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Pseudo-Allylic A1,3 Strain as a Conformational Control Element: Stereoselective Syntheses of ψ[CH2O] Pseudodipeptides.

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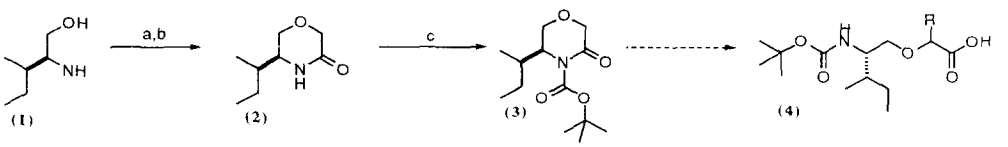
Abstract: The synthesis of methylene-oxy dipeptide isosteres has been achieved by stereoselective functionalisation of the acylmorpholinone **3**.

The major drawbacks to the use of synthetic peptides as therapeutic agents are their rapid degradation *in vivo* by numerous peptidases, and their poor transport properties through biological membranes. The isosteric replacement of an amide bond with a nonhydrolysable isostere represents a conservative modification of peptides that may improve their pharmacokinetic and physical properties.

The methylene-oxy (ψ[CH_2O]) unit offers a conformationally flexible and proteolytically resistant surrogate to the amide bond. However, in contrast to their amino[1] and thio[2] relatives, the methylene-oxy pseudodipeptides have received relatively little attention. This may be due to the paucity of synthetic methods available for the synthesis of this structural unit. The first synthesis[3] of this amide bond replacement - involving intermolecular Williamson ether synthesis - was limited to substrates that include glycine as the C-terminal component. More efficient syntheses[4-7] that involve intramolecular Williamson reaction were subsequently reported and allow for the preparation of C-terminally substituted dipeptide surrogates. In this paper, we describe alternative syntheses, which allow natural and unnatural side chains to be attached to the oxyether backbone in a stereoselective manner.

Scheme 1

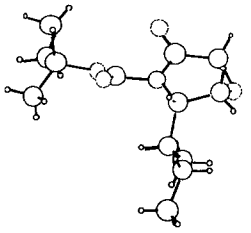


Legend. a. $ClCH_2COCl$, NEt_3, 95%; b. NaH, THF, 72%; c. Boc_2O, DMAP, 71%.

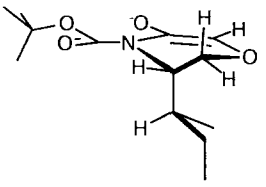
Minimisation of 1,3 allylic strain (A1,3) is one of the most powerful determinants of molecular conformation.[8] We anticipated that N-acylation of the morpholinone **2** would cause the sec-butyl side chain to adopt a pseudo-axial conformation[9] as a consequence of minimising A1,3 strain.

Furthermore, we considered that due to its axial disposition, the sec-butyl group would effect the stereoselective alkylation of an enolate anion generated from the acylmorpholinone **3** (Scheme 1). The corresponding methylene-oxy dipeptide isostere **4** could then be obtained by chemoselective hydrolysis of the endocyclic amide bond of the alkylated acylmorpholinone. To effect the synthesis of the methylene-oxy dipeptide backbone, we prepared the morpholinone **2** by intramolecular etherification.[4] The morpholinone **2** was acylated with di-t-butyldicarbonate in the presence of DMAP to afford the imide **3**. The structure of **3** was determined by single crystal X-ray crystallography.[10] The conformation observed is in accord with expectation and is shown in Figure 1. The morpholinone ring exists in a half chair conformation with the sec-butyl group adopting a pseudo-axial disposition. The C_5 C-H bond is within 9.8° of the plane defined by the exocyclic amide bond. It is interesting to note that the endocyclic amide bond is within 0.4° of planarity whereas the amide bond of the exocyclic carbamate is twisted from planarity by 27°.

Figure 1



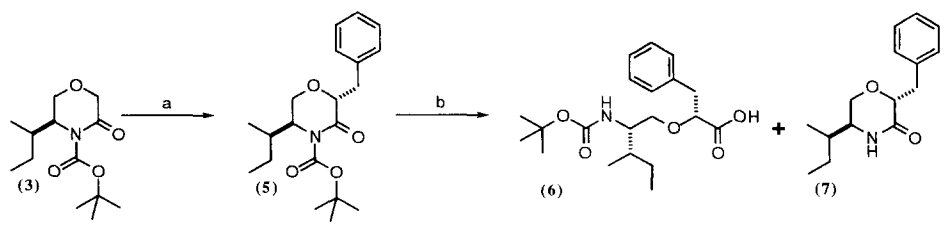
X-Ray Crystal Structure of **3**



Stereocontrol of Enolate Alkylation

Deprotonation of **3** by its addition to a solution of sodium hexamethyldisilazane and alkylation with benzyl bromide afforded the *trans*-2,5-disubstituted morpholinone **5** as a single diastereoisomer[11] (Scheme 2). The success of this reaction was dependent upon the order of addition of the reagents and the use of DME as a cosolvent. The high level of 1,4 asymmetric induction observed in this reaction may be rationalised by a combination of steric and stereoelectronic effects. The sec-butyl group, in addition to sterically shielding the *re* face of the enolate anion, may function as a conformational locking group, with reaction proceeding via preferential axial alkylation of the morpholinone ring.[12] Treatment of the imide **5** with lithium hydroperoxide effected regioselective hydrolysis of the endocyclic amide bond to afford the desired acid **6** (67%) as well as the lactam **7** (15%). The Boc-protected Ileψ[CH_2O]-D-Phe dipeptide isostere **6** was obtained as a single diastereoisomer.

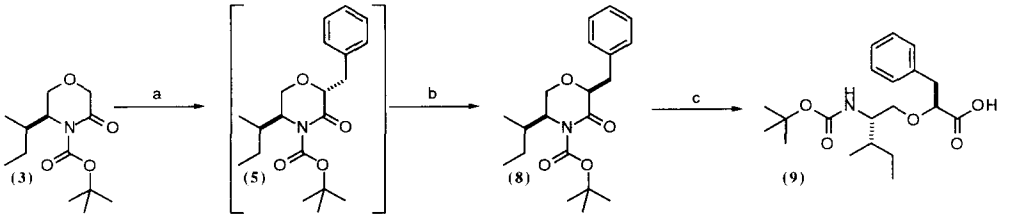
Scheme 2



Legend. a. NaHMDS, THF/DME (1:4), -78°C, then BnBr 80%; b. LiOOH, THF (aq), 67%.

The diastereomeric benzylated morpholinone **8** was prepared by deprotonation of the benzylated lactam **5** with sodium hexamethyldisilazane, and subsequent kinetic protonation of the resulting enolate anion. Conveniently, this alkylation and inversion protocol can also be achieved in a single operation (Scheme 3). Thus, without isolation, the initial alkylation product **5** was added by cannula to a second equivalent of sodium hexamethyldisilazane. The resulting enolate was quenched with aqueous ammonium chloride to afford the *cis*-2,5-disubstituted morpholinone[11] **8** in 67% yield. The principal by-products of the reaction were the corresponding *bis* benzylated lactam (15%) as well as trace amounts of the *trans* isomer **5** (3%). The Boc-protected dipeptide isostere Ileψ[CH_2O]Phe **9** was obtained as a single diastereoisomer by treatment of the purified imide **8** with lithium hydroperoxide.

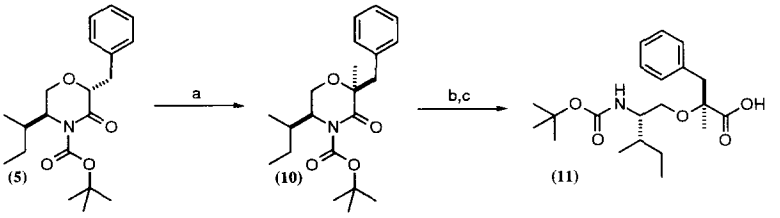
Scheme 3



Legend. a. NaHMDS, THF/DME (1:4), -78°C, then BnBr ; b.NaHMDS, THF/DME (1:4), -78°C, then NH_4Cl (aq) -78°C, 67%; c. LiOOH, THF (aq), 75%.

Stereoselective synthesis of methylene-oxy dipeptide isosteres that contain a quaternary carbon atom can also be achieved (Scheme 4). Alkylation of **5** with methyl iodide afforded the geminally substituted morpholinone **10**. The product was again obtained as a single diastereoisomer.[11] In this case, hydrolysis of the lactam with lithium hydroperoxide was sluggish, and occurred with no chemoselectivity. Therefore, the Boc-protected dipeptide isostere **11** was obtained via a two step protocol.

Scheme 4

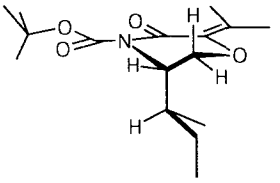


Legend. a. NaHMDS, THF/DME (1:4), -78°to -50°C, then MeI, -78°C, 71%; b. HCl / CH_3CO_2H, reflux, c. BocON, NEt_3, 69% over 2 steps.

We have found that the alkylation of morpholinone **3** is facile with allylic or benzylic halides.[13] In contrast, attempts to introduce the valine side chain through alkylation of **3** with 2-iodopropane were unsuccessful. Therefore, an alternative synthesis was developed to append β branched side chains onto the oxyether backbone (Scheme 5). Aldol reaction between the morpholinone **3** and acetone afforded a (4:1) mixture of diastereoisomeric products. Without separation, the tertiary

alcohols were treated with phosphorous oxychloride, to afford the tetrasubstituted[14] olefin **12**. Hydrogenation (Figure 2) occurred distal to the axially disposed sec-butyl group to give the *cis*-2,5-disubstituted imide **13** exclusively.[15]

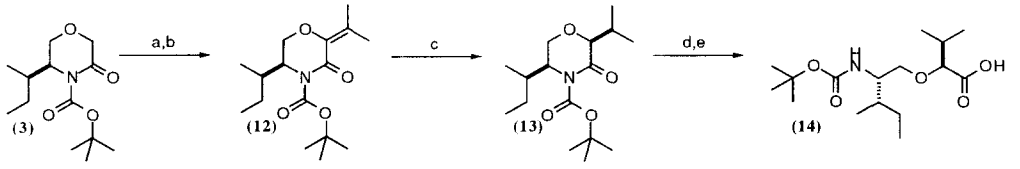
Figure 2



Stereocontrol of Hydrogenation

The lactam **13** was converted efficiently to the Boc-protected Ileψ[CH_2O]Val dipeptide isostere **14** *via* a two step protocol.

Scheme 5



Legend. a. NaHMDS, THF/DME (1:4), -78°C, then CH_3COCH_3, 67% ; b.$POCl_3$, pyridine, 70%; c. PtO_2, H_2 54 psi, 99%; d. HCl / CH_3CO_2H, reflux, e. Boc_2O, NEt_3, 75 % over 2 steps.

The morpholinone **3** has been shown to adopt a well defined conformation in which allylic strain is minimised. This synthetically versatile template can be elaborated to a variety of methyleneoxy pseudodipeptides with predictable control of stereochemistry. The incorporation of these isosteric units into biologically active peptidomimetics will be reported in due course.

References and Notes

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10. The ^1H NMR spectrum of **3** in $CDCl_3$ is also in accord with the pseudo-axial disposition of the sec-butyl group. The observed coupling constants to the C_5 methine proton are J_{obs} = 3.6 and 0.0 Hz, which are in good agreement with those calculated from the crystal structure J_{calc} = 3.7 and 0.5 Hz.
11. The assigned stereochemistry was established by appropriate NOE experiments.
12. In contrast, alkylation of the dianion of unacylated morpholinone **2** afforded, in low yield, a mixture of diastereoisomeric products slightly favouring the corresponding *cis*-2,5-disubstituted morpholinone (1.5:1, *cis:trans*). The poor stereocontrol observed in this case may be understood by the limited steric influence the pseudo-equatorially disposed isobutyl group exerts upon the stereochemical course of the reaction.
13. The alkylation inversion protocol has been performed on the following substrates and the unoptimised yields of the corresponding *cis*-2,5-disubstituted morpholinone products are given in parentheses; allyl bromide (40%); 1 bromo-2-methylprop-2-ene (32%), E-bromobut-2-ene (39%) and 1-naphthylmethyl bromide (65%).
14. A significant amount of the corresponding regioisomeric olefin (24%) was also obtained and separated by column chromatography.
15. The diastereomeric purity of the product was acertained by examination of the ^1H NMR spectrum of the crude reaction product.

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