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Synthetic Studies on Cyathins: Enantioselective Total Synthesis of (+)-Allocyathin B_2

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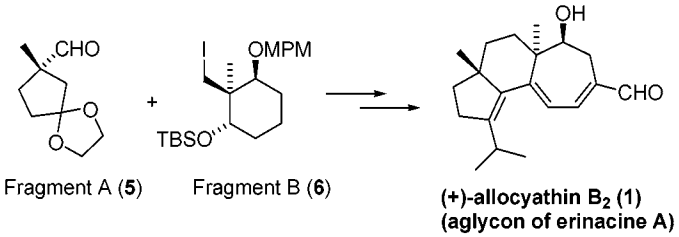
ABSTRACT



The enantioselective total synthesis of (+)-allocyathin B_2 has been achieved. Our approach features a convergent enantioselective 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.

Since the first isolation and structure elucidation of cyathins from bird nest fungi by Ayer and co-workers in 1970,[1k−m] numerous compounds possessing the cyathane skeleton, that is, cyathins,[1] allocyathins,[1a,1d,1f−j,2] striatins,[1c,3] cyafrins,[1d−f,4] sarcodonins,[1a,2,5b] erinacines (cyathane-xylosides),[5] and scabronins,[6] have been isolated and characterized. With the exception of a few compounds such as allocyathin B_2, erinacine A, and sarcodonin A, all cyathins possess an

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(4) Hirota, M.; Morimura, K.; Shibata, H. *Biosci. Biotechnol. Biochem.* **2002**, *66*, 179−184.

(5) (a) Kenmoku, H.; Tanaka, K.; Okada, K.; Kato, N.; Sassa, T. *Biosci. Biotechnol. Biochem.* **2004**, *68*, 1786−1789. (b) Kamo, T.; Imura, Y.; Hagio, T.; Makabe, H.; Shibata, H.; Hirota, M. *Biosci. Biotechnol. Biochem.* **2004**, *68*, 1362−1365. (c) Kenmoku, H.; Shimai, T.; Toyomasu, T.; Kato, N.; Sassa, T. *Biosci. Biotechnol. Biochem.* **2002**, *66*, 571−575. (d) Kenmoku, H.; Kato, N.; Shimada, M.; Omoto, M.; Mori, A.; Mitsuhashi, W.; Sassa, T. *Tetrahedron Lett.* **2001**, *42*, 7439−7442. (e) Lee, E. W.; Shizuki, K.; Hosokawa, S.; Suzuki, M.; Suganuma, H.; Inakuma, T.; Li, J.; Ohnishi-Kameyama, M.; Nagata, T.; Furukawa, S.; Kawagishi, H. *Biosci. Biotechnol. Biochem.* **2000**, *64*, 2402−2405. (f) Kenmoku, H.; Sassa, T.; Kato, N. *Tetrahedron Lett.* **2000**, *41*, 4389−4393. (g) Omori-Satoh, T.; Yamakawa, Y.; Mebs, D. *Toxicon* **2000**, *38*, 1561−1580. (h) Saito, T.; Aoki, F.; Hirai, H.; Inagaki, T.; Matsunaga, Y.; Sakakibara, T.; Sakemi, S.; Suzuki, Y.; Watanabe, S.; Suga, O.; Sujaku, T.; Smogowicz, A. A.; Truesdell, S. J.; Wong, J. W.; Nagahisa, A.; Kojima, Y.; Kojima, N. *J. Antibiot.* **1998**, *51*, 983−990. (i) Mebs, D.; Omori-Satoh, T.; Yamakawa, Y.; Nagaoka, Y. *Toxicon* **1996**, *34*, 1313−1316. (j) Kawagishi, H.; Shimada, A.; Hosokawa, S.; Mori, H.; Sakamoto, H.; Ishiguro, Y.; Sakemi, S.; Bordner, J.; Kojima, N.; Furukawa, S. *Tetrahedron Lett.* **1996**, *37*, 7399−7402. (k) Kawagishi, H.; Shimada, A.; Shizuki, K.; Mori, H.; Okamoto, K.; Sakamoto, H.; Furukawa, S. *Heterocycl. Commun.* **1996**, *2*, 51−54. (l) Kawagishi, H.; Shimada, A.; Shirai, R.; Okamoto, K.; Ojima, F.; Sakamoto, H.; Ishiguro, Y.; Furukawa, S. *Tetrahedron Lett.* **1994**, *35*, 1569−1572.

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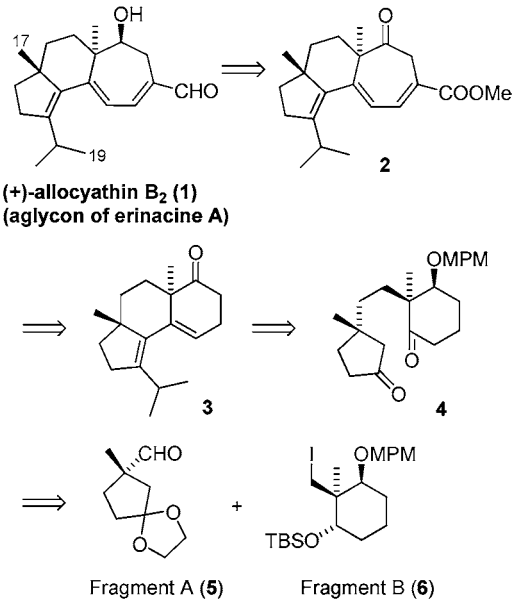
unusual 5−6−7 tricyclic carbon skeleton, including a *trans*-fused 6−7 ring system, and a common structural feature is two stereogenic quaternary carbons existing at its ring junctures.

On the other hand, the structural complexity and diversity arise from the different degrees 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 (Scheme 1). Furthermore, the striatins and erinacines possess a unique structure categorized as xylose conjugates of cyathins.

Scheme 1



Some compounds in this large cyathin family show strong antibiotic activity, and the erinacines[5j−l] and scabronines[6] have been shown to exhibit significant nerve growth factor (NGF) synthesis-stimulating activity. Moreover, erinacine E, one of the complex members of this family, was recently shown to have not only potent NGF synthesis-stimulating activity but also κ-opioid receptor agonist activity.[5h] Since NGF does not cross the blood-brain barrier (BBB) and this native peptide is rapidly metabolized in vivo,[7a] the use of small nonpeptide stimulators of NGF synthesis is perceived as a promising way to treat such neurodegenerative diseases as Alzheimer, Parkinson, and Huntington diseases.[7b−d]

The structural complexity and biological activity of the cyathins described above have drawn much attention to their synthesis, and several groups have developed different approaches to construct these attractive natural products.[8] To date, four total syntheses of cyathins have been reported; however, three of them, allocyathin B_2,[8i−k] B_3,[8a,d] and sarcodonin G,[8f] have been synthesized as a racemate. Snider reported the first synthesis of (+)-erinacine A,[8j,k] which was derived from (±)-allocyathin B_2 and (+)-xylose. Thus, no enantioselective synthesis of cyathins has been accomplished. We report herein the enantioselective total synthesis of (+)-allocyathin B_2 (**1**) through highly convergent and enantioselective construction of the 5−6−7 tricyclic core system using chiral building blocks prepared via asymmetric catalysis.

Since **1** has been derived from **2**,[8j,k] our own strategy for the synthesis of **1** is based on the retrosynthetic analysis of **2** illustrated in Scheme 1. We envisioned that **2** could be derived from **3** via installation of the ester group, followed by iodomethylation, samarium diiodide-mediated ring expansion, and subsequent introduction of the double bond. Tricyclic compound **3** would arise from diketone **4** via the intramolecular aldol reaction, followed by dehydration, installation of the isopropyl group, and dehydration. Then, **4** was disconnected to two chiral fragments, Fragments A (**5**) and B (**6**). Fragments A and B would be readily prepared via our established asymmetric catalysis for chiral building blocks;[9,10] hence, we started to prepare Fragment A via the catalytic asymmetric intramolecular cyclopropanation reaction[9] and Fragment B via baker's yeast reduction.[10]

Enantiomerically pure **7** (Scheme 2),[11] which had been prepared by the catalytic asymmetric intramolecular cyclopropanation of the corresponding α-diazo-β-keto sulfone, was reacted with thiophenol (99%), and the mesityl sulfonyl group was selectively removed by lithium naphthalenide[12] with the thiophenyl group remaining intact to generate **8** (86%). Formation of ethylene ketal (91%), following oxidation with *m*-chloroperbenzoic acid to the corresponding sulfoxide (quantitative), and Pummerer rearrangement afforded Fragment A (**5**) (87%).

As shown in Scheme 3, preparation of Fragment B (**6**) commenced with diol **9** (>99% ee), which was available by

(6) (a) Obara, Y.; Nakahata, N.; Kita, T.; Takaya, Y.; Kobayashi, H.; Hosoi, S.; Kiuchi, F.; Ohta, T.; Oshima, Y.; Ohizumi, Y. *Eur. J. Pharm.* **1999**, *370*, 79−84. (b) Kita, T.; Takaya, Y.; Oshima, Y.; Ohta, T.; Aizawa, K.; Hirano, T.; Inakuma, T. *Tetrahedron* **1998**, *54*, 11877−11886. (c) Ohta, T.; Kita, T.; Kobayashi, N.; Obara, Y.; Nakahata, N.; Ohizumi, Y.; Takaya, Y.; Oshima, Y. *Tetrahedron Lett.* **1998**, *39*, 6229−6232.

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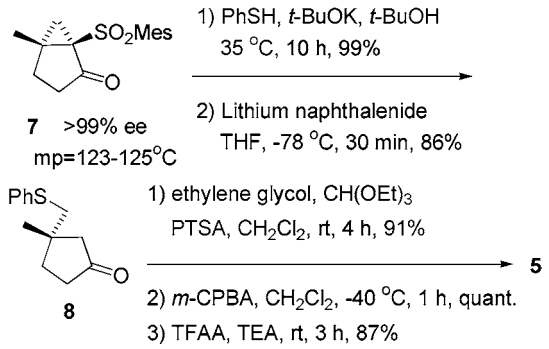
(10) Iwamoto, M.; Kawada, H.; Tanaka, T.; Nakada, M. *Tetrahedron Lett.* **2003**, *44*, 7239−7243.

(11) Enantiomerically pure **7** was easily obtained by recrystallization due to its highly crystalline nature.

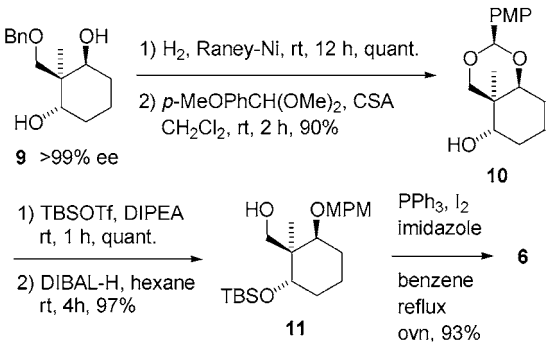
(12) Freeman, P. K.; Hutchinson, L. L. *J. Org. Chem.* **1980**, *45*, 1924−1930. Sodium amalgam, magnesium, and SmI_2 gave fruitless results.

Scheme 2



our established method,[10] that is, baker's yeast-mediated reduction and subsequent stereoselective reduction with $Me_4NBH(OAc)_3$. Removal of the benzyl ether of **9** by hydrogenolysis (quantitative) and subsequent formation of anisylidene gave **10** as the sole product (90%).[10] Formation of TBS ether (quantitative) and subsequent regioselective reduction of the anisylidene group by DIBAL-H afforded **11** (97%). Finally, alcohol **11** was converted to Fragment B (**6**) under the conventional conditions (93%).

Scheme 3



With Fragments A and B in hand, coupling of these fragments was executed (Scheme 4). Fragments B was treated with *t*-BuLi in Et_2O, and the resulting organolithium compound was reacted with Fragment A to generate **12** (41%); use of a mixture of Et_2O/THF (10:1) as a solvent greatly improved the yield to 79%.[13] **12** was converted to methyl xantate **13** (91%), followed by tin-hydride reduction[14] to produce **14** (89%). Both protective groups in **14**, TBS ether and ethylene ketal, were cleanly removed under the acidic conditions (quantitative), and subsequent Dess−Martin oxidation formed diketone **4** (93%).

Now, the stage was set for the intramolecular aldol reaction to form the six-membered ring, which is the central part of the cyathane skeleton. This reaction was challenging because both reaction points in the electrophile moiety and in the nucleophile moiety are next to the quaternary carbon. The preliminary studies on this reaction using a base in protic solvent[15] revealed that this reaction attained equilibrium between **4** and **15** probably due to the retro-aldol reaction. Accordingly, the reaction in aprotic solvent was next examined. Although no reaction occurred with amines,[16] use of potassium *t*-butoxide in benzene gratifyingly improved the yield to 94%.[17]

Dehydration of **15** with thionyl chloride and pyridine afforded a separable mixture of **16** (71%) and **17** (11%),[18] and **16** was reacted with isopropenyllithium to afford **18** (72%, at 61% conversion). Hydrogenation of the isopropenyl group and hydrogenolysis of the MPM group took place in a one-pot operation (96%), and the following Dess−Martin oxidation generated **19** (92%). Dehydration of **19** with thionyl chloride and pyridine afforded a mixture of regioisomeric alkenes; however, refluxing this mixture in benzene in the presence of *p*-toluenesulfonic acid successfully caused complete isomerization of the nonconjugated diene to afford **3** (77%, two steps).

Ring expansion of the cyclohexenone moiety of **3** employed Hasegawa's method[8f,19] because this method could easily generate the requisite ring-expanded γ-keto ester **21**. For this purpose, **3** was first converted to the corresponding β-keto ester using Mander's reagent (87%),[20] followed by iodomethylation[21] to produce **20** as a single stereoisomer (86%).[22] Exposure of **20** to samarium diiodide effectively caused ring expansion to furnish the desired γ-keto ester **21** as a mixture of diastereomers (91%, 1.9:1).

To introduce the double bond into **21**, such known one-pot methods as those using $(PhSeO)_2O$[23] or IBX[24] were examined; however, no products were obtained. Hence, we decided to find new conditions for the conversion from **21** to **2**. After several attempts, we successfully found that the dienolate formed from the keto-ester **21** could be converted to **2**. That is, **21** was first treated with excess LDA (5.0 equiv) in THF, and then the generated dienolate of **21** was treated with iodine (2.0 equiv) to afford **2** in a one-pot operation (71%). This one-pot reaction would involve the isomerization

(13) **12** was obtained as a mixture of diastereomers in ratios of 1.3:1 in Et_2O and 1:2 in Et_2O/THF.

(14) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574−1586.

(15) Intramolecular aldol reaction of **4** by K_2CO_3 in ethanol at reflux temperature afforded a mixture of **4** (42%) and **15** (47%).

(16) DBU and 1,1,3,3-tetramethylguanidine were tested.

(17) Molecular modeling suggests that this dramatic change could arise from the chelate formed between the hydroxyl and the keto groups of **15** with a potassium cation. Structure of **15** was elucidated as shown in Scheme 4 by X-ray crystallographic analysis. The CIF file is available; see Supporting Information.

(18) Dehydration of **15** with PTSA (cat.) produced only the MPM-deprotected **17** (45%).

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(20) Mander, L. N.; Sethi, S. P. *Tetrahedron Lett.* **1983**, *24*, 5425−5428.

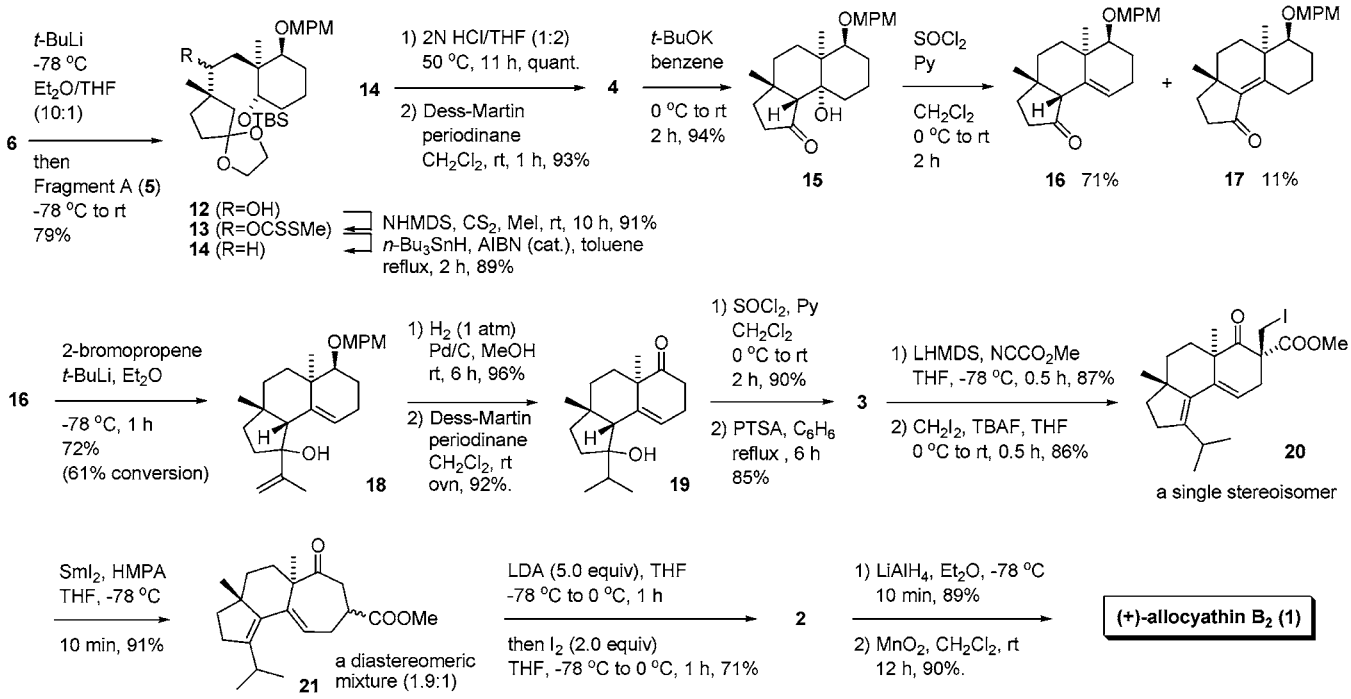
(21) Clark, J. H.; Miller, J. M. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1743−1745.

(22) Configuration was elucidated by NOE.

(23) Barton, D. H. R.; Lester, D. J.; Ley, S. V. *J. Chem. Soc., Chem. Commun.* **1978**, 130−131.

(24) (a) Nicolaou, K. C.; Zhong, Y.-L.; Baran, P. S. *J. Am. Chem. Soc.* **2000**, *122*, 7596−7597. (b) Nicolaou, K. C.; Montagnon, T.; Baran, P. S. *Angew. Chem., Int. Ed.* **2002**, *41*, 993−996. (c) Nicolaou, K. C.; Gray, D. L. F.; Montagnon, T.; Harrison, S. T. *Angew. Chem., Int. Ed.* **2002**, *41*, 996−1000.

Scheme 4



from the initially formed α,β-unsaturated ketone to the thermodynamically more stable β,γ-unsaturated ketone **2** via the enolate. This transformation is clean and easy to operate and, hence, would be advantageous for preparative purposes.

The known transformations from **2** to **1**,[8j,k] that is, stereoselective reduction of ketone and ester in **2** (89%) and selective oxidation of the resultant allylic alcohol with MnO_2 (90%), were successfully employed to complete the total synthesis of (+)-allocyathin B_2. Synthetic (+)-allocyathin B_2 proved to be identical in all respects to the reported spectral data (^{1}H NMR,[8j,k] IR,[1b] MS,[1b] $[\alpha]_D$,[1b] and ^{13}C NMR[8j,k]).

In summary, the enantioselective total synthesis of (+)-allocyathin B_2 has been achieved. This approach features the convergent enantioselective 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. Now envisioned in our laboratory is the development of a new access to the trans-fused 6−7 ring system of cyathins, which is surmised to be possible via the intermediate prepared in this synthesis. Further progress of our studies will be reported in due course.

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Supporting Information Available: Spectral data for all new compounds and X-ray data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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