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Synthesis of 1,3-bridged β-lactams embedded in a macrocyclic structure

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ABSTRACT

A new approach to N1–C3 bridged macrocyclic β-lactams has been developed. Orthogonal functional groups' protection combined with RCM has allowed the construction of the bicyclic systems bearing a β-lactam motif. These systems could represent a structural alternative to the actual lactamic antibiotics and may be further transformed into a broad variety of compounds.

1. Introduction

The ability of β-lactams to inhibit transpeptidases has focused the interest on these compounds as efficient antibacterial agents.[1] The worldwide use of penicillin and cephalosporin derivatives to treat bacterial infections has resulted in the development of bacteria resistance, which has triggered the search for novel structures bearing the 2-azetidinone ring (Fig. 1).[2]

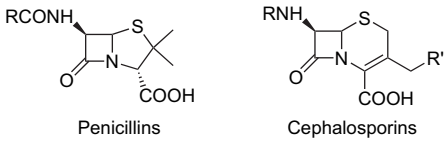

Figure 1.

Among the plethora of β-lactam derivatives having non-conventional structures,[3] N1–C3 bridgehead 2-azetidinones have been scarcely reported. Thus, short bridges between the N1–C3 atoms produced the denominated anti-Bredt 2-azetidinones.[4] In these anti-Bredt structures the amide group of the bicycle bridgehead lactam is highly twisted and this distortion from planarity affects dramatically their properties. There are only a few syntheses for this class of compounds mainly due to the intrinsic instability associated with the pyramidalization of the lactam nitrogen. As far as we are aware, macrocyclic N1–C3 bridgehead 2-azetidinones have not yet been described.

During our current work devoted to prepare macrocyclic-β-lactams[5] and metal-containing 2-azetidinone nuclei,[6] we became aware of the possibility of accessing to new macrocyclic 2-azetidinones, tethering the N1–C3 atoms of the four-membered ring, by means of ring-closing metathesis (RCM) reactions[7] on intermediates I (Fig. 2). This strategy should allow the efficient formation of macrocyclic structures based on β-lactams scaffolds, enroute to the development of new peptidic or pseudopeptidic compounds.[8,9] Reported herein is the successful development of a methodology for the synthesis of N1–C3 bridged β-lactam scaffolds based in the sequential introduction of olefin tethers in an adequate 2-azetidinone II, to form the versatile intermediates I.

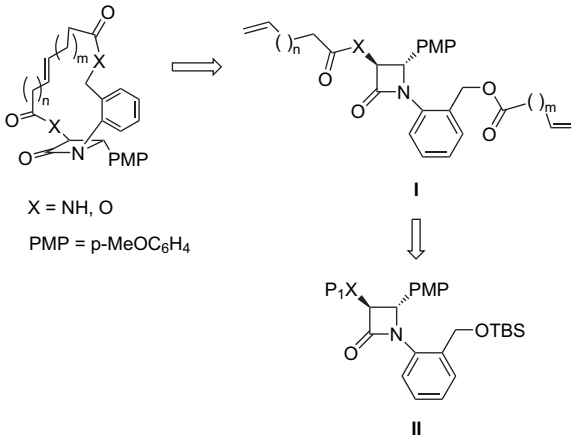

Figure 2.

2. Results and discussion

In the strategy developed for the synthesis of N1–C3 bridged β-lactam macrocyclic structures based on RCM (Fig. 2), we first synthesized a suitable β-lactam scaffold as building block. Azetidinone **4a** incorporating two different orthogonally protected

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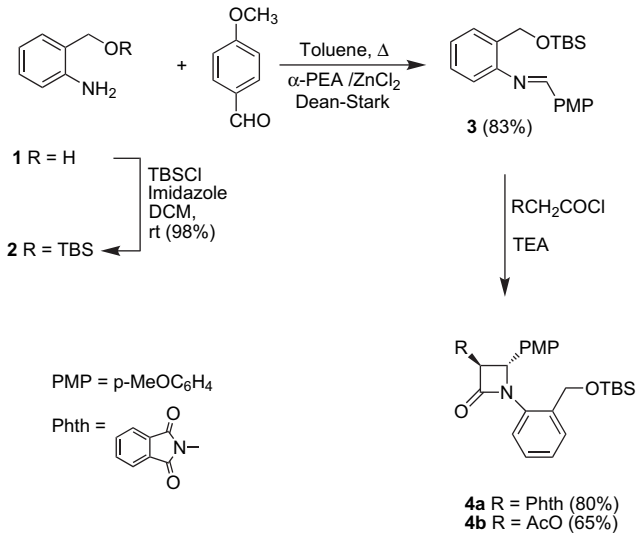
functionalities was chosen as the starting material. The functional groups in **4a** will be used as linkers to the carbon chain bearing the olefin functionality. A phenyl group in N1 was used as a restraint element in order to facilitate the RCM reactions. The synthesis of compound **4a** is shown in Scheme 1. *o*-Hydroxymethyl aniline **1** was reacted with TBSCl under standard conditions and then transformed into the corresponding imine **3** by reaction with *p*-anisaldehyde in boiling toluene, in the presence of catalytic α-phenylethanamine·$ZnCl_2$ complex. β-Lactam **4a** was synthesized as the trans isomer (80% yield) by Staudinger reaction with phthalimidylacetylchloride.[10]



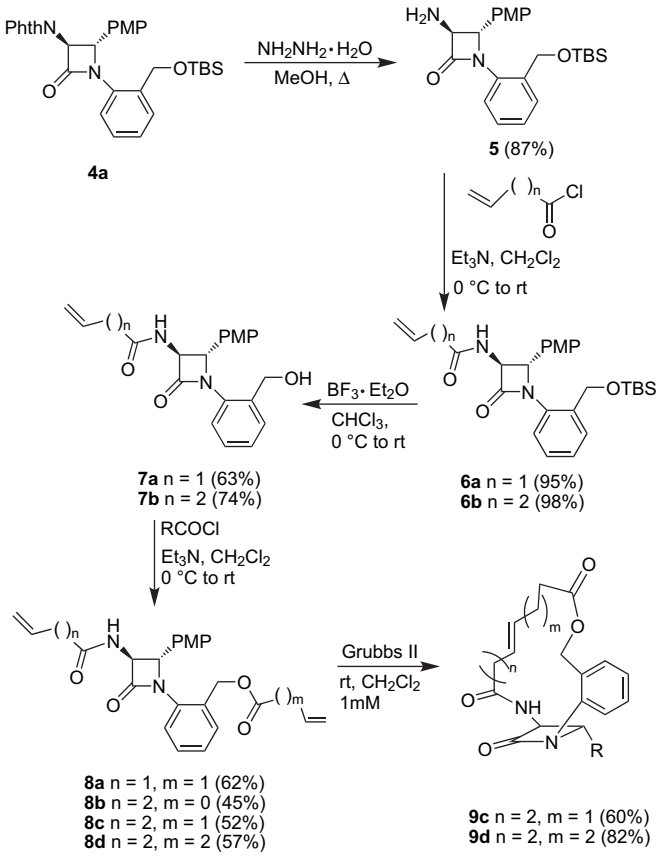
Scheme 1.

Removal of the phthalimidyl group with hydrazine gave the free amine **5** that allowed tethering the first olefinic motif by reaction with the corresponding acid chlorides yielding compounds **6** (95%, 98% yields) (Scheme 2). Removal of the silyl protecting group with NBu_4F was not effective. However, $BF_3·Et_2O$ yielded free alcohol derivatives **7** in good yield. These compounds were further transformed by reaction with acryloyl chloride, 3-butenoyl chloride, and 4-pentenoyl chloride, to give β-lactams **8** having two olefin-containing appendages.

RCM first assays were performed on compound **8d**. Treatment of 2-azetidinone **8d** with first generation Grubbs' catalyst (Grubbs 1)[11] produced no ring closure under the different conditions tested. In contrast, when this compound was heated (40 °C) in Cl_2CH_2 (1 mM) solution for 3 days in the presence of second generation Grubbs' catalyst (Grubbs 2),[12] macrocyclic compound **9d** was isolated in 82% yield. Analogously, compound **8c** formed bicyclic β-lactam **9c**, although in lower yield (60%). Compounds **8a**,**b** were inefficient in producing the cyclic products.

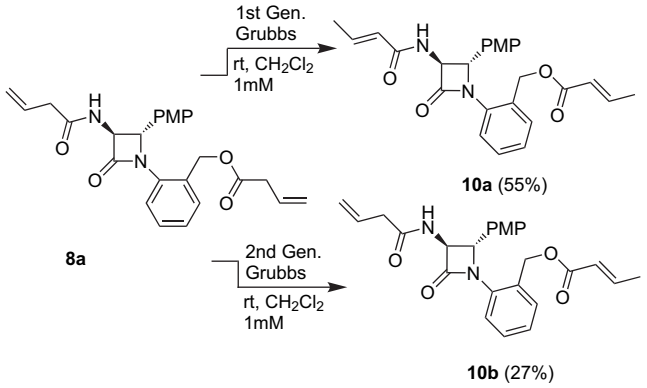
Therefore, the behavior of compounds **8** toward ring closure, strongly depends on the length of the carbon chain bearing the olefin fragment. Thus, β-lactam **8a** only led to open-chain derivatives **10** by isomerization of the C=C bonds of the starting material, either with Grubbs 1 or with Grubbs 2 catalysts (Scheme 3). Compound **8b** instead was unreactive with both catalysts, even after prolonged reaction times and different conditions tested.

RCM reactions were tested next on β-lactams **11** (Scheme 4), obtained from the orthogonally protected 2-azetidinone **4b** (Scheme 1). The synthetic sequence was similar to that employed for compounds **8**. Reaction of **3** with acetoxyacetylchloride in the presence of Et_3N (TEA) yielded *trans*-β-lactam **4b** in 65% yield. (Scheme 1). Treatment of **4b** with KOH in THF at 0 °C, efficiently removed the acetyl group without affecting the sensitive



Scheme 2.

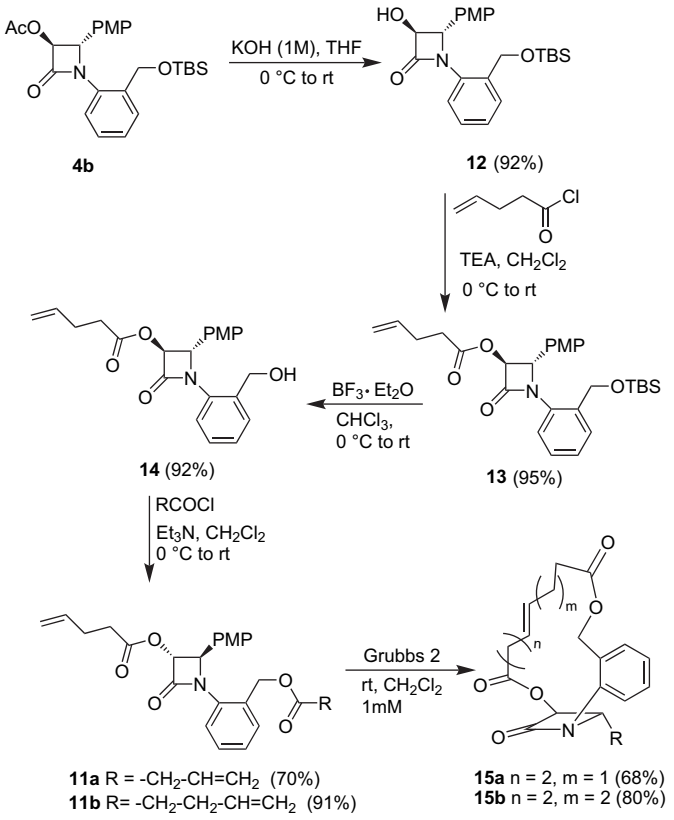
2-azetidinone ring, affording 3-hydroxy-2-azetidinone **12** in 92% yield (Scheme 4). The free hydroxyl group on C3 was used to introduce the first of the two alkene-functionalized tethers, which are necessary to effect the closure. To this end, compound **12** was reacted with 4-pentenoyl chloride to yield β-lactam **13**. Then, the benzylic position was unmasked with $BF_3·Et_2O$ and the resulting alcohol **14** reacted with the corresponding acid chlorides to form the metathesis precursors **11a**,**b**. (Scheme 4).



Scheme 3.

Again, Grubbs 1 produced no ring closure under the different conditions tested in any of the 2-azetidinones **11**. In contrast, reactions worked well with both compounds in the presence of Grubbs 2. Thus, macrocycle **15b** was isolated in 80% yield and compound **15a** in 68% yield, respectively (Scheme 4).

The structure of all macrocyclic β-lactams **9** and **15** was unequivocally established by spectroscopical and analytical methods.



Scheme 4.

2D-NMR experiments were used to unambiguously elucidate the bicyclic structures. Significantly, coupling constants (J=15.5–14.9 Hz) of the olefin hydrogens in all macrocycles denote a trans-configuration.

3. Conclusions

A new kind of N1–C3 bridged macrocyclic β-lactams has been obtained. Our approach is an easy entry to bicyclic structures bearing a β-lactam motif, which may be further transformed into a variety of compounds. Application of this approach to scaffolds incorporating peptidic moieties is now in progress in our laboratories.

4. Experimental section

4.1. General

NMR experiments were performed at 22 °C on Bruker Avance 300 (300.1 and 75.4 MHz), Bruker 200-AC (200.1 and 50 MHz), Bruker Avance AV-500 (500.1330 and 125.7722 MHz), or Bruker Avance AVIII-700 (1H: 700.1733 MHz) spectrometers. Chemical shifts are given in parts per million relative to TMS (1H, 0.0 ppm) or the specified solvent. IR spectra were taken on a Perkin–Elmer 781 or Bruker Tensor 27 spectrometer. Anhydrous solvents were obtained by distillation over the adequate drying agents. Flame-dried glassware and standard Schlenk techniques were used for moisture sensitive reactions. Merck silicagel (230–400 mesh) was used as the stationary phase for purification of crude reaction mixtures by flash column chromatography. Identification of products was made by TLC (kiesegel 60F_{254}). UV light (λ=254 nm) and 5% phosphomolybdic acid solution in 95% EtOH were used to develop the plates.

All commercially available compounds were used without further purification. The following reactants were prepared according to the literature procedures: 2-(*tert*-butyldimethyl silyloxymethyl)-aniline **2**,[13] phthalimidylacetylchloride.[14]

4.1.1. 2-((tert-Butyldimethylsilyloxy)methyl)-N-(4-methoxybenzylidene)aniline **3**

A solution of **2** (4.91 g, 21.0 mmol) in 142 mL of anhyd toluene was treated with a catalytic amount of α-phenylethanamine·$ZnCl_2$ and a solution of *p*-anisaldehyde (2.82 g, 21.0 mmol) in 22 mL of anhyd toluene. After refluxing for 48 h the crude was filtered and evaporated. Pure imine was obtained by distillation in a Büchi B-580 glass oven as thick yellow oil (6.20 g, 83%). IR (CCl_4): ν_{max}=3005, 2954, 2929, 1626, 1257, 762 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6): δ=8.42 (s, 1H), 7.88 (d, J=8.8 Hz, 2H), 7.48–7.43 (m, 1H), 7.33–7.17 (m, 2H), 7.09–7.00 (m, 3H), 4.81 (s, 2H), 3.83 (s, 3H), 0.87 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (50 MHz, DMSO-d_6): δ=161.9, 159.4, 148.9, 134.3, 130.4, 129.0, 127.8, 126.6, 125.2, 117.5, 114.2, 60.6, 55.4, 25.8, 18.0, −5.4. Anal. Calcd for $C_{21}H_{29}NO_2Si$: C, 70.94; H, 8.22; N, 3.94. Found: C, 70.72; H, 8.03; N, 4.08.

4.1.2. trans-1-(2-((tert-Butyldimethylsilyloxy)methyl)-phenyl)-4-(4-methoxyphenyl)-3-(N-phthalimidyl)azetidin-2-one **4a**

To a refluxing solution of imine **3** (0.36 g, 1.0 mmol) in 15 mL of anhyd toluene, Et_3N (0.28 mL, 2.0 mmol) was added. Then phthalimidylacetylchloride (0.27 g, 1.2 mmol) in 6 mL of anhyd toluene was added slowly dropwise. The mixture was refluxed overnight. After cooling, the solution was washed with satd $NaHCO_3$ (2×20 mL) and water. The aqueous phase was extracted with AcOEt (3×20 mL) and the combined organics dried over $MgSO_4$ and evaporated. Crude **4a** (0.43 g, 80%) was obtained as yellow oil. The product was used without further purification. IR (KBr): ν_{max}=1762, 1749, 1514, 764 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.93–7.87 (m, 2H), 7.81–7.72 (m, 3H), 7.62–7.59 (m, 1H), 7.30–7.26 (m, 2H), 7.24–7.13 (m, 2H), 6.86 (d, J=8.6 Hz, 2H), 5.54 (d, J=2.7 Hz, 1H), 5.38 (d, J=2.7 Hz, 1H), 5.10 (AB_{syst}, J_{AB}=14.4 Hz, 1H), 4.92 (AB_{syst}, J_{AB}=14.4 Hz, 1H), 3.78 (s, 3H), 0.98 (s, 9H), 0.17 (s, 3H), 0.14 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=166.9, 162.8, 160.2, 136.4, 134.5, 131.9, 131.7, 128.0, 127.5, 127.4, 127.3, 127.0, 123.7, 122.3, 114.5, 62.0, 61.7, 61.1, 55.2, 26.0, 18.4, −5.2, −5.3.

4.1.3. trans-3-Acetoxy-1-(2-((tert-butyldimethylsilyloxy)-methyl)phenyl)-4-(4-methoxyphenyl)azetidin-2-one **4b**

To a solution of acetoxyacetylchloride (2.00 g, 14.6 mmol) in 40 mL of anhyd CH_2Cl_2 cooled to −78 °C and under Ar, Et_3N (3.4 mL, 24.4 mmol) was added. The mixture was stirred for 30 min and imine **3** (4.73 g, 12.2 mmol) in CH_2Cl_2 (40 mL) was added by dropwise. The reaction was kept at 0 °C for 30 min and then was allowed to reach rt overnight. The crude was washed with satd $NaHCO_3$ (2×20 mL) and dried over $MgSO_4$. After evaporation of the solvent, crude **4b** (3.61 g, 65%, yellow oil) was obtained. The product was used without further purification. Analytical samples were obtained by chromatography (SiO_2, Hex/AcOEt 5:1) to fully characterize **4b**. IR (KBr): ν_{max}=1768, 1612, 1251, 1178, 1087, 836, 754 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.48–7.42 (m, 1H), 7.26–7.18 (m, 5H), 6.83 (d, J=8.8 Hz, 2H), 5.48 (d, J=1.9 Hz, 1H), 5.13 (d, J=1.9 Hz, 1H), 4.86 (AB_{syst}, J_{AB}=13.9 Hz, 1H), 4.81 (AB_{syst}, J_{AB}=13.9 Hz, 1H), 3.75 (s, 3H), 2.19 (s, 3H), 0.95 (s, 9H), 0.11 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=169.6, 162.3, 160.0, 134.7, 132.2, 128.3, 127.9, 127.6, 127.4, 126.6, 122.0, 114.4, 81.2, 64.2, 62.8, 55.2, 25.9, 20.5, 18.4, −5.2, −5.3. Anal. Calcd for $C_{25}H_{33}NO_5Si$: C, 65.90; H, 7.30; N, 3.07. Found: C, 66.14; H, 7.18; N, 3.24.

4.1.4. trans-3-Amino-1-(2-((tert-butyldimethylsilyloxy)-methyl)phenyl)-4-(4-methoxyphenyl)azetidin-2-one **5**[15]

A mixture of **4a** (0.50 g, 0.9 mmol), 5 mL of methanol and 0.08 mL (1.6 mmol) of hydrazine hydrate was refluxed for 1 h. After

cooling to rt, the mixture was filtered to eliminate 2,3-dihydrophthalazine-1,4-dione formed. To the filtrate was added 25 mL of H_2O and the mixture was extracted with AcOEt (3×10 mL). The organic phase was dried over $MgSO_4$ and the solvent evaporated. Pure **5** was obtained after chromatography (SiO_2, Hex/AcOEt 3:1) as a yellow solid (0.32 g, 87%). Mp: 112–114 °C. IR (KBr): ν_{max}=3392, 1735, 1749, 1514, 777 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ=7.53–7.47 (m, 1H), 7.24 (d, J=8.7 Hz, 2H), 7.20–7.13 (m, 2H), 7.11–7.05 (m, 1H), 6.84 (d, J=8.7 Hz, 2H), 4.95 (AB_{syst}, J_{AB}=13.9 Hz, 1H), 4.83 (AB_{syst}, J_{AB}=13.9 Hz, 1H), 4.83 (d, J=2.4 Hz, 1H), 4.09 (d, J=2.4 Hz, 1H), 3.77 (s, 3H), 0.96 (s, 9H), 0.12 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=168.5, 159.7, 134.8, 132.4, 128.9, 127.9, 127.5, 127.4, 126.2, 121.4, 114.3, 68.3, 67.0, 62.6, 55.2, 26.0, 18.4, −5.2. Anal. Calcd for $C_{23}H_{32}N_2O_3Si$: C, 66.95; H, 7.82; N, 6.79. Found: C, 66.77; H, 8.09; N, 6.82.

4.1.5. *trans-1-(2-((tert-Butyldimethylsilyloxy)methyl)-phenyl)-3-hydroxy-4-(4-methoxyphenyl)azetidin-2-one* ***12***[16]

To a 0 °C solution of lactam **4b** (0.58 g, 1.3 mmol) in 16 mL of THF was added 2.5 mL of 1 M KOH. The reaction was stirred for 45 min and then washed with water, extracted with AcOEt (3×20 mL), dried ($MgSO_4$), and the solvent evaporated. Purification by chromatography (SiO_2, Hex/AcOEt 3:1) yielded 0.48 g (92%) of pure **12** as a yellow oil. IR (KBr): ν_{max}=3392, 1749, 1735, 1514, 777 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=7.53–7.50 (m, 1H), 7.22–7.10 (m, 4H), 7.04–7.01 (m, 1H), 6.82 (d, J=8.8 Hz, 2H), 5.03 (d, J=1.8 Hz, 1H), 4.93 (AB_{syst}, J_{AB}=14.1 Hz, 1H), 4.81 (AB_{syst}, J_{AB}=14.1 Hz, 1H), 4.75–4.72 (m, 1H), 4.56 (d, J=5.6 Hz, 1H), 3.76 (s, 3H), 0.96 (s, 9H), 0.12 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=167.8, 159.8, 135.0, 131.8, 127.9, 127.8, 127.7, 127.4, 126.6, 121.5, 114.3, 82.1, 66.1, 62.4, 55.2, 26.0, 18.4, −5.2, −5.3. Anal. Calcd for $C_{23}H_{31}NO_4Si$: C, 66.79; H, 7.56; N, 3.39. Found: C, 66.84; H, 7.77; N, 3.54.

4.2. General procedures for the synthesis of esters or amides

4.2.1. *Method A*

To a solution of the corresponding 3-hydroxy or 3-amino-β-lactam (**12** and **5**, respectively) (1.0 mmol) in 15 mL of anhyd CH_2Cl_2, Et_3N (1.2 mmol) was added. The mixture was cooled to 0 °C and 1.2 mmol of the corresponding acid chloride was added dropwise. The reaction was stirred for 30 min at rt, washed with satd $NaHCO_3$, and extracted with AcOEt (3×20 mL). The organic phase was washed with H_2O (2×10 mL) and brine (2×10 mL), dried ($MgSO_4$), and the solvent evaporated. Purification by chromatography (SiO_2, Hex/AcOEt mixtures) yielded pure esters or amides.

4.2.2. *Method B*[17]

Butenoic acid (1.5 mmol) was dissolved in 10 mL of anhyd CH_2Cl_2. To this solution, 1.0 mmol of the corresponding β-lactam in 10 mL of CH_2Cl_2 and 1.2 mmol of 4-dimethylaminopyridine were added. The mixture was cooled to 0 °C and 1.5 mmol of DCC was added in five portions. Stirring was maintained for 1 h at 0 °C and 4 h at rt. The crude was filtered and the filtrate washed (2×2 mL of 0.5 N HCl and 2×2 mL of satd $NaHCO_3$). Further urea was eliminated by filtration, the two phases were separated and the aqueous phase was extracted with CH_2Cl_2. Combination of the organic phases was dried ($MgSO_4$) and the solvent evaporated. Purification was achieved by chromatography on silicagel.

4.2.3. *trans-1-(2-((tert-Butyldimethylsilyloxy)methyl)-phenyl)-4-(4-methoxyphenyl)-3-(but-3-enamido)azetidin-2-one* ***6a***

Following Method B (Section 4.2.2), a solution of β-lactam **5** (0.96 g, 2.3 mmol) in 37 mL of anhyd CH_2Cl_2 was treated with 0.3 mL (3.48 mmol) of 3-butenoic acid in 37 mL of anhyd CH_2Cl_2, DMAP (0.34 g, 2.78 mmol), and DCC (1.18 g, 5.7 mmol) for 2 h. Purification by chromatography (SiO_2, Hex/AcOEt 3:1) yielded pure **6a** (1.08 g, 95%) as yellow oil. IR (film): ν_{max}=3309, 3012, 2956, 2929, 1747, 1652, 1515, 1250, 750 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=7.53–7.49 (dd, J=7.3 Hz, 1.0, 1H), 7.23–7.02 (m, 6H), 6.80 (d, J=8.8 Hz, 2H), 5.90 (ddt, J=17.6, 9.6, 7.1 Hz, 1H), 5.21–5.14 (m, 3H), 4.97 (AB_{syst}, J_{AB}=14.3 Hz, 1H), 4.80 (AB_{syst}, J_{AB}=14.3 Hz, 1H), 4.71 (dd, J=7.3, 2.3 Hz, 1H), 3.73 (s, 3H), 3.00 (dt, J=7.1, 1.2 Hz, 2H), 0.95 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=171.0, 165.0, 159.6, 135.1, 132.0, 130.6, 128.0, 127.6, 127.5, 127.2, 126.4, 121.5, 119.4, 114.1, 64.0, 63.4, 62.1, 55.0, 40.7, 25.8, 18.2, −5.40, −5.42. Anal. Calcd for $C_{27}H_{36}N_2O_4Si$: C, 67.47; H, 7.55; N, 5.83. Found: C, 67.42; H, 7.44; N, 6.04.

4.2.4. *trans-1-(2-((tert-Butyldimethylsilyloxy)methyl)-phenyl)-4-(4-methoxyphenyl)-3-(pent-4-enamido)azetidin-2-one* ***6b***

Following Method A (Section 4.2.1), a 0 °C solution of **5** (0.41 g, 1.0 mmol) in 15 mL of anhyd CH_2Cl_2 was treated with Et_3N (0.17 mL, 1.2 mmol) and 4-pentenoyl chloride (0.13 mL, 1.2 mmol). Purification by chromatography (SiO_2, Hex/AcOEt 4:1) yielded pure **6b** (0.49 g, 98%) as orange oil. IR (film): ν_{max}=3315, 3009, 2958, 2934, 1748, 1662, 1516, 1251, 751 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=7.53–7.50 (m, 1H), 7.27 (d, J=8.6 Hz, 2H), 7.22–7.10 (m, 3H), 6.84 (d, J=8.6 Hz, 2H), 6.30 (d, J=6.5 Hz, 1H), 5.91–5.78 (m, 1H), 5.18 (d, J=2.2 Hz, 1H), 5.13–5.03 (m, 2H), 4.97 (AB_{syst}, J_{AB}=14.2 Hz, 1H), 4.83 (AB_{syst}, J_{AB}=14.2 Hz, 1H), 4.67 (dd, J=6.5, 2.2 Hz, 1H), 3.76 (s, 3H), 2.47–2.33 (m, 4H), 0.96 (s, 9H), 0.12 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=172.7, 164.8, 159.8, 136.7, 135.1, 132.2, 128.2, 127.9, 127.7, 127.4, 126.6, 121.7, 115.8, 114.3, 64.4, 64.1, 62.4, 55.2, 35.2, 29.2, 26.0, 18.4, −5.2. Anal. Calcd for $C_{28}H_{38}N_2O_4Si$: C, 67.98; H, 7.74; N, 5.66. Found: C, 68.19; H, 7.60; N, 5.54.

4.2.5. *trans-1-(2-((tert-Butyldimethylsilyloxy)methyl)-phenyl)-4-(4-methoxyphenyl)-3-(pent-4-enoyloxy)azetidin-2-one* ***13***

Following Method A (Section 4.2.1), a 0 °C solution of **12** (0.50 g, 1.2 mmol) in 16 mL of anhyd CH_2Cl_2 was treated with Et_3N (0.21 mL, 1.5 mmol) and 4-pentenoyl chloride (0.17 mL, 1.5 mmol). Purification by chromatography (SiO_2, Hex/AcOEt 5:1) yielded pure **13** (0.57 g, 95%) as yellow oil. IR (film): ν_{max}=3310, 2955, 2929, 1770, 1641, 1612, 1515, 1252, 755 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=7.50–7.46 (m, 1H), 7.26–7.16 (m, 5H), 6.85 (d, J=8.8 Hz, 2H), 5.85 (ddt, J=17.2, 10.6, 6.4 Hz, 1H), 5.48 (d, J=1.9 Hz, 1H), 5.12 (d, J=1.9 Hz, 1H), 5.11 (dq, J=17.2, 1.5 Hz, 1H), 5.06 (dq, J=10.6, 1.5 Hz, 1H), 4.88 (ABX_{syst}, J=13.9, 0.6 Hz, 1H), 4.83 (ABX_{syst}, J=13.9, 0.6 Hz, 1H), 3.76 (s, 3H), 2.59 (dd, J=7.0, 1.9 Hz, 2H), 2.56 (d, J=7.0 Hz, 2H), 0.96 (s, 9H), 0.12 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=171.8, 162.3, 160.0, 136.1, 134.7, 132.1, 128.2, 127.8, 127.6, 127.3, 126.6, 121.9, 115.9, 114.4, 81.2, 64.3, 62.7, 55.2, 32.9, 28.6, 25.9, 18.4, −5.2, −5.3. Anal. Calcd for $C_{28}H_{37}NO_5Si$: C, 67.85; H, 7.52; N, 2.83. Found: C, 67.66; H, 7.31; N, 2.60.

4.2.6. *trans-1-(2-(Hydroxymethyl)phenyl)-4-(4-methoxyphenyl)-3-(but-3-enamido)azetidin-2-one* ***7a***

Following the procedure described by Kelly,[18] a solution of **6a** (0.95 g, 2.0 mmol) in 10 mL of anhyd $CHCl_3$ was treated with $BF_3\cdot Et_2O$ (0.84 g, 5.9 mmol) for 30 min. Evaporation of the solvent and purification by chromatography (SiO_2, Hex/AcOEt 1:1) yielded pure **7a** (0.46 g, 63%) as orange oil. IR (film): ν_{max}=3415, 3359, 3018, 1747, 1674, 1515, 1251, 758 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=7.40 (br d, J=7.3 Hz, 1H), 7.37–7.34 (m, 1H), 7.21–7.12 (m, 4H), 7.01–6.96 (m, 1H), 6.81 (d, J=8.8 Hz, 2H), 5.84 (ddt, J=16.6, 9.8, 7.0 Hz, 1H), 5.25 (d, J=2.4 Hz, 1H), 5.16–5.10 (m, 2H), 4.76 (AB_{syst}, J_{AB}=11.8 Hz, 1H), 4.59 (dd, J=7.3, 2.4 Hz, 1H), 4.57 (AB_{syst}, J_{AB}=11.8 Hz, 1H), 3.71 (s, 3H), 3.00 (d, J=7.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=171.7, 166.9, 159.8, 135.0, 133.0, 130.9, 130.4, 128.5, 127.9, 127.6, 126.9, 122.1, 119.5, 114.3, 64.0, 62.9, 61.9, 55.1, 40.5. Anal. Calcd for $C_{21}H_{22}N_2O_4$: C, 68.84; H, 6.05; N, 7.65. Found: C, 68.52; H, 5.81; N, 7.44.

*4.2.7. trans-1-(2-(Hydroxymethyl)phenyl)-4-(4-methoxy-phenyl)-3-(pent-4-enamido)azetidin-2-one **7b***

A solution of **6b** (1.82 g, 3.68 mmol) in 10 mL of anhyd $CHCl_3$ was treated with $BF_3\cdot Et_2O$ (1.57 g, 11.0 mmol) for 30 min. Evaporation of the solvent and purification by chromatography (SiO_2, Hex/AcOEt 1:1) yielded pure **7b** (1.03 g, 74%) as orange oil. IR (film): ν_{max}=3420, 3360, 3019, 1750, 1671, 1515, 1249, 755 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=7.43–7.37 (m, 1H), 7.23 (d, J=8.7 Hz, 2H), 7.19–7.15 (m, 1H), 7.01–6.94 (m, 2H), 6.84 (d, J=8.7 Hz, 2H), 5.80 (ddt, J=17.0, 10.3, 6.3 Hz, 1H), 5.24 (d, J=2.3 Hz, 1H), 5.06 (dd, J=17.0, 1.4 Hz, 1H), 5.01 (dd, J=10.3, 1.2 Hz, 1H), 4.79 (AB_{syst}, J_{AB}=12.6 Hz, 1H), 4.58 (AB_{syst}, J_{AB}=12.6 Hz, 1H), 4.57 (dd, J=7.3, 2.3 Hz, 1H), 3.75 (s, 3H), 2.39–2.28 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=173.3, 167.0, 159.9, 136.7, 135.1, 133.3, 131.2, 128.7, 127.9, 127.8, 127.0, 122.2, 115.6, 114.4, 64.1, 63.2, 62.1, 55.2, 35.0, 29.1. Anal. Calcd for $C_{22}H_{24}N_2O_4$: C, 69.46; H, 6.36; N, 7.36. Found: C, 69.70; H, 6.54; N, 7.18.

*4.2.8. trans-1-(2-(Hydroxymethyl)phenyl)-4-(4-methoxy-phenyl)-3-(pent-4-enoyloxy)azetidin-2-one **14***

A solution of **13** (0.10 g, 0.2 mmol) in 2 mL of anhyd $CHCl_3$ was treated with $BF_3\cdot Et_2O$ (0.09 g, 0.6 mmol) for 1 h. Evaporation of the solvent and purification by chromatography (SiO_2, Hex/AcOEt 3:1) yielded pure **14** (0.07 g, 92%) as orange oil. IR (film): ν_{max}=3297, 3053, 1743, 1685, 1515, 1253, 772 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=7.49–7.46 (m, 1H), 7.27–7.20 (m, 4H), 7.00–6.93 (m, 1H), 6.87 (d, J=8.8 Hz, 2H), 5.85 (ddt, J=17.0, 10.4, 6.4 Hz, 1H), 5.51 (d, J=1.9 Hz, 1H), 5.12 (d, J=1.9 Hz, 1H), 5.11 (dq, J=17.0, 1.5 Hz, 1H), 5.07 (dq, J=10.4, 1.5 Hz, 1H), 4.82 (AB_{syst}, J_{AB}=12.6 Hz, 1H), 4.62 (AB_{syst}, J_{AB}=12.6 Hz, 1H), 3.77 (s, 3H), 2.60 (dd, J=6.8, 1.5 Hz, 1H), 2.57 (dd, J=6.8, 0.6 Hz, 1H), 2.49–2.40 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=171.7, 164.2, 160.2, 136.1, 134.6, 131.7, 128.8, 128.3, 127.9, 127.2, 126.5, 121.1, 116.0, 114.5, 80.3, 63.8, 62.3, 55.3, 32.9, 28.6. Anal. Calcd for $C_{22}H_{23}NO_5$: C, 69.28; H, 6.08; N, 3.67. Found: C, 69.60; H, 6.31; N, 3.72.

*4.2.9. trans-3-(But-3-enamido)-1-(2-((but-3-enoyloxy)-methyl)phenyl)-4-(4-methoxyphenyl)azetidin-2-one **8a***

Following Method B (Section 4.2.2), a solution of β-lactam **7a** (0.41 g, 1.1 mmol) in 18 mL of anhyd CH_2Cl_2 was treated with 0.14 mL (1.7 mmol) of 3-butenoic acid in 18 mL of anhyd CH_2Cl_2, DMAP (0.16 g, 1.3 mmol), and DCC (0.38 g, 1.9 mmol) for 2 h. Purification by chromatography (SiO_2, Hex/AcOEt 3:1) yielded pure **8a** (0.30 g, 62%) as orange oil. IR (film): ν_{max}=3350, 3018, 1751, 1739, 1683, 1515, 1257, 754 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ=7.41–7.35 (m, 1H), 7.30–7.05 (m, 5H), 6.83 (d, J=8.8 Hz, 2H), 5.92 (ddt, J=16.2, 10.2, 7.0 Hz, 1H), 5.91 (ddt, J=16.9, 9.8, 7.0 Hz, 1H), 5.42 (d, J=13.2 Hz, 1H), 5.27 (d, J=13.2 Hz, 1H), 5.24–5.11 (m, 5H), 4.67 (d, J=2.2 Hz, 1H), 3.74 (s, 3H), 3.12 (dt, J=7.0, 1.3 Hz, 2H), 3.03 (dt, J=7.0, 1.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=171.3, 171.0, 165.4, 159.7, 133.6, 130.5, 129.9, 128.9, 128.1, 127.9, 127.8, 126.6, 122.3, 122.2, 119.5, 118.6, 114.2, 63.5, 63.3, 60.2, 55.1, 40.7, 38.9. Anal. Calcd for $C_{25}H_{26}N_2O_5$: C, 69.11; H, 6.03; N, 6.45. Found: C, 68.81; H, 5.88; N, 6.61.

*4.2.10. trans-4-(4-Methoxyphenyl)-3-(pent-4-enamido)-1-(2-((prop-2-enoyloxy)methyl)phenyl)azetidin-2-one **8b***

Following Method A (Section 4.2.1), a 0 °C solution of **7b** (0.12 g, 0.3 mmol) in 7 mL of anhyd CH_2Cl_2 was treated with Et_3N (0.05 mL, 0.4 mmol) and acryloyl chloride (0.03 mL, 0.4 mmol). Purification by chromatography (SiO_2, Hex/AcOEt 3:1) yielded pure **8b** (59.0 mg, 45%) as yellow oil. IR (film): ν_{max}=3300, 2962, 1751, 1733, 1683, 1533, 1261, 754 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=7.44–7.41 (m, 1H), 7.29 (d, J=8.8 Hz, 2H), 7.24–7.17 (m, 2H), 7.10–7.07 (m, 1H), 6.84 (d, J=8.8 Hz, 2H), 6.66 (br d, J=7.1 Hz, 1H), 6.45 (dd, J=17.3, 1.5 Hz, 1H), 6.17 (dd, J=17.3, 10.4 Hz, 1H), 5.87 (dd, J=10.4, 1.5 Hz, 1H), 5.83 (ddt, J=17.1, 10.4, 6.4 Hz, 1H), 5.50 (AB_{syst}, J_{AB}=13.1 Hz, 1H), 5.39 (AB_{syst}, J_{AB}=13.1 Hz, 1H), 5.16 (d, J=2.3 Hz, 1H), 5.09 (dq, J=17.1, 1.6 Hz, 1H), 5.03 (dq, J=10.4, 1.3 Hz, 1H), 4.70 (dd, J=7.1, 2.3 Hz, 1H), 3.76 (s, 3H), 2.45–2.31 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=172.7, 165.8, 165.2, 159.8, 136.7, 133.8, 131.3, 130.3, 130.1, 129.1, 128.1, 128.0, 127.9, 126.8, 122.4, 115.8, 114.3, 64.6, 64.0, 63.6, 55.2, 35.2, 29.2. Anal. Calcd for $C_{25}H_{26}N_2O_5$: C, 69.11; H, 6.03; N, 6.45. Found: C, 68.84; H, 5.99; N, 6.33.

*4.2.11. trans-1-(2-((But-3-enoyloxy)methyl)phenyl)-4-(4-methoxyphenyl)-3-(pent-4-enamido)azetidin-2-one **8c***

Following Method A (Section 4.2.1), a 0 °C solution of **7b** (0.11 g, 0.3 mmol) in 7 mL of anhyd CH_2Cl_2 was treated with Et_3N (0.05 mL, 0.4 mmol) and freshly prepared 3-butenoyl chloride[19] (0.04 mL, 0.4 mmol). Purification by chromatography (SiO_2, Hex/AcOEt 3:1) yielded pure **8c** (70.0 mg, 52%) as yellow oil. IR (film): ν_{max}=3353, 3010, 1755, 1739, 1670, 1516, 1252, 1176, 758 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=7.39–7.36 (m, 1H), 7.28 (d, J=8.7 Hz, 2H), 7.22–7.15 (m, 2H), 7.09–7.06 (m, 1H), 6.97 (br d, J=7.3 Hz, 1H), 6.84 (d, J=8.7 Hz, 2H), 5.93 (ddt, J=17.4, 9.6, 7.0 Hz, 1H), 5.80 (ddt, J=16.7, 10.5, 6.2 Hz, 1H), 5.43 (d, J=13.3 Hz, 1H), 5.27 (d, J=13.3 Hz, 1H), 5.18 (d, J=2.3 Hz, 1H), 5.17 (dq, J=10.5, 1.2 Hz, 1H), 5.16 (dq, J=16.7, 1.4 Hz, 1H), 5.06 (dq, J=17.4, 1.6 Hz, 1H), 5.00 (dq, 1H, J=9.6, 1.4 Hz, 1H), 4.68 (dd, J=7.3, 2.3 Hz, 1H), 3.74 (s, 3H), 3.13 (dt, J=6.9, 1.4 Hz, 2H), 2.38–2.28 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=172.8, 171.2, 165.4, 159.8, 136.7, 133.7, 130.1, 130.0, 129.9, 129.0, 128.0, 127.8, 126.7, 122.4, 118.8, 115.6, 114.3, 64.4, 63.8, 63.6, 55.2, 39.0, 35.0, 29.1. Anal. Calcd for $C_{26}H_{28}N_2O_5$: C, 69.63; H, 6.29; N, 6.25. Found: C, 69.37; H, 6.45; N, 6.07.

*4.2.12. trans-4-(4-Methoxyphenyl)-3-(pent-4-enamido)-1-(2-((pent-4-enoyl-oxy)methyl)phenyl)azetidin-2-one **8d***

Following Method A (Section 4.2.1), a 0 °C solution of **7b** (0.09 g, 0.2 mmol) in 5 mL of anhyd CH_2Cl_2 was treated with Et_3N (0.04 mL, 0.3 mmol) and 4-pentenoyl chloride (0.03 mL, 0.3 mmol). Purification by chromatography (SiO_2, Hex/AcOEt 2:1) yielded pure **8d** (53.0 mg, 57%) as yellow oil. IR (film): ν_{max}=3351, 3016, 1753, 1739, 1684, 1515, 1254, 755 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=7.43–7.39 (m, 1H), 7.31 (d, J=8.8 Hz, 2H), 7.25–7.18 (m, 2H), 7.11–7.08 (m, 1H), 6.86 (d, J=8.8 Hz, 2H), 6.40 (d, J=6.9 Hz, 1H), 5.92–5.75 (m, 2H), 5.44 (d, J=13.0 Hz, 1H), 5.29 (d, J=13.0 Hz, 1H), 5.16 (d, J=2.3 Hz, 1H), 5.15–4.98 (m, 4H), 4.71 (dd, J=6.9, 2.3 Hz, 1H), 3.77 (s, 3H), 2.50–2.35 (m, 8H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=172.8, 172.7, 165.4, 159.9, 136.7, 136.5, 133.8, 130.3, 130.2, 129.0, 128.0, 127.9, 126.8, 122.6, 115.7, 115.6, 114.3, 64.5, 64.1, 63.3, 55.2, 35.2, 33.5, 29.2, 28.7. Anal. Calcd for $C_{27}H_{30}N_2O_5$: C, 70.11; H, 6.54; N, 6.06. Found: C, 70.36; H, 6.71; N, 5.94.

*4.2.13. trans-1-(2-((But-3-enoyloxy)methyl)phenyl)-4-(4-methoxyphenyl)-3-(pent-4-enoyloxy)azetidin-2-one **11a***

Following Method A (Section 4.2.1), a 0 °C solution of **14** (0.14 g, 0.4 mmol) in 16 mL of anhyd CH_2Cl_2 was treated with Et_3N (0.08 mL, 0.6 mmol) and freshly prepared 3-butenoyl chloride[20] (from 0.06 g, 0.57 mmol of 3-butenoic acid). Purification by chromatography (SiO_2, Hex/AcOEt 4:1) yielded pure **11a** (0.12 g, 70%) as yellow oil. IR (film): ν_{max}=3080, 2923, 2853, 1769, 1747, 1642, 1516, 1251, 1156, 755 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=7.33–7.30 (m, 1H), 7.22–7.03 (m, 5H), 6.78 (d, J=8.8 Hz, 2H), 5.87 (ddt, J=17.7, 9.6, 6.9 Hz, 1H), 5.78 (ddt, J=17.0, 10.5, 6.5 Hz, 1H), 5.41 (d, J=1.8 Hz, 1H), 5.35 (AB_{syst}, J_{AB}=13.3 Hz, 1H), 5.19 (AB_{syst}, J_{AB}=13.3 Hz, 1H), 5.11 (dq, J=10.5, 1.4 Hz, 1H), 5.10 (dq, J=17.0, 1.5 Hz, 1H), 5.03 (dq, J=17.7, 1.6 Hz, 1H), 5.02 (d, J=1.8 Hz, 1H), 4.98 (dq, J=9.6, 1.4 Hz, 1H), 3.68 (s, 3H), 3.07 (dt, J=6.9, 1.4 Hz, 2H), 2.51 (dd, J=6.8, 1.6 Hz, 1H), 2.49 (d, J=7.0 Hz, 1H), 2.40–2.31 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=171.7, 170.9, 162.5, 160.1, 136.1, 133.4, 130.2, 129.9, 129.7, 129.0, 128.0, 126.9, 126.8, 122.2, 118.8, 116.0, 114.4, 81.1, 64.3, 63.8, 55.2,

39.0, 32.9, 28.6. Anal. Calcd for $C_{26}H_{27}NO_6$: C, 69.47; H, 6.05; N, 3.12. Found: C, 69.25; H, 6.04; N, 3.31.

4.2.14. *trans-1-(2-((Pent-4-enoyloxy)methyl)phenyl)-4-(4-methoxyphenyl)-3-(pent-4-enoyloxy)azetidin-2-one* ***11b***

Following Method A (Section 4.2.1), a 0 °C solution of **14** (20.0 mg, 0.04 mmol) in 2 mL of anhyd CH_2Cl_2 was treated with Et_3N (0.01 mL, 0.05 mmol) and 4-pentenoyl chloride (0.01 mL, 0.05 mmol). Purification by chromatography (SiO_2, Hex/AcOEt 4:1) yielded pure **11b** (16 mg, 91%) as yellow oil. IR (film): ν_{max}=3077, 2922, 2851, 1770, 1747, 1641, 1515, 1251, 1156, 755 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=7.42–7.37 (m, 1H), 7.31–7.26 (m, 3H), 7.25–7.13 (m, 2H), 6.86 (d, J=8.8 Hz, 2H), 5.85 (ddt, J=16.9, 10.2, 6.5 Hz, 1H), 5.83 (ddt, J=17.2, 10.3, 6.2 Hz, 1H), 5.49 (d, J=1.9 Hz, 1H), 5.41 (AB_{syst}, J_{AB}=13.2 Hz, 1H), 5.26 (AB_{syst}, J_{AB}=13.2 Hz, 1H), 5.11 (dq, J=16.9, 1.5 Hz, 1H), 5.10 (d, J=1.9 Hz, 1H), 5.07 (dq, J=10.2, 1.5 Hz, 1H), 5.06 (dq, J=17.2, 0.8 Hz, 1H), 5.01 (dq, J=10.3, 1.2 Hz, 1H), 3.77 (s, 3H), 2.69–2.56 (m, 2H), 2.50–2.35 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=172.5, 171.7, 162.6, 160.1, 136.4, 136.1, 133.4, 130.3, 129.9, 128.9, 128.0, 126.9, 126.8, 122.2, 116.0, 115.6, 114.4, 81.2, 64.4, 63.5, 55.2, 33.5, 33.0, 28.8, 28.6. Anal. Calcd for $C_{27}H_{29}NO_6$: C, 69.96; H, 6.31; N, 3.02. Found: C, 70.22; H, 6.52; N, 2.89.

4.3. General procedure for the ring-closing metathesis of dienes

A solution of the corresponding diene in anhyd CH_2Cl_2 was added in a 2 h period, via syringe pump, to a degassed, refluxing CH_2Cl_2 solution of the corresponding catalyst. The reaction was continued until total disappearance of the starting diene by TLC. The crude was filtered through a short pad of SiO_2 to eliminate phosphines and pure metathesis product was then obtained by chromatography.

4.3.1. *Bicycle* ***9c***

Following the general procedure, from 60.0 mg (0.1 mmol) of β-lactam **8c** and 10 mol % of Grubbs 2 catalyst in 125 mL of anhyd CH_2Cl_2 and after 5 days at 40 °C, 25.0 mg (60%) of pure **9c** was obtained as a white solid after chromatography (SiO_2, Hex/AcOEt 3:1). Mp: 182–184 °C. IR (film): ν_{max}=3314, 2925, 2854, 1754, 1734, 1658, 1613, 1514, 1250, 977, 756 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=7.94–7.91 (m, 1H), 7.42–7.31 (m, 3H), 7.24–7.13 (m, 2H), 6.87 (d, J=8.6 Hz, 2H), 6.67 (br d, J=3.8 Hz, 1H), 5.71 ($ABX2_{syst}$, $J_{AB=}$15.3 Hz, J=6.3 Hz, 1H), 5.64 ($ABXM_{syst}$, $J_{AB=}$15.3 Hz, J=7.4, 4.3 Hz, 1H), 4.95 (AB_{syst}, J_{AB}=12.7 Hz, 1H), 4.87 (d, J=1.4 Hz, 1H), 4.85 (AB_{syst}, J_{AB}=12.7 Hz, 1H), 4.56 (dd, J=3.8, 1.4 Hz, 1H), 3.77 (s, 3H), 3.10 (d, J=6.4 Hz, 2H), 2.64–2.51 (m, 1H), 2.46–2.30 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=172.5, 170.9, 164.1, 159.9, 135.5, 132.7, 132.6, 130.1, 128.9, 127.5, 126.0, 125.3, 124.3, 124.0, 114.4, 66.6, 66.2, 65.5, 55.2, 39.1, 35.2, 29.3. Anal. Calcd for $C_{24}H_{24}N_2O_5$: C, 68.56; H, 5.75; N, 6.66. Found: C, 68.68; H, 5.88; N, 6.43.

4.3.2. *Bicycle* ***9d***

Following the general procedure, from 10.0 mg (0.02 mmol) of β-lactam **8d** and 10 mol % of Grubbs 2 catalyst in 20 mL of anhyd CH_2Cl_2 and after 5 days at rt, 7.0 mg (82%) of pure **9d** was obtained as a pale yellow oil after chromatography (SiO_2, Hex/AcOEt 2:1). IR (film): ν_{max}=3316, 2926, 2852, 1756, 1736, 1652, 1612, 1514, 1250, 972, 755 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=7.33–7.24 (m, 6H), 6.89 (d, J=8.7 Hz, 2H), 6.65 (br d, J=7.4 Hz, 1H), 5.69 (ABX_{syst}, J_{AB}=15.5 Hz, J=4.9 Hz, 1H), 5.63 (ABX_{syst}, $J_{AB=}$15.5 Hz, J=5.0 Hz, 1H), 5.47 (d, J=12.0 Hz, 1H), 5.14 (dd, J=7.4, 2.0 Hz, 1H), 4.84 (d, J=12.0 Hz, 1H), 4.69 (d, J=2.0 Hz, 1H), 3.79 (s, 3H), 2.55–2.26 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=173.5, 172.7, 165.9, 160.0, 134.5, 132.4, 131.6, 131.4, 131.2, 130.2, 128.4, 128.1, 128.0, 127.9, 114.4, 67.8, 64.9, 63.9, 55.3, 35.7, 33.2, 28.7, 27.3. Anal. Calcd for $C_{25}H_{26}N_2O_5$: C, 69.11; H, 6.03; N, 6.45. Found: C, 69.32; H, 6.18; N, 6.52.

4.3.3. *Bicycle* ***15a***

Following the general procedure, from 60.0 mg (0.1 mmol) of β-lactam **11a** and 10 mol % of Grubbs 2 catalyst in 141 mL of anhyd CH_2Cl_2 and after 3 days at 40 °C, 41.0 mg (68%) of pure **15a** was obtained as a white solid after chromatography (SiO_2, Hex/AcOEt 2:1). Mp: 185–186 °C (dec). IR (film): ν_{max}=2924, 2853, 1765, 1740, 1612, 1584, 1514, 1252, 976, 757 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ=8.16–8.14 (m, 1H), 7.46–7.43 (m, 1H), 7.24 (d, J=8.8 Hz, 2H), 7.20–7.14 (m, 2H), 6.86 (d, J=8.8 Hz, 2H), 5.77 ($ABX2_{syst}$, $J_{AB=}$14.9 Hz, J=7.4 Hz, 1H), 5.70 ($ABX2_{syst}$, J_{AB}=14.9 Hz, J=7.0 Hz, 1H), 5.10 (d, J=1.1 Hz, 1H), 4.84 (d, J=1.1 Hz, 1H), 4.82 (s, 2H), 3.77 (s, 3H), 3.16 (ABX_{syst}, J_{AB}=14.3 Hz, J=6.6 Hz, 1H), 3.09 (ABX_{syst}, $J_{AB=}$14.3 Hz, J=7.7 Hz, 1H), 2.71–2.66 (m, 1H), 2.63–2.56 (m, 1H), 2.51–2.40 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=171.8, 170.8, 162.3, 160.1, 135.3, 132.6, 132.5, 130.2, 127.9, 127.5, 125.8, 124.5, 124.1, 124.0, 114.6, 84.2, 65.9, 65.6, 55.3, 39.4, 33.3, 28.7. Anal. Calcd for $C_{24}H_{23}NO_6$: C, 68.40; H, 5.50; N, 3.32. Found: C, 68.09; H, 5.31; N; 3.17.

4.3.4. *Bicycle* ***15b***

Following the general procedure, from 10.0 mg (0.03 mmol) of β-lactam **11b** and 10 mol % of Grubbs 2 catalyst in 26 mL of anhyd CH_2Cl_2 and after 3 days at 40 °C, 8.0 mg (80%) of pure **15b** was obtained as a white solid after chromatography (SiO_2, Hex/AcOEt 2:1). Mp: 176–177 °C (dec). Yield 2.0 mg (20%) of starting **8b** was also recovered. IR (film): ν_{max}=3015, 2922, 2839, 1766, 1740, 1612, 1584, 1515, 1250, 969, 754 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ=7.64–7.63 (m, 1H), 7.30–7.27 (m, 1H), 7.19 (d, J=8.7 Hz, 2H), 7.15–7.09 (m, 2H), 6.80 (d, J=8.7 Hz, 2H), 5.66 (ABX_{syst}, J_{AB}=15.2 Hz, J=3.9 Hz, 1H), 5.64 (ABX_{syst}, J_{AB}=15.2 Hz, J=3.9 Hz, 1H), 5.18 (d, J=12.3 Hz, 1H), 5.13 (d, J=1.6 Hz, 1H), 4.65 (d, J=1.6 Hz, 1H), 4.58 (d, J=12.3 Hz, 1H), 3.69 (s, 3H), 2.54–2.48 (m, 1H), 2.43–2.35 (m, 6H), 2.29–2.23 (m, 1H); ^{13}C NMR (175 MHz, $CDCl_3$): δ=172.7, 172.4, 162.8, 160.0, 134.6, 132.5, 130.1, 129.8, 129.6, 128.0, 127.4, 127.0, 126.3, 125.8, 114.3, 83.6, 66.8, 65.0, 55.2, 34.0, 32.8, 27.6, 26.7. Anal. Calcd for $C_{25}H_{25}NO_6$: C, 68.95; H, 5.79; N, 3.22. Found: C, 68.74; H, 5.69; N, 3.06.

4.3.5. *trans-(E-But-2-enamido)-1-(2-((E-but-2-enoyloxy)-methyl)phenyl)-4-(4-methoxyphenyl)azetidin-2-one* ***10a***

Following the general procedure, from 120.0 mg (0.3 mmol) of lactam **8a** and 15 mol % of Grubbs 2 catalyst in 325 mL of anhyd CH_2Cl_2 and after 5 days at 40 °C, 72.0 mg (55%) of pure **10a** was obtained as a pale yellow oil after chromatography (SiO_2, Hex/AcOEt 5:1). Yield 6.0 mg (5%) of starting **8a** was also recovered. IR (film): ν_{max}=3307, 2930, 2863, 1761, 1722, 1633, 1552, 1515, 1250, 968, 753 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=7.44–7.41 (m, 1H), 7.32 (d, J=8.7 Hz, 2H), 7.24–7.18 (m, 2H), 7.11–7.08 (m, 1H), 7.02 (dq, J=15.5, 6.9 Hz, 1H), 6.93 (dq, J=15.3, 6.9 Hz, 1H), 6.85 (d, J=8.7 Hz, 2H), 6.45 (d, J=7.0 Hz, 1H), 5.89 (dq, J=15.5, 1.7 Hz, 1H), 5.87 (dq, J=15.3, 1.6 Hz, 1H), 5.47 (AB_{syst}, J_{AB}=13.1 Hz, 1H), 5.38 (AB_{syst}, J_{AB}=13.1 Hz, 1H), 5.19 (d, J=2.3 Hz, 1H), 4.78 (dd, J=7.0, 2.3 Hz, 1H), 3.78 (s, 3H), 1.90 (dd, J=6.9, 1.7 Hz, 3H), 1.89 (dd, J=6.9, 1.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=165.7, 165.5, 164.6, 159.4, 156.2, 145.0, 141.5, 133.5, 130.2, 130.0, 128.6, 127.6, 126.4, 123.3, 122.3, 121.9, 113.9, 64.4, 63.9, 62.8, 54.8, 17.6, 17.4. Anal. Calcd for $C_{25}H_{26}N_2O_5$: C, 69.11; H, 6.03; N, 6.45. Found: C, 68.79; H, 6.21; N, 6.33.

4.3.6. *trans-3-(But-3-enamido)-1-(2-((E-but-2-enoyloxy)-methyl)phenyl)-4-(4-methoxyphenyl)azetidin-2-one* ***10b***

Following the general procedure, from 80.0 mg (0.2 mmol) of lactam **8a** and 15 mol % of Grubbs 1 catalyst in 200 mL of anhyd CH_2Cl_2 and after 5 days at 40 °C, 20.0 mg (27%) of pure **10b** was obtained as yellow oil after chromatography (SiO_2, Hex/AcOEt 5:2). IR (film): ν_{max}=3293, 3012, 2924, 2853, 1759, 1720, 1658, 1612, 1584,

1515, 1250, 969, 754 cm^{-1}; ^1H NMR (500 MHz, C_6D_6): δ=7.30 (dd, J=7.5, 1.4 Hz, 1H), 7.25 (d, J=8.7 Hz, 2H), 7.07 (dd, J=7.8, 1.3 Hz, 1H), 6.89 (dq, J=15.5, 6.9 Hz, 1H), 6.89–6.81 (m, 2H), 6.67 (d, J=8.7 Hz, 2H), 6.14 (d, J=7.2 Hz, 1H), 5.87 (ddt, J=17.5, 9.8, 6.8 Hz, 1H), 5.84 (d, J=13.4 Hz, 1H), 5.80 (dq, J=15.5, 1.7 Hz, 1H), 5.64 (d, J=13.4 Hz, 1H), 5.25 (d, J=2.4 Hz, 1H), 5.01–4.98 (m, 2H), 4.62 (dd, J=7.2, 2.4 Hz, 1H), 3.19 (s, 3H), 2.73 (d, J=6.8 Hz, 2H), 1.31 (dd, J=6.9, 1.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=170.9, 166.1, 165.0, 159.9, 145.5, 133.9, 130.6, 130.5, 130.4, 129.3, 129.0, 128.0, 126.9, 122.8, 122.4, 120.4, 114.3, 64.7, 64.3, 63.2, 55.2, 41.1, 18.1. Anal. Calcd for $C_{25}H_{26}N_2O_5$: C, 69.11; H, 6.03; N, 6.45. Found: C, 69.35; H, 6.22; N, 6.39.

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