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Total synthesis of the naphthyridine alkaloid jasminine

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Abstract—The synthesis of (±)-jasminine (**1**), a member of a small group of naphthyridine alkaloids, has been achieved. The synthetic route takes advantage of the reactivity of dihydropyridine intermediates for the preparation of trisubstituted pyridine **4**, which gives access to the alkaloid by a reductive amination-lactamization tandem reaction.

1. Introduction

Jasminine (**1**, Fig. 1) is a monoterpene alkaloid isolated in 1968 from *Jasminum gracile* and other *Oleaceae* species,[1] which is characterized by a pyridine ring fused to a six-membered lactam moiety. This singular 2,7-naphthyridin-3-one skeleton is also present in jasminidine (**2**)[2] and dihydrojasminine (**3**),[3] which co-occur with **1** in *Syringa vulgaris* and *Osmanthus austrocaledonica*, respectively.[4] These alkaloids have attracted little synthetic attention: to our knowledge, only a biomimetic hemisynthesis of jasminine (**1**) from related secoiridoids[5] has been reported to date.

As a part of our continuing interest in the chemistry of dihydropyridines,[6] which are useful intermediates for natural product synthesis,[7] we present here a concise, total synthesis of (±)-jasminine (**1**). In planning our approach, we found it logical to close the lactam ring in the last synthetic step by a reductive amination–lactamization process from pyridine **4** (Scheme 1), which, in turn, would be prepared from commercially available 3-acetylpyridine by the sequential introduction of substituents at the 4- and 5-positions of the ring. To this end, we could take advantage of our previously reported procedure for the synthesis of substituted dihydropyridines, based on the addition of carbon nucleophiles to *N*-alkylpyridinium substrates, followed by acylation of the resultant dihydropyridine adducts.[8] This nucleophilic addition–acylation sequence would have to be combined with a final oxidative step, with concomitant or subsequent *N*-dealkylation.

2. Results and discussion

The synthesis of the pivotal intermediate **4** through dihydropyridines **6** and **7** is depicted in Scheme 2. The benzhydryl group was selected as the nitrogen substituent for the starting pyridinium salt **5** as it is easily installed in a 3-acylpyridine and can be removed in relatively mild conditions.[8d,9] Based on our own experience, we decided to use the enolate of methyl α-(methylsulfanyl)acetate[10] as the nucleophilic partner for the introduction of the acetate chain at the 4-position of the pyridine ring.[11] Satisfactorily, the reaction of this enolate with **5**, followed by acylation with trichloroacetic anhydride gave dihydropyridine **6** (70% yield, mixture of epimers) along with minor amounts of regioisomeric 1,2-dihydropyridines (not isolated). 1,4-Dihydropyridine **6** was subjected to haloform reaction with sodium methoxide and radical desulfurization with Ph_3SnH–AIBN to give **7** in 75% yield.

With 1,4-dihydropyridine **7** in hand, attention was turned to the oxidative step. We initially tested the oxidative reagent system (TFA–phenol–Pd/C, 50 °C) we had successfully used for the tandem *N*-dealkylation–oxidation of 4-unsubstituted *N*-(benzhydryl)dihydropyridines.[9,12] However, under these conditions the desired pyridine **4** was isolated in poor yields (15% yield) and pyridine **8**,[13] lacking the acetic ester, was the major product (50% yield). As

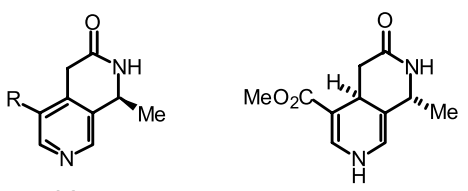

Figure 1. Jasminine and related alkaloids.

Keywords: Dihydropyridines; Pyridines; Acylation; Alkaloids.
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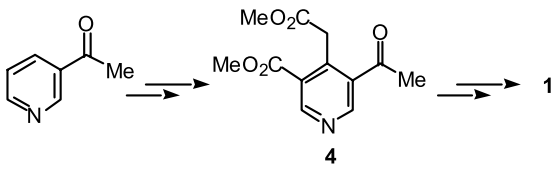
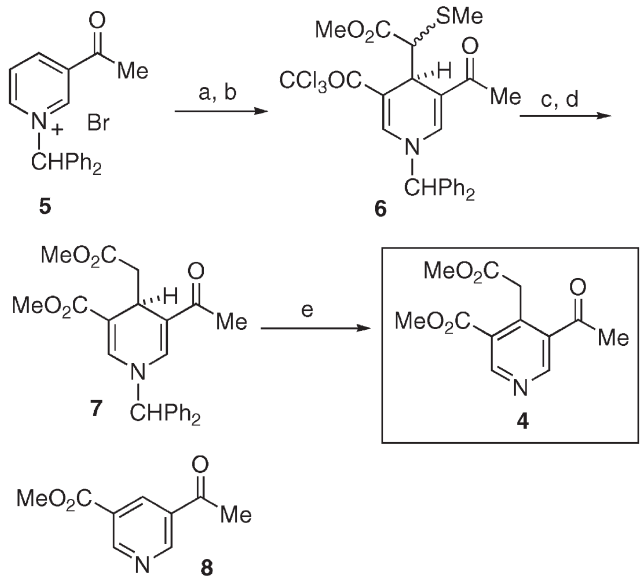


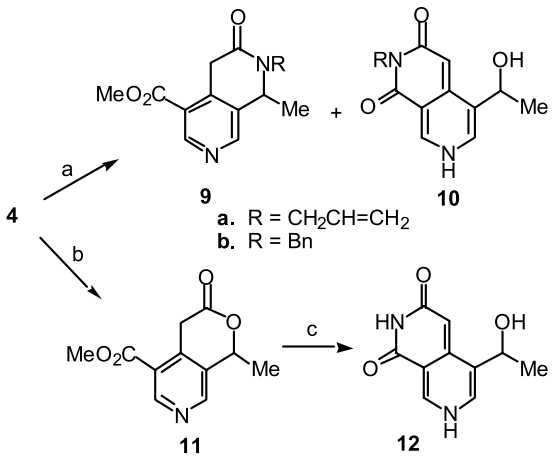
Scheme 1. Synthetic approach.

formation of **8** is presumably the result of a retroaddition reaction that occurs from the initially formed *N*-unsubstituted dihydropyridine, we reasoned that in order to minimize this undesired process oxidation should take place prior to *N*-dealkylation. We were proved right since when **7** was treated with $Mn(OAc)_3$ in TFA–acetic acid[14] and then with phenol the yield of pyridine **4** increased to 80%, with little or no formation of **8**.

Having established a functional protocol for the preparation of pyridine **4**, we then proceeded to construct the naphthyridine ring system of jasminine (**1**) using a reductive amination–lactamization tandem reaction sequence.[15] We examined first the behavior in this process of ammonia equivalents such as allylamine or benzylamine. After recovering the starting material under standard reaction conditions using $Na(CN)BH_3$[16] or $Na(AcO)_3BH$[15,17] as reducing agents, the desired jasminine lactams **9a** and **9b** were obtained, although in low yield (20%), when the reductive amination was effected in the presence of decaborane acting as both the catalyst for the imine formation and the reducing agent (Scheme 3).[18,19] Significantly, bicyclic imides **10a** and **10b** were also isolated from the reaction mixtures in 40% and 10% yields, respectively. These compounds have the 2,7-naphthyridin-1,3-dione skeleton characteristic of the alkaloid sebasnine,[20] which was shown by NMR to be in the highly conjugated 4-alkylidene-1,4-dihydropyridine tautomeric form depicted in **10**. We suspected that formation of **10** involved the initial reduction of the acetyl carbonyl group of **4**, followed by



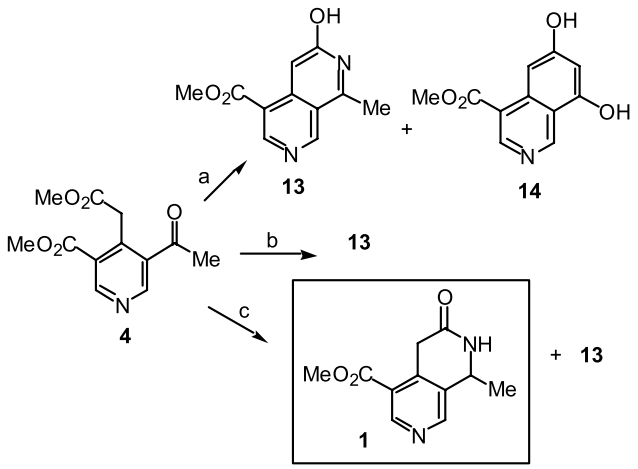
Scheme 2. Synthesis of pyridine **4**. Reagents and conditions: (a) $MeSCH_2CO_2Me$, LDA, THF, −78 °C, 30 min, then −40 °C, 2 h; (b) $(Cl_3CCO)_2O$, triethylamine, rt, 12 h, 70%; (c) MeONa, MeOH, rt, 1 min; (d) Ph_3SnH, AIBN, benzene, reflux, 2 h, 75%; (e) $Mn(OAc)_3{\cdot}2H_2O$, 1:1 TFA–AcOH, 45 °C, 1h, then phenol, 45 °C, 2 h, 80%.



Scheme 3. Reagents and conditions: (a) Allylamine or benzylamine, $B_{10}H_{14}$, MeOH, rt, 48 h, **9a**: 20%, **10a**: 40%, **9b**: 20%, **10b**: 10%; (b) $NaBH_4$, MeOH, 0 °C, 10 min, 80%; (c) NH_3, MeOH, rt, 1 h, 78%.

aminolysis of a lactone intermediate, with subsequent cyclization to the aromatic ester group. This hypothesis could be confirmed since reduction of **4** with $NaBH_4$ in methanol gave lactone **11** (80% yield), which upon a short exposure to a methanolic solution of ammonia afforded imide **12**, the *N*-unsubstituted derivative of **10**, in 78% yield.

The low yield of lactams **9** and the need for an additional *N*-deprotection step to complete the synthesis[21] motivated us to address the synthesis of jasminine (**1**) using a reductive amination with ammonia. Again this seemingly simple task was complicated by the low reactivity of the acetyl carbonyl group and the intensive functionalization of our substrate. Thus, the use of standard protocols such as $AcONH_4$–$Na(CN)BH_3$ or $AcONH_4$–$Na(AcO)_3BH$ resulted, as above, in the recovery of **4**. On the other hand, several noteworthy results were obtained when the amination reaction was carried out with more nucleophilic reagents or under more energetic conditions. Exposure of **4** to $MeAl(Cl)NH_2$[22,23] at room temperature in benzene resulted in the formation of a nearly equimolecular mixture of two fully aromatic bicycles, **13** and **14**, in 60% yield (Scheme 4). Whereas



Scheme 4. Synthesis of (±)-jasminine (**1**). Reagents and conditions: (a) $MeAl(Cl)NH_2$, C_6H_6, rt, 5 h, **13**: 30%, **14**: 30%; (b) Ammonium formate, 150 °C, 10 min, 75%; (c) NH_4Cl, Et_3N, $Ti(i\text{-}PrO)_4$, rt, overnight, then $NaBH_4$, rt, 2 h, **1**: 25%; **13**: 40%.

dihydroxyisoquinoline **14** is the result of a Claisen condensation promoted by the basic character of the reagent, formation of naphthyridinol **13**, a didehydro derivative of the natural product, is striking as it involves an intramolecular acylation at the imine stage. This premature lactamization precludes the subsequent reduction to jasminine as treatment of **4** with ammonium formate (both an ammonia source and a reducing agent)[24] at 150 °C for a short time (10 min) resulted in the exclusive formation of **13** in 75% yield. This serious drawback could be partially countered by the sequential treatment of **4** with ammonia, generated in situ from NH_4Cl and Et_3N at room temperature in the presence of Ti(*i*-PrO)$_4$, and then with $NaBH_4$.[25] Under these conditions, **13** was still the major product (40% yield), but the desired lactam **1**, (±)-jasminine, was isolated in a consistent, reproducible 25% yield. Our synthetic product displayed ^{1}H NMR data identical to those reported for the natural product,[2,3] and its ^{13}C NMR and analytical data were in full agreement with the proposed structure.

3. Conclusions

In conclusion, the present work provides the first total synthesis of the naphthyridine alkaloid jasminine, not an easy target in spite of its apparent structural simplicity. The strategy employed hinges on the straightforward preparation of a 3,4,5-trisubstituted pyridine from a 3-substituted pyridine, emphasizing the well-known utility of 1,4-dihydropyridines as intermediates for alkaloid synthesis.

4. Experimental

4.1. General

All nonaqueous reactions were performed under an argon atmosphere. All solvents were dried by standard methods. Reaction courses and product mixtures were routinely monitored by TLC on silica gel (precoated F_{254} Merck plates). Drying of organic extracts during the workup of reactions was performed over anhydrous Na_2SO_4. Evaporation of the solvents was accomplished under reduced pressure with a rotatory evaporator. Flash chromatography was carried out on SiO_2 (silica gel 60, SDS, 0.04–0.06 mm). Melting points are uncorrected. Chemical shifts of NMR spectra are reported in ppm downfield (δ) from Me_4Si.

4.1.1. 3-Acetyl-1-benzhydrylpyridinium bromide (5). A solution of 3-acetylpyridine (7 mL, 63.8 mmol) and bromodiphenylmethane (18.9 g, 76.6 mmol) in dry acetone (60 mL) was stirred at rt for a week. The white solid which appeared was collected by filtration and washed with Et_2O to give pyridinium salt **5** (12.8 g, 55%): mp 145–6 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.69 (s, 3H), 7.31 (m, 4H), 7.49 (m, 6H), 7.84 (s, 1H), 8.30 (dd, J=6, 8.1 Hz, 1H), 9.10 (d, J=8.1 Hz, 1H), 9.18 (d, J=6 Hz, 1H), 9.53 (s, 1H); ^{13}C NMR (75.4 MHz) δ 27.7, 76.0, 129.0, 129.2, 129.5, 129.7, 135.8, 136.0, 145.1, 145.4, 146.6, 194.1.

4.1.2. Methyl 3-acetyl-1-benzhydryl-α-(methylsulfanyl)-5-(trichloroacetyl)-1,4-dihydropyridine-4-acetate (6). LDA (1.5 M in cyclohexane, 4.40 mL, 6.60 mmol) was slowly added to a cooled (−78 °C) solution of methyl (methylsulfanyl)acetate (0.72 mL, 6.60 mmol) in dry THF (110 mL), and the resulting solution was stirred at −78 °C for 30 min. Pyridinium salt **5** (2 g, 5.50 mmol) was added in portions at −78 °C, and the mixture was allowed to rise to −40 °C. After 2 h at this temperature, the mixture was treated with Et_3N (4.60 mL, 33 mmol) and TCAA (6 mL, 33 mmol) and stirred at rt overnight. The reaction mixture was poured into saturated aqueous Na_2CO_3 and extracted with Et_2O. The solvent was removed and the crude product was chromatographed (75:25 hexanes–AcOEt) to give **6** (2.12 g, 70%, mixture of epimers): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.04 and 2.05 (2s, 3H), 2.20 and 2.27 (2s, 3H), 3.42 and 3.43 (2d, J=4.8, 5.1 Hz, 1H), 3.62 and 3.69 (2s, 3H), 4.88 and 4.93 (2d, J=5.1, 4.8 Hz, 1H), 6.10 (s, 1H), 7.20–7.45 (m, 11H), 7.86 and 7.90 (2s, 1H). Anal. Calcd for $C_{26}H_{24}Cl_3NO_4S$: C, 56.48; H, 4.38; N, 2.53. Found: C, 56.12; H, 4.36; N, 2.47.

4.1.3. Methyl 3-acetyl-1-benzhydryl-5-(methoxycarbonyl)-1,4-dihydropyridine-4-acetate (7). A solution of (trichloroacetyl)-1,4-dihydropyridine **6** (2 g, 3.6 mmol) in THF (65 mL) was added to a solution of MeONa (10.5 mmol) in MeOH (35 mL), and the mixture was stirred at rt for 1 min. The solvent was removed and the resulting residue was partitioned between Et_2O and H_2O, and extracted with Et_2O. After concentration of the organic extracts, the resulting residue was dissolved in C_6H_6 (100 mL) and treated with triphenyltin hydride (0.89 mL, 3.5 mmol) and AIBN (58 mg. 0.35 mmol). After stirring at reflux temperature for 1 h, triphenyltin hydride (0.89 mL, 3.5 mmol) and AIBN (58 mg. 0.35 mmol) were again added and heating was continued for 2 h. The solvent was removed and the resulting residue was partitioned between Et_2O and H_2O, and extracted with Et_2O. The organic extracts were concentrated and the residue was chromatographed (75:25 hexanes–AcOEt) to give **7** (1.13 g; 75%): ^{1}H NMR (300 MHz) δ 2.07 (s, 3H), 2.45 and 2.53 (2dd, J=5.1, 13.8 Hz, 2H), 3.55 (s, 3H), 3.67 (s, 3H), 4.36 (t, J=5.1 Hz, 1H), 5.91 (s, 1H), 7.05 (d, J=1.2 Hz, 1H), 7.23 (m, 5H), 7.39 (m, 6H); ^{13}C NMR (75.4 MHz) δ 24.6, 29.0, 39.9, 51.1, 51.3, 70.7, 107.3, 116.3, 128.2, 128.3, 128.4, 128.5, 128.9, 137.7, 137.8, 138.6, 139.6, 166.8, 172.0, 194.8. Anal. Calcd for $C_{25}H_{25}NO_5$: C, 71.58; H, 6.01; N, 3.34. Found: C, 71.28; H, 6.16; N, 3.23.

4.1.4. Methyl 3-acetyl-5-(methoxycarbonyl)pyridine-4-acetate (4). $Mn(AcO)_3{\cdot}2H_2O$ (0.54 g, 2 mmol) was added to a solution of 1,4-dihydropyridine **7** (0.42 g, 1 mmol) in AcOH–TFA (1:1, 20 mL). After stirring at 45 °C for 1.5 h, phenol (1.32 g, 14 mmol) was added in 7 portions over 2 h at 45 °C. The reaction mixture was cooled (ice bath), basified with saturated aqueous Na_2CO_3 and extracted with CH_2Cl_2. The solvent was removed and the residue was chromatographed (58:42 hexanes–AcOEt) to give pyridine **4** (0.2 g, 80% yield) as a yellow solid: mp 20–22 °C; ^{1}H NMR (400 MHz) δ 2.67 (s, 3H), 3.72 (s, 3H), 3.95 (s, 3H), 4.39 (s, 2H), 9.05 (s, 1H), 9.20 (s, 1H); ^{13}C NMR (100.6 MHz) δ 30.2, 34.8, 52.5, 53.0, 127.8, 135.0, 144.3, 152.4, 153.9, 166.1, 170.7, 200.1. For the hydrochloride: mp 60–61 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.64 (s, 3H), 3.59 (s, 3H), 3.85 (s, 3H), 4.17 (s, 2H), 9.08 (s, 1H), 9.22 (s, 1H). Anal. Calcd for $C_{12}H_{13}NO_5{\cdot}HCl$: C, 50.10; H, 4.90; N, 4.87. Found: C, 50.52; H, 4.96; N, 4.91.

4.2. Tandem reductive amination–lactamization from pyridine 4 and primary amines

A mixture of pyridine **4** (0.25 g, 1 mmol), the appropriate amine (10 mmol) and $B_{10}H_{14}$ (37 mg, 0.30 mmol) in MeOH (15 mL) was stirred at rt for 48 h. The solvent was removed and the resulting residue was chromatographed to give naphthyridines **9** and **10**.

4.2.1. Methyl 2-allyl-1,4-dihydro-1-methyl-3-oxo-2*H*−2,7-naphthyridine-5-carboxylate (9a). Elution with 99:1 CH_2Cl_2–MeOH; yield 20%; ^{1}H NMR (300 MHz) δ 1.46 (d, J=6.6 Hz, 3H), 3.68 (dd, J=6.9, 16.2 Hz, 1H), 3.79 and 4.46 (2d, J=21 Hz, 2H), 3.96 (s, 3H), 4.65 (q, J=6.6 Hz, 1H), 4.73 (dddd, J=1.8, 1.8, 4.8, 16.2 Hz, 1H), 5.20 (m, 2H), 5.78 (dddd, J=4.8, 6.9, 10.2, 17.1 Hz, 1H), 8.54 (s, 1H), 9.06 (s, 1H); ^{13}C NMR (75.4 MHz) δ 22.2, 34.7, 47.2, 52.5, 53.7, 118.0, 123.9, 132.4, 133.5, 142.3, 149.0, 150.4, 165.5, 166.7; HRMS calcd for $C_{14}H_{16}N_2O_3$ 260.1157, found 260.1151.

4.2.2. 2-Allyl-5-(1-hydroxyethyl)-2,7-naphthyridin-1,3-dione (10a). Elution with 96:4 CH_2Cl_2–MeOH; yield 40%; yellow solid; mp 205–6 °C; ^{1}H NMR (200 MHz, DMSO-d_6, HSQC and HMBC) δ 1.30 (d, J=6.5 Hz, 3H, CH_3), 4.46 (d, J=5 Hz, 2H, CH_2–CH=CH_2), 4.67 (m, 1H, CH_3CH), 4.97 and 5.01 (2m, 2H, CH_2=), 5.23 (s, 1H, 4-H), 5.33 (d, J=4.5 Hz, 1H, OH), 5.80 (m, 1H, CH=), 7.47 (s, 1H, 6-H), 8.30 (s, 1H, 8-H); ^{13}C NMR (75.4 MHz, DMSO-d_6, HSQC and HMBC) δ 22.7 (CH_3), 40.8 (CH_2–CH=CH_2), 63.2 (CH_3CH), 88.6 (C-4), 109.6 (C-8a), 115.7 (CH_2=), 128.6 (C-6), 130.7 (C-5), 133.8 (CH=), 139.1 (C-8), 141.8 (C-4a), 162.9 (C-1), 163.4 (C-3); CI-MS m/z 247 (MH^+), 229. Anal. Calcd for $C_{13}H_{14}N_2O_3.1/3H_2O$: C, 61.91; H, 5.86; N, 11.11. Found: C, 61.72; H, 5.82; N, 10.97.

4.2.3. Methyl 2-benzyl-1,4-dihydro-1-methyl-3-oxo-2*H*-2,7-naphthyridine-5-carboxylate (9b). Elution with 99:1 CH_2Cl_2–MeOH; yield 20%; ^{1}H NMR (200 MHz) δ 1.42 (d, J=7 Hz, 3H), 3.84 and 4.55 (2d, J=20.8 Hz, 2H), 3.97 (s, 3H), 4.17 and 5.44 (2d, J=15 Hz, 2H), 4.55 (q, J=7 Hz, 1H), 7.20–7.40 (m, 5H), 8.40 (s, 1H), 9.05 (s, 1H); HRMS calcd for $C_{18}H_{18}N_2O_3$ 310.1313, found 310.1324.

4.2.4. 2-Benzyl-5-(1-hydroxyethyl)-2,7-naphthyridin-1,3-dione (10b). Elution with 96:4 CH_2Cl_2–MeOH; yield 10%; ^{1}H NMR (200 MHz, DMSO-d_6) δ 1.30 (d, J=6.2 Hz, 3H), 4.69 (q, J=6.2 Hz, 1H), 5.06 (s, 2H), 5.22 (s, 1H), 7.25–7.35 (m, 5H), 7.53 (s, 1H), 8.33 (s, 1H).

4.2.5. 5-(1-Hydroxyethyl)-2,7-naphthyridin-1,3-dione (12). $NaBH_4$ (15 mg, 0.40 mmol) was added to a solution of pyridine **4** (0.1 g, 0.40 mmol) in MeOH (4 mL) cooled at 0 °C, and the mixture was stirred at 0 °C for 10 min. The solvent was removed and the residue was partitioned between H_2O_2 and CH_2Cl_2, and extracted with CH_2Cl_2. The organic extracts were concentrated and the residue was chromatographed (CH_2Cl_2) to give lactone **11** (70 mg, 80% yield): ^{1}H NMR (300 MHz) δ 1.82 (d, J=6.9 Hz, 3H), 3.98 (s, 3H), 4.08 and 4.47 (2d, J=20.1 Hz, 2H), 5.59 (q, J=6.9 Hz, 1H), 8.65 (s, 1H), 9.16 (s, 1H); ^{13}C NMR (75.4 MHz) δ 19.8, 33.1, 52.6, 73.9, 123.3, 131.8, 141.6, 147.7, 151.5, 165.1, 168.3.

Lactone **11** (0.11 g, 0.50 mmol) in a saturated methanolic solution of NH_3 (4 mL) was stirred at rt for 1 h. The solvent was removed and the residue was triturated with Et_2O to give **12** (80 mg, 78% yield) as a yellow solid: mp >300 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.28 (d, J=6.3 Hz, 3H), 4.63 (q, J=6 Hz, 1H), 5.07 (s, 1H), 5.20–5.40 (br s, 1H), 7.43 (s, 1H), 8.23 (s, 1H), 10.55 (s, 1H); ^{13}C NMR (75.4 MHz, DMSO-d_6) δ 22.5, 63.1, 88.9, 110.2, 128.5, 130.6, 138.3, 143.3, 163.8, 164.9; CI-MS m/z 207 (MH^+), 189. Anal. Calcd for $C_{10}H_{10}N_2O_3.1/2H_2O$: C, 55.81; H, 5.15; N, 13.02. Found: C, 55.73; H, 5.06; N, 12.70.

4.2.6. Methyl 3-hydroxy-1-methyl-2,7-naphthyridine-5-carboxylate (13). A mixture of pyridine **4** (0.1 g, 0.40 mmol) and ammonium formate (0.1 g, 1.59 mmol) was heated at 150 °C for 10 min. The solid residue was triturated with CH_2Cl_2 to give **13** (65 mg, 75% yield) as a yellow solid: mp >300 °C; ^{1}H NMR (200 MHz, DMSO-d_6, major tautomer) δ 2.90 (s, 3H), 3.90 (s, 3H), 7.44 (s, 1H), 8.93 (s, 1H), 9.50 (s, 1H), 12.0 (br s, 1H); ^{13}C NMR (75.4 MHz, DMSO-d_6, major tautomer) δ 20.3, 52.4, 97.3, 117.2, 140.4, 150.0, 156.6, 161.2, 163.0, 165.9; CI-MS m/z 219 (MH^+). Anal. Calcd for $C_{11}H_{10}N_2O_3{\cdot}H_2O$: C, 55.93; H, 5.12; N, 11.86. Found: C, 55.81; H, 5.26; N, 11.72.

4.2.7. Reaction of pyridine 4 with $CH_3AlClNH_2$. A solution of $CH_3AlClNH_2$[22] in C_6H_6 (0.67 M, 66 μl, 0.044 mmol) was added to a solution of pyridine **4** (10 mg, 0.040 mmol) in C_6H_6 (0.5 mL) and the mixture was stirred at rt for 5 h. The solvent was removed and the resulting residue was partitioned between saturated aqueous $NaHCO_3$ and AcOEt, and extracted with AcOEt. The organic extracts were concentrated and the residue was chromatographed (95:5 CH_2Cl_2–MeOH). First elution gave methyl 6,7-dihydroxyisoquinoline-4-carboxylate **14**: 2.6 mg (30%); ^{1}H NMR (300 MHz, CD_3OD) δ 3.96 (s, 3H), 6.56 (d, J=2.4 Hz, 1H), 7.70 (d, J=2.4 Hz, 1H), 8.85 (s, 1H), 9.36 (s, 1H); CI-MS m/z 220 (MH^+), 194; HRMS calcd for $C_{11}H_9NO_4$ 219.0529, found 219.0522. Further elution gave **13**: 2.6 mg (30%).

4.2.8. (±)-Jasminine (1). A mixture of pyridine **4** (0.1 g, 0.40 mmol), Ti(*i*-PrO)$_4$ (0.24 mL, 0.80 mmol), NH_4Cl (43 mg, 0.80 mmol) and Et_3N (0.11 mL, 0.80 mmol) in dry MeOH (1 mL) was stirred in a sealed tube at rt overnight. $NaBH_4$ (23 mg, 0.60 mmol) was then added and the resulting mixture was stirred at rt for 7 h. The reaction mixture was poured into a 2 M aqueous solution of NH_3 (3 mL), and the precipitate was filtered and washed successively with CH_2Cl_2 and 1:1 CH_2Cl_2–MeOH. Solvents were removed and the resulting residue was chromatographed. Elution with 97:3 CH_2Cl_2–MeOH gave **1** (22 mg, 25%) as a pale yellow solid; mp 163–4 °C (CH_2Cl_2); ^{1}H NMR (400 MHz) δ 1.59 (d, J=6.4 Hz, 3H), 3.96 (s, 3H), 3.99 and 4.15 (2d, J=21.6 Hz, 2H), 4.80 (br q, J=5.6 Hz, 1H), 6.77 (br s, 1H), 8.60 (s, 1H), 9.07 (s, 1H); ^{13}C NMR (100.6 MHz) δ 25.0, 34.2, 49.7, 52.8, 124.3, 132.6, 142.1, 149.9, 150.9, 165.9, 169.4. Anal. Calcd for $C_{11}H_{12}N_2O_3$: C, 59.99; H, 5.49; N, 12.72. Found: C, 59.50; H, 5.71; N, 12.61. Elution with 95:5 CH_2Cl_2–MeOH gave **13**: 35 mg (40%).

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References and notes

1. (a) Hart, N. K.; Johns, S. R.; Lamberton, J. A. *Aust. J. Chem.* **1968**, *21*, 1321–1326. (b) Hart, N. K.; Johns, S. R.; Lamberton, J. A. *Aust. J. Chem.* **1971**, *24*, 1739–1740.
2. Ripperger, H. *Phytochemistry* **1978**, *17*, 1069–1070.
3. Benkrief, R.; Ranarivelo, Y.; Skaltsounis, A.-L.; Tillequin, F.; Koch, M.; Pusset, J.; Sévenet, T. *Phytochemistry* **1998**, *47*, 825–832.
4. A closely related alkaloid, acanthicifoline, was isolated from *Acanthus ilicifolius* (*Acanthaceae*): Tiwara, K. P.; Minocha, P. K.; Masood, M. *Pol. J. Chem.* **1980**, *54*, 857–858.
5. Ranarivelo, Y.; Magiatis, P.; Skaltsounis, A.-L.; Tillequin, F. *Nat. Prod. Lett.* **2001**, *15*, 131–137.
6. For a recent review on the chemistry of dihydropyridines, see: Lavilla, R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1141–1156.
7. (a) Bennasar, M.-L.; Zulaica, E.; Juan, C.; Alonso, Y.; Bosch, J. *J. Org. Chem.* **2002**, *67*, 7465–7474. (b) Bennasar, M.-L.; Roca, T.; Monerris, M. *J. Org. Chem.* **2004**, *69*, 752–756.
8. (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.; Roca, T.; Monerris, M.; Juan, C.; Bosch, J. *Tetrahedron* **2002**, *58*, 8099–8106.
9. Bennasar, M.-L.; Zulaica, E.; Roca, T.; Alonso, Y.; Monerris, M. *Tetrahedron Lett.* **2003**, *44*, 4711–4714.
10. This type of enolate smoothly undergoes addition to *N*-alkyl-3-acylpyridinium salts with higher chemo- and regioselectivity than simple ester enolates: Bennasar, M.-L.; Zulaica, E.; Juan, C.; Llauger, L.; Bosch, J. *Tetrahedron Lett.* **1999**, *40*, 3961–3964, See also reference **7a**.
11. Several nucleophiles have been tested for this purpose: (a) Katritzky, A. R.; Zhang, S.; Kurz, T.; Wang, M.; Steel, P. J. *Org. Lett.* **2001**, *3*, 2807–2809, and references cited therein. See also: (b) Raussou, S.; Gosmini, R.; Mangeney, P.; Alexakis, A.; Commerçon, M. *Tetrahedron Lett.* **1994**, *35*, 5433–5436. (c) Yamada, S.; Misono, T.; Ichikawa, M.; Morita, C. *Tetrahedron* **2001**, *57*, 8939–8949. (d) Rudler, H.; Denise, B.; Parlier, A.; Daran, J.-C. *Chem. Commun.* **2002**, 940–941.
12. Nakamichi, N.; Kawashita, Y.; Hayashi, M. *Org. Lett.* **2002**, *4*, 3955–3957.
13. The spectroscopic data of **8** were identical to those reported in the literature: Bracher, F.; Papke, T. *Monatsh. Chem.* **1995**, *126*, 805–809.
14. Varma, R. S.; Kumar, D. *Tetrahedron Lett.* **1999**, *40*, 21–24.
15. For a precedent of this tandem process, see: Abdel-Magid, A. F.; Harris, B. D.; Maryanoff, C. A. *Synlett* **1994**, 81–83.
16. Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2897–2904.
17. Abdel-Magid, A. F.; Maryanoff, C. A.; Carson, K. G. *Tetrahedron Lett.* **1990**, *31*, 5595–5598.
18. Bae, J. W.; Lee, S. H.; Cho, Y. J.; Yoon, C. M. *J. Chem. Soc. Perkin Trans. 1* **2000**, 145–146.
19. However, no reductive amination was observed with more hindered amines such as benzhydrylamine or *tert*-butylamine.
20. (a) Wanner, M. J.; Koomen, G. J.; Pandit, U. K. *Tetrahedron* **1982**, *38*, 2741–2748. (b) Wada, M.; Nishihara, Y.; Akiba, K. *Tetrahedron Lett.* **1985**, *26*, 3267–3270.
21. Preliminary attempts to induce *N*-deprotection of **9a** or **9b** resulted in failure.
22. Levin, J. I.; Turos, E.; Weinreb, S. M. *Synth. Commun.* **1982**, *12*, 989–993.
23. For the use of aluminum amides for the conversion of C═O into C═NR functionalities, see: Gordon, J. C.; Shukla, P.; Cowley, A. H.; Jones, J. N.; Keogh, D. W.; Scott, B. L. *Chem. Commun.* **2002**, 2710–2711.
24. Wang, M.; Liu, S. Z.; Liu, J.; Hu, B. F. *J. Org. Chem.* **1995**, *60*, 7364–7365.
25. (a) Bhattacharyya, S.; Neidigh, K. A.; Avery, M. A.; Williamson, J. S. *Synlett* **1999**, 1781–1783. (b) Miriyala, B.; Bhattacharyya, S.; Williamson, J. S. *Tetrahedron* **2004**, *60*, 1463–1471.