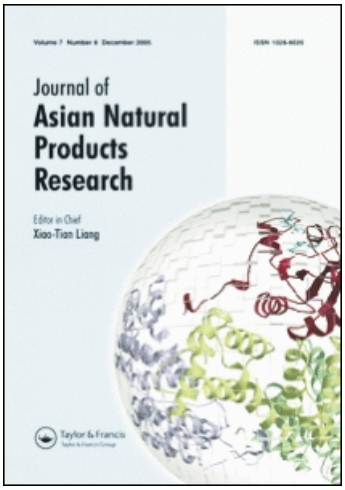

Journal of Asian Natural Products Research
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713454007

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To cite this Article Guo, Hong-Sheng , Zhao, Hong-Juan , Niu, De-Qiang and Zhao, Kang(2005) 'Stereoselective synthesis of β-amino acids', Journal of Asian Natural Products Research, 7: 2, 121 — 126
To link to this Article: DOI: 10.1080/10286020310001617219
URL: http://dx.doi.org/10.1080/10286020310001617219

Journal of Asian Natural Products Research, Vol. 7, No. 2, April 2005, 121–126

Stereoselective synthesis of β-amino acids

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(Received 30 May 2003; revised 30 June 2003; in final form 4 July 2003)

A convenient method for the stereoselective syntheses of β-amino acids with α-substitutions has been developed. This synthetic route involves the preparation of isoxazolidinones through hydroxylamine addition to unsaturated esters and subsequent hydrogenation. This procedure is also useful for the stereoselective syntheses of α-deuterated β-amino acids.

Keywords: β-Amino acids; Conjugate addition; Hydroxylamine; β-Peptides

1. Introduction

Due to their potential biomedicinal and synthetic applications, β-amino acids have attracted a great deal of attention recently [1–6]. The derived β-peptides of several amino acids have been reported to exhibit certain secondary structures and special stability against peptidase [7,8]. For example, the β-oligopeptides of six β-amino acid residues form stable helices in methanol [8]. Furthermore, α-substituted β-amino acids are often found as segments in bioactive compounds, such as paclitaxel [9] and many β-lactams [10–12]. With the increasing interest in β-peptides and other related biomedical compounds, the stereoselective synthesis of β-amino acids became desirable. Various successful methods have been developed for the synthesis of β-amino acids [1–6,13–19], including the Michael addition of amines to acrylate derivatives and homologation reactions from the corresponding α-amino acids. The efficient preparation of β-amino acids with α-substitution has also been explored [20]. The stereoselective preparation of α-substituted β-amino acids involves the alkylation of cyclic intermediates, which are either from the corresponding β-amino acids [21–23] or from the enolates generated *in situ* from the conjugate addition reaction of nucleophiles to α,β-unsaturated esters [24,25].

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Journal of Asian Natural Products Research
ISSN 1028-6020 print/ISSN 1477-2213 online © 2005 Taylor & Francis Ltd
http://www.tandf.co.uk/journals
DOI: 10.1080/10286020310001617219

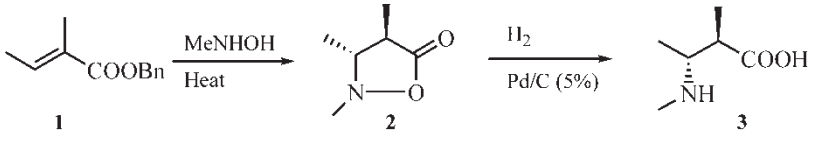
2. Results and discussion

Hydroxylamine derivatives without *O*-alkyl groups are more reactive to sp^2 centers such as in α,β-unsaturated esters than the corresponding amine compounds do, although the opposite reactivity was observed from their reactions towards the sp^3 centers. Hydroxylamine adds to unsaturated esters to give Michael addition products, which can subsequently cyclize to isoxazolidinones [26–32]. It has also been shown that isoxazolidinones can be stereoselectively prepared from trisubstituted 2-alkenoate such as **1**, one of which (**2**) has been successfully converted into the related amino acid **3** (scheme 1) [26,27]. We report herein the use of the easily prepared isoxazolidinones for their convenient conversion into β-amino acids with α-substitutions.

The addition reactions of hydroxylamines to unsaturated esters (**4a–d**) were carried out in refluxing ethanol and subsequent cyclization occurred to give the corresponding isoxazolidinones (scheme 2, table 1). Starting materials with (*E*) or (*Z*) α,β-unsaturated esters easily gave the products with *trans* or *cis* stereochemistry, respectively. The resulting isoxazolidinones were considered as the synthetic equivalents of β-amino acids due to the easy cleavage of the N–O bonds. Thus, isoxazolidinones (**5a–d**) were then converted into β-amino acids (**6a–d**) via catalytic hydrogenation in mostly quantitative yields [33–35]. This method was also useful for the preparation of *N*-unsubstituted β-amino acids (**6c**,**d**). *N*-Benzylhydroxylamine was the nucleophile for the addition step and catalytic hydrogenation at normal pressure successfully removed the *N*-benzyl group and also cleaved the N–O bond.

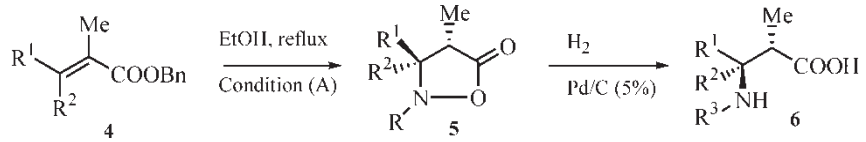
This method allows α-deuterio-β-amino acids to be prepared (scheme 3). The deuterio hydroxylamine, prepared by repeatedly dissolving the regular salt in deuterium oxide and then pumping away the solvent, reacted with **7a**,**b** and **9a** to give the corresponding isoxazolidinones. Hydrogenation produced α-deuterio-β-amino acids **8a**,**b** and **10a** with the control of stereochemistry at the α-carbon bearing the deuterium atom. By varying the olefin geometry of the starting α,β-unsaturated esters (**7a** and **9a**), the synthesis of the pair of deuterio amino acid diastereomers can be achieved by using the deuterio hydroxylamine. Alternatively, the *E*-olefin (**9b**), which is easily prepared from the corresponding Wittig reagents, can be converted into **10b** by a routine two-step procedure.

Further studies using chiral γ-oxygenated α,β-unsaturated esters (**11** and **13**) (scheme 4) led to β-amino acids with multi-chiral centers. Both reactions shown in Scheme 4 gave good



1 **2** **3**

Scheme 1.



4 **5** **6**

Scheme 2.

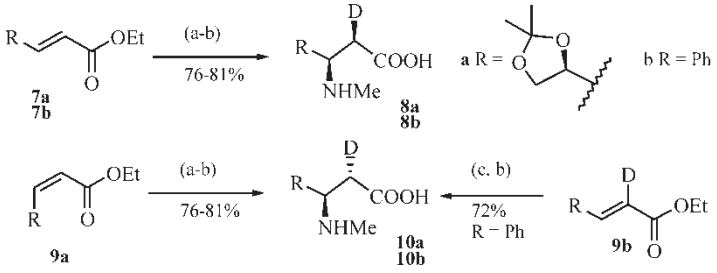
Table 1. Preparation of α-substituted β-amino acids **6**.

R	R^1	R^2	R^3	*Condition (A)*	*trans:cis*	*Yield**	*Product*
Me	Ph	H	Me	MeNHOH·HCl/MeONa	**5a** (33:1)	40%	**6a**
Me	H	Me	Me	MeNHOH·HCl/MeONa	**5b** (1:9)	84%	**6b**
Bn	Me	H	H	BnNHOH·HCl/MeONa	**5c** (30:1)	81%	**6c**
Bn	H	Me	H	BnNHOH·HCl/MeONa	**5d** (1:13)	90%	**6b**

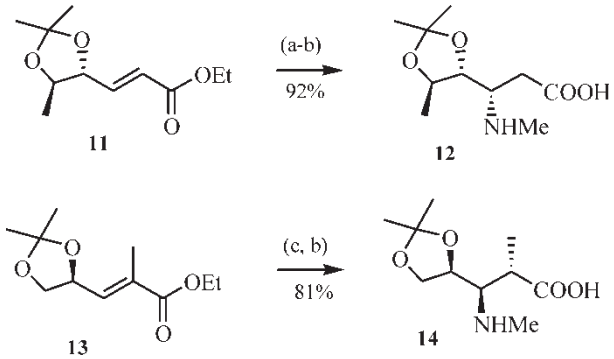
* Overall isolated yield.

yields and high stereoselectivity. The existing γ-centers in **11** and **13** are the handle for controlling the newly formed centers. The hydroxylamine addition to γ-oxygenated α,β-unsaturated esters took place in *syn* fashion, in which the β-chiral center has the *syn* configuration relative to the γ-center, and hydrogenation afforded β-amino acids **12** and **14**.

The addition of hydroxylamine derivatives is useful for the stereoselective syntheses of β-amino acids, which may bear α-substituents. The reported examples show the following features (a) trisubstituted unsaturated esters, which are normally not very reactive towards nucleophiles such as alcohols, amines or even sulfides, couple with N-hydroxylamine compounds (Scheme 2); (b) the stereochemistry of the resulting β-amino acids can be controlled by varying the olefin geometry in the α,β-unsaturated esters (Schemes 2–4); and (c) the use of deuterated hydroxylamine reagents or unsaturated esters provided two general methods for asymmetric deuterium incorporation to give a pair of deuterated amino acids (Scheme 3). These results of α-stereospecific deuteration of β-amino acids are attractive considering the potential importance of using deuterated amino acids in the mechanistic studies of enzymatic transformations and in revealing the pathways of biosyntheses [33–35].



Scheme 3. (a) MeNDODDCl/Et_3N/THF, then $ZnCl_2$; (b) H_2/Pd–C; (c) MeNHOHHCl/Et_3N/THF, then $ZnCl_2$.



Scheme 4. (a) MeNHOH·HCl/Et_3N, then $ZnCl_2$/THF; (b) H_2/Pd–C; (c) MeNHOH·HCl, NaOMe, EtOH reflux.

3. Experimental

3.1 General experimental procedure

^{1}H and ^{13}C NMR were recorded on a Varian Gemini 200 or 300 MHz spectrometer. All chemical shifts are reported relative to an internal standard of tetramethylsilane (TMS). High-pressure liquid chromatography was performed on a Shimadzu LC-10AT HPLC (column: adsorbosphere silica 5 μ, 4.6 × 250 mm) with an SPD-10Å UV-Vis detector. Thin-layer chromatography (TLC) was generally used to monitor a reaction process and was performed using precoated glass plates (silica gel 60, 0.25 mm thick) containing a 254 nm fluorescent indicator. Flash chromatography was performed (silica gel from Mallinckrodt Chemical Company) to purify the crude products.

3.2 General procedure for the synthesis of β-amino acids

3.2.1 Procedure A (for β-amino acids 6a, 6b, 6c, 6d and 14). To a solution of α,β-unsaturated ester (1 mmol) in anhydrous ethanol was added MeNHOH·HCl (5 mmol) and NaOMe (0.27 g, 5 mmol). The mixture was then allowed to boil under reflux for 8–10 h. The obtained solid (NaCl) was then filtered off and ethanol was removed under reduced pressure. The crude products were subjected to HPLC or/and ^{1}H NMR to determine the isomer ratio and then were purified by silica-gel flash-column chromatography (10–15% ethyl acetate in light petroleum) to afford pure isoxazolidinone compounds. The compounds were then hydrogenated over palladium on activated carbon (5 wt.%) in ethanol for 4 h. The resultant mixture was filtrated through a short silica-gel column; ethanol was removed under reduced pressure. The residue was then further dried under vacuum for approximately 30 min to give the β-amino acids.

6a ^{1}H NMR (200 MHz, CD_3OD) δ (ppm): 7.49 (5H, s), 4.07 (1H, d, $J = 10.7$ Hz), 2.79 (1H, m), 2.47 (3H, s), 0.98 (3H, d, $J = 7.2$ Hz). ^{13}C NMR (50 MHz, CD_3OD) δ (ppm): 16.6, 31.7, 45.1, 69.0, 130.0, 130.8, 131.0, 135.4, 180.5.

6b ^{1}H NMR (200 MHz, CD_3OD) δ (ppm): 3.38 (1H, m), 2.97 (1H, m), 2.75 (3H, s), 1.34 (3H, d, $J = 6.8$ Hz), 1.26 (3H, d, $J = 7.3$ Hz). ^{13}C NMR (50 MHz, CD_3OD) δ (ppm): 13.3, 13.9, 32.2, 42.4, 59.2, 178.2.

6c ^{1}H NMR (200 MHz, CD_3OD) δ (ppm): 3.26 (1H, dq, $J = 6.7$, 6.7 Hz), 2.32 (1H, dq, $J = 7.2$ Hz), 1.32 (3H, d, $J = 6.7$ Hz), 1.25 (3H, d, $J = 7.2$ Hz). ^{13}C NMR (50 MHz, CD_3OD) δ (ppm): 16.3, 18.3, 46.3, 52.0, 181.4.

6d ^{1}H NMR (200 MHz, CD_3OD) δ (ppm): 3.53 (1H, m), 2.77 (1H, m), 1.33 (3H, d, $J = 6.8$ Hz), 1.26 (3H, d, $J = 7.3$ Hz). ^{13}C NMR (50 MHz, CD_3OD) δ (ppm): 13.4, 16.3, 40.6, 43.5, 173.0.

14 ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 8.85 (2H, br), 4.32 (1H, dd, $J = 7.3$ Hz), 4.11 (1H, dd, $J = 6.3$, 8.5 Hz), 3.68 (1H, m), 2.89 (1H, dd, $J = 5.4$, 7.8 Hz), 2.72 (3H, s), 2.39 (1H, m), 1.38 (3H, s), 1.31 (3H, s), 1.25 (3H, d, $J = 7.4$ Hz). ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 16.8, 25.8, 27.1, 33.6, 40.4, 64.9, 67.8, 75.8, 110.1, 178.2.

3.2.2 Procedure B (for β-amino acids 8a, 8b, 10a, 10b, 12). To a suspension of hydroxylamine hydrochloride salt (1.2 mmol) in anhydrous CH_2Cl_2 (10 mL) was added α,β-unsaturated ester (1.0 mmol), followed by addition of anhydrous triethylamine

(0.17 mL, 1.2 mmol). The mixture was then stirred at room temperature overnight and the solvent removed. Anhydrous THF (10 mL) was then added, followed by the addition of anhydrous $ZnCl_2$ (0.17 g, 1.2 mmol). The resultant reaction solution was stirred for another 8 h and then quenched with water (10 mL). The so-obtained mixture was extracted with methylene chloride (3 × 10 mL), and the combined organic extracts dried over Na_2SO_4, and concentrated in vacuum. The crude products were then subjected to HPLC or/and ^{1}H NMR to determine the isomer ratio, and were then purified by silica-gel flash-column chromatography (10% ethyl acetate in light petroleum) to give isoxazolidinone compounds that were subsequently hydrogenated over palladium on activated carbon (5 wt.%) in ethanol for 4 h. The reaction mixture was filtrated through a short silica-gel column, and ethanol was removed under reduced pressure. The residue was then further dried under vacuum for approximately 30 min to give the β-amino acids.

8a ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 9.37 (2H, br), 4.33 (1H, m), 4.07 (1H, dd, $J = 6.2$, 8.5 Hz), 3.63 (1H, dd, $J = 7.7$, 7.7 Hz), 3.12 (1H, dd, $J = 3.3$, 8.7 Hz), 2.77 (3H, s), 2.29 (1H, d, $J = 3.3$ Hz), 1.38 (3H, s), 1.33 (3H, s). ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 26.1, 27.1, 32.3, 34.0, 60.2, 67.4, 76.2, 110.8, 175.6.

8b ^{1}H NMR (200 MHz, CD_3OD) δ (ppm): 7.50 (5H, m), 4.41 (1H, d, $J = 4.5$ Hz), 2.69 (1H, d, $J = 4.4$ Hz), 2.55 (3H, s). ^{13}C NMR (50 MHz, CD_3OD) δ (ppm): 31.5, 40.4, 63.0, 129.5, 130.7, 130.9, 136.4, 177.3.

10a ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 9.65 (2H, br), 4.30 (1H, dd, $J = 7.2$, 7.2 Hz), 4.01 (1H, dd, $J = 7.2$, 7.2 Hz), 3.58 (1H, dd, $J = 7.8$, 7.8 Hz), 3.06 (1H, dd, $J = 8.0$, 10.1 Hz), 2.73 (3H, s), 2.32 (1H, d, $J = 10.3$ Hz), 1.33 (3H, s), 1.28 (3H, s). ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 26.1, 27.1, 32.3, 33.9, 60.2, 67.3, 76.3, 110.7, 175.7.

10b ^{1}H NMR (200 MHz, CD_3OD) δ (ppm): 7.48 (5H, m), 4.41 (1H, d, $J = 9.6$ Hz), 3.53 (1H, m), 2.87 (1H, d, $J = 9.2$ Hz), 2.54 (3H, s). ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 31.5, 40.4, 63.1, 129.5, 130.7, 130.8, 136.5, 177.4.

12 ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 8.80 (2H, br), 3.92 (2H, m), 3.22 (1H, dt, $J = 6.6$, 7.5 Hz), 2.79 (3H, s), 2.48 (2H, dd, $J = 6.0$ Hz), 1.40 (3H, s), 1.38 (3H, s), 1.36 (3H, d, $J = 5.3$ Hz). ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 19.9, 27.4, 27.8, 32.4, 60.2, 75.5, 82.0, 109.8, 175.2.

Acknowledgements

KZ thanks the support from the Outstanding Young Scholarship from NNSFC (#30125043) and the Cheung Kong Scholars Programme, administrated by the Ministry of Education of PRC.

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