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Synthesis of a Model of Chloropeptins I, II Western Subunit by the Intramolecular S_NAr Based Methodology

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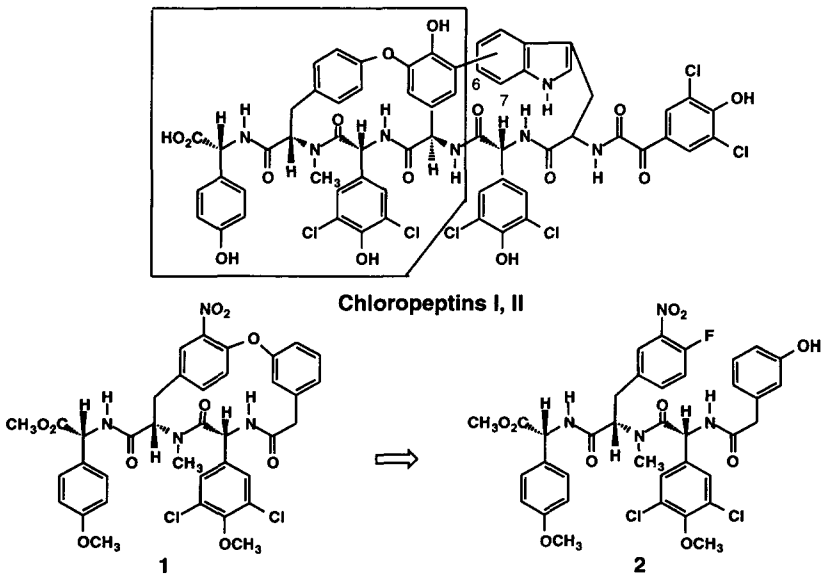
Abstract : Formation of a biaryl ether bond between the termini of a tetrapeptide containing a highly racemization prone amino acid by the intramolecular SNAr reaction afforded two diastereomeric 16-membered macrocycles along with their respective atropoisomers. The (R,S,R) and its atropoisomer constituted a model of chloropeptins I, II western part. © 1997 Published by Elsevier Science Ltd.

Chloropeptins I and II are produced by a soil actinomycete, *Streptomyces* sp. WK-3419.[1] These compounds were found to exhibit interesting biological activities.[2] Structurally, these fused polypeptidic bicyclic compounds are characterized by :

- a 16-membered ring containing a biaryl ether bond common to chloropeptins I, II (western subunit),
- a 16- or 17-membered ring linked by a carbon-carbon bond from position 7 or 6 of tryptophane (chloropeptin I or II) and by a peptidic bond to 3,5-dichloro-4-hydroxy-phenylglycine (eastern subunit).

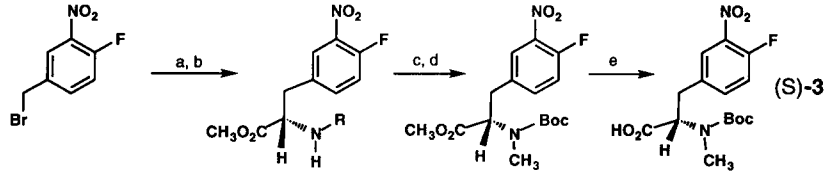
No total synthesis has been reported and we describe here an approach towards the synthesis of the subunit **1** (western part) based on ring closure of a linear peptide **2**, according to the intramolecular S_NAr based methodology[3] (Scheme 1).



Scheme 1

The linear precursor **2** consists of 3-hydroxyphenylacetic acid (as model of the central amino acid), *(R)*-*p*-methoxyphenylglycine-methyl ester and two non proteinogenic amino acids *(S)*-**3**[4] and *(R)*-**7A**.

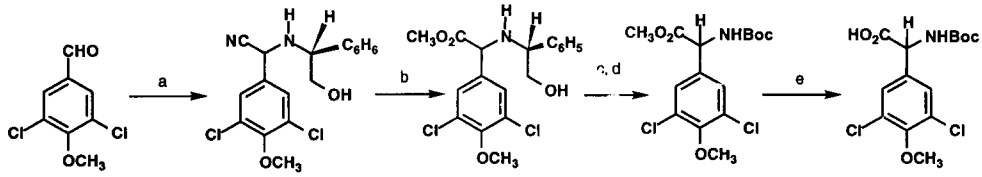
(S)-*N*-Boc-*N*-methyl-4-fluoro-3-nitrophenylalanine *(S)*-**3** was obtained in four steps by alkylation of *(S)*-Schollköpf's bislactim ether with 3-nitro-2-fluoro-bromotoluene[5] followed by *N*-Boc protection, *N*-methylation and hydrolysis (Scheme 2).



Reagents and conditions. a: *(S)*-Schollköpf's reagent, n-BuLi, CuCN, THF, -20°C, 54%; b: TFA, CH_3CN, H_2O, 65%; c: Boc_2O, NEt_3, THF, 54%; d: CH_3I, Ag_2O, DMF, 83 %; e: K_2CO_3, MeOH, H_2O, 90%

Scheme 2

(R)-*N*-Boc-3,5-dichloro-4-methoxyphenylglycine **7A**, was prepared by the standard Strecker methodology[6] from 3,5-dichloro-4-methoxybenzaldehyde using *(S)*-phenylglycinol as chiral inducing agent (Scheme 3). A mixture of diastereomeric aminonitriles **4A**, **4B** was obtained (*de* 50%), whose separation was realized after conversion to the mixture of methyl esters **5A, 5B.** The *(R)*-absolute configuration of the major aminonitrile **4A** and that of the corresponding ester **5A**, were established by ^1H NMR spectroscopy.[7] The configuration of the target compound **7A** was confirmed by dehalogenation to the known *(R)*-4-methoxyphenylglycine derivative **8b**.

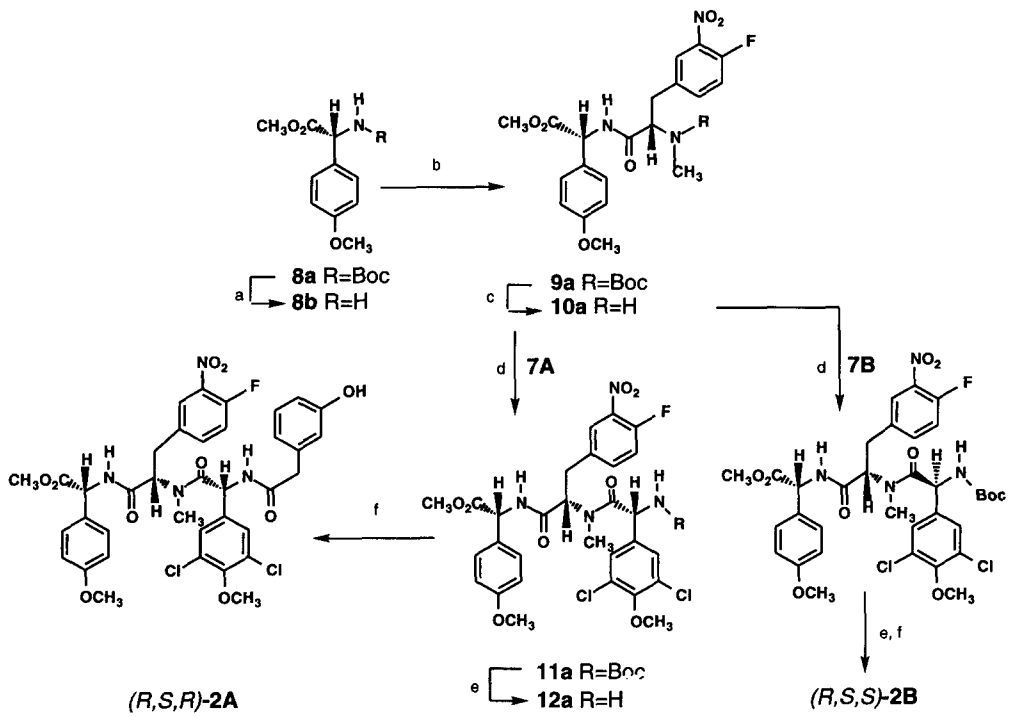


Reagents and conditions: a: (S)-Phenyl glycinol, TMSCN, $CHCl_3$, 0°C, 61%, (de 50%); b: MeOH-HCl, 88%; c: $Pb(OAc)_4$, CH_2Cl_2, MeOH, 0°C, 82%; d: Boc_2O, NEt_3, THF, 92 %; e: K_2CO_3, MeOH 67%

Scheme 3

Coupling of *(S)*-**3** with *(R)*-p-methoxyphenylglycine methyl ester **8b** yielded dipeptide **9a** (92%) in pure form. Removal of the Boc protecting group was smoothly realized by trimethylsilyl iodide. By using bromo-tris(pyrrolidino)phosphonium hexafluorophosphate (Pybrop)[8], the deprotected compound **10a** was coupled with the Boc protected amino acid *(R)*-**7A** to give **11a** in fair yield (65%), without appreciable racemization. Deprotection of the latter and coupling with *m*-hydroxyphenylacetic acid gave the expected model tetrapeptide *(R,S,R)*-**2A** in good yield (81%) (Scheme 4).

The macrocyclisation reaction of the *(R,S,R)*-tetrapeptide **2A** was first attempted under our classical conditions[3] (K_2CO_3, DMF). The reaction proceeded slowly and, after 40 h (entry 1), a mixture of six compounds was obtained. For sake of comparison, the diastereomeric tetrapeptide *(R,S,S)*-**2B**, (obtained with the enantiomer *(S)*-**7B** by the reaction sequence which had led to **2A**) was submitted to identical conditions, and found to undergo an equally slow cyclisation (entry 2). Cyclisation of **2A** under different conditions ($KHCO_3$, THF, crown ether) (entry 3) proceeded like that described in entry 1. In contrast to the first three reactions, cyclisation of **2B** (entry 4) occured much faster to give a mixture of four products **1A, 1A'** and **1B, 1B'** which were separated, purified and identified[9]. Under conditions prevailing in this reaction, the very racemization



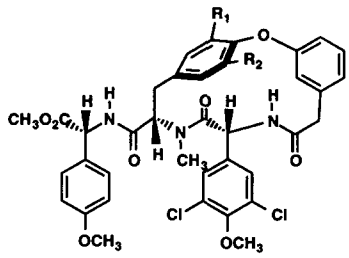
Reagents and conditions. a: HCl, MeCN, 89%; b: *(S)*-**3**, HOBT, EDC, NEt_3, CH_2Cl_2, 92%; c: TMSCl, INa, $CHCl_3$, 94%; d: PyBrOP, CH_2Cl_2, 0°C, 65%; e: TMSCl, INa, $CHCl_3$, 90 %; f: m-hydroxyphenylacetic acid, HOBT, EDC, CH_2Cl_2, 81 %

Scheme 4

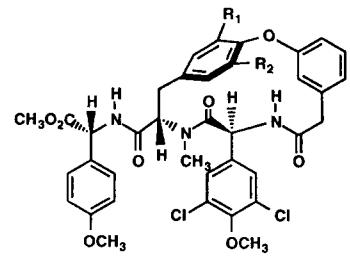
prone *(S)*-3,5-dichloro-4-methoxyphenylglycine which is part of the *(R,S,S)* peptide **2B** racemized. The mixtureof two diastereomeric peptides thus generated led to macrocycles *(R,S,R)* **1A** and *(R,S,S)* **1B**, along with their respective atropoisomers **1A'** and **1B'** (Scheme 5). With pure samples of **1A**, **1A'**, **1B**, **1B'** in hand, we were able to identify unambigously those compounds among the mixture of six products formed in the first three experiments (entry 1-3). The structures of the two products accompanying in various proportions **1A-1A'** and **1B-1B'**were assigned as diastereomeric macrocycles *(S,S,R)* **1C** and *(S,S,S)* **1D** whose predictable atropoisomers **1C'** and **1D'** could not be characterized in the NMR spectra. Formation of **1C** and **1D** indicates that *(R)*-4-methoxy-phenylglycine-methyl ester, which was stable for 5 hours (entry 4), became slowly epimerized within 40 hours (entries 1-3).

Entry	Tetrapeptide	Conditions	Conversion %[a]	Products %[a]					
				1A	**1A'**	**1B**	**1B'**	**1C**	**1D**
1	*(R,S,R)* **2A**	K_2CO_3, DMF; 40h :	90	16	10	19	12	23	20
2	*(R,S,S)* **2B**	— id — ; 40h :	70	28	12	34	14	6	6
3	*(R,S,R)* **2A**	$KHCO_3$[b], THF; 40h :	70	18	9	23	12	19	19
4	*(R,S,S)* **2B**	— id — ; 5h :	100; 60[c]	30	15	37	18	0	0

[a]Ratio obtained from ^1H NMR data. [b]18-Crown-6. [c]Yield of isolated products.



(R,S,R)



(R,S,S)

(S,S,R)

(S,S,S)

1A: R_1=H; R=NO_2
1A': R_1=NO_2; R_2=H

1B: R_1=H; R_2=NO_2
1B': R_1=NO_2; R_2=H

1C

1D

Scheme 5

Conclusion

As the intramolecular SNAr methodology is becoming more widely used,[10a-c] there is to emphasize that the minimal basic conditions required to perform the ring closure reaction might be detrimental to the diastereomeric purity of the macrocycle when a highly racemization prone amino acid is part of the polypeptidic linear precursor. However, macrocycle *(R,S,R)* **1A**, and its atropoisomer **1A'** have been obtained. Both are models of chloropeptins I, II, whose position *ortho* to the biaryl ether bond is unsubstituted.

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