Synthesis and Opioid Activity of 7-Oxygenated 2,3,4,4a,5,6,7,7a-Octahydro-1*H*-benzofuro[3,2-*e*]isoquinolin-9-ols

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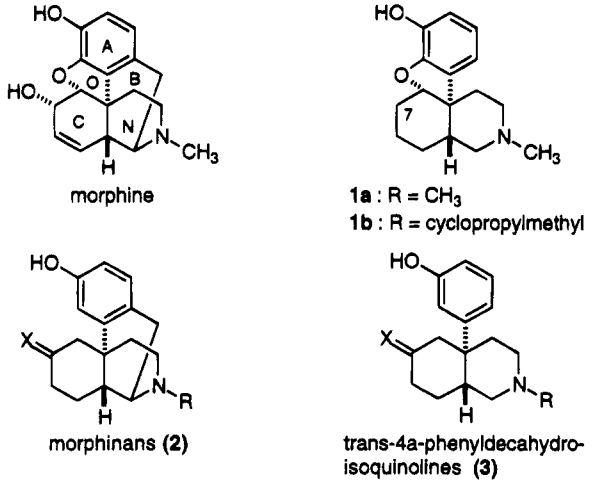
3-(Cyclopropylmethyl)-9-hydroxy-7-oxo-2,3,4,4aα,5,6,7,7aα-octahydro-1*H*-benzofuro[3,2-*e*]isoquinoline (**4b**) containing the ACNO ring system of morphine and a 7-keto function on ring C has been synthesized and found to possess potent PQW (ED_{50} = 0.15 mg/kg sc) and anti-Straub tail (ED_{50} = 0.02 mg/kg sc) activity. As compared to its 7-deoxy analog **1b**, introduction of the 7-keto group did not significantly affect binding to any of the three opioid receptors (μ, κ, and δ), but caused a 34-fold reduction in σ-binding, suggesting reduced propensity to induce psychotomimetic effects. The C/D cis isomer of **4b** (**4c**) was much less potent at the three opioid receptors, while displaying a slight increase in σ affinity. Both 7-hydroxy derivatives **4e** and **4f** were active in anti-Straub tail assay ($ED_{50} \leq 0.8$ mg/kg sc), but only the α-isomer **4e** demonstrated analgesic activity (PQW ED_{50} = 0.37 mg/kg sc) in the dose range tested. In guinea pig ileum preparations, **4e** was characterized as a selective full agonist at the κ opioid receptor (IC50 = 2.8 nM); while its β-isomer **4f** was a partial agonist (78% at 1 μM), with antagonist activity observed at both μ- and κ-opioid receptors.

Morphine is a potent analgesic alkaloid, its rigid structure consisting of five rings (ABCNO). Approaches based on simplification of the morphine skeleton for the discovery of novel analgesics have been adopted by generations of medicinal chemists.[1] Like many substructural analogs of morphine, N-substituted 2,3,4,4aα,5,6,7,7aα-octahydro-1*H*-benzofuro[3,2-*e*]isoquinolin-9-ols (**1**), which contain the ACNO ring system of morphine, have been found to retain potent analgesic activity.[2] Among them, the *N*-cyclopropylmethyl analog (**1b** or J6549) is most interesting in that it possesses potent oral analgesic and narcotic-antagonism activity and is likely to have a low potential for addiction.[2b] However, of concern is the fact that **1b** showed significant binding to the σ receptor (K_i, σ = 21 nM),[3] which indicates potential psychotomimetic effects. In morphine, the related morphinan (**2**), and *trans*-4a-phenyldecahydroisoquinoline (**3**) series, C ring functionality such as 6-oxygenation, has been found to have beneficial effects on both analgesic potency and opioid receptor selectivity.[4–6] As an effort to study the effect of placing an oxygen function in the corresponding position of the octahydrobenzofuroisoquinoline series represented by **1a** and **1b**, we report here the synthesis and opioid activity of a series of 7-oxygenated analogs of **1**, namely **4a-g**.

Chart 1



Chemistry

The first reported synthesis of **1a** was achieved via the intramolecular Diels–Alder reaction of *N*-[2-(7-methoxy-3-benzofuranyl)ethyl]-*N*-methyl-6α-pyronecarboxamide.[2] An alternative synthesis based on the regioselective acylation of the anion derived from 4-(2,3-dimethoxyphenyl)-1,2,3,6-tetrahydro-1-methylpyridine with γ-butyrolactone was reported later.[7] Neither of the above two methods can be easily adopted for the preparation of C-ring functionalized analogs of **1**. Among the reported syntheses of the ACNO system of morphine with functionalized C-ring,[8–10] the one reported by Weller et al.[10] was adopted for the preparation of our 7-keto analogs of **1** (Scheme 2). The key intermediate 4-[2-(phenylmethoxy)-3-methoxyphenyl]pyridine-3-carboxaldehyde (**8**) was synthesized by a new route (Scheme 1).[11] The starting 7-methoxy[1]benzopyrano[3,4-*c*]pyridin-5(2*H*)-one (**5**)[12] was treated with sodium methoxide followed by benzyl bromide to give 4-arylnicotinate **6**. Dibal reduction of **6** followed by oxidation of the resulting alcohol **7** with active manganese dioxide provided aldehyde **8**, which was converted by literature procedures[10] to give ester **9** in 58% overall yield from **5**. The conversion of **9** to the desired 7-keto analogs of **1**, namely **4a–c**, essentially followed the published se-

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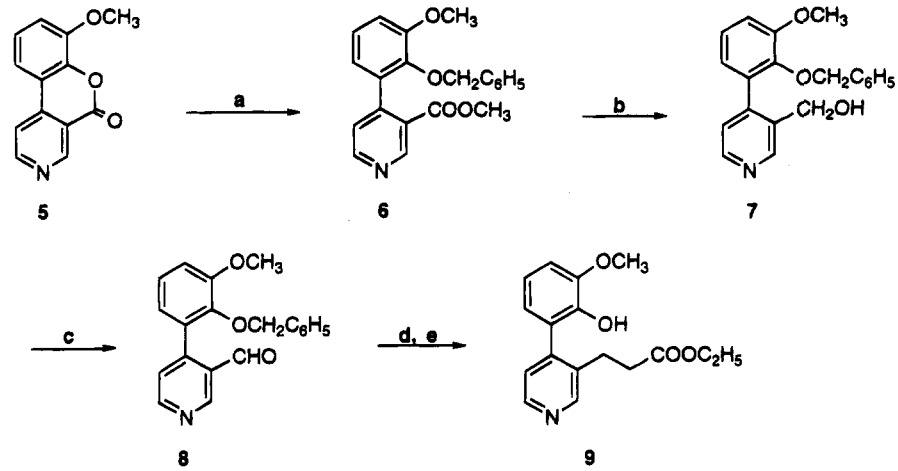
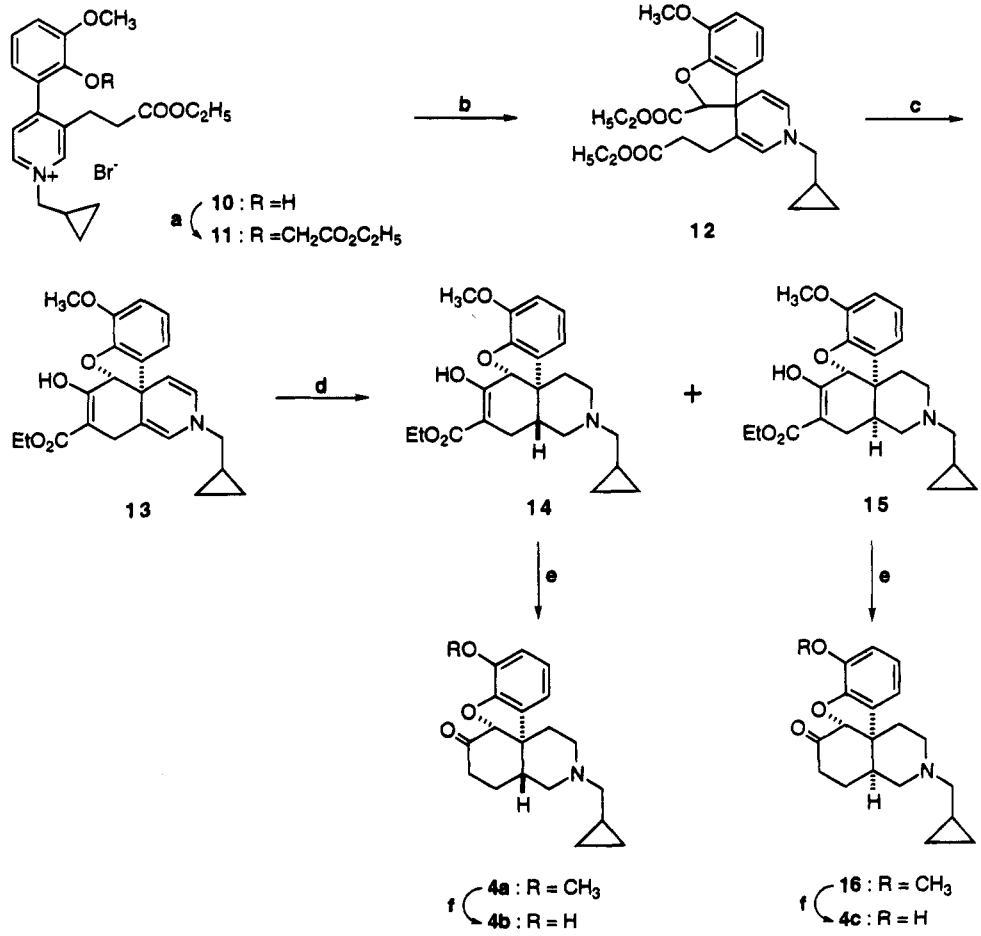
Scheme 1[a]



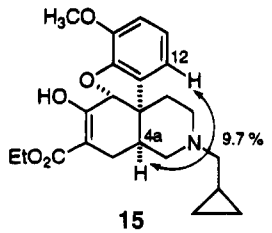
[a] Reagents, conditions, and yields: (a) NaOMe, $C_6H_5CH_2Br$, DMF; 92%; (b) DIBAL, toluene; 82%; (c) MnO_2, CH_2Cl_2; 92%; (d) monoethyl malonic acid ester, pyridine, piperidine(cat.), Δ; 91%; (e) 5% Pd/C, EtOH, H_2; 92%.

Scheme 2[a]



[a] Reagents, conditions, and yields: (a) $BrCH_2COOEt$, K_2CO_3, DMF; 93%; (b) NaOEt, EtOH; 90%; (c) NaH, 4-Å molecular sieve, THF, reflux; 72%; (d) PtO_2, EtOH, H_2; 53% (trans), 10% (cis); (e) 3 N HCl, reflux; 89%; (f) BBr_3–$S(CH_3)_2$, $ClCH_2CH_2Cl$, reflux.

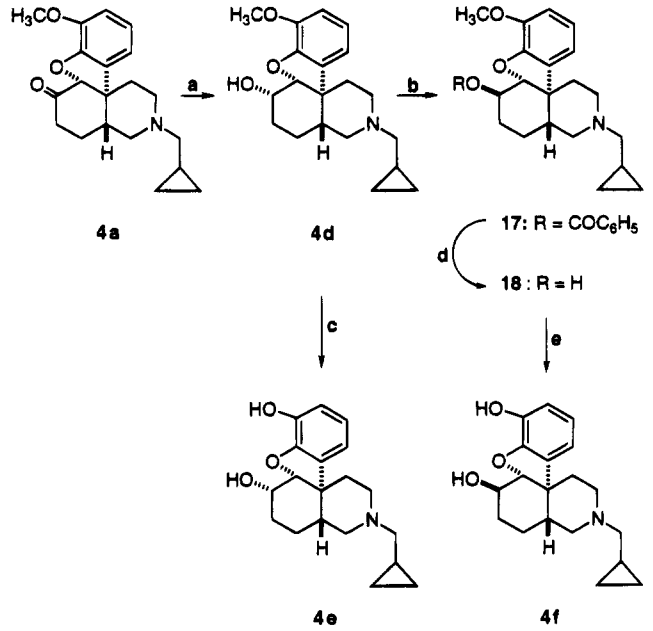
quence for the *N*-methyl analog[10] (Scheme 2). However, we found that the conversion of **11** to **12** was more efficiently carried out in ethanol. When dimethylformamide was used as the solvent, the reaction was very sluggish, probably due to the formation of a stable complex between the sodium enolate of **11** and its 3-methoxy group. In our hands, the catalytic hydrogenation of **13** over platinum afforded an 81% yield of **14** and **15** in a ratio of 83:17. The major trans isomer **14** was treated with HCl to give **4a**, which underwent O-demethylation effected by $BBr_3/S(CH_3)_2$ complex to give **4b**. The minor isomer **15** underwent similar transformations to give **4c**, the cis isomer of **4b**. The *N*-methyl analog **4g** was prepared from 1-methyl-4-(2-hydroxy-3-methoxyphenyl)-3-(3-oxo-3-ethoxypropyl)-pyridinium iodide similarly as **4b** is prepared from **10**. Our assignment of the C/D ring junction stereochemistry (cis or trans) was supported by comparison of the ^{1}H-NMR data for **4a** and **16** with that reported for the *N*-methyl analogs of these two compounds.[9,10b] An



15

Figure 1. C/D cis ring junction in **15** as revealed by NOE experiment.

Scheme 3[a]



[a] Reagents, conditions, and yields: (a) L-Selectride, THF; 80%; (b) C_6H_5COOH, DEAD, $P(C_6H_5)_3$, THF; (c) NaSPr, DMF; 75%; (d) 1% NaOH, MeOH; 54% from **4d**; (e) $BBr_3-S(CH_3)_2$, $ClCH_2CH_2Cl$, reflux; 83%.

added proof is provided by NOE experiment on compound **15**, which showed strong dipolar coupling between the angular H-4a and H-12, thus establishing the spatial proximity or the cis relationship between H-4a and the phenyl ring in **15** (Figure 1). The 7-hydroxy analogs **4d**–**f** were derived from **4a** via stereospecific transformations as shown in Scheme 3. Thus, **4a** was reduced with L-Selectride to give exclusively the α-hydroxy isomer **4d** in 80% yield, which was O-demethylated to give **4e**. Treatment of **4d** with benzoic acid under Mitsunobu's condition[13] resulted in inversion of the 7-hydroxyl function to provide the β-benzoate **17**, which was hydrolysed and O-demethylated to give the β-hydroxy analog **4f**.

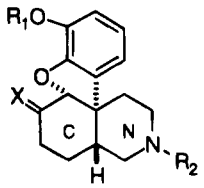
Pharmacology

Listed in Table 1 are the binding affinities (K_i, nM) of the title compounds (**4a**–**g**) for opioid receptors (μ, κ, and δ) and the σ-receptor, and the in vivo data of these compounds for analgesic activity (PQW) and narcotic antagonism (AST). The data for compound **1b**, morphine, and naloxone are included for comparison. As shown, the introduction of a 7-keto group (**4b**) did not significantly affect binding to any of the three opioid receptors but lowered the σ-binding by 34-fold over the corresponding C-ring unfunctionalized analog (**1b**). Compound **4b** also retained good activity in PQW and anti-Straub tail assays, indicating its being a potent μ-antagonist and κ-agonist similar to **1b**. Compound **4c**, the cis isomer of **4b**, is a much weaker ligand at the opioid receptors, while displaying a slight increase (2×) in σ-affinity. This is in agreement with the general observation that the degree of stereoselectivity at the σ-receptor is less than that at opioid receptors.[14] The significant anti-Straub tail activity demonstrated by **4c** indicates its being a narcotic antagonist. Replacement of the *N*-cyclopropylmethyl group in **4b** with a methyl group (**4g**) resulted in much reduced binding at all four receptors assayed, with the largest drop observed at the κ-receptor. However, the analgesic activity was only decreased 3-fold with a concomitant 63-fold decrease in anti-Straub tail activity, indicating that the *N*-methyl group confers μ agonist activity instead of antagonist activity. Both **4e** and **4f**, the 7-hydroxy analogs derived from **4b**, displayed good but reduced binding at the opioid receptors. However, some interesting stereoselectivity associated with their in vivo activity was observed. The α-hydroxy isomer **4e** was active in both PQW and anti-Straub tail assays, while its β-isomer **4f** was only active in the anti-Straub tail assay and devoid of PQW activity in the dose range tested. In order to further delineate their pharmacological profile, compounds **4e** and **4f** were also evaluated at μ- and κ- opioid receptors in guinea pig ileum preparations. Compound **4e** was found to produce a full agonist effect of inhibiting the electrically stimulated muscle contraction (IC_{50} = 2.8 nM), while **4f** behaved as a partial agonist with a maximal response of 78% at 1 μM (Table 2). The agonist activities of **4e** and **4f** in GPI preparations can be antagonized by naloxone, and the IC_{50} values were shifted similarly as that of U-50488; the agonist effect of morphine was more sensitive to antagonism by naloxone (Table 3). The data indicates that the opioid agonist effects of **4e** and **4f** are mainly due to binding at the κ-receptor, in agreement with their in vivo PQW and AST activities. Opioid antagonist activity of the β-isomer **4f** at μ- and κ-opioid receptors in guinea pig ileum was also examined. At 3 nM, **4f** was found to be an effective antagonist at both μ- and κ-opioid receptors, with higher potency for the μ-receptor (Table 4). Methylation of the 3-hydroxyl group (**4a** and **4d**) caused large reductions in opioid receptor affinities, with little effect on σ-binding. Compounds **4a** and **4d** also showed reduced potency in in vivo PQW and anti-Straub tail assays.

Conclusion

The opioid and sigma receptor binding affinities of compounds containing the ACNO partial structure of morphine as represented by **1** are sensitive to functionality in ring C. In particular, selective reduction in σ binding was realized by the introduction of a 7-keto group. Since the σ-receptor may mediate psychotomimetic effects,[15] compound **4b**, being a weaker ligand at the σ-receptor while maintaining good analgesic and narcotic antagonism activity, is likely to be superior to **1b** as a potential analgesic. Unlike binding to opioid receptors (μ, κ, and δ), binding affinity at the σ-receptor is not significantly affected by methylation of the phenolic hydroxyl group, modification of the 7-oxygen function, or stereochemistry at the C/D ring junction. As compared to the 7-keto compound **4b**, the 7α-hydroxy derivative **4e** remains a μ-antagonist and κ-agonist, although with reduced potency; while its β-isomer **4f**

Table 1. Opioid Receptor Binding and in Vivo Analgesia and Narcotic Antagonism Activity of 7-Oxygenated 2,3,4,4a,5,6,7,7a-Octahydro-1*H*-benzofuro[3,2-*e*]isoquinolin-9-ols[a]



no.	R_1	R_2	X	opioid receptor binding (K_i, nM) μ	κ	δ	σ-receptor binding (K_i, nM)	ED_{50} (mg/kg sc) PQW	AST
1b	H	CH_2-c-C_3H_5	H_2	0.57 (0.4–0.7)[b]	1.2 (1–1.5)	5.3 (1.3–20)	21 (18–26)	0.025 (0.019–0.034)	0.018 (0.014–0.023)
4a	CH_3	CH_2-c-C_3H_5	O	76 (57–102)	1760 (406–26320)	1760 (169–13700)	440 (388–496)	0.93 (0.38–2.3)	0.34 (0.17–0.68)
4b	H	CH_2-c-C_3H_5	O	0.25 (0.17–0.34)	1.73 (1.22–2.36)	2.15 (1.04–3.97)	710 (536–967)	0.15 (0.068–0.34)	0.022 (0.014–0.036)
4c		C/D cis isomer of **4b**		19 (17–22)	62 (51–77)	134 134 (77–280)	310 (113–613)	>5.4 (inactive)	1.0 (0.83–1.3)
4d	CH_3	CH_2-c-C_3H_5	····OH & —H	29 (20–40)	140 (99–197)	150 (89–246)	410 (335–504)	3.0 (0.99–8.8)	1.4 (0.60–3.5)
4e	H	CH_2-c-C_3H_5	····OH & —H	1.4 (0.8–2.1)	4.9 (2.7–8.0)	15 (12.1–17.8)	580 (236–1280)	0.37 (0.21–0.64)	0.55 (0.23–1.3)
4f	H	CH_2-c-C_3H_5	····H & —OH	3.9 (2.3–5.9)	12 (11–13)	9.5 (7.4–11.9)	300 171–508)	>4.0 (inactive)	0.80 (0.45–1.4)
4g	H	CH_3	O	7.8 (4.5–13.4)	186 (103–345)	84 (12.8–159)	2090 (695–4945)	0.40 (0.28–0.57)	1.4 (0.74–2.7)
morphine				38 (25–61)	1870 (149–7080)	375 (28–3480)	$>10^5$	0.98 (0.77–1.3)	
naloxone				1.1	12	19	$>10^5$	>100 (inactive)	0.020 (0.015–0.027)

[a] Data represents the mean of three experiments each performed in duplicate. [b] The 95% confidence limits are shown in parentheses.

Table 2. Opioid Agonist Activity of **4e** and **4f** in GPI Preparation

compd	IC_{50} (nM)	% max response[a]
4e	2.8 ± 0.7 (4)	–
4f	–	78 ± 3 (3)
morphine	79 ± 6 (4)	–
U-50488	2.2 ± 0.2 (4)	

[a] Partial agonist potency (±SE) at 1 μM.

Table 3. Effect of Naloxone on the Opioid Agonist Activity of **4e** and **4f** in GPI Preparation[a]

compd	IC_{50} ratio[b]	K_e (nM)[c]
4e	8.1 ± 1.4 (3)	14.1
4f	8.5 (2)[d]	13.3
U-50488	9.1 ± 1.3 (3)	12.3
morphine	38 ± 2.5 (4)	2.7

[a] Concentration of naloxone, 100 nM. [b] IC_{50} of the agonist in the presence of antagonist divided by the control IC_{50} in the same preparation. [c] K_e = [antagonist]/(IC_{50} ratio − 1). [d] This ratio is an estimate because the maximum agonist response of **4f** was 78%.

Table 4. Evaluation of Opioid Antagonist Activity of **4f** in GPI Preparation[a]

compd	IC_{50} ratio[b]	K_e (nM)[c]
μ, morphine	6.3 ± 0.7 (4)	0.57
κ, U-50488	2.3 ± 0.7 (3)	2.3

[a] Concentration of **4f**, 3 nM. [b] See Table 3.

was found to be only a partial agonist at the κ-receptor and an effective antagonist at both μ- and κ-receptors.

Experimental Section

Synthesis. Melting points were taken in a capillary tube by using a Yamato MP-21 melting point apparatus and are uncorrected. IR spectra were determined with a Perkin-Elmer 1760-X FT-IR spectrometer. NMR spectra were recorded on a Bruker AM-300 spectrometer; chemical shifts were recorded in parts per million downfield from Me_4Si. Mass spectra were recorded on a JEOL JMS-D300 mass spectrometer; HRMS was obtained with a JEOL JMS-HX110 spectrometer. Elemental analyses were performed with a Perkin-Elmer 240C instrument. TLC was performed on Merck (Art. 5717) silica gel plates and visualized with UV light (254 nm) or upon heating after treatment with 2% phosphomolybdic acid in ethanol. Flash column chromatography was performed with Merck 40–63-μm silica gel. Reagent grade THF was distilled from sodium benzophenone prior to use. Other anhydrous solvents were distilled from CaH_2 and stored over 4-Å molecular sieves until use.

3-(Methoxycarbonyl)-4-[2-(phenylmethoxy)-3-methoxyphenyl]pyridine (6). Lactone **5** (14.0 g, 61.6 mmol) was dissolved in DMF (180 mL) and cooled to −65 °C (CO_2/$CHCl_3$). Sodium methoxide (4.66 g, 86.3 mmol) in DMF (40 mL) was added dropwise, the mixture was stirred for 1 h, and benzyl bromide (10.2 mL, 85.9 mmol) in DMF (30 mL) was added over 30 min. The mixture was warmed to room temperature over 3 h and stirred for 2 h. The solvent was removed by vaccum distillation. To the residue were added saturated NH_4Cl(aq) (100 mL) and water (400 mL), and the resulting mixture was extracted with CH_2Cl_2 (250 mL × 3). The combined organic layer was dried ($MgSO_4$) and evaporated. The residue was chromatographed (silica gel; ether:*n*-hexane = 1:1) to afford **6** as a white solid (19.8 g, 92%): mp 76–76.5 °C (EtOAc/*n*-hexane); R_f 0.53 (ether); ^1H NMR (300 MHz, $CDCl_3$) δ 3.66 (s, 3H), 3.90 (s, 3H), 4.73 (s, 2H), 6.75–7.19 (m, 9H), 8.56 (d, J = 5.1 Hz, 1H), 8.99 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 51.0, 55.2, 73.9, 112.7, 120.5, 123.4, 124.8, 126.6, 126.9, 127.2, 127.4, 132.9, 136.2, 143.9, 145.9, 149.4, 150.9, 152.0, 165.6; IR (neat) 2955, 1730, 1582, 1265 cm^{-1}; MS (EI, 70 eV) m/e calcd for $C_{21}H_{19}NO_4^+$ 349.1314, found 349.1304; 349 (M^+), 91 (base). Anal. ($C_{21}H_{19}NO_4$) C, H, N.

[4-[2-(Phenylmethoxy)-3-methoxyphenyl]pyridin-3-yl]-methanol (7). To a solution of ester **6** (14.0 g, 40.1 mmol) in dry toluene (300 mL) at −78 °C was added DIBALH (100 mL, 1.0 M in toluene) over 30 min. The mixture was stirred and

warmed to 0 °C during 3 h. HOAc(aq) (500 mL, 1 M) was added to the reaction mixture, and the toluene layer was separated. The aqueous layer was basified to a pH of 10 with 20% NaOH(aq) and then extracted with CH_2Cl_2/2-propanol (6/1, 200 mL × 3). The organic layers were combined, washed with saturated $NaHCO_3$(aq), dried ($MgSO_4$), and evaporated. The residue was chromatographed (silica gel; ether) to afford **7** as a white solid (10.54 g, 82%): mp 94–94.5 °C (from EtOAc/*n*-hexane); R_f 0.23 (ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.85 (s, 1H, OH), 3.92 (s, 3H), 4.37 (s, 2H), 4.72 (s, 2H), 6.71–7.21 (m, 9H), 8.42 (d, J = 5.0 Hz, 1H), 8.67 (s, 1H); ^{13}C NMR (20 MHz, $CDCl_3$) δ 55.7, 60.5, 75.0, 112.8, 121.7, 124.3, 124.4, 127.8, 128.0, 128.2, 132.8, 134.9, 136.2, 144.2, 145.2, 147.6, 149.5, 152.7; IR (neat) 3238, 1467, 1218 cm^{-1}; MS (EI, 70 eV) m/e calcd for $C_{20}H_{19}NO_3^+$ 321.1365, found 321.1367; 321 (M^+), 304, 212, 91 (base). Anal. ($C_{20}H_{19}NO_3$) C, H, N.

4-[2-(Phenylmethoxy)-3-methoxyphenyl]pyridine-3-carboxaldehyde (8). To a solution of alcohol **7** (11.9 g, 37.0 mmol) in CH_2Cl_2 (150 mL) was added MnO_2 (20.9 g, 240 mmol). The mixture was brought to reflux for 14 h and then cooled to room temperature. The suspension was filtered, and the filtrate was evaporated. The residue was chromatographed (silica gel, ether/*n*-hexane = 3:1) to afford **8** as pale yellow crystals (10.9 g, 92%): mp 95.5–96 °C; R_f 0.53 (ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.95 (s, 3H), 4.79 (s, 2H), 6.75–7.19 (m, 9H), 8.61 (d, J = 5.0 Hz, 1H), 9.00 (s, 1H), 9.70 (s, 1H); ^{13}C NMR (20 MHz, $CDCl_3$) δ 56.1, 75.0, 113.9, 122.4, 125.5, 128.1, 128.2, 128.5, 128.8, 130.2, 136.2, 144.5, 148.5, 148.7, 152.9, 153.1, 191.1; IR (neat) 1698, 1589, 1476 cm^{-1}; MS (EI, 70 eV) m/e calcd for $C_{20}H_{17}NO_3^+$ 319.1209, found 319.1202; 319 (M^+), 290, 91 (base). Anal. ($C_{20}H_{17}NO_3$) C, H, N.

1-(Cyclopropylmethyl)-4-(2-hydroxy-3-methoxyphenyl)-3-(3-oxo-3-ethoxypropyl)pyridinium Bromide (10). Cyclopropylmethyl bromide (4.42 mL, 45.6 mmol) was added to a solution of **9** (6.06 g, 20.1 mmol) in DMF (15 mL), and the resulting mixture was stirred for 9 h at 78 °C. DMF and excess cyclopropylmethyl bromide were removed by Kugelrohr distillation (1 mmHg, 60 °C). The crude product was purified by recrystallization from butanone to afford **10** (6.75 g, 77%) as a white solid: mp 117–120 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.66–0.72 (m, 4H), 1.07 (t, J = 7.0 Hz, 3H), 1.42 (m, 1H), 2.50 (t, J = 7.2 Hz, 2H), 3.02 (t, J = 7.2 Hz, 2H), 3.85 (s, 3H), 3.93 (q, J = 7.1 Hz, 2H), 4.61 (d, J = 7.5 Hz, 2H), 6.62-6.65 (m, 1H), 6.85–6.92 (m, 2H), 7.73 (d, J = 6.1 Hz, 1H), 9.04–9.12 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 4.5, 11.9, 13.8, 25.8, 32.8, 56.0, 60.7, 65.2, 112.5, 120.3, 120.6, 121.6, 129.5, 140.8, 141.3, 142.7, 143.7, 147.5, 156.0, 172.1; IR (KBr) 3327, 2842, 1729, 1636 cm^{-1}. Anal. ($C_{21}H_{26}NO_4Br \cdot H_2O$) C, H, N.

1-(Cyclopropylmethyl)-4-[2-(2-ethoxy-2-oxoethoxy)-3-methoxyphenyl]-3-(3-oxo-3-ethoxypropyl)pyridinium Bromide (11). A mixture of **10** (5.41 g, 12.4 mmol), ethyl bromoacetate (2.48 g, 14.8 mmol), and finely powdered K_2CO_3 (2.57 g, 18.6 mmol) in DMF (15 mL) was stirred for 1 h at 25 °C. The solvent was removed by kugelrohr distillation. The residue was treated with CH_2Cl_2 and filtered, and the filtrate was evaporated to give **11** as an amber-colored oil (6.03 g, 93%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.72–0.81 (m, 4H), 1.11–1.27 (m, 6H), 1.52 (m, 1H), 2.63 (m, 2H), 3.05 (t, J = 7.1 Hz, 2H), 3.86 (s, 3H), 3.96–4.11 (m, 4H), 4.51–4.54 (m, 2H), 4.87 (d, J = 7.6 Hz, 2H), 6.73–6.76 (m, 1H), 7.02–7.18 (m, 2H), 7.81 (d, J = 6.2 Hz, 1H), 9.27 (s, 1H), 9.46 (d, J = 6.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 4.8, 12.3, 14.1, 25.9, 32.9, 55.9, 60.7, 60.9, 64.9, 69.0, 114.4, 120.9, 124.8, 129.0, 129.5, 141.0, 141.6, 143.3, 143.7, 151.6, 155.9, 168.6, 172.0; IR (neat) 2981, 2938, 1756, 1733, 1640 cm^{-1}.

Spiro[2-(ethoxycarbonyl)-7-methoxybenzofuran-3(2*H*),4′(1′*H*)-1′-(cyclopropylmethyl)-3′-(3-oxo-3-ethoxypropyl)pyridine] (12). To a solution of **11** (2.76 g, 5.28 mmol) in anhydrous EtOH (20 mL) was added 20% NaOEt/EtOH (6.6 mL, 17.0 mmol). The mixture was stirred at 19 °C for 30 min and quenched with saturated NH_4Cl(aq). After evaporation of EtOH, H_2O (80 mL) was added, and the mixture was extracted with ether (100 mL × 3). The combined extracts were washed with brine, dried ($MgSO_4$), and evaporated to give **12** as a yellow solid (2.1 g, 90%): R_f 0.67 (ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.12–0.17 (m, 2H), 0.46-0.52 (m, 2H), 0.81–0.93 (m, 1H), 1.11–1.25 (m, 6H), 1.86–2.28 (m, 4H), 2.95 (d, J = 6.5 Hz, 2H), 3.83 (s, 3H), 3.94–4.36 (m, 5H), 4.98 (s, 1H), 5.90–5.96 (m, 2H), 6.69–6.92 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 3.0, 3.1, 3.2, 10.9, 14.0, 14.1, 14.2, 24.8, 25.5, 33.7, 34.2, 55.3, 55.5, 55.9, 57.8, 58.0, 59.9, 60.1, 60.6, 60.8, 91.1, 95.5, 97.5, 99.3, 107.9, 111.6, 117.8, 122.0, 127.3, 129.2, 130.7, 134.8, 144.1, 145.8, 169.1, 172.9; IR (neat) 2981, 2937, 1752, 1734, 1681, 1611 cm^{-1}; MS (EI, 70 eV) m/e calcd for $C_{25}H_{31}NO_6^+$ 441.2152, found 441.2156; 441 (M^+), 368 (base), 340, 55.

Ethyl 3-(Cyclopropylmethyl)-7-hydroxy-9-methoxy-5,7a-dihydro-3*H*-benzofuro[3,2-*e*]isoquinoline-6-carboxylate (13). To a mixture of NaH (0.816 g, 34 mmol) and 4-Å molecular sieve (3.64 g) in THF (50 mL) was added a solution of **12** (3.33 g, 7.54 mmol) in THF (60 mL). The resulting mixture was brought to reflux for 2.5 h and then poured into saturated NH_4Cl(aq) (200 mL). The mixture was evaporated and redissolved in a mixture of water (50 mL) and ether (200 mL). The ether layer was separated, and the aqueous layer was extracted further with ether (200 mL × 2). The combined organic layers were washed with brine, dried ($MgSO_4$), and evaporated to give **14** as a yellow crystalline solid (2.13 g, 72%): R_f 0.48 (ether:hexane, 1:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.15–0.20 (m, 2H), 0.51-0.57 (m, 2H), 0.95 (m, 1H), 1.24 (t, J = 7.1 Hz, 3H), 2.73 (s, 2H), 2.88–3.01 (m, 2H), 3.83 (s, 3H), 4.15 (q, J = 7.1 Hz, 2H), 4.42 (d, J = 7.7 Hz, 1H), 4.76 (s, 1H), 5.85–5.91 (m, 1H), 6.11 (s, 1H), 6.68–6.88 (m, 3H), 11.86 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 3.1, 3.2, 10.9, 14.1, 26.2, 50.0, 55.9, 57.8, 60.7, 88.9, 101.7, 102.4, 103.2, 111.6, 117.1, 122.0, 126.9, 127.6, 136.3, 144.6, 144.9, 165.0, 171.4; MS (EI, 70 eV) m/e calcd for $C_{23}H_{25}NO_5^+$ 395.1733, found 395.1736; 395 (M^+), 267, 212, 55 (base).

Ethyl 3-(Cyclopropylmethyl)-7-hydroxy-9-methoxy-2,3,4,4aα,5,7aα-hexahydro-1*H*-benzofuro[3,2-*e*]isoquinoline-6-carboxylate (14) and Ethyl 3-(Cyclopropylmethyl)-7-hydroxy-9-methoxy-2,3,4,4aα,5,7aβ-hexahydro-1*H*-benzofuro[3,2-*e*]isoquinoline-6-carboxylate (15). A mixture of **13** (520 mg, 1.31 mmol) and PtO_2 (100 mg) in EtOH (20 mL) was shaken in a Parr hydrogenator under 45 psi of H_2 for 11 h. The catalyst was removed via filtration through Celite, and the filtrate was evaporated. The residue was chromatographed (silica gel; MeOH:CH_2Cl_2, 1:30) to afford 350 mg (67%) of C/D *trans* isomer **14** and 72 mg (14%) of C/D *cis* isomer **15**. **14**: pale-yellow crystals; mp 119–120 °C; R_f 0.47 (MeOH:CH_2Cl_2, 8:92); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.17–0.3 (m, 2H), 0.54–0.56 (m, 2H), 0.93 (m, 1H), 1.22 (t, J = 7.2 Hz, 3H), 1.88–2.01 (m, 3H), 2.18–2.29 (m, 2H), 2.38–2.46 (m, 3H), 2.62 (d, J = 11.6 Hz, 1H), 2.95 (d, J = 12 Hz, 1H), 3.08–3.13 (m, 1H), 3.82 (s, 3H), 4.06–4.18 (m, 2H), 4.78 (s, 1H), 6.75–6.81 (m, 2H), 7.03–7.05 (m, 1H), 11.90 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 3.99, 4.04, 8.1, 14.1, 24.5, 37.1, 37.4, 48.3, 54.5, 56.0, 60.8, 63.6, 87.5, 101.4, 112.3, 118.7, 120.7, 131.2, 145.8, 148.1, 165.7, 171.6; IR (neat) 3331, 2937, 1661, 1651, 1622, 1616 cm^{-1}; MS (EI, 70 eV) m/e calcd for $C_{23}H_{29}NO_5^+$ 399.2046, found 399.2043; 399 (M^+, base), 55. **15**: oil; R_f 0.59 (MeOH:CH_2Cl_2, 8:92); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.06-0.11 (m, 2H), 0.47–0.53 (m, 2H), 0.84 (m, 1H), 1.18–1.27 (m, 3H), 1.74–1.87 (m, 2H), 1.96–2.33 (m, 6H), 2.52 (m, 1H), 2.94 (dd, J = 11.7, 3.9 Hz, 1H), 3.06 (d, J = 12.0 Hz, 1H), 3.81 (s, 3H), 4.08–4.18 (m, 2H), 4.96 (s, 1H), 6.69–6.85 (m, 3H), 11.88 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 3.8, 4.0, 8.3, 14.0, 24.3, 35.6, 36.7, 48.2, 50.4, 55.7, 55.9, 60.8, 63.9, 82.1, 98.9, 112.0, 114.5, 121.8, 134.2, 145.2, 146.7, 163.8, 171.9; MS (EI, 70 eV) m/e calcd for $C_{23}H_{29}NO_5^+$ 399.2046, found 399.2052; 399 (M^+), 353, 55 (base).

3-(Cyclopropylmethyl)-9-methoxy-7-oxo-2,3,4,4aα,5,6,7,7aα-octahydro-1*H*-benzofuro[3,2-*e*]isoquinoline (4a). A solution of **14** (526 mg, 1.32 mmol) in CH_3CN (1.5 mL) and 3 N HCl(aq) (30 mL) was refluxed for 7 h. When cooled, the reaction mixture was basified with 20% NaOH(aq) and extracted with CH_2Cl_2 (50 mL × 3). The combined extracts were washed with brine, dried ($MgSO_4$), and evaporated to give **4a** (384 mg, 89%) as an amber oil. An analytical sample was obtained via chromatography (silica gel, MeOH:CH_2Cl_2, 7:93): mp 176.5–179 °C (HCl salt); R_f 0.37 (MeOH:CH_2Cl_2, 10:90); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.11-0.16 (m, 2H), 0.51–0.57 (m, 2H), 0.92 (m, 1H), 1.55–1.61 (m, 1H), 1.73–

1.77 (m, 1H), 1.87–1.92 (m, 1H), 2.02 (m, 1H), 2.31–2.55 (m, 6H), 2.62 (dd, J = 11.7, 11.7 Hz, 1H), 2.93 (m, 1H), 3.05 (dd, J = 11.5, 4.0 Hz, 1H), 3.87 (s, 3H), 4.42 (s, 1H), 6.76-6.83 (m, 2H), 6.98–7.03 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 3.9, 4.0, 8.3, 25.7, 38.6, 39.3, 40.1, 48.3, 52.5, 54.6, 56.1, 63.6, 91.9, 112.6, 118.7, 121.3, 130.6, 145.5, 149.1, 207.2; IR (KBr) 3419, 2931, 1724, 1489 cm^{-1}; MS (EI, 70 eV) m/e calcd for $C_{20}H_{25}NO_3^+$ 327.1835, found 327.1847; 327 (M^+, base), 270, 55. Anal. ($C_{20}H_{25}NO_3$·HCl·1.5H_2O) C, H, N.

3-(Cyclopropylmethyl)-9-methoxy-7-oxo-2,3,4,4aα,5,6,7,7aβ-octahydro-1*H*-benzofuro[3,2-*e*]isoquinoline (16). **15** was subjected to the reaction condition described above to give the C/D *cis* ketone **16**: R_f 0.56 (10:90 MeOH:CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.06–0.11 (m, 2H), 0.46–0.52 (m, 2H), 0.85 (m, 1H), 1.77–1.92 (m, 4H), 2.13–2.46 (m, 7H), 2.97 (m, 2H), 3.84 (s, 3H), 4.58 (s, 1H), 6.73 (m, 2H), 6.85 (dd, J = 8.4, 7.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 3.8, 4.0, 8.2, 24.5, 34.5, 36.5, 36.8, 50.6, 52.5, 55.6, 56.0, 63.8, 88.8, 112.3, 114.6, 122.4, 134.5, 144.8, 147.2, 207.2; MS (EI, 70 eV) m/e calcd for $C_{20}H_{25}NO_3^+$ 327.1835, found 327.1835; 327 (M^+), 55 (base).

3-(Cyclopropylmethyl)-9-hydroxy-7-oxo-2,3,4,4aα,5,6,7,7aα-octahydro-1*H*-benzofuro[3,2-*e*]isoquinoline (4b). A mixture of **4a** (10 mg, 0.031 mmol), 1-propanethiol (23 mg, 0.31 mmol), and NaH (6 mg, 0.25 mmol) in DMF (4 mL) was heated at 110 °C for 2 h. NH_4Cl (50 mg) was added to the mixture, and DMF was removed by Kugelrohr distillation. The residue was chromatographed (silica gel; MeOH:CH_2Cl_2, 15:85) to give **4b** as an oil (5 mg, 52%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.15 (m, 2H), 0.52–0.58 (m, 2H), 0.94 (m, 1H), 1.23–1.28 (m, 1H), 1.74-7.83 (m, 1H), 1.87 (dt, J = 12.9, 2.5 Hz, 1H), 2.07 (td, J = 12.8, .3.9 Hz, 1H), 2.32-2.54 (m, 6H), 2.67 (t, J = 11.7 Hz, 1H), 2.98 (d, J = 12.3 Hz, 1H), 3.12 (dd, J = 11.4, 3.8 Hz, 1H), 4.41 (s, 1H), 6.72–6.81 (m, 2H), 6.92 (dd, J = 6.9, 1.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 4.0, 4.1, 8.1, 25.7, 38.2, 39.9, 40.1, 48.2, 52.7, 54.5, 63.5, 91.8, 116.7, 118.0, 121.8, 130.2, 141.9, 147.6, 208.5; MS (EI, 70 eV) m/e calcd for $C_{19}H_{23}NO_3^+$ 313.1678, found 313.1670; 313 (M^+, base), 272.

3-Methyl-9-hydroxy-7-oxo-2,3,4,4aα,5,6,7,7aα-octahydro-1*H*-benzofuro[3,2-*e*]isoquinoline (4g). similar to the preparation of **4b** from **10**, 1-methyl-4-(2-hydroxy-3-methoxyphenyl)-3-(3-oxo-3-ethoxypropyl)pyridinium iodide was converted to **4g** (overall yield 15%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.49–2.99 (m, 11H), 2.43 (s, 3H), 4.41 (s, 1H), 6.78–6.83 (m, 2H), 7.05 (dd, J = 6.9, 1.6 Hz, 1H); IR (neat) 1720 cm^{-1}; MS (EI, 70 eV) m/e 273 (M^+, base).

3-(Cyclopropylmethyl)-9-hydroxy-7-oxo-2,3,4,4aα,5,6,7,7aβ-octahydro-1*H*-benzofuro[3,2-*e*]isoquinoline (4c). **16** was demethylated as described above to give **4c** as an oil (41%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.03–0.27 (m, 2H), 0.40–0.66 (m, 2H), 0.78–1.03 (m, 1H), 1.65–2.70 (m, 11H), 2.86–3.22 (m, 2H), 4.64 (s, 1H), 6.60-6.89 (m, 2H); MS (EI, 70 eV) m/e calcd for $C_{19}H_{23}NO_3^+$ 313.1678, found 313.1687; 313 (M^+, base), 272.

3-(Cyclopropylmethyl)-7α-hydroxy-9-methoxy-2,3,4,4aβ,5,6,7,7aβ-octahydro-1*H*-benzofuro[3,2-*e*]isoquinoline (4d). To a solution of ketone **4a** (655 mg, 2.00 mmol) in dry THF (50 mL) at −78 °C was added dropwise L-Selectride (5 mL, 1.0 M in THF). The mixture was stirred for 1.5 h, treated with water (1.5 mL), and let warm to room temperature. After evaporation of THF, the residue was treated with 1 N NaOH (50 mL), and the resulting mixture was extracted with 2-propanol/CH_2Cl_2, 1:8 (50 mL × 3). The combined extracts were washed with brine, dried ($MgSO_4$), and evaporated. The residue was chromatographed (silica gel; MeOH:CH_2Cl_2, 15:85) to afford **4d** as a white solid (528 mg, 80%): mp 171–173 °C (HCl salt); R_f 0.39 (15:85 MeOH:CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.07–0.12 (m, 2H), 0.46–0.52 (m, 2H), 0.88 (m, 1H), 1.05 (m, 1H), 1.19–1.27 (m, 1H), 1.50–1.64 (m, 2H), 1.84–1.96 (m, 2H), 2.13 (m, 1H), 2.36–2.58 (m, 4H), 2.83–2.93 (m, 2H), 3.18 (s, 1H), 3.80 (s, 3H), 3.91–3.98 (m, 1H), 4.53 (d, J = 3.8 Hz, 1H), 6.69–6.75 (m, 2H), 7.02 (dd, J = 13.1, 7.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 3.85, 3.88, 8.0, 22.2, 23.2, 34.7, 39.6, 48.2, 53.5, 54.7, 55.6, 63.4, 67.0, 90.1, 111.4, 119.0, 120.0, 132.0, 144.1, 148.9; IR (KBr) 3367, 2943, 1618, 1585, 1489, 1461 cm^{-1}; MS (EI, 70 eV) m/e calcd for $C_{20}H_{27}NO_3^+$ 329.1991, found 329.1987; 329 (M^+), 55 (base). Anal. ($C_{20}H_{27}NO_3$·HCl·$^1/_2H_2O$) C, H, N.

3-(Cyclopropylmethyl)-7α,9-dihydroxy-2,3,4,4aβ,5,6,7,7aβ-octahydro-1*H*-benzofuro[3,2-*e*]isoquinoline (4e). A mixture of **4d** (280 mg, 0.85 mmol), 1-propanthiol (0.6 mL, 6.6 mmol), and NaH (100 mg, 4.17 mmol) in DMF (7 mL) was heated at 110 °C for 3.5 h. DMF was removed by Kugelrohr distillation, and the residue was dissolved in CH_2Cl_2 (15 mL). The soluton was extracted with 1 N NaOH (20 mL × 2). The aqueous extracts were acidified to pH = 8 with 6 N HCl and extracted with 2-propanol/$CHCl_3$ (1:4). The combined organic extracts were washed with brine, dried ($MgSO_4$), evaporated, and recrystallized (2-propanol/ethyl acetate) to give **4e** as a white solid (202 mg, 75%) : mp 223–225 °C (HCl salt, dec); R_f 0.31 (20:80 MeOH:CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.04–0.09 (m, 2H), 0.43–0.49 (m, 2H), 0.80–1.01 (m, 2H), 1.14–1.22 (m, 1H), 1.45–1.54 (m, 2H), 1.84 (m, 2H), 2.04 (m, 1H), 2.34–2.41 (m, 3H), 2.50–2.59 (m, 1H), 2.77–2.89 (m, 2H), 3.90 (m, 3H), 4.42 (d, J = 3.8 Hz, 1H), 6.53–6.58 (m, 1H), 6.65 (d, J = 7.7 Hz, 1H), 6.81 (d, J = 7.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 3.8, 7.4, 22.1, 22.5, 34.1, 38.8, 48.2, 54.5, 63.2, 66.6, 89.5, 116.0, 118.0, 120.2, 131.3, 140.6, 148.3; IR (KBr) 3521, 3440, 3377, 2953, 2744, 1481 cm^{-1}; MS (EI, 70 eV) m/e calcd for $C_{19}H_{25}NO_3^+$ 315.1835, found 315.1838; 315 (M^+, base), 274, 55. Anal. ($C_{19}H_{25}NO_3$·HCl·H_2O) C, H, N.

7β-(Benzoyloxy)-3-(cyclopropylmethyl)-9-methoxy-2,3,4,4aβ,5,6,7,7aβ-octahydro-1*H*-benzofuro[3,2-*e*]isoquinoline (17). To a stirred solution of alcohol **4d** (250 mg, 0.759 mmol), triphenylphosphine, (398 mg, 1.518 mmol), and benzoic acid (185 mg, 1.518 mmol) in dry THF (25 mL) was added dropwise diethyl azodicarboxylate (0.24 mL, 1.518 mmol) in THF (1 mL) at room temperature. After 1 h, the solvent was evaporated and the residue was chromatographed (silica gel; MeOH:CH_2Cl_2, 8:92) to afford **17** as an oil: R_f 0.57 (MeOH:CH_2Cl_2, 10:90); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.10–0.15 (m, 2H), 0.50–0.54 (m, 2H), 0.91 (m, 1H), 1.41 (m, 1H), 1.52–1.62 (m, 2H), 1.84–1.89 (m, 2H), 2.00–2.04 (m, 1H), 2.17–2.41 (m, 4H), 2.64 (t, J = 11.8 Hz, 1H), 2.86 (m, 1H), 2.98–3.03 (m, 1H), 3.80 (s, 3H), 4.45 (d, J = 6.2 Hz, 1H), 5.01–5.08 (m, 1H), 6.76–6.82 (m, 2H), 7.05–7.11 (m, 1H), 7.38–7.43 (m, 2H), 7.50–7.55 (m, 1H), 8.03–8.06 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 3.9, 4.0, 8.4, 23.5, 27.6, 39.1, 39.7, 48.3, 49.3, 54.9, 56.2, 63.7, 74.7, 91.2, 112.6, 119.2, 120.4, 128.2, 129.7, 130.3, 132.9, 133.1, 146.0, 148.0, 165.8; MS (EI, 70 eV) m/e 433 (M^+), 392, 312, 105, 55 (base).

3-(Cyclopropylmethyl)-7β-hydroxy-9-methoxy-2,3,4,4aβ,5,6,7,7aβ-octahydro-1*H*-benzofuro[3,2-*e*]isoquinoline (18). A solution of benzoate **17** and NaOH (120 mg, 3 mmol) in MeOH (25 mL) was stirred for 3 h at room temperature. The solvent was evaporated, and to the residue was added 0.5 N aqueous Na_2CO_3 (15 mL). The resulting mixture was extracted with 2-propanol/$CHCl_3$, 1:4 (25 mL × 2). The combined extracts were dried ($MgSO_4$), evaporated, and chromatographed (silica gel; MeOH:CH_2Cl_2, 20:80) to give **18** as a white solid (135 mg, 54% from **4d**): mp 215–216.5 °C (HCl salt); R_f 0.38 (15:85 MeOH:CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.09–0.14 (m, 2H), 0.49–0.55 (m, 2H), 0.91 (m, 1H), 1.22–1.52 (m, 3H), 1.71–1.89 (m, 3H), 2.11 (m, 1H), 2.25–2.42 (m, 3H), 2.64 (t, J = 11.8 Hz, 1H), 2.85–2.89 (m, 1H), 2.97–3.02 (m, 1H), 3.51–3.58 (m, 1H), 3.82 (s, 3H), 4.11 (d, J = 7.1 Hz, 1H), 6.75–6.78 (m, 2H), 6.97–7.03 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 3.9, 4.0, 8.1, 24.5, 30.8, 38.4, 40.5, 48.1, 49.3, 54.7, 55.8, 63.4, 71.8, 95.5, 111.6, 119.0, 120.3, 133.9, 146.0, 147.7; IR (KBr) 3514, 3392, 2938, 1489, 1450, 1273 cm^{-1}; MS (EI, 70 eV) m/e calcd for $C_{20}H_{27}NO_3^+$ 329.1991, found 329.1974; 329 (M^+, base), 288, 55. Anal. ($C_{20}H_{27}NO_3$·HCl·0.5H_2O) C, H, N.

3-(Cyclopropylmethyl)-7β,9-dihydroxy-2,3,4,4aβ,5,6,7,7aβ-octahydro-1*H*-benzofuro[3,2-*e*]isoquinoline (4f). To a solution of BBr_3–$(CH_3)_2S$ (1.08 mmol) in $ClCH_2CH_2Cl$ (25 mL) was added alcohol **18** (79 mg, 0.24 mmol) in $ClCH_2CH_2Cl$ (5 mL). The resulting mixture was stirred for 2 h at reflux and then cooled to room temperature. The cooled mixture was treated with water (5 mL), basified to pH = 10

with aqueous Na_2CO_3, and extracted with 2-propanol/$CHCl_3$, 1:4 (25 mL × 2). The combined extracts were washed with brine, dried ($MgSO_4$), and evaporated. The residue was chromatographed (silica gel; MeOH:CH_2Cl_2, 1:4) to give **4f** as a white solid (62 mg, 83%): mp 265 °C (dec, HCl salt); R_f 0.30 (MeOH:CH_2Cl_2, 20:80); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.10 (m, 2H), 0.50 (m, 2H), 0.87 (m, 1H), 1.14–1.45 (m, 3H), 1.66–1.85 (m, 3H), 2.01 (m, 1H), 2.28–2.43 (m, 3H), 2.64 (t, J = 12.0 Hz, 1H), 2.86 (d, J = 12.2 Hz, 1H), 2.97 (dd, J = 11.5, 3.6 Hz, 1H), 3.45 (m, 1H), 4.02 (d, J = 7.3 Hz, 1H), 6.60–6.70 (m, 2H), 6.81 (d, J = 6.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 3.9, 4.0, 7.5, 24.6, 31.3, 37.5, 40.2, 48.1, 50.0, 54.3, 63.2, 71.5, 94.9, 116.3, 117.6, 120.6, 133.5, 143.0, 146.6; IR (KBr) 3415, 3198, 3145, 2935, 1055 cm^{-1}; MS (EI, 70 eV) m/e calcd for $C_{19}H_{25}NO_3^+$ 315.1835, found 315.1825; 315 (M^+).

Opioid Receptor Binding Assay. Brain membranes were prepared from male Hartley guinea pigs, 250–300 g,[16] and binding was performed with 100 mM NaCl by the method of Tam.[17] The following labeled ligands were used: 0.5 nM [^{3}H]naloxone (μ-binding);1 nM (−)-[^{3}H]ethylketocyclazocine with 500 nM 2-D-Ala-5-D-Leu-enkephalin (DADLE) and 20 nM sufentanil (κ-binding); 1 nm [^{3}H]DADLE with 4 nM sufentanil (δ-binding) and 1 nM (+)-[^{3}H]SKF 10,047 (σ binding). IC_{50}s were calculated from log–logit plots. Apparent K_i's were calculated from the equation $K_i = IC_{50}/[1 + (L/K_d)]$.

Mouse Antiphenylquinone Writhing (PQW) Test. The methods of Siegmund et al.[18] and Blumberg et al.[19] were used after modification. Fasted male CFI mice, 18–23 g, are injected with coded doses of test compound and then challenged with 1.25 mg/kg ip phenylquinone 5 min prior to the designated test time. Analgesia is indicated by a complete blockade of the writhing response during a 10-min observation period starting at the designated test time.

Anti-Straub tail (AST) Test. The test was modified from the methods of Shemano and Wendel[20] and Blumberg and Dayton.[21] Fasted male CFI mice, 18–23 g, are injected with coded doses of test compound and then challenged with 0.08 mg/kg ip etonitazene 5 min prior to the designated test time. Narcotic antagonism is indicated by a complete blockade of the narcotic Straub tail response during a 5-min observation period starting at the designated test time.

Stimulated Guinea Pig Ileum Bioassay. Male Hartley guinea pigs weighing between 250 and 400 g were used. The longitudinal muscle strips were prepared by the method of Rang.[22] Tissues were mounted in 10-mL organ baths between vertically-spaced platinum electrodes and bathed with 37 °C oxygenated Krebs solution. The composition of the Krebs solution was (mM): NaCl 117, KCl 5.9, $CaCl_2$ 2.4, $MgCl_2$·$6H_2O$ 1.2, D-glucose 11.8, Tris base 20. Preparations were stimulated electrically (0.1 Hz, 0.8 ms duration, supramaximal voltage at a resting tension of 1 g. Contractions were recorded isometrically on a polygraph. The preparation was allowed to equilibrate with continuous stimulation for 90 min. Cumulative dose–response curves for the test compounds were measured. After complete washout and reequilibration, tissue preparations were incubated with an antagonist for 30 min, and then cumulative dose–response curves for the agonists were measured again.

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