

(*endo, endo*)-9-Benzyl-9-azabicyclo[3.3.1]nonane-2,6-diol: An Intermediate for the Preparation of Indole Alkaloids of the Macroline/Sarpagine Series

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Abstract: Two intermediates **9b** and **9c** already used by Cook and Magnus in their syntheses of indole alkaloids were obtained from the title compound **1** through a Fischer indolization procedure. Related tetracyclic intermediates **6** and **8** were also prepared: **6** having substituents at position 2 or 4 were directly obtained, while **8** with substituents at position 1 or 3 were selectively obtained through a convenient protection-deprotection scheme

Key words: bicyclic compounds, indoles, natural products, macroline/sarpagine alkaloids, Fischer indolization, heterocycles

Many indole alkaloids possess the basic tetracyclic skeleton¹ (Figure) with eventually substituents such as a methyl group on nitrogen 5 or 12 and/or hydroxy or methoxy groups on carbon 1, 2, 3 or 4. Alkaloids having this skeleton have been generally prepared from tryptophane derivatives using a Pictet–Spengler² reaction. A 9-azabicyclo[3.3.1]nonanone³ has also been used during an attempted synthesis of ajmaline⁴ through a Fischer indole synthesis. However, due to the choice of a phenylcarbamate as protective group on nitrogen 12, it was not possible to introduce the desired substituents on carbon 8.

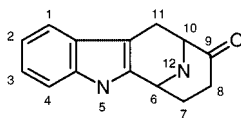
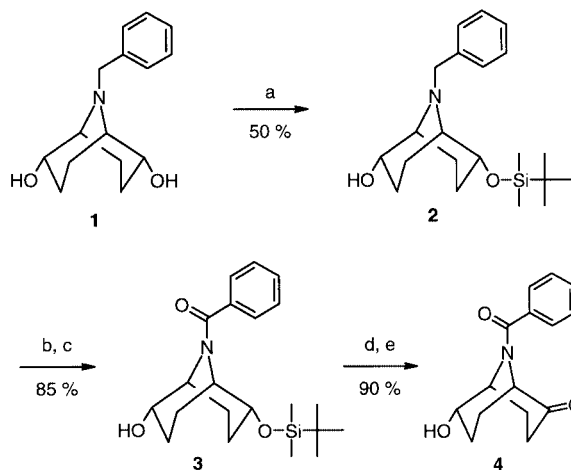


Figure Basic tetracyclic skeleton of indole alkaloids

Because (*endo,endo*)-9-benzyl-9-azabicyclo[3.3.1]nonane-2,6-diol (**1**) was easily available,⁵ we decided to re-investigate this strategy and to extend it to alkaloids having substituents on the indole nucleus. For this purpose, it was first necessary to prepare ketone **4** (Scheme 1). Diol **1** was monoprotected by *tert*-butyldimethylsilyl, and *N*-benzyl was replaced by the *N*-benzoyl group⁶ to give alcohol **3**. Ketone **4** was obtained in 37% yield from **1** after Swern oxidation followed by removal of the silyl protecting group.⁷

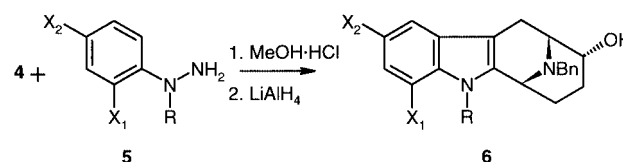
Ketone **4** was then reacted with substituted phenylhydrazines in refluxing HCl-saturated methanol (Scheme 2, Table). The corresponding derivatives **6** were easily obtained from 1-alkyl,1-phenylhydrazine (i.e. **5b** and **5c**) and from *para*- (i.e. **5g** and **5h**) and *ortho*- (i.e. **5d** and **5e**) substituted phenylhydrazines, except from *p*-methoxyphenylhydrazine (**5f**), where as expected, an abnormal



Reagents and conditions: (a) TBDMSCl/DMAP/Et₃N/CH₂Cl₂; (b) H₂/10% Pd-C MeOH; (c) BzCl/K₂CO₃/acetone; (d) Swern oxidation; (e) HF/MeCN

Scheme 1

Fischer indolization⁸ occurred. We did not investigate the use of the methods developed to overcome this problem.⁹



Scheme 2

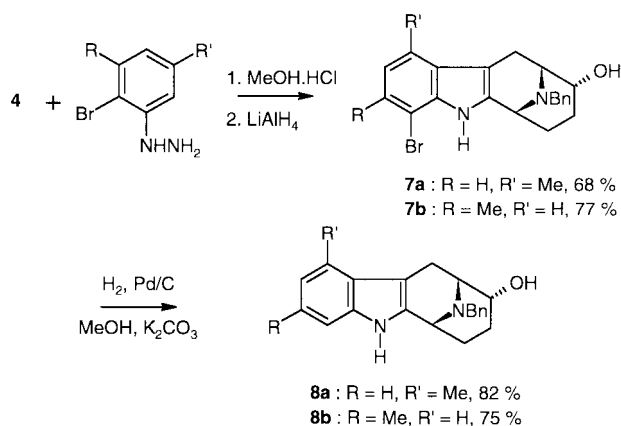
Table Indoles **6** Prepared

Phenylhydrazine	R	X ₁	X ₂	Product	Yield (%) ^a
5a	H	H	H	6a	94
5b	Me	H	H	6b	95
5c	Bn	H	H	6c	92
5d	H	Me	H	6d	83
5e	H	Br	H	6e	58
5f	H	OMe	H	6f	— ^b
5g	H	H	Me	6g	93
5h	H	H	OMe	6h	71

^a Isolated yield of purified product.

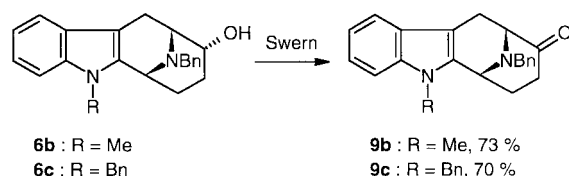
^b A mixture of several products was obtained and was not further investigated.

Reaction with *meta*-substituted phenylhydrazines obviously should lead to a mixture of 1- and 3-substituted molecules: for instance, with *m*-tolylhydrazine we obtained a 1:1 mixture of **8a** and **8b**. In order to make this reaction regioselective, we have used a temporary substitution by bromine at one *ortho*-position. After Fischer indolization and hydrogenolysis¹⁰ in the presence of Pd/C and K₂CO₃, the 1- or 3-substituted **8a** and **8b**, respectively were obtained (Scheme 3).



Scheme 3

The hydroxy ketone **4** also gives a convenient access to the two intermediates **9b**^{1a} and **9c**^{2b} previously used by Cook^{1a} and Magnus^{2b} in their total syntheses. These molecules were directly obtained by Swern oxidation of **6b** and **6c**, respectively (Scheme 4).



Scheme 4

These results demonstrate that (*endo, endo*)-9-benzyl-9-azabicyclo[3.3.1]nonane-2,6-diol (**1**) which already provided an easy access to stereoselective synthesis of indolizidine and quinolizidine alkaloids,¹¹ can also in principle be used for the synthesis of macroline/sarpagine type alkaloids.

Unless otherwise specified, materials were purchased from commercial suppliers and used without further purification. CH₂Cl₂ and Et₃N were distilled from CaH₂. THF was distilled from Na-benzophenone ketyl immediately before use. NMR spectra were recorded in CDCl₃ or DMSO at 400 MHz for ¹H and 50 MHz for ¹³C using CHCl₃ (7.30 ppm for ¹H, 77.00 ppm for ¹³C), and using H₂O (3.33 ppm for ¹H in DMSO) or DMSO (39.7 ppm for ¹³C in DMSO) as internal reference unless otherwise stated. Analytical TLC was

performed on Merck silica gel plates (60 F₂₅₄). Flash chromatography was performed using Merck silica gel (Geduran SI 60, 0.040–0.063 mm). Melting points were measured on a Büchi 535 melting point apparatus. Elemental analyses were performed by the Service Régional de Microanalyses de l'Université Pierre et Marie Curie (Paris).

(*endo, endo*)-9-Benzyl-6-[(*tert*-butyldimethylsilyl)oxy]-9-azabicyclo[3.3.1]nonan-2-ol (**2**)

A solution of the diol **1** (10.9 g, 44.13 mmol) in CH₂Cl₂ (100 mL) was cooled to 0°C under argon, and Et₃N (11.5 mL, 81.82 mmol), DMAP (2 g, 16.3 mmol) and TBDMSCl (7 g, 46.44 mmol) were added successively. After stirring the resulting mixture for 7 h at 0°C, H₂O (100 mL) was added. The aqueous layer was extracted with CH₂Cl₂ (100 mL) and the combined organic layers were dried (Na₂SO₄) and evaporated. The crude product was purified by flash chromatography (CH₂Cl₂/acetone, 95:5 then 80:20) to give **2** (8.04 g, 50%) as a white powder; mp 85°C.

¹H NMR (400 MHz, CDCl₃): δ = 0.00 (s, 3 H), 0.04 (s, 3 H), 0.89 (s, 9 H), 1.67 (br s, 1 H), 1.70–2.11 (m, 8 H), 2.61–2.67 (m, 1 H), 2.70–2.76 (m, 1 H), 3.98 (s, 2 H), 4.08–4.20 (m, 2 H), 7.20–7.40 (m, 5 H).

¹³C NMR (50 MHz, CDCl₃): δ = −4.93, −4.69, 17.95, 19.95, 20.11, 25.75, 30.04, 30.74, 54.57, 55.31, 56.30, 68.02, 68.21, 126.75, 128.02, 128.09, 139.88.

IR (KBr): ν = 3297, 3088, 3068, 3028, 2932, 2893, 2859, 1495, 1459, 1383, 1367, 1266, 1133, 1087, 1057, 863, 838 cm^{−1}.

MS (CI, NH₃): *m/z* (%) = 362 ([MH]⁺, 100), 272 (49).

Anal. Calcd for C₂₁H₃₅NO₂Si: C, 69.75; H, 9.76; N, 3.87. Found: C, 69.85; H, 9.78; N, 3.86.

(*endo, endo*)-9-Benzoyl-6-[(*tert*-butyldimethylsilyl)oxy]-9-azabicyclo[3.3.1]nonan-2-ol (**3**)

Argon was bubbled through a solution of the amine **2** (2 g, 5.5 mmol) and wet 10% Pd/C (50%, 250 mg) in MeOH (50 mL). The resultant suspension was stirred overnight under an atmosphere of H₂ maintained by fixing a balloon filled with H₂ to the flask. After filtration through Celite, the solvent was removed under reduced pressure. To the residue, acetone (50 mL), K₂CO₃ (7.7 g, 55.4 mmol) and benzoyl chloride (3.2 mL, 27.7 mmol) were successively added, and the solution refluxed for 8 h. Acetone was then evaporated under reduced pressure and CH₂Cl₂ (100 mL) was added to the residual solution. The organic layer was washed with H₂O (50 mL), dried (Na₂SO₄) and evaporated. The crude product was purified by flash chromatography (CH₂Cl₂/acetone, 80:20) to afford **3** (1.71 g, 82%) as a white solid; mp < 40°C.

Major Rotamer:

¹H NMR (400 MHz, CDCl₃): δ = −0.18 (s, 3 H), −0.08 (s, 3 H), 0.79 (s, 9 H), 1.48–1.62 (m, 1 H), 1.66–1.97 (m, 5 H), 2.05–2.12 (m, 1 H), 2.20–2.27 (m, 1 H), 3.52 (br t, 1 H, *J* = 5.39 Hz), 3.76–3.86 (m, 2 H), 3.91–4.01 (m, 1 H), 4.69 (br t, 1 H, *J* = 4.90 Hz), 7.30–7.50 (m, 5 H).

¹³C NMR (50 MHz, CDCl₃): δ = −5.27, −5.10, 17.74, 20.85, 22.11, 25.52, 28.77, 30.11, 48.02, 54.46, 66.43, 70.22, 126.14, 128.43, 129.60, 135.71, 170.20.

Minor Rotamer:

¹H NMR (400 MHz, CDCl₃): δ = 0.11 (s, 3 H), 0.14 (s, 3 H), 0.93 (s, 9 H), 1.48–1.62 (m, 1 H), 1.66–1.97 (m, 5 H), 1.97–2.05 (m, 1 H), 2.20–2.27 (m, 1 H), 3.18–3.27 (m, 1 H), 3.64 (br t, 1 H, *J* = 5.20 Hz), 3.76–3.86 (m, 1 H), 3.91–4.01 (m, 1 H), 4.59 (br t, 1 H, *J* = 4.92 Hz), 7.30–7.50 (m, 5 H).

^{13}C NMR (50 MHz, CDCl_3): $\delta = -4.89, -4.75, 17.87, 21.03, 22.23, 25.67, 29.10, 30.36, 48.08, 53.86, 66.89, 69.50, 126.28, 128.39, 129.44, 135.94, 170.07$.

IR (KBr): $\nu = 3422, 3061, 2951, 2885, 2856, 1616, 1578, 1438, 1261, 1101, 1074, 1026, 860, 837, 775, 705\text{ cm}^{-1}$.

MS (CI, NH_3): m/z (%) = 376([MH] $^+$, 100).

Anal. Calcd for $\text{C}_{21}\text{H}_{33}\text{NO}_3\text{Si}$: C, 67.16; H, 8.86; N, 3.73. Found: C, 67.23; H, 8.97; N, 3.76.

(endo)-9-Benzoyl-6-[(tert-butyldimethylsilyl)oxy]-9-azabicyclo[3.3.1]nonan-2-one

To a solution of oxalyl chloride (1.97 mL, 22.66 mmol) in CH_2Cl_2 (100 mL) was added dropwise DMSO (3.22 mL, 45.32 mmol) at -60°C . The mixture was stirred for 2 min, and a solution of alcohol **3** (7.72 g, 20.6 mmol) in CH_2Cl_2 (10 mL) was then added. After stirring for 15 min, Et_3N (8.69 mL, 61.8 mmol) was added. The mixture was stirred for 5 min and then allowed to warm to r.t. H_2O (100 mL) was then added and the aqueous layer was extracted with CH_2Cl_2 (100 mL). The organic layers were combined, washed in turn with brine (200 mL), 0.4 N HCl solution (200 mL), H_2O (100 mL), aq satd NaHCO_3 solution (200 mL) and H_2O (100 mL), dried (Na_2SO_4) and evaporated. The crude product was purified by flash chromatography (hexane/ EtOAc , 70:30) to give the corresponding ketone (7.35 g, 95%) as a white solid; mp 76°C .

^1H NMR (400 MHz, CDCl_3): $\delta = -0.15, -0.05, 0.14$ and 0.17 (s, 6 H), 0.79 and 0.93 (s, 9 H), 1.41 – 1.55 (m, 1 H), 1.63 – 1.90 (m, 2H), 1.97 – 2.72 (m, 5 H), 3.72 – 3.82 and 3.91 – 3.99 (m, 1H), 4.05 – 4.18 (m, 1 H), 5.05 – 5.13 (m, 1 H), 7.35 – 7.50 (m, 5 H).

^{13}C NMR (50 MHz, CDCl_3): $\delta = -5.31, -5.00, -4.89, -4.73, 16.72, 17.78, 25.43, 26.67, 27.90, 35.96, 36.26, 47.74, 53.93, 56.74, 62.35, 68.52, 69.64, 126.44, 126.73, 128.59, 130.09, 134.94, 170.52, 212.06, 212.33$.

IR (KBr): $\nu = 3061, 2955, 2930, 2897, 2858, 1732, 1628, 1430, 1327, 1252, 1109, 964, 835, 792\text{ cm}^{-1}$.

MS (CI, NH_3): m/z (%) = 374([MH] $^+$, 100).

Anal. Calcd for $\text{C}_{21}\text{H}_{31}\text{NO}_3\text{Si}$: C, 67.52; H, 8.36; N, 3.75. Found: C, 67.60; H, 8.32; N, 3.74.

(endo)-9-Benzoyl-6-hydroxy-9-azabicyclo[3.3.1]nonan-2-one (4)

To a solution of the above ketone (12.86 g, 34.5 mmol) in MeCN was added aq 40% HF (7.5 mL). After stirring overnight, aq satd NaHCO_3 solution (100 mL) was added and the resulting solution extracted with CH_2Cl_2 ($3 \times 100\text{ mL}$). The combined organic layers were dried (Na_2SO_4) and evaporated. The crude product was purified by flash chromatography (CH_2Cl_2 /acetone, 80:20) to afford **4** (7.35 g, 95%) as a white powder, mp 168°C .

^1H NMR (400 MHz, $\text{DMSO}-d_6$): $\delta = 1.40$ – 1.55 (m, 1 H), 1.83 – 2.02 (m, 2 H), 2.09 – 2.41 (m, 3 H), 2.47 – 2.57 (m, 1 H), 2.81 – 3.02 (m, 1 H), 3.80 – 3.90 (m, 2/3 H), 3.90 – 4.00 (m, 1/3 H), 4.03 (br s, 1/3 H), 4.14 – 4.22 (m, 2/3 H), 4.99 (br s, 2/3 H), 5.08 – 5.15 (m, 1/3 H), 5.30 (d, 2/3 H, $J = 3.82\text{ Hz}$), 5.45 (d, 1/3 H, $J = 3.44\text{ Hz}$), 7.62 – 7.72 (m, 5 H).

^{13}C NMR (50 MHz, $\text{DMSO}-d_6$): $\delta = 16.60, 17.57, 25.87, 26.48, 27.45, 35.92, 47.20, 53.55, 56.32, 61.98, 66.97, 67.80, 126.72, 128.60, 129.85, 135.41, 169.48, 212.30$.

IR (KBr): $\nu = 3333, 2990, 2972, 2954, 2920, 2867, 2843, 1724, 1603, 1576, 1437, 1342, 1080, 731\text{ cm}^{-1}$.

MS (CI, NH_3): m/z (%) = 260([MH] $^+$, 100).

Anal. Calcd for $\text{C}_{15}\text{H}_{17}\text{NO}_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.34; H, 6.53; N, 5.30.

Indoles 6 and 7; General Procedure

A solution of the ketone **4** (2 mmol) and hydrazine (or hydrazine hydrochloride) **5** (4 mmol) in MeOH saturated with HCl (30 mL) was refluxed overnight. The mixture was cooled, diluted with aq 2.5 N NaOH solution (30 mL) and extracted with CH_2Cl_2 ($3 \times 50\text{ mL}$). The combined organic layers were dried (Na_2SO_4) and evaporated.¹² The residue was dissolved in THF (5 mL) and added to a suspension of LiAlH_4 (200 mg, 5.27 mmol) in THF (30 mL) under argon at 0°C . After 15 min, the mixture was warmed to r.t., and refluxed overnight. After cooling to r.t., H_2O (200 μL), aq 15% NaOH solution (200 μL) and then H_2O (600 μL) were successively added dropwise. The resulting suspension was filtered through Celite, rinsed with Et_2O , and the solvent removed under reduced pressure. The crude product was purified by flash chromatography (CH_2Cl_2 /acetone, 90:10) to afford the corresponding indole as a white moss.

(endo)-12-Benzyl-6,7,8,9,10,11-hexahydro-6,10-imino-5H-cyclooct[b]indol-9-ol (6a)

Indole **6a** (600 mg, 94%) was obtained from **4** (518 mg, 2 mmol); mp 95 – 96°C .

^1H NMR (400 MHz, CDCl_3): $\delta = 1.22$ – 1.33 (m, 1 H), 1.65 – 1.75 (m, 3 H), 2.08 (dddd, 1 H, $J = 13.20, 13.20, 4.20, 4.20\text{ Hz}$), 2.89 – 3.01 (m, 2 H), 3.36 (br t, 1 H, $J = 5.06\text{ Hz}$), 3.73 (s, 2 H), 3.80 – 3.82 (m, 1 H), 4.11 (ddd, 1 H, $J = 11.91, 5.06, 5.06\text{ Hz}$); 7.16 – 7.24 (m, 2 H), 7.30 – 7.38 (m, 6 H), 7.59 – 7.62 (m, 1 H), 7.68 (br s, 1 H).

^{13}C NMR (50 MHz, CDCl_3): $\delta = 15.00, 25.48, 30.42, 50.84, 56.76, 57.50, 70.85, 108.06, 110.90, 118.10, 119.19, 121.11, 126.96, 127.01, 128.26, 128.67, 132.65, 135.67, 139.41$.

IR (KBr): $\nu = 3404, 3109, 3082, 3057, 2925, 2845, 1703, 1599, 1495, 1452, 1362, 1338, 1311, 1232, 1157, 1118, 1074, 1003, 922, 741, 698\text{ cm}^{-1}$.

HRMS: m/z calcd for $\text{C}_{21}\text{H}_{23}\text{N}_2\text{O}$ 319.1810, found 319.1823.

(endo)-12-Benzyl-5-methyl-6,7,8,9,10,11-hexahydro-6,10-imino-5H-cyclooct[b]indol-9-ol (6b)

Indole **6b** (631 mg, 95%) was obtained from **4** (518 mg, 2 mmol); mp 68 – 70°C .

^1H NMR (400 MHz, CDCl_3): $\delta = 1.29$ – 1.41 (m, 1 H), 1.70 – 1.80 (m, 2 H), 2.19 (dddd, 1 H, $J = 13.10, 13.10, 4.16, 4.16\text{ Hz}$), 2.51 (s, 1 H), 3.01 – 3.10 (m, 2 H), 3.41 – 3.46 (m, 1 H), 3.64 (s, 3 H), 3.79 (s, 2 H), 3.96 – 4.01 (m, 1 H), 4.17 (ddd, 1 H, $J = 12.01, 4.90, 4.90\text{ Hz}$), 7.26 – 7.32 (m, 1 H), 7.34 – 7.40 (m, 1 H), 7.40 – 7.48 (m, 6 H), 7.73 (d, 1 H, $J = 7.73\text{ Hz}$).

^{13}C NMR (50 MHz, CDCl_3): $\delta = 15.07, 25.36, 28.92, 29.92, 49.50, 56.84, 57.68, 70.82, 107.51, 108.78, 118.18, 118.81, 120.78, 126.57, 127.00, 128.27, 128.76, 133.82, 137.00, 139.39$.

IR (KBr): $\nu = 3383, 3053, 3026, 2920, 2843, 1468, 1369, 1126, 1005, 741, 725, 698\text{ cm}^{-1}$.

HRMS: m/z calcd for $\text{C}_{22}\text{H}_{25}\text{N}_2\text{O}$ 333.1967, found 333.1942.

(endo)-5,12-Dibenzyl-6,7,8,9,10,11-hexahydro-6,10-imino-5H-cyclooct[b]indol-9-ol (6c)

Indole **6c** (748 mg, 92%) was obtained from **4** (518 mg, 2 mmol); mp 72 – 74°C .

^1H NMR (400 MHz, CDCl_3): $\delta = 1.27$ – 1.38 (m, 1 H), 1.52 – 1.58 (m, 1 H), 1.63 – 1.80 (m, 2 H), 2.02 (tt, 1 H, $J = 13.11, 4.01\text{ Hz}$), 2.96 – 3.08 (m, 2 H), 3.37 (br t, 1 H, $J = 5.19\text{ Hz}$), 3.61 (d, 1 H, $J = 13.52\text{ Hz}$), 3.70 (d, 1 H, $J = 13.52\text{ Hz}$), 3.85 (br s, 1 H), 4.09 (dt, 1 H, $J = 11.82, 5.05\text{ Hz}$), 5.17 (d, 1 H, $J = 16.99\text{ Hz}$), 5.28 (d, 1 H, $J = 16.99\text{ Hz}$), 6.95 – 7.00 (m, 2 H), 7.18 – 7.33 (m, 11 H), 7.65 – 7.69 (m, 1 H).

^{13}C NMR (50 MHz, CDCl_3): $\delta = 15.01, 25.14, 29.64, 46.00, 49.60, 56.56, 57.47, 70.58, 108.20, 109.25, 118.11, 119.00, 121.02, 125.75, 126.64, 126.71, 127.12, 128.01, 128.50, 133.53, 136.67, 137.72, 139.09$.

IR (KBr): ν = 3379, 3064, 3027, 2928, 2329, 1495, 1452, 1350, 1176, 1127, 1009, 737, 697 cm^{-1} .

MS (CI, NH_3): m/z (%) = 409([MH]⁺, 100).

(endo)-12-Benzyl-4-methyl-6,7,8,9,10,11-hexahydro-6,10-imino-5H-cyclooct[b]indol-9-ol (6d)

Indole **6d** (248 mg, 83%) was obtained from **4** (230 mg, 0.89 mmol); mp 96–98 °C.

¹H NMR (400 MHz, CDCl_3): δ = 1.25–1.40 (m, 1 H), 1.64–1.80 (m, 2 H), 2.05–2.17 (m, 1 H), 2.23 (br s, 1 H), 2.55 (s, 3 H), 2.92–3.03 (m, 2 H), 3.33–3.38 (m, 1 H), 3.76 (s, 2 H), 3.85–3.88 (m, 1 H), 4.13 (ddd, 1 H, J = 11.87, 5.03, 5.03 Hz), 7.07 (br d, 1 H, J = 7.21 Hz), 7.17 (dd, 1 H, J = 7.50, 7.50 Hz), 7.32–7.44 (m, 5 H), 7.51 (br d, 1 H, J = 7.78 Hz), 7.81 (br s, 1 H).

¹³C NMR (50 MHz, CDCl_3): δ = 15.09, 16.73, 25.52, 30.51, 50.90, 56.75, 57.51, 70.92, 108.72, 115.81, 119.47, 119.97, 121.93, 126.56, 126.91, 128.21, 128.61, 132.30, 135.16, 139.36.

IR (KBr): ν = 3420, 3082, 3045, 3024, 2918, 2851, 1452, 744 cm^{-1} .

MS (CI, NH_3): m/z (%) = 333([MH]⁺, 100), 160(51), 106(100).

(endo)-12-Benzyl-4-bromo-6,7,8,9,10,11-hexahydro-6,10-imino-5H-cyclooct[b]indol-9-ol (6e)

Indole **6e** (490 mg, 58%) was obtained from **4** (554 mg, 2.13 mmol).

¹H NMR (400 MHz, CDCl_3): δ = 1.20–1.33 (m, 1 H), 1.64–1.81 (m, 3 H), 2.10 (dddd, 1 H, J = 13.15, 13.15, 4.13, 4.13 Hz), 2.89–2.99 (m, 2 H), 3.34–3.38 (m, 1 H), 3.72 (s, 2 H), 3.86–3.88 (m, 1 H), 4.12 (ddd, 1 H, J = 11.84, 5.16, 5.16 Hz), 7.06 (t, 1 H, J = 7.76 Hz), 7.27–7.38 (m, 6 H), 7.53 (d, 1 H, J = 7.81 Hz), 7.91 (br s, 1 H).

¹³C NMR (50 MHz, CDCl_3): δ = 15.09, 25.44, 30.34, 50.81, 56.52, 57.53, 70.75, 104.52, 109.59, 117.29, 120.46, 123.56, 126.98, 128.25, 128.40, 128.58, 133.46, 134.35, 139.13.

IR (KBr): ν = 3423, 3059, 3028, 2926, 2847, 1493, 1420, 1362, 1333, 1306, 1198, 1157, 1132, 1074, 1028, 1009, 773, 733, 698 cm^{-1} .

MS (CI, NH_3): m/z (%) = 399([MH]⁺, 100), 397([MH]⁺, 93), 381(24), 379(24), 319(22).

(endo)-12-Benzyl-4-methyl-6,7,8,9,10,11-hexahydro-6,10-imino-5H-cyclooct[b]indol-9-ol (6g)

Indole **6g** (310 mg, 93%) was obtained from **4** (259 mg, 1 mmol); mp 118–120 °C.

¹H NMR (400 MHz, CDCl_3): δ = 1.20–1.35 (m, 1 H), 1.63–1.73 (m, 2 H), 2.03–2.14 (m, 1 H), 2.31 (br s, 1 H), 2.61 (s, 3 H), 2.91–3.01 (m, 2 H), 3.33–3.39 (m, 1 H), 3.73–3.78 (m, 3 H), 4.11 (ddd, 1 H, J = 11.94, 4.89, 4.89 Hz), 7.11 (dd, 1 H, J = 8.18, 1.18 Hz), 7.26 (d, 1 H, J = 8.18 Hz), 7.35–7.45 (m, 5 H), 7.46 (br s, 1 H), 7.62 (br s, 1 H).

¹³C NMR (50 MHz, CDCl_3): δ = 15.01, 21.48, 25.55, 30.45, 50.86, 56.78, 57.50, 70.90, 107.62, 110.54, 117.88, 122.61, 126.93, 127.24, 128.25, 128.45, 128.65, 132.80, 133.94, 139.43.

IR (KBr): ν = 3402, 3082, 3061, 3026, 2920, 2860, 1452, 1310, 1134, 733 cm^{-1} .

MS (CI, NH_3): m/z (%) = 333([MH]⁺, 89), 160(51), 134(100), 106(96).

(endo)-12-Benzyl-2-methoxy-6,7,8,9,10,11-hexahydro-6,10-imino-5H-cyclooct[b]indol-9-ol (6h)

6h (495 mg, 71%, mp 96–98 °C) was obtained from **4** (518 mg, 2 mmol).

¹H NMR (400 MHz, CDCl_3): δ = 1.22–1.34 (m, 1 H), 1.65–1.75 (m, 3 H), 2.08 (dddd, 1 H, J = 13.18, 13.18, 4.17, 4.17 Hz), 2.86–

2.98 (m, 2 H), 3.33–3.38 (m, 1 H), 3.73 (s, 2 H), 3.77–3.81 (m, 1 H), 3.92 (s, 3 H), 4.08–4.15 (m, 1 H), 6.86 (dd, 1 H, J = 8.68, 2.46 Hz), 7.05 (d, 1 H, J = 2.46 Hz), 7.24 (d, 1 H, J = 8.68 Hz), 7.27–7.38 (m, 5 H), 7.60 (br s, 1 H).

¹³C NMR (50 MHz, CDCl_3): δ = 15.02, 25.52, 30.43, 50.96, 55.94, 56.71, 57.49, 70.81, 100.44, 107.86, 110.79, 111.54, 127.34, 126.93, 128.23, 128.67, 130.81, 133.69, 139.34, 153.74.

IR (KBr): ν = 3402, 3082, 3061, 3026, 2997, 2930, 2841, 1626, 1593, 1418, 1454, 1215, 1140, 1115, 964, 735, 700 cm^{-1} .

HRMS: m/z calcd for $\text{C}_{22}\text{H}_{25}\text{N}_2\text{O}_2$ 349.1916, found 349.1918.

(endo)-12-Benzyl-4-bromo-1-methyl-6,7,8,9,10,11-hexahydro-6,10-imino-5H-cyclooct[b]indol-9-ol (7a)

Indole **7a** (563 mg, 68%) was obtained from **4** (518 mg, 2 mmol).

¹H NMR (400 MHz, CDCl_3): δ = 1.26–1.39 (m, 1 H), 1.63 (br s, 1 H), 1.69–1.81 (m, 2 H), 2.04–2.14 (m, 1 H), 2.73 (s, 3 H), 3.11–3.23 (m, 2 H), 3.31 (br t, 1 H, J = 4.72 Hz), 3.75 (s, 2 H), 3.85 (t, 1 H, J = 3.22 Hz), 4.12 (dt, 1 H, J = 16.89, 5.23 Hz), 6.78 (d, 1 H, J = 7.85 Hz), 7.20 (d, 1 H, J = 7.85 Hz), 7.26–7.38 (m, 5 H), 7.85 (br s, 1 H).

¹³C NMR (50 MHz, CDCl_3): δ = 17.57, 19.30, 25.50, 30.38, 50.79, 56.79, 57.51, 70.87, 101.69, 109.94, 121.61, 123.31, 126.99, 127.34, 128.59, 128.27, 129.81, 132.67, 134.00, 139.19.

IR (KBr): ν = 3416, 3059, 3026, 2926, 2849, 1705, 1616, 1452, 1325, 1115, 793, 739, 698 cm^{-1} .

MS (CI, NH_3): m/z (%) = 413([MH]⁺, 93), 411([MH]⁺, 100).

(endo)-12-Benzyl-4-bromo-3-methyl-6,7,8,9,10,11-hexahydro-6,10-imino-5H-cyclooct[b]indol-9-ol (7b)

Indole **7b** (634 mg, 77%) was obtained from **4** (518 mg, 2 mmol).

¹H NMR (400 MHz, CDCl_3): δ = 1.21–1.33 (m, 1 H), 1.65–1.81 (m, 3 H), 2.09 (tt, 1 H, J = 13.1, 4.1 Hz), 2.57 (s, 3 H), 2.86–2.98 (m, 2 H), 3.34 (td, 1 H, J = 5.02, 1.3 Hz), 3.67 (s, 2 H), 3.85 (t, 1 H, J = 3.23 Hz), 4.11 (dt, 1 H, J = 11.19, 5.51 Hz), 7.06 (d, 1 H, J = 7.90 Hz), 7.27–7.37 (m, 5 H), 7.42 (d, 1 H, J = 7.90 Hz), 7.88 (br s, 1 H).

¹³C NMR (50 MHz, CDCl_3): δ = 15.05, 21.79, 25.51, 30.38, 50.79, 56.53, 57.51, 70.62, 106.58, 109.51, 116.76, 122.03, 126.10, 126.90, 128.19, 128.50, 129.75, 132.56, 134.95, 139.18.

IR (KBr): ν = 3412, 3059, 3021, 2920, 2845, 1705, 1452, 1313, 1157, 1130, 1030, 800, 738, 700 cm^{-1} .

MS (CI, NH_3): m/z (%) = 413([MH]⁺, 93), 411([MH]⁺, 100).

Hydrogenolysis of Bromoindoles 7a,b to 8a,b; General Procedure

Argon was bubbled through a solution of bromoindole **7** (1 mmol), K_2CO_3 (4 mmol) and 10% Pd/C (100 mg) in MeOH (20 mL). The resultant suspension was stirred under H_2 (balloon) for 4 h, filtered through Celite, rinsed with MeOH, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (CH_2Cl_2 /acetone 80:20) to afford **8** as a white moss.

(endo)-12-Benzyl-hexahydro-6,7,8,9,10,11-1-methyl-6,10-imino-5H-cyclooct[b]indol-9-ol (8a)

Indole **8a** (108 mg, 82%) was obtained from **7a** (164 mg, 0.4 mmol); mp 95–97 °C.

¹H NMR (400 MHz, CDCl_3): δ = 1.27–1.42 (m, 1 H), 1.63 (br s, 1 H), 1.68–1.75 (m, 2 H), 2.06 (tt, 1 H, J = 13.13, 3.98 Hz), 2.75 (s, 3 H), 3.17–3.21 (m, 2 H), 3.32 (td, 1 H, J = 4.10, 4.10 Hz), 3.74 (s, 2 H), 3.79 (t, 1 H, J = 3.22 Hz), 4.11 (dt, 1 H, J = 11.85, 4.98 Hz), 6.90 (d, 1 H, J = 7.58 Hz), 7.07 (t, 1 H, J = 7.58 Hz), 7.18 (d, 1 H, J = 7.58 Hz), 7.26–7.38 (m, 5 H), 7.61 (br s, 1 H).

^{13}C NMR (50 MHz, CDCl_3): δ = 17.70, 19.75, 25.53, 30.43, 50.76, 57.05, 57.47, 70.96, 108.36, 106.63, 120.36, 121.11, 126.14, 126.99, 128.30, 128.68, 130.40, 131.94, 135.57, 139.44.

IR (KBr): ν = 3395, 3059, 3028, 2928, 2859, 1452, 1333, 1146, 1074, 743, 700 cm^{-1} .

MS (CI, NH_3): m/z (%) = 333([MH] $^+$, 100).

(endo)-12-Benzyl-3-methyl-6,7,8,9,10,11-hexahydro-6,10-imino-5H-cyclooct[b]indol-9-ol (8b)

Indole **8b** (194 mg, 75%) was obtained from **7b** (318 mg, 0.77 mmol); mp 176–178°C.

^1H NMR (400 MHz, CDCl_3): δ = 1.22–1.34 (m, 1 H), 1.55–1.74 (m, 3 H), 2.06 (tt, 1 H, J = 4.17, 13.12 Hz), 2.51 (s, 3 H), 2.85–2.99 (m, 2 H), 3.34 (t, 1 H, J = 5.31 Hz), 3.71 (s, 2 H), 3.78 (t, 1 H, J = 3.23 Hz), 4.10 (dt, 1 H, J = 11.9, 5.31 Hz), 7.02 (dd, 1 H, J = 7.93, 0.76 Hz), 7.17 (s, 1 H), 7.26–7.37 (m, 5 H), 7.48 (d, 1 H, J = 7.93 Hz), 7.53 (br s, 1 H).

^{13}C NMR (50 MHz, CDCl_3): δ = 14.97, 21.63, 25.43, 30.36, 50.72, 56.72, 57.40, 70.83, 107.84, 110.86, 117.69, 120.79, 124.79, 126.84, 128.16, 128.56, 130.82, 131.77, 136.01, 139.38.

IR (KBr): ν = 3406, 3032, 2930, 2855, 1636, 1497, 1464, 1165, 908, 812, 742, 710 cm^{-1} .

MS (CI, NH_3): m/z (%) = 333([MH] $^+$, 100).

12-Benzyl-5-methyl-5,6,7,8,10,11-hexahydro-6,10-imino-9H-cyclooct[b]indol-9-one (9b)

To a solution of oxalyl chloride (240 μL , 2.75 mmol) in CH_2Cl_2 (25 mL) was added dropwise DMSO (370 μL , 5.21 mmol) at -60°C . The mixture was stirred for 2 min, and a solution of alcohol **8b** (550 mg, 1.65 mmol) in CH_2Cl_2 (3 mL) was then added. After stirring for 15 min, Et_3N (980 μL , 6.97 mmol) was added. The mixture was stirred again for 5 min and then allowed to warm to r.t. H_2O (25 mL) was then added and the aqueous layer was extracted with additional CH_2Cl_2 (25 mL). The organic layers were combined, dried (Na_2SO_4) and evaporated. The crude product was purified by flash chromatography (hexane/ EtOAc , 70:30) to give the corresponding ketone **9b** (400 mg, 73%) as a white moss; mp 131–132°C (Lit. 13 131.5–133°C).

^1H NMR (400 MHz, CDCl_3): δ = 1.98–2.07 (m, 1 H), 2.12–2.22 (m, 1 H), 2.46–2.56 (m, 2 H), 2.74 (d, 1 H, J = 16.87 Hz), 3.31 (dd, 1 H, J = 16.87, 6.83 Hz), 3.65 (s, 3 H), 3.78 (s, 2 H), 3.81 (d, 1 H, J = 6.83 Hz), 4.10–4.12 (m, 1 H), 7.16–7.21 (m, 1 H), 7.26–7.39 (m, 7 H), 7.57 (d, 1 H, J = 7.80 Hz).

^{13}C NMR (50 MHz, CDCl_3): δ = 20.39, 29.30, 29.74, 34.32, 48.84, 56.18, 64.80, 105.69, 108.92, 118.21, 119.25, 121.52, 126.44, 127.33, 128.45, 128.63, 133.15, 137.18, 138.26, 210.00.

IR (KBr): ν = 3090, 3064, 3032, 2967, 2935, 2850, 2802, 1715 cm^{-1} .

HRMS: m/z calcd for $\text{C}_{22}\text{H}_{23}\text{N}_2\text{O}$ 331.1810, found 331.1793.

5,12-Dibenzyl-5,6,7,8,10,11-hexahydro-6,10-imino-9H-cyclooct[b]indol-9-one (9c)

To a solution of oxalyl chloride (460 μL , 5.28 mmol) in CH_2Cl_2 (30 mL) was added dropwise DMSO (800 μL , 10.6 mmol) at -60°C . The mixture was stirred for 2 min, and a solution of the alcohol **8c** (431 mg, 1.05 mmol) in CH_2Cl_2 (5 mL) was then added. After stirring for 15 min, Et_3N (2.5 mL, 15.9 mmol) was added. The mixture was stirred again for 5 min and then allowed to warm to r.t. H_2O (30 mL) was then added and the aqueous layer was extracted with CH_2Cl_2 (30 mL). The organic layers were combined, dried (Na_2SO_4) and evaporated. The crude product was purified by flash chromatography (hexane/ EtOAc 90:10) to give **9c** (301 mg, 70%) as a white moss; mp 79–80°C.

^1H NMR (400 MHz, CDCl_3): δ = 1.74–1.88 (m, 1 H), 2.12–2.23 (m, 1 H), 2.31–2.40 (m, 1 H), 2.46 (dd, 1 H, J = 16.22, 5.08 Hz), 2.78 (d, 1 H, J = 16.80 Hz), 3.35 (dd, 1 H, J = 16.80, 6.88 Hz), 3.66 (d, 1 H, J = 13.37 Hz), 3.74 (d, 1 H, J = 13.37 Hz), 3.82 (d, 1 H, J = 6.74 Hz), 4.00–4.05 (m, 1 H), 5.22 (d, 1 H, J = 17.07 Hz), 5.33 (d, 1 H, J = 17.07 Hz), 6.92–6.97 (m, 2 H), 7.18–7.32 (m, 11 H), 7.58–7.64 (m, 1 H).

^{13}C NMR (50 MHz, CDCl_3): δ = 20.23, 29.69, 34.08, 46.23, 48.62, 55.93, 64.73, 106.37, 109.34, 118.08, 119.37, 121.70, 125.57, 126.44, 126.99, 127.26, 128.11, 128.41, 128.57, 132.77, 136.66, 137.29, 137.87, 209.66.

IR (KBr): ν = 3065, 3039, 2929, 2831, 1716, 1628, 1491, 1457, 1156, 1051, 732, 699 cm^{-1} .

MS (FAB): m/z (%) = 407([MH] $^+$, 100).

References

- (1) (a) Bi, Y.; Hamaker, L. K.; Cook, J. M. *The synthesis of macroline related alkaloids*; In *Bioactive Natural Products, Part A*; Basha, F., Rahman, A., Eds.; Elsevier Science: Amsterdam, 1993, Vol. 13; p 383.
(b) Hamaker, L. K.; Cook, J. M. *The Synthesis of Macroline Related Alkaloids*; In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Pergamon Press: London, 1995, Vol. 9; p 23.
- (2) (a) Cain, M.; Campos, O.; Guzman, F.; Cook, J. M. *J. Am. Chem. Soc.* **1983**, *105*, 907.
(b) Magnus, P.; Mugrage, B.; DeLuca, M. R.; Cain, G. A. *J. Am. Chem. Soc.* **1990**, *112*, 5220.
(c) Bailey, P. D.; McLay, N. R. *Tetrahedron Lett.* **1991**, *32*, 3895.
- (3) Calvert, B. J.; Hobson, J. D. *J. Chem. Soc.* **1964**, 5378.
- (4) Cloudsdale, I. S.; Kluge, A. F.; McClure, N. L. *J. Org. Chem.* **1982**, *47*, 919.
- (5) Michel, P.; Rassat, A., submitted to *J. Org. Chem.*
- (6) *N*-benzyl could also be used instead of *N*-benzoyl **4** in the indole syntheses, but the yield were not as good, ca 65% compared to ca 95% with **4**.
- (7) It is necessary to liberate the alcohol function at this stage, because when the protected alcohol was used in the indolization reactions, the expected formation of an indole derivative was not observed by NMR.
- (8) Ishii, H. *Acc. Chem. Res.* **1981**, *14*, 275.
- (9) (a) Szczepankiewicz, B. G.; Heathcock, C. H. *Tetrahedron* **1997**, *53*, 8853.
(b) Murakami, Y.; Watanabe, T.; Takahashi, H.; Yokoo, H.; Nakazawa, Y.; Koshimizu, M.; Adachi, N.; Kurita, M.; Yoshino, T.; Inagaki, T.; Ohishi, M.; Watanabe, M.; Tani, M.; Yokoyama, Y. *Tetrahedron* **1998**, *54*, 45.
- (10) For a example of hydrogenolysis of a bromoindole, see: Tsuji, S.; Rinehart, K. L.; Gunasekera, S. P.; Kashman, Y.; Cross, S. S.; Lui, M. S.; Pomponi, S. A.; Diaz, M. C. *J. Org. Chem.* **1988**, *53*, 5446.
- (11) Michel, P., *Thèse de Doctorat* **1999**, Université Pierre et Marie Curie, Paris.
- (12) Alternatively, the N_6 -benzoyl indoles could easily be isolated at that stage. However, conversion to the N_6 -benzyl derivatives simplified the NMR spectra.
- (13) Mashimo, K.; Sato, Y. *Tetrahedron* **1970**, *26*, 803.

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