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SYNTHESIS OF THE SPERMIDINE ALKALOID (±)-*N*(1)-ACETYL-*N*(1)-DEOXYMAYFOLINE

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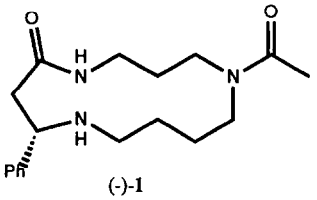
Abstract - The total synthesis of the spermidine alkaloid (±)-*N*(1)-acetyl-*N*(1)-deoxymayfoline ((±)-**1**) was achieved by expansion of rings. The 5-membered cyclic compound **2**was fused with butadiene by intermolecular Diels-Alder cycloaddition. The resulting 7-phenyl-1,6-diazabicyclo[4.3.0]nona-3,7-dien-9-one (**4**) was reductively cleaved with Raney-Ni in alcoholic KOH to afford the mono-cyclic lactam **6**. This was selectively alkylated in high yields to the cyano derivative **7**. Reduction of the nitrile group to the amine derivative **8** went smoothly by use of Adam's catalyst in the presence of acid. Intramolecular transamidation was then accomplished by acid catalysis with TsOH to furnish the 13-membered diazalactam **9**. The synthesis of (±)-**1** was completed by the selective acetylation of the more nucleophilic amino group.

N(1)-Acetyl-*N*(1)-deoxymayfoline ((-)-**1**) is a 13-membered polyamine conjugate isolated from the leaves and roots of *Maytenus buxifolia* (A. Rich.) Griseb. collected in Cuba.[1] The structure of *N*(1)-acetyl-*N*(1)-deoxymayfoline was established by chemical and spectroscopic analysis.



(-)-1

N (1)-Acetyl-*N* (1)- deoxymayfoline

Polyamine conjugates are widespread in numerous plant families,[2] and may have a significant function in plant development. Reportedly, many unique polyamine alkaloids are antibiotics,[3] antiviral and antimicrobial,[4] tumor-inhibitors,[5] antihypertensive,[6] and siderophores.[7]

Our continuing interest in the development of synthetic pathways to the polyamine macrocycles, has prompted us to investigate the synthesis of the spermidine containing alkaloid *N*(1)-acetyl-*N*(1)-deoxymayfoline (**1**).

The basic synthetic template involved the exploitation of the ring-expansion technique. For this purpose the properly functionalized pyrazolone **2** was chosen, which would be oxidized and fused with butadiene in a *Diels-Alder* type cycloaddition. The resulting bicyclic system could then be cleaved and enlarged to the 13-membered diazalactam **1**.

The intermolecular *Diels-Alder* cycloaddition of azodienophiles with 1,3-dienes is an efficient method to obtain diazabicyclo systems.[8] The unstable pyrazolone ring system of type **3** (Table 1) is formed *in situ* by the oxidation of the pyrazolone **2** with lead tetraacetate and is trapped in the presence of butadiene gas through the *Diels-Alder* reaction. Initial investigation on the oxidation of **2** showed that the reaction to 7-phenyl-1,6-diaza-

bicyclo[4.3.0]nona-3,7-dien-9-one (**4**) was more efficiently carried out with lead tetraacetate than with iodobenzene diacetate[9] (Table 1). Due to the fact that the N=N linkage in **3** tends to polymerize at higher temperatures, oxidations were done at low temperatures. This afforded better yields and cleaner products of the bicyclic compound.[10]

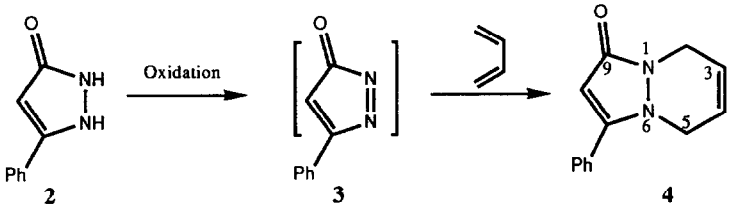
Several attempts were then made to try to cleave the N-N bond in **4** using sodium in liquid NH_3. Although the sodium in liquid NH_3 reducing system is a general one for the cleavage of N-N bonds,[11,12] in certain cases this did not work. When the bicyclic diene **4** or **5** was treated with the sodium in liquid NH_3 reducing system there resulted not the N-N cleaved product, but a hydrogenolytic C(5)-N(6) fission occurred. This concluds that upon treatment by sodium in liquid NH_3, a C-N hydrogenolytic fission takes place in preference to a N-N reductive cleavage if the latter is allylic to the double bond.

Another potential candidate for the N-N reductive cleavage is Raney-Ni. The N-N bridge cleavage by Raney-Ni in bicyclic systems to produce monocycles have been reported in several literatures;[13] but in no case were the N-N bond allylic to the double bond. Treatment of **5** with Raney-Ni in alcoholic KOH under 1 atm of H_2 not only reduces the conjugated double bond but simultaneously cleaves the N-N bridge to furnish the 9-membered lactam **6** (Scheme 1). The 9-membered lactam **6** could also be produced directly from adduct **4** by the Raney-Ni reducing system but yields were rather low due to side products. In the absence of KOH, the reductive ring opening is slow and 7-phenyl-1,6-diazabicyclo[4.3.0]nonan-9-one[11] is the major product. Lactam **6** has already been prepared in different steps,[11] but our synthetic method gives higher yields, is easy to reproduce and is straightforward with shorter synthetic steps.

Attempts were made to protect the secondary amino group in **6** by either BOC-ON or BOC_2O in CH_2Cl_2 and *N,N*-dimethylaminopyridine but without success, because of the bulkiness of the BOC group and the sterically hindered benzylic amine moiety.

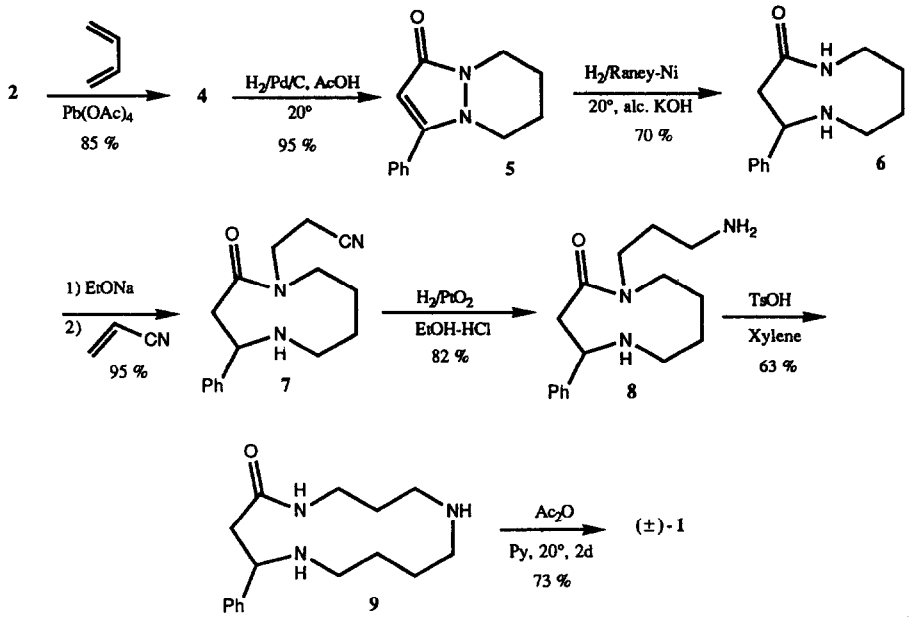
Attention was next turned to the selective alkylation of the secondary amide function in **6** without protecting the amino group. Various alkylating methods were undertaken but they were unsatisfactory.[14]

Table 1. Oxidation of the Pyrazolone **2** in the Presence of Butadiene in Dry Methylenechloride.



2 **3** **4**

Oxidizing agent	Temperature [°C]	% Yield of **4**
$PhI(OAc)_2$	20	25
$PhI(OAc)_2$	–20	30
$Pb(OAc)_4$	–5	27
$Pb(OAc)_4$	–20	85
$Pb(OAc)_4$	–35	95



Scheme1.

In our work on the *N*-alkylation of amide **6**, EtONa alkylating reagent was found to be the most successful alkylating reagent for this process. Best results were obtained when acrylonitrile was added to the sodium salt of the 9-membered azalactam **6**, prepared by adding 1.1 eq of EtONa to the dry substrate **6**, generating **7** in 95% (Scheme 1). Thus due to the difference of acidity between the benzylic amine hydrogen and that of the amide, the later is chemoselectively alkylated. The cyano derivative **7** was then catalytically reduced to the corresponding amine **8** using PtO_2 in acidic solutions.

The last stages in the synthetic sequence, the ring enlargement[15] of the 9-membered diazalactam **8** to the 13-membered diazalactam **9** proved to be troublesome. Under basic reaction conditions the ring enlargement of compound **8** was not observed: Treating **8** with 2N NaOH at 50° [11] or with 1 eq *t*-BuOK overnight gave no reaction. In contrast, refluxing **8** with 2 eq *t*-BuOK in toluene[16] or with lutidine[17] gave several decomposition products. These unsuccessful attempts to enlarge cycle **8** to **9** by bases dictated the use of acid to get an acid catalyzed ring enlargement. Thus, treating the 9-membered diazalactam **8** with 0.8 eq of TsOH in boiling xylene[18] for 3 h furnished the desired 13-membered diazalactam **9** in 63% yield. Compound **9** was synthesized earlier by different methods.[11]

The synthesis of (±)-*N*(1)-acetyl-*N*(1)-deoxymayfoline (**1**) was completed by acetylation of the more nucleophilic secondary aliphatic amino functionality, using Ac_2O / pyridine for two days, in 73% yield. The remarkable selective acetylation was the outcome of the difference in nucleophilic character between the aliphatic amino group and the benzylic one.

The synthetic product was characterized by comparing its spectroscopic data with the values cited previously.[1] The CH_3 group in the *N*(1)-acetyl moiety exhibited two singlets at 2.06 and 2.09 ppm due to two conformers. This is in accordance with the data published for the natural product. Upon heating to 55°, only one singlet was obtained at 2.06 ppm. Moreover, the ^{13}C-NMR spectrum of **1** shows doubling of nearly all signals

indicating the presence of two conformers owing to the different conformation of the amide bond. Similar doubling of signals was also observed in the NMR spectra of the 13-membered spermidine alkaloid loesenerine.[19]

EXPERIMENTAL

General Procedures. All solvents were distilled before use. Merck silica gel 60 (0.04-0.06 mm) was used for column chromatography. Merck-Si_{F254} pre-coated aluminium plates were used for TLC. Melting points were measured on a Mettler FP5/FP2 apparatus. IR spectra, in cm^{-1}, were recorded on an Perkin-Elmer 781 spectrophotometer. ^{1}H-NMR measurements were carried out on a Bruker AC 300 (300 MHz); or, as stated, on one of the following instruments: either on a Bruker AM 400 (400 MHz) or Varian XL 200 (200 MHz), in $CDCl_3$. ^{13}C-NMR measurements were carried out on a Varian XL 200 (50.4 MHz), in $CDCl_3$. Chemical shifts are given in ppm (J in Hz) relative to the deuterated solvents used. EI-MS (70 eV) and CI-MS (isobutane, 150 eV) data, given in m/z (rel.%), were measured on a Finnigan MAT 90 mass spectrometer.

7-Phenyl-1,6-diazabicyclo[4.3.0]nona-3,7-dien-9-one (4). All equipment was dried and purged with argon. Pyrazolone **2**, 20 g (0.125 mol) in 500 ml dry CH_2Cl_2 (the yields in dry acetone or acetonitrile were less satisfying) was cooled to -35° and butadiene gas condensed. (The cycloaddition reaction is independent of the amount of condensed butadiene gas). With vigorous stirring 56.4 g (0.127 mol) of lead tetraacetate was added in small portions from an addition funnel. After complete addition, stirring at this temperature was continued overnight. The reaction mixture was basicified with saturated $NaHCO_3$ solution, filtered through Celite® and washed with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and evaporated *in vacuo* at 35° to furnish **4** in good yields, and was used for the next step without further purification. However, filtration over neutral aluminium oxide (activity III, $CHCl_3$ / CCl_4 = 4:1) provides 22.5 g (85%) a purer material (greenish oil).The resulting adduct **4** is unstable and tends to decompose slowly at ambient temperatures; it is also to silica gel. IR ($CHCl_3$): 3390 (br., disubst. amide), 3060 (=C-H), 2960, 2855, 1675 (C=O), 1660 (C=C), 1490, 1450, 1385 and 1260 (C-N), 700 and 650 (arom.). ^{1}H-NMR (200 MHz): 7.45-7.24 (*m*, 5 arom. H); 6.03 (*m*, H-C(3)); 5.90 (*m*, H-C(4)); 5.74 (*s*, H-C(8)); 4.34 (*m*, 2 H-C(2)); 3.91 (*m*, 2 H-C(5)). ^{13}C-NMR: 165.11 (*s*, C(9)); 157.55 (*s*, C(7)); 129.71 (*d*, 1 arom. C); 128.46 (*d*, 2 arom. C); 128.27 (*s*, 1 arom. C); 127.76 (*d*, 2 arom. C); 120.75 (*d*, C(3)); 120.09 (*d*, C(4)); 99.22 (*d*, C(8)); 47.28 (*t*, C(2)); 41.07 (*t*, C(5)). CI-MS: 213 (100, $[M + 1]^+$). EI-MS: 212 (17, $M^{+\cdot}$), 166 (17), 145 (9), 123 (9), 102 (15), 85 (9), 81 (10), 78 (17), 72 (10), 71 (16), 69 (16), 59 (95), 56 (20), 52 (13), 43 (43), 40 (15).

7-Phenyl-1,6-diazabicyclo[4.3.0]non-7-en-9-one (5). Compound **4**, 2.25 g (0.01 mol) in 45 ml glacial AcOH was hydrogenated for 1 h over 0.1 g of 10% Pd/C under 1 atm of H_2 and at 20°. The product **5** was not sufficiently resolved on TLC, so the reaction was followed by GC. The acetic acid was evaporated under reduced pressure and the residual oil was made basic with NH_4OH and extracted with $CHCl_3$. The $CHCl_3$ layer was dried over Na_2SO_4, evaporated, and then filtered over neutral aluminium oxide (activity III, $CHCl_3$ / CCl_4 = 9:1) to afford 2.10 g (95%) of **5**. M.p. (Et_2O) 102°. IR ($CHCl_3$): 3390, 2980, 2870, 1700, 1640, 1490, 1450, 1400, 1280, 700, 660. ^{1}H-NMR (200 MHz): 7.45 (*m*, 5 arom. H); 5.71 (*s*, H-C(8)); 3.86 (*t*, 2 H-C(2)); 3.30 (*t*, 2 H-C(5)); 1.99-1.82 (*m*, 2 H-C(3), 2 H-C(4)). ^{13}C-NMR: 164.77 (*s*, C(9)); 157.63 (*s*, C(7)); 129.85 (*d*, 1 arom. C); 128.74 (*d*, 2 arom. C); 128.15 (*s*, 1 arom. C); 127.97 (*d*, 2 arom. C); 99.56 (*d*, C(8)); 49.83 (*t*, C(2)); 40.36 (*t*, C(5)); 23.16 (*t*, C(3)); 22.86 (*t*, C(4)). EI-MS: 214 (100, $M^{+\cdot}$), 185 (44), 173 (6), 158 (8), 129 (10), 116 (8), 102 (48), 91 (29), 77 (21), 55 (22), 44 (50), 42 (44).

3-Phenyl-4-azaoctanelactam (6). To 0.5 g of **5** in 30 ml EtOH and 0.5 g KOH, was added three small portions of Raney-Ni (activity W-7). Raney-Ni was washed with EtOH prior to the addition and added as a slurry. A permanent pressure of H_2 was maintained by a filled balloon of hydrogen. The reaction was followed by TLC and stopped after 32 h when no starting material could be detected. The reaction mixture was filtered through Celite® and the filtrate quenched with NH_4Cl. It was then evaporated *in vacuo* and the residual salt dissolved in water, basified with $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was dried, evaporated and chromatographed (CH_2Cl_2 / MeOH = 95:5) furnishing **6** (0.36 g) in 70% yield. M.p. (CCl_4) 94.5°. IR ($CHCl_3$): 3350 (NH), 2940 (arom.), 1670 (C=O), 1550, 1450, 700. ^{1}H-NMR (400 MHz): 7.37-7.35 (*m*, 2 arom. H);

7.34-7.23 (*m*, 3 arom. H); 6.98 (br., *d*, H-N(9)); 3.75-3.71 (*m*, H-C(8)); 3.57 (*dd*, *J* = 11.9, 2.7, H-C(3)); 2.92-2.77 (*m*, 2 H-C(5)); 2.75-2.71 (*m*, H-C(8)); 2.50 (*t*, *J* = 11.9, H-C(2)); 2.36 (*dd*, *J* = 11.9, 2.7, H-C(2)); 1.96-1.89 (*m*, H-C(7)); 1.85 (br., H-N(4)); 1.63-1.59 (*m*, H-C(7)); 1.51-1.39 (*m*, 2 H-C(6)). ^{13}C-NMR: 176.21 (*s*, C(1)); 144.56 (*s*, 1 arom. C); 129.04 (*d*, 2 arom. C); 127.53 (*d*, 1 arom. C); 125.77 (*d*, 2 arom. C); 61.46 (*d*, C(3)); 51.42 (*t*, C(2)); 46.21 (*t*, C(8)); 40.27 (*t*, C(5)); 29.17 (*t*, C(7)); 25.73 (*t*, C(6)). EI-MS: 218 (69, $M^{+\cdot}$), 201 (5), 190 (10), 178 (45), 159 (24), 146 (67), 132 (38), 118 (79), 104 (100), 91 (39), 77 (25), 70 (30), 56 (9), 41 (17). **6**·HCl: M.p. (EtOH 99.5%) 188.4-188.8°. IR (KBr): 3200, 3068, 1650 + 1610 (C=O), 1563, 1495, 1469, 1448, 1428, 761, 724, 701.

3-Phenyl-9-(2'-cyanoethyl)-4-azaoctanelactam (7). To 254 mg (1.16 mmol) of **6** was added 1.28 mmol EtONa (0.42 ml of 21% solution in EtOH) and the mixture was sonicated in a water bath till complete dissolution. Afterwards, it was evaporated to dryness taking care that no humidity gets in. To the remaining salt was added dry benzene and at 20° acrylonitrile was added dropwise under argon. The reaction was exothermic and cooling in an ice bath was required to maintain the reaction at 20°. The addition of acrylonitrile was stopped when all the starting material has been consumed judged by TLC checking. The reaction mixture was then poured into water and extracted with CH_2Cl_2. Chromatography (2% MeOH in $CHCl_3$) furnished **7** (300 mg) in quantitative yield. ^{1}H-NMR: 7.44-7.25 (5 arom. H); 4.99-4.89 (*m*, H-C(8)); 4.03-3.95 (*m*, H-C(1')); 3.75 (*dd*, H-C(3)); 3.44-3.38 (*m*, H-C(8)); 3.23-3.09 (*m*, H-C(2)); 2.99-2.74 (*m*, H-C(1'), 2 H-C(5)); 2.67-2.57 (*m*, H-C(2), 2 H-C(2')); 2.00-1.89 (*m*; H-C(7)); 1.64-1.58 (*m*, H-C(7), H-N(4)); 1.43 1.39 (*m*, 2 H-C(6)). ^{13}C-NMR: 174.02 (*s*, C(1)); 145.95 (*s*, 1 arom. C); 133.05 (*s*, CN); 128.62 (*d*, 2 arom. C); 126.89 (*d*, 1 arom. C); 125.15 (*d*, 2 arom. C); 60.66 (*d*, C(3)); 49.07 (*t*, C(2)); 48.55 (*t*, C(1')); 46.11 (*t*, C(8)); 40.94 (*t*, C(5)); 26.02 (*t*, C(7)); 21.54 (*t*, C(6)); 15.64 (*t*, C(2')). EI-MS: 271 (25, $M^{+\cdot}$), 243 (6), 228 (17), 203 (9), 159 (63), 146 (89), 132 (52), 119 (100), 104 (83), 91 (41), 77 (25), 66 (44), 54 (43), 42 (35).

3-Phenyl-9-(3'-aminopropyl)-4-azaoctanelactam (8). A solution of 250 mg of **7** in 12 ml MeOH and 0.65 ml HCl (32%) was hydrogenated overnight under 1 atm of H_2 and 20° in the presence of Adam's catalyst (73 mg). Usual work-up procedure was followed by chromatography ($CHCl_3$ / MeOH / 25% NH_4OH = 78: 19: 3) to give 210 mg (82%). The compound was detected by spraying with *Fluram*® reagent. ^{1}H-NMR: 7.36-7.25 (*m*, 5 arom. H); 4.78-4.71 (*m*, H-C(8)); 4.00-3.90 (*m*, H-C(1')); 3.79 (*dd*, *J* = 9.8, 1.3, H-C(3)); 3.30-3.24 (*m*, H-C(8)); 3.17 (*dd*, *J* = 12.6, 10.3, H-C(2)); 2.99-2.90 (m, 2 H-C(5)); 2.82-2.67 (m, H-C(1'), 2 H-C(3')); 2.62 (*dd*, *J* = 12.6, 2.60, H-C(2));1.95 (br. *m*, H-C(7), H-N(4), NH_2); 1.77 (*m*, 2 H-C(2')); 1.58-1.52 (*m*, H-C(7)); 1.48-1.40 (*m*, 2 H-C(6)). ^{13}C-NMR: 173.80 (*s*, C(1)); 146.07 (*s*, 1 arom. C); 128.56 (*d*, 2 arom. C); 126.79 (*d*, 1 arom. C); 125.23 (*d*, 2 arom. C); 60.71 (*d*, C(3)); 48.95 (*t*, C(2)); 46.98 (*t*, C(1')); 45.92 (*t*, C(8)); 40.68 (*t*, C(5)); 38.69 (*t*, C(3')); 29.64 (*t*, C(2')); 25.79 (*t*, C(7)); 21.77 (*t*, C(6)). EI-MS: 275 (24, $M^{+\cdot}$), 259 (10), 245 (16), 232 (13), 219 (30), 203 (14), 189 (8), 173 (25), 160 (73), 146 (45), 129 (46), 118 (52), 104 (61), 100 (22), 98 (60), 91 (57), 84 (66), 77 (29), 70 (100), 56 (63), 44 (72).

3-Phenyl-4,9-diazadodecanelactam (9). To 125 mg (0.45 mmol) of **7** was added 0.8 eq (69 mg) of TsOH and refluxed in xylene for 3h. The reaction mixture was then basified, extracted with CH_2Cl_2; the organic layer dried, evaporated *in vacuo* and chromatographed ($CHCl_3$ / MeOH / 25% NH_4OH = 7:3:1) to afford 79 mg of **9** (63%). ^{1}H-NMR: 8.50 (br., H-N(13)); 7.28-7.16(*m*, 5 arom. H); 4.05 (*dd*, *J* = 11.7, 3.1, H-C(3)); 3.79-3.73 (*m*, H-C(12)); 3.38 (br., H-N(9)); 3.22-3.12 (*m*, H-C(12)); 3.11-2.95 (*m*, 2 H-C(10)); 2.84-2.74 (*m*, 2 H-C(5)); 2.65 (*dd*, *J* = 14.4, 11.7, H-C(2)); 2.60-2.53 (*m*, H-C(8)); 2.48 (*dd*, *J* = 14.4, 3.1, H-C(2)); 2.35-2.28 (*m*, H-C(8)); 1.97-1.83 (*m*, H-C(6), 2 H-C(11), H-N(4)); 1.70-1.54 (*m*, H-C(6), H-C(7)); 1.50-1.46 (*m*, H-C(7)). ^{13}C-NMR: 171.60 (*s*, C(1)); 142.51 (*s*, 1 arom. C); 128.34 (*d*, 2 arom. C); 126.95 (*d*,1 arom. C); 126.21 (*d*, 2 arom. C); 59.78 (*d*, C(3)); 49.19 (*t*, C(2)); 48.67 (*t*, C(12)); 45.42 (*t*, C(10)); 44.71 (*t*, C(5)); 39.27 (*t*, C(8)); 27.37, 26.96, 26.59 (*3t*, C(11), C(7), and C(6)). EI-MS: 275 (7, $M^{+\cdot}$), 259 (14), 258 (73), 232 (7), 217 (10), 188 (13), 167 (22),160 (14), 146 (23), 149 (63), 131 (38), 126 (19), 118 (10), 104 (23), 98 (24), 84 (56), 77 (19), 70 (100), 57 (58), 44 (60).

(±)-N(1)-Acetyl-N(1)-deoxymayfoline (1). To 100 mg of **9** in 10 ml CH_2Cl_2 was added with cooling in an ice bath 1.1 eq pyridine and 1.1 eq Ac_2O. The ice bath was removed and the reaction was stirred for 48 h at 20°. The reaction was thereafter basified with NH_4OH evaporated *in vacuo* and chromatographed ($CHCl_3$ / MeOH / 25% NH_4OH = 78: 19: 3) to furnish a 73% yield of the natural product **1** (84 mg). IR ($CHCl_3$): 3450,

3000, 2930, 1660, 1630, 1550, 1520, 1440, 1240, 700. ^{1}H-NMR: 7.65 (br. *s*, H-N(5)); 7.37-7.20 (*m*, 5 arom. H); 3.94 (*2dd*, *J* = 7.7, 4, H-C(8)); 3.63-3.53 (*m*, H-C(4)); 3.51-3.21 (*m*, 2 H-C(2), 2 H-C(13)); 3.19-2.96 (*m*, H-C(4)); 2.69-2.61 (*m*, H-C(10)); 2.52-2.38 (*m*, 2 H-C(7), H-C-(10)); 2.09 and 2.06 (*2s*, two conformers for CH_3); 2.03-1.67 (*m*, 2 H-C(3), 2 H-C(12)); 1.65-1.31 (*m*, 2 H-C(11), H-N(9)). ^{13}C-NMR: 172.02 (*s*, C(6)); 169.96 (*s*, $COCH_3$)); 142.69 (*s*, 1 arom.C); 128.65 (*d*, 2 arom.C); 127.29 (*d*, 1 arom.C); 126.02 (*d*, 2 arom. C); 60.68 (*d*, C(8)); 47.16 (*t*, C(7)); 45.09 (*t*); 44.92 (*t*); 42.13 (*t*); 36.85 (*t*); 27.57 (*t*); 24.29 (*t*); 24.12 (*t*); 21.17 (*q*, CH_3). EI-MS: 318 (73, $[M + 1]^+$), 301 (11), 275 (55), 259 (9), 250 (30), 246 (31), 234 (8), 220 (21), 204 (26), 190 (60), 172 (62), 160 (69), 146 (100), 131 (29), 118 (23), 100 (37), 84 (33), 70 (45), 56 (26), 43 (94).

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Dedicated to Professor Gerhard Spiteller on the occasion of his 60th birthday.

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