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STEREOSELECTIVE INTRAMOLECULAR AZIDE 1,3-DIPOLAR CYCLOADDITION

Theodoros Markidis,[a] Emmanuel Mikros,[b] and George Kokotos[a,]*

[a] *Laboratory of Organic Chemistry, Department of Chemistry, University of Athens, Panepistimiopolis, Athens 15771, Greece*
[b] *Laboratory of Pharmaceutical Chemistry, Department of Pharmacy, University of Athens, Panepistimiopolis, Athens 15771, Greece*

E-mail: gkokotos@cc.uoa.gr

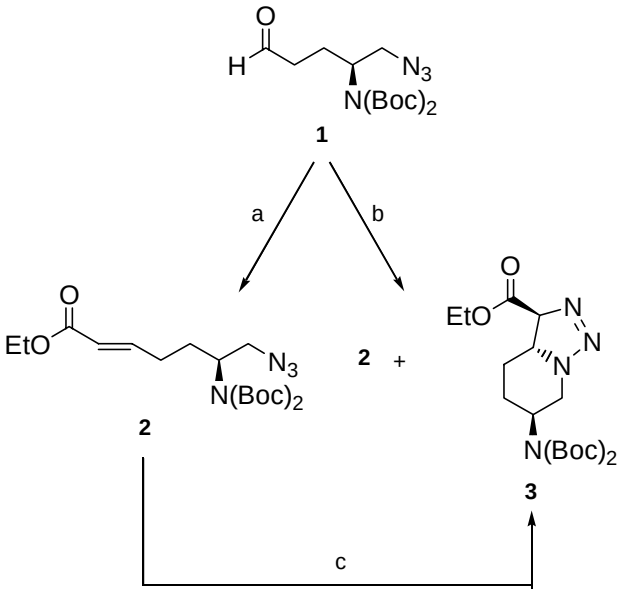
Abstract – Ethyl (*E*)-7-azido-6-[bis(*tert*-butoxycarbonyl)amino]-2-heptenoate undergoes a stereoselective intramolecular azide 1,3-dipolar cycloaddition leading to a stable triazoline. The configuration and the conformation of the triazoline obtained were determined by spectroscopic data and confirmed by molecular mechanics calculations.

Alkyl azides are well known to behave as 1,3-dipols in thermal cycloaddition reactions.[1] Triazolines and triazoles are the products of such an addition of the azido function to carbon-carbon multiple bonds. Triazoles can be readily isolated, while triazolines differ markedly in stability as a function of substituents. Most of triazolines are not stable and they decompose, after loss of nitrogen, giving products such as aziridines, diazo compounds, piperidines and pyrrolidines.[2-7] Temperature, solvent and substituents are some of the factors controlling which products are formed. Relatively few examples of aliphatic azide cyclizations have been reported in which the triazoline was isolated.[8-12] However, stereoselective intramolecular cycloaddition was observed only once.[12] Here, we report the stereoselective intramolecular cycloaddition of an aliphatic unsaturated azide leading to a stable triazoline. The configuration and conformation of triazoline were determined by spectroscopic data and molecular mechanics calculations.

During the last years we have been involved in the synthesis and study of bioactive unnatural amino acids,[13-15] 1,2-diamines and 2-amino alcohols.[16,17] Through these investigations we have shown that aldehyde (**1**) (Scheme 1) is a useful key intermediate compound leading to enantiopure terminal 1,2-

diamines.[18] In that synthetic approach, Wittig reaction of aldehyde (**1**) with 1.5 equivalents of Ph_3P=CHCOOEt at 50 °C for 2 h afforded unsaturated azide (**2**) in 81% yield. The enantiopure unsaturated azide (**2**)[18] is an excellent substrate for intramolecular thermal cycloaddition. In fact, heating of compound (**2**) in THF at 60°C for 16 h yielded the cyclized product (**3**) almost quantitatively. When the reaction was carried out at 60 °C for 16 h using 1.2 equivalents of the ylide, azide (**2**) and triazoline (**3**) were isolated, after column chromatography, in 3:2 ratio and identified by NMR spectral analysis. It is obvious that the Wittig reaction of **1** to **2** was followed by an intramolecular 1,3-dipolar cycloaddition of the azido function to the double bond. Under these conditions (elevated temperature and prolonged reaction time) the unsaturated azide (**2**) was converted, in part, to triazoline (**3**) thus resulting in a mixture of products.

Scheme 1. Preparation of Triazoline (**3**)

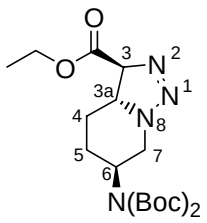


Reagents and conditions: (a) 1.5 eq. Ph_3P=CHCOOEt, THF, 50 °C, 2 h, 81%; (b) 1.2 eq. Ph_3P=CHCOOEt, THF, 60 °C, 16 h; (c) THF, 60 °C, 16 h, 96%.

In order to determine the stereoselectivity of the intramolecular cyclization of compound (**2**), the structure of triazoline (**3**) was fully characterized on the basis of NMR spectroscopy and Molecular Mechanics (MM) calculations. The COSY and NOESY correlations along with the ^3J coupling constants provided evidence for the formation of a six-membered ring. The assignment of the ^{1}H NMR spectra of triazoline (**3**) was accomplished mainly on the basis of the COSY spectra and is summarized in Table 1.

The above results consent to the formation of a six-membered ring adopting a chair conformation with the bulky Boc substituent at C_6 in the equatorial position. The expected spatial proximity of the coaxial protons H_{3a}, H_{7ax} and H_{5ax} from the one side of the ring and H_6, H_{4ax} from the other side was confirmed by

Table 1. ^{1}H NMR Spectral Data for Triazoline (**3**)



Protons	Chemical shift (ppm)	Multiplicity	Coupling constants (Hz)			
$C(CH_3)_3$	1.52	s				
CH_3CH_2COO	1.32	t	J 7.2			
$CH_3CHHCOO$	4.22	dq	J 7.2	J' 10.8		
$CH_3CHHCOO$	4.27	dq	J 7.2	J' 10.8		
H_3	4.71	d	$J_{3,3a}$ 5.3			
H_{3a}	3.76	ddd	$J_{3a,3}$ 5.3	$J_{3a,4eq}$ 4.1	$J_{3a,4ax}$ 11.9	
H_{4ax}	1.36	dtd	$J_{4ax,5eq}$ 3.5	$J_{4ax,3a}$ 11.9	$J_{4ax,4eq} = J_{4ax,5ax} = 13.1$	
H_{4eq}	1.78	dq	$J_{4eq,4ax}$ 13.1	$J_{4eq,5eq} = J_{4eq,3a} = J_{4eq,5ax} = 3.5$		
H_{5ax}	2.23	dtd	$J_{5ax,4eq}$ 3.3	$J_{5ax,6}$ 12.3	$J_{5ax,5eq} = J_{5ax,4ax} = 12.9$	
H_{5eq}	1.87	dqd	$J_{5eq,7eq}$ 1.8	$J_{5eq,5ax}$ 12.9	$J_{5eq,4ax}=J_{5eq,4eq}=J_{5eq,6}= 3.5$	
H_6	4.11	dddd	$J_{6,5eq}$ 3.5	$J_{6,7eq}$ 4.8	$J_{6,5ax}$ 11.8	$J_{6,7ax}$ 11.6
H_{7ax}	3.96	dd	$J_{6,7ax}$ 12.0	$J_{7ax,7eq}$ 12.7		
H_{7eq}	4.42	ddd	$J_{7eq,5eq}$ 1.8	$J_{7eq,6}$ 4.9	$J_{7eq,7ax}$ 12.9	

the NOE's observed in the NOESY spectrum (Figure 1), thereby verifying the chair conformation. It is also interesting to note that the two methylene protons of the ethyl ester group were not found to be equivalent,since they exhibited two signals at 4.22 and 4.27 ppm which formed a second order pattern.

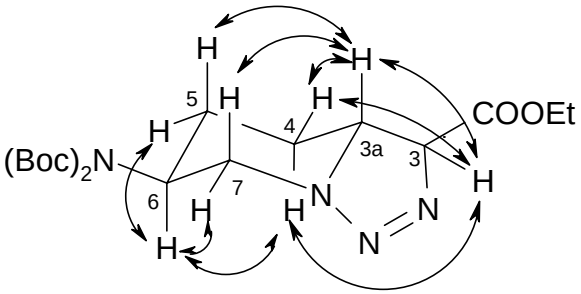
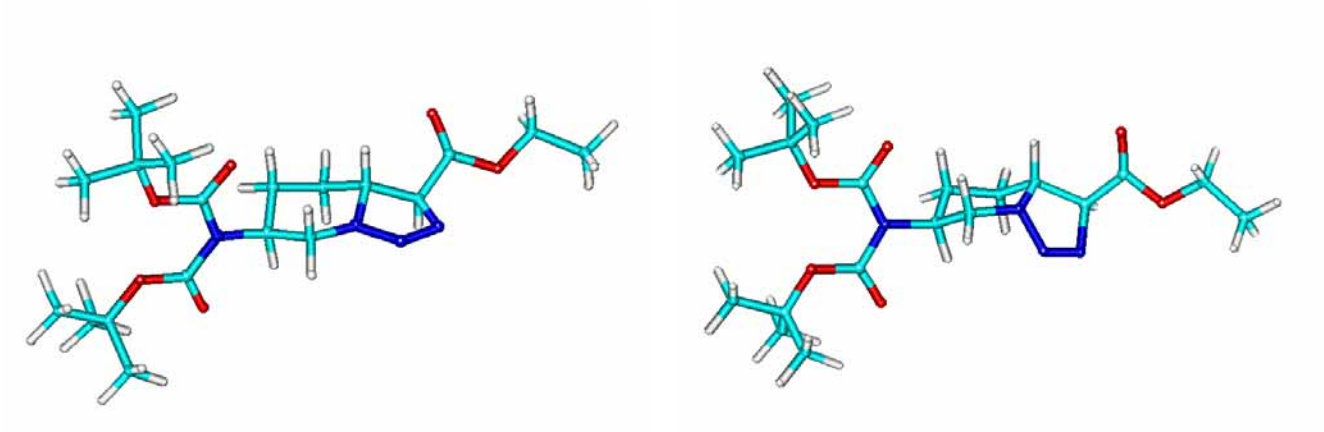


Figure 1. NOE correlations in).

To verify the configuration of chiral centers at positions 3 and 3a, theoretical calculations were performed and correlated with the experimental spectroscopic data. Protons H_3 and H_{3a} had an *E* orientation in azide

(**2**), thus two possible diastereomers could result from intramolecular cyclization: (3*S*,3a*R*,6*S*) or (3*R*,3a*S*,6*S*). Both structures of these two diastereomers were constructed, using the Macromodel software,[19] and a MonteCarlo conformational search was performed, taking into account the possible conformations of the two rings by using the MMFF force field. Two low energy conformations were revealed for isomer (3*S*,3a*R*,6*S*), with an E_{rel} difference of 0.79 kcal/mol as represented in Figures 2a and 2b. In both structures, the six-membered ring adopted a chair conformation where the bulky Boc groups had equatorial orientations, while the five-membered ring was equatorial in conformation I and axial in conformation II. The theoretical $^{3}J_{3\text{-}7}$ coupling constants were calculated on the basis of the appropriate

(a) **(b)**



E_{rel} = 0.79 kcal/mol E_{rel} = 0 kcal/mol

CONFORMER I **CONFORMER II**

Figure 2. Conformations I and II of triazoline (**3**) along with their relative Energies as resulted from Molecular Mechanics calculations.

Table 2. Theoretical ^{3}J Coupling Constants of Conformations **I** and **II** of Triazoline (**3**)

Protons	^{3}J Coupling constants of conformation I				^{3}J Coupling constants of conformation II			
H_3	$J_{3,3a}$ 10.4				$J_{3,3a}$ 1.1			
H_{3a}	$J_{3a,3}$ 10.4	$J_{3a,4eq}$ 3.2	$J_{3a,4ax}$ 11.8		$J_{3a,3}$ 1.1	$J_{3a,4eq}$ 4.1	$J_{3a,4ax}$ 11.6	
H_{4ax}	$J_{4ax,5eq}$ 3.0	$J_{4ax,3a}$ 11.8	$J_{4ax,5ax}$ 13.5		$J_{4ax,5eq}$ 3.2	$J_{4ax,3a}$ 11.6	$J_{4ax,5ax}$ 13.5	
H_{4eq}	$J_{4eq,5ax}$ 3.5	$J_{4eq,5eq}$ 3.3	$J_{4eq,3a}$ 3.2		$J_{4eq,5ax}$ 3.3	$J_{4eq,5eq}$ 3.5	$J_{4eq,3a}$ 4.1	
H_{5ax}	$J_{5ax,4eq}$ 3.5	$J_{5ax,6}$ 11.8	$J_{5ax,4ax}$ 13.5		$J_{5ax,4eq}$ 3.3	$J_{5ax,6}$ 11.8	$J_{5ax,4ax}$ 13.5	
H_{5eq}	$J_{5eq,6}$ 2.9	$J_{5eq,4ax}$ 3.0	$J_{5eq,4eq}$ 3.3		$J_{5eq,6}$ 2.6	$J_{5eq,4ax}$ 3.2	$J_{5eq,4eq}$ 3.5	
H_6	$J_{6,5eq}$ 2.9	$J_{6,7eq}$ 5.3	$J_{6,5ax}$ 11.8	$J_{6,7ax}$ 11.2	$J_{6,5eq}$ 2.6	$J_{6,7eq}$ 4.5	$J_{6,5ax}$ 11.8	$J_{6,7ax}$ 11.2
H_{7ax}	$J_{7ax,6}$ 11.2				$J_{7ax,6}$ 11.2			
H_{7eq}	$J_{7eq,6}$ 5.3				$J_{7eq,6}$ 4.5			

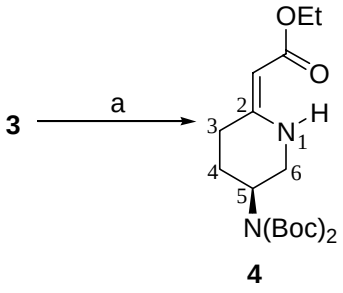
Karplus equation[20] and are summarized in Table 2. As far as the six-membered cycle is concerned, they are in full agreement with the experimental data in Table 1. Moreover, the NOE's observed are consistent with both structures.

Conformational analysis concerning isomer (3*R*,3a*S*,6*S*) revealed various low energy conformations, with E_{rel} values less than 2 kcal/mol, which were not consistent with the experimental data. All structures having the six-membered ring in the chair conformation were rejected, since either Boc groups had axial orientation or H_{3a} was equatorial. Other low energy structures revealed the six-membered ring in the twisted boat conformation with both H_6 and H_{3a} in pseudo-axial orientation at the same side of the ring. Both the calculated $^3J_{3\text{-}7}$ coupling constants (data not shown) and the expected NOE's for those low energy conformations did not agree with the experimental NMR data.

The above results corroborate the existence of one isomer, (3*S*,3a*R*,6*S*), with the six- membered ring adopting a chair conformation. The theoretical conformational analysis suggests that the five-membered ring could adopt two conformations as shown in Figures 2a and 2b. The theoretical ^3J coupling constant between H_3 and H_{3a} was calculated to be 10.4 and 1.1 Hz in conformations I and II, respectively (Table 2). The coupling constant measured from the NMR spectra of triazoline (**3**) was found to be 5.3 Hz (Table 1), suggesting that both conformations should be present in solution in an almost equal population.

Triazoline (**3**) is very stable neat or in solution at room temperature. To investigate which product is formed by heating, a solution of **3** in toluene was heated at 100 °C, and the reaction mixture was monitored by TLC. After 40 h, substituted piperidine (**4**) was isolated in 49% yield (Scheme 2) and characterized by elemental analysis, MS and NMR spectroscopy.

Scheme 2. Preparation of Piperidine (**4**)



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Reagents and conditions: (a) toluene, 100 °C, 40 h, 49%.

The assignment of the ^{1}H NMR spectrum of compound (**4**) was achieved as in the case of triazoline (**3**). The geometry of the double bond was easily determined from the presence of the NOE's between CHCO and both H_3 protons. The six-membered ring seemed to adopt a chair-like conformation as previously observed, with the bulky Boc groups in the equatorial orientation. The most deshielded broad signal at 8.61 ppm was attributed to the NH proton. The coupling constants of this proton with H_{6ax} and H_{6eq} were

found to be ^3J=1.9 Hz and ^3J=4.5 Hz, respectively, suggesting that NH is constrained to the equatorial position with the dihedral angle H_{6ax}-C_6-N-H almost orthogonal at 90°, although a nitrogen inversion is expected in this piperidine-like ring. The molecule, once constructed and geometry optimized using MM calculations, revealed that the NH proton could form a hydrogen bond with the carbonyl oxygen, thereby stabilizing the structure. The existence of such a hydrogen bond could explain the formation of only one double bond isomer leading the N_2 elimination towards a unique direction.

In conclusion, we have shown that ethyl (*E*)-7-azido-6-[bis(*tert*-butoxycarbonyl)amino]-2-heptenoate (**2**) undergoes a stereoselective thermal intramolecular cycloaddition to produce a stable triazoline derivative. Spectroscopic data together with molecular mechanics calculations showed that the triazoline derivative had a (3*S*, 3a*R*, 6*S*) configuration and adopted a chair conformation.

EXPERIMENTAL

Melting points were determined on a melting point apparatus and are uncorrected. Specific rotations were measured on a polarimeter using a 10 cm cell. NMR spectra were recorded on a 400 MHz spectrometer. COSY, and NOESY, spectra were acquired with 1024 complex points for 256 experiments with 2 s recycling delay, TPPI phase cycle and 1 s mixing time for NOESY. HSQC spectrum was obtained using B_0 gradient pulses, 128 FIDs in the t_1 domain and 1K in the t_2 domain, 8 transients for each t_1 experiment and recycling delay 1.5 s. Molecular simulations were performed with MACROMODEL 6.5 using MMFF[21] as force field implemented in MACROMODEL. Minimizations were carried out using the PRCG conjugate gradient method. Conformational search was performed by the Monte Carlo method[22] with a 5000 step. Analytical TLC plates (silica gel 60 F_{254}) and silica gel 60 (70–230 or 230–400 mesh) for column chromatography were purchased from Merck. Visualization of spots was effected with UV light and/or phosphomolybdic acid and/or ninhydrin both in ethanol stain. THF was passed through a column of aluminum oxide, distilled over CaH_2, and stored over molecular sieves. Toluene was distilled and stored over Na whereas all other solvents were of reagent grade and used without further purification. Compound (**2**) was prepared as described in the literature.[18]

Ethyl (3*S*,3a*R*,6*S*)-6-[bis(*tert*-butoxycarbonyl)amino]-3,3a,4,5,6,7-hexahydro[1,2,3]triazolo[1,5-*a*]pyridine-3-carboxylate (3). A solution of unsaturated azide (**2**) (412 mg, 1.00 mmol) in THF (10 mL) was heated at 60 °C for 16 h. The solvent was evaporated under reduced pressure and the product was purified by column chromatography using $CHCl_3$ as eluent to give **3** as a white solid. Yield 396 mg (96%); mp 106–109 °C; $[\alpha]^{25}_D$ = +360.0° (*c* 0.5, $CHCl_3$), +401.6° (*c* 0.5, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (t, 3 H, J = 7.2 Hz, CH_3), 1.52 [s, 18 H, 2 × $C(CH_3)_3$], 1.36 (dtd, 1 H, $J_{4ax,5eq}$ = 3.5 Hz, $J_{4ax,3a}$ = 11.9 Hz, $J_{4ax,4eq}$ = $J_{4ax,5ax}$ = 13.1 Hz, H_{4ax}), 1.78 (dq, 1 H, $J_{4eq,5ax}$ = $J_{4eq,5eq}$ = $J_{4eq,3a}$ = 3.5 Hz, $J_{4eq,4ax}$ = 13.1 Hz, H_{4eq}), 1.87 (dqd, 1H, $J_{5eq,7eq}$ = 1.8 Hz, $J_{5eq,5ax}$ = 12.9 Hz, $J_{5eq,4ax}$ = $J_{5eq,4eq}$ = $J_{5eq,6}$ = 3.5, H_{5eq}),

2.23 (dtd, 1 H, $J_{5ax,4eq}$ = 3.3 Hz, $J_{5ax,6}$ = 12.3 Hz, $J_{5ax,5eq}$ = $J_{5ax,4ax}$ = 12.9 Hz, H_{5ax}), 3.76 (ddd, 1 H, $J_{3a,3}$ = 5.3 Hz, $J_{3a,4eq}$ = 4.1 Hz, $J_{3a,4ax}$ = 11.9 Hz, H_{3a}), 3.96 (dd, 1 H, $J_{6,7ax}$ = 12.0 Hz, $J_{7ax,7eq}$ = 12.7 Hz, H_{7ax}), 4.11 (dddd, 1 H, $J_{6,5eq}$ = 3.5 Hz, $J_{6,7eq}$ = 4.8 Hz, $J_{6,5ax}$ = 11.8 Hz, $J_{6,7ax}$ = 11.6 Hz, H_6), 4.22 (dq, 1 H, J = 7.2 Hz, J' = 10.8 Hz, $CH_3CHHCOO$), 4.27 (dq, 1 H, J = 7.2 Hz, J' = 10.8 Hz, $CH_3CHHCOO$), 4.42 (ddd, 1 H, $J_{7eq,5eq}$ = 1.8 Hz, $J_{7eq,6}$ = 4.9 Hz, $J_{7eq,7ax}$ = 12.9 Hz, H_{7eq}), 4.71 (d, 1 H, $J_{3,3a}$ = 5.3, H_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1 (CH_3), 26.4 (C_5), 27.9 [$C(CH_3)_3$], 28.6 (C_4), 48.5 (C_7), 53.4 (C_{3a}), 56.5 (C_6), 61.9 (CH_2), 82.4 (C_3), 82.9 [$C(CH_3)_3$], 152.7 (C), 168.0 (C); FAB MS *m/z* (%): 435 (M^+ + Na, 6), 413 (M^+ + 1, 100), 385 (13), 369 (2), 339 (6), 313 (39), 257 (20), 239 (8). Anal. Calcd for $C_{19}H_{32}N_4O_6 \cdot 0.5H_2O$: C, 54.14; H, 7.89; N, 13.29. Found: C, 54.26; H, 7.87; N, 13.01.

Ethyl (5*S*,2*Z*)-2-{5-[bis(*tert*-butoxycarbonyl)amino]piperidin-2-ylidene}acetate (4). A solution of triazoline (**3**) (500 mg, 1.21 mmol) in toluene (12 mL) was heated at 100 °C for 40 h. The solvent was removed under reduced pressure and the product was purified by column chromatography using a mixture of EtOAc:petroleum ether 3:7 as eluent to give **4** as a colorless oil. Yield 228 mg (49%); $[\alpha]^{25}_D$ = +28.1° (*c* 1.05, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (t, 3 H, J = 7.2 Hz, CH_3), 1.51 [s, 18 H, 2 × $C(CH_3)_3$], 1.90 (dqd, 1 H, $J_{4eq,6eq}$ = 1.0 Hz, $J_{4eq,3ax}$ = $J_{4eq,3eq}$ = $J_{4eq,5}$ = 5.9 Hz, $J_{4eq,4ax}$ = 12.5 Hz, H_{4eq}), 2.11 (dtd, 1 H, $J_{4ax,3eq}$ = 5.6 Hz, $J_{4ax,5}$ = $J_{4ax,3ax}$ = 9.6 Hz, $J_{4ax,4eq}$ = 12.8 Hz, H_{4ax}), 2.40 (ddd, 1 H, $J_{3ax,4eq}$ = 5.6 Hz, $J_{3ax,4ax}$ = 9.3 Hz, $J_{3ax,3eq}$ = 16.3 Hz, H_{3ax}), 2.56 (dt, 1 H, $J_{3eq,4eq}$ = $J_{3eq,4ax}$ = 5.9 Hz, $J_{3eq,3ax}$ = 16.3 Hz, H_{3eq}), 3.37 (dddd, 1 H, $J_{6eq,4eq}$ = 0.8 Hz, $J_{6eq,NH}$ = 4.5 Hz, $J_{6eq,5}$ = 5.8 Hz, $J_{6eq,6ax}$ = 11.4 Hz, H_{6eq}), 3.60 (ddd, 1 H, $J_{6ax,NH}$ = 1.9 Hz, $J_{6ax,6eq}$ = 11.5 Hz, $J_{6ax,5}$ = 11.0 Hz, H_{6ax}), 4.09 (q, 2 H, J = 7.2 Hz, CH_2COO), 4.42 (ddt, 1 H, $J_{5,4eq}$ = $J_{5,6eq}$ = 6.1 Hz, $J_{5,6ax}$ = 10.6 Hz, $J_{5,4ax}$ = 10.1 Hz, H_5), 4.45 (s, 1 H, CHCO), 8.61 (br, 1 H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.6 (CH_3), 24.3 (C_4), 27.9 [$C(CH_3)_3$], 29.2 (C_3), 42.5 (C_6), 51.2 (C_5), 58.3 (CH_2), 80.5 (*C*HCO), 82.8 [$C(CH_3)_3$], 152.8 (C), 161.8 (C_2), 170.6 (C); FAB MS *m/z* (%): 385 (M^+ + 1, 43), 229 (50). Anal. Calcd for $C_{19}H_{32}N_2O_6$: C, 59.36; H, 8.39; N, 7.29. Found: C, 59.12; H, 8.33; N, 7.44.

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