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Synthesis of β-chloro α-amino acids: (2*S*,3*R*)- and (2*S*,3*S*)-3-chloroleucine

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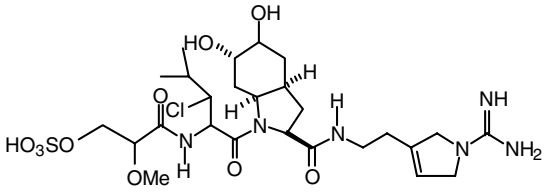
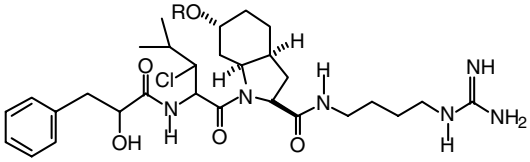
Abstract—The first syntheses of (2*S*,3*R*)- and (2*S*,3*S*)-3-chloroleucine (3-chloro-D-leucines **1** and **2**) have been achieved from D-3-hydroxyleucine and *allo*-D-3-hydroxyleucine, respectively, through the formation of the corresponding N-Cbz β-lactones, followed by a ring opening promoted by lithium chloride and a debenzylation process.

3-Chloroleucine is a novel α-amino acid, which appears in the peptide chain of a protease inhibitor of the coagulation cascade, isolated from *Dysidea* sp. sponges by a group of Pharmacia scientists[1,2] (Fig. 1). Although the configuration of this new α-amino acid has not yet been established, we have addressed our efforts to the synthesis of the two epimers of 3-chloro-D-leucine (D-Cleu), since the α-amino acid linked to the nitrogen atom of the octahydroindole core amino acid is always D in the pharmacologically and structurally related natural products of aeruginosins[3] and dysinosins,[4] isolated from cyanobacteria. Moreover, the synthesis of these new α-amino acids is of interest since we suspect that the D-Cleu residue is also present in the glycopeptides aeruginosins 205.[5] In order to test this hypothesis in our ongoing studies on the total synthesis of aeruginosins,[6] we would need to incorporate D-Cleu in the synthetic sequence devoted to the coupling of the four fragments of the aglycon part of aeruginosins 205.

In this letter, we describe the first preparation of 3-chloroleucine derivatives by chlorine-promoted ring opening of enantiopure N-protected leucine β-lactones. This type of protocol in which α-amino-β-lactones become precursors of β-substituted α-amino acids by nucleophilic ring opening (Scheme 1), is well precedented,[7,8] but it has not been applied to the synthesis of β-substituted leucine derivatives. The required attack of the nucleophile at the hindered β-position of the β-substituted β-lactones was expected to be difficult, as observed in threonine β-lactones,[9] in contrast to the facile ring opening at the methylene of the serine-derived β-lactones.[10–15]

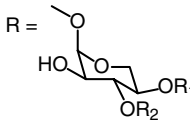


Mgs-Cleu-Cdhoi-Aaep (ref 1)



Plas-Cleu-Choi-Agma; tentative structure for aeruginosins 205

Plas-Hleu-Ccoi-Agma; proposed structure (ref 5)



Aeruginosin 205-A : L-Plas, (2*R*,3*S*)-HLeu; $R_1 = SO_3H$, $R_2 = H$

Aeruginosin 205-B : D-Plas, (2*S*,3*R*)-HLeu; $R_1 = H$, $R_2 = SO_3H$

Figure 1.

The required enantiopure N-protected α-amino-β-lactones can be prepared from β-hydroxy-α-amino acids.[16]

Keywords: β-Chloro α-amino acids; β-Lactones; 3-Chloroleucine; Ring opening; Aeruginosins.
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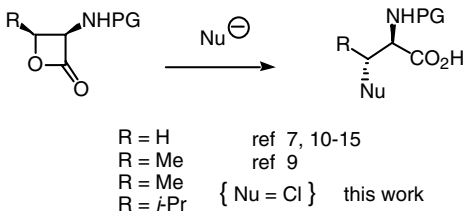


Scheme 1.

Although serine β-lactones are readily obtained by cyclization of N-protected serine derivatives under Mitsunobu conditions,[7,17]such hydroxyl group activation of the corresponding β-substituted analogues, for instance threonine derivatives, leads to a rapid stereospecific decarboxylative elimination.[9a,18] To circumvent this problem,[19] BOP reagent is used for the formation of serine and threonine β-lactones[20–24] through carboxyl activation. Recently, HBTU has been reported as a very efficient activating agent for this type of lactonization process.[12c]

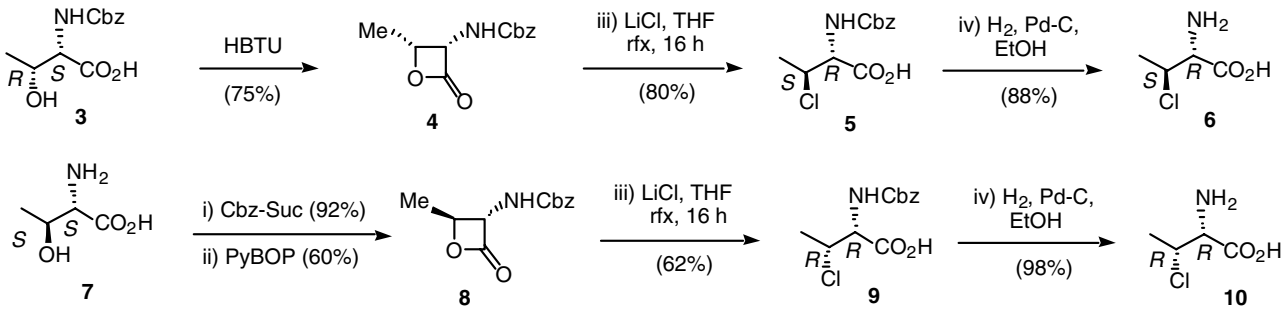
In a first series of experiments to test the β-lactone opening with the chloride anion, which is the crucial step for the synthesis of β-chloroleucines, we evaluated the ring opening using β-lactones derived from threonine as model compounds (Scheme 2).[25] Intramolecular coupling of *N*-Cbz-L-Thr (**3**) was carried out with HBTU, which proved to be a better activating agent than PyBOP for this lactonization, giving β-lactone **4** in 75% yield.[26] Treatment of **4** with LiCl at THF reflux temperature overnight gave the enantiopure chloride **5**,[27] which after hydrogenolytic cleavage of the carbamate protecting group allowed the isolation of 3-chlorothreonine **6**.[28]

N-Cbz-L-*allo*-Threonine-β-lactone (**8**) was prepared according to the protocol reported by Vederas for the synthesis of its enantiomer *ent*-**8**, but by using PyBOP instead of BOP for the lactonization process. Following the same two-step sequence as above, lactone **8** was transformed to 3-chlorothreonine **10**,[29] via its *N*-benzyloxycarbonyl derivative **9**.[27]

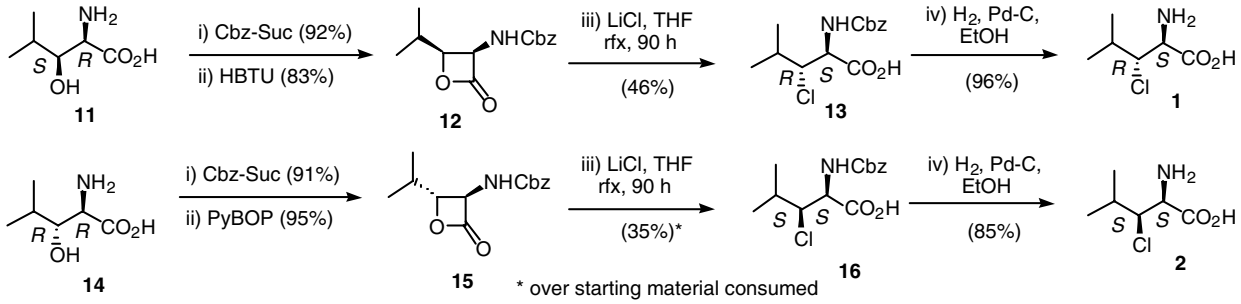
The successful lactonization of the threonine derivatives and their chloride-promoted ring opening to 3-chlorothreonines prompted us to extend this methodology to the synthesis of leucine compounds **1** and **2**. β-Lactonization[30] of (2*R*,3*S*)-hydroxyleucine (**11**) was carried out with HBTU from its corresponding Cbz derivative to afford **12** in 83% yield. As expected, the ring opening of isopropyl substituted lactone **12** required longer reaction times than those used in the methyl series to give the chloro derivative **13**, which was isolated in 46% yield. Removing the carbamate protecting group by hydrogenolysis afforded α-amino acid *anti*-(2*S*,3*R*)-(-)-**1**, which constitutes its first synthesis.[31]

We next decided to prepare the (2*S*,3*S*)-3-chloroleucine by following the same protocol. The required starting material, (2*R*,3*R*)-3-hydroxyleucine (**14**), was prepared according to the Hamada procedure[32] from 3-hydroxyleucine **11**, which was transformed into the methyl ester of the *N*-benzoyl derivative and then epimerized through an oxazoline intermediate. The β-lactone closure from the Cbz derivative of **14** was easy, even when using PyBOP, while the ring opening of **15** was as sluggish as in leucine derivative **12**. The yield in this stereocontrolled ring opening of β-lactone (**15** → **16**) was worse (20% yield, 35% based on recovered starting material) than in **12**, as occurs in the threonine series, in which the *allo* epimer also undergoes the opening in lower yield than **4**. Finally, deprotection of **16** produced *syn*-(2*S*,3*S*)-**2**.[33]

The stereoselective β-chloro-α-amino acid formation agrees with the stereochemical outcome observed in the related β-lactone formation and its ring opening, implying a stereochemical inversion in the second step. (As indicated in Schemes 2 and 3, the configuration at C(2) of the new amino acids is retained from the starting threonines and leucines, but the descriptor of its nomenclature changes due to different prelation rules of the substituents.) The stereochemistry of the β-lactones and β-chloro-α-amino acids synthesized was confirmed by 2D NMR spectra (COSY, HSQC, NOESY). Two NMR features clearly distinguished the cis (**4** and **12**) and trans (**8** and **15**) lactones: the chemical shift of H-3, which is more deshielded in the cis than in the trans isomers, and the chemical shift of C-3, which appears upfielded in the cis isomers as compared with the trans counterparts. The most significant differences in the ^{1}H NMR data of β-chloro-α-amino acids that can be used to diagnose the stereochemistry are the chemical shifts of H-3 in the Cbz derivatives, which appear at a higher field (upfielded ~0.35 ppm) in *anti* derivatives **5** and **13** than those observed in *syn* compounds **9** and **16**. For



Scheme 2. Synthesis of 3-chloro-L-threonines **6** and **10**.



Scheme 3. Synthesis of 3-chloro-D-leucines **1** and **2**.

Table 1. ^{1}H (400 MHz) and ^{13}C (75 MHz) NMR data (D_2O) for β-chloro α-amino acids **1**, **2**, **6** and **10**

	6 (L-Thr)		**10** (L-*allo*-Thr)		**1** (D-Cleu)		**2** (D-*allo*-Cleu)	
	δ_C	δ_H *J* (Hz)	δ_C	δ_H *J* (Hz)	δ_C	δ_H *J* (Hz)	δ_C	δ_H *J* (Hz)
C-1	170.0		170.9		169.6		172.3	
H-2	60.1	4.11 (d, 2.1)	60.0	4.13 (br s)	56.9	4.47 (d, 2.8)	58.0	4.19 (d, 3.6)
H-3	55.3	4.69 (qd) (6.9, 2.1)	55.8	4.79 (masked)	67.3	4.09 (dd) (9.5, 2.8)	68.4	4.30 (dd) (9.2, 3.6)
H-4	19.4	1.61 (d, 6.9)	21.6	1.67 (d, 6.8)	32.2	2.31 (dhept) (9.5, 6.5)	32.7	2.01 (dhept) (9.2, 6.3)
H-5					20.3	1.14 (d, 6.6)	20.0	1.14 (d, 6.4)
H-5′					19.6	1.12 (d, 6.6)	19.8	1.07 (d, 6.4)

NMR data of β-chloro α-amino acids reported in this work, see Table 1.

In summary, we report the first synthesis of β-chloroleucine[34] derivatives consisting of chlorine promoted ring opening of hydroxyleucine β-lactones. These new α-amino acids could enable us to develop a synthetic approach devoted to peptides incorporating 3-chloroleucine.

Acknowledgements

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26. Analytical and spectroscopic data for β-lactones (NMR data are recorded in $CDCl_3$ at 300 and 75 MHz and the assignments were aided by gCOSY, DEPT and gHSQC experiments). Compound **4**: mp 117–118 °C; $[\alpha]_D^{20}$ +17.2 (*c* 1.03, $CHCl_3$); IR (KBr): 3286, 1827, 1694 cm^{-1}; ^1H NMR 1.42 (d, $J = 6.2$ Hz, Me), 4.83 (dq, $J = 6.2$, 6.0 Hz, H-4), 5.13 (s, CH_2), 5.45 (dd, $J = 8.5$, 6 Hz, H-3), 5.78 (d, $J = 8.2$ Hz, NH), 7 (ArH); ^{13}C NMR 14.9 (Me), 60.3 (C3), 67.8 (CH_2), 74.8 (C4), 128.2, 128.5, 128.6, 135.5 (Ar), 155.4 (CO), 168.8 (C2). Compound **8**: mp 114–115 °C; $[\alpha]_D^{20}$ −40.3 (*c* 0.75, $CHCl_3$); IR (KBr): 3313, 1847, 1833, 1699 cm^{-1}; ^1H NMR 1.60 (d, $J = 6.0$ Hz, Me), 4.62 (dd, $J = 7.5$, 4.2 Hz, H-3), 4.75 (m, H-4), 5.13 (s, CH_2), 5.55 (d, $J = 6.3$ Hz, NH), 7.35 (ArH); ^{13}C NMR 18.8 (Me), 64.3 (C3), 67.7 (CH_2), 77.2 (C4), 128.3, 128.5, 128.6, 135.5 (Ar), 155.2 (CO), 167.7 (C2). Compound **12**: mp 79–80 °C; $[\alpha]_D^{20}$ −12.8 (*c* 1.01, $CHCl_3$); IR (KBr): 3326, 1830, 1701 cm^{-1}; ^1H NMR (400 MHz, NOESY): 0.86 (d, $J = 6.4$ Hz, Me), 1.05 (d, $J = 6.8$ Hz, Me), 1.88 (m, 1H, CH), 4.20 (dd, $J = 10.4$, 6.0 Hz, H-4), 5.13 (s, 2H, CH_2), 5.50 (dd, $J = 9.2$, 6.0 Hz, H-3), 5.78 (d, $J = 9.2$ Hz, NH), 7.35 (m, ArH); ^{13}C NMR 17.2 (Me), 18.4 (Me), 28.6 (CH), 59.5 (C3), 67.8 (CH_2), 82.7 (C4), 128.2, 128.4, 128.6, 135.5 (Ar), 155.3 (CO), 169.3 (C2). Compound **15**: mp 85–86 °C; $[\alpha]_D^{20}$ +27.2 (*c* 1.14, $CHCl_3$); IR (KBr): 3328, 1839, 1693 cm^{-1}; ^1H NMR 0.98 and 1.03 (2d, $J = 6.6$Hz, 2 × Me), 1.92 (m, CH), 4.29 (dd, $J = 8.5$, 4.3 Hz, H-4), 4.71 (dd, $J = 8.5$, 4.3 Hz, H-3), 5.09 (s, CH_2), 5.99 (br s, NH), 7.32 (ArH); ^{13}C NMR 16.9 (Me), 18.2 (Me), 31.8 (CH), 61.7 (C3), 67.9 (CH_2), 84.6 (C4), 128.5, 128.7, 128.8, 135.8 (Ar), 155.6 (CO), 168.8 (C2). All new compounds were characterized by HRMS or microanalysis.
27. For NMR data of *N*-Cbz-3-chlorothreonines, see: (2*R*,3*S*) isomer **5**, mp 116–118 °C; $[\alpha]_D^{20}$ +3.2 (*c* 1.02, CH_3OH); ^1H NMR (200 MHz, $CDCl_3$, gCOSY) 1.63 (d, $J = 7$ Hz, H-4), 4.37 (dq, $J = 7$, 3.1 Hz, H-3), 4.59 (d, $J = 3.1$ Hz, H-2), 5.12 (s, CH_2), 5.76 (d, $J = 8.4$ Hz, NH), 7.35 (ArH); ^{13}C NMR (75 MHz, $CDCl_3$) 21.3 (C4), 57.7 (C3), 59.3 (C2), 67.2 (CH_2), 128.0, 128.2, 128.4, 136.0 (Ar), 156.0 (NCO), 170.3 (C1). (2*R*,3*R*) isomer **9**, $[\alpha]_D^{20}$ +12.0 (*c* 1.7, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, gCOSY) 1.53 (d, $J = 6.8$ Hz, H-4), 4.88 (m, H-2 and H-3) [4.62 (dd, $J = 3.1$ Hz, H-2), 4.71 (dq, $J = 6.8$, 3.1 Hz, H-3) in CD_3OD], 5.16 (s, CH_2), 5.76 (d, $J = 9.3$ Hz, NH), 7.38 (s, ArH); ^{13}C NMR (75 MHz, $CDCl_3$, gHSQC) 22.0 (C4), 57.8 (C2), 59.1 (C3), 67.6 (CH_2), 128.0, 128.3, 128.5, 135.7 (Ar), 156.8 (NCO), 173.6 (C1).
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29. (2*R*,3*R*)-β-Chlorothreonine (**10**) has been reported by treatment of L-threonine with $SOCl_2$ in dioxane solution: Yamashita, K.; Inoue, K.; Kinoshita, K.; Ueda, Y.; Murao, H. PCT WO 9933785. The methyl esters of (2*R*,3*R*)- and (2*S*,3*S*)-2-amino-3-chlorobutanoic hydrochloride have been obtained from L- and D-allothreonine, respectively, by treatment with PCl_5: Plattner, Pl. A.; Boller, A.; Frick, H.; Fürst, A.; Hegedüs, B.; Kirchensteiner, H.; Majnoni, St.; Schläpfer, R.; Spiegelberg, H. *Helv. Chim. Acta* **1957**, *40*, 1531–1552; For related work in the racemic series, see: Srinivasan, A.; Stephenson, R. W.; Olsen, R. K. *J. Org. Chem.* **1977**, *42*, 2256–2260.
30. To our knowledge there is only one precedent of β-lactonization of 3-hydroxyleucine derivatives in the literature, involving the (2*S*,3*S*)-*N*,*N*-dibenzyl derivative: Laib, T.; Chastanet, J.; Zhu, J. *J. Am. Chem. Soc.* **2002**, *124*, 583–590.
31. Experimental procedure for **1**: *N*-Benzyloxycarbonyloxy-succinimide (539 mg, 2.16 mmol) and $NaHCO_3$ (378 mg, 4.50 mmol) were added to a solution of **11** (Acros, 265 mg, 1.80 mmol) in H_2O/THF 2:1 (6 mL). After stirring for 16 h at room temperature, the reaction mixture was extracted with Et_2O (3 × 5 mL) and the aqueous layer was acidified until pH 2 and extracted with EtOAc (4 × 15 mL). The combined organic phases were washed with 1 N HCl (2 × 30 mL) and brine (2 × 30 mL), dried with Na_2SO_4 and concentrated to afford the Cbz derivative (464 mg, 92%) as a colourless oil: $[\alpha]_D^{20}$ +3.9 (c 1.07, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, COSY): 0.89 (d, $J = 6.8$ Hz, 3H, H-5), 0.96 (d, $J = 6.8$ Hz, 3H, H-5′), 1.71 (m, H-4), 3.76 (d, $J = 9.2$ Hz, H-3), 4.55 (d, $J = 9.6$ Hz, H-2), 5.09 (s, OCH_2Ph), 6.10 (d, $J = 9.6$ Hz, NH), 7.31 (m, 5H; ArH); ^{13}C NMR (75 MHz, $CDCl_3$, HSQC): 18.8 (C-

5), 19.1 (C-5′), 30.7 (C-4), 56.3 (C-2), 67.2 (OCH_2Ph), 76.6 (C-3), 127.9 (*p*-C), 128.0 (*o*-C), 128.4 (*m*-C), 136.0 (*ipso*-Ar), 157.1 (NCO), 175.6 (C-1). A solution of the above acid (385 mg, 1.37 mmol) in CH_2Cl_2 (10 mL) was cooled to 0 °C and treated with Et_3N (954 μL, 6.85 mmol). The solution was transferred to a suspension of HBTU (975 mg, 2.57 mmol) in CH_2Cl_2 (5 mL). The cooling bath was removed and the resulting solution was stirred at room temperature for 16 h. The solution was diluted with CH_2Cl_2 (15 mL) and washed with brine (3 × 20 mL). The organic layer was dried with Na_2SO_4 and concentrated to give a residue, which was purified by column chromatography (SiO_2, hexane/EtOAc 3:1) to give **12** (375 mg, 83%) as a white solid: R_f 0.63 (SiO_2, hexane/EtOAc 1:1); for analytical and spectroscopic data, see Ref. 26. A solution of lactone **12** (95 mg, 0.36 mmol) in THF (7 mL) was added, under argon, to LiCl (153 mg, 3.61 mmol), previously dried at 80 °C under vacuum for 16 h. The reaction mixture was stirred at reflux temperature for 90 h. Then, THF was removed by evaporation, the residue was dissolved in EtOAc (6 mL) and extracted with saturated solution of $NaHCO_3$ (4 × 5 mL). The combined aqueous extracts were acidified until pH 2 with 6 N HCl and extracted with EtOAc (4 × 15 mL), and the organic layer was successively washed with H_2O (2 × 30 mL) and brine (2 × 15 mL), dried with Na_2SO_4 and concentrated to give **13** as a colourless oil (50 mg, 46%): $[\alpha]_D^{20}$ −27.1 (*c* 0.5, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, COSY): 1.10 (d, $J = 7.8$ Hz, 3H, H-5), 1.55 (d, $J = 7$ Hz, 3H, H-5′), 2.25 (m, H-4), 3.83 (dd, $J = 8.4$, 4.3 Hz, H-3), 4.89 (dq, $J = 8.8$, 4.3 Hz, H-2), 5.14 (s, OCH_2Ph), 7.36 (s, 5H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$,HSQC): 20.5 (C-5, C-5′), 32.2 (C-4), 56.8 (C-2), 67.8 (OCH_2Ph), 70.3 (C-3), 128.5 (*p*-C), 128.7(*o*-C), 128.9 (*m*-C), 136.1 (*ipso*-Ar), 155.9 (NCO), 173.8 (C-1). Pd(C) (10 mg) was added to a solution of **13** (50 mg, 0.17 mmol) in EtOH (6 mL). The mixture was stirred for 16 h under hydrogen atmospheric pressure at room temperature. The catalyst was removed by filtration through Celite®, washing several times with MeOH. The filtrate was concentrated to give **1** (27 mg, 96%) as a white solid. mp 134–136 °C (dec); $[\alpha]_D^{20}$ −7.1 (*c* 0.88, H_2O); NMR data, see Table 1.

32. For the enantioselective synthesis of the four stereoisomeric 3-hydroxyleucines, see: Makino, K.; Okamoto, N.; Hara, O.; Hamada, Y. *Tetrahedron: Asymmetry* **2001**, *12*, 1757–1762.
33. For NMR data of (2*S*,3*S*)-3-chloroleucines, see: **16**, $[\alpha]_D^{20}$ −16.7 (*c* 1.2, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, gCOSY) 1.08 (d, $J = 6.6$ Hz, H-5), 1.12 (d, $J = 7$ Hz, H-5′), 2.00 (dhept, $J = 9.6$, 6.6 Hz, H-4), 4.19 (dd, $J = 9.6$, 2.2 Hz, H-2), 4.94 (dd, $J = 10.2$, 2.2 Hz, H-3), 5.16 (s, CH_2), 5.49 (d, $J = 10$ Hz, NH), 7.35 (s, ArH); ^{13}C NMR (100 MHz, $CDCl_3$, gHSQC) 20.2 and 20.8 (C-5 and C-5′), 33.0 (C-4), 56.8 (C-2), 69.2 (C-3), 67.9 (CH_2), 128.4, 128.7, 128.9, 136.2 (Ar), 156.9 (NCO), 175.2 (C-1). Compound **2**, see Table 1. LC-MS of the product indicated that a small amount of an *N*-ethyl derivative had formed.
34. For the synthesis of (2*S*,3*S*)-(+)-3-fluoroleucine, see: Davis, F. A.; Srirajan, V.; Titus, D. D. *J. Org. Chem.* **1999**, *64*, 6931–6934.