Preparation of Protected *trans*-Olefinic Dipeptide Isosteres

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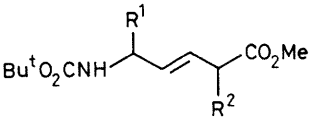
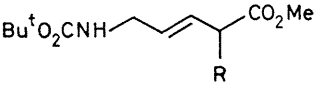
Summary Syntheses are described of several protected dipeptide isosteres, wherein the central amide linkage is replaced by a *trans*-olefinic bond.

A RECENT Communication by Sammes *et al.*[1] concerning double bond isosteres of the peptide bond prompts us to report some related work that we have carried out. In this and the accompanying Communication we confirm some of their observations and extend the concept to other hybrid peptide structures.

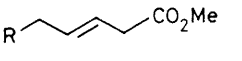
Prior to this work synthetic routes were not readily available for the preparation of protected dipeptide isosteres (**1**), which incorporate the elements of an allylic amine and a β,γ-unsaturated acid. We chose the readily available *trans*-hex-3-enedioic acid as a common starting material. Reaction with boron trifluoride–ether in dioxan containing 3 equiv. of MeOH gave a mixture of the monomethyl ester (**2**) and the diester (**3**), both of which were useful for our synthetic scheme. A modified Curtius reaction[2] of the monoester (**2**) using diphenylphosphoryl azide and triethylamine in toluene at 100 °C for 1 h, followed by the addition of Bu^{t}OH to the intermediate isocyanate, gave the protected Gly.Gly isostere (**4**) (62%), b.p. 111—112 °C at 0·1 mmHg. In principle, if this compound can be alkylated α to the ester group with an appropriate side-chain, a range of dipeptide isosteres would be available. Indeed, (**4**) reacts with LDA† and alkyl halides or aldehydes in THF to give moderate yields of alkylated products. Provided the reaction temperature is maintained below −50 °C the alkylated β,γ-unsaturated ester is the major product; some α,α-dialkylated material is also formed. If the temperature exceeds −50 °C α,β-unsaturated products are formed.[3] Thus, reaction of the anion with benzyl bromide gives the racemic, protected Gly.Phe isostere (**5**) (30%) and reaction with acetaldehyde leads to the corresponding Gly.Thr analogue (**6**) (56%).



(1)



(4) R = H
(5) R = CH_2Ph
(6) R = CH(OH)Me

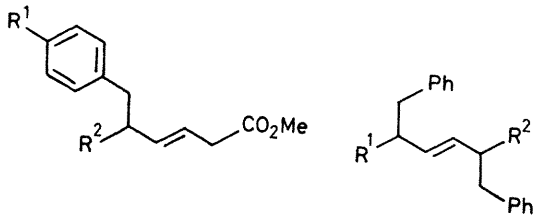


(2) R = CO_2H
(3) R = CO_2Me
(7) R = CO_2MEM
(8) R = CO_2CH_2OMe
(9) R = CO_2CH_2SMe

A series of compounds isomeric with those above is also available from the monoester (**2**), which is readily transformed into the mixed diester (**7**), b.p. 125—128 °C at 0·35 mmHg, using MEMCl–NEt_3–DMF. The monolithium enolate of (**7**) undergoes regioselective alkylation α to the MEM ester group, presumably as a result of internal

† Abbreviations used in this article: LDA = lithium di-isopropylamide; THF = tetrahydrofuran; MEM = methoxy(ethoxy)-methyl; DMF = dimethylformamide; HMPA = hexamethylphosphoric triamide; TMU = tetramethylurea.

lithium chelation ‡ The reaction is very slow at −50 °C, but addition of HMPA (5 equiv.) shortens the reaction time to about 15 min. In view of the carcinogenicity of this reagent we tried a number of alternative additives and tetramethylurea (TMU) proved to be almost as effective as HMPA in this reaction. The product of alkylation with benzyl bromide was the diester (**10**) (57%) which, with $TiCl_4$ in CH_2Cl_2, gave the mono-acid (**11**) (73%) isolated as its dicyclohexylamine salt, m.p. 120—121 °C. A modified Curtius reaction, as before, gave the protected Phe Gly isostere (**12**) (44%), m.p. 54—55 °C.



(**10**) R^1=H, R^2=CO_2MEM
(**11**) R^1=H, R^2=CO_2H
(**12**) R^1=H, R^2=$NHCO_2Bu^t$
(**13**) R^1=OBu^t, R^2=CO_2MEM
(**14**) R^1=OAc, R^2=CO_2H
(**15**) R^1=OAc, R^2=$NHCO_2C_6H_4OMe$-*p*
(**16**) R^1=R^2=CO_2Me
(**17**) R^1=CO_2H, R^2=CO_2Me
(**18**) R^1=$NHCO_2Bu^t$, R^2=CO_2Me

When the anion of (**7**), generated by using LDA–THF–TMU at −70 °C, was alkylated at −50 °C with *p*-t-butoxybenzyl bromide§ and the reaction quenched at −70 °C, analysis of the ^1H n.m.r. spectrum of the product (45%) indicated that the reaction was not completely regioselective in this case, the unwanted isomer (about 20%) was separated after the next step. We were unable to find a reagent to cleave the MEM group without cleaving the t-butyl ether, so (**13**) was treated with aqueous trifluoroacetic acid and acetylated with acetyl chloride. The resultant acid (**14**) was subjected to the modified Curtius procedure, using *p*-methoxybenzyl alcohol in this case, yielding the protected Tyr Gly isostere (**15**) (30%).

As an approach to the Phe Phe isostere (**18**), the diester (**3**) was alkylated using LDA–THF–TMU–$PhCH_2Br$ and one diastereomer (**16**) (66%) crystallised from the reaction product leaving the other essentially pure in the mother liquor. The partial hydrolysis of this material proved difficult owing to the base lability of the double bond. Eventually, 1.3 equiv. of iodotrimethylsilane in refluxing dichloroethane[4] led to the mono-acid (**17**), m.p. 100—103 °C. A modified Curtius reaction on this material gave the protected isostere (**18**) (70%).

Although these syntheses lack the stereospecificity of the approach of Sammes *et al.*,[1] they do provide access to a variety of racemic dipeptide isosteres. Also, by appropriate modification of (**7**), such as sequential alkylation, modified Curtius reaction, and alkylation, a further range of analogues of (**1**) is possible. The incorporation of some of these isosteres into peptide structures as probes for investigating the necessity of certain amide bonds for biological activity is described in the following Communication.

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‡ While this work was in progress related work on internal lithium chelation in a different context was published, see A. I. Meyers and P. J. Reider, *J. Am. Chem. Soc.*, 1979, **101**, 2501, M. Kolb and J. Barth, *Tetrahedron Lett.*, 1979, 2999. We have also obtained products of regioselective alkylation from the corresponding methoxymethyl ester (**8**), b.p. 96—98 °C at 0.05 mmHg and the methylthiomethyl ester (**9**), b.p. 105—106 °C at 0.05 mmHg.

§ Prepared from methyl *p*-hydroxybenzoate using the following reagents: i, 2-methylpropene, H^+; ii, $LiAlH_4$, Et_2O; iii, *N*-bromosuccinimide, PPh_3, CCl_4.

[1] M. M. Hann, P. G. Sammes, P. D. Kennewell, and J. B. Taylor, *J. Chem. Soc., Chem. Commun.*, 1980, 234.
[2] T. Shioiri, K. Ninomiya, and S. Yamada, *J. Am. Chem. Soc.*, 1972, **94**, 6203.
[3] For related examples of this type of reaction see M. W. Rathke and D. Sullivan, *Tetrahedron Lett.*, 1972, 4249, G. Gainelli, G. Cardillo, M. Contento, and A. Umani-Ronchi, *Gazz. Chim. Ital.*, 1974 **104** 625, A. S. Kende, D. Constantinides, S. J. Lee, and L. Liebeskind, *Tetrahedron Lett.*, 1975 405, T. J. Brocksom, M. G. Constantino and H. M. C. Ferraz, *Synth. Commun.*, 1977, **7**, 483, R. L. Cargill, D. F. Bushey, and J. J. Good *J. Org. Chem.*, 1979, **44**, 300.
[4] *Cf.* T.-L. Ho and G. A. Olah, *Angew. Chem., Int. Ed. Engl.*, 1976, **15**, 569, M. E. Jung and M. A. Lyster, *J. Am. Chem. Soc.*, 1977, **99**, 968.