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The synthesis of two diastereomeric *seco*-rhazinilams with opposite atropomeric chiralities

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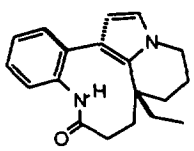
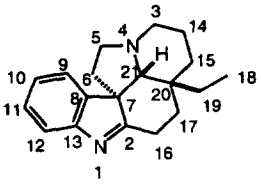
Abstract: (−)-Tabersonine **4** was submitted to quaternization and Emde degradation to yield the 3,4-*seco* derivative **5**, which was hydrolyzed and decarboxylated to the diastereomeric indolenines **8** and **9**. Oxidative rearrangement of **8** and **9** yielded the two diastereomeric *seco*-rhazinilams (−)-**10** and (+)-**11**, differing in the atropomeric conformations of their biarylic system. The results are discussed in the realm of oxidation and rearrangements in the *aspidosperma* series of indole alkaloids. © 1997 Elsevier Science Ltd. All rights reserved.

Introduction

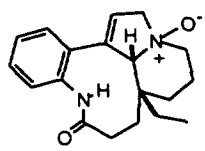
(−)-Rhazinilam (−)-**1**, a compound found in extracts of *Rhazia stricta*[1,2] and other species[3–5] has been shown to interact with tubuline, and to inhibit the growth of cultured KB, L1210 and P388 cells.[5,6] Whether or not an artefact,[2] rhazinilam is thought[7] to originate from the oxidation of (+)-1,2-dehydroaspidospermidine (+)-**2**, resulting in the cleavage of the 2,7-bond.[8]



(-)-**1**: (-)-rhazinilam



(+)-**2**: (+)-1,2-dehydro-aspidospermidine



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As indicated by the lack of conjugation[2] and further confirmed by X-ray analysis[9] the benzene and pyrrole rings are not coplanar in (−)-**1**.

A total synthesis of (±)-rhazinilam and a partial synthesis of (−)-**1** from (+)-**2** have been performed by G. F. Smith *et al.*[7] In their original paper the authors briefly report that the *m*-chloroperbenzoic acid (*m*-CPBA) oxidation of (+)-**2**, followed by treatment with aqueous iron sulfate gave (−)-**1** with 30% yield. Later on,[10] G. F. Smith isolated intermediate **3** after the oxidation step, and showed it to thermally rearrange to (−)-**1**. More recently, the synthesis of a series of tricyclic analogs of rhazinilam was reported by Thal *et al.*[11,12]

Results and discussion

Development of Smith's partial synthesis enabled us[13] to prepare (−)-**1** from (+)-**2** (and (+)-**1** from (−)-**2**) with a *ca* 50% yield, along with the isolation of **3**. This oxidative fragmentation was then applied to a hemisynthetic 3,14-*seco*-1,2-dehydroaspidospermidine with a view to preparing the two possible atropomeric tricyclic analogs of rhazinilam.

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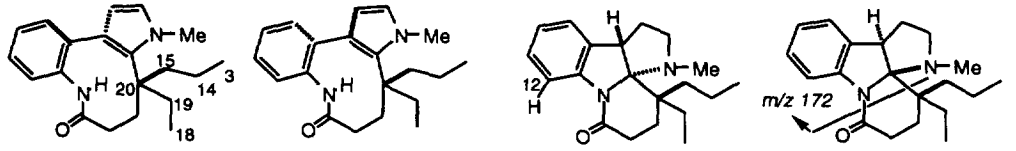
(−)-Tabersonine **4**[14] (whose configuration of the skeleton is enantiomeric with that of (+)-1,2-dehydroaspidospermidine (+)-**2** was submitted to an Emde degradation sequence used by Karrer[15] in the course of the structure elucidation of curare alkaloids: quaternization of tabersonine with methyl iodide was unusually difficult,[16] due to the bowl shape of the molecule inducing severe crowding around N-4, but it was made quantitative upon prolonged heating in a sealed tube. Catalytic hydrogenation of the methoiodide yielded (−)-4-methyl-3,4-*seco*-14,15-dihydrotabersonine **5**, which was further hydrolyzed and decarboxylated through refluxing in 2 M aqueous HCl. The ^{1}H NMR spectrum of the resulting product (87%) clearly demonstrated formation of the two diastereomeric indolenines **8** and **9** (1:1), which could not be separated: the N–Me group gave two singlets at 2.58 and 2.60 ppm, and the 3- and 18- methyl groups gave triplets at 0.64, 0.67, 0.84 and 0.94 ppm. The two upfield signals are ascribed to the 18-methyl group in **8** and to the 3-methyl in **9**, suffering the anisotropic effect of the benzene ring. Formation of **9** obviously results from the classical[17] reversible Grob's fragmentation of **8**. The initially formed nine-membered iminium **6** (with C-21 below the plane of indole) is however conformationally restricted, so that a further addition–elimination[18] of water onto/from C-21 is suspected to account for equilibration with its conformer having C-21 over the plane of indole, that finally generates **9**. Intervention of the basic N-4 in the equilibration was illustrated by hydrolysis and decarboxylation of the N-oxide of **5**, yielding N-oxide **7** with complete retention of the configuration.

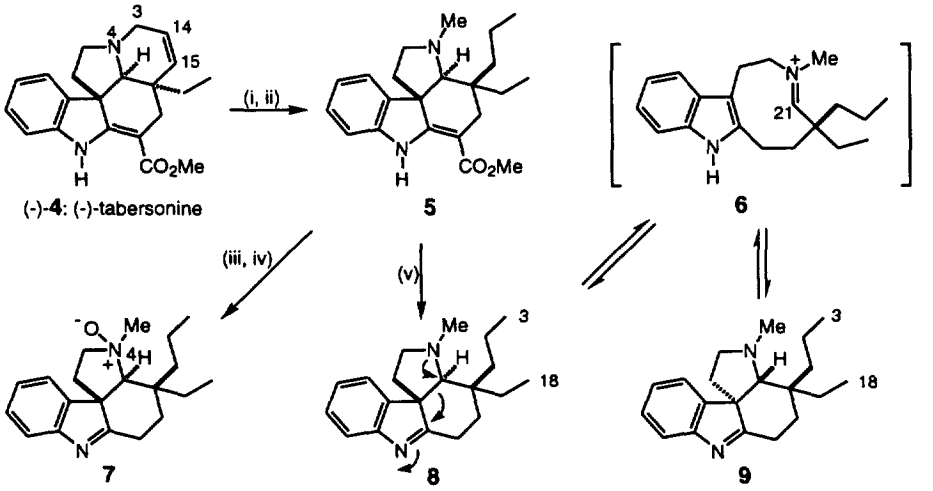


The equimolar mixture of indolenines **8** and **9** was submitted to *m*-CPBA oxidation, separation from *m*-CBA, and further thermolysis. An initial chromatography allowed separation of two couples of diastereomers, namely *seco*-rhazinilams (−)-**10** and (+)-**11** on one hand (31%, 1:1) and N-acylindolines **12** and **13** (28% 1:1) on the other. While the two N-acylindolines could not be separated, each of the two *seco*-rhazinilams was further isolated upon careful TLC. Isolation of a dextrorotatory isomer (less polar, $[\alpha]_D$ +179, $CHCl_3$) and of a levorotatory one (more polar, $[\alpha]_D$ −105, $CHCl_3$) then demonstrates the atropomeric chirality due to the biarylic system of the *seco*-rhazinilams. The ^{1}H NMR spectra ($CDCl_3$, 20°C) of (−)-**10** and of (+)-**11** were poorly resolved, probably because of the flexibility of the nine-membered lactam ring resulting in the occurence of several conformers at room temperature. However, distinct (broad) methyl signals were seen at 0.57 and 0.98 ppm for the dextrorotatory isomer, and at 0.70 and 0.90 ppm for the levorotatory isomer, disclosing a similar ring current effect as in the starting indolenines. Measuring the spectra at 80°C (DMSO-d_6) resulted in a complete equilibration to an equimolar mixture of (−)-**10** and (+)-**11**, but the signals were then well resolved with the methyls as sharp triplets centered at 0.46, 0.65, 0.89 and 0.97 ppm, respectively. A ^{1}H–^{1}H COSY experiment allowed determination of the vicinal methylenes of each methyl in the mixture, either as a non further coupled methylene (i.e. CH_2-19) or as a methylene further coupled with another one (i.e. CH_2-14, coupled with CH_2-15). Assuming that the order of chemical shifts had not suffered inversions from $CHCl_3$ (20°C) to DMSO-d_6(80°C), examination of molecular models then allows attribution of the depicted configurations for (−)-**10** and (+)-**11**, respectively. It may be pointed out that (−)-**10** is then ascribed the same (aR) configuration of the biarylic system as in (−)-rhazinilam (−)-**1**, thus confirming the assumption that the contribution of the biarylic system in the rotation should be predominant over that of the asymetric C-20 both in the tetracyclic and tricyclic series. Of interest is the fact that, although (−)-tabersonine **4** belongs to the enantiomeric series of (−)-1,2-dehydroaspidospermidine (namely the precursor of the biologically inactive (+)-rhazinilam (+)-**1** it gave rise to the *seco*-rhazinilam (−)-**10** in the enantiomeric series of the biologically active (−)-**1**.[19]

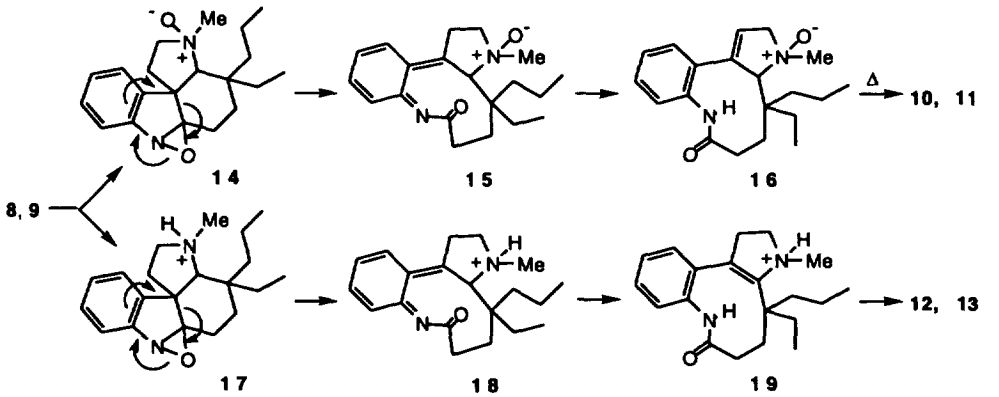
The ^{13}C NMR spectrum of the mixture of (−)-**10** and (+)-**11** (DMSO-d_6 (80°C)) was fully consistent with the structures (see experimental), as compared with literature values for rhazilinam.[4b,20]

The structures of N-acylindolines **12** and **13** rest on their characteristic UV spectrum, on their mass spectral fragmentation (base peak at m/z 172, see formula (**13**) and on the deshielding of H-12 to *ca* 8.5 ppm by the neighbouring C=O on the ^1H NMR spectrum.

As expected from the above equilibration experiment, an attempt at preparing (+)-**11** in pure diastereomeric form through oxidation and further thermolysis of the optically active indolenine N-oxide **7** (Scheme 1) was fruitless and yielded (16%) an equimolar mixture of (−)-**10** and (+)-**11**. Interestingly enough, no N-acylindolines **12** and **13** were then found in the reaction mixture. This observation is taken into account for suggesting a plausible reaction path from the starting indolenines **8** and **9** to **10–13** (Scheme 2).



Scheme 1. Reagents and conditions: (i) MeI, $CHCl_3$, sealed tube, 40°C, 36 h (100%); (ii) EtOH, PtO_2 15%, Na_2CO_3, H_2, 16 h (78%); (iii) CH_2Cl_2, *m*-CPBA 1.1 eq. 1 h (98%); (iv) 2M HCl, Δ 20 min., Ar, (70%); (v) 2 M HCl, Δ 20 min., Ar (**8**+**9**=87%).

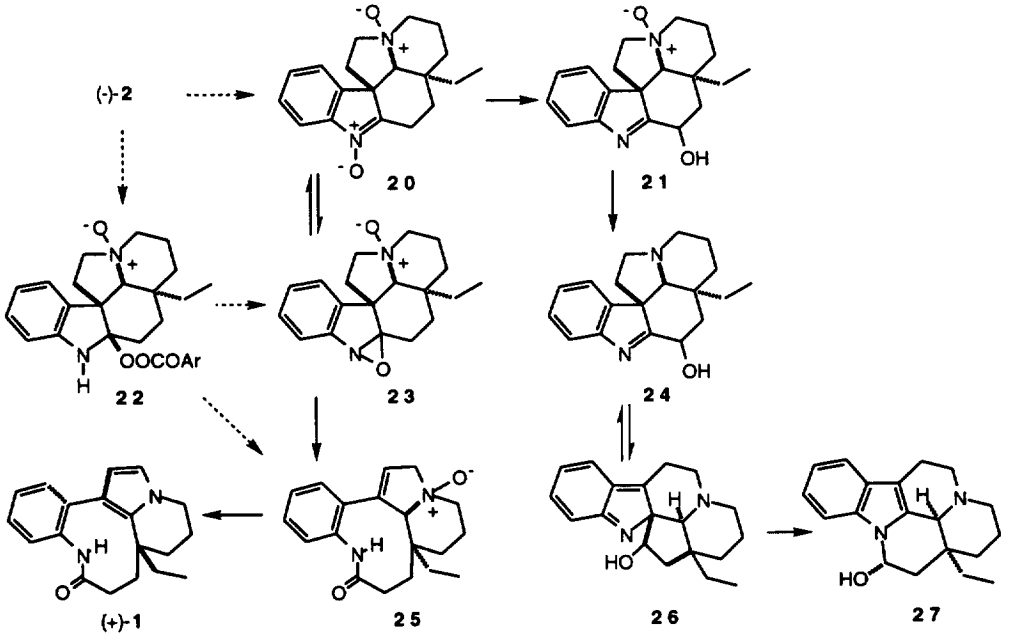


Scheme 2.

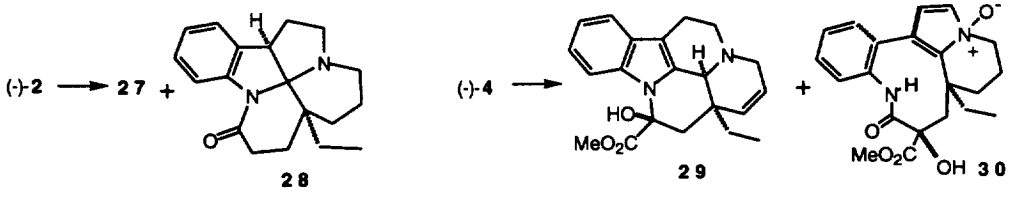
Scheme 2 is based on a study of similar reactions of 2,3,3-trimethylindolenine by Lusinchi.[21] Peracid oxidation of indolenines **8** and **9** would yield oxaziridine N-oxide **14**, thermally rearranging to **16** *via* **15** during evaporation of the solvent before the thermolysis of **16**, that yields *seco*-rhazinilams **10** and **11**. Due to formation of more acidic *m*-chlorobenzoic acid in the reaction, part of indolenines **8** and

9 is being N-4 protonated, yielding oxaziridine **17**, which escapes N-4 oxidation, and leads to **12** and **13** *via* **18** and **19**.

Finally, the above oxidative rearrangements of indolenines shed some light on our previous *aspidosperma* to *vinca* rearrangements, as illustrated (Scheme 3) in the case of (−)-1,2-dehydroaspidospermidine (−)-**2**. We had indeed shown[22] that oxidation of (−)-**2** with 2 eq of *m*-CPBA for 24 h in benzene at rt, yields the isolated and characterized 16-hydroxyindolenine N-oxide **21**, whose further chemoselective reduction (Ph_3P, AcOH) and rearrangement yields vincanol **27** *via* **24** and **26**. A shorter treatment of (−)-**2** with *m*-CPBA (in CH_2Cl_2 at 0°C), followed by thermolysis yields (+)-rhazilinam (+)-**1** as stated previously. It is then thought that, apart from the formation of the N4-oxide, the indolenine imine is first oxidized to an imine oxide **20**, immediately equilibrating with the oxaziridine precursor **23** leading to (+)-**1** *via* **25**, while prolonged standing at rt allows isomerization of the imine oxide to the 16-hydroxyindolenine **21**, namely the precursor of the vincanol (perester **22** might also be considered as a precursor of **23**, and even of **25**[23]). In agreement with the occurence of the two competitive pathways, compounds **28** and **30**, related with rhazinilam (and with leuconolam[24]), had been isolated as by-products in the oxidative rearrangements of (−)-**2** to **27**,[25] and of tabersonine (−)-**4** to 14,15-dehydrovincamine **29**,[26] respectively (Scheme 4).



Scheme 3.



Scheme 4.

Experimental

Optical rotations were measured at 20°C on a Perkin–Elmer PE 241 polarimeter. UV spectra were recorded on a Varian 634 spectrometer. IR spectra were obtained on a Beckman Acculab 4 spectrometer. NMR spectra were recorded at 300 MHz (^{1}H) and 75 MHz (^{13}C) on a Bruker AC300 spectrometer with TMS as internal reference. Mass spectra were measured on a Jeol JMS D 300 spectrometer.

*(−)-4-Methyl-3,4-*seco*-14,15-dihydrotabersonine* **5**

Tabersonine methoiodide was prepared by heating a solution of **4** in $CHCl_3$ added with 2 eq of methyl iodide in a sealed tube at 40°C for 36 h followed by evaporation of the solvent (100%): UV (MeOH) 330, 296, 224 nm; IR (film) 3350, 1680, 1610 cm^{-1}; ^{1}H NMR ($CDCl_3$) 9.15 (s, H-1), 7.55–6.90 (m, Ar), 6.38 (m, H-15), 6.25 (m, H-14), 4.95–480 (m, 2H-3), 4.35–4.10 (m, 2H-5), 3.80 (s, 3H-23), 3.78 (s, N–C*H*$_3$), 3.55 (s, H-21), 2.78 (d, J=15.5 Hz, H$_a$-17), 2.78–2.62 (m, H$_a$-6), 2.28 (d, J=15.5 Hz, H$_b$-17), 2.25–2.05 (m, H$_b$-6), 1.22 (q, J=7.5 Hz, 2H-19), 0.78 (t, J=7.5 Hz, 3H-18).

A solution of tabersonine methoiodide (350 mg, 0.71 mmol) in EtOH (10 ml) was hydrogenated in the presence of PtO_2 (53 mg) and Na_2CO_3 (17.5 mg) under atmospheric pressure for 16 h. After filtration through celite, the solvent was evaporated. Purification by preparative TLC (CH_2Cl_2:MeOH 99:1) afforded **5** (202 mg; 78%): $[\alpha]_D$ −438 ($CHCl_3$, c 0.72); UV (MeOH) 330, 303, 225 nm; IR (film) 3400, 1680, 1610 cm^{-1}; ^{1}H NMR ($CDCl_3$) 8.92 (s, H-1), 7.16 (t, J=7 Hz, H-11), 7.12 (d, J=7 Hz, H-9), 6.88 (t, J=7 Hz, H-10), 6.82 (d, J=7 Hz, H-12), 3.76 (s, 3H-23), 3.20–3.06 (m, H$_a$-5), 2.80–2.66 (m, H$_b$-5), 2.60 (s, N–C*H*$_3$, H-21), 2.40 (d, J=15.5 Hz, H$_a$-17), 2.16 (d, J=15.5 Hz, H$_b$-17), 2.12–1.97 (m, H$_a$-6), 1.68–1.20 (m, H$_b$-6, 2H-14, 2H-15), 0.95 (t, J=7.5 Hz, 3H-3), 0.90–0.70 (m, 2H-19), 0.58 (t, J=7.5 Hz, 3H-18); ^{13}C NMR ($CDCl_3$) 168.9 (C-22), 166.0 (C-2), 142.9 (C-13), 137.6 (C-8), 127.7 (C-11), 122.3 (C-9), 120.2 (C-10), 109.1 (C-12), 90.1 (C-16), 75.6 (C-21), 58.2 (C-7), 55.3 (C-5), 50.7 (C-23), 44.0 (N–*C*H$_3$), 42.4 (C-20), 42.1 (C-6), 34.9, 28.4, 26.0, 17.6 (C-14, C-15, C-17, C-19), 14.7 (C-3), 7.1 (C-18); EIMS 354 (15, M$^+$), 256 (8.5), 214 (5), 185 (5), 168 (5), 167 (5), 154 (5), 140 (100); HRMS calcd for $C_{22}H_{30}N_2O_2$ 354.2306, found 354.2199.

*4-Methyl-3,4-*seco*-1,2-dehydroaspidospermidines* **8** *and* **9**

A solution of **5** (200 mg, 0.56 mmol) in 2 M HCl (4 ml) was refluxed under argon. After 20 min, the solution was cooled, basified with NH_4OH and extracted with CH_2Cl_2. The organic layer was dried and evaporated under reduced pressure to give a residue which was purified by preparative TLC (CH_2Cl_2:MeOH 99:1), yielding a 50:50 mixture of diastereomeric compounds **8** and **9** (145 mg; 86%): $[\alpha]_D$ −1.4 ($CHCl_3$, c 1.0); UV (MeOH) 260, 220 nm; IR (film) 1580 cm^{-1}; ^{1}H NMR ($CDCl_3$) 7.60–7.10 (m, Ar), 3.35 (m, H-5), 2.70 (s, H-21), 2.60, 2.58 (2×s, N–C*H*$_3$), 0.94, 0.84, 0.67, 0.64 (4×t, J=7.5 Hz, 3H-14, 3H-18); ^{13}C NMR ($CDCl_3$) 189.4 (C-2), 154.4 (C-13), 147.1 (C-8), 127.5, 124.7, 121.4, 119.9 (C-9, C-10, C-11, C-12), 77.2, 77.0 (C-21), 64.1 (C-7), 57.4 (C-5), 44.6, 44.5 (N–*C*H$_3$), 41.5 (C-20), 35.7, 35.4, 34.1, 26.8, 26.7, 25.9, 24.7, 24.6, 16.9, 16.1 (C-6, C-14, C-15, C-16, C-17, C-19), 14.6, 8.6, 7.4 (C-3, C-18); EIMS 296 (20, M$^+$) 253 (10), 239 (10), 198 (100), 183 (20), 157 (20).

seco*-Rhazinilams* **10** *and* **11** *and N-acylindolines* **12** *and* **13**

A solution of **8** and **9** (150 mg, 0.54 mmol) in CH_2Cl_2 (6 ml) at 0°C was treated with *m*-CPBA (290 mg, 1.7 mmol). The mixture was stirred at 0°C for 1 h. The solvent was evaporated and the crude product was rapidly purified by preparative TLC (CH_2Cl_2:MeOH 95:5), in order to remove perbenzoic and benzoic acids. The residue was then dissolved in toluene and the mixture refluxed for 1 h. Evaporation of the solvent and purification of the residue (preparative TLC, CH_2Cl_2:MeOH 99:1) gave two pairs of diastereomeric compounds **10** and **11** (65 mg, 31%, R_F 0.45) and **12** and **13** (40 mg, 26%, R_F 0.83).

10$^{I)}$, **11**$^{II)}$: UV (MeOH) 270 (sh), 220 (sh), 206 nm; IR (film) 3200, 1645 cm^{-1}; ^{1}H NMR (DMSO-d$_6$, 80°C) 8.10 (br s, H-1), 7.35–7.10 (m, Ar), 6.55 (m, H-5), 5.56 (d, J=4 Hz, H-6), 3.68 (2×s, N–C*H*$_3$),

0.97 (t, J=7.5 Hz, 3H-3^{II}), 0.89 (t, J=7.5 Hz, 3H-18^{I}), 0.65 (t, J=7.5 Hz, 3H-3^{I}), 0.46 (t, J=7.5 Hz, 3H-18^{II}); ^{13}C NMR (DMSO-d_6) 173.3 (C-2), 141.3 (C-13), 137.5 (C-21), 132.7 (C-8), 129.9 (C-11), 126.9 (C-9, C-10), 126.6 (C-12), 123.8 (C-5), 121.0 (C-7), 108.8 (C-6), 42.9, 42.7 (C-$20^{I,II}$), 38.2, 38.1 (N–$CH_3^{I,II}$), 37.1, 33.3, 27.2, 16.1, 16.0 (C-14, C-15, C-16, C-17, C-19), 14.4, 13.9 (C-$3^{I,II}$), 7.7 (C-$18^{I;II}$); EIMS 310 (15, M^+), 281 (30), 267 (40), 167 (35), 149 (100).

Separation of **10** and **11** by new preparative TLC (AcOEt:Hexane:MeOH 70:29:1) yielded **10** (50%, R_F 0.46): $[\alpha]_D$ −105.0 ($CHCl_3$, c 0.82); ^{1}H NMR ($CDCl_3$) 7.40–7.15 (m, Ar), 6.46 (d, J=4 Hz, H-5), 6.30 (br s, H-1), 5.66 (d, J=4 Hz, H-6), 3.70 (s, N–CH_3), 0.90 (br s, 3H-18), 0.70 (br s 3H-3); HRMS calcd for $C_{20}H_{26}ON_2$ 310.2044, found 310.2079 and **11** (50%, R_F 0.54): $[\alpha]_D$ +178.8 ($CHCl_3$, c 0.65); ^{1}H NMR ($CDCl_3$) 7.50–7.10 (m, Ar), 6.48 (d, J=4 Hz, H-5), 6.26 (br s, H-1), 5.65 (d, J=4 Hz, H-6), 3.72 (s, N–CH_3), 0.98 (br s, 3H-3), 0.57 (br s, 3H-18); HRMS calcd for $C_{20}H_{26}ON_2$ 310.2044, found 310.2014.

12, 13: UV (MeOH) 288, 275 (sh), 254, 210 nm; IR (film) 1653 cm^{-1}; ^{1}H NMR ($CDCl_3$) 8.52–8.24 (m, H-12), 7.30–7.00 (m, H-9, H-10, H-11), 4.00–3.92 (m, H-7), 3.12–3.00 (m, H-5), 2.30 (2×s, N–CH_3), 1.05–0.73 (m, 3H-3, 3H-18); EIMS 312 (10, M^+), 269 (25), 240 (19), 226 (17), 214 (42), 172 (100), 130 (12).

N-oxide 7

A solution of **5** (300 mg, 0.85 mmol) in CH_2Cl_2 (5 ml) was treated with *m*-CPBA (160 mg, 0.94 mmol). The mixture was stirred at 0°C for 1 h. After evaporation of the solvent, the residue was purified by preparative TLC (CH_2Cl_2:MeOH 95:5) yielding **7** (301 mg, 96%): $[\alpha]_D$ −164.0 (MeOH, c 0.54); UV (MeOH) 260, 219 nm; IR (film) 1710, 1591 cm^{-1}; ^{1}H NMR ($CDCl_3$) 7.71–7.20 (m, Ar), 4.23 (m, 2H-5), 3.98 (s, H-21), 3.85 (s, N–CH_3), 1.30 (m, 2H-14), 0.97 (t, J=7.5 Hz, 3H-3), 0.73 (m, 2H-19), 0.46 (t, J=7.5 Hz, 3H-18).

Acknowledgements

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