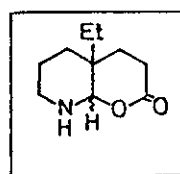


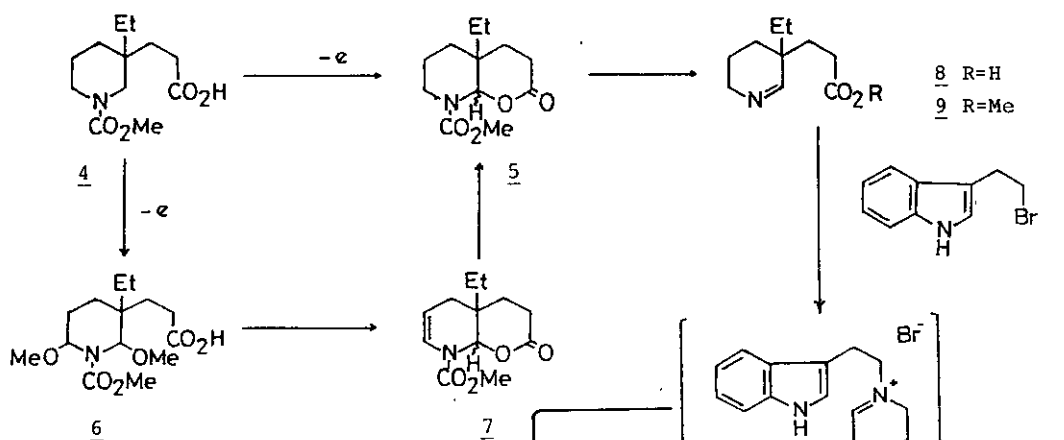
1a,b

2a,b

a: X=O, R=H
b: X=H₂, R=COOMe



10



4

-e

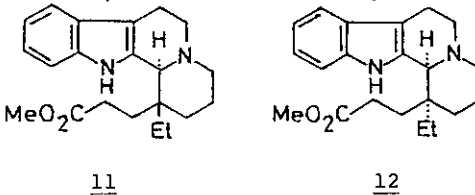
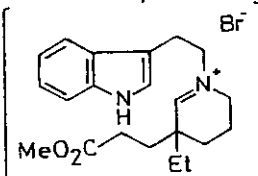
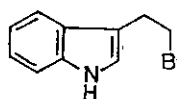
6

-e

5

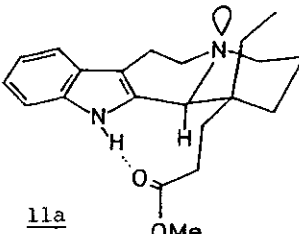
7

8 R=H
9 R=Me

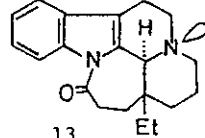


11

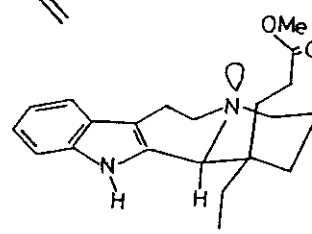
12



11a

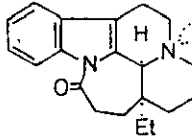


13

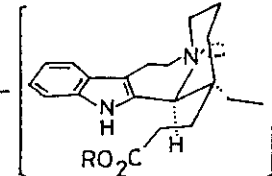


12a

(±)-Vincamine(3)



14



12b

(MeOH, rt, constant current (30 mA), $\text{Et}_4\text{N}^+\text{ClO}_4^-$, 8.2 F/mol) and the crude product was treated with formic acid in the same way as above to give the lactone 7 in 76% yield after purification by silica gel chromatography. The lactone 7 thus obtained was hydrogenated in ethyl acetate with Adams' catalyst to afford the lactone 5 in a quantitative yield. The lactone 5 was hydrolyzed with potassium hydroxide in aq dioxane containing a catalytic amount of 18-crown-6 to give the imino-acid 8, instead of the expected lactone 10. The imino-acid 8 was reacted with diazomethane to yield the methyl ester 9 (92.5% yield from 5), which was utilized as a potential intermediate for the synthesis of ($\pm$)-vincamine.

The ester 9 was reacted with tryptophyl bromide (toluene, reflux, 37 h) to give the crude product as a mixture of the isomeric octahydro-indolo[2,3-a]-quinolizidines (11 and 12), which were separated by the preparative tlc into each isomer, 11 [mp 146-147°, pale yellow needles, IR ν 3350 (broad NH), 2800, 2750 (Bohlmann's absorptions) and 1720 cm^{-1} (ester C=O); NMR δ 0.69 (3H, t, CH_3CH_2 -), 3.80 (3H, s, COOCH_3), 8.86 (1H, b, indole NH); Mass m/e 340 (M^+); 11.3% yield] and 12 [mp 138-140°, pale yellow needles; IR ν 3500 (sharp, NH), 2800, 2750 (Bohlmann's absorptions), 1730 cm^{-1} (ester C=O); NMR δ 1.16 (3H, t, CH_3CH_2 -), 3.56 (3H, s, COOCH_3), 7.80 (1H, b, indole NH); Mass m/e 340 (M^+); 13.6% yield]. As both of 11 (=11a) and 12 (=12a) indicate the Bohlmann's absorptions being characteristic of trans-quinolizidines, the C/D ring junctures of both compounds should be in trans configuration. Moreover, the hydrogen bonding between the hydrogen of NH and the oxygen of ester carbonyl was observed with 11a and not with 12a, which suggested the respective stereo-structures (11a and 12a) for both compounds. As is easily visualized, the amino acid ester (11a) was readily cyclized (NaH, THF, 0-5°, 1 h) to the product 13 as a colorless resin [IR ν 2800, 2750 (Bohlmann's absorptions), 1680 (C=O), 1615 cm^{-1} (arom); Mass m/e 309 (M^+)]. The other amino acid ester (12a), however, was not cyclized under the same conditions and resulted in the recovery of the carboxylic acid (12a: H instead of Me) as a result of hydrolysis of the starting material. It may be understood that with the former compound 11a, the distance between indole nitrogen and carbonyl oxygen is very close as the hydrogen bonding is observed, but with the latter (12a), these functional groups are remotely located as is seen in formula 12a, which should make it difficult to cyclize to the objective compound.

Finally, the ester 12a was cyclized [$(\text{Me}_3\text{Si})_2\text{NLi}$, toluene, rt, 2 h] by the procedure of Oppolzer^{3m} to the product 14 [mp 165-169° (lit.^{3m} mp 163-166°); IR ν 1690 cm^{-1} ($>\text{N}-\text{CO}-$) and the absorptions due to NH and trans-quinolizidine were not observed. Mass m/e 308 (M^+); 78% yield]. Under the present reaction conditions, the ester (12=12a) could be assumed to be cyclized to 14 via 12b generated by ring inversion of trans- to cis-quinolizidine. Thus, a formal total synthesis of ($\pm$)-vincamine was accomplished since the lactam 14 had been already converted into ($\pm$)-vincamine(3).^{3m}

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