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Enantioselective Total Synthesis of (−)-Erinacine B

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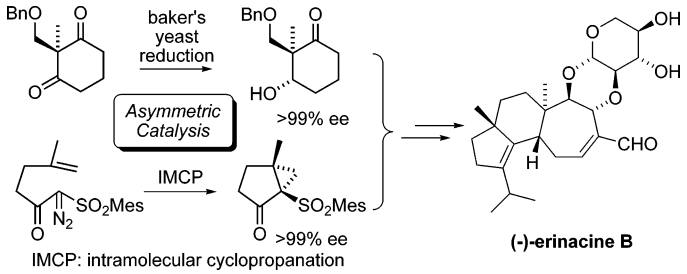
ABSTRACT



The first enantioselective total synthesis of (−)-erinacine B has been achieved. Our approach features convergent construction of the 5-6-7 tricyclic cyathane core system via chiral building blocks prepared using asymmetric catalysis developed by us and highly stereoselective construction of all stereogenic centers in the aglycon.

In 1994, Kawagishi et al. reported the isolation and structural elucidation of (−)-erinacines A, B, and C.[1a] (−)-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 located at the ring junctions. Erinacines and their congeners have been shown to exhibit significant activity in stimulating nerve growth factor (NGF) synthesis.[1,2]

Because of their structural complexity and significant biological activity, much attention has been given to the synthesis of erinacines, and several research groups have developed different approaches to the construction of these attractive polycyclic natural products.[3,4] To date, four total syntheses of cyathins[3a−f] as racemates[3c−f] or a product via optical resolution[3a,b] and four enantioselective total syntheses[4] have been reported; however, to our knowledge, no enantioselective total synthesis of a cyathane xyloside with a trans-fused 6-7 ring system such as erinacine has been reported. We report herein an enantioselective total synthesis of (−)-erinacine B in a convergent and highly stereoselective manner via chiral building blocks prepared using asymmetric catalysis developed by us.

Our synthetic strategy for (−)-erinacine B is based on the retrosynthetic analysis outlined in Scheme 1. Because it was

(1) (a) Kawagishi, H.; Shimada, A.; Shirai, R.; Okamoto, K.; Ojima, F.; Sakamoto, H.; Ishiguro, Y.; Furukawa, S. *Tetrahedron Lett.* **1994**, *35*, 1569−1572. For recently reported erinacines, see: (b) Kawagishi, H.; Masui, A.; Tokuyama, S.; Nakamura, T. *Tetrahedron* **2006**, *62*, 8463−8466. For natural products possessing a cyathane skeleton, see references cited in ref 4a.

(2) Kawagishi, H.; Furukawa, S.; Zhuang, C.; Yunoki, R. *Explore* **2002**, *11*, 46−51.

(3) (a) Snider, B. B.; Vo, N. H.; O'Neil, S. V.; Foxman, B. M. *J. Am. Chem. Soc.* **1996**, *118*, 7644−7645. (b) Snider, B. B.; Vo, N. H.; O'Neil, S. V. *J. Org. Chem.* **1998**, *63*, 4732−4740. (c) Tori, M.; Toyoda, N.; Sono, M. *J. Org. Chem.* **1998**, *63*, 306−313. (d) Piers, E.; Gilbert, M.; Cook, K. L. *Org. Lett.* **2000**, *2*, 1407−1410. (e) Ward, D. E.; Gai, Y.; Qiao, Q. *Org. Lett.* **2000**, *2*, 2125−2127. (f) Ward, D. E.; Gai, Y.; Qiao, Q.; Shen, J. *Can. J. Chem.* **2004**, *82*, 254−267. For recent synthetic studies, see: (g) Sato, A.; Masuda, T.; Arimoto, H.; Uemura, D. *Org. Biomol. Chem.* **2005**, *3*, 2231−2233. (h) Drege, E.; Morgant, G.; Desmaele, D. *Tetrahedron Lett.* **2005**, *46*, 7263−7266. For other synthetic studies, see references cited in ref 4a.

(4) (+)-Allocyathin B_2: (a) Takano, M.; Umino, A.; Nakada, M. *Org. Lett.* **2004**, *6*, 4897−4900. (b) Trost, B. M.; Dong, L.; Schroeder, G. M. *J. Am. Chem. Soc.* **2005**, *127*, 2844−2845. (c) Trost, B. M.; Dong, L.; Schroeder, G. M. *J. Am. Chem. Soc.* **2005**, *127*, 10259−10268. (+)-Cyanthiwigin U: (d) Pfeiffer, M. W. B.; Phillips, A. J. *J. Am. Chem. Soc.* **2005**, *127*, 5334−5335. (−)-Scabronine G: (e) Waters, S. P.; Tian, Y.; Li, Y.-M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2005**, *127*, 13514−13515.

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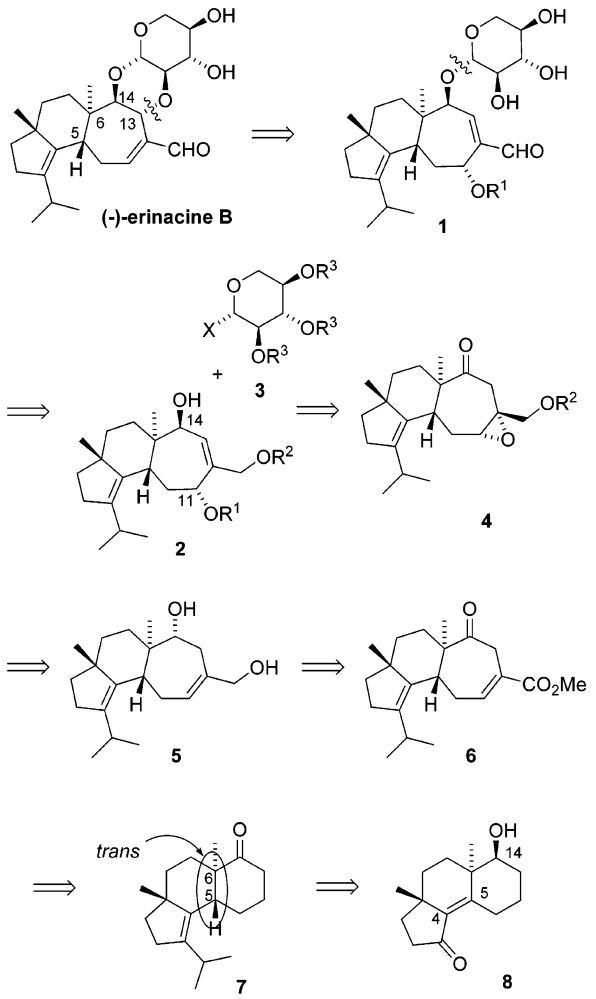
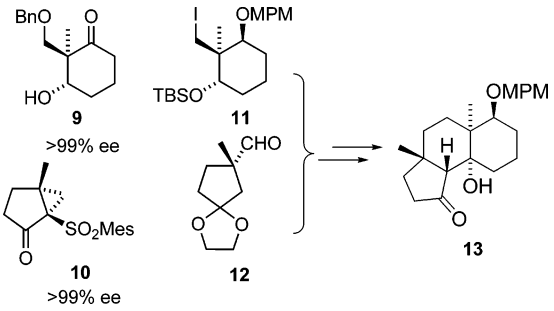
Scheme 1



Scheme 2



expected that (−)-erinacine B might be derived from **1** via a consecutive intramolecular 1,4-addition and β-elimination sequence,[5] we decided to prepare **1** by a glycosylation reaction of **2** with **3** and subsequent transformations. We envisioned that **2** would be obtained from **4** via a base-promoted β-elimination reaction and stereoselective reduction of the resulting ketone. Epoxide **4** was to be produced via stereoselective epoxidation of the homoallylic alcohol **5**, which could be prepared by stereoselective reduction of **6**. Tricyclic compound **6**, possessing a cyathane core, could be obtained from **7** by a ring-expansion reaction followed by installation of the double bond. It was expected that the trans C5−C6 stereochemistry in **7** could be attained by diastereoselective reduction of **8** utilizing the β-oriented hydroxyl at C14; hence, we commenced with asymmetric synthesis of **8**.

As shown in Scheme 2, we reported the preparation of enantiopure β-hydroxy ketone **13**[4a] via a coupling reaction of two fragments, **11** and **12**. These fragments were derived from **9** and **10** via highly enantioselective baker's-yeast-mediated reduction[6] and catalytic asymmetric intramolecular cyclopropanation,[7] respectively.

Consequently, the product **13** was dehydrated with thionyl chloride and pyridine (91%) (Scheme 3), followed by double bond isomerization using DBU (92%) and removal of MPM ether with DDQ to produce **8** (100%).

We expected that catalytic hydrogenation of alkene **8** would proceed diastereoselectively because the β-oriented hydroxyl group at C14 would direct the reaction; however, hydrogenation of **8** provided no product. We also attempted hydride reduction of **8** with various reagents, but no product or only the corresponding allylic alcohols were obtained.

Consequently, we next examined electron-transfer reduction of this enone system and found that Birch reduction of **8** afforded a mixture of **14** and its alcohol. After several attempts, we finally found that reduction of **8** with samarium diiodide in the presence of HMPA afforded **14** as a single product in 94% yield.[8] It should be noted that this diastereoselective reduction would arise from protonation of the anion generated at C5 by the β-oriented hydroxyl group at C14 because Birch reduction of the MOM ether of **8** gave the corresponding allylic alcohol as the major product.

Reaction of **14** 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 **15** (91%).

Dehydration of **15** by thionyl chloride and pyridine proceeded cleanly (100%), and double bond isomerization under acidic conditions generated ketone **7** with a thermodynamically stable alkene (100%).

The next task was to construct the 5-6-7 cyathane core from **7**, which required a one-carbon ring-expansion reaction. We employed Hasegawa's method[9] for this purpose because it was successfully applied in our first enantioselective total synthesis of (+)-allocyathin B_2.[4a] Thus, **7** was converted to the corresponding β-keto ester[10] using Mander's reagent

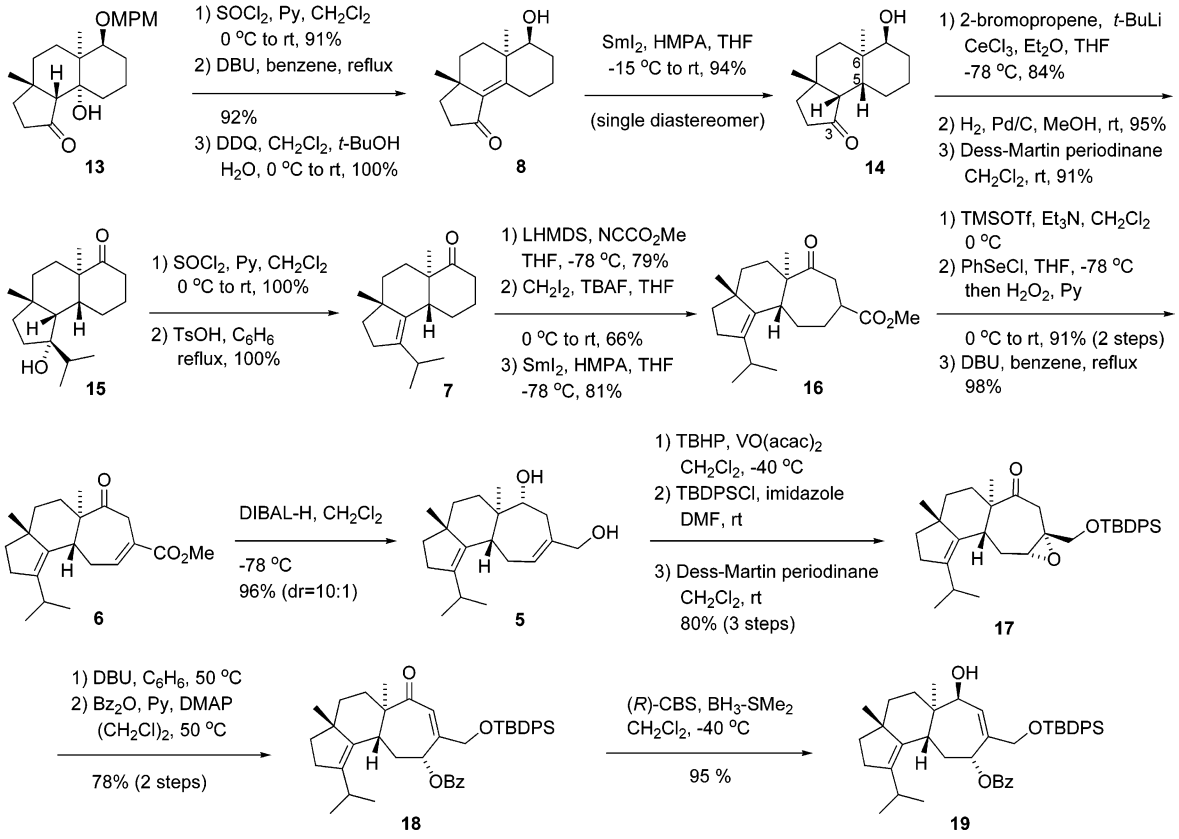
(5) Kenmoku, H.; Sassa, T.; Kato, N. *Tetrahedron Lett.* **2000**, *41*, 4389−4393.

(6) (a) Iwamoto, M.; Kawada, H.; Tanaka, T.; Nakada, M. *Tetrahedron Lett.* **2003**, *44*, 7239−7243. (b) Watanabe, H.; Iwamoto, M.; Nakada, M. *J. Org. Chem.* **2005**, *70*, 4652−4658.

(7) Honma, M.; Sawada, T.; Fujisawa, Y.; Utsugi, M.; Watanabe, H.; Umino, A.; Matsumura, T.; Hagihara, T.; Takano, M.; Nakada, M. *J. Am. Chem. Soc.* **2003**, *125*, 2860−2861.

(8) The structure of **14** was confirmed by the X-ray crystallographic analysis of the corresponding 3,5-dinitrobenzoate. See Supporting Information.

Scheme 3



(79%),[11] followed by iodomethylation (66%)[12] 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 **16** (81%, a mixture of diastereomers).

Introduction of the double bond to the seven-membered ring using the previously reported I_2/LDA method[4a] was low yielding, but reaction of the TMS enol ether of **16** with PhSeCl afforded an α-phenylselenyl ketone, which was oxidized to the corresponding selenoxide, followed by selenoxide fragmentation (91%, two steps) to install the double bond between the ketone and the ester in **16**. This double bond was easily isomerized by DBU to provide the desired compound **6** (98%).

DIBAL-H reduction of **6** exclusively provided a desired diol **5** (96%, dr = 10:1), followed by stereoselective epoxidation with TBHP/$VO(acac)_2$[13] 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 **17** (80%, three steps).

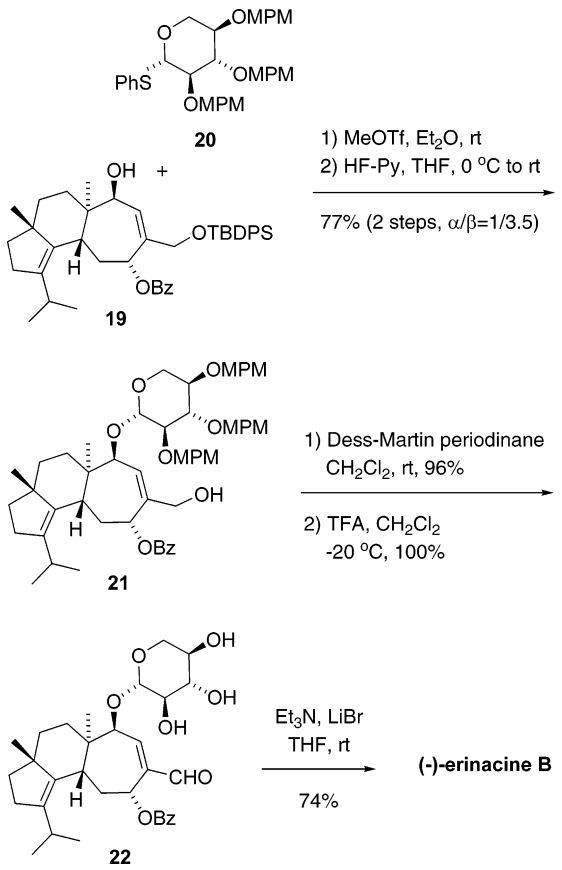
Treatment of **17** with DBU prompted a clean β-elimination reaction to provide the γ-hydroxy-α,β-unsaturated ketone, which was converted to benzoate **18** (78%, two steps) because we expected that the benzoyloxy group in **18** would be stable during the following transformations and would be a leaving group in the final consecutive intramolecular 1,4-addition and β-elimination reaction.

Diastereoselective reduction of **18** and its derivatives was investigated, but all reductions with readily available achiral reagents produced an undesired isomer as a major product. Consequently, we examined reagent-controlled stereoselective reduction and found that CBS-catalyzed reduction[14] of **18** successfully generated the desired alcohol **19** as the sole product (95%).

It was expected that glycosylation of **19** would be difficult to achieve because the hydroxyl group at C14 is highly hindered due to a quaternary carbon adjacent to C14 (Scheme 4). Most of the glycosylation reactions of **19** with several xylose derivatives under various conditions gave no glycosylated product; however, we finally found that **19** reacted with **20** in the presence of MeOTf[15] to provide the desired product, which was exposed to HF·Py to afford **21** as an inseparable mixture of anomeric isomers (77%, two steps, α/β = 1:3.5).[16]

(9) Hasegawa, E.; Kitazume, T.; Suzuki, K.; Tosaka, E. *Tetrahedron Lett.* **1998**, *39*, 4059−4062.
(10) This β-keto ester existed exclusively in its enol form.
(11) Mander, L. N.; Sethi, S. P. *Tetrahedron Lett.* **1983**, *24*, 5425−5428.
(12) Clark, J. H.; Miller, J. M. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1743−1745.
(13) Sharpless, K. B.; Michaelson, R. C. *J. Am. Chem. Soc.* **1973**, *95*, 6136−6137.
(14) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551−5553.
(15) Lönn, H. *J. Carbohydr. Chem.* **1987**, *6*, 301−306.
(16) The ratio was determined by 400 MHz ^{1}H NMR.

Scheme 4



Dess−Martin oxidation of **21** cleanly provided the corresponding aldehyde (96%), but subsequent removal of all MPM groups with DDQ was troublesome and afforded a complex mixture of products. After several attempts, we found that exposure of the substrate to TFA[17] in CH_2Cl_2 at −20 °C gratifyingly provided the key intermediate **22** (100%).

Finally, treatment of **22** with triethylamine and LiBr in THF, which were the conditions reported by Sassa,[5] furnished (−)-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.[1a]

In summary, the first enantioselective total synthesis of (−)-erinacine B has been achieved. Our approach features convergent construction of the 5-6-7 tricyclic cyathane core system via chiral building blocks prepared using asymmetric catalysis developed by us and highly stereoselective construction of all stereogenic centers in the aglycon. Further synthetic studies on other cyathanes are now in progress in our laboratory and will be reported in due course.

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Supporting Information Available: Experimental and characterization details (PDF, CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Yan, L.; Kahne, D. *Synlett* **1995**, 523−524.