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Rapid Stereoselective Access to Key Pumiliotoxin Precursors from a Common Intermediate

Gavin O'Mahony, Mark Nieuwenhuyzen, Paul Armstrong,† and Paul J. Stevenson*

School of Chemistry, Queen's University, Belfast, N. Ireland BT9 5AG

p.stevenson@qub.ac.uk

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Abstract: Epoxidation and dihydroxylation of 8-methyl-2,3,6,8a-tetrahydro-1*H*-indolizin-5-one proceeded from the concave face with good selectivity and gave advanced precursors for pumiliotoxin and allopumiliotoxin synthesis, respectively. The origin of the selectivity is believed to be stereoelectronic in nature and allows rapid entry to three different pumiliotoxin classes from a common intermediate.

Pumiliotoxin alkaloids, isolated from the defensive skin secretions of *Dendrobates* frogs[1] have attracted the attention of the synthetic organic chemistry community for a number of years.[2] The interesting structures and biological properties of these alkaloids, coupled with the fact that for all practical purposes these compounds are essentially unavailable from the natural source, make them ideal targets for synthesis and for developing new synthetic methodologies. Allopumiliotoxins are related to pumiliotoxins in that they contain an additional hydroxyl group at C7. A number of ingenious solutions to the synthesis of these molecules have been published which include iminium ion chemistry,[3] organonickel chemistry,[4] organopalladium chemistry,[5] and organochromium chemistry.[6] In other approaches, two key indolizidines **1** and **2** (Figure 1) have emerged as key intermediates in the synthesis of pumiliotoxin and allopumiliotoxin alkaloids, respectively, using aldol methodology to attach the 6-alkylidene group.

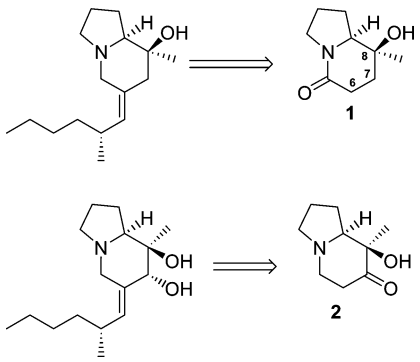

FIGURE 1. Retrosynthetic analysis showing key intermediates **1** and **2** in previous pumiliotoxin and allopumiliotoxin synthesis.

Gramain first reported the synthesis of compound **1** in racemic form,[7a] while Gallagher reported the first asymmetric synthesis of this compound[7b] and demonstrated that the 6-alkylidene unit of the target alkaloid could be attached by aldol methodology. Six additional routes to this key intermediate have been published to date.[8] Overman first reported ketone **2** as an entry to the allopumiliotoxins,[9] again with the 6-alkylidene entity being introduced by aldol methodology, and to date, three additional routes to this key indolizidine have been reported.[10]

A literature survey revealed that electrophilic additions to unsaturated indolizidin-5-ones and indolizidines usually proceed at the concave face.[11] This selectivity is opposite to what one would intuitively predict and has been independently attributed by different groups to both steric effects[12] and to the Cieplak stereoelectronic effect,[13]

† Chemical Synthesis Services (CSS), Almac House, 20 Seagoe Industrial Estate, Craigavon, N. Ireland BT63 5PW.

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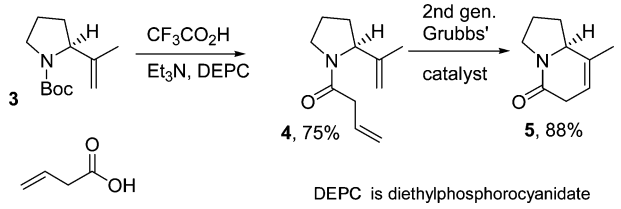
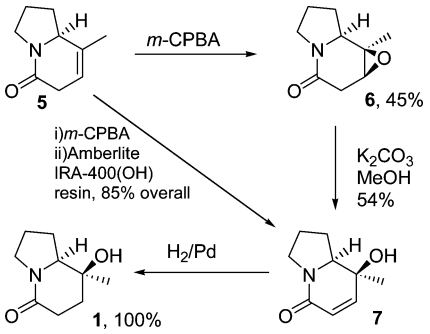
SCHEME 1. Preparation of Starting Materials



SCHEME 2. Epoxidation Studies



as recently elegantly articulated by Hanessian.[14] However, it should be noted that Cieplak's arguments have recently come under scrutiny and appear to lack a solid theoretical foundation.[15] Regardless of origin, if this remarkable face selectivity was retained in reactions of 8-methyl-2,3,6,8a-tetrahydro-1*H*-indolizin-5-one **5**, then it raised the exciting possibility that pumiliotoxin, allopumiliotoxin, 8-*epi*-pumilioxtoxin, and 8-deoxypumiliotoxin[16] alkaloids could all be prepared from a common alkene precursor.

Scheme 1 outlines the approach that was followed for synthesis of the starting material **5**. Known carbamate **3**[3g] was deprotected and coupled in situ with 3-butenoic acid using a modification of the method of Paolucci,[17] affording rotameric tertiary amide **4**. Olefin metathesis, a now well-established route for preparing indolizidinones,[18] was used to effect the key cyclization. Second-generation Grubbs' catalyst is known to be superior to first generation Grubbs' catalyst for the formation of more highly substituted cyclic alkenes.[19] Therefore, using 1.5 mol % second-generation Grubbs' catalyst, the reaction proceeded to completion after 32 h in boiling dichloromethane and the product could be isolated in 88% yield. This is the first example of the synthesis of a trisubstituted alkene-containing indolizidinone using methathesis

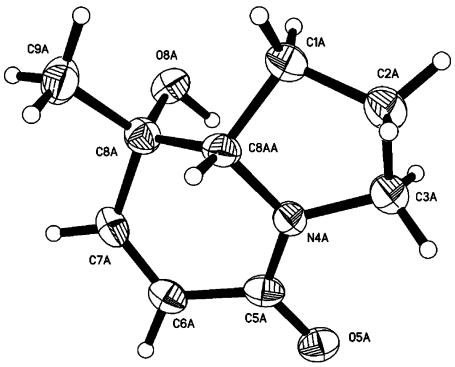


FIGURE 2. X-ray structure of alcohol **7** depicting relative stereochemistry.

methodology. On further experimentation the best method was found to be subjecting a toluene solution of diene **4** and 0.1 mol % of second generation Grubbs' catalyst to microwave irradiation for 15 min. The use of microwave heating for facilitating ring closing metathesis is well documented.[20]

Compound **5** was remarkably stable and conditions could not be found to isomerize the double bond into conjugation with the amide carbonyl group, making this a robust intermediate. With substrate **5** at hand, functionalization of the alkene was carried out. First, epoxidation with *m*-CPBA proved to be reasonably selective, affording a 10:1 mixture of diastereoisomeric epoxides (Scheme 2). Treatment of epoxide **6** with potassium carbonate resulted in a regioselective eliminative epoxide ring opening reaction to give the tertiary allylic alcohol **7** in 54% yield. Epoxide **6** proved difficult to isolate and purify in reasonable yield due to its water solubility and coelution with *m*-CPBA and derived products on silica gel column chromatography. Fortunately, conversion of alkene **5** to alcohol **7** could be performed in 85% overall yield for the two steps without isolating epoxide **6**, using strongly basic ion-exchange resin Amberlite IRA-400-(OH). The resin acted as the base for the epoxide ring-opening reaction and as a scavenger for unreacted *m*-CPBA and its byproducts. Alcohol **7** was crystallized to isomeric purity and the configuration at the tertiary alcohol center was determined by single crystal X-ray crystallography Figure 2. Gratifyingly the stereochemistry of the tertiary alcohol was correct, as anticipated, for pumiliotoxin synthesis. Hydrogenation of alkene **7** over a palladium catalyst afforded saturated compound **1**, a key intermediate in previous pumiliotoxin syntheses.[7]

Alkene **5** was next subjected to osmium tetraoxide catalyzed dihydroxylation (Scheme 3). Although this proceeded smoothly, an acetylation was necessary in order to isolate the polar, water-soluble product **8**. Only monoacetylated product **8** was detected as a single diastereoisomer (by proton NMR spectroscopy) in 84% crude yield, which dropped to 54% on chromatographic purification. It is not clear if the reaction was completely diastereoselective or if the major diastereoisomer of the diol was preferentially acylating, but in any case, iso-

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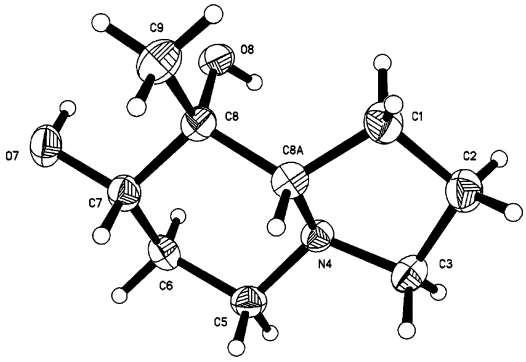
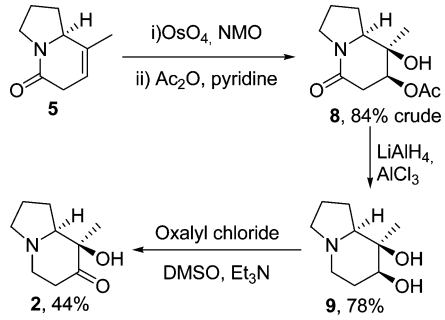


FIGURE 3. X-ray structure of diol **9** confirming stereochemical assignments.

SCHEME 3. Dihydroxylation Studies



merically pure product was obtained. Proton NMR data suggested that the dihydroxylation had proceeded from the concave face, i.e., with the (*R*)-configuration at C-8 as expected. Reduction of amide **8** gave the known crystalline amine **9**.[10c] Single-crystal X-ray crystallography, Figure 3 confirmed that the relative configuration at the three chiral centers had indeed been correctly assigned by proton NMR analysis. Finally, Swern oxidation as reported by Comins[10c] gave the key allopumiliotoxin intermediate **2**.

In conclusion, we have demonstrated that two classes of pumiliotoxin alkaloid can be readily stereoselectively obtained from a common cyclic alkene.

Experimental Section

4. Trifluoroacetic acid (7.64 g, 67.0 mmol) was added to a stirred solution of (*S*)-2-isopropenylpyrrolidine-1-carboxylic acid *tert*-butyl ester (1.41 g, 6.70 mmol) in dry dichloromethane (95 mL) and the solution stirred at rt for 2.5 h. The volatiles were removed under reduced pressure and the residue taken up in DMF (95 mL). Triethylamine (4.07 g, 40.2 mmol), diethyl cyanophosphonate (3.28 g, 20.1 mmol), and vinylacetic acid (1.73 g, 20.1 mmol) were added, and the mixture was stirred at rt for 16 h. The solvent was removed under reduced pressure and the residue dissolved in dichloromethane (50 mL) and washed with saturated aqueous sodium bicarbonate (2 × 30 mL) and water (30 mL). The combined aqueous washings were extracted with dichloromethane (20 mL) and the combined organic extracts washed with brine (30 mL) and dried over magnesium sulfate. Concentration under reduced pressure and purification by column chromatography (ether) afforded a rotameric mixture of the title compound (0.90 g, 75%) as a brown oil: R_f 0.53; $[\alpha]^{25}_D$ = 26.2 (*c* 1.3 $CHCl_3$); ν_{max} (KBr)/cm^{-1} 1647, 1416, 1193, 994, 910; δ_H (500 MHz, $CDCl_3$) 1.74 (3H, br s), 1.80−2.12 (4H, 2 × m), 3.01 (d, J = 6.7 Hz), 3.14 (d, J = 6.7 Hz), 3.45−3.59 (2H, m), 4.22−4.25 (m), 4.48−4.52 (m), 4.63 (s), 4.76 (s), 4.79 (s), 4.90 (s), 5.05−5.18 (2H, m), 5.93−6.04 (1H, m); δ_C (125 MHz, $CDCl_3$) 19.4, 19.8, 21.9, 23.8, 29.7, 31.4, 39.4, 40.3, 46.4, 47.2, 61.6, 62.7, 109.1, 111.2, 117.4, 117.8, 131.6, 132.1, 144.4, 145.0, 169.1, 170.4; *m*/*z* 179 (M^+, 27), 138 (73), 110 (43), 96 (26), 78 (24), 70 (100), 55 (29), 41 (68). Anal. Calcd for $C_{11}H_{17}NO$: C, 73.8; H, 9.5; N, 7.8. Found: C, 73.4; H, 9.5, N, 7.8.

5. Second-generation Grubbs' catalyst (76 mg, 0.09 mmol) was added to a solution of 1-((*S*)-2-isopropenyl-pyrrolidin-1-yl)but-3-en-1-one (1.62 g, 9.0 mmol) in dry dichloromethane (150 mL) and the resulting solution heated at reflux under argon for 26 h. A further portion of catalyst (38 mg) was added and the mixture refluxed for a further 6 h. Removal of the solvent under reduced pressure and purification by column chromatography (9:1 dichloromethane/methanol) afforded the title compound (1.21 g, 88%) as a brown oil: R_f 0.56; $[\alpha]^{25}_D$ = −128.9 (*c* 1.8, $CHCl_3$); ν_{max} (KBr)/cm^{-1} 1647, 1456, 1413, 1278, 805; δ_H (500 MHz, $CDCl_3$) 1.56 (1H, dq, J = 11.9, 7.5 Hz), 1.76 (3H, s), 1.89−1.94 (1H, m), 2.08−2.12 (1H, m), 2.25 (1H, quintet, J = 5.9 Hz), 2.93−2.99 (1H, m), 3.01−3.08 (1H, m), 3.51 (1H, dt, J = 12.0, 2.0 Hz), 3.82 (1H, dt, J = 12.0, 9.1 Hz), 3.99−4.02 (1H, br m), 5.42 (1H, m); δ_C (125 MHz, $CDCl_3$) 19.5, 22.5, 31.8, 33.8, 44.6, 62.3, 117.9, 132.3, 167.4; *m*/*z* 151 (M^+, 98), 150 (29), 149 (28), 136 (100), 120 (18), 108 (23), 94 (45), 80 (22); $C_9H_{13}NO$ requires M^+, 151.0997, found M^+, 151.0999

6. *m*-Chloroperoxybenzoic acid (50−55%, 736 mg, ∼2.24 mmol) was added to a solution of (*S*)-8-methyl-2,3,6,8a-tetrahydro-1*H*-indolizin-5-one (200 mg, 1.32 mmol) in dichloromethane (20 mL) and the mixture stirred at rt for 16 h. The reaction mixture was washed with saturated aqueous sodium bisulfite (3 × 10 mL), saturated aqueous potassium carbonate (10 mL, causes emulsion to form), water (10 mL), and brine (10 mL) and dried over magnesium sulfate. Concentration under reduced pressure and purification by column chromatography (9:1 dichloromethane/methanol) afforded the title compound (99 mg, 45%) as a yellow oil that solidified on standing: R_f 0.54; $[\alpha]^{25}_D$ = −47.5 (*c* 0.6, $CHCl_3$); ν_{max} (KBr)/cm^{-1} 1646, 1489, 1449, 1027, 951, 844, 695; δ_H (500 MHz, $CDCl_3$) 1.44 (3H, s), 1.76−1.81 (2H, m), 1.97−1.99 (1H, m), 2.15−2.18 (1H, m), 2.74 (1H, dd(AB), J = 18.0, 1.2 Hz), 2.91 (1H, dd(AB), J = 18.0, 2.5 Hz), 3.21 (1H, dd, J = 2.5, 1.2 Hz), 3.47−3.57 (2H, m), 3.71 (1H, dd, J = 10.8, 5.3 Hz); δ_C (125 MHz, $CDCl_3$) 18.8, 21.7, 28.9, 33.4, 45.8, 57.1, 58.3, 59.6, 165.7; *m*/*z* 168 ($M + 1^+$, 6), 167 (M^+, 59), 98 (9), 96 (18), 70 (100), 55 (19), 43 (30), 41 (31); $C_9H_{13}NO_2$ requires M^+, 167.0946, found M^+, 167.0946.

7. Potassium carbonate (4.1 mg, 0.03 mmol) was added to a stirred solution of (1a*S*,6a*S*,6b*R*)-6b-methylhexahydro-1-oxa-3a-azacyclopropa[*e*]inden-3-one (50 mg, 0.30 mmol) in dry methanol (5 mL) and the mixture stirred at rt for 6 h. The solvent was removed under reduced pressure, the residue dissolved in dichloromethane (10 mL) and washed with water (3 mL), and the aqueous washing back-extracted with chloroform (10 mL). The combined organic extracts were washed with brine (5 mL) and dried over magnesium sulfate. Concentration under reduced pressure and purification by column chromatography afforded the title compound (27 mg, 54%) as an off-white waxy solid: R_f 0.51; $[\alpha]^{25}_D$ = 294.9 (*c* 0.7, $CHCl_3$); ν_{max} (KBr)/cm^{-1} 3422, 1662, 1599, 1473, 1457, 1143, 1128, 810; δ_H (500 MHz, $CDCl_3$) 1.34 (3H, s), 1.76−1.86 (1H, m), 2.00−2.09 (2H, m), 2.12−2.19 (1H, m), 3.44 (1H, ddd, J = 11.7, 9.2, 7.2 Hz), 3.55 (1H, dd, J = 10.3, 6.2 Hz), 3.70 (1H, ddd, J = 11.7, 9.2, 2.4 Hz), 5.92 (1H, d, J = 9.7 Hz), 6.46 (1H, d, J = 9.7 Hz); δ_C (125 MHz, $CDCl_3$) 22.7, 24.4, 25.5, 45.0, 65.0, 66.8, 126.0, 145.1, 162.6; *m*/*z* 167 (M^+, 25), 149 (10), 148 (11), 120 (7), 98 (59), 70 (100), 55 (51), 43 (58); $C_9H_{13}NO_2$ requires M^+, 167.0946, found M^+, 167.0948

7. Procedure without isolation of intermediate epoxide, using Amberlite IRA-400(OH). *m*-Chloroperoxybenzoic acid (50−60%, 1.032 g, ∼2.99 mmol) was added to a solution of (*S*)-8-methyl-2,3,6,8a-tetrahydro-1*H*-indolizin-5-one (300 mg, 1.99 mmol) in dichloromethane (15 mL) and the mixture stirred at rt for 15 h. The dichloromethane was removed under reduced pressure, the residue dissolved in ethanol (9 mL), and Amberlite IRA-400-(OH) (3.00 g) added [freshly prepared by stirring Amberlite IRA-400(Cl) with 5% aqueous sodium hydroxide (∼5−6 times the volume of the resin) for 10 min and filtering off, washing the resin with distilled water until the washings were pH 7, and

drying under high vacuum]. The mixture was stirred at rt for 72 h. The resin was filtered off and the filtrate concentrated under reduced pressure affording the title compound (282 mg, 85%) as a brown oil that was pure enough to use without further purification.

1. A solution of (8*S*,8a*S*)-8-hydroxy-8-methyl-2,3,8,8a-tetrahydro-1*H*-indolizin-5-one (179 mg, 1.07 mmol) and 10% palladium on carbon (57 mg) was stirred under 1 atm of H_2 for 18 h at rt. The catalyst was filtered off through a plug of Celite and the filtrate concentrated under reduced pressure. Purification by column chromatography (9:1 dichloromethane/methanol) afforded the title compound (181 mg, 100%) as a colorless waxy solid. Analytical data were in agreement with published values:[7] R_f 0.39; $[\alpha]^{25}_D = -32.1$ (*c* 1.0, $CHCl_3$); ν_{max} (KBr)/cm^{-1} 3400, 1616, 1483, 1413, 1313, 1250, 1224, 1129; δ_H (500 MHz, $CDCl_3$) 1.31 (3H, s), 1.74−1.97 (6H, m), 2.41 (1H, dd, J = 18.5, 7.5 Hz), 2.53 (1H, ddd, J = 18.5, 11.8, 7.5 Hz), 3.38 (1H, dd, J = 10.5, 5.5 Hz), 3.51−3.55 (2H, m); δ_C (125 MHz, $CDCl_3$) 22.0, 26.3, 26.4, 28.1, 35.1, 45.7, 66.1, 67.7, 168.9; *m*/*z* 169 (M^+, 71), 154 (6), 126 (22), 112 (27), 111 (35), 99 (22), 83 (95), 70 (100), 55 (34), 43 (68), 41 (38); $C_9H_{15}NO_2$ requires M^+, 169.1103, found M^+, 169.1110.

8. Osmium tetraoxide (51 mg, 0.20 mmol) was added to a solution of (*S*)-8-methyl-2,3,6,8a-tetrahydro-1*H*-indolizin-5-one (300 mg, 2.0 mmol) and *N*-methylmorpholine (323 mg, 2.4 mmol) in acetone (7.5 mL) and water (1.5 mL) and the resulting mixture stirred at rt for 20 h. The solvents were removed under reduced pressure and the residue dried under high vacuum. The black residue was dissolved in pyridine (5 mL) and treated at 0 °C with acetic anhydride (1 mL) and the mixture stirred at rt for 16 h. The solvents were removed under reduced pressure, and the residue was redissolved in toluene (10 mL) and concentrated under reduced pressure. This was repeated three times. The residue was partitioned between brine (8 mL) and ethyl acetate (6 × 10 mL). The combined organic extracts were dried over magnesium sulfate and concentrated under reduced pressure. Purification by column chromatography (9:1 dichloromethane/methanol) afforded the title compound (244 mg, 54%) as a beige solid: R_f 0.43; $[\alpha]^{25}_D = -8.7$ (*c* 0.6, $CHCl_3$); ν_{max} (KBr)/cm^{-1} 3391, 1737, 1613, 1471, 1241, 1038, 979; δ_H (500 MHz, $CDCl_3$) 1.26 (3H, s), 1.81 (1H, m), 1.89 (1H, s), 1.95−2.04 (3H, m), 2.14 (3H, s), 2.49 (1H, dd, J = 17.5, 10.1 Hz), 2.84 (1H, dd, J = 17.5, 7.4 Hz), 3.41 (1H, dd, J = 9.8, 6.4 Hz), 3.47−3.56 (2H, m), 5.01 (1H, dd, J = 10.1, 7.4 Hz); δ_C (125 MHz, $CDCl_3$) 21.3, 22.55, 22.61, 25.9, 34.6, 46.0, 64.0, 70.0, 73.6, 166.8, 170.4; *m*/*z* 227 (M^+, 69), 209 (8), 185 (42), 184 (31), 168 (17), 112 (70), 83 (40), 70 (100); $C_{11}H_{17}O_4N$ requires M^+, 227.1158, found M^+, 227.1160. Anal. Calcd for $C_{11}H_{17}O_4N$: C, 58.2; H, 7.5; N, 6.2. Found: C, 57.8; H, 7.2; N, 6.2.

9. Aluminum chloride (357 mg, 2.67 mmol) in dry ether (5 mL) was added to a stirred suspension of lithium aluminum hydride (102 mg, 2.7 mmol) in dry ether (5 mL) under argon at rt and the mixture stirred for 25 min. A solution of acetic acid (7*S*,8*R*,8a*S*)-8-hydroxy-8-methyl-5-oxooctahydroindolizin-7-yl ester (244 mg, 1.1 mmol) in dry THF (10 mL) was added dropwise at rt (with some effervescence) and the resulting mixture stirred at rt for 45 min. The reaction mixture was cooled to 0 °C, saturated aqueous sodium hydroxide (4 mL) and water (4 mL) were carefully added, and the biphasic mixture was stirred for 1 h. The aqueous layer was separated, diluted with brine (4 mL), and extracted with chloroform (4 × 10 mL). The combined organics were dried over magnesium sulfate and concentrated under reduced pressure affording the title compound (143 mg, 78%) as an off-white solid that was used without further purification. Analytical data were in agreement with reported values:[10c] $[\alpha]^{25}_D = -2.8$ (*c* 0.6, $CHCl_3$); ν_{max} (KBr)/cm^{-1} 3481, 3424, 1635, 1264, 1078; δ_H (500 MHz, $CDCl_3$) 1.18 (3H, s), 1.54−1.62 (2H, 2 × m), 1.71−1.82 (3H, 2 × m), 1.86−1.90 (3H, 3 × m), 2.03 (1H, ddd, J = 12.6, 11.3, 3.1 Hz), 2.14−2.20 (1H, m), 2.69 (1H, br s), 2.97 (1H, ddd, J = 11.3, 5.1, 2.1 Hz), 3.00−3.06 (1H, m), 3.22 (1H, dt, J = 10.5, 5.3 Hz); δ_C (125 MHz, $CDCl_3$) 20.4, 22.3, 23.8, 31.3, 50.1, 54.7, 70.7, 71.2, 74.5; *m*/*z* 171 (M^+, 65), 154 (100), 128 (45), 126 (22), 112 (22), 97 (35), 84 (71), 70 (73), 43 (34); $C_9H_{17}NO_2$ requires M^+, 171.1259, found M^+, 171.1253. Anal. Calcd for $C_9H_{17}NO_2$: C, 63.2; H, 9.9; N, 8.2. Found: C, 63.2; H, 10.1; N, 8.0.

2. DMSO (136 mg, 1.74 mmol) was added dropwise to a solution of oxalyl chloride (147 mg, 1.16 mmol) in dry dichloromethane (1.9 mL) at −60 °C and the resulting solution stirred for 20 min at −60 °C. A solution of (7*S*,8*R*,8a*S*)-8-ethyloctahydroindolizine-7,8-diol (100 mg, 0.58 mmol) in dry dichloromethane (0.6 mL) was added dropwise and the reaction stirred at −60 °C for 20 min. Triethylamine (587 mg, 5.8 mmol) was added at −50 °C and the mixture stirred at rt for 45 min. Ethyl acetate (5 mL) was added and the dichloromethane removed under reduced pressure. A further portion of ethyl acetate (10 mL) was added and the mixture filtered. Concentration of the filtrate and purification by column chromatography (98:2 ethyl acetate/concentrated NH_3) afforded the title compound (43 mg, 44%) as a yellow oil. Spectroscopic data were in agreement with reported values:[10c] R_f 0.43; ν_{max} (KBr)/cm^{-1} 3433, 1723, 1373, 1307, 1229, 1124; δ_H (500 MHz, $CDCl_3$) 1.18 (3H, s), 1.75−1.96 (4H, 2 × m), 2.16 (1H, t, J = 7.7 Hz), 2.24 (1H, ddd, J = 14.7, 3.8, 1.4 Hz), 2.29−2.38 (2H, 2 × m), 3.06 (1H, ddd, J = 14.7, 12.4, 7.7 Hz), 3.16 (1H, m), 3.26 (1H, ddd, J = 10.8, 7.6, 1.4 Hz), 3.78 (1H, br s, O*H*); δ_C (125 MHz, $CDCl_3$) 16.82, 22.83, 23.52, 36.38, 50.18, 54.01, 72.39, 75.40, 209.24.

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Supporting Information Available: Spectra for compounds **1**, **2**, and **4**−**9** and CIF files for compounds **7** and **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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