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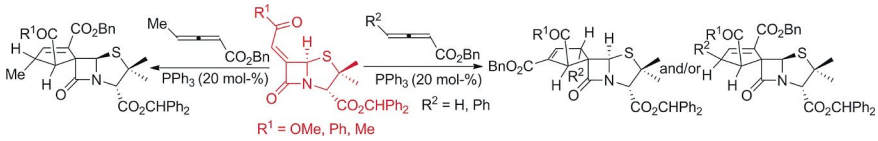

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Synthesis of Chiral Spirocyclopentenyl-β-lactams through Phosphane-Catalyzed [3+2] Annulation of Allenoates with 6-Alkylidenepenicillanates

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The first examples of phosphane-catalyzed [3+2] annulation of allenoates to 6-alkylidenepenicillanates leading to chiral spirocyclopentenyl-β-lactams are reported. The synthesis of this new type of β-lactams involved the generation of either two or three consecutive stereogenic centers, including a quaternary chiral center. Although the reported methodology is highly diastereoselective, the regioselectivity is dependent on the nature of the methylenepenicillanate derivative and on the nature of the allenoate γ-substituent.

Introduction

Since the discovery of penicillins and cephalosporins as antibiotics, the chemistry of β-lactams has attracted considerable attention. However, the extensive clinical use of these antibacterial agents has resulted in an increasing number of resistant strains of bacteria. Penicillin resistance is often caused by the action of enzymes known as β-lactamases, which cleave the reactive β-lactam bond of the antibiotic making it ineffective. Thus, the β-lactam ring is the core of the biological activity of a large class of antibiotics and also of several β-lactamase inhibitors.[1] The demand for more efficient β-lactam antibiotics and β-lactamase inhibitors has led to increasing interest in the design of new functionalized 2-azetidinones.

β-Lactams are also interesting synthons in organic synthesis, providing routes to α- and β-amino acids and peptides.[2] Structures with a spiro-β-lactam core are also interesting target molecules, because some derivatives exhibit relevant biological properties, namely cholesterol absorption inhibition, antibacterial activity and antiviral activity.[3] In peptidomimetic chemistry, spiro-β-lactams are used as β-turn mimetics.[4] Thus, the search for new spiro-β-lactam derivatives is of great interest in medicinal chemistry.

An approach to new penicillin analogues is to explore the reactivity of 6-diazopenicillanates or 6-alkylidenepenicillanates for the functionalization at C-6, keeping the penicillanate nucleus. In fact, chiral spiro-2-pyrazolinepenicillanates can be obtained from the 1,3-dipolar cycloaddition of 6-diazopenicillanates.[3a,3b,5] Our own contribution[5] established that cycloaddition with dipolarophiles such as acrylonitrile, acrylates or methyl vinyl ketone affords spiro-2-pyrazoline-β-lactams, whereas with *N*-substituted maleimides, spiro-1-pyrazoline-β-lactams are obtained. Microwave-induced denitrogenation of these spiro-1-pyrazoline-β-lactams allows the stereoselective synthesis of novel spirocyclopropyl-β-lactams. 6-Diazopenicillanates also react with electron-deficient alkynes to give the corresponding spiro-3*H*-pyrazole-β-lactam as a single product.[5] The observed stereoselectivity can be explained by considering that the major product results from addition to the sterically less hindered α-side of the β-lactam. Reaction of 6-diazopenicillanates with aromatic imines, aldehydes and ketones leading to spiro-aziridine-penicillanates[6] and spiro-epoxide-penicillanates,[7] respectively, are also known. On the other hand, 6-alkylidenepenicillanates participate in 1,3-dipolar cycloaddition reactions with diphenyldiazomethane to give spiro-1-pyrazolinepenicillanates, which undergo thermally induced ring contraction to afford spirocyclopropylpenicillanates.[3a] Spirocyclopropylpenicillanates have also been prepared through rhodium-catalyzed cyclopropanation of a 6-diazopenicillanate sulfone[8a] and by the Cu^{I}-catalyzed reaction of 6-bromopenicillanoylmagnesium bromide with α,β-unsaturated esters.[8b]

Phosphane-catalyzed [3+2] annulations of allenoates with electron-deficient alkenes is a powerful synthetic strategy for the construction of cyclopentene derivatives.[9] Cristau et al. found that in the presence of phosphanes the addition of nucleophiles to electron-deficient allenes takes place at the β,γ-carbon–carbon double bond (umpolung addition).[10] They observed that the reaction of methyl 2,3-butadienoate (**1**) with triphenylphosphane followed by the addition of NaI affords **2**, which undergoes nucleophilic attack at the γ-carbon atom leading to **3**. Lu et al. explored the reactivity of 1,3-dipoles generated from allenoates and phosphanes as the three-carbon synthon in formal [3+2] cycloaddition reactions.[11] This pioneering work included the synthesis of cyclopentene derivatives via allenoate-derived 1,3-dipoles and electron-deficient alkenes. The reac-

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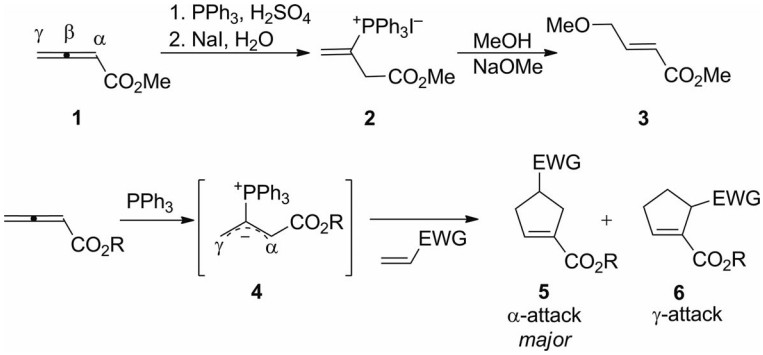
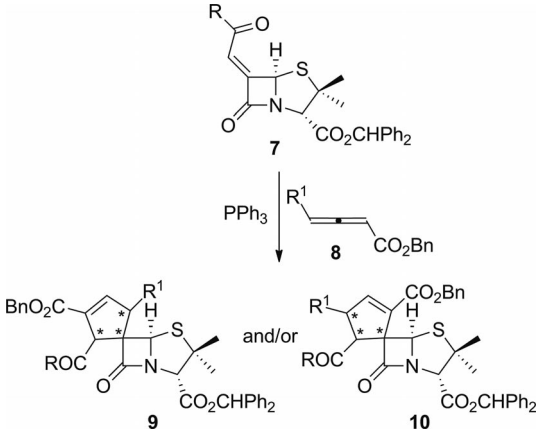


Scheme 1. Phosphane-catalyzed reactions of allenoates.

tion with alkenes such as acrylates and methyl vinyl ketone affords regioisomeric cyclopentenes **5** and **6**. The selectivity towards the former regioisomer can be rationalized as resulting from the initial conjugate addition of the α-position of the dipole to the alkene (Scheme 1).

Since this disclosure, cycloaddition of allenoates to a wide range of electron-deficient alkenes has been studied.[9,12–16] These included the use of chiral phosphanes for the enantioselective synthesis of cyclopentenes[14,15] as well as the use of chiral substrates to provide cyclopentenes in a diastereoselective manner.[16] This annulation methodology, when applied to exocyclic alkenes, provides an approach to spirocyclic compounds.[13,15,16a,16b]

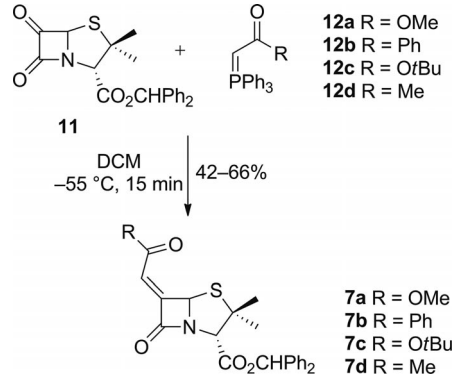
In this context, we decided to study the phosphane-catalyzed [3+2] cycloaddition of allenoates to 6-alkylidenepenicillanates **7** as a route to chiral spirocyclopentene-β-lactams (Scheme 2). This chemistry would allow the generation of two (**8**; R^1 = H) or three (**8**; $R^1 \neq$ H) consecutive stereogenic centers, including a quaternary stereocenter, leading to a new class of penicillanate derivatives **9** and **10**.



Scheme 2. Synthetic strategy for the synthesis of chiral spirocyclopentenyl-β-lactams.

Results and Discussion

6-Alkylidenepenicillanates **7** were obtained by Wittig reaction of the appropriate phosphorus ylide with 6-oxopenicillanate **11** (Scheme 3).[17] Compound **11** was initially prepared from 6-aminopenicillanic acid (6-APA) according to a known procedure.[18] This method involves the conversion of 6-APA into 6-hydroxypenicillanic acid, followed by esterification and final oxidation to the 6-oxo derivative. However, we decided to use an alternative method that proved to be a more efficient approach to 6-oxopenicillanate **11**.[19] This synthetic strategy involves the synthesis of 6-diazopenicillanate from benzhydryl 6-β-aminopenicillanate,[20] followed by rhodium-catalyzed oxidation of the diazo derivative in the presence of propylene oxide to give the target 6-oxopenicillanate.

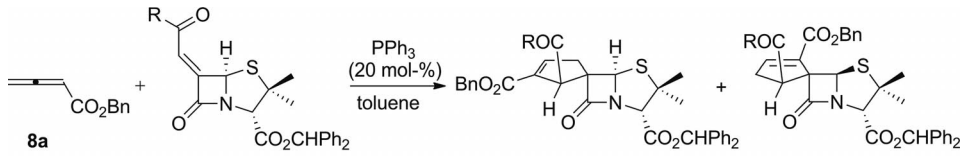


Scheme 3. Synthesis of 6-alkylidenepenicillanates **7**.

The formal [3+2] cycloaddition of benzyl 2,3-butadienoate (**8a**) with 6-alkylidenepenicillanates **7** was explored (Table 1). Allenoate **8a** reacted with 6-alkylidenepenicillanate **7a** in the presence of triphenylphosphane at room temperature for 3 h, to produce regioisomeric spiro-β-lactams **13a** and **14a**, in 48% overall yield (Entry 1). By carrying out the same reaction for 5 h, the overall yield was improved to 68% (Entry 2). The structural assignment of these chiral compounds **13a** and **14a** was made on the basis of 2D NOESY, HMQC and HMBC spectra (400 MHz). The NOESY spectra of these compounds showed cross peaks between 1′-H and the β-Me protons, but no correlation was observed between 1′-H and 5-H.

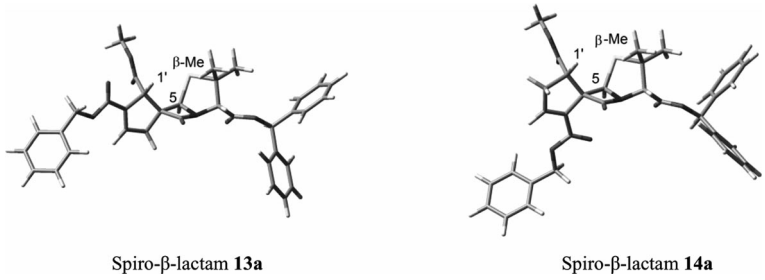
Quantum chemical calculations were carried out at the Hartree–Fock level of theory by using the 6-31G(d) basis set to determine the optimized geometries of spiro-β-lactams **13a** and **14a**, followed by harmonic frequency calcula-

Table 1. Phosphane-catalyzed [3+2] annulation of allenoate **8a** with 6-alkylidenepenicillanates **7a**–**d**.



Entry	β-Lactam **7**	Reaction conditions	Isolated yield [%] γ-Regioisomer **13**	α-Regioisomers **14**
1	**7a**	r.t., 3 h	27	21
2	**7a**	r.t., 5 h	41	27
3	**7b**	r.t., 5 h	35	53
4	**7c**	r.t., 5 h	50 (31:69)[a]	
5	**7d**	r.t., 3 h	41	–

[a] Regioisomeric ratio determined by ^{1}H NMR spectroscopic analysis.



Spiro-β-lactam **13a** Spiro-β-lactam **14a**

Figure 1. Optimized geometries of spiro-β-lactams **13a** and **14a** at the HF/6-31G(d) level.

tions, at the same level of theory, which allowed characterization of the nature of the stationary points (Figure 1). The calculated structures corroborate the stereochemistry assignment of these β-lactams and are in agreement with the NOE experiments.

The work was then extended to other 6-alkylidenepenicillanates (Table 1). Benzyl 2,3-butadienoate (**8a**) reacted with 6-alkylidenepenicillanate **7b** at room temperature for 5 h to produce the spiro-β-lactams **13b** and **14b** in 88% overall yield (Entry 3). The reaction of 6-alkylidenepenicillanate **7c** with allenoate **8a** at room temperature for 5 h also gave the regioisomeric spiro-β-lactams **13c** and **14c**, in 50% overall yield (Entry 4). Unfortunately, **13c** and **14c** could not be separated by flash chromatography. Interestingly, the reaction of 6-alkylidenepenicillanate **7d** with the same allenoate at room temperature gave spiro-β-lactam **13d** regioselectively in 41% yield (Entry 5).

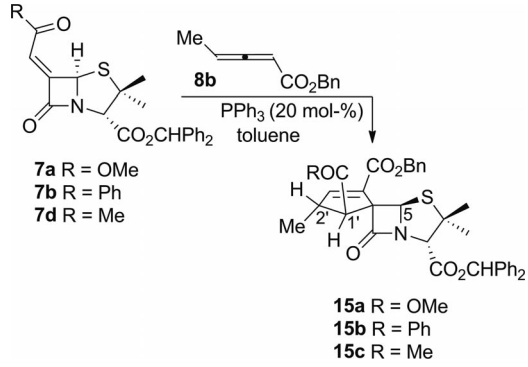
It has been previously observed that the formal phosphane-catalyzed [3+2] cycloaddition of exocyclic alkenes to allenoates can lead to a regioselection that differs from that observed in the cycloaddition with acrylates[15b] (see Scheme 1). The results on the formal [3+2] cycloaddition of **8a** with 6-alkylidenepenicillanates **7** showed that the regioselectivity depends on the nature of the methylenepenicillanate derivative. In the case of 1-methoxycarbonylmethylenepenicillanate the synthesis of the γ-regioisomer is favored, whereas the γ-regioisomer is formed exclusively from the 1-acetylmethylene derivative. However, with 1-benzoylmethylenepenicillanate the opposite regioselectivity was observed. Thus, a combination of steric and electronic effects must be considered to explain the regioselectivity of these [3+2] annulation reactions. It is noteworthy that the α- and γ-regioisomers were isolated as single stereoisomers.

The reactivity of 6-alkylidenepenicillanates towards benzyl 2,3-pentadienoate (**8b**) in the presence of triphenylphosphane was also explored (Table 2). Spirocyclopentenyl-β-lactam **15a** was prepared as the only product in 48% yield, by the [3+2] annulation reaction of allenoate **8b** with **7a** (Entry 1). The stereochemistry assignment of compound **15a** was made on the basis of 2D NOESY experiments (400 MHz). In this spectrum, 1′-H showed correlation with the β-Me protons, but no cross peaks were observed between 1′-H and 5-H nor between 1′-H and 2′-H.

Benzyl 2,3-pentadienoate (**8b**) reacted with **7b** at room temperature for 5 h to give spiro-β-lactam **15b** as a single product, in 36% yield (Table 2, Entry 2). The chiral spiro-β-lactam **15c** was also obtained regio- and stereoselectively from the reaction of allenoate **8b** with 6-alkylidenepenicillanate **7d** (Entry 3).

The study of the reactivity of 6-alkylidenepenicillanates **7** towards γ-substituted allenoate **8b** showed that the PPh_3-catalyzed [3+2] cycloaddition also proceeds, with the regioselective synthesis of the α-regioisomer being observed regardless of the nature of the methylenepenicillanate deriv-

Table 2. Phosphane-catalyzed [3+2] annulation of allenoate **8b** with 6-alkylidenepenicillanates **7a**, **7b** and **7d**.



Entry	β-Lactam **7**	Reaction conditions	Isolated yield of **15** [%]
1	**7a**	r.t., 5 h	48
2	**7b**	r.t., 5 h	36
3	**7d**	r.t., 3 h	37

ative, through a process in which three new chiral centers are formed.

The study was then extended to the reaction of benzyl 4-phenyl-2,3-butadienoate (**8c**) with 6-alkylidenepenicillanates in the presence of triphenylphosphane (Table 3). Spiro-β-lactam **16a** was prepared in 56% yield as a single product by the reaction of allene **8c** with 6-alkylidenepenicillanate **7a** at room temperature for 7 h (Entry 1). The assignment of the stereochemistry of compound **16a** was made on the basis of 2D NOESY spectra (400 MHz), in which 1′-H showed a correlation with the β-Me protons, but no cross peaks were found between 1′-H and 5-H. On the other hand, cross peaks were observed between the 4′-H and 5-H, but no correlation was observed between 1′-H and 4′-H.

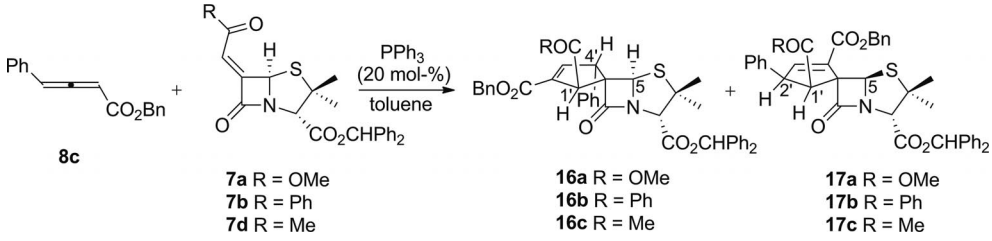
Spirocyclopentenyl-β-lactam **17b** was prepared regio- and stereoselectively in high yield (84%) by the reaction of 6-alkylidenepenicillanate **7b** with allenoate **8c** at room temperature for 7 h (Table 3, Entry 2). When the reaction was allowed to proceed for 24 h, the same regioselectivity was observed, but compound **17b** was obtained in lower yield (Entry 3). This result indicates that prolonged reaction time leads to decomposition of the product. In fact, we believe that, in general, the isolated yields of the reported reactions of 6-alkylidenepenicillanates are affected by the ease of the isolation or stability of products. It is worth noting that the cycloaddition of 1-benzoylmethylenepenicillanate (**7b**) with all the studied allenoates led to the synthesis of the α-regioisomer as either the only or the major product.

The reaction of benzyl 4-phenyl-2,3-butadienoate (**8c**) and 6-alkylidenepenicillanate **7d** at room temperature for 7 h led to the formation of spirocyclopentenyl-β-lactams **16c** and **17c**, in 43% overall yield (Table 3, Entry 4). By carrying out the same reaction for 24 h, the overall yield was improved to 60% (Entry 5). The stereochemistry assignment of compounds **17b** and **17c** was also made on the basis of 2D NOESY experiments (400 MHz). In these spectra, 1′-H showed correlation with the β-Me protons and with 2′-H. On the other hand, no correlation was observed between 5-H and either 1′-H or 2′-H. It is noteworthy that α-regioisomers **17** had a configuration at C-2′ opposite to that of compounds **15**, resulting from the PPh_3-catalyzed reaction of 6-alkylidenepenicillanates when methyl-substituted allenoate **8b** was used. Other examples are known in which the stereochemical outcome of the cycloaddition of exocyclic alkenes with allenoates bearing γ-substituents (Me vs. Ph) depends on the nature of the substituent.[16a]

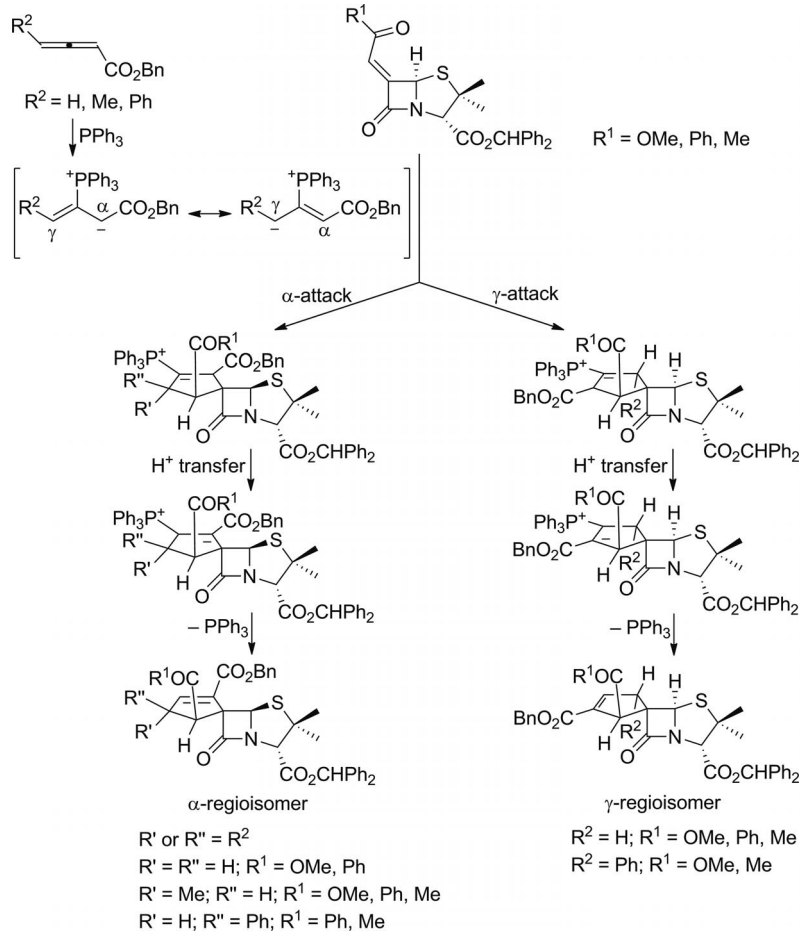
Finally, attempts to carry out the reaction of benzyl 4,4-ethylphenyl-2,3-butadienoate with 6-alkylidenepenicillanates **7a** and **7b** in the presence of triphenylphosphane were unsuccessful.

The synthesis of the new spirocyclopentenyl-β-lactams can be rationalized as shown in Scheme 4. Conjugate addition of the dipole to the 6-alkylidenepenicillanates occurs to the sterically less hindered α-side of the β-lactam, followed by ring closure, proton transfer and elimination to regenerate triphenylphosphane. The "butterfly" conformation of the penicillanate ring system ensures that reactions at the 6-position occur with high selectivity, involving the approach of the reagents from this face.[1b,3f] The formation

Table 3. Phosphane-catalyzed [3+2] annulation of allenoate **8c** with 6-alkylidenepenicillanates **7a**, **7b** and **7d**.



Entry	β-Lactam **7**	Reaction conditions	Isolated yield [%]	
			16	**17**
1	**7a**	r.t., 7 h	56	–
2	**7b**	r.t., 7 h	–	84
3	**7b**	r.t., 24 h	–	55
4	**7d**	r.t., 7 h	5	38
5	**7d**	r.t., 24 h	12	48



Scheme 4. Possible mechanism for the synthesis of spirocyclopentenyl-β-lactams.

of α- and/or γ-regioisomers will depend on the initial attack of the dipole at C-6 of the β-lactam, which can involve either the α- or the γ-position. The different stereochemical outcome observed in the synthesis of α-regioisomers **15** and **17**, obtained from methyl- or phenyl-substituted allenoates, respectively, can be explained by considering that the bulky phenyl group *trans* to the triphenylphosphonium moiety of the zwitterion will be favored, whereas the methyl substituent may accommodate a *cis* relationship.

Conclusions

Herein, a synthetic methodology leading to a new type of chiral spiro-β-lactam is described. For the first time, phosphane-catalyzed [3+2] annulation of allenoates to 6-alkylidenepenicillanates was explored, which gave access to chiral spirocyclopentenyl-β-lactams in a process involving the generation of either two or three consecutive stereogenic centers, including a quaternary chiral center.

Experimental Section

General: 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 and ^{13}C NMR spectra were recorded with a Bruker Avance III instrument operating at 400 MHz and 100 MHz, respectively; chemical shifts are expressed in ppm relatively to internal tetramethylsilane (TMS), and coupling constants (*J*) are in Hertz. IR spectra were recorded with a Perkin-Elmer 1720X FTIR spectrometer. Optical rotations were measured with an Optical Activity AA-5 electrical polarimeter. Mass spectra were recorded with a Hewlett-Packard 5989B spectrometer under electrospray ionization (ESI). HR mass spectra were obtained with an electrospray (ESI) TOF VG Autospec M spectrometer. Melting points were recorded with a Reichert hot stage. Benzhydryl 6-β-aminopenicillanate,[19] benzhydryl 6-oxopenicillinate,[20] phosphorus ylides **12a**–**d**[21] and allenes **8a**–**d**[22] were prepared as described in the literature.

General Procedure for the Synthesis of 6-Alkylidenepenicillanates: Benzhydryl 6-oxopenicillinate **11**[19] (2.73 mmol) was dissolved in dichloromethane (13 mL), the solution was cooled to –55 °C under nitrogen, and the appropriate phosphorus ylide (2.57 mmol) in dichloromethane (30 mL) was added dropwise. Stirring was continued for 10 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 product was purified by flash chromatography.

Benzhydryl 6-(*Z*)-(1-Methoxycarbonylmethylene)penicillanate (7a): Prepared from 6-oxopenicillanate **11** (0.33 g, 0.87 mmol) and phosphorus ylide **12a** (0.34 g, 0.83 mmol), as described in the general procedure. After purification by flash chromatography (hexane/ethyl acetate, 2:1), compound **7a** was obtained as a brown oil

(0.24 g, 0.55 mmol, 66%); $[\alpha]_D^{20}$ = +220 (*c* = 1, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 1779, 1743, 1732 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.27 (s, 3 H, 2α-Me), 1.56 (s, 3 H, 2β-Me), 3.81 (s, 3 H, CO_2Me), 4.66 (s, 1 H, 3-H), 6.03 (s, 1 H, 5-H), 6.31 (s, 1 H, C*H*CO_2Me), 6.96 (s, 1 H, C*H*Ph_2), 7.32–7.38 (m, 10 H, Ar-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.4, 33.6, 52.5, 63.9, 69.0, 70.7, 78.5, 115.4, 127.1, 127.6, 128.2, 128.4, 128.6, 128.7, 139.1, 139.2, 156.8, 164.2, 166.3, 166.7 ppm. MS (ESI): *m*/*z* (%) = 460 (45) [M + Na^+], 279 (7), 167 (100). HRMS (ESI): calcd. for $C_{24}H_{23}NNaO_5S$ [M + Na^+] 460.11891; found 460.11841.

Benzhydryl 6-(*Z*)-(1-Benzoylmethylene)penicillanate (7b): Prepared from 6-oxopenicillanate **11** (1.00 g, 2.62 mmol) and phosphorus ylide **12b** (0.94 g, 2.47 mmol), as described in the general procedure. After purification by flash chromatography (hexane/ethyl acetate, 2:1), compound **7b** was obtained as a yellow oil (0.57 g, 1.18 mmol, 48%); $[\alpha]_D^{20}$ = +110 (*c* = 1, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 1774, 1745, 1638 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.28 (s, 3 H, 2α-Me), 1.59 (s, 3 H, 2β-Me), 4.68 (s, 1 H, 3-H), 6.16 (s, 1 H, 5-H), 6.98 (s, 1 H, C*H*Ph_2), 7.31–7.41 (m, 10 H, Ar-H), 7.50–7.54 (m, 2 H, Ar-H), 7.62–7.66 (m, 1 H, Ar-H), 7.99 (d, ^3J = 7.6 Hz, 2 H, Ar-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.5, 33.4, 63.8, 69.7, 71.1, 78.4, 116.2, 127.1, 127.5, 128.2, 128.4, 128.6, 128.7, 129.0, 134.1, 135.0, 137.0, 139.0, 139.2, 156.3, 166.8, 167.4, 188.3 ppm. MS (ESI): *m*/*z* (%) = 506 (17) [M + Na^+], 279 (7), 167 (100). HRMS (ESI): calcd. for $C_{29}H_{25}NNaO_4S$ [M + Na^+] 506.13965; found 506.13752.

Benzhydryl 6-(*Z*)-(1-*tert*-Butoxycarbonylmethylene)penicillanate (7c): Prepared from 6-oxopenicillanate **11** (1.08 g, 2.83 mmol) and phosphorus ylide **12c** (1.00 g, 2.66 mmol), as described in the general procedure. After purification by flash chromatography (hexane/ethyl acetate, 2:1), compound **7c** was obtained as a brown oil (0.64 g, 1.33 mmol, 50%); $[\alpha]_D^{20}$ = +150 (*c* = 0.4, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 1780, 1745, 1723 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.28 (s, 3 H, 2α-Me), 1.52 (s, 9 H, CO_2tBu), 1.57 (s, 3 H, 2β-Me), 4.65 (s, 1 H, 3-H), 5.99 (s, 1 H, 5-H), 6.19 (s, 1 H, C*H*CO_2tBu), 6.95 (s, 1 H, C*H*Ph_2), 7.30–7.37 (m, 10 H, Ar-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.5, 28.1, 33.8, 63.9, 69.2, 70.7, 78.4, 82.8, 118.1, 127.1, 127.5, 128.2, 128.6, 128.7, 139.1, 139.2, 155.1, 62.9, 166.8 ppm. MS (ESI): *m*/*z* (%) = 502 (68) [M + Na^+], 167 (100). HRMS (ESI): calcd. for $C_{27}H_{29}NNaO_5S$ [M + Na^+] 502.16586; found 502.16531.

Benzhydryl 6-(*Z*)-(1-Acetylmethylene)penicillanate (7d): Prepared from 6-oxopenicillanate **11** (2.86 g, 7.50 mmol) and phosphorus ylide **12d** (2.24 g, 7.04 mmol), as described in the general procedure. After purification by flash chromatography (hexane/ethyl acetate, 2:1), compound **7d** was obtained as a brown oil (1.25 g, 2.97 mmol, 42%); $[\alpha]_D^{20}$ = +230 (*c* = 1, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 1776, 1744, 1655 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.27 (s, 3 H, 2α-Me), 1.56 (s, 3 H, 2β-Me), 2.35 (s, 3 H, CO*Me*), 4.66 (s, 1 H, 3-H), 6.03 (s, 1 H, 5-H), 6.54 (s, 1 H, C*H*COMe), 6.96 (s, 1 H, C*H*Ph_2), 7.31–7.38 (m, 10 H, Ar-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.4, 31.3, 33.6, 64.0, 69.4, 70.9, 78.5, 120.0, 127.1, 127.6, 128.2, 128.4, 128.6, 128.7, 139.1, 139.2, 154.2, 166.7, 167.7, 196.2 ppm. MS (ESI): *m*/*z* (%) = 422 (100) [M + H^+], 268 (43). HRMS (ESI): calcd. for $C_{24}H_{24}NO_4S$ [M + H^+] 422.14206; found 422.14104.

General Procedure for the Synthesis of Spirocyclopentenyl-β-lactams: To a mixture of the appropriate 6-alkylidenepenicillanate (0.40 mmol) and PPh_3 (20 mol-%) in toluene (3 mL), a solution of the allene **7** (0.40 mmol) in toluene (2 mL) was added. The reaction mixture was stirred at room temperature under nitrogen for the time 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.

(1′*R*,6*R*)-3-Benzhydryl 2′-Benzyl 1′-Methyl Spiro(cyclopent-3-enyl)-5′,6-penicillanate-1′,2′,3-tricarboxylate (13a) and (1′*R*,6*S*)-3-Benzhydryl 4′-Benzyl 1′-Methyl Spiro(cyclopent-4-enyl)-5′,6-penicillanate-1′,4′,3-tricarboxylate (14a): Obtained from allene **8a** (71 mg, 0.41 mmol) and 6-alkylidenepenicillanate **7a** (180 mg, 0.41 mmol) as described in the general procedure (reaction time: 5 h). Purification of the crude product by flash chromatography (hexane/ethyl acetate, 3:1, then hexane/ethyl acetate, 2:1), gave, in order of elution, **13a** as a yellow oil (101 mg, 0.17 mmol, 41%) and **14a** as a yellow oil (66 mg, 0.11 mmol, 27%).

Compound 13a: $[\alpha]_D^{20}$ = +210 (*c* = 1, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 1777, 1745, 1727, 1686 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.23 (s, 3 H, 2α-Me), 1.59 (s, 3 H, 2β-Me), 3.05 (dd, ^2J = 18.4, ^3J = 2.8 Hz, 1 H, 4′-H), 3.32 (pseudo-d, ^2J = 18.4 Hz, 1 H, 4′-H), 3.66 (s, 3 H, CO_2Me), 4.06 (s, 1 H, 1′-H), 4.53 (s, 1 H, 3-H), 5.12 (d, ^2J = 12.4 Hz, 1 H, CH_2Ph), 5.23 (d, ^2J = 12.4 Hz, 1 H, CH_2Ph), 5.40 (s, 1 H, 5-H), 6.93 (s, 1 H, C*H*Ph_2), 7.00 (br. s, 1 H, 3′-H), 7.32–7.36 (m, 15 H, Ar-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.0, 32.8, 40.0, 52.2, 52.5, 63.5, 66.6, 67.9, 68.7, 70.8, 78.4, 127.0, 127.6, 128.2, 128.3, 128.4, 128.5, 128.6, 134.3, 135.6, 139.2, 145.2, 162.5, 166.9, 171.7, 175.3 ppm. MS (ESI): *m*/*z* (%) = 634 (87) [M + Na^+], 492 (24), 167 (100). HRMS (ESI): calcd. for $C_{35}H_{33}NNaO_7S$ [M + Na^+] 634.18699; found 634.18726.

Compound 14a: $[\alpha]_D^{20}$ = +220 (*c* = 0.75, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 1772, 1735, 1732, 1716 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.10 (s, 3 H, 2α-Me), 1.50 (s, 3 H, 2β-Me), 2.54 (dd, ^2J = 18.8, ^3J = 2.4 Hz, 1 H, 2′-H), 3.01 (ddd, ^2J = 18.8, ^3J = 8.4 and 2.0 Hz, 1 H, 2′-H), 3.48 (pseudo-d, ^3J = 8.4 Hz, 1 H, 1′-H), 3.61 (s, 3 H, CO_2Me), 4.48 (s, 1 H, 3-H), 5.11 (s, 2 H, CH_2Ph), 6.08 (s, 1 H, 5-H), 6.86 (s, 1 H, C*H*Ph_2), 6.93 (br. s, 1 H, 3′-H), 7.18–7.39 (m, 15 H, Ar-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.6, 32.3, 35.3, 46.8, 51.4, 61.4, 65.4, 67.6, 69.7, 72.0, 77.2, 126.3, 126.4, 127.1, 127.2, 127.3, 127.5, 132.6, 134.6, 138.4, 145.0, 161.4, 165.5, 172.1, 172.4 ppm. MS (ESI): *m*/*z* (%) = 634 (100) [M + Na^+], 167 (82). HRMS (ESI): calcd. for $C_{35}H_{33}NNaO_7S$ [M + Na^+] 634.18699; found 634.18757.

(1′*R*,6*R*)-3-Benzhydryl 2′-Benzyl 1′-Benzoylspiro(cyclopent-3-enyl)-5′,6-penicillanate-3,2′-dicarboxylate (13b) and (1′*R*,6*S*)-3-Benzhydryl 4′-Benzyl 1′-Benzoylspiro(cyclopent-4-enyl)-5′,6-penicillanate-3,4′-dicarboxylate (14b): Obtained from allene **8a** (70 mg, 0.40 mmol) and 6-alkylidenepenicillanate **7b** (193 mg, 0.40 mmol) as described in the general procedure (reaction time: 5 h). Purification of the crude product by flash chromatography (hexane/ethyl acetate, 5:1), gave, in order of elution, **13b** as a yellow oil (94 mg, 0.14 mmol, 35%) and **14b** as a fluffy yellow solid (138 mg, 0.21 mmol, 53%).

Compound 13b: $[\alpha]_D^{20}$ = +280 (*c* = 1, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 1775, 1746, 1716, 1671 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.11 (s, 3 H, 2α-Me), 1.51 (s, 3 H, 2β-Me), 3.10 (dd, ^2J = 18.4, ^3J = 2.8 Hz, 1 H, 4′-H), 3.55 (pseudo-d, ^2J = 18.4 Hz, 1 H, 4′-H), 4.53 (s, 1 H, 3-H), 4.96 (s, 2 H, CH_2Ph), 5.17 (br. s, 1 H, 1′-H), 5.43 (s, 1 H, 5-H), 6.91 (s, 1 H, C*H*Ph_2), 7.06 (br. s, 1 H, 3′-H), 7.13 (m, 2 H, Ar-H), 7.25–7.41 (m, 15 H, Ar-H), 7.52–7.56 (m, 1 H, Ar-H), 8.06 (d, ^3J = 7.6 Hz, 2 H, Ar-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.0, 32.4, 40.7, 52.7, 64.1, 66.6, 69.0, 70.6, 71.1, 78.3, 127.0, 127.6, 128.2, 128.3, 128.3, 128.4, 128.5, 128.6, 128.6, 129.3, 133.5, 135.3, 135.8, 137.3, 139.1, 139.2, 145.8, 162.7, 166.9, 176.3, 201.0 ppm. MS (ESI): *m*/*z* (%) = 680 (16) [M + Na^+], 492 (8), 167 (100). HRMS (ESI): calcd. for $C_{40}H_{35}NNaO_6S$ [M + Na^+] 680.20773; found 680.20745.

Compound 14b: M.p. 110–112 °C; $[\alpha]_D^{20}$ = +385 (*c* = 1, CH_2Cl_2). IR (KBr): $\tilde{\nu}$ = 1781, 1750, 1721, 1677 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.11 (s, 3 H, 2α-Me), 1.52 (s, 3 H, 2β-Me), 2.51 (dd, ^2J = 18.8, ^3J = 2.4 Hz, 1 H, 2′-H), 3.20 (ddd, ^2J = 18.8, ^3J = 8.4 and 2.0 Hz, 1 H, 2′-H), 4.55 (s, 1 H, 3-H), 4.56 (pseudo-d, ^3J = 8.4 Hz, 1 H, 1′-H), 5.21 (s, 2 H, CH_2Ph), 6.29 (s, 1 H, 5-H), 6.91 (br. s, 1 H, 3′-H), 6.94 (s, 1 H, C*H*Ph_2), 7.29–7.51 (m, 17 H, Ar-H), 7.58–7.62 (m, 1 H, Ar-H), 7.94 (d, ^3J = 7.2 Hz, 1 H, Ar-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.7, 31.6, 34.8, 48.3, 61.5, 65.4, 68.0, 69.9, 72.8, 77.2, 126.3, 126.3, 127.0, 127.1, 127.2, 127.3, 127.4, 127.5, 127.5, 127.9, 132.5, 133.2, 134.0, 134.7, 138.5, 143.7, 161.4, 165.6, 173.2, 197.2 ppm. MS (ESI): *m*/*z* (%) = 680 (64) [M + Na^+], 658 (20), 167 (100). HRMS (ESI): calcd. for $C_{40}H_{35}NNaO_6S$ [M + Na^+] 680.20773; found 680.20760.

(1′*R*,6*R*)-3-Benzhydryl 2′-Benzyl 1′-*tert*-Butyl Spiro(cyclopent-3-enyl)-5′,6-penicillanate-1′,2′,3-tricarboxylate (13c) and (1′*R*,6*S*)-3-Benzhydryl 4′-Benzyl 1′-*tert*-Butyl Spiro(cyclopent-4-enyl)-5′,6-penicillanate-1′,4′,3-tricarboxylate (14c): Obtained from allene **8a** (72 mg, 0.41 mmol) and 6-alkylidenepenicillanate **7c** (198 mg, 0.41 mmol) as described in the general procedure (reaction time: 5 h). Purification by flash chromatography (hexane/ethyl acetate, 3:1) gave a mixture of compounds **13c** and **14c** as a colorless oil (135 mg, 0.21 mmol, 50%).

Compound 13c: IR (film): $\tilde{\nu}$ = 1774, 1746, 1720, 1631 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.16 (s, 3 H, 2α-Me), 1.30 (s, 9 H, CO_2tBu), 1.54 (s, 3 H, 2β-Me), 2.92 (dd, ^2J = 18.4, ^3J = 2.8 Hz, 1 H, 4′-H), 3.21 (pseudo-d, ^2J = 18.4 Hz, 1 H, 4′-H), 3.88 (s, 1 H, 1′-H), 4.46 (s, 1 H, 3-H), 5.13 (d, ^2J = 2.0 Hz, 1 H, CH_2Ph), 5.36 (s, 1 H, 5-H), 6.86 (s, 1 H, C*H*Ph_2), 6.93 (br. s, 1 H, 3′-H), 7.18–7.39 (m, 15 H, Ar-H) ppm. MS (ESI): *m*/*z* (%) = 654 (17) [M + H^+], 598 (14), 167 (100). HRMS (ESI): calcd. for $C_{38}H_{40}NO_7S$ [M + H^+] 654.25200; found 654.25266.

Compound 14c: IR (film): $\tilde{\nu}$ = 1774, 1746, 1720, 1631 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.13 (s, 3 H, 2α-Me), 1.35 (s, 9 H, CO_2tBu), 1.52 (s, 3 H, 2β-Me), 2.50 (dd, ^2J = 18.8, ^3J = 2.8 Hz, 1 H, 1 H, 2′H), 3.01 (ddd, ^2J = 18.8, ^3J = 8.4 and 1.6 Hz, 1 H, 1 H, 2′-H), 3.37 (pseudo-d, ^3J = 8.4 Hz, 1 H, 1′-H), 4.48 (s, 1 H, 3-H), 5.10 (s, 2 H, CH_2Ph), 6.11 (s, 1 H, 5-H), 6.86 (s, 1 H, C*H*Ph_2), 6.93 (br. s, 1 H, 3′-H), 7.26–7.36 (m, 15 H, Ar-H) ppm. MS (ESI): *m*/*z* (%) = 654 (17) [M + H^+], 598 (14), 167 (100). HRMS (ESI): calcd. for $C_{38}H_{40}NO_7S$ [M + H^+] 654.25200; found 654.25266.

(1′*R*,6*R*)-3-Benzhydryl 2′-Benzyl 1′-Acetylspiro(cyclopent-3-enyl)-5′,6-penicillanate-3,2′-dicarboxylate (13d): Obtained from allene **8a** (71 mg, 0.41 mmol) and 6-alkylidenepenicillanate **7d** (172 mg, 0.41 mmol) as described in the general procedure (reaction time: 3 h). After purification by flash chromatography (hexane/ethyl acetate, 4:1 to 2:1), **13d** was obtained as a yellow oil (99 mg, 0.17 mmol, 41%); $[\alpha]_D^{20}$ = +220 (*c* = 0.5, CH_2Cl_2). IR (KBr): $\tilde{\nu}$ = 1775, 1744, 1709, 1630 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.22 (s, 3 H, 2α-Me), 1.62 (s, 3 H, 2β-Me), 2.42 (s, 3 H, CO*Me*), 2.99 (dd, ^2J = 18.4, ^3J = 2.8 Hz, 1 H, 1 H, 4′-H), 3.33 (pseudo-d, ^2J = 18.4 Hz, 1 H, 1 H, 4′-H), 4.28 (s, 1 H, 1′-H), 4.54 (s, 1 H, 3-H), 5.15 (d, ^2J = 12.4 Hz, 1 H, CH_2Ph), 5.20 (d, ^2J = 12.4 Hz, 1 H, CH_2Ph), 5.42 (s, 1 H, 5-H), 6.93 (s, 1 H, C*H*Ph_2), 6.98 (br. s, 1 H, 3′-H), 7.26–7.36 (m, 15 H, Ar-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.1, 32.6, 32.8, 40.1, 58.4, 63.8, 66.8, 69.0, 69.7, 70.9, 78.3, 127.0, 127.8, 128.2, 128.4, 128.5, 128.6, 128.6, 134.8, 135.4, 139.1, 139.2, 145.6, 163.1, 166.9, 176.0, 209.3 ppm. MS (ESI): *m*/*z* (%) = 596 (60) [M + H^+], 568 (100), 540 (36), 351 (30). HRMS (ESI): calcd. for $C_{35}H_{34}NO_6S$ [M + H^+] 596.21013; found 596.20818.

(1′*R*,2′*R*,6*S*)-3-Benzhydryl 4′-Benzyl 1′-Methyl 2′-Methylspiro(cyclopent-4-enyl)-5′,6-penicillanate-1′,4′,3-tricarboxylate (15a): Obtained from allene **8b** (79 mg, 0.42 mmol) and 6-alkylidenepenicillanate **7a** (184 mg, 0.42 mmol) as described in the general procedure (reaction time: 5 h). After purification by flash chromatography (hexane/ethyl acetate, 7:1) to 4:1), **15a** was obtained as a yellow oil (109 mg, 0.17 mmol, 40%). $[\alpha]_D^{20}$ = +200 (*c* = 1, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 1778, 1743, 1731, 1728 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.22 (s, 3 H, 2α-Me), 1.37 (d, ^3J = 7.2 Hz, 3 H, 2′-Me), 1.59 (s, 3 H, 2β-Me), 3.28–3.32 (m, 1 H, 2′-H), 3.64 (s, 3 H, CO_2Me), 4.10 (br. s, 1 H, 1′-H), 4.53 (s, 1 H, 3-H), 5.09 (d, ^2J = 12.4 Hz, 1 H, CH_2Ph), 5.26 (d, ^2J = 12.4 Hz, 1 H, CH_2Ph), 5.49 (s, 1 H, 5-H), 6.92 (br. s, 2 H, C*H*Ph_2 and 3′-H), 7.33–7.36 (m, 15 H, Ar-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.4, 26.0, 32.7, 45.2, 52.5, 52.6, 63.3, 66.7, 68.0, 68.9, 69.5, 78.4, 127.0, 127.6, 128.2, 128.3, 128.4, 128.6, 128.6, 132.3, 135.6, 139.1, 139.3, 150.0, 162.8, 166.9, 172.0, 176.2 ppm. MS (ESI): *m*/*z* (%) = 648 (100) [M + Na^+], 626 (20), 492 (15), 196 (92). HRMS (ESI): calcd. for $C_{36}H_{35}NNaO_7S$ [M + Na^+] 648.20264; found 648.20469.

(1′*R*,2′*R*,6*S*)-3-Benzhydryl 4′-Benzyl 1′-Benzoyl-2′-methylspiro(cyclopent-4-enyl)-5′,6-penicillanate-3,4′-dicarboxylate (15b): Obtained from allene **8b** (62 mg, 0.33 mmol) and 6-alkylidenepenicillanate **7b** (158 mg, 0.33 mmol) as described in the general procedure (reaction time: 5 h). After purification by flash chromatography (hexane/ethyl acetate, 4:1 to 2:1), **15b** was obtained as a fluffy yellow solid (83 mg, 0.12 mmol, 36%); m.p. 64–66 °C; $[\alpha]_D^{20}$ = +240 (*c* = 1, CH_2Cl_2). IR (KBr): $\tilde{\nu}$ = 1769, 1743, 1717, 1678 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.10 (s, 3 H, 2α-Me), 1.48 (d, ^3J = 10 Hz, 3 H, 2′-Me), 1.56 (s, 3 H, 2β-Me), 2.81–2.84 (m, 1 H, 2′-H), 4.11 (br. s, 1 H, 1′-H), 4.55 (s, 1 H, 3-H), 5.20 (m, 2 H, CH_2Ph), 6.23 (s, 1 H, 5-H), 6.86 (d, ^3J = 2.8 Hz, 1 H, 3′-H), 6.93 (s, 1 H, C*H*Ph_2), 7.26–7.52 (m, 17 H, Ar-H), 7.60–7.63 (m, 1 H, Ar-H), 7.93 (d, ^3J = 7.2 Hz, 2 H, Ar-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.3, 25.7, 32.7, 43.6, 56.3, 62.4, 66.4, 69.2, 71.1, 73.7, 78.2, 127.4, 128.1, 128.1, 128.2, 128.4, 128.5, 128.6, 129.0, 132.9, 133.5, 135.5, 135.7, 139.6, 149.9, 162.6, 166.7, 174.0, 198.0 ppm. MS (ESI): *m*/*z* (%) = 672 (100) [M + H^+], 313 (39), 221 (32), 196 (80). HRMS (ESI): calcd. for $C_{41}H_{38}NO_6S$ [M + H^+] 672.24144; found 672.24251.

(1′*R*,2′*R*,6*S*)-3-Benzhydryl 4′-Benzyl 1′-Acetyl-2′-methylspiro(cyclopent-4-enyl)-5′,6-penicillanate-3,4′-dicarboxylate (15c): Obtained from allene **8b** (77 mg, 0.41 mmol) and 6-alkylidenepenicillanate **7d** (172 mg, 0.41 mmol) as described in the general procedure (reaction time: 3 h). After purification by flash chromatography (hexane/ethyl acetate, 4:1 to 2:1), **15c** was obtained as a yellow oil (93 mg, 0.15 mmol, 37%); $[\alpha]_D^{20}$ = +220 (*c* = 0.75, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 1769, 1741, 1711, 1638 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.16 (s, 3 H, 2α-Me), 1.42 (d, ^3J = 7.2 Hz, 3 H, 2′-Me), 1.56 (s, 3 H, 2β-Me), 2.27 (s, 3 H, CO*Me*), 2.78–2.79 (m, 1 H, 2′-H), 3.27 (br. s, 1 H, 1′-H), 4.54 (s, 1 H, 3-H), 5.15 (d, ^2J = 12.4 Hz, 1 H, CH_2Ph), 5.19 (d, ^2J = 12.4 Hz, 1 H, CH_2Ph), 6.12 (s, 1 H, 5-H), 6.83 (d, ^3J = 2.4 Hz, 1 H, 3′-H), 6.93 (s, 1 H, C*H*Ph_2), 7.26–7.46 (m, 15 H, Ar-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.1, 25.7, 29.4, 35.2, 42.6, 61.1, 62.5, 66.4, 69.0, 71.0, 73.5, 78.2, 127.3, 128.1, 128.1, 128.2, 128.4, 128.5, 132.5, 135.7, 139.5, 149.8, 162.5, 166.7, 173.6, 206.1 ppm. MS (ESI): *m*/*z* (%) = 610 (100) [M + H^+], 558 (7). HRMS (ESI): calcd. for $C_{36}H_{36}NO_6S$ [M + H^+] 610.22579; found 610.22352.

(1′*R*,4′*R*,6*R*)-3-Benzhydryl 2′-Benzyl 1′-Methyl 4′-Phenylspiro(cyclopent-3-enyl)-5′,6-penicillanate-1′,2′,3-tricarboxylate (16a): Obtained from allene **8c** (98 mg, 0.39 mmol) and 6-alkylidenepenicillanate **7a** (169 mg, 0.39 mmol) as described in the general procedure (reaction time: 7 h). After purification by flash chromatog-

raphy (hexane/ethyl acetate, 5:1), **16a** was obtained as a colorless oil (153 mg, 0.22 mmol, 56%); $[\alpha]_D^{20}$ = +105 (*c* = 1, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 1775, 1720, 1682, 1645 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.11 (s, 3 H, 2α-Me), 1.56 (s, 3 H, 2β-Me), 3.60 (s, 3 H, CO_2Me), 4.22 (s, 1 H, 1′-H), 4.46 (d, ^3J = 2.4 Hz, 1 H, 4′-H), 4.51 (s, 1 H, 3-H), 4.81 (s, 1 H, 5-H), 5.13 (d, ^2J = 12.4 Hz, 1 H, CH_2Ph), 5.31 (d, ^2J = 12.4 Hz, 1 H, CH_2Ph), 6.89 (s, 1 H, $CHPh_2$), 6.98 (br. s, 1 H, 3′-H), 7.22–7.38 (m, 20 H, Ar-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.9, 32.6, 52.3, 52.8, 57.3, 63.2, 66.9, 68.8, 68.9, 69.0, 78.2, 127.0, 127.4, 128.1, 128.2, 128.3, 128.4, 128.4, 128.6, 128.6, 128.6, 128.8, 129.5, 134.6, 135.6, 139.0, 139.3, 146.2, 162.7, 166.7, 171.7, 176.5 ppm. MS (ESI): *m*/*z* (%) = 710 (3) [M + Na^+], 460 (7), 167 (100). HRMS (ESI): calcd. for $C_{41}H_{37}NNaO_7S$ [M + Na^+] 710.21829; found 710.21877.

(1′*R*,2′*S*,6*S*)-3-Benzhydryl 4′-Benzyl 1′-Benzoyl-2′-phenylspiro(cyclopent-4-enyl)-5′,6-penicillanate-3,4′-dicarboxylate (17b): Obtained from allene **8c** (79 mg, 0.32 mmol) and 6-alkylidenepenicillanate **7b** (155 mg, 0.32 mmol) as described in the general procedure (reaction time: 7 h). After purification by flash chromatography (hexane/ethyl acetate, 7:1) to 5:1), **17b** was obtained as a fluffy yellow solid (197 mg, 0.27 mmol, 84%); m.p. 72–74 °C; $[\alpha]_D^{20}$ = +190 (*c* = 1, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 1770, 1743, 1720, 1676 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.08 (s, 3 H, 2α-Me), 1.40 (s, 3 H, 2β-Me), 3.87 (br. s, 1 H, 2′-H), 4.49 (br. s, 1 H, 1′-H), 4.52 (s, 1 H, 3-H), 5.20 (d, ^2J = 12.4 Hz, 1 H, CH_2Ph), 5.27 (d, ^2J = 12.4 Hz, 1 H, CH_2Ph), 6.22 (s, 1 H, 5-H), 6.88 (d, ^3J = 2.8 Hz, 1 H, 3′-H), 6.94 (s, 1 H, $CHPh_2$), 7.26–7.48 (m, 22 H, Ar-H), 7.60–7.62 (m, 1 H, Ar-H), 7.88 (d, ^3J = 7.6 Hz, 2 H, Ar-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.6, 31.4, 54.1, 55.2, 61.2, 65.6, 68.1, 70.8, 74.0, 77.2, 126.3, 126.3, 126.9, 127.0, 127.1, 127.2, 127.3, 127.5, 127.5, 127.6, 127.7, 127.9, 127.9, 132.6, 133.0, 134.4, 134.6, 138.3, 138.5, 145.9, 161.4, 165.7, 172.7, 197.2 ppm. MS (ESI): *m*/*z* (%) = 734 (61) [M + H^+], 167 (100). HRMS (ESI): calcd. for $C_{46}H_{40}NO_6S$ [M + H^+] 734.25709, found 734.25773.

(1′*R*,4′*R*,6*R*)-3-Benzhydryl 2′-Benzyl 1′-Acetyl-4′-phenylspiro(cyclopent-3-enyl)-5′,6-penicillanate-3,2′-dicarboxylate (16c) and (1′*R*,2′*S*,6*S*)-3-Benzhydryl 4′-Benzyl 1′-Acetyl-2′-phenylspiro(cyclopent-4-enyl)-5′,6-penicillanate-3,4′-dicarboxylate (17c): Obtained from allene **8c** (100 mg, 0.40 mmol) and 6-alkylidenepenicillanate **7d** (169 mg, 0.40 mmol) as described in the general procedure (reaction time: 24 h). Purification of the crude product by flash chromatography (hexane/ethyl acetate, 5:1), gave, in order of elution, **16c** as a colorless oil (32 mg, 0.048 mmol, 12%) and **17c** as a colorless oil (130 mg, 0.19 mmol, 48%).

Compound 16a: $[\alpha]_D^{20}$ = +67 (*c* = 0.9, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 1775, 1741, 1712, 1638 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.01 (s, 3 H, 2α-Me), 1.52 (s, 3 H, 2β-Me), 2.42 (s, 3 H, CO*Me*), 4.36 (d, ^3J = 1.6 Hz, 1 H, 4′-H), 4.42 (s, 1 H, 1′-H), 4.45 (s, 1 H, 3-H), 4.70 (s, 1 H, 5-H), 5.09 (d, ^2J = 12.4 Hz, 1 H, CH_2Ph), 5.18 (d, ^2J = 12.4 Hz, 1 H, CH_2Ph), 6.82 (s, 1 H, $CHPh_2$), 6.87 (br. s, 1 H, 3′-H), 7.15–7.29 (m, 20 H, Ar-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.2, 32.3, 33.8, 57.0, 58.8, 63.6, 67.0, 69.0, 69.1, 70.7, 78.2, 127.0, 127.4, 128.1, 128.2, 128.4, 128.5, 128.6, 128.6, 128.7, 129.8, 135.2, 135.2, 136.6, 139.0, 139.3, 146.2, 163.1, 166.7, 177.4, 208.5 ppm. MS (ESI): *m*/*z* (%) = 672 (100) [M + H^+], 644 (40), 557 (51), 501 (65), 422 (22). HRMS (ESI): calcd. for $C_{41}H_{38}NO_6S$ [M + H^+] 672.24144; found 672.23893.

Compound 17c: $[\alpha]_D^{20}$ = +130 (*c* = 1, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 1769, 1741, 1718, 1630 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.15 (s, 3 H, 2α-Me), 1.50 (s, 3 H, 2β-Me), 2.36 (s, 3 H, CO*Me*), 3.67 (br. s, 1 H, 1′-H), 3.85 (br. s, 1 H, 2′-H), 4.52 (s, 1 H, 3-H), 5.17 (d, ^2J = 12.4 Hz, 1 H, CH_2Ph), 5.23 (d, ^2J = 12.4 Hz, 1 H, CH_2Ph), 6.10 (s, 1 H, 5-H), 6.85 (d, ^3J = 2.8 Hz, 1 H, 3′-H), 6.94 (s, 1 H, $CHPh_2$), 7.25–7.48 (m, 20 H, Ar-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.6, 30.6, 33.0, 54.2, 61.3, 62.4, 66.6, 69.0, 71.6, 74.6, 78.3, 127.3, 127.4, 128.0, 128.1, 128.3, 128.4, 128.6, 129.0, 133.9, 135.6, 139.5, 139.9, 146.7, 162.3, 166.7, 173.3, 206.4 ppm. MS (ESI): *m*/*z* (%) = 672 (100) [M + H^+], 588 (21), 422 (12), 326 (18). HRMS (ESI): calcd. for $C_{41}H_{38}NO_6S$ [M + H^+] 672.24144; found 672.23885.

Supporting Information (see footnote on the first page of this article): ^1H and ^{13}C NMR spectra for compounds **7** and **13**–**17**. NOESY, HMQC and HMBC spectra of selected compounds.

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