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Halodecarboxylation Reaction of 4-Alkylidene-β-lactams

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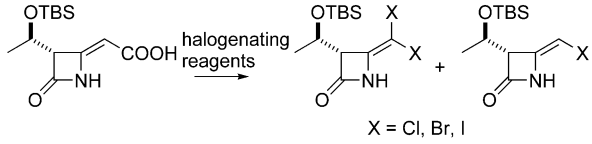
The synthesis of halo- and dihalovinyl-β-lactams by a halodecarboxylation reaction has been developed. Optimized procedures gave good yields of dibromo-, iodo- and diiodovinyl derivatives. The unprecedented synthesis of dihalo compounds by a Hunsdieker reaction was investigated in detail by ^{1}H NMR analysis, which allowed the formulation of a reaction mechanism and revealed the role of triethylamine as a deiodinating agent. The dibromo- and diiodoalkylidene-β-lactams obtained were tested in a cross-coupling reaction with dimethylzinc.

Introduction

Azetidin-2-one is one of the most important azaheterocyclic frameworks because of the biological importance of β-lactams as antibiotics[1] and their usefulness as synthons for further functionalization.[2] Our group has actively contributed to the field of new emerging β-lactam molecules through the synthesis of 4-alkylidene-β-lactams as a new scaffold for antibiotics against resistant bacteria.[3] The biological activity of 4-alkylidene-β-lactams arises from the structural characteristics of the double bond linked directly to the C-4 atom of the ring, which confers a particular propensity to ring-opening reactions by specific enzymes. Notably, the specificity towards certain enzymes can be directed by modulating the substituents on the side-chains. Specifically designed 4-alkylideneazetidinones have in fact shown biological activity as enzymatic inhibitors against human leukocyte elastase (HLE) and matrix metallo-proteases (MMPs)[4] as well as antioxidant[5] and anti-aggregating behaviour.[6]

In the course of our research devoted to the development of 4-alkylideneazetidinones and their glycoconjugates[7] as new antibiotics towards resistant bacteria, we felt the need for the further synthetic elaboration of the carboxyalkylidene side-chain at the 4-position of the β-lactam ring. Focussing on the vinylhalogenation reaction previously explored,[8] we report herein on the halodecarboxylation reaction, which led to the synthesis of 4-(mono- and dihaloalkylidene)azetidinones (Scheme 1). We have explored the scope and limits of the synthesis of the 4-(chloro-, bromo- and iodoalkylidene)-β-lactams and attempted to explain the reaction mechanism. Finally, we report the application of this reaction to the synthesis of new 4-alkylideneazetidinones.



Scheme 1.

Results and Discussion

The chemistry of the C=C double bond in 4-alkylideneazetidinones shows an unexpected low reactivity towards addition reactions, but a tendency to undergo vinyl substitution reactions. We have previously reported the reactions of 4-(ethoxycarbonylalkylidene)-β-lactams with *N*-halosuccinimides,[8] which resulted in an unexpected oxidative substitution of the vinyl hydrogen atom to give 4-(chloro-, bromo- and iodoalkylidene)-β-lactam carboxy esters. We now report on the halodecarboxylation reaction that leads to the synthesis of (mono- and dihaloalkylidene)azetidinones (Scheme 1).

Decarboxylation of carboxylic acid salts accompanied by simultaneous replacement with a halogen atom, known as the Hunsdiecker–Borodine reaction[9] (Figure 1), is a useful reaction for the synthesis of halogenated organic substances. This classic reaction has been recently modified and developed with particular attention paid to green chemistry.[10]

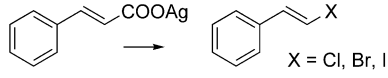


Figure 1. Hunsdiecker-type halodecarboxylation reaction of silver cinnamate.

We began our investigations by testing the halodecarboxylation reaction on the unsaturated carboxylic acid **1**. The starting compound **1** was obtained by a reported procedure in two steps starting from the commercially available

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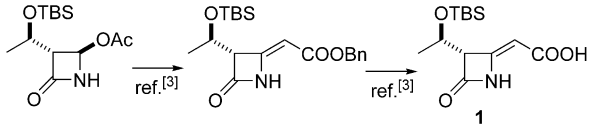
(3*R*,4*R*)-4-acetoxy-3-[(1*R*)-1-(*tert*-butyldimethylsilyloxy)-ethyl]azetidin-2-one with benzyl diazoacetate followed by hydrogenolysis with Pd/C in THF (Scheme 2).[3]



Scheme 2.

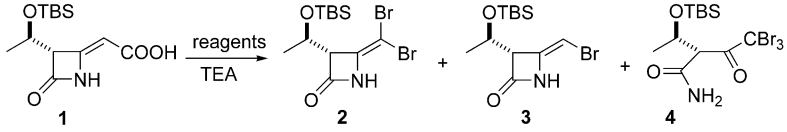
Initial attempts at the halodecarboxylation reaction were conducted with *N*-bromosuccinimide (NBS) and triethylamine (TEA), and the results are reported in Table 1.

Surprisingly, the reaction mainly furnished the dibromovinyl derivative **2** with NBS and TEA (Table 1, Entries 2–6), whereas in the absence of TEA the main product was the oxo amide **4** (Table 1, Entry 1). Only traces of the monobromovinyl derivative **3** were found (Entries 3 and 4). Tentative optimization of the procedure showed that the best results were obtained with 2 equiv. of NBS and 1 equiv. of TEA in dichloromethane (DCM), which gave the dibromoalkylidene derivative **2** in 51% isolated yield (Entry 4). Increasing the amount of NBS or TEA gave a larger amount of the byproduct **4** (Table 1, Entries 5 and 6). Investigations with other brominating agents showed that molecular bromine was not effective (Table 1, Entry 7). However, the best conditions for attaining **2** were the use of at least 2 equiv. of pyridinium tribromide with TEA in excess (Table 1, Entry 9); dibromoalkylidene derivative **2** was obtained in 68% yield after flash chromatography. A bromovinylcarboxylic acid was never detected in the crude reaction mixtures, which indicates a fast decarboxylation step.

The formation of dihalovinyl derivatives in a halodecarboxylation reaction is unprecedented. The Hunsdiecker reaction, as reported before for alkenyl- or alkynylcarboxylic acids, exclusively gives the corresponding (monobromovinyl)styrenes, but not the dibromo derivatives. Thus, it is confirmed once again as a characteristic reaction of the 4-alkylidene-β-lactam double bond.[8] To extend the scope of the reaction we then attempted the iodination reaction with *N*-iodosuccinimide or molecular iodine (Table 2).

Iododecarboxylation of **1** with 1 equiv. of NIS occurred even in the absence of TEA to give a mixture of di- and monoiodinated derivatives **5** and **6**, respectively, whereas

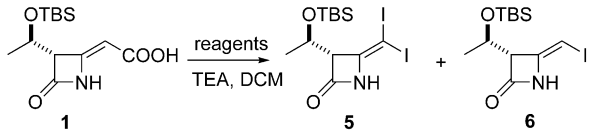
Table 1. Bromodecarboxylation of the 4-(carboxyalkylidene)azetidin-2-one **1**.



Entry	Reagent ([equiv.])	TEA [equiv.]	Conditions	Yield [%]		
				2[a]	**3**[b]	**4**[a]
1	NBS (2)	–	DCM, room temp., 22 h	13	–	45
2	NBS (1)	0.2	DCM, room temp., 5 h	23	–	–
3	NBS (2)	0.2	DCM, room temp., 3.5 h	45	4	–
4	NBS (2)	1	DCM, room temp., 3 h	51	5	–
5	NBS (5)	1	DCM, room temp., 3 h	57	–	12
6	NBS (2)	2	DCM, room temp., 3 h	51	–	18
7	Br_2 (2)	1	DCM, room temp., 3 h	25	–	21
8	$PyrHBr_3$ (1.1)	1.1	CH_3CN, 0 °C to room temp., 5.5 h	36	–	–
9	$PyrHBr_3$ (2.1)	3.3	CH_3CN, 0 °C, 1.5 h	68	–	8

[a] Isolated yields after flash chromatography. [b] Detected in the crude reaction mixture by HPLC/MS analysis.

Table 2. Iododecarboxylation of the 4-(carboxyalkylidene)azetidin-2-one **1**.



Entry	Reagent ([equiv.])	TEA [equiv.]	Conditions	Yield[a] [%]	
				5	**6**
1	NIS (1)	–	0 °C to room temp., 5.5 h	27	16
2	NIS (2)	–	0 °C, 1 h	75	–
3	NIS (1.1)	2.2	0 °C, 30 min	36	19
4	NIS (2.1)	3.2	0 °C, 40 min	42	48
5	I_2 (1)	–	0 °C to room temp., 5 h	–	–
6	I_2 (1)	1	room temp., 1 h	–	81
7	I_2 (2)	2	0 °C to room temp., 3 h	12	36

[a] Isolated yields after flash chromatography.

with 2 equiv. of NIS only the diiodinated compound **5** was obtained in 75% yield after flash chromatography. In the presence of TEA and 1 or 2 equiv. of NIS, mixtures of the mono- and diiodinated compounds were obtained (Table 2, Entries 3 and 4). Molecular iodine was effective only in the presence of TEA: 1 equiv. of I_2 and TEA afforded the monoiodo compound **6** selectively in 81% yield, whereas with 2 equiv. of I_2 and TEA a mixture of **5** and **6** was obtained (Table 2, Entries 6 and 7). Thus, we have identified the conditions in the iododecarboxylation reaction for selectively obtaining the diiodovinyl derivative **5** or the iodovinyl compound **6**. The iodo derivative **6** was obtained as a single (*Z*) stereoisomer in all cases. The (*Z*) configuration of the C=C bond was established by single-crystal X-ray diffraction analysis of compound **6** (Figure 2).[11] The formation of (*E*) isomers was not observed by ^{1}H NMR or HPLC/MS analysis of the crude reaction mixtures.

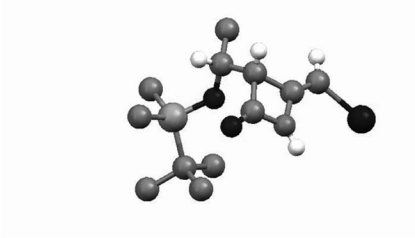
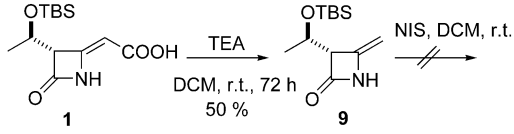


Figure 2. Molecular structure of **6**. The hydrogen atoms of the methyl groups have been omitted for the sake of clarity. Crystal data: $C_{12}H_{22}INO_2Si$, M = 367.30, monoclinic, $P2_12_12_1$, a = 7.6742(4), b = 12.3072(7), c = 18.1998(12) Å, V = 1718.93(17) Å^3, Z = 4, T = 293(2) °C, μ(Mo-K_α) = 1.926 mm^{-1}, 10161 reflections measured, 4007 unique (R_{int} = 0.0436), R_1 = 0.0905 [$I > 2\sigma(I)$], wR_2 = 0.2276.

N-Chlorosuccinimide (NCS) was not effective in the chlorodecarboxylation reaction, even in the presence of a radical initiator (AIBN), which indicates that radicals are probably not involved in this reaction (Table 3, Entry 2).[12] NCS with TEA gave mixtures of di- and monochloro derivatives **7** and **8** but in low yields (Table 3, Entries 3–5). All attempts to obtain a fluorodecarboxylation reaction with the fluorinating agent Selectfluor failed, which confirms the lack of reactivity of this reagent in vinyl substitution, as previously reported for 4-alkylidene-β-lactam carboxylic esters.[7]

The obtention of dihalovinyl compounds by the Hunsdiecker reaction, as mentioned above, is unprecedented. Thus, several attempts have been made to elucidate the reaction mechanism. In the ionic mechanism proposed by Naskar and Roy[13] for the halodecarboxylation reaction, it was assumed that the carboxylate anion is the key reactive intermediate and that it halodecarboxylates faster than the acid itself. In our case, treatment of the carboxylic acid **1** with TEA led to a rather slow reaction with the decarboxylated product **9** obtained in 50% yield. However, attempts to iodinate the vinyl moiety in the isolated 4-alkylidene-β-lactam **9** failed (Scheme 3).

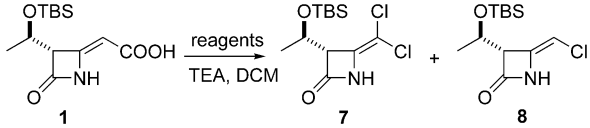


Scheme 3.

This result suggests that the halogen addition occurred before the decarboxylation step. However, in our case the reaction does not stop at the monohalo derivatives, but a further vinyl substitution occurs to give the dihalo compounds. This is particularly true for the bromodecarboxylation reaction in which the monobromo derivative was observed in only a few cases and in a very small amount. However, in the iododecarboxylation reaction, changing the reaction conditions and the amount of TEA led to mono- or diiodo compounds.

The simple procedure for the iododecarboxylation reaction with NIS and the well-differentiated ^{1}H NMR signals of **1**, **5** and **6** allowed us to monitor the reaction. ^{1}H NMR analyses were conducted at 400 MHz in NMR tubes with CD_2Cl_2 as the reaction solvent. In a first experiment, an aliquot of solid NIS (0.5 equiv.) was added to a solution of the acid **1** (13 mg, 46 μmol) in CD_2Cl_2 (0.7 mL), and suddenly the resonance peaks corresponding to the monoiodoalkene **6** and the diiodoalkene **5** appeared (Figure 3).

Table 3. Chlorodecarboxylation of the 4-(carboxyalkylidene)azetidin-2-one **1**.



Entry	Reagent ([equiv.])	TEA [equiv.]	Conditions	Yield[a] [%]	
				7	**8**
1	NCS (1)	–	room temp., 72 h	–	–
2	NCS (1)	–	AIBN 20%, room temp., 24 h	–	–
3	NCS (1)	0.5	room temp., 60 h	16	13
4	NCS (2)	3	0 °C, 1 h	22	6
5	NCS (4)	4	room temp. then reflux, 3.5 h	11	3

[a] Isolated yields after flash chromatography.

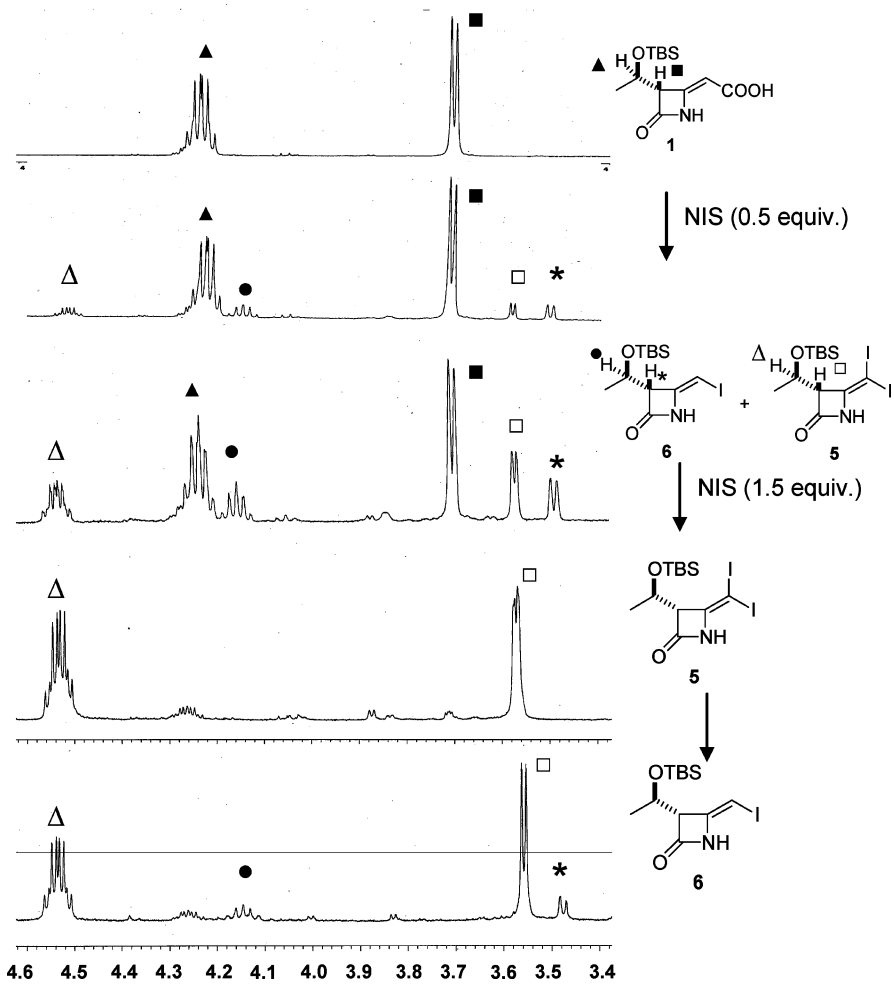


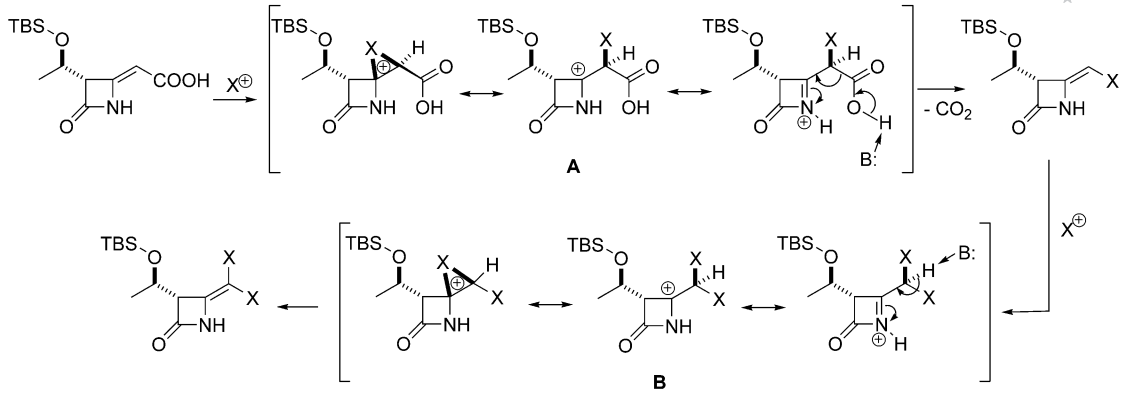
Figure 3. ^{1}H NMR (400 MHz) analysis of NIS and TEA addition to a solution of **1** in CD_2Cl_2.

We did not detect an iodovinylcarboxylic acid as a transient intermediate, which suggests that the decarboxylation step was concurrent with the iodination reaction. The presence of the diiodo derivative as well as the monoiodo compound can be accounted for by a higher reactivity of the monoiodoalkene than the acid **1** towards iodination. The addition of further aliquots of NIS increased the production of **5** and **6** to give complete conversion of the starting acid **1** to the diiodo compound **5**. At this point, addition of TEA (12.8 μL, 2 equiv.) led to the appearance of monoiodide **6**.

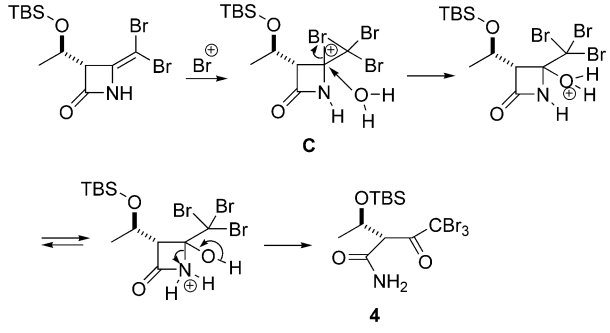
A mechanism for the halodecarboxylation reaction of the 4-alkylidene-β-lactam has thus been proposed (Scheme 4). Electrophilic halogen ion addition to the double bond gives a positively charged halogenonium intermediate **A**, which is further stabilised by the nitrogen lone-pair. A base-promoted decarboxylation occurred together with the re-establishment of the C=C double bond. A second fast addition of a halogen ion gives the intermediate **B**, which undergoes a fast base-promoted restoration of the double bond. This unusual enhanced reactivity of the monohalogenated alkylidene-β-lactams towards a further addition reaction is thus the driving force for the unprecedented formation of the dihalovinyl products.

The formation of oxo amide **4** exclusively from the dibromoalkylidene-β-lactam can be explained by the enhanced electrophilicity of the haloalkylidene-β-lactams (Scheme 5). The dibromoalkylidene-β-lactam **2** was more activated than the corresponding diiodoalkylidene-β-lactam towards a further halogen addition because of the higher electronegativity of bromine compared with iodine. The addition of water to the intermediate **C** in the reaction workup and a subsequent ring-opening reaction afforded the oxo amide **4**.

In a kinetic study, Roy and Das established that the decarboxylative halogenation of α,β-unsaturated acids with *N*-bromosuccinimide is a first-order reaction with respect to a basic catalyst such as triethylamine.[14] In our case, 4-alkylidene-β-lactam carboxylic acid **1** reacted with NIS even in the absence of an additional catalyst to give halodecarboxylation, so the succinimide anion acts as a base in the mechanism depicted in Scheme 4. However, the role of triethylamine in our conditions produced different results, depending on the conditions and amounts of reagent used: TEA with NIS gave a mixture of the mono- and diiodo compounds, whereas TEA with I_2 gave the monoiodoalkylidene-β-lactam or a mixture (Table 2, Entries 3, 4, 6 and 7). Preliminary evidence for the role of TEA in restoring the monoiodide came from the above reported NMR experi-



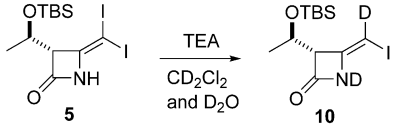
Scheme 4.



Scheme 5.

ment, but a second experiment more directly elucidated the role of TEA.

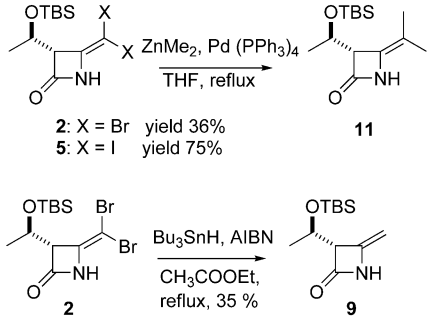
In an NMR tube filled with a solution of the diiodo derivative **5** (13 mg, 26 μmol) in CD_2Cl_2 (0.7 mL) the addition of TEA (7.2 μL, 2 equiv.) resulted in the instantaneous disappearance of the NH signal of the starting β-lactam. After 2 h, signals of the monoiodo azetidinone **6** appeared, and, after 12 h, the conversion to **6** was complete, thus supporting the action of TEA on **5** as a deiodinating agent.[15] TEA is thus responsible for the increased amount of the monoiodo compound. To confirm this finding, diiodoazetidinone **5** (13 mg, 26 μmol) was treated with TEA (7.2 μL, 2 equiv.) in CD_2Cl_2 (0.7 mL) and D_2O (20 μL) in an NMR tube to quantitatively afford the deuteriated derivative **10** (Scheme 6).



Scheme 6.

The successful halodecarboxylation reaction of the 4-alkylidene-β-lactam enables the side-chain of these derivatives to be elaborated with the aim of developing new β-lactams with specific biological activities. Vinyl halides are, in fact, interesting compounds as coupling components in a wide range of transition-metal-catalysed coupling reactions.[16]

We thus preliminarily tested the reactivity of the (haloalkylidene)azetidinones **2** and **5** in a palladium-catalysed cross-coupling reaction with organozinc reagents (Scheme 7), which gave the dimethyl derivative **11**. The dibromo compound **2** could also be fully debrominated to **9** with tributyltin hydride. However, compound **9**, obtained from the carboxylic acid **1** as described above (Scheme 3), showed a limited shelf-life even when cooled and stored under an inert atmosphere.



Scheme 7.

Conclusions

We have developed a strategy for the synthesis of a new family of halo- and dihalovinyl-β-lactams by halodecarboxylation of the unsaturated carboxylic acid **1**. Optimization of the procedures led to good yields of the dibromo, iodo and diiodo derivatives. The unprecedented formation of dihalo compounds in a Hunsdiecker reaction was investigated in depth by ^1H NMR analysis, which allowed the formulation of a reaction mechanism in which the role of triethylamine as a deiodinating agent was evidenced. The dibromo- and diiodoalkylidene-β-lactams were tested in a cross-coupling reaction with dimethylzinc, which led to new alkylidene-β-lactams. Investigations of the bioactivities of the new azetidinones are underway.

Experimental Section

General: All reactions were performed under N_2. Commercial reagents were used as received without further purification. Anhy-

drous solvents (CH_3CN, CH_2Cl_2 and THF) were obtained commercially. ^1H and ^{13}C NMR spectra were recorded with Varian MERCURY 400, Varian INOVA 300 or a GEMINI 200 instrument with a 5 mm probe. All chemical shifts are quoted relative to deuteriated solvent signals; δ values are given in ppm and J values in Hz. FTIR: Nicolet 205 spectrometer measured as films between NaCl plates; wavenumbers are reported in cm^{-1}. Melting points (uncorrected): Büchi B-540 apparatus. TLC: Merck 60 F_{254}. Column chromatography: Merck silica gel 200–300 mesh. HPLC/MS, HPLC: Agilent HP1100 instrument, ZOBRAX-Eclipse XDB-C8 column from Agilent, mobile phase: H_2O/CH_3CN, gradient from 30 to 80% of CH_3CN in 8 min, 80% of CH_3CN until 25 min, flow rate 0.4 mL/min. MS: Agilent MSD1100 single-quadrupole mass spectrometer, full-scan mode from m/z = 50 to 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, fragmenter voltage 20 V. The $[\alpha]_D^{25}$ values were determined with a Perkin–Elmer 343 polarimeter. Elemental analysis: Perkin–Elmer 2400 Series II CHNS/O analyser.

Starting Materials: 4-Alkylidene-β-lactam **1** was prepared according to a previously reported procedure.[3]

Bromodecarboxylation with NBS: NBS (160 mg, 0.9 mmol) was added to a solution of **1** (50 mg, 0.18 mmol) and TEA (0.03 mL, 0.18 mmol) in CH_2Cl_2 (3 mL). The reaction was monitored by TLC. After full conversion, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography (cyclohexane/ethyl acetate, 95:5) to afford the products.

Bromodecarboxylation with Br_2: Br_2 (58 mg, 0.36 mmol) was added to a solution of **1** (50 mg, 0.18 mmol) and TEA (0.03 mL, 0.18 mmol) in CH_2Cl_2 (3 mL). The reaction was monitored by TLC. After full conversion, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography (cyclohexane/ethyl acetate, 95:5) to afford the products.

Bromodecarboxylation with $PyHBr_3$: $PyHBr_3$ (121 mg, 0.37 mmol) was added to a solution of **1** (50 mg, 0.18 mmol) and TEA (0.08 mL, 0.6 mmol) in CH_3CN (3 mL) at 0 °C. The reaction was monitored by TLC. After full conversion, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography (cyclohexane/ethyl acetate, 95:5) to afford the products.

3-[1-(*tert*-Butyldimethylsilyloxy)ethyl]-4-(dibromomethylene)azetidin-2-one (2): White solid; m.p. 125 °C. R_f = 0.85 (cyclohexane/ethyl acetate, 8:2). $[\alpha]_D^{25}$ = +56 (c = 1, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$, 22 °C): δ = 0.09 (s, 6 H, $SiMe_2$), 0.90 (s, 9 H, Si*t*Bu), 1.37 (d, J = 6.6 Hz, 3 H, CH_3CH), 3.67 (dd, J = 1.8, J = 3.4 Hz, 1 H, C*H*CHOSi), 4.43 (dq, J = 3.4, J = 6.6 Hz, 1 H, CHC*H*OSi), 7.15 (br. s, 1 H, NH) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 22 °C): δ = –5.1, –4.5, 18.0, 21.3, 25.7, 60.5, 64.0, 64.4, 137.5, 163.7 ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 3160, 3080, 2924, 2844, 1808, 1675, 1252, 1141, 963 cm^{-1}. HPLC/MS (ESI): t_r = 13.1 min; m/z = 398.3, 400.2, 402.2 $[M + H]^+$, 422.0 $[M + Na]^+$. $C_{12}H_{21}Br_2NO_2Si$ (396.97): calcd. C 36.10, H 5.30, N 3.51; found C 36.21, H 5.33, N 3.58.

4,4,4-Tribromo-2-[1-(*tert*-butyldimethylsilyloxy)ethyl]-3-oxobutyramide (4): Yellow oil. R_f = 0.50 (cyclohexane/ethyl acetate, 8:2). ^1H NMR (200 MHz, $CDCl_3$, 22 °C): δ = 0.06 (s, 3 H, SiMe), 0.1 (s, 3 H, SiMe), 0.88 (s, 9 H, Si*t*Bu), 1.39 (d, J = 5.4 Hz, 3 H, CH_3CH), 4.40–4.50 (m, *2* H, C*H*CHOSi, CHC*H*OSi), 5.88 (br. s, 1 H, NH), 6.32 (br. s, 1 H, NH) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 22 °C): δ = –4.8, 17.8, 21.5, 25.7, 46.0, 60.0, 70.8, 168.2, 186.1 ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 3329, 3186, 2927, 2855, 1735, 1686 cm^{-1}. HPLC/MS (ESI): t_r = 11.3 min; m/z = 521, 519, 517, 515 $[M + Na]^+$.

Iododecarboxylation with NIS: NIS (45 mg, 0.20 mmol) was added to a solution of **1** (50 mg, 0.18 mmol) and TEA (0.06 mL, 0.4 mmol) in CH_2Cl_2 (3 mL) at 0 °C. The reaction was monitored by TLC. After full conversion, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography (cyclohexane/ethyl acetate, 95:5) to afford the products.

Iododecarboxylation with I_2: I_2 (91 mg, 0.36 mmol) was added to a solution of **1** (50 mg, 0.18 mmol) and TEA (0.05 mL, 0.36 mmol) in CH_2Cl_2 (3 mL) at 0 °C. The reaction was monitored by TLC. After full conversion, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography (cyclohexane/ethyl acetate, 95:5) to afford the products.

3-[1-(*tert*-Butyldimethylsilyloxy)ethyl]-4-(diiodomethylene)azetidin-2-one (5): Yellow solid; m.p. 133 °C. R_f = 0.83 (cyclohexane/ethyl acetate, 8:2). $[\alpha]_D^{25}$ = +47 (c = 0.9, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$, 22 °C): δ = 0.10 (s, 6 H, $SiMe_2$), 0.91 (s, 9 H, Si*t*Bu), 1.32 (d, J = 6.2 Hz, 3 H, CH_3CH), 3.57 (dd, J = 1.8, J = 3.6 Hz, 1 H, C*H*CHOSi), 4.54 (dq, J = 3.6, J = 6.2 Hz, 1 H, CHC*H*OSi), 7.5 (br. s, 1 H, NH) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 22 °C): δ = –4.9, –4.5, 18.0, 20.4, 25.8, 29.7, 63.9, 64.1, 145.1, 162.6 ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 3137, 3066, 2951, 2924, 1798, 1764, 1656, 1256, 837 cm^{-1}. HPLC/MS (ESI): t_r = 13.3 min; m/z = 494.1 $[M + H]^+$, 516.2 $[M + Na]^+$. $C_{12}H_{21}I_2NO_2Si$ (492.94): calcd. C 29.22, H 4.29, N 2.84; found C 29.31, H 4.34, N 2.79.

3-[1-(*tert*-Butyldimethylsilyloxy)ethyl]-4-(iodomethylene)azetidin-2-one (6): Yellow solid; m.p. 105 °C. R_f = 0.80 (cyclohexane/ethyl acetate, 8:2). $[\alpha]_D^{25}$ = +20.14 (c = 1.1, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, 22 °C): δ = 0.06 (s, 3 H, SiMe), 0.08 (s, 3 H, SiMe), 0.88 (s, 9 H, Si*t*Bu), 1.30 (d, J = 6.6 Hz, 3 H, CH_3CH), 3.49 (ddd, J = 0.6, J = 1.8, J = 3.6 Hz, 1 H, C*H*CHOSi), 4.17 (dq, J = 6.0, J = 6.6 Hz, 1 H, CHC*H*OSi), 5.06 (dd, J = 0.6, J = 1.2 Hz, 1 H, C=C*H*I), 7.06 (br. s, 1 H, NH) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 22 °C): δ = –4.9, –4.2, 17.8, 22.2, 25.6, 42.7, 62.4, 65.4, 142.4, 165.7 ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 3172, 3099, 2852, 2920, 1801, 1760, 1674, 1463, 1258, 956 cm^{-1}. HPLC/MS (ESI): t_r = 12.1 min; m/z = 368.1 $[M + H]^+$, 385.2 $[M + H_2O]^+$. $C_{12}H_{22}I_1NO_2Si$ (367.05): calcd. C 39.24, H 6.04, N 3.81; found C 39.28, H 6.06, N 3.84.

Chlorodecarboxylation with NCS: NCS (24 mg, 0.18 mmol) was added to a solution of **1** (50 mg, 0.18 mmol) and TEA (0.04 mL, 0.27 mmol) in CH_2Cl_2 (3 mL). The reaction was monitored by TLC. After full conversion, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography (cyclohexane/ethyl acetate, 95:5) to afford a mixture of the products. The spectra of **7** and **8** were recorded as the enriched column fractions.

3-[1-(*tert*-Butyldimethylsilyloxy)ethyl]-4-(dichloromethylene)azetidin-2-one (7): R_f = 0.84 (cyclohexane/ethyl acetate, 8:2). ^1H NMR (400 MHz, $CDCl_3$, 22 °C): δ = 0.08 (s, 3 H, SiMe), 0.09 (s, 3 H, SiMe), 0.90 (s, 9 H, Si*t*Bu), 1.37 (d, J = 6.4 Hz, 3 H, CH_3CH), 3.72 (dd, J = 1.6, J = 3.2 Hz, 1 H, C*H*CHOSi), 4.34 (dq, J = 3.62, J = 6.4 Hz, 1 H, CHC*H*OSi), 7.14 (br. s, 1 H, NH) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 22 °C): δ = –5.2, –4.4, 17.9, 21.8, 25.7, 30.9, 63.5, 64.7, 132.8, 164.3 ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 3182, 2929, 2856, 1803, 1691 cm^{-1}. HPLC: t_r = 12.5 min.

3-[1-(*tert*-Butyldimethylsilyloxy)ethyl]-4-(chloromethylene)azetidin-2-one (8): R_f = 0.80 (cyclohexane/ethyl acetate, 8:2). ^1H NMR (400 MHz, $CDCl_3$, 22 °C): δ = 0.07 (s, 3 H, SiMe), 0.08 (s, 3 H, SiMe), 0.88 (s, 9 H, Si*t*Bu), 1.29 (d, J = 6.4 Hz, 3 H, CH_3CH), 3.57 (dd, J = 0.8, J = 6.4 Hz, 1 H, C*H*CHOSi), 4.17 (quint, J = 6.4 Hz, 1 H, CHC*H*OSi), 5.35 (d, J = 0.8 Hz, 1 H, C*H*Cl), 7.23 (br. s, 1

H, NH) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 22 °C): δ = –4.9, –4.2, 17.9, 22.4, 25.7, 62.8, 65.4, 89.4, 135.6, 165.9 ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 3182, 2954, 2885, 1803, 1691 cm^{-1}. HPLC: t_r = 11.5 min.

3-[1-(*tert*-Butyldimethylsilyloxy)ethyl]-4-methyleneazetidin-2-one (9): This product was obtained by two different procedures. **Method a:** TEA (0.03 mL, 0.22 mmol) was added to a solution of **1** (50 mg, 0.18 mmol) in CH_2Cl_2 (3 mL). The reaction was monitored by TLC. After full conversion, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography (cyclohexane/ethyl acetate, 70:30) to afford the product (22 mg, 50% yield). **Method b:** AIBN (21 mg, 0.13 mmol) was added to a solution of **2** (50 mg, 0.13 mmol) and Bu_3SnH (0.07 mL, 0.26 mmol) in ethyl acetate (4 mL). The reaction mixture was heated at reflux and monitored by TLC. After full conversion, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography (cyclohexane/ethyl acetate, 70:30) to afford the product (11 mg, 35% yield). Colourless oil. R_f = 0.70 (cyclohexane/ethyl acetate, 8:2). $[\alpha]_D^{25}$ = +16.20 (c = 1, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$, 22 °C): δ = 0.08 (s, 6 H, $SiMe_2$), 0.90 (s, 9 H, Si*t*Bu), 1.31 (d, J = 6.2 Hz, 3 H, CH_3CH), 3.46 (d, J = 5.8 Hz, 1 H, C*H*CHOSi), 4.18 (dq, J = 5.8, J = 6.2 Hz, 1 H, CHC*H*OSi), 4.31 (d, J = 2.8 Hz, 1 H, C=C*H*), 4.39 (d, J = 2.8 Hz, 1 H, C=C*H*), 7.10 (br. s, 1 H, NH) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 24 °C): δ = –4.9, –4.2, 18.0, 22.01 25.7, 62.7, 65.7, 84.3, 140.7, 168.2 ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 3213, 2927, 2856, 1791, 1717 cm^{-1}. HPLC/MS (ESI): t_r = 10.9 min; m/z = 242 [M + H]$^+$, 259 [M + H_2O]$^+$.

3-[1-(*tert*-Butyldimethylsilyloxy)ethyl]-4-isopropylideneazetidin-2-one (11): $ZnMe_2$ (0.06 mL, 2 M in toluene, 0.12 mmol) was added to a solution of **5** (30 mg, 0.06 mmol) in THF (1 mL) and tetrakis-(triphenylphosphane)palladium (7 mg, 0.006 mmol), and the reaction mixture was heated at reflux and monitored by TLC. After full conversion, the reaction mixture was quenched by aqueous NH_4Cl and extracted with Et_2O. The organic layer was dried with Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (cyclohexane/ethyl acetate, 95:5) to afford the product (12 mg, 75% yield). The product was also obtained from dibromo compound **2** under the same reaction conditions (6 mg, 36% yield). Yellow oil. R_f = 0.80 (cyclohexane/ethyl acetate, 8:2). $[\alpha]_D^{25}$ = +12 (c = 0.8, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 24 °C): δ = 0.08 (s, 6 H, $SiMe_2$), 0.89 (s, 9 H, Si*t*Bu), 1.31 (d, J = 6 Hz, 3 H, CH_3CH), 1.67 (s, 6 H, C=CMe_2), 3.50 (m, 1 H, C*H*CHOSi), 4.21 (quint, J = 6 Hz, 1 H, CHC*H*OSi), 6.80 (br. s, 1 H, NH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 22 °C): δ = –4.7, –4.5, 17.7, 18.1, 19.3, 21.7, 25.8, 61.3, 66.4, 102.3, 126.8, 167.9 ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 3241, 2927, 2855, 1795, 1721 cm^{-1}. HPLC/MS (ESI): t_r = 12.2 min; m/z = 270 [M + H]$^+$, 292 [M + Na]$^+$. $C_{14}H_{27}NO_2Si$ (269.18): calcd. C 62.40, H 10.10, N 5.20; found C 62. 56, H 10.14, N 5.15.

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