JOC Article

Synthesis of Chiral β^3-Aminoxy Peptides

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A series of chiral β^3-aminoxy acids or amides with various side chains have been synthesized via two different approaches. One is the Arndt−Eistert homologation approach, using chiral α-aminoxy acids as starting materials. The other approach, utilizing the enantioselective reduction of β-keto esters catalyzed by baker's yeast or chiral Ru(II) complexes, produces chiral β^3-aminoxy acids with nonproteinaceous side chains. The oligomers of β^3-aminoxy acids can be readily prepared using EDCI/HOAt as the coupling reagent.

Introduction

Due to the interest in structural modifications of α-amino acids, there have been numerous explorations of unnatural oligomers with well-defined secondary structures (foldamers).[1] Extensive studies have indicated that β-peptides and γ-peptides, analogues of α-peptides, can adopt discrete secondary structures that are analogous to the secondary structures (including helices, turns, and sheets) found in proteins and peptides.[2,3]

In our endeavor to search for novel foldamers, α-aminoxy peptides and β-aminoxy peptides were designed by replacing the β-carbon of β-amino acids and the γ-carbon of γ-amino acids, respectively, with an oxygen atom. Previous studies of our group have revealed a strong eight-membered-ring hydrogen bond formed between adjacent α-aminoxy acid residues (the α-N−O turn).[4] Furthermore, homochiral and heterochiral oligomers of α-aminoxy acids formed novel 1.8_8 helices and reverse turns, respectively.[5] Compared with α-aminoxy acids, β-aminoxy acids have an extra carbon atom in the backbone, thus allowing for more variations in the substitution patterns of peptides and offering opportunities to modulate hydrogen-bonding properties. Similar to β-amino acids, β-aminoxy acids can be divided into several subclasses according to their backbone substitution patterns (Chart 1). We have reported that $\beta^{2,2}$-aminoxy peptides of 3-aminoxy-2,2-dimethyl propionic acid can adopt a helical conformation that has approximately 1.7 residues per turn and contains a network of nine-membered-ring hydrogen bonds between backbone C═O_i and NH_{i+2} (1.7_9 helix).[6a] Our recent studies showed that the β-N−O turns and β-N−O helices, which have been found in peptides of $\beta^{2,2}$-aminoxy acids, are also present in the β^3-aminoxy peptides. Also, in the β-N−O turns and β-N−O helices induced by β^3-aminoxy acids, the N−O bond could be either anti or gauche to the C_α−C_β bond depending on the size of the side chains,

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(1) For recent reviews, see: (a) Cheng, R. P.; Gellman, S. H.; DeGrado, W. F. *Chem. Rev.* **2001**, *101*, 3219. (b) Gellman, S. H. *Acc. Chem. Res.* **1998**, *31*, 173. (c) Seebach, D.; Matthews, J. L. *Chem. Commun.* **1997**, 2015.

(2) For recent examples of β-peptides, see: (a) Brückner, A. M.; Chakraborty, P.; Gellman, S. H.; Diederichsen, U. *Angew. Chem., Int. Ed.* **2003**, *42*, 4395. (b) Park, J.-S.; Lee, H.-S.; Lai, J. R.; Kim, B. M.; Gellman, S. H. *J. Am. Chem. Soc.* **2003**, *125*, 8539. (c) Raguse, T. L.; Lai, J. R.; Gellman, S. H. *J. Am. Chem. Soc.* **2003**, *125*, 5592. (d) Langenhan, J. M.; Guzei, I. A.; Gellman, S. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 2402. (e) Porter, E. A.; Weisblum, B.; Gellman, S. H. *J. Am. Chem. Soc.* **2002**, *124*, 7324. (f) LePlae, P. R.; Fisk, J. D.; Porter, E. A.; Weisblum, B.; Gellman, S. H. *J. Am. Chem. Soc.* **2002**, *124*, 6820. (g) Lee, H.-S.; Syud, F. A.; Wang, X.-F.; Gellman, S. H. *J. Am. Chem. Soc.* **2001**, *123*, 7721. (h) Daura, X.; Gademann, K.; Schäfer, H.; Jaun, B.; Seebach, D.; van Gunsteren, W. F. *J. Am. Chem. Soc.* **2001**, *123*, 2393. (i) Claridge, T. D. W.; Goodman, J. M.; Moreno, A.; Angus, D.; Barker, S. F.; Taillefumier, C.; Watterson, M. P.; Fleet, G. W. J. *Tetrahedron Lett.* **2001**, *42*, 4251. (j) Arvidsson, P. I.; Rueping, M.; Seebach, D. *Chem. Commun.* **2001**, 649. (k) Cheng, R. P.; DeGrado, W. F. *J. Am. Chem. Soc.* **2001**, *123*, 5162. (l) Motorina, I. A.; Huel, C.; Quiniou, E.; Mispelter, J.; Adjadj, E.; Grierson, D. S. *J. Am. Chem. Soc.* **2001**, *123*, 8. (m) Etezady-Esfarjani, T.; Hilty, C.; Wüthrich, K.; Rueping, M.; Schreiber, J.; Seebach, D. *Helv. Chim. Acta* **2002**, *85*, 1197. (n) Gademann, K.; Hüne, A.; Rueping, M.; Jaun, B.; Seebach, D. *Angew. Chem., Int. Ed.* **2003**, *42*, 1534.

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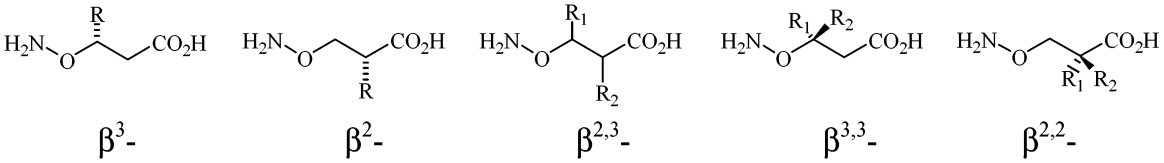
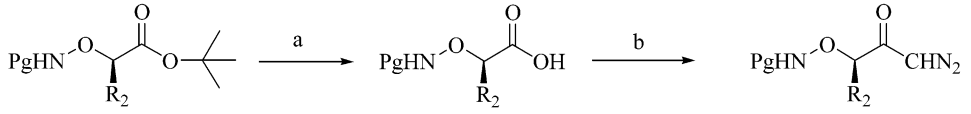
CHART 1



SCHEME 1[a]



1 Pg = Phth, R = $CH_2CH(CH_3)_2$
2 Pg = Fmoc, R = $CH_2CH(CH_3)_2$
3 Pg = Cbz, R = $CH_2CH(CH_3)_2$
4 Pg = Cbz, R = $CH(CH_3)_2$
5 Pg = EtOCO, R = $CH(CH_3)_2$

6 Pg = Phth, R = $CH_2CH(CH_3)_2$
7 Pg = Fmoc, R = $CH_2CH(CH_3)_2$
8 Pg = Cbz, R = $CH_2CH(CH_3)_2$
9 Pg = Cbz, R = $CH(CH_3)_2$
10 Pg = EtOCO, R = $CH(CH_3)_2$

[a] (a) TFA, CH_2Cl_2; (b) (i) $ClCO_2Et$, Et_3N, THF (ii) CH_2N_2, ether; 77−84% overall yield.

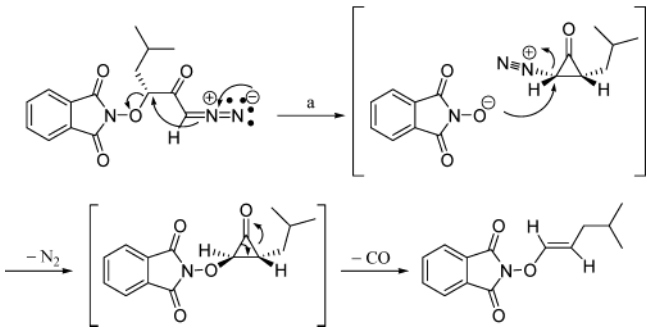
which contrasts only the anti conformation found in $\beta^{2,2}$-aminoxy peptides.[6b] To gain rapid access to chiral β^3-aminoxy peptides with a diversity of side chains, a general synthetic scheme is required. Here, we report our efforts on the synthesis of chiral β^3-aminoxy acids or amides and their oligomers.

Results and Discussion

Since the Arndt−Eistert homologation method has been successfully employed in the synthesis of β-amino acids from natural α-amino acids with nearly no racemization,[7] we applied this method to synthesize chiral β-aminoxy amides from chiral α-aminoxy acids. Following the reported procedures, we synthesized the protected chiral α-aminoxy acids **1**−**5** of proteinaceous side chains in high optical purity starting from the corresponding chiral α-amino acids.[8,9] The treatment of **1**−**5** with TFA in CH_2Cl_2 gave the free acids, which were then converted to the mixed anhydrides with $Et_3N/ClCO_2Et$. Subsequent reaction with diazomethane afforded diazoketones **6**−**10** (Scheme 1). Seebach et al. reported that the treatment of α-amino diazoketones in THF with a nucleophile in the presence of 0.1 equiv of a silver salt and Et_3N at −20 to 0 °C gave β-amino acids and their derivatives.[7b] Unfortunately, under the same experimental conditions, α-aminoxy diazoketone **6** gave an abnormal rearrangement product **12** in 69% yield instead of the desired β^3-aminoxy acids (Scheme 2).

The abnormal rearrangement product is proposed to come from cyclopropanone intermediate **11**, as shown in Scheme 2. At −20 to 0 °C, α-aminoxy diazoketone **6** might form cyclopropanone **11** rather than a ketene, and **11** then might suffer decarbonylation to give olefin **12**. As

SCHEME 2[a]



[a] (a) CF_3CO_2Ag, Et_3N, THF, −20 °C, 69% yield.

in other Wolff rearrangement reactions, the function of the silver salt is not well understood. To facilitate the ketene formation and suppress the cyclopropanone formation, the reaction temperature was further lowered to −78 °C. Diazoketone **7** underwent Wolff rearrangement in the presence of *iso*-butylamine (1.5 equiv), $PhCO_2Ag$ (0.1 equiv), and Et_3N (3.0 equiv) at −78 °C to give diamide **16** in 58% yield (Scheme 3). Treatment of diazoketones **8**−**10** with $PhCO_2Ag$ (0.1 equiv) in Et_3N (3 equiv) in the presence or absence of H_2O or MeOH at −78 °C gave β^3-aminoxy lactams **13**−**15** in 64−98% yield and 95−98% ee (Scheme 3). The lactams were formed probably because the oxy-amide anion is more nucleophilic than methanol and water. The lactams can be opened by amines in refluxing THF or toluene in the presence of DMAP to give diamides **17**−**22** in 59−97% yield. These results indicate that β^3-aminoxy amides can be synthesized in high optical purity from chiral α-aminoxy acids using the Arndt−Eistert homologation method.

Aminoxy triamide **24**, containing two β^3-aminoxy acid residues, was synthesized according to Scheme 4. Diamide **17** was deprotected at the N-terminus with HBr in acetic acid, and the resulting free β^3-aminoxy amine **23** was subsequently refluxed with DMAP and lactam **13** in THF to afford triamide **24** in 72% overall yield.

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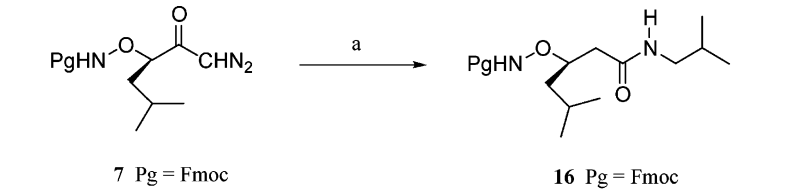
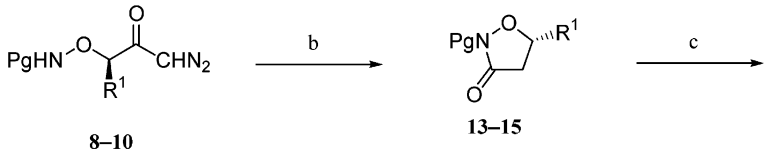
SCHEME 3[a]



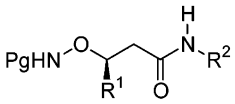
7 Pg = Fmoc **16** Pg = Fmoc



8–10 **13–15**

8 Pg = Cbz, $R^1 = CH_2CH(CH_3)_2$
9 Pg = Cbz, $R^1 = CH(CH_3)_2$
10 Pg = EtOCO, $R^1 = CH(CH_3)_2$

13 Pg = Cbz, $R^1 = CH_2CH(CH_3)_2$
14 Pg = Cbz, $R^1 = CH(CH_3)_2$
15 Pg = EtOCO, $R^1 = CH(CH_3)_2$

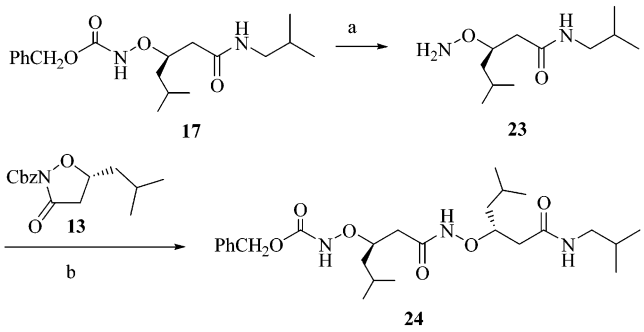


17–22

17 Pg = Cbz, $R^1 = CH_2CH(CH_3)_2$, $R^2 = CH_2CH(CH_3)_2$
18 Pg = Cbz, $R^1 = CH_2CH(CH_3)_2$, $R^2 = p$-$OMeC_6H_4$
19 Pg = Cbz, $R^1 = CH_2CH(CH_3)_2$, $R^2 = p$-MeC_6H_4
20 Pg = Cbz, $R^1 = CH(CH_3)_2$, $R^2 = CH_2C_6H_4$
21 Pg = Cbz, $R^1 = CH(CH_3)_2$, $R^2 = p$-ClC_6H_4
22 Pg = EtOCO, $R^1 = CH(CH_3)_2$, $R^2 = p$-MeC_6H_4

[a] (a) $PhCO_2Ag$, Et_3N, THF, *i*-$BuNH_2$, −78 °C, 58% yield; (b) $PhCO_2Ag$, Et_3N, THF, −78 °C, 64−98% yield; (c) DMAP, R^2NH_2, THF or toluene, reflux, 59−97% yield.

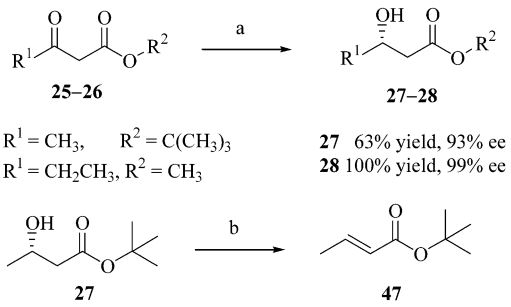
SCHEME 4[a]



17 **23** **13** **24**

[a] (a) (i) HBr, HOAc (ii) Na_2CO_3, H_2O; (b) DMAP, THF, reflux, 72% overall yield.

SCHEME 5[a]



25–26 **27–28**

25 $R^1 = CH_3$, $R^2 = C(CH_3)_3$
26 $R^1 = CH_2CH_3$, $R^2 = CH_3$

27 63% yield, 93% ee
28 100% yield, 99% ee

27 **47**

[a] (a) (i) Baker's yeast, petroleum, H_2O or (ii) $RuBr_2$[(*S*)-binap], H_2 (1 atm), MeOH; (b) PhthN−OH, DIAD, PPh_3, THF, −40 °C, 54% yield.

To synthesize chiral β^3-aminoxy acids with nonproteinaceous side chains, another scheme has been developed that utilizes chiral β-hydroxy esters rather than α-aminoxy acids as the starting materials.

Optically active β-hydroxy esters can be prepared by asymmetric reduction of β-keto esters using either chemical[10] or enzymatic methods.[11] In our study, β-keto esters were reduced to β-hydroxy esters in high optical purity using a chiral Ru(II) catalyst[10f] or baker's yeast (Scheme 5).[11f,i] The key step for introducing the N−O segment of the β-aminoxy acids was a Mitsunobu reaction[12] between *N*-hydroxyphthalimide and β-hydroxy esters; unfortunately, only elimination product **47** was formed in 54% yield at −40 °C (Scheme 5).

To avoid the undesired α,β-elimination reactions, chiral β-hydroxy esters **27** and **28** were first reduced with

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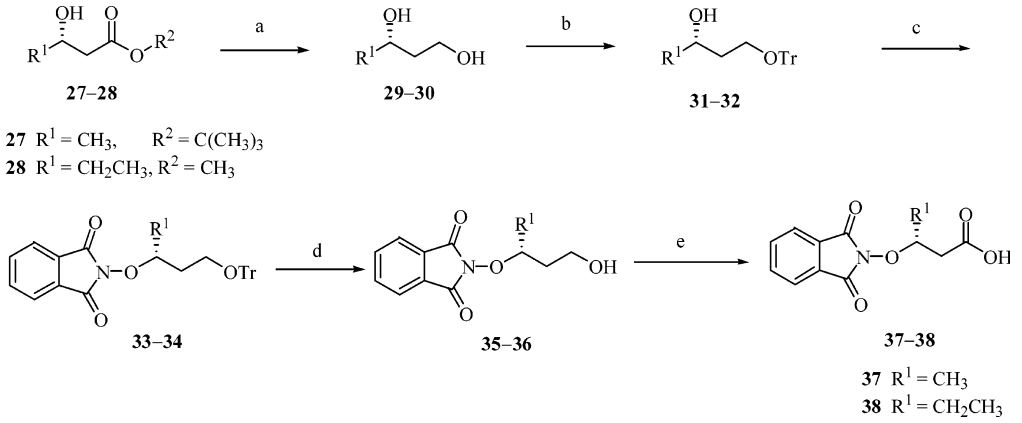
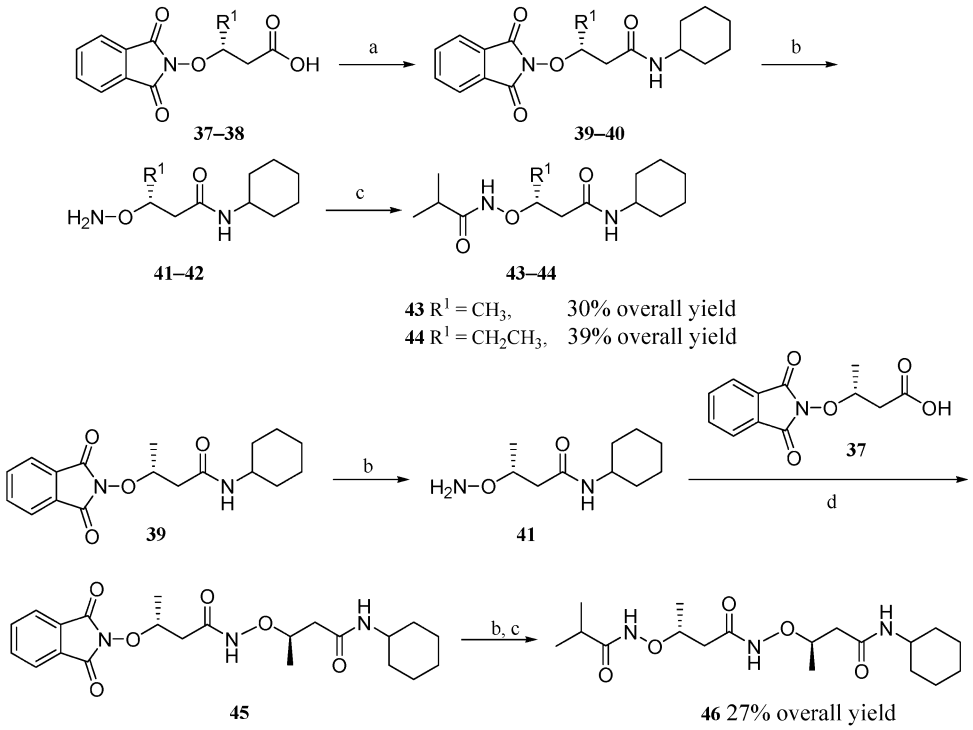
(12) Mitsunobu, O. *Synthesis* **1981**, 1.

SCHEME 6[a]



[a] (a) $LiAlH_4$, Et_2O, 56−89% yield; (b) TrCl, DMAP, DMF, Et_3N, 92−97% yield; (c) PhthN−OH, PPh_3, DIAD, THF, 74−94% yield; (d) HCOOH, CH_2Cl_2, 73−75% yield; (e) $NaIO_4$, $RuO_2 \cdot xH_2O$ and $CH_3CN/CCl_4/H_2O$/acetone (1/1/1.4/0.3).

SCHEME 7[a]



[a] (a) EDCI/HOAt/CH_2Cl_2/cyclohexylamine; (b) $NH_2NH_2 \cdot H_2O$, MeOH, CH_2Cl_2; (c) EDCI, HOAt, CH_2Cl_2, $(CH_3)_2CHCOOH$; (d) EDCI, HOAt, CH_2Cl_2.

lithium aluminum hydride to diols **29** and **30** in 56 and 89% yield, respectively (Scheme 6). Selective protection of the primary hydroxyl group of diols with a trityl group provided **31** and **32** in 92 and 97% yield, respectively. The secondary hydroxyl groups in **31** and **32** were converted to phthaloyl aminoxy groups through a Mitsunobu reaction in 74−94% yield with an inversion of the configuration at the β-carbon, and subsequent deprotection and oxidation produced N-protected β-aminoxy acids **37** and **38**, respectively. The phthaloyl group can be easily removed with hydrazine hydrate, which makes **37** and **38** ideal building blocks for peptide synthesis.

Following our previously reported protocols for α-aminoxy peptide coupling,[5a,8] we obtained diamides **43** and **44** and even triamide **46** in high overall yield using EDCI/HOAt as the coupling reagent[13] (Scheme 7).

In summary, we have developed two schemes for the efficient synthesis of chiral β^3-aminoxy acids or amides and their oligomers. These synthetic schemes should allow for the rapid construction of combinatorial libraries of peptides containing β^3-aminoxy acids for drug screening.

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Supporting Information Available: Preparation and characterization of compounds **1**−**46**, determination of optical purity of **13** and **14** by ^{1}H NMR spectroscopy, and HPLC analysis of **27**. This material is available free of charge via the Internet at http://pubs.acs.org.

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