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A NOVEL AND STEREOSELECTIVE SYNTHESIS OF (±)-CEPHALOTAXINE AND ITS ANALOGUE

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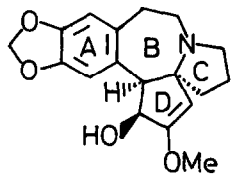
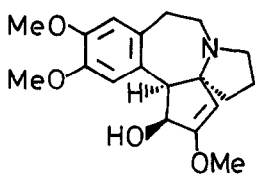
Summary: Cephalotaxine (1) and its analogue (3) were stereoselectively synthesized from proline *via* the pyrrolobenzazepine (4) through Claisen rearrangement, cationic cyclization, and regio- and stereo-selective hydroxylation.

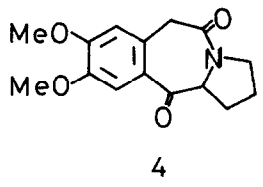
Cephalotaxine (1), a representative Cephalotaxus alkaloid,[1] possesses a unique structure having two spiro-fused five-membered rings, both of which are annular to a benzazepine system. Several ester derivatives of 1, both natural products such as harringtonine (2) and semi-synthetic ones, were found to exhibit a significant antitumor activity.[1,2] Because of above potential pharmacological activity as well as its unique structure, considerable attention has so far been paid on a synthesis of cephalotaxine (1).[1,3]

This communication deals with a novel and stereoselective synthesis of cephalotaxine (1) and its analogue (3) from proline *via* the pyrrolobenzazepine (4) by Claisen rearrangement, cationic cyclization, and regio- and stereo-selective hydroxylation as crucial steps.

Condensation of ethyl prolinate with 3,4-dimethoxyphenylacetyl chloride gave the amide-ester (5) [89%, *m/z* 321 (M^+)]. Hydrolysis of 5 with potassium hydroxide in ethanol gave the carboxylic acid (6) (100%, mp 141.5-142.5°C), which cyclized by treatment with polyphosphoric acid at 55°C to the pyrrolobenzazepine (4) [74%, mp 171-174°C, *m/z* 275 (M^+), ν 1650] accompanied with the







4

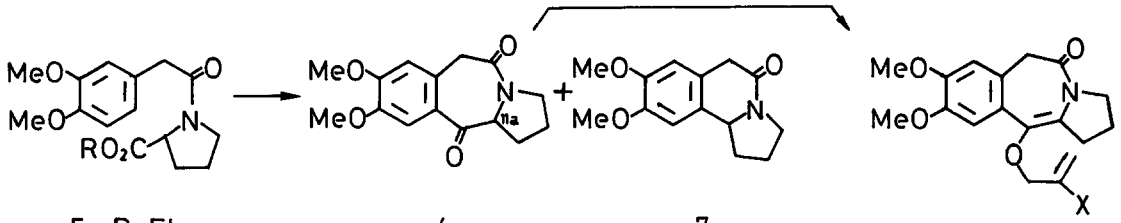
1 R=H

Cephalotaxine

3

2 R= $(CH_3)_2C(OH)(CH_2)_2\overset{OH}{\overset{|}{C}}(CH_2CO_2CH_3)-CO_2$

Harringtonine

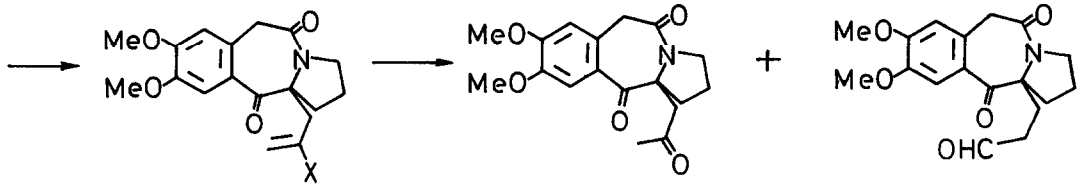


5 R= Et
6 R= H

4

7

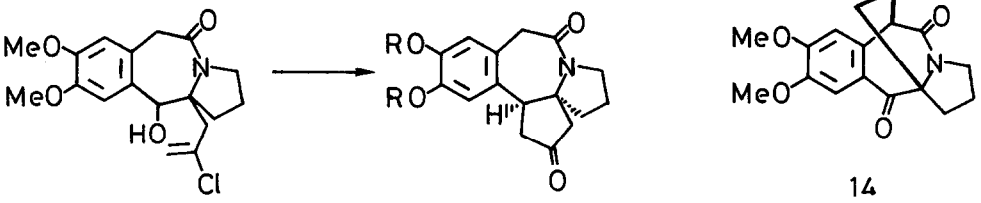
8 X= H
9 X= Cl



10 X= H
11 X= Cl

12

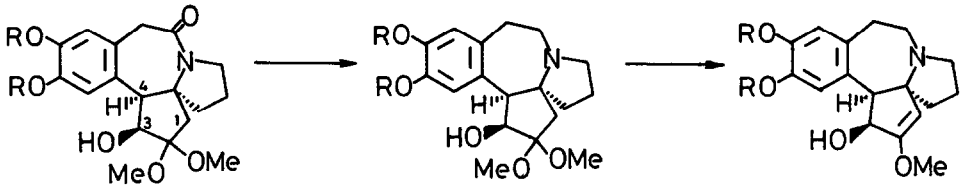
13



15

16 R= Me
19 R= H
20 R+R= CH_2

14



17 R= Me
21 R+R= CH_2

18 R= Me
22 R+R= CH_2

3 R= Me
1 R+R= CH_2

isoquinoline (7)[4] (2%). Preliminary experiments showed that exclusive *O*-alkylation of 4 occurred under various conditions. Consequently, introduction of a functionalized C_3-alkyl substituent at an angular C-11a position for construction of the ring D was successfully accomplished by *O*-allylation and subsequent Claisen rearrangement. Treatment of 4 with allyl bromide or 2,3-dichloropropene in the presence of sodium hydride in dimethylformamide (DMF) afforded the enol-ether (8) (73%) or (9) (91%), respectively. Heating of 8 or 9 at 150°C effected the Claisen rearrangement to provide *C*-allylated product (10) (81%) or (11) (97%), respectively. Wacker oxidation of 10 with palladium chloride-cuprous chloride in a stream of oxygen in DMF-water (7:1)[5] gave the diketone (12) [53%, mp 161-163°C, ν 1720, 1640, δ 2.21 (3H, s, CH_3)] along with the aldehyde (13) [24%, ν 1720, 1640, δ 9.79 (1H, br-s, CHO)]. Exposure of 12 to lithium diisopropylamide in tetrahydrofuran (THF) afforded the undesired cyclization product (14)[6] [100%, mp 110-113°C, *m/z* 331 (M^+), ν 3320, 1650, δ 1.26 (3H, s, C-CH_3)] instead of the D ring formation.

Reduction of 11 with sodium borohydride in methanol-dichloromethane at 0°C afforded the alcohol (15)[7] (100%, mp 202-204°C). On treatment with 90% sulfuric acid at 55°C, the alcohol (15) underwent cationic cyclization[8] to provide the expected tetracyclic ketone (16) [69%, mp 222-224°C, *m/z* 315 (M^+), ν 1745, 1635, δ 6.82, 6.66 (each 1H, s, Ar-H), 3.79 (1H, t, *J*=9, C_4-H), 3.75, 3.39 (2H, AB-q, *J*=14, C_{11}-H)]. Oxidation of 16 with iodosobenzene[9] in the presence of potassium hydroxide in methanol at 0°C afforded the hydroxy-ketal (17) [80%, mp 241-243°C, *m/z* 377 (M^+), δ 4.15 (1H, d, *J*=5.5, C_3-H), 3.49 (1H, d, *J*=5.5, C_4-H), 3.35, 3.31 (each 3H, s, OCH_3 x 2)] as a sole product. The stereochemistry of 17 was confirmed by the coupling constant ($J_{3H,4H}$=5.5) in its ^{1}H-NMR spectrum. The high regio- and stereo-selectivity of the hydroxylation of 16 would be due to the attack of the bulky reagent from less hindered site and side of the ring D. Lithium aluminum hydride (LAH) reduction of 17 in refluxing THF gave the amine (18) [85%, mp 178-180°C, *m/z* 363 (M^+)], which was treated with *p*-toluenesulfonic acid (*p*-TsOH) in THF to afford the cephalotaxine analogue (3) [78%, mp 155-157°C, *m/z* 331 (M^+), δ 6.70, 6.66 (each 1H, s, Ar-H), 4.94 (1H, s, C_1-H), 4.77 (1H, d, *J*=9.3, C_3-H), 3.86 (6H, s, OCH_3 x 2), 3.73 (3H, s, OCH_3), 3.69 (1H, d, *J*=9.3, C_4-H)]. The ^{1}H-NMR spectrum of 3 is very similar to that of cephalotaxine except for the aromatic methoxyl groups.

On treatment with boron tribromide in dichloromethane at -78°C, the tetracyclic ketone (16) underwent demethylation to afford the catechol (19) (79%), which was reacted with dibromomethane in the presence of potassium fluoride in DMF to give the methylenedioxy derivative (20) [33%, mp 188-189°C, *m/z* 299 (M^+), 5.94 (2H, s, OCH_2O)]. Hydroxylation of 20 with iodosobenzene at 0°C gave stereoselectively the hydroxy-ketal (21) [79%, mp 210-211°C, *m/z* 361 (M^+), δ 4.12 (1H, d, *J*=5.5, C_3-H), 3.45 (1H, d, *J*=5.5, C_4-H), 3.35, 3.30 (each 3H, s, OCH_3 x 2)], reduction of which with LAH gave the amine (22) [86%, mp 150.5-151.5°C, *m/z* 347 (M^+)]. Treatment of 22 with *p*-TsOH in THF provided (±)-cephalotaxine (1) [91%, mp 115-117°C (lit.[10a] mp 116-118°C), *m/z* 315 (M^+), δ

6.67, 6.64 (each 1H, s, Ar-H), 5.90 (2H, s, OCH_2O), 4.92 (1H, s, C_1-H), 4.76 (1H, d, J=9.3, C_3-H), 3.73 (3H, s, OCH_3), 3.67 (1H, d, J=9.3, C_4-H)]. The synthetic cephalotaxine was proved to be identical with natural cephalotaxine by comparison with ^{1}H-NMR and IR spectra, and thin-layer chromatographic behavior.

Thus, we have developed a novel and highly stereoselective synthesis of cephalotaxine (1) and its analogue (3).[11]

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6) On treatment with other base such as potassium hydroxide in methanol, 12 gave 14 (79%) and its diastereoisomer (20%).
7) This was a single product but its stereochemistry remained undetermined.
8) *cf.* P.T. Lansbury, E.J. Nienhouse, D.J. Scharf, and F. R. Hilfiker, *J. Am. Chem. Soc.*, 92, 5649 (1970).
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11) Synthesis of ester derivatives of 3 is now in progress.

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