Tetrahedron 66 (2010) 9733–9737

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

1-Aminoxymethylcyclopropanecarboxylic acid as building block of β N–O turn and helix: synthesis and conformational analysis in solution and in the solid state

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ARTICLE INFO

Article history:
Received 5 May 2010
Received in revised form 6 October 2010
Accepted 15 October 2010
Available online 9 November 2010

Keywords:
$\beta^{2,2}$-aminoxy acid
β N–O turn
Cyclopropane side chain
Secondary structure

ABSTRACT

Cyclopropane side-chained $\beta^{2,2}$-aminoxy oligopeptides were synthesized and conformationally studied. β N–O turn in solution and β N–O helix in the solid state was characterized by ^{1}H NMR, 2D NOESY and FT-IR as well as X-ray crystallography studies. Almost no changes has been observed with the disturbance at α carbon bond angle compared with dimethyl substituted one. This study provided the opportunity to design the bioactive peptidomimetics in a more elaborate way.

1. Introduction

Research of synthetic foldamers (peptidomimetics) has been attracted most attention not only on discovering predictable and well-defined secondary structures, but also on the harnessing of latent bioactivities in enzyme mimic as well as drug design and development.[1] Constrained cyclopropane ring has been served as such a useful segment in the peptidomimetic design. On the one hand, cyclopropane-containing peptides, natural or synthetic, have been found to exhibit various bioactivities, for example, to be involved in the process of the biosynthesis of ethylene, being inhibitor of the carboxypeptidase, being the hepatitis C virus NS3 protease, and so on.[1d,2–5] On the other hand, introducing the cyclopropane ring to the backbone has been employed to give the extra rigidity to the conformation or create different secondary structures.[6,7] For example, in the oligomers composed of 1-(aminomethyl)-cyclopropylcarboxylic acid (*h*Acc, a kind of $\beta^{2,2}$-amino acid), eight-membered ring intramolecular hydrogen bond was formed (Fig. 1a), while no intramolecular hydrogen bond is found in the oligomers derived from 3-amino-2,2-dimethylpropanoic acid (Fig. 1b).[7] And this eight-membered ring intramolecular hydrogen bond secondary structure hasn't been found in the known chiral β-peptides.[1c,8]

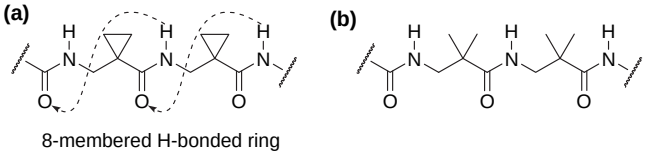

Fig. 1. Achiral $\beta^{2,2}$-peptides and intramolecular hydrogen bond form.

Aminoxy peptides are kinds of backbone-modified peptidomimetics with inserting of one oxygen atom between the nitrogen atom and one of the backbone carbon atom.[1e,9,10] Well-defined secondary structures, for example, N–O turns, N–O helices, reverse turn, etc. have been found to exhibit by short α-, β-, γ-aminoxy peptide sequences. β^3-Aminoxy peptides, a subclass of β-aminoxy peptides, possess a strong nine-membered ring intramolecular hydrogen bond, i.e., β N–O turn, (Fig. 2a) between adjacent residues,

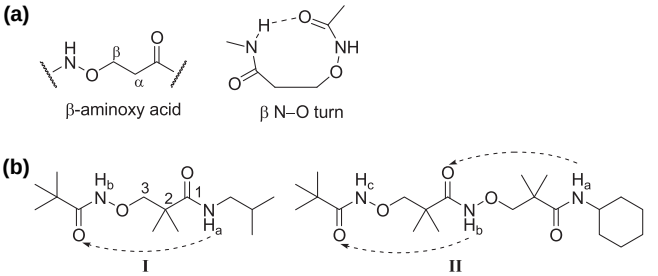

Fig. 2. (a) β-Aminoxy acid and β N–O turn; (b) Dimethyl side-chained $\beta^{2,2}$-aminoxy oligomers **I** and **II**.

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0040-4020/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2010.10.037

but the molecular conformation is side chain dependent.[10a] For the dimethyl substituted $\beta^{2,2}$-aminoxy acid (Fig. 2b), both monomer **I** and dipeptide **II** involve β N–O turn, which is coincident with one form of β N–O turns existing in β^3-aminoxy peptide.[10b] And achiral dipeptide **II** can form helix structure consisting of two consecutive homochiral β N–O turns in the solid state. Recently, we reported that the chirality of the achiral α N–O turn adopted by 1-(aminoxy) cyclopropanecarboxylic acid unit (OAcc) in the building block of chiral α-aminoxy acid/achiral cyclopropane α-aminoxy acid can be induced by the previous chiral α-aminoxy acid unit.[10d] However, this kind of induction is much weaker in chiral α-aminoxy acid/achiral 2-aminoxyacetic acid (OGly) unit. On further developing constrained cyclopropane ring incorporated bioactive peptidomimetics, we are interested in the structure and properties of cyclopropane ring substituted $\beta^{2,2}$-aminoxy peptide, which has much flexible backbone with one carbon prolonged than that of OAcc unit. Here we reported the synthesis and conformational studies of monomer **1** and dipeptide **2** (Fig. 3) derived from 1-aminoxymethyl-cyclopropanecarboxylic acid (*h*OAcc).

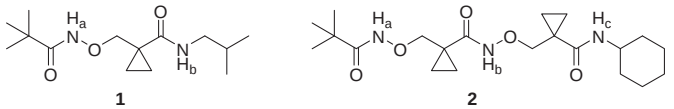


Fig. 3. Structures of cyclopropane side-chained $\beta^{2,2}$-aminoxy monomer **1** and dipeptide **2**.

2. Results and discussion

2.1. Synthesis of 1-aminoxymethylcyclopropanecarboxylic acid monomer 1 and dipeptide 2

Cyclopropane side-chained $\beta^{2,2}$-Aminoxy monomer **1** (Piv-*h*OAcc-NH-*i*-Bu) was synthesized as shown in Scheme 1. Intermediate methyl 2-(hydroxymethyl)acrylate (**3**) was obtained through Baylis–Hillman reaction from 37% formalin and methyl acrylate.[11] Then, Mitsunobu reaction transformed hydroxyl group to aminoxy group to introduce the N–O segment.[12] The key step was cyclopropanation of the ethylene group using diazomethane under reflux in toluene, but the cyclopropane compound **6** and byproduct **7** was obtained as an unseparated mixture (Scheme 2).[13] Conventional protection/deprotection, and coupling reaction were then employed to build up the amide bonds in monomer **1**.[14] Due to the low yield in the key cyclopropanation process and the difficulties in separating compound **6** from **7**, several other methods, such as photolysis[13b] and $Pd(OAc)_2$ catalyzed route[15] were tried but failed to improve the yield of compound **6**.

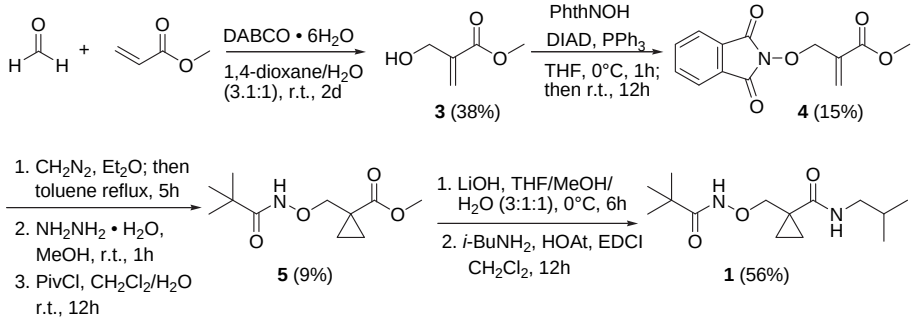
Then we changed the synthetic protocol to prepare dipeptide **2** starting from diethyl malonate as shown in Scheme 3. The cyclopropyl group was introduced via substitution by 1,2-dibromo ethane. Afterwards, compound **8** underwent hydrolysis followed by reduction to afford the key intermediate **10**, for introduction of aminoxy group in next step. $\beta^{2,2}$-Aminoxy dipeptide **2** (Piv-*h*OAcc-*h*OAcc-NH-*c*-Hex) was finally obtained in good yield through conventional protection/deprotection and coupling reactions.

2.2. Conformational studies

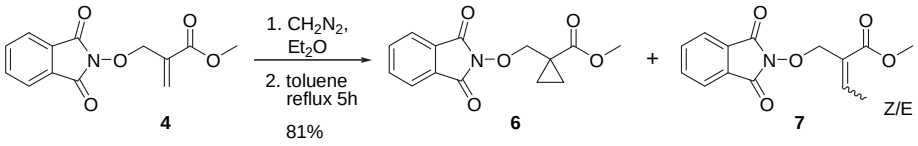
2.2.1. Conformation in solution.

*2.2.1.1. ^{1}H NMR dilution and titration studies of monomer **1** and dipeptide **2**.* The conformations of monomer **1** and dipeptide **2** in solution were studied by ^{1}H NMR spectroscopy at first. The intramolecularly hydrogen-bonded amide proton is solvent inaccessible and its chemical shift will not show significant change on dilution by $CDCl_3$ or titration by DMSO-d_6. While the chemical shift of the solvent accessible proton will move downfield dramatically in these two experiments. As shown in Fig. 4, the amide NH_b proton of monomer **1** showed little changes when its solution in $CDCl_3$ were diluted from 200 to 1.56 mM (Fig. 4a), or when DMSO-d_6 was added gradually to its 5 mM solution in $CDCl_3$ (Fig. 4b).[16]

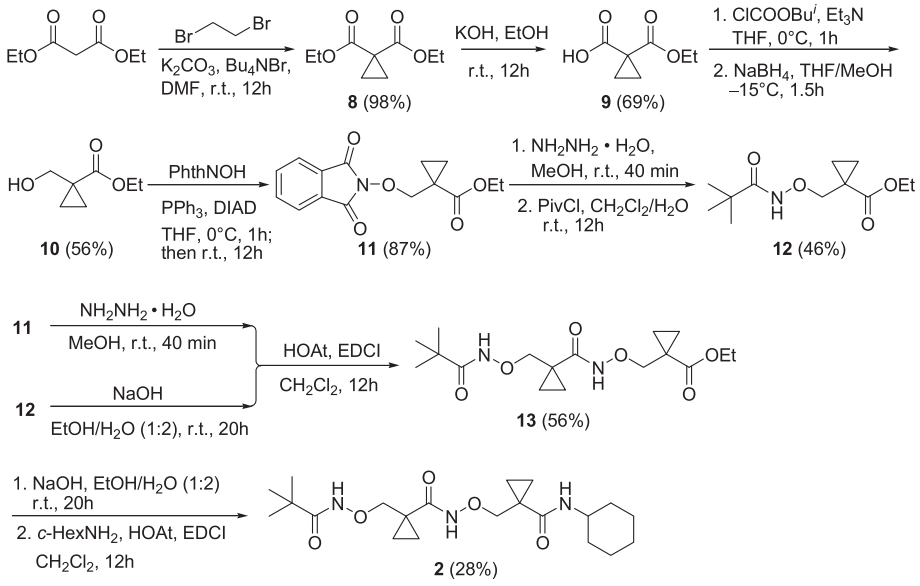
But the chemical shift of the aminoxy amide NH_a of **1** changed dramatically upon dilution in $CDCl_3$ or by DMSO-d_6 addition.[17] Table 1 summarized the chemical shifts of all the amide protons of **1** and **2** at 2 mM in $CDCl_3$ at room temperature. The chemical shifts of C-terminal regular amide NH protons of **1** (δ_{Hb} 8.63 ppm) and **2** (δ_{Hc} 8.42 ppm) were more downfield than the regular amide NHs (ca. 6.5 ppm).[17] And the chemical shift of aminoxy amide NH_b proton of dipeptide **2** (δ 12.05 ppm) was also more downfield than the non-hydrogen-bonded aminoxy amide NH (ca. 8.5 ppm). But the chemical shifts of N-terminal aminoxy amide NH_a protons of **1** (δ 8.46 ppm) and **2** (δ 8.57 ppm) were in the region of non-hydrogen-bonded aminoxy amide NHs. This result indicated that NH_b and NH_c protons are intramolecular hydrogen-bonded to form



Scheme 1. Synthesis of cyclopropane substituted $\beta^{2,2}$-aminoxy monomer **1**. Abbreviations: DABCO=1,4-diazabicyclo[2.2.2]octane; PhthNOH=*N*-hydroxyphthalimide; DIAD=diisopropyl azodicarboxylate; PivCl=pivaloyl chloride; HOAt=1-hydroxyazabenzotriazole; EDCI=1-(3-dimethylaminopropyl)-3-ethylcarbodiimide methyl hydrochloride.



Scheme 2. Cyclopropanation of compound **4** with diazomethane.



Scheme 3. Synthesis of cyclopropane substituted $\beta^{2,2}$-aminoxy dipeptide **2**.

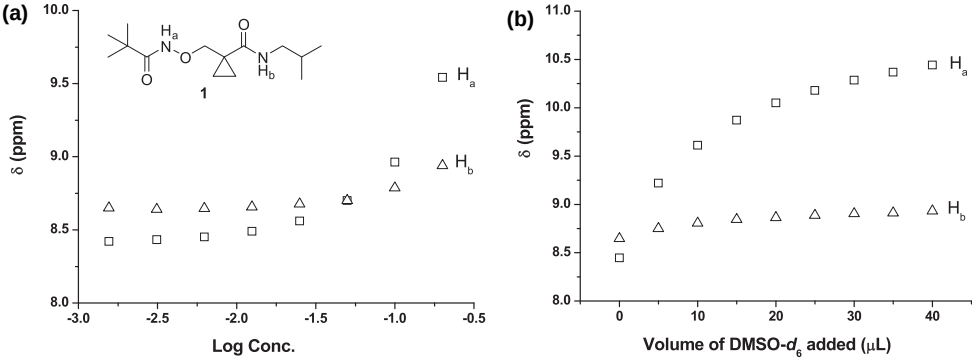


Fig. 4. ^{1}H NMR dilution study and DMSO-d_6 addition study of monomer **1**. (a) Amide proton chemical shift as a function of logarithm of concentration (in $CDCl_3$ at room temperature); (b) Amide proton chemical shift as a function of the amount of DMSO-d_6 added in a 5 mM solution (0.5 mL in $CDCl_3$ at room temperature).

Table 1
^{1}H NMR chemical shifts (δ ppm) of amide protons of **1** and **2** at 2 mM in $CDCl_3$[a]

Compound	NH_a	NH_b	NH_c
1	8.46 (s)	8.63 (br)	
2	8.57 (s)	12.05 (s)	8.42 (d)

[a] The chemical shifts underlined are those of the C-terminal regular amide NH protons, others are those of aminoxy amide NH protons.

β N–O turns, while the NH_a protons are not intramolecular hydrogen-bonded, namely, solvent accessible. Compared to those of $\beta^{2,2}$-aminoxy peptide **I** and **II**,[10b] the chemical shifts of hydrogen-bonded amide NHs of **1** and **2** were all more downfield with the differences in a range of 0.31–0.78 ppm, correspondingly. But little differences (0.06 and 0.02 ppm) existed between the chemical shifts of the N-terminal non-hydrogen-bonded NH protons of cyclopropane and dimethyl substituted one, separately. This difference could be attributed to the substituent effect. Cyclopropane substituted $\beta^{2,2}$-aminoxy peptides can form more strong intramolecular hydrogen bond than dimethyl substituted one.

2.2.1.2. FT-IR spectra studies. Fig. 5 presented the FT-IR spectra of compound **1** and **2** in the N–H stretch region. The spectra were recorded in CH_2Cl_2 at low concentration (2 mM) at which intermolecular hydrogen bond is seldom to occur. Following the principle for distinguishing the hydrogen-bonded and non-hydrogen-bonded N–H stretching frequencies,[18] the FT-IR signals of compound **1** and **2** could be assigned accordingly. The band at 3419 and 3411 cm^{-1} could be assigned to the non-hydrogen-bonded aminoxy amide N–H stretches, 3317 and 3288 cm^{-1} to the hydrogen-bonded amide N–H stretches. The absorption at 3213 cm^{-1} for compound **2** could be attributed to the hydrogen-bonded aminoxy N–H stretch. The FT-IR results were coincident with that of ^{1}H NMR experiments. The results suggested that one nine-membered ring intramolecular hydrogen bond was formed in monomer **1** and two for dipeptide **2** in aprotic solvent.

2.2.1.3. 2D NOESY studies. More information of the conformation in solution of compound **1** and **2** was obtained from 2D Nuclear Overhauser Effect Spectroscopy experiment (NOESY) recorded in $CDCl_3$.[19] Monomer **1** showed strong nuclear Overhauser effects (NOEs) between NH_b and H_β (β proton), but medium NOEs between NH_a and H_β (Fig. 6). Dipeptide **2** exhibited strong NOEs between the pairs of NH_b/H^1_β (β proton of unit 1, N-terminal), and NH_c/H^2_β (β proton of unit 2, C-terminal), but medium NOEs between NH_a/H^1_β, and NH_b/H^2_β. That is to say, the amide proton NH_i has strong NOE with the β proton $C_\beta H_{i-1}$ in adjacent residue, but medium NOE with the β proton $C_\beta H_i$ in the same residue. And two residues of dipeptide **2** possess same conformation. This kind of NOE pattern of compound **1** and **2** matched well with that of dimethyl substituted $\beta^{2,2}$-aminoxy peptides, which supported the view that similar conformation of nine-membered ring intramolecular hydrogen bond (β N–O turn) is formed of compound **1** and **2** in solution. And the absence of NOE

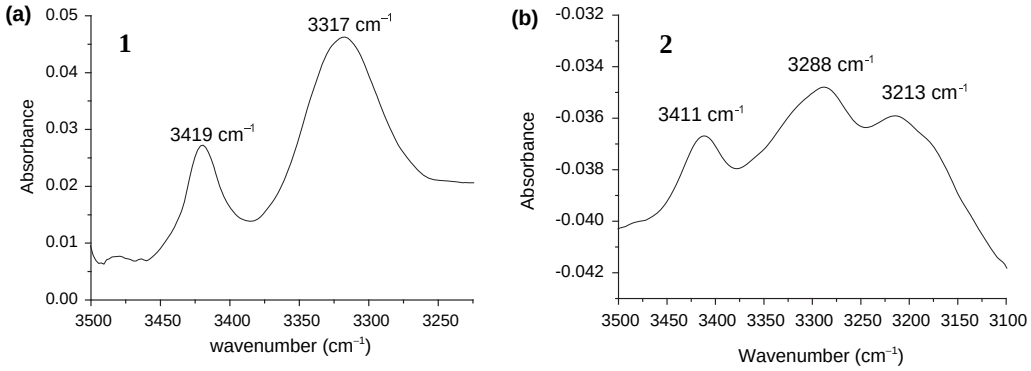


Fig. 5. N–H stretch region FT-IR data for (a) monomer **1** and (b) dipeptide **2** at 2 mM in CH_2Cl_2 at room temperature after subtraction of the spectrum of pure CH_2Cl_2.

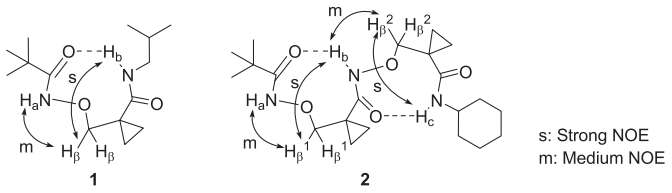


Fig. 6. The NOEs review of compound **1** and **2** according to their 2D NOESY spectra (5 mM in $CDCl_3$ at 25 °C).

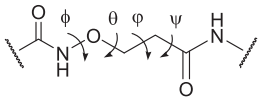
between the protons on C-terminus and on N-terminus of dipeptide **2** implied that it adopts an extended structure.

2.2.2. Conformation in the solid state: X-ray diffraction analysis. $\beta^{2,2}$-Aminoxy acid monomer **1** and dipeptide **2** adopted β N–O turn structure in solution as determined by ^{1}H NMR, 2D NOESY and FT-IR spectroscopic methods. Such high coincidence in the structure between compound **1** (**2**) and its dimethyl counterpart **I** (**II**) was also observed in the solid state as revealed by X-ray structural analysis.[20]

As shown in Fig. 7, the crystal of monomer **1** shows a strong nine-membered ring intramolecular hydrogen bond with the NH···O distance of 2.12 Å and the ∠NHO angle of 163.8°. There is also a six-membered ring intramolecular hydrogen bond formed between amide NH_b and aminoxy oxygen atom (NH···O distance of 2.39 Å and the ∠NHO angle of 121.3°), as that in monomer **I**, to further stabilize the β N–O turn conformation. The dihedral angles ϕ, θ, φ and ψ of the backbone of **1** were listed in Table 2 and found close to those of monomer **I**.[10b]

Dipeptide **2** adopted a helix structure stabilized by two consecutive homochiral β N–O turns, i.e., β N–O helix, in the solid state, which is also in accordance with the helix form of dipeptide **II**. The dihedral angles the backbone of dipeptide **2** (Table 2) and

Table 2
Dihedral angles of cyclopropane substituted $\beta^{2,2}$-aminoxy peptides **1** and **2**



Compound	Unit 1 (N-terminal)				Unit 2 (C-terminal)			
	ϕ_1	θ_1	φ_1	ψ_1	ϕ_2	θ_2	φ_2	ψ_2
1	87.4°	−169.2°	64.8°	−1.0°				
2	92.7°	−167.3°	67.0°	6.4°	90.6°	−172.1°	78.8°	−17.4°

II[10b] are comparable, except slightly differences of ϕ and ψ. The bond angles of $\angle C_{=O}C_\alpha C_\beta$ in **1** and **2** (ca. 120°) attributed to cyclopropane substituent are larger than that of dimethyl substituted **I** and **II** (ca. 109° of regular sp^3 hybrid carbon bond angle). This disturbance of backbone geometry did not change the conformations of the compound **1** and **2** in solid state, but little changes of dihedral angle ϕ and ψ of the backbone. β N–O turn and β N–O helix structure were possessed by compound **1** and **2**, respectively.

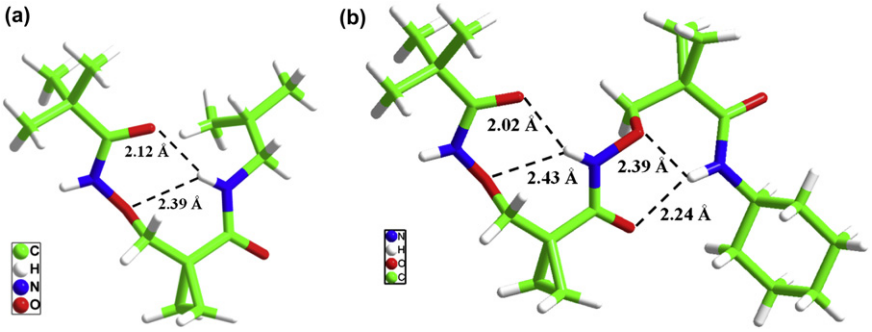


Fig. 7. X-ray structures of $\beta^{2,2}$-aminoxy (a) monomer **1** and (b) dipeptide **2**.

3. Conclusions

The monomer **1** and dipeptide **2** derived from *h*OAcc were synthesized and their conformations were characterized by ^{1}H NMR, 2D NOESY and IR spectrometries as well as X-ray crystallography. It turns out that in solution or in the solid state both of them adopted β N–O turn in the same pattern as their dimethyl counterparts **I** and **II**. This study provided us deep comprehension of the structural characteristic of β-aminoxy peptide and also lends us the opportunity to design the bioactive peptidomimetics in a more elaborate way.

4. Experimental section

4.1. *N*-Isobutyl 1-((1-(*N*-pivaloylamidoxy))methyl) cyclopropanformamide (Piv-*h*OAcc-NH-*i*-Bu, 1)

To a mixture solvent of compound **5** (83 mg, 0.36 mmol) in THF (6 mL), MeOH (2 mL) and H_2O (2 mL) was added lithium hydroxide (45.8 mg 1.09 mmol) at 0 °C. After stirring for 6 h at 0 °C, the reaction mixture was added 15 mL of EtOAc and acidified with 1 N HCl to pH=1. After extracted with EtOAc and washed with brine, the organic layer was dried over anhydrous $MgSO_4$ and concentrated. The resulting acid was azeotroped with toluene three times and directly used for the next step reaction.

Freshly distilled CH_2Cl_2 (12 mL) was added to the flask of dried free acid under nitrogen atmosphere, followed by the addition of HOAt (75 mg, 0.55 mmol), iso-butyl amine (0.07 mL, 0.7 mmol) and finally EDCI (0.21 g, 0.72 mmol). After stirring overnight, the reaction mixture was diluted with CH_2Cl_2. The organic layer was washed with 5% $NaHCO_3$, 0.1 N H_2SO_4 and brine, then dried over anhydrous $MgSO_4$ and concentrated. The residue was purified by flash column chromatography (with 2:1 hexane/EtOAc as eluent) to afford compound **1** (59 mg, 56%) as a white solid. TLC R_f 0.18 (2:1 hexane/EtOAc); mp 168–169 °C; IR (KBr) 3419, 3317, 2963, 1637, 1634 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.66 (s, br, 1H), 8.48 (s, 1H), 3.92 (s, 2H), 3.16 (dd, J=5.5, 6.9 Hz, 2H), 1.91–1.94 (m, 1H), 1.32–1.34 (m, 2H), 1.22 (s, 9H), 0.93 (d, J=6.9 Hz, 6H), 0.68–0.70 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.5, 172.4, 77.4, 47.7, 37.8, 28.4, 27.2, 22.8, 20.5, 13.6, 13.3; LRMS (EI, 20 eV) m/z 271 (M^++1, 12), 227 (20), 198 (59), 154 (100); HRMS (EI) for $C_{14}H_{26}N_2O_3$ (M^+): calcd 270.1943, found 270.1944.

4.2. Piv-*h*OAcc-*h*OAcc-NH-*c*-Hex (2)

Following the stoichiometric ratio and procedure for the synthesis of compound **13**, compound **2** (34 mg, 28%) was obtained as a white solid from cyclohexanamine (0.1 ml, 0.9 mmol) and compound **13** (107 mg, 0.3 mmol). Mp 241–244 °C; IR (CH_2Cl_2) 3411, 3288, 3213 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 12.09 (s, 1H), 8.69 (s, 1H), 8.46 (d, J=6.9 Hz, 1H), 3.96 (s, 2H), 3.85 (s, 2H), 3.70–3.80 (m, 1H), 1.86–1.92 (m, 2H), 1.68–1.78 (m, 2H), 1.23 (s, 9H), 1.17–1.41 (m, 10H), 0.72–0.78 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.2, 171.5, 170.6, 79.1, 78.9, 49.0, 37.7, 32.7, 27.1, 25.6, 25.4, 22.8, 21.5, 13.6, 13.3; LRMS (EI, 20 eV) m/z 410 (M^++1, 9), 353 (2), 212 (10), 180 (100); HRMS (EI) for $C_{21}H_{35}N_3O_5$ (M^+): calcd 409.2577, found 409.2579.

Acknowledgements

Financial support by the National Natural Science Foundation of China (Project No. 20202001), and Fok Ying Tung Education Foundation (Project No. 94023) are gratefully acknowledged. D.-W.Z. thanks Fudan University for the conferment of the Century Star Award.

Supplementary data

Synthetic schemes and characterization data of **1**, **2** and their synthetic intermediates; copies of 2D NOESY spectra of **1** and **2**; crystallographic data of **1** and **2**. Supplementary data related to this article can be found online at doi:10.1016/j.tet.2010.10.037. These data include MOL files and InChiKeys of the most important compounds described in this article.

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19. For details, please see the Supplementary data.
20. CCDC 795383 and 795384 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.