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Synthesis of nitrocyclopropyl peptidomimetics

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ABSTRACT

Nitrocyclopropanation of amino-acid derived enones has led to a series of cyclopropyl peptidomimetics suitable for further elaboration to compounds with the potential for biological activity.

The cyclopropane ring is found in numerous compounds, both naturally occurring and synthetic. These include terpenes, pheromones, and unusual amino acids, as well as synthetic antibacterials, and conformationally restricted neurotransmitters.[1] Cyclopropyl peptidomimetics have been reported to have anti-tumor, antiviral, and antidepressant activities.[2,3] While a number of compounds include the cyclopropyl as a spiro or N-substituent, there are relatively few examples incorporating the cyclopropane into the backbone of peptidomimetics, introducing a degree of rigidity to these flexible structures. Examples include Wipf's cyclopropyl dipeptide isostere, Martin's HIV protease inhibitor and the anti-tumor natural product Belactosin A which, while not a peptidomimetic, contains a cyclopropyl amino acid (Fig. 1).[4–8]

We previously reported the synthesis of a core structure of cyclopropyl peptidomimetics from protected amino acid Weinreb amides. The core is variable at three positions, allowing diversification of the template to a number of possible compounds.[9]

As shown in Figure 2, the central R^1 group is defined by the starting amino acid, deprotection of the terminal amine allows for introduction of amides (R^2) on the 'left side', and an ethyl ester affords a handle for functionalization on the 'right side' of compound **1**. An efficient approach to ester-cyclopropyl precursors of **1**, based on a sulfur-ylide cyclopropanation of amino-acid derived enones was reported previously.[9] Reported here is the extension of this methodology to afford nitrocyclopropyl peptidomimetics, allowing access to **2**, and increasing the versatility of the 'right-side' variations (R^3).

Nitrocyclopropanation using bromonitromethane was first reported for a synthesis of the antibacterial quinolone trovafloxacin, which contains a bicyclic aminocyclopropane.[10] Since that time, the reaction has been investigated by Bellini, and an enantioselective version by Ley has been reported, mostly for cyclic enones, with several examples of acyclic substrates.[11,12] Following Ballini's procedure, addition of bromonitromethane to a solution of the enone **3** in acetonitrile, with freshly ground potassium carbonate as base, afforded nitrocyclopropyl ketone **7** as a mixture of *syn* and *anti* diastereomers (Fig. 3).

The synthesis of nitrocyclopropyl analogs of a series of amino acids is summarized in Table 1.

Stereoselectivity in the nitrocyclopropanation is low, at approximately 2:1 for most of these compounds, based on HPLC. This is similar to the lack of selectivity seen in the ester series. Assignment of stereochemistry is based on analogous behavior to the ester series. In that series, absolute configuration of a derivative of the phenylalanine product was established by X-ray crystallography. As in the ester series, there is a consistent trend where the *syn* isomers elute first on HPLC, and have a much higher positive optical rotation. No racemization occurs during the cyclopropanation, as evidenced by chiral SFC analysis of the valine analog **7c**.

Reduction of the nitro group proved to be difficult, with sodium borohydride combinations (boride reductions) and aluminum hydride reductions resulting in decomposition.[14–16] Selective removal of the Cbz protecting group was carried out by palladium catalyzed hydrogenation to afford the nitro amine **9a**. This allows for selective derivatization of the 'left side' of the peptidomimetic. Reduction of both the nitro group and removal of the Cbz protecting group afforded the unstable di-amine **10a**, using either Raney nickel or transfer hydrogenation with a 48 h reaction time.[17–19]

For example, in the leucine series, cyclopropanation of the enone **3a** with EDSA, followed by ketone reduction afforded the

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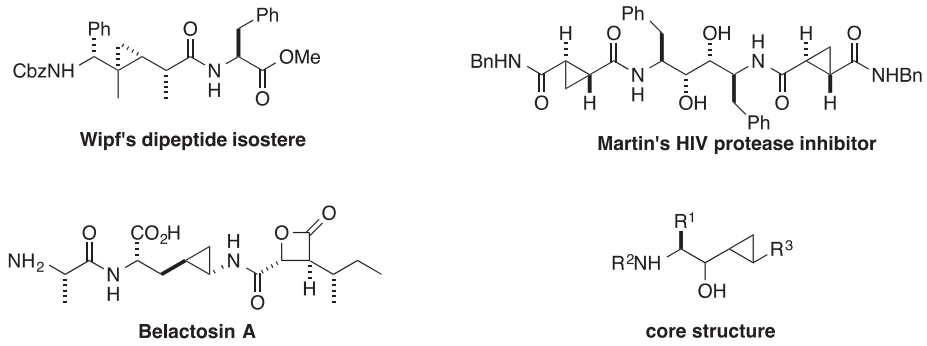


Figure 1. Examples of cyclopropyl peptidomimetics.

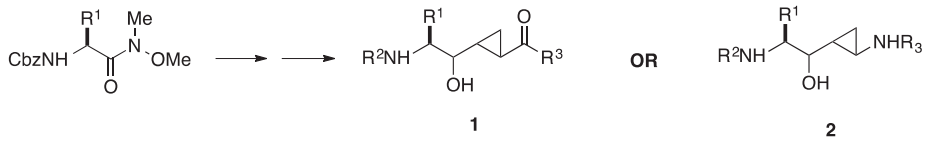


Figure 2. Conversion of amino acid Weinreb amides to cyclopropyl peptidomimetics.

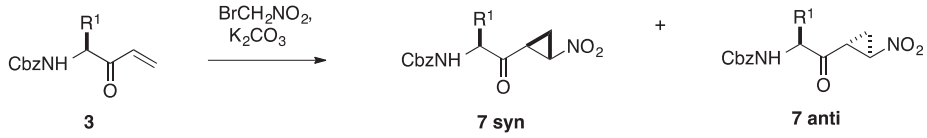
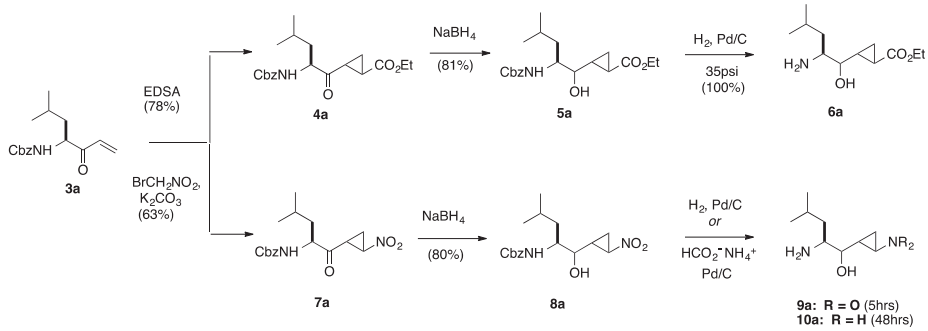


Figure 3. Nitrocyclopropanation of amino acid-derived enones.

Table 1
Nitrocyclopropanation of amino acid-derived enones

Cbz-amino acid enone (**3a–f**)	Nitrocyclopropyl ketone (**7a–f**) (%)	Ratio (*syn*/*anti*)
L-Cbz-leucine (a)	63	1.8:1.0
L-Cbz-phenylalanine (b)	78	1.0:1.0
L-Cbz-valine (c)	61	1.6:1.0
L-Cbz-proline (d)	93	2.0:1.0
L-Cbz-serine N,O acetonide[13] (e)	61	na
D-Cbz-alanine (f)	53	na

Note: *syn* and *anti* ketones **7e** and **7f** were inseparable by HPLC.



Scheme 1. Synthesis of ester, nitro, and amino-cyclopropyl peptidomimetics.

ester-cyclopropyl alcohol **5a** (Scheme 1). Conversely, cyclopropanation with bromonitromethane and subsequent reduction afforded the nitrocyclopropyl alcohol **8a**. Reductive removal of the Cbz group from compounds **5a** and **8a** afforded the aminocyclopropyl peptidomimetics **6a** and **9a**, respectively, either by direct hydrogenation or by transfer hydrogenation. Increasing the reaction time of the transfer hydrogenation also reduces the nitro to the amine **10a** without hydrogenation of the cyclopropane.

In summary, a series of nitrocyclopropyl peptidomimetics has been prepared in four steps from protected amino acids. These intermediates allow access to a variety of cyclopropyl peptidomimetics as potentially bioactive compounds.

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Supplementary data

Supplementary data (experimental procedures, spectroscopy data (NMR, IR, MS) and HPLC data for all new compounds are reported in supporting information) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.09.106.

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