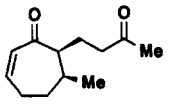
Asymmetric Synthesis of Clavularin A

Rui Tamura,*,† Ken-ichiro Watabe,† Noboru Ono,‡ and Yukio Yamamoto§

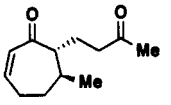
Department of Chemistry, Faculty of General Education, Ehime University, Matsuyama 790, Japan, Department of Chemistry, Faculty of Science, Ehime University, Matsuyama 790, Japan, and Graduate School of Human and Environmental Studies, Kyoto University, Kyoto 606, Japan

Received January 20, 1993

Clavularins A and B were originally isolated by Endo et al. from the Okinawa soft coral *Clavularin koellikeri* and showed significant cytotoxity and anticarcinogenicity.[1] The absolute configuration of clavularin B was unequivocally established by Kobayashi et al.,[2] whereas that of clavularin A was only estimated from the CD studies.[1] Recently, syntheses of (±)-clavularins A and B have been accomplished by Utrecht[3] and Still et al.,[4] respectively, although the former synthesis has been accompanied by the concomitant formation of 15% of the epimeric (±)-clavularin B. To our knowledge, there has been no report of stereoselective synthesis of optically active clavularins A and B, despite their simple structure. Here we describe the facile asymmetric synthesis of clavularin A with high enantio- (96% ee) and diastereoselectivity (94/6) by employing our recently reported methodology for the synthesis of optically active 3-substituted 2-*exo*-methylenecycloheptanones[5] and cis 2,3-disubstituted cycloheptanones.[6] Thus, the present work confirms the presumed absolute structure of clavularin A.[1]



Clavularin A



Clavularin B

Our synthetic approach to clavularin A is summarized in Scheme I. Requisite optically active 3-methyl-2-methylenecycloheptanone (3) was prepared in 87% chemical yield and 96% ee by addition–elimination reaction of 2, available from 1 and (*S*)-2-(methoxymethyl)pyrrolidine, with Me_2CuLi.[5] Addition of allyltrimethylsilane to 3 at −78 °C in the presence of 1 equiv of $TiCl_4$ in CH_2Cl_2[7] followed by protonation at −90 °C with various proton sources afforded a cis and trans mixture of 4 in different ratios almost quantitatively. As a consequence, the use of sterically hindered 2,4,6-collidine trifluoroacetate led to the highest cis selectivity (94/6) among proton sources such as H_2O (84/16), aqueous NH_4Cl (85/15), and AcOH (89/11). This result can be well correlated to kinetic protonation, where the least hindered approach of a sterically hindered proton donor to an enolate leads to the thermodynamically less stable stereoisomer.[6,8] The cis disubstituted cycloheptanone 4 containing 6% of the trans isomer was successively treated with LiTMP and PhSeCl[9] to provide the α-keto selenide 5. Usual oxidation of 5 with H_2O_2 in the presence of pyridine in CH_2Cl_2[9] gave the enone 6. Finally, the Wacker-type oxidation[10] of 6 resulted in the formation of clavularin A (7) with high cis selectivity (94/6) after PLC purification in overall 41% yield from 3. The CD spectrum of the obtained 7 showed a negative Cotton effect near 224 nm and a positive one near 339 nm ($[\theta]_{224}/[\theta]_{339} = -1.79$ in hexane), in good agreement with the reported pattern and value (−1.82) of clavularin A.[1]

Thus, natural-type (+)-clavularin A with high enantiomeric purity (96% ee) and diastereoselectivity (94/6) has been found to be simply produced by making use of our recently reported methodology for the stereoselective synthesis of optically active cis 2,3-disubstituted cycloheptanones.

Experimental Section

^1H NMR spectra were recorded in $CDCl_3$ solution containing TMS standard. Reactions were performed under an argon atmosphere, unless otherwise noted. All solvents were distilled before use.

Synthesis of Clavularin A. To a solution of (−)-(*S*)-3-methyl-2-methylenecycloheptanone (3) (0.152 g, 1.1 mmol) in CH_2Cl_2 (3 mL) was added dropwise $TiCl_4$ in CH_2Cl_2 (1 M solution, 1.1 mmol) and then allyltrimethylsilane (0.160 g, 1.4 mmol) in CH_2Cl_2 (3 mL) at −78 °C, and the resultant deep red-purple solution was stirred for 1 h at −78 °C. After the solution was cooled to −90 °C, a mixture of 2,4,6-collidine (0.412 g, 3.4 mmol) and CF_3COOH (0.388 g, 3.4 mmol) in THF (3 mL) was added dropwise to the reaction mixture. After the mixture was stirred for 30 min at −90 °C, 2 N HCl (30 mL) was added. The aqueous mixture was allowed to warm to 25 °C during 1 h and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phase was washed with saturated $NaHCO_3$ solution (2 × 30 mL) and brine (30 mL), dried over $MgSO_4$, and concentrated in vacuo, giving 0.200 g (ca. 100%) of the crude 4 in a high state of purity (>95%), as judged by capillary GC. The cis/trans ratio was also determined to be 94/6 by capillary GC.

4: ^1H NMR (60 MHz) δ 5.75 (m, 1H) and 5.15–4.72 (m, 2H) for CH=CH_2, 0.82 (d, J = 6.4 Hz, 3H) for Me.

A THF solution of LiTMP, prepared from 2,2,6,6-tetramethylpiperidine (0.170 g, 1.2 mmol) and *n*-BuLi (1.2 mmol) in THF (7 mL), was added dropwise to a solution of 4 (ca. 1.1 mmol) in THF (5 mL) at −78 °C, and the resultant yellow solution was stirred for 40 min at −78 °C. PhSeCl (0.229 g, 1.2 mmol) in THF (3 mL) was added at −78 °C. The reaction mixture was successively stirred for 30 min at −78 °C, allowed to warm to 0 °C during 1 h, and stirred for an additional 1 h at 0 °C. HCl (0.5 N, 30 mL) was added, and the aqueous mixture was extracted with ether (3 × 30 mL). The combined organic phase was washed with saturated $NaHCO_3$ solution (2 × 30 mL) and water (30 mL),

† Faculty of General Education, Ehime University.
‡ Faculty of Science, Ehime University.
§ Kyoto University.

(1) (a) Endo, M.; Nakagawa, M.; Hamamoto, Y.; Nakanishi, T. *J. Chem. Soc. Chem. Commun.* **1983**, 322 and 908. (b) Suntory Ltd., Jpn. Kokai Tokkyo Koho JP 5829,737 [8329,737]: *Chem. Abstr.* **1983**, *99*, 70287s.

(2) (a) Kobayashi, M.; Son, B. W.; Kido, M.; Kyogoku, Y.; Kitagawa, I. *Chem. Pharm. Bull.* **1983**, *31*, 2160; (b) **1984**, *32*, 1667.

(3) Utrecht, R. *J. Chem. Soc., Chem. Commun.* **1984**, 989.

(4) (a) Still, I.; Shi, Y. *Tetrahedron Lett.* **1987**, 2489. For the biomimetic synthesis from (±)-clavukerin A, see: (b) Kim, S. K.; Pak, C. S. *J. Org. Chem.* **1991**, *56*, 6829.

(5) Tamura, R.; Watabe, K.; Ono, N.; Yamamoto, Y. *J. Org. Chem.* **1992**, *57*, 4895.

(6) Tamura, R.; Watabe, K.; Kamimura, A.; Hori, K.; Yokomori, Y. *J. Org. Chem.* **1992**, *57*, 4903.

(7) (a) Hosomi, A.; Sakurai, H. *J. Am. Chem. Soc.* **1977**, *99*, 1673. (b) Sakurai, H.; Hasomi, A.; Hayashi, J. *Organic Syntheses*; Wiley: New York, 1990; Collect. Vol. VII, p 443.

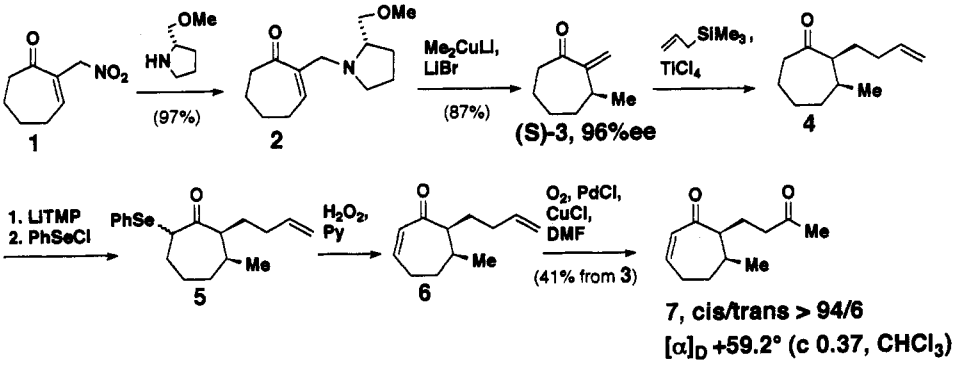
(8) For reviews, see: (a) Zimmerman, H. E. *Acc. Chem. Res.* **1987**, *20*, 263. (b) Duhamel, L.; Duhamel, P.; Launay, J.-C.; Plaquevent, J.-C. *Bull. Soc. Chem. Fr.* **1984**, 421.

(9) (a) Reich, H. J.; Renge, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97*, 5435. (b) White, J. D.; Fukuyama, Y. *Ibid.* **1979**, *101*, 226.

(10) (a) Tsuji, J.; Shimizu, I.; Yamamoto, K. *Tetrahedron Lett.* **1976**, 2975. (b) Tsuji, J.; Nagashima, H.; Nemoto, H. *Organic Syntheses*; Wiley: New York, 1990; Collect. Vol. VII, p 137.

0022-3263/93/1958-4471$04.00/0

Scheme I



dried over $MgSO_4$, and concentrated in vacuo, affording 0.380 g of **5** containing some impurities. Without purification, to the crude **5** (0.380 g) dissolved in CH_2Cl_2 (5 mL) containing pyridine (0.158 g, 2.0 mmol) was added dropwise 35% H_2O_2 (0.24 mL, 2.7 mmol) at 0 °C. After being stirred for 1 h at 25 °C, the reaction mixture was diluted with CH_2Cl_2 (30 mL), washed with 5% $NaHCO_3$ (2 × 30 mL), 2 N HCl (30 mL) and brine (30 mL), dried over $MgSO_4$, and concentrated in vacuo to give 0.132 g of the crude **6**.

6: ^1H NMR (270 MHz) δ 6.80 (ddd, J = 3.7, 7.0, 11.3 Hz, 1H), 6.08 (dd, J = 2.4, 11.3 Hz, 1H), 5.82 (m, 1H), 5.03 (d, J = 16.9 Hz, 1H), 4.98 (d, J = 9.4 Hz, 1H), 2.80 (ddd, J = 2.5, 6.2, 8.3 Hz, 1H), 2.47 (m, 2H), 2.12 (m, 2H), 2.03 (m, 2H), 1.78 (m, 2H), 1.46 (m, 1H), 0.88 (d, J = 6.6 Hz, 3H).

A stream of oxygen gas was bubbled through a mixture of $PdCl_2$ (0.027 g, 0.15 mmol) and CuCl (0.148 g, 1.5 mmol) in a mixed solvent of DMF (70 mL) and H_2O (10 mL) for 1 h with vigorous stirring. A solution of **6** (0.132 g) in a mixed solvent of DMF (17.5 mL) and H_2O (2.5 mL) was added, and the reaction mixture was stirred for 24 h at 25 °C under O_2 bubbling. HCl (2N, 100 mL) was added, and the aqueous mixture was extracted with ether (3 × 30 mL). The combined organic phase was washed with saturated $NaHCO_3$ solution (2 × 30 mL) and brine (30 mL), dried over $MgSO_4$, and concentrated in vacuo. PLC purification of the crude product gave 0.087 g (41%) of **7**. The cis/trans ratio was determined to be 94/6 by capillary GC. All spectral data of **7** showed good agreement with those of clavularin A.[1]

7: $[\alpha]_D$ +59.2° (c 0.37, $CHCl_3$); ^1H NMR (270 MHz) δ 6.76 (ddd, J = 3.9, 7.3, 11.6 Hz, 1H), 6.02 (dd, J = 2.5, 11.6 Hz, 1H), 2.81 (ddd, J = 4.3, 5.5, 9.8 Hz, 1H), 2.50 (ddd, J = 5.4, 9.0, 17.1 Hz, 1H), 2.43 (m, 2H), 2.29 (ddd, J = 6.3, 8.6, 17.1 Hz, 1H), 2.10 (s, 3H), 2.20–2.05 (m, 3H), 1.61 (m, 1H), 1.26 (m, 1H), 0.83 (d, J = 6.4 Hz, 3H); ^{13}C NMR (67.8 Hz) δ 208.8, 203.7, 148.6, 133.9, 54.1, 41.9, 35.7, 33.9, 29.9, 27.8, 22.3, 16.0.