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PROTECTED-AOE ANALOGUES of CHLAMYDOCIN

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Abstract :c[(2S,9R)8-dithianAoe*-(2R)-Pro] 1 and c[(2R,9R)8-dithianNMe-Aoe*-(2S)Pro] 2 have been prepared as protected analogues of chlamydocin.

Chlamydocin :c[(S)Aoe-Aib-(S)Phe-(R)Pro] is a very potent *in vitro* cytostatic agent (1). Unfortunately, this cyclopeptide is quickly inactivated *in vivo* (2).

Temporary protection of the activity-essential keto-epoxide function of the Aoe* side chain has been attempted giving the model cyclodipeptide 2 by direct alkylation of the cyclopeptide ring which constitutes a rather new way of cyclopeptide modification. For comparison, the very close compound 1 has been synthetized in a more usual way via preparation of a protected Aoe precursor then peptide construction followed, by cyclization.

The syntheses of chlamydocin (3-5) or related cyclotetrapeptides : HC-toxin c[(S)-Aoe-(R)Pro-(S)Ala-(R)Ala] (6,7) or WF_{3161} c[(S)-Aoe-(R)Phe-(S)Leu-(S)Pip] (8) have been always performed starting from an Aoe-precursor amino acid chosen for its stability during the subsequent peptide building-up. As the cyclisation remains very frequently the yield restricting step, we wished to develop another strategy based upon the post-modification of a cyclotetrapeptide built from readily available aminoacids. In this way, cyclosporin A has been modified on the α-carbon atom of the Sar residue by Seebach (9). The methylation has been performed after treating cyclosporin with LDA in THF containing LiBr at -78° on the resulting polyanion carrying a deprotonated Sar residue. This reaction was both regiospecific and highly stereoselective. These very good selectivities have been explained by a thermodynamically stable aggregation between the peptide polyenolate anion, the salt and the solvent (10).

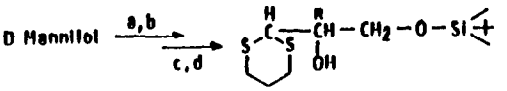
Moreover, owing to the higher stability of the cyclopeptide alternated sequence [Aib-(S)-(R)-(S)] over the epimeric one [Aib-(S)-(R)-(R)] as judged by the large difference in their cyclization yield from the two linear precursors (3,4), one can expect a high degree of stereoselectivity toward the required configuration of the new chiral center of the cyclopeptide.

* Aoe : 2-amino 8-oxo (9,10)-epoxydecanoic acid

As an example of this new strategy leading to protected chlamydocin analogues, alkylation of [Pro-Gly] and [Pro-Sar] has been performed :

Direct cyclopeptide alkylation of c[Pro-Gly] and c[Pro-Sar] :

Two strategies are outlined in Scheme 1 for protected Aoe lateral chain introduction. The dithian protected keto group can be introduced by a Corey reagent 3 derived from D-mannitol via D-glyceraldehyde :



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a)$ZnCl_2$,acetone,22h, 20° (63%); b) $NaIO_4$,CH_2Cl_2,H_2O,1h 32°(90%) ;c)HCl,$HS(CH_2)_3SH$,1h 20° (80%); d) TBDMSiCl,Et_3N,DMAP/CH_2Cl_2, 4h, 20° (96%).

Cyclopeptide alkylation has been followed by a Corey reaction (Pathway A Scheme 1): With R=CH_3, alkylation goes pretty well in the presence of LiBr (5eq), LDA and BuLi(1eq) without detectable racemization : starting from [(R)Pro-Sar], alkylation by iodopropane gives [(R)Pro-(S)NMeNorVal] (70%). Only one ^1H NMR N-CH_3 signal at δ=2.57 ppm (C_6D_6) is observed as in the case of an authentic sample obtained after (R)Pro-(S)NorVal cyclization followed by N-methylation (11).With diodopentane, the iodoalkyl product is obtained (60%) with the same high optical purity.

Conversely, with R=H, the alkylation does not take place except, but with a poor yield (20%), if complexing cations ($MgBr_2$ or $ZnCl_2$) are added.This result indicates the large influence of the remaining amidic proton next to the alkylation center.

The second step of Pathway A, in which iodine atom is substituted by the Corey dianion of 3 formed by BuLi + HMPA, gives unsatisfactory results : a poor chemical yield (30%) and above all, a complete racemization of the α carbon detected by the splitting of ^1H NMR NCH_3 signal.

This way has been discarded and Corey's reagent introduced prior to peptide alkylation has given good results (only one epimer in 70% yield) (Pathway B, Scheme 1). The title compound 2 is quickly obtained after standard deprotection, tosylation and epoxidation and gives satisfactory analytical data (12).

Amino acid synthesis and cyclization :

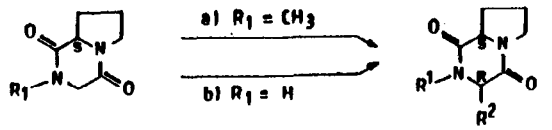
The other more common way has been followed for comparison, starting from the stereoselective alkylation of the Schiff base of pinanone (13) with the alkylation agent 4 (Scheme 2).

During the BOC deprotection step (d, Scheme 2), acetonide diol deprotection also occurs which, in the case of a larger peptide, should be avoided..

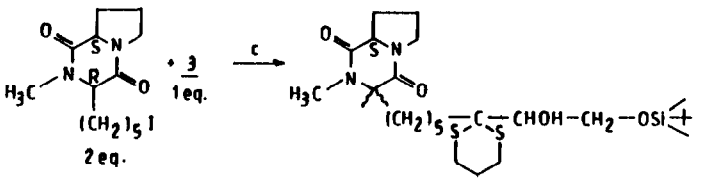
Compared with the first one, (Scheme 1 Pathway B) this route, although feasible, seems to be much longer, more complicated and less efficient.

Scheme 1

Pathway A :

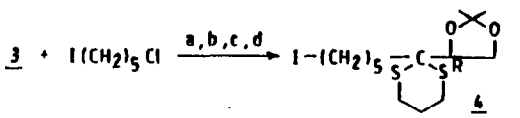


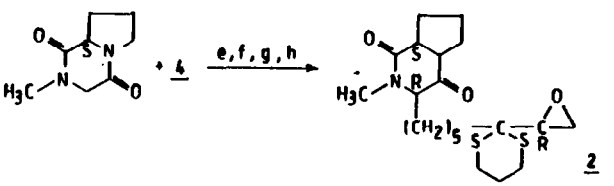
a) $R_1=CH_3$: $R_2=(C_3H_7, C_5H_{10}I)$ 2eq, LDA 1eq, BuLi 1 eq, LiBr 5 eq, THF -78° 12h;(70%).
b) $R_1=H$: $R_2=C_3H_7$ 2 eq, LDA, $MgBr_2$ 2 eq, THF -70°,24h (20%).



c) BuLi 2.2eq, HMPA 10 eq, Hexane - 78°, 3h(30%)

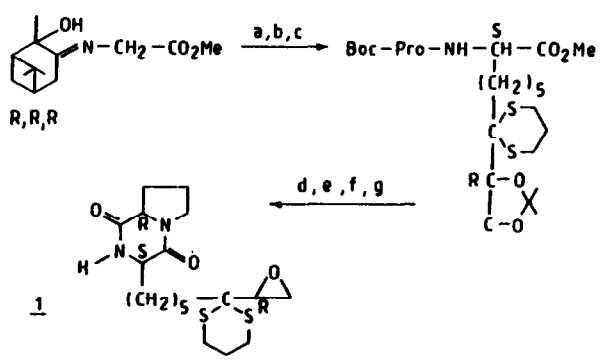
Pathway B :





a) 3 1eq, BuLi 2eq, HMPA 10 eq, $I(CH_2)_5Cl$ 2eq, THF-78° 3h (70%);b) nBu_4NF 3eq,THF, 20° 1h (98%); c) 2,2-Dimethoxypropane 1.1 eq, PTS acid 0.01 eq, $CHCl_3$ molecular sieve 4A 61°, 3h(80%); d) NaI 5 eq, acetone(95%); e) 4 2 eq, LDA 1 eq, BuLi 1eq, LiBr 5 eq, THF-78° 6h (60%); f) HCl 2N/THF (1v/1v), 0° 1H (95%); g) TsCl 1.1eq, Pyridine -5°, (90%); h)10ml NaOH 0.1N/CH_3OH (1v/1v), 1mmol monotosylate, -10°, 6h (75%).

Scheme 2



a) 4 2eq, LDA 2.2 eq, THF -78°, 12h (52%);b) Citric acid,THF,0°,96h (95%);c)(R)Boc Pro 1eq, DCC+HOBt (1eq), 20°, 12h (80%); d) TFA/CH_2Cl_2 (1v/1v),0.5h 0°(100%);e) CH_3OH /NH_3, 20°, 48 h (75%); f,g as in g and h of Scheme 1.

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