) and AIBN (0.04 g, 0.24 mmol, 1 mol%) in toluene (60 mL) was added Bu_3SnH (12.7 mL, 47.6 mmol, 2.0 equiv). The reaction mixture was stirred for 1 h at 100

^{o}C .The resulting mixture was purified directly by silica gel column chromatography (petroleum ether/Et_2O = 40/1) to afford the dehydroxylated product as a colorless oil.

To a stirred suspension of NaH (60% dispersion in mineral oil, 4.8 g, 119 mmol, 5.0 equiv) in THF (60 mL) was added dropwise a solution of the dehydroxylated product (*ca.* 23.8 mmol) in THF (20 mL) and 2-iodopropane (23.8 mL, 238 mmol, 10.0 equiv) at 0 ^{o}C. The reaction mixture was refluxed overnight. The resulting mixture was quenched at 0 ^{o}C by H_2O. Then 2 *N* HCl (65 mL) was added slowly, and the resulting mixture was stirred at room temperature for 3 h. Brine was added to the reaction mixture, and the biphasic layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 60 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/CH_2Cl_2 = 3/1) to afford **78** (2.5 g, 50% yield for 2 steps) as a colorless oil.

(*R*)-2-Isopropyl-5-methyl-5-(3-methylbut-2-en-1-yl)cyclopent-1-en-1-yl trifluoromethanesulfonate (79): Ketone **78** (2.5 g, 12.0 mmol) was dissolved in dried THF (40 mL) and the solution was cooled to -78 ^{o}C. Then LiHMDS (1.0 M in THF, 15.6 mL, 15.6 mmol, 1.3 equiv) was added and the clear solution was stirred at the same temperature for 1 h. Then a solution of $PhNTf_2$ (5.57 g, 15.6 mmol, 1.3 equiv) in dried THF (20 mL) was added slowly. The resulting reaction mixture was allowed to warm to room temperature and stirred for 3 h. Brine (50 mL) was added to the reaction mixture. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, concentrated, and purified by column chromatography on silica gel (petroleum ether/CH_2Cl_2 = 50/1) to give **79** (3.47 g, 85% yield) as a colorless oil. $[\alpha]_D^{28}$ = -32.5 (*c* = 1.0, $CDCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 5.09 (t, *J* = 7.5 Hz, 1H), 2.82 (m, 6.9 Hz, 1H), 2.26–2.16 (m, 2H), 2.09 (d, *J* = 7.5 Hz, 2H), 1.87 (ddd, *J* = 12.9, 7.8, 5.2 Hz, 1H), 1.70 (s, 3H), 1.67–1.62 (m, 1H), 1.60 (s, 3H), 1.13 (s, 3H), 1.02 (d, *J* = 6.9 Hz, 3H), 1.00 (d, *J* = 6.9 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ (ppm) 145.5, 137.8, 134.2, 120.0, 118.8 (d , J = 321 Hz), 47.1, 37.1, 33.3, 26.2, 25.9, 24.5, 24.1, 20.6, 20.4, 17.9.

(*R*)-3-(2-Isopropyl-5-methyl-5-(3-methylbut-2-en-1-yl)cyclopent-1-en-1-yl)phenol (80): To a solution of **79** (3.20 g, 9.40 mmol) in the mixed solvents of DMF (30 mL) and EtOH (30 mL) was

added arylboronic acid **23** (2.6 g, 18.8 mmol, 2.0 equiv), palladacycle **26** (0.26 g, 5 mol%), and K_2CO_3 (2.6 g, 18.8 mmol, 2.0 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was stirred at the same temperature until **79** had disappeared as monitored by TLC. The reaction mixture was then poured into water (60 mL) and extracted with ethyl acetate (3 × 60 mL). The combined organic layers were washed with brine (5 × 15 mL), dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc = 15/1) to afford **80** (2.62 g, 98% yield). $[\alpha]_D^{25}$ = + 388.2 (*c* = 0.68 in $CHCl_3$); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 9.29 (s, 1H), 7.11 (t, *J* = 7.8 Hz, 1H), 6.64 (dd, *J* = 7.8, 1.4 Hz, 1H), 6.44–6.42 (m, 2H), 5.13 (t, *J* = 7.2 Hz, 1H), 2.31(m, *J* = 6.9 Hz, 1H), 2.28–2.20 (m, 2H), 1.90 (dd, *J* = 12.0, 7.5 Hz, 2H), 1.86–1.74 (m, 1H), 1.66 (s, 3H), 1.60–1.49 (m, 1H), 1.52 (s, 3H), 0.94 (s, 3H), 0.91 (d, *J* = 6.9 Hz, 3H), 0.88 (d, *J* = 6.9 Hz, 3H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ (ppm) 155.0, 145.0, 141.9, 140.6, 132.4, 128.9, 122.5, 122.1, 116.6, 113.2, 52.0, 38.3, 36.1, 28.2, 27.8, 26.5, 26.2, 21.7, 21.5, 18.1; HRMS (ESI) m/z calcd for $C_{20}H_{27}O$ $[M-H]^-$: 283.2067; found 283.2056.

(*R*)-2-(2-(3-Hydroxyphenyl)-3-isopropyl-1-methylcyclopent-2-en-1-yl)acetaldehyde (81): To a solution of **80** (2.6 g, 9.14 mmol) in the mixed solvents of dioxane (100 mL) and H_2O (20 mL) was added $NaIO_4$ (9.77 g, 45.7 mmol, 5.0 equiv), pyridine (2.2 mL, 27.4 mmol, 3.0 equiv), and OsO_4 solution (9.1 mL, 0.04 M in H_2O). The reaction mixture was stirred at room temperature until compound **80** had disappeared as monitored by TLC. Then H_2O (100 mL) and EtOAc (200 mL) were added to the mixture. The organic phase was separated and the aqueous layer was extracted with EtOAc (3 × 60 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum. The resulting residue was purified by column chromatography on silica gel (petroleum ether/EtOAc = 10/1) to afford **81** (1.88 g, 80% yield) as a brown oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 9.74 (t, *J* = 3.1 Hz, 1H), 7.20 (t, *J* = 7.8 Hz, 1H), 6.75 (dd, *J* = 7.8, 2.4 Hz, 1H), 6.61 (d, *J* = 7.8 Hz, 1H), 6.54–6.53 (m, 1H), 4.91 (s, 1H), 2.45–2.24 (m, 5H), 2.06 (ddd, *J* = 12.9, 8.4, 5.7 Hz, 1H), 1.86 (ddd, *J* = 12.9, 8.4, 6.0 Hz, 1H), 1.15 (s, 3H), 0.92 (d, *J* = 6.9 Hz, 3H), 0.91 (d, *J* = 6.9 Hz, 3H).

(3a*R*)-1-Isopropyl-6-methoxy-3a-methyl-3,3a,4,5-tetrahydro-2*H*-cyclopenta[*a*]naphthalen-5-ol (82): To a solution of **81** (1.88 g, 7.30 mmol) in dried THF (50 mL) was added EtMgBr (1.0 M

in THF, 7.3 mL, 7.30 mmol) slowly at -78 °C. The reaction mixture was then warmed up to room temperature and stirred for 4 h. Then K_2CO_3 (2.02 g, 14.6 mmol, 2.0 equiv), MeI (2.3 mL, 36.6 mmol, 5.0 equiv), and DMF (50 mL) was added. The mixture was stirred at 45 °C for additional 6 h. The reaction mixture was then poured into water (100 mL) and extracted with ethyl acetate (4 × 125 mL). The combined organic layers were washed with brine (5 × 30 mL), dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by column chromatography on silica gel (petroleum ether/CH_2Cl_2/Et_2O = 30/3/1) to afford **82** (1.59 g, 64% yield for 2 steps) as a brown oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.22 (t, *J* = 7.8 Hz, 1H), 7.04 (d, *J* = 7.8 Hz, 1H), 6.79 (d, *J* = 7.8 Hz, 1H), 5.23–5.13 (m, 1H), 3.99 (d, *J* = 2.0 Hz, 1H), 3.90 (s, 3H), 3.19 (m, *J* = 6.9 Hz, 1H), 2.54–2.43 (m, 2H), 2.29 (dd, *J* = 12.6, 7.1 Hz, 1H), 1.84–1.69 (m, 3H), 1.16 (d, *J* = 6.9 Hz, 3H), 1.00 (d, *J* = 6.7 Hz, 3H), 0.96 (s, 3H).

(*R*)-1-Isopropyl-6-methoxy-3a-methyl-2,3,3a,4-tetrahydro-5*H*-cyclopenta[*a*]naphthalen-5-one (83): A solution of compound **82** (1.59 g, 5.85 mmol) in CH_2Cl_2 (30 mL) was added to a suspension of PCC (5.04 g, 23.4 mmol, 4.0 equiv), NaOAc (1.92 g, 23.4 mmol, 4.0 equiv), and celite (5 g) in CH_2Cl_2 (30 mL). The mixture was stirred at room temperature for 3 h. The reaction mixture was filtered through celite. The precipitates were washed thoroughly with Et_2O. The filtrate was concentrated and purified by column chromatography on silica gel (petroleum ether/EtOAc = 20/1→10/1) to give **83** (1.26 g, 80% yield) as a brown oil. $[\alpha]_D^{25}$ = + 235.7 (*c* = 0.7, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.45 (t, *J* = 8.1 Hz, 1H), 7.02 (d, *J* = 8.1 Hz,1H), 6.88 (d, *J* = 8.1 Hz, 1H), 3.91 (s, 3H), 3.14 (m, *J* = 6.9 Hz, 1H), 2.70 (d, *J* = 16.5 Hz, 1H), 2.63 (d, *J* = 16.5 Hz, 1H), 2.55 (m, 2H), 1.87–1.74 (m, 2H), 1.19 (d, *J* = 6.9 Hz, 3H), 1.06 (s, 3H), 1.01 (d, *J* = 6.9 Hz, 3H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ (ppm) 198.1, 160.5, 145.6, 140.3, 134.9, 133.9, 120.8, 120.1, 110.7, 56.5, 56.1, 49.9, 36.8, 29.6, 27.4, 25.0, 21.5, 21.4; HRMS (ESI) m/z calcd for $C_{18}H_{22}NaO_2$ $[M+Na]^+$: 293.1512; found 293.1515.

(3a*R*,5a*R*)-1-Isopropyl-6-methoxy-3a,5a-dimethyl-2,3,3a,4,5a,8-hexahydro-5*H*-cyclopenta[*a*]naphthalen-5-one (84): To a solution of **83** (0.76 g, 2.81 mmol) and *t*-butyl alcohol (0.21 mL, 2.81 mmol, 1.0 equiv) in dried THF (15 mL) and liquid ammonia (15 mL) was added potassium (0.28 g, 7.00 mmol, 2.5 equiv) under nitrogen atmosphere at -78 °C. After being stirred for 20 min, a solution of carefully dried LiBr (0.53 g, 6.18 mmol, 2.2 equiv) in THF (10 mL) was added

dropwise. By stirring for an additional 20 min, methyl iodide (0.87 mL, 14.1 mmol, 5.0 equiv) was added. The reaction mixture was stirred at -78 ^{o}C for 1 h, and then warmed to room temperature over a period of 1 h while the ammonia was evaporated. Water (50 mL) was added to the residue, and the organic phase was separated. The aqueous layer was extracted with EtOAc (2 × 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc = 30/1) to afford compound **84** (0.61 g, 76% yield). $[\alpha]_D^{25}$ = -56.9 (*c* = 1.0 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 5.47 (t, *J* = 3.1 Hz, 1H), 4.79 (t, *J* = 3.2 Hz, 1H),3.60 (s, 3H), 2.90 (m, *J* = 6.9 Hz, 1H), 2.89–2.86 (m, 2H), 2.79 (d, *J* = 12.3 Hz, 1H), 2.40 (d, *J* = 9.6 Hz, 1H), 2.38 (dd, *J* = 9.6, 2.1 Hz , 1H), 2.30 (d, *J* = 12.3 Hz, 1H), 1.89 (ddd, *J* = 12.3, 5.4, 3.7 Hz, 1H), 1.74 (m, 1H), 1.48 (s, 3H), 1.02 (d, *J* = 6.9 Hz, 3H), 1.00 (d, *J* = 6.9 Hz, 3H), 0.90 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ (ppm) 209.3, 154.7, 143.5, 137.3, 134.0, 123.0, 92.3, 54.9, 54.6, 52.6, 51.0, 39.6, 28.7, 26.9, 26.5, 24.5, 24.1, 21.7, 21.5; HRMS (ESI) m/z calcd for $C_{19}H_{26}NaO_2$ $[M+Na]^+$: 309.1825; found 309.1830.

(3a*R*,5a*R*)-1-Isopropyl-3a,5a-dimethyl-2,3,3a,4,5,5a,7,8-octahydro-6*H*-cyclopenta[*a*]naphthalen-6-one (85): To a solution of **84** (0.25 g, 0.87 mmol) in EtOH (9.0 mL) was added semicarbazide hydrochloride **52** (0.49 g, 4.35 mmol, 5.0 equiv) and NaOAc (0.36 g, 4.35 mmol, 5.0 equiv) under argon atmosphere. The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was concentrated to dryness under reduced pressure and the residue was dissolved in ethyl acetate. Water (15 mL) and EtOAc (40 mL) were added to the residue. The organic phase was separated. The organic layer was washed with water (5 × 10 mL), dried over Na_2SO_4, filtered, and evaporated under reduced pressure to give the crude semicarbazone. A mixture of the crude semicarbazone and *t*-AmOK (1.1 g, 8.7 mmol, 10.0 equiv) in degassed xylene (5.0 mL) was heated at 140 ^{o}C for 2.5 h under argon atmosphere. Then water was added to the reaction mixture, and the organic phase was separated. The aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The resulting mixture thus obtained was dissolved in THF (10 ml) and treated with aqueous HCl (2 *N*, 2.2 mL, 4.40 mmol) at room temperature for 20 min. The reaction mixture was then poured into water (30 mL) and extracted with EtOAc (3 × 20 mL). The combined organic

layers were washed successively with saturated $NaHCO_3$ (3 × 10 mL), water (2 × 10 mL), and brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc = 50/1) to afford compound **85** (146 mg, 65% yield for 3 steps). $[\alpha]_D^{25}$ = + 685.2 (*c* = 1.0 in $CHCl_3$); ^1H NMR (300 MHz, C_6D_6) δ (ppm) 5.35 (t, *J* = 4.0 Hz, 1H), 2.89 (m, *J* = 6.9 Hz, 1H), 2.42 (dt, *J* = 13.5, 7.8 Hz, 1H), 2.32–2.16 (m, 3H), 2.10–1.98 (m, 2H), 1.90–1.83 (m, 2H), 1.68 (ddd, *J* = 12.3, 7.1, 2.9 Hz, 1H), 1.56–1.45 (m, 3H), 1.13 (s, 3H), 0.98 (d, *J* = 6.9 Hz, 3H), 0.96 (d, *J* = 6.9 Hz, 3H), 0.93 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ (ppm) 216.0, 142.2, 139.5, 137.8, 121.1, 48.6, 48.3, 39.4, 36.4, 35.9, 31.4, 28.4, 26.6, 25.6, 23.0, 23.0, 21.7, 21.6; HRMS (ESI) m/z calcd for $C_{18}H_{26}NaO$ $[M+Na]^+$:281.1876; found 281.1880.

Methyl (3a*R*,5a*R*)-1-isopropyl-3a,5a-dimethyl-6-oxo-2,3,3a,4,5,5a,6,7-octahydrocyclohepta[*e*]indene-8-carboxylate (87): To a solution of **85** (110 mg, 0.43 mmol) in dried THF (4 mL) was added LiHMDS (1M in THF, 0.85 mL, 0.85 mmol, 2.0 equiv) under nitrogen atmosphere at -78 °C. The reaction mixture was stirred for 30 min at the same temperature. Then methyl carbonocyanidate (0.067 mL, 0.85 mmol, 2.0 equiv) was added and the mixture was stirred for an additional 2 h. The reaction mixture was quenched by water. The organic phase was separated, and the aqueous layer was extracted with EtOAc for three times. The combined organic layers were dried over Na_2SO_4, filtered, concentrated, and purified by column chromatography on silica gel to give a mixture of β-ketoester **86** and its enol tautomer (110 mg, 82% yield).

To a solution of diethyl zinc (1.0 M in PhMe, 1.12 mL, 1.12 mmol, 6.0 equiv) in dried CH_2Cl_2 (1 mL) was added CH_2I_2 (90 μL, 1.12 mmol, 6.0 equiv) under nitrogen atmosphere at 0 °C. After being stirred for 5 min, a solution of β-ketoester **86** (59 mg, 0.19 mmol) in CH_2Cl_2 (2 mL) was added. The resulting mixture was stirred for 1 h at room temperature. Then iodine (0.28 g, 1.12 mmol, 6.0 equiv) was added to the reaction mixture and the solution was stirred for 10 min. The saturated aqueous solution of sodium thiosulfate was added and the mixture was stirred until the pink color had disappeared. To this solution was added DBU (0.28 mL, 1.86 mmol, 10.0 equiv). The mixture was stirred for 1 h and then quenched with saturated aqueous ammonium chloride. The reaction mixture was extracted with diethyl ether for three times. The combined

organic layers were dried with Na_2SO_4, filtered, concentrated, and purified by column chromatography on silica gel (petroleum ether/EtOAc = 50/1) to give **87** (44 mg, 72% yield). $[\alpha]_D^{25}$ = + 138.6 (*c* = 0.5, $CHCl_3$); ^1H NMR (300 MHz, DMSO-d_6) δ (ppm) 7.23 (d, *J* = 6.3 Hz, 1H), 5.97 (d, *J* = 6.3 Hz, 1H), 3.72 (s, 3H), 3.69 (d, *J* = 11.7 Hz, 1H), 3.41 (d, *J* = 11.7 Hz, 1H), 2.84 (m, *J* = 6.9 Hz, 1H), 2.39 (dd, *J* = 9.0, 5.8 Hz, 2H), 2.07–1.95 (m, 1H), 1.72–1.52 (m, 4H), 1.31 (dt, *J* = 13.5, 3.6 Hz, 1H), 1.07 (s, 3H), 1.02 (d, *J* = 6.9 Hz, 3H), 1.00 (s, 3H), 0.97 (d, *J* = 6.9 Hz, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ (ppm) 205.4, 166.3, 148.9, 144.4, 139.9, 136.0, 123.8, 122.1, 57.0, 52.5, 49.5, 40.7, 38.7, 36.2, 34.4, 28.8, 27.0, 24.0, 22.5, 21.6.

(+)-Allocyathin B_2 (7): To a solution of **87** (44 mg, 0.13 mmol) in Et_2O (1 mL) was added $LiAlH_4$ (25 mg, 0.67 mmol, 5.0 equiv) at -78 °C. The reaction mixture was stirred for 30 min at -78 °C under nitrogen atmosphere and then warmed to room temperature. The reaction solution was quenched by H_2O (2 mL). Brine (10 mL) and Et_2O (20 mL) was added to the mixture and the organic layer was separated. The aqueous layer was extracted with Et_2O (2 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, concentrated, and purified by column chromatography on silica gel (petroleum ether/EtOAc = 4/1) to give the corresponding diol (37 mg, 91% yield). $[\alpha]_D^{25}$ = + 1538.2 (*c* = 0.33 in $CHCl_3$); ^1H NMR (300 MHz, DMSO-d_6) δ (ppm) 5.77 (d, *J* = 7.5 Hz, 1H), 5.41 (d, *J* = 7.5 Hz, 1H), 4.79 (t, *J* = 5.4 Hz, 1H), 4.16 (d, *J* = 6.0 Hz, 1H), 3.87 (d, *J* = 5.4 Hz, 2H), 3.44 (d, *J* = 6.0 Hz, 1H), 2.78 (m, *J* = 6.9 Hz, 1H), 2.35–2.27 (m, 4H), 2.17–2.06 (m, 1H), 1.71–1.49 (m, 4H), 1.29 (dt, *J* = 13.6, 3.6 Hz, 1H), 0.96 (d, *J* = 6.9 Hz, 3H), 0.91 (d, *J* = 6.9 Hz, 3H), 0.90 (s, 3H), 0.89 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ (ppm) 144.1, 143.3, 142.0, 138.1, 121.7, 119.4, 74.6, 69.0, 48.4, 47.3, 38.5, 36.9, 34.3, 33.1, 28.6, 26.8, 26.4, 23.7, 21.8, 21.7.

To a solution of the diol (37 mg, 0.12 mmol) in CH_2Cl_2 (3 mL) was added MnO_2 (212 mg, 2.44 mmol, 20.0 equiv). The reaction mixture was stirred at room temperature for 1 h, and then filtered. The precipitate was washed thoroughly with CH_2Cl_2. The filtrate was dried over Na_2SO_4, filtered, concentrated, and purified by column chromatography on silica gel (petroleum ether/EtOAc = 10/1) to give (+)-allocyathin B_2 (28 mg, 75% yield). $[\alpha]_D^{25}$ = + 765.1 (*c* = 0.18 in MeOH); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 9.45 (s, 1H), 6.82 (dd, *J* = 8.2, 2.4 Hz, 1H), 5.93 (d, *J* = 8.2 Hz, 1H), 3.72 (dd, *J* = 8.7, 5.7 Hz, 1H), 3.17 (dd, *J* = 18.3, 5.7 Hz, 1H), 2.83 (m, *J* = 6.9

Hz, 1H), 2.53 (dd, *J* = 18.3, 9.5 Hz, 2H), 2.46–2.36 (m, 2H), 1.78–1.61 (m, 4H), 1.34 (dt, *J* = 13.5, 3.6 Hz, 1H), 1.05 (d, *J* = 6.9 Hz, 3H), 0.99 (s, 3H), 0.96 (d, *J* = 6.9 Hz, 3H), 0.96 (s, 3H); $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$) δ (ppm) 194.3, 155.2, 146.5, 144.5, 142.0, 137.9, 119.5, 74.2, 49.3, 48.4, 38.4, 36.6, 33.9, 29.3, 29.2, 27.1, 26.6, 24.0, 21.7.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS publications website at

Copies of ^{1}H and ^{13}C NMR; HPLC chart for the determination of ee% of compound **19** (PDF).

X-ray crystallographic data for cyrneine A (CIF)

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Notes

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