Communications to the Editor

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A TOTAL SYNTHESIS OF (±)-CEPHALOTAXINAMIDE

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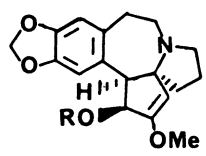
(±)-Cephalotaxinamide (**6**) was synthesized from pyroglutamic acid *via* the pyrrolobenzazepine (**4**) through the Claisen rearrangement, the Wacker oxidation, aldol condensation, and hydroxylation with iodosobenzene.

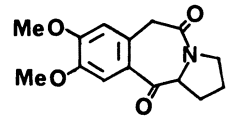
KEYWORDS —cephalotaxinamide; cephalotaxine; Cephalotaxus alkaloid; Claisen rearrangement; aldol condensation; Wacker oxidation; iodosobenzene

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]

Heating[8] 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**)



1 : R= H



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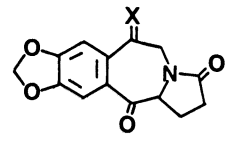
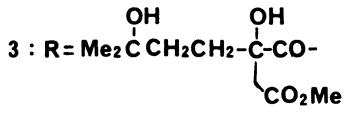
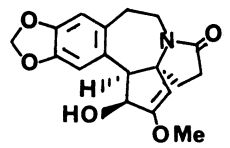


4: X= H₂
5: X= O



3 : R= $Me_2C(OH)CH_2CH_2$-C(OH)(CO₂Me)-CO-



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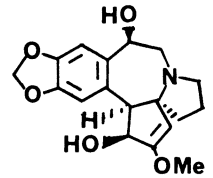

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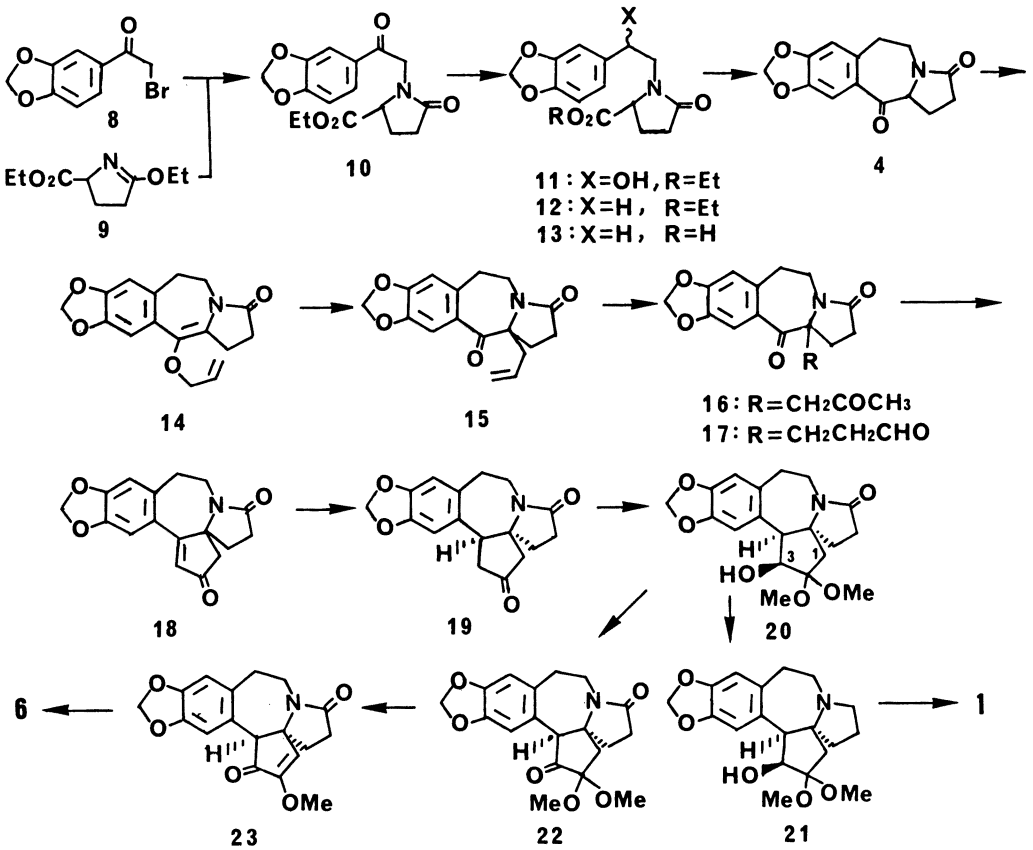

(mp 122-124°C; ν 1740, 1680) in 80% yield. Sodium borohydride reduction of **10** in methanol at -15~-18°C[10] afforded the alcohol (**11**, 98%) as a diastereoisomeric mixture which on catalytic hydrogenolysis over 10% Pd-C in acetic acid in the presence of 70% perchloric acid yielded the amide ester (**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 C-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 oxidation[11] of **15** with $PdCl_2$-CuCl in wet DMF at 75°C in a stream of oxygen for 3.5 h gave the acetonyl 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 iodosobenzene[12] 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 regioisomer[13] (24%). Reduction of **20** with aluminum hydride in tetrahydrofuran gave the amine (**21**, 65%), which was identical with the authentic sample[1] 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 [$(CF_3CO)_2O$, DMSO, in CH_2Cl_2 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]

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