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Synthesis of the first monoaromatic B-ring 13-azasteroid ring system by sequential angular annulation

Charles M. Marson,[a,*] Jennifer H. Pink[a] and Christopher Smith[b]

[a]*Department of Chemistry, University of Sheffield, Sheffield S3 7HF, UK*
[b]*Rhône-Poulenc Rorer Ltd, Rainham Road South, Dagenham, Essex RM10 7XS, UK*

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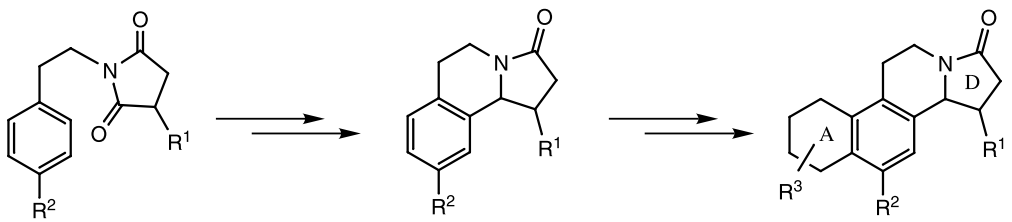
Abstract—A sequential angular annulation of an aromatic ring B is used to construct the 13-azasteroid ring system in efficient overall yield.

Azasteroids and their analogous ring systems have played important roles in medicinal chemistry.[1] 4-Azasteroids,[2] 17β-substituted aza-androstanes, and 6-azasteroids[3] can act as inhibitors of 5α-reductase. Early work on the total synthesis of 8-azasteroids included the total synthesis of (±)-8-aza-oestrone,[4] and analgesic activity has been observed with 8,13-diazasteroids.[5] 8,16-Diazasteroids and their heterocyclic variants show anti-inflammatory, anti-allergic and immunotropic activities, and can be cardiotonic and hypotensive agents.[6] However, there is a need for diversity in azasteroid synthesis, in order to generate derivatives that lack the hormonal activity that frequently complicates the use of azasteroids in medicine.

13-Azasteroids occupy a central area in heterosteroidal research; 13-aza and 13-aza-D-homo-analogues of equilenin methyl ethers were synthesised by alkylation of 6-(2-methyoxy-1-naphthyl)ethyl bromide with the respective potassium salts of succinimide and glutarimide.[7] In a synthesis of (±)-8,9-dehydro-13-aza-oestrone methyl ether, Speckamp and co-workers[8] used succinimide in an approach related to the Torgov cyclization.[9]

An elegant and flexible route to 13-azasteroids starts with a 1-halo-6-arylhex-3-ene and involves a stereospecific double cyclization.[10] We here report a new route to 13-azasteroids based on assembly of the BCD portion by acyliminium cyclization,[11] followed by angular fusion of ring A by a Haworth sequence (Scheme 1).[12] Reaction of 2-(4-methoxyphenyl)ethylamine with succinic anhydride in dichloromethane (Scheme 2) gave the intermediate *N*-[2-(4-methoxyphenyl)ethyl]-4-amidobutanoic acid which was cyclised by heating in acetyl chloride to give the imide **1** in an overall yield of 84%. Reduction of **1** with sodium borohydride was carried out in ethanol at 0–5°C, with the dropwise addition of 6 M hydrochloric acid to keep the pH at 8–10,[13] and afforded a 7:3 mixture of hydroxy- and ethoxy-lactams **2a** and **2b** in a total yield of 96%. Treatment of that mixture with trifluoromethanesulfonic acid (10% in CH_2Cl_2, 20°C, 2.5 h) afforded the tricyclic lactam **3** in almost quantitative yield. The use of trifluoromethanesulfonic acid for such cyclizations appears to be novel, and was suggested by related work involving the condensation of β,γ-unsaturated amides[14] with carbonyl compounds.[15]

The very efficient route to **3** is notable since the tetrahydropyrrolo[2,1-*a*]isoquinoline ring system has attracted widespread interest[16] and is also present in the



Scheme 1. A sequential angular annulation strategy for aromatic 13-azasteroids.

Keywords: angular annulation; cyclization; succinimide.
* Corresponding author. Present address: Department of Chemistry, University College London, Christopher Ingold Laboratories, 20 Gordon Street, London WC1H 0AJ, UK. Tel.: +44-2076794712; fax: +44-20-7679-7463; e-mail: c.m.marson@ucl.ac.uk

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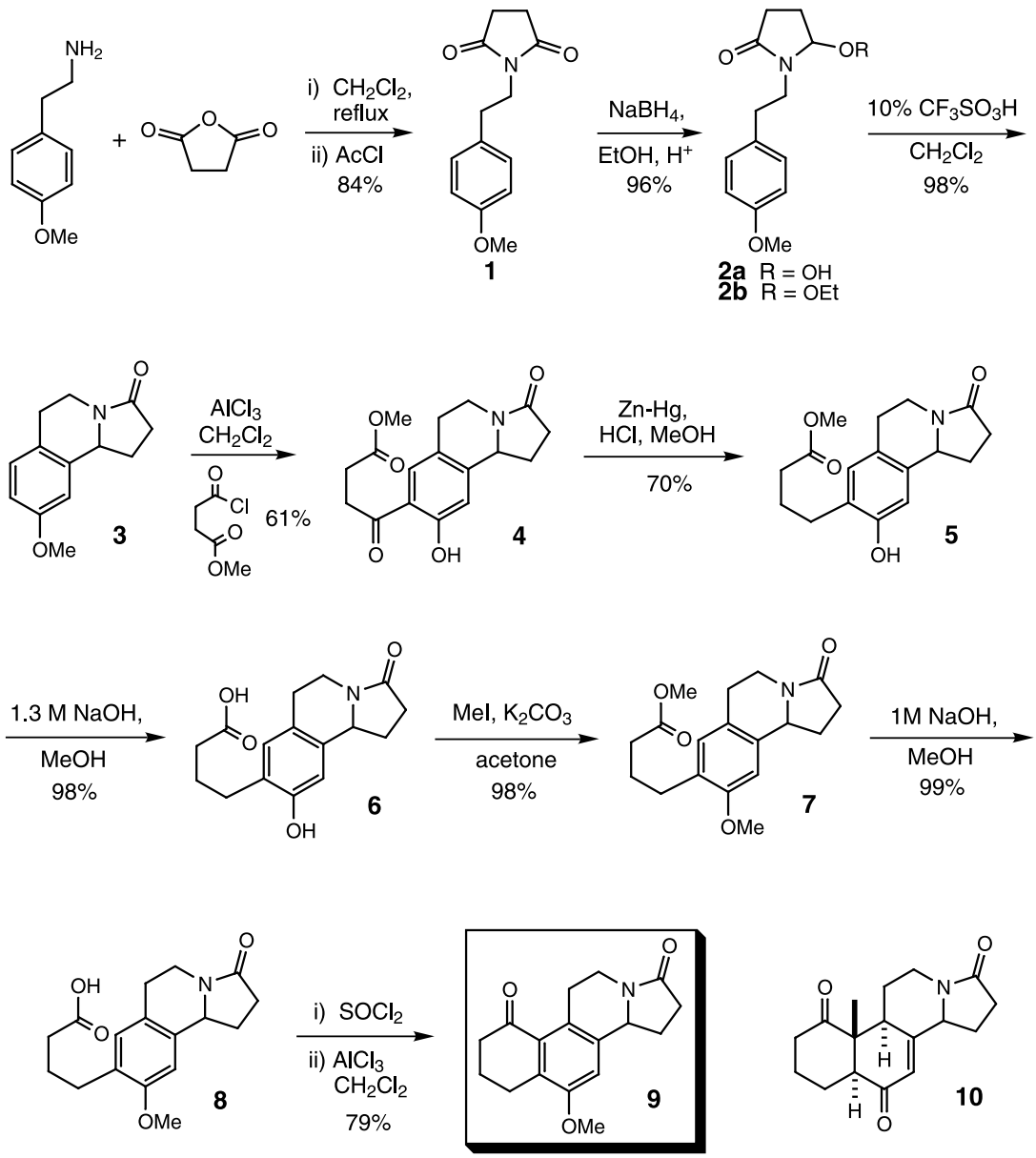

Scheme 2.

erythrina alkaloids, a skeleton that can confer sedative, hypotensive activities and the blocking of neuromuscular activity.[17] A Haworth-type cyclization[12] was envisaged as the means of appending the A ring of the azasteroid. Monomethyl succinate[18] was converted into 3-carbomethoxypropionyl chloride by treatment with thionyl chloride. As expected, Friedel–Crafts acylation of **3** occurred *ortho* to the methoxy group at the less hindered of the two unsubstituted sites activated by the phenolic hydroxyl group, and with concomitant demethylation of the methyl ether to afford the phenol **4** in 61% yield. Clemmensen reduction (Hg/Zn, 4 M HCl in 3:1 aqueous methanol) of **4** afforded a mixture of the acid **6** and its methyl ester **5**. The mixture was treated with 2:1 aqueous methanolic sodium hydroxide (1.3 M, 20°C, 16 h), resulting in saponification of the remaining ester; after neutralization, the carboxylic acid **6** was isolated in 98% yield.

In an attempt to form the tetracyclic system via a highly reactive mixed anhydride, the phenolic carboxylic acid **6** was treated with $SOCl_2$ followed by CF_3SO_3H.[19] However, a tar resulted, from which no products could be isolated. The ring closure was also attempted by treating the acid chloride with $AlCl_3$, but the desired azasteroid skeleton was not detected, and lactonisation appeared to have occurred. Accordingly, the phenolic group of **6** was protected under conditions of Williamson ether synthesis (MeI, K_2CO_3, Me_2CO; 20 h at reflux; Scheme 1) which also served to esterify the carboxylic acid group. Again, the ester **7** was smoothly hydrolyzed by stirring the crude product in aqueous methanolic 1 M sodium hydroxide for 20 h, giving a quantitative yield of the carboxylic acid **8**, the phenolic group being protected as the methyl ether. Ring closure of **8** proceeded smoothly via Lewis-acid induced cyclization of the acid chloride (5 equiv. of $AlCl_3$; 20°C, 4.5 h). The desired tetracyclic lactam **9** was isolated in 79% yield, thus demonstrating the success and efficiency of this new route to 13-azasteroid

nucleus (38% overall yield from 2-(4-methoxyphenyl)ethylamine.

It had been anticipated that dearomatization of ring B could be achieved by Birch reduction, and that quenching of the anionic intermediate would deliver the 10-methyl group of the 13-azasteroids. By this means, α-tetralone can be reductively alkylated to 8a-methyl-1,2,3,4,6,8a-hexahydronaphthalen-1-one.[20] A similar procedure was followed, in which ketone **9** in dry liquid ammonia and *tert*-butanol (1.2 equiv.) was treated with potassium (2 equiv.). After stirring for 10 min at −78°C, LiBr (2 equiv.) was added, followed by excess methyl iodide. However, proton NMR spectroscopy did not indicate formation of the desired **10**, but instead a complex mixture. Modification of this, or a related procedure, is warranted.

In conclusion, a sequential angular annulation of an aromatic ring B has been used to construct the 13-azasteroid ring system in an overall yield of 38% from a monocyclic precursor. The efficiency and flexibility of this route, particularly by using an enantiopure chiral pure chiral succinimide, e.g. derived from (*S*)-malic acid, would allow an enantioselective total synthesis of 13-azasteroids.

1. Experimental

1.1. General

All melting points were determined on a microscope hot-stage apparatus. ^{1}H and ^{13}C NMR spectra were run on a Bruker AM-250 instrument at 250 and 68.8 MHz, respectively. Microanalytical data were obtained on a Perkin–Elmer 2400 CHN elemental analyser. Mass spectra were obtained on a Kratos MS-25 or Fisons Prospec 3000 instrument. Infrared spectra were recorded on a Perkin–Elmer Paragon 100 FT-IR instrument. Thin-layer chromatography was performed on Merck 0.2 mm aluminium-backed silica gel 60 F_{254} plates and visualized using an alkaline $KMnO_4$ spray or by ultraviolet light. Flash column chromatography was performed using Sorbsil C60 40/60H silica gel. Petroleum ether (40–60 fraction) and ethyl acetate were distilled before use; tetrahydrofuran was distilled over sodium and benzophenone; dichloromethane was distilled over calcium hydride. Evaporation refers to the removal of solvent under reduced pressure.

1.1.1. *N*-[2-(4-Methoxyphenyl)ethyl]succinimide (1). A solution of 2-(4-methoxyphenyl)ethylamine (10.0 g, 66.1 mmol) and succinic anhydride (7.94 g, 79.4 mmol) in dichloromethane (300 mL) was heated under reflux for 48 h. The mixture was then cooled and the solvent evaporated. The residue was recrystallised from hot ethyl acetate, filtered and dried. The intermediate *N*-[2-(4-methoxyphenyl)ethyl]-4-amido-1-butanoic acid was treated with acetyl chloride (30 mL) under reflux for 3 h and the volatile materials were then removed by distillation to give a residue which was recrystallised from ethyl acetate to give the succinimide **1** as white prisms, (13.0 g, 84%), mp 114°C; IR (nujol) λ_{max} 1695 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.06 (2H, d, J=9.0 Hz), 6.74 (2H, d, J=9.0 Hz), 3.70 (3H, s), 3.62 (2H, t, J=8.0 Hz), 2.75 (2H, t, J=8.0 Hz), 2.57 (4H, s); ^{13}C NMR ($CDCl_3$) δ 177.0 (s), 158.4 (s) 130.0 (s), 129.8 (d), 113.9 (d), 55.2 (q), 40.1 (t), 32.6 (t), 28.1 (t). LRMS (EI) *m/e* 233 (M^+, 22%), 134 (100), 121 (57); HRMS calcd for $C_{13}H_{15}NO_3$ 233.1052, found 233.1052.

1.1.2. *N*-[2-(4-Methoxyphenyl)ethyl]-5-hydroxy-2-pyrrolidinone (2a) and *N*-[2-(4-methoxyphenyl)ethyl]-5-ethoxy-2-pyrrolidinone (2b). *N*-[2-(4-Methoxyphenyl)-ethyl]succinimide (**1**) (4.00 g, 17.1 mmol) was dissolved in ethanol (500 mL) and water (40 mL) and the solution cooled in an ice-bath. Sodium borohydride (4.00 g, 106 mmol) was added and the mixture stirred at 0–5°C. During the reaction period hydrochloric acid (6 M) was added dropwise at 10 min intervals so as to keep the pH at 8–10. After 2.5 h a further portion of sodium borohydride (4.00 g, 106 mmol) was added and stirring was continued for 3.5 h. The pH was then adjusted to 4–5 (6 M HCl) and the mixture poured into water (1.5 L). The aqueous layer was extracted with dichloromethane (5×500 mL). The combined organic extracts were dried over magnesium sulfate, filtered and the solvent was evaporated. The residue was subjected to column chromatography (9:1 ethyl acetate–light petroleum) and gave the hydroxy-2-pyrrolidinone **2a** as white prisms, (1.14 g, 28%), mp 136–139°C; ^{1}H NMR ($CDCl_3$) δ 7.07 (2H, d, J=9.0 Hz), 6.77 (2H, d, J=9.0 Hz), 4.87 (1H, bd t, J=6.0 Hz), 3.73 (3H, s), 3.60 (1H, m), 3.36 (1H, m), 2.78 (2H, t, J=7.0 Hz), 2.55–1.65 (4H, m); ^{13}C NMR ($CDCl_3$) δ 175.3 (s), 158.2 (s), 130.9 (s), 129.6 (d), 113.9 (d), 90.3 (d), 55.2 (q), 42.2 (t), 33.1 (t), 29.0 (t), 23.8 (t). Anal. calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95%; found: C, 66.26; H, 7.22; N, 5.73%; and the ethoxy-2-pyrrolidinone (**2b**) as a colourless oil, (3.06 g, 68%); IR (film) λ_{max} 1700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.12 (2H, d, J=9.0 Hz), 6.82 (2H, d, J=9.0 Hz), 4.69 (1H, dd, J=6.0, 1.0 Hz), 3.75 (3H, s), 3.70 (1H, m), 3.38 (2H, dq, J=6.0, 1.0 Hz), 3.25 (1H, m), 2.82 (2H, m), 2.60-1.30 (4H, m), 1.18 (3H, t, J=6.0 Hz); ^{13}C NMR ($CDCl_3$) δ 174.9 (s), 158.2 (s), 131.1 (s), 129.6 (d), 113.9 (d), 89.5 (d), 61.4 (t), 55.2 (q), 42.2 (t), 33.2 (t), 29.0 (t), 24.8 (t), 15.3 (q). LRMS (EI) *m/e* 263 (M^+, 31%), 217 (24), 134 (100), 121 (48), 96 (27), 68 (25); HRMS calcd for $C_{15}H_{21}NO_3$ 263.1521, found 263.1527.

1.1.3. 1,2,3,5,6,10b-Hexahydro-9-methoxy-1*H*-benzo[*g*]-indolizidin-3-one (3). A 7:3 mixture of the reduced imides **2a** and **2b** (4.30 g) was stirred in dichloromethane (23 mL) under nitrogen. The solution was cooled in an ice-bath and to it was added trifluoromethanesulfonic acid (2.5 mL). After stirring at 20°C for 2.5 h, the mixture was neutralised with saturated aqueous sodium hydrogen carbonate. The aqueous layer was separated and was extracted with dichloromethane (3×20 mL). The combined organic layers were washed with water (2×15 mL), dried over sodium sulfate and the solvent evaporated to give the lactam **3** as a viscous yellow oil (3.50 g, 98%); IR (film) λ_{max} 1685 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.06 (1H, d, J=8.5 Hz), 6.76 (1H, dd, J=8.5, 2.5 Hz), 6.63 (1H, d, J=2.5 Hz), 4.75 (1H, m), 4.26 (1H, m), 3.81 (3H, s), 2.40 (6H, m), 0.86 (1H, m); ^{13}C NMR ($CDCl_3$) δ 169.5 (s), 158.2 (s), 138.4 (s), 129.8 (d), 127.2 (s), 112.2 (d), 110.7 (d), 57.0 (d), 55.4 (q), 40.0 (t), 32.2 (t), 30.5 (t), 28.1 (t). LRMS (EI) *m/e* 217 (M^+, 88%), 216 (100), 202 (19), 186 (28), 160 (18); HRMS calcd for $C_{13}H_{15}NO_2$ 217.1103, found 217.1103.

1.1.4. 1,2,3,5,6,10b-Hexahydro-8-[3-(methoxycarbonyl)-1-oxopropyl]-9-hydroxy-1*H*-benzo[*g*]indolizidin-3-one (4). The benzo[*g*]indolizidin-3-one **3** (3.70 g, 17.1 mmol) was stirred in dichloromethane (20 mL) and the solution cooled in ice. Aluminium chloride (9.15 g, 68.6 mmol) was added, followed by the dropwise addition of 3-carbomethoxypropionyl chloride (2.31 g, 17.1 mmol) in dichloromethane (5 mL). The mixture was stirred at 20°C for 16 h. Water (50 mL) was added cautiously, the layers separated and the aqueous layer extracted with dichloromethane (3×30 mL). The combined organic extracts were washed with water (2×30 mL), dried over magnesium sulfate, filtered and the solvent was evaporated. The residue was purified by column chromatography (3% methanol in ethyl acetate) to give the benzo[*g*]indolizidin-3-one **4** as white prisms (3.29 g, 61%), mp 121–123°C; IR λ_{max} (nujol) 1735, 1690, 1645 cm^{-1}; ^1H NMR ($CDCl_3$) δ 11.9 (1H, s), 7.58 (1H, s), 6.73 (1H, s), 4.72 (1H, m), 4.27 (1H, m), 3.71 (3H, s), 3.33 (2H, t, *J*=6.5 Hz), 3.15–2.40 (8H, m) 1.88 (1H, m). Anal. calcd for $C_{17}H_{19}NO_5$: C, 64.33; H, 6.04; N, 4.42%; found: C, 64.29; H, 5.91; N, 4.68%.

1.1.5. 1,2,3,5,6,10b-Hexahydro-8-[3-(methoxycarbonyl)-propyl]-9-hydroxy-1*H*-benzo[*g*]indolizidin-3-one (5). Zinc dust (13.2 g, 0.202 mol) was amalgamated by stirring for 10 min at 20°C with a solution of mercury(II) chloride (0.92 g, 3.40 mmol) in water (66 mL) and concentrated hydrochloric acid (0.8 mL, 10 M). Decantation of the solution left the amalgam to which was added water (46 mL), followed by 10 M hydrochloric acid (46 mL) and then a solution of the keto ester **4** (3.30 g, 10.4 mmol) in methanol (33 mL). The mixture was heated under reflux for 4 h, cooled and extracted with dichloromethane (3×50 mL). The combined extracts were dried over sodium sulfate, filtered under suction, and the solvent evaporated to give a mixture of the acid **6** and its methyl ester **5**. The ester **5** was purified by dissolving in dichloromethane (200 mL), washing successively with aqueous sodium hydroxide (100 mL, 1 M), water (100 mL) and brine (100 mL), drying over sodium sulfate, followed by filtration and evaporation of the solvent to give ester **5** as a viscous oil (2.20 g, 70%); IR λ_{max} 1730, 1660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.85 (1H, s), 6.63 (1H, s), 4.70 (1H, m), 4.25 (1H, m), 3.73 (3H, s), 3.10–2.45 (8H, m), 2.41 (2H, t, *J*=6.0 Hz), 2.00–1.80 (3H, m); ^{13}C NMR ($CDCl_3$) δ 175.2 (s), 173.7 (s), 153.7 (s), 136.3 (s), 130.5 (d), 126.6 (s), 124.4 (s), 111.6 (d), 56.9 (q), 51.9 (d), 37.5 (t), 32.9 (t), 31.8 (t), 29.1 (t), 27.6 (t), 27.4 (t), 25.0 (t); LRMS (EI) *m/e* 303 (M^+, 54%), 216 (97), 202 (100), 186 (37); HRMS calcd for $C_{17}H_{21}NO_4$ 303.1471, found 303.1466.

1.1.6. 1,2,3,5,6,10b-Hexahydro-8-(3-carboxypropyl)-9-hydroxy-1*H*-benzo[*g*]indolizidin-3-one (6). The crude ester **5** (2.20 g, 7.25 mmol) was stirred in methanol (20 mL) and aqueous sodium hydroxide (40 mL, 2 M) for 20 h at 20°C. The mixture was acidified and the precipitate filtered and dissolved in methanol (50 mL). Benzene (10 mL) was added to the solution and the solvent was evaporated. Further portions of benzene (3×10 mL) were added successively. The solvent was then evaporated, and the residue dried in a desiccator overnight to give acid **6** (2.05 g, 98%), as white prisms, mp 226–228°C; IR λ_{max} (nujol) 3340, 1695, 1655 cm^{-1}; ^1H NMR ($(CD_3)_2SO$) δ 6.81 (1H, s), 6.55 (1H, s), 4.65 (1H, t, *J*=8.0 Hz), 3.98 (1H, dt, *J*=12.0, 4.0 Hz), 2.94 (1H, m), 2.70 (7H, m), 2.19 (2H, t, *J*=8.0 Hz), 1.80–1.70 (3H, m); ^{13}C NMR ($(CD_3)_2SO$) δ 174.9 (s), 172.5 (s), 154.2 (s), 136.7 (s), 130.5 (d), 127.0 (s), 123.7 (s), 111.2 (d), 56.2 (d), 37.2 (t), 33.8 (t), 31.7 (t), 29.2 (t), 27.7 (t), 27.6 (t), 25.2 (t); LRMS (EI) *m/e* 289 (M^+, 67%), 271 (38), 215 (42), 202 (100), 186 (18), 160 (14); HRMS calcd for $C_{16}H_{19}NO_4$ 289.1314, found 289.1318.

1.1.7. 1,2,3,5,6,10b-Hexahydro-8-(3-carboxypropyl)-9-methoxy-1*H*-benzo[*g*]indolizidin-3-one (7). The acid **6** (1.80 g, 5.93 mmol), methyl iodide (2.53 g, 17.8 mmol) and potassium carbonate (1.64 g, 11.9 mmol) were heated at reflux in dry acetone (20 mL) for 20 h. The solvent was then evaporated, water (50 mL) was added and the mixture extracted with dichloromethane (4×30 mL). The combined organic extracts were washed with water (50 mL) and brine (50 mL), dried over magnesium sulfate, filtered and the solvent was evaporated to give the methyl ester **7** as a viscous oil (1.85 g, 98%); IR λ_{max} (film) 1730, 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.87 (1H, s), 6.52 (1H, s), 4.74 (1H, m), 4.27 (1H, m), 3.79 (3H, s), 3.65 (3H, s), 3.00 (1H, m), 2.90–2.40 (5H, m), 2.59 (2H, t, *J*=7.5 Hz), 2.32 (2H, t, *J*=7.5 Hz), 1.96–1.80 (3H, m); ^{13}C NMR ($CDCl_3$) δ 174.1 (s), 173.3 (s), 156.4 (s), 136.0 (s), 130.6 (d), 128.9 (s), 124.9 (s), 111.4 (d), 56.9 (q), 55.4 (q), 51.5 (d), 37.3 (t), 33.6 (t), 31.8 (t), 29.2 (t), 27.6 (t), 27.5 (t), 25.0 (t); LRMS (EI) *m/e* 317 (M^+, 72%), 316 (76), 286 (31), 216 (100); HRMS calcd for $C_{18}H_{23}NO_4$ 317.1627, found 317.1621.

1.1.8. 1,2,3,5,6,10b-Hexahydro-8-(3-carboxypropyl)-9-methoxy-1*H*-benzo[*g*]indolizidin-3-one (8). The ester **7** (1.90 g, 5.93 mmol) was stirred in methanol (15 mL) and aqueous sodium hydroxide (15 mL, 2 M) for 20 h at 20°C. The methanol was then evaporated, and the residual solution was diluted with water (50 mL) and acidified (6 M HCl) before extraction with dichloromethane (3×30 mL). The combined organic extracts were washed with brine (30 mL), dried over magnesium sulfate, filtered and the solvent was evaporated to give the acid **8** as a green foam (1.75 g, 99%); IR λ_{max} (nujol) 1725, 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.88 (1H, s), 6.52 (1H, s), 4.75 (1H, bd t, *J*=8.0 Hz), 4.28 (1H, m), 3.80 (3H, s), 3.10–2.45 (8H, m), 2.36 (2H, t, *J*=7.5 Hz), 2.00–1.80 (3H, m); ^{13}C NMR ($CDCl_3$) δ 178.2 (s), 173.8 (s), 156.5 (s), 135.8 (s), 130.6 (d), 129.0 (s), 124.8 (s), 106.2 (d), 57.1 (d), 55.4 (q), 37.5 (t), 33.6 (t), 31.8 (t), 29.1 (t), 27.6 (t), 27.5 (t), 24.9 (t); LRMS (EI) *m/e* 303 (M^+, 37%), 302 (47), 216 (100); HRMS calcd for $C_{17}H_{21}NO_4$ 303.1471, found 303.1476.

1.1.9. 1,2,3,5,6,7,8,9,10,10b-Decahydro-11-methoxy-7-oxo-1*H*-naphtho[*g*]indolizidin-3-one (9). The acid **8** (1.65 g, 5.44 mmol), was stirred in thionyl chloride (12 mL) at 40°C for 3 h. The excess thionyl chloride was then distilled off under reduced pressure. The residual acid chloride, λ_{max} (liquid film) 1795 cm^{-1}, was dissolved in dichloromethane (15 mL) and cooled in an ice-bath. Aluminium chloride (3.63 g, 27.2 mmol) was added and the mixture was stirred at 20°C for 4.5 h. The mixture was then cooled in ice and water (75 mL) which was added cautiously to destroy excess aluminium chloride. The layers were separated, and the aqueous layer was extracted with dichloromethane (3×50 mL) and the combined organic

extracts washed with water (2×30 mL), saturated aqueous sodium hydrogen carbonate (30 mL) and brine (30 mL), dried over sodium sulfate and filtered. The solvent was evaporated to give lactam **9** as a green glassy solid (1.23 g, 79%); λ_{max} (nujol) 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.65 (1H, s), 4.71 (1H, m) 4.20 (1H, m), 3.80 (3H, s), 3.30–2.30 (10H, m), 2.10–1.65 (3H, m); ^{13}C NMR ($CDCl_3$) δ 200.7 (s), 173.0 (s), 155.3 (s), 136.9 (s), 134.1 (s), 132.3 (s), 127.1 (s), 110.2 (d), 57.0 (d), 55.7 (q), 40.9 (t), 37.1 (t), 31.8 (t), 28.0 (t), 27.2 (t), 23.4 (t), 22.2 (t); LRMS (EI) *m/e* 285 (M^+, 100%), 284 (82), 270 (49), 229 (85), 228 (46); HRMS calcd for $C_{17}H_{19}NO_3$ 285.1365, found 285.1364.

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