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Synthesis of diastereomerically pure 1,4,5-substituted-2-oxopiperazines on solid-phase

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Abstract—The first studies toward the solid-phase synthesis of 1,4,5-substituted-2-oxopiperazines are reported. The synthetic strategy is based on reductive alkylation of resin-bound amino acids using *N*-protected α-amino aldehydes (with concomitant epimerization), followed by acylation with α-chloroacetyl chloride. Subsequent stereoselective on-bead intramolecular cyclization has led to a diastereomerically pure 2-oxopiperazine.

Oxopiperazines constitute an important class of peptidomimetics where one of the peptide amide bonds (-CONH-) has been replaced by a non-hydrolysable ψ(-CH_2NH-) isostere. Substituted oxopiperazines are components of a variety of bioactive compounds that among the more recently reported include: substance P analogues,[1] farnesyltransferase inhibitors,[2] non-peptide GPIIb/IIIa antagonists[3] and geranylgeranyltransferase-I inhibitors.[4] Synthetic approaches to 2-oxopiperazines involve the condensation of *N*-(chloroethyl)glycinate with amines,[5] mono-protected ethylenediamines with α-haloacetic acid derivatives[6,7] or the ring closure of a linear precursor to form the piperazinone amine[8,9] or amide[10] bond. To date all solid-phase syntheses of 2-oxopiperazines have been based on the last route giving C-3[11] or C-6[12] monosubstituted derivatives and C-(3,5)[13] and C-(3,5,6)[14] multisubstituted derivatives. Among the previous precedents, both on solid or solution phase, the preparation of chiral monosubstituted piperazinones has been based on either the use of optically active starting materials or by the induction of chirality by placing a chiral auxiliary on the anilino nitrogen and using conformationally controlled stereoselective reactions.

In this paper we report the first studies toward the solid-phase synthesis of a diastereomerically pure 1,4,5-substituted-2-oxopiperazine. Our synthetic strategy is based on the on-bead cyclization of a precursor obtained by reductive alkylation of resin-bound amino acids with *N*-protected α-aminoaldehydes, followed by acylation with α-chloroacetyl chloride. As a consequence of epimerisation of α-aminoaldehydes during the reductive amination step, a diastereomeric mixture of pseudodipeptide precursor was formed. However, only one diastereomer was selectively obtained after *N*-capping and cleavage.

The synthetic route was first exemplified for the synthesis of compound **7a** (Scheme 1). Fmoc-(*S*)-leucine immobilised on Wang resin (**1**) was deprotected and subsequently reductively alkylated with *N*-Fmoc-(*S*)-phenylalaninal[15] (*S*)-**2a** to generate a diastereomeric mixture[16] of pseudodipeptides **3** and **3′**. The *indirect* reductive amination procedure[17] was used. The imine was pre-formed on solid-phase via sonication[18] and the excess aldehyde was removed by filtration. IR spectroscopy and Kaiser test analysis indicated complete imine formation. Subsequent reduction with sodium triacetoxyborohydride gave **3** and **3′** based on HPLC and LC–MS analysis of the retentate after TFA-cleavage of a resin aliquot. Diastereoisomers **3** and **3′** were acylated with chloroacetyl chloride to give resins **4** and **4′**, which were analysed after TFA-cleavage of a resin aliquot. HPLC–ELSD (evaporative light scattering detection) and (UV) LC–MS analysis of this filtrate showed two peaks of equal molecular mass at a ratio of 1:1, presumed to be the two diastereoisomers (2*S*,5*S*) and (2*S*,5*R*), generated by epimerization of the C-5 centre.[19] Subsequent Fmoc-deprotection, on-bead intramolecular cyclization and *N*-capping of the resin-bound secondary amine **6′** with *p*-toluensulfonylchloride led to the final product **7a** after TFA cleavage.

Post-cleavage analysis of **7a** by HPLC–ELSD and LC–MS gave a single peak with the expected [MH^+] molec-

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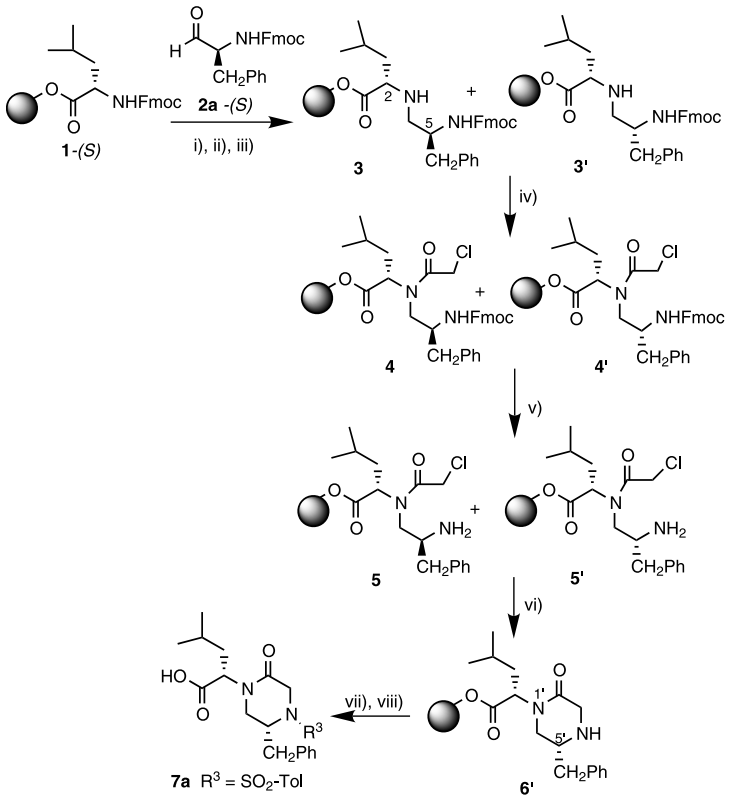


Scheme 1. *Reagents and conditions*: (i) 20% piperidine in DMF; (ii) (*S*)-*N*-Fmocphenylalaninal (**2a**); (iii) $Na(AcO)_3BH$; (iv) α-chloroacetyl chloride, DIPEA; (v) 20% piperidine in DMF; (vi) DIPEA, DCM, overnight; (vii) DIPEA, R^3Cl; (viii) TFA.

ular ion. Analysis by ^1H and ^{13}C NMR spectroscopy of the purified product (31% yield, based on initial loading) gave strong evidence that only one diastereoisomer was present in the product. X-Ray crystallography (Fig. 1) established that the C-5′ centre of the oxopiperazine ring, derived from (*S*)-phenylalaninal (**2a**), actually had *R*-configuration and that the stereocentre derived from (*S*)-leucine (**1**) (C-2) was retained.

The stereochemical configuration of single product **7a** (2*S*,5′*R*) confirmed that the C-5′ centre must have epimerised, presumably during reductive amination, and that loss of the (2*S*,5′*S*) diastereomer must have occurred during the synthetic sequence. Indeed, repeating the synthesis from Fmoc-(*S*)-leucine but using the antipode Fmoc-(*R*)-phenylalaninal also gave a single product diastereoisomer with both a HPLC–ELSD trace and ^1H NMR spectrum identical to **7a**.

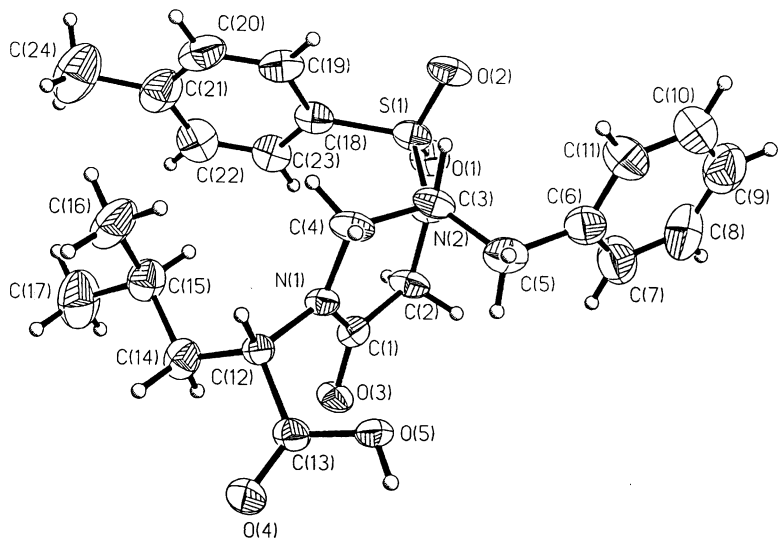
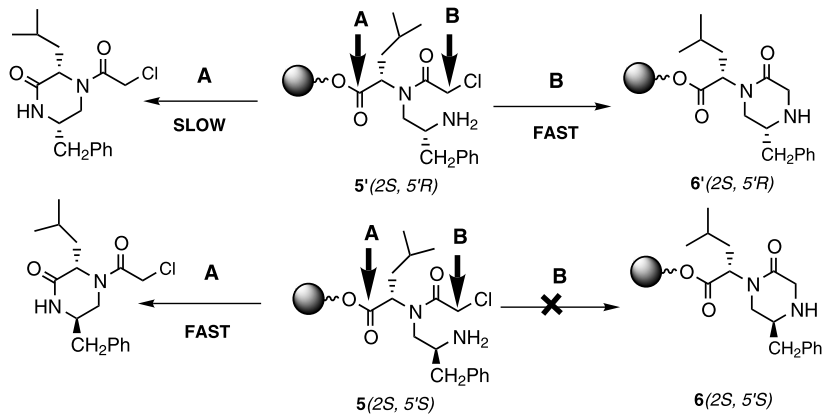


Figure 1. X-Ray structure for compound **7a**.

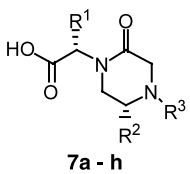
A possible explanation consistent with these observations is outlined in Scheme 2. Upon deprotection of the *N*-capped diastereoisomeric pseudodipeptides **4** and **4′** with piperidine, we propose that for the (2*S*,5′*S*) diastereomer (**5**) cyclative aminolytic cleavage of the ester linkage (route A) is faster than on-bead cyclisation (route B) whereas for the (2*S*,5′*R*) diastereomer (**5′**) on-bead S_N2 intramolecular cyclization (route B) to give a diastereomerically pure (2*S*,5′*R*)-substituted oxopiperazine **6′** is fast relative to cyclative cleavage (route A). The prematurely cleaved product **8** has been detected by LC–MS of the filtrate.[20] A related kinetically favoured *N*-alkylation or *N*-acylation process has recently been reported[5] as a side-reaction in the synthesis of substituted piperazinones via tandem reductive amination–cyclization of 2-chloro-*N*-(2-oxoethyl)-acetamide and the methyl ester of phenylalanine amino acid.

According to this hypothesis, suppression of the premature cyclative cleavage should lead to a mixture of cyclised diastereomers on-bead. The reaction sequence outlined in Scheme 1 was thus carried out using Rink amide resin in which the amide linker could not readily undergo cyclative cleavage. After reductive amination and *N*-capping with chloroacetyl chloride, the Rink amide equivalent of **4** and **4′** was TFA-cleaved and LC–MS analysis of the filtrate showed two peaks in the LC trace with the same mass, corresponding to the mixture of diastereomers. At the end of the synthetic sequence, the corresponding carboxamide derivative of **7a** was obtained after TFA cleavage. The final product appeared by ^{1}H NMR spectroscopy to be a mixture of diastereomers, as compared to the relatively simpler spectrum of the single diastereomer of acid **7a** obtained previously. This supports that the isolation of a single diastereomer when using the Wang linker is dependent



Scheme 2. Proposed mechanistic model.

Table 1.



7a - h

Entry	R^1 (resin-bound aminoacid)	R^2 (Fmoc-aminoaldehyde)	R^3Cl	Config. amino acid	Config. aldehyde	Product[a]	Yield[b] (%)	Purity[c] (%)
1	$-CH_2CH(CH_3)_2$	CH_2Ph	SO_2–Tol	*S*	*S*	**7a**	31	>95
2	$-CH_2CH(CH_3)_2$	CH_3	SO_2–Tol	*S*	*S*	**7b**	20	>95
3	CH_3	CH_3	SO_2–Tol	*S*	*S*	**7c**	26	>95
4	$-CH_2CH(CH_3)_2$	CH_2Ph	$COCH_3$	*S*	*S*	**7d**	31	>95
5	$-CH_2CH(CH_3)_2$	CH_2Ph	CH_2Ph	*S*	*S*	**7e**	26	>95
6	$-CH_2CH(CH_3)_2$	CH_2Ph	$SO_2C_6H_4(NO_2)$	*S*	*S*	**7f**	30	>95
7	$-CH_2CH(CH_3)_2$	CH_2Ph	COPh	*S*	*S*	**7g**	30	>95
8	$-CH_2CH(CH_3)_2$	CH_2Ph	$COCH(CH_3)(NH_2)$	*S*	*S*	**7h**	34	>95

[a] All products were characterised by ^{1}H, ^{13}C NMR spectroscopy and HRMS. The absolute stereochemistry of **7a** and **7b** was determined by X-ray analysis to be (2*S*,5′*R*).

[b] Yield after purification of product by preparative HPLC, based on the product expected from initial loading of resin.

[c] Purity determined by C-18 reverse-phase HPLC (monitored at 254 nm) using SEDEX ELSD. A single product peak was detected by HPLC–ELSD and LC–MS.

on selective loss of the other diastereoisomer during the synthetic sequence, thereby constituting a solid-supported self-purifying system.

To explore whether the selectivity of this cyclisation is sterically sensitive, the benzyl group of Fmoc-phenylalaninal **2a** was replaced with the methyl side chain of Fmoc-(*S*)-alaninal **2b** (entry 2, Table 1). The reaction sequence was undertaken affording compound **7b** in a purified yield of 20% as a single diastereoisomer indicated by HPLC–ELSD and ^{1}H NMR spectroscopy. The effect of replacing both side chains with a methyl group was then investigated in the synthesis of **7c** (entry 3, Table 1) using immobilised Fmoc-(*S*)-alanine and Fmoc-(*S*)-alaninal. The final product was isolated as a single diastereoisomer as indicated by HPLC–ELSD and ^{1}H NMR spectroscopy, in a purified yield of 26%. Thus, substitution of either one or both side chains with a methyl group led to the synthesis of single diastereoisomers **7b** and **7c**, respectively. This supports that the apparent selectivity for premature cleavage is controlled by the configuration of the stereoisomer even for sterically small substituents.

The resin bound cyclic secondary amine **6′** (Scheme 1) was *N*-capped with acid chlorides, sulfonyl chlorides, coupled with amino acid derivatives and reductively alkylated with an aldehyde using the borane–pyridine approach[21] to afford upon cleavage compounds **7d–h**, (entries 4–8, Table 1). Post-cleavage analysis of all compounds by HPLC–ELSD, LC–MS, ^{1}H and ^{13}C NMR spectroscopy consistently showed a single diastereoisomer of the desired product. For compound **7d**, the X-ray structure was obtained and confirmed the (2*S*,5′*R*) configuration. This is consistent with the stereochemical assignment obtained from the X-ray structure of **7a** and the mechanism proposed in Scheme 2. The absolute stereochemistry of other diastereochemically pure products may be predicted on the basis of the structural evidence obtained for **7a** and **7d** if one assumes a common mechanism. We are presently exploring whether these observations can be exploited for the stereodivergent synthesis of substituted oxopiperazines.

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