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Reduction of Piperidinoisoxazolidines: Competitive Cyclisation to Indolizidines or Epoxides

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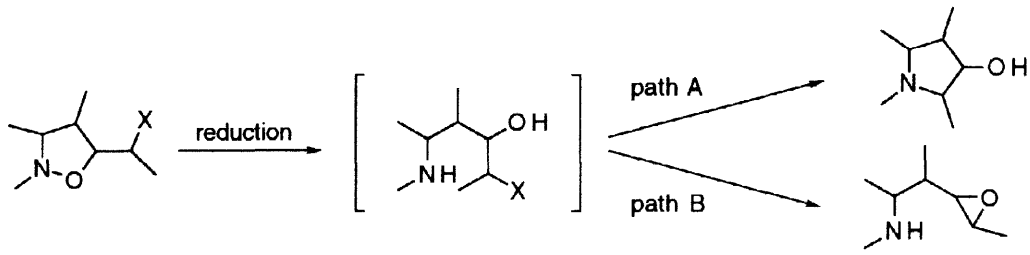
Abstract.- *In the reduction of polysubstituted piperidinoisoxazolidines, we have observed two competitive cyclisation pathways, leading to either indolizidines or epoxides. The yields of indolizidines can be optimised by an appropriate choice of the reducing agent and through a careful control of the work-up conditions.* © 1998 Elsevier Science Ltd. All rights reserved.

Introduction

Substituted isoxazolidines have been often used as crucial intermediates for the preparation of complicated target molecules.[1] Their synthetic versatility relies on the feasible reduction of the nitrogen-oxygen bond to deliver the corresponding open-chain 3-amino alcohols. This reduction has been performed with a plethora of distinct reagents, including catalytic hydrogenation, several metals in different solvents, lithium aluminum hydride, and metal complexes.[2] Usually, when the resulting amino alcohol has an electrophilic carbon atom at a suitable distance, nucleophilic addition or substitution by the amino group results in the formation of a new ring in the reaction product (Scheme 1, path A). After the pioneering work of Tufariello *et al.*[3] the overall process (reduction-cyclisation) has been successfully applied to the synthesis of many interesting compounds, mainly alkaloids[4] and β-lactams.[5] On the contrary, to the best of our knowledge, examples in which the cyclisation occurred through nucleophilic attack of the newly generated hydroxyl group to deliver an epoxide (Scheme 1, path B) have not yet been described.



Scheme 1

PII: S0040-4020(98)00677-2

We have recently reported the selective preparation of the four diastereoisomeric isoxazolidines **1-4** (Figure 1), by sequences involving the 1,3-dipolar cycloaddition of 2,3,4,5-tetrahydropyridine 1-oxide to an α,β-unsaturated ester as the key step.[6] We planned to use these compounds in the synthesis of various indolizidine alkaloids, following the strategy outlined in path A of Scheme 1. Surprisingly, in the reduction of these isoxazolidines we detected the formation of epoxides. We also found that the cyclisation process can be controlled by the appropriate choice of reducing agent and work-up conditions. Our findings are described herein.

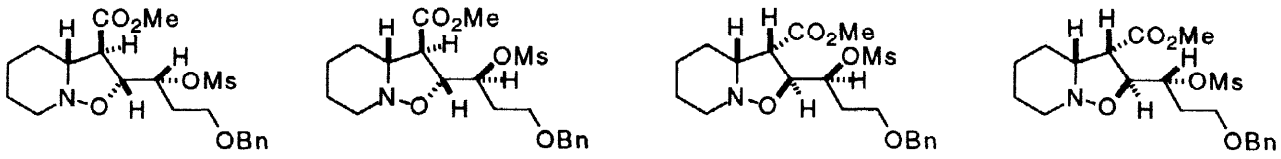


Figure 1

Results and Discussion

The results of the reduction of isoxazolidines **1-4** are collected in Table 1. First we performed the palladium catalysed hydrogenation of the *exo-syn* isomer **1** (entry 1) and we obtained the indolizidine **5** as the main product (Figure 2), but partial debenzylation leading to **6** was detrimental to the yield of the desired compound. In the NMR spectra of **5**, H_2 absorbs as a dd at δ 4.15 and H_3 presents a ddd at δ 2.21 and the corresponding carbon

Table 1. Reduction of piperidinoisoxazolidines **1-4**.

entry	substrate	method[a]	indolizidine[b]	epoxide[b]
1	**1**	A	**5** (58%), **6** (29%)	-
2	**1**	B	**5** (79%), **6** (9%)	-
3	**1**	C	**5** (67%)	**10** (12%)
4	**1**	D	**5** (85%)	-
5	**2**	B	**7** (89%)	-
6	**2**	C	**7** (64%)	**11** (21%)
7	**2**	D	**7** (91%)	-
8	**3**	B	-	-
9	**3**	C	-	**12** (85%)
10	**3**	D	**8** (84%)	-
11	**4**	A	-	-
12	**4**	B	-	-
13	**4**	C	**9** (9%)	**13** (81%)
14	**4**	D	**9** (90%)	-

[a]Method A: H_2/Pd, AcOEt-MeOH 1:1, rt. Method B: H_2/$Pd(OH)_2$, AcOEt-MeOH 1:1, rt. Method C: i) Zn (72 eq)/3M HCl/ultrasound; ii) 30% NH_3 to basicity. Method D: i) Zn (72 eq)/3M HCl/ultrasound; ii) CH_2Cl_2, vigorous stirring, slow addition of K_2CO_3 to pH 7. [b]Yields of isolated products.

atoms C_2 and C_3 appear at δ 75.9 and 72.5, respectively. The preferred *trans* fused conformation of this indolizidine is evidenced by the Δδ value between the two α-nitrogen protons at C_5, which are locked in the equatorial (δ 3.01) and axial (δ 1.90) orientation of the piperidine chair, due to the rigidity of the bicyclic system.[7] The debenzylation problem could be almost overwhelmed by changing the catalyst to $Pd(OH)_2$ (entry 2), which has been effective with other substrates where the use of Pd metal produced the reduction of a benzyl ether.[8] The hydrogenolysis of the *exo-anti* isoxazolidine **2** in these last conditions (entry 5) gave the expected indolizidine **7**, as the only reaction product, in 89% yield. Compound **7** shows signals at δ 4.43 and 3.29 for H_2 and H_3, and at δ 72.1 and 63.8 for C_2 and C_3, respectively. In contrast to its diastereoisomer **5**, the indolizidine **7** presents in solution the *cis* fused conformation, demonstrated by the close δ values (2.83 and 2.59) of the two H_5 protons.

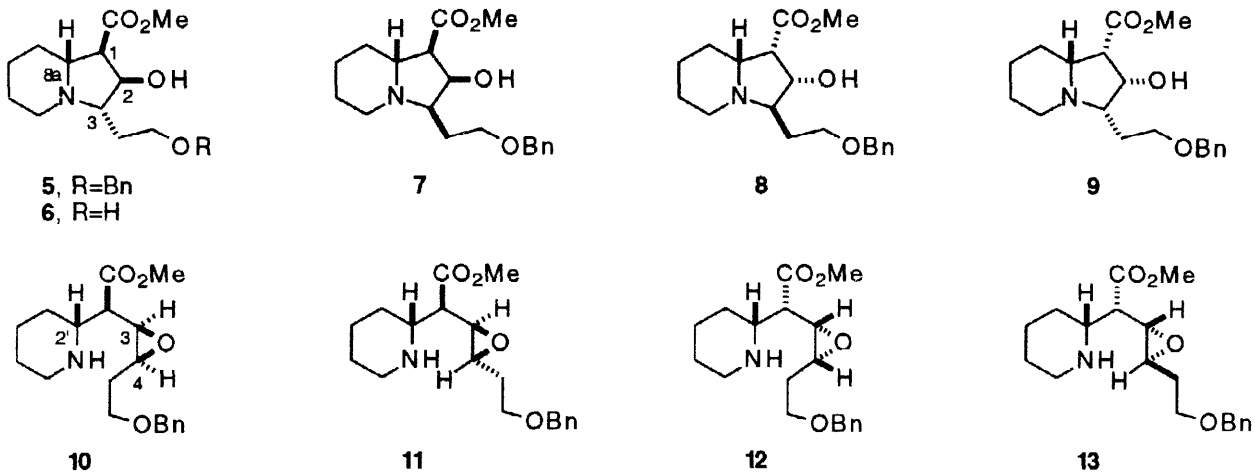


Figure 2

When the same reaction was attempted with the *endo* isoxazolidines **3** and **4** (entries 8 and 12), after several hours, most of the starting material was recovered unchanged and only traces of debenzylated isoxazolidines were observed. Hydrogenation of **4** in the presence of Pd (entry 11) let to complete debenzylation, without any nitrogen-oxygen bond cleavage. These results denote the great influence of the stereochemical features of the substrate on the hydrogenolysis process. Isoxazolidine **4** was then treated with Zn/AcOH, one of the most widely used alternative method for N-O reduction, but after 2 hours no reaction was observed. However, changing the solvent to 3M HCl and under ultrasound activation (entry 13) the starting material was rapidly consumed. Removal of the excess of Zn and basification of the filtrate with 30% NH_3 yielded the epoxide **13** as main product (81%) and only a minor amount of the expected indolizidine **9**. Compound **13** was identified through the chemical shifts of H_3, H_4 (both at δ ≈ 3.0) and C_3, C_4 (both at δ ≈ 55), that clearly indicate the presence of an oxirane ring. The NMR spectra of **9** show absorptions at δ 4.31 and 2.16 for H_2 and H_3 and at δ 71.2 and 68.0 for C_2 and C_3, respectively. The chemical shifts of the protons at C_5 (δ 3.11 and 1.85) indicate that indolizidine **9** prefers in solution a *trans* fused invertomer.

When the zinc reduction procedure was performed with the *endo-syn* isoxazolidine **3** (entry 9) we also obtained the epoxide **12** (85%), instead of the desired indolizidine **8**. On the contrary, the reduction of the *exo* isoxazolidines **1** and **2** under identical conditions (entries 3 and 6) gave the indolizidines **5** and **7** respectively, as main products, along with small percentages of the corresponding epoxides **10** and **11**.

The expected relative configuration at the new stereogenic center C_3 of the indolizidines **5**, **7** and **9** was confirmed through NOESY experiments, that allowed to establish the relative *cis* or *trans* relationship between all the hydrogen atoms of the pyrrolidine ring. The geometry of 1,2-disubstituted oxiranes can be deduced from the value of the vicinal coupling constant, which is close to 4.5 Hz for *cis* and to 3.0 Hz for *trans* protons.[9] The observed value of $J_{3,4}$ was 4.4 Hz for epoxides **10** and **12**, 2.2 Hz for **11** and it could not be measured for **13**; their relative configurations were accordingly assigned.

The comparison of the stereochemistry of each pair indolizidine-epoxide indicates that both products evolve from a common amino alcohol precursor. The different trend in the cyclisation showed by the amino alcohols derived from the *exo* (entries 3 and 6) and *endo* (entries 9 and 13) isoxazolidines is not clear, but it must be related to the steric hindrance of the transition states leading to each pentasubstituted pyrrolidine, since the *cis* or *trans* geometry of the epoxides does not appear as a decisive factor. Considering the strongly acidic reductive medium, any cyclisation must probably take place during or after the basification process; consequently we decided to explore different work-up conditions on reaction mixtures derived from isoxazolidine **4**. After wide experimentation, we found that the formation of the epoxide can be avoided if CH_2Cl_2 is added to the acidic filtrate, followed by slow addition of solid K_2CO_3 until pH 7, under vigorous stirring. In that simple way, indolizidine **9** was isolated in 90% yield (entry 14). The same work-up applied to the rest of isoxazolidines (entries 4, 7 and 10) gave also the corresponding indolizidines as exclusive products. In that way, compound **8** was obtained in 84% yield. Its ^1H NMR spectrum shows the absorption of H_2 at δ 4.31 and signals at δ 2.92 and 2.68 for the protons at C_5, denoting a clear preference for the *cis* fused invertomer.

In summary, it has been illustrated how a simple modification in the work-up conditions of the hydrogenolysis reaction of piperidinoisoxazolidines changes dramatically the relative rates of the subsequent competitive cyclisation pathways. The formation of indolizidines is promoted by avoiding local high concentrations of base, which benefit the evolution to the undesired epoxides.

Experimental

Previously described methods were used to prepare isoxazolidines **1-4**.[6] Solutions were concentrated using a rotary evaporator at 15-20 Torr. Flash column chromatographies were performed by using Merck silica gel (230-400 mesh) unless otherwise indicated. Tlc were performed by using 0.25 mm Alugram Sil plates, Macherey-Nägel. Infrared spectra were recorded on a Nicolet 5 ZDX spectrophotometer. ^1H NMR (250 MHz, unless otherwise indicated) and ^{13}C NMR (62.5 MHz) spectra were recorded by *Servei de Ressonància Magnètica Nuclear de la Universitat Autònoma de Barcelona* on Bruker AC-250-WB or AM-400-WB instruments. $CDCl_3$ was used as solvent for the NMR experiments. Elemental analyses were performed by *Servei d'Anàlisi Química de la UAB* or by *Institut de Química Bio-Orgànica de Barcelona.*

Reduction of Isoxazolidine **1** *(Method B)*

Palladium hydroxide on carbon (20 mg) was added to a solution of compound **1** (80 mg, 0.18 mmol) in MeOH/EtOAc 1/1 (3 mL) and the mixture was stirred under hydrogen atmosphere for 4 h. The hydrogen was evacuated and the mixture was filtered through Celite and rinsed with MeOH (4 mL) and EtOAc (4 mL). The

solvents were evaporated and the resulting residue was dissolved in CH_2Cl_2 (15 mL). To this vigorously stirred solution, water (10 mL) was added, and then solid K_2CO_3 until basic pH. After stirring for 15 additional minutes the organic layer was separated, dried (anh. Na_2SO_4) and concentrated. Chromatography (EtOAc/MeOH from 100/0 to 80/20) of the residue afforded 49 mg (0.15 mmol, 79% yield) of methyl (1*RS*,2*RS*,3*SR*,8a*RS*)-3-(2-benzyloxyethyl)-2-hydroxyoctahydroindolizidine-1-carboxylate, **5**, as a white solid and 4 mg (0.02 mmol, 9% yield) of methyl (1*RS*,2*RS*,3*SR*,8a*RS*)-2-hydroxy-3-(2-hydroxyethyl)octahydroindolizidine-1-carboxylate, **6**, as a colorless oil. **5**: mp 40-2 °C. IR (film): 3472, 1735 cm^{-1}; ^1H NMR: δ 7.35-7.25 (m, 5H, H-Ar), 4.49 (s, 2H, H_2C-Ph), 4.15 (dd, $J_{2,1}$=8.8 Hz, $J_{2,3}$=5.1 Hz, 1H, H-2), 3.70 (s, 3H, CH_3O), 3.68-3.52 (m, 2H, H-2'), 3.29 (br s, 1H, OH), 3.01 (m, 1H, H-5eq), 2.69 (dd, $J_{1,8a}$=10.4 Hz, $J_{1,2}$=8.8 Hz, 1H, H-1), 2.54 (td, $J_{8a,1}$=$J_{8a,8}$=10.4 Hz, $J_{8a,8}$=2.2 Hz, 1H, H-8a), 2.21 (ddd, $J_{3,1'}$=9.5 Hz, $J_{3,2}$=5.1 Hz, $J_{3,1'}$=2.6 Hz, 1H, H-3), 2.03-1.83 (m, 3H, H-5ax, H-1', H-8), 1.76-1.61 (m, 3H, H-1', H-7, H-6), 1.54-1.05 (m, 3H, H-6, H-7, H-8); ^{13}C NMR: δ 171.8 (C=O), 137.0/128.4/127.7(x2) (C-Ar), 75.9 (C-2), 73.2 (CH_2-Ph), 72.5 (C-3), 68.2 (C-2'), 65.0 (C-8a), 52.9 (C-1), 51.6 (OCH_3), 51.0 (C-5), 31.0 (C-1'), 30.0 (C-8), 25.1 (C-6), 23.8 (C-7). Anal. Calcd for $C_{19}H_{27}NO_4$: C, 68.44; H, 8.16; N, 4.20. Found: C, 68.50; H, 8.14; N, 4.18. **6**: ^1H NMR: δ 4.34 (dd, $J_{2,3}$=7.3 Hz, $J_{2,1}$=4.4 Hz, 1H, H-2), 3.87-3.63 (m, 2H, H-2'), 3.72 (s, 3H, CH_3O), 3.19 (m, 1H, H-5eq), 2.69 (dd, $J_{1,8a}$=8.0 Hz, $J_{1,2}$=7.3 Hz, 1H, H-1), 2.53 (m, 2H), 2.03-1.83 (m, 3H), 1.76-1.61 (m, 3H), 1.54-1.05 (m, 3H).

Reduction of Isoxazolidine **2** *(Method B)*

Following the above procedure, compound **2** (25 mg, 0.06 mmol) was hydrogenated in the presence of $Pd(OH)_2$ (15 mg) in MeOH/EtOAc 1/1 (2 mL). Chromatography of the reaction crude (EtOAc/MeOH 80/20) afforded 17 mg (0.05 mmol, 89% yield) of methyl (1*RS*,2*RS*,3*RS*,8a*RS*)-3-(2-benzyloxyethyl)-2-hydroxy-octahydroindolizidine-1-carboxylate, **7**, as a colorless oil: IR (film): 3444, 1735, cm^{-1}; ^1H NMR: δ 7.35-7.25 (m, 5H, H-Ar), 4.50 (s, 2H, H_2C-Ph), 4.43 (m, 1H, H-2), 3.70 (s, 3H, CH_3O), 3.62 (dt, J_{gem}=9.0 Hz, $J_{2',1'}$=4.7 Hz, 1H, H-2'), 3.45 (td, J_{gem}=$J_{2',1'}$=9.0 Hz, $J_{2',1'}$=4.5 Hz, 1H, H-2'), 3.29 (ddd, $J_{3,1'}$=10.3 Hz, $J_{3,2}$=4.8 Hz, $J_{3,1'}$=3.8 Hz, 1H, H-3), 3.17 (ddd, $J_{8a,8}$=10.7 Hz, $J_{8a,1}$=7.7 Hz, $J_{8a,8}$=3.0 Hz, 1H, H-8a), 2.83 (m, 1H, H-5), 2.73 (t, $J_{1,2}$=$J_{1,8a}$=7.7 Hz, 1H, H-1), 2.59 (td, J_{gem}=$J_{5,6}$=12.0 Hz, $J_{5,6}$=3.7 Hz, 1H, H-5), 2.00 (m, 1H, H-1'), 1.90-1.65 (m, 4H), 1.50-1.10 (m, 3H); ^{13}C NMR: δ 172.4 (C=O), 137.7/128.4/127.74/127.69 (C-Ar), 73.3 (CH_2-Ph), 72.1 (C-2), 68.7 (C-2'), 63.8 (C-3), 59.2 (C-8a), 55.0 (C-1), 51.6 (OCH_3), 46.3 (C-5), 29.9 (C-8), 24.5 (C-1'), 23.8/23.5 (C-6/C-7). Anal. Calcd for $C_{19}H_{27}NO_4$: C, 68.44; H, 8.16; N, 4.20. Found: C, 68.29; H, 8.15; N, 4.17.

Reduction of **1**. *General Procedure for Method C*

To a solution of **1** (528 mg, 1.23 mmol) in 3M HCl (40 mL), activated zinc dust (5.65 g, 86.5 mmol) was added and the resulting suspension was sonicated for 1 h. The Zn was filtered off and rinsed with 3M HCl (7 mL) and water (10 mL). The solution was basified with 30% NH_3 until pH=11, extracted with CH_2Cl_2 (3x30 mL), dried (anh. Na_2SO_4) and concentrated. Chromatography (EtOAc/MeOH from 100/0 to 80/20) of the residue afforded 278 mg (0.83 mmol, 67% yield) of **5** and 49 mg (0.15 mmol, 12% yield) of methyl (2*RS*,3*RS*,4*SR*,2'*RS*)-6-benzyloxy-3,4-epoxy-2-(2-piperidyl)hexanoate, **10**, as a colorless oil. **10**: IR (film): 3339, 1735 cm^{-1}; ^1H NMR: δ 7.35-7.25 (m, 5H, H-Ar), 4.51 (s, 2H, H_2C-Ph), 3.61 (s, 3H, CH_3O), 3.57 (m, 2H, H-6), 3.24 (dd, $J_{3,2}$=9.5 Hz, $J_{3,4}$=4.4 Hz, 1H, H-3), 3.10-2.96 (m, 3H, H-4, H-6', H-2'), 2.62 (td,

J_{gem}=$J_{6',5'}$=11.7 Hz, $J_{6',5'}$=2.9 Hz, 1H, H-6'), 2.39 (dd, $J_{2,3}$=9.5 Hz, $J_{2,2'}$=7.3 Hz, 1H, H-2), 2.02-1.62 (m, 4H, 2xH-5, H-3', H-4'), 1.58 (m, 1H, H-5'), 1.55-1.18 (m, 3H, H-3', H-4', H-5'); ^{13}C NMR: δ 171.8 (C=O), 138.1/128.3/127.5(x2) (C-Ar), 73.0 (CH_2-Ph), 67.1 (C-6), 58.5 (C-2'), 55.8 (C-3), 53.2 (C-4), 51.7 (OCH_3), 50.5 (C-2), 46.8 (C-6'), 30.3 (C-3'), 28.6 (C-5), 25.9 (C-5'), 24.4 (C-4'). Anal. Calcd for $C_{19}H_{27}NO_4$: C, 68.44; H, 8.16; N, 4.20. Found: C, 68.79; H, 7.91; N, 4.53.

Reduction of **2** *(Method C)*

Following the general procedure, isoxazolidine **2** (110 mg, 0.26 mmol) was treated with activated zinc dust (1.22 g, 18.72 mmol) in 3M HCl (8 mL). Chromatography of the reaction crude (EtOAc/MeOH 9/1) through Florisil afforded 18 mg (0.05 mmol, 21% yield) of methyl (2*RS*,3*RS*,4*RS*,2'*RS*)-6-benzyloxy-3,4-epoxy-2-(2-piperidyl)hexanoate, **11**, as a colorless oil and 55 mg (0.16 mmol, 64% yield) of **7**. **11**: IR (film): 3339, 1735 cm^{-1}; ^{1}H NMR (400 MHz): δ 7.35-7.25 (m, 5H, H-Ar), 4.53 (d, J_{gem}=12.4 Hz, 1H, *H*C-Ph), 4.49 (d, J_{gem}=12.4 Hz, 1H, *H*C-Ph), 3.67 (s, 3H, CH_3O), 3.60-3.52 (m, 2H, H-6), 3.09 (dd, $J_{3,2}$=8.2 Hz, $J_{3,4}$=2.2 Hz, 1H, H-3), 3.08 (m, 1H, H-6'), 3.02 (ddd, $J_{2',3'}$=10.7 Hz, $J_{2',2}$=6.7 Hz, $J_{2',3'}$=2.5 Hz, 1H, H-2'), 2.97 (ddd, $J_{4,5}$=6.4 Hz, $J_{4,5}$=4.9 Hz, $J_{4,3}$=2.2 Hz, 1H, H-4), 2.66 (td, J_{gem}=$J_{6',5'}$=11.5 Hz, $J_{6',5'}$=3.0 Hz, 1H, H-6'), 2.24 (dd, $J_{2,3}$=8.2 Hz, $J_{2,2'}$=6.7 Hz, 1H, H-2), 1.95-1.77 (m, 3H, 2xH-5, H-4'), 1.65-1.57 (m, 2H, H-3', H-5'), 1.50-1.30 (m, 3H, H-5', H-4', H-3'); ^{13}C NMR: δ 171.9 (C=O), 138.2/128.4/127.6(x2) (C-Ar), 73.1 (CH_2-Ph), 65.9 (C-6), 58.0 (C-2'), 56.3 (C-3), 54.5 (C-4), 54.1 (C-2), 51.6 (OCH_3), 46.9 (C-6'), 32.2 (C-5), 30.4 (C-3'), 26.0 (C-5'), 24.5 (C-4'). Anal. Calcd for $C_{19}H_{27}NO_4$: C, 68.44; H, 8.16; N, 4.20. Found: C, 68.29; H, 8.15; N, 4.17.

Reduction of Isoxazolidine **3** *(Method C)*

Following the general procedure, isoxazolidine **3** (106 mg, 0.24 mmol) was treated with activated zinc dust (1.16 g, 17.87 mmol) in 3M HCl (7 mL). Chromatography of the reaction crude (EtOAc/MeOH 9/1) through Florisil afforded 71 mg (0.21 mmol, 85% yield) of methyl (2*RS*,3*RS*,4*SR*,2'*SR*)-6-benzyloxy-3,4-epoxy-2-(2-piperidyl)hexanoate, **12**, as a colorless oil: IR (film): 3310, 1735 cm^{-1}; ^{1}H NMR: δ 7.35-7.25 (m, 5H, H-Ar), 4.48 (s, 2H, H_2C-Ph), 3.61 (s, 3H, CH_3O), 3.60-3.52 (m, 2H, H-6), 3.17 (dd, $J_{3,2}$=8.8 Hz, $J_{3,4}$=4.4 Hz, 1H, H-3), 3.11-2.93 (m, 3H, H-4, H-6', H-2'), 2.60 (ddd, J_{gem}=12.4 Hz, $J_{6',5'}$=11.7 Hz, $J_{6',5'}$=2.9 Hz, 1H, H-6'), 2.22 (dd, $J_{2,3}$=8.8 Hz, $J_{2,2'}$=7.3 Hz, 1H, H-2), 1.98-1.62 (m, 4H, 2xH-5, H-3', H-4'), 1.58 (m, 1H, H-5'), 1.45-1.12 (m, 3H, H-4', H-5', H-3'); ^{13}C NMR: δ 171.9 (C=O), 138.1/128.3/127.5(x2) (C-Ar), 73.0 (CH_2-Ph), 67.1 (C-6), 58.2 (C-2'), 55.1 (C-3), 53.8 (C-4), 51.7 (OCH_3), 50.5 (C-2), 46.8 (C-6'), 30.4 (C-3'), 28.6 (C-5), 26.3 (C-5'), 24.4 (C-4'). Anal. Calcd for $C_{19}H_{27}NO_4$: C, 68.44; H, 8.16; N, 4.20. Found: C, 68.34; H, 8.13; N, 4.32.

Reduction of Isoxazolidine **4** *(Method C)*

Following the general procedure, isoxazolidine **4** (300 mg, 0.70 mmol) was treated with activated zinc dust (3.29 g, 50.4 mmol) in 3M HCl (20 mL). Chromatography of the reaction crude (EtOAc/MeOH 9/1) through Florisil afforded 21 mg (0.06 mmol, 9% yield) of methyl (1*RS*,2*RS*,3*RS*,8a*SR*)-3-(2-benzyloxyethyl)-2-hydroxyoctahydroindolizidine-1-carboxylate, **9**, and 189 mg (0.57 mmol, 81% yield) of methyl (2*RS*,3*RS*,4*RS*,2'*SR*)-6-benzyloxy-3,4-epoxy-2-(2-piperidyl)hexanoate, **13**, both as colorless oils. **9**: IR (film): 3486, 1721 cm^{-1}; ^{1}H NMR: δ 7.35-7.25 (m, 5H, H-Ar), 4.49 (s, 2H, H_2C-Ph), 4.31 (ddd, $J_{2,OH}$=9.0 Hz,

$J_{2,1}$=8.0 Hz, $J_{2,3}$=6.0 Hz, 1H, H-2), 3.70-3.55 (m, 2H, H-2'), 3.67 (s, 3H, CH_3O), 3.19 (t, $J_{1,2}=J_{1,8a}$=8.0 Hz, 1H, H-1), 3.11 (m, 1H, H-5eq), 2.16 (ddd, $J_{3,1'}$=9.5 Hz, $J_{3,2}$=6.0 Hz, $J_{3,1'}$=4.0 Hz, 1H, H-3), 2.05 (ddd, $J_{8a,8}$=11.0 Hz, $J_{8a,1}$=8.0 Hz, $J_{8a,8}$=2.6 Hz, 1H, H-8a), 2.00-1.70 (m, 4H, 2xH-1', H-7, H-5ax), 1.70-1.35 (m, 4H, H-6, H-8), 1.20 (m, 1H, H-7); ^{13}C NMR: δ 171.8 (C=O), 138.2/128.4/127.7/127.6 (C-Ar), 73.0 (*C*H_2-Ph), 71.2 (C-2), 68.0 (C-3), 67.9 (C-2'), 65.7 (C-8a), 51.9 (C-5), 51.3 (OCH_3), 50.0 (C-1), 27.4 (C-8), 26.6 (C-1'), 24.8/24.7 (C-6/C-7). Anal. Calcd for $C_{19}H_{27}NO_4$: C, 68.44; H, 8.16; N, 4.20. Found: 68.43; H, 8.36; N, 4.29. **13**: IR (film): 3310, 1750 cm^{-1}; ^{1}H NMR: δ 7.35-7.25 (m, 5H, H-Ar), 4.51 (d, J_{gem}=11.7 Hz, 1H, *H*C-Ph), 4.45 (d, J_{gem}=11.7 Hz, 1H, *H*C-Ph), 3.64 (s, 3H, CH_3O), 3.60-3.52 (m, 2H, H-6), 3.00 (m, 1H, H-6'), 3.01-2.92 (m, 3H, H-3, H-2', H-4), 2.60 (td, $J_{gem}=J_{6',5'}$=12.0 Hz, $J_{6',5'}$=2.9 Hz, 1H, H-6'), 2.17 (t, $J_{2,3}=J_{2,2'}$=7.5 Hz, 1H, H-2), 1.94-1.68 (m, 4H, 2xH-5, H-4', H-3'), 1.55 (m, 1H, H-5'), 1.47-1.17 (m, 3H, H-4', H-5', H-3'); ^{13}C NMR (62.5 MHz): δ 172.1 (C=O), 138.1/128.3/127.6/127.5 (C-Ar), 73.0 (*C*H_2-Ph), 66.8 (C-6), 57.6 (C-2'), 56.5 (C-3), 54.8 (C-4), 54.4 (C-2), 51.8 (OCH_3), 46.8 (C-6'), 32.1 (C-5), 30.6 (C-3'), 26.5 (C-5'), 24.6 (C-4'). Anal. Calcd for $C_{19}H_{27}NO_4$: C, 68.44; H, 8.16; N, 4.20. Found: C, 68.36; H, 8.16; N, 4.11.

Reduction of **1**. *General Procedure for Method D*

To a solution of **1** (46 mg, 0.11 mmol) in 3M HCl (9 mL), activated zinc dust (522 mg, 8.07 mmol) was added and the resulting suspension was sonicated for 1 h. The Zn was filtered off and rinsed with 3M HCl (2mL), water (3 mL) and CH_2Cl_2 (13 mL). To this mixture, while vigorously stirring, solid K_2CO_3 was slowly added until pH=7. After stirring for 2 additional hours, the organic layer was separated, dried (anh. Na_2SO_4) and concentrated. Chromatography of the reaction crude (EtOAc) gave 30 mg (0.09 mmol, 85% yield) of **5**.

Reduction of **2** *(Method D)*

Following the general procedure, isoxazolidine **2** (46 mg, 0.11 mmol) was treated with activated zinc dust (522 mg, 8.07 mmol) in 3M HCl (9 mL). Chromatography of the reaction crude (EtOAc/MeOH 80/20) gave 33 mg (0.10 mmol, 91% yield) of **7**.

Reduction of **3** *(Method D)*

Following the general procedure, isoxazolidine **3** (30 mg, 0.07 mmol) was treated with activated zinc dust (343 mg, 5.25 mmol) in 3M HCl (6 mL). Chromatography of the reaction crude (EtOAc/MeOH 80/20) afforded 21 mg (0.06 mmol, 84% yield) of methyl (1*RS*,2*RS*,3*SR*,8a*SR*)-3-(2-benzyloxyethyl)-2-hydroxyoctahydro-indolizidine-1-carboxylate, **8**, as a crystalline solid: mp 65-7 °C. IR (film): 3479, 1728 cm^{-1}; ^{1}H NMR: δ 7.35-7.25 (m, 5H, H-Ar), 4.49 (s, 2H, H_2C-Ph), 4.31 (dt, $J_{2,1}$=6.2 Hz, $J_{2,3}=J_{2,OH}$=4.2 Hz, 1H, H-2), 3.85 (d, $J_{OH,2}$=4.2 Hz, 1H, OH), 3.69 (s, 3H, CH_3O), 3.58 (t, $J_{2',1'}$=7.0 Hz, 2H, H-2'), 3.21-3.13 (m, 2H, H-3, H-8a), 3.05 (t, $J_{1,2}=J_{1,8a}$=6.2 Hz, 1H, H-1), 2.92 (m, 1H, H-5), 2.68 (td, $J_{gem}=J_{5,6}$=13.0 Hz, $J_{5,6}$=2.9 Hz, 1H, H-5), 1.92 (dtd, J_{gem}=13.0 Hz, $J_{1',2'}$=7.0 Hz, $J_{1',3}$=3.5 Hz, 1H, H-1'), 1.80 (m, 1H, H-7), 1.70-1.48 (m, 3H, H-1', H-6, H-8), 1.40 (m, 1H, H-8), 1.37-1.15 (m, 2H, H-6, H-7); ^{13}C NMR: δ 172.6 (C=O), 138.3/128.3/127.6/127.5 (C-Ar), 76.5 (C-2), 73.2 (*C*H_2-Ph), 67.9 (C-2'), 65.2 (C-3), 60.9 (C-8a), 51.6 (OCH_3), 50.0 (C-1), 46.3 (C-5), 31.1 (C-1'), 25.2 (C-8), 24.4 (C-7), 21.0 (C-6). Anal. Calcd for $C_{19}H_{27}NO_4$: C, 68.44; H, 8.16; N, 4.20. Found: C, 68.25; H, 8.22; N, 4.03.

Reduction of **4** *(Method D)*

Following the general procedure, isoxazolidine **4** (42 mg, 0.10 mmol) was treated with activated zinc dust (481 mg, 7.37 mmol) in 3M HCl (8 mL). Chromatography of the reaction crude (EtOAc/MeOH 80/20) gave 29 mg (0.09 mmol, 90% yield) of **9**.

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