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A Stereoselective Synthetic Approach to N-Alkyl-4β-methyl-5-phenylmorphans

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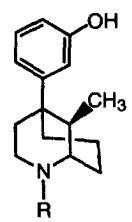
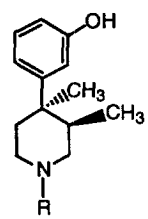
Abstract: A convergent, highly stereoselective synthetic approach to N-alkyl-4β-methyl-5-phenylmorphans has been developed utilizing alkylation of the metalloenamine of N-alkyl-1,2,3,6-tetrahydro-4-phenylpyridines with 2-(chloromethyl)-3,5-dioxahex-1-ene (Okahara's reagent) followed by Clemmensen reduction.

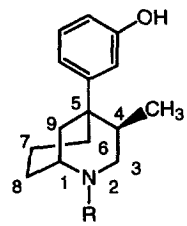
5-Phenylmorphans have been extensively investigated in search of analgesics lacking the negative side-effects associated with morphine.[1] While many agonists for the opioid receptors have been identified within this series, only the recently reported N-alkyl-9β-methyl-5-(3-hydroxyphenyl)morphans (**1a** and **1b**)[2] have been shown to possess potent antagonist activity. These compounds are believed to occupy the same site within the opioid receptors as do the N-alkyl-trans-3,4-dimethyl-4-(3-hydroxyphenyl)piperidines (**2**)[3] from which they are formally derived. Since both enantiomers of **2a** and **2b** are potent opioid receptor pure antagonists, we envisioned that N-alkyl-4β-methyl-5-(3-hydroxyphenyl)morphans (**3**) might also be potent pure antagonists for opioid receptors.[3]



1a, R= CH_3
1b, R= CH_2CH_2Ph



2a, R= CH_3
2b, R= CH_2CH_2Ph



3

The synthesis used to prepare 9β-methyl-5-(3-hydroxyphenyl)morphans[2,4] is illustrated in Scheme 1. According to this methodology, tetrahydropyridine (**5**), readily available from N-methyl-4-piperidone (**4**), is converted to the metalloenamine through treatment with n-BuLi and quenched with allyl bromide to provide enamine **6**. The key transformation then occurs via cyclization of the enamine intermediate (**6**) under acidic conditions. Important to the strategy of the present work is that the reaction terminates with an intramolecular hydride shift which produces the enamine intermediates **7** (9β CH_3:9α CH_3, 3:1).[2]

This transannular hydride shift effectively precludes the use of this reaction sequence for a stereoselective synthesis of 4β-methyl-(3-hydroxyphenyl)morphans (Scheme 2). Alkylation of tetrahydropyridine **8**, as before, would give enamine **9** which provides enamine **10** upon cyclization. In this case, the hydride shift which

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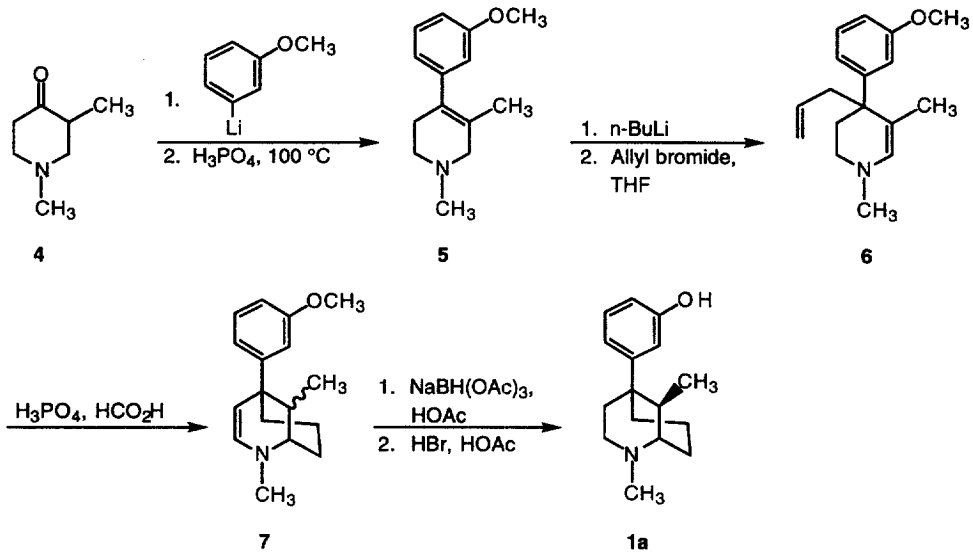
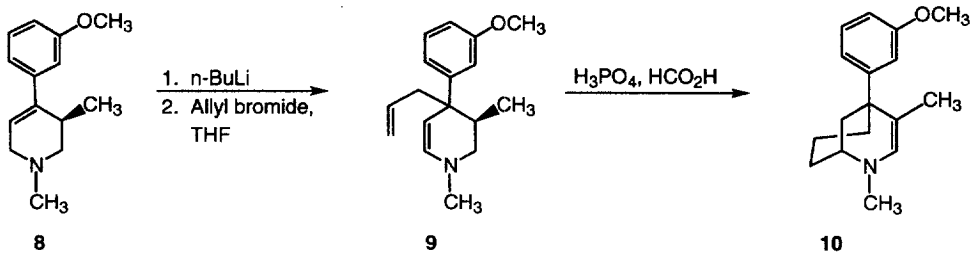
Scheme 1



4 5 6 7 1a

Scheme 2

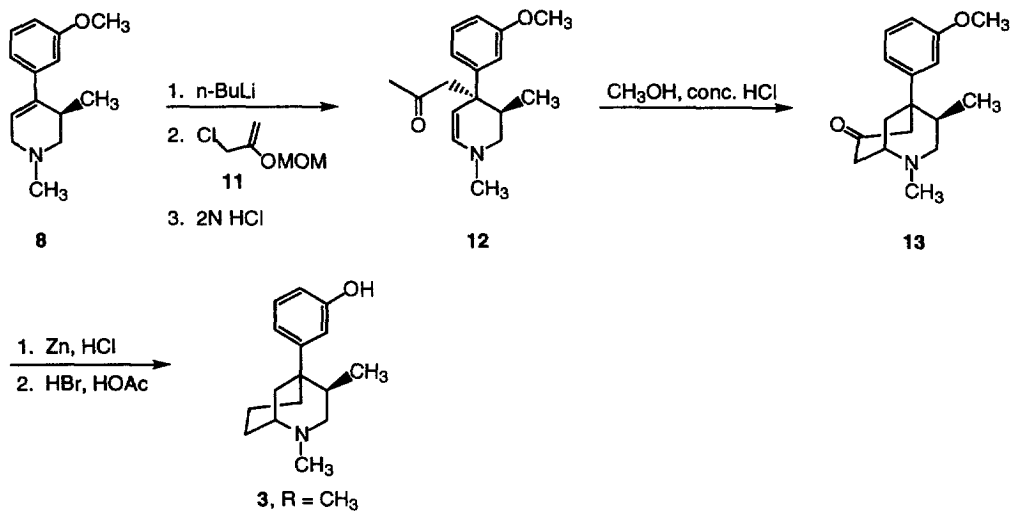


8 9 10

terminates the reaction sequence also eliminates the stereogenic center on carbon 4. While one might recover this stereocenter in a subsequent reduction, we have circumvented this potentially problematic step by modifying methodology previously reported for the synthesis of 5-phenylmorphans.[5,6] Thus, alkylation of **8**[7] with 2-(chloromethyl)-3,5-dioxohex-1-ene (Okahara's reagent)[8] followed by hydrolysis of the methoxymethyl protecting group (Scheme 3) gives enamine **12** . In the alkylation reaction, the methyl group apparently exerts a powerful directing effect since enamine **12** is the sole product. Cyclization under acidic conditions occurs regiospecifically on carbon 1 (phenylmorphan numbering) due to the specific migration of the double bond during the alkylation reaction. Furthermore, since the oxidation state of carbon 7 does not change following cyclization, no hydride shift occurs and the stereogenic center of carbon 4 is preserved providing 2,4β-dimethyl-7-oxo-5-(3-methoxyphenyl)morphan (**13**) as a single diastereomer. Clemmensen reduction[9] and deprotection of the phenol[10] then completes the synthesis of 2,4β-dimethyl-5-(3-hydroxyphenyl)morphan (**3**, R = CH_3) in 48% overall yield from **8**. The stereochemical assignments for **3** (R = CH_3) were made using NOESY spectra of a sealed degassed sample obtained with mixing time of 1.500 sec and an interpulse delay of 4 sec.[11] A strong interaction between the 4-methyl group and the 9β and 3β protons established the 4β-stereochemistry.

A requirement for significant quantities of **3** and its analogs for *in vivo* testing coupled with the usefulness of intermediates similar to **13** in the preparation of delta opioid receptor selective agonists,[12,13] directed our attention to improving the overall yield of the alkylation/ cyclization sequence relative to the one-pot procedure previously reported.[5] Experimentation with a variety of conditions revealed that addition of the metalloenamine of **8** to a solution of Okahara's reagent, rather than the reverse, gave much higher yields in the metalloenamine alkylation. In combination with an extractive workup to remove formaldehyde (formed by hydrolysis of the methoxymethyl group) and cyclization conditions similar to those defined by Bonjoch *et al.*,[14] the overall yield of the alkylation/cyclization sequence for **13** was significantly improved (75% for this work vs. 30% using the one-pot procedure).[15]

Scheme 3



In summary, we have successfully demonstrated a highly diastereoselective synthetic approach to the N-alkyl-4β-methyl-5-(3-hydroxyphenyl)morphan system as well as providing a higher yielding route to the useful 7-oxo-5-(3-methoxyphenyl)morphan opioid intermediates. Reports on the biological activity of **3** and its analogs will appear in due course.

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References and Notes

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11. Proton assignments for **3** were made using a combination of COSY and HETCORR spectra. ^{1}H NMR (d4-MeOH) δ 0.782 (d, 3H, J=7.5 Hz), 1.65 (m, 1H), 1.78 (m, 1H), 1.85 (m, 1H), 2.02 (d, 1H, J=15 Hz), 2.08 (m, 1H), 2.24 (m, 1H), 2.29 (m, 1H), 2.46 (q, 1H, J=7.5 Hz), 2.54 (d, 1H, J=15.0 Hz), 2.92 (s, 3H), 3.26 (d, 1H, J=13.6 Hz), 3.70 (m, 1H), 3.86 (dd, 1H, J=13.6 Hz, 5.3 Hz), 6.67 (m, 1H), 7.15 (t, 3H, J=7.9 Hz).
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14. Bonjoch, J.; Casamitjana, N.; Gracia, J.; Bosch, J. *Tetrahedron Lett.* **1989**, *30*, 5655-5658.
15. General Procedure for Alkylation/Cyclization Sequence: (**CAUTION:** Read reference 6 and references cited therein for information on N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, MPTP and its derivatives.) The appropriate tetrahydropyridine derivative (1 eq) is dissolved in THF (20 mL/g) and cooled to -10 °C. n-Butyl lithium (1.6M in hexanes) is slowly added until a red color is maintained followed by an addition of 1.1 eq. This material is stirred for 1 h at -10 °C and then cannulated quickly into a solution of Okahara's reagent (distilled to high purity) in THF (15 mL/g, 1.1 eq) at -78 °C followed by stirring for 2 h. The temperature should be kept below -30 °C during cannulation. This material is then poured into 2N HCl and extracted twice with ethyl ether. The aqueous layer is allowed to stand for 15 min followed by addition of 50% NaOH to pH 14 and extraction (3×) with ethyl ether. The ether is then washed (1N NaOH, H_2O) and the solvent removed under vacuum. The resulting residue of product and water is dissolved in MeOH (30 mL/g) and nitrogen is bubbled through the solution for 5 min. To this is added concentrated HCl (2 mL/g), and the mixture is allowed to stand at room temperature until the reaction is complete as indicated by TLC (up to 7 days). TLC condition: SiO_2; elution with 50 % (80% $CHCl_3$:18% CH_3OH:2% NH_4OH) in $CHCl_3$. Detection: 5% phosphomolybdic acid in ethanol. All compounds gave satisfactory ^{1}H and ^{13}C NMR and mass spectra.