DOI: 10.1002/ejoc.200801173

New Concise Route to 2-Amino-3-hydroxycycloalkanecarboxylic Acids by Imidate-Mediated Intramolecular Conjugate Addition

Yoshitaka Matsushima*[a] and Jun Kino[a]

Keywords: Amino acids / Heterocycles / Intramolecular conjugate addition / Stereoselectivity

Trichloroacetimidates, generated either in situ or prepared and isolated from methyl 3-hydroxycycloalk-1-enecarboxylates, undergo stereoselective intramolecular conjugate addition reactions to produce oxazolines. These oxazolines lead, in a novel, simple way, to 2-amino-3-hydroxycycloalkanecarboxylic acids and their derivatives.

Introduction

In recent years, alicyclic β-amino acids have attracted considerable interest because of their pharmacological activities.[1,2] Natural cispentacin, an antifungal antibiotic with a cyclopentane skeleton, is one of the most important derivatives.[3] In addition, it is noteworthy that alicyclic β-amino acids such as *trans*-2-aminocyclohexanecarboxylic acid (ACHC) and *trans*-2-aminocyclopentanecarboxylic acid (ACPC) have been used as building blocks for water-soluble β-peptides, which fold into stable helical structures.[4,5] Hydroxy-functionalized β-amino acids are an important class of amino acid because of their occurrence in many biologically active compounds.[6] Although of less biological importance than open-chain analogues, some cyclic hydroxylated β-amino acid derivatives are known to be building blocks for pharmaceutically important natural substances.[2] Recent research studies have focused on substituted ACHCs and ACPCs, and strategies for the synthesis of ACHCs and ACPCs with hydroxy groups have been reported.[2] Hydroxy groups have been introduced into the cyclohexane ring of ACHC by iodolactonization,[7] halonium-promoted intramolecular formation of oxazoline[7] or dihydrooxazole[7,8] formation via *N*-acylamines, reduction of epoxides[9] and intramolecular epoxide-opening by carboxylate,[10] and base-promoted cleavage of the oxygen bridge for oxanorbornane[11] or oxanorbornene[12] adducts derived from the Diels–Alder reaction. On the other hand, there are few reports about the installation of hydroxy groups into the cyclopentane ring of ACPC. In fact, there are only two examples: the epoxide-opening of azide ions[13] and the dihydroxylation of alkenes.[14] Very recently, it was reported that a hydroxy group was introduced into the 3-position by the NBS-promoted intramolecular formation of oxazolines via *N*-acylamines.[15]

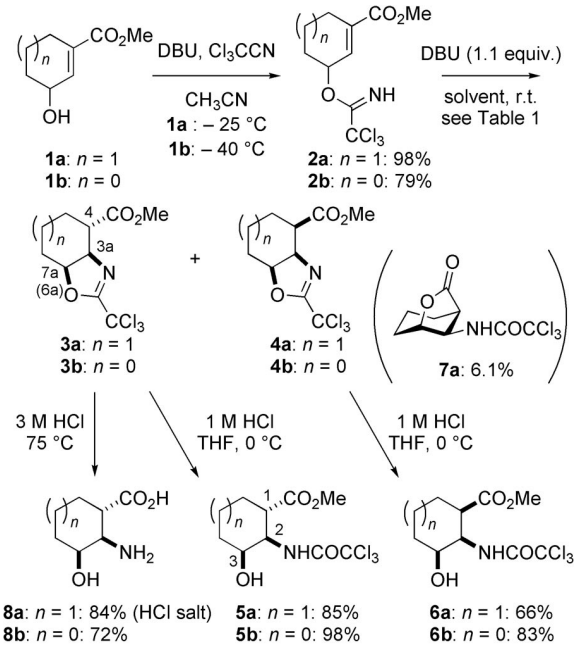
During our development of a simple synthetic strategy to deoxyamino sugars from non-sugar materials,[16,17] we noted the intramolecular conjugate addition of γ-trichloroacetimidoyloxy α,β-unsaturated esters in an acyclic system.[17,18] We reported the trichloroacetimidate-mediated functionalization as useful for the introduction of a nitrogen functionality[19] onto the β-carbon of γ- and δ-hydroxy α,β-unsaturated esters, which was a new way to construct 1,2-amino or 1,3-amino alcohol moieties in an acyclic system.[20] The purpose of this work was to use this procedure for the synthesis of polyfunctionalized carbocycles such as hydroxy-substituted 2-aminocycloalkanecarboxylates. Thus, in this paper we disclose a methodology applicable to the construction of polyfunctionalized carbocyclic systems, a novel route to 3-hydroxy-substituted ACHC and ACPC and their derivatives.

Results and Discussion

For the synthesis of polyfunctionalized carbocyclic compounds, it was anticipated that *cis*-amino alcohol moieties equipped with cycloalkanecarboxylates would be prepared by the intramolecular conjugate addition of trichloroacetimidates to cycloalkenecarboxylates. Readily available methyl 3-hydroxycyclohexenecarboxylate (**1a**) and methyl 3-hydroxycyclopentenecarboxylate (**1b**) were chosen as starting materials.[21] First, we attempted the stepwise cyclization of the trichloroacetimidates to the oxazolines (Scheme 1). The trichloroacetimidates were successfully prepared by treatment of the appropriate hydroxycyclohexenecarboxylate with a catalytic amount of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and an excess of trichloroacetonitrile in acetonitrile, and isolated by flash silica gel chromatography. The trichloroacetimidate of the six-mem-

[a] Department of Chemistry, Hamamatsu University School of Medicine,
Handayama, Hamamatsu 431-3192, Japan
Fax: +81-53-435-2319
E-mail: ymatsu@hama-med.ac.jp
Supporting information for this article is available on the WWW under http://www.eurjoc.org or from the author.

bered ring **2a** derived from 3-hydroxycyclohexenecarboxylate was stable enough to be obtained in a quantitative yield (98%). The derivative of the five-membered ring **2b** was obtained in 79% yield because of its slight susceptibility to silica gel, found during TLC analysis. Treatment of the resulting trichloroacetimidate **2a** with NaH or potassium *tert*-butoxide (*tert*-BuOK) in THF, conditions applied in acyclic systems,[20] were unsuccessful and produced a large number of products. After several experiments, it was found that a stoichiometric amount of DBU effectively afforded the cyclized products. The results of the conjugate addition reactions of **1a** and **1b** under different conditions are summarized in Table 1. The conjugate addition of **1a** and **1b** in acetonitrile at room temperature afforded oxazolines **3a** and **4a** or **3b** and **4b** in moderate yields, respectively (entries 1 and 9). The reaction yields were apparently affected by the cleavage of trichloroacetimidate groups during the cyclization in acetonitrile. The product ratio of the six-membered rings **3a** and **4a** was moderate (73:27), whereas the five-membered ring **3b** was predominantly produced from **1b** (**3b**/**4b** >99:1). The reaction of imidate **1a** was also performed under reflux, however, the yield and the stereoselectivity were barely affected (entry 2).



Scheme 1. Synthesis of 3-hydroxy-ACHC and -ACPC.

Conjugate addition using K_2CO_3 as an inorganic base in methanol was also performed (entries 3 and 10). At the beginning of the reaction, the oxazolines **4a** and **4b** seemed to be predominantly formed, as determined by TLC analysis, however, epimerization to the relatively stable isomers **3a** and **3b** occurred until the starting imidates had been completely consumed. This was also confirmed by prolonging the reaction time (entries 3 and 4). Additionally, it should be noted that the yields of the oxazolines were also severely affected by the cleavage of the trichloroacetimidate group in the alcoholic solvent. In fact, treatment with DBU in MeOH has previously been reported to be one of the methods for the cleavage of the trichloroacetimidate group.[22]

Table 1. DBU-promoted synthesis of oxazolines **3a**,**b** from imidates **2a**,**b** in different solvents.

Entry	Substrate	Conditions		Product yield [%][a]	
		Solvent	Time [h]	**3a** + **4a** (ratio **3**/**4**)	**1a**
1	**2a**	CH_3CN (25 mM)	24	67 (73:27)[b]	33
2[c]		CH_3CN (25 mM)	0.5	63 (75:25)[b]	35
3[d]		CH_3OH (25 mM)	5.5	52 (31:69)[b]	45
4[d]		CH_3OH (25 mM)	23	53 (42:58)[b]	46
5[e]		CH_2Cl_2 (25 mM)	62	71 (93:7)[b]	3
6		CH_2Cl_2 (150 mM)	21.5	69 (89:11)[b]	5
7		THF (25 mM)	42	81 (>99:1)[b]	3
8		THF (150 mM)	8	91 (99:1)[b]	1
				3b + **4b**	**1b**
9	**2b**	CH_3CN (25 mM)	3	74 (>99:1)[f]	19
10[d]		CH_3OH (25 mM)	5	69 (44:56)[f]	25
11		CH_2Cl_2 (25 mM)	24	87 (95:5)[f]	5
12		CH_2Cl_2 (150 mM)	5	92 (97:3)[f]	3
13		THF (25 mM)	18	90 (>99:1)[f]	1
14		THF (150 mM)	4	90 (>99:1)[f]	1

[a] Isolated yield; however, the yields of **1a** and **1b** when below 10% were calculated by 270 MHz ^{1}H NMR spectroscopy. [b] The isomers were not necessarily fully separated and their ratio was determined by 270 MHz ^{1}H NMR spectroscopy. [c] The reaction was performed under reflux. [d] The reaction was carried out by using K_2CO_3 (1.0 equiv.) instead of DBU. [e] Small amounts of the starting imidate were detected (ca. 4%) by 270 MHz ^{1}H NMR analysis of the crude products. [f] The product ratio was calculated from the isolated yield of each product.

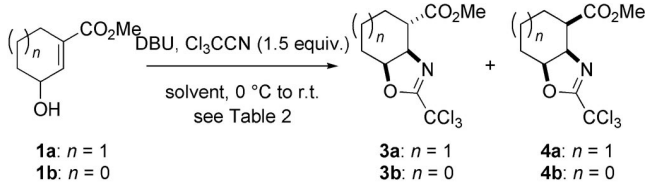
Next, we attempted to improve the intramolecular conjugate addition reaction by searching for solvents other than acetonitrile that could suppress the cleavage of the trichloroacetimidate group during the reaction and increase the stereoselectivity. We discovered that solvents such as THF or CH_2Cl_2 effectively prevented the starting imidates from being cleaved during the reaction (entries 5, 7, 11, and 13). In addition, the selectivity was increased up to >99:1 even in the case of the six-membered-ring system, especially in THF. Furthermore, the reaction was tested at higher concentrations (150 mM; entries 6, 8, 12, and14). The reaction time was generally shortened, but the product yields and ratios were not greatly affected.

The relative stereochemistries of the resultant oxazolines **3b** and **4b** were assigned on the basis of a ^{1}H NMR analysis. The values of the coupling constant between 3a-H and 6a-H (7.2–7.5 Hz) indicate the oxazoline rings of **3b** and **4b** have a *cis* stereochemistry. The small coupling constant between 3a-H and 4-H (1.3 Hz) was consistent only with the indicated 1,2-*trans*-stereochemistry, having an approximately 90° dihedral angle for the corresponding methine hydrogens of the oxazoline **3b**. In the case of oxazoline **4b**, a relatively large coupling constant (7.9 Hz) indicates a *cis* orientation for 3a-H and 4-H. For **3a** and **4a**, the values of the coupling constant between 3a-H and 7a-H (7.9–9.1 Hz) also indicate the oxazoline rings have a *cis* stereochemistry. However, the coupling constants between 3a-H and 4-H, which are similar (6.6 and 4.6 Hz, respectively), did not provide conclusive evidence of the nature of the stereoisomer.

Next, the oxazoline rings of the oxazolines **3a**,**b** and **4a**,**b** were cleaved by treatment with 1 M hydrochloric acid in THF at 0 °C over a short time to afford methyl 2-trichloroacetamido-3-hydroxycycloalkanecarboxylates **5a**,**b** and **6a**,**b**, respectively, in good-to-excellent yields. Consequently, the stereochemistries of the oxazolines **3a** and **4a** were determined by NOE analysis of compounds **5a** and **6a**, and the stereochemistries of the oxazolines **3b** and **4b** mentioned above were also confirmed by NOE experiments with **5b** and **6b**.[23] In the course of the cleavage of the oxazoline **4a**, the lactone **7a** was isolated as a byproduct (6.1%). This was strong evidence of the 1,3-*cis* relationship of the hydroxy and carboxylate groups of **4a**. With oxazoline **4b**, the corresponding lactonized compound was not detected. Note also that the ^{1}H chemical shift of the alcoholic proton peak of compound **6a** was observed to be significantly higher (ca. 1.6 ppm) than that of compound **5a**, which was also found for the five-membered case (ca. 1.2 ppm). These upfield shifts indicate intramolecular hydrogen-bonding, which is consistent with the stereochemistries of compounds **5a** and **6a**.

Finally, the methyl ester groups and oxazoline rings of compounds **3a** and **3b** were hydrolyzed by gentle heating with 3 M HCl to furnish the objective (1*S**,2*R**,3*S**)-2-amino-3-hydroxycyclohexanecarboxylic acid hydrochloride salt (**8a**) and (1*S**,2*R**,3*S**)-2-amino-3-hydroxycyclopentanecarboxylic acid (**8b**), respectively, in 84 and 72% yields. The spectral data of **8b** were identical to those reported quite recently.[15]

Furthermore, we evaluated the one-pot synthesis of oxazolines directly from allylic alcohols, as shown in Scheme 2. The one-pot procedure, which is often executed with trichloroacetonitrile and a catalytic amount of DBU,[18] was also effectively carried out. However, in our case a stoichiometric amount of DBU (1.1–1.3 equiv.) was required to achieve almost complete conjugate addition, as in the stepwise cyclization (Table 2). The allylic alcohol of the six-membered ring **1a** was transformed into oxazoline **3a** with good selectivity (90:10) and in 90% yield in CH_2Cl_2 (entry 1). It was found that the one-pot procedure in THF maintained a high selectivity (98:2), but a relatively low yield (72%) was obtained (entry 2), whereas the conjugate addition during the stepwise procedure was performed with high selectivity and an excellent yield in THF, as shown in Table 1. The allylic alcohol of the five-membered ring **1b** was also transformed into oxazoline **3b** with high selectivity (95:5) and in 92% yield in CH_2Cl_2 (entry 3). In the one-pot procedure, three contiguous stereogenic centers were simultaneously constructed with excellent stereocontrol.



Scheme 2. One-pot synthesis of oxazolines **3a**,**b** from allylic alcohols **1a**,**b**.

Table 2. One-pot synthesis of oxazolines **3a**,**b** from allylic alcohols **1a**,**b**.

Entry	Substrate	Conditions			Product Yield [%][a]	
		DBU [equiv.]	Solvent	Time [h]	**3a** + **4a** (ratio **3**/**4**)	**1a**
1[b]	**1a**	1.3	CH_2Cl_2	42	90 (90:10)[c]	3
2[b]		1.3	THF	62	72 (98:2)[c]	4
					3b + **4b**	**1b**
3	**1b**	1.1	CH_2Cl_2	27	92 (95:5)[d]	1

[a] Isolated yields, however, the yields of **1a** and **1b** were calculated by 270 MHz ^{1}H NMR spectroscopy. [b] A small amount of the intermediary imidate **2a** was detected (ca. 4%) by 270 MHz ^{1}H NMR analysis of the crude products. [c] The isomers were not necessarily fully separated and their ratio was determined by 270 MHz ^{1}H NMR spectroscopy. [d] The product ratio was calculated from the isolated yield of each product.

Conclusions

The intramolecular conjugate addition of trichloroacetimidates to cycloalkenecarboxylates provides a simple and useful method for the stereoselective synthesis of polyfunctionalized carbocycles having a vicinal *cis*-amino alcohol moiety in the cycloalkanecarboxylates, namely (1*S**,2*R**,3*S**)-2-amino-3-hydroxycycloalkanecarboxylic acids and their derivatives. The application of this methodology to other amino alcohol containing compounds is currently underway in our laboratory.

Experimental Section

General Information: All melting points are uncorrected. NMR spectra were recorded with a JEOL GSX-270 spectrometer. ^{1}H and ^{13}C NMR chemical shifts are reported in δ values based on internal tetramethylsilane (δ_H = 0 ppm) or on the solvent signal ($CDCl_3$: δ_C = 77.0 ppm) as reference unless otherwise indicated. IR spectra were recorded with a HORIBA FT-720 Fourier-transform infrared spectrometer. Mass spectra were measured with a Shimadzu LCMS-IT-TOF mass spectrometer. Flash silica gel column chromatography was carried out with Kanto Chemical Co. silica gel 60 (spherical, neutral, 40–50 mm) or Merck Kieselgel 60 (230–400 mesh, Art. Nr. 9385).

Methyl 3-(Trichloroacetimidoyloxy)cyclohex-1-enecarboxylate (2a): DBU (159 μL, 1.07 mmol) was added dropwise to a cooled (bath temp. – 25 °C) solution of the allylic alcohol **1a** (151.3 mg, 0.969 mmol) and trichloroacetonitrile (971 μL, 9.69 mmol) in anhydrous acetonitrile (4.0 mL) and the mixture was stirred for around 25 min under a dry atmosphere (calcium chloride tube). The reaction mixture was poured into cold saturated aq. NH_4Cl and extracted with EtOAc. The extract was washed successively with saturated aq. NH_4Cl and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc = 7:1) to give the trichloroacetimidate **2a** (284.2 mg; 98% yield) as a colorless oil. IR (neat): $\tilde{\nu}_{max}$ = 3342, 2951, 1720, 1662, 1437, 1323, 1265, 1242, 1086, 1001, 796, 650 cm^{-1}. ^{1}H NMR (270 MHz, $CDCl_3$: δ = 8.37 (br. s, 1 H), 6.96

(ddd, J = 1.9, 1.9, 3.7 Hz, 1 H), 5.61–5.50 (m, 1 H), 3.76 (s, 3 H), 2.49–2.19 (m, 2 H), 2.09–1.65 (m, 4 H) ppm. ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 167.3, 162.0 135.0, 134.4, 91.5, 72.6, 51.9, 26.8, 24.2, 18.8 ppm. $C_{10}H_{12}Cl_3NO_3$ (300.57): calcd. C 39.96, H 4.02, N 4.66; found C 39.98, H 4.03, N 4.53.

Methyl (3a*R,4*S**,7a*S**)-2-Trichloromethyl-3a,4,5,6,7,7a-hexahydrobenzo[*d*]oxazole-4-carboxylate (3a) and Methyl (3a*R**,4*R**,7a*S**)-2-Trichloromethyl-3a,4,5,6,7,7a-hexahydrobenzo[*d*]oxazole-4-carboxylate (4a):** DBU (50.9 μL, 0.340 mmol) was added dropwise to a solution of the trichloroacetimidate **2a** (93.0 mg, 0.309 mmol) in anhydrous THF (2.1 mL), and the mixture was stirred for around 8 h under a dry atmosphere (calcium chloride tube). The reaction mixture was poured into saturated aq. NH_4Cl and extracted with EtOAc. The extract was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc = 3:1) to give the oxazolines **3a** (colorless solid, less polar) and **4a** (colorless solid, more polar)(total: 84.7 mg, 91%). Analytical samples of **3a** (colorless powder) and **4a** (colorless powder) were respectively obtained by recrystallization from EtOAc–hexane.

Oxazoline 3a: Colorless powder; m.p. 96.0–97.5 °C. IR (KBr): $\tilde{\nu}_{max}$ = 2954, 1732, 1637, 1433, 1306, 1284, 1248, 1165, 980, 881, 800, 787, 671 cm^{-1}. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 5.01 (ddd, J = 4.9, 4.9, 8.1 Hz, 1 H), 4.56 (dd, J = 6.6, 7.9 Hz, 1 H), 3.74 (s, 3 H), 2.64 (ddd, J = 5.0, 6.6, 8.0 Hz, 1 H), 2.11–1.97 (m, 1 H), 1.95–1.76 (m, 2 H), 1.73–1.51 (m, 3 H) ppm. ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 174.3, 163.5, 87.0, 82.7, 64.8, 52.2, 44.3, 25.5, 23.9, 17.5 ppm. $C_{10}H_{12}Cl_3NO_3$ (300.57): calcd. C 39.96, H 4.02, N 4.66; found C 39.87, H 3.95, N 4.49.

Oxazoline 4a: Colorless powder; m.p. 91.0–92.0 °C. IR (KBr): $\tilde{\nu}$ = 2920, 2848, 1734, 1641, 1473, 1464, 1365, 1217, 1159, 937, 833, 791 cm^{-1}. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 5.14 (ddd, J = 4.7, 4.7, 9.3 Hz, 1 H), 4.76 (ddd, J = 1.1, 4.6, 9.1 Hz, 1 H), 3.76 (s, 3 H), 2.74 (ddd, J = 4.8, 4.8, 12.5 Hz, 1 H), 1.97–1.56 (m, 5 H), 1.52–1.38 (m, 1 H) ppm. ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 172.6, 162.9, 86.8, 82.5, 65.9, 52.0, 40.7, 25.0, 19.1, 16.1 ppm. $C_{10}H_{12}Cl_3NO_3$ (300.57): calcd. C 39.96, H 4.02, N 4.66; found C 39.99, H 3.96, N 4.55.

One-Pot Procedure: DBU (15.0 μL, 0.100 mmol) was added dropwise to an ice-cooled solution of the allylic alcohol **1a** (50.6 mg, 0.324 mmol) and trichloroacetonitrile (50.0 μL, 0.499 mmol) in anhydrous CH_2Cl_2 (2.2 mL) and the mixture was stirred for around 2 h under a dry atmosphere (calcium chloride tube). An additional amount of DBU (40.0 μL, 0.267 mmol) was added to the reaction mixture, which was stirred for around 40 h. During this time, an additional amount of DBU (10.0 μL, 0.0669 mmol) was added (total: 65.0 μL, 0.435 mmol). The reaction mixture was poured into cold saturated aq. NH_4Cl and extracted with EtOAc. The extract was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography to give the oxazolines **3a** and **4a** (total: 87.5 mg, 90%) in the same way as described above.

Methyl (1*S,2*R**,3*S**)-2-Trichloroacetamido-3-hydroxycyclohexanecarboxylate (5a):** A 1 M HCl (2.0 mL) solution was added dropwise to an ice-cooled solution of the oxazoline **3a** (94.2 mg, 0.313 mmol) in THF (7.0 mL) and the mixture was stirred for around 30 min. A 1 M NaOH (1.9 mL) solution and saturated aq. $NaHCO_3$ were successively added to the reaction mixture. The whole mixture was extracted with EtOAc. The extract was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc = 2:1) to give compound **5a** (85.0 mg, 85%) as a colorless solid. An analytical sample (colorless flake) was obtained by recrystallization from EtOAc/hexane; m.p. 113.5–114.5 °C. IR (KBr): $\tilde{\nu}_{max}$ = 3502, 3471, 3303, 2945, 1732, 1695, 1533, 1271, 1252, 1126, 843, 818, 650, 640 cm^{-1}. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 7.14 (br. d, J = 7.7 Hz, 1 H), 4.21–4.12 (m, 1 H), 4.08 (dddd, J = 0.8, 2.7, 8.7, 11.3 Hz, 1 H), 3.67 (s, 3 H), 2.90–2.73 (m, 1 H), 2.05–1.82 (m, 2 H), 1.78 (dd, J = 1.0, 4.0 Hz, 1 H), 1.75–1.52 (m, 4 H) ppm. ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 173.8, 161.3, 92.6, 67.7, 54.4, 52.1, 43.2, 31.9, 27.8, 17.8 ppm. $C_{10}H_{14}Cl_3NO_4$ (318.58): calcd. C 37.70, H 4.43, N 4.40; found C 37.62, H 4.32, N 4.24.

Methyl (1*R,2*R**,3*S**)-2-Trichloroacetamido-3-hydroxycyclohexanecarboxylate (6a) and (1*R**,5*R**,8*R**)-8-Trichloroacetamido-7-oxo-6-oxabicyclo[3.2.1]octane (7a):** A 1 M HCl solution (1.0 mL) was added dropwise to an ice-cooled solution of the oxazoline **4a** (48.2 mg, 0.160 mmol) in THF (3.5 mL) and the mixture was stirred for around 30 min. A 1 M NaOH solution (0.85 mL) and saturated aq. $NaHCO_3$ were successively added to the reaction mixture. The whole mixture was extracted with EtOAc. The extract was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was recrystallized from EtOAc to give the lactone **7a** (2.8 mg, 6.1%) as a colorless powder. The mother liquor was concentrated and purified by flash column chromatography (hexane/EtOAc = 2:1) to give compound **6a** (33.9 mg, 66%) as a colorless oil.

6a: Colorless oil. IR (neat): $\tilde{\nu}_{max}$ = 3491, 3411, 2951, 1712, 1516, 1248, 1219, 1115, 974, 822, 679 cm^{-1}. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 7.95 (br. s, 1 H), 4.11 (ddd, J = 3.2, 5.2, 8.1 Hz, 1 H), 4.06–3.97 (m, 1 H), 3.73 (s, 3 H), 3.33 (d, J = 7.3 Hz, 1 H), 3.12–3.05 (m, 1 H), 2.10–1.97 (m, 1 H), 1.96–1.41 (m, 5 H) ppm. ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 175.3, 161.9, 92.5, 68.1, 52.9, 52.4, 41.6, 31.4, 25.8, 16.3 ppm. $C_{10}H_{14}Cl_3NO_4$ (318.58): calcd. C 37.70, H 4.43, N 4.40; found C 38.08, H 4.45, N 4.23.

7a: Colorless powder; m.p. 229.0–231.0 °C. IR (KBr): $\tilde{\nu}_{max}$ = 3329, 1766, 1707, 1522, 1176, 1161, 1144, 962, 835, 818 cm^{-1}. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 6.94 (br. s, 1 H), 4.82 (dd, J = 1.0, 4.8 Hz, 1 H), 4.09 (d, J = 6.9 Hz, 1 H), 2.83 (br. d, J = 4.7 Hz, 1 H), 2.27–2.04 (m, 2 H), 1.93–1.62 (m, 4 H) ppm. ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 176.0, 162.1, 91.7, 81.0, 60.6, 44.8, 27.8, 26.0, 17.0 ppm. HRMS (ESI-TOF): calcd. for: $C_9H_{10}Cl_3NaNO_3$ [M + Na]$^+$ 307.9624; found 307.9670.

(1*S,2*R**,3*S**)-2-Amino-3-hydroxycyclohexanecarboxylic Acid Hydrochloride (8a):** A 3 M HCl solution (5.0 mL) was added to the oxazoline **3a** (56.3 mg, 0.187 mmol) and the mixture was heated at 75 °C for around 7 h. The whole mixture was concentrated in vacuo. The residue was purified by recrystallization from EtOH/Et_2O to give compound **8a** (30.6 mg, 84%) as colorless plates; m.p. 221–222.3 °C. IR (KBr): $\tilde{\nu}_{max}$ = 3398, 3174, 3043, 2893, 2605, 2495, 1967, 1701, 1595, 1485, 1410, 1242, 1186, 1132, 1053, 985, 849, 631, 534, 498 cm^{-1}. ^{1}H NMR (270 MHz, D_2O, referenced to the residual signal of HOD at δ = 4.65 ppm): δ = 4.08–4.01 (m, 1 H), 3.37 (dd, J = 2.9, 11.2 Hz, 1 H), 2.67 (ddd, J = 4.1, 11.5, 11.5 Hz, 1 H), 2.05–1.93 (m, 1 H), 1.82–1.66 (m, 1 H), 1.56–1.24 (m, 4 H) ppm. ^{13}C NMR (67.8 MHz, D_2O, acetone as internal reference at δ = 30.6 ppm): δ = 177.5, 66.0, 53.7, 41.4, 30.7, 28.0, 18.2 ppm. $C_7H_{14}ClNO_3$ (195.64): calcd. C 42.97, H 7.21, N 7.16; found C 42.64, H 7.15, N 7.07.

Methyl 3-(Trichloroacetimidoyloxy)cyclopent-1-enecarboxylate (2b): DBU (760 μL, 5.08 mmol) was added dropwise to a cooled (bath temp. –40 °C) solution of the allylic alcohol **1b** (657.0 mg, 4.62 mmol) and trichloroacetonitrile (4.63 mL, 46.2 mmol) in anhydrous acetonitrile (18 mL) and the mixture was stirred for around 20 min under a dry atmosphere (calcium chloride tube). The reac-

tion mixture was poured into cold saturated aq. NH_4Cl and extracted with EtOAc. The extract was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc = 5:1) to give the trichloroacetimidate **2b** (1.052 g; 79% yield) as a colorless solid. An analytical sample (colorless powder) was obtained by recrystallization from hexane; m.p. 47.5–50.0 °C. IR (KBr): $\tilde{\nu}_{max}$ = 3303, 2954, 1711, 1668, 1439, 1288, 1242, 1076, 1028, 991, 796, 646 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): δ = 8.34 (br. s, 1 H), 6.82 (ddd, J = 2.1, 2.1, 4.1 Hz, 1 H), 5.97–5.88 (m, 1 H), 3.78 (s, 3 H), 2.89–2.73 (m, 1 H), 2.67–2.44 (m, 2 H), 2.17–2.01 (m, 1 H) ppm. ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 165.1, 162.1, 141.7, 138.0, 91.4, 84.1, 51.8, 30.1, 29.6 ppm. $C_9H_{10}Cl_3NO_3$ (286.54): calcd. C 37.72, H 3.52, N 4.89; found C 37.53, H 3.45, N 4.83.

Methyl (3a*R,4*S**,6a*S**)-2-Trichloromethyl-4,5,6,6a-tetrahydro-3a*H*-cyclopenta[*d*]oxazole-4-carboxylate (3b) and Methyl (3a*R**,4*R**,6a*S**)-2-Trichloromethyl-4,5,6,6a-tetrahydro-3a*H*-cyclopenta[*d*]-oxazole-4-carboxylate (4b):** DBU (59.0 μL, 0.395 mmol) was added dropwise to a solution of the trichloroacetimidate **2b** (101.7 mg, 0.355 mmol) in anhydrous CH_2Cl_2 (14.0 mL) at room temp. and the mixture was stirred for around 24 h under a dry atmosphere (calcium chloride tube). The reaction mixture was poured into saturated aq. NH_4Cl and extracted with EtOAc. The extract was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc = 3:1) to give the oxazolines **3b** (colorless solid, 83.4 mg, 82%, less polar) and **4b** (colorless solid, 4.7 mg, 4.6%, more polar). Analytical samples of **3b** (colorless powder) and **4b** (colorless needles) were obtained by recrystallization from EtOAc/hexane.

Oxazoline 3b: Colorless powder; m.p. 51.5–52.5 °C. IR (KBr): $\tilde{\nu}_{max}$ = 2976, 2951, 1728, 1653, 1433, 1362, 1329, 1238, 1207, 1196, 1176, 1167, 999, 872, 812, 800, 681 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): δ = 5.39 (ddd, J = 1.7, 5.3, 7.5 Hz, 1 H), 5.04 (dd, J = 1.3, 7.5 Hz, 1 H), 3.71 (s, 3 H), 3.16–3.09 (m, 1 H), 2.19–1.79 (m, 4 H) ppm. ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 173.8, 163.2, 89.0, 86.3, 74.5, 52.2, 50.3, 32.7, 26.6 ppm. $C_9H_{10}Cl_3NO_3$ (286.54): calcd. C 37.72, H 3.52, N 4.89; found C 37.69, H 3.52, N 4.85.

Oxazoline 4b: Colorless needles; m.p. 128.0–128.5 °C. IR (KBr): $\tilde{\nu}_{max}$ = 2983, 2947, 1734, 1653, 1437, 1250, 1201, 995, 945, 850, 783, 658 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): δ = 5.35 (ddd, J = 1.5, 5.6, 7.2 Hz, 1 H), 5.00 (dd, J = 7.6, 7.6 Hz, 1 H), 3.75 (s, 3 H), 3.00 (ddd, J = 7.9, 7.9, 10.3 Hz, 1 H), 2.30–2.20 (m, 1 H), 2.00–1.70 (m, 3 H) ppm. ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 170.9, 163.5, 88.4, 86.2, 73.3, 52.0, 50.1, 33.1, 24.3 ppm. $C_9H_{10}Cl_3NO_3$ (286.54): calcd. C 37.72, H 3.52, N 4.89; found C 37.62, H 3.45, N 4.86.

One-Pot Procedure: DBU (18.6 μL, 0.124 mmol) was added dropwise to an ice-cooled solution of the allylic alcohol **1b** (58.3 mg, 0.410 mmol) and trichloroacetonitrile (62.0 μL, 0.618 mmol) in anhydrous CH_2Cl_2 (2.7 mL) and the mixture was stirred for around 17 h under a dry atmosphere (calcium chloride tube). An additional amount of DBU (49.0 μL, 0.328 mmol) was added to the reaction mixture, which was stirred for around 9 h. The reaction mixture was poured into cold saturated aq. NH_4Cl and extracted with EtOAc. The extract was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography to give the oxazolines **3b** (102.8 mg, 87%) and **4b** (5.7 mg, 4.9%) in the same way as described above.

Methyl (1*S,2*R**,3*S**)-2-Trichloroacetamido-3-hydroxycyclopentanecarboxylate (5b):** A 1 M HCl solution (1.4 mL) was added dropwise to an ice-cooled solution of the oxazoline **3b** (64.4 mg, 0.225 mmol) in THF (5.0 mL) and the mixture was stirred for around 30 min. A 1 M NaOH solution (1.3 mL) and saturated aq. $NaHCO_3$ were successively added to the reaction mixture. The whole mixture was extracted with EtOAc. The extract was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc = 1:1) to give compound **5b** (67.2 mg, 98%) as a colorless solid. An analytical sample (colorless powder) was obtained by recrystallization from EtOAc/hexane; m.p. 74.5–76.0 °C. IR (KBr): $\tilde{\nu}_{max}$ = 3496, 3323, 2956, 1736, 1697, 1522, 1431, 1365, 1223, 1165, 1053, 835, 820, 640 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): δ = 7.36 (br. d, J = 4.1 Hz, 1 H), 4.46–4.37 (m, 1 H), 4.28 (ddd, J = 4.6, 7.7, 9.5 Hz, 1 H), 3.71 (s, 3 H), 2.91 (ddd, J = 8.2, 9.2, 9.2 Hz, 1 H), 2.27–1.91 (m, 3 H), 2.00 (d, J = 3.6 Hz, 1 H), 1.88–1.73 (m, 1 H) ppm. ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 174.5, 161.8, 92.5, 72.7, 58.9, 52.3, 46.9, 32.4, 24.7 ppm. $C_9H_{12}Cl_3NO_4$ (304.55): calcd. C 35.49, H 3.97, N 4.60; found C 35.42, H 3.92, N 4.59.

Methyl (1*R,2*R**,3*S**)-2-Trichloroacetamido-3-hydroxycyclopentanecarboxylate (6b):** A 1 M HCl (1.4 mL) was added dropwise to an ice-cooled solution of the oxazoline **4b** (62.4 mg, 0.218 mmol) in THF (5.0 mL) and the mixture was stirred for around 30 min. A 1 M NaOH solution (1.3 mL) and saturated aq. $NaHCO_3$ were successively added to the reaction mixture. The whole mixture was extracted with EtOAc. The extract was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc = 1:1) to give compound **6b** (54.8 mg, 83%) as a colorless solid. An analytical sample (colorless powder) was obtained by triturating in cold EtOAc/hexane; m.p. 36.0–36.5 °C. IR (KBr): $\tilde{\nu}_{max}$ = 3365, 3236, 2951, 1711, 1520, 1441, 1375, 1227, 1209, 1173, 1003, 843, 823 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): δ = 7.70 (br. s, 1 H), 4.30–4.14 (m, 2 H), 3.71 (s, 3 H), 3.48–3.38 (m, 1 H), 3.23 (d, J = 9.8 Hz, 1 H), 2.30–1.92 (m, 4 H) ppm. ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 176.9, 161.9, 92.3, 72.8, 56.7, 52.6, 44.7, 32.7, 26.0 ppm. $C_9H_{12}Cl_3NO_4$ (304.55): calcd. C 35.49, H 3.97, N 4.60; found C 35.48, H 3.93, N 4.53.

(1*S,2*R**,3*S**)-2-Amino-3-hydroxycyclopentanecarboxylic Acid (8b):** A 3 M HCl solution (8.0 mL) was added to the oxazoline **3b** (86.4 mg, 0.302 mmol) and the mixture was heated at 75 °C for around 7 h. The whole mixture was concentrated in vacuo. The obtained crude oily hydrochloride [^1H NMR (270 MHz, D_2O, referenced to the residual signal of HOD at δ = 4.65 ppm): δ = 4.23 (ddd, J = 2.5, 4.8, 4.8 Hz, 1 H), 3.64 (dd, J = 4.7, 9.4 Hz, 1 H), 2.95 (ddd, J = 8.1, 9.8, 9.8 Hz, 1 H), 2.24–2.06 (m, 1 H), 2.00–1.85 (m, 1 H), 1.82–1.59 (m, 2 H) ppm] was treated with 1 M NH_3 and concentrated in vacuo. The residual free amino acid was purified by recrystallization from H_2O/acetone to give compound **8b** (31.7 mg, 72%) as colorless needles; m.p. 231–235 °C (dec.). IR (KBr): $\tilde{\nu}_{max}$ = 3103, 2954, 2696, 2617, 2557, 1630, 1577, 1533, 1406, 1338, 1279, 1049, 970, 781, 717, 584, 453 cm^{-1}. ^1H NMR (270 MHz, D_2O, 30 °C, referenced to the residual signal of HOD at δ = 4.65 ppm): δ = 4.28 (ddd, J = 2.7, 5.2, 5.2 Hz, 1 H), 3.57 (dd, J = 5.0, 9.5 Hz, 1 H), 2.76 (ddd, J = 9.2, 9.2, 9.2 Hz, 1 H), 2.25–1.93 (m, 2 H), 1.76–1.57 (m, 2 H) ppm. ^{13}C NMR (67.8 MHz, D_2O, 30 °C, acetone as internal reference at δ = 30.6 ppm): δ = 181.3, 71.3, 57.6, 48.2, 31.4, 25.8 ppm. HRMS (ESI-TOF): calcd. for $C_6H_{12}NO_3$ $[M + H]^+$ 146.08172; found 146.0781.

Supporting Information (see footnote on the first page of this article): Copies of ^1H and ^{13}C NMR spectra.

Acknowledgments

This work was supported by the Ministry of Education, Culture, Sports, Science and Technology of Japan (17780089, Grant-in-Aid

for Scientific Research) and the 21st Century COE Program (Hamamatsu University School of Medicine, Medical Photonics). We are grateful to Ms. N. Goto-Inoue of the Department of Molecular Anatomy for her measurement of high-resolution mass spectra. The authors also thank the technical staffs (Ms. M. Suzuki and Ms. M. Toyama) for their support.

[1] F. Fülöp, *Chem. Rev.* **2001**, *101*, 2181–2204.
[2] M. Palkó, L. Kiss, F. Fülöp, *Curr. Med. Chem.* **2005**, *12*, 3063–3083.
[3] a) M. Konishi, M. Nishio, K. Saitoh, T. Miyaki, T. Oki, H. Kawaguchi, *J. Antibiot.* **1989**, *42*, 1749–1755; b) T. Oki, M. Hirano, K. Tomatsu, K. Numata, H. Kamei, *J. Antibiot.* **1989**, *42*, 1756–1762; c) T. Iwamoto, E. Tsujii, M. Ezaki, A. Fujie, S. Hashimoto, M. Okuhara, M. Kohsaka, H. Imanaka, K. Kawabata, Y. Inamoto, K. Sakane, *J. Antibiot.* **1990**, *43*, 1–7; d) K. Kawabata, Y. Inamoto, K. Sakane, T. Iwamoto, S. Hashimoto, *J. Antibiot.* **1990**, *43*, 513–518.
[4] For the most recent paper on helical secondary structures of α/β-peptides containing β-residues derived from ACPC, see: S. H. Choi, I. A. Guzei, L. C. Spencer, S. H. Gellman, *J. Am. Chem. Soc.* **2008**, *130*, 6544–6550. 12-Helical β-peptides that incorporate 3-methoxy- or 3-phenoxy-substituted ACPC residues have also been reported, see: M. G. Woll, J. D. Fish, P. R. LePlae, S. H. Gellman, *J. Am. Chem. Soc.* **2002**, *124*, 12447–12452.
[5] For the most recent paper on helical secondary structures of β-peptides containing residues derived from ACHC, see: M. Lee, T. L. Raguse, M. Schinneri, W. C. Pomerantz, X. Wang, P. Wipf, S. H. Gellman, *Org. Lett.* **2007**, *9*, 1801–1804.
[6] M. Liu, M. P. Sibi, *Tetrahedron* **2002**, *58*, 7991–8035.
[7] Z. Szakonyi, S. Gyónfalvi, E. Forró, A. Hetényi, N. De Kimpe, F. Fülöp, *Eur. J. Org. Chem.* **2005**, 4017–4023.
[8] F. Fülöp, M. Palkó, E. Forró, M. Dervarics, T. A. Martinek, R. Sillanpää, *Eur. J. Org. Chem.* **2005**, 3214–3220.
[9] a) L. Kiss, E. Forró, T. A. Martinek, G. Bernáth, N. De Kimpe, F. Fülöp, *Tetrahedron* **2008**, *64*, 5036–5048; b) L. Kiss, E. Forró, F. Fülöp, *Tetrahedron Lett.* **2006**, *47*, 2855–2858.
[10] P. Wip, X. Wang, *Tetrahedron Lett.* **2000**, *41*, 8748–8751.
[11] E. Couché, R. Deschatrettes, K. Poumellec, M. Bortolussi, G. Mandville, R. Bloch, *Synlett* **1999**, 87–89.
[12] a) I. B. Masesane, A. S. Batsanov, J. A. K. Howard, R. Mondal, P. G. Steel, *Beilstein J. Org. Chem.* **2006**, *2*, 1–6; b) I. B. Masesane, P. G. Steel, *Tetrahedron Lett.* **2004**, *45*, 5007–5009.
[13] L. Kiss, E. Forró, R. Sillanpää, F. Fülöp, *J. Org. Chem.* **2007**, *72*, 8086–8790.
[14] L. Kiss, B. Kazi, E. Forró, F. Fülöp, *Tetrahedron Lett.* **2008**, *49*, 339–342.
[15] G. Benedek, M. Palkó, E. Wéber, T. A. Martinek, E. Forró, F. Fülöp, *Eur. J. Org. Chem.* **2008**, 3724–3730.
[16] Y. Matsushima, J. Kino, *Tetrahedron Lett.* **2005**, *46*, 8609–8612.
[17] Y. Matsushima, J. Kino, *Tetrahedron Lett.* **2006**, *47*, 8777–8780.
[18] Intramolecular conjugate addition reactions of trichloroacetimidates to an α,β-unsaturated ester in a carbocyclic system has never been reported. Two examples of such an addition in a heterocyclic system have been reported. For intramolecular conjugate addition to α,β-unsaturated nitriles, see: a) B. Fraser-Reid, C. S. Burgey, R. Vollerthum, *Pure Appl. Chem.* **1998**, *70*, 285–288; b) R. Alonso, C. S. Burgey, B. V. Rao, G. D. Vite, R. Vollerthum, M. A. Zottola, B. Fraser-Reid, *J. Am. Chem. Soc.* **1993**, *115*, 6666–6672. For intramolecular conjugate addition to α,β-unsaturated diphenyl esters, see: c) J. R. Brown, Y. Nishimura, J. D. Esko, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 532–536; d) Y. Nishimura, T. Sato, H. Adachi, S. Kondo, T. Takeuchi, M. Azetaka, H. Fukuyasu, Y. Iizuka, *J. Med. Chem.* **1997**, *40*, 2626–2633; e) Y. Nishimura, T. Sato, H. Adachi, S. Kondo, T. Takeuchi, M. Azetaka, H. Fukuyasu, Y. Iizuka, *J. Am. Chem. Soc.* **1996**, *118*, 3051–3052. For an example of intramolecular conjugate addition to α,β-unsaturated sulfones in a carbocyclic system, see: f) X. C. Li, P. L. Fuchs, *Synlett* **1994**, 629–630.
[19] Some useful reactions involving trichloroacetimidates for the introduction of nitrogen functionalities have been reported. For electrophile-promoted intramolecular aminations of trichloroacetimidates derived from allylic and homoallylic alcohols, see: a) H.-S. Lee, S. H. Kang, *Synlett* **2004**, 1673–1685, and references therein. For acid-promoted intramolecular epoxide-opening of trichloroacetimidates, see: b) B. Bernet, A. Vasella, *Tetrahedron Lett.* **1983**, *24*, 5491–5494; c) U. Schmidt, M. Respondek, A. Lieberknecht, J. Werner, O. Fischer, *Synthesis* **1989**, 256–261; d) S. Hatakeyama, H. Matsumoto, H. Fukuyama, Y. Mukugin, H. Irie, *J. Org. Chem.* **1997**, *62*, 2275–2279; e) Y. Matsushima, T. Nakayama, S. Tohyama, T. Eguchi, K. Kakinuma, *J. Chem. Soc. Perkin Trans. 1* **2001**, 569–577; f) C. Rondot, P. Retailleau, J. Zhu, *Org. Lett.* **2007**, *9*, 247–250, and references therein. For the Overman rearrangement, see: g) L. E. Overman, *Acc. Chem. Res.* **1980**, *13*, 218–224.
[20] Y. Matsushima, J. Kino, *Tetrahedron* **2008**, *64*, 3943–3952.
[21] The known starting allylic alcohols **1a** and **1b** were respectively prepared from the corresponding methyl cycloalk-1-enecarboxylates according to the following literature methods. Allylic oxidation: A. J. Catino, R. E. Forslund, M. P. Doyle, *J. Am. Chem. Soc.* **2004**, *126*, 13622–13623; 1,2-reduction: for **1a**: M.-E. Theoclitou, P. J. Duggan, C. Abell, *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1285–1288; for **1b**: L. Fonteneau, S. Rosa, D. Buisson, *Tetrahedron: Asymmetry* **2002**, *13*, 579–585.
[22] B. Yu, H. Yu, Y. Hui, X. Han, *Synlett* **1999**, 753–755.
[23] The irradiation of 1-H of compound **6a** yielded an NOE of around 8% on 2-H and around 1% on 3-H, whereas a small NOE (ca. 1%) was observed on the NH proton. In contrast, irradiation of the hydrogen corresponding to compound **5a** yielded an NOE of around 4% on the NH proton, whereas no NOE was observed on 2-H and 3-H. Irradiation of 1-H of compound **6b** yielded an NOE of around 8% on 2-H and 3-H, whereas almost no NOE was observed on the NH proton. In contrast, irradiation of the hydrogen corresponding to compound **5b** yielded an NOE of around 4% on the NH proton, whereas no NOE was observed on 2-H and 3-H.

Received: November 26, 2008
Published Online: March 4, 2009

