Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
ELSEVIER
Tetrahedron 61 (2005) 513–520

# Stereoselective synthesis of morphine fragments *trans*- and *cis*-octahydro-1*H*-benzo[4,5]furo[3,2-*e*]isoquinolines

Ling-Wei Hsin,* Li-Te Chang, Chien-Wei Chen, Chia-Huei Hsu and Hung-Wei Chen

*Institute of Pharmaceutical Sciences, College of Medicine, National Taiwan University, No. 1, Section 1, Jen-Ai Road, Room 1336, Taipei 10018, Taiwan, ROC*

Received 31 May 2004; revised 17 August 2004; accepted 11 October 2004

**Abstract**—A stereoselective synthesis of the ACNO partial structures of morphine has been developed. Palladium-catalyzed cyclization of carbamate **2** provided the tetracyclic (ACNO) 3-ethoxycarbonyl-9-methoxy-2,3,5,6,7,7a-hexahydro-1*H*-benzofuro[3,2-*e*]isoquinoline (**14**); while treatment of 5-(2-bromo-6-methoxyphenoxy)-2-methyl-1,2,3,4,5,6,7,8-octahydroisoquinoline (**8**) under the same reaction condition gave 8a-(2-hydroxy-3-methoxyphenyl)-1,2,3,4,6,7,8,8a-octahydroisoquinoline (**11**) via an unusual Claisen rearrangement. 9-Methoxy-3-methyl-2,3,5,6,7,7a-hexahydro-1*H*-benzofuro[3,2-*e*]isoquinoline (**7**) was successfully transformed to *trans*-octahydroisoquinoline **3** and *cis*-octahydroisoquinoline **4** via catalytical hydrogenation over $PtO_2$ and chemical reduction with acidic $NaBH_4$, respectively.


## 1. Introduction

The rigid structure of morphine, a potent analgesic alkaloid, consists of five rings (ABCNO, Chart 1). Although narcotic analgesics display excellent antinociceptive activity, the numerous adverse effects of opiate narcotics continue to stimulate the discovery and development of better analgesics with no abuse-liability and milder side effects.[1] Approaches based on simplification of the morphine skeleton for the development of potent and nonaddictive analgesics have been adopted by generations of medicinal chemists and have resulted in the discovery of many potent analgesics, such as meperidine, pentazocine, and levorphanol.[1–3]

Octahydro-1*H*-benzofuro[3,2-*e*]isoquinolin-9-ols, which contain the ACNO partial structure of morphine, have been found to retain potent analgesic activity.[4,5] The *N*-cyclopropylmethyl analog **1** (J-6549) displayed potent oral analgesic and narcotic-antagonism activity and therefore, is likely to have a low potential for addiction.[5] Since the first synthesis of the ACNO skeleton of morphine by Schultz et al.,[6] several synthetic strategies have been published for the construction of the ACNO fragment of morphine.[4,7–12] Nevertheless, either due to inefficiency in these synthesis or inadequate structure-activity relationship (SAR) study, these ACNO compounds have not been developed for clinical use yet.

Researches in this laboratory have been focused on the development of novel synthetic strategies for stereoselective construction of the ACNO ring system of morphine and investigation of pharmacological activities of new ACNO compounds.[11–13] Previously, we reported a convergent approach towards the construction of the ACNO fragment of morphine via an intramolecular radical cyclization.[13]

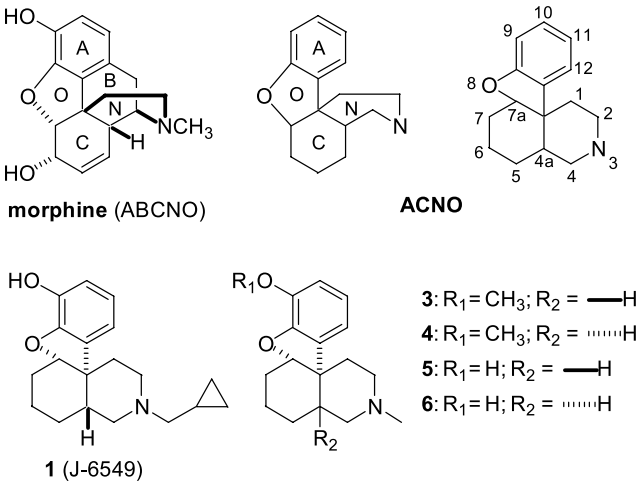



**Chart 1.**

*Keywords*: Stereoselective; Morphine; Intramolecular cyclization; Heck reaction; Claisen rearrangement.
* Corresponding author. Tel: +886 2 2395 2310; fax: +886 2 2351 2086; e-mail: lwh@ntumc.org

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.10.067

However, the difficulty in control of stereoselectivity prohibited further application.

Another attractive pathway towards the construction of the ACNO partial structure of morphine was demonstrated by Liou et al., in which a palladium-catalyzed cyclization was adopted as the key step (Chart 2).[14] However, the chirality of C-4a has not been established yet, and the stereoisomers may possess significantly different pharmacological profiles.[15–17] Therefore, to further study the SAR and the therapeutic potential of ACNO derivatives, an efficient and stereoselective synthetic route is highly desired. As a continued effort in this area, we have developed a novel synthetic approach, in which the O ring and the crucial quaternary carbon center were formed simultaneously by an intramolecular cyclization of carbamate **2** and the *trans*- and *cis*-C/N ring junctions were constructed via stereoselective catalytic hydrogenation and acidic $NaBH_4$ reduction, respectively. Here, we report this concise and stereoselective approach towards the construction of ACNO fragments of morphine, as exemplified by the synthesis of compounds **3**–**6**.

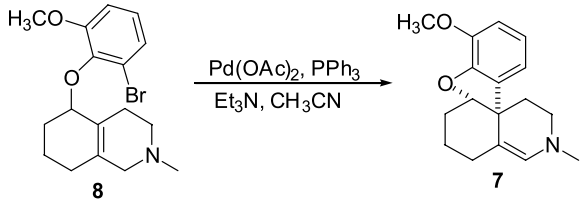



**Chart 2.** Intramolecular palladium-catalyzed cyclization.[14]

## 2. Results and discussion

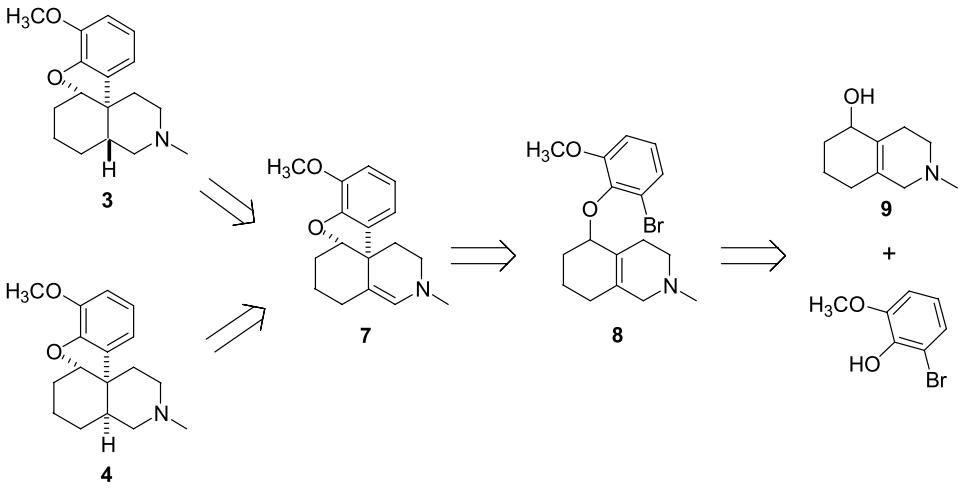
Initially, palladium-catalyzed cyclization reaction was considered as one of the key reactions in our retrosynthetic route as shown in Scheme 1. The *trans*- and *cis*-C/N ring junctions in compounds **3** and **4** could be established by stereoselective reductions of enamine **7**, which is prepared from aryl bromide **8** via the Heck reaction. Compound **8** is synthesized by coupling of compound **9** with 2-bromo-6-methoxyphenol under Mitsunobu reaction condition as previously described.[13]

Aminoalcohol **9** was prepared from 5,6,7,8-tetrahydroisoquinoline in five steps according to the previous procedures.[13] Coupling of **9** with 2-bromo-6-methoxyphenol and 2-iodo-6-methoxyphenol[18] under Mitsunobu reaction conditions provided aryl halides **8** and **10**, respectively (Scheme 2). Then the tetracyclic enamine **7** was supposed to be prepared from either bromide **8** or iodide **10** using the cyclization condition in the literature.[14] However, all attempts to convert aryl bromide **8** to enamine **7** using different Heck reaction conditions failed and afforded only one identifiable product **11**.

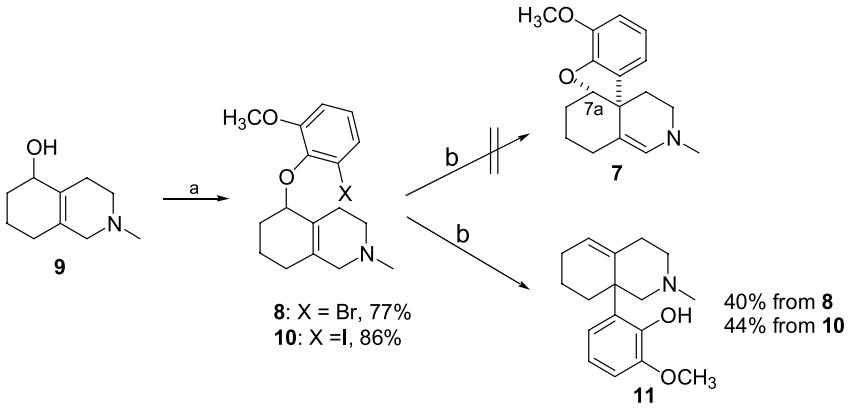
Initially, compound **11** was misinterpreted as the desired compound **7** since compound **11** and the reference compound, which was prepared and assigned as **7** in the literature,[14] showed almost identical $^{1}H$ and $^{13}C$ NMR spectra as shown in Tables 1 and 2. However, to our knowledge, the H-7a and C-7a of ACNO compounds usually display signals in the characteristic regions in the NMR spectra (i.e. $\delta$ 4.0–4.5 and 85–95, respectively). The disappearance of these typical signals prompted us to reinterpret the structure of **11**. The high-resolution mass (HRMS) data suggested that compound **11** contained two more hydrogen atoms than compound **7**. 2D NMR experiments, including COSY, NOESY, HMBC, and HMQC, were conducted and the structure of compound **11** was determined as 8a-(2-hydroxy-3-methoxyphenyl)-1,2,3,4,6,7,8,8a-octahydroisoquinoline. The X-ray diffraction analysis of the HCl salt of compound **11** confirmed the assigned structure (Fig. 1). Crystallographic data (excluding structure factors) for the structure have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 251042.

In general, the aryl iodides are more active than the aryl bromides in palladium-catalyzed cyclization. Therefore, iodide **10** was subjected to the same Heck reaction conditions as above. Again, the rearrangement product **11** was the only product isolated in a yield similar to that of using bromide **8** as Heck reaction substrate.

A [3,3]-sigmatropic-rearrangement and a reduction reaction were involved in this reaction. To study the mechanism of this unusual rearrangement, the debrominated derivative **12**




**Scheme 1.**




**Scheme 2.** Reagents and conditions: (a) 2-bromo-6-methoxyphenol or 2-iodo-6-methoxyphenol, DEAD, $Bu_3P$, THF, rt; (b) $Pd(OAc)_2$, $PPh_3$, $Et_3N$, $CH_3CN$, 125 °C.

**Table 1.** The $^1H$ NMR spectral data ($\delta$, ppm) of compounds **11**, '**7**',[14] and **7**

| **11** | '**7**'[14] | **7** |
|---|---|---|
| 1.44–1.54 (m, 3H) | 1.44–1.54 (m, 3H) | 1.10–1.26 (m, 1H), 1.35–1.45 (m, 1H), 1.55–1.62 (m, 1H) |
| 1.96–2.10 (m, 5H) | 1.96–2.10 (m, 4H) | 1.78–1.89 (m, 3H), 1.91–1.96 (m, 1H) |
| 2.12–2.21 (m, 1H) | 2.12–2.21 (m, 1H) | 2.03–2.07 (m, 1H) |
| 2.26 (s, 3H) | 2.26 (s, 3H) | 2.60 (s, 3H) |
| 2.30–2.34 (m, 1H) | 2.30–2.34 (m, 1H) | 2.68–2.74 (m, 1H) |
| 2.87–2.90 (m, 1H) | 2.87–2.90 (m, 1H) | 2.76–2.82 (m, 1H) |
| 3.84 (s, 3H) | 3.84 (s, 3H) | 3.86 (s, 3H) |
| 3.86–3.87 (m, 1H) | 3.86–3.87 (m, 1H) | 4.43 (dd, $J$=9.2, 6.1 Hz, 1H) |
| 5.62 (s, 1H) | 5.62 (s, 1H) | 5.88 (s, 1H) |
| 6.68–6.76 (m, 3H) | 6.68–6.76 (m, 3H) | 6.73–6.94 (m, 3H) |

was prepared by coupling of **9** with phenol under Mitsunobu reaction condition and then subjected to the same palladium-catalyzed reaction condition. Only starting material was recovered after heating for 72 h as shown in Chart 3. Furthermore, treatment of **8** under the same reaction condition except in the absence of $Pd(OAc)_2$ only afforded the starting material from the resulting reaction mixture. Thus, both the palladium and bromo-substituent are essential for this unusual rearrangement. Shown in Scheme 3 is the proposed mechanism for the palladium-induced rearrangement of compound **8**. Oxidative addition of **8** to the Pd(0) in the presence of ligands, such as $PPh_3$ and bromide anion, gave Pd(II) species **I**. Coordination of the long electron pair of basic nitrogen atom to Pd provided species **II**. Then an unusual Claisen rearrangement of **II** including a [3,3]-sigmatropic-rearrangement and a rearomatization of the unstable intermediate **III** gave species **IV**. Hydrolysis of **IV** provided product **11**.

The failure of the Heck reaction and the undesired rearrangement may be due to the basic amino group in compounds **8** and **10**. Therefore, a modified synthetic pathway using carbamate **2** as key intermediate for the palladium-catalyzed cyclization reaction was developed (Scheme 4). Treatment of compound **13**[18] with 2-iodo-6-methoxyphenol[14] under Mitsunobu conditions provided

**Table 2.** The $^{13}C$ NMR spectral data ($\delta$, ppm) of compounds **11**, '**7**',[14] and **7**

| **11** | '**7**'[14] | **7** |
|---|---|---|
| 19.8 | 19.7 | 22.6 |
| 25.4 | 25.5 | 29.2 |
| 33.0 | 29.6, 33.1 | 29.6 |
| 35.9 | 35.8 | 37.0 |
| 45.3 | 45.4 | 42.9 |
| 55.8 | 55.8 | 45.8 |
| 57.2 | 57.3 | 46.6 |
| 64.7 | 64.8 | 55.8 |
| 77.2 | — | 90.6 |
| 108.4 | 108.5 | 106.6 |
| 118.2 | 118.2 | 111.3 |
| 122.4 | 122.5 | 116.7 |
| 123.6 | 123.7 | 120.5 |
| 131.0 | 131.0 | 134.2 |
| 140.0 | 140.0 | 138.1 |
| 145.1 | 145.0 | 145.1 |
| 148.5 | 148.5 | 146.0 |

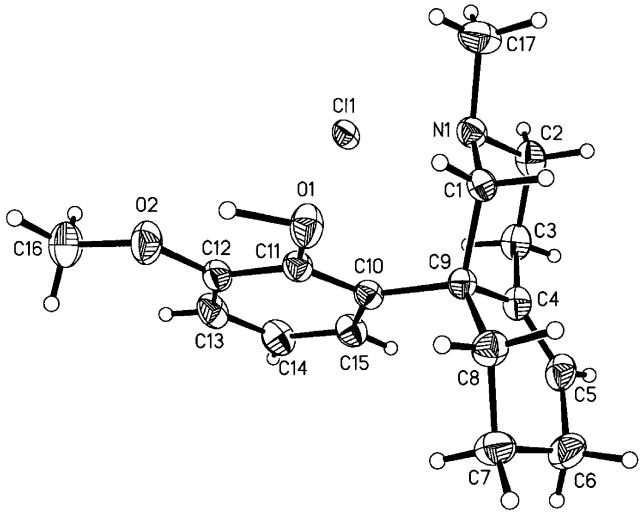



**Figure 1.**

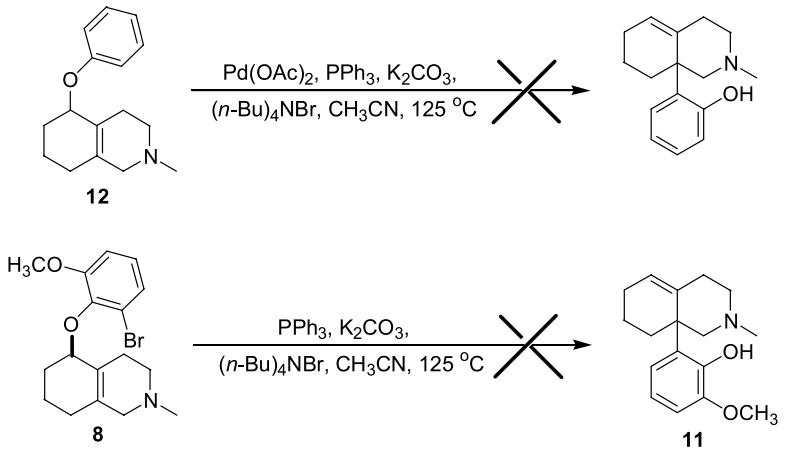
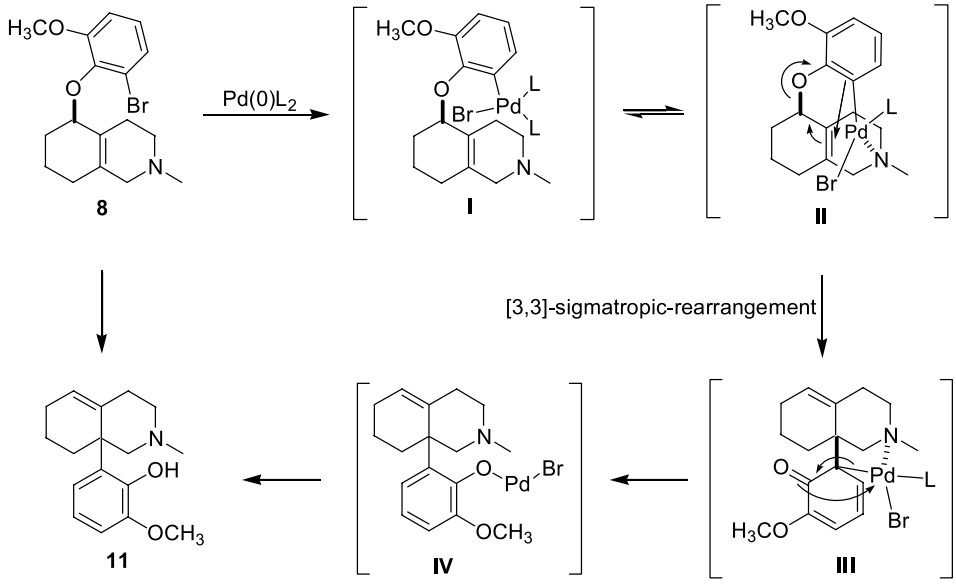
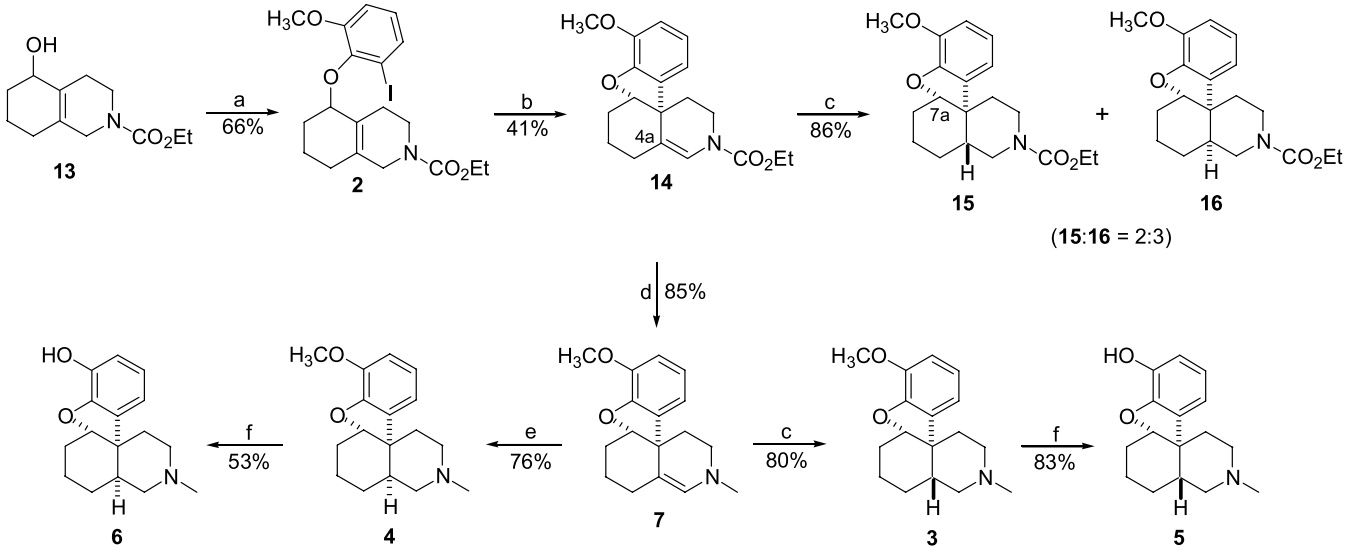



**Chart 3.**




**Scheme 3.**




**Scheme 4.** Reagents and conditions: (a) 2-iodo-6-methoxyphenol, DEAD, $Bu_3P$, THF, rt; (b) $Pd(OAc)_2$, $PPh_3$, $K_2CO_3$, $(n\text{-}Bu)_4NBr$, $CH_3CN$, 125 °C; (c) $H_2$, $PtO_2$, EtOH, rt; (d) $LiAlH_4$, ether, rt; (e) $CH_3SO_3H$, $NaBH_4$, MeOH, rt; (f) $BBr_3$–$(CH_3)_2S$, $ClCH_2CH_2Cl$, reflux.

carbamate **2**. Compound **2** was subjected to Heck reaction condition using $Pd(OAc)_2$, $PPh_3$, $(n\text{-}Bu)_4NBr$, and $K_2CO_3$ in acetonitrile at 125 °C in a sealed bottle and the tetracyclic (ACNO) carbamate **14** was successfully afforded in 41% yield. Furthermore, there was no rearrangement product observed in the crude reaction mixture. This result offered another evidence to support that the basic nitrogen atom is essential for the rearrangement.

Another task in this paper is the stereoselective establishment of the chirality of C-4a. Previously, catalytic hydrogenation was used to stereoselectively introduce H-4a into the 7-oxygenated ACNO derivatives.[11] Therefore, compound **14** was hydrogenated over platinum oxide ($PtO_2$). However, a mixture of the *trans*-carbamate **15** and *cis*-carbamate **16** in a ratio of 2:3 (the ratio was determined based on the H-7a signals in the $^1H$ NMR spectrum) was afforded. Thus, the carbamate group of **14** was removed using $LiAlH_4$ in THF to provide enamine **7**.

As mentioned above, the disappearance of the characteristic H-7a and C-7a signals in the NMR spectra of compound **11** led us to discover the unusual rearrangement and the correct structure of **11**. Therefore, the NMR spectra of enamine **7** are compared with those of compound **11**: (i) compound **7** shows a characteristic double doublet at $\delta$ 4.43 for H-7a and a tertiary carbon peak at $\delta$ 90.6 for C-7a, whereas compound **11** does not show any corresponding signals; (ii) the *N*-methyl proton signal of enamine **7** is significantly more downfield than that of amine **11** ($\delta$ 2.60 and 2.26, respectively); (iii) in DEPT spectra, enamine **7** displays five $CH_2$ and five CH carbon signals, whereas compound **11** possesses six $CH_2$ and four CH carbon signals.

Catalytic hydrogenation of enamine **7** over $PtO_2$ in ethanol provided *trans*-decahydroisoquinoline **3** as the major product (i.e. *trans*/*cis*=8:1). Stereoselective synthesis of *cis*-decahydroisoquinoline **4** was achieved by acidic $NaBH_4$ reduction[7] of **7**, which provided *cis*-**4** as the major product (i.e. *trans*/*cis*=1:12). *O*-Demethylation of compounds **3** and **4** using $BBr_3$–$(CH_3)_2S$ in 1,2-dichloroethane gave phenols *trans*-**5** and *cis*-**6**, respectively.

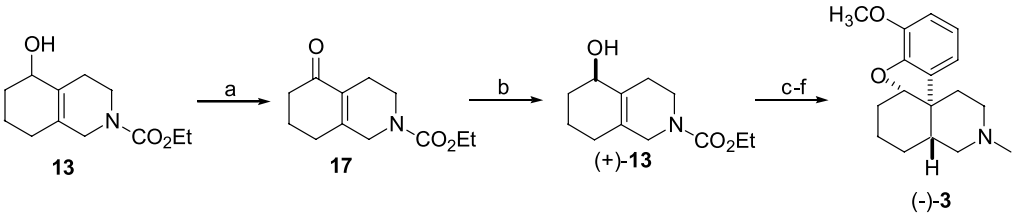
Another attractive advantage of this synthetic strategy is the feasibility of asymmetric synthesis of chiral ACNO derivatives. In our preliminary results, oxidation of racemic carbamate **13** with activated $MnO_2$ afforded ketone **17**. Asymmetric reduction of **17** with (*S*)-2-methyl-CBS-oxazaborolidine[19,20] gave optically active carbamate (+)-**13** in a moderate yield and in 64% ee as shown in Scheme 5. The chirality in (+)-**13** was then used to control the chirality of other chiral centers formed in the following steps by its directing effects. Thus, optically active (−)-**3** was successfully prepared starting from (+)-**13** via the same reaction sequence for the synthesis of racemic **3**. The hydrochloride salt of optically active (−)-**3** was recrystallized to afford optically pure (−)-**3** (ee=100%).

In summary, we have established an efficient and stereoselective synthesis for construction of the ACNO partial structure of morphine. Compounds **3** and **4** with the *trans* and *cis*-C/N ring junctions could be afforded selectively from enamine **7** via catalytical hydrogenation over $PtO_2$ and chemical reduction with acidic $NaBH_4$, respectively. Palladium-catalyzed (Heck) cyclization of carbamate **2** successfully formed the quaternary carbon center and the O ring, and provided compound **14** containing the tetracyclic ACNO skeleton. Treatment of amines **8** or **10** under the same Heck reaction conditions gave compound **11** via an unusual Claisen rearrangement. The detailed mechanism and application of this reaction in organic synthesis are currently under investigation.

## 3. Experimental

### 3.1. General procedures

Melting points were determined on a MEL-TEMP II apparatus by Laboratory Devices and are uncorrected. NMR spectra were recorded on Bruker DPX-200 and AMX-400 FT-NMR spectrometers. Chemical shifts are expressed in parts per million (ppm) on the $\delta$ scale relative to a tetramethylsilane (TMS) internal standard. Mass spectra were recorded on a Jeol JMS-D300 mass spectrometer. High-resolution mass spectroscopy (HRMS) measurements were obtained using a Jeol-HX110 mass spectrometer. Elemental analyses were performed with a Perkin–Elmer 2400-CHN instrument, and were within $\pm$0.4% for the elements indicated. The enantiomeric excess (ee) values were determined by HPLC based on the UV absorption areas of the two enantiomers using a chiral column (Daicel chiralcel OD, 0.46 cm×25 cm), a flow rate of 1 mL/min, and 1∼10% 2-propanol in *n*-hexane with 0.2% diethylamine as the mobile phase. Thin-layer chromatography (TLC) was performed on Merck (art. 5554) 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 μm silical gel 60. Anhydrous tetrahydrofuran was distilled from sodium-benzophenone prior to use. No attempt was made to optimize yields.




**Scheme 5.** Reagents and conditions: (a) $MnO_2$, $CH_2Cl_2$, reflux; (b) $BH_3$, (*S*)-MeCBS, THF, rt; (c) 2-iodo-6-methoxyphenol, DEAD, $Bu_3P$, THF, rt; (d) $Pd(OAc)_2$, $PPh_3$, $K_2CO_3$, $(n\text{-}Bu)_4NBr$, $CH_3CN$, 125 °C; (e) $LiAlH_4$, ether, rt; (f) $H_2$, $PtO_2$, EtOH, rt.

**3.1.1. 5-(2-Iodo-6-methoxyphenoxy)-2-methyl-1,2,3,4,5,6,7,8-octahydroisoquinoline (10).** To a stirred solution of **9** (429 mg, 2.56 mmol), tributylphosphine (1.9 mL, 5.13 mmol), and 2-iodo-6-methoxyphenol[14] (1.92 g, 5.13 mmol) in dry THF (10 mL) was added diethyl azodicarboxylate (DEAD, 5.13 mmol) dropwise at rt. After 40 min, the solvent was evaporated and the residue was chromatographed (silica gel; $NH_4OH/CH_3OH/CH_2Cl_2$ 0.6:5.4:94) to afford **10** (886 mg, 86%) as a pale yellow oil; $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 1.39–1.62 (m, 2H), 1.89–1.91 (m, 2H), 1.96–2.20 (m, 2H), 2.25–2.32 (m, 1H), 2.31 (s, 3H), 2.35–2.39 (m, 1H), 2.60–2.73 (m, 3H), 2.91 (d, $J$=15.7 Hz, 1H), 3.76 (s, 3H), 4.66 (s, 1H), 6.69 (t, $J$=8.0 Hz, 1H), 6.82 (dd, $J$=8.2, 1.5 Hz, 1H), 7.31 (dd, $J$=7.8, 1.6 Hz, 1H); $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 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) Calcd for $C_{17}H_{23}INO_2$ $[M+H]^+$ 400.0774, found 400.0783.

**3.1.2. 8a-(2-Hydroxy-3-methoxyphenyl)-1,2,3,4,6,7,8,8a-octahydroisoquinoline (11).** A solution of **8** (130 mg, 0.37 mmol) and a catalytic amount of $Pb(OAc)_2$ (8.3 mg, 0.037 mmol), triphenylphosphine (29.1 mg, 0.11 mmol) and triethylamine (0.15 mL, 1.11 mmol) in dry acetonitrile (11 mL) was heated in a sealed bottle at 125 °C for 38 h. The solvent was evaporated and the residue was treated with EtOAc. The EtOAc solution was washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$), filtered, and evaporated. The crude residue was chromatographed (silica gel; $CH_3OH/CH_2Cl_2$ 1:15) to afford **11** (40 mg, 40%) as a pale yellow solid; mp 126–128 °C (HCl salt, acetone); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.44–1.54 (m, 3H), 1.96–2.10 (m, 5H), 2.12–2.21 (m, 1H), 2.26 (s, 3H), 2.30–2.34 (m, 1H), 2.87–2.90 (m, 1H), 3.84 (s, 3H), 3.85–3.87 (m, 1H), 5.62 (s, 1H), 6.68–6.76 (m, 3H); $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 19.8, 25.4, 33.0, 35.9, 45.3, 55.8, 57.2, 64.7, 77.2, 108.4, 118.2, 122.4, 123.6, 131.0, 140.0, 145.1, 148.5; HRMS (EI) Calcd for $C_{17}H_{23}NO_2$ $[M]^+$ 273.1729, found 273.1721. Anal. Calcd for $C_{17}H_{23}NO_2 \cdot HCl \cdot H_2O$: C, 62.28; H, 7.99; N, 4.27. Found: C, 62.20; H, 7.83; N, 4.06.

**3.1.3. 2-Methyl-5-phenoxy-1,2,3,4,5,6,7,8-octahydroisoquinoline (12).** To a stirred solution of alcohol **9** (207 mg, 1.24 mmol), tributylphosphine (0.6 mL, 2.48 mmol) and phenol (233 mg, 2.48 mmol) in THF (6 mL) was added dropwise DEAD (1.0 mL, 2.48 mmol) at rt. After 1 h, the mixture was evaporated and the residue was chromatographed (silica gel; 6% $CH_3OH$ in $CH_2Cl_2$) to afford **12** (187 mg, 62%) as a yellow oil; $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 1.57–1.79 (m, 3H), 1.81–2.06 (m, 3H), 2.08–2.24 (m, 1H), 2.27–2.43 (m, 2H), 2.36 (s, 3H), 2.52–2.77 (m, 2H), 2.96 (d, $J$=15.8 Hz, 1H), 4.50 (s, 1H), 6.85–6.96 (m, 3H), 7.20–7.30 (m, 2H); $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 17.8, 27.5, 27.6, 27.7, 45.6, 52.3, 58.3, 73.2, 116.0, 120.6, 125.8, 129.4, 132.9, 158.6; HRMS (EI) Calcd for $C_{16}H_{21}NO$ $[M]^+$ 243.1623, found 243.1628.

**3.1.4. 5-(2-Iodo-6-methoxy-phenoxy)-3,4,5,6,7,8-hexahydro-1*H*-isoquinoline-2-carboxylic acid ethyl ester (2).** To a stirred solution of alcohol **13** (1.85 g, 8.2 mmol), tributylphosphine (6.1 mL, 24.6 mmol) and 2-iodo-6-methoxyphenol (6.15 g, 24.6 mmol) in dry THF (60 mL) was added dropwise DEAD (24.6 mmol) at rt and stirred for 1 h. The solvent was evaporated and the residue was chromatographed (silica gel; 25% EtOAc in *n*-hexane) to afford **2** (2.47 g, 66%) as a pale yellow oil; $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 1.25 (t, $J$=7.1 Hz, 3H), 1.37–1.62 (m, 2H), 1.95–2.13 (m, 5H), 2.56–2.64 (m, 1H), 3.43–3.75 (m, 1H), 3.75–3.90 (m, 3H), 3.80 (s, 3H), 4.13 (q, $J$=7.1 Hz, 2H), 4.67 (s, 1H), 6.72 (t, $J$=7.9 Hz, 1H), 6.84 (dd, $J$=7.9, 1.3 Hz, 1H), 7.33 (dd, $J$=7.9, 1.3 Hz, 1H); $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 14.8, 18.4, 26.8, 27.5, 28.3, 40.9, 46.7, 55.5, 61.1, 77.2, 93.6, 112.5, 125.2, 127.3, 131.1, 132.1, 147.3, 152.6, 155.5; HRMS (FAB) Calcd for $C_{19}H_{25}INO_4$ $[M+H]^+$ 458.0828, found 458.0826.

**3.1.5. 9-Methoxy-2,3,5,6,7,7a-hexahydro-1*H*-benzo[4,5]-furo[3,2-*e*]isoquinoline-3-carboxylic acid ethyl ester (14).** A solution of **2** (450 mg, 0.98 mmol) and a catalytic amount of $Pb(OAc)_2$ (22 mg, 0.098 mmol), triphenylphosphine (77 mg, 0.29 mmol), $K_2CO_3$ (813 mg, 5.88 mmol) and $(n\text{-}Bu)_4NBr$ (630 mg, 1.96 mmol) in dry acetonitrile (40 mL) was heated in a sealed bottle at 125 °C for 36 h. The solvent was evaporated and the residue was treated with EtOAc. The EtOAc solution was washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, filtered, and evaporated. The crude residue was chromatographed (silica gel; 17% EtOAc in *n*-hexane) to afford **14** (132 mg, 41%) as a colorless oil; $R_f$ 0.41 (40% EtOAc in *n*-hexane); $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 1.22–1.34 (q, $J$=7.3 Hz, 3H), 1.40–1.53 (m, 1H), 1.61–1.73 (m, 2H), 1.80 (dd, $J$=13.1, 4.0 Hz, 1H), 1.89–1.95 (m, 2H), 2.05 (m, 2H), 3.11–3.24 (m, 1H), 3.85 (s, 3H), 3.95–4.02 (m, 1H), 4.16–4.26 (m, 2H), 4.46 (dd, $J$=9.5, 6.3 Hz, 1H), 6.66 (dd, $J$=5.9, 2.5 Hz, 1H), 6.76–6.81 (m, 2H), (6.87, 6.98) (s, 1H); $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 14.5, 22.0, 29.3, 29.7, 35.3, (38.3, 38.5), (46.8, 46.9), 55.9, (61.8, 61.9), 90.1, 111.8, (114.9, 115.3), 116.5, 120.9, (121.6, 122.1), 135.6, 145.4, 146.1, (153.1, 153.5); HRMS (EI) Calcd for $C_{19}H_{23}NO_4$ $[M]^+$ 329.1627, found 329.1620 (since the carbamate group in compound **14** could adopt either a *cis* or *trans* configuration, some of the $^1$H and $^{13}$C signals appear as pairs).

**3.1.6. 9-Methoxy-3-methyl-2,3,5,6,7,7a-hexahydro-1*H*-benzo[4,5]furo[3,2-*e*]isoquinoline (7).** To a stirred solution of $LiAlH_4$ in diethyl ether (0.53 M, 1.5 mL) was added a solution of **14** (127 mg, 0.39 mmol) in diethyl ether (2 mL). The mixture was stirred at rt for 1 h, and then a solution of 20% $H_2O$ in THF was added and stirred for 10 min. To the solution was added 40% aqueous NaOH, and then the resulting mixture was stirred for another 10 min, dried over $MgSO_4$, filtered, and evaporated. The crude residue was chromatographed (silica gel; 30% EtOAc in *n*-hexane) to afford **7** (90 mg, 85%) as a pale yellow oil; $R_f$ 0.33 (40% EtOAc in *n*-hexane); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.10–1.26 (m, 1H), 1.35–1.45 (m, 1H), 1.55–1.62 (m, 1H), 1.78–1.89 (m, 3H), 1.91–1.96 (m, 1H), 2.03–2.07 (m, 1H), 2.60 (s, 3H), 2.68–2.74 (m, 1H), 2.76–2.82 (m, 1H), 3.86 (s, 3H), 4.43 (dd, $J$=9.2, 6.1 Hz, 1H), 5.88 (s, 1H), 6.73–6.94 (m, 3H); $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 22.6, 29.2, 29.6, 37.0, 42.9, 45.8, 46.6, 55.8, 90.6, 106.6, 111.3, 116.7, 120.5, 134.2, 138.1, 145.1, 146.0; HRMS (EI) Calcd for $C_{17}H_{21}NO_2$ $[M]^+$ 271.1572, found 271.1568.

**3.1.7. *trans*-9-Methoxy-3-methyl-2,3,4,4aβ,5,6,7,7aβ-octahydro-1*H*-benzo[4,5]furo[3,2-*e*]isoquinoline (3).** A

mixture of **7** (49 mg, 0.18 mmol) and $PtO_2$ (5 mg) in EtOH (3 mL) was shaken in a Parr hydrogenator under 10 bar of $H_2$ at rt for 18 h. The catalyst was removed via filtration through Celite and the filtrate was evaporated. The crude residue was chromatographed (silica gel; $NH_4OH/CH_3OH/CH_2Cl_2$ 0.8:8:92) to afford **3** as a pale yellow solid; mp 189–191 °C (HCl salt, 2-propanol/EtOAc); $R_f$ 0.18 ($NH_4OH/CH_3OH/CH_2Cl_2$ 0.1:1:15); $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 1.10–1.24 (m, 1H), 1.32–1.60 (m, 4H), 1.76–1.83 (m, 2H), 1.93–2.09 (m, 2H), 2.30–2.44 (m, 1H), 2.40 (s, 3H), 2.54 (t, $J$=11.6 Hz, 1H), 2.65–2.77 (m, 2H), 3.87 (s, 3H), 4.48 (t, $J$=5.6 Hz, 1H), 6.78–6.81 (m, 2H), 7.12 (t, $J$=4.3 Hz, 1H); $^{13}C$ NMR (50 MHz, $CDCl_3$) $\delta$ 19.8, 24.5, 28.1, 39.3, 39.4, 46.1, 48.0, 50.9, 55.7, 57.3, 89.4, 111.0, 119.5, 119.6, 133.0, 145.2, 148.4; HRMS (EI) Calcd for $C_{17}H_{23}NO_2$ $[M]^+$ 273.1729, found 273.1724. Anal. Calcd for $C_{17}H_{23}NO_2 \cdot HCl$: C, 65.90; H, 7.81; N, 4.52. Found: C, 65.76; H, 8.02; N, 4.26. Optically active (−)-**3** was dissolved in a solution of HCl in $CH_2Cl_2$, and then evaporated to provide (−)-**3**·HCl. Recrystallization of the hydrochloride salt of (−)-**3** afforded optically pure (−)-**3**·HCl (ee=100.0%): $[\alpha]_D = -35.6°$ ($c$=0.58, MeOH).

**3.1.8. *cis*-9-Methoxy-3-methyl-2,3,4,4aα,5,6,7,7aβ-octahydro-1*H*-benzo[4,5]furo[3,2-*e*]isoquinoline (4).** To a stirred solution of compound **7** (170 mg, 0.626 mmol) in MeOH (10 mL) cooled in an ice bath was added methanesulfonic acid (66 mg, 0.689 mmol) and the ice bath was removed after 5 min. Ten minutes later the mixture was again cooled in an ice bath, and $NaBH_4$ (284 mg, 7.51 mmol) was then added in portions over 1 min. The reaction mixture was stirred for 13 h at rt, and then brine (20 mL) was added to the resulting solution followed by 2 M aqueous HCl (9 mL), 3 M aqueous NaOH (20 mL), and $H_2O$ (20 mL). The mixture was extracted with $CHCl_3$ (50 mL×2). The combined organic layer was dried over $MgSO_4$, filtered, and evaporated. The crude residue was chromatographed (silica gel; $NH_4OH/CH_3OH/CH_2Cl_2$ 0.5:5.5:94) to afford **4** (130 mg, 76%) as a colorless oil; mp 246 °C (HCl salt, 2-propanol/EtOAc); $R_f$ 0.38 ($NH_4OH/CH_3OH/CH_2Cl_2$ 0.1:1:15); $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 1.46–1.50 (m, 1H), 1.63–1.80 (m, 7H), 1.95–2.17 (m, 2H), 2.32 (s, 3H), 2.39–2.47 (m, 1H), 2.54–2.75 (m, 2H), 3.87 (s, 3H), 4.30 (s, 1H), 6.75–6.90 (m, 2H), 7.08–7.12 (m, 1H); HRMS (EI) Calcd for $C_{17}H_{23}NO_2$ $[M]^+$ 273.1729, found 273.1727.

**3.1.9. *trans*-9-Hydroxy-3-methyl-2,3,4,4aβ,5,6,7,7aβ-octahydro-1*H*-benzo[4,5]furo[3,2-*e*]isoquinoline (5).**[4,10] A solution of **3** (51 mg, 0.19 mmol) and $BBr_3$–$(CH_3)_2S$ (0.9 mmol) in $ClCH_2CH_2Cl$ (18 mL) was brought to reflux for 3 h, and then cooled to rt. The reaction mixture was treated with $H_2O$ and basified to pH=9 with saturated aqueous $Na_2CO_3$. The solution was extracted with a solution of 2-propanol and $CH_2Cl_2$ (1:4, 75 mL×3). The organic layer was dried over $MgSO_4$, filtered, and evaporated. The crude residue was chromatographed (silica gel; $NH_4OH/CH_3OH/CH_2Cl_2$ 1.4:12.6:86) to afford **5** (40 mg, 83%) as a colorless oil; mp 268 °C (HCl salt, 2-propanol/EtOAc); $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 1.17–1.23 (m, 2H), 1.40–1.53 (m, 4H), 1.80–1.85 (m, 2H), 1.95–2.01 (m, 2H), 2.41 (s, 3H), 2.35–2.49 (m, 1H), 2.58 (t, $J$=11.8 Hz, 1H), 2.77–2.83 (m, 2H), 4.43 (t, $J$=5.3 Hz, 1H), 6.71–6.76 (m, 2H), 7.00 (dd, $J$=5.3, 3.3 Hz, 1H); $^{13}C$ NMR (50 MHz, $CDCl_3$) $\delta$ 20.3, 24.7, 28.3, 38.8, 39.1, 45.8, 48.4, 50.8, 57.1, 89.3, 115.5, 118.5, 120.1, 132.8, 142.2, 147.3; HRMS (EI) Calcd for $C_{16}H_{21}NO_2$ $[M]^+$ 259.1572, found 259.1562. Anal. Calcd for $C_{16}H_{21}NO_2 \cdot HCl$: C, 64.97; H, 7.50; N, 4.74. Found: C, 64.84; H, 7.47; N, 4.73.

**3.1.10. *cis*-9-Hydroxy-3-methyl-2,3,4,4aα,5,6,7,7aβ-octahydro-1*H*-benzo[4,5]furo[3,2-*e*]isoquinoline (6).** A solution of **4** (52 mg, 0.19 mmol) and $BBr_3$–$(CH_3)_2S$ (0.9 mmol) in $ClCH_2CH_2Cl$ (18 mL) was heated to reflux for 3 h, and then cooled to rt. The reaction mixture was treated with $H_2O$ and basified to pH=9 with $NH_4OH_{(conc.)}$. The solution was extracted with a solution of 2-propanol and $CH_2Cl_2$ (1:4, 75 mL×3). The organic layer was dried over $MgSO_4$, filtered, and evaporated. The crude residue was chromatographed (silica gel; $NH_4OH/CH_3OH/CH_2Cl_2$ 1.4:12.6:86) to afford **6** (26 mg, 53%) as a colorless oil; mp 276–278 °C (HCl salt, 2-propanol/EtOAc); $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 1.49–1.82 (m, 8H), 1.98–2.06 (m, 2H), 2.33 (s, 3H), 2.40–2.44 (m, 1H), 2.52–2.70 (m, 3H), 4.30 (s, 1H), 6.71–6.76 (m, 2H), 7.00 (t, $J$=4.3 Hz, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 20.2, 26.4, 26.5, 30.6, 38.6, 44.8, 46.7, 53.4, 57.6, 87.7, 115.0, 116.2, 120.9, 138.6, 141.3, 145.6; HRMS (EI) Calcd for $C_{16}H_{21}NO_2$ $[M]^+$ 259.1572, found 259.1571.

**3.1.11. 5-Oxo-3,4,5,6,7,8-hexahydro-1*H*-isoquinoline-2-carboxylic acid ethyl ester (17).** To a stirred solution of **13** (4.00 g, 17.8 mmol) in $CH_2Cl_2$ (250 mL) was added activated $MnO_2$ (46.0 g, 450 mmol) by portions. The mixture was stirred at rt for 48 h, filtered through Celite and the filtrate was evaporated. The residue was chromatographed (silica gel; $CH_3OH/CH_2Cl_2$ 1:20) to afford **17** (2.88 g, 43%) as a yellow oil; $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 1.18 (t, $J$=7.1 Hz, 3H), 2.01–2.05 (m, 2H), 2.29–2.34 (m, 4H), 2.45 (t, $J$=6.1 Hz, 2H), 3.54 (t, $J$=5.7 Hz, 2H), 4.05 (s, 2H), 4.17 (q, $J$=7.1 Hz, 2H); $^{13}C$ NMR (50 MHz, $CDCl_3$) $\delta$ 14.4, 21.6, 22.0, 27.7, 37.4, 40.2, 46.6, 61.2, 130.2, 152.2, 155.1, 197.4; HRMS (EI) Calcd for $C_{12}H_{17}NO_3$ $[M]^+$ 223.1208, found 223.1209.

## Acknowledgements

We acknowledge the National Science Council of the Republic of China (Grant No. NSC 91-2320-B-002-205) for partial financial support of this work.

## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2004.10.067.

## References and notes

1. Willette, R. E. Analgesic Agents. In *Wilson and Gisvold's*

*Textbook of Organic Medicinal and Pharmaceutical Chemistry*, 10th ed.; Delgado, J. N., Remers, W. A. Eds.; Lippincott-Raven: Philadelphia, 1998; pp 687–708.
2. Fries, D. S. Opioid Analgesics. In *Foye's Principles of Medicinal Chemistry*, 5th ed.; Lemke, T. L., Williams, D. A., Eds.; Lippincott Williams & Wilkins, 2002; pp 453–479.
3. Michne, W. F. Chemistry of Opiate Analgesics and Antagonists. In *Analgesics: Neurochemical, Behavioral, and Clinical Perspectives*; Kuhar, M., Pasternak, G., Eds.; Raven: New York, 1984; pp 125–148.
4. Ciganek, E. *J. Am. Chem. Soc.* **1981**, *102*, 6261–6262.
5. Ciganek, E. U.S. Patent 4,243,668, 1981; *Chem. Abstr.* **1981**, *95*, 809241.
6. Schultz, A. G.; Lucci, R. D. *J. Chem. Soc., Chem. Commun.* **1976**, 925.
7. Moos, W. H.; Gless, R. D.; Rapoport, H. *J. Org. Chem.* **1981**, *46*, 5064–5074.
8. Weller, D. D.; Weller, D. L. *Tetrahedron Lett.* **1982**, *23*, 5239–5242.
9. Weller, D. D.; Stirchak, E. P.; Weller, D. L. *J. Org. Chem.* **1983**, *48*, 4597–4605.
10. Shenvi, A. B.; Ciganek, E. *J. Org. Chem.* **1984**, *49*, 2942–2947.
11. Cheng, C. Y.; Hsin, L.-W.; Tsai, M. C.; Schmidt, W. K.; Smith, C.; Tam, S. W. *J. Med. Chem.* **1994**, *37*, 3121–3127.
12. Hsin, L.-W. Synthesis and Pharmacology of Novel Non-peptide Opioids. Ph.D. Dissertation, June 1995.
13. Cheng, C.-Y.; Hsin, L.-W.; Liou, J.-P. *Tetrahedron* **1996**, *52*, 10935–10944.
14. Cheng, C.-Y.; Liou, J.-P.; Lee, M.-J. *Tetrahedron Lett.* **1997**, *38*, 4571–4574.
15. Srinivas, N. R.; Barbhaiya, R. H.; Midha, K. K. *J. Pharm. Sci.* **2001**, *90*, 1205–1215.
16. Hsin, L.-W.; Dersch, C. M.; Baumann, M. H.; Horel, R.; Stafford, D.; Glowa, J. R.; Rothman, R. B.; Jacobson, A. E.; Rice, K. C. *J. Med. Chem.* **2002**, *45*, 1321–1329.
17. Hsin, L.-W.; Prisinzano, T.; Wilkerson, C. R.; Dersch, C. M.; Horel, R.; Jacobson, A. E.; Rothman, R. B.; Rice, K. C. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 553–556.
18. Liou, J.-P.; Cheng, C.-Y. *Tetrahedron Lett.* **2000**, *41*, 915–918.
19. Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986–2012.
20. Nettles, S. M.; Matos, K.; Burkhardt, E. R.; Rouda, D. R.; Corella, J. A. *J. Org. Chem.* **2002**, *67*, 2970–2976.