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Three-Component Synthesis of α,β-Cyclopropyl-γ-Amino Acids

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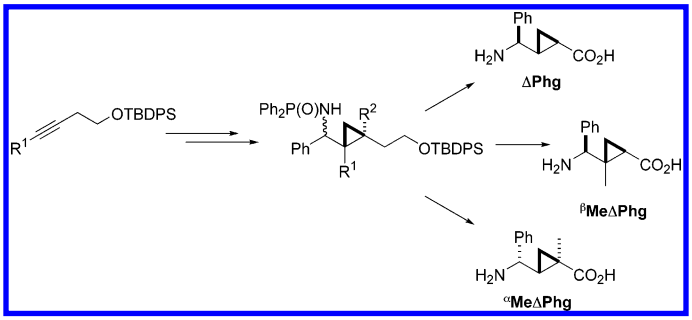
ABSTRACT



The multicomponent coupling of alkenylzirconocenes with *N*-diphenylphosphinoyl imines provides rapid access to functionalized *C*-cyclopropylalkylamides which have been readily transformed into α,β-cyclopropyl-γ-amino acids. These novel scaffolds are thus accessible in ca. 8 steps from commercially available alkynes.

The use of modified amino acids in peptide strands allows a greater control over chemical and conformational properties of oligopeptides.[1] The motivation for the development of novel peptidomimetics stems from the high affinity and selectivity of natural peptides for receptors and enzyme active sites; the failure of peptides as drug candidates is a function of their polarity and lack of stability to metabolic processes peptidases. Modification of the peptide backbone offers the promise of increased stability toward peptidases with the potential to maintain biological activity. For example, (*E*)-alkene isosteres can be used as geometric[2] and electronic[2f] replacements of the amide bond; however, alkenes are also susceptible to a number of degradation pathways such as isomerization and oxidation and in some cases even react during chain elongation.[2b]

We have recently described new methodologies for the preparation of allylic-,[3] homoallylic-,[4] *C*-cyclopropylalkyl-[3a,b] and *C*,*C*-dicyclopropylalkylamides[5] using multicomponent condensation reactions initiated by the dimethylzinc-mediated addition of alkenylzirconocenes to *N*-diphenylphosphinoyl imines. We were intrigued by the possibility of applying the methodology for *C*-cyclopropylalkylamide synthesis to the preparation of a novel family of backbone cyclopropane-extended amino acids (Figure 1).[6,7]

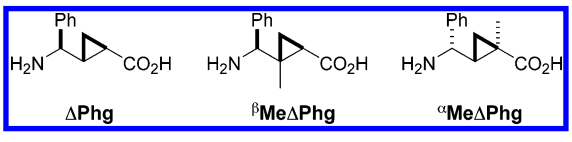


Figure 1. Backbone cyclopropane-extended amino acid residues.

The phenylglycine derivatives ΔPhg, $^{\beta}$MeΔPhg, and $^{\alpha}$MeΔPhg were chosen as representative examples that could

(1) (a) Cheng, R. P.; Gellman, S. H.; DeGrado, W. F. *Chem. Rev.* **2001**, *101*, 3219. (b) Hill, D. J.; Mio, M. J.; Prince, R. B.; Hughes, T. S.; Moore, J. S. *Chem Rev.* **2001**, *101*, 3893.

(2) (a) Liang, G.-B.; Dado, G. P.; Gellman, S. H. *J. Am. Chem. Soc.* **1991**, *113*, 3994. (b) Hagihara, M.; Anthony, N. J.; Stout, T. J.; Clardy, J.; Schreiber, S. L. *J. Am. Chem. Soc.* **1992**, *114*, 6568. (c) Liang, G.-B.; Desper, J. M.; Gellman, S. H. *J. Am. Chem. Soc.* **1993**, *115*, 925. (d) Gardner, R. R.; Liang, G.-B.; Gellman, S. H. *J. Am. Chem. Soc.* **1995**, *117*, 3280. (e) Wipf, P.; Henninger, T. C. *J. Org. Chem.* **1997**, *62*, 1586. (f) Wipf, P.; Henninger, T. C.; Geib, S. J. *J. Org. Chem.* **1998**, *63*, 6088. (g) Gardner, R. R.; Liang, G.-B.; Gellman, S. H. *J. Am. Chem. Soc.* **1999**, *121*, 1806. (h) Wipf, P.; Xiao, J. *Org. Lett.* **2005**, *7*, 103.

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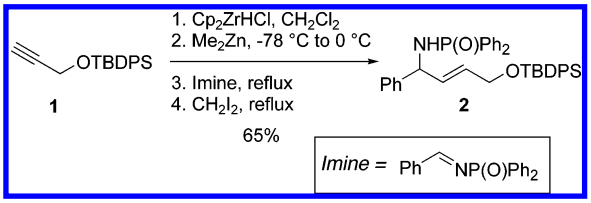
be readily prepared by multicomponent Zr→Zn methodology.[8] These compounds should also exhibit the structural rigidity that is paramount to the conformational mimicry of the peptide strand.

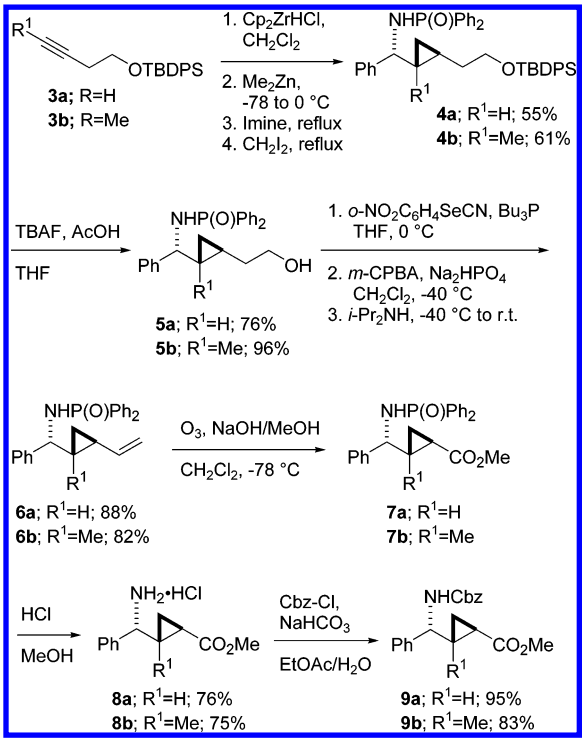
Our initial approach to α,β-cyclopropyl-γ-amino acids failed as the conversion of propargylic ether **1** stopped at the allylic amine **2** (Scheme 1). Only traces of *C*-cyclopropylalkyl amide product could be isolated after prolonged reaction times.

Scheme 1. Propargyl Ether Approach



In contrast, the TBDPS-protected *C*-cyclopropylalkylamides **4a** and **4b** were readily prepared on gram scale from homopropargylic ethers **3a** and **3b**, respectively. Desilylation (TBAF/AcOH) afforded 76% and 96% of alcohols **5a** and **5b**. Unfortunately, after conversion to the intermediate selenide, oxidation and elimination[9] afforded the desired vinyl cyclopropanes **6a** and **6b** in poor yields. However, a modification developed by Reich[10] which involved oxidation of the intermediate selenide with *m*-CPBA at low temperature (−40 °C) followed by elimination in the presence of 5 equiv of diisopropylamine afforded these alkenes in excellent yields (82−88%, two steps). Ozonolysis in the presence of basic methanol[11] followed by *N*-deprotection of the phosphinoyl group (HCl, MeOH) and precipitation with Et_2O provided the hydrochloride salts **8a** and **8b**. *N*-Protection (Cbz-Cl, $NaHCO_3$) led to the fully protected amino acids **9a** and **9b** (Scheme 2).

Scheme 2. Synthesis of Cbz-*dl*-ΔPhg-OMe and Cbz-*dl*-$^{\Delta}$MeΔPhg-OMe



The synthesis of the $^{\alpha}$MeΔPhg residue necessitated the combination of the water-accelerated methylalumination[12] reaction with the Simmons−Smith cyclopropanation (Scheme 3).[13] Carboalumination of **3a** (Me_3Al, Cp_2ZrCl_2, H_2O) followed by microwave-accelerated addition to diphenylphosphinoyl imine[14] afforded the allylic amide **10**. Treatment of **10** with $Zn(CH_2I)_2$•DME complex[15] afforded the desired *C*-cyclopropylalkylamide **4c** in excellent yield and diastereoselectivity (>19:1 by ^{1}H NMR). Desilylation (TBAF, AcOH) followed by modified Grieco elimination led to **6c** which was transformed into the Cbz-protected **9c** after ozonolysis and an *N*-protective group switch.

To examine the structural features of these new building blocks in dipeptide conjugates, we prepared enantiomerically pure derivatives by resolution of amine salts (Scheme 4).[16] Hydrogenolysis (H_2, Pd/C, MeOH) of **9a** and **9c** followed

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(4) Wipf, P.; Kendall, C. *Org. Lett.* **2001**, *3*, 2773.

(5) Wipf, P.; Stephenson, C. R. J.; Okumura, K. *J. Am. Chem. Soc.* **2003**, *125*, 14694.

(6) For reviews on the synthesis of cyclopropyl amino acids, see (a) Stammer, C. H. *Tetrahedron* **1990**, *46*, 2231. (b) Burgess, K.; Ho, K.-K.; Moye-Sherman, D. *Synlett* **1994**, 575.

(7) For examples of the use of cyclopropane-containing amino acids as peptide mimics, see: (a) Burgess, K.; Ho, K.-K.; Pal, B. *J. Am. Chem. Soc.* **1995**, *117*, 3808. (b) Martin, S. F.; Dorsey, G. O.; Gane, T.; Hillier, M. C.; Kessler, H.; Baur, M.; Matha, B.; Erickson, J. W.; Bhat, T. N.; Munshi, S.; Gulnik, S. V.; Topol, I. A. *J. Med. Chem.* **1998**, *41*, 1581. (c) North, M. *J. Peptide Sci.* **2000**, *6*, 301. (d) Martin, S. F.; Dwyer, M. P.; Hartmann, B.; Knight, K. S. *J. Org. Chem.* **2000**, *65*, 1305. (e) Hillier, M. C.; Davidson, J. P.; Martin, S. F. *J. Org. Chem.* **2001**, *66*, 1657. (f) Davidson, J. P.; Lubman, O.; Rose, T.; Waksman, G.; Martin, S. F. *J. Am. Chem. Soc.* **2002**, *124*, 205. (g) Reichelt, A.; Gaul, C.; Frey, R. R.; Kennedy, A.; Martin, S. F. *J. Org. Chem.* **2002**, *67*, 4062. (h) Headley, A. D.; Ganesan, R.; Nam, J. *Biorg. Chem.* **2003**, *31*, 99.

(8) We selected the Δ-prefix to indicate amino acid residues that have a cyclopropane ring inserted into the backbone chain between carbonyl-C and α-C.

(9) (a) Sharpless, K. B.; Young, M. W. *J. Org. Chem.* **1975**, *40*, 947. (b) Grieco, P. A.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1976**, *41*, 1485. (c) Kutney, J. P.; Singh, A. K. *Can. J. Chem.* **1983**, *61*, 1111.

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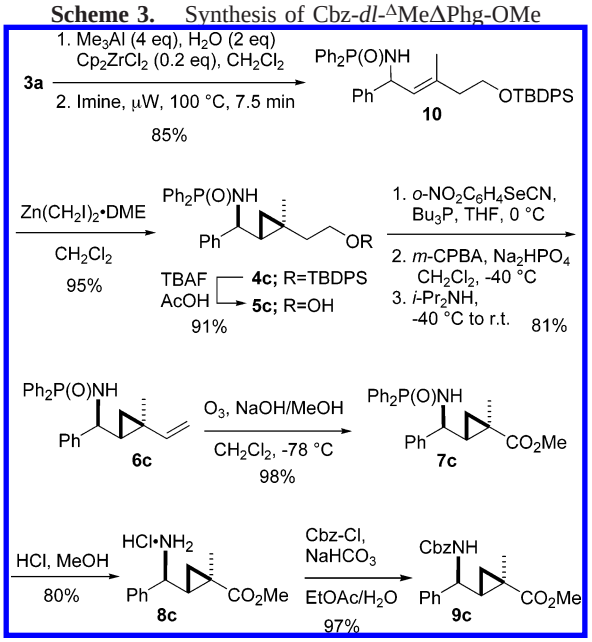
(13) (a) Simmons, H. E.; Smith, R. D. *J. Am. Chem. Soc.* **1958**, *80*, 5323. (b) Simmons, H. E.; Smith, R. D. *J. Am. Chem. Soc.* **1959**, *81*, 4256. (c) Charette, A. B.; Beauchemin, A. *Org. React.* **2001**, *58*, 1. (d) Lebel, H.; Marcoux, J.-F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977.

(14) For the diastereoselective addition of alkenylalanes to *N*-sulfinylimines using conventional reaction conditions, see: Wipf, P.; Nunes, R. L.; Ribe, S. *Helv. Chim. Acta* **2002**, *85*, 3478. Microwave reactions were performed in sealed tubes in a Biotage Emrys Optimizer at 300 W.

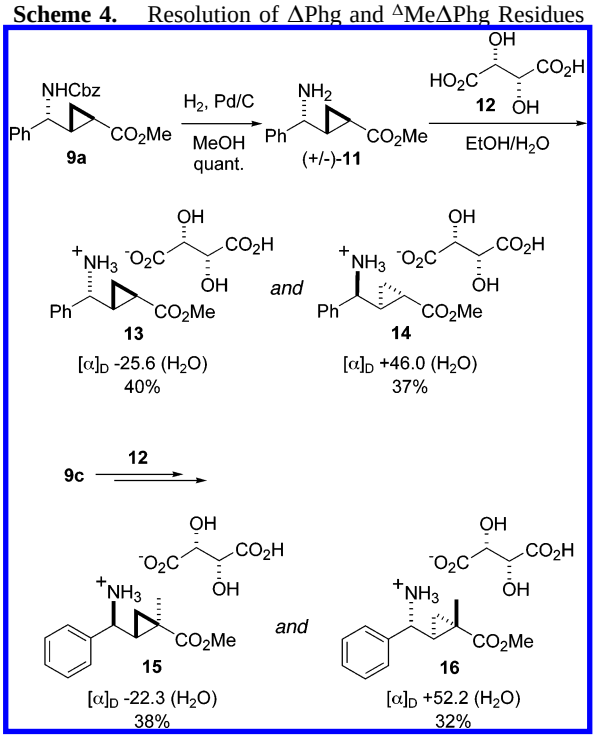
(15) Charette, A. B.; Prescott, S.; Brochu, C. *J. Org. Chem.* **1995**, *60*, 1081.

Scheme 3. Synthesis of Cbz-*dl*-$^{\Delta}$MeΔPhg-OMe

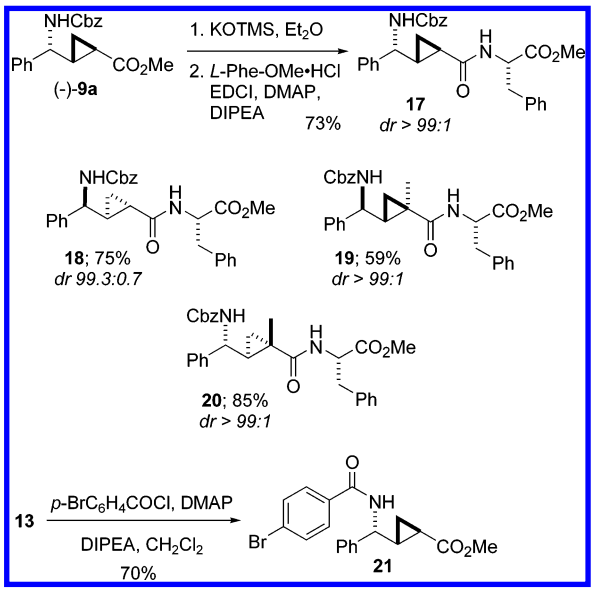


by formation of the corresponding *l*-tartaric acid ammonium salts and fractional crystallization[17] afforded the diastereomerically pure salts **13**−**16**. Subsequently, phenylalanine derivatives **17**−**20** were prepared by *N*-Cbz protection (Cbz-Cl, $NaHCO_3$) of the tartrate salts followed by saponification (KOTMS,[18] Et_2O or NaOH, MeOH/THF for **20**) and coupling with L-Phe-OMe•HCl (EDCI, DMAP, DIPEA or BOP, DIPEA, DMF for **20**, Scheme 5). HPLC analysis of the crude reaction mixtures indicated an excellent diastereomeric purity for these dipeptides. The absolute configuration[19] of the cyclopropyl residues **13** and **14** was based on the X-ray structure analysis of the *p*-bromobenzamide derivative **21**, prepared from **13** (*p*-BrC_6H_4COCl, DMAP) in good yield. The phenylalanine derivative **19** was crystallized from EtOAc/hexanes, and X-ray analysis confirmed the *syn*-stereochemistry of the *C*-cyclopropylalkylamide obtained in the Simmons−Smith step and allowed an unequivocal assignment of the absolute configuration of the amino acid precursors **15** and **16**.

Scheme 4. Resolution of ΔPhg and $^{\Delta}$MeΔPhg Residues



Scheme 5. Coupling Reactions of α,*β*-cyclopropyl-*γ*-amino Acids



The strong preference for the *syn*-diastereoisomer that was observed in the conversion of **10** to **4c** is opposite to our previous results in which (*E*)-disubstituted alkenes afforded the *anti*-diastereoisomer (>19:1) under analogous reaction conditions.[3b] The preference for the *anti*-isomer in *(E)*-disubstituted allylic amides was rationalized using a model akin to that proposed for the cyclopropanation of allylic ethers (**23**),[20] where nonbonded interactions between the olefin and the diphenylphosphinoyl substituent disfavor attack from the $A^{1,3}$-minimized conformation **22**. With (*E*)-trisubstituted alkenes, however, the 1,3-allylic strain appears to override this interaction leading to the *syn*-diastereomer via **22** (Figure 2).

Interestingly, **19** adopts an extended conformation in the solid state, crystallizing as an antiparallel dimer (Figure 3).

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(17) The salts were recrystallized until their optical rotation was constant (ca. 3 times).

(18) Laganis, E. D.; Chenard, B. L. *Tetrahedron Lett.* **1984**, *25*, 5831.

(19) Flack, H. D. *Acta Crystallogr.* **1983**, *A39*, 876.

(20) Charette, A. B.; Lebel, H.; Gagnon, A. *Tetrahedron* **1999**, *55*, 8845.

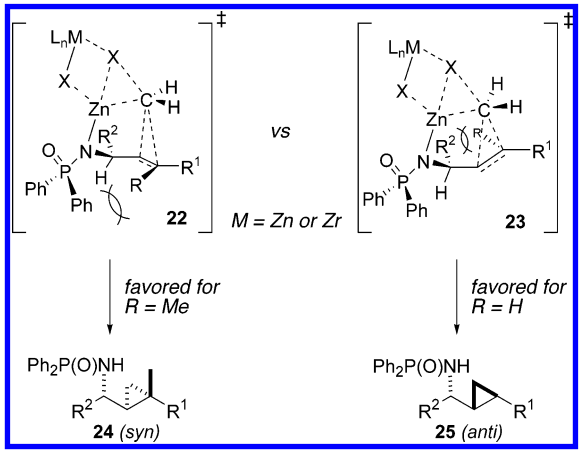

Figure 2. Proposed transition states for stereoselective cyclopropanations of allylic phosphinoylamides.

In fact, the dihedral angles about the backbone cyclopropane-extended amino acid residue are all greater than 135°, minimizing allylic strain throughout the carbon chain. The Newman projection in Figure 3b highlights the antiperiplanar positioning of the two amide groups in the solid state of **19**. This secondary structure preference is similar to that observed by Schreiber and co-workers[2b] during their studies of vinylogous amino acids. The geometric homology between naturally occurring vinylogous amino acids and novel backbone cyclopropane-extended residues such as **15** bodes well for the use of the latter building blocks in the design of conformationally preorganized peptide mimetics. β-Sheets sheets are important for protein−protein and protein−DNA interactions, and templates that induce these extended conformations are useful tools in medicinal and host−guest chemistry.[21]

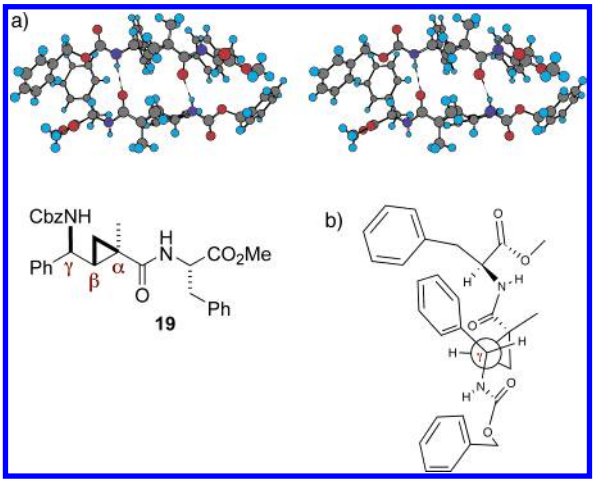

Figure 3. (a) Stereoview of the X-ray crystal structure of **19**. (b) Newman projection of the C(β)-C(γ) bond in **19**.

In summary, we have developed an efficient approach for the preparation of novel α,β-cyclopropyl-γ-amino acids utilizing the one-pot, three-component reaction of alkenylzirconocenes, diiodomethane, and benzaldimines. These backbone-modified building blocks are now accessible on multigram scale in ca. 8 steps and 35−50% overall yield from simple alkynes. As part of these synthetic studies, we have developed a new sequential water-accelerated methylalumination−imine addition−Simmons−Smith cyclopropanation strategy that provides *syn*-*C*-cyclopropylalkylamides. At least some cyclopropane substitution motifs appear to allow a control of secondary structure features. The dipeptide **19** adopts an extended, β-sheet conformation in the solid state, most likely due to a minimization of allylic strain type interactions. Further studies into the solution and solid state conformations of oligopeptides derived from α,β-cyclopropyl-γ-amino acids are currently underway in our laboratories and will be reported in due course.

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Supporting Information Available: Experimental procedures and spectral data for all new compounds, including copies of ^{1}H and ^{13}C NMR for **4b,c**, **5**−**10**, and **13**−**21** and crystal information files (CIF) for **19** and **21**. This material is available free of charge via the Internet at http://pubs.acs.org

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