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# Chiral spiro-β-lactams from 6-diazopenicillanates

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Spirocyclopropyl-β-lactams

ABSTRACT

Chiral spiro-β-lactam derivatives have been prepared via stereoselective 1,3-dipolar cycloaddition of 6-diazopenicillanates. Using dipolarophiles such as acrylonitrile, acrylates or methyl vinyl ketone spiro-2-pyrazoline-β-lactams were obtained, whereas the cycloaddition with *N*-substituted-maleimides afforded spiro-1-pyrazoline-β-lactams. 6-Diazopenicillanates also reacted with electron-deficient alkynes to give the corresponding spiro-3*H*-pyrazole-β-lactam as single product. The observed stereoselectivity can be explained considering that the major product results from the addition to the less sterically hindered α-side of the β-lactam. Microwave-induced denitrogenation of spiro-1-pyrazoline-β-lactams allowed the stereoselective synthesis of novel spirocyclopropyl-β-lactams. The rationalization of the observed selectivity was supported by electronic structure calculations.



## 1. Introduction

The β-lactam ring is the core structure of important pharmacologically active compounds, such as penicillins and cephalosporins. On the other hand, penicillin resistance is often caused by the action of enzymes known as β-lactamases, which cleave the reactive β-lactam bond of the antibiotic making it ineffective. Therefore, compounds containing the β-lactam ring are potential β-lactamase inhibitors.[1] β-Lactams can be used as synthetic intermediates in organic synthesis, providing routes to α- and β-amino acids and peptides.[2] Spiro-β-lactams are also interesting target molecules since some derivatives exhibit relevant biological properties, namely, cholesterol absorption inhibition, antibacterial activity and antiviral activity.[3] In peptidomimetic chemistry, spiro-β-lactams are used as β-turn mimetics.[4] Thus, the search for new β-lactam derivatives is a relevant research target.

It has been previously shown that spiro-2-pyrazolinepenicillanates can be obtained from the 1,3-dipolar cycloaddition of 6-diazopenicillanates with acrylamide, acrylonitrile and acrylates.[3e,g] On the other hand, spiro-1-pyrazolinepenicillanates, obtained from the addition of diphenyldiazomethane to the less hindered α-side of 6-alkylidenepenicillanates, undergo thermal induced ring contraction to afford spirocyclopropylpenicillanates.[3e] Spirocyclopropylpenicillanates have also been prepared via rhodium-catalyzed cyclopropanation of a 6-diazopenicillanate sulfone[5a] and by the Cu(I) catalyzed reaction of 6-bromopenicillanoyl magnesium bromide with α,β-unsaturated esters.[5b]

In this context, the 1,3-dipolar cycloaddition of 6-diazopenicillanates was further explored as well as the ring contraction of spiropyrazolinepenicillanates to spirocyclopropylpenicillanates, aiming to evaluate the scope and selectivity of these approaches to spiro-β-lactams.

## 2. Results and discussion

6-Diazopenicillanates have been previously prepared mainly by the diazotization of 6-aminopenicillanates with nitrous acid or by treatment of 6-β-*N*-nitrosoamidopenicillanates with pyridine.[6] We observed that an easier and efficient synthesis of 6-diazopenicillanates **2** is achieved by reacting the corresponding 6-β-aminopenicillanate **1a**[7] or **1b**[6a] with ethyl nitrite at room temperature. The diazo compounds are isolated in high yield by removing the solvent, without need of further purification (Scheme 1). In the case of **2b**, the compound was also recrystallized.

The chemical behaviour of 6-diazopenicillanates **2** in the presence of a range of dipolarophiles was studied (Table 1). Initially, we looked again into the previously reported cycloadditions of 6-diazopenicillanates with acrylonitrile and ethyl acrylate.[3e] The

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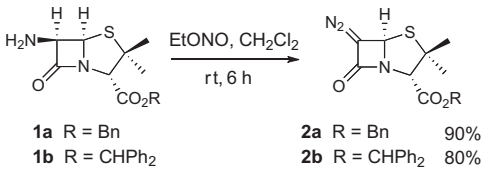
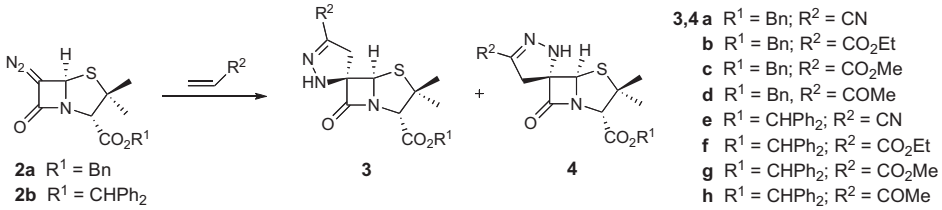



**Scheme 1.** Synthesis of 6-diazopenicillanates **2**.

The reactivity of 6-diazopenicillanates **2** towards electron-deficient alkynes was explored and led to the selective synthesis of spiro-β-lactams **5** incorporating a 3*H*-pyrazole ring (Table 2). In fact, the cycloaddition at room temperature of benzyl 6-diazopenicillanate (**2a**) and benzhydryl 6-diazopenicillanate (**2b**) with dimethyl acetylenedicarboxylate gave spiro-β-lactams **5a** (15%) and **5c** (55%), respectively (entries 1 and 6). It was again observed that the process is more efficient starting from

**Table 1**
Reaction of 6-diazopenicillanates **2** with alkenes




| Entry | $R^1$ | $R^2$ | Dipolarophile (equiv) | Reaction conditions | Yield (**3**/**4**)[a] |
|---|---|---|---|---|---|
| 1 | Bn | CN | 1.5 | rt, 16 h, DCM | 57% (76:24) |
| 2 | Bn | $CO_2Et$ | 1.5 | rt, 16 h, DCM | 34% (79:21) |
| 3 | Bn | $CO_2Me$ | 1.5 | rt, 18 h, DCM | — |
| 4 | Bn | $CO_2Me$ | 2.5 | MW, 80 °C, 1 min, Toluene | 33% (80:20) |
| 5 | Bn | COMe | 3.0 | rt, 24 h, DCM | 54% (83:17) |
| 6 | Bn | COMe | 3.0 | MW, 80 °C, 1 min, toluene | 58% (83:17) |
| 7 | $CHPh_2$ | CN | 1.5 | rt, 16 h, DCM | 85% (88:12) |
| 8 | $CHPh_2$ | $CO_2Et$ | 1.5 | rt, 16 h, DCM | 73% (85:15) |
| 9 | $CHPh_2$ | $CO_2Me$ | 1.5 | rt, 18 h, DCM | 62% (85:15) |
| 10 | $CHPh_2$ | COMe | 3.0 | rt, 24 h, DCM | 82% (83:17) |
| 11 | $CHPh_2$ | COMe | 3.0 | 45 °C, 3 h, DCM | 78% (83:17) |

[a] Isolated yield; ratio of diastereosiomers determined by $^1$H NMR.

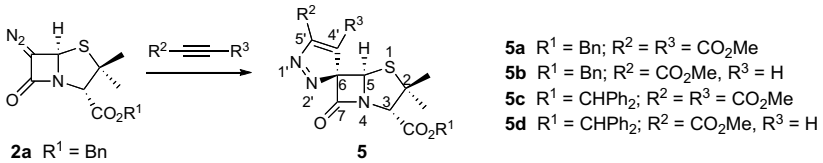
reaction at room temperature of benzyl 6-diazopenicillanate (**2a**) with acrylonitrile gave a (76:24) mixture of compounds **3a** and **4a**, in 57% overall yield (entry 1). On the other hand, starting with benzhydryl ester **2b** the corresponding cycloadducts **3e** and **4e** were obtained in significantly higher yield (85%) with a similar stereoselectivity (entry 7). It should be noted that the reported reaction of trichloroethyl 6-diazopenicillanate with acrylonitrile gave the 1,3-dipolar cycloadducts in 82% overall yield.[3e] Thus, we can conclude that the nature of the ester significantly influences the yields of the isolated products. In fact, it was observed that 6-diazopenicillanate **2a** reacted with ethyl acrylate to give a (79:21) mixture of cycloadducts **3b** and **4b** in 34% yield (entry 2) whereas starting from 6-diazopenicillanate **2b**, the corresponding isomeric spiro-β-lactams **3f** and **4f** were obtained in 73% yield (entry 8). The observed stereoselectivity can be explained considering that the major product results from the addition to the less sterically hindered α-side of the β-lactam.

The work was then extended to the cycloaddition of 6-diazopenicillanates **2** with other dipolarophiles (Table 1). Surprisingly, attempts to carry out the reaction of benzyl 6-diazopenicillanate (**2a**) with methyl acrylate at room temperature were unsuccessful (entry 3). However, under microwave irradiation at 80 °C for 1 min the expected products **3c** and **4c** were obtained in moderate yield (entry 4). In contrast with these observations, 6-diazopenicillanate **2b** reacted with methyl acrylate at room temperature to afford the expected spiro-β-lactams **3g** and **4g** in good yield (entry 9). 6-Diazopenicillanates **2** also participate in the 1,3-dipolar cycloaddition with methyl vinyl ketone, efficiently giving the corresponding chiral β-lactams with good selectivity (entries 5, 6, 10 and 11). The best results were achieved carrying out the cycloaddition of β-lactams **2a** and **2b** at room temperature, the corresponding cycloadducts being obtained in 58% and 82%, respectively (entries 5 and 10).

6-diazopenicillanate **2b**. However, the yield of **5a** was improved to 39% by carrying out the reaction with dimethyl acetylenedicarboxylate at 45 °C for 3 h (entry 2). Under microwave irradiation at 80 °C for 2 min, β-lactam **5a** was obtained in low yield (entry 3). The β-lactams **5b** (14%) and **5d** (63%) were also prepared as single products, from the reaction of the corresponding 6-diazopenicillanates **2** with methyl propiolate carried out at the reaction at room temperature (entries 4 and 8). Heating at 45 °C for 3 h cycloadducts **5b** (37%) and **5d** (73%) were obtained in higher yields (entries 5 and 9). In the NOESY spectrum of compound **5b**, 5-H shows connectivity with 4′-H, but does not show connectivity with the protons of the methyl ester group. Thus, we could conclude that the cycloaddition of 6-diazopenicillanates with methyl propiolate occurs in a regio- and stereoselective manner.

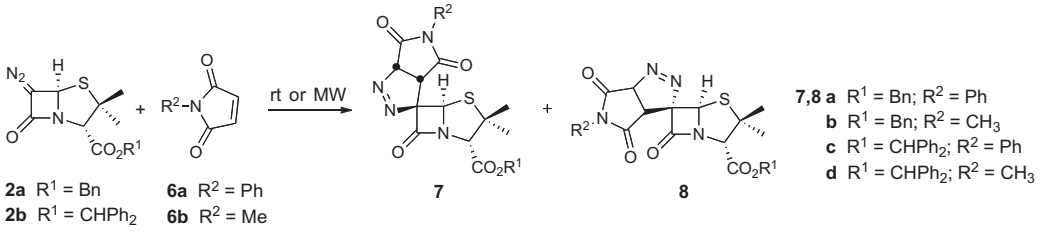
The reactivity of 6-diazopenicillanates **2** with *N*-substituted-maleimides was also studied (Table 3). Particularly interesting was to observe that the 1,3-dipolar cycloaddition of compounds **2b** with *N*-methyl- and *N*-phenylmaleimides gave a mixture of the corresponding compounds **7** and **8**, from which β-lactams **7** could be isolated in pure form by crystallization. Starting from 6-diazopenicillanate **2a** the reaction with *N*-phenylmaleimide (**6a**) led to the diastereoisomeric mixture of β-lactams **7a** and **8a** and it was again observed that the major product **7a** could be isolated in pure form by crystallization. However, the cycloaddition of 6-diazopenicillanate **2a** with *N*-methylmaleimide (**6b**) afforded a mixture of cycloadducts **7b** and **8b** that could not be separated. It should be noted that in these reactions spiro-β-lactams incorporating a 1-pyrazoline heterocycle were obtained in contrast with the products resulting from the cycloaddition of 6-diazopenicillanates with alkenes such as acrylonitrile, acrylate and methyl vinyl ketone, which led to derivatives bearing a 2-pyrazoline unit (see Table 1). This observation is in agreement with the known reactivity pattern of diazo compounds towards

**Table 2**
Reaction of 6-diazopenicillanates **2** with alkynes




| Entry | $R^1$ | $R^2$ | $R^3$ | Dipolarophile (equiv) | Reaction conditions | Isolated yield (%) |
|---|---|---|---|---|---|---|
| 1 | Bn | $CO_2Me$ | $CO_2Me$ | 1.5 | rt, 16 h, DCM | 15 |
| 2 | Bn | $CO_2Me$ | $CO_2Me$ | 1.5 | 45 °C, 3 h, DCM | 39 |
| 3 | Bn | $CO_2Me$ | $CO_2Me$ | 1.5 | MW, 80 °C, 2 min, toluene | 16 |
| 4 | Bn | $CO_2Me$ | H | 1.5 | rt, 3 h, DCM | 14 |
| 5 | Bn | $CO_2Me$ | H | 1.5 | 45 °C, 3 h, DCM | 37 |
| 6 | $CHPh_2$ | $CO_2Me$ | $CO_2Me$ | 1.5 | rt, 16 h, DCM | 55 |
| 7 | $CHPh_2$ | $CO_2Me$ | $CO_2Me$ | 1.5 | 45 °C, 3 h, DCM | 51 |
| 8 | $CHPh_2$ | $CO_2Me$ | H | 1.5 | rt, 16 h, DCM | 63 |
| 9 | $CHPh_2$ | $CO_2Me$ | H | 1.5 | 45 °C, 3 h, DCM | 73 |

**Table 3**
Reaction of 6-diazopenicillanates **2** with *N*-substituted-maleimides




| Entry | $R^1$ | $R^2$ | Dipolarophile (equiv) | Reaction conditions | Yield (**7**/**8**)[a] |
|---|---|---|---|---|---|
| 1 | Bn | Ph | 1.6 | rt, 6 h, DCM | 39% (77:23) |
| 2 | Bn | Ph | 1.1 | MW, 80 °C, 3 min, toluene | 12% (66:34) |
| 3 | Bn | $CH_3$ | 1.6 | rt, 6 h, DCM | 25% (82:18) |
| 4 | $CHPh_2$ | Ph | 1.6 | rt, 6 h, DCM | 76% (86:14) |
| 5 | $CHPh_2$ | $CH_3$ | 1.6 | rt, 6 h, DCM | 58% (80:20) |

[a] Isolated yield; ratio of diastereosiomers determined by $^1$H NMR.

dipolarophiles. In fact, diazo compounds react with α,β-unsaturated carbonyl compounds to give 1-pyrazolines, which typically undergo isomerization to give the conjugated 2-pyrazolines.[8] On the other hand, diazo compounds participate in cycloaddition reactions with *N*-substituted-maleimides affording 1-pyrazolines.[9] The reaction at room temperature of 6-diazopenicillanate **2a** with *N*-phenylmaleimide gave spiro-β-lactams **7a** and **8a** in 39% overall yield whereas the microwave induced cycloaddition was less efficient (entries 1 and 2). Starting from 6-diazopenicillanate **2b** the expected cycloadducts were obtained in 76% yield (entry 4). The assignment of the structure of compound **7a** (Fig. 1) was made on the basis of two-dimensional NOESY, HMQC and HMBC spectra (400 MHz). From the HMQC spectrum, it was established that the carbon with the 43.5 ppm chemical shift corresponds to 5′-C since it shows connectivity with the proton having a chemical shift of 3.73 ppm. On the other hand, the carbon with 96.7 ppm chemical shift corresponds to 1′-C since it shows connectivity with the proton having a chemical shift of 6.21 ppm. In the HMBC spectrum, 5′-H correlates with carbon 5-C (71.2 ppm), with 6-C (109.2 ppm) and with the carbonyl carbons (7-C, 6′-C and 8′-C). The NOESY spectrum showed cross peaks between 5′-H and 1′-H but no connectivity was observed between 5′-H and 5-H.

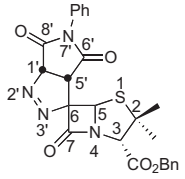


**Fig. 1.** Structure of compound **7a**.

6-Diazopenicillanates **2** also reacted with *N*-methylmaleimide to give the expected spiro-β-lactams (entries 3 and 5). It was again observed that the 1,3-dipolar cycloaddition of benzhydryl 6-diazopenicillanate (**2b**) with *N*-substituted-maleimides led to the target compounds in significantly higher yield than the corresponding cycloaddition starting from benzyl 6-diazopenicillanate (**2a**).

The formation of spiro-β-lactams **7** as the major product in the cycloaddition of 6-diazopenicillanates **2** with *N*-substituted-maleimides can be explained considering that the addition of the dipolarophile occurs selectively to the less sterically hindered α-side of the β-lactam, which is also characterized by *endo* selectivity.

Mete et al. reported that the 1,3-dipolar cycloaddition of 3-diazo-piperidin-2-one with methyl methacrylate affords the corresponding spiro-1-pyrazolines whereas in the reaction with methyl acrylate, methyl vinyl ketone and acrolein spiro-2-pyrazolines are obtained. Both types of cycloadducts extruded nitrogen under thermolysis to give spirocyclopropyl derivatives efficiently, although the ring contraction of the 2-pyrazoline derivatives required higher temperature (dioxane, reflux, 20 min vs

1,2-dichlorobenzene, reflux, 20 min).[10] These observations led us to study the thermolysis of spiro-2-pyrazoline-β-lactams **3d**, **4d** under the latter reaction conditions. However, no reaction was observed leading only to the recover of the starting β-lactam (43%). Similar result was obtained carrying out the thermolysis of compounds **3d**, **4d** in dioxane under microwave irradiation at 110 °C for 3 min.

In contrast with the less common conversion of 2-pyrazolines to cyclopropane derivatives, the synthesis of cyclopropanes via ring contraction of 1-pyrazolines is well-known.[11] Under thermal conditions the elimination of nitrogen from 1-pyrazolines can lead to the competitive formation of alkenes. The nature of the mechanism involved in the cyclopropane formation is controversial since some reactions are stereospecific, others show high stereoselectivity and yet others are not selective. These observations led to different mechanistic proposals. Thus, in some cases a concerted process has been suggested whereas in other cases a stepwise cleavage of the 1-pyrazolines ring via biradical or zwitterionic intermediates followed by ring closure has been proposed.

It has been reported that 7-substituted-6,8-dioxo-2,3,7-triazabicyclo[3.3.0]oct-2-enes, resulting from the cycloaddition of diazo compounds with *N*-substituted-maleimides, undergo thermal decomposition to give the corresponding cyclopropanes, 3-azabicyclo[3.1.0]hexane derivatives.[9,11m]

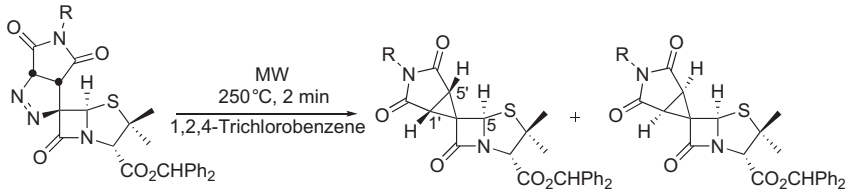
In this context, we decided to study the chemical behaviour of spiro-β-lactams **7c** and **7d**, incorporating a 7-substituted-6,8-dioxo-2,3,7-triazabicyclo[3.3.0]oct-2-ene ring system, under thermal conditions (Scheme 2). Attempts to carry out the nitrogen extrusion from compound **7c** by thermolysis in toluene (130 °C for 30 min) were unsuccessful. However, under microwave irradiation at 250 °C for 2 min, a solution of the spiro-β-lactam **7c** in 1,2,4-trichlorobenzene afforded a (77:23) mixture of cyclopropanes **9a** and **10a** in 94% yield. Interestingly, spirocyclopropane-β-lactam **9a** could be isolated from this mixture in pure form by crystallization. The ring contraction reaction of compound **7d** was also achieved under microwave irradiation at 250 °C for 2 min, to give a (72:28) mixture of cyclopropanes **9b** and **10b** in 64% yield.

Molecular mechanics (MM) and quantum chemical calculations have been carried out in order to determine the optimized geometries of the low energy conformers of spirocyclopropane-β-lactams **9a** and **10a**. A preliminary conformational search of different starting structures generated in the Avogadro package[12] for each stereoisomer was performed, with molecular mechanics, resorting to the UFF force-field. The conformational search employed random rotor search and subsequent full minimization of every internal coordinate, producing 10,000 conformations. The MM lowest energy conformations obtained in each case were refined at the PM3 level and subsequently, the lowest energy conformation obtained for each stereoisomer was further refined using the B3LYP hybrid functional[13–15] and the 6-31G(d) basis set (Fig. 2).

In the NOESY spectrum of **9a**, 5-H shows connectivity with the proton having a 3.25 ppm chemical shift, but not with the proton with a 3.16 ppm chemical shift. This observation is in agreement with the structural parameters obtained for compound **9a**, which is characterized by a distance for hydrogens 5′-H/5-H of 2.87 Å and 3.59 Å for hydrogens 1′-H/5-H. Thus, the signals at 3.25 ppm and 3.16 ppm can be assigned to protons 5′-H and 1′H, respectively. On the other hand, the optimized structure for compound **10a** presents much larger distances, 3.83 Å and 4.38 Å for hydrogens 5′-H/5-H and 1′-H/5-H, respectively, and consequently no NOE effects should be observed.

The synthesis of cyclopropanes via ring contraction of spiro-1-pyrazoline-β-lactams **7** was not stereospecific, which is an indication that a stepwise mechanism must be involved. In fact, considering the cleavage of the 1-pyrazoline ring leading to an open-chain biradical followed by the cyclopropane ring closure, a mixture of diastereoisomers would be expected (Scheme 3).

The stereoselectivity observed in the synthesis of spirocyclopropyl-β-lactams has also been rationalized by means of theoretical calculations. The optimization of structures **9a** and **10a** at the DFT level revealed that stereoisomer **10a** is the most stable but the energy difference between **9a** and **10a** is only 0.93 kcal/mol. Thus, in order to explain the formation of stereoisomer **9a** as the




**Scheme 2.** Synthesis of spirocyclopropyl-β-lactams via denitrogenation of spiro-1-pyrazoline-β-lactams **7c** and **7d**.

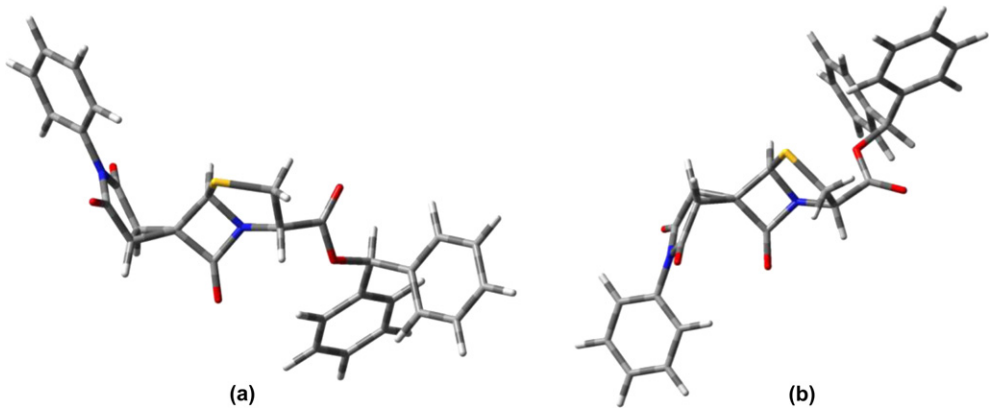
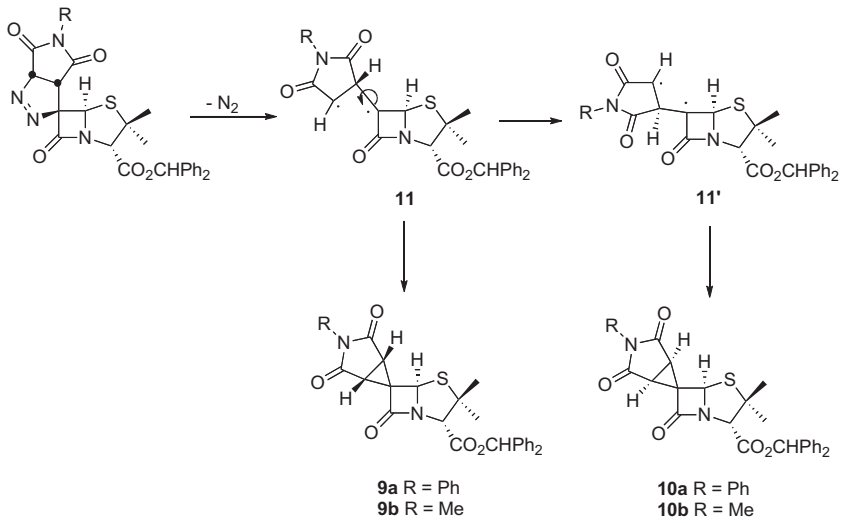



**Fig. 2.** Optimized geometries (DFT level) of the low energy conformers of compounds **10a** (panel a) and **9a** (panel b). Colour code: grey refers to carbon, red to oxygen, white to hydrogen, blue to nitrogen and yellow to sulfur atoms.




**Scheme 3.** Mechanism proposal for the ring contraction of spiro-1-pyrazoline-β-lactams.

major product it is necessary to analyze the conversion of the initially formed biradical **11** into **11′**, the rotational isomer, which undergoes cyclization to give compound **10a** (Scheme 3).

The precursor **7c**, used in the synthetic route, was optimized and the respective structure transformed into the biradical, which served as an additional input for optimization at the PM3 level. The final structure obtained was that of stereoisomer **9a**. This prompted the calculation of the energy profile presented in Fig. 3, with a scan performed on the relevant dihedral of the biradical. It shows that the formation of the structure **9a** is favoured being the energy penalty for the formation of the structure **10a** ca. 1.7 kcal/mol. Both stereoisomers are, thus, allowed.

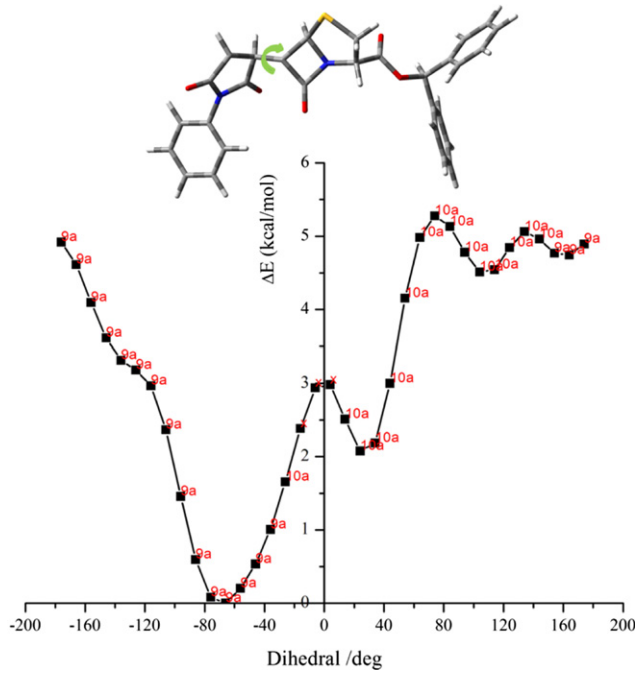



**Fig. 3.** Potential energy profile as a function of the relevant dihedral in the biradical structure, using a step size of 10°. At each point all the internal coordinates were relaxed (relaxed scan) at the MM level using the UFF force-field. The biradical structure obtained after the optimization of structure **7c** at the PM3 level was used as starting structure for the scan. The stereoisomer obtained upon optimization at the PM3 level of the biradical structure with the corresponding dihedral is also indicated for each data point.

## 3. Conclusion

Herein, we report the 1,3-dipolar cycloaddition of 6-diazopenicillanates as a route to the selective formation of new chiral spiro-β-lactams as well as the ring contraction of spiropyrazolinepenicillanates to spirocyclopropylpenicillanates.

6-Diazopenicillanates, prepared from 6-β-aminopenicillanates by an easy and efficient methodology, reacted with acrylonitrile, acrylates and methyl vinyl ketone to give spiro-2-pyrazoline-β-lactam derivatives. 6-Diazopenicillanates also participated in the 1,3-dipolar cycloaddition with *N*-substituted-maleimides to afford spiro-1-pyrazoline-β-lactams and with electron-deficient alkynes leading to the corresponding spiro-3*H*-pyrazole-β-lactams as the single product. The 1,3-dipolar cycloaddition was stereoselective, the major cycloadduct being the result of the dipolarophile addition to the less sterically hindered α-side of the β-lactam.

Stereoselective synthesis of spirocyclopropyl-β-lactams via microwave-induced denitrogenation of spiro-1-pyrazoline-β-lactams was also achieved. Computational studies corroborated the rationalization of the stereoselectivity observed in this ring contraction reaction.

The studied reactions were more efficient starting from benzhydryl 6-diazopenicillanate rather than benzyl diazopenicillanate, indicating that the nature of the ester group influences significantly the yields of the isolated products.

## 4. Experimental

### 4.1. General methods

$^{1}$H NMR spectra were recorded on an instrument operating at 400 MHz. $^{13}$C spectra were recorded on an instrument operating at 100 MHz. The solvent is deuteriochloroform except where otherwise indicated. IR spectra were recorded on a Perkin Elmer 1720X FTIR spectrometer. Optical rotations were measured on an Optical Activity AA-5 electrical polarimeter. Melting points were recorded on a Reichert hot stage and are uncorrected. Flash column chromatography was performed with Merck 9385 silica as the stationary phase. Mass spectra were recorded on an instrument operating in ESI mode. Microwave reactions were carried out in a microwave reactor CEM Focused Synthesis System, Discover S-Class. Benzyl 6-β-aminopenicillanate (**1a**)[7] and benzhydryl 6-β-aminopenicillanate (**1b**)[6a] were prepared as described in the literature.

### 4.2. General procedure for the synthesis of 6-diazopenicillanates

Ethyl nitrite (1.80 g, 24.0 mmol) was added to a solution of the appropriate 6-β-aminopenicillanate (10.9 mmol) in dichloromethane (110 mL). The resulting mixture was stirred for 6 h at room temperature and the solvent was removed under reduced pressure (without heat).

*4.2.1. Benzyl 6-diazopenicillanate (**2a**).* Prepared from ethyl nitrite (1.80 g, 24.0 mmol) and 6-β-aminopenicillanate **1a** (3.33 g, 10.9 mmol). Compound **2a** was obtained as a brown oil (3.11 g, 9.81 mmol, 90%). $\nu_{max}/cm^{-1}$ (film) 2083 (N=N), 1748 (β-lactam), 1701 (ester); $\delta_H$ 1.37 (3H, s, 2α-Me), 1.62 (3H, s, 2β-Me), 4.40 (1H, s, 3-H), 5.18 (2H, s, C*H*$_2$Ph), 6.17 (1H, s, 5-H), 7.37 (5H, m, Ph); $\delta_C$ 25.8, 34.0, 62.9, 64.2, 67.3, 69.0, 70.1, 128.6, 128.7, 134.9, 166.4, 167.9; MS (ESI) *m*/*z* 318 ($MH^+$, 45%), 308 (36), 293 (21), 280 (100), 265 (26), 250 (55), 227 (39); HRMS (ESI) *m*/*z* 318.09024 ($C_{15}H_{16}N_3O_3S$ [$MH^+$], 318.09069).

*4.2.2. Benzhydryl 6-diazopenicillanate (**2b**).* Prepared from ethyl nitrite (1.87 g, 24.9 mmol) and 6-β-aminopenicillanate **1b** (4.32 g, 11.3 mmol). Recrystallization from ether/petroleum ether afforded **2b** as a yellow solid (3.54 g, 9.0 mmol, 80%). Mp 91–92 °C (lit.[6a] 93.0–94.0 °C) (from diethyl ether/petroleum ether); $\nu_{max}/cm^{-1}$ (KBr) 2081 (N=N), 1743; $\delta_H$ 1.23 (3H, s, 2α-Me), 1.62 (3H, s, 2β-Me), 4.46 (1H, s, 3-H), 6.19 (1H, s, 5-H), 6.92 (1H, s, C*H*Ph$_2$), 7.30–7.36 (10H, m, 2×Ph); $\delta_C$ 25.6, 34.2, 63.1, 64.3, 69.1, 70.2, 78.3, 127.1, 127.5, 128.2, 128.3, 128.6, 128.6, 139.2, 139.3, 166.4, 167.2; MS (ESI) *m*/*z* 394 ($MH^+$, 100%), 366 (10), 326 (43); HRMS (ESI) *m*/*z* 394.12077 ($C_{21}H_{20}N_3O_3S$ [$MH^+$], 394.12199).

### 4.3. General procedure for the 1,3-dipolar cycloaddition of 6-diazopenicillanates

*Method A*: To a mixture of the appropriate 6-diazopenicillanate (0.50 mmol) in dichloromethane (5 mL) a solution of the corresponding dipolarophile in dichloromethane (2 mL) was added. The reaction mixture was stirred at room temperature under nitrogen. The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography [ethyl acetate/hexane] or by recrystallization, as indicated for each case.

*Method B*: A suspension of the appropriate 6-diazopenicillanate (0.50 mmol) and the corresponding dipolarophile in toluene (2 mL) was irradiated in the microwave reactor with the temperature set to 80 °C. The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography [ethyl acetate/hexane] or by recrystallization, as indicated for each case.

*Method C*: To a solution of the appropriate 6-diazopenicillanate (0.50 mmol) in dichloromethane (5 mL) a solution of the corresponding dipolarophile in dichloromethane (2 mL) was added. The reaction mixture was stirred at 45 °C under nitrogen. The solvent was removed under reduced pressure and the product was purified by flash column chromatography [ethyl acetate/hexane].

*4.3.1. Benzyl spiro[penicillanate-6,5′-(3-cyano-2-pyrazoline)] **3a** and **4a**.* Prepared by method A from 6-diazopenicillanate **2a** (172 mg, 0.54 mmol) and acrylonitrile (43 mg, 0.81 mmol). The reaction mixture was stirred for 16 h and purification by flash column chromatography [ethyl acetate/hexane (1:2)] afforded a (76:24) mixture of compounds **3a** and **4a** as a yellow oil (115 mg, 0.31 mmol, 57%). *Benzyl spiro[penicillanate-6,5′-(3-cyano-2-pyrazoline)] **3a**.* $\nu_{max}/cm^{-1}$ (film) 3337 (NH), 2225 (CN), 1784 (β-lactam), 1734 (ester); $\delta_H$ 1.33 (3H, s, 2α-Me), 1.40 (3H, s, 2β-Me), 3.18 (1H, d, *J*=18.4 Hz, 4′-H), 3.54 (1H, d, *J*=18.4 Hz, 4′-H), 4.42 (1H, s, 3-H), 5.12 (2H, s, C*H*$_2$Ph), 5.25 (1H, s, 5-H), 7.18–7.30 (5H, m, Ph); $\delta_C$ 24.7, 32.4, 37.8, 63.2, 66.7, 67.6, 80.9, 112.4, 120.6, 127.7, 127.8, 127.9, 133.5, 166.1, 170.2; MS (ESI) *m*/*z* 393 ($MNa^+$, 100%), 358 (20), 330 (44); HRMS (ESI) *m*/*z* 393.09963 ($C_{18}H_{18}N_4NaO_3S$ [$MNa^+$], 393.09918).

*4.3.2. Benzyl spiro[penicillanate-6,5′-(3-ethoxycarbonyl-2-pyrazoline)] **3b** and **4b**.* Prepared by method A from 6-diazopenicillanate **2a** (184 mg, 0.58 mmol) and ethyl acrylate (86 mg, 0.86 mmol). The reaction mixture was stirred for 16 h and purification by flash column chromatography [ethyl acetate/hexane (1:2)] afforded a (79:21) mixture of compounds **3b** and **4b** as a yellow oil (82 mg, 0.29 mmol, 34%). *Benzyl spiro[penicillanate-6,5′-(3-ethoxycarbonyl-2-pyrazoline)] **3b**.* $\nu_{max}/cm^{-1}$ (film) 3343 (NH), 1781 (β-lactam), 1740 and 1704 (esters); $\delta_H$ 1.27 (3H, t, *J*=7.2 Hz, CH$_2$C*H*$_3$), 1.31 (3H, s, 2α-Me), 1.42 (3H, s, 2β-Me), 3.22 (1H, d, *J*=18.8 Hz, 4′-H), 3.57 (1H, d, *J*=18.8 Hz, 4′-H), 4.23 (1H, q, *J*=7.2 Hz, C*H*$_2$CH$_3$), 4.41 (1H, s, 3-H), 5.10 (1H, d, *J*=12.4 Hz, C*H*$_2$Ph), 5.14 (1H, d, *J*=12.4 Hz, C*H*$_2$Ph), 5.25 (1H, s, 5-H), 6.97 (1H, s, N*H*), 7.30 (5H, br s, Ph); $\delta_C$ 14.3, 25.8, 33.4, 37.3, 53.4, 61.5, 63.9, 67.6, 68.6, 82.6, 128.7, 128.8, 128.8, 134.6, 140.9, 161.6, 167.3, 172.4; MS (ESI) *m*/*z* 418 ($MH^+$, 82%), 390 (100), 336 (13), 280 (10); HRMS (ESI) *m*/*z* 418.14167 ($C_{20}H_{24}N_3O_5S$ [$MH^+$], 418.14312).

*4.3.3. Benzyl spiro[penicillanate-6,5′-(3-methoxycarbonyl-2-pyrazoline)] **3c** and **4c**.* Prepared by method B from 6-diazopenicillanate **2a** (179 mg, 0.56 mmol) and methyl acrylate (121 mg, 1.4 mmol). The solution was irradiated for 1 min and purification by flash column chromatography [ethyl acetate/hexane (1:2)] afforded a (80:20) mixture of compounds **3c** and **4c** as a yellow oil (75 mg, 0.19 mmol, 33%). *Benzyl spiro[penicillanate-6,5′-(3-methoxycarbonyl-2-pyrazoline)] **3c**.* $\nu_{max}/cm^{-1}$ (film) 3337 (NH), 1781 (β-lactam), 1740 and 1700 (esters); $\delta_H$ 1.33 (3H, s, 2α-Me), 1.42 (3H, s, 2β-Me), 3.23 (1H, d, *J*=18.8 Hz, 4′-H), 3.58 (1H, d, *J*=18.8 Hz, 4′-H), 3.77 (3H, s), 4.42 (1H, s, 3-H), 5.11 (2H, br s, C*H*$_2$Ph), 5.22 (1H, s, 5-H), 6.99 (1H, s, N*H*), 7.30 (5H, br s, Ph); $\delta_C$ 24.7, 32.4, 36.2, 51.4, 52.4, 62.9, 66.6, 67.6, 81.6, 127.5, 127.6, 127.7, 127.8, 133.6, 139.4, 161.4, 161.0, 166.3, 171.4; MS (ESI) *m*/*z* 404 ($MH^+$, 100%), 392 (41), 376 (86), 293 (32), 280 (20), 268 (26); HRMS (ESI) *m*/*z* 404.12560 ($C_{19}H_{22}N_3O_5S$ [$MH^+$], 404.12747).

*4.3.4. Benzyl spiro[penicillanate-6,5′-(3-acetyl-2-pyrazoline)] **3d** and **4d**.* Prepared by method A from 6-diazopenicillanate **2a** (220 mg, 0.69 mmol) and methyl vinyl ketone (147 mg, 2.1 mmol). The reaction mixture was stirred for 24 h and purification by flash column chromatography [ethyl acetate/hexane (1:2)] afforded a (83:17) mixture of compounds **3d** and **4d** as a orange oil (143 mg, 0.37 mmol, 54%). The products were also prepared by method B from 6-diazopenicillanate **2a** (184 mg, 0.58 mmol) and methyl vinyl ketone (126 mg, 1.8 mmol). The solution was irradiated for 1 min and purification by flash column chromatography [ethyl acetate/hexane (1:2)] afforded a (83:17) mixture of compounds **3d** and **4d** (130 mg, 0.34 mmol, 58%). *Benzyl spiro[penicillanate-6,5′-(3-acetyl-2-pyrazoline)] **3d**.* $\nu_{max}/cm^{-1}$ (film) 3337 (NH), 1779 (β-lactam), 1744 (ester), 1666; $\delta_H$ 1.40 (3H, s, 2α-Me), 1.48 (3H, s, 2β-Me), 2.40 (3H, s), 3.21 (1H, d, *J*=18.8 Hz, 4′-H), 3.61 (1H, d, *J*=18.8 Hz, 4′-H), 4.49 (1H, s, 3-H), 5.17 (1H, d, *J*=12.4 Hz, C*H*$_2$Ph), 5.21 (1H, d, *J*=12.4 Hz, C*H*$_2$Ph), 5.33 (1H, s, 5-H), 7.04 (1H, s, N*H*), 7.37 (5H, br s, Ph); $\delta_C$ 25.5, 25.7, 33.5, 35.8, 60.4, 63.9, 67.6, 68.5, 82.8, 128.7, 128.8, 128.8, 134.6, 148.5, 167.3, 172.6, 193.6; MS (ESI) *m*/*z* 388 ($MH^+$, 100%), 376 (16), 360 (70); HRMS (ESI) *m*/*z* 388.13330 ($C_{19}H_{22}N_3O_4S$ [$MH^+$], 388.13255).

*4.3.5. Benzhydryl spiro[penicillanate-6,5′-(3-cyano-2-pyrazoline)] **3e** and **4e**.* Prepared by method A from 6-diazopenicillanate **2b** (158 mg, 0.40 mmol) and acrylonitrile (32 mg, 0.60 mmol). The

reaction mixture was stirred for 16 h and purification by flash column chromatography [ethyl acetate/hexane (1:3)] afforded a (88:12) mixture of compounds **3e** and **4e** as a yellow solid (150 mg, 0.34 mmol, 85%). *Benzhydryl spiro[penicillanate-6,5′-(3-cyano-2-pyrazoline)]* ***3e***. $\nu_{max}/cm^{-1}$ (film) 3345 (NH), 2225 (CN), 1782 (β-lactam), 1744 (ester); $\delta_H$ 1.28 (3H, s, 2α-Me), 1.48 (3H, s, 2β-Me), 3.27 (1H, d, *J*=18.4 Hz, 4′-H), 3.62 (1H, d, *J*=18.4 Hz, 4′-H), 4.56 (1H, s, 3-H), 5.31 (1H, s, 5-H), 6.94 (1H, s, C*H*Ph$_2$), 7.01 (1H, s, N*H*), 7.34–7.35 (10H, m, 2×Ph); $\delta_C$ 25.5, 33.7, 38.9, 64.4, 68.8, 78.9, 81.9, 113.3, 121.8, 127.0, 127.7, 128.4, 128.6, 128.7, 128.7, 138.8, 166.3, 171.2; MS (ESI) *m*/*z* 469 (MNa$^+$, 36%), 434 (21), 406 (100), 366 (27), 348 (19); HRMS (ESI) *m*/*z* 469.13027 ($C_{24}H_{22}N_4NaO_3S$ [MNa$^+$], 469.13048).

*4.3.6. Benzhydryl spiro[penicillanate-6,5′-(3-ethoxycarbonyl-2-pyrazoline)]* ***3f*** *and* ***4f***. Prepared by method A from 6-diazopenicillanate **2b** (159 mg, 0.40 mmol) and ethyl acrylate (60 mg, 0.60 mmol). The reaction mixture was stirred for 16 h and purification by flash column chromatography [ethyl acetate/hexane (1:3)] afforded a (85:15) mixture of compounds **3f** and **4f** as a yellow solid (144 mg, 0.29 mmol, 73%). *Benzhydryl spiro[penicillanate-6,5′-(3-ethoxycarbonyl-2-pyrazoline)]* ***3f***. $\nu_{max}/cm^{-1}$ (KBr) 3324 (NH), 1782 (β-lactam), 1742 and 1708 (esters); $\delta_H$ 1.27 (3H, s, 2α-Me), 1.35 (3H, t, *J*=7.2 Hz, $CH_2CH_3$), 1.50 (3H, s, 2β-Me), 3.31 (1H, d, *J*=18.8 Hz, 4′-H), 3.66 (1H, d, *J*=18.8 Hz, 4′-H), 3.31 (1H, q, *J*=7.2 Hz, $CH_2CH_3$), 4.55 (1H, s, 3-H), 5.32 (1H, s, 5-H), 6.93 (1H, s, C*H*Ph$_2$), 6.97 (1H, s, N*H*), 7.30–7.36 (10H, m, 2×Ph); $\delta_C$ 14.3, 25.5, 33.5, 37.3, 61.5, 64.1, 68.7, 77.7, 78.8, 82.6, 127.0, 127.7, 128.3, 128.5, 128.6, 128.7, 138.9, 141.0, 161.6, 166.6, 172.4; MS (ESI) *m*/*z* 469 (MH$^+$, 100%), 466 (7), 369 (6), 326 (5); HRMS (ESI) *m*/*z* 494.17374 ($C_{26}H_{28}N_3O_5S$ [MH$^+$], 494.17442).

*4.3.7. Benzhydryl spiro[penicillanate-6,5′-(3-methoxycarbonyl-2-pyrazoline)]* ***3g*** *and* ***4g***. Prepared by method A from 6-diazopenicillanate **2b** (132 mg, 0.34 mmol) and methyl acrylate (44 mg, 0.51 mmol). The reaction mixture was stirred for 18 h and purification by flash column chromatography [ethyl acetate/hexane (1:3)] afforded a (85:15) mixture of compounds **3g** and **4g** as a yellow solid (99 mg, 0.21 mmol, 62%). *Benzhydryl spiro[penicillanate-6,5′-(3-methoxycarbonyl-2-pyrazoline)]* ***3g***. $\nu_{max}/cm^{-1}$ (film) 3328 (NH), 1782 (β-lactam), 1742 and 1712 (esters); $\delta_H$ 1.25 (3H, s, 2α-Me), 1.50 (3H, s, 2β-Me), 3.30 (1H, d, *J*=18.8 Hz, 4′-H), 3.65 (1H, d, *J*=18.8 Hz, 4′-H), 3.84 (3H, s), 4.55 (1H, s, 3-H), 5.29 (1H, s, 5-H), 6.93 (1H, s, C*H*Ph$_2$), 6.93 (1H, s, N*H*), 7.29–7.35 (10H, m, 2×Ph); $\delta_C$ 25.6, 33.3, 37.3, 52.4, 64.1, 68.7, 77.6, 78.8, 82.6, 126.9, 127.7, 128.3, 128.5, 128.6, 128.7, 138.9, 140.3, 162.0, 167.0, 172.6; MS (ESI) *m*/*z* 480 (MH$^+$, 100%), 452 (9), 369 (4), 326 (3); HRMS (ESI) *m*/*z* 480.15715 ($C_{25}H_{26}N_3O_5S$ [MH$^+$], 480.15877).

*4.3.8. Benzhydryl spiro[penicillanate-6,5′-(3-acetyl-2-pyrazoline)]* ***3h*** *and* ***4h***. Prepared by method A from 6-diazopenicillanate **2b** (137 mg, 0.35 mmol) and methyl vinyl ketone (76 mg, 1.1 mmol). The reaction mixture was stirred for 24 h and purification by flash column chromatography [ethyl acetate/hexane (1:3)] afforded a (83:17) mixture of compounds **3d** and **4d** as a yellow oil (133 mg, 0.29 mmol, 82%). The products were also prepared by method C from 6-diazopenicillanate **2b** (150 mg, 0.38 mmol) and methyl vinyl ketone (84 mg, 1.2 mmol). The reaction mixture was stirred for 3 h and purification by flash column chromatography [ethyl acetate/hexane (1:3)] afforded a (83:17) mixture of compounds **3h** and **4h** (137 mg, 0.30 mmol, 78%). *Benzhydryl spiro[penicillanate-6,5′-(3-acetyl-2-pyrazoline)]* ***3h***. $\nu_{max}/cm^{-1}$ (film) 3326 (NH), 1780 (β-lactam), 1745 (ester), 1666; $\delta_H$ 1.28 (3H, s, 2α-Me), 1.48 (3H, s, 2β-Me), 2.39 (3H, s), 3.21 (1H, d, *J*=18.8 Hz, 4′-H), 3.61 (1H, d, *J*=18.8 Hz, 4′-H), 4.55 (1H, s, 3-H), 5.34 (1H, s, 5-H), 6.94 (1H, s, C*H*Ph$_2$), 7.16 (1H, br s, NH), 7.34–7.35 (10H, m, 2×Ph); $\delta_C$ 25.5, 25.5, 33.6, 35.8, 64.0, 68.6, 77.6, 78.7, 82.8, 127.0, 127.7, 128.3, 128.5, 128.6, 128.7, 139.0, 148.5, 166.6, 172.7, 193.6; MS (ESI) *m*/*z* 464 (MH$^+$, 100%), 436 (16), 369 (53), 340 (13); HRMS (ESI) *m*/*z* 464.16256 ($C_{25}H_{26}N_3O_4S$ [MH$^+$], 464.16385).

*4.3.9. Benzyl spiro[penicillanate-6,3′-(4,5-dimethoxycarbonyl-3H-pyrazole)]* ***(5a)***. Prepared by method A from 6-diazopenicillanate **2a** (157 mg, 0.49 mmol) and dimethyl acetylenedicarboxylate (105 mg, 0.74 mmol). The reaction mixture was stirred for 16 h and purification by flash column chromatography [ethyl acetate/hexane (1:2)] afforded compound **5a** as a yellow oil (33 mg, 0.072 mmol, 15%). The product was also prepared by method B from 6-diazopenicillanate **2a** (178 g, 0.56 mmol) and dimethyl acetylenedicarboxylate (119 mg, 0.84 mmol). The solution was irradiated for 2 min and purification by flash column chromatography [ethyl acetate/hexane (1:2)] afforded compound **5a** (42 mg, 0.091 mmol, 16%). Finally, **5a** could also be prepared by method C from 6-diazopenicillanate **2a** (167 mg, 0.53 mmol) and dimethyl acetylenedicarboxylate (113 mg, 0.80 mmol). The reaction mixture was stirred for 3 h and purification by flash column chromatography [ethyl acetate/hexane (1:2)] afforded compound **5a** (95 mg, 0.21 mmol, 39%). $\nu_{max}/cm^{-1}$ (film) 1791 (β-lactam), 1746 (ester), 1591 (N=N); $\delta_H$ 1.40 (3H, s, 2α-Me), 1.44 (3H, s, 2β-Me), 3.79 (3H, s), 3.90 (3H, s), 4.68 (1H, s, 3-H), 5.15 (1H, d, *J*=12.0 Hz, C*H*$_2$Ph), 5.22 (1H, d, *J*=12.0 Hz, C*H*$_2$Ph), 6.41 (1H, s, 5-H), 7.28–7.31 (5H, m, Ph); $\delta_C$ 25.0, 31.5, 51.4, 52.0, 59.9, 60.7, 67.0, 68.0, 109.3, 127.7, 127.8, 127.9, 133.4, 147.8, 149.2, 149.4, 159.0, 160.0, 166.3; MS (ESI) *m*/*z* 460 (MH$^+$, 100%), 266 (6); HRMS (ESI) *m*/*z* 460.11605 ($C_{21}H_{22}N_3O_7S$ [MH$^+$], 460.11730); $[\alpha]_D^{20}$ +240 (*c* 1, $CH_2Cl_2$).

*4.3.10. Benzyl spiro[penicillanate-6,3′-(5-methoxycarbonyl-3H-pyrazole)]* ***(5b)***. Prepared by method A from 6-diazopenicillanate **2a** (157 mg, 0.49 mmol) and methyl propiolate (62 mg; 0.74 mmol). The reaction mixture was stirred for 3 h and purification by flash column chromatography [ethyl acetate/hexane (1:2)] afforded compound **5b** as a yellow oil (27 mg, 0.067 mmol, 14%). The product was also prepared by method C from 6-diazopenicillanate **2a** (145 mg, 0.46 mmol) and methyl propiolate (57 mg; 0.67 mmol). The reaction mixture was stirred for 3 h and purification by flash column chromatography [ethyl acetate/hexane (1:2)] afforded **5b** (67 mg, 0.016 mmol, 37%). $\nu_{max}/cm^{-1}$ (film) 1786 (β-lactam), 1744 (ester), 1566 (N=N); $\delta_H$ 1.41 (3H, s, 2α-Me), 1.49 (3H, s, 2β-Me), 3.89 (3H, s), 4.67 (1H, s, 3-H), 5.16 (1H, d, *J*=12.0 Hz, C*H*$_2$Ph), 5.21 (1H, d, *J*=12.0 Hz, C*H*$_2$Ph), 6.28 (1H, s, 5-H), 6.78 (1H, s, 4′-H), 7.30–7.32 (5H, m, Ph); $\delta_C$ 25.1, 30.9, 51.2, 59.3, 61.1, 66.9, 68.0, 103.3, 127.8, 127.8, 127.9, 133.5, 144.6, 148.4, 150.6, 160.8, 166.4; MS (ESI) *m*/*z* 402 (MH$^+$, 100%), 302 (5); HRMS (ESI) *m*/*z* 402.11112 ($C_{19}H_{20}N_3O_5S$ [MH$^+$], 402.11182); $[\alpha]_D^{20}$ +295 (*c* 1 $CH_2Cl_2$).

*4.3.11. Benzhydryl spiro[penicillanate-6,3′-(4,5-dimethoxycarbonyl-3H-pyrazole)]* ***(5c)***. Prepared by method A from 6-diazopenicillanate **2b** (156 mg, 0.40 mmol) and dimethyl acetylenedicarboxylate (85 mg, 0.60 mmol). The reaction mixture was stirred for 16 h and purification by flash column chromatography [ethyl acetate/hexane (1:3)] afforded compound **5c** as a brown oil (117 mg, 0.22 mmol, 55%). Compound **5c** was also prepared by method C from 6-diazopenicillanate **2b** (154 mg, 0.39 mmol) and dimethyl acetylenedicarboxylate (85 mg, 0.60 mmol). The reaction mixture was stirred for 3 h and purification by flash column chromatography [ethyl acetate/hexane (1:3)] afforded compound **5c** (109 mg, 0.20 mmol, 51%). $\nu_{max}/cm^{-1}$ (film) 1789 (β-lactam), 1733 (ester), 1588 (N=N); $\delta_H$ 1.25 (3H, s, 2α-Me), 1.45 (3H, s, 2β-Me), 3.78 (3H, s), 3.89 (3H, s), 4.74 (1H, s, 3-H), 6.40 (1H, s, 5-H), 6.93 (1H, s, C*H*Ph$_2$), 7.18–7.29 (10H, m, 2×Ph); $\delta_C$ 24.8, 31.4, 51.4, 52.0, 59.9, 60.9, 68.1, 78.1, 109.3, 125.9, 126.7, 127.3, 127.6, 126.6, 127.7, 137.7,

147.8, 149.2, 149.4, 159.0, 159.9, 165.6; MS (ESI) *m/z* 436 ($MH^+$, 100%), 383 (10), 342 (13); HRMS (ESI) *m/z* 536.14744 ($C_{27}H_{26}N_3O_7S$ [$MH^+$], 536.14860); $[\alpha]_D^{20}$ +255 (*c* 1, $CH_2Cl_2$).

*4.3.12. Benzhydryl spiro[penicillanate-6,3′-(5-methoxycarbonyl-3H-pyrazole)] (**5d**).* Prepared by method A from 6-diazopenicillanate **2b** (151 mg, 0.38 mmol) and methyl propiolate (48 mg; 0.57 mmol). The reaction mixture was stirred for 16 h and purification by flash column chromatography [ethyl acetate/hexane (1:3)] afforded compound **5d** as a yellow solid (115 mg, 0.24 mmol, 63%). Compound **5d** was also prepared by method C from 6-diazopenicillanate **2b** (159 mg, 0.40 mmol) and methyl propiolate (50 mg; 0.59 mmol). The reaction mixture was stirred for 3 h and purification by flash column chromatography [ethyl acetate/hexane (1:3)] afforded **5d** (138 mg, 0.29 mmol, 73%). Mp 60–61 °C (from ethyl acetate/hexane); $\nu_{max}/cm^{-1}$ (KBr) 1785 (β-lactam), 1734 (ester), 1496 (N=N); $\delta_H$ 1.33 (3H, s, 2α-Me), 1.57 (3H, s, 2β-Me), 3.96 (3H, s), 4.81 (1H, s, 3-H), 6.34 (1H, s, 5-H), 6.85 (1H, s, C*H*$Ph_2$), 7.01 (1H, s, 4′-H), 7.32–7.38 (10H, m, 2×Ph); $\delta_C$ 25.9, 31.9, 52.6, 60.4, 62.3, 69.1, 79.0, 104.3, 127.0, 127.7, 128.3, 128.6, 128.7, 128.7, 138.9, 45.6, 149.5, 151.7, 161.8, 166.8; MS (ESI) *m/z* 478 ($MH^+$, 100%), 340 (2); HRMS (ESI) *m/z* 478.14308 ($C_{25}H_{24}N_3O_5S$ [$MH^+$], 478.14312); $[\alpha]_D^{20}$ +225 (*c* 1, $CH_2Cl_2$).

*4.3.13. Benzyl spiro[penicillanate-6,4′-(7-phenyl-6,8-dioxo-2,3,7-triazabicyclo[3.3.0]oct-2-ene)] **7a** and **8a**.* Prepared by method A from 6-diazopenicillanate **2a** (177 mg, 0.56 mmol) and *N*-phenylmaleimide (150 mg, 0.87 mmol). The reaction mixture was stirred for 6 h and purification by flash column chromatography [ethyl acetate/hexane (1:2)] afforded a (77:23) mixture of compounds **7a** and **8a** as a yellow oil (106 mg, 0.22 mmol, 39%). The products were also prepared by method B from 6-diazopenicillanate **2a** (178 mg, 0.56 mmol) and *N*-phenylmaleimide (105 mg, 0.60 mmol). The reaction mixture was irradiated for 3 min and purification by flash column chromatography [ethyl acetate/hexane (1:2)] afforded a (66:34) mixture of compounds **7a** and **8a** (34 mg, 0.069 mmol, 12%). Crystallization from ethyl acetate/hexane gave **7a** in pure form as a white solid. *Benzyl spiro[penicillanate-6,4′-(7-phenyl-6,8-dioxo-2,3,7-triazabicyclo[3.3.0]oct-2-ene)] **7a**.* Mp 194–195 °C (from ethyl acetate/hexane); $\nu_{max}/cm^{-1}$ (KBr) 1781 (β-lactam), 1747 (ester), 1735 (CO), 1723 (CO), 1500 (N=N); $\delta_H$ (DMSO-$d_6$) 1.44 (3H, s, 2α-Me), 1.69 (3H, s, 2β-Me), 3.73 (1H, d, *J*=7.2 Hz, 5′-H), 4.86 (1H, s, 3-H), 5.28 (2H, br s, C$H_2$Ph), 5.74 (1H, s, 5-H), 6.21 (1H, d, *J*=7.2 Hz, 1′-H), 7.21–7.23 (2H, m), 7.43–7.49 (8H, m); $\delta_C$ (DMSO-$d_6$) 25.6 (2α-Me), 33.2 (2β-Me), 43.5 (C-11), 64.0 (C-2), 67.0, 69.1(C-3), 71.2 (C-5), 96.7 (C-10), 109.2 (C-6), 126.7, 128.4, 128.5, 128.6, 128.8, 129.1, 131.4, 135.1, 164.9, 167.0, 168.2, 171.7; MS (ESI) *m/z* 491 ($MH^+$, 100%), 466 (9), 326 (4), 280 (5), 213 (5); HRMS (ESI) *m/z* 491.13711 ($C_{25}H_{23}N_4O_5S$ [$MH^+$], 491.13837); $[\alpha]_D^{20}$ −125 (*c* 1, $CH_2Cl_2$).

*4.3.14. Benzyl spiro[penicillanate-6,4′-(7-methyl-6,8-dioxo-2,3,7-triazabicyclo[3.3.0]oct-2-ene)] **7b** and **8b**.* Prepared by method A from 6-diazopenicillanate **2a** (174 mg, 0.55 mmol) and *N*-methylmaleimide (98 mg, 0.88 mmol). The reaction mixture was stirred for 6 h and purification by flash column chromatography [ethyl acetate/hexane (1:2)] afforded a (82:18) mixture of compounds **7b** and **8b** as a yellow oil (60 mg, 0.14 mmol, 25%). *Benzyl spiro[penicillanate-6,4′-(7-methyl-6,8-dioxo-2,3,7-triazabicyclo[3.3.0]oct-2-ene)] **7b**.* $\nu_{max}/cm^{-1}$ (film) 1794 (β-lactam), 1743 (ester), 1713 (CO), 1540 (N=N); $\delta_H$ 1.41 (3H, s, 2α-Me), 1.74 (3H, s, 2β-Me), 2.91 (3H, s), 3.53 (1H, d, *J*=8.0 Hz, 5′-H), 4.60 (1H, s, 3-H), 5.12–5.21 (2H, m, C$H_2$Ph), 5.74 (1H, s, 5-H), 5.91 (1H, d, *J*=8.0 Hz, 1′-H), 7.29–7.31 (5H, m, Ph); $\delta_C$ 24.5, 25.0, 32.8, 41.4, 65.0, 66.7, 68.8, 69.9, 94.0, 108.5, 127.5, 127.6, 127.7, 127.7, 127.8, 133.5, 162.7, 165.8, 167.0, 170.3; MS (ESI) *m/z* 451 ($MNa^+$, 100%), 431 (4); HRMS (ESI) *m/z* 451.10511 ($C_{20}H_{20}N_4NaO_5S$ [$MNa^+$], 451.10466).

*4.3.15. Benzhydryl spiro[penicillanate-6,4′-(7-phenyl-6,8-dioxo-2,3,7-triazabicyclo[3.3.0]oct-2-ene)] **7c** and **8c**.* Prepared by method A from 6-diazopenicillanate **2b** (100 mg, 0.25 mmol) and *N*-phenylmaleimide (71 mg, 0.41 mmol). The reaction mixture was stirred for 6 h and purification by flash column chromatography [ethyl acetate/hexane (1:3)] afforded a (86:14) mixture of compounds **7c** and **8c** as a yellow oil(110 mg, 0.19 mmol, 76%). Crystallization from ethyl acetate/hexane gave **7c** in pure form as a white solid. *Benzhydryl spiro[penicillanate-6,4′-(7-phenyl-6,8-dioxo-2,3,7-triazabicyclo[3.3.0]oct-2-ene)] **7c**.* mp 191–192 °C (from ethyl acetate/hexane); $\nu_{max}/cm^{-1}$ (KBr) 1778 (β-lactam), 1756 (ester), 1735 (CO), 1724 (CO), 1595 (N=N); $\delta_H$ 1.36 (3H, s, 2α-Me), 1.80 (3H, s, 2β-Me), 3.69 (1H, d, *J*=8.0 Hz, 11-H), 4.73 (1H, s, 3-H), 5.93 (1H, s, 5-H), 6.13 (1H, d, *J*=8.0 Hz, 10-H), 7.00 (1H, s, C*H*$Ph_2$), 7.25–7.47 (15H, m, 2×Ph); $\delta_C$ 26.0, 33.9, 42.6, 66.5, 70.0, 70.9, 78.8, 94.9, 110.5, 126.5, 127.2, 127.5, 128.4, 128.5, 128.7, 128.7, 129.3, 129.4, 130.8, 138.9, 163.7, 166.1, 166.7, 170.7; MS (ESI) *m/z* 567 ($MH^+$, 100%), 391 (11), 213 (14); HRMS (ESI) *m/z* 567.16873 ($C_{31}H_{27}N_4O_5S$ [$MH^+$], 567.16967); $[\alpha]_D^{20}$ −85 (*c* 1, $CH_2Cl_2$).

*4.3.16. Benzhydryl spiro[penicillanate-6,4′-(7-methyl-6,8-dioxo-2,3,7-triazabicyclo[3.3.0]oct-2-ene)] **7d** and **8d**.* Prepared by method A from 6-diazopenicillanate **2b** (158 mg, 0.40 mmol) and *N*-methylmaleimide (71 mg, 0.64 mmol). The reaction mixture was stirred for 6 h and purification by flash column chromatography [ethyl acetate/hexane (1:3)] afforded a (80:20) mixture of compounds **7d** and **8d** as a yellow oil (118 mg, 0.23 mmol, 58%). Crystallization from ethyl acetate/hexane gave **7d** in pure form as a white solid. *Benzhydryl spiro[penicillanate-6,4′-(7-methyl-6,8-dioxo-2,3,7-triazabicyclo[3.3.0]oct-2-ene)] **7d**.* Mp 171–172 °C (from ethyl acetate/hexane); $\nu_{max}/cm^{-1}$ (KBr) 1774 (β-lactam), 1745 (ester), 1710 (CO), 1494 (N=N); $\delta_H$ 1.36 (3H, s, 2α-Me), 1.83 (3H, s, 2β-Me), 3.01 (3H, s), 3.60 (1H, d, *J*=8.0 Hz, 11-H), 4.73 (1H, s, 3-H), 5.85 (1H, s, 5-H), 5.97 (1H, d, *J*=8.0 Hz, 10-H), 6.99 (1H, s, C*H*$Ph_2$), 6.90–7.37 (10H, m, 2×Ph); $\delta_C$ 25.5, 25.8, 33.9, 42.4, 66.3, 70.0, 71.0, 78.8, 95.0, 109.5, 127.2, 127.5, 128.4, 128.5, 128.7, 128.7, 138.9, 163.7, 166.1, 167.8, 171.2; MS (ESI) *m/z* 505 ($MH^+$, 100%), 464 (7), 402 (9), 241 (7); HRMS (ESI) *m/z* 505.15385 ($C_{26}H_{25}N_4O_5S$ [$MH^+$], 505.15402); $[\alpha]_D^{20}$ +20 (*c* 1, $CH_2Cl_2$).

### 4.4. General procedure for the synthesis of spirocyclopropyl-β-lactams 9 and 10

A suspension of the appropriate spiro-β-lactam **7** (50 mg) in 1,2,4-trichlorobenzene (1 mL) was irradiated in the microwave reactor with the temperature set to 250 °C for 2 min. The crude product was purified by flash column chromatography [hexane then ethyl acetate/hexane (1:2)].

*4.4.1. Benzhydryl spiro[penicillanate-6,6′-(3-phenyl-2,4-dioxo-3-azabicyclo[3.1.0]hexane)] **9a** and **10a**.* Prepared from **7c** (53 mg, 0.094 mmol). Purification by flash column chromatography afforded a (77:23) mixture of compounds **9a** and **10a** as a brown oil (47 mg, 0.088 mmol, 94%). Crystallization from ethyl acetate/hexane gave **9a** in pure form as a white solid. *Benzhydryl spiro[penicillanate-6,6′-(3-phenyl-2,4-dioxo-3-azabicyclo[3.1.0]hexane)] **9a**.* Mp 232–233 °C (from ethyl acetate/hexane); $\nu_{max}/cm^{-1}$ (film) 1786 (β-lactam), 1735 (ester), 1719 (CO); $\delta_H$ 1.22 (3H, s, 2α-Me), 1.54 (3H, s, 2β-Me), 3.16 (1H, d, *J*=5.6 Hz, 1′-H), 3.25 (1H, d, *J*=5.6 Hz, 5′-H), 4.60 (1H, s, 3-H), 5.43 (1H, s, 5-H), 6.87 (1H, s, C*H*$Ph_2$), 7.18–7.39 (15H, m, 2×Ph); $\delta_C$ 24.1, 29.8, 29.8, 33.1, 54.1, 63.7, 68.4, 69.5, 77.6, 126.0, 126.1, 126.5, 127.3, 127.5, 127.6, 127.7, 127.8, 128.1, 130.3, 138.0, 165.3, 167.8, 168.1, 170.4; MS (ESI) *m/z* 561 ($MNa^+$, 21%), 513 (14),

366 (24), 326 (100), 282 (10), 213 (7); HRMS (ESI) *m*/*z* 561.14397 ($C_{31}H_{26}N_2NaO_5S$ [$MNa^+$], 561.14546); $[\alpha]_D^{20}$ +135 (*c* 1, $CH_2Cl_2$). *Benzhydryl spiro[penicillanate-6,6′-(3-phenyl-2,4-dioxo-3-azabicyclo [3.1.0]hexane)]* ***10a***. $\delta_H$ 1.19 (3H, s, 2α-Me), 1.51 (3H, s, 2β-Me), 3.09 (1H, d, *J*=5.6 Hz), 3.33 (1H, d, *J*=5.6 Hz), 4.57 (1H, s, 3-H), 5.46 (1H, s, 5-H), 6.88 (1H, s, C*H*$Ph_2$), 7.18–7.39 (15H, m, 2×Ph).

*4.4.2. Benzhydryl spiro[penicillanate-6,6′-(3-methyl-2,4-dioxo-3-azabicyclo[3.1.0]hexane)]* ***9b***, ***10b***. Prepared from **7d** (46 mg, 0.091 mmol). Purification by flash column chromatography afforded a (72:28) mixture of compounds **9b** and **10b** as a brown oil (28 mg, 0.058 mmol, 64%). *Benzhydryl spiro[penicillanate-6,6′-(3-methyl-2,4-dioxo-3-azabicyclo[3.1.0]hexane)]* ***9b***. $\nu_{max}/cm^{-1}$ (film) 1786 (β-lactam), 1735 (ester), 1711 (CO); $\delta_H$ 1.20 (3H, s, 2α-Me), 1.51 (3H, s, 2β-Me), 2.84 (3H, s), 3.02 (1H, d, *J*=5.6 Hz, 1′-H), 3.12 (1H, d, *J*=5.6 Hz, 5′-H), 4.56 (1H, s, 3-H), 5.38 (1H, s, 5-H), 6.85 (1H, s, C*H*$Ph_2$), 7.12–7.28 (10H, m, 2×Ph); $\delta_C$ 24.8, 25.1, 30.4, 30.5, 34.1, 55.3, 64.6, 69.5, 70.4, 78.6, 127.0, 127.1, 127.5, 127.6, 128.3, 128.4, 128.6, 128.7, 139.0, 166.3, 169.7, 170.1, 171.5; MS (ESI) *m*/*z* 499 ($MNa^+$, 100%); HRMS (ESI) *m*/*z* 499.13084 ($C_{26}H_{24}N_2NaO_5S$ [$MNa^+$], 499.12981). *Benzhydryl spiro[penicillanate-6,6′-(3-methyl-2,4-dioxo-3-azabicyclo[3.1.0]hexane)]* ***10b***. $\delta_H$ 1.17 (3H, s, 2α-Me), 1.55 (3H, s, 2β-Me), 2.81 (3H, s), 2.96 (1H, d, *J*=5.6 Hz), 3.18 (1H, d, *J*=5.6 Hz), 4.52 (1H, s, 3-H), 5.26 (1H, s, 5-H), 6.88 (1H, s, C*H*$Ph_2$), 7.19–7.28 (10H, m, 2×Ph).

### 4.5. Computational details

All the calculations were performed using the Gaussian 03 program package,[16] except for the conformational search that was performed with the Avogadro package.[12] Graphical representations were produced with Gaussview.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## Supplementary data

$^1H$ and $^{13}C$ NMR spectra of selected compounds. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2012.03.022.

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