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Stereoselective synthesis of constrained norbornane-derived spiro-β-lactams

Giuseppe Cremonesi [a,*], Piero Dalla Croce [a], Alessandra Forni [b], Concetta La Rosa [a]

[a] Università degli Studi di Milano – DISFARM – Sezione di Chimica Generale e Organica 'A. Marchesini', V. Venezian 21, I-20133 Milano, Italy
[b] CNR-ISTM, V. Golgi 19, I-20133 Milano, Italy

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This paper is dedicated to the memory of Dr. Alessandro Fedeli Bernardini

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ABSTRACT

New enantiopure polycyclic norbornane-derived spiro-β-lactams were synthesized by means of a Staudinger ketene–imine reaction between unsymmetrical bicyclic chiral ketenes, generated from differently substituted norbornane carboxylic acids, and (*E*)-*N*-benzyl-*N*-(phenylmethylene)amine, with high yields and moderate to good stereoselectivities. The diastereoisomeric results were rationalized taking into account the increasing steric encumbrance present on the norbornane skeleton and the stability of the products. The configurations of the newly formed stereocenters of spiro-β-lactams were assigned on the basis of 2D NMR experiments and X-ray analysis. Spiro-β-lactams were subjected to acid hydrolysis obtaining the corresponding norbornane-derived β-amino acids.

1. Introduction

2-Azetidinones, commonly known as β-lactams, are very interesting small heterocycles present as key structure in many biologically active compounds, in particular in most widely used classes of antibiotics,[1] and also in various products with a wide variety of pharmacological activities.[2–8] In addition to its fundamental importance in medicinal chemistry, the 2-azetidinone scaffold is a versatile intermediate in synthetic organic chemistry.[9] For these reasons their synthesis has received considerable attention over recent years and, in particular, asymmetric synthesis by means of a Staudinger ketene–imine reaction has been extensively studied.[10]

Among all the structures containing β-lactam scaffolds, those in which this heterocycle is spiro-fused with another ring structure are of particular interest. Indeed spiro-β-lactams are very attractive compounds not only because of their antiviral[11a] and antibacterial activity,[11b] but also because they inhibit cholesterol absorption,[11c] so they are potential useful drugs. They can also act as β-turn mimetics.[12] Finally, spiro-β-lactams can be used as synthetic precursors for a number of useful synthetic units, such as cyclic α,α-disubstituted β-amino acids and peptidomimetics.[13] That is why the study of their synthesis and reactivity always receives an increasing interest.[14]

For many years our research group has been devoted to the synthesis of new C3 spiro-fused 2-azetidinones by means of the Staudinger reaction between heterocyclic asymmetric ketenes and imines. In this way we obtained a library of compounds in which the β-lactam ring has a spiro junction with another heterocyclic ring, such as 1,3-thiazolidine,[15a,b] pyrrolidine,[15c] pyperidine,[15c] and 1,3-oxazolidine.[15c] In particular β-lactams having a 3-spiro junction with 1,3-thiazolidine ring have proved to be useful intermediates to obtain a variety of products depending on the type of junction and experimental conditions used.[16a,b] We also realized stereoselective synthesis of spiro-β-lactams using enantiopure chiral ketenes generated from natural amino acids, such as 4-hydroxy-L-proline.[17a] Similarly, we obtained enantiomerically pure 1,3-thiazolidine-spiro-β-lactams starting from optically active 1,3-thiazolidine-2-carboxylic acid synthesized from L-cysteine[17b] and L-valine.[17b] Then we transformed these lactams in enantiopure monobactam derivatives by 1,3-thiazolidine moiety ring opening.[18a] Recently, we have also utilized enantiopure pyrroline-spiro-β-lactams, obtained from protected 4-hydroxy-L-prolines, as substrates toward a series of olefin reactions obtaining polyheterocyclic-spiro-β-lactam derivatives.[18b]

Our interest in the stereoselective synthesis of new enantiopure spiro-β-lactams by means of the Staudinger ketene–imine reaction between chiral ketenes and imine led us to investigate the

* Corresponding author. Tel.: +39 02 503 14473; fax: +39 02 503 14476; e-mail address: giuseppe.cremonesi@gmail.com (G. Cremonesi).

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reactivity of norbornene- or norbornane carboxylic acids as precursor of bicyclic ketenes intermediates (Fig. 1).

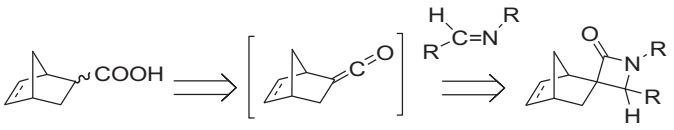


Fig. 1. Synthetic pathway for norbornane/ene-C3-spiro-β-lactams.

In the literature only one example of a norbornene-C3-spiro-β-lactam has been reported but its synthesis was accomplished by means of a Diels–Alder reaction between 3-methylidene-β-lactams and cyclopentadiene.[19] Similarly, norbornane-C3-spiro-azetidine-2,4-diones were synthesized with a completely different way, i.e., the photochemical isomerization of succinimides.[20] Some reports regard other synthesis of norbornene- or norbornane-C4-spiro-β-lactams: Plumet et al. have reported the preparation of 7-oxanorbornene-C4-spiro-β-lactams by means of the Staudinger ketene–imine reaction between imines deriving from the 7-oxa-norbornen-2-one and acyl chlorides.[21] However, in this case, the norbornene-moiety was the imine partner in the Staudinger reaction and consequently this led to a spiro junction at the C-4 position of the 2-azetidinone ring. A C-4 spiro-fused 2-azetidinone was also obtained by means of the reaction between 5-ethylidene-2-norbornene[22a] or camphene[22b] and chlorosulfonyl isocyanate, or between the 3-phenylimino-camphorquinone and diphenylketene.[23] In no case, has the reaction of a norbornane- or norbornene-derived ketene with an imine been reported in the synthesis of spiro-β-lactams. For this reason we decided to investigate this reaction.

These spiro-β-lactams are very attractive scaffolds because they join the rigid structure of norbornane skeleton with the β-lactam ring versatility. For example, the hydrolysis of the lactam bond could afford β-amino acids. Moreover, in the case of norbornene derived β-lactams, the presence of the cyclic double bond could lead to further transformations, such as 1,3-cycloaddition reactions with 1,3-dipoles,[18b] potentially giving interesting polycyclic-β-lactam derivatives, or ring-opening-metathesis-cross metathesis reactions (ROM-CM) in presence of a suitable catalyst.[21b]

In order to produce different typologies of spiro-β-lactams and to evaluate the steric effect on the diastereoselectivity of the Staudinger reaction of the substituents present at different position of the bicyclic framework, we planned the use of four different ketenes deriving from carboxylic acids **1a**–**d** having differently substituted norbornane skeletons (Fig. 2).

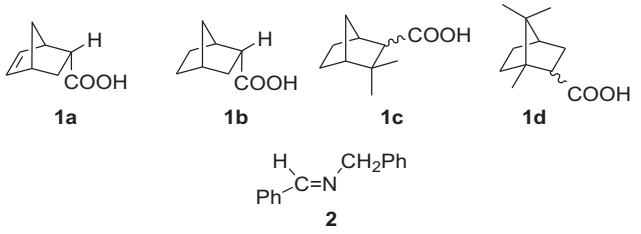


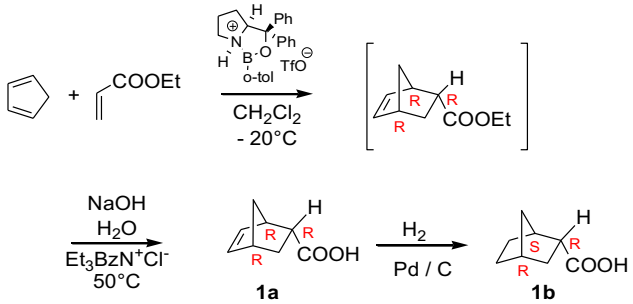
Fig. 2. Selected substrates.

Though the Staudinger reaction was first described more than 100 years ago,[24] its rationalization (and, consequently, its stereochemical course) are still debated.[25] In general, the stereochemistry of the products depends on the nature of the substrates (stereoelectronic aspects) and the experimental conditions. Also the geometry and electronic properties of imines play a key role in this reaction: we decided to use the (*E*)-*N*-benzyl-*N*-(phenylmethylene) amine **2** (Fig. 2) as a convenient imine partner, already widely used by us,[16b,17b] due to its good nucleophilicity.[14a]

2. Results and discussion

2.1. Synthesis of carboxylic acids 1a–d

All the carboxylic acids were prepared from commercial reagents using catalytic stereoselective synthesis or from chiral natural products. The synthesis of (1*R*,2*R*,4*R*)-bicyclo[2.2.1]hept-5-ene-2-carboxylic acid **1a**, in 98% ee, was accomplished by means of a Diels–Alder reaction between cyclopentadiene and ethyl acrylate, using (*S*)-*o*-tolyl-CBS-oxazaborolidine as chiral catalyst,[26a] followed by basic hydrolysis[26b] under phase-transfer conditions (Scheme 1). Carboxylic acid **1a** was catalytically reduced leading to the corresponding saturated (1*S*,2*R*,4*R*)-bicyclo[2.2.1]heptane-2-carboxylic acid[27] **1b** (Scheme 1).



Scheme 1.

The more encumbered carboxylic acids, the (1*S*,4*R*)-3,3-dimethyl-bicyclo[2.2.1]heptane-2-carboxylic acid **1c** and the (1*S*,4*R*)-1,7,7-trimethyl-bicyclo[2.2.1]heptane-2-carboxylic acid **1d**, were obtained as a mixture of *endo*/*exo* stereoisomers starting from the natural bicyclic diterpenes (+)-camphene and (+)-camphor, respectively, using, in this case, their chiral information as already extensively done.[28] (Scheme 2).

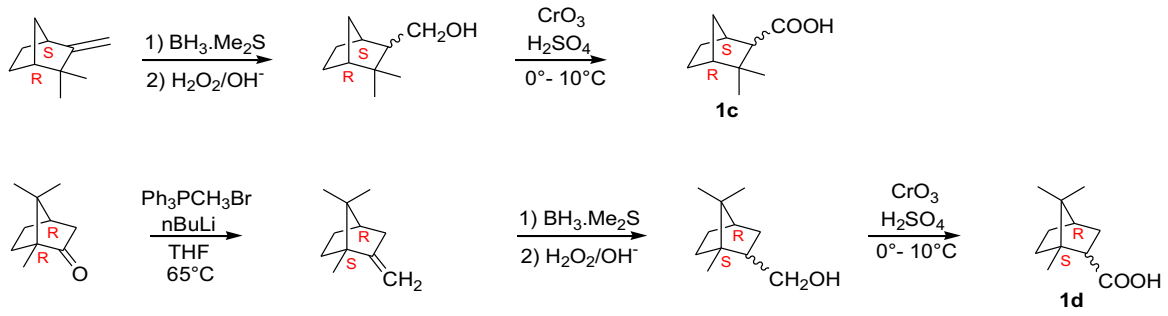
As described for (±)-camphene,[29] (+)-camphene was subjected to oxidative hydroboration giving a 85/15 *endo*/*exo* mixture of camphanol, which following Jones oxidation provided carboxylic acid **1c**.

(+)-Camphor was first transformed into the corresponding (−)-2-methylenebornane,[30a] by means of a Wittig reaction with Ph_3PCH_3Br/*n*BuLi. The latter, similarly to (+)-camphene, was subjected to an oxidative hydroboration leading to the corresponding 2-(hydroxymethyl)bornane,[30b] which was directly oxidized with Jones' reagent to a 30/70 *endo*/*exo* mixture of carboxylic acid **1d**[30c] (Scheme 2).

The formation of *endo*/*exo* mixtures of carboxylic acids **1c**,**d** does not constitute a problem since their C-2 configuration is lost when the ketene is formed or when the intermediate *N*-acyl-iminium salt, resulting from the condensation of the activated acid with the imine, was deprotonated by the base.

2.2. Generation of ketenes and spiro-β-lactams synthesis

We first investigated the best conditions for generating the intermediate ketenes and carrying out the reaction with the imine **2**. Various activation methods were tried using the commercially available racemic 80/20 *endo*/*exo* norbornane-2-carboxylic acid (±)-**1b**. With *N*,*N*-dimethylchlorosulfitemethaniminium chloride ($SOCl_2$-DMF), a dehydrating reagent that is also used to prepare β-lactams,[31] the reaction of (±)-**1b** with **2**, run in refluxing dichloromethane solution in presence of Et_3N, led to unreacted (±)-**1b** and poor yields of a mixture of diastereoisomeric spiro-β-lactams **3**–**6b** and the *endo*/*exo* bicycle[2.2.1]heptane-2-carboxylic acid benzylamide **7b**.[32] This latter is obtained as a consequence of the hydrolysis

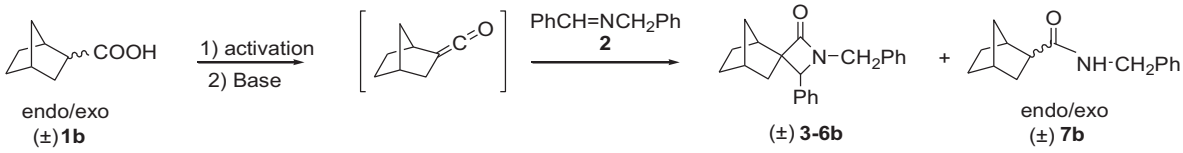


Scheme 2.

of the iminium salt resulting from the reaction of the activated acid and imine (Scheme 3 and Table 1, entry 1). Only benzylamide and unreacted (±)-**1b** were also obtained running the reaction in toluene solution and heating at T=90 °C (Table 1, entry 2).

ketene so preformed with imine **2** in toluene solution at 90 °C (Table 1, entry 8).

This protocol was then applied to the reaction of enantiomerically pure **1a**–**d** with imine **2** leading to mixtures of the corre-



Scheme 3.

Table 1
Optimization of the reaction of (±) **1b** with **2** under different activation conditions

Entry	Reaction conditions	Total yield of β-lactams **3**–**6b** (%)	Yield of amide **7b** (%)	Unreacted (±) **1b** (%)
1	1) $SOCl_2$–DMF T=0 °C 2) Et_3N–CH_2Cl_2–reflux	14	37	45
2	1) $SOCl_2$–DMF T=0 °C 2) Et_3N–toluene–T=90 °C	—	13	67
3	*Mukaiyama's* reagent Et_3N–CH_2Cl_2–reflux	8	16	62
4	*Mukaiyama's* reagent DABCO–CH_2Cl_2–reflux	15	24	50
5	*Mukaiyama's* reagent DIPEA–CH_2Cl_2–reflux	—	10	80
6	*Mukaiyama's* reagent Et_3N–toluene–T=90 °C	—	21	64
7	1) $(COCl)_2$–DMF 0.1 mol %. T=−5 °C-rt 2) Et_3N–CH_2Cl_2–rt	—	—	80
8	1) $(COCl)_2$–DMF 0.1 mol %. T=−5 °C-rt 2) Et_3N–toluene–T=90 °C	70	—	—

We also applied our usual protocol to activate the carboxylic group and generate in situ the intermediate ketene[17b] by heating a mixture of carboxylic acid (±)-**1b**, imine **2** and 2-chloro-1-methylpyridinium iodide, *Mukaiyama's* reagent, in the presence of different bases, such as Et_3N, DABCO or DIPEA, but also in this case the reactions afforded poor yields of β-lactams and benzylamide (Table 1, entries 3–5). As already observed (Table 1, entry 2), replacement of dichloromethane with toluene as solvent and heating at T=90 °C resulted only in amide formation (Table 1, entry 6).[14a]

So we switched to using the more reactive acyl chloride as ketene precursor: the acyl chloride was obtained by reacting the acid (±)-**1b** with oxalyl chloride in presence of a catalytic amount of DMF.[33] Subsequent treatment with Et_3N and imine **2** in dichloromethane solution at room temperature did not afford β-lactams (Table 1, entry 7). On the contrary, the mixture of diastereoisomeric β-lactams **3**–**6b** was obtained in good yield adding a toluene solution of TEA to the acyl chloride at T=0 °C, and then reacting the sponding spiro-β-lactams. With **1a** and **1b** the reactions afforded all the four possible diastereoisomers whose ratio was determined from integration of the H-4 signals in the ^{1}H NMR spectra of the crude reaction mixtures (4.0–4.5 δ) (Scheme 4 and Table 2). In the case of **1c** the reaction afforded only two diastereoisomers in nearly equal amounts beside to a 23% yield of the *endo*/*exo*-*N*-benzyl-3,3-dimethylbicyclo[2.2.1]heptane-2-carboxamide **7c**, while in the case of **1d** a greater diastereoselectivity was observed only one diastereoisomer being obtained in 73% yield, together with a 12% total yield of the other three diastereoisomers in 2.6:1:1 ratio.

2.3. Assignment of the absolute configurations to spiro-β-lactams

The mixtures of spiro-β-lactams were partially separated by means of column chromatography: only the more abundant products **3a**–**c**, **4b**–**c**, and **5d** were obtained pure enough to be

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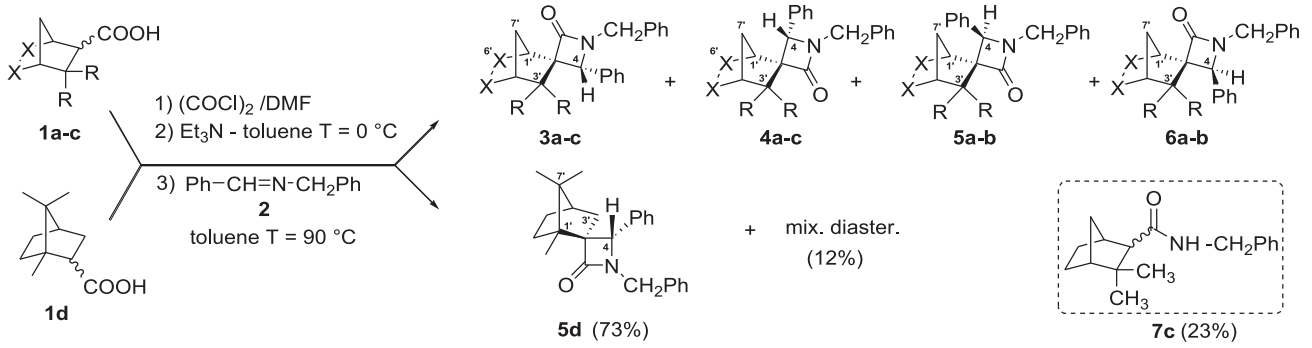


Scheme 4.

Table 2
Total yields and ratios of spiro-β-lactams **3**–**6(a**–**c)**

Carboxylic acid	X–X	R	Total yield (%)	Diastereoisomers ratio (%)			
				3	**4**	**5**	**6**
1a	CH=CH	H	98	46	27	20	7
1b	CH_2–CH_2	H	94	53	29	9	9
1c	CH_2–CH_2	CH_3	68	47	53	—	—

fully characterized by means of analytical and spectroscopic data (see Experimental section). The absolute configurations of the newly formed C-3 and C-4 stereocenters were assigned by means of suitable NOESY, COSY, HSQC, and HMBC experiments or by X-ray analysis. In particular, in the NOESY spectra of the major diastereoisomer **3a**, H-4 (δ=4.17) shows positive effect only with one of the two H-3′ (δ=1.45), while in the NOESY spectra of the minor diastereoisomer **4a**, H-4 (δ=4.48) shows positive effects with both H-3′ (δ=1.81 and 2.07) and also with H-1′ (δ=2.61) and one H-7′ (δ=0.94). With the aid of Dreiding's molecular models, these observations allowed us to assign (3*S*,4*R*) and (3*R*,4*S*) configurations to **3a** and **4a**, respectively. It is noteworthy that H-6′ proton in **3a** is shielded by the C-4 phenyl and thereby its chemical shift drops more than 1 ppm (δ=4.74) with respect to the corresponding value of H-6′ in **4a** (δ=6.02). In the NOESY spectra of diastereoisomer **5a**, H-4 (δ=4.26) shows positive effects with H-7′ (δ=1.18–1.22) and with H-1′ (δ=3.08) but not with H-3′: as a consequence the (3*R*,4*R*) configurations were assigned to **5a** and (3*S*,4*S*) to the remaining compound **6a**. The NOESY spectra of compound **3b** showed no useful positive effects in the determination of the absolute configurations. On the contrary in the NOESY spectra of compound **4b** positive effects were observed between H-4 (δ=4.03) and H-3′ (δ=1.91) and H-7′ (δ=0.82–0.90) similarly to **4a**. The configurations of **3**–**5b** were confirmed by means of catalytic hydrogenation (Pd/C, AcOEt, rt) of compound **3a** that afforded **3b** and of the mixture **4a**/**5a**=2:1 that allowed obtaining a mixture with the same ratio of **4b** and **5b**, respectively, so determining the assignment of the same (3*R*,4*R*) configurations to **5b** and, consequently, (3*S*,4*S*) to **6b**. The absolute configurations (3*R*,4*R*) were assigned to compound **3c** by means of the X-ray analysis (see Supplementary data), while in the NOESY spectra of **4c** positive effects were observed between H-4 (δ=4.51) and H-7′ (δ=1.14–1.19) and one of the methyl groups (δ=1.13) allowing to assign the (3*S*,4*S*) configurations. Finally the same (3*S*,4*S*) configurations were assigned to **5d**: in the NOESY spectra H-4 (δ=4.28) shows positive effects with two methyl groups: one on C-7′ and the other on C-1′. On the contrary, it was not possible to assign the absolute configurations to compounds **3**,**4**,**6d** because they were inseparable.

2.4. Diastereoselectivity of Staudinger reaction on norbornane ketenes

The mechanism of the Staudinger reaction has been the subject of extensive studies.[25] Although an asynchronous concerted reaction pathway cannot be excluded, according to both experimental and theoretical[25c,d] studies, using a nucleophilic imine, such as (*E*)-**2**, the [2+2] ketene–imine cycloaddition reaction occurs with a stepwise mechanism. The attack of the imine on the least hindered side of the ketene gives a zwitterionic intermediate, which undergoes a subsequent conrotatory ring closure to generate the spiro-β-lactam. In the reactions of unsymmetrical ketenes with imines the stereoselectivity could be controlled by the torquoelectronic effects that become more pronounced when the carbon–carbon double bond of the ketene is substituted with a heteroatom.[14a,25b,25f,25m] In addition, also the steric effects play an important role in the stereoselectivity of the Staudinger reaction.[25i] In the case of our norbornene/ane-derived substrates **1a**–**d**, the stereochemical outcome of the reactions showed a moderate diastereoselectivity as, except for **1c**, all the four possible diastereoisomers were obtained. However, in the case of **1d** the reaction was more diastereoselective than in the other cases.

In Fig. 3 are reported the approaches of the imine to the ketene leading to zwitterionic intermediates **A**–**D** whose ring closure affords spiro-β-lactams **3**–**6**. Taking into account the obtained results, it is quite clear that the steric hindrance present on the norbornane skeleton on the different approaches has little influence. In fact, from this point of view, the zwitterionic intermediates **C** and **D** should be favorite, especially with **1c** (R=Me). Instead the two more abundant products **3a**–**c** and **4a**–**c** derive from the zwitterionic intermediates **A** and **B** showing that the element governing the reaction is the stability of the products. In fact the Dreiding models show that compounds **3a**–**c** and **4a**–**c** suffer of minor steric hindrance respect to **5a**–**c** and **6a**–**c** and therefore they should be more stable. With **1d**, the prevalent compound **5d** derives from a zwitterionic intermediate analogous to **C**: in this case the major diastereoselectivity observed could be ascribed to the fact that the more stable compound derives also from the more favorable approach. On the other hand, the experimental conditions adopted, high temperatures and prolonged reaction times, provide for a thermodynamic control of the reaction thus leading to the more stable compounds even if they do not derive from the more favorable approaches.

2.5. Hydrolysis of spiro-β-lactams

Spiro-β-lactams were subjected to numerous experimental conditions of hydrolysis, either basic or acidic, to obtain the corresponding norbornane-derived β-amino acids (Scheme 5). In

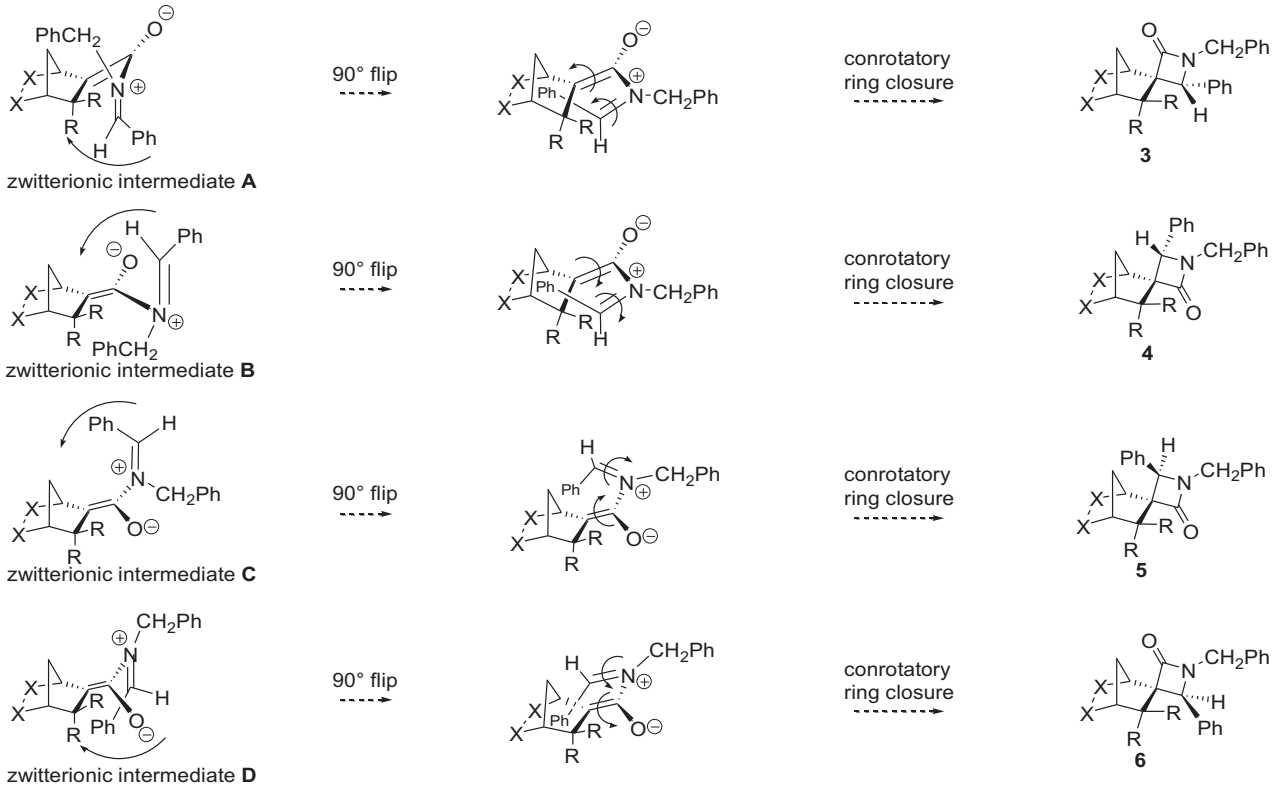
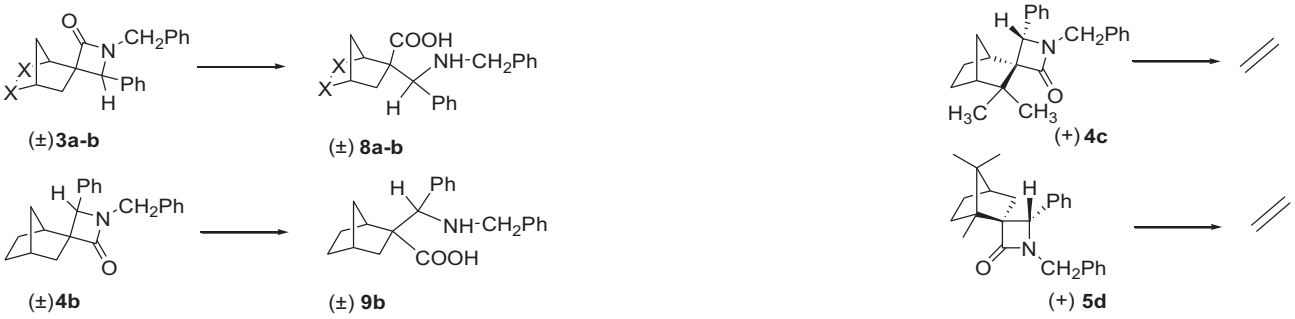


Fig. 3. Conrotatory ring closure of zwitterionic intermediates **A**–**D**.



Scheme 5.

particular, racemic **3a** was treated with different bases, such as NaOH, LiOH, Cs_2CO_3 or CH_3ONa or acids, such as HCl or HBr. The lactam ring of (±)-**3a** was completely stable under basic hydrolysis conditions (Table 3, entries 1–5) or acid catalyzed at room temperature (Table 3, entry 6). By heating with HCl to 50 °C, or higher temperatures, or treating with HBr at room temperature, the norbornene scaffold of (±)-**3a** underwent complete degradation (Table 3, entries 7–9) leading to a mixture of unidentified products presumably deriving from the reactive C–C double bond (as shown by the disappearance of the olefinic system in ^{1}H NMR). The norbornane spiro-β-lactam (±)-**3b** showed to be more stable under acid hydrolysis conditions and among the different acids tested, (Table 3, entries 10–14), the better results were obtained with HBr in acetic acid at room temperature: in these conditions the amino acid (±)-**8b** was obtained in 73% yield. The same protocol applied to spiro-β-lactam (±)-**4b** afforded the diastereoisomeric amino acid (±)-**9b** in 71% yield (Table 3, entry 15). Finally, the enantiomerically pure spiro-β-lactams (+)-**4c** and (+)-**5d** were subjected to a variety of hydrolytic conditions including an enzymatic one,[34] but they were stable in each case (Table 3, entries 16–21).

3. Conclusions

We have synthesized new, enantiomerically pure, highly constrained norbornane-derived spiro-β-lactams by reacting optically active, non-symmetrical, bicyclic ketenes in a Staudinger ketene–imine reaction. This is the first example of the generation of norbornane-C3-spiro-β-lactams through the reaction between norbornane-derived ketenes and imines. The stereochemical outcome of the reaction is influenced by the presence of encumbering groups in the cyclic ketenes. In fact a better selectivity was obtained when some methyl groups are present near to the carbon bearing the carboxylic functionality. These spiro-β-lactams showed to be very resistant to β-lactam ring hydrolysis; only with HBr in AcOH the amidic bond was broken affording the corresponding norbornane-derived amino acids. The particular skeletons of these

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Table 3
Hydrolysis of spiro-β-lactams

Entry	Spiro-β-lactam	Base/acid	Experimental conditions	Products (%)	
				3/4	**8/9**
1	(±)-**3a**	NaOH 5%	THF/65 °C/6 h	100	0
2	(±)-**3a**	NaOH 32%	Dioxane/100 °C/10 h	100	0
3	(±)-**3a**	LiOH	H_2O/THF/65 °C/6 h	100	0
4	(±)-**3a**	Cs_2CO_3	H_2O/Dioxane/50 °C/24 h	100	0
5	(±)-**3a**	CH_3ONa	CH_3OH/50 °C/24 h	100	0
6	(±)-**3a**	HCl_{aq} 10 N	Dioxane/rt/72 h	100	0
7	(±)-**3a**	HCl_{aq} 10 N	Dioxane/50 °C/4 h	15	0
8	(±)-**3a**	HCl_{aq} 10 N	Dioxane/100 °C/10 h	0	0
9	(±)-**3a**	HBr 32%	AcOH/rt/16 h	0	0
10	(±)-**3b**	Dowex 50X8	THF/60 °C/7 h	100	0
11	(±)-**3b**	HCl_{aq} 10 N	Dioxane/100 °C/24 h	0	trace
12	(±)-**3b**	HI_{aq} 57%	AcOH/rt/24 h	100	0
13	(±)-**3b**	$H_2SO_{4\ aq}$ 50%	AcOH/rt/72 h	100	0
14	(±)-**3b**	HBr 32%	AcOH/rt/16 h	0	73
15	(±)-**4b**	HBr 32%	AcOH/rt/16 h	0	71
16	(+)-**4c**	HCl_{aq} 10%	Dioxane/100 °C/24 h	100	0
17	(+)-**4c**	HBr 32%	AcOH/rt/48 h	100	0
18	(+)-**4c**	Lipase from *Candida antarctica*	Toluene/60 °C/48 h	100	0
19	(+)-**5d**	HBr 32%	AcOH/rt/48 h	100	0
20	(+)-**5d**	HCl_{aq} 10%	AcOH/100 °C/48 h	100	0
21	(+)-**5d**	HCl_{aq} 10%	Dioxane/150 °C/*mw*/3 h	100	0

spiro-β-lactams and of the corresponding amino acids are of interest for the synthesis of peptides conformational restricted. In fact their incorporation in the amino acid chains may alter the secondary structure of the peptide as their rigid structure results in a constrained conformation, with consequent variation of the peptide properties itself.

4. Experimental section

4.1. General

^1H and ^{13}C NMR spectra were recorded using a 300 MHz spectrometer. Chemical shifts (δ) are given in parts per million in relation to TMS; the solvent was $CDCl_3$ unless otherwise specified. All of the coupling constants (J) are in Hertz. IR spectra (in cm^{-1}) were determined using a FT-IR spectrometer. The optical rotation values were measured at 25 °C. Carboxylic acids **1a**–**d** were prepared as previously reported. (+)-Camphene, (+)-camphor, and imine **2** were obtained from commercial sources.

4.2. General procedure for the synthesis of spiro-β-lactams 3–6

To a solution of the carboxylic acid **1a**–**d** (7 mmol) in dry CH_2Cl_2 (20 mL), cooled at $T=-5$ °C, was added a solution of oxalyl chloride (35 mmol) and *N*,*N*-dimethylformamide (0.7 mmol) in dry CH_2Cl_2 (20 mL) dropwise over 1 h, under a nitrogen atmosphere. The mixture was stirred at room temperature for 3 h. The solvent and the oxalyl chloride excess was removed by evaporation at reduced pressure and the residue was dissolved in dry toluene (10 mL), cooled at $T=0$ °C and added with a solution of TEA (7 mmol) in dry toluene (10 mL). After 30 min the mixture was added, over 30–40 min, to a solution of imine 2 (3.5 mmol) in dry toluene (10 mL) heated at $T=90$ °C. The reaction was heated at reflux temperature for 20 h. After cooling, the solution was washed with 5% aq HCl, and then with H_2O. The organic layer was dried (Na_2SO_4) and the solvent was removed under reduced pressure. The crude products were purified by flash chromatography (SiO_2, *n*-hexane/AcOEt=97:3 for **3**–**6a**, *n*-hexane/AcOEt=95:5 for **3**–**6b**, CH_2Cl_2/AcOEt=99:1 for **3**–**4c** and for **4d**).

*4.2.1. (1′R,3S,4R,4′R)-1-Benzyl-4-phenyl-2H-spiro[azetidine-3,2′-bicyclo[2.2.1]hept[5]en]-2-one (**3a**).* Colorless solid (45%); mp 103–104 °C (hexane). $[\alpha]_D^{20}$ +47.7 (*c* 3.0, EtOH). ^1H NMR: δ 1.22–1.33 (m, 1H, H-7′); 1.45 (dd, *J* 11.9, 2.6, 1H, H-3′); 1.82 (d, *J* 8.5, 1H, H-7′); 2.29 (dd, *J* 11.9, 3.6, 1H, H-3′); 2.81–2.85 (m, 1H, H-4′); 2.89–2.93 (m, 1H, H-1′); 3.86 (d, *J* 15.0, 1H, CH_2Ph); 4.17 (s, 1H, H-4); 4.74 (dd, *J* 5.6, 2.7, 1H, H-6′); 4.87 (d, *J* 15.0, 1H, CH_2Ph); 6.03 (dd, *J* 5.6, 3.0, 1H, H-5′); 7.15–7.40 (m, 10H, Ph). ^{13}C NMR: δ 36.9/44.0 (C-3′/C-7′); 42.1/46.3 (C-1′/C-4′); 47.3 (*C*H_2Ph); 65.3 (C-4); 66.7 (C-3); 127.3–128.6 (Ph); 133.3/138.6 (C-6′/C-5′); 135.8/136.5 (Ph); 174.4 (C-2). IR (Nujol): 1746 (ν_{CO}, N–CO). Anal. Calcd for $C_{22}H_{21}NO$: C, 83.78; H, 6.71; N, 4.44. Found: C, 83.67; H 6.45; N, 4.31. MS-EI (*m*/*z*): 315 $[M]^+$.

*4.2.2. (1′R,3R,4S,4′R)-1-Benzyl-4-phenyl-2H-spiro[azetidine-3,2′-bicyclo[2.2.1]hept[5]en]-2-one (**4a**).* (26.5%). ^1H NMR (in mixture with **5a**): δ 0.94 (broad d, *J* 8.6, 1H, H-7′); 1.13 (broad d, *J* 8.6, 1H, H-7′); 1.81 (dd, *J* 12.0, 2.7, 1H, H-3′); 2.07 (dd, *J* 12.0, 3.6, 1H, H-3′); 2.61 (broad s, 1H, H-1′); 2.90 (broad s, 1H, H-4′); 3.94 (d, *J* 15.0, 1H, CH_2Ph); 4.48 (s, 1H, H-4); 4.95 (d, *J* 15.0, 1H, CH_2Ph); 6.02 (dd, *J* 5.6, 2.8, 1H, H-6′); 6.21 (dd, *J* 5.6, 3.1, 1H, H-5′); 7.15–7.40 (m, 10H, Ph). ^{13}C NMR: δ 37.5/44.6 (C-3′/C-7′); 42.1/46.0 (C-1′/C-4′); 47.7 (*C*H_2Ph); 65.7 (C-3); 66.9 (C-4); 127.6–129.2 (Ph); 133.1/139.3 (C-6′/C-5′); 135.7/136.1 (Ph); 173.6 (C-2). HRMS (FT-ICR)-(ESI$^+$) calcd for $C_{22}H_{21}NNaO^+$338.1515; found 338.1511.

*4.2.3. (1′R,3R,4R,4′R)-1-Benzyl-4-phenyl-2H-spiro[azetidine-3,2′-bicyclo[2.2.1]hept[5]en]-2-one (**5a**).* (19.5%); ^1H NMR (in mixture with **4a**): δ 1.18–1.22 (m, 1H, H-7′); 1.23–1.25 (m, 1H, H-3′); 1.31–1.33 (m, 1H, H-3′); 1.47–1.49 (m, 1H, H-7′); 2.77 (broad s, 1H, H-4′); 3.08 (broad s, 1H, H-1′); 3.85 (d, *J* 14.9, 1H, CH_2Ph); 4.26 (s, 1H, H-4); 4.97 (d, *J* 14.9, 1H, CH_2Ph); 6.15–6.19 (m, 1H, H-6′); 6.31–6.36 (m, 1H, H-5′); 7.15–7.40 (m, 10H, Ph). ^{13}C NMR: δ 32.6/44.3 (C-3′/C-7′); 43.4/52.3 (C-1′/C-4′); 48.7 (*C*H_2Ph); 66.8 (C-4); 67.1 (C-3); 127.6–129.2 (Ph); 133.5/139.6 (C-6′/C-5′); 136.1/137.4 (Ph); 173.3 (C-2). HRMS (FT-ICR)-(ESI$^+$) calcd for $C_{22}H_{21}NNaO^+$338.1515; found 338.1511.

*4.2.4. (1′S,3S,4R,4′R)-1-Benzyl-4-phenyl-2H-spiro[azetidine-3,2′-bicyclo[2.2.1]heptan]-2-one (**3b**).* Colorless solid (50%); mp 94–96 °C (pentane). $[\alpha]_D^{20}$ −33.5 (*c* 0.52, CH_2Cl_2). ^1H NMR: δ 0.58–0.64 (m, 1H, H-6′); 0.79–0.91 (m, 1H, H-5′); 1.00–1.11 (m, 1H, H-6′); 1.19 (d, *J* 9.8,

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1H, H-7′); 1.21–1.42 (m, 1H, H-5′); 1.47 (dd, *J* 12.7, 2.8, 1H, H-3′); 1.96 (d, *J* 9.8, 1H, H-7′); 2.20 (dt, *J* 12.7, 3.1, 1H, H-3′); 2.23–2.32 (m, 1H, H-4′); 2.43 (d, *J* 4.6, 1H, H-1′); 3.74 (d, *J* 15.0, 1H, CH_2Ph); 4.31 (s, 1H, H-4); 4.80 (d, *J* 15.0, 1H, CH_2Ph); 7.07–7.36 (m, 10H, Ph). ^{13}C NMR: δ 22.6/29.1/37.7 (C-3′/C-5′/C-6′/C-7′); 36.4/39.3 (C-1′/C-4′); 43.2 (*C*H_2Ph); 64.9 (C-4); 66.5 (C-3); 127.1–128.5 (Ph); 135.8/136.7 (Ph); 174.1 (C-2). IR (Nujol): 1746 (ν_{CO}, N–CO). Anal. Calcd for $C_{22}H_{23}NO$: C, 83.24; H, 7.30; N, 4.41. Found: C, 83.05; H 7.18; N, 4.28. MS-EI (*m*/*z*): 317[M]$^+$.

*4.2.5. (1′S,3R,4S,4′R)-1-Benzyl-4-phenyl-2H-spiro[azetidine-3,2′-bicyclo[2.2.1]heptan]-2-one (**4b**).* Colorless solid (27%); mp 112–113 °C (hexane). $[\alpha]_D^{20}$ +65.8 (*c* 1.43, CH_2Cl_2). ^{1}H NMR: δ 0.82–0.90 (m, 2H, H-7′); 1.23–1.34 (m, 1H, H-6′); 1.36–1.52 (m, 2H, H-5′); 1.91 (broad s, 2H, H-3′); 2.05 (d, *J* 4.3, 1H, H-1′); 2.06–2.18 (m, 1H, H-6′); 2.29 (broad s, 1H, H-4′); 3.89 (d, *J* 15.0, 1H, CH_2Ph); 4.03 (s, 1H, H-4); 4.93 (d, *J* 15.0, 1H, CH_2Ph); 7.15–7.42 (m, 10H, Ph). ^{13}C NMR: δ 23.6/29.1/38.1/39.4 (C-3′/C-5′/C-6′/C-7′); 36.5/40.1 (C-1′/C-4′); 44.1 (*C*H_2Ph); 66.5 (C-3); 69.9 (C-4); 127.5–128.8 (Ph); 135.7/135.9 (Ph); 173.7 (C-2). IR (Nujol): 1746 (ν_{CO}, N–CO). Anal. Calcd for $C_{22}H_{23}NO$: C, 83.24; H, 7.30; N, 4.41. Found: C, 83.12; H 7.21; N, 4.29. MS-EI (m/z): 317[M]$^+$.

*4.2.6. (1′S,3R,4R,4′R)-1-Benzyl-3′,3′-dimethyl-4-phenyl-2H-spiro[azetidine-3,2′-bicyclo[2.2.1]heptan]-2-one (**3c**).* Colorless solid (32%); mp 107–109 °C (hexane). $[\alpha]_D^{20}$ −3.8 (*c* 1, CH_2Cl_2). ^{1}H NMR: δ 0.46–0.51 (m, 1H); 0.71–0.88 (m, 1H); 1.05 (s, 3H, Me); 1.04–1.18 (m, 2H); 1.17 (s, 3H, Me); 1.39–1.45 (m, 1H); 1.78 (broad s, 1H, H-1′/H-4′); 2.25 (d, *J* 10.0, 1H); 2.45 (d, *J* 4.9, 1H, H-4′/H-1′); 3.66 (d, *J* 15.1, 1H, CH_2Ph); 4.41 (s, 1H, H-4); 4.86 (d, *J* 15.1, 1H, CH_2Ph); 7.08–7.36 (m, 10H, Ph). ^{13}C NMR: δ 21.4/24.7/35.7 (C-5′/C-6′/C-7′); 26.7/27.8 (2Me); 39.9 (C-3′); 43.2 (*C*H_2Ph); 42.8/49.0 (C-1′/C-4′); 60.4 (C-4); 74.2 (C-3); 127.5–128.9 (Ph); 136.2/136.9 (Ph); 172.5 (C-2). IR (Nujol): 1747 (ν_{CO}, N–CO). Anal. Calcd for $C_{24}H_{27}NO$: C, 83.44; H, 7.88; N, 4.05. Found: C, 83.37; H 7.76; N, 3.97. MS-FAB$^+$ (*m*/*z*): 346[MH]$^+$. Single crystals suitable for X-ray structure determination were obtained by precipitation from hexane. Crystallographic data (excluding structure factors) for **3c** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 891441. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

*4.2.7. (1′S,3S,4S,4′R)-1-Benzyl-3′,3′-dimethyl-4-phenyl-2H-spiro[azetidine-3,2′-bicyclo[2.2.1]heptan]-2-one (**4c**).* Colorless solid (36%); mp 131–133 °C (hexane). $[\alpha]_D^{20}$ +1.78 (*c* 0.2, CH_2Cl_2). ^{1}H NMR: δ 0.77 (d, *J* 10.1, 1H); 1.13 (s, 3H, Me); 1.14–1.19 (m, 1H, H-7′); 1.24 (s, 3H, Me); 1.21–1.27 (m, 2H); 1.70 (broad s, 1H); 1.75–1.84 (m, 1H); 2.02 (broad s, 1H); 2.15–2.25 (m, 1H); 3.74 (d, *J* 15.0, 1H, CH_2Ph); 4.51 (s, 1H, H-4); 4.97 (d, *J* 15.0, 1H, CH_2Ph); 7.12–7.40 (m, 10H, Ph). ^{13}C NMR: δ 22.3/24.5/35.9 (C-5′/C-6′/C-7′); 24.1/29.6 (2Me); 42.1 (C-3′); 43.7 (*C*H_2Ph); 42.4/49.2 (C-1′/C-4′); 61.1 (C-4); 73.4 (C-3); 127.5–128.5 (Ph); 135.9/136.0 (Ph); 172.3 (C-2). IR (Nujol): 1745 (ν_{CO}, N–CO). Anal. Calcd for $C_{24}H_{27}NO$: C, 83.44; H, 7.88; N, 4.05. Found: C, 83.39; H 7.80; N, 3.95. MS-FAB$^+$ (*m*/*z*): 346[MH]$^+$.

*4.2.8. (1′R,3S,4S,4′R)-1-Benzyl-1′,7′,7′-trimethyl-4-phenyl-2H-spiro[azetidine-3,2′-bicyclo[2.2.1]heptan]-2-one (**5d**).* Colorless solid (58%); mp 161–162 °C (hexane). $[\alpha]_D^{20}$ +23.5 (*c* 1.1, CH_2Cl_2). ^{1}H NMR: δ 0.47 (s, 3H, Me); 0.80 (s, 3H, Me); 0.94 (s, 3H, Me); 1.19–1.69 (m, 6H); 2.48–2.62 (m, 1H); 3.57 (d, *J* 14.78, 1H, CH_2Ph); 4.28 (s, 1H, H-4); 4.84 (d, *J* 14.8, 1H, CH_2Ph); 7.07–7.37 (m, 10H, Ph). ^{13}C NMR: δ 11.8/18.9/20.0 (3Me); 27.7/33.8 (C-5′/C-6′); 31.3 (C-3′); 43.6 (*C*H_2Ph); 45.9 (C-4′); 48.6 (C-7′); 51.7 (C-1′); 63.9 (C-4); 70.1 (C-3); 127.5–128.6 (Ph); 135.5/136.0 (Ph); 173.3 (C-2). IR (Nujol): 1733 (ν_{CO}, N–CO). Anal. Calcd for $C_{25}H_{29}NO$: C, 83.52; H, 8.13; N, 3.90. Found: C, 83.29; H 8.26; N, 3.87. MS-FAB$^+$ (*m*/*z*): 360[MH]$^+$.

*4.2.9. endo/exo-(1S,4R)-N-Benzyl-3,3-dimethylbicyclo[2.2.1] heptane-2-carboxamide (**7c**).* Amorphous solid (23%). ^{1}H NMR: δ 0.95 (s, 3H, Me); 1.10 (s, 3H, Me); 0.87–1.45 (m, 6H); 1.60–1.70 (m, 1H); 2.15 (d, *J* 9.9, 1H); 2.34 (broad s, 1H); 4.32–4.44 (m, 2H, CH_2Ph); 5.78 (broad s, 1H); 7.24–7.33 (m, 5H, Ph). ^{13}C NMR: δ 23.9/29.0/37.6 (C-5/C-6/C-7); 25.4/28.0 (2Me); 41.3/47.8 (C-1/C-4); 42.2 (C-3); 43.3 (*C*H_2Ph); 60.8 (C-2); 127.3–128.5 (Ph); 138.6 (Ph); 173.5 (C=O). IR (Nujol): 1651 (ν_{CO}, N–CO). Anal. Calcd for $C_{17}H_{23}NO$: C, 79.33; H, 9.01; N, 5.44. Found: C, 79.25; H 8.87; N, 5.28.

4.3. General procedure for the hydrolysis of spiro-β-lactams

A solution of spiro-β-lactam **3b** or **4b** (2.5 mmol) in HBr 32% in AcOH (5 mL) was stirred at room temperature for 16 h. The mixture was added with water (5 mL) and extracted with CH_2Cl_2. The organic layer was washed with NH_3 7% until basic pH, dried (Na_2SO_4) and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (SiO_2, AcOEt).

4.3.1. (1S,2S*,4R*)-2-[(R*)-(Benzylamino)(phenyl)methyl] bicyclo[2.2.1]heptane-2-carboxylic acid (**8b**).* Colorless solid (73%); mp 103–105 °C. ^{1}H NMR (CD_3OD): δ 1.22–2.23 (m, 10H); 3.79 (AB syst., 2H, N–CH_2); 4.32 (s, 1H, N–C*H*); 7.33–7.53 (m, 10H, Ph). ^{13}C NMR (CD_3OD): δ 24.4/29.8/40.4/44.0 (C-3/C-5/C-6/C-7); 37.5/44.2 (C-1/C-4); 50.2 (*C*H_2Ph); 56.5 (C-2); 67.6 (N–C*H*); 129.7–130.7 (Ph); 134.0/135.3 (Ph); 183.3 (C=O). IR (Nujol): 1636 (ν_{CO}, N–CO). Anal. Calcd for $C_{22}H_{25}NO_2$: C, 78.77; H, 7.51; N, 4.18. Found: C, 78.65; H 7.37; N, 4.06. MS-FAB$^+$ (*m*/*z*): 336[MH]$^+$.

4.3.2. (1S,2R*,4R*)-2-[(S*)-(Benzylamino)(phenyl)methyl] bicyclo[2.2.1]heptane-2-carboxylic acid (**9b**).* Amorphous solid (71%). ^{1}H NMR (CD_3OD): δ 1.00–2.44 (m, 10H); 3.81 (AB syst., 2H, N–CH_2); 3.96 (s, 1H, N–C*H*); 7.26–7.43 (m, 10H, Ph). ^{13}C NMR (CD_3OD): δ 28.6/28.8/38.9/39.3 (C-3/C-5/C-6/C-7); 38.7/42.5 (C-1/C-4); 51.6 (*C*H_2Ph); 58.9 (C-2); 68.7 (N–*C*H); 128.9–131.2 (Ph); 135.2/136.5 (Ph); 180.3 (C=O). IR (Nujol): 1641 (ν_{CO}, N–CO). Anal. Calcd for $C_{22}H_{25}NO_2$: C, 78.77; H, 7.51; N, 4.18. Found: C, 78.54; H 7.31; N, 4.03. MS-FAB$^+$ (*m*/*z*): 336[MH]$^+$.

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Supplementary data

Copies of ^{1}H and ^{13}C NMR of all compounds, NOESY experiments and X-ray figure. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2012.11.048.

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