Morphine

Topic Review

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May 31st, 2012

Opium

Extracted from *Papaverum Somniferum*

Known since 3000 AC (Sumerians)

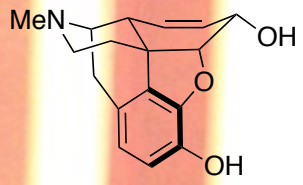
Traditional drug for its sedative and analgesic effects

XVI^{e}, Paracelsius used it as a medicine in alcoholic solution: Laudanum

Widely prescript in the XIX^{e} century for a simple cold, a meningite or even cardiovascular deseases, to adults as to babies (they sleep better…)

40 000 tons of opium produced in 1906, 8000 in 2008

Morphine



Named after Morpheus, the greek god of the dreams

Isolated by A. Seguin, B. Courtois, in the 1804

But first F. W. Sertürner showed it was a “vegetal alkali”: the first alkaloid.

Many famous morphine addicts: Baudelaire, Bismarck, Alphonse Daudet.

1874: A. Wright prepared diacetylmorphine: heroin, quickly a success.

Extraction from poppy is still by far cheaper than synthetic morphine

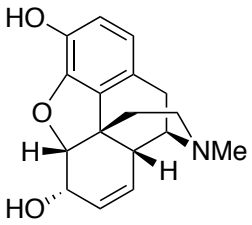
France and Australia are the main producer of legal morphine

Effects

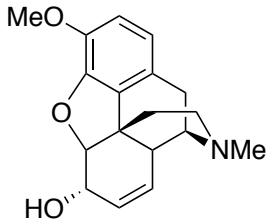
Morphine and its derivative are important analgesic and anaesthetic.

μ-opioid receptor agonist in the CNS.

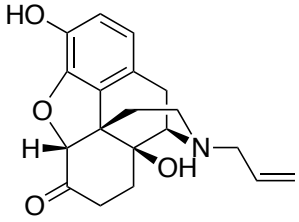
Cough medecine, induces constipation, nausea, dependence and tolerance.



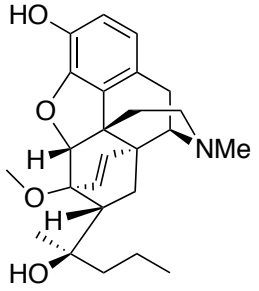
morphine



codeine

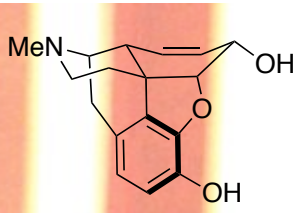


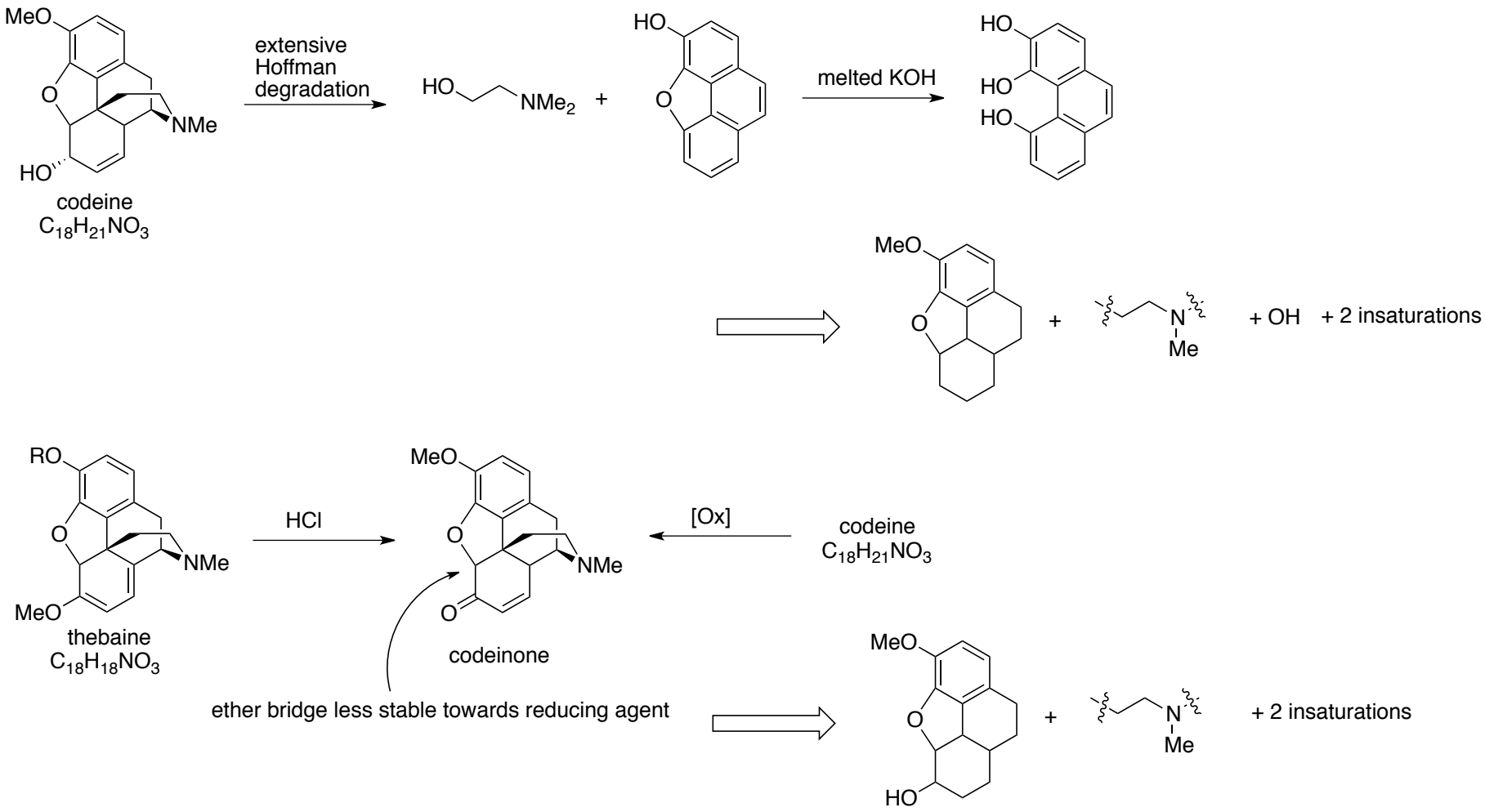
naxolone
antagonist



ethorphine
1000 times more potent

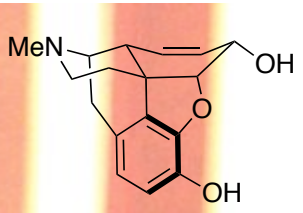
Structure Elucidation

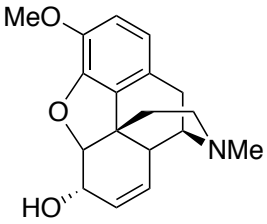




J. M. Gulland R. Robinson, *J. Chem. Soc.* **1923**, 980 – 998.
J. M. Gulland R. Robinson, *J. Chem. Soc.* **1923**, 998 – 1011.

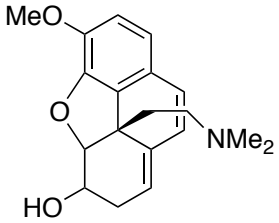
Structure Elucidation



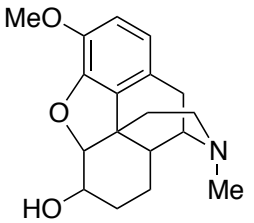


codeine
$C_{18}H_{21}NO_3$

1) MeI, NaOH
2) RONa



$C_{19}H_{23}NO_3$



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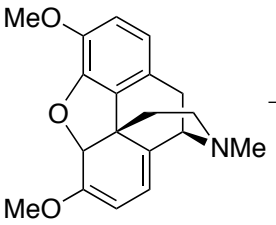
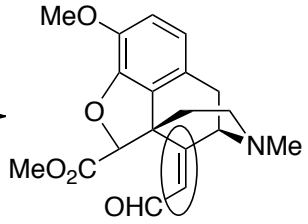
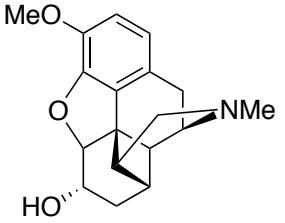


thebaine

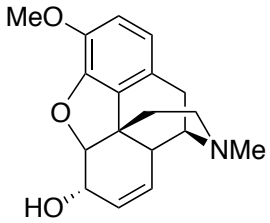
O_3



No double bond?

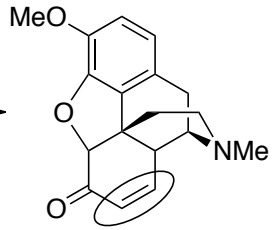


?



codeine

$KMnO_4$
acetone



codeinone

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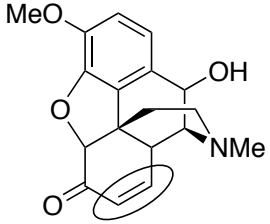
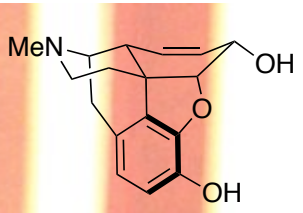
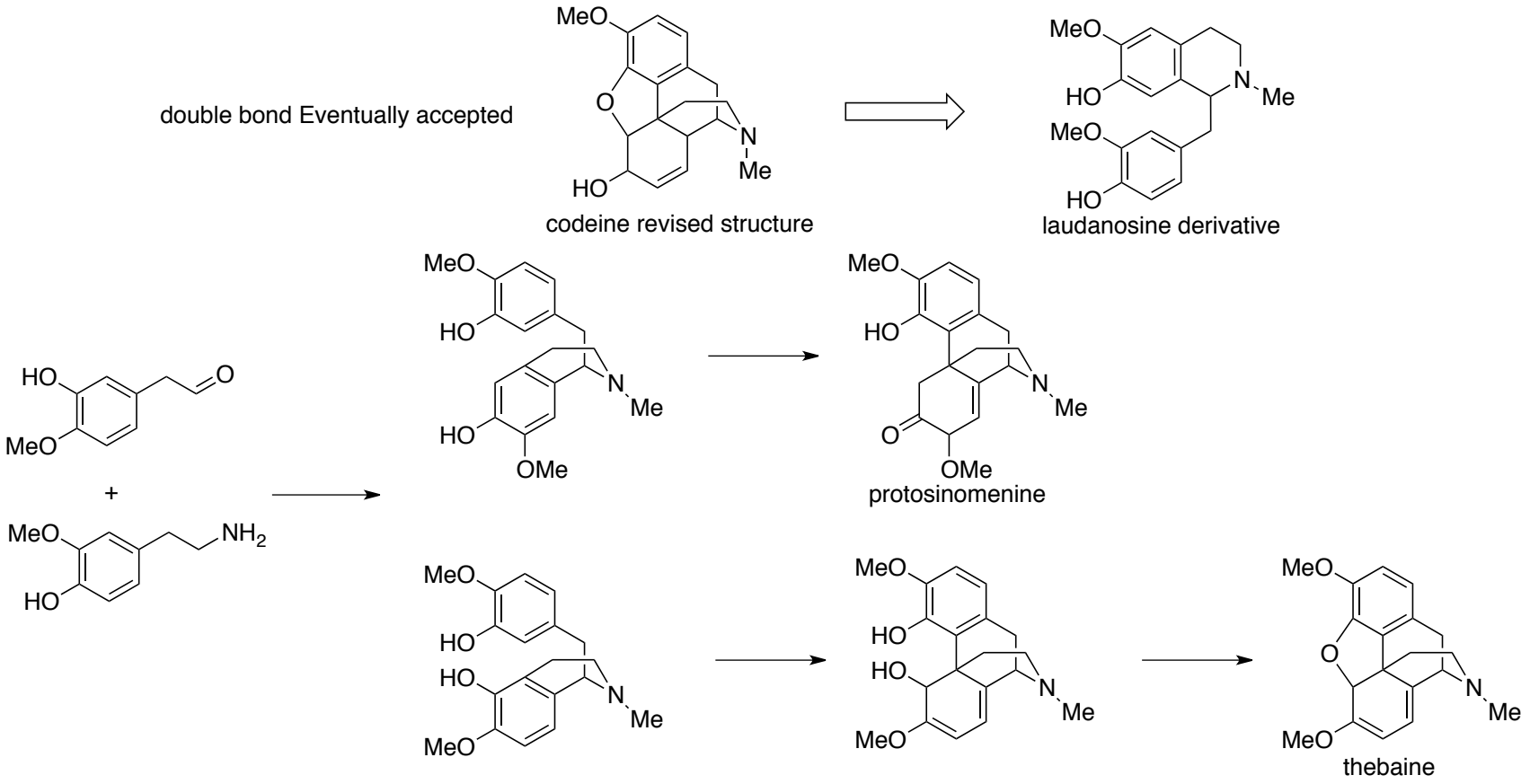


J. M. Gulland R. Robinson, *J. Chem. Soc.* **1923**, 980 – 998.
J. M. Gulland R. Robinson, *J. Chem. Soc.* **1923**, 998 – 1011.

Biosynthetic Hypothesis

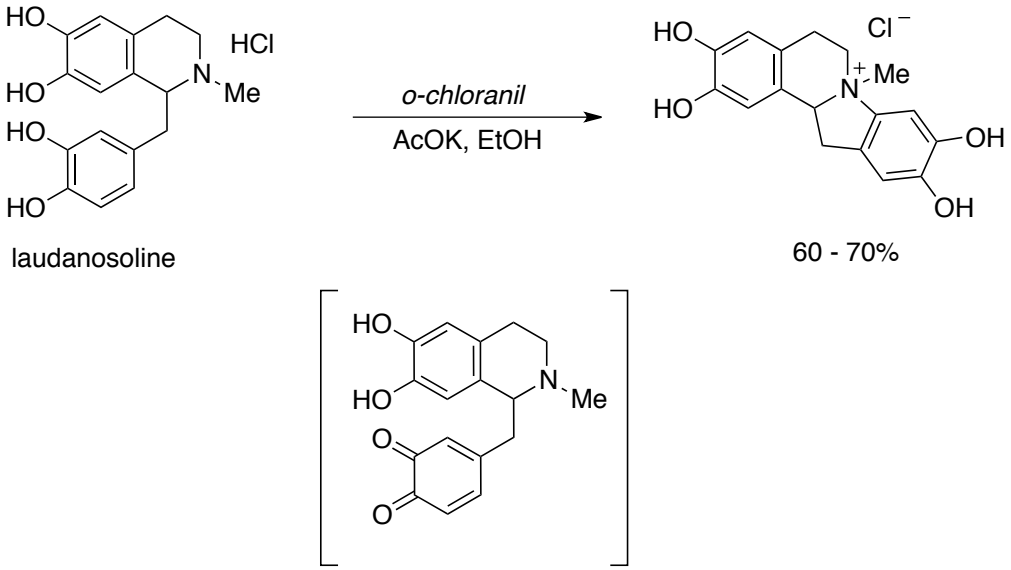




"It is strongly held that the only promising route to an ultimate synthesis of morphine and its congeners is by a path already laid down by Nature." R. Robinson

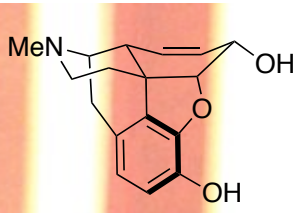
R. Robinson, S. Sugasawa, *J. Chem. Soc.* **1931**, 3163 – 3172.

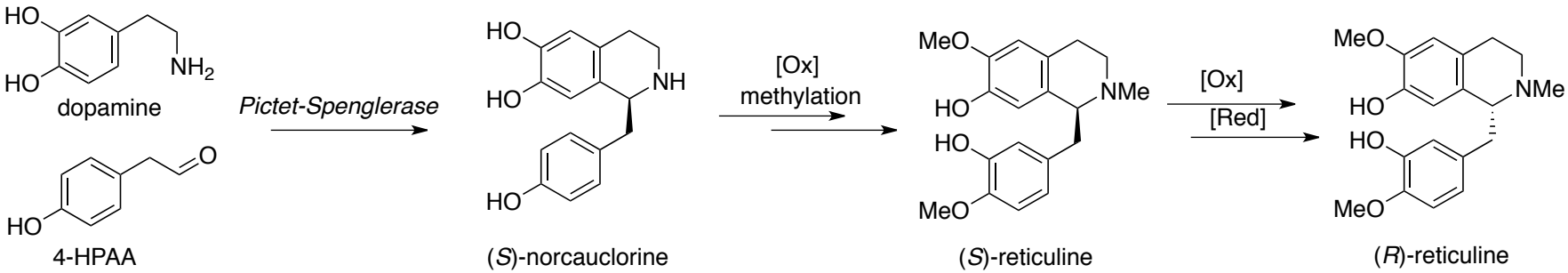
Oxidative Coupling



R. Robinson, S. Sugasawa, *J. Chem. Soc.* **1932**, 785 – 789.
R. Robinson, S. Sugasawa, *J. Chem. Soc.* **1932**, 789 – 805.

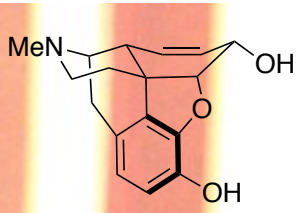
Modern Biogenesis

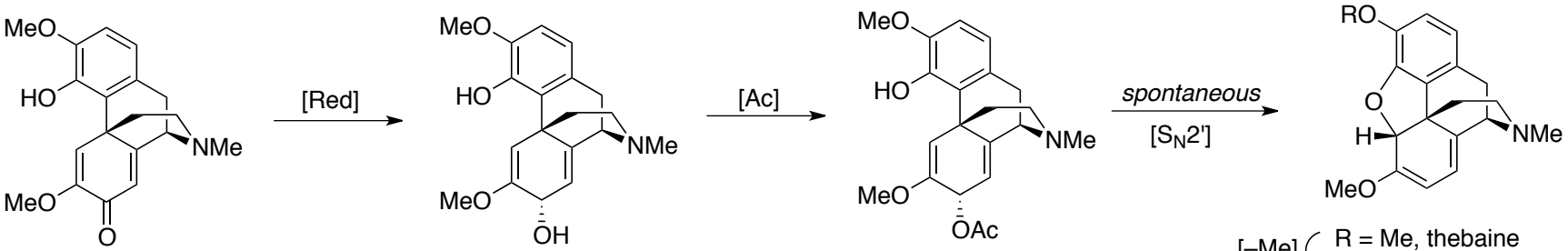




W. Brandt *et al.*, *Phytochemistry* **2009**, *70*, 1696 – 1707.
T. Kutchan *et al.*, *J. Biol. Chem.* **2009**, *284*, 24432 – 24442.

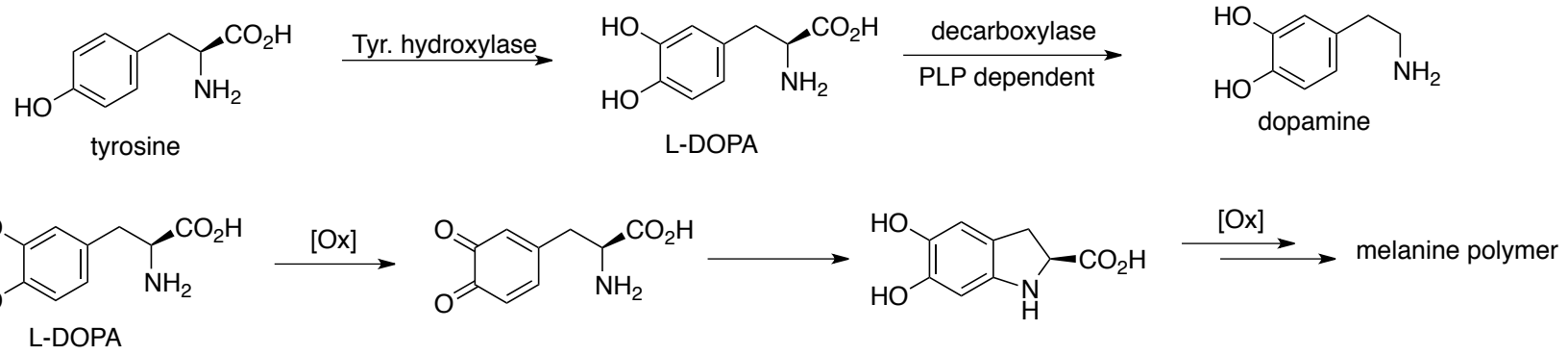
Morphine Biosynthesis





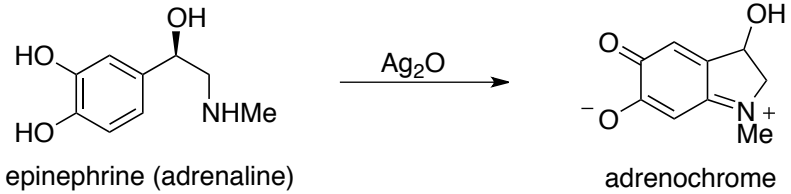
W. Brandt *et al.*, *Phytochemistry* **2009**, *70*, 1696 – 1707.
T. Kutchan *et al.*, *J. Biol. Chem.* **2009**, *284*, 24432 – 24442.

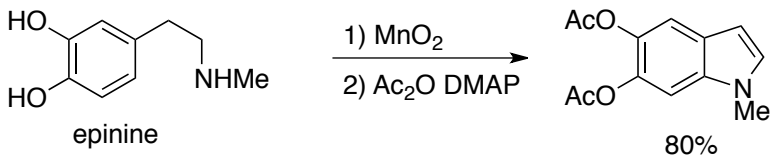
Dopamine



P. M. Dewick *in* Medicinal Natural Products: A Biosynthetic Approach. 2nd Ed. John Wiley & Sons, Inc., New. York, **2002**

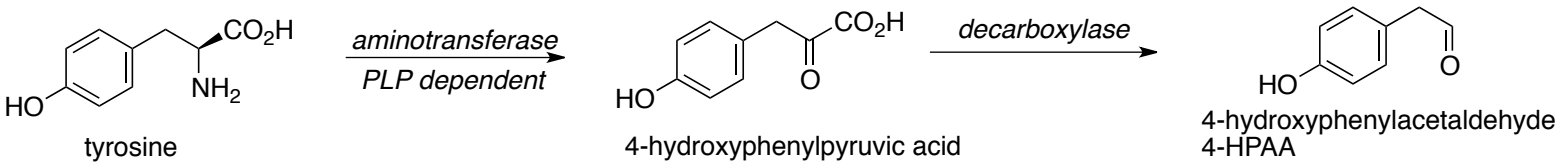
examples





J. F. Carpenter *J. Org. Chem.* **1993**, *58*, 1607 – 1609.

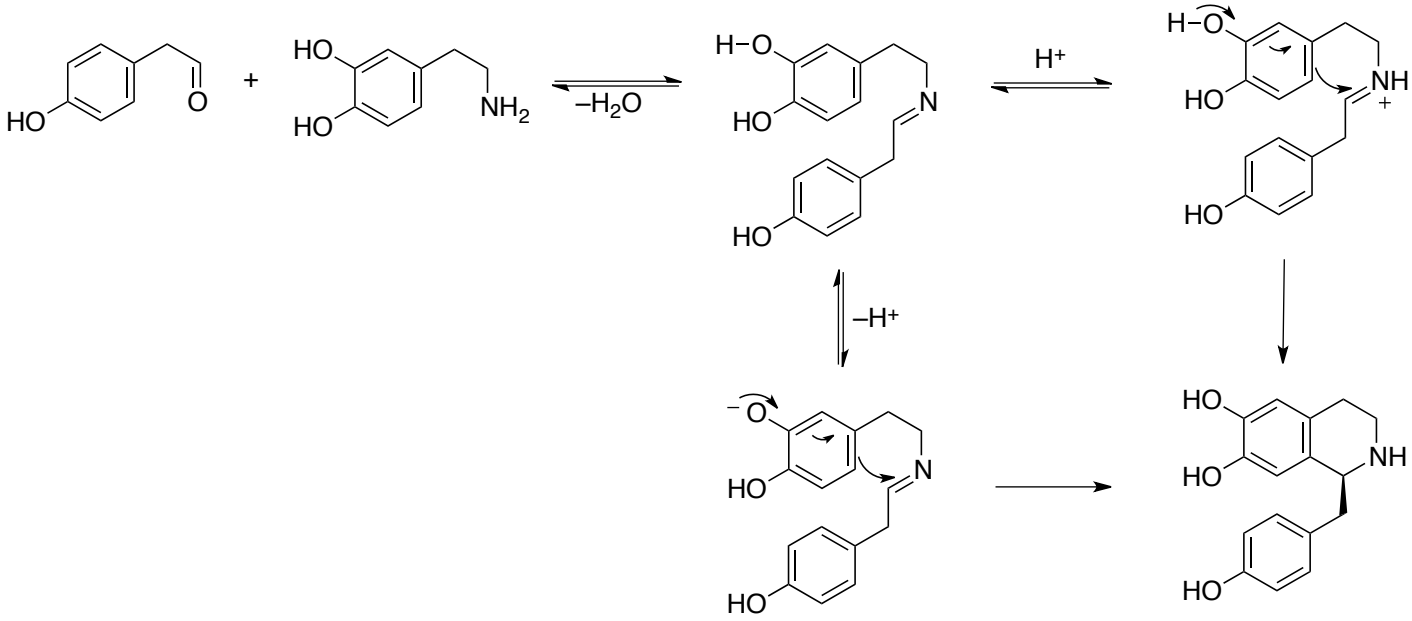
Pictet Spengler



tyrosine

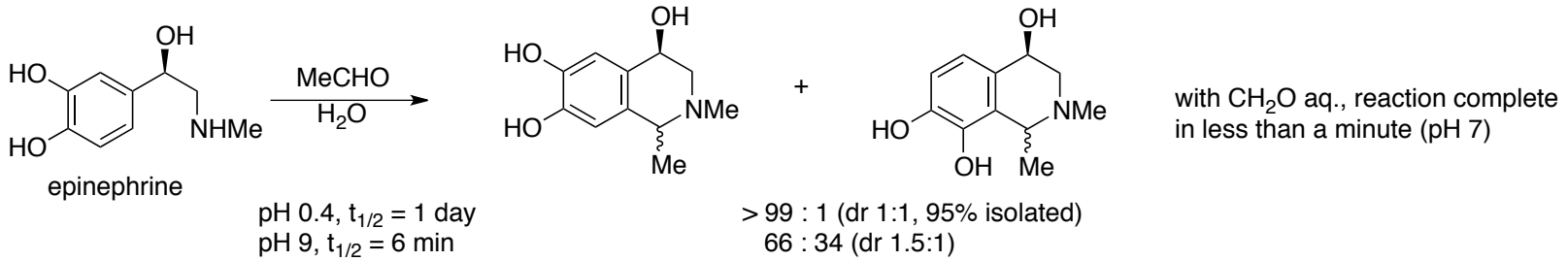
4-hydroxyphenylpyruvic acid

4-hydroxyphenylacetaldehyde
4-HPAA

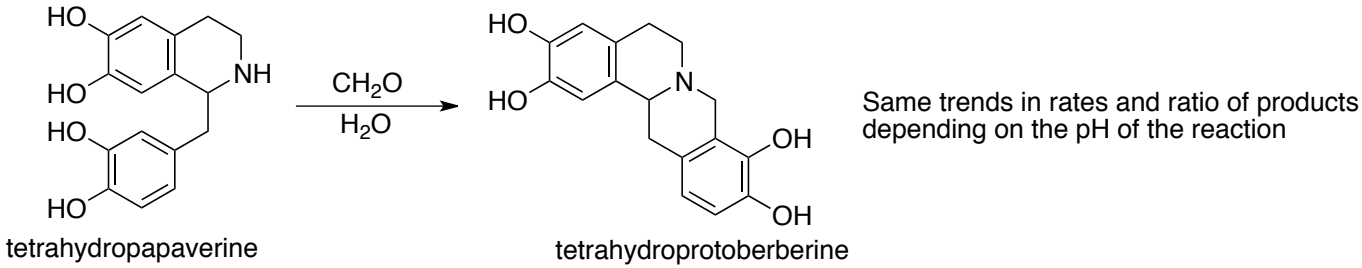


(*S*)-norcauclorine

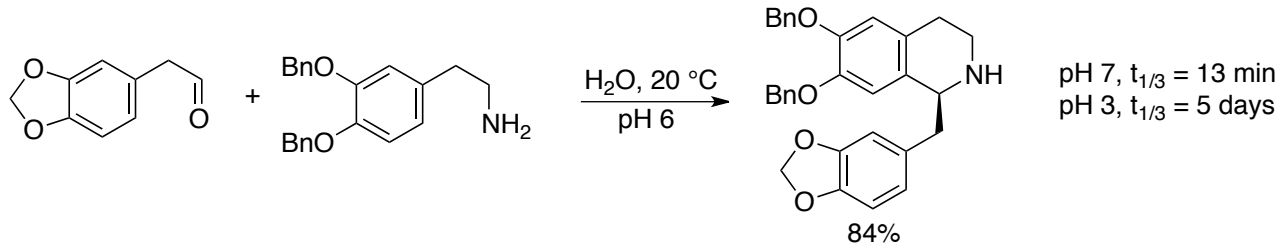
In Aqueous Media



H. A. Bates, *J. Org. Chem.* **1981**, *46*, 4931 – 4935. H. A. Bates, *J. Org. Chem.* **1983**, *48*, 1932– 1934

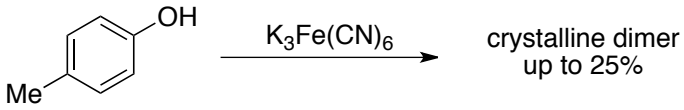


K. D. McMurtrey, L. R. Meyerson, J. L. Cashaw, V. E. Davis, *J. Org. Chem.* **1984**, *49*, 948 – 950.



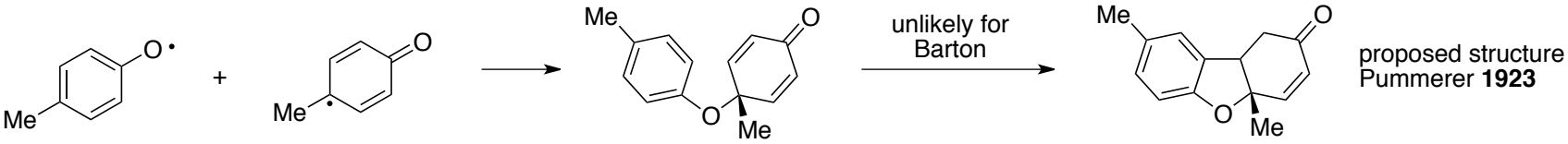
C. Schöpf, W. Salzer, *Justus Liebigs Ann. Chem.* **1940**, *544*, 1 – 30.

Pummerer's Ketone:
a Model for Morphine Biosynthesis

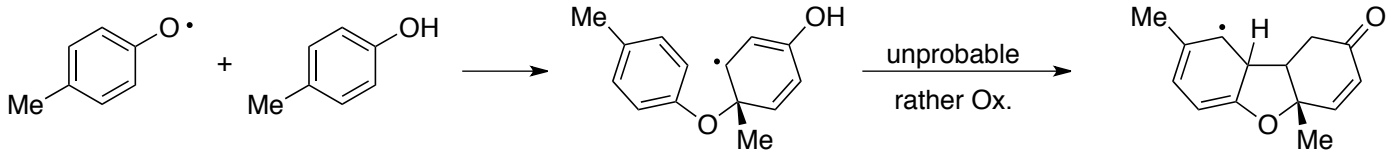


Pummerer proposed a *p*-O coupled intermediate

Radical pairing

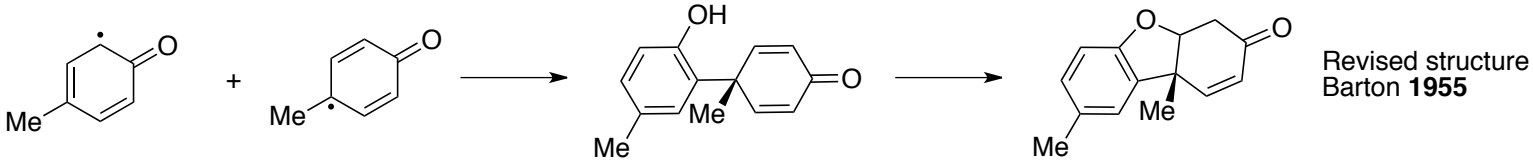


radical substitution



Barton's revision

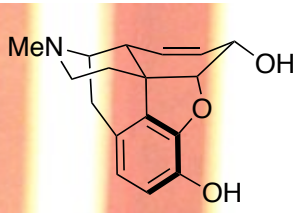
Phenolic coupling *ortho-para*

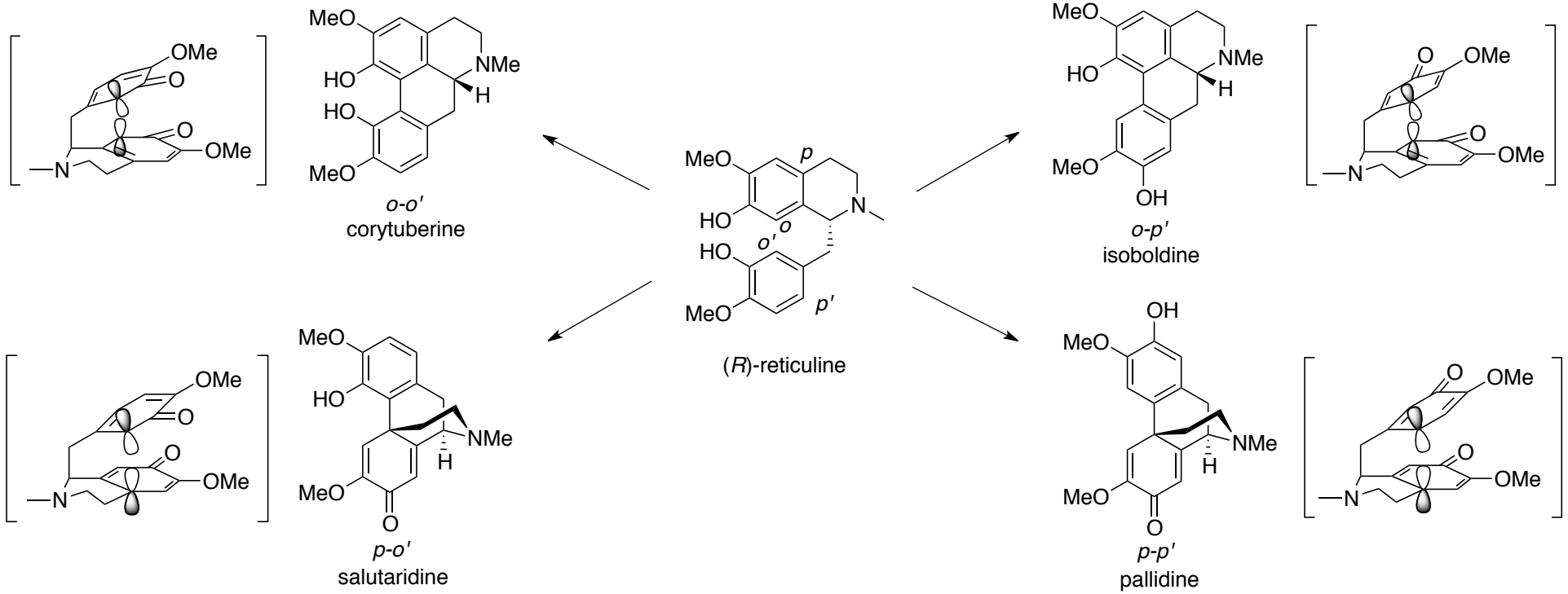


Radical coupling preferred but substitution not discarded.

D. H. R. Barton, A. M. Deflorin, O. E. Edwards, *J. Chem. Soc.* **1956**, 530 – 534.

Barton's Hypothesis

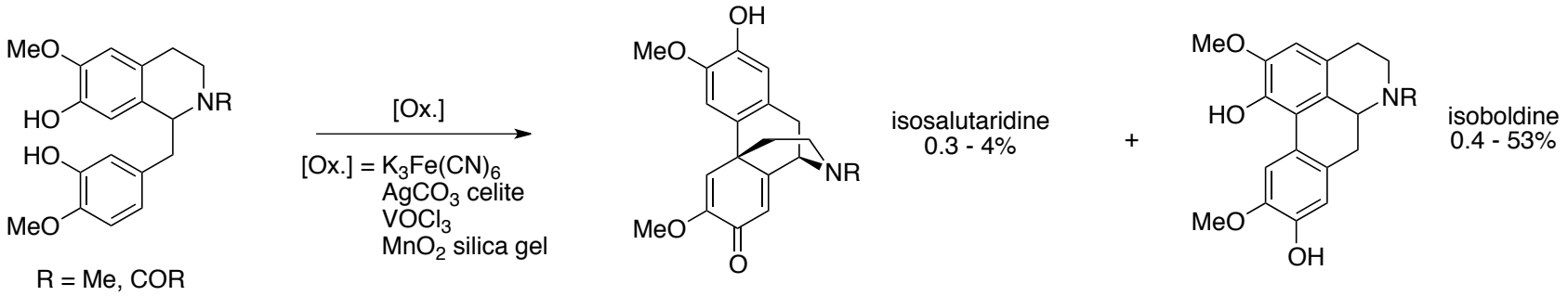




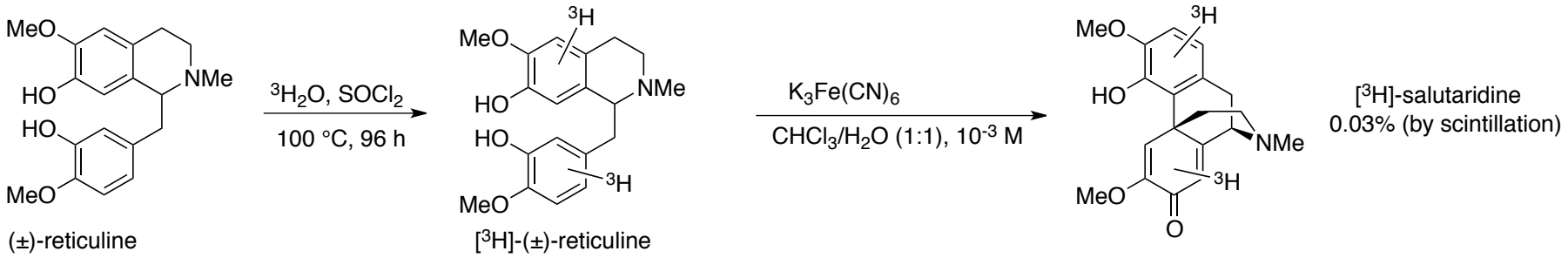
Revision of the biogenesis of morphine and aporphines, and proposal of a key phenolic coupling also for amaryllidaceae and erythrina alkaloids as well as fungal metabolites (usnic acid).

D. H. R. Barton, T. Cohen, *Festschrift Arthur Stoll* **1957**, 177 – 142.

Ox. Phenolic Coupling

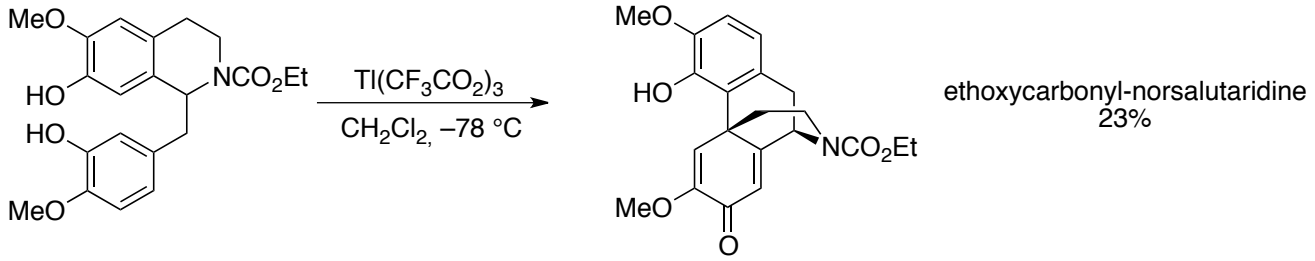


T. Kametani, A. Kozuka, K. Fukumoto, *J. Chem. Soc. C* **1971**, 1021 – 1023.



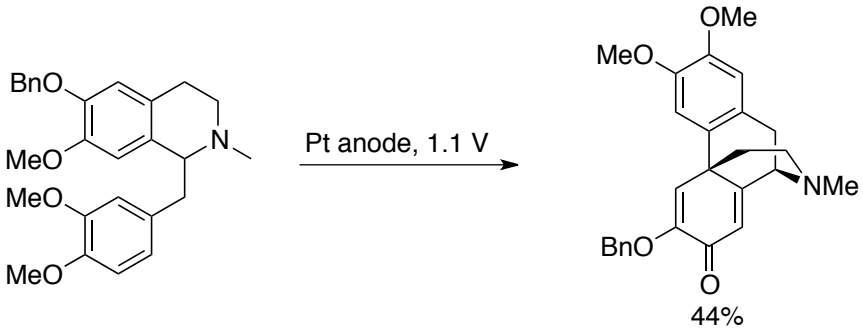
D. H. R. Barton, D. S. Bhakuni, R. James, G. W. Kirby,, *J. Chem. Soc. C* **1967**, 128 – 132.

Oxidative Coupling



M. A. Schwartz, I. S. Mami, *J. Am. Chem. Soc.* **1975**, *97*, 1239 – 1240.

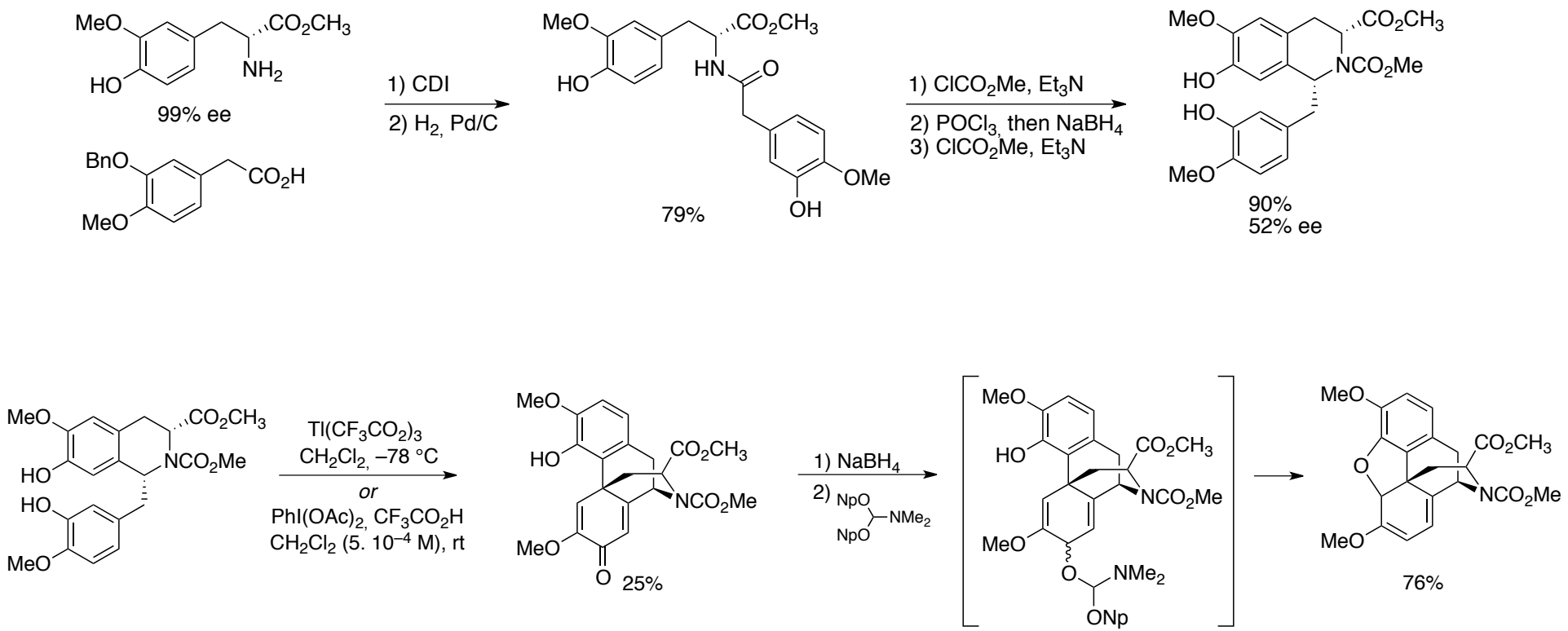
See also: C. Szàntay, *et al.*, *J. Org. Chem.* **1982**, *47*, 594 – 596. M. A. Schwartz, *et al. J. Org. Chem.* **1985**, *50*, 743 – 747. D. A. Burnett, D. J. Hart, *J. Org. Chem.* **1987**, *52*, 5662 – 5667. H. Hara, S. Komoriya, T. Miyashita, O. Hoshino, *Tetrahedron asym.* **1995**, *6*, 1683 – 1692.



L. L .Miller, F. Stermitz, J. R. Falck, *J. Am. Chem. Soc.* **1973**, *95*, 2651 – 2656.

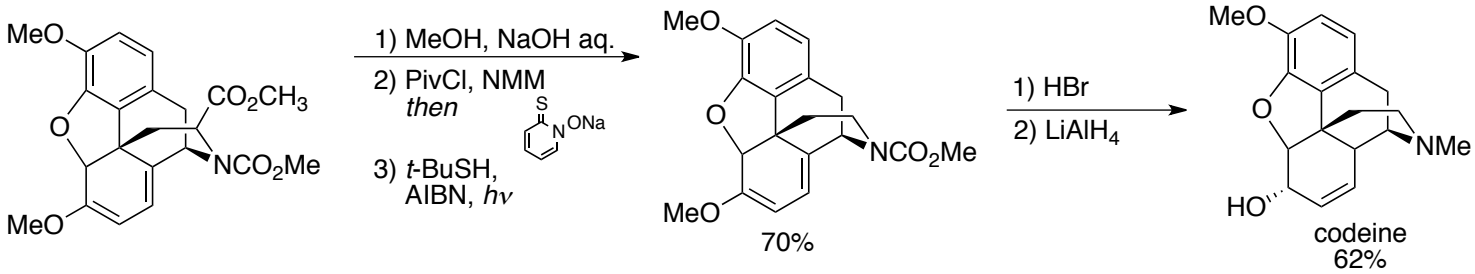
For electrochemical approaches see also: Ronlàn *et al.*, *J. Org. Chem.* **1979**, *44*, 196 – 203.
S. M .Kupchan *et al. J. Am. Chem. Soc.* **1975**, *97*, 5622 – 5623.

Schwartz Codeine Synthesis



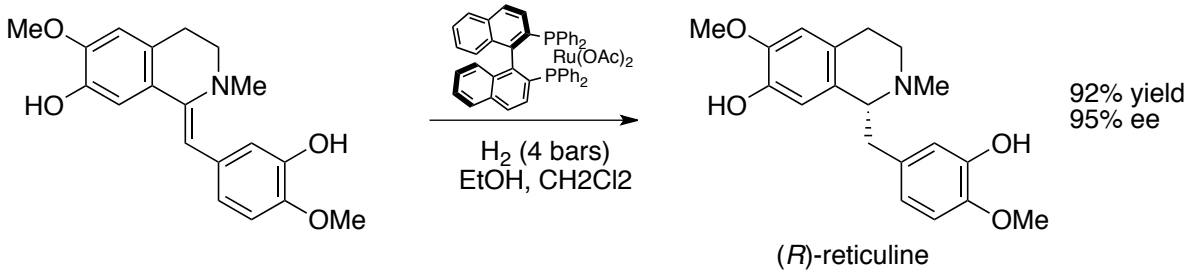
M. A. Schwartz, P. T. K. Pham, *J. Org. Chem.* **1988**, *53*, 2318 – 2322.

Schwartz Codeine Synthesis



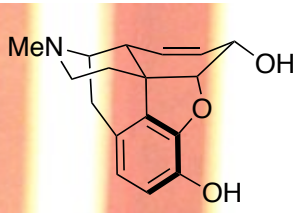
M. A: Schwartz, P. T. K. Pham, *J. org. Chem.* **1988**, *53*, 2318 – 2322.

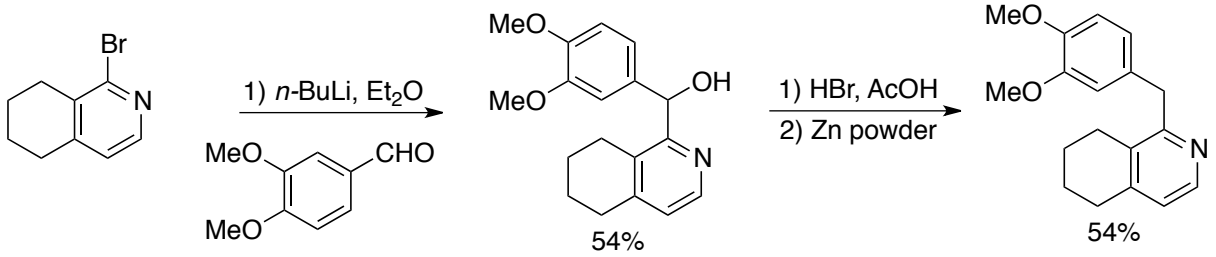
Noyori's synthesis of (*R*)-reticuline in high optical purity ([Ru] cat. Hydrogenation of enamides): access to a rapid asymmetric version.

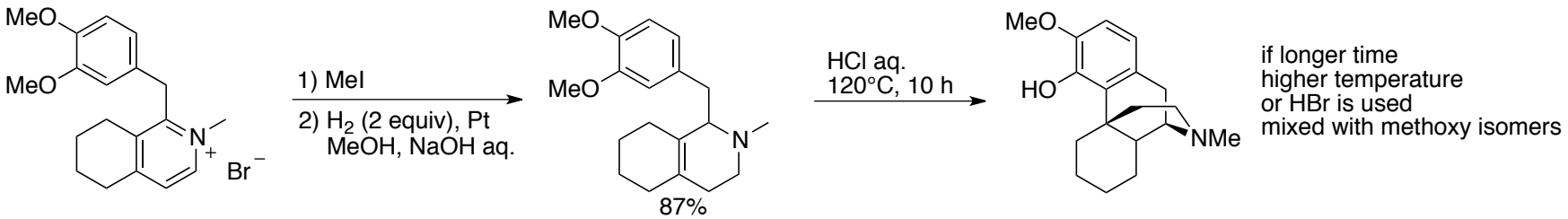


R. Noyori, M. Otha, Y. Hsiao, M. Kitamura, T. Otha, H. Takaya, *J. Am. Chem. Soc.* **1986**, *108*, 7117 – 7119.

Grewe Cyclisation

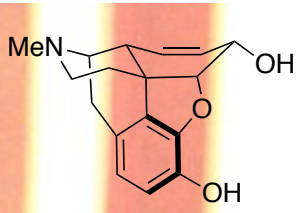


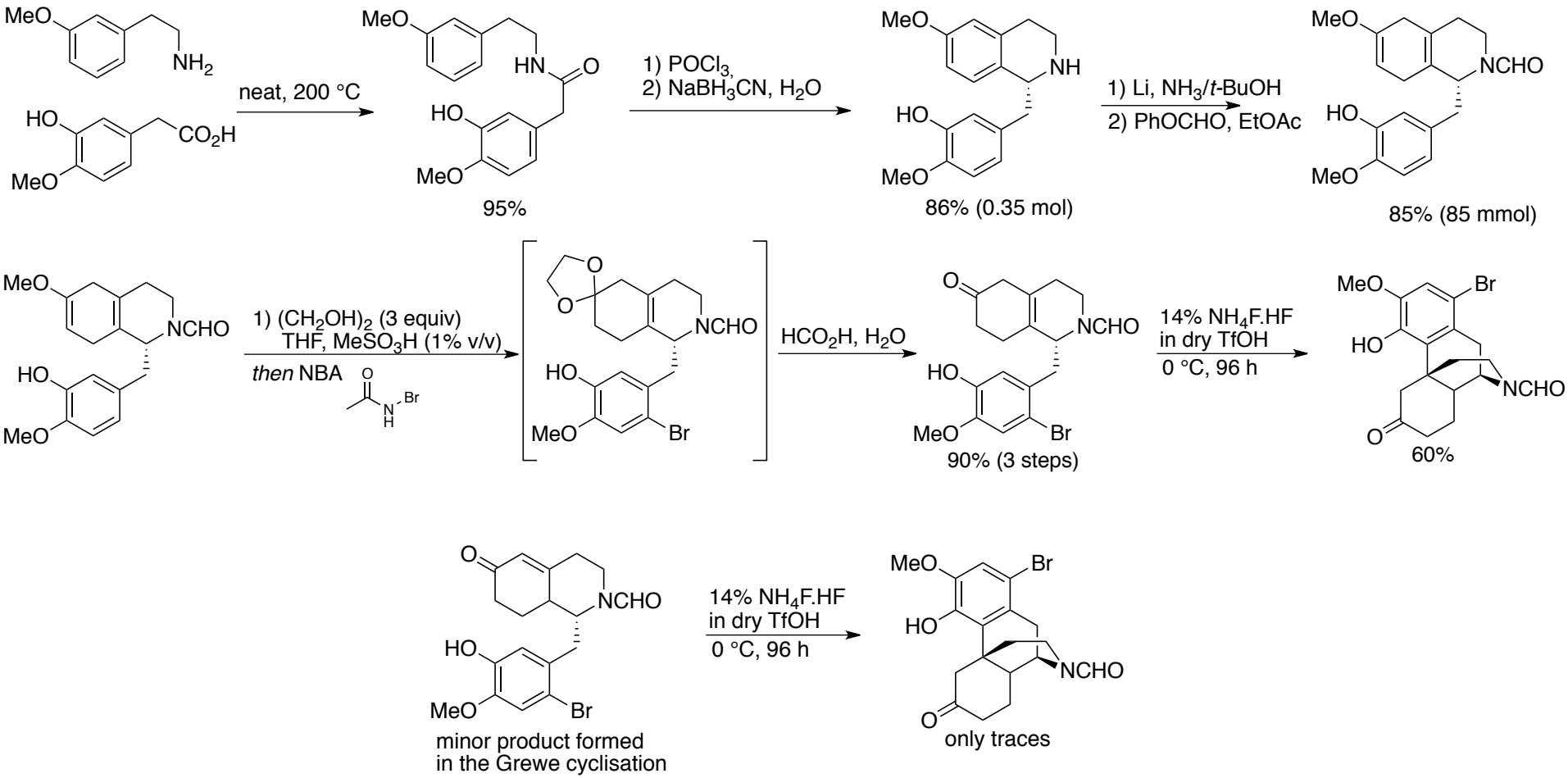




R. Grewe, A. Mondon, E. Nolte, *justus Liebigs Ann. Chem.* **1949,** *564*, 12 – 161 – 198.

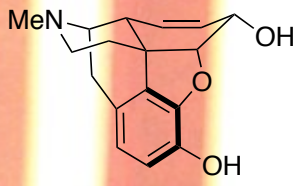
Rice Synthesis

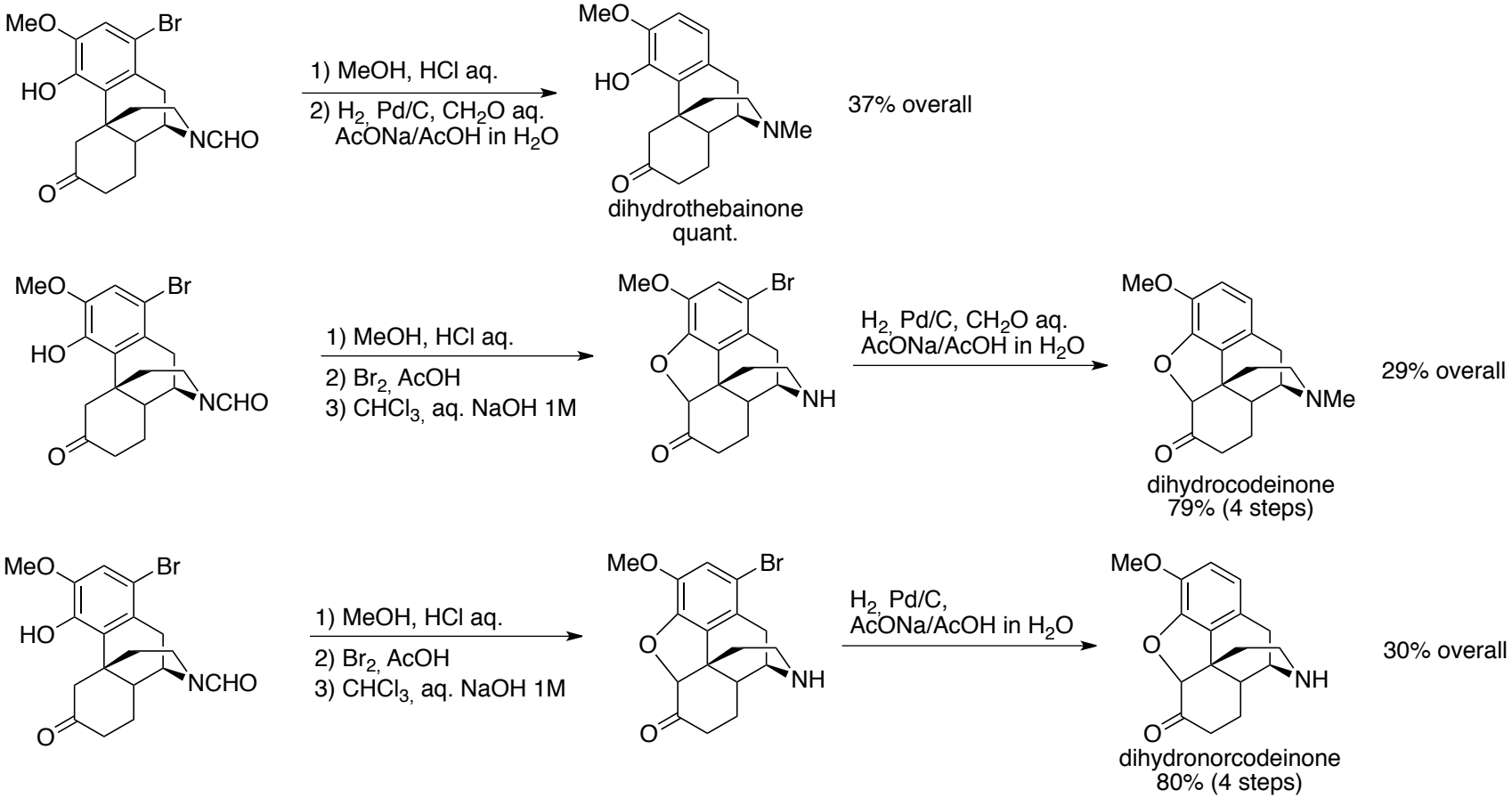




K. C. Rice, *J. Org. Chem.* **1980**, *45*, 3137 – 3139.

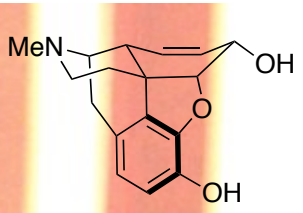
Rice Synthesis

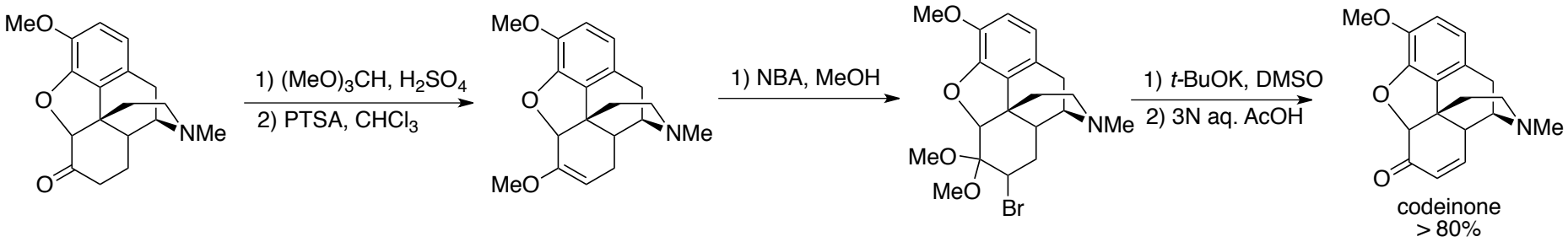




K. C. Rice, *J. Org. Chem.* **1980**, *45*, 3137 – 3139.

End Game to Morphine





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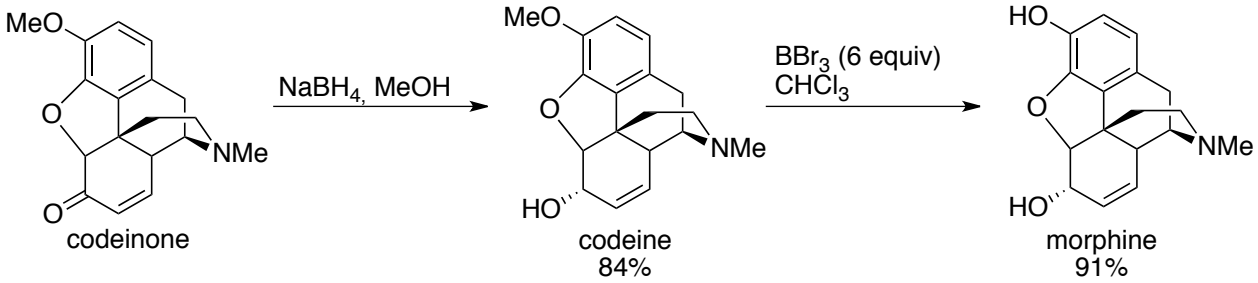
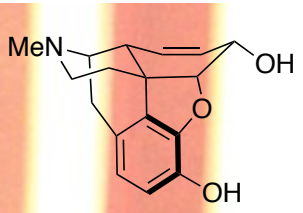
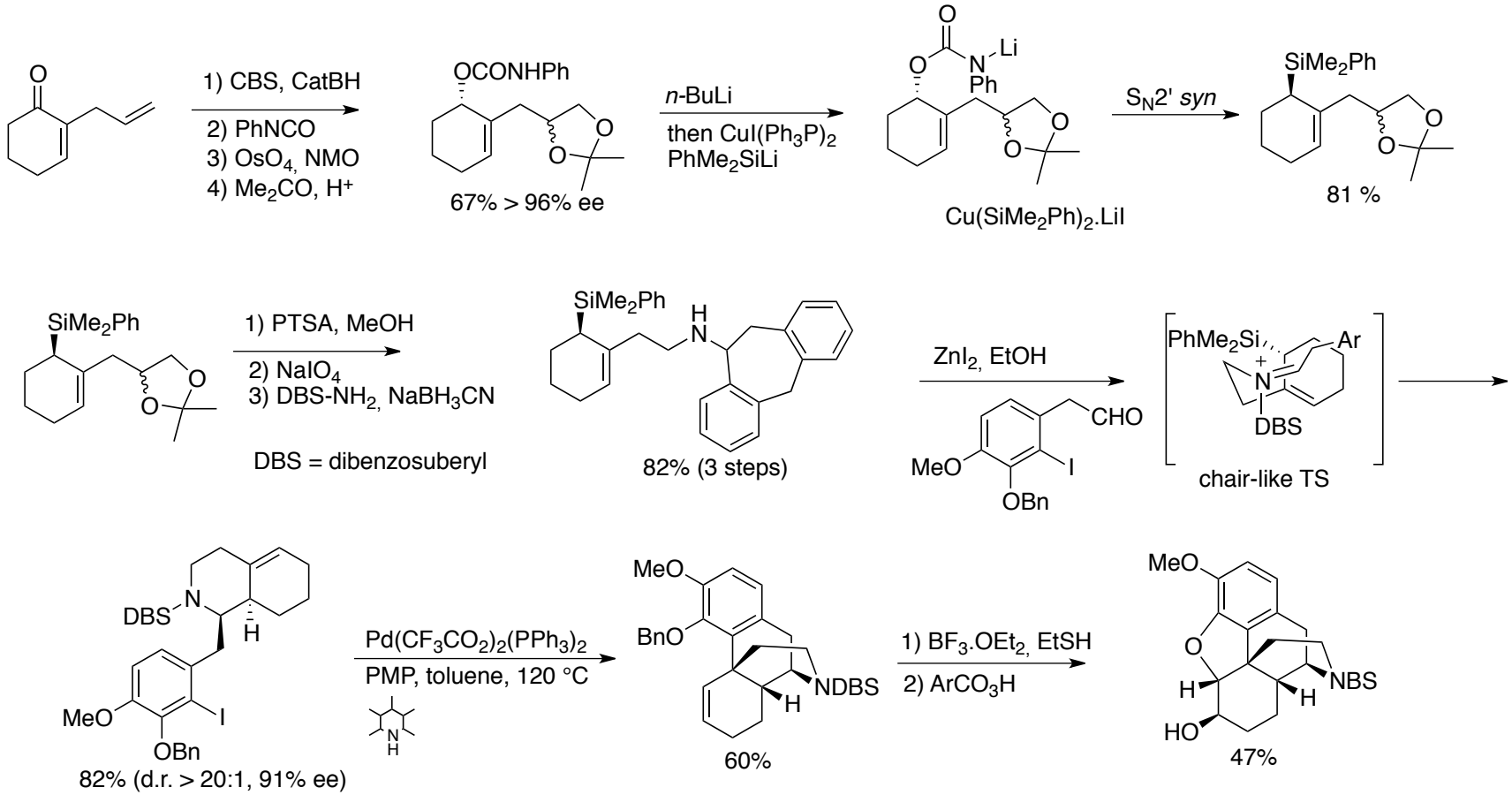


M. Gates *J. Am. Chem. Soc.* **1953**, *75*, 4340 – 4341.

K. C: Rice, *J. Med. Chem.* **1977**, *20*, 164 – 165.

Overman Synthesis





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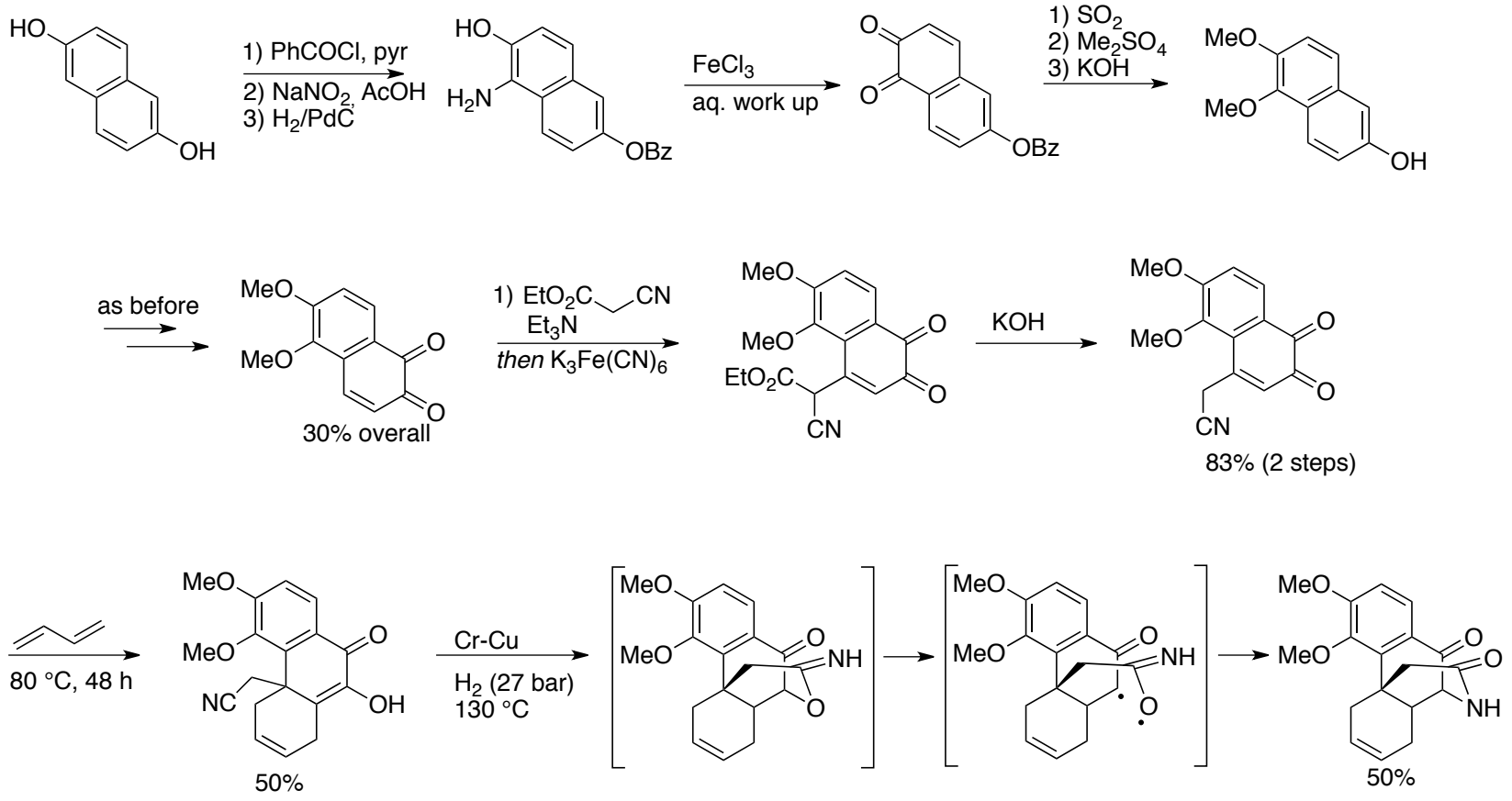
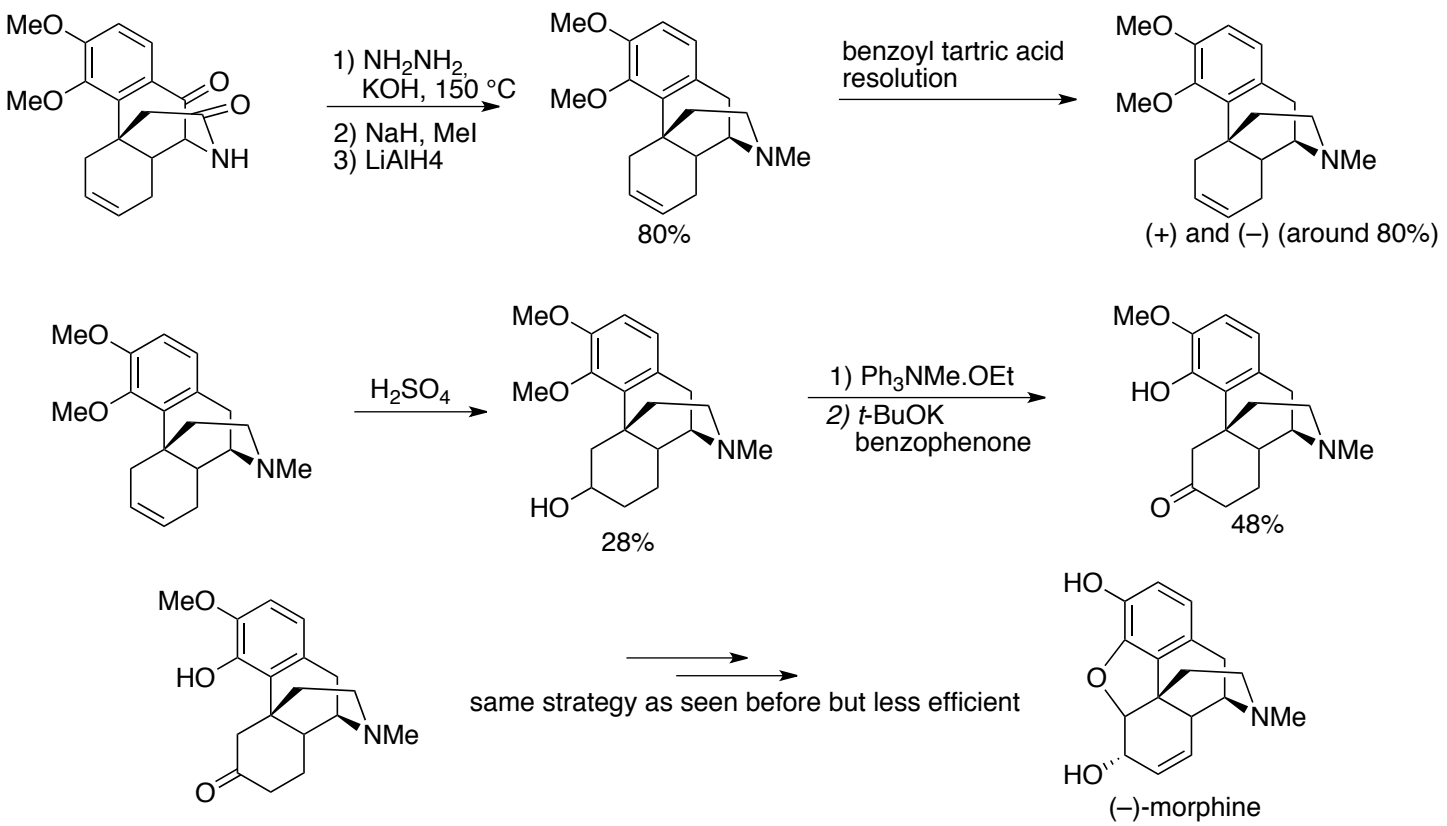
The First Synthesis of Morphine



M. Gates, *J. Am. Chem. Soc.* **1950**, *72*, 228 – 234.
M. Gates, G. Tschudi, *J. Am. Chem. Soc.* **1952**, *74*, 1109 – 1110.

Gates Synthesis



Definitely proved the structure proposed by Robinson

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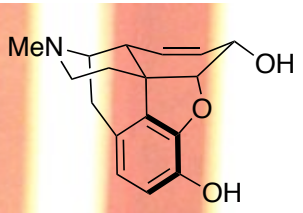
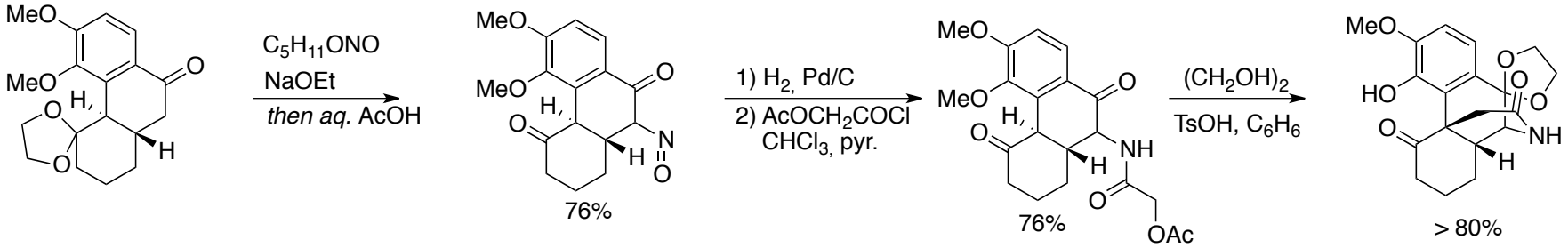
The Phenanthrene Route



Ginsburg unexpected cyclisation



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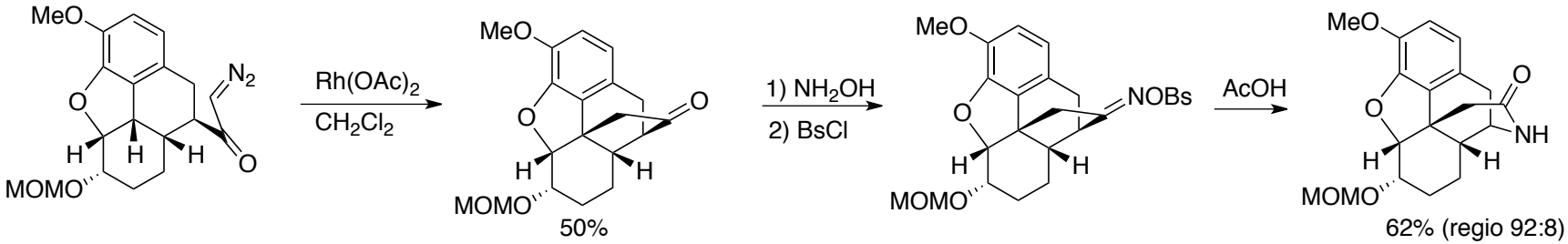
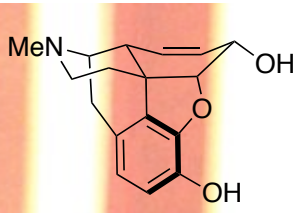
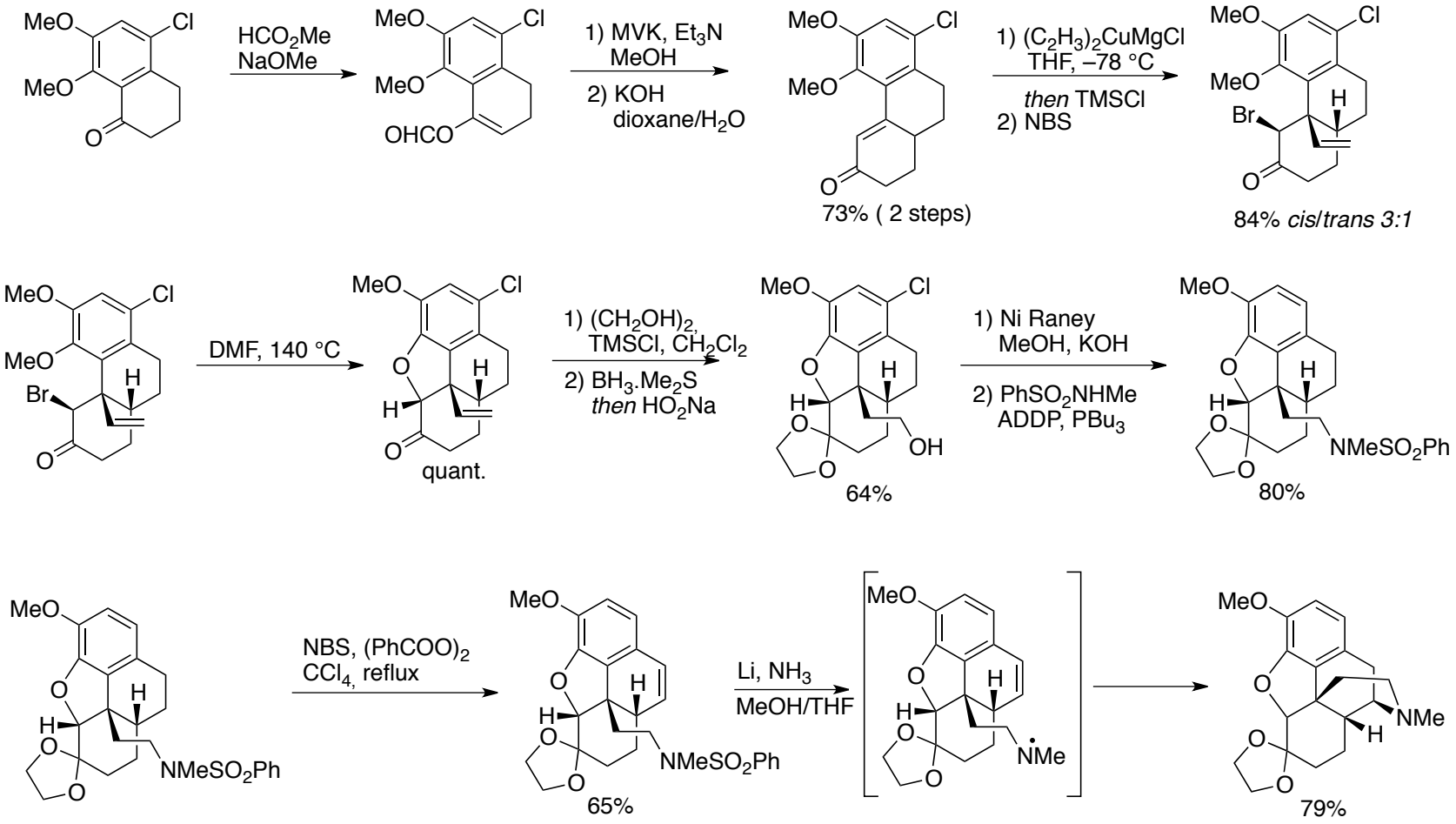
White's C-H insertion



J. D. White, P. Hrnciar, *J. Org. Chem.* **1999**, *64*, 7871 – 7884.

Mulzer Approach





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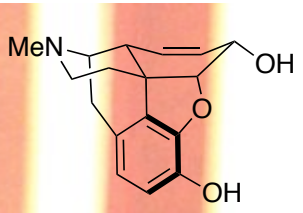
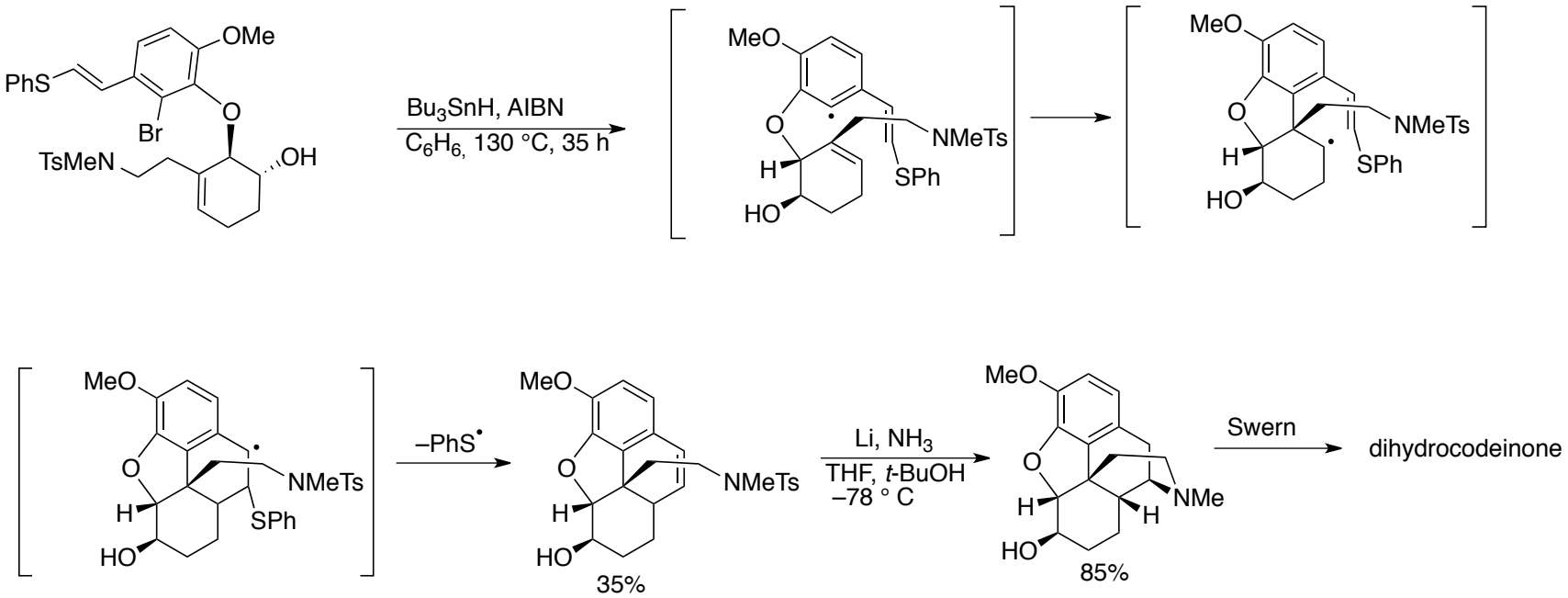
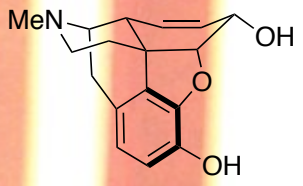
Radical Cyclisation

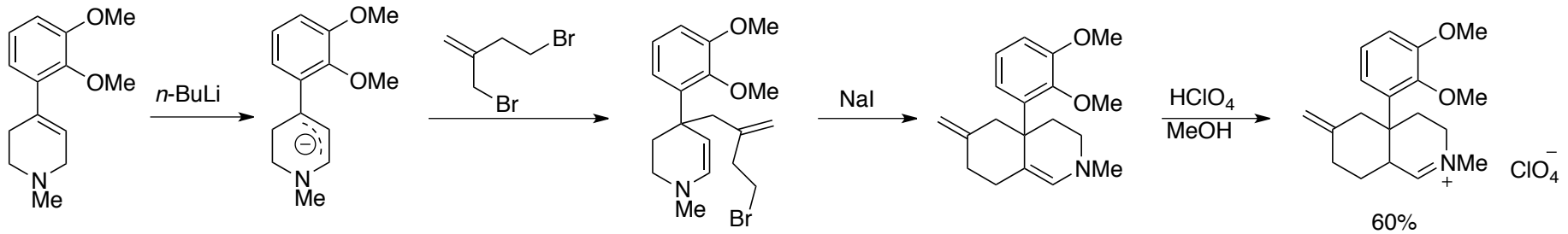


Parker's formal synthesis



Evans Route





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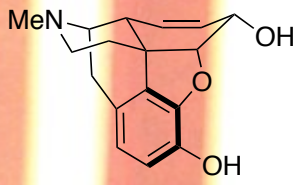
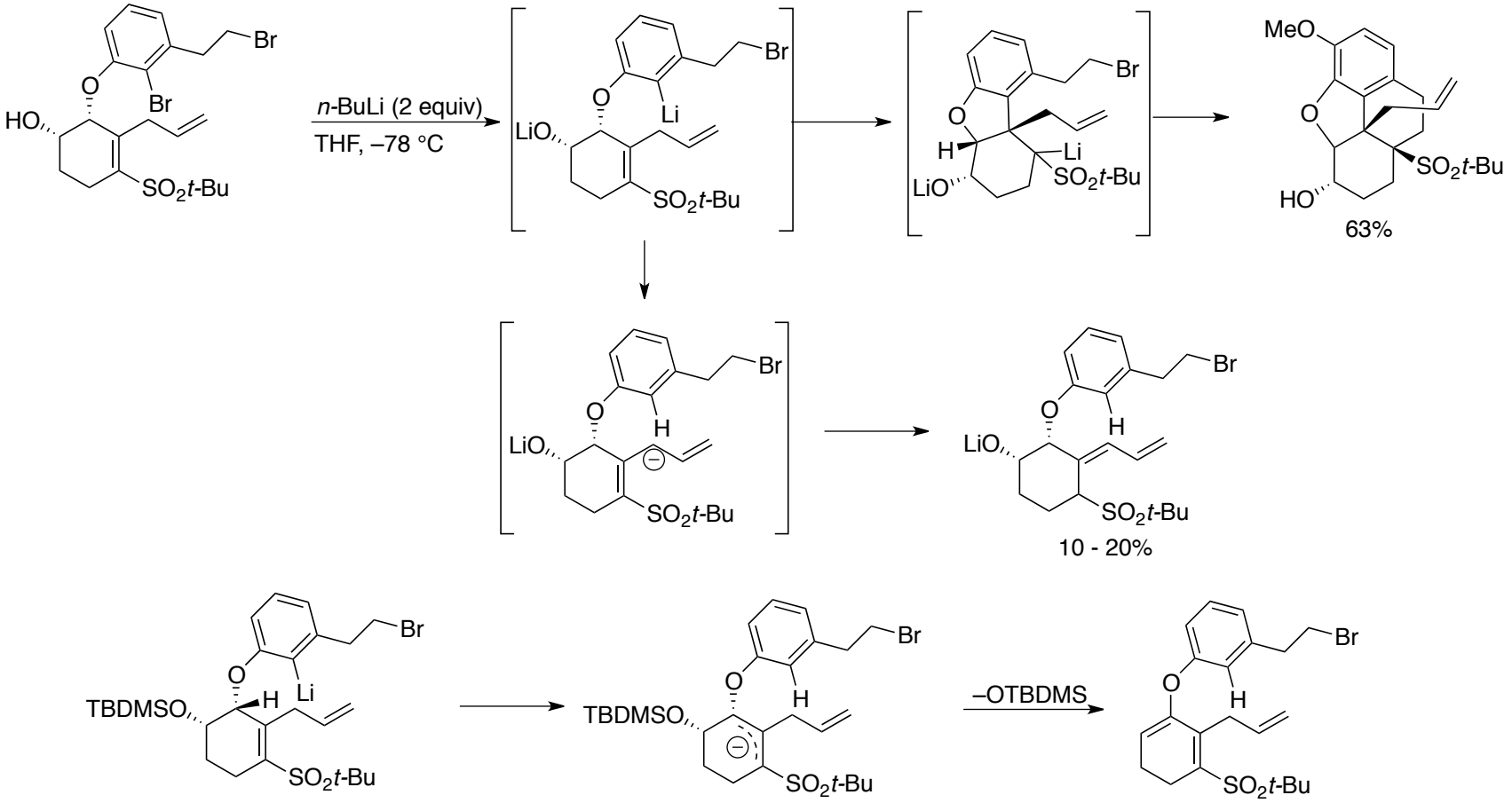
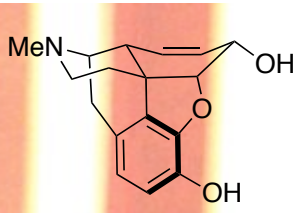
Fuchs Double Cyclisations



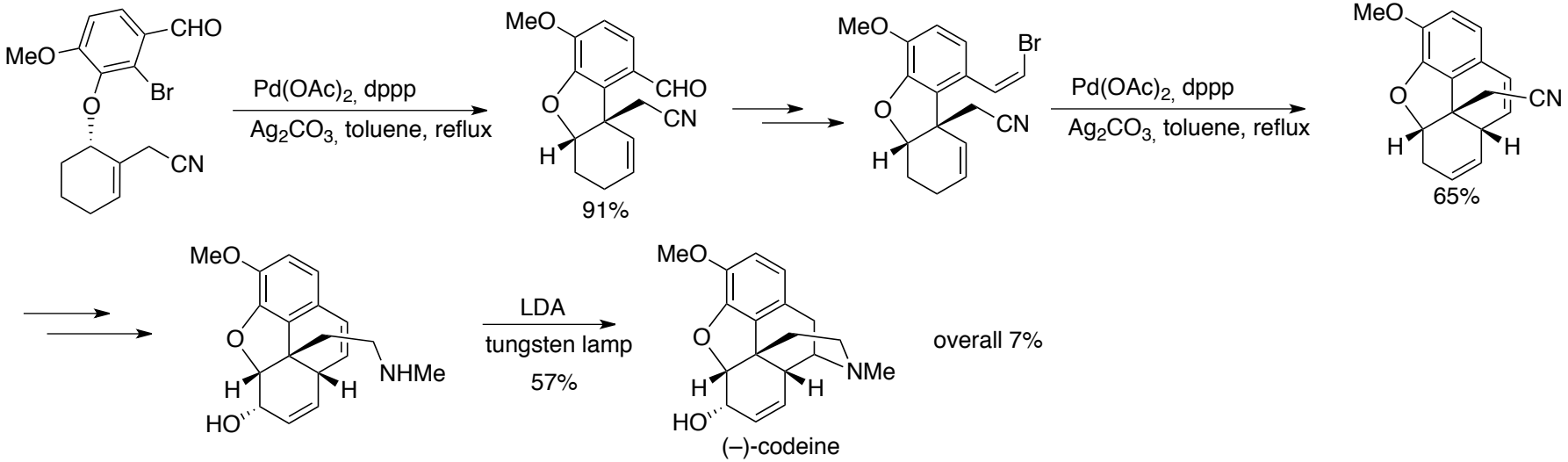


J. E. Toth, P. R. Hamann, P. L. Fuchs, *J. Org. Chem.* **1988**, *53*, 4694 – 4708.

Heck Cyclisations

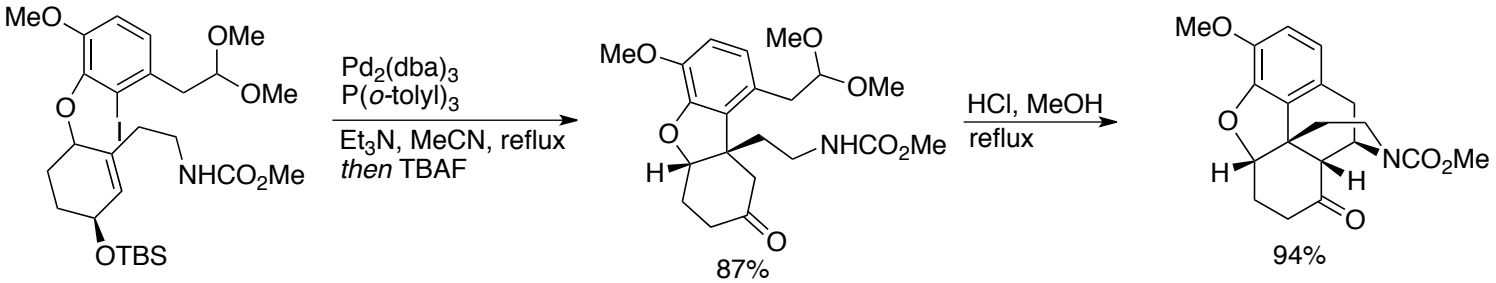


Trost



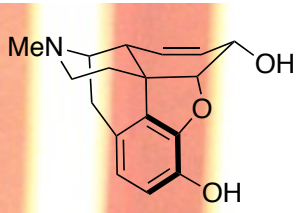
B. M. Trost, W. Tang, *J. Am. Chem. Soc.* **2005**, *127*, 14785 – 14803.

Fukuyama

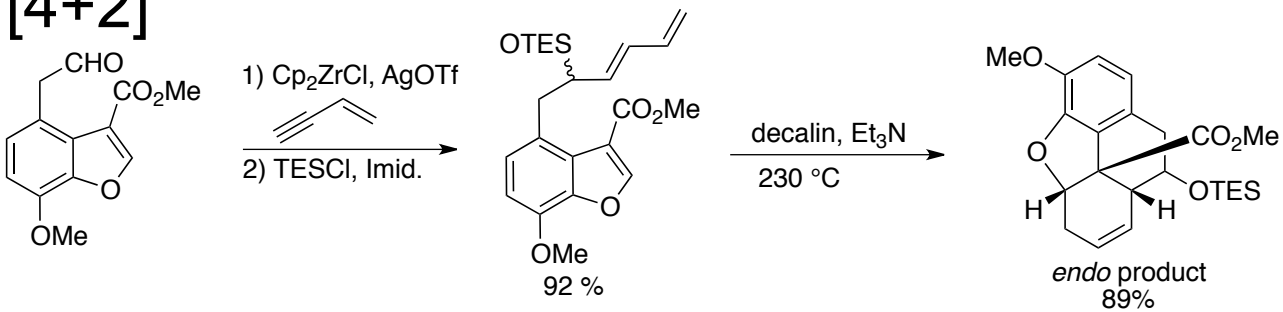


K. Ushida, S. Yokoshima, T. Kan, T. Fukuyama, *Org. Lett.* **2006**, *8*, 5311 – 5313.

Miscellanous



Storck's [4+2]



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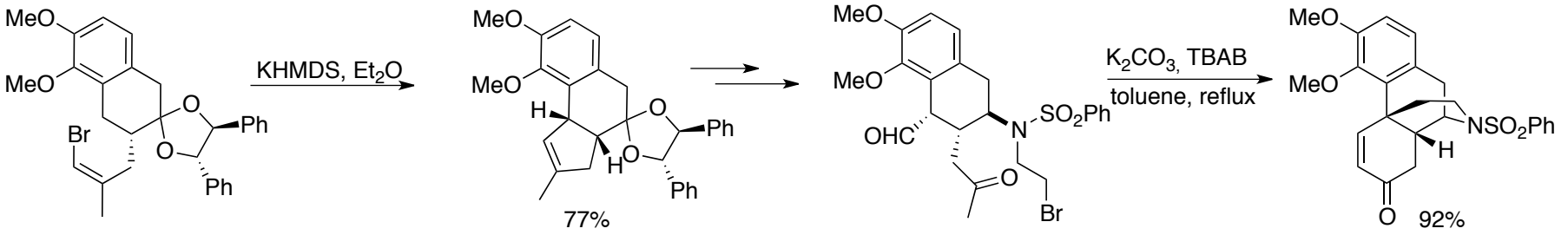
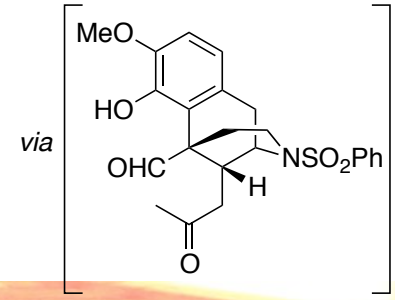
Taber





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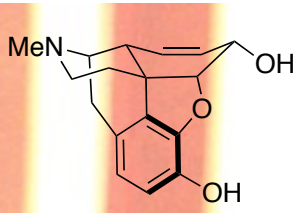
And many others…



Principle author	Date	Product (no. of steps)	Yield (%)
Gates	1952	(–)-Morphine (23)	0.01[6]
Ginsberg	1954	*rac*-Dihydrothebainone (21)	8.86[a,7]
Grewe	1967	*rac*-Dihydrothebainone (9)	0.81[8]
Rice	1980	(–)-Dihydrocodeinone (10)	29.00[9]
Evans	1982	*rac*-*O*-Me-thebainone-A (12)	16.67[10]
Rapoport	1983	*rac*-Codeine (26)	1.15[11]
Fuchs	1988	*rac*-Codeine (22)	1.53[12]
Tius	1992	*rac*-Thebainone-A (28)	0.97[13]
Parker	1992	*rac*-Dihydrocodeinone (12)	9.42[14]
Overman	1993	(–)-Dihydrocodeinone (14)	4.43[15]
Mulzer	1996	(–)-Dihydrocodeinone (15)	11.50[16]
Parsons	1996	Morphine	0.88[b,17]
White	1997	(+)-Morphine (28)	3.00[18]
Hudlicky	1998	10-Hydroxy-*ent*-epi-dihydro-codeinone (14)	2.70[19]
Cheng	2000	*rac*-Desoxycodeine-D (15)	13.26[20]
Ogasawara	2000	*rac*-3,4-Dimethoxy-6-mor-phinanone (29)	0.25[21]
Ogasawara	2001	(–)-Dihydrocodeinone ethyl-ene ketal (24)	0.37[22]
Taber	2002	(–)-Morphine (27)	0.51[23]
Trost	2002	(–)-Codeine (15)	6.78[24]

Guillou synthesis of *rac*-codeine

M. Varin, E. Barré, B. Lorga, C. Guillou, *Chem. Eur. J.*, **2008**, *14* , 6606-6608

Metz synthesis of *rac*-codeine

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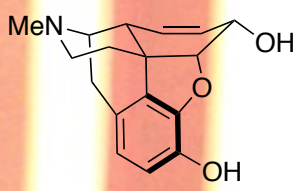
Conclusions



"It is strongly held that the only promising route to an ultimate synthesis of morphine and its congeners is by a path already laid down by Nature." R. Robinson

The most efficient synthesis does not always require the most sophisticated tools.

Still a long way untill the ultimate synthesis…