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Synthesis of 9β-Methyl-2-alkyl-7-oxo-5-arylmorphans

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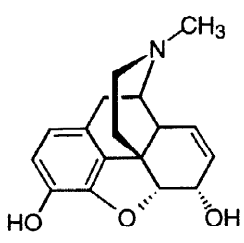
Abstract: A convergent synthetic approach to 9β-methyl-2-alkyl-7-oxo-5-arylmorphans has been developed utilizing alkylation of the metalloenamine of 1,2,3,6-tetrahydro-4-aryl-1-alkylpyridines with 2-(chloromethyl)-3,5-dioxahex-1-ene (Okahara's reagent).

The 5-arylmorphans have been extensively investigated as potential small-molecule analogs of the prototypical mu opioid agonist, morphine **1**.[1-4] Recently, Rice and coworkers used the 7-oxo derivative **2**, which was prepared by the method reported by Bosch and coworkers (see Scheme 1),[5] as starting material in the synthesis of novel delta opioid receptor subtype-selective agonists.[6,7] *N*-Substituted 9β-methyl-5-(3-hydroxyphenyl)morphans (**3**) can be viewed as conformationally rigid analogs of the important *N*-substituted trans-3,4-dimethylphenylpiperidine (**4**) class of opioid antagonists.[8] In this study, we report a stereoselective synthesis of 9β-methyl-7-oxo-5-arylmorphans, a conformationally stable analog of **4**, which can be converted to opioid receptor-selective antagonists.



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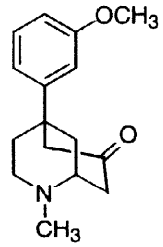

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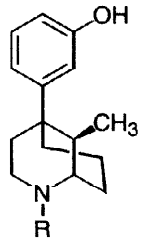

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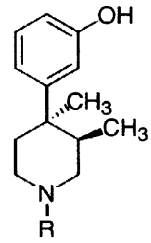

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While the route shown in Scheme 1 is a useful source of **2**, it is not applicable to a synthesis of the 9β-methyl derivatives based on the findings of Martinelli and coworkers.[9] In their synthesis of the analgesic Picenadol **14** (Scheme 2), it was clearly demonstrated that a 3-methyl group (phenyl piperidine numbering) exerts a dramatic directing effect in the conjugate addition reaction of enone **11** as only compound **12** was obtained with none of **13** being detected. This is completely opposite the facial selectivity required for the preparation of the title compound. Compound **12**, if carried forward according to Bosch's method, would give the 9α isomer. Martinelli's results, therefore, firmly established the need for an alternative synthetic approach to the 7-oxo-9β-methylphenylmorphan derivatives.

In 1980, Evans[10] and coworkers prepared the parent phenylmorphan system by treating metalloenamines generated from compounds similar to **15b,c** (Scheme 3) with allylbromide followed by cyclization in 1:1

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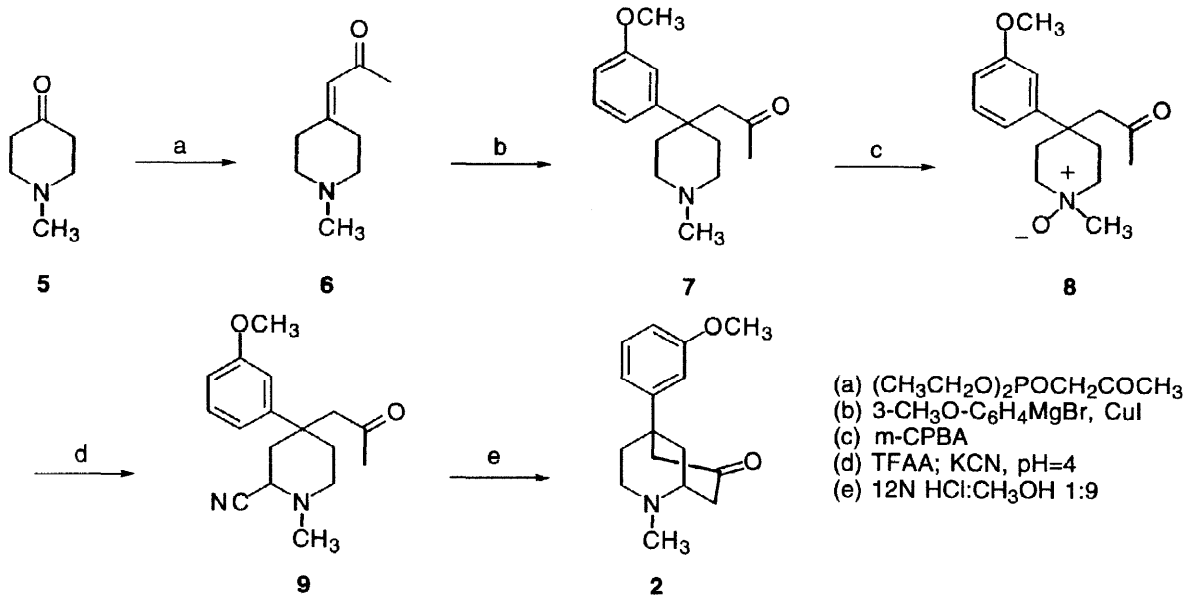
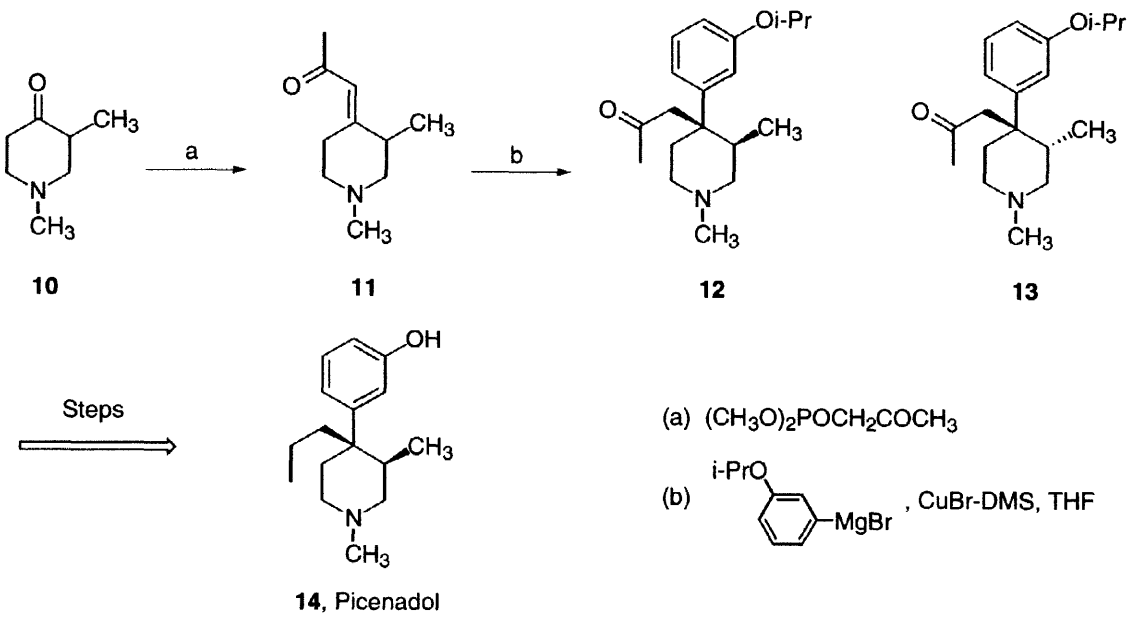


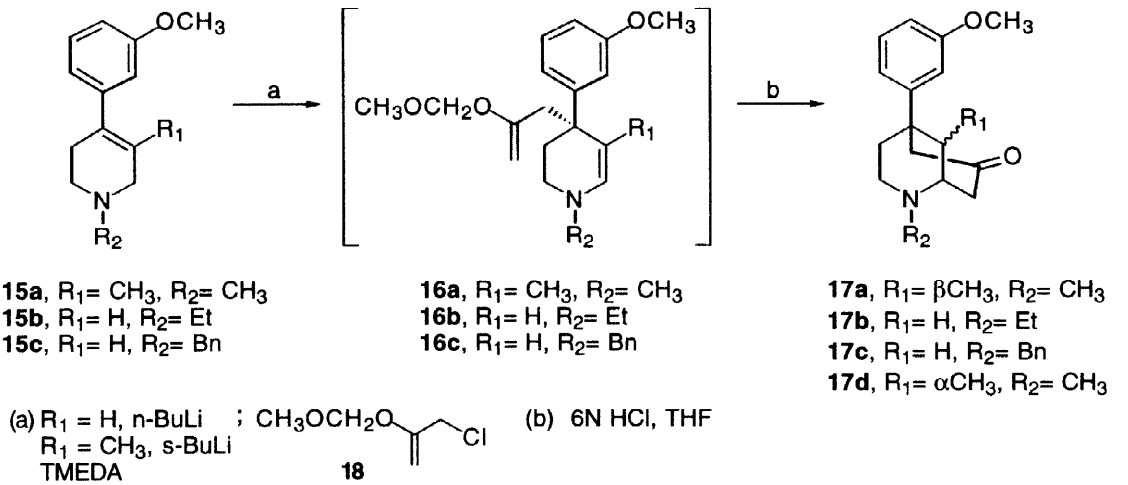
Scheme 1. Bosch's Synthetic Route to 2-Methyl-5-Phenylmorphan



Scheme 2. Martinelli's Synthesis of Picenadol

mixture of phosphoric and formic acids. Therefore, it seemed reasonable that a properly masked acetonyl equivalent might also alkylate such metalloenamines and that under acidic conditions the acetonyl equivalent could be unmasked and cyclized in a single step. Most importantly, since this product arises from the intermediate that places the alkyl group opposite the face of cyclization, we reasoned that a substituent R_1 in **16a** would favor the 9β stereochemistry in the final product **17a**. While many acetonyl equivalents are available, 2-(chloromethyl)-3,5-dioxahex-1-ene **18** (Okahara's reagent)[11,12] was most suited to the reaction conditions. Thus, treatment of the lithium salt of **15a** with **18** provided **16a** (not isolated) which cyclized on acidification with hydrochloric acid in tetrahydrofuran to give a 10:1 mixture of **17a** and **17d** as determined by

^{1}H NMR analysis. Separation by silica gel chromatography provided 43% of **17a.** Proton assignments were made using a combination of HMQC, HMBC, and COSY. The 9β stereochemical assignments for **17a** were made using NOESY techniques. In particular, the axial 9β-methyl group was observed to show an NOE interaction with the 4β proton.[13]



Scheme 3

To expand this method to the ring unsubstituted derivatives and to explore potential limitations of the chemistry, compounds **17b** (47%) and **17c** (42%) were also prepared. It was shown earlier that differences in reactivities exist between unsubstituted and substituted systems, **15b,c** and **15a**. For example, s-BuLi is needed to effectively deprotonate **15a** as opposed to **15b** and **15c** which require only n-BuLi.[14] In our studies we found that only the simple *N*-alkyl analogs of **15** (methyl) could be alkylated when the compounds possessed a 3-methyl substituent. Neither the *N*-benzyl nor the *N*-(3-phenylpropyl) derivative could be alkylated with **18**. Furthermore, it was found that **15a** required tetramethylethylene diamine (TMEDA) addition during deprotonation. To our knowledge no other alkylations of this type have required this additive. Nevertheless, this is a convenient route to the 7-oxo-phenylmorphan derivatives from either substituted or unsubstituted 4-phenyl-1,2,3,6-tetrahydropyridines from intermediates which can be prepared in bulk and stored for long periods of time.

Compounds **17b** and **17c** can be used as more readily available starting materials to prepare the opioid receptor delta subtype selective agonists reported by Rice and coworkers.[6,7] In addition, the ready availability of **17a** opens the opportunity to develop potential opioid subtype-selective antagonists. Studies along these lines are underway and will be reported in due course.

In summary, we have shown that the 9β-methyl-7-oxo-5-arylmorphan **17a** can be prepared in a convergent manner from tetrahydropyridine **15a** by alkylation with 2-(chloromethyl)-3,5-dioxahex-1-ene **18** followed by cyclization under acidic conditions. This method provides the first reported access to the 9β-methyl substituted system with good control of the stereochemistry. Application of the method to **15b** and **15c** provides a higher yielding route to the unsubstituted 7-oxo-phenylmorphan ring system and is amenable to large-scale synthesis.

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13. ^{1}H NMR ($CDCl_3$) δ 0.92 (d, 3H, 9-CH_3), 1.76 (d, 1H, H4α), 2.23 (dd, 1H, H8), 2.33 (s,3H, NCH_3), 2.37 (dd, 1H, H4β), 2.38 (dd, 1H, H3), 2.43 (d, 1H, H6), 2.50 (q, 1H, H9), 2.62 (d, 1H, H6), 2.72 (m, 1H, H3), 2.97 (d, 1H, H8), 3.10 (m, 1H, H1), 3.78 (s, 3H, OCH_3), 6.75 (dd, 1H, ArH), 6.87 (s, 1H, ArH), 6.92 (d, 1H, ArH), 7.25 (dd, 1H, ArH).
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