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Asymmetric Total Synthesis and Revised Structure of Cephalezomine H

Tsuyoshi Taniguchi, Shin'ichi Yokoyama, and Hiroyuki Ishibashi*

School of Pharmaceutical Sciences, Institute of Medical, Pharmaceutical and Health Sciences, Kanazawa University, Kakuma-machi, Kanazawa 920-1192, Japan

isibasi@p.kanazawa-u.ac.jp

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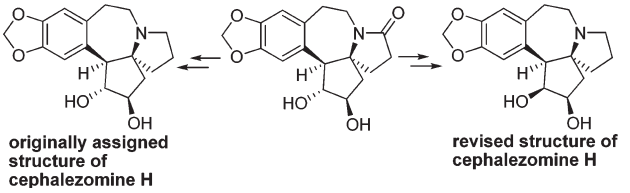

A revised structure of cephalezomine H, *Cephalotaxus* alkaloids, is presented. The originally assigned and revised structures of cephalezomine H were synthesized from the key intermediate for the synthesis of (−)-cephalotaxine.

Cephalezomines G and H were isolated from the leaves of *Cephalotaxus harringtonia* var. *nana* and their structures were elucidated by Kobayashi and co-workers (Figure 1).[1] It has been shown that these alkaloids have a 1,2-cyclopentanediol in the cephalotaxan skeleton and show cytotoxic activity against murine lymphoma L 1210 cells and human epidermoid carcinoma KB cells, respectively.[2]

We have recently reported a concise synthesis of optically active (−)-cephalotaxine (**8**) using a radical cascade that involves Bu_3SnH-mediated 7-*endo*-selective aryl radical cyclization of enamide **3**, prepared from diethyl D-tartrate, followed by 5-*endo-trig* cyclization of the resulting α-amidoyl radical to give **4** (Scheme 1).[3] *tert*-Butyldiphenylsilyl groups of the cyclized product **4** were removed and the resulting diol **5** was oxidized to give diketone **6**, which was then converted into (−)-cephalotaxine (**8**) through methylated compound **7**.

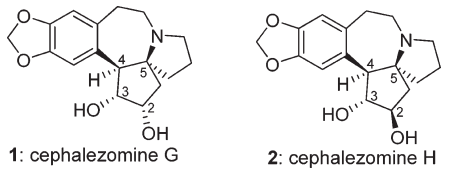

FIGURE 1. Originally assigned structure of cephalezomines G and H.

Subsequently, in the hope of obtaining cephalezomine H (**2**), we reduced the lactam carbonyl group of **5** with $LiAlH_4$, but ^1H NMR spectroscopic data of the synthesized compound did not match the literature values for compound **2**. We wish to report that the true structure of cephalezomine H is not **2** but **10**, whose hydroxy group at the 3-position is a β-orientation.

Reduction of **5** with $LiAlH_4$ gave compound **2** in 98% yield (Scheme 2). ^1H NMR spectroscopic data of **2** [(CD_3OD, 500 Mz) δ 2.74 (d, J = 9.8 Hz, 1H, H-4), 3.73−3.79 (m, 1H, H-2), 3.88 (dd, J = 9.5, 8.5 Hz, 1H, H-3)], however, did not agree with those reported for the originally assigned cephalezomine H [(CD_3OD, 600 MHz) δ 3.48 (d, J = 5.6 Hz, 1H, H-4), 4.16 (dd, J = 5.6, 4.9 Hz, 1H, H-3), 4.23 (m, 1H, H-2)].

The significant difference in the spin−spin coupling constant between H-3 and H-4 of the synthetic compound **2** (9.8 Hz) and reported cephalezomine H (5.6 Hz) prompted us to investigate the synthesis of compound **10** (Scheme 3).

Reduction of compound **6** with $NaBH_4$ gave, in 72% yield, diol **9**, the carbonyl group of which was reduced by alane to give the desired amine **10** in 52% yield. Compound **9** was also synthesized from **5** (vide infra). ^1H NMR spectroscopic data of **10** [(CD_3OD, 500 MHz) δ 3.25 (d, J = 5.9 Hz, 1H, H-4), 4.08 (t, J = 5.4 Hz, 1H, H-3), 4.11−4.16 (m, 1H, H-2)], however, again did not agree with the literature values for cephalezomine H. The signals of the ^1H NMR spectrum for cephalezomine H appeared in relatively low field. Therefore, trifluoroacetic acid salt of **10**, i.e., compound **11**, was prepared, whereupon, ^1H NMR spectral data of **11** [(CD_3OD, 500 MHz) δ 3.48 (d, J = 5.9 Hz, 1H, H-4), 4.17 (t, J = 5.1 Hz, 1H, H-3), 4.21−4.26 (m, 1H, H-2)] were found to be in good accord with the values reported for natural cephalezomine H.

It was reported that the isolation step of caphalezomine H included HPLC, using a mixture of 15% acetonitrile and 0.1% trifluoroacetic acid as a solvent.[1] This isolation step of caphalezomine H was probably due to obtaining a trifluoroacetic acid salt of this alkaloid.[4]

Kobayashi and co-workers made a stereochemical assignment of cephalezomine H by a comparison of the spectroscopic data of cephalezomine G (**1**).[1] H-3 of cephalezomine H was assigned as β-configuration on the basis of the similarity of $^1H-^1H$ spin coupling (5.6 Hz) between H-3

(1) Morita, H.; Yoshinaga, M.; Kobayashi, J. *Tetrahedron* **2002**, *58*, 5489.
(2) For reviews on Cephalotaxus alkaloids, see: (a) Weinreb, S. M.; Semmelhack, M. F. *Acc. Chem. Res.* **1975**, *8*, 158−164. (b) Huang, L.; Xue, Z. *The Alkaloids*: Academic Press: New York, 1984; Vol. 23, pp 157−226. (c) Jalil Miah, M. A.; Hudlicky, T.; Reed, J. W. *The Alkaloids*: Academic Press: San Diego, CA, 1998; Vol. 51, pp 199−269. (d) Hudlicky, T.; Reed, J. W. *The Way of Synthesis: Evolution of Design and Methods for Natural Products*; Wiley-VCH: Weinheim, Germany, 2007; Part 4.5, pp 655−687.
(3) Taniguchi, T.; Ishibashi, H. *Org. Lett.* **2008**, *10*, 4129.

(4) There are some cases in which alkaloids are isolated as a salt by using an acid. For example, Kibayashi and co-workers reported that a tricyclic marine alkaloid, lepadiformine, was isolated as hydrochloride salt in their total synthesis of this compound, see: Abe, H.; Aoyagi, S.; Kibayashi, C. *J. Am. Chem. Soc.* **2000**, *122*, 4583.

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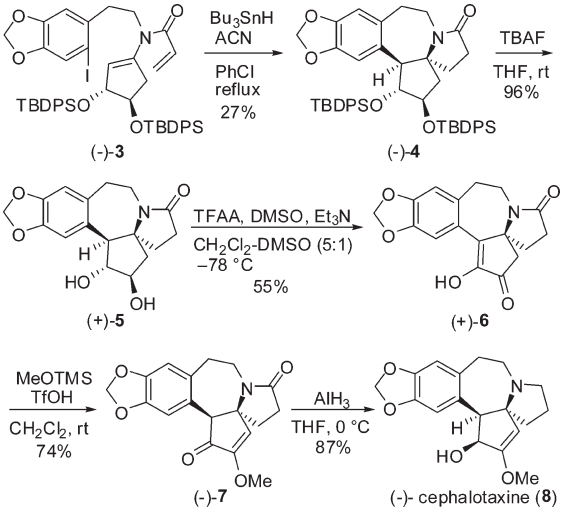
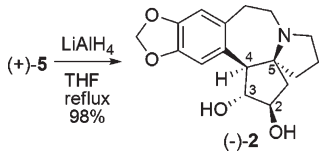
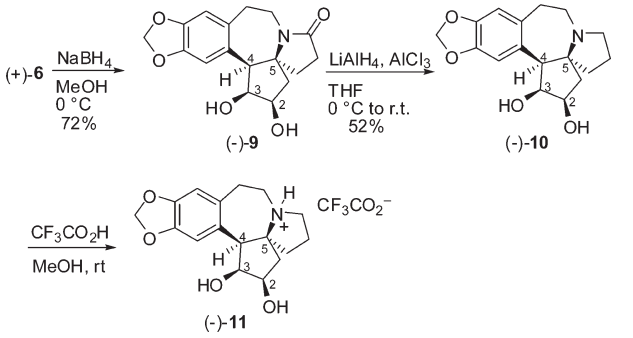
SCHEME 1. Synthesis of (−)-Cephalotaxine (8)



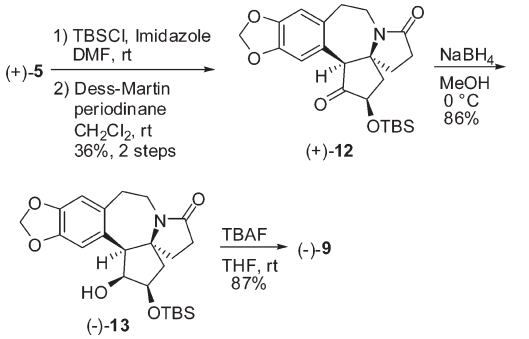
SCHEME 2. Reduction of 5



SCHEME 3. Synthesis of Cephalezomine H (10)



SCHEME 4. Independent Synthesis of Compound 9

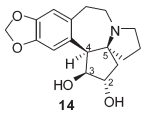


and H-4 to that (6.6 Hz) of cephalezomine G (**1**). If H-3 and H-4 of cephalezomine G (**1**) have a *trans*-configuration as shown in Figure 1 (H-3 being β-configuration and H-4 being α-configuration.), $^1H-^1H$ spin coupling between H-3 and H-4 might be ~10 Hz (for compound **2**, $J_{H\text{-}3,H\text{-}4}$ = 9.8 Hz: cf., for compound **10**, $J_{H\text{-}3,H\text{-}4}$ = 5.9 Hz), and hence the structure of **1** still remains to be solved.[5]

The structure of compound **9** was further confirmed by an independent synthesis from **5** (Scheme 4). Silylation of the less hindered OH group of **5** followed by oxidation with Dess−Martin periodinane[6] gave compound **12**. Reduction of the cyclopentanone ring of **12** with $NaBH_4$ followed by desilylation of the resulting **13** gave compound **9**.

If silylation of the OH group of **5** occurred at the 3-position, H-4 of the oxidation product might appear as a doublet, whereas H-4 of the observed compound **12** appeared as a singlet, and if hydride attack occurred on the β-face of the cyclopentanone ring of **12**, compound **5** might be recovered after desilylation.

(5) Synthesis of cephalezomine G (**1**) has already been reported for the total synthesis of cephalotaxine before isolation, see: (a) Burkholder, T. P.; Fuchs, P. L. *J. Am. Chem. Soc.* **1988**, *110*, 2341. (b) Isono, N.; Mori, M. *J. Org. Chem.* **1995**, *60*, 115. However, a comparison of the ^1H NMR spectra of the synthesized compound with that of the natural product was difficult due to the difference of the solvent used. We assumed that the true structure of cephalezomine G is (2*S*,3*S*,4*S*,5*S*)-2,3-dihydroxycephalotaxane (**14**).



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An attempt to convert compound **5** into compound **14** with use of the Mitsunobu reaction failed.

(6) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.

In summary, we have revealed that the true structure of cephalezomine H is not **2** but **10**. The optical rotations of compounds **10** and **11** were $[\alpha]_D$ −132 (*c* 0.1, MeOH) and $[\alpha]_D$ −30 (*c* 0.3, MeOH), respectively, whereas that of natural cephalezomine H was $[\alpha]_D$ +58 (*c* 0.9, MeOH).[1] The reason for this difference in symbols (− and +) for the optical rotation of synthesized and natural cephalezomine H is, however, unknown at present

Experimental Section

(2*R*,3*R*,4*S*,5*S*)-2,3-Dihydroxycephalotaxane (2). To a solution of lactam **5** (50 mg, 0.16 mmol) in THF (2 mL) was added $LiAlH_4$ (30 mg, 0.79 mmol) at 0 °C and the mixture was heated at reflux for 60 min. After the solution was cooled to 0 °C, a few drops of a saturated NH_4Cl solution were added and the mixture was filtered through a pad of Celite. The solvent was removed under reduced pressure and the residue was purified by column chromatography on alumina ($MeOH/CH_2Cl_2$, 1:10) to give **2** (47 mg, 98%), mp 173−174 °C: $[\alpha]^{23}_D$ −60 (*c* 0.2, MeOH); ^1H NMR (500 MHz, CD_3OD) δ 1.55−1.70 (m, 4H), 1.83 (t, *J* = 11.7 Hz, 1H), 1.91 (t, *J* = 8.3 Hz, 1H), 2.29−2.35 (m, 1H), 2.48−2.55 (m, 2H), 2.74 (d, *J* = 9.8 Hz, 1H), 2.78−2.86 (m, 2H), 3.02−3.10 (m, 1H), 3.73−3.79 (m, 1H), 3.88 (dd, *J* = 9.5, 8.5 Hz, 1H), 5.77 (br s, 2H), 6.51 (s, 1H), 6.62 (s, 1H); ^{13}C NMR (500 MHz, CD_3OD) δ 20.2, 31.7, 32.8, 44.6, 54.4, 61.7, 63.9, 76.0, 82.5, 102.0, 111.4, 113.2, 131.7, 133.3, 147.6, 147.9; HRMS (EI) *m*/*z* calcd for $C_{17}H_{21}NO_4$ 303.1471, found 303.1473.

(2*R*,3*S*,4*S*,5*S*)-2,3-Dihydroxy-8-oxocephalotaxane (9): Preparation from 6. A solution of diketone **6** (30 mg, 0.096 mmol) in MeOH (1 mL) was treated with $NaBH_4$ (36 mg, 0.96 mmol) at 0 °C, and the mixture was stirred at the same temperature for 60 min. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel (AcOEt/acetone, 1:1) to give **9** (22 mg, 72%),

mp 116−117 °C: $[\alpha]^{25}_{D}$ −103 (*c* 0.02, MeOH); IR ($CHCl_3$) ν 1674 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 1.90 (dd, J = 12.0, 6.1 Hz, 1H), 2.07−2.14 (m, 2H), 2.17−2.23 (m, 2H), 2.47 (ddd, J = 14.5, 6.1, 1.8 Hz, 1H), 2.63 (t, J = 12.2 Hz, 1H), 3.20 (dd, J = 12.9, 6.3 Hz, 1H), 3.32 (d, J = 5.9 Hz, 1H), 3.92 (td, J = 13.0, 6.2 Hz, 1H), 4.07 (td, J = 14.3, 6.9 Hz, 1H), 4.12 (t, J = 5.1 Hz, 1H), 4.17−4.21(m, 1H), 5.86 (br s, 2H), 6.65 (s, 1H), 6.68 (s, 1H); ^{13}C NMR (500 MHz, CD_3OD) δ 30.5, 31.5, 40.0, 40.6, 41.2, 61.7, 68.2, 71.9, 77.4, 102.2, 111.3, 113.0, 130.7, 134.3, 147.6, 148.2 177.6; HRMS (EI) m/z calcd for $C_{17}H_{19}NO_5$ 317.1263, found 317.1266.

Preparation from 13. To a solution of **13** (31 mg, 0.07 mmol) in THF (1 mL) was added a 1.0 M solution of tetrabutylammonium fluoride (TBAF) in THF (0.09 mL, 0.09 mmol) at room temperature and the mixture was stirred at the same temperature for 2 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel (AcOEt/acetone, 1:1) to give **9** (20 mg, 87%), whose physical data were identical with those of the compound obtained from **6**.

(2*R*,3*S*,4*S*,5*S*)-2,3-Dihydroxycephalotaxane (10). To a solution of **9** (20 mg, 0.06 mmol) in THF (1 mL) were added successively $AlCl_3$ (67 mg, 0.5 mmol) and $LiAlH_4$ (28 mg, 0.76 mmol) at 0 °C, and the mixture was stirred at the same temperature for 60 min. The reaction mixture was quenched with 3 drops of water and the mixture was filtered through a pad of Celite. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel ($MeOH/CH_2Cl_2$, 1:10) to give **10** (10 mg, 52%), mp 70−71 °C: $[\alpha]^{25}_{D}$ −132 (*c* 0.1, MeOH); ^1H NMR (500 MHz, CD_3OD) δ 1.64−1.80 (m, 4H), 2.02 (t, J = 9.0 Hz, 1H), 2.13 (t, J = 11.7 Hz, 1H), 2.36 (dd, J = 14.6, 6.3 Hz, 1H), 2.47−2.53 (m, 1H), 2.65 (dd, J = 11.5, 7.6 Hz, 1H), 2.91−2.99 (m, 2H), 3.25 (d, J = 5.9 Hz, 1H), 4.04 (td, J = 14.2, 8.3 Hz, 1H), 4.08 (t, J = 5.2 Hz, 1H), 4.11−4.16 (m, 1H), 5.85 (br s, 2H), 6.65 (s, 1H), 6.68 (s, 1H); ^{13}C NMR (500 MHz, CD_3OD) δ 20.3, 30.7, 32.0, 33.3, 44.2, 55.4, 60.2, 67.5, 72.4, 77.2, 102.0, 111.2, 113.1, 131.3, 134.9, 147.4, 147.8; HRMS (EI) m/z calcd for $C_{17}H_{21}NO_4$ 303.1471, found 303.1467.

TFA Salt of (2*R*,3*S*,4*S*,5*S*)-2,3-Dihydroxycephalotaxane (11). Triofluoroacetic acid (TFA) (0.1 mL) was added to a solution of amine **10** in MeOH (1 mL) at 0 °C, and the mixture was stirred at the same temperature for 10 min. The solvent and an excess of TFA were removed under reduced pressure to give **11**. The existence of two diasteromers of **11**, which differ in the configuration on the nitrogen, was observed in the ^1H NMR and ^{13}C NMR spectra, mp 170−200 °C: $[\alpha]^{24}_{D}$ −30 (*c* 0.3, MeOH); IR ($CHCl_3$) ν 1682 cm^{-1}; ^1H NMR (500 MHz, CD_3OD, for major isomer) δ 1.90−1.95 (m, 2H), 2.00−2.03 (m, 1H), 2.04−2.20 (m, 1H), 2.36−2.46 (m, 3H), 2.57 (dd, J = 15.1, 6.3 Hz, 1H), 3.20 (td, J = 11.5, 6.3 Hz, 1H), 3.34 (d, J = 8.1 Hz, 1H), 3.41 (td, J = 12.9, 6.6 Hz, 1H), 3.48 (d, J = 5.9 Hz, 1H), 3.51−3.57 (m, 1H), 4.17 (t, J = 5.1 Hz, 1H), 4.21−4.26 (m, 1H), 4.27−4.35 (m, 1H), 5.94 (br s, 2H), 6.80 (s, 1H), 6.81 (s, 1H); ^{13}C NMR (500 MHz, CD_3OD, for major isomer) δ 19.3, 29.4, 34.6, 41.0, 55.5, 57.4, 71.5, 72.1, 76.6, 102.7, 112.0, 113.7, 128.6, 131.4, 148.8, 149.2; HRMS (EI) m/z calcd for $C_{17}H_{21}NO_4$ (for compound **10**) 303.1471, found 303.1465.

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Supporting Information Available: Experimental procedures for **12** and **13** and ^1H and ^{13}C NMR spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.