Tetrahedron 70 (2014) 3812–3821

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis of chiral spiropyrazoline-β-lactams and spirocyclopropyl-β-lactams from 6-alkylidenepenicillanates

Bruna S. Santos [a], Clara S.B. Gomes [b], Teresa M.V.D. Pinho e Melo [a,*]

[a] Department of Chemistry, University of Coimbra, 3004-535 Coimbra, Portugal
[b] Centro de Química Estrutural, Departamento de Engenharia Química, Instituto Superior Técnico, Universidade de Lisboa, 1049-001 Lisboa, Portugal

ARTICLE INFO

Article history:
Received 15 February 2014
Received in revised form 25 March 2014
Accepted 28 March 2014
Available online 12 April 2014

Keywords:
6-Alkylidenepenicillanates
Spiropyrazolinepenicillanates
Spirocyclopropylpenicillanates
1,3-Dipolar cycloaddition
Ring contraction
Microwave-induced reactions

ABSTRACT

Chiral spiropyrazolinepenicillanates were obtained in a stereoselective fashion via 1,3-dipolar cycloaddition reactions of 6-alkylidenepenicillanates with diphenyldiazomethane, phenyldiazomethane, and diazomethane. Microwave-induced ring contraction of spiro-1-pyrazoline-β-lactams leading to chiral spirocyclopropylpenicillanates is also described.

1. Introduction

The β-lactam ring is the core structure of the biological activity of a large class of antibiotics and also of several β-lactamase inhibitors.[1] Spiro-β-lactams are also particularly interesting target molecules since some derivatives exhibit relevant biological properties, namely, cholesterol absorption inhibition, antibacterial activity, and antiviral activity.[2] Therefore, the search for new spiro-β-lactam derivatives is of great interest in medicinal chemistry.

In the recent past, we have been interested in exploring the reactivity of 6-diazopenicillanates and 6-alkylidenepenicillanates as an approach to new spirocyclic penicillin analogues.[3] In fact, we reported the first examples of phosphane-catalyzed [3+2] annulation of allenoates to 6-alkylidenepenicillanates **1** leading to chiral spirocyclopentenyl-β-lactams **2** having either two or three consecutive stereogenic centers, including a quaternary chiral center.[3b] The stereoselective 1,3-dipolar cycloaddition reactions of 6-diazopenicillanates was also explored.[3a,4a,b] Chiral spiro-2-pyrazoline-β-lactams, spiro-1-pyrazoline-β-lactams, and spiro-3*H*-pyrazole-β-lactams could be obtained in a stereoselective fashion, the major products resulting from the addition to the less sterically hindered α-side of the β-lactam. Spiro-1-pyrazoline-β-lactams **4** obtained from the cycloaddition reaction of 6-diazopenicillanates **3** with *N*-substituted maleimides, undergo microwave-induced nitrogen extrusion allowing the stereoselective synthesis of spirocyclopropyl-β-lactams **5** (Scheme 1).[3a]

An alternative strategy to spiropyrazolinepenicillanates via 1,3-dipolar cycloaddition reactions of 6-alkylidenepenicillanates is also known.[4a,c] Häbich et al. described the reaction of 6-alkylidenepenicillanates with diazomethane leading to spiro-2-pyrazolinepenicillanates.[4c] On the other hand, diphenyldiazomethane reacted with 6-(1-benzyloxicarbonylmethylene)penicillanates **6** to give spiro-1-pyrazolinepenicillanates **7**, which underwent thermally induced ring contraction to afford spirocyclopropylpenicillanates **8** (Scheme 2).[4a] The synthesis of spirocyclopropylpenicillanates via rhodium-catalyzed cyclopropanation of a 6-diazopenicillanate sulfone[5b] and via Cu(I) catalyzed reaction of 6-bromopenicillanoyl magnesium bromide with α,β-unsaturated esters[5a] has also been reported.

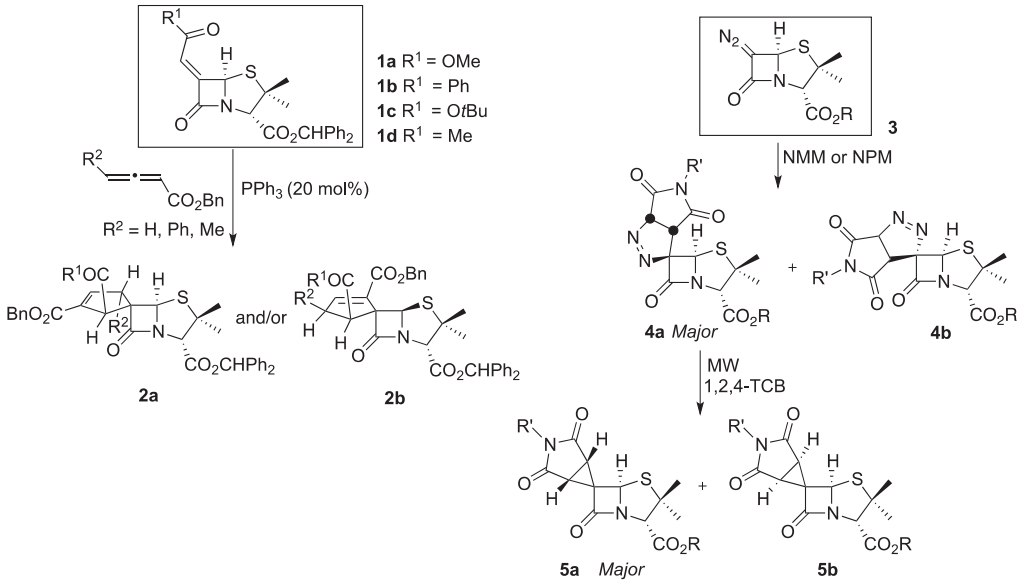
As part of our continuing investigations, this paper describes the evaluation of the scope and selectivity of the 1,3-dipolar cycloaddition of 6-alkylidenepenicillanates with diazo compounds as a route to chiral spiropyrazolinepenicillanates, as well as the stereoselective microwave-induced ring contraction of spiro-1-pyrazolinepenicillanates to spirocyclopropylpenicillanates.

2. Results and discussion

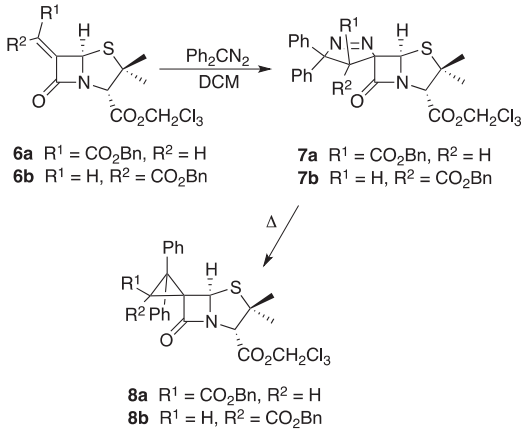
6-(*Z*)-Alkylidenepenicillanates **1a**–**1d** were obtained by the Wittig reaction of the appropriate phosphorous ylide **9** with

* Corresponding author. E-mail address: tmelo@ci.uc.pt (T.M.V.D. Pinho e Melo).

0040-4020/$ – see front matter © 2014 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tet.2014.03.109

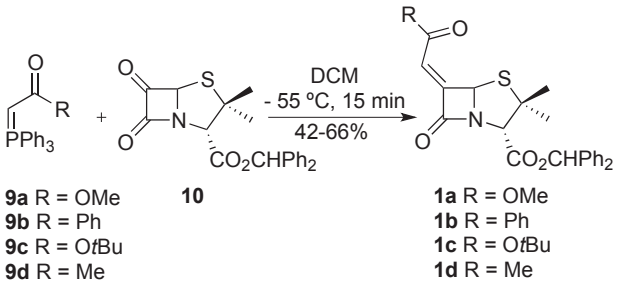


Scheme 1. Synthesis of spiro-β-lactams from 6-alkylidenepenicillanates and 6-diazopenicillanates.[3]



Scheme 2. Synthesis of spirocyclopropylpenicillanates from 6-alkylidenepenicillanates.[4a]

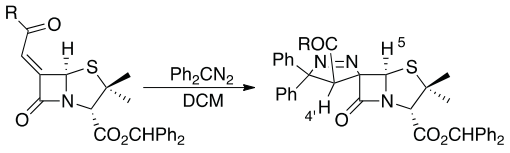
benzhydryl 6-oxopenicillanate (**10**), which was prepared by a known procedure (Scheme 3).[3b,6,7]



Scheme 3. Synthesis of 6-(*Z*)-alkylidenepenicillanates **1**.

Initially, we looked again into the cycloaddition of 6-(*Z*)-alkylidenepenicillanates with diphenyldiazomethane (Table 1). The 1,3-dipolar cycloaddition of benzhydryl 6-(*Z*)-(1-methoxycarbonyl methylene)penicillanate (**1a**) with diphenyldiazomethane at room temperature for 48 h, gave the spiro-1-pyrazolinepenicillanate **11a** regio- and stereoselectively in 60% yield (entry 1). By carrying out

Table 1
1,3-Dipolar cycloaddition reaction of diphenyldiazomethane with 6-alkylidenepenicillanates **1a** and **1b**

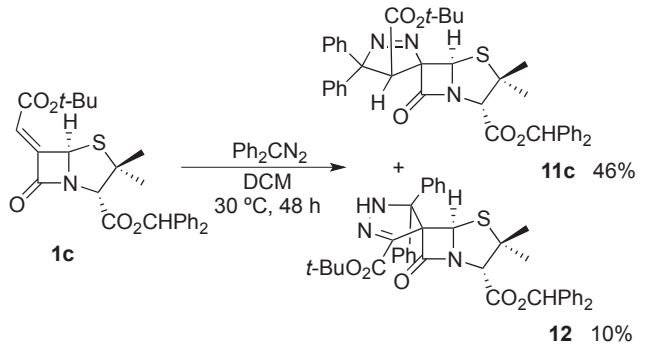


Entry	β-Lactam **1**	Reaction conditions	Isolated yield
1	**1a**	rt, 48 h	**11a**, 60%
2	**1a**	30 °C, 24 h	**11a**, 75%
3	**1b**	30 °C, 24 h	**11b**, 9%

the same reaction at 30 °C for 24 h, the yield was improved to 75% (entry 2). The 2D NOESY spectrum (400 MHz) of chiral compound **11a** showed cross peaks between H-4′ and the β-Me protons, but no correlation was observed between H-4′ and H-5. The observed stereoselectivity can be explained considering that the product results from the addition to the less sterically hindered α-side of the β-lactam. On the other hand, the cycloaddition with less steric hindrance allowed the selective synthesis of regioisomer **11a**. This result is in agreement with the previously reported cycloaddition of β,β,β-trichloroethyl 6-(1-benzyloxycarbonylmethylene)penicillanate with diphenyldiazomethane.[4a]

Diphenyldiazomethane also reacted with 6-(*Z*)-(1-benzoylmethylene)penicillanate **1b** to afford spiro-β-lactam **11b**. However, carrying out the reaction at 30 °C for 24 h, the target molecule could only be obtained in low yield (9%) (Table 1, entry 3). Several attempts made to obtain compound **11b** with higher yield were unsuccessful.

The cycloaddition of 6-(*Z*)-(1-*tert*-butoxycarbonylmethylene) penicillanate **1c** with diphenyldiazomethane was stereoselective but led to the formation of two products resulting from opposite regiochemistries (Scheme 4). The reaction was carried out at 30 °C for 48 h producing chiral spiro-1-pyrazolinepenicillanate **11c** (46%), as the major product, together with spiro-β-lactam **12** (10%). Thus, compound **12** was formed by isomerization of the initially formed cycloadduct, regiosiomer of **11c**, which could not be isolated under



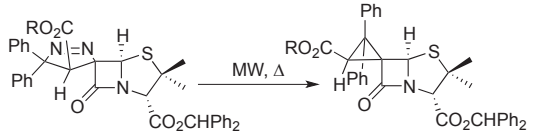
Scheme 4. 1,3-Dipolar cycloaddition reaction of diphenyldiazomethane with 6-alkylidenepenicillanate **1c**.

the reaction conditions. The structural assignment of compound **12** was made on the basis of 2D HMQC and HMBC spectra (400 MHz). In the HMQC spectrum, no connectivity was observed for a proton with the chemical shift of 6.30 ppm confirming that this proton is attached to a nitrogen atom. This result indicates that the presence of the bulky 1-*tert*-butoxycarbonyl group makes the addition of the diphenyldiazomethane with the phenyl groups pointing away from the thiazolidine ring less favorable.

Unfortunately, attempts to carry out the 1,3-dipolar cycloaddition of benzhydryl 6-(*Z*)-(1-acetylmethylene)penicillanate (**1d**) with diphenyldiazomethane were unsuccessful.

The microwave-induced reactivity of spiro-1-pyrazoline penicillanates **11a**–**11c** was explored (Table 2). The attempt to carry out the nitrogen extrusion from compound **11a** in toluene under microwave irradiation at 80 °C for 2 min did not lead to the target molecule (entry 1). However, when the reaction was performed at 100 °C for 2 min, spirocyclopropylpenicillanate **13a** was obtained in 37% yield (entry 2). Increasing the reaction time to 4 min afforded cyclopropane derivative **13a** in 64% yield (entry 3). The target compound could be obtained in 99% yield by carrying out the ring contraction reaction of **11a** under microwave irradiation at 120 °C for 2 min (entry 4). Performing this reaction at higher temperature, using 1,2,4-trichlorobenzene (1,2,4-TCB) as solvent, resulted in lower yield (entries 5 and 6). The optimized reaction conditions were applied to the synthesis of cyclopropane **13b** in high yield via microwave-induced nitrogen extrusion of spiro-β-lactam **11c** (entry 7). It should be noted that compounds **13** were isolated by simple evaporation of the solvent, without need of further purification.

Table 2
Synthesis of spirocyclopropyl-β-lactams **13** via ring contraction of the corresponding spiro-1-pyrazoline-β-lactam **11**



11a R = Me
11c R = *t*-Bu

13a R = Me
13b R = *t*-Bu

Entry	β-Lactam **11**	Reaction conditions	Isolated yield
1	**11a**	80 °C, 2 min, Toluene	**13a**, 0%
2	**11a**	100 °C, 2 min, Toluene	**13a**, 37%
3	**11a**	100 °C, 4 min, Toluene	**13a**, 64%
4	**11a**	120 °C, 2 min, Toluene	**13a**, 99%
5	**11a**	200 °C, 2 min, 1,2,4-TCB	**13a**, 89%
6	**11a**	250 °C, 2 min, 1,2,4-TCB	**13a**, 74%
7	**11b**	120 °C, 2 min, Toluene	**13b**, 91%

The preparation of cyclopropanes via ring contraction of 1-pyrazolines is a well-known method.[8] The nature of the mechanism involved in the cyclopropane formation is controversial since some reactions are stereospecific, some show high stereoselectivity and others are not selective. 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.

We previously reported that spiro-1-pyrazoline-β-lactams obtained from the cycloaddition reaction of 6-diazopenicillanates with *N*-substituted maleimides, undergo microwave-induced ring contraction to afford spirocyclopropyl-β-lactams.[3a] In this case the reaction was not stereospecific, which was rationalized considering a stepwise mechanism via cleavage of the 1-pyrazoline ring leading to an open-chain biradical followed by cyclopropane ring closure. In contrast with these observations, the synthesis of spirocyclopropylpenicillanates **13** was stereospecific, which is an indication that a concerted mechanism must be involved in the elimination of nitrogen from the spiro-1-pyrazoline-β-lactams **11**.

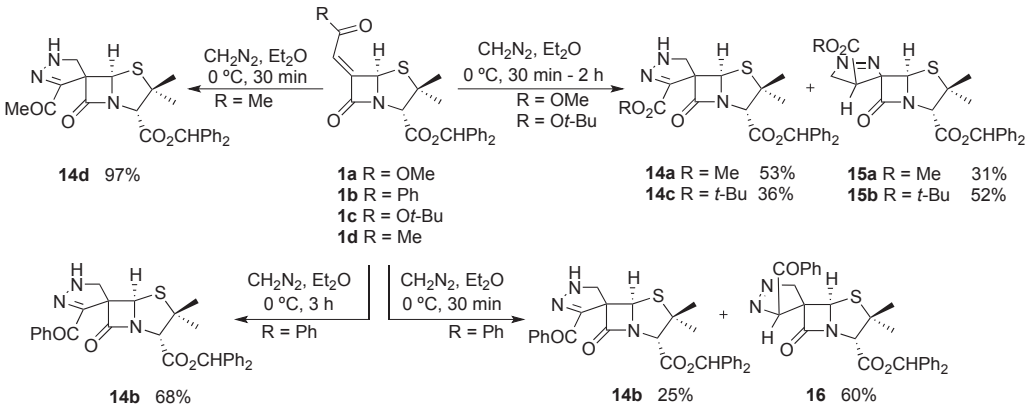
The reactivity of 6-alkylidenepenicillanates towards diazomethane was then explored (Scheme 5). Diazomethane reacted with **1a** at 0 °C for 2 h to afforded β-lactams **14a** and **15a** resulting from both regiochemistries, isolated as single stereoisomers in each case, in 84% overall yield. Note that spiro-β-lactam **14a** results from the conversion of the initially formed cycloadduct that could not be isolated under these reaction conditions. The same behavior was observed in the reaction of 6-alkylidenepenicillanate **1c** with diazomethane at 0 °C for 30 min, which produced β-lactams **14c** and **15b** in 88% overall yield.

Interestingly, the reaction of **1b** with diazomethane at 0 °C for only 30 min was regio- and stereoselective, leading to the cycloadduct **16** and the isomeric derivative **14b**, in 85% overall yield (Scheme 5). By carrying out the same reaction for 3 h, β-lactam **14b** was obtained as the only product in 68% yield (Scheme 5).

The structure of spiro-β-lactam **16** was determined by X-ray crystallography (Fig. 1). This compound crystallized as colorless needles in the monoclinic system within *C*2 space group, showing one molecule per asymmetric unit. In the molecule, there are four chiral centers, C3, C5, C6, and C3′, with relative configuration *S*, *R*, *R* and *S*, respectively. The hydrogen atoms bonded to carbons C3 and C5 of the penicillanate moiety are placed on opposite faces of the fused rings. All distances and angles are within the expected values for similar compounds.[9]

The reaction of 6-(*Z*)-alkylidenepenicillanate **1d** with diazomethane gave chiral spiro-β-lactam **14d** as the only product, in 97% yield (Scheme 5). Compound **14d** was isolated by simple evaporation of the solvent, without need of further purification. The structural assignment of **14d** was made on the basis of 2D COSY, HMQC, HMBC, and DEPT spectra (400 MHz). In the HMQC spectrum, no connectivity was observed for a proton with the chemical shift of 6.43 ppm confirming that this proton is attached to a nitrogen atom. The COSY spectrum showed cross peaks between the NH and H-5′ protons. Finally, the DEPT spectrum confirmed that the protons with the 4.06 ppm chemical shift are geminal, belonging to the methylene group.

It is worth noting that the 1,3-dipolar cycloaddition reactions of diazomethane with 6-(*Z*)-alkylidenepenicillanates bearing carboxylate groups in the double bond were not regiospecific, whereas with the acetyl and benzoyl 6-alkylidenepenicillanate derivatives regiospecificity was observed. The expected regioselectivity for the 1,3-dipolar cycloaddition of diazomethane with electron-deficient alkenes is the one observed for compounds **1b** and **1d**, with the carbon end of the dipole becoming bonded to the β-carbon of the substituted alkene.[10] Thus, a combination of electronic and steric factors must be considered to explain the outcome of the reactions of diazomethane with β-lactams **1a** and **1c**. It is noteworthy that the regioselectivity of the reaction of diphenyldiazomethane with 6-(*Z*)-alkylidenepenicillanates is determined by steric factors. Nevertheless, all the 6-



Scheme 5. 1,3-Dipolar cycloaddition reaction of diazomethane with 6-alkylidenepenicillanates **1a**–**d**.

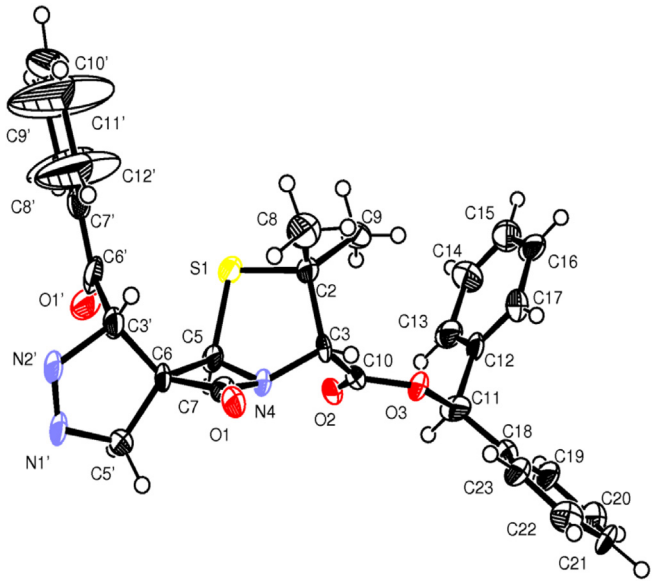
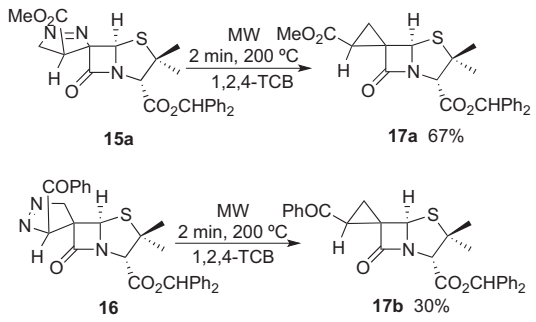


Fig. 1. ORTEP-3 diagram of spiropyrazolinepenicillanate **16**, using 50% probability level ellipsoids.

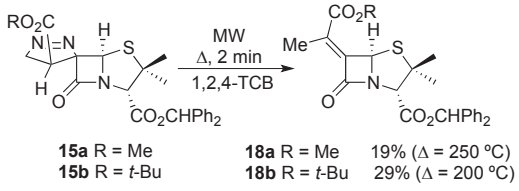
alkylidenepenicillanates studied reacted with diazomethane in a stereoselective fashion leading to products resulting from the addition to the less sterically hindered α-side of the β-lactam.

Several unsuccessful attempts were made in order to carry out the microwave-induced nitrogen extrusion from compound **15a** at 120, 140 or even at 160 °C. However, spirocyclopropylpenicillanates **17a** and **17b** could be obtained from spiro-β-lactams **15a** and **16**, respectively, carrying out the microwave irradiation at 200 °C for 2 min (Scheme 6).



Scheme 6. Synthesis of spirocyclopropyl-β-lactams **17** via nitrogen extrusion of the corresponding spiro-1-pyrazoline-β-lactam.

It is known that under thermal conditions the elimination of nitrogen from 1-pyrazolines can lead to the formation of alkenes.[8] Corbett also described that the thermolysis of spirocyclic carbapenems in toluene, prepared by the addition of diazomethane to 6-ethylidene olivanic acids, produce isopropylidene derivatives instead of spirocyclopropanes.[11] We also observed that by carrying out the microwave irradiation of spiro-1-pyrazolinepenicillanate **15b** at 200 °C for 2 min 6-alkylidenepenicillanate **18b** was obtained in 29% yield (Scheme 7). Interestingly, the same behavior was observed when a solution of spiro-β-lactam **15a** in 1,2,4-trichlorobenzene was irradiated at 250 °C for 2 min giving β-lactam **18a** in 19% yield.



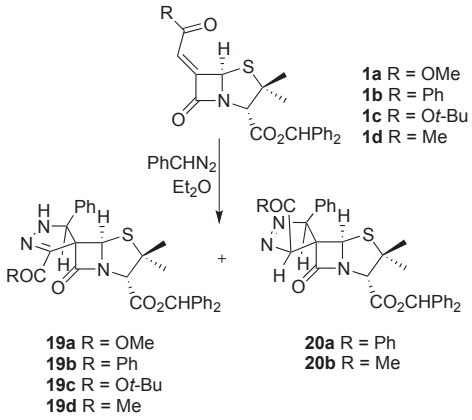
Scheme 7. Synthesis of β-lactams **18** via microwave irradiation of the corresponding spiro-1-pyrazoline-β-lactam **15**.

The reactivity of 6-alkylidenepenicillanates towards phenyldiazomethane was also studied (Table 3). Dipolar cycloaddition of 6-(methoxycarbonylmethylene)penicillanate **1a** with phenyldiazomethane at 0 °C for 30 min allowed the regio- and stereoselective synthesis of chiral β-lactam **19a** in 40% yield (entry 1). When the reaction was performed with a longer reaction time the same product was obtained in lower yield (entry 2). We observed the same behavior for 6-(*tert*-butoxycarbonylmethylene)penicillanate **1c** in the reaction with phenyldiazomethane. Carrying out the reaction at 0 °C for 30 min gave β-lactam **19c** in 52% yield (entry 6), whereas with a longer reaction time the yield was lower (entry 7). These results indicate that β-lactams **19a** and **19c** are not very stable under these reaction conditions.

The 1,3-dipolar cycloaddition of 6-benzoylmethylene penicillanate **1b** with phenyldiazomethane at 0 °C for 30 min afforded β-lactam **19b** (30%) together with the cycloadduct **20a** isolated in 11% yield (entry 3). The structural assignment of compound **20a** was made on the basis of 2D NOESY, COSY, HMQC, and HMBC spectra (400 MHz). The NOESY spectrum showed cross peaks between H-3′ and the β-Me protons and between the H-5′ and H-5 protons.

The molecular structure of compound **19b** was unambiguously established by X-ray crystallography (Fig. 2). This derivative crystallized in the monoclinic system within $P2_1$ space group, as colorless plates. In the molecule present in the asymmetric unit, there

Table 3
1,3-Dipolar cycloaddition reaction of phenyldiazomethane with 6-alkylidene penicillanates **1a**–**1d**



Entry	β-Lactam	Reaction conditions	Isolated yield (%)	
			19	**20**
1	**1a**	0 °C, 30 min	40	—
2	**1a**	0 °C, 1 h	34	—
3	**1b**	0 °C, 30 min	30	11
4	**1b**	0 °C, 4 h	35	0,9
5	**1b**	0 °C, 6 h	45	—
6	**1c**	0 °C, 30 min	52	—
7	**1c**	0 °C, 1 h	33	—
8	**1d**	0 °C, 30 min	65	12
9	**1d**	0 °C, 4 h	71	7
10	**1d**	0 °C, 6 h	67	—

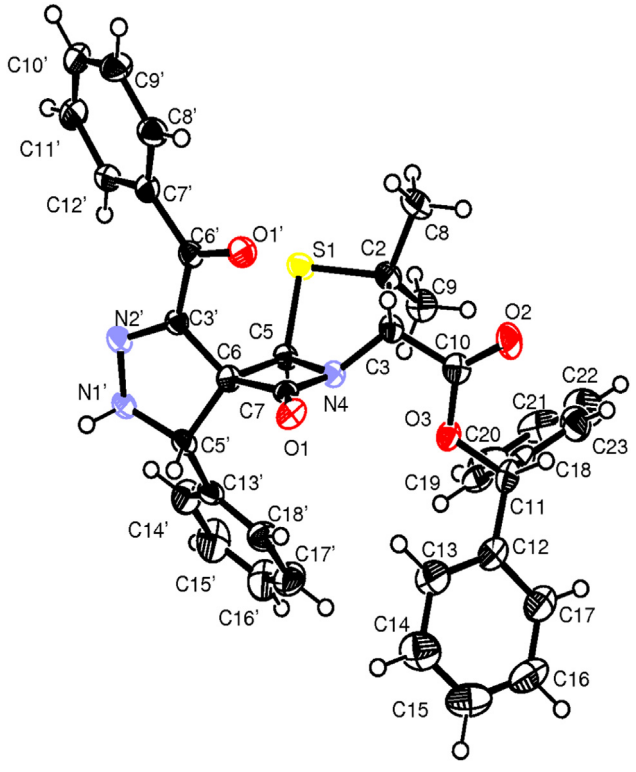
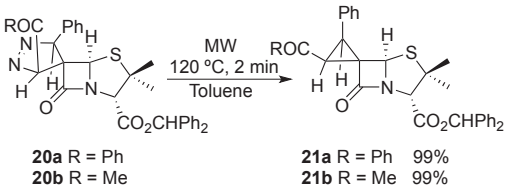


Fig. 2. ORTEP-3 diagram of compound **19b**, using 50% probability level ellipsoids.

are four chiral centers, C3, C5, C6, and C5′, with relative configuration *S*, *R*, *R* and *S*, respectively. The hydrogen atoms bonded to the C3 and C5 carbons of the penicillanate moiety are placed on opposite faces of the fused rings. All distances and angles are within the expected values for similar compounds.

Phenyldiazomethane reacted with 6-acetylmethylene penicillanate **1d** at 0 °C for 30 min, also giving two products, β-lactam **19d** and cycloadduct **20b** in 77% overall yield (entry 8). Spiro-β-lactams **19b** and **19d** were obtained in higher yield when the corresponding 6-alkylidenepenicillanate was allowed to react with phenyldiazomethane for 4 h (entries 4 and 9). Furthermore, by increasing the reaction time to 6 h, β-lactams **19b** and **19d** could be isolated as the only product (entries 5 and 10).

Finally, the quantitative synthesis of chiral spirocyclopropylpenicillanates **21a** and **21b** was also achieved under microwave irradiation (120 °C for 2 min) via the ring contraction reaction of **20a** and **20b**, respectively (Scheme 8). These compounds were isolated by removing the solvent, without need of further purification. The structural assignment of compound **21b** was made on the basis of 2D NOESY, HMQC, and HMBC spectra (400 MHz). From the HMBC spectrum, it was established that the carbon with 38.3 ppm chemical shift corresponds to C-1′, since it shows correlation with the CO*Me* protons. On the other hand, the carbon with 37.8 ppm chemical shift corresponds to C-2′ since it shows correlation with the H-5 proton. Finally, the NOESY spectrum of the compound showed cross peaks between H-2′ and H-5.



Scheme 8. Synthesis of spirocyclopropyl-β-lactams **21** via ring contraction of the corresponding spiro-1-pyrazoline-β-lactams **20**.

3. Conclusion

Spiro-1-pyrazolinepenicillanates were prepared regio- and stereoselectively by the reaction of 6-(*Z*)-(1-methoxycarbonyl methylene)- and 6-(*Z*)-(1-benzoylmethylene)penicillanates with diphenyldiazomethane. However, starting from 6-(*Z*)-(1-*tert*-butoxycarbonylmethylene)penicillanate two products resulting from both regiochemistries were obtained. The 1,3-dipolar cycloaddition reactions of diazomethane with 6-(1-*tert*-butoxycarbonylmethylene)- and 6-(1-methoxycarbonylmethylene)penicillanates also led to two regioisomers, whereas with the acetyl and benzoyl derivatives regiospecificity was observed. Finally, phenyldiazomethane reacted with 6-alkylidenepenicillanates to afford spiropyrazolinepenicillanates regio- and stereoselectively.

All of these cycloaddition reactions of 6-alkylidene penicillanates were stereoselective, which can be explained considering that addition to the less sterically hindered α-side of the β-lactam has occurred.

Finally, microwave-induced ring contraction of spiro-1-pyrazolinepenicillanates to new spirocyclopropylpenicillanates was also achieved. The process was stereospecific, which is an indication that a concerted mechanism must be involved.

4. Experimental section

4.1. General

Microwave reactions were carried out in a microwave reactor CEM Focused Synthesis System Discover S-Class using 10 mL microwave tubes. The reaction temperatures were measured by infrared surface detector during microwave heating. Thin-layer chromatography (TLC) was performed on precoated silica gel plates. Flash chromatography was performed on silica gel 60 as the

stationary phase. ^{1}H NMR spectra were recorded on an instrument operating at 400 MHz. ^{13}C NMR spectra were recorded on an instrument operating at 100 MHz. Chemical shifts are expressed in parts per million (ppm) relatively to internal tetramethylsilane (TMS), and coupling constants (*J*) are in hertz (Hz). Infrared spectra (IR) were recorded on a Fourier Transform spectrometer. Mass spectra were recorded under electrospray ionization (ESI). High-resolution mass spectra (HRMS) spectra were obtained on an electron impact (EI) or electrospray (ESI) TOF mass spectrometer. Melting points were determined in open glass capillaries. Benzhydryl 6-β-aminopenicillanate,[12] benzhydryl 6-oxopenicillinate,[7] 6-alkylidenepenicillanates[3b,6,7] **1a**–**c**, phosphorus ylides,[13] diphenyldiazomethane,[14] phenyldiazomethane,[15] and diazomethane[16] were prepared as described in the literature.

4.2. General procedure for the 1,3-dipolar cycloaddition of 6-alkylidenepenicillanates with diphenyldiazomethane

To a mixture of the appropriate 6-alkylidenepenicillanate (0.40 mmol) in dichloromethane (2 mL), a solution of the diphenyldiazomethane (0.48 mmol) in dichloromethane (3 mL) was added dropwise. The reaction mixture was stirred under nitrogen for the time and temperature indicated in each case. The reaction was monitored by TLC. Upon completion, the solvent was removed under reduced pressure and the crude product was purified by flash chromatography.

*4.2.1. (4′S,6S)-3-Benzhydryl 4′-methoxycarbonyl-5′,5′-diphenyl-4′,5′-dihydrospiro[penicillanate-6,3′-(3H-pyrazole)]-3-carboxylate (**11a**).* Obtained from compound **1a** (509 mg, 1.16 mmol) as described in the general procedure (reaction time: 24 h, temperature reaction: 30 °C). After purification by flash chromatography (hexane/ethyl acetate, 4:1), **11a** was obtained as a yellow oil (552 mg, 0.87 mmol, 75%); $[\alpha]_D^{20}$ +150 (*c* 1, CH_2Cl_2); IR (film) 1786, 1743, 1739, 1600 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (s, 3H, 2α-Me), 1.62 (s, 3H, 2β-Me), 3.06 (s, 3H, CO_2*Me*), 4.22 (s, 1H, H-4′), 4.60 (s, 1H, H-3), 6.19 (s, 1H, H-5), 6.97 (s, 1H, C*H*Ph$_2$), 7.187.36 (m, 18H, Ar–H), 7.55 (d, 2H, ^3J=7.6 Hz, Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.9, 33.1, 50.5, 51.9, 63.2, 69.7, 70.0, 78.5, 105.3, 110.7, 127.2, 127.3, 127.4, 127.6, 127.9, 127.9, 128.3, 128.4, 128.6, 128.6, 128.7, 139.1, 139.1, 139.6, 140.5, 166.1, 166.3, 168.8; HRMS (ESI) *m*/*z*: calcd for $C_{37}H_{33}N_3NaO_5S$ [M+Na$^+$] 654.20331, found 654.20473.

*4.2.2. (4′S,6S)-3-Benzhydryl 4′-benzoyl-5′,5′-diphenyl-4′,5′-dihydrospiro[penicillanate-6,3′-(3H-pyrazole)]-3-carboxylate (**11b**).* Obtained from compound **1b** (243 mg, 0.50 mmol) as described in the general procedure (reaction time: 24 h, temperature reaction: 30 °C). After purification by flash chromatography (hexane/ethyl acetate, 7:1), **11b** was obtained as a yellow oil (31 mg, 0.046 mmol, 9%); IR (film) 1782, 1743, 1673, 1597 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01 (s, 3H), 1.13 (s, 3H), 4.50 (s, 1H), 4.63 (s, 1H), 5.27 (s, 1H), 6.24 (s, 1H), 7.09–8.33 (m, 25H, Ar–H); HRMS (ESI) *m*/*z*: calcd for $C_{42}H_{36}N_3O_4S$ [M+H$^+$] 678.24210, found 678.24237.

*4.2.3. (4′S,6S)-3-Benzhydryl 4′-tert-butoxycarbonyl-5′,5′-diphenyl-4′,5′-dihydrospiro[penicillanate-6,3′-(3H-pyrazole)]-3-carboxylate (**11c**) and (6R)-3-benzhydryl 3′-tert-butoxycarbonyl-5′,5′-diphenyl-1′,5′-dihydrospiro[penicillanate-6,4′-(4H-pyrazole)]-3-carboxylate (**3**).* Obtained from compound **1c** (231 mg, 0.48 mmol) as described in the general procedure (reaction time: 48 h, temperature reaction: 30 °C). Purification of the crude product by flash chromatography (hexane/ethyl acetate, 5:1), gave, in order of elution, **11c** as a yellow oil (148 mg, 0.22 mmol, 46%) and **12** as a yellow oil (32 mg, 0.047 mmol, 10%).

*4.2.3.1. Compound **11c**.* $[\alpha]_D^{20}$ +155 (*c* 1.4, CH_2Cl_2); IR (film) 1786, 1743, 1721, 1601 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (s, 9H, CO_2*t-Bu*), 1.29 (s, 3H, 2α-Me), 1.63 (s, 3H, 2β-Me), 4.15 (s, 1H, H-4′), 4.56 (s, 1H, H-3), 6.23 (s, 1H, H-5), 6.96 (s, 1H, C*H*Ph$_2$), 7.22–7.39 (m, 18H, Ar–H), 7.52 (d, 2H, ^3J=7.6 Hz, Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.2, 27.4, 32.7, 51.2, 63.4, 69.9, 70.0, 78.5, 82.8, 104.4, 110.9, 126.6, 127.0, 127.2, 127.4, 127.6, 127.9, 128.0, 128.4, 128.5, 128.5, 128.7, 128.7, 139.1, 140.7, 143.9, 166.3, 166.5, 167.4; HRMS (ESI) *m*/*z*: calcd for $C_{40}H_{40}N_3O_5S$ [M+H$^+$] 674.26832, found 674.26934.

*4.2.3.2. Compound **12**.* $[\alpha]_D^{20}$ +220 (*c* 0.25, CH_2Cl_2); IR (film) 3415, 1782, 1741, 1736 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07 (s, 3H, 2α-Me), 1.60 (s, 9H, CO_2*t-Bu*), 1.66 (s, 3H, 2β-Me), 4.61 (s, 1H, H-3), 4.78 (s, 1H, H-5), 6.30 (s, 1H, N*H*), 6.79 (s, 1H, C*H*Ph$_2$), 7.16–7.46 (m, 20H, Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.7, 28.2, 29.8, 65.1, 68.4, 69.9, 73.8, 78.1, 82.7, 83.6, 127.2, 127.2, 127.3, 127.4, 127.5, 128.1, 128.2, 128.3, 128.3, 128.4, 128.5, 128.6, 130.1, 138.7, 139.2, 139.3, 142.3, 143.6, 160.9, 166.8, 167.2; HRMS (ESI) *m*/*z*: calcd for $C_{40}H_{40}N_3O_5S$ [M+H$^+$] 674.26832, found 674.26928.

4.3. General procedure for the 1,3-dipolar cycloaddition of 6-alkylidenepenicillanates with diazomethane

To a solution of the appropriate 6-alkylidenepenicillanate (0.40 mmol) in diethyl ether (3 mL) at 0 °C was added an excess of ethereal diazomethane. The reaction mixture was manually stirred for the time indicated in each case and monitored by TLC. Excess of diazomethane was purged with nitrogen and the crude product was purified by flash chromatography.

*4.3.1. (6R)-3-Benzhydryl 3′-methoxycarbonyl-1′,5′-dihydrospiro[penicillanate-6,4′-(4H-pyrazole)]-3-carboxylate (**14a**) and (4′S,6S)-3-benzhydryl 4′-methoxycarbonyl-4′,5′-dihydrospiro[penicillanate-6,3′-(3H-pyrazole)]-3-carboxylate (**15a**).* Obtained from compound **1a** (142 mg, 0.32 mmol) as described in the general procedure (reaction time: 2 h). Purification of the crude product by flash chromatography (hexane/ethyl acetate, 2:1), gave, in order of elution, **15a** as a brown oil (80 mg, 0.17 mmol, 53%) and **14a** as a colorless oil (47 mg, 0.10 mmol, 31%).

*4.3.1.1. Compound **14a**.* $[\alpha]_D^{20}$ +133 (*c* 0.75, CH_2Cl_2); IR (film) 3338, 1790, 1743, 1732 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (s, 3H, 2α-Me), 1.71 (s, 3H, 2β-Me), 3.83 (s, 3H, CO_2*Me*), 4.05 (d, 1H, ^2J=11.6 Hz, H-5′), 4.10 (d, 1H, ^2J=11.6 Hz, H-5′), 4.67 (s, 1H, H-3), 5.34 (s, 1H, H-5), 6.59 (br s, 1H, N*H*), 6.96 (s, 1H, C*H*Ph$_2$), 7.32–7.35 (m, 10H, Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.7, 29.6, 52.4, 57.5, 65.6, 67.3, 69.9, 72.7, 78.5, 126.9, 127.8, 128.2, 128.5, 128.6, 128.7, 138.9, 139.0, 139.2, 162.1, 167.2, 169.8; HRMS (ESI) *m*/*z*: calcd for $C_{25}H_{26}N_3O_5S$ [M+H$^+$] 480.15877, found 480.15859.

*4.3.1.2. Compound **15a**.* $[\alpha]_D^{20}$ +380 (*c* 0.75, CH_2Cl_2); IR (film) 1782, 1743, 1736, 1545 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (s, 3H, 2α-Me), 1.59 (s, 3H, 2β-Me), 3.29 (dd, 1H, ^3J=8.8 and 1.6 Hz, H-4′), 3.67 (s, 3H, CO_2*Me*), 4.63 (dd, 1H, ^2J=18 Hz, ^3J=8.8 Hz, H-5′), 4.64 (s, 1H, H-3), 5.03 (dd, 1H, ^2J=18 Hz, ^3J=1.6 Hz, H-5′), 6.19 (s, 1H, H-5), 6.99 (s, 1H, C*H*Ph$_2$), 7.31–7.38 (m, 10H, Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.7, 32.4, 39.3, 51.7, 62.6, 68.2, 68.4, 77.6, 80.4, 107.5, 126.2, 126.4, 127.3, 127.4, 127.6, 127.7, 138.0, 138.0, 165.1, 166.2, 169.7; HRMS (ESI) *m*/*z*: calcd for $C_{25}H_{26}N_3O_5S$ [M+H$^+$] 480.15877, found 480.15944.

*4.3.2. (6R)-3-Benzhydryl 3′-benzoyl-1′,5′-dihydrospiro[penicillanate-6,4′-(4H-pyrazole)]-3-carboxylate (**14b**) and (3′S,6R)-3-benzhydryl 3′-benzoyl-3′,4′-dihydrospiro[penicillanate-6,4′-(5H-pyrazole)]-3-carboxylate (**16**).* Obtained from compound **1b** (68 mg, 0.14 mmol) as described in the general procedure (reaction time: 30 min). Purification of the crude product by flash chromatography (hexane/ethyl acetate, 3:1), gave, in order of elution, **16** as a white solid

(44 mg, 0.084 mmol, 60%) and **14b** as a yellow pale solid (18 mg, 0.034 mmol, 25%)

*4.3.2.1. Compound **14b**.* Mp 170.9–172.5 °C (decomposes >150 °C) (from hexane/ethyl acetate); $[\alpha]_D^{20}$ +130 (*c* 0.5, CH_2Cl_2); IR (film) 3419, 1786, 1745, 1637 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.22 (s, 3H, 2α-Me), 1.68 (s, 3H, 2β-Me), 4.07–4.15 (m, 2H, H-5′), 4.82 (s, 1H, H-3), 5.40 (s, 1H, H-5), 6.56 (br s, 1H, N*H*), 6.97 (s, 1H, C*H*Ph_2), 7.30–7.55 (m, 13H, Ar–H), 7.99 (d, 2H, ^3J=7.6 Hz, Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.8, 29.7, 56.9, 65.9, 68.1, 70.1, 72.9, 78.4, 126.9, 127.8, 128.1, 128.1, 128.4, 128.6, 128.6, 129.9, 132.5, 137.0, 139.1, 139.2, 146.6, 167.4, 169.8, 187.1; HRMS (ESI) *m*/*z*: calcd for $C_{30}H_{28}N_3O_4S$ [M+H^+] 526.17921, found 526.17950.

*4.3.2.2. Compound **16**.* Mp 183.6–185.0 °C (decomposes> 169 °C) (from hexane/ethyl acetate); $[\alpha]_D^{20}$ +333 (*c* 0.3, CH_2Cl_2); IR (KBr) 1770, 1738, 1664, 1597 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.15 (s, 3H, 2α-Me), 1.49 (s, 3H, 2β-Me), 4.50 (s, 1H, H-3), 5.51 (dd, 1H, ^2J=18 Hz, ^4J=2 Hz, H-5′), 5.36 (d, 1H, ^2J=18 Hz, H-5′), 5.56 (s, 1H, H-5), 6.79 (d, 1H, ^4J=2 Hz, H-3′), 6.94 (s, 1H, C*H*Ph_2), 7.31–7.38 (m, 10H, Ar–H), 7.56–7.60 (m, 2H, Ar–H), 7.67–7.71 (m, 1H, Ar–H), 8.28 (d, 2H, ^4J=7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.3, 31.4, 63.3, 63.5, 69.3, 69.4, 78.5, 82.9, 94.5, 127.0, 127.7, 128.3, 128.5, 128.6, 128.7, 129.1, 129.4, 134.6, 136.1, 138.9, 139.1, 166.8, 174.7, 191.4; HRMS (ESI) *m*/*z*: calcd for $C_{30}H_{28}N_3O_4S$ [M+H^+] 526.17950, found 526.18050.

*4.3.3. (6R)-3-Benzhydryl 3′-tert-butoxycarbonyl-1′,5′-dihydrospiro [penicillanate-6,4′-(4H-pyrazole)]-3-carboxylate (**14c**) and (4′S,6S)-3-benzhydryl 4′-tert-butoxycarbonyl-4′,5′-dihydrospiro[penicillanate-6,3′-(3H-pyrazole)]-3-carboxylate (**15b**).* Obtained from compound **1c** (108 mg, 0.23 mmol) as described in the general procedure (reaction time: 30 min). Purification of the crude product by flash chromatography (hexane/ethyl acetate, 3:1), gave, in order of elution, **14c** as a yellow oil (60 mg, 0.12 mmol, 52%) and **15b** as a yellow solid (43 mg, 0.082 mmol, 36%).

*4.3.3.1. Compound **14c**.* Mp 82.8–84.7 °C; $[\alpha]_D^{20}$ +130 (*c* 1, CH_2Cl_2); IR (KBr) 3350, 1793, 1751, 1701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.24 (s, 3H, 2α-Me), 1.56 (s, 9H, CO_2t-*Bu*), 1.70 (s, 3H, 2β-Me), 4.02 (d, 1H, ^2J=11.2 Hz, H-5′), 4.08 (d, 1H, ^2J=11.2 Hz, H-5′), 4.69 (s, 1H, H-3), 5.34 (s, 1H, H-5), 6.18 (br s, 1H, N*H*), 6.96 (s, 1H, C*H*Ph_2), 7.35 (br s, 10H, Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.8, 28.1, 29.5, 57.3, 65.6, 67.7, 69.9, 72.4, 78.4, 82.3, 126.9, 127.7, 128.2, 128.4, 128.6, 128.6, 139.0, 139.2, 141.5, 161.0, 167.3, 169.6; HRMS (ESI) *m*/*z*: calcd for $C_{28}H_{31}N_3NaO_5S$ [M+Na^+] 544.18766, found 544.18678.

*4.3.3.2. Compound **15b**.* $[\alpha]_D^{20}$ +347 (*c* 0.75, CH_2Cl_2); IR (film) 1776, 1743, 1597 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.31 (s, 3H, 2α-Me), 1.41 (s, 9H, CO_2t-*Bu*), 1.61 (s, 3H, 2β-Me), 3.19 (d, 1H, ^3J=8.4 Hz, H-4′), 4.56 (dd, 1H, ^2J=17.6 Hz, ^3J=8.4 Hz, H-5′), 4.64 (s, 1H, H-3), 4.98 (d, 1H, ^2J=17.6 Hz, H-5′), 6.23 (s, 1H, H-5), 6.99 (s, 1H, C*H*Ph_2), 7.31–7.81 (m, 10H, Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.9, 26.8, 32.2, 40.9, 62.6, 68.3, 68.6, 77.6, 80.2, 82.0, 107.1, 126.1, 126.4, 127.2, 127.4, 127.6, 127.7, 138.1, 165.3, 166.4, 168.0; HRMS (ESI) *m*/*z*: calcd for $C_{28}H_{32}N_3O_5S$ [M+H^+] 522.20572, found 522.20581.

*4.3.4. (6R)-3-Benzhydryl 3′-acetyl-1′,5′-dihydrospiro[penicillanate-6,4′-(4H-pyrazole)]-3-carboxylate (**14d**).* Obtained from compound **1d** (143 mg, 0.34 mmol) as described in the general procedure (reaction time: 30 min). The solvent was removed under reduced pressure and **14d** was obtained as a yellow oil (153 mg, 0.33 mmol, 97%); $[\alpha]_D^{20}$ +120 (*c* 1, CH_2Cl_2); IR (film) 3348, 1784, 1747, 1666 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.22 (s, 3H, 2α-Me), 1.73 (s, 3H, 2β-Me), 2.40 (s, 3H, CO*Me*), 4.03–4.10 (m, 2H, H-5′), 4.76 (s, 1H, H-3), 5.30 (s, 1H, H-5), 6.43 (br s, 1H, N*H*), 6.96 (s, 1H, C*H*Ph_2), 7.31–7.35 (m, 10H, Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.0, 27.8, 29.4, 57.6, 65.5, 66.6, 70.1, 72.5, 78.3, 126.9, 127.8, 128.1, 128.4, 128.6, 128.6, 139.1, 139.3, 147.3, 167.4, 169.9, 192.3; HRMS (ESI) *m*/*z*: calcd for $C_{25}H_{26}N_3O_4S$ [M+H^+] 464.16385, found 464.16386.

4.4. General procedure for the 1,3-dipolar cycloaddition of 6-alkylidenepenicillanates with phenyldiazomethane

To a solution of the appropriate 6-alkylidenepenicillanate (0.40 mmol) in diethyl ether (3 mL) at 0 °C was added an excess of ethereal phenyldiazomethane. The reaction mixture was stirred under nitrogen for the time indicated in each case. The reaction was monitored by TLC. Upon completion, excess of phenyldiazomethane was destroyed with acetic acid. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography, except otherwise indicated.

*4.4.1. (5′S,6R)-3-Benzhydryl 3′-methoxycarbonyl-5′-phenyl-1′,5′-dihydrospiro[penicillanate-6,4′-(4H-pyrazole)]-3-carboxylate (**19a**).* Obtained from compound **1a** (250 mg, 0.57 mmol) as described in the general procedure (reaction time: 30 min). After purification by flash chromatography (hexane/ethyl acetate, 6:1 to hexane/ethyl acetate, 2:1), **19a** was obtained as a colorless oil (130 mg, 0.23 mmol, 40%); $[\alpha]_D^{20}$ +115 (*c* 1.3, CH_2Cl_2); IR (film) 3344, 1786, 1736 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.06 (s, 3H, 2α-Me), 1.64 (s, 3H, 2β-Me), 3.85 (s, 3H, CO_2Me), 4.55 (s, 1H, H-3), 4.76 (s, 1H, H-5), 5.48 (d, 1H, ^3J=2.4 Hz, H-5′), 6.75 (d, 1H, ^3J=2.4 Hz, N*H*), 6.79 (s, 1H, C*H*Ph_2), 7.187.42 (m, 15H, Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.7, 29.5, 59.4, 65.7, 66.7, 69.8, 70.9, 71.7, 78.2, 127.0, 127.3, 127.3, 120.1, 128.3, 128.5, 128.6, 129.1, 132.7, 139.2, 139.3, 140.1, 162.0, 166.7, 169.7; HRMS (ESI) *m*/*z*: calcd for $C_{31}H_{30}N_3O_5S$ [M+H^+] 556.19007, found 556.18920.

*4.4.2. (5′S,6R)-3-Benzhydryl 3′-benzoyl-5′-phenyl-1′,5′-dihydrospiro [penicillanate-6,4′-(4H-pyrazole)]-3-carboxylate (**19b**) and (3′S,5′S,6R)-3-benzhydryl 3′-benzoyl-5′-phenyl-3′,4′-dihydrospiro [penicillanate-6,4′-(5H-pyrazole)]-3-carboxylate (**20a**).* Obtained from compound **1b** (194 mg, 0.40 mmol) as described in the general procedure (reaction time: 30 min). Compound **20a** precipitates during reaction and was recovered by filtration at the end as a white solid (26 mg, 0.043 mmol, 11%). Purification of the crude product by flash chromatography (hexane/ethyl acetate, 6:1 to hexane/ethyl acetate, 2:1), gave **19b** as a white solid (72 mg, 0.12 mmol, 30%).

*4.4.2.1. Compound **19b**.* Mp 172.3–173.5 °C (decomposes >130 °C) (from hexane/ethyl acetate); $[\alpha]_D^{20}$ +120 (*c* 0.5, CH_2Cl_2); IR (KBr) 3330, 1766, 1741, 1628 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.06 (s, 3H, 2α-Me), 1.61 (s, 3H, 2β-Me), 4.70 (s, 1H, H-3), 4.85 (s, 1H, H-5), 5.52 (d, 1H, ^3J=2.4 Hz, H-5′), 6.78 (d, 1H, ^3J=2.4 Hz, N*H*), 6.79 (s, 1H, C*H*Ph_2), 7.187.59 (m, 18H, Ar–H), 8.06 (d, 2H, ^3J=7.2 Hz, Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.9, 29.8, 66.1, 66.9, 70.0, 71.2, 71.7, 78.2, 126.9, 127.3, 128.0, 128.1, 128.2, 128.5, 128.5, 129.2, 130.0, 132.6, 132.9, 136.8, 139.2, 139.4, 147.8, 166.8, 169.9, 187.1; HRMS (ESI) *m*/*z*: calcd for $C_{36}H_{32}N_3O_4S$ [M+H^+] 602.21080, found 602.21162.

*4.4.2.2. Compound **20a**.* Mp 140.8–141.7 °C (from hexane/diethyl ether); $[\alpha]_D^{20}$ +514 (*c* 0.35, CH_2Cl_2); IR (KBr) 1770, 1739, 1670, 1597 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.12 (s, 3H, 2α-Me), 1.43 (s, 3H, 2β-Me), 4.31 (s, 1H, H-3), 5.71 (s, 1H, H-5), 6.14 (br s, 1H, H-5′), 6.82 (s, 1H, C*H*Ph_2), 7.30 (br s, 1H, H-3′), 7.31–7.36 (m, 10H, Ar–H), 7.58-7.62 (m, 2H, Ar–H), 7.68–7.72 (m, 1H, Ar–H), 8.34 (d, 2H,

^3J=7.6 Hz, Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.0, 32.5, 63.5, 68.5, 69.2, 71.2, 78.2, 95.9, 96.1, 127.0, 127.3, 128.0, 128.2, 128.3, 128.6, 128.6, 128.8, 129.0, 129.1, 129.5, 133.3, 134.7, 136.1, 139.1, 139.2, 166.3, 171.8, 191.4; HRMS (ESI) *m/z*: calcd for $C_{36}H_{32}N_3O_4S$ [M+H$^+$] 602.21080, found 602.21202.

*4.4.3. (5′S,6R)-3-Benzhydryl 3′-tert-butoxycarbonyl-5′-phenyl-1′,5′-dihydrospiro[penicillanate-6,4′-(4H-pyrazole)]-3-carboxylate (**19c**).* Obtained from compound **1c** (121 mg, 0.25 mmol) as described in the general procedure (reaction time: 30 min). After purification by flash chromatography (hexane/ethyl acetate, 2:1), **19c** was obtained as a yellow oil (75 mg, 0.13 mmol, 52%); $[\alpha]_D^{20}$ +115 (*c* 1, CH_2Cl_2); IR (film) 3342, 1786, 1735, 1709 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06 (s, 3H, 2α-Me), 1.57 (s, 9H, CO_2t-*Bu*), 1.64 (s, 3H, 2β-Me), 4.57 (s, 1H, H-3), 4.75 (s, 1H, H-5), 5.46 (d, 1H, ^3J=2.8 Hz, H-5′), 6.51 (d, 1H, ^3J=2.8 Hz, N*H*), 6.79 (s, 1H, C*H*Ph$_2$), 7.16–7.43 (m, 15H, Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.8, 28.2, 29.3, 65.6, 66.7, 69.8, 71.1, 71.4, 78.2, 82.5, 127.0, 127.2, 127.4, 128.1, 128.2, 128.5, 128.6, 129.0, 129.1, 133.1, 139.2, 139.4, 142.1, 161.0, 166.8, 169.9; HRMS (ESI) *m/z*: calcd for $C_{34}H_{36}N_3O_5S$ [M+X$^+$] 598.23702, found 598.23766.

*4.4.4. (5′S,6R)-3-Benzhydryl 3′-acetyl-5′-phenyl-1′,5′-dihydrospiro[penicillanate-6,4′-(4H-pyrazole)]-3-carboxylate (**19d**) and (3′S,5′S,6R)-3-benzhydryl 3′-acetyl-5′-phenyl-3′,4′-dihydrospiro[penicillanate-6,4′-(5H-pyrazole)]-3-carboxylate (**20b**).* Obtained from compound **1d** (169 mg, 0.40 mmol) as described in the general procedure (reaction time: 30 min). Compound **20b** precipitates during reaction and is recovered by filtration at the end as a white solid (26 mg, 0.048 mmol, 12%). Purification of the crude product by flash chromatography (hexane/ethyl acetate, 5:1 to hexane/ethyl acetate, 1:1) gave **19d** as a white solid (141 mg, 0.26 mmol, 65%).

*4.4.4.1. Compound **19d**.* Mp 142.8–144.2 °C (from hexane/diethyl ether); $[\alpha]_D^{20}$ +171 (*c* 0.35, CH_2Cl_2); IR (KBr) 3344, 1768, 1753, 1662 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.03 (s, 3H, 2α-Me), 1.66 (s, 3H, 2β-Me), 2.43 (s, 3H, CO*Me*), 4.65 (s, 1H, H-3), 4.72 (s, 1H, H-5), 5.44 (d, 1H, ^3J=2.0 Hz, H-5′), 6.64 (d, 1H, ^3J=2.0 Hz, N*H*), 6.80 (s, 1H, C*H*Ph$_2$), 7.187.41 (m, 15H, Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.9, 27.9, 29.3, 65.7, 66.3, 70.0, 70.2, 71.9, 78.1, 126.9, 127.3, 127.4, 128.0, 128.2, 128.5, 128.5, 129.1, 129.2, 133.0, 139.2, 139.4, 148.3, 166.9, 170.0, 192.5; HRMS (ESI) *m/z*: calcd for $C_{31}H_{30}N_3O_4S$ [M+H$^+$] 540.19515, found 540.19425.

*4.4.4.2. Compound **20b**.* Mp 142.4–143.8 °C (from hexane/diethyl ether); $[\alpha]_D^{20}$ +590 (*c* 1, CH_2Cl_2); IR (KBr) 1770, 1738, 1710, 1595 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.18 (s, 3H, 2α-Me), 1.54 (s, 3H, 2β-Me), 2.66 (s, 3H, CO*Me*), 4.32 (s, 1H, H-3), 5.60 (s, 1H, H-5), 5.93 (s, 1H, H-5′), 6.27 (s, 1H, H-3′), 6.82 (s, 1H, C*H*Ph$_2$), 7.187.33 (m, 15H, Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.0, 32.4, 33.0, 63.6, 68.3, 69.1, 70.6, 78.3, 95.7, 99.7, 127.0, 127.3, 127.9, 128.2, 128.4, 128.6, 128.8, 129.0, 133.1, 139.0, 139.2, 166.2, 171.4, 199.8; HRMS (ESI) *m/z*: calcd for $C_{31}H_{30}N_3O_4S$ [M+H$^+$] 540.19515, found 540.19424.

4.5. General procedure for the synthesis of spirocyclopropyl-β-lactams

A suspension of the appropriate spiro-β-lactam (0.10 mmol) in the appropriate solvent (1 mL) was irradiated in the microwave reactor with the time and temperature indicated in each case. The solvent was removed under reduced pressure, except otherwise indicated.

*4.5.1. (2′S,6S)-3-Benzhydryl 2′-methoxycarbonyl-1′,1′-diphenylspiro[cyclopropane-3′,6-penicillanate]-3-carboxylate (**13a**).* Obtained from compound **11a** (107 mg, 0.17 mmol) as described in the general procedure (reaction time: 2 min, temperature reaction: 120 °C, solvent: toluene). The solvent was removed under reduced pressure and **13a** was obtained as a white solid (100 mg, 0.17 mmol, 99%). Mp 83.9–85.9 °C (from hexane/ethyl acetate); $[\alpha]_D^{20}$ +175 (*c* 1, CH_2Cl_2); IR (KBr) 1788, 1736, 1685 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (s, 3H, 2α-Me), 1.58 (s, 3H, 2β-Me), 3.23 (s, 1H, H-2′), 3.60 (s, 1H, CO_2Me), 4.57 (s, 1H, H-3), 5.87 (s, 1H, H-5), 6.98 (s, 1H, C*H*Ph$_2$), 7.16–7.42 (m, 20H, Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.4, 31.4, 34.2, 48.2, 52.1, 54.3, 62.6, 68.3, 69.3, 78.3, 127.0, 127.6, 127.7, 127.7, 128.1, 128.2, 128.4, 128.6, 128.6, 128.7, 128.8, 128.9, 137.9, 139.2, 139.5, 140.3, 167.4, 167.9, 174.3; HRMS (ESI) *m/z*: calcd for $C_{37}H_{34}NO_5S$ [M+H$^+$] 604.21522, found 604.21668.

*4.5.2. (2′S,6S)-3-Benzhydryl 2′-tert-butoxycarbonyl-1′,1′-diphenylspiro[cyclopropane-3′,6-penicillanate]-3-carboxylate (**13b**).* Obtained from compound **11c** (75 mg, 0.11 mmol) as described in the general procedure (reaction time: 2 min, temperature reaction: 120 °C, solvent: toluene). The solvent was removed under reduced pressure and **13b** was obtained as a yellow oil (63 mg, 0.10 mmol, 91%); $[\alpha]_D^{20}$ +150 (*c* 0.5, CH_2Cl_2); IR (film) 1786, 1743, 1720 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (s, 3H, 2α-Me), 1.33 (s, 3H, CO_2t-*Bu*), 1.58 (s, 3H, 2β-Me), 3.13 (s, 1H, H-2′), 4.56 (s, 1H, H-3), 5.91 (s, 1H, H-5), 6.97 (s, 1H, C*H*Ph$_2$), 7.25–7.40 (m, 20H, Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.7, 26.9, 30.4, 34.2, 47.1, 53.4, 61.6, 67.6, 68.4, 77.2, 81.5, 125.5, 126.0, 126.4, 126.5, 126.5, 126.6, 127.0, 127.1, 127.4, 127.5, 127.6, 127.6, 127.7, 127.8, 127.9, 137.2, 138.2, 138.4, 139.6, 142.8, 165.5, 166.5, 173.7; HRMS (ESI) *m/z*: calcd for $C_{40}H_{40}NO_5S$ [M+H$^+$] 646.26217, found 646.26119.

*4.5.3. (1′S,6R)-3-Benzhydryl 1′-methoxycarbonylspiro[cyclopropane-3′,6-penicillanate]-3-carboxylate (**17a**).* Obtained from compound **15a** (30 mg, 0.063 mmol) as described in the general procedure (reaction time: 2 min, temperature reaction: 200 °C, solvent: 1,2,4-trichlorobenzene). After purification by flash chromatography (hexane to hexane/ethyl acetate, 1:1), **17a** was obtained as a yellow oil (19 mg, 0.042 mmol, 67%); $[\alpha]_D^{20}$ +146 (*c* 1.3, CH_2Cl_2); IR (film) 1784, 1732, 1639 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (s, 3H, 2α-Me), 1.56 (s, 3H, 2β-Me), 1.78 (dd, 1H, ^2J=8.4 Hz, ^3J=6.0 Hz, H-2′), 1.87 (pseudo-t, 1H, ^3J=6.0 Hz, H-1′), 2.40 (dd, 1H, ^2J=8.4 Hz, ^3J=6.0 Hz, H-2′), 3.74 (s, 3H, CO_2Me), 4.55 (s, 1H, H-3), 5.49 (s, 1H, H-5), 6.19 (s, 1H, H-5), 6.95 (s, 1H, C*H*Ph$_2$), 7.30–7.36 (m, 10H, Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.9, 22.9, 24.9, 31.6, 46.5, 51.4, 62.0, 68.2, 68.4, 77.3, 126.0, 126.6, 127.1, 127.3, 127.3, 127.5, 127.6, 129.0, 131.4, 138.2, 138.2, 166.0, 169.2, 174.6; HRMS (ESI) *m/z*: calcd for $C_{25}H_{25}NNaO_5S$ [M+Na$^+$] 474.13456, found 474.13395.

*4.5.4. (1′S,6R)-3-Benzhydryl 1′-benzoylspiro[cyclopropane-3′,6-penicillanate]-3-carboxylate (**17b**).* Obtained from compound **16** (39 mg, 0.074 mmol) as described in the general procedure (reaction time: 2 min, temperature reaction: 200 °C, solvent: 1,2,4-trichlorobenzene). After purification by flash chromatography (hexane to hexane/ethyl acetate, 1:1), **17b** was obtained as a brown oil (11 mg, 0.022 mmol, 30%); $[\alpha]_D^{20}$ +200 (*c* 0.2, CH_2Cl_2); IR (film) 1778, 1745, 1668 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.16 (s, 3H, 2α-Me), 1.47 (s, 3H, 2β-Me), 1.92 (dd, 1H, ^2J=8.4 Hz, ^3J=5.2 HZ, H-2′), 2.09 (pseudo-t, 1H, ^3J=5.2 HZ, H-1′), 3.44 (dd, 1H, ^2J=8.4 Hz, ^3J=5.2 HZ, H-2′), 4.49 (s, 1H, H-3), 5.56 (s, 1H, H-5), 6.95 (s, 1H, C*H*Ph$_2$), 7.28–7.39 (m, 10H, Ar–H), 7.48–7.52 (m, 2H, Ar–H), 7.59–7.63 (m, 1H, Ar–H), 7.99 (d, 1H, ^3J=8.0 Hz, Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.1, 26.0, 26.5, 31.8, 50.9, 63.1, 69.2, 78.3, 126.5, 127.0, 127.6, 128.1, 128.3, 128.3, 128.6, 128.6, 128.7, 133.6, 137.7, 139.2, 139.3, 167.2, 176.2, 196.2; HRMS (ESI) *m/z*: calcd for $C_{30}H_{27}NNaO_4S$ [M+Na$^+$] 520.15530, found 520.15493.

*4.5.5. 3-Benzhydryl 6-(Z)-(1-methoxycarbonylethylene)penicillanate-3-carboxylate (**18a**).* Obtained from compound **15a**

(69 mg, 0.14 mmol) as described in the general procedure (reaction time: 2 min, temperature reaction: 250 °C, solvent: 1,2,4-trichlorobenzene). After purification by flash chromatography (hexane to hexane/ethyl acetate, 4:1), **18a** was obtained as a brown oil (12 mg, 0.027 mmol, 19%); $[\alpha]_D^{20}$ +100 (*c* 0.2, CH_2Cl_2); IR (film) 1768, 1751, 1726 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.25 (s, 3H, 2α-Me), 1.56 (s, 3H, 2β-Me), 2.20 (s, 3H, C1′-*Me*), 3.81 (s, 3H, CO_2Me), 4.63 (s, 1H, H-3), 5.95 (s, 1H, H-5), 6.96 (s, 1H, *CH*Ph_2), 7.34–7.38 (m, 10H, Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.5, 25.6, 33.4, 52.5, 63.5, 69.8, 70.4, 78.3, 126.5, 127.1, 127.6, 128.2, 128.4, 128.5, 128.6, 128.6, 139.2, 139.3, 149.3, 165.6, 167.1, 167.7; HRMS (ESI) *m*/*z*: calcd for $C_{25}H_{25}NNaO_5S$ [M+Na^+] 474.13456, found 474.13425.

*4.5.6. 3-Benzhydryl 6-(Z)-(1-tert-butoxycarbonylethylene)penicillanate-3-carboxylate (**18b**).* Obtained from compound **15b** (36 mg, 0.069 mmol) as described in the general procedure (reaction time: 2 min, temperature reaction: 200 °C, solvent: 1,2,4-trichlorobenzene). After purification by flash chromatography (hexane to hexane/ethyl acetate, 5:1), **18a** was obtained as a brown oil (10 mg, 0.020 mmol, 29%); $[\alpha]_D^{20}$ +75 (*c* 0.15, CH_2Cl_2); IR (film) 1770, 1720, 1697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.28 (s, 3H, 2α-Me), 1.52 (s, 9H, CO_2t-*Bu*), 1.56 (s, 3H, 2β-Me), 2.16 (s, 3H, C1′-*Me*), 4.63 (s, 1H, H-3), 5.92 (s, 1H, H-5), 6.94 (s, 1H, *CH*Ph_2), 7.30–7.39 (m, 10H, Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.5, 25.6, 33.9, 63.6, 70.1, 70.5, 78.3, 82.8, 127.0, 127.5, 128.2, 128.3, 128.6, 130.1, 130.8, 139.3, 148.1, 164.2, 167.0, 168.2; HRMS (ESI) *m*/*z*: calcd for $C_{28}H_{32}NO_5S$ [M+H^+] 494.19957, found 494.20000.

*4.5.7. (1′S,2′R,6R)-3-Benzhydryl 1′-benzoyl-2′-phenylspiro[cyclopropane-3′,6-penicillanate]-3-carboxylate (**21a**).* Obtained from compound **20a** (31 mg, 0.052 mmol) as described in the general procedure (reaction time: 2 min, temperature reaction: 120 °C, solvent: toluene). The solvent was removed under reduced pressure and **21a** was obtained as a yellow oil (27 mg, 0.050 mmol, 99%); $[\alpha]_D^{20}$ +100 (*c* 0.2, CH_2Cl_2); IR (film) 1778, 1747, 1666 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.19 (s, 3H, 2α-Me), 1.50 (s, 3H, 2β-Me), 3.50 (d, 1H, ^3J=6.4 Hz), 3.82 (d, 1H, ^3J=6.4 Hz), 4.50 (s, 1H, H-3), 5.65 (s, 1H, H-5), 6.94 (s, 1H, *CH*Ph_2), 7.24–7.50 (m, 18H, Ar–H), 8.02 (d, 2H, ^3J=7.6 Hz, Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.4, 31.3, 34.9, 38.6, 56.6, 63.1, 69.2, 69.3, 78.3, 127.0, 127.6, 127.7, 127.8, 128.1, 128.4, 128.6, 128.8, 133.7, 135.3, 137.6, 139.2, 139.3, 167.3, 174.2, 195.4; HRMS (ESI) *m*/*z*: calcd for $C_{36}H_{32}NO_4S$ [M+H^+] 574.20466, found 574.20676.

*4.5.8. (1′S,2′R,6R)-3-Benzhydryl 1′-acetyl-2′-phenylspiro[cyclopropane-3′,6-penicillanate]-3-carboxylate (**21b**).* Obtained from compound **20b** (30 mg, 0.056 mmol) as described in the general procedure (reaction time: 2 min, temperature reaction: 120 °C, solvent: toluene). The solvent was removed under reduced pressure and **21b** was obtained as a yellow oil (29 mg, 0.056 mmol, 99%); $[\alpha]_D^{20}$ +222 (*c* 0.45, CH_2Cl_2); IR (film) 1778, 1747, 1701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.23 (s, 3H, 2α-Me), 1.60 (s, 3H, 2β-Me), 2.41 (s, 3H, CO*Me*), 3.12 (d, 1H, ^3J=6.4 Hz), 3.28 (d, 1H, ^3J=6.4 Hz), 4.51 (s, 1H, H-3), 5.53 (s, 1H, H-5), 6.93 (s, 1H, *CH*Ph_2), 7.25–7.34 (m, 15H, Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.4, 31.7, 32.6, 37.8, 38.3, 56.2, 63.2, 69.1, 78.3, 127.0, 127.5, 127.7, 128.2, 128.4, 128.5, 128.6, 128.6, 135.1, 139.1, 139.2, 167.2, 173.9, 203.5; HRMS (ESI) *m*/*z*: calcd for $C_{31}H_{30}NO_4S$ [M+H^+] 512.18901, found 512.18908.

4.6. X-ray diffraction

Crystals of compounds **16** and **19b** were selected, covered with polyfluoroether oil, and mounted on a nylon loop. Crystallographic data for both compounds were collected at the IST using graphite monochromated Mo Kα radiation (λ=0.71073 Å) on a Bruker AXS-KAPPA APEX II diffractometer equipped with an Oxford Cryosystem open-flow nitrogen cryostat, at 150 K. Cell parameters were retrieved using Bruker SMART software and refined using Bruker SAINT on all observed reflections. Absorption corrections were applied using SADABS.[17] Structure solution and refinement were performed using direct methods with the programs SIR97[18] and SIR2004[19] included in the package of programs WINGX-Version 1.80.05[20] and SHELXL.[21] Both crystal structures were refined to convergence, even though the crystal of compound **16** was of poor quality, presenting relatively high R_{int} (0.1269) and low ratio of observed/unique reflections. Non-hydrogen atoms were refined with anisotropic thermal parameters. Except for the NH groups, all hydrogen atoms were inserted in idealized positions and allowed to refine riding on the parent carbon atom with C–H distances of 0.95, 0.98, 0.99, and 1.0 Å for aromatic, methyl, methylene, and methine H atoms, respectively, and with $U_{iso}(H)=1.2U_{eq}(C)$. Graphic presentations were prepared with ORTEP-III.[22] CCDC 993025 (for **16**) and 993026 (for **19b**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

*4.6.1. Crystallographic data for (3′S,6R)-3-benzhydryl 3′-benzoyl-3′,4′-dihydrospiro[penicillanate-6,4′-(5H-pyrazole)]-3-carboxylate (**16**).* $C_{30}H_{27}N_3O_4S$, *M*=525.62, monoclinic, *C* 2 with unit cell, *a*=29.915(6) Å, *b*=5.897(2) Å, *c*=17.503(6) Å, α=90°, β=121.91(2)°, γ=90°, *V*=2621.0(15) $Å^3$. ρ_{calcd}=1.332 g cm^{-3}, *Z*=4, μ=0.165 mm^{-1}. *R*[*I*>2σ(*I*)]=0.1030 and R_w=0.2485 for 2247 independent reflections.

*4.6.2. Crystallographic data for (5′S,6R)-3-benzhydryl 3′-benzoyl-5′-phenyl-1′,5′-dihydrospiro[penicillanate-6,4′-(4H-pyrazole)]-3-carboxylate (**19b**).* $C_{36}H_{31}N_3O_4S$, *M*=601.70, monoclinic, $P2_1$ with unit cell, *a*=10.9401(4) Å, *b*=10.2024(4) Å, *c*=13.9470(6) Å, α=90°, β=94.678(2)°, γ=90°, *V*=1551.51(11) $Å^3$. ρ_{calcd}=1.288 g cm^{-3}, *Z*=2, μ=0.149 mm^{-1}. *R*[*I*>2σ(*I*)]=0.0369 and R_w=0.0781 for 4409 independent reflections.

Acknowledgements

Thanks are due to Fundação para a Ciência e a Tecnologia (SFRH/BD/63622/2009, SFRH/BPD/64423/2009, RECI/QEQ-QIN70189/2012, PEst-OE/QUI/UI0313/2014 and PEst-OE/QUI/UI0100/2013) for financial support. We acknowledge the Nuclear Magnetic Resonance Laboratory of the Coimbra Chemistry Center (www.nmrccc.uc.pt), University of Coimbra for obtaining the NMR data. C.S.B.G. thanks Prof. M. Teresa Duarte for valuable discussions on X-ray crystallography.

Supplementary data

^1H NMR, ^{13}C NMR, NOESY, COSY, HMQC, HMBC and DEPT spectra for selected compounds. ORTEP, bond lengths and angles of compounds **16** and **19b** determined by X-ray crystallography. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2014.03.109.

References and notes

1. (a) Knowles, J. R. *Acc. Chem. Res.* **1985**, *18*, 97–104; (b) Jastrzebski, J. T. B. H.; VanKoten, G. Penicillins In*Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.. Comprehensive Heterocyclic Chemistry II*; Elsevier: Oxford, UK, 1996; Vol. 1B; Chapter 1.20, pp 623–658; (c) Fisher, J. F.; Meroueh, S. O.; Mobashery, S. *Chem. Rev.* **2005**, *105*, 395–424; (d) Pérez-Llarena, F. J.; Bou, G. *Curr. Med. Chem.* **2009**, *16*, 3740–3765; (e) Bebrone, C.; Lassaux, P.; Vercheval, L.; Sohier, J.-S.; Jehaes, A.; Sauvage, E.; Galleni, M. *Drugs* **2010**, *70*, 651–679.
2. (a) Skiles, J. W.; McNeil, D. *Tetrahedron Lett.* **1990**, *31*, 7277–7280; (b) Chen, L.-Y.; Zaks, A.; Chackalamannil, S.; Dugar, S. *J. Org. Chem.* **1996**, *61*, 8341–8343; (c) Wu, G.; Tormos, W. *J. Org. Chem.* **1997**, *62*, 6412–6414; (d) Bari, S. S.; Bhalla, A.

Top. Heterocycl. Chem. **2010**, *22*, 49–99; (e) Singh, G. S.; D'hooghe, M.; De Kimpe, N. *Tetrahedron* **2011**, *67*, 1989–2012; (f) Dadiboyena, S. *Eur. J. Med. Chem.* **2013**, *63*, 347–377.
3. (a) Santos, B. S.; Nunes, S. C. C.; Pais, A. A. C. C.; Pinho e Melo, T. M. V. D. *Tetrahedron* **2012**, *68*, 3729–3737; (b) Santos, B. S.; Pinho e Melo, T. M. V. D. *Eur. J. Org. Chem.* **2013**, *18*, 3901–3909.
4. (a) Sheehan, J. C.; Chacko, E.; Lo, Y. S.; Ponzi, D. R.; Sato, E. *J. Org. Chem.* **1978**, *43*, 4856–4859; (b) Campbell, M. M.; Harcus, R. G.; Ray, S. J. *Tetrahedron Lett.* **1979**, *20*, 1441–1444; (c) Häbich, D.; Metzger, K. *Heterocycles* **1986**, *24*, 289–296.
5. (a) Arrowsmith, J. E.; Greengrass, C. W.; Newman, M. J. *Tetrahedron* **1983**, *39*, 2469–2475; (b) Sandanayaka, V. P.; Prashad, A. S.; Yang, Y.; Thomas Williamson, R.; Lin, Y. I.; Mansour, T. S. *J. Med. Chem.* **2003**, *46*, 2569–2571.
6. (a) Buynak, J. D.; Geng, B.; Bachmann, B.; Hua, L. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1513–1518; (b) Ruddle, C. C.; Smyth, T. P. *Org. Biomol. Chem.* **2007**, *5*, 160–168.
7. Buynak, J. D.; Rao, A. S.; Nidamarthy, S. D. *Tetrahedron Lett.* **1998**, *39*, 4945–4946.
8. (a) Engel, P. S. *Chem. Rev.* **1980**, *80*, 99–150; (b) Pellíssier, H. *Tetrahedron* **2008**, *64*, 7041–7095; (c) Cruz Cruz, D.; Yuste, F.; Rosario Martin, M.; Tito, A.; Garcia Ruano, J. L. *J. Org. Chem.* **2009**, *74*, 3820–3826; (d) Abe, M.; Iwakura, I.; Yabushita, A.; Yagi, S.; Liu, J.; Okamura, K.; Kobayashi, T. *Chem. Phys. Lett.* **2012**, *527*, 79–83.
9. Allen, F. H. *Acta Crystallogr., Sect. B: Struct. Sci.* **2002**, *58*, 380–388.
10. Houk, K. N. *J. Am. Chem. Soc.* **1972**, *94*, 8953–8955.
11. Corbett, D. F. *J. Chem. Soc., Perkin Trans. 1* **1996**, 421–428.
12. Sheehan, J. C.; Commons, T. J. *J. Org. Chem.* **1978**, *43*, 2203–2208.
13. (a) Ramirez, F.; Dershowitz, S. *J. Org. Chem.* **1957**, *22*, 41–45; (b) Giese, B.; Schoch, J.; Rüchardt, C. *Chem. Ber.* **1978**, *111*, 1395–1403.
14. Javed, M. I.; Brewer, M. *Org. Synth.* **2008**, *85*, 189–195.
15. Overberger, C. G.; Anselme, J.-P. *J. Org. Chem.* **1963**, *28*, 592–593.
16. Furniss, B. S.; Hannaford, A. J.; Rogers, V.; Smith, P. W. G.; Tachell, A. R. *Vogel's Textbook of Practical Chemistry*, 4th ed.; Longman: London, UK, 1978; pp 291–292.
17. Sheldrick, G. M. *SADABS, Program for Empirical Absorption Correction*; University of Göttingen: Göttingen, Germany, 1996.
18. Altomare, A.; Burla, M. C.; Camalli, M.; Cascarano, G. L.; Giacovazzo, C.; Guagliardi, A.; Moliterni, A. G. G.; Polidori, G.; Spagna, R. *J. Appl. Crystallogr.* **1999**, *32*, 115–119.
19. SIR 2004 Burla, M. C.; Caliandro, R.; Camalli, M.; Carrozzini, B.; Cascarano, G. L.; De Caro, L.; Giacovazzo, C.; Polidori, G.; Spagna, R. *J. Appl. Crystallogr.* **2005**, *38*, 381–388.
20. Farrugia, L. J. *J. Appl. Crystallogr.* **1999**, *32*, 837–838.
21. (a) Sheldrick, G. M. *SHELX97-Programs for Crystal Structure Analysis (Release 97-2)*; Institüt für Anorganische Chemie der Universität: Tammanstrasse 4, D-3400 Göttingen, Germany, 1998; (b) Sheldrick, G. M. *Acta Crystallogr.* **2008**, *A64*, 112–122.
22. Farrugia, L. J. *J. Appl. Crystallogr.* **1997**, *30*, 565.