Efficient Biomimetic Synthesis of Indole Alkaloids of the Vallesiachotamine Group by a Domino Knoevenagel Hetero Diels-Alder Hydrogenation Sequence

Lutz F. Tietze*, Jürgen Bachmann, Jürgen Wichmann, Yifa Zhou, and Thomas Raschke

Institut für Organische Chemie der Georg-August Universität,
Tammannstraße 2, D-37077 Göttingen, Germany
Fax: (internat.) +49(0)551 399476

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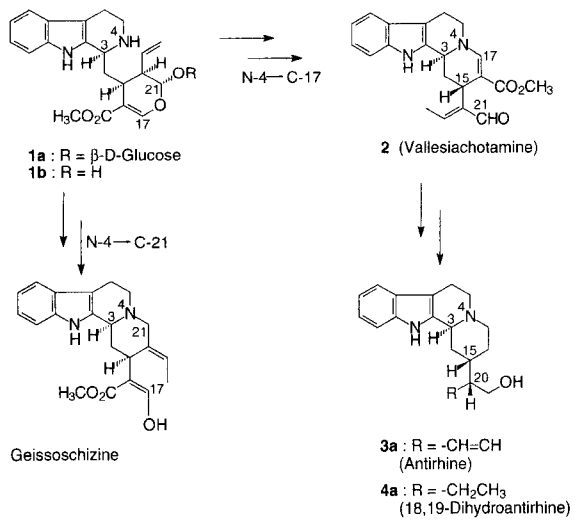
An efficient three-step biomimetic synthesis of the four diastereomeric 18,19-dihydroantirhines **4a–d** starting from the tetrahydrocarboline aldehydes **5a** and **5b** is described. Domino reaction of the aldehydes **5a** and **5b**, respectively, with Meldrum's acid (**6**) and the enol ethers **8a** and **8b** in the presence of catalytic amounts of ethylenediammonium diacetate leads to the strictosidine analogues **10a–d** and **11a–h**, respectively, in 74–86% yield, hydrogenation of which gives mainly **15** and **16** with the skeleton of the vallesiachotamine indole alkaloids (55–86%). In addition, small amounts of **17** and **18** with the corynanthe skeleton are also formed (10–12%). Reduction of both **15** and **16** with $LiAlH_4$ yields the diastereomeric *rac*-18,19-dihydroantirhines **4a–d** in 78–86% yield.

In the biosynthesis[1] of the over 2000 monoterpenoid indole alkaloids, strictosidine (**1a**), formed from secologanin[2] and tryptamine under catalysis by the enzyme strictosidine synthetase[3], is the key intermediate. Enzymatic glycolysis[4] of strictosidine **1a** provides the highly reactive aglucon **1b**, which reacts in vivo via its open dialdehyde form either by an N-4/C-17 cyclization to the give indole alkaloids of the vallesiachotamine (**2**) group, or alternatively by a competitive N-4/C-21 cyclization with formation of indole alkaloids of the corynanthe group, e.g. geissoschizine. Interestingly, the in vitro treatment of strictosidine **1a** with emulsine (β-glucosidase) gives almost exclusively vallesiachotamine (**2**) as the thermodynamically more stable product[1].



Vallesiachotamine (**2**), as well as the two other best-known alkaloids of this family, antirhine (**3a**) and 18,19-dihydroantirhine (**4a**), belong to a small group of monoterpenoid indole alkaloids with the less stable C-3/C-15 *anti* arrangement (15-β-H). Antirhine (**3a**) was first isolated[5] in 1967 from *Antirhea putaminosa* (*F. Muell.*) and later also from *Strychnos camptonuera*[6], *Aspidosperma oblongum*[7] and *Rhazya stricta*[8]. 18,19-Dihydroantirhine (**4a**) was found in *Aspidosperma marcgravium*[7] in 1983, and 3-epi-antirhine (**4c**) in *Guettarda heterosepala*[9] in 1985. Since then, antirhine (**3a**) and 18,19-dihydroantirhine (**4a**) have been the target of many total syntheses[10].

Recently, we have shown that a domino Knoevenagel hetero Diels-Alder hydrogenation sequence[11] can be used for the synthesis of indole alkaloids of the corynanthe family[12]. Herein, we report a highly efficient three-step biomimetic synthesis of the four diastereomeric 18,19-dihydroantirhines **4a–d** with the vallesiachotamine skeleton, using a similar approach. In this synthesis, the key intermediates are the strictosidine analogues **10** and **11**, which are obtained from the aldehydes **5a** and **5b**, Meldrum's acid (**6**), and the enol ethers **8a** and **8b**. Knoevenagel condensation of **5a** and **5b**, respectively, with Meldrum's acid (**6**) in the presence of catalytic amounts of ethylenediammonium diacetate (EDDA)[13] resulted in the formation of the 2-alkylidene-1,3-dicarbonyl compounds **7a** and **7b**, which reacted in situ with the enol ethers **8a** and **8b** to give the primary Diels-Alder products **9a** and **9b**, respectively. However, these cycloadducts were quite unstable and could not be isolated. Under the reaction conditions, they lost acetone and probably CO_2 as well, presumably by reaction with the water eliminated in the Knoevenagel condensation, to afford the stable lactones **10** and **11** as diastereomeric mixtures. The yields of these domino reactions, which were performed in an ultrasonic bath at 50–60 °C, varied between 74 and 86%.

As expected, the *endolexo* selectivity (simple diastereoselectivity) of the intermolecular hetero Diels-Alder reactions

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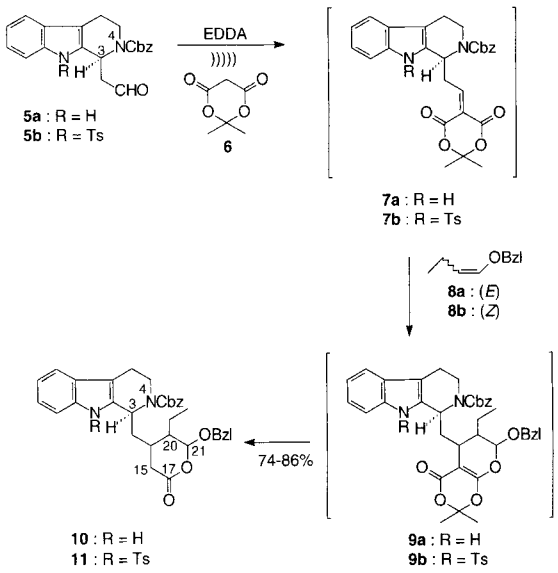
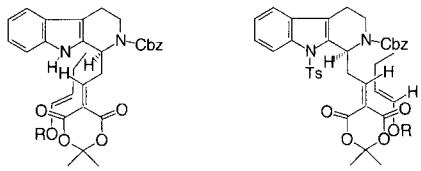


10/11	C-15	C-20	C-21
a	R(α-H)	S(β-H)	S(α-H)
b	R(α-H)	R(α-H)	R(β-H)
c	S(β-H)	R(α-H)	R(β-H)
d	S(β-H)	S(β-H)	S(α-H)
e	R(α-H)	R(α-H)	S(α-H)
f	R(α-H)	S(β-H)	R(β-H)
g	S(β-H)	S(β-H)	R(β-H)
h	S(β-H)	R(α-H)	S(α-H)

was quite low in all cases[14] (HPLC: **10a/10b** = **10c/10d** = 1.1:1; **11a/11b** = **11c/11d** = 1.2:1; **11e/11f** = **11g/11h** = 1.6:1). In contrast, the induced diastereoselectivity (1,3-induction) caused by the stereogenic center C-3 in **5a** and **5b**, respectively, was much better, even allowing the possibility of facial differentiation by employing either **5a** with a free, or **5b** with an *N*-tosyl-protected indole nitrogen atom. Thus, reaction of the aldehyde **5a**, Meldrum's acid (**6**) and the (*E*)-enol ether **8a** provided mainly the cycloadducts **10a** and **10b** with a 1,3-induction of 3:1 (HPLC: **10a/10b/10c/10d** = 3.3:3.0:1.1:1.0). The transformation proceeded with retention of the configuration of the employed enol ether. In contrast, with the aldehyde **5b** under identical conditions, the enol ether **8a** provided predominantly the cycloadducts **11c** and **11d** (HPLC: **11a/11b/11c/11d** = 1.2:1.0:7.4:7.1), whereas use of the enol ether **8b** yielded mainly the products **11g** and **11h** (HPLC: **11e/11f/11g/11h** = 1.6:1.0:11.7:7.1). The lactones **11g** and **11h** could be isolated in a pure state by column chromatography on silica gel, but the other diastereomeric mixtures were not separable.

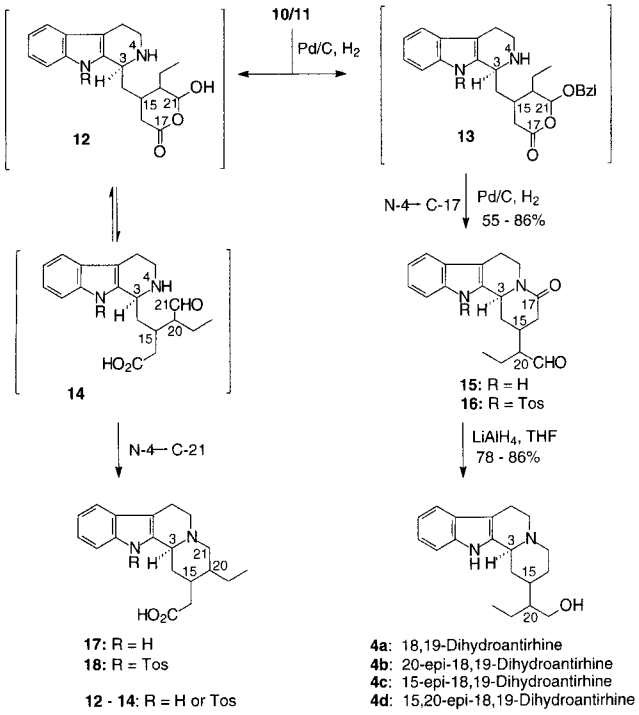
The interesting facial differentiation of the 1-oxa-1,3-butadienes **7a** and **7b** is difficult to explain since two different 1-oxa-1,3-butadiene moieties exist in these molecules. Thus, the cycloaddition could take place either via an (*E*) or via a (*Z*) geometry of the heterodiene whereby the *exo-(E)-syn* and the *endo-(Z)-syn* transition structure would give the *trans* cycloadducts, while the *endo-(E)-syn* and the *exo-(Z)-syn* transition structure would lead to the *cis* compounds[15]. Since (*Z*)-heterodienes are generally less reactive[16], we assume that in both alkylidene-1,3-dicarbonyl compounds **7a** and **7b** the reaction takes place at the (*E*)-1-oxa-1,3-butadiene moiety, but in different conformations. Thus, for **7a**, conformation **C-1** should be preferred in the transition structure possibly eventually due to a weak hydrogen bond of the NH group of the indole moiety and the carbonyl group of the oxabutadiene[12c,17] or simply due to some steric interaction of the alkylidene-1,3-dicarbonyl moiety with the Cbz group in conformation **C-2**. For **7b**, conformation **C-2** should clearly be preferred due to a strong steric repulsion between the alkylidene-1,3-dicarbonyl moiety and the tosyl group in conformation **C-1**. Furthermore, the stabilizing effect in conformation **C-1** as discussed for **7a** does not exist in this case due to the absence of the indole NH group in **7b**. In both systems, the attack of the enol ether should take place preferentially from below, this being the less hindered side. Thus, the following transition structures can be assumed: *Re-endo-(E)-syn* for **10a**, **11a**, **11e**; *Si-endo-(E)-syn* for **10c**, **11c**, **11g**; *Re-exo-(E)-anti* for **10b**, **11b**, **11f** and *Si-exo-(E)-anti* for **10d**, **11d**, **11h**[18].



C-1 C-2

For the synthesis of dihydroantirhine and its epimers **4a–b**, the protecting groups at N-4 and, as in the enzymatic glycolysis of strictosidine (**1a**), at C-21 of the lactones **10** and **11** have to be removed. Both the benzyloxy carbonyl group at N-4 and the benzyl group at C-21 can be cleaved by hydrogenolysis using $Pd/C/H_2$. However, for this transformation and the subsequent reaction sequence two different pathways have to be discussed, in view of the formation of the products **15** and **16**, respectively, (55–86%) and of **17** and **18** (10–12%). The products **17a–b** and **18a–b**, containing the skeleton of the indole alkaloids of the corynanthe group, are obtained by a twofold deprotection of **10** and **11** to give the hemiacetals **12**, which are then transformed by a reductive amination via the aldehydes **14**. The main products **15a–d** and **16a–d** of the hydrogenation sequence, displaying the skeleton of the indole alkaloids of the vallesiachotamine group, originate from a preferred removal of the protecting group at N-4 to give **13**, followed by a nucleophilic attack of N-4 at the carbonyl group C-17 with opening of the acetal moiety. Reduction of **15** and **16** with lithium aluminium hydride provided directly the diastereomeric 18,19-dihydroantirhine isomers **4a–d** in 78–86% yield. In the reaction of **16** not only are the amide and the aldehyde functions reduced, as in **15**, but also simultaneous removal of the *p*-toluenesulfonyl group is achieved.

Hydrogenolysis and reduction of the mixtures of the diastereomeric cycloadducts **10a–d**, **11a–d** and **11e–h** generated a mixture of the diastereomeric 18,19-dihydroantirhines **4a–d**. Chromatography on silica gel allowed sep-



aration of the C-15 isomers (**4a**, **b**/**4c**, **d** = 3:1 for **10** and 1:7 for **11**) but separation of the C-20 isomers **4a**, **b** and **4c**, **d** was not possible. However, hydrogenolysis and reduction of the separated cycloadducts **11g** and **11h** provided 15-epi-dihydroantirhine **4c** and 3-epi-dihydroantirhine **4d**, respectively, as pure compounds.

The configuration of the products was determined mainly by ^{1}H-NMR spectroscopy[19]. Thus, the *cis*-quinolizidine geometry of **4a** and **4b** could clearly be deduced from the 3-H resonances at δ = 4.21 and 4.36, respectively, whereas for the *trans*-quinolizidines **4c** and **4d**, the 3-H signals were found at δ = 3.32 and 3.38. The NMR data were in agreement with both published data[1] and those of an authentic sample.

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Experimental Section

^{1}H NMR and ^{13}C NMR: Varian XL-500 and VXR-200, multiplicities were determined with an APT pulse sequence; the numbering of the indole alkaloids was used for the correlation of the NMR data. – MS: Varian MAT 311A; high resolution: Varian MAT 731. – IR: Bruker IFS 25. – UV: Varian Cary 219. – Melting points: Mettler FP 61 or Kofler hot stage. – Ultrasound: Bandolin Sonorex RK102 (50 kHz). – Elemental analyses were carried out in the analytical laboratory of the university Göttingen. – All solvents were distilled prior to use. Reagents and materials were obtained from commercial suppliers and were used without further purification. All reactions were carried out under a positive pressure of nitrogen and monitored by TLC (Macherey-Nagel & Co., Polygram SIL G/UV$_{254}$). Products were isolated by column chromatography on silica gel (ICN Silica 63–200, 60 A, ICN Biomedicals).

Domino Knoevenagel Hetero Diels-Alder Reactions

(1′S,4R*,5S*,6S*)-, (1′S*,4R*,5R*,6R*)-, (1′S*,4S*,5R*,6R*)- and (1′S*,4S*,5S*,6S*)-(±)-6-Benzyloxy-4-{[1-(2-benzyloxycarbonyl)-1,2,3,4-tetrahydro-β-carbolinyl]methyl}-5-ethyl-2,3,4,5-tetrahydro-4H-pyran-2-one* (**10a–d**): Reaction of **5a** (1.04 g, 2.99 mmol), Meldum's acid (**6**) (516 mg, 3.58 mmol) and (*E*)-1-benzyloxy-1-butene (**8a**) (1.50 g, 9.26 mmol) in the presence of a few crystals of ethylenediammonium diacetate (EDDA) in 1 ml of dry benzene under nitrogen in an ultrasonic bath (H_2O, 50–60 °C) for 16 h gave a clear, red solution. The solvent was then evaporated and the residue was purified by column chromatography, eluting first with pentane in order to separate the enol ether **8a**, then with CH_2Cl_2/Et_2O/pentane (1:1:3), and finally with Et_2O, to give the cycloadducts **10a–d** (1.42 g, 2.57 mmol, 86%) as a white foam. – HPLC [Nucleosil 5CN, 5 μm (Knauer), heptane/*tert*-butyl methyl ether/acetonitrile, 50:45:5; flow rate: 0.5 ml/min, 278 nm): R_t = 6.1 min (**10d**: 1.0), 16.8 min (**10b**: 3.0), 17.2 min (**10a**: 3.3), 19.1 min (**10c**: 1.2). – R_f = 0.21 (CH_2Cl_2/Et_2O/pentane, 1:1:3). – UV (CH_3CN): λ_{max} (lg ε) = 209 nm (4.56), 217 (4.55), 225 (4.58). – IR (KBr): $\tilde{\nu}$ = 3300 cm^{-1} (NH, indole), 1740 (C=O, lactone), 1700 (C=O, urethane), 1115 (C–O, acetal), 750 (C–H, phenyl), 705 (C–H, phenyl). – ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.72–1.10 (m, 3H, CH_3), 1.18–3.56 (m, 11H, 1″-H, CH_2, 5-H, 4-H, 3-H, 4′-H, 3′-H_{ax}), 4.12–4.78 (m, 2H, 3′-H_{eq}, OCH_2), 4.84–5.58 (m, 5H, OCH_2, CO_2CH_2Ph, 6-H, 1′-H), 6.78–8.50 (m, 15H, Ph-H, NH indole). – MS (70 eV): *m/z* (%) = 552 (0.2) [M$^+$], 461 (2) [M$^+$ – C_7H_7], 417 (2) [M$^+$ – $C_8H_7O_2$], 91 (100) [$C_7H_7^+$]. – $C_{34}H_{36}N_2O_5$ (552.7): calcd. C 73.89, H 6.57, N 5.07; found C 73.93, H 6.76, N 5.06.

(1′S,4R*,5S*,6S*)-, (1′S*,4R*,5R*,6R*)-, (1′S*,4S*,5R*,6R*)- and (1′S*,4S*,5S*,6S*)-(±)-6-Benzyloxy-4-{[1-(2-benzyloxycarbonyl)-N-p-toluenesulfonyl-1,2,3,4-tetrahydro-β-carbolinyl]methyl}-5-ethyl-2,3,4,5-tetrahydro-4H-pyran-2-one* (**11a–d**): Reaction of **5b** (502 mg, 1.00 mmol), Meldrum's acid (**6**) (173 mg, 1.20 mmol) and (*E*)-1-benzyloxy-1-butene (**8a**) (518 mg, 3.20 mmol) in the presence of a few crystals of ethylenediammonium diacetate (EDDA) under nitrogen in an ultrasonic bath (H_2O, ca. 60 °C) for 16 h gave a clear, red solution. The solvent was then evaporated and the residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:2) affording a diastereomeric mixture of the cycloadducts **11a–d** (548 mg, 0.78 mmol, 78%) as a white foam. – HPLC [System of LiChrosorb 100 RP-18, 5 μm and LiChrospher 100 RP-18, 5 μm (Merck), acetonitrile/water, 75:25, flow rate: 1.5 ml/min, 257 nm]: **11c/d**: R_t = 39 min (14.5), **11a**: R_t = 37 min (1.2), **11b**: R_t = 32 min (1.0). – R_f = 0.39 (EtOAc/hexane, 1:2). – UV (CH_3CN): λ_{max} (lg ε) = 253 nm (4.16). – IR (KBr): $\tilde{\nu}$ = 2956 cm^{-1}, 2926, 2878 (CH), 1746, 1698 (C=O). – ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.74–1.16 (m, 3H, CH_3), 1.18–3.30 (m, 11H, 1″-H, CH_2, 5-H, 4-H, 3-H, 4′-H, 3′-H_{ax}), 2.19, 2.27 (2 s, 3H, Tos-CH_3), 4.21–5.39 (m, 6H, 3′-H_{eq}, OCH_2, 6-H), 5.87–6.19 (m, 1H, 1′-H), 6.69–6.84 (m, 1H, Tos-H), 7.02–7.80 (m, 16H, Ph-H, Tos-H, 5′-H, 6′-H, 7′-H), 8.06–8.22 (m, 1H, 8′-H). – MS (70 eV): *m/z* (%) = 551 (1) [M$^+$ – Tos], 459 (29) [$C_{26}H_{23}N_2O_4S^+$], 415 (18) [M$^+$ – Tos – Cbz], 169 (11) [$C_{11}H_9N_2^+$], 133 (2) [$C_9H_{10}O^+$], 91 (100) [$C_7H_7^+$]. – $C_{41}H_{42}N_2O_7S$ (706.9): calcd. C 69.66, H 5.99; found C 69.64, H 6.01.

(1′S,4R*,5R*,6S*)-, (1′S*,4R*,5S*,6R*)-, (1′S*,4S*,5S*,6R*)- and (1′S*,4S*,5R*,6S*)-(±)-6-Benzyloxy-4-{[1-(2-benzyloxycarbonyl)-N-p-toluenesulfonyl-1,2,3,4-tetrahydro-β-carbolinyl]methyl}-5-ethyl-2,3,4,5-tetrahydro-4H-pyran-2-one* (**11e–h**): Re-

action of **5b** (502 mg, 1.00 mmol), Meldrum's acid (**6**) (173 mg, 1.20 mmol) and (*Z*)-1-benzyloxy-1-butene (**8b**) (518 mg, 3.20 mmol) in the presence of a few crystals of ethylenediammonium diacetate (EDDA) under nitrogen in an ultrasonic bath (H_2O, ca. 60°C) for 16 h gave a clear, red solution. The solvent was then evaporated and the residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:2), affording a mixture of cycloadducts **11e–h** (520 mg, 0.74 mmol, 74%) as a white foam. A second column chromatography of this product mixture on silica gel (EtOAc/hexane, 2:3) gave 88 mg of a mixture of **11e–g** as an oil, R_f = 0.67 (EtOAc/hexane, 2:3), 207 mg of **11g** as a white foam, R_f = 0.59 (EtOAc/hexane, 2:3), and 146 mg of **11h** as a white foam, R_f = 0.46 (EtOAc/hexane, 2:3). – HPLC [System of LiChrosorb 100 RP-18, 5 µm and LiChrospher 100 RP-18, 5 µm (Merck), acetonitrile/water, 75:25, flow rate: 1.5 ml/min, 257 nm]: **11e**: R_t = 32 min (1.6), **11f**: R_t = 38 min (1.0), **11g**: R_t = 36 min (11.7), **11h**: R_t = 33 min (7.1). – UV (CH_3CN): λ_{max} (lg ε) = 253 nm (4.17). – IR (KBr): $\tilde{\nu}$ = 2958 cm^{-1}, 2934, 2878 (CH), 1744, 1698 (C=O). – ^1H NMR (200 MHz, $CDCl_3$): δ = 0.72–0.94 (m, 2H, CH_3), 1.06 (t, *J* = 7.0 Hz, 1H, CH_3), 1.18–3.30 (m, 11H, 1″-H, CH_2, 5-H, 4-H, 3-H, 4′-H, 3′-H_{ax}), 2.20, 2.45 (2 s, 3H, Tos-CH_3), 4.22–5.39 (m, 6H, 3′-H_{eq}, OCH_2Ph, 6-H), 5.81–6.15 (m, 1H, 1′-H), 6.72–6.87 (m, 1H, Tos-H), 7.04–7.80 (m, 16H, Ph-H, Tos-H, 5′-H, 6′-H, 7′-H), 8.08–8.23 (m, 1H, 8′-H). – High-temperature NMR of **11g**: ^1H NMR (200 MHz, $C_2D_2Cl_4$, 100°C): δ = 0.84 (t, *J* = 7.0 Hz, 3H, CH_3), 1.42–3.29 (m, 11H, 1″-H, CH_2, 5-H, 4-H, 3-H, 4′-H, 3′-H_{ax}), 2.21 (s, 3H, Tos-CH_3), 4.35 (m_c, 1H, 3′-H_{eq}), 4.60, 4.86 (2 d, *J* = 12 Hz, 2H, OCH_2), 5.17 (s, 2H, OCH_2), 5.33 (d, *J* = 2.5 Hz, 1H, 6-H), 5.99 (m_c, 1H, 1′-H), 6.97 (d, *J* = 8.0 Hz, 2H, Tos-H), 7.12–7.42 (m, 13H, Ph-H, 5′-H, 6′-H, 7′-H), 7.53 (d, *J* = 8.0 Hz, 2H, Tos-H), 8.06 (dd, *J* = 2.0, 7.0 Hz, 1H, 8′-H). – High-temperature NMR of **11h**: ^1H NMR (200 MHz, $C_2D_2Cl_4$, 100°C): δ = 1.04 (t, *J* = 7.0 Hz, 3H, CH_3), 1.42–3.29 (m, 11H, 1″-H, CH_2, 5-H, 4-H, 3-H, 4′-H, 3′-H_{ax}), 2.21 (s, 3H, Tos-CH_3), 4.35 (m_c, 1H, 3′-H_{eq}), 4.58, 4.90 (2 d, *J* = 12 Hz, 2H, OCH_2), 5.18 (m, 2H, OCH_2), 5.26 (d, *J* = 2.5 Hz, 1H, 6-H), 5.93 (m_c, 1H, 1′-H), 6.97 (d, *J* = 8.0 Hz, 2H, Tos-H), 7.12–7.42 (m, 13H, Ph-H, 5′-H, 6′-H, 7′-H), 7.53 (d, *J* = 8.0 Hz, 2H, Tos-H), 8.07 (dd, *J* = 2.0, 7.0 Hz, 1H, 8′-H). – MS (70 eV): *m/z* (%) = 551 (1) [M^+ – Tos], 459 (30) [$C_{26}H_{23}N_2O_4S^+$], 415 (22) [M^+ – Tos – Cbz], 169 (5) [$C_{11}H_9N_2^+$], 133 (6) [$C_9H_{10}O^+$], 91 (100) [$C_7H_7^+$]. – $C_{41}H_{42}N_2O_7S$ (706.9): calcd. C 69.66, H 5.99; found C 69.50, H 5.88.

Hydrogenation of the Lactones **10** *and* **11**: 1.00 g of the catalyst (Pd/C, 10%) was suspended in anhydrous EtOH and saturated with H_2 by stirring at room temp. (30–60 min). The mixture of **10a–d** (1.03 g, 1.87 mmol), dissolved in 5 ml of EtOH, was then added by syringe and stirring was continued under hydrogen for 4 h. After separation of the catalyst by filtration through silica gel ($CHCl_3$/MeOH, 5:1), the solvent was removed in vacuo and the residue was purified by column chromatography on silica gel (first $CHCl_3$/MeOH, 5:1, then MeOH) to afford two fractions: Fraction 1: *(1′β,2β,12bα)-, (1′α,2β,12bα)-, (1′β,2α,12bα)- and (1′α,2α,12bα)-(±)-2-(1-Formyl-1-propyl)-1,2,3,4,6,7,12,12b-octahydro-4-oxoindolo[2,3-a]quinolizine* (**15a–d**): 495 mg, 1.60 mmol, 86% as a white foam which was crystallized from THF/pentane, m.p. 190°C. – R_f = 0.90 ($CHCl_3$/MeOH, 5:1). – UV (MeOH): λ_{max} (lg ε) = 223 nm (4.57), 273 (3.87), 289 (3.78). – IR (KBr): $\tilde{\nu}$ = 3280 cm^{-1} (NH, indole), 1725 (C=O, aldehyde), 1625 (C=O, lactam), 750 (C–H, phenyl). – ^1H NMR (200 MHz, $CDCl_3$): δ = 0.83 (t, *J* = 7.5 Hz, 1.5H, 18-H), 0.97 (t, *J* = 7.5 Hz, 1.3H, 18-H), 0.79–1.05 (m, 0.2H, 18-H), 1.44–3.12 (m, 11H, 19-H, 14-H, 6-H, 20-H, 15-H, 16-H, 5-H_{ax}), 4.56–5.24 (m, 2H, 3-H, 5-H_{eq}), 7.06–7.54 (m, 4H, Ph-H), 8.19 (br s, 0.06H, NH indole), 8.27 (br s, 0.4H, NH indole), 8.31 (br s, 0.5H, NH indole), 8.17–8.43 (br s, 0.04H, NH indole), 9.62 (d, *J* = 2.8 Hz, 0.5H, CHO), 9.65 (d, *J* = 2.2 Hz, 0.4H, CHO), 9.67 (d, *J* = 2.8 Hz, 0.06H, CHO), 9.73 (d, *J* = 2.2 Hz, 0.04H, CHO). – ^{13}C NMR ([D_6]DMSO): δ (relat. intensities) = 11.01 (0.4) (C-18), 11.24 (0.1) (C-18), 11.35 (0.5) (C-18), 18.31 (0.05) (C-19), 18.62 (0.4) (C-19), 18.68 (0.5) (C-19), 18.85 (0.05) (C-19), 20.49 (0.8) (C-14), 20.62 (0.1) (C-14), 20.71 (0.1) (C-14), 28.47 (0.4) (C-15), 28.95 (0.4) (C-5), 29.08 (0.6) (C-15), 29.64 (0.6) (C-5), 35.58 (0.5) (C-6), 35.71 (0.1) (C-6), 36.40 (0.4) (C-6), 40.89 (C-16), 51.93 (0.4) (C-3), 52.06 (0.05) (C-3), 52.21 (0.5) (C-3), 53.34 (0.05) (C-3), 55.09 (0.4) (C-20), 55.35 (0.5) (C-20), 56.52 (0.1) (C-20), 106.9 (0.1) (C-7), 108.0 (0.4) (C-7), 108.1 (0.5) (C-7), 111.1 (0.5) (C-12), 111.2 (0.5) (C-12), 117.5 (C-9), 118.5 (C-11), 120.9 (C-10), 126.7 (C-8), 134.3 (0.4) (C-2), 134.4 (0.6) (C-2), 136.0 (0.85) (C-13), 136.2 (0.07) (C-13), 136.3 (0.08) (C-13), 167.1 (0.1) (C-17), 167.6 (0.4) (C-17), 167.8 (0.5) (C-17), 205.0 (0.1) (C-21), 205.3 (0.4) (C-21), 205.3 (0.5) (C-21). – MS (70 eV): *m/z* (%) = 310 (53) [M^+], 309 (6) [M^+ – H], 282 (5) [M^+ – CO], 239 (14) [M^+ – C_4H_7O], 238 (24) [M^+ – C_4H_8O], 237 (100) [M^+ – C_4H_9O], 91 (24). – $C_{19}H_{22}N_2O_2$ (310.4): calcd. C 73.52, H 7.14, N 9.02; found C 73.67, H 7.02, N 8.91.

Fraction 2: *Methyl (2α,3α,12bα)-, (2α,3β,12bα)-, (2β,3α,12bα)- and (2β,3β,12bα)-(±)-2-Ethyl-1,2,3,4,6,7,12,12b-octahydro-4-oxoindolo[2,3-a]quinolizine-2-carboxylate* (**17a–d**): 73 mg, 0.23 mmol, 12% as a white solid. – R_f = 0.24 and 0.12 (1:3) ($CHCl_3$/MeOH, 5:1). – UV (MeOH): λ_{max} (lg ε) = 223 nm (4.50), 273 (3.82), 280 (3.82), 289 (3.75). – IR (KBr): $\tilde{\nu}$ = 3500–3000 cm^{-1} (O–H, acid), 3410 (NH, indole), 1710 (C=O, carboxylic acid), 1625 (N–H^+), 1570 (C=O, COO^-), 750 (C–H, arom.). – ^1H NMR (200 MHz, [D_6]DMSO, 35°C): δ = 0.86 (t, *J* = 7.0 Hz, 2.2H, CH_3), 1.08–3.62 (m, 13.3H), 4.70–5.00 (m, 0.7H, 3-H), 6.92–7.48 (m, 4H, Ph-H), 10.6–11.0 (several s, 1H, NH indole). – MS (70 eV): *m/z* (%) = 312 (86) [M^+], 311 (100) [M^+ – H], 283 (5) [M^+ – C_2H_5], 253 (15) [M^+ – $C_2H_3O_2^+$], 169 (41) [$C_{11}H_{11}N_2^+$]. – $C_{19}H_{22}N_2O_2 \cdot [CHCl_3]_{0.5}$ (349.8): calcd. C 64.70, H 6.78; found C 64.59, H 6.73.

(1′β,2β,12bα)-, (1′α,2β,12bα)-, (1′β,2α,12bα)- and (1′α,2α,12bα)-(±)-2-(1-Formyl-1-propyl)-1,2,3,4,6,7,12,12b-octahydro-4-oxo-N-(p-tolylsulfonyl)-indolo[2,3-a]quinolizine (**16a–d**): The mixture of **11a–d** (300 mg, 0.42 mmol) was stirred with 10% Pd/C (300 mg) in 30 ml MeOH/EtOH (1:1) under hydrogen for 12 h at room temp. The catalyst was then separated by filtration throuh silica gel (MeOH/$CHCl_3$, 1:4) and the solvent was removed in vacuo. The residue was purified by column chromatography (first EtOAc/$CHCl_3$, 1:1, then MeOH/$CHCl_3$, 1:4) to give two fractions: Fraction 1 (R_f = 0.51; EtOAc/$CHCl_3$, 1:1) containing an inseparable mixture of the aldehydes **16a–d** (108 mg, 0.23 mmol, 55%), and Fraction 2, containing an inseparable mixture of the carboxylic acids **18a–d** (24 mg, 0.05 mmol, 12%), both in the form of white foams. – Hydrogenation of the mixture **11e–h** (300 mg, 0.42 mmol) afforded after column chromatography on silica gel (EtOAc/$CHCl_3$, 1:1) a mixture of cycloadducts **16a–d** (104 mg, 0.22 mmol, 53%) as a white foam, and as a second fraction an inseparable mixture of the carboxylic acids **18a–d** (24 mg, 0.05 mmol, 12%), also as a white foam.

Hydrogenation of pure **11h** (200 mg, 0.28 mmol) gave after column chromatography on silica gel (EtOAc/$CHCl_3$, 1:1) *(1′β,2α,12bα)-(±)-2-(1-Formyl-1-propyl)-1,2,3,4,6,7,12,12b-octahydro-4-oxo-N-(p-tolylsulfonyl)indolo[2,3-a]quinolizine* (**16c**) (70 mg, 0.15 mmol, 53%) as a white foam.

Hydrogenation of pure **11g** (200 mg, 0.28 mmol) gave after column chromatography on silica gel (EtOAc/$CHCl_3$, 1:1) *(1′β,2α,12bα)-(±)-2-(1-Formyl-1-propyl)-1,2,3,4,6,7,12,12b-octa-*

hydro-4-oxo-N-(p-tolylsulfonyl)indolo[2,3a]quinolizine (**16d**) (71 mg, 0.15 mmol, 54%) as a white foam.

Fraction 1 (**16a–d**): R_f = 0.51 (EtOAc/$CHCl_3$, 1:1). – UV (CH_3CN): λ_{max} (lg ε) = 246 nm (4.17). – IR (KBr): $\tilde{\nu}$ = 2964 cm^{-1}, 2924, 2876 (CH), 1720, 1646 (C=O). – ^1H NMR (200 MHz, $CDCl_3$): δ = 0.96, 0.97 (2 t, *J* = 7.5 Hz, 3H, 18-H), 1.19–1.86 (m, 4H, 6-H_{ax}, 14-H_{ax}, 19-H), 2.12–2.82 (m, 6H, 5-H_{ax}, 6-H_{eq}, 14-H_{eq}, 15-H, 16-H_{ax}, 20-H), 2.29 (s, 3H, Tos-CH_3), 3.12, 3.19 (2 m_c, 1H, 16-H_{eq}), 4.95–5.21 (m, 2H, 3-H, 5-H_{eq}), 7.08 (d, *J* = 8.0 Hz, 2H, Tos-H), 7.18–7.49 (m, 5H, 9-H, 10-H, 11-H, Tos-H), 8.11 (dd, *J* = 2.0, 7.5 Hz, 1H, 12-H), 9.62–9.80 (4 d, *J* = 3.0 Hz, 1H, 21-H). – ^1H NMR (500 MHz, C_6D_6) of **16c**: δ = 0.71 (t, *J* = 7.0 Hz, 3H, 18-H), 0.90 (ddd, *J* = 11.5, 11.5, 12.0 Hz, 1H, 14-H_{ax}), 1.21–1.38 (m, 3H, 19-H, 14-H_{eq}), 1.52–1.61 (m, 1H, 16-H_{ax}), 1.57 (s, 3H, Tos-CH_3), 1.86 (m_c, 1H, 16-H_{eq}), 2.02–2.11 (m, 1H, 15-H), 2.21–2.34 (m, 2H, 6-H), 2.73 (m_c, 1H, 20-H), 3.09 (m_c, 1H, 5-H_{ax}), 4.82 (m_c, 1H, 5-H_{eq}), 5.25 (dd, *J* = 5.0, 12.0 Hz, 1H, 3-H), 6.45 (d, *J* = 8.0 Hz, 2H, Tos-H), 6.85 (dd, *J* = 1.5, 7.5 Hz, 1H, 9-H), 6.97 (ddd, *J* = 1.5, 7.5, 7.5 Hz, 1H, 10-H), 7.11 (ddd, *J* = 1.5, 7.5, 7.5 Hz, 1H, 11-H), 7.39 (d, *J* = 8.0 Hz, 2H, Tos-H), 8.36 (dd, *J* = 1.5, 7.5 Hz, 1H, 12-H), 9.22 (d, *J* = 2.5 Hz, 1H, 21-H). – ^1H NMR (500 MHz, C_6D_6) of **16d**: δ = 0.65 (t, *J* = 7.5 Hz, 3H, 18-H), 1.03–1.12 (m, 1H, 14-H_{ax}), 1.21–1.38 (m, 3H, 19-H, 14-H_{eq}), 1.56 (s, 3H, Tos-CH_3), 1.60 (m_c, 1H, 16-H_{ax}), 1.85 (m_c, 1H, 16-H_{eq}), 2.03–2.12 (m, 1H, 15-H), 2.22–2.36 (m, 2H, 6-H), 2.53 (m_c, 1H, 20-H), 3.09 (m_c, 1H, 5-H_{ax}), 4.82 (m_c, 1H, 5-H_{eq}), 5.25 (dd, *J* = 5.0, 12.0 Hz, 1H, 3-H), 6.45 (d, *J* = 8.0 Hz, 2H, Tos-H), 6.85 (dd, *J* = 1.5, 7.5 Hz, 1H, 9-H), 6.96 (ddd, *J* = 1.5, 7.5, 7.5 Hz, 1H, 10-H), 7.11 (ddd, *J* = 1.5, 7.5, 7.5 Hz, 1H, 11-H), 7.39 (d, *J* = 8.0 Hz, 2H, Tos-H), 8.36 (dd, *J* = 1.5, 7.5 Hz, 1H, 12-H), 9.26 (d, *J* = 2.5 Hz, 1H, 21-H). – ^{13}C NMR (50 MHz, $CDCl_3$) of **16a–d**: δ = 10.97, 11.03, 11.23, 11.64 (C-18), 18.91, 19.14 (C-19), 21.53 (Tos-CH_3), 21.72, 21.97 (C-6), 30.96, 31.16 (C-15), 35.45, 35.89 (C-14), 36.56 (C-16), 38.71, 38.78 (C-5), 55.82, 56.00 (C-3), 57.27, 57.46 (C-20), 116.4, 116.6 (C-12), 118.8 (C-9), 124.2, 124.3 (C-7), 124.6, 124.8 (C-11), 125.4 (C-10), 126.5 (C-2-Tos), 129.4 (C-3-Tos), 130.5 (C-8), 132.8, 132.9 (C-2), 135.2, 135.3 (C-13), 138.4 (C-4-Tos), 145.0 (C-1-Tos), 167.7, 168.6, 168.7 (C-17), 203.7, 203.8 (C-21). – MS (70 eV): *m/z* (%) = 464 (7) [M^+], 391 (16) [M^+ – C_4H_9O], 309 (100) [M^+ – Tos], 237 (65) [M^+ – Tos – C_4H_8O], 169 (53) [$C_{11}H_9N_2^+$], 143 (17) [$C_{10}H_{10}N^+$], 91 (52) [$C_7H_7^+$]. – $C_{26}H_{28}N_2O_4S$ (464.6): calcd. C 67.22, H 6.07; found C 67.26, H 6.08.

Methyl (2α,3α,12bα)-, (2α,3β,12bα)-, (2β,3α,12bα)- and (2β,3β,12bα)-(±)-3-Ethyl-1,2,3,4,6,7,12,12b-octahydro-4-oxo-N-(p-tolylsulfonyl)indolo[2,3-a]quinolizine-2-carboxylate (**18a–d**): R_f = 0.82 (MeOH/$CHCl_3$, 1:4). – UV (CH_3CN): λ_{max} (lg ε) = 223 nm (4.28), 252 (4.05). – IR (KBr): $\tilde{\nu}$ = 3432 cm^{-1} (br., OH), 2958, 2926, 2872 (CH), 1726 (C=O), 1642 (R_3NH^+), 1598 (C=C). – ^1H NMR (200 MHz, $CDCl_3$/[D_4]methanol): δ = 1.88, 1.94 (2 t, *J* = 7.0 Hz, 3H, 18-H), 1.10–1.64 (m, 3H, 14-H_{ax}, 19-H), 1.98–3.22 (m, 11H, 5-H, 6-H, 14-H_{eq}, 15-H, 16-H, 20-H, 21-H), 2.24 (s, 3H, Tos-CH_3), 4.20–4.33 (m, 1H, 3-H), 6.98–7.67 (m, Tos-H, 9-H, 10-H, 11-H), 7.94–8.16 (m, 1H, 12-H). – MS (70 eV): *m/z* (%) = 466 (3) [M^+], 311 (100) [M^+ – Tos], 251 (4) [M^+ – Tos – $C_2H_3O_2$], 169 (50) [$C_{11}H_9N_2^+$], 143 (2) [$C_{10}H_{10}N^+$], 91 (70) [$C_7H_7^+$], 44 (94) [CO_2^+]. – $C_{26}H_{28}N_2O_4S$: calcd. 466.19263; found 466.19263 (MS).

Reduction of the Formyllactams **15** *and* **16** *with Lithium Aluminium Hydride:* A solution of **15a–d** (311 mg, 1.00 mmol) in 5 ml THF was added dropwise under nitrogen to a vigorously stirred suspension of lithium aluminium hydride (846 mg, 21.4 mmol) in 10 ml of dry THF at –50 °C. The rection mixture was allowed to warm to room temp. over a period of 4 h and then refluxed for 3 h. After cooling to 0 °C, the reaction was quenched by the dropwise addition of water (10 ml), aqueous NaOH (10 ml, 15%), water (25 ml) and THF (40 ml). The mixture was stirred for an additional 30 min, and the precipitate formed was filtered off and washed with THF (20 ml). The combined filtrate and washings were concentrated in vacuo and the remaining oil was purified by chromatography on deactivated neutral alumina (first EtOAc, then EtOAc/MeOH, 20:1) to afford two fractions:

Fraction 1: *(2β,2'α,12b'α)-(±)-2-(1,2,3,4,6,7,12,12b-Octahydroindolo[2,3-a]quinolizin-2-yl)butan-1-ol (15-epi-18,19-Dihydroantirhine,* **4c***) and (2α,2'α,12b'α)-(±)-2-(1,2,3,4,6,7,12,12b-Octahydroindolo[2,3-a]quinolizin-2-yl)butan-1-ol (15,20-epi-18,19-Dihydroantirhine,* **4d***)*: 62 mg, 0.21 mmol, 21% as a yellow solid. – R_f = 0.39 (MeOH/EtOAc, 1:4). – UV (CH_3CN): λ_{max} (lg ε) = 225 nm (4.54), 282 (3.86), 290 (3.76). – IR (KBr): $\tilde{\nu}$ = 3420 cm^{-1}, 3264 (NH, OH), 2956, 2918, 2854 (CH), 2816, 2756 (Bohlmann peaks), 1628 (C=C), 736 (CH–Ph). – ^1H NMR (200 MHz, $CDCl_3$/[D_4]methanol): δ = 0.95, 0.96 (2 t, *J* = 7.0 Hz, 3H, 18-H), 1.21–1.94 (m, 7H, 14-H, 15-H, 16-H, 19-H), 2.21–3.21 (m, 7H, 5-H, 6-H, 17-H, 20-H), 3.29–3.44 (m, 1H, 3-H), 3.37–3.72 (m, 2H, 21-H), 7.05 (ddd, *J* = 1.5, 7.0, 7.0 Hz, 1H, 10-H), 7.12 (ddd, *J* = 1.5, 7.0, 7.0 Hz, 1H, 11-H), 7.34 (dd, *J* = 1.5, 7.0 Hz, 1H, 9-H), 7.45 (dd, *J* = 1.5, 7.0 Hz, 1H, 12-H). – MS (70 eV): *m/z* (%) = 298 (90) [M^+], 297 (100) [M^+ – H], 267 (5) [M^+ – CH_3O], 225 (47) [M^+ – C_4H_9O]. – $C_{19}H_{26}N_2O$: calcd. 298.20451; found 298.20451 (MS).

Fraction 2: *(2β,2'β,12b'α)-(±)-2-(1,2,3,4,6,7,12,12b-Octahydroindolo[2,3-a]quinolizin-2-yl)butan-1-ol (18,19-Dihydroantirhine,* **4a***) and (2α,2'β,12b'α)-(±)-2-(1,2,3,4,6,7,12,12b-Octahydroindolo[2,3-a]quinolizine-2-yl)butan-1-ol (20-epi-18,19-Dihydroantirhine,* **4b***)*: 194 mg, 0.65 mmol, 65% as a yellow foam. – R_f = 0.12 (MeOH/EtOAc, 1:4). – UV (MeOH): λ_{max} (lg ε) = 225 nm (4.42), 282 (3.788), 289 (3.72). – IR (KBr): $\tilde{\nu}$ = 3420 cm^{-1}, 3280 (NH, OH), 2928, 2854 (CH), 1624, 1576 (C=C), 740 (CH–Ph). – ^1H NMR (200 MHz, $CDCl_3$/[D_4]methanol): δ = 0.93, 0.94 (2 t, *J* = 7.0 Hz, 3H, 18-H), 1.21–1.99 (m, 7H, 14-H, 15-H, 19-H), 2.12–3.32 (m, 7H, 5-H, 6-H, 17-H, 20-H), 3.57–3.73 (m, 2H, 21-H), 4.21–4.36 (m, 1H, 3-H), 7.04 (ddd, *J* = 1.5, 7.0, 7.0 Hz, 1H, 10-H), 7.12 (ddd, *J* = 1.5, 7.0, 7.0 Hz, 1H, 11-H), 7.32–7.54 (m, 2H, 9-H, 12-H). – MS (70 eV): *m/z* (%) = 298 (90) [M^+], 297 (100) [M^+ – H], 267 (5) [M^+ – CH_3O], 225 (47) [M^+ – C_4H_9O]. – $C_{19}H_{26}N_2O$ calcd. 298.20451; found 298.20451 (MS).

A solution of **16a–d** (100 mg, 0.22 mmol) in 10 ml of THF was added dropwise under nitrogen to a vigorously stirred suspension of lithium aluminium hydride (250 mg, 6.58 mmol) in 20 ml of dry THF at –50 °C. The reaction mixture was allowed to warm to room temp. over a period of 4 h and then refluxed for 3 h. After cooling to 0 °C, the reaction was quenched by the dropwise addition of 30 ml of aqueous THF (containing 20% water) and the mixture was refluxed for 15 min. The precipitate thus produced was filtered off and washed with THF (20 ml), and then refluxed with THF (50 ml). The combined filtrates were concentrated in vacuo, and the residue was dissolved in $CHCl_3$, washed with 30 ml of satd. aqueous NaCl solution and dried with Na_2SO_4. The solvents were removed in vacuo and the remaining oil was purified by chromatography on silica gel (EtOAc/MeOH, 4:1) to afford two fractions.

Fraction 1: *15-epi-18,19-Dihydroantirhine* (**4c**) and *15,20-epi-18,19-Dihydroantirhine* (**4d**) (44 mg, 0.15 mmol, 68%) as a yellow solid.

Fraction 2: *18,19-Dihydroantirhine* (**4a**) and *20-epi-18,19-Dihydroantirhine* (**4b**) (6.3 mg, 0.02 mmol, 10%) as a yellow foam.

Using the same procedure, pure **16c** and **16d** (10 mg, 0.022 mmol of each) were reduced with $LiAlH_4$ to yield pure **4c** and **4d**, respectively.

15-epi-18,19-Dihydroantirhine (**4c**): ^{1}H NMR (500 MHz, $CDCl_3$/[D_4]methanol): δ = 0.95 (t, *J* = 7.0 Hz, 3H, 18-H), 1.25–1.51 (m, 4H, 19-H, 14-H), 1.61–1.73 (m, 2H, 16-H), 1.84 (m_c, 1H, 15-H), 2.25 (m_c, 1H, 20-H), 2.51 (ddd, *J* = 11.5, 11.5, 3.5 Hz, 1H, 17-H_{ax}), 2.70 (ddd, *J* = 11.5, 11.5, 4.5 Hz, 1H, 5-H_{ax}), 2.80 (m_c, 1H, 6-H_{ax}), 3.04 (m_c, 1H, 6-H_{eq}), 3.10–3.18 (m, 2H, 5-H_{eq}, 17-H_{eq}), 3.38 (m_c, 1H, 3-H), 3.60–3.64 (m, 2H, 21-H), 7.05 (dt, *J* = 7.0, 1.5 Hz, 1H, 10-H), 7.12 (dt, *J* = 7.0, 1.5 Hz, 1H, 11-H), 7.34 (dd, *J* = 7.0, 1.5 Hz, 1H, 9-H), 7.45 (dd, *J* = 7.0, 1.5 Hz, 1H, 12-H).

15,20-epi-18,19-Dihydroantirhine (**4d**): ^{1}H NMR (500 MHz, $CDCl_3$/[D_4]methanol): δ = 0.94 (t, *J* = 7.0 Hz, 3H, 18-H), 1.26–1.82 (m, 7H, 19-H, 14-H, 16-H, 15-H), 2.30 (m_c, 1H, 20-H), 2.47 (ddd, *J* = 11.5, 11.5, 3.5 Hz, 1H, 17-H_{ax}), 2.65 (ddd, *J* = 11.5, 11.5, 4.5 Hz, 1H, 5-H_{ax}), 2.78 (m_c, 1H, 6-H_{ax}), 3.02 (m_c, 1H, 6-H_{eq}), 3.07–3.15 (m, 2H, 5-H_{eq}, 17-H_{eq}), 3.32 (m_c, 1H, 3-H), 3.63 (dd, *J* = 11.0, 5.0 Hz, 1H, 21-H), 3.68 (dd, *J* = 11.0, 4.0 Hz, 1H, 21-H), 7.05 (dt, *J* = 7.0, 1.5 Hz, 1H, 10-H), 7.12 (dt, *J* = 7.0, 1.5 Hz, 1H, 11-H), 7.34 (dd, *J* = 7.0, 1.5 Hz, 1H, 9-H), 7.45 (dd, *J* = 7.0, 1.5 Hz, 1H, 12-H).

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