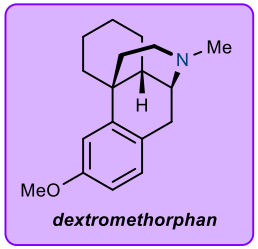
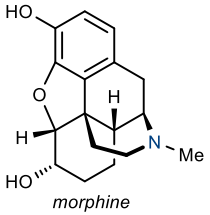
Dextromethorphan

Background and Uses

- Dextromethorphan (DXM) is of the most common OTC antitussives (cough suppressant)
- Thought to work by inhibiting the cough center of the brain, but the precise mechanism is still unknown
- Recent studies have brought the effectiveness of antitussives into question
- Has been used as a recreational drug, at high doses can produce dissociative and hallucinogenic effects
- Recently approved in a combination therapy (dextromethorphan / quinidine) for treatment of Pseudobulbar Affect.
- Also studied as an antidepressant and for opioid withdrawal treatment



dextromethorphan

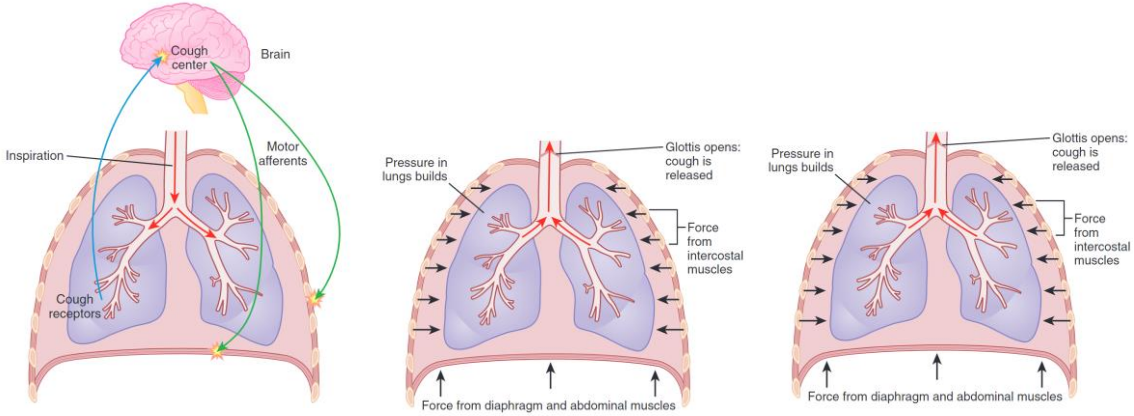


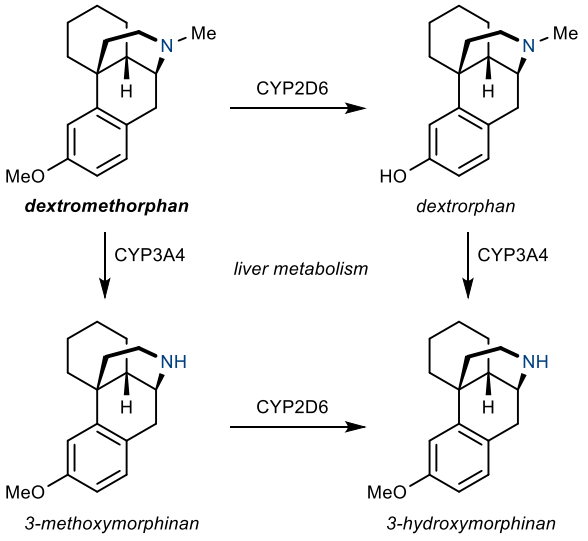
morphine

Smith, S. M. *Cochrane Database Syst. Rev.* **2014**, *11*. https://doi.org/10.1002/14651858.CD001831.pub5
Matsumoto, R. R. *Pharmacol. Ther.* **2016**, *159*, 1. https://doi.org/10.1016/j.pharmthera.2016.01.016

Pharmacology and Mechanism of Action

- DXM is a prodrug of the active metabolite dextrophan
- The low μ-opioid receptor activity renders DXM a non-opioid antitussive
- As such, there is no risk of physical dependence like with codeine or hydrocodone
- At high doses, DXM acts as a NMDA receptor antagonist, similar to PCP and ketamine
- It is also a nonselective serotonin reuptake inhibitor



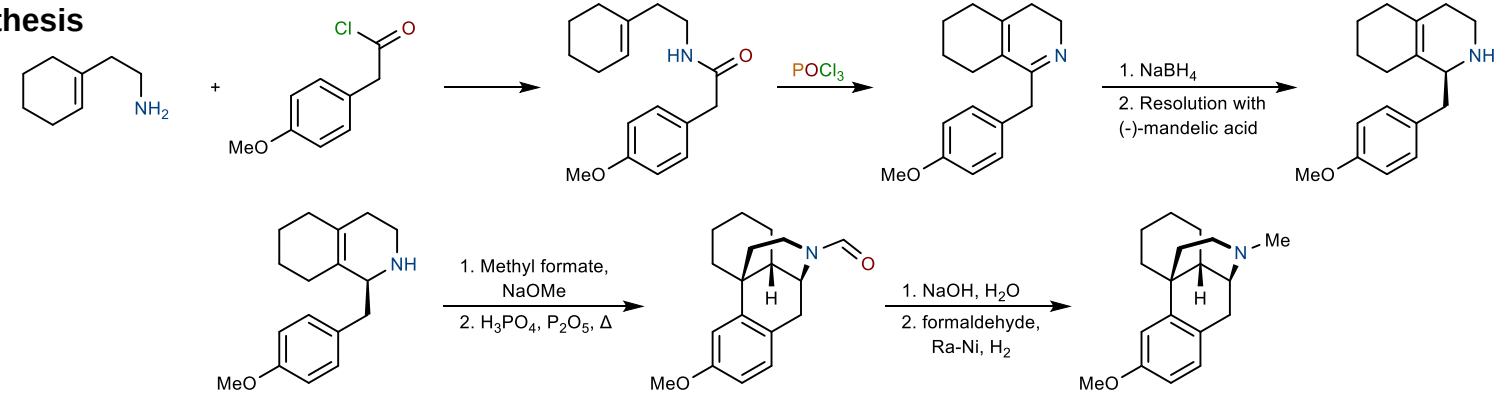


dextromethorphan *dextrorphan*
3-methoxymorphinan *3-hydroxymorphinan*

Bardal, S. K.; Waechter, J. E.; Martin, D. S. *Applied Pharmacology*; Elsevier:Amsterdam, 2011. ISBN: 978-1-4377-0310-8

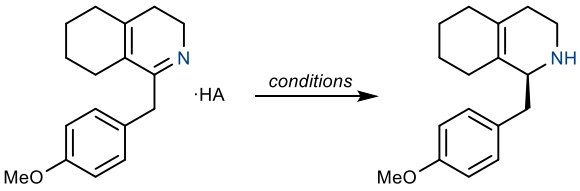
Dextromethorphan

Early Synthesis

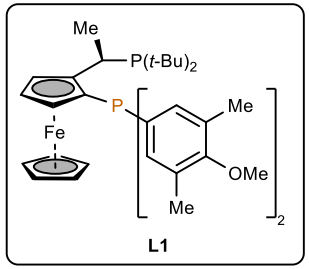


Patent: US3634429A

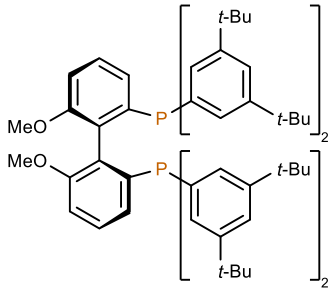
Asymmetric Hydrogenation



Lonza conditions	***Hoffmann-La Roche conditions***
$Ir(cod)_2BF_4$, **L1**	Rh(**L2**)(cod)Cl
70 bar H_2	40 atm H_2
toluene, H_2O, NaOH	1:1 toluene:MeOH,
$(Bu_4N)X$	Et_3N (10 mol%)$(Bu_4N)I$
HA = H_3PO_4	HA = H_2SO_4
1500 S/C	10000 S/C
89.2% *ee*	97% yield, 94% ee



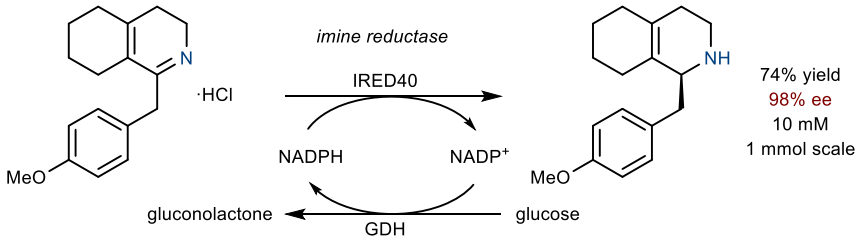
L1



(*S*)-3,5-*t*-Bu-MeOBIPHEP (**L2**)

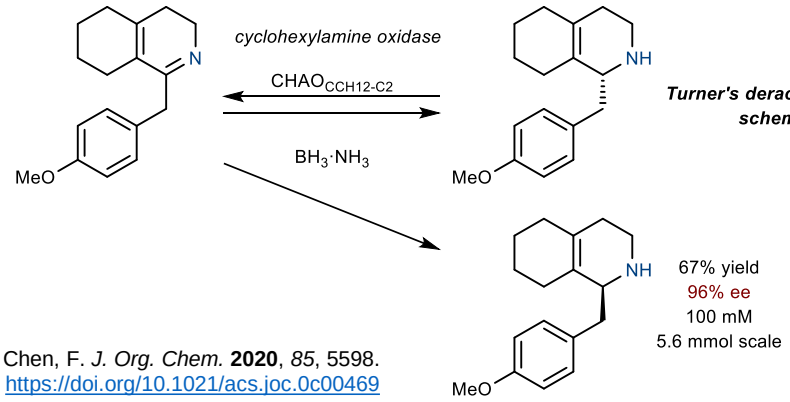
Imwinkelried, R. *Chimia* **1997**, *51*, 300. https://www.ingentaconnect.com/contentone/scs/chimia/1997/00000051/00000006/art00012
Hoffmann-La Roche, *New Processes for Existing Compounds*. In *Asymmetric Catalysis on Industrial Scale: Challenges, Approaches and Solutions*, 2nd Edition, Blaser, H. U.; Federsel, H.-J. VCH:New York, 2011. ISBN: 978-3-527-64216-8

Chemoenzymatic Reduction



74% yield
98% ee
10 mM
1 mmol scale

Zhu, D. *Adv. Synth. Catal.* **2018**, *361*, 556. https://doi.org/10.1002/adsc.201801326



Turner's deracemization scheme

Chen, F. *J. Org. Chem.* **2020**, *85*, 5598. https://doi.org/10.1021/acs.joc.0c00469