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Novel Spiroheterocycles by Aziridination of α-Methylene-γ- and -δ-lactams

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New potentially bioactive α-spiroaziridino-γ- and -δ-lactams have been prepared by treatment of α-methylene-γ- and -δ-lactams with ethyl *N*-{[(4-nitrophenyl)sulfonyl]oxy}-carbamate ($NsONHCO_2Et$) in the presence of CaO. These compounds, through reductive aziridine ring opening, can be intermediates for the synthesis of α- and β-aminolactams, which are useful as conformational constraints in peptides. The above procedure has been successfully extended to one α-methyleneoxindole to obtain a new spirooxindole derivative, a potential precursor of natural alkaloids.

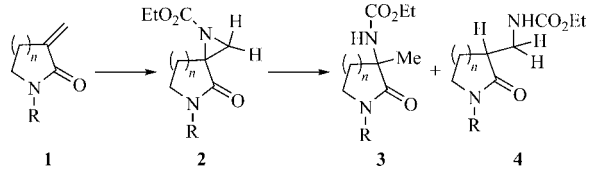
Introduction

Molecules with strained, three-membered heterocycles have been arousing the interest of chemists for more than 100 years thanks to the varied reactivity of these rings. Among them, aziridines are valuable intermediates in organic synthesis: the regio- and stereochemical control of the ring-opening reactions can be a useful tool in the synthesis of unnatural amino acids and other nitrogen-containing compounds of biological importance.[1] In particular, spiroaziridines, where the aziridine ring is fused with a heterocycle, are of synthetic interest because the presence of a spiro carbon atom induces steric strain and allows for possible rearrangements.[2] Among these molecules, we turned our attention to spiroaziridino-γ- and -δ-lactams.

In general, the insertion of a spiranic moiety in a γ- or δ-lactam results in interesting biological activities. For example, marine amathaspiramides and pseudoindoxyl alkaloids from plants are potent antiviral agents with potential anticancer properties.[3] In addition, some L-proline-derived spirolactams have been studied for their use in constraining peptides with L-proline residues to mimic a β-turn, an important component of peptide secondary structures.[4] Nevertheless, to the best of our knowledge, spiroaziridino lactams are not reported in the literature, except for one paper concerning the synthesis of unsaturated spiroaziridino-δ-lactams.[2b] On these grounds, we felt that spiroaziridino-γ- and -δ-lactams could be intriguing synthetic targets and useful intermediates for the synthesis of valuable α- and β-aminolactams, the latter resulting from the aziridine ring-opening reaction of the former.

For some years our research program has been focused on the synthesis of aziridines starting from electron-poor olefins, such as α,β-unsaturated esters, phosphonates, and amides.[5] In this field, we have recently succeeded in the synthesis of *N*-(ethoxycarbonyl)spiroaziridino-γ-lactones from simple α-ylidene-γ-butyrolactones with $NsONHCO_2Et$ and CaO.[6] The subsequent regio- and stereoselective aziridine ring opening provided simple access to interesting homoserine lactone derivatives, which are present in certain biologically active molecules.[7]

On the basis of the good results we obtained with α-ylidene-γ-butyrolactones, we felt that the extension of our synthetic procedure to other heterocyclic compounds like α-methylene-γ- and -δ-lactams **1** (Scheme 1) could result in the obtention of the spiroaziridinolactams **2** and, after aziridine ring opening, the corresponding amino derivatives **3** or **4**.



Scheme 1.

Results and Discussion

Keeping in mind this program, our first objective was the preparation of substrates **1** (Scheme 2). Compound **1a** was obtained according to a procedure reported in the literature.[8] The same procedure was extended to the synthesis

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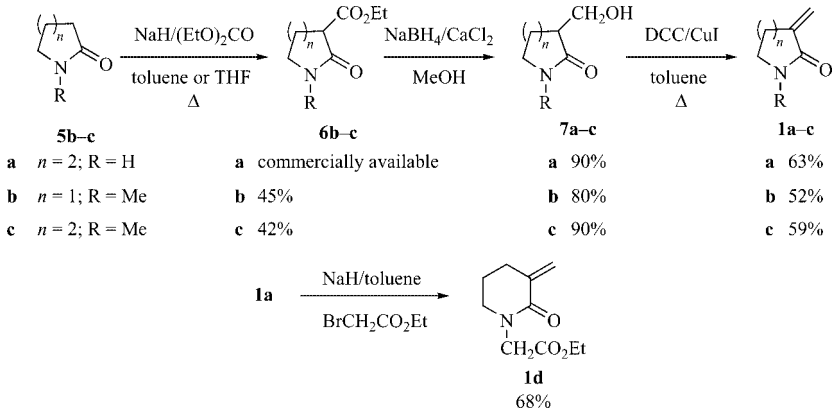


Scheme 2. Synthesis of substrates **1a**–**d**.

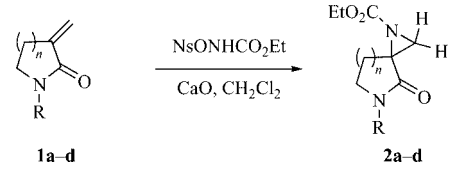
of compounds **1b**–**c**, although their preparation by a different route has been already reported.[9] While for substrate **1a** the procedure starts directly from the commercially available ester **6a**, in the case of substrates **1b**–**c**, we prepared the corresponding esters with the ethoxycarbonylation reaction reported by Rapoport for 1-methylpyrrolidin-2-one (**5b**).[10] The reduction of esters **6a**–**c** with calcium tetrahydridoborate, afforded the known alcohols **7a**[8] and **7b**[11] and the novel alcohol **7c**, which were obtained pure and in good yields.

α-Methylenelactams **1a**–**c** were finally prepared by direct dehydration of **7a**–**c** with dicyclohexylcarbodiimide (DCC) in the presence of catalytic amounts of cuprous iodide in an aprotic solvent such as toluene.[8] Olefins **1a**–**c** were purified by chromatography on silica gel and their structures were confirmed by ^{1}H and ^{13}C NMR analysis.

In addition, we wanted to extend our aziridination procedure to the α-methylene-δ-lactam **1d**, carrying a ethoxycarbonylmethyl group at the nitrogen atom as a suitable anchor for an amino acid chain. Indeed, it is known that some lactam derivatives are useful conformational constraints in peptides and limit the number of available conformers. In particular, five- and six-membered lactams with amino acid chains at the lactam nitrogen atom are important scaffolds in conformationally restricted peptidomimetics.[12]

Substrate **1d** was prepared starting from **1a** according to a reported alkylation reaction at the nitrogen atom[8] (Scheme 2).

With the α-methylene-γ- and -δ-lactams **1a**–**d** in hand, we proceeded to the aziridination reaction, which was carried out in CH_2Cl_2, according to the reported procedure,[6] by adding $NsONHCO_2Et$ and CaO portionwise, to reach the molar ratios shown in Table 1. After the addition of a few equivalents of reagents, we observed the complete disappearance of the starting material and the formation of the expected *N*-(ethoxycarbonyl)spiroaziridines (Scheme 3), detected in the crude mixture by the characteristic NMR aziridine proton signals. Compounds **2a**–**d** were purified by chromatography on silica gel and fully characterized.



Scheme 3. Synthesis of spiroaziridino-γ- and -δ-lactams.

The good results obtained in the synthesis of spiroaziridino lactams **2a**–**d** prompted us to start studying the amination of more complex α-methylene-γ-lactams, characterized by the oxindole moiety. To the best of our knowledge, only one synthesis of spiroaziridinooxindole derivatives is reported.[13]

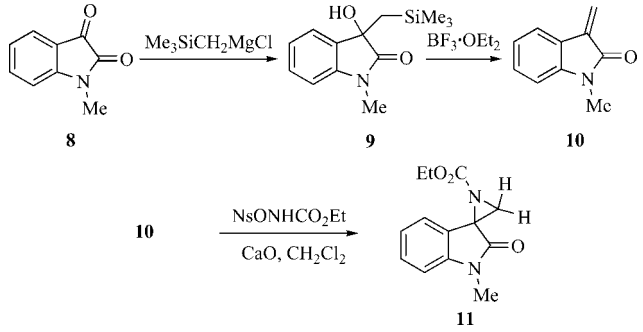
The oxindole ring system is found at the core of a number of natural alkaloids, which are interesting, challenging targets for chemical synthesis.[14] Most of these alkaloids are characterized by a spirooxindole structure.[15]

Table 1. Synthesis of spiroaziridinolactams **2a**–**d**: conditions and yields.

Entry	R	*n*	Molar ratio **1**/$NsONHCO_2Et$/CaO	**2** Isolated yields [%]	^{1}H NMR Aziridine protons
a	H	2	1:3:3	50	δ = 2.11 (d, J = 1.5 Hz, 1 H); 2.91 (d, J = 1.5 Hz, 1 H)
b	Me	1	1:3:3	48	δ = 2.33 (d, J = 1.1 Hz, 1 H); 2.76 (d, J = 1.1 Hz, 1 H)
c	Me	2	1:3:3	46	δ = 2.10 (d, J = 1.5 Hz, 1 H); 2.96 (d, J = 1.5 Hz, 1 H)
d	CH_2CO_2Et	2	1:2.5:2.5	56	δ = 2.11 (d, J = 1.5 Hz, 1 H); 2.90 (d, J = 1.5 Hz, 1 H)

Their appealing spiro architecture is often associated with biological activity, such as the antineoplastic activity discovered for the spirotryprostatins.[16]

As a model compound we took into consideration 1-methyl-3-methylene-1,3-dihydro-2*H*-indol-2-one (**10**, Scheme 4). This compound was prepared by Peterson's isatin olefination, proposed by Rossiter for the preparation of the α-methyleneoxindole itself.[17] It is reported that α-methyleneoxindoles are very unstable compounds because they can polymerize to afford dimers or higher-order polymers.[18]



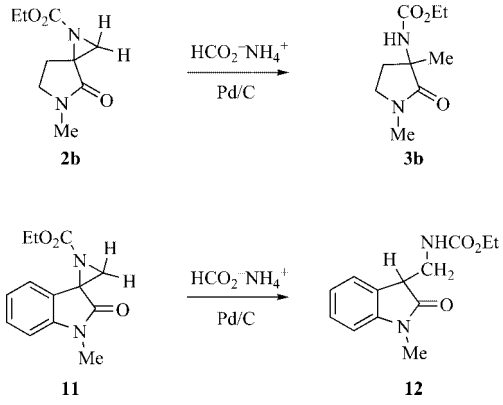
Scheme 4. Synthesis and aziridination of **10**.

Accordingly, compound **10** proved to be unstable and not isolable. Thus, after extraction with dichloromethane (solvent to be used in the subsequent reaction), the solution containing **10** was only partially concentrated and rapidly used for the aziridination reaction. After the addition of only 1 equiv. of the $NsONHCO_2Et/CaO$ mixture, we obtained a total conversion of **10** into the new spiroaziridinooxindole **11** (Scheme 4), isolated in good yield (72%) by chromatography and characterized.

Aziridine ring opening in spiroaziridinolactams **2a**–**d** and **11** could be a suitable way to obtain the corresponding α- or β-aminolactams, key components of many peptidomimetic structures.[12] In this context, in order to study the regiochemistry of the aziridine ring-opening reaction, we treated the spiroaziridines **2a**–**d** and **11** with ammonium formate and Pd/C under the conditions[19] previously used successfully for the ring-opening reaction of spiroaziridino-γ-lactones.

With regard to the spiroaziridino-δ-lactams **2a**, **2c**, and **2d**, we showed they were poorly reactive towards the reductive ring opening. Despite long reaction times (8 d) we observed only a partial disappearance of the starting material and the formation of a mixture of products. These results indicate that this method is not suitable for converting spiroaziridines from α-methylene-δ-lactams into α- or β-aminolactams.

Starting from the simple spiroaziridino-γ-lactam **2b**, as previously found for the corresponding spiroaziridino-γ-lactones,[6] we obtained, after 4 h, the α-aminolactam derivative **3b** (Scheme 5) as the main product, together with a very small amount of a byproduct, which we suggest to be the β-amino isomer **4b**. In fact, we observed singlets attributable to additional N-CH_3 and N-H groups in the ^1H NMR spectrum of the crude reaction mixture and found a minor peak with the same mass of **3b** by GC-MS coupling. However, only compound **3b** was separated and purified by chromatography on silica gel. Spectroscopic data confirmed the structure. In contrast, carrying out the reaction on the spiroaziridinooxindole **11**, we obtained the β-amino derivative **12** as the only product after 1 h (Scheme 5).



Scheme 5. Ring-opening reactions of aziridine **2b** and **11**.

The opposite regiochemistry observed in the aziridine ring opening for compounds **2b** and **11** could be explained in terms of the relative stabilities of the respective intermediates involved. The ring-opening reaction can occur through the competitive formation of an intermediate Pd complex[20a] or a radical involving either the spiranic carbon atom or the aziridine methylene group. The former intermediate could be stabilized by the aromatic ring in **11**, as reported for benzylic and allylic aziridines and epoxides,[20] while the corresponding intermediate for **2b** could be disfavored both by the absence of aromatic stabilization and the presence of more steric hindrance.

Compounds like **12** are very interesting targets, as some of them are natural antibiotics produced by plants,[21] potential antileukemics, and important intermediates in the synthesis of other spirooxindole systems.[22]

Conclusion

We present herein an easy procedure for the synthesis of new spiroaziridinolactams starting from easily accessible α-methylene-γ- and -δ-lactams, and we have confirmed the possibility of using novel spiroaziridino-γ-lactams as precursors of α- and β-aminolactams. Considering the efficiency of the aziridination protocol, when applied to the α-methyleneoxindole **10** and the current interest in spirooxindoles in chemical synthesis, we are encouraged to carry on our research work in this field.

Experimental Section

General Experimental Methods: Solvents and common reagents were purchased from commercial sources and used without further purification. All reactions were monitored by GC-MS analysis with

an HP 5890 system equipped with a phenylmethylsilicon capillary column (15 m, 0.25 mm i.d.), and by thin layer chromatography (TLC) carried out on Merck F-254 silica glass plates and visualized with UV light and I_2. Chromatographic separations were performed on Merck silica gel 60 (70–230 mesh). ^1H and ^{13}C NMR spectra were recorded with a Varian Gemini 200 (200 MHz) spectrometer; chemical shifts are expressed in ppm (δ) and are referenced to the carbon and residual proton signals of the NMR solvent ($CHCl_3$: δ = 7.26 ppm for ^1H NMR, δ = 77.0 ppm for ^{13}C NMR). IR spectra were obtained with a Perkin-Elmer 1600 (FT-IR) spectrometer; data are presented in wavenumbers (cm^{-1}). HRMS data were recorded with a Micromass Q-TOF micro Mass Spectrometer (Waters).

Ethyl 1-Methyl-2-oxopyrrolidine-3-carboxylate (6b):[10] To a suspension of NaH (2.9 g, 120 mmol, 60% suspension in mineral oil) in anhydrous toluene (160 mL), a solution of **5b** (4 g, 40 mmol) and diethyl carbonate (18.8 g, 160 mmol) in anhydrous toluene (40 mL) was added dropwise under argon at room temperature. After 8 h at reflux, the mixture was cooled to room temperature, and glacial acetic acid (5 g, 83 mmol) was added. After 1 h of stirring, the resulting slurry was filtered, the solid phase was washed with CH_2Cl_2, and the organic phase was washed with a little water. The aqueous phase was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were dried with anhydrous Na_2SO_4. After solvent evaporation, the crude product was purified by chromatography on silica gel (diethyl ether/methanol, 99:1) to obtain **6b** as a yellow viscous oil (3.1 g, 18 mmol, 45% yield). IR ($CHCl_3$): $\tilde{\nu}$ = 1740, 1680 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz, 25 °C): δ = 1.25 (t, J = 7.1 Hz, 3 H, OCH_2CH_3), 2.13–2.56 (m, 2 H, CH_2CH), 2.83 (s, 3 H, NCH_3), 3.25–3.60 (m, 3 H, CH_2CH_2CH), 4.17 (q, J = 7.1 Hz, 2 H, OCH_2CH_3) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz, 25 °C): δ = 14.1 (OCH_2CH_3), 21.0 (CH_2CH), 32.3 (NCH_3), 45.5 (NCH_2), 49.3 (CH), 62.2 (OCH_2CH_3), 169.2 ($CO_2CH_2CH_3$.), 171.1 (NC=O) ppm. GC-MS: m/z (%) = 171 (63) $[M]^+$, 98 (100).

Ethyl 1-Methyl-2-oxopiperidine-3-carboxylate (6c): To a suspension of NaH (7.0 g, 160 mmol, 60% suspension in mineral oil) in anhydrous THF (70 mL), a solution of **5c** (4.5 g, 40 mmol) and diethyl carbonate (28.3 g, 360 mmol) in anhydrous THF (30 mL) was added dropwise under argon at room temperature. After 7 h at reflux, the mixture was cooled to room temperature and stirred for 14 h. To the resulting mixture, water (150 mL) was added, and the aqueous phase was extracted with diethyl ether (4 × 200 mL). The organic phase was dried with Na_2SO_4, and after solvent evaporation, the crude product was purified by chromatography on silica gel (diethyl ether/methanol, 99:1) to obtain **6c** as a yellow viscous oil (3.1 g, 16.80 mmol, 42% yield). IR ($CHCl_3$): $\tilde{\nu}$ = 1730, 1640 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz, 25 °C): δ = 1.25 (t, J = 7.1 Hz, 3 H, OCH_2CH_3), 1.70–2.20 (m, 4 H, CH_2CH_2CH), 2.93 (s, 3 H, NCH_3), 3.18–3.45 (m, 3 H, NCH_2, CH), 4.09–4.28 (m, 2 H, OCH_2CH_3) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz, 25 °C): δ = 14.1 (OCH_2CH_3), 20.9 ($CH_2CH_2CH_2$), 25.2 (CH_2CH), 34.9 (NCH_3), 49.1 (CH), 50.0 (NCH_2), 61.2 (OCH_2CH_3), 165.8 ($CO_2CH_2CH_3$), 171.1 (NC=O) ppm. GC-MS: m/z (%) = 185 (95) $[M]^+$, 83 (100). HRMS: calcd. for $C_9H_{15}NNaO_3$ 208.0950; found 208.0947.

3-(Hydroxymethyl)piperidin-2-one (7a):[8] A suspension of **6a** (1 g, 6.00 mmol) and $CaCl_2$ (700 mg, 6.00 mmol) in methanol (12 mL) was cooled to 0–5 °C and treated with sodium tetrahydridoborate (500 mg, 12 mmol), and cooling was continued for 2 h. After an additional 14 h at room temperature, the solvent was removed under vacuum, and a solution of 3 N citric acid was added dropwise until the mixture was completely soluble (pH = 3.5–4). The aqueous phase was extracted with CH_2Cl_2 (3 × 40 mL), the organic extracts were dried with Na_2SO_4, and the solvent was removed under vacuum to give pure **7a** as a white solid (700 mg, 5.43 mmol, 90% yield). IR ($CHCl_3$): $\tilde{\nu}$ = 3340, 1700 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz, 25 °C): δ = 1.35–1.95 (m, 4 H, $NCH_2CH_2CH_2$), 2.36–2.59 (m, 1 H, CH), 3.16–3.41 (m, 2 H, NCH_2), 3.61 (br., 1 H, OH), 3.60–3.84 (m, 2 H, CH_2OH), 6.67 (br., 1 H, NH) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz, 25 °C): δ = 21.2 (NCH_2CH_2), 23.1 ($NCH_2CH_2CH_2$), 41.7 (NCH_2), 42.0 (CH), 63.5 (CH_2OH), 175.3 (NC=O) ppm. GC-MS: m/z (%) = 129 (12) $[M]^+$, 99 (100).

3-(Hydroxymethyl)-1-methylpyrrolidin-2-one (7b):[11] Compound **7b** was prepared from **6b** (2 g, 11.70 mmol) according to the procedure described for **7a**. The product was obtained as a pure yellow liquid (1.2 g, 9.36 mmol, 80% yield). IR ($CHCl_3$): $\tilde{\nu}$ = 1705 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz, 25 °C): δ = 1.65–1.90 (m, 1 H, NCH_2CHHCH), 2.05–2.25 (m, 1 H, NCH_2CHHCH), 2.54–2.80 (m, 1 H, CH), 2.85 (s, 3 H, NCH_3), 3.24–3.48 (m, 2 H, NCH_2), 3.67 (dd, J = 11.0 Hz, J = 7.3 Hz, 1 H, $CHHOH$), 3.87 (dd, J = 11.0 Hz, J = 5.1 Hz, 1 H, $CHHOH$) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz, 25 °C): δ = 21.2 (NCH_2CH_2), 29.5 (NCH_3), 43.5 (CH), 48.0 (NCH_2), 62.6 (CH_2OH), 174.6 (NC=O) ppm. GC-MS: m/z (%) = 129 (9.3) $[M]^+$, 99 (100).

3-(Hydroxymethyl)-1-methylpiperidin-2-one (7c): Compound **7c** was prepared from **6c** (360 mg, 2.16 mmol) according to the procedure described for **7a**. The product was obtained as a pure white solid (278 mg, 1.94 mmol, 90% yield). IR ($CHCl_3$): $\tilde{\nu}$ = 1710 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz, 25 °C): δ = 1.35–1.60 (m, 1 H, $CHHCH_2CH$), 1.70–2.00 (m, 3 H, $CHHCH_2CH$), 2.33–2.59 (m, 1 H, CH), 2.94 (s, 3 H, NCH_3), 3.19–3.34 (m, 2 H, NCH_2), 3.46 (s, 1 H, OH), 3.55–3.80 (m, 2 H, CH_2OH) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz, 25 °C): δ = 22.1 (NCH_2CH_2), 26.0 ($NCH_2CH_2CH_2$), 34.4 (CH), 42.9 (NCH_3), 49.7 (NCH_2), 64.7 (CH_2OH), 173.1 (NC=O) ppm. GC-MS: m/z (%) = 143 (39) $[M]^+$, 113 (100). HRMS: calcd. for $C_7H_{13}NNaO_2$ 166.0844; found 166.0840.

Synthesis of α-Methylene-γ- and -δ-lactams 1a–d

3-Methylenepiperidin-2-one (1a):[8] Cuprous iodide (190 mg, 1.00 mmol) was added at 110 °C to a stirred solution of **7a** (1.6 g, 12.00 mmol) and *N*,*N*-dicyclohexylcarbodiimide (3.1 g, 15.00 mmol) in toluene (18 mL). The mixture was heated at reflux for 70 min and cooled. Water (15 mL) was added, and the mixture was stirred for 1 h. Diethyl ether (37 mL) was added, and the mixture was filtered. The aqueous phase was separated and extracted with CH_2Cl_2 (2 × 40 mL). The combined organic phases were dried with K_2CO_3, filtered, and concentrated to give pure **1a** as a solid (839 mg, 7.56 mmol, 63% yield). IR ($CHCl_3$): $\tilde{\nu}$ = 3240, 1673, 1628 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz, 25 °C): δ = 1.75–1.95 (m, 2 H, NCH_2CH_2), 2.48–2.64 (m, 2 H, CH_2CH_2C), 3.30–3.46 (m, 2 H, NCH_2), 5.26–5.37 (m, 1 H, C=C*H*H), 6.16–6.24 (m, 1 H, C=CH*H*), 6.68 (br., 1 H, NH) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz, 25 °C): δ = 22.7 (NCH_2CH_2), 29.4 (CH_2CH_2C), 42.1 (NCH_2), 121.3 (C=CH_2), 137.3 (C=CH_2), 166.0 (NC=O) ppm. GC-MS: m/z (%) = 111 (100) $[M]^+$.

1-Methyl-3-methylenepyrrolidin-2-one (1b):[9a] Compound **1b** was prepared from **7b** (1 g, 7.75 mmol), according to the procedure described for **1a**. The product was obtained as a pure yellow liquid (447 mg, 4.03 mmol, 52% yield). IR ($CHCl_3$): $\tilde{\nu}$ = 1680, 1638 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz, 25 °C): δ = 2.55–2.70 (m, 2 H, NCH_2CH_2), 2.78 (s, 3 H, NCH_3), 3.20–3.35 (m, 2 H, NCH_2), 5.09–5.20 (m, 1 H, C=C*H*H), 5.68–5.78 (m, 1 H, C=CH*H*) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz, 25 °C): δ = 23.8 (NCH_2CH_2), 33.5 (NCH_3), 49.2 (NCH_2), 120.3 (C=CH_2), 140.9 (C=CH_2), 164.3 (NC=O) ppm. GC-MS: m/z (%) = 111 (100) $[M]^+$.

1-Methyl-3-methylenepiperidin-2-one (1c):[9b] Compound **1c** was prepared from **7c** (270 mg, 1.89 mmol), according to the procedure described for **1a**. The product was obtained as a pure clear liquid (140 mg, 1.12 mmol, 59% yield). IR ($CHCl_3$): $\tilde{\nu}$ = 1680, 1630 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz, 25 °C): δ = 1.88 (p, J = 6.0 Hz, 2 H, $NCH_2CH_2CH_2$), 2.49–2.62 (m, 2 H, CH_2CH_2C), 3.01 (s, 3 H, NCH_3), 3.37 (t, J = 5.9 Hz, 2 H, NCH_2), 5.21–5.28 (m, 1 H, C=CHH), 6.14–6.21 (m, 1 H, C=CHH) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz, 25 °C): δ = 22.8 ($NCH_2CH_2CH_2$), 29.8 (CH_2CH_2C), 34.8 (NCH_3), 50.1 (NCH_2), 120.5 (C=CH_2), 137.6 (C=CH_2), 164.0 (NC=O) ppm. GC-MS: m/z (%) = 125 (100) $[M]^+$.

Ethyl (3-Methylene-2-oxopiperidin-1-yl)acetate (1d):[8] To a suspension of NaH (218 mg, 4.54 mmol, 50% suspension in mineral oil) in anhydrous THF (10 mL), a solution of **1a** (504 mg, 4.54 mmol) in toluene (1 mL) was added dropwise at 0 °C. After 3 h at room temperature, the mixture was cooled again to 0 °C, and ethyl bromoacetate (0.5 mL, 4.54 mmol) was added. After stirring of the mixture for 2 h, diethyl ether (10 mL) was added to the residue, and the solids were filtered off and washed with diethyl ether. The organic phase was concentrated to give a crude product, which was purified by chromatography on silica gel (hexane/ethyl acetate, 1:1) to give **1d** as a yellowish viscous liquid (608 mg, 3.09 mmol, 68% yield). IR ($CHCl_3$): $\tilde{\nu}$ = 1730, 1680, 1635 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz, 25 °C): δ = 1.18 (t, J = 7.3 Hz, 3 H, $CO_2CH_2CH_3$), 1.79–2.01 (m, 2 H, $NCH_2CH_2CH_2$), 2.52–2.68 (m, 2 H, CH_2CH_2C), 3.39–3.50 (m, 2 H, NCH_2), 4.10–4.26 (m, 4 H, NCH_2CO_2, $CO_2CH_2CH_3$), 5.27–5.33 (m, 1 H, C=CHH), 6.17–6.23 (m, 1 H, C=CHH) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz, 25 °C): δ = 14.2 ($CO_2CH_2CH_3$), 23.2 ($NCH_2CH_2CH_2$), 30.1 (CH_2CH_2C), 49.3 (NCH_2), 49.8 (NCH_2CO_2), 60.4 ($CO_2CH_2CH_3$), 122.4 (C=CH_2), 137.4 (C=CH_2), 166.2 ($CO_2CH_2CH_3$), 170.9 (NC=O) ppm. GC-MS: m/z (%) = 197 (5) $[M]^+$, 124 (100).

Synthesis of Spiroaziridinolactams 2a–d

Ethyl 4-Oxo-1,5-diazaspiro[2.5]octane-1-carboxylate (2a): To a stirred solution of the substrate **1a** (96 mg, 0.87 mmol) in CH_2Cl_2 (0.5 mL), $NsONHCO_2Et$ (252 mg, 0.87 mmol) and CaO (49 mg, 0.87 mmol) were added portionwise every hour, reaching a substrate/$NsONHCO_2Et$/CaO molar ratio of 1:3:3. Because the reaction was exothermic, the flask was cooled in a water bath during the addition to avoid overheating. After 4 h, pentane was added. The organic phase was filtered, and the solid residue was washed again with pentane/CH_2Cl_2 (1:1) and then with CH_2Cl_2. The combined organic phases were concentrated under vacuum and chromatographed on silica gel (hexane/ethyl acetate, 4:6) to obtain **2a** as a yellow oil (86 mg, 0.43 mmol, 50% yield). IR ($CHCl_3$): $\tilde{\nu}$ = 3240, 1733, 1680 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz, 25 °C): δ = 1.24 (t, J = 7.3 Hz, 3 H, OCH_2CH_3), 1.74–2.22 (m, 5 H, $CH_2CH_2CH_2C$, $CHHNCO_2$), 2.91 (d, J = 1.5 Hz, 1 H, $CHHNCO_2$), 3.26–3.56 (m, 2 H, NCH_2CH_2), 4.13 (q, J = 7.3 Hz, 2 H, OCH_2CH_3), 6.81 (br., 1 H, NH) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz, 25 °C): δ = 14.3 (OCH_2CH_3), 21.6 (NCH_2CH_2), 29.8 (CH_2NCO_2), 37.0 (CH_2CH_2C), 42.3 (CH_2CCH_2), 42.8 (NCH_2CH_2), 62.3 (OCH_2CH_3), 161.0 (NCO_2), 167.6 (NHCO) ppm. GC-MS: m/z (%) = 198 (7) $[M]^+$, 125 (100). HRMS: calcd. for $C_9H_{14}N_2NaO_3$ 221.0902; found 221.0900.

Ethyl 5-Methyl-4-oxo-1,5-diazaspiro[2.4]heptane-1-carboxylate (2b): Compound **2b** was prepared from **1b** (300 mg, 2.70 mmol), according to the procedure described for **2a**. The crude product was purified by chromatography on silica gel (hexane/ethyl acetate, 4:6) to obtain **2b** as a pale yellow oil (257 mg, 1.30 mmol, 48% yield). IR ($CHCl_3$): $\tilde{\nu}$ = 1730, 1680 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz, 25 °C): δ = 1.24 (t, J = 7.3 Hz, 3 H, OCH_2CH_3), 2.09–2.49 (m, 3 H, NCH_2CH_2, $CHHNCO_2$), 2.76 (d, J = 1.1 Hz, 1 H, $CHHNCO_2$), 2.93 (s, 3 H, NCH_3), 3.35–3.64 (m, 2 H, NCH_2CH_2), 4.16 (q, J = 7.3 Hz, 2 H, OCH_2CH_3) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz, 25 °C): δ = 14.2 (OCH_2CH_3), 23.8 (NCH_2CH_2), 30.6 (NCH_3), 35.2 (CH_2NCO_2), 45.2 (CH_2CCH_2), 45.7 (NCH_2CH_2), 62.4 (OCH_2CH_3), 160.8 (NCO_2), 168.9 (NCH_3CO) ppm. GC-MS: m/z (%) = 198 (<0.1) $[M]^+$, 126 (100). HRMS: calcd. for $C_9H_{14}N_2NaO_3$ 221.0902; found 221.0899.

Ethyl 5-Methyl-4-oxo-1,5-diazaspiro[2.5]octane-1-carboxylate (2c): Compound **2c** was prepared from **1c** (140 mg, 1.20 mmol), according to the procedure described for **2a**. The crude product was purified by chromatography on silica gel (hexane/ethyl acetate, 1:1) to obtain **2c** as a pale yellow oil (117 mg, 0.55 mmol, 46% yield). IR ($CHCl_3$): $\tilde{\nu}$ = 1732, 1660 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz, 25 °C): δ = 1.23 (t, J = 7.3 Hz, 3 H, OCH_2CH_3), 1.82–2.24 (m, 5 H, CH_2CH_2C, $CHHNCO_2$), 2.96 (d, J = 1.5 Hz, 1 H, $CHHNCO_2$), 2.98 (s, 3 H, NCH_3), 3.36–3.53 (m, 2 H, NCH_2CH_2), 4.00–4.27 (m, 2 H, OCH_2CH_3) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz, 25 °C): δ = 14.3 (OCH_2CH_3), 21.4 (NCH_2CH_2), 30.1 (CH_2NCO_2), 35.3 (NCH_3), 37.0 (CH_2CH_2C), 42.8 (CH_2CCH_2), 50.4 (NCH_2CH_2), 62.2 (OCH_2CH_3), 161.0 (NCO_2), 165.5 (NCH_3CO) ppm. GC-MS: m/z (%) = 211 (17) $[M - 1]^+$, 138 (100). HRMS: calcd. for $C_{10}H_{16}N_2NaO_3$ 235.1059; found 235.1057.

Ethyl 5-(2-Ethoxy-2-oxoethyl)-4-oxo-1,5-diazaspiro[2.5]octane-1-carboxylate (2d): Compound **2d** was prepared from **1d** (290 mg, 1.47 mmol), according to the procedure described for **2a**, reaching a substrate/$NsONHCO_2Et$/CaO molar ratio of 1:2.5:2.5. The crude product was purified by chromatography on silica gel (hexane/ethyl acetate, 3:7) to obtain the product **2d** as a pale yellow oil (234 mg, 0.82 mmol, 56% yield). IR ($CHCl_3$): $\tilde{\nu}$ = 1725, 1657 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz, 25 °C): δ = 1.10–1.31 (m, 6 H, $NCO_2CH_2CH_3$, $CH_2CO_2CH_2CH_3$), 1.84–2.23 (m, 5 H, CH_2CH_2C, $CHHNCO_2$), 2.90 (d, J = 1.5 Hz, 1 H, $CHHNCO_2$), 3.40–3.59 (m, 2 H, NCH_2CH_2), 3.87 (d, J = 17.2 Hz, 1 H, $NCHHCO_2$), 4.31 (d, J = 17.2 Hz, 1 H, $NCHHCO_2$), 3.99–4.23 (m, 4 H, $NCO_2CH_2CH_3$, $CH_2CO_2CH_2CH_3$) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz, 25 °C): δ = 13.9 ($NCO_2CH_2CH_3$), 14.1 ($CH_2CO_2CH_2CH_3$), 21.3 (NCH_2CH_2), 29.9 (CH_2CH_2C), 37.2 (CH_2NCO_2), 42.5 (CH_2CCH_2), 49.1 (NCH_2CH_2), 49.7 (NCH_2CO), 61.1 ($CH_2CO_2CH_2CH_3$), 62.2 ($NCO_2CH_2CH_3$), 160.8 ($NCO_2CH_2CH_3$), 166.3 ($CH_2CO_2CH_2CH_3$), 168.5 (NCO) ppm. GC-MS: m/z (%) = 284 (1) $[M]^+$, 29 (100). HRMS: calcd. for $C_{13}H_{20}N_2NaO_5$ 307.1270; found 307.1267.

3-Hydroxy-1-methyl-3-[(trimethylsilyl)methyl]-1,3-dihydroindol-2-one (9): 1-Methylisatin (**8**, 1 g, 6.21 mmol) was suspended in dry diethyl ether (24 mL) and the mixture cooled to –78 °C. [(Trimethylsilyl)methyl]magnesium chloride (12 mL of a 1 M solution in diethyl ether, 12.42 mmol) was added whilst stirring. The mixture was stirred at –78 °C for 15 min and then warmed to room temperature with stirring for a further 18 h. The reaction was quenched with methanol, and then the mixture was concentrated in vacuo to give a dark green solid, which was triturated first with hexane/ethyl acetate (1:1) and then with ethyl acetate. After filtration, the combined organic phases were concentrated in vacuo to give pure **9** as a solid (1.5 g, 6.21 mmol, quantitative yield). IR ($CHCl_3$): $\tilde{\nu}$ = 1700 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz, 25 °C): δ = –0.30 [s, 9 H, $Si(CH_3)_3$], 1.55 (s, 2 H, $SiCH_2$), 2.20 (br., 1 H, OH), 3.18 (s, 3 H, NCH_3), 6.80–7.40 (m, 4 H, CH_{arom}) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz, 25 °C): δ = –2.5 [$Si(CH_3)_3$], 24.9 ($SiCH_2$), 27.3 (NCH_3), 74.4 (COH), 35.3 (NCH_3), 107.1 ($CH_{arom.}$), 121.9 ($CH_{arom.}$), 122.9 ($CH_{arom.}$), 128.3 ($CH_{arom.}$), 130.1 ($C_{arom.}$), 141.6 ($C_{arom.}$), 177.3 (C=O) ppm. GC-MS: m/z (%) = 249 (26) $[M - 1]^+$, 75 (100). HRMS: calcd. for $C_{13}H_{19}NNaO_2Si$ 272.1083; found 272.1079.

1-Methyl-3-methylene-1,3-dihydro-2*H*-indol-2-one (10): 3-Hydroxy-3-[(trimethylsilyl)methyl]-1-methyloxindole (**9**, 1.5 g, 6.21 mmol) in dry CH_2Cl_2 (120 mL) was cooled to –78 °C, and boron trifluoride–diethyl ether (7.5 mL, 30 mmol) was added. The mixture was stirred at –78 °C for 2 h, and then at 0 °C for a further 1 h. The mixture was poured into saturated aqueous $NaHCO_3$ solution and extracted with CH_2Cl_2 (4 × 300 mL). The combined organic layers were washed again with $NaHCO_3$, dried with Na_2SO_4, and the solvent was partially evaporated to give a concentrated solution of pure product **10**, which was immediately treated as described below. An analytical sample was concentrated to dryness for spectroscopic characterization. ^{1}H NMR ($CDCl_3$, 200 MHz, 25 °C): δ = 3.24 (s, 3 H, NCH_3), 6.10 (s, 1 H, C=C*H*H), 6.40 (s, 1 H, C=CH*H*), 6.80–7.47 (m, 4 H, CH_{arom}) ppm. GC-MS: *m*/*z* (%) = 159 (98) $[M]^+$, 130 (100).

Ethyl 1′-Methyl-2′-oxospiro[aziridine-2,3′-indoline]-1-carboxylate (11): To a stirred solution of the substrate **10** (900 mg, 5.66 mmol) in CH_2Cl_2 (2 mL), $NsONHCO_2Et$ (1.6 g, 5.66 mmol) and CaO (317 mg, 5.66 mmol) were added portionwise. After 3 h, pentane was added, and the mixture was stirred for a further 1 h. The organic phase was filtered, and the solid residue was washed first with pentane/CH_2Cl_2 (8:2) and then with pentane/CH_2Cl_2 (1:1). The combined organic phases were concentrated under vacuum and chromatographed on silica gel (hexane/ethyl acetate, 7:3) to obtain **11** as a pale yellow solid (1 g, 4.07 mmol, 72% yield). IR ($CHCl_3$): $\tilde{\nu}$ = 1732, 1621 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz, 25 °C): δ = 1.25 (t, *J* = 7.3 Hz, 3 H, OCH_2CH_3), 2.84 (d, *J* = 1.5 Hz, 1 H, NC*H*H), 3.12 (d, *J* = 1.5 Hz, 1 H, NCH*H*), 3.30 (s, 3 H, NCH_3), 4.20 (q, *J* = 7.3 Hz, 2 H, OCH_2CH_3), 6.94–7.43 (m, 4 H, CH_{arom}) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz, 25 °C): δ = 14.6 (OCH_2CH_3), 27.1 (NCH_3), 39.4 (NCH_2C), 45.2 ($NCCH_2$), 63.4 (OCH_2CH_3), 109.1 (CH_{arom}), 122.0 (CH_{arom}), 123.2 (CH_{arom}), 123.7 (C_{arom}), 130.1 (CH_{arom}), 144.7 (C_{arom}), 160.0 (NCO_2), 170.4 (NCH_3CO) ppm. GC-MS: *m*/*z* (%) = 246 (100) $[M]^+$. HRMS: calcd. for $C_{13}H_{14}N_2NaO_3$ 269.0902; found 269.0899.

Aziridine Ring-Opening Reactions

Ethyl (1,3-Dimethyl-2-oxopyrrolidin-3-yl)carbamate (3b): To a stirred suspension of **2b** (40 mg, 0.20 mmol) and 10% Pd/C (80 mg) in dry methanol (1 mL), anhydrous ammonium formate (63 mg, 1 mmol) was added in a single portion, and the resulting mixture was stirred at room temperature under argon for 4 h. The catalyst was removed by filtration through a Celite pad and washed with methanol. The filtrate was concentrated under reduced pressure, and the residue was triturated with water and extracted with ethyl acetate (5 mL). The combined organic phases were dried with Na_2SO_4 and concentrated in vacuo. The crude product was purified by chromatography on silica gel (hexane/ethyl acetate, 2:8) to obtain **3b** as a yellow oil (24 mg, 0.12 mmol, 60% yield). IR ($CHCl_3$): $\tilde{\nu}$ = 1735, 1675 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz, 25 °C): δ = 1.23 (t, *J* = 7.3 Hz, 3 H, OCH_2CH_3), 1.37 (s, 3 H, CH_2CCH_3), 2.09–2.55 (m, 2 H, CH_2CH_2C), 2.89 (s, 3 H, NCH_3), 3.20–3.44 (m, 2 H, NCH_2), 4.08 (q, *J* = 7.3 Hz, 2 H, OCH_2CH_3), 5.23 (br., 1 H, NH) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz, 25 °C): δ = 13.3 (OCH_2CH_3), 21.7 (CH_2CCH_3), 29.9 (CH_2CH_2C), 34.6 (NCH_3), 35.9 (NCH_2), 57.9 (OCH_2CH_3), 64.4 (CH_2CCH_3), 159.2 (NCO_2), 178.4 (NCH_3CO) ppm. GC-MS: *m*/*z* (%) = 200 (7) $[M]^+$, 111 (100). HRMS: calcd. for $C_9H_{16}N_2NaO_3$ 223.1059; found 223.1056.

Ethyl [(1-Methyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl)methyl]carbamate (12): Compound **12** was prepared from **11** (50 mg, 0.20 mmol), according to the procedure described for **3b**. The mixture was stirred at room temperature under argon for 1 h, and the crude product was purified by chromatography on silica gel (hexane/ethyl acetate, 1:1) to give **12** as a yellow solid (22 mg, 0.09 mmol, 44% yield). IR ($CHCl_3$): $\tilde{\nu}$ = 1709, 1613 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz, 25 °C): δ = 1.23 (t, *J* = 7.3 Hz, 3 H, OCH_2CH_3), 3.20 (s, 3 H, NCH_3), 3.28–3.49 (m, 1 H, CHC*H*HNH), 3.52–3.66 (m, 1 H, COC*H*CH_2), 3.84–4.04 (m, 1 H, CHCH*H*NH), 4.10 (q, *J* = 7.3 Hz, 2 H, OCH_2CH_3), 5.55 (br., 1 H, NH), 6.80–7.40 (m, 4 H, CH_{arom}) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz, 25 °C): δ = 14.4 (OCH_2CH_3), 26.0 (NCH_3), 41.1 (NCH_2CH), 45.5 ($CHCH_2N$), 60.8 (OCH_2CH_3), 108.0 (CH_{arom}), 123.2 (CH_{arom}), 124.1 (CH_{arom}), 125.9 (C_{arom}), 128.4 (CH_{arom}), 144.3 (C_{arom}), 156.5 (NCO_2), 176.6 (NCH_3CO) ppm. GC-MS: *m*/*z* (%) = 248 ( ) $[M]^+$, 159 (100). HRMS: calcd. for $C_{13}H_{16}N_2NaO_3$ 271.1059; found 271.1055.

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