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A STEREOCONTROLLED SYNTHESIS OF TRANS-ALKENE ISOSTERES OF DIPEPTIDES

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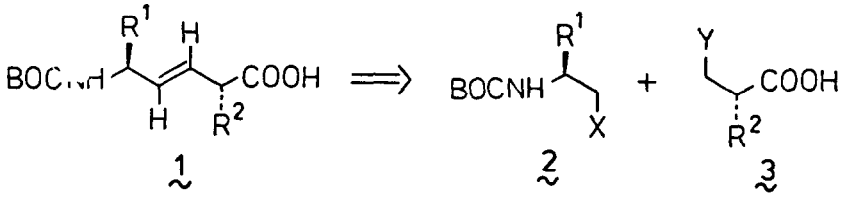
Summary: A general synthetic route to trans-alkene isosteres of protected dipeptides is reported. This sequence permits the fully stereocontrolled preparation of these isosteres in optically active form and in quantities sufficient for further biological study. Prepared in this manner were alkene isosteres of TyrAla, PhePhe, and LeuLeu.

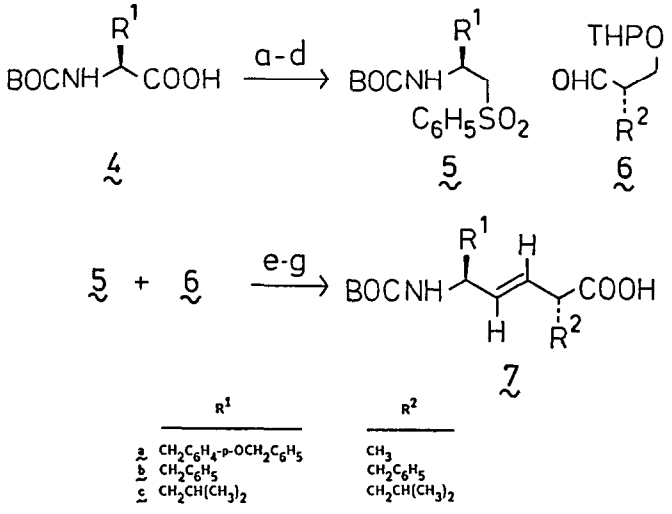
The central role played by peptides and proteins in biological systems has resulted in considerable interest in the preparation and biochemical properties of structural analogs of these substances. Numerous peptide analogs which possess a modified amide backbone have been previously studied.[2] Among these, the substances in which one or more amide linkages are replaced by a trans-alkene are particularly interesting by virtue of both their close stereochemical resemblance to the parent peptide and their inertness to enzymatic hydrolysis.[2,3] Previously described syntheses of oligopeptides which incorporate the alkene isostere have proceeded *via* the intermediacy of a protected dipeptide isostere, **1**[3]. Unfortunately, existing procedures for the synthesis of substances of general form **1** do not permit the stereocontrolled preparation of alkene isosteres which bear non-glycine mimics at both termini.[3] Our own interest in this area prompted us to explore stereocontrolled synthetic sequences to trans-alkene isosteres of dipeptides. A convergent solution to this synthetic problem was sought to permit the separate preparation of a family of



N-terminal fragments **2** and a family of C-terminal fragments **3**. The union of various combinations of these two families would then be expected to provide for the preparation of a wide variety of dipeptide analogs. Reported here, in preliminary form, is a solution to this problem which involves the stereocontrolled coupling of two chiral, non-racemic, synthetic fragments, sulfone **5** and aldehyde **6**. This solution is illustrated in the context of syntheses of trans-alkene isosteres of TyrAla, PhePhe, and LeuLeu in a protected form suitable for direct elaboration, using standard peptide synthesis methodology, to oligopeptide analogs.

The requisite chiral, non-racemic sulfones **5** were readily prepared from commercial t-BOC-α-amino acids, **4**. This was accomplished (without purification of the intermediates) by the illustrated four step sequence, affording the sulfones **5a-c**[4] in 60 to 80% overall yield.

Coupling of the dilithium dianion of **5a**, formed by treatment of **5a** in THF with 2 equivalents of methyl lithium, to the aldehyde **6a**[9] gave poor yields of β-hydroxysulfone[10] under a variety of experimental conditions (temperature and order of addition variation), the yield rarely exceeding 30%. Fortunately, an improvement was found in precomplexation of 2 equivalents of the aldehyde component with 2 equivalents of diisobutylaluminum methoxide, prepared *in situ* by the reaction of 1 equivalent of methanol with diisobutylaluminum hydride,[11] followed by addition of the resulting complex to 1 equivalent of the dilithium dianion of **5a** at -78°. The resulting crude β-hydroxysulfone was not characterized, but was directly reduced to the corresponding trans-alkene in 65% overall yield.[10] Hydrolysis of the THP ether and oxidation to the acid were accomplished in a single operation[12] with Jones reagent, affording the TyrAla analog **7a** in 65% yield. In order to unequivocally verify that racemization at neither terminus had occurred, a sample of **7a** as a mixture of diastereoisomers was prepared by analogous coupling of optically

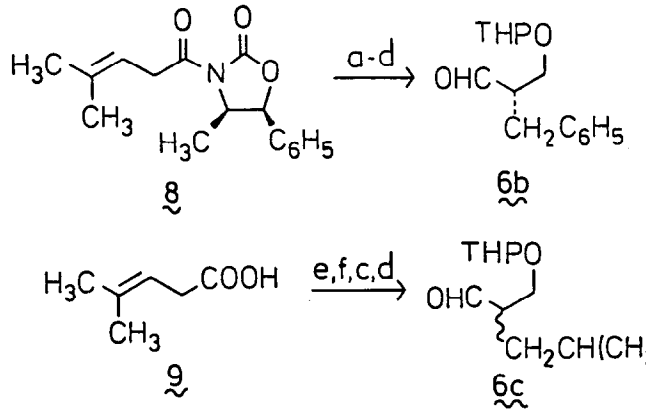


a) i. C_2H_5OCOCl, Et_3N, THF, 0°. ii. $NaBH_4$, H_2O, 0°[5]; b) CH_3SO_2Cl, Et_3N, CH_2Cl_2, 0°[6]; c) $NaSC_6H_5$, CH_3OH, THF, 50°; d) MCPBA, CH_2Cl_2, 25°; e) i. 5/THF, -78° + 2.0 CH_3Li/Et_2O; ii. 6/CH_3OAl-i-Bu_2, 0.5 h, -78°; f) 5% Na(Hg), Na_2HPO_4, CH_3OH, 0°, 4 h[7]; g) i. $PyrH^+OTs^-$, CH_3OH, 25°, 12 h[8]; ii) CrO_3, H_2SO_4, H_2O, CH_3COCH_3, 0°, 0.5 h.

active **5a** and *racemic* **6a**. The ^1H NMR signals of the resulting pair of diastereoisomers were clearly resolved at 500 MHz, proving that the stereochemical homogeneity of **7a**, prepared from optically active **6a**, exceeded 95%.

The utility of this peptide isostere synthesis would be enhanced by the availability of a general synthetic approach to optically active aldehydes **6**. One such route has been devised and used for the synthesis of a C-terminal Phe isostere. The oxazolidone **8**[13] was alkylated as shown (88% de),[14] and the product processed to **6b** in 44% yield from **8**. Coupling of the dianion of sulfone **5b** to the aluminum complex of **6b** afforded, ultimately, the PhePhe isostere **7b** in 40% overall yield from **5b** and **6b**. For biological applications in which it is anticipated that the presence of a mixture of epimers at the C-terminus will be inconsequential, one can rely upon the more readily available *racemic* C-terminal aldehyde to afford a final isostere mixture containing *ca.* 50% of the natural stereochemistry. This was

demonstrated by the synthesis of LeuLeu isostere **7c** from **5c** and the racemate of **6c**, prepared as shown (48% from **9**). In this instance, the diastereoisomers obtained after the sodium amalgam reduction could be separated by column chromatography and independently oxidized to the corresponding acids.



a) i. 1.2 LDA, THF, -78°, 0.5 h; ii. 2.0 $C_6H_5CH_2Br$, -78°(0.5 h), -78°→25°(5 h)[13]; b) $LiAlH_4$, Et_2O, -78°→0°(0.5 h); c) DHP, $PyrH^+OTs^-$, CH_2Cl_2, 25°, 10 h; d) i. O_3, CH_2Cl_2:CH_3OH(5:1), -78°; ii. $(CH_3)_2S$, -78°→25°, 0.25 h; e) i. 2.2 LDA, THF, -78°→-20°, (0.25 h); ii. 2.0 $(CH_3)_2CHCH_2I$, -78°→25° (4 h)[15]; f) $LiAlH_4$, THF, 50°, 1 h.

The synthetic pathway to trans-alkene isosteres of dipeptides described herein is the only fully stereocontrolled method for the preparation of these substances which is currently in the literature. The approach is readily conducted on a scale which provides gram-quantities of the protected dipeptide isosteres. It is expected that this sequence will provide previously unavailable substances of considerable biological interest. The isostere **7a**, for example, mimics a portion of the dominant immunogenic site of the influenza virus hemagglutinin[16]; isostere **7b** is a mimic for a dipeptide unit found in a number of peptide inhibitors of renin.[17] A detailed procedure for the key coupling of **5** and **6** follows:

Representative Procedure: Coupling of **5b** and **6b**. A solution of **5b** (0.30 g, 0.80 mmol) in 5.0 mL of THF at -78° was treated over 5 min. with 1.0 mL (1.6 mmol) of methyl lithium (1.6 M in ether). The resulting yellow solution was stirred 0.33 h at -78°. In a separate flask, 0.50 g (2.0 mmol) of aldehyde **6b** in 2.0 mL of THF at -78° was treated with 1.8 mL (1.8 mmol) of diisobutylaluminum methoxide (~1 M in THF; prepared by the addition of 1 equiv. of methanol to a 1.0 M solution of diisobutylaluminum hydride in THF). The resulting cold solution of the aluminum complex was transferred via cannula into the cold, metallated sulfone solution, and the whole was stirred 0.5 h at -78°. The reaction was quenched at -78° with saturated aqueous ammonium chloride, and the product was extracted with ether, dried over magnesium sulfate, and concentrated *in vacuo*. The crude β-hydroxysulfone was dissolved in 10 mL of methanol and cooled to 0°. Disodium hydrogen phosphate (0.5 g, 3 mmol)[7] was added, followed by 5 g (10.0 mmol) of 5% sodium amalgam. The mixture was stirred 4 h at 0°, diluted with water, and extracted with dichloromethane. Drying over $MgSO_4$ and concentration *in vacuo* followed by chromatography on silica gel (10% ethyl acetate-hexanes) afforded 275 mg (74%) of the THP-protected trans-homoallylic alcohol as a colorless oil which solidified upon standing at 25°.[18]

References and Endnotes

1. (a) Searle Scholar (1984-1987); (b) Recipient of a Procter & Gamble Exploratory Research Grant (1983-1986); (c) Petroleum Research Fund Summer Research Associate, 1984.

2. Spatola, A. in "Chemistry and Biochemistry of Amino Acids, Peptides and Proteins," Vol. 7, B. Weinstein, Ed. (New York: Marcel Dekker, 1983), pp. 267-358.

3. (a) Hann, M.M.; Sammes, P.B. J. Chem. Soc. Chem. Commun. 1980, 234; (b) Hann, M.M.; Sammes, P.G.; Kennewell, P.D.; Taylor, J.B. J. Chem. Soc. Perkin I 1982, 307; (c) Cox, M.T.; Heaton, D.W.; Horbury, J. J. Chem. Soc. Chem. Commun. 1980, 799; (d) Cox, M.T.; Gormley, J.J.; Hayard, C.F.; Petter, N.N. J. Chem. Soc. Chem. Commun. 1980, 800; (e) Miles, N.J.; Sammes, P.G.; Kennewell, P.D.; Westwood, R. J. Chem. Soc. Perkin Trans. I. 1985, 2299; and (f) Johnson, R. J. Med. Chem. 1984, 27, 1351.

4. All new substances were characterized by ^{1}H NMR (500 MHz or 80 MHz), IR, and low resolution MS. Selected intermediates were further characterized by high resolution MS.

5. Ishizumi, K.; Koga, K.; Yamada, S.-I. Chem. Pharm. Bull. 1968, 16, 492.

6. Crossland, R.K.; Servis, K.L. J. Org. Chem. 1970, 35, 3195.

7. Trost, B.M.; Arndt, H.C.; Strege, P.E.; Verhoeven, T.R. Tetrahedron Lett. 1976, 3477.

8. Miyashita, M.; Yoshikoshi, A.; Grieco, P.A. J. Org. Chem. 1977, 42, 3772.

9. Prepared from commercially available (S)-(+)-methyl-3-hydroxy-2-methylpropionate (Aldrich) by protection as the THP ether (DHP, $PyrH^+$ OTs^-, CH_2Cl_2) followed by reduction (DIBAL).

10. (a) Julia, M.; Paris, J.-M. Tetrahedron Lett. 1973, 4833; (b) Kocienski, P.J.; Lythgoe, B.; Ruston, S. J. Chem. Soc. Perkin Trans. I 1978, 829; (c) Kocienski, P.J.; Lythgoe, B.; Waterhouse, I. J. Chem. Soc. Perkin Trans. I 1980, 1045. We have not detected the corresponding cis isomer.

11. The aluminum complex of the aldehyde is labile. It must be formed at -78° and used immediately.

12. Hanessian, S.; Frenette, R.; Tetrahedron Lett. 1979, 3391.

13. Evans, D.A.; Ennis, M.D.; Mathre, D.J. J. Am. Chem. Soc. 1982, 104, 1727. The oxazolidone **8** was contaminated with *ca.* 30% of the corresponding α,β-unsaturated isomer which was recovered unchanged from the alkylation reaction. The de for this alkylation was determined by ^{1}H NMR. We thank Professor D.A. Evans and Dr. Marcello DiMare for providing unpublished results regarding the preparation and alkylation of oxazolidone **8**.

14. The absolute configuration and optical purity (88%) of **8** after benzylation and $LiAlH_4$ reduction was verified by conversion to the known (R)-2-benzyl-3-benzyloxypropanol. See: Aebi, J.P.; Sutter, M.A.; Wasmuth, D.; Seebach, D. Liebigs Ann. Chem. 1983, 2114.

15. (a) Creger, P.L. J. Am. Chem. Soc. 1967, 89, 2500; (b) Pfeffer, P.E.; Silbert, L.S.; Chirinko, J.M., Jr. J. Org. Chem. 1972, 37, 451.

16. (a) Wilson, I.A.; Niman, H.L.; Houghten, R.A.; Cherenson, A.R.; Connolly, M.L. and Lerner, R.A. Cell 1984 37, 767-778 and (b) Wilson, I.A.; Wiley, D.C. and Skehel, J.J. Nature (London) 1981, 289, 366-373.

17. Petrillo, E.W.; Ondetti, M.A. in "Medicinal Research Reviews," Vol. 2 (New York: Wiley, 1982), pp. 1-41.

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