Efficient Synthesis of (±)-Horsfiline through the MgI_2-Catalyzed Ring-Expansion Reaction of a Spiro[cyclopropane-1,3′-indol]-2′-one

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Dedicated to Prof. Dr. *José Barluenga* on the occasion of his 60th birthday

We report a short synthetic route to (±)-horsfiline that provides the racemate in five steps from commercially available, substituted isatin in 41% overall yield. Efficient entry into the spiro[oxindole-pyrrolidine] ring system is possible through the application of the cyclopropane opening/ring expansion chemistry we have described with MgI_2 as a bifunctional catalyst.

1. Introduction. – The spiro[indole-pyrrolidine] nucleus is a key structural component found in a number of pharmacologically important natural products such as vinblastine and vincristine. These compounds are cell-cycle-specific cytostatic agents that arrest mitosis at metaphase by acting as spindle poisons. Because they disproportionately affect proliferating cells, they have become of prime importance in cancer chemotherapy [1]. The related spiro[indole-pyrrolidin]-2-one ring system has been identified in a number of other cytostatic alkaloids of potential interest to human medicine, such as spirotryprostatin A and strychnophylline [2]. These natural products embody stereochemical and structural complexities that provide a challenge in the evolution of modern synthetic chemistry [3][4]. In combination, these factors provide an impetus for the development of novel, versatile, and efficient reaction methods and strategies aimed at the synthesis of the spiro[indole-pyrrolidin]-2-one moiety, as exemplified recently in the elegant total synthesis of spirotryprostatin A by *Danishefsky* and co-workers [5].

As part of our interest in developing novel approaches for the stereoselective synthesis of alkaloids, we have recently reported a number of useful strategies [6]. In this regard, we have documented a new approach to spiro[indole-pyrrolidines], involving the reaction of spiro[cyclopropane-indol]-2′-one **1** and *N*-alkyl- as well as *N*-arylsulfonyl aldimines **2** (*Scheme 1*) [7]. The successful implementation of this cyclopropane ring-expansion strategy resulted from the unique properties of MgI_2 as a bifunctional catalyst wherein the electrophilic metal center (Mg^{II}) and nucleophilicity of the counterion (I^-) appear to operate synergistically, leading to the formation of a reactive γ-iodo enolate **3**[2]). The ambiphilic character of this intermediate allows for

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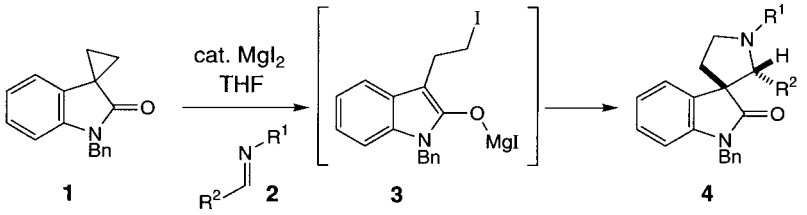
[1]) Part of the Diploma Thesis of *C.F.*, ETH-Zürich, 2000.

[2]) MgI_2 has been observed to function as a uniquely effective catalyst in asymmetric *Diels-Alder* and aldol addition reactions. Its superiority has been attributed to the facile dissociation of I^- from L_2MgI_2 [8].

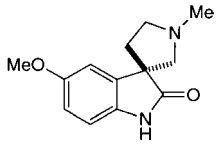
efficient reaction with imines, leading to the formation of spiro[indole-pyrrolidin]-2-ones. Our preliminary work in this area has been focussed primarily on the use of *N*-tosyl and *N*-allyl imines derived from aromatic and aliphatic aldimines derived from propionaldehyde, isobutyraldehyde, and α,β-unsaturated aldehydes.

Scheme 1



1 **2** **3** **4**

The successful application of this methodology to structures typified by horsfiline **5** necessitates that the methodology we have delineated be successfully executed with formaldehyde-derived aldimines. In this regard, we initiated a project aimed at the total synthesis of (±)-horsfiline (**5**) with the dual goals of expanding the methodology to include *N*-methylmethanimine, or its equivalent, and of applying the method to an efficient synthesis strategy for a spiro[indole-pyrrolidin]-2-one.



(–)-Horsfiline

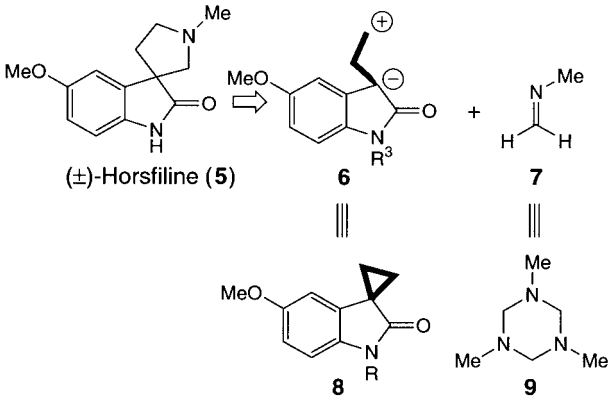
(–)-**5**

Background. – Horsfiline (**5**) is one of the structurally simpler oxindole alkaloids isolated in 1991 by *Bodo* and co-workers from *Horsfieldia superba*, a tree from Malaysia, whose extracts are commonly employed in local medicine [9]. In the context of confirming the proposed structure, these workers carried out a synthesis of the racemate through oxidative rearrangement reaction of 1,2,3,4-tetrahydro-*N*-methyl-6-methoxy-β-carboline. Subsequent to the isolation work, additional syntheses have been reported of the natural product, employing a variety of strategies [10–14]. The most general approach to the installation of the requisite spirocyclic core such as that found in (–)-horsfiline ((–)-**5**) is typified by an annulation sequence wherein a tryptamine derivative is subjected to a *Pictet-Spengler* condensation to afford the corresponding tetrahydrocarbolines followed by oxidative rearrangement [15][16].

In our retrosynthetic analysis, we envisioned a different approach to such ring systems wherein **5** is disconnected to synthon **6** and aldimine **7** (*Scheme 2*). The dissonant charge-affinity pattern manifest in **6** is congruent with that of spiro[cyclopropane-indol]-2′-one **8**. Indeed, this pattern is manifest in the well-known reactivity of

cyclopropanes, when substituted with electron-withdrawing groups[3]), to serve as homo-*Michael* acceptors [17][18]. The strategy plan we had envisioned for the synthesis of horsfiline would necessitate the nucleophilic ring opening of a *singly* activated cyclopropane ring. As a way of implementing the synthetic plan, we speculated that the use of a catalyst exhibiting dual electrophilic and nucleophilic activation would furnish an intermediate possessing the ambiphilic reactivity (*i.e.*, **3**), which could be intercepted by the imine, thus enabling the desired reaction [8]. It is important to note, however, that the use of such a strategy would lead to the desired spiro[indole-pyrrolidin]-2-ones, provided competitive self-immolative consumption of the intermediate species *via* intramolecular *O*-alkylation is precluded. In this regard, the fact that the horsfiline synthesis would employ the aldimine derived from formaldehyde, *i.e.*, methanimine, posed a potential problem. Because methanimines typically are handled as the corresponding trimeric triazines, the success of the annulation strategy would depend on the stability of reactive intermediate **3**, in light of potential intramolecular *O*-alkylation, under the thermal conditions prescribed for the triazine fragmentation reaction to give methanimine.

Scheme 2

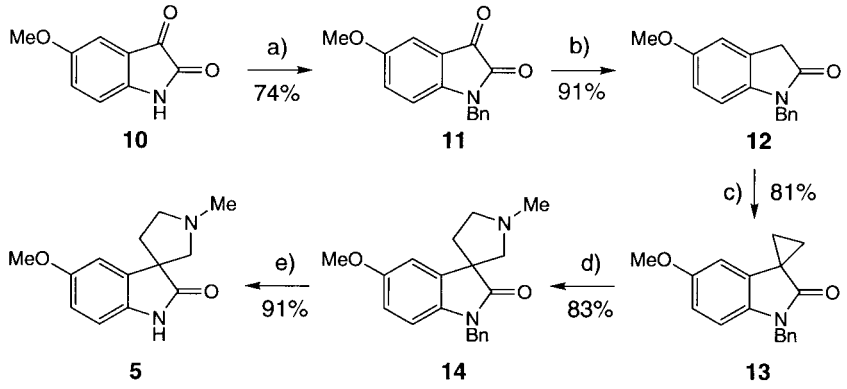


Results and Discussion. – The synthesis route commenced with the *N*-benzylation of the commercially available 5-methoxyisatin **10** to furnish **11** as a red crystalline solid (m.p. 117–118°) in 74% yield (*Scheme 3*). Subsequent subjection of **11** to the *Wolff-Kishner* reduction ($NH_2NH_2 \cdot H_2O$, reflux) afforded oxindole **12** (91%). The success of the strategy outlined above depends on the availability of the spiro[cyclopropane-indol]-2′-one ring system. In this regard, we were pleased to observed that, as reported, the Na-enolate derived from **12** underwent clean alkylative cyclization with 1,2-dibromoethane to afford **13** as a crystalline solid (m.p. 112–113°) in 81% yield.

The stage was set for the key cyclopropane fragmentation/ring-expansion reaction. Treatment of **13** with 1,3,5-trimethyl-1,3,5-triazinane (**9**) and 5.5 mol-% MgI_2 in THF at reflux furnished the desired spiro[indole-pyrrolidin]-2-one **14** in 83% yield. Removal

[3]) The reactivity of cyclopropanes towards nucleophiles is typically limited to those activated by two electron-withdrawing groups or those that are highly strained. Exceptions to this generalization occur with strong nucleophiles such as metal selenides and Ni-catalyzed additions of organoaluminums (see [18]).

Scheme 3



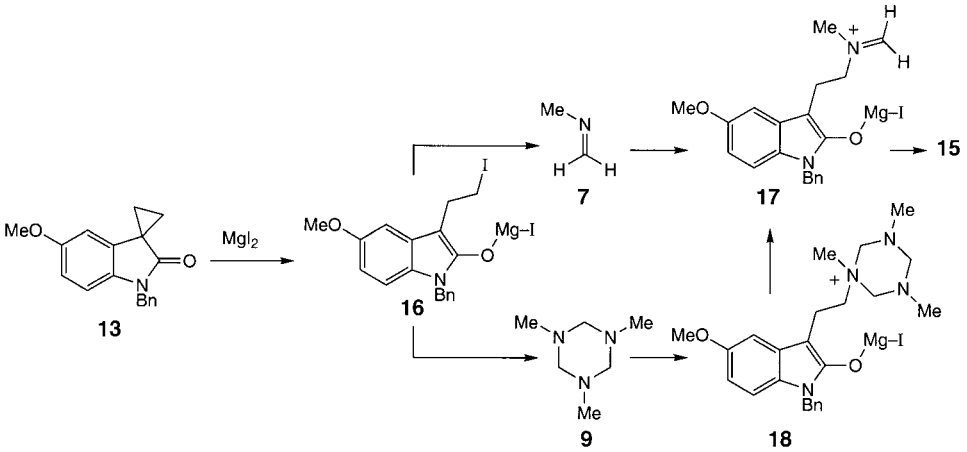
a) NaH, BnBr, DMF, 23°. b) $N_2H_4 \cdot H_2O$, reflux. c) 1,2-Dibromoethane, NaH, DMF, 23°. d) MgI_2 (5.5 mol-%), 1,3,5-trimethyl-1,3,5-triazinane (**9**), THF, 125°. e) Na/NH_3, −78°.

of the *N*-Bn protecting group was effected by subjecting **14** to dissolving metal reduction (Na/NH_3), affording (±)-horsfiline (**5**) in 91% yield. The racemic horsfiline obtained from the synthetic sequence displayed spectroscopic properties (^{1}H-NMR, ^{13}C-NMR, IR, MS) identical in all respects with that reported for the authentic material.

In the synthesis of (±)-horsfiline (**5**) reported herein, we have demonstrated the use of 1,3,5-trimethyl-1,3,5-triazinane as an equivalent for *N*-methylmethanimine under the conditions of the ring-expansion reaction of spiro[cyclopropane-indol]-2′-ones. The conversion of 1,3,5-trimethyl-1,3,5-triazinane to *N*-methyl methanimine has been reported to take place at $T > 250°$ under conditions of flash-vacuum-pyrolysis [19][20]. These conditions are considerably harsher than those we utilized in the construction of the spiro[indole-pyrrolidin]-2-one. At least two putative mechanistic pathways for the annulation reaction can be envisioned: reaction of free *N*-methyl methanimine with **16**, directly affording iminium **17**, or alkylation of the triazinane to give cationic quaternized amine **18** (*Scheme 4*). This latter intermediate could subsequently undergo fragmentation to **17**. Although it is not possible at this time to differentiate between mechanistic alternatives involving reaction of free *N*-methylmethanimine *vs.* 1,3,5-trimethyl-1,3,5 triazinane itself, we favor the latter mechanism, as it is unlikely that in refluxing a significant quantitity of *N*-methyl methanimine is generated (*Scheme 4*).

Conclusion. – We have reported a short synthetic route to (±)-horsfiline with which the natural product can be accessed as its racemate in five steps from commercially available substituted isatin in 41% overall yield. Efficient entry into the spiro[indole-pyrrolidin]-2-one ring system is possible through the application of the cyclopropane opening/ring expansion chemistry we have described with MgI_2 as a bifunctional catalyst. This synthesis thus demonstrates the viability of the process to generate adducts formally derived from *N*-alkyl methanimines. Additional studies of this process are ongoing, particularly as it pertains to asymmetric induction, and these will be reported as they become available.

Scheme 4



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Experimental Part

General. All reactions were carried out in oven-dried glassware under an atmosphere or Ar or N_2. The solvents used for reactions were reagent grade and purchased from commercial suppliers; THF was degassed with Ar, then passed through two 4×36 inch columns of anh. neutral *A-2* alumina (8×14 mesh; *La Roche Chemicals*; activated under a flow of Ar at 350° for 3 h) to remove H_2O. For chromatography, technical-grade solvents, distilled prior to use, were used. All chemicals were purchased from *Fluka* or *Aldrich* in *purum* or higher quality, 5-methoxyisatin (> 99.8%) was purchased from *Spectrum Laboratory Products*, Gardena, CA, USA. Chromatographic purification was performed as flash chromatography using *Fluka* silica gel *60* (40–63 μm) or neutral *Merck* silica *60* (40–63 μm), with 0.2–0.4 bar N_2 pressure. TLC: *Merck* silica gel *60* F_{254} TLC glass plates; visualized with UV light or ceric ammonium molybdate (CAM stain; 500 ml of 10% H_2SO_4 soln., 25 g of $(NH_4)Mo_7O_{24} \cdot 6H_2O$, 1 g of $Ce(SO_4)_2$). M.p.: *Büchi 510* with open glass capillaries; uncorrected. IR: *Perkin Elmer Spectrum RX-I FT-IR* spectrophotometer as KBr pellets. NMR: *Varian-Mercury-300* or *Varian-Gemini-300* (^{1}H: 300 MHz, ^{13}C: 75 MHz) in $CDCl_3$, with the internal $CHCl_3$ signal as reference (^{1}H: 7.27 ppm, ^{13}C: 77.0 ppm). MS: *VG ZAB2-SEQ* spectrometer (FAB: bombardment with 35 keV Cs-atoms (3-nitrobenzyl-alcohol (NOBA) matrix)); in *m/z* (rel. %). Elemental analyses were conducted by the Microanalytical Laboratory of the Laboratorium für Organische Chemie, ETH-Zürich.

*1-Benzyl-5-methoxy-1*H*-indol-2,3-one* (**11**). *5-Methoxy-1*H*-indole-2,3-dione* (**10**; 1.000 g, 5.645 mmol) was placed in a two-neck flask, and dry DMF (10 ml, over 4-Å molecular sieves) was added. NaH (142 mg, 5.92 mmol) was added portionwise to the brown soln., which changed color to dark blue. After the H_2 evolution had ceased, BnBr (771 μl, 6.49 mmol) was added dropwise *via* a syringe, the color changed back to brown-red. After stirring for 1 h at 23°, H_2O (30 ml) was added, and a red sticky solid was observed to precipitate. The aq. layer was extracted with AcOEt (8×40 ml), and the combined org. layers were dried (anh. Na_2SO_4). The solvent was evaporated *in vacuo*. The remaining residual DMF was removed under high vacuum/60°. The sticky red solid was purified by chromatography on silica gel (hexane/AcOEt 2:1), and 140 mg of **10** and 1.114 g (74%) of **11** as red solid were obtained. Recrystallization from hexane afforded a pure sample as red needles. M.p. 117–118°. IR: 1723*s*, 1621*m*, 1602*m*, 1494*s*, 1472*w*, 1437*w*, 1349*w*, 1336*m*, 1313*w*, 1271*w*, 1238*w*, 1175*m*, 1145*w*, 1080*w*, 1047*w*, 1018*w*, 836*m*, 773*m*, 695m, 473*w*. ^{1}H-NMR: 7.37–7.31 (*m*, 5 arom. H); 7.16 (*d*, $J = 2.8$, 1 arom. H); 7.03 (*dd*, $J = 8.4$, 2.8, 1 arom. H); 6.68 (*d*, $J = 8.4$, 1 arom. H); 4.91 (*s*, CH_2N); 3.78 (*s*, MeO). ^{13}C-NMR: 183.8; 158.5; 156.6; 144.6; 134.6; 129.1; 128.1; 127.4; 124.7; 118.1; 112.0; 109.6; 56.0; 44.1. MS: 269.1 (30.4, $[M+2H]^+$), 268.1(100.0, $[M+H]^+$), 267.0 (32.7, M^+). Anal. calc. for $C_{16}H_{13}NO_3$ (267.30): C 71.90, H 4.90, N 5.24; found: C 71.84, H 5.09, N 5.25.

*1-Benzyl-2,3-dihydro-1*H*-indol-2-one* (**12**). Compound **11** (702 mg, 2.63 mmol) was dissolved in $N_2H_4 \cdot H_2O$ (5 ml) and the soln. heated to reflux. After 45 min., the mixture was allowed to cool to 23°, and a greenish yellow oil separated. The mixture was diluted with H_2O (40 ml) and extracted with Et_2O (30 ml). The org. layer was dried (anh. Na_2SO_4) and the solvent evaporated *in vacuo*. Crude **12** (647 mg, 97%) was obtained as a yellow oil and used without further purification. A pure sample (91%) could be obtained by chromatography on silica gel (hexane/AcOEt 3:1). IR: 1708*s*, 1602*w*, 1494*s*, 1454*w*, 1436*w*, 1359*w*, 1345*w*, 1289*w*, 1220*w*, 1180*m*, 1142*w*, 1037*w*, 806*w*, 746*w*, 705*w*, 676*w*, 621*w*. ^{1}H-NMR: 7.33–7.25 (*m*, 5 arom. H); 6.90–6.89 (*m*, 1 arom. H); 6.72–6.68 (*m*, 1 arom. H); 6.62–6.59 (*m*, 1 arom. H); 4.90 (*s*, CH_2N); 3.76 (*s*, MeO); 3.61 (*s*, CH_2(3)). ^{13}C-NMR: 175.0; 156.0; 136.1; 128.8; 127.7; 127.4; 125.9; 112.2; 112.0; 109.4; 55.7; 43.7; 36.0. HR-MS: 253.1104 (MH^+, $C_{16}H_{16}NO_2^+$; calc. 253.1103).

5′-Methoxy-1′,3′-dihydrospiro-[cyclopropane-1,3′-indol]-2′-one (**13**). A soln. of **12** (402 mg, 1.59 mmol) in Et_2O was concentrated in a two-neck flask and dried under high vacuum. After the addition of DMF (2 ml, over 4 Å molecular sieves) and 1,2-dibromoethane (0.15 ml, 1.7 mmol), the mixture was cooled to 0°, NaH (114 mg, 5.75 mmol) was portionwise added, and the color of the mixture turned from yellow to orange to red to brown-red upon addition. After 3 h, H_2O (40 ml) was added, and the aq. layer was extracted with AcOEt (2 × 25 ml). The combined org. layers were washed with H_2O (4 × 20 ml) and brine, dried (anh. Na_2SO_4), and the solvent was evaporated *in vacuo*. The brown-red oil obtained was purified by chromatography on silica gel (hexane/AcOEt 9:1 → 8:1) to yield 358 mg (81%) of **13**. Colorless, slightly yellowish crystals. Recrystallization from hexane/AcOEt gave colorless crystals. M.p. 112–113°. IR: 3060*w*, 3037*w*, 3009*w*, 2916*w*, 2838*w*, 1692*s*, 1602*m*, 1491*s*, 1475*m*, 1454*m*, 1438*m*, 1382*s*, 1350*m*, 1334*m*, 1286*w*, 1239*s*, 1077*w*, 1056*w*, 1031*m*, 1003*w*, 954*w*, 892*w*, 882*m*, 806*m*, 745*m*, 732*w*, 698*m*, 652*w*, 596*m*, 558*w*, 458*w*. ^{1}H-NMR: 7.34–7.24 (*m*, 5 arom. H); 6.67 (*m*, 2 arom. H); 6.47–6.46 (*m*, 1 arom. H); 4.98 (*s*, CH_2N); 3.75 (*s*, MeO); 1.84–1.80 (*m*, 2 cyclopropyl H); 1.55–1.51 (*m*, 2 cyclopropyl H). ^{13}C-NMR: 177.1; 156.0; 136.4; 132.4; 128.8; 127.6; 127.4; 111.1; 111.0; 109.3; 106.1; 55.8; 44.1; 27.3; 19.4. MS 281.1 (23.6, $[M+2H]^+$), 280.1 (71.3, $[M+H]^+$), 279.1 (100.0, M^+). Anal. calc. for $C_{18}H_{17}NO_2$ (279.34): C 77.40, H 6.13, N 5.01; found: C 77.31, H 6.30, N 4.96.

*1-Benzyl-5-methoxy-1′-methylspiro[1*H*-indole-3,3′-pyrrolidin]-2-one* (**14**). A 10-ml sealed tube was charged with **13** (50 mg, 0.18 mmol) and anh. MgI_2 (2.5 mg, 9.0 μmol). The tube was closed, evacuated, and backfilled with Ar. 1,3,5-Trimethyl-1,3,5-triazinane (26 μl, 0.18 mmol) and THF (0.3 ml) were added, and the tube was sealed, before it was submerged in a preheated oil bath at 125°. The mixture turned pale orange, and, after a few min, a colorless solid was observed to precipitate. After 60 h, the mixture was allowed to cool to 23° and was then further cooled in an ice bath. H_2O (1 ml), a single crystal of $Na_2S_2O_3$, and AcOEt (2 ml) were added, whereupon more of the precipitate was formed. The reaction vessel was decanted and extracted with AcOEt (3 × 10 ml), the layers were separated, and the combined org. layers were washed with brine, dried (anh. Na_2SO_4), and concentrated *in vacuo*. Purification of the yellow oil by chromatography on silica gel (AcOEt/acetone 4:1) afforded 48 mg (83%) of **14** as a colorless, slightly yellowish oil. Repeated purification by chromatography on silica gel (AcOEt/acetone 4:1) yielded a pure sample as a colorless, viscous oil. IR: 2944*w*, 2836*w*, 2789*w*, 1707*s*, 1603*w*, 1496*s*, 1456*m*, 1436*m*, 1359*w*, 1346*m*, 1303*w*, 1282*w*, 1176*m*, 1030*w*, 807*w*, 739*w*, 697*w*, 668*m*. ^{1}H-NMR: 7.34–7.22 (*m*, 5 arom. H); 7.10 (*d*, J = 2.5, 1 arom. H); 6.67 (*dd*, J = 8.4, 2.5, 1 arom. H); 7.10 (*d*, J = 8.4, 1 arom. H); 4.89 (*s*, CH_2N); 3.77 (*s*, MeO); 3.14–3.07 (*m*, H–C(5′)); 2.96 (*d*, J = 9.3, H–C(2′)); 2.88 (*d*, J = 9.3, H–C(2′)); 2.81–2.72 (*m*, H–C(5′)); 2.49 (*s*, MeN); 2.47–2.39 (*m*, H–C(4′)); 2.18–2.08 (*m*, H–C(4′)). ^{13}C-NMR: 180.3; 156.5; 138.9; 136.2; 135.5; 128.8; 127.6; 127.3; 112.1; 110.4; 109.1; 66.4; 56.6; 55.8; 53.7; 43.8; 41.8; 38.1. MS: 324.1 (29.9, $[M+2H]^+$), 323.1 (100.0, $[M+H]^+$), 322.1 (26.3, M^+). Anal. calc. for $C_{20}H_{22}N_2O_2$ (322.41): C 74.51, H 6.88, N 8.69; found: C 74.36, H 6.62, N 8.45.

(±)-Horsfiline (**5**). NH_3 (*ca.* 5 ml) was condensed at −78°, and Na was added with vigorous stirring at −42°, until the blue color persisted. Compound **14** (32 mg, 0.10 mmol) was added in THF (0.5 ml). After 13 min, H_2O (25 ml) and a small amount of NH_4Cl were added. Then, the pH of the mixture was adjusted to pH 11 with 6N HCl. The mixture was extracted with CH_2Cl_2 (6 × 20 ml) and washed with brine. The combined org. layers were dried (anh. Na_2SO_4), and the solvent was evaporated *in vacuo*. Recrystallization from hexane yielded 21 mg (91%) of **5** as a colorless solid. M.p. 151°. IR: 3173*w*, 2785*w*, 1702*s*, 1638*w*, 1619*w*, 1602*w*, 1480*m*, 1442*w*, 1319*w*, 1279*w*, 1258*w*, 1229*w*, 1210*w*, 1183*w*, 1161*w*, 1138*w*, 1058*w*, 1036*w*, 907*w*, 883*w*, 791*w*, 681*w*, 668*w*, 641*w*. ^{1}H-NMR: 8.9 (br. *s*, NH); 7.02 (*d*, J = 2.5, 1 arom. H); 6.82 (*d*, J = 8.3, 1 arom. H); 6.72 (*dd*, J = 8.3, 2.5, 1 arom. H); 3.79 (*s*, MeO); 3.04–2.97 (*m*, H–C(5′)); 2.89 (*d*, J = 9.3, H–C(2′)); 2.84 (*d*, J = 9.3, H–C(2′)); 2.81–2.73 (*m*, H–C(5′)); 2.46 (*s*, MeN); 2.43–2.37 (*m*, H–C(4′)); 2.13–2.04 (*m*, H–C(4′)). ^{13}C-NMR: 183.3; 156.3; 137.8; 133.7; 112.4; 110.3; 110.0; 66.3; 56.7; 55.8; 54.1; 41.7; 37.9. MS: 234.1 (20.4, $[M+2H]^+$), 233.1 (100.0, $[M+H]^+$), 232.1 (24.0, $[M]^+$). Anal. calc. for $C_{13}H_{16}N_2O_2$ (232.28): C 67.22, H 6.94, N 12.06; found: C 67.37, H 6.94, N 11.86.

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