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Three-Step Synthesis of Cyclopropyl Peptidomimetics

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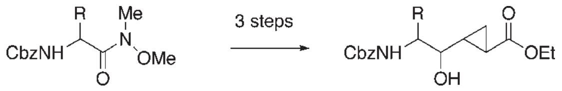
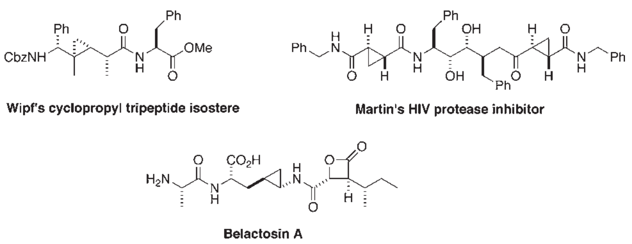
ABSTRACT



An efficient approach to novel cyclopropyl peptidomimetics has been developed. The synthetic route involves a cyclopropanation using ethyl (dimethylsulfuranylidene)acetate (EDSA) as the key step and affords a cyclopropyl peptidomimetic core in three steps from protected amino acid Weinreb amides.

The hydroxyethylene peptidomimetic core structure is central to numerous drugs both on the market and in development for a diverse number of conditions. Some examples include HIV protease inhibitors, BACE inhibitors, and renin inhibitors.[1−3] Cyclopropyl peptidomimetics, in particular, have been reported to have antitumor, antiviral, and antidepressant activity.[4−7] Incorporation of the cyclopropyl ring into the backbone of peptidomimetics has been shown to increase stability toward degradation, as well as decreasing conformational flexibility.[8,9] Some examples include Martin's Ras farnesyltransferase and HIV protease inhibitors, the natural product belactosin, and Wipf's cyclopropyl tripeptide isosteres (Figure 1).[5−7,10]


Wipf's cyclopropyl tripeptide isostere

Martin's HIV protease inhibitor

Belactosin A

Figure 1. Cyclopropyl peptidomimetics and natural products.

Prior approaches to cyclopropyl peptidomimetics include carbenoid cyclopropanations, as well as ylide additions to electron-deficient alkenes. As a general target, the

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(1) Abdel-Rahman, H. M.; Al-Karamany, G. S.; El-Koussi, N. A.; Youssef, A. F.; Kiso, Y. *Curr. Med. Chem.* **2002**, *9*, 1905.

(2) (a) Choi, S.; Cho, J.; Im, I.; Lee, S.; Jang, J.; Oh, Y.; Jung, Y.; Jeon, E.; Kin, Y. *Eur. J. Med. Chem.* **2010**, *45*, 2578. (b) Hom, R. K.; Gailunas, A. F.; Mamo, S.; Yang, L. Y.; Tung, J. S.; Walker, D. E. *J. Med. Chem.* **2004**, *47*, 158.

(3) Rahuel, J.; Rasetti, V.; Maibaum, J.; Rueger, H.; Goschke, R.; Cohen, N.-C.; Stutz, S.; Cumin, F.; Guhrer, W.; Wood, J. M.; Grutter, M. G. *Chem. Biol.* **2000**, *7*, 493.

(4) (a) Asai, A.; Hasegawa, A.; Ochiai, K.; Yamashita, Y.; Mizukami, T. *J. Antibiot.* **2000**, *53*, 81. (b) Vanier, S. F.; Lauroche, G.; Wurz, R. P.; Charette, A. B. *Org. Lett.* **2010**, *12*, 672 and references therein.

(5) (a) Wipf, P.; Xiao, J. *Org. Lett.* **2005**, *7*, 103. (b) Wipf, P.; Kendall, C.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2001**, *123*, 5122.

(6) (a) Martin, S. F.; Dorsey, G. O.; Gane, T.; Hillier, M. C. *J. Med. Chem.* **1998**, *41*, 1581. (b) Reichelt, A.; Gaul, C.; Frey, R. R.; Kennedy, A.; Martin, S. F. *J. Org. Chem.* **2002**, *67*, 4062.

(7) (a) Kazuta, Y.; Tsujita, R.; Yamashita, K.; Uchino, S.; Kohsaka, S.; Matsuda, A.; Shura, S. *Bioorg. Med. Chem.* **2002**, *10*, 3829. (b) Monn, J. A.; Balli, M. J.; Massey, S. M.; Wright, R. A.; Salhoff, C. R.; Johnson, B. G.; Howe, T.; Atl, C. A.; Rhodes, G. A.; Robey, R. L.; Griffer, K. R.; Tizzano, J. P.; Kallman, M. J.; Helton, D. R.; Schoepp, D. D. *J. Med. Chem.* **1997**, *40*, 528.

(8) Burgess, K.; Lim, D.; Ho, K.-K.; Ke, C.-Y. *J. Org. Chem.* **1994**, *59*, 2179.

(9) Zhu, Y. F.; Yamazaki, T.; Tsang, J. W.; Lok, S.; Goodman, M. *J. Org. Chem.* **1992**, *57*, 1074.

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peptidomimetic shown in Figure 2, with three variable positions, would allow access to a variety of potential medicinal agents starting from the known Weinreb amides of protected amino acids.[11]

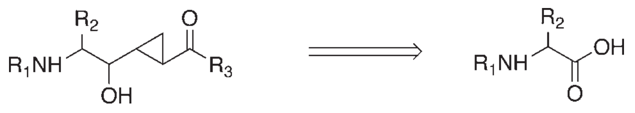
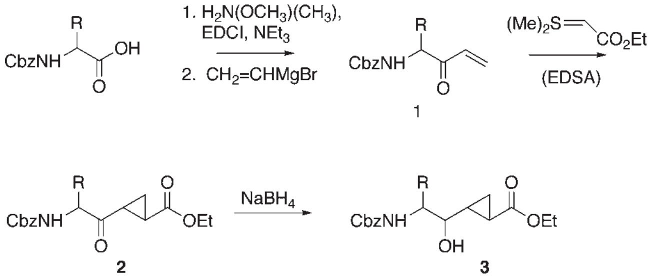


Figure 2. Cyclopropyl peptidomimetic core.

A number of carbenoid approaches were investigated, as well as Corey ylide cyclopropanation of an unsaturated ester; however all suffered from low yields and numerous steps.[12] The most efficient route was found to be addition of an enone to the stabilized sulfur ylide EDSA, followed by ketone reduction, affording the cyclopropyl backbone in just three steps.

As outlined in Scheme 1, conversion of Cbz-protected amino acids to the corresponding Weinreb amides, followed by addition of vinylmagnesium bromide, afforded the enones **1**. Cyclopropanation using EDSA afforded the protected cyclopropyl ketones **3** in good yield as a 1:1 mixture of *syn* and *anti* isomers. In most cases, the ketones were separable by HPLC. Reduction of the ketones afforded the protected cyclopropyl peptidomimetics.

Scheme 1. General Synthesis of Cyclopropyl Peptidomimetics **3**



As expected for addition to the terminal methylene, none of the *cis*-cyclopropyl analog of **2** was observed.[10b] Reduction of the ketones with sodium borohydride was only mildly stereoselective, typically affording a 2:1 mixture of the 4*R* and 4*S* isomers of alcohol **3**. Although not previously reported in peptidomimetic syntheses, EDSA and chiral sulfur ylides have been used in the synthesis of many cyclopropyl derivatives.[10] The lack of stereocontrol at this point is not an issue, since eventual conversion of compounds such as **3** to products with potential bioactivity may benefit from access to multiple stereoisomers.

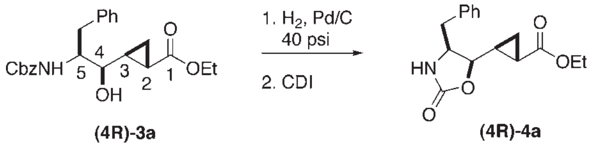
This procedure allows for very efficient access to a cyclopropyl peptidomimetic core from a variety of amino acids. Five series have been completed, as shown in Table 1.

Table 1. Yields for Conversion of Protected Amino Acids to Compounds **1**−**3**

amino acid	enone **1a**−**e**	ketone **2a**−**e**	alcohol **3a**−**e**
L-Cbz-phenylalanine (a)	62%	69%	95%
L-Cbz-leucine (b)	70%	78%	81%
L-Cbz-valine (c)	66%	76%	96%
D-Cbz-alanine (d)	99%	57%	95%
L-Cbz-proline (e)	41%	31%	53%

Stereochemistry of the phenylalanine series was confirmed by conversion of a pure alcohol (***syn*-4*R*-3a**) to the corresponding oxazolidinone, as shown in Scheme 2.

Scheme 2. Confirmation of Stereochemistry



Final confirmation by X-ray crystallography (Figure 3) established the stereochemistry of the cyclopropyl ring relative to the benzyl group. Assignment of stereochemistry in the other series is based on similarities in the HPLC behavior of the ketone isomers and in the ^{1}H NMR pattern of the cyclopropyl CH_2. In particular, the *syn* isomers elute first and show a separation of 0.7 ppm of the methylene hydrogens, whereas the *anti* ketone isomers show one multiplet for both of those hydrogens.[13]

The choice of base for ylide generation was found to be critical in order to avoid racemization of the cyclopropyl ketones. Initial conditions involved generation of the ylide using DBU as base in chloroform, followed by addition of the enone at room temperature. These conditions resulted

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(10) (a) Riches, S. L.; Saha, C.; Filjueira, N. F.; Grange, E.; McGarrigle, E. M.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2010**, *132*, 7626 and references therein. (b) Payne, G. B. *J. Org. Chem.* **1967**, *32*, 3351. (c) Curley, R. W., Jr.; DeLuca, H. F. *J. Org. Chem.* **1983**, *49*, 1944. (d) Collado, I.; Dominguez, C.; Ezquerra, J.; Pedregal, C.; Monn, J. A. *Tetrahedron Lett.* **1997**, *38*, 2133. (e) Yong, S. R.; Ung, A. T.; Pyne, S. G.; Skelton, B. W.; White, A. H. *Tetrahedron* **2007**, *63*, 1191.

(11) (a) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815. (b) Leucine amide: Kratzel, M.; Hiessböck, R.; Bernkop-Schnürch, A. *J. Med. Chem.* **1998**, *41*, 2339–2344. (c) Phenylalanine amide and enone: De Lucca, G. V.; Linag, J.; Aldrich, P. E.; Calabrese, J.; Cordova, B.; Klabe, R. M.; Rayner, M. M.; Chang, C.-H. *J. Med. Chem.* **1997**, *40*, 1707. (d) See also: Li, H.; Yang, H.; Liebeskind, L. S. *Org. Lett.* **2008**, *10*, 4375. (e) Proline amide and enone: De Luca, L.; Giacomelli, G.; Porcheddu, A. *Org. Lett.* **2001**, *3*, 1519. (f) Alanine amide and enone: Wuts, P. G.; Putt, S. R.; Ritter, A. R. *J. Org. Chem.* **1988**, *53*, 4503.

(12) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *83*, 417.

(13) See Table 1 in the Supporting Information.

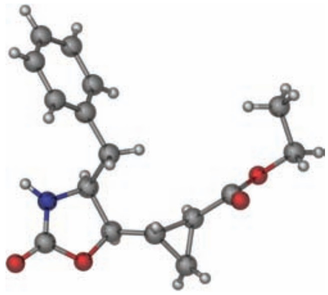

Figure 3. X-ray crystal structure of oxazolidinone (4*R*)-**4a**.

in varying degrees of racemization. However, using either LDA or sodium hydride as base, and a reduced temperature and reaction time, led to optically pure materials as verified by chiral HPLC. The ketones were also found to racemize upon storage for long periods of time, so subsequent reduction is best carried out soon after preparation of the ketones.

In summary, a very efficient synthesis of a series of novel cyclopropyl peptidomimetics from amino acids has been developed. The core structures should prove to be useful intermediates for the synthesis of potential medicinal agents.

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Supporting Information Available. Experimental procedures, characterization, NMR spectra, X-ray, and HPLC information are included in the Supporting Iinformation. This material is available free of charge via the Internet at http://pubs.acs.org.