Pergamon

Tetrahedron, Vol. 52, No. 33, pp. 10935-10944, 1996

0040-4020/96 $15.00 + 0.00

PII: S0040-4020(96)00649-7

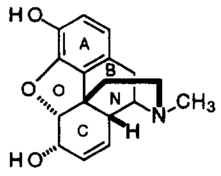
Novel Radical Synthesis of Morphine Fragments Spiro[benzofuran-3(2H),4'-piperidine] and Octahydro-1H-benzofuro[3,2-e]isoquinoline

Chen-Yu Cheng*, Ling-Wei Hsin, and Jing-Ping Liou

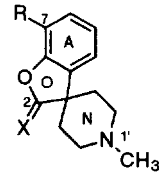
Institute of Pharmaceutical Sciences, National Taiwan University, 1, Sec 1,
Jen-Ai Road, Taipei, Taiwan 10018

Abstract: A new strategy for the synthesis of oxide-containing fragments of morphine has been developed. Thus, the tricyclic (ANO) morphine fragment spiro[7-methoxybenzofuran-3(2H),4'-1'-methylpiperidine] (**1**) was obtained as the sole product via an intramolecular radical cyclization of 4-[(2'-bromo-6'-methoxyphenoxy)methyl]-1-methyl-1,2,5,6,-tetrahydropyridine (**9**); while the tetracyclic (ACNO) fragment 9-methoxy-3-methyl-2,3,4,4aα,5,6,7,7aα-octahydro-1H-benzofuro[3,2-e]isoquinoline (**3**) and its 4-oxo analog **4** were synthesized in a similar fashion starting from 5,6,7,8-tetrahydroisoquinoline (**10**).Copyright © 1996 Elsevier Science Ltd

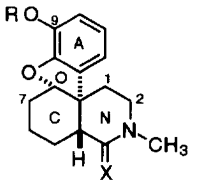
Morphine is a potent analgesic alkaloid, its rigid structure consisting of five rings (ABCNO). Approaches based on simplification of the morphine skeleton for the discovery of novel analgesics have been adopted by generations of medicinal chemists.[1] Clinically important analgesics which can be viewed as partial structures of morphine include morphinan derivatives such as levorphanol (ABCN), benzomorphan derivatives such as pentazocine (ABN), 4-phenylpiperidines such as meperidine or pethidine (AN), and phenyl propylamines such as methadone (A). Nevertheless, there remain several interesting classes of morphine fragments, including the ANO spiro[benzofuran-3(2H),4'-piperidines] and the ACNO octahydro-1H-benzofuro[3,2-e]isoquinolines, which have not been developed for clinical use, either due to inefficiency in their synthesis or inadequate structure-activity relationship study.[2,3] To extend the SAR of oxide(O)-containing partial structures of morphine, we have recently reported the synthesis of a series of 7-oxygenated octahydro-1H-benzofuro[3,2-e]isoquinoline (ACNO) derivatives with improved pharmacological profile.[3e] As a continued effort in this area, we have now developed an efficient radical approach for the construction of oxide-containing fragments of morphine, as exemplified by the synthesis of compounds **1**, **3**, and **4**. The potent analgesic activity of the ACNO fragment compound **5** or the 9-O-demethylated analog of **3** has been reported.[3b] However, the synthesis and pharmacological activity of either compound **1** or its 7-O-demethylated analog has not been documented, despite the fact that the closely related ANO fragment 4-(2'-hydroxyphenyl)-1-methylpiperidine-4-carboxylic acid lactone (**2**) has been reported to retain weak analgesic activity.[4] The application of radical cyclization reactions in the construction of polycyclic compounds has been well documented.[5] Recently a formal total synthesis of (±)-morphine based on a tandem radical cyclization strategy has been reported.[6]



Morphine



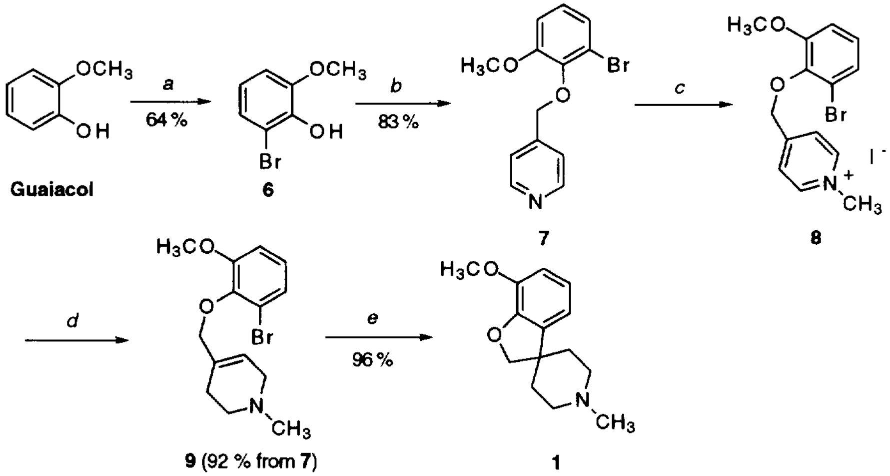
1 : R = OCH_3 ; X = H_2
2 : R = H ; X = O



3 : R = CH_3 ; X = H_2
4 : R = CH_3 ; X = O
5 : R = H ; X = H_2

In formulating our synthetic strategy, we envisioned that a 5-exo-trig intramolecular cyclization of an aryl radical to the 4-position of a tetrahydropyridine derivative such as **9** would provide a facile construction of the ANO fragment. As shown in Scheme 1, the key intermediate **9** was readily prepared from guaiacol in 4 steps. Regioselective *ortho*-bromination of guaiacol following a literature procedure[7,8] gave 6-bromoguaiacol (**6**) in 64% yield. Picolylation of **6** afforded an 83% yield of aryl picolyl ether **7**, which was treated with methyl iodide followed by $NaBH_4$ reduction to give **9** in 92% yield. To our satisfaction, the radical reaction of **9** with Bu_3SnH and AIBN (cat.) in benzene at 130 °C in a sealed vessel afforded the desired spiro[7-methoxybenzofuran-3(2H),4'-1'-methylpiperidine] (**1**) in 96% yield as the sole product.

Scheme 1

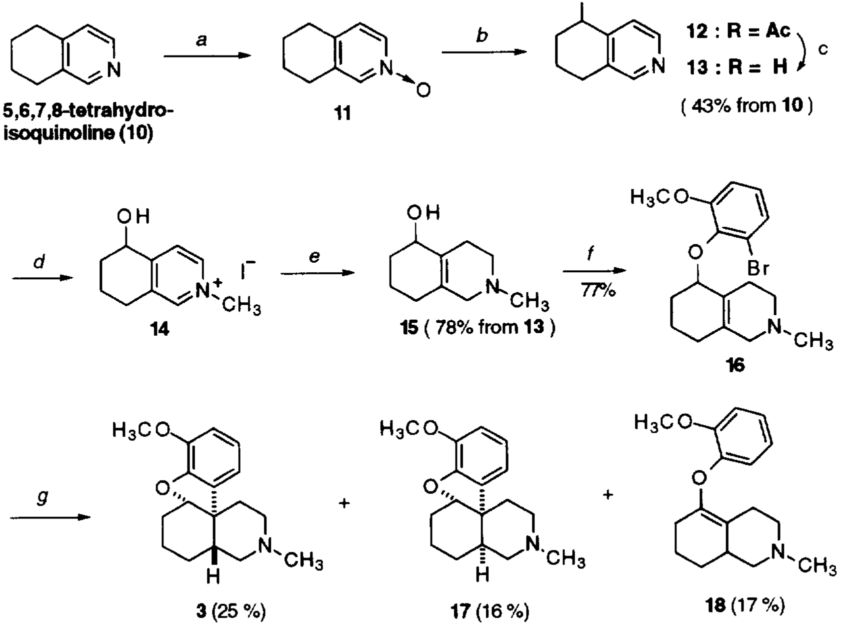


Scheme 1 (*a*) Br_2, *t*-butylamine, toluene, -60 °C. (*b*) picolyl chloride, K_2CO_3, acetone, reflux. (*c*) CH_3I, CH_2Cl_2, r.t. (*d*) $NaBH_4$, $CH_3COOH_{(cat.)}$, CH_3OH, r.t. (*e*) Bu_3SnH, $AIBN_{(cat.)}$, benzene, 130 °C, sealed vessel, 20 h.

We then extended the above methodology to the construction of ACNO fragments of morphine, with 5-aryloxy-1,2,3,4,5,6,7,8-octahydroisoquinoline derivative **16** as the key intermediate. As shown in Scheme 2, the commercially available 5,6,7,8-tetrahydroisoquinoline (**10**) was first oxidized with H_2O_2 in acetic acid to give N-oxide **11**, which underwent Polonovski rearrangement [9] in refluxing acetic anhydride to provide acetate

12. Hydrolysis of **12** with NaOH/MeOH afforded 5-hydroxy-5,6,7,8-tetrahydroisoquinoline (**13**)[10] in 43% yield from **10**. Treatment of **13** with methyl iodide, followed by $NaBH_4$ reduction of the intermediate pyridinium salt **14**, yielded exclusively 5-hydroxy-2-methyl-1,2,3,4,5,6,7,8-octahydroisoquinoline (**15**), which was then condensed with 6-bromoguaiacol (**6**) under Mitsunobu reaction condition[11] to afford the requisite intermediate **16** in 77% yield. The use of triethylphosphine instead of triphenylphosphine in the above condensation resulted in higher yield. The radical reaction of **16** under conditions similar to those for the formation of **1** resulted in the formation of three products, namely the desired 9-methoxy-3-methyl-2,3,4,4aα,5,6,7,7aα-octahydro-1H-benzofuro[3,2-e]isoquinoline (**3**), its C/N *cis*-isomer **17**, and a debrominated rearrangement product **18**, in yields of 25%, 16%, and 17% respectively. We have also tried to use tris(trimethylsilyl)silane[12] instead of tributyltin hydride as the chain carrier in the radical reaction of **16**. However, no reaction was observed even after heating for 72 h.

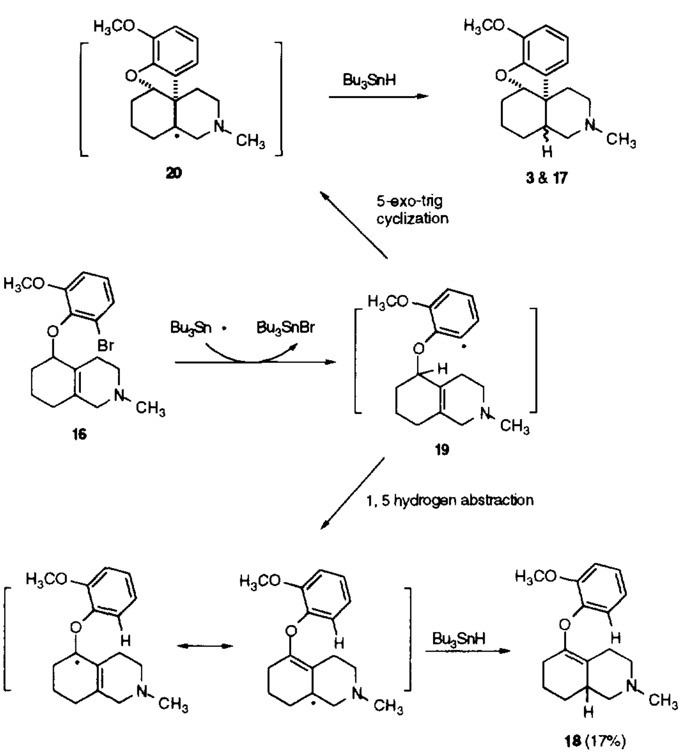
Scheme 2



Scheme 2 (*a*) H_2O_2, HOAc, 70 °C. (*b*) Ac_2O, reflux. (*c*) NaOH/MeOH, r.t. (*d*) CH_3I, 2-propanol, reflux. (*e*) $NaBH_4$, MeOH, r.t. (*f*) **6**, Et_3P, diethyl azodicarboxylate, THF, r.t. (*g*) Bu_3SnH, AIBN(cat.), benzene, 130 °C, sealed vessel, 15 - 17 h.

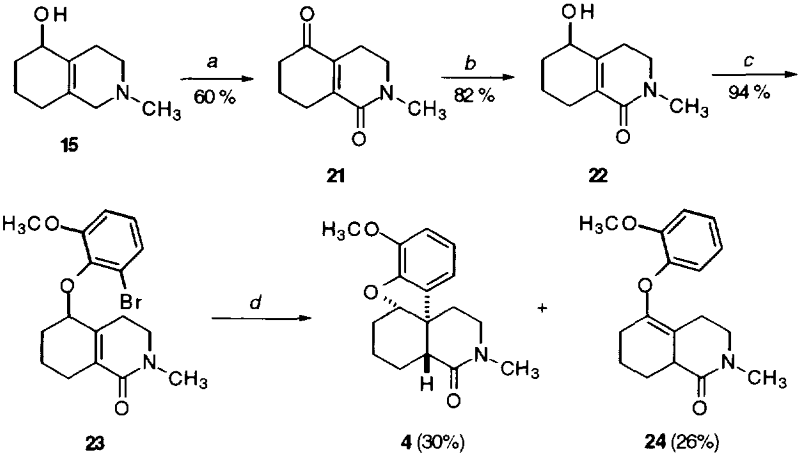
Shown in Scheme 3 is the proposed mechanism for the radical reaction of **16**. A bromine atom is abstracted from compound **16** by tributyltin radical to form aryl radical **19**, which may undergo two alternative reaction pathways. The first pathway is the desired 5-exo-trig cyclization to the tertiary radical **20**, which then abstracts a hydrogen atom preferentially from Bu_3SnH approaching from the face trans to the phenyl ring to provide a mixture of **3** and **17** in a ratio of about 3 to 2. As compared to the radical reaction of **9**, the desired cyclization of the radical intermediate **19** is less favored due to the steric bulk and the higher electron density of the tetrasubstituted olefin moiety in **16**. Therefore, a second reaction pathway involving 1,5-hydrogen atom abstraction, also occurs and leads to the formation of **18** as shown

Scheme 3



We then attempted to improve the radical synthesis of the ACNO ring system as described above by introducing a carbonyl function at C-1 of the octahydroisoquinoline intermediate **16**. The carbonyl function was introduced as shown in Scheme 4. Thus, compound **15** was first oxidized with MnO_2 to give keto-enamide **21**, which was then selectively reduced to alcohol **22** with $NaBH_4$. Mitsunobu reaction between **22** and 6-bromoguaiacol (**6**) proceeded smoothly to provide the requisite intermediate **23** in 94% yield. It was anticipated that the electron-withdrawing enamide moiety in **23** would facilitate the intramolecular addition of the nucleophilic aryl radical to the sterically congested 4a position. However, results obtained from the radical reaction of **23** under the same condition for **16** were only partially satisfactory. Although the desired C/N *trans* isomer **4** was obtained in 30% yield and in the absence of its *cis* isomer, the 1,5-hydrogen abstraction product **24** was also obtained in higher yield. It remains to be determined if the exclusive formation of the C/N *trans* isomer **4** is the result of kinetic or thermodynamic control; while the more facile formation of **24** is apparently due to the added resonance stabilization of the intermediate radical by the carbonyl group.

Scheme 4



Scheme 4 (*a*) MnO_2, CH_2Cl_2 , r.t. (*b*) $NaBH_4$, 2-propanol, 0 °C (*c*) **6**, PPh_3, diethyl azodicarboxylate, THF, r.t. (*d*) Bu_3SnH, $AIBN_{(cat.)}$, benzene, 130 °C, sealed vessel, 20 h.

The amide function in **4** can be further elaborated for the construction of ring B as documented in the related ACN series,[13] while the availability of chiral reducing agents, catalysts for asymmetric reduction, and enzymatic kinetic resolution offers the possibility of obtaining alcohol **22** in enantiomerically pure form. Therefore, with the introduction of suitable functionality into ring C of intermediate **23**, the above methodology may be adopted for the chiral synthesis of typical morphine alkaloids, when further optimization of the intramolecular radical cyclization can be realized.

EXPERIMENTAL

General

Melting points were taken in a capillary tube by using the Laboratory Devices, MEL-TEMP II melting point apparatus and are uncorrected. NMR spectra were recorded on a Bruker AMX-400, AM-300 FT-NMR spectrometers; chemical shifts were recorded in parts per million downfield from Me_4Si. IR spectra were determined with a Perkin-Elmer 1760-X FT-IR spectrometer. Mass spectra were recorded on a Jeol JMS-D300 and Finnigan TSQ-46C mass spectrometers; HRMS was obtained with a Jeol JMS-HX110 spectrometer. TLC was performed on Merck (Art. 5715) silica gel plates and visualized under UV light (254 nm), upon treatment with iodine vapor, or upon heating after treatment with 5% phosphomolybdic acid in ethanol. Flash column chromatography was performed with Merck (Art. 9385) 40-63 mm silica gel 60. Medium pressure liquid chromatography (MPLC) was performed with a Büchi B-680 instrument, with Merck (Art. 15111) 15-40 mm silica gel 60 as the stationary phase. High performance liquid chromatography was conducted using a Jasco model 880 series.

2-Bromo-6-methoxyphenol (6). Br_2 (13.7 mL, 0.266 mol) was added dropwise to a solution of *t*-butylamine (51 mL, 0.484 mol) in toluene (500 mL) at -30 °C. After being stirred for 0.5 h, the reaction mixture was cooled to -60 °C , and a solution of guaiacol (30.0 g, 0.242 mol) in CH_2Cl_2 (30 mL) was added dropwise. The resulting mixture was let warm to room temperature during 10 h, and then treated with 10% $Na_2S_2O_3$, followed by extraction with 10 % aqueous sodium hydroxide (200 mL + 100 mL). The combined alkaline extracts were acidified with conc. hydrochloric acid in an ice bath, and then extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and filtered. The filtrate was evaporated to afford an oily residue, which was distilled under reduced pressure (143-147 °C, 3.75 mmHg) to provide **3** (31.3 g, 64%) as a white solid: R_f 0.32 (ether : *n*-hexane = 1 : 2); ^{1}HNMR (300 MHz, $CDCl_3$) δ 3.84 (s, 3H), 5.96 (s, 1H), 6.70 (t, J = 8.0 Hz, 1H), 6.77 (dd, J = 8.1, 1.6 Hz, 1H), 7.06 (dd, J = 7.9, 1.7 Hz, 1H); ^{13}CNMR (75 MHz, $CDCl_3$) δ 56.2, 108.2, 109.9, 120.5, 124.7, 143.1, 147.3; IR (KBr) 3402, 1478, 1268, 1055 cm^{-1}; MS (EI, 70 eV) *m/e* 202 (M^+), 204 (M^+).

4-(2-Bromo-6-methoxyphenoxymethyl)pyridine (7) To a stirred mixture of 6-bromoguaiacol (5.00 g, 24.6 mmol), potassium carbonate (5.57 g, 40.3 mmol), and acetone (60 ml), was added slowly a solution of picolyl chloride in acetone (10 ml) at 0 °C. The reaction mixture was brought to reflux for 16 h, then cooled and evaporated. The crude residue was chromatographed (silica gel; EtOAc : *n*-hexane = 5 : 1) to give **7** (5.99 g, 83 %) as a white solid: m.p. 49-54 °C; R_f 0.16 (ether : n-hexane = 2 : 1); ^{1}HNMR (300 MHz, $CDCl_3$) δ 3.81 (s, 3H), 5.25 (s, 2H), 6.87 (dd, J = 8.1 Hz, 1H), 6.99 (t, J = 8.4 Hz, 1H), 7.13 (dd, J = 8.5, 1.7 Hz, 1H), 8.07 (d, J = 6.2 Hz, 2H), 8.81 (d, J = 6.2 Hz, 1H); ^{13}CNMR (75 MHz, $CDCl_3$) δ 56.0, 71.4, 111.7, 117.3, 124.1, 124.9, 126.1, 141.2, 144.1, 153.3, 157.6; MS (EI, 70 eV) *m/e* calc'd for $C_{13}H_{12}NO_2Br^+$: 293.0015, found 293.0033; 293 (M^+), 214 (base).

4-(2-Bromo-6-methoxyphenoxymethyl)-1,2,5,6-tetrahydropyridine (9) A solution of **7** (5.00 g, 17.06 mmol) and methyl iodide (5.31 ml, 85.30 mmol) in dry CH_2Cl_2 (10 ml) was stirred for 15 h at room temperature, and then evaporated to give crude **8** as a pale yellow solid. The crude (1.00 g, 2.3 mmol) was dissolved in CH_3OH (50 ml), followed by the portionwise addition of sodium borohydride (0.35 g, 9.20 mmol) at room temperature. After 0.5 h, acetic acid (1 ml) was added to the reaction mixture which was then evaporated. The residue was treated with H_2O (30 ml), and the resulting mixture was basified to pH = 10 with aqueous sat. $NaHCO_3$. The aqueous solution was extracted with isopropanol-$CHCl_3$ (1:4). The combined extracts were washed with brine, dried ($MgSO_4$), and evaporated to give a pale yellow oil (**6**, 0.97 g, 92 % from **7**): R_f 0.5 (CH_2Cl_2 : MeOH = 6 : 1); ^{1}HNMR (400 MHz, $CDCl_3$) δ 2.29 (s, 3H), 2.39 (m, 2H), 2.55 (t, J = 11.5 Hz, 2H), 2.92 (m, 2H), 3.78 (s, 3H), 4.34 (s, 2H), 5.74 (m, 1H), 6.76 (dd, J = 8.2, 1.4 Hz, 1H), 6.85 (t, J = 8.1 Hz, 1H), 7.06 (dd, J = 8.0 Hz, 1H); ^{13}CNMR (100 MHz, $CDCl_3$) δ 45.5, 51.8, 54.0, 55.9, 64.0, 75.9, 111.6, 117.9, 123.4, 124.8, 132.7, 145.3, 153.8; MS (EI, 70eV) *m/e* calc'd for $C_{14}H_{18}NO_2Br^+$: 311.0533, found 311.0527; 312 (M^+), 110 (base).

Spiro[7-methoxybenzofuran-3(2H),4'-1'-methylpiperidine] (1) A solution of **6** (0.20 g, 0.64 mmol), tributyltin hydride (0.2 ml, 0.74 mmol), and a catalytic amount of AIBN (52 mg) in dry benzene (64 ml) was heated in a sealed round bottle at 130-135 °C for 20h. The resulting mixture was evaporated to give a crude, which was chromatographed (silica gel; CH_2Cl_2 : MeOH : 40 % $NH_{3(aq)}$ = 30 : 1 : 0.01) to afford **1**

(0.14 g, 96 %) as a white solid: m.p. 54-59 °C; Rf 0.28 (benzene : EtOH = 30 : 1); ^{1}HNMR (400 MHz, $CDCl_3$) δ 1.71–1.74 (m, 2H), 1.93-2.02 (m, 4H), 2.29 (s, 3H), 2.81-2.83 (m, 2H), 3.84 (s, 3H), 4.40 (s, 2H), 6.72 (dd, *J* = 4.4, 0.9 Hz, 1H), 6.74 (d, *J* = 3.1 Hz, 1H), 6.81 (t, *J* = 7.6 Hz, 1H); ^{13}CNMR (100 MHz, $CDCl_3$) δ 36.4, 44.5, 46.4, 53.0, 55.8, 80.9, 111.2, 115.0, 121.2, 136.0, 144.5, 147.4; MS (EI, 70eV) *m/e* calc'd for $C_{14}H_{19}NO_2^+$: 233.1406, found 233.1411; 233 (M^+, base).

5,6,7,8-Tetrahydroisoquinoline-*N*-oxide (11). A solution of 5,6,7,8-tetrahydroisoquinoline (**10**) (25.6 g, 0.192 mol) and H_2O_2 (35%, 50 mL) in AcOH (120 mL) was heated for 4 h at 70-80 °C. After cooled, the mixture was evaporated to one-quarter of the starting volume, water (50 mL) was added, and the mixture was evaporated again to the same volume. To the residue, CH_2Cl_2 (100 mL) was added and the solution was neutralized with anhydrous K_2CO_3 and filtered. The filtrate was evaporated to afford crude **11** (28.1 g, 98%). An analytical sample was obtaind via distillation (156-16°C, 0.5 mbar) to give a hygroscopic white solid: R_f 0.26 (CH_3OH : CH_2Cl_2 = 1 : 15); ^{1}HNMR (300 MHz, $CDCl_3$) δ 1.69-1.73 (m, 4H), 2.58-2.62 (m, 4H), 6.87 (d, *J* = 6.5 Hz, 1H), 7.85 (d, *J* = 6.7 Hz, 1H), 7.88 (s, 1H); ^{13}CNMR (75 MHz, $CDCl_3$) δ 21.5, 21.9, 26.1, 27.6, 125.8, 135.8, 136.0, 137.2, 138.2; MS (EI, 70 eV) *m/e* 149 (M^+, base).

5-Hydroxy-5,6,7,8-tetrahydroisoquinoline (13). To boiling Ac_2O (45 mL) was added dropwise a solution of **11** (35.2 g, 236 mmol) in Ac_2O (230 mL) during 30 min, and the mixture was then heated for an additional 30 min under reflux. The excess Ac_2O was distilled (103-122 °C; 1 torr) to give crude 5-acetoxy-5,6,7,8-tetrahydroisoquinoline (**12**, 29.9 g), which was dissolved in 0.5 M methanolic sodium hydroxide solution (250 mL), and stirred at room temperature for 2 h. The reaction mixture was evaporated and extracted five times with CH_2Cl_2. The combined extracts were dried ($MgSO_4$), filtered, and evaporated to give an oily residue. The residue was distilled to give **13** (15.2 g, 43%) as a white solid: b.p. 134-136° C at 1 torr; ^{1}HNMR (300 MHz, $CDCl_3$) δ 1.61-1.74 (m, 2H), 1.85-2.03 (m, 2H), 2.57-2.61 (m, 2H), 4.59 (t, *J* = 5.9 Hz, 1H), 5.30 (s, 1H), 7.32 (d, *J* = 5.0 Hz, 1H), 8.07 (s, 1H), 8.11 (d, *J* = 5.0 Hz, 1H); ^{13}CNMR (75 MHz, $CDCl_3$) δ 19.2, 25.8, 31.8, 66.6, 122.3, 132.4, 146.2, 148.8, 149.2; IR (neat) 3350, 2940 cm^{-1}; MS (EI, 70 eV) *m/e* 150 (MH^+, base).

5-Hydroxy-2-methyl-1,2,3,4,5,6,7,8-octahydroisoquinoline (15). A stirred solution of **13** (6.80 g, 45.6 mmol) and methyl iodide (3.1 mL, 50.1 mmol) in anhydrous isopropanol (20 mL) was brought to reflux. Refluxing was continued for 2 h, then the solution was cooled and evaporated to give **14** as a pale yellow solid. The crude **14** was dissolved in CH_3OH (200 mL) and H_2O (10 mL), and then sodium borohydride (6.56 g, 173 mmol) was added in portions at room temperature. The reaction mixture was stirred for another 30 min, and then evaporated. The residue was treated with H_2O (100 mL), and the resulting mixture extracted with isopropanol-$CHCl_3$ (1:4). The combined extracts were washed with brine, dried ($MgSO_4$), filtered, and evaporated. The oily residue was chromatographed (MPLC, silica gel; $MeOH/CH_2Cl_2/NH_4OH_{(aq)}$ = 1:9:0.1) to afford **15** (5.94 g, 78%) as a pale yellow solid: ^{1}HNMR (400 MHz, $CDCl_3$) δ 1.37-1.41 (m, 1H), 1.43-1.49 (m, 1H), 1.54-1.66 (m, 4H), 1.82-1.88 (m, 1H), 2.12 (s, 3H), 2.27-2.37 (m, 3H), 2.56 (s, 2H), 3.69 (s, 1H), 4.12 (s, 1H); ^{13}CNMR (100 MHz, $CDCl_3$) δ 18.3, 26.8, 27.5, 32.3, 45.2, 52.2, 57.9, 67.0, 128.9, 129.2; IR (neat) 3366, 2932, 1461 cm^{-1}; MS (EI, 70 eV) *m/e* 167 (M^+).

5-(2-Bromo-6-methoxyphenoxy)-2-methyl-1,2,3,4,5,6,7,8-octahydroisoquinoline (16). To a stirred solution of alcohol **15** (1.00 g, 5.98 mmol), triethylphosphine (17.9 mmol) and 2-bromo-6-methoxyphenol (**6**) (3.60 g, 17.9 mmol) in dry THF (35 mL) was added dropwise diethyl azodicarboxylate (2.8 mL, 17.9 mmol) at room temperature. After 0.5 h, the solvent was evaporated and the oily residue was dissolved in diethyl ether. The resultant solution was extracted with 0.5 N hydrochloric acid, and the combined aqueous extracts were basified to pH = 10 with aqueous sodium hydroxide. The basic solution was extracted with CH_2Cl_2. The combined extracts were washed with brine, dried ($MgSO_4$), filtered, and evaporated. The residue was chromatographed (MPLC, silica gel; 8% MeOH in CH_2Cl_2) to afford ether **16** (1.63 g, 77%) as a pale yellow oil: ^{1}HNMR (400 MHz, $CDCl_3$) δ 1.32-1.38 (m, 1H), 1.49-1.53 (m, 1H), 1.79-1.94 (m, 3H), 2.00-2.04 (m, 1H), 2.21-2.25 (m, 1H), 2.27 (s, 3H), 2.28-2.32 (m, 1H), 2.61 (d, *J* = 15.6 Hz, 1H), 2.68-2.72 (m, 2H), 2.88 (d, *J* = 15.8 Hz, 1H), 3.73 (s, 3H), 4.55 (s, 1H), 6.75 (dd, *J* = 8.2, 1.6 Hz, 1H), 6.80 (t, *J* = 8.0 Hz, 1H), 7.04 (dd, *J* = 7.8, 1.6 Hz, 1H); ^{13}CNMR (100 MHz, $CDCl_3$) δ 17.9, 27.6, 27.8, 28.0, 45.5, 52.5, 55.5, 58.4, 77.5, 111.3, 118.3, 124.1, 124.9, 126.3, 132.8, 144.7, 153.8; IR (neat) 2938, 1471, 1261, 1036 cm^{-1}; MS (EI, 70 eV) *m/e* calc'd for $C_{17}H_{22}BrNO_2^+$: 351.0834, found 351.0812; 352 (MH$^+$).

***trans*-9-Methoxy-3-methyl-2,3,4,4aα,5,6,7,7aα-octahydro-1*H*-benzo[4,5]furo[3,2-*e*]isoquinoline (3), *cis*-9-Methoxy-3-methyl-2,3,4,4aβ,5,6,7,7aα-octahydro-1*H*-benzo[4,5]furo[3,2-*e*]isoquinoline (17), & 5-(2-Methoxyphenoxy)-2-methyl-1,2,3,4,6,7,8,8a-octahydroisoquinoline (18)** A solution of **16** (293 mg, 0.832 mmol), tributyltin hydride (0.32 ml, 1.18 mmol), and a catalytic amount of AIBN (13 mg) in dry benzene (50 mL) was heated in a degassed sealed round bottle at 120-130 °C for 15 h. The solvent was evaporated and the resulting residue was dissolved in diethyl ether. The ethereal solution was extracted with 1 N hydrochloric acid. The combined aqueous extracts were basified with 20% aqueous sodium hydroxide. The aqueous layer was then extracted with CH_2Cl_2, and the combined extracts were washed with brine, dried ($MgSO_4$), filtered, and evaporated. The crude residue was chromatographed (MPLC, silica gel; $MeOH/CH_2Cl_2/NH_4OH_{(aq)}$ = 5.5 : 94 : 0.5) to afford the *trans* adduct **3** (56 mg, 25%) as a white solid, the *cis* adduct **17** (36 mg, 16%) as an oil, and the enol ether **18** (39 mg, 17%). **3**: ^{1}HNMR (400 MHz, $CDCl_3$) δ 1.09-1.13 (m, 1H), 1.33-1.41 (m, 2H), 1.46-1.54 (m, 2H), 1.73-1.77 (m, 2H), 1.89-2.01 (m, 2H), 2.31-2.35 (m, 1H), 2.35 (s, 3H), 2.49 (t, *J* = 11.7 Hz, 1H), 2.63 (dt, *J* = 11.9, 2.8 Hz, 1H), 2.68 (dd, *J* = 11.5, 4.0 Hz, 1H), 3.82 (s, 3H), 4.42 (t, *J* = 5.8 Hz, 1H), 6.737 (d, *J* = 5.2 Hz, 1H), 6.739 (d, *J* = 3.4 Hz, 1H), 7.06 (dd, *J* = 5.1, 3.5 Hz, 1H); ^{13}CNMR (100 MHz, $CDCl_3$) δ 19.7, 24.5, 28.1, 39.2, 39.4, 46.0, 48.0, 50.8, 55.7, 57.3, 89.4, 111.1, 119.5, 119.6, 133.0, 145.2, 148.5; MS (EI, 70 eV) *m/e* calc'd for $C_{17}H_{23}NO_2^+$: 273.1729, found 273.1740; 273 (M$^+$). **17**: ^{1}HNMR (400 MHz, $CDCl_3$) δ 1.43-1.47 (m, 1H), 1.59-1.78 (m, 6H), 1.96-2.00 (m, 1H), 2.06-2.10 (m, 1H), 2.27 (s, 3H), 2.30-2.32 (m, 1H), 2.43-2.49 (m, 1H), 2.57 (td, *J* = 11.2, 3.5 Hz, 1H), 2.63-2.67 (m, 1H), 3.83 (s, 3H), 4.25 (s, 1H), 6.73 (dd, *J* = 8.1, 1.0 Hz, 1H), 6.78 (t, *J* = 7.7 Hz, 1H), 7.05 (d, *J* = 7.2 Hz, 1H); ^{13}CNMR (100 MHz, $CDCl_3$) δ 20.1, 26.2, 26.4, 30.5, 38.8, 44.3, 46.8, 53.3, 55.7, 57.7, 87.6, 110.7, 116.7, 120.5, 138.9, 145.0, 146.9; MS (EI, 70 eV) *m/e* calc'd for $C_{17}H_{23}NO_2^+$: 273.1729, found 273.1727; 273 (M$^+$). **18**: ^{1}HNMR (400 MHz, $CDCl_3$) δ 1.09-1.18 (m, 1H), 1.56-1.60 (m, 1H), 1.60 (t, *J* = 11.0 Hz, 1H), 1.75-1.82 (m, 3H), 1.91-1.95 (m, 1H), 1.97-2.01 (m, 1H), 2.10-2.12 (m, 1H), 2.23 (s, 3H), 2.41-2.45 (m, 1H), 2.69 (dt, *J* = 14.0, 2.4 Hz, 1H), 2.75-2.79 (m, 1H), 2.89 (ddd, *J* = 10.8, 4.7, 1.7 Hz, 1H), 3.85 (s, 3H), 6.73-6.77 (m, 1H), 6.80-6.84 (m, 1H), 6.86-6.92 (m, 2H); ^{13}CNMR (100 MHz, $CDCl_3$) δ 21.6, 25.4, 26.3, 27.5, 36.2, 46.1, 55.9, 56.0, 63.3, 112.1, 114.4, 120.7, 121.6, 122.9, 143.2, 146.0, 149.4; MS (EI, 70 eV) *m/e* calc'd for $C_{17}H_{23}NO_2^+$: 273.1729, found 273.1724; 274 (MH$^+$).

1,5-Dioxo-2-methyl-1,2,3,4,5,6,7,8-octahydroisoquinoline (21) A suspension of alcohol **15** (3.0 g, 0.018 mol) and activated manganese dioxide (108.9 g, 1.25 mol) in CH_2Cl_2 (300 ml) was stirred vigorously for 24 h at room temperature. The reaction mixture was filtered, and the precipitate was washed four times with 200 ml CH_2Cl_2. The filtrate and washings were combined and evaporated to afford **20** (1.92 g, 60%) as a pale yellow oil.: Rf 0.7 (CH_2Cl_2 : MeOH = 6 : 1); ^{1}HNMR (400 MHz, $CDCl_3$) δ 1.95 (m, 2H), 2.40 (m, 2H), 2.48 (m, 2H), 2.55 (m, 2H), 2.98 (m, 3H), 3.34 (t, *J*=7.2 Hz, 2H); ^{13}CNMR (100 MHz, $CDCl_3$) δ 20.1, 21.8, 23.8, 35.0, 37.4, 46.9, 137.7, 144.9, 164.9, 199.5; IR (neat) 1680, 1660, 1620 cm^{-1}; MS (EI, 70 eV) *m/e* 179 (M$^+$), 149, 100, 85 (base).

5-Hydroxy-2-methyl-1-oxo-1,2,3,4,5,6,7,8-octahydroisoquinoline (22) Ketone **21** (0.24 g, 1.34 mmol) was dissolved in isopropanol (20 ml), and then sodium borohydride (0.056 g, 1.47 mmol) was added to the solution at 0 °C. The reaction mixture was stirred for another 30 min, and then evaporated. The residue was treated with H_2O (50 ml), and the resulting mixture extracted with isopropanol-$CHCl_3$ (1 : 4). The combined extracts were dried with $MgSO_4$, filtered, and evaporated. The oily residue was chromatographed (silica gel; CH_2Cl_2 : MeOH = 50 : 1) to afford **21** (0.2 g, 82.4%) as a white solid.: Rf 0.3 (CH_2Cl_2 : MeOH = 6 : 1) ^{1}HNMR (400 MHz, $CDCl_3$) δ 1.82 (m, 1H), 2.24 (m, 1H), 2.29 (m, 3H), 2.59 (m, 1H), 2.94 (s, 3H), 3.33 (m, 2H), 4.10 (m, 1H); ^{13}CNMR (100 MHz, $CDCl_3$) δ 18.5, 23.6, 25.1, 31.6, 34.7, 47.1, 67.9, 128.9, 144.2, 166.1; IR (neat) 1620, 1660, 3400 cm^{-1}; MS (EI, 70ev) *m/e* calc'd for $C_{10}H_{15}NO_2^+$: 181.1103, found 181.1097; 181 (M$^+$, base), 164.

5-(2-Bromo-6-methoxyphenoxy)-2-methyl-1-oxo-1,2,3,4,5,6,7,8-octahydroisoquinoline (23). To a stirred solution of alcohol **22** (0.1 g, 0.55 mmol), triphenylphosphine (0.18 g, 0.72 mmol) and 2-bromo-6-methoxyphenol (0.12 g, 0.61 mmol) in dry THF (12 ml) was added dropwise diethyl azodicarboxylate (0.12 ml, 0.71 mmol) at room temperature. After 1 h, the solvent was evaporated, and the residue was chromatographed (silica gel; CH_2Cl_2 : MeOH = 80 : 1) to afford **22** (0.20 g, 94%) as a pale yellow solid.: R_f 0.48 (CH_2Cl_2 : MeOH = 50: 1); ^{1}HNMR (400 MHz, $CDCl_3$) δ 1.44 (m, 1H), 1.54 (m, 1H), 1.89 (m, 2H), 2.14 (m, 1H), 2.39 (m, 2H), 2.76 (m, 1H), 2.92 (s, 1H), 3.27 (m, 1H), 3.40 (m, 1H), 4.75 (m, 1H), 6.78 (dd, *J*= 8.28, 1.52 Hz, 1H), 6.84 (t, *J*=8.12 Hz, 1H), 7.05 (dd, *J*=7.96, 1.52 Hz, 1H); ^{13}CNMR (100 MHz, $CDCl_3$) δ 18.1, 13.6, 15.1, 27.5, 34.5, 47.0, 55.5, 77.2, 111.3, 118.1, 124.5, 124.9, 130.5, 141.6, 144.0, 153.5, 165.7; MS (EI, 70eV) *m/e* calc'd for $C_{17}H_{20}NO_3Br^+$: 366.0705, found 366.0690; 366 (M$^+$), 164 (base).

***trans*-9-Methoxy-3-methyl-4-oxo-2,3,4,4aα,5,6,7,7aα-octahydro-1H-benzo[4,5]furo[3,2-e]isoquinoline (4) & 5-(2-Methoxyphenoxy)-2-methyl-1-oxo-1,2,3,4,6,7,8,8a-octahydroisoquinoline (24).** A solution of **23** (50 mg, 0.14 mmol), tributyltin hydride (0.04 ml, 0.16 mmol), and a catalytic amount of AIBN (12 mg) in dry benzene (22 ml) was heated in a sealed round bottle at 130-135 °C for 20 h. The solvent was evaporated and the resulting residue was chromatographed (silica gel; EtOAc : n-hexane = 1 : 3) to give a pale yellow oil, which was chromatographed with preparative HPLC (RP-18 column, 21.2 x 250 mm; CH_3OH : H_2O = 7 : 3 ; 10 ml/min) to afford **4** (11.7 mg, 30%) and **24** (10.2 mg, 26%): **4**: R_f 0.43 (benzene : ethanol = 12 : 1); ^{1}HNMR (400 MHz, $CDCl_3$) δ 1.13-1.64 (m, 4H), 1.92-2.05

(m, 3H), 2.21 (m, 1H), 2.43 (dd, J=12.0, 4.0 Hz, 1H), 3.14 (td, J=12.0, 5.8 Hz, 1H), 3.22 (qd, J=12.4, 6.5, 1.4 Hz, 1H), 3.85 (s, 3H), 4.51 (dd, J=7.8, 6.0 Hz, 1H), 6.46 (m, 1H), 6.79 (m, 2H); ^{13}CNMR (100 MHz, $CDCl_3$) δ 20.8, 21.3, 28.0, 34.2, 34.5, 44.6, 46.1, 48.6, 55.9, 88.5, 111.9, 116.4, 121.3, 130.1, 145.8, 147.5, 170.6; MS (EI, 70 eV) *m/e* calc'd for $C_{17}H_{21}NO_3^+$: 287.1521, found 287.1542; 287 (M^+), 121 (base). **24**: ^{1}HNMR (400 MHz, $CDCl_3$) δ 1.61-1.67 (m, 2H), 1.89 (m, 1H), 2.06-2.24 (m, 2H), 2.25-2.28 (m, 2H), 2.80 (m, 1H), 2.90 (s, 3H), 3.03 (m, 1H), 3.24 (m, 2H), 3.86 (s, 3H), 6.74-6.76 (m, 1H), 6.82-6.84 (m, 1H), 6.89-6.95 (m, 2H); ^{13}CNMR (100 MHz, $CDCl_3$) δ 21.9, 23.7, 25.1, 25.6, 34.8, 41.9, 48.0, 55.9, 112.2, 115.2, 118.4, 120.8, 122.3, 145.0, 145.4, 149.7, 171.2; MS (EI, 70 eV) *m/e* calc'd for $C_{17}H_{21}NO_3^+$: 287.1522, found 287.1544; 287 (M^+), 164 (base).

Acknowledgement: We thank Prof. Yung-Son Hon for helpful discussion and the National Science Council of the R.O.C. for financial support (NSC 84-2331-B002-265).

REFERENCES AND NOTES

1. Michne, W. F.; Chemistry of Opiate Analgesics and Antagonists. In *Analgesics: Neurochemical, Behavioral, and Clinical Perspectives*; Kuhar, M.; Pasternak, G. Eds.; Raven Press: New York, 1984; pp. 125-148.
2. For syntheses of ANO fragments of morphine, see: (*a*) Bergel, F.; Haworth, J. W.; Morrison, A. L.; Rinderknecht, H. *J. Chem. Soc.* **1944**, 261-265. (*b*) Moos, W. H.; Gless, R. D.; Rapoport, H. *J. Org. Chem.* **1981**, *46*, 5064-5074. (*c*) Rosenberg, S. H.; Rapoport, H. *J. Org. Chem.* **1984**, *49*, 56-62.
3. For syntheses of ACNO fragments of morphine, see: (*a*) Ciganek, E. *J. Am. Chem. Soc.* **1981**, *103*, 6261-6262. (*b*) Ciganek, E. U.S. Patent 4 243 668, 1981; *Chem. Abstr.* **1981**, *95*, 809241. (*c*) Weller, D. D.; Weller, D. L. *Tetrahedron Lett.* **1982**, *23*, 5239-5242. (*d*) Weller, D. D.; Stirchak, E. P.; Weller, D.L. *J. Org. Chem.* **1983**, *48*, 4597-4605. (*e*) Cheng, C.Y.; Hsin, L. W.; Tsai, M. C.; Schmidt, W. K.; Smith, C.; Tam, S. W. *J. Med. Chem.* **1994**, *37*, 3121-3127. and 2(*b*).
4. Macdonald, A. D.; Woolfe, G.; Bergel, F.; Morrison, A. L.; Rinderknecht, H. *Brit. J. Pharmacol.* **1946**, *1*, 4-14.
5. For a review, see: Jasperse, C.; Curran, D. P.; Ferig, T. L. *Chem. Rev.* **1991**, *91*, 1237-1286.
6. (a) Parker, K. A.; Fokas, D. *J. Am. Chem. Soc.* **1992**, *114*, 9688. (b) Parker, K. A.; Fokas, D. *J. Org. Chem.* **1994**, *59*, 3933-3938.
7. Pearson, D. E.; Wysong, R. D.; Breder, C.V. *J. Org. Chem.* **1967**, *32*, 2358-2360.
8. Ishizaki, M.; Ozaki, K.; Kanematsu, A.; Isoda, T.; Hoshino, O. *J. Org. Chem.* **1993**, *58*, 3877-3885.
9. Polonovski, M. *Bull. Soc. Chim. Fr.* **1927**, *41*, 1190.
10. Epsztajn, J.; Bieniek, A. *J. Chem. Soc., Perkin Trans. 1* **1985**, 213-219.
11. Mitsunobu, O. *Synthesis* **1981**, 1-28.
12. Kanabus-Kaminska, J. M.; Hawari, J. A.; Griller, D.; Chatgilialoglu, C. *J. Am. Chem. Soc.* **1987**, *109*, 5267-5268.
13. (a) Evans, D. A.; Mitch, C. H.; Thomas, R. C. *J. Am. Chem. Soc.* **1980**, *102*, 5955-5956. (b) Evans, D. A.; Mitch, C. H. *Tetrahedron Lett.* **1982**, *23*, 285-288. (c) Moos, W. H.; Gless, R. D.; Rapoport, H. *J. Org. Chem.* **1983**, *48*, 227-238.

(*Received in China* 29 *April* 1996; *accepted* 24 *May* 1996)