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Palladium-Catalyzed Ullmann Cross-Coupling/Tandem Reductive Cyclization Route to Key Members of the Uleine Alkaloid Family

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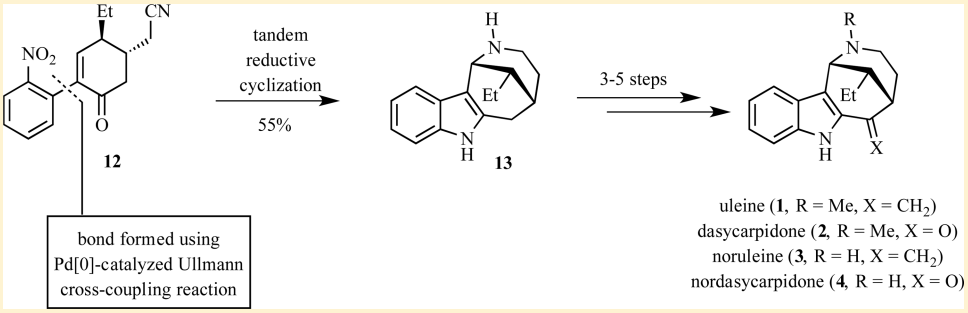
Supporting Information



ABSTRACT: The trisubstituted cyclohexenone **12**, generated through a palladium-catalyzed Ullmann cross-coupling reaction between *o*-iodonitrobenzene and a 4,5-*trans*-disubstituted 2-iodo-2-cyclohexen-1-one, engaged in a tandem reductive cyclization process upon exposure to hydrogen gas in the presence of Raney cobalt. As a result, the 1,5-methanoazocino[4,3-*b*]indole **13** was obtained and this could be readily elaborated to the racemic modifications of the alkaloids uleine, dasycarpidone, noruleine, and nordasycarpidone (**1**−**4**, respectively).

INTRODUCTION

Like the more well-known *Strychnos* alkaloids, the uleine-type natural products embody the tetracyclic 1,5-methanoazocino-[4,3-*b*]indole framework.[1] Uleine (**1**),[2,3] dasycarpidone (**2**),[3] noruleine (**3**),[3] and nordasycarpidone (**4**)[3] (Figure 1), all of which have been isolated from a range of plant sources, including the bark of the South American shrub *Aspidosperma dasycarpon* A. DC., are the "original" and representative members of the family, but others have since been identified, including, for example, C20-epimers[4] and more highly oxygenated variants.[5]

A range of interesting biological properties has been attributed to uleine and its congeners. These include analgesic, anti-inflammatory, bactericidal, antimalarial, and acetylcholinesterase (AChE)-inhibiting activities.[6] In addition, the capacity of compound **1** to promote the synthesis of nitric oxide has prompted investigations on the use of the source plants as adjuvants in the treatment of patients with compromised immune systems.[7]

Since the completion of the key studies[2,4,8] on the elucidation of the structures of the uleines, there have been numerous reports on the development of often ingenious total syntheses of compounds **1**−**4**.[9,10] These have delivered both racemic and enantiomerically enriched forms of the target compounds. The presence of the 1,5-methanoazocino[4,3-*b*]indole framework within other alkaloids has also prompted the more general development of approaches to this scaffold.[11] As part of our own efforts in the area, in 2012 we described[10f] a Raney cobalt mediated tandem reductive cyclization route to this framework and the elaboration of it to the ABCDE-ring system of the *Strychnos* alkaloids. This work was an extension of slightly earlier studies on the application of related processes to the assembly of the *Aspidosperma* alkaloids limaspermidine and 1-acetylaspidoalbidine[12] that also exploited the capacity of the palladium-catalyzed Ullmann cross-coupling reaction[13] to generate the relevant substrates for the reductive cyclization events.

Herein, we report the extension of both these earlier studies[10f] to stereocontrolled total syntheses of the racemic forms of uleine, dasycarpidone, noruleine, and nordasycarpidone. We also identify seemingly straightforward means by which this work could be extended to the enantioselective assembly of these same alkaloids.

RESULTS AND DISCUSSION

The reaction sequence leading to the substrate required for the pivotal tandem reductive cyclization event is shown in Scheme 1. Thus, 4-ethylcyclohexanone (**5**) was converted into the corresponding (and racemic) unsaturated analogue **6** (60%)[14] by treating the former compound with iodoxybenzoic acid (IBX) in DMSO under conditions defined by Nicoloau and coworkers.[15] Nucleophilic cyclopropanation of the latter compound could be achieved using the Corey−Chaykovsky ylide that had been generated in situ by well-established methods.[16] As a result, the diastereoselective formation of the

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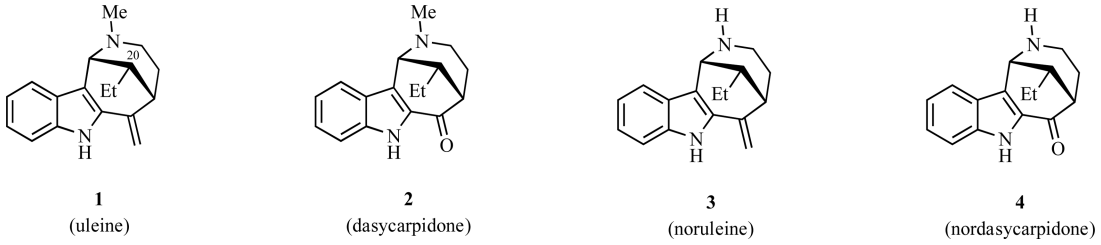
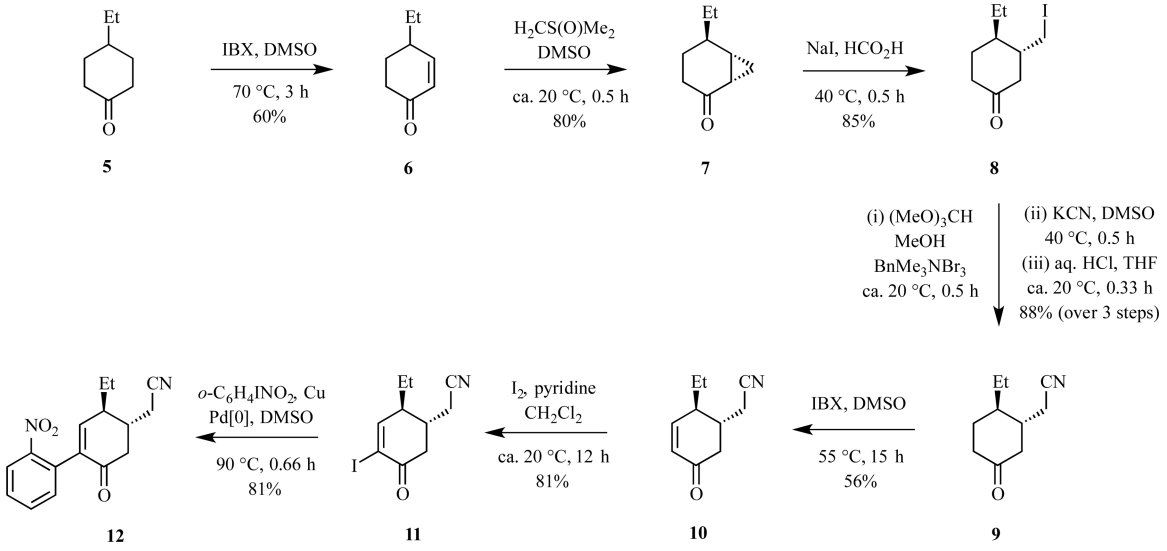


Figure 1. Structures of uleines **1**−**4**.

Scheme 1. Synthesis of Substrate 12 Required for the Tandem Reductive Cyclization Reaction



bicyclo[4.1.0]heptanone **7** (80%) was achieved, although the presence of a ca. 10% of an isomeric material (presumably the corresponding *cis*-compound) was evident in the ^{13}C NMR spectrum of this material. Treament of compound **7** with sodium iodide in formic acid resulted in a homoconjugate addition reaction[17] and formation of ca. 10:1 mixture of the desired iodomethylated product **8** (85%) and a chromatographically inseparable isomer. The substitution of the iodine within compound **8** by a nitrile residue could not be achieved directly by, for example, treating it with sodium cyanide. Rather, a 3-(enol-*exo*)-*exo*-*tet* cyclization reaction[18] took place under all conditions employed, thus regenerating the precursor cyclopropane **7**. Accordingly, and in a telescoped-type reaction sequence, compound **8** was converted into the corresponding dimethyl ketal that could now be engaged in the desired nucleophilic substitution reaction with sodium cyanide. The ensuing dimethyl ketal of the required nitrile was immediately treated with aqueous hydrochloric acid, thereby affording the targeted compound **9** in 88% yield over the three steps involved. Various attempts to effect the direct conversion of enone **6** into nitrile **9**, including through addition of the acetonitrile anion to the former compound, all failed.

Dehydrogenation of cyclohexanone **9** could be achieved with some levels of regiocontrol using IBX in DMSO[15] and the 4,5-disubstituted-2-cyclohexen-1-one **10** was thus obtained in 56% yield. Even after chromatographic purification, this material contained IBX-derived impurities. There was also some evidence for the coproduction of minor amounts of the regioisomeric enone. The (albeit modest) regioselectivity observed in this conversion is presumably the result of the steric effects exerted by the cyanomethyl group in substrate **9**. In anticipation of perfoming a palladium-catalyzed Ullmann cross-coupling reaction,[13] cyclohexenone **10** was subjected to a Johnson-type α-iodination reaction,[19] thus affording the iodo derivative **11** (81%) that was readily obtained in spectroscopically pure form after flash chromatography. The pivotal cross-coupling of compound **11** with *o*-iodonitrobenzene proceeded smoothly when a DMSO solution of the two reaction partners was treated with copper powder and $Pd_2(dba)_3$ (ca. 8 mol % wrt **11**) and the ensuing mixture heated at 90 °C for 0.66 h. As a result, and after chromatographic purification, the crystalline product **12** was obtained in 81% yield.

All of the conventional spectroscopic data acquired on compound **12** were in complete accord with the assigned structure, but final confirmation of this followed from a single-crystal X-ray analysis, some details of which are provided in the Experimental Section and the Supporting Information. Most importantly, this analysis confirmed the *trans* relationship between the ethyl and cyanomethyl residues within the compound. Such a relationship was essential for establishing the correct relative stereochemistry of the ethyl group at C-20 in target **1** (a vexing issue encountered in a number of earlier synthetic studies[9c]).

With compound **12** in hand, its capacity to engage in the pivotal tandem reductive cyclization reaction could be explored. When a THF/methanol solution of compound **12** containing *p*-toluenesulfonic acid monohydrate (*p*-TsOH·H_2O, introduced to suppress intermolecular reductive alkylation reactions) was treated with 200 wt % of freshly prepared Raney cobalt[20] and exposed to an atmosphere of hydrogen gas then the desired transformation took place such that after chromatographic purification the anticipated 1,5-methanoazocino[4,3-*b*]indole

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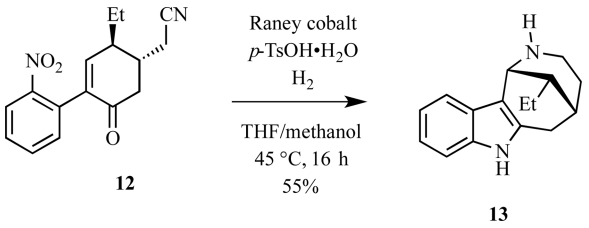
13 was obtained in 55% yield (Scheme 2). The modest yields observed during this conversion are attributed to the rather unstable nature of the product and, for example, the apparent ready propensity of it to oxidize on standing. All of the spectral data acquired on compound 13 were in accord with the assigned structure, but final confirmation of this followed from a single-crystal X-ray analysis of a Boc derivative (see below).

Scheme 2. Pivotal Tandem Reductive Cyclization Reaction



Interestingly, compound 13 has served as an advanced intermediate in a total synthesis of the *Strychnos* alkaloid tubotaiwine reported by Bosch and co-workers.[11a]

The route used in elaborating compound 13 to noruleine (3) and then, through *N*-methylation, to uleine (1) is shown in Scheme 3. Thus, the 2°-amine 13 was first converted into the corresponding Boc derivative 14 (80%), the structure of which was confirmed through a single-crystal X-ray analysis (see the Experimental Section and the Supporting Information for details). In $CDCl_3$ solutions at room temperature, this material existed as a ca. 1:1 mixture of rotamers. Upon treating a dichloromethane solution of carbamate 14 with pyridinium chlorochromate (PCC), a relatively smooth oxidation reaction took place to deliver ketone 15 (75%), and on reacting this with methyllithium at −78 °C, the 3°-alcohol 16 was produced. This last compound was not isolated but simply treated with a ca. 4-fold excess of trifluoroacetic acid at ambient temperature. As a result, both dehydration and cleavage of the Boc group took place (no specific order of events implied). After workup and chromatographic purification, noruleine (3) was obtained in 75% yield.

A comparison of the ^1H and ^{13}C NMR spectral data acquired on this material with those recorded by Patir and Ertürk[9e] on their (synthetically derived) material revealed an excellent match (see Table 1 for a comparison of the ^{13}C NMR data sets).

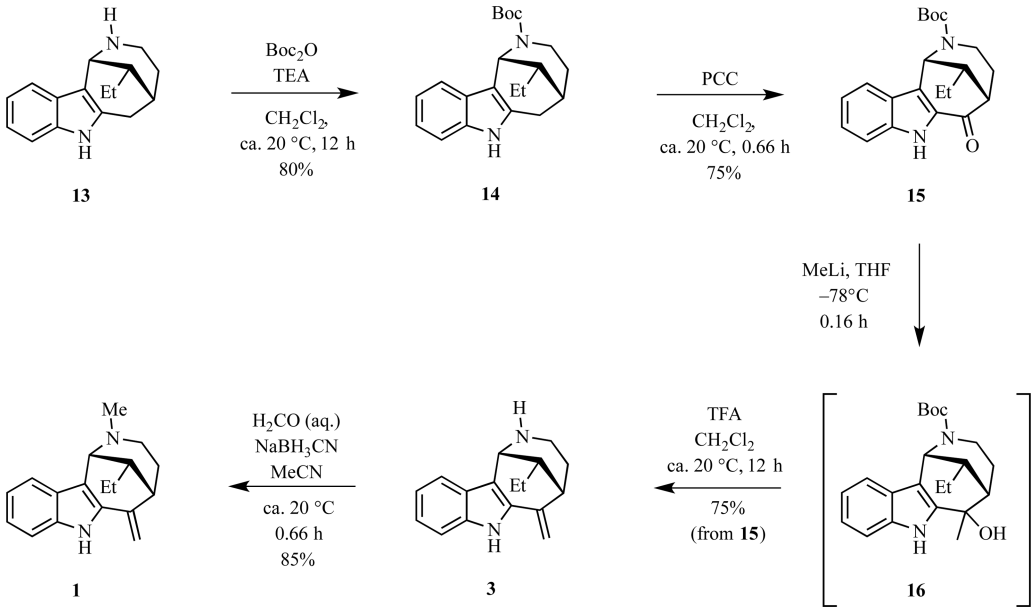
Table 1. Comparison of the ^{13}C NMR Data Recorded for Synthetically Derived Compounds 3 and 1 with Those Reported for Noruleine (3) and Uleine (1)

^{13}C NMR data for compd 3 (δ_C)[a]	^{13}C NMR data for noruleine (δ_C)[b]	^{13}C NMR data for compd 1 (δ_C)[a]	^{13}C NMR data for uleine (δ_C)[b]
138.7	138.6	138.7	138.7
137.1	137.1	136.6	136.6
134.9	135.0	135.2	135.2
126.8	126.8	129.4	129.4
123.0	122.9	122.8	122.7
119.8	119.7	119.9	119.9
118.6	118.5	119.6	119.5
111.5	111.2	110.8	110.7
110.9	110.9	107.7	107.7
106.7	106.9	106.9	106.8
49.3	49.3	56.6[c]	55.6[c]
45.8	45.6	46.3	46.1
40.6	40.5	46.1	46.3
37.4	37.3	44.3	44.3
35.0	34.8	39.5	39.5
24.6	24.6	34.7	34.7
11.8	11.7	24.4	24.4
		11.8	11.8

[a]Spectrum recorded in $CDCl_3$ at 100 MHz. [b]Data obtained from ref 9e; spectrum recorded in $CDCl_3$ at 125 or 150 MHz. [c]The difference in these δ_C values could arise from variations in the pH of the medium in which each spectrum was acquired.

The conversion of noruleine (3) into uleine (1) proved a straightforward matter and simply involved (Scheme 3) subjecting the former compound to a reductive methylation reaction using a combination of formaldehyde and sodium

Scheme 3. Elaboration of the Tandem Reductive Cyclization Product 13 to Noruleine (3) and Uleine (1)



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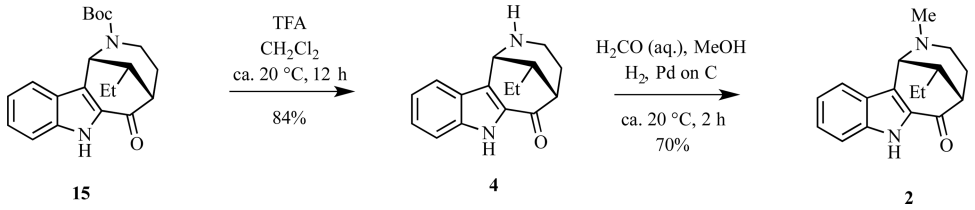
Scheme 4. Completion of Syntheses of Nordasycarpidon (4) and Dasycarpidone (2)



cyanoborohydride. By such means, parent compound **1** was obtained in 85% yield and all the derived spectral data were, once again, a good match with those reported by others (see Table 1, for example).

Completion of syntheses of nordasycarpidone (**4**) and dasycarpidone (**2**) proved equally straightforward and involved, as shown in Scheme 4, TFA-induced cleavage of compound **15** to give, in 84% yield, the former natural product. Reductive methylation of this product (viz. **4**) using formaldehyde and hydrogen gas in the presence of palladium on carbon then gave dasycarpidone (**2**) in 70% yield.

As before, all of the spectroscopic data obtained on compounds **2** and **4** were in accord with the assigned structures and, with one minor discrepancy (see Table 2), matched those reported by Bosch and co-workers.[9a]

Table 2. Comparison of the ^{13}C NMR Data Recorded for Synthetically Derived Compounds 4 and 2 with Those Reported for Nordasycarpidone (4) and Dasycarpidone (2)

^{13}C NMR data for compd **4** (δ_C)[a]	^{13}C NMR data for nordasycarpidone (δ_C)[b]	^{13}C NMR data for compd **2** (δ_C)[a]	^{13}C NMR data for dasycarpidone (δ_C)[b]
193.2[c]	193.9[c]	193.2	193.5
138.7	139.0	138.0	138.1
132.8	132.9	132.8	132.9
127.1	127.0	127.7	127.8
125.1	125.1	126.8	126.9
122.8[c]	123.8[c]	121.9	122.0
121.0	121.0	121.1	121.1
121.0	120.8	119.7	119.9
112.9	113.0	112.6	112.7
49.0	49.0	56.4	56.2
48.7	49.0	49.7	49.6
47.2	47.4	46.4	46.3
37.2	37.2	46.1	46.0
29.8	30.2	44.1	44.0
25.2	25.0	30.2	30.1
11.7	11.5	25.0	24.8
		11.8	11.8

[a]Spectrum recorded in $CDCl_3$ at 100 MHz. [b]Data obtained from ref 9a; spectrum recorded in $CDCl_3$ at 125 MHz. [c]The difference in these δ_C values could arise from variations in the pH of the medium in which each spectrum was acquired.

CONCLUSION

The work reported here, when considered in conjunction with our previous studies,[10f,12,21] serves to emphasize the considerable utility of both the palladium-catalyzed Ullmann cross-coupling reaction and certain tandem reductive cyclization processes, especially when these are applied together within a given synthetic sequence. The capacity to exploit such processes in the assembly of other biologically relevant heterocyclic frameworks is the subject of ongoing studies in our laboratories.

It should also be noted that rather efficient methods for the synthesis of optically active 4-substituted 2-cyclohexenones, including the *S*-enantiomer of **6**, have been reported.[22] Accordingly, there is every prospect that the work reported here could be applied in a straightforward manner to the enantioselective synthesis of the uleines and, perhaps even, the *Strychnos* alkaloids.

EXPERIMENTAL SECTION

General Protocols. Unless otherwise specified, proton (^1H) and carbon (^{13}C) NMR spectra were recorded at room temperature in base-filtered $CDCl_3$ on a spectrometer operating at 400 MHz for proton and 100 MHz for carbon nuclei. The signal due to residual $CHCl_3$ appearing at δ_H 7.26 and the central resonance of the $CDCl_3$ "triplet" appearing at δ_C 77.0 were used to reference ^1H and ^{13}C NMR spectra, respectively. ^1H NMR data are recorded as follows: chemical shift (δ) [multiplicity, coupling constant(s) J (Hz), relative integral] where multiplicity is defined as s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet or combinations of the above. Infrared spectra (ν_{max}) were recorded on an FTIR spectrometer. Samples were analyzed as thin films on KBr plates. Low-resolution ESI mass spectra were recorded on a single quadrupole liquid chromatograph−mass spectrometer, while high-resolution measurements were conducted on a time-of-flight instrument. Low- and high-resolution EI mass spectra were recorded on a magnetic-sector machine. Melting points were measured on an automated melting point system and are uncorrected. Analytical thin-layer chromatography (TLC) was performed on aluminum-backed 0.2 mm thick silica gel 60 F_{254} plates. Eluted plates were visualized using a 254 nm UV lamp and/or by treatment with a suitable dip followed by heating. These dips included phosphomolybdic acid/ceric sulfate/sulfuric acid (concd)/water (37.5 g/7.5 g/37.5 g/720 mL), potassium permanganate/potassium carbonate/5% sodium hydroxide aqueous solution/water (3 g/20 g/5 mL/300 mL), *p*-anisaldehyde or vanillin/sulfuric acid (concd)/ethanol (15 g/2.5 mL/250 mL). Flash chromatographic separations were carried out following protocols defined by Still et al.[23] with silica gel 60 (40−63 μm) as the stationary phase and using the AR- or HPLC-grade solvents indicated. Starting materials, reagents, drying agents, and other inorganic salts were generally commercially available and were used as supplied. Tetrahydrofuran (THF), methanol, and dichloromethane were dried using a solvent purification system that is based upon a technology originally described by Grubbs et al.[24] Where necessary, reactions were performed under a nitrogen atmosphere.

Specific Chemical Transformations. *4-Ethylcyclohex-2-en-1-one (6).* A magnetically stirred solution of 4-ethylcyclohexanone (2.00 g, 15.9 mmol) in DMSO (50 mL) was treated with IBX (9.10 g, 32.5 mmol) and the resulting mixture heated at 70 °C for 3 h and then cooled to room temperature and quenched with $NaHCO_3$ (50 mL of a saturated aqueous solution). The ensuing mixture was filtered through diatomaceous earth, and the solids thus retained washed with diethyl ether (3 × 20 mL). The aqueous phase was extracted with diethyl ether (3 × 40 mL), and the combined organic phases were washed with brine (1 × 50 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The ensuring black oil was subjected to flash chromatography (silica, 1:50 → 1:20 v/v ethyl acetate/hexane gradient elution), and concentration of relevant

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fractions (R_f = 0.4 in 1:7 v/v ethyl acetate/hexane elution) afforded the title compound **6**[14] (1.18 g, 60%) as a clear, colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.88 (ddd, J = 10.2, 2.6, and 1.4 Hz, 1H), 5.98 (dd, J = 10.2 and 2.2 Hz, 1H), 2.50 (dt, J = 16.7 and 4.7 Hz, 1H), 2.42−2.27 (complex m, 2H), 2.16−2.08 (complex m, 1H), 1.76−1.62 (complex m, 1H), 1.62−1.39 (complex m, 2H), 1.01 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 200.0, 155.0, 129.0, 37.7, 37.0, 28.2, 27.5, 11.4; IR ν_{max} 2963, 1683, 1461, 1390, 1148, 942, 854, 742 cm^{-1}; MS (ESI, + ve) m/z 125 [(M + H)$^+$, 100]; HRMS (M + Na)$^+$ calcd for $C_8H_{12}NaO$ 147.0786, found 147.0787.

*rac-(1S,5R,6S)-5-Ethylbicyclo[4.1.0]heptan-2-one (**7**).* A magnetically stirred suspension of NaH (82 mg, 3.4 mmol) in dry DMSO (10 mL) was treated with Me_3SOI (441 mg, 2.0 mmol), and after being maintained at room temperature for 0.17 h, the reaction mixture was warmed to 50 °C and stirred for a further 0.34 h. The cooled mixture was treated with enone **6** (224 mg, 1.8 mmol) and then stirred at room temperature for 0.5 h before being quenched with H_2O (15 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic phases were washed with brine (1 × 50 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The ensuing yellow oil was subjected to flash chromatography (silica, 1:15 → 1:10 v/v ethyl acetate/hexane gradient elution) and concentration of relevant fractions (R_f = 0.3 in 1:7 v/v ethyl acetate/hexane) afforded a ca. 10:1 mixture of the title compound **7** and the diastereoisomeric cyclopropane (224 mg, 90%) as a clear, colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.17−2.05 (complex m, 2H), 1.93−1.83 (complex m, 1H), 1.82−1.65 (complex m, 2H), 1.66−1.32 (complex m, 4H), 1.27−1.09 (complex m, 2H), 0.97 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 209.8, 33.5, 33.1, 27.4, 25.5, 24.2, 23.8, 12.8, 12.0; IR ν_{max} 2960, 1686, 1462, 1345, 1246, 1197, 939, 883, 824 cm^{-1}; MS (ESI, + ve) m/z 161 [(M + Na)$^+$, 3%], 139 [(M + H)$^+$, 100]; HRMS (M + Na)$^+$ calcd for $C_9H_{14}NaO$ 161.0942, found 161.0939.

*rac-(3R,4R)-4-Ethyl-3-(iodomethyl)cyclohexan-1-one (**8**).* A magnetically stirred solution of ketone **7** (510 mg, 4.0 mmol) and NaI (2.20 g, 14.7 mmol) in HCOOH (10 mL) was heated at 40 °C for 0.5 h and then cooled to room temperature and quenched with H_2O (15 mL). The resulting mixture was extracted with ethyl acetate (3 × 20 mL), and the combined organic phases were washed with $NaHCO_3$ (1 × 50 mL of a saturated aqueous solution) and brine (1 × 50 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The ensuing yellow oil was subjected to flash chromatography (silica, 1:18 v/v ethyl acetate/hexane elution), and concentration of relevant fractions (R_f = 0.5 in 1:7 v/v ethyl acetate/hexane) afforded a ca. 10:1 mixture of the title compound **8** and a diastereoisomer (930 mg, 95%) as a clear, colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.41 (dd, J = 10.3 and 4.9 Hz, 1H), 3.24 (dd, J = 10.3 and 2.9 Hz, 1H), 2.46−2.25 (complex m, 4H), 2.16−2.04 (complex m, 1H), 1.73−1.40 (complex m, 3H), 1.36−1.14 (complex m, 2H), 0.95 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 210.7, 47.1, 41.6, 40.9, 40.7, 28.8, 24.2, 15.2, 10.4; IR ν_{max} 2960, 2873, 1716, 1461, 1427, 1318, 1218, 1177 cm^{-1}; MS (ESI, + ve) m/z 289 [(M + Na)$^+$, 100], 267 [(M + H)$^+$, 23]; HRMS (M + Na)$^+$ calcd for $C_9H_{15}INaO$ 289.0065, found 289.0067.

*rac-2-[(1R,2R)-2-Ethyl-5-oxocyclohexyl]acetonitrile (**9**). Step i.* A magnetically stirred solution of iodide **8** (1.08 g, 4.1 mmol) in anhydrous MeOH (10 mL) was treated with trimethyl orthoformate (480 μL, 4.5 mmol) and benzyltrimethylammonium tribromide (30 mg, 0.08 mmol). The resulting mixture was stirred at room temperature for 0.5 h, quenched with $NaHCO_3$ (10 mL of a saturated aqueous solution), and extracted with ethyl acetate (3 × 20 mL). The combined organic phases were washed with brine (1 × 50 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The resulting yellow oil, presumed to contain the dimethyl ketal of compound **8**, was immediately subjected to the reaction conditions defined in step ii.

Step ii. A magnetically stirred solution of crude material obtained from step i in DMSO (6 mL) was treated with KCN (480 mg, 7.4 mmol). The resulting solution was stirred at 40 °C for 0.5 h and then quenched with H_2O (15 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic phases were concentrated under reduced pressure, and the yellow oil thus obtained, and presumed to contain the dimethyl ketal of compound **9**, was immediately subjected to the reaction conditions defined in step iii.

Step iii. A magnetically stirred solution of the oil obtained from step ii in THF (10 mL) was treated with HCl (5 mL of a 1 M aqueous solution) (CAUTION: possibility of HCN generation) and the resulting mixture stirred at room temperature for 0.33 h before being quenched with $NaHCO_3$ (20 mL of a saturated aqueous solution) and then extracted with ethyl acetate (3 × 20 mL). The combined organic phases were washed with brine (1 × 50 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The ensuing yellow oil was subjected to flash chromatography (silica, 1:9 v/v ethyl acetate/hexane elution), and concentration of relevant fractions (R_f = 0.2 in 1:3 v/v ethyl acetate/hexane) afforded the title compound **9** (590 mg, 88%) as a clear, colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.50 (dd, J = 17.1 and 6.3 Hz, 1H), 2.45−2.25 (complex m, 5H), 2.13−2.03 (complex m, 1H), 1.93−1.85 (complex m, 1H), 1.66−1.59 (complex m, 2H), 1.49−1.32 (complex m, 1H), 1.31−1.15 (complex m, 1H), 0.90 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 209.2, 117.5, 45.6, 40.4, 39.9, 38.3, 29.1, 24.5, 21.9, 10.5; IR ν_{max} 2964, 2877, 2245, 1715, 1464, 1426, 1328, 1250, 1193, 954, 853 cm^{-1}; MS (ESI, + ve) m/z 188 [(M + Na)$^+$, 45], 166 [(M + H)$^+$, 30], 122 (100); HRMS (M + Na)$^+$ calcd for $C_{10}H_{15}NNaO$ 188.1051, found 188.1052.

*rac-2-[(1R,2S)-2-Ethyl-5-oxocyclohex-3-en-1-yl]acetonitrile (**10**).* A magnetically stirred solution of ketone **9** (280 mg, 1.7 mmol) in DMSO (10 mL) was treated with p-TsOH·H_2O (90 mg, 0.5 mmol) and IBX (960 mg, 3.4 mmol) and then heated at 55 °C for 15 h. The cooled reaction mixture was quenched with $NaHCO_3$ (15 mL of a saturated aqueous solution) and then filtered through a pad of diatomaceous earth. The solids thus retained were washed with ethyl acetate (3 × 20 mL), and the separated aqueous phase associated with the filtrate was extracted with ethyl acetate (3 × 40 mL). The combined organic phases were washed with brine (1 × 50 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The yellow oil thus obtained was subjected to flash chromatography (silica, 1:9 → 1:4 v/v ethyl acetate/hexane gradient elution), and concentration of relevant fractions (R_f = 0.3 in 1:3 v/v ethyl acetate/hexane) afforded the title compound **10** (150 mg, 56%) as a clear, colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.81 (dd, J = 10.2 and 2.9 Hz, 1H), 6.00 (dd, J = 10.2 and 2.1 Hz, 1H), 2.58 (dd, J = 16.2 and 4.0 Hz, 1H), 2.46 (t, J = 6.0 Hz, 2H), 2.42−2.21 (complex m, 3H), 1.73−1.63 (complex m, 1H), 1.59−1.43 (complex m, 1H), 0.94 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 197.1, 152.4, 129.3, 117.5, 41.5, 40.9, 34.9, 24.4, 21.6, 10.4; IR ν_{max} 2966, 2257, 1679, 1389, 1249, 868, 504 cm^{-1}; MS (ESI, + ve) m/z 186 [(M + Na)$^+$, 100]; HRMS (M + Na)$^+$ calcd for $C_{10}H_{13}NNaO$ 186.0895, found 186.0897.

*rac-2-[(1R,2S)-2-Ethyl-4-iodo-5-oxocyclohex-3-en-1-yl]-acetonitrile (**11**).* A magnetically stirred solution of enone **10** (140 mg, 0.48 mmol) in CH_2Cl_2/pyridine (4 mL of a 1:1 v/v mixture) maintained at room temperature was treated dropwise with a solution of molecular iodine (330 mg, 1.20 mmol) in CH_2Cl_2/pyridine (4 mL of a 1:1 v/v mixture). The ensuing solution was stirred at room temperature for 12 h and then treated with H_2O (10 mL). The separated aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL), and the combined organic phases were washed, sequentially, with HCl (1 × 20 mL of a 1 M aqueous solution), $Na_2S_2O_3$ (1 × 20 mL of a 10% w/w aqueous solution), and brine (1 × 20 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The yellow oil thus obtained was subjected to flash chromatography (silica, 1:6 → 1:3 v/v ethyl acetate/hexane gradient elution), and concentration of relevant fractions (R_f = 0.4 in 1:3 v/v ethyl acetate/hexane) afforded the title compound **11** (190 mg, 81%) as a clear, colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.63 (d, J = 3.2 Hz, 1H), 2.90 (dd, J = 16.3 and 4.1 Hz, 1H), 2.72−2.49 (complex m, 4H), 2.46−2.33 (complex m, 1H), 1.81−1.71 (complex m, 1H), 1.68−1.53 (complex m, 1H), 1.04 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 190.0, 160.8, 117.0, 103.0, 45.3, 40.5, 35.1, 24.3, 21.4, 10.6; IR ν_{max} 2964, 2245, 1686, 1589, 1461, 1421, 1329, 1191, 1116, 948, 899,

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772 cm^{-1}; MS (ESI, + ve) m/z 312 [$(M + Na)^+$, 100], 290 [$(M + H)^+$, 14]; HRMS $(M + Na)^+$ calcd for $C_{10}H_{12}INNaO$ 311.9861, found 311.9862.

Compound **12**. A magnetically stirred solution of iodide **11** (240 mg, 0.86 mmol) and *o*-iodonitrobenzene (420 mg, 1.7 mmol) in DMSO (4 mL) was treated with $Pd_2(dba)_3$ (60 mg, 0.07 mmol) and Cu powder (260 mg, 4.1 g.atom). The resulting mixture was heated at 90 °C for 0.66 h before being cooled to room temperature and then diluted with ethyl acetate (10 mL). The mixture thus obtained was filtered through diatomaceous earth, and the solids thus retained were washed with ethyl acetate (3 × 10 mL). The combined filtrates were washed with water (2 × 30 mL) and the combined aqueous phases extracted with ethyl acetate (3 × 30 mL). The combined organic phases were washed with brine (1 × 30 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The ensuing yellow oil was subjected to flash chromatography (silica, 1:10 → 1:5 v/v ethyl acetate/hexane gradient elution) and concentration of relevant fractions (R_f = 0.2 in 1:3 v/v ethyl acetate/hexane) afforded the title compound **12** (190 mg, 81%) as a yellow, crystalline solid: mp = 109−113 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.07 (dd, J = 8.2 and 1.2 Hz, 1H), 7.65 (td, J = 7.9 and 1.3 Hz, 1H), 7.53 (td, J = 7.9 and 1.5 Hz, 1H), 7.36−7.18 (complex m, 1H), 6.89 (d, J = 3.5 Hz, 1H), 2.81 (dd, J = 16.1 and 4.0 Hz, 1H), 2.76−2.43 (complex m, 5H), 1.95−1.78 (complex m, 1H), 1.76−1.67 (complex m, 1H), 1.11 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 193.9, 148.5, 148.0, 139.3, 133.6, 131.6, 131.3, 129.3, 124.5, 117.6, 41.3, 41.2, 34.8, 24.9, 21.6, 10.8; IR ν_{max} 2971, 2245, 1683, 1524, 1353, 1184, 854, 788 cm^{-1}; MS (ESI, + ve) m/z 307 [$(M + Na)^+$, 100], 285 [$(M + H)^+$, 22]; HRMS $(M + Na)^+$ calcd for $C_{16}H_{16}N_2NaO_3$ 307.1059, found 307.1059.

Compound **13**. A magnetically stirred solution of nitrile **12** (200 mg, 0.70 mmol), *p*-TsOH·H_2O (700 mg, 3.7 mmol), and Raney cobalt (430 mg, 200% w/w) in THF/methanol (15 mL of a 1:1 v/v mixture) was heated at 45 °C for 16 h while being maintained under an atmosphere of hydrogen. The resulting mixture was cooled to room temperature then filtered through diatomaceous earth, and the solids thus retained were washed with methanol (3 × 20 mL). The combined filtrates were concentrated under reduced pressure to afford a yellow oil that was subjected to flash chromatography (silica, 1:20 → 1:5 v/v methanol/dichloromethane gradient elution). Concentration of relevant fractions (R_f = 0.4 in 1:4 v/v methanol/dichloromethane) afforded the title compound **13**[9a,11a] (93 mg, 55%) as a clear, unstable yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.20 (s, 1H), 7.43 (d, J = 7.6 Hz, 1H), 7.25 (d, J = 7.5 Hz, 1H), 7.03 (m, 2H), 2.91 (dd, J = 17.4 and 6.6 Hz, 1H), 2.67−2.35 (complex m, 3H), 2.20 (broad s, 1H), 2.01−1.75 (complex m, 2H), 1.54 (d, J = 13.4 Hz, 2H), 1.31−1.01 (complex m, 3H), 0.81 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 136.3, 136.0, 126.8, 121.1, 119.4, 117.4, 110.6, 107.2, 48.8, 43.4, 37.1, 34.0, 29.9, 25.6, 24.0, 11.8; IR ν_{max} 2958, 2925, 2873, 1617, 1456, 1304, 1238, 1010, 906, 727 cm^{-1}; MS (ESI, + ve) m/z 241 [$(M + H)^+$, 100], 224 (45), 198 (30); HRMS $(M + H)^+$ calcd for $C_{16}H_{21}N_2$ 241.1705, found 241.1702.

Compound **14**. A magnetically stirred solution of amine **13** (87 mg, 0.36 mmol) in dichloromethane (5 mL) was treated with Boc_2O (157 mg, 0.72 mmol) and triethylamine (300 μL, 2.2 mmol). The ensuing mixture was stirred at room temperature for 12 h, quenched with H_2O (20 mL), and extracted with dichloromethane (3 × 20 mL). The combined organic phases were washed with brine (1 × 30 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The yellow oil thus obtained was subjected to flash chromatography (silica, 1:10 → 1:5 v/v ethyl acetate/hexane gradient elution), and concentration of relevant fractions (R_f = 0.5 in 1:3 v/v ethyl acetate/hexane) afforded the title compound **14** (98 mg, 80%) as a white, crystalline solid and a ca. 1:1 mixture of rotamers: mp = 216 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ (mixture of rotamers) 10.91 (s, 0.5H), 10.85 (s, 0.5H), 7.41 (d, J = 7.6 Hz, 1H), 7.27 (dd, J = 10.7 and 7.8 Hz, 1H), 7.02−6.89 (complex m, 2H), 5.36 (s, 0.5H), 5.27 (s, 0.5H), 3.62 (dd, J = 13.2 and 5.5 Hz, 0.5H), 3.52 (dd, J = 13.3 and 5.7 Hz, 0.5H), 2.96 (dd, J = 17.8 and 6.7 Hz, 1H), 2.60 (dd, J = 17.7 and 13.1 Hz, 1H), 2.46−2.35 (complex m, 1H), 2.25 (broad s, 1H), 1.85−1.59 (complex m, 3H), 1.52 (s, 4.5H), 1.35 (s, 4.5H), 1.25−1.10 (complex m, 2H), 0.89 (t, J = 7.4 Hz, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ (mixture of rotamers) 154.6, 154.1, 136.8, 136.7, 126.9, 126.8, 120.7(1), 120.6(5), 118.8, 118.2, 117.6, 111.3, 111.1, 105.9, 105.5, 78.9, 78.6, 48.1, 46.9, 43.6, 43.2, 37.2, 36.0, 33.4, 33.2, 29.3, 28.7, 28.5, 25.0, 23.7, 23.6, 12.2, 12.1; IR ν_{max} 3402, 3301, 2961, 2929, 2874, 1662, 1462, 1416, 1365, 1308, 1169, 1127, 864, 742 cm^{-1}; MS (ESI, + ve) m/z 363 [$(M + Na)^+$, 100%], 341 [$(M + H)^+$, 33]; HRMS $(M + Na)^+$ calcd for $C_{21}H_{28}N_2NaO_2$ 363.2048, found 363. 2047.

Compound **15**. A magnetically stirred solution of compound **14** (45 mg, 0.13 mmol) in dichloromethane (5 mL) was treated with PCC (57 mg, 0.27 mmol), and the ensuing mixture stirred at room temperature for 0.66 h then quenched with isopropyl alcohol (3 mL). The resulting mixture was treated with water (15 mL) and then extracted with dichloromethane (3 × 20 mL). The combined organic phases were washed with brine (1 × 30 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The ensuing yellow oil was subjected to flash chromatography (silica, 1:10 → 1:5 v/v ethyl acetate/hexane gradient elution), and concentration of relevant fractions (R_f = 0.5 in 1:3 v/v ethyl acetate/hexane) afforded the title compound **15** (35 mg, 75%) as a clear, yellow oil and a ca. 1:1 mixture of rotamers: ^{1}H NMR ($CDCl_3$, 400 MHz) δ (mixture of rotamers) 9.89 (s, 0.5H), 9.81 (s, 0.5H), 7.95 (d, J = 8.2 Hz, 0.5H), 7.80 (d, J = 8.1 Hz, 0.5H), 7.53 (t, J = 9.3 Hz, 1H), 7.41 (t, J = 7.8 Hz, 1H), 7.21 (m, 1H), 5.85 (s, 0.5H), 5.67 (s, 0.5H), 3.99 (dd, J = 14.0 and 5.5 Hz, 0.5H), 3.79 (dd, J = 14.3 and 5.7 Hz, 0.5H), 2.86 (s, 1H), 2.79−2.60 (complex m, 1H), 2.22 (t, J = 7.3 Hz, 1H), 2.15−1.87 (complex m, 2H), 1.65 (s, 4.5H), 1.45 (s, 4.5H), 1.43−1.34 (complex m, 2H), 0.96 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (mixture of rotamers) 193.0, 155.0, 154.3, 138.6, 132.4, 127.3, 125.4, 125.3, 123.0, 122.7, 122.3, 121.6, 121.1, 112.9, 112.5, 80.3, 79.9, 48.3, 48.1, 47.8, 47.0, 46.7, 36.9, 35.7, 31.6, 30.2, 28.7, 28.4, 24.9, 24.8, 22.7, 11.8; IR ν_{max} 3268, 2964, 2932, 2876, 1649, 1470, 1407, 1366, 1277, 1254, 1154, 1127, 1019, 867, 747 cm^{-1}; MS (ESI, + ve) m/z 731 [$(2M + Na)^+$, 100], 377 [$(M + Na)^+$, 50]; HRMS $(M + Na)^+$ calcd for $C_{21}H_{26}N_2NaO_3$ 377.1841, found 377.1843.

Noruleine (**3**). *Step i.* A magnetically stirred solution of ketone **15** (14 mg, 0.04 mmol) in THF (4 mL) was cooled to −78 °C and then treated with methyllithium (40.0 μL of a 3.0 M solution in diethoxymethane). The resulting mixture was stirred at −78 °C for 0.16 h and then quenched with water (15 mL). After the resulting mixture was warmed to room temperature, the aqueous phase was extracted with dichloromethane (3 × 20 mL), and the combined organic phases were washed with brine (1 × 30 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The ensuing yellow oil, presumed to contain the anticipated *tert*-alcohol, was subjected to step ii of the reaction sequence as described immediately below.

Step ii. A magnetically stirred solution of the yellow oil obtained from step i in dichloromethane (4 mL) was treated with trifluoroacetic acid (15 μL, 0.19 mmol). The resulting mixture was stirred at room temperature for 12 h and then concentrated under reduced pressure to afford a yellow oil that was subjected to flash chromatography (silica, 1:25 → 1:7 v/v methanol/dichloromethane gradient elution). Concentration of relevant fractions (R_f = 0.5 in 1:4 v/v methanol/dichloromethane) afforded the title compound **3**[9e] (7.5 mg, 75%) as a clear, yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.13 (s, 1H), 7.51 (d, J = 7.8 Hz, 1H), 7.29 (d, J = 7.8 Hz, 1H), 7.13 (t, J = 7.8 Hz, 1H), 7.04 (t, J = 7.8 Hz, 1H), 5.20 (s, 1H), 4.93 (s, 1H), 4.32 (s, 1H), 2.89−2.36 (complex m, 3H), 2.26−1.88 (complex m, 3H), 1.60 (d, J = 12.6 Hz, 1H), 1.18−0.98 (complex m, 2H), 0.79 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ see Table 1; IR ν_{max} 3230, 2960, 2930, 1672, 1613, 1454, 1325, 1201, 1179, 1134, 906, 798, 740 cm^{-1}; MS (ESI, + ve) m/z 253 [$(M + H)^+$, 40], 236 (100); HRMS $(M + H)^+$ calcd for $C_{17}H_{21}N_2$ 253.1705, found 253.1701.

Uleine (**1**). A magnetically stirred solution of amine **3** (15 mg, 0.06 mmol) in acetonitrile (4 mL) was treated, sequentially, with formaldehyde (100 μL of a 35% w/w aqueous solution, 1.2 mmol) and $NaCNBH_3$ (8 mg, 0.13 mmol). The resulting mixture was stirred at room temperature for 0.66 h and then quenched with $NaHCO_3$ (10 mL of a saturated aqueous solution). The separated aqueous phase was

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extracted with dichloromethane (3 × 20 mL), and the combined organic phases were washed with brine (1 × 30 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The resulting yellow oil was subjected to flash chromatography (silica, 1:25 → 1:7 v/v methanol/dichloromethane gradient elution), and concentration of relevant fractions (R_f = 0.6 in 1:4 v/v methanol/dichloromethane) afforded the title compound **1**[9e] (13 mg, 85%) as a clear, yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.27 (s, 1H), 7.58 (d, J = 7.9 Hz, 1H), 7.37 (d, J = 7.9 Hz, 1H), 7.21 (t, J = 7.9 Hz, 1H), 7.12 (t, J = 7.9 Hz, 1H), 5.29 (s, 1H), 5.02 (s, 1H), 4.12 (d, J = 2.0 Hz, 1H), 2.72 (d, J = 2.0 Hz, 1H), 2.58−2.42 (complex m, 1H), 2.32 (s, 3H), 2.25−1.96 (complex m, 3H), 1.72 (d, J = 7.6 Hz, 1H), 1.22−1.04 (complex m, 2H), 0.87 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ see Table 1; IR ν_{max} 3231, 2957, 2926, 1668, 1456, 1320, 1050, 880, 738 cm^{-1}; MS (ESI, + ve) m/z 267 [(M + H)$^+$, 85], 236 (100); HRMS (M + H)$^+$ calcd for $C_{18}H_{23}N_2$ 267.1861, found 267.1860.

*Nordasycarpidone (**4**).* A magnetically stirred solution of ketone **15** (17 mg, 0.05 mmol) in dichloromethane (4 mL) was treated with trifluoroacetic acid (15 μL, 0.19 mmol) and the ensuing mixture stirred at room temperature for 12 h before being concentrated under reduced pressure to afford a yellow oil. Subjection of this material to flash chromatography (silica, 1:25 → 1:7 v/v methanol/dichloromethane gradient elution) and concentration of relevant fractions (R_f = 0.6 in 1:4 v/v methanol/dichloromethane) afforded the title compound **4**[9a] (10 mg, 84%) as a clear, yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.89 (s, 1H), 7.72 (d, J = 8.0 Hz, 1H), 7.45 (d, J = 8.0 Hz, 1H), 7.34 (t, J = 8.0 Hz, 1H), 7.13 (t, J = 8.0 Hz, 1H), 6.14 (broad s, 1H), 4.83 (s, 1H), 2.97 (broad s, 1H), 2.75 (s, 2H), 2.49 (s, 1H), 2.17 (m, 1H), 1.86 (d, J = 12.7 Hz, 1H), 1.31−1.23 (complex m, 2H), 0.83 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ see Table 2; IR ν_{max} 3255, 2960, 1654, 1541, 1474, 1328, 1199, 1132, 908, 800, 746 cm^{-1}; MS (ESI, + ve) m/z 255 [(M + H)$^+$, 55], 238 (100); HRMS (M + H)$^+$ calcd for $C_{16}H_{19}N_2O$ 255.1497, found 255.1499.

*Dasycarpidone (**2**).* A magnetically stirred solution of compound **4** (15 mg, 0.06 mmol) in methanol (5 mL) was treated with 10% Pd on carbon (3 mg) and formaldehyde (200 μL of a 35% w/v aqueous solution, 2.3 mmol). The resulting mixture was stirred at room temperature for 2 h while being maintained under an atmosphere of hydrogen. The mixture thus obtained was filtered through diatomaceous earth, and the solids thus retained were washed with methanol (3 × 10 mL). The combined filtrates were diluted with water (30 mL) and dichloromethane (30 mL), and the separated aqueous phase was extracted with dichloromethane (3 × 30 mL). The combined organic phases were washed with brine (1 × 30 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The yellow oil thus obtained was subjected to flash chromatography (silica, 1:25 → 1:7 v/v methanol/dichloromethane gradient elution), and concentration of relevant fractions (R_f = 0.7 in 1:4 v/v methanol/dichloromethane) afforded the title compound **2**[9a] (11 mg, 70%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.20 (s, 1H), 7.63 (d, J = 8.1 Hz, 1H), 7.41 (d, J = 8.1 Hz, 1H), 7.31 (m, 1H), 7.12 (m, 1H), 4.24 (s, 1H), 2.63 (broad s, 1H), 2.55 (d, J = 7.0 Hz, 1H), 2.32 (s, 1H), 2.27 (s, 3H), 2.15−1.94 (complex m, 2H), 1.85 (d, J = 9.7 Hz, 1H), 1.34−1.04 (complex m, 2H), 0.82 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ see Table 2; IR ν_{max} 3262, 2929, 1650, 1531, 1467, 1325, 1151, 1021, 744, 489 cm^{-1}; MS (ESI, + ve) m/z 269 [(M + H)$^+$, 73], 238 (100); HRMS (M + H)$^+$ calcd for $C_{17}H_{21}N_2O$ 269.1654, found 269.1655.

Crystallographic Studies. *Crystallographic Data for Compound **12**:* $C_{16}H_{16}N_2O_2$, M = 284.31, T = 150 K, orthorhombic, space group $P2_12_12_1$, Z = 4, a = 8.56836(10) Å, b = 12.02612 (14) Å, c = 14.15115(14) Å; V = 1458.19(3) Å^3, D_x = 1.295 g cm^{-3}, 2890 unique data ($2\theta_{max}$ = 144.8°), R = 0.027 [for 2828 reflections with $I > 2.0\sigma(I)$]; R_w = 0.069 (all data), S = 1.0.

*Crystallographic Data for Compound **14**:* $C_{21}H_{28}N_2O_2$, M = 340.47, T = 150 K, monoclinic, space group $P2_1/n$, Z = 4, a = 10.1738(2) Å, b = 10.6826(1) Å, c = 17.3464(3) Å; β = 103.2796(16)°; V = 1834.84(5) Å^3, D_x = 1.232 g cm^{-3}, 3623 unique data ($2\theta_{max}$ = 144.6°), R = 0.031 [for 3271 reflections with $I > 2.0\sigma(I)$]; R_w = 0.075 (all data), S = 0.99.

Structure Determinations. Images were measured on a diffractometer (Cu Kα, mirror monochromator, λ = 1.54184 Å) fitted with an area detector and data extracted using the CrysAlis package.[25] The structure solutions were solved by direct methods (SIR92).[26] The structures of compounds **12** and **14** were refined using the CRYSTALS program package.[27] Atomic coordinates, bond lengths and angles, and displacement parameters for compounds **12** and **14** have been deposited at the Cambridge Crystallographic Data Centre (CCDC nos. 1450903 and 1450904). These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: + 44 1223 336033.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00240.

X-ray crystallographic data for compound **12** (CIF)
X-ray crystallographic data for compound **14** (CIF)
Anisotropic displacement ellipsoid plot derived from the single-crystal analyses of compounds **12** and **14**; ^{1}H and ^{13}C NMR spectra for compounds **1**−**4** and **6**−**15** (PDF)

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Notes

The authors declare no competing financial interest.

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