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Synthesis of *E*- and *Z*-alkene Dipeptide Isosteres

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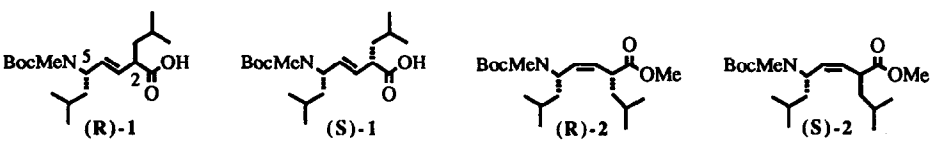
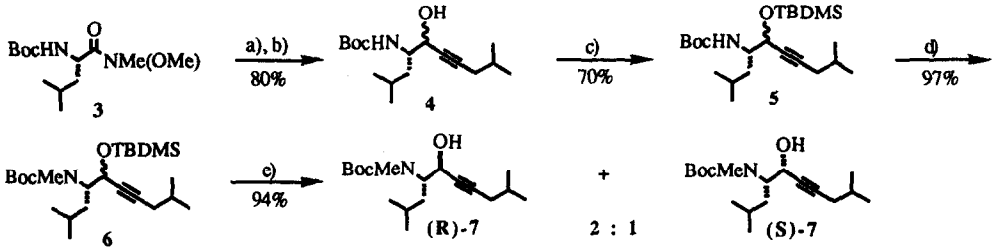
Abstract: The syntheses of MeLeu-Leu and MeLeu-D-Leu alkene dipeptide isosteres are described. Isosteres with an *E*-alkene bond were synthesized stereoselectively by employing the [2, 3] Wittig rearrangement to control double bond geometry and C-2 configuration. *Z*-Alkene isosteres were obtained as an easily separable mixture of diastereomers *via* alkylation of a *Z*-alkene MeLeu-Gly isostere that was obtained using a *Z*-selective Wittig reaction as the key step. All isosteres are isolated with high stereochemical purity.

Recently, it was shown that cyclosporin A (CsA) contains a *trans* MeLeu-MeLeu amide bond in the 9, 10 position when bound to cyclophilin[1] and that this conformation is required before tight-binding can occur.[2] CsA analogs which have *E*- and *Z*-alkene replacements of the 9, 10 peptide bond could provide an experimental test of the different cyclophilin inhibition activities of the *trans* and *cis* MeLeu[9]-MeLeu[10] CsA conformations. The *E*-alkene replacement of the peptide bond, one of the first dipeptide isosteres reported,[3] has been the focus of several synthetic efforts since first introduced by Sammes *et al.*[4] We report here a synthesis of Boc-MeLeu-Ψ[*E*-CH=CH]-Leu-OH[5] ((**R**)-**1**) and the epimer (**S**)-**1** that utilizes the [2, 3] Wittig rearrangement as the key step for introducing chirality at C-2. The synthesis of the corresponding *Z*-alkene dipeptide isosteres, Boc-MeLeu-Ψ[*Z*-CH=CH]-Leu-OMe ((**R**)-**2**) and its epimer (**S**)-**2** is also described.[6]



The synthesis of (**R**)-**1** and (**S**)-**1** begins with the aldehyde generated from Boc-Leu-N(Me)OMe (**3**) (Scheme 1).[7] Addition of the aldehyde to 2.2 eq. of *iso*-butyl magnesium acetylide gave the propargylic alcohol **4** in 80% yield as a 2:1 mixture of diastereomers (> 95% e.e.).[8] Protection under standard conditions[9] gave the silyl ether **5** in 70% yield which was N-methylated to give **6** in 97% yield.[10] Deprotection[11] of **6** gave the 2:1 mixture of diastereomers (**R**)-**7** and (**S**)-**7** in 94% yield. These compounds were easily separable by flash chromatography (R_f((**R**)-**7**) 0.33, R_f((**S**)-**7**) 0.39, 1:3 EtOAc:hexanes).[12]

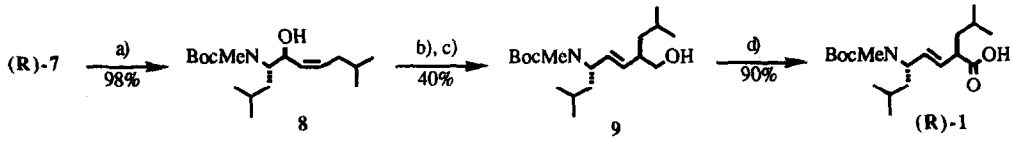
Scheme 1



Reagents: a)$LiAlH_4$, 0° C, Et_2O, 0.5 H.; b) $(CH_3)_2CHCH_2CCMgBr$, Et_2O, 0° C, 2 H.; c) TBDMSCl, imidazole, DMF/CH_2Cl_2, R.T., 24 H.; d) NaH, CH_3I, R.T., THF, 12 H.; e) HF, CH_3CN, -20° C --> 0° C, 1.5 H.

Hydrogenation of **(R)-7** with $Pd/BaSO_4$ in pyridine[13] gave 98% of a mixture consisting primarily of *Z*-alkene **8** (Scheme 2) along with 5% of the corresponding *E*-isomer as determined by HPLC analysis.[14a] Alkylation of the mixture with ICH_2SnBu_3[15,16] gave the expected ethers which were filtered through silica gel (1:49 EtOAc:hexanes) and used in the next reaction without further purification. Addition of BuLi at -78° C gave the homoallylic alcohol **9** in 30 - 40% yields and 90% d.e. from **8**.[14b,17,18] The undesired diastereomer could be separated from **9** by conversion of the mixture to THP ethers followed by silica gel chromatography.[19] Jones oxidation gave Boc-MeLeu-Ψ[*E*-CH=CH]-Leu-OH (**(R)-1**) in 90% yield. Boc-MeLeu-Ψ[*E*-CH=CH]-D-Leu-OH (**(S)-1**) was obtained in exactly the same manner and in analogous yields from **(S)-7**.

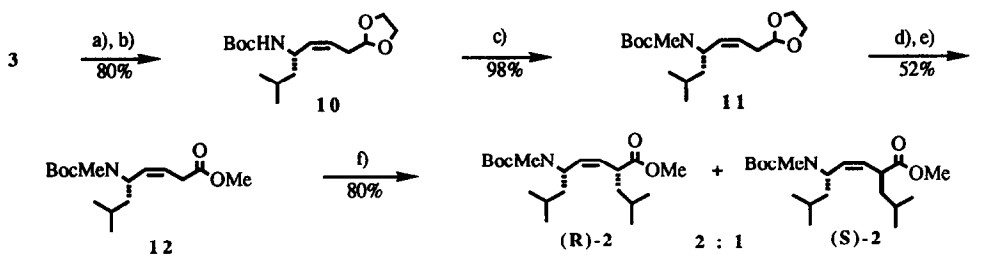
Scheme 2



Reagents: a) H_2, Pd / $BaSO_4$, Pyr., R.T., 2 H.; b) KH, ICH_2SnBu_3, 18-cr-6, THF, -30° C --> -20° C, 1 H.; c) BuLi, THF, -78° C, 24 H.; d) Jones, 0° C, 1 H.

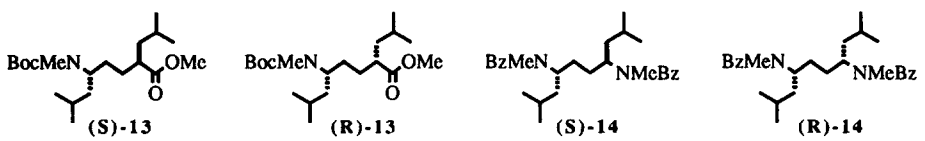
The synthesis of the *Z*-alkene dipeptide isosteres **(R)-2** and **(S)-2** is shown in Scheme 3. The aldehyde derived from **3** underwent the *Z*-selective Wittig reaction[20] with the ylide obtained from the commercially available phosphonium bromide (Aldrich®) and KHMDS to give the *Z*-alkene **10** in 80% yield and > 95% e.e.[21] **10** was N-methylated in 95% yield to give **11** which was both deprotected and oxidized by the addition of Jones reagent. Esterification of the derived acid with CH_2N_2 gave Boc-MeLeu-Ψ[Z-CH=CH]-Gly-OMe (**12**) in 52% yield from **11**. Methyl ester **12** was alkylated to give isosteres **(R)-2** and **(S)-2** in a 2:1 ratio and 80% overall yield. We discovered that these diastereomers were easily separable by flash chromatography (R_f(**(R)-2**) 0.48, R_f(**(S)-2**) 0.55, 1:3 EtOAc:hexanes).

Scheme 3



Reagents: a) $LiAlH_4$, 0° C, Et_2O, 0.5 H.; b) $Ph_3P{=}CHCH_2CH(OCH_2)_2$, -78° C --> R.T., THF, 12 H.; c) NaH, CH_3I, R.T., THF, 12 H.; d) Jones, 0° C, 1 H.; e) CH_2N_2, Et_2O, 0° C; f) LDA, -78° C, THF/DMPU, 1 H., then iBuI, -78° C --> R.T., 12 H.

The stereochemical assignments of **(R)-1** and **(S)-1** as well as **(R)-2** and **(S)-2** were confirmed as follows: Esterification (CH_2N_2) of **(R)-1** followed by reduction (H_2, Pd/C) gave **(S)-13**, which was identical to the product obtained from hydrogenation of **(R)-2**. **(S)-13** was easily distinguishable from **(R)-13**,[22] obtained from **(S)-1** and **(S)-2**. Employing a Curtius rearrangement as the key step, **(S)-13** was converted[23] to meso compound **(S)-14** (no optical rotation). In the same way, **(R)-13** gave optically active **(R)-14** ($[\alpha]_D$ -29.7 (c = 1.0, CH_2Cl_2). Since the Curtius rearrangement is known to proceed with retention of configuration,[24] the stereochemical assignments based on [2, 3] Wittig rearrangement precedent[25] is independently confirmed by these experiments.



Few *diastereoselective* routes to *E*-alkene isosteres have been reported due to the difficulty with the stereoselective introduction of the C-2 center.[26] We have found that the [2, 3] Wittig rearrangement can be used to set predictably the double bond geometry and the newly formed chiral center in one reaction. While this work was in progress, Bol and Liskamp reported the use of the [2, 3] Wittig rearrangement to prepare racemic "Gly-Xxx" and non-racemic "Xxx-Gly" isosteres,[27a] and an abstract by Lipton and Koscho appeared that suggests a related synthetic approach.[27b] Our results demonstrate that this method may be used for the stereoselective synthesis of non-glycine-containing *E*-alkene dipeptide isosteres. It is also worth noting that this method is nicely complementary to the route devised by Ibuka *et al*[26] in that chelation-controlled addition of organometallic reagents to protected α-amino aldehydes gives major products (i.e. **(R)-7**) that lead to 2-(R), 5-(S) isosteres (**(R)-1**) and non-chelation-controlled addition (**(S)-7**) leads to 2-(S), 5-(S) isosteres (**(S)-1**).

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6. All isosteres and intermediates gave satisfactory ^{1}H-NMR, HRMS and C, H, N data.
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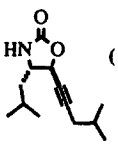
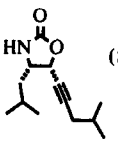
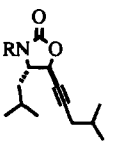
8. Compound **4** was treated with NaH in THF (ambient, 12 H.) to obtain the separable oxazolidinones **(R)-15** and **(S)-15** (2:1, 89%). ^{1}H-NMR(300 MHz, $CDCl_3$), **(R)-15:** δ 4.74 (dt, 1H, J = 7, 2 Hz, C_5H), **(S)-15:** δ 5.28 (dt, 1H, J = 8, 2 Hz, C_5H). The data is characteristic for analogous compounds (see ref. 26). Lithiated **(R)-15** (addition of BuLi, -78° C) was treated with (R)-MTPA-Cl and also (S)-MTPA-Cl to give the diastereomerically pure N-acylated derivatives **16** and **17** *via* ^{1}H-NMR analysis of the crude reaction mixtures. Dale, J.A.; Dull, D.L.; Mosher, H.S. *J. Org. Chem.* **1969**, *34*, 2543-2549.



(R)-15



(S)-15



16: R = (R)-MTPA

17: R = (S)-MTPA

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12. The stereochemistry was determined by cyclization of **(R)-7**, **(S)-7** and ^{1}H-NMR analysis (see note 8).
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14. Zorbax SIL 4.6 mm x 25 cm, 214 nm, 1.2 ml/min. a) 1:4 *t*-butyl methyl ether:hexanes. b) 1:9 *t*-butyl methyl ether (the diastereomeric mixture was protected as THP ethers to ease separation, see ref. 19).
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16. We found that it is crucial to keep the temperature between -30° and -20° C during this reaction to prevent cyclization forming the undesired oxazolidinone (see also ref. 27a).
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21. The acid derived from **11** was coupled (EDCI/HOBT) with (R)-methylbenzylamine and also the (S)-enantiomer. ^{1}H-NMR analysis of the crude derived amides showed them to be diastereomerically pure.
22. For example: ^{1}H-NMR(300 MHz, $CDCl_3$), **(S)-13:** δ 2.40 (m, 1H, $CHCO_2Me$), **(R)-13:** δ 2.49 (m, 1H, $CHCO_2Me$).
23. Reaction series: a) 4N HCl / dioxane, R.T., 0.5 H. then 3N HCl(aq.), reflux, 3 H.; b) BzCl, Et_3N, CH_2Cl_2, R.T., 0.5 H.; c) DPPA, Et_3N, $PhCH_3$, reflux, 2-4 H. then 0.2 N HCl(aq), R.T., 24 H.; d) BzCl, Et_3N, CH_2Cl_2, R.T., 0.5 H.; e) NaH, CH_3I, THF, R.T., 12 H.
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