Synthesis of Novel Chiral Spiroisoxazolidine-β-Lactams from 6-Alkylidenepenicillanates: A 1,3-Dipolar Cycloaddition Approach

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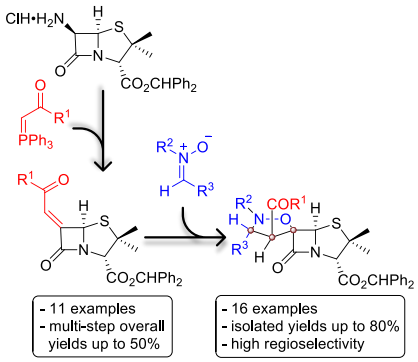


Abstract – The synthesis of a library of 6-alkylidene-β-lactams, derived from 6-aminopenicillanic acid is reported. The 1,3-dipolar cycloaddition of these 6-alkylidenepenicillanates with nitrones was explored as an approach to synthesize novel chiral spiroisoxazolidine-β-lactams. Quantum chemical calculations, at the DFT level of theory, were carried out to elucidate the 3D structure of the synthesized compounds. The reported methodology, which involves the generation of three new consecutive stereogenic centers, proved to be regio- and stereoselective, leading to novel chiral spiroisoxazolidine-penicillanates efficiently.

Keywords: Spiro-β-lactams; Isoxazolidines; Penicillanates; Nitrones; 1,3-Dipolar Cycloaddition.

Introduction

The β-lactam ring is one of the most studied moieties from a synthetic and medicinal chemistry point of view. Since the discovery of penicillins that had a huge impact on medicine, many researchers were inspired and turned their mind to the study of β-lactams.[1]

The use of spirocyclic frameworks is a broadly used strategy in drug design to rigidify a molecule by the fusion of two rings in one shared atom. The three-dimensional nature of spirocyclic compounds provides a good balance of conformational rigidity and flexibility for efficient interaction with a given molecular target. In fact, important interactions of a molecule with a three-dimensional binding site can be achieved more easily using a rigid core (*e.g.* spirocyclic) than a planar one (*e.g.* aromatic systems), making spiro containing compounds relevant in medicinal chemistry.[2]

In the last few years, spiro-β-lactams have attracted the attention of organic chemists since they can be used as building blocks for the synthesis of amino acids, alkaloids and other relevant

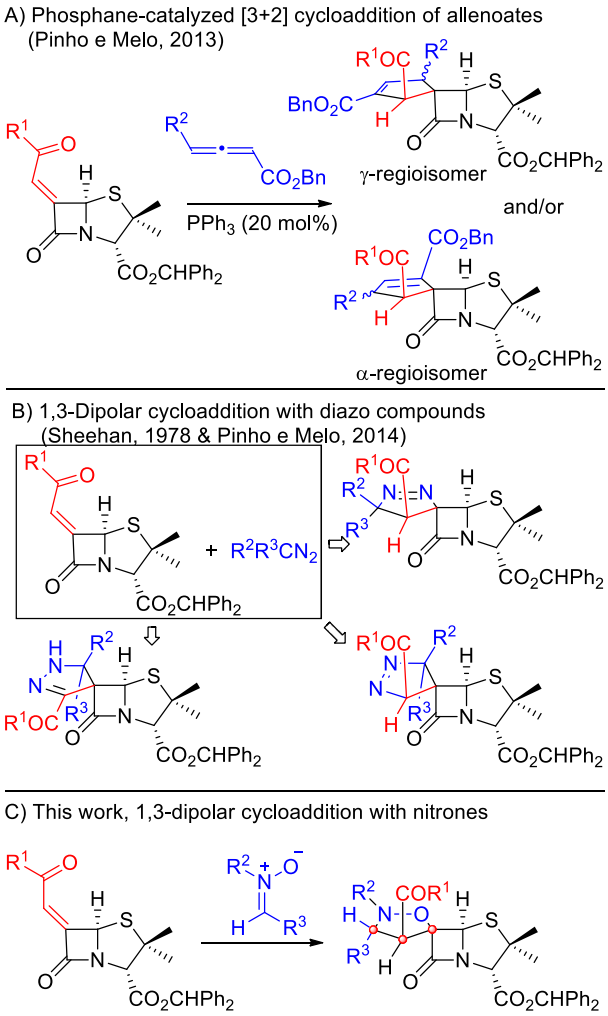
compounds.[3] Furthermore, it is known that spiro-β-lactams are also interesting target molecules due to their relevant biological properties, namely as antibacterial and antiviral agents, and as cholesterol absorption inhibitors.[3a, 3b] Thus, the search of new methodologies for the synthesis of novel spiro-β-lactam derivatives is a relevant research topic.

Pinho e Melo and co-workers described the first and unprecedented phosphine-catalyzed [3+2] annulation of allenoates to 6-alkylidenepenicillanates leading to chiral spirocyclopentenyl-β-lactams (Scheme 1A).[4] On the other hand, 6-alkylidenepenicillanates react with diazo compounds via 1,3-dipolar cycloaddition reactions to afford chiral spiropyrazolinepenicillanates (Scheme 1B).[5] The microwave-induced denitrogenation of the spiro-1-pyrazoline-β-lactams leading to spirocyclopropyl-β-lactams was also reported.[5] Among the set of synthesized spiro-penicillanates, lead compounds with remarkable anti-HIV and anti-*Plasmodium* properties were identified.[6a] The considerable geographic overlap between HIV and *Plasmodium infections*, mainly in sub-Saharan Africa, where coinfection is common, contributes to the spread of both diseases. Moreover, there is a significant risk of drug-drug interactions between anti-retroviral and antimalarial regimens making the identification of this novel class of compounds with potent activity against both infectious agents holds a particularly relevant contribution for the fight against both AIDS and malaria. Several other spiro-penicillanates as well as spiro-γ-lactams, corresponding to the replacement of the four-membered β-lactam ring by the five-membered γ-lactam ring, with moderate to good activity against either HIV or *Plasmodium* were identified. The results suggest that the β-lactam ring is an important structural feature for the activity of these compounds against both HIV and *Plasmodium*.[6b]

We envisaged that adding an additional medicinal chemistry structural motif (*e.g.* isoxazolidines) to the spiro-penicillanate core would lead to interesting scaffolds. Isoxazolidines are heterocyclic compounds known for having a labile N-O bond in the five-membered ring system. Taking advantage of this structural feature it is possible to explore their use as building blocks in organic synthesis namely in the synthesis of 1,3-aminoalcohols.[7] Furthermore, the isoxazolidine system is considered a mimetic of ribose, and can be found as constituent of biologically active compounds, namely nucleoside analogues with anticancer and/or antiviral activities.[8]

The [3+2] nitrone-olefin cycloaddition is an important and versatile synthetic route for the construction of the isoxazolidine ring, being the most explored approach to isoxazolidines.[9] In the late 80s and 90s, some distinct research groups have reported their work on the synthesis of spiroisoxazolidines through dipolar cycloaddition reactions of alkylidene-β-lactams with nitrones.[10] More recently, while exploring the reactivity of alkylidene-β-lactams, Wang and Dao Thi have described the synthesis of novel spiroisoxazolidines from benzaldehyde-derived nitrones.[11] Nevertheless, all these advances were exclusively focused on the reactivity of alkylidenes derived from mono-β-lactams.

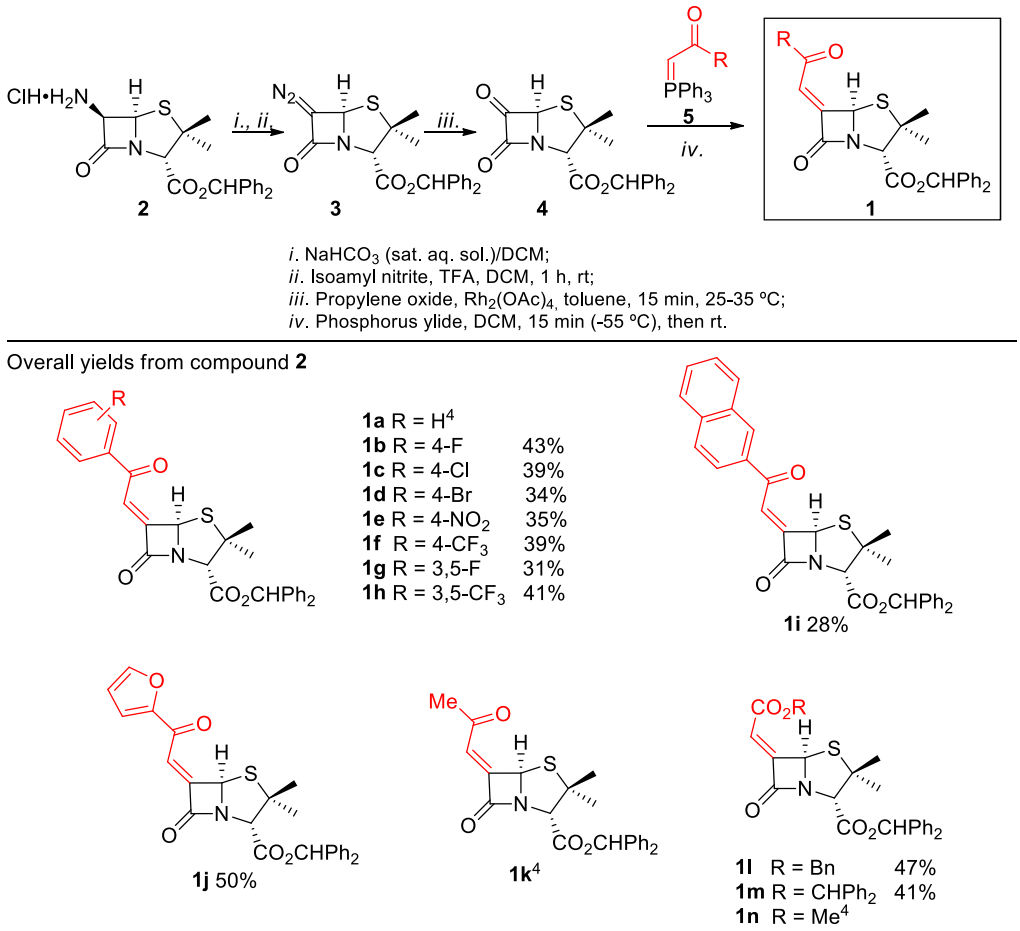
In this context, the 1,3-dipolar cycloaddition of 6-alkylidenepenicillanates with nitrones was explored as a strategy to synthesize novel chiral spiroisoxazolidine-β-lactams incorporating the penicillanate nucleus, a process involving the generation of three new consecutive stereogenic centers, including a quaternary chiral center (Scheme 1C).



Scheme 1. Synthesis of chiral spiro-β-lactams from 6-alkylidenepenicillanates.

Results and Discussion

Our study started with the synthesis of a wide range of 6-alkylidenepenicillanates **1**. 6-Alkylidenepenicillanates **1b-m** were prepared and isolated by a known procedure, having 6-aminopenicillanic acid (6-APA) as starting material, a well-known raw material used for the synthesis of compounds containing the penicillanic core (Scheme 2).[4] This synthetic strategy involves the synthesis of 6-diazopenicillanate **3** from benzhydryl 6-β-aminopenicillanate hydrochloride salt **2** (obtained from 6-APA by a known procedure),[4] followed by rhodium catalyzed oxidation of the diazo derivative in the presence of propylene oxide to give 6-oxopenicillanate **4**. The Wittig reaction of the oxo derivative **4** with the appropriate phosphorus ylide **5** afforded the expected 6-alkylidenepenicillanates **1** in overall yields ranging from 28% to 50% (starting from 6-β-aminopenicillanate **2**). We also carried out the synthesis of the previously described alkylidenes **1a**, **1k** and **1n**.[4]



Scheme 2. Synthesis of 6-alkylidenepenicillanates from benzhydryl 6-β-aminopenicillanate hydrochloride.

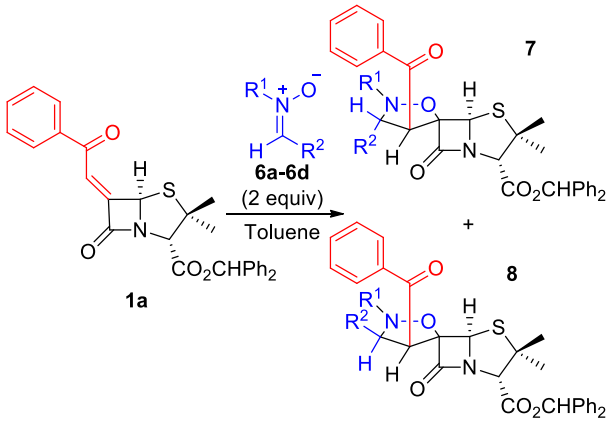
Initial screening of four *C*-aryl-*N*-substituted nitrones **6a**-**6e** with 6-alkylidenepenicillanate **1a** was carried out (Table 1).[12] The synthesis of nitrones **6a**-**6e** was performed following a known procedure, and their structure was assigned as described in the literature and confirmed by NOESY experiments (see supporting information).[13] The reaction of **6a** with **1a** was carried out with excess of nitrone (2 equiv) in toluene at room temperature for 16 hours, and the expected spirocyclic compound **7aa** was obtained in 30% yield together with stereoisomer **8aa** (6% yield). To further optimize the reaction conditions, the temperature was increased to 80 ºC enabling the isolation of compounds **7aa**/**8aa** in 80% overall yield. It is noteworthy that a slight increase in the reaction time to 24 h led to compound **7aa** in even higher yield (70%).

The cycloaddition reaction of nitrone **6b**, bearing a nitro group in *para* position of the aromatic ring, with alkylidene **1a** was also explored under the optimized conditions (Table 1, entry 4), leading to compound **7ba** in 56% yield. However, the analysis of the ^{1}H NMR spectrum of crude of reaction mixture showed that alkylidene **1a** was not all consumed. Therefore, the reaction was carried out with longer reaction time giving, after 70 h, compound **7ba** in 64% yield together with the formation of stereoisomer **8ba** isolated in 10% yield (Table 1, entry 5).

Next, we extended the study to the reactivity of 6-alkylidenepenicillanate **1a** towards other nitrones (**6c**-**6e**). Unfortunately, complex mixtures were obtained from the attempts to carry out the cycloaddition with nitrones **6d** and **6e**. Interestingly, the reaction with nitrone **6c** led to the target spiro-β-lactam **7ca** in 41% yield.

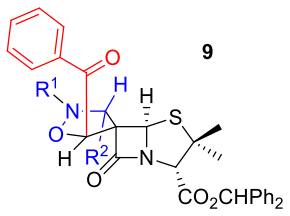
The studied reactions proved to be regioselective. Nevertheless, the formation of regioisomers **9aa** (R^1 = Me, R^2 = Ph), **9ba** (R^1 = Me, R^2 = 4-$NO_2C_6H_4$), and **9ca** (R^1 = Ph, R^2 = Ph) in trace amounts could be detected in the ^{1}H NMR spectra of spiro-β-lactams **8aa**, **7ba** and **8ca** respectively (purification by silica gel flash chromatography was ineffective).

Table 1. Screening of the reactivity of a 6-alkylidenepenicillanate towards different nitrones**.**



Entry	**6** R^1, R^2	Reaction Conditions		Isolated Yields
1	**6a** Me, Ph	rt, 16 h	**7aa**, 30%	**8aa**, 6%[a,b]
2	**6a** Me, Ph	80 ºC, 16 h	**7aa**, 57%	**8aa**, 23%[a,b]
3	**6a** Me, Ph	80 ºC, 24 h	**7aa**, 70%	**8aa**, 11%[a,b]
4	**6b** Me, 4-$NO_2C_6H_4$	80 ºC, 24 h	**7ba**, 56%[a,b]	---
5	**6b** Me, 4-$NO_2C_6H_4$	80 ºC, 70 h	**7ba**, 64%[a,b]	**8ba**, 10%
4	**6c** Ph, Ph	80 ºC, 24 h	**7ca**, 41%[a,b]	---
5	**6d** *t*-Bu, Ph	80 ºC, 24 h		Complex Mixture
6	**6e** Bn, Ph	80 ºC, 24 h		Complex Mixture

[a] Isolated together with the corresponding regioisomer **9**
[b] Yield of the major product determined by ^{1}H NMR

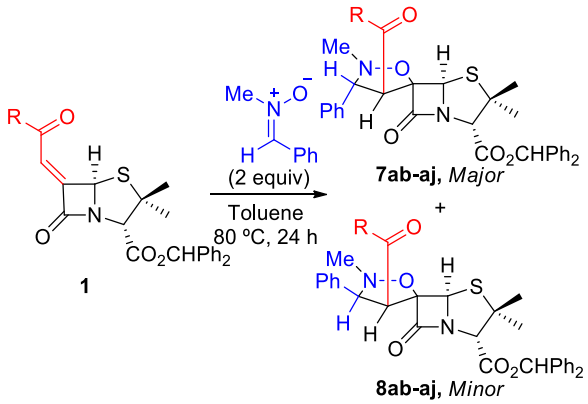


Considering the results obtained regarding the screening of different nitrones, the work was extended to 1,3-dipolar cycloaddition reactions of nitrone **6a** with 6-alkylidenepenicillanates bearing different substituted benzoyl groups (**1b-h**), and derivatives where the aryl group was replaced by other aromatic systems such as naphthalene (**2i**) and furan (**2j**) (Table 2, entries 1-9). To our delight, spiroisoxazolidine-β-lactams **7ab-7ag**, **7ai-7aj** were obtained as major products,

which were isolated as pure stereoisomers in yields ranging from 43 to 69%. In contrast, spiroisoxazolidine-β-lactam **7ah** was obtained in lower yield (26%) and could not be isolated in pure form. From these reaction stereoisomers **8ab**-**8aj** were also obtained as minor products (9-27%).

The reactivity of 6-alkylidenepenicillanate **1k**, bearing an acetyl group substituent, towards nitrone **6a** was also studied (Table 2, entry 10). The same stereoselectivity pattern was observed with the synthesis of chiral spiroisoxazolidine-β-lactams **7ak** and **8ak** in 30% and 7% yields, respectively.

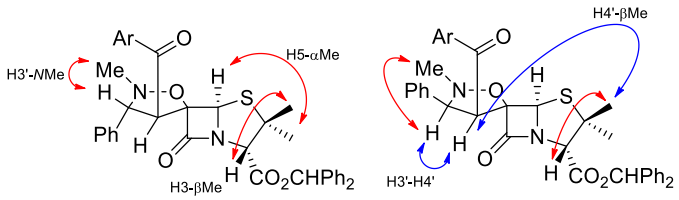
Table 2. 1,3-Dipolar cycloaddition of nitrone **6a** with alkylidenes **1b-k**.



Entry	**1**, R		Products, Isolated Yields	
1	**1b**	*p*-FC_6H_4	**7ab**, 66%	**8ab**, 13%[a,b]
2	**1c**	*p*-ClC_6H_4	**7ac**, 69%	**8ac**, 10%
3	**1d**	*p*-BrC_6H_4	**7ad**, 43%	**8ad**, 12%
4	**1e**	*p*-$NO_2C_6H_4$	**7ae**, 57%	**8ae**, 27%[a,b]
5	**1f**	*p*-$CF_3C_6H_4$	**7af**, 53%	**8af**, 11%
6	**1g**	3,5-$(F)_2C_6H_3$	**7ag**, 62%	**8ag**, 14%
7	**1h**	3,5-$(CF_3)_2C_6H_3$	**7ah**, 26%[a,b]	**8ah**, 9%[a,b]
8	**1i**	2-Naphthyl	**7ai**, 73%	**8ai**, 10%[a,b]
9	**1j**	2-Furyl	**7aj**, 67%	**8aj**, 13%[a,b]
10	**1k**	Me	**7am**, 30%	**8am**, 7%

[a] Isolated together with the corresponding regioisomer **9**
[b] Yield of the major product determined by ^{1}H NMR

The stereochemistry of the *major* (**7**) and *minor* (**8**) adducts was determined based on two-dimensional NOE spectra (NOESY) (Figure 1). The NOESY spectrum of compound **7af** did not show any correlation between isoxazolidine ring protons and penicillanate core protons. However, cross-peaks were observed between protons within the penicillanate core (H3-βMe and H5-αMe) as well as between protons of the isoxazolidine ring (H3'-*N*Me). Some of these correlations were also observed in the NOESY spectrum of compound **8af** (shown as red arrows) which further revealed cross-peaks between proton H3' (δ = 4.47 ppm) and proton H4' (δ = 4.78 ppm) confirming their *cis* configuration, and the latter proton showed correlation with protons of the β-methyl group of the penicillanate core (δ = 1.44 ppm). However, no cross-peaks were observed between protons H5 and α-Me. The observed correlations were in agreement with the estimated internuclear distances values (see below).



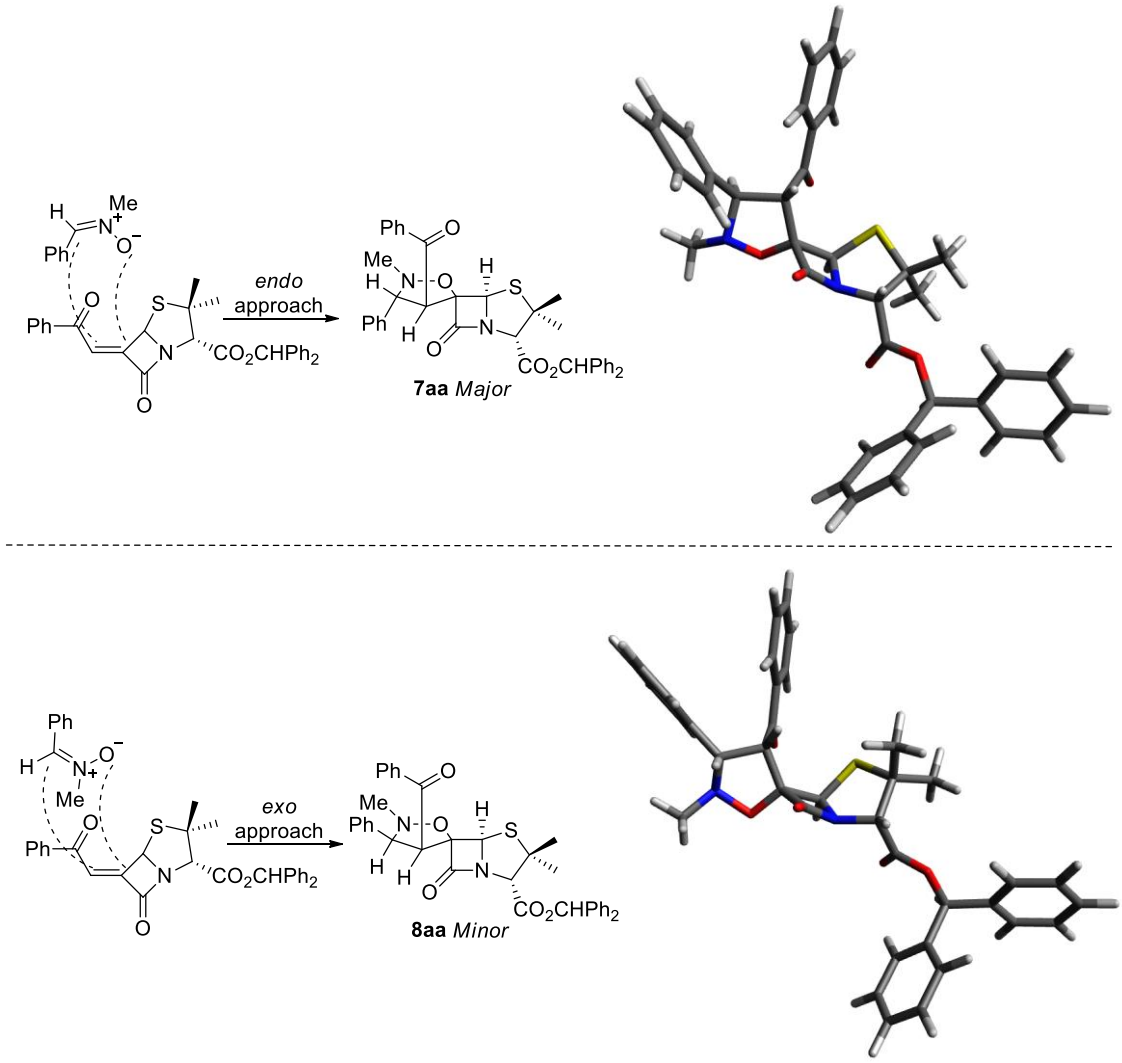
7af Ar = *p*-$CF_3C_6H_4$ **8af** Ar = *p*-$CF_3C_6H_4$

Figure 1. NOESY correlations of compounds **7af** and **8af**.

The bicyclic β-lactam-thiazolidine ring system of the penicillin core exists in a butterfly-like structure. This has been supported by X-ray crystallography studies, namely by the X-ray structure of 6-APA[14] and by the X-ray structure of some spiropyrazolinepenicillanates.[12] Thus, the approach of a given reactant by the convex face (α-side) of the penicillin derivative is usually more favourable. This is in agreement with the stereoselectivity observed in the 1,3-dipolar cycloaddition of 6-alkylidenepenicillanates with nitrones where the major product results from the addition of the dipole to the less sterically hindered α-side of the penicillanates. Furthermore, these spiroisoxazolidine-β-lactams **7** were obtained via an *endo* cycloaddition.

Quantum chemical calculations, at the DFT level of theory (B3LYP/6-31G(d)), were carried out to determine the 3D structure of spiroisoxazolidine-β-lactams **7aa** and **8aa**. The optimized geometries revealed that these novel structures also have a butterfly-like structure with a more open shape in the case of β-lactam **7aa**. Moreover, the *endo* product (**7aa**) was estimated to be 7.03 kJ/mol more stable than the *exo* adduct (**8aa**) which corroborates the experimental results (Scheme 3).

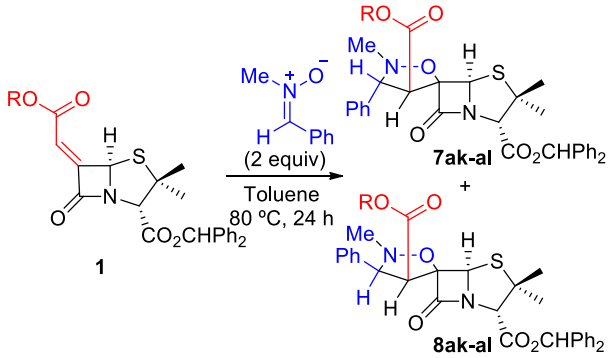
In order to support the NOESY correlations, internuclear distance values were estimated from the optimized structures of derivatives **7aa** and **8aa**. The distance between H3'-*N*Me and H3-βMe, in which cross-peaks were observed for both spiroisoxazolidine-β-lactams **7af** and **8af**, are similar in both cases (**7aa:** 2,376 Å; **8aa**: 2,387 Å and **7aa:** 2,416 Å; **8aa**: 2, 576 Å, respectively). Major differences were observed in the distances between H5-αMe and H4'-βMe (**7aa:** 2,713 Å; **8aa**: 4,126 Å and **7aa:** 4,824 Å; **8aa**: 3,025 Å, respectively) resulting from the more folded structure of the penicillanate core in **8aa**. Therefore, cross-peaks between H5-αMe were only observed for compound **7aa** whereas the correlation H4'-βMe was only observed for compound **8aa**.



Scheme 3. *Endo* and *exo*-cycloaddition of alkylidene **1a** with nitrone **6a**, considering the approach of the dipole by the α-face. Optimized geometries (B3LYP/6-31G(d) level) of *endo*-adducts **7aa** and **8aa**.

The reaction could be readily extended to alkylidenes bearing a carboxylate substituent (**1l-n**), as exemplified by the synthesis of spiro-β-lactams **7al-an** and **8al-an** (Table 3). The major products **7al-an** were obtained efficiently (51-80% yield) and also resulted from an *endo* 1,3-dipolar cycloaddition with addition of the nitrone to the α-side of the β-lactams. The stereoisomeric *exo*-cycloadducts **8al-an** were isolated as minor products (10 -16% yield). Noteworthy is the cycloaddition with the most hindered 6-alkylidenepenicillanate **1m**, bearing a benzhydryl group, which led to our best result (entry 2), affording compound **7am** in 80% yield and its stereoisomer **8am** in 10% yield, corresponding to 90% overall yield.

Table 3. 1,3-Dipolar cycloaddition of nitrone **6a** with alkylidenes **1l-n**



Entry	**1**, R		Products, Isolated Yields	
1	**1l**	Bn	**7al**, 51%	**8al**, 15%[a,b]
2	**1m**	$CHPh_2$	**7am**, 80%	**8am**,10%[a,b]
3	**1n**	Me	**7an**, 57%	**8an**,16%[a,b]

[a] Isolated together with the corresponding regioisomer **9**

[b] Yield of the major product determined by ^{1}H NMR

Conclusions

In summary, we have described the synthesis of a wide range of alkylidenepenicillanates which were used to explore the synthesis of novel spiro-β-lactams through a 1,3-dipolar cycloaddition approach. The novel spiroisoxazolidine-penicillanates, containing four consecutive stereogenic centers, were synthesized in high overall yield using mild conditions. Due to the nature of the final products, the reported synthetic methodology opens the way to the construction of novel molecules with potential biological activity.

Experimental Section

Chemistry

General Information

Thin-layer chromatography (TLC) analyses were performed using precoated silica gel plates. Flash column chromatography was performed with silica gel 60 as the stationary phase. ^{1}H NMR spectra were recorded on an instrument operating at 400 MHz and ^{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. Infrared spectra (IR) were recorded in a Fourier Transform spectrometer coupled with a diamond Attenuated Total Reflectance (ATR) sampling accessory. Elemental analyses were carried out with an Elemental Vario Micro Cube analyser. High-resolution mass spectra (HRMS) were obtained on a TOF VG Autospect M spectrometer with electrospray ionization (ESI) or electronic impact (EI). Benzhydryl 6-β-aminopenicillanate hydrochloride salt (**2**), benzhydryl 6-diazopenicillinate (**3**), benzhydryl 6-oxopenicillinate (**4**), and nitrones **6a-d** and **11** were prepared as described in the literature.[4, 12]

General Procedure for the Synthesis of 6-Alkylidenepenicillanates

Benzhydryl 6-oxopenicillinate **4** (2.38 mmol) was dissolved in dichloromethane (12 mL), the solution was cooled to –55 °C under nitrogen, and the appropriate phosphorus ylide (2.26 mmol) in dichloromethane (30 mL) was added dropwise. Stirring was continued for 15 min, then the

solution was warmed to room temperature and washed with water (20 mL). The organic layer was separated, dried, and concentrated under reduced pressure. The products were purified by flash chromatography. The presented yields were global and calculated from benzhydryl 6-β-aminopenicillanate hydrochloride.

(2*S*,5*R*,*Z*)-Benzhydryl 6-(2-(4-fluorophenyl)-2-oxoethylidene)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate (1b)

Prepared from 6-oxopenicillanate (2.38 mmol) and the corresponding phosphorus ylide (0.90 g, 2.26 mmol), as described in the general procedure. After purification by flash chromatography (hexane/ethyl acetate, 3:1), compound **1b** was obtained as a yellow solid (509 mg, 1.015 mmol, 43%). mp low melting point solid. $[\alpha]_D^{25}$= + 290 (*c* 0.5 in CH_2Cl_2) IR (ATR): ν = 1011, 1154, 1228, 1593, 1636, 1735, 1741, 1770 and 1772 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.28 (s, 3H), 1.58 (s, 3H), 4.68 (s, 1H), 6.15 (s, 1H), 6.97 (s, 1H), 7.19 (t, *J* = 8.6 Hz, 2H), 7.29-7.42 (m, 11H), 8.02 (dd, *J* = 5.3 and 8.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.6, 33.6, 63.9, 69.8, 71.3, 78.6, 115.9, 116.4 (d, *J* = 22 Hz, 1C), 127.2, 127.7, 128.4, 128.5, 128.8, 128.8, 131.6 (d, *J* = 10 Hz, 1C), 133.6 (d, *J* = 3 Hz, 1C), 139.2, 139.3, 156.8, 166.5 (d, *J* = 256 Hz, 1C), 166.9, 167.4, 186.8. ^{19}F NMR (376 MHz, $CDCl_3$): 102.74 (s, 1F). Anal. Calcd for $C_{29}H_{24}NO_4SF$: C, 69.45; H, 4.82; N, 2.79; S, 6.39. Found: C, 69.43; H, 5.04; N, 2.76; S, 6.28.

(2*S*,5*R*,*Z*)-Benzhydryl 6-(2-(4-chlorophenyl)-2-oxoethylidene)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate (1c)

Prepared from 6-oxopenicillanate (2.38 mmol) and the corresponding phosphorus ylide (0.937 g, 2.26 mmol), as described in the general procedure. After purification by flash chromatography (hexane/ethyl acetate, 3:1), compound **1c** was obtained as a yellow solid (486 mg, 0.938 mmol, 39%). mp low melting point solid. $[\alpha]_D^{25}$= + 280 (*c* 0.5 in CH_2Cl_2) IR (ATR): ν = 1007, 1233, 1587, 1636, 1735, 1741 and 1772 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.29 (s, 3H), 1.58 (s, 3H), 4.69 (s, 1H), 6.15 (d, *J* = 0.9 Hz, 1H), 6.98 (s, 1H), 7.30-7.42 (m, 11H), 7.48-7.52 (m, 2H), 7.91-7.95 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.6, 33.6, 63.9, 69.8, 71.2, 78.6, 115.8, 127.2, 127.7, 128.4, 128.5, 128.8, 128.8, 129.5, 130.1, 135.4, 139.2, 140.9, 157.0, 166.8, 167.3, 187.2. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{29}H_{25}ClNO_4S$ $[M+H]^+$ 518.1187; found 518.1188.

(2*S*,5*R*,*Z*)-Benzhydryl 6-(2-(4-bromophenyl)-2-oxoethylidene)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate (1d)

Prepared from 6-oxopenicillanate (2.38 mmol) and the corresponding phosphorus ylide (1.038 g, 2.26 mmol), as described in the general procedure. After purification by flash chromatography (hexane/ethyl acetate, 3:1), compound **1d** was obtained as a light yellow solid (461 mg, 0.82 mmol, 34%). mp 135.4 – 137.2 ºC. $[\alpha]_D^{25}$= + 220 (*c* 0.5 in CH_2Cl_2). IR (ATR): ν = 1005, 1265, 1583, 1631, 1719, 1749 and 1758 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.28 (s, 3H), 1.58 (s, 3H), 4.68 (s, 1H), 6.14 (d, *J* = 0.9 Hz, 1H), 6.97 (s, 1H), 7.30-7.42 (m, 11H), 7.67 (d, *J* = 8.6 Hz, 2H), 7.85 (d, *J* = 8.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.6, 33.6, 64.0, 69.8, 71.3, 78.6, 115.7, 127.3, 127.7, 128.4, 128.5, 128.8, 128.8, 129.8, 130.2, 132.6, 135.8, 139.2, 139.3, 157.1, 166.8, 167.3, 187.4. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{29}H_{25}BrNO_4S$ $[M+H]^+$ 562.0682; found 562.0693.

(2*S*,5*R*,*Z*)-Benzhydryl 6-(2-(4-nitrophenyl)-2-oxoethylidene)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate (1e)

Prepared from 6-oxopenicillanate (2.38 mmol) and the corresponding phosphorus ylide (0.96 g, 2.26 mmol), as described in the general procedure. After purification by flash chromatography (hexane/ethyl acetate, 3:1), compound **1e** was obtained as a yellow solid (445 mg, 0.842 mmol, 35%). mp 68,3 – 70,3 ºC. $[\alpha]_D^{25}$= + 270 (*c* 0.5 in CH_2Cl_2). IR (ATR): ν = 1009, 1223, 1341, 1523, 1735, 1741 and 1773 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.29 (s, 3H), 1.59 (s, 3H), 4.71 (s, 1H), 6.15 (d, *J* = 0.9 Hz, 1H), 6.98 (s, 1H), 7.31-7.41 (m, 11H), 8.11-8.16 (m, 2H), 8.35-8.39 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.5, 33.8, 64.1, 69.8, 71.3, 78.7, 115.2, 124.4, 127.2, 127.7, 128.4, 128.6, 128.8, 128.8, 129.8, 139.2, 139.3, 141.3, 150.9, 158.6, 166.7, 166.8, 187.0. Anal. Calcd for $C_{29}H_{24}N_2O_6S$: C, 65.90; H, 4.58; N, 5.30; S, 6.07. Found: C, 66.02; H, 4.83; N, 5.11; S, 6.07.

(2*S*,5*R*,*Z*)-Benzhydryl 3,3-dimethyl-7-oxo-6-(2-oxo-2-(4-(trifluoromethyl)phenyl)ethylidene)-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate (1f)

Prepared from 6-oxopenicillanate (2.38 mmol) and the corresponding phosphorus ylide (1.013 g, 2.26 mmol), as described in the general procedure. After purification by flash chromatography (hexane/ethyl acetate, 4:1), compound **1f** was obtained as a yellow solid (518 mg, 0.94 mmol, 39%). mp low melting point solid. $[\alpha]_D^{25}$= + 270 (*c* 0.5 in CH_2Cl_2). IR (ATR): ν = 1010, 1168, 1319, 1735, 1741, 1744 and 1773 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.29 (s, 3H), 1.59 (s, 3H), 4.70 (s, 1H), 6.16 (d, *J* = 0.9 Hz, 1H), 6.98 (s, 1H), 7.30-7.40 (m, 11H), 7.79 (d, *J* = 8.3 Hz, 2H), 8.09 (d, *J* = 8.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.6, 33.7, 64.0, 69.8, 71.3, 78.7, 115.6, 126.2, 126.3, 127.3, 127.7, 128.4, 128.6, 128.8, 128.8, 129.1, 139.2, 139.3, 139.6, 157.8, 166.8, 187.6. ^{19}F NMR (376 MHz, $CDCl_3$): 63.24 (s, 3F). Anal. Calcd for $C_{30}H_{24}F_3NO_4S$: C, 65.33; H, 4.39; N, 2.54; S, 5.81. Found: C, 65.60; H, 4.39; N, 2.47; S, 5.05.

(2*S*,5*R*,*Z*)-Benzhydryl 6-(2-(3,5-difluorophenyl)-2-oxoethylidene)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate (1g)

Prepared from 6-oxopenicillanate (2.38 mmol) and the corresponding phosphorus ylide (0.94 g, 2.26 mmol), as described in the general procedure. After purification by flash chromatography (hexane/ethyl acetate, 3:1), compound **1g** was obtained as a white solid (386 mg, 0.743 mmol, 31%). mp 150,8 – 152,8 ºC. $[\alpha]_D^{25}$= + 290 (*c* 0.5 in CH_2Cl_2). IR (ATR): ν = 1066, 1121, 1251, 1297, 1593, 1640, 1719 and 1758 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.29 (s, 3H), 1.58 (s, 3H), 4.69 (s, 1H), 6.14 (d, *J* = 1.0 Hz, 1H), 6.97 (s, 1H), 7.09 (tt, *J* = 2.3 and 8.3 Hz, 1H), 7.25 (d, *J* = 1.0 Hz, 1H), 7.27-7.42 (m, 10H), 7.46-7.52 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.6, 33.7, 64.0, 69.8, 71.3, 78.7, 109.6 (t, *J* = 25 Hz, 1C), 111.7 (d, *J* = 19 Hz, 1C), 111.8 (d, *J* = 18 Hz, 1C), 115.1, 127.2, 127.7, 128.4, 128.6, 128.8, 128.8, 139.2, 139.3, 139.8 (t, *J* = 8 Hz, 1C), 158.2, 163.3 (d, *J* = 251 Hz, 1C), 163.4 (d, *J* = 251 Hz, 1C), 166.8, 166.9, 186.0. ^{19}F NMR (376 MHz, $CDCl_3$): 106.90 (s, 2F). Anal. Calcd for $C_{29}H_{23}F_2NO_4S$: C, 67.04; H, 4.46; N, 2.70; S, 6.17. Found: C, 66.93; H, 4.33; N, 2.63; S, 5.61.

(2*S*,5*R*,*Z*)-Benzhydryl 6-(2-(3,5-bis(trifluoromethyl)phenyl)-2-oxoethylidene)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate (1h)

Prepared from 6-oxopenicillanate (2.38 mmol) and the corresponding phosphorus ylide (1.167 g, 2.26 mmol), as described in the general procedure. After purification by flash chromatography (hexane/ethyl acetate, 4:1), compound **1h** was obtained as a yellow solid (601 mg, 0.97 mmol, 41%). mp low melting point solid. $[\alpha]_D^{25}$= + 230 (*c* 0.5 in CH_2Cl_2). IR (ATR): ν = 1074, 1132, 1277, 1456, 1647, 1744 and 1773 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.30 (s, 3H), 1.59 (s, 3H), 4.72 (s, 1H), 6.17 (d, *J* = 0.8 Hz, 1H), 6.98 (s, 1H), 7.30-7.41 (m, 11H), 8.13 (s, 1H), 8.42

(s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.5, 33.9, 64.0, 69.8, 71.3, 78.7, 114.5, 122.9 (q, *J* = 273 Hz, 2C), 124.2, 127.2, 127.7, 128.4, 128.6, 128.7, 128.8, 128.8, 133.0 (q, *J* = 34 Hz, 2C), 138.4, 139.2, 139.3, 159.4, 166.6, 166.7, 185.8. ^{19}F NMR (376 MHz, $CDCl_3$): 63.02 (s, 6F). HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{31}H_{24}F_6NO_4S$ $[M+H]^+$ 620.1325; found 620.1321.

(2*S*,5*R*,*Z*)-Benzhydryl 3,3-dimethyl-6-(2-(naphthalen-2-yl)-2-oxoethylidene)-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate (1i)

Prepared from 6-oxopenicillanate (2.38 mmol) and the corresponding phosphorus ylide (0.973 g, 2.26 mmol), as described in the general procedure. After purification by flash chromatography (hexane/ethyl acetate, 3:1), compound **1i** was obtained as a yellow solid (355 mg, 0.66 mmol, 28%). mp 100,7 – 102,7 ºC. $[\alpha]_D^{25}$= + 250 (*c* 0.5 in CH_2Cl_2). IR (ATR): ν = 997, 1126, 1252, 1457, 1623, 1719, 1769 and 1771 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.30 (s, 3H), 1.60 (s, 3H), 4.70 (s, 1H), 6.21 (d, *J* = 0.9 Hz, 1H), 6.98 (s, 1H), 7.32-7.40 (m, 10H), 7.57-7.68 (m, 3H), 7.88-8.00 (m, 3H), 8.05 (dd, J = 1.7 and 8.6 Hz, 1H), 8.52 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.6, 33.6, 63.9, 69.9, 71.3, 78.6, 116.4, 123.9, 127.2, 127.3, 127.7, 128.1, 128.3, 128.5, 128.7, 128.8, 129.2, 129.4, 130.0, 131.1, 132.6, 134.6, 136.1, 139.3, 139.4, 156.3, 166.9, 167.7, 188.2. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{33}H_{28}NO_4S$ $[M+H]^+$ 534.1734; found 534.1734.

(2*S*,5*R*,*Z*)-Benzhydryl 6-(2-(furan-2-yl)-2-oxoethylidene)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate (1j)

Prepared from 6-oxopenicillanate (2.38 mmol) and the corresponding phosphorus ylide (0.837 g, 2.26 mmol), as described in the general procedure. After purification by flash chromatography (hexane/ethyl acetate, 3:1), compound **1j** was obtained as a yellow solid (562 mg, 1.18 mmol, 50%). mp low melting point solid. $[\alpha]_D^{25}$= + 290 (*c* 0.5 in CH_2Cl_2). IR (ATR): ν = 1153, 1251, 1458, 1560, 1566, 1629, 1636, 1735, 1741, 1770 and 1772 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.28 (s, 3H), 1.57 (s, 3H), 4.68 (s, 1H), 6.18 (d, *J* = 1.0 Hz, 1H), 6.62 (dd, *J* =1.6 and 3.6 Hz, 1H), 6.97 (s, 1H), 7.23 (d, *J* = 1.1 Hz, 1H), 7.31-7.41 (m, 11H), 7.68 (dd, *J* = 0.5 and 1.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.5, 33.8, 63.8, 69.8, 71.2, 78.6, 113.3, 116.4, 119.5, 127.2, 127.7, 128.3, 128.5, 128.7, 128.8, 139.3, 139.4, 148.0, 153.4, 156.2, 166.9, 167.4, 176.2. Anal. Calcd for $C_{27}H_{23}NO_5S$: C, 68.48; H, 4.90; N, 2.96; S, 6.77. Found: C, 68.44; H, 5.02; N, 3.09; S, 6.66.

(2*S*,5*R*,*Z*)-benzhydryl 6-(2-(benzyloxy)-2-oxoethylidene)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate (1l)

Prepared from 6-oxopenicillanate (2.38 mmol) and the corresponding phosphorus ylide (0.927 g, 2.26 mmol), as described in the general procedure. After purification by flash chromatography (hexane/ethyl acetate, 4:1), compound **1m** was obtained as a white oil (576 mg, 0.976 mmol, 41%). $[\alpha]_D^{25}$= + 270 (*c* 0.5 in CH_2Cl_2). IR (film): ν = 1066, 1153, 1170, 1249, 1453, 1496, 1719, 1774 and 2966 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.25 (s, 3H), 1.55 (s, 3H), 4.64 (s, 1H), 5.22 (s, 2H), 6.00 (d, *J* = 1.0 Hz, 1H), 6.33 (d, *J* =1.1 Hz, 1H), 6.94 (s, 1H), 7.32-7.38 (m, 15H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.5, 33.8, 64.1, 67.6, 69.3, 70.9, 77.5, 115.8, 127.2, 127.6, 128.4, 128.5, 128.7, 128.8, 128.8, 128.8, 128.8, 135.1, 139.2, 139.3, 157.1, 163.7, 166.4, 166.8. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{30}H_{28}NO_5S$ $[M+H]^+$ 514.1683; found 514.1688.

(2*S*,5*R*,*Z*)- Benzhydryl 6-(2-(benzhydryloxy)-2-oxoethylidene)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate (1m)

Prepared from 6-oxopenicillanate (2.38 mmol) and the corresponding phosphorus ylide (1.099 g, 2.26 mmol), as described in the general procedure. After purification by flash chromatography

(hexane/ethyl acetate, 3:1), compound **1l** was obtained as a white solid (579 mg, 0.982 mmol, 41%). mp low melting point solid. $[\alpha]_D^{25}$= + 200 (*c* 0.5 in CH_2Cl_2). IR (ATR): ν = 981, 1065, 1170, 1248, 1449, 1496, 1719, 1735 and 1773 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.25 (s, 3H), 1.56 (s, 3H), 4.64 (s, 1H), 6.01 (d, *J* = 1.0 Hz, 1H), 6.40 (d, *J* =1.1 Hz, 1H), 6.94 (s, 1H), 6.97 (s, 1H), 7.30-7.36 (m, 20H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.5, 33.7, 64.3, 69.3, 71.0, 78.6, 78.7, 115.9, 127.2, 127.3, 127.6, 128.4, 128.4, 128.5, 128.8, 128.8, 129.3, 139.3, 139.4, 139.4, 157.1, 163.0, 166.4, 166.8. Anal. Calcd for $C_{36}H_{31}NO_5S$: C, 73.32; H, 5.30; N, 2.38; S, 5.44. Found: C, 73.12; H, 5.67; N, 2.31; S, 4.94.

General Procedure for the Synthesis of Spiroisoxazolidine Penicillanates

To a mixture of the appropriate 6-alkylidenepenicillanate **1** (1 equiv.) in toluene (2.5 or 5 mL), the corresponding nitrone **6** or **10** (2 equiv.) was added. The reaction mixture was stirred at 80 ºC for the time indicated in each case. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography.

(2*S*,3'*R*,4'*S*,5*R*,5'*S*)-Benzhydryl 4'-benzoyl-2',3,3-trimethyl-7-oxo-3'-phenyl-4-thia-1-azaspiro[bicyclo[3.2.0]heptane-6,5'-isoxazolidine]-2-carboxylate (7aa) and (2*S*,3'*S*,4'*S*,5*R*,5'*S*)-Benzhydryl 4'-benzoyl-2',3,3-trimethyl-7-oxo-3'-phenyl-4-thia-1-azaspiro[bicyclo[3.2.0]heptane-6,5'-isoxazolidine]-2-carboxylate (8aa)

Obtained from *N*-methylphenylnitrone **6a** (55.6 mg, 0.412 mmol) and 6-alkylidenepenicillanate **1a** (100 mg, 0.412 mmol) as described in the general procedure (reaction time: 24 h). Purification of the crude product by flash chromatography (hexane/ethyl acetate, 5:1 → 3:1), gave, in order of elution, **7aa** as a white solid (90 mg, 0.145 mmol, 70%) and a mixture of **8aa**/**9aa** as a yellow oil (**8aa**: 11%).

7aa: mp low melting solid. $[\alpha]_D^{25}$= + 280 (*c* 0.5 in CH_2Cl_2). IR (ATR): ν = 981, 1179, 1258, 1449, 1456, 1676, 1741 and 1776 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.13 (s, 3H), 1.33 (s, 3H), 2.71 (s, 3H), 3.61 (d, *J* = 6.9 Hz, 1H), 4.52 (s, 1H), 4.69 (d, *J* = 7.3 Hz, 1H), 5.66 (s, 1H), 6.94 (s, 1H), 7.27-7.37 (m, 15H), 7.44-7.50 (m, 3H), 7.56 (d, *J* = 7.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.9, 32.0, 43.3, 60.4, 62.8, 69.3, 71.6, 78.5, 79.5, 96.6, 127.3, 127.6, 128.3, 128.4, 128.7, 128.7, 128.8, 128.9, 129.1, 129.1, 133.9, 137.0, 139.3, 139.4, 166.8, 173.8, 198.9. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{37}H_{35}N_2O_5S$ $[M+H]^+$ 619.2261; found 619.2253.

8aa: ^1H NMR (400 MHz, $CDCl_3$): δ = 1.12 (s, 3H), 1.44 (s, 3H), 2.79 (s, 3H), 4.45 (d, *J* = 6.2 Hz, 1H), 4.57 (s, 1H), 4.81 (d, *J* = 6.2 Hz, 1H), 5.79 (s, 1H), 6.93 (s, 1H), 7.00-7.53 (m, 20H). MS (ESI-TOF) m/z: $[M+H]^+$ found 619.23.

(2*S*,3'*R*,4'*S*,5*R*,5'*S*)-Benzhydryl 4'-benzoyl-2',3,3-trimethyl-3'-(4-nitrophenyl)-7-oxo-4-thia-1-azaspiro[bicyclo[3.2.0]heptane-6,5'-isoxazolidine]-2-carboxylate (7ba) and (2*S*,3'*R*,4'*S*,5*R*,5'*S*)-Benzhydryl 4'-benzoyl-2',3,3-trimethyl-3'-(4-nitrophenyl)-7-oxo-4-thia-1-azaspiro[bicyclo[3.2.0]heptane-6,5'-isoxazolidine]-2-carboxylate (8ba)

Obtained from *N*-methyl-*C*-4-nitrophenyl nitrone **6b** (74 mg, 0.412 mmol) and 6-alkylidenepenicillanate **1a** (100 mg, 0.206 mmol) as described in the general procedure (reaction time: 24 h). Purification of the crude product by flash chromatography (hexane/ethyl acetate, 5:1 → 3:1), gave, in order of elution, a mixture of **7ba**/**9ba** as a yellow oil (**7ba**: 64%) and **8ba** as a yellow oil (14 mg, 0.020 mmol, 10%).

7ba: ^1H NMR (400 MHz, $CDCl_3$): δ = 1.13 (s, 3H), 1.34 (s, 3H), 2.72 (s, 3H), 3.73 (d, *J* = 6.9 Hz, 1H), 4.53 (s, 1H), 4.63 (d, *J* = 6.9 Hz, 1H), 5.66 (s, 1H), 6.95 (s, 1H), 7.20-7.64 (m, 15H), 7.66 (d, *J* = 8.7 Hz, 2H), 8.20 (d, *J* = 8.8 Hz, 2H). MS (ESI-TOF) m/z: $[M+H]^+$ found 664.21.

8ba: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.14 (s, 3H), 1.47 (s, 3H), 2.79 (s, 3H), 4.56 (d, *J* = 6.3 Hz, 1H), 4.59 (s, 1H), 4.88 (d, *J* = 6.3 Hz, 1H), 5.78 (s, 1H), 6.94 (s, 1H), 7.17 (t, *J* = 7.8 Hz, 2H), 7.29-7.36 (m, 11H), 7.41 (d, *J* = 8.7 Hz, 2H), 7.45 (d, *J* = 8.5 Hz, 2H), 7.88 (d, *J* = 8.8 Hz, 2H). HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{37}H_{34}N_3O_7S$ $[M+H]^+$ 664.2112; found 664.2111.

(2*S*,3'*R*,4'*S*,5*R*,5'*S*)-Benzhydryl 4'-benzoyl-3,3-dimethyl-7-oxo-2',3'-diphenyl-4-thia-1-azaspiro[bicyclo[3.2.0]heptane-6,5'-isoxazolidine]-2-carboxylate (7ca)

Obtained from diphenylnitrone **6c** (81 mg, 0.412 mmol) and 6-alkylidenepenicillanate **1a** (100 mg, 0.206 mmol) as described in the general procedure (reaction time: 24 h). Purification of the crude product by flash chromatography (hexane/ethyl acetate, 5:1 → 3:1), gave a mixture of **7ca/9ca** as a white solid (**7ca**: 41%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.15 (s, 3H), 1.36 (s, 3H), 4.31 (d, *J* = 6.0 Hz, 1H), 4.56 (s, 1H), 4.74 (d, *J* = 6.0 Hz, 1H), 5.81 (s, 1H), 6.96-6.99 (m, 4H), 7.14-7.18 (m, 3H), 7.31-7.64 (m, 19H). MS (ESI-TOF) m/z: $[M+H]^+$ found 681.24.

(2*S*,3'*R*,4'*S*,5*R*,5'*S*)-Benzhydryl 4'-(4-fluorobenzoyl)-2',3,3-trimethyl-7-oxo-3'-phenyl-4-thia-1-azaspiro[bicyclo[3.2.0]heptane-6,5'-isoxazolidine]-2-carboxylate (7ab) and (2*S*,3'*S*,4'*S*,5*R*,5'*S*)-Benzhydryl 4'-(4-fluorobenzoyl)-2',3,3-trimethyl-7-oxo-3'-phenyl-4-thia-1-azaspiro[bicyclo[3.2.0]heptane-6,5'-isoxazolidine]-2-carboxylate (8ab)

Obtained from *N*-methylphenylnitrone **6a** (55.6 mg, 0.412 mmol) and 6-alkylidenepenicillanate **1b** (103 mg, 0.412 mmol) as described in the general procedure (reaction time: 24 h). Purification of the crude product by flash chromatography (hexane/ethyl acetate, 5:1 → 3:1), gave, in order of elution, **7ab** as a white solid (86 mg, 0.135 mmol, 66%) and a mixture of **8ab**/**9ab** as a yellow oil (**8ab**: 13%).

7ab: mp 139,8 – 141,5 ºC. $[\alpha]_D^{25}$= + 240 (*c* 0.25 in CH_2Cl_2). IR (ATR): ν = 849, 1151, 1180, 1194, 1303, 1593, 1676, 1752 and 1774 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.14 (s, 3H), 1.35 (s, 3H), 2.70 (s, 3H), 3.58 (d, *J* = 7.0 Hz, 1H), 4.52 (s, 1H), 4.63 (d, *J* = 7.2 Hz, 1H), 5.63 (s, 1H), 6.94-6.99 (m, 3H), 7.30-7.36 (m, 14H), 7.46 (dd, *J* = 6.6 and 2.9 Hz, 2H), 7.58 (dd, *J* = 8.8 and 5.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.0, 32.0, 43.3, 60.4, 62.8, 69.3, 71.5, 78.5, 79.5, 96.5, 116.0 (d, *J* = 22 Hz, 1C), 127.3, 127.6, 128.4, 128.5, 128.6, 128.7, 128.8, 129.2, 131.6 (d, *J* = 10 Hz, 2C), 133.5 (d, *J* = 3 Hz, 2C), 136.9, 139.3, 139.3, 166.3 (d, *J* = 257 Hz, 1C), 166.8, 173.7, 197.3. ^{19}F NMR (376 MHz, $CDCl_3$): 103.59 (s, 1F). HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{37}H_{34}FN_2O_5S$ $[M+H]^+$ 637.2167; found 637.2185.

8ab: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.13 (s, 3H), 1.45 (s, 3H), 2.78 (s, 3H), 4.45 (d, *J* = 6.1 Hz, 1H), 4.57 (s, 1H), 4.73 (d, *J* = 6.2 Hz, 1H), 5.78 (s, 1H), 6.81 (t, *J* = 8.6 Hz, 2H), 6.93 (s, 1H), 7.03-7.50 (m, 17H). ^{19}F NMR (376 MHz, $CDCl_3$): 105.09 (s, 1F). MS (ESI-TOF) m/z: $[M+H]^+$ found 637.22.

(2*S*,3'*R*,4'*S*,5*R*,5'*S*)-Benzhydryl 4'-(4-chlorobenzoyl)-2',3,3-trimethyl-7-oxo-3'-phenyl-4-thia-1-azaspiro[bicyclo[3.2.0]heptane-6,5'-isoxazolidine]-2-carboxylate (7ac) and (2*S*, 3'*S*,4'*S*,5*R*,5'*S*)-Benzhydryl 4'-(4-chlorobenzoyl)-2',3,3-trimethyl-7-oxo-3'-phenyl-4-thia-1-azaspiro[bicyclo[3.2.0]heptane-6,5'-isoxazolidine]-2-carboxylate (8ac)

Obtained from *N*-methylphenylnitrone **6a** (55.6 mg, 0.412 mmol) and 6-alkylidenepenicillanate **1c** (106,7 mg, 0.412 mmol) as described in the general procedure (reaction time: 24 h). Purification of the crude product by flash chromatography (hexane/ethyl acetate, 5:1 → 3:1), gave, in order of elution, **7ac** as a white solid (93 mg, 0.143 mmol, 69%) and **8ac** as a yellow oil (13 mg, 0.020 mmol, 10%).

7ac: mp 140,6 – 142,6 ºC. $[\alpha]_D^{25}$= + 310 (*c* 0.5 in CH_2Cl_2). IR (ATR): ν = 1006, 1089, 1181, 1303, 1584, 1677, 1753 and 1772 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.13 (s, 3H), 1.35 (s, 3H), 2.70 (s, 3H), 3.59 (d, *J* = 7.0 Hz, 1H), 4.52 (s, 1H), 4.62 (d, *J* = 7.2 Hz, 1H), 5.64 (s, 1H), 6.95 (s, 1H), 7.26-7.38 (m, 15H), 7.43-7.51 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.0, 32.1, 43.3, 60.5, 62.9, 69.3, 71.5, 78.5, 79.5, 96.6, 127.3, 127.6, 128.4, 128.5, 128.6, 128.7, 128.8, 129.1, 129.3, 130.2, 135.4, 136.8, 139.3, 139.3, 140.6, 166.8, 173.7, 197.8. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{37}H_{34}ClN_2O_5S$ $[M+H]^+$ 653.1871; found 653.1873.
8ac: ^1H NMR (400 MHz, $CDCl_3$): δ = 1.13 (s, 3H), 1.43 (s, 3H), 2.78 (s, 3H), 4.45 (d, *J* = 6.1 Hz, 1H), 4.57 (s, 1H), 4.73 (d, *J* = 6.2 Hz, 1H), 5.77 (s, 1H), 6.93 (s, 1H), 7.04-7.06 (m, 2H), 7.11-7.13 (m, 2H), 7.18-7.21 (m, 2H), 7.30-7.40 (m, 13H). HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{37}H_{34}ClN_2O_5S$ $[M+H]^+$ 653.1871; found 653.1867.

(2*S*,3'*R*,4'*S*,5*R*,5'*S*)-Benzhydryl 4'-(4-bromobenzoyl)-2',3,3-trimethyl-7-oxo-3'-phenyl-4-thia-1-azaspiro[bicyclo[3.2.0]heptane-6,5'-isoxazolidine]-2-carboxylate (7ad) and (2*S*,3'*S*,4'*S*,5*R*,5'*S*)-Benzhydryl 4'-(4-bromobenzoyl)-2',3,3-trimethyl-7-oxo-3'-phenyl-4-thia-1-azaspiro[bicyclo[3.2.0]heptane-6,5'-isoxazolidine]-2-carboxylate (8ad)
Obtained from *N*-methylphenylnitrone **6a** (27.8 mg, 0.206 mmol) and 6-alkylidenepenicillanate **1d** (57.9 mg, 0.103 mmol) as described in the general procedure (reaction time: 24 h). Purification of the crude product by flash chromatography (hexane/ethyl acetate, 5:1 → 3:1), gave, in order of elution, **7ad** as a white solid (31 mg, 0.044 mmol, 43%) and **8ad** as a yellow oil (8.7 mg, 0.012 mmol, 12%).
7ad: mp 134,4 – 136,4 ºC. $[\alpha]_D^{25}$= + 280 (*c* 0.75 in CH_2Cl_2). IR (ATR): ν = 846, 1004, 1182, 1303, 1577, 1676, 1752 and 1772 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.13 (s, 3H), 1.34 (s, 3H), 2.70 (s, 3H), 3.59 (d, *J* = 7.0 Hz, 1H), 4.52 (s, 1H), 4.62 (d, *J* = 7.2 Hz, 1H), 5.63 (s, 1H), 6.94 (s, 1H), 7.29-7.37 (m, 13H), 7.39-7.47 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.0, 32.1, 43.3, 60.5, 62.9, 69.3, 71.5, 78.5, 79.5, 96.6, 127.3, 127.6, 128.4, 128.5, 128.6, 128.7, 128.8, 129.3, 129.4, 130.3, 132.1, 135.8, 136.8, 139.3, 139.3, 166.8, 173.7, 198.0. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{37}H_{34}BrN_2O_5S$ $[M+H]^+$ 697.1366; found 697.1367.
8ad: ^1H NMR (400 MHz, $CDCl_3$): δ = 1.13 (s, 3H), 1.42 (s, 3H), 2.78 (s, 3H), 4.44 (d, *J* = 6.1 Hz, 1H), 4.57 (s, 1H), 4.72 (d, *J* = 6.2 Hz, 1H), 5.76 (s, 1H), 6.93 (s, 1H), 7.05-7.07 (m, 3H), 7.18-7.20 (m, 2H), 7.27-7.36 (m, 14H). HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{37}H_{34}BrN_2O_5S$ $[M+H]^+$ 697.1366; found 697.1364.

(2*S*,3'*R*,4'*S*,5*R*,5'*S*)-Benzhydryl 4'-(4-nitrobenzoyl)-2',3,3-trimethyl-7-oxo-3'-phenyl-4-thia-1-azaspiro[bicyclo[3.2.0]heptane-6,5'-isoxazolidine]-2-carboxylate (7ae) and (2*S*,3'*S*,4'*S*,5*R*,5'*S*)-Benzhydryl 4'-(4-nitrobenzoyl)-2',3,3-trimethyl-7-oxo-3'-phenyl-4-thia-1-azaspiro[bicyclo[3.2.0]heptane-6,5'-isoxazolidine]-2-carboxylate (8ae)
Obtained from *N*-methylphenylnitrone **6a** (27.8 mg, 0.206 mmol) and 6-alkylidenepenicillanate **1e** (54.4 mg, 0.103 mmol) as described in the general procedure (reaction time: 24 h). Purification of the crude product by flash chromatography (hexane/ethyl acetate, 5:1 → 3:1), gave, in order of elution, **7ae** as a white solid (39 mg, 0.059 mmol, 57%) and a mixture of **8ae**/**9ae** as a yellow oil (**8ae**: 27%).
7ae: mp 143,1 – 144,0 ºC. $[\alpha]_D^{25}$= + 330 (*c* 0.5 in CH_2Cl_2). IR (ATR): ν = 1150, 1179, 1299, 1456, 1669, 1749 and 1773 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.13 (s, 3H), 1.33 (s, 3H), 2.72 (s, 3H), 3.63 (d, *J* = 7.2 Hz, 1H), 4.54 (s, 1H), 4.68 (d, *J* = 7.3 Hz, 1H), 5.63 (s, 1H), 6.95 (s, 1H), 7.30-7.40 (m, 13H), 7.45-7.48 (m, 2H), 7.69 (d, *J* = 8.8 Hz, 2H), 8.14 (d, *J* = 8.9 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.9, 32.3, 43.2, 61.2, 63.3, 69.2, 71.4, 78.6, 79.7, 96.9, 124.0,

127.3, 127.6, 128.4, 128.5, 128.5, 128.8, 128.8, 129.4, 129.5, 129.7, 136.4, 139.2, 139.3, 141.4, 150.7, 166.6, 173.3, 198.1.

8ae: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.13 (s, 3H), 1.44 (s, 3H), 2.81 (s, 3H), 4.49 (d, *J* = 6.1 Hz, 1H), 4.59 (s, 1H), 4.79 (d, *J* = 6.2 Hz, 1H), 5.77 (s, 1H), 6.94 (s, 1H), 7.04-7.36 (m, 15H), 7.58 (d, *J* = 8.9 Hz, 2H), 7.99 (d, *J* = 8.9 Hz, 2H). MS (ESI-TOF) m/z: $[M+H]^+$ found 664.21.

(2*S*,3'*R*,4'*S*,5*R*,5'*S*)-Benzhydryl 2',3,3-trimethyl-7-oxo-3'-phenyl-4'-(4-(trifluoromethyl)benzoyl)-4-thia-1-azaspiro[bicyclo[3.2.0]heptane-6,5'-isoxazolidine]-2-carboxylate (7af) and (2*S*,3'*S*,4'*S*,5*R*,5'*S*)-Benzhydryl 2',3,3-trimethyl-7-oxo-3'-phenyl-4'-(4-(trifluoromethyl)benzoyl)-4-thia-1-azaspiro[bicyclo[3.2.0]heptane-6,5'-isoxazolidine]-2-carboxylate (8af)

Obtained from *N*-methylphenylnitrone **6a** (27.8 mg, 0.206 mmol) and 6-alkylidenepenicillanate **1f** (56.9 mg, 0.103 mmol) as described in the general procedure (reaction time: 24 h). Purification of the crude product by flash chromatography (hexane/ethyl acetate, 5:1 → 3:1), gave, in order of elution, **7af** as a white solid (37,4 mg, 0.054 mmol, 53%) and **8af** as a yellow oil (7.7 mg, 0.011 mmol, 11%).

7af: mp 153,6 – 155,6 ºC. $[\alpha]_D^{25}$= + 280 (*c* 0.25 in CH_2Cl_2). IR (ATR): ν = 1066, 1128, 1259, 1321, 1456, 1685, 1748 and 1776 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.13 (s, 3H), 1.33 (s, 3H), 2.71 (s, 3H), 3.62 (d, *J* = 7.0 Hz, 1H), 4.53 (s, 1H), 4.68 (d, *J* = 7.2 Hz, 1H), 5.64 (s, 1H), 6.95 (s, 1H), 7.29-7.38 (m, 13H), 7.45-7.48 (m, 2H), 7.56 (d, *J* = 8.4 Hz, 2H), 7.65 (d, *J* = 8.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.9, 32.2, 43.2, 60.9, 63.1, 69.3, 71.4, 78.5, 79.6, 96.8, 123.5 (q, *J* = 273 Hz, 1C), 125.8, 125.9, 127.3, 127.6, 128.4, 128.5, 128.6, 128.8, 128.8, 129.1, 129.3, 129.4, 136.6, 139.2, 139.3, 139.7, 166.7, 173.5, 198.4. ^{19}F NMR (376 MHz, $CDCl_3$): 63.24 (s, 3F). HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{38}H_{34}F_3N_2O_5S$ $[M+H]^+$ 687.2135; found 687.2129.

8af: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.13 (s, 3H), 1.44 (s, 3H), 2.80 (s, 3H), 4.47 (d, *J* = 6.1 Hz, 1H), 4.58 (s, 1H), 4.78 (d, *J* = 6.2 Hz, 1H), 5.78 (s, 1H), 6.94 (s, 1H), 7.02-7.04 (m, 3H), 7.17-7.20 (m, 2H), 7.30-7.36 (m, 10H), 7.40 (d, *J* = 8.3 Hz, 2H), 7.53 (d, *J* = 8.2 Hz, 2H). . ^{19}F NMR (376 MHz, $CDCl_3$): 63.27 (s, 3F). HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{38}H_{34}F_3N_2O_5S$ $[M+H]^+$ 687.2135; found 687.2162.

(2*S*,3'*R*,4'*S*,5*R*,5'*S*)-Benzhydryl 4'-(3,5-difluorobenzoyl)-2',3,3-trimethyl-7-oxo-3'-phenyl-4-thia-1-azaspiro[bicyclo[3.2.0]heptane-6,5'-isoxazolidine]-2-carboxylate (7ag) and (2*S*,3'*S*,4'*S*,5*R*,5'*S*)-Benzhydryl 4'-(3,5-difluorobenzoyl)-2',3,3-trimethyl-7-oxo-3'-phenyl-4-thia-1-azaspiro[bicyclo[3.2.0]heptane-6,5'-isoxazolidine]-2-carboxylate (8ag)

Obtained from *N*-methylphenylnitrone **6a** (55.6 mg, 0.412 mmol) and 6-alkylidenepenicillanate **1g** (107 mg, 0.206 mmol) as described in the general procedure (reaction time: 24 h). Purification of the crude product by flash chromatography (hexane/ethyl acetate, 5:1 → 3:1), gave, in order of elution, **7ag** as a white solid (83.6 mg, 0.128 mmol, 62%) and **8ag** as a yellow oil (19 mg, 0.029 mmol, 14%).

7ag: mp 140,4 – 141,4 ºC. $[\alpha]_D^{25}$= + 260 (*c* 0.5 in CH_2Cl_2). IR (ATR): ν = 977, 1250, 1265, 1438, 1596, 1688, 1720 and 1772 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.15 (s, 3H), 1.37 (s, 3H), 2.71 (s, 3H), 3.58 (d, *J* = 7.1 Hz, 1H), 4.54 (s, 1H), 4.54 (d, *J* = 7.1 Hz, 1H), 5.62 (s, 1H), 6.95 (s, 1H), 6.95 (dt, *J* = 16.5 and 2.3 Hz, 1H), 7.03 (d, *J* = 5.7 Hz, 2H), 7.30-7.40 (m, 13H), 7.45-7.49 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.0, 32.3, 43.2, 61.0, 63.2, 69.3, 71.4, 78.5, 79.6, 96.7, 109.2 (t, *J* = 25 Hz, 1C), 111.7 (d, *J* = 19 Hz, 1C), 111.8 (d, *J* = 19 Hz, 1C), 127.3, 127.6, 128.4, 128.5, 128.8, 128.8, 129.4, 129.5, 136.4, 139.2, 139.3, 163.0 (d, *J* = 252 Hz, 1C), 163.1 (d,

J = 252 Hz, 1C), 166.7, 173.4, 196.9. ^{19}F NMR (376 MHz, $CDCl_3$): 107.47 (s, 2F). HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{37}H_{33}F_2N_2O_5S$ $[M+H]^+$ 655.2073; found 655.2075.

8ag: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.14 (s, 3H), 1.46 (s, 3H), 2.80 (s, 3H), 4.46 (d, *J* = 6.1 Hz, 1H), 4.59 (s, 1H), 4.64 (d, *J* = 6.1 Hz, 1H), 5.76 (s, 1H), 6.76 (tt, *J* = 8.3 and 2.3 Hz, 1H), 6.92-6.94 (m, 3H), 7.08-7.10 (m, 3H), 7.19-7.22 (m, 2H), 7.29-7.36 (m, 10H). ^{19}F NMR (376 MHz, $CDCl_3$): 108.52 (s, 2F). HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{37}H_{33}F_2N_2O_5S$ $[M+H]^+$ 655.2073; found 655.2073.

(2*S*,3'*R*,4'*S*,5*R*,5'*S*)-Benzhydryl 4'-(3,5-bis(trifluoromethyl)benzoyl)-2',3,3-trimethyl-7-oxo-3'-phenyl-4-thia-1-azaspiro[bicyclo[3.2.0]heptane-6,5'-isoxazolidine]-2-carboxylate (7ah) and (2*S*,3'*S*,4'*S*,5*R*,5'*S*)-Benzhydryl 4'-(3,5-bis(trifluoromethyl)benzoyl)-2',3,3-trimethyl-7-oxo-3'-phenyl-4-thia-1-azaspiro[bicyclo[3.2.0]heptane-6,5'-isoxazolidine]-2-carboxylate (8ah)

Obtained from *N*-methylphenylnitrone **6a** (55.6 mg, 0.412 mmol) and 6-alkylidenepenicillanate **1h** (127.6 mg, 0.206 mmol) as described in the general procedure (reaction time: 24 h). Purification of the crude product by flash chromatography (hexane/ethyl acetate, 5:1 → 3:1), gave, in order of elution, **7ah/9h** as a yellow oil (**7ah**: 26%) and **8ah/9ah** as a yellow oil (**8ah**: 9%).

7ah: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.16 (s, 3H), 1.38 (s, 3H), 2.72 (s, 3H), 3.55 (d, *J* = 7.3 Hz, 1H), 4.54 (s, 1H), 4.64 (d, *J* = 7.4 Hz, 1H), 5.66 (s, 1H), 6.96 (s, 1H), 7.23-7.47 (m, 15H), 7.90 (s, 1H), 7.98 (s, 1H), 8.06 (s, 1H). ^{19}F NMR (376 MHz, $CDCl_3$): 63.11 (s, 6F). MS (ESI-TOF) m/z: $[M+H]^+$ found 755.20.

8ah: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.15 (s, 3H), 1.47 (s, 3H), 2.82 (s, 3H), 4.51 (d, *J* = 6.1 Hz, 1H), 4.61 (s, 1H), 4.75 (d, *J* = 6.2 Hz, 1H), 5.78 (s, 1H), 6.95 (s, 1H), 7.00-7.06 (m, 3H), 7.17-7.19 (m, 2H), 7.33-7.37 (m, 10H), 7.79 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$): 63.11 (s, 6F). MS (ESI-TOF) m/z: $[M+H]^+$ found 755.20.

(2*S*,3'*R*,4'*S*,5*R*,5'*S*)-Benzhydryl 4'-(2-naphthoyl)-2',3,3-trimethyl-7-oxo-3'-phenyl-4-thia-1-azaspiro[bicyclo[3.2.0]heptane-6,5'-isoxazolidine]-2-carboxylate (7ai) and (2*S*,3'*S*,4'*S*,5*R*,5'*S*)-Benzhydryl 4'-(2-naphthoyl)-2',3,3-trimethyl-7-oxo-3'-phenyl-4-thia-1-azaspiro[bicyclo[3.2.0]heptane-6,5'-isoxazolidine]-2-carboxylate (8ai)

Obtained from *N*-methylphenylnitrone **6a** (55.6 mg, 0.412 mmol) and 6-alkylidenepenicillanate **1i** (110 mg, 0.206 mmol) as described in the general procedure (reaction time: 24 h). Purification of the crude product by flash chromatography (hexane/ethyl acetate, 5:1 → 3:1), gave, in order of elution, **7ai** as a white solid (101 mg, 0.151 mmol, 73%) and a mixture of **8ai/9ai** as a yellow oil (**8ai**: 10%).

7ai: mp 138,3 – 139,0 ºC. $[\alpha]_D^{25}$= + 300 (*c* 0.5 in CH_2Cl_2). IR (ATR): ν = 1124, 1152, 1178, 1258, 1457, 1670, 1741 and 1773 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.13 (s, 3H), 1.33 (s, 3H), 2.74 (s, 3H), 3.65 (d, *J* = 7.0 Hz, 1H), 4.52 (s, 1H), 4.83 (d, *J* = 7.2 Hz, 1H), 5.71 (s, 1H), 6.95 (s, 1H), 7.30-7.38 (m, 13H), 7.46-7.52 (m, 4H), 7.57 (ddd, *J* = 8.1, 6.4 and 1.7 Hz, 1H), 7.74 (s, 1H). 7.81 (dd, *J* = 8.3 and 5.2 Hz, 2H), 7.86 (dd, *J* = 8.7 and 1.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.0, 31.8, 43.3, 60.8, 62.7, 69.4, 71.5, 78.4, 79.6, 96.5, 124.1, 127.0, 127.3, 127.6, 127.8, 128.3, 128.4, 128.7, 128.8, 128.8, 129.1, 129.2, 129.9, 131.4, 132.3, 134.3, 135.9, 137.2, 139.3, 139.4, 166.9, 174.0, 198.5. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{41}H_{37}N_2O_5S$ $[M+H]^+$ 669.2418; found 669.2413.

8ai: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.10 (s, 3H), 1.42 (s, 3H), 2.81 (s, 3H), 4.52 (d, *J* = 6.7 Hz, 1H), 4.57 (s, 1H), 4.96 (d, *J* = 6.2 Hz, 1H), 5.81 (s, 1H), 6.82-8.11 (m, 32H). MS (ESI-TOF) m/z: $[M+H]^+$ found 669.24.

(2*S*,3'*R*,4'*S*,5*R*,5'*S*)-Benzhydryl 4'-(2-furoyl)-2',3,3-trimethyl-7-oxo-3'-phenyl-4-thia-1-azaspiro[bicyclo[3.2.0]heptane-6,5'-isoxazolidine]-2-carboxylate (7aj) and (2*S*,3'*S*,4'*S*,5*R*,5'*S*)-Benzhydryl 4'-(2-furoyl)-2',3,3-trimethyl-7-oxo-3'-phenyl-4-thia-1-azaspiro[bicyclo[3.2.0]heptane-6,5'-isoxazolidine]-2-carboxylate (8aj)

Obtained from *N*-methylphenylnitrone **6a** (55.6 mg, 0.412 mmol) and 6-alkylidenepenicillanate **1j** (97,5 mg, 0.206 mmol) as described in the general procedure (reaction time: 24 h). Purification of the crude product by flash chromatography (hexane/ethyl acetate, 4:1 → 3:1), gave, in order of elution, **7aj** as a white solid (84 mg, 0.138 mmol, 67%) and a mixture of **8aj**/**9aj** as a yellow oil (**8aj**: 13%).

7aj: mp 137,2 – 138,5 ºC. $[\alpha]_D^{25}$= + 270 (*c* 0.5 in CH_2Cl_2). IR (ATR): ν = 1155, 1179, 1297, 1463, 1660, 1744 and 1786 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.14 (s, 3H), 1.37 (s, 3H), 2.70 (s, 3H), 3.72 (s, 1H), 4.47 (d, *J* = 7.1 Hz, 1H), 4.54 (s, 1H), 5.61 (s, 1H), 6.45 (dd, *J* = 3.5 and 1.6 Hz, 1H), 6.82 (s, 1H), 6.94 (s, 1H), 7.29-7.37 (m, 13H), 7.45 (dd, *J* = 7.3 and 2.1 Hz, 2H), 7.54 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.9, 32.5, 43.2, 60.6, 62.9, 69.2, 71.6, 78.5, 79.3, 96.1, 112.7, 119.3, 127.3, 127.6, 128.3, 128.5, 128.7, 128.7, 129.0, 129.0, 139.3, 139.3, 147.8, 152.9, 166.8, 173.4, 186.4. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{35}H_{33}N_2O_6S$ $[M+H]^+$ 609.2054; found 609.2068.

8aj: ^1H NMR (400 MHz, $CDCl_3$): δ = 1.14 (s, 3H), 1.45 (s, 3H), 2.78 (s, 3H), 4.43 (d, *J* = 6.3 Hz, 1H), 4.58 (s, 1H), 4.64 (d, *J* = 5.8 Hz, 1H), 5.77 (s, 1H), 6.22 (d, *J* = 1.9 Hz, 1H), 6.78 (s, 1H), 6.93 (s, 1H), 7.09-7.50 (m, 16H). MS (ESI-TOF) m/z: $[M+H]^+$ found 609.20.

(2*S*,3'*R*,4'*S*,5*R*,5'*S*)-Benzhydryl 4'-acetyl-2',3,3-trimethyl-7-oxo-3'-phenyl-4-thia-1-azaspiro[bicyclo[3.2.0]heptane-6,5'-isoxazolidine]-2-carboxylate (7ak) and (2*S*,3'*S*,4'*S*,5*R*,5'*S*)-Benzhydryl 4'-acetyl-2',3,3-trimethyl-7-oxo-3'-phenyl-4-thia-1-azaspiro[bicyclo[3.2.0]heptane-6,5'-isoxazolidine]-2-carboxylate (8ak)

Obtained from *N*-methylphenylnitrone **6a** (55.6 mg, 0.412 mmol) and 6-alkylidenepenicillanate **1ak** (87.6 mg, 0.206 mmol) as described in the general procedure (reaction time: 24 h). Purification of the crude product by flash chromatography (hexane/ethyl acetate, 4:1 → 3:1), gave, in order of elution, **7ak** as a white solid (34 mg, 0.061 mmol, 30%) and **8ak** as a yellow oil (7.8 mg, 0.014 mmol, 7%).

7ak: mp 122,8 – 124,5 ºC. $[\alpha]_D^{25}$= + 250 (*c* 0.5 in CH_2Cl_2). IR (ATR): ν = 968, 978, 1258, 1267, 1718 and 1774 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.21 (s, 3H), 1.53 (s, 3H), 2.13 (s, 3H), 2.65 (s, 3H), 3.49 (d, *J* = 6.9 Hz, 1H), 3.90 (d, *J* = 7.3 Hz, 1H), 4.57 (s, 1H), 5.56 (s, 1H), 6.95 (s, 1H), 7.28-7.44 (m, 13H), 7.52 (dd, *J* = 7.9 and 1.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.0, 32.7, 33.5, 43.1, 63.0, 65.4, 69.2, 71.2, 78.5, 79.0, 95.9, 127.3, 127.6, 128.4, 128.4, 128.5, 128.7, 128.8, 129.2, 129.3, 137.2, 139.3, 139.3, 166.8, 173.4, 207.0. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{32}H_{33}N_2O_5S$ $[M+H]^+$ 557.2105; found 557.2108.

8ak: ^1H NMR (400 MHz, $CDCl_3$): δ = 1.20 (s, 3H), 1.52 (s, 3H), 1.58 (s, 3H), 2.77 (s, 3H), 3.91 (d, *J* = 6.2 Hz, 1H), 4.36 (d, *J* = 6.2 Hz, 1H), 4.58 (s, 1H), 5.68 (s, 1H), 6.93 (s, 1H), 7.31-7.36 (m, 15H). HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{32}H_{33}N_2O_5S$ $[M+H]^+$ 557.2105; found 557.2107.

(2*S*,3'*R*,4'*S*,5*R*,5'*S*)-Benzhydryl 4'-benzyl-2',3,3-trimethyl-7-oxo-3'-phenyl-4-thia-1-azaspiro[bicyclo[3.2.0]heptane-6,5'-isoxazolidine]-2,4'-dicarboxylate (7al) and (2*S*,3'*S*,4'*S*,5*R*,5'*S*)-Benzhydryl 4'-benzyl-2',3,3-trimethyl-7-oxo-3'-phenyl-4-thia-1-azaspiro[bicyclo[3.2.0]heptane-6,5'-isoxazolidine]-2,4'-dicarboxylate (8al)

Obtained from *N*-methylphenylnitrone **6a** (55.6 mg, 0.412 mmol) and 6-alkylidenepenicillanate **1l** (105.8 mg, 0.206 mmol) as described in the general procedure (reaction time: 24 h). Purification of the crude product by flash chromatography (hexane/ethyl acetate, 5:1 → 3:1), gave, in order of elution, **7al** as a white solid (68.7 mg, 0.106 mmol, 51%) and a mixture of **8al/9al** as a yellow oil (**8al**: 15%).

7al: mp low melting solid. $[\alpha]_D^{25}$= + 190 (*c* 0.5 in CH_2Cl_2). IR (ATR): ν˜ = 979, 1155, 1256, 1456, 1731, 1735 and 1779 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.18 (s, 3H), 1.40 (s, 3H), 2.65 (s, 3H), 3.66 (t, *J* = 8.4 Hz, 2H), 4.57 (s, 1H), 5.15 (d, *J* = 12.3 Hz, 1H), 5.20 (d, *J* = 12.3 Hz, 1H), 5.54 (s, 1H), 6.95 (s, 1H), 7.29-7.39 (m, 20H). ^{13}C NMR (100 MHz, $CDCl^3$): δ = 25.5, 33.4, 43.2, 62.7, 67.3, 68.8, 71.5, 78.5, 78.9, 95.0, 127.3, 127.6, 128.3, 128.4, 128.5, 128.6, 128.7, 128.7, 128.7, 128.8, 129.0, 129.1, 135.3, 139.3, 139.3, 166.7, 170.8, 172.7. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{38}H_{37}N_2O_6S$ $[M+H]^+$ 649.2367; found 649.2362.

8al: ^1H NMR (400 MHz, $CDCl_3$): δ = 1.21 (s, 3H), 1.49 (s, 3H), 2.79 (s, 3H), 3.40 (s, 2H), 3.70 (d, *J* = 6.3 Hz, 1H), 4.33 (d, *J* = 6.2 Hz, 1H), 4.58 (s, 1H), 5.69 (s, 1H), 6.94 (s, 1H), 7.22-7.43 (m, 20H). MS (ESI-TOF) m/z: $[M+H]^+$ found 649.24.

(2*S*,3'*R*,4'*S*,5*R*,5'*S*)-Dibenzhydryl 2',3,3-trimethyl-7-oxo-3'-phenyl-4-thia-1-azaspiro[bicyclo[3.2.0]heptane-6,5'-isoxazolidine]-2,4'-dicarboxylate (7am)

Obtained from *N*-methylphenylnitrone **6a** (55.6 mg, 0.412 mmol) and 6-alkylidenepenicillanate **1m** (121 mg, 0.206 mmol) as described in the general procedure (reaction time: 24 h). Purification of the crude product by flash chromatography (hexane/ethyl acetate, 5:1 → 3:1), gave, in order of elution **7am** as a white solid (119 mg, 0.164 mmol, 80%) and a mixture of **8am/9am** as a yellow oil (**8am:** 10%).

7am: mp low melting solid. $[\alpha]_D^{25}$= + 190 (*c* 0.5 in CH_2Cl_2). IR (ATR): ν˜ = 953, 978, 1155, 1254, 1449, 1453, 1494, 1735 and 1777 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.08 (s, 3H), 1.20 (s, 3H), 2.66 (s, 3H), 3.70 (t, *J* = 7.7 Hz, 2H), 4.52 (s, 1H), 5.52 (s, 1H), 6.92 (s, 1H), 6.97 (s, 1H), 7.10-7.13 (m, 2H), 7.27-7.36 (m, 23H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.4, 33.1, 43.2, 62.6, 68.8, 71.4, 78.0, 78.5, 79.1, 95.2, 126.9, 127.3, 127.6, 128.0, 128.2, 128.3, 128.5, 128.6, 128.7, 128.8, 129.0, 136.6, 139.3, 139.3, 139.5, 139.5, 166.6, 170.5, 172.9. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{44}H_{41}N_2O_6S$ $[M+H]^+$ 725.2680; found 725.2683.

8am: ^1H NMR (400 MHz, $CDCl_3$): δ = 1.21 (s, 3H), 1.25 (s, 3H), 2.75 (s, 3H), 3.79 (d, *J* = 6.1 Hz, 1H), 4.34 (d, *J* = 6.1 Hz, 1H), 4.49 (s, 1H), 5.58 (s, 1H), 6.71 (s, 1H), 6.92 (s, 1H), 7.08-7.42 (m, 25H). MS (ESI-TOF) m/z: $[M+H]^+$ found 725.27.

(2*S*,3'*R*,4'*S*,5*R*,5'*S*)-Benzhydryl 4'-methyl-2',3,3-trimethyl-7-oxo-3'-phenyl-4-thia-1-azaspiro[bicyclo[3.2.0]heptane-6,5'-isoxazolidine]-2,4'-dicarboxylate (7an) and (2*S*,3'*S*,4'*S*,5*R*,5'*S*)-Benzhydryl 4'-methyl-2',3,3-trimethyl-7-oxo-3'-phenyl-4-thia-1-azaspiro[bicyclo[3.2.0]heptane-6,5'-isoxazolidine]-2,4'-dicarboxylate (8an)

Obtained from *N*-methylphenylnitrone **6a** (55.6 mg, 0.412 mmol) and 6-alkylidenepenicillanate **1n** (90 mg, 0.206 mmol) as described in the general procedure (reaction time: 24 h). Purification of the crude product by flash chromatography (hexane/ethyl acetate, 4:1 → 3:1), gave, in order of elution, **7an** as a white solid (67 mg, 0.117 mmol, 57%) and a mixture of **8an/9an** as a yellow oil (**8an**: 16%).

7an: mp low melting solid. $[\alpha]_D^{25}$= + 220 (*c* 0.5 in CH_2Cl_2). IR (ATR): ν = 980, 1169, 1199, 1255, 1434, 1454, 1495, 1735 and 1779 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.22 (s, 3H), 1.48 (s, 3H), 2.67 (s, 3H), 3.64 (d, *J* = 7.2 Hz, 1H), 3.73 (br s, 4H), 4.59 (s, 1H), 5.54 (s, 1H), 6.95 (s, 1H), 7.30-7.37 (m, 13H), 7.47 (dd, *J* = 7.8 and 1.5 Hz, 2H). ^{13}C NMR (100 MHz, CDCl3): δ = 25.6, 33.4, 43.1, 52.6, 62.8, 68.8, 71.5, 78.6, 127.3, 127.6, 128.3, 128.4, 128.5, 128.7, 128.8, 129.0,

129.1, 139.2, 139.3, 166.7, 171.3, 172.7. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{32}H_{33}N_2O_6S$ $[M+H]^+$ 573.2054; found 573.2062.
8an: ^1H NMR (400 MHz, $CDCl_3$): δ = 1.21 (s, 3H), 1.49 (s, 3H), 2.79 (s, 3H), 3.40 (s, 2H), 3.70 (d, *J* = 6.3 Hz, 1H), 4.33 (d, *J* = 6.2 Hz, 1H), 4.58 (s, 1H), 5.69 (s, 1H), 6.94 (s, 1H), 7.22-7.43 (m, 15H). MS (ESI-TOF) m/z: $[M+H]^+$ found 573.21.

Computational Methodology

Quantum chemical calculations were carried out in order to explore the structure and the preferred conformations of molecules **7aa** and **8aa**. The structures were optimized at the Density Functional (DFT) level of theory, using the B3LYP hybrid functional[15] and the standard 6-31G(d) basis set. All calculations were performed using the GAMESS program package[16] and graphical representations were produced with GaussView. The optimized structures are depicted in Scheme 3 and in Figs. (S62 and S63) of the Supporting Information. Energy values and Cartesian coordinates are given in Supporting Information.

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References

[1] a) N. Arya, A. Y. Jagdale, T. A. Patil, S. S. Yeramwar, S. S. Holikatti, J. Dwivedi, C. J. Shishoo, K. S. Jain, *Eur. J. Med. Chem.* **2014**, *74*, 619-656; b) P. D. Mehta, N. P. Sengar, A. K. Pathak, *Eur. J. Med. Chem.* **2010**, *45*, 5541-5560.

[2] a) G. Chaubet, T. Coursindel, X. Morelli, S. Betzi, P. Roche, Y. Guari, A. Lebrun, L. Toupet, Y. Collette, I. Parrot, J. Martinez, *Org. Biomol. Chem.* **2013**, *11*, 4719-4726; b) Y. Zheng, C. M. Tice, S. B. Singh, *Bioorg. Med. Chem. Lett.* **2014**, *24*, 3673-3682; c) E. Chupakhin, O. Babich, A. Prosekov, L. Asyakina, M. Krasavin, *Molecules* **2019**, *24*.

[3] a) A. Jarrahpour, E. Ebrahimi, E. De Clercq, V. Sinou, C. Latour, L. Djouhri Bouktab, J. M. Brunel, *Tetrahedron* **2011**, *67*, 8699-8704; b) T. Opatz, M. Dhooghe, H. D. Thi, *Arkivoc* **2019**, *2018*, 314-347; c) G. S. Singh, M. D'hooghe, N. De Kimpe, *Tetrahedron* **2011**, *67*, 1989-2012.

[4] B. S. Santos, T. M. V. D. Pinho e Melo, *Eur. J. Org. Chem.* **2013**, *2013*, 3901-3909.

[5] a) J. C. Sheehan, E. Chacko, Y. S. Lo, D. R. Ponzi, E. Sato, *J. Org. Chem.* **1978**, *42*, 4856-4859; b) D. Habich, K. Metzger, *Heterocycles* **1986**, *24*, 289-296; c) B. S. Santos, C. S. B. Gomes, T. M. V. D. Pinho e Melo, *Tetrahedron* **2014**, *70*, 3812-3821.

[6] a) T. M. V. D. Pinho e Melo, B. S. Santos, I. Bártolo, M. Prudêncio, N. Taveira, Novel Spiro-Lactam Compounds, Process and Uses Thereof, WO/2018/207165, **2018;** b) A. J. S. Alves, N. G. Alves, C. C. Caratao, M. I. M. Esteves, D. Fontinha, I. Bartolo, M. I. L. Soares, S. M. M. Lopes, M. Prudencio, N. Taveira, T. M. V. D. Pinho e Melo, *Curr. Top. Med. Chem.* **2020**, *20*, 140-152;

[7] a) S. Cicchi, A. Goti, A. Brandi, A. Guarna, F. De Sarlo, *Tetrahedron Lett.* **1990**, *31*, 3351-3354; b) S. M. Lait, D. A. Rankic, B. A. Keay, *Chem. Rev.* **2007**, *107*, 767-796.

[8] a) G. Romeo, U. Chiacchio, A. Corsaro, P. Merino, *Chem. Rev.* **2010**, *110*, 3337-3370; b) P. Quadrelli, M. Mella, S. Carosso, B. Bovio, *J. Org. Chem.* **2013**, *78*, 516-526.

[9] a) M. Berthet, T. Cheviet, G. Dujardin, I. Parrot, J. Martinez, *Chem. Rev.* **2016**, *116*, 15235-15283; b) K. V. Gothelf, K. A. Jørgensen, *Chem. Commun.* **2000**, 1449-1458; c) L. Maiuolo, V. Algieri, F. Olivito, A. De Nino, *Catalysts* **2020**, *10*, 65; d) M. A. Chiacchio, S. V. Giofrè, R. Romeo, G. Romeo, U. Chiacchio, *Curr. Org. Synth.* **2016**, *13*, 726-749.

[10] a) J. E. Baldiwn, M. Otsuka, M. P. Wallace, *Tetrahedron* **1986**, *42*, 3097-3110; b) A. Basak, H. M. M. Bdour, G. Bhattacharya, *Tetrahedron Lett.* **1997**, *38*, 2535-2538; c) A. Strauss, H.-H. Otto, *Helv. Chim. Acta* **1997**, *80*, 1823-1830; d) S. Anklam, J. Lisbscher, *Tetrahedron* **1998**, *54*, 6369-6384.

[11] a) H. Dao Thi, B. Danneels, T. Desmet, K. Van Hecke, T. Van Nguyen, M. D'Hooghe, *Asian J. Org. Chem.* **2016**, *5*, 1480-1491; b) X. Wang, F. Meng, Y. Wang, Z. Han, Y. J. Chen, L. Liu, Z. Wang, K. Ding, *Angew. Chem. Int. Ed. Engl.* **2012**, *51*, 9276-9282.

[12] M. M. Andrade, M. T. Barros, R. C. Pinto, *Tetrahedron* **2008**, *64*, 10521-10530.

[13] A. Hassan, M. I. M. Wazeer, S. A. Ali, *J. Chem. Soc. Perkin Trans. 2* **1998**, 393-399.

[14] S. Saouane, G. Buth, F. P. A. Fabbiani, *Acta Crystallogr. Sect. C* **2013**, *69*, 1238-1242.

[15] a) A. D. Becke, *Phys. Rev. A* **1988**, *38*, 3098-3100; b) A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 5648-5652; c) C. Lee, W. Yang, R. G. Parr, *Phys. Rev. B* **1988**, *37*, 785-789.

[16] M. W. Schmidt, K. K. Baldridge, J. A. Boatz, S. T. Elbert, M. S. Gordon, J. H. Jensen, S. Koseki, N. Matsunaga, K. A. Nguyen, S. Su, T. L. Windus, M. Dupuis, J. A. Montgomery Jr, *J. Comput. Chem.* **1993**, *14*, 1347-1363.