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Total Synthesis of (+)-Benzastatin E via Diastereoselective Grignard Addition to 2-Acylindoline

Narihiro Toda, Mayuko Ori, Kazuko Takami, Keiko Tago, and Hiroshi Kogen*

Exploratory Chemistry Research Laboratories, Sankyo Co., Ltd., 1-2-58 Hiromachi, Shinagawa-ku, Tokyo 140-8710, Japan

hkogen@shina.sankyo.co.jp

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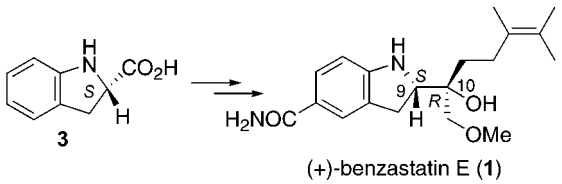
ABSTRACT



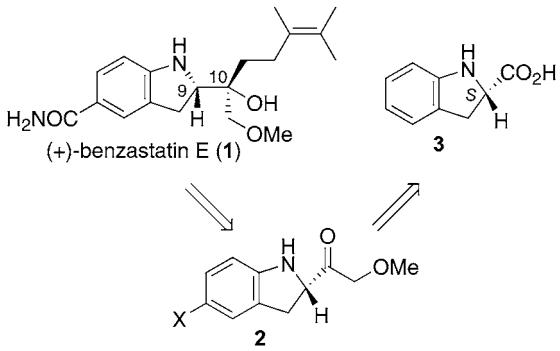
A stereoselective total synthesis of (+)-benzastatin E (1) is described. The synthesis involves a diastereoselective Grignard addition to 2-acylindoline 2, which is derived from commercially available (*S*)-2-indolinecarboxylic acid (3). The unknown absolute configuration of (+)-1 is determined as (9*S*,10*R*).

Benzastatin E (**1**) and its congeners, a family of indoline alkaloids that were isolated from *Streptomyces nitrosporeus* 30643 in 1997,[1] show neuronal cell protecting activity that can be used to prevent brain ischemia injury.[2] Benzastatin E (**1**) is the most potent inhibitor of glutamate toxicity using neuronal hybridoma N18-RE-10[5] among the benzastatin family.[1] The relative stereochemistry of benzastatin E (**1**) was elucidated by extensive NMR spectroscopic analysis.[1] However, the absolute stereochemistry of **1** was undetermined. Herein, we wish to report the first total synthesis of (+)-benzastatin E (**1**) and its absolute configuration.

The key step is a diastereoselective Grignard addition to 2-acylindoline **2**, which is readily prepared from commercially available (*S*)-(−)-indoline-2-carboxylic acid (**3**) as shown in Scheme 1.

Key intermediate 2-acylindoline **7** was prepared as shown in Scheme 2. Carboxylic acid **3** was treated with sulfuric acid in methanol, followed by nitrogen protection with di-*tert*-butyl dicarbonate to provide methyl ester **4** in 92% yield. Bromination of **4** with NBS (1 equiv) in DMF afforded bromide **5** in 93% yield. The bromide was converted to Weinreb amide[3] **6** by treatment with *N*,*O*-dimethylhydroxylamine hydrochloride and isopropylmagnesium chloride[4] in 83% yield. Coupling of methoxymethyllithium,[5] derived from Sn−Li exchange of methyl tributylstannylmethyl ether, with **6** afforded ketone **7** in 61% yield.

Scheme 1



(1) Kim, W. G.; Kim, J.-P.; Koshino, H.; Shin-Ya, K.; Seto, H.; Yoo, I.-D. *Tetrahedron* **1997**, *53*, 4309.

(2) Kim, W. G.; Kim, J. P.; Lim, C. J.; Lee, K. H.; Yoo, I. D. *J. Antibiot.* **1996**, *49*, 20. Kim, W. G.; Kim, J. P.; Yoo, I. D. *J. Antibiot.* **1996**, *49*, 26.

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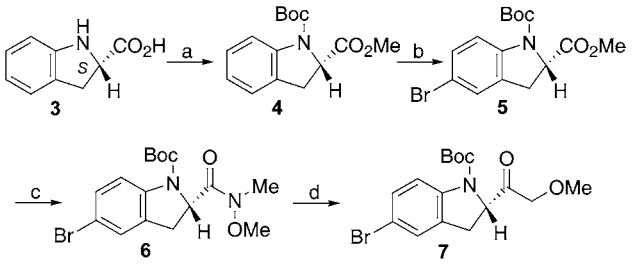
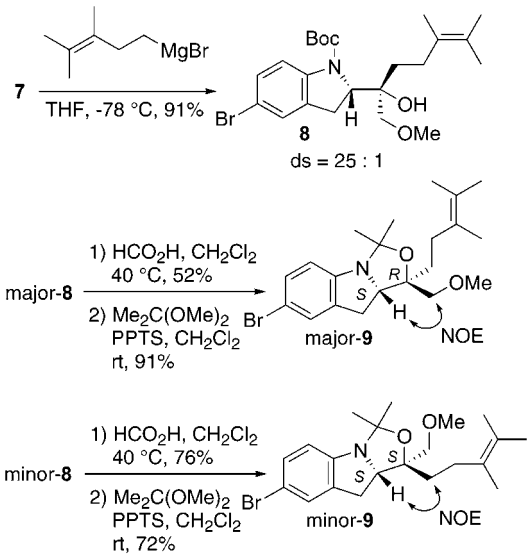
Scheme 2[a]



[a] Key: (a) (i) MeOH, H_2SO_4, 80 °C, (ii) Boc_2O, CH_2Cl_2, rt, 92% (two steps); (b) NBS, DMF, 0 °C, 93%; (c) *i*-PrMgCl, Me(MeO)-NH·HCl, THF, −20 to −10 °C, 83%; (d) $MeOCH_2Sn(n\text{-}Bu)_3$, *n*-BuLi, THF, −78 °C, 61%.

Construction of the *tert*-alcohol moiety was efficiently achieved by diastereoselective Grignard addition to **7**. Reaction of ketone **7** with 3,4-dimethyl-3-pentenylmagnesium bromide[6] in THF at −78 °C gave *tert*-alcohols in a 25:1 ratio of separable isomers major-**8** and minor-**8** as determined by HPLC analysis of the product mixture (Scheme 3). Configurations of the newly created stereo-

Scheme 3



centers in major-**8** and minor-**8** were determined with NOE experiments of the acetonides major-**9** and minor-**9**, which were derived from major-**8** and minor-**8** in a two-step sequence, respectively, as shown in Scheme 3. Thus, the absolute configuration of major-**8** was assigned as (9*S*,10*R*).

This diastereoselective Grignard addition was successfully extended to a variety of substrates and Grignard reagent combinations.[7] The results are summarized in Table 1. Inspection of the data in Table 1 demonstrates that the additions are quite diastereoselective. Moreover, as shown in runs 1 and 2, either diastereomer can be easily obtained by exchanging the order of the metal reagent addition to Weinreb amide. The enantiomer of **8** can also be readily prepared by using (*R*)-(+)-indoline-2-carboxylic acid[8] as a starting material (run 3). The chiral HPLC analysis[9] of **8a** shows that no racemization occurs during these manipulations (from **4** to **8**). The stereochemical outcome of these facially selective additions can be rationalized in terms of a Felkin−Anh model[10] as depicted in Figure 1.

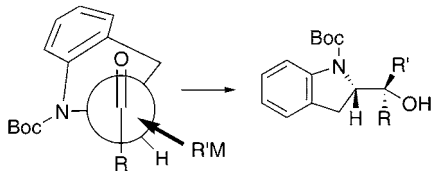
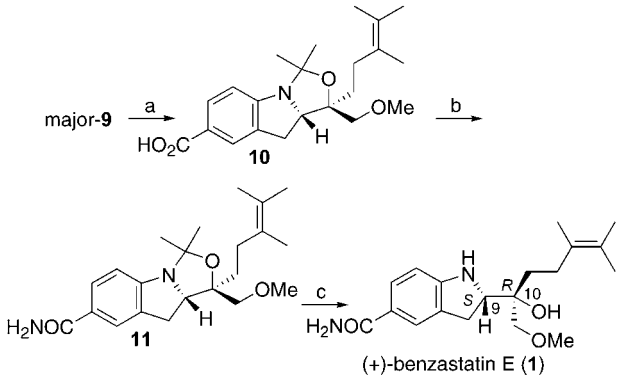


Figure 1.

Finally, total synthesis of (+)-**1** was accomplished in three steps from major-**9** as shown in Scheme 4. Conversion of

Scheme 4[a]

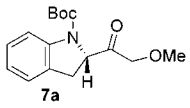
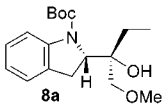
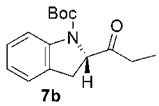
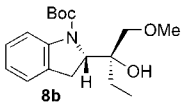
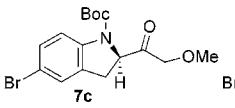
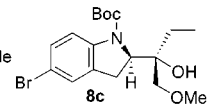
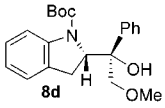
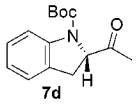
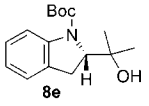
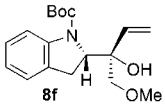
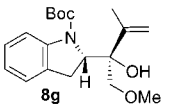
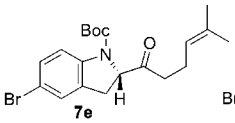
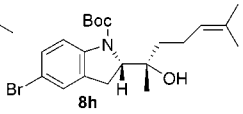
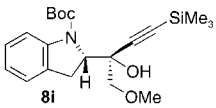
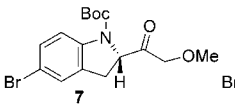
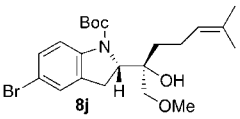
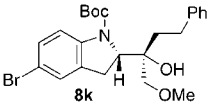
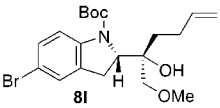


[a] Key: (a) *t*-BuLi, CO_2, Et_2O, −78 to 0 °C, 53%; (b) CDI, 28% aq NH_3, THF, rt, 74%; (c) PPTS, MeOH, rt, 64%.

major-**9** to the corresponding aryllithium species followed by carboxylation with CO_2 provided **10**. Amidation of **10** with aqueous ammonia and 1,1′-carbonyldiimidazole (CDI)

(3) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815.
(4) Williams, J. M.; Jobson, R. B.; Yasuda, N.; Marchesini, G.; Dolling, U.-H.; Grabowski, E. J. J. *Tetrahedron Lett.* **1995**, *36*, 5461.
(5) Kaufman, T. S. *Synlett* **1997**, 1377.
(6) De Silva, A. N.; Francis, C. L.; Ward, D. *Aust. J. Chem.* **1993**, *46*, 1657.
(7) Ding et al. reported the diastereoselective addition of lithium ethyl propiolate to an 2-acetylpyrrolidine derivative. Ni, Y.; Zhao, G.; Ding, Y. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3264.
(8) Gross, K. M. B.; Jun, Y. M.; Beak, P. *J. Org. Chem.* **1997**, *62*, 7679.
(9) DAICEL CHIRALCEL OD (0.46 cm ∅ × 25 cm), *n*-hexane−*i*-PrOH (95:5), 1 mL/min.
(10) Anh, N. T. *Top. Curr. Chem.* **1980**, *88*, 145.

Table 1. Diastereoselective Grignard Addition to 2-Acylindolines

run	substrate [a]	product [b]	yield [c,d]
1	 **7a**	 **8a**	57% (ds = 16:1)
2	 **7b**	 **8b**	86% (ds = 13:1)
3	 **7c**	 **8c**	75% (ds = 16:1)
4	**7a**	 **8d**	94% (ds = 15:1)
5	 **7d**	 **8e**	62%
6	**7a**	 **8f**	97% (ds = 12:1)
7	**7a**	 **8g**	100% (ds = 13:1)
8	 **7e**	 **8h**	47% (ds = 10:1)
9	**7a**	 **8i**	63% (ds = 38:1)
10	 **7**	 **8j**	67% (ds = 9:1)
11	**7**	 **8k**	68% (ds = 8:1)
12	**7**	 **8l**	82% (ds = 11:1)

[a] Readily prepared from the corresponding Weinreb amide and either Grignard reagent or alkyllithium by the same method for preparation of **7** except for **7c**. Substrate **7c** was prepared from (*R*)-(+)-indoline-2-carboxylic acid. [b] Absolute configuration of the major isomer was determined by NOE experiments of the corresponding acetonide derivative. [c] Isolated yield of a mixture of diastereoisomers. [d] Diastereomeric ratios determined by HPLC analysis of crude product mixtures.

gave amide **11**. Removal of the acetonide protecting group was effected by treatment of **11** with PPTS in MeOH to furnish (+)-benzastatin E (**1**) [$[\alpha]^{24}_{D}$ +21.3 (*c* 0.10, MeOH) (lit.[1] $[\alpha]^{18}_{D}$ +17 (*c* 0.1, MeOH))] in 64% yield. Spectral data (IR, ^{1}H NMR, and ^{13}C NMR) for synthetic (+)-**1** are identical to that reported for the natural product.

In summary, the first total synthesis of (+)-benzastatin E (**1**) has been accomplished in 11 steps from **3** via diastereoselective Grignard addition to **7**. The unknown absolute stereochemistry of (+)-**1** was determined as (9*S*,10*R*).

Supporting Information Available: Representative experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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