

A Novel One-Step Approach for the Preparation of α -Amino Acids, α -Amino Amides, and Dipeptides from Azetidine-2,3-diones

Benito Alcaide,* Pedro Almendros, and Cristina Aragoncillo^[a]

Abstract: A remarkable reaction of azetidine-2,3-diones with primary as well as secondary amines, and water is presented. Simply by varying the nucleophile, an unprecedented one-step synthesis of α -amino acids, α -amino amides, and dipeptides, was developed in both the racemic and optically pure forms. The current mechanistic hypothesis invokes a concerted process involving CO extrusion. However, a stepwise pathway can also account for these novel transformations.

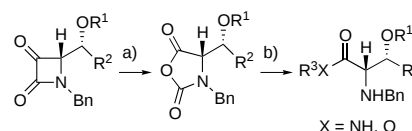
Keywords: amino acids • asymmetric synthesis • cleavage reactions • β -lactams • peptides

Introduction

α -Amino acids play a central role in chemistry and biology. α -Amino amides, like α -amino acids, are of medicinal value.^[1] α -Amino acids can be found almost anywhere in nature, most evident as the building blocks of peptides and proteins, but also extensively in other natural products.^[2] The unusual structures are mainly produced by microorganisms and have evolved to interfere with biochemical pathways of other organisms. In close analogy, a large number of unusual man-designed amino acids have pharmaceutical applications or are used to control plant growth and plant diseases. In addition, the use of both natural and unnatural α -amino acids and their derivatives as chiral reagents, auxiliaries, catalyst and ligands for asymmetric synthesis is widely spread.^[3] As a consequence of their application to the fine chemical, agrochemical, and pharmaceutical business sectors, the development of new synthetic methods for the preparation of amino acids and their derivatives in enantiomerically pure form has attracted much attention.^[4]

Recently, a number of investigations has been centered on the preparation and reactivity of monocyclic azetidine-2,3-diones, because of their use as building blocks in the synthesis of biologically important β -lactam products.^[5] In this context, the antibiotics nocardicin A and sulphazecin, as well as enzyme inhibitors, such as tabtoxin, are representative

examples. In addition to their interest in β -lactam antibiotics synthesis, azetidine-2,3-diones are important starting materials for the preparation of amino-acid derivatives. However, little was known about their application in synthesis of the C2–C3 bond cleavage of the β -lactam nucleus until Palomo and colleagues elegantly merged into this field; they utilized an azetidine-2,3-dione approach to α -amino acids.^[6] This two-step route starts with the Baeyer–Villiger oxidation of azetidine-2,3-diones to give *N*-carboxy anhydrides (NCA), which, after coupling with amines or alcohols, produced α -amino acid derivatives (Scheme 1).



Scheme 1. Palomo's two-step route from azetidine-2,3-diones to α -amino acids. a) *m*CPBA, dichloromethane, -40°C . b) MeOH, room temperature or R^3NH_2 , room temperature.

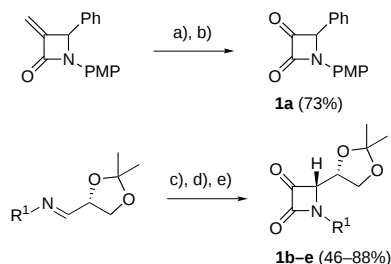
As part of our ongoing project on the synthesis of natural products and derivatives of 2-azetidinones,^[7] we decided to pursue approaches to 3-substituted 3-amino- β -lactams because of their importance both as substrates for the “ β -lactam synthon method” and for studies of biological activity. In connection with this work, we wish to report here the unexpected manner in which azetidine-2,3-diones and a variety of primary as well as secondary amines undergo reaction to give α -amino amides and dipeptides.^[8] In addition, a one-step metal-promoted synthesis of α -amino acids from azetidine-2,3-diones is also described. The concise and convergent approach described herein presents a practical opportunity to connect the rapidly expanding fields of β -lactam chemistry with α -amino acids and peptides.^[9]

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Supporting information for this article is available on the WWW under <http://www.chemurj.org> or from the author. It contains spectroscopic and analytical data for compounds ($\pm$)-**2a**, ($\pm$)-**2c**, ($\pm$)-**2d**, (–)-**2f**, (–)-**2i**, (–)-**2n**, (+)-**8a**, (+)-**8b**, ($\pm$)-**10a**, and (–)-**10c**; as well as experimental procedures for compound (+)-**10b**.

Results and Discussion

Starting substrates, azetidine-2,3-diones **1**, were prepared both in racemic and in optically pure forms following our previously reported methods. Racemic compound **1a** was obtained from 3-methylidene-4-phenyl-2-azetidinone by dihydroxylation followed by oxidative cleavage with NaIO_4 .^[10] Azetidine-2,3-diones **1b–e** were efficiently prepared in the optically pure form from imines of (*R*)-2,3-*O*-isopropylidene-glyceraldehyde, by a Staudinger reaction with acetoxyacetyl chloride in the presence of Et_3N , followed by sequential transesterification and Swern oxidation (Scheme 2).^[7e]



Scheme 2. Preparation of azetidine-2,3-diones **1a–d**. a) OsO_4 , Me_3NO , acetone/water, RT. b) NaIO_4 , NaHCO_3 , dichloromethane, RT. c) Et_3N , $\text{AcOCH}_2\text{COCl}$, dichloromethane, RT. d) NaOCH_3 , CH_3OH , 0°C . e) i) $(\text{CO})_2\text{Cl}_2$, DMSO, dichloromethane, -78°C , 2 h, ii) Et_3N .

Our initial aim was to explore the reactivity of azetidine-2,3-diones **1** with various primary amines in order to obtain the corresponding imines. However, to our surprise, under the usual conditions utilized for imine formation, the reaction of azetidine-2,3-dione (+)-**1b** with benzylamine provided the enantiomerically pure α -amino acid derivative (–)-**2e** in a reasonable yield (50%), instead of the expected imino- β -lactam. When azetidine-2,3-dione (–)-**1c** was used instead of the α -keto lactam (+)-**1b**, the reaction proceeded in the same manner, giving α -amino amide (–)-**2m** in good yield (58%). Similar results to those observed for the coupling of benzylamine with azetidine-2,3-diones (+)-**1b** and (–)-**1c** were obtained in the amine-mediated reaction of different substituted azetidine-2,3-diones **1** with allylamine as well as propargylamine and *p*-anisidine (Table 1, Scheme 3).

Preliminary experiments were carried out under the usual anhydrous conditions utilized for the formation of imines, namely with MgSO_4 , but we then realized that this was not necessary. Also, initial experiments with the most volatile amines were carried out in a large excess (10 equiv). However,

we later performed the reaction with equimolecular amounts of amine/substrate and obtained the same results as previously. Additionally, we carried out the experiments either with or without argon and with or without rigorously dry and degassed THF, obtaining similar results in all cases. This result is in sharp contrast with the smooth reaction of related indoline-2,3-diones with primary amines to afford imino- γ -lactams.^[11] The different behavior of azetidine-2,3-diones and pyrrolidine-2,3-diones may be caused by differences in the carbinolamine presumably involved in the reaction, perhaps the more strained four-membered ring has a greater tendency to open.^[12] Of particular interest was the reaction of azetidine-2,3-diones with α -amino esters, such as glycine methyl ester, alanine methyl ester, phenylglycine methyl ester, or β -alanine methyl ester, showing the utility of this approach in the rapid synthesis of optically pure dipeptides (Table 1, entries 8–11 and 16). As a good example, the treatment of azetidine-2,3-dione (+)-**1b** with (*S*)-phenylglycine methyl ester affords a 65% yield of peptide (+)-**2k** (entry 11) that has three chiral centers. Compound (+)-**2k** showed a single set of signals in the ^1H NMR spectrum, thus proving that this transformation proceeded without diminishing the stereochemical integrity. In this way, α -amino amides and dipeptides can be smoothly prepared in both the racemic and enantiopure forms (Table 1, Scheme 3). The optical purities of the compounds **2** were confirmed by the use of $[\text{Eu}(\text{hcf})_3]$ in CDCl_3 according to the literature procedure.^[13] Notably, the incorporation of functionality into the ketone or the amine substrates does not retard the reaction. In addition, both aryl and alkyl amines can be employed. Thus, it now appears that the initial Baeyer–Villiger oxidation of the azetidine-2,3-dione moiety in the Palomo's two-step route to amino acids is superfluous.^[14]

From a mechanistic point of view, our results could be explained as illustrated in Scheme 4 (stepwise process) or Scheme 5 (concerted process). According to Scheme 4, this transformation could be rationalized through an initial nucleophilic addition of the amine to the ketone moiety of the azetidine-2,3-dione **1** to form an intermediate carbinolamine **3**. This intermediate **3** may react through two different pathways to give the expected 3-imino- β -lactam **4** or the intermediate **5**, but presumably evolves to the fused aziridine- β -lactam **5**. We believe that the N1–C2 bond of intermediate **5** should be very labile, evolving to aziridinone **6**. Under the reaction conditions employed, compound **6** furnishes the *N*-formyl-amide **7**. Intermediate **7** appears as the final, not isolable product, in the reaction. It is well-known that *N*-formyl amides that are related to **7** smoothly lose CO under basic conditions to give the corresponding NH amides.^[15]

We thought that the reaction could proceed with rate enhancement by heating in a sealed tube at 90°C . Indeed, we found that in most of the tested cases the thermal process proceeded faster than the reaction at room temperature, which may well favor a concerted CO extrusion (Scheme 5). However, as the temperature increased there was concomitant formation of unidentified side products.

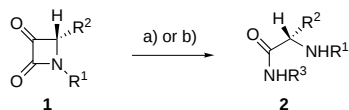
In order to obtain more information about the correct mechanism, we decided to carry out the reaction between azetidine-2,3-diones **1** and secondary amines. Indeed, we

Abstract in Spanish: Se describe una notable reacción de azetidin-2,3-dionas con aminas primarias o secundarias, o con agua. Con un simple cambio del nucleófilo se puede conseguir una síntesis sin antecedentes de derivados de α -aminoácidos en una etapa. Se pueden preparar α -aminoácidos, α -aminoamidas y dipéptidos, tanto en forma racémica como ópticamente pura. El mecanismo más probable debe ser un proceso concertado con extrusión de CO. Sin embargo, un camino de reacción por etapas también podría justificar esta novedosa transformación.

Table 1. One-step synthesis of α -amino amides and dipeptides **2** from azetidine-2,3-diones **1**.^[a]

Entry	Substrate	R ¹	R ²	R ³	Product	Yield [%] ^[b]
1	($\pm$)- 1a	PMP	Ph	PhCH ₂	($\pm$)- 2a	45
2	($\pm$)- 1a	PMP	Ph		($\pm$)- 2b	77
3	($\pm$)- 1a	PMP	Ph		($\pm$)- 2c	49
4	($\pm$)- 1a	PMP	Ph	MeO ₂ C- 	($\pm$)- 2d	60
5	(+)- 1b	PMP		PhCH ₂	(-)- 2e	50
6	(+)- 1b	PMP			(-)- 2f	45
7	(+)- 1b	PMP			(-)- 2g	48
8	(+)- 1b	PMP		MeO ₂ C- 	(-)- 2h	50
9	(+)- 1b	PMP		MeO ₂ C- 	(-)- 2i	55
10	(+)- 1b	PMP		MeO ₂ C- 	(-)- 2j	48
11	(+)- 1b	PMP		MeO ₂ C- 	(+)- 2k	65
12	(+)- 1b	PMP		MeO- 	(-)- 2l	59
13	(-)- 1c	2-propenyl		PhCH ₂	(-)- 2m	58
14	(-)- 1c	2-propenyl			(-)- 2n	42
15	(-)- 1d	2-propynyl		PhCH ₂	(-)- 2o	50
16	(-)- 1e	benzyl		MeO ₂ C- 	(-)- 2p	43

[a] PMP = 4-MeOC₆H₄. [b] Yield of pure, isolated product with correct analytical and spectral data.

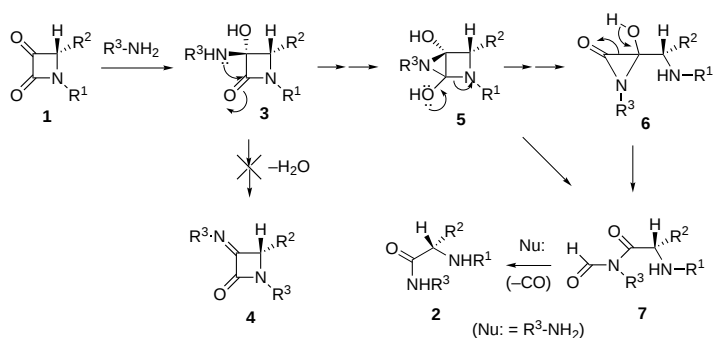


Scheme 3. One-step preparation of α -amino amides and dipeptides from azetidine-2,3-diones and primary amines. a) R³NH₂, THF, room temperature. b) R³NH₂, THF, sealed tube, 90 °C.

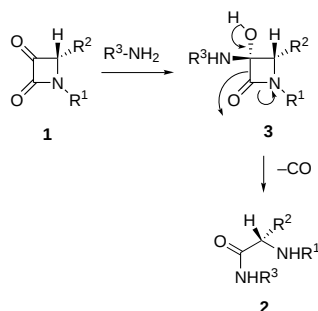
observed disappearance of the α -keto lactam moiety and appearance of tertiary α -amino amides **8** (Scheme 6). As before, this new transformation that involves secondary

amines was amenable to the preparation of enantiomerically pure α -amino amides (**8a–c**) and dipeptides (**8d**). Thus, proving again that this reaction proceeded without detectable racemization. If the corresponding tertiary α -amino amides were formed by a stepwise pathway, quaternary ammonium salt intermediates (compound types **5–7** in Scheme 4) should be involved. This is hard to believe, and points to the concerted process (Scheme 5) as the more likely pathway.

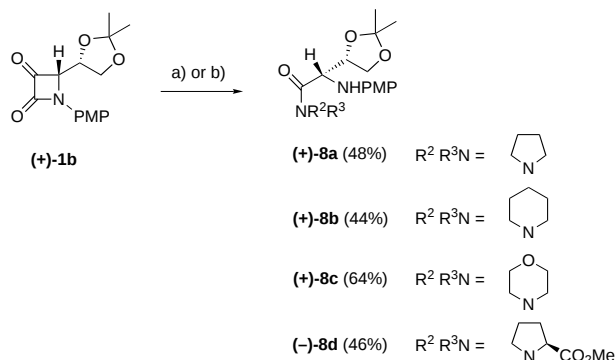
We sought to explore the reactivity of α -keto lactams **1** with different nucleophiles, taking into account the smooth reaction between azetidine-2,3-diones and primary and secondary



Scheme 4. Mechanistic explanation for the formation of α -amino acids derivatives by a stepwise process.

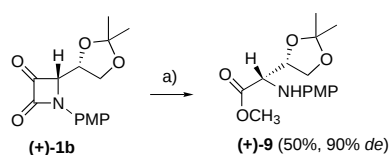


Scheme 5. Mechanistic explanation for the formation of α -amino acids derivatives by a concerted process.



Scheme 6. One-step preparation of tertiary α -amino amides and dipeptides from azetidine-2,3-diones and secondary amines. a) R^2R^3NH , THF, RT. b) R^2R^3NH , THF, sealed tube, 90 °C.

amines. This is not the case for the use of alcohols or water. Fortunately, the treatment of azetidine-2,3-dione (+)-1b with sodium methoxide/methanol led to the clean coupling of these fragments into the α -amino ester (+)-9 (Scheme 7). However, analysis of the crude by 1H NMR spectrum revealed concurrent partial epimerization (5 %) in compound (+)-9.



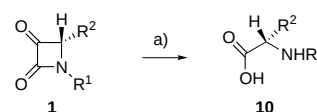
Scheme 7. One-step preparation of α -amino ester **9** from azetidine-2,3-dione **1a** and sodium methoxide/methanol. a) MeONa, MeOH, RT.

From the variety of synthetic transformations mediated by transition metals, processes involving cleavage of C–C single bonds are among the most difficult to achieve.^[16] Hence, their development remains an important challenge in organic chemistry. We attempted the reaction with water in the presence of some transition metals because the substrates **1** presently employed benefit from relief of the structural strain. Among the various metals and conditions studied, the best combination seemed to be cadmium/ammonium chloride in wet methanol (5 % water). Addition of metal is essential to obtain compounds **10**. In the absence of metallic promoter, no α -amino acid was formed. Increasing the reaction temperature from 20 to 65 °C lowered the conversion of azetidine-2,3-diones **1** to α -amino acids **10**, because a high proportion of reduction product of the ketone moiety was obtained. The presence of ammonium chloride is crucial; this may be attributed to changes in the ionic strength of the solvent.^[17] The azetidine-2,3-dione moiety then reacts with water to form the corresponding α -amino acids **10** (Table 2, Scheme 8). Other examples of the metal-promoted α -amino acid formation are listed in Table 2. Indium and manganese gave erratic results because sometimes the reaction proceeded efficiently, but complex mixtures of unidentified products were obtained

Table 2. Metal-promoted one-step synthesis of α -amino acids **10** from azetidine-2,3-diones **1**.^[a]

Entry	Substrate	R ¹	R ²	Metal	Product	Yield [%] ^[b]
1	(±)-1a	PMP	Ph	Cd	(±)-10a	45
2	(+)-1b	PMP		Cd	(+)-10b	58
3	(+)-1b	PMP		In	(+)-10b	42
4	(+)-1b	PMP		Mn	(+)-10b	33
4	(-)-1d	2-propynyl		Cd	(-)-10c	35
5	(-)-1e	benzyl		Cd	(-)-10d	57

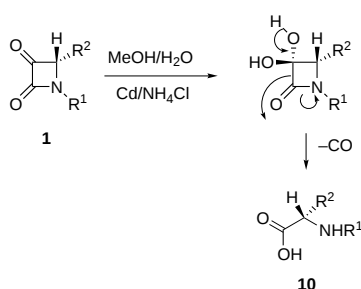
[a] PMP = 4-MeOC₆H₄. [b] Yield of pure, isolated product with correct analytical and spectral data.



Scheme 8. Metal-promoted one-step preparation of α -amino acids **10** from azetidine-2,3-diones **1**. a) Metal, NH₄Cl, MeOH (containing 5 % water), RT.

in the majority of the tested cases. When zinc was used instead of cadmium, reduction products of the ketone moiety were always isolated. Tin and bismuth failed to produce any desired product when they were used as metal promoters.

Because water is an economical solvent, we decided to increase the amount of water in the coupling reaction by the use of a MeOH/NH₄Cl (aq. satd.) (1:5) or THF/NH₄Cl (aq. satd.) (1:5) mixed solvents. Although complete conversion was observed by TLC and ¹H NMR analysis of the crude reaction mixtures, the isolated yields (12–18% yield) were not as good as before. The high polarity of α -amino acids **10** and subsequent high water solubility may be responsible for the modest isolated yields in the aqueous reaction media. A plausible rationale for this azetidine-2,3-dione behavior is that chelation of the ketone and amide moieties in the metal presence activates the ketone group as effectively as required for water attack. Concerted CO extrusion produces the α -amino acids **10** (Scheme 9).



Scheme 9. Mechanistic explanation for the formation of α -amino acids **10** by a concerted process.

Conclusion

In conclusion, the reaction of azetidine-2,3-diones with primary as well as secondary amines, and water is a novel method for the one-step production of α -amino acids, α -amino amides, and dipeptides from azetidine-2,3-diones. This unprecedented transformation allows variability of the structure and facile incorporation of functional groups. The coupling reaction into an amino-acid unit is extremely simple in execution and workup, and is of considerable potential for the synthesis of α -amino acid derivatives, in both the racemic and optically pure forms.

Experimental Section

General methods: ¹H NMR and ¹³C NMR spectra were recorded on a Bruker AMX-500, Bruker Avance-300, Varian VRX-300S or Bruker AC-200. NMR spectra were recorded in CDCl₃ solutions, unless otherwise stated. Chemical shifts are given in ppm relative to TMS (¹H, δ = 0.0), or CDCl₃ (¹³C, δ = 76.9). Low- and high-resolution mass spectra were recorded on a HP5989 A spectrometer operating in the chemical ionization mode (CI) unless otherwise stated. Specific rotation [α]_D is given in ° at 20 °C, and the concentration (*c*) is expressed in g 100 mL^{−1}. All commercially available compounds were used without further purification.

Reactions between primary amines and azetidine-2,3-diones 1. General procedure for the synthesis of α -amino amides and dipeptides 2:

Method A: A solution of the appropriate amine (0.5 mmol) in THF (0.1 mL) was added to a solution of the corresponding azetidine-2,3-dione **1**

(0.5 mmol) in THF (5 mL) and the solution was stirred at room temperature for 2–24 h. Compounds ($\pm$)-**2b** and (−)-**2m** required a longer reaction time (3 and 4 d, respectively). The solvent was removed under reduced pressure and the residue was purified by flash chromatography (hexanes/ethyl acetate or dichloromethane/ethyl acetate) to give analytically pure **2**. Spectroscopic and analytical data for some representative pure forms of **2** are given below.^[18]

Method B: A solution of the appropriate amine (0.5 mmol) in THF (1 mL) was added to a solution of the azetidine-2,3-dione **1** (0.5 mmol) in THF (5 mL) and the solution was heated in a sealed tube at 90 °C for 2–6 h. The reaction mixture was allowed to cool to room temperature, the solvent was removed under reduced pressure, and the residue was purified by flash chromatography (hexanes/ethyl acetate or dichloromethane/ethyl acetate) to give analytically pure **2**.

(SR)-2-(4-Methoxyphenylamino)-2-phenyl-N-allyl-methanecarboxamide [(±)-2b]:

Method B: The reaction of azetidine-2,3-dione [(±)-**1a**, 44 mg, 0.17 mmol] gave (±)-**2b** (39 mg, 77%) as a colorless oil after purification by flash chromatography (hexanes/ethyl acetate 2:1). ¹H NMR (200 MHz, CDCl₃, 25 °C): δ = 7.24 (m, 5H), 6.91/6.79 (dd, *J* = 6.6, 2.2 Hz, each 2H), 5.75 (m, 1H), 5.15 (m, 2H), 4.89 (s, 1H), 3.81 (t, *J* = 1.2 Hz, 1H), 3.77 (s, 3H), 3.75 (brs, 1H); ¹³C NMR (50 MHz, CDCl₃, 25 °C): δ = 162.3, 158.8, 136.1, 134.6, 133.1, 128.9, 128.4, 127.9, 127.7, 116.9, 114.1, 55.2, 54.9, 41.6; IR (CHCl₃): $\tilde{\nu}$ = 3350, 3202, 1651 cm^{−1}; MS (CI): *m/z* (%): 297 (100) [*M*+H]⁺, 296 (17) [*M*]⁺; elemental analysis calcd (%) for C₁₈H₂₀N₂O₂ (346.4): C 72.95, H 6.80, N 9.45; found: C 72.87, H 6.82, N 9.48.

Method A: Azetidine-2,3-dione [(±)-**1a**, 44 mg, 0.17 mmol] and chromatography of the residue (hexanes/ethyl acetate 2:1) gave (±)-**2a** (37 mg, 73%) as a colorless oil.

(−)-(2S)-2-(4-Methoxyphenylamino)-2-[(S)-2,2-dimethyl-1,3-dioxolan-4-yl]-N-benzyl-methanecarboxamide [(−)-2e]:

Method A: Azetidine-2,3-dione [(+)-**1b**, 183 mg, 0.624 mmol] and purification by flash chromatography (hexanes/ethyl acetate 6:4) gave (−)-**2e** as a colorless solid (112 mg, 50%). M.p. 111–112 °C (hexanes/ethyl acetate). [α]_D = −41.7 (*c* = 1.0 in CHCl₃); ¹H NMR (300 MHz, CDCl₃, 25 °C): δ = 7.39 (brs, 1H), 7.26 (m, 5H), 6.79/6.59 (d, *J* = 9.0 Hz, each 2H), 4.62 (dd, *J* = 11.1, 5.7 Hz, 1H), 4.53 (dd, *J* = 15.1, 5.7 Hz, 1H), 4.43 (dd, *J* = 15.1, 5.7 Hz, 1H), 4.31 (brs, 1H), 4.13 (dd, *J* = 8.8, 6.7 Hz, 1H), 4.01 (dd, *J* = 8.8, 5.7 Hz, 1H), 3.74 (s, 3H), 3.70 (d, *J* = 4.4 Hz, 1H), 1.47/1.38 (s, each 3H); ¹³C NMR (75 MHz, CDCl₃, 25 °C): δ = 171.1, 153.3, 140.9, 137.9, 128.5, 127.4, 127.3, 115.1, 114.9, 109.8, 75.7, 66.8, 62.4, 55.7, 43.1, 26.5, 24.7; IR (KBr): $\tilde{\nu}$ = 3350, 3200, 1650 cm^{−1}; MS (CI): *m/z* (%): 371 (100) [*M*+H]⁺, 300 (29) [*M*]⁺; elemental analysis calcd (%) for C₂₁H₂₆N₂O₄ (370.5): C 68.09, H 7.07, N 7.56; found: C 68.17, H 7.09, N 7.58.

(−)-(2S)-2-(4-Methoxyphenylamino)-2-[(S)-2,2-dimethyl-1,3-dioxolan-4-yl]-N-propargyl-methanecarboxamide [(−)-2g]:

Method B: Azetidine-2,3-dione [(+)-**1b**, 65 mg, 0.22 mmol] gave (−)-**2g** as a colorless oil (34 mg, 48%) after purification by flash chromatography (hexanes/ethyl acetate 2:1). [α]_D = −8.5 (*c* = 0.8 in CHCl₃); ¹H NMR (300 MHz, CDCl₃, 25 °C): δ = 6.60/6.81 (dd, *J* = 6.6, 2.2 Hz, each 2H), 4.58 (dd, *J* = 10.9, 5.6 Hz, 1H), 4.31 (d, *J* = 3.4 Hz, 1H), 4.09 (m, 2H), 4.07 (dd, *J* = 5.6, 2.7 Hz, 1H), 3.96 (dd, *J* = 8.8, 5.6 Hz, 1H), 3.76 (s, 3H), 3.65 (t, *J* = 4.1 Hz, 1H), 2.19 (t, *J* = 2.7 Hz, 1H), 1.48/1.37 (s, each 3H); ¹³C NMR (75 MHz, CDCl₃, 25 °C): δ = 171.0, 153.5, 140.9, 115.3, 115.0, 109.9, 75.4, 71.6, 66.8, 62.3, 55.7, 26.6, 26.1, 24.8; IR (CHCl₃): $\tilde{\nu}$ = 3345, 3202, 1655 cm^{−1}; MS (CI): *m/z* (%): 319 (100) [*M*+H]⁺, 318 (23) [*M*]⁺; elemental analysis calcd (%) for C₁₇H₂₂N₂O₄ (318.4): C 64.13, H 6.97, N 8.80; found: C 64.20, H 6.96, N 8.82.

Peptide (−)-2h: **Method A:** from azetidine-2,3-dione [(+)-**1b**, 61 mg, 0.21 mmol] gave (−)-**2h** as a colorless oil (37 mg, 50%) after purification by flash chromatography (hexanes/ethyl acetate 1:1). [α]_D = −2.5 (*c* = 0.8 in CHCl₃); ¹H NMR (500 MHz, CDCl₃, 25 °C): δ = 7.56 (t, *J* = 5.4 Hz, 1H), 6.79/6.65 (dd, *J* = 6.6, 2.2 Hz, each 2H), 4.58 (q, *J* = 5.6 Hz, 1H), 4.34 (d, *J* = 3.4 Hz, 1H), 4.09 (dd, *J* = 8.8, 6.6 Hz, 1H), 4.05 (m, 2H), 3.99 (dd, *J* = 8.8, 5.6 Hz, 1H), 3.75 (s, 3H), 3.73 (s, 3H), 3.67 (t, *J* = 4.1 Hz, 1H), 1.47/1.36 (s, each 3H); ¹³C NMR (125 MHz, CDCl₃, 25 °C): δ = 171.7, 169.8, 153.4, 140.9, 115.4, 114.9, 109.9, 75.5, 66.8, 62.4, 55.7, 52.2, 41.0, 26.6, 24.8; IR (CHCl₃): $\tilde{\nu}$ = 3342, 3208, 1738, 1656 cm^{−1}; MS (CI): *m/z* (%): 353 (100) [*M*+H]⁺, 352 (25) [*M*]⁺; elemental analysis calcd (%) for C₁₇H₂₄N₂O₆ (352.4): C 57.94, H 6.86, N 7.95; found: C 57.87, H 6.87, N 7.97.

Peptide (−)-2j: **Method A:** Azetidine-2,3-dione [(+)-**1b**, 54 mg, 0.18 mmol] gave (−)-**2j** as a colorless oil (48 mg, 48%) after purification

by flash chromatography (hexanes/ethyl acetate 1:1). $[\alpha]_D = -17.3$ ($c = 0.7$ in CHCl_3); ^1H NMR (300 MHz, CDCl_3 , 25°C): $\delta = 7.48$ (m, 1H), 6.76/6.56 (dd, $J = 6.6, 2.2$ Hz, each 2H), 4.52 (q, $J = 5.6$ Hz, 1H), 4.04 (m, 3H), 4.01 (d, $J = 7.1$ Hz, 1H), 3.74 (s, 3H), 3.52 (m, 3H), 2.49 (t, $J = 6.1$ Hz, 2H), 1.46/1.35 (s, each 3H), 1.17 (t, $J = 7.3$ Hz, 1H); ^{13}C NMR (75 MHz, CDCl_3 , 25°C): $\delta = 171.8, 171.2, 153.3, 140.8, 115.0, 114.9, 109.8, 75.5, 66.8, 62.3, 60.6, 55.7, 34.7, 34.1, 26.5, 24.8, 14.0$; IR (CHCl_3): $\tilde{\nu} = 3340, 3205, 1742, 1658\text{ cm}^{-1}$; MS (CI): m/z (%): 381 (100) $[M+\text{H}]^+$, 380 (36) $[M]^+$; elemental analysis calcd (%) for $\text{C}_{19}\text{H}_{28}\text{N}_2\text{O}_6$ (380.4): C 59.99, H 7.42, N 7.36; found: C 60.07, H 7.44, N 7.35.

Peptide (+)-2k: *Method A:* Azetidine-2,3-dione [(+)-1b, 48 mg, 0.164 mmol] gave (+)-2k as a colorless oil (45 mg, 65%) after purification by flash chromatography (hexanes/ethyl acetate 3:1). $[\alpha]_D = +11.0$ ($c = 0.6$ in CHCl_3); ^1H NMR (300 MHz, CDCl_3 , 25°C): $\delta = 7.94$ (d, $J = 6.8$ Hz, 1H), 7.34 (m, 5H), 6.83/6.69 (dd, $J = 6.6, 2.4$ Hz, each 2H), 5.53 (d, $J = 7.1$ Hz, 1H), 4.53 (m, 1H), 4.30 (brs, 1H), 4.01 (m, 2H), 3.78 (m, 1H), 3.77 (s, 3H), 3.69 (s, 3H), 1.46/1.34 (s, each 3H); ^{13}C NMR (75 MHz, CDCl_3 , 25°C): $\delta = 171.1, 170.7, 153.5, 141.1, 135.8, 128.9, 128.5, 127.1, 115.7, 114.9, 109.8, 75.5, 66.7, 62.6, 56.6, 55.7, 52.6, 26.5, 24.8$; IR (CHCl_3): $\tilde{\nu} = 3338, 3204, 1740, 1657\text{ cm}^{-1}$; MS (CI): m/z (%): 429 (100) $[M+\text{H}]^+$, 428 (44) $[M]^+$; elemental analysis calcd (%) for $\text{C}_{23}\text{H}_{28}\text{N}_2\text{O}_6$ (428.5): C 64.47, H 6.59, N 6.54; found: C 64.40, H 6.60, N 6.52.

Peptide (–)-2l: *Method A:* Azetidine-2,3-dione [(+)-1b, 46 mg, 0.16 mmol] gave (–)-2l as a colorless solid (36 mg, 59%) after purification by flash chromatography (dichloromethane/ethyl acetate 8:1). M.p. 117–118°C (hexanes/ethyl acetate). $[\alpha]_D = -53.1$ ($c = 0.7$ in CHCl_3); ^1H NMR (300 MHz, CDCl_3 , 25°C): $\delta = 8.87$ (brs, 1H), 6.86/6.81 (d, $J = 7.1$ Hz, each 2H), 7.46/6.68 (dd, $J = 6.6, 2.4$ Hz, each 2H), 4.66 (dd, $J = 11.2, 5.4$ Hz, 1H), 4.14 (dd, $J = 8.8, 6.4$ Hz, 1H), 4.02 (dd, $J = 8.8, 5.6$ Hz, 1H), 3.79/3.76 (s, each 3H), 3.71 (d, $J = 4.9$ Hz, 1H), 1.49/1.38 (s, each 3H); ^{13}C NMR (75 MHz, CDCl_3 , 25°C): $\delta = 169.0, 156.5, 153.7, 140.7, 130.2, 121.4, 115.6, 115.1, 114.1, 109.9, 75.5, 66.9, 63.2, 55.7, 55.5, 26.6, 24.8$; IR (KBr): $\tilde{\nu} = 3344, 3203, 1743, 1670\text{ cm}^{-1}$; MS (CI): m/z (%): 387 (100) $[M+\text{H}]^+$, 386 (48) $[M]^+$; elemental analysis calcd (%) for $\text{C}_{21}\text{H}_{26}\text{N}_2\text{O}_5$ (386.5): C 65.27, H 6.78, N 7.25; found: C 65.21, H 6.76, N 7.26.

(–)-(2S)-2-(Allylamino)-2-[(S)-2,2-dimethyl-1,3-dioxolan-4-yl]-N-benzyl-methanecarboxamide [(–)-2m]: *Method A:* Azetidine-2,3-dione [(–)-1c, 58 mg, 0.257 mmol] gave (–)-2m as a colorless oil (45 mg, 58%) after purification by flash chromatography (hexanes/ethyl acetate 2:1). $[\alpha]_D = -34.0$ ($c = 0.8$ in CHCl_3); ^1H NMR (300 MHz, CDCl_3 , 25°C): $\delta = 7.78$ (brs, 1H), 7.29 (m, 5H), 5.80 (m, 1H), 5.11 (m, 2H), 4.45 (d, $J = 6.1$ Hz, 1H), 4.21 (m, 1H), 4.09 (brs, 1H), 4.08 (d, $J = 6.6$ Hz, 1H), 3.21 (m, 2H), 3.19 (d, $J = 6.8$ Hz, 1H), 1.84 (brs, 1H), 1.42/1.34 (s, each 3H); ^{13}C NMR (75 MHz, CDCl_3 , 25°C): $\delta = 171.3, 138.3, 135.7, 128.6, 127.5, 127.4, 116.7, 109.4, 76.2, 67.1, 64.8, 51.2, 42.9, 26.6, 25.2$; IR (CHCl_3): $\tilde{\nu} = 3344, 3208, 1652\text{ cm}^{-1}$; MS (CI): m/z (%): 305 (100) $[M+\text{H}]^+$, 304 (28) $[M]^+$; elemental analysis calcd (%) for $\text{C}_{17}\text{H}_{24}\text{N}_2\text{O}_3$ (304.4): C 67.08, H 7.95, N 9.20; found: C 67.16, H 7.93, N 9.21.

(–)-(2S)-2-[(S)-2,2-Dimethyl-1,3-dioxolan-4-yl]-2-(propargylamino)-N-benzyl-methanecarboxamide [(–)-2o]: *Method A:* Azetidine-2,3-dione [(–)-1d, 40 mg, 0.18 mmol] gave (–)-2o as a colorless oil (28 mg, 50%) after purification by flash chromatography (hexanes/ethyl acetate 1:1). $[\alpha]_D = -38.1$ ($c = 1.8$ in CHCl_3); ^1H NMR (300 MHz, CDCl_3 , 25°C): $\delta = 7.65$ (m, 1H), 7.31 (m, 5H), 4.46 (d, $J = 6.1$ Hz, 2H), 4.25 (m, 1H), 4.10 (m, 2H), 3.49/3.30 (td, $J = 17.3, 2.4$ Hz, each 1H), 2.20 (t, $J = 2.4$ Hz, 1H), 1.44/1.34 (s, each 3H); ^{13}C NMR (75 MHz, CDCl_3 , 25°C): $\delta = 170.8, 138.2, 128.6, 127.5, 127.4, 109.6, 80.9, 76.1, 72.2, 66.9, 64.0, 43.0, 37.2, 26.6, 25.0$; IR (CHCl_3): $\tilde{\nu} = 3338, 3204, 1654\text{ cm}^{-1}$; MS (CI): m/z (%): 303 (100) $[M+\text{H}]^+$, 302 (19) $[M]^+$; elemental analysis calcd (%) for $\text{C}_{17}\text{H}_{22}\text{N}_2\text{O}_3$ (302.4): C 67.53, H 7.33, N 9.26; found: C 67.60, H 7.32, N 9.25.

Peptide (–)-2p: *Method A:* Azetidine-2,3-dione [(–)-1e, 96 mg, 0.43 mmol] gave (–)-2p as a colorless solid (69 mg, 43%) after purification by flash chromatography (hexanes/ethyl acetate 1:1). $[\alpha]_D = -34.3$ ($c = 0.6$ in CHCl_3); ^1H NMR (300 MHz, CDCl_3 , 25°C): $\delta = 8.04$ (d, $J = 8.5$ Hz, 1H), 7.31 (m, 5H), 4.59 (m, 1H), 4.00 (m, 5H), 3.76 (s, 3H), 3.20 (d, $J = 7.6$ Hz, 1H), 2.48 (brs, 1H), 1.42 (d, $J = 7.3$ Hz, 3H), 1.35/1.32 (s, each 3H); ^{13}C NMR (75 MHz, CDCl_3 , 25°C): $\delta = 173.1, 170.7, 128.5, 128.4, 127.4, 109.5, 76.0, 66.9, 64.9, 52.5, 52.4, 47.4, 26.7, 25.3, 18.3$; IR (CHCl_3): $\tilde{\nu} = 3344, 3202, 1742, 1654\text{ cm}^{-1}$; MS (CI): m/z (%): 351 (100) $[M+\text{H}]^+$, 350 (15) $[M]^+$; elemental analysis calcd (%) for $\text{C}_{18}\text{H}_{26}\text{N}_2\text{O}_5$ (350.4): C 61.70, H 7.48, N 7.99; found: C 61.78, H 7.47, N 8.00.

Reactions between secondary amines and azetidine-2,3-dione [(+)-1b]. General procedure for the synthesis of α -amino amides and dipeptides 8:

Method A: A solution of the appropriate amine (0.5 mmol) in THF (0.1 mL) was added to a solution of the azetidine-2,3-dione (+)-1b (0.5 mmol) in THF (5 mL) and the solution was stirred at room temperature for 20–72 h. The solvent was removed under reduced pressure and after flash chromatography (hexanes/ethyl acetate or dichloromethane/ethyl acetate), compounds 8 were obtained in analytically pure form. Spectroscopic and analytical data for some representative pure forms of 8 are given below.

Method B: A solution of the appropriate amine (0.5 mmol) in THF (1 mL) was added to a solution of the azetidine-2,3-dione (+)-1b (0.5 mmol) in THF (5 mL) and the solution was heated in a sealed tube at 90°C for 2 h. The reaction mixture was allowed to cool to room temperature, the solvent was removed under reduced pressure and after flash chromatography (hexanes/ethyl acetate or dichloromethane/ethyl acetate), compounds 8 were obtained in analytically pure form.

(+)-(2S)-2-(4-Methoxyphenylamino)-2-[(S)-2,2-dimethyl-1,3-dioxolan-4-yl]-N-morpholinyl-methanecarboxamide [(+)-8c]: *Method A:* Azetidine-2,3-dione [(+)-1b, 49 mg, 0.167 mmol] gave (+)-8c as a colorless oil (37 mg, 64%) after purification by flash chromatography (hexanes/ethyl acetate 1:1). $[\alpha]_D = +13.8$ ($c = 0.8$ in CHCl_3); ^1H NMR (200 MHz, CDCl_3 , 25°C): $\delta = 6.97$ (brs, 1H), 6.76/6.51 (dd, $J = 6.6, 2.4$ Hz, each 2H), 4.44 (m, 1H), 4.32 (d, $J = 5.1$ Hz, 1H), 4.18 (dd, $J = 8.3, 7.1$ Hz, 1H), 3.97 (dd, $J = 8.3, 6.6$ Hz, 1H), 3.36 (m, 2H), 3.35 (s, 3H), 3.19 (m, 5H), 2.92 (m, 1H), 1.31/1.23 (s, each 3H); ^{13}C NMR (50 MHz, CDCl_3 , 25°C): $\delta = 169.2, 153.0, 140.6, 115.5, 114.9, 109.8, 75.9, 66.7, 65.9, 56.4, 55.7, 46.5, 42.6, 26.6, 25.1$; IR (CHCl_3): $\tilde{\nu} = 3337, 1660\text{ cm}^{-1}$; MS (CI): m/z (%): 351 (100) $[M+\text{H}]^+$, 350 (25) $[M]^+$; elemental analysis calcd (%) for $\text{C}_{18}\text{H}_{26}\text{N}_2\text{O}_5$ (350.4): C 61.70, H 7.48, N 7.99; found: C 61.78, H 7.47, N 8.01.

(–)-(2S)-2-(4-Methoxyphenylamino)-2-[(S)-2,2-dimethyl-1,3-dioxolan-4-yl]-N-(L-prolinyl methyl ester)-methanecarboxamide [(–)-8d]: *Method A:* Azetidine-2,3-dione [(+)-1b, 121 mg, 0.414 mmol] gave (–)-8d as a colorless oil (75 mg, 46%) after purification by flash chromatography (hexanes/ethyl acetate 1:1). $[\alpha]_D = -60.6$ ($c = 0.8$ in CHCl_3); ^1H NMR (500 MHz, CDCl_3 , 25°C): $\delta = 6.76/6.64$ (dd, $J = 6.6, 2.4$ Hz, each 2H), 4.45 (m, 1H), 4.26 (d, $J = 5.4$ Hz, 1H), 4.08 (td, $J = 6.3, 1.7$ Hz, 1H), 3.96 (dd, $J = 8.5, 6.3$ Hz, 1H), 3.73/3.72 (s, each 3H), 2.16 (m, 2H), 1.98 (m, 3H), 1.51/1.37 (s, each 3H); ^{13}C NMR (125 MHz, CDCl_3 , 25°C): $\delta = 172.1, 169.9, 152.9, 140.8, 115.7, 114.9, 109.6, 76.7, 66.1, 59.2, 59.1, 55.7, 52.1, 47.3, 28.8, 26.4, 25.2, 24.9$; IR (CHCl_3): $\tilde{\nu} = 3337, 1735, 1660\text{ cm}^{-1}$; MS (CI): m/z (%): 393 (100) $[M+\text{H}]^+$, 392 (31) $[M]^+$; elemental analysis calcd (%) for $\text{C}_{20}\text{H}_{28}\text{N}_2\text{O}_6$ (392.5): C 61.21, H 7.19, N 7.14; found: C 61.13, H 7.18, N 7.16.

Reaction between sodium methoxide and azetidine-2,3-dione (+)-1b. Preparation of α -amino ester [(+)-9]: Sodium methoxide (12 mg, 0.22 mmol) was added in portions at room temperature to a solution of the azetidine-2,3-dione (+)-1b (43 mg, 0.15 mmol) in methanol (5 mL), and the solution was heated at reflux temperature for 1 h. The reaction mixture was allowed to cool to room temperature and then water was added (2 mL). The methanol was removed under reduced pressure, the aqueous residue was extracted with ethyl acetate ($3 \times 10\text{ mL}$), and the organic layer was dried (MgSO_4). The solvent was removed under reduced pressure to give (+)-9 (which contained $\approx 5\%$ of its (1S)-epimer) as a colorless oil (22 mg, 50%) after purification by flash chromatography (dichloromethane/ethyl acetate 9:1).

(+)-(2S)-2-(4-Methoxyphenylamino)-2-[(S)-2,2-dimethyl-1,3-dioxolan-4-yl] methyl acetate [(+)-9]: $[\alpha]_D = +11.0$ ($c = 0.6$ in CHCl_3); ^1H NMR (300 MHz, CDCl_3 , 25°C): $\delta = 6.78/6.60$ (dd, $J = 6.6, 2.4$ Hz, each 2H), 4.54 (td, $J = 6.3, 3.2$ Hz, 1H), 4.12 (dd, $J = 8.3, 6.6$ Hz, 1H), 3.99 (m, 3H), 3.76/3.75 (s, each 3H), 1.49/1.38 (s, each 3H); ^{13}C NMR (75 MHz, CDCl_3 , 25°C): $\delta = 172.4, 153.0, 140.8, 115.3, 114.8, 110.1, 75.9, 66.3, 58.9, 55.7, 52.4, 26.3, 25.1$; IR (CHCl_3): $\tilde{\nu} = 3332, 1738\text{ cm}^{-1}$; MS (CI): m/z (%): 280 (100) $[M+\text{H}]^+$, 279 (21) $[M]^+$; elemental analysis calcd (%) for $\text{C}_{15}\text{H}_{21}\text{NO}_4$ (279.3): C 64.50, H 7.58, N 5.01; found: C 64.58, H 7.56, N 5.00.

Cadmium-promoted reaction between azetidine-2,3-diones 1 and water. General procedure for the synthesis of α -amino acids 10: A suspension of the appropriate azetidine-2,3-dione 1 (0.5 mmol), granulated cadmium (5 mmol), and solid ammonium chloride (3 mmol) in wet methanol (10 mL, 5% water) was stirred at room temperature for 2–4 d. The solvent was removed under reduced pressure and after flash chromatography (hexanes/

ethyl acetate), compounds **10** were obtained in analytically pure form. Spectroscopic and analytical data for some representative pure forms of **10** are given below.

(+)-(2S)-2-(4-Methoxyphenylamino)-2-[(S)-2,2-dimethyl-1,3-dioxolan-4-yl]-acetic acid [(+)-10b]: Azetidine-2,3-dione [(+)-**1b**, 44 mg, 0.15 mmol] gave (+)-**10b** as a colorless solid (24 mg, 48%) after purification by flash chromatography (hexanes/ethyl acetate 1:1). M.p. 185–186 °C (hexanes/ethyl acetate). $[\alpha]_D^{25} = +34.8$ ($c = 1.1$ in CHCl_3); ^1H NMR (300 MHz, CDCl_3 , 25 °C): $\delta = 6.93$ (brs, 1H), 6.80/6.62 (d, $J = 8.9$ Hz, each 2H), 5.63 (brs, 1H), 4.59 (m, 1H), 4.11 (dd, $J = 8.6$, 6.6 Hz, 1H), 3.97 (dd, $J = 8.6$, 5.6 Hz, 1H), 3.76 (s, 3H), 3.64 (d, $J = 4.1$ Hz, 1H), 1.49/1.38 (s, each 3H); ^{13}C NMR (75 MHz, CDCl_3 , 25 °C): $\delta = 174.2$, 153.4, 140.9, 115.1, 109.9, 75.5, 66.8, 61.9, 55.8, 26.6, 24.8; IR (CHCl_3): $\tilde{\nu} = 3345$, 3130, 1710 cm^{-1} ; MS (CI): m/z (%): 282 (100) $[M+H]^+$, 281 (14) $[M]^+$; elemental analysis calcd (%) for $\text{C}_{14}\text{H}_{19}\text{NO}_5$ (281.3): C 59.78, H 6.81, N 4.98; found: C 59.85, H 6.79, N 5.00.

(-)-(2S)-2-(Benzylamino)-2-[(S)-2,2-dimethyl-1,3-dioxolan-4-yl]-acetic acid [(-)-10d]: From azetidine-2,3-dione [(-)-**1e**, 46 mg, 0.17 mmol] gave (-)-**10d** as a colorless oil (25 mg, 57%) after purification by flash chromatography (hexanes/ethyl acetate 1:2). $[\alpha]_D^{25} = -77.8$ ($c = 1.0$ in CHCl_3); ^1H NMR (300 MHz, CDCl_3 , 25 °C): $\delta = 7.33$ (m, 5H), 5.72 (brs, 1H), 4.24 (m, 1H), 4.03 (dd, $J = 5.9$, 3.2 Hz, 1H), 3.91/3.74 (d, $J = 13.4$ Hz, each 1H), 3.20 (d, $J = 7.3$ Hz, 1H), 1.37/1.33 (s, each 3H); ^{13}C NMR (75 MHz, CDCl_3 , 25 °C): $\delta = 174.2$, 139.1, 128.6, 128.1, 127.4, 109.5, 75.9, 66.9, 64.8, 52.6, 26.6, 25.2; IR (CHCl_3): $\tilde{\nu} = 3342$, 3122, 1708 cm^{-1} ; MS (CI): m/z (%): 266 (100) $[M+H]^+$, 265 (17) $[M]^+$; elemental analysis calcd (%) for $\text{C}_{14}\text{H}_{19}\text{NO}_4$ (265.3): C 63.38, H 7.22, N 5.28; found: C 63.47, H 7.21, N 5.27.

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- [1] a) A. Gringauz, *Introduction to Medicinal Chemistry: How Drugs Act and Why*, Wiley-VCH, New York, **1997**; b) A. N. Collins, G. N. Sheldrake, J. Crosby, *Chirality in Industry: The Commercial Manufacture and Applications of Optically Active Compounds*, Wiley, Chichester, **1992**.
- [2] I. Wagner, H. Musso, *Angew. Chem.* **1983**, 95, 827; *Angew. Chem. Int. Ed. Engl.* **1983**, 22, 816.
- [3] a) G. M. Coppola, H. F. Schuster, *Asymmetric Synthesis: Construction of Chiral Molecules Using Amino Acids*, Wiley, New York, **1987**; b) F. J. Sardina, H. Rapoport, *Chem. Rev.* **1996**, 96, 1825; c) M. T. Reetz, *Angew. Chem.* **1991**, 103, 1559; *Angew. Chem. Int. Ed. Engl.* **1991**, 30, 1531; d) P. I. Dalko, L. Moisan, *Angew. Chem.* **2001**, 113, 3840; *Angew. Chem. Int. Ed.* **2001**, 40, 3726.
- [4] For reviews, see: a) R. O. Duthaler, *Tetrahedron* **1994**, 50, 1539; b) R. M. Williams, *Synthesis of Optically Active α -Amino Acids*, Pergamon, Oxford, **1989**; c) M. J. O'Donell, *Tetrahedron* **1988**, 44, 5253.
- [5] For a review, see: B. Alcaide, P. Almendros, *Org. Prep. Proced. Int.* **2001**, 33, 315.
- [6] a) F. P. Cossio, C. López, M. Oiarbide, C. Palomo, D. Aparicio, G. Rubiales, *Tetrahedron Lett.* **1988**, 29, 3133; b) C. Palomo, J. M. Aizpurua, I. Ganboa, F. Carreaux, C. Cuevas, E. Maneiro, J. M. Ontoria, *J. Org. Chem.* **1994**, 59, 3123; c) C. Palomo, J. M. Aizpurua, I. Ganboa, M. Oiarbide, *Amino Acids* **1999**, 16, 321; d) C. Palomo, J. M. Aizpurua, I. Ganboa, M. Oiarbide, *Synlett* **2001**, 1813.
- [7] a) B. Alcaide, P. Almendros, C. Aragoncillo, *Chem. Eur. J.* **2002**, 8, 1719; b) B. Alcaide, P. Almendros, *Chem. Soc. Rev.* **2001**, 30, 226; c) B. Alcaide, P. Almendros, C. Aragoncillo, *J. Org. Chem.* **2001**, 66, 1612; d) B. Alcaide, P. Almendros, J. M. Alonso, M. F. Aly, *J. Org. Chem.* **2001**, 66, 1351; e) B. Alcaide, P. Almendros, J. M. Alonso, M. F. Aly, M. R. Torres, *Synlett* **2001**, 1531; f) B. Alcaide, P. Almendros, C. Aragoncillo, R. Rodríguez-Acebes, *J. Org. Chem.* **2001**, 66, 5208; g) B. Alcaide, P. Almendros, J. M. Alonso, M. F. Aly, *Org. Lett.* **2001**, 3, 3781.
- [8] For a preliminary communication of a part of this work, see: B. Alcaide, P. Almendros, C. Aragoncillo, *Chem. Commun.* **2000**, 757.
- [9] Ojima and co-workers found that cleavage of the C4–N1 bond in 2-azetidinones proceeds exclusively in a palladium-catalyzed hydrogenolysis when an aryl substituent is attached to the C4 position. This finding led Ojima's group to develop the β -lactam synthon method for the synthesis of α -amino acid derivatives. See: a) I. Ojima, F. Delaloge, *Chem. Soc. Rev.* **1997**, 26, 377; b) I. Ojima, *Adv. Asym. Synth.* **1995**, 1, 95.
- [10] B. Alcaide, G. Esteban, Y. Martín-Cantalejo, J. Plumet, J. Rodríguez-López, A. Monge, V. Pérez-García, *J. Org. Chem.* **1994**, 59, 7994.
- [11] J. W. Skiles, D. McNeil, *Tetrahedron* **1990**, 31, 7277.
- [12] For a review on the application in stereocontrolled synthesis involving selective bond cleavage of the β -lactam nucleus, see: B. Alcaide, P. Almendros, *Synlett* **2002**, 381.
- [13] A. Solladié-Cavallo, J. Suffert, *Magn. Reson. Chem.* **1985**, 23, 739.
- [14] Palomo's group has also developed an alternative procedure to synthesize NCAs. According to this approach, from the ring expansion of α -hydroxy β -lactams by means of sodium hypochlorite and a catalytic amount of TEMPO, NCAs are obtained. The process occurs through a regioselective Baeyer–Villiger rearrangement of an in situ generated azetidine-2,3-dione. This strategy was recently documented as an access to β,γ -dihydroxy α -amino acid-derived peptides: C. Palomo, M. Oiarbide, A. Landa, A. Esnal, A. Linden, *J. Org. Chem.* **2001**, 66, 4180.
- [15] In the β -lactam series, it has been reported that *N*-formyl- β -lactams gives *NH*- β -lactams under slightly basic conditions. For treatment with Et_3N (cat.) in methanol, see: J. M. Aizpurua, F. P. Cossio, C. Palomo, *Tetrahedron Lett.* **1986**, 27, 4359. For *N*-deformylation on treatment with the system $\text{NaHCO}_3/\text{Na}_2\text{CO}_3$, see: C. Palomo, J. M. Aizpurua, M. Legido, A. Mielgo, R. Galarza, *Chem. Eur. J.* **1997**, 3, 1432.
- [16] Reviews: a) R. H. Crabtree, *Chem. Rev.* **1985**, 85, 245; b) B. Rybtchinski, D. Milstein, *Angew. Chem.* **1999**, 111, 918; *Angew. Chem. Int. Ed.* **1999**, 38, 870; c) M. Murakami, Y. Ito in *Activation of Unreactive Bonds and Organic Synthesis* (Ed.: S. Murai), Springer, Berlin, **1999**, p. 97.
- [17] It was reported for the Barbier-type allylation or allenylation of 2-aminocarbonyls in aqueous media that changes in the ionic strength of the solvent can provide modification in the diastereomeric ratio or accelerated the process: a) M. D. Chappell, R. L. Halcomb, *Org. Lett.* **2000**, 2, 2003; b) B. Alcaide, P. Almendros, C. Aragoncillo, *Org. Lett.* **2000**, 2, 1411.
- [18] Full spectroscopic and analytical data for compounds not included in the Experimental Section are described in the Supporting Information.

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