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Stereoselective Synthesis of a trans-Octahydroindole Derivative, Precursor of Trandolapril (RU 44 570), an Inhibitor of Angiotensin Converting Enzyme.

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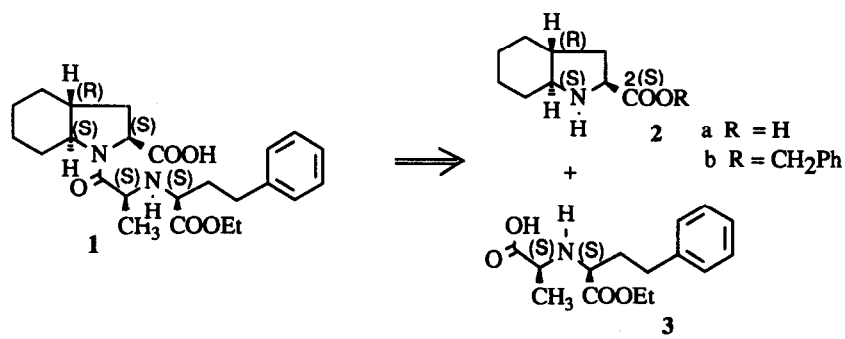
Abstract : *We describe a stereoselective synthesis of the trans-octahydroindole-2-carboxylic acid* **2** *a key intermediate in the elaboration of Trandolapril (RU 44 570)* **1**. *The optically active starting material used was obtained by an enzymatic hydrolysis.*

Orally active inhibitors of Angiotensine Converting Enzyme (ACE) have received much attention in the treatment of hypertension since the 1980s[1]. Our interest in this subject was focused on Trandolapril (RU 44 570) **1**, an optically active ACE inhibitor.

The retrosynthetic scheme adopted for the synthesis of **1** is shown below. In this paper, we describe a stereoselective synthesis of the trans-octahydroindole derivative **2**. This compound was already obtained in a racemic form by R. Henning and H. Urbach[2].

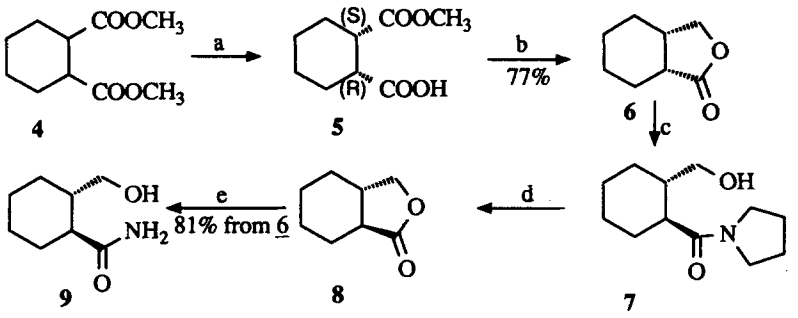


Synthesis of the optically active key intermediate **2** presents two major difficulties due to the presence of

- a trans fused ring junction[3],
- an epimerisable center at C2.

The optically active starting material used in our approach was obtained from the meso diester **4** using an enantioselective enzymatic hydrolysis with Pig Liver Esterase (PLE)[4,5]. Chemoselective reduction of the ester group of **5** with sodium diethyldihydroaluminate afforded the cis-lactone **6**[4c] (b.p. 80°/0.8 mm Hg) $[\alpha]_D^{20}$ = - 42° (c 1.00, CH_3OH).

Isomerisation of **8** to the corresponding trans-lactone **8** $[\alpha]_D^{20}$ = -28° (c 1.00, CH_3OH) could be performed efficiently through the amide **7**. Aminolysis of **8** yielded the corresponding trans amido-alcohol **9**[6] (m.p. 172°C) $[\alpha]_D^{20}$ = + 52° (c 1.00, CH_3OH).



a) PLE, pH 8.0 phosphate buffer, 35°C (5) ; b) $NaAlH_2(C_2H_5)_2$ (1.4 equiv.) toluene, r.t., 3 hr ; c) CH_3ONa (0.25 equiv.), pyrrolidine (1.3 equiv.), toluene, 100°C, 2 hr ; d) toluene/H_2O 1:1; conc H_2SO_4 (3.5 equiv.), reflux, 2.5 hr ; e) toluene, NH_4OH, r.t., 15 hr.

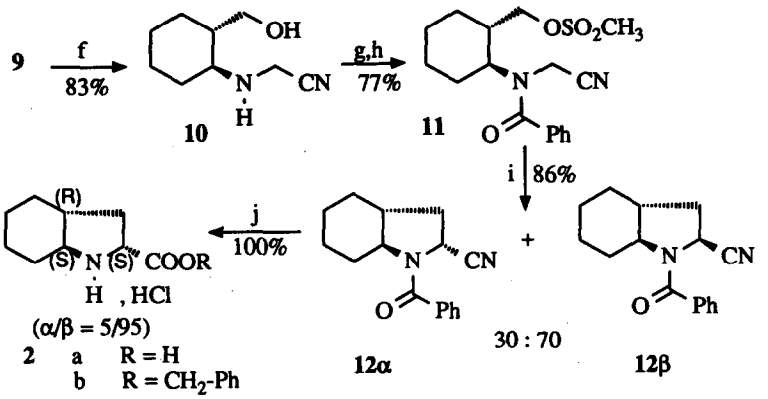
Conversion of compound **9** to the cyanoamine **10** (m.p. 62-64°C) $[\alpha]_D^{20}$ = + 75.5° (c 1.00, CH_3OH) was realized in a "one pot" reaction[7] (overall yield 83% from **9**).

In situ protection of the alcohol function of **10** with trimethylsilylchloride followed by benzoylation of the amino group, desilylation and mesylation of the alcohol smoothly afforded compound **11** (m.p. 116°C) $[\alpha]_D^{20}$ = - 11.5° (c 1.00, CH_3OH) (overall yield 77% from **10**).

Upon treatment with sodium hydride in dimethylformamide, **11** underwent cyclisation to afford a mixture of diastereoisomeric bicyclic nitriles **12α/12β** (30/70)[8].

The amide and nitrile functions of the mixture **12α** and **12β** were then submitted to acid hydrolysis. Carefully controlled experimental conditions permitted us to obtain the amino-acid in a ratio α/β 5/95. The amino-nitrile **14** is probably the intermediate of the reaction[9]. Treatment of amino-acid **2a** with thionyl chloride in the presence of benzyl alcohol (dichloroethane, r.t., 4 hr) gave the desired benzyl ester **2b** (78%) (m.p 170-172°C) $[\alpha]_D^{20}$ = - 49° (c 1.00, CH_3OH).

Finally the ACE inhibitor **1** was obtained from **2b** according to the procedure described earlier by H.G. Eckert et al[10].



f) see ref. 7 ; g) Et_3N (3 equiv.), Me_3SiCl (1.2 equiv.), CH_2Cl_2, r.t., 1 hr ; C_6H_5COCl, r.t., 1 hr ; CH_3OH (0.5 equiv.), aqueous HCl (pH 1), r.t., 3 hr ; h) Et_3N (1.5 equiv.), CH_3SO_2Cl (1.3. equiv.), CH_2Cl_2, r.t., 15 hr ; i) NaH (2 equiv.), DMF, r.t., 4.5 hr ; j) dioxane, aqueous HCl (2.65 equiv.), reflux, 1.5 hr then addition of 2.35 equiv. of conc. HCl, reflux, 1hr.

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References and notes :

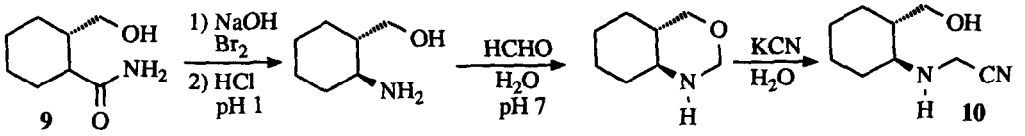
All new compounds have been fully characterised by elemental analyses and/or mass spectroscopy. Spectral data are in full accord with the structural assignments.

1. Wyvratt, M.J.; Patchett, A.A.; *Medicinal Research Reviews*, 1985, *5*, 483.
2. Henning, R.; Urbach, H.; *Tet. Letters*, 1983, *24*, 5339 and 5343. Henning, R.; Urbach, H.; Paulus, E.F.; *Tet. Letters*, 1983, *24*, 5347.
3. Catalytic hydrogenation of (S)2-carboxyindoline affords the corresponding cis perhydroindole derivative, see Vincent,M.; Remond, G.; Serkiz, B.; Laubie, M.; *Tet. Letter*,1982, *23*, 1677.
4. a) Mohr, P.; Waespe-Sarcevic, N.; Tamm, C.; Gawronska, K.; Gawronski, J.K.; *Helv. Chim. Acta*, 1983, *66*, 2501. b) Gais, H-J.; Lukas, K.L.; Angew. *Chem. Int. Ed. Engl.*,1983, *23*, 142. c) Schneider, M.; Engel, N.; Honicke, P.; Heinemann, G.; Gorisch, H.; *Angew. Chem. Int. Ed. engl.*, 1984, *23*, 67. d) Laumen, K.; Reimerdes, E.H.; Schneider, M.; *Tet. Letters*, 1985, *26*, 407. e) Kobayashi, S.; Kamiyama, K., Iimori, T.; Ohno, M.; *Tet. Letters*, 1984, *24*, 2557. For a review see Zhu, L-M.; Tedford, M.C.; *Tetrahedron*, 1990, *46*, 6587.

5. The enzymatic hydrolysis affords **5** with a yield of 95% (ee 80%). Optical pure **5** $[\alpha]_D^{20} = +5°$ (c 2.00, CH_3OH) could be obtained by chemical resolution with (+) chloramphenicol.

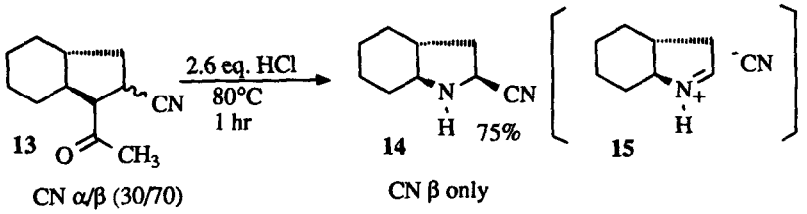
6. Nohira, H.; Ehara, K.; Miyashita, A.; *Bull. Chem. Soc. Jap.*,1970, *43*, 2230.

7. The sequence observed during the transformation of **9** to **10** was demonstrated to be the following.



8. Evans, D.A.; Biller, S.A.; *Tet. Letters*,1985, *26*, 1907.

9. The amino-nitrile **14** could be isolated during the hydrolysis of the N-acetyl analogues **13α** and **13β**. Furthermore, pure **13** submitted to hydrolysis affords **2a** as the major compound. One possible explanation to this surprising result is the formation of the iminium **15** with preferential axial addition by the cyanide anions[11].



CN α/β (30/70) CN β only

10. Eckert, H.G.; Badian, M.J., Gantz, D.; Kellner, H.M.; Volz, M.; *Arzneim. Forsch./Drug Res.*1984, Nr 10b, *34* (11), (1984).

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