

Communications to the Editor

[Chem. Pharm. Bull.]
36(10)4229—4231(1988)]

A TOTAL SYNTHESIS OF (+)-CEPHALOTAXINAMIDE

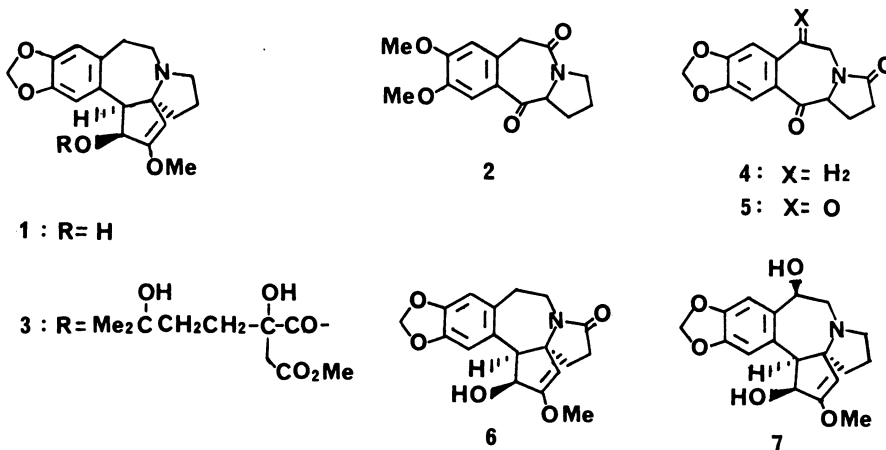
Shingo Yasuda, Youichi Yamamoto, Shuji Yoshida, and Miyoji Hanaoka*
Faculty of Pharmaceutical Sciences, Kanazawa University,
Takara-machi, Kanazawa 920, Japan

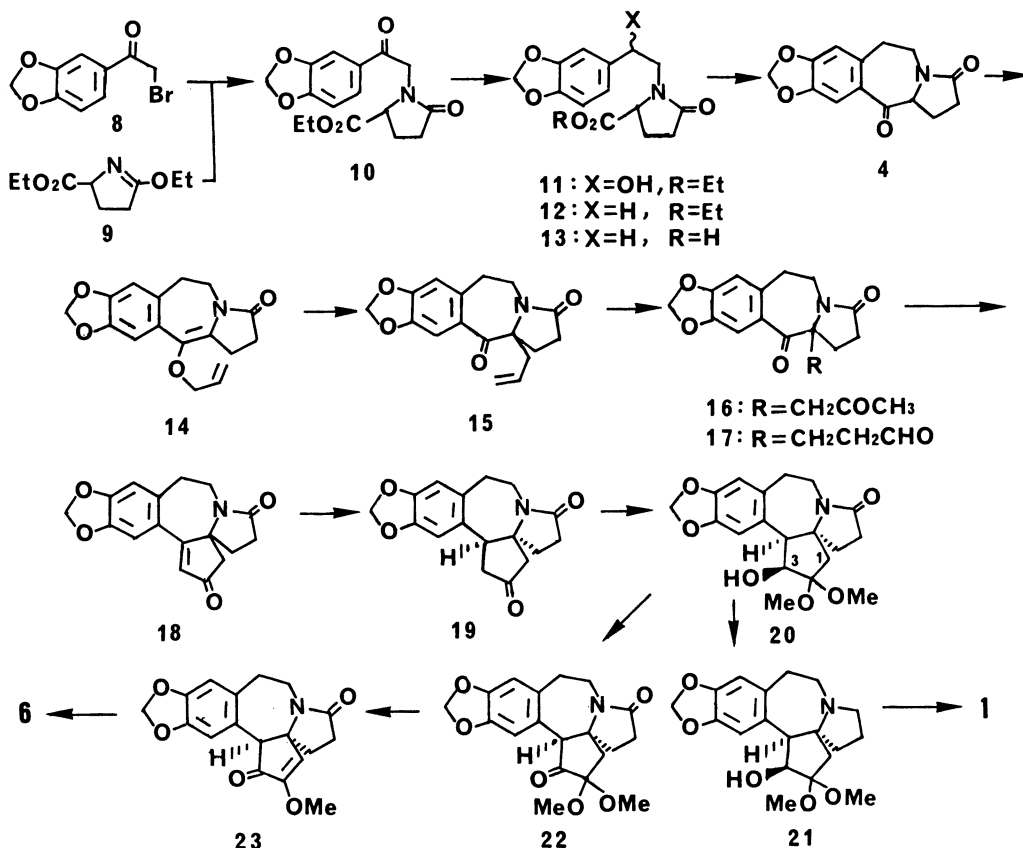
(+)-Cephalotaxinamide (6) was synthesized from pyroglutamic acid via the pyrrolobenzazepine (4) through the Claisen rearrangement, the Wacker oxidation, aldol condensation, and hydroxylation with iodosobenzene.

KEYWORDS — cephalotaxinamide; cephalotaxine; Cephalotaxus alkaloid; Claisen rearrangement; aldol condensation; Wacker oxidation; iodosobenzene

In a previous paper,¹⁾ we reported a stereoselective synthesis of cephalotaxine (1), a representative Cephalotaxus alkaloid,²⁾ through the pyrrolobenzazepine (2). Cephalotaxine has attracted many synthesis chemists because of its unique ring system and the significant antitumor activity of its ester derivatives such as harringtonine (3).²⁾ Among five total syntheses^{1,3~6)} of this alkaloid, our method may be one of the most practical. In order to improve the versatility of our method, we postulate new synthetic intermediates (4 and 5), which will provide not only cephalotaxine but also other Cephalotaxus alkaloids, cephalotaxinamide (6) and 11-hydroxycephalotaxine (7). We describe here a new synthesis of cephalotaxinamide, an alkaloid from *Cephalotaxus hainanensis*,⁷⁾ from 4. Recently cephalotaxinamide was synthesized in a different method.⁶⁾

Heating⁸⁾ of 3,4-methylenedioxybromoacetophenone (8) with the lactim ether (9), derived from ethyl pyroglutamate,⁹⁾ at 85°C for 4 h gave the amide ester (10)





(mp 122–124°C; ν 1740, 1680) in 80% yield. Sodium borohydride reduction of **10** in methanol at $-15 \sim -18^\circ\text{C}$ ¹⁰) afforded the alcohol (**11**, 98%) as a diastereoisomeric mixture which on catalytic hydrogenolysis over 10% Pd-C in acetic acid in the presence of 70% perchloric acid yielded the amide ester (**12**) (mp 90–92°C) in 82% yield. Saponification of **12** with potassium hydroxide in aqueous ethanol gave the carboxylic acid (**13**) (100%; mp 111–112°C). After several unsuccessful experiments using various reagents, **13** was cyclized by treating it with a large excess of trifluoroacetic anhydride and boron trifluoride etherate in 1,2-dichloroethane under reflux for 4 h to give efficiently the expected pyrrolobenzazepine (**4**) [75%; mp 172–175°C; m/z 259 (M^+); ν 1680; δ 7.27, 6.67 (each 1H, s)].

Treatment of **4** with allyl bromide in the presence of sodium hydride in dimethylformamide (DMF) afforded the enol-ether (**14**) (73%; mp 100–101°C) accompanied with the α -allyl derivative (**15**) (23%; mp 188–189°C). Heating of **14** at 120°C caused the Claisen rearrangement to give **15** in 80% yield. The Wacker oxidation¹¹) of **15** with PdCl₂-CuCl in wet DMF at 75°C in a stream of oxygen for 3.5 h gave the acetyl derivative (**16**) [69%; mp 175–177°C; m/z 315 (M^+); δ 2.25 (3H, s)] along with the aldehyde (**17**) [20%; mp 173–175°C; m/z 315 (M^+); δ 9.84 (1H, s)]. On exposure to 10% potassium hydroxide in refluxing methanol for 1 h, **16** cyclized through aldol condensation to give the enone (**18**) (94%; mp 268–270°C; m/z 297 (M^+); ν 1710, 1680; δ 6.70 (2H, s), 6.21 (1H, s)]. Hydrogenation of **18** over 10% Pd-C in

acetic acid gave stereoselectively the *cis*-fused cyclopentanone (**19**) [64%; m/z 299 (M^+); mp 192-193°C] due to hydrogen attack from the less hindered α -side.

Oxidation of **19** with iodosobenzene¹²⁾ in the presence of potassium hydroxide in methanol at -5~-8°C gave the desired hydroxy-ketal (**20**) [58%; mp 180-181°C; m/z 361 (M^+); δ 4.14 (1H, d, $J=6$), 3.40 (1H, d, $J=6$)] accompanied with its regio-isomer¹³⁾ (24%). Reduction of **20** with aluminum hydride in tetrahydrofuran gave the amine (**21**, 65%), which was identical with the authentic sample¹⁾ converted to (+)-cephalotaxine (**1**). Thus the stereochemistry of **20** was completely established and this synthesis amounts to a formal synthesis of (+)-**1**.

The Swern oxidation [(CF₃CO)₂O, DMSO, in CH₂Cl₂ at -60°C] of **20** afforded the ketone (**22**) [43%; m/z 335 (M^+); ν 1760, 1680] and the enone (**23**) [10%; m/z 327 (M^+); ν 1730, 1680, 1640; δ 6.07 (1H, s)]. Heating **22** in dimethyl sulfoxide eliminated methanol to produce **23** in 51% yield. Finally, sodium borohydride reduction of **23** in methanol-dichloromethane (1:1) at 0°C stereoselectively furnished (+)-cephalotaxinamide (**6**) [83%; mp 258-259°C; m/z 329 (M^+); ν 3325, 1675; δ 6.64, 6.61 (each 1H, s), 5.91 (2H, s), 4.77 (1H, d, $J=9$), 4.68 (1H, s), 3.78 (3H, s), 3.63 (1H, d, $J=9$)]. The spectral data of the product (**6**) were in good agreement with those reported for natural cephalotaxinamide.⁷⁾

REFERENCES AND NOTES

- 1) S. Yasuda, T. Yamada, and M. Hanaoka, *Tetrahedron Lett.*, **27**, 2023 (1986).
- 2) L. Huang and Z. Xue, "The Alkaloids: Chemistry and Pharmacology," Vol. 23, ed. by A. Brossi, Academic Press, New York, 1984, Chapter 3; M. Suffness and G.A. Cordell, "The Alkaloids: Chemistry and Pharmacology," Vol. 25, ed. by A. Brossi, Academic Press, New York, 1985, pp. 57-69; pp. 295-298.
- 3) S.M. Weinreb and J. Auerbach, *J. Am. Chem. Soc.*, **97**, 2503 (1975).
- 4) M.F. Semmelhack, B.P. Chong, R.D. Stauffer, T.D. Rogerson, A. Chong, and L.D. Jones, *J. Am. Chem. Soc.*, **97**, 2507 (1975).
- 5) T.P. Burkholder and P.L. Fuchs, *J. Am. Chem. Soc.*, **110**, 2341 (1988).
- 6) M.E. Kuehne, W.G. Bornmann, W.H. Parsons, T.D. Spitzer, J.F. Blount, and J. Zubieta, *J. Org. Chem.*, **53**, 3439 (1988).
- 7) Z. Xue, L. Xu, D. Chen, and L. Huang, *Acta Pharm. Sin.*, **16**, 752 (1981).
- 8) The alkylation of lactim ether with phenacyl bromide was reported: *cf.* T. Fujii, S. Yoshifuji, and K. Yamada, *Chem. Pharm. Bull.*, **26**, 2071 (1978).
- 9) U. Schmidt and R. Scholm, *Synthesis*, **1978**, 290.
- 10) At higher temperature the ester group was also reduced with sodium borohydride to afford the corresponding diol.
- 11) J. Tsuji, *Pure Appl. Chem.*, **53**, 2371 (1981).
- 12) R.M. Moriarty, H. Hu, and S.C. Gupta, *Tetrahedron Lett.*, **22**, 1283 (1981); R.M. Moriarty and O. Prakash, *Acc. Chem. Res.*, **19**, 244 (1986).
- 13) The structure of this regioisomer is 1-hydroxyl derivative.

(Received August 15, 1988)