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Synthesis of (±)-aphanorphine: a new approach to tricyclic 3-benzazepine scaffold using two radical C–C bond-forming reactions

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ABSTRACT

An expeditious approach to (±)-aphanorphine has been established using readily available starting materials. The present synthesis relies on the direct assembly between *N*-methylpyrrolidone (NMP) and 2-bromoanisaldehyde, which takes place through Et_3B/air-mediated transformation of the α-nitrogen-substituted sp^3C–H bond, and features a new design concept for the synthesis of the tricyclic 3-benzazepine skeleton.

(−)-Aphanorphine (**1**), a unique tricyclic 3-benzazepine alkaloid isolated from the freshwater blue-green alga *Aphanizomenon flos-aquae*, has attracted considerable attention over the past two decades because of the biological interest stemming from its structural similarity to benzomorphane analgesics such as pentazocine (Fig. 1).[1] Accordingly, many synthetic approaches to this natural product have appeared in the literature, showing various concepts for the construction of the tricyclic 3-benzazepine skeleton.[2]

The prospect that aphanorphine (**1**) serves as a potential lead compound for the discovery of new analgesics has prompted us to devise an expeditious route to this class of compounds, which, hopefully, would be applicable to the synthesis of a wide range of tricyclic 3-benzazepine derivatives. In this context, we envisaged that the Et_3B/air-mediated hydroxyalkylation reaction of *N*-methylpyrrolidone (NMP) with aldehyde **4**, recently devised in this laboratory,[3,4] would provide 5-benzylated pyrrolidinone **3** that constitutes an ideal intermediate for aphanorphine (**1**) synthesis (Scheme 1). Recent reports from the laboratories of Ishibashi[2n,q] and Gallagher,[2v,z] who have shown that the quaternary stereocenter of (−)-aphanorphine (**1**) could be constructed by the radical cyclization of alkenylated pyrrolidinone scaffolds, suggested the relevance of our strategic interpretations.

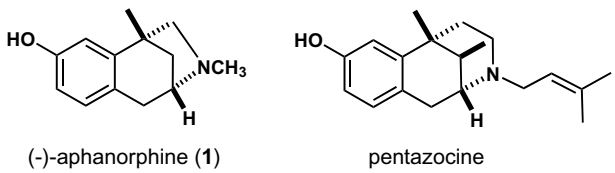

Figure 1.

We describe here a new concise approach to (±)-aphanorphine (**1**) that features two strategic radical C–C bond-forming reactions on NMP, involving sp^3C–H hydroxyalkylation and Bu_3SnH-mediated cyclization, the latter of which has been employed as a key bond-forming reaction in Gallagher's synthesis.[2v,z]

Our synthesis started with readily available NMP (**5**), employing radical sp^3C–H bond transformation chemistry (Scheme 2).[5–7] Thus, lactam **5** was directly hydroxybenzylated with 2-bromoanisaldehyde (**4**)[8] using Et_3B/air[9] at room temperature to afford desired compound **3a/b** as an inseparable diastereomixture, slightly favoring the production of *erythro*-type adduct **3a**, along with regioisomer **3c** in 64% combined yield (**3a**:**3b**:**3c** = 5:3:1) (Fig. 2).[10] The hydroxyalkylation took place predominantly at the methylene position alpha to the nitrogen atom, thereby enabling the direct installation of the arylmethyl motif at the 5-position of NMP (**5**).

The benzylic hydroxyl group of each of compounds **3a/b** was easily removed by treatment with Et_3SiH in the presence of $BF_3{\cdot}OEt_2$ to provide 5-benzylated pyrrolidone **6** in 94% yield. Although the methylenation of compound **6**, in an attempt to deliver key 3-methylenepyrrolidone **2**, was unfruitful under various conditions,[11] pyrrolidone **6** could eventually be converted in three steps into pyrrolidone **2** via the following sequence: compound **6** was initially subjected to LiHMDS and then to diethyl carbonate to effect ethoxycarbonylation, giving ester **7** in 85% yield. Reduction of ester **7** with $NaBH_4$ in the presence of $CaCl_2$ provided alcohol **8** (95%), which, by subsequent dehydration reaction using *N*,*N*′-dicyclohexylcarbodiimide (DCC) and CuI in refluxing chlorobenzene, was efficiently transformed into olefin **2** (84%).[12] Since olefin **2** has already been utilized as an intermediate in Gallagher's

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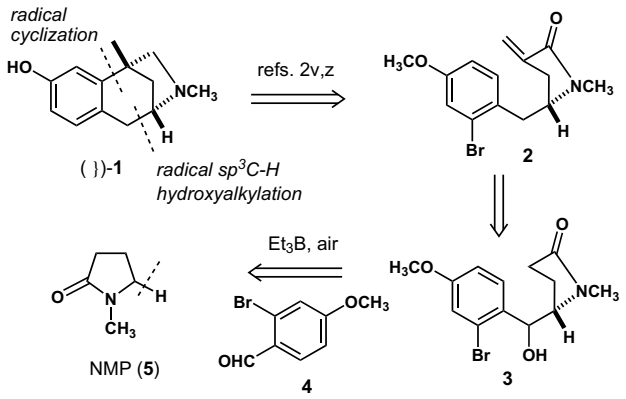
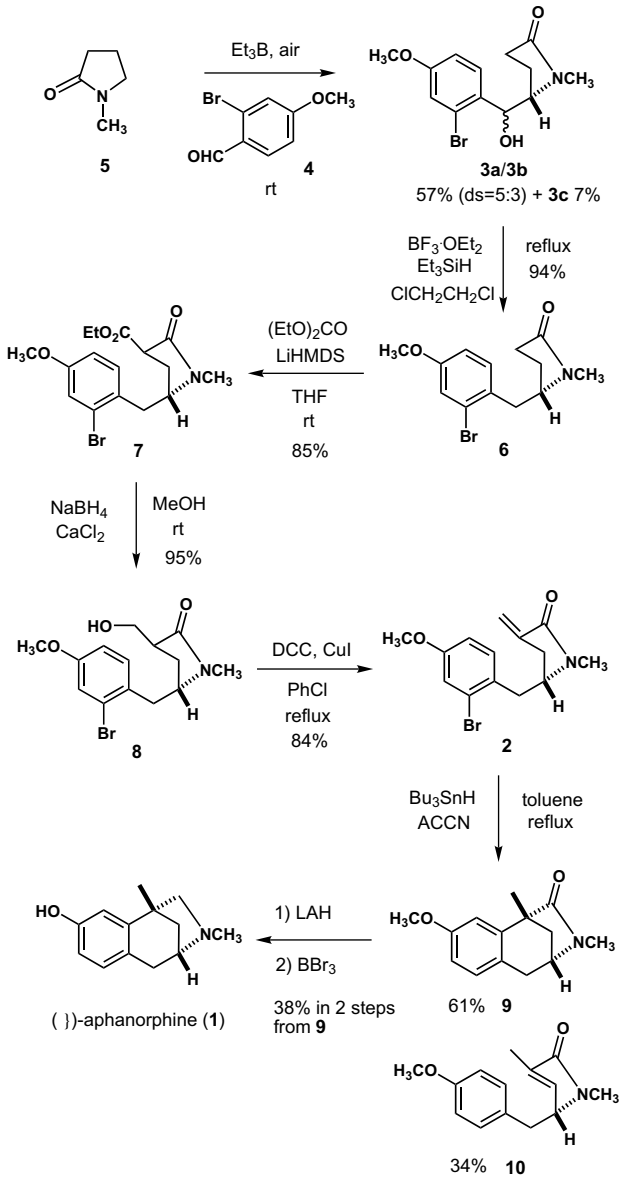


Scheme 1. Bridgehead annulation approach to (±)-aphanorphine (**1**) using two radical C–C bond-forming reactions.



Scheme 2. Total synthesis of (±)-aphanorphine (**1**).

total synthesis, this constitutes the formal synthesis of (±)-aphanorphine (**1**).[2v,z] Following a slight modification of Gallagher's protocol for the radical annulation reaction, 3-methylenepyrrolidone **2** was further converted into tricyclic lactam **9**: a diluted solution of pyrrolidone **2**, Bu_3SnH, and 1,1′-azobis(cyclohexylcarbonitrile) (ACCN)[13] in toluene was heated at reflux for a short period (ca. 5 min) to yield annulated compound **9** (61%) accompanied by isomerized internal alkene **10** (34%). The previously reported two-step transformation process from this compound **9**, involving LAH reduction and BBr_3-mediated demethylation, enabled us to access final target molecule **1**. The ^1H NMR, ^{13}C NMR, IR, and analytical data obtained for compounds **2**, **9**, and **1** were in full agreement with those reported in the literature.[14]

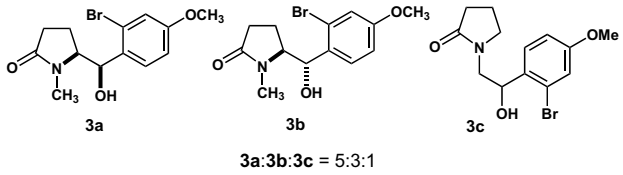


Figure 2. Hydroxyalkylation products.

In conclusion, we have established a new expeditious route to (±)-aphanorphine (**1**), which relies on the radical-based direct assembly between *N*-methylpyrrolidone (NMP) (**5**) and 2-bromoanisaldehyde (**4**). The present synthesis provides a new concept for the construction of the tricyclic 3-benzazepine skeleton from readily available NMP, which would be applicable to the short syntheses of a diverse array of aphanorphine derivatives simply by switching starting aldehydes. Further work along this line, which would allow us to discover new potent analgesics, is avidly being undertaken in this laboratory.

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14. Spectral data of compound **3a** (major isomer): colorless needles of mp 156–157 °C (EtOAc–CH_2Cl_2); IR (neat) ν 3299, 2931, 1662 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.60–1.71 (m, 1H), 2.02–2.12 (m, 1H), 2.22 (ddd, 1H, J = 16.8, 10.4, 4.1 Hz), 2.52 (dt, 1H, J = 15.7, 9.5 Hz), 3.00 (s, 3H), 3.80 (s, 3H), 3.77–3.87 (m, 1H), 5.30 (s, 1H), 5.35 (d, 1H, J = 1.7 Hz), 6.91 (dd, 1H, J = 8.6, 2.5 Hz), 7.08 (d, 1H, J = 2.5 Hz), 7.56 (d, 1H, J = 8.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.0, 28.0, 30.8, 55.5, 63.7, 69.5, 113.5, 117.9, 121.5, 128.9, 131.2, 159.5, 176.5; MS m/z: 314 (MH^+); HRMS (FAB) calcd for $C_{13}H_{17}O_3N^{79}Br$ (MH^+): 314.0392, found: 314.0384. m/z: 316 (MH^+); HRMS (FAB) calcd for $C_{13}H_{17}O_3N^{81}Br$ (MH^+): 316.0372, found: 316.0369. Compound **6**: colorless solid of mp 77–78 °C; IR (neat) ν 2927, 1662 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.73–1.82 (m, 1H), 1.84–2.05 (m, 1H), 2.21–2.46 (m, 2H), 2.57 (dd, 1H, J = 13.5, 9.2 Hz), 2.89 (s, 3H), 3.24 (dd, 1H, J = 13.4, 4.3 Hz), 3.79 (s, 3H), 3.75–3.89 (m, 1H), 6.82 (dd, 1H, J = 8.4, 2.6 Hz), 7.09 (d, 1H, J = 8.4 Hz), 7.13 (d, 1H, J = 2.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.2, 28.0, 29.5, 38.2, 55.4, 59.8, 113.6, 118.1, 124.7, 128.3, 131.6, 158.9, 174.9; MS m/z: 298 (MH^+); HRMS (FAB) calcd for $C_{13}H_{17}O_2N^{79}Br$ (MH^+) 298.0443, found: 298.0421. m/z: 300 (MH^+); HRMS (FAB) calcd for $C_{13}H_{17}O_2N^{81}Br$ (MH^+) 300.0423, found: 300.0411. Compound **7** (ca. 1:1 diastereomixture): pale yellow oil; IR (neat) ν 2927, 1738, 1693 cm^{-1}; ^1H NMR (300 MHz $CDCl_3$) δ 1.28 (t, 1.5H, J = 7.2 Hz), 1.33 (t, 1.5H, J = 7.2 Hz), 2.00–2.22 (m, 1.5H), 2.36 (dt, 0.5H, J = 13.2, 8.1 Hz), 2.57 (dd, 0.5H, J = 13.6, 9.0 Hz), 2.68 (dd, 0.5H, J = 13.3, 10.2 Hz), 2.92 (s, 1.5H), 2.94 (s, 1.5H), 3.25 (dd, 0.5H, J = 13.6, 4.4 Hz), 3.35–3.43 (m, 1.5H), 3.79 (s, 3H), 3.80–3.95 (m, 1H), 4.16–4.30 (m, 2H), 6.80–6.84 (m, 1H), 7.06–7.27 (m, 2H); MS m/z: 370 (MH^+); HRMS (FAB) calcd for $C_{16}H_{21}O_4N^{79}Br$(MH^+): 370.0654, found: 370.0631, m/z: 372 (MH^+); HRMS (FAB) calcd for $C_{16}H_{21}O_4N^{81}Br$ (MH^+): 372.0634, found: 372.0612. Compound **8** (ca. 1:1 diastereomixture): pale yellow oil; IR (neat) ν 3396, 2927, 1670 cm^{-1}; ^1H NMR (300 MHz $CDCl_3$) δ 1.44–1.81 (m, 1H), 1.89–2.08 (m, 1H), 2.47–2.71 (m, 2H), 2.89–2.93 (s × 2, 3H), 3.16–3.46 (m, 2H), 3.53–3.85 (m, 2H), 3.79 (s, 3H), 6.82 (m, 1H), 7.07–7.20 (m, 2H); MS m/z: 328 (MH^+); HRMS (FAB) calcd for $C_{14}H_{19}O_3N^{79}Br$ (MH^+): 327.0470; found: 328.0531, m/z: 330 (MH^+); HRMS (FAB) calcd for $C_{14}H_{19}O_3N^{81}Br$ (MH^+): 329.0450; found: 330.0506. Compound **2** (Refs. 2v and 2z): colorless oil; IR (neat) ν 2931, 1693 cm^{-1}; ^1H NMR (300 MHz $CDCl_3$) δ 2.46–2.53 (m, 2H), 2.68 (dddd, 1H, J = 17.9, 8.0, 2.8, 2.8 Hz), 3.01 (s, 3H), 3.30 (dd, 1H, J = 13.5, 4.1 Hz), 3.80 (s, 3H), 3.83–3.88 (m, 1H), 5.97 (t, 1H, J = 2.6 Hz), 5.29 (s, 1H), 6.83 (dd, 1H, J = 8.4, 2.6 Hz), 7.09 (d, 1H, J = 8.4 Hz), 7.13 (d, 1H, J = 2.6 Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ 28.8, 30.4, 39.3, 55.6, 56.9, 113.7, 115.3, 118.3, 124.8, 128.1, 131.7, 138.9, 159.2, 168.2. Compound **9** (Refs. 2o, 2v, and 2z): colorless solid of mp 142–143 °C; IR (neat) ν 2936, 1686 cm^{-1}; ^1H NMR (300 MHz $CDCl_3$) δ 1.55 (s, 3H), 2.03 (d, 1H, J = 10.6 Hz), 2.18 (dd, 1H, J = 10.6, 5.5 Hz), 2.83 (s, 3H), 2.92–2.94 (m, 2H), 3.78 (s, 3H), 3.82–3.86 (m, 1H), 6.73 (dd, 1H, J = 8.4, 2.5 Hz), 6.99 (d, 1H, J = 8.4 Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ 17.5, 27.6, 30.0, 40.7, 45.2, 54.9, 55.3, 110.1, 112.8, 124.4, 130.7, 141.5, 158.1, 177.1. *O*-Methylaphanorphine (Refs. 2o, 2v, and 2z): colorless oil; IR (neatl) ν 2934, 1493 cm^{-1}; ^1H NMR (300 MHz $CDCl_3$) δ 1.48 (s, 3H), 1.86 (d, 1H, J = 11.0 Hz), 2.02 (ddd, 1H, J = 11.0, 5.5, 1.0 Hz), 2.47 (s, 3H), 2.77 (d, 1H, J = 9.5 Hz), 2.83 (dd, 1H, J = 9.5, 1.3 Hz), 2.85 (dd, 1H, J = 16.5,3.1 Hz), 3.02 (d, 1H, J = 16.5 Hz), 3.42–3.44 (m, 1H), 3.78 (s, 3H), 6.69 (dd, 1H, J = 8.5, 2.4 Hz), 6.78 (d, 1H, J = 2.4 Hz), 7.02 (d, 1H, J = 7.9 Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ 21.5, 35.7, 41.5, 41,7, 43.2, 55.2, 61.2, 71.3, 109.4, 110.8, 126.1, 130.2, 148.1, 157.7. (±)-Aphanorphine (**1**) (Refs. 2n, 2o, and 2x): colorless solid of mp 210–215 °C; IR (neat) ν 2928, 1576 cm^{-1}; ^1H NMR (300 MHz CD_3OD) δ 1.45 (s, 3H), 1.84 (d, 1H, J = 11.0 Hz), 2.00 (ddd, 1H, J = 11.0, 5.8, 1.3 Hz), 2.42 (s, 3H), 2.64 (d, 1H, J = 9.6 Hz), 2.82–2.89 (m, 2H), 3.00 (d, 1H, J = 16.6 Hz), 3.40 (q, 1H, J = 2.6 Hz), 6.56 (dd, 1H, J = 8.2, 2.5 Hz), 6.67 (d, 1H, J = 2.5 Hz), 6.89 (d, 1H, J = 8.2 Hz); ^{13}C NMR (68 MHz, CD_3OD) δ 21.5, 36.5, 41.9, 42.8, 44.3, 64.0, 72.6, 110.9, 114.6, 124.8, 131.3, 148.1, 156.7.