Novel Reversed Chain Modified Oligopeptides via Sequential α-*N*-Mitsunobu Condensation of a Functionalized C-glycoside

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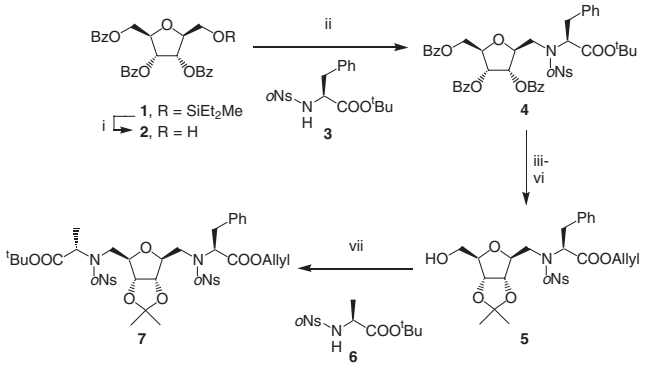
The synthesis of a novel reversed chain modified oligopeptide via sequential α-*N*-Mitsunobu condensation reactions on a C-glycoside with amino acid derived nitrobenzenesulfonamides is described. Structural analysis of the target compound **11** using NMR techniques indicates a folded structure.

The design and synthesis of peptidomimetic scaffolds has received growing interest over the last two decades.[1–7] Peptidomimetic scaffolds can be incorporated in specific peptide sequences with the aim of inducing particular conformations.[1–8] In addition, the incorporated moiety can be designed in such a way that pharmacophoric groups can be attached. The use of rigidified, functionalised molecules as scaffolds has found application in the search for surrogates for therapeutic peptides with favourable properties in terms of potency, bioavailability, and biostability.[1–5]

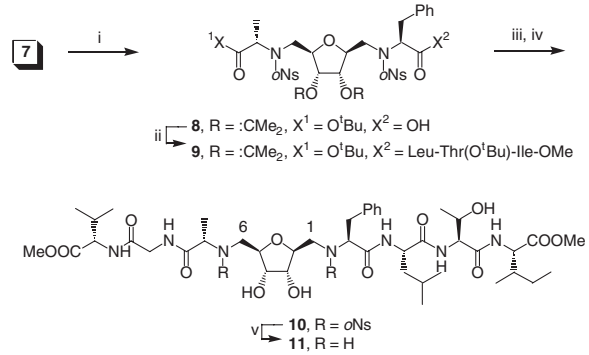
A frequently used class of scaffold in peptide chemistry is derived from monosaccharides. Monosaccharides can be readily manipulated to provide attachment points for connection to the peptide backbone.[3,4] Remaining hydroxy moieties are amenable to further elaboration or can be left unmodified, thus imparting saccharide-like physical properties to the peptide. Usually, these scaffolds, known as sugar amino acids (SAAs) containing one amine and one carboxyl moiety, can be incorporated into peptide sequences via solid phase peptide synthesis. As an alternative strategy, scaffolds have been designed that have peptide strands appended to either two carboxyl groups or two amino groups, leading to peptide-like material having a reversed chain sequence.[9,10] We reasoned that reversed chain modified oligopeptides can be obtained by performing a double α-*N*-Mitsunobu condensation with a suitably functionalized C-glycoside.[12,13] We here present the incorporation of a didehydroxy-D-allitol derived scaffold into a reversed peptide-chain sequence and its structural analysis using variable temperature and 2-D NMR.

The synthesis of orthogonally protected scaffold **7** commences with the desilylation of known 2,5-anhydro-1-*O*-(diethylmethylsilyl)-D-allitol tribenzoate (**1**) (Scheme 1),[14] under mild acidic conditions to give **2** in excellent yield. Condensation of **2** with *o*Ns(2-nitrobenzenesulfonyl)–Phe–O*t*-Bu (**3**)[15] under Mitsunobu conditions at room temperature furnished *N*-alkylated amino acid **4** in near quantitative yield. The *tert*-butyl ester in **4** was converted to the corresponding carboxylate by treatment with neat TFA. Ensuing debenzoylation (potassium carbonate in anhydrous methanol), transformation of the carboxylate to the corresponding allyl ester (silver carbonate, allyl bromide) and installment of the 2,3-*O*-isopropylidene (acetone, cat. pTsOH) afforded compound **5** in 71% overall yield starting from **4**. Treatment of **5** with *o*Ns–Ala–O*t*-Bu **6** in the presence of triphenylphosphine and DEAD at elevated temperature provided the desired product **7** (98% yield).



Scheme 1. Reagents and conditions: (i) AcOH/H_2O/THF (1/1/1, v/v/v), rt, 2 h, 97%. (ii) Ph_3P (1.5 equiv.), DEAD (1.5 equiv.), THF, 0°C to rt, 16 h, 98%. (iii) TFA, rt, 1 h. (iv) K_2CO_3 (1.1 equiv.), MeOH, rt, 4 h. (v) Ag_2CO_3 (1.3 equiv.), allyl bromide (3 equiv.), DMF, rt, 3 h. (vi) *p*TsOH (cat.), acetone, rt, 24 h, 71% (4 steps from **4**). (vii) Ph_3P (1.5 equiv.), DEAD (1.5 equiv.), THF, reflux, 4 h, 98%.

Having suitably protected compound **7** in hand, attention was focussed on the synthesis of oligomer **11**. Compound **7** was subjected to allyl ester cleavage conditions[16] to obtain the free carboxylic acid **8** which was condensed with an equimolar amount of the tripeptide ester H–Leu–Ser(O*t*-Bu)–Ile–OMe[17] under the agency of EDC and HOBt affording the desired prod-



Scheme 2. Reagents and conditions: (i) $(Ph_3P)_4Pd(0)$ (cat.), $PhSiH_3$ (2 equiv.), DCM, rt, 6 h, 75%. (ii) H–Leu–Ser(O*t*-Bu)–Ile–OMe (1 equiv.), EDC (1.5 equiv.), HOBt (1.5 equiv.), DCM, rt, 4 h, 33%. (iii) TFA/H_2O (99/1, v/v), rt, 2 h. (iv) HCl.H–Gly–Val–OMe (1.2 equiv.), EDC (1.5 equiv.), HOBt (1.5 equiv.), DIPEA (1.6 equiv.), DCM, rt, 16 h, 64% (2 steps from **9**). (v) PhSH (3 equiv.), K_2CO_3 (6 equiv.), DMF, rt, 4 h, 92%.

uct **9** in modest yield (33%).

The acid labile protective groups in **9** were removed with a mixture of TFA/water (99/1) and the resulting free acid was condensed with HCl.H–Gly–Val–OMe to give compound **10** in 64% over the two steps. Finally, cleavage of the *o*Ns groups in **10** afforded **11** in excellent yield.

In the NOESY spectrum of **11** ($CDCl_3$) several inter-residue interactions can be observed, the most significant crosspeaks of medium intensity corresponding to NH Leu/H_2, NH Leu/H_3, NH Gly/H_4, and NH Gly/H_5 (Figure 1). We conclude that the second amino acid residues (i.e. Leu and Gly) are in close proximity to the scaffold, indicating a folded structure.

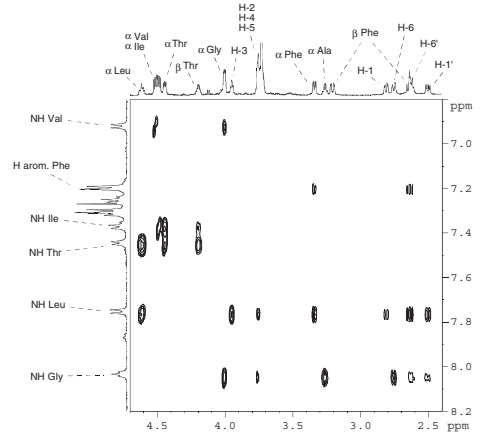


Figure 1. Expansion of NOESY spectrum of **11** in $CDCl_3$.

Next we investigated the presence of hydrogen bonding interactions that may be responsible for the observed folded conformation. The temperature dependence of chemical shifts of the amide protons in **11** using DMSO-d_6 (Figure 2) indicate that two amides are partially shielded from the solvent and involved in 'intermediate' hydrogen bonding interactions. The amides concerned, NH Gly (−2.7 ppb/K) and NH Leu (−3.3 ppb/K), both belong to the second amino acid residues (counting from the scaffold) in their respective strands.

These findings may be explained by the presence of a weak hydrogen bonding interaction between the NHs of the second amino acid residues and its nearest scaffold OHs. Such an H-bonding interaction is supported by the observations made by Chakraborty and co-workers for molecules with similar structure.[9,10,18] Current research activities are aimed at the futher development of carbohydrate derived scaffolds that induce a predetermined structure and their incorporation into biologically relevant oligopeptide sequences.[19]

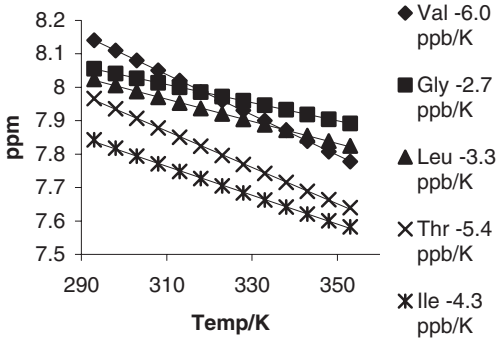


Figure 2. Temperature dependence of the chemical shifts of NHs in **11**.

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References and Notes

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15 All new compounds were fully characterised by ^{1}H and ^{13}C NMR spectroscopy as well as mass spectrometry. Data for compound **11**: ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.03 (m, 1H, NH Gly), 7.75 (d, 1H, NH Leu, $J_{NH,\alpha} = 8.9$ Hz), 7.45 (d, 1H, NH Thr, $J_{NH,\alpha} = 7.6$ Hz), 7.37 (d, 1H, NH Ile, $J_{NH,\alpha} = 8.3$ Hz), 7.32–7.19 (m, 5H, H_{arom} Ph), 6.92 (d, 1H, NH Val, $J_{NH,\alpha} = 8.6$ Hz), 4.61 (m, 1H, H_α Leu), 4.51 (dd, 1H, H_α Val, $J_{\alpha,\beta} = 4.9$ Hz), 4.49 (dd, 1H, H_α Ile, $J_{\alpha,\beta} = 5.0$ Hz), 4.44 (dd, 1H, H_α Thr, $J_{\alpha,\beta} = 4.1$ Hz), 4.19 (m, 1H, H_β Thr), 4.00 (m, 2H, H_α and $H_{\alpha'}$ Gly), 3.95 (m, 1H, H_3), 3.75–3.71 (m, 9H: 2 × OMe, H_2, H_4, and H_5), 3.34 (dd, 1H, H_α Phe, $J_{\alpha,\beta} = 3.7$ Hz, $J_{\alpha,\beta'} = 9.9$ Hz), 3.26 (q, 1H, H_α Ala, $J_{\alpha,\beta} = 6.9$ Hz), 3.20 (1/2ABX, 1H, H_β Phe), 2.75 (1/2ABX, 1H, H_6), 2.66 (ABX, 2H, H_1 and $H_{1'}$, $J_{1,2} = 3.5$ Hz, $J_{1',2} = 5.2$ Hz), 2.66–2.62 (m, 2H, $H_{6'}$ and $H_{\beta'}$ Phe), 2.16 (m, 1H, H_β Val), 1.91 (m, 1H, H_β Ile), 1.61–1.55 (m, 3H: 2 × H_β and H_γ Leu), 1.44–1.15 (m, 2H, 2 × H_γ Ile), 1.34 (d, 3H, H_β Ala), 1.16 (d, 3H, H_γ Thr, $J_{\gamma,\beta} = 6.4$ Hz), 0.97–0.90 (m, 18H: 6 × H_γ Val, 6 × H_δ Leu, 3 × $H_{\gamma'}$ Ile, 3× H_δ Ile). ^{13}C NMR (150 MHz, $CDCl_3$): δ 176.1, 174.3, 173.4, 172.3, 172.0, 170.2, 169.5 (7 × C=O), 137.0 (C_q Ph), 129.0, 128.8, 127.1 (CH_{arom} Ph), 83.1, 82.6 (C_5/C_2), 73.1 (C_4), 72.0 (C_3), 66.9 (C_β Thr), 64.6 (C_α Phe), 58.3 (C_α Ala), 57.6 (C_α Thr), 57.2 (C_α Val), 56.8 (C_α Ile), 52.3, 52.2 (2 × OMe), 51.1 (C_α Leu), 50.6 (C_6), 50.1 (C_1), 42.9 (C_α Gly), 41.7 (C_β Leu), 39.6 (C_β Phe), 37.2 (C_β Ile), 31.1 (C_β Val), 25.0 (C_γ Ile), 24.8 (C_γ Leu), 23.0 (CH_3), 21.8 (CH_3), 19.2 (C_β Ala), 18.9 (CH_3), 18.1 (C_γ Thr), 17.7 (CH_3), 15.5 (CH_3), 11.6 (CH_3). MS (ESI): m/z 894.5 $[M + H]^+$, 916.5 $[M + Na]^+$.
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