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A GENERAL ROUTE TO "CARBA" PEPTIDE BOND REPLACEMENTS : UNEQUIVOCAL SYNTHESIS OF BOC-L-PHE-Ψ(CH_2-CH_2)-L-ALA-OH AND BOC-L-PHE-Ψ(CH_2-CH_2)-D-ALA-OH.

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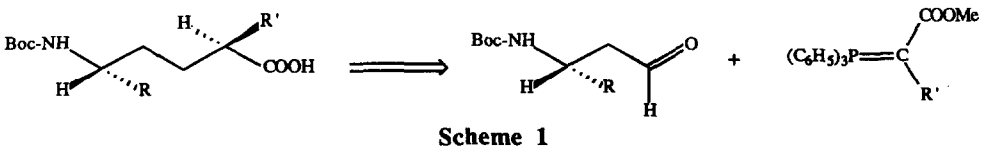
Abstract: An unambiguous synthesis of Boc-L-Phe-Ψ(CH_2-CH_2)-L-Ala-OH and Boc-L-Phe-Ψ(CH_2-CH_2)-D-Ala-OH from Boc-L-phenylalanine, through lactame intermediates (3R,6R)-3-methyl 6-benzyl-piperidin-2-one and (3S,6R)-3-methyl 6-benzyl-piperidin-2-one, is described.

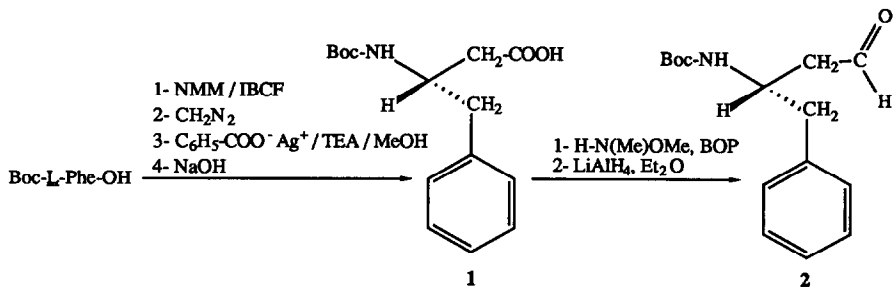
In peptide chemistry, isosteric peptide bond replacements have attracted considerable interest. Increased stability towards enzymatic degradation can thus be achieved, leading to pseudo-peptides analogues able to exhibit a prolonged duration of action as compared to the parent peptide hormone[1]. We have also shown that modifications of the peptide bonds can lead to peptide antagonists[2], a strategy which has since been widely followed. Some of the common backbone modifications are of general use, such as the retro-inverso Ψ(NH-CO) or the reduced peptide bond Ψ(CH_2-NH) approaches. The carba [Ψ(CH_2-CH_2)] replacement was applied in a limited number of structures, and no general methodology has been published to date, although it has been demonstrated in some examples to be an excellent mimic of the peptide bond[3]. For instance, we have synthesized in an earlier work the carba analogue of the protected dipeptide Boc-Nle-Gly-OH, i.e. 5(S)-(N-tert-butyloxycarbonyl)amino-nonanoic acid (Boc-Nle-Ψ(CH_2-CH_2)-Gly-OH) and described its incorporation in positions 28 and 29 of cholecystokinin[4].

We now report a general synthetic approach to carba bond replacements which is retrosynthetically illustrated in Scheme 1. It implies the reaction of the N-protected aldehyde of a homologated amino acid with a subtituted methyl (triphenylphosphoranylidene) acetate, followed by catalytic hydrogenation of the double bond formed. This pathway leads to a diastereomeric mixture of N-protected dipeptides, as no significant chiral induction can occur during the reduction of the ethylenic bond.



Scheme 1

In order to demonstrate the feasability of that method, we investigated the synthesis of Boc-Phe-Ψ(CH_2-CH_2)-Ala-OH. Homologation of Boc-L-phenylalanine was carried out by the classical Arndt-Eistert procedure to produce Boc-βhomo-L-Phe-OH **1**[5], which was converted to the corresponding aldehyde **2**[6] according to Fehrentz and Castro[7] (Scheme 2).



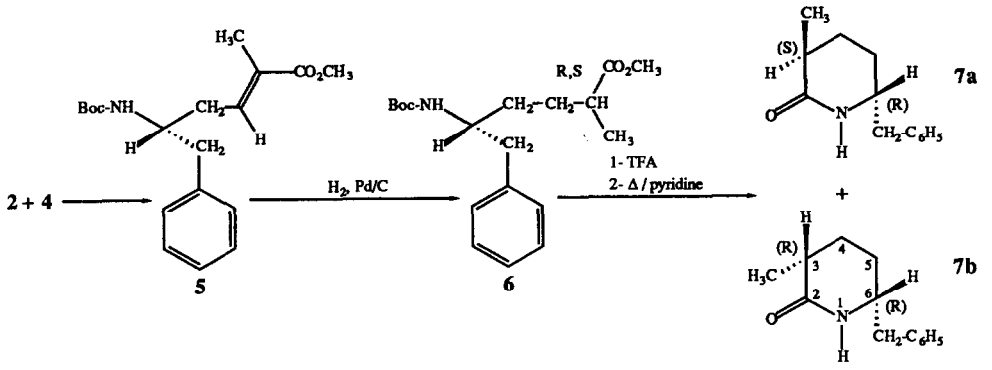
Scheme 2

Reaction of methyl iodide with methyl (triphenylphosphoranylidene)acetate afforded in fair yields the corresponding phosphonium salt **3** (Scheme 3) as described by Bestmann and Schultz[8]. It was treated with a molar equivalent of aqueous sodium hydroxide to lead, after extraction with ethyl acetate to the ylide **4**, which was immediately used without purification in the next step.

$$(C_6H_5)_3P{=}CH\text{-}COOCH_3 \xrightarrow{CH_3I} \underset{\mathbf{3}}{(C_6H_5)_3P^+\text{-}CH(CH_3)\text{-}COOCH_3, I^-} \xrightarrow{NaOH} \underset{\mathbf{4}}{(C_6H_5)_3P{=}C(CH_3)\text{-}COOCH_3}$$

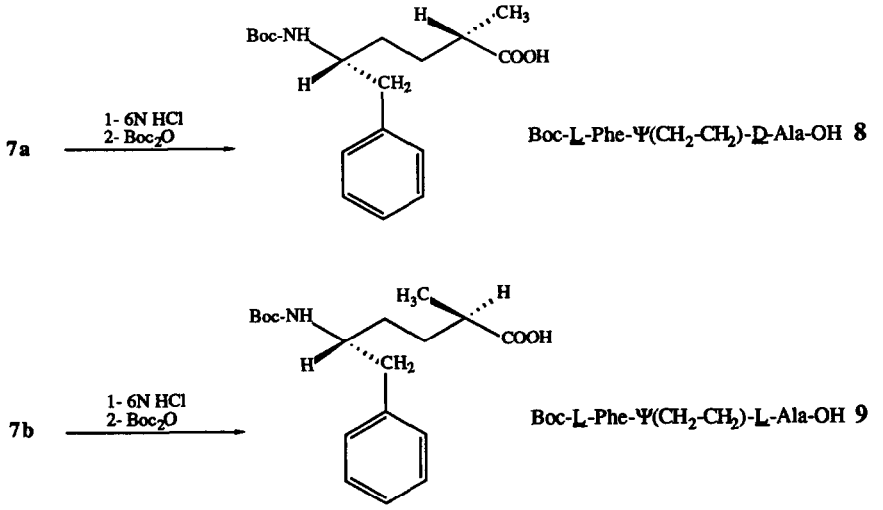
Scheme 3

Ylide **4** reacted with aldehyde **2** (Scheme 4) to produce the unsaturated compound **5**[9] (E isomer predominantly) which was submitted to catalytic hydrogenation to afford the 1/1 diastereomeric mixture **6**[10] (Boc-L-Phe-Ψ(CH_2-CH_2)-L-Ala-OMe + Boc-L-Phe-Ψ(CH_2-CH_2)-D-Ala-OMe), as shown by ^{1}H-NMR spectroscopy. In order to assign the absolute configuration of each diastereomer, the mixture **6** was submitted to partial deprotection with trifluoroacetic acid, followed by cyclisation in refluxing pyridine to lead to lactames **7a** and **7b**, which were separated by silica gel chromatography. The structure of lactames **7a** and **7b**[11] was unambiguously assigned by ^{1}H-NMR spectroscopy[12]: a nuclear Overhauser effect (NOE) was observed between H-3 and H-6 protons of compound **7b** at 305 and 320 K, whereas no effect was detected in compound **7a**, suggesting that H-3 andH-6 protons of compound **7b** are located on the same side of the piperidinone ring. As the absolute configuration of the carbon atom in position 6 is R (since the synthesis started from Boc-L-phenylalanine), the configuration of C-3 is R in compound **7b**.



Scheme 4

Acid hydrolysis of (3S,6R)-3-methyl-6-benzyl-piperidin-2-one **7a** and subsequent reaction with (di-tert-butyl)-dicarbonate (Boc_2O) (Scheme 5) afforded Boc-L-Phe-Ψ(CH_2-CH_2)-D-Ala-OH **8**[13], whereas (3R,6R)-3-methyl 6-benzyl-piperidin-2-one **7b** led to Boc-L-Phe-Ψ(CH_2-CH_2)-L-Ala-OH **9**[14].



Scheme 5

This work constitutes an unequivocal method for preparing stereochemically definite carba dipeptide isosteres. This methodology, which mainly involves stable and storable reagents, should be applicable to most of dipeptide units, and is in developement in our laboratory.

References and notes:

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3. C. Mendre, M. Rodriguez, M. F. Lignon, M. C. Galas, P. Worms & J. Martinez, *Eur. J. Pharmacol.*, in press.

4. C. Mendre, M. Rodriguez, J. Laur, A. Aumelas & J. Martinez, *Tetrahedron*, 1988, **44**, 4415-4430.

5. All yields refer to chromatographically pure materials. **1**: Yield 65% (overall from Boc-L-Phe-OH); mp 100-105 °C; Rf 0.40 ($CHCl_3$/MeOH/AcOH, 120/10/5); $[\alpha]_D$ = - 16 (c 0.98, MeOH).

6. **2**: Yield 81% (overall from **1**); mp 88-90 °C; Rf 0.71 (EtOAc/Hexane, 1/1); $[\alpha]_D$ = - 8 (c 0.97, MeOH); ^{1}H-NMR (DMSO-d^6) δ ppm 9.58 (s, 1H, CHO), 7.32 to 7.15 (m, 5H, arom.), 6.90 (d, 1H, ^3J = 8.0 Hz, NH), 4.11 (m, 1H, H α), 2.75 and 2.69 (m, 1H each, ^3J = 7.7 and 6.3 Hz respectively, ^2J = 13.5 Hz, H ββ'), 2.52 and 2.46 (m, 1H each, ^3J = 5.0 and 8.2 Hz respectively, ^2J = 16.2 Hz, H βhomo), 1.31 (s, 9H, Boc).

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8. H.J. Bestman & H. Schultz, Tetrahedron Lett., 1960, 5-6.

9. **5**: Yield 95% (from **2**); mp 68-69°C; Rf 0.55 (EtOAc/Hexane, 3/7); $[\alpha]_D$ = - 26 (c 0.93, MeOH); ^{1}H-NMR (DMSO-d^6) δ ppm 7.32 to 7.13 (m, 5H, arom.), 6.83 (d, 1H, ^3J = 8.8 Hz, NH), 6.71 (t, 1H, ^3J = 6.9 Hz, CH), 3.73 (m, 1H, Hα), 3.64 (s, 3H, O-CH_3), 2.34 and 2.26 (m, 1H each, allylic CH_2), 1.73 (s, 3H, CH_3), 1.31 (s, 9H, Boc), E structure shown by a NOE between allylic CH_2 and CH_3.

10. **6**: 1/1 mixture of diastereomers. Yield 97%; mp 62-64°C; Rf 0.55 (EtOAc/Hexane, 3/7); $[\alpha]_D$ = - 9 (c 1.11, MeOH); ^{1}H-NMR (DMSO-d^6) δ ppm 7.30 to 7.13 (m, 5H, arom.), 6.65 (d, 1H, ^3J = 8.9 Hz, NH), 3.55 (m, 1H, Hα), 3.53 and 3.56 (2s, 1H, O-CH_3), 2.63 (m, 2H, Hββ'), 2.37 (m, 1H, CH), 1.66-1.21 (m, 4H, CH_2-CH_2), 1.31 (s, 9H, Boc), 1.01 and 1.02 (2d, 3H, ^3J = 6.8 Hz, CH_3).

11. **7a**: Yield 40%; mp 112-114 °C; Rf 0.23 (EtOAc/Hexane, 1/1); $[\alpha]_D$ = + 17 (c 1.1, MeOH); ^{1}H-NMR (DMSO-d^6) δ ppm 7.40 to 7.10 (m, 5H, arom.), 7.20 (d, 1H, NH), 3.49 (m, 1H, H_6), 2.88 and 2.56 (dd, 2H, ^3J = 4.6 and 8.8 Hz respectively, ^2J = 13.0 Hz, benzylic Hs), 2.06 (m, 1H, H_3), 1.82 (m, 1H, H_4), 1.61 (m, 1H, H_5), 1.27 (m, 2H, $H_{4',5'}$), 1.02 (d, 3H, ^3J = 7.0 Hz, CH_3).

7b: Yield 40%; mp 124-126°C; Rf 0.12 (EtOAc/Hexane, 1/1); $[\alpha]_D$ = + 16 (c 0.98, MeOH); ^{1}H-NMR (DMSO-d^6) δ ppm 7.40 to 7.10 (m, 5H, arom.), 7.21 (d, 1H, NH), 3.51 (m, 1H, H_6), 2.85 and 2.62 (dd, 2H, ^3J = 4.6 and 9.0 Hz respectively, ^2J = 13.2 Hz, benzylic Hs), 2.17 (m, 1H, H_3), 1.70 (m, 1H, H_4), 1.52 (m, 1H, H_5), 1.46 (m, 1H, $H_{4'}$), 1.41 (m, 1H, $H_{5'}$), 1.03 (d, 3H, ^3J = 7.3 Hz, CH_3).

12. ^{1}H-NMR data were recorded on a Bruker WM 360 WB spectrometer at 360 MHz, in DMSO-d^6, the residual signal of which was taken as reference at 2.50 ppm. NOE difference was obtained by substracting two types of spectra, one in which the desired signal was saturated at low power during 4 seconds and the other in which the irradiation was on the left side of the spectrum. Saturation power was turned off during acquisition time. The resultant spectrum was compared with a standard one for localizing the NOE. The steady state was obtained with two dummy scans.

13. **8**: Yield 79%; mp 95-97 °C; Rf 0.49 ($CHCl_3$/MeOH/AcOH, 120/10/5); $[\alpha]_D$ = + 11 (c 2.06, EtOAc); ^{1}H-NMR (DMSO-d^6) δ ppm 11.93 (s, 1H, COOH), 7.30 to 7.10 (m, 5H, arom.), 6.62 (d, 1H, ^3J = 9.0 Hz, NH), 3.57 (m, 1H, H αPhe), 2.64 (m, 2H, H ββ'Phe), 2.29 (m, 1H, HαAla), 1.62-1.35 (m, 4H, CH_2-CH_2), 1.31 (s, 9H, Boc), 1.01 (d, 3H, ^3J = 6.9 Hz, CH_3).

14. **9**: Yield 76%; mp 100-102 °C; Rf 0.47 ($CHCl_3$/MeOH/AcOH, 120/10/5); $[\alpha]_D$ = - 12 (c 1.98, EtOAc); ^{1}H-NMR (DMSO-d^6) δ ppm 11.93 (s, 1H, COOH), 7.30 to 7.10 (m, 5H, arom.), 6.63 (d, 1H, ^3J = 9.0 Hz, NH), 3.54 (m, 1H, H αPhe), 2.64 (m, 2H, H ββ'Phe), 2.25 (m, 1H, HαAla), 1.52-1.37 (m, 4H, CH_2-CH_2), 1.31 (s, 9H, Boc), 1.00 (d, 3H, ^3J = 6.3 Hz, CH_3).

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