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Synthesis of (3,4) β-Methylenecepham and (3,4) β-Methylenecarbacepham Via Intramolecular Carbene Addition to Double Bond

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Abstract—A series of new (3,4) β-methylenecepham and carbacepham analogues were synthesised as potential antibacterial agents. The key step of the synthesis included presumed generation of the carbene species from the oxalimide substrate effected by triethylphosphite and its intramolecular addition to the double bond. The stereochemistry of the tricyclic system has been elucidated by NMR and X-ray crystallography. In preliminary screening, two of the synthesised compounds exhibited modest antibacterial activity at 1.5–2.0 mg/mL against a number of bacterial strains.

Introduction

For nearly 50 years, β-lactam antibiotics have proven to be of enormous importance for treatment of bacterial diseases. Many structural modifications of the typical nuclei were prepared, their therapeutic performance elucidated and conclusions drawn about the factors influencing the antibacterial action. As part of this effort, we present a novel, simple method for the construction of tricyclic compounds structurally related to cephems, namely (3,4) β-methylenecepham and (3,4) β-methylenecarbacepham.

There have been a few reports describing synthesis and chemistry of (2,3) α- and β-methylenepenams.[1,2] β-Methylene isomer was significantly less biologically active than the penam analogue, while the α-isomer exhibited much higher antibacterial potency and against selected bacterial strains could be compared to penicillin G. Thus it was argued that stereochemistry of the tricyclic system is crucial for the antibacterial properties. Similar conclusions have been drawn from the analysis of β-lactamase inhibiting properties of (2,3)-methylene analogues of sulbactam.[3,4] In the study related to olivanic acids, (2,3) α- and β-methylenecarbapenam compounds have been synthesized and their cyclopropane stereochemistry assigned, but no antibacterial or β-lactamase inhibiting properties were assessed.[5–8]

Much less attention has been given to (3,4)-methylenecephams. Long[9] has reported that cyclopropanecepham (**I**) (Fig. 1) with 7-acylamido substituent and typical *cis* configuration of β-lactam protons lacks antibacterial activity nor do related oxacephams bearing a dichlorosubtituted cyclopropane.[10] On the other hand, (2,3) α- and β-methylenecephams (**II**) in a standard disk assay tested active at 2.0 mg/mL against a number of typical bacterial strains.[11]

Syntheses of the described cyclopropane structures have comprised relatively long multistep procedures. The penam analogues were prepared from penicillin sulfoxide via azetidinone disulfides, and 2β-halomethylpenicillins through their intramolecular cyclisation.[2,4] Carbapenam[5–7] and cepham[11] compounds were formed upon thermolysis of appropriate tricyclic pyrazoline esters prepared from available azetidinone starting materials in at least 10 steps. Oxa and carbacephams were obtained in a series of reactions involving palladium catalysed ene-halogenocyclisation to form γ-iodoketones or esters and their 1,3 elimination to yield cyclopropane ring.[12,13] Similar iodine substituted substrate obtained in laborious transformations of penicillin G served for the synthesis of **I**.[9]

In view of these findings, we have developed synthetic strategy to make target tricyclic molecules, which are hybrids of thienamycin related antibiotics and cephalosporins, that is they have a hydroxyethyl group and trans proton configuration of the β-lactam ring, which is fused with the six-membered ring and the cyclopropane.

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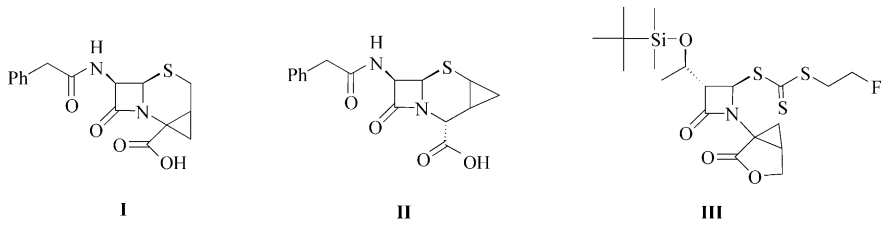
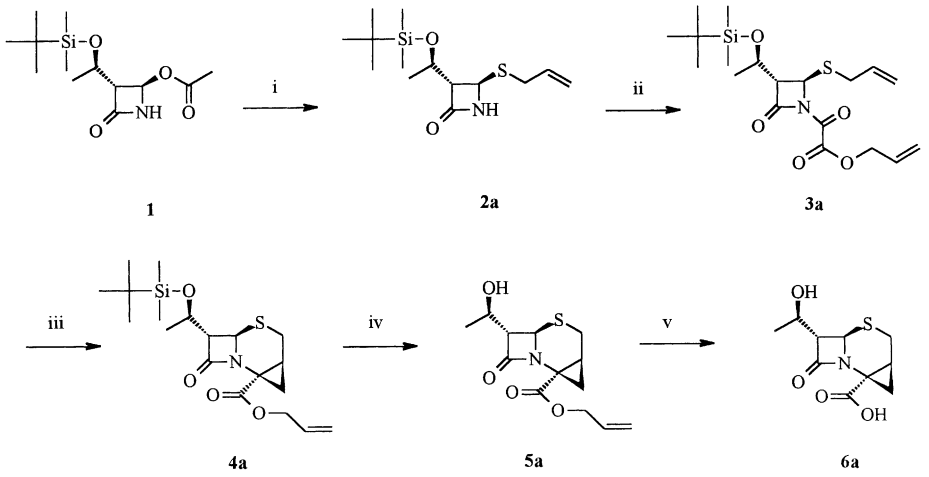


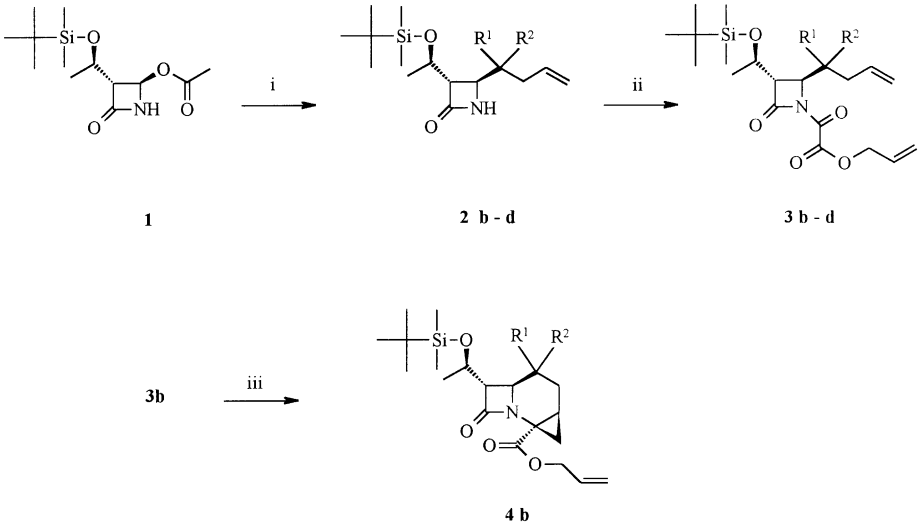
Figure 1. Structures of compounds **I–III**.

Chemistry

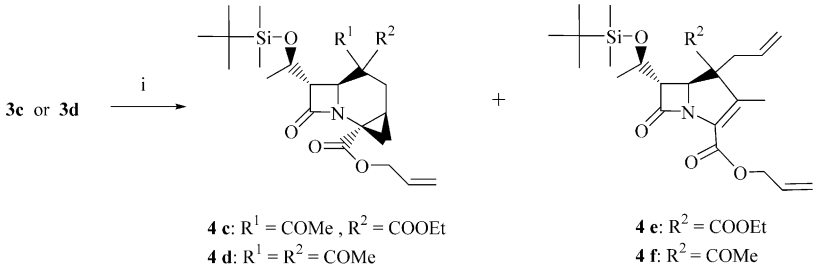
To synthesise target compounds (3*R*,4*R*)-3-[(*R*)-1-*tert*-butyldimethylsilyloxyethyl)-4-acetoxyazetidin-2-one (**1**) was used as the starting material. Substitution of the acetyl group using sodium hydride generated anions of appropriate allyl derivatives (allyl mercaptan, 2-allylmalonic acid diethyl ester, 2-acetylpent-4-enoic acid ethyl ester, 3-allylpentane-2,4-dione) provided more stable *trans* substituted azetidinones (**2a–d**) (Schemes 1 and 2). Their reaction with allyl chloro-oxalate, afforded the expected oxalimides (**3a–d**) in overall yield of 55–67% from (**1**). Compounds **3a–d** were cyclised in the presence of triethylphosphite in refluxing xylene. Under these conditions oxalimide substrates bearing carbonyl group at C-4 side chain of azetidinone form bicyclic compounds with unsaturated ring (penem synthesis being the most abundant example). In the mechanistic considerations of oxalimide cyclisation, a carbene intermediate has been postulated based, among other evidence, on the isolation of cyclopropane compounds of type **III**, which were formed by trapping of the carbene



Scheme 1. Reagents: (i) allyl mercaptan, NaH, EtOH, (0 °C/2 h, rt/18 h); (ii) allyl chlorooxalate, Et_3N, CH_2Cl_2 (−20 °C/1 h); (iii) $P(OEt)_3$, xylene (reflux/9 h); (iv) (*i*-Pr)$_2$EtN·3HF, AcOEt (50 °C/10 h); (v) $Pd(PPh_3)_4$, PPh_3, sodium 2-ethyl hexanoate, AcOEt,(rt/3 h) H_2O, H_3PO_4.



Scheme 2. Reagents: (i) (b) 2-allylmalonic acid diethyl ester or (c) 2-acetyl-pent-4-enoic acid ethyl ester or (d) 3-allylpentane-2,4-dione, NaH, THF (0 °C→rt/2 h); (ii) allyl chlorooxalate, Et_3N, CH_2Cl_2 (−20 °C/1 h); (iii) $P(OEt)_3$, xylene (reflux/9 h).

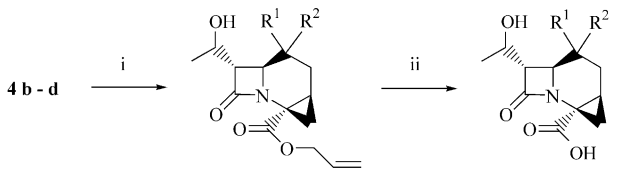


Scheme 3. Reagents: (i) $P(OEt)_3$, xylene (reflux/9 h).

by the double bond of the allyl ester group.[14–16] We have successfully applied this process to the synthesis of tricyclic cepham and carbacepham compounds and obtained tricyclic compounds **4a–d** from the oxalimides (**3a–d**) in yields of 25–50%. Reaction of oxalimides (**3c**,**d**) which had a suitable ketone group competitively produced both possible cyclised products: tricyclic compounds with cyklopropane ring (**4c**,**d**) and bicyclic carbapenems (**4e**,**f**) (Scheme 3). Cyclised compounds (**4a–d**) were subsequently deprotected: hydroxyl group in the presence of di-isopropyl ethyl amine trifluorohydride which afforded compounds **5a–d**; and carboxyl group in the presence of $Pd(PPh_3)_4$ (Scheme 4). Thus, the desired acids (**6a–d**) were obtained from (**1**) in five steps.

The present approach demonstrates a possible pathway to various types of interesting novel tricyclic cephams and carbacephams and provides additional evidence that carbene species play significant role in the cyclisation processes effected by trialkylphosphites.

Stereochemical assignments of the final compounds were made on the basis of 1-D and 2-D NMR spectroscopy and X-ray crystallography. The *trans* configuration of β-lactam ring protons is confirmed by their typical coupling constant of 2–2.5 Hz. The NOESY spectra of compound **6a** (Fig. 2) show correlation, between the 3-CH proton and the 5-CH proton. However, there is no correlation between either of 3-CH protons and the protons of the β-lactam ring (7-CH or 8-CH), which previously gave grounds for stereochemical assignments made for similar carbapenam tricyclic compounds.[7] Thus, to unambiguously assign the configuration of cyclopropane ring the X-ray crystal structure of **6a** was measured (Fig. 3).[17] It provides conclusive evidence for the syn-fusion of rings that is both β-lactam and cyclopropyl rings are located above



Scheme 4. Reagents: (i) $(i\text{-Pr})_2EtN{\cdot}3HF$, anisole (50 °C/10 h); (ii) $Pd(PPh_3)_4$, PPh_3, sodium 2-ethyl hexanoate, AcOEt, (rt/3 h) H_2O, H_3PO_4.

the plane of the six-membered ring. As other synthesised molecules (**6b–d**) exhibit very similar pattern of cyclopropyl protons in ^1H NMR spectra as **6a** we think the X-ray findings for the latter molecule are also valid for **6b–d** meaning they are all syn-fused tricyclic structures.

Antibacterial Activity

The β-lactam compounds synthesized were tested for in vitro antibacterial activity against a panel of susceptible and resistant Gram-positive and Gram-negative organisms (Agar Diffusion Well Method). In a standard disk assay test acids **6a** and **6d** at 1.5–2.0 mg/mL exhibited activity against *Escherichia coli* (β-lactam susceptible, cephalosporin susceptible ampicyllin resistant) *Klebsiella pneumoniae* (cephalosporin susceptible, ampicyllin resistant*) Providencia rettgeri* (β-lactam susceptible), *Morganella morgani* (ampicyllin and II generation cephalosporin resistant), *Staphylococcus aureus* (methycillin resistant). Of the two compouds **6d** consistently showed slightly better activity. Acids **6b** and **6c** that is compounds having an ethyl ester group or groups at C-6 exhibited no activity against the panel of bacteria tested.

In conclusion, we have synthesised a series of syn-fused tricyclic β-lactam compounds related to cephams amd carbacephams using novel synthetic methodology of intramolecular carbene addition to double bond and evaluated their structure, conformation and biological activity.

Experimental

General

Solvents were reagent grade and were obtained from POCH Gliwice Poland Company. 3-allylpentane-2,4-dione, 2-acetyl-pent-4-enoic acid ethyl ester, allyl chloro-oxalate, sodium 2-ethyl hexanoate, palladium tetrakis triphenylphosphine and di-i-propylethyl amine trifluorohydride were synthesized according to literature procedures. Azetidinone (**1**) was purchased from Kaneka Co., other reagents and chemicals were purchased from Aldrich or Fluka Chemical Companies.

Melting points are uncorrected. NMR spectra were recorded with Mercury 400 spectrometer. Chemical shifts are expressed in ppm, coupling constants are expressed in Hz, LSIMS and EI mass spectra were

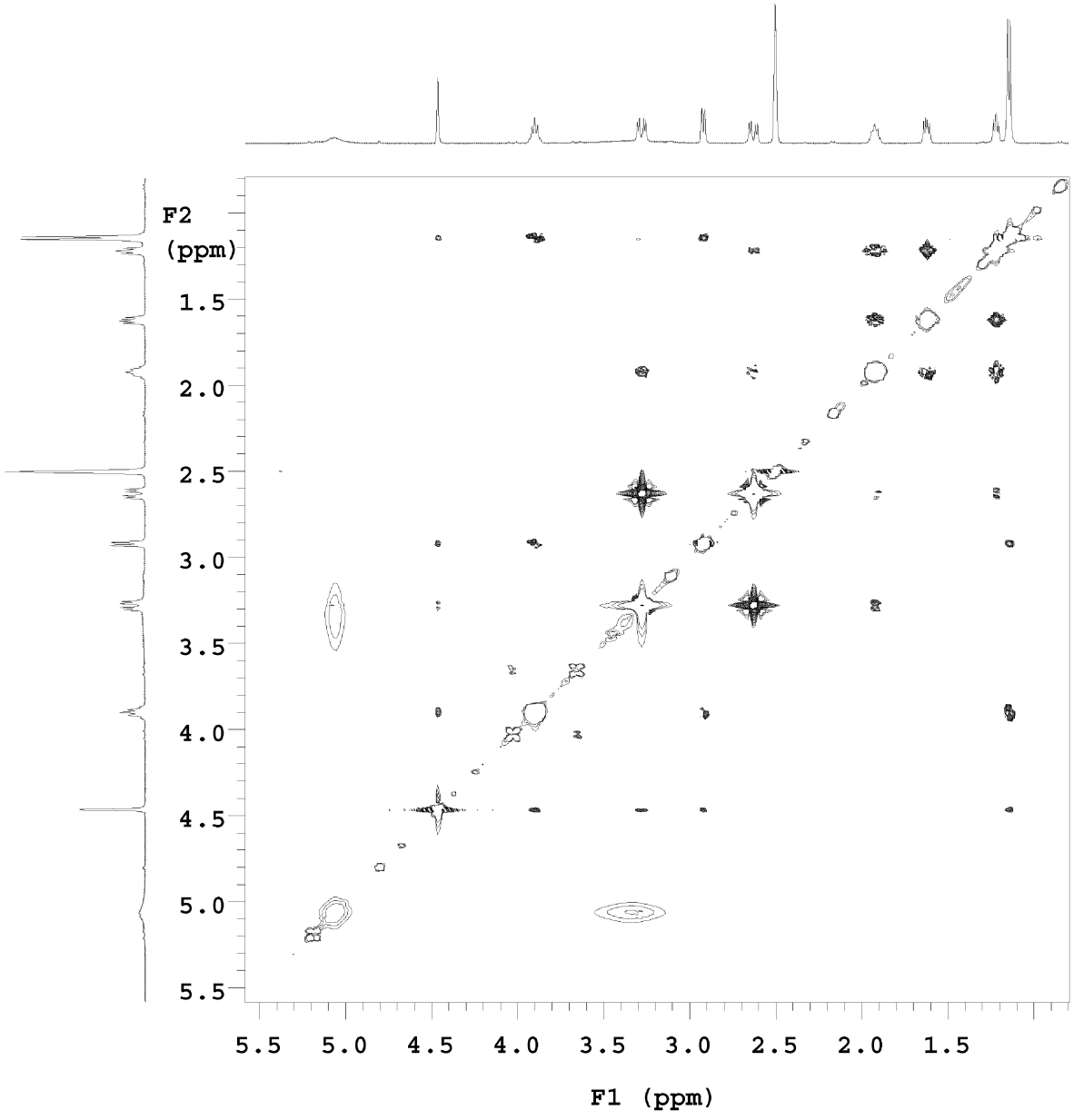


Figure 2. 2-D NOESY of compound **6a**.

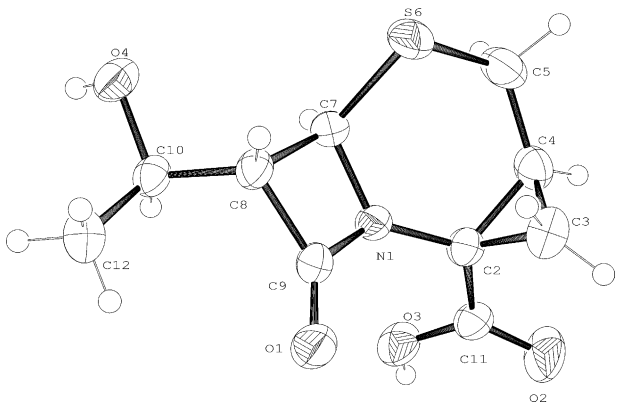


Figure 3. X-ray crystal structure of compound **6a**.

obtained on MASPEC II system. Optical rotations were measured on a Jasco DIP-360 digital polarimeter. Column chromatography was performed on Merck silica gel 60 (230–400 mesh)

(3*S*,4*R*)-4-Allylsulfanyl-3-[(*R*)-1-*tert*-butyldimethylsilyloxyethyl]-azetidin-2-one (2a). Sodium hydride (60% suspension in mineral oil, 6.0 g 0.15 mol, washed with hexane) was added in portions to ethanol (150 mL) precooled to 0 °C and allyl mercaptan (9.3 g, 0.12 mol) was added dropwise to the mixture maintaining temperature at 0 °C. To the above the solution of (3*R*,4*R*)-3 - [(*R*) - 1 - *tert* - butyldimethylsilyloxyethyl) - 4 - acetoxyazetidin-2-one (**1**) (28.7 g, 0.1 mol) in ethanol (50 mL) was added dropwise and the mixture was stirred at 0 °C for 2 h, warmed up to ambient temperature and left

overnight. The solvent was evaporated under reduced pressure and the resultant oil was partitioned between water (200 mL) and ethyl acetate (200 mL). The water layer was twice extracted with ethyl acetate. (2×30 mL) The combined organic extracts were dried over $MgSO_4$ and concentrated to give crude product **2a** (29.2 g) as oil, which was without purification subjected to acylation with allyl chloro-oxalate. A sample for analytical purposes was purified by column chromatography on silica gel (9:1 *n*-hexane–AcOEt).

^{1}H NMR ($CDCl_3$) δ 0.065 (s, 3H, $SiCH_3$), 0.076 (s, 3H, $SiCH_3$), 0.876 (s, 9H, *t*-Bu), 1.226 (d, J = 6.2 Hz, 3H, CH_3), 3.138 (ddd, J = 3.5, 2.4, 0.9 Hz; 1H, 3-CH), 3.258 (ddt, J = 14.1, 6.4 Hz, 1.3 Hz; 1H, SCH_2), 3.314 (ddt, J = 14.1, 7.5, 1.1 Hz; 1H, SCH_2), 4.245 (dq, J = 6.2, 3.5 Hz; 1H, $OC\underline{H}CH_3$) 4.827 (d, J = 2.4 Hz; 1H, 4-CH), 5.138 (dq, J = 10.1, 1.3 Hz; 1H, H_2C=), 5.220 (dq, J = 17.0, 1.3 Hz; 1H, H_2C=), 5.891 (ddt, J = 17.0, 10.1, 6.6 Hz; 1H, H_2C=C$\underline{H}$), 5.995 (br s, 1H, NH).

^{13}C NMR ($CDCl_3$) −5.12, −4.31, 17.92, 22.32, 25.68, 34.29, 54.13, 64.13, 66.20, 117.51, 134.92, 167.09.

MS HR (LSIMS) for $C_{14}H_{27}O_2NSiS$ $(M+Na)^+$, found 324.14246, calcd 324.14295.

(3*S*,4*S*)-4-(1,l-Dietoxycarbonyl-but-3-enyl)-3-[(*R*)-1-*tert*-butyldimethylsilyloxyethyl]-azetidin-2-one (2b). Sodium hydride (60% suspension in mineral oil, 4.0 g, 0.10 mol, washed with hexane) was suspended in tetrahydrofurane (200 mL) precooled to 0 °C and 2-allylmalonic acid diethylester (17.9 g, 0.09 mol) was added dropwise to the mixture maintaining temperature at 10 °C. To the above, the solution of (**1**) (23.2 g, 0.08 mol) in THF (80 mL) was added dropwise and the mixture was stirred at rt for 2 h. The solvent was evaporated under reduced pressure and the resultant oil was partitioned between water (100 mL) and ethyl acetate (100 mL). The organic extract was dried over $MgSO_4$ and concentrated in vacuo. The crude product **2b** (33.2 g) was subjected without purification to acylation with allyl chloro-oxalate.

A sample for analytical purposes was purified by column chromatography on silica gel (3:1 *n*-hexane–AcOEt).

^{1}H NMR ($CDCl_3$) δ 0.070 (s, 3H, $SiCH_3$), 0.073 (s, 3H, $SiCH_3$), 0.880 (s, 9H, *t*-Bu), 1.188 (d, J = 6.4 Hz, 3H, CH_3), 1.253 (t, J = 7.1 Hz, 3H, $C\overline{H_3}CH_2$), 1.257 (t, J = 7.1 Hz, 3H, $C\overline{H_3}CH_2$), 2.612 (ddt, J = 14.5, 6.6, 1.3 Hz; 1H, $CC\underline{H_2}C\overline{H}$=), 2.736 (ddt, J = 14.5, 7.9, 1.1 Hz; 1H, $CC\underline{H_2}CH$=), 3.071 (ddd, J = 3.3, 2.2, 1.3 Hz; 1H, 3-CH), 4.186–4.261 (m, 6H, $CH_3C\overline{H_2}$, $OC\underline{H}CH_3$, 4-CH), 5.130 (dq, J = 8.6, 1.5 Hz; 1H, $\overline{H_2}C$=), 5.151 (dq, J = 13.7, 1.5 Hz; 1H, H_2C=), 5.779 (ddt, J = 17.0, 10.1, 6.8 Hz; 1H, H_2C=C$\underline{H}$), 6.002 (br s, 1H, NH).

MS HR (LSIMS) $C_{21}H_{37}O_6NSi$ for $(M+H)^+$ found 428.24712 calcd 428.24683.

According to the same procedure, compounds **2c** and **d** were prepared.

(3*S*,4*S*)-4-(1-acetyl,1-etoxycarbonyl-but-3-enyl)-3-[(*R*)-1-*tert*-butyldimethyl-silyloxy-ethyl]-azetidin-2-one (2c). From **1**, (11.5 g, 0.04 mol) and 2-acetyl-pent-4-enoic acid ethyl ester (7.0 g, 0.045 mol). Crude product **2c** (15.8 g) was subjected without purification to acylation with allyl chloro-oxalate.

A sample for analytical purposes was purified by chromatography on silica gel (3:1 *n*-hexane–AcOEt) giving **2c** as two diastereoisomers:

^{1}H NMR ($CDCl_3$) δ 0.063 (s, 3H, $SiCH_3$), 0.068 (s, 6H, $SiCH_3$), 0.072 (s, 3H, $SiCH_3$), 0.876 (s, 9H, *t*-Bu), 0.882 (s, 9H, *t*-Bu), 1.152 (d, J = 6.4 Hz, 3H, CH_3), 1.200 (d, J = 6.4 Hz, 3H, CH_3), 1.273 (t, J = 7.2 Hz, 3H, $C\overline{H_3}CH_2$), 1.309 (t, J = 7.2 Hz, 3H, $C\overline{H_3}CH_2$), 2.169 (s, 3$\overline{H}$, CH_3C=O), 2.186 (s, 3H, CH_3C=$\overline{O}$), 2.566–2.685 (m, 4H, $CC\underline{H_2}CH$=), 2.964–2.300 (m, 2H, 3-CH), 4.192–4.300 (m, 4H, $OC\underline{H}CH_3$, 4-CH), 5.113–5.193 (m, 4H, H_2C=) 5.640–5.777 (m, 2H, H_2C=C$\underline{H}$) 5.855 (br s, 1H, NH), 5.964 (br s 1H, NH).

^{13}C NMR −4.81, −4.38, 13.95, 14.06, 17.93, 22.44, 22.85, 25.71, 25.78, 28.02, 29.56, 35.55, 51.20, 51.52, 60.29, 60.42, 61.91, 62.06, 64.48, 64.90. 65.18, 119.65, 131.44, 132.13, 167.46, 168.00, 169.82, 170.73, 204.06, 204.34.

MS HR (LSIMS) $C_{20}H_{35}O_5NSi$ for $(M+H)^+$, found 398.23481, calcd 398.23628.

(3*S*,4*S*)-4-(1,1-Diacetyl-but-3-enyl)-3-[(*R*)-1-*tert*-butyldimethylsilyloxyethyl]-azetidin-2-one (2d). From (**1**) (16.7 g, 0.058 mol) and 3-allylpentane-2,4-dione (9.1 g, 0.065 mol) The crude product was purified by column chromatography on silica gel (3:1 *n*-hexane–AcOEt) giving (**2d**) (9.8 g, 0.029 mol, 44%).

^{1}H NMR ($CDCl_3$) δ 0.050 (s, 3H, $SiCH_3$), 0.056 (s, 3H, $SiCH_3$), 0.866 (s, 9H, *t*-Bu), 1.163 (d, J = 6.4 Hz, 3H, CH_3), 2.176 (s, 3H, CH_3C=O), 2.181 (s, 3H, CH_3C=O), 2.787 (dd, J = 3.5, 2.4 Hz, 1H, 3-CH), 2.624 (ddt, J = 15.6, 6.4, 1.5 Hz, 1H, $CC\underline{H_2}CH$=), 2.729 (ddt, J = 15.6, 8.0, 1.1 Hz, 1H, $CC\overline{H_2}CH$=), 4.215 (dq, J = 6.4, 3.5 Hz; 1H, $OC\underline{H}CH_3$), 4.2$\overline{18}$ (d, J = 2.4 Hz; 1H, 4-CH), 5.138 (dq, J = 10.1, 1.3 Hz, 1H, H_2C=), 5.181 (dq, J = 16.8, 1.3 Hz, 1H, H_2C=), 5.623 (ddt, J = 16.8, 10.1, 6.6 Hz; 1H, H_2C=C$\underline{H}$), 6.028 (br s, 1H, NH).

^{13}C NMR ($CDCl_3$) −4.82, −4.40, 17.94, 22.81, 25.67, 25.75, 25.83, 28.42, 30.30, 34.70, 51.28, 60.37, 64.87, 71.15, 119.87, 131.64, 167.80, 205.16, 206.03.

MS HR (LSIMS) for $C_{19}H_{33}O_4NSi$ $(M+Na)^+$, found 390.20905, calcd 390.20766.

(3*S*,4*R*)-4-Allylsulfanyl-3-[(*R*)-1-*tert*-butyldimethylsilyloxyethyl]-1-[(1-allyloxy)-2-methyl-1-oxo]-azetidin-2-one (3a). Crude (**2a**) (29.2 g) was dissolved in dichloromethane (300 mL) and the solution was cooled to −20 °C. Triethylamine (21.8 mL, 15.8 g, 0.16 mol) was added and allyl chloro-oxalate (21.8 g, 0.15 mol) was added dropwise maintaining temperature at −20 °C. The mixture was stirred for 1 h and warmed up to

ambient temperature. Water (100 mL) was added and the layers were separated. Water layer was extracted with additional methylene chloride (30 mL), organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (10:1 *n*-hexane–AcOEt) giving **3a** as an oil (22.7 g, 0.055 mol, 55% yield from **1**).

^{1}H NMR ($CDCl_3$) δ 0.012 (s, 3H, $SiCH_3$), 0.064 (s, 3H, $SiCH_3$), 0.833 (s, 9H, *t*-Bu), 1.210 (d, $J=6.4$ Hz, 3H, CH_3), 3.233 (dd, $J=3.8$, 2.5 Hz; 1H, 3-CH), 3.351 (ddt, $J=13.7$, 5.3, 1.5 Hz; 1H, $SCH_2CH=$), 3.820 (dd, $J=13.7$, 9.3 Hz; 1H, $SCH_2CH=$), 4.339 (dq, $J=6.4$, 2.4 Hz; 1H, $OCHCH_3$), 4.811 (ddt, $J=6.2$, 4.7 1.3 Hz; 2H, $OCH_2CH=$), 5.234 (dq, $J=10.0$, 1.1 Hz, 1H, $H_2C=CHCH_2S$), 5.315 (dq, $J=17.0$, 1.0 Hz; 1H, $H_2C=CHCH_2S$), 5.331–5.472 (m, 2H, $H_2C=CHCH_2O$), 5.407 (d, $J=3.8$ Hz, 1H, 4-CH), 5.845 (ddt, $J=17.0$, 10.0, 5.3 Hz; 1H, $H_2C=CHCH_2S$), 5.973 (ddt, $J=17.2$, 10.4, 6.0 Hz, 1H, $H_2C=CHCH_2O$).

^{13}C NMR ($CDCl_3$) δ −4.39, −3.66, 8.56, 17.71, 17.94, 21.75, 25.59, 35.95, 46.00, 64.01, 64.45, 67.35, 67.50, 67.85, 120.31, 120.49, 130.25, 130.37, 157.33, 158.15, 158.31.

According to the same procedure, compounds **3b–d** were prepared.

(3*S*,4*S*)-4-(1,l-Dietoxycarbonyl-but-3-enyl)-3-[(*R*)-1-*tert*-butyldimethylsilyloxyethyl]-1-[(1-allyloxy)-2-methyl-1-oxo]-azetidin-2-one (3b). From crude **2b** (33.2 g). Product was purified by column chromatography on silica gel (5:1 *n*-hexane–AcOEt) giving (**3b**) (27.6 g, 0.051 mol, 64% yield from **1**).

^{1}H NMR ($CDCl_3$) δ 0.075 (s, 6H, $SiCH_3$), 0.849 (s, 9H, *t*-Bu), 1.290 (d, $J=6.4$ Hz, 3H, CH_3), 1.271 (t, $J=7.1$ Hz; 3H, CH_3CH_2), 1.275 (t, $J=7.1$ Hz; 3H, CH_3CH_2), 2.756 (ddt, $J=14.1$, 7.3, 1.1 Hz; 1H, $CCH_2CH=$), 2.960 (ddt, $J=14.1$, 7.3, 1.1 Hz; 1H, $CCH_2CH=$), 3.540 (t, $J=3.0$ Hz; 1H, 3-CH), 4.189–4.252 (m, 4H, CH_3CH_2) 4.357 (dq, $J=6.4$, 2.9 Hz; 1H, $OCHCH_3$), 4.760–4.788 (m, 2H $OCH_2CH=$), 4.837 (d, $J=2.9$ Hz, 1H, 4-CH), 5.168 (dq, $J=10.0$, 1.8 Hz; 1H, $H_2C=CHCH_2S$), 5.257 (dq, $J=17.0$, 1.8 Hz; 1H, $H_2C=CHCH_2S$), 5.303 (dq, $J=10.3$, 1.3 Hz; 1H, $H_2C=CHCH_2O$), 5.393 (dq, $J=17.1$, 1.3 Hz; 1H, $H_2C=CHCH_2O$), 5.812 (ddt, $J=17.0$, 10.0, 7.3 Hz; 1H, $H_2C=CHCH_2S$), 5.945 (ddt, $J=17.1$, 10.3, 6.2 Hz, 1H, $H_2C=CHCH_2O$).

^{13}C NMR ($CDCl_3$) −5.20, −4.53, 13.83, 13.92, 17.69, 22.69, 25.59, 38.19, 55.25, 59.52,61.88, 61.92, 62.14, 65.67, 67.58, 119.99, 120.10, 130.51, 132.00, 156.05, 159.88, 166.16, 168.10, 168.45.

MS HR (LSIMS) $C_{26}H_{41}O_9NSi$ for $(M+H)^+$, found 540.26077, calcd 540.26289.

(3*S*,4*S*)-4-(1-acetyl,1-etoxycarbonyl-but-3-enyl)-3-[(*R*)-1-*tert* - butyldimethyl - silyloxyethyl] - 1 - [(1 - allyloxy) - 2 - methyl-1-oxo]-azetidin-2-one (3c). From crude **2c** (15.8 g). Product was purified by column chromatography on silica gel (5:1 *n*-hexane–AcOEt) giving (**3c**) as two diastereoisomers (14.0 g, 0.028 mol, 67% yield from **1**).

^{1}H NMR ($CDCl_3$) δ −0.024 (s, 3H, $SiCH_3$), 0.014 (s, 3H, $SiCH_3$), 0.054 (s, 6H, $SiCH_3$), 0.064 (s, 3H, $SiCH_3$), 0.823 (s, 9H, *t*-Bu), 0.834 (s, 9H, *t*-Bu), 1.261 (d, $J=6.4$ Hz, 3H, CH_3), 1.283 (t, $J=7.1$ Hz, 3H, CH_3CH_2), 1.292 (t, $J=7.1$ Hz, 3H, CH_3CH_2), 1.306 (d, $J=6.4$ Hz, 3H, CH_3), 2.202 (s, 3H, $CH_3C=O$), 2.234 (s, 3H, $CH_3C=O$), 2.466 (dd, $J=13.7$, 8.4 Hz; 1H, $CCH_2CH=$), 2.733 (ddt, $J=14.5$, 7.0, 1.1 Hz; 1H, $CCH_2CH=$), 2.783 (ddt, $J=13.7$, 6.0, 1.4 Hz; 1H, $CCH_2CH=$), 3.078 (ddt, $J=14.4$, 7.7, 1.0 Hz; 1H, $CCH_2CH=$), 3.386 (t, $J=3.3$ Hz; 1H, 3-CH), 3.466 (t, $J=2.6$ 1H, 3-CH Hz), 4.212–4.250 (m, 6H, CH_3CH_2, $OCHCH_3$), 4.803 (d, $J=3.1$ Hz, 1H, 4-CH), 4.869 (d, $J=3.3$ Hz, 1H, 4-CH), 4.739–4.773 (m, 4H, $OCH_2CH=$), 5.110–5.290 (m, 4H, $H_2C=CHCH_2C$), 5.286 (dq, $J=10.2$, 1.0 Hz, 1H, $H_2C=CHCH_2O$), 5.373 (dq, $J=17.2$, 1.0 Hz, 1H, $H_2C=CHCH_2O$), 5.589–5.693 (m, 1H, $H_2C=CHCH_2C$), 5.703–5.808 (m, 1H, $H_2C=CHCH_2C$), 5.872–5.975 (m, 2H, $H_2C=CHCH_2O$).

^{13}C NMR ($CDCl_3$) −5.22, −5.12, −4.52, −4.46, 13.81, 13.84, 17.69, 17.72, 22.13, 22.44, 25.60, 25.62, 28.14, 29.41, 37.34, 38.17, 54.95, 56.41, 61.24, 61.97, 62.32, 62.44, 63.98, 65.46, 67.19, 120.05, 120.34, 130.46, 131.48, 155.98, 159.86, 165.30, 169.57, 202.88, 203.36.

MS HR (LSIMS) $C_{25}H_{39}O_8NSi$ for $(M+H)^+$, found 510.25221, calcd 510.25232.

(3*S*,4*S*)-4-(1,1-Diacetyl-but-3-enyl)-3-[(*R*)-1-*tert*-butyldimethylsilyloxyethyl]-1-[(1-allyloxy)-2-methyl-1-oxo]-azetidin-2-one (3d). From crude **2d** (9.6 g). Product was purified by column chromatography on silica gel (4:1 *n*-hexane–AcOEt) giving **3d** (7.47 g, 0.016 mol, 60% yield from **1**).

^{1}H NMR ($CDCl_3$) δ 0.006 (s, 3H, $SiCH_3$), 0.084 (s, 3H, $SiCH_3$), 0.852 (s, 9H, *t*-Bu), 1.345 (d, $J=6.4$ Hz, 3H, CH_3), 2.227 (s, 3H, $CH_3C=O$), 2.296 (s, 3H, $CH_3C=O$), 2.619 (ddt, $J=14.6$, 8.3, 1.0 Hz; 1H, $CCH_2CH=$), 3.138 (ddt, $J=14.6$, 6.1, 1.6 Hz; 1H, $CCH_2CH=$), 3.366 (dd, $J=3.2$, 2.5 Hz; 1H, 3-CH), 4.372 (dq, $J=6.4$, 2.4 Hz; 1H, $OCHCH_3$), 4.883 (d, $J=3.2$ Hz, 1H, 4-CH), 4.786 (dq, $J=6.0$, 1.5 Hz; 1H, $OCH_2CH=$), 5.172 (dq, $J=10.1$, 1.0 Hz; 1H, $H_2C=CHCH_2C$), 5.283 (dq, $J=17.1$, 1.2 Hz; 1H, $H_2C=CHCH_2C$), 5.316 (dq, $J=10.4$, 1.2 Hz; 1H, $H_2C=CHCH_2O$), 5.395 (dq, $J=17.2$, 1.3 Hz; 1H, $H_2C=CHCH_2O$), 5.623 (ddt, $J=17.1$, 10.1, 6.1 Hz; 1H, $H_2C=CHCH_2C$), 5.942 (ddt, $J=17.2$, 10.4, 6.0 Hz, 1H, $H_2C=CHCH_2O$).

^{13}C NMR −4.91, −4.50, 17.96, 22.83, 25.76, 28.44, 30.31, 34.70, 51.29, 60.39, 64.89, 71.18, 119.89, 131.65, 167.80, 205.18, 206.05.

MS HR (LSIMS) for $C_{24}H_{37}O_7NSi$ dla $(M+H)^+$, found 480.24212, calcd 480.24176.

(2*R*,7*R*,8*S*)-9-oxo-8$_t$-[(*R*)-1-*tert*-Butyldimethylsilyloxyethyl]-6-thia-1-azatricyclo-[5.2.0.0^{2,4}]-nonane-2-carboxylic acid allyl ester (4a). To the solution of **3a** (11.50 g, 27.8

mmol) in xylene (250 mL) was added triethylphosphite (9.23 g, 0.056 mol) and the mixture was heated at reflux for 9 h. The mixture was concentrated at reduced pressure and the residue was purified by column chromatography on silica gel (6:1 *n*-hexane–AcOEt) to give **4a** as an oil (4.58 g, 11.5 mmol, 41% yield).

^{1}H NMR ($CDCl_3$) δ 0.089 s (s, 3H, $SiCH_3$), 0.094 (s, 3H, $SiCH_3$), 0.895 (s, 9H, *t*-Bu), 1.240 (d, $J=6.1$ Hz, 3H, CH_3), 1.483 (dd, $J=7.1$ Hz, $J=5.5$ Hz, 1H, 3-CH), 1.824 (dd, $J=9.0$, 5.7 Hz, 1H, 3-CH), 2.041 (tt, $J=9.0$, 5.7 Hz, 1H, 4-CH), 2.497 (dd, $J=14.6$, 5.8 Hz; 1H, 5-CH), 3.022 (dd, $J=4.7$, 2.0 Hz; 1H, 8-CH), 3.211 (dd, $J=14.6$, 5.3 Hz; 1H, 5-CH), 4.217 (dq, $J=6.1$, 4.7 Hz; 1H, OC<u>H</u>CH_3), 4.578 (d, $J=1.8$ Hz; 1H, 7-CH), 4.635 (dq, $J=5.7$, 1.1 Hz; 2H, OC<u>H_2</u>CH=), 5.235 (dq, $J=10.4$, 2.5 Hz; 1H, <u>H_2</u>C=CH), 5.320 (dq, $J=17.2$, 1.5 Hz; 1H, <u>H_2</u>C=CH), 5.891 (ddt, $J=17.2$, 10.6, 5.7 Hz, 1H, H_2C=C<u>H</u>).

^{13}C NMR ($CDCl_3$) 17.95, 20.35, 22.56, 23.08, 24.91, 25.75, 34.63, 51.02, 64.90, 66.11, 68.35, 118.41, 131.75, 167.75, 170.30.

MS HR (LSIMS) for $C_{19}H_{31}O_4NSiS$ $(M+Na)^+$, found 420.16661, calcd 420.16408.

IR (film from $CHCl_3$) 2955, 2930, 2886, 1769, 1732, 1399, 1375, 1279, 1252, 1185, 1144, 837, 778.

According to the same procedure compounds **4b–f** were prepared.

(2*R*,7*S*,8*S*)-9-oxo-8$_t$-[(*R*)-1-*tert*-Butyldimethylsilyloxyethyl]-1-azatricyclo-[5.2.0.0^{2,4}]nonane-2,6,6-tricarboxylic acid, 2-allyl ester, 6,6-diethyl ester (4b). (5.2 g, 9.9 mmol, 52% yield) from (**3b**) (10.2 g, 18.9 mmol) (column chromatography conditions: silica gel, 2:1 *n*-hexane–AcOEt).

^{1}H NMR ($CDCl_3$) δ 0.082 (s, 3H, $SiCH_3$), 0.101 (s, 3H, $SiCH_3$), 0.925 (s, 9H, *t*-Bu), 1.051 (d, $J=6.2$ Hz, 3H, CH_3), 1.160 (dd, $J=14.8$, 8.8 Hz, 1H, 5-CH), 1.248 (t, $J=7.1$ Hz, 3H, C<u>H_3</u>CH_2), 1.259 (t, $J=7.1$ Hz, 3H, CH_3C<u>H_2</u>), 1.424 (t, $J=5.9$ Hz, 1H, 3-CH), 1.613 (tt, $J=8.8$, 6.2 Hz, 1H, 4-CH), 1.795 (dd, $J=8.8$, 5.7 Hz, 1H, 3-CH), 2.770 (t, $J=5.7$ Hz; 1H, 8-CH), 2.793 (dd, $J=14.9$, 6.8 Hz, 1H, 5-CH), 3.971 (dq, $J=11.0$, 7.1 Hz, 1H, CH_3C<u>H_2</u>), 4.20–4.26 (m, 1H, OC<u>H</u>CH_3), 4.236 (q, $J=7.1$ Hz, 2H, CH_3C<u>H_2</u>), 4.330 (dq, $J=11.0$, 7.1 Hz, 1H, CH_3C<u>H_2</u>), 4.575 (ddt, $J=13.2$, 5.8, 1.3 Hz; 1H, OC<u>H_2</u>CH=), 4.633 (d, $J=2.4$ Hz; 1H, 7-CH), 4.686 (ddt, $J=13.2$, 5.7, 1.5 Hz; 1H, OC<u>H_2</u>CH=), 5.231 (dq, $J=10.4$, 1.3 Hz; 1H, <u>H_2</u>C=CH), 5.346 (dq, $J=17.2$, 1.5; 1H, <u>H_2</u>C=CH), 5.87–5.98 (m, 1H, H_2C=C<u>H</u>).

^{13}C NMR ($CDCl_3$) δ −5.05, −4.58, 13.82, 14.02, 18.01, 21.94, 22.98, 23.22, 25.79, 28.67, 34.67, 50.56, 54.01, 55.80, 61.98, 62.08, 63.70, 66.06, 118.21, 132.06, 169.23, 169.29, 169.71, 170.79.

MS HR (LSIMS) $C_{26}H_{41}NO_8Si$ for $(M+Na)^+$, found 546.25049, calcd 546.24992.

IR (film from $CHCl_3$) 2980, 2957, 2931, 2857, 1170, 1732, 1447, 1399, 1375, 1283, 1268, 1256, 1186, 1148, 838, 778.

(2*R*,7*S*,8*S*)-9-oxo-8$_t$-[(*R*)-1-*tert*-Butyldimethylsilyloxyethyl]-6-acetyl-1-azatricyclo-[5.2.0.0^{2,4}]nonane-2,6-dicarboxylic acid, 2-allyl ester, 6-ethyl ester (4c). (3.44 g, 7.0 mmol, 25% yield) from **3c** (14.0 g, 27.5 mmol), also penem, **4e** is formed in this reaction. The products were separated by means of column chromatography on silica gel (6:1 *n*-hexane–AcOEt) R_f being 0.4 for **4c** and 0.6 for **4e** (TLC, Merck silica gel 60 F_{254}aluminum plates, 3:1 *n*-hexane–AcOEt).

^{1}H NMR ($CDCl_3$) δ 0.101 (s, 3H, $SiCH_3$), 0.115 (s, 3H, $SiCH_3$), 0.914 (s, 9H, *t*-Bu), 1.110 (dd, $J=14.8$, 8.8 Hz, 1H, 5-CH), 1.149 (d, $J=6.3$ Hz, 3H, CH_3), 1.277 (t, $J=7.1$ Hz, 3H, C<u>H_3</u>CH_2), 1.449 (t, $J=5.9$ Hz, 1H, 3-CH), 1.612 (tt, $J=8.8$, 6.2 Hz, 1H, 4-CH), 1.806 (dd, $J=8.7$, 5.8 Hz, 1H, 3-CH) 2.203 (s, 3H, CH_3C=O), 2.576 (dd, $J=5.6$, 2.3 Hz; 1H, 8-CH), 2.653 (dd, $J=14.9$, 6.6 Hz, 1H, 5-CH), 4.200 (quintet, $J=7.0$ Hz, 1H, OC<u>H</u>CH_3), 4.236 (q, $J=7.1$ Hz, 1H, CH_3C<u>H_2</u>), 4.286 (q, $J=7.1$ Hz, 1H, CH_3C<u>H_2</u>), 4.578 (ddt, $J=13.2$, 5.6, 1.5 Hz; 1H, OC<u>H_2</u>CH=), 4.612 (d, $J=2.2$ Hz; 1H, 7-CH), 4.677 (ddt, $J=13.2$, 5.6, 1.5 Hz; 1H, OC<u>H_2</u>CH=), 5.251 (dq, $J=10.4$, 1.4 Hz; 1H, <u>H_2</u>C=CH), 5.357 (dq, $J=17.2$, 1.5 Hz; 1H, <u>H_2</u>C=CH), 5.927 (ddt, $J=17.2$, 10.4, 5.7 Hz, 1H, H_2C=C<u>H</u>).

^{13}C NMR ($CDCl_3$) δ −4.70, −4.51, 14.00, 18.04, 22.91, 23.02, 23.46, 25.86, 28.10, 28.70, 34.56, 51.69, 59.66, 60.88, 62.34, 65.60, 65.99, 118.22, 131.94, 168.83, 170.60, 170.83, 202.20.

MS HR (LSIMS) for $C_{25}H_{39}NO_7Si$ $(M+Na)^+$, found 516.2388, calcd 516.2380.

IR (film from $CHCl_3$) 2983, 2957, 2933, 2859, 1810, 1755, 1738, 1712, 1371, 1343, 1253, 1204, 1150, 839, 810.

(2*R*,7*S*,8*S*)-9-oxo-8$_t$-[(*R*)-1-*tert*-Butyldimethylsilyloxyethyl]-6,6-diacetyl-1-azatricyclo-[5.2.0.0^{2,4}]nonane-2-carboxylic acid allyl ester (4d). (3.30 g, 7.1 mmol, 49% yield) from **3c** (6.90g, 14.4 mmol). Also penem **4f** is formed in this reaction. The products were separated by means of column chromatography on silica gel (5:1 *n*-hexane–AcOEt) R_f being 0.07 for **4d** and 0.5 for **4f** (TLC, Merck silica gel 60 F_{254}aluminum plates, 3:1 *n*-hexane–AcOEt).

^{1}H NMR ($CDCl_3$) δ 0.110 (s, 3H, $SiCH_3$), 0.116 (s, 3H, $SiCH_3$), 0.908 (s, 9H, *t*-Bu), 1.149 (dd, $J=15.6$, 8.8 Hz, 1H, 5-H), 1.205 (d, $J=6.4$ Hz, 3H, CH_3), 1.453 (dd, $J=11.5$, 6.0 Hz, 1H, 3-H), 1.493 (tt, $J=8.8$, 6.2 Hz, 1H, 4-CH), 1.794 (dd, $J=8.2$, 5.5 Hz, 1H, 3-CH) 2.174 (s, 3H, CH_3C=O), 2.207 (s, 3H, CH_3C=O) 2.491 (dd, $J=6.6$, 2.4 Hz; 1H, 8-CH), 2.755 (ddd, $J=15.5$, 6.4, 0.7 Hz, 1H, 5-CH), 4.125 (ddt, $J=13.2$, 5.5, 1.4 Hz; 1H, OC<u>H_2</u>CH=), 4.209 (quintet, $J=6.4$ Hz, 1H, OC<u>H</u>CH_3), 4.558 (ddt, $J=13.2$, 5.5, 1.4 Hz; 1H, OC<u>H_2</u>CH=), 4.661 (d, $J=2.0$ Hz; 1H, 7-CH), 5.277 (dq, $J=10.4$, 1.3 Hz;

1H, $\underline{H_2}C{=}CH$), 5.392 (dq, $J=17.2$, 1.5 Hz; 1H, $\underline{H_2}C{=}CH$), 5.957 (ddt, $J=17.2$, 10.4, 5.7 Hz, 1H, $H_2C{=}C\underline{H}$).

^{13}C NMR ($CDCl_3$) −4.72, −4.38, 18.06, 22.84, 22.87, 23.06, 25.88, 26.89, 27.27, 29.22, 34.56, 50.83, 59.76, 66.11, 66.49, 67.99, 118.26, 131.87, 168.68, 170.43, 203.33, 203.50.

MS HR (LSIMS) for $C_{24}H_{37}N\,O_6Si\,(M+Na)^+$, found 486.22770, calcd 486.22879.

IR (film from $CHCl_3$) 2956, 2931, 2858, 1764, 1727, 1702, 1402, 1362, 1296, 1283, 1258, 1195, 1175, 1149, 836, 778.

(5*S*,6*S*)-4-allyl-7-oxo-8$_t$-[(*R*)-1-*tert*-Butyldimethylsilyloxyethyl]-3-methyl-1-azabicyclo[3.2.0]hept-2-ene-2,4-dicarboxylic acid, 2-allyl ester, 4-ethyl ester (4e). (4.45 g, 9.3 mmol, 33% yield) as two diastereoisomers from **3c** (14.0 g, 27.5 mmol).

^{1}H NMR ($CDCl_3$) δ 0.065 (s, 3H, $SiCH_3$), 0.070 (s, 3H, $SiCH_3$), 0.072 (s, 3H, $SiCH_3$), 0.076 (s, 3H, $SiCH_3$), 0.870 (s, 9H, *t*-Bu), 0.888 (s, 9H, *t*-Bu), 1.186 (d, $J=6.2$ Hz, 3H, CH_3), 1.243 (d, $J=6.2$ Hz, 3H, CH_3), 1.268 (t, $J=7.1$ Hz, 3H, CH_3CH_2), 1.298 (t, $J=7.0$ Hz, 3H, CH_3CH_2), 2.060 (s, 3H, 3-CCH_3), 2.107 (s, 3H, 3-CCH_3), 2.470 (ddt, $J=15.3$, 6.0, 1.6 Hz; 1H, $CC\underline{H_2}CH{=}$), 2.610 (ddt, $J=14.7$, 6.5, 1.5 Hz, 1H, $CC\underline{H_2}CH{=}$), 2.750 (dd, $J=14.6$, 7.7 Hz, 1H, $CC\underline{H_2}CH{=}$), 2.764 (ddt, $J=15.3$, 7.3, 1.2 Hz; 1H, $CC\underline{H_2}CH{=}$), 3.013 (dd, $J=5.2$, 3.0 Hz, 1H, 6-CH), 3.358 (dd, $J=6.3$, 2.9 Hz, 1H, 6-CH), 4.095 (d, $J=3.0$ Hz, 1H, 5-CH), 4.205 (q, $J=7.1$ Hz, 1H, $CH_3C\underline{H_2}$), 4.211 (q, $J=7.1$ Hz, 1H, $CH_3C\underline{H_2}$), 4.234 (q, $J=7.1$ Hz, 1H, $CH_3C\underline{H_2}$), 4.239 (q, $J=7.1$ Hz, 1H, $CH_3C\underline{H_2}$), 4.611 (d, $J=2.9$ Hz; 1H, 5-CH), 4.700 (ddt, $J=13.5$, 5.6, 1.4 Hz; 1H. $OC\underline{H_2}CH{=}$), 4.703 (ddt, $J=13.6$, 5.5, 1.5 Hz, 1H, $OC\underline{H_2}CH{=}$), 4.774 (dd, $J=9.5$, 5.4 Hz; 1H, $OC\underline{H_2}CH{=}$), 4.783 (ddt, $J=13.7$, 5.4, 1.5 Hz, 1H, $OC\underline{H_2}CH{=}$), 4.80 (m, 2H, $OC\underline{H}CH_3$), 5.22 (m, 2H, $H_2C{=}CHCH_2C$), 5.142 (dq, $J=10.2$, 1.5 Hz; 1H, $\underline{H_2}C{=}CHCH_2C$), 5.165 (dq, $J=17.2$, 1.6 Hz; 1H, $\underline{H_2}C{=}CHCH_2C$), 5.250 (dq, $J=10.5$, 1.4 Hz, 1H, $\underline{H_2}C{=}CHCH_2O$), 5.259 (dq, $J=10.4$, 1.4 Hz; 1H, $\underline{H_2}C{=}CHCH_2O$), 5.440 (dq, $J=17.2$, 1.5 Hz; 1H, $\underline{H_2}C{=}CHCH_2O$), 5.445 (dq, $J=17.2$, 1.5 Hz, 1H, $\underline{H_2}C{=}CHCH_2O$), 5.664 (ddt, $J=17.7$, 10.2, 6.6 Hz, 1H, $H_2C{=}C\underline{H}CH_2C$), 5.670 (ddt $J=17.2$, 10.2, 6.2 Hz; 1H, $H_2C{=}C\underline{H}CH_2C$), 5.961 (ddt $J=17.2$, 10.4, 6.2 Hz; 1H, $H_2C{=}C\underline{H}CH_2O$), 5.967 (ddt, $J=17.2$, 10.6, 5.5 Hz, 1H, $H_2C{=}C\underline{H}CH_2O$).

^{13}C NMR ($CDCl_3$) δ −5.01, −4.34, 12.35, 14.14, 17.87, 22.58, 25.66, 25.70, 36.40, 58.67, 60.89, 61.86, 62.65, 65.65, 66.40, 118.39, 119.65, 128.41, 131.51, 132.23, 144.75, 161.04, 171.74, 173.05.

MS HR (LSIMS) for $C_{25}H_{39}O_6NSi\,(M+H)^+$, found 478.26306, calcd 478.262449.

IR (film from $CHCl_3$) 3452, 2956, 2932, 2858, 1736, 1446, 1368, 1254, 1215, 1100, 1051, 836, 778.

(5*S*,6*S*)-4-allyl-4-acetyl-7-oxo-8$_t$-[(*R*)-1-*tert*-Butyldimethylsilyloxyethyl]-3-methyl-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid allyl ester (4f). (1.92 g, 4.3 mmol, 30% yield) from **3d** (6.9g, 14.0 mmol). ^{1}H NMR ($CDCl_3$) δ 0.057 (s, 3H, $SiCH_3$), 0.070 (s, 3H, $SiCH_3$), 0.868 (s, 9H, *t*-Bu), 1.212 (d, $J=6.2$ Hz, 3H, CH_3), 2.015 (s, 3H, 3-CCH_3), 2 252 (s, 3H, $CH_3C{=}O$), 2.564 (ddt, $J=15.5$, 6.4, 1.6 Hz; 1H, $CC\underline{H_2}CH{=}$), 2.697 (ddt, $J=15.6$, 6.6, 1.4 Hz; 1H, $CC\underline{H_2}CH{=}$), 3.485 (dd, $J=6.9$, 3.0 Hz, 1H, 6-CH), 4.80 (m, 1H, $OC\underline{H}CH_3$), 4.303 (d, $J=3.0$ Hz, 1H, 5-CH), 4.715 (ddt, $J=13.5$, 5.6, 1.4 Hz; 1H, $OC\underline{H_2}CH{=}$), 4.798 (ddt, $J=13.5$, 5.5, 1.4 Hz; 1H, $OC\underline{H_2}CH{=}$), 5.272 (dq, $J=10.5$, 1.4 Hz; 1H, $\underline{H_2}C{=}CHCH_2O$), 5.451 (dq, $J=17.2$, 1.5 Hz; 1H, $\underline{H_2}C{=}CHCH_2O$), 5.618 (ddt, $J=17.0$, 10.1, 6.5 Hz, 1H, $H_2C{=}C\underline{H}CH_2O$).

^{13}C NMR ($CDCl_3$) δ −4.93, −4.32, 12.71, 17.85, 22.64, 26.68, 35.25, 58.24, 61.69, 65.75, 66.21, 68.27, 118.48, 119.66, 129.91, 131.42, 132.79, 144.06, 160.92, 173.49, 205.97.

MS HR (LSIMS) for $C_{24}H_{37}NO_5Si\,(M+Na)^+$, found 470.23237, calcd 470.23387.

IR (film from $CHCl_3$) 3376, 2955, 2931, 1737, 1714, 1380, 1361, 1255, 1192, 1093, 836, 778.

(2*R*,7*R*,8*S*)-9-oxo-8$_t$-[(*R*)-1-Hydroxyethyl]-6-thia-1-azatricyclo[5.2.0.0^{2,4}]nonane-2-carboxylic acid allyl ester (5a). Compound **4a** (4.0 g, 10.0 mmol) was dissolved in ethyl acetate (50 mL) and di-i-propylethyl amine trifluorohydride (7.7 g, 40.0 mmol) was added at rt .The mixture was stirred with heating at 50 °C for 5–10 h (TLC monitoring). After the reaction was completed, the mixture was washed with water, organic layer was dried over $MgSO_4$, filtered and evaporated under reduced pressure. The residue was chromatographed on silica gel (1:1 *n*-hexane–AcOEt) giving (**5a**) (2.2 g, 7.8 mmol, 78% yield).

^{1}H NMR ($CDCl_3$) δ 1.319 (d, $J=6.4$ Hz, 3H, CH_3), 1.503 (dd, $J=7.3$, 5.5 Hz, 1H, 3-CH), 1.815 (dd, $J=9.1$, 5.3 Hz, 1H, 3-CH), 1.990 (tt, $J=7.3$, 4.8 Hz, 1H, 4-CH), 2.674 (dd, $J=14.5$, 4.6 Hz; 1H, 5-CH), 3.055 (dd, $J=5.7$, 1.6 Hz; 1H, 8-CH), 3.257 (dd, $J=14.6$, 4.9 Hz; 1H, 5-CH), 4.258 (qvintet, $J=6.0$ Hz, 1H, $OC\underline{H}CH_3$), 4.508 (d, $J=1.7$ Hz; 1H, 7-CH), 4.620 (dq, $J=3.3$, 1.0 Hz; 2H, $OC\underline{H_2}CH{=}$), 5.232 (dq, $J=10.4$, 1.5 Hz; 1H, $\underline{H_2}C{=}CH$), 5.332 (dq, $J=17.2$, 1.6 Hz; 1H, $\underline{H_2}C{=}CH$), 5.882 (ddt, $J=17.2$, 10.4, 5.5 Hz, 1H, $H_2C{=}C\underline{H}$).

^{13}C NMR ($CDCl_3$) δ 19.65, 21.70, 21.97, 23.74, 33.85, 51.03, 63.79, 65.19, 67.11, 117.22, 132.15, 167.70, 169.91.

MS HR (LSIMS) for $C_{13}H_{17}NO_4S\,(M+H)^+$, found 284.09541, calcd 284.09566.

IR (film from $CHCl_3$) 3453, 2971, 1761, 1734, 1402,1377, 1282, 1185.

The same procedure except that anisole was used as a solvent was applied to obtain compounds **5b**–**d**.

(2*R*,7*S*,8*S*)-9-oxo-8$_t$-[(*R*)-1-Hydroxyethyl]-1-azatricyclo[5.2.0.0^{2,4}]nonane-2,6,6-tricarboxylic acid, 2-allyl ester, 6,6-diethyl ester (5b). (6.2 g, 15.1 mmol, 83% yield) from **4b** (9.5 g, 18.2 mmol).

^{1}H NMR ($CDCl_3$) δ 1.251 (t, J = 7.1 Hz, 3H, CH_3CH_2), 1.256 (t, J = 7.1 Hz, 3H, CH_3CH_2), 1.267 (dd, J = 14.6, 6.0 Hz; 1H, 5-CH), 1.285 (d, J = 6.0 Hz, 3H, CH_3), 1.424 (t, J = 6.0 Hz, 1H, 3-CH), 1.653 (tt, J = 8.4, 6.4 Hz, 1H, 4-CH), 1.830 (dd, J = 8.8, 5.7 Hz, 1H, 3-CH), 2.806 (dd, J = 6.6, 2.6 Hz; 1H, 8-CH), 2.811 (ddd, J = 15.0 Hz, 6.6, 0.7; 1H, 5-CH), 4.057–4.322 (m, 5H, CH_3CH_2, $OCHCH_3$), 4.422 (d, J = 2.4 Hz; 1H, 7-CH), 4.596 (ddt, J = 13.5, 5.7, 1.6 Hz, 1H, OCH_2CH=), 4.659 (ddt, J = 13.4, 5.5, 1.5 Hz, 1H, OCH_2CH=) 5.248 (dq, J = 10.6, 1.5 Hz; 1H, H_2C=CH), 5.367 (dq, J = 17.2, 1.6, Hz; 1H, H_2C=CH), 5.922 (ddt, J = 17.2, 10.4, 5.6 Hz, 1H, H_2C=CH).

^{13}C NMR ($CDCl_3$) δ 13.84, 13.98, 14.15, 20.98, 22.76, 23.10, 28.28, 34.71, 52.80, 54.00, 60.11, 60.37, 62.31, 65.42, 66.04, 118.09, 131.73, 168.19, 169.00, 169.56, 170.39.

MS HR (LSIMS) for $C_{20}H_{27}NO_8$ $(M+H)^+$, found 410.18040, calcd 410.18149.

IR (film from $CHCl_3$) 3475, 2978, 1764, 1742, 1713, 1396, 1367, 1300, 1280, 1265, 1186.

(2*R*,7*S*,8*S*)-9-oxo-8$_t$-[(*R*)-1-Hydroxyethyl]-6-acetyl-1-azatricyclo[5.2.0.0^{2,4}]nonane-2,6-dicarboxylic acid, 2-allyl ester, 6-ethyl ester (5c). (1.8 g, 4.7 mmol, 94% yield) from **4c** (2.5 g, 5.1 mmol). ^{1}H NMR ($CDCl_3$) δ 1.124 (dd, J = 15.0, 8.6 Hz; 1H, 5-CH), 1.276 (t, J = 7.1 Hz, 3H, CH_3CH_2), 1.329 (d, J = 6.2 Hz, 3H, CH_3), 1.428 (t, J = 5.8 Hz, 1H, 3-CH), 1.648 (tt, J = 8.8, 6.2 Hz, 1H, 4-CH), 1.826 (dd, J = 7.8, 5.9 Hz, 1H, 3-CH), 2.230 (s, 3H, CH_3C=O), 2.572 (dd, J = 8.6, 2.4 Hz; 1H, 8-CH), 2.685 (ddd, J = 14.8, 6.6, 0.7 Hz; 1H, 5-CH), 4.130 (qvintet, J = 7.1 Hz, 1H, $OCHCH_3$), 4.244 (q, J = 7.1 Hz, 1H, CH_3CH_2), 4.274 (q, J = 7.1 Hz, 1H, CH_3CH_2), 4.536 (d, J = 2.4 Hz; 1H, 7-CH), 4.600 (ddt, J = 13.4, 5.7, 1.5 Hz; 1H, OCH_2CH=), 4.651 (ddt, J = 13.4, 5.5, 1.5 Hz, 1H, OCH_2CH=) 5.258 (dq, J = 10.7, 1.5 Hz; 1H, H_2C=CH), 5.337 (dq, J = 17.2, 1.6 Hz; 1H, H_2C=CH), 5.923 (ddt, J = 17.2, 10.4, 5.5 Hz, 1H, H_2C=CH).

^{13}C NMR ($CDCl_3$) −4.58, 13.95, 22.11, 23.06, 23.43, 25.60, 27.72, 28.32, 34.58, 53.50, 59.42, 60.67, 62.40, 65.98, 66.31, 118.17, 131.72, 168.28, 170.41, 170.63, 202.39.

MS HR (LSIMS) for $C_{19}H_{25}O_7N$ $(M+H)^+$, found 380.17108, calcd 380.17093.

IR (film from $CHCl_3$) 3483, 2978, 1762, 1712, 1400, 1369, 1298, 1283, 1263, 1179.

(2*R*,7*S*,8*S*)-9-oxo-8$_t$-[(*R*)-1-Hydroxyethyl]-6,6-diacetyl-1-azatricyclo[5.2.0.0^{2,4}]nonane-2-carboxylic acid allyl ester (5d). (1.31 g, 3.8 mmol, 65% yield) from (**4d**) (2.66 g, 5.7 mmol).

^{1}H NMR ($CDCl_3$) δ 1.143 (dd, J = 15.6, 8.9 Hz; 1H, 5-CH), 1.354 (d, J = 6.2 Hz, 3H, CH_3), 1.418 (t, J = 6.0 Hz, 1H, 3-CH), 1.544 (tt, J = 8.8, 6.2 Hz, 1H, 4-CH), 1.809 (dd, J = 8.8, 6.2 Hz, 1H, 3-CH), 2.206 (s, 3H, CH_3C=O), 2.213 (s, 3H, CH_3C=O), 2.521 (dd, J = 8.8, 2.4 Hz; 1H, 8-CH), 2.779 (ddd, J = 15.4, 6.6, 0.7 Hz; 1H, 5-CH), 4.112 (quintet, J = 7.0 Hz, 1H, $OCHCH_3$), 4.585 (ddt, J = 13.4, 5.7, 1.5 Hz; 1H, OCH_2CH=), 4.602 (d, J = 2.7 Hz; 1H, 7-CH), 4.683 (ddt, J = 13.4, 5.5, 1.5 Hz, 1H, OCH_2CH=) 5.277 (dq, J = 10.6, 1.5 Hz; 1H, H_2C=CH), 5.373 (dq, J = 17.4, 1.6 Hz; 1H, H_2C=CH), 5.942 (ddt, J = 17.3, 10.4, 5.5 Hz, 1H, H_2C=CH).

^{13}C NMR ($CDCl_3$) δ 16.02, 16.09, 22.18, 22.99, 23.01, 26.73, 26.86, 28.86, 34.52, 52.54, 59.41, 63.60, 63.66, 66.12, 66.70, 68.04, 118.26, 131.71, 168.20, 170.29, 203.53, 203.67.

MS HR (LSIMS) for $C_{18}H_{23}O_6N$ $(M+Na)^+$, found 372.14324, calcd 372.14231.

IR (film from $CHCl_3$) 3473, 2973, 1760, 1700, 1363, 1299, 1284, 1197, 1175, 1151.

(2*R*,7*R*,8*S*)-9-oxo-8$_t$-[(*R*)-1-Hydroxyethyl]-6-thia-1-azatricyclo[5.2.0.0^{2,4}]nonane-2-carboxylic acid (6a). To the solution of sodium 2-ethylhexanoate (1.5 g, 9.0 mmol), triphenylphosphine (0.08 g, 0.3 mmol) and $Pd(PPh_3)_4$ (0.08 g, 0.07 mmol) in ethyl acetate (10 mL) was added dropwise a solution of **5a** (2.1 g, 7.4 mmol) in ethyl acetate (10 mL) at rt. The mixture was stirred for 1–3 h with TLC monitoring. After the reaction was completed the mixture was extracted with water (2×10 mL). The water layer was acidified with H_3PO_4 (pH = 3.0) while a jelly-like precipitate was formed which was extracted with ethyl acetate (2×20 mL). The organic layer was dried with $MgSO_4$ and evaporated under reduced pressure. The resultant solid was treated with diethyl ether (15 mL) filtered and dried giving **6a** (0.84 g, 3.1 mmol, 42% yield); mp 154 °C, $[\alpha]_D^{25}$ = 154.8 (*c* 1%, CH_3Cl).

^{1}H NMR (DMSO-d_6) δ 1.142 (d, J = 6.2 Hz, 3H, CH_3), 1.219 (dd, J = 7.1, 5.1 Hz, 1H, 3-CH), 1.622 (dd, J = 9.1, 5.1 Hz, 1H, 3-CH), 1.924 (tt, J = 9.0, 5.3 Hz, 1H, 4-CH), 2.630 (dd, J = 14.6, 5.3 Hz; 1H, 5-CH), 2.924 (dd, J = 7.1, 1.6 Hz; 1H, 8-CH), 3.279 (dd, J = 14.5, 5.1 Hz; 1H, 5-CH), 3.900 (quintet, J = 6.6 Hz, 1H, $OCHCH_3$), 4.464 (d, J = 1.7 Hz; 1H, 7-CH), 5.61 (brs, 1H, OH), 12.63 (brs, 1H, COOH).

^{13}C NMR ($CDCl_3$) δ 19.07, 21.47, 21.74, 23.91, 33.70, 51.14, 63.90, 67.20, 167.53, 171.96.

MS HR (EI) for $C_{10}H_{13}NO_4S$ for M^+, found 243.05666, calcd 243.05653 Elemental analysis: calcd %C 49.37, %H 5.38, %N 5.76, %S 13.18, found %C 49.14, %H 5.36, %N 5.62, %S 13.17.

IR (KBr) 3312, 2979.2920, 1744, 1720, 1393, 1381, 1255, 1196, 1185.

According to the same procedure compounds **6b–d** were prepared.

(2*R*,7*S*,8*S*)-9-oxo-8$_t$-[(*R*)-1-Hydroxyethyl]-1-azatricyclo[5.2.0.0^{2,4}]nonane-2,6,6-tricarboxylic acid, 6,6-diethyl ester (6b). (1.8 g, 4.9 mmol 51% yield) from (**5b**) (3.9 g, 9.5 mmol); mp 182 °C, $[\alpha]_D^{25} = -88.2$ (*c* 1%, CH_3Cl). ^1H NMR ($CDCl_3$) δ 1.258 (t, *J* = 7.0 Hz, 3H, $C\underline{H_3}CH_2$), 1.259 (d, *J* = 6.4 Hz, 3H, CH_3), 1.280 (t, *J* = 7.0 Hz, 3H, $CH_3\underline{CH_2}$), 1.295 (dd, *J* = 14.6, 8.2 Hz, 1H, 5-CH), 1.449 (t, *J* = 6.0 Hz, 1H, 3-CH), 1.720 (tt, *J* = 8.2, 6.4 Hz, 1H, 4-CH), 1.865 (dd, *J* = 8.8, 5.7 Hz, 1H, 3-CH), 2.818 (dd, *J* = 14.6, 6.4 Hz, 1H, 5-CH), 2.855 (dd, *J* = 5.8, 2.6 Hz, 1H, 8-CH), 4.077 (dq, *J* = 10.8, 7.1 Hz, 1H, $OC\underline{H}CH_3$), 4.21-4.35 (m, 4H, $CH_3C\underline{H_2}$), 4.443 (d, *J* = 2.6 Hz, 1H, 7-CH).

^{13}C NMR ($CDCl_3$) δ 13.86, 13.96, 20.91, 23.24, 23.72, 28.36, 34.55, 52.37, 53.92, 60.04, 62.40, 62.59, 64.92, 168.94, 169.03, 169.72, 174.42.

MS HR (LSIMS) for $C_{17}H_{23}NO_8$ for $(M+Na)^+$, found 392.11428, calcd 392.11428.

Elemental analysis: calcd %C 55.28, %H 6.27, %N 3.79, found %C 55.23, %H 6.34, %N 3.85.

IR (KBr) 3407, 2995, 2974, 1770, 1730, 1716, 1451, 1390, 1372, 1285, 1260, 1201, 1168, 1147, 1096, 1029.

(2*R*,7*S*,8*S*)-9-oxo-8$_t$-[(*R*)-1-Hydroxyethyl]-6-acetyl-1-azatricyclo[5.2.0.0^{2,4}]nonane-2,6-dicarboxylic acid, 6-ethyl ester (6c). (0.57 g, 1.7 mmol, 34% yield) from **5c** (1.9 g, 5.0 mmol); mp 98 °C, $[\alpha]_D^{25} = -162.4$ (*c* 1%, CH_3Cl).

^1H NMR ($CDCl_3$) δ 1.157 (dd, *J* = 15.2, 8.8 Hz, 1H, 5-CH), 1.303 (t, *J* = 7.1 Hz, 3H, $C\underline{H_3}CH_2$), 1.318 (d, *J* = 6.2 Hz, 3H, CH_3), 1.472 (t, *J* = 6.0 Hz, 3H, 3-CH), 1.712 (tt, *J* = 8.8, 6.4 Hz, 1H, 4-CH), 1.866 (dd, *J* = 8.8, 5.8 Hz, 1H, 3-CH), 2.235 (s, 3H, $CH_3C{=}O$), 2.618 (dd, *J* = 8.1, 2.4 Hz, 1H, 8-CH), 2.699 (dd, *J* = 14.5, 6.7 Hz, 1H, 5-CH), 4.197 (dq, *J* = 8.1, 6.4 Hz, 1H, $OC\underline{H}CH_3$), 4.296 (dq, *J* = 7.1, 5.7 Hz, 4H, $CH_3C\underline{H_2}$), 4.550 (d, *J* = 2.4 Hz, 1H, 7-CH).

^{13}C NMR ($CDCl_3$) 13.99, 22.02, 23.71, 24.07, 27.94, 28.47, 34.44, 53.21, 59.49, 60.58, 62.74, 66.01, 168.93, 170.84, 175.36, 202.55.

MS HR (EI) $C_{16}H_{21}NO_7$ for M^+, found 339.13146, calcd 339.13180.

Elemental analysis: calcd %C 56.63, %H 6.24, %N 4.13, found %C 56.54, %H 6.22, %N 4.06.

IR (KBr) 3417, 2979, 1770, 1741, 1714, 1450, 1370, 1298, 1271, 1189.

(2*R*,7*S*,8*S*)-9-oxo-8$_t$-[(*R*)-1-Hydroxyethyl]-6,6-diacetyl-1-azatricyclo[5.2.0.0^{2,4}]nonane-2-carboxylic acid (6d). (0.40 g, 1.3 mmol, 35%) from **5d** (1.3 g, 3.7 mmol); mp 163–165 °C, $[\alpha]_D^{25} = -238.2$ (*c* 1%, CH_3Cl).

^1H NMR ($CDCl_3$) δ 1.165 (dd, *J* = 15.6, 8.9 Hz; 1H, 5-CH), 1.361 (d, *J* = 6.2 Hz, 3H, CH_3), 1.465 (t, *J* = 6.0 Hz, 1H, 3-CH), 1.859 (dd, *J* = 8.6, 5.9 Hz, 1H, 3-CH), 2.211 (s, 3H, $CH_3C{=}O$), 2.246 (s, 3H, $CH_3C{=}O$), 2.288 (tt, *J* = 8.6, 5.5 Hz, 1H, 4-CH), 2.552 (dd, *J* = 8.6, 2.4 Hz; 1H, 8-CH), 2.803 (dd *J* = 15.5, 6.2 Hz; 1H, 5-CH), 4.215 (dq, *J* = 8.6, 6.2 Hz, 1H, $OC\underline{H}CH_3$), 4.631 (d, *J* = 2.2 Hz; 1H, 7-CH).

^{13}C NMR ($CDCl_3$) δ 22.27, 23.59, 26.85, 28.92, 35.24, 52.49, 59.50, 66.65, 68.00, 168.50, 174.15, 203.59, 203.89.

MS HR (EI) $C_{15}H_{20}O_6N$ for M^+ found 310.12848, calcd 310.12906.

Elemental analysis: calcd %C 58.05, %H 6.50, %N 4.51, found %C 58.06, %H 6.34, %N 4.59.

IR (KBr) 3340, 2973, 2926, 17726, 1698, 1420, 1365, 1305, 1256, 1203, 1182.

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17. Crystallographic data (excluding structure factors) for structure **6a** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication No. CCDC 196221. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).