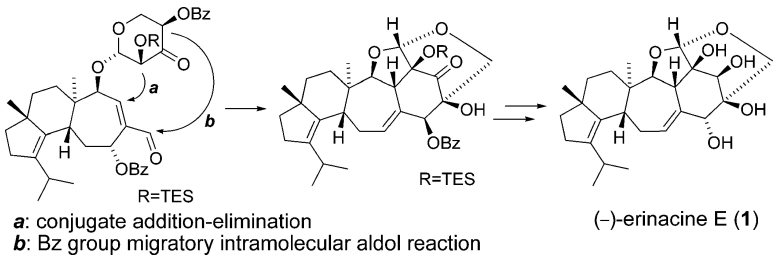
Communication

Biomimetic Total Synthesis of (–)-Erinacine E

Hideaki Watanabe, and Masahisa Nakada

J. Am. Chem. Soc., **2008**, 130 (4), 1150-1151 • DOI: 10.1021/ja7102795



a: conjugate addition-elimination
b: Bz group migratory intramolecular aldol reaction

More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Links to the 2 articles that cite this article, as of the time of this article download
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

J|A|C|S
COMMUNICATIONS

Published on Web 01/09/2008

Biomimetic Total Synthesis of (−)-Erinacine E

Hideaki Watanabe and Masahisa Nakada*

Department of Chemistry and Biochemistry, Advanced School of Science and Engineering, Waseda University, 3-4-1 Ohkubo, Shinjuku-ku, Tokyo 169-8555, Japan

Received November 13, 2007; E-mail: mnakada@waseda.jp

In 1996, (−)-erinacine E (**1**) (Figure 1) was reported to be a strong stimulator of nerve growth factor (NGF) synthesis from the mycelia of *Hericium erinaceum* whose fruiting bodies have been known as Chinese medicine or food.[1] Two years later, a Pfizer research group isolated **1** from a different source, the fermentation broth of *Hericium ramosum* CL24240, and disclosed that **1** was a potent, highly selective κ-opioid receptor agonist.[2]

Single-crystal X-ray crystallographic analysis unambiguously elucidated the absolute structure of **1**.[1] 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 **1** a strained and largely different compound compared with other cyathane diterpenoids and erinacines.[3]

Since striatals, exemplified as striatal A (**2**) and striatal D (**3**), and (−)-erinacine P (**4**) (Figure 1) have been isolated,[4] it was proposed that the C−C bond-forming reaction ***a*** (Scheme 1) between the C2′ and C13 positions of keto aldehyde **6**, which could be derived from **4**, could provide striatals, and subsequent intramolecular aldol reaction ***b*** (Scheme 1) between the C4′ and C15 positions could yield erinacines. However, to the best of our knowledge, none of these transformations have been reported.[5]

The complex structure, significant biological activity, and biogenesis of **1** are features that make it a fascinating target. Nevertheless, although enantioselective total syntheses of (+)-erinacine A,[6] (−)-erinacine B (**5**),[7] and some cyathane diterpenoids[8] have been published, the total synthesis of **1** has not been reported. Since we had already achieved the enantioselective total synthesis of **5** via enantiopure alcohol **7** (Scheme 2),[7] we investigated the enantioselective total synthesis of **1** via alcohol **7** and report herein the biomimetic total synthesis of **1**.

We first examined the glycosylation of alcohol **7** with thioglycoside **8**[9] (Scheme 2). The glycosylation with MeOTf[7,10] successfully provided glycoside **9** in 84% overall yield with high selectivity (α/β = 1/14) using the recycling technique.[11,12] Deprotection of glycoside **9** afforded diol **10** and subsequent Swern oxidation provided keto aldehyde **11**, which was found to be gradually converted in situ to ketone **12** as the sole product, probably due to the catalysis by Et_3N.[12]

We anticipated that the aldol reaction of ketone **12** 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 ketone **12** under any conditions resulted in no reaction or in decomposition,[13] suggesting that this process needed an exceptional procedure to provide the product.

Considering the structure of **2**, a proposed biosynthetic intermediate of **1**, we were inspired by the acetyl group at the C4′ position and we decided to examine the aldol reaction of ketone **17** possessing a benzoate at the C4′ position (Scheme 3).[14] Thus, we conceived that the enolate **18** generated from ketone **17** would

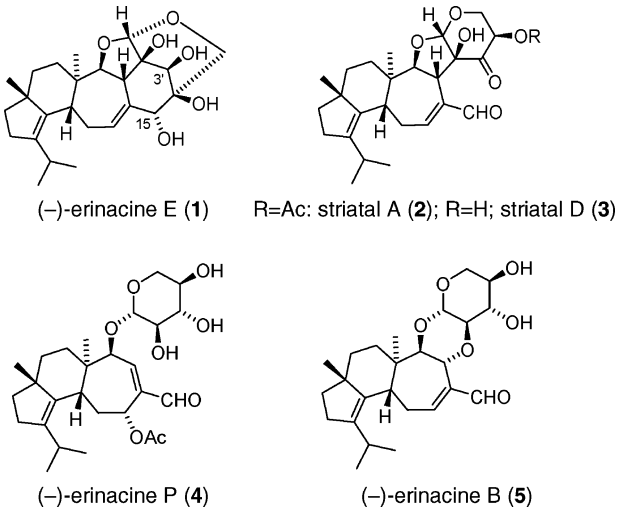
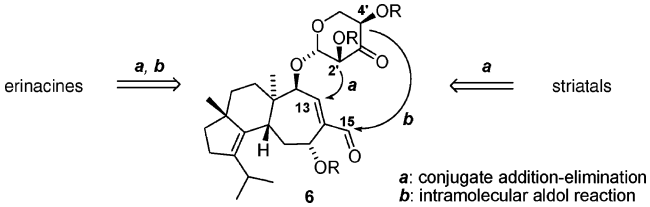


Figure 1. Structures of (−)-erinacine E (**1**), striatal A (**2**), striatal D (**3**), (−)-erinacine P (**4**), and (−)-erinacine B (**5**).

Scheme 1. Proposed Biosynthesis of Erinacines and Striatals



provide the initial aldol product **19**, in which the benzoyl group could migrate to the secondary C15 hydroxyl to provide stable ketone **20**, which would not revert to ketone **17**.

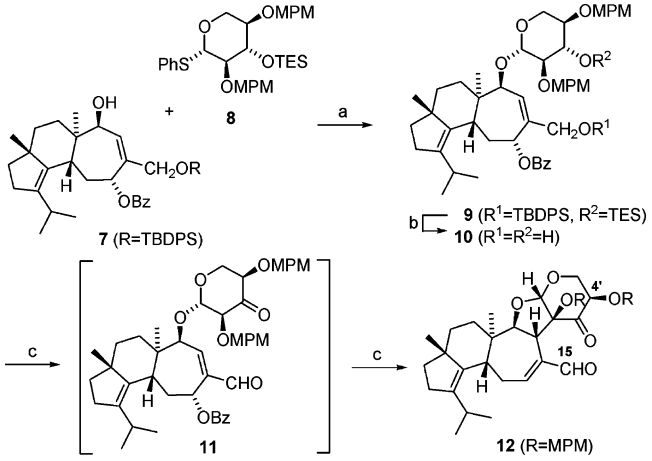
Deprotection of ketone **12** caused decomposition under any conditions, hence, ketone **17** was prepared from diol **10** (Scheme 3). Deprotection of diol **10** provided tetraol **13**, which was monoprotected with a TES group to provide a separable mixture of TES ethers **14** and **15**. Recycling TES ether **15** to tetraol **13** was successfully achieved. Selective benzoylation of TES ether **14**, subsequent deprotection of the C15 TES group, and Swern oxidation of the resultant diol to keto aldehyde **16**, followed by in situ cyclization/elimination gave ketone **17** directly.

Initial attempts of the intramolecular aldol reaction of ketone **17** using bases containing a metal cation (*t*-BuOK, LiBr/Et_3N, $CsCO_3$)[13] resulted in no reaction or decomposition. However, DBU effectively provided a product in 85% yield, and the detailed NMR studies[12] of the product confirmed its structure as ketone **20**, proving that the aldol reaction of ketone **17** proceeded as expected with concomitant 1,2-migration of the benzoyl group.

Reduction of ketone **20** with $NaBH_4$ occurred as anticipated at the less hindered side to provide alcohol **21**,[12] which was deprotected to afford diol **22**. Mitsunobu reaction of alcohol **22** did not proceed; hence, the oxidation and stereoselective reduction sequence

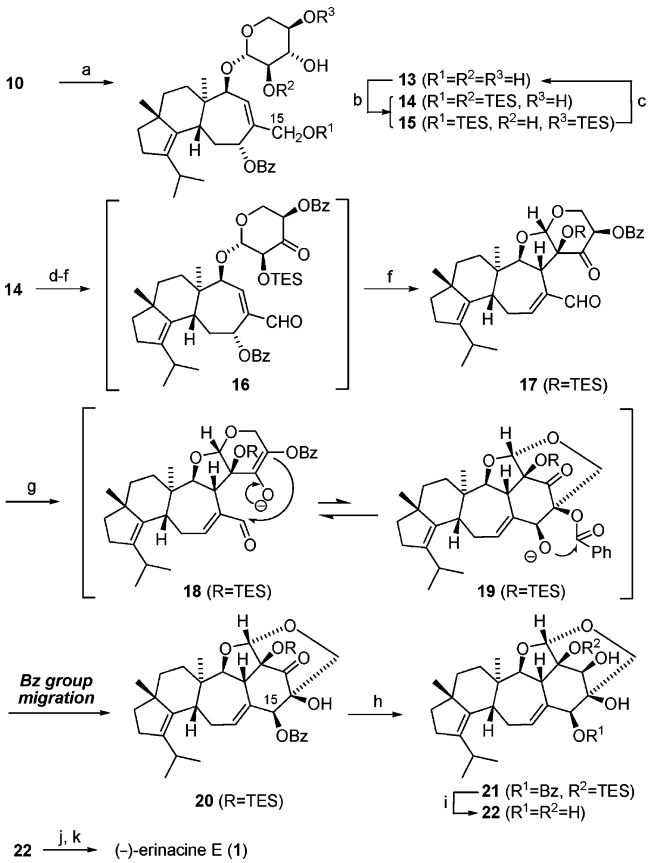
10.1021/ja7102795 CCC: $40.75

Scheme 2. Enantioselective Synthesis of **12**[a]



[a] Conditions: (a) MeOTf, Et_2O, MS 4 Å, room temp, 1 d, 84% (one recycling), (α/β = 1/14); (b) TBAF, NH_4Cl, room temp, 12 h; (c) DMSO, $(COCl)_2$, CH_2Cl_2, −78 °C, 2 h, then Et_3N, room temp, 12 h, 80% (two steps).

Scheme 3. Biomimetic Total Synthesis of **1**[a]



[a] Conditions: (a) TFA, CH_2Cl_2, −20 °C, 2 h, 93% from **9**; (b) TESCl, Et_3N, CH_2Cl_2, 0 °C, 2 h, **14** (44%), **15** (44%); (c) HF·Py, 0 °C to room temp, 1 h, 98%; (d) Bz_2O, Et_3N, DMAP (catalyst), CH_2Cl_2, 0 °C, 5 h, 92%; (e) 10% citric acid, saturated NH_4Cl, THF, room temp, 1.5 h, 91%; (f) DMSO, $(COCl)_2$, CH_2Cl_2, −78 °C, 2 h, then Et_3N, room temp, 12 h, 93%; (g) DBU, C_6H_6, room temp, 2 h, 85%; (h) $NaBH_4$, MeOH, −78 °C to 0 °C, 1 h; (i) K_2CO_3, MeOH, room temp, 2 h, 96% (two steps); (j) IBX, CH_2Cl_2, DMSO, room temp, 2 h; (k) $Me_4NBH(OAc)_3$, AcOH, CH_3CN, 0 °C, 30 min, 70% (two steps).

was investigated. *o*-Iodoxybenzoic acid (IBX) oxidation[15] of alcohol **22** 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 $Me_4NBH(OAc)_3$[16] was found to provide the desired 1,2-reduction product as a single isomer, which was identical to the natural product **1** in all respects (^{1}H NMR, IR, MS, $[\alpha]_D$, and ^{13}C NMR).[1]

In summary, highly stereoselective total synthesis of **1** has been achieved in 12 steps from the enantiopure alcohol **7**. The intramolecular aldol reaction of ketone **17**, 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 **1**. Considering the structure of a putative biosynthetic intermediate **2**, striatal A, the intramolecular aldol reaction driven by the C4′ acetyl group could be involved in the biosynthesis of **1**. This acyl group migratory ring-closing reaction would be applicable to the synthesis of other strained molecules.

Acknowledgment. This work is dedicated to Emeritus Professor Masaji Ohno (University of Tokyo, Japan) on the occasion of his 77th birthday. We thank Professor Yoshikazu Kawagishi (Shizuoka University, Japan) for kindly giving us copies of ^{1}H NMR and ^{13}C NMR of (−)-erinacine E. This work was financially supported in part by a Waseda University Grant for Special Research Projects, a Grant-in-Aid for Scientific Research on Priority Areas (No. 17035082), Young Scientists (No. 18850023), and the Global COE program "Center for Practical Chemical Wisdom" by MEXT.

Supporting Information Available: Complete ref 2. Experimental and characterization details. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) 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.
(2) IC_{50} values of **1** in the binding experiments of [^{3}H] CI-977, [^{3}H] DAGO, and [^{3}H] DPDPE (1 nM) to guinea pig brain membrane were 0.8 μM, >200 μM, and >200 μM, respectively. For the details, see: Saito, T.; et al. *J. Antibiot.* **1998**, *51*, 983−990.
(3) Recently isolated erinacines: Kawagishi, H.; Masui, A.; Tokuyama, S.; Nakamura, T. *Tetrahedron* **2006**, *62*, 8463−8466. For examples of erinacines isolated before this report, see ref. 7.
(4) (a) Anke, T.; Oberwinkler, F. *J. Antibiot.* **1977**, *30*, 221−225. (b) Hecht, H. J.; Hoefle, G.; Steglich, W.; Anke, T.; Oberwinkler, F. *J. Chem. Soc., Chem. Commun.* **1978**, 665−666. (c) Anke, T.; Rabe, U.; Schu, P.; Eizenhofer, T.; Schrage, M.; Steglich, W. *Z. Naturforsch., C: Biosci.* **2002**, *57*, 263−271.
(5) Kenmoku, H.; Sassa, T.; Kato, N. *Tetrahedron Lett.* **2000**, *41*, 4389−4393.
(6) (+)-Erinacine A: (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.
(7) (−)-Erinacine B: Watanabe, H.; Takano, M.; Umino, A.; Ito, T.; Ishikawa, H.; Nakada, M. *Org. Lett.* **2007**, *9*, 359−362.
(8) Enantioselective total synthesis of cyathane diterpenoids. (+)-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. (−)-Cyathin A_3: (f) Ward, D. E.; Shen, J. *Org. Lett.* **2007**, *9*, 2843−2846.
(9) For preparation of thioglycoside **8**, see Supporting Information.
(10) Lönn, H. *J. Carbohydr. Chem.* **1987**, *6*, 301−306.
(11) The glycosylation for 2 days afforded glycoside **9** in 73% yield (α/β = 1/7), but the reaction after 1 day gave glycoside **9** in 55% yield (α/β = 1/14) and recycling a recovered mixture of alcohol **7** and thioglycoside **8** provided glycoside **9** in 29% yield (α/β = 1/14).
(12) See Supporting Information for the detail.
(13) Stabilizing the product with a metal chelate was very effective in the total syntheses of (−)-erinacine B[7] and (+)-allocyathin B_2,[8a] but this method was fruitless in this synthesis.
(14) A benzoyl group was used because of its stability.
(15) Frigerio, M.; Santagostino, M. *Tetrahedron Lett.* **1994**, *35*, 8019−8022.
(16) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560−3578.

JA7102795