Synthesis of Highly Functionalized *trans*-Alkene Isosteres of Dipeptides

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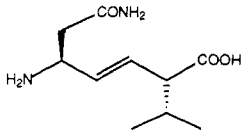
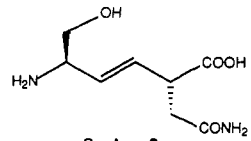
During the course of our studies on peptide inhibitors of protein kinases,[1] we wanted to investigate the contribution, if any, of amide backbone linkages to the potency of these inhibitors. Replacement of specific amide linkages with *trans*-alkene isosteres would allow us to mimic the three-dimensional geometry provided by the backbone amide but eliminate any possible hydrogen-bonding contribution. Since we had determined that α carbon stereochemistry was essential for enzyme inhibition, the stereocontrolled synthesis of *trans*-alkene isosteres of dipeptides recently described by Hopkins and co-workers[2] seemed to be an attractive strategy. This convergent strategy which applied the Julia olefin synthesis as the key carbon–carbon bond formation step provided four dipeptide analogues with alkyl (Ala, Leu) or aryl (Phe, Tyr) side chains. It seemed to us, and was suggested,[2] that this strategy could be applied to more functionalized isosteres with the judicious choice of protecting groups. Herein we detail the preparation of protected forms of the highly functionalized dipeptide isosteres, AsnVal 1 and SerAsn 2.



AsnVal 1

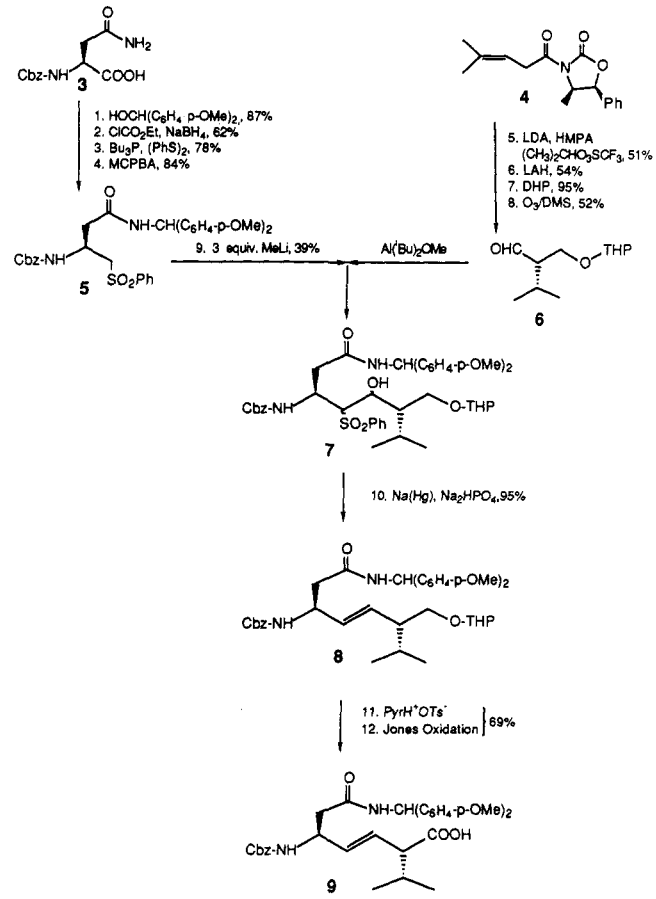


SerAsn 2

Our synthetic approach to a protected version of *trans*-alkene 1 is outlined in Scheme I. Two key aspects of this approach are (1) the incorporation of the Asn side chain protected with the 4,4′-bis-*p*-methoxybenzhydryl group before conversion to sulfone **5** and (2) the preparation of a sterically hindered β,β-dialkyl amino acid (i.e., Val) surrogate. Alkylation of the Evans oxazolidone **4** with the secondary isopropyl halides, in the manner previously used,[2] failed in our hands. Use of isopropyl triflate and HMPA successfully produced the desired oxazolidone in high diastereomeric excess, >97%, which was converted to the desired aldehyde **6**. Treatment of the homochiral sulfone **5** with 3 equiv of methyllithium, condensation of this trianion with the aldehyde **6**, and subsequent reduction of the β-hydroxy sulfone **7** with sodium amalgam gave the desired *trans*-alkene **8**. This alkene was converted to the protected dipeptide mimic **9** by removal of the THP ether and oxidation of the alcohol to an acid.

The successful strategy to obtain a protected form of the highly oxygenated SerAsn **2** *trans*-alkene isostere is shown in Scheme II. The key strategic steps in this Scheme are (1) the choice of the Cbz and *O*-benzyl ether protecting groups on the sulfone **11** which are stable during the manipulations to obtain the amide side chain and backbone

Scheme I. AsnVal *trans*-Alkene Isostere



acid functionalities and (2) the formation of the lactone **14** which was treated with ammonia to obtain the amide side chain. This alcohol **15** could then be selectively oxidized to the acid, yielding the protected SerAsn isostere **16**.

In summary, we report the preparation of protected *trans*-alkene isosteres which contain highly functionalized and sterically hindered side chains. These isosteres may be incorporated into peptides by utilizing standard peptide coupling methods to add amino acids or fragments to the carboxy terminus. Removal of remaining protecting groups with TFA/thioanisole allows addition to the amino terminus of the isosteres.

Experimental Section

General experimental protocol was the same as for ref 2. All reactions were carried out under an inert atmosphere. ^{1}H NMR spectra were recorded on a Varian XL200 spectrometer. FAB mass spectra were recorded on a Varian MAT 312 instrument. Short-path chromatography refers to the procedures described by Hunt and Rigby.[3]

Sulfone 5. N^{α}-Cbz-L-asparagine **3** was protected as the N^{γ}-bis(*p*-methoxyphenyl)methyl derivative according to the procedure of Konig et al.[4] The sulfone was prepared by following a modification of the procedures described,[2,5] the major modification being the direct conversion, in a single step, of the intermediate alcohol into the phenyl thioether using diphenyl disulfide and tri-*n*-butylphosphine, following ref 6. Purification by short-path chromatography, eluting with CH_2Cl_2–MeOH (95:5), gave a white solid product. ^{1}H NMR (DMSO): δ 3.30–3.70 (4 H, m, CH_2SO_2, CH_2CON), 3.70, 3.75 (6 H, s, 2 OCH_3), 4.22 (1 H,

(1) Presented in part at The Third Chemical Congress of North America, Toronto, Canada, June 1988.

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(3) Hunt, B. J.; Rigby, W. *Chem. Ind. (London)* **1967**, 1868.

(4) Konig, W.; Geiger, R. *Chem. Ber.* **1970**, *103*, 2041.

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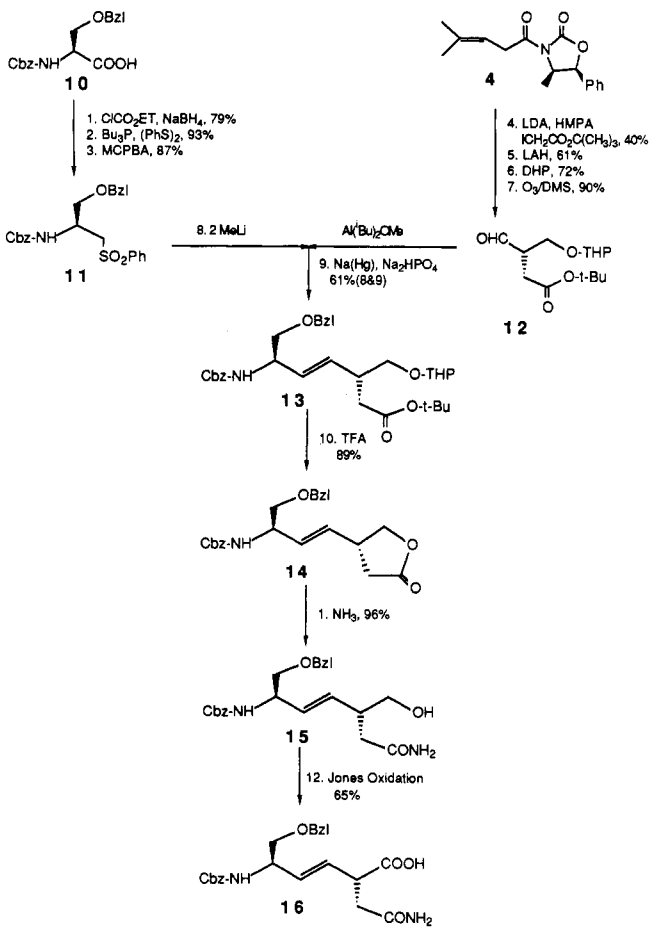
Scheme II. SerAsn *trans*-Alkene Isostere



m, C*H*$(CH_2)_2$), 4.88 (2 H, s, CH_2Ph), 5.95 (1 H, m, NCHAr_2), 6.84, 7.10 (8 H, m, 2 ArOCH_3), 7.36 (6 H, m, *Ph*CH_2, NH), 7.55–7.83 (5 H, m, SO_2Ph), 8.71 (1 H, d, NH). FAB mass spectrum: (M + 1)$^+$ = 603.

Aldehyde 6. Oxazolidinone **4** was alkylated, reduced with lithium aluminum hydride, protected as the THP ether, and ozonolyzed as previously described[2] to give **6**. Successful alkylation required the use of isopropyl triflate and the addition of 1 equiv of HMPA. The isopropyl triflate was prepared according to Beard et al.[7] Purification on short-path chromatography, eluting with EtOAc–hexane (1:9), gave the product as a clear oil. ^{1}H NMR ($CDCl_3$): δ 1.01 (6 H, dd, 2 CH_3), 1.41–1.94 (7 H, s, $(CH_2)_3$, C*H*$(CH_3)_2$), 2.40 (1 H, m, C*H*CHO), 3.30–3.95 (4 H, m, 2 CH_2O), 4.61 (1 H, m, OCHO), 9.74 (1 H, m, CHO). FAB mass spectrum: (M + 1)$^+$ = 201.

***trans*-Alkene 8.** A suspension of 0.482 g (0.8 mmol) of **5** in 5 mL of THF at −78 °C was treated with 1.7 mL (2.4 mmol) of 1.4 M MeLi in hexane to form the trianion of **5**. The temperature was raised to −20 °C whereupon the sulfone went into solution; additional cooling was then applied until the temperature returned to −78 °C. In a separate flask, 0.159 g (0.8 mmol) of **6** in 2 mL of THF at −78 °C was treated with 0.7 mmol of diisobutylaluminum methoxide and then cannulated into the solution containing the trianion. The reaction mixture was stirred for 1 h at −78 °C and the solution allowed to warm to room temperature overnight. The reaction was quenched and saturated aqueous NH_4Cl and the product extracted with CH_2Cl_2, dried over Na_2SO_4, filtered, and concentrated in vacuo. The hydroxy sulfone **7** was purified on short-path chromatography, eluting with EtOAc–hexane (1:1). To the hydroxy sulfone dissolved in 6 mL of MeOH at 0 °C was added 0.5 g (3 mmol) of disodium hydrogen phosphate followed by 5 g (10 mmol) of 5% sodium amalgam. The mixture was stirred for 2 h, diluted with H_2O, extracted with CH_2Cl_2, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification on short-path chromatography, eluting with EtOAc–hexane (1:1), gave the diastereomeric mixture as a clear oil. ^{1}H NMR ($CDCl_3$): δ 1.75–1.91 (6 H, dd, 2 CH_3), 1.41–1.94 (7 H, s, $(CH_2)_3$, C*H*$(CH_3)_2$), 2.10 (1 H, m, C*H*CH_2O), 3.22–3.90 (4 H, m, 2 CH_2), 3.78 (6 H, s, 2 OCH_3), 4.50 (2 H, m, NC*H*CH=, OCHO), 5.04 (2 H, s, CH_2Ph), 5.51 (2 H, m, CH=CH), 5.85 (1 H, m, NH), 6.10 (1 H, m, NCHAr_2), 6.21 (1 H, m, NH), 6.78–7.15 (8 H, m, 2 *Ar*OCH_3), 7.32 (5 H, s, Ph). FAB mass spectrum: (M + 1)$^+$ = 645.

AsnVal *trans*-Alkene[8] Isostere 9. In 5 mL of MeOH, 0.115 g (0.2 mmol) of **8** was stirred with 0.010 g (0.04 mmol) of pyridinium *p*-toluenesulfonate overnight and then the solvent removed in vacuo. The residue was dissolved in 15 mL of acetone, cooled to 0 °C, and treated with 6 mL of 1.92 M Jones reagent. After stirring for 2 h, 100 mL of both saturated aqueous NaCl and Et_2O were added, and the organic layer was washed with additional aqueous NaCl, dried over Na_2SO_4, filtered, and concentrated in vacuo, to give a clear oil product. ^{1}H NMR ($CDCl_3$): δ 0.77–1.00 (6 H, dd, 2 CH_3), 1.90–2.11 (1 H, m, C*H*$(CH_3)_2$), 2.45–2.75 (3 H, m, CH_2CON, C*H*COOH), 3.80 (6 H, s, 2 OCH_3), 4.50 (1 H, m, NC*H*CH=), 5.05 (2 H, s, CH_2Ph), 5.55–5.74 (2 H, m, CH=CH), 6.08 (1 H, m, NCHAr_2), 6.35 (1 H, m, NH), 6.84–7.11 (8 H, m, 2 *Ar*OCH_3), 7.34 (6 H, m, Ph, NH). FAB mass spectrum: (M + 1)$^+$ = 575.

Lactone 14. The intermediate **13** was obtained similarly as described above, with the exception that the intermediate hydroxy sulfone was not isolated. In 20 mL of CH_2Cl_2, 0.35 g (0.9 mmol) of this tetraprotected *trans*-alkene **13** was treated with 0.5 mL of TFA. After 2 h, the solvent was removed in vacuo. Purification by short-path chromatography, eluting with EtOAc–hexane (1:1), gave the product as an oil. ^{1}H NMR ($CDCl_3$): δ 2.32, 2.65 (2 H, dd, CH_2CO_2 of lactone), 3.20 (1 H, m, CH of lactone), 3.52 (2 H, m, CH_2OBzl), 3.95 (1 H, m, NCH), 4.30–4.45 (2 H, m, CH_2O of lactone), 4.51 (2 H, d, CH_2OCH_2Ph), 5.10 (2 H, s, PhCH_2OCO), 5.20 (1 H, d, NH), 5.61 (2 H, m, CH=CH), 7.26–7.41 (10 H, m, Ar). FAB mass spectrum: (M + 1)$^+$ = 396.

Alcohol 15. To 0.150 g of **14** was added 5 mL of MeOH saturated with gaseous ammonia. Stirring for 12 h at room temperature yielded the product as a clear oil which needed no further purification. ^{1}H NMR ($CDCl_3$): δ 2.31 (2 H, m, CH_2CON), 3.12 (1 H, m, C*H*CH_2OH), 3.54 (4 H, m, CH_2OBzl, C*H*$_2$OH), 4.30 (1 H, m, NCH), 4.48 (H, d, *J* = 14 Hz, OCH_2Ph), 4.52 (H, d, *J* = 14 Hz, OCH_2Ph), 5.11 (2 H, s, CH_2OCO), 5.35 (3 H, m, 3 NH), 5.59 (2 H, m, CH=CH), 7.36 (10 H, m, Ar). FAB mass spectrum: (M + 1)$^+$ = 413.

SerAsn *trans*-Alkene[8] Isostere 16. The isostere **16** was prepared by the oxidation of **15** to the acid as described for the preparation of **9** and was isolated as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 2.22–2.70 (2 H, m, CH_2CON), 3.51 (3 H, m, C*H*CO_2H, CH_2OBzl), 4.33 (1 H, m, NCH), 4.49 (2 H, dd, OCH_2Ph), 5.09 (2 H, s, CH_2OCO), 5.43 (3 H, m, 3 NH), 5.71 (2 H, m, CH=CH), 7.30 (10 H, m, Ar). FAB mass spectrum: (M + 1)$^+$ = 427.

(7) Beard, C. D.; Baum, K.; Grakauskas, V. *J. Org. Chem.* **1973**, *38*, 3073.

(8) Trans stereochemistry in these highly functionalized dipeptide isosteres was confirmed after their incorporation into pentapeptide target molecules. ^{1}H NMR spectra recorded at 400 MHz in DMSO-d_6 and MeOH-d_4 gave vicinal coupling constants of the olefinic protons measured as *J* = 10–14 Hz, consistent with the desired stereochemistry.

Synthesis and Novel Properties of *N*-Phosphoryl Peptides

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Introduction

Since N-phosphorylated proteins and amino acids play important roles in the regulation of enzyme activity, protein biosynthesis, etc.,[1,2] it is of great significance for us

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