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Preparation of 'carba' dipeptides bearing a basic side-chain at the C-terminus: synthesis of enantiopure Boc-D-Phe-Ψ[CH_2CH_2]-L-Arg(NO_2)-OH and Boc-D-Phe-Ψ[CH_2CH_2]-D-Arg(NO_2)-OH

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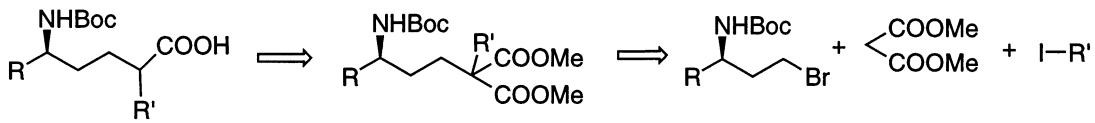
Abstract—A new approach to synthesize 'carba' Ψ[CH_2CH_2] dipeptides, e.g. Boc-D-Phe-Ψ[CH_2CH_2]-L-Arg(NO_2)-OH and Boc-D-Phe-Ψ[CH_2CH_2]-D-Arg(NO_2)-OH, is described.

Peptidomimetic research is an increasingly important feature of drug design, given the wealth of therapeutically useful natural peptide leads currently available. Work continues in the field to develop diverse non-peptidic scaffolds[1] to restrict conformational freedom of short peptides or offer 3-dimensional mimicry of peptide motifs such as β-turns, γ-turns[2] and helices.[2,3] An important aspect of this research is the design and synthesis of novel isosteric dipeptide mimetics as building blocks for longer peptides. This term describes structures which retain a 1,4-relationship between centers corresponding to the α-carbons in a dipeptide, while the amide bond is replaced with a different functionality. These structures vary in properties and degrees of conformational constraint, as in the Phe-Gly analogs recently reported by Gillespie.[4] Kaltenbronn[5] described synthesis of renin inhibitors containing any of 13 peptide bond isosteres. The chemical and enzymatic reactivities of such pseudopeptide linkages as Ψ[CH_2CH_2] and Ψ[CH=CH] are generally lower than those of the typical peptide bond and they generally do not form a hydrogen bond under physiological conditions. Hydrogen bonding in the peptide backbone has been implicated in inhibiting peptide transport through the intestinal wall.[6] Consequently, certain isosteric replacements of the amide bond may also facilitate oral bioavailability.

The synthesis of certain Ψ[CH_2CH_2] dipeptides, in which CH_2CH_2 replaces the amide bond, has been reported by Martinez[7] and by Wilson.[8] Typically the CH_2CH_2 unit in these syntheses was constructed by Horner–Wadsworth–Emmons or Wittig olefination of an enantiopure aldehyde, followed by reduction of the internal ethylene to an ethane segment. These sequences generally lead to a protected δ-amino ester, which may be cyclized to a pair of diastereomeric piperidones. Chromatographic separation of these epimers, followed by ring cleavage, leads to the free pseudo dipeptides. More recently, Guichard[9] has disclosed the stereoselective synthesis of pseudo dipeptides bearing aliphatic or aralkyl side-chains by direct C(2)-alkylation of a preformed *N*-Boc-piperidone with reactive primary halides.



Scheme 1.

Keywords: 'carba' dipeptide; arginine; guanidination.
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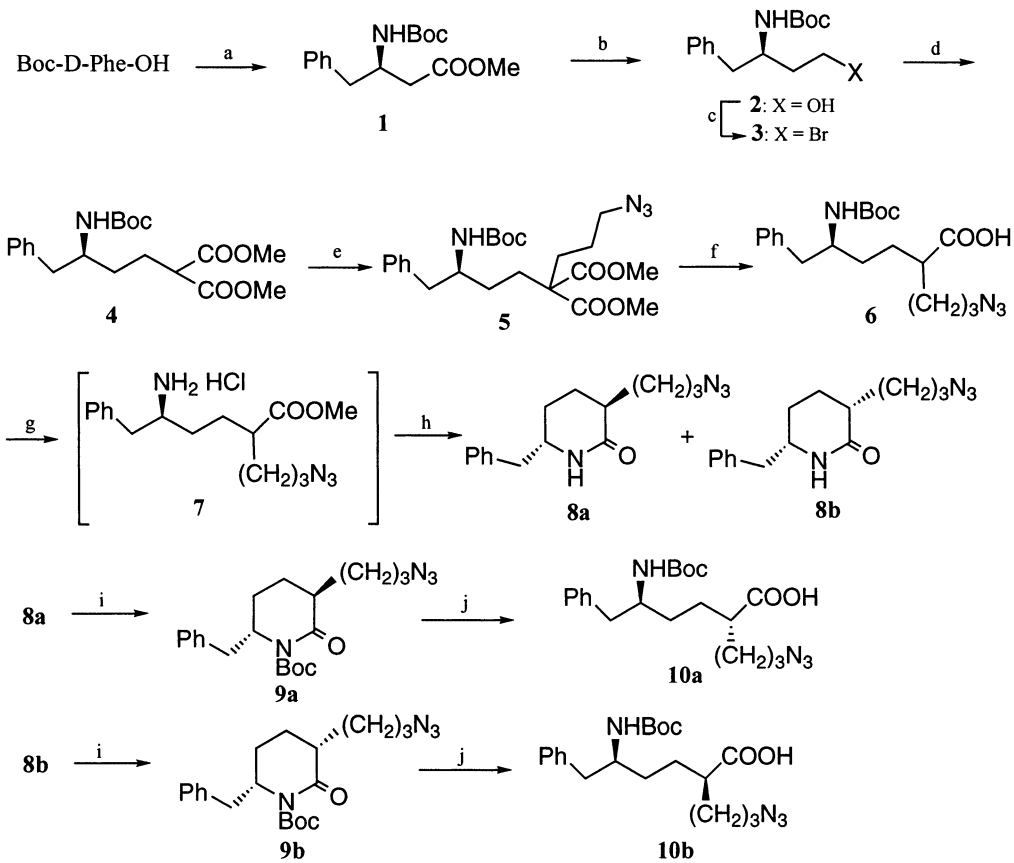
We have independently explored the synthesis of novel $\Psi[CH_2CH_2]$ dipeptides bearing a guanidine side-chain, in which there are orthogonally protected guanidine and N-terminal NH_2 groups, allowing convenient synthesis of longer peptides. Specifically, we illustrate a useful strategy for the synthesis of α,δ-disubstituted δ-amino acids containing a pendant guanidine unit. Our sequence utilizes a new 'carba' $\Psi[CH_2CH_2]$ replacement method to achieve this goal, and permits the rigorous identification of stereochemically pure isomers for basic researchers to scan for 3-D requirements in any given dipeptide pharmacophore. This work has resulted in the first synthesis of pure Boc-D-Phe-$\Psi[CH_2CH_2]$-L-Arg(NO_2)-OH and Boc-D-Phe-$\Psi[CH_2$-$CH_2]$-D-Arg(NO_2)-OH. Our synthetic strategy for such 'carba' peptides is shown in Scheme 1.

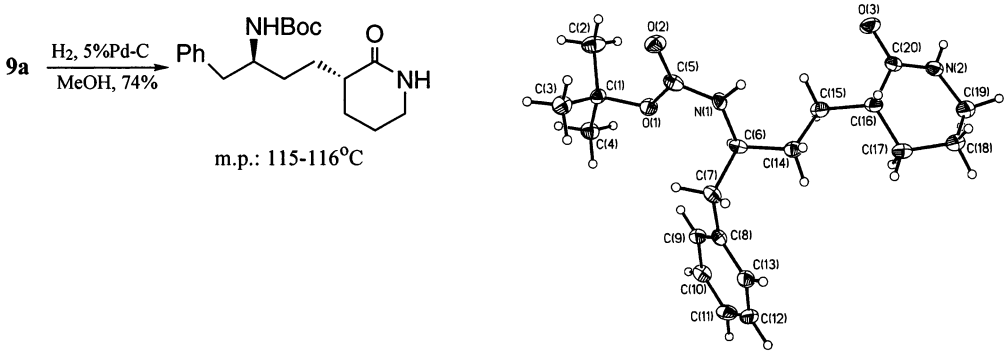
Starting from Boc-D-phenylalanine, homologation with the classical Arndt–Eistert procedure afforded ester **1**,[10] which could be reduced by sodium borohydride to give alcohol **2** in quantitative yield. Bromination of **2** with carbon tetrabromide and triphenylphosphine, followed by alkylation with dimethyl malonate, produced **4**.[11] The requirement of a guanidine residue led us to choose the azido group as a potential amine. This side-chain, 3-azido-propyl, was successfully introduced using 1-azido-3-iodopropane[12] as the alkylating reagent. Treatment of **5** with excessive 1N aqueous lithium hydroxide in methanol at room temperature resulted in the hydrolysis of one methyl ester; the second methyl ester was readily hydrolyzed when the reaction temperature was raised to reflux. The crude diacid was heated in toluene for 7 h to give an unseparable 1:1 diasteromeric mixture **6**[13] in 86% overall yield, as shown in Scheme 2.

The diastereomeric mixture **6** was subjected to acetyl chloride in methanol;[14] esterification and deprotection of *N*-Boc resulted in **7**. Cyclization of **7** occurred in refluxing pyridine to give lactams **8a** and **8b**,[15] which could be separated by flash chromatography, in 40 and 36% yield, respectively. Hydrolysis of the lactams **8a** and **8b** in refluxing aqueous HCl solution destroyed the azido group, while an alternative way via the Boc-protected lactams **9a** and **9b** proceeded smoothly with LiOOH in THF/H_2O to produce the optically pure δ-azido acids **10a** and **10b** without epimerization at α-position as shown in their ^1H and ^{13}C NMR spectra.[16] The structure of the compounds in series **a** and **b** was unambiguously assigned by X-ray crystallography of the derivative from **9a** as shown in Scheme 3.

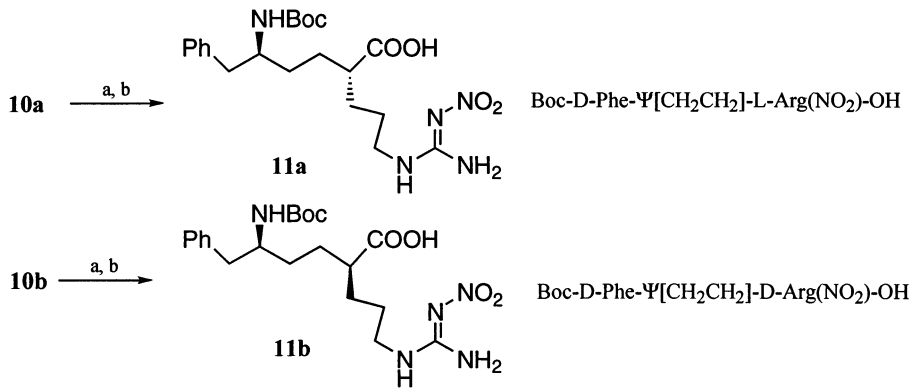
With both optically pure δ-azido acids **10a** and **10b** in hand, hydrogenation with 5% Pd-C and subsequent guanidination[17] using 3,5-dimethyl-*N*-nitro-1*H*-pyra-



Scheme 2. *Reagents and conditions:* (a) (i) $ClCO_2Et$, Et_3N, THF, then CH_2N_2, 93%, (ii) PhCOOAg, MeOH, 100%; (b) $NaBH_4$, THF/MeOH (20/1), 100%; (c) CBr_4, Ph_3P, CH_2Cl_2, 84%; (d) MeONa, $CH_2(COOMe)_2$, DME, 86%; (e) MeONa, $I(CH_2)_3N_3$, DME, 90%; (f) (i) 1N aq. LiOH, MeOH, reflux, (ii) toluene, reflux, 86% (from **5**); (g) AcCl, MeOH; (h) pyridine, reflux, 40% for **8a**, 36% for **8b** (from **6**); (i) Boc_2O, DMAP, MeCN, 80%; (j) 1N LiOH, H_2O_2, THF/H_2O (4:1), then Na_2SO_3, 98%.



Scheme 3.



Scheme 4. *Reagents and conditions*: (a) 5% Pd–C, H_2, MeOH; (b) 3,5-dimethyl-*N*-nitro-1*H*-pyrazole-1-carboximidamide, Et_3N, MeOH, 55–60% (two steps).

zole-1-carboximidamide afforded Boc-D-Phe-Ψ[CH_2-CH_2]-L-Arg(NO_2)-OH (**11a**) and Boc-D-Phe-Ψ[CH_2CH_2]-D-Arg(NO_2)-OH (**11b**),[18,19] respectively. (Scheme 4). These two convenient building blocks are now being utilized within peptidomimetic strategies in our laboratory in effort to scan for effective three-dimensional requirements of active peptide leads. Unlike earlier Wittig methodology, our route to 'carba' Ψ[CH_2CH_2] dipeptides proceeds through the 'modular' malonate intermediate **4**, which can be readily alkylated by a diverse range of electrophiles.

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11. Compound **4**: $[\alpha]_D = -3.9$ ($c = 1.14$, MeOH); mp 73–74°C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.33–1.55 (m, 2H), 1.42 (s, 9H), 1.91–2.03 (m, 2H), 2.73 (dd, $J = 13.3$, 6.9 Hz, 1H), 2.82 (m, 1H), 3.39 (t, $J = 7.4$ Hz, 1H), 3.71 (s, 3H), 3.73 (s, 3H), 3.84 (m, 1H), 4.38 (br d, $J = 8.0$ Hz, 1H), 7.17–7.32 (m, 5H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ: 25.3 (t), 28.3 (q), 31.4 (t), 41.3 (t), 51.1 (d), 52.41 (q), 52.44 (q), 79.1 (s), 126.3 (d), 128.3 (d), 129.4 (d), 137.8 (s), 155.4 (s), 169.6 (s) ppm. Anal. calcd for $C_{20}H_{29}NO_6$: C, 63.31; H, 7.70; N, 3.69. Found: C, 63.04; H, 7.87; N, 3.64%.
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13. Compound **6**: ^{1}H NMR (CD_3OD, 400 MHz): δ 1.20–1.66 (m, 8H), 1.39 (s, 9H), 2.31–2.38 (m, 1H), 2.71 (m, 2H), 3.29 (m, 2H), 3.70 (m, 1H), 7.16–7.28 (m, 5H) ppm.
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15. Compound **8a** (less polar): $[\alpha]_D = +33.2$ ($c = 0.74$, $CHCl_3$); mp 57–58°C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.46–1.68 (m, 5H), 1.98–2.03 (m, 3H), 2.25 (m, 1H), 2.62, 2.87

(ABX, $J_{AB}=13.5$ Hz, $J_{AX}=8.7$ Hz, $J_{BX}=5.2$ Hz, 2H), 3.29 (t, $J=6.7$ Hz, 2H), 3.60 (m, 1H), 5.71 (br, 1H), 7.18–7.36 (m, 5H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 26.1 (t), 26.3 (t), 28.4 (t), 29.1 (t), 40.7 (d), 43.5 (t), 51.5 (t), 54.6 (d), 127.0 (d), 128.9 (d), 129.1 (d), 136.6 (s), 173.9 (s) ppm. Anal. calcd for $C_{15}H_{20}N_4O$: C, 66.15; H, 7.40; N, 20.57. Found: C, 66.00; H, 7.54; N, 20.42%. Compound **8b** (more polar): a colorless oil, $[\alpha]_D=+86.7$ ($c=0.81$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.50–1.75 (m, 5H), 1.82–1.88 (m, 3H), 2.31 (m, 1H), 2.68, 2.84 (ABX, $J_{AB}=13.4$ Hz, $J_{AX}=8.4$ Hz, $J_{BX}=5.7$ Hz, 2H), 3.32 (m, 2H), 3.62 (m, 1H), 5.86 (br, 1H), 7.17–7.35 (m, 5H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 23.7 (t), 25.3 (t), 26.8 (t), 29.1 (t), 40.0 (d), 43.1 (t), 51.4 (t), 53.8 (d), 126.9 (d), 128.8 (d), 129.2 (d), 136.9 (s), 174.5 (s) ppm. Anal. calcd for $C_{15}H_{20}N_4O$: C, 66.15; H, 7.40; N, 20.57. Found: C, 66.05; H, 7.61; N, 20.19%.

16. Compound **10a**: a colorless oil, $[\alpha]_D=-3.4$ ($c=1.73$, $CHCl_3$); ^{1}H NMR (CD_3OD, 400 MHz): δ 1.38 (s, 9H), 1.48–1.69 (m, 8H), 2.37 (m, 1H), 2.71 (d, $J=7.0$ Hz, 2H), 3.29 (t, $J=6.2$ Hz, 2H), 3.74 (m, 1H), 7.16–7.33 (m, 5H) ppm; ^{13}C NMR (CD_3OD, 100 MHz): δ 26.4 (t), 27.3 (q), 28.4 (t), 29.2 (t), 31.8 (t), 41.4 (t), 44.4 (d), 50.8 (t), 51.5 (d), 78.3 (s), 125.7 (d), 127.8 (d), 129.0 (d), 138.7 (s), 156.7 (s), 178.1 (s) ppm. HRMS (M+H): calcd 391.2345; found: 391.2354. Compound **10b**: a colorless oil, $[\alpha]_D=-0.5$ ($c=1.48$, $CHCl_3$), ^{1}H NMR (CD_3OD, 400 MHz): δ 1.39 (s, 9H), 1.51–1.63 (m, 8H), 2.30 (m, 1H), 2.72 (d, $J=7.0$ Hz, 2H), 3.28 (t, $J=6.1$ Hz, 2H), 3.69 (m, 1H), 7.16–7.33 (m, 5H) ppm; ^{13}C NMR (CD_3OD, 100 MHz): δ 26.3 (t), 27.4 (q), 28.5 (t), 28.8 (t), 31.8 (t), 41.1 (t), 44.7 (d), 50.8 (t), 52.0 (d), 78.3 (s), 125.7 (d), 127.8 (d), 129.0 (d), 138.7 (s), 156.6 (s), 178.1 (s) ppm. HRMS (M+H) calcd: 391.2345; found: 391.2364.
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18. Compound **11a**: $[\alpha]_D=-5.6$ ($c=0.45$, MeOH), mp 75–77°C, ^{1}H NMR (CD_3OD, 400 MHz): δ 1.38 (s, 9H), 1.43–1.72 (m, 8H), 2.38 (m, 1H), 2.71 (d, $J=7.0$ Hz, 2H), 3.24 (t, $J=6.3$ Hz, 2H), 3.75 (m, 1H), 7.16–7.28 (m, 5H) ppm; ^{13}C NMR (CD_3OD, 100 MHz): δ 27.3 (q), 28.4 (t), 29.1 (t), 31.9 (t), 40.6 (t), 41.4 (t), 44.5 (d), 51.6 (d), 78.3 (s), 125.7 (d), 127.8 (d), 129.0 (d), 138.7 (s), 156.7 (s), 159.5 (s), 178.3 (s) ppm. HRMS (M+Na): calcd 474.2329; found: 474.2341. Compound **11b**: $[\alpha]_D=-1.3$ ($c=0.38$, MeOH), mp 80–82°C, ^{1}H NMR (CD_3OD, 400 MHz): δ 1.38 (s, 9H), 1.54–1.61 (m, 8H), 2.33 (m, 1H), 2.72 (d, $J=7.6$ Hz, 2H), 3.23 (t, $J=6.4$ Hz, 2H), 3.68 (m, 1H), 7.16–7.28 (m, 5H) ppm; ^{13}C NMR (CD_3OD, 100 MHz): δ 27.4 (q), 28.6 (t), 28.7 (t), 31.9 (t), 40.6 (t), 41.1 (t), 44.8 (d), 52.0 (d), 78.3 (s), 125.7 (d), 127.8 (d), 129.0 (d), 138.7 (s), 156.7 (s), 159.5 (s), 178.3 (s) ppm. HRMS (M+Na): calcd 474.2329; found: 474.2338.
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