DOI: 10.1002/ejoc.200900188

Synthesis of 2-Azetidinones Incorporating Carbenechromium(0) Moieties and Their Use in the Preparation of Penicillin- and Cephalosporin-Containing Peptides

Miguel A. Sierra,*[a] Mamen Rodríguez-Fernández,[a] Luis Casarrubios,[a] Mar Gómez-Gallego,[a] and María José Mancheño*[a]

Keywords: Chromium / Peptides / Lactams / Photochemistry / Carbonylation / Carbenes

A series of β-lactams incorporating a carbenechromium(0) moiety in their structures have been prepared. These stable compounds are suitable precursors for the preparation of α-amino esters, dipeptides and tripeptides tethered to a 2-azetidinone ring. The methodology has also been extended to the synthesis of carbenechromium(0) complexes of penicillin G, cephalosporin and 6-aminopenicillanic acid. All these new metalla-β-lactam derivatives are stable compounds and can be transformed into antibiotic structures with tripeptide side-chains. The methodology relies on the compatibility of the β-lactam ring with the carbenechromium(0) moiety and on the stability of the four-membered ring during the photocarbonylation of the resulting chromium complex.

Introduction

The efforts devoted to the synthesis of new 2-azetidinones with unprecedented structures[1] are only paralleled by the use of 2-azetidinone derivatives as intermediates in the synthesis of non-β-lactam products.[2] The pivotal role of β-lactams in the treatment of bacterial diseases, together with the appearance of antibiotic-resistant bacteria,[3] justify the unabated reporting of the preparation of new 2-azetidinone-derived compounds and the study of their antibiotic properties.[4] Moreover, it is now known that 2-azetidinone-derived drugs show other interesting biological properties. In fact, they are potent inhibitors of mammalian serine proteases[5] and cholesterol absorption inhibitors.[6] Other monocyclic 2-azetidinones are inhibitors of the human cytomegalovirus (HCMV, a β-herpes virus).[7] Recently, the role of β-lactam antibiotics as neuroprotectors has also been reported as they increase the expression of glutamate carriers.[8]

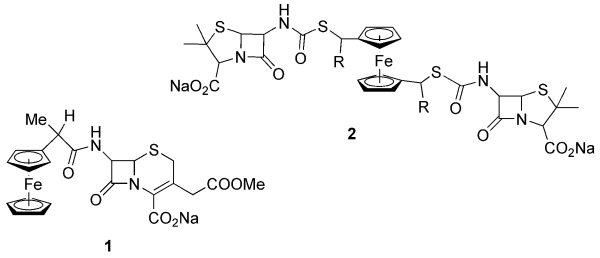
Following the developments in the synthesis of new 2-azetidinones, their use as intermediates in organic synthesis led to the term "β-lactam synthon method" being coined by Ojima and co-workers more than 20 years ago.[9] In fact, the key role of these compounds in the preparation of β-amino alcohols and acids is well recognized.[10] β-Lactams are also building blocks for the preparation of non-proteinogenic amino acids and have been used to introduce the C-13 side-chain into Taxol and its analogues.[11] The incorporation of the 2-azetidinone nucleus as part of an organotransition-metal complex, susceptible to further manipulation, may be an alternative route to the preparation of β-lactam derivatives and other structures retaining the original β-lactam ring. In this context, the presence of group 6 metal–carbene complexes[12] bearing the 2-azetidinone ring (as a monolactam, penam or cepham derivative) in their structures will allow the generation of ketenes[13] using the well-known photochemistry of these compounds.[14] The mild reaction conditions in which this process occurs may provide the necessary conditions to manipulate these sensitive compounds.

Structures in which a β-lactam nucleus is embedded in an organometallic complex are scarce,[15] and of those that exist, metallocene-derived 2-azetidinones are possibly the most abundant group.[16] Cephalosporin and penicillin derivatives **1** and **2**, bearing a ferrocene nucleus at the 7- and 6-positions, respectively, are representative examples.[16f,16g] The role of the ferrocene nucleus as a redox marker is the main reason for the interest in this type of compound. It is remarkable that ferrocene derivatives **1** and **2** are strong β-lactamase inhibitors.

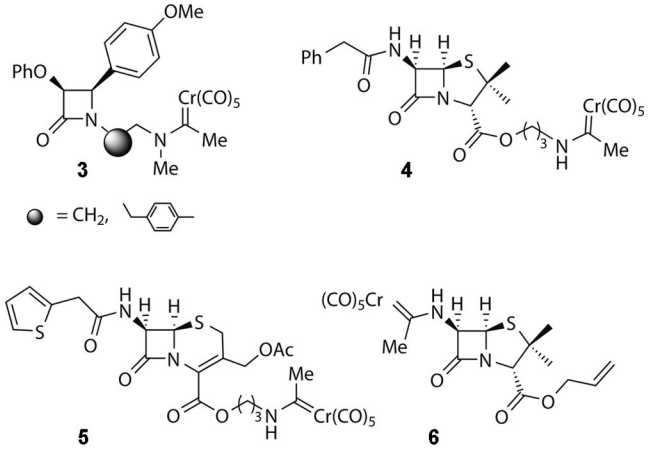
In this paper we report the sequential synthesis of mononuclear 2-azetidinones **3** bearing a Fischer-type carbenechromium(0) moiety in the chain attached to the β-lactam nitrogen, the synthesis of penicillin G and cephalosporin derivatives **4** and **5** bearing a carbenechromium(0) attached to the carboxylic acid at the 3- and 4-positions of the bicyclic systems, respectively, as well as the preparation of a

[a] Departamento de Química Orgánica, Facultad de Química, Universidad Complutense,
28040 Madrid, Spain
Fax: +34-91-3944310

Supporting information for this article is available on the WWW under http://www.eurjoc.org/ or from the author.

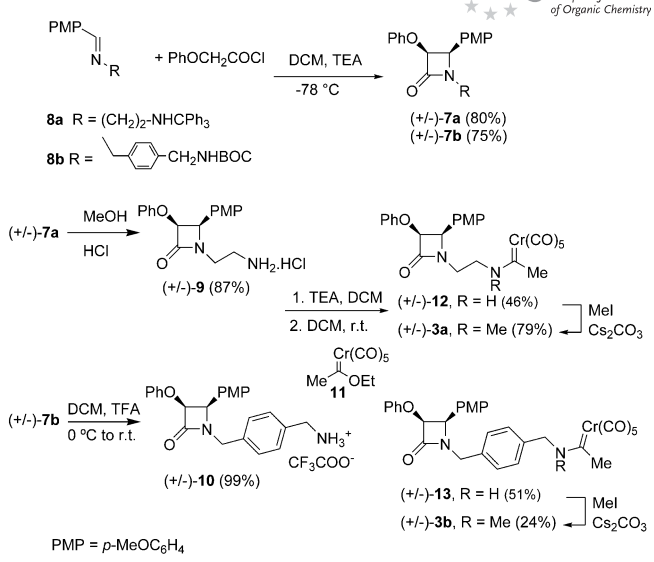


penicillin derivative **6** directly tethered to the carbene carbon through the 6-amino group. Irradiation of these compounds in the presence of alcohols, amino esters and dipeptides renders several new types of peptide derivatives. The use of carbenechromium(0) complexes in the thermal[17] and photochemical[14] preparation of amino acids and small peptides is of long-standing interest.



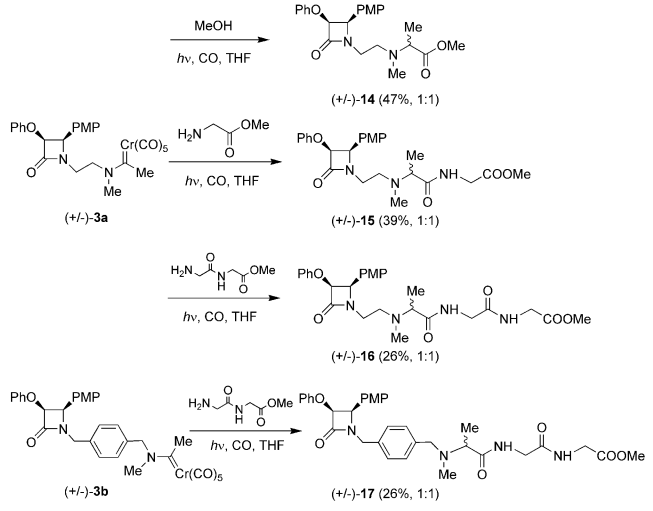
Results and Discussion

The racemic mononuclear β-lactams **7** were synthesized by reaction of monoprotected imines **8** with phenoxyacetyl chloride in the presence of TEA at –78 °C by using the standard procedure for the Staudinger reaction. Compounds **7** were obtained as the *cis* isomers (determined by a $J_{3,4}$ value of 4.4 and 4.3 Hz) in good yields. The trityl group of **7a** was removed by treatment with MeOH/HCl to give the hydrochloride **9**, whereas the Boc group of **7b** was quantitatively removed to form the trifluoroacetate **10** by treatment with TFA/DCM at 0 °C. Compounds **9** and **10** were attached to the pentacarbonylcarbenechromium(0) fragment by standard aminolysis with complex **11** to give the NH complexes **12** and **13**. Finally, the carbene nitrogen was methylated with MeI/Cs_2CO_3 to yield the desired metalla-2-azetidinones **3** as mixtures of *syn*/*anti* isomers at the aminocarbene centre (Scheme 1).



Scheme 1.

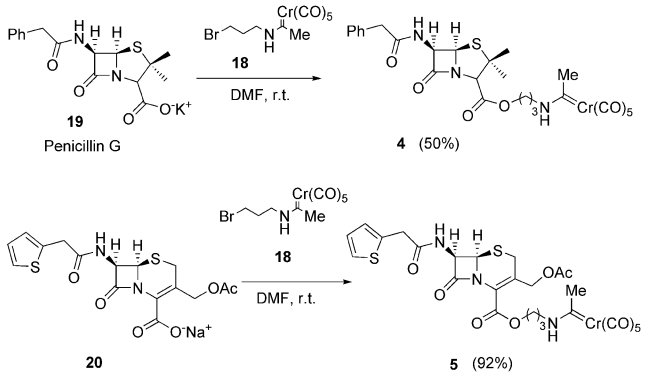
Irradiation (400 W, medium-pressure Hg lamp, Pyrex filter and Pyrex tube) of complex **3a** in the presence of MeOH and under a low CO pressure gave the α-amino ester **14** in 47% yield and as a 1:1 mixture of diastereomers at the newly formed stereogenic centre. Although the instability of β-lactams towards light is generally accepted,[18] the 2-azetidinone nucleus remains unaltered during the photochemical process. Subsequently, complex **3a** was irradiated in the presence of methyl glycinate or methyl glycinylglycinate (TEA was used to obtain the free amine prior to the photochemical reaction).[19] The corresponding dipeptide **15** and tripeptide **16** were obtained in acceptable-to-moderate yields as a 1:1 mixture of diastereomers at the newly formed stereogenic centres. Analogously, irradiation of complex **3b** in the presence of methyl glycinylglycinate formed the β-lactamic tripeptide **17** as a 1:1 diastereomeric mixture (Scheme 2).



Scheme 2.

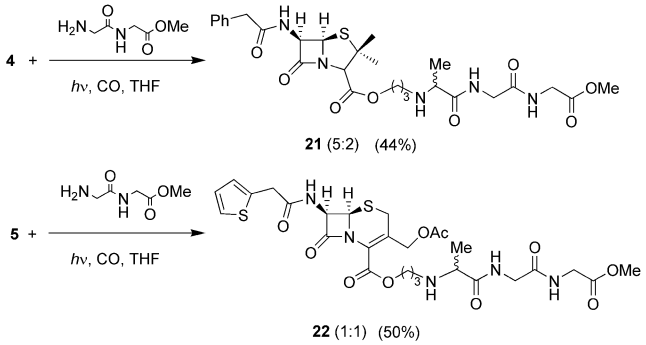
There are two major points to note in the approach to metalla-β-lactams and β-lactam-containing peptides reported herein. First, it is possible to incorporate the metal fragment into the side-chain of the β-lactams **3**. Secondly, the resulting complexes can photocarbonylate to produce ketene derivatives that react with nucleophiles maintaining the integrity of the 2-azetidinone ring. To explore the scope of this methodology, the incorporation of the metal–car-

bene fragment into the more sensitive penicillin and cephalosporin antibiotics was studied next. Thus, penicillin G (**19**) was alkylated at the carboxy group with carbenechromium(0) complex **18**. Complex **18** was prepared in 67% yield by standard aminolysis of the carbenechromium(0) complex **11** with 3-bromopropan-1-amine hydrobromide in the presence of TEA. The reaction between penicillin G and complex **18** was carried out in DMF at room temp. and resulted in an acceptable 50% yield of pure metalla-penicillin **4**. Analogously, the reaction of cephalosporin **20** (cephalotin) with complex **18** yielded metalla-cephalosporin **5** (92%) as a 1:1 mixture of *syn*/*anti* isomers. Note that no decomposition of the starting materials was observed in these processes. The final products **4** and **5** are fairly stable compounds and represent a new class of metalla-antibiotics (Scheme 3).



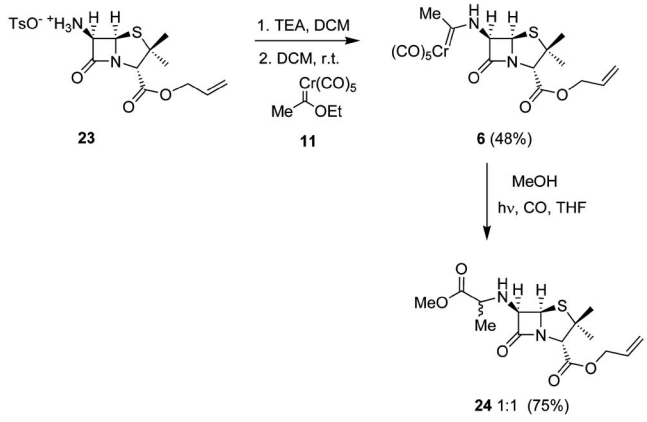
Scheme 3.

Compounds **4** and **5** were irradiated in the presence of methyl glycinylglycinate under the conditions described above. Penicillin G and cephalosporin tripeptide derivatives **21** and **22** were obtained in 44 and 50% isolated yields, respectively. Compound **21** was produced as a 5:2 mixture of diastereomers at the newly formed stereocentre. The stereochemical integrity of the penam nucleus remained unaffected. Furthermore, compound **22** was obtained as a 1:1 mixture of diastereomers also with the integrity of the cephem nucleus unaltered (Scheme 4).



Scheme 4.

Finally, the incorporation of a carbenechromium(0) fragment into the 6-amino group of 6-aminopenicillanic acid (6-APA) was explored. 6-APA was transformed into the 6-APA allyl ester **23** following a literature procedure[20] and then the ester was treated with complex **11** in DCM for 16 h. A quantitative transformation (TLC) to the new product **6** was observed. However, complex **6** is slightly unstable and upon chromatography only 48% of the product could be recovered. Irradiation of **6** using THF/MeOH as the solvent provided a 75% isolated yield of the penicillin derivative **24** as a 1:1 diastereomeric mixture. Again, the integrity of the labile penam moiety was maintained through the irradiation and isolation processes (Scheme 5).



Scheme 5.

Conclusions

We have demonstrate that β-lactams containing carbenechromium(0) moieties are stable compounds and suitable precursors for the preparation of peptides incorporating the 2-azetidinone ring. Thus, β-lactam-derived α-amino esters, dipeptides and tripeptides are available by this procedure. Analogously, the carbenechromium(0)-containing tether may be incorporated into penicillin G (**19**) or cephalotin (**20**) by using the (bromopropylamino)carbenechromium(0) complex **18**. The synthesized metalla-penicillin and -cephalosporin derivatives are also stable compounds and can be transformed into antibiotic derivatives bearing tripeptide side-chains. Finally, a carbenechromium(0) can be incorporated into the 6-APA allyl ester moiety in very good yield by solvolysis. This compound is also stable and generates penicillin derivatives bearing an α-amino ester chain. The photochemical reactions give acceptable-to-good yields, but with poor or no stereoselectivity. The compounds reported in this work form a new class of metalla-β-lactams.

Experimental Section

General: Methods and procedures have been reported elsewhere.[14d] All commercially available compounds were used without further purification. The following chemicals were prepared according to literature procedures: *N*-tritylethane-1,2-diamine,[21] 6-APA allyl ester tosylate **23**,[20] pentacarbonyl[(ethoxy)(methyl)carbene]chromium(0).[22]

Imine 8a: A solution of *N*-tritylethane-1,2-diamine (4.00 g, 13.0 mmol) and a catalytic amount of 1-phenylethanamine–$ZnCl_2$ in toluene (90 mL) was treated with *p*-anisaldehyde (1.80 g, 13.0 mol). The mixture was heated at reflux for 48 h, filtered and the solvent eliminated under vacuum. The thus obtained crude was purified by vacuum distillation to give pure **8a** (3.45 g, 62%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.15 (s, 1 H), 7.57 (d, J = 8.7 Hz, 2 H), 7.39–7.36 (m, 5 H), 7.17–7.03 (m, 10 H), 6.81 (d, J = 8.7 Hz, 2 H), 3.71 (s, 3 H), 3.61 (t, J = 5.6 Hz, 2 H), 2.37 (t, J = 5.9 Hz, 2 H), 1.94 (br. s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.5, 161.2, 146.1, 129.6, 129.1, 128.6, 127.7, 126.1, 113.9, 70.7, 61.8, 55.3, 44.4 ppm. IR (CCl_4): $\tilde{\nu}$ = 3061, 3018, 2963, 2937, 1645, 1578, 1252 cm^{-1}.

Imine 8b: A solution of *tert*-butyl 4-(aminomethyl)benzylcarbamate (0.70 g, 2.96 mmol) in anhydrous Et_2O (5 mL) was treated with *p*-anisaldehyde (0.40 g, 2.96 mmol) in the presence of anhydrous $MgSO_4$ (4.99 g) under Ar. The reaction mixture was stirred at room temp. for 16 h, filtered and the solvent eliminated under vacuum to give **8b** (1.04 g, 99%), which was used without further purification. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.30 (s, 1 H), 7.70 (d, J = 8.8 Hz, 2 H), 7.29–7.22 (m, 4 H), 6.91 (d, J = 8.8 Hz, 2 H), 4.80 (br. s, 1 H), 4.75 (s, 2 H), 4.28 (d, J = 5.6 Hz, 2 H), 3.82 (s, 3 H), 1.44 (s, 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.7, 161.3, 155.8, 138.7, 137.5, 129.8, 129.1, 128.2, 127.6, 114.0, 79.4, 64.6, 55.3, 44.5, 28.4 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3349, 3018, 2976, 1703, 1644, 1577, 1250, 1166 cm^{-1}.

General Procedure for the Synthesis of β-Lactams 7: A solution of phenoxyacetyl chloride (1.20 mmol) in anh. DCM (3 mL) cooled to –78 °C under Ar was treated with TEA (2.00 mmol). The mixture was stirred for 30 min and a solution of imine **8** (1.00 mmol) in DCM (1 mL) was added dropwise. The cooling bath was replaced with an ice/H_2O bath and the reaction was kept at 0° for 30 min and allowed to warm to room temp. overnight. The mixture was washed with saturated $NaHCO_3$ (2 × 20 mL), dried with $MgSO_4$, the solvent evaporated and the residue purified by chromatography (SiO_2, Hex/AcOEt mixtures).

***cis*-β-Lactam 7a:** Following the general procedure, from imine **8a** (2.52 g, 6.00 mmol) and after purification by chromatography (SiO_2, Hex/AcOEt, 3:1), pure *cis*-**7a** (2.64 g, 80%) was obtained as a yellow solid; m.p. 92–94 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.44–7.38 (m, 5 H), 7.33–7.10 (m, 14 H), 6.93–6.84 (m, 1 H), 6.80–6.71 (m, 4 H), 5.36 (d, J = 4.4 Hz, 1 H), 4.70 (d, J = 4.4 Hz, 1 H), 3.74 (s, 3 H), 3.56 (ddd, J = 14.0, 7.4, 4.9 Hz, 1 H), 3.09 (dt, J = 14.0, 4.9 Hz, 1 H), 2.42–2.17 (m, 2 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 166.3, 159.9, 157.0, 145.6, 129.9, 129.2, 128.5, 127.9, 126.4, 124.8, 121.9, 115.5, 113.7, 81.9, 70.8, 62.3, 55.1, 41.5, 41.3 ppm. IR (KBr): $\tilde{\nu}$ = 3058, 2913, 2837, 1759, 1597, 1514, 1248, 1176, 833, 748 cm^{-1}. $C_{37}H_{34}N_2O_3$ (554.68): calcd. C 80.12, H 6.18; found C 80.34, H 6.38.

***cis*-β-Lactam 7b:** Following the general procedure, from imine **8b** (1.29 g, 3.63 mmol) and after purification by chromatography (SiO_2, Hex/AcOEt, 3:1), pure *cis*-**7b** (1.33 g, 75%) was obtained as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.27–7.17 (m, 4 H), 7.11–7.06 (m, 4 H), 6.86–6.77 (m, 3 H), 6.70 (d, J = 8.6 Hz, 2 H), 5.33 (d, J = 4.3 Hz, 1 H), 5.11 (br. s, 1 H), 4.82 (d, J = 14.7 Hz, 1 H), 4.70 (d, J = 4.3 Hz, 1 H), 4.28 (d, J = 5.6 Hz, 2 H), 3.80 (d, J = 14.7 Hz, 1 H), 3.73 (s, 3 H), 1.46 (s, 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.4, 159.6, 156.7, 155.8, 138.8, 133.5, 129.7, 129.0, 128.6, 127.6, 124.2, 121.7, 115.3, 113.5, 81.8, 79.3, 60.7, 55.0, 44.0, 43.4, 28.2 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3355, 2977, 1757, 1704, 1596, 1513, 1248, 1173, 831, 753 cm^{-1}. $C_{29}H_{32}N_2O_5$ (488.58): calcd. C 71.29, H 6.60; found C 71.53, H 6.84.

***cis*-β-Lactam Hydrochloride 9:** A solution of β-lactam **7a** (0.50 g, 0.90 mmol) in MeOH (5 mL) was treated with conc. HCl (0.88 mL, 10.0 mmol). The reaction was heated at reflux for 1 h and the white precipitate formed was filtered, washed with MeOH (2 × 5 mL) and characterized as pure **9**. Yield: 0.27 g (87%); m.p. 200–202 °C. ^{1}H NMR (300 MHz, D_2O): δ = 7.33 (d, J = 8.7 Hz, 2 H), 7.20–7.15 (m, 2 H), 7.02–6.93 (m, 1 H), 6.89 (d, J = 8.7 Hz, 2 H), 6.75 (d, J = 8.0 Hz, 2 H), 5.70 (d, J = 4.0 Hz, 1 H), 5.27 (d, J = 4.0 Hz, 1 H), 3.73 (s, 3 H), 3.57 (t, J = 6.1 Hz, 1 H), 3.39 (t, J = 5.5 Hz, 1 H), 3.18 (t, J = 6.3 Hz, 2 H) ppm. ^{13}C NMR (50 MHz, [D_6]DMSO): δ = 165.7, 159.2, 156.5, 129.7, 129.3, 125.0, 121.6, 114.9, 113.5, 81.4, 60.6, 54.9, 37.6, 36.4 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3437, 2932, 1919, 1743, 1518, 1257, 1256, 752 cm^{-1}. $C_{18}H_{21}ClN_2O_3$ (348.92): calcd. C 61.98, H 6.07; found C 62.13, H 6.26.

***cis*-β-Lactam Trifluoroacetate 10:** A solution of β-lactam **7b** (0.47 g, 0.97 mmol) in CH_2Cl_2 (12 mL) was cooled to 0 °C under Ar and treated with TFA (0.24 mL, 3.14 mmol). After the addition, the cooling bath was removed and stirring was continued until total disappearance of the starting material (TLC). Evaporation of the solvent yielded pure **9** as a red oil. Yield: 0.45 g (99%). ^{1}H NMR (300 MHz, CD_3OD): δ = 7.41 (d, J = 8.2 Hz, 2 H), 7.28 (d, J = 8.2 Hz, 2 H), 7.18–7.07 (m, 4 H), 6.86–6.69 (m, 5 H), 5.55 (d, J = 4.2 Hz, 1 H), 4.93 (d, J = 4.2 Hz, 1 H), 4.73 (d, J = 15.4 Hz, 1 H), 4.11–4.08 (m, 2 H), 4.08 (d, J = 15.4 Hz, 1 H), 3.71 (s, 3 H) ppm. ^{13}C NMR (75 MHz, CD_3OD): δ = 168.2, 161.4, 158.1, 137.5, 134.1, 131.1, 130.4, 130.3, 130.2, 125.6, 122.9, 116.2, 114.6, 82.8, 63.2, 55.6, 44.9, 43.9 ppm. IR (KBr): $\tilde{\nu}$ = 2927, 1749, 1676, 1515, 1202, 1177, 1139, 1033, 755 cm^{-1}. $C_{26}H_{25}F_3N_2O_5$ (502.48): calcd. C 62.15, H 5.01; found C 62.38, H 5.33.

General Procedure for the Synthesis of Metalla-β-Lactams 6, 12 and 13: A solution of the corresponding β-lactam amine hydrochloride (1.00 mmol) in CH_2Cl_2 (15 mL) was treated with TEA (2.50 mmol) for 2 h. This mixture was added to a solution of pentacarbonyl-[(ethoxy)(methyl)]carbenechromium(0)[11] (1.00 mmol) in CH_2Cl_2 (20 mL). The reaction was stirred at room temp. overnight, the solvent evaporated and the crude purified by chromatography (SiO_2, Hex/AcOEt mixtures).

Metalla-β-Lactam 12: Following the general procedure, from **9** (0.55 g, 1.58 mmol) and complex **11** (0.41 g, 1.58 mmol), pure compound **12** (0.39 g, 46%) was obtained as a yellow solid after purification by chromatography (SiO_2, Hex/AcOEt, 4:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.76 (br. s, 1 H), 7.29 (d, J = 8.8 Hz, 2 H), 7.18–7.13 (m, 2 H), 6.93–6.86 (m, 3 H), 6.74 (d, J = 7.8 Hz, 2 H), 5.49 (d, J = 4.3 Hz, 1 H), 4.94 (d, J = 4.3 Hz, 1 H), 3.79 (s, 3 H), 3.66 (q, J = 5.5 Hz, 2 H), 3.52–3.38 (m, 2 H), 2.63 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 284.3, 222.9, 217.7, 167.3, 160.3, 156.6, 129.8, 129.3, 123.9, 122.2, 115.4, 114.0, 81.8, 63.2, 55.2, 45.6, 40.7, 35.7 ppm. IR (KBr): $\tilde{\nu}$ = 3437, 2054, 1911, 1751, 1541, 1520, 1251, 756 cm^{-1}. $C_{25}H_{22}CrN_2O_8$ (530.45): calcd. C 56.61, H 4.18; found C 56.93, H 4.59.

Metalla-β-lactam 13: Following the general procedure, from **10** (0.46 g, 0.91 mmol) and complex **11** (0.24 g, 0.91 mmol), pure compound **13** (0.28 g, 51%) was obtained as a yellow oil after purification by chromatography (SiO_2, Hex/AcOEt, 4:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.99 (br. s, 1 H), 7.25–7.20 (m, 6 H), 7.16–7.10 (m, 2 H), 6.91–6.81 (m, 3 H), 6.74 (d, J = 7.8 Hz, 2 H), 5.42 (d, J = 4.3 Hz, 1 H), 4.85 (d, J = 15.0 Hz, 1 H), 4.77 (d, J = 4.3 Hz, 1 H), 4.63 (d, J = 5.3 Hz, 2 H), 3.92 (d, J = 15.0 Hz, 1 H), 3.78 (s, 3 H), 2.76 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 284.0, 222.7, 217.7, 165.7, 159.9, 156.8, 135.6, 134.1, 129.9, 129.6, 129.2, 128.4, 127.9, 124.1, 115.5, 113.8, 82.1, 61.3, 55.2, 51.7, 43.6, 36.1 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3282, 2932, 2053, 1909, 1754, 1515,

1249, 755 cm^{-1}. $C_{31}H_{26}CrN_2O_8$ (606.55): calcd. C 61.39, H 4.32; found C 61.78, H 4.98.

6-Aminopenicillin Allyl Ester Chromium(0) Complex Derivative 6: Following the general procedure, from ester **23** (1.05 g, 2.46 mmol) and complex **11** (0.65 g, 2.46 mmol), pure compound **6** (0.56 g, 48%) was obtained as a yellow solid after purification by chromatography (SiO_2, Hex/AcOEt, 3:1). ^1H NMR (300 MHz, $CDCl_3$): δ = 9.43 (br. s, 1 H), 6.01–5.87 (m, 1 H), 5.77 (d, J = 3.0 Hz, 1 H), 5.44–5.31 (m, 3 H), 4.70 (d, J = 4.8 Hz, 2 H), 4.61 (s, 1 H), 2.89 (s, 3 H), 1.67 (s, 3 H), 1.59 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 293.2, 222.7, 217.1, 166.9, 166.6, 130.7, 120.2, 69.6, 67.2, 66.5, 65.6, 64.8, 38.3, 34.1, 25.8 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3282, 2976, 2056, 1908, 1783, 1744, 1492, 1304, 1206, 1158 cm^{-1}. $C_{18}H_{18}CrN_2O_8S$ (474.40): calcd. C 45.57, H 3.82; found C 45.92, H 3.98.

Complex 18: TEA (0.16 mL, 1.14 mmol) was added dropwise to a solution of **11** (0.30 g, 1.14 mmol) and 3-bromopropan-1-amine hydrobromide (0.25 g, 1.14 mmol). The reaction was stirred at room temp. for 6 h, filtered through Celite and the solvents evaporated. Pure **18** (0.27 g, 67%) was obtained as a yellow solid after purification by chromatography (SiO_2, Hex/EtOAc, 5:1). ^1H NMR (300 MHz, $CDCl_3$): δ = 8.85 (br. s, 1 H), 3.69 (q, J = 6.5 Hz, 2 H), 3.50 (t, J = 6.0 Hz, 2 H), 2.73 (s, 3 H), 2.28 (q, J = 6.4 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 284.2, 222.7, 217.7, 46.4, 35.6, 31.2, 29.1 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2055, 1889, 1530 cm^{-1}.

General Procedure for the Preparation of Penam and Cepham Derivatives 4 and 5: A solution of complex **18** (1.10 mmol) in anh. DMF (7 mL) was treated with the corresponding carboxylate (1.00 mmol). The reaction mixture was stirred until total disappearance of the starting material (TLC), diluted with cold H_2O (14 mL) and extracted with cold Et_2O (3 × 20 mL). The combined organic extracts were washed with brine (3 × 20 mL), dried with $MgSO_4$ and the solvents evaporated. Purification was achieved by chromatography (SiO_2) or precipitation with appropriate solvents.

Preparation of Penicillin G Chromium Complex Derivative 4: Following the general procedure, a solution of the penicillin G potassium salt **19** (0.26 g, 0.69 mmol) and complex **18** (0.27 g, 0.76 mmol) in DMF (5 mL) was stirred at room temp. for 16 h. Pure **4** (0.21 g, 50%) was obtained as a yellow solid after work-up and chromatography (SiO_2, Hex/AcOEt, 1:1). ^1H NMR (300 MHz, $CDCl_3$): δ = 9.04 (br. s, 1 H), 7.42–7.32 (m, 3 H), 7.31–7.26 (m, 2 H), 6.09 (d, J = 8.9 Hz, 1 H), 5.66 (dd, J = 8.9, 4.2 Hz, 1 H), 5.51 (d, J = 4.2 Hz, 1 H), 4.42 (s, 1 H), 4.42–4.28 (m, 2 H), 3.65 (s, 2 H), 3.54 (q, J = 6.5 Hz, 2 H), 2.69 (s, 3 H), 2.08 (quint., J = 6.4 Hz, 2 H), 1.46 (s, 3 H), 1.45 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 274.4, 222.6, 217.7, 173.4, 170.3, 167.7, 133.7, 129.5, 129.2, 127.7, 70.2, 68.1, 64.3, 62.1, 59.0, 44.5, 43.4, 35.5, 32.0, 28.2, 26.7 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3294, 2971, 2053, 1902, 1781, 1747, 1668, 1536, 1456, 1262, 732 cm^{-1}. $C_{26}H_{27}CrN_3O_9S$ (609.57): calcd. C 51.23, H 4.46; found C 51.57, H 4.80.

Preparation of Cephalotin Sodium Salt Chromium Complex Derivative 5: Following the general procedure, a solution of the cephalotin sodium salt **20** (0.25 g, 0.60 mmol) and complex **18** (0.23 g, 0.66 mmol) in DMF (5 mL) was stirred at room temp. for 48 h. Pure **5** (0.37 g, 92%) was obtained as a 1:1 mixture of isomers as a yellow solid after work-up and purification by chromatography (SiO_2, Hex/AcOEt, 1:1). Mixture of isomers: ^1H NMR (300 MHz, $CDCl_3$): δ = 9.46 (br. s, 2 H), 7.28–7.26 (m, 2 H), 7.02–6.99 (m, 4 H), 6.53 (br. d, J = 8.5 Hz, 1 H), 6.43 (br. s, 1 H), 5.86 (dd, J = 9.1, 4.9 Hz, 1 H), 5.67 (dd, J = 8.5, 3.8 Hz, 1 H), 5.24 (d, J = 3.8 Hz, 1 H), 5.18 (d, J = 13.7 Hz, 1 H), 5.00 (d, J = 4.9 Hz, 1 H), 4.97 (m, 4 H), 4.83 (d, J = 12.8 Hz, 1 H), 4.76 (d, J = 13.7 Hz, 1 H), 4.52 (d, J = 12.8 Hz, 1 H), 4.47–4.36 (m, 1 H), 4.36–4.27 (m, 3 H), 3.86 (s, 4 H), 3.68–3.54 (m, 3 H), 3.39 (d, J = 18.9 Hz, 1 H), 2.68 (s, 3 H), 2.65 (s, 3 H), 2.10–2.02 (m, 4 H), 2.09 (s, 3 H), 2.04 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 283.0, 281.4, 222.9, 222.8, 217.9, 217.8, 170.9, 170.7, 170.1, 169.9, 167.2, 165.1, 164.2, 161.2, 134.5, 127.9, 127.6, 127.6, 126.5, 126.1, 126.1, 125.0, 122.2, 118.9, 65.1, 63.0, 62.8, 62.6, 60.4, 59.1, 57.4, 53.3, 49.7, 44.3, 44.0, 37.1, 35.2, 35.2, 28.2, 27.8, 26.4, 20.8, 20.7 ppm. IR (KBr): $\tilde{\nu}$ = 3309, 2815, 2053, 1909, 1777, 1739, 1673, 1540, 1380, 1227, 1028, 802 cm^{-1}. $C_{26}H_{25}CrN_3O_{11}S$ (639.55): calcd. C 46.50, H 3.75; found C 46.71, H 3.83.

General Procedure for the *N*-Methylation of Metalla-β-lactams 12 and 13: A solution of the corresponding chromium complex (1.0 mmol) in deoxygenated acetone (0.025 M) was treated with methyl iodide (2.0 mmol), Cs_2CO_3 (3.0 mmol) and a few drops of H_2O. The mixture was stirred for 16 h at room temp., filtered through Celite and the solvent evaporated. Pure products were obtained by SiO_2 chromatography.

Complex 3a: Following the general procedure, from **12** (1.08 g, 2.03 mmol) and after purification by chromatography (SiO_2, Hex/AcOEt, 4:1), pure isomer I (0.52 g, 47%) and a mixture of syn and *anti* isomers (0.35 g, 32%) were obtained as yellow solids. Isomer I: ^1H NMR (300 MHz, $CDCl_3$): δ = 7.26 (d, J = 8.7 Hz, 2 H), 7.18–7.13 (m, 2 H), 6.94–6.88 (m, 1 H), 6.86 (d, J = 8.7 Hz, 2 H), 6.73 (d, J = 7.8 Hz, 2 H), 5.44 (d, J = 4.4 Hz, 1 H), 4.86 (d, J = 4.4 Hz, 1 H), 4.14–3.99 (m, 1 H), 3.83 (s, 3 H), 3.79 (s, 3 H), 3.70–3.59 (m, 2 H), 3.36–3.25 (m, 1 H), 2.73 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 277.9, 222.9, 217.4, 166.6, 160.1, 156.6, 129.9, 129.2, 124.2, 122.0, 115.4, 113.8, 82.0, 63.0, 55.1, 53.4, 41.2, 40.5, 38.6 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2935, 2053, 1899, 1762, 1612, 1515, 1494, 1401, 1354, 1250, 1033, 755 cm^{-1}. $C_{26}H_{24}CrN_2O_8$ (544.48): calcd. C 57.35, H 4.44; found C 57.66, H 4.73. Mixture of isomers: ^1H NMR (300 MHz, $CDCl_3$): δ = 7.26 (d, J = 8.7 Hz, 2 H), 7.18–7.13 (m, 5 H), 6.94–6.83 (m, 6 H), 6.75–6.72 (m, 5 H), 5.47 (d, J = 4.4 Hz, 1 H), 5.44 (d, J = 4.4 Hz, 1 H), 5.01 (d, J = 4.4 Hz, 1 H), 4.86 (d, J = 4.4 Hz, 1 H), 4.44–4.23 (m, 2 H), 4.08–3.99 (m, 1 H), 3.83 (s, 6 H), 3.80–3.74 (m, 1 H), 3.79 (s, 3 H), 3.78 (s, 3 H), 3.70–3.46 (m, 3 H), 3.36–3.25 (m, 1 H), 2.73 (s, 3 H), 2.69 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 279.3, 277.9, 223.1, 222.9, 217.6, 217.4, 166.6, 166.3, 160.3, 160.1, 156.7, 156.6, 130.0, 129.9, 129.3, 129.2, 124.2, 123.6, 122.2, 122.0, 115.4, 115.3, 114.0, 113.8, 82.2, 82.0, 63.1, 63.0, 55.1, 53.4, 52.0, 50.9, 41.2, 40.5, 39.8, 38.6, 37.5 ppm. IR (KBr): $\tilde{\nu}$ = 2935, 2053, 1899, 1762, 1612, 1515, 1494, 1401, 1354, 1250, 1033, 755 cm^{-1}.

Complex 3b: Following the general procedure, from **13** (0.44 g, 0.73 mmol) and after purification by chromatography (SiO_2, Hex/AcOEt, 1:1), pure **3b** (0.11 g, 24%) was obtained as a 1:1 mixture of isomers as a yellow solid. Mixture of isomers: ^1H NMR (200 MHz, $CDCl_3$): δ = 7.23–7.09 (m, 14 H), 7.03–6.88 (m, 3 H), 6.84–6.71 (m, 9 H), 5.45 (s, 2 H), 5.41 (dd, J = 4.4, 2.0 Hz, 2 H), 4.89 (s, 1 H), 4.79–4.71 (m, 2 H), 4.72 (d, J = 4.4 Hz, 2 H), 3.95 (d, J = 15.1 Hz, 2 H), 3.85 (s, 1 H), 3.78 (s, 6 H), 3.11 (s, 6 H), 2.82 (s, 3 H), 2.81 (s, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 276.6, 276.5, 223.2, 217.8, 217.4, 165.6, 159.8, 156.8, 135.2, 134.1, 132.7, 129.9, 129.5, 129.3, 129.1, 127.7, 126.4, 124.2, 121.9, 115.4, 113.7, 82.1, 68.7, 61.3, 57.9, 55.1, 51.3, 43.7, 43.6, 40.4, 40.2 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2923, 1912, 1761, 1646, 1613, 1515, 1495, 1401, 1353, 1248, 1032, 755 cm^{-1}.

General Procedure for the Photochemical Reactions: A solution of the corresponding nucleophile (2.00 mmol) and the chromium complex (1.00 mmol) in dry-degassed THF and in a sealed Pyrex tube filled with CO (80 psi) was irradiated for 16 h using a 400 W

medium-pressure Hg lamp, through a Pyrex filter. The temperature was maintained at 25 °C by forced circulation air in the irradiation box. After irradiation, the solution was filtered through a short pad of Celite, the solvent was evaporated and the crude purified by SiO_2 flash chromatography.

β-Lactam 14: Following the general procedure, a solution of **3a** (0.15 g, 0.28 mmol) and MeOH (5 mL) in THF (20 mL) was irradiated for 16 h under CO. A 1:1 diastereomeric mixture of the ester **14** (0.05 g, 47%) was obtained as a colourless oil after purification by chromatography (SiO_2, Hex/AcOEt, 2:1). Mixture of isomers: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.27 (d, J = 8.8 Hz, 2 H), 7.26 (d, J = 8.8 Hz, 2 H), 7.14 (d, J = 8.6 Hz, 2 H), 7.12 (d, J = 8.6 Hz, 2 H), 6.90–6.73 (m, 10 H), 5.41 (d, J = 4.4 Hz, 1 H), 5.40 (d, J = 4.4 Hz, 1 H), 5.05 (d, J = 4.4 Hz, 1 H), 5.02 (d, J = 4.4 Hz, 1 H), 3.76 (s, 6 H), 3.69 (s, 3 H), 3.68 (s, 3 H), 3.71–3.60 (m, 2 H), 3.40 (q, J = 7.1 Hz, 1 H), 3.38 (q, J = 7.0 Hz, 1 H), 2.98 (t, J = 6.1 Hz, 1 H), 2.94 (t, J = 6.1 Hz, 1 H), 2.78–2.57 (m, 4 H), 2.25 (s, 3 H), 2.24 (s, 3 H), 1.28 (d, J = 7.1 Hz, 3 H), 1.25 (d, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.5, 173.4, 166.1, 166.1, 159.8, 157.0, 129.8, 129.1, 125.1, 125.0, 121.8, 115.5, 113.6, 82.0, 82.0, 62.4, 62.2, 61.3, 61.2, 55.1, 51.5, 51.4, 51.3, 51.3, 37.8, 37.7, 37.4, 37.3, 14.8, 14.7 ppm. IR (KBr): $\tilde{\nu}$ = 2951, 2839, 1759, 1612, 1598, 1514, 1495, 1247, 1175, 983, 755 cm^{-1}. $C_{23}H_{28}N_2O_5$ (412.48): calcd. C 66.97, H 6.84; found C 67.07, H 7.01.

β-Lactam 15: Following the general procedure, a solution of **3a** (0.30 g, 0.55 mmol) and methyl glycinate[21] (0.11 g, 1.10 mmol) in THF (20 mL) was irradiated for 16 h under CO. A 1:1 diastereomeric mixture of **15** (0.11 g, 39%) was obtained as a slightly coloured oil after purification by chromatography (SiO_2, Hex/AcOEt, 2:3). Mixture of isomers: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.77 (br. s, 2 H), 7.28–7.23 (m, 4 H), 7.14–7.06 (m, 4 H), 6.88–6.73 (m, 10 H), 5.54 (d, J = 4.4 Hz, 1 H), 5.49 (d, J = 4.4 Hz, 1 H), 5.03 (d, J = 4.4 Hz, 1 H), 5.00 (d, J = 4.4 Hz, 1 H), 4.19 (q, J = 7.2 Hz, 2 H), 4.17 (q, J = 7.2 Hz, 2 H), 4.15–4.04 (m, 2 H), 3.99–3.82 (m, 2 H), 3.74 (s, 6 H), 3.27 (q, J = 7.1 Hz, 2 H), 3.05 (dt, J = 14.4, 5.6 Hz, 2 H), 2.98 (dt, J = 14.3, 5.4 Hz, 2 H), 2.60 (t, J = 4.8 Hz, 2 H), 2.57 (t, J = 4.8 Hz, 2 H), 2.24 (s, 3 H), 2.23 (s, 3 H), 1.26 (t, J = 7.2 Hz, 3 H), 1.25 (t, J = 7.2 Hz, 3 H), 1.19 (d, J = 7.1 Hz, 3 H), 1.17 (d, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 173.7, 173.6, 170.2, 166.7, 166.6, 160.0, 159.9, 157.0, 129.9, 129.8, 129.1, 124.9, 124.8, 121.8, 121.8, 115.5, 113.8, 81.9, 81.8, 63.3, 62.6, 62.4, 62.0, 61.3, 55.1, 52.5, 41.1, 41.0, 38.7, 38.6, 37.5, 37.1, 14.1, 9.1, 8.9 ppm. IR (KBr): $\tilde{\nu}$ = 3344, 2937, 1752, 1674, 1613, 1598, 1514, 1495, 1240, 1197, 1033, 754 cm^{-1}. $C_{26}H_{33}N_3O_6$ (483.56): calcd. C 64.58, H 6.88; found C 64.83, H 6.99.

β-Lactam 16: Following the general procedure, a solution of **3a** (0.26 g, 0.48 mmol) and methyl *N*-glycylglycinate[21] (0.14 g, 0.96 mmol) in THF (20 mL) was irradiated for 16 h under CO. A 1:1 diastereomeric mixture of **16** (0.06 g, 26%) was obtained as a yellow oil after purification by chromatography (SiO_2, AcOEt/MeOH, 5:1). Mixture of isomers: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.02–7.97 (m, 2 H), 7.28–7.25 (m, 4 H), 7.14–7.09 (m, 4 H), 7.01 (br. s, 2 H), 6.92–6.71 (m, 10 H), 5.57 (d, J = 4.2 Hz, 1 H), 5.55 (d, J = 4.3 Hz, 1 H), 5.06 (d, J = 4.2 Hz, 1 H), 5.02 (d, J = 4.3 Hz, 1 H), 4.17–3.89 (m, 8 H), 3.76 (s, 3 H), 3.75 (s, 3 H), 3.70–3.56 (m, 2 H), 3.68 (s, 3 H), 3.65 (s, 3 H), 3.45–3.31 (m, 2 H), 3.12–2.95 (m, 2 H), 2.63–2.57 (m, 4 H), 2.23 (s, 6 H), 1.21 (d, J = 6.9 Hz, 3 H), 1.19 (d, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.1, 169.5, 169.3, 167.1, 167.0, 159.9, 156.9, 156.8, 129.9, 129.9, 129.1, 124.8, 124.6, 121.8, 115.5, 115.4, 113.8, 113.7, 81.8, 62.4, 62.3, 55.2, 52.3, 52.2, 43.0, 42.9, 41.1, 41.1, 37.8, 37.3, 8.5 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3325, 2929, 2853, 1751, 1663, 1613, 1598, 1589, 1515, 1495, 1239, 1033, 834, 754 cm^{-1}. $C_{27}H_{34}N_4O_7$ (526.58): calcd. C 61.58, H 6.51; found C 61.75, H 6.80.

β-Lactam 17: Following the general procedure, a solution of **3b** (0.11 g, 0.18 mmol) and methyl *N*-glycylglycinate (0.05 g, 0.35 mmol) in THF (10 mL) was irradiated for 16 h under CO. A 1:1 diastereomeric mixture of **17** (0.03 g, 26%) was obtained as a yellow solid after purification by chromatography (SiO_2, AcOEt/MeOH, 5:1). Mixture of isomers: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.95 (br. s, 1 H), 7.30 (d, J = 7.7 Hz, 2 H), 7.21 (dd, J = 8.8, 3.1 Hz, 2 H), 7.16–7.10 (m, 4 H), 6.87 (t, J = 7.4 Hz, 1 H), 6.81 (dd, J = 8.8, 1.9 Hz, 2 H), 6.73 (d, J = 8.0 Hz, 2 H), 6.68 (br. s, 1 H), 5.40 (d, J = 4.3 Hz, 1 H), 4.84 (d, J = 14.8 Hz, 1 H), 4.76 (d, J = 4.3 Hz, 1 H), 4.20–3.90 (m, 2 H), 4.05 (d, J = 5.3 Hz, 2 H), 3.84 (dd, J = 14.8, 3.3 Hz, 1 H), 3.77 (s, 3 H), 3.74 (s, 3 H), 3.75–3.50 (m, 2 H), 3.39–3.31 (m, 1 H), 2.23 (s, 3 H), 1.29 (d, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.0, 169.3, 169.3, 165.6, 165.6, 159.9, 156.9, 130.0, 129.9, 129.3, 129.1, 128.9, 128.8, 124.4, 121.9, 121.9, 115.5, 115.5, 113.7, 113.7, 82.1, 82.1, 61.7, 61.6, 61.1, 61.1, 58.8, 55.1, 52.4, 43.6, 43.0, 41.1, 37.9, 37.8, 9.05 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3359, 3014, 1754, 1662, 1613, 1598, 1514, 1495, 1238, 1216, 984, 832 cm^{-1}. $C_{33}H_{38}N_4O_7$ (602.68): calcd. C 65.77, H 6.35; found C 65.96, H 6.64.

Penicillin Derivative 21: Following the general procedure, a solution of **4** (0.21 g, 0.34 mmol) and methyl *N*-glycylglycinate (0.10 g, 0.69 mmol) in THF (20 mL) was irradiated for 16 h under CO. A 5:2 diastereomeric mixture of pure **21** (0.10 g, 44%) was obtained as a brown oil after purification by chromatography (SiO_2, fast elution with hexane and then AcOEt). Mixture of isomers: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.39–7.28 (m, 10 H), 6.22 (br. d, J = 8.7 Hz, 1 H), 6.12 (br. d, J = 9.0 Hz, 1 H), 5.80 (br. s, 1 H), 5.77 (br. s, 1 H), 5.65 (dd, J = 9.0, 4.2 Hz, 1 H), 5.51 (d, J = 4.2 Hz, 1 H), 5.08 (d, J = 3.9 Hz, 1 H), 4.64 (dd, J = 8.7, 3.9 Hz, 1 H), 4.37 (s, 2 H), 4.28–4.13 (m, 2 H), 4.13–4.06 (m, 2 H), 3.73 (s, 6 H), 3.66–3.59 (m, 8 H), 3.64 (br. s, 4 H), 3.64 (s, 2 H), 3.38–3.24 (m, 6 H), 1.98 (d, J = 5.9 Hz, 3 H), 1.97 (d, J = 5.0 Hz, 3 H), 1.91–1.85 (m, 4 H), 1.45 (s, 6 H), 1.44 (s, 6 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.5, 173.4, 170.9, 170.4, 170.3, 170.3, 169.5, 167.7, 167.5, 134.6, 133.8, 129.5, 129.5, 129.1, 129.0, 127.6, 127.4, 72.8, 70.3, 70.3, 68.1, 66.0, 64.4, 63.2, 62.8, 62.7, 62.7, 58.8, 58.6, 56.9, 52.6, 43.6, 43.4, 36.3, 36.2, 31.9, 31.9, 28.8, 28.7, 26.7, 26.5, 23.3, 23.2 ppm. IR (KBr): $\tilde{\nu}$ = 3300, 2930, 1785, 1743, 1657, 1540, 1371, 1260, 1207, 758 cm^{-1}. $C_{27}H_{37}N_5O_8S$ (591.67): calcd. C 54.81, H 6.30; found C 54.98, H 6.63.

Cephalotin Derivative 22: Following the general procedure, a solution of **5** (0.17 g, 0.25 mmol) and methyl *N*-glycylglycinate (0.11 g, 0.75 mmol) in THF (20 mL) was irradiated for 16 h under CO. A 1:1 diastereomeric mixture of pure **22** (0.08 g, 50%) was obtained as an orange solid after purification by chromatography (SiO_2, AcOEt/MeOH, 5:1). Mixture of isomers: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.88 (br. s, 1 H), 7.71 (br. s, 3 H), 7.26–7.21 (m, 2 H), 7.01–6.96 (m, 4 H), 6.61 (br. d, J = 8.7 Hz, 1 H), 6.61 (br. d, J = 8.6 Hz, 1 H), 5.69 (dd, J = 8.7, 4.4 Hz, 1 H), 5.67 (dd, J = 8.6, 4.2 Hz, 1 H), 5.27 (d, J = 4.5 Hz, 1 H), 5.25 (d, J = 4.2 Hz, 1 H), 5.05–4.44 (m, 3 H), 4.56 (d, J = 12.8 Hz, 1 H), 4.32–4.23 (m, 4 H), 4.08–3.92 (m, 8 H), 3.86 (s, 4 H), 3.78–3.67 (m, 2 H), 3.73 (s, 6 H), 3.54 (d, J = 18.4 Hz, 1 H), 3.36 (d, J = 18.4 Hz, 1 H), 3.28–3.17 (m, 2 H), 2.76–2.59 (m, 4 H), 2.10–1.80 (m, 4 H), 2.06 (s, 6 H), 1.32 (d, J = 6.6 Hz, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.5, 170.5, 170.1, 170.0, 170.0, 169.3, 167.0, 164.2, 164.1, 134.7, 127.8, 127.4, 125.9, 125.4, 125.4, 119.1, 119.1, 65.4, 64.2, 64.1, 62.9, 60.3, 60.3, 58.2, 58.1, 53.3, 52.3, 44.9, 44.8, 42.6, 41.1, 37.0, 36.9, 29.0, 26.3, 20.8, 19.5, 19.4 ppm. IR (KBr): $\tilde{\nu}$ = 3314, 2929, 1777,

1741, 1662, 1530, 1438, 1378, 1223, 1029 cm^{-1}. $C_{27}H_{35}N_5O_{10}S_2$ (653.72): calcd. C 49.61, H 5.40; found C 49.78, H 5.86.

Penicillin Derivative 24: Following the general procedure, a solution of **6** (0.14 g, 0.29 mmol) and MeOH (5 mL) in THF (20 mL) was irradiated for 16 h under CO. A 1:1 diastereomeric mixture of **24** (0.08 g, 75%) was obtained as a yellow oil after purification by precipitation (Hex/DCM, 10:2). Mixture of isomers: ^1H NMR (300 MHz, $CDCl_3$): δ = 5.91 (ddt, J = 18.0, 10.4, 6.0 Hz, 2 H), 5.51 (d, J = 4.0 Hz, 2 H), 5.39–5.26 (m, 4 H), 4.64 (d, J = 6.0 Hz, 2 H), 4.63 (d, J = 6.0 Hz, 2 H), 4.51–4.43 (m, 2 H), 4.41 (s, 1 H), 4.40 (s, 1 H), 3.72 (s, 3 H), 3.69 (s, 3 H), 3.63–3.43 (m, 2 H), 1.63 (s, 6 H), 1.49 (s, 6 H), 1.36 (d, J = 7.0 Hz, 3 H), 1.32 (d, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.6, 175.9, 175.2, 174.6, 167.8, 167.7, 131.1, 131.1, 119.6, 70.8, 70.3, 70.0, 68.2, 66.3, 66.0, 63.9, 63.6, 54.7, 52.1, 31.8, 31.6, 27.2, 27.0, 18.7, 18.5 ppm. IR (KBr): $\tilde{\nu}$ = 3336, 2925, 2854, 1780, 1739, 1452, 1373, 1261, 1203, 1184, 1155, 985 cm^{-1}. $C_{15}H_{22}N_2O_5S$ (342.40): calcd. C 52.62, H 6.48; found C 52.84, H 6.62.

Supporting Information (see footnote on the first page of this article): ^1H and ^{13}C NMR spectra of the newly synthesized compounds.

Acknowledgments

Support for this work from the Spanish Ministerio de Educación y Ciencia (MEC) (CTQ2007-67730-C02-01/BQU and Programa Consolider-Ingenio 2010, CSD2007-0006) and from the Comunidad Autónoma de Madrid (CCG07-UCM-PPQ-2596) is gratefully acknowledged. M.R.-F. thanks the MEC for an FPU fellowship.

[1] M. Gómez-Gallego, M. J. Mancheño, M. A. Sierra, *Tetrahedron* **2000**, *56*, 5743–5774.

[2] a) I. Ojima, F. Delaloge, *Chem. Soc. Rev.* **1997**, *26*, 377–386; b) C. Palomo, J. M. Aizpurua, I. Gamboa, M. Oiarbide, *Synlett* **2001**, *12*, 1813–1826; c) B. Alcaide, P. Almendros, *Chem. Soc. Rev.* **2001**, *30*, 226–240; d) B. Alcaide, P. Almendros, *Curr. Med. Chem.* **2004**, *11*, 1921–1949; e) B. Alcaide, P. Almendros, C. Aragoncillo, *Chem. Rev.* **2007**, *107*, 4437–4492.

[3] a) The following articles give an up-to-date description of the necessity of obtaining new antibacterial agents: D. J. Payne, *Science* **2008**, *321*, 1644–1645; b) C. T. Walsh, G. Wright, *Chem. Rev.* **2005**, *105*, 391–394; c) J. F. Fisher, S. O. Meroueh, S. Mobashery, *Chem. Rev.* **2005**, *105*, 395–424.

[4] For recent reviews, see: a) J. Spencer, T. Walsh, *Angew. Chem. Int. Ed.* **2006**, *45*, 1022–1026; b) , J. M. Thomson, A. M. Distler, F. Pratl, R. A. Bonomo, *J. Biol. Chem.* **2006**, *281*, 26734–26744; c) K. Bush, S. Mobashery, in: *Resolving the Antibiotic Paradox* (Eds.: B. P. Rosen, S. Mobashery), Kluwer Academic, Plenum Publishers, New York, **1999**, vol. 456.

[5] For reviews, see: a) O. A. Mascaretti, C. E. Boschetti, G. O. Danelon, E. G. Mata, O. A. Roveri, *Curr. Med. Chem.* **1995**, *1*, 441–470; b) P. D. Edwards, P. R. Bernstein, *Med. Res. Rev.* **1994**, *14*, 127–194.

[6] a) S. B. Rosenblum, T. Huynh, A. Afonso, H. R. Davis, N. Yumibe, J. W. Clader, D. A. Burnett, *J. Med. Chem.* **1998**, *41*, 973–980; b) J. W. Clader, D. A. Burnett, M. A. Caplen, M. S. Domalski, S. Dugar, W. Vaccaro, R. Sher, M. E. Browne, H. Zhao, R. E. Burrier, B. Salisbury, H. R. Davis, *J. Med. Chem.* **1996**, *39*, 3684–3693.

[7] For examples, see: a) P. R. Bonneau, F. Hasani, C. Plouffe, E. Malenfant, S. R. LaPlante, I. Guse, W. W. Ogilvie, R. Plante, W. C. Davidson, J. L. Hopkins, M. M. Morelock, M. G. Cordingley, R. Déziel, *J. Am. Chem. Soc.* **1999**, *121*, 2965–2973; b) A. D. Borthwick, G. Weingarten, T. M. Haley, M. Tomaszewski, W. Wand, Z. Hu, J. Bédard, H. Jin, L. Yuen, T. S. Mansour, *Bioorg. Med. Chem. Lett.* **1998**, *8*, 365–370; c) C. Yoakim, W. W. Ogilvie, D. R. Cameron, C. Chabot, I. Guse, B. Haché, J. Naud, J. A. O'Meara, R. Plante, R. Déziel, *J. Med. Chem.* **1998**, *41*, 2882–2891.

[8] J. D. Rothstein, S. Patel, M. R. Regan, C. Haenggeli, Y. H. Huang, D. E. Bergles, L. Jin, M. Dykes Hoberg, S. Vidensky, D. S. Cheng, S. V. Toan, L. I. Bruijn, Z. Su, P. Gupta, P. B. Fisher, *Nature* **2005**, *433*, 73–77.

[9] N. Hatanaka, R. Abe, I. Ojima, *Chem. Lett.* **1982**, 445–448.

[10] a) S. Hetch (Ed.), *Bioorganic Chemistry: Peptides and Proteins*, Oxford University Press, Oxford, **1998**; b) M. Hesse, in: *Alkaloids: Nature's Curse or Blessing*, Wiley-VCH, New York, **2000**.

[11] For reviews, see: a) T. C. Boge, G. I. Georg, in: *Enantioselective Synthesis of β-Amino Acids* (Ed.: E. Juaristi), Wiley-VCH, New York, **1997**, chapter 1, pp. 1–43; b) C. Palomo, J. M. Aizpurua, I. Gamboa, in: *Enantioselective Synthesis of β-Amino Acids* (Ed.: E. Juaristi), Wiley-VCH, New York, **1997**, chapter 14, pp. 279–357; c) I. Ojima, in: *The Organic Chemistry of β-Lactams* (Ed.: G. I. Georg), New York, **1993**, chapter 4, pp. 197–255.

[12] For selected reviews of the chemistry and synthetic applications of Fischer carbene complexes, see: a) K. H. Dötz, H. Fischer, P. Hofmann, R. Kreissel, U. Schubert, K. Weiss, *Transition Metal Carbene Complexes*, Verlag Chemie, Weinheim, Germany, **1983**; b) W. D. Wulff, in: *Comprehensive Organic Synthesis* (Eds.: B. M. Trost, I. Fleming), Pergamon Press, Oxford, **1991**, vol. 5, pp. 1065–1113; c) W. D. Wulff, in: *Comprehensive Organometallic Chemistry II* (Eds.: E. W. Abel, F. G. A. Stone, G. Wilkinson), Pergamon Press, Oxford, **1995**, vol. 12, pp. 470–547; d) D. F. Harvey, D. M. Sigano, *Chem. Rev.* **1996**, *96*, 271–288; e) R. Aumann, H. Nienaber, *Adv. Organomet. Chem.* **1997**, *41*, 163–242; f) B. Alcaide, L. Casarrubios, G. Domínguez, M. A. Sierra, *Curr. Org. Chem.* **1998**, *2*, 551–574; g) M. A. Sierra, *Chem. Rev.* **2000**, *100*, 3591–3638; h) J. Barluenga, F. J. Fañanás, *Tetrahedron* **2000**, *56*, 4597–4628; i) M. Gómez-Gallego, M. J. Mancheño, M. A. Sierra, *Acc. Chem. Res.* **2005**, *38*, 44–53; j) M. A. Sierra, M. Gómez-Gallego, R. Martínez-Álvarez, *Chem. Eur. J.* **2007**, *13*, 736–744.

[13] a) L. S. Hegedus, G. deWeck, S. D'Andrea, *J. Am. Chem. Soc.* **1988**, *110*, 2122–2126; b) A. Arrieta, F. P. Cossío, I. Fernández, M. Gómez-Gallego, B. Lecea, M. J. Mancheño, M. A. Sierra, *J. Am. Chem. Soc.* **2000**, *122*, 11509–11510; c) I. Fernández, M. A. Sierra, M. J. Mancheño, M. Gómez-Gallego, F. P. Cossío, *Chem. Eur. J.* **2005**, *11*, 5988–5996; d) I. Fernández, M. A. Sierra, M. J. Mancheño, M. Gómez-Gallego, F. P. Cossío, *J. Am. Chem. Soc.* **2008**, *130*, 13892–13899.

[14] a) L. S. Hegedus, M. A. McGuire, L. M. Schultze, C. Yijun, O. P. Anderson, *J. Am. Chem. Soc.* **1984**, *106*, 2680–2687; for reviews see: b) M. A. Schwindt, J. R. Miller, L. S. Hegedus, *J. Organomet. Chem.* **1991**, *413*, 143–153; c) L. S. Hegedus, in: *Comprehensive Organometallic Chemistry II* (Eds.: E. W. Abel, F. G. A. Stone, G. Wilkinson), Pergamon Press, Oxford, **1995**, vol. 12, pp. 549–576; d) L. S. Hegedus, *Acc. Chem. Res.* **1995**, *28*, 299–305; e) L. S. Hegedus, *Tetrahedron* **1997**, *53*, 4105–4127.

[15] a) B. Alcaide, J. Pérez-Castells, B. Sánchez-Vigo, M. A. Sierra, *J. Chem. Soc., Chem. Commun.* **1994**, 587–588; b) B. Alcaide, C. Polanco, M. A. Sierra, *J. Org. Chem.* **1998**, *63*, 6786–6796; c) C. Baldoli, P. Del Buttero, E. Licandro, S. Maiorana, A. Papagni, *Synlett* **1994**, 183–185; d) C. Baldoli, P. Del Buttero, E. Licandro, S. Maiorana, A. Papagni, *Tetrahedron: Asymmetry* **1994**, *5*, 809–812; e) C. Baldoli, P. Del Buttero, E. Licandro, A. Papagni, *Tetrahedron* **1996**, *52*, 4849–4856; f) P. Del Buttero, G. Molteni, A. Papagni, *Tetrahedron: Asymmetry* **2003**, *14*, 3949–3956.

[16] a) M. A. Sierra, M. J. Mancheño, R. Vicente, M. Gómez-Gallego, *J. Org. Chem.* **2001**, *66*, 8920–8923; b) E. I. Edwards, R. Epton, G. Marr, *J. Organomet. Chem.* **1975**, *85*, C23–C25; c) E. I. Edwards, R. Epton, G. Marr, *J. Organomet. Chem.* **1976**, *107*, 351–357; d) D. Scutaru, I. Mazilu, M. Vata, L. Tataru, A. Vlase, *J. Organomet. Chem.* **1991**, *401*, 87–90; e) C. Simionescu,

T. Lixandru, L. Tataru, I. Mazilu, M. Vata, S. Luca, *J. Organomet. Chem.* **1983**, *252*, C43–C46; f) Y.-Y. Tong, J. J. R. Fraústo da Silva, A. J. L. Pombeiro, G. Wagner, R. J. Herrmann, *J. Organomet. Chem.* **1998**, *552*, 17–21; g) A. Gatak, F. F. Becker, B. K. Banik, *Heterocycles* **2000**, *53*, 2769–2773.
[17] a) K. Weiss, E. O. Fischer, *Chem. Ber.* **1973**, *106*, 1277–1284; b) K. Weiss, E. O. Fischer, *Chem. Ber.* **1976**, *109*, 1868–1886.
[18] R. Alcazar, P. Ramírez, R. Vicente, M. J. Mancheño, M. A. Sierra, M. Gómez-Gallego, *Heterocycles* **2001**, *55*, 511–521, and references cited therein.
[19] Commercial methyl glycinate or *N*-glycylclycinate hydrochlorides (1.0 equiv.) was stirred with 2.5 equiv. of TEA in diethyl ether for 2 h. The mixture was then filtered and the solvents were evaporated. The free base thus obtained was used in the photochemical reactions.
[20] M. S. Manhas, K. Gala, S. S. Bari, A. K. Bose, *Synthesis* **1983**, 549–552.
[21] J. W. Tilley, P. Levitan, R. W. Kierstead, M. Cohen, *J. Med. Chem.* **1980**, *23*, 1387–1392.
[22] L. S. Hegedus, M. A. McGuire, L. Schultze, *Org. Synth.*, *Coll. Vol. VIII*, 216–218.

Received: February 23, 2009
Published Online: May 7, 2009

