Total Synthesis of (+)-Allocyathin B₂, (–)-Erinacine B, and (–)-Erinacine E

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Abstract: This article describes the enantioselective total synthesis of (+)-allocyathin B₂ and (–)-erinacine B via the convergent approach using new chiral building blocks prepared by the asymmetric catalysis developed in our research, and also describes the biomimetic total synthesis of (–)-erinacine E. The convergent approach developed in these studies would enable the divergent synthesis of optically pure cyathane diterpenoids and their derivatives for SAR.

1. Introduction

Since the first isolation and structure elucidation of cyathins from bird nest fungi by Ayer and coworkers in 1970^{1k-m}, numerous compounds possessing the cyathane skeleton, that is, cyathins,¹ allocyathins,^{1b,1e,1g-k,2} striatins,^{1d,3} cyafrins,^{1c-g,4} sarcodonins,^{1a,1b,2,5c} erinacines,⁵ scabronins,⁶ glaucopines,⁷ cyrneines,^{7a,8} and cyanthiwigins,⁹ have been isolated and characterized (Figure 1). With the exception of some compounds, all cyathane diterpenoids possess an unusual 5-6-7 tricyclic carbon skeleton including a *trans*-fused 6-7 ring system, and a common structural feature is two stereogenic quaternary carbons existing at its ring junctions.

On the other hand, structural complexity and diversity

arise from the different degree of oxidation not only around the five-membered and seven-membered rings, but also at the C19 position of sarcodonins and the C17 position of scabronins. Moreover, striatins and erinacines possess a unique structure categorized as xylose conjugates of cyathins, and cyanthiwigins have the *epi*-cyathane skeleton with the reversed C9 stereogenic quaternary carbon.⁹

Some compounds in this large family show strong antibiotic activity, and the erinacines^{5a,5k-m} and scabronines⁶ have been shown to be strong stimulators of nerve growth factor (NGF) synthesis. Since NGF does not cross the blood-brain barrier (BBB) and this native peptide is rapidly metabolized *in vivo*,^{10a} the use of small non-peptide stimulators of NGF synthesis is perceived as a promising way to treat such neurodegenerative diseases as Alzheimer, Parkinson, and Hunt-

Figure 1. Structure of selected cyathane diterpenoids.

ington diseases.^{10b-d}

Moreover, erinacine E, one of the more complex members of this family, was recently shown to have not only potent NGF synthesis-stimulating activity, but also to possess κ -opioid receptor agonist activity.⁵ⁱ Furthermore, cyanthiwins show toxicity against HBV, HIV-1, and human primary tumor cells.⁹

The structural complexity and diverse biological activity of the cyathane diterpenoids have drawn much attention to their synthesis,¹¹⁻¹³ leading to a number of total syntheses¹² including enantioselective ones.¹¹

Considering the structural diversity of this family, a rational synthetic approach to all the compounds and their derivatives would be a convergent synthesis, namely, the preparation and assembly of chiral building blocks. For the preparation of chiral building blocks, asymmetric catalysis is a powerful method because it allows the enantiodivergent synthesis of desired compounds. For example, Fragment A and *ent*-Fragment A (Scheme 1), which arose from the corresponding retrosynthetic analysis of (+)-allocyathin B₂ and cyanthiwigin F, would be derived from (–)-CP and (+)-CP, respectively, which could be prepared by our originally developed catalytic asymmetric intramolecular cyclopropanation (CAIMCP) with the appropriate chiral ligand.¹⁴

We wish to review herein our enantioselective total synthesis of (+)-allocyathin B₂^{11h} and (–)-erinacine B^{11c}

Scheme 1. Enantiodivergent approach to cyathane diterpenoids.

through highly convergent and stereoselective construction of the 5–6–7 tricyclic core system, and the biomimetic total synthesis of (–)-erinacine E.^{11a}

2. Enantioselective Total Synthesis of (+)-Allocyathin B₂^{11h}

Our own strategy for the enantioselective synthesis of (+)-allocyathin B₂ is based on the retrosynthetic analysis of keto ester **1** illustrated in Scheme 2 because (+)-allocyathin B₂ has been derived from keto ester **1**.^{12c,f} We envisioned that keto ester **1** could be derived from ketone **2** via installation of the ester group, followed by iodomethylation, samarium diiodide-mediated ring expansion, and subsequent introduction of the double bond. Ketone **2** would be derived from diketone **3** via the intramolecular aldol reaction, followed by dehydration, installation of the isopropyl group, and dehydration. Then, diketone **3** was disconnected into two chiral fragments, Fragments A (**4**) and B (**5**), which would be readily prepared from the chiral building blocks prepared in our research,^{14,15} hence, we started to prepare Fragment A (**4**) utilizing CAIMCP^{14g} and Fragment B (**5**) utilizing baker's yeast reduction.^{15c,d}

Enantiomerically pure cyclopropane **6** (Scheme 3),^{14g} which had been prepared by CAIMCP of the corresponding α -diazo- β -keto sulfone, was made to react with thiophenol (99%), and the mesityl sulfonyl group was selectively removed by lithium naphthalenide¹⁶ with the thiophenyl group remaining intact to generate ketone **7** (86%). Ethylene ketal was formed (91%), followed by oxidation with *m*-chloroperbenzoic acid (quantitative), and finally, Pummerer rearrangement to furnish Fragment A (**4**) (87%).

Preparation of Fragment B (**5**) commenced with diol **8** (Scheme 4, >99% ee), which was prepared by the baker's yeast-mediated reduction of 2-benzoyloxymethyl-2-methyl-1,3-cyclohexanedione and subsequent stereoselective reduction with Me₄NBH(OAc)₃.^{15c,d} Removal of the benzyl ether of diol **8** by hydrogenolysis (quantitative) and subsequent formation of anisylidene gave acetal **9** as the sole product (90%). Formation of TBS ether (quantitative) and subsequent regioselective reduction of the anisylidene group by

Scheme 2. Retrosynthetic analysis of (+)-allocyathin B₂.

Scheme 3. Preparation of Fragment A (4).

Scheme 4. Preparation of Fragment B (5).

DIBAL-H afforded alcohol **10** (97%), which was finally converted to Fragment B (**5**) under the conventional conditions (93%).

With Fragments A (**4**) and B (**5**) in hand, they were then coupled (Scheme 5). Fragment B (**5**) was treated with *t*-BuLi in Et₂O, and the resulting organolithium compound was made to react with Fragment A (**4**) to generate alcohol **11** (41%), but use of a mixture of Et₂O/THF (10:1) as a solvent greatly improved the yield to 79%. Alcohol **11** was converted to methyl xantate **12** (91%), followed by tin-hydride reduction¹⁷ to produce compound **13** (89%). Both protective groups in compound **13**, TBS ether and ethylene ketal, were cleanly removed under the acidic conditions (quantitative), and subsequent Dess–Martin oxidation provided diketone **3** (93%).

Now, the stage was set for the intramolecular aldol reaction to form the six-membered ring in the cyathane skeleton. This reaction was challenging because both reaction points in the electrophile and in the nucleophile are next to the quaternary carbon. The preliminary studies revealed that this reaction using a base in protic solvent¹⁸ attained equilibrium between diketone **3** and β -hydroxy ketone **14**, probably due to the retro-aldol reaction. Accordingly, the reaction in aprotic solvent was examined next. Although no reaction

occurred with amines,¹⁹ use of potassium *t*-butoxide in benzene gratifyingly improved the yield to 94%.²⁰ Molecular modeling suggests that this dramatic change could arise from the chelate formed between the hydroxyl and the keto groups of β -hydroxy ketone **14** with a potassium cation. The structure of the β -hydroxy ketone **14** was elucidated as shown in Scheme 5 by X-ray crystallographic analysis.^{11h}

Dehydration of the β -hydroxy ketone **14** with thionyl chloride and pyridine afforded a separable mixture of β,γ -unsaturated ketone **15** (71%) and its regio isomer **16** (11%),²⁰ and ketone **15** was made to react with isopropenyl lithium to afford alcohol **17** (72%, at 61% conversion). Hydrogenation of the isopropenyl group took place with concomitant hydrogenolysis of the PMB group (96%) and the following Dess–Martin oxidation generated the hydroxyl ketone **18** (92%). Dehydration of the hydroxyl ketone **18** with thionyl chloride and pyridine afforded a mixture of regioisomeric alkenes; however, the acid catalyzed alkene isomerization in refluxing benzene proceeded completely to provide conjugated diene **2** (77%, two steps).

Ring expansion of the cyclohexenone moiety of ketone **2** employed Hasegawa's method^{12c,21} because this method could easily generate the requisite ring-expanded γ -keto ester **20**. For this purpose, **2** was first converted to the corresponding β -keto ester using Mander's reagent (87%),²² followed by iodomethylation²³ to produce iodide **19** as a single stereoisomer (86%).²⁴ Exposure of iodide **19** to samarium diiodide effectively caused ring expansion to furnish the desired γ -keto ester **20** (91%, dr=1.9:1).

To introduce the double bond into γ -keto ester **20**, such known one-pot methods as those using (PhSeO)₂O²⁵ or IBX²⁶ were examined; however, no products were obtained. Hence, we decided to find new conditions for this transformation, and after several attempts, we successfully found that the dienolate formed from γ -keto ester **20** could be converted to ketone **1**. That is, γ -keto ester **20** was first treated with excess LDA (5.0 equiv) in THF, followed by the treatment with iodine (2.0 equiv) to afford ketone **1** (71%). This one-pot reaction would involve the isomerization from the initially formed α,β -unsaturated ketone to the thermodynamically more stable β,γ -unsaturated ketone **1** via the enolate. This transformation is clean and easy to operate, hence, advantageous for preparative purposes.

The known transformations from ketone **1** to (+)-allocyathin B₂,^{12c,f} that is, stereoselective reduction of ketone and ester in ketone **1** (89%) and selective oxidation of the resultant allylic alcohol with MnO₂ (90%), were successfully employed to complete the total synthesis of (+)-allocyathin B₂. Synthetic (+)-allocyathin B₂ proved to be identical in all respects to the reported spectral data (¹H NMR,^{12c,f} IR,^{1c} MS,^{1c} [α]_D,^{1c} and ¹³C NMR^{12c,f}).

This total synthesis features the convergent construction of the 5–6–7 tricyclic core system using the originally developed chiral building blocks via asymmetric catalysis, the intramolecular aldol reaction in high yield, successful samarium diiodide mediated ring expansion, and a newly developed double bond installation method. As a synthetic approach to the 5–6–7 tricyclic core system of cyathane diterpenoids had been established, next we developed a new access to the *trans*-fused 6–7 ring system of cyathane diterpenoids, which is surmised to be possible via the intermediate **14** prepared in

Scheme 5. Enantioselective total synthesis of (+)-allocyathin B₂.

this synthesis.

3. Enantioselective Total Synthesis of (–)-Erinacine B^{11c}

In 1994, Kawagishi et al. reported the isolation and structural elucidation of (–)-erinacines A, B, and C.^{5m} (–)-Erinacine B is the first xylose-conjugated terpenoid possessing a cyathane core, which features an unusual 5–6–7 tricyclic carbon skeleton incorporating a *trans*-fused 6–7 ring system and 1,4-*anti* quaternary methyl groups at the ring junctions. As described in Introduction, erinacines and their congeners have been shown to exhibit significant activity in stimulating nerve growth factor (NGF) synthesis.

Our synthetic strategy for (–)-erinacine B is based on the retrosynthetic analysis outlined in Scheme 6. Because it was expected that (–)-erinacine B might be derived from xyloside **21** via a consecutive intramolecular 1,4-addition and β -elimination sequence,²⁷ we decided to prepare xyloside **21** by a glycosylation reaction of aglycon **22** with xylose derivative **23** and subsequent transformations. We envisioned that aglycon **22** would be obtained from epoxy ketone **24** through a base promoted β -elimination reaction and stereoselective reduction of the resulting ketone. Epoxide **24** was to be produced via stereoselective epoxidation of the homoallylic alcohol **25**, which could be prepared by stereoselective reduction of ketone **26**. Tricyclic compound **26** could be obtained from ketone **27** by a ring-expansion reaction followed by installation of the double bond. It was expected that the *trans* C5–C6 stereochemistry in ketone **27** could be attained by

diastereoselective reduction of enone **28** utilizing the β -oriented hydroxyl at C14; hence, we commenced with preparation of enone **28**.

Since we established the preparation method of enantiopure β -hydroxy ketone **14** in the total synthesis of (+)-allocyathin B₂,^{11h} preparation of enone **28** was started from β -hydroxy ketone **14** (Scheme 7). β -Hydroxy ketone **14** was dehydrated with thionyl chloride and pyridine (91%), followed by double bond isomerization using DBU (92%) and removal of PMB ether with DDQ to produce enone **28** (100%).

We expected that catalytic hydrogenation of enone **28** would proceed with high diastereoselectivity because the β -oriented hydroxyl group at C14 would direct the reaction; however, hydrogenation of enone **28** provided no product. We also attempted the conjugate reduction of **28** with various reagents, but no product was obtained.

We next examined electron-transfer reduction of this enone system and found that Birch reduction of enone **28** afforded a mixture of ketone **29** and its alcohol. After several attempts, we finally found that reduction of enone **28** with samarium diiodide in the presence of HMPA successfully afforded ketone **29** as a single product in 94% yield.²⁸ It should be noted that this stereoselectivity would be attributed to the diastereoselective protonation of the anion generated at C5 with the β -oriented hydroxyl group at C14 because reduction of the MOM ether of enone **28** under the same conditions gave the corresponding allylic alcohol exclusively.

Scheme 6. Retrosynthetic analysis of (–)-erinacine B.

Scheme 7. Preparation of aglycon 35.

Reaction of ketone **29** with isopropenyl lithium resulted in low conversion; however, this problem was settled by use of the isopropenyl cerium reagent (84%). The product with an isopropenyl group was subjected to hydrogenation (95%), followed by Dess–Martin oxidation to afford hydroxy ketone **30** (91%). Dehydration of hydroxy ketone **30** by thionyl chloride and pyridine proceeded cleanly (100%), and subsequent double bond isomerization under acidic conditions generated

ketone **27** with a thermodynamically stable alkene (100%).

The next task was to construct the 5–6–7 cythane core from ketone **27**, which required a one-carbon ring-expansion reaction. We employed Hasegawa's method²⁰ for this purpose because it was successfully applied in our first enantioselective total synthesis of (+)-allocyathin B.^{11h} Thus, ketone **27** was converted to the corresponding β -keto ester²⁹ using Mander's reagent (79%), followed by iodomethylation (66%)

and reaction with samarium diiodide in the presence of HMPA. As expected, this resulted in a ring-expansion reaction, generating the desired γ -keto ester **31** (81%, a mixture of diastereomers).

Introduction of the double bond to the seven-membered ring by the previously reported I_2/LDA method^{11h} was low-yielding, but reaction of the TMS enol ether of γ -keto ester **31** with PhSeCl afforded an α -phenylselenyl ketone, which was subjected to the selenoxide fragmentation (91%, two steps), successfully installing the desired double bond in γ -keto ester **31**. This double bond was easily isomerized by DBU to provide the desired keto-ester **26** (98%).

DIBAL-H reduction of keto-ester **26** exclusively provided a desired diol **32** (96%, dr = 10:1), followed by stereoselective epoxidation with TBHP/ $VO(acac)_2$ ³⁰ to afford the desired epoxide as a single diastereomer. The primary alcohol of this epoxide was converted to a TBDPS ether, and Dess-Martin oxidation of the remaining secondary alcohol provided β,γ -epoxy ketone **33** (80%, three steps).

Treatment of epoxy ketone **33** with DBU prompted a clean β -elimination reaction to provide the γ -hydroxy- α,β -unsaturated ketone, which was converted to benzoate **34** (78%, two steps) because we expected that the benzyloxy group in **34** would be stable during the following transformations and would be a good leaving group in the final consecutive intramolecular 1,4-addition and β -elimination reaction.

Diastereoselective reduction of benzoate **34** with achiral reagents was extensively investigated, but all the reductions produced an undesired isomer as a major product. Consequently, we examined the chiral reagent-controlled reduction and found that CBS-catalyzed reduction³¹ of **34** successfully generated the desired alcohol **35** as the sole product (95%).

It was expected that glycosylation of alcohol **35** would be difficult because the hydroxyl group at C14 is greatly hindered due to a quaternary carbon adjacent to C14 (Scheme 8). Most of the glycosylation reactions of alcohol **35** with several xylose derivatives under various conditions gave no glycosylated product; however, we finally found that alcohol **35** reacted with thioglycoside **36** in the presence of MeOTf³² to provide the desired product, which was exposed to HF·Py to afford alcohol **37** as an inseparable mixture of anomeric isomers (77%, two steps, $\alpha/\beta=1:3.5$).

Dess-Martin oxidation of alcohol **37** cleanly provided the corresponding aldehyde (96%), but subsequent removal of all PMB groups with DDQ was troublesome and afforded a complex mixture of products. After several attempts, we found that exposure of the substrate to TFA³³ in CH_2Cl_2 at $-20^\circ C$ gratifyingly provided the key intermediate **38** (100%).

Finally, treatment of the key intermediate **38** with triethylamine and LiBr in THF, which were the conditions reported by Sassa,²⁷ caused sequential oxy-Michael addition and β -elimination in a highly stereoselective manner to furnish (–)-erinacine B (74%), which was successfully isolated as a single diastereomer. Synthetic (–)-erinacine B proved to be identical in all respects to the natural product on the reported spectral data.^{5m}

This total synthesis established the convergent construction of the xylose conjugated 5–6–7 tricyclic cyathane core system with the *trans* 6–7 ring junction using chiral building blocks prepared by the asymmetric catalysis developed in our research. Encouraged by this highly stereoselective total syn-

Scheme 8. Enantioselective total synthesis of (–)-erinacine B.

thesis, we proceeded to study the total synthesis of erinacine E, one of the more complex compounds in the xylose-conjugated cyathanes.

4. Biomimetic Total Synthesis of (–)-Erinacine E^{11a}

In 1996, (–)-erinacine E (Figure 2) was reported to be a strong stimulator of nerve growth factor (NGF) synthesis from the mycelia of *Herichium erinaceum* whose fruiting bodies have been used in Chinese medicine or as food.^{5k} Two years later, a Pfizer research group isolated (–)-erinacine E from a different source, the fermentation broth of *Herichium ramosum* CL24240, and disclosed that (–)-erinacine E was a potent, highly selective κ -opioid receptor agonist.^{5i,34}

Single-crystal X-ray crystallographic analysis unambiguously elucidated the absolute structure of (–)-erinacine E.^{5k} Its unique hexacyclic ring system includes ten stereogenic centers as well as a 5–6–7 tricyclic cyathane skeleton, which is fused with a highly oxygenated tricyclic 2,9-dioxatricyclo[5.2.2.0^{4,10}]undecane system. These structural features make (–)-erinacine E a strained and largely different compound compared with other cyathane diterpenoids and erinacines.^{1–9}

Since striatals, exemplified as striatal A and striatal D, and (–)-erinacine P (Figure 2) have been isolated,³⁵ it was proposed that the C–C bond-forming reaction **a** (Scheme 9) between the C2' and C13 positions of keto aldehyde **39**, which could be derived from keto aldehyde **39**, could provide striatals, and the subsequent intramolecular aldol reaction **b** (Scheme 9) between the C4' and C15 positions could yield erinacines. However, to the best of our knowledge, none of these transformations have been reported.

The complex structure, significant biological activity, and

Figure 2. Structure of (–)-erinacine E, striatal A, D, (–)-erinacine P.

Scheme 9. Proposed biosynthesis of erinacines and striatals.

biogenesis of (–)-erinacine E are features that make it a fascinating target. Since we had already achieved the enantioselective total synthesis of (–)-erinacine B, we started to investigate the enantioselective total synthesis of (–)-erinacine E via alcohol **35**, an intermediate in the total synthesis of (–)-erinacine B.

We first examined the glycosylation of alcohol **35** with thioglycoside **40**⁹ (Scheme 10). The glycosylation with MeOTf^{11c} successfully provided glycoside **41** in 84% overall yield with high selectivity ($\alpha/\beta=1/14$) using the recycling technique.³⁶ Deprotection of glycoside **41** afforded diol **42** and subsequent Swern oxidation provided keto aldehyde **43**, which was found to be gradually converted in situ to PMB-protected striatal **44** as the sole product (80%, two steps), probably due to the catalysis by Et₃N.

We anticipated that the aldol reaction of PMB-protected striatal **44** would be difficult to achieve because the product was energetically unfavorable owing to its strained structure and would easily undergo a retro-aldol reaction. Indeed, despite extensive studies, the aldol reaction of PMB-protected striatal **44** under any conditions resulted in either no reaction or in decomposition,³⁷ suggesting that this process needed an exceptional procedure to provide the product.

Considering the structure of striatal A (Figure 2), a proposed biosynthetic intermediate of (–)-erinacine E, we were inspired by the acetyl group at the C4' position and we decided to examine the aldol reaction of ketone **49** possessing a benzoate at the C4' position (Scheme 12).³⁸ Thus, we conceived that the enolate **50** generated from ketone **49** would provide the initial aldol product **51**, in which the benzoyl group could migrate to the secondary C15 hydroxyl to provide stable ketone **52**, which would not revert to ketone **49**.

Deprotection of PMB-protected striatal **44** caused decomposition under any conditions, hence, ketone **49** was prepared from diol **42** (Scheme 11, 12). Deprotection of diol **42** provided tetraol **45** (93%), which was protected with TES groups to provide a separable mixture of TES ethers **46** (44%) and **47** (44%). Recycling TES ether **47** to tetraol **45** was successfully achieved. Selective benzylation of TES ether **46** (92%), subsequent deprotection of the C15 TES

Scheme 10. Enantioselective synthesis of PMB-protected striatal **44**.

group (91%), and Swern oxidation of the resultant diol to keto aldehyde **48**, followed by in situ cyclization/elimination gave ketone **49** directly (93%).

Scheme 11. Preparation of diol 46.

Initial attempts of the intramolecular aldol reaction of ketone **49** using bases containing a metal cation (*t*-BuOK, LiBr/Et₃N, CsCO₃)³⁷ resulted in no reaction or decomposition. However, DBU effectively provided a product in 85% yield, and the detailed NMR studies^{11a} of the product confirmed its structure as ketone **52**, proving that the aldol reaction of ketone **49** proceeded as expected with concomitant 1,2-migration of the benzoyl group.

Reduction of ketone **52** with NaBH₄ occurred as anticipated at the less-hindered side to provide alcohol **53**, which was deprotected to afford diol **54** (96%, two steps). Mitsunobu reaction of alcohol **54** did not proceed and all attempts to invert the stereochemistry at C15 failed; hence, the oxidation and stereoselective reduction sequence was investigated. *o*-Iodoxybenzoic acid (IBX) oxidation³⁹ of alcohol **54** provided the desired enone, but reduction of the enone with most reducing reagents resulted in decomposition or only provided the 1,4-reduction product, probably due to its *s-cis* structure. After several attempts, the reduction with Me₄NBH(OAc)₃⁴⁰ was found to provide the desired 1,2-reduction product (70%, two steps) as a single isomer, which was identical to the natural (–)-erinacine E in all respects (¹H NMR, IR, MS, [α]_D, and ¹³C NMR).^{5m}

In this total synthesis, highly stereoselective total synthesis of (–)-erinacine E has been achieved in 12 steps from the enantiopure alcohol **35**. The intramolecular aldol reaction of ketone **49**, driven by the rationally designed 1,2-migration of a benzoyl group, is the crucial step in this synthesis that

Scheme 12. Biomimetic total synthesis of (–)-erinacine E.

effectively prevented the retro-aldol reaction and permitted the successful construction of the strained skeleton of (–)-erinacine E. Considering the structure of a putative biosynthetic intermediate, striatal A, the intramolecular aldol reaction driven by the C4' acetyl group could be involved in the biosynthesis of (–)-erinacine E. This acyl group migratory ring-closing reaction would be applicable to the synthesis of other strained molecules.

5. Conclusion

We have achieved the first enantioselective total synthesis of (+)-alloyathin B₂, (–)-erinacine B, and (–)-erinacine E via the convergent approach using chiral building blocks prepared by the asymmetric catalysis developed in our research. This convergent approach incorporates the enantiodivergent synthesis of chiral building blocks by asymmetric catalysis, allowing not only enantioselective total synthesis of all the cyathane diterpenoids with divergent structures but also preparation of their various derivatives for SAR. Further synthetic studies now undertaken feature an efficient and short access to the key intermediate revealed in the total syntheses achieved in our research, and will be reported in the future.

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