Pergamon

Tetrahedron 57 (2001) 1883–1890

TETRAHEDRON

Synthesis of β-lactams and cyclo-β-dipeptides from β-amino acids: experimental observations and theoretical analysis

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Received 4 February 2000; accepted 11 December 2000

Abstract—The cyclization of β-amino acids by means of activating agents is one of the most useful approaches for the construction of β-lactams; however, we found that when $PhP(O)Cl_2$ (in Et_3N) is employed as the activating agent, cyclization of the derived 'active ester' affords varying amounts of cyclo-β-dipeptides, depending on reactions conditions (solvent, temperature, and concentration), as well as on the substitution pattern in the starting β-amino acid. Theoretical rationalization of the experimental results was achieved by modeling studies of the presumed intermediates, both at semi-empirical (MNDO, AM1, and PM3) and at ab initio (HF/3-21G) levels. In the latter calculations, simulation of solvents was accomplished by means of self-consistent reaction field theory (Onsager's method).

1. Introduction

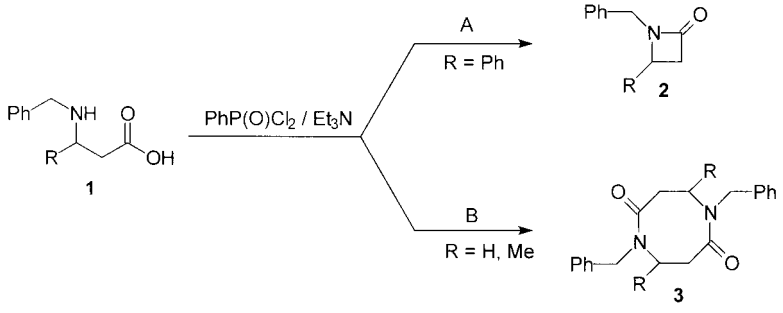
The chemistry of β-amino acids is of continuing interest in modern organic chemistry.[1] Application to β-lactam synthesis[2] and to the synthesis of structurally rich β-peptides[3] has led to growing attention to the area. In particular, β-dipeptides have been shown to possess interesting biological properties[4] as well as greater enzyme-inhibiting abilities than β-lactams.[5] Furthermore, short oligomers made of β-amino acids give rise to stabilized helical structures and can exhibit a resistance to enzymatic hydrolysis.[6]

Activation of the carboxyl group on a β-amino acid by means of an organophosphorus reagent[7] is one of the most common methods for the construction of β-lactams via intramolecular condensation (pathway A in Scheme 1).[8] However, we have found that when the activating agent is $PhP(O)Cl_2$ in the presence of excess triethylamine, two β-amino acids, 3-(benzylamino)propanoic acid and 3-(benzylamino)-3-methylpropanoic acid, afford cyclic β-dipeptides (pathway B in Scheme 1).

2. Results and discussion

2.1. β-Lactam formation

3-(Benzylamino)-3-phenylpropanoic acid (*rac*-**1a**) was



Scheme 1.

Keywords: azetidinones; peptides and polypeptides; theoretical studies; solvent effects; amino acids and derivatives.

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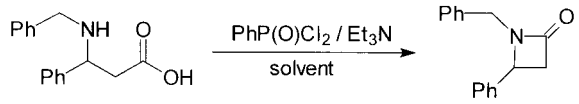
Table 1. Lactamization of 3-(benzylamino)-3-phenylpropanoic acid (**1a**) under varying reaction conditions

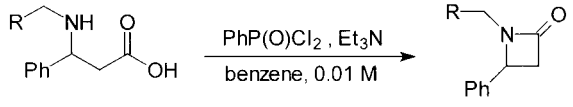


rac-**1a** *rac*-**2a**

Entry	Concentration (M) of *rac*-**1a**	Solvent	Temperature (°C)	Time (h)	Yield[a] (%)
1	0.1	Benzene	80	20	78
2	0.01	Benzene	80	20	99
3	0.01	Benzene	40	20	49
4	0.005	Benzene	80	20	99
5	0.01	MeCN	82	20	75
6	0.01	CH_2Cl_2	40	96	55
7	0.01	CH_2Cl_2	25	96	31

[a] β-Lactam (±)-**2a** is the only product found in this reaction.

Table 2. β-Lactam formation with various *N*-substituents in the β-amino-β-phenyl-propanoic acid substrate



(±)-**1a-d** (±)-**2a-d**

Entry	R	Yield (%)
1	C_6H_5	99
2	*p*-C_6H_5–C_6H_4	95
3	*o*-CH_3O–C_6H_4	72
4	$CH_3(CH_2)_3$	62

treated with 1.5 equiv. of phenylphosphonic dichloride in the presence of excess triethylamine under varying reaction conditions (Table 1). Benzene, especially under high dilution, gave the best yields of β-lactam formation (*rac*-**2a**) and is therefore generally recommended as a solvent. Acetonitrile (at 82°C) was also an effective solvent for β-lactam formation (Table 1); by contrast, dichloromethane afforded low yields, even at long reaction times (T=25 or 40°C).

Some of the data presented in Table 1 give evidence of significant concentration and temperature effects. So, comparison of entries 1 and 2 (or 4) show increased yields of β-lactam at lower concentration. This result can be interpreted in terms of intramolecular lactamization, being favored over intermolecular peptide formation. On the other hand, examination of entries 2 and 3, as well as entries 6 and 7, show clearly that higher yields of lactam **2a** are achieved at higher reaction temperatures. Finally, it is important to point out that no evidence for dipeptide formation was found; that is, only starting β-amino acid *rac*-**1a** accompanies the product in those cases where conversion was not complete.

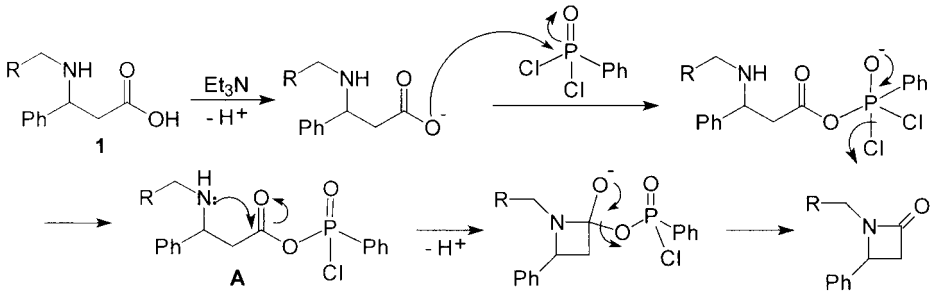
The possible effect of the substituent at nitrogen was explored (Table 2). We can see that when R is an aryl group, higher yields are obtained than when R is an alkyl group; thus, β-lactamization is facilitated by incorporation of a phenyl group in the *N*-substituent of the β-amino acid. Nevertheless, even when R=$CH_3(CH_2)_3$, this method is compared favorably with the other methods for β-lactamization of *rac*-**1a**.[9]

β-Lactam formation in this reaction (Tables 1 and 2) may proceed via intermediate **A**, as shown in Scheme 2. The reaction is run with 2 mol equiv. of triethyl amine; therefore, the conjugate base of the amino acid must be the initial species of the mechanism.

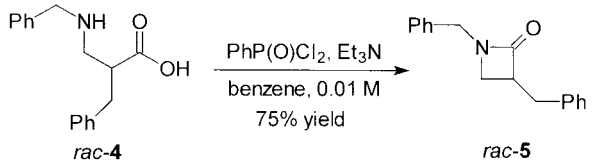
In order to explore the effect of substitution at C(2) in the starting β-amino acid, we carried out the reaction with (±)-*N*,α-dibenzyl-β-alanine, *rac*-**4**, in benzene at 0.01 M concentration, and under reflux. (Scheme 3). In this case, a *syn*-periplanar aromatic stacking effect may facilitate formation of the β-lactam.[10]

2.2. Cyclo-β-dipeptide formation

As indicated in Scheme 1, an alternative route, for the reaction of β-amino acids with $PhP(O)Cl_2$, affords



Scheme 2.



Scheme 3.

cyclo-β-dipeptides, presumably via cyclization of linear β-dipeptides. In particular, β-amino acids **6a** and *rac*-**6b** provided cyclo-β-dipeptides **3a** and *rac*-**3b** in moderate yields (Table 3). These dipeptides are formed in similar yields at high and low concentrations of the reaction media (see entries 1–3 and 6–8 in Table 3). While best yields of **3a** and *rac*-**3b** were found in benzene, acetonitrile and CH_2Cl_2 were also effective solvents for cyclo-β-dipeptide formation (cf. entries 4, 5 and 9 in Table 3). Reaction temperature seems to be important in the yield; thus, no cyclo-β-dipeptide *rac*-**3b** is observed in the reaction of *rac*-**6b** in CH_2Cl_2 at ambient temperature (compare entries 10 and 11 in Table 3).

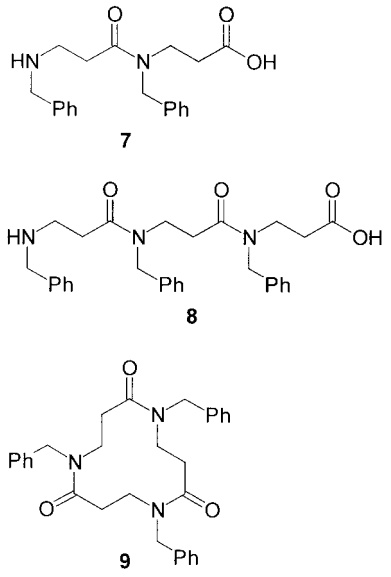


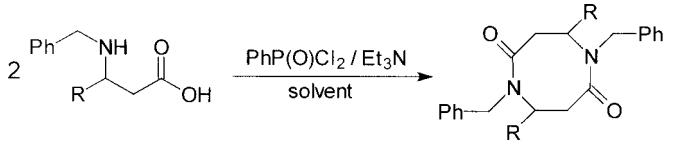
Chart 1.

Other researchers apparently missed the identification of cyclo-β-dipeptides in reactions, attempting the lactamization of β-amino acids with activating agents.[11] Nevertheless, the preparation of cyclo-β-dipeptides has been described in a few cases.[12] Although, ordinary ^1H and ^{13}C NMR spectra, and even EI mass spectra, may be unsuitable for distinction between β-lactams **2** and cyclo-β-dipeptides **3**, characteristic infrared bands allow easy differentiation.[13] In particular, whereas, β-lactams **2** and **5** present carbonyl stretch absorptions around 1730–1750 cm^{-1} (see Section 4), cyclo-β-dipeptides **3** exhibit C=O values close to 1640 cm^{-1}.

Importantly, the infrared spectra for the crude products in the reactions described in Table 3 showed the presence of cyclo-β-dipeptides **3a** and *rac*-**3b** (ν=1640 cm^{-1}) and of the carbonyl band that corresponds to β-lactams (ν= 1730–1750 cm^{-1}); nevertheless, HPLC analysis (μporasil stationary phase) established that the latter are only a minor side product, 6% in the case of **6a** and 20% in the case of *rac*-**6b**. On the other hand, ^1H NMR and infrared spectroscopic analysis of the crude product obtained from the reaction of **6a** with $PhP(O)Cl_2$ discards, by comparison with authentic samples,[14] the presence of linear dipeptide **7**, linear tripeptide **8**, and cyclo-β-tripeptide **9** (Chart 1).

Interestingly, the formation of cyclo-β-dipeptide *rac*-**3b** from β-amino acid *rac*-**6b** appears to be highly diastereoselective. Indeed, ^1H and ^{13}C NMR spectra, and HPLC analyses (μporasil 125 Å column) of the crude product indicate the presence of a single diastereoisomer. Although, the relative configuration of this product has not been securely established, molecular modeling (see Section 2.3) does lead to the conclusion that cyclic β-dipeptide *like*-**3b** should be more stable than the *unlike* isomer,[15] that is, (*R*,*R*)- and (*S*,*S*)-**3b** are of lower energy than (*R*,*S*)-**3b**. Therefore, it

Table 3. Cyclo-β-dipeptide formation of *N*-benzyl-β-alanine (**6a**) and (±)-*N*-benzyl-3-methyl-β-alanine (*rac*-**6b**) under various reaction conditions



6a, R = H; *rac*-**6b**, R = CH_3 **3a**, R = H; *rac*-**3b**, R = CH_3

Entry	Starting material	Concentration (M)	Solvent	Temperature (°C)	Time (h)	Yield[a] (%)
1	**6a**	0.1	Benzene	80	20	48
2	**6a**	0.01	Benzene	80	20	54
3	**6a**	0.005	Benzene	80	20	41
4	**6a**	0.01	CH_3CN	82	20	48
5	**6a**	0.1	CH_2Cl_2	40	96	43
6	*rac*-**6b**	0.1	Benzene	80	20	66
7	*rac*-**6b**	0.01	Benzene	80	20	68
8	*rac*-**6b**	0.005	Benzene	80	20	63
9	*rac*-**6b**	0.01	CH_3CN	82	20	35
10	*rac*-**6b**	0.1	CH_2Cl_2	40	96	26
11	*rac*-**6b**	0.1	CH_2Cl_2	25	96	~0

[a] Yield after flash chromatography.

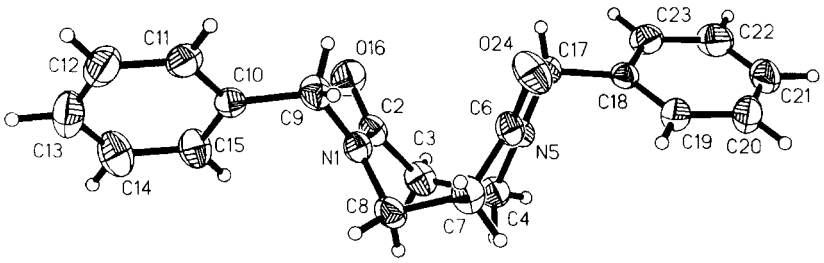
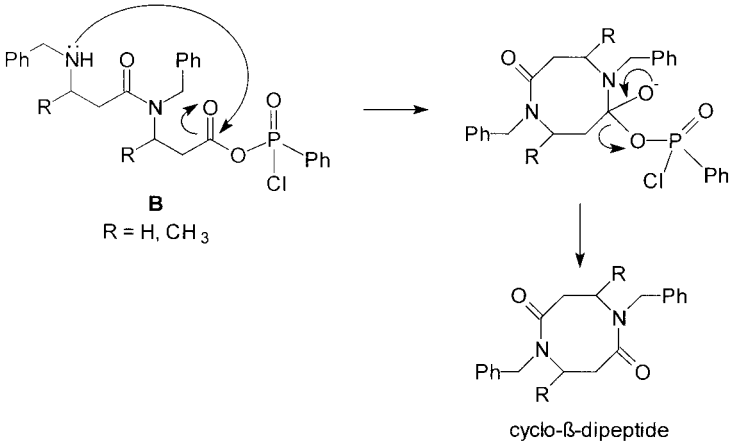


Figure 1. Structure and solid-state conformation of unsubstituted *N*-benzylated cyclo-β-dipeptide **3a**.



Scheme 4.

can be argued that late, product-like transition states in the reactions leading to β-dipeptide formation discriminate in favor of *like* diastereomers.

In order to confirm that the β-lactam is stable under the reaction conditions, a control experiment was carried out with equimolar amounts of β-amino acid **6a** and β-lactam *rac*-**2a**, under the established conditions [$PhP(O)Cl_2$, Et_3N/benzene, 80°C, 20 h]. While most of the starting β-lactam was recovered, the yield of cyclo-β-dipeptide **3a** was again (cf. Table 3) ca. 50%. These observations demonstrate that the β-lactam is stable under the reactions conditions, with excess amino acid present.

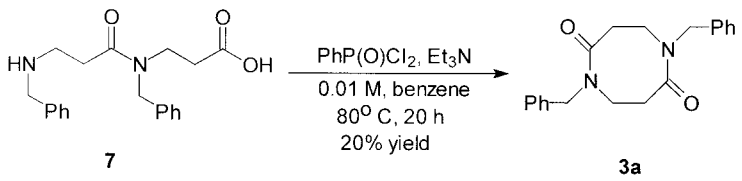
Recrystallization of cyclo-β-dipeptide **6a**, afforded a suitable crystal for X-ray diffraction analysis. The observed structure and solid-state conformation is presented in Fig. 1. Salient features in this crystallographic structure are (1) the slightly twisted boat conformation of the eight membered ring[16] and (2) the close proximity between the basic amide nitrogen and the carbonyl carbon situated across the ring, that allows for intramolecular electrostatic stabilization of the boat conformation.

Scheme 4 presents a reasonable reaction mechanism for cyclo-β-dipeptide formation. Two molecules of intermediate **A** (see Scheme 2) react to form a β-dipeptide, **B**, which undergoes intramolecular amide bond formation to afford the corresponding cyclo-β-dipeptide.

Some support for the proposal that β-amino acids **6** generate initially an open-chain β-dipeptide, which then cyclizes to give the final product, comes from the confirmation that β-dipeptide **7** reacts under the established conditions [0.01 M in benzene solvent, $PhP(O)Cl_2$, Et_3N, 80°C, 20 h] to give cyclo-β-dipeptide **3a**, albeit in low yield. (Scheme 5).

2.3. Molecular modeling

With the aim of understanding the contrasting reactivity behavior of β-amino acids **1** and **6**, the former giving the



Scheme 5.

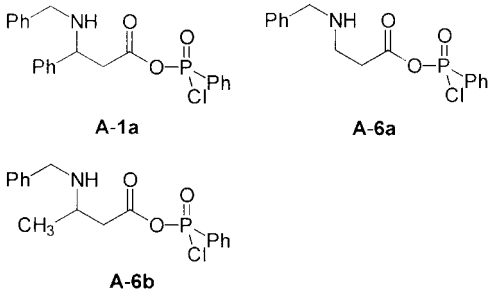


Chart 2.

anticipated β-lactams **2**, while the latter affording mainly cyclo-β-dipeptides **3**, a series of theoretical studies were carried out.

Initial geometries for presumed intermediates **A-1a**, **A-6a** and **A-6b** (Chart 2) were calculated by means of semi-empirical methods (MNDO, AM1 and PM3), accessible in the GAUSSIAN 94 package of programs.[17]

The structures of lowest energy selected from the semi-empirical calculations were then optimized at ab initio HF/3-21G level,[18] as available in GAUSSIAN 98.[19] Furthermore, the role of the solvent was taken into account by means of the general self-consistent reaction field (SCRF) model proposed for quantum chemical computations on solvated molecules.[20] In this model, the solvent is represented by an infinite dielectric continuum, characterized by its dielectric relative permittivity ϵ, in which a cavity is created and the solute is placed in it. The charge distribution of the solute polarizes the continuum, which in turn creates an electrostatic field inside the cavity.[21]

Fig. 2 shows the ab initio HF/3-21G calculated most stable structures for **A-1a**, **A-6a** and **A-6b** in a solvent of ϵ=2.3.[22] Most interestingly, unsubstituted β-amino acid phosphorylated intermediate **A-6a** presents an 'extended' conformation, with a considerably large distance between the nitrogen and the activated carbonyl, r=3.77 Å, which should be unfavorable for lactam formation, as experimentally found. By contrast, C(3)-substituted **A-1a** and **A-6b** present 'folded' conformations, with short N···C=O distances (r=2.71 and 2.61 Å, respectively), which should facilitate β-lactamization. This interpretation is in agreement with experimental observation in the case of substrate **1a** (Table 1), but seems to be at odds with **6b** as the starting β-amino acid.

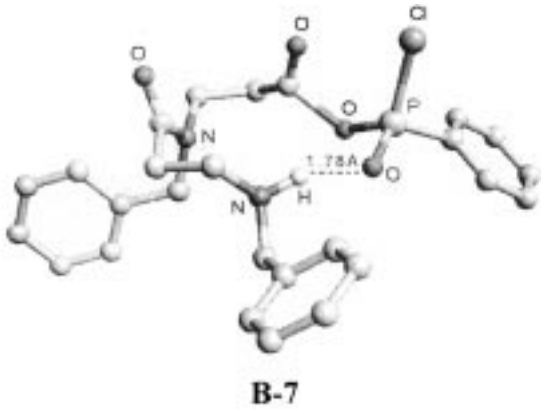


Figure 3. Ab initio HF/3-21G conformation of lowest energy for activated β-dipeptide **B-7**. Hydrogen bonding between the amino N-H group and the phosphoryl oxygen helps in stabilizing the 'folded' conformation and renders the phosphorus more electron deficient.

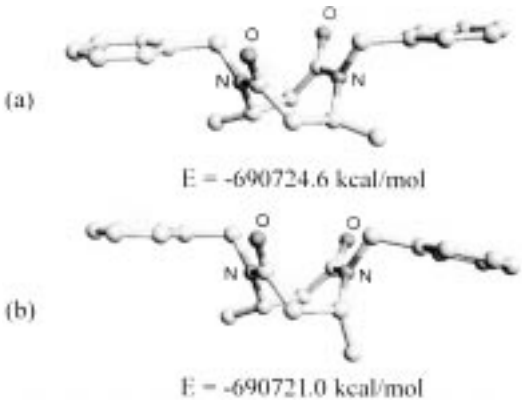


Figure 4. Ab initio HF/3-21G conformations of minimum energy for (a) *like*-cyclo-β-dipeptide *l*-**3b**, and (b) *unlike*-cyclo-β-dipeptide *u*-**3b**. The *like* diastereoisomer is calculated to be 3.6 kcal/mol more stable.

As it was indicated above, substrate **6a** affords cyclo-β-dipeptide **3a** in good yield (Table 3) and this experimental finding, i. e. the lack of β-lactam formation, can be understood in view of the preferred 'extended' conformation of the activated derivative **A-1a** (Fig. 2). In order to examine the propensity of open-chain phosphorylated β-dipeptide **B-7** for cyclization, we next calculated the conformation of minimum energy for this intermediate (Fig. 3). Pleasingly, **B-7** is estimated to adopt a 'folded' conformation with a relatively short N···C=O distance, r=3.72 Å, that should favor cyclization to give **3a**, as experimentally observed. Most interestingly, this folded conformation is stabilized

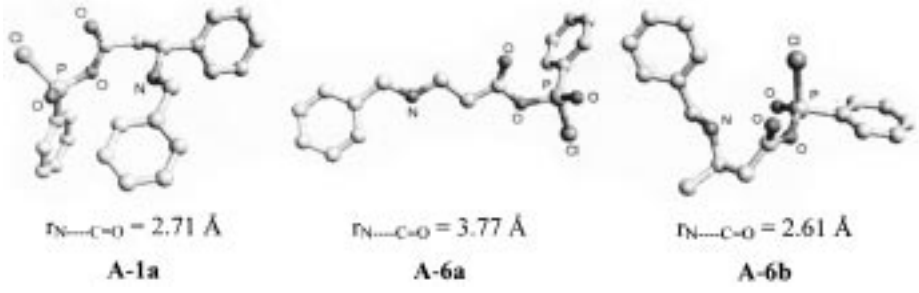


Figure 2. Ab initio HF/3-21G conformations of minimum energy, in a solvent of ϵ=2.3, for activated β-amino acids **A-1a**, **A-6a** and **A-6b**.

Table 4. Infrared carbonyl frequencies for representative β-lactams and cyclo-β-dipeptides prepared in this work ($\nu_{C=O}$, in cm^{-1})

Compound	Experimental	Calculated[a]
Lactam **2a**	1747	1751
Lactam **4**	1740	1743
Cyclo-β-dipeptide **3a**	1639	1639
Cyclo-β-dipeptide **3b**	1641	1639

[a] Ab initio HF/3-21G level (scaling factor to 0.9085), GAUSSIAN 98.[21]

by hydrogen-bonding between the N-H and the phosphoryl oxygen (Fig. 3). This hydrogen bonding might render the phosphorus more electron deficient, further activating dipeptide **B-7** towards cyclization.[23]

The relative energy between *like* and *unlike* cyclo-β-dipeptides **3b** was estimated. In apparent agreement with experiment (see Section 2.2), the *like* diastereoisomer [(*R*,*R*)-**3b** and (*S*,*S*)-**3b**] is calculated to be ca. 3.6 kcal/mol more stable than the *unlike* [(*R*,*S*)-**3b**] isomer. Examination of Fig. 4 offers a ready explanation for the above observation, since the methyl substituents in *like*-**3b** take both pseudo-equatorial positions in the eight-membered ring, whereas one of the methyls necessarily exists as pseudo-axial in the boat conformation of *unlike*-**3b**.[24]

Finally, it was also gratifying to confirm that ab initio calculations at the HF/3-21G level do reproduce the experimental infrared carbonyl bands for typical β-lactams and cyclo-β-dipeptides described in this work (Table 4).

3. Conclusions

Phenylphosphonic dichloride, $PhP(O)Cl_2$, activates (±)-(benzylamino)-3-phenylpropanoic acids, *rac*-**1a**–**d**, towards β-lactamization. 2-Substituted β-amino acid *rac*-**4** is also converted to β-lactam *rac*-**5** in 75% yield, in the presence of $PhP(O)Cl_2$. In contrast, 3-(benzylamino)-3-methylpropanoic acid **6a** and (±)-3-(benzylamino)-3-methylpropanoic acid *rac*-**6b** afford cyclo-β-dipeptides **3a** and *rac*-**3b**, respectively, as the main products.

X-Ray diffraction analysis of cyclo-β-dipeptides **3a** shows a slightly twisted boat conformation for this interesting analog of the well-known diketopiperazines, commonly generated during peptide synthesis from α-amino acids. Semi-empirical (AM1, MNDO, PM3) and ab initio (HF/3-21G) calculations reproduce with great accuracy the solid-state conformation of cyclic β-dipeptide **3a**.

Ab initio calculations at the HF/3-21G level help in understanding the contrasting reactivity behavior of activated (phosphorylated) β-amino acid derivatives **A-1a** and **A-6a**. The former is estimated to adopt a 'folded' conformation that should facilitate β-lactam formation, whereas the latter prefers an 'extended' conformation that apparently inhibits β-lactamization. Indeed, modeling of the activated open-chain β-dipeptide **B-7** provides a 'folded' conformation that should favor cyclization to give cyclo-β-dipeptide **3a**, as experimentally observed. Most interestingly, the 'folded' conformation of activated dipeptide **B-7** is stabilized by hydrogen-bonding between the amino N-H group and the phosphoryl oxygen, and this renders the phosphorus more electron deficient, further activating dipeptide derivate **B-7** towards cyclization.

Finally, both semi-empirical and ab initio calculations indicate that the *like*-diastereoisomer of disubstituted cyclo-β-dipeptide **3b** is significantly more stable than the *unlike* isomer, because the former places both methyl substituents pseudo-equatorial, whereas one of the methyl groups in *u*-**3b** adopts a pseudo-axial orientation in the eight-membered ring.

4. Experimental[25]

4.1. General procedure for the cyclization of *N*-substituted β-amino acids

In a flask provided with magnetic stirrer and condenser was placed the *N*-substituted β-amino acid (prepared by the reductive amination method developed by Simpkins[26]), the appropriate solvent, 2 mol equiv. of triethylamine and 1.5 mol equiv. of phenylphosphonic dichloride. The reaction mixture was refluxed at the chosen temperature and time (see Tables 1–3). Concentration in a rotatory evaporator gave the crude product which was purified on a silica gel column (hexane/AcOEt, 10:0⟶0:10) to get the product as a colorless oil, or white crystals (in the case of **3a**).

4.1.1. (±)-*N*-Benzyl-4-phenyl-2-azetidinone (*rac*-2a). 99% Yield. ^{1}H NMR ($CDCl_3$, 270 MHz) δ 2.85 (dd, ^3J= 2.2 Hz, J_{gem}=14.5 Hz, 1H), 3.32 (dd, ^3J=5.1 Hz, J_{gem}= 14.5 Hz, 1H), 4.38 (dd, ^1J=2.5 Hz, ^2J=5.1 Hz, 1H), 3.74, 4.79 (AB, J=J'=14.5 Hz, 2H), 7.33 (m, 10H). ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ 44.8, 47.0, 53.6, 126.6, 127.8, 128.6, 128.8, 129.1, 135.6, 138.0, 167.3. MS, *m*/*z* 237 (M^+). IR (ν_{max} cm^{-1}) 1747. Pure compound was confronted with ^{1}H NMR previously reported.[27]

4.1.2. (±)-*N*-*p*-Phenylbenzyl-4-phenyl-2-azetidinone (*rac*-2b). 95% Yield. ^{1}H NMR ($CDCl_3$, 270 MHz) δ 2.89 (dd, ^3J=2.1 Hz, J_{gem}=14.7 Hz, 1H), 3.36 (dd, ^3J=5.2 Hz, J_{gem}=14.6 Hz, 1H), 3.82, 4.83 (AB, J=J'=15.0 Hz, 2H), 4.45 (dd, ^1J=2.2 Hz, ^2J=5.2 Hz, 1H), 7.2–7.58 (m, 14H). ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ 44.5, 47.0, 53.7, 126.7, 127.1, 127.5, 128.6, 128.9, 129.1, 129.1, 134.6, 138.0, 140.7, 140.7, 167.3. MS, *m*/*z* 313 (M^+). IR (ν_{max} cm^{-1}) 1753. HRMS (FAB): calcd for $[M+H]^+$ $C_{22}H_{20}NO$: 314.1545; found: 314.1552.

4.1.3. (±)-*N*-*o*-Methoxybenzyl-4-phenyl-2-azetidinone (*rac*-2c). 72% Yield. ^{1}H NMR ($CDCl_3$, 270 MHz) δ 2.78 (dd, ^3J=1.5 Hz, J_{gem}=14.6 Hz, 1H), 3.28 (dd, ^3J=5.2 Hz, J_{gem}=14.6 Hz, 1H), 3.62 (s, 3H), 3.96, 4.67 (AB, J=J'=14.6 Hz, 2H), 4.39 (dd, ^1J=2.2 Hz, ^2J=5.2 Hz, 1H), 7.1–7.32 (m, 9H). ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ 39.9, 47.0, 54.3, 55.1, 110.3, 120.6, 123.8, 126.4, 128.2, 128.8, 129.3, 130.5, 138.8, 157.5, 167.4. MS, *m*/*z* 267 (M^+). IR (ν_{max} cm^{-1}) 1753. HRMS (FAB): calcd for $[M+H]^+$ $C_{17}H_{18}NO_2$: 268.1338; found: 268.1345.

4.1.4. (±)-*N*-*n*-Pentyl-4-phenyl-2-azetidinone (*rac*-2d). 62% Yield. ^{1}H NMR ($CDCl_3$, 270 MHz) δ 0.79 (t, J=

6.8 Hz, 3H), 1.20 (m, 4H), 1.39 (q, J=7.1 Hz, 2H), 2.76 (m, 2H), 3.32 (m, 2H), 5.0 (dd, ^1J=2.2 Hz, ^2J=4.9 Hz, 1H), 7.27 (m, 5H). MS, *m/z* (relative intensity) 217 (85.4), 178 (26), 146 (33), 122 (58.5), 107 (100). IR (ν_{max} cm^{-1}) 1728. HRMS (FAB): calcd for $[M+H]^+$ $C_{14}H_{20}NO$: 218.1545; found: 218.1553.

4.1.5. (±)-*N*-3-Dibenzyl-2-azetidinone (*rac*-5). 75% Yield. ^1H NMR ($CDCl_3$, 399.7 MHz) δ 3.0 (dd, ^3J= 5.0 Hz, J_{gem}=14.5 Hz, 2H), 3.1 (dd, ^3J=5.1 Hz, J_{gem}= 14.3 Hz, 2H), 3.5 (m, 1H), 4.2–5.0 (d, J=15.0 Hz, 2H), 7.2 (m, 10H). ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ 34.2, 43.9, 45.7, 50.7, 126.6, 127.6, 127.9, 128.6, 128.7, 129.1, 135.5, 138.0, 169.7. MS, *m/z* 251 (M^+). IR (ν_{max} cm^{-1}) 1740. HRMS (FAB): calcd for $[M+H]^+$ $C_{17}H_{18}NO$: 252.1388; found: 252.1390.

4.1.6. Perhydro-1,5-(*N*,*N*-dibenzyl)-diazocine-2,6-dione 3a. 49% Yield. Colorless crystals, mp=161–162°C. ^1H NMR ($CDCl_3$, 300 MHz) δ 2.95 (t, J=6.9 Hz, 2H), 3.54 (t, J=6.9 Hz, 2H) 4.61 (s, 2H), 7.31 (m, 5H). ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 36.7, 42.4, 49.3, 128.1, 128.7, 129.1, 137.2, 170.6. MS, *m/z* 322 (M^+). IR (ν_{max} cm^{-1}) 1639 and 1742. HRMS (FAB): calcd for $[M+H]^+$ $C_{20}H_{22}N_2O_2$: 322.1681; found: 322.1700. X-Ray crystallographic structure in Fig. 1.[28]

4.1.7. (±)-Perhydro-1,5-(*N*,*N*-dibenzyl)-4,8-dimethyl-diazocine-2,6-dione (*rac*-3b).[29] 68% Yield. ^1H NMR ($CDCl_3$, 270 MHz) δ 1.17 (d, J=5.9 Hz, 3H), 2.50 (dd, ^3J=2.2 Hz, J_{gem}=14.3 Hz, 1H), 3.03 (dd, ^3J=4.9 Hz, J_{gem}=14.5 Hz, 1H), 3.54 (m, 1H), 4.06, 4.55 (AB, J= J'=15.2 Hz, 2H), 7.24 (m, 5H). ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ 18.6, 44.2, 44.4, 47.1, 127.7, 128.3, 128.8, 136.1, 166.9. MS, *m/z* 350 (M^+). IR (ν_{max} cm^{-1}) 1641 and 1747. HRMS (FAB): calcd for $[M+H]^+$ $C_{22}H_{27}N_2O_2$: 351.2073; found: 351.2066.

Acknowledgements

We are indebted to the editor, Professor S. F. Martin, and the reviewers for many important observations. The financial support from Conacyt-México, via grants 3559P-E9607 and 33023-E2000, is gratefully acknowledged.

References

1. For reviews: (a) Drey, C. N. C. In *Chemistry and Biochemistry of the Amino Acids*; Barret, G. C., Ed.; Chapman and Hall: London, 1985; pp 25. (b) Juaristi, E.; Quintana, D.; Escalante, J. *Aldrichim. Acta* **1994**, *27*, 3. (c) Cole, D. C. *Tetrahedron* **1994**, *50*, 9517. (d) Cardillo, G.; Tomasini, C. *Chem. Soc. Rev.* **1996**, *23*, 117. (e) In *Enantioselective Synthesis of β-Amino Acids*; Juaristi, E., Ed.; Wiley-VCH: New York, 1997. (f) Juaristi, E.; López-Ruiz, H. *Curr. Med. Chem.* **1999**, *6*, 983.
2. For reviews: (a) *The Chemistry of β-Lactams*; Page, M. I., Ed.; Chapman and Hall: London, 1992. (b) Craig, W. A.; Ebert, S. C. *Antimicrob. Agents Chemother.* **1992**, *36*, 2577. (c) In *The Organic Chemistry of β-Lactams*; Georg, G. I., Ed.; Verlag Chemie: New York, 1993. (d) Southgate, R.; Branch, C.; Coulton, S.; Hunt, E. In *Recent Progress in the Chemical Synthesis of Antibiotics and Related Microbial Products*; Lukacs, G.; Springer: Berlin, 1993; Vol. 2, pp 621. For the preparation of β-lactams from β-amino acids: (e) Huang, H.; Iwasawa, N.; Mukaiyama, T. *Chem. Lett.* **1984**, 1465. (f) Kumieda, T.; Nagamatsu, T.; Kiguchi, T.; Hirobe, M. *Tetrahedron Lett.* **1988**, *29*, 2203. (g) Tanner, D.; Somfai, P. *Tetrahedron* **1988**, *44*, 613. (h) Mayachi, N.; Shibasaki, M. *J. Org. Chem.* **1990**, *55*, 1975. (i) Murayama, T.; Kobayashi, T.; Miura, T. *Tetrahedron Lett.* **1995**, *36*, 3703.
3. (a) Seebach, D.; Matthews, J. L. *Chem. Commun.* **1997**, 2015 (and references cited therein). (b) Gellman, S. H. *Acc. Chem. Res.* **1998**, *31*, 173 (and references cited therein). (c) Gademann, K.; Hintermann, T.; Schreiber, J. V. *Curr. Med. Chem.* **1999**, *6*, 905.
4. Palomo, C.; Aizpurua, J. M.; Cuevas, C. *J. Chem. Soc., Chem Commun.* **1994**, 1957.
5. Samy, R.; Kim, H. K.; Brady, M.; Toogood, P. L. *J. Org. Chem.* **1999**, *64*, 2711.
6. Seebach, D.; Gademann, K.; Ernst, M.; Hoyer, D. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 1223.
7. Veda, M.; Mori, H. *Bull. Chem. Soc. Jpn* **1992**, *65*, 1636.
8. Palomo, C.; Aizpurua, J. M.; Urchegui, R.; Iturburu, M.; Ochoa, A.; Cuevas, C. *J. Org. Chem.* **1991**, *56*, 2244.
9. (a) Kim, S.; Chang, S. B.; Lee, P. H. *Tetrahedron Lett.* **1987**, *28*, 2735. (b) Kim, S.; Lee, P. H.; Lee, T. A. *J. Chem. Soc., Chem. Commun.* **1988**, 1242.
10. Aromatic π–π interactions facilitating cyclizations; e.g. Diels–Alder reactions[12a] and Claisen Rearrangements[12b] have been postulated before: (a) Siegel, C.; Thornton, E. R. *J. Am. Chem. Soc.* **1989**, *111*, 5722. (b) Kallmerten, J.; Gould, T. J. *J. Org. Chem.* **1986**, *51*, 1152.
11. Nagao, Y.; Kumagai, T.; Tamai, S.; Matsunaga, H.; Abe, T.; Inoue, Y. *Heterocycles* **1996**, *42*, 849.
12. (a) Rothe, M.; Timler, R. *Chem. Ber.* **1962**, *95*, 783. (b) Aversa, M. C.; Bonaccorsi, P.; Giannetto, P.; Beagley, B.; Leigh, D. A.; Pritchard, R.; Truscello, A. M. *J. Heterocycl. Chem.* **1992**, *29*, 317. (c) Sutton, P. W.; Bradley, A.; Farrás, J.; Romea, P.; Urpí, F.; Vilarrasa, J. *Tetrahedron* **2000**, *56*, 7947.
13. Gordon, A. J.; Ford, R. A. *The Chemist's Companion*; Wiley: New York, 1972; pp 196, 200.
14. Full experimental and spectroscopic data for **7**–**9** will be reported separately.
15. For a definition of the *like/unlike* stereochemical descriptors: (a) Seebach, D.; Prelog, V. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 654. (b) Juaristi, E. In *Introduction to Stereochemistry and Conformational Analysis*; Wiley: New York, 1991; pp 52–54.
16. Moore, J. A.; Anet, F. A. L. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon: Oxford, 1984; Vol. 7, pp 783.
17. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T.; Petersson, G. A.; Montgomery, J. A.; Aghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Cioslowski, J.; Stefanov, B. B.; Nanayakkara, A.; Challacombe, M.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andres, J. L.; Replogle, E. S.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Binkley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. P.; Head-Gordon, M.; Gonzalez, C.; Pople, J. A. *GAUSSIAN 94* (Revision D.4); Gaussian: Pittsburgh, PA, 1995.
18. Hehre, W. J.; Schleyer, P. v. R.; Pople, J. A. *Ab Initio Molecular Orbital Theory*; Wiley: New York, 1986.
19. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A.; Stratmann, R. E., Jr.; Burant, J. C.;

Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Peterson, G. A.; Ayala, P. Y.; Cui, Q.; Ortiz, J. V.; Baboul, A. G.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, D. J.; Al-Lahman, M. A.; Peng, C. Y.; Nanyakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *GAUSSIAN 98* (Revision A.7); Gaussian, Pittsburgh, PA, 1998.

20. Rivail, J. L.; Rinaldi, D. *Chem. Phys.* **1976**, *18*, 233.
21. (a) Onsager, L. *J. Am. Chem. Soc.* **1938**, *60*, 1486. (b) Wong, M. W.; Frisch, M.; Wiberg, K. B. *J. Am. Chem. Soc.* **1991**, *113*, 4776. (c) Miertus, S.; Tomassi, J. *Chem. Phys.* **1982**, *65*, 239.
22. Optimized structures of **A-1a**, **A-6a**, and **A-6b** proved relatively insensitive to changes in solvent polarity.
23. Smith III, A. B.; Ducry, L.; Corbett, R. M.; Hirschmann, R. *Org. Lett.* **2000**, *2*, 3887.
24. *Conformational Analysis of Medium-sized Heterocycles*; Glass, R., Ed.; VCH: New York, 1988.
25. For general experimental procedures, see Juaristi, E.; Balderas, M.; Ramírez-Quirós, Y. *Tetrahedron: Asymmetry* **1998**, *9*, 3881.
26. Simpkins, N. S.; Cain, C. M.; Cousins, R. P. C.; Coumbarides, G. *Tetrahedron* **1990**, *46*, 523.
27. Barrow, K. D.; Spotswood, T. M. *Tetrahedron Lett.* **1965**, *37*, 3325.
28. Crystallographic data are deposited at Cambridge Crystallographic Data Center (CDDC 152942).
29. Relative configuration of *rac*-**3b** not yet securely established (see text).