Staudinger reactions of unsymmetrical cyclic ketenes: a synthetically useful approach to spiro β-lactams and derivatives. Reaction mechanism and theoretical studies †

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An efficient and operationally simple synthesis of tetrahydrofuran-derived spiro-β-lactams using the ketene–imine cycloaddition route is described. Also the preparation of spiro-*N*-sulfonyl-β-lactam derivatives, which are analogs of monobactams, is reported. As far as we know, this is the first time that an unsymmetrical cyclic ketene is used in a Staudinger-type reaction. The experimental evidence suggests the involvement of a ketene derived from the acyl chloride precursor in the reaction. High-level *ab initio* calculations have been performed in order to get insight into the electronic effects controlling the stereochemical outcome of the reactions.

Introduction

The β-lactam ring is a very interesting backbone in organic chemistry and is responsible for the antibacterial properties of penicillins and cephalosporins.[1] More specifically, spiro-β-lactams are interesting compounds due to their antiviral[2a] and antibacterial properties.[2b] Recently, it has been shown that some spiro-β-lactams also exhibit activity as cholesterol absorption inhibitors (CAI),[3] making them potentially useful compounds not only for the development of drugs for the treatment of patients with high levels of cholesterol, but also due to recent evidence indicating that the activity of the enzymes responsible of the cleavage of the amyloid precursor protein (a protein thought to be involved in the pathogenesis of Alzheimer's disease) is coupled to cholesterol regulation.[4]

On the other hand, β-lactams have received wide use as synthetic intermediates in organic synthesis (the β-Lactam Synthon Method),[5] thus providing a very useful route to a number of α- and β-amino acid derivatives and peptides. In this context, the 4-spiro-β-lactams can also be synthetic precursors of α,α-disubstituted β-amino acids.

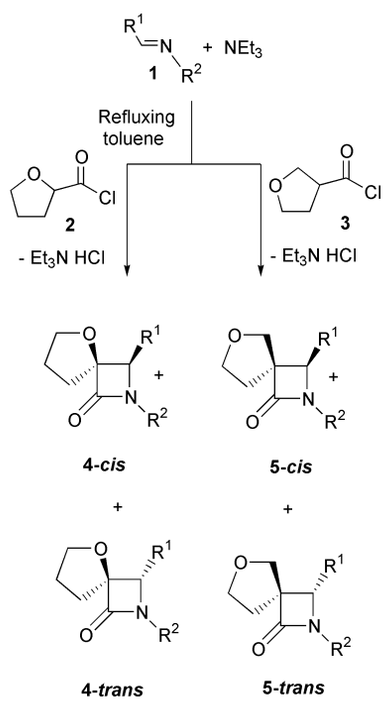
Several syntheses of spiro-β-lactams have been described in the literature,[6] but only in one case, was a cyclic ketene (2-carbonyl-1,3-dithiolane) employed in the ketene–imine cycloaddition.[7]

In this paper, we present the results obtained in the synthesis of tetrahydrofuran-derived spiro-β-lactams **4** (5-oxa-2-azaspiro-[3.4]octan-1-ones) and **5** (6-oxa-2-azaspiro[3.4]octan-1-ones) (Scheme 1), using the Staudinger reaction.[8] The synthesis of spiro-analogs of monobactams is described and the results of preliminary *ab initio* studies on the reaction mechanism of cyclic ketenes are reported.

Results and discussion

(i) [2+2] Cycloaddition of imines 1 with 2- and 3-tetrahydrofuroyl chlorides 2 and 3

The β-lactams **4** and **5** were prepared by reaction of either 2-tetrahydrofuroyl chloride **2** or 3-tetrahydrofuroyl chloride **3** with imines **1** (Scheme 1 and Table 1). The acid chloride was added to a stirred, refluxing solution of the imine and triethylamine in toluene. After refluxing of the solution overnight and aqueous work-up, a mixture of *cis*- and *trans*-spiro-β-lactams **4** or **5** was obtained in good to moderate yields. When other solvents such as dichloromethane and lower temperatures were used, the starting materials were always recovered. The β-lactams **4** and **5** are the expected products of the [2+2] cycloaddition reaction of imines with the cyclic ketenes **6** and **7** (Fig. 1).



Scheme 1 See Table 1 for R^1 and R^2.

In all cases, the diastereomeric mixtures of spiro-β-lactams **4** and **5** were separated by column chromatography. The relative configuration in the stereochemical centres of the azetidinone ring was established by nuclear overhauser effect (NOE) difference NMR experiments. The *cis*/*trans* ratio and the chemical yield are shown in Table 1. The *N*-unsubstituted azetidin-1-ones

† Electronic supplementary information (ESI) available: Spectral data for compounds **4b**–**4m** and **5b**–**5d** and Cartesian coordinates and energies (hartrees) of zwitterionic intermediates (**IZ1**, **IZ2**, **IZ3**, and **IZ4**) and transition structures (**TS1**, **TS2**, **TS3** and **TS4**). See http://www.rsc.org/suppdata/p1/b1/b103279h/

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Table 1

	R^1	R^2	*cis* : *trans* Ratio [a]	Yield (%) [b]
4a	*p*-$CH_3OC_6H_4$	*p*-$CH_3OC_6H_4$	15 : 1	76
4b	C_6H_5	*p*-$CH_3OC_6H_4$	12 : 1	75
4c	C_6H_5	C_6H_5	6 : 1	49
4d	2-Furyl	*p*-$CH_3OC_6H_4$	8 : 1	64
4e	3-Pyridyl	*p*-$CH_3OC_6H_4$	4 : 1	63
4f	$C_6H_5CH{=}CH$	*p*-$CH_3OC_6H_4$	5 : 1	56
4g	C_6H_5	CH_3	14 : 1	66
4h	C_6H_5	$C_6H_5CH_2$	5 : 1	77 [c]
4i	C_6H_5	*p*-$NO_2C_6H_4$	1 : 1	66
4j	*p*-$NO_2C_6H_4$	C_6H_5	1 : 4	58
4k	*p*-$NO_2C_6H_4$	CH_3	1 : 2	71
4l	*p*-$NO_2C_6H_4$	*p*-$NO_2C_6H_4$	1 : 5	52
4m	*p*-$NO_2C_6H_4$	*p*-$CH_3OC_6H_4$	1 : 3	74
5a	*p*-$CH_3OC_6H_4$	*p*-$CH_3OC_6H_4$	3 : 1	69
5b	C_6H_5	*p*-$CH_3OC_6H_4$	3 : 1	66
5c	C_6H_5	C_6H_5	2 : 1	69
5d	*p*-$NO_2C_6H_4$	C_6H_5	1 : 2	68

[a] Determined by integration of the ^{1}H NMR spectra of the crude reaction mixture. [b] Refers to the mixture of the pure diastereomers, after their isolation. [c] The reaction was carried out by adding NEt_3 to the acyl chloride **2** in refluxing toluene, and after 10 minutes *N*-benzylbenzaldimine was added.

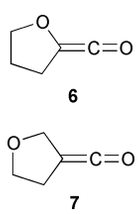
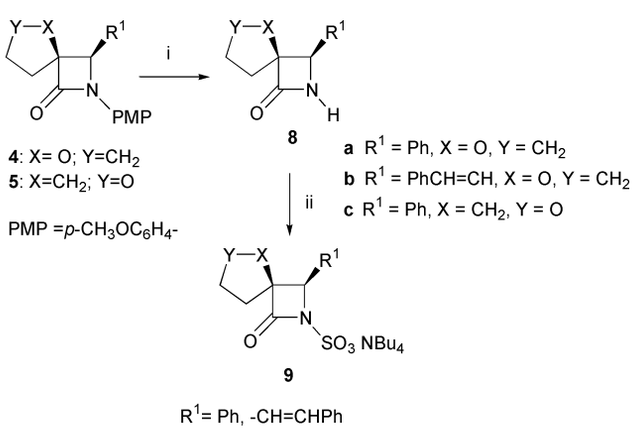


Fig. 1 Unsymmetrical ketenes derived from 2- and 3-tetrahydrofuroyl chlorides.

8 can be prepared by oxidative cleavage of the corresponding *N*-*p*-methoxyphenyl derivatives, following a previously described procedure (see Scheme 2 and Experimental section).[9]



Scheme 2 *Reagents and conditions*: (i) CAN, CH_3CN–water, 0 °C, (ii) SO_3–pyridine complex, pyridine, 90 °C, then $HNBu_4SO_4$.

When analysing the stereochemistry of the reactions of **2** or **3** with imines, it should be noted that the *cis*/*trans* ratio is strongly influenced by two factors: the position of the oxygen on the acyl chloride precursor and the electronic nature of the substituents R^1 and R^2 on the imine. Thus, the reaction of 2-tetrahydrofuroyl chloride with imines is more stereoselective than that of 3-tetrahydrofuroyl chloride, as can be seen from entries **4b** and **5b** in Table 1. On the other hand, the presence of an electron-withdrawing group can decrease (entries **4c** *vs.* **4i**) or reverse (entries **4c** *vs.* **4j**) the stereoselectivity of the reaction, while the presence of electron-donating groups on the imine leads to an increase in stereoselectivity.

In addition to the electronic factors described above, steric effects also play a role in the stereoselectivity, as can be seen from the *cis*/*trans* ratio in the reaction of the 2-tetrahydrofuroyl chloride **2** with *N*-benzyl- or *N*-methylbenzaldimine (entries **4g** *vs.* **4h**).

(ii) Synthesis of spiro-*N*-sulfonyl-β-lactam derivatives 9

The monobactams are monocyclic β-lactams containing a sulfamate group, produced by different types of bacteria (*e.g.*, *Chromobacterium*) with the interesting feature of their utility in the treatment of infectious diseases in patients allergic to penicillins (Fig. 2).[10] Synthetic analogs such as Aztreonam (Fig. 2)

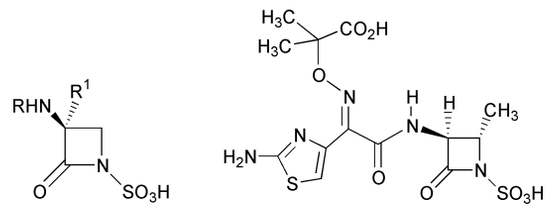
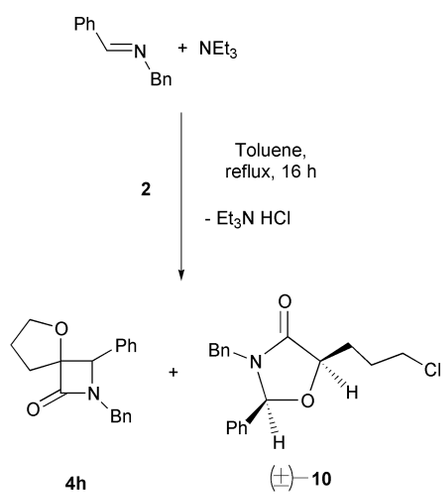


Fig. 2

are active against gram-negative bacteria and show a high resistance to the degradative action of β-lactamases. Here we report the synthesis of spiro-*N*-sulfonyl-β-lactams **9**, which can be viewed as analogs of monobactams. Compounds **9** (Scheme 2) were prepared by reaction of the *N*-unsubstituted spiro-β-lactams **8** with the SO_3–pyridine complex, and isolated as the tetrabutylammonium salts.[11]

(iii) Reaction mechanism

In order to understand the factors controlling the stereochemical outcome of the reaction, some experimental studies were carried out. We have found that in the reaction involving 2-tetrahydrofuroyl chloride **2** with *N*-benzylbenzaldimine, different products are obtained depending upon the order of addition of the reagents. Thus, when the previously described conditions for the synthesis of these β-lactams were employed, the spiro-β-lactam **4h** and another compound, **10**, were obtained in a 1 : 1 ratio (as can be determined by integration of the ^{1}H NMR signals of the crude reaction mixture) (Scheme 3).

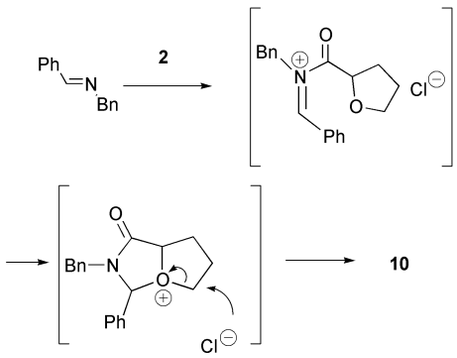


Scheme 3

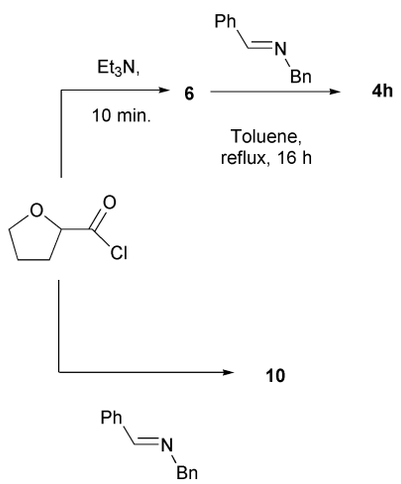
The formation of compound **10** can be explained by assuming the initial acylation of the imine to give an *N*-acyliminium intermediate, which in turn undergoes a rearrangement by internal nucleophilic attack of the tetrahydrofuran oxygen on the iminiun carbon, followed by the chloride ring-opening to

give **10** (Scheme 4). Alternatively, the β-lactam **4h** is formed from the competitive ketene–imine cycloaddition route.

This mechanistic proposal was tested as follows (Scheme 5):



Scheme 4



Scheme 5

when the cyclic ketene was generated *in situ* from the reaction of a toluene solution of **2** with triethylamine and, after 10 min, the *N*-benzylbenzaldimine was added, only the β-lactam **4h** was obtained. On the other hand, the reaction of *N*-benzylbenzaldimine with **2**, in the absence of base, leads exclusively to **10**, as a 95 : 5 mixture of diastereomers.[12] The reaction of 3-tetrahydrofuroyl chloride **3**, in the absence of base, does not lead to the analog of **10** but to the hydrolysis products of the imine. This result can be understood by taking into account that the rearrangement of the *N*-acyliminium intermediate derived from **3** is, for geometrical reasons, more difficult than in the case of the reaction of **2**.

According to these results, which are in good agreement with previous findings of Duran and Ghosez,[13] we can assume that in the reaction of the acid chlorides **2** or **3** with imines, a true cyclic ketene **6** or **7** (Fig. 1) is formed[14] by dehydrohalogenation of the acid chloride, and then the [2+2] ketene–imine cycloaddition takes place to give the β-lactam.

(iv) *Ab initio* calculations

The mechanism of the [2+2] ketene–aimine cycloaddition reaction is still a subject of controversy. According to both experimental[15] and theoretical studies,[16] the ketene–imine cycloaddition is a stepwise reaction, in which a solvent-stabilized zwitterionic intermediate is formed. The conrotatory ring-closure of this zwitterionic intermediate produces the β-lactam. However, at present, an asynchronous concerted reaction pathway or a diradical mechanism cannot be excluded for these reactions.[17]

According to previous theoretical studies,[16c] when an unsymmetrical ketene reacts with imines the stereoselectivity will be controlled, at least in part, by the torquoelectronic effect, as happens for the thermal ring-opening of 3-substituted cyclobutenes.[18] In our case, the difference in stereoselectivity between the reactions carried out using the 2- and 3-tetrahydrofuroyl chloride could be explained by the fact that, in the ring closure of the intermediate formed from the ketene **6**, the oxygen atom will have a strong electronic preference for the outward closure (see Fig. 3). The preference of the oxygen atom for

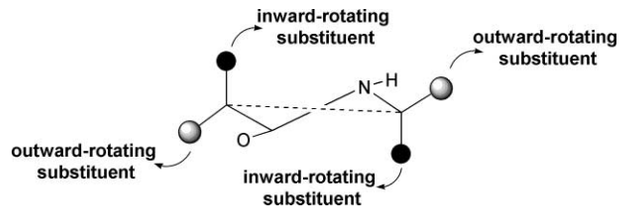


Fig. 3 Definition of inward and outward positions in the conrotatory ring-closure transition state of the zwitterionic intermediate.

the outward position in the transition state of the conrotatory ring-closure of the zwitterionic intermediate has been reported before,[16c] and is quite similar to the preference observed in the ring-opening of the 3-substituted cyclobutenes.[18b] In the case of the reaction of 3-tetrahydrofuroyl chloride, there is no important difference, from the electronic point of view, between the inward and outward carbon atoms, so the stereoselectivity of the ring-closure is expected to be significantly lower.

In order to test the influence of the torquoelectronic effect in determining the stereoselectivity observed in the reactions of the ketene **6**, compared with the analogous reactions of **7**, we carried out preliminary theoretical studies. The potential-energy surfaces corresponding to the model reaction of formaldimine with 2-carbonyltetrahydrofuran **6**, or with 3-carbonyltetrahydrofuran **7**, were explored at the MP2/6-31+G* level of theory.[19] The stationary points corresponding to the inward and outward reaction pathways were located. The reaction is predicted to take place through a two-step mechanism involving the formation of a zwitterionic intermediate. In Fig. 4, the

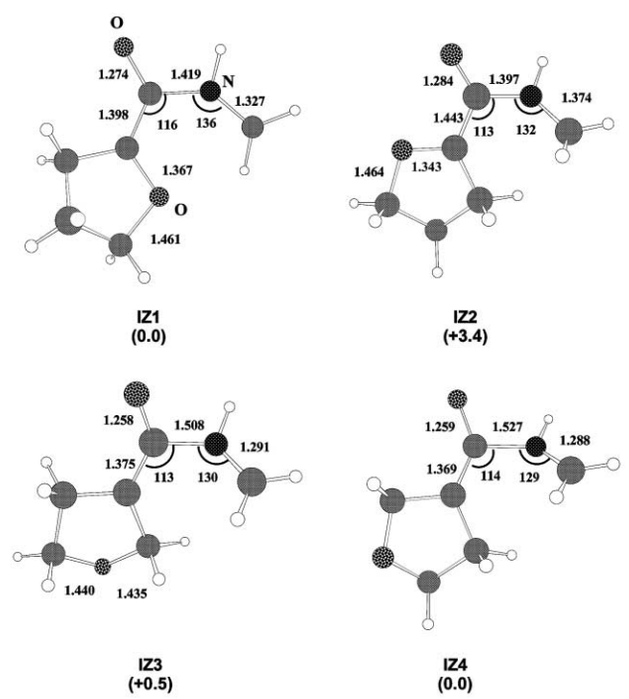


Fig. 4 Selected bond-lengths (Å) and angles (°) of the MP2/6-31+G*-optimized zwitterionic intermediates of the Staudinger reaction of **6** (**IZ1** and **IZ2**) or **7** (**IZ3** and **IZ4**) with formaldimine. The relative energies are in kcal mol^{-1}.

geometries corresponding to the zwitterionic intermediates (**IZ1** to **IZ4**) are shown. The transition structures (**TS1** to

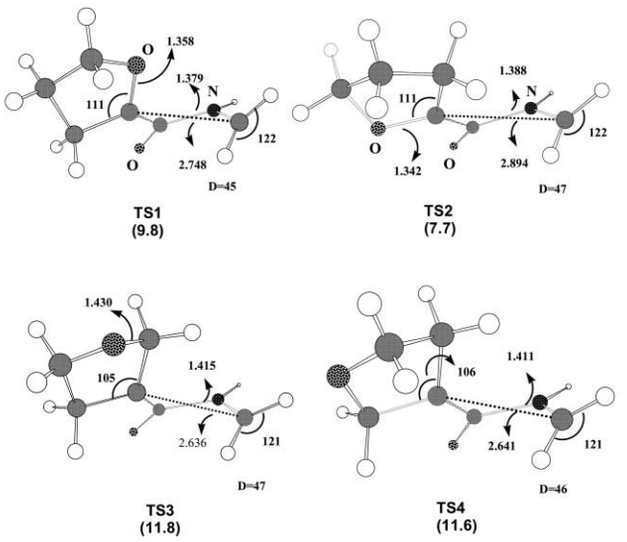


Fig. 5 Selected bond-lengths (Å) and angles (°) of the MP2/6-31+G*-optimized transition structures for the conrotatory ring-closure of the zwitterionic intermediates of the Staudinger reaction of **6** (**TS1** and **TS2**) or **7** (**TS3** and **TS4**) with formaldimine. D is the dihedral angle around the forming ring. The energies of the transition structures, relative to the lowest zwitterionic intermediate, are in kcal mol^{-1}.

TS4) for the ring-closure of the zwitterionic intermediates are presented in Fig. 5.

As can be seen in Fig. 5, in the case of the 2-carbonyltetrahydrofuran **6**, the transition structure having the oxygen atom rotating inward (**TS1**) is 2.1 kcal mol^{-1} ‡ less stable than the transition structure in which the oxygen is placed outward (**TS2**). Assuming that the configuration of the imine (the imines are present only as the *E*-isomer, as explained below) does not change during the reaction, the outward transition structure **TS2** will lead to the *cis*-β-lactams. On the other hand, in the reaction of 3-carbonyltetrahydrofuran **7**, the difference in energy between the inward (**TS3**) and outward (**TS4**) transition structures was found to be significantly smaller (0.2 kcal mol^{-1}). This result is in good agreement with the experimental results: the reactions of 3-tetrahydrofuroyl chloride **3** show less stereoselectivity than the corresponding reactions of 2-tetrahydrofuroyl chloride **2** (see, for example, entries **4b** and **5b** in Table 1).

In addition to the torquoelectronic effect, it is evident from an analysis of the results shown in Table 1 that other electronic effects (*e.g.*, the electronic nature of the substituents of the imines) are also important in determining the stereochemistry of these reactions. In this regard, we have to take into account the configurational purity of the starting imines, because this could determine, at least in some cases, the final stereochemistry. However, our analysis of the NMR spectra of the imines shows that these compounds are obtained exclusively as the *E* isomer, in good agreement with previous studies.[21] The decrease or reversal of the reaction stereoselectivity when using imines bearing strongly electron-withdrawing groups could be due to a change in the reaction mechanism, from the stepwise process, involving a zwitterionic intermediate, to a concerted and probably asynchronous reaction. The reduced nucleophilicity of the imines may cause the reaction to take place through a concerted [2+2] cycloaddition rather than through a reaction pathway involving an initial attack of the imine lone pair on the ketene.[22]

Conclusions

We have developed a simple method for the synthesis of spiro-β-lactams, which are now being studied as precursors of modified β-amino acids and β-peptides. These spiro compounds can be also employed in the synthesis of monobactam analogs. In addition, the results presented here raise interesting points about the mechanism of the [2+2] ketene–imine cycloaddition and the factors controlling the stereochemistry of the products. According to preliminary *ab initio* calculations, the torquoelectronic effect is an important factor in determining the stereochemistry of the [2+2] cycloadditions of unsymmetrical ketenes with imines, but, as the experimental data show, steric and other electronic effects are important in determining the reaction stereoselectivity.

Experimental

Reagents

Toluene was dried by distillation from sodium–benzophenone. Dichloromethane (DCM) was refluxed over phosphorus pentaoxide and distilled immediately prior to use. Chromatographic purifications were performed on silica gel (230–400 mesh) by flash technique. Analytical TLC plates (covered with silica gel 60 F_{254}) were viewed by UV light or developed by heating after treatment with an acidic solution of Ce(IV) and Mo(VI). ^1H and ^{13}C NMR spectra were recorded on a Bruker AC-300 or DPX-300 spectrometer. Chemical shifts (**8**) refer to tetramethylsilane (TMS) in ^1H experiments and to deuterated solvent in ^{13}C experiments. IR analyses were performed on a Mattson 3000 FTIR spectrometer. Elemental analyses were obtained on a Perkin-Elmer 240-B analyser. Standard benchtop techniques were employed for handling air-sensitive reagents. The imines **1** were prepared according to the procedure published by Westheimer[23] and were used without further purification.

Preparation of 2-tetrahydrofuroyl chloride 2 and 3-tetrahydrofuroyl chloride 3

To a stirred solution of 2- or 3-tetrahydrofuroic acid (2.0 g, 17.24 mmol) in 25 mL of CH_2Cl_2 at room temperature was added dropwise a solution of oxalyl dichloride (4.5 mL, 51.57 mmol) in 10 mL of dry CH_2Cl_2. When the addition was finished, two drops of dry DMF were added, and the reaction mixture was stirred overnight at room temperature. Solvent and excess of oxalyl dichloride were removed *in vacuo*, and distillation under reduced pressure afforded the desired acid chlorides (2-tetrahydrofuroyl choride **2**, bp 39 °C at 1 Torr; 3-tetrahydrofuroyl chloride **3**, bp 36 °C at 1 Torr).

General procedure for the preparation of spiro-β-lactams 4 and 5

To a solution of the appropriate imine **1** (2 mmol) and dry Et_3N (0.41 mL, 3 mmol) in refluxing toluene (15 mL) was added dropwise a solution of the corresponding tetrahydrofuroyl chloride **2** or **3**, (0.269 g, 2 mmol) in toluene (5 mL) (a white precipitate of triethylammonium chloride was formed as soon as the addition was started). The reaction mixture was refluxed overnight, cooled to room temperature, and diluted with CH_2Cl_2 (30 mL). The resultant solution was washed successively with 5% aq. sodium bicarbonate (20 mL) and brine (20 mL). The organic layer was dried (Na_2SO_4), and concentrated *in vacuo*. Flash chromatography of the crude reaction mixtures over silica gel (EtOAc–hexanes) afforded the final spiro-β-lactams **4** and **5**.

2,3-Bis(4-methoxyphenyl)-5-oxa-2-azaspiro[3.4]octan-1-one 4a. Prepared according to the general procedure described above, to afford after flash chromatography (25% EtOAc–hexanes) compound **4a** (487 mg of the *cis* diastereomer and 30 mg of the *trans* diastereomer, 76% overall yield) as a white solid *cis*: mp 147 °C; ν_{max}/cm^{-1} 1734 (β-lactam C=O); ^1H NMR (300 MHz; $CDCl_3$) δ_H 7.28 (d, J = 8.7 Hz, 2H), 7.22 (d, J = 8.7 Hz, 2H), 6.87 (d, J = 8.7 Hz, 2H), 6.77 (d, J = 8.7 Hz, 2H),

‡ 1 cal = 4.184 J.

4.88 (s, 1H), 3.91–3.84 (m, 1H), 3.80 (s, 3H), 3.73 (s, 3H), 3.59–3.51 (m, 1H), 2.44 (m, 1H), 2.33 (m, 1H), 2.05–1.90 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 167.0, 159.3, 155.9, 130.6, 128.3, 126.3, 118.6, 114.0, 113.7, 92.6, 69.6, 69.2, 55.1, 54.9, 32.0, 25.1 (Calc. for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24. Found: C, 70.54; H, 6.28%).

2,3-Bis(4-methoxyphenyl)-6-oxa-2-azaspiro[3.4]octan-1-one 5a. Prepared according to the general procedure described above, to afford after flash chromatography (25% EtOAc–hexanes) compound **5a** (360 mg of the *cis* diastereomer and 122 mg of the *trans* diastereomer, 69% overall yield) as a white solid *cis*: mp 147 °C; ν_{max}/cm^{-1} 1742 (β-lactam C=O); ^{1}H NMR (300 MHz; $CDCl_3$) δ_H 7.24 (d, J = 8.7 Hz, 2H), 7.12 (d, J = 8.7 Hz, 2H), 6.90 (d, J = 8.7 Hz, 2H), 6.78 (d, J = 9.1 Hz, 2H), 4.97 (s, 1H), 3.92 (m, 2H), 3.79 (d, J = 9.6 Hz, 1H), 3.79 (s, 3H), 3.74 (s, 3H), 3.37 (d, J = 9.6 Hz, 1H), 2.58 (m, 1H), 2.40 (m, 1H); ^{13}C NMR (75 MHz; $CDCl_3$) δ_C 167.6, 159.6, 155.8, 130.8, 127.6, 126.6, 118.4, 114.4, 114.1, 68.2, 68.0, 66.6, 55.3, 55.2, 34.6 (Calc. for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24. Found: C, 71.06; H, 6.35%). *trans*: mp 142 °C; ν_{max}/cm^{-1} 1744 (β-lactam C=O); ^{1}H NMR (300 MHz; $CDCl_3$) δ_H 7.25 (d, J = 9.7 Hz, 2H), 7.16 (d, J = 8.7 Hz, 2H), 6.89 (d, J = 8.7 Hz, 2H), 6.79 (d, J = 8.7 Hz, 2H), 4.97 (s, 1H), 4.27 (d, J = 9.2 Hz, 1H), 4.13 (d, J = 9.2 Hz, 1H), 3.80 (s, 3H), 3.77 (m, 1H), 3.74 (s, 3H), 3.59 (m, 1H), 2.11 (m, 1H), 1.54 (m 1H); ^{13}C NMR (75 MHz; $CDCl_3$) δ_C 167.2, 159.5, 155.8, 130.8, 127.9, 126.8, 118.4, 114.3, 114.1, 73.2, 68.2, 66.2, 65.8, 55.3, 55.1, 29.0 (Calc. for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24. Found: C, 70.98; H, 6.39%).

Synthesis of the *N*-unsubstituted spiro-β-lactams 8

The *N*-unsubstituted β-lactams **8a–c** were prepared according to the published procedure,[9] employing 1 mmol of the spiro-β-lactam **4** or **5**.

3-Phenyl-5-oxa-2-azaspiro[3.4]octan-1-one 8a. Prepared from **4b *cis*** according to the published procedure to afford, after flash chromatography (50% AcOEt–hexanes), compound **8a** (167 mg, 82%); ν_{max}/cm^{-1} 1750 (β-lactam C=O); ^{1}H NMR (300 MHz; $CDCl_3$) δ_H 7.38–7.25 (m, 5H), 6.81 (br s, 1H), 4.61 (s, 1H), 3.82 (m, 1H), 3.56 (m, 1H), 2.49–2.23 (m, 2H), 1.81–2.09 (m, 2H); ^{13}C NMR (75 MHz; $CDCl_3$) δ_C 171.6, 136.7, 128.2, 127.9, 126.8, 94.6, 69.7, 65.8, 32.1, 25.1 (Calc. for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.45. Found: C, 70.77; H, 6.25%).

3-Styryl-5-oxa-2-azaspiro[3.4]octan-1-one 8b. Prepared from **4f *cis*** according to the published procedure to afford, after flash chromatography (50% AcOEt–hexanes), compound **8b** (96 mg, 42%); ν_{max}/cm^{-1} 1746 (β-lactam C=O); ^{1}H NMR (300 MHz; $CDCl_3$) δ_H 7.41–7.28 (m, 5H), 6.59 (d, J = 15.9 Hz, 1H), 6.45 (br s, 1H), 6.34 (dd, J = 15.9 Hz, J = 8.2 Hz, 1H), 4.15 (d, J = 8.2 Hz, 1H), 3.90 (m, 2H), 2.34 (m, 1H), 2.22–1.84 (m, 3H); ^{13}C NMR (75 MHz; $CDCl_3$) δ_C 171.2, 136.6, 134.0, 128.5, 126.5, 126.0, 94.5, 69.9, 64.5, 31.7, 25.1 (Calc. for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59. Found: C, 73.57; H, 6.75%).

3-Phenyl-6-oxa-2-azaspiro[3.4]octan-1-one 8c. Prepared from **5b *cis*** according to the published procedure to afford, after flash chromatography (50% AcOEt–hexanes), compound **8c** (188 mg, 93%), ν_{max}/cm^{-1} 1742 (β-lactam C=O); ^{1}H NMR (300 MHz; $CDCl_3$) δ_H 7.40–7.13 (m, 5H), 7.12 (br s, 1H), 4.57 (s, 1H), 3.82 (m, 2H), 3.62 (d, J = 9.7 Hz, 1H), 3.21 (d, J = 9.7 Hz, 1H), 2.53–2.26 (m, 2H); ^{13}C NMR (75 MHz; $CDCl_3$) δ_C 172.0, 136.8, 128.6, 128.0, 125.8, 68.3, 67.7, 66.2, 63.0, 33.9 (Calc. for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.45. Found: C, 70.67; H, 6.25%).

Synthesis of the sulfamate tetrabutylammonium salts 9

These compounds were prepared according to the published procedure,[11] employing 0.3 mmol of the corresponding *N*-unsubstituted β-lactam **8**.

Tetrabutylammonium 1-oxo-3-phenyl-5-oxa-2-azaspiro[3.4]-octane-2-sulfonate 9a. Prepared from **8a** according to the published procedure to afford **9a** (120 mg, 76%) as a colorless oil, ν_{max}/cm^{-1} 1769 (β-lactam C=O); ^{1}H NMR (300 MHz; $CDCl_3$) δ_H 7.38–7.16 (m, 5H), 4.87 (s, 1H), 3.71 (m, 1H), 3.43 (m, 1H), 3.08 (m, 8H), 2.26 (m, 2H), 1.95–1.79 (m, 2H), 1.48 (m, 8H), 1.27 (m, 8H), 0.89 (t, J = 7.4 Hz, 12H); ^{13}C NMR (75 MHz; $CDCl_3$) δ_C 167.3, 136.4, 127.5, 127.0, 91.9, 70.9, 69.5, 57.9, 32.2, 24.8, 23.4, 19.2, 13.3 (Calc. for $C_{28}H_{48}N_2O_5S$: C, 64.09; H, 9.22. Found: C, 64.37; H, 9.45%).

Tetrabutylammonium 1-oxo-3-styryl-5-oxa-2-azaspiro[3.4]-octane-2-sulfonate 9b. Prepared from **8b** according to the published procedure to afford **9b** (136 mg, 82%) as a pale yellow oil, ν_{max}/cm^{-1} 1773 (β-lactam C=O); ^{1}H NMR (300 MHz; $CDCl_3$) δ_H 7.33–7.11 (m, 5H), 6.61 (d, J = 15.9 Hz, 1H), 6.30 (dd, J = 15.9 Hz, J = 8.2 Hz, 1H), 4.37 (d, J = 8.2 Hz, 1H), 3.91–3.68 (m, 2H), 3.12 (m, 8H), 2.29–2.05 (m, 2H), 1.98–1.71 (m, 2H), 1.48 (m, 8H), 1.27 (m, 8H), 0.88 (t, J = 7 Hz, 12H); ^{13}C NMR (75 MHz; $CDCl_3$) δ_C 166.5, 136.4, 133.4, 128.0, 127.3, 126.3, 125.9, 91.7, 69.5, 69.1, 57.9, 31.6, 24.8, 23.4, 19.2, 13.3 (Calc. for $C_{30}H_{50}N_2O_5S$: C, 64.42; H, 9.15. Found: C, 65.0; H, 9.32%).

Tetrabutylammonium 1-oxo-3-phenyl-6-oxa-2-azaspiro[3.4]-octane-2-sulfonate 9c. Prepared from **8c** according to the published procedure to afford **9c** (133 mg, 85%) as a colorless oil, ν_{max}/cm^{-1} 1763 (β-lactam C=O); ^{1}H NMR (300 MHz; $CDCl_3$) δ_H 7.29–7.11 (m, 5H), 4.91 (s, 1H), 3.70 (m, 2H), 3.46 (d, J = 9.5 Hz, 1H), 3.01 (m, 9H), 2.41–2.16 (m, 2H), 1.42 (m, 8H), 1.22 (m, 8H), 0.83 (t, J = 7 Hz, 12H); ^{13}C NMR (75 MHz; $CDCl_3$) δ_C 168.1, 148.7, 136.4, 136.1, 127.9, 127.1, 126.1, 123.5, 68.1, 67.6, 67.5, 63.3, 57.8, 33.9, 23.2, 19.0, 13.1 (Calc. for $C_{28}H_{48}N_2O_5S$: C, 64.09; H, 9.22. Found: C, 64.29; H, 9.42%).

3-Benzyl-5-(3-chloropropyl)-2-phenyloxazolidin-4-one 10

To a stirred solution of *N*-benzylbenzaldimine (0.39 g, 2 mmol) in refluxing toluene (10 mL) was added dropwise a toluene solution of 2-tetrahydrofuryl chloride **2** (0.269 g, 2 mmol). The reaction mixture was refluxed overnight, cooled to room temperature, and diluted with CH_2Cl_2 (20 mL). The resultant solution was washed with brine (2 × 25 mL). The organic layer was dried over sodium sulfate and concentrated *in vacuo*. Flash chromatography (25% EtOAc–hexanes) afforded compound **10** (0.45 g, 77%) as white solid, mp 57 °C; ν_{max}/cm^{-1} 1698 (amide C=O); ^{1}H NMR (300 MHz; $CDCl_3$) δ_H 7.41–7.09 (m, 10H), 5.72 (d, J = 2.1 Hz, 1H), 5.05 (d, J = 14.8 Hz, 1H), 4.66 (m, 1H), 3.58 (m, 2H), 3.50 (d, J = 14.8, 1H), 2.1–1.8 (m, 4H); ^{13}C NMR (75 MHz; $CDCl_3$) δ_C 170.8, 136.4, 134.9, 130.0, 128.8, 128.6, 128.0, 127.8, 127.0, 90.8, 77.0, 44.3, 43.5, 29.7, 27.9; MS (EI) 328 ($M - H^+$) (Calc. for $C_{19}H_{20}ClNO_2$: C, 69.19; H, 6.11. Found: C, 68.97; H, 6.24%).

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References

1 For a detailed review of the biological properties of β-lactams, see: *The Chemistry of β-Lactams*, ed. M. I. Page, Blackie, Glasgow, 1992.

2 (*a*) J. W. Skiles and D. McNeil, *Tetrahedron Lett.*, 1990, **31**, 7277; (*b*) J. C. Sheehan, E. Chacko, Y. S. Lo, D. R. Ponzi and E. Sato, *J. Org. Chem.*, 1978, **43**, 4856 and references cited therein.

3 (*a*) G. Wu and W. Tormos, *J. Org. Chem.*, 1997, **62**, 6412; (*b*) L.-Y. Chen, A. Zarks, S. Chackalamamil and S. Dugar, *J. Org. Chem.*, 1996, **61**, 8341.
4 B. M. Austen, E. R. Frears and H. Davies, in *International Symposium on Proteinase Inhibitors and Activators*, University of Oxford, UK, April 2000, Abstract Book, p. 6.
5 I. Ojima, *Acc. Chem. Res.*, 1995, **28**, 383.
6 (*a*) P. Dalla Croce, R. Ferraccioli and C. La Rosa, *Tetrahedron*, 1999, **55**, 201; (*b*) S. Anklam and J. Liebscher, *Tetrahedron*, 1998, **54**, 6369; (*c*) A. W. Guest and J. H. Bateson, *Tetrahedron Lett.*, 1993, **34**, 1799; (*d*) S. Le Blanc, J. P. Pete and O. Piva, *Tetrahedron Lett.*, 1992, **33**, 1993; (*e*) I. Ishibashi, N. Nakamura, T. Sato, M. Takeuchi and M. Ikeda, *Tetrahedron Lett.*, 1991, **32**, 1725; (*f*) M. Ikeda, T. Uchino, H. Ishibashi, Y. Tamura and M. Kido, *J. Chem. Soc., Chem. Commun.*, 1984, 758.
7 W. Abramsky, C. Belzecki and M. Chielewski, *Bull. Pol. Acad. Sci. Chem.*, 1985, **33**, 451.
8 For a review of the Staudinger reaction, see: G. I. Georg and V. T. Ravikumar, in *The Organic Chemistry of β-Lactams*, ed. G. I. Georg, VCH, New York, 1992, pp. 295–368.
9 D. R. Kronenthal, C. Y. Han and M. K. Taylor, *J. Org. Chem.*, 1982, **47**, 2765.
10 See, H. C. Neu, in *The Chemistry of β-Lactams*, ed. M. I. Page, BlackieGlasgow, 1992, pp. 121–122.
11 D. M. Floyd, A. W. Fritz, J. Pluscec, E. R. Weaver and C. M. Cimarusti, *J. Org. Chem.*, 1982, **47**, 5160.
12 Determined by GC-MS analysis of the crude reaction mixture. The relative stereochemistry of the chiral centres of the related compound **12** were assigned as *cis* owing to a nuclear overhauser enhancement (NOE) observed between the two protons of the tertiary carbons of the molecule.
13 F. Duran and L. Ghosez, *Tetrahedron Lett.*, 1970, 245.
14 T. Tidwell, *Ketenes*, Wiley, New York, 1995, p. 57.
15 (*a*) A. M. Hafez, A. E. Taggi, H. Wack and T. Lectka, *Org. Lett.*, 2000, **2**, 3963; (*b*) C. Palomo, I. Ganboa, A. Kot and L. Dembkowski, *J. Org. Chem.*, 1998, **63**, 6398; (*c*) J. Podlech and M. R. Linder, *J. Org. Chem.*, 1997, **62**, 5873; (*d*) J. Pacansky, J. S. Chang, D. W. Brown and W. J. Swaarz, *J. Org. Chem.*, 1982, **47**, 2233.
16 (*a*) J. A. Sordo, J. González and T. L. Sordo, *J. Am. Chem. Soc.*, 1992, **114**, 6249; (*b*) X. Assfeld, M. F. Ruiz-López, J. González, R. López, J. A. Sordo and T. L. Sordo, *J. Comp. Chem.*, 1994, **15**, 479; (*c*) R. López, T. L. Sordo, J. A. Sordo and J. González, *J. Org. Chem.*, 1993, **58**, 7036; (*d*) F. P. Cossío, A. Arrieta, B. Leccea and J. M. Ugalde, *J. Am. Chem. Soc.*, 1994, **116**, 2058; (*e*) A. Arrieta, F. P. Cossío and B. Leccea, *J. Org. Chem.*, 2000, **65**, 8458.
17 C. C. Lim, Z. P. Xu, H. H. Huang, C. Y. Mok and W. S. Chin, *Chem. Phys. Lett.*, 2000, **325**, 433.
18 (*a*) N. G. Rondan and K. N. Houk, *J. Am. Chem. Soc.*, 1985, **107**, 2099; (*b*) W. Kirmse, N. G. Rondan and K. N. Houk, *J. Am. Chem. Soc.*, 1984, **106**, 7989.
19 The theoretical studies described in this paper were carried out with the Gaussian 98 program.[20] The transition structures located were fully optimized and characterized by the corresponding frequency calculation, showing an imaginary frequency. The scaled zero-point vibrational energies have been included in the calculation of the relative energies. The scale factor used was 0.9646, as proposed by Pople *et al.*: J. A. Pople, A. P. Scott, M. W. Wong and L. Radom, *Isr. J. Chem.*, 1993, **33**, 345; the geometries and energies of the optimized zwitterionic intermediates and transition structures are available as supplementary material.
20 Gaussian 98 (Revision A8), M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, V. G. Zakrzewski, J. A. Montgomery, Jr., R. E. Stratmann, J. C. Burant, S. Dapprich, J. M. Millam, A. D. Daniels, K. N. Kudin, M. C. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G. A. Petersson, P. Y. Ayala, Q. Cui, K. Morokuma, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. Cioslowski, J. V. Ortiz, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, C. Gonzalez, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, J. L. Andres, C. Gonzalez, M. Head-Gordon, E. S. Replogle, and J. A. Pople, Gaussian, Inc., Pittsburg, PA, 1998.
21 J. Bjorgo, D. R. Boyd, C. G. Watson, W. B. Jennings and D. M. Jerina, *J. Chem. Soc., Perkin Trans. 2*, 1974, 1081.
22 X. Wang and K. N. Houk, *J. Am. Chem. Soc.*, 1990, **112**, 1754.
23 K. Taguchi and F. H. Westheimer, *J. Org. Chem.*, 1971, **36**, 1570.