A New Access to Pyrrolizidine Derivatives: Ring Contraction of Methyl (*E*)-[1,2-Oxazin-3-yl]propenoates

Reinhold Zimmer,*[a] Markus Collas,[b,1] Regina Czerwonka,[b] Ute Hain,[b] Hans-Ulrich Reissig*[a]

[a] Institut für Chemie und Biochemie, Freie Universität Berlin, Takustraße 3, 14195 Berlin, Germany
Fax +49(30)83855367; E-mail: hans.reissig@chemie.fu-berlin.de

[b] Institut für Organische Chemie, Technische Universität Dresden, Bergstraße 66, 01016 Dresden, Germany

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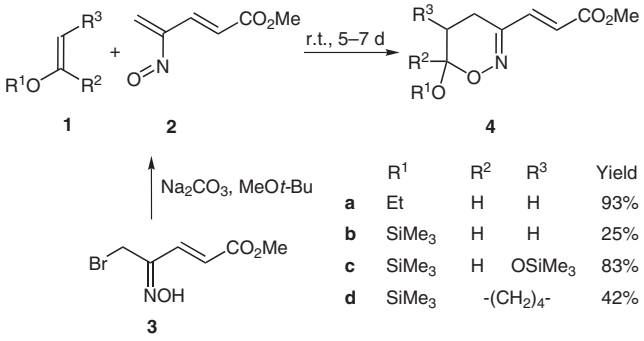
Dedicated to Professor Volker Jäger on the occasion of his 65th birthday

Abstract: Nitrosoalkene **2** generated in situ from oxime **3** underwent smooth hetero Diels–Alder reaction with enol ethers **1** to afford 1,2-oxazine derivatives **4** bearing an exocyclic C=C bond. Methoxyallene **8** and **2** provided 6*H*-1,2-oxazine **10** in good overall yield. The exocyclic double bond of this type of 1,2-oxazines can be employed for addition reactions as demonstrated by dihydroxylation of **4a** with potassium permanganate, smoothly delivering 1,2-diol **11**. A reductive cascade reaction involving ring cleavage at the N–O bond followed by cyclization steps furnished pyrrolizidinone derivatives **12** in good yields. In the case of **12b** this transformation proceeded with excellent stereoselectivity. Finally, the lactam moiety of **12** could be reduced with borane to provide the corresponding pyrrolizidine derivatives **19** in good yield.

Key words: 1,2-oxazines, pyrrolizidines, hydrogenation, lactams, pyrroles, hetero Diels–Alder reaction

A common strategy for the construction of functionalized heterocyclic compounds involves ring contraction of easily available precursor heterocycles. For this purpose, a moiety allowing smooth ring opening is required, a property which is given with the relatively weak N–O bond.[2] The compound class of 1,2-oxazines fulfils this prerequisite and hence it is frequently employed in organic synthesis.[3] Ring cleavages and ring transformations could be exploited for the synthesis of a variety of nitrogen-containing heterocycles such as pyrroles,[4] proline derivatives,[4f,5] pyrrolidines,[6] cyclic five-membered nitrones,[4i,5a,7] aziridines,[8] γ-lactams,[4i,9] pyridines,[10] and indolizidines.[11] To date, not much is known about the preparation of pyrrolidizines starting from 1,2-oxazine derivatives.[12] The pyrrolizidine core is found in many alkaloids including examples with interesting pharmacological activity.[13] Polyhydroxylated pyrrolidizine alkaloids are of particular importance as inhibitors of glycosidases and glycosyltransferases.[14] The present report deals with the preparation of methyl (*E*)-3-[1,2-oxazin-3-yl]propenoates and their simple transformation into pyrrolizidinone and pyrrolizidine derivatives.

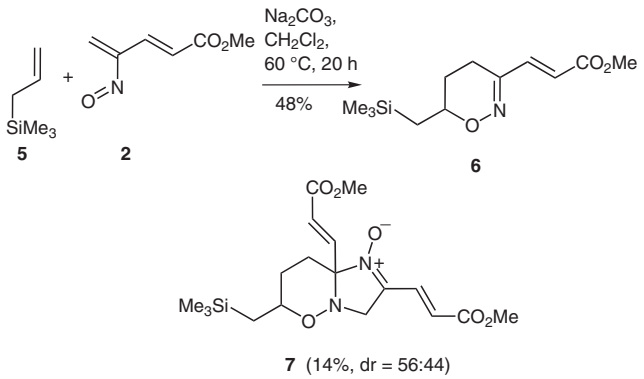
1,2-Oxazines **4** with an exocyclic C=C bond at position 3 can easily be prepared by hetero Diels–Alder reaction of electron-rich olefins **1** and nitrosoalkene **2**, which are generated in situ from the corresponding α-bromooxime **3** by treatment with a base such as sodium carbonate (Scheme 1).[15] Cycloadducts **4** were generally obtained in moderate to excellent yields. Dienophile **1c** was used as an *E*/*Z* mixture of isomers (60:40), however, only the more reactive *E*-isomer underwent cycloaddition with **2** providing **4c** in good yield and with *trans*-orientated trimethylsiloxy groups. The high kinetic preference for *E*-configured dienophiles is a common feature of nitrosoalkene cycloadditions.[16]



	R^1	R^2	R^3	Yield
a	Et	H	H	93%
b	$SiMe_3$	H	H	25%
c	$SiMe_3$	H	$OSiMe_3$	83%
d	$SiMe_3$	$-(CH_2)_4-$		42%

Scheme 1 Hetero Diels–Alder reactions of enol ethers **1** with nitrosoalkene **2**

Allyltrimethylsilane (**5**) is also a suitable dienophile for hetero Diels–Alder reactions with nitrosoalkenes, although the reactivity of **5** is lower in comparison with olefins **1**.[16] The cycloaddition of **2** and **5** under standard conditions (see Scheme 1) gave the 1,2-oxazine **6** only in



Equation 1 Hetero Diels–Alder reaction of allyltrimethylsilane with nitrosoalkene **2**

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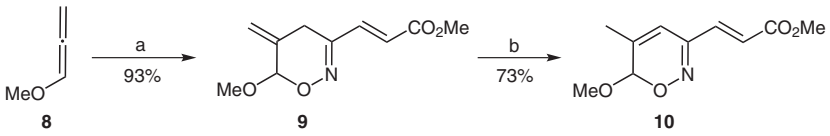
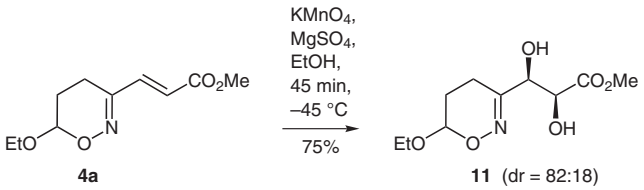


Scheme 2 Preparation of 6*H*-1,2-oxazine **10**; *Reagents and conditions:* a) **2**, Na_2CO_3, *t*-BuOMe, r.t., 6 d; b) DBU, CH_2Cl_2, r.t., 6 h.

low yield (4–30%).[17] However, the yield of **6** could be improved when the reaction was performed at 60 °C in an ACE pressure tube (Equation 1). The reaction time was dramatically decreased under these conditions, but the expected product **6** was accompanied by bicyclic nitrone **7**, which was obtained as a mixture of two diastereomers (ca. 1:1). The formation of nitrone **7** can be explained by a subsequent [3+2] cycloaddition of the primary adduct **6** with nitrosoalkene **2**.[7a] It cannot be ruled out that **2** and **6** first undergo a [4+2] cycloaddition and the primary 2:1 adduct then rearranges to nitrone **7**. This type of transformation of 1,2-oxazines into nitrones was reported earlier.[4f,7b]

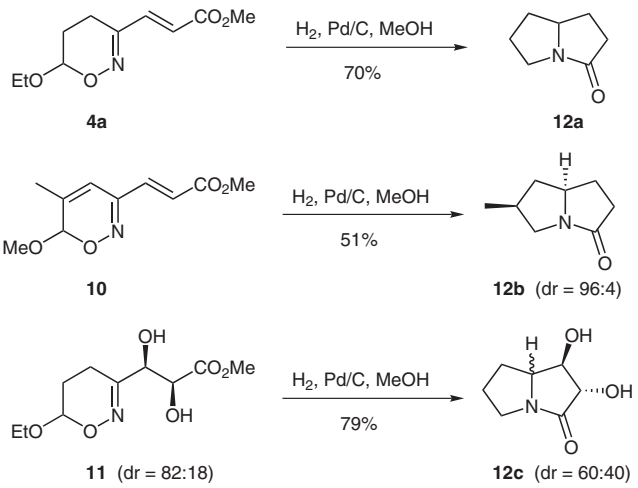
Donor-substituted allenes, in particular alkoxyallenes, are synthetically very useful dienophiles in [4+2] cycloadditions with nitrosoalkenes.[18] Gratifyingly, the hetero Diels–Alder reaction of nitrosoalkene **2** with methoxyallene (**8**)[19] led to 5-methylene-5,6-dihydro-4*H*-1,2-oxazine **9** in excellent yield. Primary adduct **9** was smoothly converted into the 6*H*-1,2-oxazine **10** containing two C=C bonds on treatment with DBU at room temperature (Scheme 2).

The C=C bonds of 1,2-oxazines such as **4** or **10** can be used to add new substituents or functional groups to the heterocycle.[17] This option is demonstrated in the dihydroxylation of 1,2-oxazine **4a** with potassium permanganate as the oxidizing reagent in the presence of magnesium sulfate.[20] The expected 1,2-diol **11** was obtained in good yield and with surprisingly high diastereoselectivity (Equation 2). Although we could not determine the relative configuration of the obtained diastereomers, the high stereoselection exhibited by the axial 6-ethoxy group[21] is quite remarkable. The asymmetric induction operates in a 1,5/1,6 fashion with respect to the dihydroxylated C=C bond.[22]



Equation 2 Dihydroxylation of 4*H*-1,2-oxazine **4a**

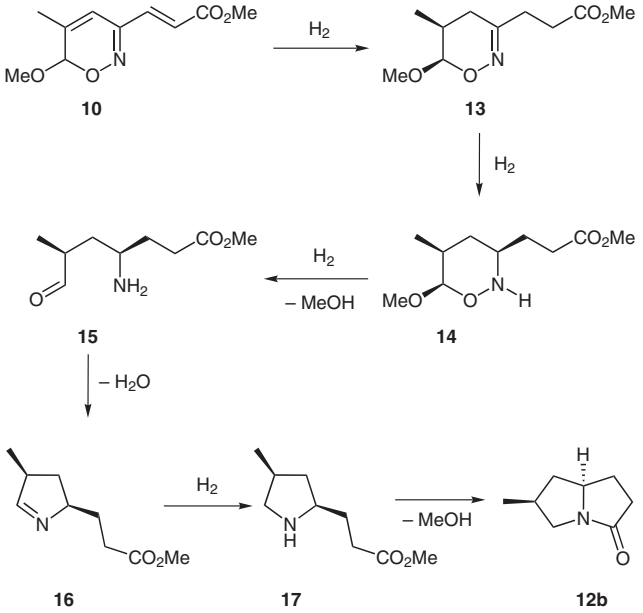
Having attained a good access to heterocyclic precursors **4a**, **10**, and **11**, we turned our attention to their conversion into pyrrolizidinones. The hydrogenolysis of these 1,2-oxazines furnished pyrrolizidinones **12a–c** in good yields (Scheme 3). We applied palladium on charcoal as catalyst for this multi-step reaction.[4i] Interestingly, the diastereoselectivity in the case of 7-methyl-substituted pyrrolizidinone **12b** is excellent, whereas the reduction and lactamization of **11** afforded the dihydroxylated pyrrolizidinone **12c** as a 60:40 mixture of isomers. This strongly differing stereoselectivity can be explained by the sequence of steps during this reductive ring contraction cascade (see below).



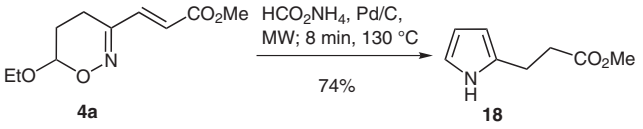
Scheme 3 Reductive ring contraction and lactamization of 1,2-oxazines leading to pyrrolizidinones **12**

A plausible mechanism for the formation of pyrrolizidinone **12b** from 1,2-oxazine **10** is illustrated in Scheme 4. The first step probably involves reduction of both C=C bonds. Intermediate **13** is very likely generated with the relative configuration as depicted, since the axial 6-methoxy group of **10** should lead to a high induction for the reduction of the 4,5-double bond. The subsequent reduction of the C=N bond of **13** is strongly influenced by the two existing stereogenic centers to preferentially form intermediate **14** with all-*cis* configuration as shown. This step determines the high diastereoselectivity of the overall process. Reductive cleavage of the N–O bond, ring closure, and water elimination to give cyclic imine **16** followed by a reduction of the C=N bond and finally lactamization of intermediate **17** furnishes pyrrolizidinone **12b**. This sequence of reduction steps explains the observed relative configuration, whereas the mechanism as proposed in earlier examples[4i] should lead to lower diastereoselectivity. Since 1,2-oxazine **11** bears no substituent at C-5, but only the more flexible stereogenic centers at the side chain, no comparable stereoselectivity of the C=N reduction occurs and **12c** is generated as a 60:40 mixture of diastereomers.

We also attempted to prepare pyrrolizidinones by microwave-assisted transfer hydrogenolysis, but failed. Treatment of 1,2-oxazine **4a** with ammonium formate in the presence of palladium on charcoal furnished pyrrole de-



Scheme 4 Proposed mechanism for the stereoselective formation of pyrrolizidinone **12b**

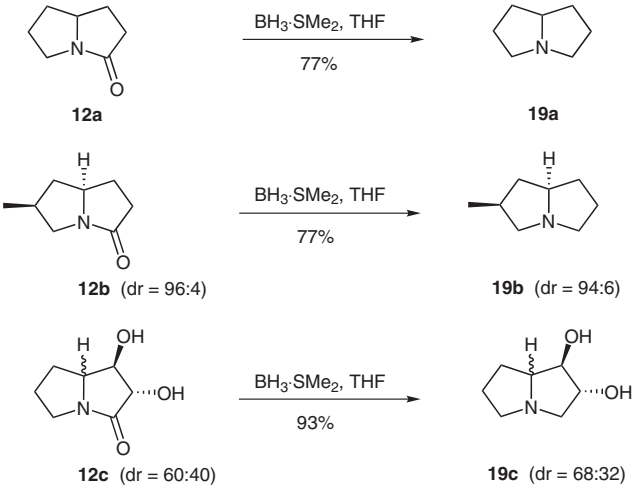


Equation 3 Transfer hydrogenation of 1,2-oxazine **4a** under microwave condition

rivative **18**[23] as a single product in good yield instead of the expected pyrrolizidinone **12a** (Equation 3). Apparently, only the C=C bond of **4a** was saturated, the N–O bond was reductively cleaved, and subsequent condensation led to the pyrrole.

Finally, pyrrolizidinones **12a–c** were smoothly converted into the corresponding pyrrolizidines **19a–c** in high yields by treatment of **12a–c** with borane-dimethyl sulfide complex in tetrahydrofuran at room temperature (Scheme 5).[24] As to be expected, the ratios of diastereomers of the products are comparable to those of the starting bicyclic lactams **12**. The relative configuration of **19b** was established by comparison of the NMR data of the minor diastereomer of **19b** with those reported in the literature.[25] Similar transformations leading to pyrrolizidinones and pyrrolizidines should also be possible with the other 1,2-oxazine derivatives as shown in Scheme 1.

In conclusion, we have established a simple, efficient and selective route for the synthesis of pyrrolizidine derivatives starting from enol ethers **1** and oxime **3** with the corresponding 1,2-oxazines **4** as crucial intermediates.[26] The overall yields for pyrrolizidinones are generally good: 65% **12a** (2 steps), 35% **12b** (3 steps), and 55% **12c** (3 steps). This convenient, reliable, and potentially very flexible procedure will enable rapid access to a variety of pharmacologically significant pyrrolizidine derivatives.



Scheme 5 Reduction of the pyrrolizidinones **12** to pyrrolizidines **19**

All reactions were performed under argon in flame-dried flasks, and the components were added by means of syringes. All solvents were dried by standard methods. IR spectra were measured with a Perkin-Elmer IR-325 or Nicolet 205 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on Bruker instruments (AC 200 or AC 300) in $CDCl_3$ solution. The chemical shifts are given relative to the TMS or $CDCl_3$ signals (δ_H = 7.27, δ_C = 77.0). Missing signals of the minor isomer are either hidden by signals of the major isomer or they could not be unambiguously identified due to low intensity. Neutral alumina (activity III, Merck) was used for column chromatography. Boiling points of compounds obtained in small-scale experiments refer to the temperature in a Büchi Kugelrohr oven. Melting points (uncorrected) were measured with an apparatus from Rapido (Boëtius). Na_2CO_3 was freshly pulverized (electric coffee mill, Braun KSM 1G) before use. All solvents were dried by standard methods.

Syntheses of starting materials were done according to literature: silyl enol ethers **1b**,**d**[27] and **1c**,[28] oxime **3**,[15] and methoxyallene (**8**).[29]

4*H*-1,2-Oxazines; General Procedure 1

Freshly ground Na_2CO_3 (6 equiv) was added to a solution of the corresponding olefin (10 equiv) and α-bromoketoxime **3** (1 equiv) in *t*-BuOMe (12–16 mL/mmol of oxime **3**). After stirring at r.t. for the time indicated in the individual reaction, the suspension was filtered through a pad of Celite to remove inorganic salts. The resulting filtrate was concentrated in vacuo and the excess of olefin was distilled off by Kugelrohr distillation. The residue was purified by chromatography (alumina, elution with hexane–EtOAc, 4:1 or 9:1) to furnish the 4*H*-1,2-oxazine.

Methyl (*E*)-3-(6′-Ethoxy-5′,6′-dihydro-4′*H*-1′,2′-oxazin-3′-yl)propenoate (4a)

According to general procedure 1, a mixture of **1a** (26.0 g, 360 mmol), oxime **3** (7.99 g, 36.0 mmol), and Na_2CO_3 (22.9 g, 216 mmol) in *t*-BuOMe (400 mL) was stirred for 5 d at r.t. The resulting crude product was purified by column chromatography (hexane–EtOAc, 4:1) to give 1,2-oxazine **4a** (7.16 g, 93%) as colorless crystals; mp 52–53 °C.

IR (KBr): 3040–2800 (=C–H, C–H), 1715 (C=O), 1640 (C=C), 1570 cm^{-1} (C=N).

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.34, 6.17 (2 d, *J* = 16 Hz, 1 H each, 3-H, 2-H), 5.16 (t, *J* = 2.5 Hz, 1 H, 6′-H), 3.85, 3.62 (2 qd, *J* = 7, 10 Hz, 1 H each, OCH_2CH_3), 3.79 (s, 3 H, CO_2CH_3), 2.45 (ddd, *J* = 7.5, 12.5, 17.5 Hz, 1 H, 4′-H_a), 2.26 (ddd, *J* = 2.5, 6.5, 17.5

Hz, 1 H, 4′-H_e), 2.06 (tdd, J = 2.5, 7.5, 13.5 Hz, 1 H, 5′-H_e), 1.91 (dddd, J = 2.5, 6.5, 12.5, 13.5 Hz, 1 H, 5′-H_a), 1.19 (t, J = 7 Hz, 3 H, OCH_2CH_3).

^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 166.4, 51.8 (s, q, CO_2CH_3), 155.4 (s, C-3′), 141.6 (d, C-3), 121.5 (d, C-2), 95.7 (d, C-6′), 63.8, 14.9 (t, q, OCH_2CH_3), 22.0 (t, C-5′), 15.1 (t, C-4′).

Anal. Calcd for $C_{10}H_{15}NO_4$ (213.2): C, 56.33; H, 7.09; N, 6.57. Found: C, 56.54; H, 7.43; N, 6.56.

Methyl (*E*)-3-[5′,6′-Dihydro-6′-(trimethylsiloxy)-4′*H*-1′,2′-oxazin-3′-yl]propenoate (4b)

According to general procedure 1, a mixture of **1b** (2.88 g, 24.8 mmol), oxime **3** (1.10 g, 4.96 mmol), and Na_2CO_3 (3.07 g, 29.8 mmol) in *t*-BuOMe (50 mL) was stirred for 5 d at r.t. The resulting crude product was purified by column chromatography (hexane–EtOAc, 4:1) to give 1,2-oxazine **4b** (0.317 g, 25%) as colorless crystals; mp 97–98 °C.

IR (KBr): 3060–2850 (=C–H, C–H), 1715 (C=O), 1635 (C=C), 1570 cm^{-1} (C=N).

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.33, 6.16 (2 d, J = 16 Hz, 1 H each, 3-H, 2-H), 5.47 (t, J = 2.5 Hz, 1 H, 6′-H), 3.77 (s, 3 H, CO_2CH_3), 2.44 (ddd, J = 7.5, 12, 17.5 Hz, 1 H, 4′-H_a) 2.23 (ddd, J = 2.5, 6.5, 17.5 Hz, 1 H, 4′-H_e), 1.86–1.76 (m, 1 H, 5′-H_e), 1.81 (dddd, J = 2.5, 6.5, 12, 13 Hz, 1 H, 5′-H_a), 0.15 [s, 9 H, $OSi(CH_3)_3$].

^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 166.5, 51.9 (s, q, CO_2CH_3), 154.7 (s, C-3′), 141.7 (d, C-3), 121.4 (d, C-2), 91.1 (d, C-6′), 23.8 (t, C-5′), 14.7 (t, C-4′), –0.2 [q, $OSi(CH_3)_3$].

Anal. Calcd for $C_{11}H_{19}NO_4Si$ (257.3): C, 51.34; H, 7.44; N, 5.44. Found: C, 51.45; H, 7.58; N, 5.46.

Methyl (*E*)-3-[5′,6′-Dihydro-*t*-5′,*r*-6′-bis(trimethylsiloxy)-4′*H*-1′,2′-oxazin-3′-yl]propenoate (4c)

According to general procedure 1, a mixture of **1c** (1.19 g, 5.80 mmol, *E*/*Z* = 60:40), oxime **3** (0.444 g, 2.00 mmol), and Na_2CO_3 (0.636 g, 12.0 mmol) in *t*-BuOMe (75 mL) was stirred for 10 d at r.t. The resulting crude product was purified by column chromatography (hexane–EtOAc, 4:1) to give 1,2-oxazine **4c** (0.572 g, 83%) as colorless crystals; mp 101–103 °C.

IR (KBr): 3060–2900 (=C–H), 1715 (C=O), 1635 (C=C), 1580 cm^{-1} (C=N).

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.39, 6.15 (2 d, J = 16.5 Hz, 1 H each, 3-H, 2-H), 5.08 (d, J = 3 Hz, 1 H, 6′-H), 3.92 (ddd, J = 2.5, 3, 5 Hz, 1 H, 5′-H_e), 3.79 (s, 3 H, CO_2CH_3), 2.56 (dd, J = 5, 17.5 Hz, 1 H, 4′-H_a), 2.17 (dd, J = 2.5, 17.5 Hz, 1 H, 4′-H_e), 0.17, 0.13 [2 s, 9 H each, $OSi(CH_3)_3$].

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 166.4, 51.9 (s, q, CO_2CH_3), 153.1 (s, C-3′), 141.9 (d, C-3), 121.5 (d, C-2), 93.3 (d, C-6′), 62.6 (d, C-5′), 24.5 (t, C-4′), 0.0, –0.2 [2 q, $OSi(CH_3)_3$].

Anal. Calcd for $C_{14}H_{27}NO_5Si_2$ (345.6): C, 48.66; H, 7.88; N, 4.05. Found: C, 47.98; H, 7.78; N, 4.01.

Methyl (*E*)-3-[4a′,5′,6′,7′,8′,8a′-Hexahydro-8a′-(trimethylsiloxy)-4′*H*-1′,2′-benzoxazin-3′-yl]propenoate (4d)

According to general procedure 1, a mixture of **1d** (1.36 g, 8.00 mmol), oxime **3** (0.222 g, 1.00 mmol), and Na_2CO_3 (0.318 g, 6.00 mmol) in *t*-BuOMe (10 mL) was stirred for 6 d at r.t. The resulting crude product was purified by column chromatography (hexane–EtOAc, 9:1) to give 1,2-oxazine **4d** (0.130 g, 42%) as colorless crystals; mp 117–118 °C.

IR (KBr): 3080–2800 (=C–H, C–H), 1715 (C=O), 1640 (C=C), 1580 cm^{-1} (C=N).

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.36, 6.13 (2 d, J = 16 Hz, 1 H each, 3-H, 2-H), 3.77 (s, 3 H, CO_2CH_3), 2.63 (dd, J = 7, 17.5 Hz, 1 H, 4′-H), 2.19–2.15, 1.91–1.79, 1.66–1.43, 1.29–0.96 (4 m, 1 H, 1 H, 5 H, 2 H, 4a′-H, 5′-H, 6′-H, 7′-H, 8′-H), 1.90 (br d, J = 17.5 Hz, 1 H, 4′-H), 0.08 [s, 9 H, $OSi(CH_3)_3$].

^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 166.5, 51.8 (s, q, CO_2CH_3), 153.2 (s, C-3′), 142.0 (d, C-3), 121.2 (d, C-2), 97.4 (d, C-8a′), 37.3 (t, C-8′), 34.8 (d, C-4a′), 29.3 (t, C-4′), 24.6, 23.6, 23.3 (3 t, C-5′, C-6′, C-7′), 1.4 [q, $OSi(CH_3)_3$].

Anal. Calcd for $C_{15}H_{25}NO_4Si$ (311.5): C, 57.85; H, 8.09; N, 4.50. Found: C, 58.09; H, 8.65; N, 4.39.

Methyl (*E*)-3-[5′,6′-Dihydro-6′-[(trimethylsilyl)methyl]-4′*H*-1′,2′-oxazin-3′-yl]propenoate (6) and (*E*,*E*)-5,6,7,7a-Tetrahydro-2,7a-bis[2-(methoxycarbonyl)ethenyl]-1-oxy-5-[(trimethylsilyl)methyl]-3*H*-4-oxa-1,3a-diazaindole (7)

Analogous to general procedure 1, a mixture of **5** (1.14 g, 10.0 mmol), oxime **3** (0.111 g, 0.50 mmol), and Na_2CO_3 (0.318 g, 6.00 mmol) in CH_2Cl_2 (20 mL) was stirred for 20 h at 60 °C in an ACE pressure tube. The resulting crude product was purified by column chromatography (hexane–EtOAc, 4:1) to provide 3 fractions: fraction 1, 1,2-oxazine **6** (0.052 g, 41%) as colorless crystals; fraction 2, a 1:2 mixture of **6** and **7** (0.029 g); and fraction 3, product **7** (0.009 g, 5%) as a colorless oil.

Compound 6

Mp 79–81 °C.

IR (KBr): 3080–2800 (=C–H, C–H), 1720 (C=O), 1635 (C=C), 1560 cm^{-1} (C=N).

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.30, 6.06 (2 d, J = 16 Hz, 1 H each, 3-H, 2-H), 3.84 (dtd, J = 2, 7.5, 10.5 Hz, 1 H, 6′-H), 3.74 (s, 3 H, CO_2CH_3), 2.34–2.24, 2.00–1.87, 1.69–1.52 (3 m, 2 H, 1 H, 1 H, 4′-H, 5′-H), 1.09, 0.86 (2 dd, J = 7.5, 14.5 Hz, 1 H each, CH_2SiMe_3), 0.50 [s, 9 H, $Si(CH_3)_3$].

^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 166.5, 51.8 (s, q, CO_2CH_3), 153.7 (s, C-3′), 141.9 (d, C-3), 120.9 (d, C-2), 75.2 (d, C-6′), 26.2, 22.7, 20.4 (3 t, C-4′, C-5′, CH_2SiMe_3), –0.9 [q, $Si(CH_3)_3$].

Anal. Calcd for $C_{12}H_{21}NO_3Si$ (255.4): C, 56.44; H, 8.29; N, 5.48. Found: C, 56.80; H, 8.22; N, 5.21.

Compound 7

Mixture of two diastereomers, 56:44.

IR (KBr): 3050–2800 (=C–H, C–H), 1725, 1720 (C=O), 1645, 1635 (C=C), 1525 cm^{-1} (C=N).

Major Isomer

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.61, 6.88, 6.34, 6.22 (4 d, J = 16 Hz, 1 H each, HC=), 4.21–3.84 (m, 3 H, 3-H, 5-H), 3.79, 3.76 (2 s, 3 H each, CO_2CH_3), 2.74–2.66, 2.36–2.26, 2.07–1.81 (3 m, 1 H, 1 H, 2 H, 6-H, 7-H), 1.31 (dd, J = 8, 14.5 Hz, 1 H, CH_2SiMe_3), 0.97 (dd, J = 6.5, 14.5 Hz, 1 H, CH_2SiMe_3), 0.05 [s, 9 H, $Si(CH_3)_3$].

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 166.4, 165.6, 52.0 (2 s, q, CO_2CH_3), 141.7, 128.4, 123.5, 123.2 (4 d, HC=), 135.2 (s, C-2), 95.9 (s, C-7a), 75.1 (d, C-5), 57.2 (t, C-3), 27.9, 26.5, 23.2 (3 t, C-6, C-7, CH_2SiMe_3), –0.8 [q, $CH_2Si(CH_3)_3$].

Additional Signals Assigned to the Minor Isomer

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.66, 6.82, 6.36, 6.13 (4 d, J = 16 Hz, 1 H each, HC=), 3.80, 3.74 (2 s, 3 H each, CO_2CH_3), 0.82, 0.71 (2 dd, J = 7, 14.5 Hz, 1 H each, CH_2SiMe_3), 0.02 [s, 9 H, $Si(CH_3)_3$].

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 166.5, 165.7, 51.7 (2 s, q, CO_2CH_3), 139.9, 128.0, 123.8, 123.0 (4 d, HC=), 134.3 (s, C-2), 98.2 (s, C-7a), 74.5 (d, C-5), 56.4 (t, C-3), 26.1, 25.5, 23.1 (3 t, C-6, C-7, CH_2SiMe_3), –1.0 [q, $Si(CH_3)_3$].

MS (FD): *m*/*z* (%) = 398 (14, $[M + 2]^+$), 397 (40, $[M + 1]^+$), 396 (100, M^+), 323 (31).

Anal. Calcd for $C_{18}H_{28}N_2O_6Si$ (396.5): C, 54.52; H, 7.12; N, 7.06. Found: C, 55.11; H, 7.53; N, 6.11. Due to the low amount of product available no correct elemental analysis could be obtained.

Methyl (*E*)-3-[(5′,6′-Dihydro-6′-methoxy-5′-methylene)-4′*H*-1′,2′-oxazin-3′-yl]propenecarboxylate (9)

According to general procedure 1, a mixture of methoxyallene (**8**; 4.20 g, 60.0 mmol), oxime **3** (2.70 g, 12.2 mmol), and Na_2CO_3 (3.88 g, 73.2 mmol) in *t*-BuOMe (180 mL) was stirred for 7 d at r.t. The resulting crude product (2.40 g, 93%) was used in the next step without further purification.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.37, 6.19 (2 d, *J* = 16 Hz, 1 H each, 3-H, 2-H), 5.24, 5.13 (2 d, *J* = 2.5 Hz, 1 H each, $=CH_2$), 5.20 (s, 1 H, 6′-H), 3.80 (s, 3 H, CO_2CH_3), 3.49 (s, 3 H, 6′-OCH_3), 3.31 (td, *J* = 2.5, 19.5 Hz, 1 H, 4′-H), 2.95 (d, *J* = 19.5 Hz, 1 H, 4′-H).

Methyl (*E*)-3-[(6′-Methoxy-5′-methyl)-6′*H*-1′,2′-oxazin-3′-yl]propenecarboxylate (10)

To a solution of 1,2-oxazine **9** (0.440 g, 2.09 mmol) dissolved in CH_2Cl_2 (10 mL) was added dropwise DBU (0.185 g, 1.20 mmol). After stirring for 6 h at r.t., the solution was diluted with CH_2Cl_2 (10 mL), then successively washed with aq 1 N HCl solution (10 mL) and H_2O (2 × 10 mL), and the organic phase was dried ($MgSO_4$). Evaporation of the solvent under reduced pressure and purification of the crude product by column chromatography (alumina III, hexane–EtOAc, 4:1) gave **10** (0.320 g, 73%) as colorless crystals; mp 84–85 °C.

IR (KBr): 3050–2800 (=C–H, C–H), 1720 (C=O), 1640 (C=C), 1575 cm^{-1} (C=N).

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.36, 6.33 (2 d, *J* = 16 Hz, 1 H each, 3-H, 2-H), 6.14 (q, *J* = 1.5 Hz, 1 H, 4′-H), 5.29 (s, 1 H, 6′-H), 3.78 (s, 3 H, CO_2CH_3), 3.50 (s, 3 H, 6′-OCH_3), 2.02 (d, *J* = 1.5 Hz, 3 H, 5′-CH_3).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 166.2, 52.0 (s, q, CO_2CH_3), 152.3 (s, C-3′), 138.6, 122.5 (2 d, C-2, C-3), 137.3 (s, C-5′), 109.5 (d, C-4′), 97.8 (d, C-6′), 56.1 (q, 6′-OCH_3), 19.2 (q, 5′-CH_3).

Anal. Calcd for $C_{10}H_{13}NO_4$ (211.2): C, 56.87; H, 6.20; N, 6.63. Found: C, 56.86; H, 6.05; N, 6.29.

Methyl 2,3-Dihydroxy-3-(6′-ethoxy-5′,6′-dihydro-4′*H*-1′,2′-oxazin-3′-yl)propanecarboxylate (11)

To a vigorously stirred solution of 6*H*-1,2-oxazine **4a** (2.00 g, 9.38 mmol) in EtOH (200 mL) was added over a period of 20 min at –45 °C a solution of $KMnO_4$ (2.21 g, 14.0 mmol) and $MgSO_4$ (1.70 g, 14.2 mmol) dissolved in H_2O (100 mL). The resulting mixture was stirred for further 30 min at this temperature. Then 40% aq $NaHSO_3$ (30 mL) was added, and the mixture was allowed to warm up to r.t. After filtration of the suspension and evaporation of the alcohol, the residue was saturated with NaCl. The resulting mixture was extracted with EtOAc (3 × 30 mL) and the combined organic phases were dried ($MgSO_4$). Evaporation of the solvent under reduced pressure gave the 2,3-dihydroxylated compound **11** (1.73 g, 75%) as a mixture of two diastereomers (82:18), which was NMR spectroscopically pure.

Major Isomer

IR (neat): 3670–3180 (O–H), 3040–2830 (C–H), 1745 (C=O), 1640 cm^{-1} (C=N).

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 5.11 (t, *J* = 2.5 Hz, 1 H, 6′-H), 4.55, 4.42 (2 d, *J* = 2 Hz, 2 H each, 2 OH), 3.85 (s, 3 H, OCH_3), 3.83, 3.61 (2 qd, *J* = 7, 10 Hz, 1 H each, O*C*$H_2$$CH_3$), 3.80–3.59, 3.40–3.28 (2 m, 1 H each, 2-H, 3-H), 2.47–1.89 (m, 4 H, 4′-H, 5′-H), 1.20 (t, *J* = 7 Hz, 3 H, OCH_2C*H*$_3$).

^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 172.6, 52.8 (s, q, CO_2CH_3), 157.2 (s, C-3′), 95.4 (d, C-6′), 73.6, 72.0 (2 d, C-2, C-3), 63.7, 14.9 (t, q, OCH_2CH_3), 22.4, 15.9 (2 t, C-5′, C-4′).

Additional Signals Assigned to the Minor Isomer

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 4.52, 4.47 (2 d, *J* = 2 Hz, 2 H, 2 OH).

^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 172.5, 52.8 (s, q, CO_2CH_3), 157.0 (s, C-3′), 95.3 (d, C-6′), 74.0, 71.5 (2 d, C-2, C-3), 63.5, 14.9 (t, q, OCH_2CH_3), 22.2, 16.0 (2 t, C-5′, C-4′).

Anal. Calcd for $C_{10}H_{17}NO_6$ (247.2): C, 48.58; H, 6.93; N, 5.67. Found: C, 48.17; H, 7.11; N, 5.68.

Hydrogenolysis of 1,2-Oxazines; General Procedure 2

A suspension of 10% Pd/C in MeOH (8–20 mL/mmol substrate) was saturated with H_2. The corresponding 1,2-oxazine dissolved in MeOH (25 mL/mmol substrate) was added, and the mixture was stirred under H_2 at atmospheric pressure and r.t. for the time indicated in the individual experiment. The suspension was then filtered through Celite, eluting with MeOH. The resulting filtrate was concentrated in vacuo and the crude product was purified as described.

1,2,5,6,7,8-Hexahydro-3*H*-pyrrolizin-3-one (12a)[30]

According to general procedure 2, a mixture of 1,2-oxazine **4a** (0.426 g, 2.00 mmol) and 10% Pd/C (0.200 g) in MeOH (20 mL) was stirred for 2 d at r.t. The resulting crude product was purified by Kugelrohr distillation (70 °C/0.03 mbar) to give 1,2-oxazine **12a** (0.176 g, 70%) as a colorless oil.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 3.87 (m_c, 1 H, 8-H), 3.53 (td, *J* = 8, 11.5 Hz, 1 H, 5-H_a), 3.04 (m_c, 1 H, 5-H_b), 2.72 (td, *J* = 10, 16.5 Hz, 1 H, 2-H_a), 2.43 (ddd, *J* = 2, 8.5, 16.5 Hz, 1 H, 2-H_b), 2.29 (m_c, 1 H, 1-H_a), 2.15–2.06, 2.04–1.96 (2 m, 1 H, 2 H, 6-H, 7-H_a), 1.75–1.67 (m, 1 H, 1-H_b), 1.31 (m_c, 1 H, 7-H_b).

6-Methyl-1,2,5,6,7,8-hexahydro-3*H*-pyrrolizin-3-one (12b)[31]

According to general procedure 2, a mixture of 1,2-oxazine **10** (0.130 g, 0.62 mmol) and 10% Pd/C (0.150 g) in MeOH (15 mL) was stirred for 3 d at r.t. The resulting crude product was purified by column chromatography (alumina, hexane–EtOAc, 2:1 to 1:3) to give 1,2-oxazine **12b** (0.044 g, 51%; mixture of two diastereomers, 96:4) as a colorless oil.

Major Isomer

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.96 (m_c, 1 H, 8-H), 3.27, 3.02 (2 dd, *J* = 9, 11 Hz, 1 H each, 5-H), 2.80–2.64 (m, 1 H, 2-H_a), 2.54 (dddd, *J* = 1.5, 4.5, 9, 13 Hz, 1 H, 1-H_a), 2.44 (ddd, *J* = 1.5, 9.5, 16.5 Hz, 1 H, 2-H_b), 2.20 (dddd, *J* = 1.5, 6.5, 9.5, 13 Hz, 1 H, 1-H_b), 2.12 (m_c, 1 H, 6-H), 1.81–1.71 (m, 1 H, 7-H_a), 1.11 (d, *J* = 7 Hz, 3 H, CH_3), 1.02 (q, *J* = 11 Hz, 1 H, 7-H_b).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 174.6 (s, C=O), 62.5 (d, C-8), 48.3 (t, C-5), 41.5, 35.1, 27.4 (3 t, C-1, C-2, C-7), 36.6 (d, C-6), 18.7 (q, CH_3).

Additional Signals Assigned to the Minor Isomer

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 49.4 (t, C-5), 34.8, 28.5 (2 t, C-1, C-7), 19.6 (q, CH_3).

The ^{13}C NMR data of the minor isomer are in agreement with those given in ref.[31a]

***r*-1,*t*-2-Dihydroxy-1,2,5,6,7,8-hexahydro-3*H*-pyrrolizin-3-one (12c)[32]**

According to general procedure 2, a mixture of 1,2-oxazine **11** (0.525 g, 2.12 mmol) and 10% Pd/C (0.250 g) in MeOH (50 mL) was stirred for 21 h at r.t. The resulting crude product was purified by crystallization from CH_2Cl_2 to give 1,2-oxazine **12c** (0.264 g,

79%; two diastereomers, 60:40) as colorless crystals; mp 112–114 °C.

IR (KBr): 3620–3180 (O–H), 3030–2850 (C–H), 1760 cm^{-1} (C=O).

^1H NMR (DMSO-d_6, 300 MHz): δ = 5.95–5.15 (m, 2 H, 2 OH), 4.12 (d, *J* = 8.5 Hz, 0.6 H, 2-H), 4.01 (m_c, 0.4 H, 1-H), 3.85 (d, *J* = 4 Hz, 0.4 H, 2-H), 3.80–3.30, 2.95–2.80 (2 m, 2.6 H, 1 H, 1-H, 5-H, 8-H), 2.05 (sext, *J* = 6 Hz, 0.6 H, 7-H), 1.91–1.40 (m, 3.4 H, 6-H, 7-H).

^{13}C NMR (DMSO-d_6, 75.5 MHz): δ (major isomer) = 171.8 (s, C=O), 81.2 (d, C-2), 78.2 (d, C-1), 62.4 (d, C-8), 41.6 (t, C-5), 29.7, 25.2 (2 t, C-6, C-7); δ (minor isomer) = 171.9 (s, C=O), 81.0 (d, C-2), 72.1 (d, C-1), 63.7 (d, C-8), 40.9 (t, C-5), 26.4, 22.6 (2 t, C-6, C-7).

^1H NMR ($CDCl_3$/CD_3OD, 300 MHz): δ (major isomer) = 4.11–4.07 (m, 1 H, 2-H), 3.84 (dd, *J* = 7.5, 8 Hz, 1 H, 1-H), 3.56 (td, *J* = 6.5, 12.5 Hz, 1 H, 5-H_a), 3.15–3.06 (m, 1 H, 5-H_b), 2.25 (dtd, *J* = 4, 6.5, 12.5 Hz, 1 H, 7-H_a), 2.18–1.88 (m, 2 H, 6-H), 1.58 (tdd, *J* = 8.5, 12.5, 17.5 Hz, 1 H, 7-H_b). The signal of 8-H is hidden under the signal of 5-H_a; δ (additional signals assigned to the minor isomer) = 4.42 (d, *J* = 10 Hz, 1 H, 2-H), 4.21 (ddd, *J* = 4, 6.5, 9 Hz, 1 H, 8-H), 3.48 (td, *J* = 7.5, 11.5 Hz, 1 H, 5-H_a), 1.78 (dtd, *J* = 4, 6.5, 12.5 Hz, 1 H, 7-H_b).

^{13}C NMR ($CDCl_3$/CD_3OD, 75.5 MHz): δ (major isomer) = 173.4 (s, C=O), 82.9 (d, C-2), 80.2 (d, C-1), 64.1 (d, C-8), 43.0 (t, C-5), 31.1, 26.9 (2 t, C-6, C-7); δ (minor isomer) = 174.6 (s, C=O), 83.3 (d, C-2), 73.5 (d, C-1), 66.4 (d, C-8), 42.3 (t, C-5), 28.1, 23.8 (2 t, C-6, C-7).

Anal. Calcd for $C_7H_{11}NO_3$ (157.2): C, 53.49; H, 7.05; N, 8.91. Found: C, 53.31; H, 7.07; N, 8.67.

Methyl 3-(2-Pyrrolyl)propanoate (18)[23]

A suspension of 1,2-oxazine **4a** (0.213 g, 1.00 mmol), 10% Pd/C (80 mg) and ammonium formate (0.948 g, 15.0 mmol) in ethylene glycol (8 mL) was heated at 130 °C under microwave irradiation (200 W) for 8 min. Then, the cooled suspension was filtered through a pad of Celite and washed with EtOAc (20 mL). The combined organic phases were successively washed with H_2O (3 × 10 mL) and brine (3 × 10 mL), and dried (Na_2SO_4). The crude product was purified by Kugelrohr distillation (80–85 °C/0.1 mbar) to yield pyrrole **18** as a colorless oil.

^1H NMR ($CDCl_3$, 300 MHz): δ = 8.57 (br s, 1 H, NH), 6.66 (dd, *J* = 1, 1.5 Hz, 1 H, 5-H), 6.15 (dd, *J* = 1.5, 2 Hz, 1 H, 5-H), 5.89 (br s, 1 H, 3-H), 3.71 (s, 3 H, CO_2CH_3), 2.91, 2.63 (2 t, *J* = 8 Hz, 2 H each, 2 × CH_2).

The ^1H NMR data of **18** are in agreement with those given in ref.[23]

Reduction of Pyrrolizidinones with BH_3·SMe_2; General Procedure 3

To a solution of the corresponding pyrrolizidinone (1 equiv) in THF (10 mL/mmol of substrate) was added BH_3·SMe_2 (10 equiv) under argon. The mixture was stirred at r.t., then MeOH (1 mL/mmol of substrate) was slowly added. After further 10 min at r.t., the mixture was concentrated in vacuo and the crude product was purified as described in the individual experiment.

2,3,5,6,7,8-Hexahydro-1*H*-pyrrolizidine (19a)[33]

According to general procedure 3, a mixture of pyrrolizidinone **12a** (0.160 g, 1.28 mmol) and BH_3·SMe_2 (1.23 mL, 12.8 mmol) in THF (15 mL) was stirred for 16 h at r.t. The resulting crude product was purified by Kugelrohr distillation (80–90 °C/2 mbar) to give pyrrolizidine **19a** (0.107 g, 77%) as a colorless oil.

^1H NMR ($CDCl_3$, 300 MHz): δ = 3.68 (m_c, 1 H, 8-H), 3.24, 2.88 (2 td, *J* = 6.5, 11.5 Hz, 2 H each, 3-H, 5-H), 2.17 (dtd, *J* = 6.5, 7, 12.5 Hz, 2 H, 1-H_a, 7-H_a), 1.98 (m_c, 2 H, 2-H_a, 6-H_a), 1.90 (m_c, 2 H, 2-H_b, 6-H_b), 1.57 (dtd, *J* = 6, 6.5, 12.5 Hz, 2 H, 1-H_b, 7-H_b).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 73.3 (d, C-8), 63.5 (t, C-3, C-5), 32.0 (t, C-1, C-7), 25.3 (t, C-2, C-6).

The NMR data of **19a** are in agreement with those given in ref.[33]

2-Methyl-2,3,5,6,7,8-hexahydro-1*H*-pyrrolizidine (19b)[25]

According to general procedure 3, a mixture of pyrrolizidinone **12b** (0.065 g, 0.467 mmol) and BH_3·SMe_2 (0.45 mL, 4.68 mmol) in THF (6 mL) was stirred for 16 h at r.t. The resulting crude product was purified by Kugelrohr distillation (65 °C/0.02 mbar) to give pyrrolizidine **19b** (0.045 g, 77%, mixture of two diastereomers, 94:6) as a colorless oil.

^1H NMR ($CDCl_3$, 300 MHz): δ = 3.79–3.71 (m, 1 H, 8-H), 3.43–3.38, 3.15–3.03, 3.00–2.93, 2.59 (3 m, m_c, 1 H each, 3-H, 5-H), 2.34–2.23, 2.13–2.03, 2.00–1.80, 1.66–1.47 (4 m, 2 H, 1 H, 2 H, 1 H, 1-H_a, 2-H, 6-H, 7-H), 1.11 (dt, *J* = 10, 12 Hz, 1 H, 1-H_b), 1.01 (d, *J* = 6.5 Hz, 3 H, CH_3); δ (additional signals assigned to minor isomer) = 1.04 (d, *J* = 6.5 Hz, 3 H, CH_3).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ (major isomer) = 74.1 (d, C-8), 70.7, 64.4 (2 t, C-3, C-5), 42.1, 31.4, 24.0 (3 t, C-1, C-6, C-7), 33.2 (d, C-2), 16.3 (q, CH_3); δ (minor isomer) = 73.8 (d, C-8), 39.5, 33.7, 25.2 (3 t, C-1, C-6, C-7), 16.1 (q, CH_3).

The NMR data of **19b** are in agreement with those given in ref.[25]

trans-1,2-Dihydroxy-2,3,5,6,7,8-hexahydro-1*H*-pyrrolizidine (19c)[24,32a,b,34]

According to general procedure 3, a mixture of pyrrolizidinone **12c** (0.134 g, 0.852 mmol) and BH_3·SMe_2 (0.82 mL, 8.50 mmol) in CH_2Cl_2 (10 mL) was stirred for 2 d at r.t. to give the spectroscopically pure pyrrolizidine **19c** (0.114 g, 93%, two diastereomers, 68:32) as a colorless resin.

Major Isomer

IR (KBr): 3620–3180 (O–H), 3030–2850 (C–H), 1760 cm^{-1} (C=O).

^1H NMR ($CDCl_3$, 300 MHz): δ = 4.30–4.15, 3.85–3.77, 3.70–3.51, 3.45–3.35 (4 m, 1 H, 1 H, 2 H, 1 H, 1-H, 2-H, 8-H, OH), 3.30–3.04, 3.02–2.80 (2 m, 2 H each, 3-H, 5-H), 2.20–1.70 (m, 4 H, 6-H, 7-H).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 82.0, 77.8, 77.7 (3 d, C-1, C-2, C-8), 66.0, 65.1 (2 t, C-3, C-5), 30.0, 24.5 (2 t, C-6, C-7).

Additional Signals Assigned to the Minor Isomer

^1H NMR ($CDCl_3$, 300 MHz): δ = 4.50–4.38, 4.00–3.92 (2 m, 1 H, 1 H, 1-H/2-H/8-H).

^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 77.9, 75.9, 75.2 (3 d, C-1, C-2, C-8), 66.7, 65.6 (2 t, C-3, C-5), 26.2, 24.8 (2 t, C-6, C-7).

HRMS: *m*/*z* calcd for $C_7H_{13}NO_2$: 143.0946; found: 143.0959.

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