Stereoselective Synthesis of Tetrahydrofuran Spiro-β-Lactams by Ru-Catalyzed Metathesis of 7-Oxabicyclo[2.2.1]heptenes

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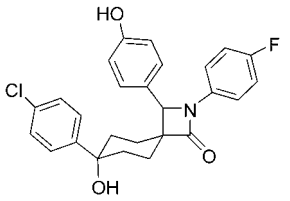
Dedicated to Professor *Rolf Huisgen* on the occasion of his 85th birthday

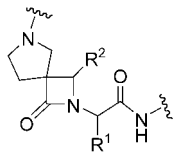
A new method for the synthesis of spiro-β-lactams tethered to tetrahydrofuran rings is described. The procedure is based on Ru-catalyzed metathesis sequences with oxanorbornene precursors easily obtained by the *Staudinger* [2 + 2] cycloaddition of related imines.

Introduction. – The interest in the development of new versatile syntheses of β-lactam derivatives continues due to the biological activity of these molecules[1]). On the other hand, these compounds have also been found to be valuable intermediates in organic synthesis[2]).

Although various examples of β-lactams with spiro structures deriving from penicillins or cephalosporins have been reported [3], only a few examples of simple spiro β-lactams were known until 1990 [4]. More recently, the discovery of compounds such as Sch 58053 (**1**) [5], a cholesterol absorption inhibitor, the proline derived β-lactams **2** [6], designed as β-turn mimetics and used for synthetic applications for the preparation of α,α-disubstituted β-amino esters [7], diazabicyclic compounds [8] and other densely functionalized, nitrogenated five-membered-ring systems [9], have renewed the interest in these compounds.



1
Sch 58053



2
Proline derived β-turn mimetics

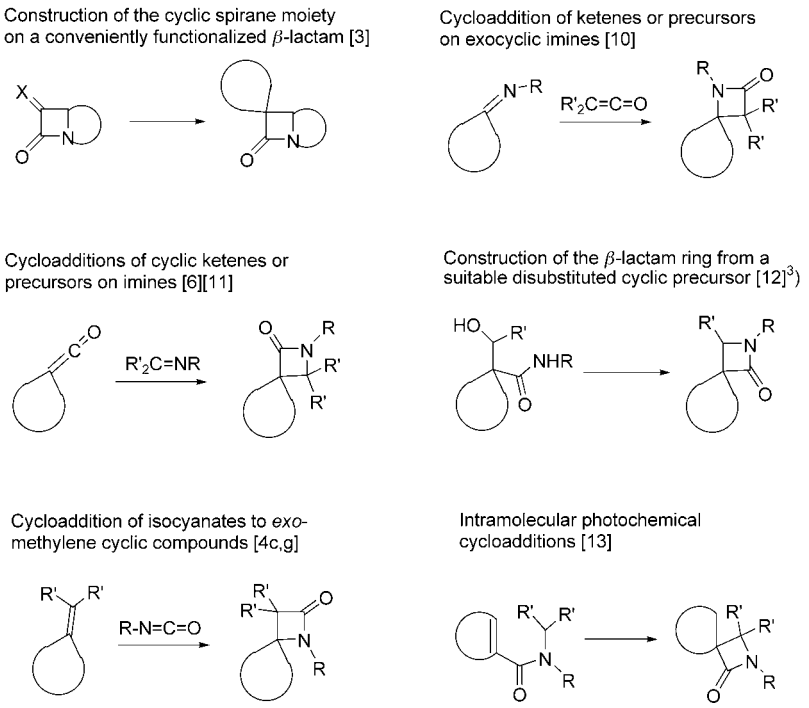
From a synthetic point of view, spiro β-lactam derivatives have been obtained using different methodologies, as summarized in *Scheme 1* [3][4c,g][6][10–13][3]).

[1]) For reviews on β-lactams as antibiotic agents, see [1a,b]. For the use of β-lactams as enzymatic inhibitors, see [1c].

[2]) For selected reviews on the use of β-lactams as synthetic intermediates, see [2].

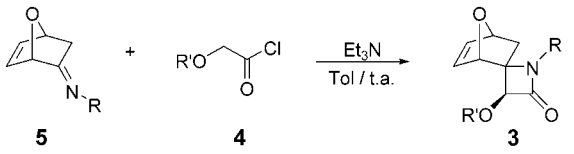
[3]) Using the methodology reported in [12], compound **1** has been synthesized on 1.5-kg scale.

Scheme 1



In a preliminary account [14], we have described the synthesis of oxabicyclic spiro-β-lactams **3** *via* [2+2] cycloaddition reaction (*Staudinger* reaction)[4]) of the appropriate acyl chlorides **4** and oxanorbornene imines **5**[5]) in the presence of Et_3N (*Scheme 2*).

Scheme 2



5 **4** **3**

As oxabicyclic compounds may be considered masked 2,5-*cis*-disubstituted tetrahydrofuran derivatives after a sequence of ring-opening-metathesis and cross-metathesis (ROM-CM) reactions [17], we speculate that compounds **3** should be suitable precursors of the hitherto unknown spiro-β-lactams **6** by reaction with ethylene as CM partner, and in the presence of an appropriate Ru catalyst[6]) (*Scheme 3*).

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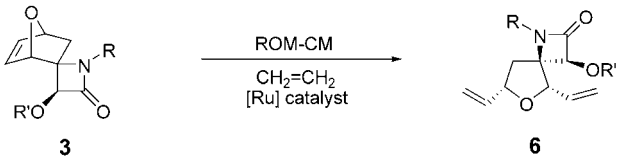
[4]) For reviews on *Staudinger* reactions, see [15a,b] (general) and [15c] (asymmetric variant).

[5]) For some aspects related to the synthesis and reactivity of oxanorbornene imines, see [16].

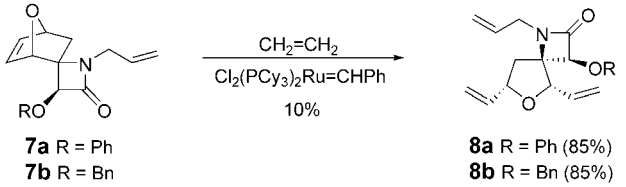
[6]) Metathesis reactions have been applied to the synthesis of fused β-lactams. For some recent reports, see [18].

Scheme 3



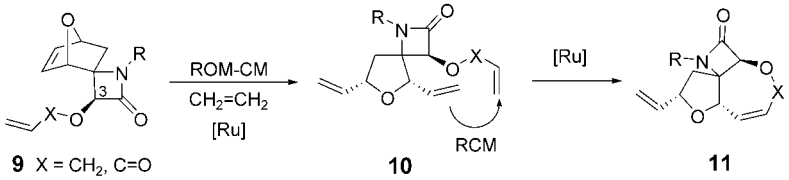
Results and Discussion. – In a preliminary assay, the *N*-allyl-*β*-lactams **7a** and **7b** were tested in the ROM-CM sequence. Thus, treatment of both compounds with *Grubb*'s Ru catalyst (10 mol-%) under ethene pressure afforded compounds **8a** and **8b**, respectively (*Scheme 4*).

Scheme 4



Once the feasibility of this method was confirmed, the next objective was the introduction of new substituents attached to the O-atom at position 3 of the *β*-lactam nucleus to extend the scope of the reaction. Also, such modified precursors should additionally promote the sequence ring-opening–cross–ring-closing metathesis (ROM-CM-RCM)[7]). For this last purpose, a terminal C=C bond on these substituents is necessary (*Scheme 5*). The products resulting from this sequence are tricyclic *β*-lactams such as **11** [20][8]).

Scheme 5



For the synthesis of compounds **9** (R = Bn), the starting material was compound **12** prepared, in turn, by reaction of the imine **13** with 3-oxobutanoyl chloride, followed by cleavage of the Ac moiety of the resulting spiro-*β*-lactam **14** (*Scheme 6*).

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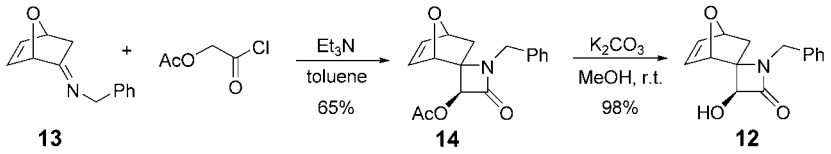
[7]) For the sequence ROM-CM-RCM in oxa- and azanorbornene derivatives, see [19].

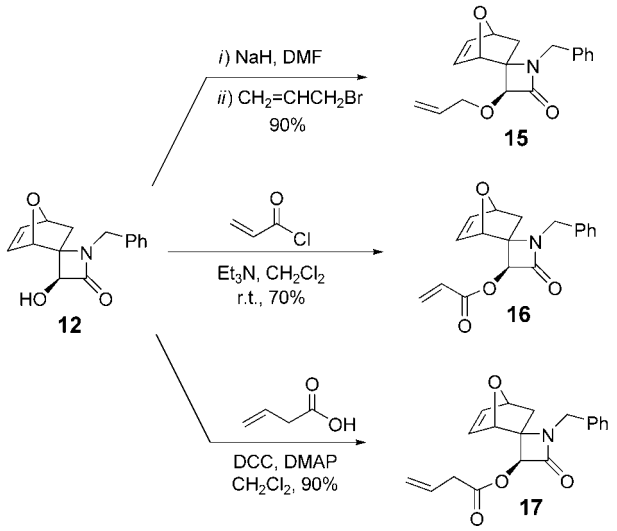
[8]) Tricyclic *β*-lactams are synthetic antibacterial agents featuring good resistance to *β*-lactamases and dehydropeptidases.

Scheme 6



From the hydroxy compound **12**, the ether **15** and the esters **16** and **17** were prepared using standard methods (*Scheme 7*).

Scheme 7



Treatment of compounds **15**–**17** with *Grubb*'s Ru catalyst gave different results. Thus, compound **15** afforded the tricyclic β-lactam **18** in almost quantitative yield. In sharp contrast, compounds **16** and **17** afforded, under the same conditions, the bicyclic spiro-β-lactams **19** and **20** (*Scheme 8*). Attempts to induce the last metathesis step (RCM) on the isolated compounds were unsuccessful. Also, the use of the second-generation *Grubb*'s catalyst **21** only improved the yield of **19** and **20**.

Substitution of the O-atom attached to C(3) in compound **9** (*Scheme 5*) by and S-atom was also carried out[9]). For this purpose, mesylation of **12** followed by reaction of the resulting mesylate **22** with prop-2-ene-1-thiol afforded compound **23**. Alternatively, isomerization of **22** with NaH and prop-2-en-1-amine, followed by treatment of the resulting epimer **24**[10]) with allylmercaptane, gave the spiro-β-lactam **25** (*Scheme 9*).

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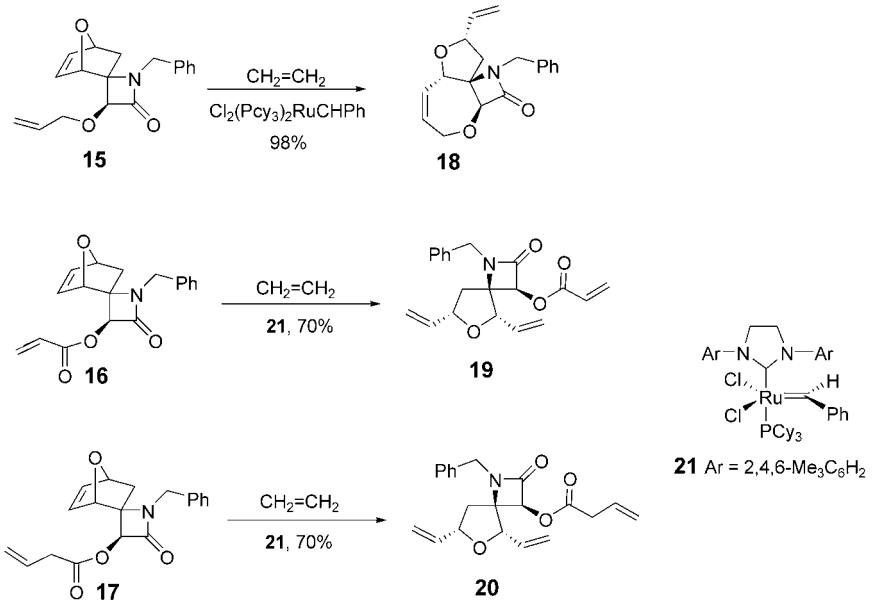
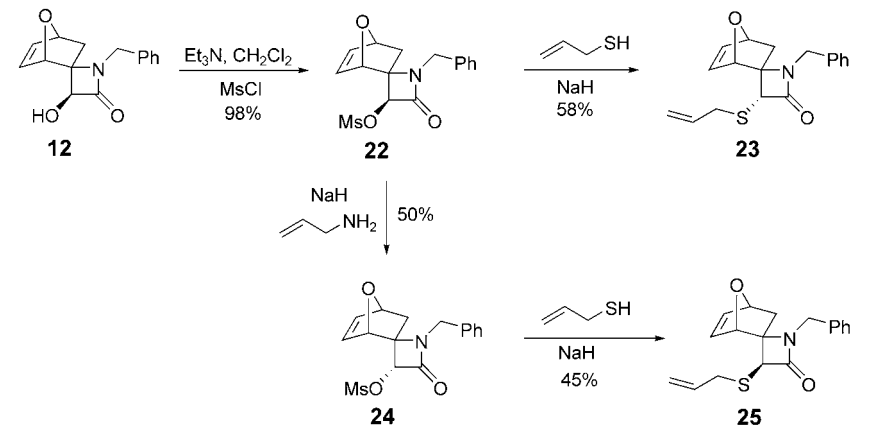
[9]) Many sulfur-containing bicyclic β-lactams are potent antibiotics and inhibitors of serine proteases (for the synthesis and transformation of sulfur-containing mono- and bicyclic β-lactams, see [21]; in particular see Chapt. 2 p. 82–86, 90, 91, 96, 101, 104, and 105, Chapt. 5 p. 281, and Chapt. 6 p. 356).

[10]) Complete isomerization of **22**–**24** was not possible, even in the presence of different basic reagents.

Scheme 8



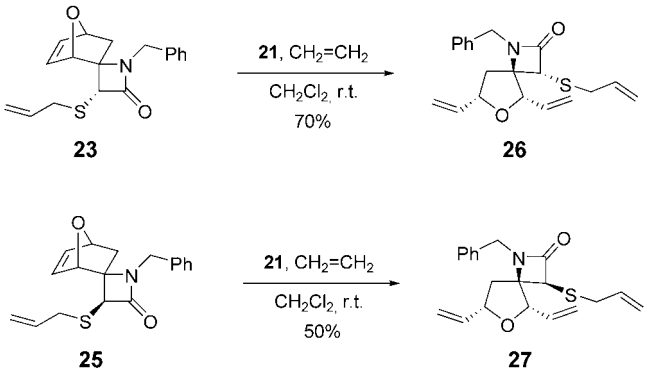
Scheme 9



Compounds **23** and **25** were submitted to ROM-CM reaction using catalyst **21** to afford the spiro-β-lactams **26** and **27**, respectively, in moderate yields (*Scheme 10*).

Conclusions. – We have developed a new procedure for the stereoselective synthesis of new spiro-β-lactams by means of metathesis reactions as the key procedure. This method allows the introduction of different substituents on the β-lactam nucleus, and may be considered a convenient and versatile alternative for the synthesis of this kind of compounds.

Scheme 10



Experimental Part

General. Commercially available reagents were used as received, and solvents were dried prior to use. Silica gel *60* F_{254} was used for TLC, and the spots were detected under UV light or by dipping into $KMnO_4$ soln. Flash chromatography (FC) was carried out on silica gel *60*. Melting points (m.p.) were determined on a *Büchi 512* apparatus and are uncorrected. IR Spectra were recorded on a *Perkin-Elmer 781* spectrophotometer; in cm^{-1}. ^1H- and ^{13}C-NMR spectra were recorded on a *Bruker AM-300* instrument in $CDCl_3$ soln., with Me_4Si as internal reference; δ in ppm, J in Hz. Elemental analyses were performed at the Universidad Complutense de Madrid.

Syntheses of β-Lactams **7a**, **7b**, *and* **14**. *General Procedure.* To a soln. of the imine **5** (R = allyl) or **13** (R = benzyl) (1 mmol) in toluene, Et_3N (3 mmol) was added. Then, a soln. of the corresponding acid chloride (1.5 mmol) in toluene (4.5 ml) was added dropwise. The mixture was stirred for 12 h at r.t., diluted with CH_2Cl_2, and washed with aq. sat. $NaHCO_3$ soln. and brine. The org. layer was dried ($MgSO_4$) and concentrated under reduced pressure to give a crude residue, which was purified by FC (hexane/AcOEt 3:1).

*Data of (1′*S**,2*R**,3*S**,4′*S**)-3-Phenoxy-1-(prop-2-enyl)-4*H*-spiro[azetidine-2,2′-[7]oxabicyclo[2.2.1]hept-5-en]-4-one* (**7a**). Yield: 80%. Colorless solid. M.p. 82–85° (hexane/Et_2O). IR (KBr): 1740, 1660, 1590, 1230. ^1H-NMR (300 MHz, $CDCl_3$): 1.75 (*d*, *J* = 12.4, 1 H); 2.10 (*dd*, *J* = 12.4, 4.6, 1 H); 3.80 (*m*, 2 H); 4.90 (*s*, 1 H); 5.00 (*s*, 2 H); 5.10 (*d*, *J* = 9.0, 1 H); 5.20 (*d*, *J* = 17.1, 1 H); 5.75 (*m*, 1 H); 6.50 (*m*, 2 H); 6.90 (*m*, 3 H); 7.20 (*m*, 2 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 35.2; 42.3; 70.2; 78.4; 83.3; 84.6; 116.6; 118.3; 122.3; 129.5; 133.7; 134.1; 139.1; 157.6; 165.6. Anal. calc. for $C_{17}H_{17}NO_3$: C 72.07, H 6.05, N 4.94; found: C 72.11, H 6.12, N 4.92.

*Data of (1′*S**,2*R**,3*S**,4′*S**)-3-(Phenylmethyl)-1-(prop-2-enyl)-4*H*-spiro[azetidine-2,2′-[7]oxabicyclo[2.2.1]hept-5-en]-4-one* (**7b**). Yield: 80%. Colorless solid. M.p. 58–60° (hexane/ Et_2O). IR (KBr): 1745, 1640, 1580, 1230. ^1H-NMR (300 MHz, $CDCl_3$): 1.60 (*d*, *J* = 12.4, 1 H); 2.05 (*dd*, *J* = 12.4, 4.6, 1 H); 3.80 (*m*, 2 H); 4.50 (*s*, 1 H); 4.65 (*d*, *J* = 11.8, 1 H); 4.85 (*s*, 1 H); 4.95 (*d*, *J* = 11.8, 1 H); 5.05 (*d*, *J* = 4.6, 1 H); 5.15 (*d*, *J* = 9.0, 1 H); 5.25 (*d*, *J* = 17.1, 1 H); 5.90 (*m*, 1 H); 6.50 (*m*, 2 H); 7.25 (*m*, 5 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 35.3; 42.2; 69.7; 72.7; 78.5; 83.4; 85.2; 118.1; 127.7; 128.1; 128.8; 132.8; 134.4; 137.4; 138.8; 167.4. Anal. calc. for $C_{18}H_{19}NO_3$: C 72.71, H 6.44, N 4.71; found: C 72.75, H 6.52, N 4.75.

*Data of (1′*S**,2*R**,3*S**,4′*S**)-4-Oxo-1-(phenylmethyl)-4*H*-spiro[azetidine-2,2′-[7]oxabicyclo[2.2.1]hept-5-en]-3-yl Acetate* (**14**). Yield: 65%. Pale yellow oil. IR ($CHCl_3$): 1740, 1650, 1230. ^1H-NMR (300 MHz, $CDCl_3$): 1.65 (*d*, *J* = 12.4, 1 H); 1.90 (*dd*, *J* = 12.4, 4.6, 1 H); 2.02 (*s*, 3 H); 4.35 (*d*, *J* = 15.1, 2 H); 4.55 (*s*, 1 H); 4.95 (*d*, *J* = 4.6, 1 H); 5.75 (*s*, 1 H); 6.05 (*dd*, *J* = 5.8, 1.6, 1 H); 6.40 (*dd*, *J* = 5.8, 1.6, 1 H); 7.30 (*m*, 5 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 20.4; 32.5; 57.4; 70.1; 78.7; 84.2; 85.1; 127.7; 128.1; 129.2; 134.1; 136.6; 137.8; 167.4; 171.2. Anal. calc. for $C_{17}H_{17}NO_4$: C 68.21, H 5.72, N 4.68; found: C 68.25, H 5.68, N 4.65.

*(1′*S**,2*S**,3*S**,4′*S**)-3-Hydroxy-1-(phenylmethyl)-4*H*-spiro[azetidine-2,2′-[7]oxabicyclo[2.2.1]hept-5-en]-4-one* (**12**). To a soln. of **14** (70 mg, 0.23 mmol) in MeOH (2.5 ml), K_2CO_3 (160 mg, 1.20 mmol) was added in one portion. The mixture was stirred for 12 h at r.t., quenched with NH_4Cl (150 mg), and then filtered through *Celite*. The crude was concentrated under reduced pressure to give a residue, which was purified by FC (CH_2Cl_2/MeOH 96:4): 54 mg (98%) of **12**. Pale yellow oil. IR ($CHCl_3$): 3640, 1660, 1650, 1230. ^1H-NMR (300 MHz, $CDCl_3$): 1.60 (*d*, *J* = 12.4, 1 H); 1.90 (*dd*, *J* = 12.4, 4.6, 1 H); 4.40 (*d*, *J* = 15.0, 2 H); 4.70 (*m*, 2 H); 5.05 (*d*, *J* = 4.6, 1 H);

6.45 (*dd*, *J* = 5.8, 1.6, 1 H); 6.55 (*dd*, *J* = 5.8, 1.6, 1 H); 7.30 (*m*, 5 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 35.5; 47.4; 70.1; 78.6; 83.1; 84.2; 127.7; 128.1; 129.2; 133.4; 136.6; 138.2; 167.5. Anal. calc. for $C_{15}H_{15}NO_3$: C 68.21, H 5.72, N 4.68; found: C 68.25, H 5.68, N 4.65.

*(1′*S*,2*S*,3*S*,4′*S*)-1-(Phenylmethyl)-3-(prop-2-enyloxy)-4*H*-spiro[azetidine-2,2′-[7]oxabicyclo[2.2.1]-hept-5-en]-4-one* (**15**). To a soln. of **12** (50 mg, 0.20 mmol) in DMF (2 ml) at 0°, NaH (60% in mineral oil; 8.5 mg, 0.36 mmol) and allyl bromide (0.035 ml, 0.40 mmol) were added. The mixture was stirred at 0° for 30 min, and then for 24 h at r.t. The reaction was quenched with H_2O, and the mixture was extracted with Et_2O. The org. layer was dried ($MgSO_4$) and concentrated under reduced pressure to give a crude residue, which was purified by FC (hexane/AcOEt 2:1): 52 mg (90%) of **15**. Pale yellow oil. IR ($CHCl_3$): 1665, 1650, 1235. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.60 (*d*, *J* = 12.4, 1 H); 1.90 (*dd*, *J* = 12.4, 4.6, 1 H); 4.10 (*d*, *J* = 15.2, 1 H); 4.35 (*d*, *J* = 15.2, 1 H); 4.40 (*d*, *J* = 13.8, 2 H); 4.50 (*s*, 1 H); 4.70 (*s*, 1 H); 4.95 (*d*, *J* = 4.4, 1 H); 5.20 (*d*, *J* = 9.2, 1 H); 5.30 (*d*, *J* = 17.2, 1 H); 5.90 (*m*, 1 H); 6.45 (*m*, 2 H); 7.30 (*m*, 5 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 35.4; 43.7; 70.1; 72.1; 78.7; 83.4; 85.7; 117.8; 127.9; 128.9; 129.1; 134.1; 134.5; 137.4; 139.1; 167.7. Anal. calc. for $C_{18}H_{19}NO_3$: C 72.71, H 6.44, N 4.71; found: C 72.75, H 6.47, N 4.75.

*(1′*S*,2*R*,3*S*,4′*S*)-4-Oxo-1-(phenylmethyl)-4*H*-spiro[azetidine-2,2′-[7]oxabicyclo[2.2.1]hept-5-en]-3-yl Prop-2-enoate* (**16**). To a soln. of **12** (33 mg, 0.13 mmol) in CH_2Cl_2 (1.3 ml) at 0°, Et_3N (0.026 ml, 0.19 mmol) and acryloyl chloride (0.015 ml, 0.19 mmol) were added. The mixture was stirred for 12 h at r.t., quenched with H_2O, and extracted with CH_2Cl_2. The org. layer was dried ($MgSO_4$) and concentrated under reduced pressure to give a crude residue, which was purified by FC (hexane/AcOEt 2:1): 28 mg (70%) of **16**. Pale yellow oil. IR ($CHCl_3$): 1720, 1665, 1240. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.77 (*d*, *J* = 12.6, 1 H); 1.97 (*dd*, *J* = 12.4, 4.6, 1 H); 4.39 (*d*, *J* = 15.1, 1 H); 4.51 (*d*, *J* = 15.1, 1 H); 4.70 (*d*, *J* = 1.0, 1 H); 5.00 (*d*, *J* = 4.4, 1 H); 5.90 (*s*, 1 H); 5.98 (*dd*, *J* = 10.5, 1.5, 1 H); 6.17 (*m*, 2 H); 6.51 (*dd*, *J* = 5.8, 1.7, 1 H); 6.52 (*ddd*, *J* = 16.8, 10.2, 1.7, 1 H); 7.35 (*m*, 5 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 34.7; 43.8; 70.4; 77.9; 78.6; 82.7; 127.0; 127.7; 128.6; 128.7; 132.2; 133.1; 136.5; 140.7; 163.9; 164.4. Anal. calc. for $C_{18}H_{17}NO_4$: C 69.44, H 5.50, N 4.50; found: C 69.49, H 5.58, N 4.45.

*(1′*S*,2*R*,3*S*,4′*S*)-4-Oxo-1-(phenylmethyl)-4*H*-spiro[azetidine-2,2′-[7]oxabicyclo[2.2.1]hept-5-en]-3-yl But-3-enoate* (**17**). To a soln. of **12** (75 mg, 0.29 mmol) in CH_2Cl_2 (1.0 ml), 1,3-dicyclohexylcarbodiimide (DCC; 60 mg, 0.29 mmol), 4-(dimethylamino)pyridine (DMAP; cat. amount), and a soln. of but-3-enoic acid (0.025 ml, 0.29 mmol) in CH_2Cl_2 (1.0 ml) were added. The mixture was stirred for 12 h at r.t., filtered, and concentrated under reduced pressure. The crude residue was dissolved in Et_2O and washed with aq. 0.5N HCl soln., aq. 10%. $NaHCO_3$ soln., and H_2O. The org. layer was dried ($MgSO_4$) and concentrated under reduced pressure to give a crude residue, which was purified by FC (hexane/AcOEt 1:1): 85 mg (90%) of **17**. Pale yellow oil. IR ($CHCl_3$): 1745, 1665, 1235. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.73 (*d*, *J* = 12.4, 1 H); 1.95 (*dd*, *J* = 12.4, 4.6, 1 H); 3.18 (*dd*, *J* = 7.1, 1.4, 2 H); 4.36 (*d*, *J* = 15.1, 1 H); 4.48 (*d*, *J* = 15.1, 1 H); 4.67 (*d*, *J* = 1.0, 1 H); 4.99 (*d*, *J* = 4.4, 1 H); 5.22 (*dd*, *J* = 16.3, 1.2, 1 H); 5.23 (*dd*, *J* = 10.5, 1.2, 1 H); 5.82 (*s*, 1 H); 5.93 (*m*, 1 H) 6.17 (*dd*, *J* = 5.9, 1.7, 1 H); 6.50 (*dd*, *J* = 5.9, 1.7, 1 H); 7.34 (*m*, 5 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 34.6; 38.7; 43.7; 70.1; 78.0; 78.4; 82.5; 119.6; 127.7; 128.5; 128.6; 129.0; 132.1; 136.5; 140.6; 164.3; 169.2. Anal. calc. for $C_{19}H_{19}NO_4$: C 70.14, H 5.89, N 4.31; found: C 70.20, H 5.92, N 4.35.

*(1′*S*,2*R*,3*R*,4′*S*)-4-Oxo-1(phenylmethyl)-4*H*-spiro[azetidine-2,2′-[7]oxabicyclo[2.2.1]hept-5-en]-3-yl Methanesulfonate* (**22**). To a soln. of **12** (40 mg, 0.15 mmol) in CH_2Cl_2 (1.0 ml) at 0°, Et_3N (0.024 ml, 0.17 mmol) and methanesulfonyl chloride (MsCl; 0.024 ml, 0.30 mmol) were added. The mixture was stirred for 12 h at r.t., quenched with H_2O, and extracted with CH_2Cl_2. The org. layer was dried ($MgSO_4$) and concentrated under reduced pressure to give a crude residue, which was purified by FC (hexane/AcOEt 2:1): 48 mg (98%) of **22**. Pale yellow oil. IR ($CHCl_3$): 1740, 1660, 1230. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.75 (*d*, *J* = 12.4, 1 H); 1.95 (*dd*, *J* = 12.4, 4.6, 1 H); 3.25 (*s*, 3 H); 4.40 (*d*, *J* = 15.1, 2 H); 4.60 (*s*, 1 H); 5.05 (*d*, *J* = 4.6, 1 H); 5.35 (*s*, 1 H); 6.52 (*dd*, *J* = 5.8, 1.6, 2 H); 7.35 (*m*, 5 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 35.2; 39.6; 44.1; 70.2; 78.6; 82.5; 83.6; 127.9; 128.5; 128.8; 132.9; 136.1; 140.1; 162.7. Anal. calc. for $C_{16}H_{17}NO_5S$: C 57.30, H 5.11, N 4.18; found: C 57.38, H 5.18, N 4.25.

*(1′*S*,2*S*,3*R*,4′*S*)-1-(Phenylmethyl)-3-(prop-2-enylsulfanyl)-4*H*-spiro[azetidine-2,2′-[7]oxabicyclo[2.2.1]-hept-5-en]-4-one* (**23**). To a soln. of prop-2-ene-1-thiol (0.024 ml, 0.30 mmol) in THF (0.5 ml) at 0°, NaH (60% in mineral oil; 12 mg, 0.30 mmol) and **22** (50 mg, 0.15 mmol) in THF (0.5 ml) were added. The mixture was stirred at 0° for 30 min, and then for 24 h at r.t. The reaction was quenched with H_2O, and the mixture was extracted with Et_2O. The org. layer was dried ($MgSO_4$) and concentrated under reduced pressure to give a crude residue, which was purified by FC (hexane/AcOEt 2:1): 27 mg (58%) of **23**. Pale yellow oil. IR ($CHCl_3$): 1665, 1650, 1235. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.50 (*d*, *J* = 12.4, 1 H); 1.80 (*dd*, *J* = 12.4, 4.6, 1 H); 3.15 (*dd*, *J* = 15.2, 5.8, 1 H); 3.35 (*dd*, *J* = 15.2, 5.8, 1 H); 3.80 (*s*, 1 H); 4.40 (*d*, *J* = 13.8, 2 H); 4.60 (*s*, 1 H); 4.95 (*d*, *J* = 4.4, 1 H); 5.10

(*d*, *J* = 9.2, 1 H); 5.15 (*d*, *J* = 17.2, 1 H); 5.80 (*m*, 1 H); 6.25 (*dd*, *J* = 5.8, 1.6, 1 H); 6.55 (*dd*, *J* = 5.8, 1.6, 1 H); 7.30 (*m*, 5 H). Anal. calc. for $C_{18}H_{19}NO_2S$: C 68.98, H 6.11, N 4.47; found: C 68.95, H 6.17, N 4.35.

*(1′*S**,2*R**,3*R**,4′*S**)-4-Oxo-1-(phenylmethyl)-4*H*-spiro[azetidine-2,2′-[7]oxabicyclo[2.2.1]hept-5-en]-3-yl Methanesulfonate* (**24**). To a soln. of **22** (50 mg, 0.15 mmol) in THF (0.5 ml), NaH (60% in mineral oil; 8 mg, 0.20 mmol) and prop-2-ene-1-amine (0.015 ml, 0.20 mmol) were added at 0°. The mixture was stirred at 0° for 30 min, and then for 24 h at r.t. The reaction was quenched with H_2O, and the mixture was extracted with Et_2O. The org. layer was dried ($MgSO_4$) and concentrated under reduced pressure to give a crude residue, which was purified by FC (hexane/AcOEt 2:1): 25 mg of **24** (50%). Pale yellow oil. IR ($CHCl_3$): 1740, 1660, 1230. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.76 (*d*, *J* = 12.4, 1 H); 1.92 (*dd*, *J* = 12.4, 4.6, 1 H); 3.20 (*s*, 3 H); 4.35 (*d*, *J* = 15.1, 2 H); 4.55 (*s*, 1 H); 4.65 (*d*, *J* = 4.6, 1 H); 5.15 (*s*, 1 H); 6.35 (*dd*, *J* = 5.8, 1.6, 1 H); 6.60 (*dd*, *J* = 5.8, 1.6, 1 H); 7.30 (*m*, 5 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 31.2; 39.5; 43.9; 70.4; 78.6; 81.3; 82.2; 128.2; 128.7; 128.9; 131.6; 136.2; 141.3; 162.2. Anal. calc. for $C_{16}H_{17}NO_5S$: C 57.30, H 5.11, N 4.18; found: C 57.32, H 5.17, N 4.22.

*(1′*S**,2*S**,3*S**,4′*S**)-1-(Phenylmethyl)-3-(prop-2-enylsulfanyl)-4*H*-spiro[azetidine-2,2′-[7]oxabicyclo[2.2.1]-hept-5-en]-4-one* (**25**). To a soln. of prop-2-ene-1-thiol (0.024 ml, 0.30 mmol) at 0°, NaH (60% mineral oil; 12 mg, 0.30 mmol) and **24** (50 mg, 0.15 mmol) in THF (0.5 ml) were added. The mixture was stirred at 0° for 30 min, and then for 24 h at r.t. The reaction was quenched with H_2O, and the mixture was extracted with Et_2O. The org. layer was dried ($MgSO_4$) and concentrated under reduced pressure to give a crude residue, which was purified by FC (hexane/AcOEt 2:1): 21 mg (45%) of **25**. Pale yellow oil. IR ($CHCl_3$): 1665, 1655, 1235. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.75 (*d*, *J* = 12.4, 1 H); 1.95 (*dd*, *J* = 12.4, 4.6, 1 H); 3.10 (*dd*, *J* = 15.2, 5.8, 1 H); 3.30 (*dd*, *J* = 15.2, 5.8, 1 H); 3.70 (*s*, 1 H); 4.30 (q, *J* = 13.8, 2 H); 4.50 (*s*, 1 H); 4.90 (*d*, *J* = 4.4, 1 H); 5.05 (*d*, *J* = 9.2, 1 H); 5.10 (*d*, *J* = 17.2, 1 H); 5.70 (*m*, 1 H); 6.25 (*dd*, *J* = 5.8, 1.6, 1 H); 6.45 (*dd*, *J* = 5.8, 1.6, 1 H); 7.30 (*m*, 5 H). Anal. calc. for $C_{18}H_{19}NO_2S$: C 68.98, H 6.11, N 4.47; found: C 68.95, H 6.17, N 4.35.

Metatheses of β-Lactams **7a**,**b**, **15**–**17**, **23** *and* **25** *with Ethene. General Procedure.* A soln. of the corresponding *β*-lactam (0.25 mmol) in CH_2Cl_2 (5.5 ml) was saturated with ethene and left under ethene pressure (1 atm). Either the classical *Grubb*'s Ru catalyst or **21** (see text; 0.025 mmol) dissolved in CH_2Cl_2 (1.5 ml) was added, and the mixture was stirred for 12 h at r.t. The solvent was removed under reduced pressure, and the residue was purified by FC (hexane/AcOEt 2:1) to afford **8a**,**b**, **18**–**20**, **26**, or **27**, resp.

*Data of (3*S**,4*R**,5*S**,7*S**)-5,7-Diethenyl-3-phenoxy-1-(prop-2-enyl)-6-oxa-1-azaspiro[3.4]octan-2-one* (**8a**). Yield: 85%. Pale yellow oil. IR ($CHCl_3$): 1710, 1600, 1240. ^{1}H-NMR (300 MHz, $CDCl_3$): 2.25 (*dd*, *J* = 13.6, 8.7, 1 H); 2.45 (*dd*, *J* = 13.6, 7.2, 1 H); 4.05 (*d*, *J* = 10.1, 2 H); 4.60 (*m*, 1 H); 4.70 (*d*, *J* = 6.5, 1 H); 5.10 (*s*, 1 H); 5.20–5.40 (*m*, 6 H); 5.90 (*m*, 2 H); 6.15 (*m*, 1 H); 7.00 (*m*, 3 H); 7.30 (*m*, 2 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 39.6; 43.1; 73.8; 78.6; 83.7; 86.5; 116.4; 117.3; 118.4; 119.1; 122.3; 129.5; 133.1; 134.5; 138.5; 157.9; 165.6. Anal. calc. for $C_{19}H_{21}NO_3$: C 73.29, H 6.80, N 4.50; found: C 73.25, H 6.86, N 4.55.

*Data of (3*S**,4*R**,5*S**,7*S**)-5,7-Diethenyl-3-(phenylmethoxy)-1-(prop-2-enyl)-6-oxa-1-azaspiro[3.4]octan-2-one* (**8b**). Yield: 85%. Pale yellow oil. IR ($CHCl_3$): 1705, 1600, 1230. ^{1}H-NMR (300 MHz, $CDCl_3$): 2.05 (*dd*, *J* = 13.6, 8.7, 1 H); 2.30 (*dd*, *J* = 13.6, 7.2, 1 H); 3.95 (*d*, *J* = 10.1, 2 H); 4.55 (*m*, 2 H); 4.60 (*s*, 1 H); 4.75 (*q*, *J* = 12.0, 2 H); 5.20–5.40 (*m*, 6 H); 5.90 (*m*, 2 H); 6.25 (*m*, 1 H); 7.35 (*m*, 5 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 39.4; 42.7; 73.3; 73.8; 78.6; 83.3; 87.5; 116.4; 117.8; 118.7; 128.1; 128.3; 128.8; 133.3; 134.8; 137.2; 138.7; 166.9. Anal. calc. for $C_{20}H_{23}NO_3$: C 73.82, H 7.12, N 4.30; found: C 73.85, H 7.16, N 4.35.

*(2a*S**,6a*S**,8*S**,9a*R**)-8-Ethenyl-4,6a,8,9-tetrahydro-1-(phenylmethyl)-1*H*-furo[3′,2′:3,4]oxepino[3,2-*b*]-azet-2(2a*H*)-one* (**18**). Yield: 98%. Pale yellow oil. IR ($CHCl_3$): 1735, 1600, 1230. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.95 (*dd*, *J* = 13.4, 7.1, 1 H); 2.20 (*dd*, *J* = 13.4, 9.4, 1 H); 4.05 (*d*, *J* = 18.0, 1 H); 4.30 (*d*, *J* = 14.8, 1 H); 4.35 (*m*, 1 H); 4.50 (*d*, *J* = 18.0, 1 H); 4.58 (*d*, *J* = 14.8, 1 H); 4.60 (*s*, 1 H); 4.80 (br. *s*, 1 H); 5.05 (*d*, *J* = 7.0, 1 H); 5.15 (*d*, *J* = 12.1, 1 H); 5.50 (*m*, 2 H); 5.78 (*m*, 1 H); 7.25 (*m*, 5 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 37.9; 44.3; 70.2; 78.1; 80.1; 80.3; 86.2; 116.1; 127.1; 127.7; 127.9; 128.6; 131.4; 136.5; 139.5; 164.2. Anal. calc. for $C_{18}H_{19}NO_3$: C 72.71, H 6.44, N 4.71; found: C 72.74, H 6.46, N 4.75.

*(3*S**,4*R**,5*S**,7*S**)-5,7-Diethenyl-2-oxo-1-(phenylmethyl)-6-oxa-1-azaspiro[3.4]oct-3-yl Prop-2-enoate* (**19**). Yield: 70%. Pale yellow oil. IR ($CHCl_3$): 1720, 1705, 1600, 1240. ^{1}H-NMR (300 MHz, $CDCl_3$): 2.18 (*dd*, *J* = 13.7, 7.3, 1 H); 2.29 (*dd*, *J* = 13.7, 8.8, 1 H); 4.33 (*m*, 2 H); 4.44 (*d*, *J* = 15.8, 1 H); 4.62 (*d*, *J* = 15.8, 1 H); 5.05 (*d*, *J* = 10.9, 1 H); 5.09 (*d*, *J* = 17.3, 1 H); 5.10 (*d*, *J* = 10.0, 1 H); 5.15 (*d*, *J* = 17.3, 1 H); 5.56–5.81 (*m*, 2 H); 5.84 (*s*, 1 H); 5.92 (*dd*, *J* = 10.5, 1.5, 1 H); 6.27 (*dd*, *J* = 16.8, 10.2, 1 H); 6.46 (*dd*, *J* = 16.8, 1.7, 1 H) 7.37 (*m*, 5 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 39.1; 44.0; 73.4; 78.5; 78.9; 83.1; 116.7; 118.3; 127.1; 128.1; 128.1; 128.9; 132.9; 133.1; 136.3; 138.3; 164.4; 164.7. Anal. calc. for $C_{20}H_{21}NO_4$: C 70.78, H 6.24, N 4.13; found: C 70.81, H 6.30, N 4.17.

*(3*S**,4*R**,5*S**,7*S**)-5,7-Diethenyl-2-oxo-1-(phenylmethyl)-6-oxa-1-azaspiro[3.4]oct-3-yl But-3-enoate* (**20**). Yield: 80%. Pale yellow oil. IR ($CHCl_3$): 1740, 1705, 1600, 1235. ^{1}H-NMR (300 MHz, $CDCl_3$): 2.16 (*dd*, *J* = 13.9,

7.5, 1 H); 2.26 (*dd*, *J* = 13.9, 8.5, 1 H); 3.03 (*ddt*, *J* = 17.3, 7.1, 1.5, 1 H); 3.16 (*ddt*, *J* = 17.3, 6.8, 1.5, 1 H); 4.31 (*m*, 2 H); 4.42 (*d*, *J* = 15.6, 1 H); 4.60 (*d*, *J* = 15.4, 1 H); 5.07–5.23 (*m*, 6 H); 5.60–5.98 (*m*, 3 H); 5.76 (*s*, 1 H); 7.36 (*m*, 5 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 38.5; 39.1; 44.0; 73.3; 78.4; 78.9; 83.0; 116.6; 118.1; 119.4; 128.1; 128.1; 128.9; 129.0; 133.4; 136.2; 138.3; 164.3; 170.2. Anal. calc. for $C_{21}H_{23}NO_4$: C 71.37, H 6.56, N 3.96; found: C 71.41, H 6.50, N 4.03.

*(3*R*,4*R*,5*S*,7*S*)-5,7-Diethenyl-1-(phenylmethyl)-3-(prop-2-enylsulfanyl)-6-oxa-1-azaspiro[3.4]octan-2-one* (**26**). Yield: 70%. Pale yellow oil. IR ($CHCl_3$): 1710, 1600, 1230. ^{1}H-NMR (300 MHz, $CDCl_3$): 2.02 (*dd*, *J* = 13.9, 7.5, 1 H); 2.25 (*dd*, *J* = 13.9, 8.5, 1 H); 3.15 (*dd*, *J* = 13.3, 7.1, 1 H); 3.36 (*dd*, *J* = 13.3, 7.1, 1 H); 4.10 (*s*, 1 H); 4.22 (*m*, 2 H); 4.50 (*s*, 2 H); 5.10–5.23 (*m*, 6 H); 5.65 (*m*, 1 H); 5.85 (*m*, 2 H); 7.35 (*m*, 5 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 35.5; 36.1; 44.0; 53.8; 55.1; 73.3; 79.9; 82.9; 117.6; 119.1; 119.8; 128.1; 128.3; 128.9; 129.0; 133.4; 136.2; 137.3; 164.5. Anal. calc. for $C_{20}H_{23}NO_2S$: C 70.35, H 6.79, N 4.10; found: C 70.41, H 6.84, N 4.05.

*(3*S*,4*R*,5*S*,7*S*)-5,7-Diethenyl-1-(phenylmethyl)-3-(prop-2-enylsulfanyl)-6-oxa-1-azaspiro[3.4]octan-2-one* (**27**). Yield: 50%. Pale yellow oil. IR ($CHCl_3$): 1710, 1660, 1610, 1230. ^{1}H-NMR ($CDCl_3$, 300 MHz): 1.98 (*dd*, *J* = 13.9, 7.5, 1 H); 2.22 (*dd*, *J* = 13.9, 8.5, 1 H); 3.17 (*dd*, *J* = 13.3, 7.1, 1 H); 3.31 (*dd*, *J* = 13.3, 7.1, 1 H); 4.12 (*s*, 1 H); 4.20 (*m*, 2 H); 4.42 (*s*, 2 H); 5.05–5.20 (*m*, 6 H); 5.60–5.90 (*m*, 3 H); 7.35 (*m*, 5 H). Anal. calc. for $C_{20}H_{23}NO_2S$: C 70.35, H 6.79, N 4.10; found: C 70.44, H 6.82, N 4.15.

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