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SYNTHESIS OF HYDROXYLATED PYRROLIDINES DERIVATIVES AS POTENTIAL INHIBITORS OF SAH/MTA NUCLEOSIDASE.

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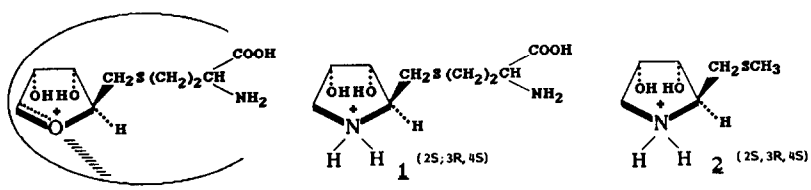
Summary : A enantioselective synthesis of a new series of dihydroxylated pyrrolidines derivatives is described.

S-adenosyl-L homocysteine (SAH) is an important metabolic product in a variety of processes (1,2) in procaryotes. This compound as well as 5'-methyl thioadenosine (MTA) are substrates for SAH/MTA nucleosidase which catalyses their splitting into adenine and S-ribosyl L-homocysteine or 5'-methylthioribose, respectively (3,4,5). This enzyme plays a fundamental role in these cells (-recovery of enzymatic activity of methylase through the splitting of SAH (3,4) -regulation of in vivo concentration of MTA, a potent inhibitor of spermine and spermidine synthase) (6,7) and may be considered as an attractive target for the design of antibacterial agents.

On the basis of the mechanism proposed for the acid solvolysis of adenine nucleosides (8) a plausible mechanism, for catalytic cleavage of the glycosidic bound of SAH and MTA, passing through an oxocarbanium ion intermediate can be hypothesized.

Our first experiments directed to inhibit this enzyme (9) and several exemples of specific inhibition of glycosidase by piperidine derivatives (10) led us to consider that hydroxylated pyrrolidines 1, 2 bearing homocysteinyl or methylthio residues should be good candidates as "transition state analogue" inhibitors (11) of SAH/MTA nucleosidase.



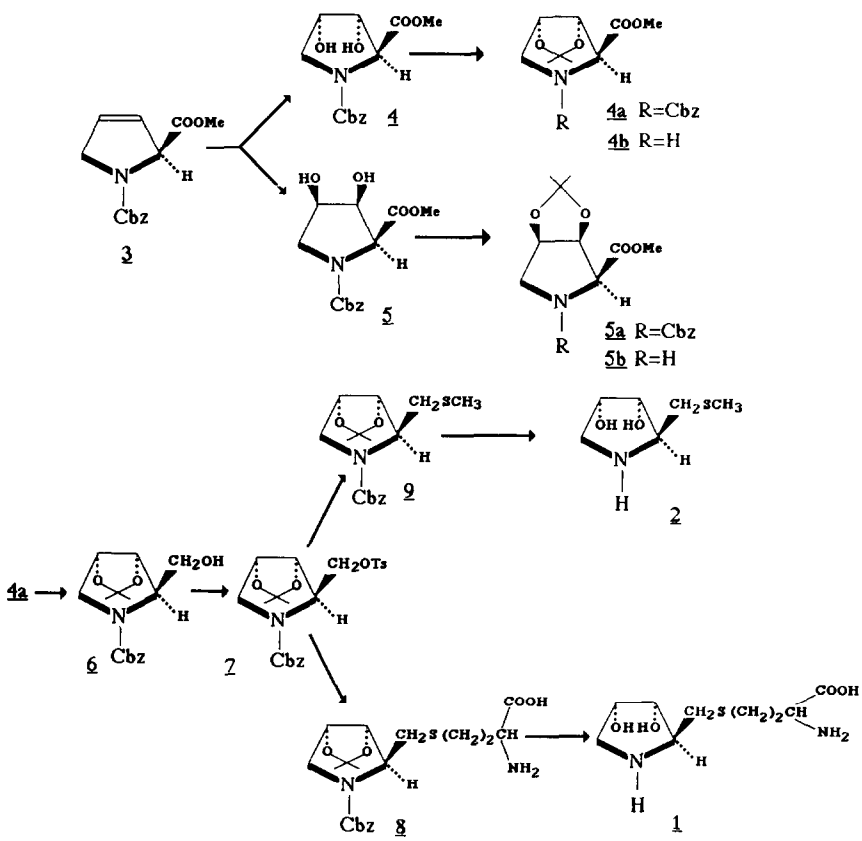
Scheme 1

The ammonium group of these derivatives should of course act by mimicking the oxocarbonium ion involved in the catalytic process of the target enzyme (Scheme 1).

The route selected (scheme 2) for the enantioselective synthesis of 1 and 2 is based on the stereoselective cis-glycosylation (12) of the suitabely protected (S)-3,4 dehydroproline 3 $[\alpha]_D^{20}$=-210.5 (c 1.7, $CHCl_3$). This compound was prepared in five high yield steps from (2S, 4R)-4 hydroxyproline 3 according to the method described by M.H. Benn (13).

Catalytic osmium tetroxyde cis-dihydroxylation of 3 (MNO-OsO_4, aq. acetone, tBuOH (14)) gave in 78 % yield a mixture 4, 5 (97:3, NMR determination).

Subsequent protection of hydroxyl groups of 4 + 5 as isopropylidene derivatives (quantitative yield) permitted an efficient separation of 4a (15) $[\alpha]_D^{20}$=-34.0 (c 1.0, $CHCl_3$) and 5a $[\alpha]_D^{20}$=-46.5 (c 2.3, $CHCl_3$) by flash chromatography (silicagel : AcOEt/Hexane : 1.3/2).



Scheme 2

Reduction of 4a by lithium borohydride in dry ether afforded the alcool 6 (95 %) $[\alpha]_D^{20}$=-46.0 (c 1.08, $CHCl_3$). Treatment of 6 with paratoluenesulfonyl chloride gave the key intermediate 7 mp : 84.5°C, mass spectrum DCI/NH_3, m/z : 462, $[\alpha]_D^{20}$=-108.4 (c 1.03, $CHCl_3$).

Nucleophilic displacement of the tosylate group with sodium L-homocysteinate (generated from L-homocysteine) or sodium methyl sulfide in liquid ammonia afforded in satisfactory yield 8 (72 %) $[\alpha]_D^{25}$=-5.8 (c 2.04, H_2O) and 9 (84 %) $[\alpha]_D^{20}$=-41.6 (c 0.9, $CHCl_3$) respectively.

At this stage, the same procedure was applied for the removal of the protecting group. 8 and 9 were treated with trimethylsilyl iodide for the splitting of N.Cbz according to litterature method (17). Usual work up gave crude N deprotected derivatives which were treated without furter purification with Dowex 50WX4 H^+ for removal of isopropylidene groups.

The pyrrolidine derivatives were eluted from the resin with NH_4OH 1N after washing with water. The ninhydrin positive fractions (for compound 1) and 4-dimethylaminobenzaldehyde positive fractions (for 2) gave after lyophilysation pure 1 (76 %) (19) and 2 (70 %) (20).

Biological activity of these compounds will be reported elsewhere.

References and Notes

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15. The two conformers (16) resulting from hindered rotation of N-C=O bound of N-CBz proline are obstacles to complete NMR analysis. Subsequent hydrogenolis (16) of N-CBz group of 4a and 5a (10 % Pd/C, ammonium formate in methanol) gave 4b and 5b respectively (98 %). 4b, ^{1}H NMR ($CDCl_3$, 250 MHz) δ ppm : 4.92 (H3, d, J=6 and ≅0.1 Hz); 3.90 (H2, s broad, J≅0.1 Hz) ; 3.75 (s, $COOCH_3$) ; 3.15 (N-CH_2, 1H, dd, J=14 (gem) and 4 Hz) ; 2.95 (N-CH_2, 1H, J=14 (gem) and 0.1 Hz) ; 1.50 + 1.34 (s, $O(CH_3)_2$). 5b, 1H NMR ($CDCl_3$, 250 MHz) δ ppm : 4.72 (H3, dd, J=5.2 and 4.7 Hz) ; 4.64 (H4, dd, J=3.3 and ≅0.1 Hz) ; 3.78 (s, $COOCH_3$) ; 3.64 (H2, d, J=4.7 Hz) ; 3.24 (N-CH_2, 1H, d broad, J(gem)=13.6 Hz) ; 3.01 (NH) ; 2.73 (N-CH_2, 1H, dd, J=13.6 (gem) and 3.3 Hz) ; 1.42 + 1.22 (2s, $C(CH_3)_2$). In both case coupling constants are consistant (17) with the assigned structures.

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19. Mass spectrum (DCI ; NH_3) m/z : 251 ; 1H NMR (D_2O, 250 MHz) δ ppm : 4.21 (H4, m) ; 3.95 (H3, dd, J=8 and 4.8 Hz) ; 3.65 (H2, m) ; 3.40 + 3.14 (m, 3H, -CH + -CH_2-N) ; 2.85 + 2.90 (m, CH_2-S) ; 2.54 (t, S-CH_2, J=7 Hz) ; 1.85 + 2.15 (m, 2H, CH_2-CH_2-CH).

20. Mass spectrum (DCI ; NH_3) m/z : 164 ; α D=76.92 (c 0.48, H_2O) ; 1H NMR (D_2O, 250 MHz). δ ppm : 4.20 (H4, m) ; 2.95 (H3, dd, J=8 and 4.8 Hz) ; 3.50 (H2, m, J=9.6, 4.8 and 4.6 Hz) ; 3.35 (H5, dd, J=14.4 (gem) and 4.8 Hz) ; 3.14 (H5, dd, J=14.4 and 1.6 Hz) ; 2.85 (dd, 1H, CH_2-S, J=14 (gem) and 9.6 Hz) ; 2.60 (dd, 1H, CH_2-S, J=14 (gem) and 4.6 Hz) ; 1.96 (s, S-CH_3).

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