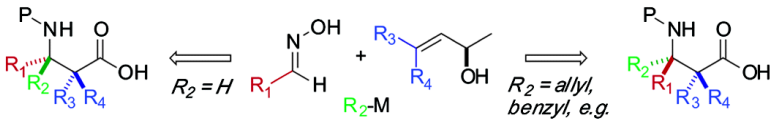
Communication

A Concise Approach to Structurally Diverse β-Amino Acids

Aaron R. Minter, Amelia A. Fuller, and Anna K. Mapp

J. Am. Chem. Soc., **2003**, 125 (23), 6846-6847• DOI: 10.1021/ja0298747 • Publication Date (Web): 15 May 2003



More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Links to the 4 articles that cite this article, as of the time of this article download
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

J|A|C|S
COMMUNICATIONS

Published on Web 05/15/2003

A Concise Approach to Structurally Diverse β-Amino Acids

Aaron R. Minter, Amelia A. Fuller, and Anna K. Mapp*

Departments of Chemistry and Medicinal Chemistry, University of Michigan, Ann Arbor, Michigan 48109

Received December 21, 2002; E-mail: amapp@umich.edu

The importance of stereochemically defined β-amino acids (**1**) as synthetic targets continues to grow as successful applications in drug development, molecular recognition, and structure/function studies of biomolecular processes rapidly increase in number.[1] The widespread interest in β-amino acids stems both from enhanced proteolytic stability relative to their α-amino acid counterparts[2] and from the tendency of many to promote the formation of stable secondary structures such as β turns, β sheets, and helices.[1b,c,g] These unique characteristics of β-amino acids are dependent upon the substitution pattern and the stereochemistry at the C2 (α) and C3 (β) positions, and much attention has thus been brought to bear on the stereoselective synthesis of this important class of compounds (Figure 1).[3] The greatest challenge has been the development of methods applicable to amino acids highly substituted at the C2 and/or C3 positions ($\beta^{3,3}$ and $\beta^{2,3,3}$, for example),[4] the point at which virtually all approaches suffer in yield and/or selectivity.[5,6] Although oligomers of $\beta^{3,3}$- and $\beta^{2,3,3}$-amino acids are predicted to have unique secondary structural properties and should exhibit increased proteolytic stability,[5] they have remained virtually unexamined due to the difficulties associated with preparing stereoisomerically pure samples of the individual residues.[3,6] We report here a conceptually unique synthetic approach that is applicable to a diverse array of β-amino acids, including highly substituted variants not accessible by previously reported methodologies.

We recognized that isoxazolines (**3**), readily available as single stereoisomers from the 1,3-dipolar cycloaddition of variously substituted oximes (**4**) and allylic alcohols (**5**),[7] contain the requisite stereochemical information and substitution pattern for ready transformation into β-amino acids (Figure 1); the C2 and C3 positions of **1** correspond to C4 and C3 of **2**, respectively. The C4 stereochemistry would be set in the cycloaddition reaction to form **3**, and the C3 stereochemistry would arise from nucleophilic addition to the C=N bond with facial selectivity dictated by the C5 substituent in either a directed or a sterically controlled manner. Cleavage of the N−O bond followed by an oxidative cleavage of the resulting diol would then provide the target β-amino acid. This allows ready access to a variety of substitution patterns, functional groups (R_1−R_4), and stereochemical relationships based upon the choice of starting materials and reaction conditions. Furthermore, a unique advantage of this approach is that it provides access to β-amino acids in which R_1 and R_2 are sterically similar, a class of β-amino acids not available in stereoisomerically pure form using existing methods.[8]

We first investigated hydride addition to isoxazolines **3** for the preparation of a β^3-amino acid that has seen widespread use in peptidomimetic design, Boc-β-leucine (Scheme 1).[1,9] The synthesis was initiated by a 1,3-dipolar cycloaddition between oxime **6a** and (*R*)-3-buten-2-ol to provide isoxazoline **7a**. Access to the (*S*)-stereochemistry of **10** required a reduction of the C=N bond *directed* by the C5 1′-hydroxyethyl group. Directed reductions of isoxazolines remain largely unexplored;[10] Jäger, for example, reported the reduction of an isoxazoline with a C5 hydroxymethyl

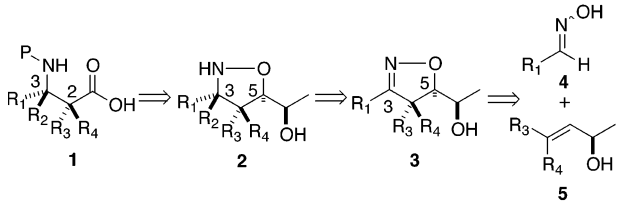
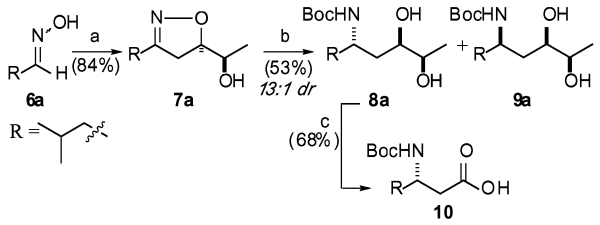


Figure 1. The isoxazoline approach to β-amino acids.

Scheme 1 [a]



$[\alpha]_D$ = -34.1 (c = 0.41, $CHCl_3$)

[a] (a) (i) *t*-BuOCl, CH_2Cl_2; (ii) (*R*)-3-buten-2-ol, EtMgBr, *i*-PrOH. (b) (i) $LiAlH_4$, THF; (ii) Boc_2O. (c) $NaIO_4/RuCl_3$.

group using $LiAlH_4/Et_2O$ to provide a 1.5:1 diastereomeric mixture.[10c] In our system, poor conversion to product was observed under conditions commonly used for directed reductions (e.g., $Me_4NB(OAc)_3H$, $NaCNBH_4$, $Zr(BH_4)_2$), and more reactive reagents ($LiAlH_4/Et_2O$, BH_3, $Zn(BH_4)_2$) provided good yields of diol **8a** (60−85%) with poor to moderate diastereoselectivity (1:1−4:1).

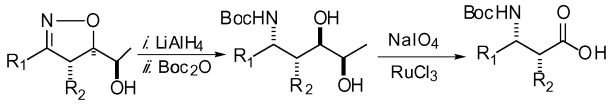
We noted that the intermediate isoxazolidine was not isolated under any of the conditions examined. This was somewhat unexpected because O-alkyl oxime reductions under similar conditions often provide the hydroxylamine product.[11] We reasoned that in our system chelation between O1 and the side chain hydroxyl was likely activating the N−O bond for cleavage and that this chelation might be the culprit in the poor selectivity observed. To test this, we carried out the $LiAlH_4$ reduction in THF, in which intramolecular chelation would presumably be less favored. Gratifyingly, a dramatic increase in diastereoselectivity (13:1) was the result. Diol **8a** was then cleaved to provide **10**[12] as a single stereoisomer.

This approach can be used to prepare β^3- and $\beta^{2,3}$-amino acids with a variety of substitutions (Table 1). Alkyl, aryl, and alkynyl substituents were well tolerated with the overall yield for the three chemical steps (C=N reduction, N−O reduction, and protection) ranging from 40% to 64% with good to excellent diastereoselectivity (7:1 to 15:1) in all cases. Oxidative cleavage of the amino diols also proceeded smoothly to give the target acids **11** in good overall yields.

Highly substituted β-amino acids can also be prepared using this approach by replacing hydride with carbon nucleophiles (Table 2). Remarkably, the addition of Grignard reagents[13] such as allylmagnesium chloride occurs with high yields and up to 20:1 diastereoselectivity (**13d**). In contrast to hydride addition, the facial

10.1021/ja0298747 CCC: $25.00

Table 1. Synthesis of β^{3}- and $\beta^{2,3}$-Amino Acids

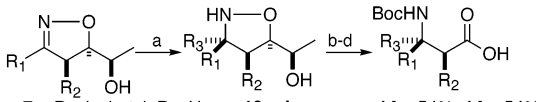


7b-f **8b-f** **11b-f**

substrate[a]	R_1	R_2	dr (% yield)[b]	yield of **11**
7b	Et	H	7:1[c] (44)	70%
7c	*i*-Pr	H	7:1[d] (64)	76%
7d	TIPS—≡—§–	H	10:1[d] (40)	59%[e]
7e	Ph	H	15:1[c] (54)	72%
7f	Et	Et	12:1[d] (63)	67%

[a] Yield of isoxazolines: **7b** (69%), **7c** (96%), **7d** (69%), **7e** (85%), **7f** (50%). [b] Combined yield of diastereomers; only **8** was carried on to the oxidative cleavage. [c] Determined by ^{1}H NMR spectral integration prior to separation. [d] Due to poorly dispersed resonances, determined by comparison of the isolated components. [e] $NaIO_4$ followed by $NaClO_2$ provided **11d**.

Table 2. Synthesis of Highly Substituted β-Amino Acids



7a: R_1=isobutyl, R_2=H
7b: R_1=ethyl, R_2=H
12: R_1=ethyl, R_2=Ph

13a-d

14a: 54% **14c**: 54%
14b: 69% **14d**: 48%

product	R_1	R_2	R_3	yield of **13**	dr[e,f]
13a	*i*-Bu	H	allyl	90%	9:1
13b	Et	H	allyl	95%	10:1
13c	*i*-Bu	H	benzyl	90%[g,h]	18:1
13d[i]	Et	Ph	allyl	81%[g]	>20:1

[a] R_3MgCl, $BF_3{\cdot}OEt_2$, THF, $-78 \rightarrow 0$ °C. [b] (i) $LiAlH_4$, Et_2O; (ii) Boc_2O. [c] $NaIO_4$. [d] $NaClO_2$, 2-methyl-2-butene. [e] The facial selectivity of addition was confirmed by NOE difference experiments; see the Supporting Information for details. [f] Determined by ^{1}H NMR analysis of the crude reaction mixture. [g] Isolated as the HCl salt. [h] N−O bond reduction was accomplished with 10% Pd/C, NH_4O_2CH. [i] Prepared in 67% yield.

selectivity is dictated by steric constraints, with the C5 substituent blocking the top face of the ring. The resulting isoxazolidines **13** are readily transformed into the corresponding $\beta^{3,3}$- and $\beta^{2,3,3}$-amino acids by N−O bond reduction, protection of the free amine, and oxidative cleavage of the diol. In preliminary experiments, we have also found that *nonstabilized* organometallic reagents add to isoxazolines such as **7a** in good yields and excellent diastereoselectivity (PhLi: 78%, 20:1 dr; MeLi: 63%, 10:1 dr) upon masking of the side chain hydroxyl as a silyl ether, increasing the range of accessible substitution patterns.

The highly selective addition of carbon nucleophiles provides access to a class of β-amino acids not readily prepared by existing methods, those in which the β-substituents are *sterically similar*. In addition, the allyl group can be readily transformed by oxidation[14] or reduction, for example, to access additional functional group diversity within the final β-amino acid product. Furthermore, isoxazolidines **13** contain four contiguous stereocenters, one of which is a quaternary stereogenic center,[15] and will thus serve as useful intermediates for a variety of synthetically challenging structures such as amino alcohols, amino alkenes, and β-lactams.[1f,3a,b,d]

In summary, we have demonstrated that the high yields and selectivities of 1,3-dipolar cycloadditions can be translated into facile stereoselective syntheses of a variety of β-amino acids. Simply by choosing different combinations of three readily available starting materials − an oxime, a chiral allylic alcohol, and a nucleophile − the reaction sequence can be extended to the synthesis of *either enantiomer* of a wide range of β-amino acid structural types. Finally, this approach is unique in that it can be used to synthesize previously inaccessible, sterically encumbered $\beta^{3,3}$- and $\beta^{2,3,3}$-amino acids. Studies of the structural properties of oligomers of this amino acid class are underway and will be reported in due course.

Acknowledgment. A.K.M. is grateful for financial support from the NIH (GM65330), the Burroughs Wellcome Fund, and the March of Dimes. A.R.M. was supported by the Chemistry/Biology Interface Training Program (GM09597).

Supporting Information Available: Experimental procedures and characterization data for all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Recent reviews on β-amino acids applications: (a) Steer, D. L.; Lew, R. A.; Perlmutter, P.; Smith, A. I.; Aguilar, M. I. *Curr. Med. Chem.* **2002**, *9*, 811−822. (b) Hill, D. J.; Mio, M. J.; Prince, R. B.; Hughes, T. S.; Moore, J. S. *Chem. Rev.* **2001**, *101*, 3893−4011. (c) Gellman, S. H. *Acc. Chem. Res.* **1998**, *31*, 173−180. (d) Cheng, R. P.; Gellman, S. H.; DeGrado, W. F. *Chem. Rev.* **2001**, *101*, 3219−3232. (e) Gademann, K.; Hintermann, T.; Schreiber, J. V. *Curr. Med. Chem.* **1999**, *6*, 905−925. (f) Juaristi, E., Ed. *Enantioselective Synthesis of β-Amino Acids*; Wiley-VCH: New York, 1997. (g) Seebach, D.; Matthews, J. L. *Chem. Commun.* **1997**, 2015−2022.

(2) Griffith, O. W. *Annu. Rev. Biochem.* **1986**, *55*, 855−878.

(3) See: (a) Juaristi, E.; López-Ruiz, H. *Curr. Med. Chem.* **1999**, *6*, 983−1004. (b) Liu, M.; Sibi, M. P. *Tetrahedron* **2002**, *58*, 7991−8035. (c) Abele, S.; Seebach, D. *Eur. J. Org. Chem.* **2000**, 1−15. (d) Cole, D. C. *Tetrahedron* **1994**, *50*, 9517−9582 and references therein.

(4) The nomenclature of Seebach in which the superscript after "β" describes the substitution pattern of a β-amino acid is used throughout. According to this system, for example, a $\beta^{2,3,3}$-amino acid has a single substituent at the C2 position and two substituents at the C3 position. See ref 3c.

(5) For a discussion of this point, see ref 3c.

(6) For elegant approaches in which R_1 and R_2 are sterically dissimilar, see: (a) Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **2002**, *67*, 7819−7832. (b) Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 12−13. (c) Kobayashi, K.; Matoba, T.; Irisawa, S.; Takanohashi, A.; Tanmatsu, M.; Morikawa, O.; Konishi, H. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 2805−2809. (d) Ishitani, H.; Ueno, M.; Kobayashi, S. *J. Am. Chem. Soc.* **2000**, *122*, 8180−8186.

(7) (a) Kanemasa, S.; Nishiuchi, M.; Kamimura, A.; Hori, K. *J. Am. Chem. Soc.* **1994**, *116*, 2324−2339. (b) Bode, J. W.; Fraefel, N.; Muri, D.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2001**, *40*, 2082−2085.

(8) For a rare exception, see the example in: Espino, C. G.; Wehn, P. M.; Chow, J.; Du Bois, J. *J. Am. Chem. Soc.* **2001**, *123*, 6935−6936.

(9) For a recent example, see: Hamuro, Y.; Schneider, J. P.; DeGrado, W. F. *J. Am. Chem. Soc.* **1999**, *121*, 12200−12201.

(10) Good selectivity has only been observed when steric hindrance is also a contributing factor: (a) Jäger, V.; Buss, V.; Schwab, W. *Tetrahedron Lett.* **1978**, 3133−3136. (b) Jäger, V.; Müller, I.; Paulus, E. F. *Tetrahedron Lett.* **1985**, *26*, 2997−3000. (c) Jäger, V.; Schwab, W.; Buss, V. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 601−603.

(11) (a) Williams, D. R.; Benbow, J. W.; Sattleberg, T. R.; Ihle, D. C. *Tetrahedron Lett.* **2001**, *42*, 8597−8601. (b) Williams, D. R.; Osterhout, M. H. *J. Am. Chem. Soc.* **1992**, *114*, 8750−8751. (c) Feuer, H.; Vincent, B. F., Jr.; Bartlett, R. S. *J. Org. Chem.* **1965**, *30*, 2877−2880. (d) Zhu, Q.-C.; Hutchins, R. O. *Org. Prep. Proced. Int.* **1994**, *26*, 193−236.

(12) El Marini, A.; Roumestant, M. L.; Viallefont, P.; Razafindramboa, D.; Bonato, M.; Follet, M. *Synthesis* **1992**, 1104−1108.

(13) For a rare example of an organometallic addition to an isoxazoline, see: Huang, K. S.-L.; Lee, E. H.; Olmstead, M. M.; Kurth, M. J. *J. Org. Chem.* **2000**, *65*, 499−503.

(14) **13a** was subjected to reductive ozonolysis to introduce a hydroxyethyl side chain in 77% yield, for example. See the Supporting Information for details.

(15) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388−401.

JA0298747