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, numerous compounds possessing the cyathane skeleton, that is, cyathins, allocyathins, striatins, cyafrins, sarcodonsins, erinacines, scabronins, glaucopines, cyrneines, and cyanthiwigins, 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 sarcodonsins 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. Some compounds in this large family show strong antibiotic activity, and the erinacines and scabronines 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, 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-
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 \( \kappa \)-opioid receptor agonist activity. Furthermore, cyanthiwigin \( G \) show toxicity against HBV, HIV-1, and human primary tumor cells.

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

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 B 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.

We wish to review herein our enantioselective total synthesis of (+)-allocyathin B and (-)-erinacine B through highly convergent and stereoselective construction of the 5-6-7 tricyclic core system, and the biomimetic total synthesis of (-)-erinacine E.

Scheme 1. Enantiodivergent approach to cyathane diterpenoids.

\[ (+)-\text{allocyathin B}_2 \]  
\[ \text{cyanthiwigin } F \]  
\[ \text{Fragment A} \]  
\[ \text{ent-Fragment A} \]  
\[ (-)-\text{CP} \]  
\[ (+)-\text{CP} \]  
\[ > 99\% \text{ ee} \]  
\[ \text{CAIMCP with (+)-Ligand} \]  
\[ \text{CAIMCP with (-)-Ligand} \]  
\[ \text{achiral} \]  
\[ \text{(-)-Ligand} \]  
\[ \text{(+)-Ligand} \]  

Our own strategy for the enantioselective synthesis of (+)-allocyathin B is based on the retrosynthetic analysis of keto ester 1 illustrated in Scheme 2 because (+)-allocyathin B has been derived from keto ester 1. 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; hence, we started to prepare Fragment A (4) utilizing CAIMCP and Fragment B (5) utilizing baker’s yeast reduction.

Enantiomerically pure cyclopropane 6 (Scheme 3), which had been prepared by CAIMCP of the corresponding \( \alpha \)-diazoo-\( \beta \)-keto sulfone, was made to react with thiophenol (99%), and the mesityl sulfonyl group was selectively removed by lithium naphthalenide 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-benzyloxymethyl-2-methyl-1,3-cyclohexanedione and subsequent stereoselective reduction with Me4NBH(OAc)3. 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...
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 Et_2O, and the resulting organolithium compound was made to react with Fragment A (4) to generate alcohol 11 (41%), but use of a mixture of Et_2O/THF (10:1) as a solvent greatly improved the yield to 79%. Alcohol 11 was converted to methyl xanthate 12 (91%), followed by tin-hydride reduction 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 solvent attained equilibrium between diketone 3 and γ-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, use of potassium t-butoxide in benzene gratifyingly improved the yield to 94%. 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.

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%). 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 alkeno 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 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%), followed by iodomethylation to produce iodide 19 as a single stereoisomer (86%). 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)2 or IBX 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) and t-BuLi, 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 B3, 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 B3. Synthetic (+)-allocyathin B3 proved to be identical in all respects to the reported spectral data (1H NMR, IR, MS, [α]D, and 13C NMR). 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
3. Enantioselective Total Synthesis of (-)-Erinacine B\(^\text{1c}\)

In 1994, Kawagishi et al. reported the isolation and structural elucidation of (-)-erinacines A, B, and C;\(^\text{5m}\) (-)-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 \(\beta\)-elimination sequence,\(^\text{27}\) 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 \(\beta\)-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 \textit{trans} C5-C6 stereochemistry in ketone 27 could be attained by diastereoselective reduction of enone 28 utilizing the \(\beta\)-oriented hydroxyl at C14; hence, we commenced with preparation of enone 28.

Since we established the preparation method of enantiopure \(\beta\)-hydroxy ketone 14 in the total synthesis of (+)-allocyathin B\(^\text{11}\), preparation of enone 28 was started from \(\beta\)-hydroxy ketone 14 (Scheme 7). \(\beta\)-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 \(\beta\)-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.\(^\text{28}\) It should be noted that this stereoselectivity would be attributed to the diastereoselective protonation of the anion generated at C5 with the \(\beta\)-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.

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 cyathane core from ketone 27, which required a one-carbon ring-expansion reaction. We employed Hasegawa’s method for this purpose because it was successfully applied in our first enantioselective total synthesis of (+)-allocyathin B. Thus, ketone 27 was converted to the corresponding β-keto ester 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 \( \gamma \)-keto ester 31 (81%, a mixture of diastereomers).

Introduction of the double bond to the seven-membered ring by the previously reported \( \text{I}_2/\text{LDA} \) method\(^{1,1b} \) was low-yielding, but reaction of the TMS enol ether of \( \gamma \)-keto ester 31 with \( \text{PhSeCl} \) afforded an \( \alpha \)-phenylethylketone, which was subjected to the selenoxide fragmentation (91%, two steps), successfully installing the desired double bond in \( \gamma \)-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%, \( \text{dr} = 10:1 \)), followed by stereoselective epoxidation with TBHP/VO(acac)\(^2 \) 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 \( \beta \gamma \)-epoxy ketone 33 (80%, three steps).

Treatment of epoxy ketone 33 with DBU prompted a clean \( \beta \)-elimination reaction to provide the \( \gamma \)-hydroxy-\( \alpha \beta \)-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 \( \beta \)-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 reduction\(^3 \) 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 \( \text{McOTf} \) 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, \( \text{ao}=1:3.5 \)).

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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 (Scheme 10). The glycosylation with MeOTf\(^{[12]}\) successfully provided glycoside 41 in 84% overall yield with high selectivity (\(a/\beta = 1/14\)) 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 Et\(_3\)N.

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 tetratol 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 tetratol 45 was successfully achieved. Selective benzoylation of TES ether 46 (92%), subsequent deprotection of the C15 TES group (91%), and Swern oxidation of the resultant diol to keto aldehyde 48, followed by in situ cyclization/elimination gave ketone 49 directly (93%).
Initial attempts of the intramolecular aldol reaction of ketone 49 using bases containing a metal cation (t-BuOK, LiBr/Et3N, CsCO3) resulted in no reaction or decomposition. However, DBU effectively provided a product in 85% yield, and the detailed NMR studies 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). Mitsuobu 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) oxidation 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) 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).

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
effectively prevented the retro-aldol reaction and permitted the successful construction of the strained skeleton of
(−)–eranacine E. Considering the structure of a putative biosynthetic intermediate, triastrial A, the intramolecular aldol reaction driven by the C4′ acetyl group could be involved in the biosynthesis of (−)–eranacine 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 (+)-allocyathin B2, (−)–eranacine B, and (−)–eranacine 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 synthesis achieved in our research, and will be reported in the future.

References


35 and thioglucose 40 provided glycoside 41 in 29% yield (α/β=1/14).
37 Stabilizing the product with a metal chelate in the aldol reaction was very effective in the total syntheses of (+)-allocyathin B₁ and (-)-erinacine B, but the method was fruitless in this synthesis.
38 A benzoyl group was used because of its stability.

PROFILE

Hideaki Watanabe received his B.S. (2003), M.S. (2005), and Ph.D. (2008) degrees from Waseda University under the supervision of Prof. Masahisa Nakada. In 2008, he joined Daiichi Sankyo Co., Ltd. where he is currently a researcher. His current research interests are in the areas of medicinal chemistry.

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Masahisa Nakada received his B.S. (1982), M.S. (1984), and Ph.D. degrees (under the supervision of Prof. Masaji Ohno) from The University of Tokyo, and was appointed Assistant Professor during his Ph.D. course in 1987. He joined Prof. Shibasaka’s group in 1991 and spent one year and four months from the beginning of FY1992 as a postdoctoral fellow with Prof. K. C. Nicolaou at The Scripps Research Institute. In 1995, he was promoted to Associate Professor of Department of Chemistry at Waseda University, and has been Professor since FY2000. In 1997, he received the Pharmaceutical Society of Japan Award for Young Scientists. His research interests include total syntheses of bioactive natural products, asymmetric catalysis, new synthetic reactions, and chemical biology.