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Intramolecular substitution reactions involving π-nucleophiles and *N*-acyliminium cations generated from azetidin-2-ones

Barbara Grzeszczyk, Barbara Szechner, Bartłomiej Furman, Marek Chmielewski *

Institute of Organic Chemistry of the Polish Academy of Sciences, Kasprzaka 44/52, 01-224 Warsaw, Poland

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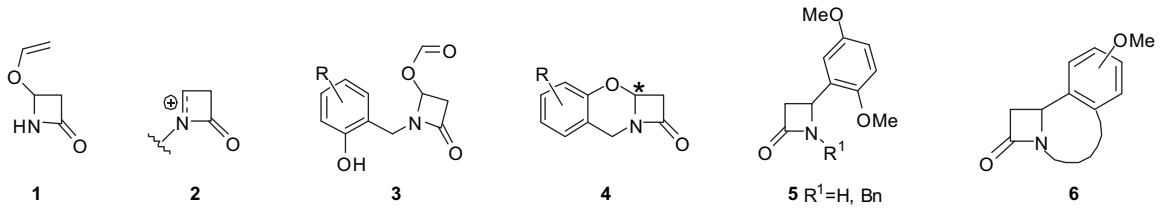
ABSTRACT

The Lewis acid-catalyzed intramolecular substitution reactions of 4-vinyloxy- or 4-acyloxy-azetidin-2-ones with nitrogen-bound allyl-, propargyl- and vinyl-silanes leading to the carbacephams or carbacephems, are reported. The formation of carbapenams was not observed. To illustrate the potential of these reactions to be carried out under solid-phase conditions, a synthesis of diastereomeric 5-vinyl-carbacephams via the cyclization/cleavage methodology was performed.

1. Introduction

The *N*-acyliminium ions are important reactive intermediates in organic synthesis, which can act as electron-deficient *C*-electrophiles toward weak, soft nucleophiles providing useful methodologies for both the inter- and intramolecular carbon–carbon and carbon–heteroatom bond formation.[1] *N*-Acyliminium species can be generated in acidic media from lactams bearing a leaving group in the α-position to the nitrogen atom. Over the last 40 years, the cationic cyclization involving benzenoid, alkene, or alkyne nucleophiles and *N*-acyliminium ions has found a broad application in the synthesis of a variety of ring systems.[2] It should be noted, however, that as a rule, the cyclic *N*-acyliminium cations have been generated from five- or six-membered ring lactams,[2] and only a few reported examples have referred to 4-substituted β-lactams.[3] We have shown that the 4-vinyloxyazetidin-2-one (**1**) is an attractive starting material for the synthesis of 5-oxacephams since it allows for N-alkylation of the substrate prior to the nucleophilic substitution at the C-4 carbon atom.[4] Subsequently, the vinyloxyl group itself, or formyloxyl (readily available by ozonolysis), in the presence of a Lewis acid, undergoes intramolecular displacement leading to the ring closure.[5] The acid-catalyzed nucleophilic substitution at C-4 of the azetidinone ring proceeds via a flat intermediate **2**, which in the presence of a chiral reagent may allow discrimination of its faces thus providing a configurationally enriched product. The intramolecular diastereoselective process involving chiral *N*-substituent offers high asymmetric induction,[6] whereas the commonly used intermolecular reaction proceeds usually with poor stereoselectivity.[6b,7]

A search for the enantioselective formation of bicyclic β-lactams prompted us to investigate the chiral Lewis acid-catalyzed intramolecular formation of the 5-oxa-3,4-benzocephams **4** from compounds **3**.[8] The observed moderate yield, which never exceeded 50%, in parallel with a high asymmetric induction, suggested a kinetic asymmetric destruction of the initially formed racemic oxacepham **4**. This has been proved independently by the asymmetric degradation of racemic **4** in the presence of a chiral catalyst.[8]



1 **2** **3** **4** **5** R^1=H, Bn **6**

Recently, we have also shown that the *N*-acyliminium ions **2** generated from β-lactams can be used as electrophilic agents to

* Corresponding author. Tel.: +4822 631 87 88; fax: +4822 632 66 81; e-mail address: chmiel@icho.edu.pl (M. Chmielewski).

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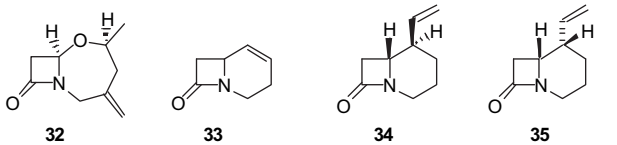
substitute nucleophilic arenes in both inter- and intramolecular processes.[9] The former reaction was successfully carried out only with *p*-dimethoxybenzene to provide compounds **5** in moderate yield, whereas the latter can be done with a variety of nucleophilic arenes affording bicyclic compounds **6** in a good yield. Reactions of *N*-acyliminium cations generated from **1** with simple π-nucleophiles, such as vinylsilanes, allylsilanes, and propargylsilanes are logical continuation of our investigation. It should be noted that reactions of allyltrimethylsilane with *N*-acyliminium cations derived from alkoxylactams have been investigated in the past provide the corresponding *C*-allylated product.[10] A Similar reaction involving the trimethylsilyl trifluoromethanesulfonate-mediated allyl transfer from an *N*-allyldimethylsilylated β-lactam to C-4 carbon atom of 4-acetoxyazetidinone fragment has also been reported.[11]

2. Result and discussion

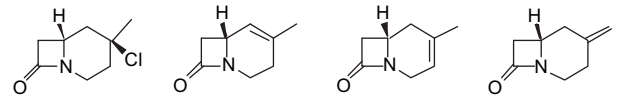
The known vinyl- **7**[12], allyl- **8**[13], **10**[14], **11**–**12**,[15] and propargylsilanes **13**[13] were transformed into the corresponding *p*-chlorobenzenesulfonates **14**–**19**. Subsequently, the 4-vinyloxyazetidin-2-one (**1**) was *N*-alkylated with chloride **9** and sulfonates **14**–**19** to afford azetidinones **20**–**26**, using our general procedure.[16] Since we have previously shown[5a–c] that in the presence of acid catalysts, vinyloxyl played the role of a leaving group, compounds **20**–**26** were directly subjected to the cyclization. To demonstrate that the 4-acyloxy congeners provide the similar result of cyclization, compounds **21**, **23**, and **26** were oxidized to corresponding acetates **27**, **28**, and **30** using the standard PCC procedure, whereas compound **26** was also treated with ozone to give formate **31**.

The intramolecular nucleophilic substitution at C-4 carbon atom of the azetidinone residue was performed in the presence of Lewis acids $SnCl_2$/TMSCl, $Yb(OTf)_3$, $SnCl_4$, and TiF_4. Reactions were performed on both 4-vinyloxy-(**20**–**26**) and 4-acyloxy-azetidinones (**27**,**28**, **30**, and **31**). In all feasible cases (**22**, **23**, and **28**), the formation of carbapenams (five-membered pyrrolidine ring fused to the four-membered ring) was unsuccessful. This result may be explained as a 5-*endo* process, which is disfavored by the Baldwin rule.[17] The cyclization of compound **28** led to slow decomposition of the substrate and we were able to isolate only a minute amount of desilylated product **29**. Compounds **22** and **23** with 4-vinyloxy substituents afforded oxazepane **32** resulting from addition of the allylsilane fragment to the vinyloxy group. Oxazepane **32** was formed with a high stereoselectivity providing a single isomer with both bridgehead protons *syn* located. This was corroborated by NOE spin–spin interaction between both protons. The cyclization of 4-acyloxy-azetidinones **27**, **30**, and **31** did not offer any advantage in comparison with the corresponding vinyloxy congeners. Slightly better yields were realized in the former reactions but at the cost of one additional synthetic step (oxidation).

Cyclization of vinyl silane **20** led to the carbacephem **33** in 78% yield, whereas the (*Z*)-allylsilanes **21** and **27** gave a mixture of carbacephams **34** and **35** in a ratio of about 1.0:1.3, respectively, as determined by the HPLC. The relative configuration of both diastereomers was assigned using NOE to show a spin–spin interaction between H-5 and H-6 protons in the case of **35**.

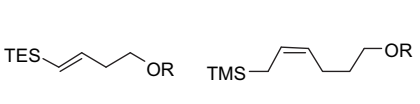


32 **33** **34** **35**



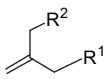
36 **37a** **37b** **37c**

The cyclization of allylsilanes **24** and **25** proceeded in somewhat unanticipated manner. In the presence of $SnCl_2$ or $SnCl_4$, the 4-chloro-4-methylcarbacepham **36** was formed. The configuration at C-3 carbon in **36** was assigned assuming that the addition of

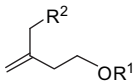


7 R=H
14 R=*p*-$C_6H_4SO_2$

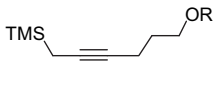
8 R=H
15 R=*p*-$C_6H_4SO_2$



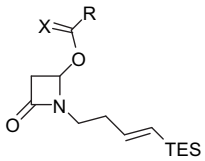
9 R^1=Cl, R^2=TMS
10 R^1=OH, R^2=Me_2PhSi
16 R^1=*p*-$C_6H_4SO_2$; R^2=Me_2PhSi



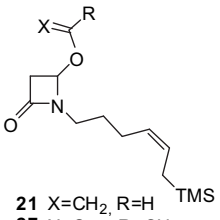
11 R^1=H, R^2=TMS
12 R^1=H, R^2=Me_2PhSi
17 R^1=*p*-$C_6H_4SO_2$; R^2=TMS
18 R^1=*p*-$C_6H_4SO_2$; R^2=Me_2PhSi



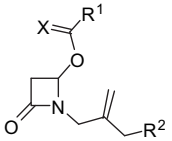
13 R=H
19 R=*p*-$C_6H_4SO_2$



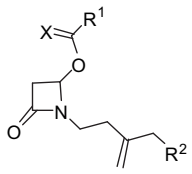
20 X=CH_2, R=H



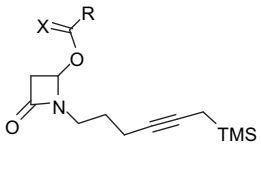
21 X=CH_2, R=H
27 X=O, R=CH_3



22 X=CH_2, R1=H, R^2=TMS
23 X=CH_2, R^1=H, R^2=Me_2PhSi
28 X=O, R^1=CH_3, R^2=Me_2PhSi
29 X=O, R^1=CH_3, R^2=H



24 X=CH_2, R^1=H, R^2= TMS
25 X=CH_2, R^1=H, R^2= Me_2PhSi



26 X=CH_2, R = H
30 X=O, R=CH_3
31 X=O, R=H

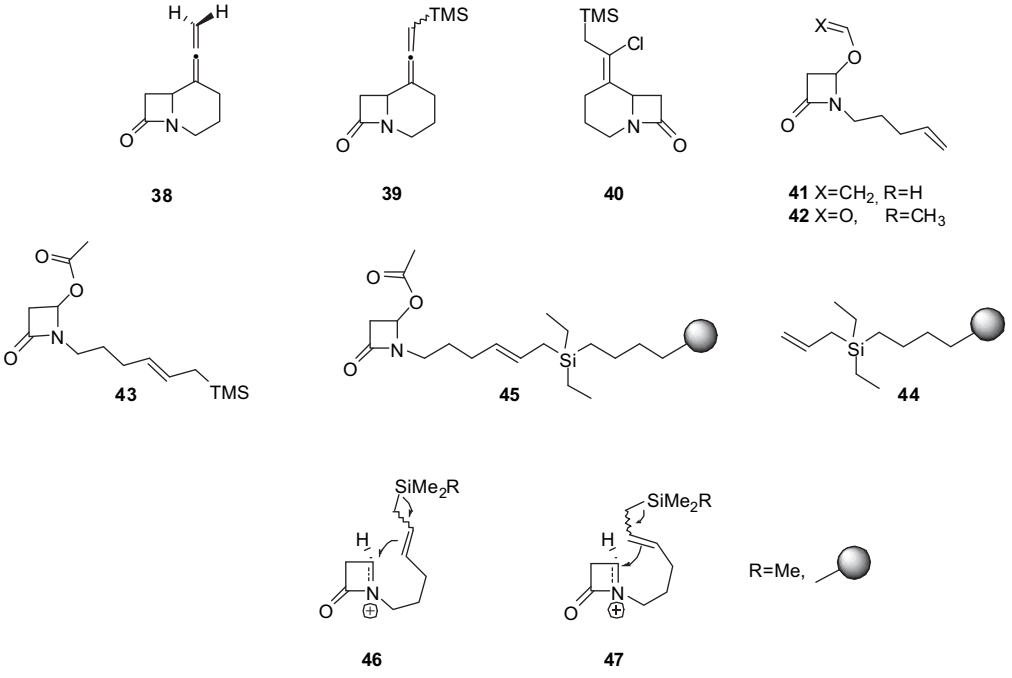
chloride anion to the tertiary carbocation proceeded from the *exo* side of the bicyclic cepham skeleton. In the presence of $Yb(OTf)_3$, both silanes **24** and **25** afforded a mixture of carbacephams **37b** and **37a** in a ratio of about 1.3:1.0. Both regioisomers were separated by chromatography. The signals due to a minute amount of the expected cepham **37c** were detected only in the ^1H NMR spectrum of the post reaction mixture. This unexpected pathway of the reaction is likely a result of a low stability of the initially formed cepham **37c**. One could speculate that in the presence of acids bearing chlorine atoms the cepham **37c** forms **36**, whereas other acids induce migration of the double bond.[18]

The intermolecular reaction of 4-acetoxy-azetidinone with propargyl silane to provide 4-allenyl-azetidinone is a known process.[19] The corresponding intramolecular process involving propargylsilanes **26** and **30** should proceed more readily. Indeed, both compounds easily underwent the cyclization in an analogous yield, however, the structure of the final product depended on which Lewis acid was used. In the presence of titanium tetrafluoride allene **38** was obtained as a sole product in a good yield from both silanes **26** and **30**. In the presence of $Yb(OTf)_3$, compounds **26** and **31** afforded allene **38** (50% yield) accompanied by the TMS-substituted diastereomers **39** (29% yield) in a ratio of about 3:1. The relative configuration of diastereomers **39** was not assigned. The cyclization of **26** and **31** in the presence of $SnCl_2$/TMSCl catalyst gave expected allene **38** (43%) accompanied only by the chloro-trimethylsilyl compound **40** (21%).[20] The configuration of the double bond in **40** was not assigned.

resin according to the literature method.[22] Cyclization involving **43**, under conditions used for the cyclization of its (*Z*) isomer **27**, afforded a mixture of **34**, and **35** in the same ratio as cyclization of **27**. This result shows that the *endo* approach of the double bond (structure **47**) to acyliminium cation is slightly preferred over the *exo* approach (structure **46**) owing to the overlapping of the nucleophilic double bond with electrophilic acyliminium cation. The configuration of the double bond, (*Z*) **27** and (*E*) **43**, does not affect the stereochemical pathway of the reaction. The cyclization/cleavage performed on solid support **45**, however, led to a mixture of cephams **34** and **35** in a ratio 1.3:1.0, respectively, being reversed to that observed for reactions performed in solution. This indicates that the spatial requirements of the silyl substituent bound to the resin make the *exo* approach (structure **46**) preferred.

3. Conclusion

It was demonstrated that the vinyloxy group at C-4 of the azetidinone ring is an attractive substituent. It is stable under basic conditions allowing alkylation of the nitrogen atom, whereas in the presence of a Lewis acid catalyst it plays a role of a leaving group, which promotes a nucleophilic substitution. We have shown that cyclization reactions involving *N*-acyliminium cations generated from the azetidinone fragment and π-nucleophiles, such as vinylsilanes, allylsilanes, and propargylsilanes proceeds smoothly only if a six-membered cepham ring can be formed. The formation of



To demonstrate that cyclizations involving π-nucleophiles to *N*-acyliminium cations can be performed using solid-phase methodology, we chose the intramolecular alkylation of the (*E*) allylsilane **43**. The reaction should proceed via the cyclization/cleavage methodology.[21] Starting material, *N*-(pent-4-enyl)azetidin-2-one **41** was obtained from **1** by a standard alkylation procedure. In order to compare the reaction performed in solution and on a solid support, the vinyloxy group in compound **41** was oxidized to the acetoxy group to afford compound **42**. The latter was coupled with trimethylallylsilane in the presence of Grubbs catalyst second generation to give compound **43**. The same cross-metathesis reaction was performed using the allylsilane resin **44**, synthesized from Merrifield carbapenam skeletons was never observed. Instead, if the substrate contains 4-vinyloxy group, addition of the nucleophile to vinyl ether takes place.

4. Experimental section

4.1. General

^1H and ^{13}C NMR spectra were recorded on a Brucker DRX 500 Avance Spectrometer at 500 MHz and 125 MHz, respectively, in $CDCl_3$ unless otherwise stated. TMS was used as an internal standard. Chemical shifts are reported as δ values in parts per million

and coupling constants are in hertz. Proton assignment was done based on COSY experiments. Infrared spectra were recorded on a FT-IR-1600 Perkin–Elmer spectrophotometer. High-resolution mass spectra were recorded on ESI-TOF Mariner Spectrometer (Perspective Biosystem) or AMD 604 mass spectrometer. Thin layer chromatography was performed on Merck aluminum sheet Silica Gel 60 F_{254}. Column chromatography was carried out using Merck silica gel (230–400 mesh) and Florisil (100–200 mesh). All reactions were performed under argon in predried glassware. All solvents were purified by standard techniques. 5-Bromo-1-pentene was obtain according to literature method.[23] Diastereomeric ratios of cephams obtained were determined by HPLC of crude post reaction mixtures on Kromasil Si 60 column.

4.2. Sulfonylation of compounds 7, 8, 10–13

4.2.1. Method A. To a solution of hydroxy compound (**7**, **8**, **10**–**13**; 1.0 mmol), DMAP (0.024 g, 0.2 mmol), and NEt_3 (0.42 mL, 3.0 mmol) in dry dichloromethane (5 mL/mmol) cooled to 0 °C 4-chlorobenzenesulfonyl chloride (0.317 g, 1.5 mmol) was added and the reaction mixture was allowed to warm to room temperature. The reaction progress was monitored by TLC. After 1.5 h, the reaction mixture was diluted with ethyl acetate (100 mL), washed with water (50 mL), dried ($MgSO_4$), and the solvent evaporated in vacuo. Pure products were obtained by flash chromatography (10% ethyl acetate/hexane).

*4.2.1.1. (E)-4-Triethylsilylbut-1-enyl-4-chlorobenzenesulfonate (**14**).* Yield (0.141 g, 76%) from **7**. ^{1}H NMR δ: 7.85–7.83 (m, 2H, aromatic), 7.53–7.51 (m, 2H, aromatic), 5.86 (dt, 1H, *J* 18.8, 6.2 Hz, H-3), 5.65 (dt, 1H, *J* 18.8, 1.4 Hz, H-4), 4.12 (t, 2H, *J* 6.7 Hz, H-1a, H-1b), 2.48 (dq, 2H, *J* 6.7, 1.4 Hz, H-2a, H-2b), 0.89 (t, 9H, *J* 8.0 Hz, 3×CH_3), 0.52 (q, 6H, *J* 8.0 Hz, 2×CH_2); ^{13}C NMR δ: 140.9, 140.4, 134.8, 131.1, 129.6, 129.3, 69.8, 36.0, 7.3, 3.3. IR (neat) ν: 2941, 1590, 1367, 1187 cm^{-1}. HRMS (ESI): calcd for $C_{16}H_{25}NO_3NaSiCl$ $[M+Na]^+$: 383.0874; found: 383.0860.

*4.2.1.2. 2-[(Dimethylphenylsilyl)methyl]prop-2-enyl 4-chlorobenzenesulfonate (**16**).* Yield (0.138 g, 67%) from **10**. ^{1}H NMR δ: 7.77–7.73 (m, 2H, aromatic), 7.50–7.46 (m, 2H, aromatic), 7.45–7.43 (m, 2H, aromatic), 7.38–7.30 (m, 3H aromatic), 4.91 (d, 1H, *J* 1.0 Hz, H-3a), 4.73 (s, 1H, H-3b), 4.19 (s, 2H, H-4a, H-4b), 1.69 (s, 2H, H-1a, H-1b), 0.27 (s, 6H, 2×CH_3); ^{13}C NMR δ: 140.3, 138.9, 137.8, 134.8, 133.5, 129.5, 129.3, 127.9, 113.5, 74.1, 22.2, -3.2. IR (neat) ν: 2951, 1589, 1369, 1186, 829 cm^{-1}. HRMS (ESI): calcd for $C_{18}H_{21}O_3NaSiSCl$ $[M+Na]^+$: 403.0561. found: 403.0542.

*4.2.1.3. 3-[(Trimethylsilyl)methyl]but-3-enyl-4-chlorobenzenesulfonate (**17**).* yield (0.079 g, 50%) from **11**. ^{1}H NMR (C_6D_6) δ: 7.48–7.40 (m, 2H, aromatic), 6.76–6.70 (m, 2H, aromatic), 4.50–4.41 (m, 2H, H-5a, H-5b), 3.90 (t, 2H, *J* 7.0 Hz, H-1a, H-1b), 2.00 (bt, 2H, *J* 6.9 Hz, H-2a, H-2b), 1.20 (d, 2H, *J* 1.0 Hz H-4a, H-4b), −0.14 (s, 9H, TMS); ^{13}C NMR δ: 141.7, 135.2, 129.1, 129.0, 127.8, 127.6, 127.5, 109.7, 68.6, 37.0, 26.5, −1.9. IR (neat) ν: 2956, 1637, 1478, 1366, 1186, 853 cm^{-1}. HRMS (ESI): calcd for $C_{14}H_{21}O_3NaSiSCl$ $[M+Na]^+$: 355.0561; found: 355.0579.

*4.2.1.4. 3-[(Dimethylphenylsilyl)methyl]but-3-enyl 4-chlorobenzenesulfonate (**18**).* Yield (0.200 g, 91%) from **12**. ^{1}H NMR δ: 7.82–7.78 (m, 2H, aromatic), 7.54–7.44 (m, 4H, aromatic), 7.38–7.30 (m, 3H, aromatic,), 4.60 (br s, 1H, H-4a), 4.58–4.55 (m, 1H, H-4b), 4.03–4.07 (m, 2H, H-2a, H-2b), 2.10–2.04 (m 2H, H-1a, H-1b), 1.66 (d, 2H, *J* 0.7 Hz, H-5a, H-5b), 0.28 (s, 6H, 2×CH_3); ^{13}C NMR δ: 141.1, 140.4, 133.5, 129.5×2, 129.3, 129.2, 127.8, 110.7, 69.1, 36.9, 26.1, -0.0, −3.2. IR (neat) ν: cm^{-1} 2958, 1636, 1365, 1186, 832 cm^{-1}. HRMS (ESI): calcd for $C_{19}H_{23}O_3NaSiSCl$ $[M+Na]^+$: 417.0718; found: 417.0726.

4.2.2. Method B[24]. To a solution of hydroxy compound (**7**, **8**, **10**, **11**–**13**; 1.0 mmol) in dry dichloromethane (5 mL/mmol) were added DABCO (0.224 g, 2.0 mmol) and 4-chlorobenzenesulfonyl chloride (0.317 g, 1.5 mmol). The reaction progress was monitored by TLC. After 1.5 h, the reaction mixture was diluted with ethyl acetate (100 mL), washed with water (50 mL), dried ($MgSO_4$), and the solvent evaporated in vacuo. Pure products were obtained by flash chromatography (10% ethyl acetate/hexane).

*4.2.2.1. (Z)-6-Trimethylsilylhex-4-en-1-yl-4-chlorobenzenesulfonate (**15**).* Yield (0.141 g, 82%) from **8**. ^{1}H NMR δ: 7.87–7.82 (m, 2H, aromatic), 7.55–7.51 (m, 2H, aromatic), 5.47–5.38 (m, 1H, H-5), 5.16–5.10 (m, 1H, H-4), 4.08 (t, 2H, *J* 6.5 Hz, H-1a, H-1b), 2.02 (m, 2H, H-3a, H-3b), 1.74–1.68 (m, 2H, H-2a, H-2b), 1.40 (dm, 2H, *J* 8.7 Hz, H-6a, H-6b), −0.02 (s, 9H, TMS); ^{13}C NMR δ: 140.3, 134.8, 129.5, 129.3, 127.4, 124.8, 70.7, 28.9, 22.8, 18.5, −1.8. IR ($CHCl_3$) ν: 2957, 1366, 1185 cm^{-1}. HRMS (ESI): calcd for $C_{15}H_{23}O_3NaSiSCl$ $[M+Na]^+$: 369.0718; found: 369.0700.

*4.2.2.2. 6-Trimethylsilylhex-4-yn-1-yl-4-chlorobenzenesulfonate (**19**).* Yield (0.122 g, 71%) from **13**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88–7.84 (m, 2H, aromatic), 7.55–7.52 (m, 2H, aromatic), 4.17 (t, 2H, *J* 6.2 Hz, H-1a, H-1b), 2.25–2.20 (m, 2H, H-3a, H-3b), 1.81 (dt, 2H, *J* 13.0, 6.5 Hz, H-2a, H-2b), 1.34 (t, 2H, *J* 2.7 Hz, H-6a, H-6b), 0.04 (s, 9H, TMS); ^{13}C NMR δ: 140.4, 134.6, 129.6, 129.3, 79.0, 76.1, 69.7, 28.6, 15.1, 6.8, −0.02, −2.1. IR (CH_2Cl_2) ν: 2952, 1590, 1368, 1186, 850 cm^{-1}. HRMS (ESI): calcd for $C_{15}H_{21}O_3NaSiSCl$ $[M+Na]^+$: 367.0561; found: 367.0548.

4.3. Alkylation of 4-vinyloxyazetidin-2-one

General method.[16] 4-Vinyloxyazetidin-2-one **1** (0.113 g, 1.0 mmol) was added to a suspension of Bu_4NHSO_4 (0.373 g, 1.1 mmol) in dry THF (20 mL) cooled to −70 °C. Butyllithium (2.5 M in hexanes, 0.88 mL, 2.2 mmol) was then added dropwise at such a rate that the temperature did not exceed −60 °C. Afterward stirring at −70 °C was continued for 1 h and then alkylating agent (4-chlorobenzenesulfonate chloride) in THF (2 mL) was added. The reaction mixture was left overnight for slow warming up. Then it was diluted with ether (20 mL) and quenched with NH_4Cl solution (10 mL). After separation, the water layer was extracted with ether (20 mL) and combined organic layers were washed with water until neutral. Drying (Na_2SO_4), evaporation of solvents, and flash-chromatography afforded pure product.

*4.3.1. (E)-1-(4″-Triethylsilylbut-3″-enyl)-4-vinyloxyazetidin-2-one (**20**).* Yield (0.059 g, 21%) from **14**. ^{1}H NMR δ: 6.40 (dd, 1H, *J* 14.3, 6.7 Hz, H-1′), 5.98 (dt, 1H, *J* 18.7, 6.2 Hz, H-3″), 5.69 (dt, 1H, *J* 18.7, 1.5 Hz, H-4″), 5.27 (dd, 1H, *J* 3.6, 1.1 Hz, H-4), 4.35 (dd, 1H, *J* 14.3, 2.2 Hz, H-2′a), 4.21 (dd, 1H, *J* 6.7, 2.2 Hz, H-2′b), 3.44–3.37 (m, 1H, H-1″a), 3.28–3.21 (m, 1H, H-1″b), 3.10 (dd, 1H, *J* 14.8, 3.6 Hz, H-3a), 2.85 (d, 1H, *J* 14.8 Hz, H-3b), 2.49–2.36 (m, 2H, H-2″a, H-2″b), 0.92 (s, 9H, TMS), 0.55 (q, 6H, *J* 7.9 Hz, 3×CH_2); ^{13}C NMR δ: 165.3, 147.7, 143.8, 129.7, 91.2, 80.2, 44.8, 39.8, 35.3, 7.31, 3.4. IR (neat) ν 2953, 1774, 1619, 1195 cm^{-1}. HRMS (ESI): calcd for $C_{15}H_{27}NO_2NaSi$ $[M+Na]^+$: 304.1703; found: 304.1698.

*4.3.2. (Z)-1-(6″-Trimethylsilylhex-4″-enyl)-4-vinyloxyazetidin-2-one (**21**).* Yield (0.139 g, 52%) from **15**. ^{1}H NMR δ: 6.39 (dd, 1H, *J* 14.3, 6.7 Hz, H-1′), 5.46–5.40 (m, 1H, H-4″), 5.26 (dd, 1H, *J* 3.6, 1.1 Hz, H-4), 5.25–5.19 (m, 1H, H-5″), 4.34 (dd, 1H, *J* 14.3, 2.2 Hz, H-2′a), 4.20 (dd, 1H, *J* 6.7, 2.2 Hz, H-2′b), 3.27–3.16 (m, 2H, H-1″a, H-1″b), 3.12 (dd, 1H, *J* 14.8, 3.6 Hz, H-3a), 2.85 (d, 1H, *J* 14.8 Hz, H-3b), 2.22 (dq,

2H, *J* 7.5, 1.3 Hz, H-2″a, H-2″b), 1.70–1.55 (m, 2H, H-3″a, H-3″b), 1.45 (dd, 2H, *J* 8.6, 1.0 Hz, H-6″a, H-6″b), −0.1 (s, 9H, TMS); ^{13}C NMR *δ*: 165.3, 147.8, 126.7, 125.7, 91.1, 80.2, 44.8, 40.6, 28.1, 24.5, 18.5, −1.8. IR ($CHCl_3$) *ν*: 2957, 1759, 1642, 1621, 855 cm^{-1}. HRMS (ESI): calcd for $C_{14}H_{25}NO_2NaSi$ $[M+Na]^+$: 290.1547; found: 290.1550.

*4.3.3. 1-[2″-(Trimethylsilylmethyl)-prop-2″enyl]-4-vinyloxyazetidin-2-one (**22**).* Yield (0.072 g, 30%) from **9**. ^{1}H NMR *δ*: 6.38 (dd, 1H, *J* 14.2, 6.7 Hz, H-1′), 5.26 (dd, 1H, *J* 3,6, 1.0 Hz, H-4), 4.78 (d, 1H, *J* 1.2 Hz, H-4″a), 4.72 (br s, 1H, H-4″b), 4.37 (dd, 1H, *J* 14.2, 2.2 Hz, H-2′a), 4.18 (dd, 1H, *J* 6.7, 2.2 Hz, H-2′b), 3.90 (d, 1H, *J* 15.8 Hz, H-1″a), 3.52 (d, 1H, *J* 15.8 Hz, H-1″b), 3.18 (dd, 1H, *J* 14.9, 3.7 Hz, H-3a), 2.91 (d, 1H, *J* 14.9 Hz, H-3b), 1.58–1.43 (m, 2H, H-3″a, H-3″b), 0.05 (s, 9H, TMS); ^{13}C NMR *δ*: 165.6, 148.2, 141.1, 110.6, 91.1, 79.9, 47.0, 44.8, 24.2, −1.5. IR (CH_2Cl_2) *ν*: 2955, 1774, 1640, 1621 cm^{-1}. HRMS (ESI): calcd for $C_{12}H_{21}NO_2NaSi.[M+Na]^+$: 262.1234; found: 262.1241.

*4.3.4. 1-[(2″-Dimethylphenylsilylmethyl)-prop-2″enyl]-4-vinyloxyazetidin-2-one (**23**).* Yield (0.238 g, 79%) from **16**. ^{1}H NMR *δ*: 7.53–7.49 (m, 2H, aromatic), 7.37–7.34 (m, 3H, aromatic), 6.31 (dd, 1H, *J* 14.2, 6.7 Hz, H-1′), 5.14 (dd, 1H, *J* 3.6, 1.0 Hz, H-4), 4.75 (d, 1H, *J* 1.3 Hz, H-1″a), 4.70 (br s, 1H, H-1″b), 4.32 (dd, 1H, *J* 14.2, 2.2 Hz, H-2′a), 4.16 (dd, 1H, *J* 6.6, 2.2 Hz, H-2′b), 3.72 (d, 1H, *J* 15.7 Hz, H-4″a), 3.40 (d, 1H, *J* 15.7 Hz, H-4″b), 3.12 (dd, 1H, *J* 14.8, 3.6 Hz, H-3a), 2.86 (d, 1H, *J* 14.8, H-3b), 1.72 (ABq, 2H, *J* 13.9 Hz, H-3″a, H-3″b), 0.33 (s, 6H, 2×CH_3); ^{13}C NMR *δ*: 165.5, 148.2, 140.6, 138.1, 133.6, 129.2, 127.9, 111.4, 91.0, 79.9, 47.1, 44.8, 23.4, −3.0, −3.2. IR (neat) *ν*: 2957, 1771, 1640, 1621. 1392, 1195, 837 cm^{-1}. HRMS (ESI): calcd for $C_{17}H_{23}NO_2NaSi$ $[M+Na]^+$: 324.1390; found: 324.1386.

*4.3.5. 1-[(3″-Trimethylsilylmethyl)-but-3″-enyl]-4-vinyloxyazetidin-2-one (**24**).* Yield (0.076 g, 30%) from **17**. ^{1}H NMR *δ*: 6.40 (dd, 1H, *J* 14.3, 6.7 Hz, H-1′), 5.29 (dd, 1H, *J* 3.6, 1.2 Hz, H-4), 4.65 (q, 1H, *J* 2.8, 1.4 Hz, H-5″a), 4.61 (br s, 1H, H-5″b), 4.36 (dd 1H, *J* 14.3, 2.2 Hz, H-2′a), 4.21 (dd 1H, *J* 6.7, 2.2 Hz, H-2′b), 3.44 (ddd, 1H, *J* 14.5, 8.1, 6.7 Hz, H-1′a), 3.28 (ddd, 1H, *J* 14.5, 7.3, 0.8 Hz, H-1′b), 3.11 (dd, 1H, *J* 14.8, 3.6 Hz, H-3a), 2.85 (d, 1H, *J* 14.8 Hz, H-3b), 2.31–2.15 (m, 2H, H-2″a, H-2″b), 1.58–1.50 (m, 2H, H-4″a, H-4″b), 0.22 (s, 9H, TMS); ^{13}C NMR *δ*: 165.2, 147.8, 144.0, 109.2, 91.2, 80.3, 44.8, 39.0, 36.3, 26.5, −1.4. IR (neat) *ν*: 2955, 1771, 1194, 850 cm^{-1}. HRMS (ESI): calcd for $C_{13}H_{23}NO_2NaSi$ $[M+Na]^+$: 276.1390; found: 276.1385.

*4.3.6. 1-[(3″-Dimethylphenylsilylmethyl)-but-3″-enyl]-4-vinyloxyazetidin-2-one (**25**).* yield (0.095 g, 30%) from **18**. ^{1}H NMR *δ*: 7.52–7.48 (m, 2H, aromatic), 7.37–7.34 (m, 3H, aromatic), 6.33 (dd, 1H, *J* 14.3, 6.7 Hz, H-1′), 5.16 (dd, 1H, *J* 3.7, 1.0 Hz, H-4), 4.66–4.65 (m, 1H, H-5″a), 4.61 (br s, 1H, H-5″b), 4.33 (dd, 1H, *J* 14.3, 2.2 Hz, H-2′a), 4.19 (dd, 1H, *J* 6.7, 2.2 Hz, H-2′b), 3.36 (dt, 1H, *J* 14.3, 7.6 Hz, H-1″a), 3.17 (dt, 1H, *J* 14.3, 7.2 Hz, H-1″b), 3.07 (dd, 1H, *J* 14.8, 3.6 Hz, H-3a), 2.81 (br d, 1H, *J* 14.8, H-3b), 2.11–2.04 (m, 2H, H-2″a, H-2″b), 1.77 (dd, 2H, *J* 0.8, 3.2 Hz, H-4″a, H-4″b), 0.311 (s, 3H, CH_3), 0.308 (s, 3H, CH_3); ^{13}C NMR *δ*: 165.2, 147.7, 138.6, 133.6, 129.1, 127.8, 109.9, 91.1, 80.1, 44.7, 38.7, 36.0, 25.7, −3.0, −3.1. IR (neat) *ν*: 2961, 1760, 1641, 1402, 1195, 837 cm^{-1}. HRMS (ESI): calcd for $C_{18}H_{25}NO_2NaSi$ $[M+Na]^+$: 338.1547; found: 338.1560.

*4.3.7. (6″-Trimethylsilyl-hex-4″-ynyl)-4-vinyloxyazetidin-2-one (**26**).* Yield (0.153 g, 58%) from **19**. ^{1}H NMR *δ*: 6.40 (dd, 1H, *J* 14.3, 6.7 Hz, H-1′), 5.27 (dd, 1H, *J* 3.6, 1.1 Hz, H-4), 4.25 (dd, 1H, *J* 14.3, 2.2 Hz, H-2′a), 4.21 (dd, 1H, *J* 6.7, 2.2 Hz, H-2′b), 3.32 (br d, 2H, *J* 7.3 Hz, H-1″a, H-1″b), 3.13 (dd, 1H, *J* 14.8, 5.6 Hz, H-3a), 2.86 (br d, 1H, *J* 14.8 Hz, H-3b), 2.25–2.18 (m, 2H, H-2″a, H-2″b), 1.83–1.69 (m, 2H, H-3″a, H-3″b), 1.42 (t, 2H, *J* 2.7 Hz, H-6″a, H-6″b), 0.09 (s, 9H, TMS); ^{13}C NMR *δ*: 165.4, 147.8, 91.1, 80.4, 78.6, 77.1, 44.8, 40.2, 27.8, 16.7, 6.9, −2.1. IR (neat) *ν*: 2956, 2221, 1770, 1641, 1621 cm^{-1}. HRMS (ESI): calcd for $C_{14}H_{23}NO_2NaSi$ $[M+Na]^+$: 288.1363; found: 288.1391.

4.4. Oxidation of the vinyloxy group to the acetoxy one. General procedure

PCC on silica gel (2.2 g, 3 mmol/g) was added to a solution of 1-alkyl-4-vinyloxyazetidin-2-one (1.0 mmol) in dry CH_2Cl_2 (20 mL). The reaction mixture was refluxed for 3 h and then filtered through Celite and evaporated to dryness. Flash chromatography (20% ethyl acetate/hexane) afforded pure products.

*4.4.1. (Z)-4-Acetoxy-1-(6″-trimethylsilylhex-4″-enyl)-azetidin-2-one (**27**).* Yield (0.175 g, 62%) from **21**. ^{1}H NMR *δ*: 5.98 (dd, 1H, *J* 3.9, 1.2 Hz, H-4), 5.46–5.39 (m, 1H, H-5″), 5.25–5.18 (m, 1H, H-4″), 3.27 (ddd, 1H, *J* 14.2, 8.3, 6.8 Hz, H-1″a), 3.21 (dd, 1H, *J* 15.0, 4.0 Hz, H-3a), 3.11 (ddd, 1H, *J* 14.1, 8.2, 6.1 Hz, H-1″b), 2.89 (d, 1H, *J* 15.0 Hz, H-3b), 2.10 (s, 3H, Ac), 2.03–1.97 (m, 2H, H-3″a, H-3″b), 1.69–1.54 (m, 2H, H-2″a, H-2″b), 1.44 (br d, 2H, *J* 8.6 Hz, H-6″a, H-6″b), −0.01 (s, 9H, TMS); ^{13}C NMR *δ*: 170.7, 165.3, 126.7, 125.7, 76.1, 44.6, 41.0, 28.1, 24.4, 20.9, 18.6, −1.8. IR ($CHCl_3$) *ν*: 1763, 1252, 1038, 856 cm^{-1}. HRMS (ESI): calcd for $C_{14}H_{25}NO_3NaSi$ $[M+Na]^+$: 306.1496; found: 306.1509.

*4.4.2. 4-Acetoxy-1-[(2″-dimethylphenylsilyl-methyl)-prop-2″-enyl]-azetidin-2-one (**28**).* Yield (0.237 g, 75%) from **23**. ^{1}H NMR *δ*: 7.54–7.49 (m, 2H, aromatic), 7.37–7.34 (m, 3H, aromatic), 5.93 (dd, 1H, *J* 1.3, 4.0 Hz, H-4), 4.75 (q, 1H, *J* 1.2 Hz, H-4″a), 4.66 (q, 1H, *J* 1.2 Hz, H-4″b), 3.62 (d, 1H, *J* 16.0 Hz, H-1′a), 3.48 (d, 1H, *J* 16.0, Hz, H-1′b), 3.23 (dd, 1H, *J* 15.0, 4.0 Hz, H-3a), 2.91 (d, 1H, *J* 15.0 Hz, H-3b), 2.04 (s, 3H, CH_3), 1.72 (ABq, 2H, *J* 13.9 Hz, H-3″a, H-3″b), 0.34 (s, 3H, CH_3), 0.33 (s, 3H, CH_3); ^{13}C NMR *δ*: 170.5, 165.4, 140.8, 138.2, 133.6, 129.2, 127.8, 110.5, 76.1, 47.6, 44.7, 23.5, 20.7–3.2, −3.1. IR (neat) *ν*: 2957, 1777, 1750, 1391, 1235, 1038, 837 cm^{-1}. HRMS (ESI): calcd for $C_{17}H_{23}NO_3NaSi$ $[M+Na]^+$: 340.1355; found: 340.1355.

*4.4.3. 4-Acetoxy-1-(2″-methyl-prop-2″-enyl)-azetidin-2-one (**29**).* Yield 0.011 g, 6%. ^{1}H NMR *δ*: 6.01 (dd, 1H, *J* 1.3, 4.0 Hz, H-4), 4.90–4.85 (m, 2H, H-1″a, H-1″b), 3.82–3.69 (m, 2H, H-4′a, H-4′b), 3.28 (dd, 1H, *J* 15.0, 4.0 Hz, H-3a), 2.96 (d, 1H, *J* 15.0 Hz, H-3b), 2.08 (s, 3H, Ac), 1.73 (s, 3H, CH_3); ^{13}C NMR *δ*: 170.7, 165.5, 139.7, 113.2, 76.1, 47.3, 44.7, 20.7, 20.2. IR (neat) *ν*: 2922, 1774, 1750, 1393, 1234, 1037, 922 cm^{-1}. HRMS (ESI): calcd for $C_9H_{13}NO_3Na$ $[M+Na]^+$: 206.0788; found: 206.0778.

*4.4.4. 4-Acetoxy-1-(6″-trimethylsilylhex-4″-ynyl)-azetidin-2-one (**30**).* Yield (0.210 g, 75%) from **26**. ^{1}H NMR *δ*: 5.99 (dd, 1H, *J* 3.9, 1.2 Hz, H-4), 3.38–3.31 (m, 1H, H-1′a), 3.23 (dd, 1H, *J* 14.8, 3.7 Hz, H-3 a), 3.23–3.19 (m, 1H, H-1′b), 2.89 (d, 1H, *J* 14.8 Hz, H-3b), 2.23–2.18 (m, 2H, H-2′a, H-2′b), 2.12 (s, 3H, Ac), 1.79–1.70 (m, 2H, H-3′a, H-3′b), 1.41 (t, 2H, *J* 2.7 Hz, H-6′a, H-6′b); ^{13}C NMR *δ*: 170.6, 165.3, 78.5, 77.0, 76.2. 44.7, 40.6, 27.8, 20.9, 16.6, 6.9, −2.1. IR ($CHCl_3$) *ν*: 2959, 1764, 1400, 1039, 853 cm^{-1}. HRMS (ESI): calcd for $C_{14}H_{23}NO_3NaSi$ $[M+Na]^+$: 304.1339; found: 304.1325.

*4.4.5. 4-Formyloxy-1-(6″-trimethylsilylhex-4″-ynyl)-azetidin-2-one (**31**).* A solution of **26** (0.280 g, 1.05 mmol) in CH_2Cl_2 (5 mL) was placed in a three-necked flask equipped with a thermometer, bubbling tube, and ozone outlet. The solution was stirred and upon cooling to −78 °C ozone was bubbled. After about 15 min TLC showed the disappearance of substrate, and the solution turned light blue. The ozone generator was switched off, and oxygen was passed through the solution for 5 min to remove the excess of ozone. Dimethyl sulfide (0.5 mL) was added in one portion and stirring was continued at −78 °C for 20 min. Subsequently the reaction mixture was slowly brought to room temperature and the

solvent was evaporated. Purification on silica gel (20% ethyl acetate/hexane) gave **31** (0.210 g, 77.0%). ^{1}H NMR δ: 8.1 (br s, 1H, CHO), 6.3–6.0 (m, 1H, H-4), 3.38 (dt, 1H, *J* 14.3, 7.3 Hz, H-1″a), 3.29 (dd, 1H, *J* 15.1, 3.9 Hz, H-3a), 3.24 (dt, 1H, *J* 14.3, 6.9 Hz, H-1″b), 2.94 (d, 1H, *J* 15.1 Hz, H-3b), 2.23–2.19 (m, 2H, H-2″a, H-2″b), 1.95–1.72 (m, 2H, H-3″a, H-3″b), 1.42 (t, 2H, *J* 2.7 Hz, H-6″a, H-6″b), 0.09 (9H, s, TMS); ^{13}C NMR δ: 165.0, 160.2, 78.7, 76.9, 76.2, 44.9, 40.7, 27.6, 16.6, 6.9, −2.08. IR (CH_2Cl_2) ν: 2956, 1775, 1730, 1397, 1157 cm^{-1}. HRMS (ESI): calcd for $C_{13}H_{21}NO_3NaSi$ $[M+Na]^+$: 290.1183; found: 290.1197.

4.5. Cyclization. General procedure

To a stirred solution of β-lactam (0.1 mmol) in CH_2Cl_2 (2 mL) at 0 °C or at −20 °C was added Lewis acid (0.1 mmol). The reaction mixture was brought to 20 °C and kept at this temperature until disappearance of substrate (TLC). The reaction was quenched by the addition of saturated solution of $NaHCO_3$ (2 mL) and stirring was continued for 10 min. The organic phase was separated, washed with water, dried ($MgSO_4$), and evaporated. The crude product was purified on silica gel.

*4.5.1. 5-Methyl-3-methylene-6-oxa-1-azabicyclo[5.2.0]nonan-9-one (**32**).* Obtained according to the general procedure. $SnCl_2$/TMSCl catalysed—0.015 g, 88% yield from **22** (0.024 g, 0.1 mmol), 0.008 g, 50% from **23** (0.031 g, 0.1 mmol); $Yb(OTf)_3$ catalysed—0.012 g, 70% yield from **22** (0.024 g, 0.0 mmol), 0.009 g, 57% from **23** (0.031 g, 0.1 mmol). ^{1}H NMR δ: 5.03 (br d, 2H, *J* 8.5 Hz, H-10), 4.94 (dd, 1H, *J* 3.8, 0.8 Hz, H-7), 4.09 (br d, 1H, *J* 13.6 Hz, H-2a), 3.80 (br d, 1H, *J* 13.6 Hz, H-2b), 3.62–3.51 (m, 1H, H-5), 3.06 (ddd, 1H, *J* 14.6, 3.8, 2.0 Hz, H-8a), 2.78 (dd, 1H, *J* 14.6, 1.0 Hz, H-8b), 2.53 (d, 1H, *J* 13.7 Hz, H-4a), 2.20 (dd, 1H, *J* 13.6, 9.8 Hz, H-2b), 1.30 (d, 1H, *J* 6.3 Hz, H-11); ^{13}C NMR δ: 165.7, 141.0, 118.1, 80.7, 79.1, 49.0, 46.5, 44.0, 22.1. IR (neat) ν 2924, 1766, 1385, 1079 cm^{-1}. HRMS (EI): calcd for $C_9H_{13}NO_2$ (M^+): 167.0946; found: 167.0940.

*4.5.2. 1-Azabicyclo[4.2.0]oct-4-en-8-one (**33**).* Cyclization of compound **20** (0.028 g, 0.1 mmol) was performed according to the general procedure. $SnCl_2$/TMSCl catalysed—0.010 g, 78% yield, $SnCl_4$ catalysed—0.005 g, 44% yield. ^{1}H NMR δ: 5.94–5.92 (m, 1H, H-5), 5.90–5.87 (m, 1H, H-4), 3.93 (dd, 1H, *J* 13.8, 7.8 Hz, H-2a), 3.91–3.88 (m, 1H, H-6), 3.19 (ddd, 1H, *J* 14.7, 5.2, 0.9 Hz. H-7a), 2.89 (dddd, 1H, *J* 13.8, 10.5, 5.5, 0.5 Hz, H-2b), 2.61 (dd, 1H, *J* 14.7, 2.3 Hz, H-7b), 2.36–2.37 (m, 1H, H-3a), 2.07–2.00 (m, 1H, H-3b); ^{13}C NMR δ: 176.6, 127.1, 127.0, 45.0, 43.4, 36.5, 23.5; ^{1}H NMR (500 MHz, C_6D_6) δ: 5.40–5.34 (m, 2H, H-4, H-5), 3.65 (dd, 1H, *J* 13.7, 7.7 Hz, H-2a), 3.23–3.18 (m, 1H, H-6), 2.64 (ddd, 1H, *J* 14.5, 5.3, 0.7 Hz., H-7a), 2.29 (dddd, 1H, *J* 13.6, 10.6, 5.0, 0.7 Hz, H-2b), 2.15 (dd, 1H, *J* 14.5, 2.3 Hz, H-7b), 2.00–1.91 (m, 1H, H-3a), 1.32–1.25 (m, 1H, H-3b). IR (CH_2Cl_2) ν: 2927, 1756, 1378, 1097 cm^{-1}. HRMS (EI): calcd for C_7H_9NO $[M]^+$: 123.0684; found 123.0680.

4.5.3. (5R,6R*) and (5S*,6R*)-5-Vinyl-1-azabicyclo[4.2.0]octan-8-one (**34** and **35**).* Cyclization of compound **21** (0.053 g, 0.2 mmol) was performed according to the general procedure. TiF_4 catalysed reaction afforded as less polar product (5*R**,6*R**)-5-vinyl-1-azabicyclo[4.2.0]octan-8-one (**34**) in 0.010 g, 32% yield: ^{1}H NMR (500 MHz, C_6D_6) δ: 5.27 (ddd, 1H, *J* 17.4, 10.5, 7.0 Hz, H-9), 4.79 (ddd, 1H, *J* 10.4, 1.5, 1.1 Hz, H-10a), 4.71 (ddd, 1H, *J* 17.4, 1.5, 0.6 Hz, H-10b), 3.58–3.52 (m, 1H, H-2a), 2.65 (ddd, 1H, *J* 14.3, 4.6, 1.7 Hz, H-7a), 2.45 (ddd, 1H, *J* 9.6, 4.7, 1.8 Hz, H-6), 2.25 (dd, 1H, *J* 14.3, 1.8 Hz, H-7b), 2.1–2.0 (m, 1H, H-2b), 1.40–1.33 (m, 1H, H-5), 1.32–1.26 (m, 1H, H-4a), 1.03–0.91 (m, 2H, H-3), 0.74–0.65 (m, 1H, H-4b); ^{13}C NMR δ: 164.6, 138.9, 115.0, 51.0, 46.5, 44.3, 38.1, 28.7, 24.9. IR ($CHCl_3$) ν: 2946, 1734, 1411, 1396, 1094 cm^{-1}. HRMS (ESI): calcd for $C_9H_{13}NONa$ $[M+Na]^+$: 174.0889; found: 174.0883. More polar product: (5*S**,6*R**)-5-vinyl-1-azabicyclo[4.2.0]octan-8-one (**35**) in 0.011 g, 36% yield: ^{1}H NMR δ: 6.04 (dt, 1H, *J* 16.8, 10.2 Hz, H-9), 5.20–5.14 (m, 2H, H-10a, H-10b), 3.84–3.78 (m, 1H, H-2a), 3.52 (dt, 1H, *J* 4.7, 2.0 Hz, H-6), 2.88 (ddd, 1H, *J* 14.6, 4.7, 1.9 Hz, H-7a), 2.82–2.75 (m, 1H, H-2b), 2.77 (dd, 1H, *J* 14.6, 1.9 Hz, H-7b), 2.57 (m, 1H, H-5), 1.90–1.68 (m, 3H, H-3a, H-3b, H-4a), 1.51–1.37 (m, 1H, H-4b); ^{13}C NMR δ: 165.5, 134.6, 117.8, 49.3, 41.0, 39.4, 38.3, 28.8, 18.3. IR ($CHCl_3$) ν: 2948, 1735, 1409, 1104 cm^{-1}. HRMS (ESI): calcd for $C_9H_{13}NONa$ $[M+Na]^+$: 174.0889; found: 174.0892.

*4.5.4. Cyclization of acetoxy compound **27**.* Cyclization was performed analogously to the procedure described for **21** to afford compounds: (5*R**,6*R**)—**34** (0.004 g, 27% yield) and (5*S**,6*R**)—**35** (0.005 g, 30%).

*4.5.5. 4-Chloro-4-methylo-1-azabicyclo[4.2.0]octan-8-one (**36**).* Cyclization of compound **24** or compound **25** was performed according to the general method. From **24** (0.051 g, 0.2 mmol), $SnCl_2$/TMSCl catalysed 0.010 g, 30% yield. From **25** (0.063 g, 0.2 mmol) $SnCl_2$/TMSCl catalysed—0.020 g, 57% yield, $SnCl_4$ catalysed—0.020 g, 57% yield. ^{1}H NMR δ: 3.82 (dd, 1H, *J* 13.7, 5.9 Hz, H-2a), 3.76–3.70 (m, 1H, H-6), 3.18 (ddd, 1H, *J* 1.6, 4.6, 14.6 Hz, H-7a), 3.11 (dddd, 1H, *J* 4.0, 1.5, 11.9, 13.7 Hz, H-2b), 2.60 (dd, 1H, *J* 1.6, 14.6 Hz, H-7b), 2.33 (ddd, 1H, *J* 1.5, 4.0, 13.6 Hz, H-5a), 1.91–1.86 (m, 1H, H-3a), 1.67 (s, 3H, CH_3), 1.62 (ddd, 1H, *J* 14.0, 11.8, 5.9 Hz, H-3b), 1.41 (dd, 1H, *J* 10.2, 13.6 Hz, H-5b); ^{13}C NMR δ: 166.0, 68.2, 44.8, 44.4, 44.3, 38.9, 35.7, 34.1. IR (neat) ν 2929, 1750, 1390, 1135, 786, 561 cm^{-1}. HRMS (ESI): calcd for $C_8H_{12}NONaCl$ $[M+Na]^+$: 196.0500; found 196.0498.

*4.5.6. 1-Azabicyclo[4.2.0]oct-4-en-4-methyl-8-one (**37a**) and 1-azabicyclo[4.2.0]oct-3-en-4-methyl-8-one (**37b**).* Cyclization of compound **25** (0.063. 0.2 mmol) was performed according to the general method. Catalysed $Yb(OTf)_3$ afforded less polar product compound **37a**, 0.006 g, 21% yield and more polar product **37b**, 0.008 g, 28% yield.

*4.5.7. 1-Azabicyclo[4.2.0]oct-4-en-4-methyl-8-one (**37a**).* ^{1}H NMR δ: 5.64 (br s, 1H, H-5), 3.92 (dd, 1H, *J* 13.8, 7.8 Hz, H-2a), 3.85–3.83 (m, 1H, H-6), 3.14 (ddd, 1H, *J* 14.6, 5.1, 0.8 Hz, H-7a), 2.84 (dddd, 1H, *J* 13.8, 10.6, 5.5, 0.7 Hz, H-2b), 2.53 (dd, 1H, *J* 14.6, 2.2 Hz, H-7b), 2.38–2.26 (m, 1H, H-3a), 1.89–1.81 (m, 1H, H-3b), 1.72 (br s, 3H, CH_3); ^{13}C NMR δ: 169.8, 134.7, 120.9, 45.2, 43.8, 36.6, 28.3. 24.1. IR (CH_2Cl_2) ν 2925, 1730, 1025, 996 cm^{-1}. HRMS (EI): calcd for $C_8H_{11}NO$ $[M]^+$: 137.0841; found 137.0843.

*4.5.8. 1-Azabicyclo[4.2.0]oct-3-en-4-methyl-8-one (**37b**).* ^{1}H NMR δ: 5.43–5.39 (m, 1H, H-3), 4.09–4.02 (m, 1H, H-2a), 3.49–3.41 (m, 2H, H-6, H-2b), 3.20 (ddd, 1H, *J* 14.5, 4.4, 2.0 Hz. H-7a), 2.54 (dd, 1H, *J* 14.5, 1.5 Hz, H-7b), 2.26 (dd, 1H, *J* 14.8, 5.1 Hz, H-5a), 2.09–2.01 (m, 1H, H-5b), 1.75 (br s, 3H, CH_3); ^{13}C NMR δ: 167.1, 131.3, 116.1, 45.0, 45.4, 38.5, 33.7, 24.2. IR (CH_2Cl_2) ν: 2926, 1750, 1389, 866 cm^{-1}. HRMS (EI): calcd for $C_8H_{11}NO$ $[M]^+$: 137.0846; found 137.0846. ^{1}H NMR (500 MHz, C_6D_6) δ: 4.85 (br s, 1H, H-3), 3.95–3.84 (m, 1H, H-2a); 3.04–2.96 (m, 1H, H-2b), 2.76–2.71 (m, 1H, H-6); 2.67 (ddd, 1H, *J* 14.1, 4.6, 1.9 Hz, H-7a), 2.01 (dd, 1H, *J* 14.1, 1.4 Hz, H-7b), 1.51–1.45 (m, 1H, H-5a), (s, 3H, CH_3), 1.34–1.22 (m, 1H, H-5b).

*4.5.9. 4-Methylene-1-azabicyclo[4.2.0]octan-8-one (**37c**).* Selected signals taken from the spectrum of a crude post-reaction mixture: ^{1}H NMR δ: 4.90–4.88 (m, 2H,=CH_2), 3.96 (dd, 1H, *J* 13.0,.6.6 Hz, H-2), 3.38 (ddd, 1H, *J* 10.5, 1.0, 4.5 Hz, H-6), 3.13 (ddd, 1H, *J* 14.5, 4.5, 1.8 Hz, H-7a), 2.65 (dd, 1H, *J* 14.5, 1.6 Hz, H-7b).

*4.5.10. 5-Vinylidene-1-azabicyclo[4.2.0]octan-8-on (**38**).* Cyclization of compound **26** (0.053 g, 0.2 mmol) was performed according to the general method, TiF_4 catalysed—0.017 g, 56% yield. From

compound **30** (0.056 g, 0.2 mmol), TiF_4 catalysed, **38** was obtained in 0.018 g, 61% yield. ^{1}H NMR δ: 4.86 (dt, 1H, *J* 10.3, 3.8 Hz, H-10a), 4.73 (ddt, 1H, *J* 10.3, 4.3, 0.5 Hz, H-10b), 3.96–3.90 (m, 1H, H-6), 3.83 (dd, 1H, *J* 13.7, 5.5 Hz, H-2a), 3.12 (ddd, 1H, *J* 14.6, 4.6, 1.7 Hz, H-7a), 2.87 (dd, 1H, *J* 14.6, 1.9 Hz, H-7b), 2.76 (dddd, 1H, *J* 13.7, 12.1, 4.3, 1.7 Hz, H-2b), 2.46–2.24 (m, 1H, H-4a), 2.17–2.09 (m, 1H, H-4b), 1.76–1.70 (m, 1H, H-3a), 1.66–1.57 (m, 1H, H-3b); ^{13}C NMR δ: 202.8, 167.3, 99.4, 77.1, 47.7, 43.7, 39.2, 27.6, 25.9. IR (CH_2Cl_2) ν: 2952, 2923, 1962, 1748, 1384, 848 cm^{-1}. HRMS (ESI): calcd for $C_9H_{11}NONa$ $[M+Na]^+$: 172.0733; found: 172.0729.

*4.5.11. 5-Vinylidene-1-azabicyclo[4.2.0]octan-8-on (**38**) and 5-(2-trimethylsilylvinylidene)-1-azabicyclo-[4.2.0]octan-8-on (**39**).* Cyclization of compound **26** (0.053 g, 0.2 mmol) was performed according to the general method. Yb(OTf)$_3$ catalysed provided **38** in 0.016 g, 50% yield, and **39** in 0.013 g, 29%. From **31** (0.054 g, 0.2 mmol) using Yb(OTf)$_3$ as a catalyst compounds **38** (0.012 g, 38%) and **39** (0.003 g, 7%) were obtained NMR spectrum of two diastereoisomers (**39**) in the approx. ratio 3:1. ^{1}H NMR δ: 5.12 (t, 1H *J* 4.5 Hz, H-10), 3.99–3.95 (m, 1H, H-6), 3.86 (bdd, 1H, *J* 13.5, 5.5 Hz, H-2a), 3.12 (ddd, 1H, *J* 14.6, 4.6, 1.7 Hz, H-7a), 2.85 (dd, 1H, *J* 14.6, 1.8, H-7b), 2.80–2.73 (m, 1H, H-2b), 2.44–2.38 (m, 1H, H-4a), 2.16–2.10 (m, 1H, H-4b), 1.77–1.69 (m, 1H, H-3a), 1.66–1.56 (m, 1H, H-3b); ^{13}C NMR δ: 204.2, 93.0, 85.8, 77.2, 47.5, 43.6, 39.3, 27.1, 25.9, 0.03, 0.02, −0.9. IR (CH_2Cl_2) ν 2954, 1946, 1756 cm^{-1}. HRMS (ESI): calcd for $C_{12}H_{19}NONaSi$ $[M+Na]^+$: 244.1128; found: 244.1126. Selected ^{1}H NMR data of the less abundant isomer: 5.06 (t, 1H, *J* 4.8 Hz, H-10), 3.13 (ddd, 1H, *J* 14.6, 4.6, 1.6 Hz, H-7a).

*4.5.12. 5-Vinylidene-1-azabicyclo[4.2.0]octan-8-on (**38**) and 5-([1′-chloro-2′-trimethylsilyl-ethylidene)-1-azabicyclo[4.2.0]octan-8-one (**40**).* Cyclization of compound **26** (0.032 g, 0.2 mmol) was performed according to the general procedure. Using $SnCl_2$/TMSCl, compounds **38** (0.012 g, 43%), and **40** (0.010 g, 21%) were obtained. Cyclization of **31** was performed according to the general method. Using $SnCl_2$/TMSCl compounds **38** (0.016 g, 53%) and **40** (0.008 g, 17%) were obtained. ^{1}H NMR δ: 4.21–4.18 (m, 1H, H-6), 3.69 (ddd, 1H, *J* 12.6, 9.0, 6.7 Hz, H-2a), 3.39 (ddd, 1H, *J* 15.0, 4.7, 1.8 Hz, H-7a), 3.0 (dddd, 1H, *J* 12.6, 6.3, 4.6, 1.7 Hz, H-2a), 2.81 (dd, 1H, *J* 15.0, 2.2 Hz, H-7b), 2.32 (ddd, 1H, *J* 15.3, 6.8, 3.1 Hz, H-4a), 2.18–2.12 (m, 1H, H-4b), 1.99 (br d, 1H, *J* 14.4 Hz, H-10a), 1.90 (br d, 1H, *J* 14.4 Hz, H-10b), 1.84–1.77 (m, 1H, H-3a), 1.70–1.61 (m, 1H, H-3b), 0.09 (s, 9H, TMS); ^{13}C NMR δ: 168.7, 127.9, 128.3, 48.9, 45.9, 38.5, 26.6, 26.3, 22.5, −1.0. IR (CH_2Cl_2) ν: 2917, 1738, 1249, 851 cm^{-1}. HRMS (ESI): calcd for $C_{12}H_{20}NONaSiCl$ $[M+Na]^+$: 280.0895; found: 280.0903.

*4.5.13. 1-(Pent-4′-enyl)-4-vinyloxyazetidin-2-one (**41**).* Compound **41** was obtained according to the general method of alkylation 0.129 g, 71% yield from 5-bromo-1-pentene. ^{1}H NMR δ: 6.41 (dd, 1H, *J* 14.3, 6.7 Hz, H-1′), 5.84–5.75 (m, 1H, H-4″), 5.28 (dd, 1H, *J* 3.6, 1.0 Hz, H-4), 5.09–4.98 (m, 2H, H-5″a, H-5″b), 4.37 (dd, 1H, *J* 14.3, 2.2 Hz, H-2′a), 4.22 (dd, 1H, *J* 6.7, 2.2 Hz, H-2′b), 3.30–3,19 (m, 2H, H-3″a, H-3″b), 3.14 (dd, 1H, *J* 14.8, 3.6 Hz, H-3a), 2.88 (d, 1H, *J* 14.8, H-3b), 2.14–2.08 (m, 2H, H-1″a, H-1″b), 1.77–1.66 (m, 2H, H-2″a. H-2″b); ^{13}C NMR δ: 165.4, 147.7, 137.2, 115.5, 91.1, 80.3, 44.8, 40.3, 31.0, 27.2. IR (neat) ν: 2932, 1769, 1641, 1195 cm^{-1}. HRMS (ESI): calcd for $C_{10}H_{15}NO_2Na$ $[M+Na]^+$: 204.0995; found: 204.1004.

*4.5.14. 4-Acetoxy-1-(pent-4″-enyl) azetidin-2-one (**42**).* Compound **42** was obtained according to the general procedure of oxidation of the vinyloxy group to the acetoxy one, 0.154 g, 78% yield from **41** (0.181 g, 1.0 mmol). ^{1}H NMR δ: 5.99 (dd, 1H, *J* 3.1, 0.7 Hz, H-4), 5.83–5.74 (m, 1H, H-4″), 5.04 (dd, 1H, *J* 17.1, 1.6 Hz, H-5″a), 4.99 (dd, 1H, *J* 10.1, 1.1 Hz, H-5″b), 3.32–3.26 (m, 1H, H-3″a), 3.23 (dd, 1H, *J* 3.9, 15.0 Hz, H-3a), 3.16–3.11 (m, 1H, H-3″b), 2.90 (d, 1H, *J* 15.0, H-3b), 2.12 (s, 3H, CH_3), 2.08–2.05 (m 2H, H-2″a, H-2″b), 1.74–1.63 (m, 2H, H-1″a, H-1″b); ^{13}C NMR δ: 170.8, 165.4, 137.2, 115.4, 76.1, 44.9, 40.7, 30.9, 27.2, 20.9. IR (CH_2Cl_2) ν: 2955, 1772, 1749, 1399, 1225, 1037 cm^{-1}. HRMS (ESI): calcd for $C_{10}H_{15}NO_3Na$ $[M+Na]^+$: 220.0944; found: 220.0936.

*4.5.15. (E)-4-Acetoxy-1-(6″-trimethylsilylhex-4″-enyl)azetidin-2-one (**43**).* Compound **42** (0.035 g, 0.18 mmol) was dissolved in CH_2Cl_2 (10 mL) and trimethylallylsilane (0.14 mL) and Grubbs catalyst second generation (5 mg) was added. The reaction mixture was refluxed for 12 h. Evaporation of solvent and flash chromatography of the residue afforded product **43** as an oil (0.038 g, 75%). ^{1}H NMR δ: 5.98 (dd, 1H, *J* 1.2, 3.9 Hz, H-4), 5.44–5.37 (m, 1H, H-4′), 5.26–5.17 (m, 1H, H-5′), 3.32–3.18 (m, 2H, H-1′a, H-3a), 3.15–3.05 (m, 1H, H-1′b), 2.89 (d, 1H, *J* 15.0 Hz, H-3b), 2.10 (s, 3H, OAc), 2.03–1.96 (m, 2H, H-3′a, H-3′b), 1.68–1.54 (m, 2H, H-2′a, H-2′b), 1.46–1.38 (m, 2H, H-6′a, H-6′b), 0.01 (s, 9H, TMS); ^{13}C NMR δ: 170.7, 165.4, 127.4, 127.0, 76.0, 44.6, 40.7, 30.1, 27.2, 20.9, 18.5, −2.0. IR (CH_2Cl_2) ν: 2955, 1777, 1751, 1247, 1223, 1036, 854; cm^{-1}. HRMS (ESI): calcd for $C_{14}H_{25}NO_3NaSi$ $[M+Na]^+$: 306.1496; found. 306.1490.

4.6. Cyclization of compound 43

Performed according to the procedure described for **27** afforded (5*R**,6*R**) and (5*S**,6*R**)-5-vinyl-1-azabicyclo[4.2.0]octan-8-one (**34** and **35**) in a ratio of about 1.0:1.3.

*4.6.1. (E)-4-Acetoxy-1-(6″-diethylsilylhex-4″-enyl)-azetidin-2-one bound to the resin (**45**).* Compound **42** (0.17 g; 0.95 mmol) was dissolved at CH_2Cl_2 (20 mL) and allylsilane resin **44**[22] (0.4 g) and Grubbs catalyst second generation (0.005 g) was added and the reaction mixture was refluxed overnight. Solvent was evaporated, and the resin was washed with THF (3×2 mL), THF/H_2O (1:1) (3×2 mL), THF (3×2 mL), and CH_2Cl_2 (3×2 mL) and dried under reduced pressure. IR (KBr) ν: 1777, 1751 cm^{-1}.

4.6.2. (5R,6R*) and (5S*, 6R*)-5-Vinyl-1-azabicyclo [4.2.0]octan-8-one (**34** and **35**).* A solution of $SnCl_2$ (0.0095 g, 0.05 mmol) in CH_2Cl_2 (1.5 mL) was cooled to −10 °C and added TMSCl (25 μL, 0.2 mmol). After 10 min, when solution became clear (*E*)-1-(6-trimethylsilyl)hex-4-enyl-4-acetoxyazetidin-2-one resin (**45**) was added. After 2 h the saturated solution of $NaHCO_3$ (1 mL) was added and stirring was continued for 10 min. The solvent was evaporated and the resin was washed with H_2O (2×1 mL) and CH_2Cl_2 (3×2 mL). The crude product was purified on silica gel. Elution 30% Et_2O in CH_2Cl_2 gave mixture of diastereoisomers **34** and **35**, 1.3:1.0, respectively.

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Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2010.03.108.

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