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TOTAL SYNTHESIS OF (-)-DIHYDROCELACINNINE AND (±)-CELABENZINE

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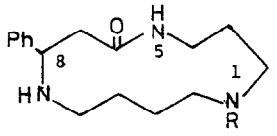
Summary : (S)-3-amino-3-phenylpropionic acid, as an intermediate, was converted to dihydrocelacinnine and celabenzine.

The macrocyclic alkaloids celacinnine (1) and celabenzine (3) were isolated from Maytenus arbutifolia[1], Tripterygium wilfordii[1], and Pleurostylia africana[2], members of the plant family Celastraceae. Their structures have in common a 13-membered ring composed of a spermidine. Celacinnine (1) and celallocinnine (2) were converted to dihydrocelacinnine (4) by hydrogenation[1,2], mp 176-178°C; $[\alpha]_D^{25}$ -16°. Celabenzine (3) had a mp 163-167°C[3]; $[\alpha]_D^{25}$ ±0°. Three other syntheses of celabenzine (3) have appeared in the recent literature[4,5,6]. Celabenzine in its natural form has never been synthesized. In this paper, we report the syntheses of the natural forms of dihydrocelacinnine (4) and celabenzine (3).

First, the conjugate addition of 4-aminobutanol (5) to acrylonitrile gave the N-(cyanoethyl)-4-aminobutanol (6) in 95% yield. Treatment of (6) with two equivalents of cinnamoyl chloride yielded (7), which was converted to the amine derivative (9) by hydrogenation of cyano and olefin groups over platinum oxide, in 90% yield.

Treatment of (S)-3-amino-3-phenylpropionic acid (11)[7] with BOC-S gave the urethane acid (12)[8], mp 130-132°C; $[\alpha]_D^{25}$ -42.2° (c=0.54 EtOH).

Condensation of the amine (9) with urethane acid (12) in the presence of 2-chloro-1-methylpyridinium iodide afforded the amide (13) in 80% yield; this was hydrolyzed with K_2CO_3 to give the alcohol (14)[10] in 90% yield. Oxidation of 14 with pyridinium chlorochromate afforded the aldehyde (17)[11] in 70% yield. The amino salt (18) was obtained in 90% yield by the trifluoroacetic acid cleavage of the BOC group and gave the 13-membered ring lactum in 80-85% yield from (17) on treatment with a 5% solution of $NaHCO_3$ at room temperature. Subsequent reduction of the lactam with $NaBH_4$ afforded the dihydrocelacinnine (4)[12] in 80% yield.

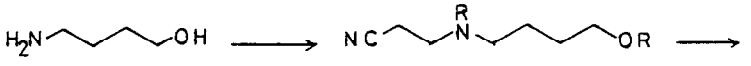


1:R=PhCH=CHCO(trans)

2:R=PhCH=CHCO(cis)

3:R=PhCO

4:R=$PhCH_2CH_2CO$

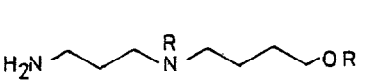


5

6:R=H

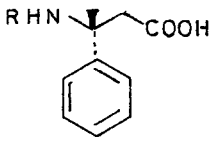
7:R=PhCH=CHCO(trans)

8:R=PhCO



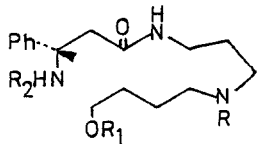
9:R=$PhCH_2CH_2CO$

10:R=PhCO



11:R=H

12:R=BOC

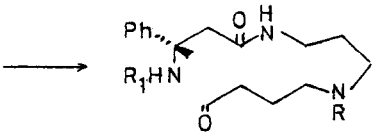


13:R=R_1=$PhCH_2CH_2CO$, R_2=BOC

14:R=$PhCH_2CH_2CO$, R_1=H R_2=BOC

15:R=R_1=PhCO, R_2=BOC

16:R=PhCO, R_1=H, R_2=BOC



4 and 3

17:R=$PhCH_2CH_2CO$, R_1=BOC

18:R=$PhCH_2CH_2CO$, R_1=$CF_3CO_2H_2^+$

19:R=PhCO, R_1=BOC

20:R=PhCO, R_1=$CF_3CO_2H_2^+$

The synthetic dihydrocelacinnine (4) was identical in all respects, i.e., $[\alpha]_D^{25}$, mp, NMR, IR, and TLC to natural dihydrocelacinnine (4)[2]. On the basis of the data presented above, the authors conclude that the configuration of C-8 of the 13-membered ring in celacinnine (1) is the (S)-configuration.

Celabenzine (3) was obtained by the following route: Treatment of (6) with two equivalents of benzoylchloride yielded 8 (90%) which, by hydrogenation of cyano group over platinum oxide, was converted to the amine derivative (10) in 90% yield. Condensation of the amine (10) with the acid (12) in the presence of 2-chloro-1-methyl pyridinium iodide afforded the amide (15)[13] in 80% yield. On hydrolysis with K_2CO_3, it afforded the alcohol (16)[14] in 90% yield, which was subsequently oxidized with pyridinium chlorochromate to the aldehyde (19)[15] in 70% yield. Trifluoroacetic acid was added to remove the BOC protecting group and the amino salt (20) was cyclized with $NaHCO_3$ to give the 13-membered ring lactum. Its reduction with $NaBH_4$ afforded celabenzine (3)[16] in 70% yield.

Synthetic celabenzine (3) was found identical in all respects, i.e. $[\alpha]_D^{25}$, NMR, IR, and TLC to natural celabenzine.

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References and Notes.

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M. Furukawa, T. Okawara, Y. Noguchi, and Y. Terawaki, Chem. Pharm. Bull., 27, 2223 (1979).
8. mp 130-132°C; $[\alpha]_D^{25}$ -42.2° (c=0.54 EtOH); IR (nujol): 3360, 1680cm^{-1}; NMR ($CDCl_3$): δ 1.4 (s, 9H), 2.85 (d, J=7Hz, 2H), 5.0 (m, 1H), 7.3 (s, aromatic-H)
9. IR (neat): 3350, 1700, 1620cm^{-1}; NMR ($CDCl_3$): δ 1.4 (s, 9H), 5.0 (m, 1H), 6.7-7.7 (m, aromatic-H); MS: m/e 657 (M^+).

10. oil; $[\alpha]_D^{25}$ -15.0° (c=0.72 $CHCl_3$); IR (neat): 3350, 1690, 1620cm^{-1}; NMR ($CDCl_3$): δ 1.4 (s, 9H), 5.0 (m, 1H), 6.7- 7.7 (aromatic-H); MS: m/e 525 (M^+).
11. oil; IR (neat): 3350, 1700, 1620cm^{-1}; NMR ($CDCl_3$); δ 1.4 (s, 9H), 5.0 (m, 1H), 6.8-7.4 (m, aromatic-H), 9.8 (s, 1H); MS: m/e 523 (M^+).
12. mp 180-183°C; $[\alpha]_D^{25}$ -17.7° (c=0.23 $CHCl_3$); CD (MeOH) 224, 261, 268, (Δε -4.8, 0.23, 0.23); IR (nujol) 3330, 1630, 1560cm^{-1}; NMR ($CDCl_3$): δ 1.1-4.0 (m, 22H), 3.97 (t, J=7Hz, 1H), 2.50 (d, J=7Hz, 2H), 7.15-7.50 (m, aromatic-H); MS: m/e 407 (M^+).
13. oil; $[\alpha]_D^{25}$ -10.5° (c=0.32 $CHCl_3$); IR (neat): 3300-3400, 1720cm^{-1}; NMR ($CDCl_3$): δ 1.40 (s, 9H), 5.0 (m, 1H), 7.2-7.6 (m, aromatic-H), 7.9-8.1 (d-d, 2H); MS: m/e 601 (M^+).
14. mp 108-110°C; $[\alpha]_D^{25}$ -13.2° (c=0.44 $CHCl_3$); IR (nujol) 3330, 1670, 1640, 1620cm^{-1}; NMR ($CDCl_3$): δ 1.40 (s, 9H), 5.0 (m, 1H), 7.2-7.5 (m, aromatic-H), 7.8-8.0 (d-d, 2H); MS: m/e 497 (M^+).
15. oil; IR (neat): 3350, 1710, 1700, 1650, 1610cm^{-1}, NMR ($CDCl_3$): δ 1.40 (s, 9H), 5.0 (m, 1H), 7.1-7.5 (m, aromatic-H), 9.6 (s, 1H); MS: m/e 495 (M^+).
16. mp 170-173°C; $[\alpha]_D^{25}$ ±0° (c=0.73 $CHCl_3$); CD (MeOH) 233, 250, 262, 268 (Δε -2.9, 0.64, 0.47, 0.32): IR (nujol): 3300, 1660, 1610cm^{-1}; NMR ($CDCl_3$): δ 1.2-2.2 (m, 7H), 2.25-2.75 (m, 4H), 2.8-3.9 (m, 6H), 3.95 (m, 1H), 7.2-7.5 (m, aromatic-H, 10H); MS: m/e 379 (M^+).

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