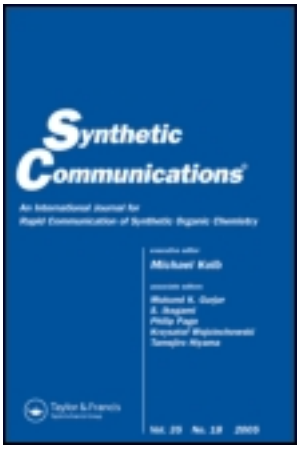

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Sonia B. Parsekar [a], Chandan P. Amonkar [a], Peruninakulath S. Parameswaran [b] & Santosh G. Tilve [a]

[a] Department of Chemistry, Goa University, Goa, India

[b] National Institute of Oceanography, Dona Paula, Goa, India

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CONVENIENT SYNTHESIS OF 2,2-DIMETHYL-3,4-DIHYDRO-2*H*-PYRANO[2,3-*b*]QUINOLINES

Sonia B. Parsekar,[1] Chandan P. Amonkar,[1] Peruninakulath S. Parameswaran,[2] and Santosh G. Tilve[1]

[1]*Department of Chemistry, Goa University, Goa, India*
[2]*National Institute of Oceanography, Dona Paula, Goa, India*

A convenient general synthesis of 2,2-dimethyl-3,4-dihydro-2H-pyrano[2,3-b]quinolines using the Wittig reaction is described. The o-nitrobenzaldehydes (1a–d) on reaction with phosphorane 2 provided (E)-ethyl-α-(2,2-dimethylprop-2-ene)-2-nitrocinnamates (3a–d) in excellent yields, which on cyclization with polyphosphoric acid followed by reductive cyclization using Fe/HCl afforded dihydropyranoquinolines (5a–d). Alternatively, the pyranoquinolines 5a–d were also synthesised from esters 3a–d by employing domino reductive cyclization in a single step.

Keywords: Domino reaction; lactones; pyranoquinoline; reductive cyclization; Wittig reaction

Quinoline and its annulated derivatives are important compounds for synthetic and biological chemists.[1] These alkaloids are useful as antimalarial, antihypertensive, anti-inflammatory, antiasthamatic, antibacterial, and tyrosine kinase inhibiting agents.[2] Significant numbers of quinoline alkaloids have 2,2-dimethylpyran units attached to the quinoline rings. These pyranoquinoline alkaloids display a wide range of biological activities.[3] *Balfourodendron riedelianum* (Rutaceae), a small Brazilian tree, is a rich source of pyrano[2,3-*b*]quinolines and furo[2,3-*b*]quinolines.[4] The extract of this plant is used in folk medicine for the treatment of gastrointestinal ailments.[5] Flindersin, ribalinine, helietidine, and dutadrupine are some examples of quinoline alkaloids containing the pyran unit (Fig. 1).

Because of their potent biological activities, numerous methods have been developed for these alkaloids.[6]

RESULTS AND DISCUSSION

In continuation of our studies exploiting phosphorous chemistry,[7] we report herein a convenient general synthesis of 2,2-dimethyl-3,4-dihydro-2*H*-pyrano[2,3-*b*]quinolines (**5a–d**). Wittig reaction of the phosphorane[8] (**2**) with *o*-nitrobenzaldehydes

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Address correspondence to Santosh G. Tilve, Department of Chemistry, Goa University, Goa 403 206, India. E-mail: stilve@unigoa.ac.in

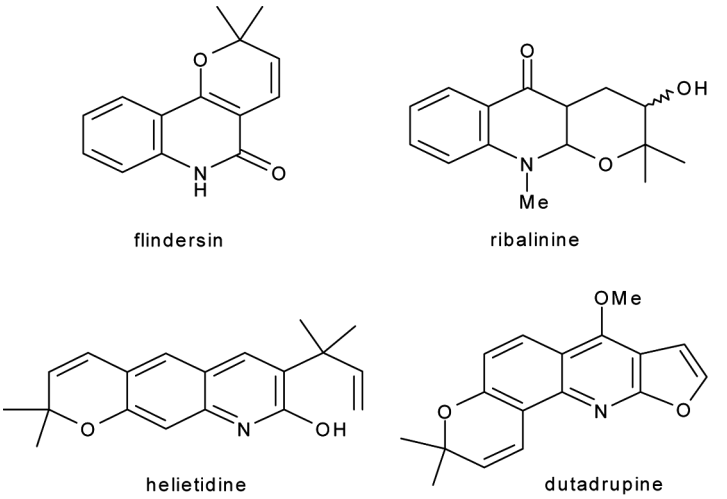
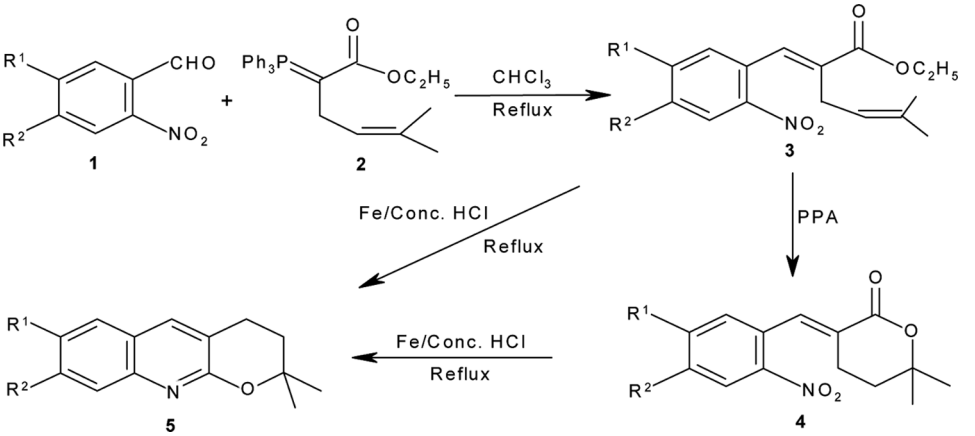


Figure 1. Natural pyranoquinolines.

(**1a–d**) gave exclusively ethyl (2*E*)-5-methyl-2[(2-nitrophenyl)methylidene]hex-4-enoates (**3a–d**). The unsaturated esters (**3a–d**) were further cyclized to δ-(*E*)-lactones (**4a–d**) using polyphosphoric acid (PPA). No isomerization of the *E*-lactone to *Z*-lactone was observed during this acid-mediated cyclization.

The lactones (**4a–d**) were then subjected to reductive cyclization[9] using Fe and conc. HCl to furnish corresponding dihydropyranoquinolines (**5a–d**), and reduction of nitro to amino, isomerization of *E* to *Z*-lactone, and cyclization took place in one pot in a domino fashion[10] (Scheme 1). Furthermore, to make our synthesis more concise, an alternate method was attempted, wherein Wittig product (**3a–d**) was directly subjected to reductive cyclization by Fe and conc. HCl to get the corresponding dihydropyranoquinolines (**5a–d**) without isolating the lactone intermediates (**4a–d**). However, the yield of isolated product (**5a–d**) during this one



Scheme 1. Synthesis of dihydropyranoquinolines.

Table 1. Yields in the synthesis of dihydropyranoquinolines

			Yield (%)			
Entry	R^1	R^2	**3**	**4**	**5**	**5** from **3**
a	H	H	90	85	54	19
b	OR	H	82 (R=COOEt)	95 (R=COOEt)	85 (R=OH)	36 (R=OH)
c	OCH_3	OCH_3	66	80	76	25
d	-OCH_2O-		68	82	83	33

pot concurrent lactonization/isomerization/reductive cyclization was somewhat less than the overall yield from the two-step strategy mentioned previously. The results are summarized in Table 1.

In conclusion, we have developed a new and effective methodology for the synthesis of 2,2-dimethyl-3,4-dihydro-2*H*-pyrano[2,3-*b*]quinolines using phosphorane chemistry. The noteworthy step is the one-pot reductive cyclization to yield directly the annulated tricyclic ring system.

EXPERIMENTAL

Thin-layer chromatography (TLC) was performed on silica gel G (13% $CaSO_4$ as binder). Column chromatography was performed on silica gel (60–120 mesh). Infrared (IR) spectra were recorded on a Shimadzuu Fourier transform (FT)–IR spectrophotometer (KBr pellets). ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) were recorded on a Bruker instrument. The multiplicities of carbon signals were obtained from distortionless enhancement by polarization transfer (DEPT) experiments. Chemical shift (ppm) are relative to the internal standard Me_4Si (0 ppm). High-resolution mass spectra (HRMS) were recorded on a MicroMass ES-QTOF.

General Procedure for the Preparation of Ethyl (2*E*)-5-Methyl-2[(2-nitrophenyl)methylidene]hex-4-enoates (3a–d)

A solution of aldehyde (1 mmol) **1a–d** in chloroform (10 mL) was refluxed with phosphorane[6] **2** (1 mmol) for 3 h. The solvent was removed under reduced pressure to give a residue, which was purified by column chromatography (silica gel, hexane-EtOAc, 9:1) to give pure **3a–d** as viscous liquids.

Data

Ethyl (2*E*)-5-Methyl-2[(2-nitrophenyl)methylidene]hex-4-enoate (3a). Yield: 90%; thick viscous yellow liquid; IR (KBr): 1713 cm^{-1} (C=O). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.35$ (t, $J = 7.2$ Hz, 3H), 1.42 (s, 3H), 1.64 (s, 3H), 2.98 (d, $J = 6.3$ Hz, 2H), 4.30 (q, $J = 7.2$ Hz, 2H), 5.03 (m, 1H), 7.37 (d, $J = 7.5$ Hz, 1H), 7.51 (t, $J = 7.5$ Hz, 1H), 7.65 (t, $J = 7.8$ Hz, 1H), 7.9 (s, 1H), 8.13 (d, $J = 8.1$ Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 14.23$ (CH_3), 17.64 (CH_3), 25.66 (CH_3), 27.06 (CH_2), 61.04 (OCH_2), 120.97 (CH), 124.72 (CH), 128.90 (CH), 131.18 (CH), 132.07 (C),

132.81 (C), 133.28 (CH), 133.91 (C), 135.59 (CH), 147.71 (C), 167.28 (C=O). GC/MS: m/z 289 [M^+].

Ethyl (2*E*)-2-({5-[(Ethoxycarbonyl)oxy]-2-nitrophenyl}methylidene)-5-methylhex-4-enoate (3b). Yield: 82%; thick viscous yellow liquid; IR (KBr): 1722, 1770 cm^{-1} (C=O). ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.26$–1.43 (m, 6H), 1.64 (s, 6H), 2.93 (d, $J = 6.6$ Hz, 2H), 4.19–4.33 (m, 4H), 4.95 (br s, 1H), 7.15 (d, $J = 2.4$ Hz, 1H), 8.14 (d, $J = 9.0$ Hz, 1H), 7.29 (dd, $J = 9.0$, 2.4 Hz, 1H), 7.79 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 14.11$ (CH_3), 14.20 (CH_3), 17.54 (CH_3), 25.61 (CH_3), 26.99 (CH_2), 61.11 (OCH_2), 65.56 (OCH_2), 120.65 (CH), 121.23 (CH), 123.52 (CH), 126.56 (CH), 133 (C), 134.11 (C), 134.40 (C), 134.72 (CH), 144.71 (C), 152.32 (C), 154.06 (C), 167.03 (C=O). GC/MS: m/z 377 [M^+].

Ethyl (2*E*)-2-[(4,5-Dimethoxy-2-nitrophenyl)methylidene]-5-methylhex-4-enoate (3c). Yield: 66%; thick viscous yellow liquid. IR (KBr): 1709 cm^{-1} (C=O). ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.37$ (t, $J = 7.2$ Hz, 3H), 1.49 (s, 3H), 1.67 (s, 3H), 3.00 (d, $J = 6.0$ Hz, 2H), 3.92 (s, 3H), 4.00 (s, 3H), 4.31 (q, $J = 7.2$ Hz, 2H), 5.1 (m, 1H), 6.77 (s, 1H), 7.75 (s, 1H), 7.94 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 14.24$ (CH_3), 17.85 (CH_3), 25.62 (CH_3), 27.28 (CH_2), 56.33 (OCH_3), 56.40 (OCH_3), 60.99 (OCH_2), 107.70 (CH), 112.42 (CH), 121.77 (CH), 126.66 (C), 132.75 (C), 132.83 (C), 136.82 (CH), 140.15 (C), 148.55 (C), 152.97 (C), 167.41 (C=O). GC/MS: m/z 349 [M^+].

Ethyl (2*E*)-5-Methyl-2-[(6-nitro-1,3-benzodioxol-5-yl)methylidene]hex-4-enoate (3d). Yield: 68%; thick viscous yellow liquid. IR (KBr): 1713 cm^{-1} (C=O). ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.35$ (t, $J = 7.2$ Hz, 3H), 1.51 (s, 3H), 1.67 (s, 3H), 3.00 (d, $J = 6.6$ Hz, 2H), 4.29 (q, $J = 7.2$ Hz, 2H), 5.06 (m, 1H), 6.17 (s, 2H), 6.74 (s, 1H), 7.65 (s, 1H), 7.83 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 14.21$ (CH_3), 17.68 (CH_3), 25.66 (CH_3), 27.15 (CH_2), 60.99 (OCH_2), 103.20 (CH_2), 105.50 (CH), 109.74 (CH), 121.02 (CH), 128.74 (C), 132.74 (C), 133.05 (C), 136.22 (CH), 141.87 (C), 147.78 (C), 151.77 (C), 167.30 (C=O). GC/MS: m/z 333 [M^+].

General Procedure for the Preparation of (3*E*)-6,6-Dimethyl-3-[(2-nitrophenyl)methylidene]tetrahydro-2*H*-pyran-2-ones (4a–d)

Compounds **3a–d** (1 mmol) were added to the stirred solution of polyphosphoric acid (2 mL). The reaction mixture was warmed on water bath for 5 min. Chilled water (15 mL) was added to the reaction mixture, and it was subsequently extracted with diethyl ether (3×10 mL). The organic layer was washed with saturated $NaHCO_3$ solution (2×30 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (silica gel, hexane–EtOAc, 9:1) to give pure **4a–d**.

Data

(3*E*)-6,6-Dimethyl-3-[(2-nitrophenyl)methylidene]tetrahydro-2*H*-pyran-2-one (4a). Yield: 85%; white solid; mp 96–98 °C. IR (KBr): 1692 cm^{-1}(C=O). ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.46$ (s, 6H), 1.85 (t, $J = 6.9$ Hz, 2H), 2.56 (dt,

$J = 6.9$, 2.4 Hz, 2H), 7.39 (d, $J = 7.5$ Hz, 1H), 7.55 (t, $J = 7.5$ Hz, 1H), 7.69 (t, $J = 7.5$ Hz, 1H), 8.11 (br s, 1H), 8.17 (d, $J = 8.1$ Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 21.66$ (CH_2), 27.96 ($2 \times CH_3$), 33.13 (CH_2), 80.94 (C), 125 (CH), 127.04 (C), 129.41 (CH), 130.66 (CH), 131.21 (C), 133.43 (CH), 138.15 (CH), 147.72 (C), 165.79 (C=O). HRMS: m/z $[M + Na]^+$ calcd. for $C_{14}H_{15}NNaO_4$: 284.0899; found: 284.0893.

3-[(*E*)-(6,6-Dimethyl-2-oxodihydro-2*H*-pyran-3(4*H*)-ylidene)methyl]-4-nitrophenyl Ethyl Carbonate (4b). Yield: 95%; white solid; mp 104–106 °C. IR (KBr): 1774, 1717 cm^{-1} (C=O). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.34$ (t, $J = 7.2$ Hz, Hz, 3H), 1.40 (s, 6H), 1.78 (t, $J = 6.9$ Hz, 2H), 2.53 (dt, $J = 6.9$, 2.4 Hz, 2H), 4.30 (q, $J = 7.2$ Hz, 2H), 7.18 (d, $J = 2.4$ Hz, 1H), 7.32 (dd, $J = 9.0$, 2.4 Hz, 1H), 8.03 (br s, 1H), 8.17 (d, $J = 9.0$ Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 14.11$ (CH_3), 21.60 (CH_2), 27.95 ($2 \times CH_3$), 33.08 (CH_2), 65.68 (CH_2), 81.00 (C), 121.56 (CH), 123.08 (CH), 126.89 (CH), 127.63 (C), 133.22 (C), 137.22 (CH), 144.66 (C), 152.31 (C), 154.10 (C), 165.48 (C=O). HRMS: m/z $[M + Na]^+$ calcd. for $C_{17}H_{19}NNaO_7$: 372.1059; found: 372.1059.

(3*E*)-3-[(4,5-Dimethoxy-2-nitrophenyl)methylidene]-6,6-dimethyltetrahydro-2*H*-pyran-2-one (4c). Yield: 80%; yellow solid; mp 181–182 °C. IR (KBr): 1692 cm^{-1} (C=O). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.46$ (s, 6H), 1.85 (t, $J = 6.9$ Hz, Hz, 2H), 2.55 (dt, $J = 6.6$, 2.1 Hz, 2H), 3.98 (s, 3H), 4.00 (s, 3H), 6.73 (s, 1H), 7.76 (s, 1H), 8.11 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 21.75$ (CH_2), 27.98 ($2 \times CH_3$), 33.20 (CH_2), 56.47 (OCH_3), 56.62 (OCH_3), 80.83 (C), 107.97 (CH), 111.63 (CH), 125.75 (C), 126.16 (C), 139.17 (CH), 140.33 (C), 148.88 (C), 153.14 (C), 166.02 (C=O). HRMS: m/z $[M + Na]^+$ calcd. for $C_{16}H_{19}NNaO_6$: 344.1110; found 344.1113.

(3*E*)-6,6-Dimethyl-3-[(6-nitro-1,3-benzodioxol-5-yl)methylidene]tetrahydro-2*H*-pyran-2-one (4d). Yield: 82%; yellow solid; mp 176–177 °C. IR (KBr): 1697 cm^{-1}(C=O). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.45$ (s, 6H), 1.85 (t, $J = 6.9$ Hz, Hz, 2H), 2.56 (dt, $J = 6.9$, 2.4 Hz, 2H), 6.18 (s, 2H), 6.73 (s, 1H), 7.67 (s, 1H), 8.04 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 21.65$ (CH_2), 27.94 ($2 \times CH_3$), 33.11 (CH_2), 80.83 (C), 103.38 (OCH_2O), 105.79 (CH), 109.00 (CH), 126.14 (C), 127.84 (C), 138.91 (CH), 142 (C), 148.13 (C), 151.94 (C), 165.9 (C=O). HRMS: m/z $[M + Na]^+$ calcd. for $C_{15}H_{15}NNaO_6$: 328.0797; found 328.0800.

General Procedure for the Preparation of 2,2-Dimethyl-3,4-dihydro-2*H*-pyrano[2,3-*b*]quinolines (5a–d)

Concentrated HCl (8 mL) was added to a magnetically stirred mixture of esters **3a–d** or **4a–d** (1 mmol) and Fe powder (15 mmol). The reaction mixture was allowed to stir for 15 min and was subsequently refluxed on a water bath. After completion of the reaction (the progress of the reaction was monitored by thin-layer chromatography, TLC), the reaction mixture was filtered, and the residue was washed with water (3×5 mL). This combined filtrate washed with diethyl ether (2×10 mL) and filtered on celite. The filtrate was basified with solid NaOH pellets (liquid ammonia was used to basify compound **3b** and **4b**), and the compound was subsequently extracted in diethyl ether (3×15 mL). The combined organic extracts were dried over anhydrous

Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (silica gel, hexane–EtOAc, 8:2) to give pure **5a–d**.

Data

2,2-Dimethyl-3,4-dihydro-2*H*-pyrano[2,3-*b*]quinoline (5a). Yield: 19% (from **3**), 54% (from **4**); white solid; mp 103–105 °C. IR (KBr): 1622, 1562, 1492, 1415 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.50$ (s, 6H), 1.96 (t, $J = 6.6$ Hz, 2H), 3.04 (t, $J = 6.3$ Hz, 2H), 7.36 (t, $J = 7.8$, 7.2 Hz, 1H), 7.58 (t, $J = 8.1$, 7.2 Hz, 1H), 7.68 (d, $J = 7.5$ Hz, 1H), 7.85 (d, $J = 8.7$ Hz, 1H), 7.88 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 22.62$ (CH_2), 27.36 ($2 \times CH_3$), 32.41 (CH_2), 77.08 (C), 117.66 (C), 123.88 (CH), 125.19 (C), 126.56 (CH), 127.22 (CH), 129.02 (CH), 137.51 (CH), 146.42 (C), 159.72 (C). HRMS: m/z $[M + Na]^+$ calcd. for $C_{14}H_{15}NNaO$: 236.1051; found: 236.1049.

2,2-Dimethyl-3,4-dihydro-2*H*-pyrano[2,3-*b*]quinoline-7-ol (5b). Yield: 36% (from **3**), 85% (from **4**); white solid; mp 223–225 °C. IR (KBr): 3300 (OH), 1612, 1517, 1434, 1367 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.41$ (s, 6H), 1.87 (t, $J = 6.9$ Hz, 2H), 2.93 (t, $J = 6.9$ Hz, 2H), 5.11 (br s, 1H), 6.96 (d, $J = 2.7$ Hz, 1H), 7.13 (dd, $J = 9.0$, 2.7 Hz, 1H), 7.67 (s, 1H), 7.69 (d, $J = 9.0$ Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 22.59$ (CH_2), 27.28 ($2 \times CH_3$), 32.39 (CH_2), 70.19 (C), 108.46 (CH), 118.06 (CH), 120.69 (CH), 125.83 (CH), 128.52 (C), 136.16 (C), 141.62 (C), 152.02 (C), 158.20 (C). HRMS: m/z $[M + Na]^+$ calcd. for $C_{14}H_{15}NNaO_2$: 252.1; found: 252.0999.

7,8-Dimethoxy-2,2-dimethyl-3,4-dihydro-2*H*-pyrano[2,3-*b*]quinoline (5c). Yield: 25% (from **3**), 76% (from **4**); white solid; mp 156–158 °C. IR (KBr): 1612, 1496, 1458, 1381 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.47$ (s, 6H), 1.93 (t, $J = 6.6$ Hz, 2H), 2.97 (t, $J = 6.6$ Hz, 2H), 3.98 (s, 3H), 3.99 (s, 3H), 6.95 (s, 1H), 7.2 (s, 1H), 7.7 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 22.43$ (CH_2), 27.28 ($2 \times CH_3$), 32.51 (CH_2), 55.87 ($2 \times CH_3$), 76.53 (C), 104.69 (CH), 106.62 (CH), 114.85 (C), 119.92 (C), 136 (CH), 143.05 (C), 147.81 (C), 152.07 (C), 158.66 (C). HRMS: m/z $[M + Na]^+$ calcd. for $C_{16}H_{19}NNaO_3$: 296.1263; found: 296.1263.

7,8-Methylenedioxy-2,2-dimethyl-3,4-dihydro-2*H*-pyrano[2,3-*b*]quinoline (5d). Yield: 33% (from **3**), 83% (from **4**); white solid; mp 177–179 °C. IR (KBr): 1620, 1480, 1465, 1388 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.44$ (s, 6H), 1.89 (t, $J = 6.6$ Hz, 2H), 2.92 (t, $J = 6.6$ Hz, 2H), 6.02 (s, 2H), 6.91 (s, 1H), 7.15 (s, 1H), 7.65 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 22.32$ (CH_2), 27.26 ($2 \times CH_3$), 32.44 (CH_2), 76.65 (C), 101.26 (CH_2), 102.08 (CH), 104.40 (CH), 114.78 (C), 121.10 (C), 136.57 (CH), 144.24 (C), 145.83 (C), 150.21 (C), 158.60 (C). HRMS: m/z $[M + Na]^+$ calcd. for $C_{15}H_{15}NNaO_3$: 280.0950; found: 280.0958.

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