Tetrahedron Letters,Vol.28,No.41,pp 4829-4832,1987 0040-4039/87 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

GENERAL ASYMMETRIC SYNTHESIS OF BENZOMORPHANS AND MORPHINANS VIA ENANTIOSELECTIVE HYDROGENATION

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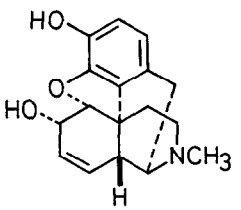
Summary: A variety of optically active benzomorphans including metazocine and pentazocine as well as dextromethorphan, a morphinan, are obtainable by using the BINAP—ruthenium(II) catalyzed enantioselective hydrogenation as key operation.

Naturally occurring morphine (**1**) is important as an analgesic[1] but exhibits undesired addicting side effect. The structural modification can overcome this problem to a considerable extent. For example, certain artificial benzomorphans,[2] such as metazocine (**2a**)[3] or pentazocine (**2b**)[4] are potent but nonaddictive narcotic analgesics. Dextromethorphan (**3a**)[5] which possesses the opposite absolute configuration has powerful antitussive property. Described herein is the asymmetric synthesis of such artificial morphines utilizing the recently discovered enantioselective hydrogenation of enamides as key step.[6]



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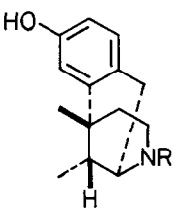
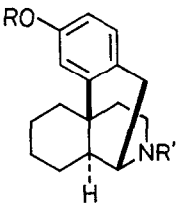


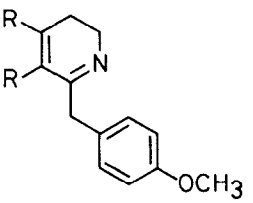
2a, R = CH_3
2b, R = $CH_2CH{=}C(CH_3)_2$
2c, R = cyclopropylmethyl
2d, R = $CH_2CH_2C_6H_5$



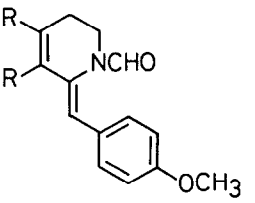
3a, R = R' = CH_3
3b, R = H; R' = CH_3

The dihydropyridine **4a** was prepared in a straightforward manner from tiglic acid by using the Bischler-Napieralski cyclodehydration.[7] The imine hydrochloride[8] was reacted with 10 equiv of formic pivalic mixed anhydride (benzene-pyridine, 0 °C, 8 h) to give a 6:1 stereoisomeric mixture of **5a** and the *E* isomer in 60% yield. Homogeneous hydrogenation was then effected with the major crystalline (*Z*)-enamide **5a**,[9] mp 96—98 °C, in methanol with 0.5 mol% of $Ru(OCOCF_3)_2$[(*R*)-tolbinap][6,10] under initial hydrogen pressure of 100 atm (25 °C, 120 h), affording the *R*-configurated **6a** in 98% ee and in 98% yield. The ruthenium-catalyzed hydrogenation was completely regioselective; the enamide moiety was saturated, whereas the tetrasubstituted olefinic bond remained intact. The enantiomeric excess of (*R*)-**6a**, $[\alpha]_D^{27}$ -35.6° (*c* 1.67, CH_3OH), was determined by reversed phase HPLC analysis[11] of (*R*)-**8a**, an adduct of (*R*)-

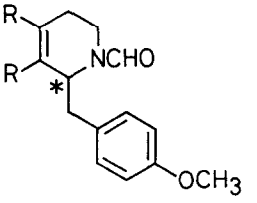
7a obtained by the treatment with 2 N NaOH at 80 °C and 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl isothiocyanate (GITC).[12] The chiral tetrahydropyridine derivatives, (*R*)-**6a** and (*R*)-**7a**, are useful intermediates for synthesis of (-)-metazocine (**2a**), (-)-pentazocine (**2b**),[13] (-)-cyclazocine (**2c**),[1c,4a] (-)-phenazocine (**2d**),[3a,14] etc. When $Ru(OCOCF_3)_2$[(*S*)-tolbinap] was used as the hydrogenation catalyst (0.5 mol%, methanol, 100 atm, 30 °C, 120 h), (*S*)-**6a** in 97% ee, $[\alpha]_D^{23}$ +34.4° (*c* 1.95, CH_3OH), was obtained in 98% yield. This compound is convertible to the dextrorotatory isomers of **2a—d**.



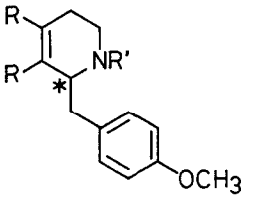
4a, R = CH_3
4b, R—R = $(CH_2)_4$



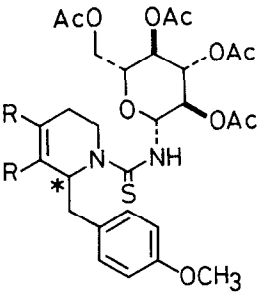
5a, R = CH_3
5b, R—R = $(CH_2)_4$



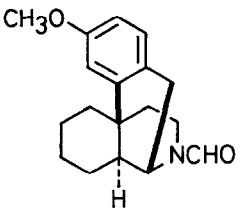
6a, R = CH_3
6b, R—R = $(CH_2)_4$



7a, R = CH_3; R' = H
7b, R—R = $(CH_2)_4$; R' = H



8a, R = CH_3
8b, R—R = $(CH_2)_4$



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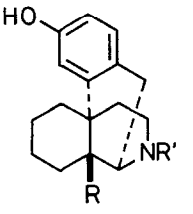

10a, R = H; R' = $CH_2CH{=}CH_2$
10b, R = OH; R' = cyclopropylmethyl
10c, R = OH; R' = cyclobutylmethyl

This method has been successfully extended to the enantioselective synthesis of dextromethorphan (**3a**), an extremely important bronchodilating agent. The starting imine, **4b**, is available from 2-(1'-cyclohexenyl)ethylamine and 4-methoxyphenylacetic acid by the standard procedure.[15] The *N*-formylation with formic pivalic mixed anhydride (3 equiv, pyridine-THF, 0 °C, 8 h) produced the (*Z*)-enamide **5b**[9] and its *E* isomer in 6:1 ratio in 78% combined yield. When the (*Z*)-enamide was hydrogenated in methanol containing 0.5 mol% of $Ru(OCOCF_3)_2$[(*S*)-tolbinap][6,10] (100 atm, 30 °C, 100 h), the desired (*S*)-**6b**, $[\alpha]_D^{22}$ +21.4° (*c* 1.33, CH_3OH),[16] was obtained quantitatively and in 97% ee (HPLC assay[11] of (*S*)-**8b** formed from (*S*)-**7b** and GITC). The formyl base, (*S*)-**6b**, can be subjected directly to the acid-catalyzed Grewe type cyclization[17] giving the tetracyclic compound **9**, reduction of which completes the asymmetric synthesis of **3a**. Since the existing commercial production of **3a** involves optical resolution of an amine intermediate, this asymmetric catalysis would enhance greatly the synthetic efficiency. In addition, (*S*)-**7b** acts as an intermediate leading to optically active dextrorphan (**3b**),[18] an anticough agent. The levorotatory isomer, (*R*)-**6b**, $[\alpha]_D^{27}$ -18.0° (*c* 2.03, CH_3OH), can be derived to levallorphan (**10a**)[5] and oxilorphan (**10b**),[19] narcotic antagonists, and analgesic butorphanol (**10c**),[19] etc.

Although we have demonstrated the utility of the ruthenium-catalyzed enantioselective hydrogenation in the synthesis of natural morphine precursors,[6] this is now recognized also as a powerful tool for asymmetric entry to clinically effective, artificial morphine-based analgesics.[20] This method allows flexible synthesis of both enantiomers. The new procedure is general and efficient, and finds a wide applicability.

Acknowledgment. We thank Professor A. I. Meyers (Colorado State University) and Dr. M. Takeda (Tanabe Pharmaceutical Co.) for suggestions and encouragement. We also acknowledge the generous supply of samples of racemic and optically active **6b** and **7b** and valuable information from Hoffmann-La Roche Inc., Nutley, New Jersey, USA.

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7. The hydrochloride of **4a** was prepared as follows. Reduction of tiglic acid ($LiAlH_4$, ether, 0—40 °C) gave (*E*)-2-methyl-2-buten-1-ol (bp 65—70°C/76 mmHg, 85% yield), whose bromination (PBr_3, 0 °C, 91% yield) followed by cyanation (CuCN, DMF, 26 °C, 76% yield) furnished (*E*)-3-methyl-3-pentenenitrile. Reduction ($LiAlH_4$ + $AlCl_3$, ether, 0—26 °C) of the cyanide gave (*E*)-3-methyl-3-pentenylamine (bp 35—40 °C/25 mmHg). *N*-(3'-Methyl-3'-pentenyl)-4-methoxyphenylacetamide (mp 66—68 °C) was obtained by condensation of the amine with 4-methoxyphenylacetic acid (toluene, reflux) followed by recrystallization (1:4 ethyl acetate-hexane) in 69% yield. Bischler-Napieralski cyclization of the amide ($POCl_3$, toluene, 110 °C, 15 h, 95% crude yield)) gave the hydrochloride of **4a**, which was immediately used for the *N*-formylation without purification.

8. Because the free imine is labile, the hydrochloride should be used.
9. **5a**: ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.84 and 1.93 (s, each, 6, CH_3 x 2), 2.28 (bt, 2, J = 6.0 Hz, CH_2), 3.78 (s, 3, OCH_3), 3.84 (t, 2, J = 6.1 Hz, CH_2), 6.24 (s, 1, CH=), 6.83 (d, 2, J = 8.9 Hz, aromatic), 7.23 (d, 2, J = 8.6 Hz, aromatic), 8.00 (s, 1, CHO). **5b**: ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.6—1.8 (m, 4, CH_2 x 2), 2.07, 2.20, and 2.28 (m, each, 6, CH_2 x 3), 3.78 (s, 3, OCH_3), 3.86 (t, 2, J = 5.9 Hz, CH_2), 6.16 (s, 1, CH=), 6.83 (d, 2, J = 8.9 Hz, aromatic), 7.23 (d, 2, J = 8.6 Hz, aromatic), 8.01 (s, 1, CHO). In general the (*Z*)-enamides give the NMR signals due to the formyl protons at higher field (δ 8.0—8.2) than the (*E*)-isomers (δ 8.5—8.7) (ref 6).
10. TolBINAP = 2,2'-bis(di-*p*-tolylphosphino)-1,1'-binaphthyl. Takaya, H.; Mashima, K.; Koyano, K.; Yagi, M.; Kumobayashi, H.; Taketomi, T.; Akutagawa, S.; Noyori, R. *J. Org. Chem.* **1986**, *51*, 629. The complex, $Ru(OCOCF_3)_2$[(*R*)-tolbinap], was prepared by treatment of $Ru(OCOCH_3)_2$[(*R*)-tolbinap] with 2 equiv of trifluoroacetic acid in dichloromethane and then removal of the solvent: ^{31}P NMR ($CDCl_3$) 59.91 ppm (standard, 85% H_3PO_4).
11. Conditions of HPLC analysis for **8a**: column, Nomura Chemical Co., Develosil ODS-5; eluent, 1/1 CH_3CN-H_2O containing $NH_4H_2PO_4$ (1.4 g/L); flow rate, 1 mL/min; detection, 254-nm light. Acetonitrile-water (3/2) containing $NH_4H_2PO_4$ (1.4 g/L) was used as eluent for analysis of **8b**.
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13. Commercial pentazocine is a racemic mixture.
14. May, E. L.; Eddy, N. B. *J. Org. Chem.* **1959**, *24*, 294.
15. Heating 2-(1'-cyclohexenyl)ethylamine with 4-methoxyphenylacetic acid (150 °C, 5 h) followed by removal of the resulting water and recrystallization (1:4 ethyl acetate-hexane) afforded *N*-2-(1'-cyclohexenyl)ethyl-4-methoxyphenylacetamide, mp 76.5—78.5 °C. Its Bischler-Napieralski type cyclization ($POCl_3$, benzene, reflux) gave after basic workup 3,4,5,6,7,8-hexahydro-1-(4-methoxyphenylmethyl)isoquinoline. This was immediately used for the subsequent reaction.
16. Authentic sample from Hoffmann-La Roche showed $[\alpha]_D^{25}$ +22.2° (*c* 1.33, CH_3OH).
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(Received in Japan 18 June 1987)