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Tandem-Selective Bond Cleavage of the Lactam Nucleus and Michael Reaction

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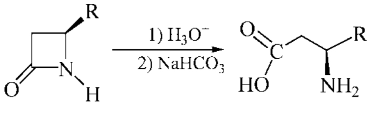
The reactivity of the β-lactam ring towards nucleophiles has been investigated. Ring-opening reactions were performed on 3-allyl-β-lactams with CH_3O^-/CH_3OH at room temperature and/or reflux. Lactam nucleus isomerization followed by N1–C2 bond cleavage and methanol Michael addition afforded substituted amino esters. The reactivity of the four-membered ring towards nucleophiles was found to depend on the substituents at the lactamic nitrogen and the C3 and C4 atoms. The ring-opening path is highlighted in this report.

Introduction

The importance of the monocyclic 2-azetidinone ring, the most widely employed family of antimicrobial agents,[1,2] has led to the development of efficient approaches to the construction of substituted β-lactams with stereochemical and functional group control.[3–5]

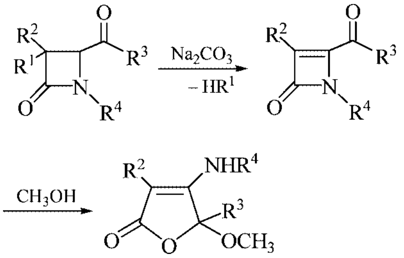
The enhanced ring strain of these compounds facilitates the cleavage of any of the four single bonds. For instance, selective bond cleavage of the 2-azetidinone ring, coupled with further transformations, makes these molecules powerful synthetic building blocks.[6–8]

Cleavage of the 2-azetidinone ring at the N1–C2 bond usually takes place with nucleophilic reagents and exemplifies the synthesis of β-amino acids,[9,10] which is the more obvious synthetic application. The rigidity of the four-membered ring often makes this methodology highly stereoselective,[11] and it has become an exceptionally efficient entry to enantiomerically pure nonproteinogenic amino acids and peptides (Scheme 1).[12–14]

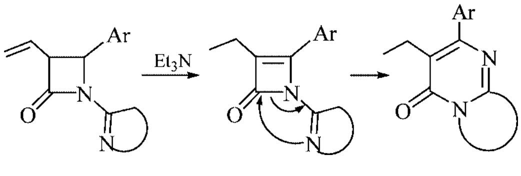


Scheme 1.

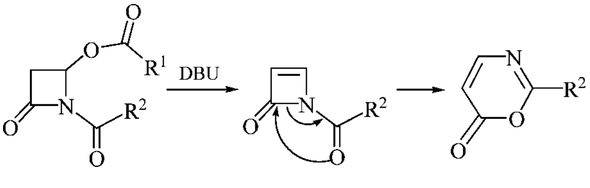
Ring expansion to enamine lactones and lactams is also possible with 4-acyl-β-lactams through a tandem-E1cB-elimination–rearrangement process,[15] as well as with *N*-α-azaheteroaryl-β-lactams[16] and *N*-acyl-4-acyloxy-β-lactams,[17] as shown in Schemes 2, 3 and 4, respectively. In all these cases, a highly strained azet-2(1*H*)-one intermediate can be hypothesized.



Scheme 2.



Scheme 3.



Scheme 4.

C2–C3,[18–20] C3–C4[21–24] and also the C4–N1[25–27] bond cleavages have been widely reported in the literature. The preference for each one of the ring-opening paths seems to be related to the substituents on the β-lactam ring and is also dependent on the reagent employed for the reaction. We further investigate this interesting aspect of the reactivity of this reaction and present in this paper the re-

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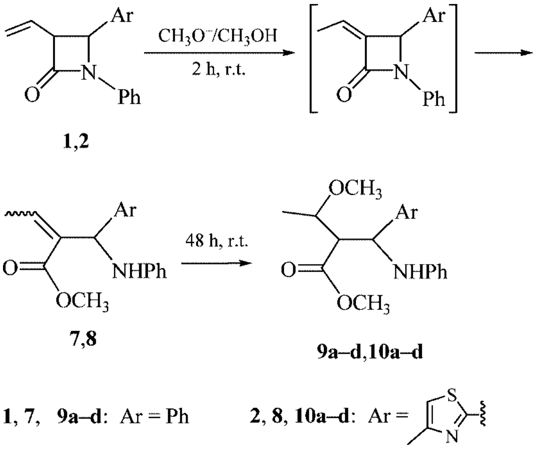
sults of the ring-opening reaction of 3-allyl-β-lactams with CH_3O^-/CH_3OH at room temperature and/or reflux.

Results and Discussion

The β-lactams **1**–**5** were prepared according to a methodology improved by our group; the full characterization of these lactams has previously been reported by us.[5,16,28,29] The 2-azetidinone **6** was prepared following the same procedure and the experimental details are reported in the Exp. Sect. The latter was isolated as a mixture of four diastereomers, with only the (1′*R*,3*R*,4*S*)-**6** isomer being used in our investigations.

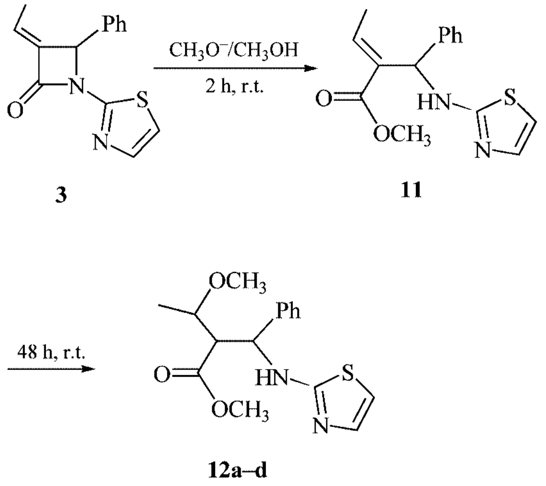
When the racemic β-lactam *trans*-**1** was treated at room temp. with CH_3O^-/CH_3OH the major reaction product after 2 h was **7**, which was transformed into the β-amino esters **9a**–**d** in quantitative yield (>99%) after 48 h (Scheme 5). Analogous results were observed starting from the racemic *cis*-**1** substrate.



Scheme 5.

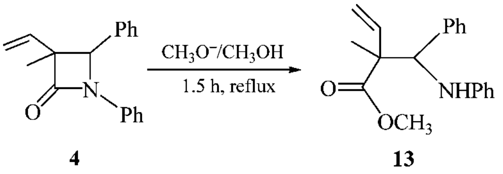
It seems evident that the deprotonation of C3–H leads firstly to the isomerization of **1** through a C=C double bond shift, followed by amidic bond cleavage to give the more stable α,β-unsaturated carbonyl compound **7** as two diastereomers, (*E*) and (*Z*), in a 1:1 ratio (yield >99%). These two isomers then underwent a Michael addition reaction with methanol to afford the final products **9a**–**d** as a mixture of four diastereomers in diastereomeric ratios as detailed in the Exp. Sect. The analogous reaction performed under reflux for 1.5 h led directly to the same compounds **9a**–**d** in quantitative yield (>99%).

The results observed for **1** were also found for the 2-azetidinone **2** (*trans* or *cis*) bearing an α-aza-heteroaryl moiety on the C4 atom: the β-amino esters **10a**–**d** were isolated as a mixture of four diastereomers via the intermediate **8** which was isolated as almost totally the (*E*) isomer (Scheme 5). Analogous results were observed starting directly from the α,β-unsaturated β-lactam (*E*)-**3** with the heteroaryl moiety linked to the N1 atom (Scheme 6). The carbonyl compound (*E*)-**11** was isolated as the only diastereomer after 2 h at room temp. (yield >99%). This compound then underwent the Michael addition reaction to afford the β-amino esters **12a**–**d** quantitatively as a mixture of four diastereomers (overall yield >99%) after 48 h.



Scheme 6.

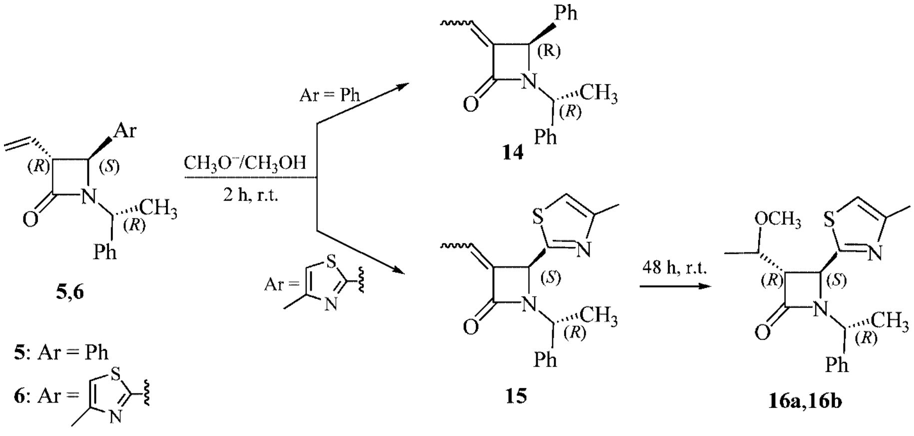
When the β-lactam *cis*-**4**, with no hydrogen atoms at the C3 position, was treated under the same conditions (48 h at room temp. or 1.5 h under reflux), the β-amino ester **13** was isolated as the only reaction product (yield >99%) without the addition of methanol to the vinyl group, which could not conjugate with the C=O group (Scheme 7). From these results we can assume that isomerization is not a necessary condition for the amidic bond cleavage.



Scheme 7.

Starting from alkenyl-β-lactams like **1**,**2** or directly from the isomerized β-lactam such as **3**, the isolated products were the same. Similarly, the presence of an aryl or an α-aza-heteroaryl substituent at the C4 or N1 position does not influence the reaction pathway.

These considerations are further supported by the results obtained by treating the 2-azetidinones (1′*R*,3*R*,4*S*)-**5** and (1′*R*,3*R*,4*S*)-**6** with CH_3O^-/CH_3OH (Scheme 8). The presence of an alkyl group at the N1 position and a phenyl or an α-aza-heteroaryl substituent at the C4 position makes β-lactams **5** and **6** inert to the ring-opening reaction. For instance, when the substrate bears a phenyl group at C4, as in (1′*R*,3*R*,4*S*)-**5**, the β-lactam underwent only isomerization leading to the α,β-unsaturated carbonyl compound **14** as a mixture of two diastereomers [(*E*) >> (*Z*), overall yield >99%]. No ring-opened and/or Michael addition products were found in this case, not even for longer reaction times. The presence of an α-aza-heteroaryl moiety at C4, such as in the compound (1′*R*,3*R*,4*S*)-**6**, led to the isomerization product **15** as a mixture of two diastereomers [(*E*) > (*Z*), overall yield >99%]. For longer reaction times, the subse-



Scheme 8.

quent Michael addition of methanol gave β-lactams **16a** and **16b** functionalized by the methoxy group on the side-chain. The presence of the α-azaheteroaryl moiety instead of the phenyl on the C4 atom should activate the vinylic C3 carbon atom to the Michael addition in this latter reaction, with no β-lactam ring-opening. Compounds **16a** and **16b** were isolated as a mixture of two *trans* diastereomers showing a new stereogenic centre at the carbon atom bearing the methoxide and retaining the absolute configuration of the pre-existing chiral carbon atoms (*dr* = 7:3, by GC-MS; overall yield >99%, see Exp. Sect.). From this behaviour we can assume that the nature of the substituent linked to the lactamic nitrogen atom plays a strategic role in the ring-opening reaction. For instance, the phenyl or the heteroaryl moiety, relative to the alkyl group, has a bigger electron-withdrawing effect which could activate the carbonyl carbon atom making the Michael addition and the ring-opening reactions easier.

The absolute configurations of the four diastereomers of compound **6** were assigned by ^{1}H NMR spectroscopy, comparing the data with those obtained for analogous structures previously reported and characterized also by X ray diffraction.[29] The two isomeric forms of **7**, **8**, **11**, **14** and **15** were assigned by ^{1}H NMR spectroscopy. For instance, the (*Z*) isomer exhibited a vinylic proton with an upfield chemical shift, whereas the (*E*) compound showed a downfield chemical shift as this proton is in the deshielding region of the neighbouring carbonyl group.[29–31] The *trans* configurations of the β-lactams **16a** and **16b** were assigned by ^{1}H NMR spectroscopy on the basis of the coupling constants between the protons linked to the C3 and the C4 atoms ($J_{cis} > J_{trans}$).[28,29]

Conclusions

In conclusion, our results appear to be in agreement with those reported by other authors[32,33] for 2-azetidinones having different substituents. The nature of the groups on the lactamic nitrogen and the C3 and C4 carbon atoms influences the reactivity of the four-membered ring towards nucleophiles. Thus, groups that inhibit the amidic resonance, such as an aryl linked to the nitrogen atom, facilitate nucleophilic addition to the carbonyl carbon atom and, consequently, make the 2-azetidinone ring-opening reaction easier while an alkyl group, as in compound **5** or **6**, by increasing the nitrogen basicity, strengthens the amidic conjugation which makes the N1–C2 bond stronger and prevents β-lactam ring-opening.

Experimental Section

General Remarks: Methyl alcohol, sodium methoxide, allyl bromide, 2-thiazolecarbaldehyde, (*R*)-1-phenylethylamine and all other chemicals were of commercial grade (Aldrich) and were used without further purification. The β-lactam **6** was prepared by the [2+2] carbonylative cycloaddition reaction of (*R*)-[1-(4-phenylthiazol-2-yl)ethylidene](1-phenylethyl)amine and allyl bromide following our methodology.[5] The starting imine was prepared by the coupling reaction of (*R*)-1-phenylethylamine and 2-thiazolecarbaldehyde according to the protocol of Taguchi and Westheimer.[34] Petroleum ether refers to the 40–60 °C boiling fraction. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker Avance 400 spectrometer (400.13 and 100.62 MHz for ^{1}H and ^{13}C NMR, respectively) with $CDCl_3$ as solvent and TMS as the internal standard (δ = 7.24 ppm for ^{1}H NMR; δ = 77.0 ppm for ^{13}C NMR). The IR spectra were recorded with an Digilab Scimitar Series FTS 2000 FTIR spectrophotometer. GC-MS analyses were performed with an Agilent Technologies 6850 series II gas chromatograph (5% phenyl-polymethylsiloxane capillary column, 30 m, 0.25 mm i.d.), equipped with an Agilent Technologies 5973 Network mass-selective detector operating at 70 eV (EI). The electrospray ionisation (ESI HRMS) experiments were carried out with a hybrid Q*q*TOF mass spectrometer (PE SCIEX-QSTAR) equipped with an ion-spray ionisation source. MS(+) spectra were acquired by direct infusion (5 μL/min) of a solution containing the appropriate sample (10 pmol/μL) dissolved in a solution of 0.1% acetic acid in methanol/water (50:50) at the optimum ion voltage of 4800 V. The pressure of nitrogen gas was set to 30 psi and the potentials of the orifice, the focusing ring and the skimmer were kept at 30, 50 and 25 V relative to the ground, respectively. Elemental analyses were performed on a Carlo Erba CHN analyzer. Melting points were determined using an Electrothermal melting point apparatus and are uncorrected. TLC was performed on Merck silica gel plates with an F-254 indicator and was viewed by UV light (254 nm). Column chromatography was performed on silica gel (63–200 mm) using petroleum ether/

diethyl ether (Et_2O) mixtures as eluents. All reactions involving air-sensitive reagents were performed under nitrogen in oven-dried glassware using syringe/septum cap techniques.

General Procedure for the Preparation of Compounds 7–16: Compounds **1**–**6** (1 mmol) dissolved in CH_3OH (5 mL) was added dropwise to a solution of $NaOCH_3$ (3 mmol) in CH_3OH (20 mL) under nitrogen. The mixture was stirred under nitrogen until complete disappearance of the starting reagent. Then, the excess $NaOCH_3$ was neutralized with aqueous NH_4Cl (10 mL). The product was extracted with Et_2O (3×20 mL) and the combined organic layers were dried with anhydrous Na_2SO_4 and concentrated in vacuo. The crude products were purified by column chromatography (silica gel, petroleum ether/Et_2O, 8:2) to afford the pure products **7**–**16** in total yields of >99%. The spectral characterizations of the different isomers of each compound are listed in the order of GC-MS elution.

Methyl 2-[Phenyl(phenylamino)methyl]-2-butenoate (7): (*Z*): Yield: 140 mg (50%), oil. ^1H NMR (400.13 MHz, $CDCl_3$): δ = 2.02 (d, J = 7.2 Hz, 3 H), 3.67 (s, 3 H), 4.17 (s, 1 H), 5.34 (br. s, exchanges with D_2O, 1 H), 6.34 (q, J = 7.1 Hz, 1 H), 6.57 (d, J = 8.4 Hz, 2 H), 6.71 (t, J = 7.0 Hz, 1 H), 7.15 (t, J = 7.6 Hz, 2 H), 7.25–7.34 (m, 5 H) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 15.5, 51.3, 60.4, 113.3, 117.7, 127.5, 127.6, 128.6, 129.2, 132.5, 137.7, 141.2, 146.8, 167.7 ppm. GC-MS (70 eV): *m*/*z* (%) = 281 (30) $[M]^+$, 266 (15), 182 (39), 129 (100), 77 (33). IR ($CHCl_3$): $\tilde{\nu}$ = 3431, 3030, 3010, 2954, 2926, 2855, 1711, 1602, 1503, 1453, 1248 cm^{-1}. HRMS: calcd. for $C_{18}H_{20}NO_2$ 282.1495; found 282.1490.

(*E*): Yield: 140 mg (50%), oil. ^1H NMR (400.13 MHz, $CDCl_3$): δ = 2.03 (d, J = 7.3 Hz, 3 H), 3.65 (s, 3 H), 5.10 (br. d, exchanges with D_2O, J = 9.0 Hz, 1 H), 5.73 (d, J = 9.0 Hz, 1 H), 6.65 (d, J = 7.9 Hz, 2 H), 6.70 (t, J = 7.4 Hz, 1 H), 7.07 (q, J = 7.3 Hz, 1 H), 7.16 (t, J = 7.9 Hz, 2 H), 7.21–7.40 (m, 5 H) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 14.7, 51.7, 53.8, 113.5, 117.7, 126.3, 126.9, 128.4, 129.3, 133.5, 139.6, 141.2, 147.4,166.9 ppm. GC-MS (70 eV): *m*/*z* (%) = 281 (45) $[M]^+$, 266 (23), 182 (41), 129 (100), 77 (36). IR ($CHCl_3$): $\tilde{\nu}$ = 3431, 3030, 3010, 2954, 2926, 2855, 1711, 1602, 1503, 1453, 1248 cm^{-1}. HRMS: calcd. for $C_{18}H_{20}NO_2$ 282.1495; found 282.1498.

Methyl 3-Methoxy-2-[phenyl(phenylamino)methyl]butanoates 9a–d: **9a**: Yield: 106 mg (34%), white solid. M.p. 69–70 °C (*n*-hexane). ^1H NMR (400.13 MHz, $CDCl_3$): δ = 1.15 (d, J = 6.0 Hz, 3 H), 2.90 (dd, J = 9.7, 3.9 Hz, 1 H), 3.26 (s, 3 H), 3.47 (s, 3 H), 3.73–3.80 (m, 1 H), 5.03 (d, J = 3.9 Hz, 1 H), 5.42 (br. s, exchanges with D_2O, 1 H), 6.55–6.62 (m, 3 H), 7.08 (t, J = 7.6 Hz, 2 H), 7.20–7.27 (m, 5 H) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 17.4, 51.5, 54.7, 57.2, 59.2, 74.6, 113.1, 116.9, 126.2, 127.1, 128.5, 129.1, 141.5, 147.0, 173.3 ppm. GC-MS (70 eV): *m*/*z* (%) = 313 (5) $[M]^+$, 182 (100), 104 (60), 77 (11). IR ($CHCl_3$): $\tilde{\nu}$ = 3414, 3300, 2928, 2855, 1718, 1602, 1509, 1170, 1097 cm^{-1}. $C_{19}H_{23}NO_3$ (313.40): C 72.81, H 7.39, N 4.47; found C 73.05, H 7.50, N 4.35.

9b: Yield: 106 mg (34%), white solid. M.p. 111–113 °C (*n*-hexane). ^1H NMR (400.13 MHz, $CDCl_3$): δ = 1.26 (d, J = 6.0 Hz, 3 H), 2.82 (dd, J = 9.0, 4.9 Hz, 1 H), 3.30 (s, 3 H), 3.46 (s, 3 H), 3.77–3.83 (m, 1 H), 4.70 (d, J = 4.9 Hz, 1 H), 5.37 (br. s, exchanges with D_2O, 1 H), 6.52 (d, J = 7.9 Hz, 2 H), 6.61 (t, J = 7.3 Hz, 1 H), 7.07 (t, J = 7.7 Hz, 2 H), 7.19–7.29 (m, 5 H) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 16.3, 51.5, 55.6, 56.8, 59.0, 73.7, 113.1, 117.2, 126.2, 127.3, 128.7, 129.1, 140.7, 146.5, 174.0 ppm. GC-MS (70 eV): *m*/*z* (%) = 313 (15) $[M]^+$, 182 (100), 104 (11), 77 (18). IR ($CHCl_3$): $\tilde{\nu}$ = 3414, 3300, 2928, 2855, 1718, 1602, 1509, 1170, 1097 cm^{-1}. $C_{19}H_{23}NO_3$ (313.40): C 72.81, H 7.39, N 4.47; found C 72.63, H 7.25, N 4.37.

9c: Yield: 50 mg (16%), white solid. M.p. 102–104 °C (*n*-hexane). ^1H NMR (400.13 MHz, $CDCl_3$): δ = 1.30 (d, J = 6.4 Hz, 3 H), 2.98 (dd, J = 8.3, 3.1 Hz, 1 H), 3.38 (s, 3 H), 3.51 (s, 3 H), 3.58–3.64 (m, 1 H), 4.80 (d, J = 8.3 Hz, 1 H), 5.32 (br. s, exchanges with D_2O, 1 H), 6.50 (d, J = 7.7 Hz, 2 H), 6.62 (t, J = 7.2 Hz, 1 H), 7.02 (t, J = 7.4 Hz, 2 H), 7.20–7.38 (m, 5 H) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 16.2, 51.6, 56.8, 57.1, 57.7, 75.9, 113.5, 117.3, 127.1, 127.4, 128.5, 129.0, 141.8, 147.3, 171.3 ppm. GC-MS (70 eV): *m*/*z* (%) = 313 (5) $[M]^+$, 182 (100), 104 (7), 77 (12). IR ($CHCl_3$): $\tilde{\nu}$ = 3414, 3300, 2928, 2855, 1718, 1602, 1509, 1170, 1097 cm^{-1}. $C_{19}H_{23}NO_3$ (313.40): C 72.81, H 7.39, N 4.47; found C 72.89, H 7.45, N 4.52.

9d: Yield: 50 mg (16%), white solid. M.p. 133–134 °C (*n*-hexane). ^1H NMR (400.13 MHz, $CDCl_3$): δ = 1.18 (d, J = 6.1 Hz, 3 H), 2.97 (t, J = 8.2 Hz, 1 H), 3.41 (s, 3 H), 3.46 (s, 3 H), 3.65–3.69 (m, 1 H), 4.81 (d, J = 8.2 Hz, 1 H), 5.30 (br. s, exchanges with D_2O, 1 H), 6.51 (d, J = 7.8 Hz, 2 H), 6.62 (t, J = 7.3 Hz, 1 H), 7.06 (t, J = 7.5 Hz, 2 H), 7.20–7.37 (m, 5 H) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 16.7, 51.4, 56.0, 58.4, 58.8, 76.3, 113.5, 117.4, 127.1, 127.5, 128.3, 129.0, 141.1, 147.3, 171.6 ppm. GC-MS (70 eV): *m*/*z* (%) = 313 (4) $[M]^+$, 182 (100), 104 (6), 77 (10). IR ($CHCl_3$): $\tilde{\nu}$ = 3414, 3300, 2928, 2855, 1718, 1602, 1509, 1170, 1097 cm^{-1}. $C_{19}H_{23}NO_3$ (313.40): C 72.81, H 7.39, N 4.47; found C 72.75, H 7.35, N 4.40.

Methyl 2-[(4-Methylthiazol-2-yl)(phenylamino)methyl]-2-butenoate (8): (*E*): Yield: 296 mg (98%), oil. ^1H NMR (400.13 MHz, $CDCl_3$): δ = 2.04 (d, J = 7.2 Hz, 3 H), 2.39 (s, 3 H), 3.69 (s, 3 H), 5.34 (d, exchanges with D_2O, J = 9.8 Hz, 1 H), 5.86 (d, J = 9.8 Hz, 1 H), 6.68–6.78 (m, 4 H), 7.01–7.26 (m, 3 H) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 15.3, 17.4, 51.7, 54.1, 113.7, 114.3, 118.8, 129.3, 131.8, 141.5, 146.5, 152.7, 166.7, 172.6 ppm. GC-MS (70 eV): *m*/*z* (%) = 302 (100) $[M]^+$, 241 (65), 227 (57), 178 (58), 150 (67), 77 (42). IR ($CHCl_3$): $\tilde{\nu}$ = 3410, 2983, 3010, 2954, 1719, 1602, 1507, 1453, 1438, 1258 cm^{-1}. HRMS: calcd. for $C_{16}H_{19}N_2O_2S$ 303.12587; found 303.12582.

(*Z*): Isolated in traces and identified by GC-MS (70 eV): *m*/*z* (%) = 302 (100) $[M]^+$, 241 (60), 227 (60), 178 (55), 150 (63), 77 (40).

Methyl 3-Methoxy-2-[(4-methylthiazol-2-yl)(phenylamino)methyl]-butanoates 10a–d: **10a**: Yield: 110 mg (33%), oil. ^1H NMR (400.13 MHz, $CDCl_3$): δ = 1.17 (d, J = 6.1 Hz, 3 H), 2.41 (s, 3 H), 3.13 (s, 3 H), 3.32 (dd, J = 9.4, 3.6 Hz, 1 H), 3.60 (s, 3 H), 3.67–3.73 (m, 1 H), 5.33 (dd, J = 8.8, 3.6 Hz, 1 H), 5.39 (d, exchanges with D_2O, J = 8.8 Hz, 1 H), 6.65–6.77 (m, 4 H), 7.15 (t, J = 7.5 Hz, 2 H) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 17.1, 17.2, 51.8, 54.4, 56.6, 56.9, 74.4, 113.5, 118.1, 128.9, 129.2, 146.8, 153.1, 172.9, 173.7 ppm. GC-MS (70 eV): *m*/*z* (%) = 334 (7) $[M]^+$, 243 (9), 203 (100), 100 (18), 77 (7). IR ($CHCl_3$): $\tilde{\nu}$ = 3414, 3386, 3031, 3007, 2954, 2927, 2854, 1703, 1603, 1517, 1438, 1303 cm^{-1}. HRMS: calcd. for $C_{17}H_{23}N_2O_3S$ 335.14309; found 335.14313.

10b+10c: Isolated as an inseparable mixture (*dr* = 1:1 by ^1H NMR spectroscopy). Overall yield: 114 mg (34%), oil. ^1H NMR (400.13 MHz, $CDCl_3$): δ = 1.17 (d, J = 6.2 Hz, 3 H), 1.32 (d, J = 6.2 Hz, 3 H), 2.40 (s, 3 H), 2.41 (s, 3 H), 3.14 (t, J = 6.8 Hz, 1 H), 3.32 (dd, J = 7.2, 3.2 Hz, 1 H), 3.32 (s, 3 H), 3.42 (s, 3 H), 3.622 (s, 3 H), 3.624 (s, 3 H), 3.68–3.72 (m, 1 H), 3.83–3.87 (m, 1 H), 5.17 (t, J = 7.2 Hz, 1 H), 5.25 (t, J = 6.8 Hz, 1 H), 5.30 (d, exchanges with D_2O, J = 7.2 Hz, 1 H), 5.34 (d, exchanges with D_2O, J = 6.8 Hz, 1 H), 6.62–6.78 (m, 8 H), 7.12–7.25 (m, 4 H) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 14.1, 16.5, 17.0, 17.2, 51.7, 51.8, 55.6, 56.3, 56.4, 56.6, 56.7, 75.1, 75.8, 113.6, 113.8, 114.3, 118.4, 129.2, 146.7, 146.9, 152.8, 153.0, 170.8, 171.3, 172.3, 173.2 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3414, 3386, 3031, 3007, 2954, 2927, 2854, 1703, 1603, 1517, 1438, 1303 cm^{-1}. HRMS: calcd. for $C_{17}H_{23}N_2O_3S$ 335.14309; found 335.14306. Distinguishable signals: **10b**: GC-MS (70 eV): *m*/*z* (%) = 334 (5) [M]$^+$, 243 (11), 203 (100), 100 (21), 77 (8). **10c**: GC-MS (70 eV): *m*/*z* (%) = 334 (8) [M]$^+$, 243 (13), 203 (100), 100 (20), 77 (11).

10d: Yield: 110 mg (33%), white solid. M.p. 91–93 °C (*n*-hexane). ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.24 (d, *J* = 6.3 Hz, 3 H), 2.42 (s, 3 H), 3.24 (dd, *J* = 8.3, 4.5 Hz, 1 H), 3.30 (s, 3 H), 3.59 (s, 3 H), 3.75–3.80 (m, 1 H), 5.03 (dd, *J* = 8.5, 4.5 Hz, 1 H), 5.39 (d, exchanges with D_2O, *J* = 8.5 Hz, 1 H), 6.62–6.72 (m, 4 H), 7.14 (t, *J* = 7.5 Hz, 2 H) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 16.5, 17.2, 51.8, 54.9, 56.7, 56.8, 76.1, 113.2, 118.3, 128.4, 129.3, 146.2, 153.1, 173.1, 173.4 ppm. GC-MS (70 eV): *m*/*z* (%) = 334 (8) [M]$^+$, 243 (10), 203 (100), 100 (22), 77 (10). IR ($CHCl_3$): $\tilde{\nu}$ = 3414, 3386, 3031, 3007, 2954, 2927, 2854, 1703, 1603, 1517, 1438, 1303 cm^{-1}. $C_{17}H_{22}N_2O_3S$ (334.46): C 61.07, H 6.63, N 8.38; found C 61.29, H 6.70, N 8.40.

Methyl 2-[Phenyl(thiazol-2-ylamino)methyl]-2-butenoate (11): (*E*): Yield: 282 mg (98%), oil. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 2.10 (d, *J* = 7.2 Hz, 3 H), 3.65 (s, 3 H), 6.11 (d, *J* = 9.7 Hz, 1 H), 6.47 (d, *J* = 3.6 Hz, 1 H), 6.61 (d, exchanges with D_2O, *J* = 9.7 Hz, 1 H), 7.10 (d, *J* = 3.6 Hz, 1 H), 7.14 (q, *J* = 7.2 Hz, 1 H), 7.23–7.54 (m, 5 H) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 14.7, 51.8, 55.2, 106.6, 125.8, 127.1, 128.5, 132.2, 139.1, 140.1, 140.7, 166.8, 169.2 ppm. GC-MS (70 eV): *m*/*z* (%) = 288 (45) [M]$^+$, 229 (33), 129 (100), 77 (20). IR ($CHCl_3$): $\tilde{\nu}$ = 3412, 2990, 3010, 2950, 1720, 1608, 1500, 1450, 1438, 1258 cm^{-1}. HRMS: calcd. for $C_{15}H_{17}N_2O_2S$ 289.10121; found 289.10125.

Methyl 3-Methoxy-2-[phenyl(thiazol-2-ylamino)methyl]butanoates 12a–d: **12a**: Yield: 48 mg (15%), oil. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.18 (d, *J* = 6.1 Hz, 3 H), 3.05 (t, *J* = 8.2 Hz, 1 H), 3.41 (s, 3 H), 3.48 (s, 3 H), 3.67–3.74 (m, 1 H), 4.89 (d, *J* = 8.2 Hz, 1 H), 6.40 (d, *J* = 3.8 Hz, 1 H), 6.90 (d, exchanges with D_2O, *J* = 8.2 Hz, 1 H), 7.08 (d, *J* = 3.8 Hz, 1 H), 7.25–7.34 (m, 5 H) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 16.7, 51.7, 56.1, 57.8, 60.6, 76.2, 107.2, 127.5, 128.1, 128.4, 138.7, 139.1, 169.5, 171.1 ppm. GC-MS (70 eV): *m*/*z* (%) = 320 (11) [M]$^+$, 229 (16), 189 (100), 129 (20), 100 (14), 59 (39). IR ($CHCl_3$): $\tilde{\nu}$ = 3388, 3031, 2977, 2931, 1720, 1536, 1495, 1380, 1153, 1094 cm^{-1}. HRMS: calcd. for $C_{16}H_{21}N_2O_3S$ 321.12743; found 321.12746.

12b: Yield: 48 mg (15%), oil. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.32 (d, *J* = 6.4 Hz, 3 H), 3.06 (dd, *J* = 8.5, 2.8 Hz, 1 H), 3.37 (s, 3 H), 3.53 (s, 3 H), 3.63 (dd, *J* = 6.4, 2.8 Hz, 1 H), 4.97 (d, *J* = 8.5 Hz, 1 H), 6.40 (d, *J* = 3.5 Hz, 1 H), 6.90 (br. s, exchanges with D_2O, 1 H), 7.07 (d, *J* = 3.5 Hz, 1 H), 7.27–7.39 (m, 5 H) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 15.9, 51.7, 56.5, 56.8, 59.3, 75.7, 107.0, 127.4, 127.8, 128.5, 138.8, 139.8, 169.3, 170.7 ppm. GC-MS (70 eV): *m*/*z* (%) = 320 (10) [M]$^+$, 229 (16), 189 (100), 129 (25), 100 (17), 59 (32). IR ($CHCl_3$): $\tilde{\nu}$ = 3388, 3031, 2977, 2931, 1720, 1536, 1495, 1380, 1153, 1094 cm^{-1}. HRMS: calcd. for $C_{16}H_{21}N_2O_3S$ 321.12743; found 321.12740.

12c+12d: Isolated as an inseparable mixture (*dr* = 1:1 by ^{1}H NMR spectroscopy). Overall yield: 224 mg (70%), oil. ^{1}H NMR (400.13 MHz, $CDCl_3$): 1.16 (d, *J* = 6.1 Hz, 3 H), 1.29 (d, *J* = 6.1 Hz, 3 H), 2.85 (dd, *J* = 8.8, 4.9 Hz, 1 H), 2.92 (dd, *J* = 9.6, 4.0 Hz, 1 H), 3.29 (s, 3 H), 3.30 (s, 3 H), 3.50 (s, 3 H), 3.51 (s, 3 H), 3.68–3.73 (m, 2 H), 4.98 (t, *J* = 4.9 Hz, 1 H), 5.19 (dd, *J* = 8.2, 4.0 Hz, 1 H), 6.41 (d, *J* = 3.5 Hz, 1 H), 6.42 (d, *J* = 3.6 Hz, 1 H), 6.85 (d, exchanges with D_2O, *J* = 4.0 Hz, 1 H), 6.92 (d, exchanges with D_2O, *J* = 8.2 Hz, 1 H), 7.04 (d, *J* = 3.6 Hz, 1 H), 7.07 (d, *J* = 3.5 Hz, 1 H), 7.21–7.30 (m, 10 H) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 15.9, 51.7, 56.5, 56.8, 59.3, 75.7, 106.6, 106.8, 126.2, 127.5, 127.6, 128.5, 128.6, 139.0, 139.7, 168.8, 169.4, 172.7, 173.6 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3388, 3031, 2977, 2931, 1720, 1536, 1495, 1380, 1153, 1094 cm^{-1}. HRMS: calcd. for $C_{16}H_{21}N_2O_3S$ 321.12743; found 321.12745. Distinguishable signals: **12c**: GC-MS (70 eV): *m*/*z* (%) = 320 (12) [M]$^+$, 229 (25), 189 (100), 129 (22), 100 (15), 59 (30). **12d**: GC-MS (70 eV): *m*/*z* (%) = 334 (8) [M]$^+$, 243 (13), 203 (100), 100 (20), 77 (11).

Methyl 2-Methyl-2-[phenyl(phenylamino)methyl]-3-butenoate (13): Yield: 293 mg (>99%), oil. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.29 (s, 3 H), 3.67 (s, 3 H), 4.30 (br. s, exchanges with D_2O, 1 H), 4.71 (s, 1 H), 5.20 (d, *J* = 17.5 Hz, 1 H), 5.31 (d, *J* = 10.7 Hz, 1 H), 6.22 (dd, *J* = 17.5, 10.7 Hz, 1 H), 6.47 (d, *J* = 8.2 Hz, 2 H), 6.63 (t, *J* = 7.4 Hz, 1 H), 7.04 (t, *J* = 7.7 Hz, 2 H), 7.22–7.35 (m, 5 H) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 16.5, 52.2, 54.0, 63.7, 113.8, 116.8, 117.7, 127.6, 128.0, 128.1, 129.0, 138.8, 139.1, 147.2, 174.4 ppm. GC-MS (70 eV): *m*/*z* (%) = 295 (2) [M]$^+$, 281 (55), 182 (70), 129 (100), 104 (15), 77 (40). IR ($CHCl_3$): $\tilde{\nu}$ = 3410, 3300, 2928, 2856, 1723, 1602, 1504, 1260, 1113 cm^{-1}. HRMS: calcd. for $C_{19}H_{22}NO_2$ 296.16516; found 296.16512.

3-Ethylidene-4-phenyl-1-(1-phenylethyl)azetidin-2-one (14): (1′*R*,4*S*)-(*Z*): Yield: 17 mg (6%), oil. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.80 (d, *J* = 7.3 Hz, 3 H), 2.03 (d, *J* = 7.4 Hz, 3 H), 4.38 (q, *J* = 7.3 Hz, 1 H), 4.66 (s, 1 H), 5.44 (q, *J* = 7.4 Hz, 1 H), 7.16–7.31 (m, 10 H) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 14.3, 20.2, 54.3, 61.8, 124.9, 126.8, 127.3, 127.4, 128.3, 128.5, 128.6, 137.6, 141.7, 142.6, 164.9 ppm. GC-MS (70 eV): *m*/*z* (%) = 277 (9) [M]$^+$, 262 (100), 194 (31), 157 (62), 132 (40). IR ($CHCl_3$): $\tilde{\nu}$ = 3032, 3011, 1737, 1603, 1455, 1377 cm^{-1}. $[\alpha]_D^{22}$ = –9.5 (*c* = 0.012, $CHCl_3$). HRMS: calcd. for $C_{19}H_{20}NO$ 278.15460; found 278.15457.

(1′*R*,4*S*)-(*E*): Yield: 260 mg (94%), white solid. M.p. 108–109 °C (*n*-hexane). ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.43 (d, *J* = 7.1 Hz, 3 H), 1.77 (d, *J* = 7.1 Hz, 3 H), 4.34 (q, *J* = 7.1 Hz, 1 H), 4.78 (s, 1 H), 6.17 (q, *J* = 7.4 Hz, 1 H), 7.16–7.30 (m, 10 H) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 13.2, 20.2, 54.2, 61.5, 121.1, 126.7, 127.3, 127.5, 128.3, 128.5, 128.6, 136.9, 141.5, 143.1, 164.2 ppm. GC-MS (70 eV): *m*/*z* (%) = 277 (8) [M]$^+$, 262 (100), 194 (27), 157 (36), 132 (67). IR ($CHCl_3$): $\tilde{\nu}$ = 3032, 3011, 1737, 1603, 1455, 1377 cm^{-1}. $[\alpha]_D^{22}$ = –37.0 (*c* = 0.024, $CHCl_3$). $C_{19}H_{19}NO$ (277.37): C 82.30, H 6.90, N 5.05; found C 82.48, H 6.86, N 5.03.

4-(4-Methylthiazol-2-yl)-1-(1-phenylethyl)-3-vinylazetidin-2-one (6): (1′*R*,3*S*,4*R*): Yield: 149 mg (50%), oil. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.80 (d, *J* = 7.2 Hz, 3 H), 2.40 (s, 3 H), 3.85 (dd, *J* = 2.3, 7.3 Hz, 1 H), 4.52 (q, *J* = 7.2 Hz, 1 H), 4.56 (d, *J* = 2.3 Hz, 1 H), 5.27 (d, *J* = 10.4 Hz, 1 H), 5.34 (d, *J* = 17.2 Hz, 1 H), 5.87–5.99 (m, 1 H), 6.83 (s, 1 H), 7.22–7.30 (m, 5 H) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 16.9, 19.8, 54.8, 57.4, 62.6, 114.3, 119.7, 126.8, 127.0, 128.6, 130.1, 140.8, 153.3, 167.5, 168.0 ppm. GC-MS (70 eV): *m*/*z* (%) = 298 (2) [M]$^+$, 150 (100), 132 (7), 105 (55), 77 (48). IR ($CHCl_3$): $\tilde{\nu}$ = 3060, 3020, 2980, 2920, 1740, 1440, 1300, 750, 700 cm^{-1}. $[\alpha]_D^{22}$ = –20.50 (*c* = 0.018, $CHCl_3$). HRMS: calcd. for $C_{17}H_{19}N_2OS$ 299.12197; found 299.12193.

(1′*R*,3*R*,4*S*): Yield: 89 mg (30%), oil. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.44 (d, *J* = 7.2 Hz, 3 H), 2.43 (s, 3 H), 3.89 (dd, *J* = 2.2, 7.7 Hz, 1 H), 4.52 (d, *J* = 2.2 Hz, 1 H), 5.02 (q, *J* = 7.2 Hz, 1 H), 5.22 (d, *J* = 10.3 Hz, 1 H), 5.31 (d, *J* = 17.1 Hz, 1 H), 5.78–5.83 (m, 1 H), 6.87 (s, 1 H), 7.24–7.38 (m, 5 H) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 16.9, 18.7, 52.8, 57.5, 62.7, 114.4, 119.7, 127.1, 127.8, 128.7, 129.9, 139.7, 153.1, 167.7, 168.3 ppm. GC-MS (70 eV): *m*/*z* (%) = 298 (2) [M]$^+$, 150 (100), 132 (10), 105 (64), 77 (41). IR ($CHCl_3$): $\tilde{\nu}$ = 3060, 3020, 2980, 2920, 1740, 1440, 1300, 750, 700 cm^{-1}. $[\alpha]_D^{22}$ = +42.6 (*c* = 0.020, $CHCl_3$). HRMS: calcd. for $C_{17}H_{19}N_2OS$ 299.12197; found 299.12102.

(1′*R*,3*S*,4*S*): Yield: 42 mg (14%), oil. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.87 (d, *J* = 7.2 Hz, 3 H), 2.43 (s, 3 H), 4.13 (dd, *J* = 6.0, 6.1 Hz, 1 H), 4.53 (q, *J* = 7.2 Hz, 1 H), 4.96 (d, *J* = 6.0 Hz, 1 H), 5.13 (d, *J* = 10.2 Hz, 1 H), 5.33 (d, *J* = 17.0 Hz, 1 H), 5.43–5.51 (m, 1 H), 6.83 (s, 1 H), 7.23–7.32 (m, 5 H) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 17.0, 19.9, 55.3, 56.3, 58.7, 114.2, 121.3, 126.9, 127.8, 128.2, 128.7, 141.0, 153.4, 166.5, 167.7 ppm. GC-MS (70 eV): *m*/*z* (%) = 298 (3) [M]$^+$, 193 (4), 150 (100), 105 (67), 77 (41). IR ($CHCl_3$): $\tilde{\nu}$ = 3060, 3020, 2980, 2920, 1740, 1440, 1300, 750, 700 cm^{-1}. $[\alpha]_D^{22}$ = +94.8 (*c* = 0.028, $CHCl_3$). HRMS: calcd. for $C_{17}H_{19}N_2OS$ 299.12197; found 299.12100.

(1′*R*,3*R*,4*R*): Yield: 18 mg (6%), oil. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.54 (d, *J* = 7.2 Hz, 3 H), 2.42 (s, 3 H), 4.07 (dd, *J* = 6.0, 6.1 Hz, 1 H), 4.53 (q, *J* = 7.2 Hz, 1 H), 4.96 (d, *J* = 6.0 Hz, 1 H), 5.13 (d, *J* = 10.2 Hz, 1 H), 5.33 (d, *J* = 17.0 Hz, 1 H), 5.43–5.51 (m, 1 H), 6.83 (s, 1 H), 7.23–7.32 (m, 5 H) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 17.0, 19.9, 55.3, 56.3, 58.7, 114.2, 121.3, 126.9, 127.8, 128.2, 128.7, 141.0, 153.4, 166.5, 167.7 ppm. GC-MS (70 eV): *m*/*z* (%) = 298 (3) [M]$^+$, 193 (4), 150 (100), 105 (67), 77 (41). IR ($CHCl_3$): $\tilde{\nu}$ = 3060, 3020, 2980, 2920, 1740, 1440, 1300, 750, 700 cm^{-1}. $[\alpha]_D^{22}$ = –88.8 (*c* = 0.022, $CHCl_3$). HRMS: calcd. for $C_{17}H_{19}N_2OS$ 299.12197; found 299.12195.

3-Ethylidene-4-(4-methylthiazol-2-yl)-1-(1-phenylethyl)azetidin-2-one (15): (1′*R*,4*S*)-(*Z*): Yield: 45 mg (15%), oil. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.81 (d, *J* = 7.1 Hz, 3 H), 2.04 (d, *J* = 7.1 Hz, 3 H), 2.39 (s, 3 H), 4.67 (q, *J* = 7.1 Hz, 1 H), 5.11 (s, 1 H), 5.68 (q, *J* = 7.1 Hz, 1 H), 6.80 (s, 1 H), 7.19–7.33 (m, 5 H) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 14.3, 20.2, 54.3, 61.8, 124.9, 126.8, 127.3, 127.4, 128.3, 128.5, 128.6, 137.6, 141.7, 142.6, 164.9 ppm. GC-MS (70 eV): *m*/*z* (%) = 298 (<1) [M]$^+$, 215 (1), 193 (13), 179 (100), 151 (60), 105 (21), 77 (11). IR ($CHCl_3$): $\tilde{\nu}$ = 3031, 2986, 2928, 1745, 1450, 1304 cm^{-1}. $[\alpha]_D^{22}$ = +19.4 (*c* = 0.007, $CHCl_3$). HRMS: calcd. for $C_{17}H_{19}N_2OS$ 299.12197; found 299.12101.

(1′*R*,4*S*)-(*E*): Yield: 253 mg (85%), oil. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.60 (d, *J* = 7.0 Hz, 3 H), 1.79 (d, *J* = 7.0 Hz, 3 H), 2.39 (s, 3 H), 4.66 (q, *J* = 7.0 Hz, 1 H), 5.25 (s, 1 H), 6.23 (q, *J* = 7.0 Hz, 1 H), 6.82 (s, 1 H), 7.15–7.28 (m, 5 H) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 13.5, 16.8, 19.4, 53.9, 58.5, 114.7, 123.2, 126.7, 127.4, 128.4, 140.8, 141.5, 152.6, 163.6, 167.7 ppm. GC-MS (70 eV): *m*/*z* (%) = 298 (<1) [M]$^+$, 215 (2), 193 (24), 179 (100), 151 (89), 105 (33), 77 (18). IR ($CHCl_3$): $\tilde{\nu}$ = 3031, 2986, 2928, 1745, 1450, 1304 cm^{-1}. $[\alpha]_D^{22}$ = –18.6 (*c* = 0.019, $CHCl_3$). HRMS: calcd. for $C_{17}H_{19}N_2OS$ 299.12197; found 299.12195.

3-(1-Methoxyethyl)-4-(4-methylthiazol-2-yl)-1-(1-phenylethyl)-azetidin-2-ones 16a,b: 16a: Yield: 234 mg (71%), oil. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.22 (d, *J* = 6.2 Hz, 3 H), 1.78 (d, *J* = 7.1 Hz, 3 H), 2.39 (s, 3 H), 3.25 (dd, *J* = 1.9, 6.2 Hz, 1 H), 3.36 (s, 3 H), 3.77 (quintet, *J* = 6.2 Hz, 1 H), 4.53 (q, *J* = 7.1 Hz, 1 H), 4.80 (d, *J* = 1.9 Hz, 1 H), 6.78 (s, 1 H), 7.20–7.26 (m, 5 H) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 17.0, 17.5, 19.9, 53.5, 54.7, 56.6, 64.8, 73.5, 114.0, 126.9, 127.4, 128.4, 140.8, 153.2, 167.9, 168.3 ppm. GC-MS (70 eV): *m*/*z* (%) = 330 (2) [M]$^+$, 271 (25), 184 (42), 168 (100), 152 (68), 105 (33), 77 (10). IR ($CHCl_3$): $\tilde{\nu}$ = 3031, 2983, 2932, 2875, 1747, 1455, 1377, 1306 cm^{-1}. $[\alpha]_D^{22}$ = +35.6 (*c* = 0.007, $CHCl_3$). HRMS: calcd. for $C_{18}H_{23}N_2O_2S$ 331.14819; found 331.14815.

16b: Yield: 96 mg (29%), oil. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.31 (d, *J* = 6.4 Hz, 3 H), 1.79 (d, *J* = 7.1 Hz, 3 H), 2.39 (s, 3 H), 3.30–3.37 (m, 4 H), 3.72 (dd, *J* = 2.2, 6.4 Hz, 1 H), 4.52 (q, *J* = 7.1 Hz, 1 H), 4.69 (d, *J* = 2.2 Hz, 1 H), 6.80 (s, 1 H), 7.20–7.26 (m, 5 H) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 16.2, 16.9, 20.0, 53.4, 54.8, 56.6, 63.9, 73.3, 114.1, 127.0, 127.5, 128.4, 140.8, 153.0, 167.5, 168.7 ppm. GC-MS (70 eV): *m*/*z* (%) = 330 (2) [M]$^+$, 271 (23), 184 (21), 168 (100), 152 (61), 152 (50), 105 (41), 77 (12). IR ($CHCl_3$): $\tilde{\nu}$ = 3031, 2983, 2932, 2875, 1747, 1455, 1377, 1306 cm^{-1}. $[\alpha]_D^{22}$ = +14.3 (*c* = 0.006, $CHCl_3$). HRMS: calcd. for $C_{18}H_{23}N_2O_2S$ 331.14819; found 331.14812.

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