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NEW ROUTES TO CLAVINE-TYPE ERGOT ALKALOIDS. PART 1. FIRST TOTAL SYNTHESIS OF THREE NATURAL PRODUCTS: (+)-SETOCLAVINE, (+)-ISOSETOCLAVINE, (-)-9,10-DIHYDROISOSETO-CLAVINE, AND STRUCTURE CORRECTION OF THE LATTER [#]

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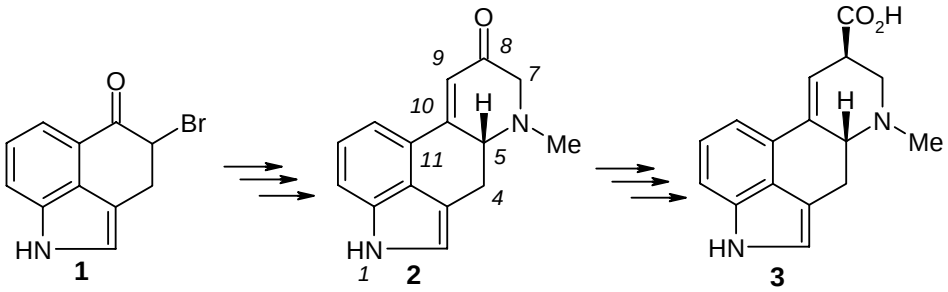
[#]*We dedicate this paper to Professor Barry M. Trost on the occasion of his 65th birthday.*

Abstract – The double bond in ring D of (+)-9,10-didehydro-6-methylergolin-8-one (**2**) was reduced selectively by catalytic hydrogenation to yield (-)-6-methylergolin-8-one (**6**). Grignard reaction of **6** has been performed with methylmagnesium iodide to afford two isomers (**5** and **7**). The main isomer having an 8α-methyl group at C8 with a C/D-*trans* junction (**5**; (-)-dihydro-isosetoclavine) proved to be identical with the natural product, hence its name and structure should be corrected. As a minor isomer (**7**) a C/D-*cis* clavine derivative was also isolated which can be regarded as unnatural (+)-8α-hydroxy-costaclavine. (+)-Setoclavine (**8**) and (+)-isosetoclavine (**9**) have also been prepared from **2**, thus achieving the first total synthesis of these natural products. Detailed structure elucidation of **5**-**9** has been carried out as well.

INTRODUCTION

In our previous publication[1] we described the first direct synthesis of (+)-lysergic acid (**3**, Scheme 1). In our procedure (+)-9,10-didehydro-6-methylergolin-8-one (**2**) prepared from 4-bromo-Uhle's ketone (**1**) proved to be the main key intermediate. This optically active key compound (**2**) with (5*R*)-configuration opened the way to elaborate new routes toward further ergot alkaloids.



Scheme 1

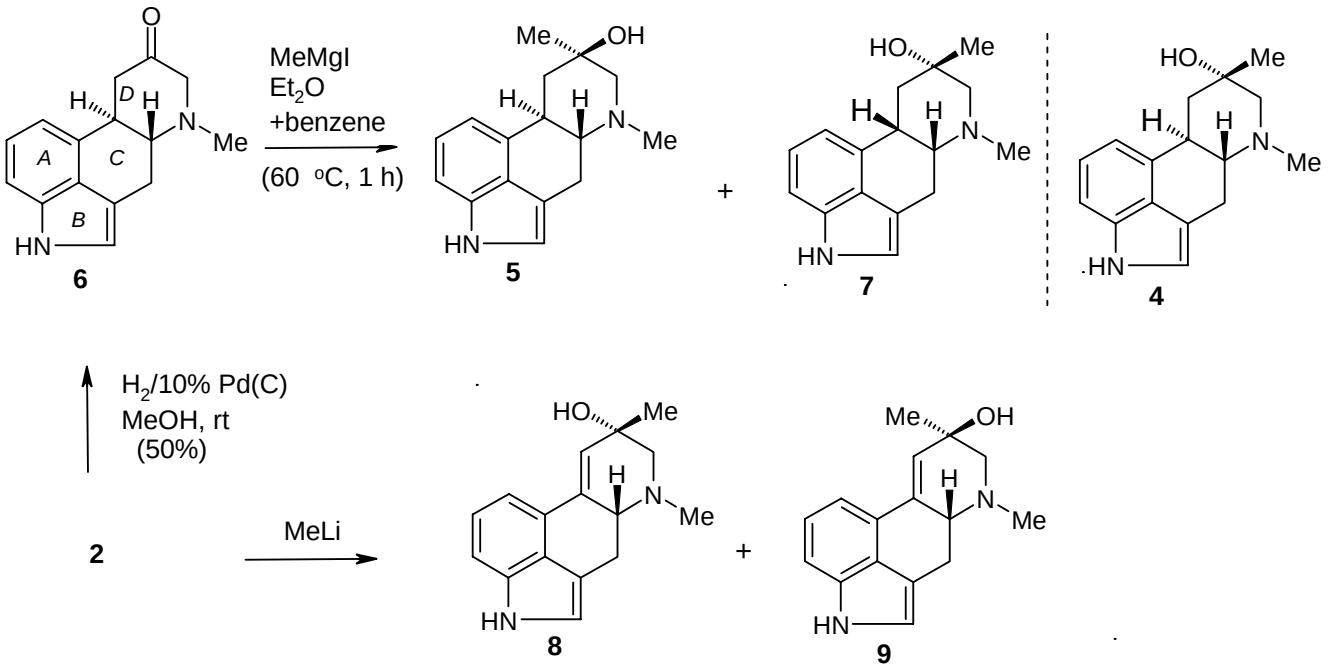
Ergot alkaloids have attracted the attention of synthetic chemists for decades. Certainly the pivotal representatives of this class have been **3** and its amide derivatives, peptide-type ergot alkaloids, as they possess a very wide spectrum of biological activity. However other members, clavine-type ergot alkaloids, have also played an important role in natural product chemistry. On the other hand, several therapeutically important compounds can be formally regarded as derivatives of clavine alkaloids.[2] Thus, continued research into this field is driven by both chemical and biological interest.[3]

RESULTS AND DISCUSSION

From saprophytic cultures of *Claviceps paspali Stevens et Hall* a C8-disubstituted (OH, Me groups) tetracyclic clavine-type ergot alkaloid was isolated by Sandoz researchers in 1973,[4] which was named (-)-dihydrosetoclavine with formula (**4**) (Scheme 2). Later, Natsume's group elaborated two total syntheses[5,6] of (±)-**4** and its C8-epimer [(±)-**5**]. In the second alternative route[6] tetracyclic ketone [(±)-**6**],[7] prepared from their commonly used tricyclic nitrovinyl derivative, was allowed to react with methyllithium to yield (±)-**4** and (±)-**5**. The Japanese group regarded **4** as the racemic form of the natural product. Unfortunately, the NMR spectral instrumentation at that time was not sophisticated enough to provide unambiguous stereochemical assignments.

The optically active **2**, synthesized by us, seemed to be suitable for preparing the natural product. The first step of our recent synthesis was to reduce the C9-C10 double bond by catalytic hydrogenation (H_2/10% Pd-C, MeOH, rt, 50% yield) to afford the optically active ketone (**6**). The α-position of C10-H and hence the *trans* junction of rings C and D followed were verified by NMR spectral measurements. Specifically, the proton-proton coupling values of C10-H with the C5-H and C-9H_{ax} protons (9.1 and 12.8 Hz, respectively) reflect the *trans* arrangement of these protons. In the second step ketone (**6**) was allowed to react with methylmagnesium iodide in a Grignard reaction to afford two isomers (**5**, yield: 22%; **7**, yield: 9%) after separation of the components by column chromatography; **5** and **7** showed the same molecular weight (M^+=256) as determined from the MS spectra. The structure elucidation of **5** and **7** by high-resolution NMR spectral techniques gave surprising results in both cases (see: below). It is worth mentioning here that the natural product isolated by the Sandoz group[4] is a *laevo* rotatory (-)

compound. By comparison with the optical rotations of our synthetic **5** ($[\alpha]_D$ = - 48°) with the isolated compound from natural sources ($[\alpha]_D$ = - 51 ± 5°) we had to assume to obtain the natural material in the Grignard reaction. After a detailed structure elucidation by NMR spectral measurements, the obtained results unambiguously proved that the natural product should be characterized with formula (**5**) and named as (-)-dihydro**iso**setoclavine instead of the published structure (**4**) which should be called (-)-dihydrosetoclavine.



Scheme 2

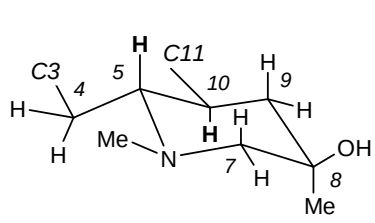
The *dextro* rotating (+) minor isomer (**7**) showed a curious feature, the *cis* junction of ring C and D. [Compound (**7**) has been prepared racemic form earlier by Natsume's group[6] from a C/D-*cis* ketone derivative and can be regarded as 8α-hydroxycostaclavine]. To explain the intriguing epimerization that leads to C/D-*cis* ring junction from a *trans* compound (**6**), requires further investigation. Preliminary epimerization of either the C5 or the C10 chiral centers could result in C/D-*cis* ketone, before the Grignard reaction of the keto function.

Ketone (**2**) was allowed to react with methyllithium, as described by Italian researchers[8] to yield (+)-setoclavine (**8**)[9] and (+)-isosetoclavine (**9**).[10] As this reaction sequence was performed earlier only with semisynthetic ketone (**2**) obtained from natural sources, our approach represents the first total syntheses of these two natural products. The stereochemistry, mainly the configuration at C8 of **8** and **9** has been reinvestigated by NMR spectral techniques; the data and thus the structures were in good accordance with the published ones.

In the proton spectrum of **8** the assignment of the steric orientation of the C7-H protons was obtained from the NOE enhancement observed on the C7-H_β proton (2.47 ppm) upon irradiation of the C5-H

proton. The subsequent irradiation of the C8-Me protons gave NOE on the same, C7-H_β proton. For **9** a similar experiment assigned the resonance at 2.51 ppm to the C7-H_β proton. Irradiation of the C8-OH resonance (4.36 ppm) resulted in a noteworthy NOE on the proton signal of this proton. In addition, the C8-Me protons gave an NOE with the C7-H_α proton (2.78 ppm), which determined the stereochemistry at C8 as depicted in Scheme 2.

It is well documented that ring D of lysergic acid derivatives can be characterized by two dominant conformers[11] and the situation is expected to be similar in the case of 9,10-dehydroclavine type alkaloids.[12] As for the 9,10-dihydroclavine alkaloids, two all-chair conformations seems to be imaginable as well. [13] On the basis of NMR spectral studies our synthetic products (**5**, **7**, **8**, **9**) can be found mainly in the conformers drawn on Scheme 3. The stereostructure of **5** is of special interest. Both the ^{1}H and ^{13}C spectral parameters of rings C and D were rather good agreement with those of some parent compounds[14] for which the configuration and conformations were inferred from X-Ray studies. In the respective stereochemistry ring D is in a chair form where the methyl group is close to the C10-H proton, which explains the significant enhancement of this hydrogen upon irradiation of the methyl resonance. The *trans* C/D ring junction is also corroborated by the coupling value of the C10-H with C5-H proton (10.0 Hz). In accordance with the *trans* arrangement of these protons, no NOE was observed between them.



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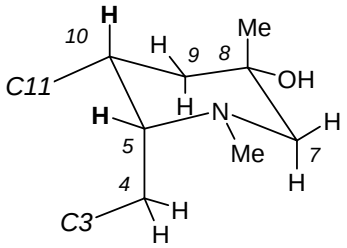

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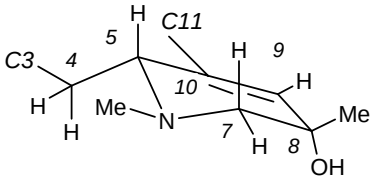

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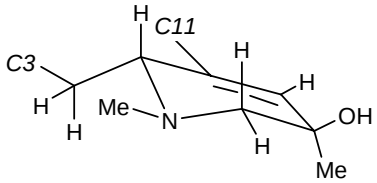

9

	C-4	C-5	C-7
5	27.28	68.15	70.03
6	27.25	65.38	67.24
7	*13.91*	*60.87*	*61.75*
8	27.26	63.45	66.81
9	26.82	63.28	66.21

Scheme 3

On the contrary, the NMR parameters confirmed the *cis* stereochemistry at the C10-C5 ring junction for **7**. The *cis* relationship between the C10-H and C5-H protons follows from also scalar proton coupling (4.0 Hz). The configuration at C8, as depicted in Schemes 2 and 3, was assigned on the basis of the NOE observed on the C10-H signal upon irradiation of the methyl resonance. The C/D ring stereochemistry basically affects the ^{13}C chemical shifts, as the γ-gauche relations cause noteworthy shifts of the C4, C5 and C7 carbons in comparison with their values in the *trans* C/D ring systems.

The novel chemical proofs and correlations of the above compounds will be published in the near future. Further examination of the reactions of **1** and **2** to synthesize other ergot alkaloids or derivatives is in progress.

EXPERIMENTAL

Mps are uncorrected. MS spectra were run on an AEI-MS-902 (70 eV; direct insertion) and on a Kratos-MS-902 mass spectrometer. FAB-MS spectra were measured on a ZAB 2SEQ spectrometer. IR spectra were taken on a Nicolet 7795 FT-IR spectrophotometer. NMR spectroscopy measurements were carried out on a Varian Unity Inova (400 MHz for ^{1}H and 100 MHz for ^{13}C) instrument. Chemical shifts are given relative to TMS=0.00 ppm. Elemental analyses (C, H, N, S) were carried out by Vario EL III (Elementar Analysen System Gmbh) automatic microanalyzer. Preparative separations were performed by column chromatography on Merck Kieselgel 60 (0.063-0.200).

(-)-6-Methylergolin-8-one (6)

To a solution of **2**[1] (200 mg; 0.839 mmol) in dry MeOH (30 mL) 10% Pd/C (100 mg) was added at rt and the suspension stirred under H_2 atmosphere for 8 h. The catalyst was removed by filtration, washed with MeOH (3x20 mL), the filtrate was evaporated under reduced pressure and the residue was purified by column chromatography (eluent: $CHCl_3$ – MeOH, 10/1) to yield **6** (100 mg; 50%) as a pale semisolid product, mp 182-190 ^{o}C (from ether/hexane; decomp); $[\alpha]_D$ = - 64^{o} (c=0.25, MeOH). IR (KBr): 3408, 2930, 2794, 1661, 1618, 1445, 1346, 1062 cm^{-1}. MS (*m*/*z*, %): 241 (100, M^+), 212 (33), 197 (10), 181 (9), 168 (23), 154 (26) 127 (9). ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6), δ: 2.50 (3H, s, N-Me), 2.51 (1H, dd, *J*= 15.2 + 12.8 Hz, H-9_{ax}), 2.67 (1H, ddd, *J*= 11.1 + 9.1 + 4.0 Hz, H-5), 2.76 (1H, ddd, *J*= 14.4 + 11.1 + 1.6 Hz, H-4_{ax}), 3.06 (1H, d, *J*= 14.5 Hz, H-7_{ax}), 3.26 (1H, ddd, *J*= 15.2 + 5.0 + 2.1 Hz, H-9_{eq}), 3.35 (1H, ddd, *J*= 12.8 + 9.1 + 5.0 Hz, H-10), 3.35 (1H, dd, *J*= 14.5 + 2.1 Hz, H-7_{eq}), 3.42 (1H, dd, *J*= 14.4 + 4.0 Hz, H-4_{eq}), 6.74 (1H, dd, *J*= 7.2 + 1.2 Hz, H-14), 6.93 (1H, t, *J*= 1.6 Hz, H-2), 7.10 (1H, dd, *J*= 7.2 + 8.1 Hz, H-13), 7.20 (1H, dd, *J*= 8.1 + 1.2 Hz, H-12), 9.82 (1H, d, *J*= 1.6 Hz, NH). ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6), δ: 27.25 (C-4), 40.57 (C-10), 41.89 (N-Me), 43.00 (C-9), 65.38 (C-5), 67.24 (C-7), 109.59 (C-14), 110.63 (C-3), 112.67 (C-12), 118.79 (C-2), 122.80 (C-13), 126.44 (C-16), 131.93 (C-11), 133.80 (C-15), 206.13 (C-8). Anal. Calcd for $C_{15}H_{16}N_2O$: C, 74.97, H, 6.71, N, 11.65. Found: C, 74.85, H, 6.79, N, 11.61.

(-)-9,10-Dihydroisosetoclavine (5) and (+)- 8α-hydroxycostaclavine (7)

Grignard reagent was prepared from Mg (120 mg, 049 mg atom) and MeI (1.1 g, 8.03 mmol) in dry ether (20 mL). The formed methylmagnesium iodide was dropped into a solution of **6** (160 mg, 0.66 mmol) in benzene (20 mL) at 50 ^{o}C and the reaction mixture was stirred for 1 h at 60 ^{o}C, then was cooled to 0 ^{o}C.

The mixture was decomposed by adding aqueous saturated NH_4Cl solution (5 mL). The phases were separated and the aqueous layer was extracted with $CHCl_3$ (2x20 mL). The combined organic phase was washed with saturated NaCl solution (10 mL) and dried (Na_2SO_4). The filtrate was evaporated under reduced pressure, the residue was separated by column chromatography (eluent: $CHCl_3$ – MeOH, 5/1; R_f of **7** ≈ 0.3, R_f of **5** ≈ 0.5).

Compound (**5**): white crystals (38 mg; 22%), mp 245-250 °C (decomp) (from ether) [lit.,[4] mp 276-278 °C]; $[\alpha]_D$ = - 48° (c=0.25, MeOH) [lit.,[4] $[\alpha]_D$ = - 51° ± 5° (c=0.2, pyridine)]. IR (KBr): 3404, 3099, 2847, 2792, 1609, 1444, 1328, 1126 cm^{-1}. MS (*m*/*z*, %): 256 (100, M^+), 197 (15), 167 (9), 154 (26), 127 (9). ^1H NMR (400 MHz, $CDCl_3$, + DMSO-d_6), δ: 1.43 (3H, s, C8-Me), 1.48 (1H, dd, *J*= 13.0 + 12.2 Hz, H-9_{ax}), 1.98 (1H, ddd, *J*= 10.2 + 10.0 + 4.2 Hz, H-5), 2.14 (1H, d, *J*= 10.7 Hz, H-7_{ax}), 2.38 (3H, s, N-Me), 2.51 (1H, ddd, *J*= 13.0 + 4.0 + 2.0 Hz, H-9_{eq}), 2.57 (1H, dd, *J*= 14.6 + 10.2 Hz, H-4_{ax}), 2.69 (1H, dd, *J*= 10.7 + 2.0 Hz, H-7_{eq}), 2.86 (1H, ddd, *J*= 12.2 + 10.0 + 4.0 Hz, H-10), 3.32 (1H, dd, *J*= 14.6 + 4.2 Hz, H-4_{eq}), 4.42 (1H, s, OH), 6.75 (1H, dd, *J*= 7.2 + 1.2 Hz, H-12), 6.87 (1H, br s, H-2), 7.02 (1H, dd, *J*= 8.1 + 7.2 Hz, H-13), 7.12 (1H, dd, *J*= 8.1 + 1.2 Hz, H-14), 10.24 (1H, br s, NH). ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6), δ: 26.91 (C8-Me), 27.28 (C-4), 39.65 (C-10), 42.44 (C-9), 43.75 (N-Me), 68.00 (C-8), 68.15 (C-5), 70.03 (C-7), 109.11 (C-14), 111.03 (C-3), 112.40 (C-12), 118.64 (C-2), 122.60 (C-13), 126.73 (C-16), 133.36 (C-11), 133.72 (C-15). Anal. Calcd for $C_{16}H_{20}N_2O$: C, 74.96, H, 7.86, N, 10.92. Found: C, 74.91, H, 7.89, N, 10.83.

Compound (**7**): white crystals (15 mg; 9%), mp 165-170 °C (decomp) (from ether); $[\alpha]_D$ = + 24° (c=0.54, MeOH). IR (KBr): 3410, 2929, 2852, 1667, 1444, 1108. cm^{-1}. MS (*m*/*z*, %): 256 (100, M^+), 197 (14), 167 (9), 154 (27), 127 (7). ^1H NMR (400 MHz, $CDCl_3$, 70 °C), δ: 1.37 (3H, s, C8-Me), 1.83 (1H, dd, *J*= 13.4 + 5.0 Hz, H-9_β), 2.22 (1H, dd, *J*= 13.4 + 9.4 Hz, H-9_α), 2.37 (1H, d, *J*= 11.0 Hz, H-7_β), 2.40 (3H, s, N-Me), 2.62 (1H, d, *J*= 11.0 Hz, H-7_α), 2.92 (1H, ddd, *J*= 15.4 + 3.7 + 1.0 Hz, H-4_β), 2.98 (1H, ddd, *J*= 6.7 + 4.0 + 3.7 Hz, H-5), 3.18 (1H, ddd, *J*= 15.4 + 6.7 + 1.5 Hz, H-4_α), 3.34 (1H, ddd, *J*= 9.4 + 5.0 + 4.0 Hz, H-10), 3.85 (1H, br s, in $CDCl_3$ + DMSO-d_6), 6.84 (1H, dd, *J*= 1.5 + 1.0 Hz, H-2), 6.97 (1H, m, H-13), 7.12 (2H, m, H-12 + H-14), 7.80 (1H, br s, NH). ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6, 80 °C), δ: 13.91 (C-4) 27.31 (C8-Me), 38.59 (C-10), 43.07 (N-Me), 43.73 (C-9), 60.87 (C-5), 61.75 (C-7), 68.87 (C-8), 108.87 (C-14), 110.53 (C-3), 114.92 (C-12), 119.07 (C-2), 122.44 (C-13), 126.69 (C-16), 134.52 (C-15), 135.05 (C-11). Anal. Calcd for $C_{16}H_{20}N_2O$: C, 74.96, H, 7.86, N, 10.92. Found: C, 74.90, H, 7.84, N, 11.03.

(+)-Setoclavine (**8**) and **(+)-isosetoclavine** (**9**)

To cold solution of THF (5 mL, -50°C) and methyllithium (2 mL in THF, 2 mmol) a solution of **2** (160 mg, 0.67 mmol) in anisole (5 mL) was added. The temperature of the reaction mixture was allowed to

warm up to 0 °C and stirred for 1 h then was cooled again to - 40 °C. The mixture was decomposed by adding water (3 mL) and the organic solvent was removed by evaporation in reduced pressure (bath: 30 °C). The residue was dissolved in a mixture of $CHCl_3$ (100 mL) and water (7 mL). The phases were separated and the organic layer was washed with saturated NaCl solution (20 mL). The filtrate was evaporated under reduced pressure (4 g). The residue was purified by column chromatography (eluent: hexane - AcOEt, 1/1) to remove anisole. The residue was separated by column chromatography (eluent: hexane – AcOEt - MeOH, 5/5/1; R_f of **8** ≈ 0.4, R_f of **9** ≈ 0.6) to yield yield **8** and **9**.

Compound (**8**): white crystals (40 mg; 24%), mp 216-222 °C (from ether; decomp) [lit.,[9] mp 229-234 °C]; $[\alpha]_D$ = +160° (c=0.25, pyridine) [lit.,[9] $[\alpha]_D$ = + 174° (c= 1.1, pyridine)]. IR (KBr): 3537, 2929, 2844, 1650, 1601, 1450, 1341, 1103, 928 cm^{-1}. MS (*m*/z, %): 254.1424 (calcd 254.1419, $C_{16}H_{18}N_2O$, 100, M^+), 235 (8), 211 (29), 196 (34), 181 (22), 168 (28), 154 (72), 127 (7). ^1H NMR (400 MHz, $CDCl_3$), δ: 1.91 (3H, s, C8-Me), 2.47 (1H, d, *J*= 11.3, H-7_{ax}), 2.54 (3H, s, N-Me), 2.66 (1H, ddd, *J*= 14.6 + 11.3 + 1.7 Hz, H-4_{ax}), 2.78 (1H, dd, *J*= 11.4 + 1.3 Hz, H-7_{eq}), 2.98 (1H, ddd, *J*= 11.3 + 5.5 + 1.9 Hz, H-5), 3.51 (1H, dd, *J*= 14.6 + 5.5, H-4_{eq}), 3.63 (1H, br s, OH), 6.30 (1H, dd, *J*= 1.9 + 1.3 Hz, H-9), 6.90 (1H, dd, *J*= 1.7 + 1.7 Hz, H-2), 7.08 (2H, m, H-13 + H-14), 7.18 (1H, m, H-12), 10.22 (1H, d, *J*= 1.7 Hz, NH). ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6), δ: 26.09 (C8-Me), 27.26 (C-4), 43.88 (N-Me), 63.45 (C-5), 66.58 (C-8), 66.81 (C-7), 109.67 (C-3), 110.47 (C-14), 111.87 (C-12), 119.33 (C-2), 122.79 (C-13), 126.86 (C-16), 127.01 (C-9), 127.60 (C-11), 134.40 (C-15), 135.90 (C-10).

Compound (**9**): white crystals (64 mg; 38%), mp 208-226 °C (from ether; decomp) [lit.,[9] mp 234-237 °C]; $[\alpha]_D$ = + 102° (c=0.25, pyridine) [lit.,[9] $[\alpha]_D$ = + 107° (c=0.5, pyridine)]. IR (KBr): 3374, 2777, 1660, 1604, 1446, 1378, 1220, 1109, 922 cm^{-1}. MS (*m*/z, %): 254.1424 (calcd 254.1419, $C_{16}H_{18}N_2O$, 100, M^+), 235 (11), 211 (37), 196 (34), 181 (24), 168 (32), 154 (79), 127 (9). ^1H NMR (400 MHz, $CDCl_3$ + DMSO-d_6), δ: 1.44 (3H, s, C8-Me), 2.51 (1H, d, *J*= 10.6, H-7_{ax}), 2.53 (3H, s, N-Me), 2.58 (1H, ddd, *J*= 14.5 + 11.4 + 1.7 Hz, H-4_{ax}), 2.78 (1H, dd, *J*= 10.6 + 1.3 Hz, H-7_{eq}), 3.07 (1H, ddd, *J*= 11.4 + 5.6+ 2.1 Hz, H-5), 3.46 (1H, dd, *J*= 14.5 + 5.6 Hz, H-4_{eq}), 4.36 (1H, br s, OH), 6.29 (1H, dd, *J*= 2.1 + 1.3 Hz, H-9), 6.90 (1H, dd, *J*= 1.7 + 1.7 Hz, H-2), 7.07 (2H, m, H-13 + H-14), 7.17 (1H, m, H-12), 10.05 (1H, d, *J*= 1.7 Hz, NH). ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6), δ: 26.82 (C-4), 28.24 (C8-Me), 43.80 (N-Me), 63.28 (C-5), 66.21 (C-7), 67.97 (C-8), 110.09 (C-3), 110.12 (C-14), 111.56 (C-12), 119.19 (C-2), 122.80 (C-13), 126.78 (C-16), 126.20 (C-11), 129.01 (C-9), 134.0 (C-10), 134.39 (C-15).

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