DOI: 10.1002/ejoc.200601095

# Vinylic Halogenation in 4-Alkylidenazetidin-2-ones

**Gianfranco Cainelli,[a] Paola Galletti,*[a] Daria Giacomini,[a] Sebastiano Licciulli,[a] and Arianna Quintavalla[a]**

**Keywords:** Halogenation / 4-Alkylidenazetidin-2-ones / Vinylic substitution / Lactams / Azetidinones

The synthesis of a new family of halogenated β-lactams by oxidative substitution of vinylic hydrogen in conjugated double bonds of 4-alkylidenazetidinones is reported. Optimised procedures give good to excellent yields of chloro, bromo, iodo and nitro derivatives. A mechanism to explain the direct vinylic substitution is proposed.

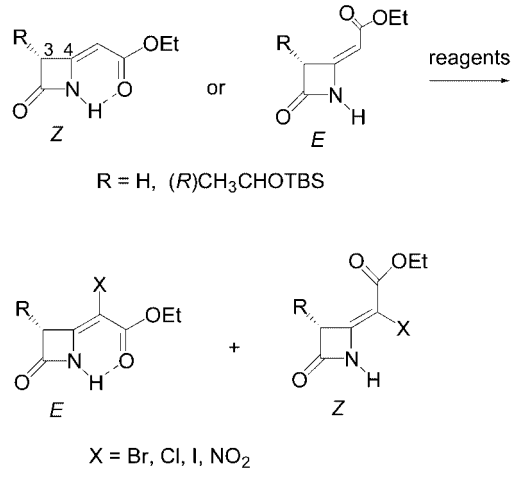

## 1. Introduction

β-Lactams are an important and extremely large class of compounds, the synthesis of which has been intensively investigated because of their effective biological activity[1] and their usefulness as intermediates in the syntheses of important compounds like β-amino acids,[2] aminols[3] and heterocycles of various sizes.[4]

4-Alkylidenazetidin-2-ones in particular represent a new class of monocyclic β-lactam compounds that show promising biological activity both as antibiotics[5] and as enzyme inhibitors.[6] Their biological and chemical reactivity is attributed to the direct connection of the conjugated double bond to the β-lactam ring: in fact, these compounds have been found to be highly activated towards ring-opening by nucleophilic acyl substitution and can act as enzymatic inhibitors of serine-dependent enzymes or can be functionalised and used as chemical synthons.

Here we report our results in a further derivatisation of 4-alkylidene-β-lactams designed to produce highly functionalised azetidinones by substitution of vinylic hydrogen in conjugated double bond to form chloro, bromo, iodo or nitro derivatives (Scheme 1).

α-Halogenation of simple α,β-unsaturated carbonyl compounds has been little reported in the literature.[7] α-Bromo enones are generally synthesised by a two-step procedure: dibromination followed by bromide elimination in the presence of a base. The few examples of direct vinylic bromination that exist are mainly restricted to unsaturated ketones. One-step preparation of α-bromo α,β-unsaturated carbonyl compounds, for example, has been achieved with the expensive Dess–Martin periodinane coupled with $Et_4NBr$,[8] whereas iodination has recently been accomplished with $I_2$




Scheme 1.

in aqueous THF with DMAP catalysis in a Baylis–Hillman-type reaction.[9] Direct bromination of more complex substrates such as uracils[10] or β-amino- and β-alkoxy α,β-unsaturated compounds, has been accomplished more frequently,[11] as in the cases of the bromination of 2-alkylidenetetrahydrofurans and 2-alkylidenepyrrolidines,[12] β-butoxyvinyl trifluoromethyl ketone[13] and β-aminovinyl chlorodifluoromethyl ketones.[14] To the best of our knowledge, vinylic substitution on β-amido α,β-unsaturated esters has never been reported in the literature.

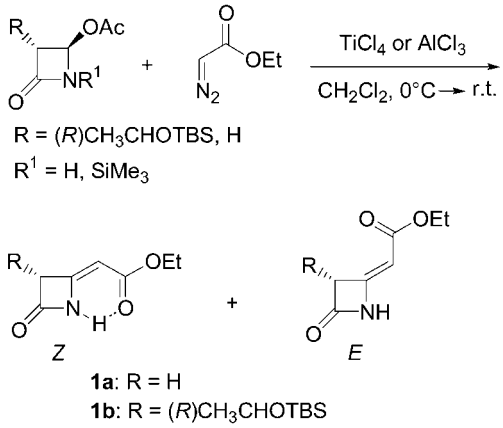
## 2. Results and Discussion

As previously reported by our group, 4-alkylidene-β-lactams are easily prepared by Lewis acid-promoted addition of diazocarbonyl compounds to 4-acetoxyazetidin-2-ones variously functionalised at the C-3 position (see Scheme 2).[15] Depending on the starting materials and

[a] Department of Chemistry "G. Ciamician", University of Bologna,
Via Selmi 2, 40126 Bologna, Italy
Fax: +39-051-2099456
E-mail: paola.galletti@unibo.it

Lewis acid used, 4-alkylidene-β-lactams can be obtained with *Z* or *E* diastereoselectivity. Diastereoisomers are easily separated by flash chromatography: *Z* isomers are configurationally stable whereas *E* isomers slowly convert into *Z* isomers, which are more stable because of the formation of an intramolecular hydrogen bond.[15]




Scheme 2.

In addition to evaluation of the biological activity of this new class of compounds, we were also interested in their chemical reactivity. The double bond on C-4 proved particularly unreactive, especially towards addition reactions, but attempted C-3 bromination with NBS (*N*-bromosuccinimide) resulted in unexpected oxidative substitution of double bond vinylic hydrogen, prompting us to take a closer look at the reaction (see Table 1).

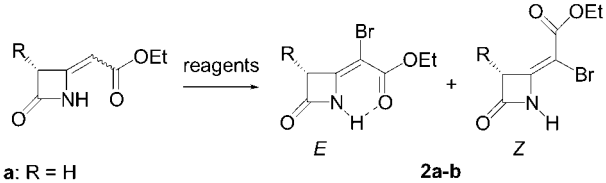
Bromination was initially achieved with NBS in chlorinated solvents (see Table 1). In $CH_2Cl_2$, the reaction proceeded in a few minutes with excellent yield (Entry 4). The presence of TEA was not essential, although it seemed to accelerate the reaction with 3-substituted β-lactams (Entries 7 and 8). In $CCl_4$, bromination appeared to be slower and less efficient (Entries 1–3).

Good results were also obtained with use either of $Br_2$ in chlorinated solvents or of pyridinium tribromide ($PyHBr_3$) in $CH_3CN$, in the presence of an equimolecular amount of TEA. The reaction with bromine was immediate (Entry 11) and could be monitored through decolouration of bromine drops added to the reaction vessel. Reactions with $Br_2$ proceeded with almost quantitative yields with **1a**, and with formation of *O*-desilylated product when conducted on **1b** in absence of the base (Entry 10). Reaction yields remained high with $PyHBr_3$[16] and TEA (Entries 12–15), with the major advantage of an easier to handle bromination reagent.

Bromination with NBS was also carried out with an *N*-Bn-protected 4-alkylidene-β-lactam.[17] At room temperature the reaction proceeded in low yield, whereas the use of higher temperatures allowed the brominated products to be obtained in 75% isolated yield, with the formation of equal amounts of *Z* and *E* bromo derivatives.

The double bond configurations of the halogenated compounds were assigned by comparison with spectral and HPLC data for the starting materials (see Experimental Section, Table 4). Once separated by preparative HPLC, pure *Z* or *E* isomers were configurationally stable, whereas bases, acids or silica gel were able to promote *Z*/*E* interconversion.

Table 1. Bromination of 4-alkylidenazetidin-2-ones **1a**–**b**.




| Entry | Starting material | Reagents (equiv.) and conditions | Yield (%) | *Z*/*E* Products[a] |
|---|---|---|---|---|
| 1 | (*E*)-**1a** | NBS (1), $CCl_4$, room temp., 15 h | 69[b] | 30:70 |
| 2 | (*Z*)-**1a** | NBS (1), $CCl_4$, room temp., 15 h | 90 | 33:67 |
| 3 | (*Z*)-**1a** | NBS (1), $CCl_4$, 0 °C, 15 h | 71[b] | 70:30 |
| 4 | (*E*)-**1a** | NBS (1), $CH_2Cl_2$, room temp., 15 min | 95 | 59:41 |
| 5 | (*E*)-**1a** | NBS (1), TEA (1) $CH_2Cl_2$, room temp., 15 min | 95 | 80:20 |
| 6 | (*Z*)-**1b** | NBS (1.1), $CCl_4$, AIBN cat, reflux, 9 h | 21[b] | 30:70 |
| 7 | (*Z*)-**1b** | NBS (1), $CH_2Cl_2$, room temp., 22 h | 82 | 17:83 |
| 8 | (*Z*)-**1b** | NBS (1), TEA (1) $CH_2Cl_2$, room temp., 15 min | 95 | 40:60 |
| 9 | (*E*)-**1a** | $Br_2$ (1), $CCl_4$, room temp., 18 h | 90 | 63:37 |
| 10 | (*Z*)-**1b** | $Br_2$ (1.5), $CH_2Cl_2$, room temp., 15 min | 90[c] | – |
| 11 | (*Z*)-**1b** | $Br_2$ (1.1), TEA (1.1), $CH_2Cl_2$, 0 °C, 15 min | 95 | 45:55 |
| 12 | (*Z*)-**1a** | $PyHBr_3$ (1.1), TEA (1.1), $CH_3CN$, 0 °C, 2 h | 95 | 80:20 |
| 13 | (*E*)-**1a** | $PyHBr_3$ (1.1), TEA (1.1), $CH_3CN$, 0 °C, 5.5 h | 90 | 95:5 |
| 14 | (*Z*)-**1b** | $PyHBr_3$ (1.1), TEA (1.1), $CH_3CN$, 0 °C, 1.5 h | 95 | 65:35 |
| 15 | (*E*)-**1b** | $PyHBr_3$ (1.1), TEA (1.1), $CH_3CN$, 0 °C, 1.5 h | 78 | 63:37 |
| 16 | (*Z*)-**1b** | $PyHBr_3$ (1.1), $CH_3CN$, 0 °C, 2 h | 90[c] | – |

[a] Diastereomeric ratios were evaluated by HPLC or $^1H$ NMR on crude reaction mixtures. [b] Isolated yields after chromatography; all other yields were evaluated by $^1H$ NMR on crude reaction mixtures. [c] Complete bromination but concurrent *O*-desilylation.

With regard to the diastereoselectivity outcome reflected in the data reported in Table 1, stereochemistry was not preserved, since mixtures of diastereoisomers were always obtained whether starting from pure (*Z*)- or (*E*)-4-alkylidenazetidin-2-ones. Moreover, the results were not easy to interpret because of the large number of parameters influencing the diastereomeric ratios of products: configurations of starting materials, steric hindrance of substituents on C-3, formation of intramolecular hydrogen bonds in product *E* isomers, reagent type, coordinating ability of reaction solvents, reaction times and temperatures. Even the partial double bond isomerisations of *E* starting materials and/or *Z* products during the reaction course should be taken into consideration, especially in cases in which TEA was used.

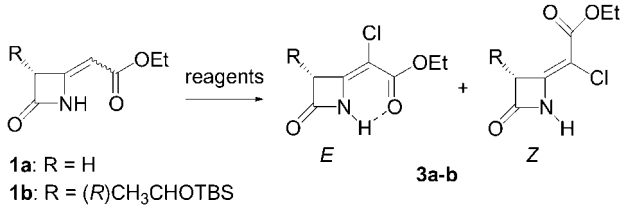
As a general trend, when the starting materials were C-3-substituted β-lactams **1b**, *E* isomers seemed to be preferred in noncoordinating chlorinated solvents, because of the steric hindrance of the side chain, together with the formation of the intramolecular hydrogen bond. In $CH_3CN$, however, the preference was for formation of the *Z* isomers. When the starting materials were C-3 unsubstituted β-lactams **1a**, *Z* isomers were preferred in most cases.

In view of the good results obtained with bromination, we also tested the reactivity of other halogens. The first attempts were made with chlorination (Table 2) with *N*-chlorosuccinimide (NCS) in various chlorinated solvents, but in all cases only traces of the products were obtained (Entries 1–3), even in the presence of TEA and/or AIBN (2,2′-azobisisobutyronitrile).

Better results were obtained with a saturated solution of chlorine in $CH_2Cl_2$. Once prepared at 0 °C, the yellow chlorine solution was added dropwise to the β-lactam solution and the conversion was monitored by drop-decolouration and TLC. In this case, addition of TEA did not improve reaction yield or rate, but instead gave rise to side products.

As in the bromination, C-3-unsubstituted starting materials **1a** preferentially gave (*Z*)-chlorinated compounds (Entries 7 and 8), whereas C-3-substituted ones **1b** preferen-

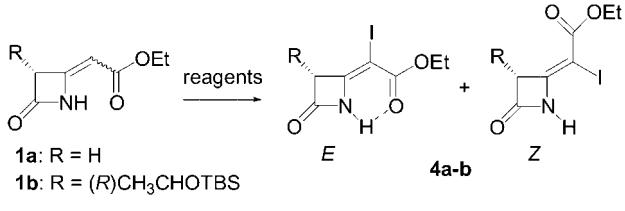
Table 2. Chlorination of 4-alkylidenazetidin-2-ones **1a**–**b**.




| Entry | Starting material | Reagents (equiv.) and conditions | Isolated yield (%) | *Z*/*E* Products[a] |
|---|---|---|---|---|
| 1 | (*Z*)-**1b** | NCS (1.5), $CH_2Cl_2$, room temp., 8 d | – | – |
| 2 | (*E*)-**1b** | NCS (1.5), $CH_2Cl_2$, room temp., 8 d | traces | – |
| 3 | (*E*)-**1b** | NCS (2), TEA (1), $CH_2Cl_2$, room temp., 2 d | traces | – |
| 4 | (*Z*)-**1b** | $Cl_2$ (satd. sol.), $CH_2Cl_2$, 0 °C, 30 min | 67 | 80:20 |
| 5 | (*Z*)-**1b** | $Cl_2$ (satd. sol.), TEA (1.1), $CH_2Cl_2$, 0 °C, 2 h | traces | – |
| 6 | (*E*)-**1b** | $Cl_2$ (satd. sol.), $CH_2Cl_2$, 0 °C, 30 min | 39 | 36:64 |
| 7 | (*E*)-**1a** | $Cl_2$ (satd. sol.), $CH_2Cl_2$, 0 °C, 30 min | 64 | 67:33 |
| 8 | (*Z*)-**1a** | $Cl_2$ (satd. sol.), $CH_2Cl_2$, 0 °C, 30 min | 60 | 83:17 |

[a] Diastereomeric ratios were evaluated by HPLC or $^1$HNMR on crude reaction mixture.

Table 3. Iodination of 4-alkylidenazetidin-2-ones **1a**–**b**.




| Entry | Starting material | Reagents (equiv.) and conditions | Yield (%) | *Z*/*E* Products[a] |
|---|---|---|---|---|
| 1 | (*Z*)-**1a** | NIS (1.5), $CH_2Cl_2$, room temp., 2 h | 90 | 75:25 |
| 2 | (*E*)-**1a** | NIS (1.3), $CH_2Cl_2$, room temp., 3 h | 82[b] | 75:25 |
| 3 | (*E*)-**1a** | NIS (1),TEA (1), $CH_2Cl_2$, room temp., 15 min | 95 | 54:46 |
| 4 | (*Z*)-**1a** | $I_2$ (2.5), TEA (2.2), $CH_2Cl_2$, room temp., 72 h | 95 | 73:27 |
| 5 | (*E*)-**1a** | $I_2$ (2.0), TEA (1.3), $CH_2Cl_2$, room temp., 19 h | 84[b] | 83:17 |
| 6 | (*Z*)-**1b** | $I_2$ (2.5), TEA (1.2), $CH_2Cl_2$, room temp., 12 h | 52[b] | 44:56 |
| 7 | (*E*)-**1b** | $I_2$ (2.5), TEA (1.2), $CH_2Cl_2$, room temp., 12 h | 27 | 49:51 |

[a] Diastereomeric ratios were evaluated by HPLC or $^1$H NMR on crude reaction mixtures. [b] Isolated yields after chromatography; all other yields are evaluated by $^1$H NMR on the crude reaction mixtures.

tially give either *Z* or *E* products, depending on the starting material configuration (Entries 4 and 6).

Even iodination gave good yields with use of *N*-iodosuccinimide (NIS) or molecular $I_2$ in the presence of TEA. The results are reported in Table 3.

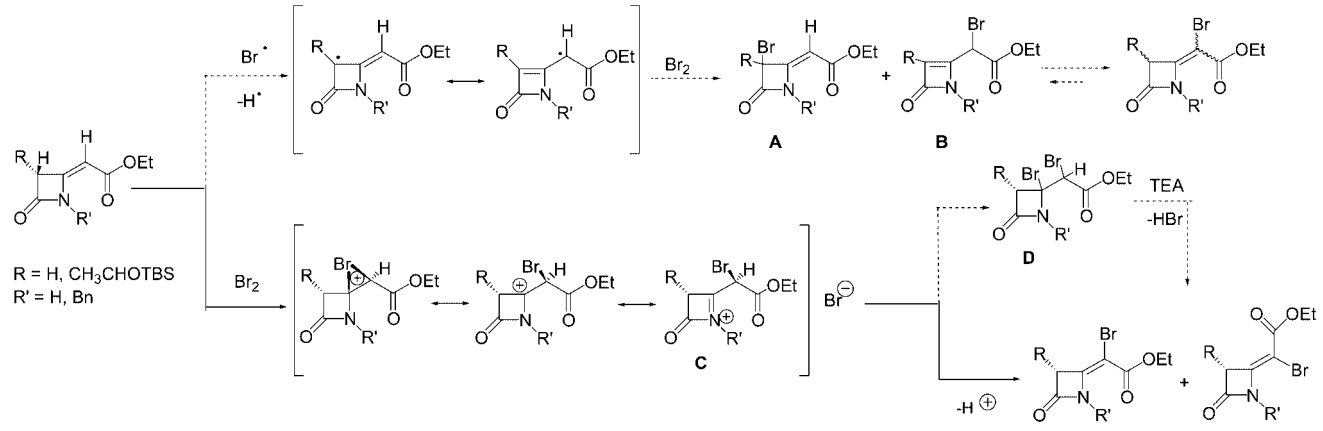
With C-3-unsubstituted starting materials **1a**, iodination always produced good yields with either NIS or $I_2$ in the presence of TEA (Entries 3 and 4). As in bromination, the base was not essential to formation of the product, though it very much raised reaction rates and yields (Entries 2 and 3). Preferential formation of *Z* isomers was always observed regardless of the double bond configurations in the reactants. From **1b**, iodination still proceeded but with much lower yields.

Two hypotheses can be advanced for the reaction mechanism (Scheme 3).

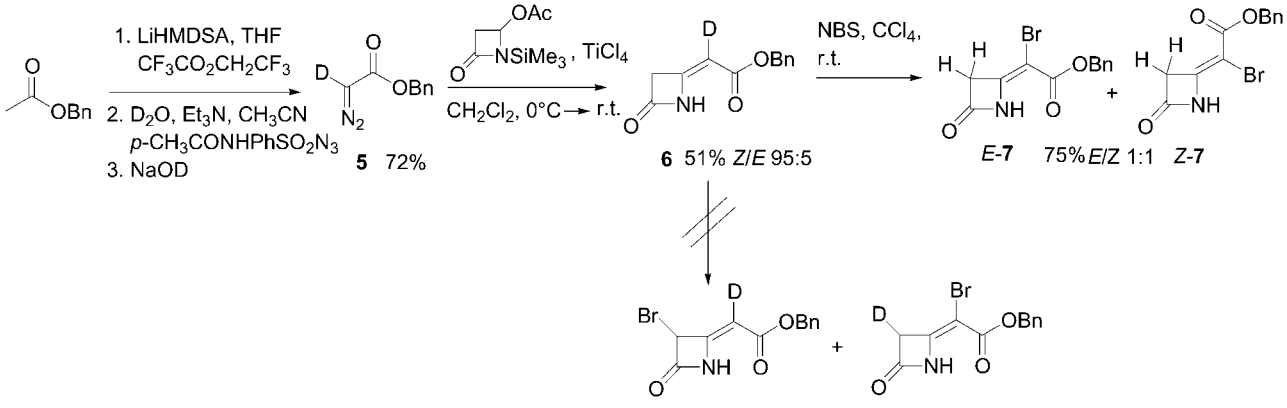
(i) Radical Allylic Bromination. In this case the formation of the final vinyl brominated product is considered to take place through a radical allylic bromination followed by an allylic rearrangement. Although reported by other authors,[12] this mechanism seemed improbable in our case since the use of AIBN did not improve yields and no traces of the 3-bromo derivatives (**A**, Scheme 3) were detected in crude reaction mixtures. Moreover, the final product should derive from an allylic rearrangement of **B**, the formation of which should be strongly disfavoured by the endocyclic carbon–carbon double bond. A reaction pathway through **B** should even result in racemisation at the C-3 position, but the presence of diastereoisomers was never observed in reactions performed with enantiomerically pure **1b**.

To exclude a radical mechanism more emphatically, we also carried out the bromination reaction with a deuterium-labelled 4-alkylidene-β-lactam (Scheme 4). For this, we prepared the deuteriodiazoacetate **5**, which was treated with 4-acetoxyazetidin-2-one in the presence of $TiCl_4$ to give the 4-(1-deuterio-alkyliden)azetidin-2-one **6**. The bromination reaction with **6** proceeded as usual in high yields to furnish products **7** with no deuterium incorporated in any position.

(ii) NBS as Source of Molecular Bromine. In this case, NBS is taken to be a source of molecular bromine (analogously to $PyHBr_3$). It is known that NBS can provide a constant concentration of $Br_2$ through HBr bromide ion attack on NBS.[18] Addition of bromine results in the formation of a positively charged bromonium intermediate, further stabilised by the nitrogen lone pair (**C**, Scheme 3); a contribution of an iminium ion to the stabilisation of a C-4 cationic intermediate in substitution reactions of 4-acetoxyazetidinones has in fact already been suggested.[19] Intermediate **C** could then undergo bromide addition or β-hydrogen elimination. Bromide addition would give rise to




Scheme 3.



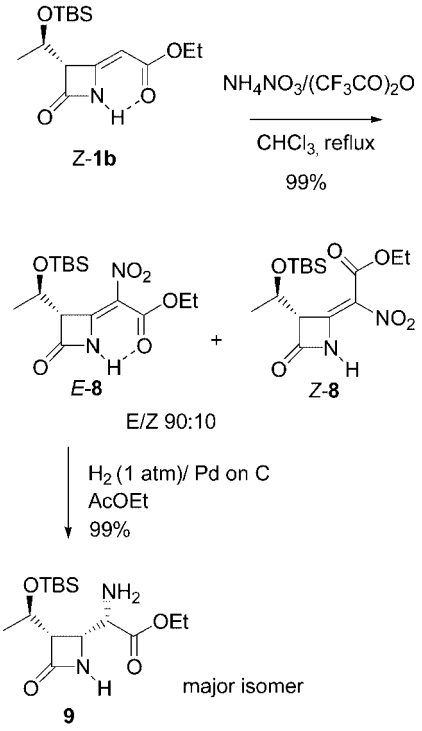

Scheme 4.

a 1,2-dibromo adduct (**D**, Scheme 3), in which a base-mediated elimination would be needed to provide the final vinyl bromide.[20] However, no 1,2-dibromo intermediate **D** was ever isolated, even in the presence of an excess of bromide ion by addition of a soluble bromide salt such as $Et_4NBr$, and moreover we observed that the base was not strictly necessary for formation of the product (see Table 1, Entries 7 and 9). Evolution of the bromonium intermediate towards the final vinyl bromide by β-hydrogen elimination therefore appeared to be the most likely mechanism, assisted by the formation of an extended conjugated system. The role of the base would just be to favour the hydrogen elimination and to buffer the hydrobromic acid. Furthermore, formation of a long-lived, freely rotatable intermediate **C** helps explain the lack of stereocontrol.

The same mechanism (ii) could be advanced for chlorine and iodine substitution, and was confirmed by the lack of reactivity with use of NCS, which has a weaker tendency to generate $Cl_2$ than the tendency of NBS and NIS to behave as active sources of their molecular halogens.[19]

To extend the scope of the vinylic substitution, we also attempted to perform the reaction with various electrophiles. Fluorination, acylation and alkylation did not take place even on experimentation with reaction conditions and reagents, though we did successfully achieve nitration with use of trifluoroacetic anhydride/$NH_4NO_3$ in $CHCl_3$ (see Scheme 5).[21] Nitrovinyl derivatives **8** were isolated and characterised, and a 90:10 diastereoisomerically enriched mixture was reduced to give the corresponding *cis* α-amino ester **9** as prevalent isomer. In this compound, the stereochemistry has been tentatively assigned as shown in Scheme 5, under the hypothesis that the stereochemistry of the starting material **8** was predominantly *E* and that the hydrogen *syn* addition to the double bond occurred at the less hindered face.[22]




Scheme 5.

## 3. Conclusion

We have developed the synthesis of a new family of halogenated β-lactams by direct vinylic substitution on 4-alkylidenazetidinones. Optimised procedures gave good to excellent yields of chloro, bromo and iodo derivatives. An extended procedure gave a nitrovinyl compound, which was stereoselectively hydrogenated to provide the corresponding α-amino ester.

All new vinyl-substituted 4-alkylidene-β-lactams are currently under pharmacological screening and further research on the reactivity of the new halogenated-β-lactams is in progress.

## Experimental Section

**General:** $^1H$ and $^{13}C$ NMR: recorded on a Varian INOVA 300 or a GEMINI 200 instrument with a 5 mm probe. All chemical shifts have been quoted relative to deuterated solvent signals, $\delta$ in ppm, $J$ in Hz. Spectra of products **2**–**4** and **8** were recorded on diastereomerically enriched column fractions. FT-IR: Nicolet 380 FT measured as films between NaCl plates, wavenumbers reported in $cm^{-1}$. Melting points: collected on a Büchi B-540 and uncorrected. TLC: Merck 60 $F_{254}$. Column chromatography: Merck silica gel 200–300 mesh. HPLC: Agilent Technologies HP1100, column ZORBAX-Eclipse XDB-C8 Agilent Technologies, mobile phase: $H_2O/CH_3CN$, gradient: from 10% to 100% of $CH_3CN$ in 25 min, then 100% of $CH_3CN$, 0.5 mL $min^{-1}$. MS: Agilent Technologies MSD1100 single-quadrupole mass spectrometer, full-scan mode from *m/z* 50 to *m/z* 2600, scan time 0.1 s in positive ion mode, ESI spray voltage 4500 V, nitrogen gas 35 psi, drying gas flow 11.5 mL $min^{-1}$, fragmentor voltage 20 V. HRMS: Thermo Finnigan mat 95 xp, 70 eV, 10000 resolution (Mass Spectrometry Centre, Faculty of Industrial Chemistry, University of Bologna). Elemental analysis: performed at the Istituto di Biologia Marina, CNR, Bologna, Italy.

**Starting Materials:** 4-Alkylidene-β-lactams **1a**–**b** were prepared by the already reported procedure.[15]

**Halogenation Procedures**

**Bromination with NBS:** NBS (89 mg, 0.5 mmol) was added to a solution of **1a** (72 mg, 0.5 mmol) or **1b** (156 mg, 0.5 mmol) and TEA (0.07 mL, 0.5 mmol) in $CH_2Cl_2$ (10 mL). The reaction was monitored by TLC. After full conversion, a saturated solution of $NH_4Cl$ (10 mL) was added. The mixture was extracted with $CH_2Cl_2$ (3 × 10 mL), dried with $Na_2SO_4$ and concentrated. If necessary, residues of succinimide were eliminated by trituration with $CCl_4$.

**Bromination with $PyHBr_3$:** $PyHBr_3$ (176 mg, 0.55 mmol) was added to a solution of **1a** (72 mg, 0.5 mmol) or **1b** (156 mg, 0.5 mmol) and TEA (0.08 mL, 0.55 mmol) in $CH_3CN$ (10 mL). After full conversion, a saturated solution of $NH_4Cl$ (10 mL) was added. The mixture was extracted with EtOAc (3 × 10 mL), dried with $Na_2SO_4$ and concentrated.

**Bromination with $Br_2$:** A solution of $Br_2$ (88 mg, 0.55 mmol) in $CH_2Cl_2$ (2 mL) was added dropwise to a solution of **1a** (72 mg,

0.5 mmol) or **1b** (156 mg, 0.5 mmol) and TEA (0.08 mL, 0.55 mmol) in $CH_2Cl_2$ (10 mL). The reaction was monitored by drop discoloration and TLC. After full conversion, a saturated solution of $NH_4Cl$ (10 mL) was added. The mixture was extracted with $CH_2Cl_2$ (3 × 10 mL), dried with $Na_2SO_4$ and concentrated.

**Chlorination with $Cl_2$:** Saturated chlorine solution was prepared by bubbling gaseous chlorine into dichloromethane at 0 °C until the solution became yellow. This solution was added dropwise at 0 °C to a solution of $CH_2Cl_2$ (10 mL) containing **1a** (72 mg, 0.5 mmol) or **1b** (156 mg, 0.5 mmol). The reaction was monitored by TLC, and after full conversion the reaction mixture was concentrated. The products were isolated by flash chromatography.

**Iodination with NIS:** NIS (112 mg, 0.5 mmol) was added to a solution of **1a** (72 mg, 0.5 mmol) or **1b** (156 mg, 0.5 mmol) and TEA (0.07 mL, 0.5 mmol) in $CH_2Cl_2$ (10 mL). The reaction was monitored by TLC. After full conversion, a saturated solution of $NH_4Cl$ (10 mL) was added. The mixture was extracted with $CH_2Cl_2$ (3 × 10 mL), dried with $Na_2SO_4$ and concentrated. Where necessary, residues of succinimide were eliminated by trituration with $CCl_4$.

**Iodination with $I_2$:** $I_2$ (318 mg, 1.25 mmol) was added to a solution of **1a** (72 mg, 0.5 mmol) or **1b** (156 mg, 0.5 mmol) and TEA (0.15 mL, 1.1 mmol) in $CH_2Cl_2$ (10 mL). The reaction was monitored by drop discoloration and TLC. After full conversion, a saturated solution of $NH_4Cl$ (10 mL) was added. The mixture was extracted with $CH_2Cl_2$ (3 × 10 mL), dried with $Na_2SO_4$ and concentrated.

**Ethyl (*E*,*Z*)-Bromo-(4-oxoazetidin-2-yliden)acetate (2a):** Pale yellow solid. IR ($CH_2Cl_2$): $\tilde{\nu}$ = 3500, 3250, 1823, 1668 $cm^{-1}$. HRMS (EI) calculated for $C_7H_8BrNO_3$: 232.9687; found: 232.9683. $C_7H_8BrNO_3$ (234.05) calculated: C 35.92, H 3.45, N 5.98; found: C 35.99, H 3.38, N 5.91.

**Isomer (*E*)-2a:** $R_f$ = 0.61 (cyclohexane/ethyl acetate, 6:4). $^1H$ NMR (300 MHz, $CDCl_3$, 22 °C): $\delta$ = 1.36 (t, $J$ = 6.9 Hz, 3 H, C$H_3$CH$_2$), 3.63 (s, 2 H, $CH_2$), 4.28 (q, $J$ = 6.9 Hz, 2 H, CH$_3$C$H_2$), 8.31 (br s, 1 H, NH) ppm. $^{13}C$ NMR ($CDCl_3$, 75 MHz, 22 °C): $\delta$ = 14.1, 47.3, 62.2, 83.7, 148.9, 162.2, 163.8 ppm. HPLC-MS (ESI): $R_t$ = 15.9 min; $m/z$ = 234.0–236.0 $[M + H]^+$, 256.1–258.1 $[M + Na]^+$.

**Isomer (*Z*)-2a:** $R_f$ = 0.53 (cyclohexane/ethyl acetate, 6:4). $^1H$ NMR (300 MHz, $CDCl_3$, 22 °C): $\delta$ = 1.32 (t, $J$ = 6.9 Hz, 3 H, C$H_3$CH$_2$), 3.79 (s, 2 H, $CH_2$), 4.26 (q, $J$ = 6.9 Hz, 2 H, CH$_3$C$H_2$), 7.58 (br s, 1 H, NH) ppm. $^{13}C$ NMR ($CDCl_3$, 75 MHz, 22 °C): $\delta$ = 14.1, 46.9, 62.2, 84.5, 147.8, 162.4, 162.9 ppm. HPLC-MS (ESI): $R_t$ = 14.3 min; $m/z$: 234.0–236.0 $[M + H]^+$, 256.1–258.1 $[M + Na]^+$.

**Ethyl (*E*,*Z*)-Bromo-{(3*S*)-3-[(1*R*)-1-(*tert*-butyldimethylsilanyloxy)-ethyl]-4-oxoazetidin-2-ylidene}acetate (2b):** Pale yellow oil. IR ($CH_2Cl_2$): $\tilde{\nu}$ = 3400, 1820, 1650 $cm^{-1}$. $C_{15}H_{26}BrNO_4Si$ (392.36) calculated: C 45.92, H 6.68, N 3.57; found: C 45.85, H 6.62, N 3.54.

**Isomer (*E*)-2b:** $R_f$ = 0.63 (cyclohexane/ethyl acetate, 8:2). $^1H$ NMR ($CDCl_3$, 300 MHz, 22 °C): $\delta$ = 0.09 (s, 6 H, SiMe$_2$), 0.87 (s, 9 H, Si$t$Bu), 1.20 (d, $J$ = 6.3 Hz, 3 H, C$H_3$CH), 1.24 (t, $J$ = 7.2 Hz, 3 H, C$H_3$CH$_2$), 3.88 (dd, $^4J_{H3,NH}$ = 1.2 Hz, $J$ = 3.3 Hz, 1 H, C$H$CHOSi), 4.24 (q, $J$ = 7.2 Hz, 2 H, CH$_3$C$H_2$), 4.53 (dq, $J$ = 3.3, 6.3 Hz, 1 H, CHC$H$OSi), 8.77 (br s, 1 H, NH) ppm. $^{13}C$ NMR ($CDCl_3$, 75 MHz, 22 °C): $\delta$ = –5.1, –4.6, 14.2, 17.9, 20.8, 25.6, 62.2, 64.1, 64.6, 82.9, 151.4, 163.4, 164.9 ppm. HPLC-MS (ESI): $R_t$ = 27.0 min; $m/z$: 392.0–394.1 $[M + H]^+$.

**Isomer (*Z*)-2b:** $R_f$ = 0.60 (cyclohexane/ethyl acetate, 8:2). $^1H$ NMR ($CDCl_3$, 300 MHz, 22 °C): $\delta$ = 0.08 (s, 6 H, SiMe$_2$), 0.88 (s, 9 H, Si$t$Bu), 1.33 (d, $J$ = 6.3 Hz, 3 H, C$H_3$CH), 1.33 (t, $J$ = 7.2 Hz, 3 H, C$H_3$CH$_2$), 4.04 (dd, $^4J_{H3,NH}$ = 1.8 Hz, $J$ = 3.9 Hz, 1 H, C$H$CHOSi), 4.27 (q, $J$ = 7.2 Hz, 2 H, CH$_3$C$H_2$), 4.58 (dq, $J$ = 3.9, 6.3 Hz, 1 H, CHC$H$OSi), 7.98 (br s, 1 H, NH) ppm. $^{13}C$ NMR ($CDCl_3$, 75 MHz, 22 °C): $\delta$ = –5.0, –4.7, 14.3, 17.9, 19.9, 25.6, 61.9, 64.5, 66.5, 84.8, 150.3, 162.1, 165.0 ppm. HPLC-MS (ESI): $R_t$ = 26.1 min; $m/z$: 392.0–394.1 $[M + H]^+$.

**Ethyl (*E*,*Z*)-Chloro-(4-oxoazetidin-2-yliden)acetate (3a):** White solid. IR ($CH_2Cl_2$): $\tilde{\nu}$ = 3244, 1825, 1661 $cm^{-1}$. HRMS (EI) calculated for $C_7H_8ClNO_3$: 189.0193; found: 189.0185. $C_7H_8ClNO_3$ (189.60) calculated: C 44.34, H 4.25, N 7.39; found: C 44.41, H 4.21, N 7.46.

**Isomer (*E*)-3a:** $R_f$ = 0.68 (cyclohexane/ethyl acetate, 1:1). $^1H$ NMR ($CDCl_3$, 300 MHz, 22 °C): $\delta$ = 1.35 (t, $J$ = 6.9 Hz, 3 H, C$H_3$CH$_2$), 3.66 (s, 2 H, $CH_2$), 4.29 (q, $J$ = 6.9 Hz, 2 H, CH$_3$C$H_2$), 8.54 (br s, 1 H, NH) ppm. $^{13}C$ NMR ($CDCl_3$, 75 MHz, 22 °C): $\delta$ = 14.2, 45.6, 62.1, 96.3, 146.6, 162.6, 163.4 ppm. HPLC-MS (ESI): $R_t$ = 15.0 min; $m/z$: 190.1 $[M + H]^+$.

**Isomer (*Z*)-3a:** $R_f$ = 0.66 (cyclohexane/ethyl acetate, 1:1). $^1H$ NMR ($CDCl_3$, 300 MHz, 22 °C): $\delta$ = 1.31 (t, $J$ = 6.9 Hz, 3 H, C$H_3$CH$_2$), 3.81 (s, 2 H, $CH_2$), 4.26 (q, $J$ = 6.9 Hz, 2 H, CH$_3$C$H_2$), 7.95 (br s, 1 H, NH) ppm. $^{13}C$ NMR ($CDCl_3$, 75 MHz, 22 °C): $\delta$ = 14.2, 46.1, 61.9, 96.6, 145.6, 162.5, 163.6 ppm. HPLC-MS (ESI): $R_t$ = 13.6 min; $m/z$: 190.1 $[M + H]^+$.

**Ethyl (*E*,*Z*)-{(3*S*)-3-[(1*R*)-1-(*tert*-Butyldimethylsilanyloxy)ethyl]-4-oxoazetidin-2-ylidene}-chloroacetate (3b):** Pale yellow oil. IR ($CH_2Cl_2$): $\tilde{\nu}$ = 3283, 1823, 1652 $cm^{-1}$. $C_{15}H_{26}ClNO_4Si$ (347.91) calculated: C 51.78, H 7.53, N 4.03; found: C 51.71, H 7.48, N 4.07.

**Isomer (*E*)-3b:** $R_f$ = 0.67 (cyclohexane/ethyl acetate, 7:3). $^1H$ NMR ($CDCl_3$, 300 MHz, 22 °C): $\delta$ = 0.08 (s, 6 H, SiMe$_2$), 0.87 (s, 9 H, Si$t$Bu), 1.35 (t, $J$ = 7.0 Hz, 3 H, C$H_3$CH$_2$), 1.38 (d, $J$ = 6.6 Hz, 3 H, C$H_3$CH), 3.92 (m, 1 H, C$H$CHOSi), 4.29 (q, $J$ = 7.0 Hz, 2 H, CH$_3$C$H_2$), 4.47 (dq, $J$ = 3.4, 6.6 Hz, 1 H, CHC$H$OSi), 8.39 (br s, 1 H, NH) ppm. $^{13}C$ NMR ($CDCl_3$, 75 MHz, 22 °C): $\delta$ = –5.2, –4.5, 14.2, 18.0, 21.6, 25.7, 62.0, 64.5, 65.9, 95.9, 149.5, 163.7, 164.6 ppm. HPLC-MS (ESI): $R_t$ = 26.8 min; $m/z$: 348.3–350.3 $[M + H]^+$, 370.2–372.1 $[M + Na]^+$.

**Isomer (*Z*)-3b:** $R_f$ = 0.65 (cyclohexane/ethyl acetate, 7:3). $^1H$ NMR ($CDCl_3$, 200 MHz, 22 °C): $\delta$ = 0.10 (s, 3 H, SiMe), 0.11 (s, 3 H, SiMe), 0.91 (s, 9 H, Si$t$Bu), 1.33 (d, $J$ = 6.6 Hz, 3 H, C$H_3$CH), 1.34 (t, $J$ = 7.0 Hz, 3 H, C$H_3$CH$_2$), 4.10 (dd, $^4J_{H3,NH}$ = 1.8 Hz, $J$ = 4.0 Hz, 1 H, C$H$CHOSi), 4.31 (q, $J$ = 7.0 Hz, 2 H, CH$_3$C$H_2$), 4.58 (dq, $J$ = 4.0, 6.6 Hz, 1 H, CHC$H$OSi), 7.56 (br s, 1 H, NH) ppm. $^{13}C$ NMR ($CDCl_3$, 50 MHz): $\delta$ = –5.0, –4.6, 14.3, 18.0, 19.9, 25.6, 61.8, 64.7, 65.9, 96.8, 148.0, 162.1, 164.6 ppm. HPLC-MS (ESI): $R_t$ = 26.0 min; $m/z$: 348.3–350.3 $[M + H]^+$, 370.2–372.1 $[M + Na]^+$.

**Ethyl (*E*,*Z*)-Iodo-(4-oxoazetidin-2-yliden)acetate (4a):** White solid. IR ($CH_2Cl_2$): $\tilde{\nu}$ = 3227, 1823, 1650 $cm^{-1}$. HRMS (EI) calculated for $C_7H_8INO_3$: 280.9549; found: 280.9552. $C_7H_8INO_3$ (281.05) calculated: C 29.91, H 2.87, N 4.98; found: C 29.81, H 2.80, N 4.91.

**Isomer (*E*)-4a:** $R_f$ = 0.45 (cyclohexane/ethyl acetate, 7:3). $^1H$ NMR ($CDCl_3$, 200 MHz, 22 °C): $\delta$ = 1.33 (t, $J$ = 7.0 Hz, 3 H, C$H_3$CH$_2$), 3.56 (s, 2 H, $CH_2$), 4.24 (q, $J$ = 7.0 Hz, 2 H, CH$_3$C$H_2$), 8.53 (br s, 1 H, NH) ppm. $^{13}C$ NMR ($CDCl_3$, 50 MHz, 22 °C): $\delta$ = 14.3, 45.1, 53.2, 62.3, 152.6, 162.7, 163.7 ppm. HPLC-MS (ESI): $R_t$ = 16.3 min; $m/z$: 282.1 $[M + H]^+$.

**Isomer (*Z*)-4a:** $R_f$ = 0.42 (cyclohexane/ethyl acetate, 7:3). $^1H$ NMR ($CDCl_3$, 200 MHz, 22 °C): $\delta$ = 1.31 (t, $J$ = 7.0 Hz, 3 H, C$H_3$CH$_2$), 3.77 (s, 2 H, $CH_2$), 4.24 (q, $J$ = 7.0 Hz, 2 H, CH$_3$C$H_2$), 7.35 (br s, 1 H, NH) ppm. $^{13}C$ NMR ($CDCl_3$, 50 MHz): $\delta$ = 14.2, 49.7, 57.2,

62.4, 153.4, 162.3, 163.3 ppm. HPLC-MS (ESI): $R_t$ = 14.8 min; *m/z*: 282.1 $[M + H]^+$.

**Ethyl (*E*,*Z*)-{(3*S*)-3-[(1*R*)-1-(*tert*-Butyldimethylsilanyloxy)ethyl]-4-oxoazetidin-2-ylidene}-iodoacetate (4b):** Pale yellow oil. IR ($CH_2Cl_2$): $\tilde{\nu}$ = 3277, 1822, 1634 $cm^{-1}$. $C_{15}H_{26}INO_4Si$ (439.36) calculated: C 41.01, H 5.96, N 3.19; found: C 40.95, H 5.88, N 3.11.

**Isomer (*E*)-4b:** $R_f$ = 0.67 (cyclohexane/ethyl acetate, 8:2). $^1H$ NMR ($CDCl_3$, 300 MHz, 22 °C): $\delta$ = 0.11 (s, 6 H, $SiMe_2$), 0.89 (s, 9 H, Si*t*Bu), 1.19 (d, *J* = 6.3 Hz, 3 H, C*H*$_3$CH), 1.36 (t, *J* = 7.0 Hz, 3 H, C*H*$_3$CH$_2$), 3.82 (dd, $^4J_{H3,NH}$ = 1.0 Hz, *J* = 3.6 Hz, 1 H, C*H*CHOSi), 4.22 (q, *J* = 7.0 Hz, 2 H, CH$_3$C*H*$_2$), 4.63 (m, 1 H, CHC*H*OSi), 8.85 (br s, 1 H, NH) ppm. $^{13}C$ NMR ($CDCl_3$, 75 MHz, 22 °C): $\delta$ = –5.0, –4.6, 14.3, 17.9, 19.9, 25.7, 57.0, 62.5, 63.8, 67.5, 155.5, 163.8, 164.5 ppm. HPLC-MS (ESI): $R_t$ = 27.2 min; *m/z*: 440.0 $[M + H]^+$, 457.1 $[M + H_2O]^+$, 462.0 $[M + Na]^+$.

**Isomer (*Z*)-4b:** $R_f$ = 0.65 (cyclohexane/ethyl acetate, 8:2). $^1H$ NMR ($CDCl_3$, 300 MHz, 22 °C): $\delta$ = 0.10 (s, 6 H, $SiMe_2$), 0.91 (s, 9 H, Si*t*Bu), 1.29 (d, *J* = 6.2 Hz, 3 H, C*H*$_3$CH), 1.37 (t, *J* = 7.0 Hz, 3 H, C*H*$_3$CH$_2$), 4.04 (dd, $^4J_{H3,NH}$ = 1.8 Hz, *J* = 6.0 Hz, 1 H, C*H*CHOSi), 4.24 (q, *J* = 7.0 Hz, 2 H, CH$_3$C*H*$_2$), 4.61 (dq, *J* = 6.0, 6.2 Hz, 1 H, CHC*H*OSi), 7.58 (br s, 1 H, NH) ppm. $^{13}C$ NMR ($CDCl_3$, 75 MHz, 22 °C): $\delta$ = –4.9, –4.6, –14.2, 17.9, 19.9, 25.7, 52.1, 62.2, 63.6, 67.5, 154.8, 163.8, 164.5 ppm. HPLC-MS (ESI): $R_t$ = 26.4 min; *m/z*: 440.0 $[M + H]^+$, 462.0 $[M + Na]^+$.

**Benzyl 2-Deuterio-diazoacetate (5):** Deep yellow liquid. The diazo ester was prepared as reported in the literature[23] by quenching of the reaction mixture with $D_2O$ and NaOD. $^1H$ NMR ($CDCl_3$, 200 MHz, 22 °C): $\delta$ = 5.23 (s, 2 H, C*H*$_2$Ph), 7.38 (m, 5 H, Ph) ppm. $^{13}C$ NMR ($CDCl_3$, 75 MHz, 22 °C): $\delta$ = 45.4 (t, $J_{C,D}$ = 31.5 Hz), 66.1, 127.7, 127.8, 129.1, 135.8, 166.1 ppm.

**Benzyl Deuterio-(4-oxoazetidin-2-yliden)acetate (6):** This compound was prepared from **5** as reported in Ref.[6]. Pale yellow oil. $^1H$ NMR ($CDCl_3$, 300 MHz, 22 °C): $\delta$ = 3.55 (s, 2 H,C*H*$_2$), 5.19 (s, 2 H, C*H*$_2$Ph), 7.35 (m, 5 H, Ph), 8.65 (br s, 1 H, NH) ppm. $^{13}C$ NMR ($CDCl_3$, 75 MHz, 22 °C): $\delta$ = 44.8, 66.0, 90.3 (t, $J_{C,D}$ = 25.2 Hz), 128.1, 128.3, 128.6, 135.9, 150.4, 164.7, 166.8 ppm.

**Benzyl (*E*,*Z*)-Bromo-(4-oxoazetidin-2-yliden)acetate (7):** Pale yellow oil.

**Isomer (*E*)-7:** $^1H$ NMR ($CDCl_3$, 300 MHz, 22 °C): $\delta$ = 3.64 (s, 2 H, C*H*$_2$), 5.25 (s, 2 H, C*H*$_2$Ph), 7.39 (m, 5 H, Ph), 8.2 (br s, 1 H, NH) ppm.

**Isomer (*Z*)-7:** $^1H$ NMR ($CDCl_3$, 300 MHz, 22 °C): $\delta$ = 3.75 (s, 2 H, C*H*$_2$), 5.23 (s, 2 H, C*H*$_2$Ph), 7.39 (m, 5 H, Ph), 7.5 (br s, 1 H, NH) ppm.

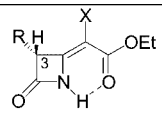
**Ethyl (*E*,*Z*)-{(3*S*)-3-[(1*R*)-1-(*tert*-Butyldimethylsilanyloxy)ethyl]-4-oxoazetidin-2-ylidene}-nitroacetate (8):** Trifluoroacetic anhydride (0.178 mL, 1.25 mmol) and solid $NH_4NO_3$ (40 mg, 0.5 mmol) were added to a solution of **1b** (156 mg, 0.5 mmol) in $CHCl_3$ (10 mL), and the reaction mixture was heated to reflux with monitoring by HPLC and then poured into saturated NaCl (10 mL) and extracted with $CH_2Cl_2$ (3 × 10 mL). The product was obtained as a pale yellow oil and could be further purified by flash chromatography, although the diastereoselectivity ratio changed. IR ($CH_2Cl_2$): $\tilde{\nu}$ = 1842, 1564, 1515 $cm^{-1}$. $R_f$ = 0.7 (cyclohexane/ethyl acetate, 7:3). HPLC-MS (ESI): $R_t$ = 24.9 min; *m/z*: 359.4 $[M + H]^+$, 381.5 $[M + Na]^+$, 397.2 $[M + K]^+$. $C_{15}H_{26}N_2O_6Si$ (358.46) calculated: C 50.26, H 7.31, N 7.81; found: C 50.14, H 7.42, N 7.75.

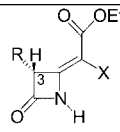
**Isomer (*Z*)-8:** $^1H$ NMR ($CDCl_3$, 200 MHz, 22 °C): $\delta$ = 0.09 (s, 6 H, $SiMe_2$), 0.88 (s, 9 H, Si*t*Bu), 1.23 (d, *J* = 5.8 Hz, 3 H, C*H*$_3$CH), 1.33 (t, *J* = 7.4 Hz, 3 H, C*H*$_3$CH$_2$), 4.45 (m, 4 H, CH$_3$C*H*$_2$, C*H*CHOSi, CHC*H*OSi), 8.73 (br s, 1 H, NH) ppm. $^{13}C$ NMR ($CDCl_3$, 50 MHz, 22 °C): $\delta$ = –5.3, –4.5, 14.0, 17.8, 21.1, 25.5, 62.3, 64.8, 67.3, 106.1, 157.3, 159.9, 163.6 ppm.

**Isomer (*E*)-8:** $^1H$ NMR ($CDCl_3$, 200 MHz, 22 °C): $\delta$ = 0.09 (s, 6 H, $SiMe_2$), 0.88 (s, 9 H, Si*t*Bu), 1.19 (d, *J* = 5.8 Hz, 3 H, C*H*$_3$CH), 1.33 (t, *J* = 7.4 Hz, 3 H, C*H*$_3$CH$_2$), 4.45 (m, 4 H, CH$_3$C*H*$_2$, C*H*CHOSi, CHC*H*OSi), 8.95 (br s, 1 H, NH) ppm. $^{13}C$ NMR ($CDCl_3$, 50 MHz, 22 °C): $\delta$ = –5.4, –4.54, 14.1, 17.8, 21.3, 25.5, 62.5, 64.8, 68.0, 106.0, 159.6, 160.7, 164.0 ppm.

**Ethyl (*S*)-Amino{(2*S*,3*S*)-3-[(1*R*)-1-(*tert*-butyldimethylsilanyloxy)-ethyl]-4-oxoazetidin-2-yl}acetate (9):**[22] Compound **8** (35 mg, 0.1 mmol) was dissolved in EtOAc (5 mL), and Pd (10 wt.% on activated carbon, 3 mg) was added. The reaction mixture was

Table 4. Selected $^1H$ NMR and HPLC data for compounds **1**–**4**.




| Comp. | R | X | Config.[a] | HPLC r.t. [min] | δ NH [ppm] | δ 3-H [ppm] | Config.[a] | HPLC r.t. [min] | δ NH [ppm] | δ 3-H [ppm] |
|---|---|---|---|---|---|---|---|---|---|---|
| **1a** | H | H | *Z* | 12.0 | 8.47 | 3.56 | *E* | 11.3 | 7.6 | 3.78 |
| **2a** | H | Br | *E* | 15.9 | 8.31 | 3.63 | *Z* | 14.3 | 7.58 | 3.79 |
| **3a** | H | Cl | *E* | 15.0 | 8.54 | 3.66 | *Z* | 13.6 | 7.95 | 3.81 |
| **4a** | H | I | *E* | 16.3 | 8.53 | 3.56 | *Z* | 14.8 | 7.35 | 3.78 |
| **1b** | (*R*)CH$_3$CHOTBS | H | *Z* | 25.9 | 8.31 | 3.63 | *E* | 25.1 | 7.90 | 4.10 |
| **2b** | (*R*)CH$_3$CHOTBS | Br | *E* | 27.0 | 8.77 | 3.88 | *Z* | 26.1 | 7.98 | 4.04 |
| **3b** | (*R*)CH$_3$CHOTBS | Cl | *E* | 26.8 | 8.39 | 3.92 | *Z* | 26.0 | 7.56 | 4.10 |
| **4b** | (*R*)CH$_3$CHOTBS | I | *E* | 27.2 | 8.85 | 3.82 | *Z* | 26.4 | 7.58 | 4.04 |

[a] In halogenated compounds (X = Cl, Br, I) a change in the priority order of C=C substituents causes an apparent inversion of configuration respect to starting materials (X = H).

treated with $H_2$ (1 atm) and stirred at room temperature until full conversion (1 h). The catalyst was filtered off and the solution was concentrated to give **9** (33 mg) as a yellow oil. $^1$H NMR ($CDCl_3$, 300 MHz, 22 °C): $\delta$ = 0.17 (s, 6 H, $SiMe_2$), 0.94 (s, 9 H, Si*t*Bu), 1.34 (t, $J$ = 7.2 Hz, 3 H, $CH_3CH_2$), 1.47 (d, $J$ = 6.3 Hz, 3 H, $CH_3CH$), 2.0–2.3 (br s, 2 H, $NH_2$), 3.37 (ddd, $^4J_{H3,NH}$ = 1.5 Hz, $J$ = 5.4, 5.4 Hz, 1 H, CHCHCHOSi), 3.89 (dd, $J$ = 5.4, 8.4 Hz, 1 H, $OCOCHCHNH_2$), 4.23 (m, 1 H, $OCOCHCHNH_2$), 4.27 (q, $J$ = 7.2 Hz, 2 H, $CH_3CH_2$), 4.51 (m, 1 H, $CH_3CH$), 6.20 (br s, 1 H, NH) ppm. $^{13}$C NMR ($CDCl_3$, 75 MHz, 22 °C): $\delta$ = –4.3, –4.8, 14.2, 18.1, 22.8, 25.9, 54.7, 54.9, 60.9, 61.7, 65.8, 167.6, 172.8 ppm. HPLC-MS (ESI): $R_t$ = 22.9 min; *m/z*: 332 $[M + H]^+$. $C_{15}H_{30}N_2O_4Si$ (330.49) calculated: C 54.51, H 9.15, N 8.48; found: C 54.63, H 9.23, N 8.41.

**Double Bond Configuration Assignment**

Double bond configurations of halogenated products **2**–**4** were assigned by comparison with $^1$H NMR and HPLC data for their starting materials[15] (see Table 4).

In particular, diastereoisomers with stronger intramolecular hydrogen bonds [*E* diastereoisomers in products, *Z* in starting materials according to IUPAC rules] have longer HPLC retention times and more powerfully unshielded NH resonances in the $^1$H NMR spectra in $CDCl_3$. Proton chemical shifts on C-3 are downfield in *E* halogenated-β-lactams and in *Z* starting materials.

In nitro derivatives **8** the double bond configuration has been tentatively assigned on the hypothesis that in chlorinated solvents the intramolecular hydrogen bond between NH and ester C=O group is stronger than that between NH and nitro group.[24]

## Acknowledgments

We would like to thank Mr. Paolo Bedonni for experimental assistance and Mr. Andrea Garelli for technical assistance. We also acknowledge the Ministero dell'Università e della Ricerca (MIUR) and the University of Bologna for funding.

[1] a) G. S. Singh, *Mini-Rev. Med. Chem.* **2004**, *4*, 93–109; b) A. J. Wright, *Mayo Clin. Proc.* **1999**, *74*, 290–307; c) M. I. Konaklieva, *Curr. Med. Chem.-Anti-Infective Agents* **2002**, *1*, 215–238.
[2] a) A. R. A. S. Deshmukha, B. M. Bhawal, D. Krishnaswamy, V. V. Govande, B. A. Shinkre, A. Jayanth, *Curr. Med. Chem.* **2004**, *11*, 1889–1920; b) C. Palomo, J. Aizpurua, I. Ganboa, M. Oiarbide, *Synlett* **2001**, 1813–1826.
[3] M. Suffness, *Taxol, Science and Applications*, CRC Press, Boca Raton, FL, USA, **1995**.
[4] B. Alcaide, P. Almendros, *Curr. Med. Chem.* **2004**, *11*, 1921–1949.
[5] F. Broccolo, G. Cainelli, G. Caltabiano, C. E. A. Cocuzza, C. G. Fortuna, P. Galletti, D. Giacomini, G. Musumarra, R. Musumeci, A. Quintavalla, *J. Med. Chem.* **2006**, *49*, 2804–2811.
[6] a) G. Cainelli, P. Galletti, S. Garbisa, D. Giacomini, L. Sartor, A. Quintavalla, *Bioorg. Med. Chem.* **2003**, *11*, 5391–5399; b) G. Cainelli, P. Galletti, S. Garbisa, D. Giacomini, L. Sartor, A. Quintavalla, *Bioorg. Med. Chem.* **2005**, *13*, 6120–6132.
[7] C. Ye, J. M. Shreeve, *J. Org. Chem.* **2004**, *69*, 8561–8563.
[8] G. V. Ramanarayanan, V. G. Shukla, K. G. Akamanchi, *Synlett* **2002**, 2059–2061.
[9] M. E. Krafft, J. W. Cran, *Synlett* **2005**, 1263–1266.
[10] a) F. Fernandez, X. Garcia-Mera, C. Lopez, M. Morales, J. E. Rodriquez-Borges, *Synthesis* **2005**, 3549–3554; b) S.-Y. Wang, *Nature* **1957**, *180*, 91–92.
[11] a) M. E. F. Braibante, H. T. S. Braibante, G. B. Rosso, J. K. da Roza, *Synthesis* **2001**, 1935–1937; b) N. Amishiro, A. Okamoto, M. Okabe, H. Saito, *Bioorg. Med. Chem.* **2000**, *8*, 1195–2001; c) E. N. Koz'minykh, A. O. Belyaev, V. O. Koz'minykh, R. R. Makhmudov, *Pharm. Chem. J.* **2003**, *37*, 71–75.
[12] E. Bellur, P. Langer, *Eur. J. Org. Chem.* **2005**, 4815–4828.
[13] A. Y. Rulev, S. V. Fedorv, V. G. Nenajdenko, E. S. Balenkova, M. G. Voronkov, *Russ. Chem. Bull. Int. Ed.* **2003**, *52*, 2287–2289.
[14] M. Médebielle, O. Onomura, R. Keirouz, E. Okada, H. Yano, T. Terauchi, *Synthesis* **2002**, 2601–2608.
[15] a) G. Cainelli, P. Galletti, D. Giacomini, A. Quintavalla, *Eur. J. Org. Chem.* **2003**, 1765–1774; b) G. Cainelli, P. Galletti, M. Gazzano, D. Giacomini, A. Quintavalla, *Tetrahedron Lett.* **2002**, *43*, 233–235.
[16] a) C. Djerassi, C. R. Scholz, *J. Am. Chem. Soc.* **1948**, *70*, 417–418; b) L. C. McKenzie, L. M. Huffman, J. E. Hutchison, *J. Chem. Educ.* **2005**, *82*, 306.
[17] For the synthesis of *N*-benzyl-4-alkylidene-β-lactams, see ref.[6].
[18] a) M. A. Lischwe, M. T. Sung, *J. Biol. Chem.* **1977**, *252*, 4976–4980; b) M. B. Smith, J. March, *March's Advanced Organic Chemistry*; **2001**, John Wiley & Sons, New York, chapter 14, p. 913.
[19] For a discussion on the iminium ion in azetidin-2-ones, see for example: a) R. P. Attrill, A. G. M. Barrett, P. Quayle, J. van der Westhuizen, *J. Org. Chem.* **1984**, *49*, 1679 ; b) F. Gavina, A. M. Costero, M. R. Andreu, *J. Org. Chem.* **1990**, *55*, 434.
[20] I. I. Gerus, L. M. Kacharova, S. I. Vdovenko, *Synthesis* **2001**, 431–436.
[21] J. V. Crivello, *J. Org. Chem.* **1981**, *46*, 3056–3060.
[22] The *cis* stereochemistry in the β-lactam ring has been assigned by analysis of $^1$H NMR coupling constants. On starting materials **1**, the same hydrogenation procedure stereospecifically affords the *cis* isomer, thus suggesting a stereospecific *syn* addition from the less hindered face, G. Cainelli, P. Galletti, D. Giacomini, A. Quintavalla, unpublished results.
[23] R. L. Danheiser, R. F. Miller, R. G. Brisbois, S. Z. Park, *J. Org. Chem.* **1990**, *55*, 1959–1964.
[24] A. Konopacka, A. Filarowski, Z. Pawelka, *J. Solution Chem.* **2005**, *34*, 929–945.

Received: December 18, 2006
Published Online: March 28, 2007