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Synthesis of Xaa-Gly-Xaa' Keto-Methylene Tri-peptide Isosteres Incorporating Phenylalanine, Tyrosine and Valine Units.

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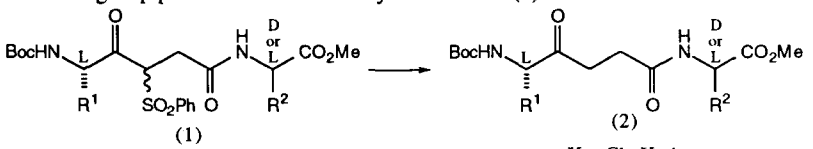
Abstract: *The utility of amino-acid derived β-ketosulfones in the synthesis of keto-methylene tri-peptide isosteres Xaa-Gly-Xaa', incorporating phenylalanine, tyrosine and valine units is reported. Both L,L and L,D forms of the tripeptide systems have been prepared using this methodology.*

The replacement of key amide bonds in peptide fragments by isosteric groups has received considerable attention recently as a possible means of generating novel bio-active substances[1]. As part of a programme designed towards the synthesis of new protease inhibitors we have been concerned with the synthesis of modified tripeptides in which one amide bond has been replaced by a keto-methylene group. We recently outlined the use of an alanine-derived β-ketosulfone in the construction of such amide isosteres and now wish to report extension of this methodology to more complex modified tri-peptides of the general type Xaa-Gly-Xaa' (2), in which Xaa, Xaa' is either phenylalanine, tyrosine or valine, compounds that are structurally related to known inhibitors of HIV protease[2].

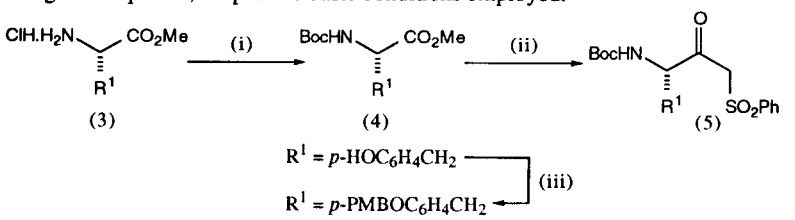
Our synthetic approach[3] to these isosteres proceeds through a β-ketosulfone intermediate (1) which on direct reduction of the sulfone group provides the keto-methylene isostere (2).



Scheme 1

Intermediates of type (1) should be available *via* the coupling of amino-acid derived β-ketosulfone (5) and bromoacetates (6), consequently we first considered synthesis of these units. The sulfones (5) derived from L-valine and L-phenylalanine were readily prepared from the corresponding amino-acid derivatives (3) as outlined in scheme 2. Thus blocking of the amino function as a *tert*-butoxycarbonyl urethane gave intermediate (4) which could then be reacted with the dianion derived from methylphenylsulfone to give the desired products (5a-b). Purification of the intermediates (4) was generally unnecessary, and good overall yields of the crystalline sulfones were obtained. In the case of L-tyrosine, it was also necessary to protect the phenolic function as a *p*-methoxybenzyl ether, immediately prior to formation of the sulfone, and this was readily achieved under standard

conditions[4]. As far as we were able to determine[5] the sulfone products (5a-c) were not racemised to any significant extent during this sequence, despite the basic conditions employed.

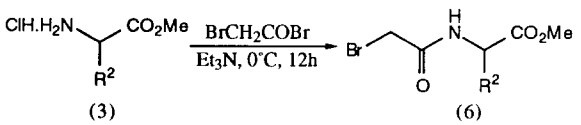


Reagents and conditions:
(i) $(Boc)_2O$, $NaHCO_3$, MeOH/THF (1:4), RT, 20h;
(ii) $PhSO_2CH^{2-}$, THF, -78°C to -30°C, 5h;
(iii) PMB-Cl, K_2CO_3, acetone, reflux, 24h.

Entry	R^1	Overall Yield
(a)	$C_6H_5CH_2$	67%
(b)	$CHMe_2$	68%
(c)	p-$PMBOC_6H_4CH_2$	83%

Scheme 2

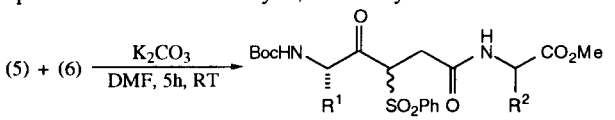
The desired bromoacetate derivatives (6a-d) were readily prepared in good yields by acylation of the requisite amino acid methyl ester hydrochlorides (3) with bromoacetyl bromide (scheme 3)[6]. It was found that good yields of the L-tyrosine derived bromoacetate (6e) could be obtained without protection of the phenol function.



Entry	R^2	Yield
(a)	L-$C_6H_5CH_2$	87%
(b)	L-$CHMe_2$	78%
(c)	D-$C_6H_5CH_2$	89%
(d)	D-$CHMe_2$	85%
(e)	L-p-$HOC_6H_4CH_2$	69%

Scheme 3

Coupling of the two fragments (5) and (6) was investigated under a variety of base-mediated conditions, including sodium hydride/tetrahydrofuran[6], potassium carbonate/acetonitrile[7] and lithium chloride/ diisopropylethylamine[8], which have proved successful in related reactions, however it could only be effectively achieved using anhydrous potassium carbonate in dry N,N-dimethylformamide.

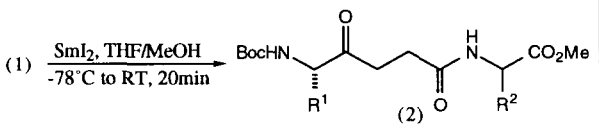


Entry	R^1	R^2	Yield	Entry	R^1	R^2	Yield
(aa)	$C_6H_5CH_2$	L-$C_6H_5CH_2$	80%	(bd)	$CHMe_2$	D-$CHMe_2$	82%
(ab)	$C_6H_5CH_2$	L-$CHMe_2$	92%	(be)	$CHMe_2$	L-p-$HOC_6H_4CH_2$	50%
(ac)	$C_6H_5CH_2$	D-$C_6H_5CH_2$	68%	(ca)	p-$PMBOC_6H_4CH_2$	L-$C_6H_5CH_2$	89%
(ad)	$C_6H_5CH_2$	D-$CHMe_2$	75%	(cb)	p-$PMBOC_6H_4CH_2$	L-$CHMe_2$	98%
(ae)	$C_6H_5CH_2$	L-p-$HOC_6H_4CH_2$	62%	(cc)	p-$PMBOC_6H_4CH_2$	D-$C_6H_5CH_2$	57%
(ba)	$CHMe_2$	L-$C_6H_5CH_2$	84%	(cd)	p-$PMBOC_6H_4CH_2$	D-$CHMe_2$	50%
(bb)	$CHMe_2$	L-$CHMe_2$	77%	(ce)	p-$PMBOC_6H_4CH_2$	L-p-$HOC_6H_4CH_2$	50%
(bc)	$CHMe_2$	D-$C_6H_5CH_2$	58%				

Scheme 4

Under these conditions coupling was usually complete after 5h at room temperature, giving the products (1) in good yield as a *ca.* 1:1 mixture of diastereoisomers at the sulfone centre. It is worth noting that using these reaction conditions coupling was successful, even in the presence of the free phenol group in the tyrosine-derived bromoacetate (6e), although the yields of the products incorporating this moiety were generally lower.

With the key β-ketosulfone intermediates (1) readily available we next considered conversion into the desired keto-methylene (2) systems. In our earlier studies in this area we had accessed the keto-methylene isostere by reductive removal of the sulfone group using aluminium amalgam in refluxing methanol, and although application of this procedure to the intermediates (1aa-ce) gave the desired products, yields were irreproducible and often low (≥10%). This appears to be partly a consequence of the increased reaction times required to reduce these relatively hindered sulfone functions, and partly because of difficulties in extracting the products from the heterogeneous reaction mixture. As a consequence we investigated a range of other methods for the reductive removal of the sulfone group. The best results to-date have been obtained employing freshly prepared samarium diiodide in dry tetrahydrofuran[9]. Under these conditions the desired keto-methylene isosteres are produced in reasonable isolated yields with relatively short reaction times (scheme 5). No other identifiable products could be isolated from this reaction system. As can be seen from the table, the presence of a benzyl substituent (R^1) adjacent to the β-ketosulfone unit (2aa-2ae, 2ca-2ce) generally results in noticeably lower yields than those obtained with an *iso*-propyl substituent (2ba-2be), whereas the nature of substituent R^2 appears to have relatively little effect.



Substrate	Yield 2[a]	Substrate	Yield 2[a]
1aa	44%	1bd	70%
1ab	43%	1be	55%
1ac	33%	1ca	54%
1ad	47%	1cb	41%
1ae	36%	1cc	27%
1ba	61%	1cd	34%
1bb	66%	1ce	47%
1bc	73%	a - after chromatographic purification	

Scheme 5

The preparation of both possible diastereoisomers of most of the the keto-methylene isostere systems (2) has allowed us to check the levels of racemisation obtained during this synthetic sequence. This can be achieved by investigation of the high-field ^1H nmr spectra of the diastereoisomers[10], which in the majority of cases is sufficiently different.[11] We have found that in general d.e. values for the products are high ≥90% although they do vary from run to run, and can drop as low as 85% in some instances. The epimerisation appears to be associated with the coupling reaction using K_2CO_3/DMF, and prolonged exposure of the reactants to these reaction conditions is reflected in a lowering of stereochemical purity in the final products.

In conclusion, we have developed a very short synthetic route to keto-methylene tri-peptide isosteres, which allows the preparation of Xaa-Gly-Xaa' systems incorporating phenylalanine, tyrosine and valine amino acid units. We are now examining the extension of this chemistry to the synthesis of other potential protease inhibitor systems.

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References and Notes

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5. The optical rotation of the sulfone products was not altered by differing reaction times, nor by repeated recrystallisation of the product.
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10. Selected ^{1}H nmr data (300MHz, $CDCl_3$):

    Compound 2ba - δ 7.30-7.20(3H, m, Ar-*H*), 7.10-7.08(2H, m, Ar-*H*), 6.02(1H, br.d, J=7.5Hz, N*H*) 5.08(1H, br.d, J=8.0Hz, N*H*), 4.86-4.79(1H, m, C*H*Bn), 4.24(1H, dd, J=3.5, 8.0Hz, C*H*i-Pr), 3.69(3H, s, CO_2CH_3), 3.12-3.03(2H, m, CH_2Ph), 2.94(1H, ddd, J=6.5, 6.5, 18.5Hz, CH_aH_bCO), 2.70(1H, ddd, J=6.0, 6.0, 18.5Hz, CH_aH_bCO), 2.54-2.37(2H, m, CH_2CO), 2.28-2.10(1H, m, C*H*Me$_2$) 1.41(9H, s, $C(CH_3)_3$), 0.98(3H, d, J=7.0Hz, CH_3), 0.76(3H, d, J=7.0Hz, CH_3).

    Compound 2bc - δ 7.30-7.20(3H, m, Ar-*H*), 7.09-7.06(2H, m, Ar-*H*), 6.04(1H, br.d, J=7.5Hz, N*H*), 5.08(1H, br.d, J=8.5Hz, N*H*), 4.86-4.80(1H, m, C*H*Bn), 4.23(1H, dd, J=4.0, 8.5Hz, C*H*i-Pr), 3.69(3H, s, CO_2CH_3), 3.11(1H, dd, J=6.0, 14.0Hz, CH_aH_bPh), 3.05(1H, dd, J=6.5, 14.0Hz, CH_aH_bPh), 2.87(1H, ddd, J=6.5, 6.5, 18.5Hz, CH_aH_bCO), 2.73(1H, ddd, J=6.5, 6.5, 18.5Hz, CH_aH_bCO), 2.53-2.37(2H, m, CH_2CO), 2.23-2.17(1H, m, C*H*Me$_2$), 1.41(9H, s, $C(CH_3)_3$), 0.98(3H, d, J=7.0Hz, CH_3), 0.75(3H, d, J=7.0Hz, CH_3).

    Compounds 2cb/2cd - δ 7.32(2H, d, J=8.5Hz, *o*-Ar-*H*), 7.04(2H, d, J=8.5Hz, *o*-Ar-*H*), 6.89(2H, d, J=8.5Hz, *m*-Ar-*H*), 6.86(2H, d, J=8.5Hz, *m*-Ar-*H*), 6.10(1H, br.d, J=8.5Hz, N*H*), 5.05(1H, br.d, J=8.5Hz, N*H*), 4.92(2H, s, OCH_2Ar), 4.51(1H, dd, J=5.0, 9.0Hz, C*H*i-Pr), 4.49-4.42(1H, m, C*H*CH2Ar), 3.79(3H, s, ArOCH_3), 3.73(3H, s, CO_2CH_3), 3.05(1H, dd, J=6.0, 14.0Hz, CH_aH_bAr), 2.89-2.69(3H, m, CH_aH_bAr, CH_2CO), 2.51-2.46(2H, m, CH_2CO), 2.17-2.06(1H, m, C*H*Me$_2$), 1.37(9H, s, $C(CH_3)_3$), 0.90(3H, d, J=7.0Hz, CH_3), 0.88(3H, d, J=7.0Hz, CH_3).

    Compound 2ce - δ 7.31(2H, d, J=8.5Hz, *o*-Ar-*H*), 7.04(2H, d, J=8.5Hz, *o*-Ar-*H*), 6.93(2H, d, J=8.5Hz, *o*-Ar-*H*), 6.89(2H, d, J=8.5Hz, *m*-Ar-*H*), 6.86(2H, d, J=8.5Hz, *m*-Ar-*H*), 6.71(2H, d, J=8.5Hz, *m*-Ar-*H*), 6.14-6.10(2H, m, O*H*, N*H*), 5.08(1H, br.d, J=7.5Hz, N*H*), 4.91(2H, s, OCH_2Ar), 4.82-4.76(1H, m, C*H*CH_2Ar), 4.46-4.39(1H, m, C*H*CH_2Ar), 3.79(3H, s, ArOCH_3), 3.70(3H, s, CO_2CH_3), 3.07-2.64(6H, m, 2xCH_2Ar, CH_2CO), 2.42-2.37(2H, m, CH_2CO), 1.38(9H, s, $C(CH_3)_3$).
11. We obtained coincident spectra for diastereoisomers 2cb/2cd, and to-date have been unable to find a method that enables us to determine d.e. values for these compounds, however, due to the similarity between these compounds and the others reported it would seem likely that similar levels of stereochemical purity are present.

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