A Practical Asymmetric Synthesis of the ACNO Fragment of Morphine Alkaloids

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Abstract: Asymmetric total synthesis of the ACNO skeleton of morphine alkaloids has been achieved in excellent overall yields and optical purities using the Ru-catalyzed asymmetric transfer hydrogenation, Pd-catalyzed cyclization, and Pt-catalyzed hydrogenation as key steps.

Key words: asymmetric catalysis, total synthesis, transition metals, hydrogenation, Heck reaction

Morphine alkaloids have been widely used in clinics as analgesics, antidiarrheals, and antitussives for decades.[1] Although morphine is a potent and inexpensive pain killer, its abuse liability and undesired adverse effects continue to stimulate the search for nonaddictive and safer analgesics. *trans*-Octahydro-1*H*-benzo[4,5]-furo[3,2-*e*]-isoquinolin-9-ol, which contains the ACNO partial structure of morphine (Figure 1), is an attractive class of morphine fragment. The *N*-cyclopropylmethyl derivative **1** has potent oral analgesic and narcotic-antagonism activities and thus, might have a low potential for addiction similar to nalbuphine and buprenorphine.[2]

To further study the structure-activity relationship (SAR) and evaluate the therapeutic potential of ACNO compounds as novel nonaddictive analgesics, preparation of optically pure ACNO derivatives for pharmacological studies is essential and therefore, an efficient route for the preparation of various ACNO derivatives is highly desired. Despite several synthetic strategies that have been reported in the literature,[3–6] the need for a practical and stereoselective synthetic strategy has not been met. Herein we report a concise asymmetric synthesis of the ACNO fragment of morphine alkaloids starting from commercially available 5,6,7,8-tetrahydroisoquinoline.

Retrosynthetic analysis of the ACNO ring system of morphine alkaloids is briefly depicted in Scheme 1. Stereoselective reduction of enamine **4** yields **3** with the desired *trans* CN ring junction. The O ring of **4** could be formed by treatment of haloaryl ethers **5** or **6** via Pd-catalyzed cyclization reactions. Coupling of aminoalcohol **9** with aryl halides **7** and **8** provides **5** and **6**, respectively. Alcohol **9** is accessible via N-methylation of compound **10** followed by partial reduction. Asymmetric reduction of ketone **11** provides optically active compound **10**. In this strategy, the chirality of C-7a in compound **10** could be used to control the chirality of other chiral centers in ACNO skeleton formed in the following steps by its directing effect.

Asymmetric transfer hydrogenation of ketone **11**, which was synthesized in two steps according to the literature procedure,[7] using Noyori and Hashiguchi's chiral Ru(II) catalysts[8] provided alcohol **10** in high optical purity. Treatment of ketone **11** with Et_3N and formic acid at room temperature in the presence of a catalytic amount (substrate/catalyst = 200) of Ru(II) catalyst, RuCl[(*R*,*R*)-Tsdpen](*p*-cymene) [(*R*,*R*)-**17**; Tsdpen: *N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine], afforded alcohol (–)-**10** in quantitative yield with 96% ee (Scheme 2).[9]

Initial attempts to transform alcohol (–)-**10** to compound (+)-**9** using the same reaction conditions for the preparation of compound (±)-**9** from (±)-**10**[4] yielded (+)-**9** with a poor ee (<70%). A possible mechanism is shown in Scheme 3.

After *N*-methylation of (–)-**10**, the acidity of H-5 in the pyridinium ion was substantially increased. An equilibrium between the pyridinium ion and the dihydropyridine intermediate might have existed in the presence of basic

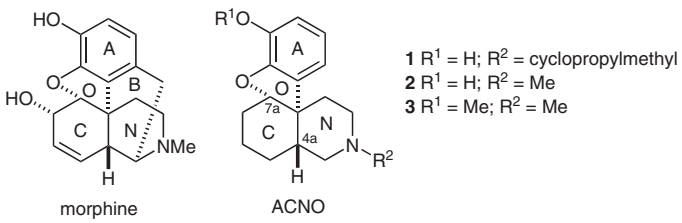

Figure 1 Morphine and its ACNO partial structure

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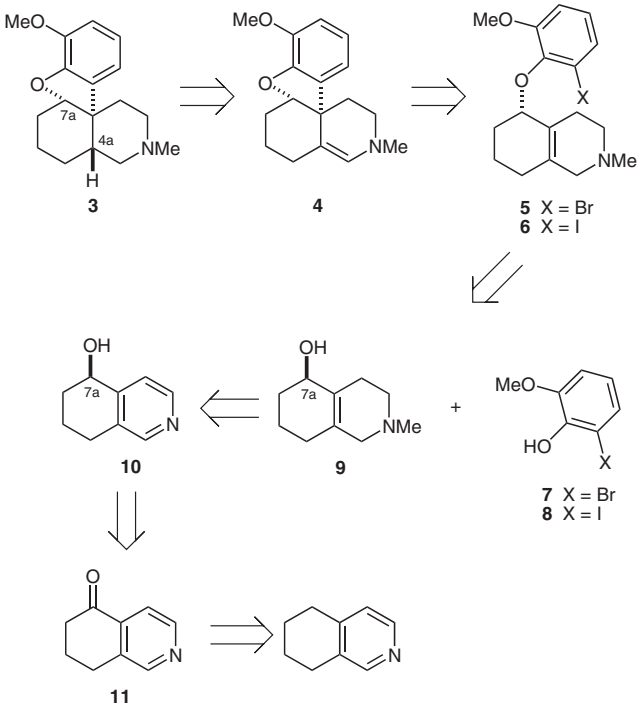
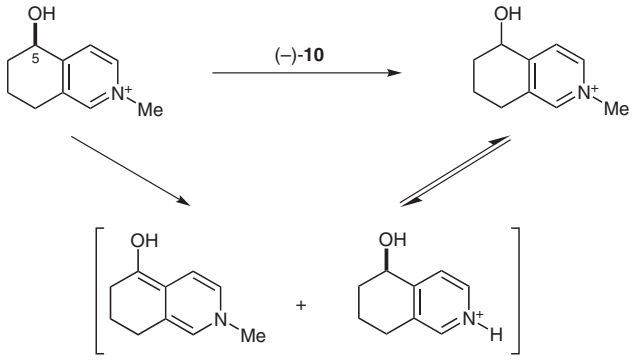


Scheme 1 Retrosynthetic analysis of compound **3**

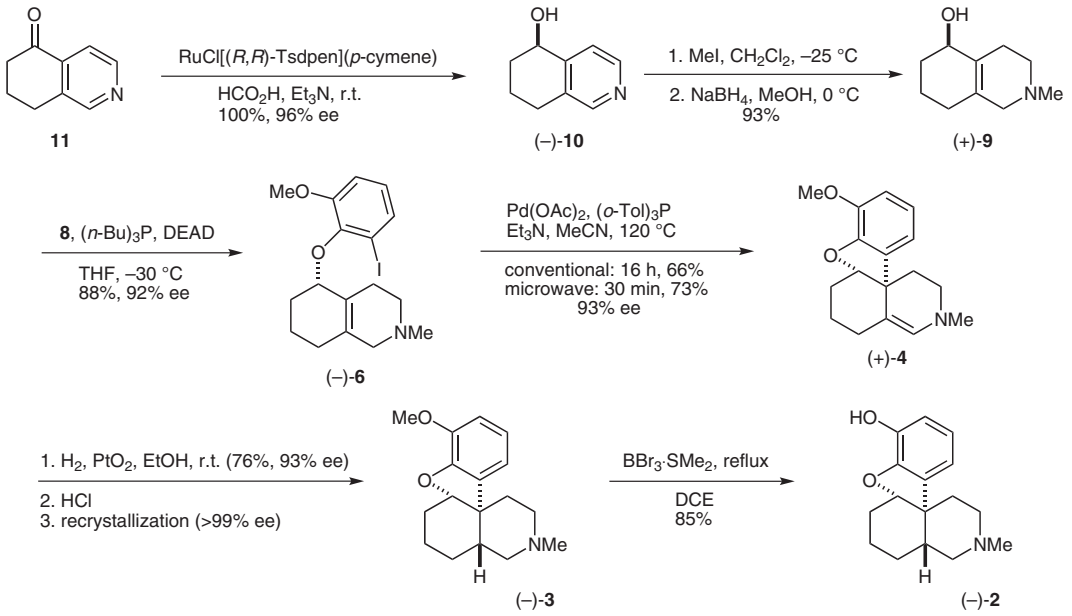
(–)-**10** and resulted in significant racemization. Therefore, alcohol (–)-**10** was methylated in CH_2Cl_2 at –25 °C and then reduced with $NaBH_4$ in MeOH at 0 °C to yield (+)-**9**. Coupling of compound (+)-**9** with aryl iodide **8** under Mitsunobu reaction conditions provided aryl ether (–)-**6** in 88% yield and 92% ee when the reaction was conducted at –30 °C. Higher reaction temperature was detrimental to the optical purity of compound (–)-**6**.

Previously, intramolecular radical cyclization of bromide **5** provided a mixture of *trans* isomer **3**, *cis* isomer **12**, and a rearranged product **13** (Scheme 4).[4] In another approach, treatment of halides **5** or **6** under palladium-catalyzed (Heck) reaction conditions yielded phenol **14** via a Claisen rearrangement.[5] We thought that the basic nitrogen atoms in halides **5** and **6** might be responsible for the failure of the cyclization reactions. Therefore, carbamate **15** was synthesized and subjected to the Heck reaction condition, and compound **16** with the ACNO ring system was obtained in a moderate yield.[5] Based on this key transformation, the first asymmetric synthesis of the ACNO fragment of morphine alkaloids was achieved in 12 steps with a total yield of 4.2%.[6] However, this lengthy synthetic route and the low overall yield were not satisfactory for the preparation and pharmacological studies of various ACNO derivatives.

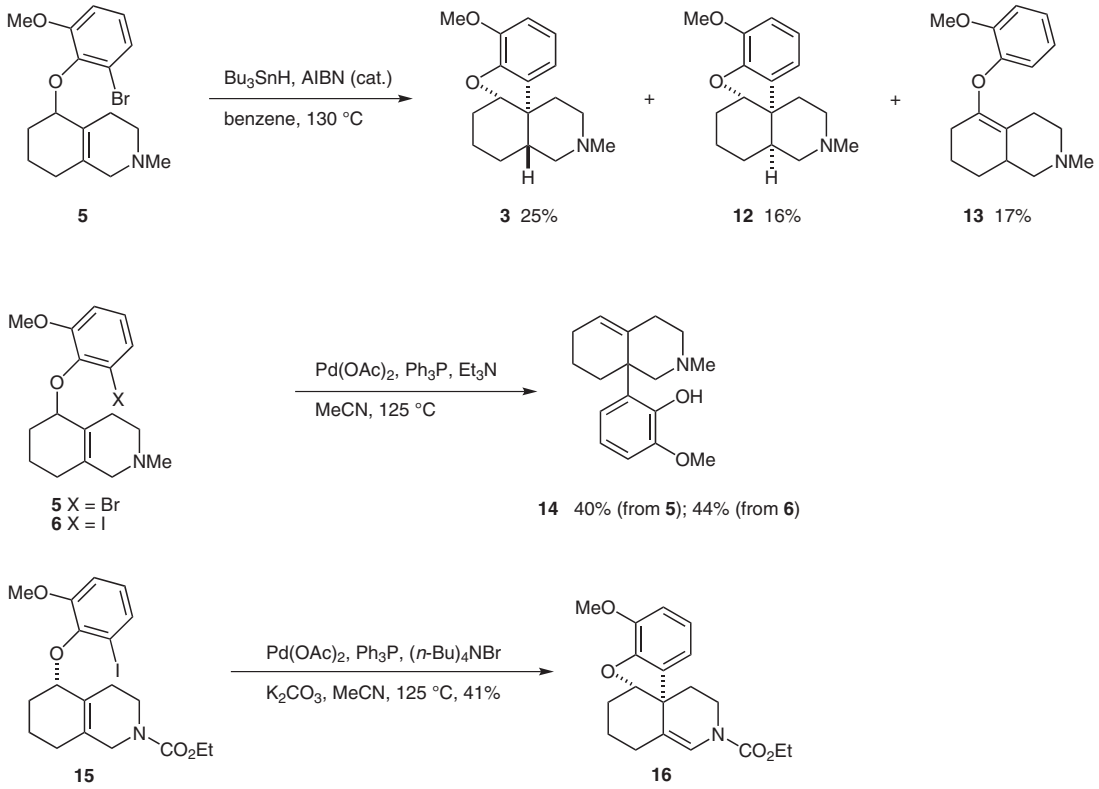


Scheme 3 Possible mechanism of racemization

To avoid the production of phenol **14** and identify the critical reaction parameters for successful Heck reaction, iodide **6** was treated with various Pd catalysts, phosphine ligands, bases, and solvents. It is interesting to note that the tetracyclic enamine **4** was obtained when PPh_3 was replaced with $(o\text{-tolyl})_3P$ in this Pd-catalyzed cyclization, and there was no rearranged product **14** formed in the reaction mixture. Thus, treatment of iodide (–)-**6** with



Scheme 2 A concise total synthesis of (–)-**2**



Scheme 4 Intramolecular radical cyclization,[4] palladium-catalyzed Claisen rearrangement,[5] and palladium-catalyzed Heck cyclization[5]

$Pd(OAc)_2$, (*o*-Tol)$_3$P, and Et_3N in acetonitrile at 120 °C in a sealed bottle gave the Heck reaction product (+)-**4** with the tetracyclic ACNO ring system. By using microwave-assisted heating,[10] the yield of enamine (+)-**4** was increased from 66% to 73% and the reaction time was shorten from 16 hours to 30 minutes. In contract to the preceding steps, conducting this palladium-catalyzed reaction at high reaction temperature by either conventional or microwave-assisted heating did not affect the ee of (+)-**4** (93%).

Catalytic hydrogenation of enamine (+)-**4** over PtO_2 afforded (–)-**3**[6] with the desired *trans* CN ring junction. This optically active (–)-**3** (ee = 93%) was transformed to its hydrochloride salt and then recrystallized to obtain optically pure (–)-**3** (ee >99%).[6] *O*-Demethylation of compound (–)-**3** using $BBr_3 \cdot SMe_2$ in 1,2-dichloroethane furnished *trans*-octahydro-1*H*-benzo[4,5]furo[3,2-*e*]isoquinolin-9-ol (–)-**2**[6] in 85% yield.[11] In contrast to the previous carbamate pathway (12 steps; 4.2% yield),[6] this new synthetic route provided compound (–)-**2** in eight steps with a total yield of 27.4% starting from commercially available 5,6,7,8-tetrahydroisoquinoline.

In conclusion, a practical asymmetric synthesis of the ACNO fragment of morphine alkaloids was demonstrated. The three chiral centers in *trans*-octahydro-1*H*-benzo[4,5]furo[3,2-*e*]isoquinolin-9-ol were stereoselectively established via metal-catalyzed asymmetric transfer hydrogenation, Heck reaction, and hydrogenation, respectively as exemplified by the synthesis of (–)-**2**. In addition, a catalytic amount of Ru(II) catalyst (*R*,*R*)-**17** was the only chiral reagent used in this asymmetric total synthesis. Application of this synthetic strategy for the preparation of other morphine fragments and related alkaloids such as galanthamine are currently under investigation.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(9) **Chiral HPLC Analysis**: The free base of the sample was dissolved in 1% isopropanol (IPA) in *n*-hexane. Then the sample solution (10 μL) was eluted using 1.5% [for compound (+)-**4**], 2.5% [for compounds (–)-**3** and (–)-**6**], or 8% [for compound (–)-**10**] IPA in *n*-hexane in the presence of 0.2% diethylamine as mobile phase on the CHIRALCEL OD column (250 × 4 mm, DAICEL). The ee values were calculated based on the UV absorption (λ = 254 nm) areas of the two enantiomers.

(10) **Microwave Experiments**: The reactions under microwave irradiation were conducted in sealed heavy-walled Pyrex tubes. Microwave heating was carried out with a single mode cavity Discover Microwave Synthesizer (CEM Corporation, P.O. Box 200, Matthews, NC 28106, USA), producing continuous irradiation at 2.45 GHz. The reaction temperature was measured and feedback controlled with an infrared device under the reaction vessel.

(11) **Spectral Data**: Compound (–)-**10**: pale yellow solid; $[\alpha]_D^{24}$ –31.1 (*c* = 1.00, MeOH); ee = 96.3%. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.61–1.74 (m, 2 H), 1.85–2.03 (m, 2 H), 2.57–2.61 (m, 2 H), 4.59 (t, *J* = 5.9 Hz, 1 H), 5.30 (s, 1 H), 7.32 (d, *J* = 5.0 Hz, 1 H), 8.07 (s, 1 H), 8.11 (d, *J* = 5.0 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.2, 25.8, 31.8, 66.6, 122.3, 132.4, 146.2, 148.8, 149.2. HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_9H_{11}NO$: 149.0841; found: 149.0839.
Compound (+)-**9**: yellow oil; $[\alpha]_D^{20}$ +60.0 (*c* = 0.10, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.37–1.41 (m, 1 H), 1.43–1.49 (m, 1 H), 1.54–1.66 (m, 4 H), 1.82–1.88 (m, 1 H), 2.12 (s, 3 H), 2.27–2.37 (m, 3 H), 2.56 (s, 2 H), 3.69 (s, 1 H), 4.12 (s, 1 H). ^{13}C NMR (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. HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{10}H_{17}NO$: 167.1310; found: 167.1317.
Compound (–)-**6**: pale yellow oil; $[\alpha]_D^{20}$ –51.1 (*c* = 1.90, MeOH); ee = 92%. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.39–1.62 (m, 2 H), 1.89–1.91 (m, 2 H), 1.96–2.20 (m, 2 H), 2.29 (m, 1 H), 2.31 (s, 3 H), 2.35–2.39 (m, 1 H), 2.60–2.73 (m, 3 H), 2.91 (d, *J* = 15.7 Hz, 1 H), 3.76 (s, 3 H), 4.66 (s, 1 H), 6.69 (t, *J* = 8.0 Hz, 1 H), 6.82 (dd, *J* = 1.5, 8.2 Hz, 1 H), 7.31 (dd, *J* = 1.6, 7.8 Hz, 1 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 18.4, 27.80, 27.84, 28.3, 45.6, 52.5, 55.3, 58.4, 77.5, 93.5, 112.4, 124.9, 126.4, 130.9, 132.6, 147.4, 152.5. HRMS (FAB): *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{23}INO_2$: 400.0774; found: 400.0783.
Compound (+)-**4**: pale yellow oil; $[\alpha]_D^{20}$ +105.0 (*c* = 0.92, MeOH); ee = 92.5%. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.10–1.26 (m, 1 H), 1.35–1.47 (m, 1 H), 1.50–1.68 (m, 1 H), 1.84–1.93 (m, 4 H), 2.00–2.17 (m, 1 H), 2.62 (s, 3 H), 2.71–2.82 (m, 2 H), 3.88 (s, 3 H), 4.46 (dd, *J* = 6.1, 9.4 Hz, 1 H), 5.91 (s, 1 H), 6.74–6.90 (m, 3 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 22.7, 29.3, 29.7, 37.1, 43.0, 45.9, 46.7, 55.9, 90.8, 106.8, 111.4, 116.8, 120.6, 134.2, 138.2, 145.2, 146.2. HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{17}H_{21}NO_2$: 271.1572; found: 271.1569.