JOC Article

# Total Synthesis of the Proposed Structures of Indole Alkaloids Lyaline and Lyadine

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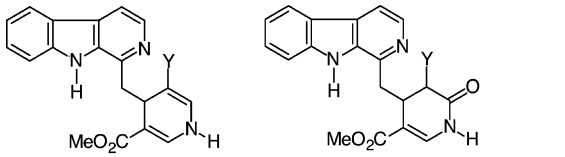
The harman-1,4-dihydropyridines **1** and **2**, which constitute the originally proposed structures for the indole alkaloids lyaline and lyadine, have been synthesized, and their NMR data have been compared with those available for the natural products. Due to the discrepancies in the spectral data, the structures of lyadine and lyaline should be revised.

## Introduction

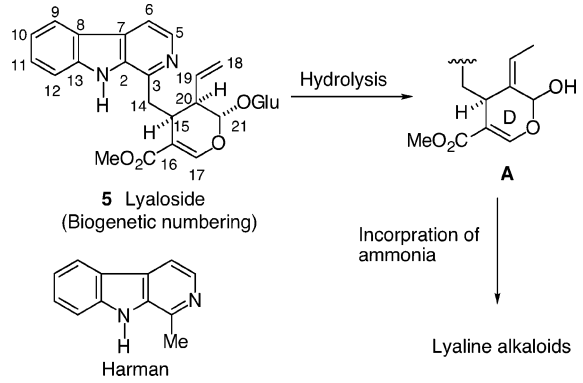
In 1974, Cavé and co-workers reported the isolation of a small subgroup of monoterpenoid indole alkaloids from *Pauridiantha lyalli* (Rubiaceae),[1] a Madagascan plant whose roots have been traditionally used for their febrifuge properties. The spectroscopic data of these alkaloids revealed a particular skeletal arrangement, with a fully aromatic harman nucleus connected to the 4-position of a 3,5-disubstituted pyridine ring: 1,4-dihydropyridine in the major components lyaline (**1**, Chart 1) and lyadine (**2**)[2] and dihydro-2-pyridone in the minor components lyalidine (**3**) and hydroxylyalidine (**4**).[3] These structures suggested a clear relationship with lyaloside (**5**, Scheme 1), a glucoindole alkaloid belonging to the Vincosan biogenetic type,[4] which co-occurs in the same plant.[5] Thus, the lyaline alkaloids would derive biogenetically (or would be simple artifacts) from **5**, by hydrolysis of the glucosidic bond, followed by incorporation of ammonia into the D-ring.[6] In the context of biomimetic transformations in this field, it has been reported that **5** can be converted into the ethylidene hemiacetal **A** by treatment with $\beta$-glucosidase.[7] However, subsequent attempts to reproduce this result were unsuccessful since only simple harman, a main constituent of *Pauridiantha lyalli* and other Rubiaceous plants, was recovered from the reaction mixtures.[8] From a synthetic standpoint, only the structure of lyaloside (**5**) has been confirmed by total synthesis.[9]

**CHART 1. Monoterpenoid Indole Alkaloids from *Pauridiantha lyally***




**1** Y = CH=CH$_2$ Lyaline
**2** Y = CH(OH)CH$_3$ Lyadine
**3** Y = =CHCH$_3$ Lyalidine
**4** Y = CH(OH)CH$_3$ Hydroxylialidine

**SCHEME 1**




**5** Lyaloside (Biogenetic numbering)

The structural type proposed for lyaline (**1**) and lyadine (**2**) attracted our interest due to the fact that N-unsubstituted 4-alkyl-1,4-dihydropyridines,[10] carrying only one electron-withdrawing group at the $\beta$-position, are supposed to be very sensitive, perhaps too much so to

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(1) Pousset, J. L.; Levesque, J.; Cavé, A.; Picot, F.; Potier, P.; Paris, R. R. *Plantes Med. Phytother.* **1974**, *8*, 51−56.

(2) Levesque, J.; Pousset, J. L.; Cavé, A.; Cavé, A. *C. R. Acad. Sci. Paris C* **1974**, *278*, 959−961.

(3) Levesque, J.; Pousset, J. L.; Cavé, A. *C. R. Acad. Sci. Paris C* **1974**, *279*, 1053−1055.

(4) Kisakürek, M. V.; Leeuwenberg, A. J. M.; Hesse, M. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, 1983; Chapter 5.

(5) (a) Levesque, J.; Pousset, J.-L.; Cavé, A. *C. R. Acad. Sci. Paris C* **1975**, *280*, 593−595. (b) Levesque, J.; Jacquesy, R.; Foucher, J. P. *Tetrahedron* **1982**, *38*, 1417−1424.

(6) This two-step biogenetic transformation is believed to operate in other indolopyridine alkaloids. For a recent example, see: Takayama, H.; Tsutsumi, S.; Kitajima, M.; Santiarworn, D.; Liawruangrth B.; Aimi, N. *Chem. Pharm. Bull.* **2003**, *51*, 232−233.

(7) Levesque, J.; Jacquesy, R.; Merienne, C. *J. Nat. Prod.* **1983**, *46*, 619−625.

(8) Aimi, N.; Murakami, H.; Tsuyuki, T.; Nishiyama, T.; Sakai, S.; Haginiwa, J. *Chem. Pharm. Bull.* **1986**, *34*, 3064.

(9) Aimi, N.; Seki, H.; Sakai, S. *Chem. Pharm. Bull.* **1992**, *40*, 2588−2590.

(10) For reviews on the chemistry of dihydropyridines, see: (a) Eisner, U.; Kuthan, J. *Chem. Rev.* **1972**, 72, 1−42. (b) Stout, D.; Meyers, A. I. *Chem. Rev.* **1982**, *82*, 223−243. (c) Sausins, A.; Duburs, G. *Heterocycles* **1988**, *27*, 291−314. (d) Lavilla, R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1141−1156.

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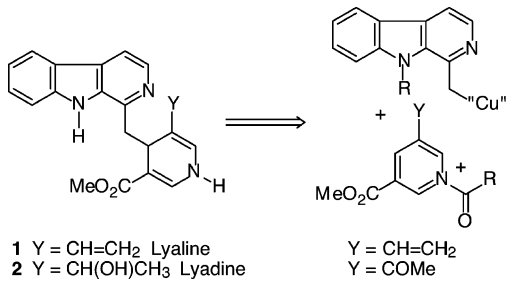
**SCHEME 2. Synthetic Approach**



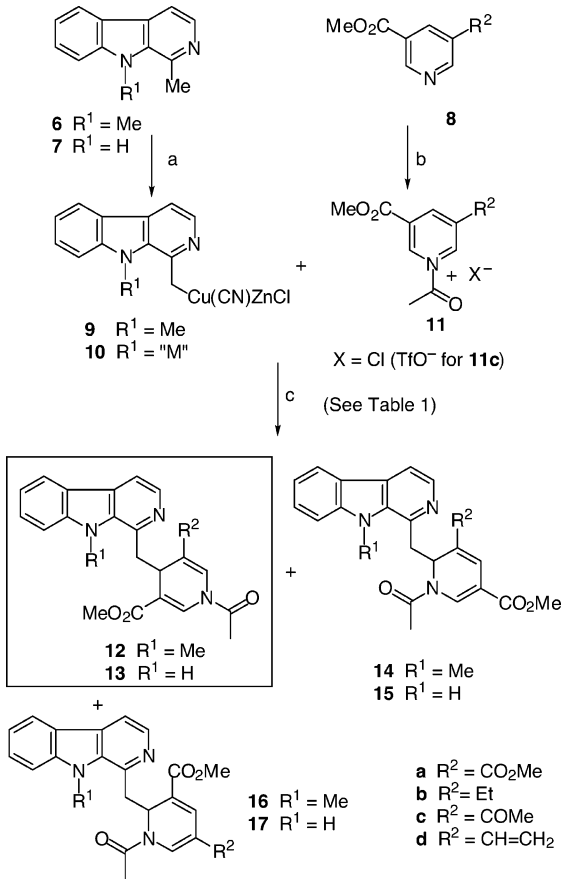

withstand the rigorous conditions when being extracted from natural sources. The above observation together with the fact that partial NMR data are given in the original paper[1,2] prompted us to develop a synthetic sequence for these alkaloids in order to verify their structure.

The literature data[11] and our own experience[12] in the synthesis of 4-substituted 1,4-dihydropyridines by regioselective addition of carbon nucleophiles to suitably activated pyridines led us to envisage the use of an organocopper derivative of harman in this reaction as a logical approach to the target molecules. With the aim of assembling the harman−dihydropyridine skeleton of **1** and **2** in a straightforward and convergent way, we selected 3,5-disubstituted *N*-acylpyridinium salts,[13] such as those depicted in Scheme 2, as electrophilic partners. Afterward, we should be able to carefully induce *N*-deacylation to gain access to the desired *N*-unsubstituted derivatives. In the lyadine (**2**) series, an additional reduction of the acetyl group would be required to complete the synthesis.

## Results and Discussion

We set out to explore the feasibility of this proposal using $N_a$-methylharman (**6**)[14] as a model organometallic precursor and easily available pyridines **8a**, **8b**,[15] and **8c**,[15,16] which bear one or two electron-withdrawing substituents at the $\beta$-positions (Scheme 3). After some experimentation with different organometallic species,[17] it was found that the mixed copper−zinc organometallic

**SCHEME 3. Synthesis of Harman−Dihydropyridines 12 and 13**[a]




[a] Reagents and conditions: (a) (i) *n*-BuLi, THF, 0 °C, 30 min, (ii) CuCN, THF, 0 °C, then $ZnCl_2$, −78 °C; (b) acetyl chloride, THF, or $CH_2Cl_2$, then TMSOTf (for **11c**); (c) −78 °C to rt, 12 h.

**9**, prepared from **6** by sequential treatment with *n*-Buli, CuCN, and $ZnCl_2$, was the best reagent in terms of yield and regioselectivity.[18] Pyridines **8a** and **8b** were converted into *N*-acetylpyridinium chlorides **11a** and **11b** by treatment with acetyl chloride and then allowed to react in situ with **9**. In the 3-acetyl (**c**) series, better yields were observed when using a triflate counterion, prepared by the exchange of chloride with trimethylsilyl triflate.[19] The results of this preliminary study are summarized in Table 1. As can be observed, reaction of **9** with pyridinium salt **11a** took place with moderate yield and acceptable regioselectivity to give a 4.5:1 mixture of separable 1,4-dihydropyridine **12a** and 1,2-dihydropyridine **14a** in 50% overall yield (entry 1). Starting from 3-ethylpyridinium salt **11b** (entry 2), which bears only one acyl group at the $\beta$-position, the regioselectivity of the addition was clearly lower. In this case, from the 4:1:1 mixture of dihydropyridines we were able to isolate the major component **12b**. Finally, pyridinium triflate **11c** (entry 3) was a more convenient electrophilic substrate as it led to 1,4-dihydropyridine **12c** as the main product (40%).

(11) See inter alia: (a) Comins, D. L.; Abdullah, A. H. *J. Org. Chem.* **1982**, *47*, 4315−4319. (b) Comins, D. L.; Stroud, E. D.; Herrick, J. J. *Heterocycles* **1984**, *22*, 151−157. (d) Akiba, K.; Iseki, Y. Wada, M. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 1994−1999. (e) Mangeney, P.; Gosmini, R.; Raussou, S.; Commerçon, M.; Alexakis, A. *J. Org. Chem.* **1994**, *59*, 1877−1888. (f) Yamada, S.; Misono, T.; Ichikawa, M.; Morita, C. *Tetrahedron* **2001**, *57*, 8939−8949.

(12) (a) Bennasar, M.-L.; Vidal, B.; Bosch, J. *J. Org. Chem.* **1997**, *62*, 3597−3609. (b) Bennasar, M.-L.; Juan, C.; Bosch, J. *Tetrahedron Lett.* **1998**, *39*, 9275−9278. (c) Bennasar, M.-L.; Vidal, B.; Kumar, R.; Lázaro, A.; Bosch, J. *Eur. J. Org. Chem.* **2000**, 3919−3925. (d) Bennasar, M.-L.; Zulaica, E.; Juan, C.; Alonso, Y.; Bosch, J. *J. Org. Chem.* **2002**, *67*, 7465−7474. (e) Bennasar, M.-L.; Roca, T.; Monerris, M.; Juan, C.; Bosch, J. *Tetrahedron* **2002**, *58*, 8099−8106.

(13) For the use of an *intramolecular* enamide addition to a 3,5-disubstituted *N*-acylpyridinium salt in the synthesis of indolopyridine alkaloids, see: (a) Lavilla, R.; Gullón, F.; Bosch, J. *Eur. J. Org. Chem.* **1999**, *373*, 3−378.

(14) (a) Karrer, P.; Müller, H. *J. Org. Chem.* **1957**, *22*, 1433−1434. (b) Seki, H.; Hashimoto, A.; Hino, T. *Chem. Pharm. Bull.* **1993**, *41*, 1169−1172.

(15) Bracher, F.; Papke, T. *Monatsh. Chem.* **1995**, *126*, 805−809.

(16) Bennasar, M.-L.; Zulaica, E.; Roca, T. Alonso, Y.; Monerris, M. *Tetrahedron Lett.* **2003**, *44*, 4711−4744.

(17) The corresponding copper-catalyzed Grignard reagent and the lower order cyanocuprate gave mixtures of dihydropyridines in poor yields.

(18) For the use of this type of organometallic in the synthesis of 4-benzylpyridines, see: (a) Chia, W.-L.; Shiao, M.-J. *Tetrahedron Lett.* **1991**, *32*, 2033−2034. (b) Shing, T.-L.; Chia, W.-L.; Shiao, M.-J.; Chau, T.-Y. *Synthesis* **1991**, 849−850.

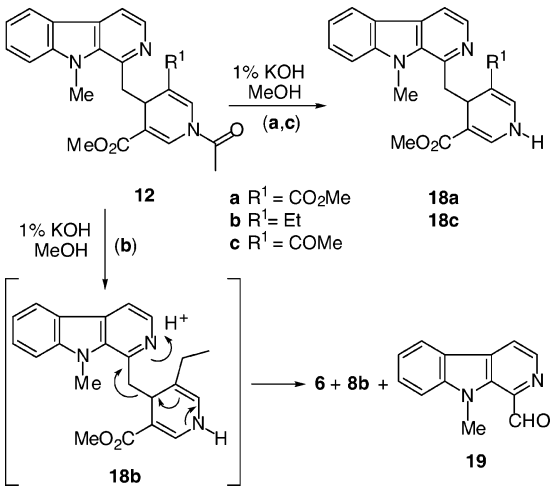
(19) Pabel, J.; Hösl, C. E.; Maurus, M.; Ege, M.; Wanner, K. Th. *J. Org. Chem.* **2000**, *65*, 9272−9275.

**TABLE 1. Reaction of Mixed Copper−Zinc Organometallic Derivatives 9 and 10 with Pyridinium Salts 11**

| entry | organometallic | pyridinium salt | products (ratio) | overall yield (%) |
|---|---|---|---|---|
| 1 | **9** | **11a** | **12a** + **14a** (4.5:1) | 50 |
| 2 | **9** | **11b** | **12b** + **14b** +**16b** (4:1:1) | 40 |
| 3 | **9** | **11c** | **12c**[a] | 40 |
| 4 | **10** | **11c** | **13c** + **17c** (9:1) | 30 |
| 5 | **10** | **11d** | **13d** + **15d** (10:1) | 30 |

[a] Trace amounts of a regioisomeric 1,2-dihydropyridine.

**SCHEME 4. *N*-Deprotection of 1,4-Dihydropyridines 12**

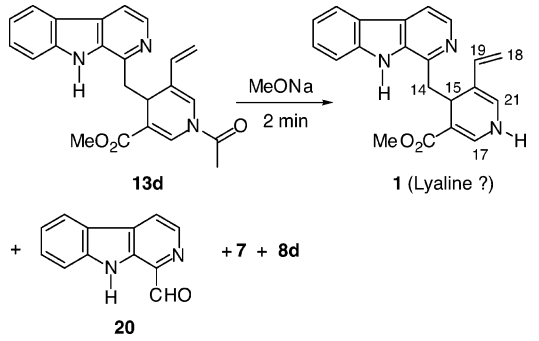



This result was particularly satisfactory considering the structural relationship of **12c** with **2**.

With the aim of fully understanding the harman−dihydropyridine spectroscopic pattern, **12a**−**c** were exhaustively analyzed by mono- and bidimensional (HSQC and HMBC) NMR. A similar spectroscopic study was performed with all intermediate 1,4-dihydropyridines prepared in this work.

With the model 1,4-dihydropyridines **12a**−**c** in hand, attention was turned to the *N*-deprotection reaction. Satisfactorily, treatment of 3,5-diacyl derivatives **12a** and **12c** with 1% KOH in MeOH for a short period of time (15 min)[20] smoothly gave **18a** (85%) and **18c** (80%, Scheme 4). As expected from their substitution pattern, **18a** and **18c** were stable enough to be purified by column chromatography, and they could be stored for several months at −20 °C. However, exposure of **12b**, bearing *only one* acyl group at the pyridine *β*-position, to the above deprotection conditions did not provide the desired ethyldihydropyridine **18b**. Instead, the crude product was shown by $^1$H NMR to be a 4:3:1 mixture of pyridine **8b**, harman **6,** and aldehyde **19.** This result indicated that under the reaction conditions (or during the extractive workup) dihydropyridine **18b** undergoes cleavage of the C-14/C-15 bond, probably through a retroaddition reaction, to give **6** and **8b**. Oxidation at the benzylic position at any stage would account for the minor formation of **19**.

**SCHEME 5. Synthesis of 1**




At this point, access to the natural products required the extension of the chemistry outlined above to $N_a$-unsubstituted harman (**7**, Scheme 3) or to a protected derivative. We wanted to avoid protection techniques as they would involve an increase in the number of reactions to perform on sensitive dihydropyridines. Hence, we were pleased to find that the mixed copper−zinc organometallic **10**, prepared in situ from **7**, underwent regioselective addition to 3-acetylpyridinium salt **11c** to give 1,4-dihydropyridine **13c** along with minor amounts of regioisomer **17c** in an overall yield only slightly lower (30%) than in the above $N_a$-methyl series (Table 1, entry 4). The reaction was satisfactorily extended to vinylpyridinium salt **11d**, prepared as above from pyridine **8d**, to give **13d** as the major product (30%, entry 5).

The only remaining transformation required to complete the synthesis of **1** from **13d** was the removal of the *N*-acetyl group (Scheme 5). Given the experience acquired in the model series, we had to find conditions mild enough to avoid, if possible, the concomitant cleavage that had taken place from the closely related dihydropyridine **12b**. To this end, **13d** was treated with NaOMe in MeOH for 2 min. After extractive workup with AcOEt (chlorinated solvents were deliberately excluded), the crude product was shown by $^1$H NMR to be the desired harman−dihydropyridine **1** along with minor amounts (10%) of fragmentation products (pyridine **8d**, harman **7**, and aldehyde **20** in a 4:1:3 relationship). To minimize the undesired decomposition, the deprotection experiment was reproduced in an NMR tube using $CD_3OD$ as the solvent. In this manner, we were able to extensively examine the structure of our pure synthetic product by $^1$H (500 MHz) and $^{13}$C NMR (100.6 MHz) with the aid of bidimensional (HSQC, HMBC) techniques. We also measured NMR spectra in $CDCl_3$, although in this solvent significant fragmentation to **7**, **8d**, and **20** took place. Not surprisingly, all our recorded data perfectly confirmed the structure **1**. However, the comparison of our $^1$H NMR data with those published for lyaline[1,2] revealed differences in the chemical shifts of some protons of the dihydropyridine ring and its substituents (Table 2). Most notably, the protons of the vinyl methylene group of **1** appear much more shielded than those reported for lyaline (entry 4).

We then focused our attention on dihydropyridine **13c**, which was envisaged as a precursor of **2** (lyadine) by *N*-deprotection followed by reduction of the acetyl group

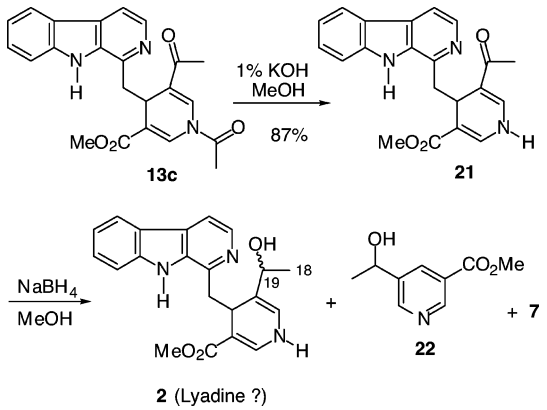
(20) Lavilla, R.; Gotsens, T.; Guerrero, M.; Bosch, J. *Synthesis* **1995**, 382−384.

**TABLE 2. Comparison of the $^1$H NMR Data of 1 with Those Reported for Lyaline**

| entry | proton[a] | **1** ($CD_3OD$, $\delta$) | **1** ($CDCl_3$, $\delta$) | lyaline[b] $\delta$ |
|---|---|---|---|---|
| 1 | 14-H | 3.17 | 3.19 | 3.23 |
| | | 3.20 | 3.43 | 3.57 |
| 2 | 15-H | 4.32 | 4.33 | 4.17 |
| 3 | 17-H | 7.33 | 7.40 | 7.15 |
| 4 | 18-H | 4.48 | 3.77 | 5.37 |
| | | 4.60 | 4.29 | |
| 5 | 19-H | 6.17 | 6.12 | 5.99 |
| 6 | 21-H | 6.25 | 6.22 | 6.40 |
| 7 | OMe | 3.43 | 3.85 | 3.60 |

[a] Biogenetic numbering, see Scheme 1. [b] Reference 2. Solvent not given.

**SCHEME 6. Synthesis of 2**




(Scheme 6). As anticipated, **13c** could be easily converted (87%) into the *N*-unsubstituted 1,4-dihydropyridine **21** in conditions identical (1% KOH in MeOH) to those that had been effective for model 3,5-diacyldihydropyridines **12a** and **12c**. The next step was the reduction of the vinylogous amide carbonyl group of **21**, which was expected to be problematic as it involved the suppression of one stabilizing substituent of the dihydropyridine ring. In accord with this expectation, preliminary attempts to reduce **21** with $NaBH_4$−$CeCl_3$ in MeOH resulted in a clean and fast fragmentation to harman **7** and pyridine **22**, even at −40 °C. It is worth mentioning that aldehyde **20** was not detected.

We reasoned that $CeCl_3$ not only could favor the carbonyl reduction but also the leaving group ability of the harman moiety by interaction with the basic ($N_b$) nitrogen. Thus, dihydropyridine **21** was treated with $NaBH_4$ in MeOH without any additive at 0 °C for 15 min. After the extractive workup and trituration with $Et_2O$, the crude product was shown by $^1$H NMR in $CD_3OD$ (400 MHz) or $CDCl_3$ (300 MHz) to be the target harman−dihydropyridine **2** (1:1 mixture of epimers) together with variable amounts (10−30% depending on the assay) of **7** and **22**.

We extensively examined the NMR spectra of this mixture in $CD_3OD$. Significantly, harman **7** appeared partially deuterated at the benzylic methyl group, thus indicating that cleavage of the C-14/C-15 bond had also taken place during the short $^1$H NMR measurement time (approximately 6 min). Confirming this fast decomposition, dihydropyridine **2** was the minor component of the mixture after the $^{13}$C NMR measurement time (2 h). Despite all these difficulties, we successfully characterized our synthetic product **2**. Disappointingly, our recorded spectroscopic data did not match those published for lyadine.[1,2] The protons of the hydroxyethyl chain in the $^1$H NMR of the natural product, presumably recorded in $CDCl_3$, are reported[2] to appear at $\delta$ 1.42 (18-H) and $\delta$ 5.28[21] (19-H). However, our synthetic product **2** (mixture of epimers) displayed a different chemical shift pattern as the methyl group 18-H resonates at $\delta$ 1.11 or $\delta$ 1.34 in $CD_3OD$ and at $\delta$ 0.90 or $\delta$ 1.09 in $CDCl_3$. The methine proton 19-H is much more shielded, appearing at $\delta$ 4.21 or $\delta$ 4.35 in $CD_3OD$ and $\delta$ 4.26 in $CDCl_3$.

In conclusion, we have synthesized the harman−dihydropyridines **1** and **2**, which constitute the originally proposed structures for lyaline and lyadine. As could be expected considering their dihydropyridine nature, both compounds were very sensitive, being difficult to isolate in pure form. In fact, in our hands these compounds (in particular **2**) were prone to undergo fragmentation in solution into harman and pyridine. The incomplete NMR data published for these alkaloids exhibit serious discrepancies with our recorded data for **1** and are definitely not in accordance with structure **2**. A final decision about the structure of these natural products requires a new structure elucidation on authentic material.

## Experimental Section

**Organometallic Derivative 10.** *n*-BuLi (1.6 M in hexane, 1.40 mL, 2.24 mmol) was slowly added to a cooled (0 °C) solution of harman (**7**, 186 mg, 1 mmol) in dry THF (18 mL), and the resulting red solution was stirred at 0 °C for 30 min. After the solution was cooled to −78 °C, a suspension of CuCN (183 mg, 2 mmol) in dry THF (10 mL) was added. The resulting mixture was stirred until the reaction temperature rose to 0 °C and then cooled again to −78 °C. $ZnCl_2$ (1 M in $Et_2O$, 2 mL, 2 mmol) was added, and the mixture was stirred for 10 min. Then was used in the next reaction.

**Methyl 1-Acetyl-4-[(β-carbolin-1-yl)methyl]-5-vinyl-1,4-dihydropyridine-3-carboxylate (13d).** Acetyl chloride (36 μL, 0.51 mmol) was added to a solution of pyridine **8d** (83 mg, 0.51 mmol) in anhydrous $CH_2Cl_2$ (5 mL) cooled at 0 °C. The mixture was stirred at 0 °C for 30 min and then cooled to −78 °C. Organometallic **10** (1 mmol) was added by cannula, and the mixture was allowed to slowly warm to rt for 12 h. The reaction mixture was poured into a 1:1 mixture of 20% $NH_4OH$ and saturated aqueous $NH_4Cl$ (25 mL) and extracted with $CH_2Cl_2$ (3 × 30 mL). The organic extracts were concentrated, and the resulting residue was chromatographed (99:1 $CH_2Cl_2$−MeOH) to give a 10:1 mixture of dihydropyridines **13d** and **15d** (59 mg, 30%). Both dihydropyridines were separated by an additional chromatography (AcOEt). 1,2-Dihydropyridine **15d**: $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 2.44 (s, 3H), 3.33 (dd, $J$ = 3, 13.0 Hz, 1H), 3.44 (dd, $J$ = 9.9, 13.0 Hz, 1H), 3.83 (s, 3H), 4.14 (d, $J$ = 17.4 Hz, 1H), 4.50 (d, $J$ = 11.4 Hz, 1H), 5.97 (m, 1H), 6.16 (dd, $J$ = 11.4, 17.4 Hz, 1H), 6.50 (s, 1H), 7.30 (m, 1H), 7.58 (ddd, $J$ = 1.2, 7.2, 8.1 Hz, 1H), 7.67 (d, $J$ = 8.1 Hz, 1H), 7.69 (s, 1H), 7.83 (d, $J$ = 5.4 Hz, 1H), 8.12 (d, $J$ = 7.5 Hz, 1H), 8.24 (d, $J$ = 5.4 Hz, 1H), 9.94 (s, 1H). 1,4-Dihydropyridine **13d**: $^1$H NMR ($CDCl_3$, 500 MHz, 50 °C, assignment aided by HSQC and HMBC) $\delta$ 2.28 (s, 3H, $CH_3CO$), 3.28 (br t, 1H, $CH_2$), 3.44 (dd, $J$ = 2.5, 14 Hz, 1H, $CH_2$), 3.86 (s, 3H, OMe), 4.23 (dd, $J$ = 2.5, 8.5 Hz, 1H, pyr 4-H), 4.32 (br m, 1H, $CH_2$=), 4.64 (d, $J$ = 10.5 Hz, 1H, $CH_2$=), 6.18 (dd, $J$ = 10.5, 17.5 Hz, 1H, CH=), 6.84 (br s, 1H, pyr 6-H), 7.28 (t, $J$ = 7.5 Hz, 1H, 6-H), 7.56 (t, $J$ = 8 Hz, 1H, 7-H), 7.63 (d, $J$ = 8 Hz, 1H, 8-H), 7.82 (d, $J$ = 5.0 Hz, 1H, 4-H), 8.05 (br s, 1H, pyr 2-H), 8.10 (d, $J$ = 8 Hz, 1H, 5-H), 8.22 (d, $J$ = 5.0 Hz, 1H, 3-H), 10.04 (br s, 1H, NH); $^{13}$C NMR ($CDCl_3$, 100.6 MHz, assignment aided by HSQC

(21) 19-H is reported to appear at $\delta$ 5.7 in ref 1.

and HMBC) $\delta$ 21.8 ($CH_3CO$), 31.3 (pyr C-4), 43.4 ($CH_2$), 52.3 (OMe), 111.9 (C-9), 112.7 (pyr C-3), 113.4 ($CH_2$=), 113.5 (C-4′), 119.9 (C-6′), 121.6 (C-4b), 121.7 (C-5′), 122.9 (pyr C-6), 123.8 (pyr C-5), 128.3 (C-7), 128.4 (C-4a), 132.0 (pyr C-2), 133.8 (CH=), 134.8 (C-9a), 137.6 (C-3), 140.4 (C-8a), 143.2 (C-1), 167.1 (CO), 168.3 (CO); HRMS calcd for $C_{23}H_{21}N_3O_3$ 387.1583, found 387.1584.

**Methyl 4-[(β-Carbolin-1-yl)methyl]-5-vinyl-1,4-dihydropyridine-3-carboxylate (1).** $Na^0$ (5 mg) was added to a solution of 1,4-dihydropyridine **13d** (20 mg, 0.052 mmol) in MeOH (1.5 mL). The mixture was stirred at rt for 2 min, quenched with $H_2O$, and extracted with AcOEt. Concentration of extracts gave **1** (15 mg) as an orange solid (impure with 10% of fragmentation products **8d**, **7** and **20**, see text). The deprotection experiment was reproduced in an NMR tube in $CD_3OD$: $^1H$ NMR ($CD_3OD$, 500 MHz, assignment aided by HSQC and HMBC) $\delta$ 3.17 (dd, $J$ = 7, 13 Hz, 1H, $CH_2$), 3.20 (dd, $J$ = 5.5, 13 Hz, 1H, $CH_2$), 3.43 (s, 3H, OMe), 4.32 (dd, $J$ = 7 and 5.5 Hz, 1H, pyr 4-H), 4.48 (d, $J$ = 17.5 Hz, 1H, $CH_2$=), 4.60 (d, $J$ = 11 Hz, 1H, $CH_2$=), 6.17 (dd, $J$ = 11, 17.5 Hz, 1H, CH=), 6.25 (s, 1H, pyr 6-H), 7.22 (t, $J$ = 7.5 Hz, 1H, 6-H), 7.33 (s, 1H, pyr 2-H), 7.52 (t, $J$ = 7.5 Hz, 1H, 7-H), 7.60 (d, $J$ = 8 Hz, 1H, 8-H), 7.87 (d, $J$ = 5.5 Hz, 1H, 4-H), 8.11 (m, 2H, 3-H, 5-H); $^{13}C$ NMR ($CD_3OD$, 100.6 MHz, assignment aided by HSQC and HMBC) $\delta$ 32.8 (pyr C-4), 42.9 ($CH_2$), 51.5 (OMe), 101.4 (pyr C-3), 108.5 ($CH_2$=), 113.0 (C-8), 114.1 (C-4), 118.0 (pyr C-5), 120.6 (C-6), 122.5 (C-4b, C-5), 127.5 (pyr C-6), 129.3 (C-7), 129.8 (C-4a), 136.4 (CH=), 136.9 (C-9a), 137.8 (C-3), 139.5 (pyr C-2), 142.3 (C-8a), 145.5 (C-1), 171.0 (CO); $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 3.19 (dd, $J$ = 9.3, 13.0 Hz, 1H, $CH_2$), 3.34 (d, $J$ = 13.0 Hz, 1H, $CH_2$), 3.77 (d, $J$ = 17.4 Hz, 1H, $CH_2$=), 3.85 (s, 3H, OMe), 4.29 (d, $J$ = 11.1 Hz, 1H, $CH_2$=), 4.33 (d, $J$ = 9.3 Hz, 1H, pyr 4-H), 6.12 (dd, $J$ = 11.1, 17.4 Hz, 1H, CH=), 6.22 (s, 1H, pyr 6-H), 7.28 (t, $J$ = 8.1 Hz, 1H, 6-H), 7.40 (s, 1H, pyr 2-H), 7.56 (ddd, $J$ = 0.9, 7.8, 8.1 Hz, 1H, 7′-H), 7.70 (d, $J$ = 7.8 Hz, 1H, 8-H), 7.82 (d, $J$ = 5.1 Hz, 1H, 4-H), 8.12 (d, $J$ = 8.1 Hz, 1H, 5-H), 8.18 (d, $J$ = 5.1 Hz, 1H, 3-H), 10.65 (br s, 1H, NH); $^{13}C$ NMR ($CDCl_3$, 75.4 MHz, intensive fragmentation) $\delta$ 30.5, 45.5, 51.6, 102.3, 109.3, 112.1, 113.2, 118.1, 119.5, 121.6, 121.6, 125.2, 127.8, 127.9, 134.6, 134.9, 137.0, 137.6, 140.4, 145.0, 169.5; ESI-MS $m/z$ 345 ($M^+$), 182, 163.

**Methyl 1,5-Diacetyl-4-[(β-carbolin-1-yl)methyl]-1,4-dihydropyridine-3-carboxylate (13c).** Acetyl chloride (36 μL, 0.51 mmol) was added to a solution of pyridine **8c** (90 mg, 0.50 mmol) in anhydrous $CH_2Cl_2$ (5 mL) cooled at −10 °C, and the mixture was stirred at −10 °C for 5 min. Trimethylsilyl triflate (90 μL, 0.50 mmol) was added, and the mixture was stirred at −10 °C for 1 h. The resulting pyridinium triflate (**11c**) was allowed to react as above with **10** (1 mmol). After the extractive workup and chromatography of the residue (98:2 AcOEt−MeOH), a 9:1 mixture of **13c** and **17c** (60 mg, 30%) was obtained. Pure **13c** was obtained after an additional chromatography (98:2 AcOEt−MeOH): $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 2.41 (sa, 3H), 2.44 (s, 3H), 3.05 (dd, $J$ = 8.7, 13 Hz, 1H), 3.22 (br s, 3H), 3.28 (dd, $J$ = 3, 13 Hz, 1H), 4.37 (dd, $J$ = 3, 8.7 Hz, 1H), 7.28 (ddd, $J$ = 0.9, 6.9, 8 Hz, 1H), 7.56 (ddd, $J$ = 1.2, 6.9, 8.1 Hz, 1H), 7.69 (d, $J$ = 8.1 Hz, 1H), 7.7−7.9 (br s, 2H), 7.82 (d, $J$ = 5.4 Hz, 1H), 8.11 (d, $J$ = 8 Hz, 1H), 8.20 (d, $J$ = 5.4 Hz, 1H), 10.15 (s, 1H); $^{13}C$ NMR ($CDCl_3$, 75.4 MHz) $\delta$ 21.8, 25.4, 30.7, 43.9, 51.8, 111.9, 113.4, 115.8, 119.6, 121.6, 121.7, 123.4, 128.0, 128.0, 131.1, 132.4, 134.7, 137.4, 140.3, 143.2, 166.1, 167.3, 197.7; HRMS calcd for $C_{23}H_{21}N_3O_4$ 403.1532, found 403.1518.

**Methyl 5-Acetyl-4-[(β-carbolin-1-yl)methyl]-1,4-dihydropyridine-3-carboxylate (21).** Dihydropyridine **13c** (80 mg, 0.2 mmol) was added to a solution of KOH in MeOH (1%, 6 mL) and stirring was maintained at rt for 15 min. The reaction mixture was poured into 5% $Na_2CO_3$ (15 mL) and extracted with $CH_2Cl_2$ (6 × 20 mL). The organic extracts were dried and concentrated. Pure **21** was obtained after flash chromatography (9:1 AcOEt−MeOH): 63 mg (87%); mp 118−119 °C; $^1H$ NMR (DMSO-$d_6$, 400 MHz, assignment aided by HSQC and HMBC) $\delta$ 2.08 (s, 3H, COMe), 2.94 (dd, $J$ = 6.4, 12.8 Hz, 1H, $CH_2$), 2.98 (dd, $J$ = 5.2, 12.8 Hz, 1H, $CH_2$), 3.23 (s, 3H, OMe), 4.31 (dd, $J$ = 6.4, 5.2 Hz, 1H, pyr 4-H), 7.12 (s, 1H, pyr 2-H), 7.19 (dd, $J$ = 8, 7.5 Hz, 1H, 6-H), 7.35 (s, 1H, pyr 6-H), 7.49 (dd, $J$ = 8, 7.5 Hz, 1H, 7-H), 7.58 (d, $J$ = 8 Hz, 1H, 8-H), 7.84 (d, $J$ = 5.2 Hz, 1 H, 4-H), 8.12 (d, $J$ = 5.2 Hz, 1H, 3-H), 8.15 (d, $J$ = 8 Hz, 1H, 5-H), 9.12 (s, 1H, pyr NH), 11.0 (s, 1H, NH); $^{13}C$ NMR (DMSO-$d_6$, 100.6 MHz, assignment aided by HSQC and HMBC) $\delta$ 24.6 (COMe), 30.1 (pyr C-4), 41.5 ($CH_2$), 50.6 (OMe), 106.0 (pyr C-3), 111.9 (C-8), 112.5 (C-4), 115.0 (pyr C-5), 119.0 (C-6), 121.1 (C-4b), 121.5 (C-5), 126.7 (C-4a), 127.5 (C-7), 135.0 (C-9a), 135.5 (pyr C-2), 137.3 (C-3), 138.5 (pyr C-6), 140.2 (C-8a), 143.9 (C-1), 166.9 (CO), 195.3 (CO); HRMS calcd for $C_{21}H_{19}N_3O_3$ 361.1426, found 361.1442. Anal. Calcd for $C_{21}H_{19}N_3O_3 \cdot {}^1/_2H_2O$: C, 68.10; H, 5.44: N, 11.34. Found: C, 68.08; H, 5.74; N, 11.21.

**Methyl 4-[(β-Carbolin-1-yl)methyl]-5-(1-hydroxyethyl)-1,4-dihydropyridine-3-carboxylate (2).** $NaBH_4$ (5 mg) was added to a suspension of 1,4-dihydropyridine **21** (15 mg, 0.041 mmol) in MeOH (2 mL), and the mixture was stirred at rt for 15 min. The solvent was removed, and the resulting residue was partitioned between saturated aqueous NaCl and $CH_2Cl_2$ and extracted with $CH_2Cl_2$. After concentration of the organic extracts, the resulting residue was triturated with anhydrous $Et_2O$ (10 mL) to give **2** (10 mg) as a white solid (mixture of epimers, impurified with 10% of fragmentation products **7** and **22**): $^1H$ NMR ($CD_3OD$, 400 MHz, assignment aided by HSQC and HMBC) $\delta$ 1.11 and 1.34 (2 d, $J$ = 6.4 Hz, 3H, $CH_3$), 3.15−3.30 (m, 2H, $CH_2$), 3.36 and 3.45 (2 s, 3H, OMe), 3.94 and 4.20 (2 t, $J$ = 6 Hz, 1H, pyr 4-H), 4.21 and 4.35 (2 q, $J$ = 6.4 Hz, 1H, CHOH), 6.09 and 6.17 (2 s, 1H, pyr 6-H), 7.23 and 7.27 (2 s, 1H, pyr 2-H), 7.24 (m, 1H, 6-H) 7.53 (m, 1H, 7-H), 7.61 (d, $J$ = 8.4 Hz, 1H, 8-H), 7.90 (d, $J$ = 5.6 Hz, 1H, 4-H), 8.13 (m, 2H, 3-H, 5-H); $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 0.90 and 1.09 (2 d, $J$ = 6.6 Hz, 3H, $CH_3$), 3.43 (m, 2H, $CH_2$), 3.86 and 3.87 (2 s, 3H, OMe), 4.13 (dd, $J$ = 3.6, 5.7 Hz, 1H, pyr 4-H), 4.26 (q, $J$ = 6.6 Hz, 1H, CHOH), 5.58 and 5.75 (2 br s, 1H, OH), 6.10 and 6.27 (2 d, $J$ = 4.2, 1H, pyr 6-H), 7.27 (m, 2H, pyr 2-H, 6-H), 7.56 (m, 1H, 7-H), 7.62 and 7.66 (2 d, $J$ = 8.1 and 8.4 Hz, 1H, 8-H), 7.84 (m, 1H, 4-H), 8.12 (d, $J$ = 7.5 Hz, 1H, 5-H), 8.25 and 8.28 (2 d, $J$ = 5.4 Hz, 1H, 3-H), 10.37 and 10.80 (2 br s, 1H, NH); $^{13}C$ NMR ($CD_3OD$, 100.6 MHz, assignment aided by HSQC and HMBC) $\delta$ 21.8 and 22.2 ($CH_3$), 33.0 and 35.8 (pyr C-4), 43.6 and 43.9 ($CH_2$), 51.3 and 51.4 (OMe), 68.7 and 70.2 (CHOH), 99.7 and 100.6 (pyr C-3), 112.8 (C-8), 114.2 (C-4), 120.3 and 121.6 (pyr C-5), 120.6 and 120.7 (C-6), 122.4 (C-4b), 122.5 (C-5), 123.6 (pyr C-6), 129.2 and 129.3 (C-7), 129.6 (C-4a), 136.9 and 137.0 (C-9a), 137.4 and 137.6 (C-3), 140.1 and 140.3 (pyr C-2), 142.3 (C-8a), 145.5 (C-1), 171.0 and 171.3 (CO); ESI-MS $m/z$ 363, 345, 182.

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**Supporting Information Available:** General experimental protocols and detailed experimental procedures for the preparation of **12a**−**c**, **18a**,**d**. $^1H$ and $^{13}C$ NMR spectra of all new compounds. ESI-MS spectra of **1** and **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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