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SYNTHESIS OF PEPTIDE ALKALOIDS-III[1)]. AMINO ACIDS AND PEPTIDES-XXXII. SYNTHESIS OF DIHYDRO-ZIZYPHINE A AND B

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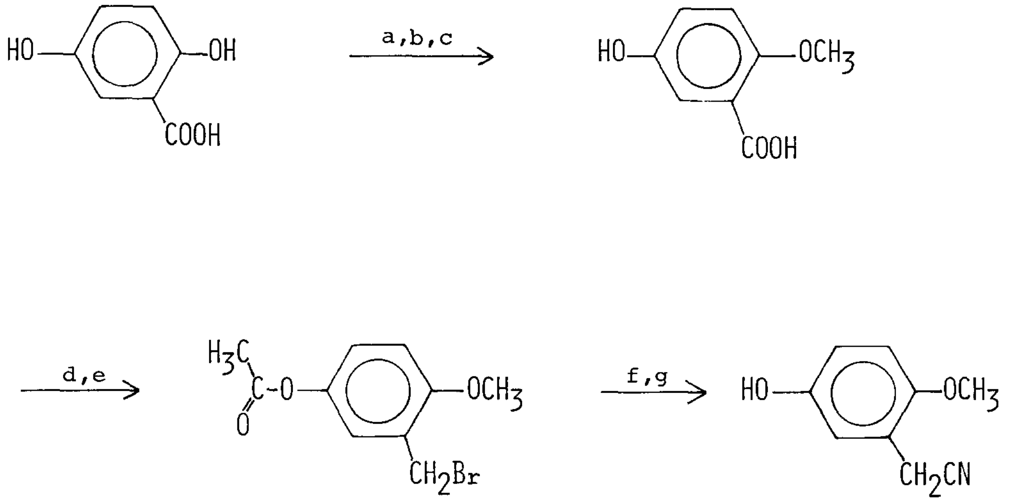
Summary: Recently we described[2] a new cyclisation method for the synthesis of ansa peptides by hydrogenolysis of Z-pentafluorophenyl ester and ring closure on the surface of the palladium catalyst. We applied this reaction to the synthesis of the 14-membered ansa peptide dihydro-zizyphine G[1]. Here we wish to report the synthesis of the 13-membered ansa peptides dihydro-zizyphine A (8a) and B (9a)[3].

The phenol 1 was prepared using conventional methods (a-g) (65 % yield from gentisic acid) and was reacted[4] with bromodehydroproline ester forming the corresponding phenoxydehydroproline ester 2. Saponification and treatment with dimethylamine borane gave a mixture of cis- and trans-phenoxyproline derivatives 3, which were transformed into the BOC-esters 4 (90 % yield) and separated by medium pressure chromatography using silicagel and petrolether/ethylacetate. Saponification of the trans-methyl ester, hydrogenation of the nitrile group (Rh/Al_2O_3; 84 % yield) and coupling with S-Z-proline-hydroxysuccinimide ester provided an inseparable mixture of the two diastereomers 5a + 5b (94 % yield), which were reacted with pentafluorophenol/DCC to the substrate 6a + 6b of the ring forming reaction (70 % yield). The ring closure was achieved by dropping the pentafluorophenyl ester using dilution conditions into a rapidly stirred suspension of Pd/C in dioxane at 95°C containing pyrrolidinopyridine, ethanol and alumina into which hydrogen was passed.

In view of our experience[1] we believed that probably the "desired" SSS-ring product 7a would be formed in a better yield than the RRS one, 7b. The SSS-isomer 7a (which corresponds to the configuration of the natural compounds) indeed was isolated from the mixture of the two diastereomers in a 98 % yield by medium pressure chromatography using silicagel and ethylacetate (yield of the RRS-isomer was 65 % only). Removal of the BOC-group by trifluoroacetic acid, coupling with BOC-isoleucine/DCC (60 % yield), deblocking of the BOC-group and reaction with activated dimethyl-isoleucine gave dihydrozizyphine A 8a (60 % yield). Reaction of 7a after deblocking of the BOC-group with BOC-N--methyl-isoleucyl-isoleucine/DCC and subsequent removal of the BOC-group lead to dihydro-zizyphine B 9a (60 % yield from 7a). - All new compounds reported gave satisfactory NMR and MS spectra.

Scheme



1

a: $PhCH_2Cl/KOH$

b: Me_2SO_4, K_2CO_3/acetone - saponification: $NaOH/H_2O$

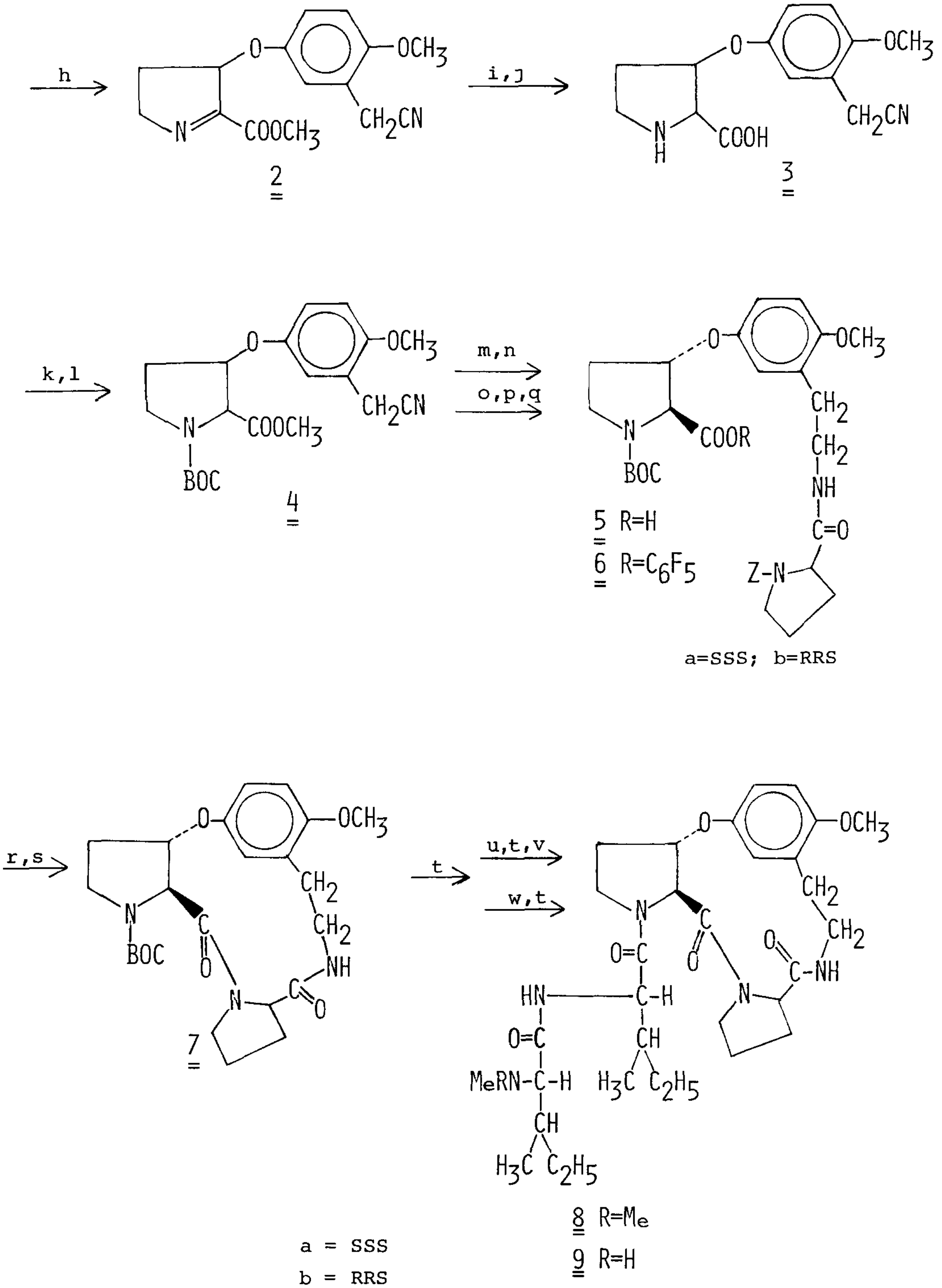
c: Pd/C-5%/EtOH

d: B_2H_6/THF

e: AcBr

f: $Et_4N{\cdot}CN/CH_2Cl_2$

g: NH_3/H_2O


h
OCH3
COOCH3
CH2CN
2
i,j
COOH
3
k,l
BOC
4
m,n
o,p,q
COOR
NH
C=O
Z-N
5 R=H
6 R=C6F5
a=SSS; b=RRS
r,s
7
a = SSS
b = RRS
t
u,t,v
w,t
HN
C-H
MeRN-C-H
H3C C2H5
8 R=Me
9 R=H

h: Bromodehydroproline ester/DMF. - i: H_2O/OH^-. - j: $Me_2NH{\cdot}BH_3/AcOH$. - k: $(t\text{-}BuO)_2C_2O_3$. - l: CH_2N_2/Et_2O. - m: separation of the resulting cis-trans BOC-phenoxyproline esters 4 by medium pressure chromatography: silicagel, petrolether/ethylacetate 1:1, cis:trans = 1:1. - n: OH^-/H_2O. - o: $H_2/Rh\text{-}Al_2O_3$. p: Z-Pro-OSUCC. - q: C_6F_5OH/DCC. - r: cyclisation by hydrogenation conditions[2]. s: separation of the ring-diastereomers 7 by medium pressure chromatography: silicagel, ethylacetate. - t: TFA. - u: BOC-Ile/DCC. - v: activated dimethyl isoleucine. - w: BOC-Me-Ile-Ile/DCC.

Comp.	m.p.	[α]	MS	NMR [δ (ppm)] ($CHCl_3$)
1	109°C			3.70(s,2), 3.87(s,3), 6.7-7.1(m,3)
2				1.8-2.6(m,2), 3.65(s,2), 4.25(t,2), 5.40-5.60(m,1), 3.80(s,3), 3.90(s,3), 6.75-7.05(m,3)
7a		$[\alpha]_D^{20}$ -178.7° (c=0.904;MeOH)	m/e 459(M^+)	
7b		$[\alpha]_D^{20}$ +164.1° (c=1.03;MeOH)	m/e 459(M^+)	
8a		$[\alpha]_D^{26}$ -160° (c=0.21;$CHCl_3$)	m/e 613(M^+)	
9a		$[\alpha]_D^{20}$ -133° (c=0.12;$CHCl_3$)	m/e 599(M^+)	

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References and Footnotes

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