Current Topics in Organic Chemistry

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Lecture notes:
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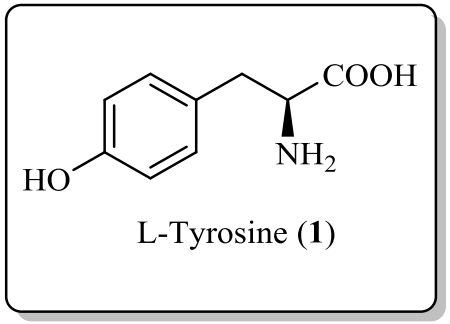
Scheduled meeting times:

Dienstag, 10.03	10:15 – 12:45
Mittwoch, 11.03	10:15 – 12:45
Dienstag, 17.03	10:15 – 12:45
Mittwoch, 18.03	10:15 – 12:45
Dienstag, 31.03	10:15 – 12:45
Mittwoch, 01.04	10:15 – 12:45

Course outline:

The biosynthesis and synthesis of tyrosine-derived alkaloids will be covered.

For a better comparison of total syntheses, several approaches towards the same target are discussed.



L-Tyrosine (**1**)

Phenylethylamines	mescaline, adrenaline
Simple Tetrahydroiso-quinoline alkaloids	salsolinol, lophocorine, tubocurarine
Modified benzyltetrahydro-isoquinoline alkaloids	morphine, codeine, isothebaine, berberine
Modified phenethyltetra-hydroisoquinoline alkaloids	autumnaline, colchicine
Amaryllidaceae alkaloids	galantamine, lycorine, crinine

Examination:

Term paper describing the total synthesis of a tyrosine-derived natural product.

Please find a target of interest to you (and optionally a specific total synthesis) and discuss the topic with me before the end of the class.

A template will be provided at my webpage which should be used for the term paper.

General guideline:
The term paper should follow the typical organization of a review article in the area of total synthesis.

- Introduction: Short introduction on the importance and relevance of the topic
- Biosynthetic considerations: Very short outline of the biosynthesis of the target compound or the alkaloid family.
- The main section should cover a retrosynthetic analysis and the detailed description of the synthetic achievement,
- The conclusion should highlight the key features of the work and also outline problematic steps.
- The final section of the paper is the reference section

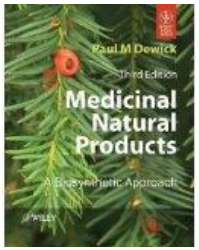
Examination - continued:

Length of the term paper: 7 pages (for example 4 to 5 pages of text and 2 to 3 pages of chemical schemes.

Schemes: Please use ChemDraw or an equivalent drawing program (no copy/paste from journals or any other sources). Apply ACS settings in ChemDraw and reduce the size of the schemes to 80% in Word

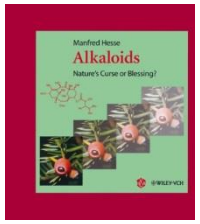
The term paper has to be submitted by June 30 as word file

Recommended Reading:



Medicinal Natural Products: A Biosynthetic Approach.
Paul M. Dewick
John Wiley & Sons Ltd.
ISBN: 978-0-470-74167-2

Naturstoffe der chemischen Industrie
Bernd Schäfer
Elsevier, Spektrum Akademischer Verlag
ISBN: 978-3-8274-1614-8



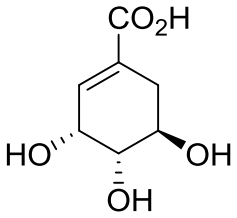
Alkaloids: Nature‘s Curse or Blessing?
Manfred Hesse
Wiley-VCH
ISBN: 3-906390-24-1

The Organic Chemistry of Biological Pathways
John McMurry, Tadhg Begley
Roberts and Company Publishers
ISBN: 0-9747077-1-6

Biosynthesis of tyrosine:

Tyrosine (as well as tryptophane and phenylalanin) are derived by the shikimate pathway.

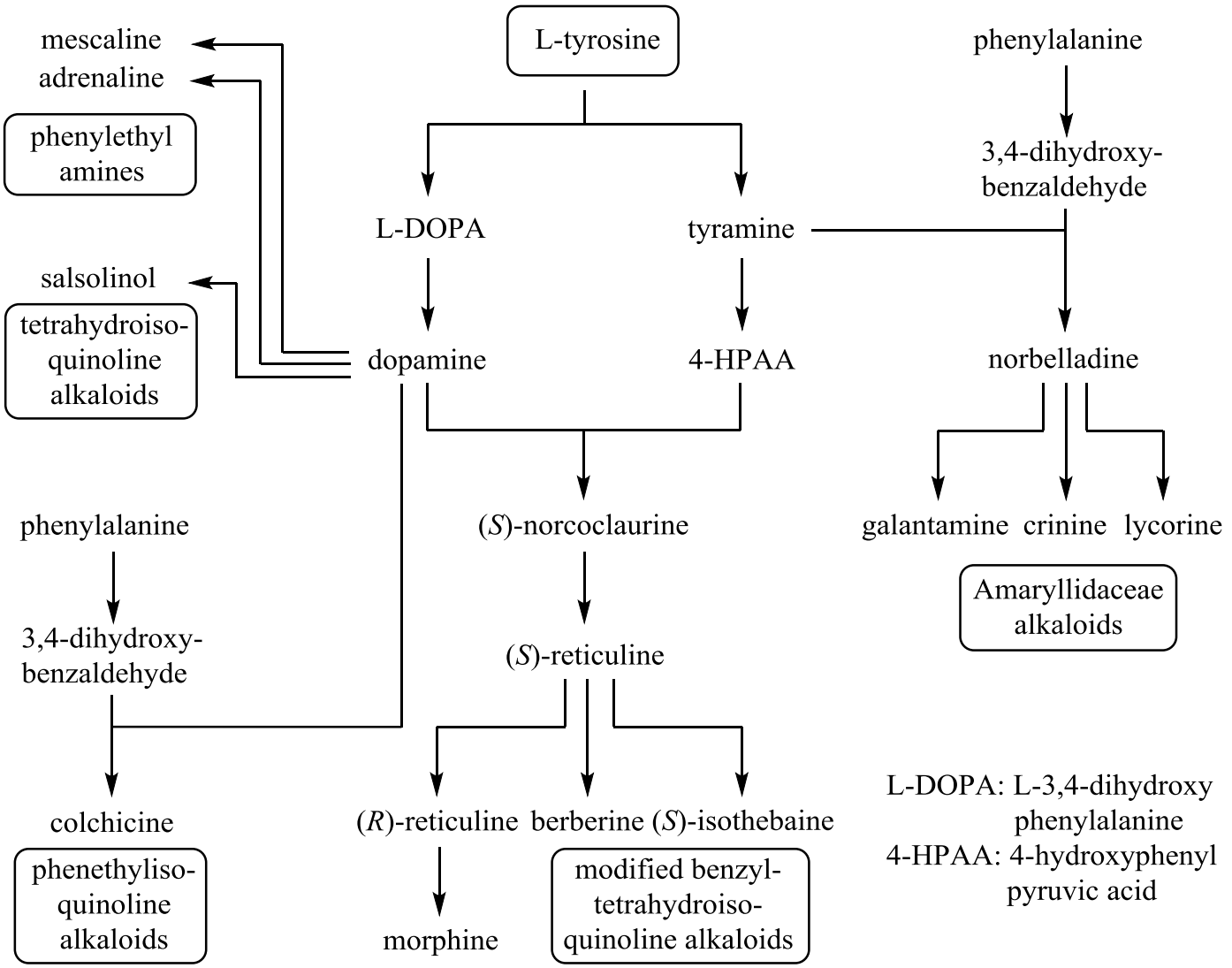
As the shikimate pathway is only active in microorganisms and plants, tyrosine belongs to the class of essential amino acids and has to be obtained in the diet.



Shikimic acid

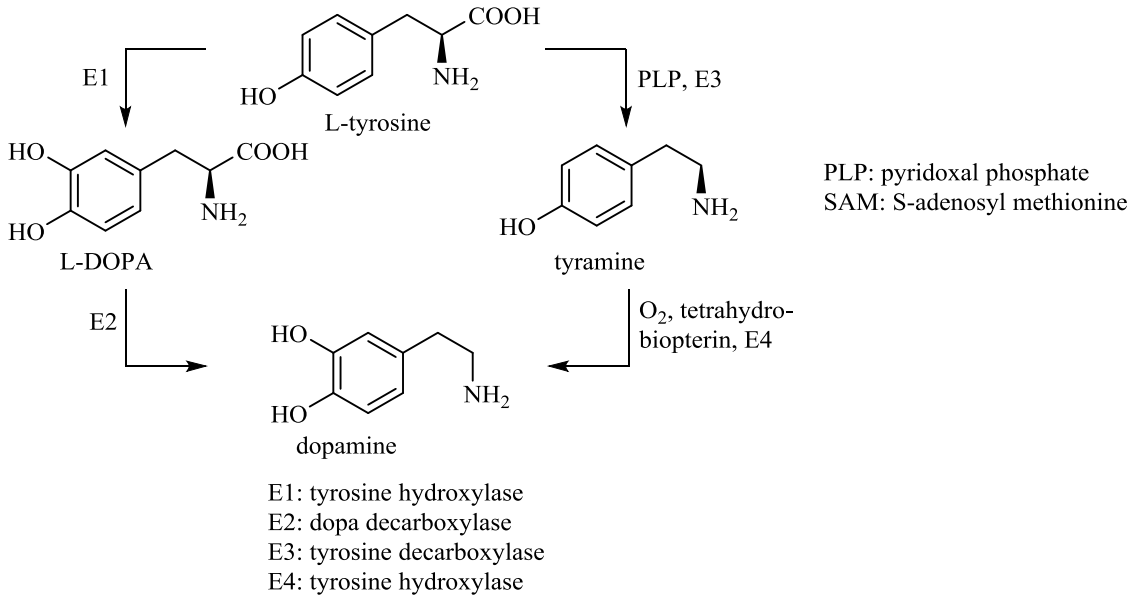
The shikimate pathway is also used for the biosynthesis of simple aromatic compounds such as cinnamic acids, coumarins, or gallic acid. The name of the biosynthetic pathway is derived from a key intermediate, namely shikimic acid, which has been derived from plants of the *Illicium* family (Japanese shikimi).

Tyrosine is an important starting material for a variety of natural products:



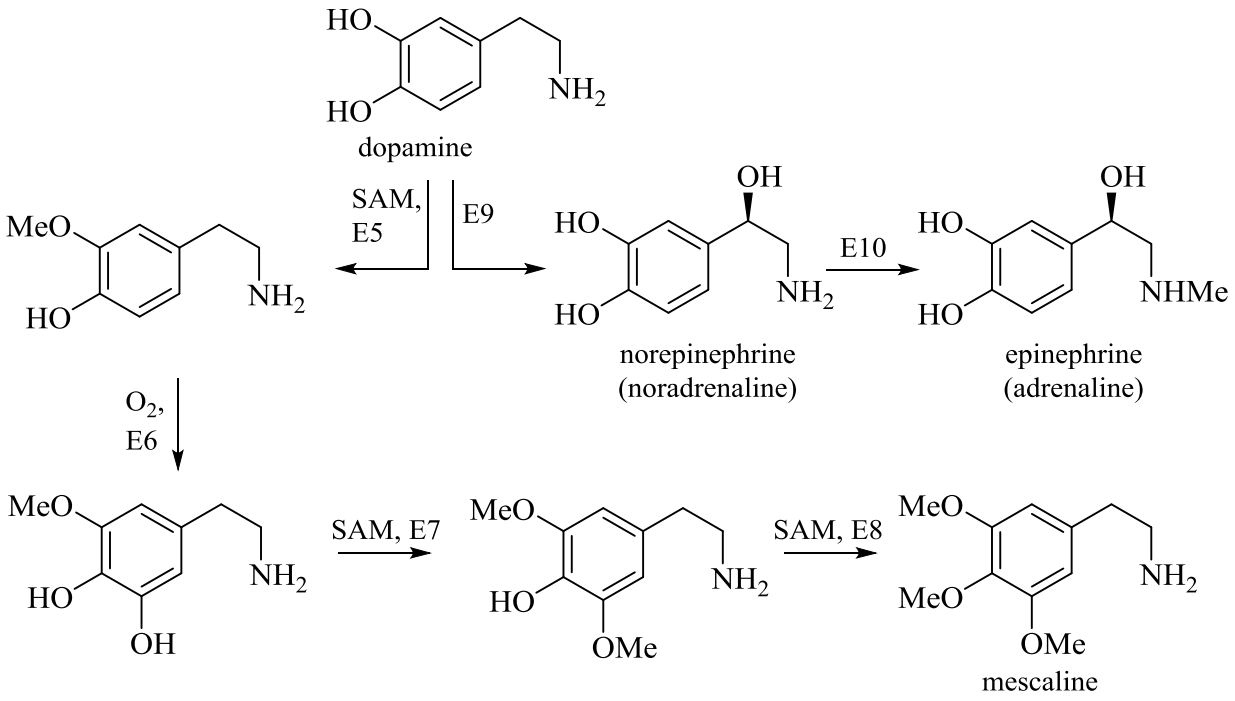
Phenylethylamine derivatives:

Phenylethylamines play an important role as messengers and hormones. The synthesis of these derivatives proceeds via dopamine which can be biosynthesized accroding to the scheme below:



Phenylethylamine derivatives:

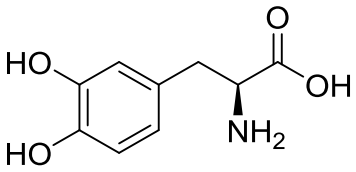
Further functionalization of dopamine results in the formation of a variety of bioactive natural products



E5: catechol *O*-methyl transferase (COMT)
E6: hydroxylase
E7: catechol *O*-methyl transferase (COMT)
E8: guaiacol *O*-methyl transferase (GOMT)
E9: dopamine β-monooxygenase
E10: phenylethanolamine *N*-methyltransferase

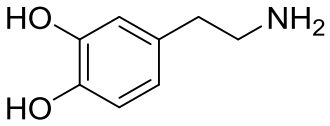
Phenylethylamine derivatives:

L-DOPA (L-3,4-**D**ihydr**o**xy**p**henyl**a**lanin)



Precursor for important neurotransmitters (dopamine, noradrenaline and arenaline).
L-DOPA is able to cross the blood-brain barrier and can be used as medication to increase the level of dopamine in the brain.
L-DOPA is used in the treatment of Parkinson‘s disease.

Dopamine (3,4-dihydroxyphenethylamine)



Dopamine is one of the most versatile biomolecules and the compound plays an important role in controling various completely different and unrelated biological processes.

Phenylethylamine derivatives:

Dopamine (3,4-dihydroxyphenethylamine), continued

Dopamine does not cross the blood-brain barrier. Thus, dopamine can be biosynthesized in different areas of the body and act locally.

Brain: important neurotransmitter responsible for motor control, arousal and the reward system

Immune system: Exact mode of acton is unknown, but dopamine plays a role in the activation and deactivation of responses of the immune system

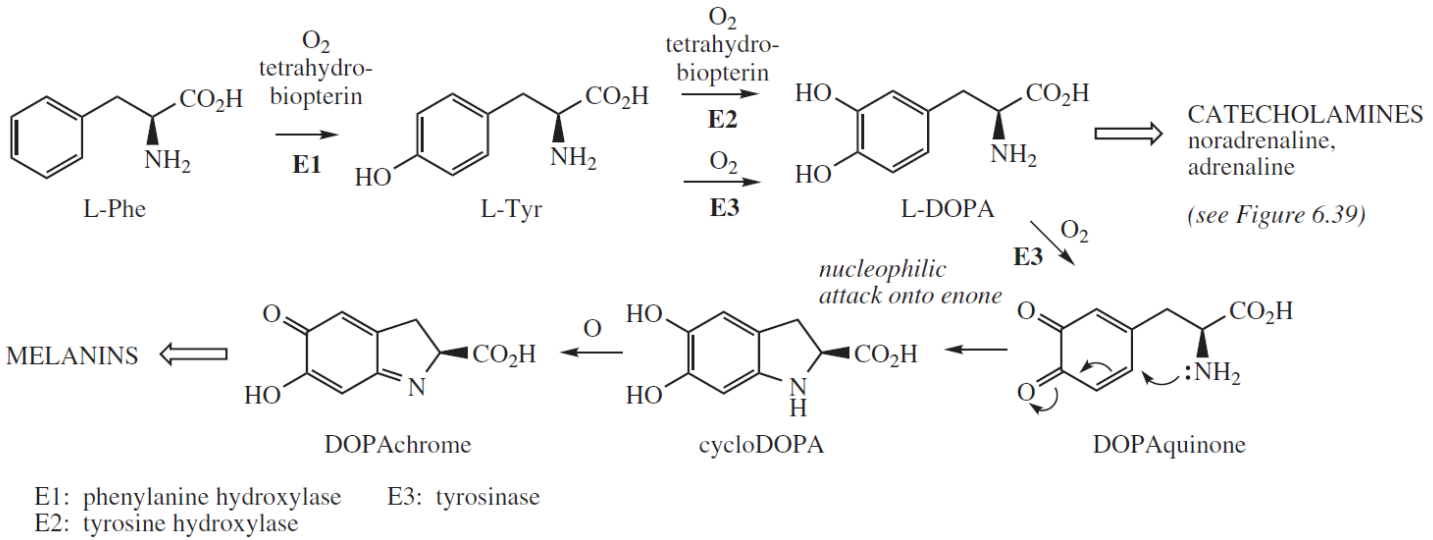
Kidneys: Controls to some part production of urine and the concentration of ions in urine (sodium concentration)

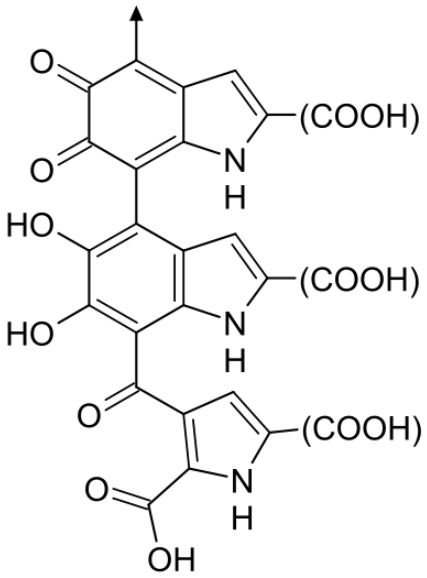
Pancreas: Not fully understood. The pancreas produces dopamine and releases the compound in the bloodstream. Also, dopaine is released into the small intestine where it supposedly protects the intestinal mucosa.

Phenylethylamine derivatives:

Dopamine (3,4-dihydroxyphenethylamine), continued

An interesting side product of dopamine is melanin. Thus, the neurotransmitter is also responsible for sun-induced tanning of the skin.

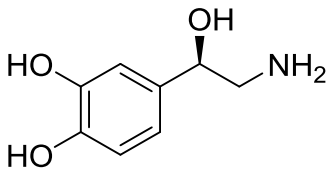




Partial structure of eumelanin

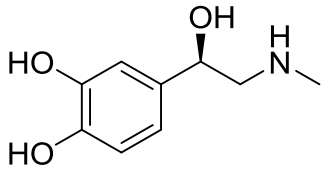
Phenylethylamine derivatives:

Noradrenaline (norepinephrine)



Noradrenaline acts as hormone and neurotransmitter and precursor of adrenaline. The catecholamine is medicinally used to treat acute low blood pressure.

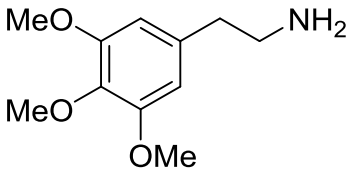
Adrenaline (epinephrine)



Adrenaline is known as stress hormone and related to physiological response to stress of any kind. Medicinally, adrenaline has various potential applications: used to treat cardic arrest; reduces immune response and serves as medication in case of anaphylaxis; bronchodilator used to treat asthma; added to local anesthesia to increase the effect of the medication

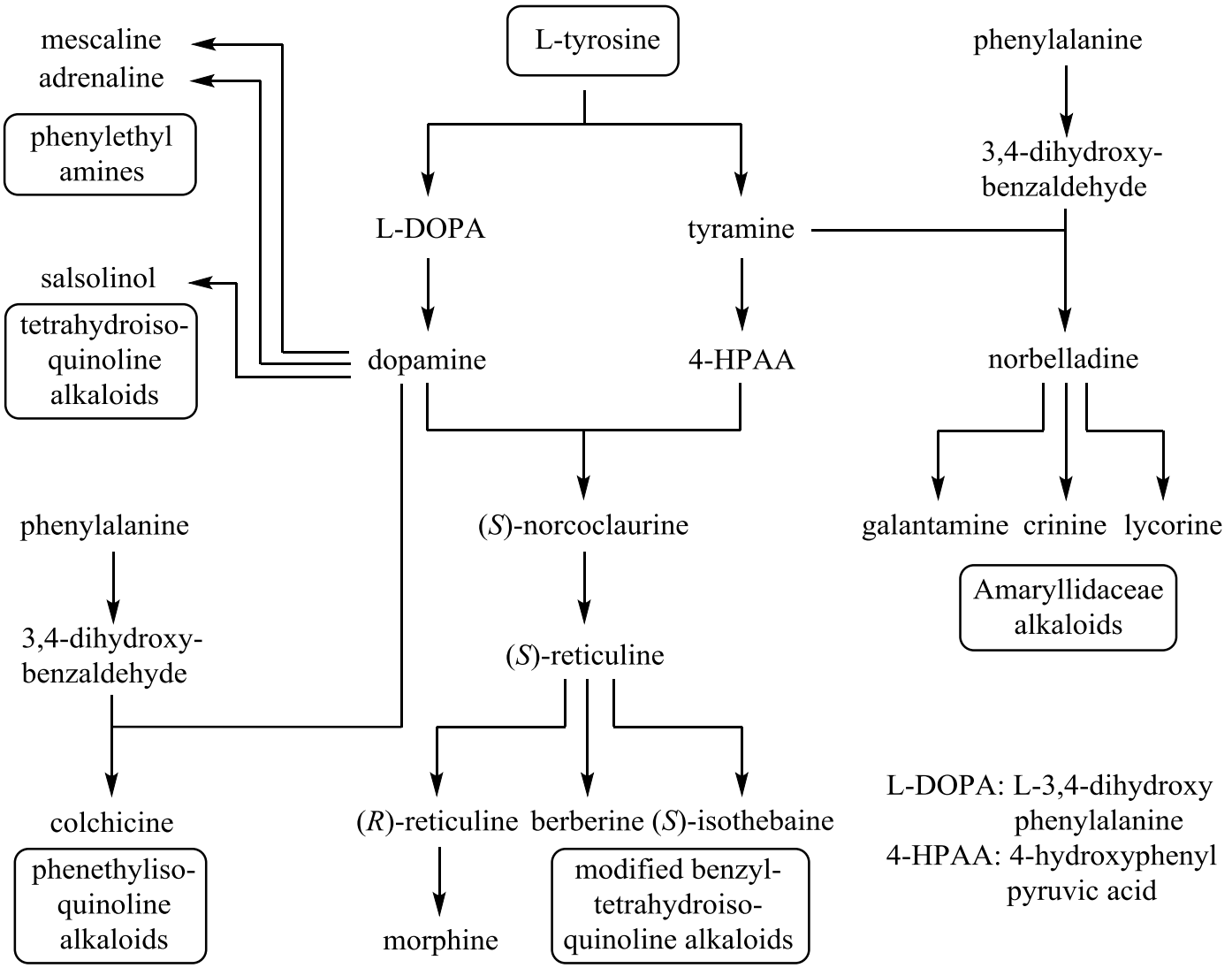
Phenylethylamine derivatives:

Mescaline

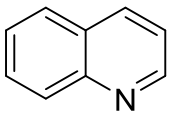


Naturally occurring psychedelic drug with hallucinogenic properties similar to LSD and psilocybin; isolated from the peyote cactus.
Mescalin has been used by Native americans for at least 5700 years.
The compound hs great potential for medical usage; however, ist application is limited because of limited legal access to researchers and patients.

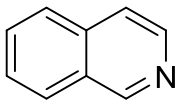
Tyrosine is an important starting material for a variety of natural products:



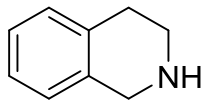
Tetrahydroisoquinoline alkaloids:



Quinoline



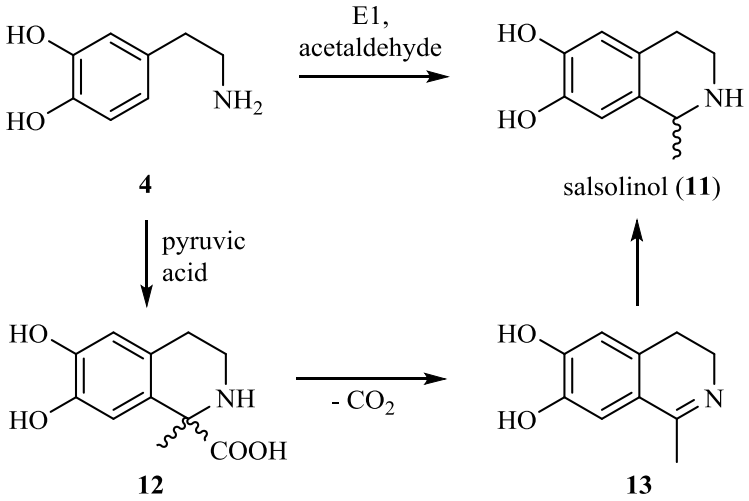
Isoquinoline



Tetrahydroisoquinoline

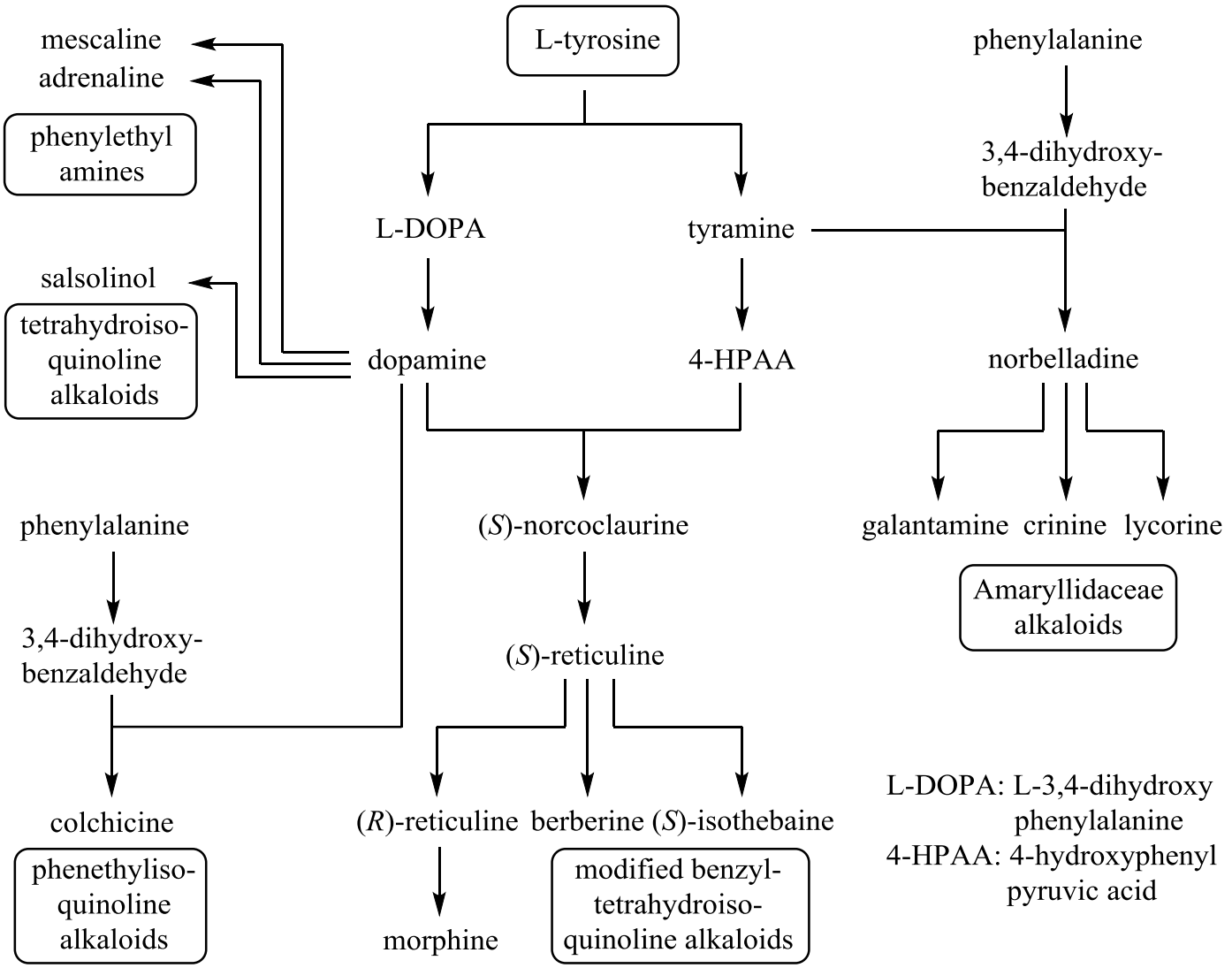
Tetrahydroisoquinline alkaloids are characteristic and representative tyrosine-derived secondary metabolites

Salsolinol is one the structurally simplest tetrahydroisoquinoline alkaloids



E1: salsolinol synthase

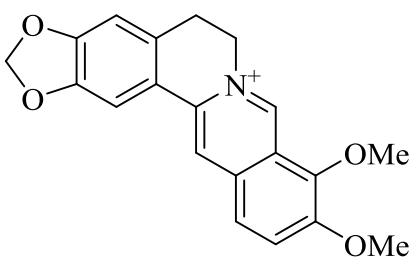
Tyrosine is an important starting material for a variety of natural products:



Modified benzyltetrahydroisoquinoline alkaloids:

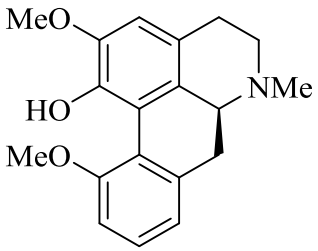
A great variety of structurally complex and intriguing secondary metabolites are derived from benzyltetrahydroisoquinoline derivatives.

Protoberberine, aporphine, and opium alkaloids belong to the most important modified benzyltetrahydroisoquinoline alkaloids which are biosynthesized from a common simple precursor.



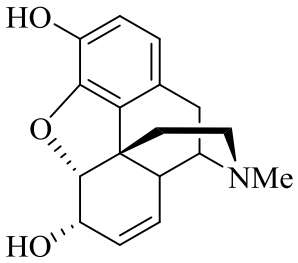
berberine

protoberberine alkaloids



(*S*)-isothebaine

aporphine alkaloids

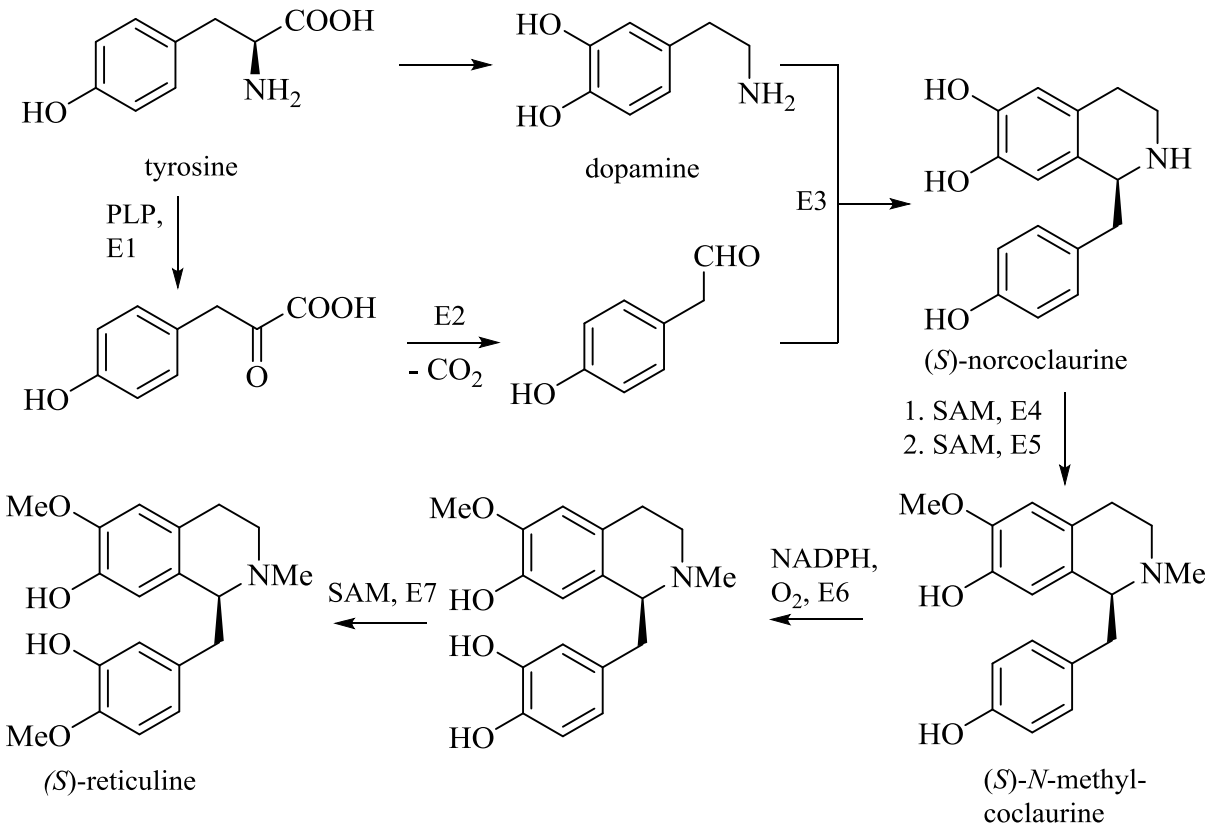


morphine

opium alkaloids

Modified benzyltetrahydroisoquinoline alkaloids:

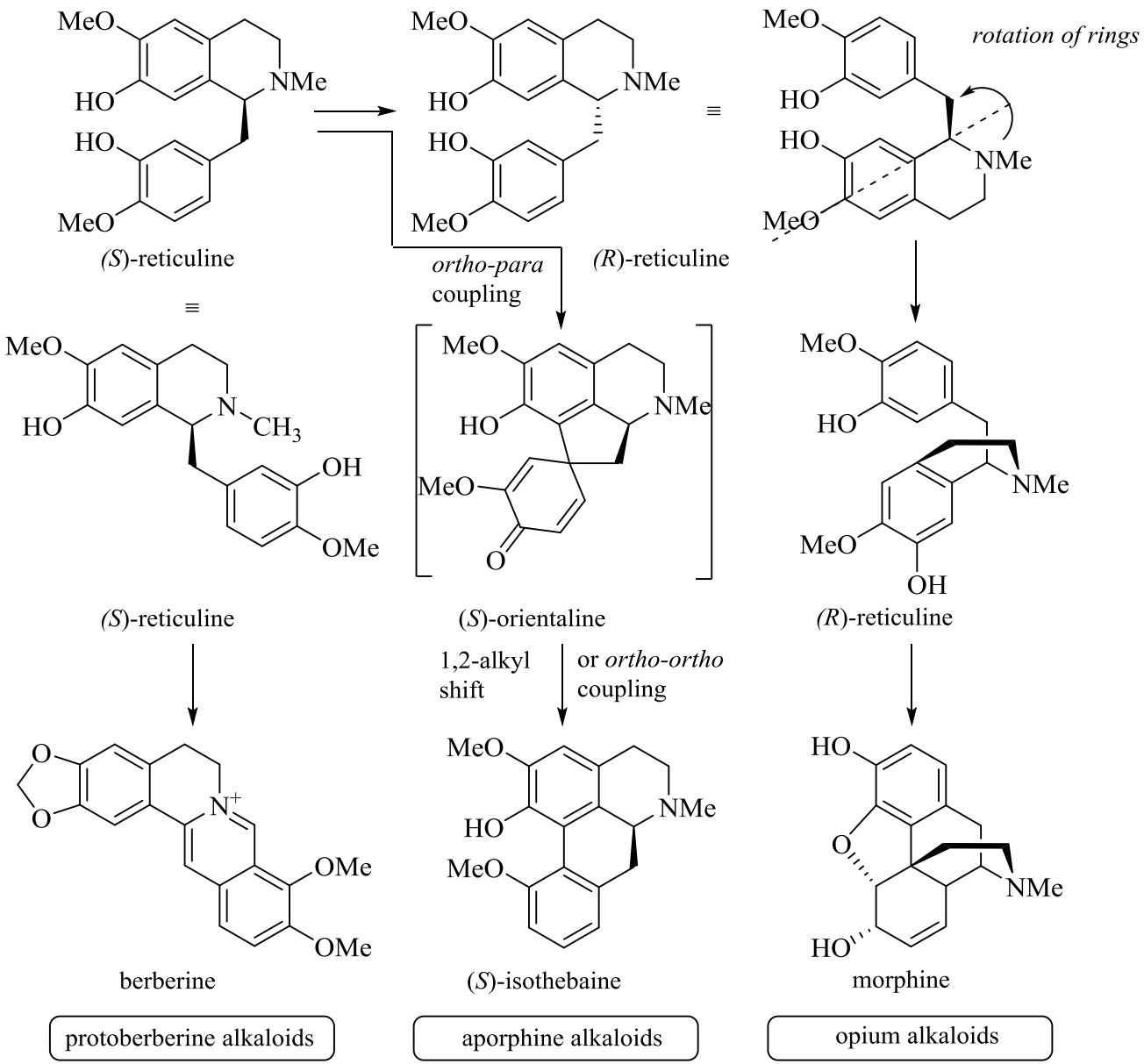
Reticuline is the key intermediate in the biosynthesis of modified benzyltetrahydroisoquinoline alkaloids



E1: tyrosine transaminase
E2: 4-hydroxyphenylpyruvic acid decarboxylase
E3: norcoclaurine synthase
E4: norcoclaurine 6-*O*-methyltransferase
E5: (*RS*)-coclaurine *N*-methyltransferase
E6: (*S*)-*N*-methylcoclaurine 3'-hydroxylase
E7: (*S*)-3'-hydroxy-*N*-methylcoclaurine 4'-*O*-methyltransferase

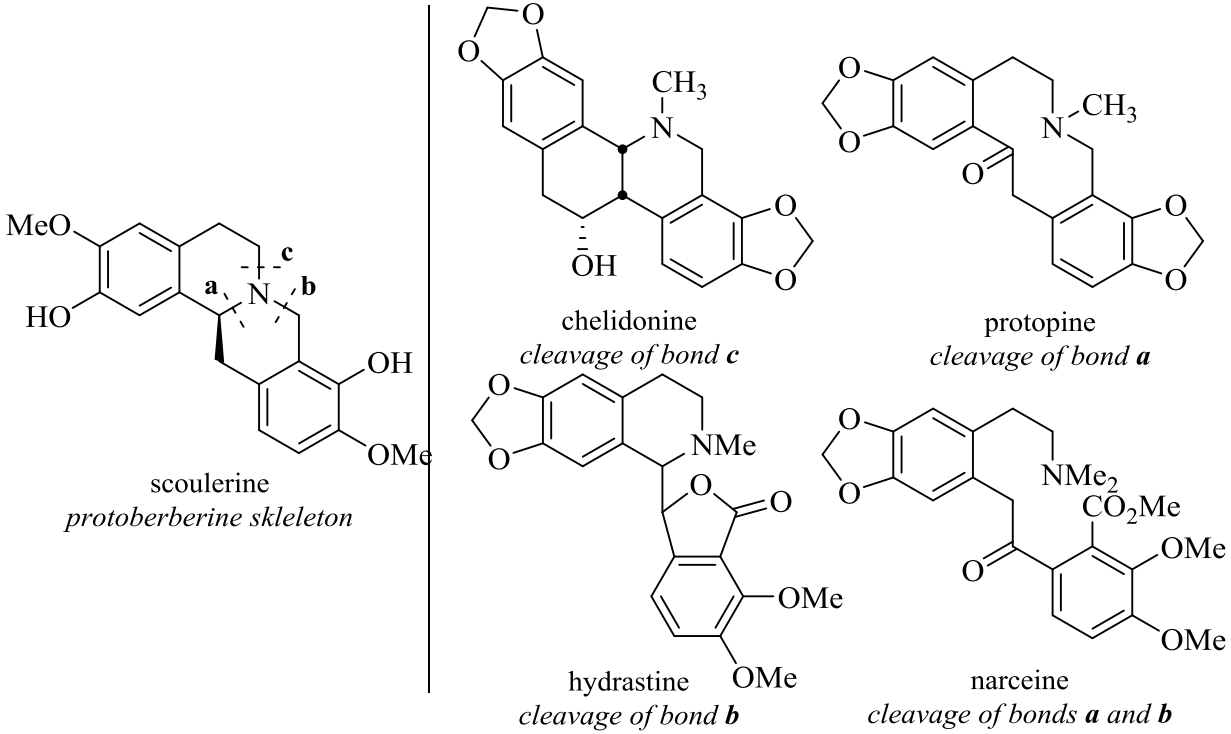
PLP: pyridoxal phosphate
SAM: S-adenosyl methionine

Modified benzyltetrahydroisoquinoline alkaloids:



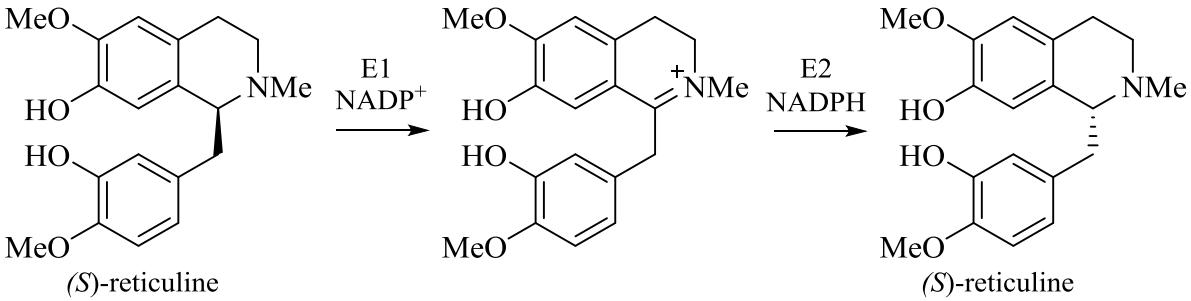
Modified benzyltetrahydroisoquinoline alkaloids:

Structural diversity in protoberberine alkaloids is generated via selective cleavage of C-N bonds in the parent compound



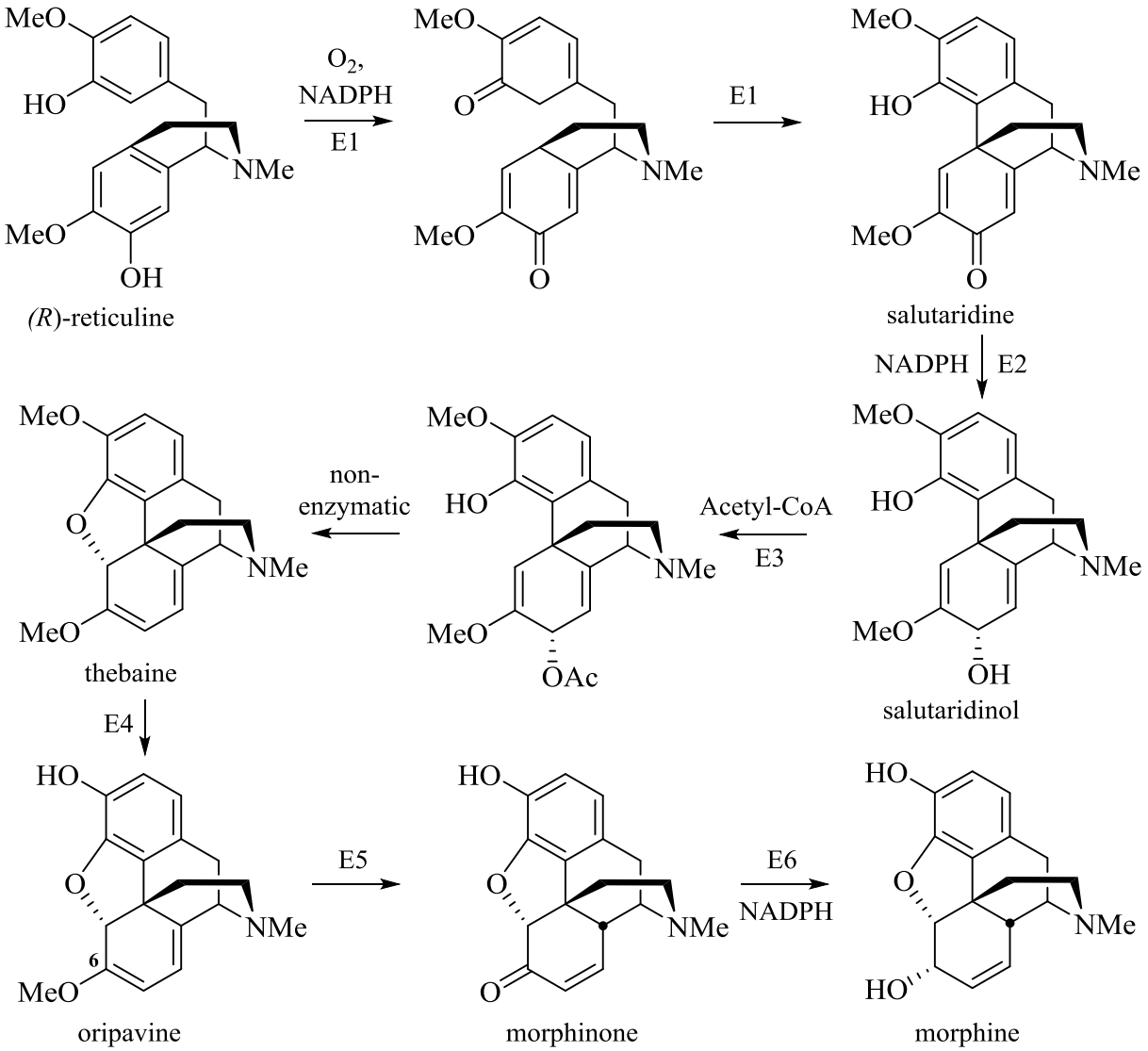
Modified benzyltetrahydroisoquinoline alkaloids:

The biosynthesis of opium alkaloids requires the correction configuration of the stereocenter in (S)-reticuline.



E1: 1,2-dehydroreticuline synthase
E2: 1,2-dehydroreticuline reductase

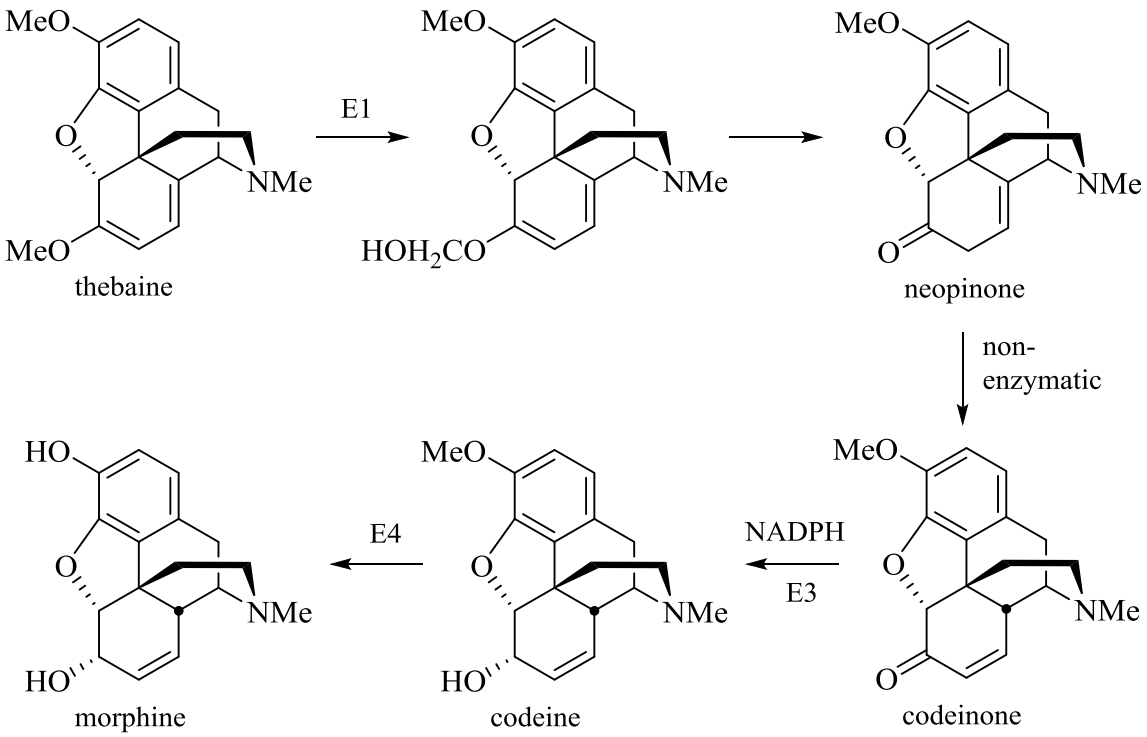
Modified benzyltetrahydroisoquinoline alkaloids – biosynthesis of morphine:



E1: salutaridine synthase
E2:salutaridine NADPH 7-oxidorectuase
E3:salutaridinol 7-O-acyltransferase
E4: codeine-O-demethylase
E5: thebaine 6-O-demethylase
E6: codeinone reductase

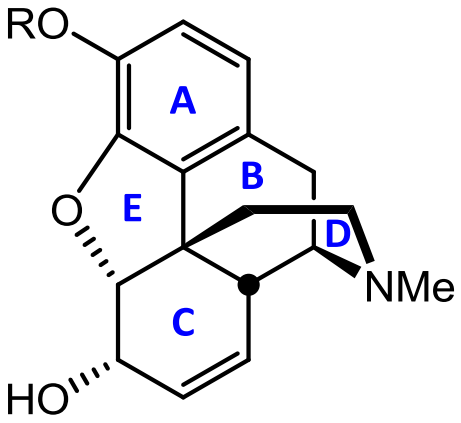
Modified benzyltetrahydroisoquinoline alkaloids – biosynthesis of morphine:

Alternative (and more common) route from thebaine:

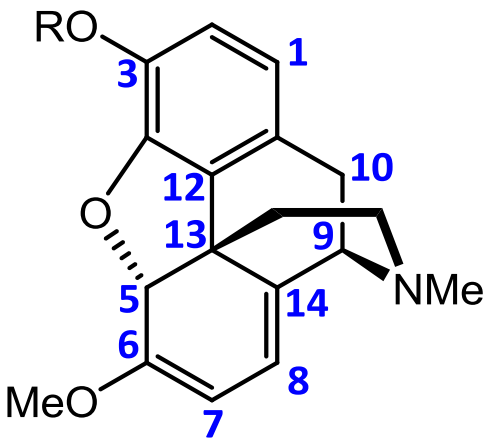


Opium alkaloids:

Opium alkaloids belong to the most important natural products as they exhibit pronounced biological activity.
Additionally, morphine is (still) one of the most attractive synthetic targets.



morphine (**1**), R = H
codeine (**2**), R = Me



thebaine (**3**), R = Me
oripavine (**4**), R = H

Origin of Morphine: *Papaver somniferum* and related poppy plants:

More than 700 different members of this plant family are known.

Papaver lateritium

Origin of Morphine: *Papaver somniferum* and related poppy plants:

Papaver radicatum

Papaver somniferum

Origin of Morphine: *Papaver somniferum* and related poppy plants:

Papaver somniferum

Papaver hybridum

Opium – historic aspects:

First indication of the cultivation of poppy plants can be traced back to the Stone Age. Poppy seed was found in ancient settlements in the Bodensee area (Switzerland). Interestingly, the species found in these settlements was not endemic in Switzerland – one of the earliest examples of international trade…
Poppy plants need warm climate for the production of narcotics)

Poppy plants and poppy seeds were common and highly valued „food additives“ in Mesopotamia, Ancient Rome and Greece. The plant was used for nutrition, medicial treatments and „religious“ rites.

Morphine – biological activity:

Morphine acts as agonist for morphine receptors (mainly μ-opioid receptor), predominantly in the central nervous system but also in muscle cells

- used to treat acute and chronic pain
- traditionally used for the treatment of acute pulmonary edema
- releases symptoms of shortness of breath
- used as analgetic (3 to 4 hours, maximum 6 hours)
- substitution therapy for drug addicts (if buprenorphine or methadone does not give satisfactory results)
- muscle relaxant
- euphoria

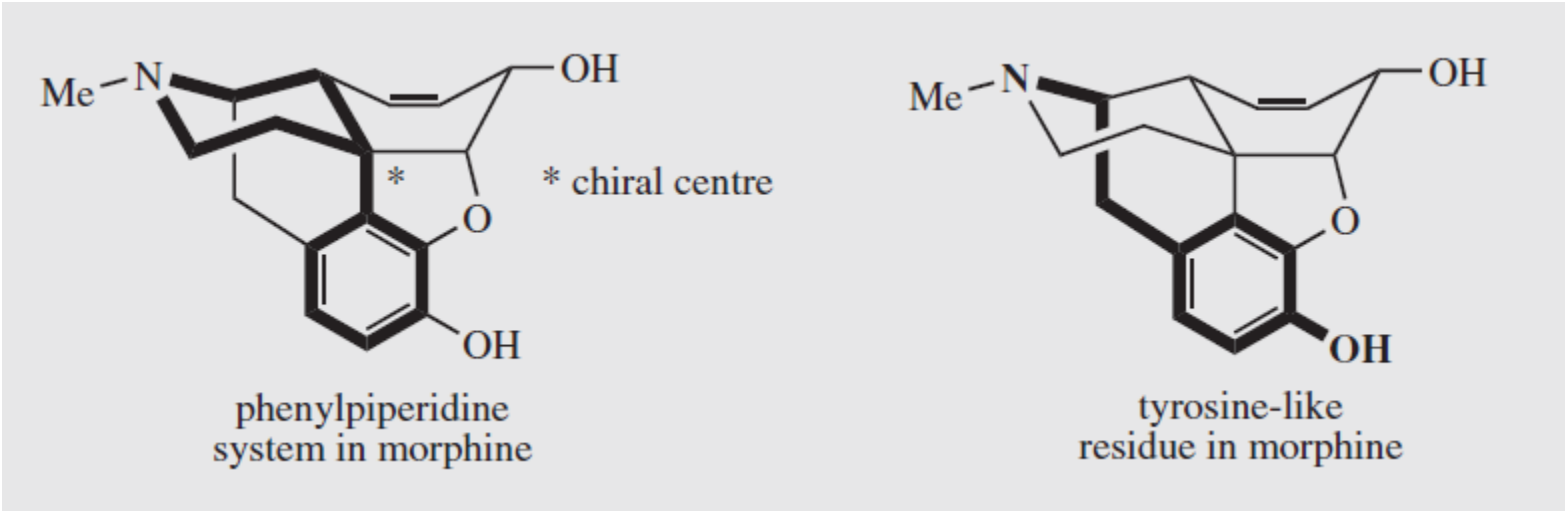
Morphine – biological activity:

Side effects:

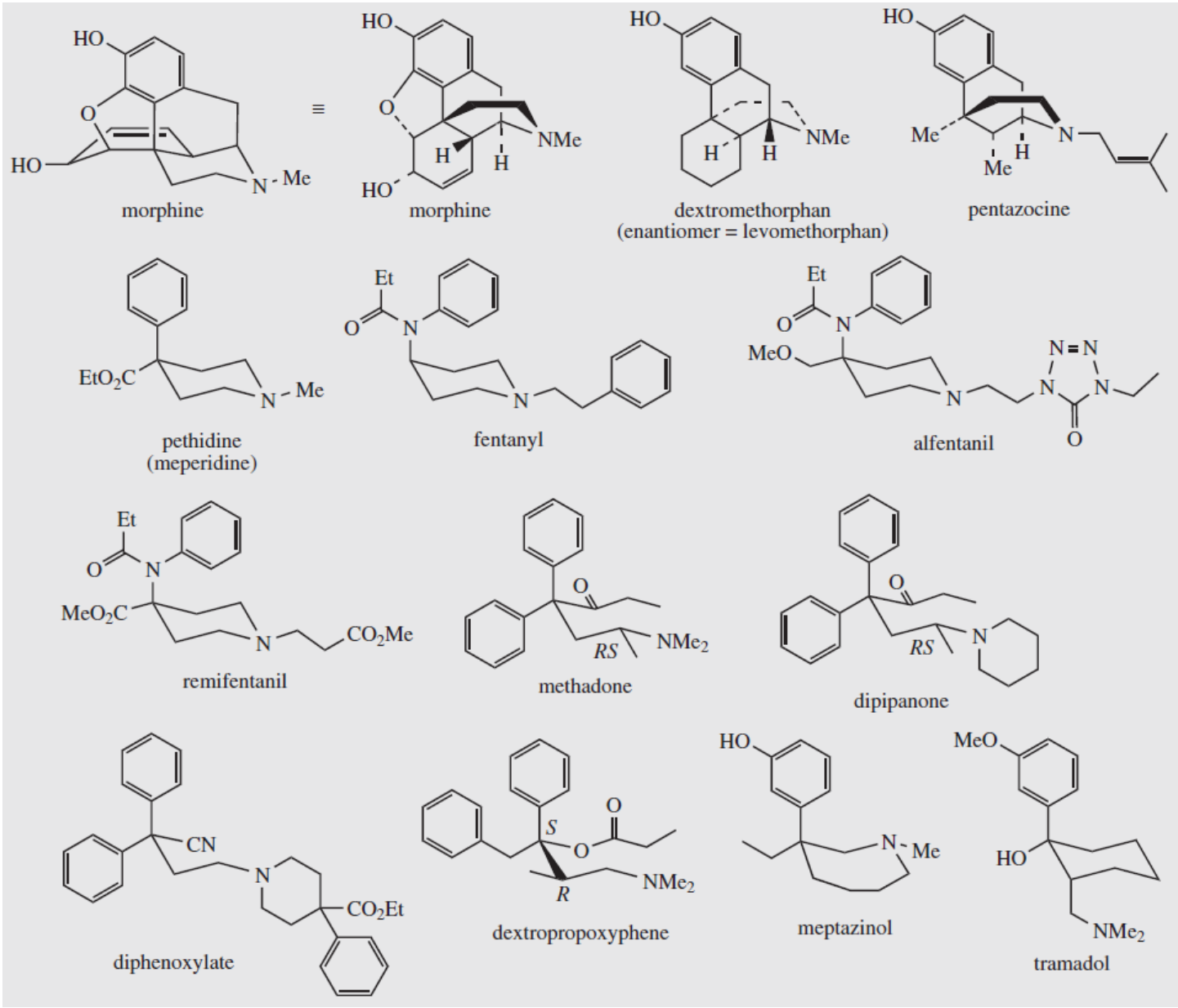
- strongly addicitve
- strong increase in dosage needed for desired results
- possible respiratory depression and apnoea
- renal failure (toxic metabolites)
- raised intracranial pressure
- euphoria
- nightmares and depression

Morphine – biological activity:

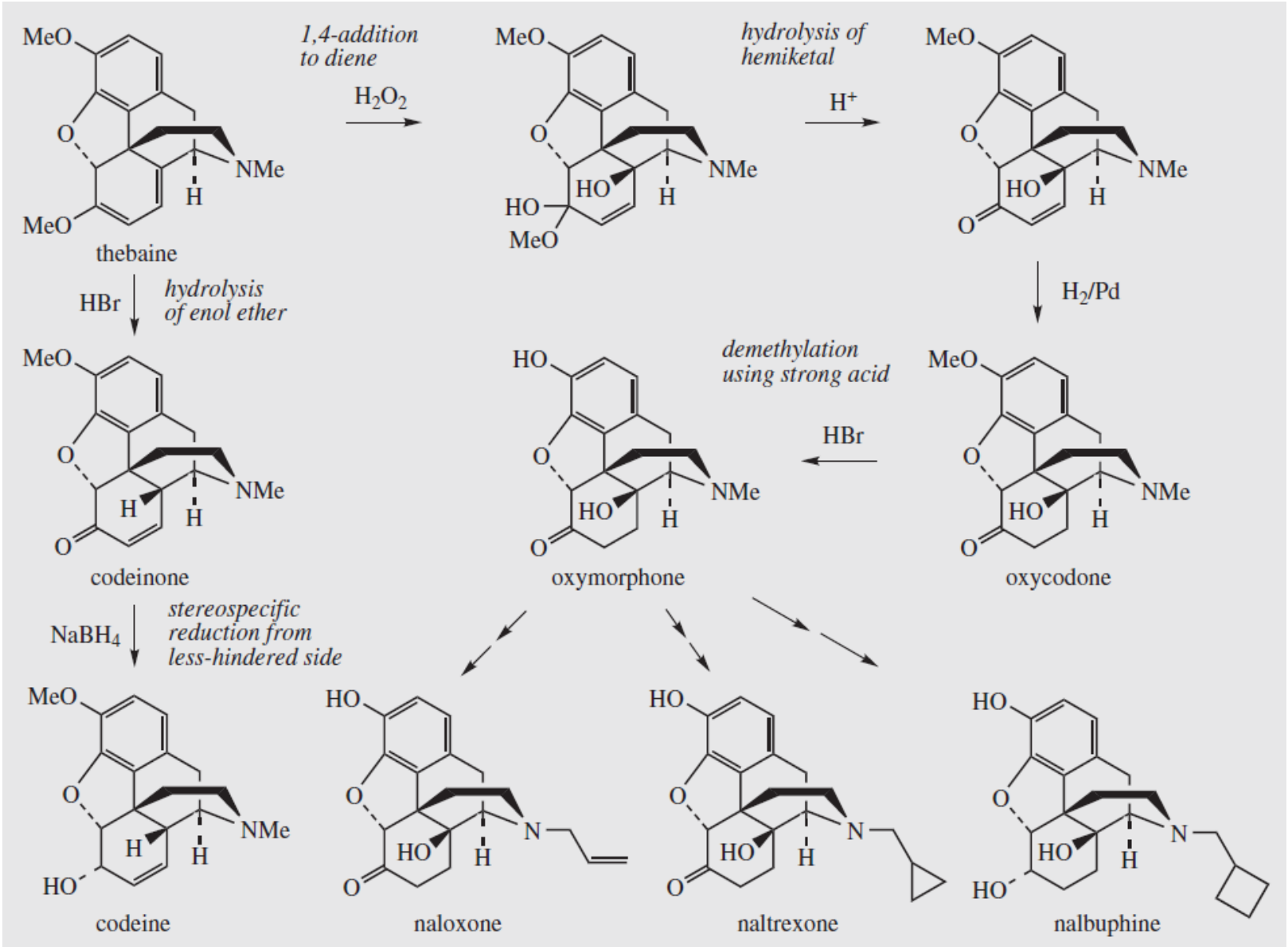
Morphine binds to opioid receptors in the brain. The natural substrates for those receptors are opioid peptides, including endorphins, dynorphins, endomorphins. The natural substrates are by a terminal tyrosine unit, mimicked by the morphine structure



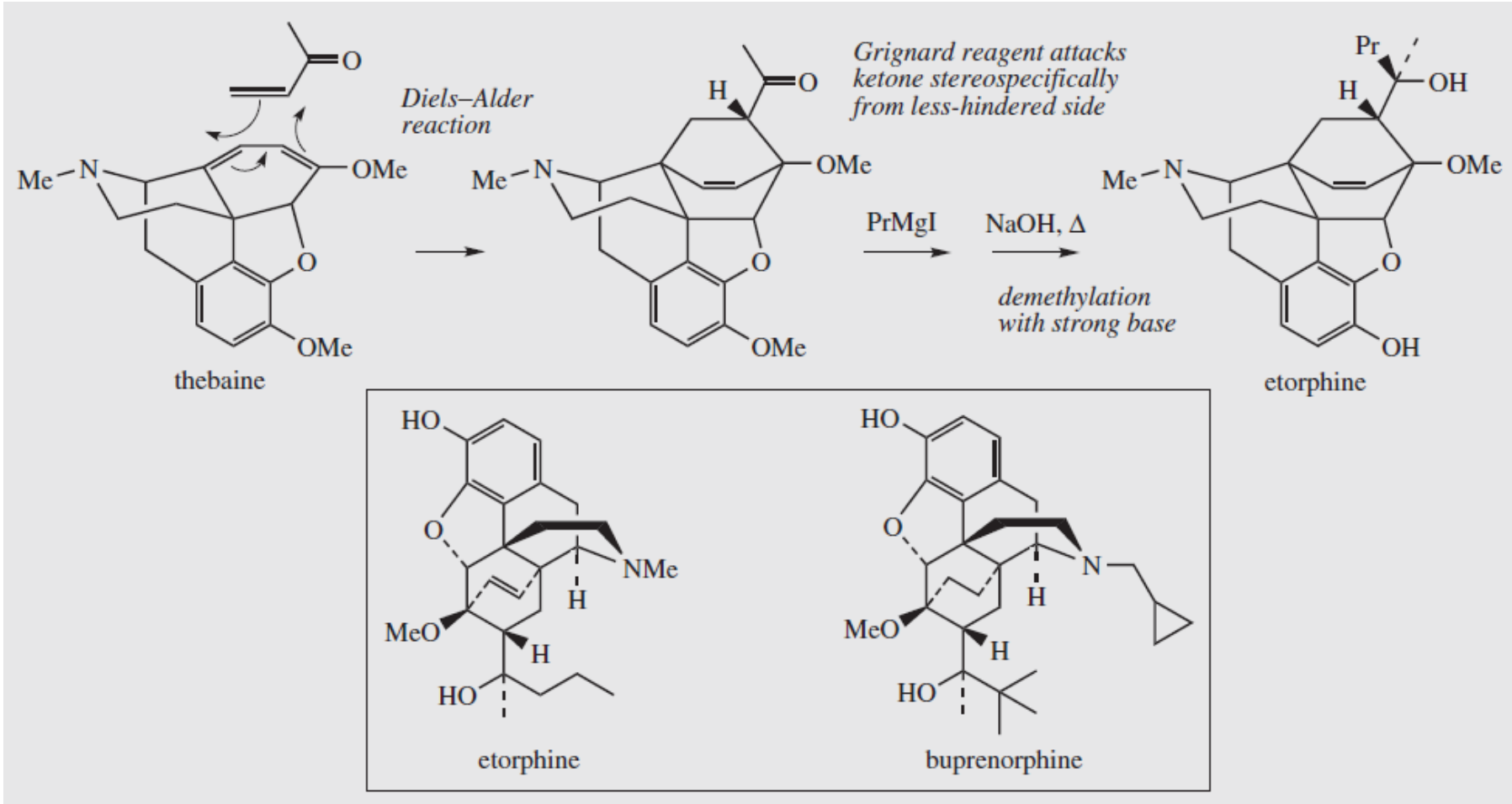
Morphine – biologically active derivatives:



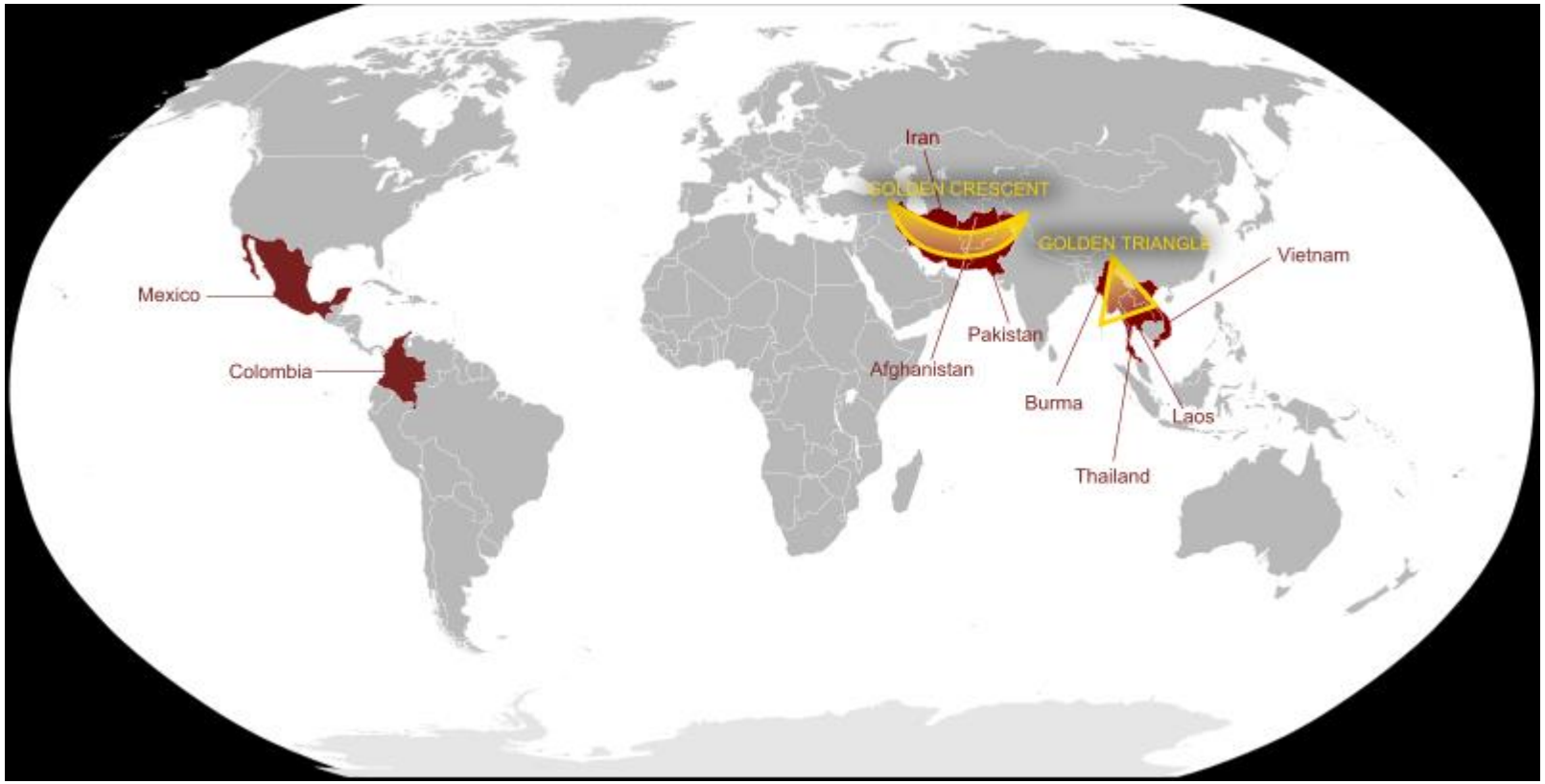
Morphine – biologically active derivatives:



Morphine – biologically active derivatives:



Cultivation of *Papaver somniferum*; Production of Opium:

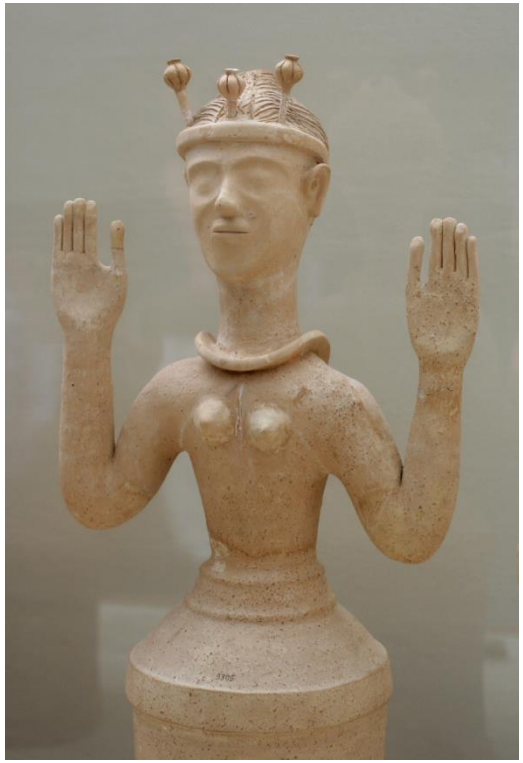


Origin of Morphine: *Papaver somniferum* and related poppy plants:

Harvest of raw opium:

Origin of Morphine: *Papaver somniferum* and related poppy plants:

Poppy plants in ancient art:



Goddess Gazi
(Kreta, minoic period)

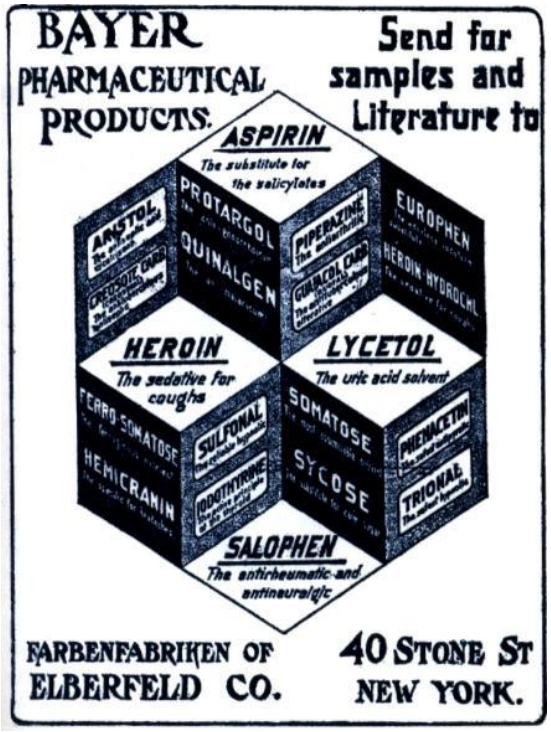
Dionysos
Greek vase

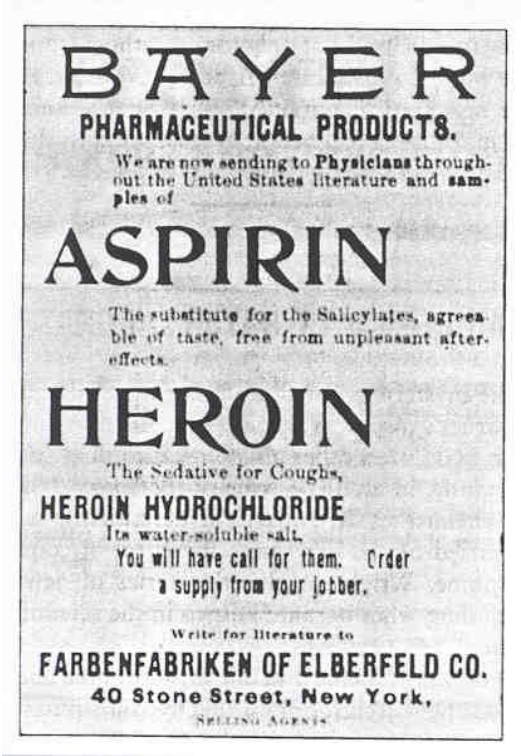
Poppy plants in ancient art:

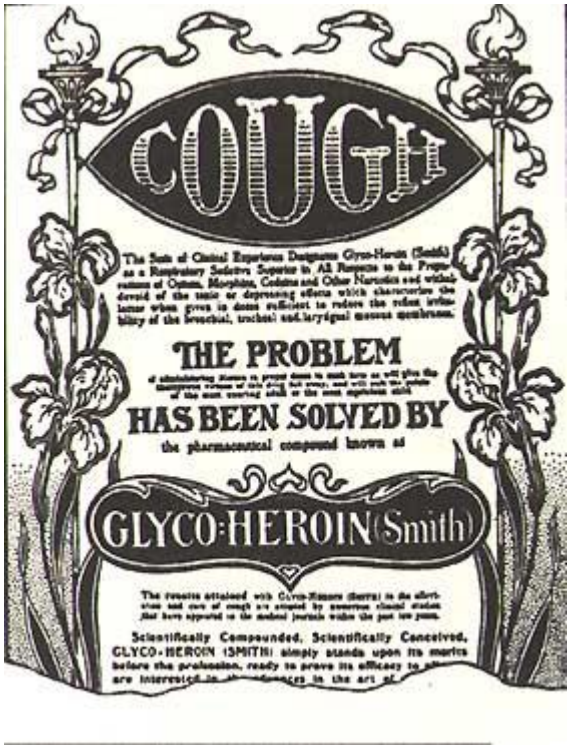
Demeter with wheat and poppy plants

Early advertisments…

In the early 1900‘s, Bayer wanted to stop the production of aspirin because other pain killers, such as heroin and cocain were cheaper and more effective…
Between 1910 and 1920, aspirin became more popular because heroin was slowly banned from the marked







Not so long ago…

Not so long ago…

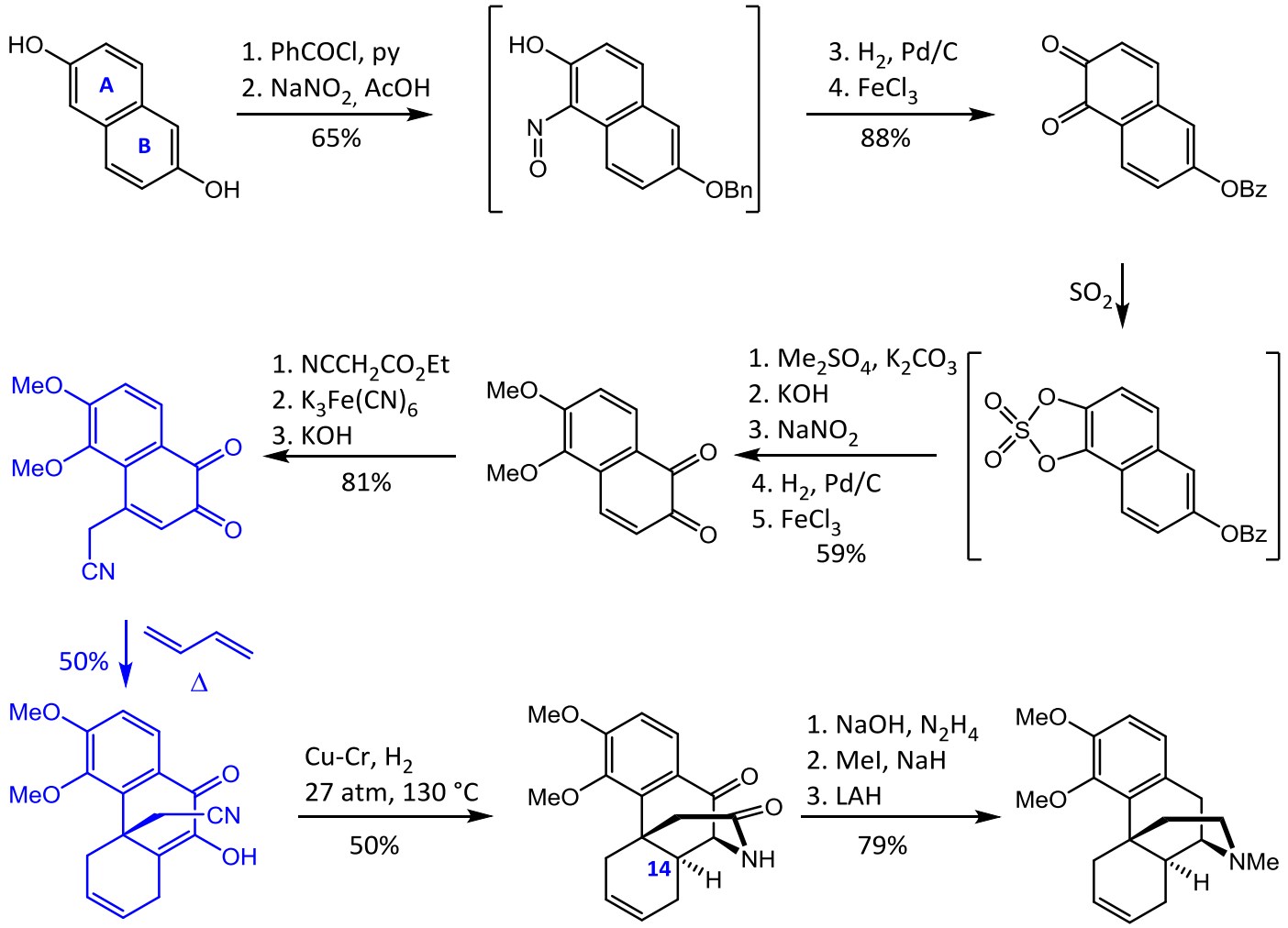
Syntheses of morphine and related alkaloids:

Even after more than 60 years of total syntheses, morphine still is one of the most attractive targets (historical, economic and societal importance)

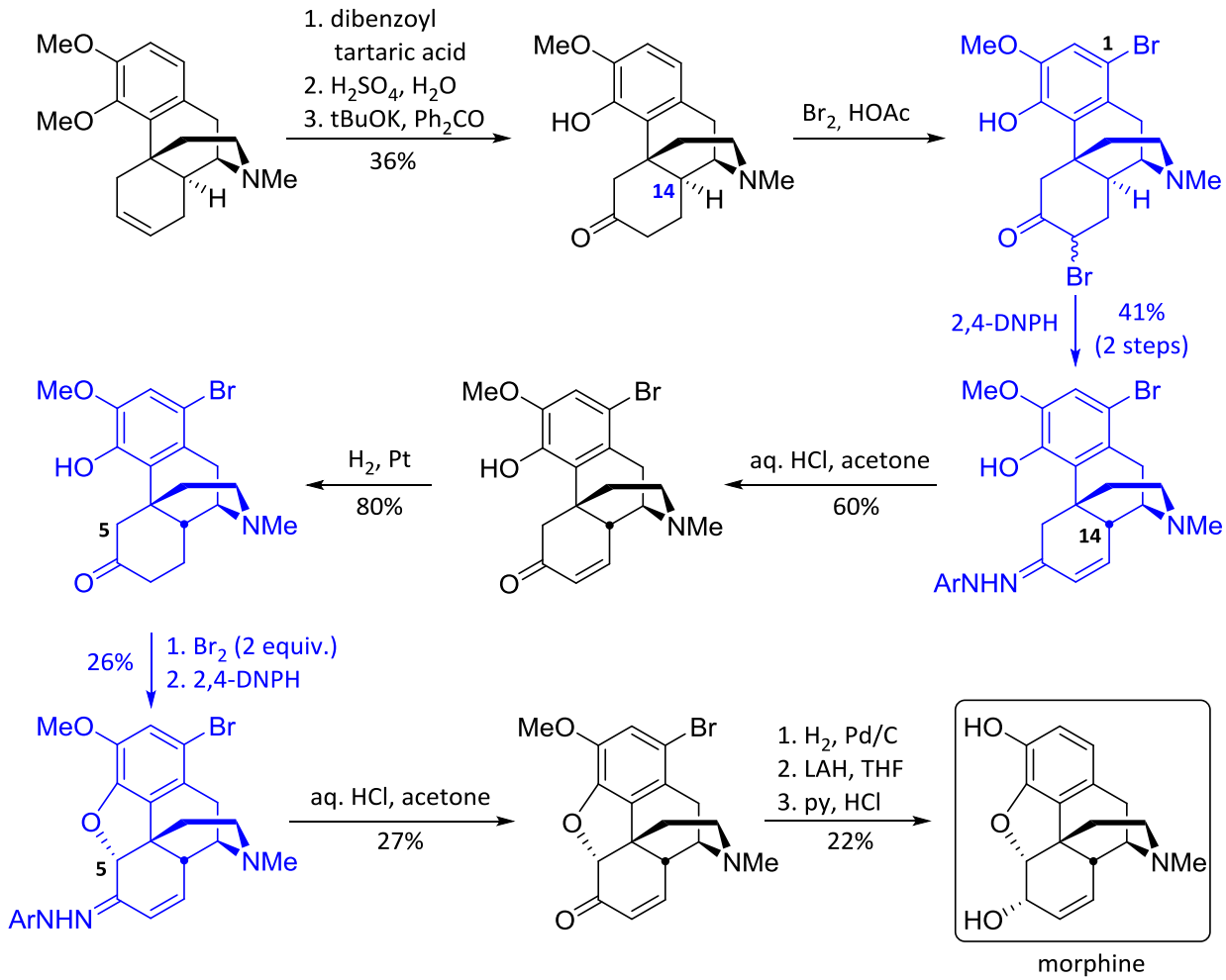
Table 3 Summary of syntheses of morphine and derivatives

Principal author	Year	Target	Steps	Overall yield (as reported)
Gates	1952	Morphine	31	0.06
Ginsburg	1954	*rac*-Dihydrothebainone	21	8.9
Grewe	1967	*rac*-Dihydrothebainone	9	0.81
Rice	1980	Dihydrocodeinone	14	29.7
Evans	1982	*rac*-*O*-Me-thebainone A	12	16.7
White	1983	Codeine	8	1.8
Rapoport	1983	*rac*-Codeine	26	1.2
Fuchs	1987	*rac*-Codeine	23	1.3
Tius	1992	*rac*-Thebainone-A	24	1.1
Parker	1992	*rac*-Dihydrocodeinone	11	11.1
Overman	1993	Dihydrocodeinone	14	1.9
Mulzer	1996	Dihydrocodeinone	15	9.1
Parsons	1996	Morphine	5	1.8
White	1997	*ent*-Morphine	28	3.0
Mulzer	1997	Dihydrocodeinone	18	5.7
Ogasawara	2001	Dihydrocodeineone ethylene ketal	21	1.5
Taber	2002	Morphine	27	0.51
Trost	2002	Codeine	15	6.8
Fukuyama	2006	*rac*-Morphine	25	6.7
Hudlicky	2007	*ent*-Codeine	15	0.23
Iorga/Guillou	2008	*rac*-Codeine	17	0.64
Chida	2008	*rac*-Dihydroisocodeine	24	3.8
Hudlicky	2009	Codeine	18	0.19
Magnus	2009	*rac*-Codeine	13	20.1
Stork	2009	*rac*-Codeine	22	2.0
Fukuyama	2010	Morphine	18	4.8

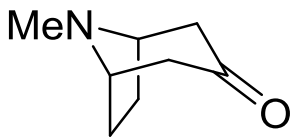
Early syntheses of morphine and codeine – Gates (1952) part 1:



Early syntheses of morphine and codeine – Gates (1952) part 2:



Where everyting started – the beginning of modern organic synthesis



Tropinone

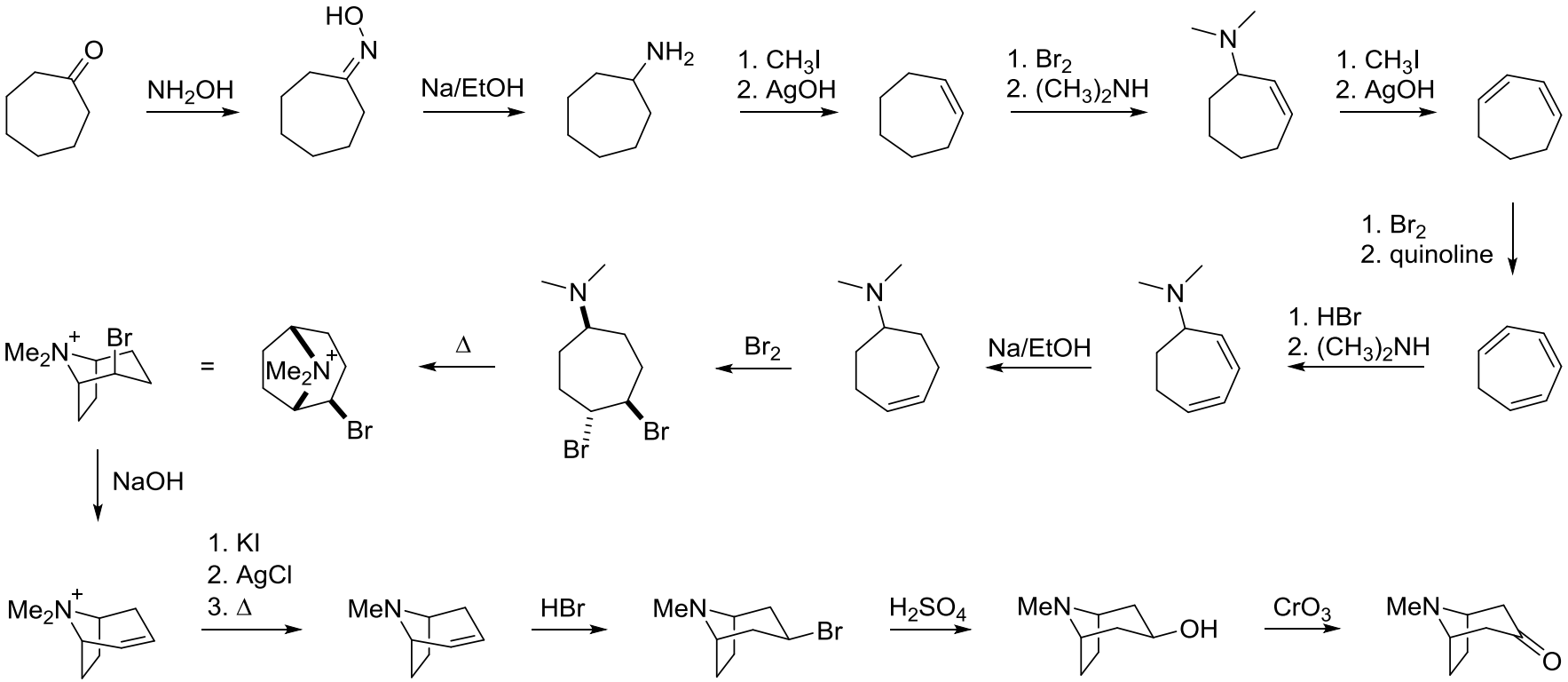
Tropinone is the parent compounds of important alkaloids (atropine, cocaine...)

One of the earliest targets for total synthesis

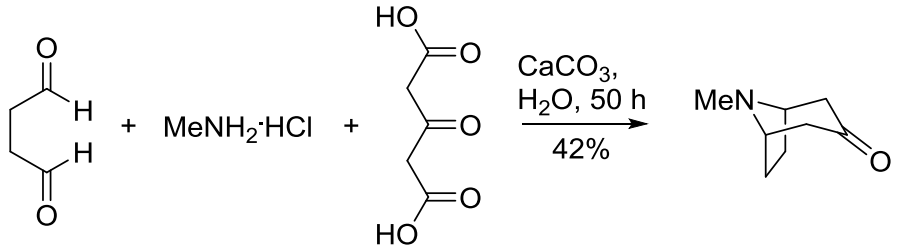
Atropos, Greek Goddess of Faith

Deadly nightshade (*Atropa belladonna*)

First total synthesis of tropinone by Willstätter in 1901:



In 1917, Robinson presented a one-step synthesis of tropinone:



Perfect Synthesis: One Step
100% yield of the desired material
Inexpensive and readily available starting materials
No purification required / easy work-up

- **First example of a biomimetic process!**
- Chemists started believing in the concept of synthesis

Recommended reading:
Medley, J. W.; Movassaghi, M. *Chem.Commun*. **2013**, *49*, 10775.

Biomimetic synthesis:

A biomimetic synthesis contains a specific reaction or sequence of reactions that **mimic a proposed biological pathway.** The process being imitated usually **has solid biochemical background**.

Biomimetic chemistry is the branch of organic **chemistry which attempts to imitate natural reactions and enzymatic processes as a way to improve the power of organic chemistry**.

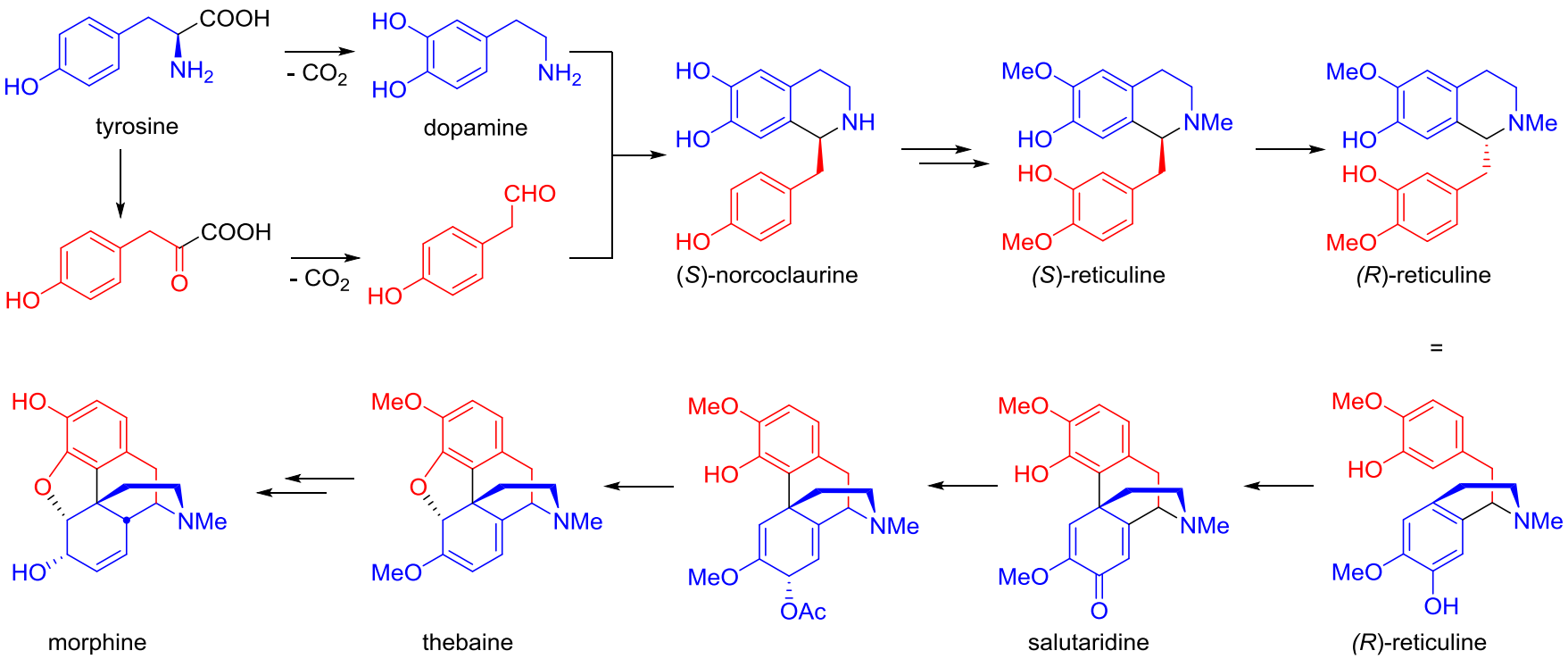
Important:
Not every target might be accessible by means of a biomimetic approach. However, it's always worth to investigate this option.

In order to be able to design a biomimetic synthesis you need to know biochemistry.

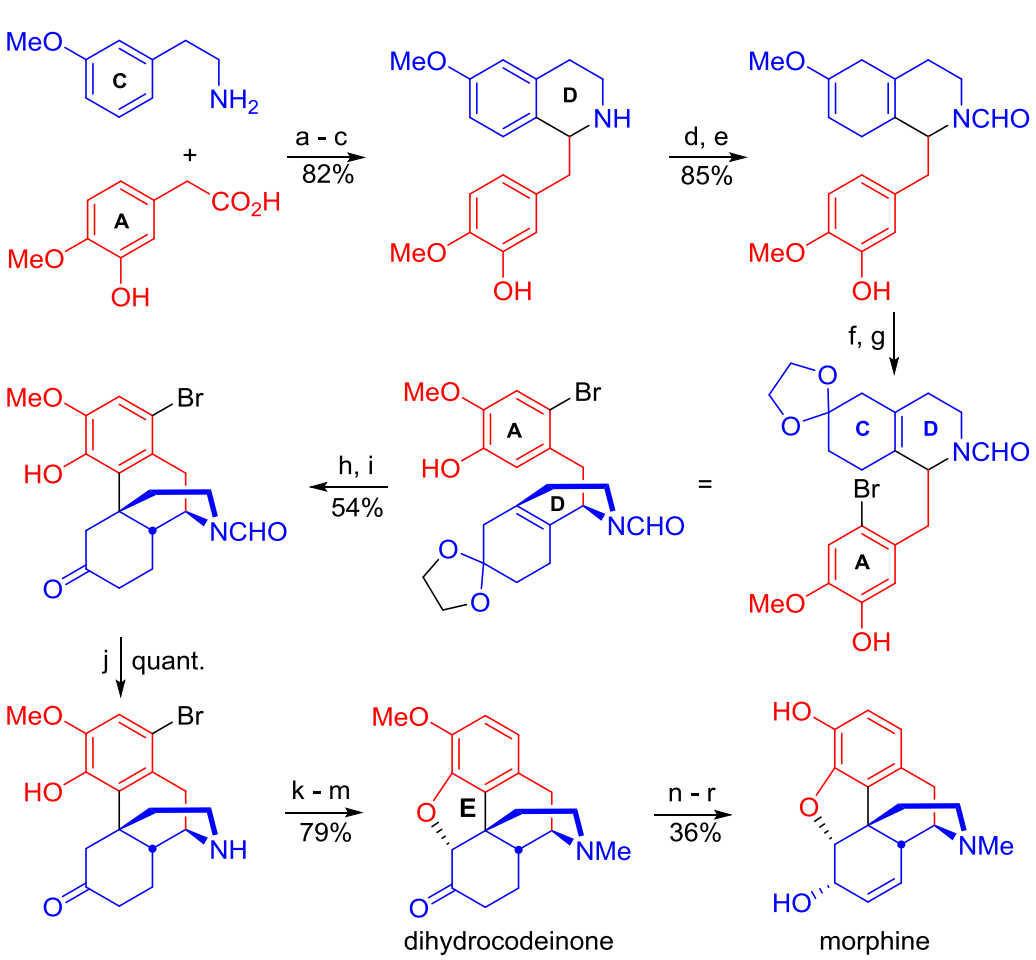
Further reading:

Torre, M. C.; Sierra, M. A. *Angew. Chem. Int. Ed*. **2004**, *43*, 160.
Breslow, R. Chem. Soc. Rev. **1972**, *1*, 553
Van Tamelen, E. E. *Fortschr. Chem. Org. Naturst*. **1961**, *4*, 242.

Biosynthesis of morphine (abbreviated):



Biomimetic synthesis of morphine by Rice:



Key reactions:

Bischler-Napieralski reaction
Birch reduction

installation of bromide to prevent undesired regiochemistry in cyclization reaction

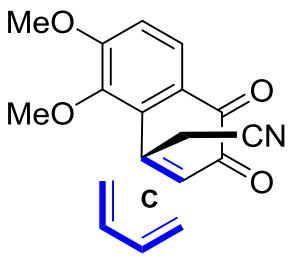
Grewe cyclization - nucleophilic attack of aromatic ring onto activated double bond (or corresponding cation)

E-ring formation by bromination and nucleophilic displacement α-selenation
BBr_3-mediated demethylation

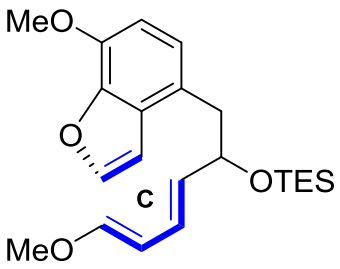
Reagents and conditions: a) 200 °C, 2h; **b)** $POCl_3$, MeCN; **c)** $NaCNBH_3$, MeOH; **d)** Li, NH_3, THF, *t*BuOH; **e)** PhOCHO, EtOAc, D; **f)** $(CH_2OH)_2$, THF, $MeSO_3H$; **g)** $CH_3CONHBr$, 0 °C; **h)** HCO_2H, H_2O; **i)** $NH_4F.HF$, CF_3SO_3H; **j)** (i) MeOH, HCl, reflux, (ii) NH_3, H_2O, *i*PrOH; **k)** Br_2, HOAc; **l)** NaOH, $CHCl_3$; **m)** H_2, HOAc, HCHO; **n**) EtOCOCl, C_6H_6, reflux; n) PhSeCl, EtOAc, HCl; **o)** $NaIO_4$, EtOAc, H_2O; p) LAH, THF, reflux; **q)** (i) BBr_3, $CHCl_3$, (ii) NH_3.

Diels-Alder approaches towards morphine:

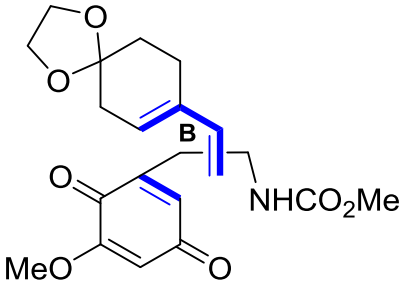
The Diels-Alder reaction is a highly versatile method for the elaboration of six-membered rings and has already been used in the first total synthesis of morphine by Gates. Additionally, Stork, Tius and Hudlicky employed this reaction in their routes to the title alkaloid.



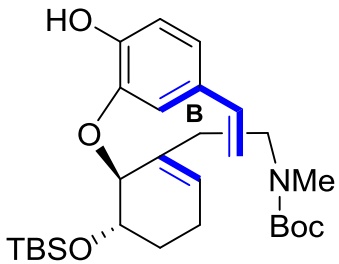
Gates



Stork



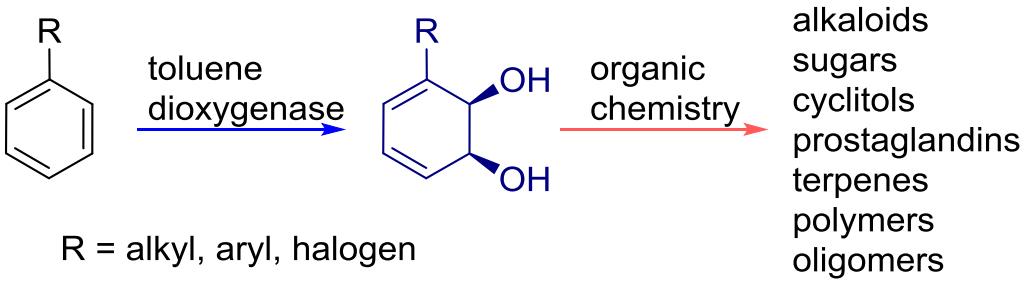
Tius



Hudlicky

Hudlicky's synthesis of *ent*-hydromorphone:

Cyclohexadiene diol as starting material for the preparation of morphine (and other natural products):

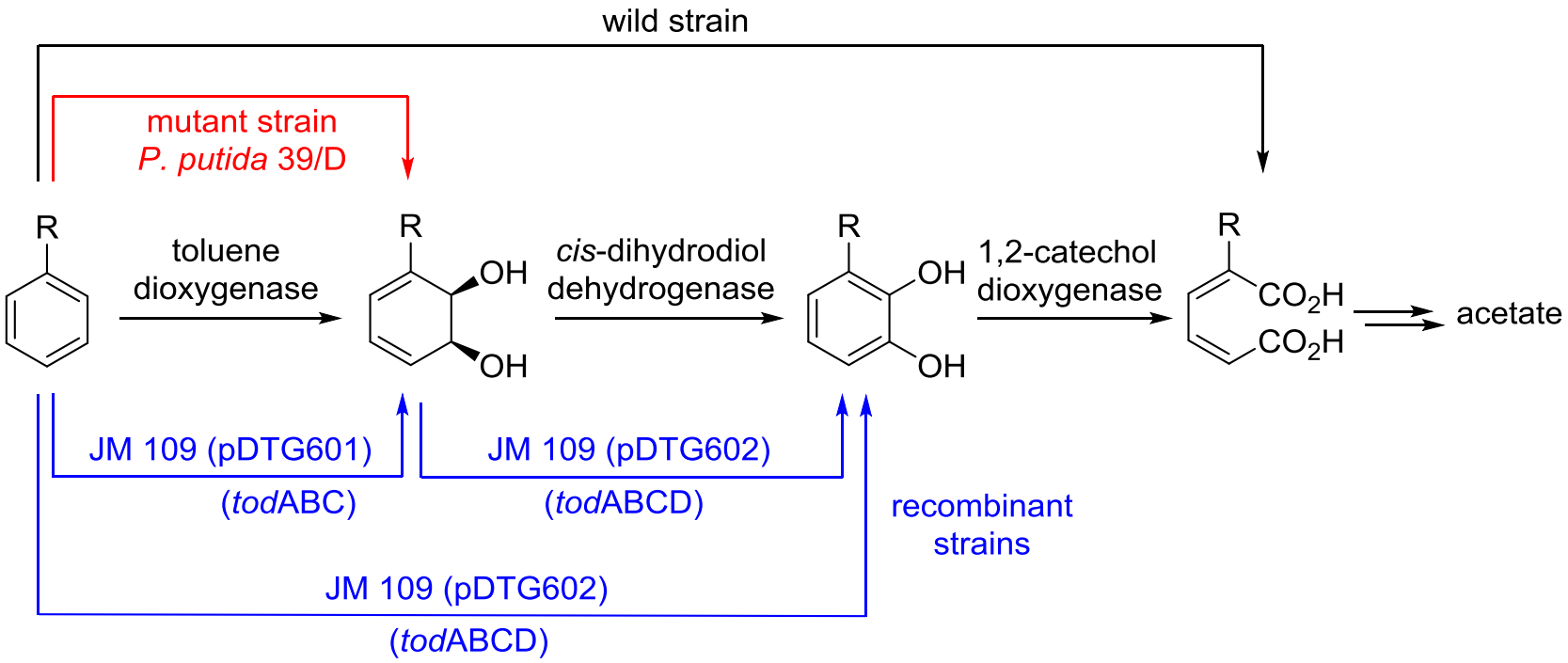


Reviews:

Hudlicky, T.; Gonzalez, D.; Gibson, D. T. *Aldrichimica Acta* **1999**, 32, 35;
Rinner, U. Chiral Pool Syntheses from *cis-Cyclohexadiene* Diols. In Comprehensive Chirality, Eds. Carreira, E. M.; Yamamoto, H. Elsevier, Amsterdam 2012, p 240-267.

Hudlicky's synthesis of *ent*-hydromorphone:

Metabolism of Aromatic Compounds by Soil Organisms:

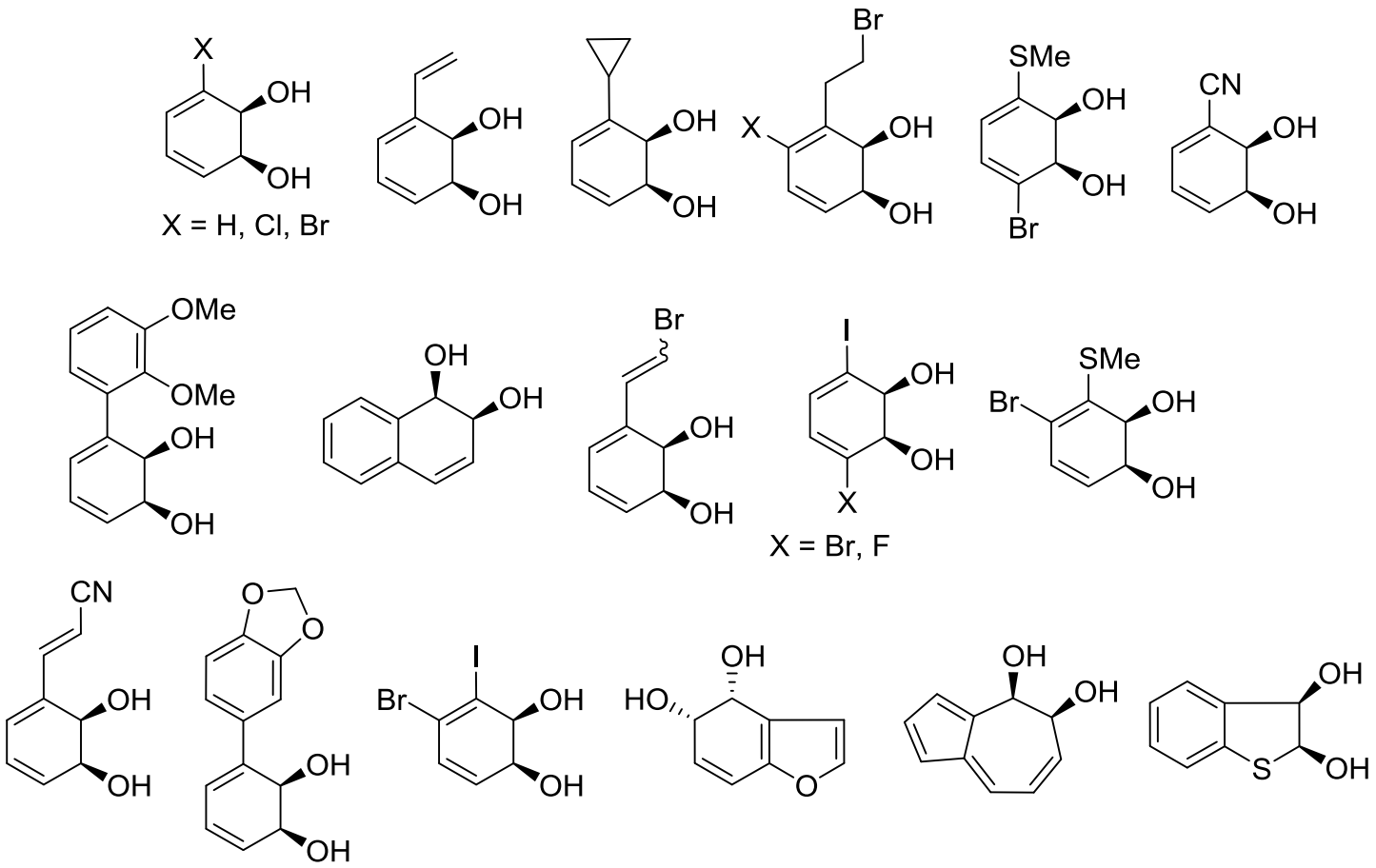


> 420 diversely functionalized metabolites known

Gibson, D. T.; Koch, J. R.; Schuld, C. L.; Kallio, R.E. *Biochemistry*, **1968**, *7*, 3795.
Zylstra, G.; Gibson, D.T. *J. Biol. Chem.* **1989**, *264*, 14940.
Johnson, R. A. *Org. React.* **2004**, *63*, 117.
Hudlicky, T.; Reed, J. W. *Synlett* **2009**, 685.

Hudlicky's synthesis of *ent*-hydromorphone:

Examples of Known Dioxygenase Metabolites:



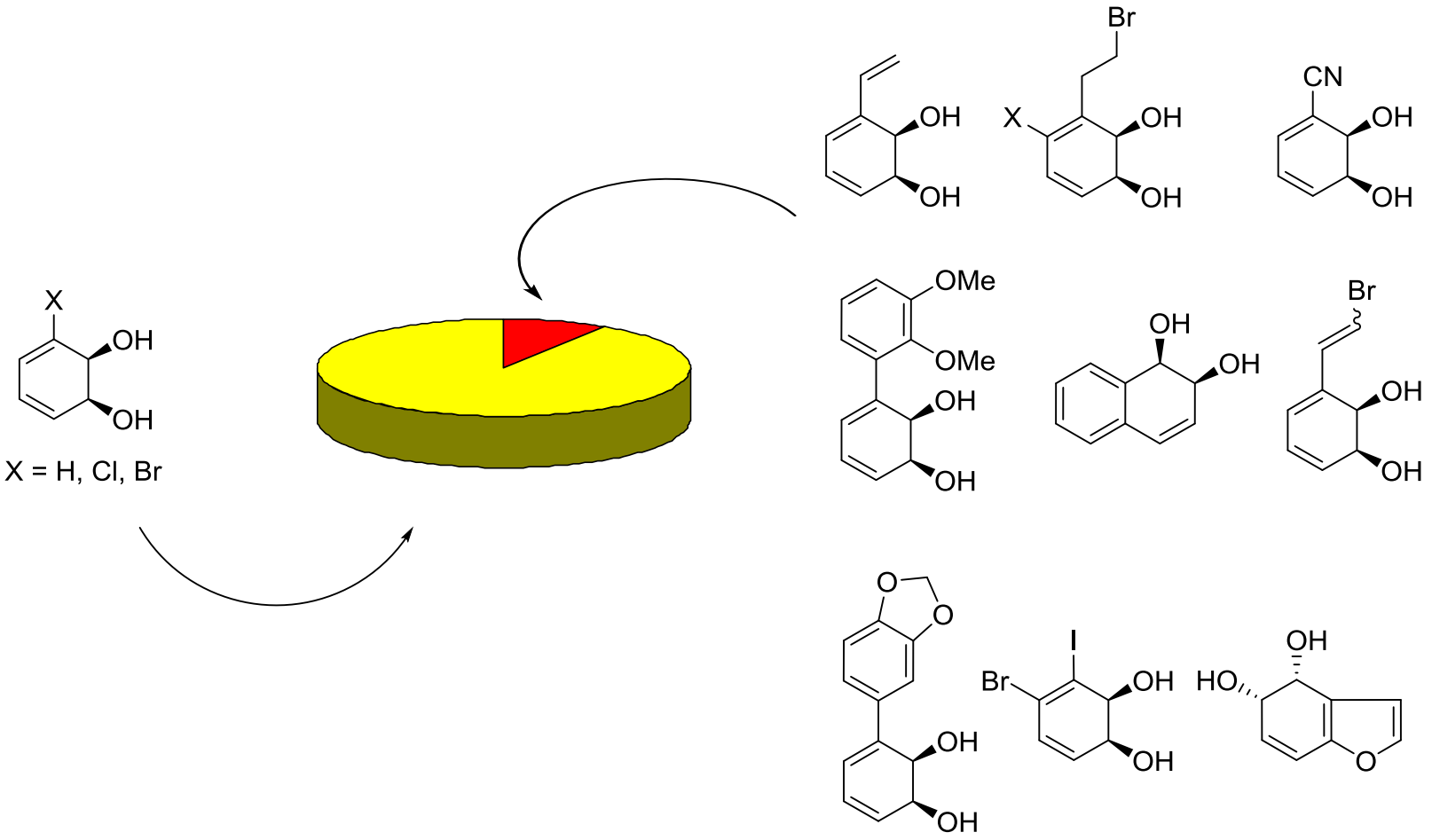
Finn, K.J.; Cankar, P.; Jones, R.T.B.; Hudlicky, T. *Tetrahedron. Asym.* **2004**, *15*, 2833.

Hudlicky, T.; Gonzalez, D.; Gibson, D.T. *Aldrichim. Acta,* **1999**, *32*, 35.

Yildirum, S.; Zezula, J.; Hudlicky, T.; Witholt, B.; Schmid, A. *Adv. Synth. Catal.* **2004**, *346*, 933.

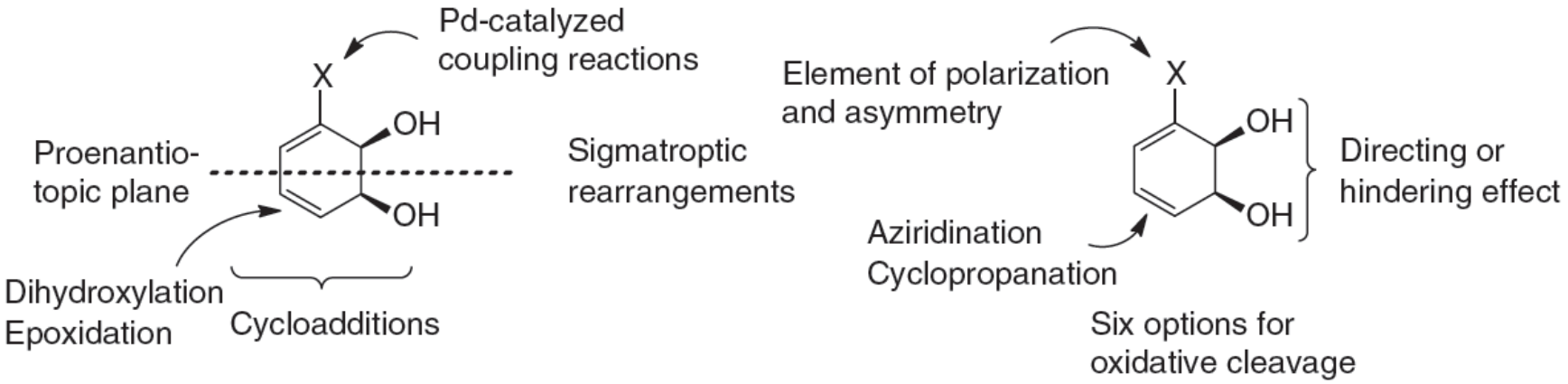
Hudlicky's synthesis of *ent*-hydromorphone:

Cyclohexadiene diols in organic synthesis:



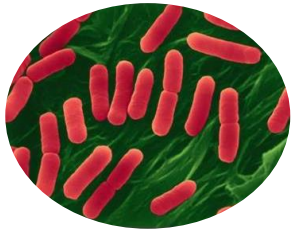
Hudlicky's synthesis of *ent*-hydromorphone:

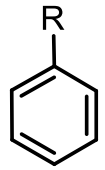
Cyclohexadiene diols in organic synthesis:



Hudlicky's synthesis of *ent*-hydromorphone:

Biotransformations with *E. coli*:





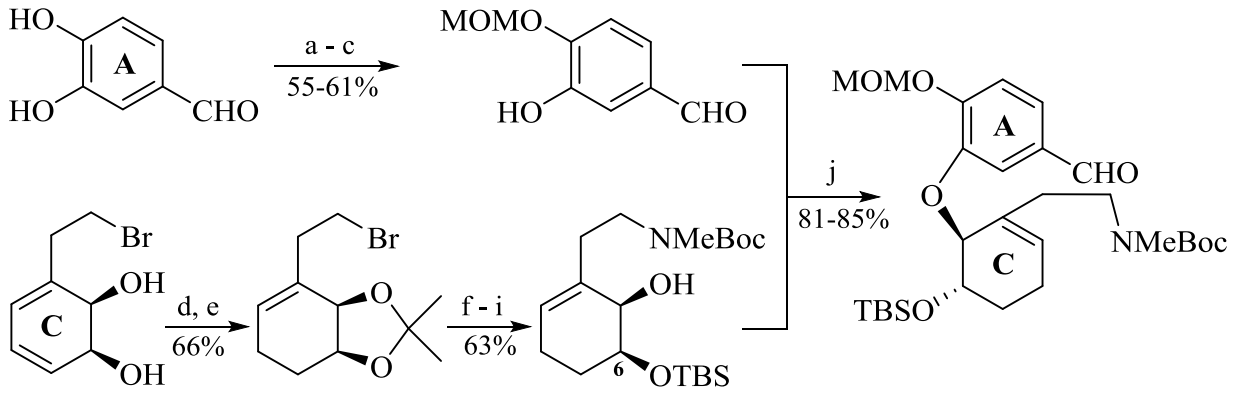
Total Time: 3 days

Total Hands-on Time: 4 hours

~20-30 g/L/h

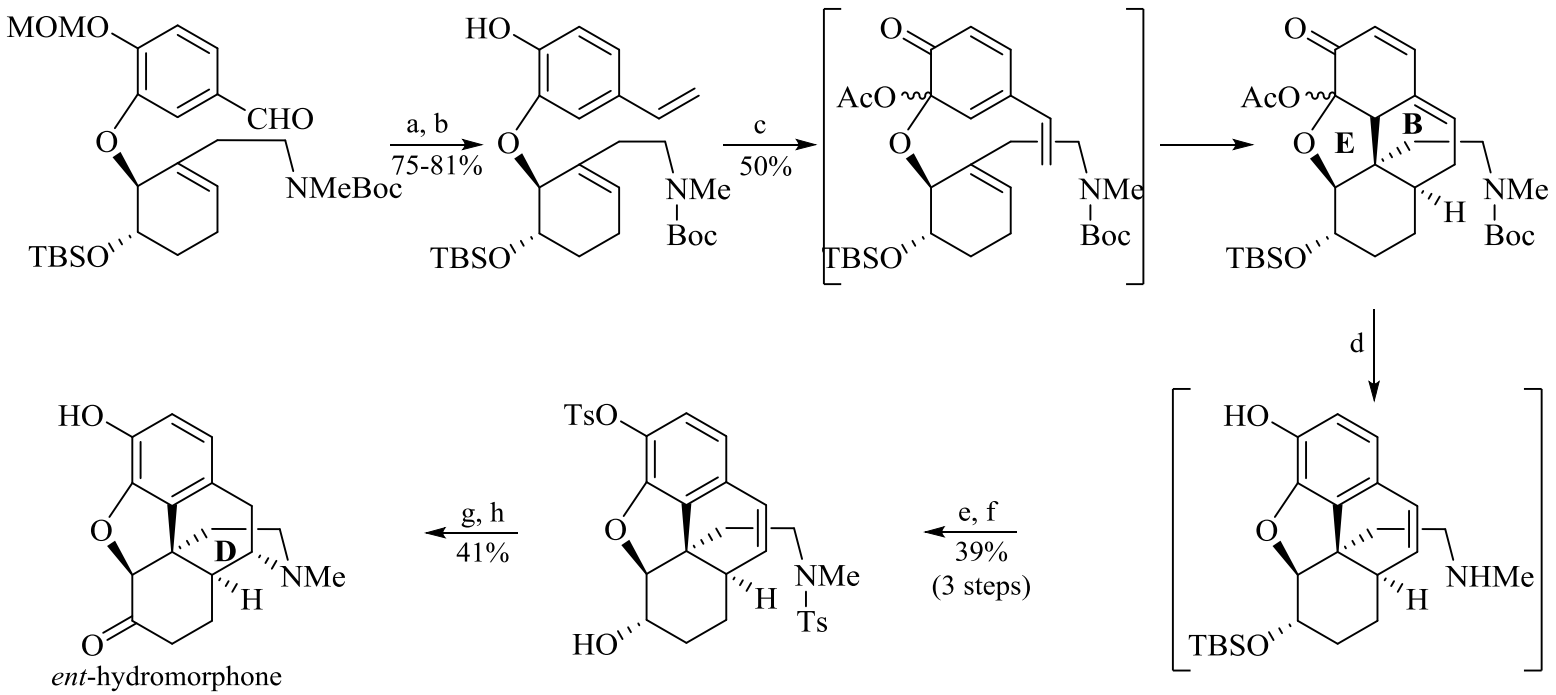
Hudlicky's synthesis of *ent*-hydromorphone – part 1:

Cychohexadiene derived diols served as starting material for Hudlicky's latest synthesis of *ent*-hydromorphone



Reagents and conditions: a) Ac_2O, NaOH, THF, 0 °C, 82-85%; **b)** MOMCl, K_2CO_3, DMF, 0 °C to rt, 76-80%; **c)** K_2CO_3, MeOH, 88-90%; **d)** potassium azadicarboxylate, AcOH, MeOH, 0 °C, 83%; **e)** 2,2-dimethoxypropane, acetone, *p*-TsOH, 80%; **f)** $MeNH_2$, K_2CO_3, THF, sealed tube, 93%; **g)** HCl (1.3M), EtOH; **h)** $(Boc)_2O$, $NaHCO_3$, EtOH, 74% (2 steps); **i)** TBSCl, imidazole, CH_2Cl_2, -78 °C to rt, 92%; **j)** TMAD, PBu_3, 81-85%.

Hudlicky's synthesis of *ent*-hydromorphone – part 2:

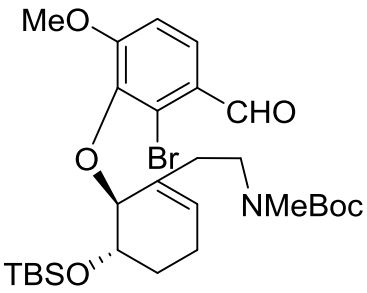


Reagents and conditions: a) CH_3PPh_3Br, *n*-BuLi, THF, -78 °C to rt, then reflux, 82-88%; **b)** $ZnBr_2$, $CH_3(CH_2)_{10}CH_2SH$, CH_2Cl_2, 10 min, 92%; **c)** $Pb(OAc)_4$, $ClCH_2CH_2Cl$, reflux, 50%; **d)** TFA, CH_2Cl_2, 0 °C; **e)** TsCl, Et_3N, CH_2Cl_2, 0 °C to rt, 45% (2 steps); **f)** TBAF, THF, 86%; **g)** Li, *t*-BuOH, NH_3 (liq), THF, -78 °C, 10 min, 93%; **h)** *t*-BuOK, PhCOPh, toluene, 85 °C, 44%.

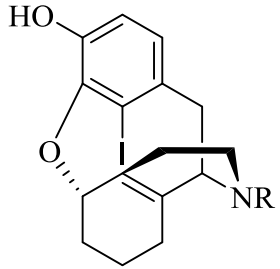
Palladium catalysis in morphine syntheses:

Palladium-catalyzed reactions have been employed in the total synthesis of morphine. Several approaches utilize either the Heck or the Suzuki reacton to connect the A and C ring of the alkaloid

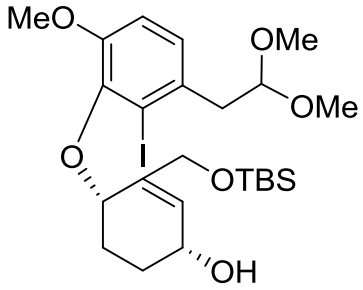
Heck reaction:



Hudlicky

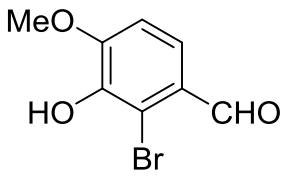


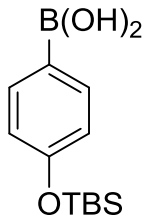
Overman



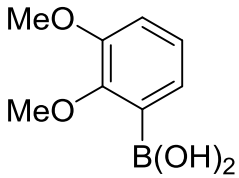
Fukuyama

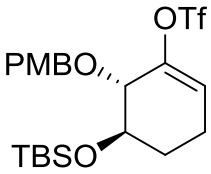
Suzuki reaction:





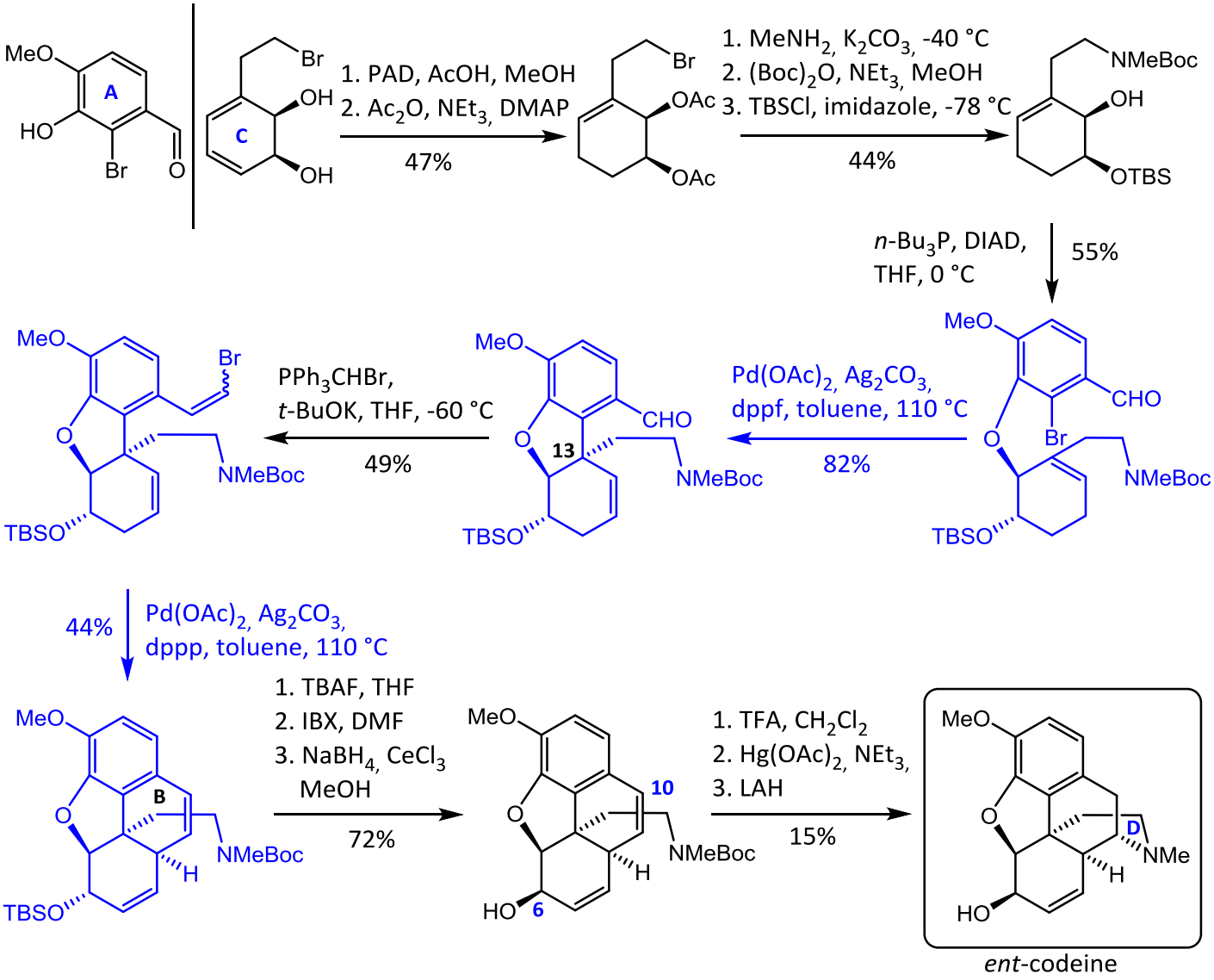
Magnus



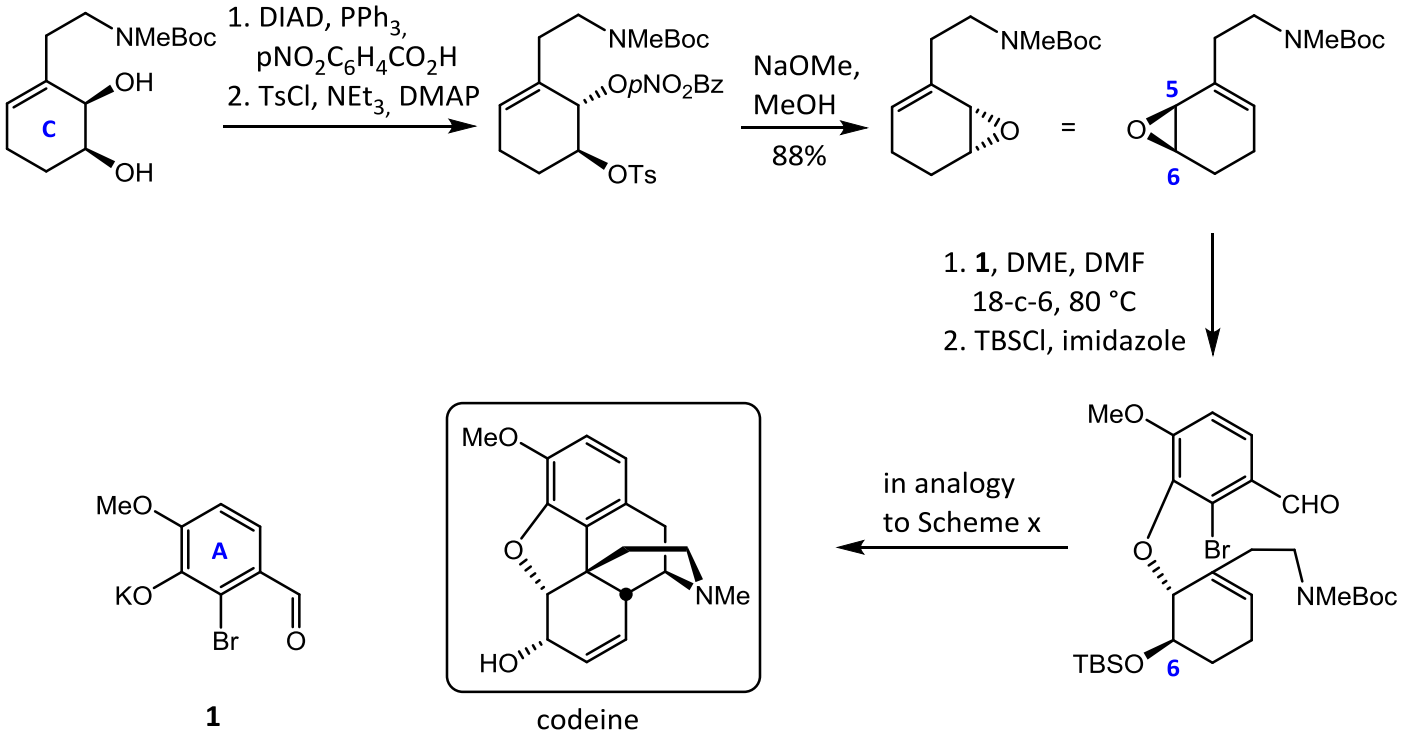


Chida

Palladium catalysis in morphine syntheses:

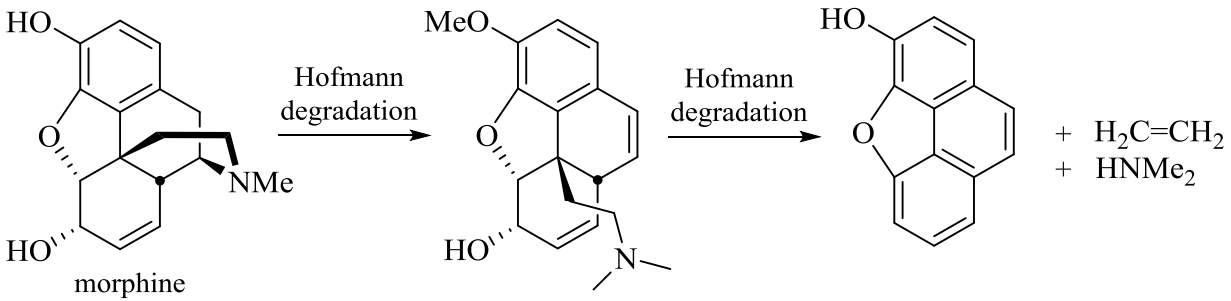


Palladium catalysis in morphine syntheses:



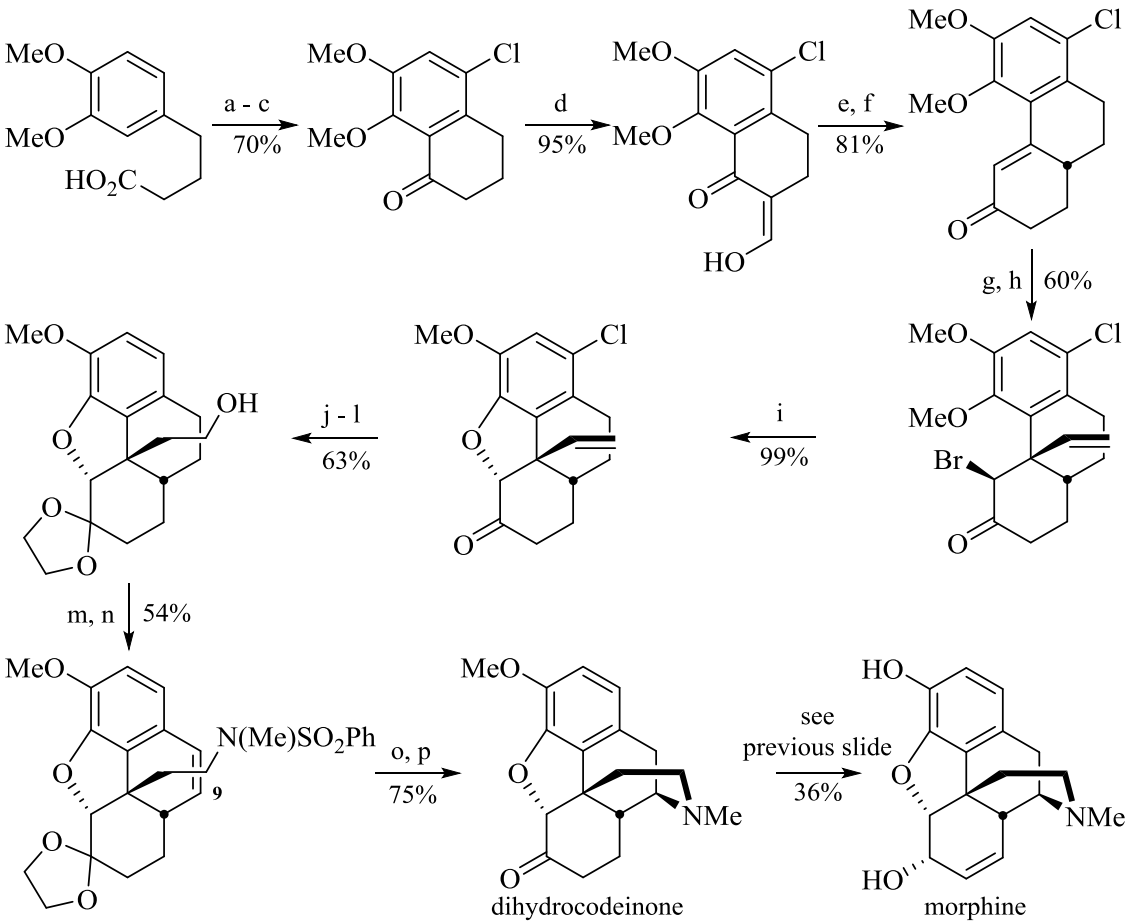
Mulzer's synthesis of morphine:

Retrosynthesis based on an early degradation study of morphine:



Mulzer's synthesis of morphine:

Alternative approach featuring a conjugate cuprate addition as key step



Reagents and conditions: a) Cl_2, AcOH, 99%; **b)** $(COCl)_2$, C_6H_6, reflux; **c)** $SnCl_4$, C_6H_6, 0 °C, 71% (2 steps); **d)** HCO_2Me, NaOMe, C_6H_6, 95%; **e)** methyl vinyl ketone, NEt_3, MeOH, **f)** KOH, dioxane, H_2O, 81% (2 steps); **g)** $(H_2C{=}CH_2)CuMgCl$, THF, -78 °C to 0 °C; TMSCl, NEt_3, 0 °C to 25 °C; **h)** NBS, THF, 60% (2 steps) **i)** DMF, 140 °C, 99%; **j)** TMSCl, $(CH_2OH)_2$, CH_2Cl_2, 92%; **k)** $BH_3{\bullet}SMe_2$, THF; H_2O_2, NaOH, 70%; **l)** Raney-Ni, MeOH, KOH, 98%; **m)** $PhSO_2NHMe$, ADDP, Bu_3P, 81%; **n)** NBS, $(PhCO_2)_2$, CCl_4, NEt_3, reflux, 67%; **o)** Li, NH_3, THF, *t*-BuOH, -78 °C, 79%; **p)** HCl (3N), 90 °C, 95%.