Pergamon

Tetrahedron Letters, Vol. 38, No. 49, pp. 8439-8442, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)10274-X

Pyridinomorphinans: Asymmetric Synthesis of Either Enantiomer and Opioid Receptor Binding Selectivity

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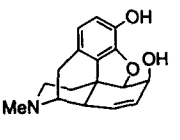
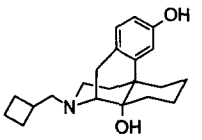
Abstract. Either enantiomer of a new class of morphinans in which the aryl ring is replaced by a pyridine ring can be prepared by sequential iminium ion–allylsilane cyclization and intramolecular Heck insertion. Pyridinomorphinan **5** exhibits high affinity for the μ opioid receptor. © 1997 Elsevier Science Ltd.

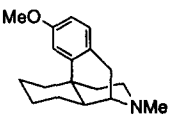
Morphine (**1**), and its simpler morphinan and benzomorphan analogs, remain the most widely used analgesics for the treatment of severe pain.[2] The numerous side effects of opiate narcotics, of which physical dependence is undoubtedly the most serious, continue to stimulate the search for better analgesics.[3] The likelihood that improved analgesics can be found has been heightened by growing understanding of opioid receptor subtypes.[4] Since the first synthesis of morphinans 50 years ago,[5] a wide variety of these tetracyclic congeners of morphine have been prepared and pharmacologically characterized.[6,7] Both enantiomers of morphinans find clinical utility, with butorphanol (**2**), a mixed opioid agonist–antagonist, and dextromethorphan (**3**), an antitussive, being two examples.[2] In this letter, we describe the synthesis and initial pharmacological characterization of representative members of a new family of morphinans (**4**, **5**, and *ent*-**4**) in which the aromatic ring is replaced with a pyridine. To our knowledge, these are the first heteroaromatic morphinans.



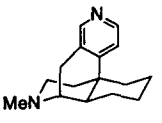
(–)-morphine (**1**)



butorphanol (**2**)



dextromethorphan (**3**)



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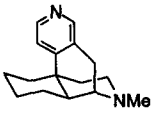
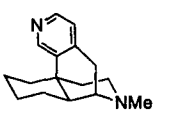


ent-**4**



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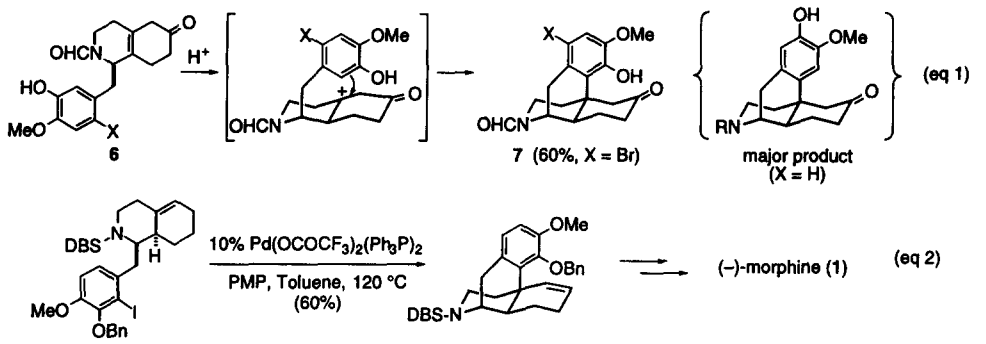
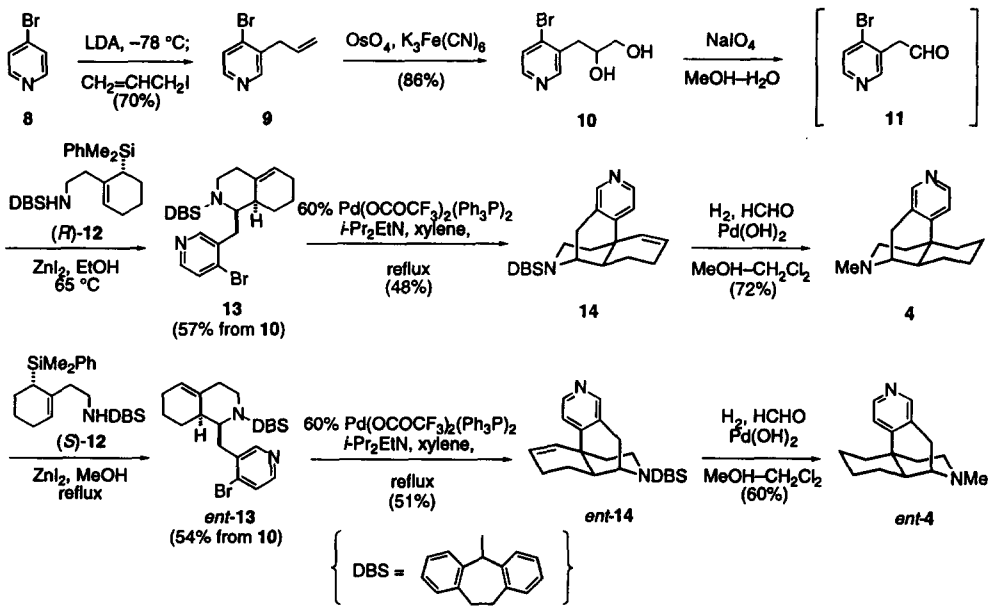
Almost all morphinans synthesized to date contain electron-rich aromatic rings, stemming from their preparation by the route pioneered by Grewe.[5] The intramolecular aromatic substitution step of the Grewe synthesis can be remarkably efficient when the aromatic ring is electron-rich and only a single *ortho* position is available for substitution. This situation is exemplified in the key step (**6** → **7**, eq 1) of Rice's efficient



synthesis of dihydrocodeinone, where the bromine substituent in **6** was incorporated to regulate regioselection.[8] In 1993, we introduced an alternate method to control regiochemistry in the assembly of morphinans which employed an intramolecular Heck cyclization to forge the critical quaternary carbon–aryl bond (eq 2).[9] An additional attraction to this organometallic strategy, which was not illustrated in our earlier work, is its expected applicability for the synthesis of morphinans containing electron-deficient aromatic rings. To exemplify this feature of our sequential iminium ion-allylsilane cyclization–intramolecular Heck asymmetric synthesis strategy and to introduce a structurally unusual family of morphinans, we pursued the enantioselective synthesis of representative pyridinomorphinans.[10]

Since 2-, 3-, and 4-halopyridines can be regioselectively lithiated at low temperature and trapped with reactive electrophiles,[11] we chose these lithium reagents as starting points for assembling the halopyridinyl octahydroisoquinoline Heck cyclization substrates. Lithiation of 4-bromopyridine (**8**), followed by trapping the derived lithium intermediate with allyl iodide at –78 °C provided **9** in moderate yield (Scheme 1).[12] Dihydroxylation of this crude product yielded diol **10**,[13] which could be cleaved with $NaIO_4$ in aqueous methanol to generate bromopyridineacetaldehyde **11**.[14] Although this aldehyde was sufficiently unstable that

Scheme 1

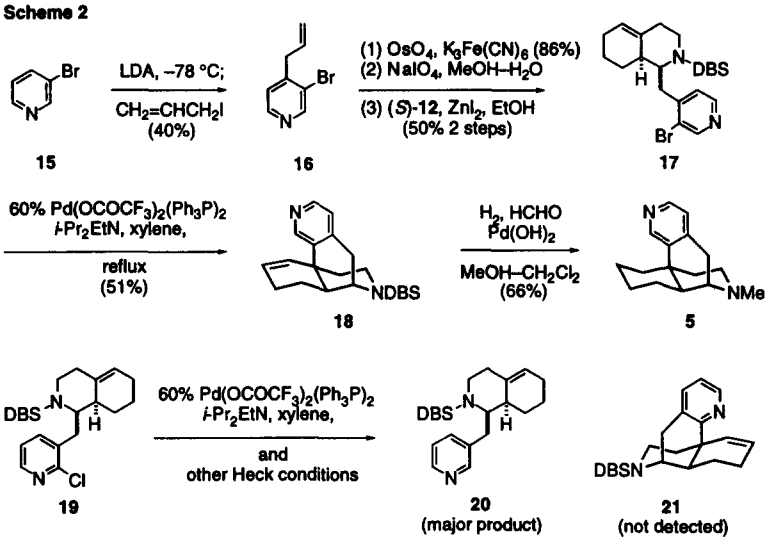


isolation in pure form was difficult, the crude periodate product could be directly coupled in the presence of ZnI_2 with either (*R*)- or (*S*)-allylsilane amines **12**[9,15] to generate enantiomeric octahydroisoquinolines **13** and *ent*-**13**.[16] As in our earlier development of this allylsilane–iminium ion cyclization route to octahydroisoquinolines, only a single stereoisomer was produced, in this case in 50-57% overall yield from diol **10**.[9,17]

Cyclization of **13** was investigated under a variety of standard Heck reaction conditions (Scheme 1). Forcing conditions were required and best results were obtained using 60 mol% of the catalyst generated from the precatalyst $Pd(O_2CCF_3)_2(Ph_3P)_2$ and *i*-Pr_2EtN in xylene at 140 °C. This procedure provided **14** and *ent*-**14** in ~50% yield. These products could be transformed in one step to the *N*-methyl pyridinomorphinans **4** and *ent*-**4** by catalytic hydrogenation in the presence of formalin.[16]

Using an identical strategy, pyridinomorphinan **5** was prepared from 3-bromopyridine (**15**) and (*S*)-**12** as summarized in Scheme 2.[16] Unfortunately, we were not able to access pyridinomorphinan **21** derived from 2-chloropyridine, since attempted Heck cyclizations of octahydroisoquinoline **19** were unsuccessful. That the oxidative addition step was not responsible for this failure is suggested by isolation of reduction product **20**.

Scheme 2



Pyridinomorphinans **4**, *ent*-**4** and **5** were evaluated in ligand binding assays at μ, δ and κ opioid receptors in monkey cortex.[18] Pyridinomorphinan **5** exhibited nanomolar affinity for the μ opioid receptor (EC_{50} = 14 ± 2 nM, ~20 fold lower affinity than the standard μ peptide DAMGO) and showed modest selectivity for this opioid receptor: δ/μ = 70 and κ/μ = 25 (EC_{50} ratios). The other two morphinans showed no binding to the δ and κ receptors and only weak binding to the μ opioid receptor. It is likely significant that the nitrogen of pyridinomorphinan **5** is oriented in the analogous relative position as the phenolic hydroxyl group of morphine. Since affinity to the μ opioid receptor is typically observed in the natural opiate series, the enantiomer of **5** would be expected to exhibit even higher affinity for the μ receptor.[2,3]

In summary, sequential iminium ion–allylsilane cyclization and intramolecular Heck insertion allows morphinans that are not accessible by classical Grewe cyclization to be prepared efficiently and in either enantiomeric series. This strategy can potentially access a wide variety of novel morphinan and opium alkaloid analogs.

Acknowledgment. Support of this investigation by NIH Grant GM-30859 and Roche Biosciences is gratefully acknowledged. NMR and mass spectra were determined at Irvine using instruments acquired with the assistance of the NSF and NIH shared instrumentation programs. We particularly thank Dr. Arthur E.

Jacobsen, Biological Coordinator, Drug Evaluation Committee, College of Problems of Drug Dependence, Inc. and Dr. J. H. Woods, Department of Pharmacology, University of Michigan Medical School for the *in vitro* opioid binding assays and Dr. Kenner Rice, NIDDK, NIH for helpful discussion.

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13. Intermediates were fully characterized by ^{1}H, ^{13}C, IR, and mass spectrometric analysis. The elemental composition of analytical samples of new compounds was confirmed by combustion analysis or high-resolution mass spectrometry. Unless noted otherwise, yields refer to isolated, purified products.
14. Initial attempts to access 2-pyridineacetaldehydes by reaction of pyridyllithium reagents with two carbon electrophiles (e.g., ethylene oxide, methyl α-bromoacetate or bromoacetaldehyde dimethyl acetal) failed.
15. The enantiomeric purity of (*R*)- and (*S*)-**12** was ~90% (Chiracel OJ, 9:1 hexane-EtOH, non-baseline separation).
16. Selected characterization data for key compounds: **13**: $[\alpha]_D^{25}$ +105° (*c* 1.3, $CHCl_3$) and *ent*-**13**: $[\alpha]_D^{25}$ −110° (*c* 1.3, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.46 (m, 1H), 1.57 (m, 2H), 1.70 (m, 1H), 1.77 (d, *J* = 13.8 Hz, 1H), 1.98 (m, 2H), 2.29 (m, 1H), 2.40 (m, 2H), 2.55 (dd, *J* = 5.1, 14.0 Hz, 1H), 2.70 (m, 1H), 2.83-2.88 (m, 2H), 2.95 (dt, *J* = 4.1, 13.5 Hz, 1H), 3.02 (m, 1H), 3.43 (m, 2H), 4.85 (s, 1H), 5.60 (s, 1H), 6.85-7.20 (m, 8H), 7.32 (d, *J* = 5.2 Hz, 1H), 8.15 (s, 1H), 8.20 (d, *J* = 5.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.0, 25.1, 26.0, 29.8, 30.4, 30.8, 31.7, 34.1, 37.2, 42.1, 57.1, 71.1, 121.9, 124.9, 125.6, 127.6, 129.8, 130.0, 130.7, 131.6, 134.4, 135.8, 136.8, 138.6, 139.4, 139.6, 140.2, 147.4, 150.8, 151.6; MS (CI) *m/e* 499.1738 (MH, 499.1749 calcd for $C_{30}H_{32}BrN_2$). **18**: $[\alpha]_D^{25}$ +12° (*c* 1.3, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.20 (m, 1H), 1.35 (m, 1H), 1.45 (d, *J* = 12.5 Hz, 1H), 1.62 (m, 1H), 1.78 (m, 1H), 1.95 (m, 2H), 2.24 (m, 1H), 2.40 (m, 1H), 2.41 (dd, *J* = 6.2, 19.0 Hz, 1H), 2.80-2.90 (m, 3H), 3.17 (d, *J* = 19.0 Hz, 1H), 3.95 and 4.05 (m, 2H), 4.46 (s, 1H), 5.75 (d, *J* = 9.9 Hz, 1H), 6.14 (d, *J* = 9.9 Hz, 1H), 7.00-7.25 (m, 9H), 8.29 (d, *J* = 5.0 Hz, 1H), 8.36 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.2, 23.6, 25.8, 31.4, 31.7, 36.2, 40.3, 42.8, 43.0, 51.9, 74.4, 122.1, 125.3, 125.7, 127.6, 127.7, 129.7, 130.6, 130.8, 131.1, 133.1, 139.3, 139.4, 139.5, 139.7, 146.0, 149.3; MS (CI) *m/e* 419.2461 (MH, 419.2487 calcd for $C_{30}H_{31}N_2$). **4**: $[\alpha]_D^{25}$ −77° (*c* 1.1, $CHCl_3$) and *ent*-**4**: $[\alpha]_D^{25}$ +38° (*c* 0.83, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.02 (dq, *J* = 3.8, 12.9 Hz, 1H), 1.17 (m, 1H), 1.35-1.70 (m, 6H), 1.92 (dt, *J* = 4.5, 13.0 Hz, 1H), 2.11 (d, *J* = 12.9 Hz, 1H), 2.21 (dt, *J* = 2.8, 12.4 Hz, 1H), 2.37 (d, *J* = 14.2 Hz, 1H), 2.51 (s, 3H), 2.63 (m, 1H), 2.74 (dd, *J* = 5.6, 18.8 Hz, 1H), 3.03 (s, 1H), 3.06 (d, *J* = 18.8 Hz, 1H), 7.15 (d, *J* = 5.1 Hz, 1H), 8.39 (br s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.9, 22.1, 26.3, 26.7, 35.7, 37.0, 41.4, 42.8, 44.9, 46.8, 57.3, 120.2, 133.6, 147.6 149.2, 150.0; MS (EI) *m/e* 242.1788 (M, 242.1783 calcd for $C_{16}H_{22}N_2$). **5**: $[\alpha]_D^{25}$ +9.0° (*c* 1.1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.01 (m, 1H), 1.20-1.30 (m, 10H), 2.43 (s, 3H), 2.50 (m, 2H), 2.65 (dd, *J* = 5.5, 19.1 Hz, 1H), 2.91 (s, 1H), 3.01 (d, *J* = 19.1 Hz, 1H), 7.03 (d, *J* = 9.9 Hz, 1H), 8.32 (d, *J* = 5.0 Hz, 1H), 8.48 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.9, 23.7, 26.4, 26.6, 35.6, 35.8, 41.7, 42.7, 45.1, 46.9, 57.5, 122.4, 136.2, 146.3, 146.9, 147.8; MS (CI) *m/e* 243.1860 (MH, 243.1861 calcd for $C_{16}H_{23}N_2$).
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(*Received in USA* 13 *August* 1997; *revised* 23 *September* 1997; *accepted* 24 *September* 1997)