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Enantiopure *N*-Acyldihydropyridones as Synthetic Intermediates: Asymmetric Synthesis of Benzomorphans

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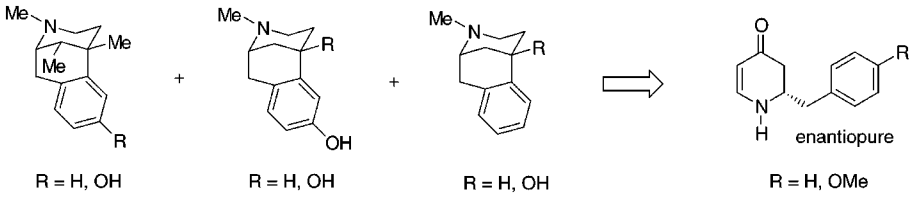
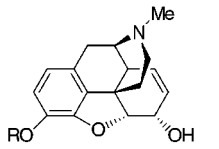
ABSTRACT

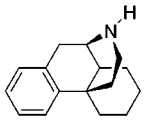


Concise asymmetric syntheses of several benzomorphan derivatives have been accomplished using enantiopure 2,3-dihydro-4-pyridones as chiral building blocks.

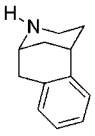
The natural opium alkaloids (−)-morphine (**1a**) and (−)-codeine (**1b**), and the simpler analogues morphinan (**2**) and benzomorphan (**3**), are important analgesics or antitussive agents.[1] Although morphine is an important narcotic analgesic, it exhibits undesired addicting side effects. Structural



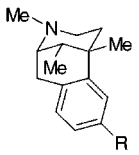
1a R = H, (-)-morphine
1b R = Me, (-)-codeine



2 morphinan



3 benzomorphan



4a R = H
4b R = OH, (+)-metazocine

modification can reduce this problem to a considerable extent. Synthetic analogues containing the benzomorphan ring system, i.e., **4**, have proven to be particularly interesting and hold promise in the search for nonaddictive narcotic analgesics.[2] Several racemic syntheses of the benzomorphan **4a** and metazocine **4b** have been achieved.[1,2] In contrast, the only enantioselective syntheses of benzomorphans **4** without using optical resolution were accomplished by the groups of Meyers[3] and Marazano.[4] Using chiral dihydropyridones as building blocks, we have developed a versatile asymmetric route to various benzomorphan derivatives. Syntheses of **4a** and **4b** were carried out as shown in Scheme 1.

The appropriate benzylic Grignard reagent was added to a mixture of 4-methoxy-3-(triisopropylsilyl)pyridine[5] and the

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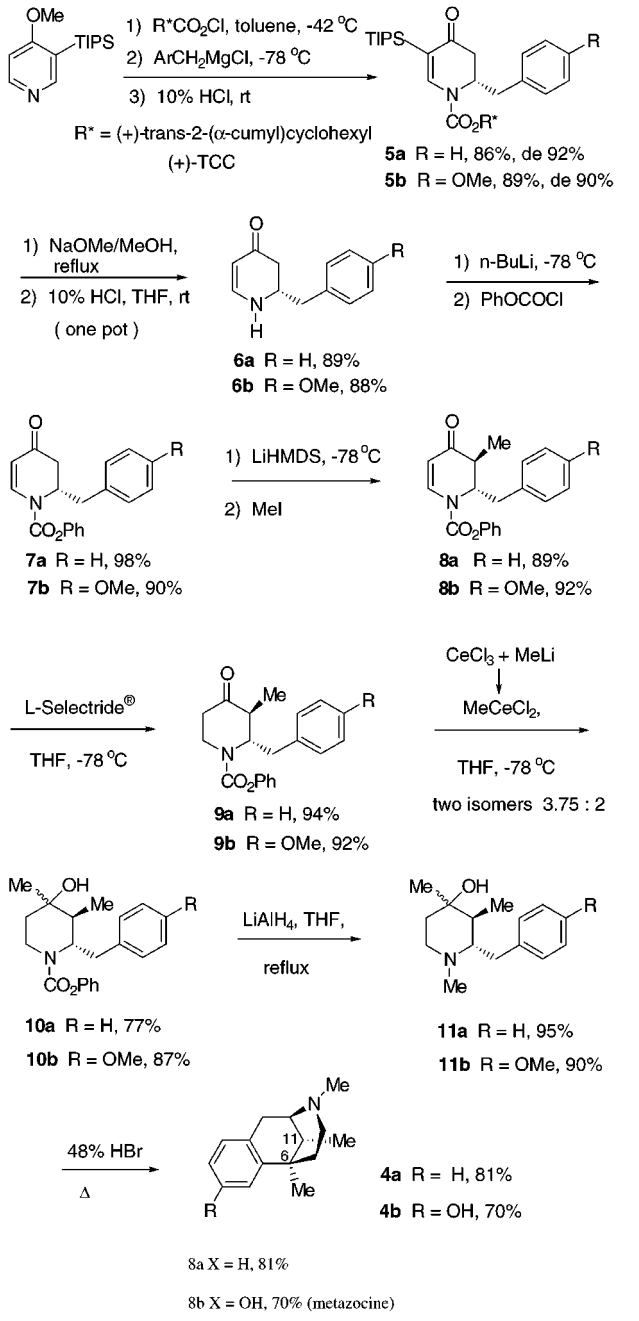
Scheme 1

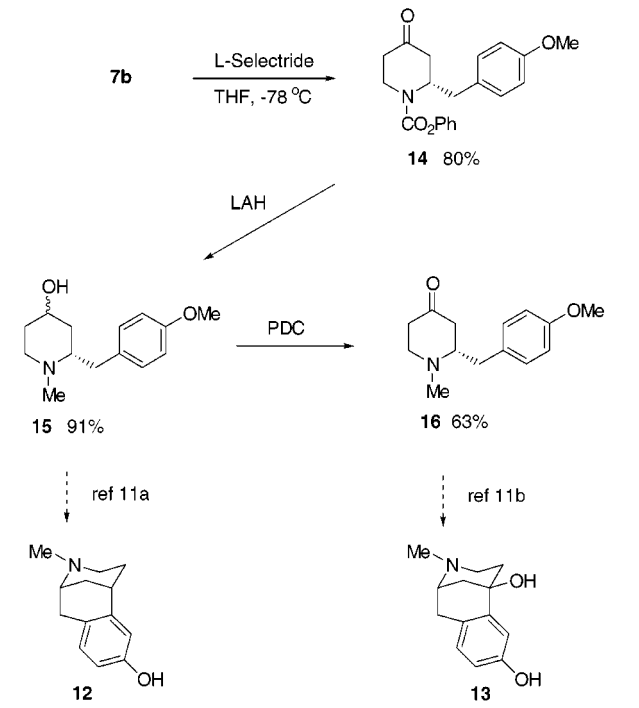


chloroformate of (+)-TCC.[6] After purification, dihydropyridones **5a** and **5b** were obtained in 86% and 89% yields, respectively. The de was determined by HPLC analysis of the crude products to be 92% for **5a** and 90% for **5b**. One-pot cleavage of the chiral auxiliary (>98%) and the C-5 triisopropylsilyl group[7] afforded an 89% yield of **6a** and 88% yield of **6b**, which were deprotonated by *n*-butyllithium and acylated with phenyl chloroformate. The resulting dihydropyridones **7** were methylated at C-3[8] (LiHMDS, THF, −78 °C; MeI) to give **8a** and **8b** in 89% and 92% yields, respectively. Subjection of **8** to basic conditions (K_2CO_3/THF) gave the cis 2,3-disubstituted compounds due to epimerization at C-3. By comparison of the ^{1}H NMR spectra of crude **8** with that of the epimerized cis product, it was determined that only the trans 2,3-disubstitued product was formed in the enolate alkylation reaction. Treatment of **8** with L-Selectride effected regioselective 1,4-reduction to give piperidones **9** in high yields.[9] Regioselective 1,2-addition was realized by adding a methylcerium species, generated from a mixture of methyllithium and anhydrous cerium chloride in THF.[10]

A mixture of diastereomeric 1-acyl-4-piperidinols **10** in a ratio of 3.75:2 was then reduced by lithium aluminum hydride to give 1-methyl-4-piperidinols **11** in 90−95% yield. Diastereoisomers **11** were separated by radial PLC; however, the stereochemistry at the C-4 position of the isomers was not determined in this case since it is unimportant for the subsequent reaction. Both isomers of **11a** and **11b** were subjected to acid-catalyzed cyclization to afford α-benzomorphans **4a** and **4b** in 81% and 70% yields, respectively [**4a**, $[\alpha^{22}_D]$ +62 (*c* 0.81, $CHCl_3$); lit.[4] $[\alpha]_D$ +63 (*c* 0.6, $CHCl_3$); **4b**, $[\alpha]^{25}_D$ + 82.6 (*c* 0.91, EtOH); lit.[3] $[\alpha]^{25}_D$ + 81.8 (*c* 0.83, EtOH)]. In both cases, a small quantity (5−8%) of *β*-isomers (C-11 *β*-methyl) was detected by ^{1}H NMR analysis of the crude products. The overall yield is 37% for **4a** and 33% for **4b** in eight steps starting from 4-methoxy-3-(triisopropylsilyl)pyridine.

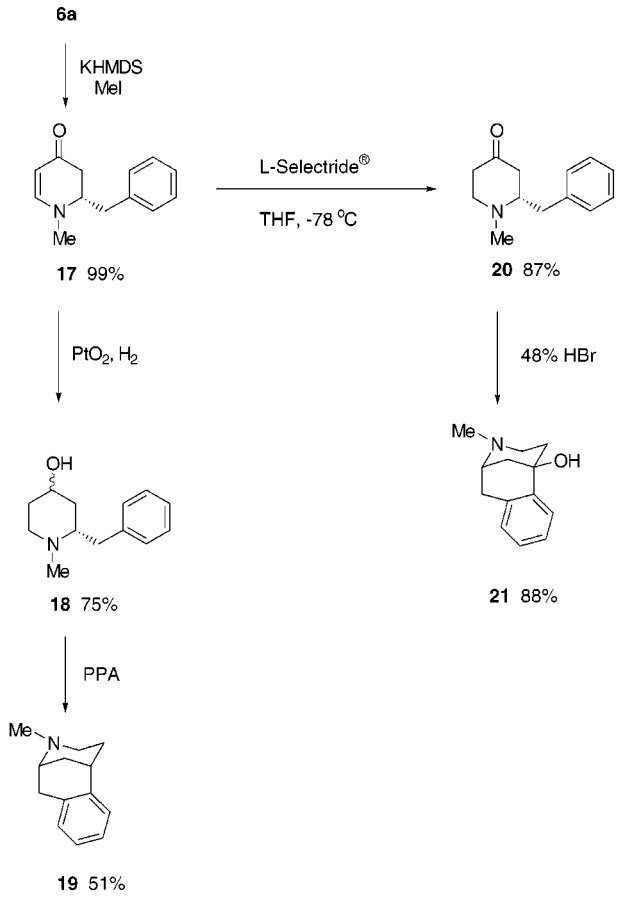
The benzomorphans **12** and **13** can also be synthesized from intermediate **7b** as described in Scheme 2. The 1,4-reduction of enantiopure **7b** with L-Selectride gave piperidone **14**, which on treatment with lithium aluminum hydride

Scheme 2



(6) Comins, D. L.; Salvador, J. M. *J. Org. Chem.* **1993**, *58*, 4656. (b) The (+)- and (−)-TCC alcohols are available from Aldrich Chemical Co.
(7) Comins, D. L.; Libby, A. H.; Al-awar, R. S.; Foti, C. J. *J. Org. Chem.* **1999**, *64*, 2184.

Scheme 3



(THF, reflux) provided a 91% yield of cis and trans 4-piperidinols **15** in a ratio of 2:1 with the trans 2,4-disubstitued isomer as the major product. Determination of stereochemistry at C-4 was assigned by an HOMO decoupling experiment. The chemical shift of the axial proton at C-4 is 3.48 ppm whereas the equatorial proton is found at 4.04 ppm. Conversion of **15** to benzomorphan **12** has been reported by May using a Grewe-type carbocation cyclization.[11] Subjection of **15** to pyridinium dichromate (PDC) oxidation gave 1-methyl-4-piperidone **16** $[\alpha]^{23}_{D}$ +17.1 (*c* 0.21, $CHCl_3$). Again, the last step leading to 2′,5-dihydroxy-6,7-benzomorphan **13** is a literature procedure.[11b] Therefore, analgesics **12** and **13** can be prepared from 2,3-dihydro-4-pyridone **7** in a concise, asymmetric fashion.

Benzomorphans **19** and **21** were prepared in three steps from enantiopure dihydropyridone **6a** as shown in Scheme 3. *N*-Methylation of **6a** gave a near quantitative yield of **17**, which on catalytic hydrogenation provided piperidinols **18** (>7:1, cis:trans) in good yield. A Grewe-type cyclization gave the target benzomorphan[11b,12] **19**, $[\alpha]^{23}_{D}$ +116 (*c* 0.1, $CHCl_3$).

Alternatively, dihydropyridone **17** could be reduced with L-Selectride in 87% yield to give piperidone **20**, which on treatment with HBr provided the enantiopure benzomorphan **21**,[11c] $[\alpha]^{26}_{D}$ +24.6 (*c* 0.39, $CHCl_3$).

The concise asymmetric syntheses of **4**, **12**, **13**, **19**, and **21** have amply demonstrated the versatility of our new approach to benzomorphan derivatives using enantiopure 2,3-dihydro-4-pyridones as chiral building blocks.[13] The route is practical as it uses the readily available chiral auxiliary TCC, which can be prepared economically on a large scale as either antipode[6] and easily recycled.

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Supporting Information Available: Characterization data for compounds **4**−**9**, **11**, **14**−**15**, and **17**−**21** and comparison tables of NMR data for synthetic **4a**,**b**, **19**, and **21**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) The structure assigned to each new compound is in accordance with its IR, ^{1}H NMR, and ^{13}C NMR spectra and elemental analysis or high-resolution mass spectra.