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

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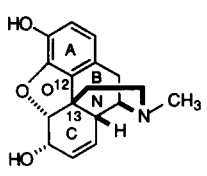
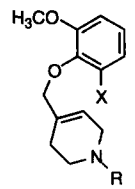
Abstract: As a better alternative to radical cyclization, 5-(2-bromo-6-methoxyphenoxy)-2-methyl-1,2,3,4,5,6,7,8-octahydroisoquinoline (**2**) and its 1-oxo analog **3** underwent Pd-catalyzed intramolecular cyclization to give the tetracyclic (ACNO) morphine fragments **5** and **6** respectively. 4-[(2'-Iodo-6'-methoxyphenoxy)methyl]-1-ethoxycarbonyl-1,2,5,6,-tetrahydropyridine (**11**) reacted similarly to provide the tricyclic ANO fragment **12** in 70% yield and 45% e.e. when a Pd-(S)-BINAP complex was used as the catalyst.

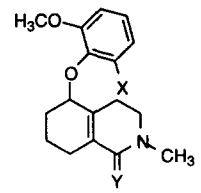
Although the first total synthesis of morphine was reported more than 40 years ago by Gates and Tschudi,[1] the rigid pentacyclic (ABCNO) structure of morphine continues to attract the efforts of modern synthetic chemists.[2] Among the published total syntheses of morphine, the one reported by Parker et al.[3] was the first that utilized a radical approach, in which the O and B rings were formed via tandem radical cyclization. Recently we have developed a facile construction of morphine ANO and ACNO fragments via intramolecular radical cyclization of 4-[(2'-bromophenoxy)methyl]-1,2,5,6-tetrahydropyridine **1** and the corresponding 1,2,3,4,5,6,7,8-octahydroisoquinolines **2** and **3** respectively,[4] during our efforts to explore the structure-activity relationship of the relatively less-explored oxide-containing fragments of morphine.[5] Hudlicky et al.[6] recently reported a chemoenzymatic synthesis of the morphine skeleton, using a similar radical approach for the formation of C_{12}-C_{13} bond.



Morphine



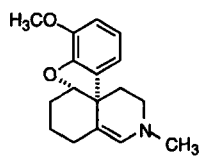
1 : X = Br ; R = CH_3
10 : X = I ; R = CH_3
11 : X = I ; R = CO_2Et



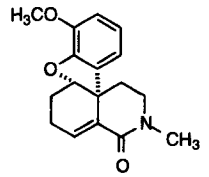
2 : X = Br; Y = H_2
3 : X = Br; Y = O
4 : X = I; Y = H_2

As a continuation to our efforts in this area, we now report that, for the synthesis of morphine ANO and ACNO fragments, the key furan-forming step can also be achieved via a Pd-catalyzed intramolecular cyclization of basically the same intermediates used in our previously described radical cyclizations.[7] A total synthesis of morphine via the Heck cyclization of a benzylisoquinoline intermediate has been reported by Overman et al.[8] Recent developments in the synthesis of morphine partial structures include a novel indolenine approach to the ACNO fragment.[9]

Since the radical cyclization of compounds **2** and **3** was accompanied by the undesired 1,5-hydrogen abstraction,[4] we first focused our efforts on the Pd-catalyzed intramolecular cyclization of these two intermediates. When a solution of compound **2** in acetonitrile was heated in a sealed vessel at 120 °C in the presence of $Pd(OAc)_2$ (5 mol%), $P(C_6H_5)_3$ (20 mol%), and triethylamine for 24 h, the desired cyclization product **5** was obtained in 48% yield as the only identifiable product. [10] When the iodo analog **4** was subjected to the same cyclization conditions, the yield of **5** was raised to 72%. It is noteworthy that compounds **2** and **4**, being unprotected amines, underwent the intramolecular Heck reaction without much complication, since most literature examples of alkaloid synthesis via Heck reaction involved neutral amide or carbamate intermediates.[11] However, when we subjected the neutral lactam intermediate **3** to the above reaction conditions at a slightly higher temperature (130 °C), the yield of the corresponding ACNO fragment **6** remained a modest 43%.[10]



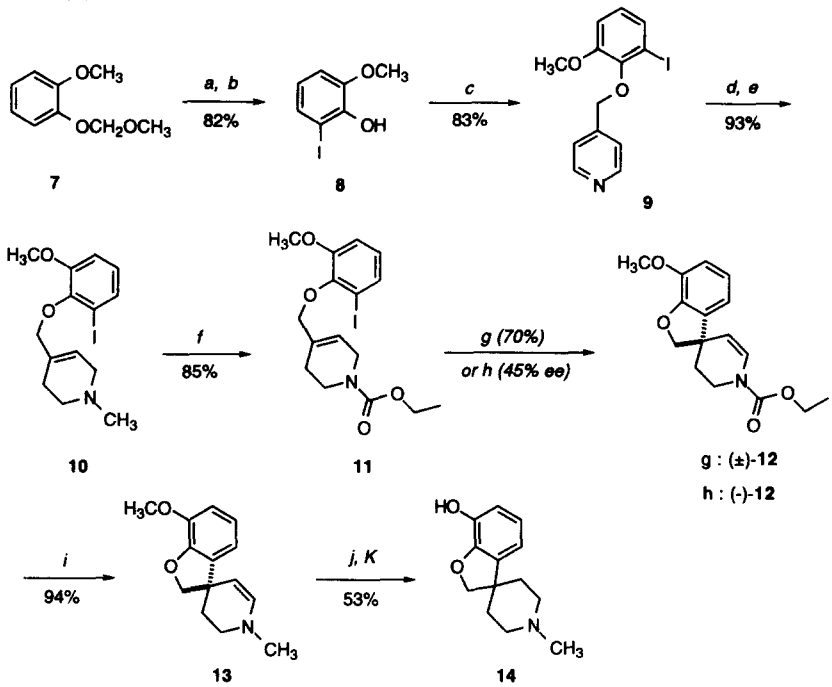
5 (48% from **2** or 72% from **4**)



6 (43% from **3**)

We then turned our attention to the synthesis of the ANO fragment **13** via Heck cyclization. (Scheme 1) Compound **13** has an enamine function, and is well suited to serve as an intermediate for the preparation of pharmacologically interesting morphine ANO fragments with substitution on the piperidine (N) ring[12] and the ABNO fragment. To anticipate better reactivity with the Pd catalyst so that milder reaction conditions can be attempted for the asymmetric versions of the Heck cyclization described below, 6-bromoguaiacol was replaced with 6-iodoguaiacol (**8**), which was prepared from MOM-protected guaiacol (**7**) via ortho-lithiation followed by iodination. Compound **8** was then coupled with 4-picolyl chloride and further converted to tetrahydropyridine **10** as shown. In contrast to what's observed with compounds **2** and **4**, when amine **10** was subjected to Heck reaction conditions, only un-identifiable products were obtained, probably due to the reactive nature of the enamine intermediate formed during the reaction. Therefore, compound **10** was converted to the neutral carbamate **11**, which then underwent the desired Pd-catalyzed cyclization to provide the ANO fragment **12** in 70% yield.[10] LAH reduction of **12** then delivered the enamine intermediate **13**. Among the possibilities for further transformation, compound **13** has been converted to the morphine ANO partial structure **14**[13] via $NaBH_4$ reduction followed by O-demethylation. Since compound **12** has a chiral center at C-4, the feasibility of asymmetric induction during the intramolecular cyclization of **11** to **12** has been examined with chrial Pd(BINAP[14]) complexes as catalysts.[15] The enantiomeric excess obtained with (S)-BINAP, tris(dibenzylideneacetone)dipalladium, and Ag_3PO_4 was 45-50%.[16]

Scheme 1



Scheme 1 (*a*) n-BuLi, THF, I_2, -40 °C. (*b*) 6 N HCl. (*c*) 4-picolyl chloride, K_2CO_3, acetone, reflux. (*d*) CH_3I, CH_2Cl_2, r.t. (*e*) $NaBH_4$, CH_3OH, r.t. (*f*) $ClCO_2Et$, $KHCO_3$, $ClCH_2CH_2Cl$, reflux. (*g*) $Pd(OAc)_2$ (10 mole %), PPh_3 (40 mole %), 2 eq Ag_2CO_3, THF, 120-130 °C. (*h*) $Pd(dba)_2$ (10 mole %), (S)-BINAP (20 mole %), 2 eq Ag_3PO_4, DMA, 50 °C. (*i*) $LiAlH_4$, Et_2O , r.t. (*j*) $NaBH_4$, CH_3COOH, r.t. (*k*) BBr_3, $(CH_3)_2S$, $ClCH_2CH_2Cl$

In summary, we have demonstrated that intramolecular Heck reaction can be effectively applied to the construction of morphine ANO and ACNO fragments. Notable features not obtainable with the corresponding radical cyclizations are the presence of a C-C double bond in the products and the possibility of asymmetric induction. Further derivatization based on these features, including the synthesis of an ABNO fragment, is currently being explored in our laboratory.

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10. Selected spectral and analytical data : **5**: pale yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44-1.54 (m, 3H), 1.96-2.10 (m, 4H), 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), 3.86-3.87 (m, 1H), 5.62 (s, 1H), 6.68-6.76 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.7, 25.5, 29.6, 33.1, 35.8, 45.4, 55.8, 57.3, 64.8, 108.5, 118.2, 122.5, 123.7, 131.0, 140.0, 145.0, 148.5; MS (EI, 70 eV) *m/e* calc'd for $C_{17}H_{21}NO_2^+$: 271.1590, found 271.1566. **6**: white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.80-2.10 (m, 4H), 2.17-2.32 (m, 2H), 3.09 (s, 3H), 3.27 (qd, *J* = 12.8, 6.1, 1.2 Hz, 1H), 3.59 (td, *J* = 12.4, 5.4 Hz, 1H), 3.85 (s, 3H), 4.63 (dd, *J* = 7.6, 4.6 Hz, 1H), 6.57 (dd, *J* = 6.2, 2.1 Hz, 1H), 6.77 (m, 2H), 7.01 (t, *J* = 4.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 24.8, 33.4, 34.7, 45.6, 47.1, 55.9, 87.6, 111.7, 116.6, 121.3, 131.4, 132.4, 135.2, 145.2, 146.7, 164.1; MS (EI, 70 eV) *m/e* calc'd for $C_{17}H_{19}NO_3^+$: 285.1365, found 285.1378. (±)-**12**: oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (dd, *J* = 8.5, 8.2 Hz, 1H), 6.91-6.69 (m, 3H), 4.86 (dd, *J* = 8.7, 8.3 Hz, 1H), 4.34 (d, *J* = 8.9 Hz, 2H), 4.24 (q, *J* = 7.1 Hz, 2H), 3.94-3.84 (m, 1H), 3.85 (s, 3H), 3.54-3.41 (m, 1H), 2.00-1.80 (m, 2H), 1.29 (t, *J* = 3.54 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (157.5, 156.3), 147.7, 144.7, 135.5, (127.1, 126.6), 121.5, 115.8, 111.7, (108.4, 108.2), 82.8, 62.1, 56.0, 44.9, (39.4, 39.2), 33.8; MS (EI, 70 eV) *m/e* calc'd for $C_{16}H_{19}NO_4^+$: 289.13425, found 289.1314. (Since the carbamate function in **12** adopts a *cis* or *trans* conformation, some of the ^{13}C signals appear as pairs.)
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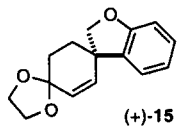
16. The e.e. was determined by HPLC analysis: ChiralCel OD; hexane/isopropanol = 9:1; UV: 254 nm; flow rate: 0.8 mL/min. The absolute configuration of (-)-**12** was assigned based on analogy with (+)-**15**, which was synthesized in 49-55% e.e. under similar reaction conditions with (R)-(+)-BINAP. See: Ashimori, A.; Overman, L. E. *J. Org. Chem.* **1992**, *57*,4571-4572.



(+)-**15**

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