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SYNTHESIS OF UNNATURAL AMINO ACIDS : (S,S,S)-2-AZABICYCLO[3.3.0]OCTANE-3-CARBOXYLIC ACID

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Summary:

(S,S,S)-2-Azabicyclo[3.3.0]octane-3-carboxylic acid 1, a structural element of the very potent ACE inhibitor HOE 498, is readily available via a diastereo selective synthesis starting from serine or cystine.

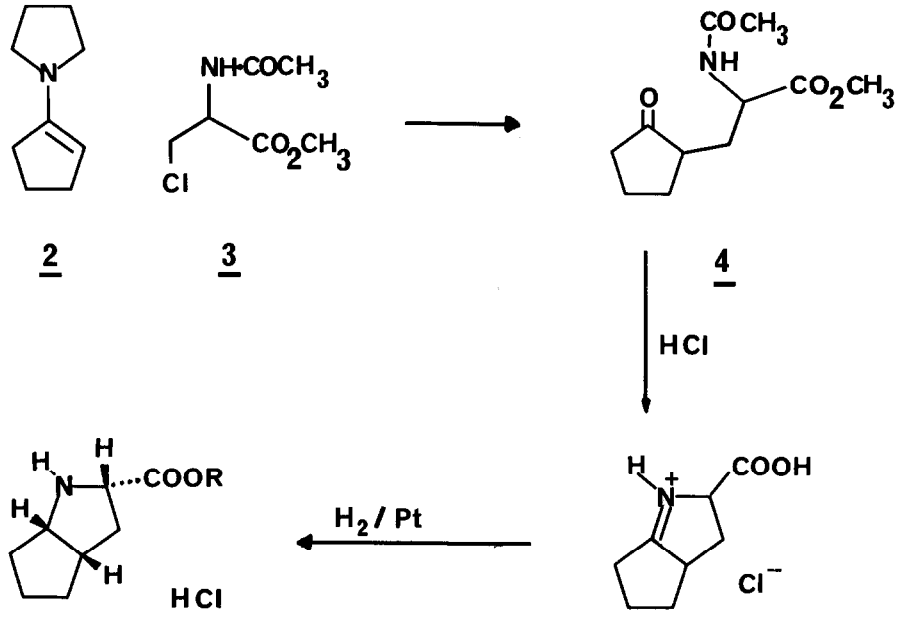
Introduction:

Hydrophobic interactions are known to play an important role in the binding of substrates or inhibitors to the active site of an enzyme. In persuit of this general knowledge some lipophilic and sterically demanding amino acids have been synthesized [1,2,3] to substitute proline residues in peptides, thereby improving bioavailability and pharmacokinetics as well as selectivity of these compounds.
(S,S,S)-2-Azabicyclo[3.3.0]octane-3-carboxylic acid 1 with 3 defined centres of asymmetry represents a crucial substructure of HOE 498, a very powerful inhibitor of the angiotensin converting enzyme (ACE), which currently undergoes preclinical and clinical investigations [5-10].

Chemistry:

The bicyclic amino acid 1 is synthesized via an enamine reaction (scheme). Starting from cyclopentenopyrrolidine 2 and the chloroalanine derivative 3, which can be obtained from N-acetyl-serine methylester by treatment with phosphorus pentachloride [15] or chlorination of cystine-diester [14], the intermediate 4 is generated [16].

During this reaction the α-chirality of serine is lost via double bond formation by elimination of HCl by the basic enamine (the dehydroalanine derivative can be detected by t.l.c). This facile formation of an α,β-unsaturated ester alters the reaction pathway normally encountered with chloroethanolamines [4] thereby making the reaction feasible.



2 3 4 5

1 R = H, (all S)
1a R = H, (R,S)
6 R = C_7H_7, (R,S)
6a R = C_7H_7, (all S)

On reflux in 2N HCl for 1 h compound 4 cyclises to the racemic imino acid 5 under cleavage of all protecting groups. The iminoacid can be isolated in crystalline form by evaporation of the solvent. Hydrogenation of compound 5 with Pd/C in acetic acid at 5 bar yields cis,endo-2-azabicyclo[3.3.0]-octane-3-carboxylic acid hydrochloride 1a, which remains as a racemic mixture after filtration and evaporation of the solvent. It can be re-crystallized from chloroform/diisopropyl ether [^{1}H NMR (D_2O), δ(ppm): 1.55 (1H, m), 1.65-1.90 (3H, m), 1.95 (1H, m), 2.62 (1H, m), 2.98 (1H, m), 4.17 (1H, m), 4.26 and 4.30 (1H, dd)].

The racemate is then transformed into the benzylester 6 (m.p.185°C) via the thionylchloride procedure [11, 17] and the optical resolution of the R,R,R- and S,S,S- form is achieved by crystallization of the diastereomeric salt with benzyloxycarbonyl-L-phenyl-alanine [18]. The (S,S,S)-benzylester hydrochloride 6 is hydrogenated in methanol with Pd/C as catalyst at r.t. and 0.1 MPa. On addition of diisopropylether to the filtered and concentrated solution the amino acid 1 (hydrochloride) precipitates in nearly quantitative yield; $[\alpha]^{30}_{D}$ -31.5° (c=1, 0.1N HCl).

Reference and notes

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(16) 1-Acetylamino-2-(2-oxo-cyclopentyl)propionic acid methylester : 269 g 3-chloro-2-acetylamino-propionic acid methylester 2 and 257 g freshly distilled cyclopentenopyrrolidine 3 are dissolved under nitrogen in 1.5 l DMF or alcohol and 1 equivalent of triethylamine is added. After 24 h at r.t. the organic solvent is evaporated i.vac. and the residue is dissolved in a small amount of water. The pH is adjusted with conc. HCl to pH 2 and the ester 4 extracted two times with 4 l ethyl acetate. Evaporation of the organic layer leaves a light yellow oil. Yield: 290 g

(17) cis,endo-2-Azabicyclo[3.3.0]octane-3-carboxylic acid benzylester hydrochloride : 120 ml benzylalcohol are cooled to 0°C. At this temperature 13 ml thionylchloride followed by 13 g of bicyclic amino acid hydrochloride 6 are added while stirring. The temperature is allowed to rise at r.t.. After about 15 h the solution is given into 400 ml diisopropylether. The crystallin precipitate is treated with ether and dried i.vac.. From the mother liquor some additional product can be obtained by moderate concentration. Yield: 17 g (91%); mp. 185 °C .

(18) (S,S,S)-2-Azabicyclo[3.3.0]octane-3-carboxylic acid benzylester hydrochloride 6a : 166 g racemic benzylester hydrochloride 6 are treated with 250 ml aqueous 10% sodium hydroxide. The free base is extracted with 500 ml and 100 ml methylene chloride. The organic layer is concentrated i.vac. and the remaining oil is dissolved in 100 ml ethyl acetate. After addition of a solution of 117 g N-benzyloxycarbonyl-L-phenylalanine in 200 ml ethylacetate and 1.6 l of cyclohexane 133 g diastereomeric salt (all S-form) precipitates:
m.p. 103-04 °C, $[\alpha]^{27}_D$ -6.1° (c=1, methanol).
The salt is dissolved in 600 ml methylene chloride and treated with 9.5 g sodium hydroxide in 300 ml water. The organic layer is dried over anhydrous sodium sulfate and concentrated to 200 ml. On addition of 200 ml diisopropylether and 50 ml of 6N HCl in ether compound 6 precipitates.
Yield:67.8 g, m.p. 180°C, $[\alpha]^{30}_D$ -38.4° (c=1, water).

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