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"CARBA" PEPTIDE BOND SURROGATES: SYNTHESIS OF BOC-L-LEU-Ψ(CH_2-CH_2)-L-PHE-OH AND BOC-L-LEU-Ψ(CH_2-CH_2)-D-PHE-OH THROUGH A HORNER-EMMONS REACTION.

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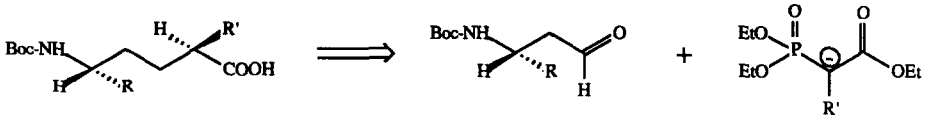
Abstract: A synthesis of Boc-L-Leu-Ψ(CH_2-CH_2)-L-Phe-OH and Boc-L-Leu-Ψ(CH_2-CH_2)-D-Phe-OH from Boc-βhomo-L-leucinal, through a Horner-Emmons reaction with ethyl 2-(diethylphosphono)-3-phenylpropionate is described. Intermediate cyclisation into lactames (3S,6R)-3-benzyl 6-isobutyl-piperidin-2-one and (3R,6R)-3-benzyl 6-isobutyl-piperidin-2-one allowed a facile and unambiguous identification of diastereomers.

We recently reported on a general route leading to "carba" peptide bonds replacements, which involved the reaction of a phosphorus ylide with a N-Boc-protected β-substituted β-aminoaldehyde[1]. As an example, we described the unambiguous synthesis of the two diastereomeric pseudodipeptides Boc-L-Phe-Ψ(CH_2-CH_2)-L-Ala-OH and Boc-L-Phe-Ψ(CH_2-CH_2)-D-Ala-OH.

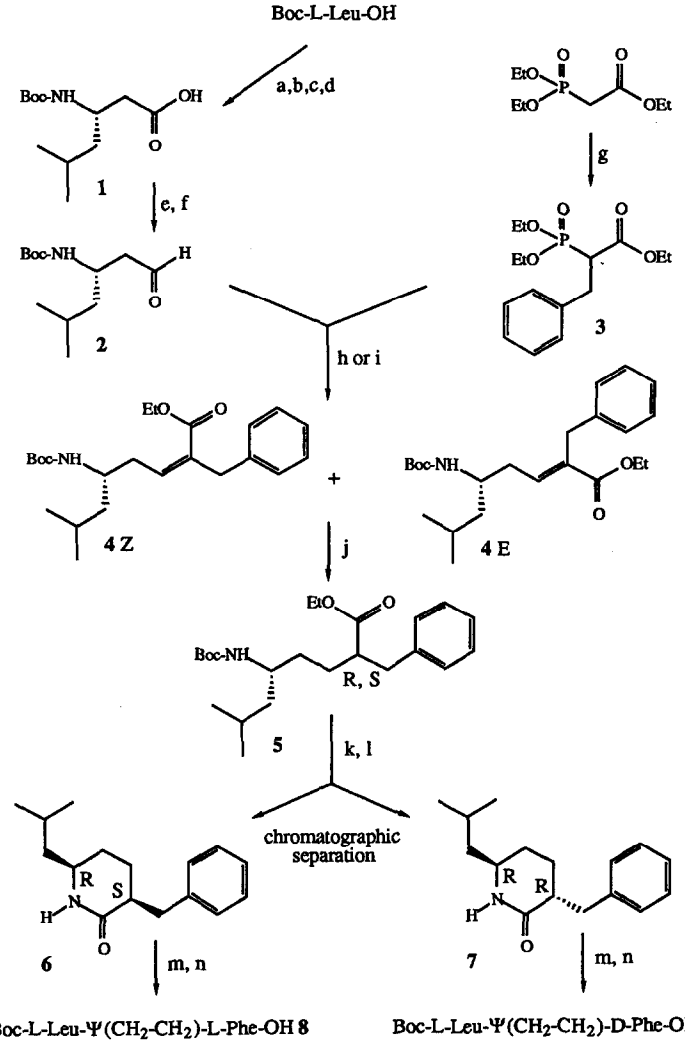
It has been demonstrated[2] that phosphonate anions have a number of advantages over the classical "Wittig reagents". They are usually rather inexpensive and they react with a wide variety of aldehydes and ketones under mild conditions. They can be alkylated to give α-substituted phosphonates[3], which can in turn react with bases to yield new anions which lead to olefins upon treatment with aldehydes or ketones. We thus investigated the obtention of "carba" peptide bonds replacements, by reacting the anion of an α-substituted phosphonoacetate with a N-Boc-protected β-substituted β-aminoaldehyde, according to the retrosynthetical scheme outlined below (Scheme 1).



Scheme 1

As an example, we report herein the synthesis (Scheme 2) of the two diastereomers of the "carba" analog of the N-protected dipeptide Boc-Leu-Phe-OH which represent one of the HIV protease cleavage site, i.e. Boc-L-Leu-Ψ(CH_2-CH_2)-L-Phe-OH and Boc-L-Leu-Ψ(CH_2-CH_2)-D-Phe-OH.

Boc-L-leucine was homologated as previously described[4] through a Arndt-Eistert reaction to lead to Boc-βhomo-L-Leu-OH **1**[5], which was converted to the aldehyde **2**[6], according to Fehrentz and Castro[7].

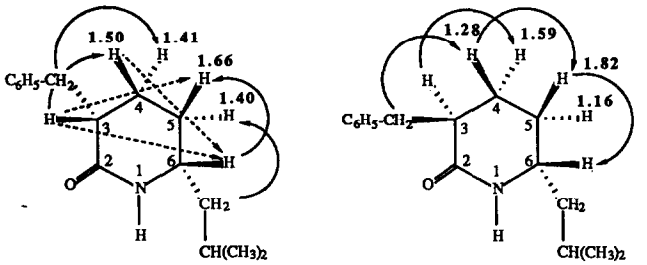


a: N-methylmorpholine, isobutylchloroformate; b: CH_2N_2; c: C_6H_5COOAg, triethylamine, MeOH; d: NaOH; e: HCl . H-N(Me)OMe, BOP, N-methylmorpholine; f: $LiAlH_4$; g: EtONa/EtOH, BzlBr; h: K_2CO_3, H_2O; i: NaH, dimethoxyethane; j: H_2, Pd/C; k: trifluoroacetic acid; l: Δ, pyridine; m: Δ, 6N HCl; n: Boc_2O.

Scheme 2

The triethyl phosphonoacetate anion was generated either in ethanol (0.5 molar solution) by sodium ethoxide, or in THF (5 molar solution) by sodium hydride, and then reacted with benzyl bromide to lead to the α-substituted phosphonoacetate 3[8]. This reaction, when carried out in THF, proceeded in very good yields (over 90%) after purification by column chromatography (TLC plates were monitored by UV light and iodine).

Ther substituted phosphonoacetate **3** was treated with sodium hydride in dry dimethoxyethane and subsequently reacted with aldehyde **2**, to afford in 30 minutes a mixture of Z and E isomers (Z/E = 45/55) of the alkene **4**[9], in a 83% yield. Alternatively, the reaction was carried out in water in the presence of potassium carbonate (3 days, room temperature), as described by Villeras and Rambaud[10], leading to the same mixture of isomers, although in a much lower yield (44%). Catalytic hydrogenation of mixture **4** over palladium on charcoal in 95% ethanol at room temperature afforded quantitatively a diastereomeric mixture **5**[11] of Boc-L-Leu-Ψ(CH_2-CH_2)-D,L-Phe-OEt. TFA deprotection followed by heating in pyridine, as already described[1], afforded in 88% yield a mixture of lactames **6** and **7**[12], which were easily separated by column chromatography. The more polar compound was identified as (3S,6R)-3-benzyl 6-isobutyl-piperidin-2-one **6** by NOE experiments as shown in Scheme 3. Isomer **7**, less polar, was identified on the same basis.



6 **7**

⌒ : strong NOE; ------ : weak NOE; bold numbers refer to chemical shifts

Scheme 3

Acid hydrolysis of **6** and **7**, followed by treatment with (di-tert-butyl)-dicarbonate (Boc_2O) led respectively to the N-protected pseudo-dipeptides Boc-L-Leu-Ψ(CH_2-CH_2)-L-Phe-OH **8** and Boc-L-Leu-Ψ(CH_2-CH_2)-D-Phe-OH **9**[13]. It is interesting to mention that, as already observed[1], the more polar lactame corresponds to the pseudo-dipeptide of L,L configuration.

This synthesis, which has been carried out on about ten millimoles of final compounds, can be generalized to the obtention of "carba" pseudo-dipeptide units, since the use of α-substituted phosphonoacetates allows the introduction of a wide variety of side chains.

References and notes:

1. M. Rodriguez, A. Aumelas & J. Martinez, *Tetrahedron Lett.*, 1990, **31**, 5153-5156.
2. W.S. Wadsworth, Jr. & W.D. Emmons, *J. Amer. Chem. Soc.*, 1961, **83**, 1733-1738.
3. R. D. Clark, L. G. Kozar & C. H. Heathcock, *Synthesis*, 1975, 635-636.
4. C. Mendre, M. Rodriguez, J. Laur, A. Aumelas & J. Martinez, *Tetrahedron*, 1988, **44**, 4415-4430.
5. 1: Yield 80% overall from Boc-Leu; oil; Rf 0.67 ($CHCl_3$/MeOH/AcOH, 120/10/5); ^{1}H-NMR (DMSO-d_6) δ ppm 12.08 (s, 1H, COOH), 6.60 (d, 1H, ^3J = 8.8 Hz, NH), 3.81 (m, 1H, Hα), 2.32 and 2.23 (dd, 1H each, ^3J = 6.8 Hz, ^2J = 15.1 Hz, Hβhomo), 1.57 (m, 1H, ^3J = 4.8, 9.3 Hz, Hγ), 1.37 (s, 9H, Boc), 1.32 (m, 1H, Hβ), 1.14 (m, 1H, ^3J = 9.3 Hz, ^2J = 14.2 Hz, Hβ'), 0.85 (d, 6H, ^3J = 6.8 Hz, Hδ). ^{1}H-NMR experiments were performed on a Bruker WM 360 WB

spectrometer. Chemical shifts are given relative to the residual signal of DMSO-d_6 (2.5 ppm). Resonance assignements are made by decoupling experiments and 2D spectra (COSY). NOEs were measured in the difference mode.

6. **2**: Yield 70% overall from **1**; mp 75-77°C; $[\alpha]_D$ = -5 (c = 1.2; MeOH); Rf 0.49 (EtOAc/Hexane, 3/7); ^{1}H-NMR (DMSO-d_6) δ ppm 9.60 (dd, 1H, ^3J = 3.4, 2.0 Hz, CHO), 6.77 (d, 1H, ^3J = 8.8 Hz, NH), 3.97 (m, 1H, Hα), 2.49 and 2.34 (ddd, 1H each, ^3J = 5.4, 2.0 and 8.3, 3.4 Hz respectively, ^2J = 15.6 Hz, Hβhomo), 1.58 (m, 1H, ^3J = 5.4, 8.8 Hz, Hγ), 1.38 and 1.15 (ddd, 1H each, ^3J = 5.4, 9.8 and 5.4, 8.8 Hz respectively, ^2J = 13.7 Hz, Hββ'), 1.36 (s, 9H, Boc), 0.86 and 0.85 (d, 3H each, ^3J = 6.8, Hδ).

7. J.A. Fehrentz & B. Castro, *Synthesis*, 1983, 676.

8. **3**: Yield 92% (THF), 55% (ethanol); oil; Rf 0.37 (EtOAc/Hexane, 5/5); ^{1}H-NMR (DMSO-d_6) δ ppm 7.31 to 7.17 (m, 5H, Ar), 4.08 (qd, 4H, ^3J = 7.1 Hz, J_{PH} = 8.3 Hz, $(EtO)_2$ CH_2), 4.00 (qd, 2H, ^3J = 7.1 Hz, J_{PH} = 3.0 Hz, COOEt CH_2), 3.39 (ddd, 1H, ^3J = 4.9, 10.7 Hz, J_{PH} = 22.5 Hz, CH), 3.09 and 3.02 (m, 1H each, ^2J = 13.6 Hz, J_{PH} = 6.9 Hz, CH_2), 1.25 (td, 6H, ^3J = 7.1 Hz, J_{PH} = 2.5 Hz, $(EtO)_2$ CH_3), 1.05 (t, 3H, ^3J = 7.1 Hz, COOEt CH_3).

9. **4**: Yield 83% (DME), 44% (H_2O); oil; Rf 0.52 and 0.43 (EtOAc/Hexane, 1/5); ^{1}H-NMR (DMSO-d_6) δ ppm: **4E**: 7.30 to 7.10 (m, 5H, Ar), 6.85 (t, 1H, ^3J = 7.3 Hz, vinylic CH), 6.70 (d, 1H, ^3J = 8.8 Hz, NH), 4.06 (q, 2H, ^3J = 6.8 Hz, Et CH_2), 3.65 and 3.62 (d, 2H, ^2J = 14.6 Hz, benzylic CH_2), 3.58 (m, 1H, Hα), 2.39 and 2.29 (ddd, 1H each, ^3J = 5.4 and 8.8 Hz respectively, ^2J = 14.6 Hz, allylic CH_2), 1.57 (m, 1H, Hγ), 1.37 (s, 9H, Boc), 1.32 (m, 1H, ^3J = 9.8 Hz, ^2J = 14.6 Hz, Hβ), 1.14 (m, 1H, Hβ'), 1.12 (t, 3H, Et CH_3), 0.84 and 0.82 (d, 3H each, Hδ); **4Z**: 7.30 to 7.10 (m, 5H, Ar), 6.62 (d, 1H, ^3J = 8.8 Hz, NH), 6.04 (t, 1H, ^3J = 7.3 Hz, vinylic CH), 4.04 (q, 2H, ^3J = 6.3 Hz, Et CH_2), 3.58 (m, 1H, Hα), 3.52 (s, 2H, benzylic CH_2), 2.54 and 2.43 (ddd, 1H each, ^3J = 5.9 and 7.8 Hz respectively, ^2J = 15.1 Hz, allylic CH_2), 1.57 (m, 1H, Hγ), 1.37 (s, 9H, Boc), 1.32 and 1.14 (m, 1H each, Hββ'), 1.14 (t, 3H, Et CH_3), 0.85 and 0.83 (d, 3H each, Hδ), a NOE between vinylic CH and benzylic CH_2 proves Z structure.

10. J. Villeras & M. Rambaud, *Synthesis*, 1983, 300-303.

11. **5**: Yield 97%; oil; Rf 0.48 (EtOAc/Hexane, 1/5); ^{1}H-NMR (DMSO-d_6) δ ppm: (55/45 mixture of diastereomers) 7.30 to 7.10 (m, 5H, Ar), 6.48 and 6.47 (d, ^3J = 9.3 Hz, NH), 3.97 (q, 4H, ^3J = 7.1 Hz, Et CH_2), 3.46 and 3.38 (m, HαLeu), 2.79 and 2.71 (dd, ^3J = 8.8 and 6.8 Hz respectively, ^2J = 13.2 Hz, Hββ'Phe), 2.70 and 2.57 (m, HαPhe), 1.53 (m, HγLeu), 1.49 (m, 2H, Leu/CH_2), 1.30 (m, 2H, Phe/CH_2), 1.37 and 1.35 (s, Boc), 1.27 and 1.05 (m, Hββ'Leu), 1.06 and 1.05 (t, Et CH_3), 0.83 (d, 6H, ^3J = 6.4 Hz, HδLeu).

12. Yield 88%, ratio **6/7** ≈ 55/45; **6**: mp 88-90°C; $[\alpha]_D$ = -38 (c = 1.9; MeOH); Rf 0.46 (EtOAc/Hexane, 5/5); ^{1}H-NMR (DMSO-d_6) δ ppm: 7.38 (m, 1H, NH), 7.32 to 7.15 (m, 5H, Ar), 3.28 (m, 1H, H_6), 3.06 and 2.63 (dd, 1H each, ^3J = 3.9 and 9.8 respectively, ^2J = 13.2 Hz, benzylic Hs), 2.39 (m, 1H, H_3), 1.66 (m, 1H, H_5), 1.62 (m, 1H, Hγ), 1.50 (m, 1H, H_4), 1.41 (m, 1H, $H_{4'}$), 1.40 (m, 1H, $H_{5'}$), 1.26 and 1.11 (m, 1H each, ^3J = 7.3 and 6.8 Hz respectively, ^2J = 13.7 Hz, Hββ'), 0.83 and 0.81 (d, 3H each, ^3J = 6.8 Hz, Hδ); **7**: mp 105-106°C; $[\alpha]_D$ = +31 (c = 1.2; MeOH); Rf 0.26 (EtOAc/Hexane, 5/5); ^{1}H-NMR (DMSO-d_6) δ ppm: 7.30 to 7.10 (m, 5H, Ar), 7.23 (1H, NH), 3.22 (m, 1H, H_6), 3.19 and 2.57 (dd, 1H each, ^3J = 4.4 and 9.3 Hz respectively, ^2J = 13.7 Hz, benzylic Hs), 2.32 (m, 1H, H_3), 1.82 (m, 1H, H_5), 1.68 (m, 1H, ^3J = 7.4 Hz, Hγ), 1.59 (m, 1H, H_4), 1.34 (m, 1H, ^3J = 7.8 Hz, ^2J = 12.7 Hz, Hβ), 1.28 (m, 1H, $H_{4'}$), 1.16 (m, 1H, $H_{5'}$), 1.16 (m, 1H, Hβ'), 0.84 and 0.82 (d, 3H each, ^3J = 6.8 Hz, Hδ).

13. **8**: Yield 82% overall from **6**; Rf 0.66 ($CHCl_3$/MeOH/AcOH, 120/10/5); mp 98-100°C; $[\alpha]_D$ = -11 (c = 2.0; MeOH); ^{1}H-NMR (DMSO-d_6) δ ppm: 12.04 (s, 1H, COOH), 7.30 to 7.10 (m, 5H, Ar), 6.47 (m, 1H, ^3J = 9.2 Hz, NH), 3.36 (m, 1H, HαLeu), 2.81 and 2.66 (dd, 1H each, ^3J = 8.5 and 6.1 Hz respectively, ^2J = 13.4 Hz, Hββ'Phe), 2.47 (m, 1H, HαPhe), 1.53 (m, 1H, HγLeu), 1.41 (m, 2H, Phe/CH_2), 1.35 (s, 9H, Boc), 1.25 (m, 2H, Leu/CH_2), 1.25 (m, 1H, HβLeu), 1.06 (m, 1H, ^3J = 8.5 Hz, ^2J = 13.4 Hz, Hβ'Leu), 0.83 (d, 6H, ^3J = 6.7 Hz, HδLeu); **9**: Yield 85% overall from **7**; Rf 0.66 ($CHCl_3$/MeOH/AcOH, 120/10/5); mp 101-102°C; $[\alpha]_D$ = -4 (c = 1.6; MeOH); ^{1}H-NMR (DMSO-d_6) δ ppm: 12.03 (s, 1H, COOH), 7.30 to 7.10 (m, 5H, Ar), 6.48 (m, 1H, ^3J = 9.2 Hz, NH), 3.44 (m, 1H, HαLeu), 2.79 and 2.64 (dd, 1H each, ^3J = 8.5 and 6.1 Hz respectively, ^2J = 13.4 Hz, Hββ'Phe), 2.57 (m, 1H, HαPhe), 1.54 (m, 1H, HγLeu), 1.49 and 1.42 (m, 1H each, Phe/CH_2), 1.37 (s, 9H, Boc), 1.31 (m, 2H, Leu/CH_2), 1.27 (m, 1H, HβLeu), 1.06 (m, 1H, ^3J = 8.5 Hz, ^2J = 13.4 Hz, Hβ'Leu), 0.83 (d, 6H, ^3J = 6.7 Hz, HδLeu).

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