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A SIMPLE AND VERSATILE ROUTE TO KETOMETHYLENE DIPEPTIDE ANALOGS

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Summary: A facile and versatile procedure for the synthesis of ketomethylene dipeptides by using N^{α}-Z-amino acid halomethyl ketones and dimethyl malonate as starting materials is reported. By application of this method, alanyl and phenylalanyl derivatives containing C-terminal Gly, Ala, Asp, Phe and Trp residues have been prepared.

Dipeptides in which the amide -CONH- linkage has been replaced by an isosteric ketomethylene $-COCH_2-$ group[1] have been used to prepare metabolically stable peptides[2] and various enzyme inhibitors[3]. For the synthesis of these pseudodipeptides, two procedures involving a modified Dakin-West reaction[4,5] and the use of Grignard reagents[5-7] respectively have been described. In the course of our studies concerning analgesic dipeptides[8], we desired a facile route to a variety of ketomethylene analogs which would: (1) simplify the reported methods from the standpoints of readily available starting materials and minimal steps of protection and deprotection; (2) assess the chiral integrity of the C-5 center; and (3) be easily applicable to those pseudodipeptides containing chemically labile side chains.

In a communication Umezawa et al[9] reported the synthesis of the first naturally occuring carba analogs of peptides, namely, Arg $\psi(COCH_2)$Phe and Arg $\psi(COCH_2)$-D-Phe (Arphamenine A and epi-Arphamenine A) from protected arginine bromomethyl ketone and ditetrahydropyranyl benzyl malonate. However, in spite of the simplicity of this synthesis, neither this pathway nor any modification of it have been applied to the preparation of other related compounds. With this in mind, a route, outlined in Scheme I, involving the use of N^{α}-Z-amino acid chloromethyl ketones and dimethyl malonate as starting compounds has now been developed. To test this route, the following pseudodipeptide derivatives have been prepared: Z-Phe$\psi(COCH_2)$X [X= Gly (4a), (RS) Ala(9a)] and Z-Ala$\psi(COCH_2)$Y [Y= Gly (4b), (RS) Ala(9b), (RS) Asp(10b), (RS) Phe (11b), (RS) Trp(12b)]. For biological purposes, to be reported elsewhere, compounds 9a and 11b have been deprotected.

As shown in Scheme I conversion of chloromethyl ketones 1[10,11] to iodomethyl ketones by transhalogenation with 1 equiv of sodium iodide in 1,2-dimethoxyethane, followed by in situ reaction with 1.1 equiv of the sodium derivative of dimethyl malonate (2) in 1,2-dimethoxyethane afforded, after silica gel chromatography (1:2 EtOAc/hexane), the 4-ketodiesters 3 (3a: 73% as a syrup; 3b: 90%, m.p. 99-100°C)[11]. Saponification of 3 and acidification to pH 3 with concentrated HCl, followed by decarboxylation in refluxing dioxane and flash chromatography (12:1 $CHCl_3$/MeOH) led to the N-protected ketomethylene glycine analogs 4[11] (Table 1). In order to introduce the C-2 substituent in ketomethylene dipeptide 9, 10b-12b, the sodium derivative of the corresponding 4-ketodiester 3 was treated with 1.1 equiv of the appropiate alkylating agent. Thus, alkylation of 3a with methyl iodide at room temperature led to 5a (97%) as a syrup.

A similar alkylation of 3b with methyl iodide, methyl bromoacetate and benzyl bromide provided 5b (93%), 6b (89%) and 7b (87%) respectively as syrups. The 3-methylindole substituted compound 8b was obtained as a syrup in 72% yield when methiodide of gramine, which was in situ formed by addition of 2 equiv of methyl iodide to a cooled solution (0°C) of gramine in 1,2-dimethoxyethane, was treated with the sodium derivative of 3a for 1h. Hydrolysis and decarboxylation of 5a, 5b-8b in a similar manner to that described for 4 gave the desired Z-protected ketomethylene dipeptides 9a, 9b-12b[11] (Table 1) in which the C-terminal amino acids are fully racemic. Finally, hydrogenation of 9a and 11b (0.01 mol) in 6N HCl/MeOH (1:20) at room temperature and 25 psi for 1.5 h, using Pd/C (0.1g) as catalyst afforded 13a and 14b after silica gel chromatography (6:1 $CHCl_3$/MeOH). Separation of the S,R and S,S diastereomers of 9a, 9b-12b, 13a and 14b was not observed in any of our chromatography experiments. In this synthetic route to ketomethylene dipeptides, the asymmetric centre of the starting amino acid derivatives is not affected. Therefore, the configuration at C-5 for all the compounds here reported was assigned as S. Support for the assignment came from the ^{1}H-NMR spectra of 9a, 9b-12b, 13a and 14b which indicated that, within the limits of ^{1}H-NMR, racemization of the N-terminal amino acid did not take place.

SCHEME I

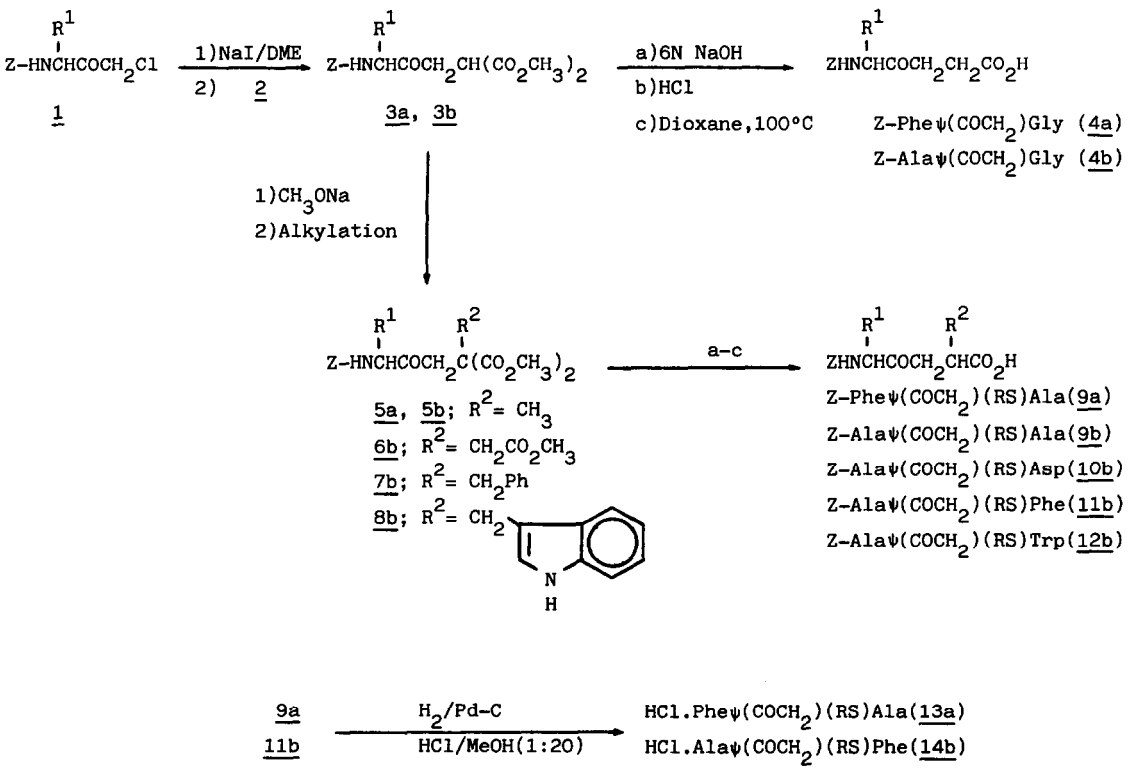
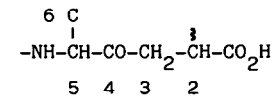


Table 1. Protected and unprotected ketomethylene dipeptides 4,9,10b-12b and 13a, 14b prepared[11]



No	Yield % [a]	m.p. °C [b]	^{1}H-NMR[c] (ppm); J(Hz)
4a	95	63-64	2.41(t,2H,H-2,$J_{2,3}$=6.4); 2.69(t,2H,H-3); 2.69 and 3.07(2dd,2H,H-6, $J_{6,6'}$=14.0, $J_{5,6}$=4.0, $J_{5,6'}$=10.7); 4.26(m,1H,H-5); 7.77(d,1H,NH).
4b	83	69-70	1.18(d,3H,H-6,$J_{5,6}$=7.5); 2.40(t,2H,H-2,$J_{2,3}$=6.3); 2.70(t,2H,H-3); 4.09(q,1H,H-5); 7.71(d,1H,NH).
9a	81	syrup	1.03 and 1.07(2d,6H,Ala CH_3); 2.49-3.17(m,10H,H-2,H-3 and H-6); 4.24 (m,2H,H-5); 7.76 and 7.80(2d,2H,NH).
9b	85	syrup	1.04 and 1.05(2d,6H,C-terminal Ala CH_3); 1.16(2d,6H,H-6,$J_{5,6}$=6.8); 2.43-2.86(m,6H,H-2 and H-3); 4.06 and 4.09(2q,2H,H-5); 7.67 and 7.71 (2d,2H,NH).
10b	71	syrup	1.17(2d,6H,H-6,$J_{5,6}$=7.3); 2.30-3.17(m,10H,H-2,H-3 and Asp CH_2); 4.07(m,2H,H-5); 7.75 and 7.77(2d,2H,NH).
11b	77	syrup	1.13 and 1.14(2d,6H,H-6,$J_{5,6}$=7.1); 2.40-3.00(m,10H,H-2,H-3 and Phe CH_2); 4.00 and 4.06(2q,2H,H-5); 7.14-7.38(m,20H,Z and Phe C_6H_5); 7.70 and 7.76(2d,2H,NH).
12b	67	foam	1.14 and 1.15(2d,6H,H-6,$J_{5,6}$=7.4 and 7.1); 2.48-3.06(m,10H,H-2,H-3 and Trp CH_2); 4.07 and 4.09(2q,2H,H-5); 6.97-7.57(m,10H,Z C_6H_5 and Trp C_8H_5); 7.67 and 7.73(2d,2H,NH).
13a	72	foam	1.30 and 1.33(2d,6H,Ala CH_3); 2.70-3.70(m,10H,H-2,H-3 and H-6); 4.63 (dd,2H,H-5,$J_{5,6}$=6.0, $J_{5,6}$=9.0).
14b	67	foam	1.50 and 1.53(2d,6H,H-6,$J_{5,6}$=7.7 and 7.9); 2.75-3.10(m,8H,H-3 and Phe CH_2); 3.25(m,2H,H-2); 4.24(m,2H,H-5); 7.35(m,5H Phe C_6H_5)

[a] Yield of pure isolated compounds. Overall yield of 9a and 9b-12b from 3a and 3b, respectively. [b] Not corrected. [c] Recorded at 300 MHz using Me_2SO-d_6 (for compounds 4, 9, 10b-12b) or D_2O (for compounds 13a and 14b) as sample solvents.

The synthetic method here reported has been extended to the preparation of ketomethylene dipeptides containing basic amino acids analogs as C-terminal residues. The synthesis and biological data of these compounds will be reported elsewhere.

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References and notes

1. The standard three-letter notation for amino acid residues preceded by the symbols $\psi(COCH_2)$ represents the ketomethylene modified residue of the pseudodipeptide. IUPAC-IUB Joint Commission on Biochemical Nomenclature Eur. J. Biochem. 1984, 138, 9.

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10. Compound 1a is commercially available from Bachem.
Compound 1b (m.p. 67°C, crystallized from EtOAc/hexane) was prepared in 74% by bubbling dry HCl into a solution (Et_2O) of the corresponding diazoketone which was in situ obtained from Z-Ala and isobutyl chloroformate in THF, and then treatment with CH_2N_2 in Et_2O.

11. All new compounds gave satisfactory microanalytical and spectral data.

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