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STEREOSELECTIVE SYNTHESIS OF A NEW PERHYDROINDOLE DERIVATIVE OF CHIRAL IMINODIACID, A POTENT INHIBITOR OF ANGIOTENSIN CONVERTING ENZYME

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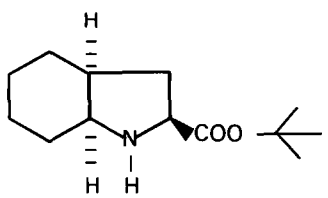
Abstract.The stereoselective synthesis of N-[(S) 1 - carbethoxybutyl)] (S) alanine and of (2S, 3aS, 7aS) 2-t.butoxycarbonyl perhydroindole are described. Their coupling produces the title compound.

With the view to preparing 1 - [(2S) 2 - [(1S) 1-carbethoxybutyl) amino] 1-oxo propyl] (2S, 3aS, 7aS) perhydroindole 2-carboxylic acid 1, by coupling (2S, 3aS, 7aS) 2 - t.butoxy-carbonyl perhydroindole 2 with N-[(S) 1-carbethoxybutyl] (S) alanine 3, we had to synthetize these original compounds 2 and 3 in a pure state and at the same time to be sure of their configuration.



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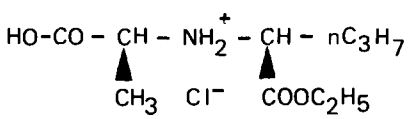

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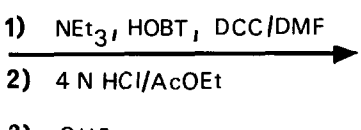

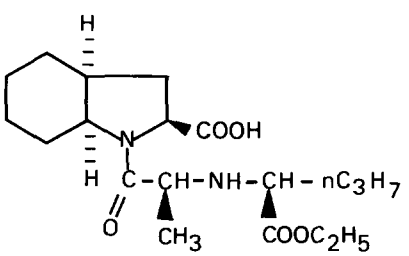

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These goals were simultaneously attained by using an approach close to that used by BIELLMANN et al. for octopine (1).

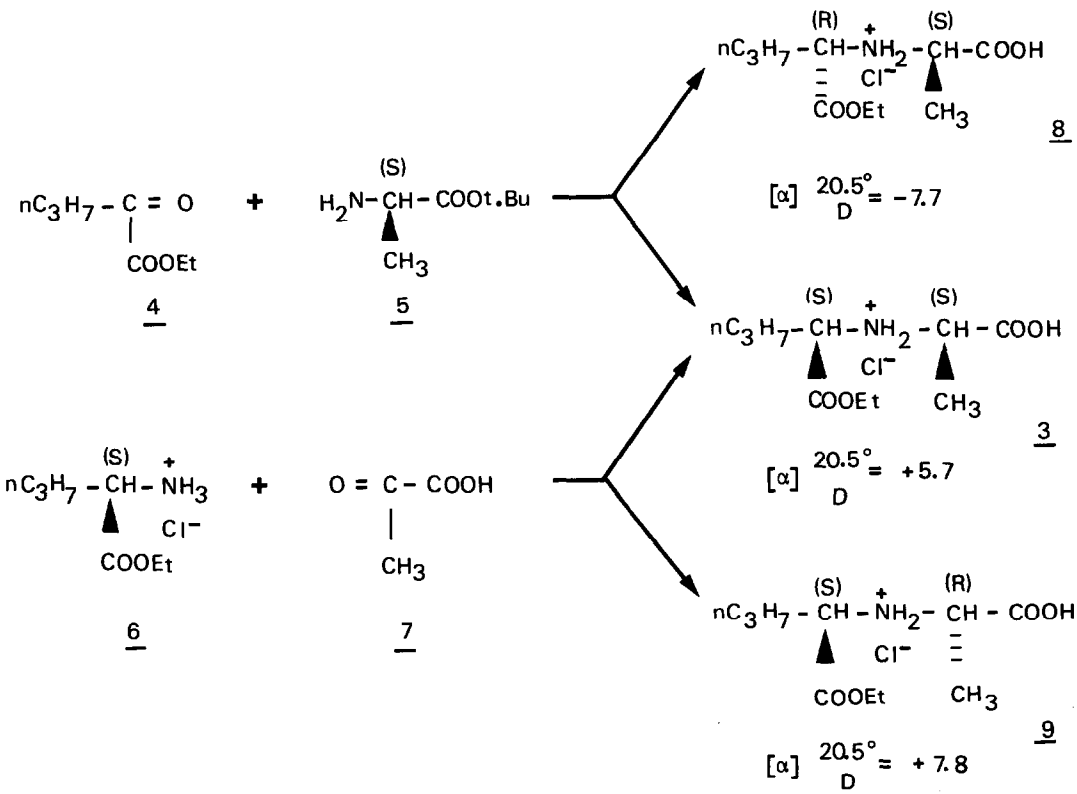
On the one hand, prochiral keto ester 4 was coupled with (S) alanine t.Bu ester 5 by reductive amination (Na BH_3 CN, EtOH), using the procedure described by C.F. LANE et al. (2). The mixture of epimeric t.Bu esters so obtained was treated as described in note (3) producing after separation the expected two epimeric hydrochlorides 8 et 3. The chemical

yield was high (80 %) and the coupling was stereoselective in favour of 3 (65/35 by GLC on OV 17 5 %, Θ 150°C derivatization with BSA).

On the other hand, freshly distilled prochiral pyruvic acid 7 was coupled with (S) norvaline ethyl ester hydrochloride 6 by catalytic reductive amination in EtOH (chemical yield : 92 %, asymmetric induction : 70/30 in favour of 3) according to the procedure described by S.I. YAMADA (4). After treatment and separation as described in note (3) two epimeric hydrochlorides 9 and 3 were obtained.

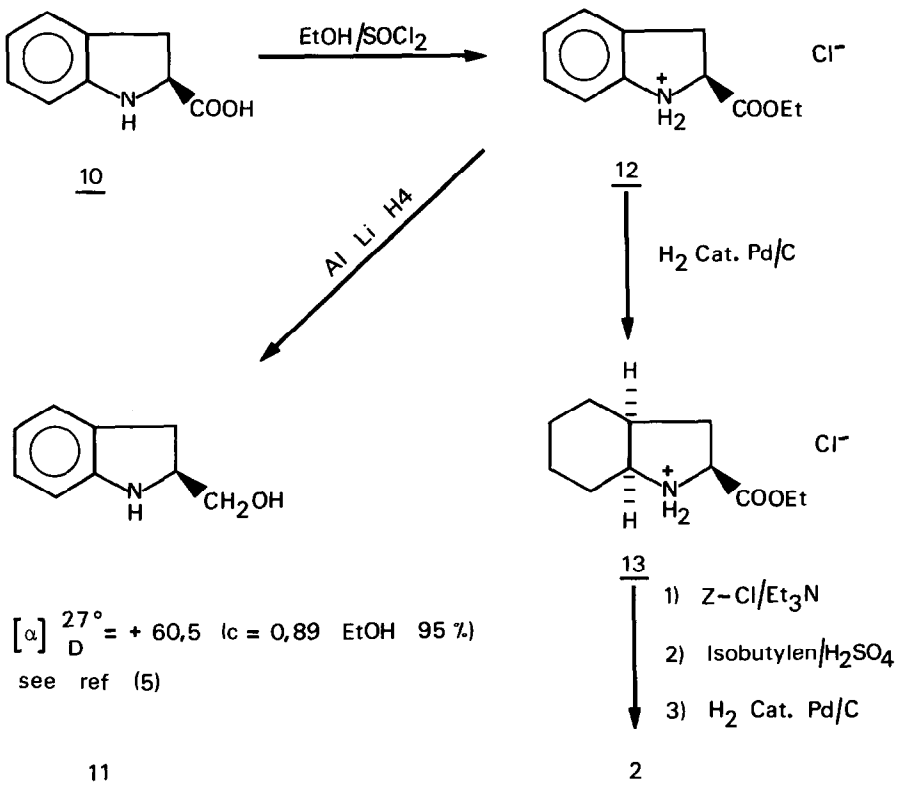
The attributions of configurations to 3, 8 and 9 were easily performed by measuring their respective optical rotations (c = 1, EtOH).

As expected, the diastereoisomer having the desired (S,S) configuration was 3, compound 8 and 9 being antipodes of the other diastereoisomer.



Compound 2 was synthetized as follows : (S) 2-carboxy indoline 10 was obtained in a pure state ($[\alpha]_D^{20.5°}$ = - 114 c = 1, HCl 2N) by fractional crystallization of its (+) α methyl benzylamine salt (first EtOH, then Iso PrOH). (S) 2-carbethoxy indoline hydrochloride 12 was prepared (EtOH , $SOCl_2$) from the preceding acid without racemization (checked by capillary GLC of the (-) camphanamide) and its (S) configuration was established by reduction (Al LiH4) to the corresponding alcool which was identified with authentic (S) 2-hydroxy methyl indoline 11 described by E.J. Corey (5). 12 was catalytically hydrogenated

(Pd/C) in EtOH to (2S, 3aS, 7aS) 2-carbethoxy perhydroindole hydrochloride 13 which was purified by crystallization from AcOEt ($[\alpha]_D^{20.5°}$ = - 25,7 c = 1, H_2O F = 139-140°dec). This ester was saponified (NaOH, H_2O, EtOH, 25°) and the resulting acid ($[\alpha]_D^{20.5°}$ = - 47,7 c = 1,MeOH F = 268-271°dec) successively treated with Z - Cl (CH_2Cl_2, NEt_3, C_6H_6), Isobutylen - H_2SO_4, and cat. hydrogenation (Pd/C, EtOH) to produce 2 ($[\alpha]_D^{20.5°}$ = - 26,3 c = 1, MeOH), whose purity (>98 %) was measured by capillary GLC of the (-) camphanamide. The configurations of carbons 2, 3a and 7a in 2 were studied by NMR (SY 250 BRUKER). Out of the possible configurations, the values of the observed coupling constants are preferential to configuration 2S, 3aS, 7aS (note 8).



Compound 1 is a potent long-lasting and orally active inhibitor of Angiotensin Converting Enzyme (ACE). The form for testing was t.Bu NH_2 salt ($[\alpha]_D^{20.5°}$ = - 64,8 c = 1, EtOH F = 134°dec.) (6).

Notes and references

1. J.F. BIELLMANN, G.B. BRANLANT, L. WALLEN. Bioorganic Chemistry 6, 89-93 (1977)
2. C.F. LANE. Synthesis 135-146 (1975)

3. The product was treated with 4N HCl in AcOEt. Spontaneously precipitated pure (GLC) 8 or 9 was separated by filtration. The filtrate was evaporated in vacuo to dryness. The residue (impure 3, 90 % by GLC) was purified by successively applying it to Dowex 50 H+, eluting with NH_4 OH, crystallizing the so obtained free amino acid ester from MeCN and transforming it again into hydrochloride.

4. SUN-ICHI YAMADA and SUN-ICHI HASHIMOTO Tetrahedron letters 13, 997-1000 (1976)

5. E.J. COREY, R.J. Mc CAULLY, H.S. SACHDEV J. Amer. Chem. Soc. 92 (8) 2476-2488 (1970)

6. In vivo ACE inhibition has been determined in dogs as described by Gross et al. (7). In vagotomized anesthetized dogs, intravenous administration of 1 produced a dose dependent inhibition of the pressor response to angiotensin I and was found to have an ID 50 = 125 (94-155) µg/kg i.v.. In unanesthetized dogs, oral administration of 1 (0.1-1 mg kg p.o.) inhibited the pressor response to angiotensin I in a dose dependent manner. The peak of inhibition (90 %) was reached approximatively 60 min. after administration. ACE inhibition (40 %) was observed 24-30 hr in dogs treated with 1 mg/kg p.o..

7. D.M. GROSS, C.S. SWEET, E.H. ULM, E.P. BACKLUND, A.A. MORRIS, D. WEITZ, D.L. BOHN, H.C. WENGER, T.C. VASSIL and C.A. STONE. J. Pharmacol. Exp. Ther.. 216, 552-557 (1981)

8. A detailed article on the results of the NMR and RX studies will be published later.

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