Microwave-Assisted Synthesis of β-Lactams and Cyclo-β-dipeptides

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Dedicated to Professor *Dieter Seebach* on the occasion of his 75th birthday

Different cyclo-β-dipeptides were prepared from corresponding *N*-substituted β-alanine derivatives under mild conditions using $PhPOCl_2$ as activating agent in benzene and Et_3N as base. To evaluate β^3-substituent influence, the amino acids **7**–**26** were synthesized, and a β-lactam formation reaction was carried out instead of cyclo-β-dipeptide formation. The crystal structures of three derivatives of cyclo-β-peptides and one β-lactam are presented.

1. Introduction. – In the last few decades, several methods have been developed for enantioselective preparation of β-amino acids [1] due to their biological properties [2], and their application in the synthesis of β-lactams [3] and β-peptides [4], which have been shown to possess biological activities [5], and also because many β-amino acids have been identified as building blocks in natural occurring peptides and antibiotics mainly in plants [6a], microorganisms [6b][6c], and some mammalians [6d].

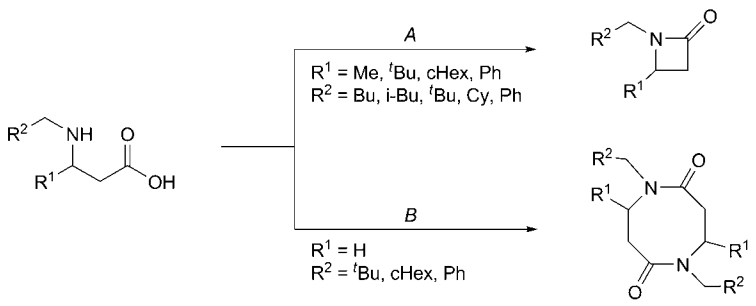
After the discovery of penicillin by *Alexander Fleming*, numerous reviews on chemistry and biology of β-lactam antibiotics have been published. The key feature of this kind of antibiotics is the β-lactam ring, and because of the growing bacterial resistance [7] due to unconscious use of antibiotics, demand for more potent analogs is increasing. To achieve this goal, a wide range of synthetic methods to form the β-lactam ring, *i.e.*, the final step, have been developed [3][8].

On the other hand, β-peptides have shown to possess interesting properties such as the ability to fold into stable secondary structures [9]. They also exhibit proteolytic stability against enzymes [10], which is due to lack of recognition by the peptidase [11], even though environmental microbial samples have been shown to use β-peptides as nitrogen and carbon source [5b][12]. To increase stability against certain peptidases in some peptides, an α-amino acid residue was replaced by a β-amino acid [13]. Due these properties, β-peptidic drugs could be synthesized and would probably have an excellent bioavailability and long-term activity. Moreover, cyclo-β-peptides can adopt, in solid state, tubular structures [14] of pleated-sheet-type H-bonds, which have potential application to promote ion-selective channel transport [14b][15]; also they have been

found to mimic β-peptide hormones as the cyclo-β-tetrapeptide (β-HPhe-β-HThr-β-HLys-β-HTrp) [16], with an affinity for human somatostatin receptors. Furthermore, cyclo-β-tripeptides [17] have been synthesized, and successful growth against human cancer cell lines were carried out.

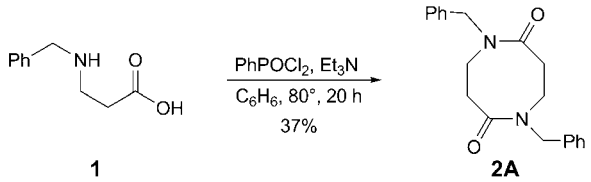
We found that the more versatile way to prepare either β-lactams or cyclo-β-dipeptides is activation of the C=O group with an organophosphorus reagent [18] or using *Mukaiyama*'s reagent [3b], depending upon the solvent used. With phenylphosphonic dichloride, $PhPOCl_2$, the reaction follows two possible pathways depending on the β-substituent: in *Pathway A*, an intramolecular reaction occurs to form the β-lactam, whereas, in *Pathway B*, a cyclic bis-amide is formed through an intramolecular amide bond-formation in the intermediate linear β-peptide[1]) (*Scheme 1*).

Scheme 1



2. Results and Discussion. – 2.1. *Preparations of Cyclo-β-dipeptides.* For comparison with microwave (MW)-assisted synthesis, cyclo-β-dipeptide **2A** was prepared first by conventional heating as reported in [18] (*Scheme 2*). After purification, a crystalline solid was obtained (37% yield).

Scheme 2

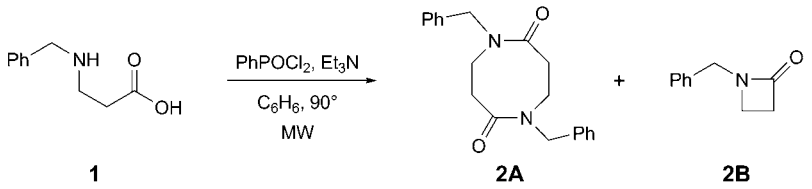


1 **2A**

We performed the same reaction by using MWs (*Scheme 3*), which have been established as auxiliaries in organic synthesis by decreasing reaction times, increasing yields, and even enhancing product purities [19]. Several experiments were carried out under different conditions; the results are compiled in *Table 1.*

[1]) Several combinations of R^1 and R^2 were examined.

Scheme 3



1 **2A** **2B**

Table 1. *Microwave-Assisted Formation of Cyclo-β-dipeptide* **2A**

Entry	Volume [ml]	Concentration [M]	Power [W]	$PhPOCl_2$ [equiv.]	Time [min]	Yield [%] **2A**[a])	**2B**[a])
1	80	0.0125	90	1.5	120	37	–
2	40	0.025	130	1.5	60	18	–
3	40	0.025	130	1.5	30	30	–
4	40	0.025	130	1.5	15	16	–
5	20	0.05	130	1.5	30	16	9
6	80	0.0125	130	0.5	30	27	trace[b])
7	40	0.025	130	0.5	30	27	8
8	20	0.05	130	0.5	30	23	11
9	10	0.1	130	0.5	30	24	10

[a]) Yield after column chromatography. [b]) Detected by TLC.

Entry 1 indicates that using microwaves gives cyclo-β-dipeptide in yields comparable to those reported in the literature [18][20], but with a considerable reduction in the reaction time and solvent volume used. Also good yields of cyclo-β-dipeptide are obtained by increasing the concentration and the MW accompanied by a furthermore reduction in the reaction time (*Entries 2–4*).

Surprisingly, at a higher concentration (*Entry 5*), β-lactam **2B** is formed, which was not isolated by the conventional heating [18]. In *Fig. 1*, the differences between the ^{1}H-NMR spectra of **2A** and **2B** are depicted. Decreasing the number of equiv. of $PhPOCl_2$ favored β-lactam formation (*Entries 6–9*). *Entry 6* indicates that decreasing $PhPOCl_2$ equivalents gave at least traces of β-lactam at higher dilutions. According to our criteria, the best conditions with respect to time, yield, and volume relations for the preparation of the cyclo-β-dipeptide **2A** are those of *Entry 3* which are used in the following experiments.

Once the optimal reaction conditions were established (*Entry 3*), reactions starting from amino acids **3** and **4** were carried out to form cyclo-β-dipeptides **5A** and **6A** (*Scheme 4* and *Table 2*), respectively.

After purification by column chromatography, both compounds were obtained, and their crystal structures were determined (*Figs. 2* and *3*). In solid state, both adopt a twisted boat conformation with *N*-substituents in pseudo-axial orientations which is the preferred conformation [18][21][22]. Although the CH_2 H-atoms are partially eclipsed, this is avoided by the slightly twisted boat conformation and is favored, because *Prelog* strain (*i.e.*, transannular strain) is null due to the presence of amide group.

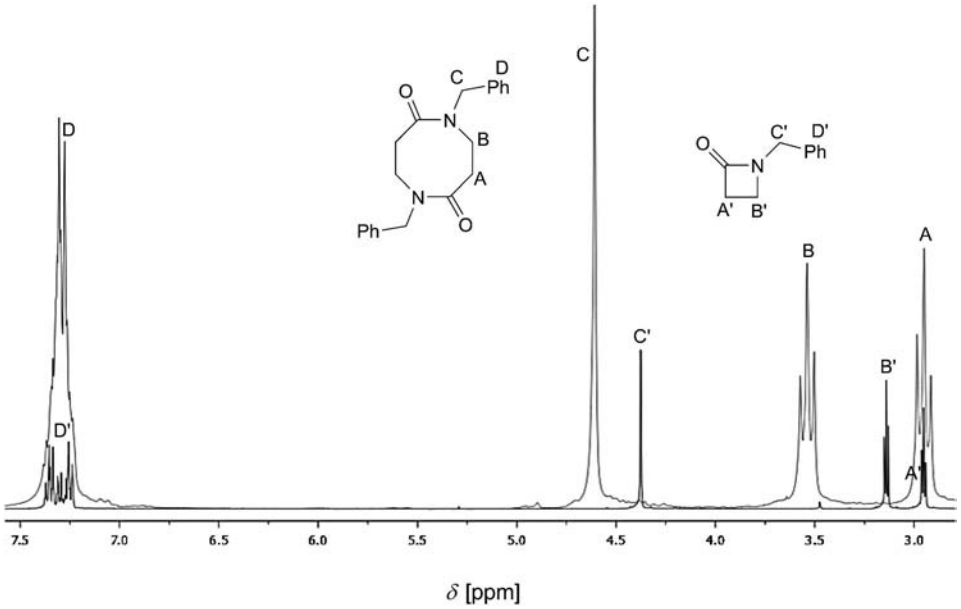


Fig. 1. Comparison of *^{1}H-NMR spectra of cyclo-β-dipeptide* **2A** *and β-lactam* **2B**. α-N- and benzylic H-atom signals are shifted to higher field in β-lactam. If only NMR spectrum of either cyclo-β-dipeptide or β-lactam is available, IR serves for identification.

Scheme 4

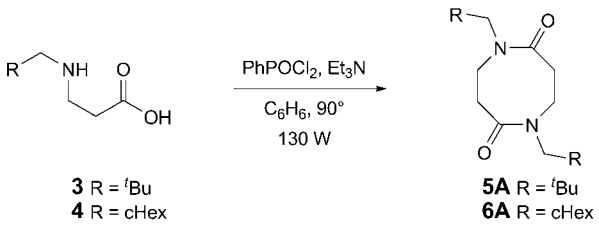


Table 2. *Cyclo-β-dipeptides* **5A** *and* **6A** *from Amino Acids* **3** *and* **4**, *Respectively*

Entry	Starting material	R	Product	Yield [%]	IR (C=O) [cm^{-1}]
1	**3**	^{t}Bu	**5A**	25	1641
2	**4**	cHex	**6A**	28	1637

2.2. *Preparation of β-Lactams.* Amino acids **7**–**26** were prepared to evaluate the β^3-substituent effect in cyclo-β-dipeptide formation. Interestingly, no cyclo-β-dipeptide formation was observed; instead, intramolecular reactions occured to form β-lactams (*Scheme 5* and *Table 3*).

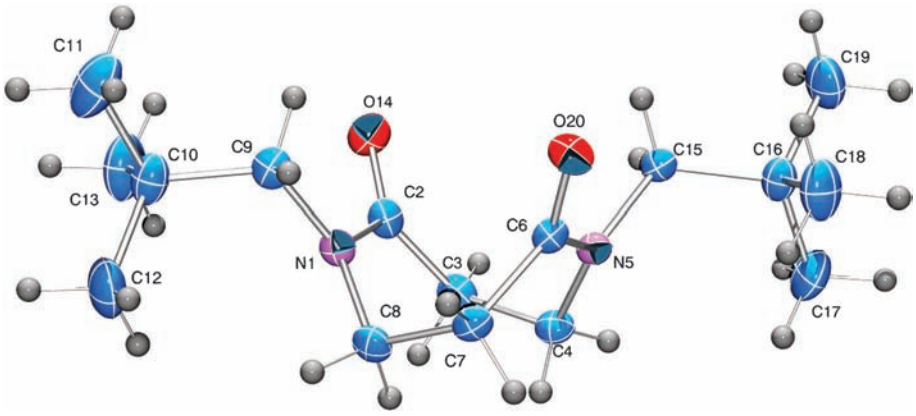


Fig. 2. *Solid-state conformation of cyclo-β-dipeptide* **5A**[2]). The thermal ellipsoids are drawn at 50% probability level with ORTEP and rendered using POV-Ray.

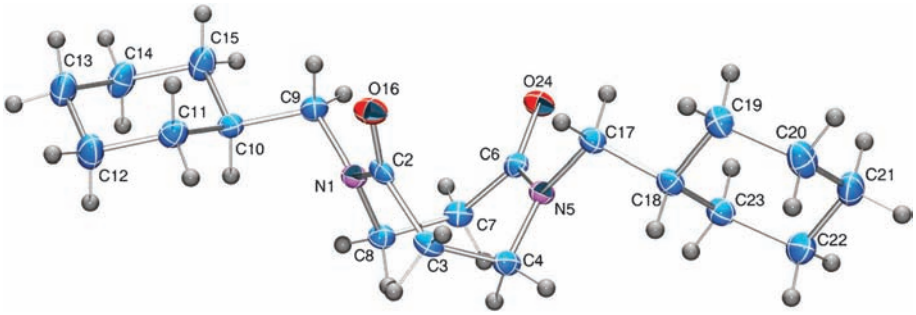
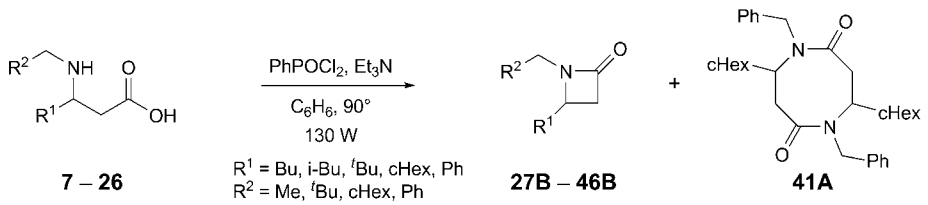


Fig. 3. *Solid-state conformation of cyclo-β-dipeptide* **6A**[2]). The thermal ellipsoids are drawn at 50% probability level with ORTEP and rendered using POV-Ray.

Scheme 5



Outstanding features of *Table 3: i*) The bulkier R^1 becomes, the higher yield is obtained (higher yields were achieved with $R^1 = {}^t$Bu (*Entries 8* and *9*) also high yields were detected with R^1 = cHex (= cyclohexyl; *Entries 12* and *15*)). *ii*) It seems that R^2 has little effect on the yield when R^1 = Me (*Entries 1–5*), but bulky R^2 lowers the yield

[2]) CCDC-894799–894802 contain the supplementary crystallographic data for this article. These data can be obtained free of charge *via* http://www.ccdc.cam.ac.uk/data_request/cif.

Table 3. *β-Lactams* **27B**–**46B** *from Amino Acids* **7**–**26**, *Respectively*

Entry	Raw material	R^1	R^2	Product	Yield [%]	IR (C=O) [cm^{-1}]
1	**7**	Me	Bu	**27B**	65	1736
2	**8**	Me	i-Bu	**28B**	64	1738
3	**9**	Me	^{t}Bu	**29B**	65	1737
4	**10**	Me	cHex	**30B**	55	1737
5	**11**	Me	Ph	**31B**	69	1730
6	**12**	^{t}Bu	Bu	**32B**	86	1725
7	**13**	^{t}Bu	i-Bu	**33B**	65	1744
8	**14**	^{t}Bu	^{t}Bu	**34B**	70	1725
9	**15**	^{t}Bu	cHex	**35B**	90	1745
10	**16**	^{t}Bu	Ph	**36B**	53	1740
11	**17**	cHex	Bu	**37B**	76	1742
12	**18**	cHex	i-Bu	**38B**	81	1742
13	**19**	cHex	^{t}Bu	**39B**	56	1753
14	**20**	cHex	cHex	**40B**	64	1739
15	**21**	cHex	Ph	**41A**	trace	1628
16	**21**	cHex	Ph	**41B**	72	1749
17	**22**	Ph	Bu	**42B**	18	1753
18	**23**	Ph	i-Bu	**43B**	62	1753
19	**24**	Ph	^{t}Bu	**44B**	78	1629
20	**25**	Ph	cHex	**45B**	52	1751
21	**26**	Ph	Ph	**46B**	50	1751

with R^1 = Ph (*Entry 18*). *iii*) This *β*-lactam formation can be interpreted as a related phenomenon to *Thorpe–Ingold* effect [23], where the substituents R^1 and R^2 tend to bring N-atom closer to C=O group the bulkier they are, favoring intramolecular reaction.

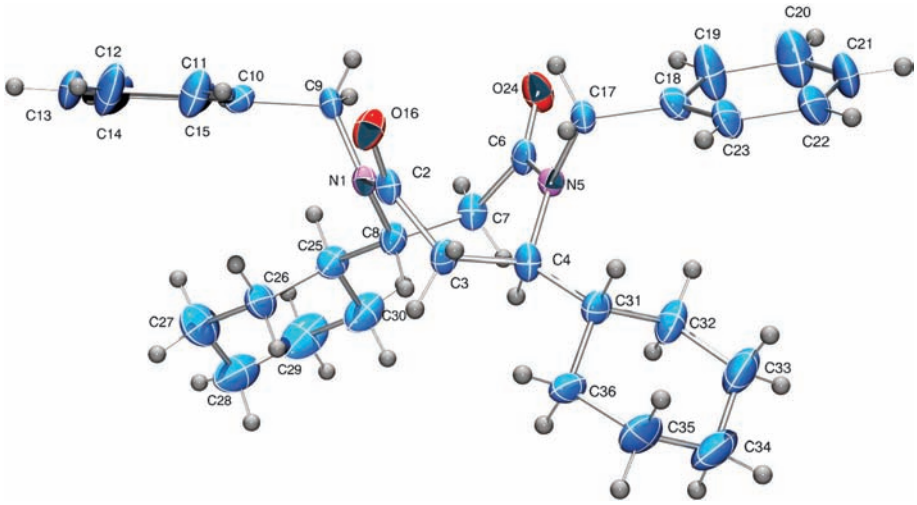


Fig. 4. *Solid-state conformation of cyclo-β-dipeptide* **41A**[2]). The thermal ellipsoids are drawn at 25% probability level with ORTEP and rendered using POV-Ray.

Interestingly, it was possible to obtain the cyclo-β-dipeptide **41A** from amino acid **21**. A single crystal was obtained, and the crystal structure (*Fig. 4*) revealed that it adopts a twisted boat conformation, with *N*-substituents in pseudo-axial orientations and ring substituents occupying pseudo-equatorial positions. Furthermore, ring substituents slightly decrease distances between amide N-atom and C=O C-atom across the ring, allowing an intramolecular electrostatic interaction.

Furthermore, it was deduced from the crystal structure of β-lactam **34B** (*Fig. 5*) that it has a planar ring conformation, where the N(1)–C(5) bond is also in the same plane of the ring as expected for an amide. This finding was also supported by the bond length N(1)–C(2), which is slightly shorter than N–C distance (1.47 Å); this behavior is also observed in the cyclo-β-dipeptides **5A**, **6A**, and **47A** due to the tendency of the N-atom to be in resonance with C=O group, leading to a slightly longer C=O bond.

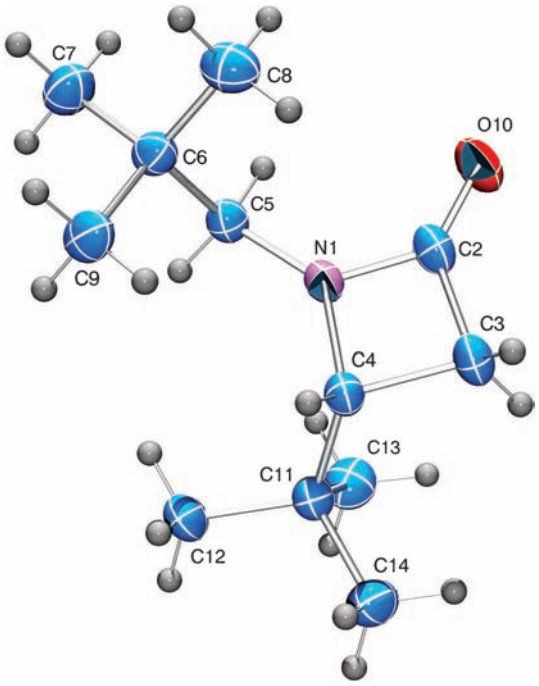


Fig. 5. *Solid-state conformation of β-lactam* **34B**[2]). The thermal ellipsoids are drawn at 50% probability level with ORTEP and rendered using POV-Ray.

Additionally, several experiments were carried out (see *Table 4*) using *Mukaiyama*'s reagent to confirm that compounds **31B** and **41B** were in fact β-lactams. This, because *i*) amino acid **11** was reported to form a cyclo-β-dipeptide by conventional heating [18], and the IR spectrum of the product matches that of a β-lactam; *ii*) amino acid **21** forms a cyclo-β-dipeptide (*Fig. 4*), which would not be formed by this method; and *iii*) we wanted to prepare β-lactams from compounds **3** and **4** to compare their properties with those of cyclo-β-dipeptides **5A** and **6A**.

The reactions were carried out with 1.0 mmol of amino acid (*Table 4*) in 40 ml of MeCN, 1.1 mmol of 2-chloro-1-methylpyridinium iodide, and 2.2 mmol of Et_3N. Reaction mixture was exposed to MWs (*Scheme 6*).

Scheme 6

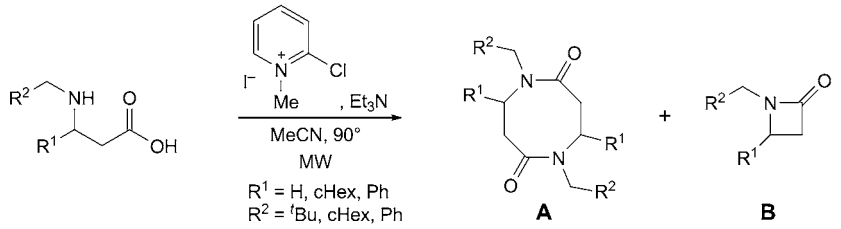


Table 4. *β-Lactams Obtained Using 2-Chloro-1-methylpiridium Iodide*

Entry	Starting material	Product	Solvent	2-$ClC_5H_4N^+Me \cdot I^-$ [equiv.]	Time [min]	Yield [%]	
						A	**B**
1	**1**	**2B**	MeCN	1.1	10	–	62
2	**1**	**2A**, **2B**	C_6H_6	1.1	30	12	31
3	**1**	**2A**, **2B**	MeCN	[c])	30	17	22
4	**3**	**5B**	MeCN	1.1	10	–	64
5	**4**	**6B**	MeCN	1.1	10	–	48
6	**11**	**31B**	MeCN	1.1	10	–	74
7	**21**	**41B**	MeCN	1.1	10	–	87
8	**24**	**44B**	MeCN	1.1	10	–	46

[c]) $PhPOCl_2$ was used.

The *β*-lactams **5B** and **6B** also have slightly similar ^{1}H-NMR spectra as their cyclo-*β*-dipeptide counterparts. As in the case of **2A** and **2B**, signals of both pairs of CH_2 H-atom in *α*-position to the N-atom are shifted to higher fields in *β*-lactams. For **31B**, **41B**, and **44B**, ^{1}H- and ^{13}C-NMR, IR, and MS (FAB^+) data match those of the compounds obtained, when $PhPOCl_2$ was used. Crystals from **41A** could not be obtained, since the cyclo-*β*-dipeptide was only obtained when $PhPOCl_2$ was used as activating agent.

Noteworthy results collected in *Table 4* are *i*) MeCN generally favors *β*-lactam formation with high yields and avoids the formation of the cyclo-*β*-dipeptide, *ii*) MeCN also favors *β*-lactam formation in cases where cyclo-*β*-dipeptide is generated in lower yields (*Entry 2*), and *iii*) the yield of the cyclo-*β*-dipeptide is slightly higher when $PhPOCl_2$ is used.

3. Conclusions. – Several *β*-amino acids were prepared and evaluated, by using $PhPOCl_2$, to form *β*-lactams or cyclo-*β*-dipeptides. *N*-Substituted *β*-amino acids have the tendency to form cyclo-*β*-dipeptides, while β^3-substituted amino acids form *β*-lactams under reaction conditions indicated in *Table 1*, *Entry 3*. However, it was possible to obtain a cyclo-*β*-dipeptide starting from amino acid **21** (*Fig. 4*).

From *N*-substituted, β-amino acids, it is possible to obtain either β-lactams or cyclo-β-dipeptides, or even a mixture of both just by changing the solvent used, when the *Mukaiyama*'s reagent is used, benzene favors cyclo-β-dipeptide formation, whereas MeCN affords β-lactam. Moreover, the yields achieved were slightly higher when MeCN is used; however, this solvent seemed to have no effect on the reaction of β^3-substituted amino acids.

Experimental Part

General. β^3-Amino acids were prepared according to the *Rodionov* synthesis [24a], and *N*-alkylation of β^3-amino acids and β-alanine derivatives were conducted by the reductive amination method developed by *Simpkins* and co-workers [24b]. All chemicals used for the synthesis of β-amino acids were obtained commercially (*Aldrich*) and used without further purification. Solvents were dried using standard techniques. Reactions were monitored by TLC on Al plates coated with silica gel with fluorescent indicator (*60 F_{254}*). Column chromatography (CC) was performed on silica gel (70–230 and 230–400 mesh). The reactions with microwaves were carried out in *Discover CEM* equipment. IR Spectra: *Perkin-Elmer FT-IR Spectrum One*; $\tilde{\nu}_{max}$ in cm^{-1}. NMR Spectra: *Varian Gemini* at 200 (^{1}H) and 50 MHz (^{13}C), with $CDCl_3$ as solvent, unless stared otherwise; δ in ppm rel. to Me_4Si as internal standard, *J* in Hz. HR-MS: *MStation JMS-700 JEOL* apparatus; in *m*/*z*. The X-ray structures were obtained using *APEX-Brucker* apparatus.

General Procedure for the Cyclization of N-*Substituted* β-*Amino Acids*. Into a 100-ml flask provided with magnetic stirrer, the *N*-substituted β-amino acid (1 mmol) and benzene (40 ml) were placed. Under N_2, Et_3N (2 mmol) and $PhPOCl_2$ (1.5 mmol) were added. The mixture was placed in a *Discover CEM* equipment at 90° and 130 W during 30 min. After completion, H_2O (5 ml) was added, and the mixture was concentrated in a rotatory evaporator. Extractions with AcOEt (3×10 ml) were carried out, and after evaporation the crude was purified by CC (silica gel; hexane/AcOEt, 9:1 → 5:5) to yield the products.

1,5-Dibenzyl-1,5-diazocane-2,6-dione (**2A**). Yield: 30%. IR: 1633 (C=O). ^{1}H-NMR: 2.95 (*t*, $^3J = 7.4$, 2 H); 3.54 (*t*, $^3J = 6.6$, 2 H); 4.6 (*s*, 2 H); 7.28 (*m*, 5 H). ^{13}C-NMR: 36.5; 42.2; 49.1; 127.8; 128.4; 128.8; 136.9; 170.2. FAB-MS: 323 ($[M+H]^+$). HR-FAB-MS: 322.1700 (M^+, $C_{20}H_{22}N_2O_2^+$; calc. 322.1681). Spectroscopic data were compared with those reported in [18].

1-Benzylazetidin-2-one (**2B**). Yield: 11%. IR: 1728 (C=O). ^{1}H-NMR: 2.95 (*t*, $^3J = 4.0$, 2 H); 3.14 (*t*, $^3J = 4.0$, 2 H); 4.37 (*s*, 2 H); 7.31 (*m*, 5 H). ^{13}C-NMR: 37.0; 38.7; 46.4; 127.8; 128.2; 128.9; 135.7; 167.7. FAB-MS: 162 ($[M+H]^+$). Spectroscopic data were compared with those reported in [25].

1,5-Bis(2,2-dimethylpropyl)-1,5-diazocane-2,6-dione (**5A**). Yield: 25%. IR: 1641 (C=O). ^{1}H-NMR: 0.91 (*s*, 9 H); 2.94 (*t*, $^3J = 7.4$, 2 H); 3.15 (*s*, 2 H); 3.71 (*t*, $^3J = 7.4$, 2 H). ^{13}C-NMR: 28.5; 34.2; 37.0; 46.0; 58.0; 171.1. FAB-MS: 283 ($[M+H]^+$). HR-FAB-MS: 283.2389 ($[M+H]^+$, $C_{16}H_{31}N_2O_2^+$; calc. 283.2386).

1-(2,2-Dimethylpropyl)azetidin-2-one (**5B**). Yield: 64%. IR: 1738 (C=O). ^{1}H-NMR: 0.86 (*s*, 9 H); 2.86 (*s*, 2 H); 2.87 (*t*, $^3J = 4.4$, 2 H); 3.26 (*t*, $^3J = 4.0$, 2 H). ^{13}C-NMR: 27.9; 33.2; 37.0; 42.3; 54.7; 168.4. HR-FAB-MS: 142.1244 ($[M+H]^+$, $C_8H_{16}NO^+$; calc. 142.1232).

1,5-Bis(cyclohexylmethyl)-1,5-diazocane-2,6-dione (**6A**). Yield: 28%. IR: 1632 (C=O). ^{1}H-NMR: 0.90 (*m*, 6 H); 1.22 (br., 6 H); 1.63 (br., 10 H); 2.91 (*t*, $^3J = 7.0$, 4 H); 3.17 (*d*, $^3J = 6.6$, 4 H); 3.61 (*t*, $^3J = 6.6$, 4 H). ^{13}C-NMR: 14.5; 26.1; 26.6; 31.1; 36.9; 37.3; 44.5; 53.2; 170.3. FAB-MS: 335 ($[M+H]^+$). HR-FAB-MS: 335.2684 ($[M+H]^+$, $C_{20}H_{35}N_2O_2^+$; calc. 335.2699).

1-(Cyclohexylmethyl)azetidin-2-one (**6B**). Yield: 48%. IR: 1738 (C=O). ^{1}H-NMR: 0.96 (br., 2 H); 1.22 (br., 3 H); 1.71 (br., 6 H); 2.93 (*t*, $^3J = 4.4$, 2 H); 3.03 (*d*, $^3J = 7.0$, 2 H); 3.26 (*t*, $^3J = 4.0$, 2 H). ^{13}C-NMR: 25.7; 26.2; 30.9; 36.5; 36.6; 39.9; 48.5; 167.7. HR-FAB-MS: 168.1407 ($[M+H]^+$, $C_{10}H_{18}NO^+$; calc. 168.1388).

(±)-4-Methyl-1-pentylazetidin-2-one (**27B**). Yield: 65%. IR: 1736 (C=O). ^{1}H-NMR: 0.89 (*t*, $^3J = 6.0$, 3 H); 1.34 (*d*, $^3J = 6.2$, 9 H); 1.53 (*t*, $^3J = 7.0$, 2 H); 2.47 (*d*, $J_{gem} = 14.3$, $^3J = 1.6$, 1 H); 3.01 (*m*, 2 H); 3.30 (*m*, 1 H); 3.66 (*m*, 1 H). ^{13}C-NMR: 14.1; 18.8; 22.4; 27.9; 29.4; 40.4; 43.8; 47.3; 167.0. FAB-MS: 156 ($[M+H]^+$). HR-FAB-MS: 156.1370 ($[M+H]^+$, $C_9H_{18}NO^+$; calc. 156.1388).

(±)-4-Methyl-1-(3-methylbutyl)azetidin-2-one (**28B**). Yield: 64%. IR: 1738 (C=O). ^{1}H-NMR: 0.91 (*d*, ^3J = 3.6, 3 H); 0.94 (*d*, ^3J = 3.2, 3 H); 1.33 (*m*, 3 H); 1.43 (*m*, 2 H); 1.52 (*m*, 1 H); 2.47 (*dd*, ^3J = 2.0, J_{gem} = 14.3, 1 H); 3.03 (*m*, 2 H); 3.34 (*m*, H); 3.66 (*m*, 1 H). ^{13}C-NMR: 18.9; 22.5; 22.6; 26.1; 36.9; 38.7; 43.9; 47.3; 166.9. EI-MS: 155 (M^+).

(±)-1-(2,2-Dimethylpropyl)-4-methylazetidin-2-one (**29B**). Yield: 65%. IR: 1737 (C=O). ^{1}H-NMR: 0.87 (*s*, 9 H); 1.24 (*d*, ^3J = 6.2, 3 H); 2.41 (*dd*, ^3J = 1.8, J_{gem} = 15, 1 H); 2.49 (*d*, J_{gem} = 15, 1 H); 3.04 (*dd*, ^3J = 4.8, J_{gem} = 14.2, 1 H); 3.16 (*d*, J_{gem} = 14.4, 1 H); 3.71 (*m*, 1 H). ^{13}C-NMR: 18.0; 28.1; 32.3; 44.2; 49.4; 51.8; 167.8. EI-MS: 155 (M^+).

(±)-1-(Cyclohexylmethyl)-4-methylazetidin-2-one (**30B**). Yield: 55%. IR: 1737 (C=O). ^{1}H-NMR: 0.95 (*m*, 3 H); 1.21 (br., 2 H); 1.31 (*d*, ^3J = 6.2, 3 H); 1.61 (br., 6 H); 2.47 (*dd*, ^3J = 2.2, J_{gem} = 14.2 H, 1 H); 2.78 (*dd*, ^3J = 6.2, J_{gem} = 13.8, 1 H); 3.05 (*dd*, ^3J = 3.8, J_{gem} = 14.4, 1 H); 3.15 (*dd*, ^3J = 7.8, J_{gem} = 14.4, 1 H); 3.64 (*m*, 1 H). ^{13}C-NMR: 18.5; 25.8; 25.8; 26.4; 31.1; 31.2; 37.0; 43.8; 46.7; 47.9; 167.1. FAB-MS: 182 ($[M+H]^+$). HR-FAB-MS: 182.1532 ($[M+H]^+$, $C_{11}H_{20}NO^+$; calc. 182.1545).

(±)-1-Benzyl-4-methylazetidin-2-one (**31B**). Yield: 69%. IR: 1730 (C=O). ^{1}H-NMR: 1.20 (*d*, ^3J = 6.2, 3 H); 2.52 (*dd*, ^3J = 1.4, J_{gem} = 14.2, 1 H); 3.05 (*dd*, ^3J = 5, J_{gem} = 14.6, 1 H); 3.57 (*m*,1 H); 4.10 (*d*, J_{gem} = 15.4, 1 H); 4.57 (*d*, J_{gem} = 15.4, 1 H); 7.3 (*m*, 5 H). ^{13}C-NMR: 18.5; 44.1; 44.3; 47.1; 127.5; 128.1; 128.6; 136.0; 166.7. FAB-MS: 176 ($[M+H]^+$). HR-FAB-MS: 176.1093 ($[M+H]^+$, $C_{11}H_{14}NO^+$; calc. 176.1075). Spectroscopic data were compared with those reported in [25][26].

*(±)-4-(*tert*-Butyl)-1-pentylazetidin-2-one* (**32B**). Yield: 86%. IR: 1746 (C=O). ^{1}H-NMR: 0.76 (*t*, ^3J = 7.0, 3 H); 0.82 (*s*, 9 H); 1.16 (*m*, 4 H); 1.43 (*m*, 2 H); 2.43 (*dd*, ^3J = 2.0, J_{gem} = 14.8, 1 H); 2.64 (*dd*, ^3J = 5.2, J_{gem} = 14.6, 1 H); 2.80 (*m*, 1 H); 3.28 (*m*, 1 H); 3.41 (*m*, 1 H). ^{13}C-NMR: 13.9; 22.2; 25.8; 27.2; 29.1; 32.7; 37.8; 42.2; 60.3; 167.8. HR-FAB-MS: 198.1856 ($[M+H]^+$, $C_{12}H_{24}NO^+$; calc. 198.1858).

*(±)-4-(*tert*-Butyl)-1-(3-methylbutyl)azetidin-2-one* (**33B**). Yield: 65%. IR: 1744 (C=O). ^{1}H-NMR: 0.91 (*d*, ^3J = 6.4, 6 H); 0.95 (*s*, 9 H); 1.47 (*m*, 3 H); 2.57 (*dd*, ^3J = 1.4, J_{gem} = 14.6, 1 H); 2.77 (*dd*, ^3J = 5.2, J_{gem} = 14.6, 1 H); 2.93 (*dt*, ^3J = 7, J_{gem} = 14, 1 H); 3.41 (*dd*, $^3J_1$ = 2.6, $^3J_2$ = 5.2); 3.58 (*dt*, ^3J = 7.6, J_{gem} = 13.8). ^{13}C-NMR: 22.2; 22.6; 25.9; 25.9; 32.8; 36.2; 37.9; 40.6; 60.3; 168.0. FAB-MS: 198 ($[M+H]^+$). HR-FAB-MS: 198.1887 ($[M+H]^+$, $C_{12}H_{24}NO^+$; calc. 198.1858).

*(±)-4-(*tert*-Butyl)-1-(2,2-dimethylpropyl)azetidin-2-one* (**34B**). Yield: 70%. IR: 1725 (C=O). ^{1}H-NMR: 0.91 (*d*, 18 H); 2.48 (*dd*, ^3J = 2.2, J_{gem} = 14.6); 2.61 (*d*, J_{gem} = 14.6); 2.81 (*dd*, ^3J = 5.2, J_{gem} = 15); 3.43 (*d*, J_{gem} = 14.4); 3.57 (*dd*, $^3J_1$ = 2.2, $^3J_2$ = 5). ^{13}C-NMR: 26.5; 28.6; 33.4; 34.6; 38.6; 53.5; 62.9; 168.5. FAB-MS: 198 ($[M+H]^+$). HR-FAB-MS: 198.1854 ($[M+H]^+$, $C_{12}H_{24}NO^+$; calc. 198.1858).

*(±)-4-(*tert*-Butyl)-1-(cyclohexylmethyl)azetidin-2-one* (**35B**). Yield: 90%. IR: 1745 (C=O). ^{1}H-NMR (400 MHz, $CDCl_3$): 0.95 (*s*, 11 H); 1.21 (*m*, 3 H); 1.69 (*m*, 7 H); 2.58 (*dd*, ^3J = 2, J_{gem} = 14.8, 1 H); 2.79 (*m*, 2 H); 3.36 (*dd*, ^3J = 5.6, J_{gem} = 14.4, 1 H); 3.41 (*dd*, $^3J_1$ = 2.8, $^3J_2$ = 5.2, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 25.8; 25.9; 26.0; 26.4; 30.9; 31.2; 32.9; 36.3; 38.0; 48.9; 61.1; 168.5. FAB-MS: 224 ($[M+H]^+$). HR-FAB-MS: 224.2012 ($[M+H]^+$, $C_{14}H_{26}NO^+$; calc. 224.2014).

(±)-1-Benzyl-4-(tert-butyl)azetidin-2-one (**36B**). Yield: 53%. IR: 1740 (C=O). ^{1}H-NMR: 0.88 (*s*, 9 H); 2.66 (*dd*, ^3J = 2.5, J_{gem} = 15, 1 H); 2.82 (*dd*, ^3J = 5.2, J_{gem} = 14.6, 1 H); 3.3 (*dd*, $^3J_1$ = 2.8, $^3J_2$ = 5, 1 H); 4.04 (*d*, J_{gem} = 15.4, 1 H); 4.82 (*d*, J_{gem} = 15.4); 7.28 (*m*, 5 H). ^{13}C-NMR: 26.0; 32.7; 38.4; 46.5; 60.5; 127.6; 128.3; 128.7; 136.2; 168.5. FAB-MS: 218 ($[M+H]^+$). HR-FAB-MS: 218.1551 ($[M+H]^+$, $C_{14}H_{20}NO^+$; calc. 218.1545).

(±)-4-Cyclohexyl-1-pentylazetidin-2-one (**37B**). Yield: 76%. IR: 1742 (C=O). ^{1}H-NMR: 0.89 (*t*, ^3J = 6.6, 3 H); 1.06 (*m*, 2 H); 1.25 (*m*, 7 H); 1.59 (*m*, 8 H); 2.59 (*dd*, ^3J = 2, J_{gem} = 14.8, 1 H); 2.82 (*dd*, ^3J = 5.2, J_{gem} = 14.2, 1 H); 2.96 (*dd*, ^3J = 6.6, J_{gem} = 13.6, 1 H); 3.42 (*m*, 2 H). ^{13}C-NMR: 14.1; 22.4; 25.9; 26.0; 26.4; 27.6; 27.7; 29.3; 30.0; 38.9; 40.4; 41.6; 56.0; 167.7. FAB-MS: 224 ($[M+H]^+$). HR-FAB-MS: 224.2012 ($[M+H]^+$, $C_{14}H_{26}NO^+$; calc. 224.2014).

(±)-4-Cyclohexyl-1-(3-methylbutyl)azetidin-2-one (**38B**). Yield: 81%. IR: 1742 (C=O). ^{1}H-NMR: 0.79 (*d*, ^3J = 6.4, 6 H); 0.99 (*m*, 5 H); 1.47 (*m*, 9 H); 2.45 (*dd*, ^3J = 2.2, J_{gem} = 14.6, 1 H); 2.68 (*dd*, ^3J = 5.2, J_{gem} = 14.6, 1 H); 2.82 (*m*, 1 H); 3.32 (*m*, 2 H). ^{13}C-NMR: 21.9; 22.2; 25.5; 25.6; 26.2; 27.2; 29.5; 36.2; 38.5; 39.4; 40.0; 55.5; 167.0. FAB-MS: 224 ($[M+H]^+$). HR-FAB-MS: 224.2029 ($[M+H]^+$, $C_{14}H_{26}NO^+$; calc. 224.2014).

(±)-4-Cyclohexyl-1-(2,2-dimethylpropyl)azetidin-2-one (**39B**). Yield: 56%. IR: 1753 (C=O). ^{1}H-NMR: 0.95 (*s*, 9 H); 1.07 (*m*, 2 H); 1.28 (*m*, 3 H); 1.67 (*m*, 6 H); 2.56 (*d*, J_{gem} = 14.2, 1 H); 2.63

(*dd*, $^3J = 2.2$, $J_{gem} = 14.3$, 1 H); 2.88 (*dd*, $^3J = 5.2$, $J_{gem} = 14$, 1 H); 3.35 (*d*, $J_{gem} = 14.4$, 1 H); 3.64 (*m*, 1 H). ^{13}C-NMR: 25.9; 26.3; 26.5; 26.6; 28.3; 29.9; 33.9; 38.5; 38.5; 52.5; 58.1; 168.2. FAB-MS: 224 ($[M+H]^+$). HR-FAB-MS: 224.2000 ($[M+H]^+$, $C_{14}H_{26}NO^+$; calc. 224.2014).

(±)-4-Cyclohexyl-1-(cyclohexylmethyl)azetidin-2-one (**40B**). Yield: 64%. IR: 1739 (C=O). ^{1}H-NMR: 0.98 (*m*, 4 H); 1.21 (*m*, 7 H); 1.68 (*m*, 11 H); 2.61 (*dd*, $^3J = 1.8$, $J_{gem} = 14$, 1 H); 2.79 (*m*, 2 H); 3.30 (*dd*, $^3J = 8.4$, 14.2, 1 H); 3.42 (*m*, 1 H). ^{13}C-NMR: 25.9; 25.9; 26.1; 26.5; 27.6; 30.0; 31.1; 31.4; 36.8; 38.9; 40.1; 47.9; 56.7; 167.9. FAB-MS: 250 ($[M+H]^+$). HR-FAB-MS: 250.2187 ($[M+H]^+$, $C_{16}H_{28}NO^+$; calc. 250.2171).

(±)-1,5-Dibenzyl-4,8-dicyclohexyl-1,5-diazocane-2,6-dione (**41A**). The crystal of this compound was isolated from the recrystallization of **41B**. In ^{1}H- and ^{13}C-NMR only one compound was detected (also GC-MS and TLC). IR: 1628 (C=O). FAB-MS: 487 ($[M+H]^+$). HR-FAB-MS: 487.3282 ($[M+H]^+$, $C_{32}H_{43}N_2O_2^+$; calc. 487.3325).

(±)-1-Benzyl-4-cyclohexylazetidin-2-one (**41B**). Yield: 72%. IR: 1741 (C=O). ^{1}H-NMR: 1.03 (*m*, 5 H); 1.55 (*m*, 6 H); 2.66 (*dd*, $^3J = 2.8$, $J_{gem} = 14.6$, 1 H); 2.86 (*dd*, $^3J = 5$, $J_{gem} = 14.4$, 1 H); 3.29 (*m*, 1 H); 4.05 (*d*, $J_{gem} = 15$, 1 H); 4.73 (*d*, $J_{gem} = 15$, 1 H); 7.31 (*m*, 5 H). ^{13}C-NMR: 25.9; 26.0; 26.4; 27.6; 30.0; 39.5; 40.3; 45.8; 55.9; 127.7; 128.3; 128.4; 128.8; 136.2; 167.9; 191.8. FAB-MS: 244 ($[M+H]^+$). HR-FAB-MS: 244.1729 ($[M+H]^+$, $C_{16}H_{22}NO^+$; calc. 244.1701).

(±)-1-Pentyl-4-phenylazetidin-2-one (**42B**). Yield: 18%. IR: 1753 (C=O). ^{1}H-NMR: 0.85 (*t*, $J = 6.6$, 3 H); 1.24 (*m*, 3 H); 1.45 (*m*, 3 H); 2.81 (*m*, 2 H); 3.38 (*m*, 2 H); 4.55 (*dd*, $^3J_1 = 2.6$, $^3J_2 = 5.2$, 1 H); 7.30 (*m*, 5 H). ^{13}C-NMR: 14.2; 22.4; 27.6; 29.7; 41.0; 46.9; 54.3; 126.5; 128.6; 129.1; 138.6; 167.5. CI-MS: 218 ($[M+H]^+$). HR-CI-MS: 218.1543 ($[M+H]^+$, $C_{14}H_{20}NO^+$; calc. 218.1545).

(±)-1-(3-Methylbutyl)-4-phenylazetidin-2-one (**43B**). Yield: 62%. IR: 1753 (C=O). ^{1}H-NMR: 0.83 (*d*, $J = 3.0$, 3 H); 0.86 (*d*, $J = 3.0$, 3 H); 1.47 (*m*, 3 H); 2.81 (*m*, 2 H); 3.35 (*dd*, $^3J = 5.0$, $J_{gem} = 14.2$, 1 H); 3.48 (*dd*, $^3J = 8.0$, $J_{gem} = 14.2$, 1 H); 4.53 (*dd*, $^3J_1 = 2.2$, $^3J_2 = 5.2$, 1 H); 7.35 (*m*, 5 H). ^{13}C-NMR: 22.4; 22.6; 26.1; 36.5; 26.1; 36.5; 39.4; 46.9; 54.3; 126.5; 128.6; 129.1; 138.6; 167.5. CI-MS: 218 ($[M+H]^+$). HR-CI-MS: 218.1529 ($[M+H]^+$, $C_{14}H_{20}NO^+$; calc. 218.1545).

(±)-1-(2,2-Dimethylpropyl)-4-phenylazetidin-2-one (**44B**). Yield: 20%. IR: 1629 (C=O). ^{1}H-NMR: 0.87 (*s*, 9 H); 2.28 (*d*, $J_{gem} = 14.2$, 1 H); 2.79 (*d*, $J_{gem} = 14.8$, 1 H); 3.37 (*m*, 2 H); 4.62 (*m*, 1 H); 7.32 (*m*, 5 H). ^{13}C-NMR: 28.1; 33.4; 47.1; 52.3; 56.9; 126.7; 128.6; 129.0; 137.8; 168.2. CI-MS: 218 ($[M+H]^+$). HR-CI-MS: 218.1557 ($[M+H]^+$, $C_{14}H_{20}NO^+$; calc. 218.1545).

(±)-1-(Cyclohexylmethyl)-4-phenylazetidin-2-one (**45B**). Yield: 52%. IR: 1751 (C=O). ^{1}H-NMR: 1.28 (*m*, 11 H); 2.58 (*dd*, $^3J = 6.0$, $J_{gem} = 14.0$, 1 H); 2.81 (*dd*, $^3J = 2.0$, $J_{gem} = 14.8$, 1 H); 3.28 (*dd*, $^3J = 7.6$, $J_{gem} = 13.8$, 1 H); 3.38 (*dd*, $^3J = 5.2$, $J_{gem} = 14.6$, 1 H); 2.55 (*dd*, $^3J_1 = 2.2$, $^3J_2 = 5.2$, 1 H); 7.36 (*m*, 5 H). ^{13}C-NMR: 25.8; 26.4; 31.1; 31.2; 36.8; 46.9; 47.2; 55.1; 126.5; 128.6; 129.0; 138.4; 167.7. CI-MS: 244 ($[M+H]^+$). HR-CI-MS: 244.1669 ($[M+H]^+$, $C_{16}H_{22}NO^+$; calc. 244.1701).

(±)-1-Benzyl-4-phenylazetidin-2-one (**46B**). Yield: 50%. IR: 1751 (C=O). ^{1}H-NMR: 2.87 (*dd*, $^3J = 1.4$, $J_{gem} = 14.6$, 1 H); 3.35 (*dd*, $^3J = 5.2$, $J_{gem} = 14.6$, 1 H); 3.76 (*d*, $J_{gem} = 14.8$, 1 H); 4.40 (*dd*, $^3J_1 = 2.2$, $^3J_2 = 5.2$, 1 H); 4.81 (*d*, $J_{gem} = 15.2$, 1 H); 7.29 (*m*, 10 H). ^{13}C-NMR: 45.0; 47.1; 53.8; 126.7; 127.8; 128.7; 128.9; 129.1; 135.7; 138.0; 167.3. CI-MS: 238 ($[M+H]^+$). HR-CI-MS: 238.1230 ($[M+H]^+$, $C_{16}H_{16}NO^+$; calc. 238.1232). Spectroscopic data were compared with those reported in [18][26].

We would like to thank Dr. *Gaurau Tibhe* for his suggestions, also we are grateful to *CONACYT* for financial support (Project CB2010/151875) and for scholarships to *L. G. H.-V.*

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Received August 10, 2012