OPIOIDS - STRUCTURE AND SYNTHESIS

by

Milovan D. Ivanović

University of Belgrade, Faculty of Chemistry

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OPIOIDS - STRUCTURE AND SYNTHESIS

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OPIOID ANALGESICS. CHAPTER 1.

1.1 General Aspects

The main subject of the present treatise is the structure and synthesis of opioids, including natural, semi-synthetic and fully synthetic componds.[1] Also, it briefly describes other aspects of the opioids, such as pharmacology, opioid receptors, mechanism of action, theoretical modeling and biological testing. The literature sources of the treatise, cited at the end of each Chapter, encompass relevant papers, patents, reviews, chapters and monographs. Both the most recent and earlier references have been included, providing a thorough coverage of the topic. In addition, in-depth analysis of the patent literature revealed many important synthetic and isolation procedures, not reported elsewhere.

The term *opioid* refers to any compound, regardless of the structure or origin, having the pharmacological action similar to opium. In the recent literature, it usually denotes any exogenous substance, not normally present in the organism of mammals (and other animal groups), causing opium-like effects. Endogenous opioids (i.e. endogenous opioid peptides), also exist and are the normal constituents of certain tissues, as detailed later (p. 3-4). Historically, the term *opiate* was used specifically for the compounds extracted from opium, e.g. morphine and codeine, or their semi-synthetic derivatives, such as heroin. It has been largely replaced by the more general term *opioid*.

By far the best known property of opioids is to temporarily alleviate or abolish pain, without inducing loss of consciousness. Therefore, they are pharmacologically completely different from the general anesthetics.[2] (On the molecular level, the mechanism of action is also entirely different). As the drugs acting upon central nervous system (CNS), opioids cause a variety of physiological, psychological, and neurological effects, including euphoria, dysphoria and the life-threatening respiratory depression (cessation of spontaneous breathing).

Opioids selectively abolish only the painful sensations (an effect also known as antinociception). In that respect, they differ from the local anesthetics,[3] which typically cause the loss of any senses in the affected area of the body (i.e. numbness).

Through their mechanism of action, as briefly shown in the following pages, opioids are also entirely different from other widely used analgesics, which have no action upon CNS. The later categories include nonsteroidal anti-inflammatory drugs, NSAIDs,[4] (which inhibit prostaglandin synthesis) and glucocorticoids.[5] These drugs can substantially reduce the inflammatory painful stimuli, without affecting CNS, but have significant limitations, both in terms of the intensity and type of pain they can manage as well as the numerous side effects .

Opioids are the most powerful analgesics known to science, and are often the only drugs capable of controlling various extremely painful conditions, including cancer pain. However, the acute and chronic risk of using opioids is also high, particularly in non-terminal conditions. As already mentioned, they severely impair spontaneous breathing, which is the main cause of death in addicts and can also present a risk in pain management.

Also, any chronic use of the opioids inevitably results in a gradual development of tolerance and addiction. If opioid tolerance develops, then higher doses of the drug are required to achieve the same analgesic effect. Addiction represents the physical and psychological dependence on the opioids, which causes severe and often lethal abstinence syndrome, if the drug intake is abruptly discontinued. While the tolerance and addiction are usually encountered among the drug abusers, they can also arise during the prolonged medical treatment. Tolerance and addiction represent the major drawback of the opioids as analgesics, requiring strict control in dosing and duration of therapy, except in terminal cases.[6]

It is interesting to note that there is a very large number of exogenous compounds, particularly semi-synthetic and fully synthetic, which are potent opioid analgesics. While the cause of that phenomenon is not clear, some of the compounds (e.g. morphine, oxymorphone, oxycodone, fentanyl etc.) have become highly useful analgesics.

It is also known that certain compounds can "cancel" the action of opioids, rapidly terminating their analgesic effect as well as the side effects. Typically, such compounds have little or no pharmacological effects on their own and are denoted as opioid antagonists. Virtually all known antagonists are semi-synthetic morphine derivatives, with naloxone being especially effective (Chapter 2). Medical application of antagonists is limited to the treatment of opioid overdose, since they immediately reverse the life-threatening respiratory depression. Also, when given to the addicts, they rapidly precipitate the abstinence syndrome.[1a,6]

Research also revealed that some opioids are mixed agonist-antagonists or partial agonists.[1a] At least one such compound, buprenorphine, has found important use in the treatment of opioid addiction.[1,6]

1.2. Opioid Receptors

Parallel to the development of new semi-synthetic and synthetic opioid drugs, as discussed in Chapters 2 and 3, there has been an extensive ongoing research of opioid analgesia mechanisms. Thus, it has long been known that opioids act by binding to the specific receptors - protein molecules located in various parts of CNS and also in some periferal tissues. The binding is normally non-covalent and it is reversible. Outside CNS, opioid receptors are significantly expressed in intestines (e.g. *ileum*) and sperm ducts (*vas deferens*).[1]

At present, four types of opioid receptors types are recognized: μ (MOR), κ (KOR), δ (DOR) and ORL-1 (or NOP). (The opioid receptor types are sometimes refered to as sub-types). While many of the natural physiological roles of those receptors remain poorly understood or unknown, a number of facts have been established with solid certainty. Thus all opioid receptor types are G-protein coupled, transmembrane proteins. As such, they are tightly embedded into the cell wall, with the active site facing outward.

Upon forming a complex with agonist ligands (either endogenous opioid peptides or exogenous compounds), the receptors initiate an intracellular sequence of events, eventually resulting in the reduction of painful sensations. (ORL-1 receptor type is considerably different from the other three).[1]

Much effort has been invested in the theoretical modeling of receptor-ligand interactions. The most significant general approach is known as docking, although other methods are also used.[7] Apart from the practical aspects, in designing novel opioid drugs, the studies have significantly contributed to the present knowledge of receptor-ligand interactions and to the general understanding of opioid action on molecular level.

Prior to 2012, the 3D structures of opioid receptors were unknown, since the purified opioid receptor proteins could not be crystalized. Therefore, the extensive homology modeling, based on the experimentally determined 3D structures of the related receptors ("homologues"), was used to predict probable 3D structures of the opioid receptors and their active sites.[8] (The active sites are often denoted as binding pockets). The interactions of the presumed active sites and the various ligands were then calculated and compared to the experimental pharmacological results, particularly binding affinities. While insufficiently accurate, the homology approach offered a significant and generally correct insight into the mechanism of opioid action on molecular level. In some instances, binding affinities of novel compounds could be predicted qualitatively.[8]

Since 2012, all 4 opioid receptors, in various complexes, were crystalized and their 3D structures determined using single crystal X-ray diffraction.[9] Significantly, one of the structures is the complex μ-receptor-agonist, having the binding pocket in the activated state.[9a] (Other complexes are with the antagonist ligands and have inactive binding pockets).[9b-e] Detailed knowledge of the activated binding pocket can also facilitate the development of novel opioids, having higher potency and/or improved pharmacological profile.

As already noted, opioid endogenous peptides are the natural ligands of opioid receptors, normally present in the tissues containing opioid receptors. The following endogenous opioid peptides are known: 1) Met-enkephalin, 2) Leu-enkephalin, 3) β-Endorphin, 4) Dynorphin A, 5) Dynorphin B, 6) α-Neoendorphin, 7) Endomorphin-1 and 8) Nociceptin (orphanin FQ), Scheme 1. Their structure, biosynthesis and biological roles have been the subject of extensive research in the past three decades.[1a]

1. **Tyr-Gly-Gly-Phe-Met**

Met-enkephalin

2. **Tyr-Gly-Gly-Phe-Leu**

Leu-enkephalin

3. **Tyr-Gly-Gly-Phe-Met-Thr-Ser-Glu-Lys-Ser-Gln-Thr-Pro-Leu-Val-Thr-Leu-Phe-Lys-Asn-Ala-Ile-Ile-Lys-Asn-Ala-Tyr-Lys-Lys-Gly-Glu**

β-Endorphin

4. **Tyr-Gly-Gly-Phe-Leu-Arg-Arg-Ile-Arg-Pro-Lys-Leu-Lys-Trp-Asp-Asn-Gln**

Dynorphin A

5. **Tyr-Gly-Gly-Phe-Leu-Arg-Arg-Gln-Phe-Lys-Val-Val-Thr**

Dynorphin B

6. **Tyr-Gly-Gly-Phe-Leu-Arg-Lys-Tyr-Pro-Lys**

α-Neoendorphin

7. **Tyr–Pro–Trp–Phe–NH_2**

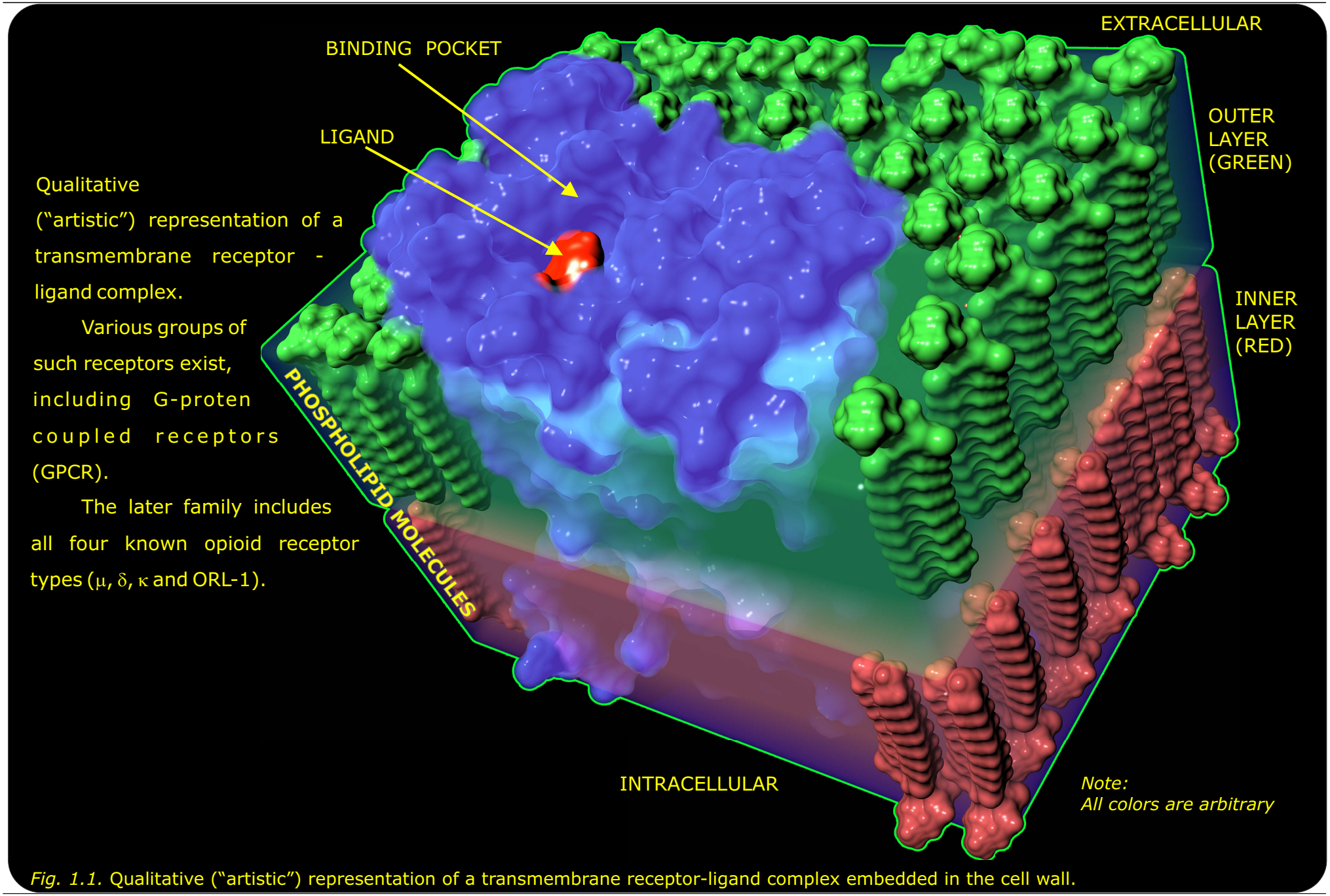
Endomorphin-1

8. **Phe-Gly-Gly-Phe-Thr-Gly-Ala-Arg-Lys-Ser-Ala-Arg-Lys-Leu-Ala-Asn-Gln**

Nociceptin (orphanin FQ)

Scheme 1.1. Known endogenous opioid pepties

Figures 1.1-1.3, (p. 5-7), are qualitative ("artistic") representations of opioid receptors and their environment. Exact experimental structures of μ-opioid receptors, Figures 1.4-1.6, were rendered from the original PDB files, using dedicated molecular visualizing applications. For more detailed information on the opioid receptor structures, readers are refered to the original literature and the PDB files. (To avoid ambiguities, CAS Registry Numbers are provided for certain small molecules, e.g. ligands).



Qualitative ("artistic") representation of a transmembrane receptor - ligand complex.

Various groups of such receptors exist, including G-proten coupled receptors (GPCR).

The later family includes all four known opioid receptor types (μ, δ, κ and ORL-1).

Fig. 1.1. Qualitative ("artistic") representation of a transmembrane receptor-ligand complex embedded in the cell wall.

It has been determined experimenatally that opioid receptors consist of seven transmembrane α-helical folds (TM-1 to TM-7) and three extra-cellular loops (ECL1-ECL3).[9] *N*-terminus is in the extracelluar space and C-terminus is inside the cell. The receptor is coupled to G-protein in the intracellular space, *Fig. 1.2*. When activated by an agonist ligand, the receptor generates signal, mediated by G-protein. The signal initiates the chain of intracelular events, eventually resulting in temporary analgesia.

Other G-protein coupled receptors have a broadly similar structure and mechanism of action. (For a detailed discussion see ref. 9a).

Note: *Fig.1.2* was created using a dedicated application, by an extensive manual modification of the experimental structure (activated μ-opioid receptor, PDB: 5C1M). While the basic shape was preserved, α-helical folds (TM-1 to TM-7) were stretched apart to make the receptor structure clearly visible.

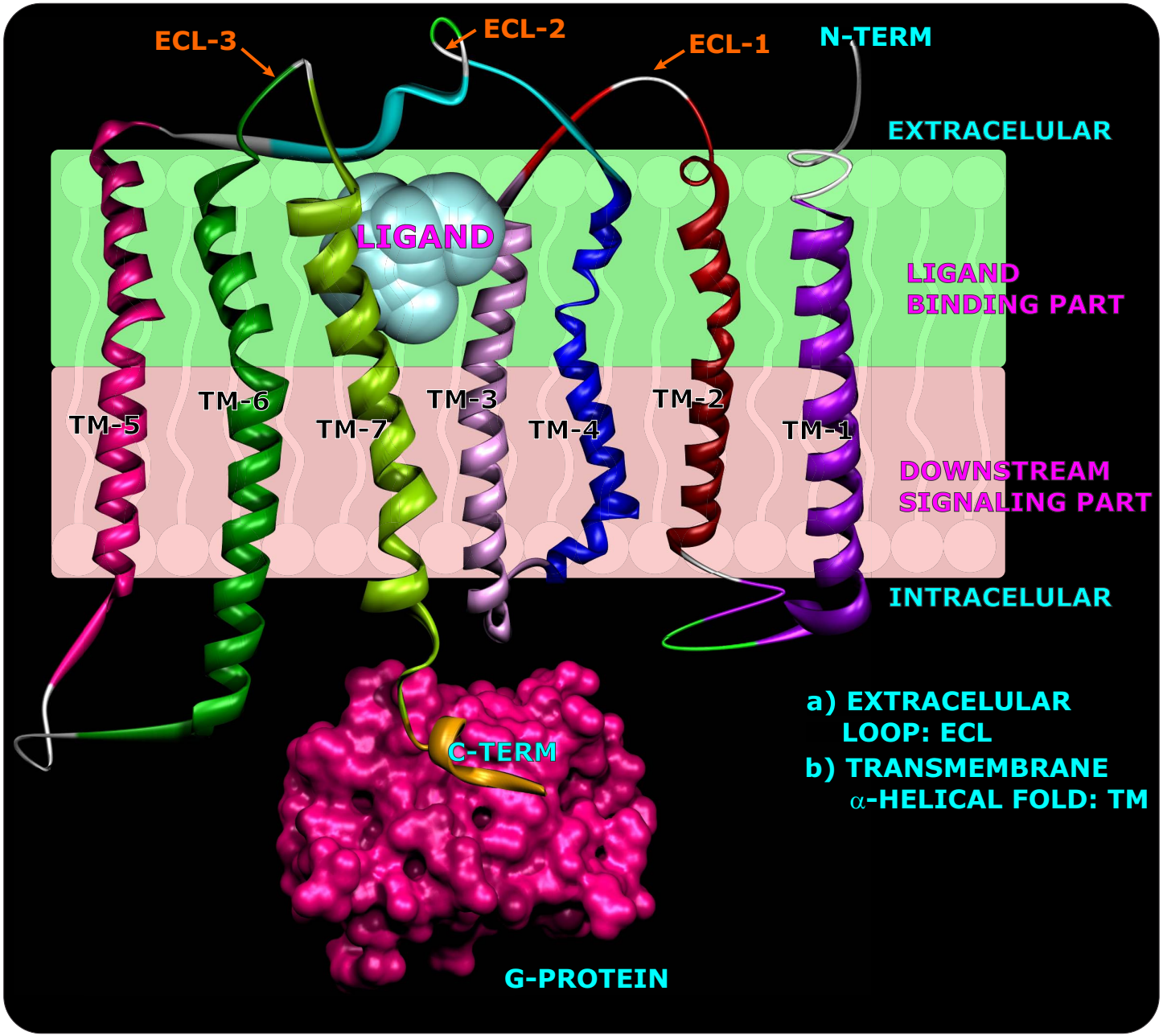


Fig. 1.2. Shematic qualitative representation of an opioid receptor (μ, κ, δ or ORL-1) in the cell membrane bilayer.

Artistic representation of an opioid ligand (e.g. morphine), penetrating into the brain tissue, Fig. 1.3. ***A***. The ligand is delivered to the brain via bloodstream. ***B***. The ligand crosses the "Blood-Brain Barrier" (BBB), entering the brain tissue. ***C***. Inside the tissue, it forms a reversible complex ***D-E*** with an opioid receptor ***E*** (represented by the magenta circle). The complex formation initiates chain of events resulting in temporary analgesia. As the complex dissociates, the analgesic effect terminates.

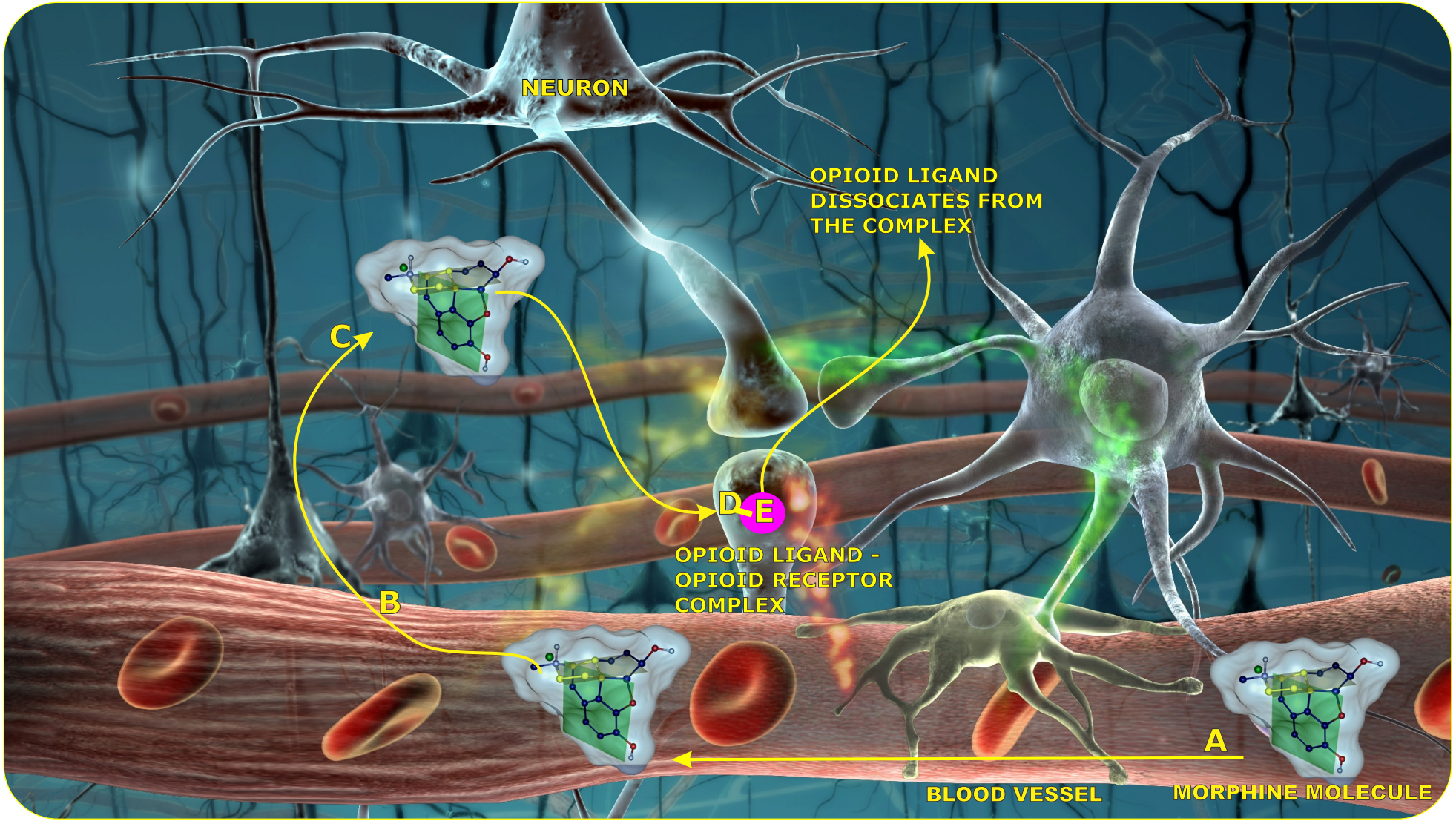
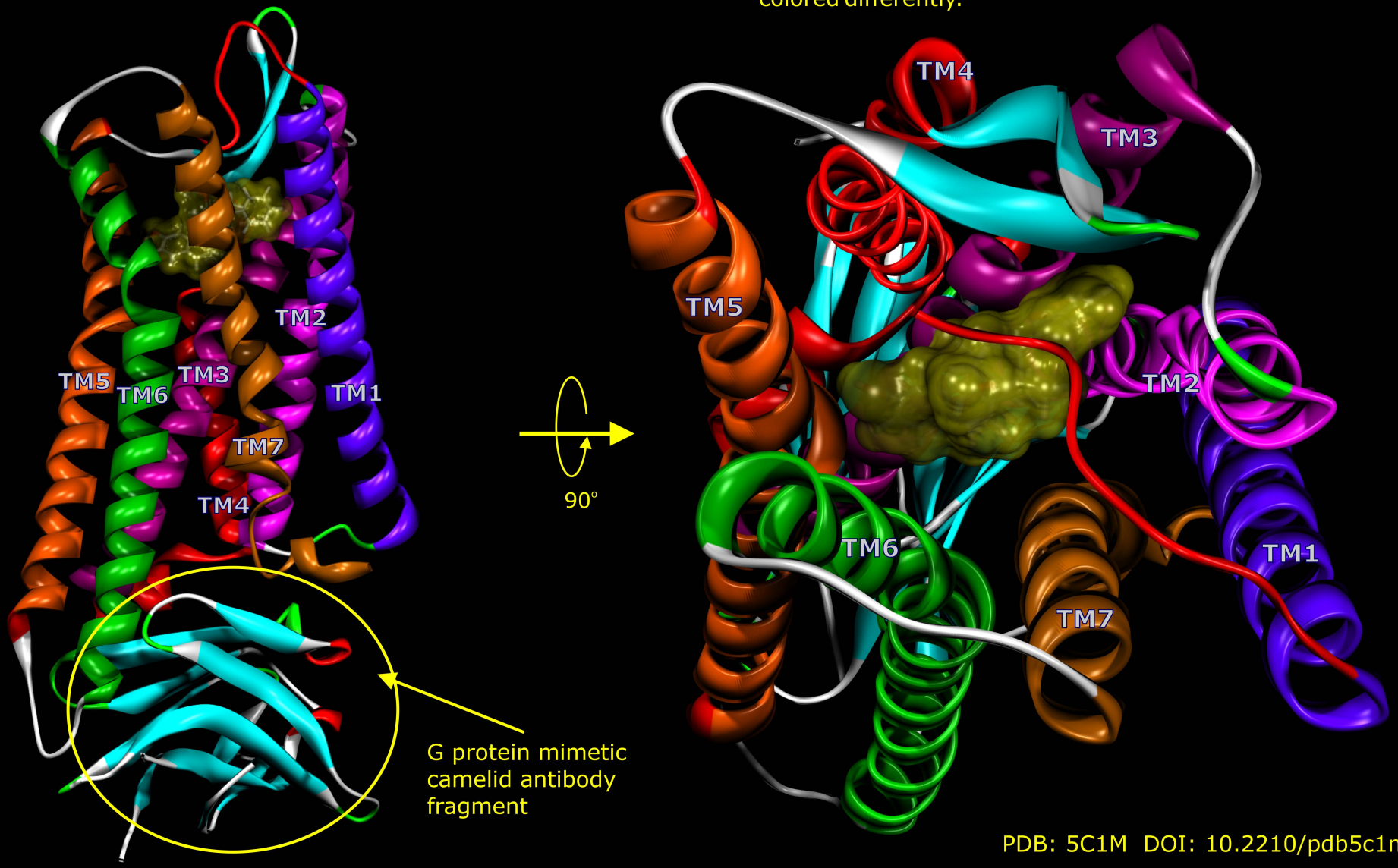


Fig. 1.3 Artistic representation of an opioid ligand penetrating into the brain tissue and the sequence of ensuing events.

X-ray crystal structure of the mouse μ-opioid receptor bound to morphinan agonist BU72 and a G-protein mimetic camelid antibody fragment, *Fig. 1.4*.[9a] It is a shematic representation of the *exact, activated structure of μ–opiod receptor.* Each of the seven transmembrane α-helical folds, TM1-TM7, is colored differently.



PDB: 5C1M DOI: 10.2210/pdb5c1m/pdb

Fig. 1.4 X-ray crystal structure of the activated μ-opioid receptor bound to agonist (shematic representation).

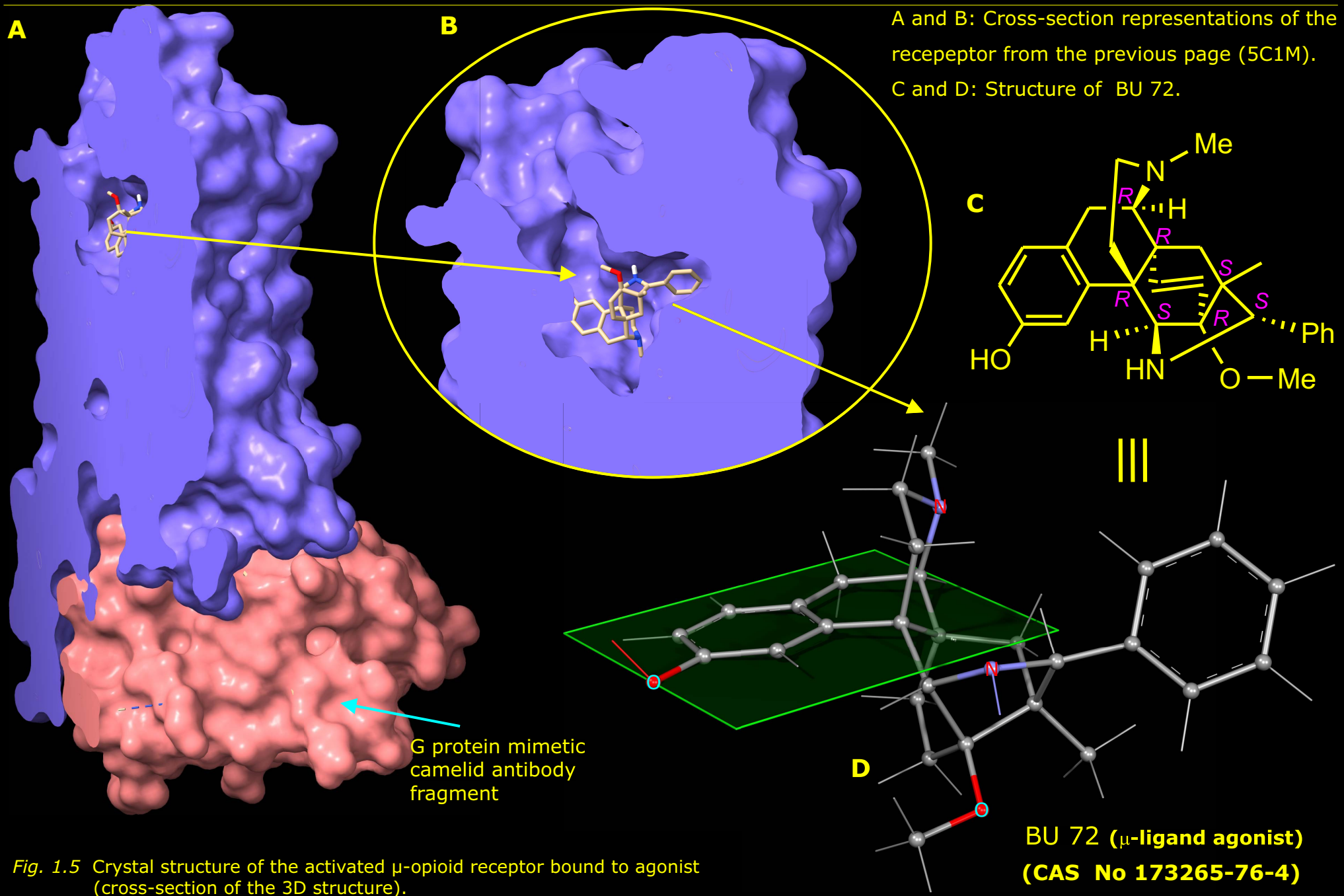
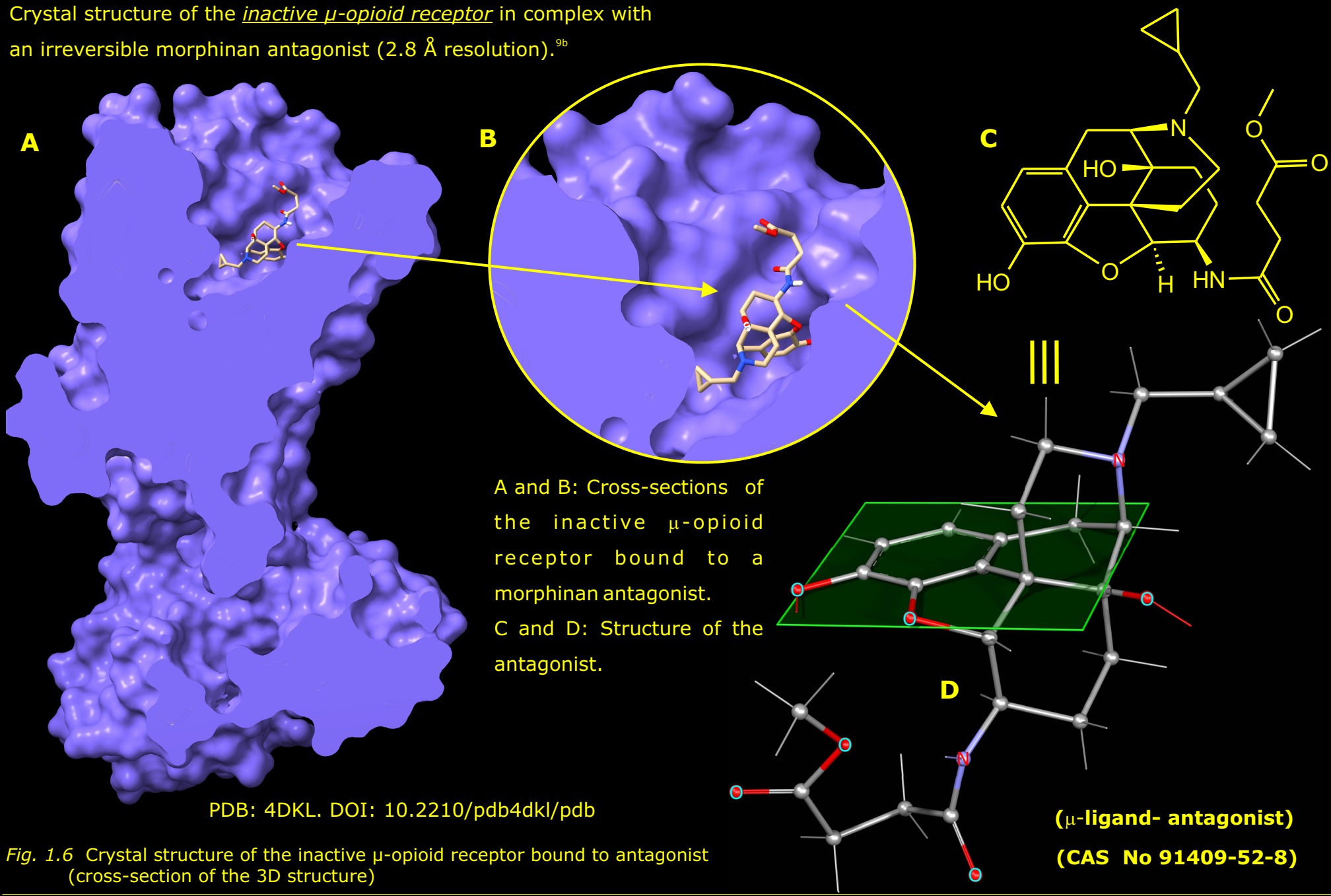


Fig. 1.5 Crystal structure of the activated μ-opioid receptor bound to agonist (cross-section of the 3D structure).

Crystal structure of the *inactive μ-opioid receptor* in complex with an irreversible morphinan antagonist (2.8 Å resolution).[9b]



A and B: Cross-sections of the inactive μ-opioid receptor bound to a morphinan antagonist.
C and D: Structure of the antagonist.

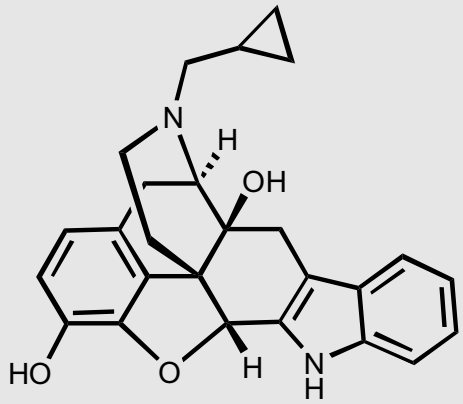
PDB: 4DKL. DOI: 10.2210/pdb4dkl/pdb

(μ-ligand- antagonist)

(CAS No 91409-52-8)

Fig. 1.6 Crystal structure of the inactive μ-opioid receptor bound to antagonist (cross-section of the 3D structure)

As already noted, besides μ receptor structure, crystalline structures of δ, κ and ORL-1 receptors, in complexes with the respective antagonist ligands, were also determined.[9c,d,e] Although the each receptor and its binding pocket have a distinct 3D structure, they are visually similar, as expected from the closely homologous proteins. Therefore, structures of the three receptors are not represented here; only their antagonist ligands are shown, *Scheme 1.2.* (The receptor structures can be directly retrived using DOI numbers).

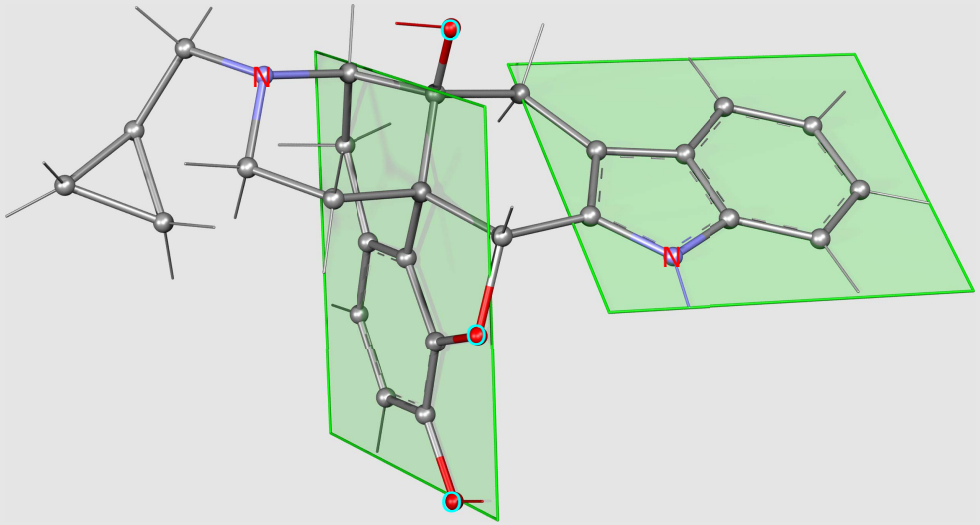


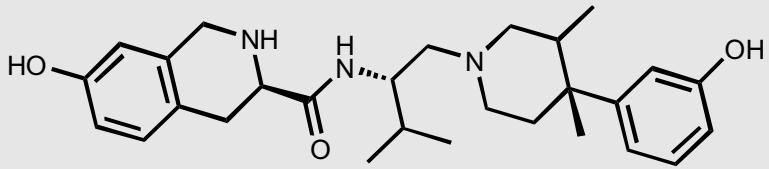
1

(Naltrindole;δ-ligand- antagonist)

(CAS No. 111555-53-4);PDB: DOI: 10.2210/pdb4ej4/pdb

≡

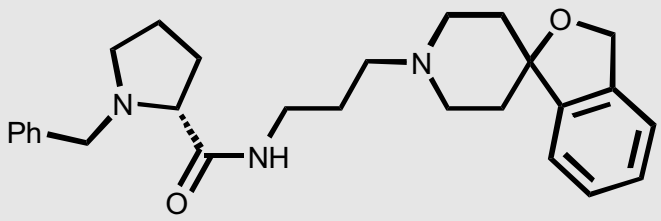




2

JDTic; (κ ligand antagonist)

(CAS No. 361444-66-8); PDB: DOI: 10.2210/pdb4djh/pdb



3

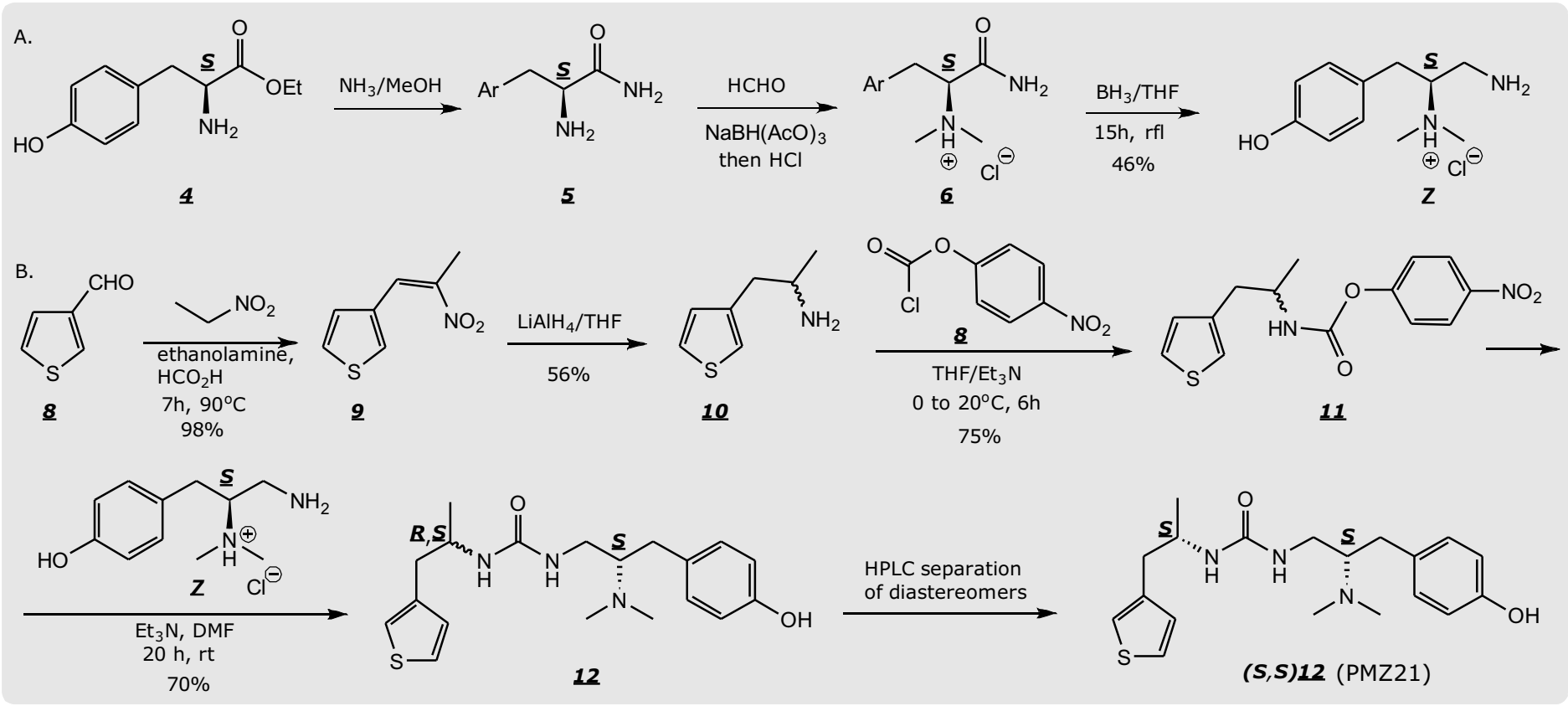
(ORL-1 ligand- antagonist)

(CAS No 475150-69-7);PDB: DOI: 10.2210/pdb4ea3/pdb

*Scheme 1.2. A*ntagonist ligands ***1***, ***2*** and ***3***, used to obtain crystalline complexes with δ, κ and ORL-1 receptors, respectively.

Very recently, the crystalline structure of the μ-receptor-ligand complex was used in the rational drug design, providing entirely novel μ-opioid agonist, PZM21.[10] While the compound has similar analgesic potency as morphine, adverse side effects appear to be substantially reduced, thus providing a significant pharmacological lead in development of the next-generation opioid drugs. The synthesis of the compound (***S***,***S)12*** (PZM21) is shown in *Scheme 1.3*.[10]

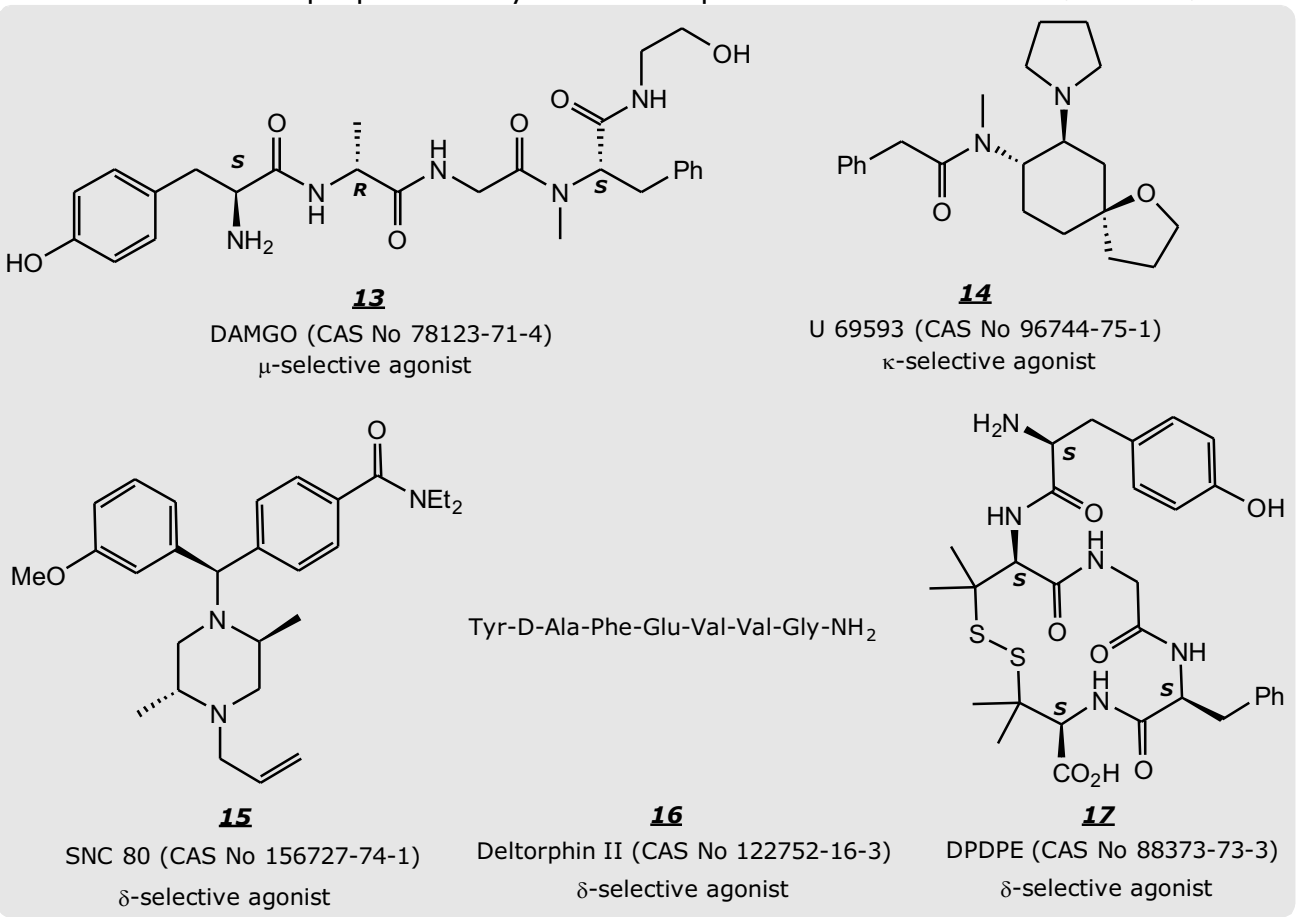
The synthetic approach is straightforward, based on the standard reactions used in synthesis of peptidomimetics and related compounds. Commercial precursors, L-tyrosine ethyl ester ***4*** and thiophene-3-carbaldehyde ***8*** were elaborated to the intermediates ***7*** and ***11*** respectively. Direct aminolysis of the activated carbamate ***11*** by primary amine ***7*** secured the final product, urea ***12*** as a diastereomeric mixture. HPLC separation provided the active μ-opiod ligand (***S***,***S)12***. Despite simplicity of the synthetis, the ligand design process was qute complex and sophisticated.[10]



Scheme 1.3. Synthesis of novel, μ-selective opioid ligand (***S***,***S)12*** (PMZ21).

1.3. Ligands Selective For μ, κ and δ Opioid Receptors

In general, opioid ligands have preferential selectivity for one of the three receptor types (μ, κ, δ). (ORL-1 ligands are discussed at p. 14). However, the selectivity is relative and they also bind, with various affinities, to other opioid receptor types. Ligands highly selective for the each opioid receptor type do exist and are used for research purposes only. The compounds have no therapeutic use, since they cannot penetrate blood-brain barier and/or have serious side effects. Prominent examples are shown in *Scheme 1.4*. Thus, synthetic peptide DAMGO ***13*** is highly selective μ-receptor agonist, widely used in the reasearch of opioid-related phenomena.[11-13] Compound ***14*** (U 69,593)[14] is a selective κ-receptor agonist, while compounds ***15***,[15] ***16***[16] and ***17***,[17,18] are all δ-selective agonist ligands. (Deltorphine II, structure ***16***, is a naturally-occuring peptide, which is normally obtained synthetically, as [3H] radioligand).

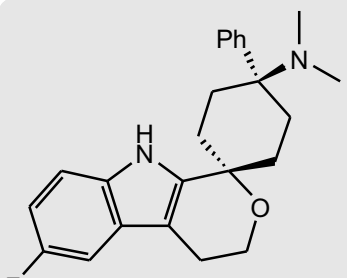


Scheme 1.4. Structure of some significant, μ, κ and δ-selective opioid ligands, used in the research of opioid receptor related phenomena.

Pharmacological profiles of the three opioid receptor types are significantly different. Thus μ-receptors are responsible for the most powerful analgesia and are clinically most significant. Almost all opioid analgesic in the current clinical use are primarily μ-agonists. Unfortunately, their activation also causes severe respiratory depression, tolerance and addiction. Various κ-selective agonists have been tested as analgesics, however, except for pentazocine, cannot be used as drugs, because of the serious psychotomimetic effects (otherwise they produce powerful analgesia and little tolerance and dependence). At present, selective δ-opioid agonists appear to have limited therapeutic potentials.

ORL-1 receptors apparently have significantly different biological roles from μ, κ and δ receptors. Consequently, their exogenous ligands, both agonists and antagonists, induce diverse pharmacological responses.

There are several ongoing clinical trials or preclinical investigations of both ORL-1 agonists and antagonists.[19] ORL-1 agonists have been examined in preclinical models for the potential treatment of anxiety, cough, substance abuse, pain (spinal and peripheral) as well as urinary incontinence. ORL-1 antagonists have promising potentials in the treatment of pain, depression, and motor symptoms in Parkinson's disease.[19] At present, there are no approved drugs, acting on ORL-1 receptors. Cebranopadol,[20] structure ***18***, which is the full ORL-1 agonist and full μ-agonist, is currently undergoing Clinical Phase III trials, as a potential analgesic. Other ORL-1 agonist or antagonists are in a less advanced clinical trials or preclinical investigations.[19]



Cebranopadol ***18***
(CAS No. 863513-91-1)

1.4. Biological Testing Of Opioids

Biological testing of the opioid ligands has evolved greatly in the past several decades. Initially, only *in vivo* tests were available.

Typical tests for measuring analgesic effects (not necessarily caused by opioids) are: 1) *mouse hot-plate test* (MHP), 2) *rat-tail withdrawal test* (RTW) and 3) *The Randall–Selitto test or paw pressure test*. They are still extensively performed in rodents. *Rotarod performance test* is used to examine balance and coordination, which can be seriously affected by various substances, including opioids.

Description of the tests and statistical methods for results evaluation can be found in the relevant literture.[21] Some of the tests are illustrated in the *Figures 1.7-1.10*.

Fig. 1.7. **Mouse hot plate test**

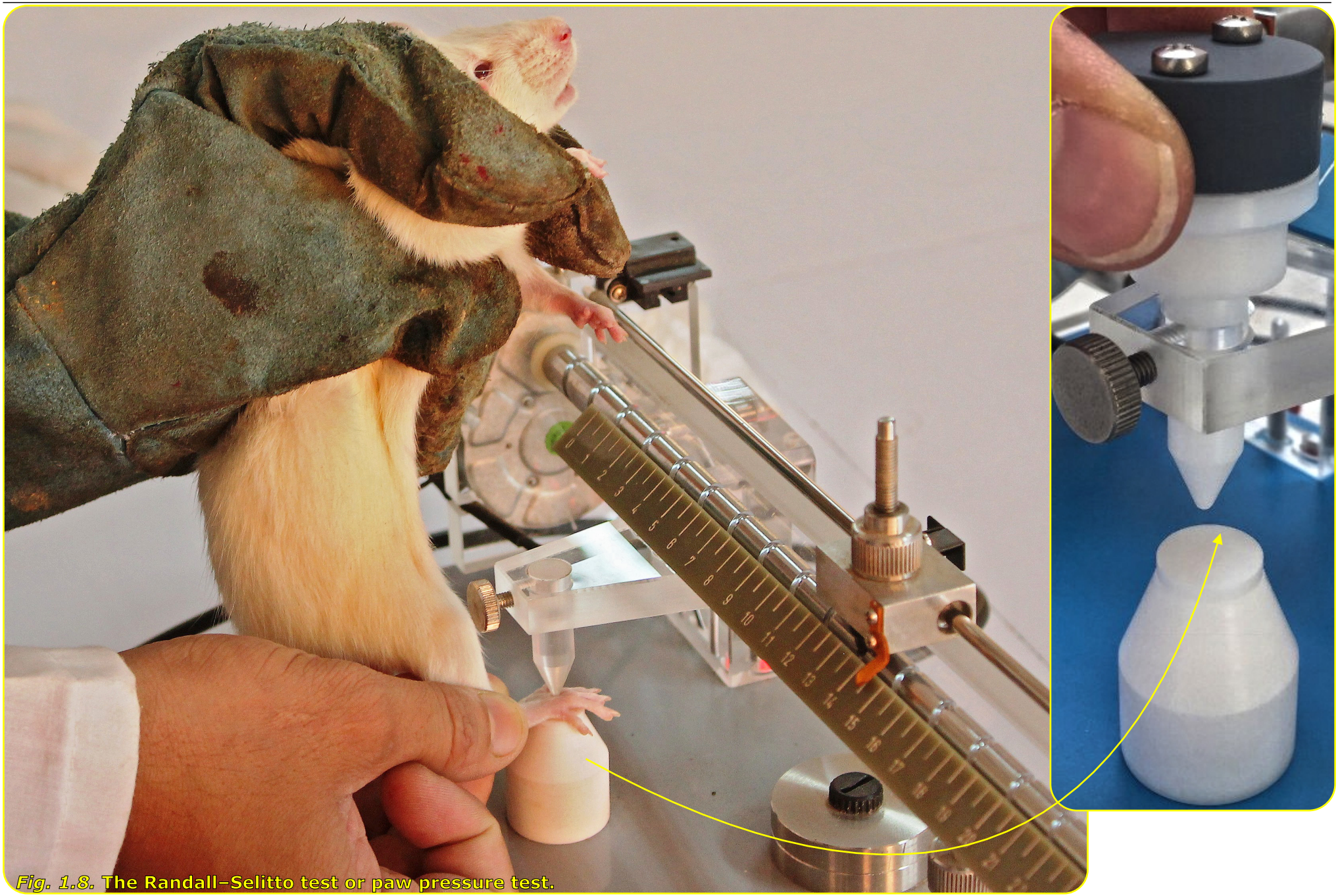


Fig. 1.8. **The Randall–Selitto test or paw pressure test.**

Fig. 1.9. Rat-tail withdrawal test.

Fig. 1.10. **Rotarod performance test**

More advanced tests, including the electrical stimulation of the tooth pulp in healthy human volunteers were developed.[22] While usually efficient, they are time-consuming, costly and depend on numerous pharmacokinetic factors (e.g. some compounds cannot penetrate brain-blood barrier etc.). Furthermore, any tests in humans are clinical trials, requiring long preparations, previous animal tests and safety considerations. Therefore, various *in vitro* tests were developed. One group of tests involve isolated animal organs, rich in opioid receptors, usually intestines or sperm ducts (e.g. guinea-pig isolated *ileum*[23] or rat *vas deferens*[24]). Electrical stimulation[25] of these isolated organs can efficiently identify opioid agonists or antagonists, without interference from pharmacokinetic factors.

Binding assays become essential, first-line tests in estimating opioid activity of the novel compounds.[26] With the advances in receptor cloning, much larger amounts of the cloned receptor proteins, including all four human opioid receptors, become available. Using various radiolabeled reference ligands (e.g. [3H] naloxone), it is relatively expedient to measure binding affinity of the novel compounds towards specific receptors. Yet, high costs of the cloned receptors, reference radioligands and the dedicated equipment are often prohibitive.[26]

Another useful tool in studding opioid receptors and their ligands are receptor-specific ligands. They are used extensively in various tests, usually *in vitro*, to measure the receptor selectivity of new compounds (see *Scheme 1.4*).

1.5. Structure of Exogenous Opioid Ligands

As evident from the available literature (papers and patents), there are thousands of the known exogenous opioid agonists and a far smaller number of the opioid antagonists. Many of them a structurally quite diverse, encompassing, among others, morphine-like compounds, relatively simple piperidines and peptides. An overwhelming majority of the opioids are obtained either by semi-synthesis from morphine alkaloids or are fully synthetic, including many peptides and peptidomimetics. In fact, morphine is the only opioid drug obtained exclusively by isolation. (Codeine is predominantly prepared by semi-synthesis, Chapter 2). A small number of compounds are naturally occurring non-morphine opioids, as detailed later. In the present, short treatise of the topic, it was not possible to include even the structures of all opioid classes, much less their synthesis.

Therefore, the author chose to cover mainly opioids used as the drugs, either currently or in the past. These compounds are easily identified, as all countries worldwide are obliged to report to UN agencies (primarily to International Narcotic Control Board, INCB) the exact quantities of the opioid drugs they produce annually, as well as the consumption, utilization and import/export.

Medically used opioid drugs can be simply classified as:

1) immediate morphine derivatives and

2) all others.

On the industrial scale, morphine derivatives are exclusively obtained by semi-synthesis from morphine, thebaine and oripavine (Chapter 2). Almost all other opioids are fully synthetic, e.g. pentazocine, methadone, pethidine, fentanyl and its analogues and several others (Chapter 3).

1.6. Natural Non-Morphine Opioids

There is a relatively small number of natural products, structurally unrelated to morphine, which are proven opioids. At present, their significance is only academic.

Almost forty years ago, it was found that the skin of several species of frogs (genus *Phyllomedusinae*), contained peptides which were selective μ-opioid agonists.[27] A total of seven naturally occurring peptides, named dermorphins, were isolated and numerous analogues synthesized.

Representative examples are Dermorphin and hydroxyproline[6]-Dermorphin, *Fig. 1.11*. Generally, they are potent and selective opioids, however most of them cannot penetrate brain-blood barrier (BBB), thus requiring direct injection into the brain (ICV, intracerebro-ventricularly). Like other opioid peptides, both natural and synthetic, dermorphins have only academic significance, with no therapeutic potential. In addition to dermorphins, the same genus of frogs (spec. *Phyllomedusa bicolor*) was the source of several heptapeptides, possessing high agonist activity and exceptionally high selectivity for δ-opioid receptors, Fig. *1.12*. The peptides were named deltorphins and, like dermorphins, all have D-alanine in the position 2.[28] Initial studies, using various *in vitro* tests, confirmed that Deltorphin I was the most potent and δ-selective ligand, with Ki= 0.15 nM.

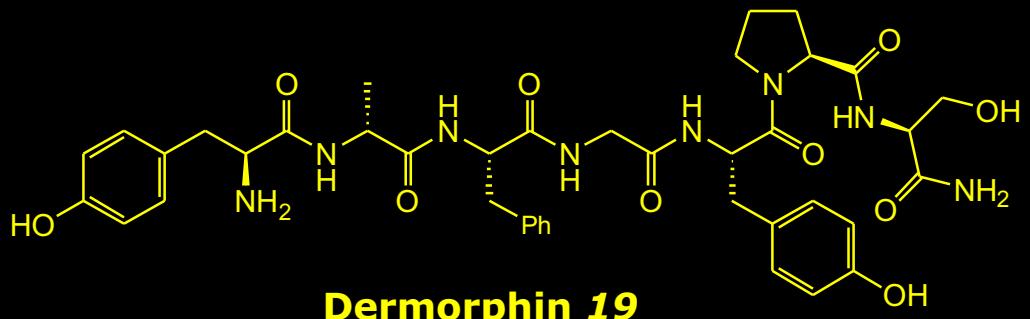
Thus, the synthetically prepared and [3H] labeled compound is a useful probe in binding studies. Subsequently, it was determined that deltorphins significantly penetrate blood-brain barrier, via specific transportation mechanism, producing *in vivo* analgesia in rodents. Nonetheless, like more recent, non-peptide δ-agonists, their overall therapeutic potential is low.[28]

The South Asian plant, known as "kratom" (*Mitragyna speciosa*), has been used for centuries by the local population, because of its pronounced psychoactive properties, Fig. *1.13*.[1a,29] The most active constituent is the alkaloid mitragynine, which shows distinct opioid-like activity (ca ½ that of morphine, when measured *in vitro*). However, other pharmacological properties are different from morphine and it is unlikely that the compound or its analougues will find therapeutic use.

Probably the most intriguing example of naturally occurring opioids is Salvinorin A, isolated from the Central American plant, *Salvia divinorum*, *Fig. 1.14*.[30] The compound is a terpenoid rather than alkaloid, since it has no nitrogen atoms. Yet, it is probably the most potent κ-agonists known to science. It is also a well-known and extremly potent halucinogen, being active in sub-milligram quantities in humans. The plant has been used for centuries, by Mazatecs, an indigenous group from Oaxaca, Mexico, in shamanistic rituals.[30]

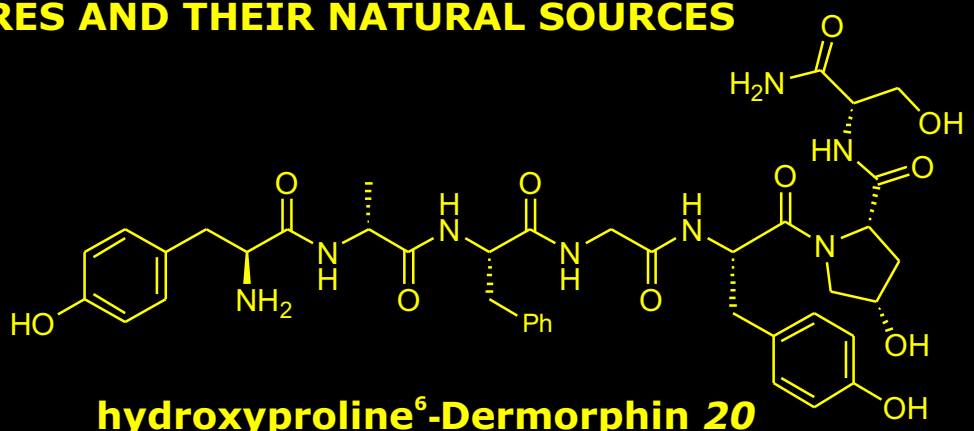
Despite more than three decades of research efforts, many aspects of its action remain poorly understood.[30] However, the fact that it causes hallucinations is not surprising, since κ-receptor activation almost always has strong psychomimetic effects.[1a,30c] This is the principal reason that prevents medical use of the selective κ-agonists, including Salvinorin A and its numereous analogues. However, the compounds are useful tools in pharmacological research.

DERMORPHINS - REPRESENTATIVE STRUCTURES AND THEIR NATURAL SOURCES



Dermorphin *19*

Tyr-D-Ala-Phe-Gly-Tyr-Pro-Ser-NH_2



hydroxyproline^6-Dermorphin *20*

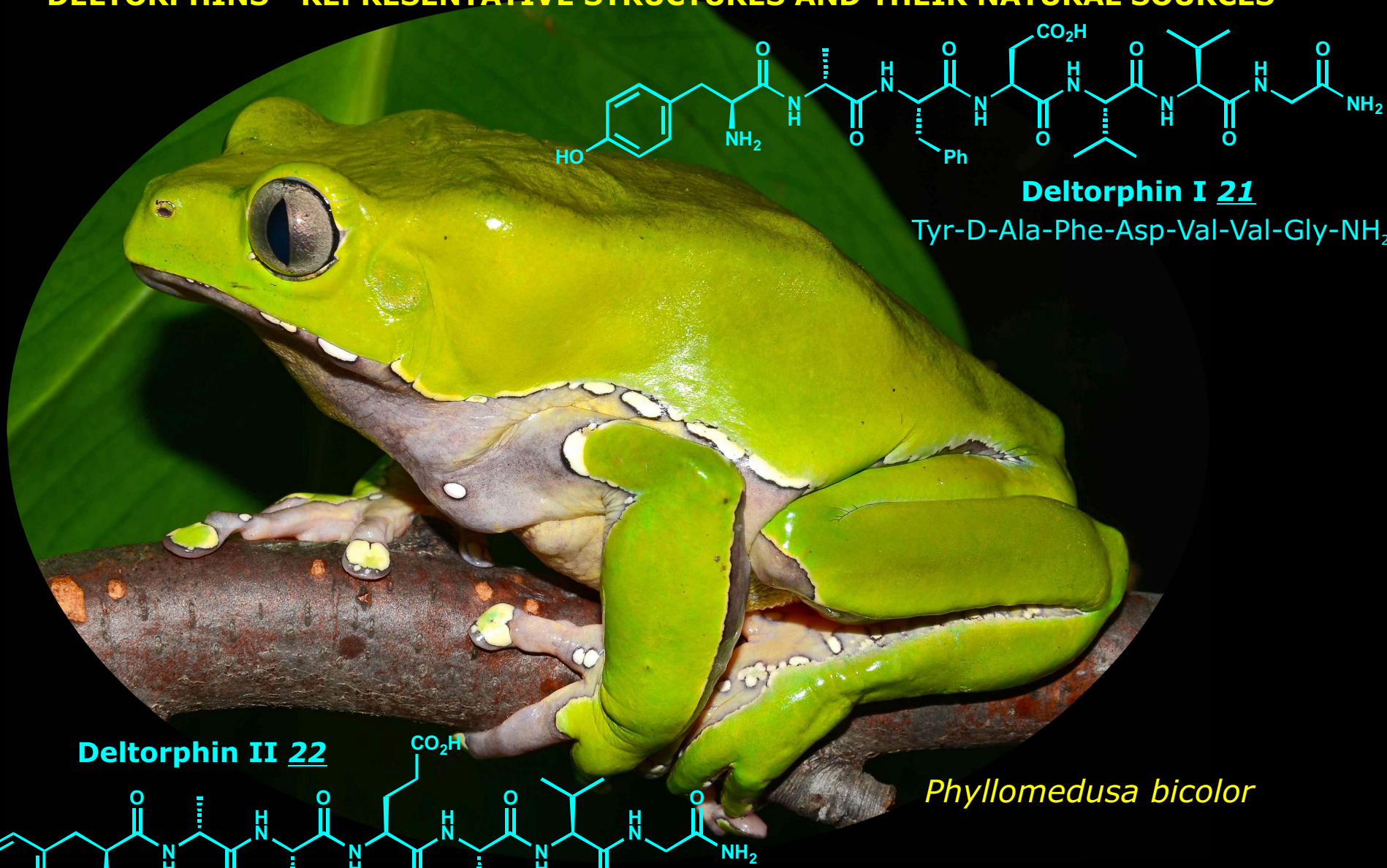
Tyr-D-Ala-Phe-Gly-Tyr-Hyp-Ser-NH_2

Phyllomedusa sauvagei

Phyllomedusa rohdei Mertens, 1926

Fig. 1.11. **Dermorphins**

DELTORPHINS - REPRESENTATIVE STRUCTURES AND THEIR NATURAL SOURCES



Deltorphin I *21*

Tyr-D-Ala-Phe-Asp-Val-Val-Gly-NH_2

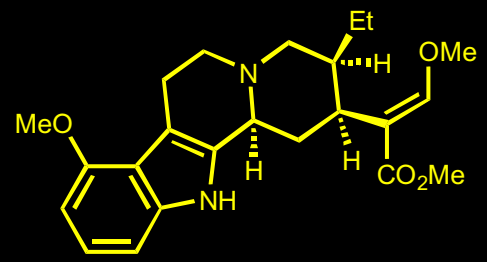
Deltorphin II *22*

Tyr-D-Ala-Phe-Glu-Val-Val-Gly-NH_2

Phyllomedusa bicolor

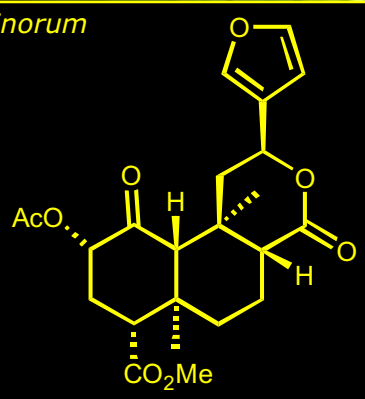
Fig. 1.12. **Deltorphins**

Fig.1.13 Mitragyna speciosa



Mitragynin *23* (CAS No. 4098-40-2)

Fig.1.14 Salvia divinorum



Salvinorin A *24* (CAS No 83729-01-5)

1.7 References

1. For the recent general references see:

a) Tony L. Yaksh; Mark S. Wallace. Chapter 18: Opioids, Analgesia, and Pain Management. pp. 481-522. In Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 12e. Ed. Laurence L. Brunton, Bruce A. Chabner, Björn C. Knollmann. The McGraw-Hill Companies 2011. New York.
ISBN 978-0-07-176939-6.

b) Del Vecchio, G., Spahn, V., & Stein, C. (2017). Novel Opioid Analgesics and Side Effects. ACS Chemical Neuroscience. doi:10.1021/acschemneuro.7b00195.

c) Pellissier, L. P., Gandía, J., Laboute, T., Becker, Jô. A. J., and Le Merrer, J. (2017) μ- opioid receptor, social behaviour and autism spectrum disorder: reward matters. British Journal of Pharmacology, doi: 10.1111/bph.13808.

d) Luigi, A. M., Damiana, S., Laura, R., Hirokazu, M., & Giacinto, B. (2017). Opioids Resistance in Chronic Pain Management. Current Neuropharmacology, 15(3), 444-456. doi:http://dx.doi.org/10.2174/1570159X14666161101092822.

e) Kratom and Other Mitragynines. The Chemistry and Pharmacology of Opioids from a Non-Opium Source. Edited by Robert B. Raffa. CRC Press 2014. eBook ISBN: 978-1-4822-2519-8. https://doi.org/10.1201/b17666.

2. Piyush M. Patel. Hemal H. Patel, and David M. Roth Chapter 19: General Anesthetics and Therapeutic Gase. pp. 527-564. In Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 12e. Ed. Laurence L. Brunton, Bruce A. Chabner, Björn C. Knollmann. The McGraw-Hill Companies 2011. New York. ISBN 978-0-07-176939-6.

3. William A. Catterall and Kenneth Mackie. Chapter 20: Local Anesthetics. pp. 565-582. In Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 12e. Ed. Laurence L. Brunton, Bruce A. Chabner, Björn C. Knollmann. The McGraw-Hill Companies 2011. New York. ISBN 978-0-07-176939-6.

4.Tilo Grosser, Emer Smyth, and Garret A. FitzGerald. Chapter 34: Anti-Inflamatory, Antipyretic, and, Analgesic Agents; Pharmacotherapy of Gout. pp. 959-1004. Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 12e. Ed. Laurence L. Brunton, Bruce A. Chabner, Björn C. Knollmann. The McGraw-Hill Companies 2011. New York. ISBN 978-0-07-176939-6.

5. Alan M. Krensky, William M. Bennett, and Flavio Vincenti. Chapter 35: Immunosupressants, Tolerogens, and Immunostimulants. pp. 1005-1029. Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 12e. Ed. Laurence L. Brunton, Bruce A. Chabner, Björn C. Knollmann. The McGraw-Hill Companies 2011. New York. ISBN 978-0-07-176939-6.

6.Charles P. O'BrienIn Chapter 24: Drug Addiction. pp. 649-668. Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 12e. Ed. Laurence L. Brunton, Bruce A. Chabner, Björn C. Knollmann. The McGraw-Hill Companies 2011. New York. ISBN 978-0-07-176939-6.

7.a) Anna, E. L., Stephan, M. L., Billy, W.-N., & Stephanie, S. S. (2017). A Practical Guide to Molecular Docking and Homology Modelling for Medicinal Chemists. Current Topics in Medicinal Chemistry, 17(18), 2023-2040. doi:http://dx.doi.org/10.2174/1568026617666170130110827.

b) Bartuzi, Damian; Kaczor, Agnieszka A.; Targowska-Duda, Katarzyna M.; Matosiuk, Dariusz. (2017). "Recent Advances and Applications of Molecular Docking to G Protein-Coupled Receptors." Molecules 22, no. 2: 340. doi:10.3390/molecules22020340

c) Leelananda, S. P.; Lindert, S. Computational methods in drug discovery. Beilstein J. Org. Chem. 2016, 12, 2694–2718. doi:10.3762/bjoc.12.267.

d) Liu, Z., Su, M., Han, L., Liu, J., Yang, Q., Li, Y., & Wang, R. (2017). Forging the Basis for Developing Protein–Ligand Interaction Scoring Functions. Accounts of Chemical Research, 50(2), 302-309. doi:10.1021/acs.accounts.6b00491.

8.See for example:
a) Senćanski, M., Ivanović, M. & Došen-Mićović, L. (2014). Modelling of ORL1 receptor-ligand interactions. Chemical Papers, 68(10), pp. 1305-1316. doi:10.2478/s11696-014-0577-z.

b) Senćanski Milan, Ivanović Milovan D., Vučković Sonja, Došen-Mićović Ljiljana. Journal of the Serbian Chemical Society 2011 Volume 76, Issue 9, Pages: 1247-1262. doi.org/10.2298/JSC110120110S.

c) Mićović Vuk I., Ivanović Milovan D., Došen-Mićović Ljiljana. Structural requirements for ligands of the δ-opioid receptor. Journal of the Serbian Chemical Society 2009 Volume 74, Issue 11, Pages: 1207-1217. doi.org/10.2298/JSC0911207M.

d) Mićović, V., Ivanović, M. D., & Došen-Mićović, L. (2009). Docking studies suggest ligand-specific δ-opioid receptor conformations. Journal of Molecular Modeling, 15(3), 267-280. doi:10.1007/s00894-008-0396-7.

e) Došen-Mićović Ljiljana, Ivanović Milovan, Mićović Vuk. Location of the hydrophobic pocket in the binding site of fentanyl analogs in the μ-opioid receptor. Journal of the Serbian Chemical Society 2007 Volume 72, Issue 7, Pages: 643-654. doi.org/10.2298/JSC0707643D.

8f) Došen-Micovic, L., Ivanovic, M., & Micović, V. (2006). Steric interactions and the activity of fentanyl analogs at the μ-opioid receptor. Bioorganic & Medicinal Chemistry, 14(9), 2887-2895. doi:http://dx.doi.org/10.1016/j.bmc.2005.12.010.

9.a) Huang, W.; Manglik, A.; Venkatakrishnan, A. J.; Laeremans, T.; Feinberg, E. N.; Sanborn, A. L.; Kato, H. E.; Livingston, K. E.; Thorsen, T. S.; Kling, R. C.; Granier, S.; Gmeiner, P.; Husbands, S. M.; Traynor, J. R.; Weis, W. I.; Steyaert, J.; Dror, R. O.; Kobilka, B. K., Structural insights into μ-opioid receptor activation. Nature 2015, 524, 315-321. doi:10.1038/nature14886.

b) Manglik, A.; Kruse, A. C.; Kobilka, T. S.; Thian, F. S.; Mathiesen, J. M.; Sunahara, R. K.; Pardo, L.; Weis, W. I.; Kobilka, B. K.; Granier, S., Crystal structure of the μ-opioid receptor bound to a morphinan antagonist. Nature 2012, 485, 321-326. doi:10.1038/nature10954.

c) Granier, S.; Manglik, A.; Kruse, A. C.; Kobilka, T. S.; Thian, F. S.; Weis, W. I.; Kobilka, B. K., Structure of the δ-opioid receptor bound to naltrindole. Nature 2012, 485, 400-404. doi:10.1038/nature11111

d) Wu, H.; Wacker, D.; Mileni, M.; Katritch, V.; Han, G. W.; Vardy, E.; Liu, W.; Thompson, A. A.; Huang, X.-P.; Carroll, F. I.; Mascarella, S. W.; Westkaemper, R. B.; Mosier, P. D.; Roth, B. L.; Cherezov, V.; Stevens, R. C., Structure of the human κ-opioid receptor in complex with JDTic. Nature 2012, 485, 327-332. doi:10.1038/nature10939.

e) Thompson, A. A.; Liu, W.; Chun, E.; Katritch, V.; Wu, H.; Vardy, E.; Huang, X.-P.; Trapella, C.; Guerrini, R.; Calo, G.; Roth, B. L.; Cherezov, V.; Stevens, R. C., Structure of the nociceptin/orphanin FQ receptor in complex with a peptide mimetic. Nature 2012, 485, 395-399. doi:10.1038/nature11085.

10.Manglik, A.; Lin, H.; Aryal, D. K.; McCorvy, J. D.; Dengler, D.; Corder, G.; Levit, A.; Kling, R. C.; Bernat, V.; Hübner, H.; Huang, X.-P.; Sassano, M. F.; Giguère, P. M.; Löber, S.; Da, D.; Scherrer, G.; Kobilka, B. K.; Gmeiner, P.; Roth, B. L.; Shoichet, B. K., Structure-based discovery of opioid analgesics with reduced side effects. Nature 2016, 537, 185-190. 10.1038/nature19112.

11.Araldi, D., Ferrari, L. F., & Levine, J. D. (2017). Hyperalgesic priming (type II) induced by repeated opioid exposure: maintenance mechanisms. PAIN, 158(7), 1204-1216. doi:10.1097/j.pain.0000000000000898.

12.Lindqvist, A., Jönsson, S., & Hammarlund-Udenaes, M. (2016). Exploring Factors Causing Low Brain Penetration of the Opioid Peptide DAMGO through Experimental Methods and Modeling. Molecular Pharmaceutics, 13(4), 1258-1266. doi:10.1021/acs.molpharmaceut.5b00835

13.a) Lefever, M.; Li, Y.; Anglin, B.; Muthu, D.; Giuvelis, D.; Lowery, J. J.; Knapp, B. I.; Bidlack, J. M.; Bilsky, E. J.; Polt, R., Structural Requirements for CNS Active Opioid Glycopeptides. Journal of Medicinal Chemistry 2015, 58, 5728-5741. DOI: 10.1021/acs.jmedchem.5b00014

b) Dang, V. C., & Christie, M. J. (2012). Mechanisms of rapid opioid receptor desensitization, resensitization and tolerance in brain neurons. British Journal of Pharmacology, 165(6), 1704-1716. doi:10.1111/j.1476-5381.2011.01482.x

14. McElroy, T., Thomas, J. B., Brine, G. A., Navarro, H. A., Deschamps, J., & Carroll, F. I. (2008). A Practical Synthesis of the Kappa Opioid Receptor Selective Agonist (+)-5R,7S,8S-N-Methyl- N-[7-(1-pyrrolidinyl)-1- oxospiro[4,5]dec-8-yl]benzeneacetamide (U69,593). Synthesis, 2008(06), 943-947. doi:10.1055/s-2008-1032185.

15. a) Thomas, J. B.; Herault, X. M.; Rothman, R. B.; Burgess, J. P.; Wayne Mascarella, S.; Xu, H.; Horel, R. B.; Dersch, C. M.; Ivy Carroll, F., (±)-4-[(N-allyl-cis-3-methyl-4-piperidinyl)phenylamino] -N,N-diethylbenzamide displays selective binding for the delta opioid receptor. Bioorganic & Medicinal Chemistry Letters 1999, 9, 3053-3056. doi.org/10.1016/S0960-894X(99)00525-9.

b) Calderon, S. N.; Rothman, R. B.; Porreca, F.; Flippen-Anderson, J. L.; McNutt, R. W.; Xu, H.; Smith, L. E.; Bilsky, E. J.; Davis, P.; Rice, K. C., Probes for Narcotic Receptor Mediated Phenomena. 19. Synthesis of (+)-4-[(.alpha.R)-.alpha.-((2S,5R)-4-Allyl-2,5-dimethyl-1-piperazinyl)-3-methoxybenzyl]-N,N-diethylbenzamide (SNC 80): A Highly Selective, Nonpeptide delta Opioid Receptor Agonist. Journal of Medicinal Chemistry 1994, 37, 2125-2128. DOI: 10.1021/jm00040a002.

16.Pescatore, R.; Marrone, G. F.; Sedberry, S.; Vinton, D.; Finkelstein, N.; Katlowitz, Y. E.; Pasternak, G. W.; Wilson, K. R.; Majumdar, S., Synthesis and Pharmacology of Halogenated δ-Opioid-Selective [d-Ala2]Deltorphin II Peptide Analogues. ACS Chemical Neuroscience 2015, 6, 905-910. DOI: 10.1021/acschemneuro.5b00060.

17.Dolle, R. E., Michaut, M., Martinez-Teipel, B., Belanger, S., Graczyk, T. M., & DeHaven, R. N. (2007). Further studies of tyrosine surrogates in opioid receptor peptide ligands. Bioorganic & Medicinal Chemistry Letters, 17(9), 2656-2660. doi:https://doi.org/10.1016/j.bmcl.2007.01.092.

18.Maruyama, T., Ikeo, T., & Ueki, M. (1999). A rapid and facile method for the preparation of peptide disulfides. Tetrahedron Letters, 40(27), 5031-5034. doi:http://dx.doi.org/10.1016/S0040-4039(99)00926-0.

19. Zaveri, N. T. (2016). Nociceptin Opioid Receptor (NOP) as a Therapeutic Target: Progress in Translation from Preclinical Research to Clinical Utility. Journal of Medicinal Chemistry, 59(15), 7011-7028. doi:10.1021/acs.jmedchem.5b01499.

20.Schunk, S.; Linz, K.; Hinze, C.; Frormann, S.; Oberbörsch, S.; Sundermann, B.; Zemolka, S.; Englberger, W.; Germann, T.; Christoph, T.; Kögel, B.-Y.; Schröder, W.; Harlfinger, S.; Saunders, D.; Kless, A.; Schick, H.; Sonnenschein, H., Discovery of a Potent Analgesic NOP and Opioid Receptor Agonist: Cebranopadol. ACS Medicinal Chemistry Letters 2014, 5, 857-862. DOI: 10.1021/ml500117c

21.a) Lavich, T. R., Cordeiro, R. S. B., Silva, P. M. R., & Martins, M. A. (2005). A novel hot-plate test sensitive to hyperalgesic stimuli and non-opioid analgesics. Brazilian Journal of Medical and Biological Research, 38, 445-451. http://dx.doi.org/10.1590/S0100-879X2005000300016.

b) Le Bars, D., Gozariu, M., & Cadden, S. W. (2001). Animal Models of Nociception. Pharmacological
Reviews, 53(4), 597-652. http://pharmrev.aspetjournals.org/content/by/year

c) Drug discovery and evaluation: pharmacological assays. Hans Gerhard Vogel, Wolfgang H. Vogel. (Eds.). ISBN 978-3-662-03335-7 ISBN 978-3-662-03333-3 (eBook) DOI 10.1007/978-3-662-03333-3. Springer-Verlag Berlin Heidelberg 1997. Originally published by Springer-Verlag Berlin Heidelberg New York in 1997.

d) Staahl, C., & Drewes, A. M. (2004). Experimental Human Pain Models: A Review of Standardised Methods for Preclinical Testing of Analgesics. Basic & Clinical Pharmacology & Toxicology, 95(3), 97-111. doi:10.1111/j.1742-7843.2004.950301.x

22. Fernandes de Lima, V. M.; Chatrian, G. E.; Lettich, E.; Canfield, R. C.; Miller, C. R.; Soso, M. J., Electrical stimulation of tooth pulp in humans. I. Relationships among physical stimulus intensities, psychological magnitude estimates and cerebral evoked potentials. PAIN 1982, 14, 207-232. doi: 10.1016/0304-3959(82)90130-0.

22. Mundey, M. K., Ali, A., Mason, R., & Wilson, V. G. (2000). Pharmacological examination of contractile responses of the guinea-pig isolated ileum produced by μ-opioid receptor antagonists in the presence of, and following exposure to, morphine. British Journal of Pharmacology, 131(5), 893-902. doi:10.1038/sj.bjp.0703659

24.Koslov, D. S., & Andersson, K.-E. (2013). Physiological and pharmacological aspects of the vas deferens—an update. Frontiers in Pharmacology, 4, 101. doi:10.3389/fphar.2013.00101

25.Jespersen, B., Tykocki, N. R., Watts, S. W., & Cobbett, P. J. (2015). Measurement of Smooth Muscle Function in the Isolated Tissue Bath-applications to Pharmacology Research. Journal of Visualized Experiments : JoVE(95), 52324. doi:10.3791/52324.

26.a) Marrone, G. F., Majumdar, S., & Pasternak, G. W. (2015). Radioligand Binding Assay for an Exon 11-Associated Mu Opioid Receptor Target. In M. Filizola (Ed.), G Protein-Coupled Receptors in Drug Discovery: Methods and Protocols (pp. 241-249). New York, NY: Springer New York.
DOI: 10.1007/978-1-4939-2914-6_16.

b) Newman, L. C., Wallace, D. R., & Stevens, C. W. (2000). Selective opioid agonist and antagonist competition for [(3)H]-naloxone binding in amphibian spinal cord. Brain research, 884(1--2), 184-191. https://doi.org/10.1016/S0006-8993(00)02967-X.

c) Taylor, D. A. (2011). In Vitro Opioid Receptor Assays Current Protocols in Pharmacology: John Wiley & Sons, Inc. ISBN 9780471141754. DOI: 10.1002/0471141755.ph0408s55.

27.Melchiorri, P., & Negri, L. (1996). The dermorphin peptide family. General Pharmacology: The Vascular System, 27(7), 1099-1107. doi:http://dx.doi.org/10.1016/0306-3623(95)02149-3

28. Filira, F., Biondi, B., Biondi, L., Giannini, E., Gobbo, M., Negri, L., & Rocchi, R. (2003). Opioid peptides: synthesis and biological properties of [(N^{γ}-glucosyl, N^{γ}-methoxy)-α,γ-diamino-(*S*)-butanoyl]^{4}-deltorphin-1-neoglycopeptide and related analogues. Organic & Biomolecular Chemistry, 1(17), 3059-3063. doi:10.1039/B306142F; and the literature cited therin.

29. Raffa, R. B.; Beckett, J. R.; Brahmbhatt, V. N.; Ebinger, T. M.; Fabian, C. A.; Nixon, J. R.; Orlando, S. T.; Rana, C. A.; Tejani, A. H.; Tomazic, R. J., Orally Active Opioid Compounds from a Non-Poppy Source. Journal of Medicinal Chemistry 2013, 56, 4840-4848. DOI: 10.1021/jm400143z

30. a) Cruz, A., Domingos, S., Gallardo, E., & Martinho, A. (2017). A unique natural selective kappa-opioid receptor agonist, salvinorin A, and its roles in human therapeutics. Phytochemistry, 137, 9-14. doi:https://doi.org/10.1016/j.phytochem.2017.02.001.

b) Line, N. J., Burns, A. C., Butler, S. C., Casbohm, J., & Forsyth, C. J. (2016). Total Synthesis of (−)-Salvinorin A. Chemistry – A European Journal, 22(50), 17983-17986. doi:10.1002/chem.201604853.

c) Butelman, E. R.; Kreek, M. J., Salvinorin A, a kappa-opioid receptor agonist hallucinogen: pharmacology and potential template for novel pharmacotherapeutic agents in neuropsychiatric disorders. Frontiers in Pharmacology 2015, 6. 10.3389/fphar.2015.00190.

OPIOID ANALGESICS. CHAPTER 2.

2.1. Morphine alkaloids: introduction

Morphine alkaloids[1] are formally classified as a distinct group of isoquinoline alkaloids, since they all possess isoquinoline structural motif. While various groups of isoquinoline alkaloids are structurally diverse and numerous, there are only four significant, naturally occurring morphine alkaloids.[2,3] These are: morphine,[4,5] ***1***, thebaine,[4,6] ***2***, oripavine[4] ***3*** and codeine,[4,5] ***4***, all found as single enantiomers only, *Fig. 2.1.* (The opposite enantiomers can be obtained exclusively by total synthesis). Structure A represents the usual numeration of morphine molecule and its congeners, whereas B emphasizes the presence of isoquinoline ring system.

The compounds are often denoted as 4,5-epoxymorphinans, indicating the presence of furan ring as the common feature.[7] Morphine alkaloids are most abundant in *Papaver somniferum* (opium poppy), and, to a lesser extent, in many related species, including *Papaver bracteates* (Persian poppy)[8] and *Papaver orientale*.[9] Usually they are accompanied with other isoquinoline alkaloids,[1] such as noscapine,[4,10] ***5***, papaverine[4] ***6*** and berberine,[4,11] ***7***, *Fig 2.1.* These "non-morphine" alkaloids have complex pharmacology and some therapeutic potentials,[1] however they are not opioids and have no significant analgesic effect.

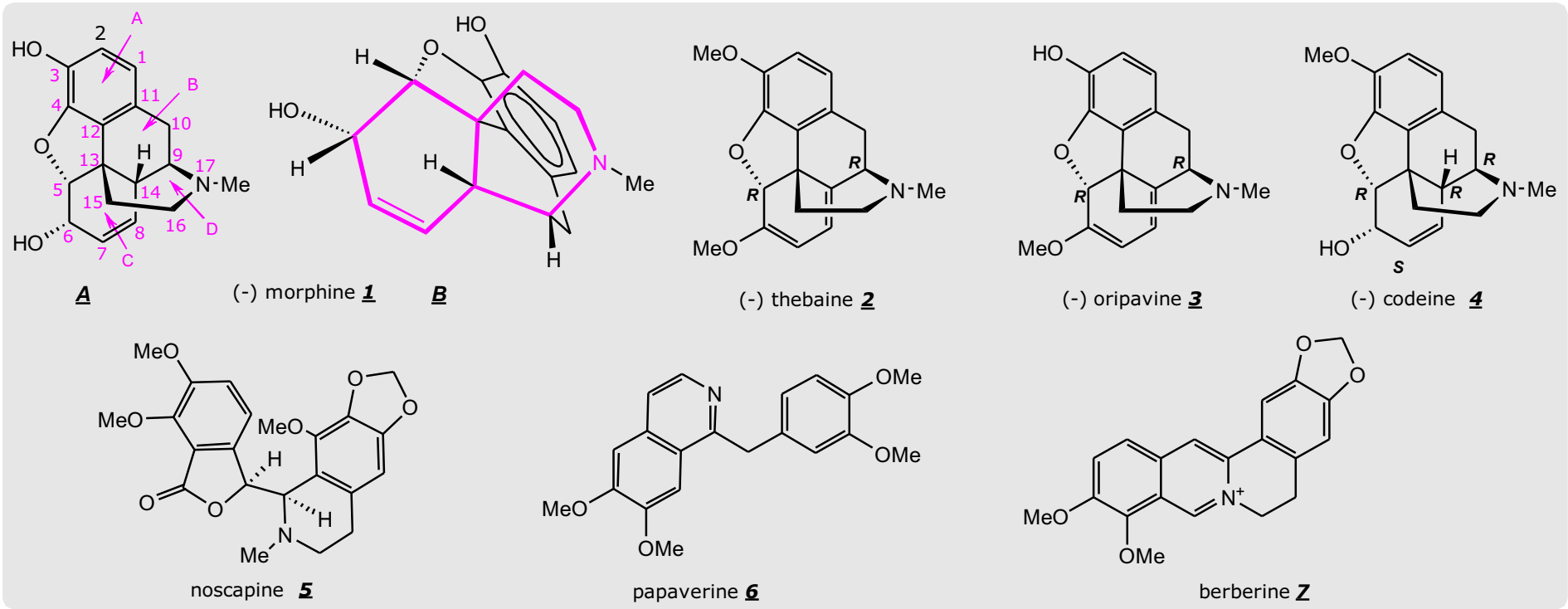


Fig. 2.1 Structures and the absolute configurations of some isoquinoline alkaloids found in various *Papaver* species (*Papaveraceae*)

2.2. Pharmacological properties of morphine alkaloids

Morphine alkaloids are best known because morphine is a highly potent opioid analgesic.[4,12] Since the 19th century, morphine salts (mainly sulphate), have been used extensively to treat moderate to severe pain, both acute and chronic. Because of the poor oral effectiveness, it is predominantly injected intravenously, (IV), under the skin (subcutaneously) or intramuscularly (into muscle). A usual therapeutic dose is 10 mg in adults, although it can vary substantially, depending on the individual's sensitivity and concrete conditions (e.g. intensity of the pain).

Morphine has serious side effects, with the respiratory depression (cessation of the spontaneous breathing) being the most dangerous, often resulting in death. Prolonged use inevitably results in tolerance and physical addiction, which is difficult to treat (see Chapter 1).

Thebaine[4,12] is practically devoid of any useful pharmacological activity, however it is a significant precursor in various semi-synthesis of morphine derivatives.

Oripavine[4] has analgesic potency similar to morphine,[13] but it is severely toxic, often causing death in experimental animals. It is used only as a precursor in several semi-synthesis of morphine derivatives.

Codeine is a very effective antitussive, widely used to supress cough, although there are alternative, non-opioid drugs. It is also a weak analgesic, about 10 times less potent than morphine. While it is relatively safe drug, its prolonged use can result in some tolerance and addiction.

2.3. Sources of morphine alkaloids

Morphine, thebaine, and oripavine have been obtained commercially only from the various strains of opium poppy, *Papaver somniferum*. Codeine is much less abundant than morphine in the ordinary poppy strains, approximately in the ratio 10:1.[4,14,15] Since it is needed in multi-ton quantities as the antitussive drug, it has been in short supply since the late 19th century. However, development of the efficient semi-synthesis from morphine in the past decades, provided sufficient quantities of the drug. [14,15]

The total amounts of the morphine alkaloids produced worldwide in 2014, are presented below.[14,15]

1. Morphine: exclusively from natural sources (>90% from poppy straw, <10% from opium). Total world production: 463.6 t (from poppy straw and opium).

2. Thebaine: exclusively from natural sources (poppy straw, opium). Total world production: 102.6 t.

3. Oripavine: exclusively from natural sources (poppy straw, opium). Total world production: 25.4 t.

4. Codeine: almost exclusively from morphine. Small but growing amounts: from the poppy straw. Total world production: 379.0 t.

2.4. Opium poppy: basic facts

Papaver somniferum is a species of annual herb in the family *Papaveraceae*, *Fig 2.2.* There are a number of strains as well the artificially mutated variants. Detailed information can be found in the cited reference.[16] Various strains of *Papaver somniferum* are extensively cultivated for the edible seeds and, to lesser extent, the oil.[17] According to FAO data,[17] poppy seed production is almost exclusively limited to European countries. Thus, in 2014, the leading producer was Czech Republic (24 665 t), followed by Turkey (16 223 t) and Spain (~11 000 t). No data are available for poppy seed oil, which is much less significant, mainly culinary product. As explained below, after harvesting the seeds, the dry plant residue is usually used to extract morphine alkaloids.

Opium poppy is also legally cultivated in other countries, particularly India and Australia (Tasmania), only to obtain morphine alkaloids, rather than the seeds.[14,15]

The alkaloids are present in the whole plant both during the maturation period and in the dry plant residue, known as the poppy straw. The highest alkaloid concentration is in the seed-free capsules, and much lower in the stems. However, the ripe poppy seeds are completely devoid of the alkaloids and therefore safe for human consumption. *Figures 2.2-2.6* illustrate the appearance of opium poppy.

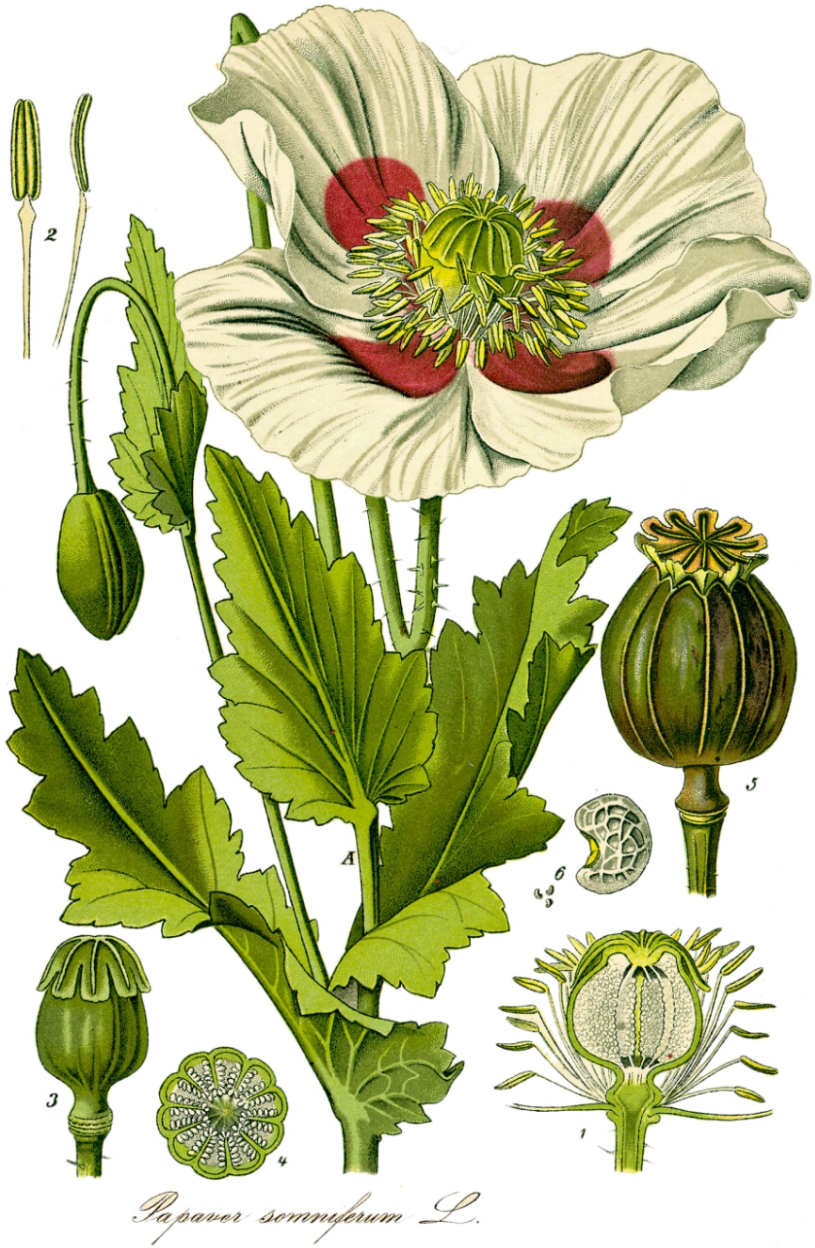


Fig. 2.2. Opium poppy plant, drawing

Fig.2.3. A: Opium poppy with a flower and unripe capsules (pods). B: Sliced unripe capsule; unripe seeds are white.

Fields Of Papaver Somniferum Convar Opiiferum

Fig.2.4. Fields of opium poppy (*Papaver Somniferum*)

Fig.2.5. Opium poppy plant: ripe capsules and seeds

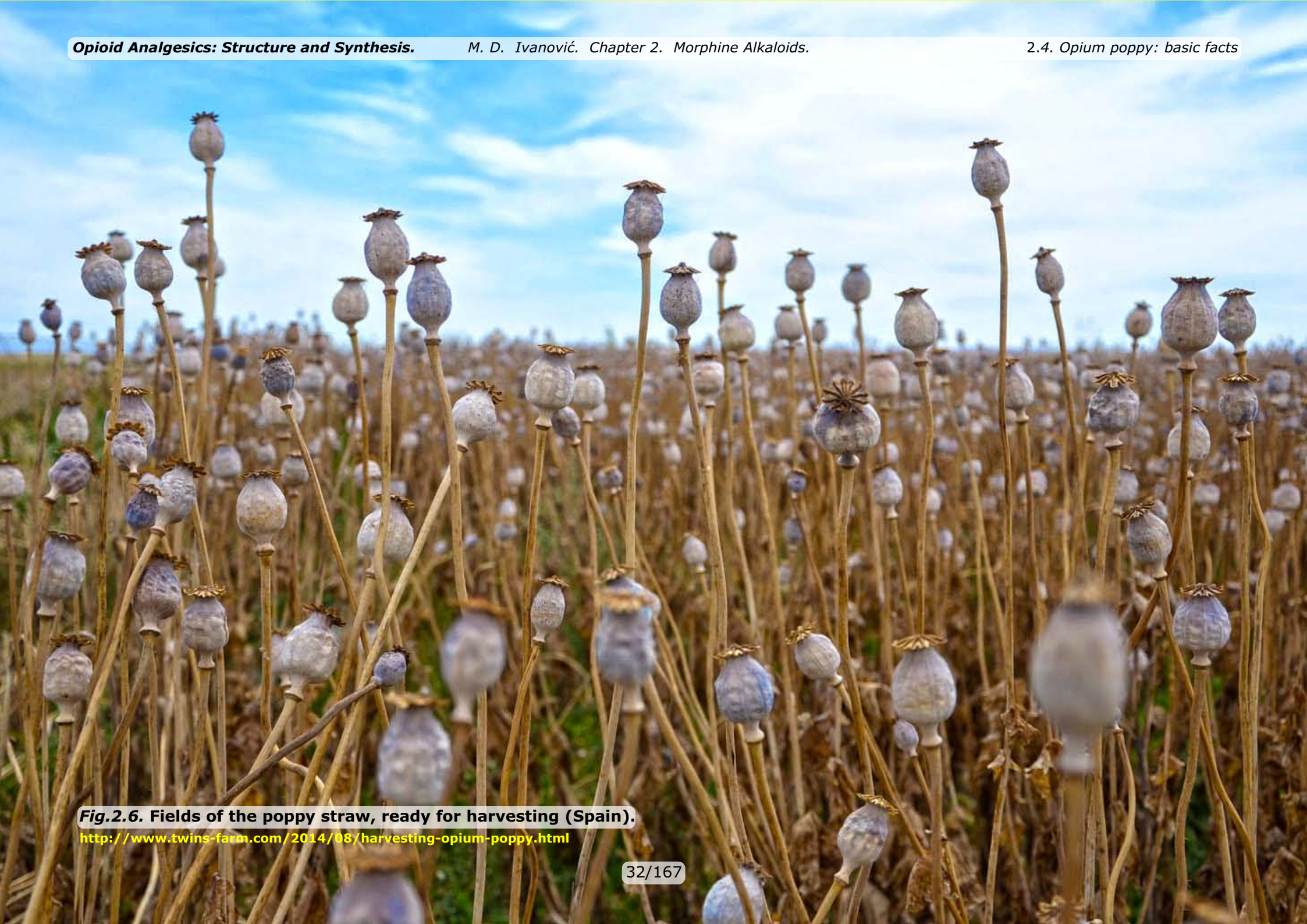


Fig.2.6. **Fields of the poppy straw, ready for harvesting (Spain).**
http://www.twins-farm.com/2014/08/harvesting-opium-poppy.html

2.5. Extraction of morphine alkaloids: opium[1,2,4]

When the unripe capsules of opium poppy (and related species), are accidentally damaged or deliberately incised, they secrete a milky exudation, *Fig. 2.7*. The viscous liquid gradually solidifies into the yellow-brown, resinous solid, known as opium. The substance is rich in various isoquinoline alkaloids (about 20), including morphine and its congeners, as well as papaverine, noscapine and others (see Chapter 1).[1] While the early historic records of opium are scarce, the analgesic properties of opium were known and documented in the antiquity.[2,4,18] However, a significant production, use and abuse of opium started much later and it became more widely available in the European countries since the early 19th century.

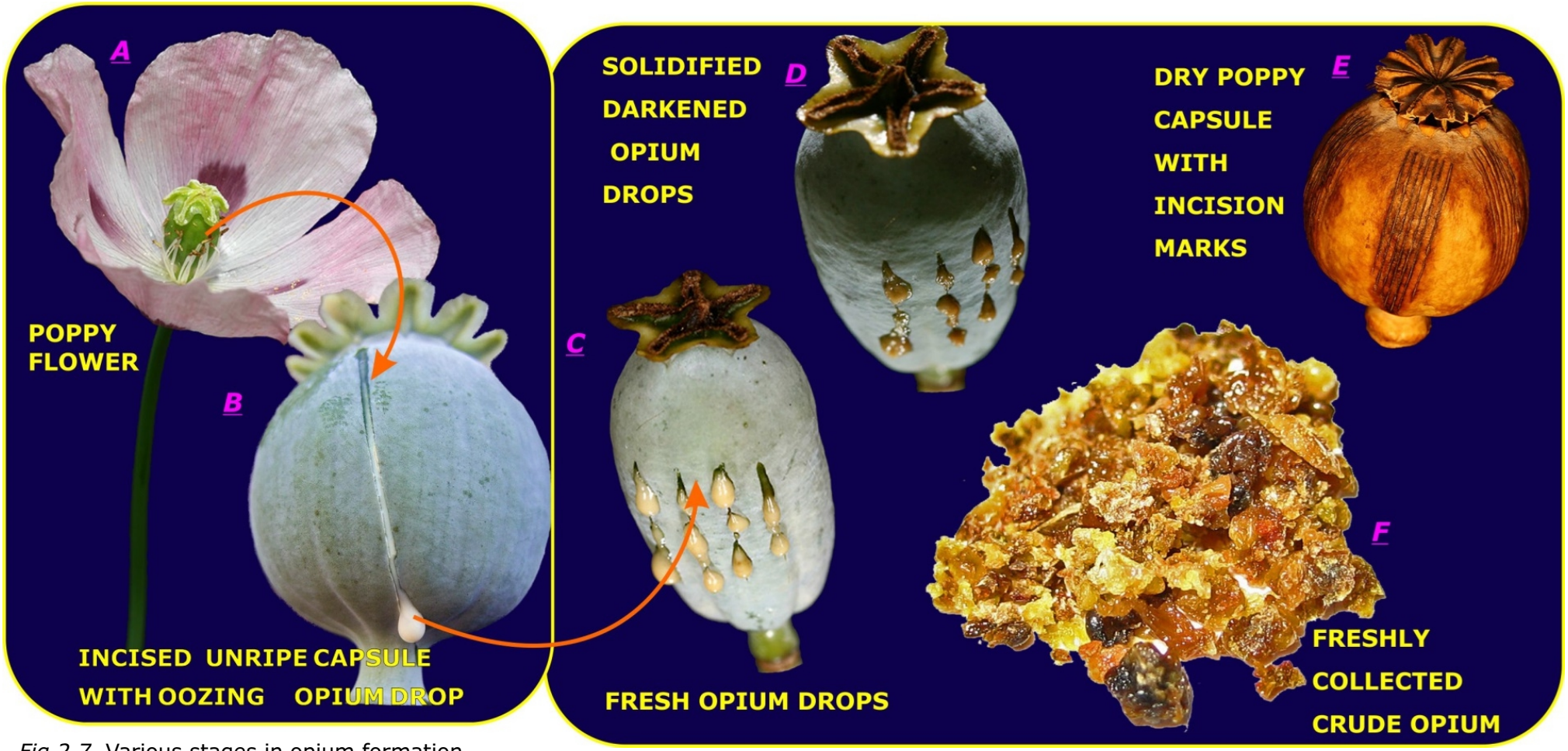


Fig.2.7. Various stages in opium formation

Opium is usually further processes by drying and pressing, resulting in compact cakes or lustrous black resin, Fig. 8 A and B.

Alcoholic extracts of opium, then known as laudanum[4] were widely prescribed as an analgesic, hypnotic and for various ailments, often with no therapeutic justification. The easy availability of the drug led to severe addictions, health issues and deaths. Opium also became the subject of scientific interest, leading to the isolation of morphine by the German pharmacist F. W. Sertürner in 1803/4. (The results were published in several later papers).[19] Incidentally, it was also the first known organic base, hence the name alkaloid ("alkali-like" or similar to inorganic bases). It was isolated exclusively from the opium, using various extraction and precipitation procedures, affording the final product, water-soluble morphine sulphate or hydrochloride.[4]

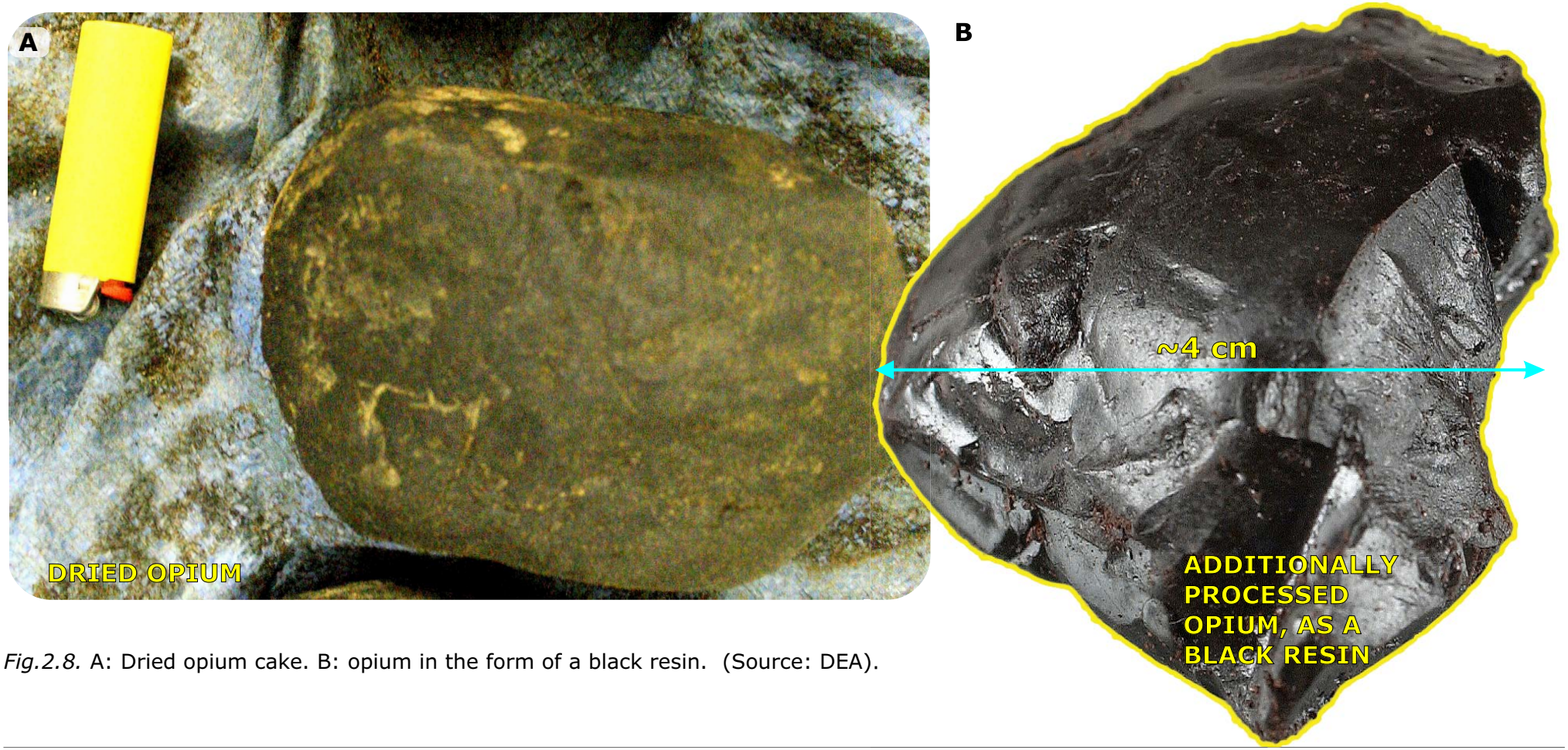


Fig.2.8. A: Dried opium cake. B: opium in the form of a black resin. (Source: DEA).

The increased need for the morphine, since the 19th century, resulted in the manifold increase in opium production. At the time, it was the only source of morphine alkaloids, and also used in medical preparations of opium tinctures (alcoholic solutions of opium). It should be noted that the appropriately purified opium is still prescribed by various Pharmacopoeias, including the European, in the form of several tinctures (alcoholic extracts). Almost exclusively, it is used as antidiarrheal medication.[4]

The whole process of opium production has always been extremely labour-intensive, as it is to this day. It requires manual incision of unripe poppy capsules ("pod scoring"), with primitive, 1-5 blade "knifes", *Fig. 2.9* A and B. Then, on the next day, the semi-solid opium drops are scraped from the surface of the pods with a short-handled, flat, iron blade 10-15 cm wide, *Fig. 2.10* A and B.[20,21] Further processing of the raw opium includes various drying and pressing methods, providing opium cakes or lumps (*Fig. 8*).

Fig.2.9. A: Current licit production of opium in India. B: Manual incision of unripe poppy capsule. Source: DEA

It was only in the early 1930s that opium was gradually replaced by poppy straw as the practical source of morphine alkaloids (see below). Consequently, the licit opium production decreased dramatically, to only 287 t in 2014. India remains the only country in the world still producing the licit opium, mainly for the export.[14,15] This is profitable, in part, due to the very cheap labour force. (The illicit opium is much more expensive).

Regrettably, in the same year, the illicit opium production reached an estimated ~7100 t, with the sole purpose of criminal production of heroin.[20,21] (Global illicit production of heroin was estimated at 526 t in 2014, as opposed to ~0.6 t of the licit production in the same year). Tree main regions in the world are prime sources of the illicit opium (2014.): a) South-West Asia (Afghanistan, Pakistan and India; b) South-East Asia (Myanmar and Laos) and; c) The Americas (especially Colombia, Mexico and Guatemala).[20,21]

Fig.2.10. A. Incision (scoring tools). B. Collecting fresh opium resin from the incised poppy capsules. (Source: DEA)

2.6. Extraction of morphine alkaloids: poppy straw

As explained previously, the production of opium is laborious and expensive. Hence, the alternative approaches to extracting morphine from poppy plant were sought for decades. While it was well known that poppy straw, remaining after harvesting the ripe seeds, contained very significant amounts of the morphine alkaloids, no practical isolation procedure existed, and the straw was burnt as a waste. However, in the late 1920s, Hungarian chemist Janos Kabay solved the problem on an industrial scale.[22] In the following decades, the process has been extensively modified and several substantially different variants emerged (with critical details kept as trade secrets).

Consequently, the contemporary licit production of morphine alkaloids starts almost exclusively from the poppy straw, (well above 90%), instead from the opium.[14,15] Poppy straw is usually collected by mechanical harvesting, *Fig. 2.11*.

Fig.2.11. Mechanical harvesting of the opium poppy straw. It is used both for the seed production and extraction of the alkaloids, Spain.

According to the original Kabay's procedure (patented in 1935), the extraction of morphine from dried poppy straw, relied on the initial acid extraction of the powdered plant material, followed by the several basification and acidification cycles of the aqueous extracts.[22] In addition, the procedure required several tons of water per ton of the straw, vacuum concentrations of the extracts, filtrations and crystallization, *Fig. 2.12.* With the final yield of 0.7-0.8 Kg of the purified morphine per ton of the dried poppy straw, the process did not appear cost-effective. Nonetheless, it was, since Hungary soon stopped importing morphine, relying entirely on the domestic production.[23]

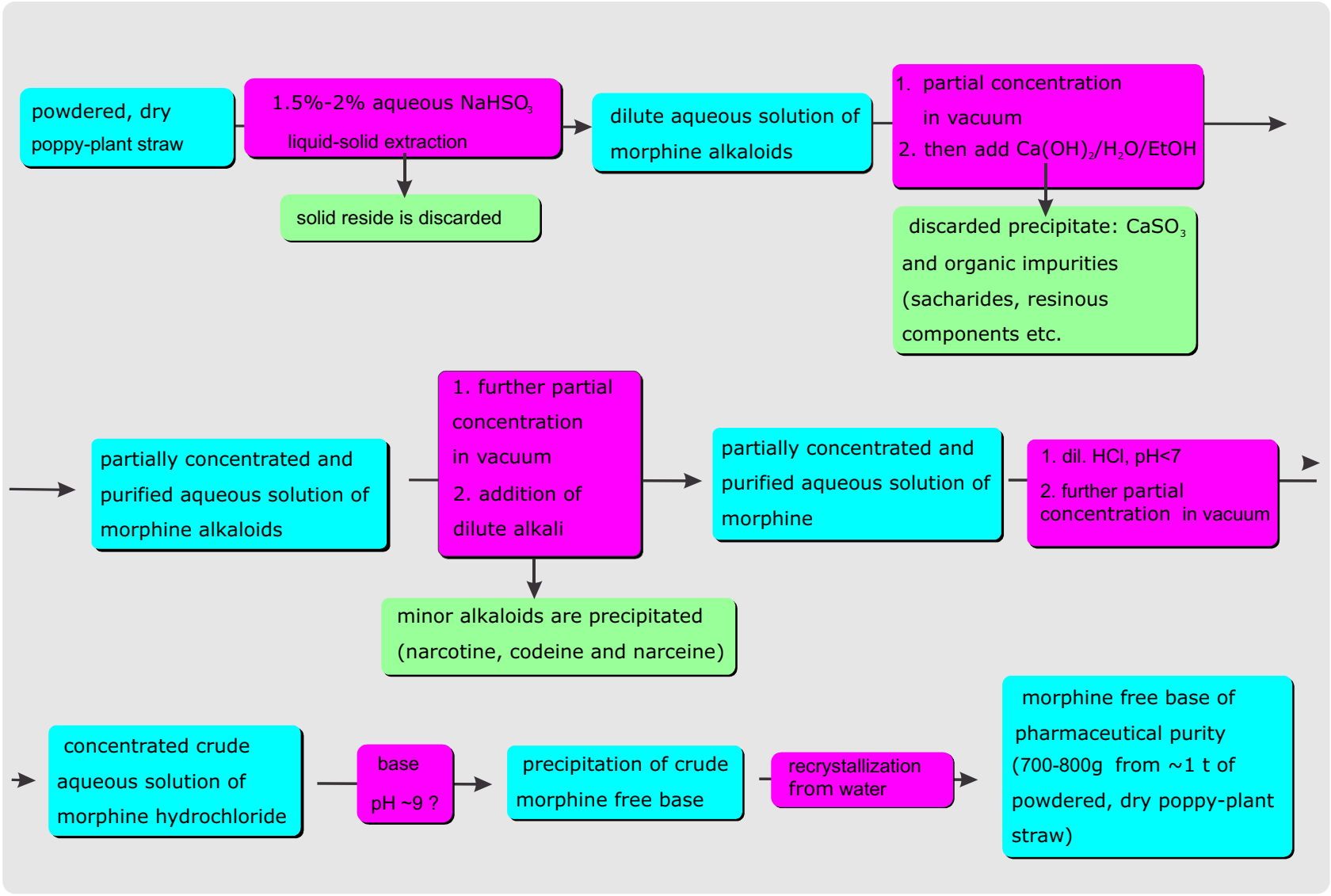


Fig.2.12. Simplified Flow chart diagram of crude morphine isolation from powdered, dry poppy-plant acc.to the patent

Following the initial Kabay's discovery, various procedures for the isolation of morphine alkaloids form the straw have been patented in the past several decades. An early example, shown below, illustrates the use of *i*-butanol, (inexpensive, poorly water-miscible solvent) for the poppy straw extraction,[24] *Fig. 2.13*. An apparent advantage of the method is the limited amount of the organic solvent used, no need for vacuum concentration and the simple liquid-liquid extraction. Thus, free alkaloids, dissolved in *i*-butanol, were extracted into water as salts, using dil. sulphuric acid. Upon basification, the solid, crude alkaloid mixtures precipitated as "Concentrate of Poppy Straw", CPS.[14,15]

Additional steps, including passing the liquid extracts through cationic and anionic ion-exchange beds, facilitate the separation of non-alkaloid impurities and some alkaloids. Final purification of the separated morphine alkaloids to the pharmaceutical grade (usually >98% purity), required further steps, involving crystallizations, extractions etc

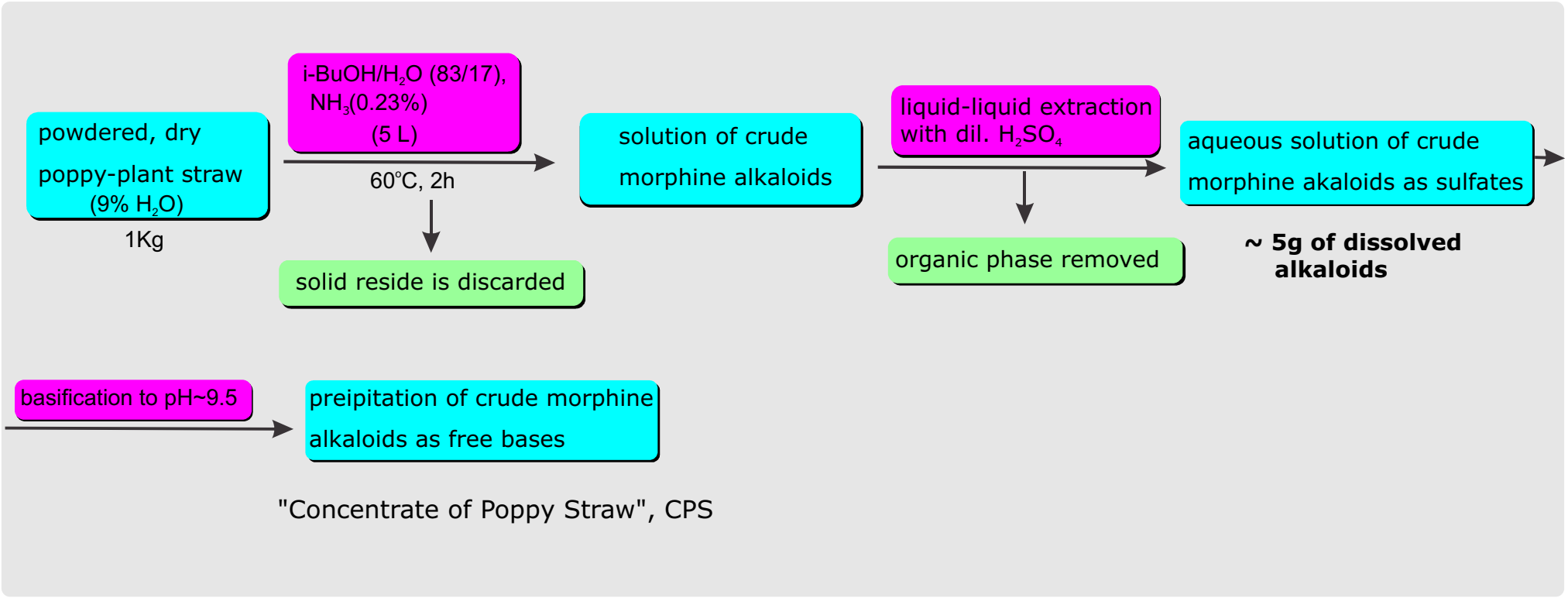


Fig. 2.13. Simplified Flow chart diagram: isolation of the crude morphine from powdered dry poppy-plant.

Numerous refinements and modifications, introduced over the next several decades, fully justified the basic concept.

All modern processes for the preparation of pure morphine alkaloids from poppy straw, involve the stage where concentrated mixtures of the alkaloids are obtained. The mixtures, usually in the powdered form, are denoted as "concentrate of poppy straw" or CPS. Although it is commercially advantageous to refine CPS to the pure alkaloids, it is often not the case either because of the manufacturer's lack the expertise or other reasons. Hence, various grades of CPSs are traded as such, as documented in INCB reports.[14,15]

According to INCB reports, before the late 1990s, the only cultivated strains of opium poppy were those rich in morphine, containing only small amounts of thebaine, codeine and oripavine. Consequently, the single type of "concentrate of poppy straw" existed, i.e. the variant rich in morphine ("CPS–morphine").

Since then, several novel strains of opium poppy, rich in thebaine and later in codeine were introduced. Their current cultivation provides four grades of commercial CPS, classified according to the main morphine alkaloid present in the product. These are: a) CPS-morphine; b) CPS-thebaine; c) CPS-codeine and d) CPS-oripavine. (The last one results from the modified processing and not from the specific opium poppy strain). In the past several years, the amounts of poppy straw concentrates are usually expressed as the quantity of the principal alkaloid they contain. For example, in 2014, Australia produced morphine poppy straw concentrate containing 163.5 t of anhydrous (i.e. pure) morphine. (The actual weight of the concentrate was considerably higher, since it also contained other alkaloids, water and various impurities). Consequently, the term "poppy straw concentrate" is being replaced by the more accurate terms: AMA (anhydrous morphine alkaloid), ATA (anhydrous thebaine alkaloid), AOA (anhydrous oripavine alkaloid) and ACA (anhydrous codeine alkaloid).

Production of thebaine has increased substantially in the past two decades.[14,15] There is a high demand for that alkaloid, since it is the key precursor in several industrial semi-synthesis of various opioid drugs. Until the late 1990s (and, to a lesser extent, as of 2016), it has been in short supply and expensive, since it is only a minor opium alkaloid in the standard opium poppy strains. Although thebaine is the principal alkaloid in the perennial poppy *Papaver bracteatum*, the large-scale production from that plant proved impractical. Therefore, several new opium poppy strains, rich in thebaine, were obtained through the artificial mutations. One of the several such strains, e.g. the "Norman" poppy, produces 1.68% thebaine, 0.74% oripavine, 0.05% codeine and no morphine, by weight of the dry straw.[25] Newer mutated strains, introduced in 2009-10, have even higher thebaine contents and less other alkaloids.[26] Currently, they are the main source of thebaine, while the rest is isolated from the standard opium poppy strains.

As already mentioned, the bulk of codeine is still being produced from morphine. However, in the past several years, new opium poppy strains, rich in codeine, have gradually being cultivated. (Like the thebaine-producing strains, these too were obtained through the artificial mutations).[27] Thus, the total world production of the concentrate (expressed as anhydrous codeine alkaloid) was ~58 t in 2014, although the quantity of pure codeine obtained from the concentrate was not reported.

It should be noted that the alkaloid contents in the concentrates are relatively simple to determine accurately, using standardized HPLC procedures.[27] Nevertheless, there are always very significant losses in the purification of the concentrates, resulting in the much lower amounts of the isolated pure product. (As already mentioned, details of the purification processes are kept confidential). Laboratory-scale extraction of codeine is represented in *Fig. 2.14*.

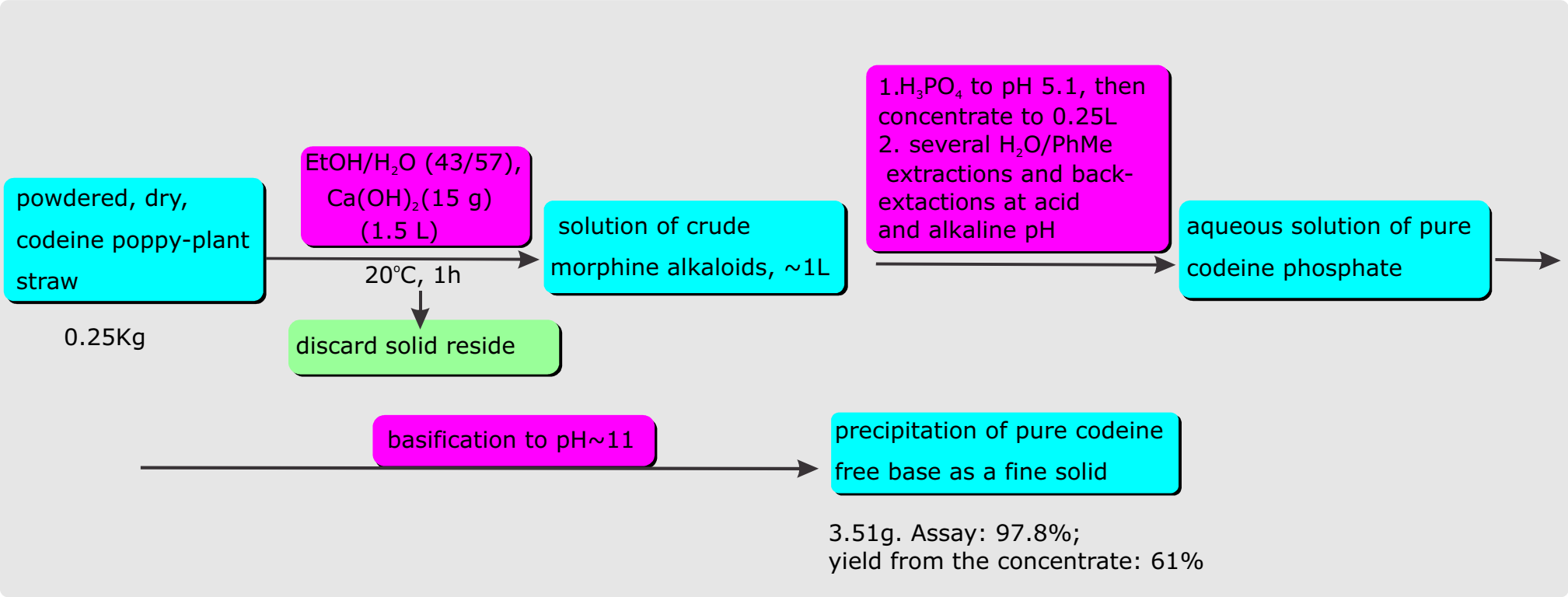


Fig. 2.14. Simplified flow chart diagram: isolation of crude codeine from powdered, dry poppy-plant.[27]

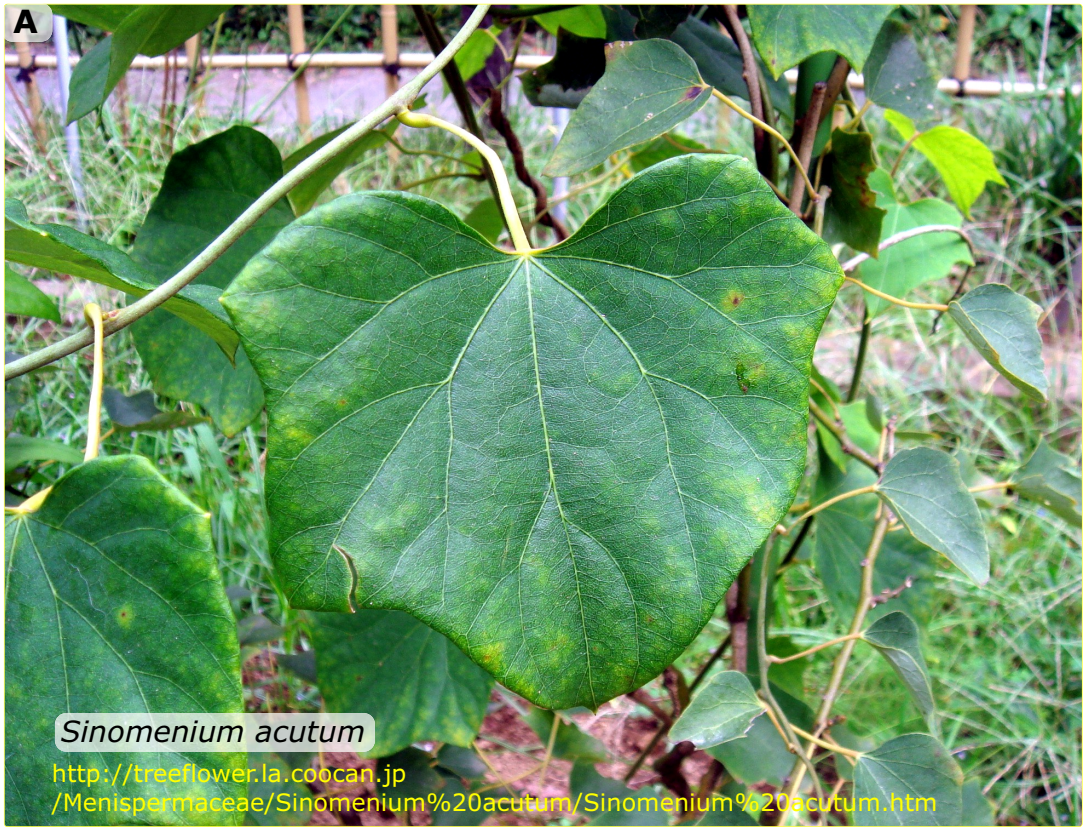
2.7. 3D structure of (-) morphine and the related "opposite"alkaloids

It is well-known that most natural products occur as single enantiomers only, and morphine alkaloids are no exception in that respect. Interestingly, several plant species native to Far East, such as *Sinomenium acutum*, (*Fig. 2.15 A*), produce a group of closely related alkaloids, having almost the same scaffold as morphine, but with the opposite absolute configuration.

The representative examples include sinomenine ***8***,[4] hasubanonine ***9***,[4] and oreobeiline ***10***,[4] *Fig. 2.15*.

In the case of (-) morphine, configuration at the relevant stereocenters is: ***9R***, ***13S*** and ***14R*** while sinomenine and oreobeline have the configuration ***9S***, ***13R*** and ***14S***.

The compounds are not opioids, having only moderate anti-rheumatic activity with various side effects.[28] Molecules of (-) morphine and sinomenine, represented as 3D and 2D "mirror images", are shown in *Fig 2.16*. Three key stereocenters are coloured violet.



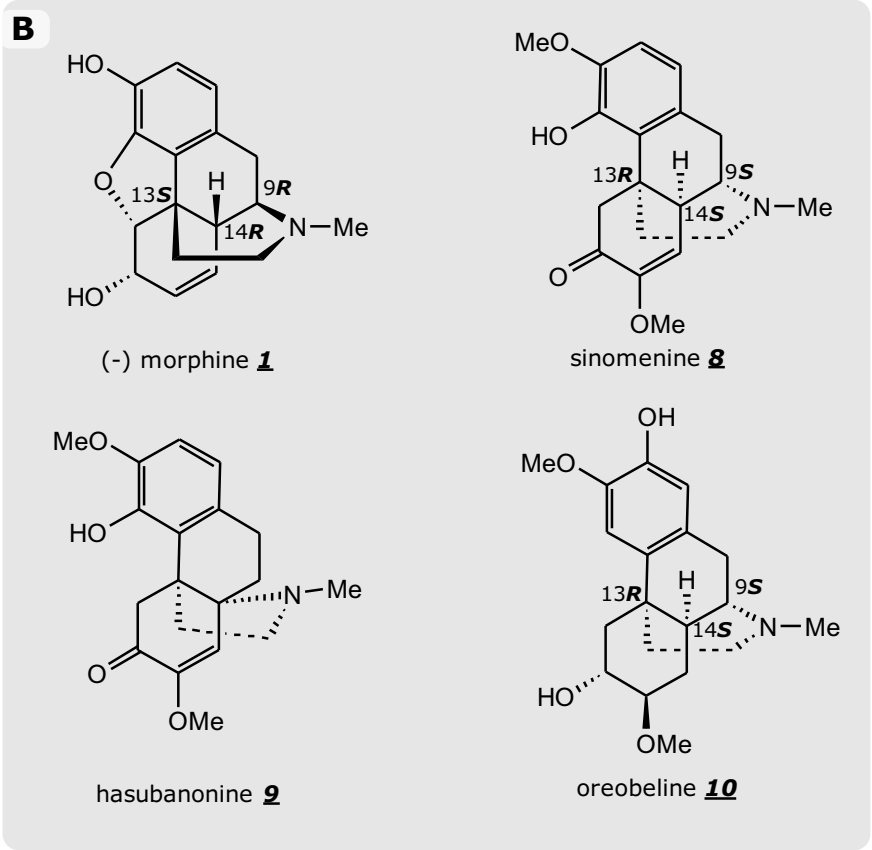
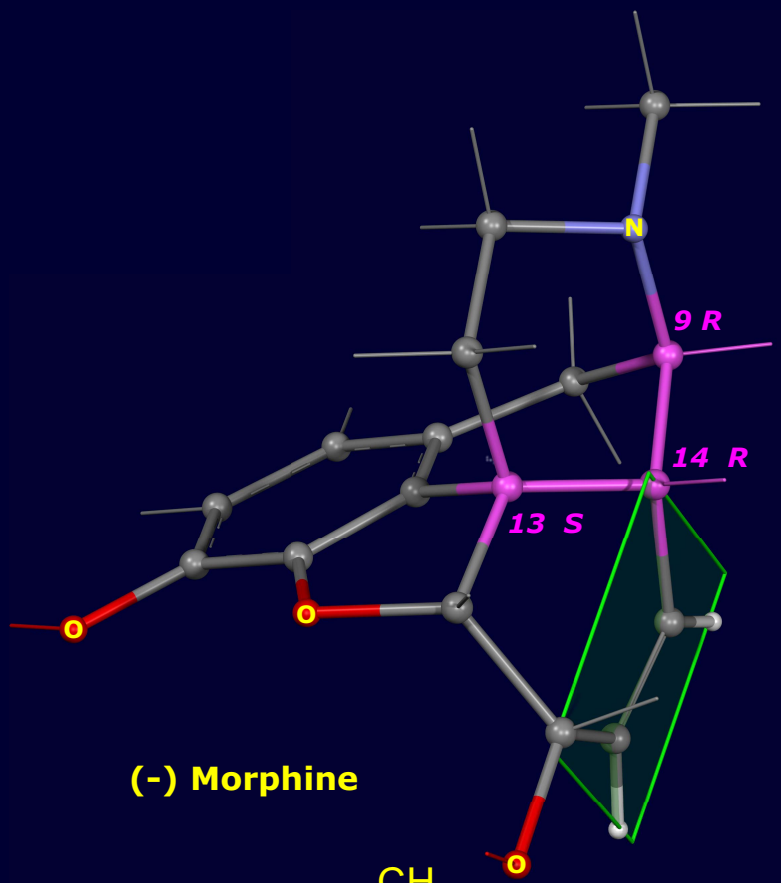
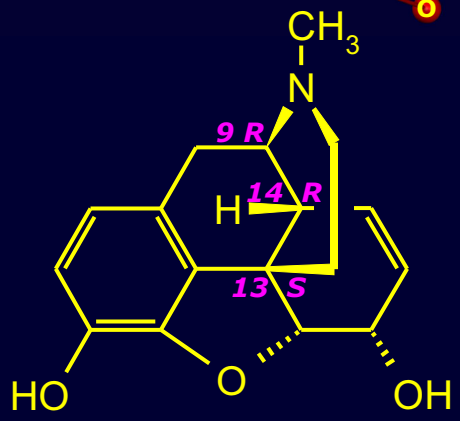


Fig.2.15. A. *Sinomenium acutum*. B. Structures of the natural, (-) morphine, compared to the alkaloids sinomenine,[4] hasubanonine,[4] and oreobeiline



(-) Morphine



Sinomenine

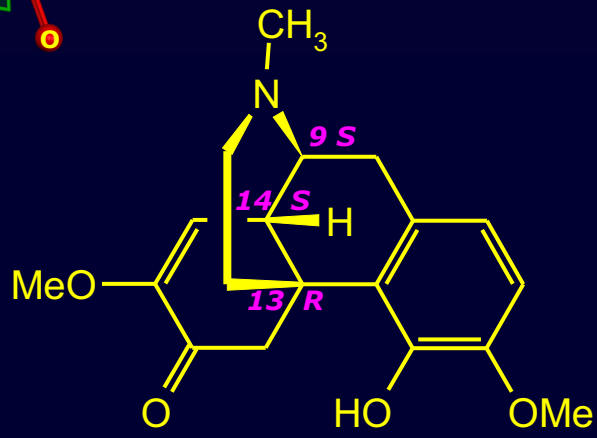


Fig.2.16. Structure of (-) morphine and sinomenine arranged as mirror images.

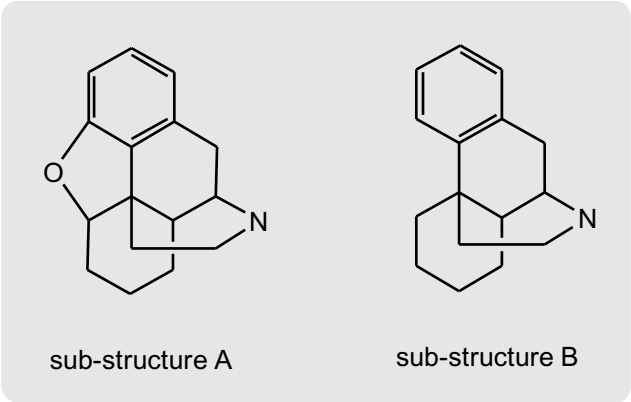
2.8. Use of Morphine Alkaloids

As explained previously, morphine alkaloids are obtained exclusively from the various strains of opium poppy, either from opium or, more recently, from the straw.

The anticipated commercial total syntheses of morphine alkaloids have never materialized, and are not expected to be achieved in a foreseeable future.[29] (On the other hand, over 30 academic total synthesis of morphine alkaloids have been disclosed, as of 2016, as discussed later).

The exceptional importance of morphine as analgesic and codeine as antitussive is well-known[12] In addition, all four natural morphine alkaloids are key precursors in the semi-synthesis of numerous derivatives, having therapeutic and/or academic significance.

It should be emphasized that numerous semi-syntheses of the morphine derivatives, published since the late 19th century, produced a very large number of compounds, possessing the complete morphine scaffold. Thus, sub-structure search of the SciFinder, using the shown sub-structure A (the basic morphine scaffold), returned the total of 12816 compounds, including 745 of those containing isotopes.[30] (Salts and mixtures were not included). Almost all of those compounds were prepared by semi-syntheses from morphine alkaloids, except a relatively small number, obtained via total syntheses. The additional search, excluding the furan ring, (sub-structure B), gave 4706 structures,[30] also predominantly prepared by the semi-synthesis. (Many of the compounds, generally known as morphinanes,[7] are important opioids, particularly as pharmacological research tools).



sub-structure A sub-structure B

The vast number of the derivatives and the invested research efforts testify to the practical and scientific significance of morphine alkaloids. However, of all these compounds, probably less than 100, have ever found any practical use, including several dozens of the approved drugs (opioids, opioid antagonists and others).[12] Consequently, only the most important morphine derivatives are considered herein.

Schemes 2.1-2.3 summarize the use of oripavine, morphine, and thebaine as the key precursors in semi-synthesis of major, commercial drugs. Codeine has only a limited use as a precursor in semi-synthesis of other derivatives. It is mainly used to prepare antitussive drug formulations, as shown in *Scheme 2.4*.

2.9. Opiates, drug development, and patents

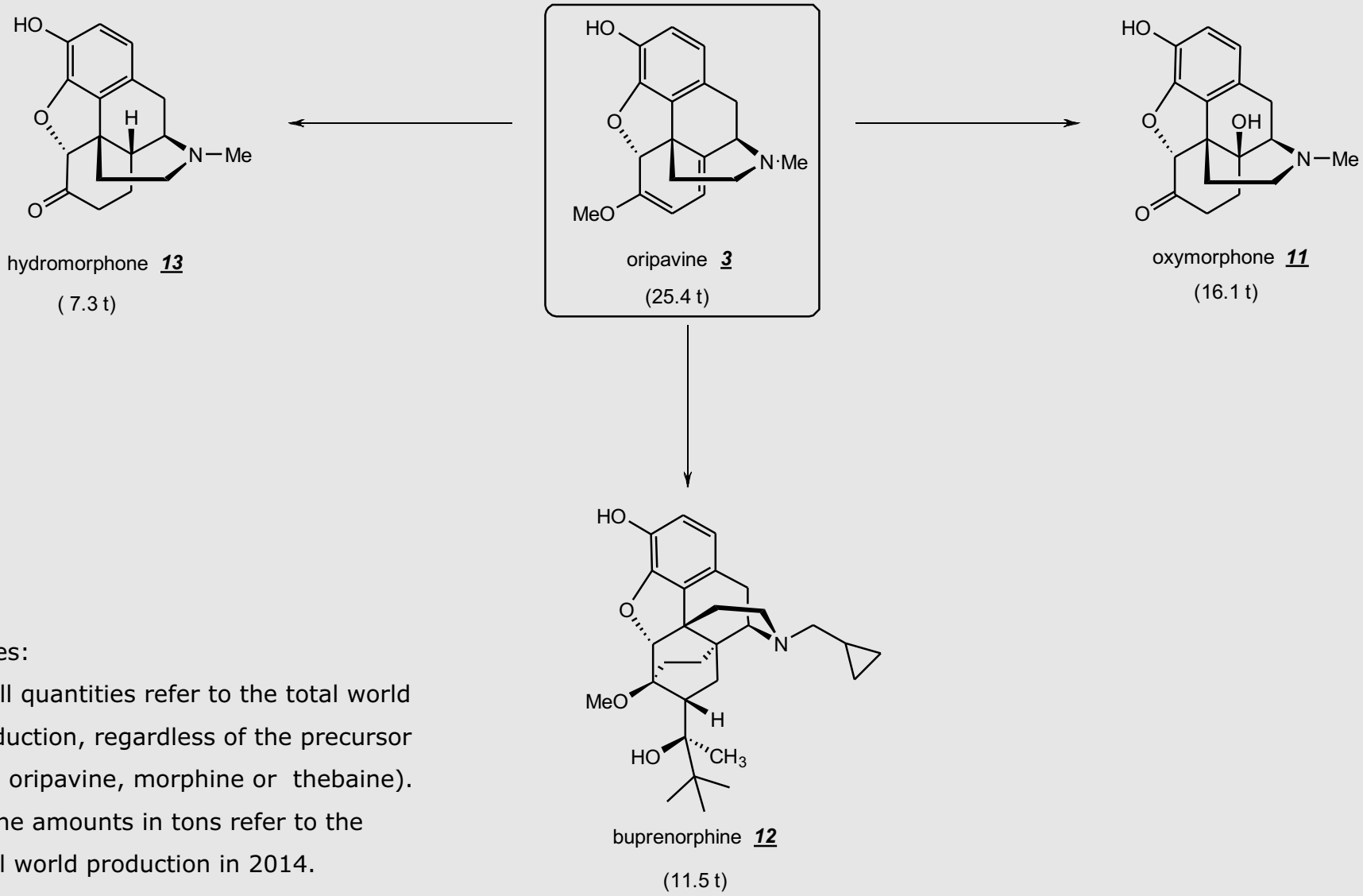
The results presented in Schemes 1-4, are official and accurate, as far as they go.[14,15] However, the actual industrial procedures for isolation of morphine alkaloids and the semi-synthesis of morphine derivatives, may only be guessed from the relevant patents and some papers. It is well-known that information in the patents[31] is generally significantly less reliable than in the papers. In addition, the detailed protocols are closely guarded trade secrets, since the patents provide only limited legal protection, even during the patent term (15-20 years). After the patent expires, any legal protection ceases to exist, leaving the firm with its confidential "know-how" procedures, as the only barrier against the competition. (Even this is often ineffective, as competitor firms can develop their own production methods. Also, the "know-how" procedures are often obtained through economic espionage).[32] It is generally known that the development a new drug, including all clinical trials and the regulatory approvals, is far more expensive then the production itself.[33,34] According to a study published in 2016, average overall cost of getting a new drug on the market, presently stands at nearly three billion dollars![35] If a drug is commercially successful, the profits exceed the development cost manyfold, before the patent expires. The expiration of profitable patents results in the sharp drop in the profits, as cheaper generic forms of the drug, produced by the competitors, appear on the market. This is referred to as a "patent cliff" and is quite relevant to all drugs, including opioids.[36]

Thus, while the chemistry of morphine alkaloids and opiates in general, is continuously being developed and patented, the commercially significant aspects usually remain confidential. On the other hand, papers typically report small-scale procedures, many of which are too expensive or unsuitable for the scale-up, including, for example, all total syntheses of morphine alkaloids published up to present. (In that particular case, the absence of commercial total syntheses reflects the current limitations of the synthetic organic chemistry).[29]

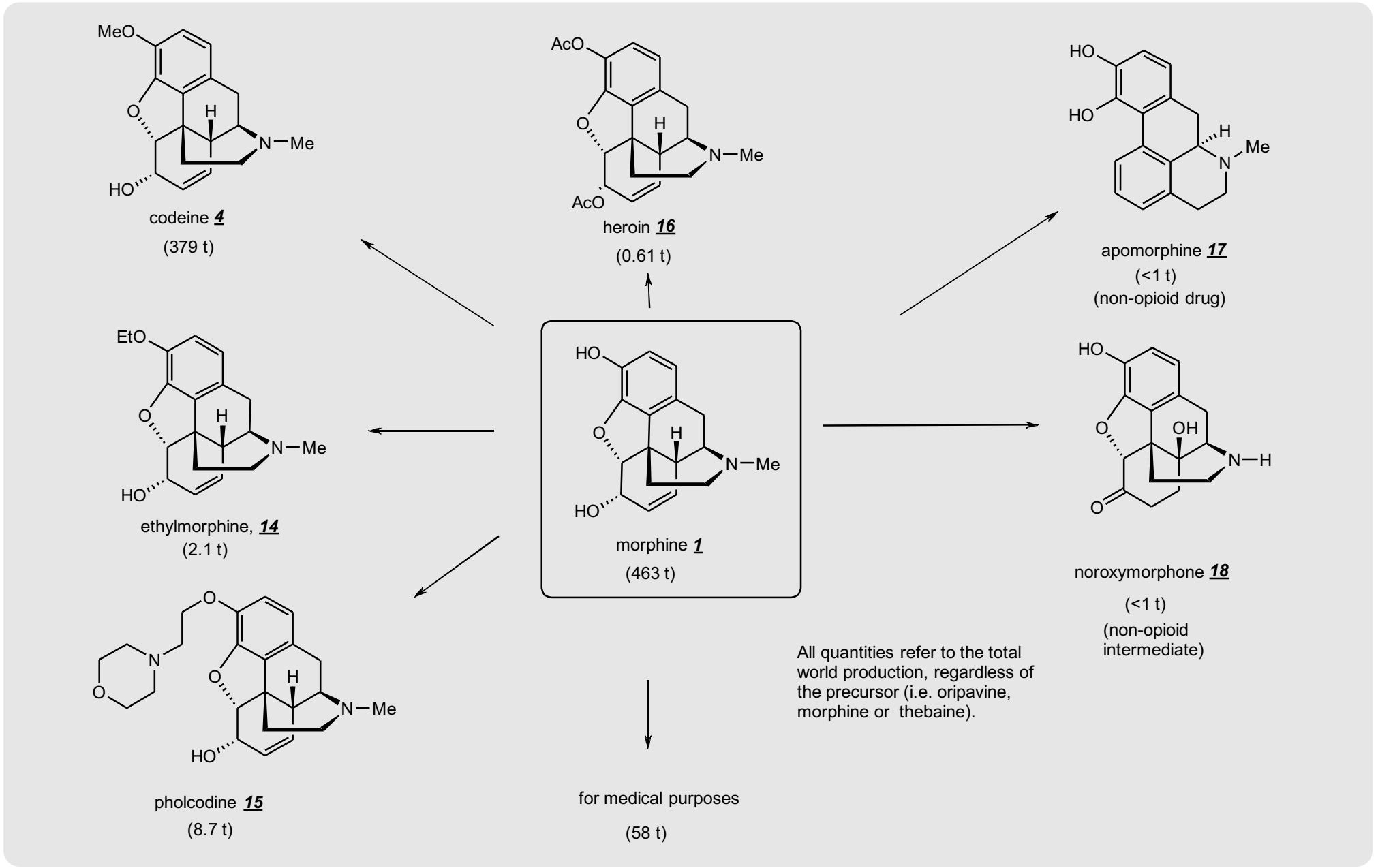
2.10. Morphine alkaloids as precursors in commercial semi-synthesis of opioid agonists

Oripavine ***3***, (total annual production ~25 t), is used as a key precursor in the semi-syntheses of several clinically significant opioids. Particularly important are oxymorphone ***11***, buprenorphine ***12*** and hydromorphone ***13*** [4,12] (The same drugs are also prepared from other precursors). As explained previously, oripavine is very toxic and cannot be used as a drug.[13] Morphine ***1*** (total annual production ~463 t) is mainly used as precursor in semi-syntheses of opioids[12] codeine ***4***, ethylmorphine ***14***, pholcodine ***15*** and heroin ***16*** as well as non-opioid drugs, apomorphine ***17*** and noroxymophone ***18***, *Scheme 2.2* [4].

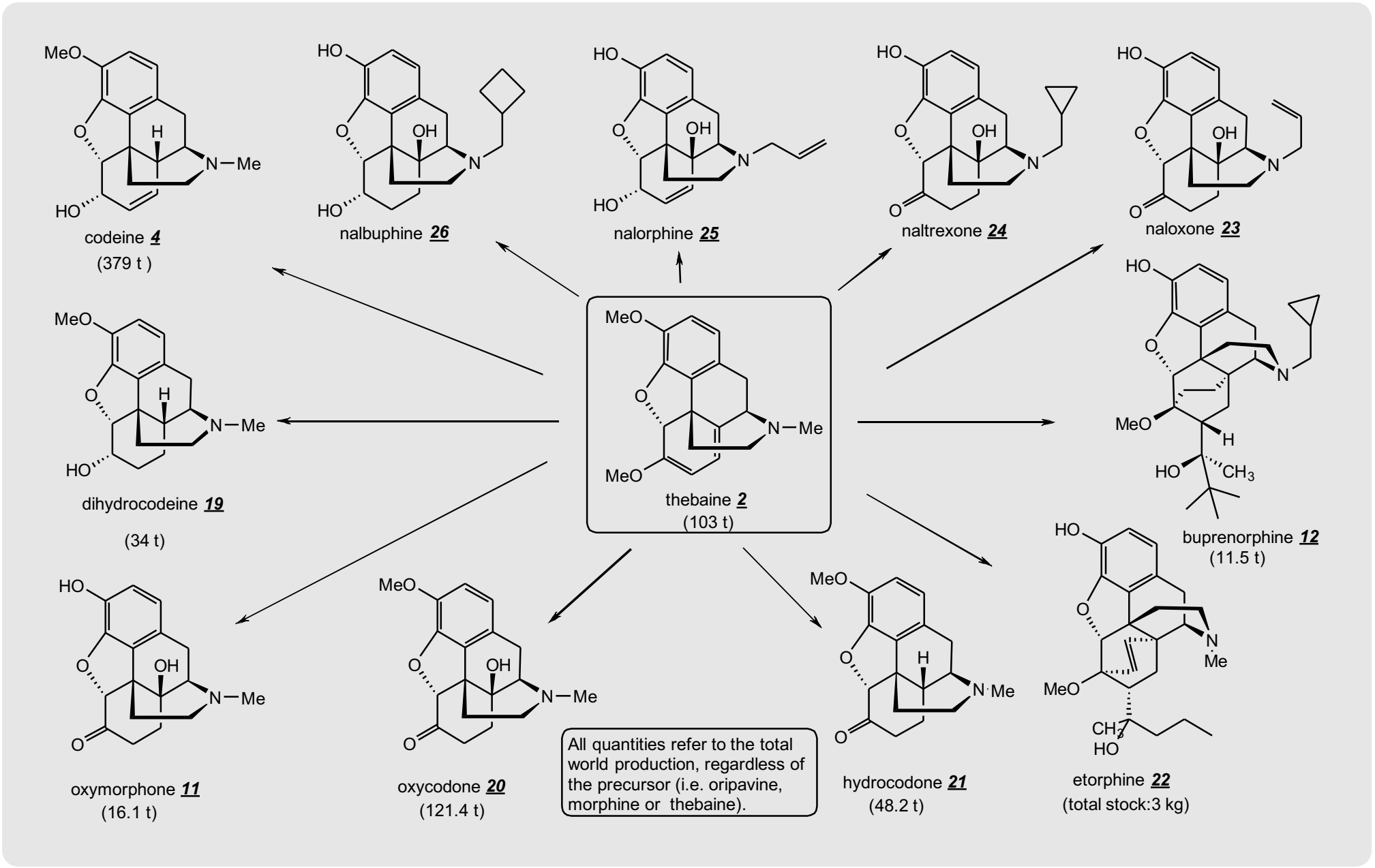
Only 58 t of morphine is used directly for medical purposes, mainly as morphine sulphate.



Scheme 2.1. Use of oripavine in large-scale preparation of opioid drugs[14,15]



Scheme 2.2. The use of morphine in large-scale preparation of opioid drugs and for medical purposes[14,15]

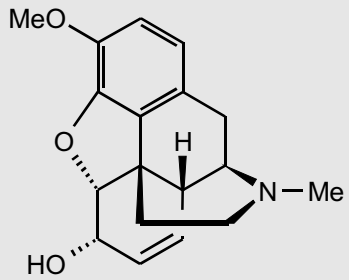


Scheme 2.3. The Use Of Thebaine in Large-scale Preparation of Opioid Drugs[14,15]

Thebaine ***2*** (total annual production ~103 t) is used exclusively as a key precursor in the semi-syntheses of several clinically significant opioids, *Scheme 2.3*. Those include opioids: codeine ***4***, dihydrocodeine ***19***, oxymorphone ***11***, oxycodone ***20***, hydrocodone ***21***, etorphine ***22***, buprenorphine ***12*** and opioid antagonists naloxone ***23***, naltrexone ***24***, nalorphine ***25*** and nalbuphine ***26***.

Codeine ***4***, (total annual consumption ~287 t) is used almost exclusively (98%) in various preparations of antitussive and analgesic drugs,[14,15,37] *Scheme 2.4*. Since the free base is water insoluble (as all other morphine alkaloids), it is first converted into salts (phosphate, hydrochloride) which are APIs, followed by the preparation of various antitussive and analgesic medication. Only 2% (<6 t) of codeine is chemically transformed into other opioids annually.

A



Codeine Base

ACID

Codeine Phosphate

(Codeine)xH_3PO_4 x 1/2 H_2O

Codeine Hydrochloride

(Codeine) x HCl x $2H_2O$

Active Pharmaceutical Ingredients (APIs)

Total cocsumption (2014): 286.5 t
Use: ~98% in preparation of antitussive and analgesic drugs; ~2% in semi-synthesis of morphine derivatives

VARIOUS FORMULATIONS OF ANALGESIC AND ANTITUSSIVES, OFTEN COMBINED WITH OTHER DRUGS

(some as over-the-counter medications)

B

http://www.narconon.org/drug-abuse/codeine-effects.html

Scheme 2.4. A. A general procedure for converting codeine base into commercial antitussives and analgesics. B. Codeine Linctus acc. to British Pharmacopoeia (BP).

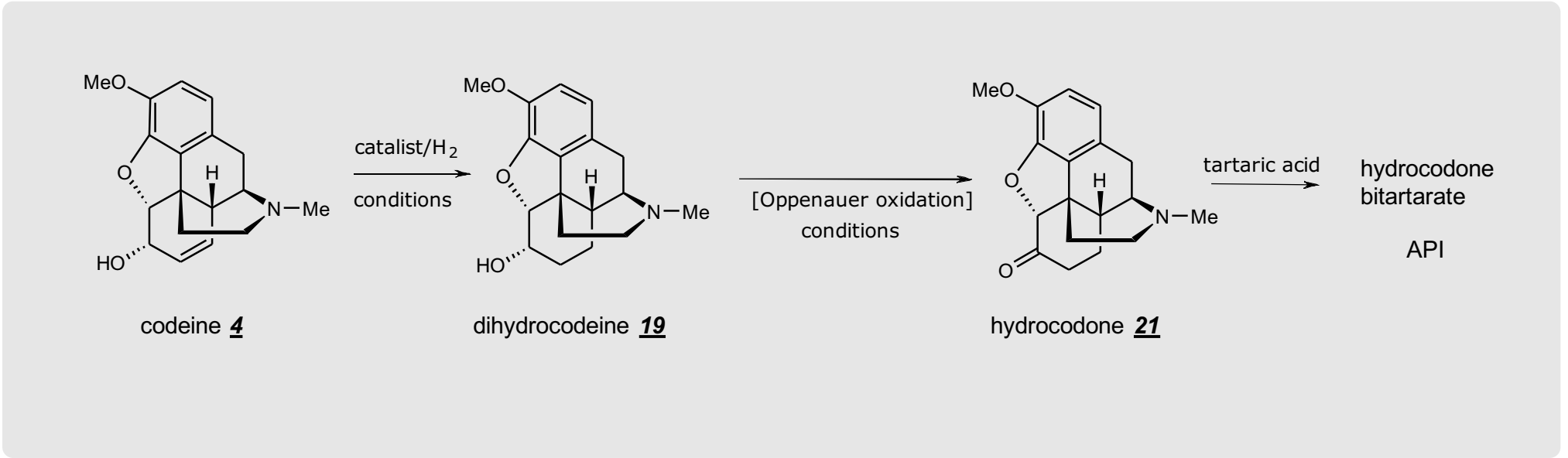
Although codeine is generally insignificant industrial precursor, it has been used in semi-synthesis of dihydrocodeine ***19*** and hydrocodone ***21***, *Scheme 2.5.*[27]

First, catalytic hydrogenation of codeine produces dihydrocodeine, which is then converted to hydrocodone by Oppenauer oxidation. No specific reaction conditions or the yields were given.

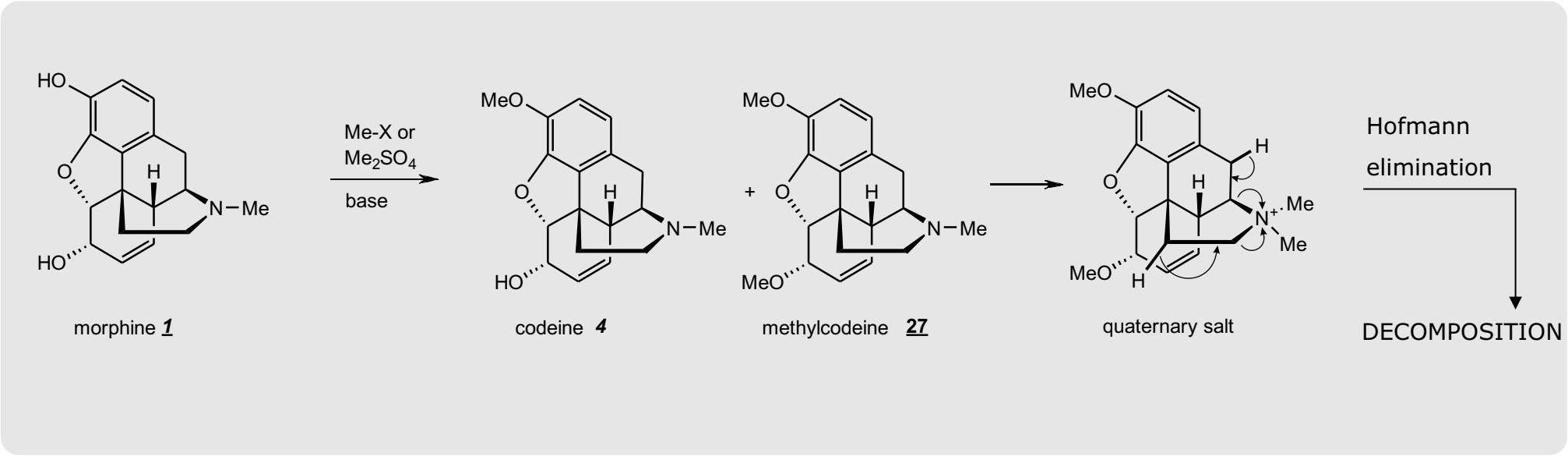
Both compounds, water insoluble free bases, form stable bitartrate salts, i.e. dihydrocodeine bitartrate and hydrocodone bitartrate, which are APIs, found in various commercial analgesic drugs.

Hydrocodone is particularly important, orally active analgesic, used to treat moderate to severe pain.[12] It is predominantly synthesized from thebaine.[14,15]

The main source of codeine is the industrial semi-synthesis, since only small amount are obtained by the extraction from natural sources (poppy straw).[38,39] While the chemical transformation appears trivial, involving methylation of phenol group, it requires special conditions and reagents to provide optimal yields and purity. Early attempts to use conventional methylating agents, such as methyl halides or dimethyl sulphate, invariably resulted in the formation of "methylcodeine" ***27*** as well as the *N*-quaternary salts, further producing Hofmann elimination products, *Scheme 2.6*.



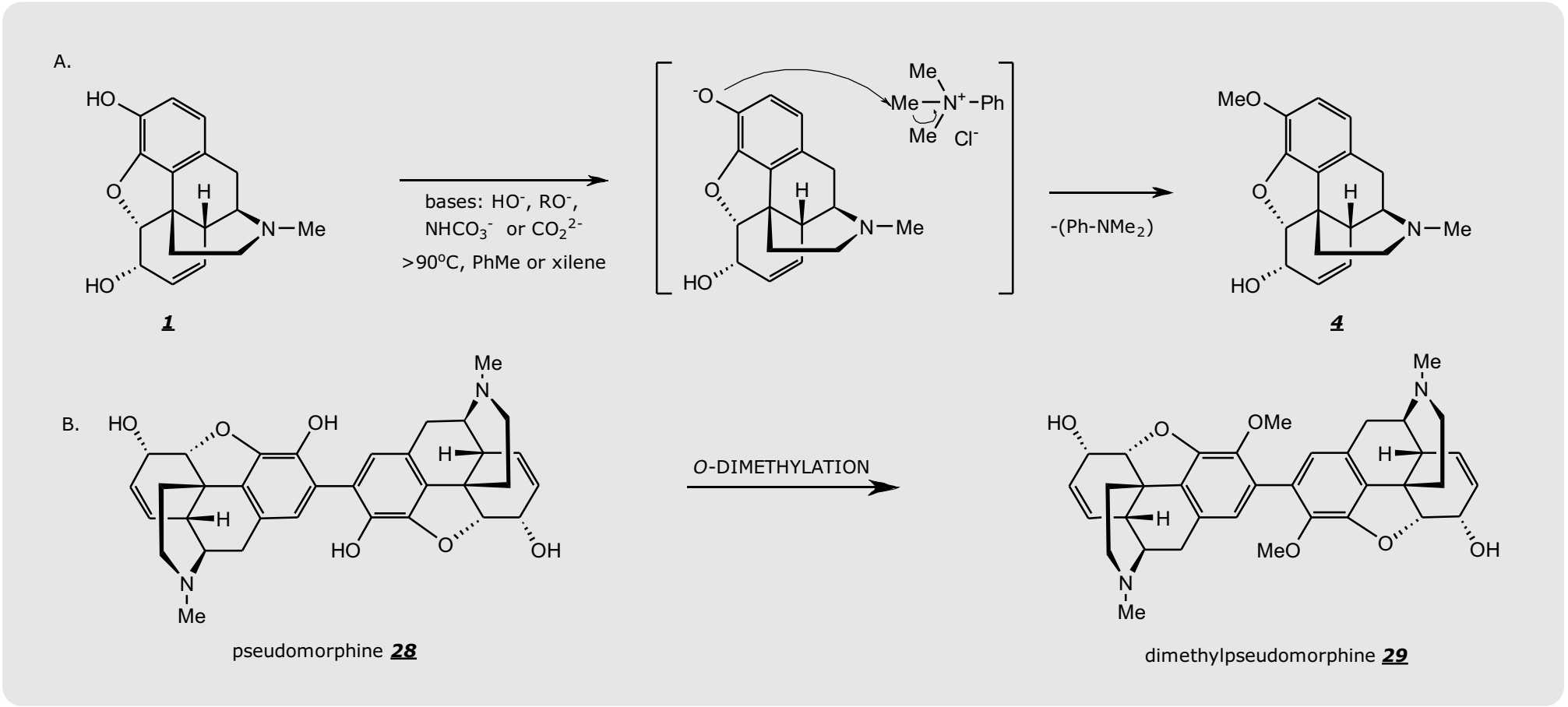
Scheme 2.5. Semi-synthesis of Hydrocodone from Codeine[27]



Scheme 2.6. Early Attempts of Codeine Semi-synthesis[38,39]

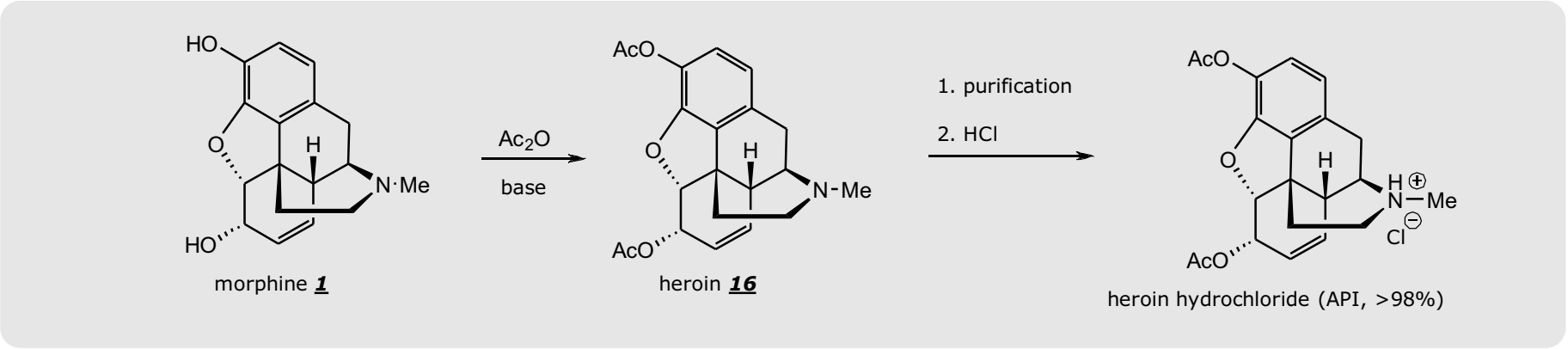
The only practical methylating reagents are quaternary ammonium salts, typically trimethyl-phenylammonium chloride, in the presence of various bases such as alkali hydroxides, alkoxides, carbonates or bicarbonates.[40] Use of the quaternary ammonium methylating agents is mandatory, as it greatly diminishes the side reactions, Scheme 2.7A. The reaction proceeds efficiently because phenoxide anion is easily formed, it is much stronger nucleophile then the tertiary amine or free hydroxyl group and particularly because ~~the~~ quaternary ammonium salts are weak and selective electrophiles. Numerous patents were dedicated to the improvements of codeine manufacturing, however always using the quaternary ammonium salts as the methylating agent.[41,42] The serious shortcoming of the process is the formation of toxic and difficult-to-remove *N,N*-dimethylaniline. Nonetheless, there are no literature references to the alternative quaternary ammonium salts, e.g. $Me_4N^+X^-$ or others.

A natural impurity, pseudomorphine ***28*** often present in the crude morphine, presents a particular problem in codeine synthesis, since it is also methylated to dimethyl-pseudomorphine ***29***, *Scheme 2.7B*.[27] The latter is particularly difficult to remove, requiring additional purification steps, with consequent yield losses.



Scheme 2.7. (A and B): General Approach to Semi-synthesis of Codeine from morphine[38-42]

Simple bis-*O*-acetylation of morphine produces the diester derivative, 2-3 times more powerful analgesic then morphine, *Scheme 2.8*. The compound, widely known as heroin ***16***, also has significantly stronger side effects compared to morphine, including life-threatening respiratory depression and, in some instances, euphoria, irrational behaviour and aggression. Because of the side effects and particularly high addiction potential, it has been prohibited as a medical analgesic in most countries.[14,15] Yet, if administered in proper doses, it is very effective in suppressing severe pain and it is still a legal medication in Great Britain, Switzerland and elsewhere.

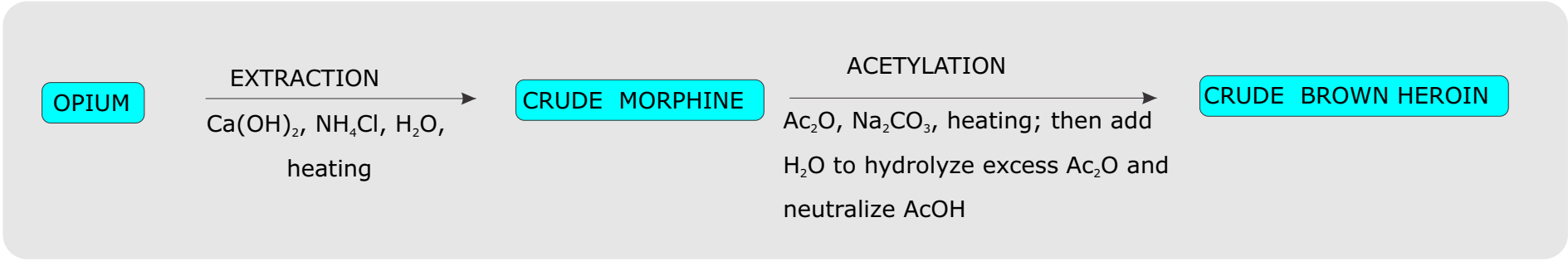


Scheme 2.8. General Procedure for the Synthesis of Pharmaceutical Heroin (diamorphine hydrochloride)

As such, it is prescribed by The British Pharmacopoeia (BP), exclusively under the name diamorphine. While the exact details of the pharmaceutical heroin production are not available, the general procedure is simple, *Scheme 2.8*. Tragically, the illicit heroin production is very high, standing at estimated 526 t in 2014.[20,21] The general protocol for the production of illicit heroin invariably starts from opium.[20,21] A detailed, genuine procedure of the illicit heroin manufacturing in Afghanistan, including photos of all stages and laboratory analysis of the samples, was published by Federal Criminal Police Office, Wiesbaden, Germany.[43]

The production starts with the isolation of crude morphine base from opium, followed by the acetylation using acetic anhydride, *Scheme 2.9.* Excess anhydride is hydrolysed by the alkaline work-up, yielding heroin of variable purity, depending on the quality of the opium, crude morphine, reaction conditions and the additional purification. The product is normally obtained as a brown or off-white solid, with the heroin content of ~80% or less. Acetic anhydride is the key precursor in the process, since there are no practical alternative procedures for the acetylation step. Without access to the chemical, there would be no illicit production of heroin. Although the trade of acetic anhydride is strictly controlled, it is still available through many illegal channels. (Because the anhydride has great industrial significance, it is legally produced in multi-thousand metric tons. Thus in 2015/2016, the licit global export of acetic anhydride was close to 500 000 t and it is not too difficult to divert quantities needed for the illicit use).[44] Illicit heroin comes in various forms and purity, from a black tar to the very pure, white heroin known as "china white" (the latter is rare), *Fig. 2.17*. The street samples are typically mixed with the adulterants, usually paracetamol and/or caffeine, having the heroin content often below 40%. Particularly deadly mixtures also contain illicitly produced fentanyl (50-100 more potent than morphine).[45]

Such mixtures are very easily overdosed, resulting in the exceptionally high death rate among the addicts. Illicit morphine is practically never marketed, as it is 2-3 times less potent than heroin. Also, the addicts are specifically interested in heroin, as it often produces strong euphoria.



Scheme 2.9. General procedure for the production of illicit heroin.[43]

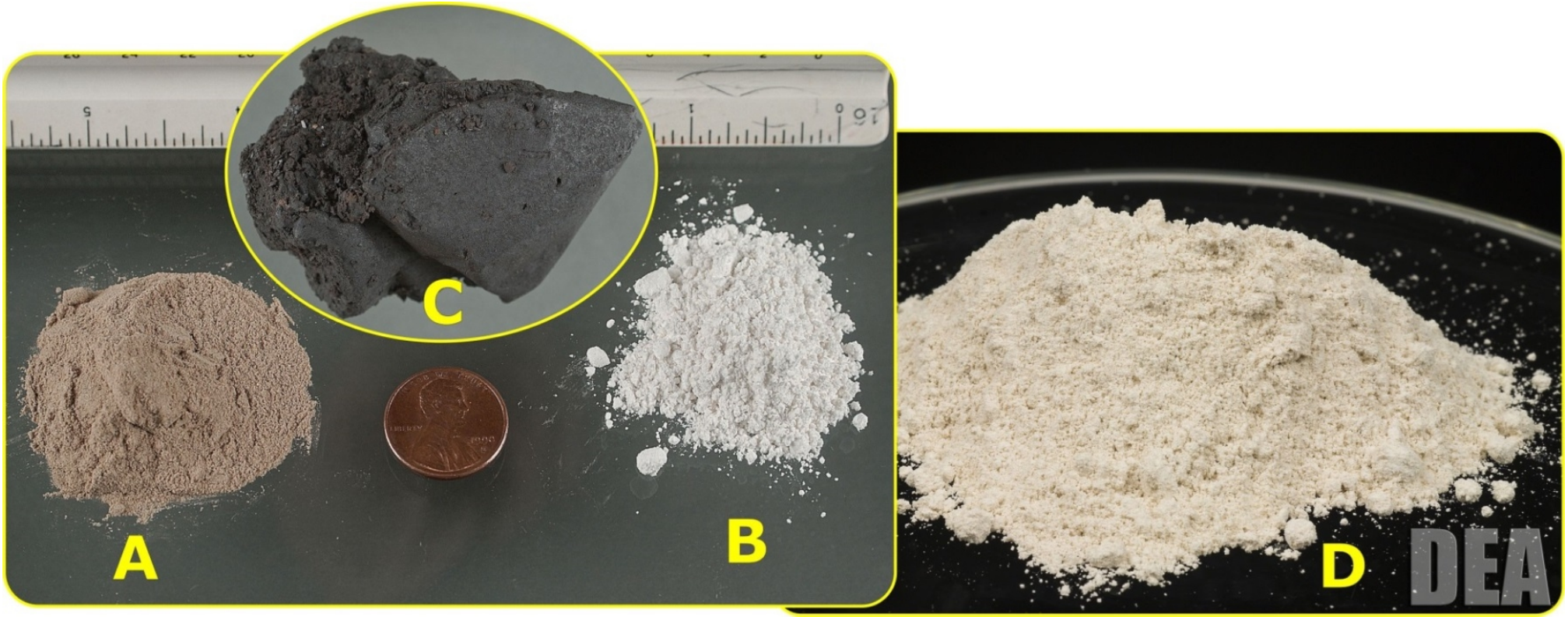


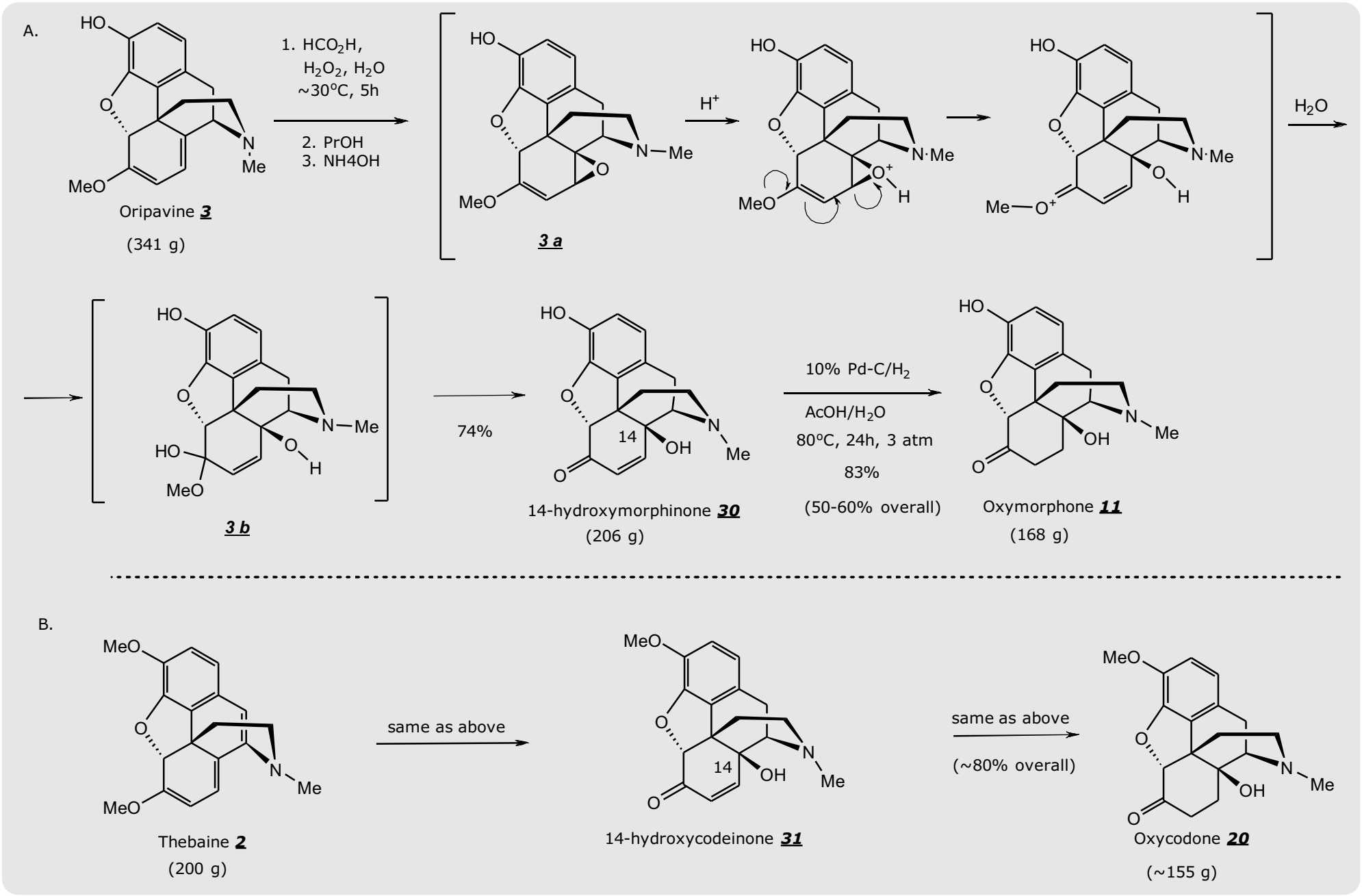
Fig.2.17. Various samples of impounded illicit heroin (A-D). Source: DEA

Oxymorphone ***11*** and oxycodone ***20*** were first prepared more than a century ago, by semi-synthesis from morphine alkaloids. Both compounds are strong opioids.[12] In the past several decades, they have become widely used (and abused) drugs, primarily due to the very good oral bioavailability. (Most morphine derivatives are poorly active when taken orally, largely restricting their use to the intravenous or intramuscular injections).[12] More recently, both oxymorphone and oxycodone also became available as the extended release formulations.[46,47] The drugs are strongly addictive, as most opioids, and have caused a significant number of deaths, usually due to the accidental overdose. (As explained in Chapter 1, lethal outcome is almost exclusively caused by respiratory depression. However, the illicit, "street" opioids, primarily heroin, are often highly contaminated with various adulterants, which can cause serious intoxication and death on their own, particularly when abused by intravenous injections).

Despite all the drawbacks, oxymorphone and oxycodone continue to be used extensively, to control various painful conditions, where other types of analgesics, like NSAIDs, are insufficiently effective. Numerous large-scale semi-syntheses have been patented, starting from the naturally occurring morphine alkaloids. A very recent patent application claims improved procedures for the semi-syntheses of oxymorphone and oxycodone, starting from the readily available oripavine and thebaine, respectively, *Scheme 2.10,* A and B.[48]

The synthesis relies on the known chemical transformations characteristic for thebaine, oripavine and the related morphine alkaloids. The initial epoxidation of 8:14 double bond, structure ***3a***, using aqueous performic acid, proceeded with the complete regio- and stereospecificity. While the precise mechanism is probably not known, it almost certainly involves the acid-catalyzed epoxide opening, with the simultaneous double bond migration. The keto group forms via spontaneous hydrolysis of hemiacetal ***3b***, affording intermediate 14-hydroxymorphinone ***30***. Following the known, selective protocol for the catalytic hydrogenation, the oxymorphone base was isolated in ca. 50-60% overall yield. The claimed advantage of the method is a high purity of the product, operational simplicity and the scalability, making it suitable for the industrial production. Oxycodone was obtained analogously from thebaine, via 14-hydroxycodeinone intermediate ***31***, in ca. 80% overall yield, *Scheme 2.10 B*.

As noted in Chapter 1, both oripavine and thebaine became more accessible and less expensive in recent years, due to the introduction of novel, thebaine rich strains of opium poppy. This is likely to result in the reduced costs of various semi-synthetic drugs, including oxymorphone and oxycodone.

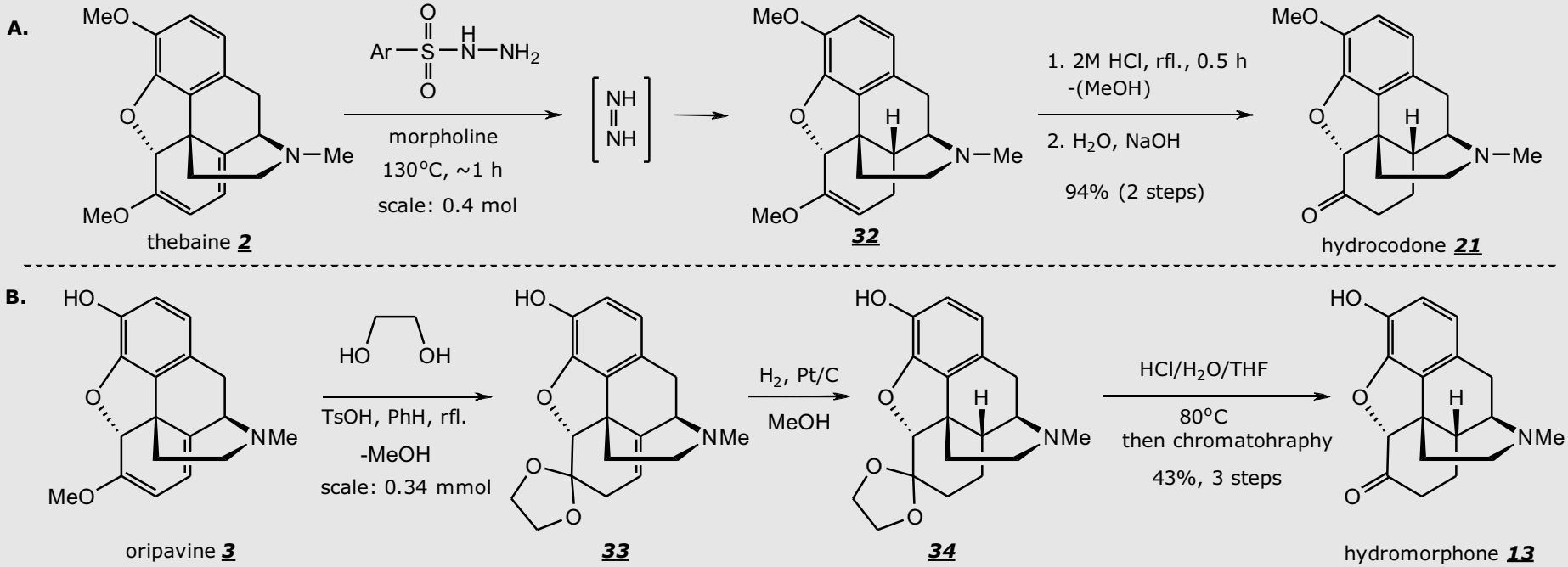


Scheme 2.10. A and B: Semi-synthesis of oxymorphone ***11*** and oxycodone ***20***.

Hydrocodone ***21*** and hydromorphone ***13*** are also significant semi-synthetic analgesics,[12] usually obtained from thebaine and oripavine, respectively. As already shown, both drugs are produced in multi-ton quantities annually, although the actual industrial protocols remain trade secrets and may only be guessed from the patents and papers.

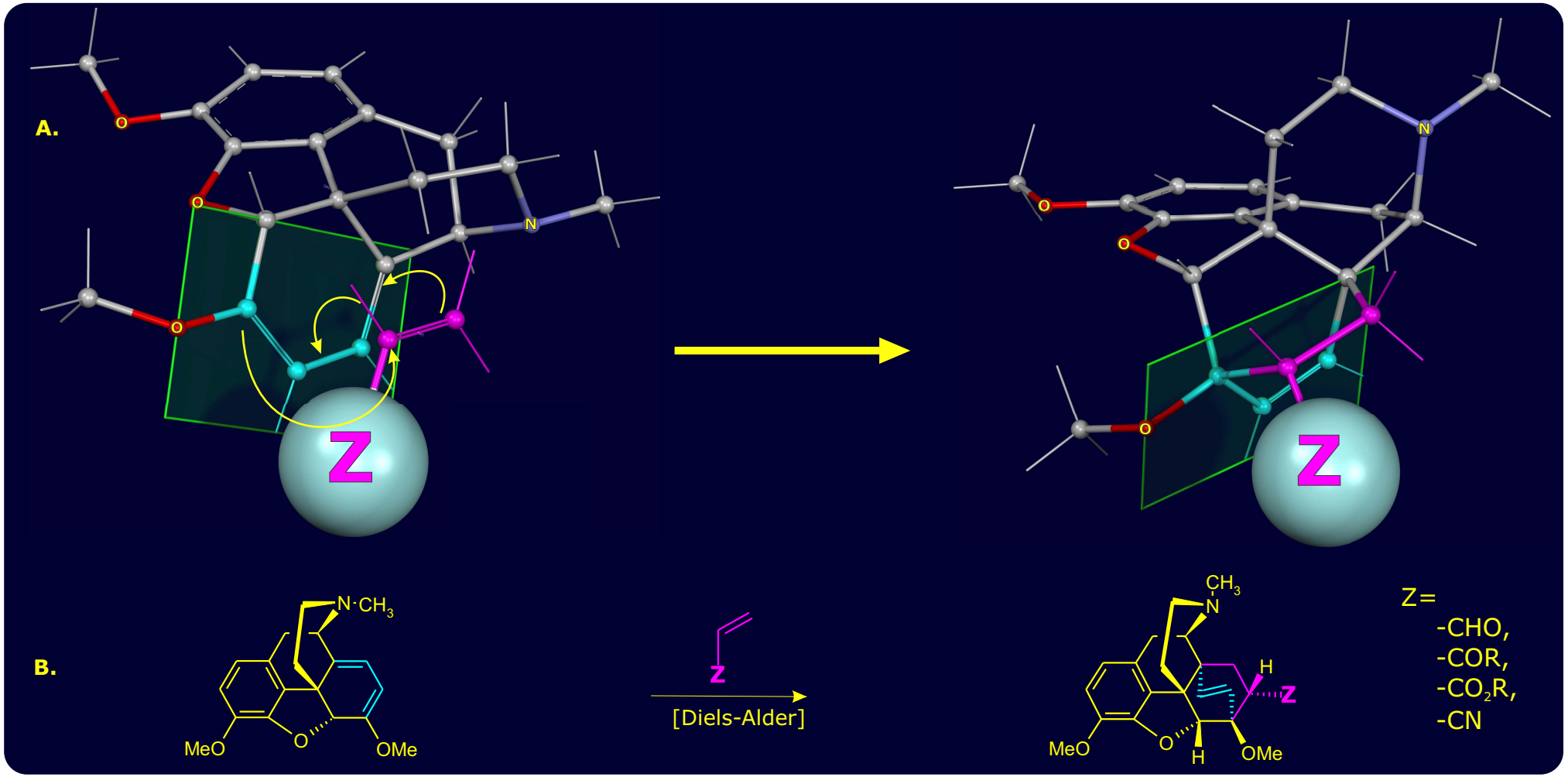
An interesting, scalable method, involved the selective reduction of 8:14 double bond in thebaine ***2***, using p-toluene sulphonyl-hydrazide in various basic solvents. The actual reducing agent was considered to be a highly unstable species, the diimine, *Scheme 2.11 A*.[49] Subsequent acid hydrolysis of the vinyl ether[32] afforded hydrocodone ***21*** in nearly quantitative yields.

A recent patent discloses the synthesis of hydromorphone ***13*** from oripavine ***3***, *Scheme 2.11 B*.[50] After conversion to cyclic acetal ***33***, 8:14 double bond was reduced catalytically to ***34***, in the presence of Pt/C. After acid hydrolysis of acetal group, the obtained mixture was purified chromatographically, providing ~41 mg (43% overall yield) of hydromorphone. However, modest yields, the need for purification by chromatography and use of the expensive platinum catalyst are all serious drawbacks in the possible scale-up.



Scheme 2.11. Semi-synthesis of Hydrocodone (A) and Hydromorphone (B)[49,50]

During the 1950s, it was discovered that thebaine was an active diene in Diels-Alder reaction, reacting with various active dienophiles including conjugated ketones, aldehydes, esters and nitriles.[51] The resulting products, possessing additional cyclohexene ring and a carbonyl or nitrile group, were structurally radically different from the starting morphine scaffold, with no parallel to the known natural (or synthetic) products. The synthesis and various chemical transformations of the compounds were examined extensively in 1960s, mainly by Bentley and co-workers.[52] The general reaction is shown in *Scheme 2.12 A* and *B*, as 3D and 2D representation, respectively.[52]

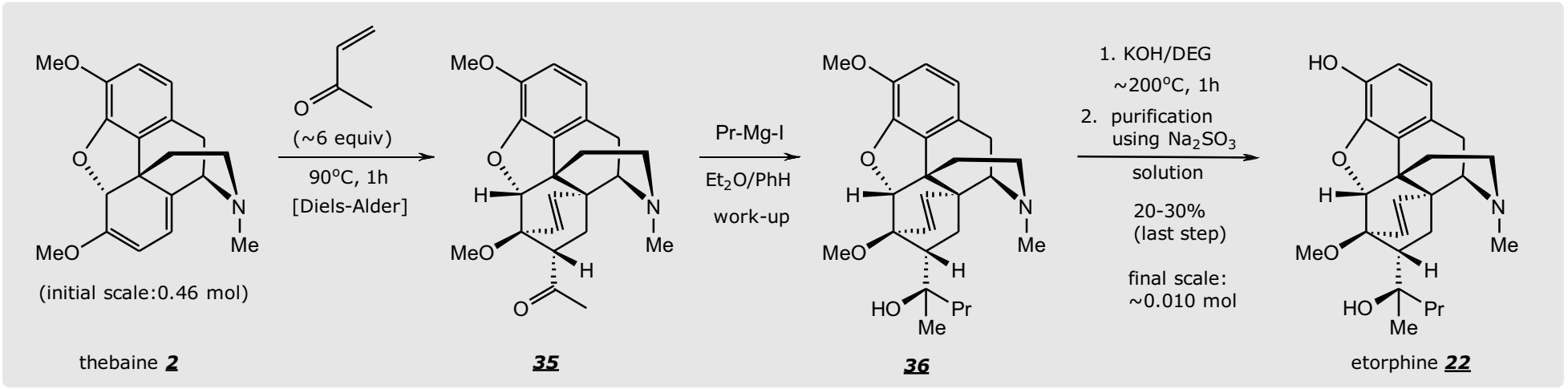


Scheme 2.12. Diels-Alder Reaction of Thebaine and Active Dienophiles. A: 3D representation. B: 2D representation.

Various Diels-Alder adducts, obtained acc. to the general reaction, *Scheme 2.12* were elaborated further. Thus, the addition of organometallics to the carbonyl group gave tertiary alcohols, e.g. etorphine ***22***, *Scheme 2.13*. Several of the compounds were thousands of the times stronger opioids than morphine. (The potency greatly depends on the animal species and the tests employed, with the humans being particularly sensitive). This level of activity remains among the highest among the μ agonists known to science. The most active analogue, etorphine (also known as M99)[53] is unsuitable as analgesic in humans, due to the serious side effects. However, it is widely used to immobilize large animals, particularly herbivores such as elephants and rhinos.[54,55] (It may be noted that salvinorine A,[4] a naturally occurring terpenoid, is still more active opioid, but it is a selective κ agonist, having very different pharmacological profile and strong hallucinogenic activity).

The patented synthesis of etorphine ***22***, started with 4+2 cycloaddition of thebaine and methyl-vinyl ketone, as outlined in *Scheme 2.13*.[51,56] (The reaction conditions, yields, and purity of the intermediates were often incomplete or missing in the patents). The obtained adduct ***35*** was first reacted with propylmagnesium iodide affording alcohol ***36***. The cleavage of aryl-methoxy group using potassium hydroxide, under extremely vigorous conditions, apparently gave low yields of impure etorphine ***22***. After extensive purification, the product was obtained in ~10-15% overall yields.

While the actual manufacturing procedures have probably been improved, the total annual consumption of the drug is minimal, possibly well below 1 Kg (the registered total world stock was~3 Kg in 2014).[14,15]



Scheme 2.13. Synthesis of etorphine ***22***.

Etorphine, in combination with other drugs, is currently being used to sedate large animals, both in captivity and in the wild, *Fig 2.18.*[57] The sedation is necessary for medical treatment, tagging and often for the relocation to other areas. Typically, animals are shot with the tranquilising darts, kept sedated as short as possible, and then treated with opioid antagonists. The procedure is far from benign, as the animal can die or suffer serious ill-effects from deep sedation. Thus, each case requires careful planning and the choice of optimal drug combinations, depending on the animal species and other factors. Often, it is necessary to provide an artificial respiration and the appropriate physical support (particularly for giraffes). Thus, "recreational tranquilising" of the wild animals in photo safaris, must be strictly avoided.

Fig.2.18. Some examples of etorphine use (A, B, C and D). Note: other, higly potent opioids are also used, instead of etorphine (see Chapter 3).

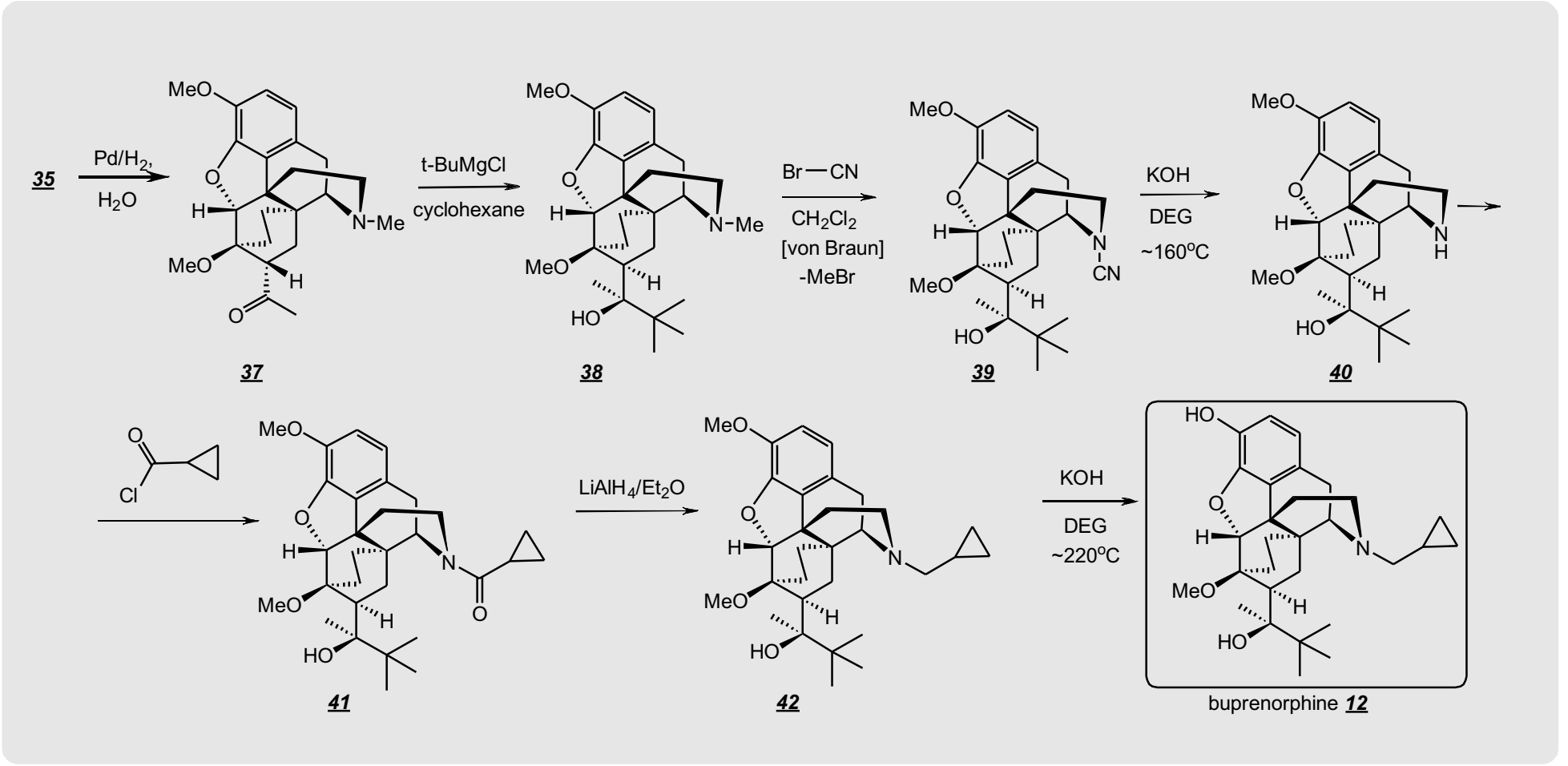
Buprenorphine ***12*** was first prepared in the late 1960s, by semi-synthesis from thebaine[58] and it is structurally closely related to etorphine ***22***. However, buprenorphine is much less potent opioid analgesic, acting primarily as a partial μ-agonist (and to some extent as partial δ-agonist, as well as κ-competitive antagonist).[59] Thus, it reaches a limit (plateau) in the receptor activation, when higher doses do not elicit higher activity. While buprenorphine has some use in the pain management,[60] its prime role is in the treatment of opioid dependence via the substitution therapy. (An alternative drug, methadone[4,12] has been on the market since the early 1950s, and is orally active, unlike buprenorphine). Yet, buprenorphine is considered to have generally more favourable pharmacological profile, resulting in the continuous production increase and use in recent years. (Methadone production slowly decreases).[14,15]It should be noted that buprenorphine is considerably more difficult and expensive to synthesize, requiring thebaine, as a key precursor, while fully synthetic methadone is relatively easy to prepare.[7] Buprenorphine formulations include sublingual tablets, transdermal patches and a long lasting depot form.[12]

The original synthesis of buprenorphine used Diels-Alder adduct ***35*** as the precursor, *Scheme 2.14*.[58] The current industrial production was claimed to be based on the original protocol.[59] The elaboration of ***35*** included hydrogenation of the double bond in the cyclohexene ring, followed by the addition of *t*-butylmagnesium bromide to the keto group, providing tertiary alcohol ***38***. The removal of *N*-methyl group was effected using highly toxic cyanogen bromide, (von Braun reaction), resulting in *N*-cyano intermediate ***39***. (It is possible that alternative, less toxic reagents, e.g. various chloroformates, would be more suitable).

Basic hydrolysis of the *N*-cyano group, under vigorous conditions, gave the secondary piperidine ***40***. (While it is known that *N*-cyano group is much easier to hydrolyse in acidic medium, it was not an option in the particular synthesis, as it would also result in the dehydration of the tertiary hydroxyl group and the cleavage of the furan ring).

Significantly, under the reaction conditions, the methoxy group remained intact, while in the last synthetic step, under similar conditions, it was demethylated. Presumably, the selectivity was achieved by performing the reaction at lower temperature. *N*-cyclopropilmethyl group was then introduced in two steps. First, the acylation of the piperidine ***40*** gave carboxamide ***41***, followed by the reductive deoxygenation with LAH, securing *N*-cycloproylmethyl amine ***42***. This protocol was preferred to the more conventional, direct *N*-alkylation, due to the slow reaction and low yields. (While the simple secondary piperidines are generally very nucleophilic and easily alkylated, the particular ring system is highly hindered and a poor nucleophile).

In the final step, buprenorphine ***12*** was obtained via cleavage of the aromatic methoxy group using KOH solution in diethylene glycol (DEG) at ~220°C. While it seems unusual that the molecule was stable under the extreme conditions, the protocol was successfully used in the synthesis of other morphine derivatives. (The demethylation mechanism is not clear and may involve the aromatic nucleophilic substitution). The 3D structure of buprenorphine is represented in *Fig.2.19*.



Scheme 2.14. Semi-synthesis of buprenorphine.

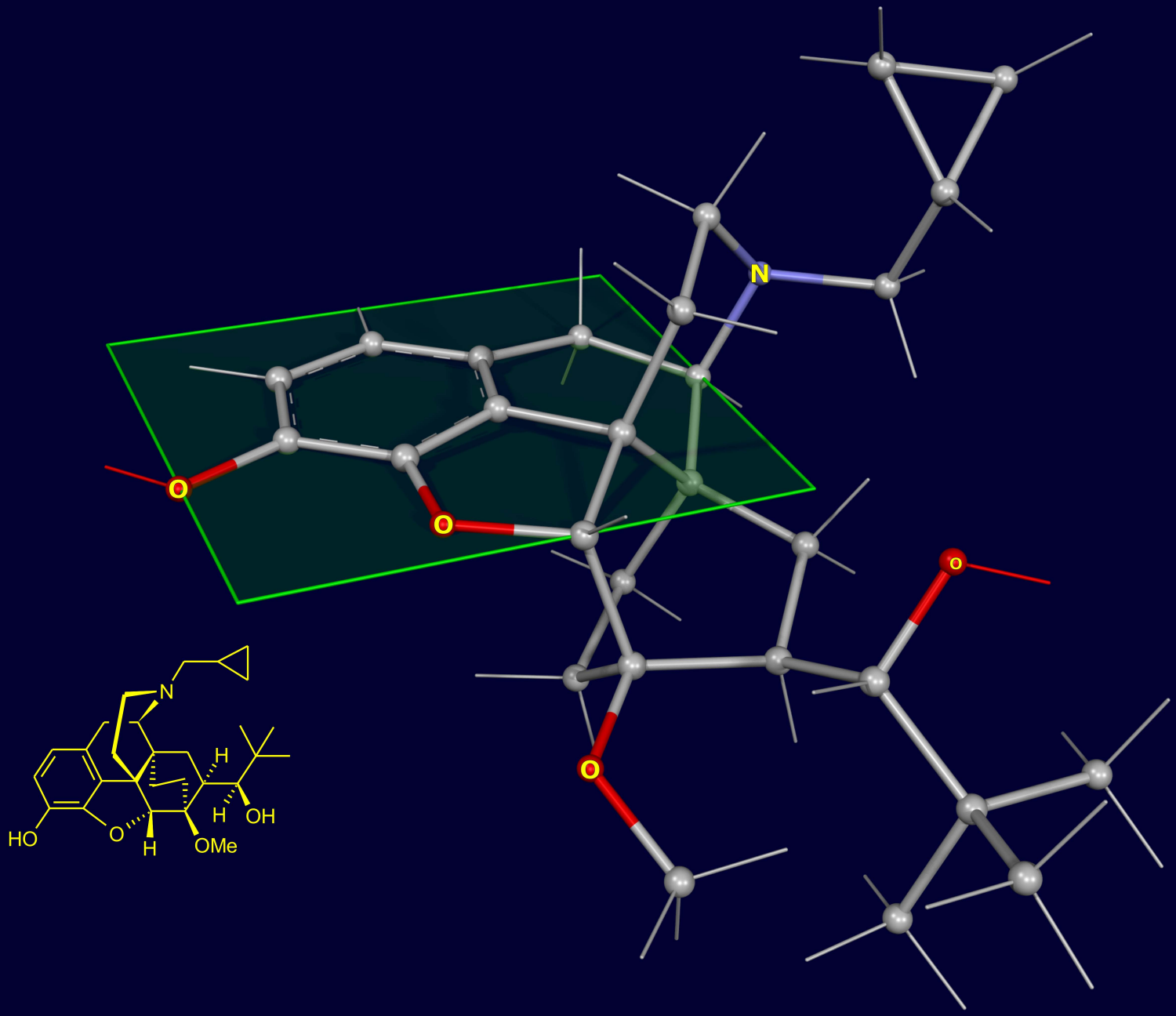
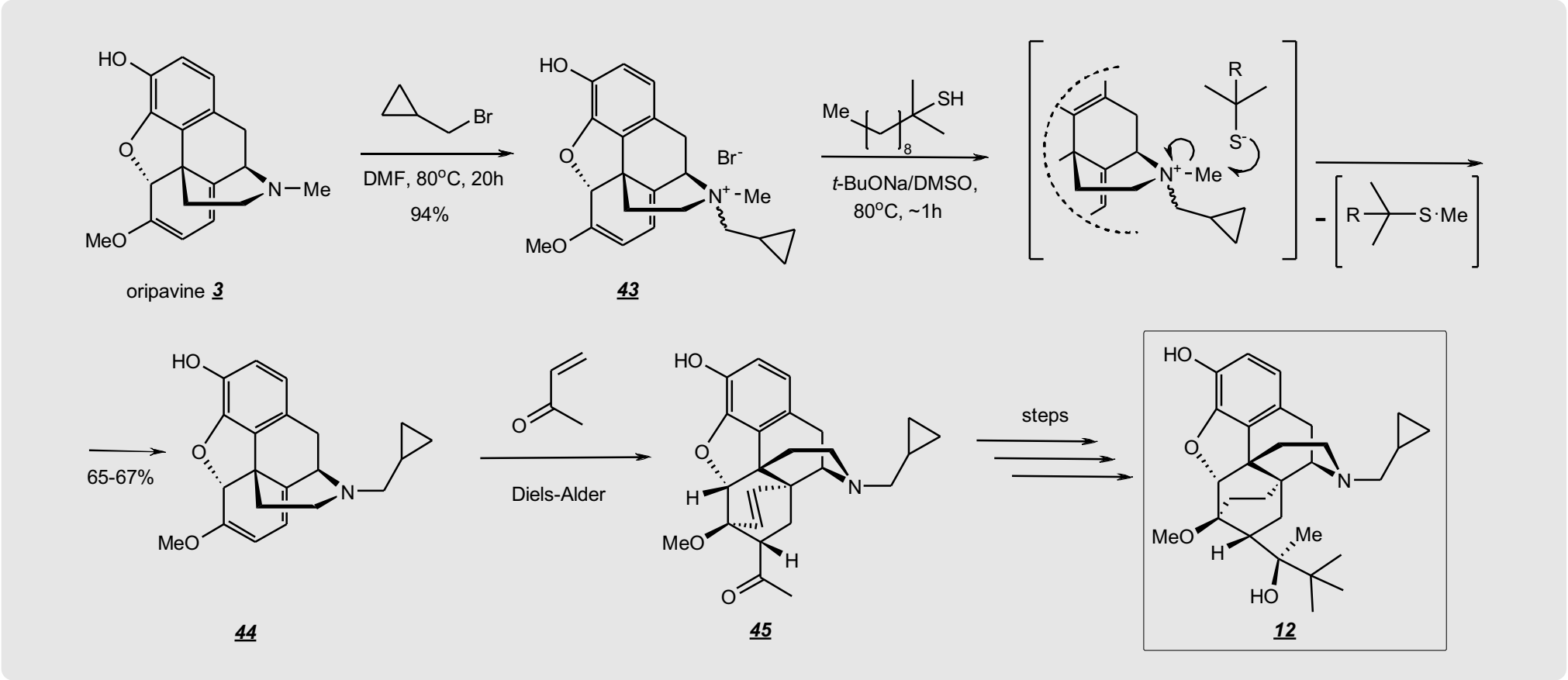


Fig.2.19. Buprenorphine *12*: 2D and 3D representations of the structure.

An alternative, recently published[59] and patented[61] semi-synthesis of buprenorphine starts from oripavine, *Scheme 2.15*.

The approach is significant primarily because of the initial, two stage transformation. First, the tertiary amino group was nearly quantitatively alkylated and the resulting quaternary salt ***43*** isolated. The salt was then selectively *N*-demethylated, providing the requisite *N*-cyclopropylmethyl intermediate ***44***. Although similar transformations were reported previously, the achieved chemo-and regioselectivity on such a complex molecule is remarkable. Apparently, the key to the successful demethylation was the use of sterically hindered sodium t-dodecanethiolate. As a weak base and strong nucleophile, it substitutes *N*-alkyl group, in preference to a much more common Hofmann elimination. In addition, because the reagent is bulky, the substitution is strictly regioselective, removing the least voluminous methyl group.



Scheme 2.15. Alternative semi-synthesis of buprenorphine.

The main advantages of the approach, compared to the earlier syntheses, are the omission of highly toxic cyanogen bromide and higher yields with fewer steps. Also, *t*-dodecanethiol is non-toxic and available in bulk quantities. While performed on a small scale, the synthesis appears to be readily scalable, with the potential to become production procedure. After obtaining Diels Alder adduct ***45***, the remaining steps (not shown), leading to buprenorphine ***12***, are largely modifications of the known protocols

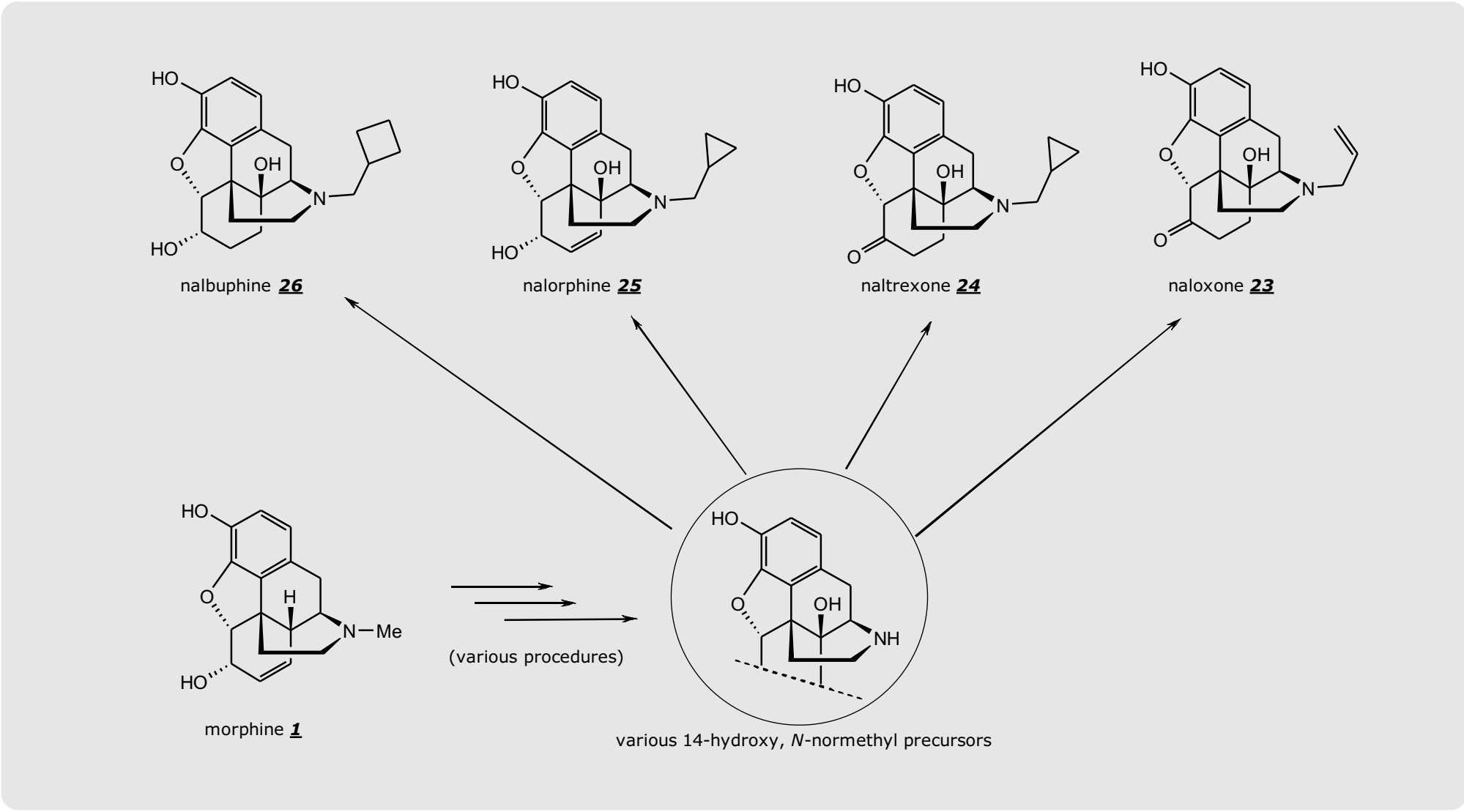
2.11. Morphine alkaloids as precursors in commercial semi-synthesis of opioid antagonists

Compounds binding to the opioid receptors, without eliciting typical analgesic effects, are generally denoted as the opioid antagonists.[12] The antagonist-receptor complexes form reversibly, analogously to the agonist complexes, except that they are usually more stable. Therefore, the antagonists displace agonists from the receptors, effectively terminating their action.

Clinically, most opioid antagonists produce little, if any, pharmacological effects in animals and healthy individuals. However, they can rapidly reverse the opioid analgesic effects, including life-threatening respiratory depression, the most common cause of death in opioid overdosing. Agonist also quickly precipitate the abstinence syndrome in addicts. However, the general therapeutic potential of opioid agonists is quite limited, compared to agonists. Besides clinical use, the antagonists are important tools in pharmacological research of the opioids.

The common structural characteristics of antagonists are: a) the presence of 14-hydroxy group and b) various *N*-alkyl groups, notably *N*-cyclobutylmethyl, *N*-cyclopropylmethyl and *N*-allyl group.

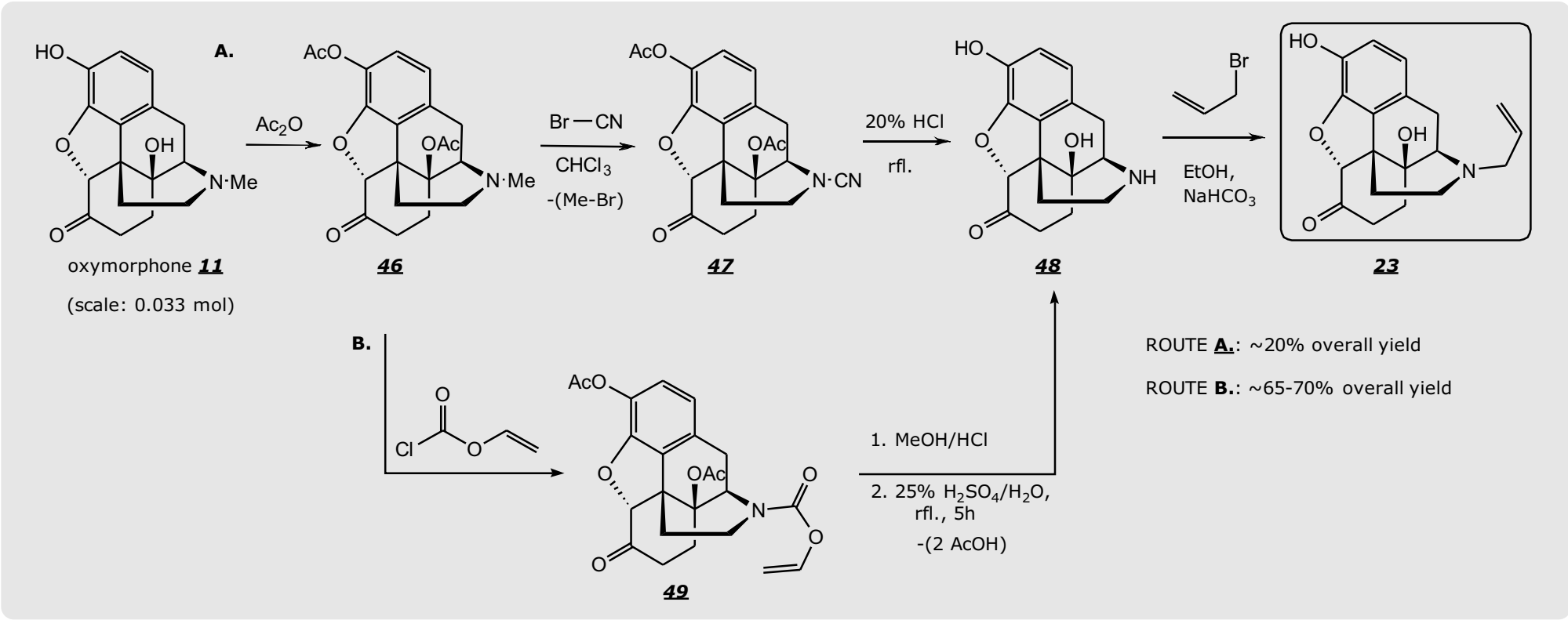
The most significant antagonist, all of them morphine derivatives, are naloxone ***23***, naltrexone ***24***, nalorphine ***25***, and nalbuphine ***26***, *Scheme 2.16*.



Scheme 2.16. Structures and general synthetic approaches to the significant opioid antagonists

Commercially, opioid antagonists are always prepared by semi-synthesis from morphine alkaloids and their derivatives. The multistep procedures always involve replacement of *N*-methyl group with allyl or other alkyl groups, often using reagents like cyanogen bromide. Typical examples are illustrated in *Schemes 2.17* and *2.18*.

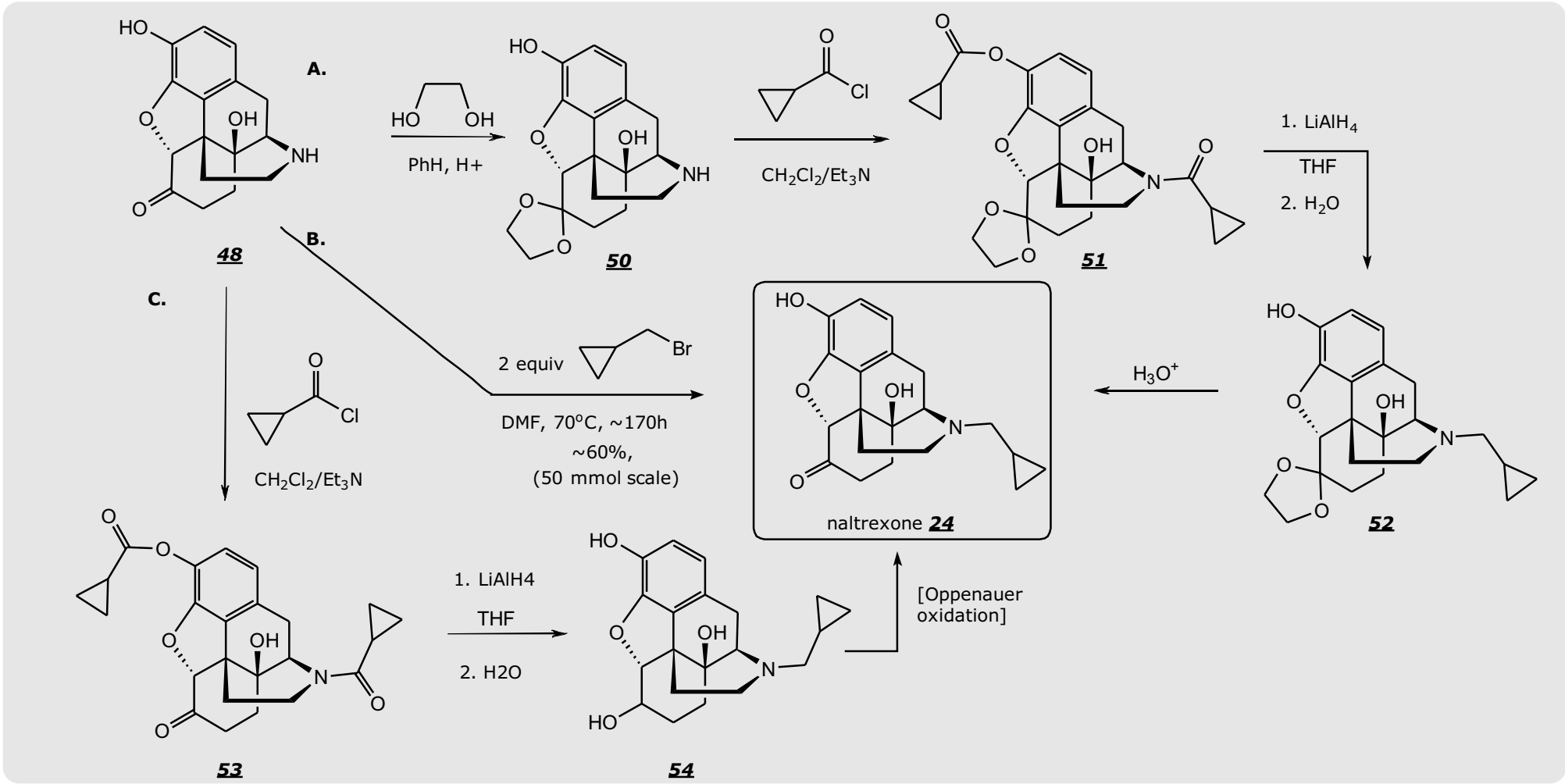
The original, patented synthesis of naloxone, started from the readily available oxymorphone ***11***, *Scheme 2.17*, route A.[62] After the hydroxyl groups were protected as acetates, *N*-demethylation with cyanogen bromide, produced the stable *N*-cyano intermediate ***47***. (The procedure, known as von Braun reaction, has limited selectivity, often resulting in low to moderate yields and side products, depending on the substrate). Vigorous acid hydrolysis removed both the cyano and the acetate groups, providing *N*-noroxymorphone ***48***. (Unexpectedly, it seems that the acid-sensitive furane ring and tert-hydroxyl group remained largely unaffected. However, the base-catalysed hydrolysis is often preferred, e.g. Scheme 2.14). After *N*-allylation, naloxone ***23*** was obtained in only 20% overall yields. A modified synthesis, using vinyl chloroformate, proved to be far more selective, affording nearly quantitative demethylation, *Scheme 2.17*, route B.[63] (More recently, vinyl chloroformate was largely replaced with a more stable and similarly efficient 1-chloroethyl chloroformate).[64]



Scheme 2.17. Synthesis of Naloxone ***23*** via Two Different Routes.

The patented semi-synthesis of naltrexone ***24***, via three different approaches, is represented in the *Scheme 2.18*.[65]

All three routes start from *N*-noroxymorphone ***48***, a key intermediate in the preparation of naloxone. Direct *N*-alkylation of ***48***, route B, appears to be the most practical, despite very long reaction time and modest yields (7 days, 60%). The alkylation rate is slow due to the steric hindrance of both the nucleophile and the alkylating agent. The alternative, multi-step routes A and C are likely to be less efficient (it is a known fact that the patent procedures are often unreliable, particularly regarding the reaction conditions, yields and purity).



Scheme 2.18. Synthesis of Naltrexone ***24*** via Three Different Routes.

2.12. Morphine alkaloids in semi-synthesis of opioid ligands as pharmacological research tools

While the commercial research in opioids continues unabated, new opioid drugs have not reached the market in recent years.[14,15] There are already many powerful opioid analgesics in the therapeutic use, leaving little room for novel, yet pharmacologically similar drugs.[12] Successful new opioids would need, besides high potency, far better general tolerance, including much lower addiction potential, weak or absent respiratory depression, sedation and other side effects, compared to the current opioid drugs. This is particularly important in the treatment of non-malignant, chronic pain (such as back pain), which can last for years and requires continuous management. At present, there are no such opioids and they are unlikely to appear in a foreseeable future. (Alternative treatments are also limited).

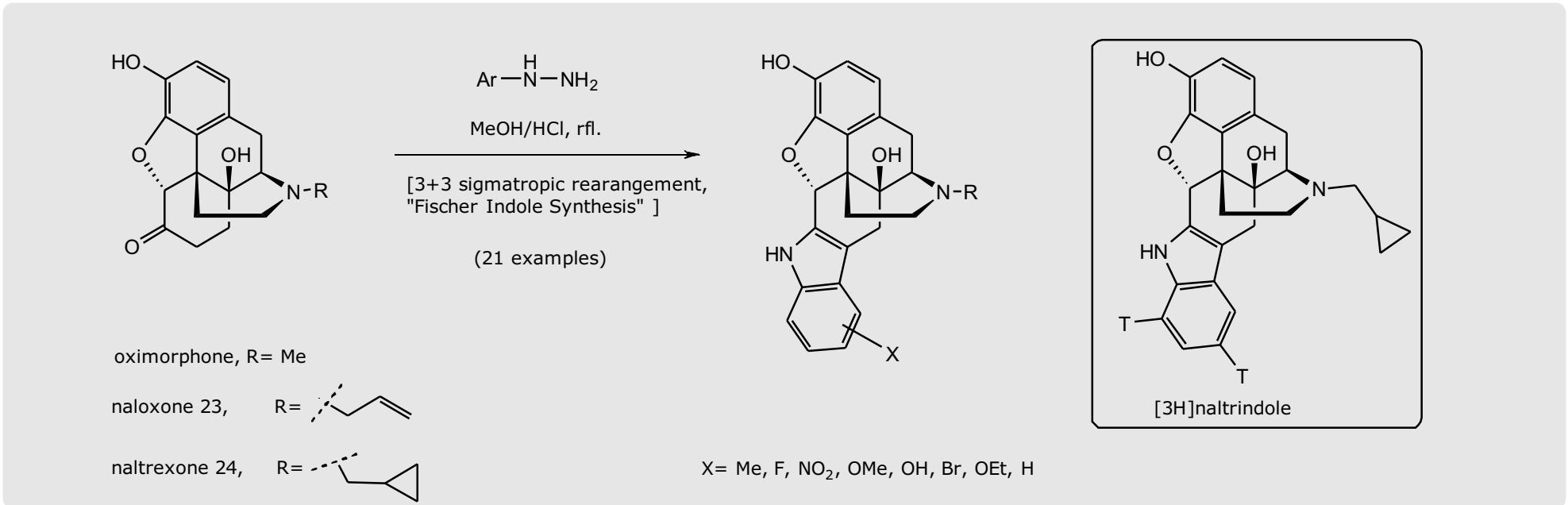
Consequently, the present commercial research in opioids is focused primarely to improving production procedures for the drugs already on the market, developing new opium poppy strains for higher yields of the specific morphine alkaloids and finding novel drug formulations, often combining several active ingredients. In addition, new drug delivery methods have been investigated, such as various systems for continuous drug delivery (Chapter 3, p. 124).

Basic research in opioids is generally far more diverse than the industrial and it is certainly more transparent. Besides other aspects, it includes synthesis of various new opioid ligands and studding receptor-ligand interactions. The interactions have been extensively examined experimentally, by various pharmacological tests (*in vitro* and *in vivo*), and theoretically, particularly using docking simulation methods. Since 2012, accurate structures of the crystalline opioid receptor-ligand complexes were obtained, (Chapter 1, p. 3, 8-11). Thus, a significant new avenue in this research field became available.

This section includes only several examples (out of the thousands), where opioid ligands were prepared by semi-synthesis from morphine alkaloids, followed by the pharmacological characterization (*in vitro* and, in some instances, *in vivo*). The theoretical studies, docking in particular, were often included, comparing experimental results and the calculated predictions. The main goal of these investigations was to gain deeper insights into the biological roles of the opioid receptors and mechanisms of their action.

Besides the immediate receptor-ligand interactions, the investigations also encompassed interactions between different receptor types, transmission pathways of painful stimuli and related phenomena.

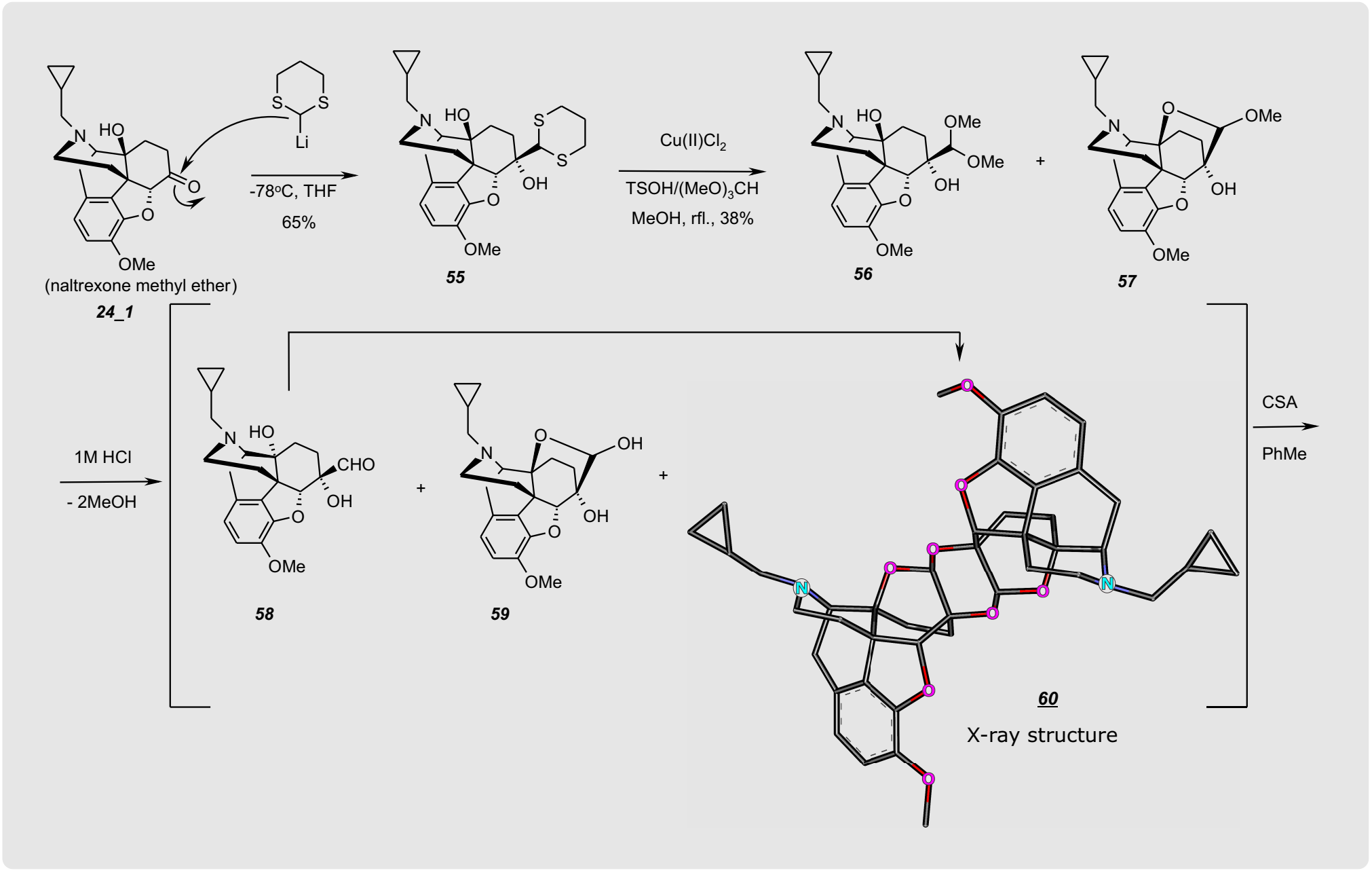
Several semi-syntheses of morphine analogues, dedicated to the pharmacological research, are presented herein. Thus, the reaction of oxymorphone, naloxone or naltrexone with variously substituted aryl hydrazines, produced the expected indole derivatives, via Fischer indole synthesis, *Scheme 2.19*.[66].



Scheme 2.19. Morphine derivatives as highly active and selective antagonists of δ-opioid receptors

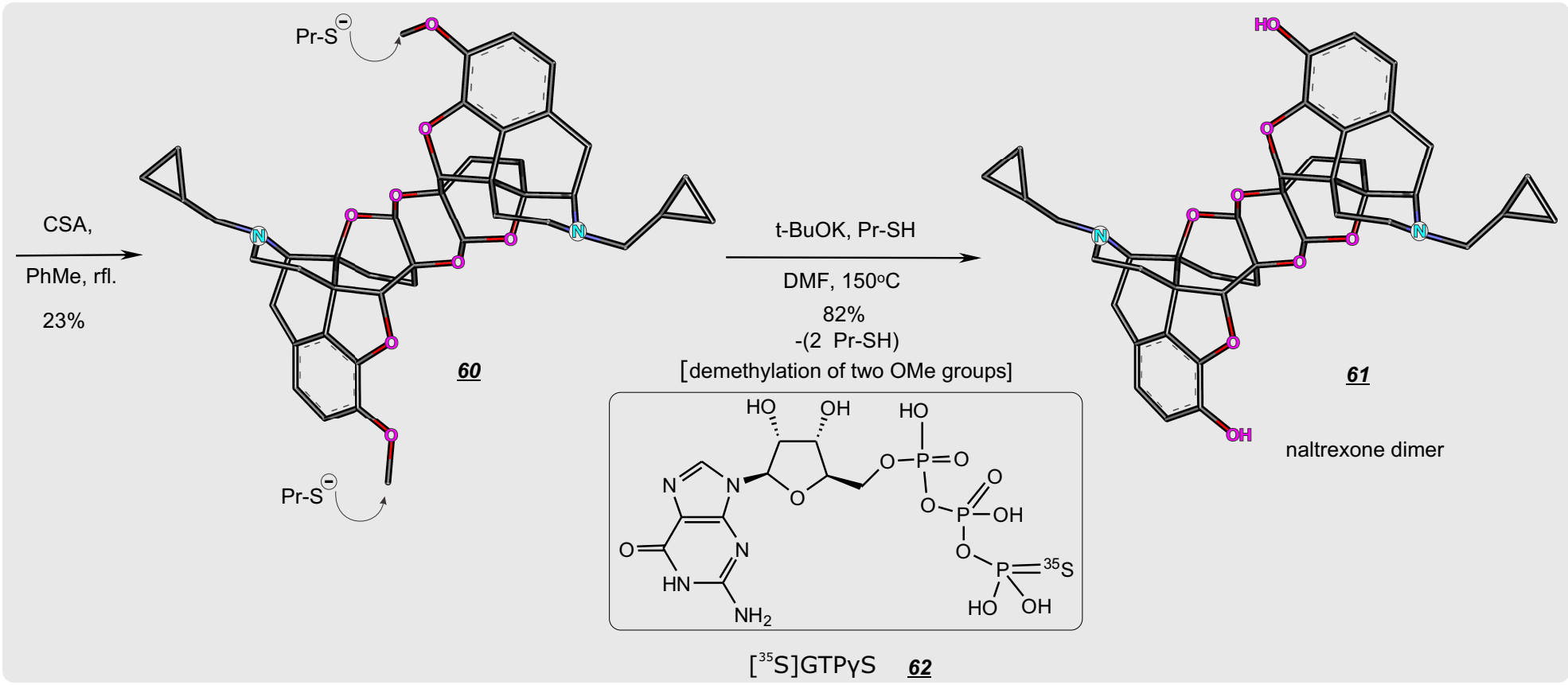
The compounds, prepared as potential opioid antagonists, indeed demonstrated the remarkable affinity and selectivity for δ-opioid receptors. The most potent antagonist in the series was naltrindole, active in the sub-nanomolar concentrations and also highly selective for δ-opioid receptors. Because of the activity and selectivity, it has often been used as a research tool, particularly as tritiated radioligand.[67]

Besides the numerous modifications of morphine alkaloids, they have also been used to synthesize more complex molecules, primarily aimed for pharmacological research. Thus relatively short, but rather unusual syntheses of the dimers and trimers possessing morphine scaffold, produced compounds having significant effects on the opioid receptors. The synthesis of the dimers started from naltrexone methyl ether ***24.1***, *Scheme 2.20*.[68] The addition of excess dithiane anion to the carbonyl group, gave α-hydroxy-thioacetal ***55***. Thioacetal group was removed oxidatively, using Cu^{2+}, affording a mixture of normal acetal ***56*** and the bridged, mixed acetal ***57***. After acid hydrolysis, the three-component mixture was obtained, consisting of α-hydroxy-aldehyde ***58***, bridged hemiacetal ***59*** and dimeric acetal ***60***, originated from ***58***. (The compound ***60*** is represnted as the experimentaly determined 3D structure, since 2D formula is ambiguous).



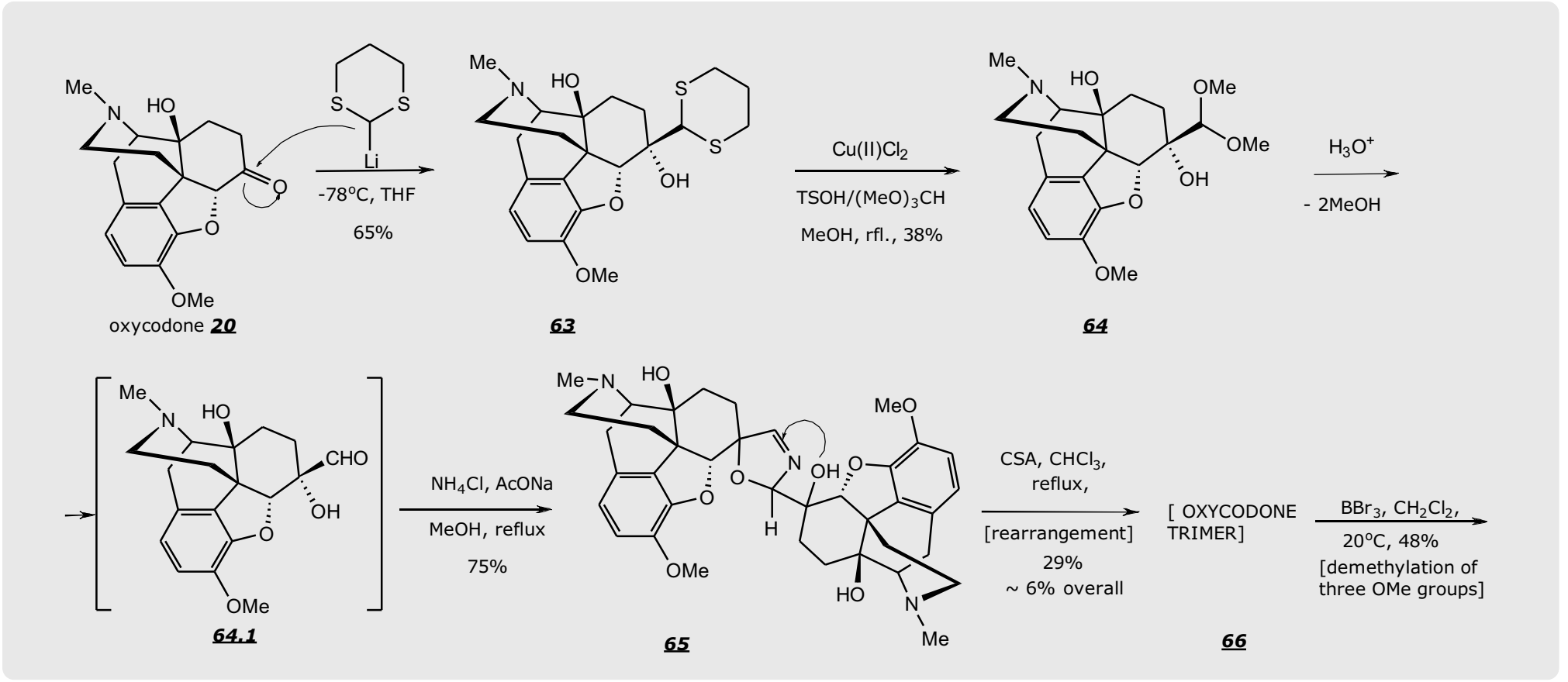
Scheme 2.20. Synthesis of Morphine Dimers: Naltrexone Dimer (part 1).

Exposing the mixture of ***58***, ***59*** and ***60*** to anhydrous camphorsulfonic acid, the dimeric acetal ***60*** was obtained as the main product, albeit only in low yields. Structurally, the compound is a rigid dimer of two naltrexone molecules, having the common dioxane ring. In the final step, demethylation of aryl methoxy groups required the use of thiolate anions as hypernucleophilic regents, because electrophilic reagents (e.g. BBr_3), would also cleave the acetal groups. Thus, potassium propanethiolate, generated *in situ*, gave ***61***, possessing free phenolic groups, *Scheme 2.21*. Despite the synthesis has no preparative significance, because of the very low overall yields, it provided sufficient amounts of ***61*** for several binding assays, using [^{35}S]GTPγS ***62***. The results demonstrated a significant antagonist activity for μ and κ opioid receptors, but not for δ receptors, indicating that the compound could be a useful tool in opioid receptor research.[68]

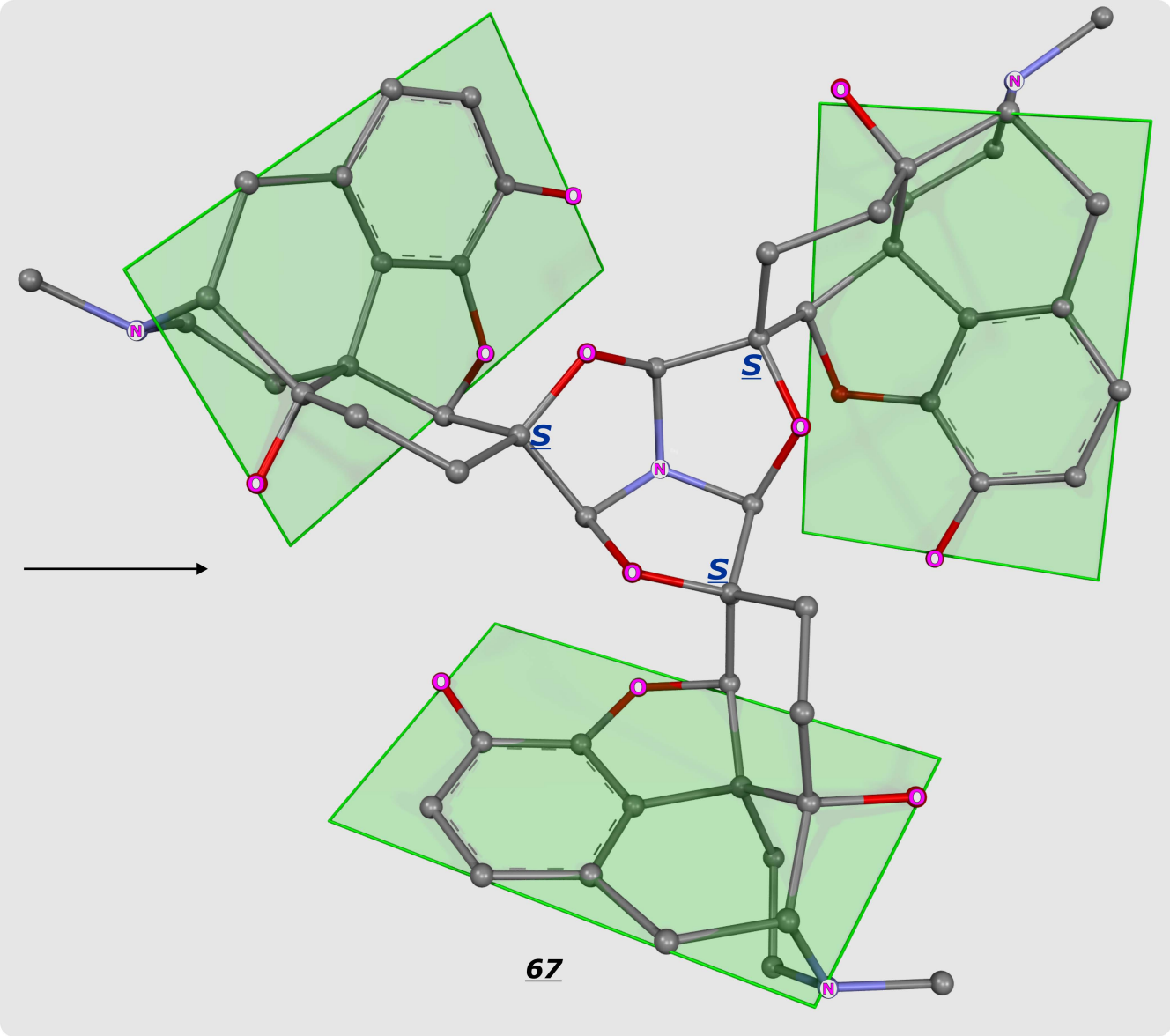


Scheme 2.21. Synthesis of Morphine Dimers: Naltrexone Dimer (part 2).

In the continuation of previous work, novel rigid trimers, possessing the morphine scaffold, were prepared in a 5-step synthesis, *Scheme 2.22* and *Scheme 2.23.*[69] The trimers possessed a central, 1,3,5-trioxazatriquinane ring, symmetrically connecting three oxymorphone molecules. The synthesis, starting from oxycodone, involved two key steps. Dimerization of α-hydroxy-aldehyde ***64.1***, in the presence of ammonium ion, resulted in the formation of the oxycodone dimer ***65***, incorporating 2,5-dihydrooxazole ring. Then, in the presence of strong acid, rearrangement of ***65*** produced symmetrical oxycodone trimer ***66*** (structure not shown), having the central 1,3,5-trioxaza-triquinane ring. (The overall yield, for 5 steps, was just 6%). Finally, the methoxy groups were cleaved, securing ***67*** (*Scheme 2.23*). In this case, the use of BBr_3 was feasible, as the other groups in the molecule were stable to this electrophilic reagent.



Scheme 2.22. Synthesis of Morphine Trimers (part 1).



Scheme 2.23. Synthesis of Morphine Trimers (part 2). (Adapted from X-ray file, hence hydrogen atoms are absent).

The structure of symmetrical oxymorphone trimer ***67*** was determined by X-ray diffraction, *Scheme 2.23*. Surprisingly, only one diastereomer was obtained, with the absolute configuration ***S*** at all three shown stereocenters. A number of examples confirmed that the trimerization of various α-hydroxy aldehydes is a relatively general reaction, permitting preparation of both symmetric and non-symmetric trimers. Pharmacological tests revealed that ***67*** was potent *in vivo* analgesic in rodents. Thus, acetic acid writhing assay gave ED_{50}=0.037 mg/kg, about 20 times more potent than morphine (ED_{50}= 0.6 mg/kg).[70]

Given the size and rigidity of the molecule, the result is rather unexpected, both in terms of the formation of ligand-receptor complex and penetration of the brain-blood barrier. Additional test would be necessary to confirm the activity. In addition, there is a possibility that the trimer undergoes *in vivo* hydrolysis, producing the actual active species, possibly oxymorphone itself.

Another intriguing research area, involving morphine derivatives, are bivalent opioid ligands. The concept of bivalent (or bidentate) ligands, possessing at least one opioid pharmacophore, has been examined in the past three decades.[71,72] Initially it was assumed that the opioid receptors were uniformly spaced in the tissues (e.g. various parts of the brain). Consequently, if two ligand molecules are interconnected by a linker ("spanner"), such as a linear hydrocarbon chain, they could simultaneously bind to two adjacent receptors. The simultaneous binding would occur only if a linker has the correct length, resulting in the stronger binding, as measured by various pharmacological test (such as binding constants). In general, the bidentate ligands could provide significant insights into the receptor spacing, distribution and other properties in a given tissue type. The approach was pioneered by Portoghese group, which prepared the bivalent ligands by connecting two β-naltrexamine molecules (opioid antagonist), using oxyethylene units.[73] The general concept is represented in *Fig. 2.20*. (The receptor molecules in *Fig. 2.20* were modelled acc. to the recently published 3D structure of μ-receptor, obtained by X-ray analysis of the crystalline protein-ligand complex).[74]

The synthesis of the ligands is shown in *Scheme 2.24*.

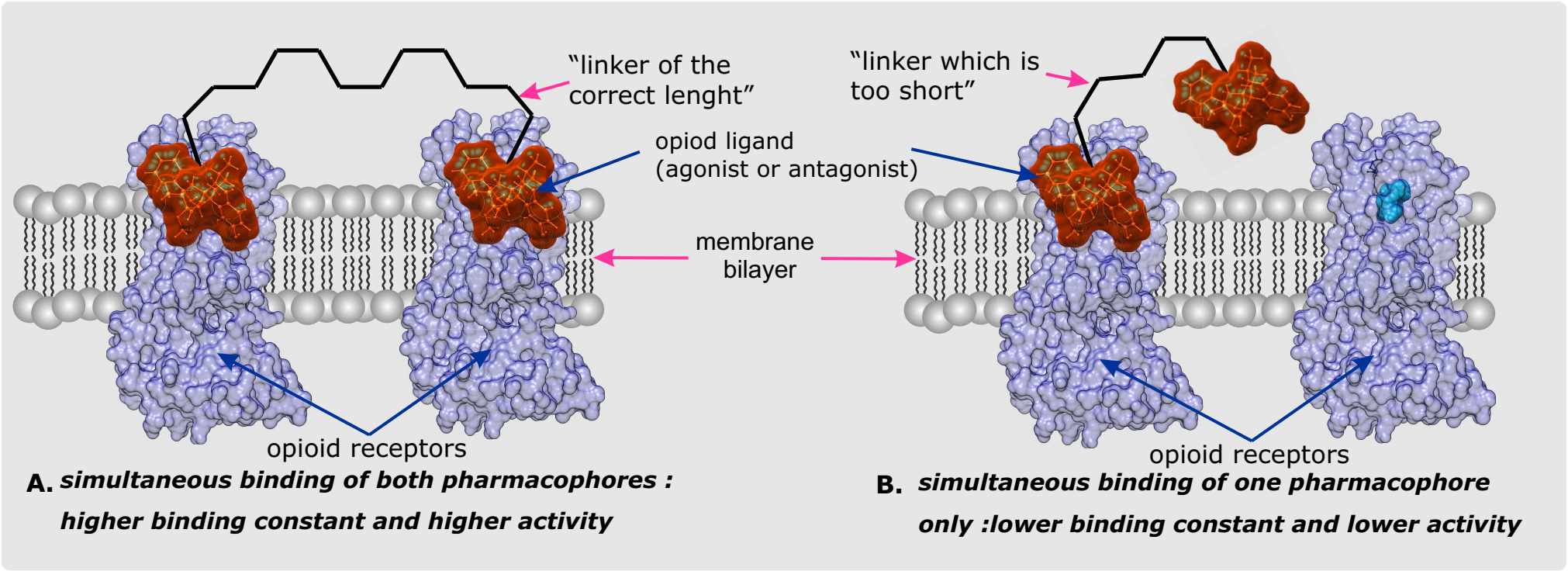
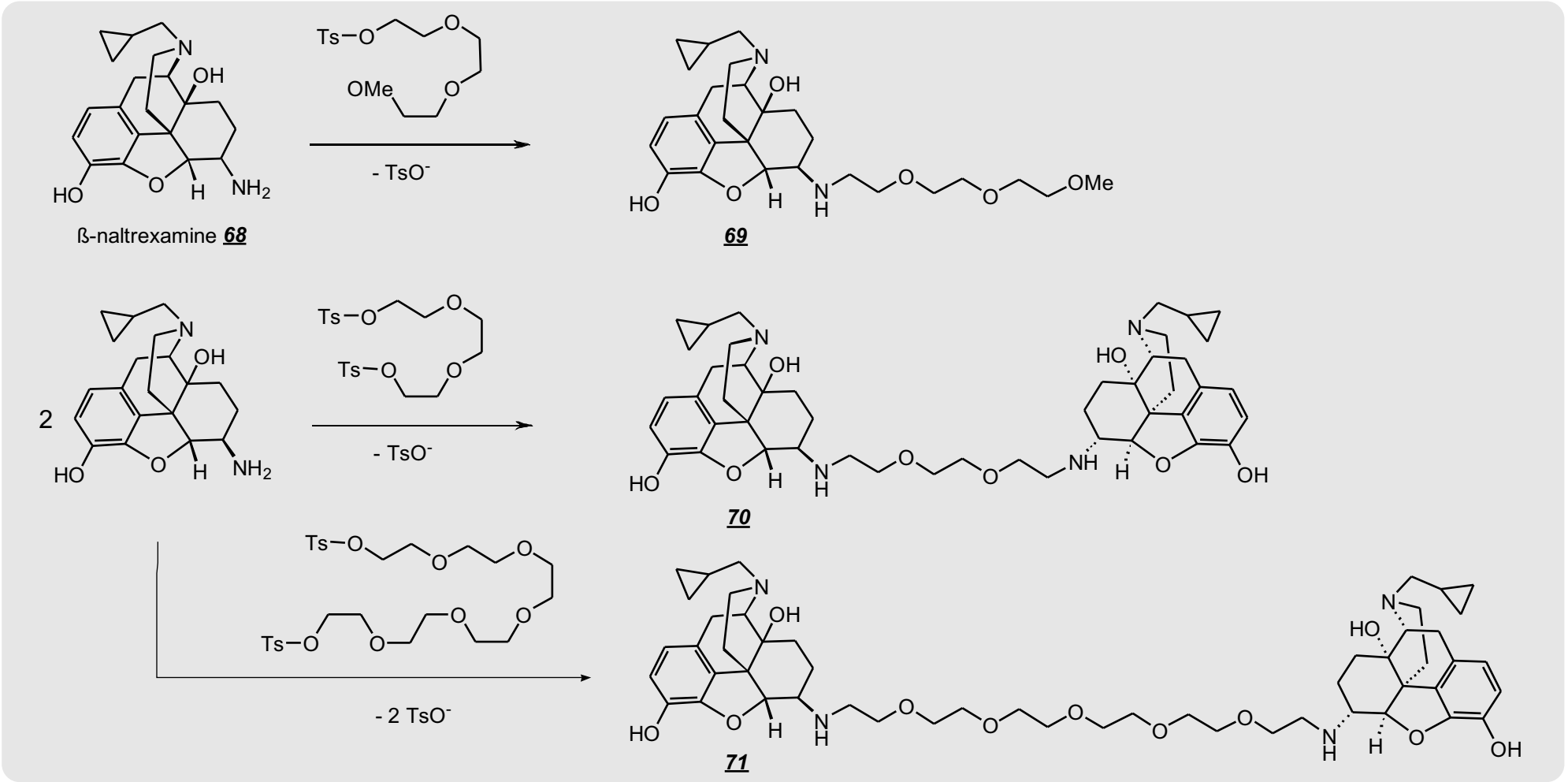


Fig.2.20. Highly Simplified Representation of Bidentate Ligand Binding (not drawn to scale).

Opioid antagonist β-naltrexamine ***68*** was alkylated using triethylene glycol monotosylate methyl ether, triethylene glycol ditosylate or hexaethylene glycol ditosylate, *Scheme 2.24*. It was shown that bivalent ligands ***70*** and ***71*** exhibited 10-15 times higher antagonist activity than β-naltrexamine or monodentate (monovalent) ligand ***69***. Although not fully conclusive at the time, pharmacological tests corroborated the basic concept. Later, many more elaborated experiments, confirmed the findings, offering new insights into the pharmacology of opioid receptors.



Scheme 2.24. Synthesis of Monodentate and Bidentate Opioid ligands prepared from β-naltrexamine

A large number of structurally and pharmacologically diverse bivalent opioid ligands have been synthesized and tested in the past three decades.[71,72] A particular attention was paid to the ligands combining two different pharmacophores, each specific for a given opioid receptor type (μ, κ or δ), or non-opioid receptors.

One of the significant finding was that simultaneous activation of μ-receptors by specific agonists and blocking δ-receptors by specific antagonist resulted in a strong analgesia, with the significantly reduced tolerance and dependence.[75,76] Further investigation in that direction involved the synthesis of numerous bivalent ligands, combining known, specific μ-agonist and δ-antagonist (3α-amino derivative of oxymorphone ***72*** and 7'-amino naltrindole ***73***, respectively).

The ligands were then examined in rodents, using various in vivo tests.[77] One of the tested compounds, ***74***, designated MDAN-21, was found to be 50-fold more potent analgesic than morphine by the intravenous route, while causing little or no tolerance and dependence, *Fig.2.21*. (Number 21 refers to the total number of atoms in the linker).

This remarkable pharmacology was attributed to the simultaneous binding to both μ and δ receptors, because of the optimal length of the spacer. (Longer or shorter spacers resulted in lower activities or were inactive). However, it seems that this type of drugs has never been tested clinically.

The general synthetic approach, illustrating the synthesis of ***74*** is self-explanatory, *Scheme 2.25*. The two pharmacophores, μ-agonist ***72*** and δ-antagonists ***73*** were coupled, using standard methods for the synthesis of peptidomimetics.

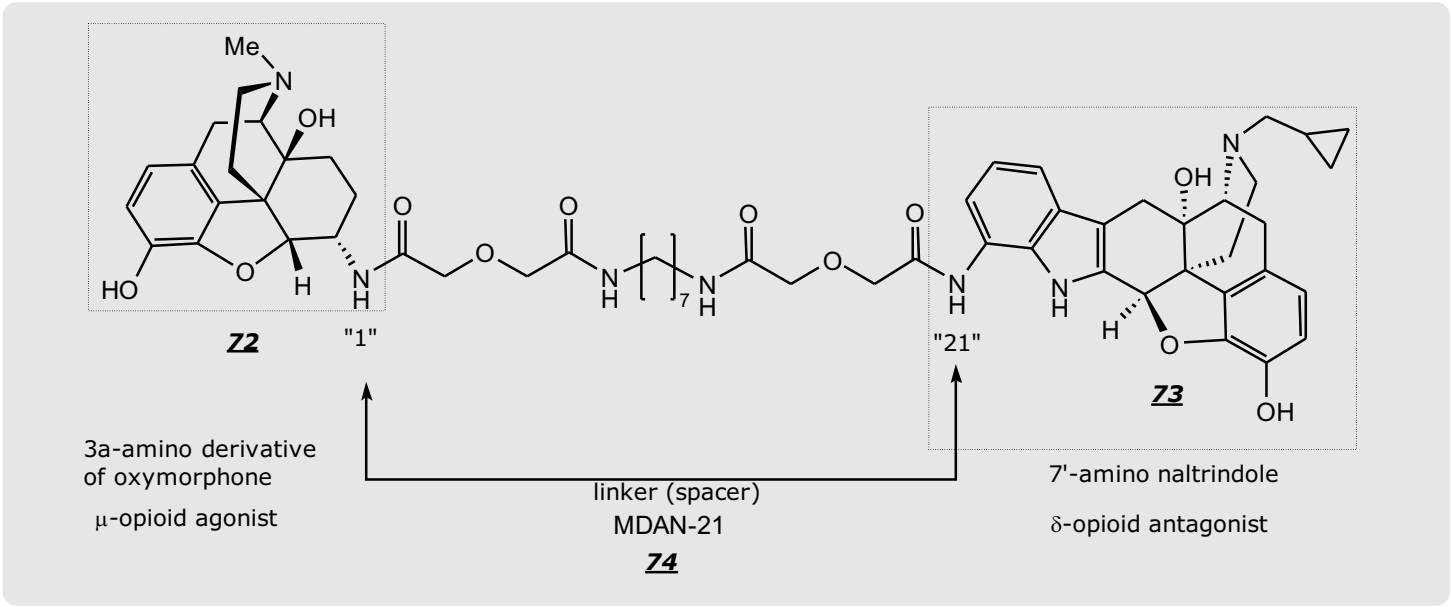
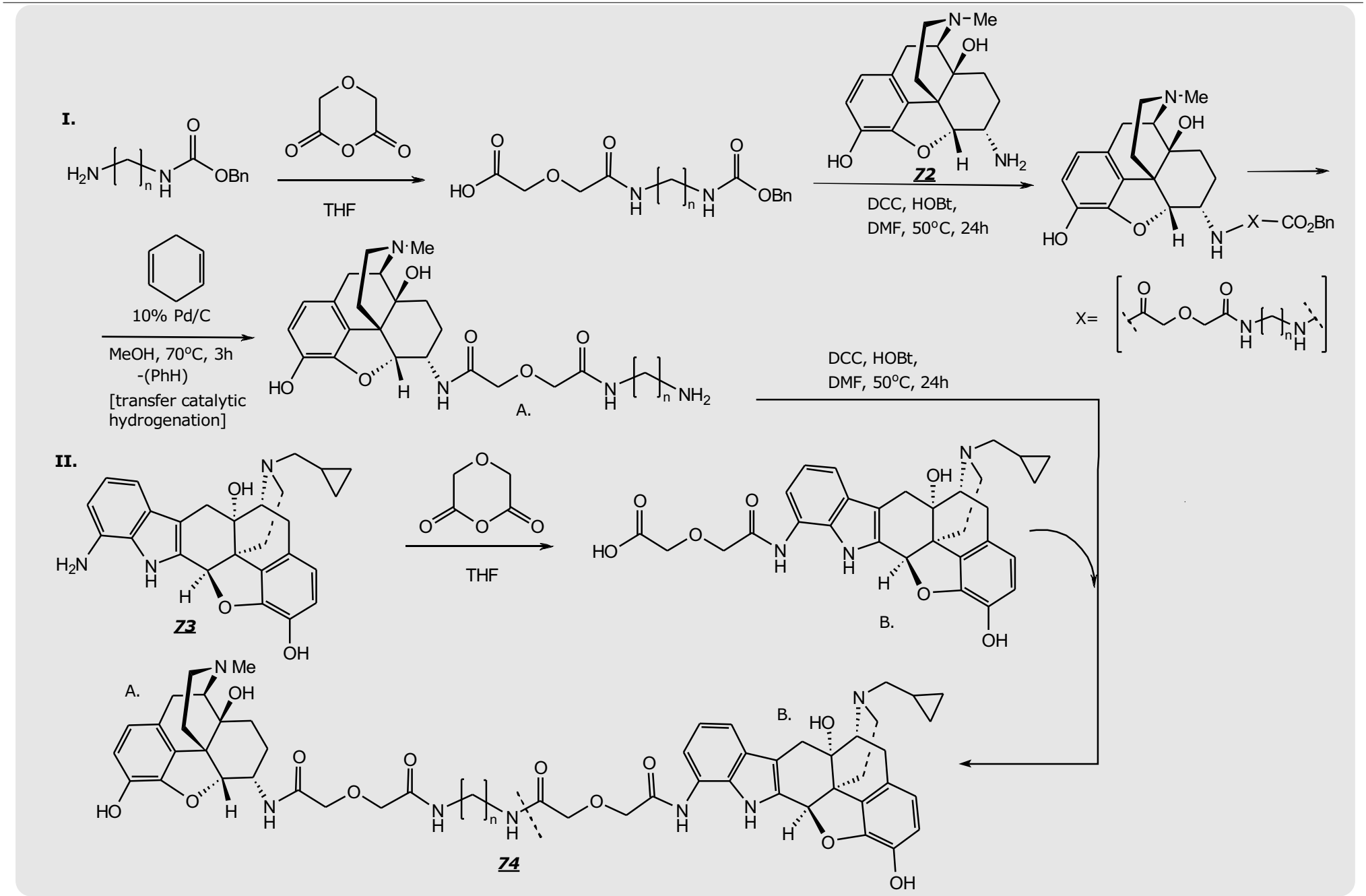


Fig.2.21. Structure of the ligand MDAN-21 (***74***).



Scheme 2.25. Synthesis of bidentate μ-agonist/δ-antagonist ligands

Any detailed discussion of the ligand-receptor interactions, either in terms of pharmacology or the theoretical modelling, exceeds the scope of this treatise. Nonetheless, where appropriate, brief notes and references are given.

Generally, it has long been understood that bivalent ligands have far too short linkers to simultaneously bind to two adjacent, physically separated, membrane receptors. (The receptors, being protein molecules, are quite voluminous). Therefore, based on the pharmacological and other evidence, concepts of the various receptor dimers (both homo- and heterodimers) have been advanced.[71,72](Heterodimers are also denoted as heteromers). Essentially, two receptor protein molecules are believed to form a complex, "bivalent" receptor, capable of simultaneously binding certain bivalent ligands, eliciting the pharmacological response. In the case of homodimers, the response would be simply enhanced compared to monovalent ligands, a phenomenon often evidenced in pharmacological tests.

Receptor heterodimers however, when complexed to hetero bivalent ligands, would send simultaneous, but different signals. Potentially, the effect may have a therapeutic significance. For example, as already shown for hetero bivalent ligand MDAN-21, the result could be the enhanced opioid analgesia with the reduced or absent tolerance. Results of several *in vitro* studies were consistent with the presence of opioid heterodimers receptors. Thus, it seems likely that some of heterodimers are actually present *in vivo*, causing diverse pharmacological phenomena such as tolerance and the addiction.[71,72]

Concept of the opioid heterodimer, as previously proposed,[77] is illustrated in *Fig 2.22.* The representation is entirely hypothetical and qualitative. It was composed from the actual X-ray structures, obtained from the μ-opioid receptor/agonist complex (with morphinane BU72)[74,78]and the δ-opioid receptor/antagonist complex (with naltrindole).[79,80] The two receptors were manually connected to the 3D model of the ligand ***74***, using the appropriate software.[81] The active site of μ-opioid receptor received the agonist side of the model while δ-opioid receptor was connected to the antagonist side of 3D model. Thus, the original ligands in the X-ray structures were approximately replaced by the corresponding parts of the ligand ***74***. Also, the linker was rotated manually, as needed, to obtain a rough fit. The sole purpose of producing this composite 3D model (no calculations were performed), was to visualize the appearance of the heterodimer, complexed to bivalent ligand ***74***. The levels of the upper and the lower cell membranes were taken from the respective X-ray structures, using estimates from PDB site.[82]

The question if such heterodimers actually exist, particularly *in vivo*, either constitutively (i.e. as a normal part of certain cell walls) or induced by the ligands, remains the matter of debate and further investigations.[71,72]

Opioid Heterodimer Structure, Manually Composed From The Actual X-ray Structures Of μ-Opioid Receptor/Agonist Complex And δ-Opioid Receptor/Antagonist Complex.

A and B: different representations of the same strructure

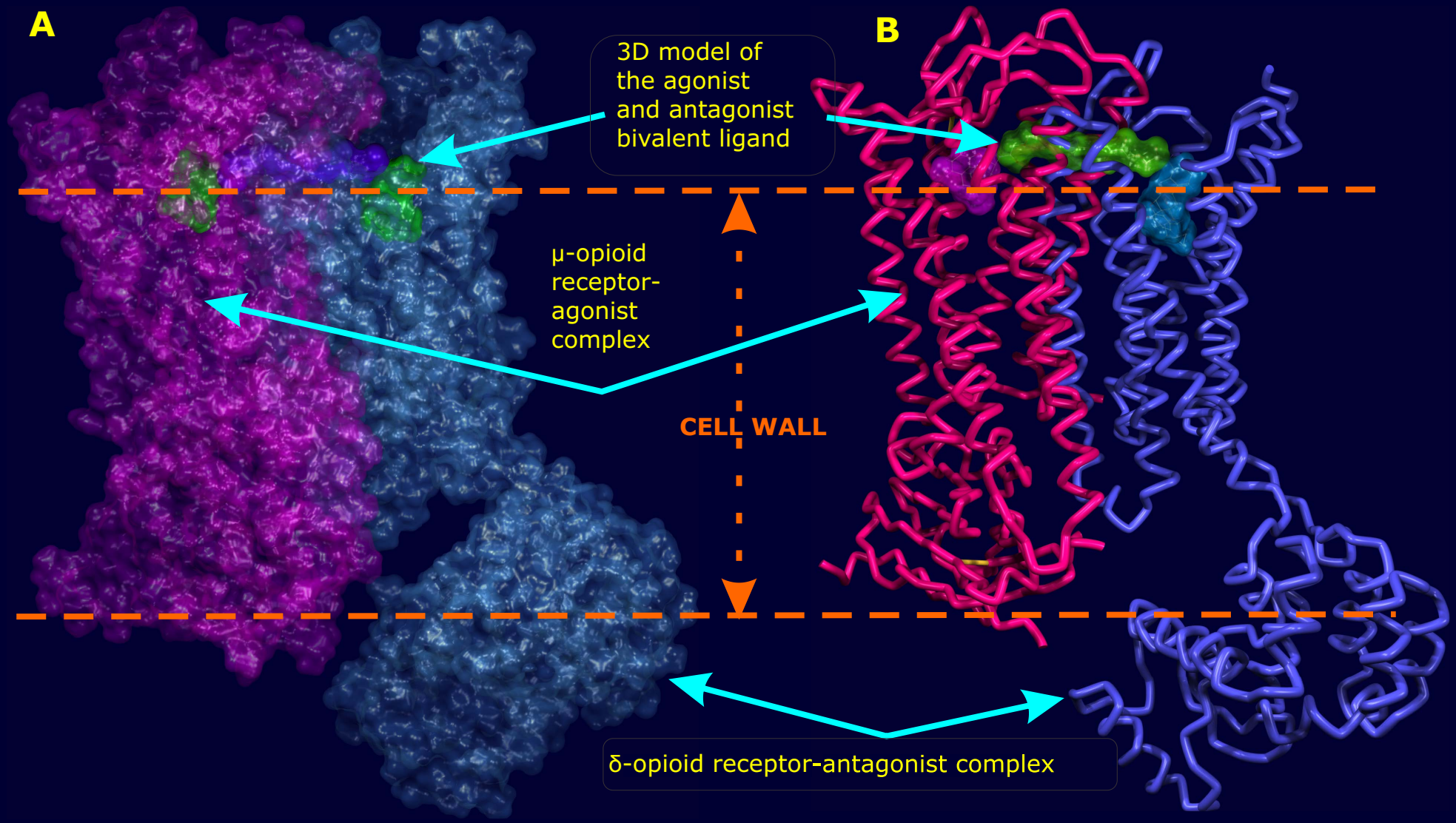
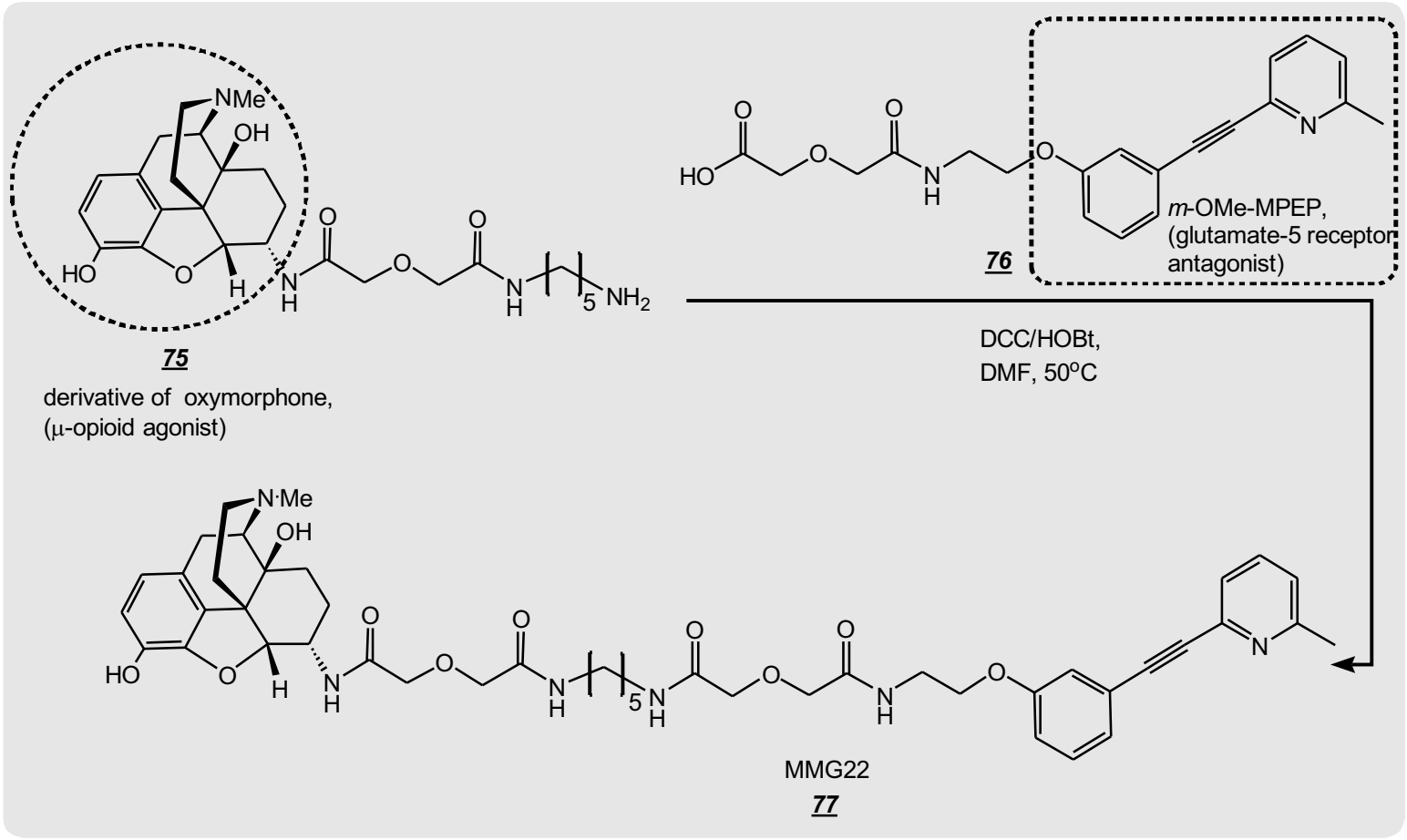


Fig.2.22. Hypothetical, qualitative representation of μ/ δ-opioid heterodimer complexed to the common ligand ***72*** (MDAN-21).

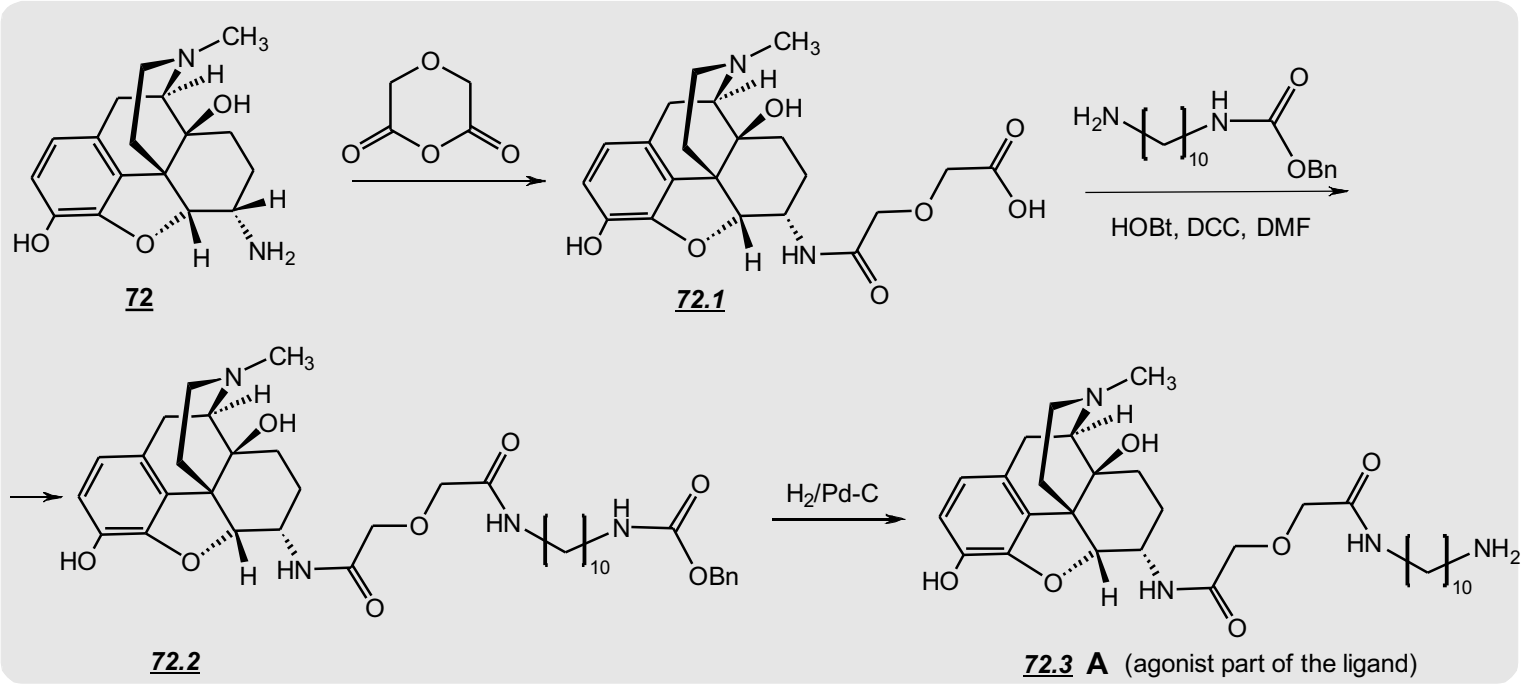
Putative heterodimers, combining μ-opioid and glutamate-5 receptors were also investigated.[83] The natural ligand of the glutamate receptors in the central nervous system is glutamate, the excitatory neurotransmitter known as an important mediator in pain-related phenomena, dependence and the withdrawal syndrome. Specifically designed bivalent ligands produced *in vivo* pharmacological results consistent with the presumed receptor heterodimers. However, the actual interactions at the molecular level remain highly uncertain. The synthesis involved preparation of the series of potential bivalent ligands, possessing the opioid agonist pharmacophore and antagonist pharmacophore for the glutamate-5 receptor. As in the previous examples, the opioid agonist part of the ligands was derived from 3α-amino-oxymorphone ***72***, while the antagonist moiety from the previously known glutamate antagonist, m-OMe-MPEP. The most active derivative ***77***, (MMG22), was obtained by simple coupling of the immediate precursors ***75*** and ***76***, *Scheme 2.26*. When administered intraspinally to the rodents, ***77*** showed the highest analgesic activity, compared to other ligands in the series. The observed potency was attributed to the optimal spacer length, as the analogues with shorter or longer spacers were significantly less active or inactive.



Scheme 2.26. Synthesis of a bivalent ligand ***77*** (putative μ-agonist/glutamate-5 receptor antagonist).

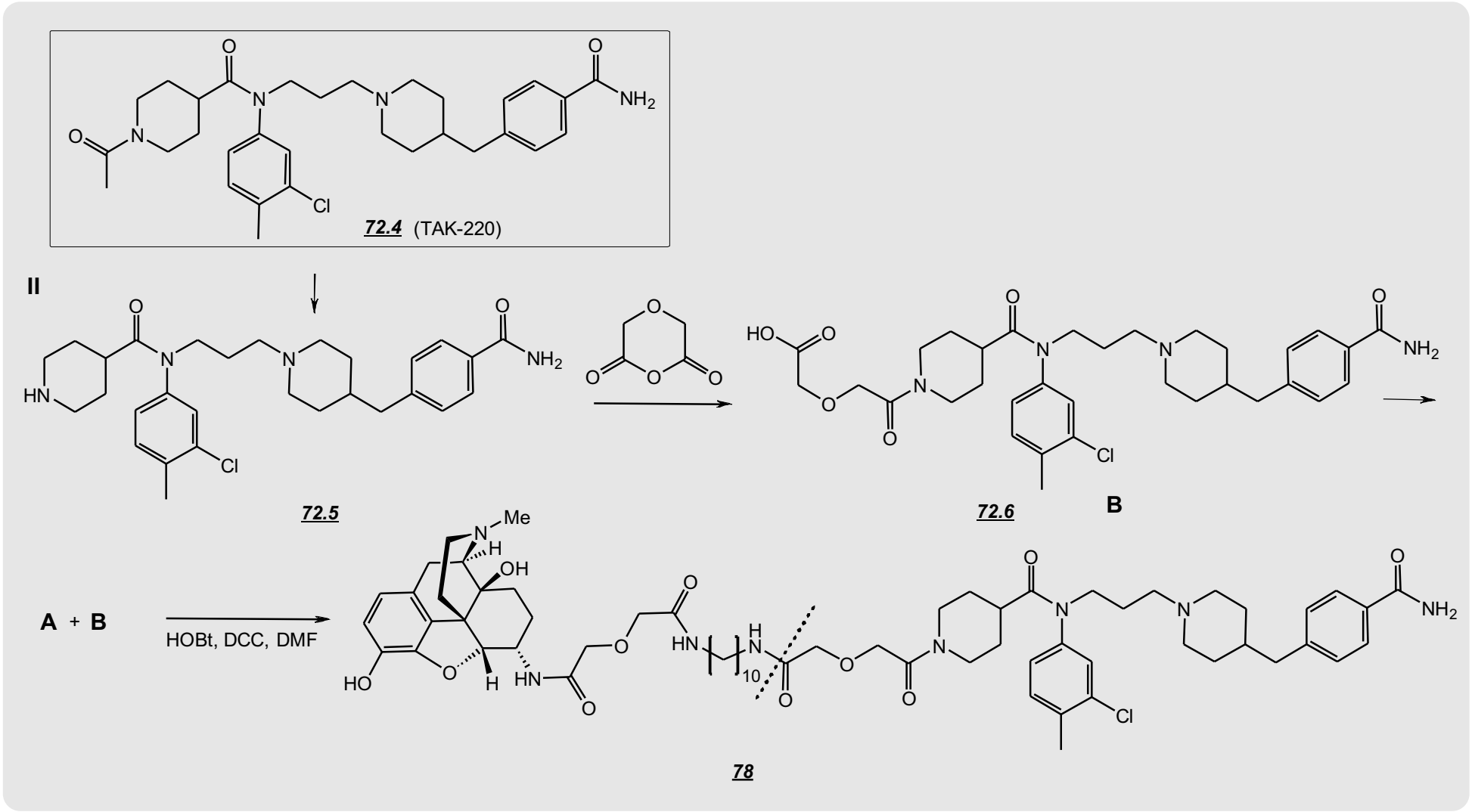
Recent investigations have suggested that μ-opioid receptors also interact with the chemokine receptor CCR5, both i*n vitro* and *in vivo*. Presumably, the release of chemokine (small signalling protein) initiates the receptor-receptor interaction, effectively reducing the analgesic effects of opioid drugs, especially in the treatment of chronic pain.[84]

The observations suggest that a hypothetical heteromer consisting of the μ-opioid receptor and chemokine receptor CCR5 may exist *in vivo*, located in the neuron regions responsible for the pain processing. To explore the possibility, the authors prepared a series of homologous bivalent ligands, consisting of the opioid agonist ***72***, the antagonist of CCR5 receptor and the linear spacers of various lengths, connecting the two pharmacophores. (The antagonist ***72.5*** was a derivative of the known compound ***72.4*** i.e. TAK-220). Also, monovalent ligands were prepared as controls.[84] The synthesis (analogous to those presented in *Scheme 2.25* and *Scheme 2.26*), involved connecting the two pharmacophores, via linear spacers, *Scheme 2.27* and *Scheme 2.28*. The agonist part A (structure ***72.3***), *Scheme 2.27* and the antagonist part ***72.6*** (structure B, *Scheme 2.28*) were prepred separately, then linked together, via the amide bond, into the bivalent ligand ***78***.



Scheme 2.27. Synthesis of bivalent ligand ***78***. Synthesis of agonist part (structure A).

The antagonist part was derived from the previously known CCR5-antagonist, compound ***72.4*** (TAK-220), by replacing the acetyl group with the linker residue, structure ***72.6*** i.e. B, *Scheme 2.28*. The direct coupling of A and B then afforded the final bivalent ligand ***78***.



Scheme 2.28. Synthesis of bivalent ligand ***78***. Synthesis of the antagonist part (structure B) and coupling of fragments A and B.

Pharmacological tests revealed that the compound ***78*** (*Scheme 2.28*), elicited the exceptional *in vivo* analgesia, some 2000 times greater than morphine, when given intrathecally (into the spinal canal). Also, it was about 3500 more potent than a mixture of the control monovalent ligands (i.e. μ-agonist and CCR5 antagonist). The results support hypothesis that μ-opioid/CCR5 heteromer may actually exist *in vivo*, representing a potential, novel target in the treatment of chronic pain.

In addition to the extensive pharmacological tests, theoretical modelling and simulations were also in agreement with the proposed heteromer. Docking studies, using X-ray crystallographic structures of μ-opioid receptor-antagonist complex and CCR5 receptor-antagonist complex, revealed that a suitable bivalent ligand can simultaneously bind to the receptor heteromer. The binding would concomitantly activate the μ-opioid receptor and inhibit the CCR5 receptor, thus potentiating the analgesic action. The calculated structure of the proposed μ-opioid/CCR5 heteromer complexed to bivalent ligand ***78***, is represented in *Fig.2.23.* (The 3D model and the images were prepared for the present treatise, to approximate the geometry calculated in the original reference.).[84]

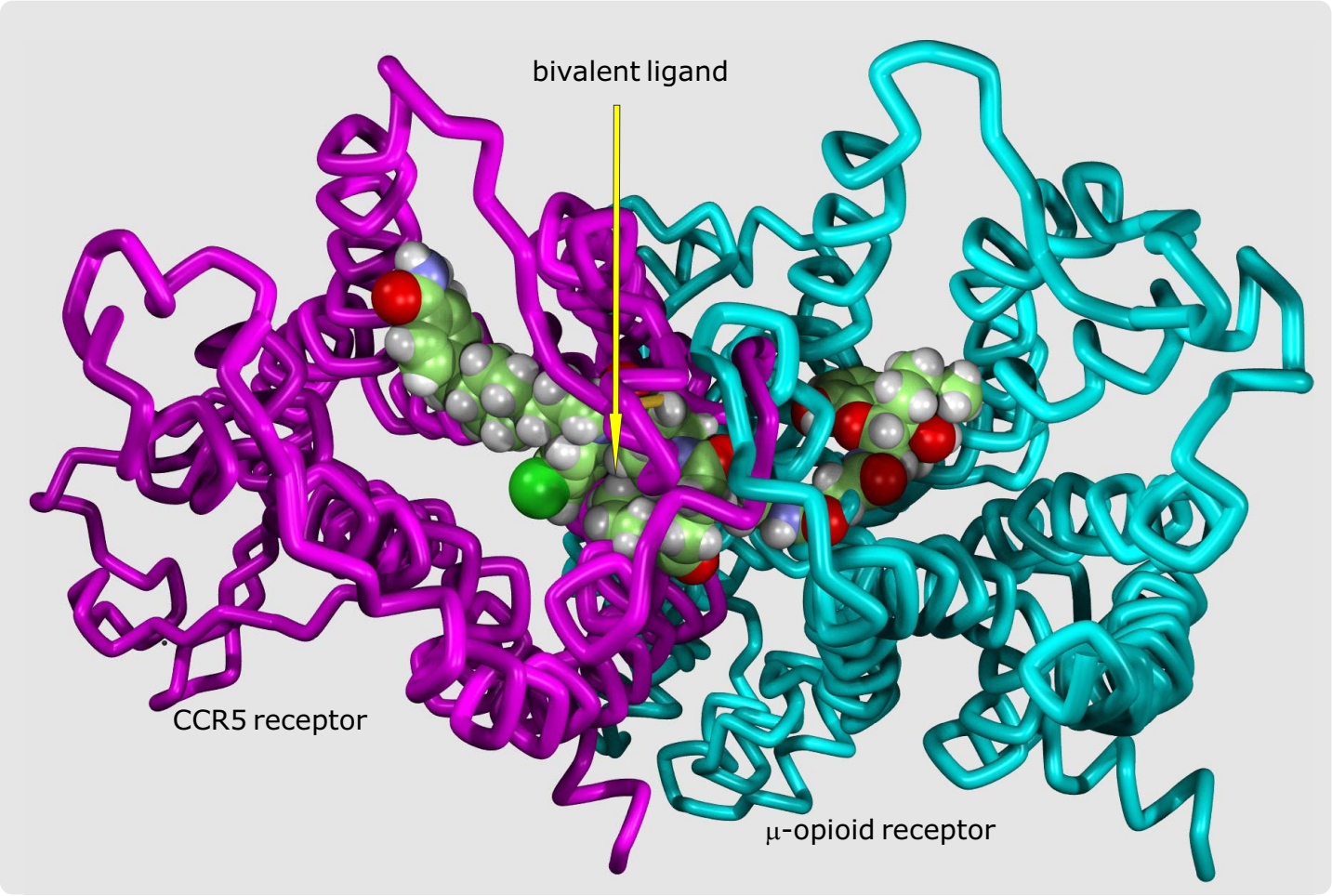


Fig.2.23. Calculated structure of μ-Opioid/CCR5 heteromer receptor in complex with bivalent ligand ***78.***

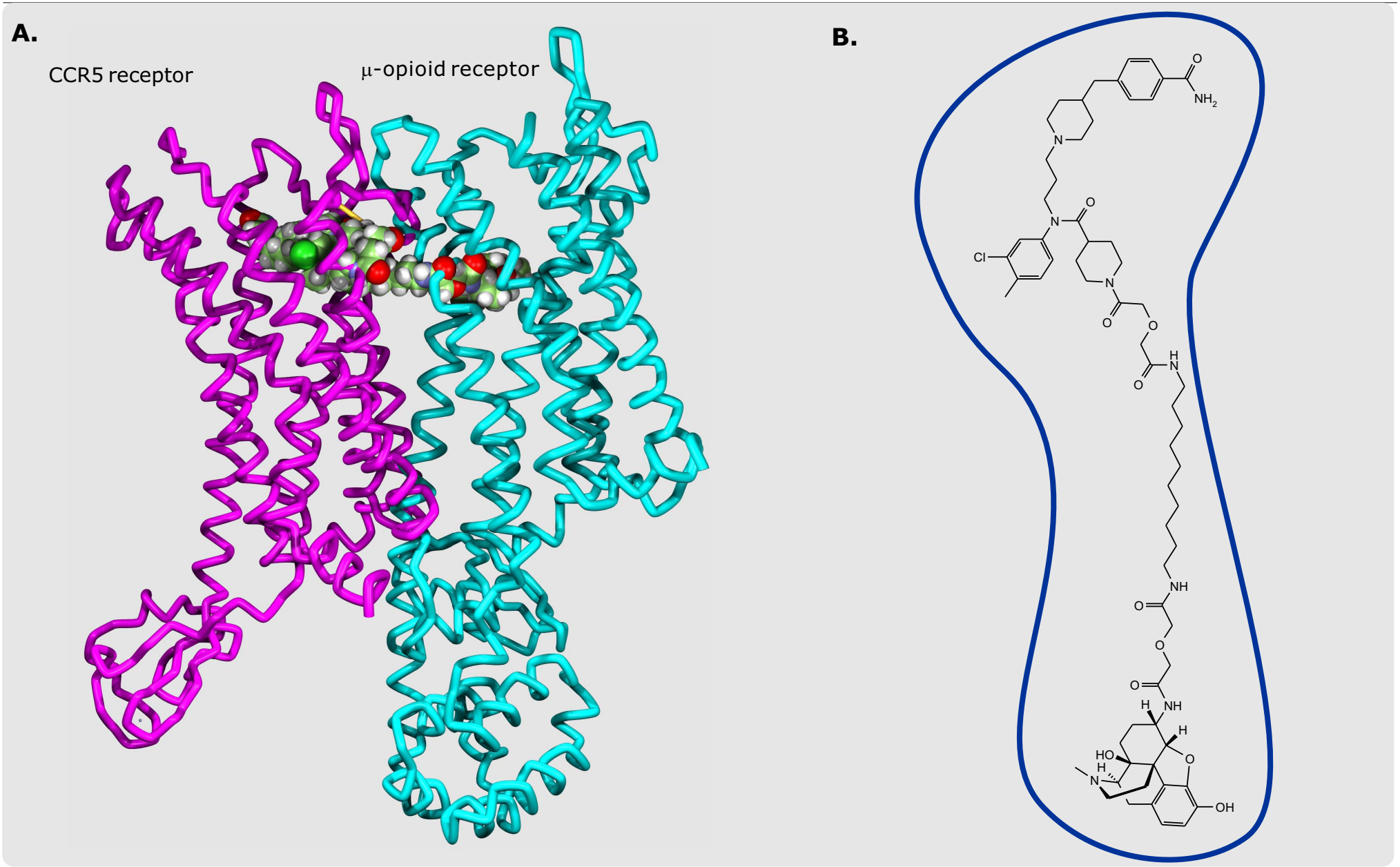


Fig.2.24. A: Horizontal projection of the heteromer-ligand complex from *Fig. 23.* B: Simplified 2D schematic representation of the ligand ***78*** inside the heteromer (adapted from the original publication).

2.13. Total syntheses of morphine alkaloids.

As already discussed, the chemistry and structure of morphine alkaloids have been investigated since the second half of the 19th century. Early research was mainly directed towards discovering derivatives with higher potency and/or less side effects (heroin was probably the first, highly active morphine derivative). Also, numerous studies attempted to elucidate the structure of morphine scaffold. Only the chemical transformations were available for the task, as no instrumental methods existed at the time. Finally, the correct constitutional formulas of morphine alkaloids were deduced by Robinson and Gulland in 1923-25.[85] Further investigations revealed the relative stereochemistry,[86] confirmed by the first total synthesis in 1952.[87] First X-ray analysis of the morphine derivative (+) laudanosine implied the absolute configuration common to all morphine alkaloids.[88] Subsequent X-ray of morphine hydroiodide dihydrate confirmed the constitution, the absolute configuration and provided an approximate 3D structure.[89]

Historically, the main interest in total synthesis of various natural products, including morphine alkaloids, was to prove the structure of a molecule, through the rationally designed synthetic approach. However, advances in instrumental methods (X-ray, NMR and MS), enabled that the relative and absolute structure of almost any molecule can be determined accurately and expediently. (The crystalline structures obtained by X-ray diffraction are published in open-access databases).[90,91] Consequently, the proof of the structure by total synthesis has long lost significance. Nevertheless, contemporary total syntheses in general, including the syntheses of morphine alkaloids, represent a highly significant part of organic chemistry. They constantly advance our knowledge in novel synthetic strategies, reactions and mechanisms.

The other important aspect of total syntheses is the preparation of new analogues of natural products, not accessible through the semi-synthesis. Many potent opioids, structurally related to morphine alkaloids (e.g. various morphinanes), were prepared by the total synthesis. The unnatural enantiomers of morphine alkaloids, as well as various diastereomers can only be obtained by total synthesis. Such compounds are of particular interest in pharmacological studies, since they provide valuable insights into structure-activity relationship (SAR).

Finally, the industrial-scale syntheses could be developed for the drugs like morphine, currently obtained only from the biological sources . However, in that respect, present-day synthesis usually cannot compete with the biosynthesis in terms of yields, purity, stereoselectivity and the overall cost.

The total syntheses of morphine alkaloids illustrate the problem. Since the first one,[87] more than 30 syntheses of morphine alkaloids, involving quite diverse strategies, have been published (as of 2016).[92] As explained previously, the morphine alkaloids can only be obtained from the several species and strains of the poppy, as there are no other natural sources.

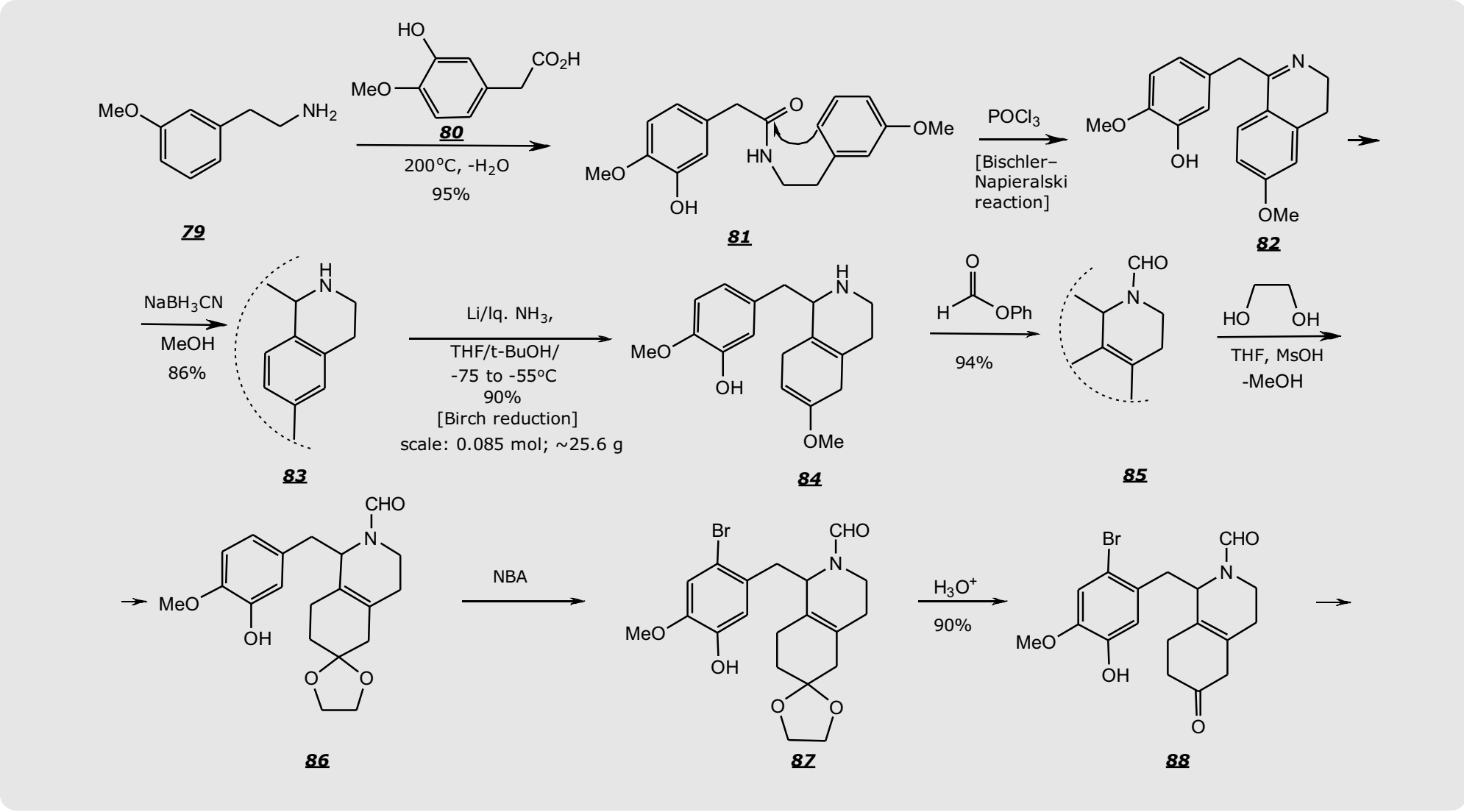
It has long been argued that a potential unavailability of the opium poppy, either because of the climatic changes or other factors, could result in critical shortages of the morphine alkaloids. The argument was also a driving force behind the attempts to develop the industrial-scale, total synthesis of morphine alkaloids. However, all of them proved futile.

Several recent, comprehensive analyses of all the published syntheses concluded that commercial total syntheses of morphine alkaloids will not be feasible in a foreseeable future, due to the fundamental limitations of the current organic synthesis. As noted by Hudlicky, "The interest in this fascinating molecule will no doubt continue, yet a truly practical synthesis of the title alkaloid still remains a distant dream.[29]

In this treatise, the total syntheses of morphine alkaloids are illustrated by three examples, representing the continuing and extensive efforts in this subject. The syntheses, published in 1980, 1997 and 2016 respectively, reflect the enormous advances in synthetic organic chemistry, during the past four decades.

The communication, published by Rice in 1980,[93] presented a formal synthesis of morphine and its derivatives, since it afforded (±)-nordihydrocodeinone ***91***, a morphinane previously shown to be the precursor of (±) morphine (*Schemes 2.29* and 2.*30*). The synthesis was also significant, since it was performed on a multigram scale, although the amount of the final product was not reported. (Other syntheses were on the mmol scale).

The synthesis started with the thermal condensation of phenethyl amine ***79*** and phenylacetic acid ***80***, providing amide ***81***, on 0.35 mol scale, *Scheme 2.29*. The amide was a suitable substrate for the Bischler-Napieralski-type cyclization in the presence of $POCl_3$. The resulting cyclic imine ***82*** was easily reduced to isoquinoline derivative ***83***. In the next step, it was possible to selectively reduce the condensed aromatic ring only, applying low-temperature Birch reduction. Vinyl ether ***84*** was obtained on a preparative scale (0.085 mol, ~26 g), indicating attempt to achieve a practical synthesis of morphine derivatives. After protecting the piperidine nitrogen by *N*-formylation (structure ***85***), vinyl ether was converted to the cyclic acetal ***86***, under typical acid-catalysed conditions, analogously to transacetalization. (The step was necessary, since vinyl ether would react during the bromination of the aromatic ring. Likewise, the free keto group would also react). The aromatic bromination was used to block the reactive position para to OH group, which would otherwise react in the following steps. The regioselective bromination of the highly reactive aromatic ring was achieved using *N*-bromoacetamide (other reagents would likely produced mixtures. Mild acid hydrolysis liberated the keto group, providing ***88*** as a suitable substrate for Grewe-type cyclization, *Scheme 2.30*.

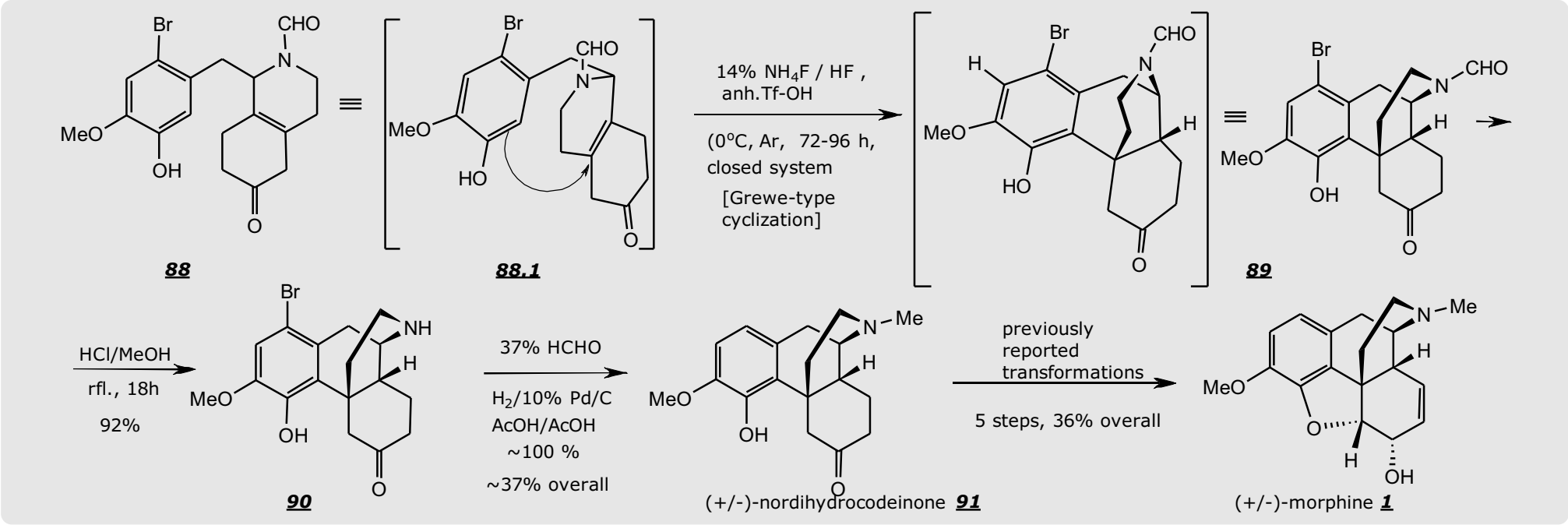


Scheme 2.29. Formal synthesis of (±) morphine by Rice (part 1).

Mechanistically, Grewe-type cyclization is an intramolecular electrophilic aromatic substitution, with the double bond serving as an electrophile. However, under the general acidic conditions, various products usually arise, thus requiring the carefully optimized conditions.

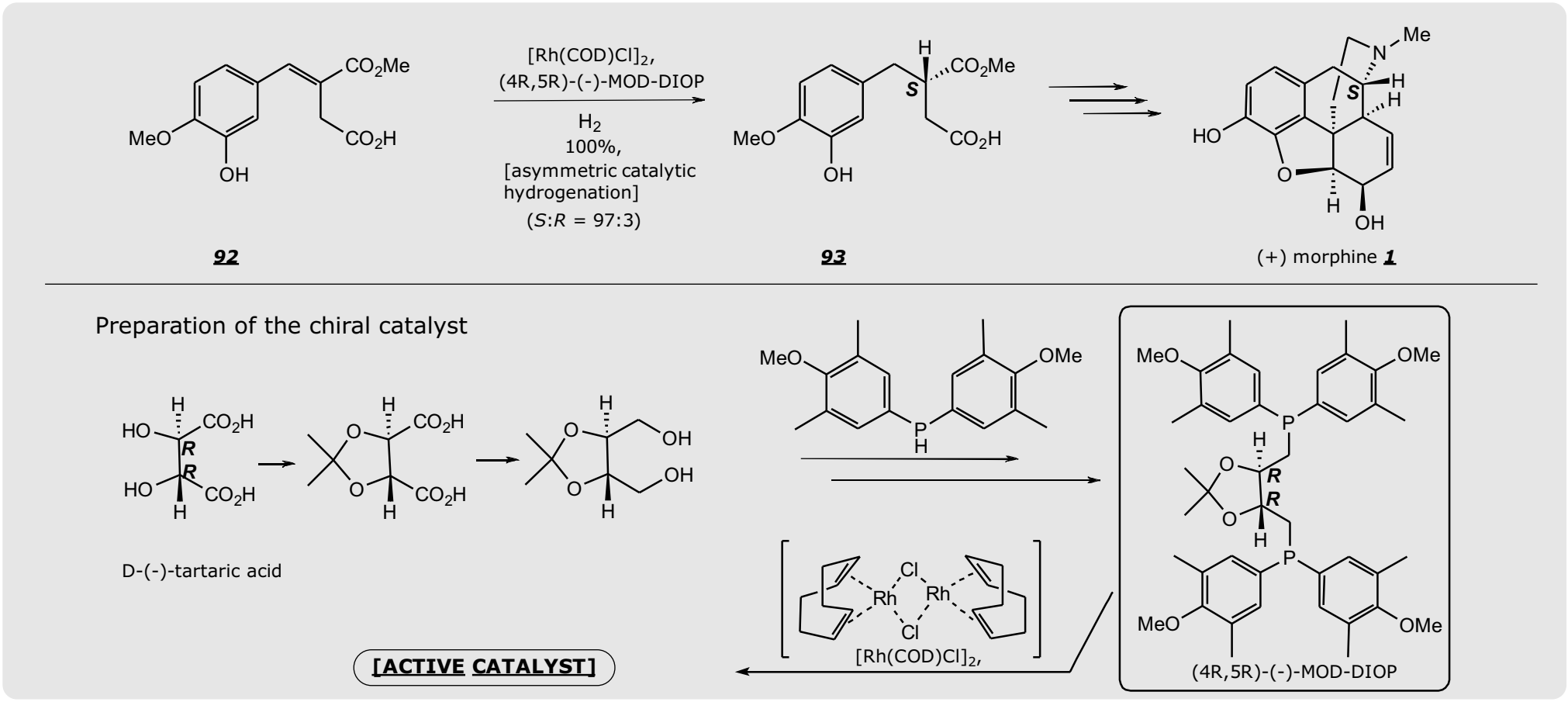
Previous experiments revealed that the cyclization proceeds in acceptable yields, using anh. triflic acid as a solvent, in the presence of NH_4F/HF mixture. After running the reaction for 3-4 days at 0°C, the expected product ***89*** was obtained in ~60% yields (scale not reported). The final steps included vigorous acid-catalysed formamide hydrolysis to piperidine ***90***, followed by two transformations combined in one operational step. Thus, hydrogenation in the presence of formaldehyde, resulted in the *N*-methylation (reductive methylation via iminium ion intermediate), while hydrogenolysis cleaved the aromatic C-Br bond. The desired morphinane, (±)-nordihydrocodeinone ***91*** was obtained in 10 operational steps (37% overall yield, the scale not reported), *Scheme 2.30*. The compound can be converted into morphine in five additional steps, reported previously. The synthesis is relatively concise, operationally not too complex and performed at a considerable scale (at least some steps). Nonetheless, the synthetic morphine obtained via this procedure, would have been immensely more expensive than the natural one (possibly two to three orders of magnitude if not more). In addition, it provides the racemic morphine, while the unnatural enantiomer, i.e. (+) morphine is inactive as analgesic.

Thus, the synthesis, like all the others, has only academic significance.



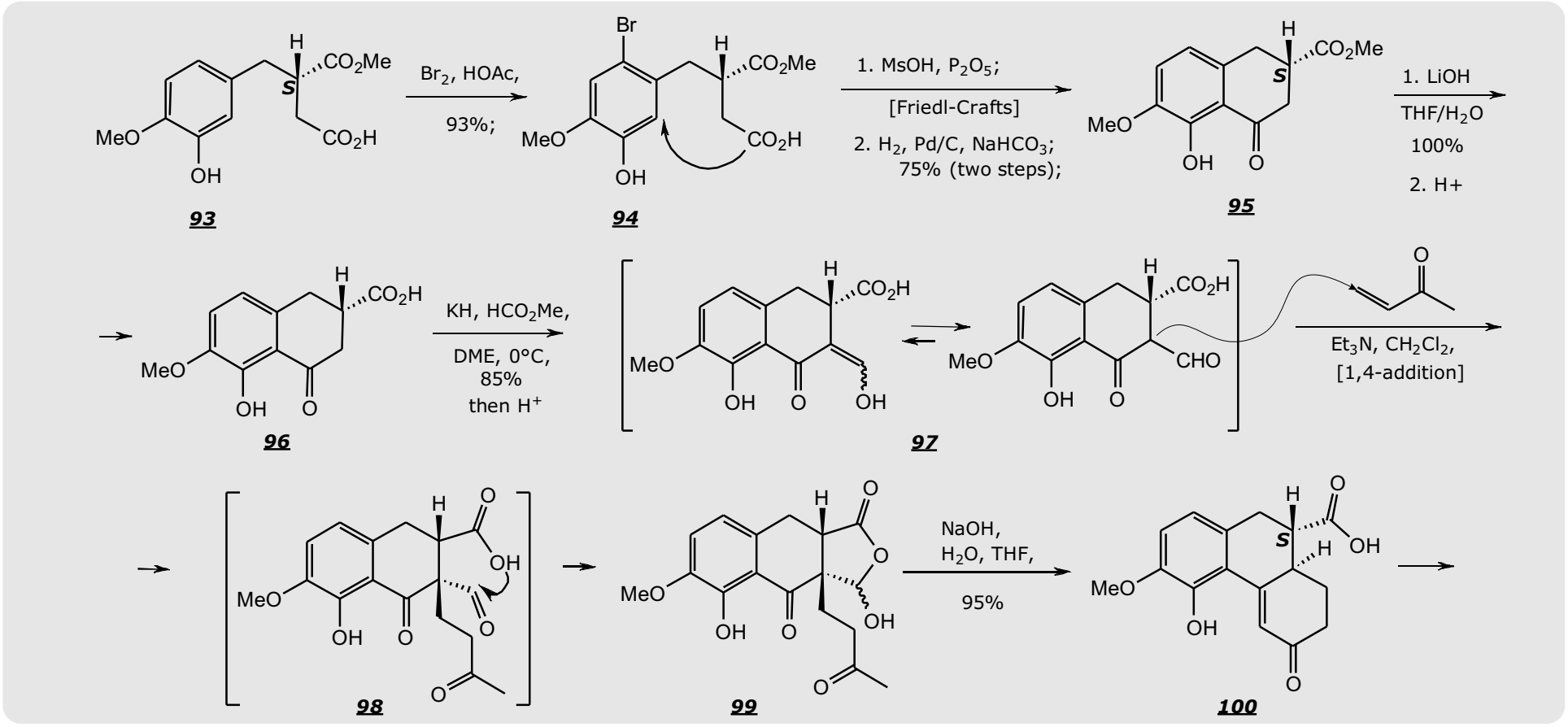
Scheme 2.30. Formal synthesis of (±) morphine by Rice (part 2).

The total asymmetric synthesis of (+) morphine, disclosed by White at. al, in 1997,[94] considered the phenanthrene ring system as a central structural motif in the construction of morphine scaffold. The synthesis was accomplished in 28 steps, affording the unnatural, (+) morphine in the total yield of 3%, *Scheme 2.31* to *Scheme 2.36*. The starting compound ***92*** was obtained by Stobbe condensation of isovaniline and dimethyl succinate. Asymmetric catalytic hydrogenation of the conjugated double bond quantitatively provided the chiral succinate ***93***, in high optical purity (S/R=97/3). The obtained chiral centre was retained throughout the synthesis and used to effectively induce all other chiral centres, formed at various stages of the synthesis, *Scheme 2.31*. The chiral hydrogenation was achieved using homogeneous, rhodium-based catalyst with the chiral ligand. The chiral phosphine ligand, (4R,5R)-(-)-MOD-DIOP, was prepared acc. to the previously published procedure, starting from D-(-) tartaric acid.



Scheme 2.31. Asymmetric Total Synthesis of unnatural (+) morphine (part 1).

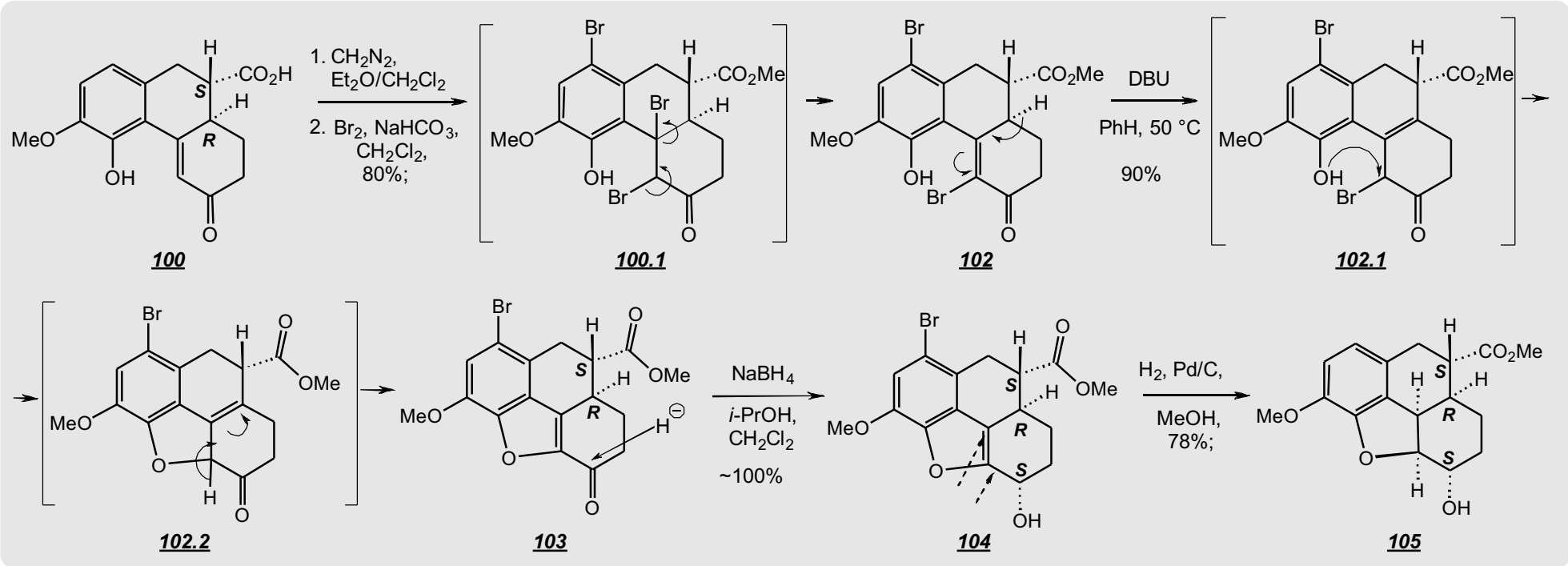
The selective p-bromination gave ***94*** and forced the intramolecular Friedl-Crafts acylation in the o-position, *Scheme 2.32*. (Otherwise, p-position was acylated). The obtained cyclohexanone ring corresponded to the ring B in the morphine scaffold. Catalytic hydrogenolysis removed bromine, followed by the selective ester hydrolysis to the acid ***96***. The hydrolysis was necessary, since the ester group in ***95***, when exposed to KH, gave enolate anion and the racemization. The next stage was the construction of the ring C, achieved by the Robinson annulation. It involved three steps, starting with α-formylation of the keto group in ***96***. The formylated ketone ***97***, mainly in enol form, reacted quantitatively and diastereoselectively with methyl-vinyl ketone, via Michael-addition, providing the stable lactol ***99***. The correct configuration at the new stereocenter (***R***), was induced by the existing stereocenter, and also aided by the conformational rigidity of the reactant ***97***, *Scheme 2.32*.



Scheme 2.32. Asymmetric Total Synthesis of unnatural (+) morphine (part 2).

Exposing lactol ***99*** to aqueous hydroxide resulted in the intramolecular aldol condensation, while the formyl group cleaved spontaneously. Cyclohexenone ring in ***100*** corresponds to the morphine C ring, *Scheme 2.32*.

In the next stage, furan ring was added to the scaffold, using the previously developed protocols, *Scheme 2.33*. After protecting the carboxyl group as methyl ester, addition of Br_2 gave the unstable intermediate ***101.1*** which spontaneously transformed into α-bromo enone ***102***. (Aromatic p-bromination proceed concomitantly). In the presence of DBU, ***102*** furnished furan ***103***. The spontaneous transformation likely involved base-catalyzed double bond isomerization, followed by the intramolecular S_N2 substitution and the second double bond migration, via unstable intermediates ***102.1*** and ***102.2***. Significantly, the configuration at both stereocenters of ***103*** was retained. The stereocenters and the rigidity of the molecule exerted a high degree of the strereocontrol in the next two steps. Thus, the sodium borohydride reduction gave only ***S***-alcohol ***104***, followed by the selective hydrogenation of double bond from the side indicated by the arrows. Simultaneously, hydrogenolysis removed the aromatic bromine, structure ***105***, *Scheme 2.33*.



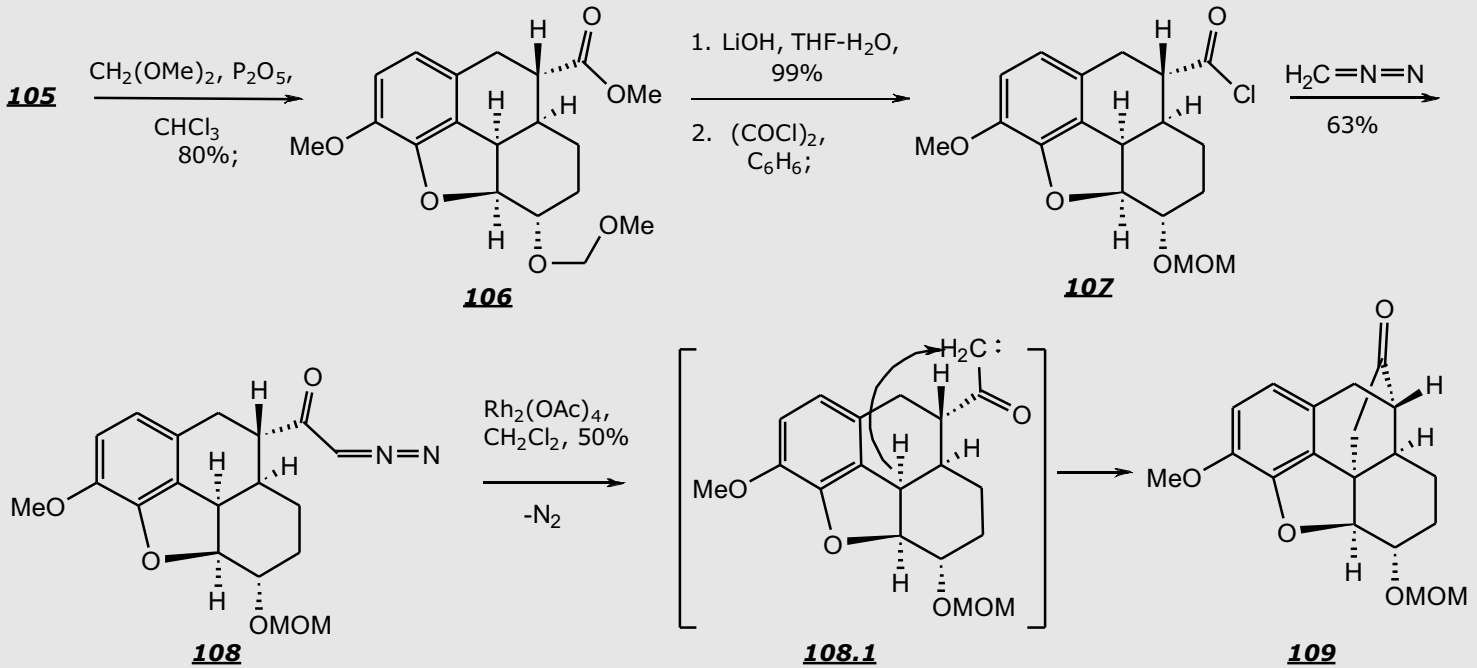
Scheme 2.33. Asymmetric Total Synthesis of unnatural (+) morphine (part 3).

Thus, the two consecutive transformations introduced three new stereocenters, all with the correct configuration (opposite to that in the natural morphine), *Scheme 2.33*.

After protecting the hydroxyl group as MOM ether ***106***, the carbomethoxy function was converted to acid chloride ***107***, *Scheme 2.34*. Direct acylation with diazomethane provided the requisite diazo ketone ***108*** (potentially a highly hazardous operation). The compound was an immediate precursor in the two key transformations, leading to the formation of the last segment of the morphine scaffold, the bridged piperidine ring.

The first transformation involved catalytic decomposition of the diazo group, providing reactive carbenoid intermediate ***108.1***. (The catalyst was Rh (II) cation, i.e. rhodium acetate dimer). As anticipated, the carbenoid ***108.1*** reacted intramolecularly, forming a new C-C bond through C-H bond insertion. The main product, bridged cyclopentanone ***109***, was obtained in modest yields (~50%, 0.13 mmol scale), together with various side products (~30%), *Scheme 2.34*.

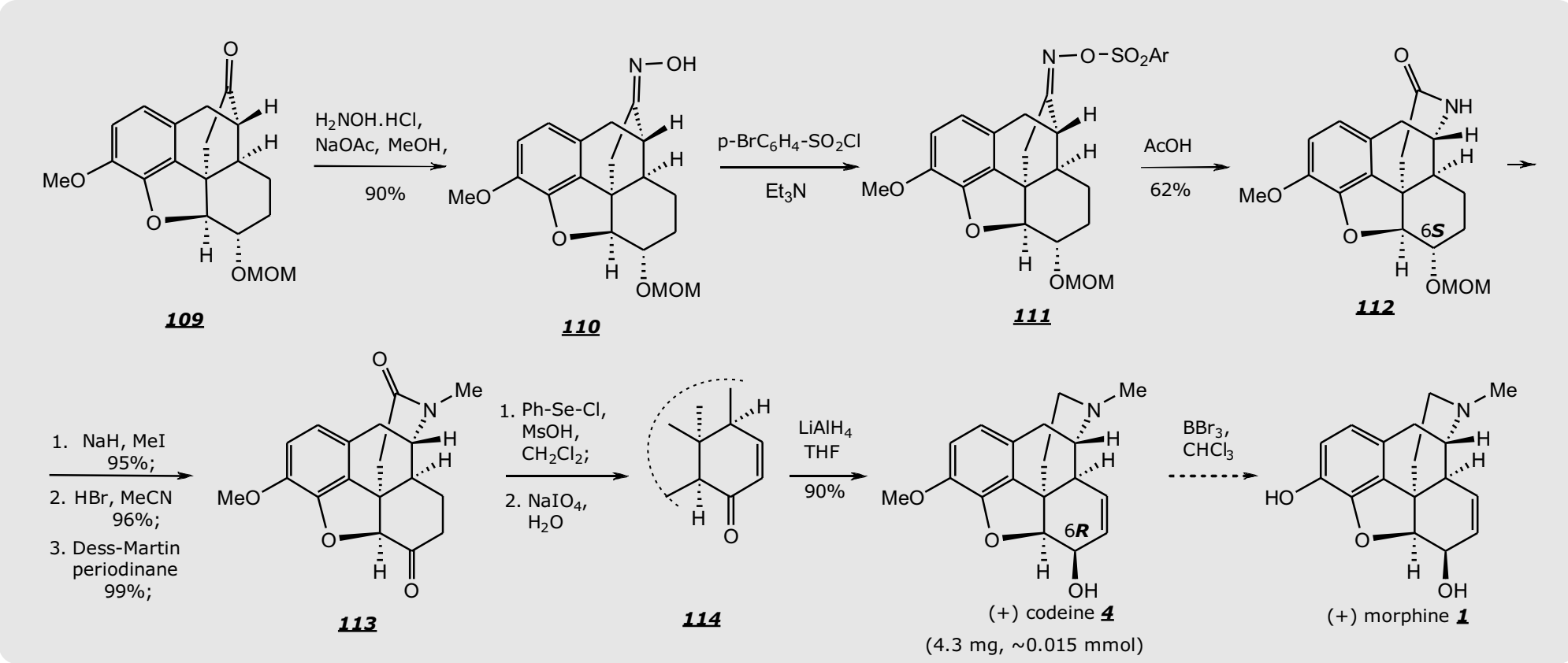
The second transformation was Beckmann rearrangement of ***109*** to the δ-lactam ***112***. It required two steps, since the oxime ***110*** failed to rearrange, *Scheme 2.35*. However, the rearrangement of brosylate ester ***111*** proceeded under mild conditions, affording the required δ-lactam ***112***. The remaining synthetic stages involved established transformations of the functional groups and proceeded as expected.



Scheme 2.34. Asymmetric Total Synthesis of unnatural (+) morphine (part 4).

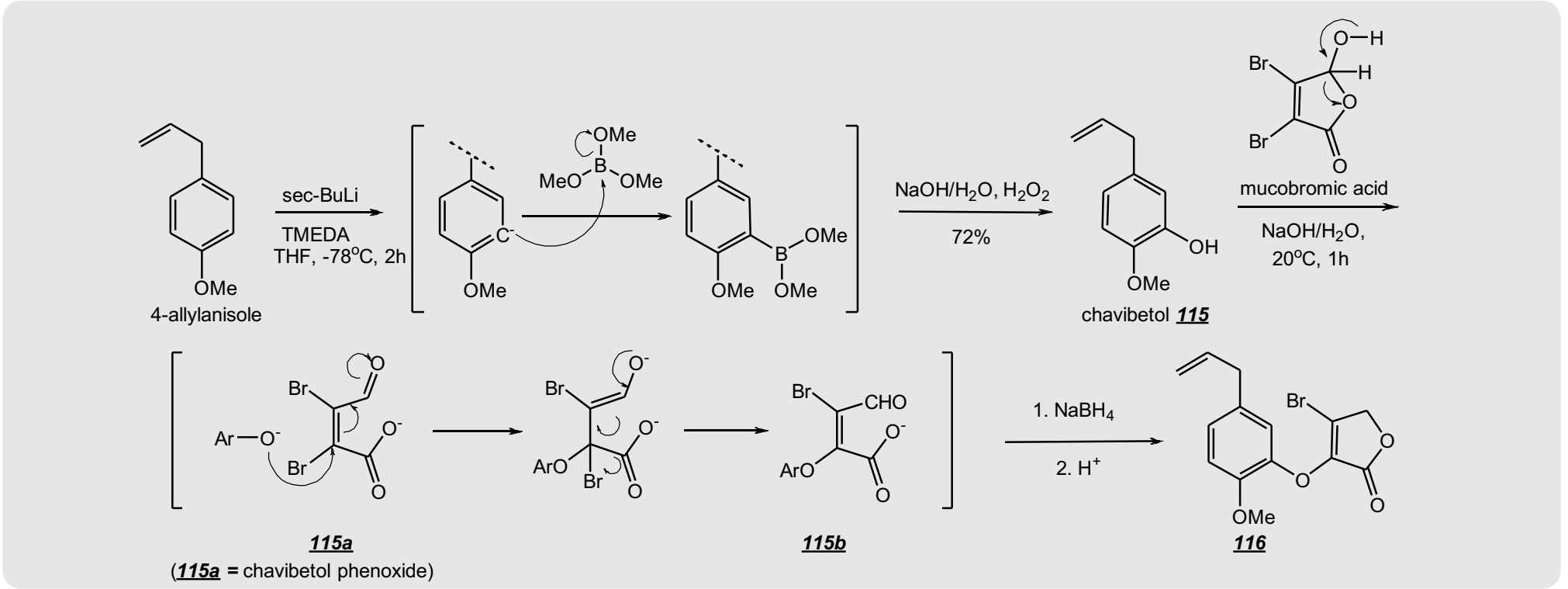
After *N*-methylation of lactam ***112*** and the removal of the MOM protecting group, the hydroxyl group was oxidized to ketone ***113***, using Dess-Martin periodinane, *Scheme 2.35*. The enone function in ***114*** was introduced by α-phenylselenylation of the carbonyl group, followed by the oxidative elimination. In the final step, the lactam and enone functions were reduced simultaneously with LAH, to (+)-codeine ***4***. The transformation followed the expected course, providing the piperidine ring and 6***R*** allyl alcohol.

It was known from the previous work that the 1,2 enone reduction of morphine alkaloids proceeded from α-face. Thus, conversion of ***112*** to ***4*** resulted in the configuration inversion at the possition 6. The obtained (+)-codeine ***4*** was not converted to (+) morphine ***1***, since the transformation was published previously. As already noted (Chapter 1), the unnatural codeine and morphine enantiomers have no analgesic properties.

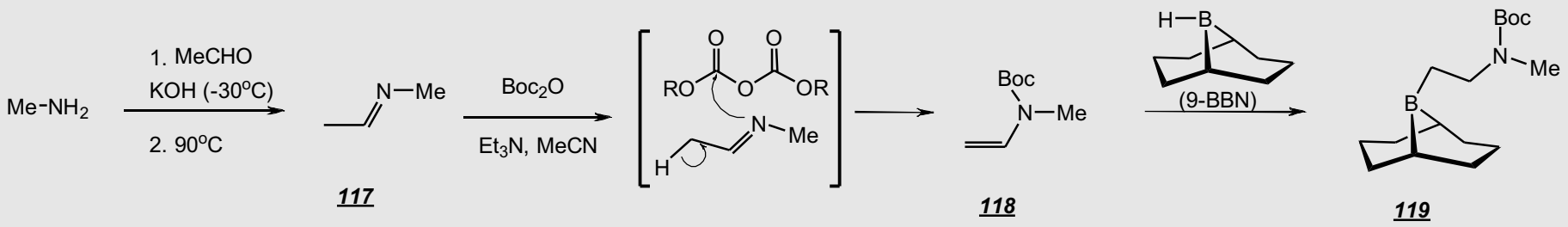


Scheme 2.35. Asymmetric Total Synthesis of unnatural (+) morphine (part 5).

A very recently published total synthesis of (±) morphine ***1***, adopted a radically novel strategy, by assembling rings B and C of the morphine scaffold in a cascade ene–yne–ene ring closing metathesis.[95] The piperidine ring, as a final part of the scaffold, was introduced by the intramolecular 1,6 aza Michael addition. The synthesis involved 9 "one pot" stages or 15 discrete steps, with the overall yield of 6.5% (8.6 mg). Since only the natural (-) morphine is an active opioid, the yield of that enantiomer is 3.25% (~4 mg), comparable to other recent total synthesis. The synthesis started from the natural product chavibetol ***115***. The compound can be prepared from 4-allylanisole, in "one pot" procedure, combining ortho metalation, aryl boronation and alkaline peroxide oxidation, *Scheme 2.36*. The reaction of chavibetol phenoxide ***115a*** and mucobromic acid provided butyrolactone ***116*** in three steps. The first step probably proceeded acc. to the shown mechanism, (intermediates ***115a*** and ***115b***), followed by the reduction of aldehyde ***115b*** (not isolated) and acid-catalyzed lactonization.

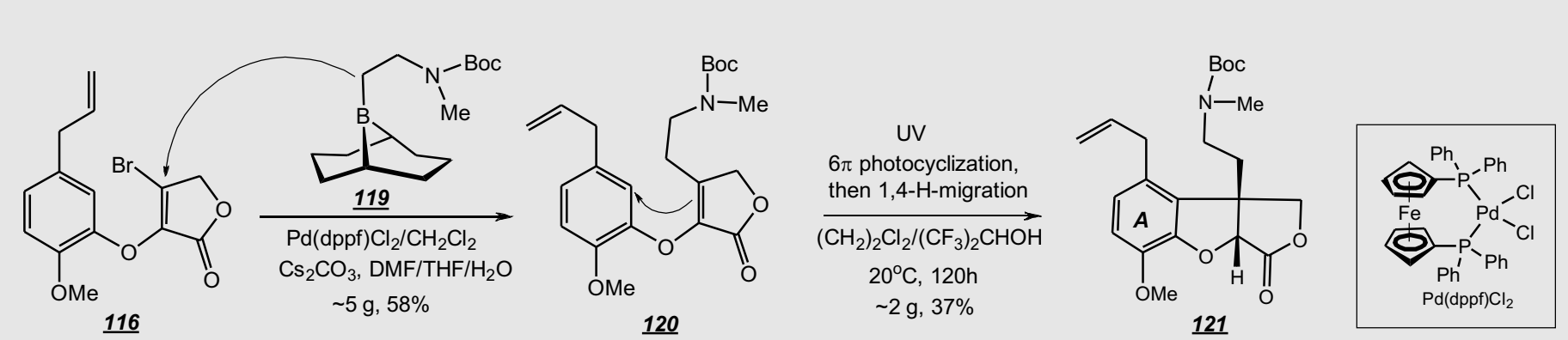


Scheme 2.36. A Cascade Strategy to (±) Morphine (part 1).



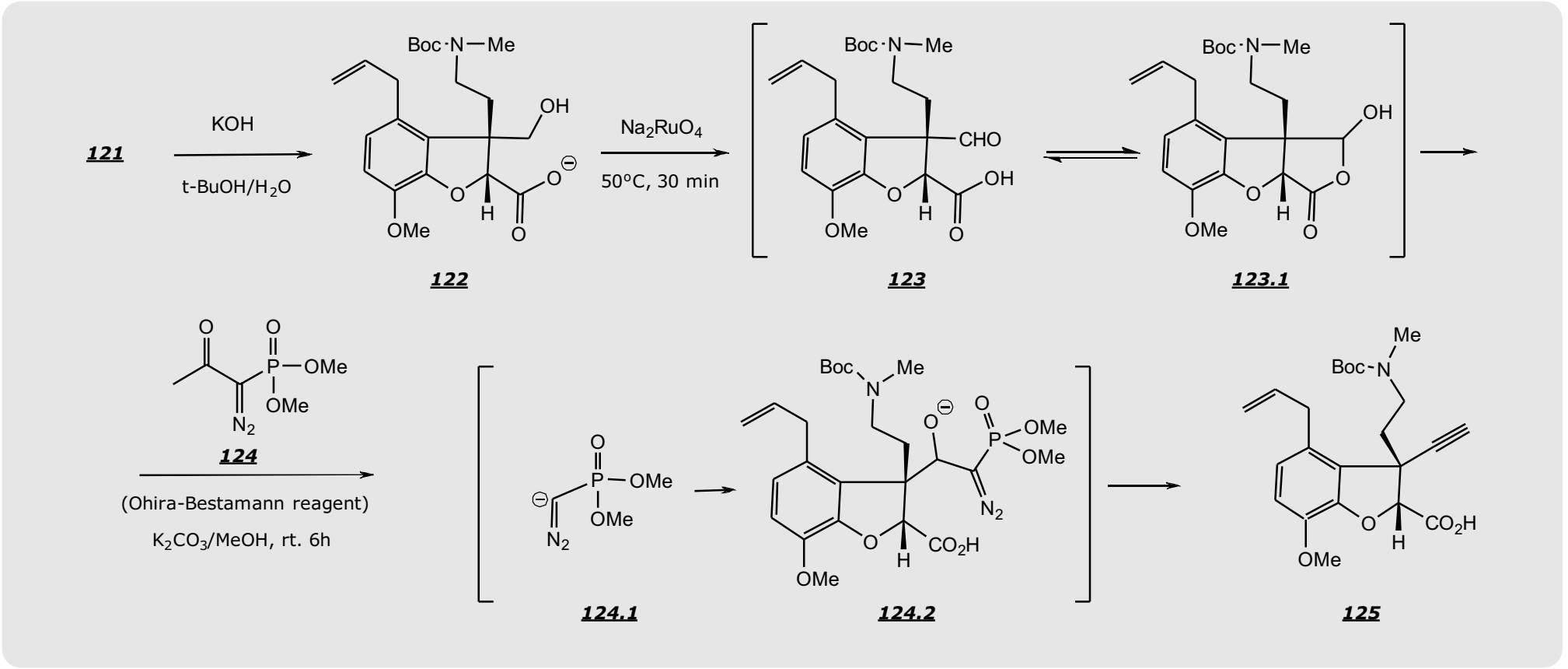
Scheme 2.37. A Cascade Strategy to (±) Morphine (part 2).

Separately, *N*-acylation of the aldimine ***117*** with Boc_2O provided enamide ***118***. The expected regioselective addition of 9-BBN to the double bond gave the requisite borane ***119***, *Scheme 2.37*.Suzuki-Miyaura reaction of borane ***119*** and vinyl bromide ***116*** established a new carbon-carbon bond, involving sp2-sp3 coupling, structure ***120***, *Scheme 2.38*. The reaction required extensive optimization, including examination of the various catalysts, solvents and bases. Next, a known photocyclization, provided the required benzofuran ***121***. (After 5 days of the irradiation, the yield was only 37%). The reaction involves 6π-photo-electrocyclization, followed by a concerted 1,4-hydrogen shift. Thus, the two consecutive steps, established two rings of the morphine scaffold, structure ***121***.

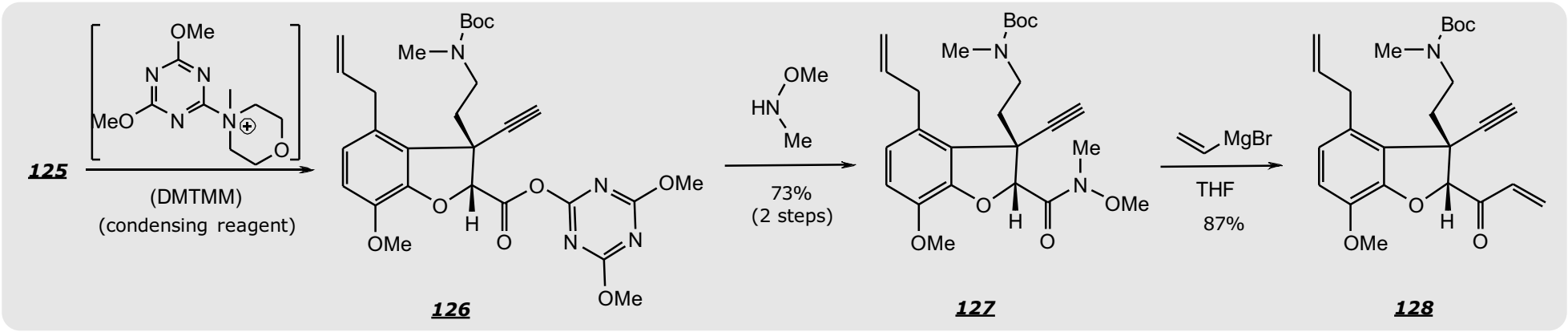


Scheme 2.38. A Cascade Strategy to (±) Morphine (part 3).

The compound ***121*** was elaborated to the next key intermediate, benzofuran ***125***, via standard transformations of the functional groups. The selective sodium ruthenate oxidation afforded aldehyde ***123*** in equilibrium with lactol ***123.1***, *Scheme 2.39*. Then, the aldehyde group was converted to alkyne ***125*** using Ohira-Bestmann reagent ***124*** ((1-diazo-2-oxopropyl)-phosphonic acid dimethyl ester). The known reaction mechanism is represented by the structures of two intermediates, ***124.1*** and ***124.2***. Transformation of the carboxyl group in ***125*** to the enone function in ***128*** was achieved via Weinreb amide ***127***, prepared by a standard protocol, *Scheme 2.40*. (The Weinreb amides have been used extensively to prepare ketones from carboxylic acids, since they react with only one equivalent of an organometallic reagent, producing no alcohols). Thus, reaction of ***127*** and vinylmagnesium bromide furnished enone ***128*** in high yields.

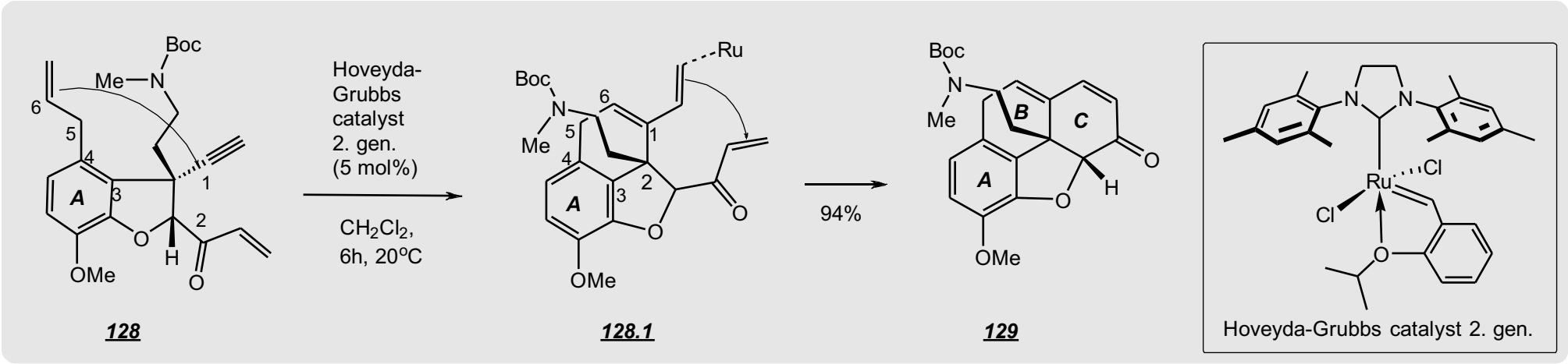


Scheme 2.39. A Cascade Strategy to (±) Morphine (part 4).



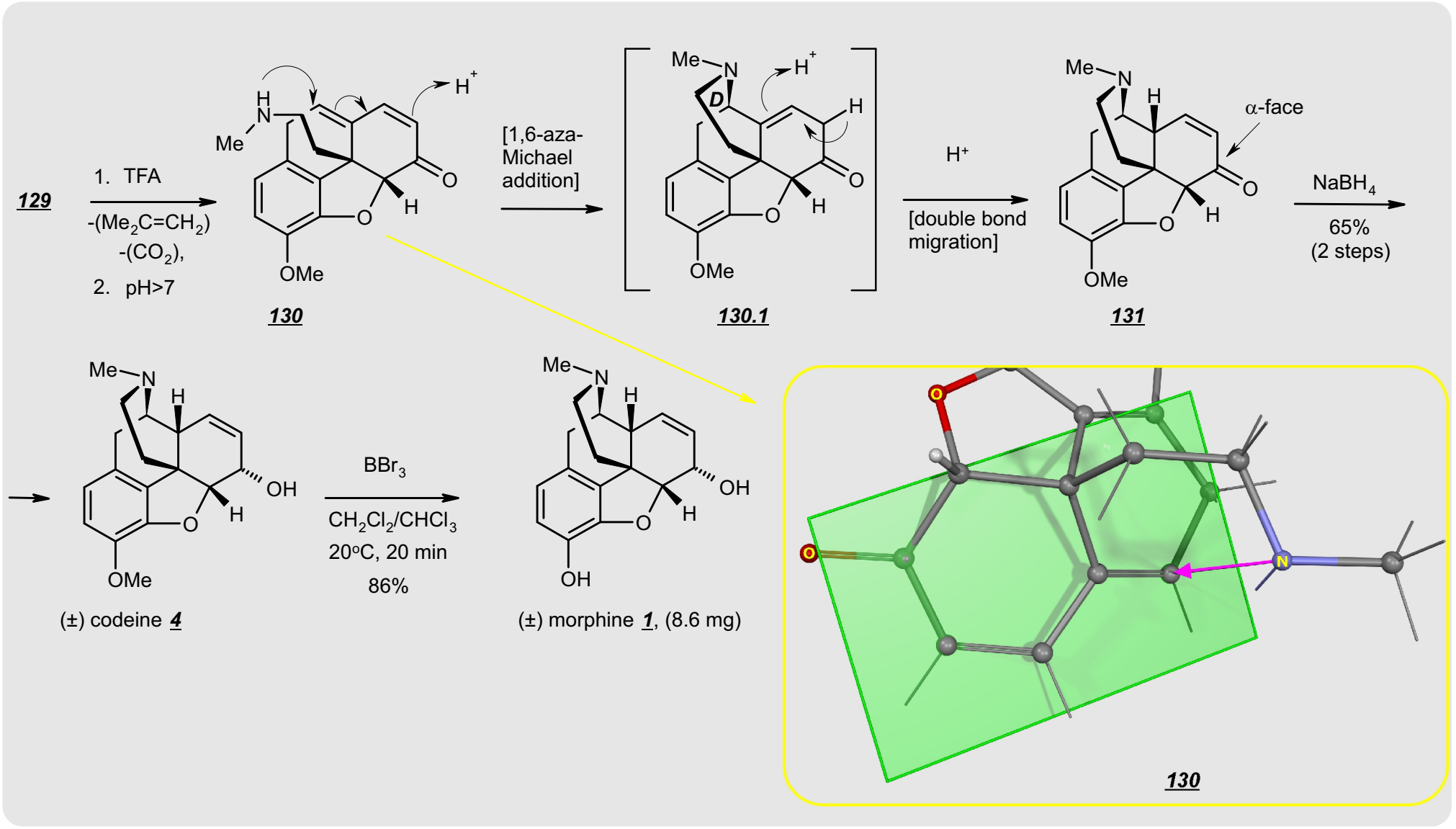
Scheme 2.40. A Cascade Strategy to (±) Morphine (part 5).

The correctly positioned double and triple bonds in ***128*** enabled the intramolecular, cascade ene–yne–ene metathesis. The initial ene–yne metathesis resulted in the formation of ring B, spontaneously followed by ene–ene metathesis and the introduction of ring C. Thus, rings B and C of the morphine scaffold were installed in the single synthetic step, in near quantitative yield, requiring only 5 mol% of Hoveyda–Grubbs 2nd generation catalyst.



Scheme 2.41. A Cascade Strategy to (±) Morphine (part 6)

After deportation of the amino group in ***129***, the morphine scaffold was completed by intramolecular 1,6-aza-Michael reaction of α,β,γ,δ-conjugated dienone ***130***, affording piperidine ***131***. (The intramolecular addition is also shown in 3D, yellow frame). Elaboration of ***131*** in two simple, known transformations, secured (±) morphine on 0.03 mmol scale.



Scheme 2.42. A Cascade Strategy to (±) Morphine (part 7)

2.14. References.

1. J. D. Phillipson, M. F. Roberts, & M. H. Zenk (Eds.), (1985). The Chemistry and Biology of Isoquinoline Alkaloids. Berlin, Heidelberg: Springer Berlin Heidelberg. ISBN-13: 978-3-642-70130-6; DOI: 10.1007/978-3-642-70128-3.

2. Bisset, N. G. (1985). Plants as a Source of Isoquinoline Alkaloids. In J. D. Phillipson, M. F. Roberts, & M. H. Zenk (Eds.), The Chemistry and Biology of Isoquinoline Alkaloids (pp. 1-22). Berlin, Heidelberg: Springer Berlin Heidelberg, DOI: 10.1007/978-3-642-70128-3_1.

3. Brossi, A. (1985). The Chemistry and Pharmacology of Morphinan Alkaloids. In J. D. Phillipson, M. F. Roberts, & M. H. Zenk (Eds.), The Chemistry and Biology of Isoquinoline Alkaloids (pp. 171-190). Berlin, Heidelberg: Springer Berlin Heidelberg, DOI: 10.1007/978-3-642-70128-3_1.

4. ([4.1]) (2001). The Merck Index: An Encyclopedia of Chemicals, Drugs, and Biologicals (13th ed.). NJ: Merck. NOTE: Please search by the compound name.

([4.2]) The Merck Index Online:https://www.rsc.org/Merck-Index/

5. https://www.pharmacopoeia.com/

6. Sandor, B., Csaba, C., & Attila, S. (2009). Recent Developments in the Chemistry of Thebaine and its Transformation Products as Pharmacological Targets. Current Medicinal Chemistry, 16(25), 3215-3242. doi:http://dx.doi.org/10.2174/092986709788803295

7. Alan F. Casy, Robert T. Parfitt (1986) Opioid Analgesics_Chemistry and Receptors. DOI 10.1007/978-1-4899-0585-7 ISBN 9781489905871

8.Vincent, P. G., Gentner, W. A., Küppers, F. J. E. M., & Salemink, C. A. Papaver bracteatum Lindi.: Quantitative Extraction and Determination of Thebaine. Journal of Pharmaceutical Sciences, (1979) 68(1), 87-89. doi:10.1002/jps.2600680127

9. Phillipson, J. D., Scutt, A., Baytop, A., Özhatay, N., & Sariyar, G. (1981). Alkaloids from Turkish Samples of Papaver orientale and P. pseudo-orientale. Planta Med, 43(11), 261-271. doi:10.1055/s-2007-971507

10. Chen, X., Dang, T.-T. T., & Facchini, P. J. (2015). Noscapine comes of age. Phytochemistry, 111, 7-13. doi:http://doi.org/10.1016/j.phytochem.2014.09.008

11.Sharma Preeti, Upadhyay Prabhat, Mishra Shardendu, Sadhu Ananya, Purohit Suresh. Berberine A Potent Substance for Researcher: A Review. World Journal Of Pharmacy And Pharmaceutical Sciences Vol 4, Issue 07, 2015

12. Tony L. Yaksh and Mark S. Wallace. (2011) Opioids, Analgesia, and Pain Management, Ch. 18, 481-525 in Goodman & Gilman's The Pharmacological Basis Of Therapeutics 12th Edition The McGraw-Hill Companies, Inc., ISBN: 978-0-07-176939-6.

13. Yeh SY. Analgesic activity and toxicity of oripavine and phi-dihydrothebaine in the mouse and rat. Arch Int Pharmacodyn Ther. 1981 Dec;254(2):223-40.

14. http://www.incb.org/

15.http://www.incb.org/incb/en/narcoticdrugs/Technical_Reports/narcotic_drugs_reports.html; International Narcotics Control Board, Narcotic Drugs 2015, Narcotic Drugs Estimated World Requirements for 2016 Statistics for 2014 e-ISBN: 978-92-1-057171-5

16. Kapoor L. (1995). *Opium Poppy: Botany, Chemistry, and Pharmacology*. United States: CRC Press. ISBN 1-56024-923-4

17.http://www.fao.org/faostat/en/#data/QC

18. Brook, K., Bennett, J., & Desai, S. P. The Chemical History of Morphine: An 8000-year journey, from resin to de-novo synthesis. Journal of Anesthesia History. doi: 10.1016/j.janh.2017.02.001

19. Klockgether-Radke, A. P. (2002). F. W. Sertürner und die Entdeckung des Morphins. [F. W. Sertürner and the Discovery of Morphine]. Anästhesiol Intensivmed Notfallmed Schmerzther, 37(05), 244-249. doi:10.1055/s-2002-30132.

20. European Monitoring Centre for Drugs and Drug Addiction and Europol (2016), *EU Drug Markets Report: In-Depth Analysis*, EMCDDA–Europol Joint publications, Publications Office of the European Union, Luxembourg.

21. United Nations Office on Drugs and Crime, World Drug Report 2016. eISBN: 978-92-1-057862-2

22. Janos Kabay. Process For Obtaining Opium Alkaloids From Dried Poppy Straw US. 2,009,181 (1935).

23. https://www.unodc.org/unodc/en/data-and-analysis/bulletin/bulletin_1961-01-01_1_page005.html; Istvan Bayer Manufacture of alkaloids from the poppy plant in Hungary (1961).

24. Charles L. Mehltretter and Francis B. Weakley. Solvent Extraction Of Opium Alkaloids US. 2,715,627 (1955).

25. ([25.1]) Anthony John Fist, Christopher James Byrne, Wayne Lyle Gerlach. Papaver Somniferum Strain with High Concentration Of Thebaine And Oripavine. US 6,067,749. (2000).

([25.2]) Anthony John Fist, Christopher James Byrne, Wayne Lyle Gerlach. Production Of Thebaine And Oripavine. US 6,376,221 (2002).

([25.3]) Anthony John Fist, Christopher James Byrne, Wayne Lyle Gerlach. Production Of Thebaine And Oripavine. US 6, 723,894 (2004).

26. Fist, Anthony J. Papaver Somniferum with High Concentration Of Thebaine. WO 2009/109012 (2009).

27. Anthony John Fist, James A.C. Miller, Davina Gregory. Papaver Somniferumwith High Concentration of Codeine. WO 2009/143574 (2009).

28. Abbas Mollataghi, Emilie Coudiere, A. Hamid A. Hadi, Mat Ropi Mukhtar, Khalijah Awang, Marc Litaudon, Athar Ata. *Anti-acetylcholinesterase, anti-a-glucosidase, anti-leishmanial and anti-fungal activities of chemical constituents of Beilschmiedia species*, Fitoterapia, Volume 83, Issue 2, 2012, 298. ISSN 0367-326X, http://doi.org/10.1016/j.fitote.2011.11.009.

29. Uwe Rinner and Tomas Hudlicky Synthesis of Morphine Alkaloids and Derivatives Top Curr Chem (2012) 309: 33–66, DOI: 10.1007/128_2011_133. Springer-Verlag Berlin Heidelberg.

30.SciFinder search performed on 24. 04 2017.

31.http://www.wipo.int/treaties/en/text.jsp?file_id=283854

32.https://www.justice.gov/sites/default/files/usao/legacy/2009/12/10/usab5705.pdf.

33.https://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/

34.https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/default.htm

35. DiMasi, J. A., Grabowski, H. G., & Hansen, R. W. (2016). Innovation in the pharmaceutical industry: New estimates of R&D costs. Journal of Health Economics, 47, 20-33. doi:http://doi.org/10.1016/j.jhealeco.2016.01.012.

36. Song, C. H. and J.-W. Han. "Patent cliff and strategic switch: exploring strategic design possibilities in the pharmaceutical industry." Springerplus. 2016; 5(1): 692. DOI: 10.1186/s40064-016-2323-1

37. F. J. Muhtadi, M. M. A. Hassan. Codeine Phosphate in *Anal. Profiles Drug Subs.* **10,** 93-138. (1981). 10.1016/S0099-5428(08)60640-1

38. Walter R. Heumann. The manufacture of codeine from morphine. Bull. Narcotics, 1958, vol. 3, p. 15. (https://www.unodc.org/unodc/en/data-and-analysis/bulletin/bulletin_1958-01-01_3_page006.html)

39. Charles A. Francis. Process for The Production Of Opiates. US 2005/0261500 (2005), and the references cited therin.

40. Per H.J. Carlsen, Katerina Liberkova, Rachel Harrex and Johan Roe. O-Methylation with Phenyltrimethylammonium chloride. Acta Chemica Scandinavica. 1997: 51: 343.

41. Ayyangar Nagaraj R, Choudhary Anil R, Uttam R, Sharma Vasant K. Process for the preparation of codeine from morphine. US 4,764,615 (1988).

42. Lloyd P. Hill. Preparation of Codeine from Morphine. US 6,579,985 (2003).

43. U. Zerell, B. Ahrens and P. Gerz Documentation of a heroin manufacturing process in Afghanistan. Bulletin On Narcotics Volume LVII, 11-31, 2005. ISBN 978-92-1-148221-8. https://www.unodc.org/unodc/data-and-analysis/bulletin/

44. ([44.1]) International Narcotics Control Board Precursors and chemicals frequently used in the illicit manufacture of narcotic drugs and psychotropic substances 2016. eISBN: 978-92-1-060067-5.

([44.2]) https://www.incb.org/documents/PRECURSORS/TECHNICAL_REPORTS/2016/PRE-AR_E_ebook_r.pdf

45.https://www.getsmartaboutdrugs.gov/sites/getsmartaboutdrugs.com/files/files/dea-heroin-brochure.pdf

45.https://www.getsmartaboutdrugs.gov/sites/getsmartaboutdrugs.com/files/files/dea-heroin-brochure.pdf

46.Craig, D. S. (2010). Oxymorphone Extended-Release Tablets (Opana ER) For the Management of Chronic Pain: A Practical Review for Pharmacists. Pharmacy and Therapeutics, 35(6), 324-357. ISSN:1052-1372

47.https://www.fda.gov/downloads/drugs/drugsafety/ucm208530.pdf

48. Saroop Singh Matharu; Brian W. Heinrich; Ewart Grant; Hongzhi Zhang. Processes for Making Opioids Including 14-Hydroxycodeinone And 14-Hydroxymorphinone. US 2016/0052932 A1; (2016).

49. Edward Leon Grew and Alastair Agnew Robertson. Reduction of Thebaine. US 3,812,132 (1974).

50. Tomas Hudlicky; Mary Ann Endoma-Arias; Brennan Augusta Murphy; Ivan Snajdr; Ales Machara. Methods for The Preparation of Hydromorphone. US 2015/0225419 (2015).

51. Kenneth Walter Bentley. Oripavine Derivatives. GB 937,214 (1963).

52. ([52.1]) Bentley, K. W., & Hardy, D. G. (1967). Novel analgesics and molecular rearrangements in the morphine-thebaine group. I. Ketones derived from 6,14-endo-ethenotetrahydrothebaine. Journal of the American Chemical Society, 89(13), 3267-3273. doi:10.1021/ja00989a030

([52.2]) Bentley, K. W., Hardy, D. G., & Meek, B. (1967). Novel analgesics and molecular rearrangements in the morphine-thebaine group. II. Alcohols derived from 6,14-endo-etheno- and 6,14-endo-ethanotetrahydrothebaine. Journal of the American Chemical Society, 89(13), 3273-3280. doi:10.1021/ja00989a031.

([52.3]) Bentley, K. W., & Hardy, D. G. (1967). Novel analgesics and molecular rearrangements in the morphine-thebaine group. III. Alcohols of the 6,14-endo-ethenotetrahydrooripavine series and derived analogs of N-allylnormorphine and -norcodeine. Journal of the American Chemical Society, 89(13), 3281-3292. doi:10.1021/ja00989a032

([52.4]) Bentley, K. W., Hardy, D. G., & Meek, B. (1967). Novel analgesics and molecular rearrangements in the morphine-thebaine group. IV. Acid-catalyzed rearrangements of alcohols of the 6,14-endo-ethenotetrahydrothebaine series. Journal of the American Chemical Society, 89(13), 3293-3303. doi:10.1021/ja00989a033

([52.5]) Bentley, K. W., Hardy, D. G., Howell, C. F., Fulmor, W., Lancaster, J. E., Brown, J. J., Hardy, R. A. (1967). Novel analgesics and molecular rearrangements in the morphine-thebaine group. V. Derivatives of 7,8-dihydrocyclohexeno [1',2':8,14] codeinone. Journal of the American Chemical Society, 89(13), 3303-3311. doi:10.1021/ja00989a034

([52.6]) Bentley, K. W., Hardy, D. G., Crocker, H. P., Haddlesey, D. I., & Mayor, P. A. (1967). Novel analgesics and molecular rearrangements in the morphine-thebaine group. VI. Base-catalyzed rearrangements in the, 14-endo-ethenotetrahydrothebaine series. Journal of the American Chemical Society, 89(13), 3312-3321. doi:10.1021/ja00989a035

([52.7]) Bentley, K. W. (1967). Morphine-thebaine group of alkaloids. IX. Reaction of thebaine with magnesium iodide. Journal of the American Chemical Society, 89(10), 2464-2469. doi:10.1021/ja00986a039

([52.8]) Bentley, K. W., Burton, M., & Uff, B. C. (1984). Preparation of 7-(1,3,4-oxadiazolyl)-6,14-endo-etheno-6,7,8,14-tetrahydrothebaines and related compounds as potential analgesics. Journal of Medicinal Chemistry, 27(10), 1276-1280. doi:10.1021/jm00376a008

53. Blane, G. F., Boura, A. L., Fitzgerald, A. E., & Lister, R. E. (1967). Actions of etorphine hydrochloride, (M99): a potent morphine-like agent. British Journal of Pharmacology and Chemotherapy, 30(1), 11-22; https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1557229/

54. Schumacher, J. (2008). Chapter 56 - Side Effects of Etorphine and Carfentanil in Nondomestic Hoofstock A2 - Fowler, Murray E. In R. E. Miller (Ed.), Zoo and Wild Animal Medicine (Sixth Edition) (pp. 455-461). Saint Louis: W.B. Saunders.

55.http://wildpharm.com/medications/wildlife/item/38-etorphine-hci-m99-cii-10ml-10mgml.html

56. William R. Hydro; Process of Purifying Oripavines, US 3,763,167 (1973).

57 ([57.1]) http://www.lilongwewildlife.org/category/weru-blog/

([57.2]) http://www.uidaho.edu/cnr/research/stories/ryan-long

([57.3]) http://bushvet.blogspot.rs/2011_04_01_archive.html

([57.4]) https://fossilrimblog.wordpress.com/2014/02/24/animal-capture-and-restraint-chemical-immobilization/

([57.5]) http://www.prnewswire.com/news-releases/colorado-sanctuary-rescues-lions-tigers--bears-from-argentina-300409926.html

58. Kenneth Walter Bentley. Endoethano Nor Oripavines And Nor Thebaines. US 3,433,791 (1969).

59.Werner, L., Machara, A., Adams, D. R., Cox, D. P., & Hudlicky, T. (2011). Synthesis of Buprenorphine from Oripavine via N-Demethylation of Oripavine Quaternary Salts. The Journal of Organic Chemistry, 76(11), 4628-4634. doi:10.1021/jo200567n

60. Gordon, A., Callaghan, D., Spink, D., Cloutier, C., Dzongowski, P., O'Mahony, W., Michalko, K. J. Buprenorphine transdermal system in adults with chronic low back pain: A randomized, double-blind, placebo-controlled crossover study, followed by an open-label extension phase. Clinical Therapeutics, 32(5), 844-860. doi: 10.1016/j.clinthera.2010.04.018

61.Hudlicky, T.; Carroll, R.; Leisch, H.; Machara, A.; Werner, L.; Adams, D. R. Processes for the preparation of morphinane and morphinone compounds. WO 2010121369 (2010).

62. Mozes Juda Lewenstein and Jack Fishman. Morphine Derivative. US 3,254,088 (1966).

63. Olofson, R. A., Schnur, R. C., Bunes, L., & Pepe, J. P. (1977). Selective N-dealkylation of tertiary amines with vinyl chloroformate: An improved synthesis of naloxone. Tetrahedron Letters, 18(18),1567-1570. doi:http://dx.doi.org/10.1016/S0040-4039(01)93104-1

64. Armstrong, A. (2001). 1-Chloroethyl Chloroformate Encyclopedia of Reagents for Organic Synthesis: John Wiley & Sons, Ltd. DOI: 10.1002/047084289X.rc102

65. Harold Blumberg, Irwin J. Pachter, Zaven Matossian. 14-Hydroxydihydronormorphinone Derivatives. US 3,332,950. (1967).

66. Portoghese, P. S., Sultana, M., & Takemori, A. E. (1990). Design of peptidomimetic delta opioid receptor antagonists using the message-address concept. Journal of Medicinal Chemistry, 33(6), 1714-1720. doi:10.1021/jm00168a028

67. Dorn, C. R., Markos, C. S., Dappen, M. S. and Pitzele, B. S. (1992), Synthesis of [3H] naltrindole [1]. J Label Compd Radiopharm, 31: 375–380. doi:10.1002/jlcr.2580310506

68. Fujii, H., Watanabe, A., Nemoto, T., Narita, M., Miyoshi, K., Nakamura, A.,. Nagase, H. (2009). Synthesis of novel twin drug consisting of 8-oxaendoethanotetrahydromorphides with a 1,4-dioxane spacer and its pharmacological activities: μ, κ, and putative ε opioid receptor antagonists. Bioorganic & Medicinal Chemistry Letters, 19(2), 438-441. doi:https://doi.org/10.1016/j.bmcl.2008.11.050

69. Nagase, H., Watanabe, A., Harada, M., Nakajima, M., Hasebe, K., Mochizuki, H.,. Fujii, H. (2009). Novel Synthesis of a 1,3,5-Trioxazatriquinane Skeleton Using a Nitrogen Clamp. Organic Letters, 11(3), 539-542. doi:10.1021/ol8024988

70. Nagase, H., Watanabe, A., Nemoto, T., Nakajima, M., Hasebe, K., Mochizuki, H., & Fujii, H. (2011). Synthesis of novel triplet drugs with 1,3,5-trioxazatriquinane skeletons and their pharmacologies. 1: Synthesis of triplet drugs with morphinan skeletons. Bioorganic & Medicinal Chemistry Letters, 21(13), 4023-4026. doi:https://doi.org/10.1016/j.bmcl.2011.04.134

71. Portoghese, P. S., Akgün, E., & Lunzer, M. M. (2017). Heteromer Induction: An Approach to Unique Pharmacology? ACS Chemical Neuroscience, 8(3), 426-428. doi:10.1021/acschemneuro.7b00002

72. Remesic, M., Hruby, V. J., Porreca, F., & Lee, Y. S. (2017). Recent Advances in the Realm of Allosteric Modulators for Opioid Receptors for Future Therapeutics. ACS Chemical Neuroscience. doi:10.1021/acschemneuro.7b00090

73. Erez, M., Takemori, A. E., & Portoghese, P. S. (1982). Narcotic antagonistic potency of bivalent ligands which contain beta-naltrexamine. Evidence for simultaneous occupation of proximal recognition sites. Journal of Medicinal Chemistry, 25(7), 847-849. doi:10.1021/jm00349a016

74. http://www.rcsb.org/pdb/explore/explore.do?structureId=5C1M 5C1M. Crystal structure of active mu-opioid receptor bound to the agonist BU72. DOI: 10.2210/pdb5c1m/pdb

75. Ananthan, S., Kezar, H. S., Carter, R. L., Saini, S. K., Rice, K. C., Wells, J. L., Rothman, R. B. (1999). Synthesis, Opioid Receptor Binding, and Biological Activities of Naltrexone-Derived Pyrido- and Pyrimidomorphinans. Journal of Medicinal Chemistry, 42(18), 3527-3538. doi:10.1021/jm990039i

76. Wells, J. L., Bartlett, J. L., Ananthan, S., & Bilsky, E. J. (2001). In Vivo Pharmacological Characterization of SoRI 9409, a Nonpeptidic Opioid μ-Agonist/δ-Antagonist That Produces Limited Antinociceptive Tolerance and Attenuates Morphine Physical Dependence. Journal of Pharmacology and Experimental Therapeutics, 297(2), 597-605.

77. Daniels, D. J., Lenard, N. R., Etienne, C. L., Law, P.-Y., Roerig, S. C., & Portoghese, P. S. (2005). Opioid-induced tolerance and dependence in mice is modulated by the distance between pharmacophores in a bivalent ligand series. Proceedings of the National Academy of Sciences of the United States of America, 102(52), 19208-19213. doi:10.1073/pnas.0506627102

78. Huang, W., Manglik, A., Venkatakrishnan, A. J., Laeremans, T., Feinberg, E. N., Sanborn, A. L., Kobilka, B. K. (2015). Structural insights into [micro]-opioid receptor activation. Nature, 524(7565), 315-321. doi:10.1038/nature14886. http://www.nature.com/nature/journal/v524/n7565/abs/nature14886.html#supplementary-information

79. http://www.rcsb.org/pdb/explore/explore.do?structureId=4EJ4. Structure of the delta opioid receptor bound to naltrindole. DOI: 10.2210/pdb4ej4/pdb

80. Granier, S., Manglik, A., Kruse, A. C., Kobilka, T. S., Thian, F. S., Weis, W. I., & Kobilka, B. K. (2012). Structure of the δ-opioid receptor bound to naltrindole. Nature, 485(7398), 400-404. doi:http://www.nature.com/nature/journal/v485/n7398/abs/nature11111.html#supplementary-information

81. http://accelrys.com/products/collaborative-science/biovia-discovery-studio/visualization.html

82. The model was composed by Milovan D. Ivanovic for visualization purposes only. It was not published.

83. Akgün, E., Javed, M. I., Lunzer, M. M., Smeester, B. A., Beitz, A. J., & Portoghese, P. S. (2013). Ligands that interact with putative MOR-mGluR5 heteromer in mice with inflammatory pain produce potent antinociception. Proceedings of the National Academy of Sciences, 110(28), 11595-11599. doi:10.1073/pnas.1305461110

84. Akgün, E., Javed, M. I., Lunzer, M. M., Powers, M. D., Sham, Y. Y., Watanabe, Y., & Portoghese, P. S. (2015). Inhibition of Inflammatory and Neuropathic Pain by Targeting a Mu Opioid Receptor/Chemokine Receptor5 Heteromer (MOR-CCR5). Journal of Medicinal Chemistry, 58(21), 8647-8657. doi: 10.1021/acs.jmedchem.5b01245

85. ([85.1]) Gulland, J. M., & Robinson, R. (1923). CXII.-The morphine group. Part I. A discussion of the constitutional problem. *Journal of the Chemical Society, Transactions, 123*(0), 980-998. doi:10.1039/CT9232300980

([85.2]) Gulland, J. M., & Robinson, R. (1923). CXIII.-The morphine group. Part II. Thebainone, thebainol, and dihydrothebainone. *Journal of the Chemical Society, Transactions, 123*(0), 998-1011. doi:10.1039/CT9232300998

([85.3]) Gulland, J. M., & Robinson, R. (1925). Mem. Proc. Manchester Lit. Philos. Soc., 69, 79– 86.

86. Rapoport, H., & Payne, G. B. (1950). Stereochemical Studies In The Morphine Series. The Relative Configuration At Carbons Five And Six. *The Journal of Organic Chemistry, 15*(5), 1093-1102. doi:10.1021/jo01151a028

87. Gates, M., & Tschudi, G. (1952). The Synthesis Of Morphine. *Journal of the American Chemical Society, 74*(4), 1109-1110. doi:10.1021/ja01124a538

88. Bick, I. R. C. (1952). Absolute Stereochemical Configuration of Morphine. *Nature, 169*(4305), 755-756. doi:10.1038/169755a0

89. Mackay, M., & Hodgkin, D. C. (1955). A crystallographic examination of the structure of morphine. *Journal of the Chemical Society (Resumed)* (0), 3261-3267. doi:10.1039/JR9550003261

90. https://www.ccdc.cam.ac.uk/

91.http://www.rcsb.org/pdb/home/home.do

92. A noninclusive list of morphine alkaloids total syntheses:

([92.1]) Grewe, R., & Friedrichsen, W. (1967). Die Cyclisierung von Octahydro-isochinolinderivaten durch Morphinan-Ringschluß. Synthese des Dihydrothebainons. *Chemische Berichte, 100*(5), 1550-1558. doi:10.1002/cber.19671000521

([92.2]) Schwartz, M. A., & Mami, I. S. (1975). Biogenetically patterned synthesis of the morphine alkaloids. *Journal of the American Chemical Society, 97*(5), 1239-1240. doi:10.1021/ja00838a046

([92.3]) Evans, D. A., & Mitch, C. H. (1982). Studies directed towards the total synthesis of morphine alkaloids. *Tetrahedron Letters, 23*(3), 285-288. doi:http://dx.doi.org/10.1016/S0040-4039(00)86810-0

([92.4]) Moos, W. H., Gless, R. D., & Rapoport, H. (1983). Codeine analogs. Synthesis of 4a-aryldecahydroisoquinolines containing nitrogen ring functionality and of octahydro-1H-indeno[1,2,3-ef] isoquinolines. A total synthesis of codeine. *The Journal of Organic Chemistry, 48*(2), 227-238. doi:10.1021/jo00150a017

([92.5]) White, J. D., Caravatti, G., Kline, T. B., Edstrom, E., Rice, K. C., & Brossi, A. (1983). Biomimeic total synthesis of (−)-codeine. *Tetrahedron, 39*(14), 2393-2397. doi: http://dx.doi.org/10.1016/S0040-4020(01)91965-9

([92.5]) Toth, J. E., & Fuchs, P. L. (1987). Synthesis via vinyl sulfones. 21. Total synthesis of dl-morphine. *The Journal of Organic Chemistry, 52*(3), 473-475. doi:10.1021/jo00379a038

([92.6]) Parker, K. A., & Fokas, D. (1992). Convergent synthesis of (+-.)-dihydroisocodeine in 11 steps by the tandem radical cyclization strategy. A formal total synthesis of (+-.)-morphine. *Journal of the American Chemical Society, 114*(24), 9688-9689. doi:10.1021/ja00050a075

([92.7]) Tius, M. A., & Kerr, M. A. (1992). A novel approach to the synthesis of morphine alkaloids: the synthesis of (*d,l*)-thebainone-A. *Journal of the American Chemical Society, 114*(15), 5959-5966. doi:10.1021/ja00041a008

([92.8]) Hong, C. Y., Kado, N., & Overman, L. E. (1993). Asymmetric synthesis of either enantiomer of opium alkaloids and morphinans. Total synthesis of (-)- and (+)-dihydrocodeinone and (-)- and (+)-morphine. *Journal of the American Chemical Society, 115*(23), 11028-11029. doi:10.1021/ja00076a086

([92.9]) Mulzer, J., Dürner, G., & Trauner, D. (1996). Formal Total Synthesis of (-)-Morphine by Cuprate Conjugate Addition. *Angewandte Chemie International Edition in English, 35*(23-24), 2830-2832. doi:10.1002/anie.199628301

([92.10]) Parsons, P. J., Penkett, C. S., & Shell, A. J. (1996). Tandem Reactions in Organic Synthesis:□ Novel Strategies for Natural Product Elaboration and the Development of New Synthetic Methodology. *Chemical Reviews, 96*(1), 195-206. doi:10.1021/cr950023

([92.11]) Mulzer, J., Bats, J. W., List, B., Opatz, T., & Trauner, D. (1997). The Phenanthrenone Approach to Opium Alkaloids: Formal Total Synthesis of Morphine by Sigmatropic Rearrangement. *Synlett, 1997*(Sup. I), 441-444. doi:10.1055/s-1997-6135

([92.12]) Mulzer, J., & Trauner, D. (1999). Practical synthesis of (−)-morphine. *Chirality, 11*(5-6), 475-482. doi:10.1002/(SICI)1520-636X (1999)

([92.13]) Nagata, H., Miyazawa, N., & Ogasawara, K. (2001). A concise route to (-)-morphine. *Chemical Communications* (12), 1094-1095. doi:10.1039/B101668G

([92.14]) Taber, D. F., Neubert, T. D., & Rheingold, A. L. (2002). Synthesis of (−)-Morphine. *Journal of the American Chemical Society, 124*(42), 12416-12417. doi:10.1021/ja027882h

([92.15]) Trost, B. M., & Tang, W. (2002). Enantioselective Synthesis of (−)-Codeine and (−)-Morphine. *Journal of the American Chemical Society, 124*(49), 14542-14543. doi:10.1021/ja0283394

([92.16]) Uchida, K., Yokoshima, S., Kan, T., & Fukuyama, T. (2006). Total Synthesis of (±)-Morphine. *Organic Letters, 8*(23), 5311-5313. doi:10.1021/ol062112m

([92.17]) Omori, A. T., Finn, K. J., Leisch, H., Carroll, R. J., & Hudlicky, T. (2007). Chemoenzymatic Total Synthesis of (+)-Codeine by Sequential Intramolecular Heck Cyclizations via C-B-D Ring Construction. *Synlett, 2007*(18), 2859-2862. doi:10.1055/s-2007-990833

([92.18]) Tanimoto, H., Saito, R., & Chida, N. (2008). Formal synthesis of (−)-morphine from d-glucal based on the cascade Claisen rearrangement. *Tetrahedron Letters, 49*(2), 358-362. doi:http://doi.org/10.1016/j.tetlet.2007.11.037

([92.19]) Varin, M., Barré, E., Iorga, B., & Guillou, C. (2008). Diastereoselective Total Synthesis of (±)-Codeine. *Chemistry – A European Journal, 14*(22), 6606-6608. doi:10.1002/chem.200800744

([92.20]) Fujii, H., Watanabe, A., Nemoto, T., Narita, M., Miyoshi, K., Nakamura, A., Nagase, H. (2009). Synthesis of novel twin drug consisting of 8-oxaendoethanotetrahydromorphides with a 1,4-dioxane spacer and its pharmacological activities: μ, κ, and putative ε opioid receptor antagonists. *Bioorganic & Medicinal Chemistry Letters, 19*(2), 438-441. doi:https://doi.org/10.1016/j.bmcl.2008.11.050

([92.21]) Leisch, H., Omori, A. T., Finn, K. J., Gilmet, J., Bissett, T., Ilceski, D., & Hudlický, T. (2009). Chemoenzymatic enantiodivergent total syntheses of (+)- and (−)-codeine. *Tetrahedron, 65*(47), 9862-9875. doi:http://doi.org/10.1016/j.tet.2009.09.052

([92.22]) Magnus, P., Sane, N., Fauber, B. P., & Lynch, V. (2009). Concise Syntheses of (−)-Galanthamine and (±)-Codeine via Intramolecular Alkylation of a Phenol Derivative. *Journal of the American Chemical Society, 131*(44), 16045-16047. doi:10.1021/ja9085534

([92.23]) Stork, G., Yamashita, A., Adams, J., Schulte, G. R., Chesworth, R., Miyazaki, Y., & Farmer, J. J. (2009). Regiospecific and Stereoselective Syntheses of (±) Morphine, Codeine, and Thebaine via a Highly Stereocontrolled Intramolecular 4+2 Cycloaddition Leading to a Phenanthrofuran System. *Journal of the American Chemical Society, 131*(32), 11402-11406. doi:10.1021/ja9038505

([92.24]) Koizumi, H., Yokoshima, S., & Fukuyama, T. (2010). Total Synthesis of (−)-Morphine. *Chemistry – An Asian Journal, 5*(10), 2192-2198. doi:10.1002/asia.201000458

([92.25]) Duchek, J., Piercy, T. G., Gilmet, J., & Hudlicky, T. (2011). Chemoenzymatic total synthesis of ent-neopinone and formal total synthesis of ent-codeinone from β-bromoethylbenzene*. *Canadian Journal of Chemistry, 89*(6), 709-729. doi:10.1139/v11-071

([92.26]) Erhard, T., Ehrlich, G., & Metz, P. (2011). A Total Synthesis of (±)-Codeine by 1,3-Dipolar Cycloaddition. *Angewandte Chemie International Edition, 50*(17), 3892-3894. doi:10.1002/anie.201007448

([92.27]) Ichiki, M., Tanimoto, H., Miwa, S., Saito, R., Sato, T., & Chida, N. (2013). Synthesis of (−)-Morphine: Application of Sequential Claisen/Claisen Rearrangement of an Allylic Vicinal Diol. *Chemistry – A European Journal, 19*(1), 264-269. doi:10.1002/chem.201203284

([92.28]) Li, J., Liu, G.-L., Zhao, X.-H., Du, J.-Y., Qu, H., Chu, W.-D., Fan, C.-A. (2013). Formal Synthesis of (±)-Morphine. *Chemistry – An Asian Journal, 8*(6), 1105-1109. doi:10.1002/asia.201300139

([92.29]) Varghese, V., & Hudlicky, T. (2013). Total Synthesis of Dihydrocodeine and Hydrocodone via a Double Claisen Rearrangement and C-10/C-11 Closure Strategy. *Synlett, 24*(03), 369-374. doi:10.1055/s-0032-1318114

([92.30]) Endoma-Arias, M. A. A., Hudlicky, J. R., Simionescu, R., & Hudlicky, T. (2014). Chemoenzymatic Formal Total Synthesis of ent-Codeine and Other Morphinans via Nitrone Cycloadditions and/or Radical Cyclizations. Comparison of Strategies for Control of C-9/C-14 Stereogenic Centers. *Advanced Synthesis & Catalysis, 356*(2-3), 333-339. doi:10.1002/adsc.201400016

([92.31]) Geffe, M., & Opatz, T. (2014). Enantioselective Synthesis of (−)-Dihydrocodeine and Formal Synthesis of (−)-Thebaine, (−)-Codeine, and (−)-Morphine from a Deprotonated α-Aminonitrile. *Organic Letters, 16*(20), 5282-5285. doi:10.1021/ol5023849

([92.32]) Tissot, M., Phipps, R. J., Lucas, C., Leon, R. M., Pace, R. D. M., Ngouansavanh, T., & Gaunt, M. J. (2014). Gram-Scale Enantioselective Formal Synthesis of Morphine through an ortho–para Oxidative Phenolic Coupling Strategy. *Angewandte Chemie International Edition, 53*(49), 13498-13501. doi:10.1002/anie.201408435

([92.33]) Varghese, V., & Hudlicky, T. (2014). Short Chemoenzymatic Total Synthesis of ent-Hydromorphone: An Oxidative Dearomatization/Intramolecular [4+2] Cycloaddition/Amination Sequence. *Angewandte Chemie International Edition, 53*(17), 4355-4358. doi:10.1002/anie.201400286

([92.34]) Li, Q., & Zhang, H. (2015). Total Synthesis of Codeine. *Chemistry – A European Journal, 21*(46), 16379-16382. doi:10.1002/chem.201503594

93. Rice, K. C. (1980). Synthetic opium alkaloids and derivatives. A short total synthesis of (.+-.)-dihydrothebainone, (.+-.)-dihydrocodeinone, and (.+-.)-nordihydrocodeinone as an approach to a practical synthesis of morphine, codeine, and congeners. The Journal of Organic Chemistry, 45(15), 3135-3137. doi:10.1021/jo01303a045

94. White, J. D., Hrnciar, P., & Stappenbeck, F. (1997). Asymmetric Synthesis of (+)-Morphine. The Phenanthrene Route Revisited. The Journal of Organic Chemistry, 62(16), 5250-5251. doi:10.1021/jo9710994

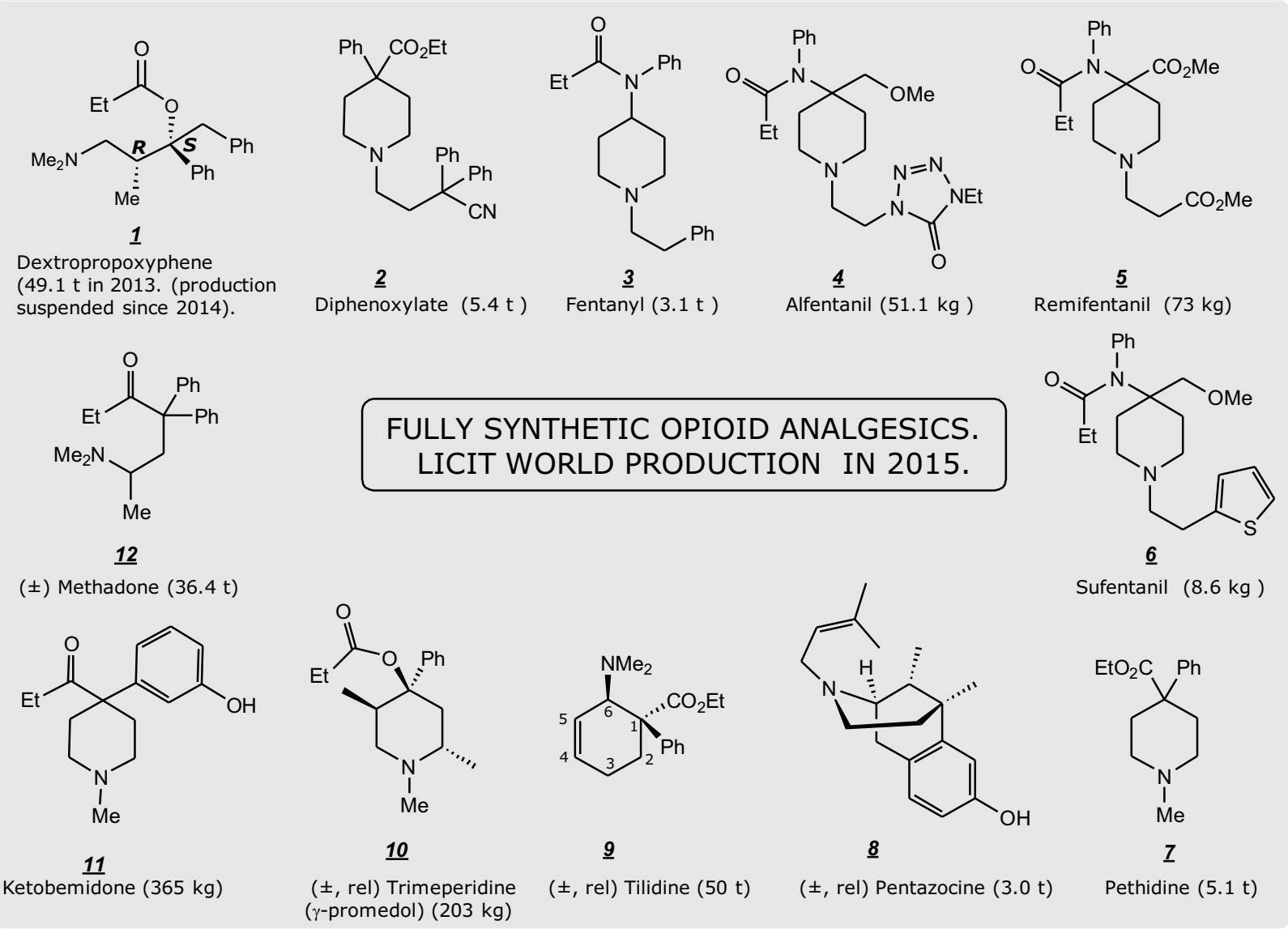
95. Chu, S., Münster, N., Balan, T., & Smith, M. D. (2016). A Cascade Strategy Enables a Total Synthesis of (±)-Morphine. *Angewandte Chemie International Edition, 55*(46), 14306-14309. doi:10.1002/anie.201608526.

SYNTHETIC OPIOID ANALGESICS. CHAPTER 3.

3.1. Introduction

As shown in Chapter 2, the only naturally occurring opioid analgesics in the current medical use are morphine and codeine. Other two natural morphine alkaloids (thebaine and oripavine) are used exclusively as the precursors in semi-synthesis of opioid drugs (e.g. oxycodone, oxymorphone, hydro-morphone, hydrocodone, buprenorphine, etc.) and some and non-opioids (e.g apomor-phine).

While many of those semi-synthetic drugs are highly effective and widely used opioids, their prepa-ration depends exclusively on the availability of the precursors, i.e. natural morphine alkaloids. Since steady supply of the natu-ral alkaloids could not be guaranteed, there have been numerous attempts to design fully synthetic opioids, as a replacement or supplement to the natu-ral or semi-synthetic opioid drugs.



Scheme 3.1. Synthetic opioid analgesics currently used in humans: world production in 2015.(refs. 14,15; p. 100).

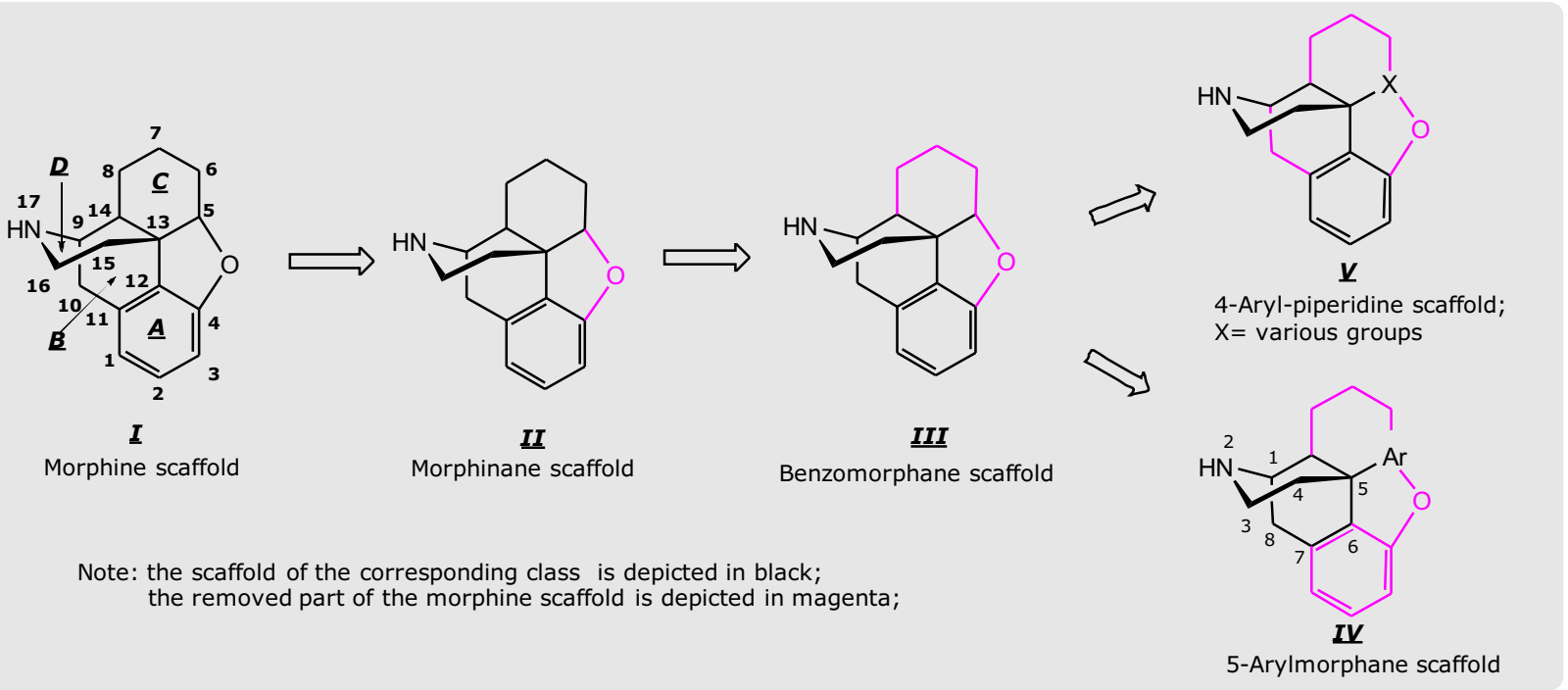
Numerous attempts towards practical, industrial synthesis of morphine alkaloids were unsuccessful, (Chapter 2) and have actually proved that it is beyond the capabilities of the contemporary organic synthesis. (There are current attempts to employ the methods of genetical engineering to that purpose).[1] Other goals in developing synthetic opioids were to design more powerful drugs with less side effects.

Those efforts eventually succeeded, resulting in the tens of opioid drugs used clinically since the late 1930s. While many of those drugs were later withdrawn from the market, due to the serious side effects or insufficient potency, new synthetic opioids emerged, having more favorable pharmacological profile.

At present (as of 2017), there are about 12 fully synthetic opioids in human use, *Scheme 3.1*. Several more are used as veterinary drugs only. It is noteworthy that the first three significant opioid drugs, synthesized in the late 1930s and during the World War II, are still being used as analgesics. Those are pethidine ***7***, ketobemidone ***11*** and methadone ***12***, Scheme 3.1.

Historically, the quest for the fully synthetic and clinically useful opioids, started with the simplification of the morphine molecule.

The general approach was to remove the selected rings from the morphine scaffold, establish the structure-activity relationship and to identify regions of the molecule responsible for the activity (the opioid pharmacophores). Ideally, further refinements would improve the activity and reduce side effects. The general concept is shown in *Scheme 3.2.*



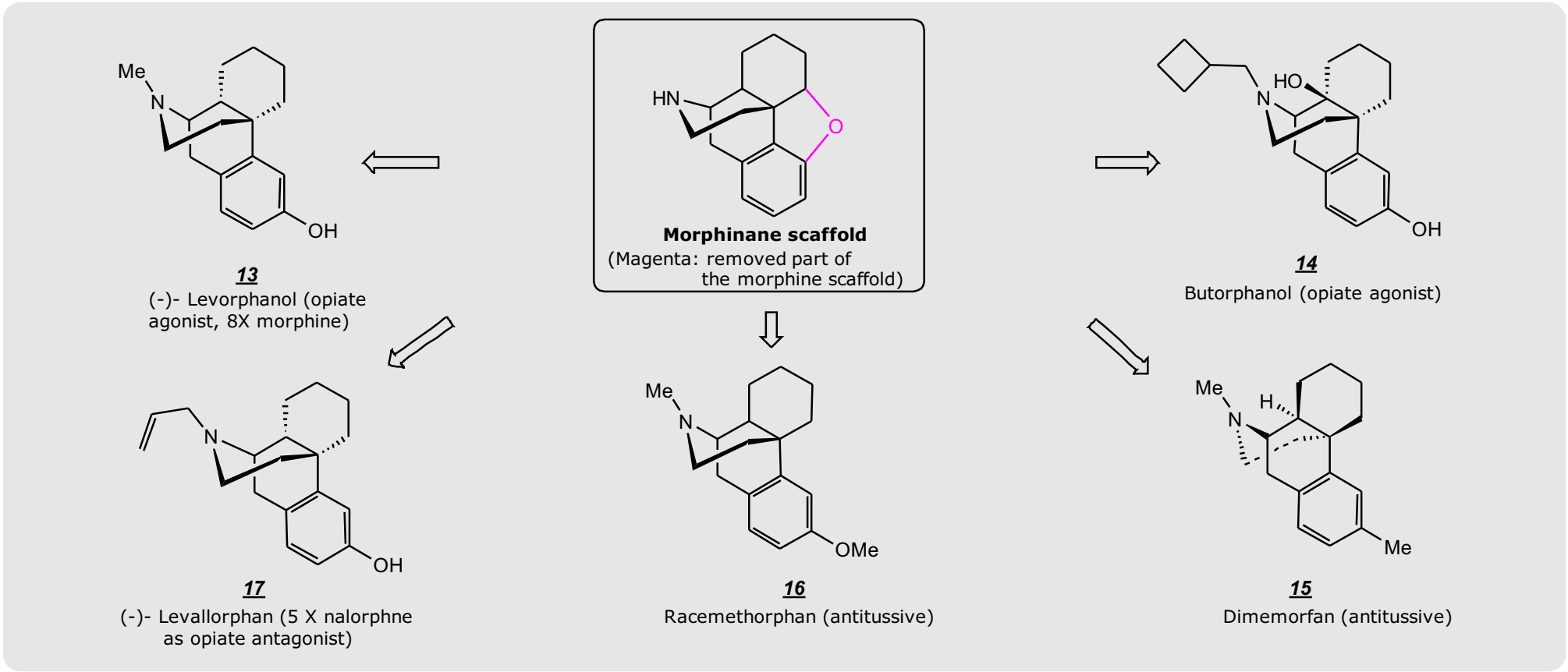
Scheme 3.2. Simplification of the morphine scaffold: morphinanes, benzomorphanes and arylmophanes.

3.2. Morphinanes

The removal of furan ring from the morphine scaffold produced a novel class of "simplified morphines" denoted morphinanes.[2] The compounds, with no direct parallel to any natural products, often exhibited significant opioid activity, particularly towards μ and κ receptors.

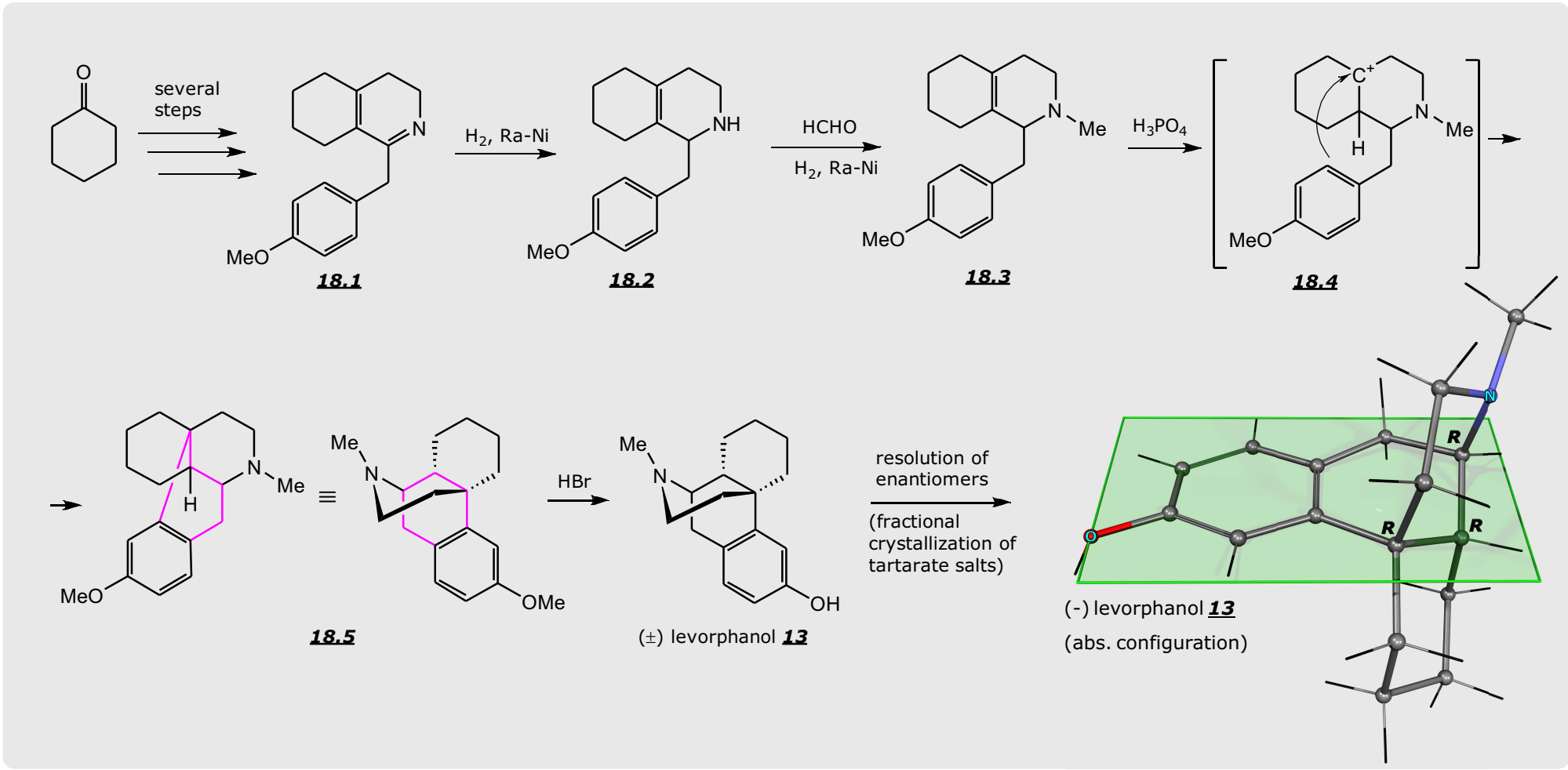
Some morphinanes were formerly used as drugs, notably levorphanol ***13***[3] and butorphanol ***14***[4] as analgesics, dimemorfan ***15***[5] and racemethorphan ***16***[6] as antitussives and levallorphan ***17***[7] as opioid antagonist. However, all of them have been withdrawn from the market, mainly due to significant side effects and better pharmacological alternatives. At present, there are no morphinans in clinical use.

Morphinanes were prepared either by semi-synthesis from morphine alkaloids or by the total synthesis. Some of the significant examples are shown in the *Scheme 3.3*.



Scheme 3.3. Structures of significant morphinanes

A classical synthesis of levorphanol is depicted in *Scheme 3.4*. (No yields were reported in the original literature).[8] The imino group in isoquinoline derivative ***18.1***, prepared in several steps from cyclohexanone, was selectively reduced by catalytic hydrogenation to ***18.2***, followed by the reductive *N*-methylation using formaldehyde. Acid-catalyzed Grewe-type cyclization[9] formed new cyclohexane ring (magenta), structure ***18.5***. The synthesis was completed by the cleavage of methoxy group using hydrogen bromide, securing (±) levorphanol ***13***. The racemate was resolved by fractional crystallization of the tartrate salt, providing (-) levorphanol ***13***.



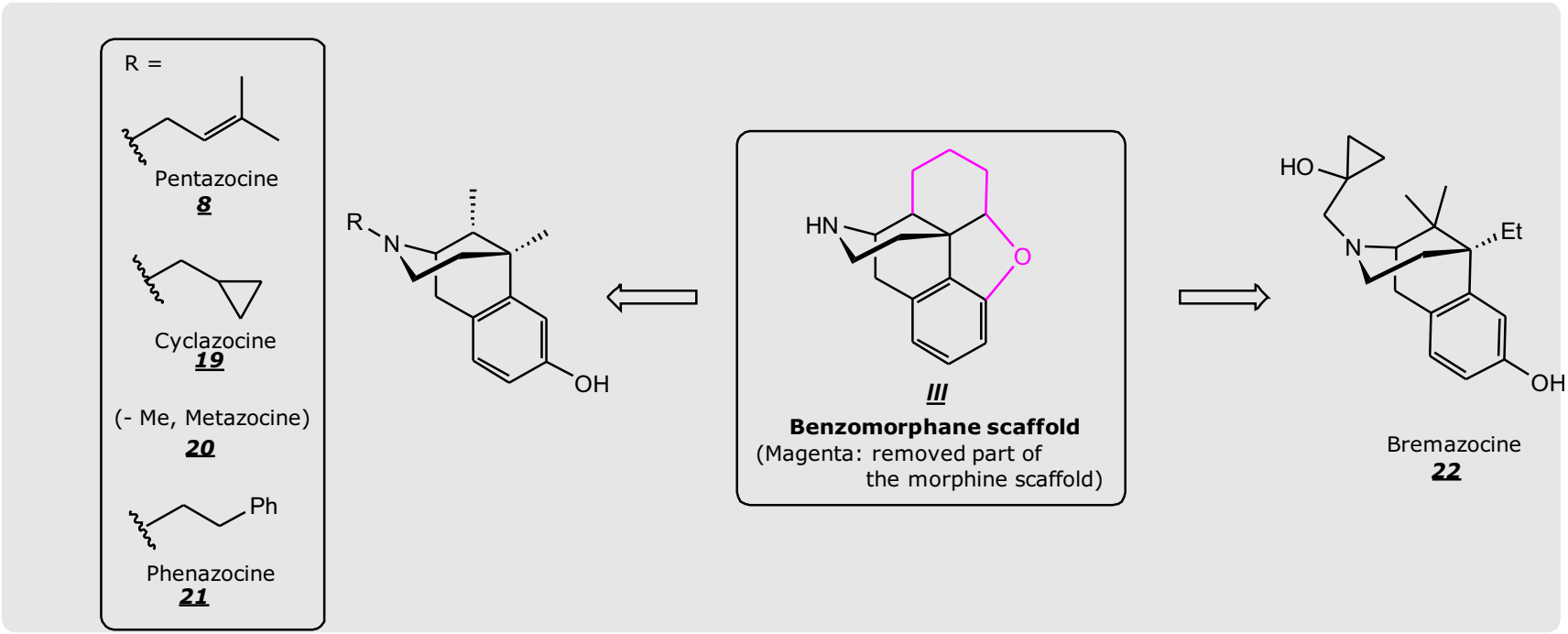
Scheme 3.4. Simplified representation of the classical synthesis of levorphanol ***13***.

3.3. Benzomorphanes and Arylmophanes.

The removal of both furan and the ring C from the morphine scaffold gave the class of opioid analgesics known as benzomorphanes,[10] general structure III, *Scheme 3.5*. Significant representatives include pentazocine ***8***, cyclazocine ***19***,[12] metazocine ***20***[13]and phenazocine ***21***[14] which differ only in the nitrogen substituent.

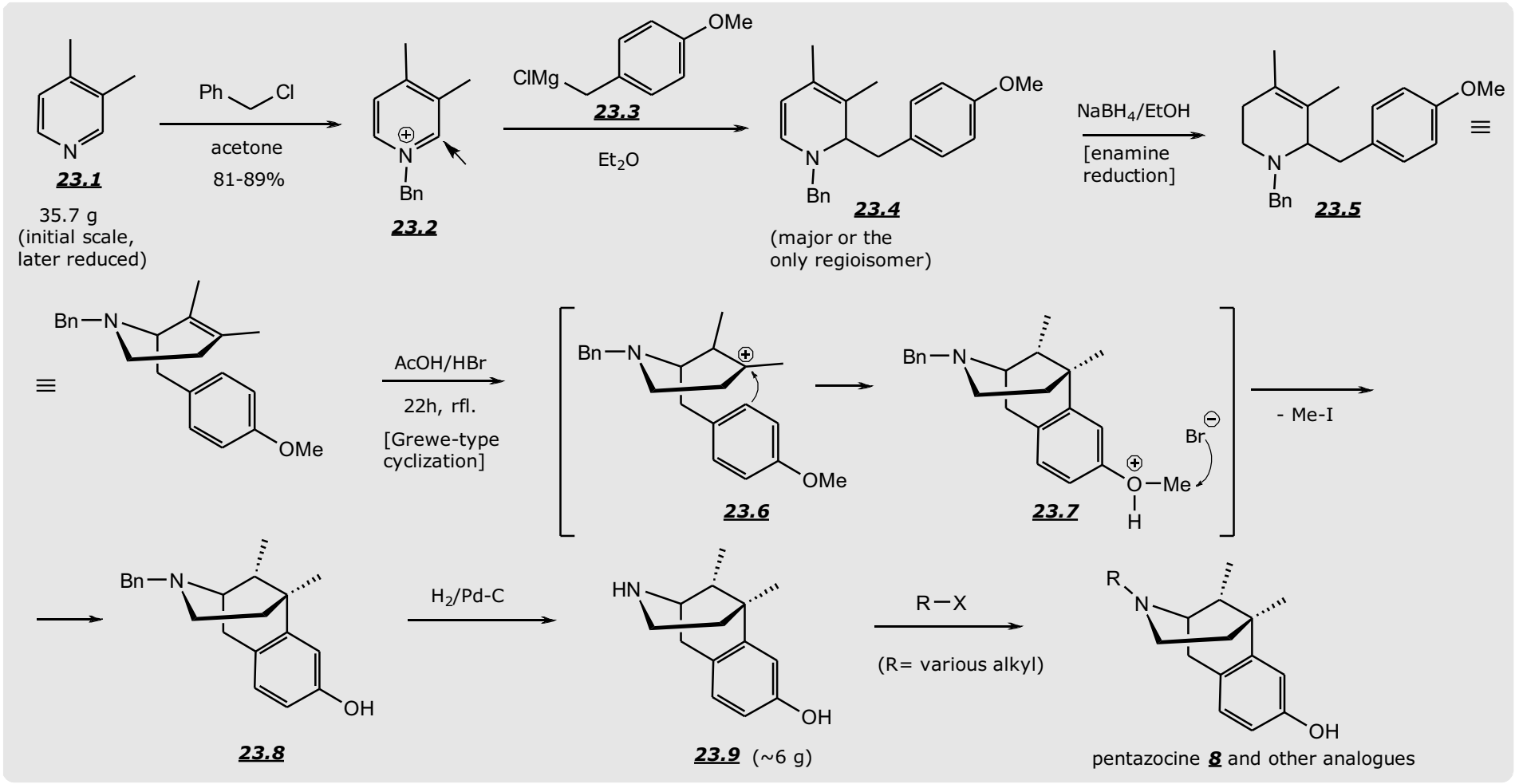
Structurally closely similar drug, bremazocine ***22***,[15,16] has also received considerable attention due to its opioid activity.[17] Most benzomorphanes are mixed μ/κ or κ-only agonists. Many are potent analgesics, largely devoid of the side effects typical for μ-opioid agonist (respiratory depression, physical and psychological dependence).

While those properties make benzomorphanes attractive candidates as analgesics, only pentazocine is currently used as a drug. This is because of the side effects associated with κ-receptors activation, including dysphoria and a range of psychotomimetic disorders (disturbance in the perception of space and time, abnormal visual experience, disturbance in body image perception, de-personalization, de-realization and loss of self-control).[16] Two closely similar, general approaches to benzomorphanes (e.g. pentazocine ***8***) were published almost simultaneously by two research groups,[18] *Scheme 3.6*.



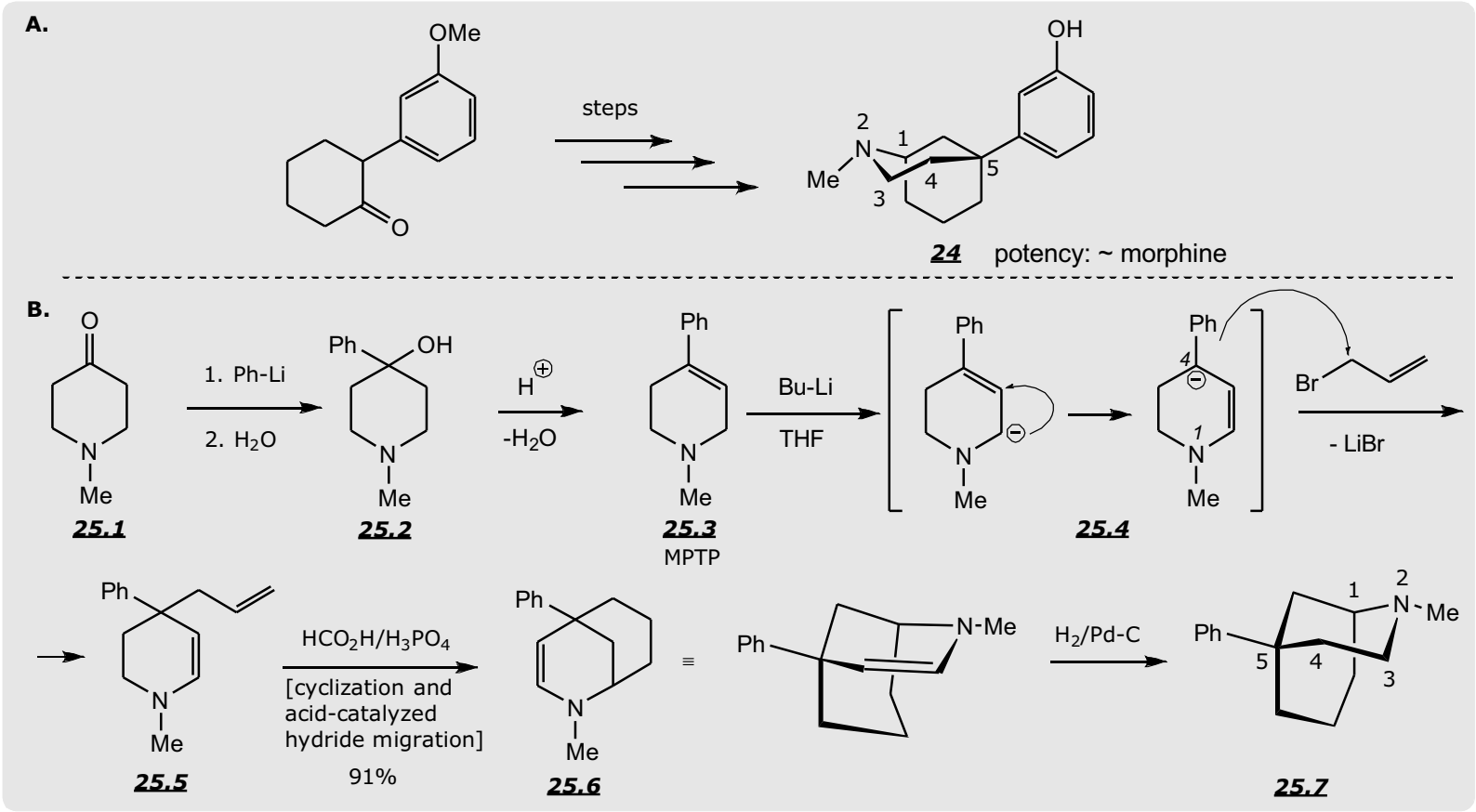
Scheme 3.5. Structure of benzomorphane scaffold and the significant representatives

The addition of benzyl Grignard reagent ***23.3*** to the quaternary pyridinium salt ***23.2*** proceeded regioselectively, affording enamine ***23.4***. The enamine was reduced using $NaBH_4$ and the resulting piperidine derivative ***23.5***, exposed to strong acid (AcOH/HBr). Upon the prolonged heating, Grewe-type cyclization (via intermediates ***23.6*** and ***23.7***), formed the cyclohexane ring, together with the *O*-demethylation, structure ***23.8***. The key intermediate, piperidine ***23.9***, was obtained by hydrogenolysis of *N*-benzyl group. (The reaction scale was reduced in several synthetic steps. Subsequent *N*-alkylation, acc. to the previously reported procedure, provided various benzomorphanes, including pentazocine ***8*** and others.[18]



Scheme 3.6. Practical synthesis of penazocine and its *N*-alkyl analogues.

Numerous 5-arylmorphanes[19] and the structurally related compounds were synthesized over the course of several decades. Some of the compounds exhibited significant opioid analgesic activity when tested *in vivo*, at least equivalent to morphine. Despite the extensive research efforts, no clinical tests were reported and arymorphahes have never been used as drugs. Apparently, the complex syntheses and only moderate activity ruled them out as potential drug candidates. *Scheme 3.7 A* represents the conceptual synthesis and structure of arylmorpahane ***24***, having the opioid potency similar to morphine.[20] Much later, an efficient and simple approach to the same ring system was disclosed, *Scheme 3.7 B*.[21] The synthesis involved metalation of enamine ***25.3***, base-promoted double bond migration and the allylation of the carbanion ***25.4*** at the position 4. The acid-catalyzed cyclization and hydride migration of ***25.5*** (mechanism not shown) furnished bicyclic enamine ***25.6***. In the final step, hydrogenation secured arylmorphane ***25.7***. (The scale was not reported).

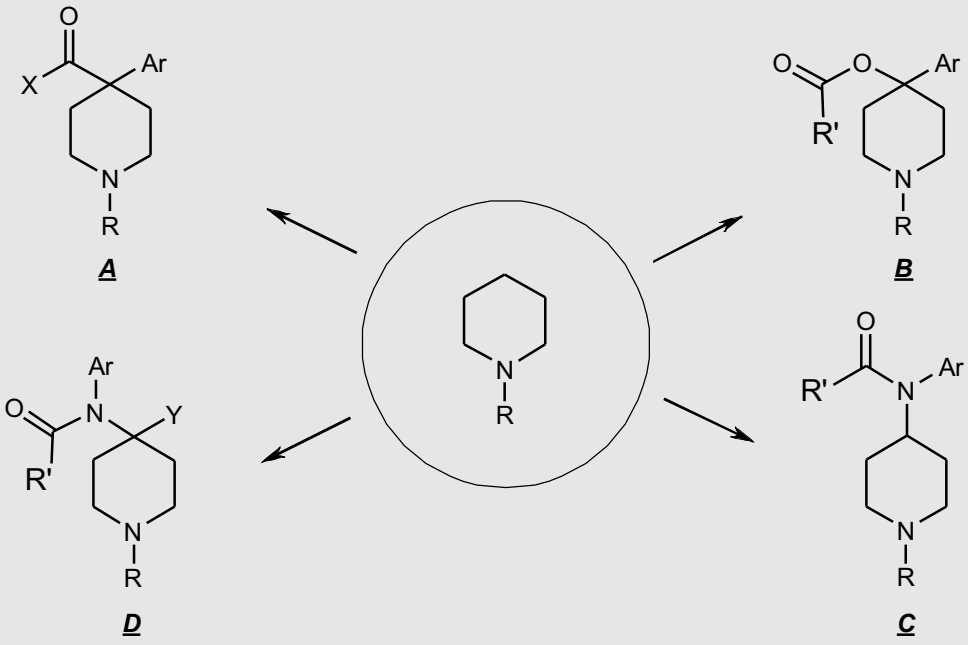


Scheme 3.7. 5-Arylmorphanes: structure and a general synthetic approach.

It is noteworthy that the key intermediate ***25.3*** (MPTP) is extremely neurotoxic, causing the irreversible symptoms of parkinsonism in humans and monkeys.[22] While the compound has been known for decades and used extensively as synthetic intermediate, this unusual property was only discovered by accident in mid-1982.

The illicit preparations of "reverse esters of pethidine" (p. 120), sold as heroin, were significantly contaminated with MPTP. (It originated by spontaneous dehydration of alcohol ***25.2*** in acidic medium). It was then discovered that the addicts who abused this "heroin", suffered from the irreversible Parkinson-like symptoms.

Incidentally, it was the first known example that the Parkinsonism could be caused by any compound, sparking the extensive research efforts in that direction that last to the present time.[23]



Scheme 3.8. General structures of opioid piperidines

3.4.Simple opioid piperidines: pethidines (meperidines), "reverse esters of meperidine" and 4-anilidopiperidines

As it is apparent from the previous discussion, most of the clinically significant opioids possess piperidine ring as an essential part of their structure. This is true not only for the immediate morphine derivatives, i.e. 4,5-epoxymorphinans, but also for all morphinans, benzomorphans and the related classes of opioids. Since they were developed as structural simplification of the morphine scaffold, it become apparent that the piperidine ring was an essential part of the opioid pharmacophore. The extensive pharmacological results, over many decades, demonstrated that the cleavage of piperidine ring always abolished the opioid activity. (However, there are many potent "open-chain" opioids, including peptides, which have no heterocyclic rings). Consequently, the morphine structure was finally simplified to various functionalized piperidines. Experiments performed since 1930s, demonstrated that a specific class of the substituted piperidines included moderately potent and clinically useful opioids, *Scheme 3.8*, general structure ***A***. Further structure-activity relationship studies identified a number of more active analogues, as detailed later. Nonetheless, only two members of the group, including pethidine (meperidine), remained in a significant clinical use to the present time (as of 2017).

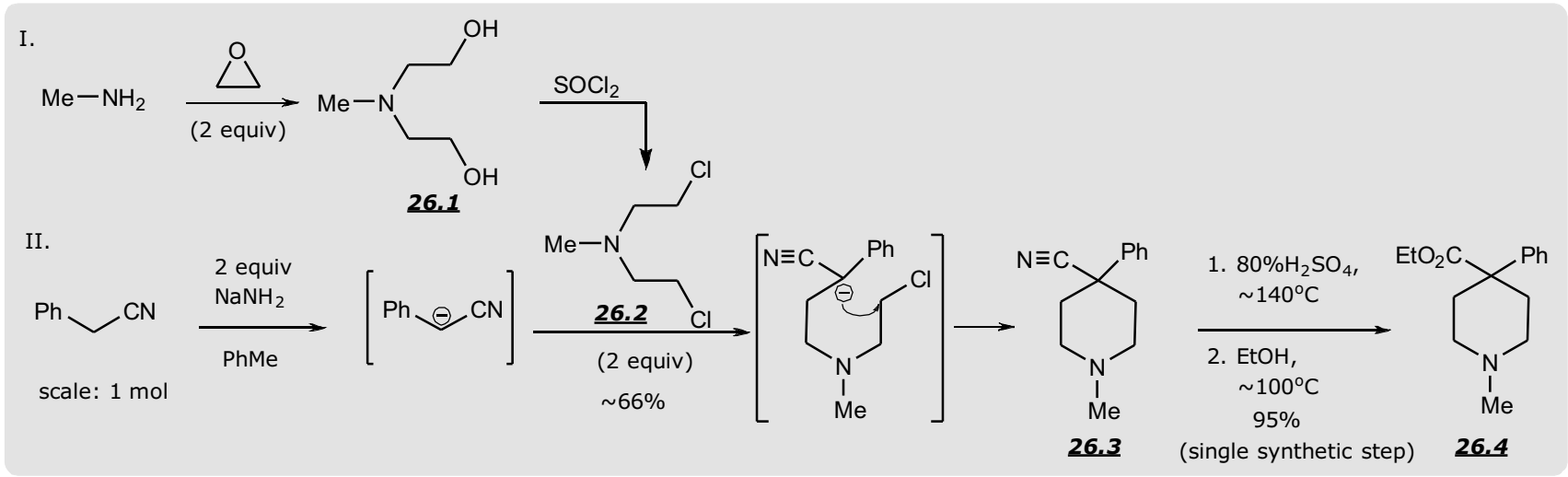
Soon after, several more classes of the opioid piperidines were discovered, including "reverse esters of pethidine", structure ***B***, 4-anilidopiperidines, structure ***C***, and the related derivatives structure ***D***, *Scheme 3.8*. While the "reverse esters" are no longer in medical use, except for trimeperidine (γ-promedol, p. 120),[24] anilidopiperidines ***C*** and ***D*** are used extensively, both as analgesics and in various anesthetic formulations.

In addition, all classes of opioid piperidines are valuable pharmacological tools in the research of opioid-related phenomena. In that respect, 4-anilidopiperidines have the most prominent role, in part because of their exceptional potency.

3.4.1 Simple opioid piperidines: pethidines (meperidines)

The original synthesis of pethidines is shown in *Scheme 3.9A*.[25] It involved bis-alkylation of benzyl cyanide with "nitrogen mustard" ***26.2***, in the presence of sodium amide. (The "nitrogen mustards" are simple to prepare on the industrial scale, using ammonia, primary or secondary amines and oxiranes, such as ethylene or propylene oxide. The resulting amino-diols (e.g. ***26.1***) are then converted to amino-dichlorides or dibromides. However, the compounds are stable only as salts, otherwise undergoing spontaneous *N*-alkylation). Subsequent acid hydrolysis and esterification of the resulting 4-cyano-piperidine ***26.3***, was performed in one synthetic operation, providing pethidine ***26.4*** in ~60% overall yields.

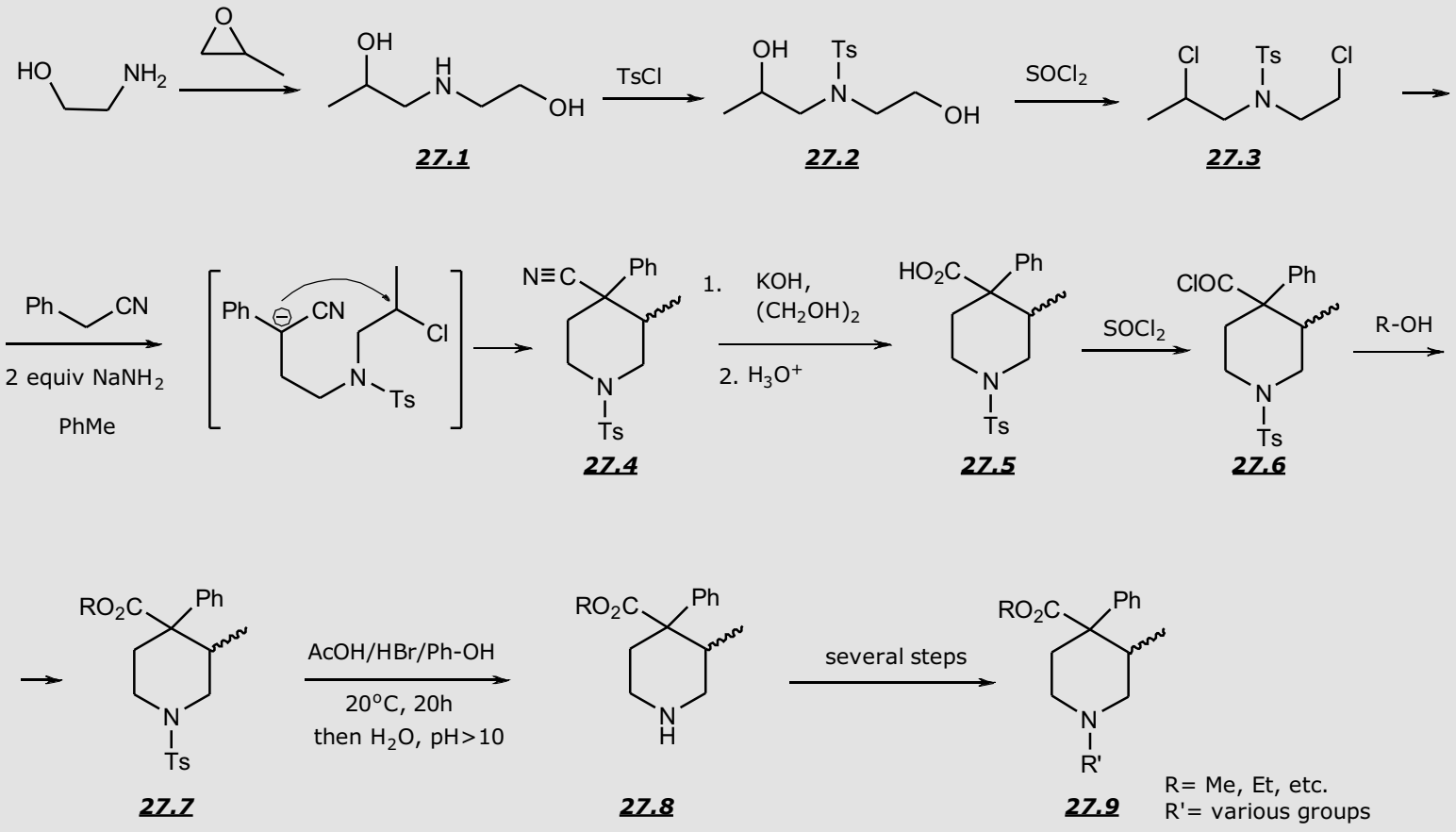
While efficient and scalable, the synthesis was highly hazardous, due to the extreme toxicity of "nitrogen mustards" (like sulphur mustard gas yperite, the are vesicants, mutagens and carcinogens). Thus, various alternative methods were devised,[26] such as the one presented in *Scheme 3.9 B*.[27]



Scheme 3.9A. Original synthetic approach to pethidines.

Diethanolamine ***27.1*** was *N*-tosylated and the hydroxyl groups converted to dichloride ***27.3***. (Compounds of this structure are not vesicants). The dichloride was used for bis-alkylation of benzyl cyanide, analogously to *Scheme 3.9B*, resulting in the diastereomeric mixture of piperidine ***27.4***. Vigorous basic hydrolysis secured carboxyl derivative ***27.5***, leaving the sulfonamide unchanged. (Sulfonamides are generally removed either by acid hydrolysis or by the reduction). The free carboxyl group was esterified, via acid chloride intermediate ***27.6***, followed by the selective, removal of the *N*-tosyl function. In the final steps, secondary piperidine ***27.8*** was elaborated by introducing various functionalized *N*-alkyl groups, general structure ***27.9***.

Since no yields or the reaction scale were indicated for any step, the practical applicability of the procedure cannot be ascertained.

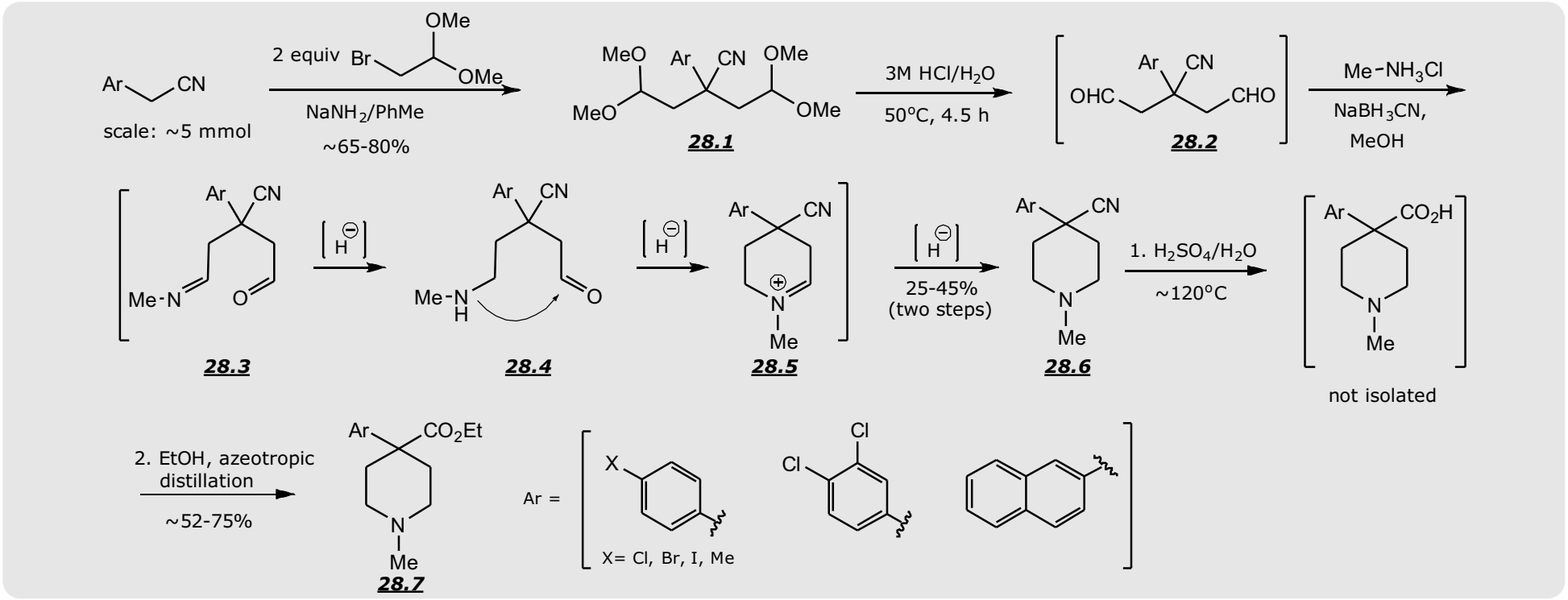


Scheme 3.9B. Modified synthetic approach to pethidines.

The key modification was the use of relatively non-toxic *N*-tosylated dichloride ***27.3***, although it later required selective removal of the sulfonamide protecting group.

However, the current industrial procedures for meperidine production have not been published and are apparently trade secrets.

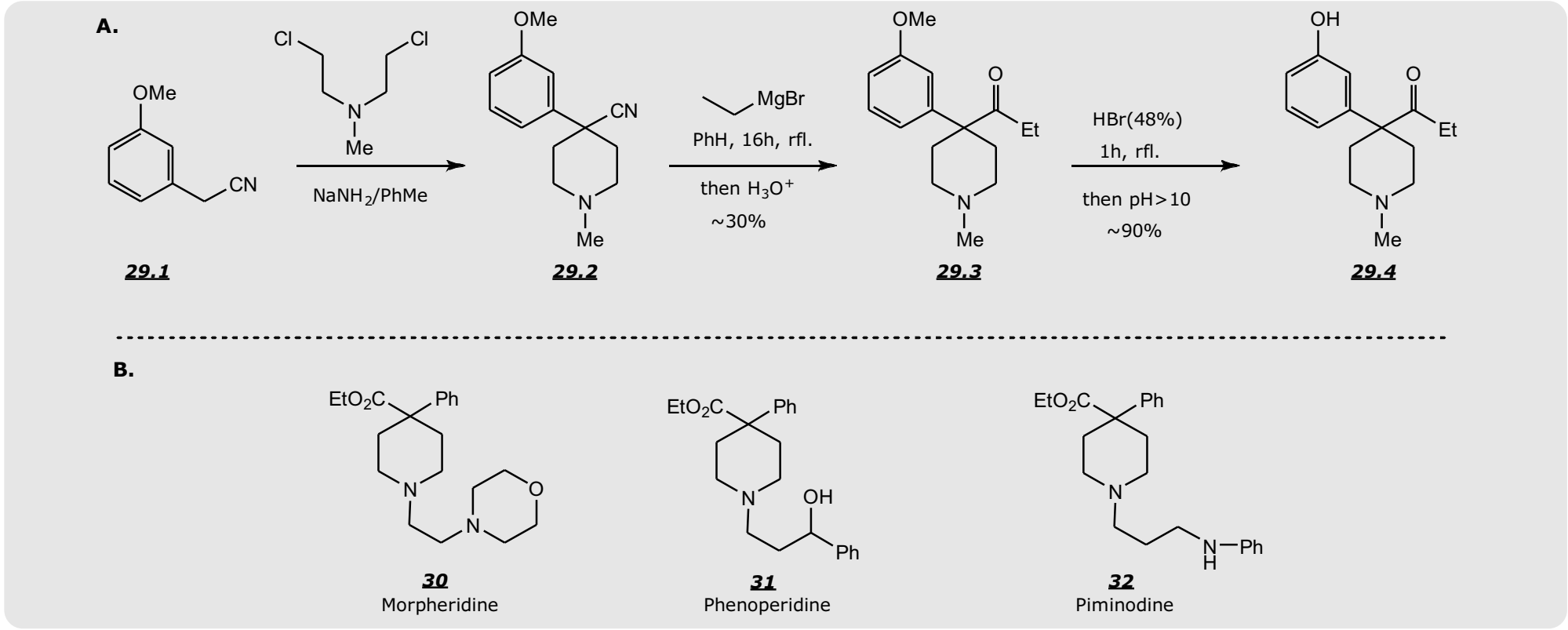
A modified laboratory method for the synthesis of meperidine analogues was reported more recently,[28] *Scheme 3.10*. The first step corresponds to *Scheme 3.9*, except that the alkylating agent was a protected aldehyde, 2-bromo-1,1-dimethoxyethane. Afer bis-alkylation and acid hydrolisis, the obtained di-aldehyde ***28.2*** was not isolated, but used directely in the consecutive reductive aminations, via intermediates ***28.3***, ***28.4*** and ***28.5***. The reductive aminations, selectively achieved by $NaBH_3CN$, secured the requsite piperidines, general structure ***28.6***. However, only relatively low yields were obtained, (25-45%), also requiring chromatographic purification. The synthesis was completed by the standard procedure, converting nitrile ***28.6*** to ethyl ester ***28.7*** in one synthetic step. (The procedure, acc. to *Sheme 3.9A*, involved acid-catalyzed hydrolisis of the nitrile group to free carboxylic acid, which was not isolated, but directly esterified, removing excess water by azeotropic distillation. Thus, tedious isolation of the free amino-acid intermediate was avoided). Although the method is suitable for the small-scale synthesis of various meperidine analogues of the general structure ***28.7***, it is probably not amenable for the scale-up. The compounds were used in SAR studies.[28]



Scheme 3.10. Laboratory procedure for the synthesis of pethidine analogues ***28.7.***

A closely related derivative of pethidine, ketobemidone ***29.4*** was first prepared by O. Eisleb, during the World War II (codename Hoechst 10720). The synthesis, published later by other authors,[29] is presented in *Scheme 3.11A*. The key step is the addition of ethylmagnesium bromide to the nitrile function, structure ***29.3*** which is one of the standard methods for the preparation of ketones. The reported yield for the particular step was low (~30%), although it could likely be improved using alternative reagents (e.g. ethyllithium) and/or solvents. Clevage of methyl ether by hydrobromic acid, provided the free phenol group, necessary for the optimal opioid activity. Presumably, the same general approach is still employed for the preparation of the drug.

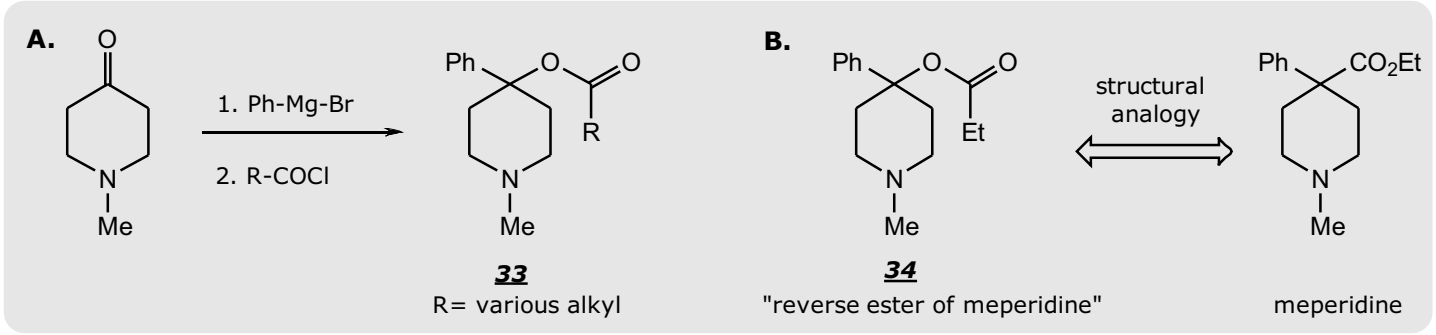
Structures of some significant pethidine derivatives, i.e. morpheridine ***30***,[30] phenoperidine ***31***,[31] and piminodine ***32***,[32] are shown in *Scheme 3.11B*. All three compounds were used as opioid drugs in some countries, but have been withdrawn from the global market because of serious side effects and/or insufficient potency.



Scheme 3.11. A. General synthetic approach to ketobemidone. B. Structures of some significant pethidine derivatives

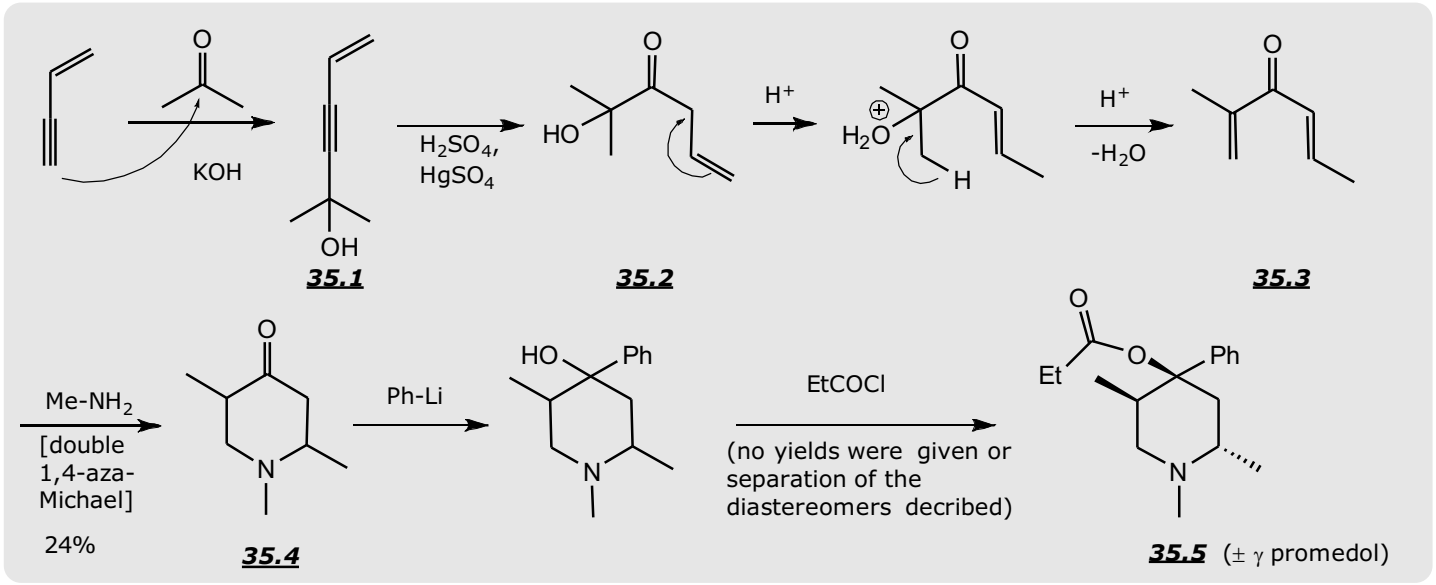
3.4.2 Simple opioid piperidines: reverse esters of pethidines.

Soon after the discovery of pethidine, it was found that "reverse esters of pethidine", *Scheme 3.12*, general structure ***33***, were also powerful opioid analgesics.[33] Particularly potent was ***34*** (about the potency of morphine). The compounds received much attention in the following decades, both because of the high, morphine-like potency and relative simplicity of the synthesis, *Scheme 3.12*.



33 ***34***

Scheme 3.12. A. General synthesis of "reverse esters". B. Structural analogy between "reverse esters" and meperidine.

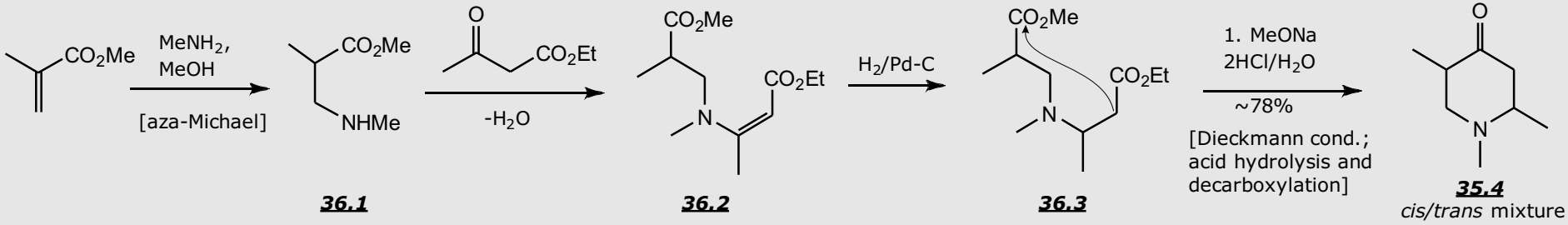


35.1 ***35.2*** ***35.3*** ***35.4*** ***35.5*** (± γ promedol)

Scheme 3.13. Original synthesis of promedol ***35.5***

Later, the Russian researchers developed a related opioid analgesic, similar in potency to morphine, named γ-promedol (± trimeperidine) ***35.5***, *Scheme 3.13*.[34] At present, (as of 2017), the drug is still used, mainly in the former USSR republics.

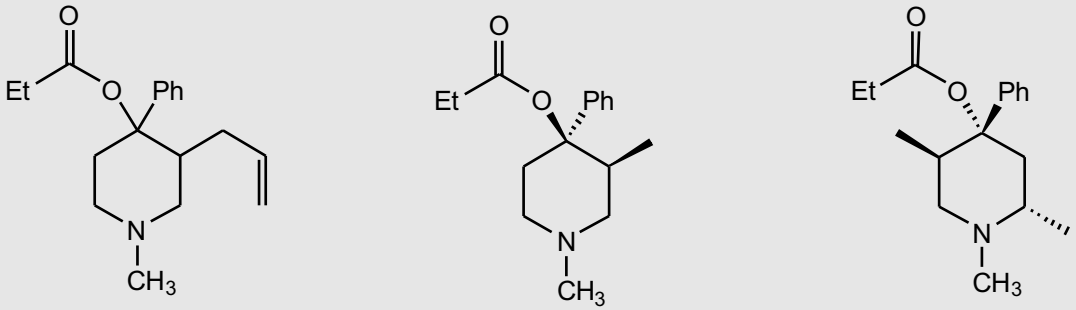
The initial manufacturing technology, developed in early 1950s, provided the key intermediate, piperidone ***35.4***, in relatively low yields and required toxic Hg^{2+} catalyst, *Scheme 3.13*.[35] The separation of diastereomers was not disclosed.



Scheme 3.14. Alternative synthesis of piperidone ***35.4*** as promedol precursor.

While piperidone ***35.4*** can be prepared acc. to *Scheme 3.16*, recently published paper revealed a different approach, *Scheme 3.14*.[36] Simple aza-Michael addition, acc. to the previously published protocol,[37] provided β-amino-ester ***36.1***, followed by the condensation with ethyl acetoacetate. Catalytic hydrogenation of the enamine ***36.2***, followed by the Dieckmann cyclization, acid hydrolysis and spontaneous decarboxylation afforded piperidone ***35.4*** as *cis*/*trans* mixture (~78% yield). However, further elaboration to γ-promedol was not published. As already noted, a great deal of effort has been paid, over past several decades, to the synthesis and pharmacological evaluation of various "reverse meperidiene esters" (According to the sub-structure searches of SciFinder, about 1400 derivatives were prepared, as of 2017). Of those compounds, several entered the market as opioid drugs, however all except γ-promedol ***35.5*** have been withdrawn, as better pharmacological alternatives emerged.

Prominent examples are: allyprodine ***37***,[38] (+) alphaprodine ***38***[39] and (±) α-promedole ***39***,[40] Scheme 3.15.



Scheme 3.15. Examples of the significant "reverse esters of meperidine" (formerly used as opioid drugs).

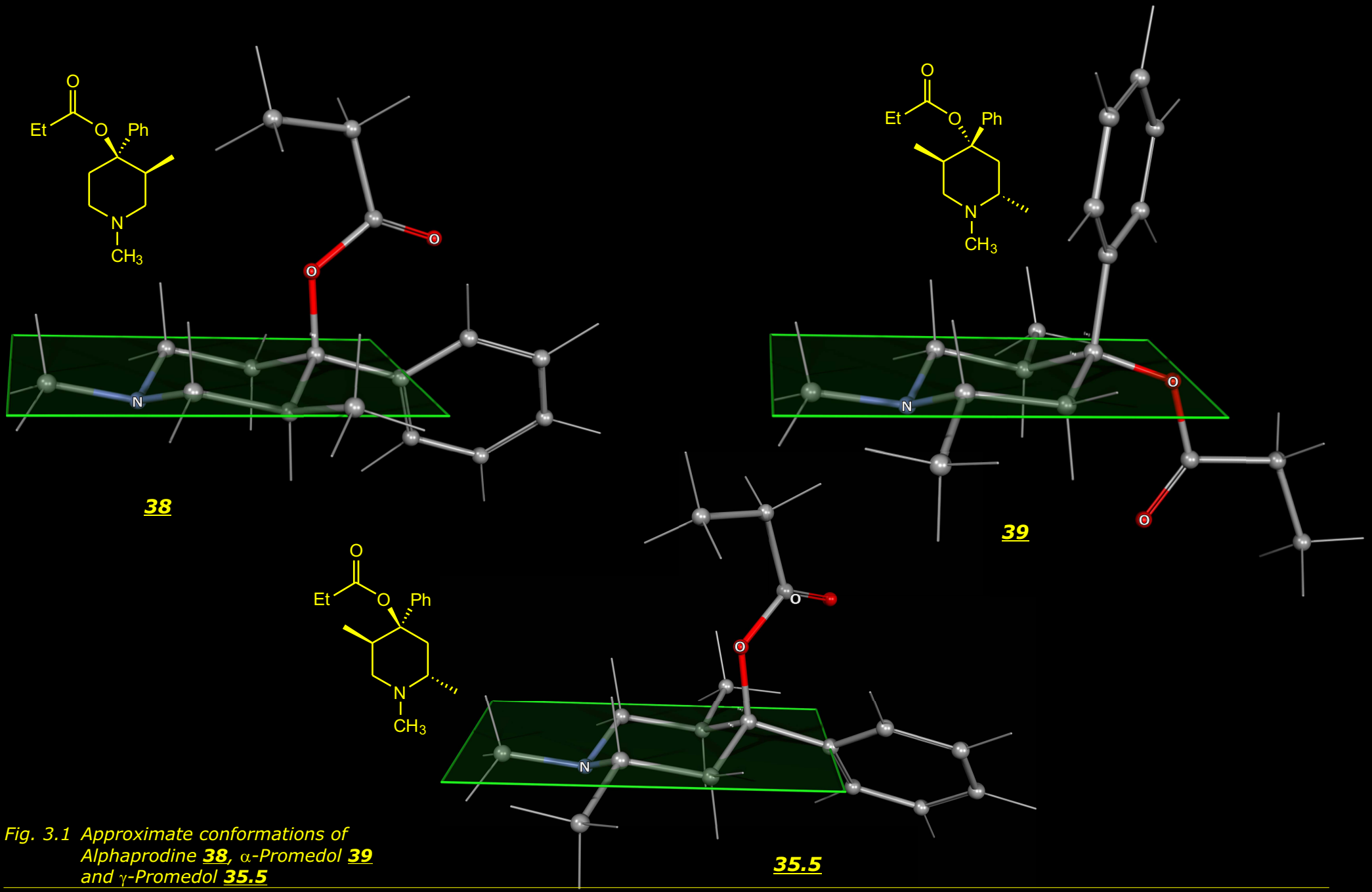


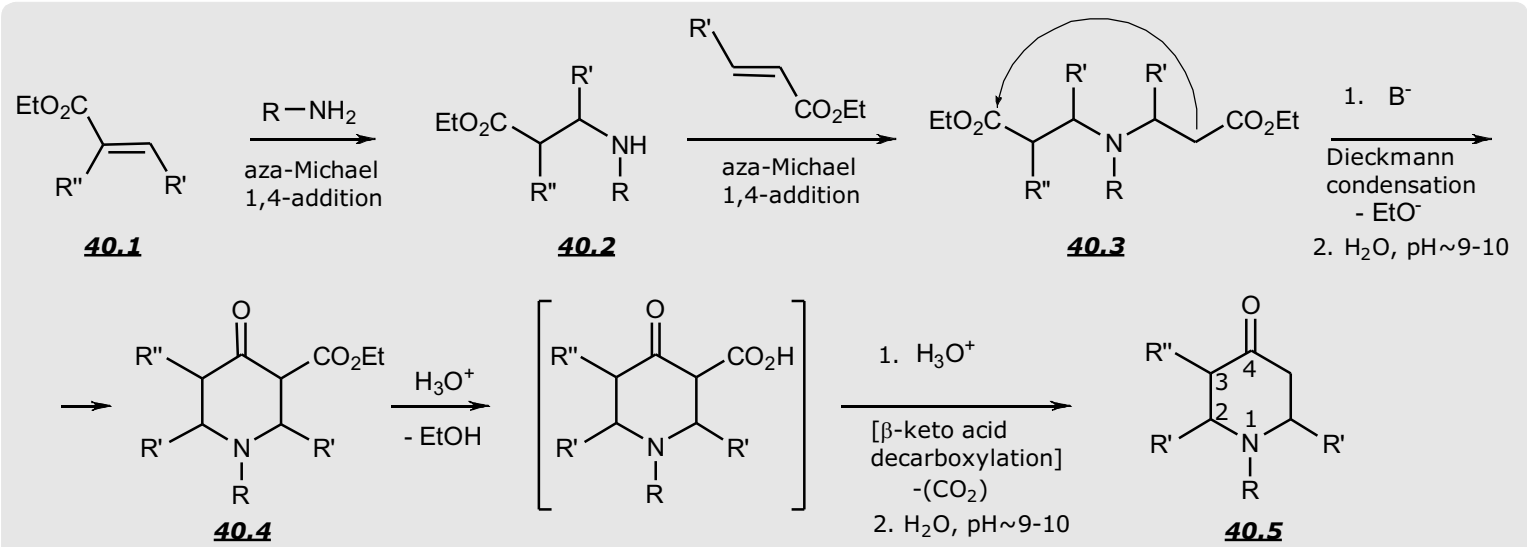
*Fig. 3.1 Approximate conformations of Alphaprodine **38**, α-Promedol **39** and γ-Promedol **35.5***

3.4.3 Simple opioid piperidines: 4-Piperidone Precursors

The extensive research in "reverse esters of meperidine", anilido-piperidines and the related groups, (structures B, C and D, *Scheme 3.1*) was possible because the immediate precursors, various 4-piperidones were accessible through a relatively simple synthesis, involving 3 to 4 steps, *Scheme 3.16*.[41,42,43] The aza-Michael addition of primary amines to conjugated esters may be performed step-wise, producing symmetric or non-symmetric β-amino diesters ***40.3***. The compounds are suitable substrates for Dieckmann condensation, resulting in the six-membered β-keto esters ***40.4*** (5-membered analogues are obtained as ~1:1 mixtures of two regio-isomers). Although the β-keto esters are useful intermediates in heterocyclic synthesis, they are usually converted to 4-piperidones of the general structutre ***40.5***, by a simple acid hydrolysis and decarboxylation. (The compounds are acid-stable, while prone to base-catalyzed decomposition). Despite the apparent simplicity, both the aza-Michel addition and Dieckmann condensation can be incomplete, often resulting in the mixtures and modest yields. The Dieckmann condensation may be difficult to perform, particularly on a large scale, since it requires mechanical stirring and the prolonged reflux. Also, depending on the reactant structure, solid gels can form, effectively blocking the reaction.

Recently, a modification of Dieckmann condensation was reported, using DMSO or DMSO/THF as a solvent and NaH as base.[44]

The reaction proceeds to completion at ambient temperature, typically in 15-45 min, no gels are formed and pure heterocyclic β-keto esters ***40.4*** are isolated in 80-95% yields on a multi-gram scale (e.g. 50-500 mmol). Even t-Bu diesters react quantitatively, albeit at slower rate (~2 h).



40.1 ***40.2*** ***40.3*** ***40.4*** ***40.5***

R= Me, Bn, 2-Phenethyl; R', R''= H, Me. *Note*: Me, *t*-Bu and other esters can also be used

Scheme 3.16. General procedure for the preparation of 4-piperidones ***40.5***.

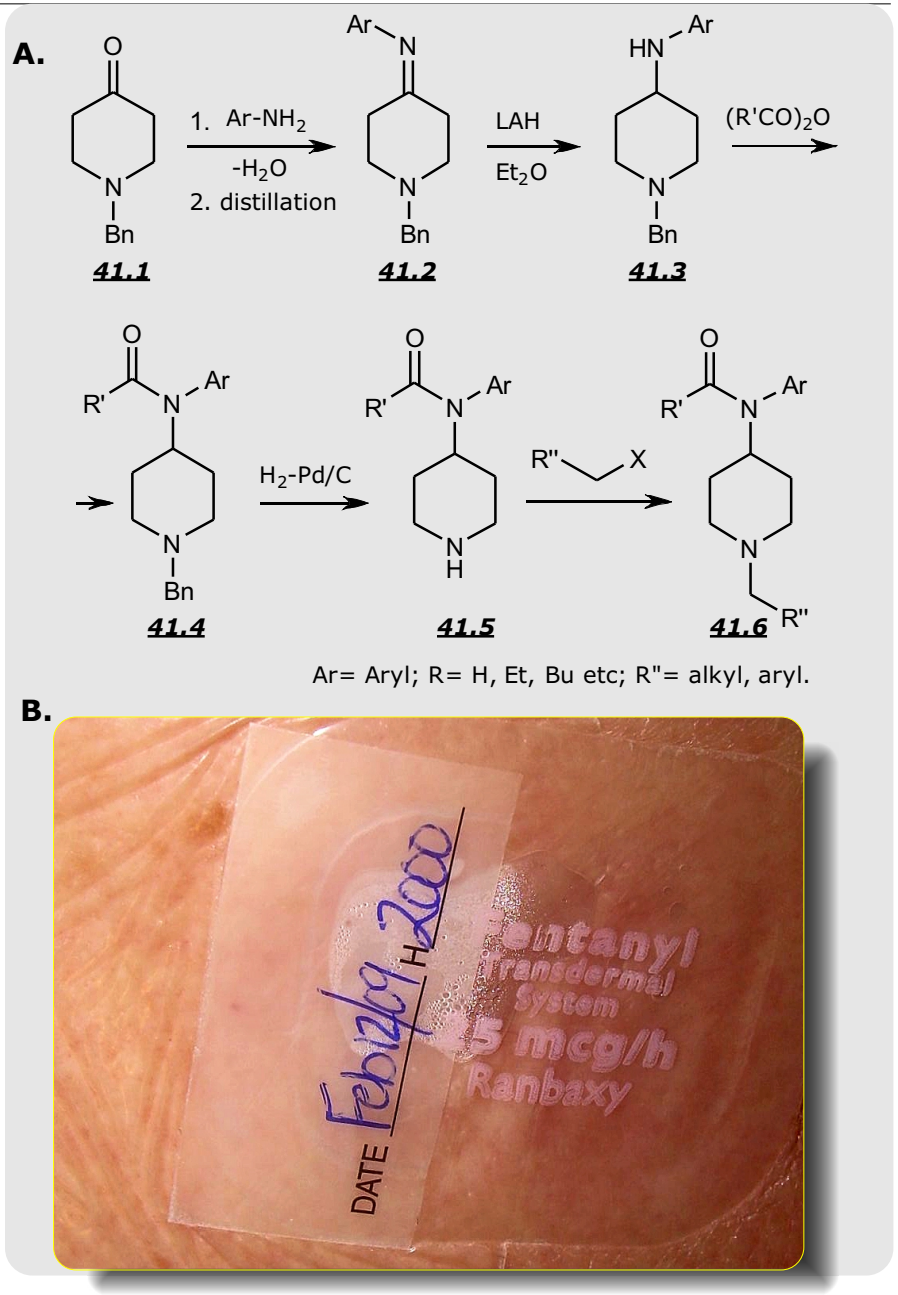
3.4.4 Simple opioid piperidines: 4-anilido-piperidines.[45a,46]

In the late 1950s, Paul A. J. Janssen and coworkers discovered that some of the novel 4-anilido-piperidines possessed significant opioid analgesic activity. Their research efforts resulted in the general, patented synthesis[47] of these compounds, *Scheme 3.17A*. (No yields were given in the patent). Condensation of piperidone ***41.1*** with various aromatic amines gave imines ***41.2***, purified by distillation. Reduction of the imino group with LAH furnished secondary arylamines ***41.3***, Acylation of the secondary amino group using simple acid anhydrides (e.g. propionic anhydride), followed by the catalytic hydrogenolysis of *N*-benzyl group, afforded the secondary piperidines ***41.5***. In the final step, the desired 4-anilido-piperidines ***41.6*** were obtained by direct *N*-alkylation .

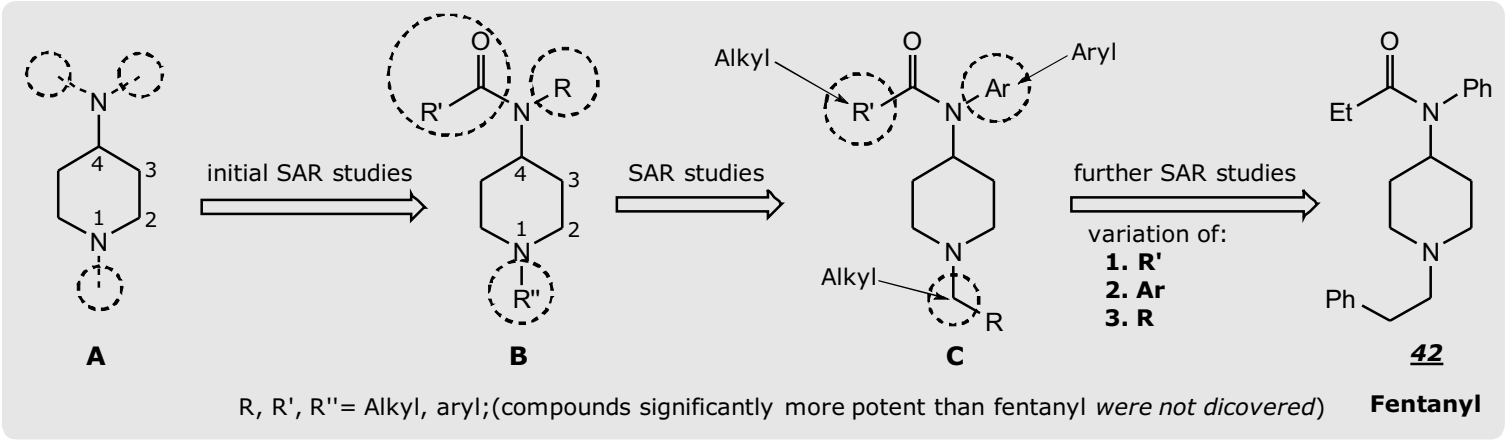
Detailed pharmacological tests revealed that one of the prepared compounds was 50-100 times more potent analgesic than morphine, with the significant clinical potentials. It received the INN (International Nonproprietary Name) fentanyl, (structure ***42***, *Scheme 3.18*). The compound eventually become widely used and essential active pharmaceutical ingridient (API) of various anesthetic formulations and opioid analgesics, including transdermal patches, *Scheme 3.17 B*.[45b,c]

Early structure-relationship studies (SAR) of 4-anilido-piperidines focused on the variation of three substituents on the piperidine ring: 1) the acyl group, R'CO, 2) R group and 3) R'' group, structure A, *Scheme 3.18*. It was found that a compound must satisfy at least four general structural requirements, in order to possess any analgesic activity, structure C.

(The first SAR study actually resulted in the original patent).[45,47]



Scheme 3.17. A. General synthetic procedure for the synthesis of 4-anilido-pipredines ***41.6***. B. Applied fentanyl transdermal patch.



Scheme 3.18. General structural requirements for the opioid activity in 4-anilido-piperidines, Structure C.

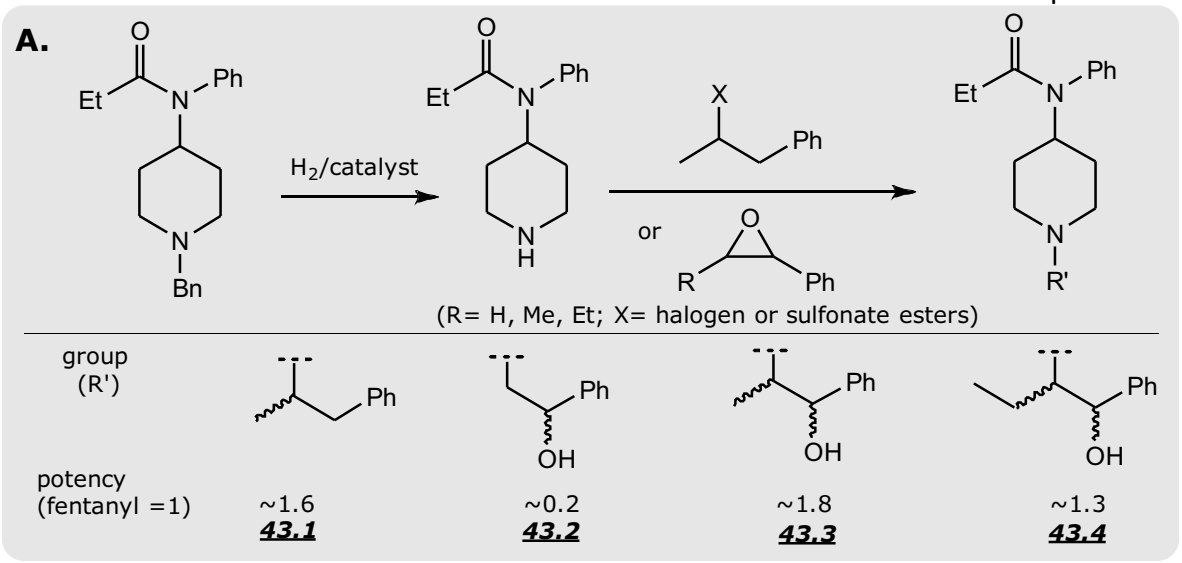
Minimal structural requirements for the opioid activity of anilido-piperidines are:

1. 4-amino group must by acylated, i.e. the structure must be a tertiary carboxamide.

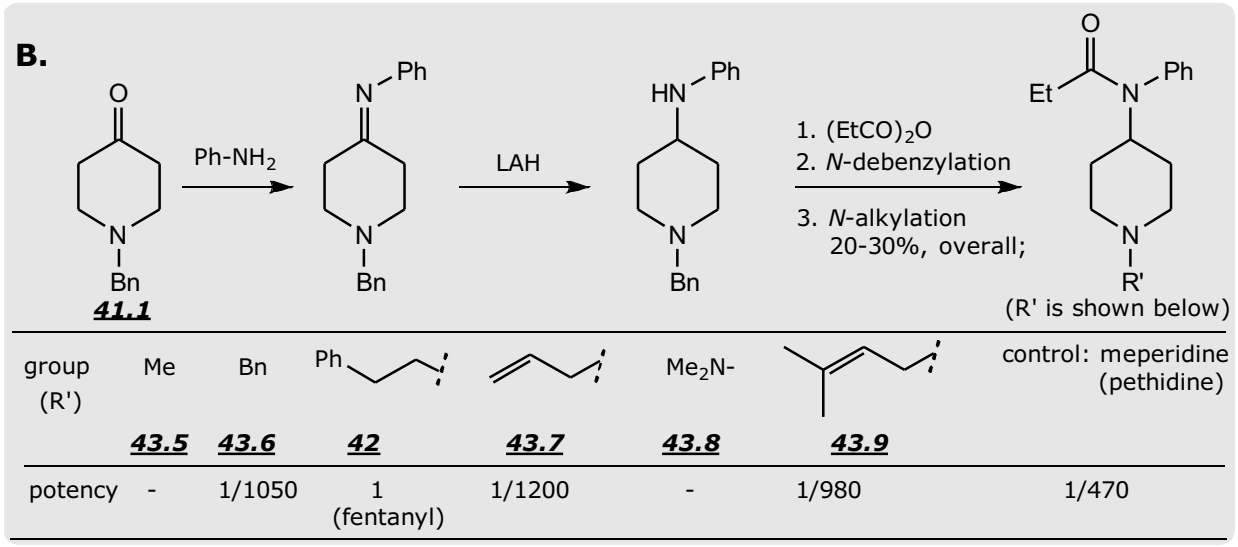
2. 4-amino group must be arylated (R= aryl). Phenyl group confers the highest activity, while substituted aryl groups always diminish the potency. Alkyl groups or hydrogen abolish the activity.

3. Acyl group must be alkanoyl, (R'= alkyl, simple or with some functional groups). Propionyl derivatives are the most potent, at least 10 times more than the acetyl or butyryl analogues. Aroyl derivatives (R'= aryl) are generally inactive.

4. Piperidine nitrogen must be alkylated (R''= alkyl, simple or with some functional groups, e.g. aryl). Most alkyl derivatives possess some activity, however only 2-arylethyl analogues are highly potent analgesics. Aryl derivatives (R''= aryl) are inactive. During the 1960s and later, numerous new analogues of the general structure B, *Scheme 3.18,* were prepared and tested pharmacologically. Interestingly, only a few derivatives were reported to be slightly more potent than fentanyl, with the majority much less potent or inactive. Several of those more active derivatives possess substituted *N*-phenethyl moiety, as shown in *Scheme 3.19A*.[48] However, the potency enhancement, relative to fentanyl, was small and practically insignificant.



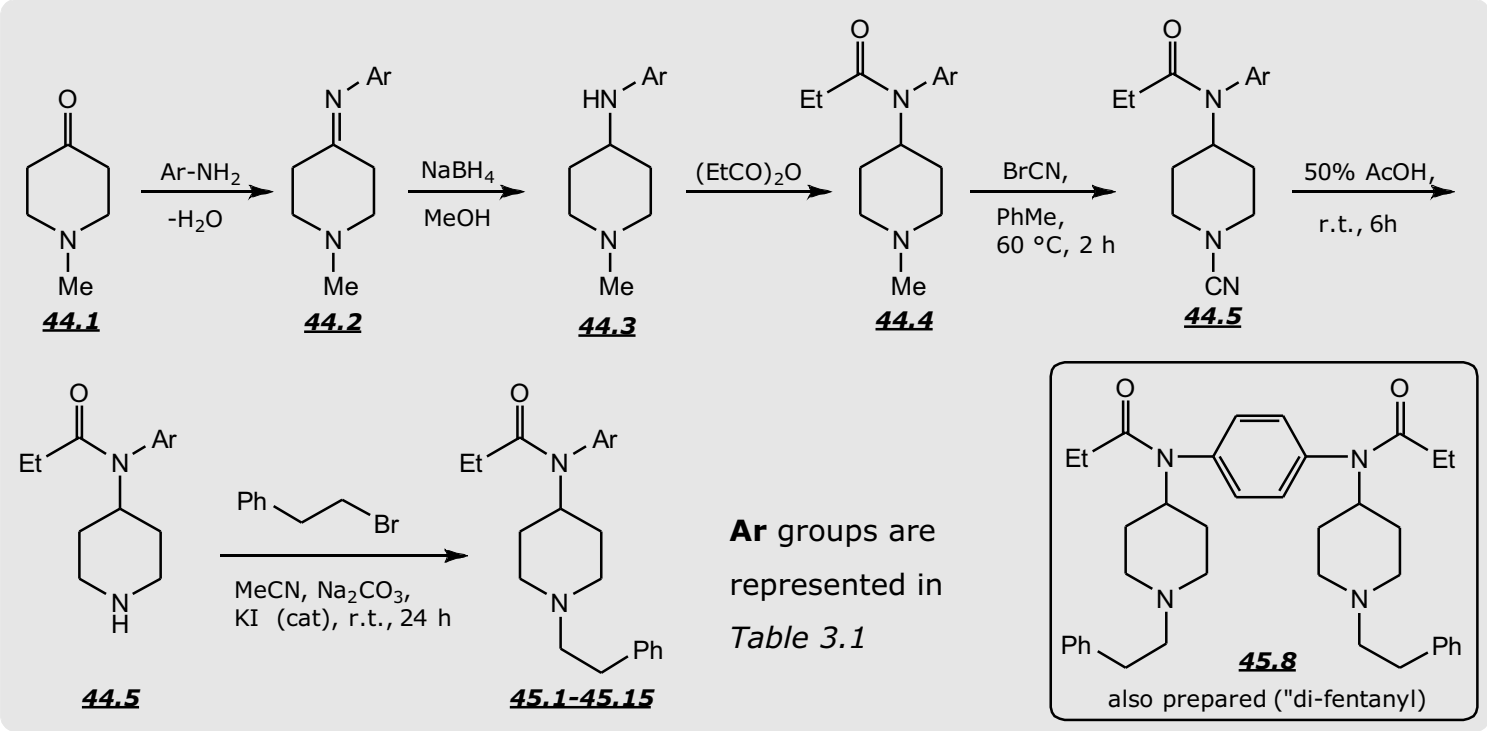
Scheme 3.19A. Fentanyl analogues with various *N*-alkyl substituents



Scheme 3.19 B. Fentanyl analogues with various alkyl substituents at the piperidine nitrogen.

Groups other than 2-arylethyl severely diminished or completely abolished the analgesic activity,[49] as exemplified in *Scheme 3.19 B*.

The influence of 4-*N*-aryl substituents to the pharmacological activity was examined in detail. General synthetic approach to those derivatives is shown in *Scheme 3.20*.[50] The synthesis followed the general procedure, starting from the readily available *N*-methyl piperidone ***44.1***. The imines were reduced using $NaBH_4$ in methanol, rather than LAH. After removal of *N*-methyl group via classical von Braun reaction, the expected fentanyl analogues ***45.1***-***45.8*** were prepared by *N*-alkylation with 2-phenylethyl bromide. Compounds ***45.9***-***45.15*** (*Table 3.1*) were prepared using similar protocol.[51] The only enhancement in analgesic activity, observed with the o-OMe group, was statistically insignificant (1.3 times fentanyl, *Table 3.1*, entry 10).



Scheme 3.20. Alternative synthesis of fentanyl analogues with various alkyl substituents at the piperidine nitrogen.

All other substituents, either diminished the analgesic potency to various extents or completely abolished it (*Table 3.1*, entries 1-9 and 11-15).

Two major studies[52a, 52b] examined the influence of 4-*N*-heteroaryl groups to analgesic and other pharmacological properties of fentanyl analogues, *Scheme 3.21 A and B*. The most efficient synthesis of 4-*N*-heteroaryl derivatives at the time (in 1980s), involved direct *N*-arylation of the intermediate amines ***46.3*** with various heteroaryl chlorides and bromides (Ullmann-type reaction). The relatively harsh reaction conditions, in the presence of elemental copper, provided *N*-aryl amines of the general structure ***47***, mainly in modest yields. The final products, carboxamides ***48***, were obtained by simple *N*-acylation.

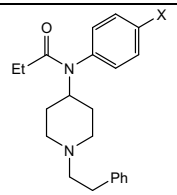
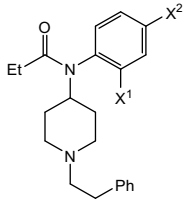
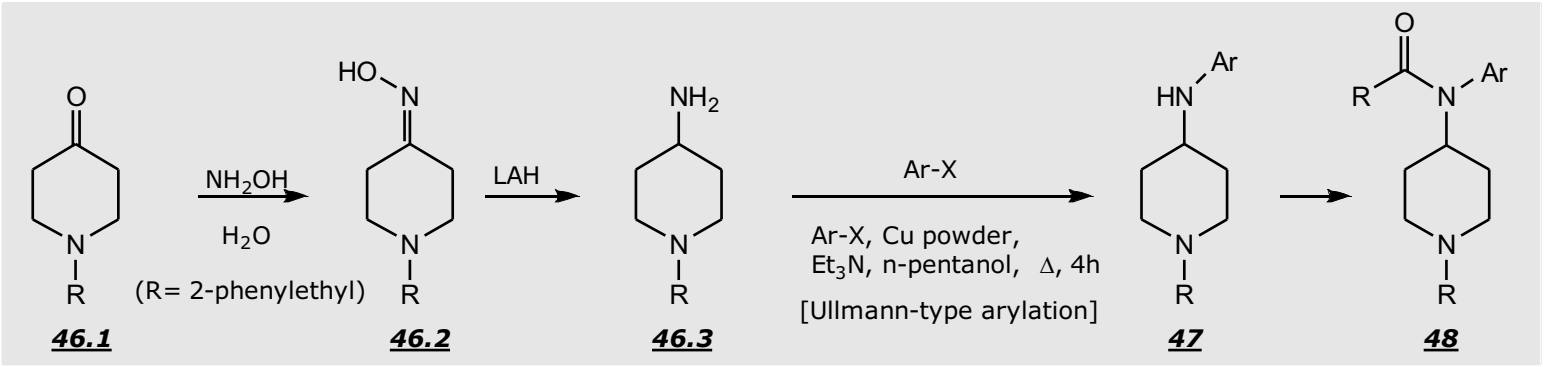
No	COMPOUND	ACTIVITY (fentanyl =1)	No	COMPOUND	ACTIVITY (fentanyl =1)
					
1	X = F; ***45.1***	0.5	9	X^1 = OH, X^2 = H; ***45.9***	0.1
2	X = Cl; ***45.2***	0.02	10	X^1 = OMe, X^2 = H; ***45.10***	1.3
3	X = Br; ***45.3***	0.01	11	X^1 = OEt, X^2 = H; ***45.11***	0.6
4	X = I; ***45.4***	0.06	12	X^1 = OMe, X^2 = OMe; ***45.12***	0.25
5	X = CF_3; ***45.5***	0.01	13	X^1 = OMe, X^2 = OH; ***45.13***	0.8
6	X = Me; ***45.6***	0.03	14	X^1 = Me, X^2 = H; ***45.14***	0.7
7	X = NHCOEt; ***45.7***	0	15	X^1 = Me, X^2 = Me; ***45.15***	0.5
8	"di-fentanyl'; ***45.8***	0	-	-	-

Table 3.1. Relative opioid potencies of 4-aryl substituted fentanyl analogues

Representative structures, A[52a] and B[52b] are shown in *Scheme 3.21 B.* (In the past two decades, the *N*-arylation is usually performed using Pd-catalyzed protocol, known as Buchwald-Hartwig Cross Coupling Reaction).[53]

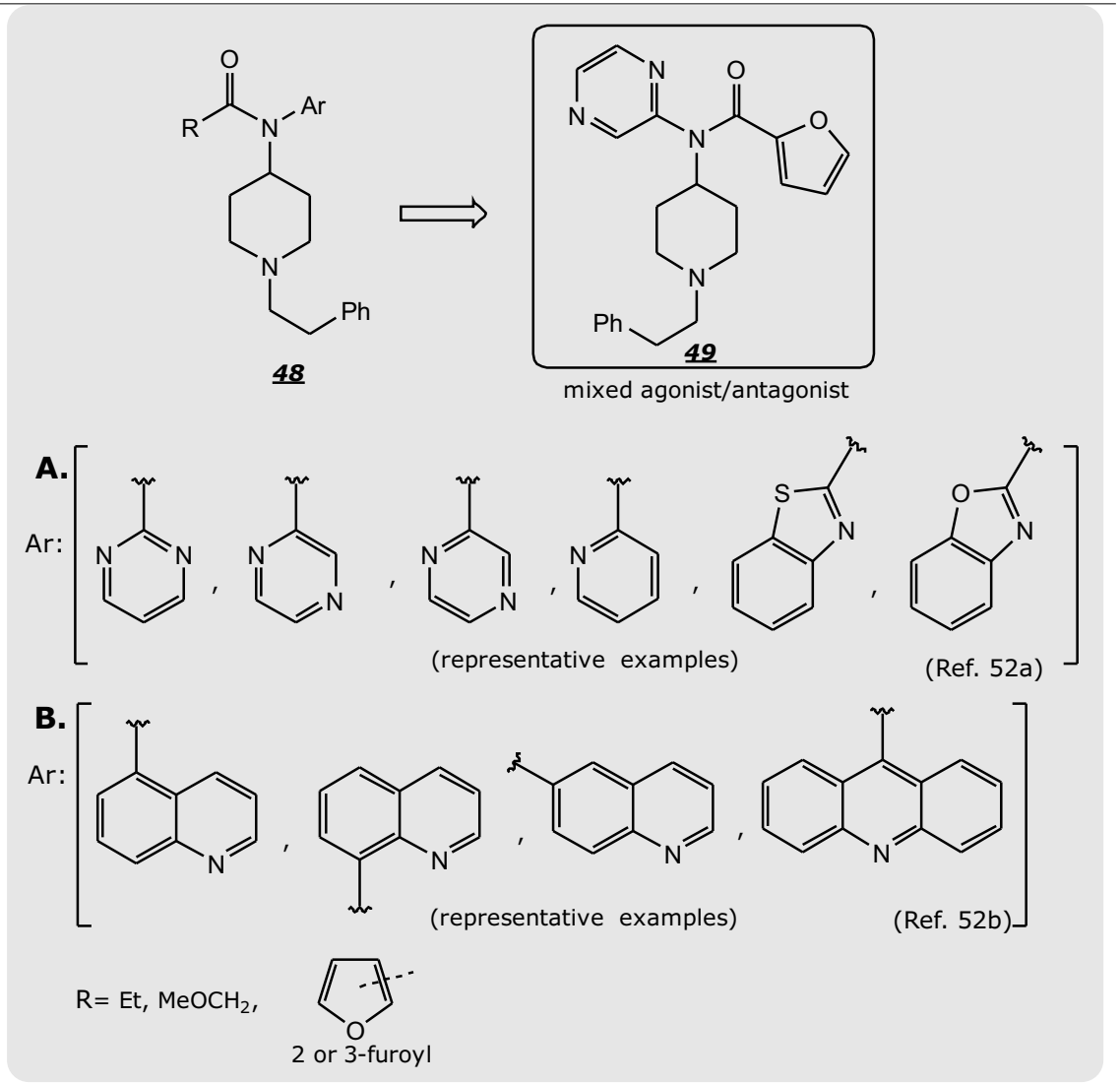
The studies, which also included variations of acyl groups, generally resulted in the pharmacologically inactive compounds, proving that *N*-heteroaryl groups could not effectively substitute the *N*-phenyl group in fentanyl analogues.



Scheme 3.21 A. General approach to fentanyl analogues having 4-*N*-heteroaryl groups[52]

A notable exception was compound ***49***,[52a] *Scheme 3.21 B*, which exhibited unusual pharmacology, best described as a mixed opioid agonist/antagonist. However, it seems that similar compounds were not investigated further.

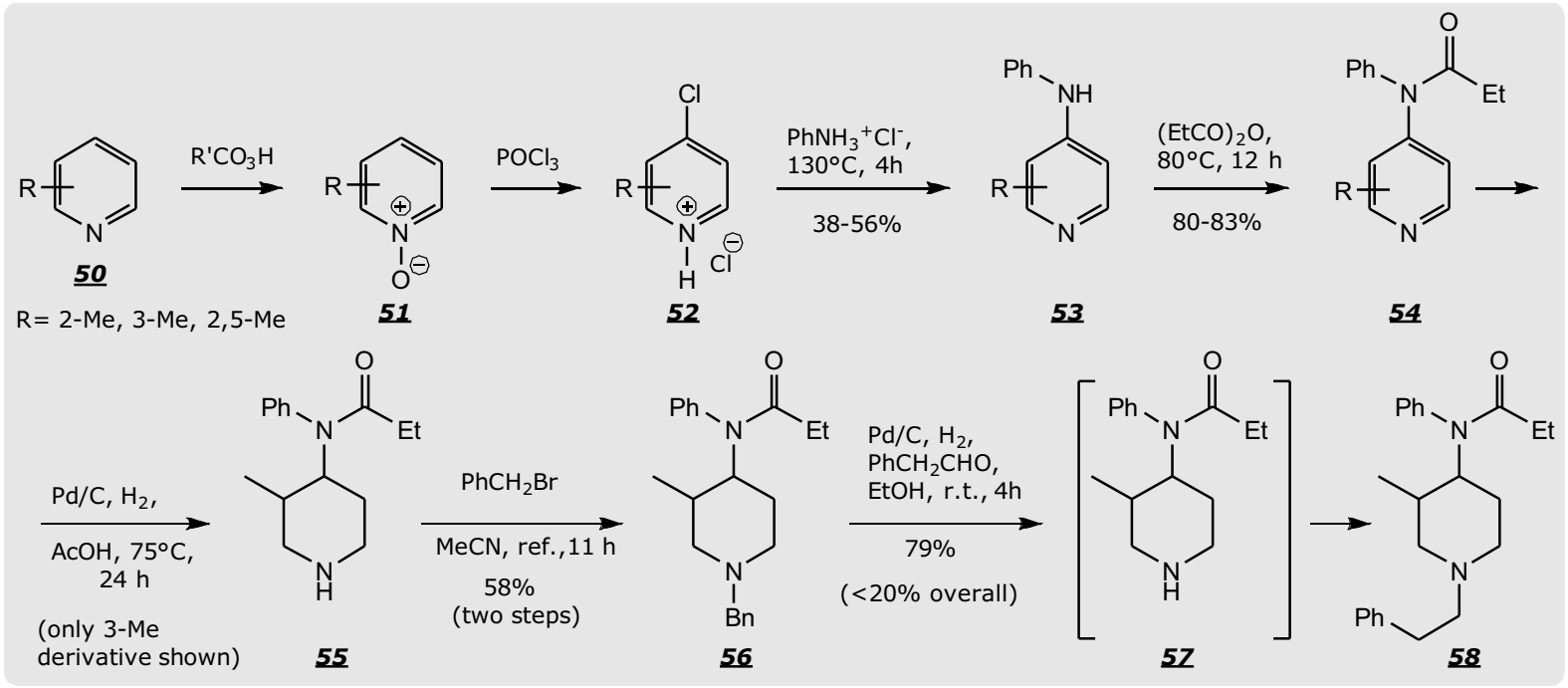
While most of the 4-anildo-piperidines have been synthesized from 4-piperidones, pyridines were also used as the precursors. One of the first reported synthesis from pyridine precursors, is shown *Scheme 3.22.*[54] Thus, methyl substituted pyridines ***50*** were converted into *N*-oxides ***51***, followed by the regioselective 4-chlorination using $POCl_3$. (The standard protocol for introducing halogens into the pyridine ring, since free pyridines are quite unreactive, unlike the *N*-oxides). Nucleophilic substitution with aniline, in a sealed vessel, gave 4-phenylamino pyridines ***53*** in modest yields. After *N*-propionylation and catalytic hydrogenation of the pyridine ring, secondary piperidines were obtained, such as 3-methyl derivative ***55***. The products were *N*-benzylated, to facilitate isolation and purification. In the final step, simultaneous catalytic hydrogenolysis and the reductive amination with 2-phenylacetaldehyde furnished the corresponding methyl fentanyls (2-Me, 3-Me and 2,5-di-Me). Only the structure of 3-methyl fentanyl ***58*** is shown in *Scheme 3.22.* (The stereochemistry was not determined).



Scheme 3.21 B. Structures of fentanyl analogues having 4-*N*-heteroaryl rings[52]

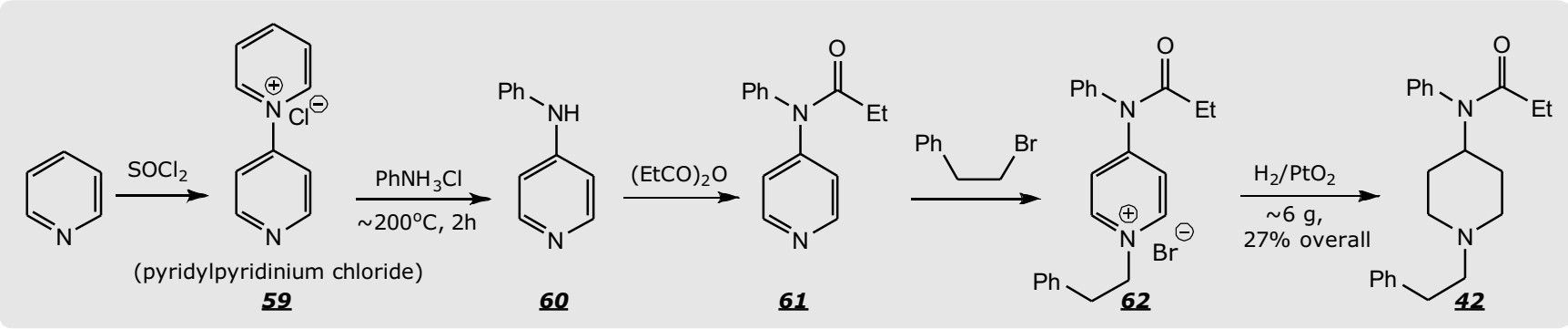
In practical terms, the general synthetic approach is clearly inferior to the 4-piperidone route, due to the very low overall yields, multitude of side products and the need for pressure vessel.

Despite synthetic limitations, the research demonstrated that, unexpectedly, 3-methyl fentanyl ***58*** (presumably *cis* dia-stereomer) was about 10 times more potent than the parent compound. (Presumably, the compound was *cis* dia-stereomer). It was later confirmed by more detailed synthetic and pharmaco-logical studies. A similar approach to fentany ***42***l used readily accessible pyridylpyridinum chloride ***59***, *Scheme 3.23.*[55] Thus, heating ***59*** with aniline hydrochloride pro-duced *N*-phenyl-pyridin-4-amine ***60***. After acylation and alkylation, the resulting quaternary pyridinium salt ***62*** was hydrogenated to afford ~6 g of fentanyl in 27% overall yield.



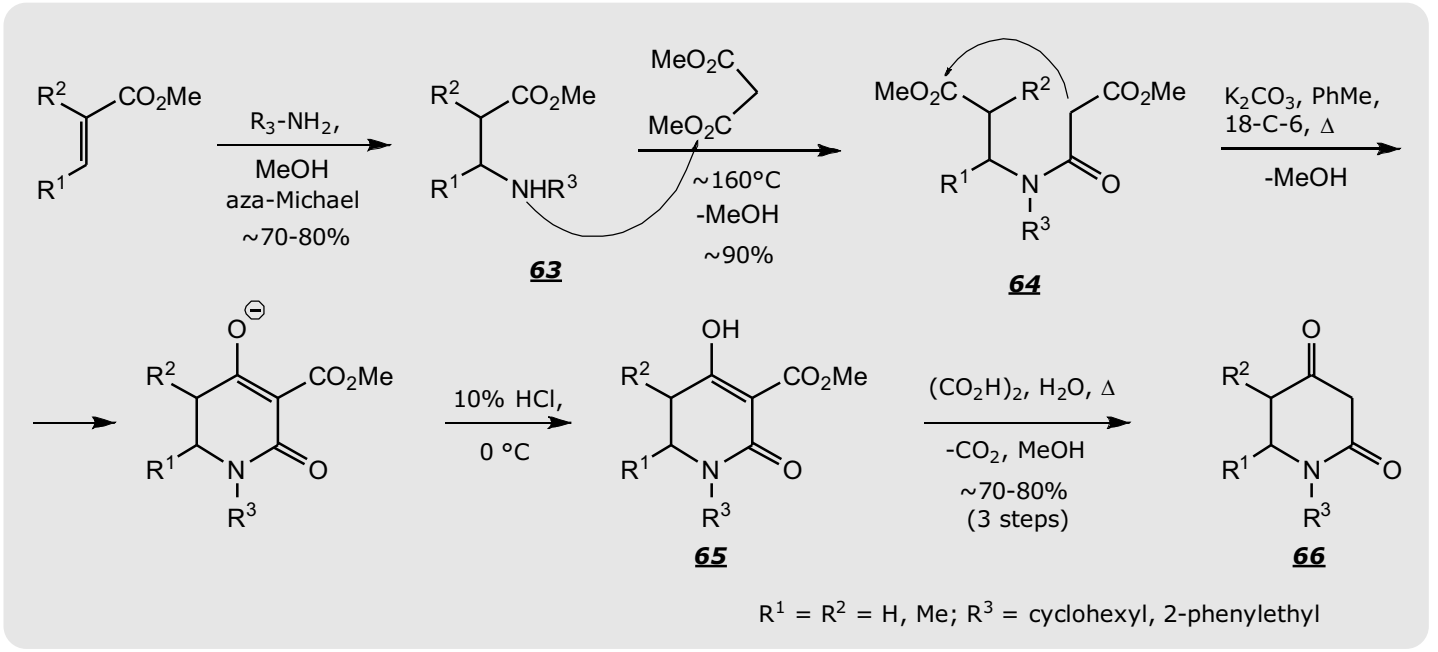
Scheme 3.22. Synthesis of 2-Me, 3-Me and 2,5-di-Me fentanyl analogues from pyridine precursors

The method appears to be less effective than 4-piperidone approach, particularly because it requires costly Pt catalyst.



Scheme 3.23. Synthesis of fentanyl from pyridine.

A substantially different approach to 4-anilido-piperidines involved piperidine-2,4-diones as the key intermediates, *Scheme 3.24*. Although the compounds were known for decades, a phase-catalyzed modification made their preparation simple and efficient.[56] After the selective aza-Michael addition, the resulting β-amino esters ***63*** were smoothly *N*-acylated at elevated temperature, using dimethyl malonate. Dieckmann-type cyclization of the resulting diesters ***64*** proceeded to completion in the presence of K_2CO_3 as base and 10 mol% of 18-C-6. Apparently, the active methylene group was sufficiently acidic to form enolate anion in the presence of a weak base and crown ether catalyst. (Earlier methods used molten sodium as a base). Hydrolysis of ester ***65*** in a moderately acidic medium (aqueous oxalic acid) resulted in selective and quantitative decarboxylation, providing pure piperidine-2,4-diones ***66*** in good overall yields. (Use of the mineral acids resulted in the lactam hydrolysis).

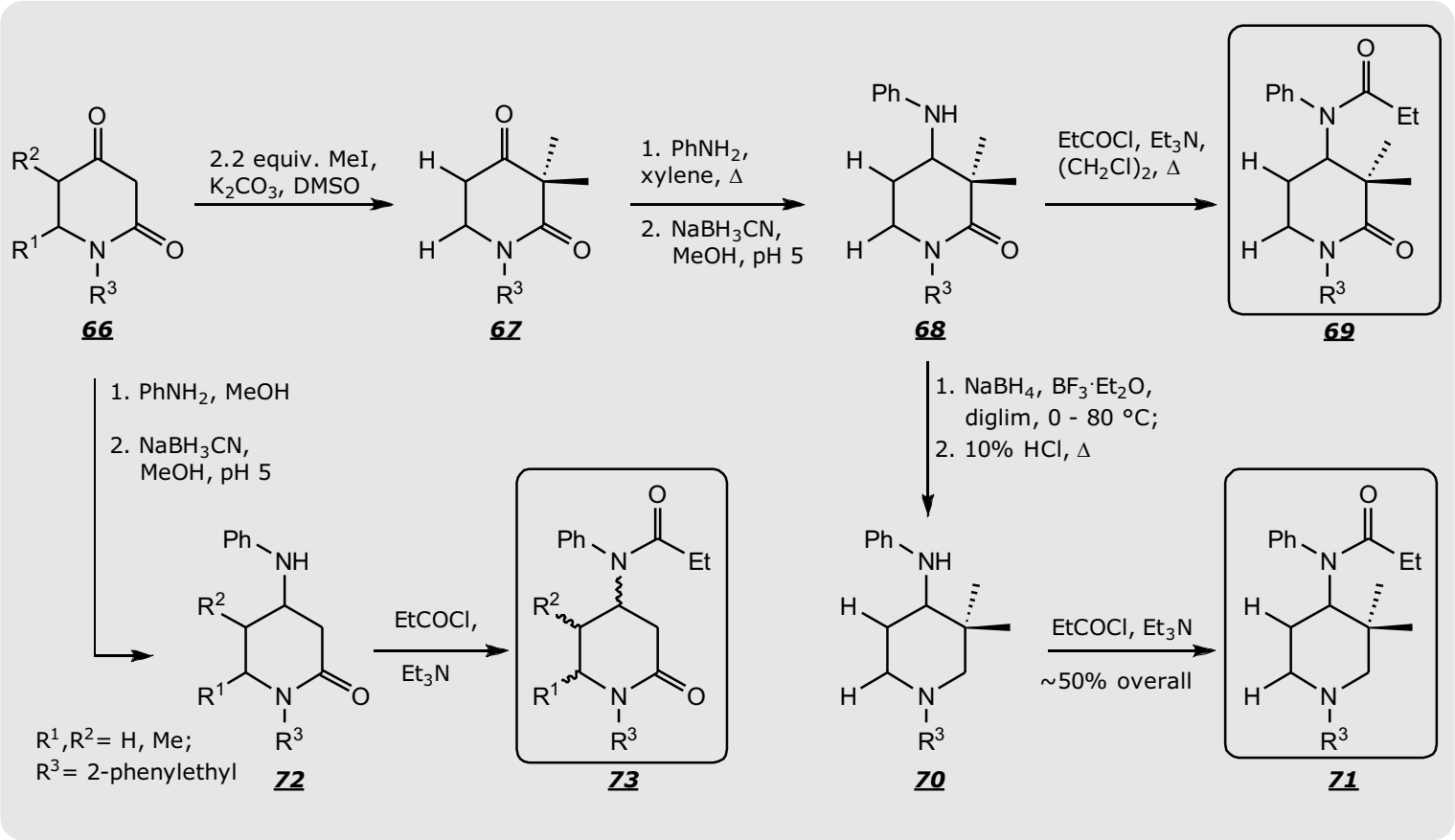


Scheme 3.24. Improved synthesis of piperidine-2,4-diones.

Piperidine-2,4-diones proved to be versatile intermediates in the synthesis of 4-anilido-piperidines and their derivatives, *Scheme 3.25.*[55] Methylation in the position 3 gave 3,3-dimethyl derivative ***67***. Condensation with aniline, followed by the enamine reduction, produced anilino-lactam ***68***. The compound was converted to 4-anilido-lactam ***69*** by simple *N*-propionylation. Alternatively, ***68*** was first reduced to piperidine ***70***, using *in situ* generated borane.

The final product, 3,3-dimethyl fentanyl ***71*** was obtained in good overall yield (~50%). Substituted 4-anilido-lactams of the general structure ***73*** were synthesized analogously to ***69***. In all instances, the obtained *cis*/*trans* diastereomers were separated chromatographically.

It is apparent that the general synthetic approach has a considerable potential in the synthesis of various heterocycles, including 4-anilido-piperidines, particularly because it was performed on a considerable scale (10-20 mmols of the final products). However, it was not developed further, nor the compounds were tested pharmacologically. (The lactam derivatives are highly unlikely to be opioid analgesics, since they do not possess the basic nitrogen – an almost universal requirement for the opioid activity of any type).



Scheme 3.25. Piperidine-2,4-diones in the synthesis of 4-anildo-piperidines and their lactam analogues.

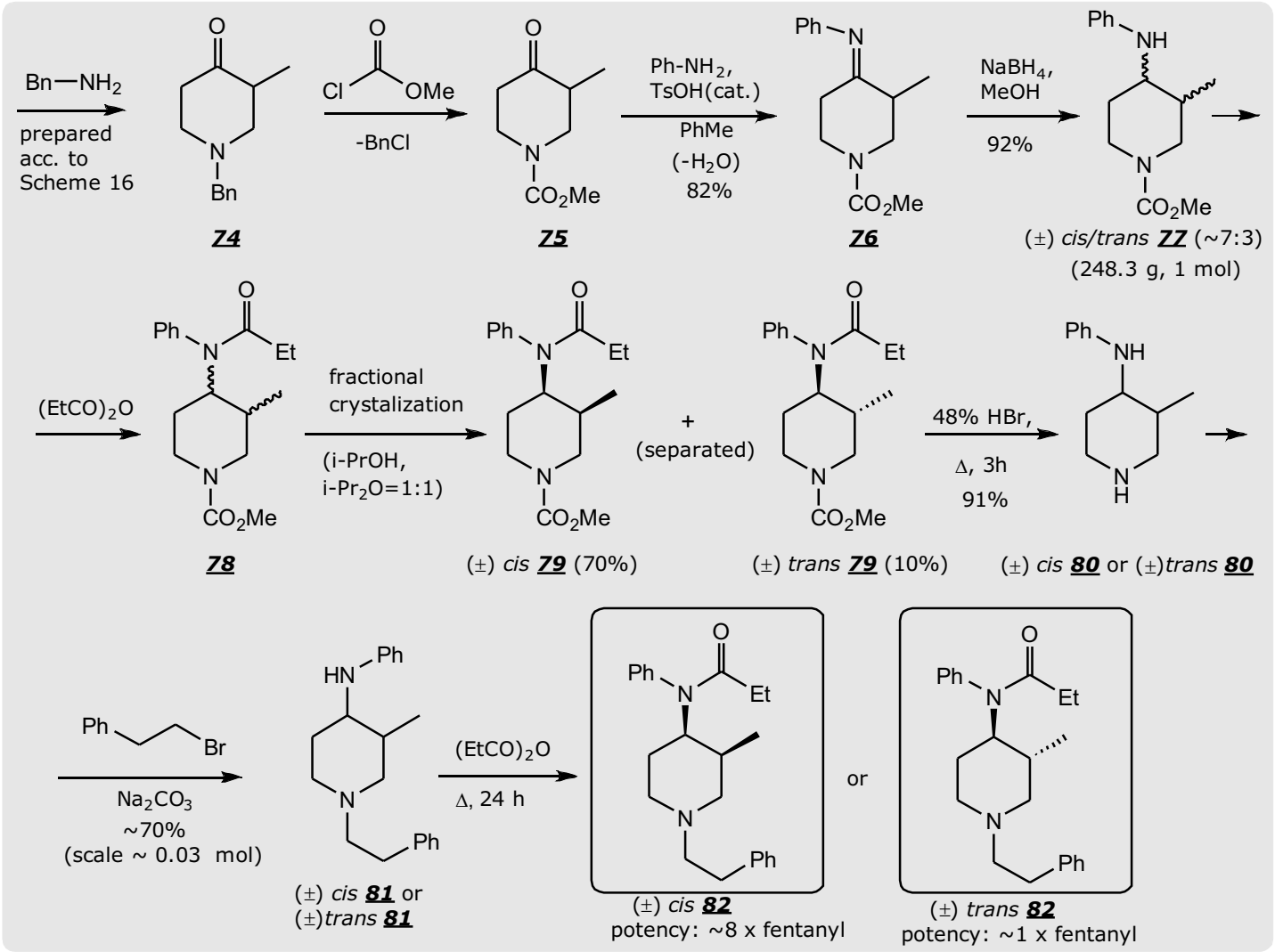
3.4.5 Anilido-piperidines: modifications of the piperidine ring.

As already shown, structural variations of opioid anildo-piperidines were essentially restricted to three regions of the molecule: a) acyl substituents, b) 4-*N*-aryl groups and c) substituents at the piperidine nitrogen. A chance discovery[50] that 3-methyl fentanyl ***58*** was several times more potent than the parent compound, (p. 129), prompted researchers to modify the piperidine ring.

The simplest modification involved the introduction of alkyl groups in the position 3 and/or 2 of the ring.

Thus, the alternative synthesis of 3-methyl fentanyl is shown in *Scheme 3.26*.[57]

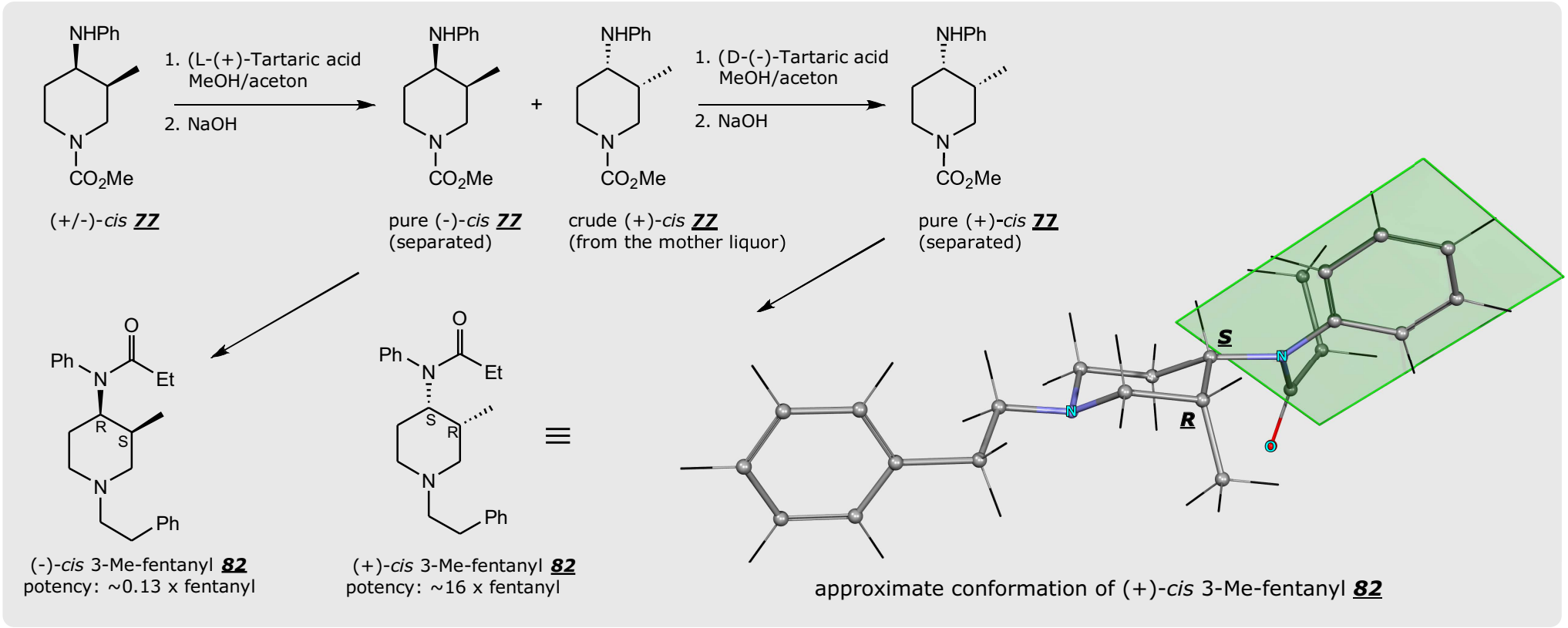
The starting piperidone ***74***, prepared acc. to *Scheme 16*, was debenzylated with methyl chloroformate and the resulting carbamate ***75*** converted to cis/trans anilines ***77*** in the two known synthetic steps, *Scheme 3.26.* After *N*-propionylation, the *cis*/*trans* mixture of anilido-piperidines ***78*** was separated by fractional crystallization, providing pure (±) *cis* and (±) *trans* anilido-piperidines ***79***. (The crystallization, rather than chromatography, was necessary because the reaction was performed on 1 mol scale). Acid hydrolysis secured *cis* and *trans* diamines ***80*** in near quantitative yields. (Attempts to remove the *N*-carbomethoxy group selectively, under either acidic or basic conditions, were unsuccessful). Selective alkylation of piperidine nitrogen with 2-phenylethyl chloride or bromide afforded tertiary amines ***81***. (Derivatives with other 1-*N*-alkyl groups were also prepared). No alkylation of the aromatic nitrogen was observed, since aromatic amines are much weaker nucleophiles than the secondary piperidines. Simple *N*-propionylation provided the final products (±) *cis* ***82*** and (±) ***trans*** ***82***, with the *cis*/*trans* relative opioid potency 8:1 (fentanyl=1), *Scheme 3.26.*



Scheme 3.26. Synthesis of (±) *cis* and (±) *trans* 3-methyl fentanyl ***82***.

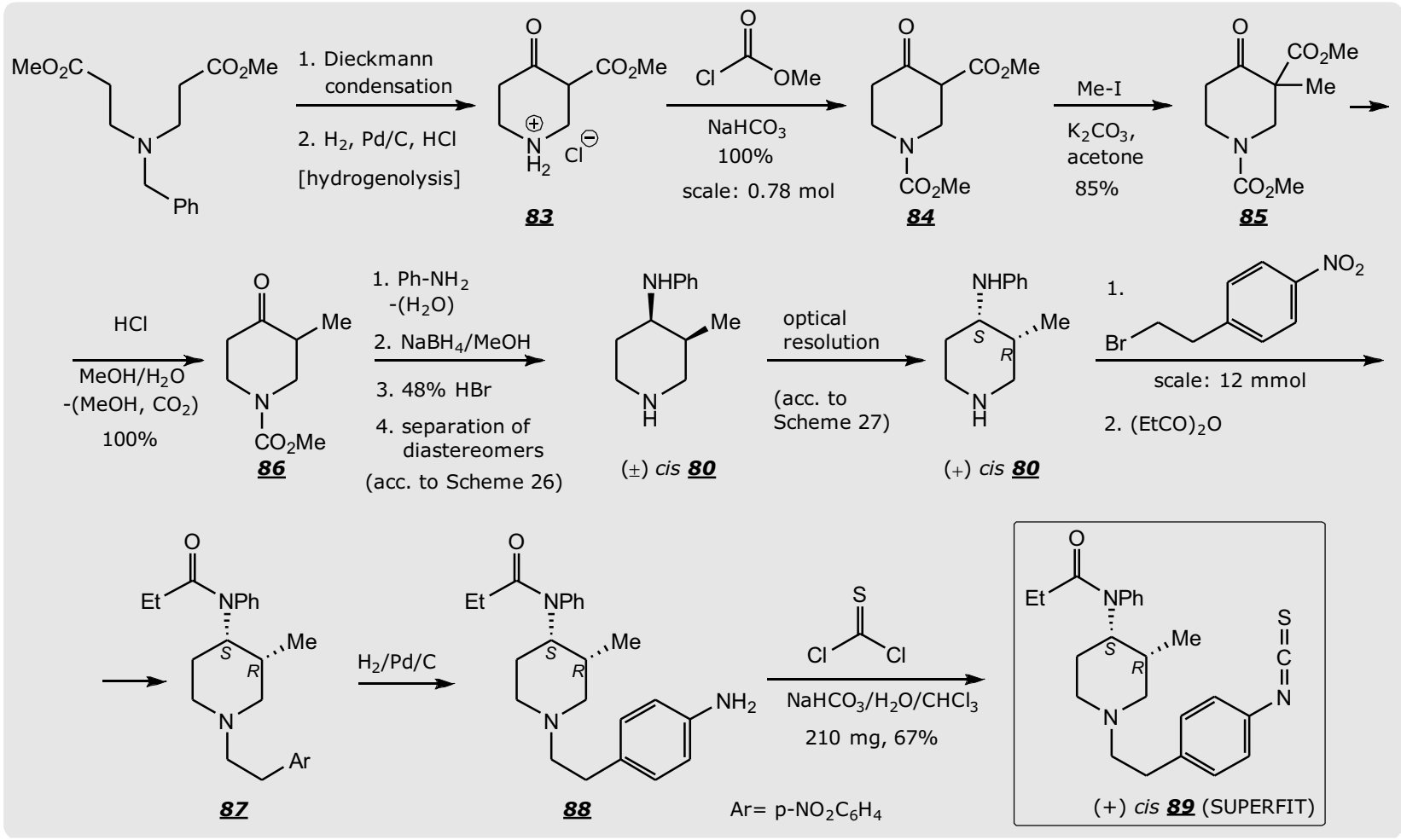
The authors also prepared pure enantiomers, to establish the influence of the absolute configuration to the analgesic activity, Scheme 3.27. The intermediate (±) *cis* ***77*** was separated into pure (-) *cis* 77 and pure (+) *cis* ***77*** enantiomers, using L-(+) tartaric acid and D-(-) tartaric acid, respectively. Elaboration acc. to *Scheme 3.26*., gave (+) *cis* 3-Me-fentanyl (absolute configuration *3R,4S*, 16 times fentanyl potency) and (-) *cis* 3-Me-fentanyl (absolute configuration *3S,4R*, 0.13 times fentanyl potency).

(The absolute configuration was determined in the later research by standard X-ray diffraction technique).[58] The difference in activity between the two enantiomers (over 100 times) is not unusual, since only one enantiomer can effectively fit into the receptor active site. It parallels the case of morphine, where only the natural, (-) enantiomer is an active analgesic. Later, other research groups prepared derivatives of 3-Me-fentanyl which are selective, highly active and irreversible ligands for δ-opioid receptors (*Schemes 3.28* and 3.*29*).

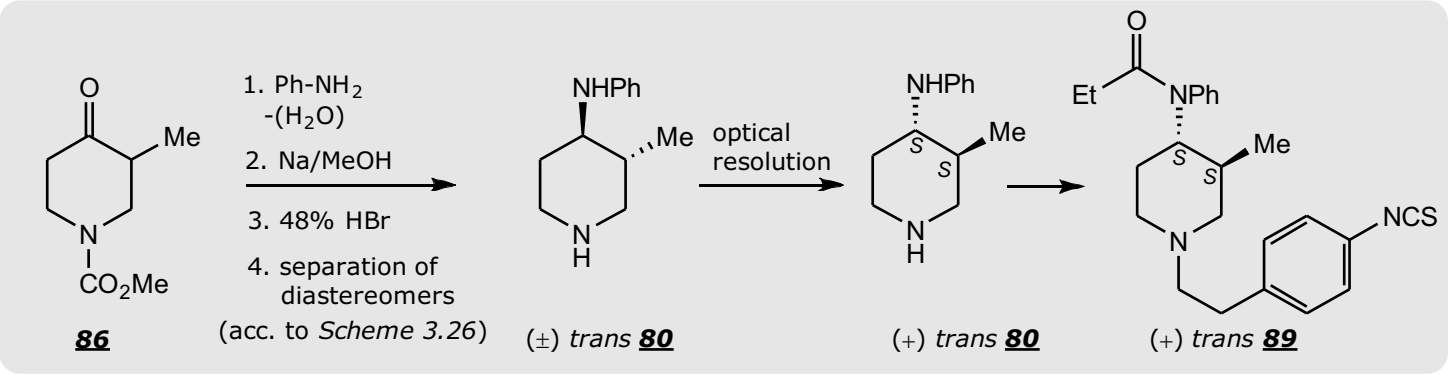


Scheme 3.27. Synthesis of (+) *cis* and (-) *cis* 3-methyl fentanyl ***82***.

The synthesis of one such ligand, denoted as SUPERFIT (structure (+) *cis* ***89***), is presented in *Scheme 3.28*. The general approach mainly relied on the previously published procedure (*Scheme 3.26*), except that methyl group was introduced by the alkylation of β-keto ester ***84***. (It should be pointed out that the successful alkylation was possible only in the presence of a neutral nitrogen i.e. carbamate. In general, tertiary amines rapidly form quaternary salts with the active alkylating agents). An important selectivity was achieved in transformation of of ***85*** to ***86***. Thus, only the ester group hydrolyzed in the presence of HCl, leaving *N*-metoxycarbonyl function intact. It was only in 48% HBr, that the carbamate function hydrolyzed, affording *cis* ***80***. (Carbamates are generally much more resistant to acid and alkaline hydrolysis than esters). In the final synthetic step, isothiocyanato group was introduced by the standard reaction of a primary amine and thiophosgene, structure (+) *cis* ***89***, *Scheme 3.28*.



Scheme 3.28. Synthesis of SUPERFIT, (+) *cis* ***89***.



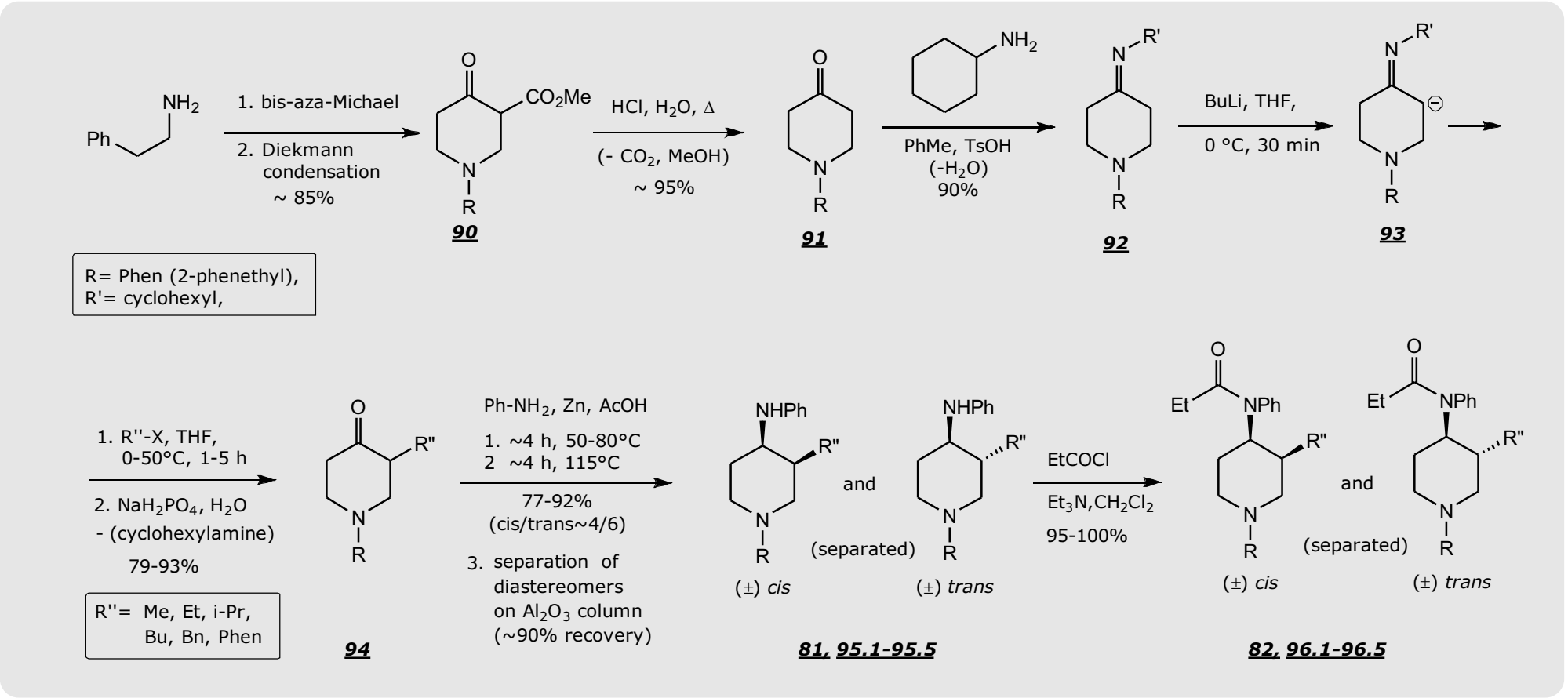
Scheme 3.29. Synthesis of (+) *trans* ***89***.

The ligand SUPERFIT, is a selective and irreversible δ-opioid agonist, used for *in vitro* studies of opioid receptors. The corresponding *trans* diastereomer was also prepared, according to the same general protocol.[59] The imine intermediate was reduced using metallic sodium in methanol, resulting in *trans*/*cis* ratio ~6/4 rather than ~3/7 with $NaBH_4$, *Scheme 3.29*. The more active, (+)-trans ***89*** enantiomer has the absolute configuration 3S,4S, as determined by the single-crystal X-ray analysis.

While the introduction of 3-methyl group in the fentanyl scaffold was relatively simple, derivatives having other alkyl groups were considerably more difficult to obtain. The compounds were significant in determining structure-activity relationship for various 3-alkyl fentanyls, including the influence of *cis* and *trans* configuration to opioid activity. The problem was solved by developing a novel approach, as shown in the *Scheme 30*.[60] β-Keto ester ***90*** and piperidone ***91*** were prepared acc. to the general *Scheme 3.16*. Condensation with cyclohexylamine furnished stable imine ***92***, which was then quantitatively deprotonated to anion ***93*** using BuLi as a base. (No 1,2-addition was observed). The anion reacted quantitatively with primary and secondary halogen alkanes, providing exclusively C-monoalkylated products. (The alkylated imines were not isolated, while a significant hydrolysis was observed on TLC). Upon a mild acidic workup, the mono-alkylated piperidones ***94*** were obtained in high isolated yields, without side products or the starting piperidone ***90***. Reductive alkylation with aniline, was effected utilizing previously developed protocol, utilizing metallic zinc in acetic acid.[61] It provided good isolated yields of 4-anilino-piperidines ***81*** and ***96.1***-***96.5***, as (±) *cis*/*trans* mixtures. The predominance of *trans* isomer (ca. 3/7 to 4/6), probably reflected the thermodynamic control, in parallel to Na/MeOH imine reduction.[58] (Conversely, $NaBH_4$ reduction of the preformed aryl imines gave the opposite diastereomeric ratio, indicating partial kinetic control, i.e. hydride attack from the less hindered side, *Schemes 3.26 and 3.28*).

It should be noted that similar results were obtained employing an alternative reductive amination procedure. It involved reduction with metallic magnesium in a buffered medium (MeOH, AcOH, Et_3N).[62] Unlike Zn/AcOH method, it can also reduce aliphatic imines, formed reversibly during the reductive amination. Both methods have the advantage that imines need not to be preformed, they secure complete conversion with little or no side products and the carbonyl groups are not reduced to alcohols. (Reductive amination with $NaBH_3CN$ in these experiments always gave alcohols as side products, significantly reducing the yields). A considerable disadvantage of the magnesium method is that the product isolation is relatively laborious.

The formation of *cis/trans* mixtures did not present a drawback, since both diastereomers were needed for pharmacological tests and SAR studies, S*cheme 3.30*.



Scheme 3.30. General method for synthesis of (±) *cis* and (±) *trans* 3-alkyl fentanyl analogues (***82***, ***96.1***-***96.5***)

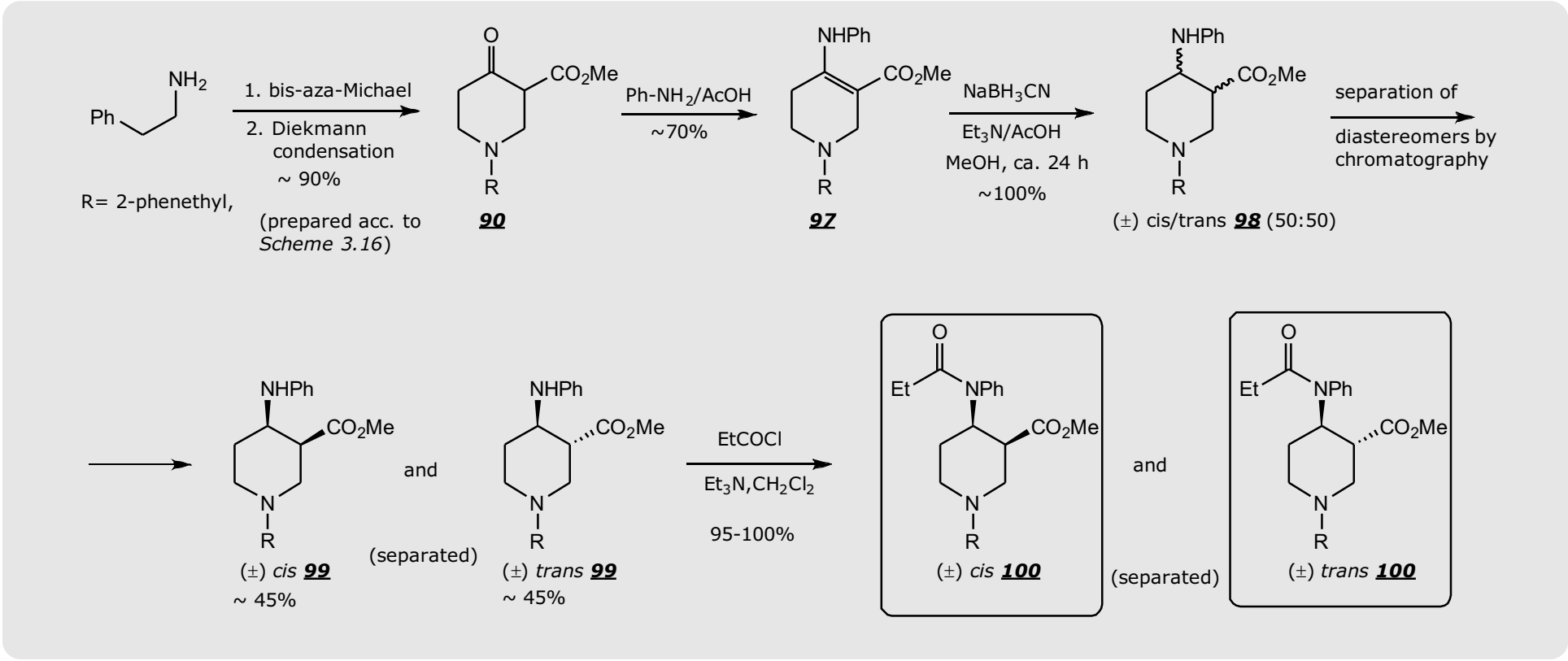
The compounds synthesized acc. to *Scheme 3.30* were examined pharmacologically as opioid agonists, using the standard *in vivo* animal tests (rat-tail withdrawal test, RTW, mouse hot-plate test, MHP and others).[62,63a] The analgesic potencies, relative to fentanyl, are presented in *Table 3.2.* (For the detailed discussion of pharmacological results see ref. 63a). Of the novel 3-alkyl derivatives, only (±)-*cis*-3-Et fentanyl ***96.1*** was slightly more potent than the parent compound (entry 6), while other compounds in the series were less active than fentanyl or inactive. The results made it possible to establish the basic structure activity relationship, proving that larger alkyl groups reduce or abolish the opioid activity.[63] The relative configuration also influences activity, since the *cis* diastereomers were significantly more active than the *trans*. The results demonstrated that *cis*-3-Me group has the optimal size and relative configuration to confer the highest opioid activity (entry 2, compound ***81***). The activities of *cis* and *trans* 3-carbomethoxy fentanyl (entries 17 and 18) as well as carfentanil and 4-methyl fentanyl[63a,b] (entries 19 and 20) are also included. The later two compounds were added for comparison only, as they have no substituents in the possition 3. (Syntheses of 3-carbomethoxy fentanyl, carfentanil and 4-methyl fentanyl are presented at p. 138, 144 and 151 respectively).

No	Compound	Potency ratio	No	Compound	Potency ratio	No	Compound	Potency ratio	No	Compound	Potency ratio
1	Fentanyl ***42***	1[a]	6	(±)-*cis*-3-Et Fentanyl ***96.1***	1.5[a]	11	(±)-*cis*-3-*i*-Pr Fentanyl ***96.2***	-[a]	16	(±)-*cis*-3-(2-Phen) Fentanyl ***96.5***	-[a]
2	(±)-*cis*-3-Me Fentanyl ***81***	~7[a]	7	(±)-*trans*-3-Et Fentanyl ***96.1***	0.9[a]	12	(±)-*cis*-3-Bu Fentanyl ***96.3***	0.06[a]	17	(±)-*cis*-3-carbomethoxy Fentanyl ***100***	0.5[a]
3	(±)-*trans*-3-Me Fentanyl ***81***	2[a]	8	(±)-*cis*-3-allyl Fentanyl -	0.14[b]	13	(±)-*trans*-3-Bu Fentanyl ***96.3***	0.03[a]	18	(±)-*trans*-3-carbomethoxy Fentanyl ***100***	0.1[a]
4	(-)-*cis*-3-Me Fentanyl ***81***	0.16[b]	9	9 (±)-*cis*-3-Pr Fentanyl -	0.6[b]	14	(±)-*cis*-3-Bn Fentanyl ***96.4***	0.008[a]	19	Carfentanil	27[b]
5	(+)-*cis*-3-Me Fentanyl ***81***	19[b]	10	(±)-*trans*-3-Pr Fentanyl -	0.3[b]	15	(±)-*trans*-3-Bn Fentanyl ***96.4***	0.005[a]	20	4-methyl-Fentanyl ***167***	4[a]

Table 3.2. Opioid potency of 3-substituted fentanyl derivatives and other fentanyl analogues.[62,63]

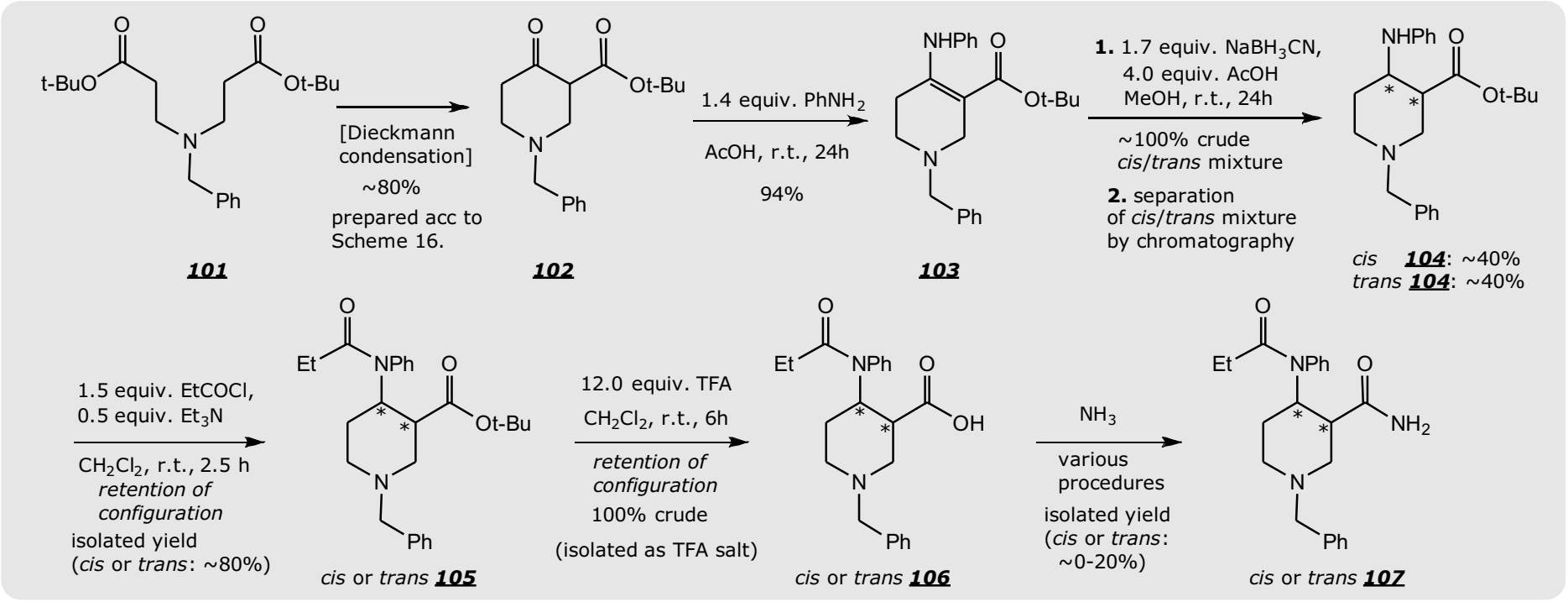
a) Experimentaly determined *in vivo*, using RTW and MHP tests. b) Retrieved from the literature sources.[63]

Groups other than alkyl were also introduced in the position 3 of fentanyl scaffold. Thus, the synthesis of (±) *cis* and (±) *trans* 3-carbomethoxy fentanyl ***100*** was achieved according to *Scheme 3.31*.[64] Condensation of β-keto-ester ***90*** and aniline resulted in a very stable enamine ***97***, which could be reduced only using $NaBH_3CN$ in a buffered medium ($AcOH/Et_3N$, MeOH). Other methods, including catalytic hydrogenation (with PtO_2 or Pd/C catalysts), $NaBH_4$/AcOH and dissolving metals (Na/*i*-PrOH, Li/R-OH, Zn/AcOH or Mg/MeOH/buffer) all failed, resulting either in the reactant recovery or decomposition. Also, in the strongly acidic medium (e.g. formic acid), enamine ***97*** hydrolyzed quantitatively.[46,64] The obtained equimolar *cis*/*trans* mixture of anilino-esters ***99*** was separated chromatographically and after *N*-propionylation, provided (±) *cis* and (±) *trans* 3-carbomethoxy fentanyl derivatives *cis* ***100*** and *trans* ***100***. *In vivo p*harmacological tests reviled moderate opioid activity, *Table 3.2* (entries 17,18), albeit much lower than (±) *cis* 3-methyl-fentanyl and carfentanil (entries 2, 19).



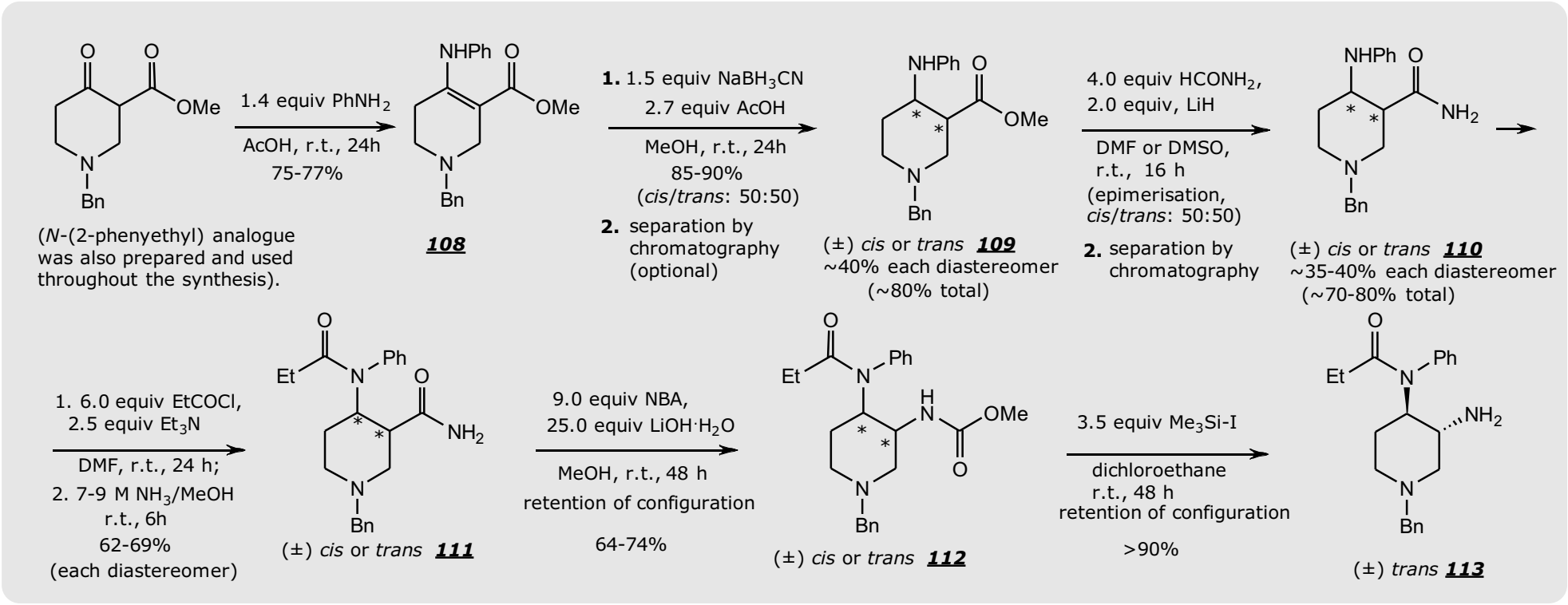
Scheme 3.31. Synthesis of "iso-carfentanil" ***100***.

Very recently, the enamine approach was extensively modified, as to introduce other functional groups in the position 3, acc. to *Schemes 3.32A*, *32B* and *3.33*.[65] The initial approach started from diester ***101***, *Scheme 3.32A*. Modified Dieckmann condensation (*t*-BuOH, NaH, DMSO), acc. to the previously published procedure, (*Scheme 3.16*),[44] provided hitherto unknown β-keto-ester ***102***. (Dieckmann condensation with *t*-Bu-diesters proceeds only very slowly, except in DMSO). After condensation with aniline, the resulting enamine ***103*** was quantitatively reduced to the *cis*/*trans* mixture of β-anilino-esters ***104***, in the ratio ~50:50. The diastereomers were separated chromatographically, followed by *N*-propionylation (structure ***105***) and the standard, acid-catalyzed cleavage of *t*-butyl ester. The anilido-acids, *cis* or *trans* ***106***, were obtained quantitatively as TFA-salts. Significantly, the ester cleavage proceeded with the full configuration retention. (The relative configuration was determined unequivocally using HSQC/NOESY/COSY 2D NMR techniques). Unexpectedly, the condensation of *cis* or *trans* anilido-acid ***106*** with ammonia, using the standard peptide coupling reagents (e.g. DCC and others) was not successful, yielding only minimal amounts of the desired carboxamide ***107***. However, the method may have wider applicability, since it provides access to various stereodefined heterocyclic β-amino acids.[65]



Scheme 3.32A . Synthesis of 3-amino-4-anilido-piperidines. Part 1.

An alternative approach to various 3-substituted 4-anilido-piperidines is shown in *Scheme 3.32B.*[65] Enamine ***108***, was reduced and the resulting *cis*/*trans* mixture of anilino-esters ***109*** separated. Attempted aminolysis of the ester group failed unexpectedly, even under the forcing conditions (pressure vessel, ~9 M NH_3/MeOH, 150°C, 15 bar). The known alternative protocol, using formamide as a nitrogen source, proceeded quantitatively to carboxamide ***110***, however with the extensive epimerization. Consequently, the transformation was performed on the *cis*/*trans* mixture, followed by the diastereomer separation. Surprisingly, *N*-propionylation of the *cis* and *trans* carboxamide ***110*** was also unsuccessful under any usual conditions (e.g. propionyl chloride in chloroform), resulting in the recovered reactant and decomposition products. (It also failed with propionic anhydride in boiling pyridine, in the presence of DMAP). Finally, the acylation proceeded quantitatively in DMF, albeit accompanied by the *N*-acylation of the carboxamido group. The imido group (not shown in *Scheme 3.32B*), was cleaved by simple aminolysis, affording *cis* and *trans* anilido-carboxamide ***111***, without any epimerization.

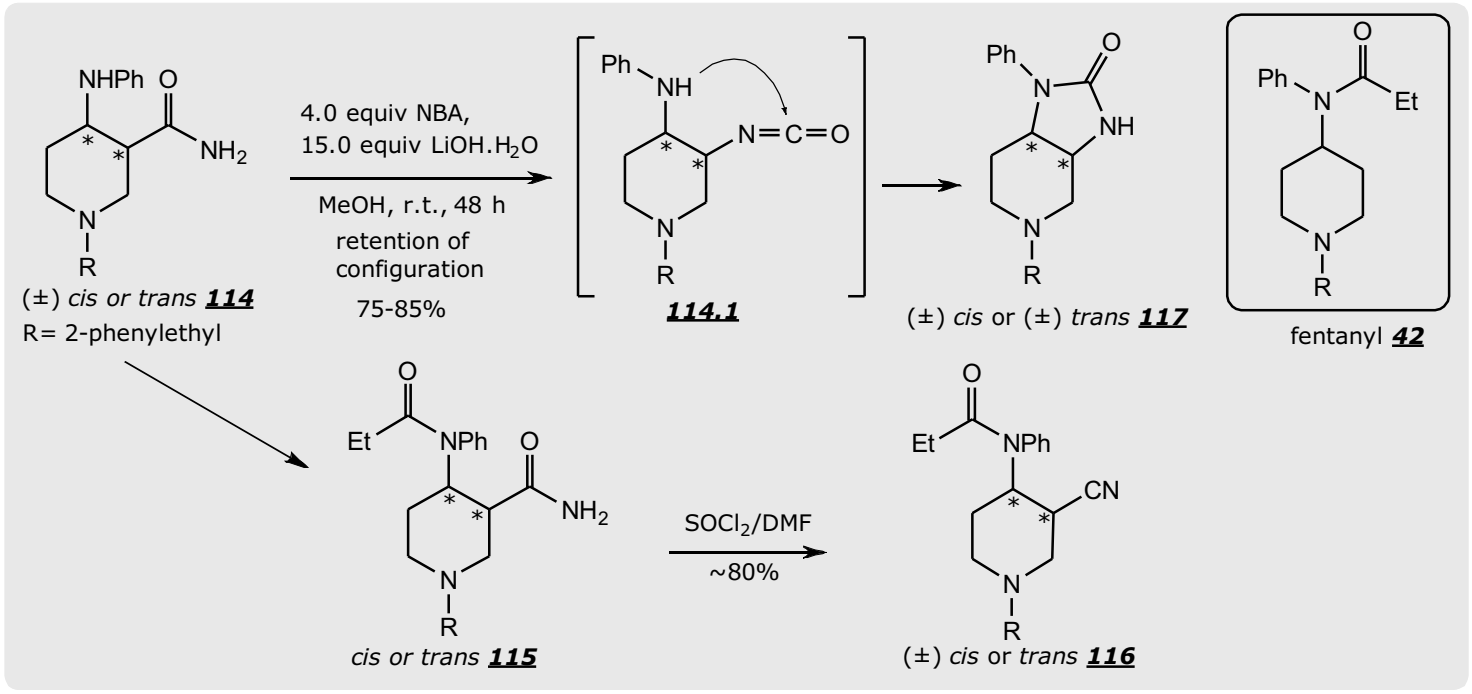


Scheme 3.32B . Synthesis of 3-amino-4-anilido-piperidines. Part 2.

When the Hofmann rearrangement of ***111*** was attempted with various known reagents, only low yields and large amounts of side products were obtained. (Hypervalent iodine reagents, e.g. PIDA, resulted in the complete decomposition).

Therefore, in a separate research, a new method for the Hofmann rearrangement was developed, utilizing *N*-bromoacetamide in MeOH, in the presence of LiOH or MeOLi.[66] The method proved to be of a considerable scope and well suited for the relatively sensitive substrates, including carboxamide ***111***. While the reaction was relatively slow at r.t., it provided good yields of the carbamate ***112*** with the complete retention of the configuration. As expected, the cleavage of the methoxycarbonyl group, mediated by trimethylsylil iodide, proceed smoothly to 3-amino derivative ***113*** (only *trans* diastereomer is shown in Scheme *3.32B)*. No epimerization was observed. This general approach also permits the introduction of other alkyl groups at the piperidine nitrogen, as well as the selective preparation of *cis* and *trans* diastereomers. In addition, other analogues were obtained by the variations of the general approach, *Scheme 3.33*. For example, the Hofmann rearrangement of the anilino-carboxamide ***114*** stereospecifically gave novel cyclic ureas ***117***, which are closed-ring analogues of fentanyl. However, the preliminary *in vivo* tests did not show any analgesic activity, in parallel to the numerous fentanyl analogues possessing fused rings, p. 155. Alternatively, dehydration of carboxamide ***115***, in the presence of $SOCl_2$, resulted in the stereospecific formation of nitrile ***116***.

Most of those novel compounds (including various *N*-substituted 3-amino derivatives), are currently undergoing pharmacological testing (as of 2017.) and the results will be published in a due course.

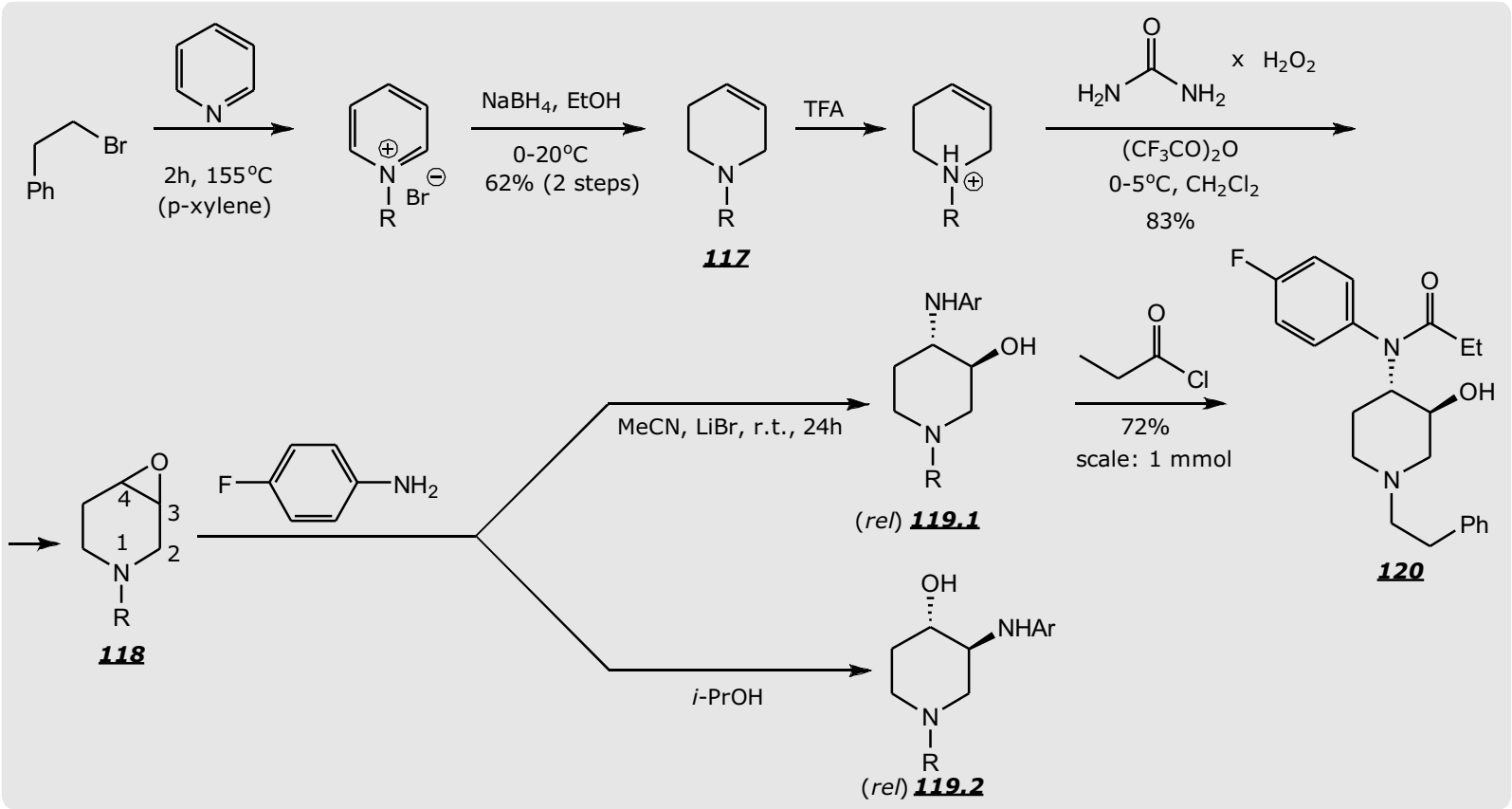


Scheme 3.33 . Synthesis of some novel classes of 3-substituted derivatives of fentanyl.

Hydroxy and alkoxy groups were also introduced in the position 3 of 4-anilido-piperidines.

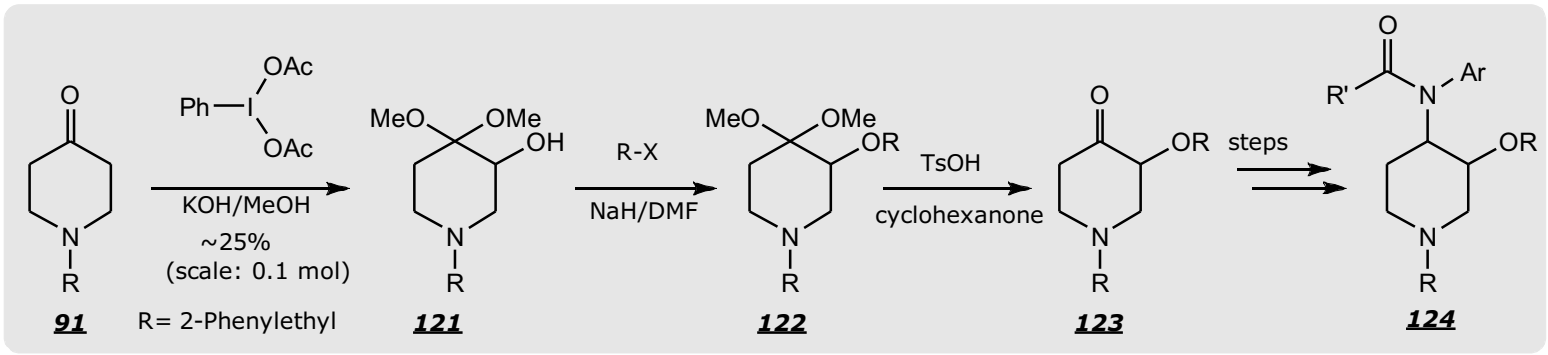
One of the more recent procedure involved the regioselective epoxide opening, permitting synthesis of both 3-hydroxy-4-anilido-piperidines as well as the regioisomers (4-hydroxy-3-anilido-piperidines), depending of the reaction conditions, *Scheme 3.34*.[67]

The method appears to be efficient and versatile, although limited to *trans* isomers only. All key steps were chemo, regio and/or stereoselective. Chemoselective hydride reduction of the quaternary piridinium salts gave derivative ***117*** (the other two double bonds were reduced as imine/enamine function). Epoxidation of the double bond was achieved using particularly mild conditions, providing epoxide ***118***. (Formation of *N*-oxides and other side products was completely suppressed). An efficient regioselective protocols for the epoxide ring opening were developed, directing nucleophylic attack at the possition 4 or 3, depending on the conditions. Attack of the aromatic amine at the possition 4 resulted in the regioisomer ***119.1***, which, after *N*-acylation, provided trans-3-hydroxy-4-anilido-piperidine ***120***. The regioisomer ***119.2*** was also obtained and *N*-acylated with other groups.



Scheme 3.34 . Synthesis of *trans*-3-hydroxy fentanyl derivative ***120***.

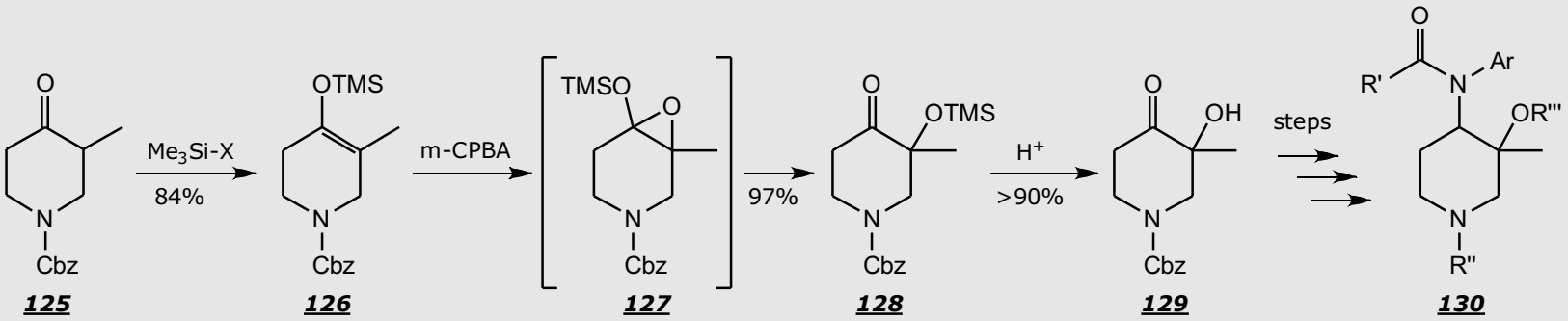
However, no pharmacological results were reported.



Scheme 3.35 . Synthesis of trans-3-hydroxy fentanyl derivative ***124***.

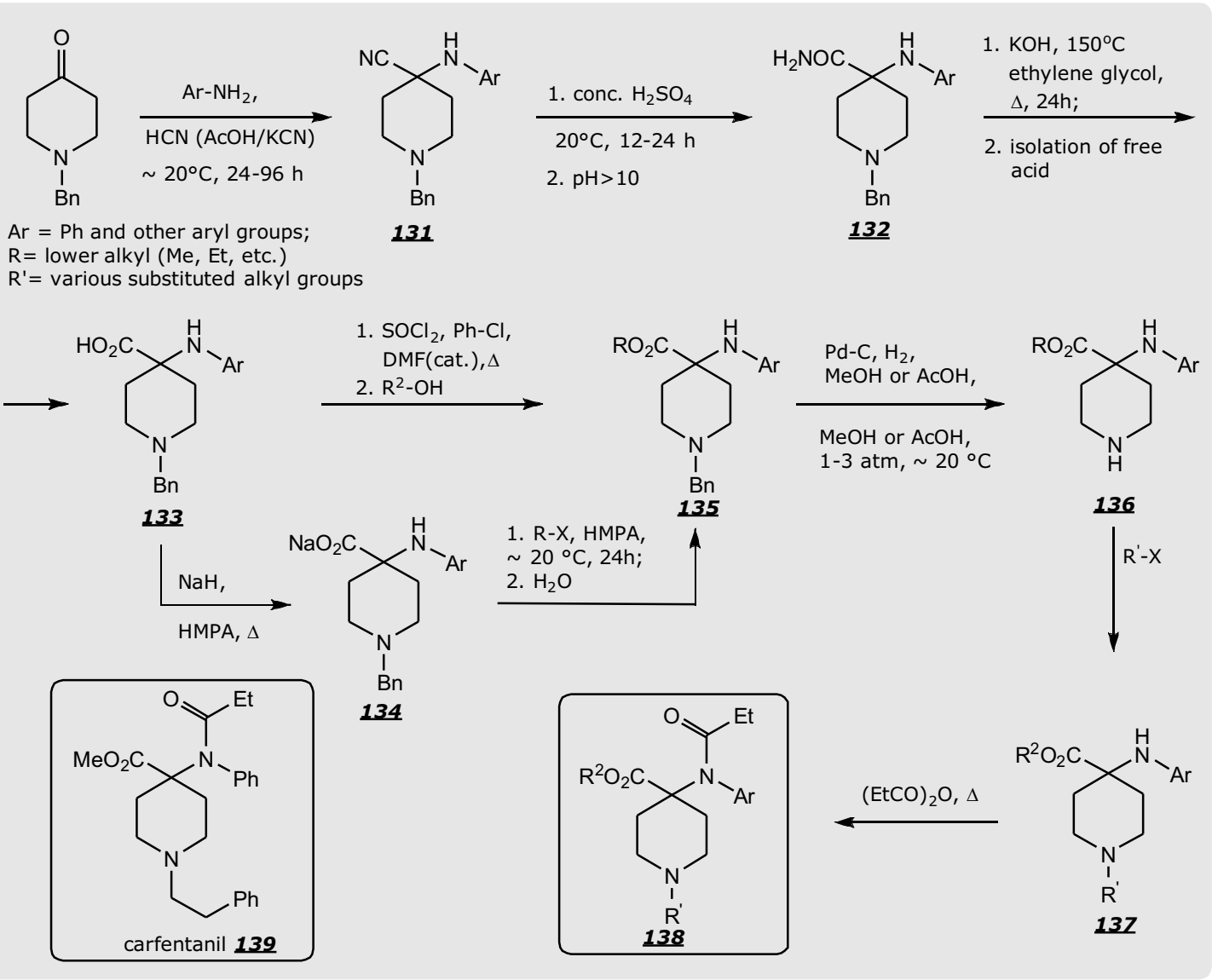
Earlier methods, published in the patent literature, were based on the classical procedures for α-hydroxylation of ketones, applied to 4-piperidones. Thus, α-hydroxylation of 4-piperidone ***91*** was achieved using (diacetoxyiodo)benzene, however only in 25% yield, *Scheme 3.35*. After *O*-alkylation and transketalisation, the obtained α-alkoxy 4-piperidone ***123*** was further elaborated, to various 4-anilido-piperidines ***124***, acc. to the procedures shown previously (e.g. *Schemes 3.17, 3.20*). More than 30 final compounds of the general structure ***124*** were synthesiszed, generally having significantly lower opioid activity then fentanyl (as estimated by mouse hot-plate test).[68]

An alternative approach to similar compounds is shown in *Scheme 3.36*.[69] One of the standard procedures for α-hydroxylation of ketones was applied to 4-piperidone ***125***. After conversion of the keto group to trimethylsilyl enol-ether ***126*** and epoxidation, the unstable epoxide ***127*** spontaneously rearranged to α-keto-silyl ether ***128***. Mild acid hydrolysis secured hydroxy-ketone ***129***. It should be emphasized that the protocol is applicable only to the ketones having no amino groups, since *N*-oxides and other side products predominate (carbamates and amides are stable, since the nitrogen is non-basic). As in the previous example, a number of the 3-alkoxy-4-anilido-piperidines of the general structure ***130*** were obtained via the known transformations.



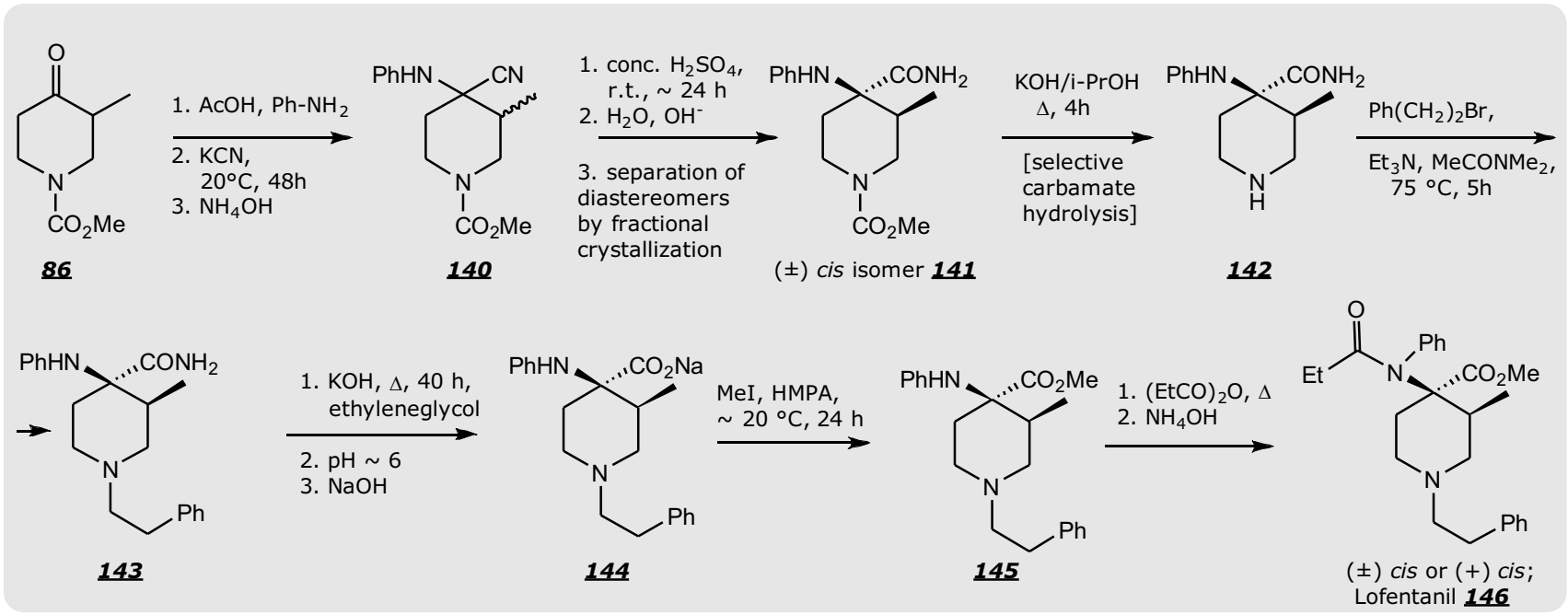
Scheme 3.36. Synthesis of various 3-alkyloxy-4-anilido-piperidines ***130***.

From the pharmacological point of view, the most successful modification of fentanyl scaffold was the introduction of various substituents in the position 4 of the piperidine ring. A general approach to 4-alkoxycarbonyl derivatives, acc. to the original patent,[70] is presented in *Scheme 3.37.* (No yields were reported). Strecker reaction of various 4-piperidones, primary arylamines and HCN generated *in situ*, resulted in the expected amino-nitriles ***131***. Selective acid hydrolysis of the nitrile group gave stable amino-amide ***132***. After vigorous basic hydrolysis and the aqueous work-up, α-amino-acid ***133*** were isolated by precipitation and then converted to the esters ***135***, via two different routes. One route involved formation of the acid chlorides followed by the reaction with alcohols. Alternatively, the same esters were prepared by direct O-alkylation of carboxylate anions ***134*** in hexamethylphosphoramide (HMPA). Catalytic hydrogenolysis secured secondary piperidines ***136***, which are reactive nucleophiles and can be readily alkylated with haloalkanes or sulfonate esters, general structure ***137***.



Scheme 3.37. Synthesis of various 4-alkoxycarbonyl-4-anilido-piperidines of the general structure ***138***.

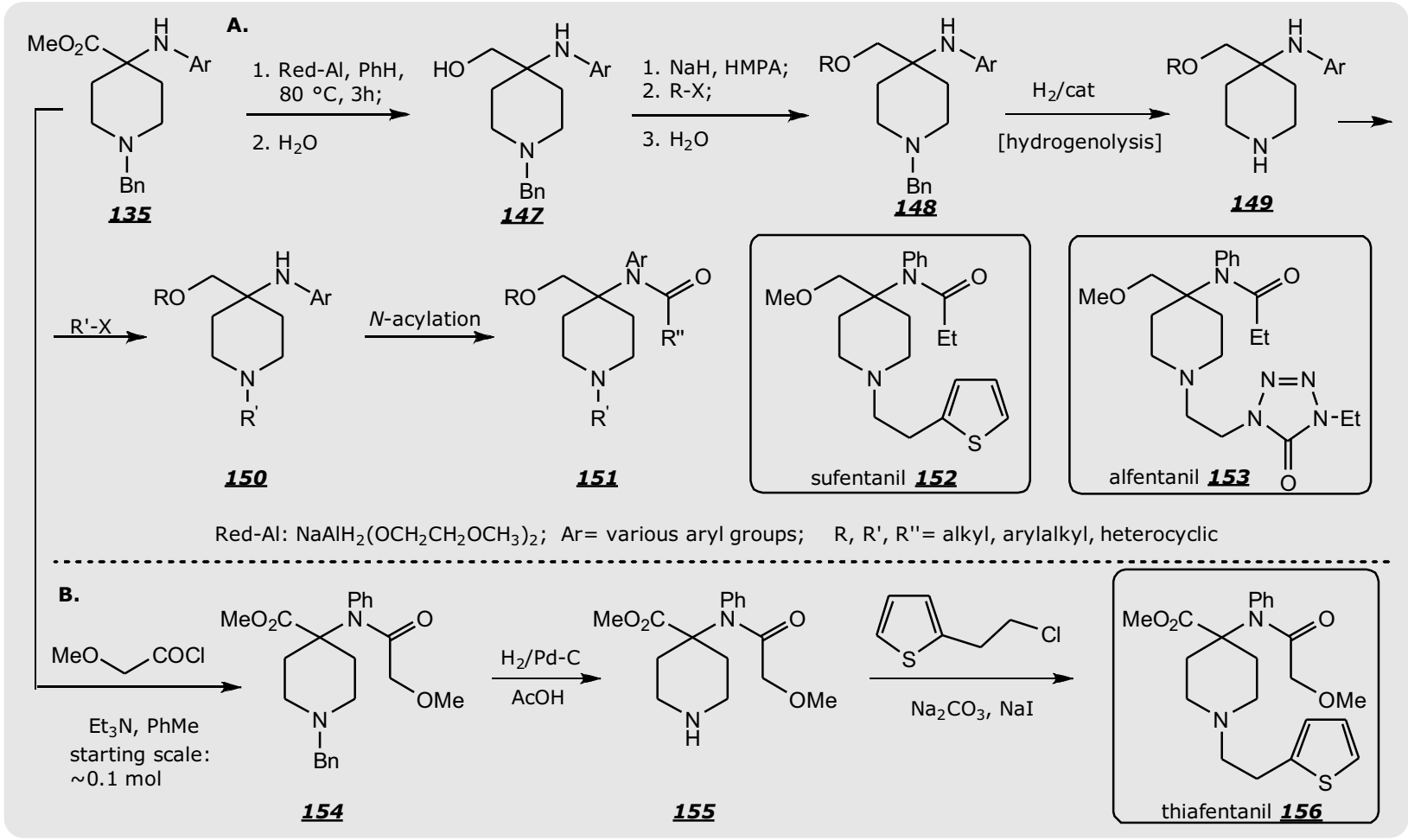
In the last step, *N*-acylation of ***137*** furnished anilido-piperidines ***138***, mainly having *N*-propionyl group. (As already noted, numerous SAR studies confirmed that propionyl group confers the highest activity). The most potent compound in the series, structure ***139***., was ~30 times more active than fentanyl. Various *in vivo* tests revealed that it was unsuitable for human use, due to the side effects, but useful as a veterinary analgesic. The compound received the INN carfentanil and it has been used in the past three decades to sedate large animals in the wild and in the captivity, as an alternative to etorphine. The compound 3-methyl carfentanil ***146*** was synthesized similarly, *Scheme 3.38*.[70] The exposure of the nitrile ***140*** to conc. sulfuric acid gave amide ***141***, with the intact carbamate group. After separation of the diastereomers by fractional crystallization, the carbamate function was removed by the selective basic hydrolysis. *N*-alkylation of the resulting secondary piperidine ***142***, using 2-phenylethyl bromide, followed by vigorous basic hydrolysis of the carboxamide ***143***, afforded sodium salt of the amino acid ***144.*** The carboxylate anion was O-alkylated with MeI, providing the ester ***145*** and the synthesis completed by *N*-propionylation, structure ***146***. The compound, named lofentanil (INN), exhibited the opioid activity somewhat lower than carfentanil (about 20 times more potent than fentanyl), but with less side effects. It was successfully tested in surgical procedures in humans, however, it has never entered the market.[71]



Note: HMPA is a known carcinogen and can be replaced by less hazardous solvents or co-solvents, e.g. DMF).

Scheme 3.38. Synthesis of lofentanil ***146***.

Yet another class of 4-subsituted anilido-piperidines were reported in the same patent, *Scheme 3.39 A*.[70] Reduction of α-arylamino-esters, general structure ***135***, using Red-Al or the related hydrides, produced alcohols ***147***. Direct alkylation of the corresponding alkoxides (Williamson ether synthesis) gave 4-alkoxymethyl ethers ***149***. Straightforward elaboration of ***149*** produced anilido-piperidines of the general structure ***151***. After preliminary tests, one compound was chosen for the further examination. The compound ***152***, named sufentanil (INN), exhibited generally favorable pharmacological profile and high opioid potency (ca. 7.5 times fentanyl in humans). At present, it is the most potent opioid analgesic in medical use.



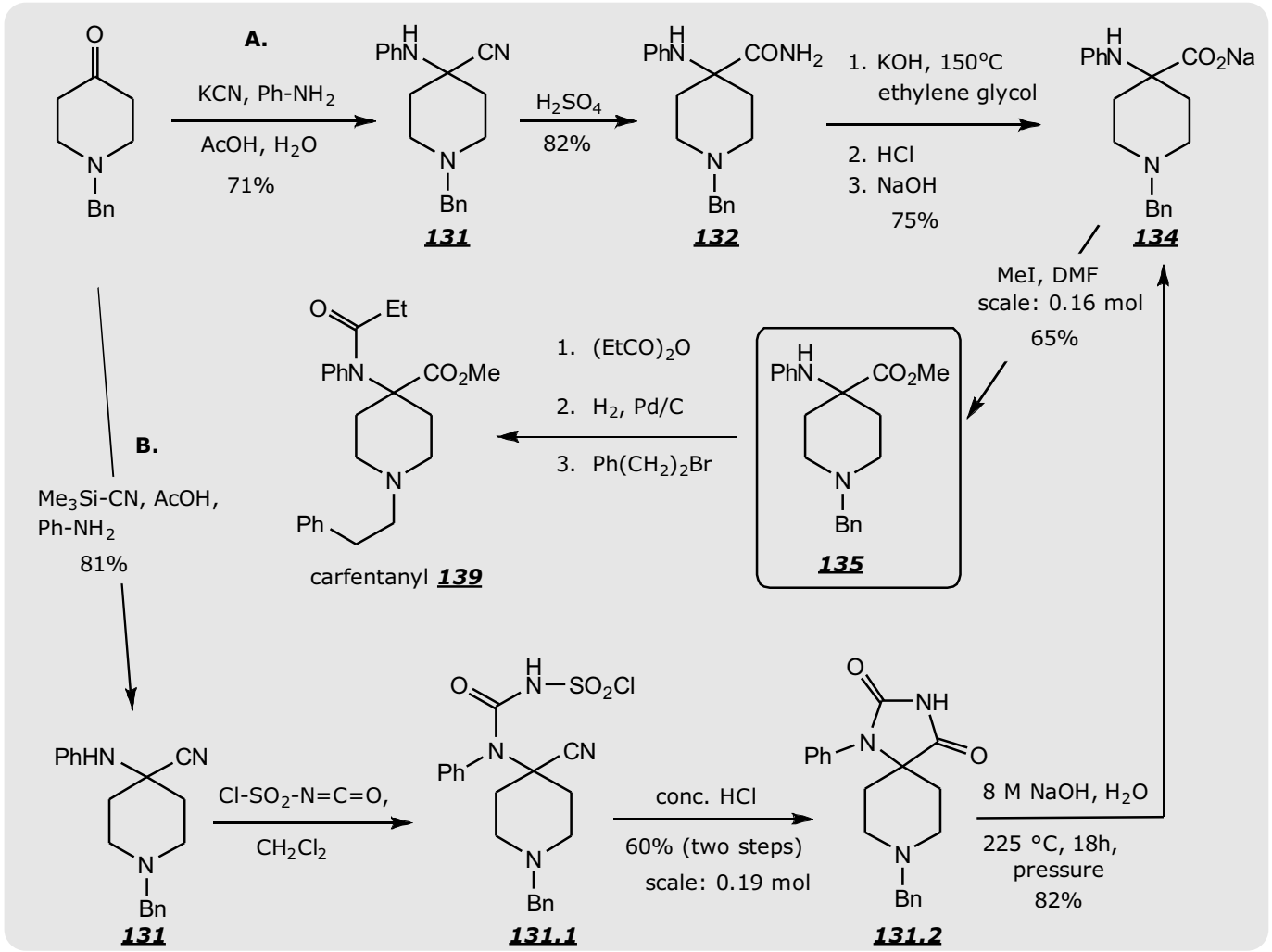
135 ***147*** ***148*** ***149*** ***150*** ***151*** ***154*** ***155***

Scheme 3.39. A. Synthesis of sufentanyl ***152*** and alfentanil ***153***. B.Synthesis of thiafentanil ***156***

A compound structurally closely related to sufentanil was reported in the later patent,[73] prepared analogously to sufentanyl. Pharmacological tests reveiled significant opioid activity, short duration of action and high safety margin. The compound, named alfentanil ***153*** (INN), has become significant opioid analgesis, widely used in short surgical procedurs.

Essentialy the same procedure as shown in *Shemes 3.37-3.38*, was used to prepare carfentanil analogue ***156***, Scheme *3.39B*.[74] The compound, named thiafentanil (INN), has similar potency to carfentanil, however the overall pharmacological effects are more favourable. While unsuitable as analgesic in humans, it has found considerable use as an alternative to etorphine or carfentanil in veterinary medicine.[75]

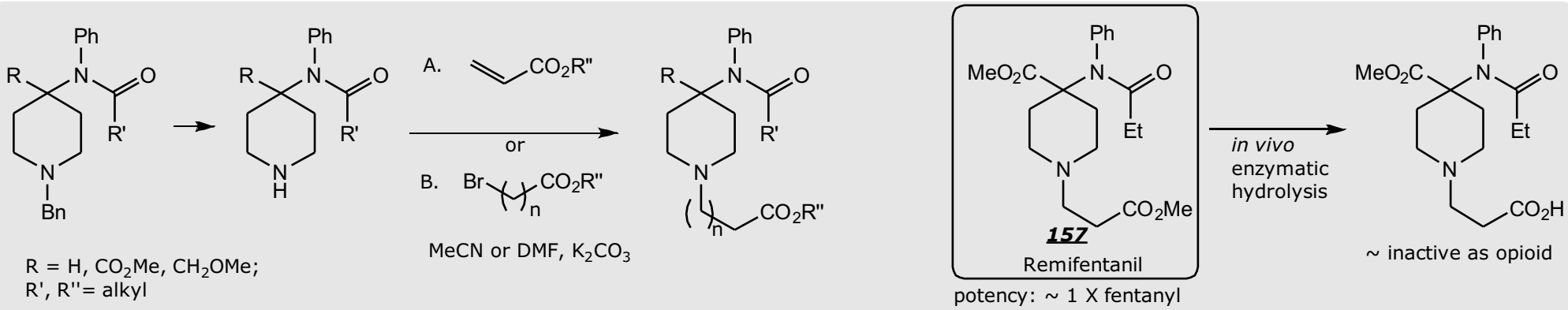
Later research, published in numerous patents and papers, reported various improved preparation procedures, as well as many new 4-anilido-piperidines, substituted in the position 4.



Scheme 3.40. Improved synthesis of carfentanil precursors[76]

For example, *Scheme 3.40* presents two approaches to carfentanil precursor, structure ***135***.[76] The approach ***A***, was an optimization of the original procedure (presented in *Scheme 3.36*), securing the key intermediate ***135*** in ~43% overal yield. (The experimental procedure and reaction scale was not given). The approach ***B*** employed trimethylsilyl cyanide for the anhydrous Strecker reaction, followed by the reaction with chlorosulfonyl isocyanate, intermediate ***131.1***. After the successive acid and basic hydrolysis (the later performed in a pressure vessel), the intermediate ***135*** was obtained in the yields comparable to the procedure ***A***.

Thus, except for the first step, it is unclear if the approach ***B*** offers any advantage.



*Scheme 3.41. Synthesis of remifentanil **157**.*

Secondary piperidines, obtained acc. to the previously published methods (e.g. *Schemes 3.36, 3.37, 3.39*) were used to prepare series of novel analogues, via simple N-alkylation or aza Michael addition, *Scheme 3.41*.[77a, 77b] As in the previous examples, one of compounds, structure ***157***, showed opioid potency close to fentanyl, few side effects and, of a particular significance, very short duration of the analgesia. It is also important that, unlike most opioids, it readily undergoes *in vivo* inactivation, since the less hindered ester group is rapidly hydrolyzed enzymatically. Thus, there is no significant risk of renarcotization, a potentially life-threatening phenomenon, causing unexpected and recurring respiratory depression.

The compound received INN remifentanil and eventually become a clinically significant, short-acting opioid.

Solutions of remifentanil hydrochloride salt (ULTIVA®) are not stable, due to the hydrolysis of the ester group. Thus, the drug is marketed as a dry hydrochloride salt, in the vials containing 1, 2

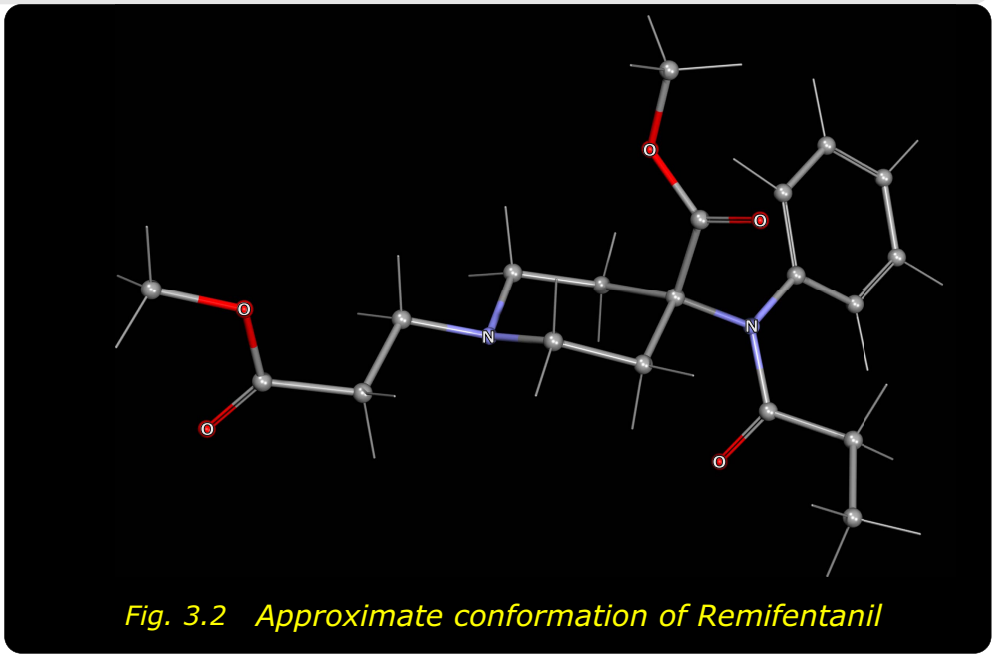
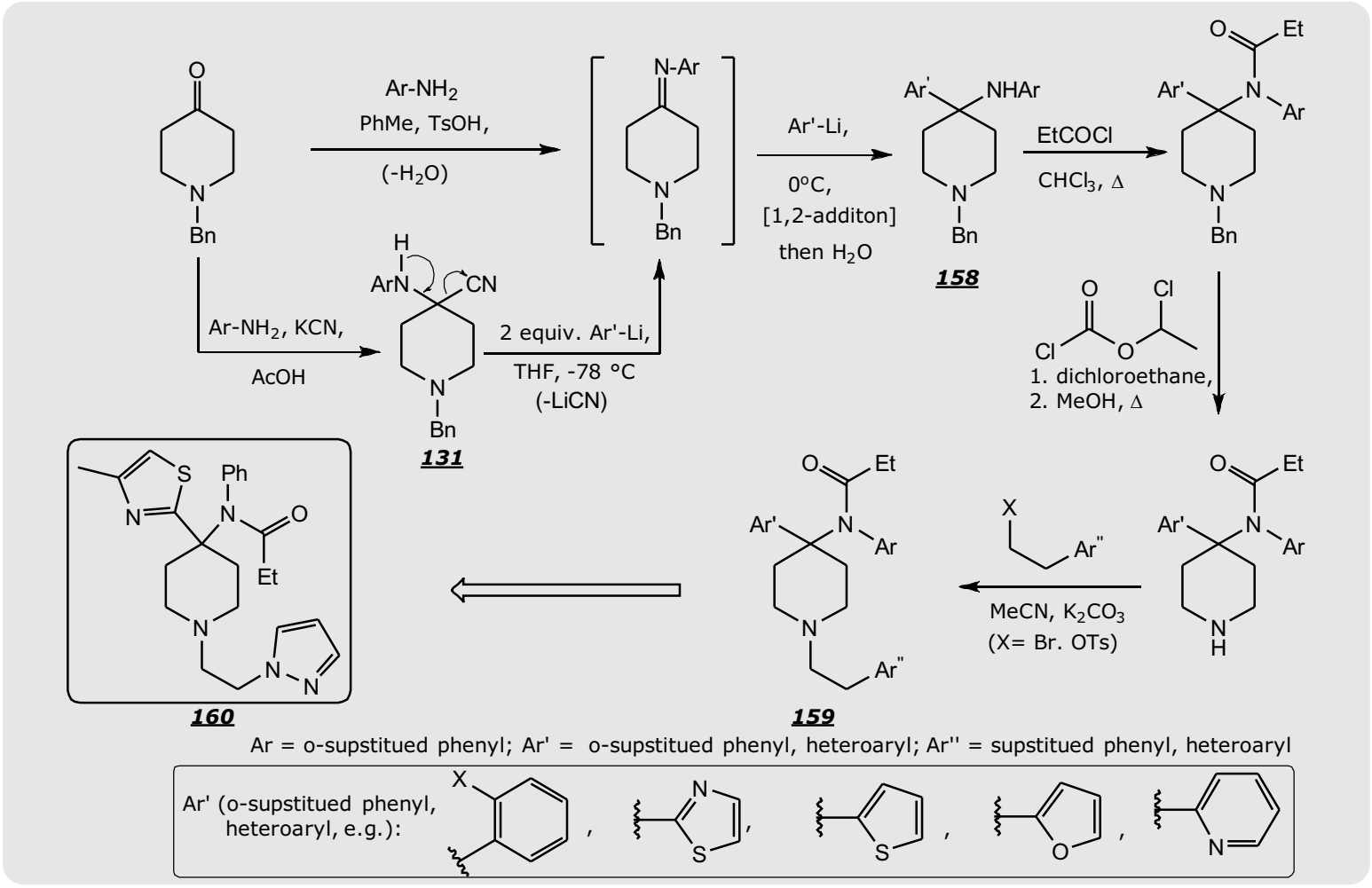


Fig. 3.2 Approximate conformation of Remifentanil

or 5 mg of the solid. Immediately before the use for injection or infusion, the solid is dissolved (reconstituted) and diluted as prescribed. If used for infusion, usually during surgeries in the spontaneously breathing patients, it is normally administered in doses between 0.025-0.1 μg/kg/min.[77c,d]

Aryl groups were also introduced in the position 4 of 4-anilido-piperidines, acc. to the approach represented in *Scheme 3.42*.[78] It was found that various aryl and heteroaryl organolithium reagents react with the imino group via 1,2 addition, providing derivatives of the general structure ***158***. The same derivatives can also be obtained from the Strecker-type aminonitrile, general structure ***131***, in one synthetic step. Aryllithium reagents, as strong bases, promote retro-Strecker elimination, followed by the sponaneous 1,2-addition of the excess reagent to the intermediate imine. The synthesis was completed by the standard transformations, i.e. *N*-propionylation, debenzylation and *N*-alkylation of the piperidine nitrogen. The debenzylation step was perfomed using 1-chloro-ethyl chloroformate since it is usually much faster than the hydrogenolysis. The compound ***160*** exibited favourable pharmacological profile, comparable to fentanyl and alfentanil, in terms of high analgesic potency, short duration of action, rapid recovery of motor coordination following anesthetic doses, and good cardiovascular and respiratory safety during anesthesia. However, it seems that such compounds have not been examined clinically.

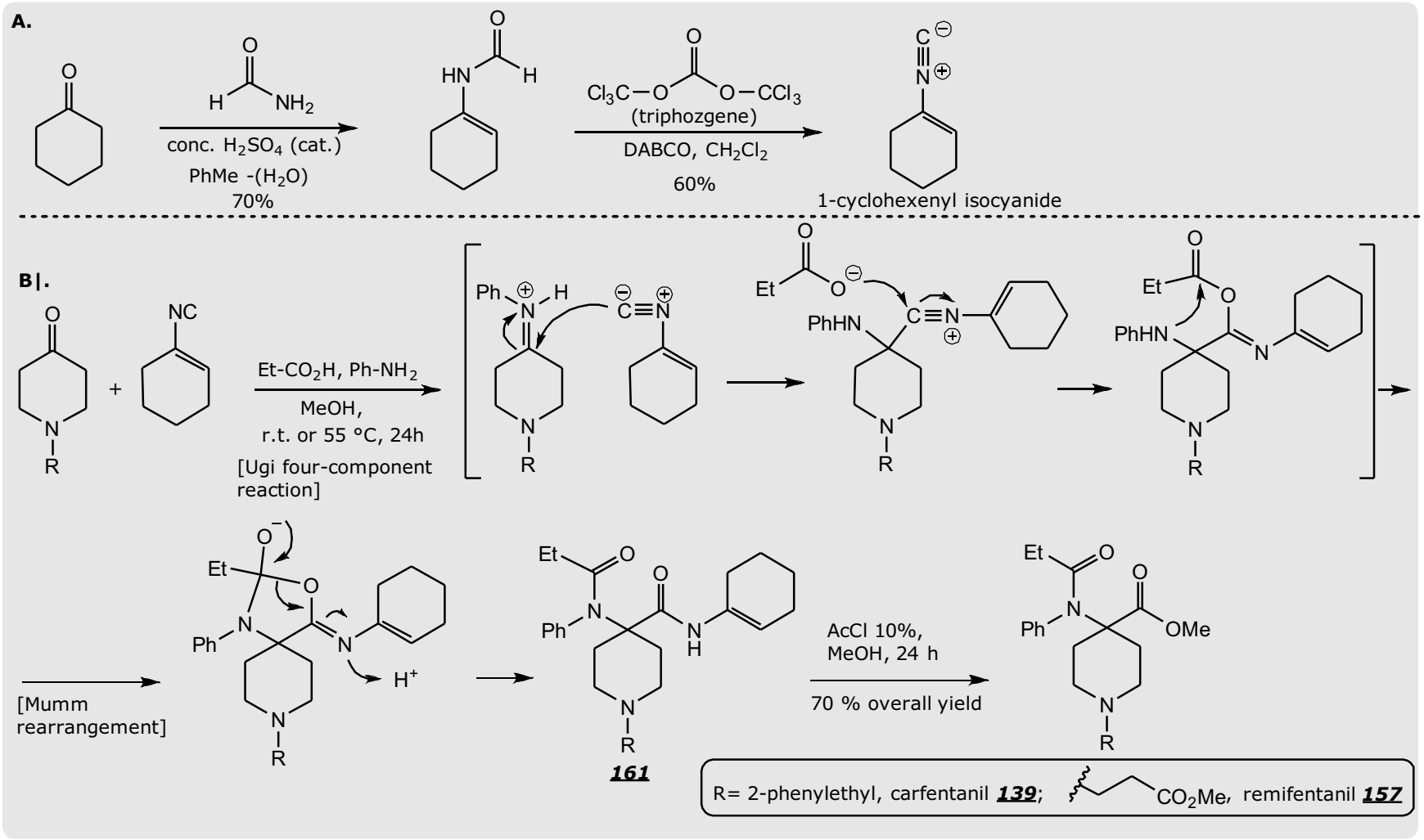


131 ***158*** ***159*** ***160***

Scheme 3.42. Synthesis of 4-aryl-4-anildopiperidines, general structure ***159***.

Recently, a radically different approach to 4-carbomethoxy-4-anilido-piperidines was disclosed.[79] It involves Ugi four-component reaction,[80] providing the key intermediate ***161*** in a single synthetic step, *Scheme 3.43*. The mechanism is complex, probably proceeding as shown, including the spontaneous Mumm rearrangement in the final stage. However, the synthesis is operationally simple, only requiring heating of the components in methanol, followed by acid-catalyzed methanolysis of the isolated intermediate ***161*** The overall yields, on 0.5 mmol scale, exceeded 70%. It appears that the synthesis is scalable and potentially economically viable, particularly because the key precursor, 1-cyclohexenyl isocyanide, is readily and inexpensively available on large scale.

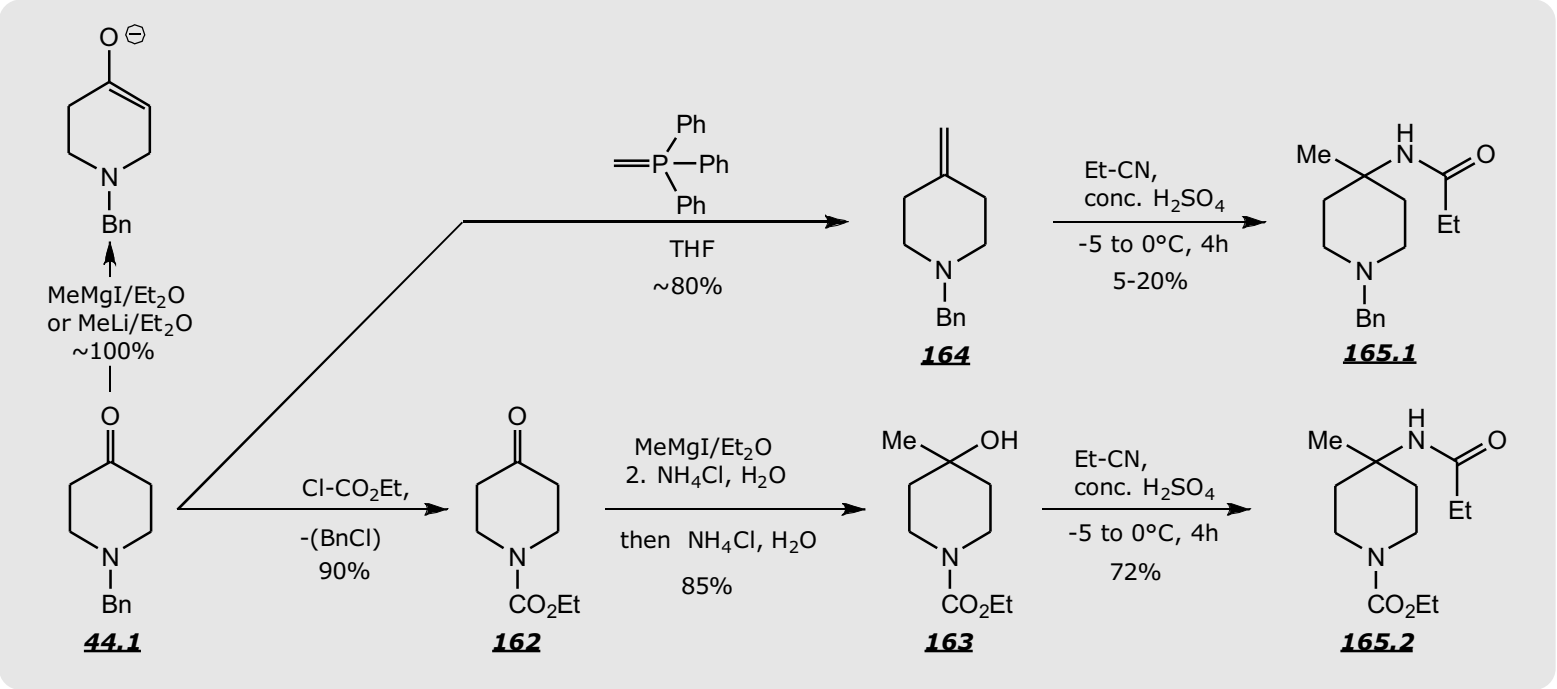
(Triphosgene can be replaced by phosgene).[81]



Scheme 3.43. Synthesis of carfentanil and remifentanil via Ugi four-component reaction.

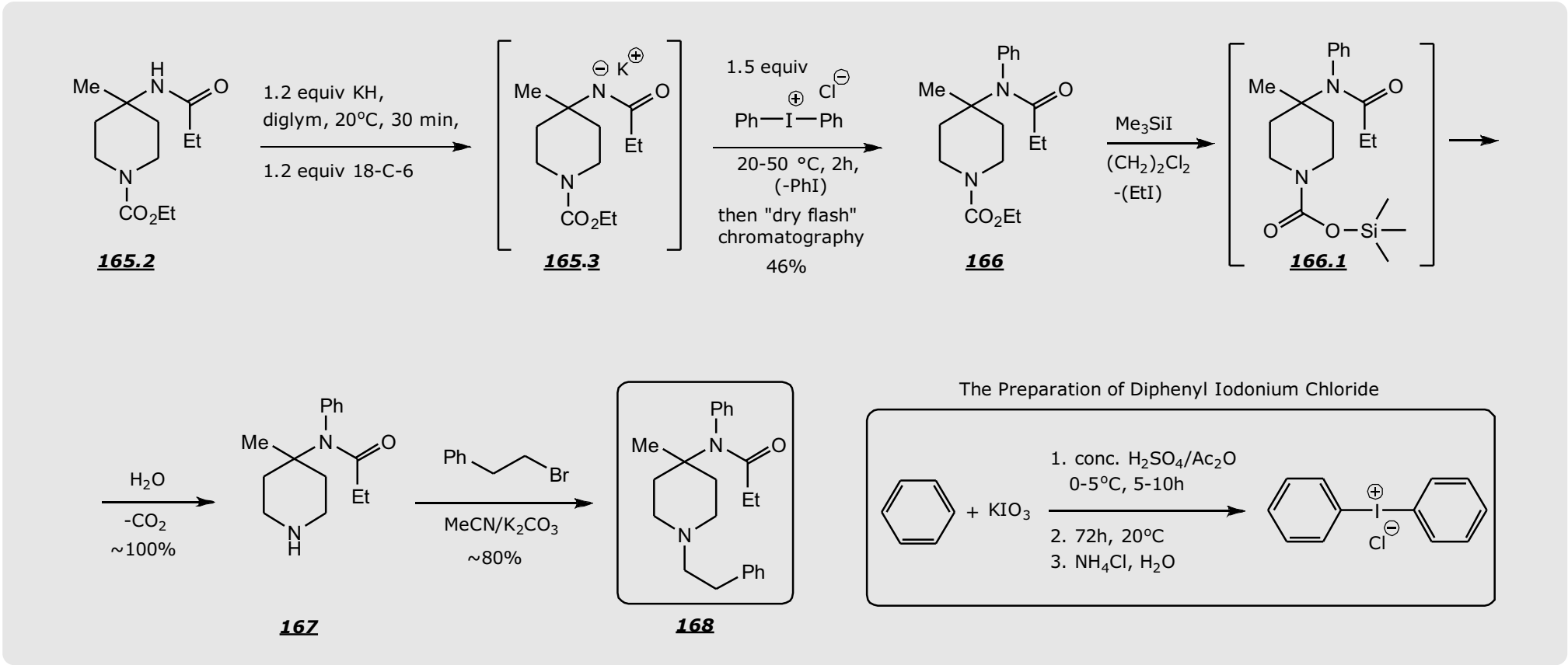
The extensive literature search did not identify simple alkyl groups (e.g. methyl, ethyl etc.) in the position 4 of the 4-anilido-piperidines. In fact, reports of the 1,2-addition of simple alkyllithium, alkylmagnesium and the related organometallic species to ketimines were not found, while aldimines are known to react, in the presence of various catalysts. The experiments with the ketimines (e.g. ***41.2***, *Scheme 3.17* and ***92***, *Scheme 3.30*) by the present author, exclusively resulted in α-deprotonation, i.e. formation of imine "enolates". In order to examine the influence of simple 4-alkyl groups to the opioid activity, relative to 4-alkoxycarbonyl and other, previously introduced groups, a novel synthetic approach was designed, acc. to *Scheme 3.44 A* and *B*.[63b]

Attempts to achieve normal 1,2-addition of methyl-magnesium bromide or methyllithium to piperidone ***44.1*** failed. Unexpectedly, only the enolate anion was obtained, apparently due to the extensive base-catalyzed enolization and deprotonation of the enol. When piperidone ***44.1*** was converted into a non-basic carbamate ***162***, the addition proceeded normally, providing alcohol ***163***. An alternative approach, using piperidone ***44.1*** and the Wittig reagent, gave good yields of alkene ***164***. However, in the following step, involving the Ritter reaction, desired carboxamide ***165.***1 was obtained in minimal yields (5-20%), regardless of the conditions. While acetic acid is often used as solvent in Ritter reaction, in these experiments acetate esters were isolated as sole products, with no traces of the carboxamides. (Apparently, the intermediate carbocation preferentially reacted with acetic acid). Consedquently, the protocol was modified, using conc. H_2SO_4 as a solvent. Under these conditions, alcohol ***163*** (but not alkene ***164***) reacted normally, providing moderate yields of carboxamide ***165.2***.



Scheme 3.44A. Synthesis of 4-methyl fentanyl

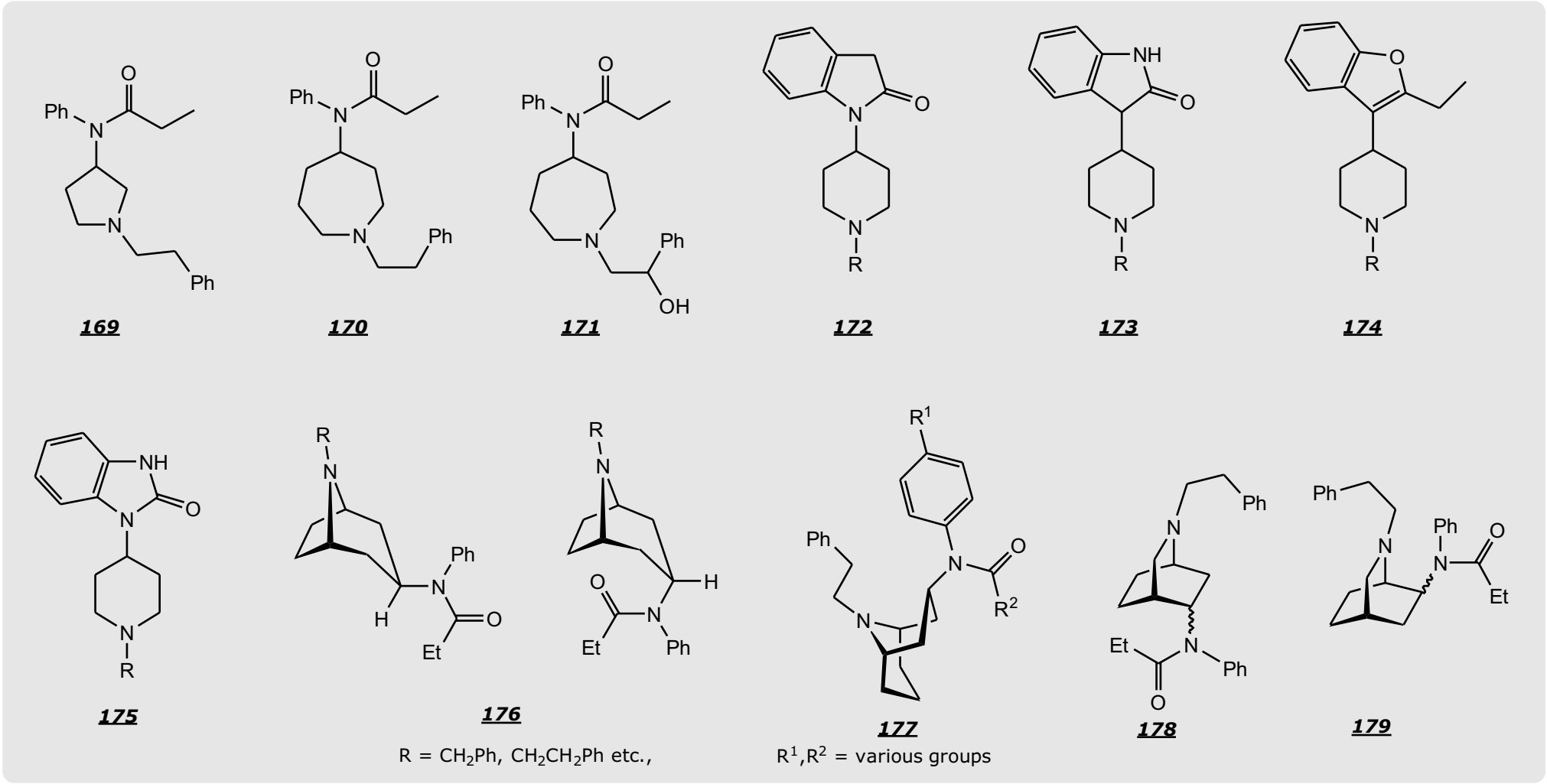
The *N*-phenylation of the secondary carboxamide proved challenging. Thus, the attempted use of triphenylbismuth carbonate,[82] or several variants of Goldberg reaction were uniformly unsuccessful.[83] Fortunately, diphenyl-iodonium chloride,[84a] gave the acceptable yields of *N*-phenylated product ***166***, thus solving the key step in the synthesis, *Scheme 3.44 B*. While the reagent was used previously for C-phenylation of various enolate anions, in modest yields,[84b] no *N*-phenylation was reported. (Recently, the modified method was applied to various secondary N-aryl amides, providing good yields of tertiary *N*,*N*-di-arylamides).[85] The key intermediate ***165*** was transformed into 4-methyl-fentanyl ***167*** in two routine steps.[63b] A preliminary *in vivo* tests found that it was about four times more potent analgesic than fentanyl.[63] However, higher homologues have not been prepared, thus precluding SAR studies.



Scheme 3.44 B. Synthesis of 4-methyl fentanyl

3.4.6 Structural variation of fentanyl scaffold

Numereous structural variations of the original fentanyl scaffold were examined, including replacing the piperidine ring with pyrrolidine analogue ***169***[86] or azepane analogues ***170***[87] and ***171***[87] , as well as the synthesis of conformationally restricted structures ***172***-***174***,[88] ***175***,[89] ***176***,[90] ***177***,[91] ***178*** - ***179***[92] and many others, possessing one or more additional rings, *Scheme 3.45*. However, all the prepared compounds were only feebly active or inactive as opioids.



Scheme 3.45. Examples of structural variations of the fentanyl scafold.

3.4.7 General SAR for anilido-piperidines

Analyzing the structures of hundreds of fentanyl analogues in a broader sense, i.e. not only those having the original fentanyl scaffold, and taking into account the results of various molecular modelings, some SAR conclusions can be made. The conclusions are summarized in *Fig. 3.3*.

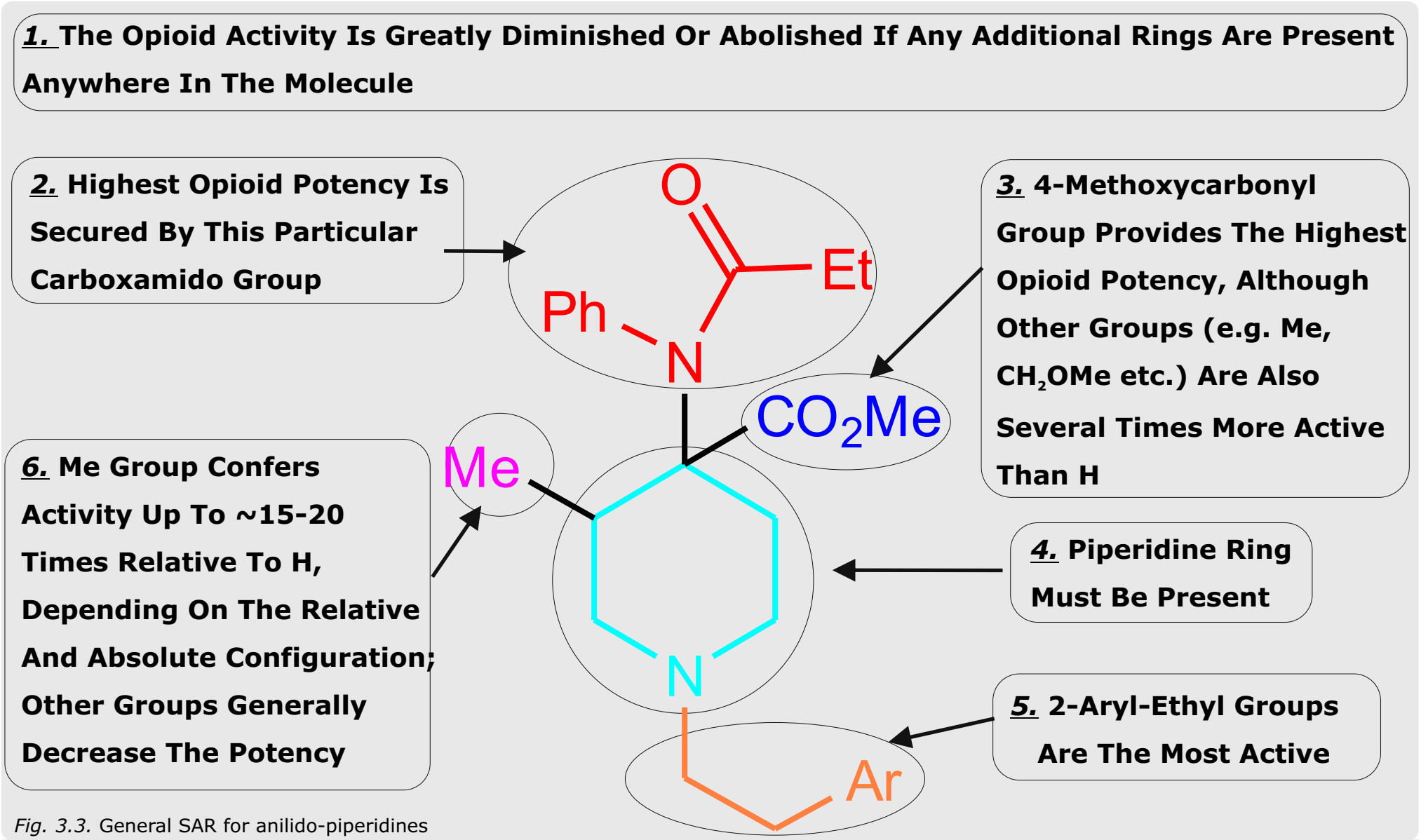
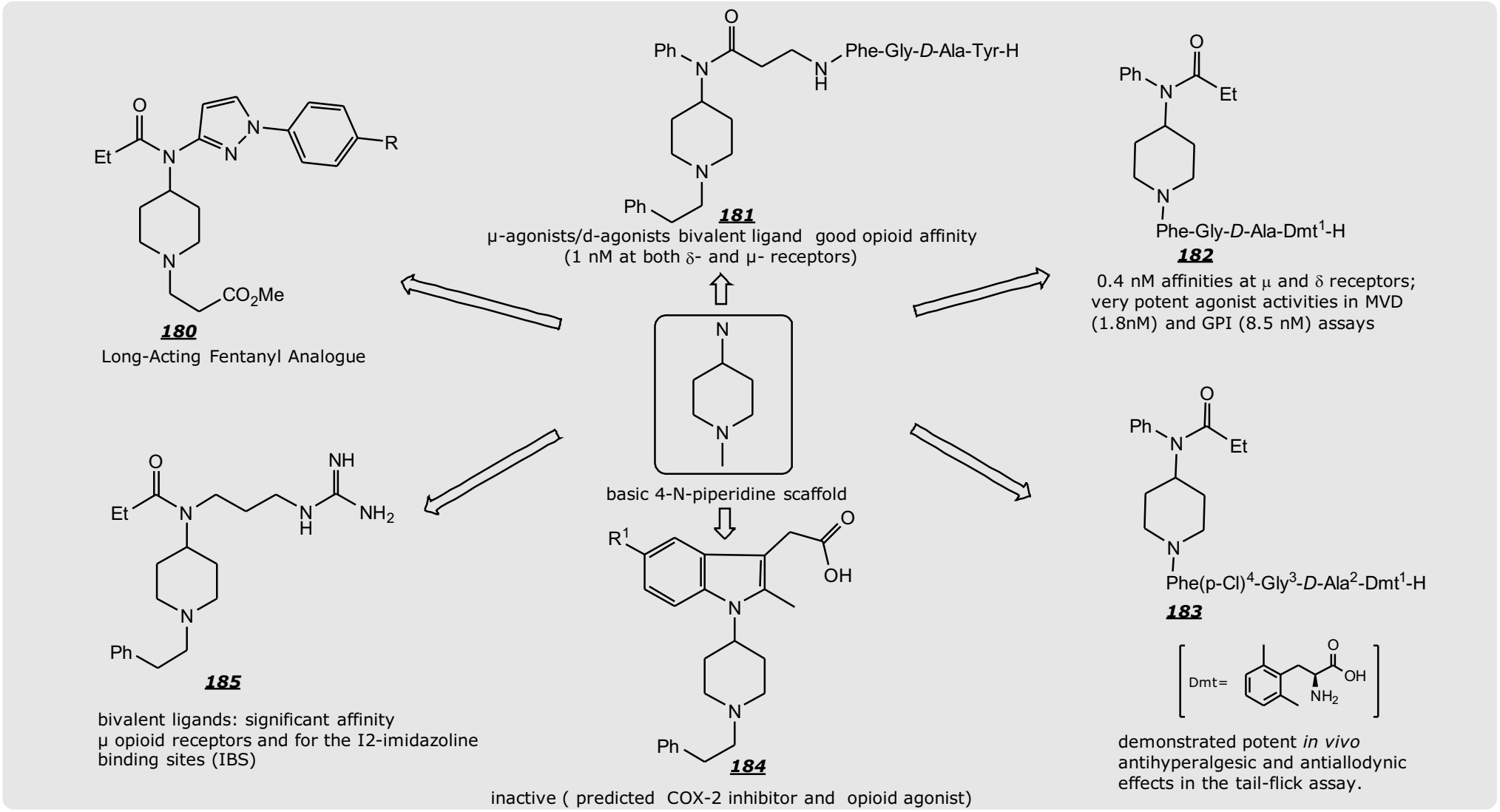


Fig. 3.3. General SAR for anilido-piperidines

3.4.8 Anildo-piperidines as bivalent ligands.

In recent years, simple 4-amino-piperidine structural motifs (mainly fentanyl analogues), have been incorporated into more complex molecules, in attempts to change the pharmacological profile or to obtain various bivalent ligands. Some of the more prominent examples, structures ***180***,[93] ***181***,[94] ***182***,[95] ***183***,[96] ***184***,[97] and ***185***,[98] are shown in *Scheme 3.46*. For detailed discussion of the synthesis and pharmacology, see relevant references (93-98).



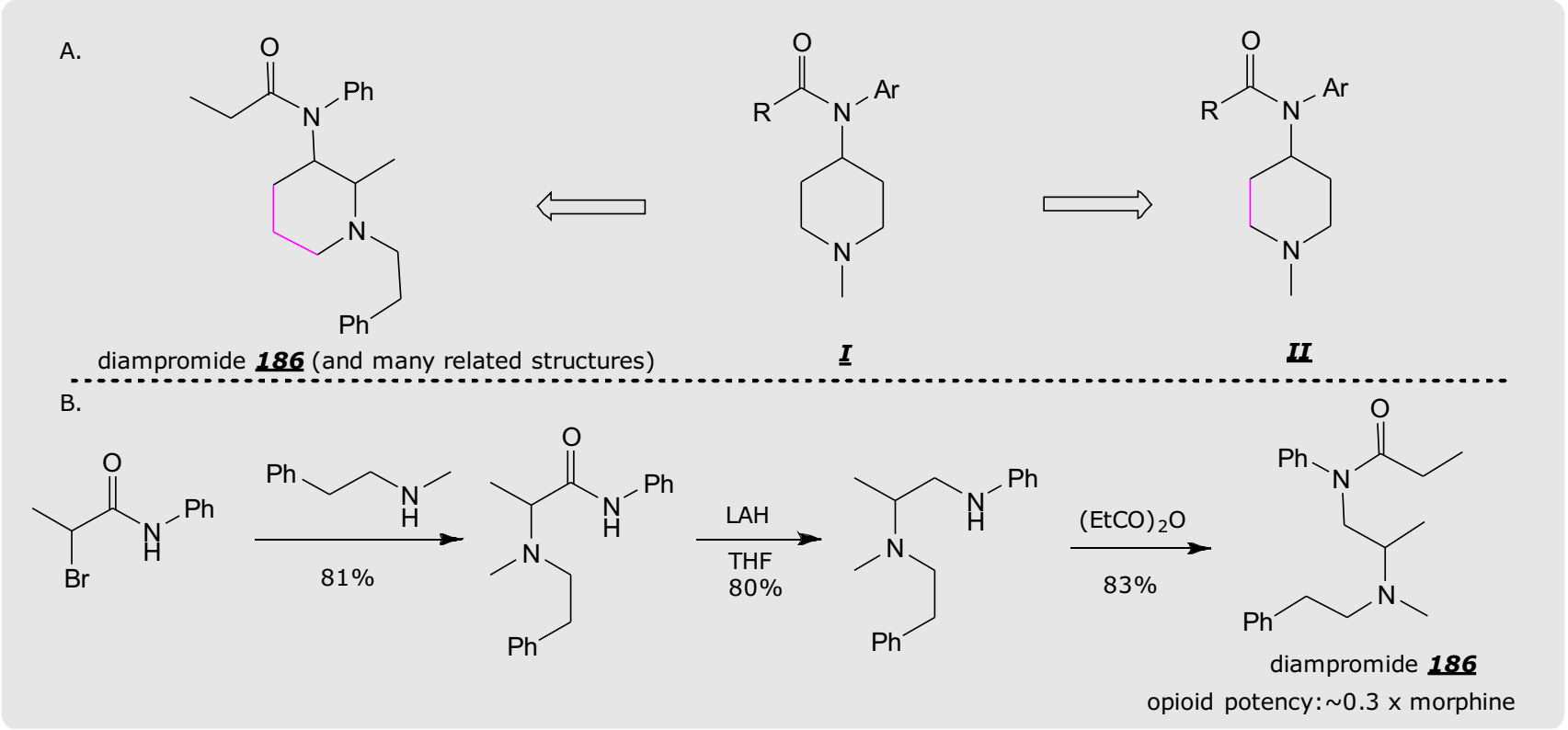
Scheme 3.46. Various potential bivalent ligands and other pharmacologically active compounds possessing fentanyl-like scaffold.

3.5. Simple opioids possessing no heterocyclic rings.

As it is evident from the previous discussion, the overwhelming majority of non-peptide opioids possesses piperidine ring. Extensive empirical results have shown that piperidine ring is highly significant opioid pharmacophore, together with amino groups (usually tertiary) and, at least one, aryl moiety. Nonetheless, a number of potent opioids have no heterocyclic rings.

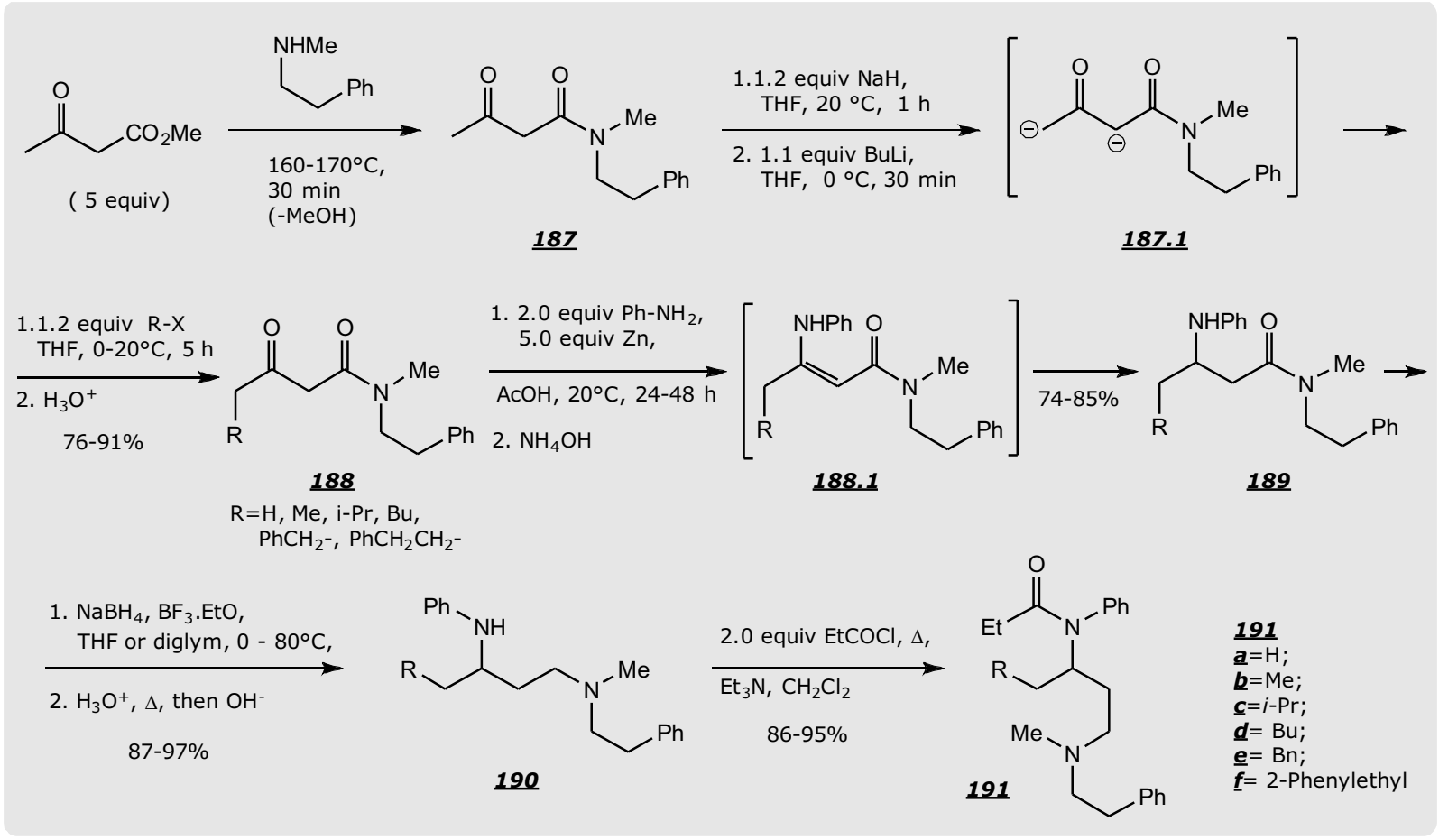
Some of the compounds share many structural features with anilido-piperidines, general structure ***I***, e.g. diampromide ***186***,[99,100] yet they are not exact open-chain analogs, general structure ***II*** *Scheme 3.47A*. (Diampromide, which has never been used as a drug, was synthesized via simple transformations, acc. to *Scheme 3.47B*. Many similar compounds were prepared in the late 1950s).[99]

It was considered significant for SAR studies to synthesize compounds, hitherto unknown, which represent exact open-chain anilido-piperidine analogues, general structure ***II***. The aproach is outlined in *Scheme 3.48*.



Scheme 3.47. A. General structure of anilido-piperidines and open-chain derivatives. B. Synthesis of diampromide ***186***.

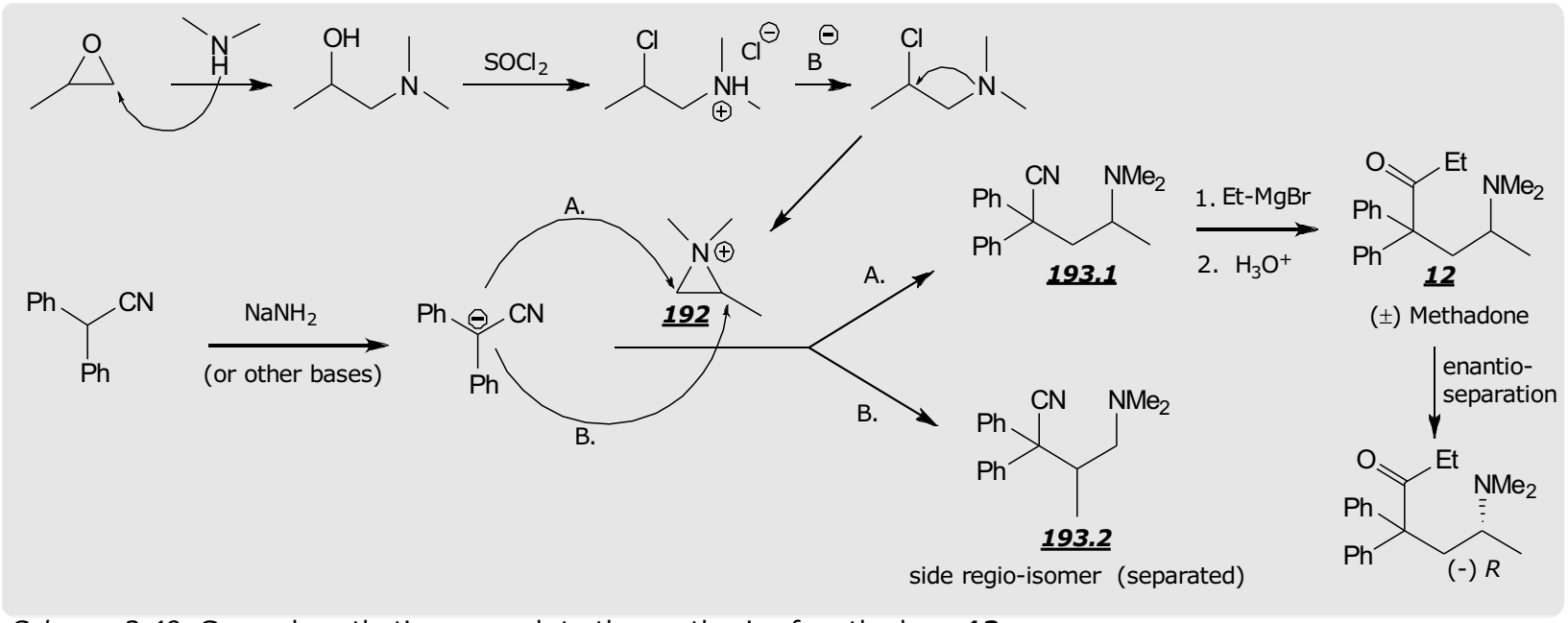
The synthesis of open-chain anilido-piperidine analogues of the general structure ***191*** ("seco-fentanyls"), was achieved acc. to *Scheme 3.48*.[101] Thermally promoted aminolysis of methyl acetoacetate gave β-keto carboxamide ***187*** in nearly quantitative yields (respective to the amine). Dianion ***187.1*** was generated analogously to the dianions from β-keto esters, followed by the strictly regioselective γ-alkylation. The obtained β-keto carboxamides (general structure ***188***) were reacted with aniline and metallic zinc in acetic acid, providing relatively stable enamine intermediates ***188.1***, which were quantitatively reduced to β-anilino-carboxamides ***189***. The carboxamido group was then reductively deoxygenated to diamine ***190***, using *in situ* generated borane. (Decomposition of the stable amine-borane complex required acid treatment). The final products, anilides of the general structure ***191*** were obtained by direct *N*-propionylation. Pharmacological tests, performed *in vivo*, found that only the parent compound (***191a***, R=H), was an active opioid, about ~40 times less active than fentanyl, but still 5-6 times more active than morphine.[101] (In this test, fentanyl to morphine potency ratio is ~250:1).



Scheme 3.48. Synthetic approach to "seco" analogues of anilido-piperidines, general structure ***191***.

The extensive SAR results have proved that the piperidine ring highly potentiates opioid activity but it is not an absolute requrement, even among the structurally closely related compounds, such as fentanyl and "seco" fentanyl.

Several other, open-chain opioid drugs, are in the current therapeutic use or were used formerly. The best known of these compounds is methadone ***12***,[102] first synthesized by Hoechst chemists, G. Ehrhart and M. Bockmühl, in the late 1939. The synthesis was later refined; however, acc. to the literature reports, it seems that the fundamental approach has not changed substantially, *Scheme 3.49*.[103] Of the two enantiomers, (-) *R* is much more active (approximately as morphine in humans) and has fewer side effects.[104] Because of the less favorable pharmacological profile than morphine, it has not been used extensively as analgesic, but mainly in the treatment of opioid dependence, as heroin substitute.[105] (It is well-known that the addicts who developed physical dependence, must not abruptly discontinue the opioid use, since it typically results in the severe and life-threatening abstinence syndrome. In that respect, methadone's main advantage is the orally activity (unlike heroin) and less pronounced respiratory depression. However, as an opioid, methadone too has dependence liability and has been abused on a considerable scale. Methadone is prepared starting from 2,2-diphenylacetonitrile, which is first deprotonated using various bases (originally sodium amide), *Scheme 3.49*. Under the reaction conditions, 2-chloro-N,N-dimethyl-propan-1-amine form the reactive intermediate, unsymmetrical aziridinium cation ***192***, which is the actual electrophile. The ring opening is not regioselective, typically producing similar amounts of regio-isomers ***193.1*** and ***193.2.***

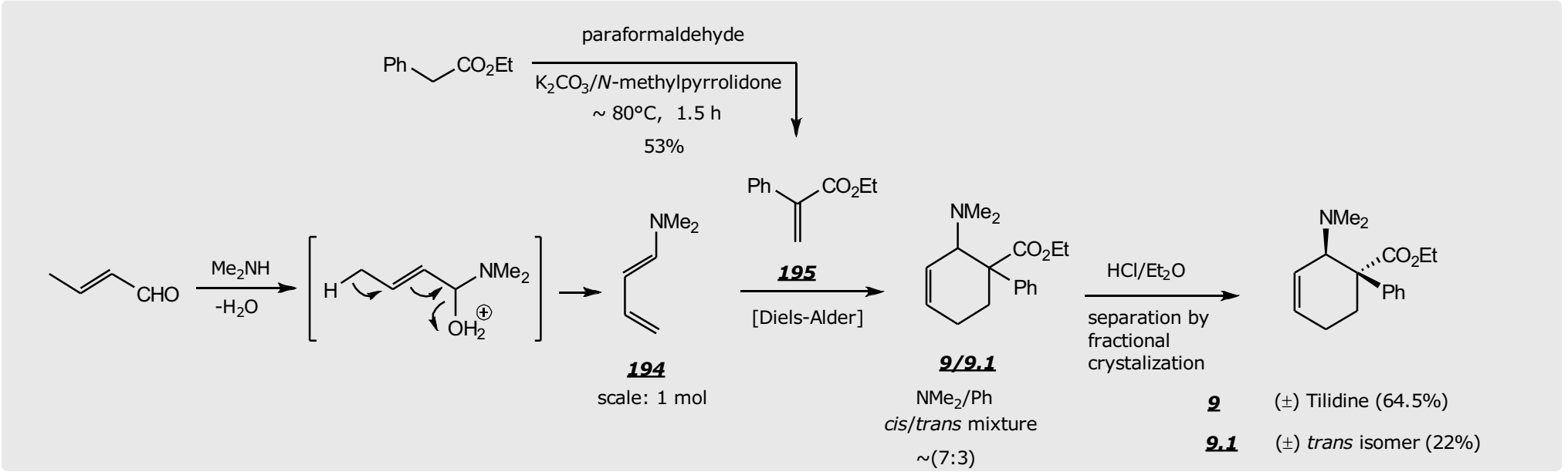


Scheme 3.49. General synthetic approach to the synthesis of methadone ***12***.

Usually, the regioisomers are separated by fractional crystallization of the salts, prior to the next step. Addition of ethylmagnesium bromide to the nitrile function of ***193.1***, followed by acid hydrolysis, secures racemic methadone ***12*** (reported yields vary substantially, depending on the literature source, and are not quoted in the *Scheme 3.49*). The requred (-) R enantiomer is obtained by fractional crystalyzation of the salts, using various optically active acids, e.g. (1S)-(+)-3-bromocamphor-10-sulfonic acid[103e] etc.

The final example in this treatise is tilidine ***9***, wich can be considered as "open-chain opioid" since it contains no heterocyclic rings. While it is relatively weak opioid (~20% potency of morphine in humans, when taken orally), it has relatively few serious side effects and it is used extensively for the management of moderate to severe pain.

The synthesis is shown in *Sheme 3.50*.[106] The compound was prepared in two, relatively simple steps. Spontaneous condensation of dimethylamine and crotonaldehyde produced the conjugated enamine ***194*** ,resulting from the concomitant double bond migration. Diels-Alder reaction with atropic acid ethyl ester ***195*** gave *cis*/*trans* mixture of the adduct ***9***/***9.1***, which was separated by fractional crystalization to afford (±) Tilidine ***9*** and *trans* diastereomer ***9.1*** (in 64.5% and 22% yields respectively). The requsite precursor ***195*** can be obtained from ethyl 2-phenylacetate and paraformaldehyde, acc. to the patented procedure.[107]



Scheme 3.50. Synthesis of Tilidine ***9***.

3.6 References

1. Galanie, S., Thodey, K., Trenchard, I. J., Filsinger Interrante, M., & Smolke, C. D. (2015). Complete biosynthesis of opioids in yeast. Science, 349(6252), 1095-1100. doi:10.1126/science.aac9373.

2. a) Haddou, T. B.; Malfacini, D.; Calo, G.; Aceto, M. D.; Harris, L. S.; Traynor, J. R.; Coop, A.; Schmidhammer, H.; Spetea, M., Exploring Pharmacological Activities and Signaling of Morphinans Substituted in Position 6 as Potent Agonists Interacting with the μ Opioid Receptor. Molecular Pain 2014, 10, 1744-8069-10-48. doi:10.1186/1744-8069-10-48.
b) Bidlack, J. M. (2014). Mixed Kappa/Mu Partial Opioid Agonists as Potential Treatments for Cocaine Dependence. Advances in Pharmacology, 69, 387-418. doi:http://dx.doi.org/10.1016/B978-0-12-420118-7.00010-X
c) Mariana, S., Muhammad Faheem, A., Gerhard, W., & Helmut, S. (2013). The µ Opioid Receptor and Ligands Acting at the µ Opioid Receptor, as Therapeutics and Potential Therapeutics. Current Pharmaceutical Design, 19(42), 7415-7434. doi:http://dx.doi.org/10.2174/13816128113199990362.
d) Filer, C. N. (2013). Morphinan alkaloids labeled with tritium: synthesis and applications. Journal of Labelled Compounds and Radiopharmaceuticals, 56(13), 639-648. doi:10.1002/jlcr.3094.
e) Decker, M., Si, Y.-G., Knapp, B. I., Bidlack, J. M., & Neumeyer, J. L. (2010). Synthesis and Opioid Receptor Binding Affinities of 2-Substituted and 3-Aminomorphinans: Ligands for μ, κ, and δ Opioid Receptors. Journal of Medicinal Chemistry, 53(1), 402-418. doi:10.1021/jm9013482.
f) Decker, M., Si, Y.-G., Knapp, B. I., Bidlack, J. M., & Neumeyer, J. L. (2010). Synthesis and Opioid Receptor Binding Affinities of 2-Substituted and 3-Aminomorphinans: Ligands for μ, κ, and δ Opioid Receptors. Journal of Medicinal Chemistry, 53(1), 402-418. doi:10.1021/jm9013482.

3. a) Gudin, J., Fudin, J., & Nalamachu, S. (2016). Levorphanol use: past, present and future. Postgraduate Medicine, 128(1), 46-53. doi:10.1080/00325481.2016.1128308
b) Pham, T. C., Fudin, J., & Raffa, R. B. (2015). Is levorphanol a better option than methadone? Pain Medicine, 16(9), 1673-1679. doi:10.1111/pme.12795.

4. Kataoka, H., & Ueno, S. (2013). Butorphanol-midazolam combination therapy for the treatment of intracranial hypertension in a patient with tuberculous meningitis: a case study. SpringerPlus, 2(1), 442. doi:10.1186/2193-1801-2-442.

5.a) Schnider, Otto; Grussner, Andre. Optically active 3-methoxy-*N*-methylmorphinans and their salts. US 2676177 (1954).
b) Benson, Wilbur M.; Stefko, Paul L.; Randall, Lowell O. Comparative pharmacology of levorphan, racemorphan, and dextrorphan and related methyl ethers Journal of Pharmacology and Experimental Therapeutics (1953). 109, 189-200. CAN48:4612.
6. a) Ida H.; Inukai N.; Iwamoto H.; Kawahara S.; Murakami M.; Nagano N. 3-Methyl-N-Methylmorphinans. US 3786054 (1974).
b) Shen, Y., Luo, Z., Yu, Q., Wang, Y., Xiang, J., & Miao, J. (2017). Pharmacokinetics of dimemorfan phosphate tablets in healthy Chinese volunteers. European Journal of Clinical Pharmacology, 73(6), 709-715. doi:10.1007/s00228-017-2211-9.
7. Yuan, S., Palczewski, K., Peng, Q., Kolinski, M., Vogel, H., & Filipek, S. (2015). The Mechanism of Ligand-Induced Activation or Inhibition of μ- and κ-Opioid Receptors. Angewandte Chemie International Edition, 54(26), 7560-7563. doi:10.1002/anie.201501742

8. a) Schnider, O. and A. Grüssner (1949). "Synthese von Oxy-morphinanen." Helvetica Chimica Acta 32(3): 821-828. DOI: 10.1002/hlca.19490320325
b) Schnider, O. and J. Hellerbach (1950). "Synthese von Morphinanen. (2. Mitteilung)." Helvetica Chimica Acta 33(6): 1437-1448.DOI: 10.1002/hlca.19500330606.
c)Schnider, O., & Grüssner, A. (1951). Oxy-morphinane. (3. Mitteilung). Optisch aktive 3-Oxy-morphinane. Helvetica Chimica Acta, 34(7), 2211-2217. doi:10.1002/hlca.19510340715

9. a) Grewe, R. and A. Mondon (1948). "Synthesen in der Phenanthren-Reihe, VI. Mitteil.: Synthese des Morphinans." Chemische Berichte 81(4): 279-286. 10.1002/cber.19480810402.
b) Grewe, R. and W. Friedrichsen (1967). "Die Cyclisierung von Octahydro-isochinolinderivaten durch Morphinan-Ringschluß. Synthese des Dihydrothebainons." Chemische Berichte 100 (5): 1550-1558. 10.1002/cber.19671000521.

10. Bidlack, J. M., & Knapp, B. I. (2013). Mixed Mu/Kappa Opioid Agonists Research and Development of Opioid-Related Ligands (Vol. 1131, pp. 257-272): American Chemical Society. doi:10.1021/bk-2013-1131.ch014

11. a) Archer, S., Albertson, N. F., Harris, L. S., Pierson, A. K., & Bird, J. G. (1964). Pentazocine.1 Strong Analgesics and Analgesic Antagonists in the Benzomorphan Series2. Journal of Medicinal Chemistry, 7(2), 123-127. doi:10.1021/jm00332a001
b)Wilson, T. D. (1984). Pentazocine. Analytical Profiles of Drug Substances, 13, 361-416. doi:http://dx.doi.org/10.1016/S0099-5428(08)60197-5

12. Archer, S., Glick, S. D., & Bidlack, J. M. (1996). Cyclazocine revisited. Neurochemical Research, 21(11), 1369-1373. doi:10.1007/bf02532378

13. Hori, M.; Ban, M.; Imai, E.; Iwata, N.; Suzuki, Y.; Baba, Y.; Morita, T.; Fujimura, H.; Nozaki, M.; Niwa, M., Novel nonnarcotic analgesics with an improved therapeutic ratio. Structure-activity relationships of 8-(methylthio)- and 8-(acylthio)-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocines. Journal of Medicinal Chemistry 1985, 28, 1656-1661. doi:10.1021/jm00149a020.

14. Prezzavento, O.; Arena, E.; Sánchez-Fernández, C.; Turnaturi, R.; Parenti, C.; Marrazzo, A.; Catalano, R.; Amata, E.; Pasquinucci, L.; Cobos, E. J., (+)-and (−)-Phenazocine enantiomers: Evaluation of their dual opioid agonist/σ1 antagonist properties and antinociceptive effects. European Journal of Medicinal Chemistry 2017, 125, 603-610. doi.org/10.1016/j.ejmech.2016.09.077

15. Note: while bremazocine has been commercially available for decades, its original synthesis was not well documented See: https://depatisnet.dpma.de/DepatisNet/depatisnet?action=bibdat&docid=NL00 0007804509A; (Acf Chemiefarma Nv. Nieuwe 6,7-Benzomorfanderivaten En Zuuradditiezouten Daarvan. NL7804509 (1979).

16. Matsuo, J.-i.; Okado, R.; Ishibashi, H., A New Synthesis of 2,3-Di- or 2,3,3-Trisubstituted 2,3-Dihydro-4-pyridones by Reaction of 3-Ethoxycyclobutanones and N-p-Toluenesulfonyl Imines Using Titanium(IV) Chloride: Synthesis of (±)-Bremazocine. Organic Letters 2010, 12, 3266-3268. DOI: 10.1021/ol1012313

17. Dortch-Carnes, J., & Potter, D. E. (2005). Bremazocine: A κ-Opioid Agonist with Potent Analgesic and Other Pharmacologic Properties. CNS Drug Reviews, 11(2), 195-212. doi:10.1111/j.1527-3458.2005.tb00270.x

18. a) Kametani, T., Takano, S., Hibino, S., & Terui, T. (1969). Ochotensine and related compounds. II. A synthesis of iso-ochotensine. (Studies on the syntheses of heterocyclic compounds. CCLXXV). Journal of Heterocyclic Chemistry, 6(1), 49-51. doi:10.1002/jhet.5570060109
b) Albertson, N. F., & Wetterau, W. F. (1970). Synthesis of pentazocine. Journal of Medicinal Chemistry, 13(2), 302-303. doi:10.1021/jm00296a036.

19. a) Thomas, J. B.; Zheng, X.; Brieaddy, L. E.; Burgess, J. P.; Wayne Mascarella, S.; Fix, S. E.; Cantrell, B. E.; Zimmerman, D. M.; Ivy Carroll, F., Synthesis of 9β-methyl-2-alkyl-7-oxo-5-arylmorphans. Tetrahedron Letters 1998, 39, 7001-7004. doi.org/10.1016/S0040-4039(98)01549-4.
b) Awaya, H.; May, E. L.; Aceto, M. D.; Merz, H.; Rogers, M. E.; Harris, L. S., Racemic and optically active 2,9-dimethyl-5-(m-hydroxyphenyl) morphans and pharmacological comparison with the 9-demethyl homologs. Journal of Medicinal Chemistry 1984, 27, 536-539. DOI: 10.1021/jm00370a019
c) Burke, T. R.; Jacobson, A. E.; Rice, K. C.; Weissman, B. A.; Huang, H. C.; Silverton, J. V., Probes for narcotic receptor mediated phenomena. 9. Synthesis of (+/-)-(3 alpha, 6a alpha, 11a beta)- 1,3,4,5,6,11a-hexahydro-2-methyl-2H-3,6a-methanobenzofuro[2,3-c]azocin-10-ol, and oxide-bridged 5-(m-hydroxyphenyl)morphan. Journal of Medicinal Chemistry 1986, 29, 748-751. DOI: 10.1021/jm00155a026.

20. a) May, E. L., & Murphy, J. G. (1954). Structures Related To Morphine.. An Isomer Of *N*-Methylmorphinan. The Journal of Organic Chemistry, 19(4), 618-622. doi:10.1021/jo01369a021.
b) May, E. L., & Murphy, J. G. (1955). Structures Related To Morphine. IV.1 M-Substituted Phenylcyclohexane Derivatives. The Journal of Organic Chemistry, 20(9), 1197-1201. doi:10.1021/jo01126a008
c) Cochran, T. G. (1974). Stereochemistry and absolute configuration of the analgesic agonist-antagonist (-)-5-m-hydroxyphenyl-2-methylmorphan. Journal of Medicinal Chemistry, 17(9), 987-989. doi:10.1021/jm00255a017

21. Evans, D. A., Mitch, C. H., Thomas, R. C., Zimmerman, D. M., & Robey, R. L. (1980). Application of metalated enamines to alkaloid synthesis. An expedient approach to the synthesis of morphine-based analgesics. Journal of the American Chemical Society, 102(18), 5955-5956. doi:10.1021/ja00538a065

22. a) Langston, J., Ballard, P., Tetrud, J., & Irwin, I. (1983). Chronic Parkinsonism in humans due to a product of meperidine-analog synthesis. Science, 219(4587), 979-980. doi:10.1126/science.6823561
b) Machado, V., Zöller, T., Attaai, A., & Spittau, B. (2016). Microglia-Mediated Neuroinflammation and Neurotrophic Factor-Induced Protection in the MPTP Mouse Model of Parkinson's Disease-Lessons from Transgenic Mice. International Journal of Molecular Sciences, 17(2), 151.
c) Abushouk, A. I., Negida, A., Ahmed, H., & Abdel-Daim, M. M. (2017). Neuroprotective mechanisms of plant extracts against MPTP induced neurotoxicity: Future applications in Parkinson's disease. Biomedicine & Pharmacotherapy, 85, 635-645. doi:https://doi.org/10.1016/j.biopha.2016.11.074
d) Potts, L. F., Wu, H., Singh, A., Marcilla, I., Luquin, M. R., & Papa, S. M. (2014). Modeling Parkinson's disease in monkeys for translational studies, a critical analysis. Experimental Neurology, 256, 133-143. doi:https://doi.org/10.1016/j.expneurol.2013.09.014.

23. Porras, G.; Li, Qin; Bezard, E. Modeling Parkinson's disease in primates: the MPTP model. Cold Spring Harb Perspect Med (2012);2:a009308. General Review; Online Computer File . DOI:10.1101/cshperspect.a009308

24. Lukashov, O. I., Kazakov, P. V., & Mirzabekova, N. S. (2015). Optimization of the Manufacturing Technology for Promedone. Synthesis of 1,2,5-trimethylpiperidin-4-one. Pharmaceutical Chemistry Journal, 49(1), 51-54. doi:10.1007/s11094-015-1220-1

25. Eisleb, O. (1941). Neue Synthesen mittels Natriumamids. Berichte der deutschen chemischen Gesellschaft (A and B Series), 74(8), 1433-1450. doi:10.1002/cber.19410740814.

26. a) Bergel, F., Morrison, A. L., & Rinderknecht, H. (1944). 69. Synthetic analgesics. Part II. A new synthesis of pethidine and similar compounds. Journal of the Chemical Society (Resumed) (0), 265-267. doi:10.1039/JR9440000265.
b) Thorp, R. H., & Walton, E. (1948). 114. Search for new analgesics. Part II. Further homologues of pethidine and the pharmacology of these and other compounds. Journal of the Chemical Society (Resumed)(0), 559-561. doi:10.1039/JR9480000559

27. Paul A. J. Janssen. Lower Alkyl Esters Of 1-(2-Benzoylethyl)-3-Methyl-4-Phenylpiperidine-4–Carboxylic Acid And 1-(3-Hydroxy-3-Phenylpropyl)-3-Methyl-4-Phenylpiperidine-4 - Carboxylic Acid. US Patent 3,004,977 (1961).

28. Lomenzo, S. A., Rhoden, J. B., Izenwasser, S., Wade, D., Kopajtic, T., Katz, J. L., & Trudell, M. L. (2005). Synthesis and Biological Evaluation of Meperidine Analogues at Monoamine Transporters. Journal of Medicinal Chemistry, 48(5), 1336-1343. doi:10.1021/jm0401614

29. Avison, A. W. D., & Morrison, A. L. (1950). 303. Synthetic analgesics. Part VI. The synthesis of ketobemidone. Journal of the Chemical Society (Resumed)(0), 1469-1471. doi:10.1039/JR9500001469

30. a) Blair, A. M. J. N., Stephenson, R. P., With an Addendum By, R. E. L., & R. P, S. (1960). Analgesic Action Of Ethyl 4-Phenylpiperidine-4-Carboxylates With Oxygenated 1-Substituents. British Journal of Pharmacology and Chemotherapy, 15(2), 247-253. doi:10.1111/j.1476-5381.1960.tb01239.x
b) Anderson, R. J., Frearson, P. M., & Stern, E. S. (1956). 788. Some new analogues of pethidine. Part I. Journal of the Chemical Society (Resumed)(0), 4088-4091. doi:10.1039/JR9560004088.

31. a) Duc, C. L., Charlon, C., Delord, C. A., Cros, J., & Monsarrat, B. (1978). Synthesis of pethidine derivatives: 14C labelled DL-phenoperidine. Journal of Labelled Compounds and Radiopharmaceuticals, 15(S1), 693-696. doi:10.1002/jlcr.2580150182
b) Auguy-Valette, A., Cros, J., Gouarderes, C., Gout, R., & Pontonnier, G. (1978). Morphine Analgesia And Cerebral Opiate Receptors: A Developmental Study. British Journal of Pharmacology, 63(2), 303-308. doi:10.1111/j.1476-5381.1978.tb09761.x
c) Jennett, S., Barker, J. G., & Forrest, J. B. (1968). A Double-Blend Controlled Study Of The Effects On Respiration Of Pentazocine, Phenoperidine And Morphine In Normal Man. BJA: British Journal of Anaesthesia, 40(11), 864-875. doi:10.1093/bja/40.11.864

32. a) Elpern, B., Carabateas, P., Soria, A. E., Gardner, L. N., & Grumbach, L. (1959). Strong Analgesics. The Preparation of Some Ethyl 1-Anilinoalkyl-4-Phenylpiperidine-4-Carboxylates. Journal of the American Chemical Society, 81(14), 3784-3786. doi:10.1021/ja01523a073.
b) Dornette, W. H. L.; Poe, Mary F.; Jones, J. P.; Hughes, B. H. A comparison of three new synthetic analgesics and demerol. Anesthesia & Analgesia (Hagerstown, MD, United States) (1961), 40, 307-13. DOI:10.1213/00000539-196105000-00013. CAN57:79229.

33. Jensen, K. A.; Lindquist, F.; Rekling, E.; Wolffbrandt, C. G. A new type of piperidine derivative with analgesic and spasmolytic activity. Dansk Tidsskrift for Farmaci. 1943, 17, 173- 82. CAN 39:16043.

34. a) Casy, A. F., & McErlane, K. (1971). Analgesic potency and stereochemistry of trimeperidine and its isomers and analogues. Journal of Pharmacy and Pharmacology, 23(1), 68-69. doi:10.1111/j.2042-7158.1971.tb12786.x.
b) Fries, D., & Portoghese, P. S. (1974). Stereochemical studies on medicinal agents. 18. Absolute configuration and analgetic potency of trimeperidine enantiomers. Journal of Medicinal Chemistry, 17(9), 990-993. doi:10.1021/jm00255a018

35. Nazarov, I. N.; Prostakov, N. S.; Shvetsov, N. I. Heterocyclic compounds. XXXIX. Synthetic analgesic substances. 4. Esters of 1,2,5-trimethyl-4-phenyl-4-piperidol with aliphatic acids. Synthesis of Promedol and Isopromedol. Zhurnal Obshchei Khimii. (1956), 26, 2798-2811. CAN51:43339.

36. Lukashov, O. I., Kazakov, P. V., & Mirzabekova, N. S. (2015). Optimization of the Manufacturing Technology for Promedone. Synthesis of 1,2,5-trimethylpiperidin-4-one. Pharmaceutical Chemistry Journal, 49(1), 51-54. doi:10.1007/s11094-015-1220-1.

37. Howton, D. R. (1945). 1,3-Dimethylpiperidone-4. The Journal of Organic Chemistry, 10(4), 277-282. doi:10.1021/jo01180a003.

38. a) Portoghese, P. S., Alreja, B. D., & Larson, D. L. (1981). Allylprodine analogs as receptor probes. Evidence that phenolic and nonphenolic ligands interact with different subsites on identical opioid receptors. Journal of Medicinal Chemistry, 24(7), 782-787. doi:10.1021/jm00139a004.
b) Portoghese, P. S., & Shefter, E. (1976). Stereochemical studies on medicinal agents. 19. The x-ray crystal structures of two (+-)-allylprodine diastereomers. Role of the allyl group in conferring high stereoselectivity and potency at analgetic receptors. Journal of Medicinal Chemistry, 19(1), 55-57. doi:10.1021/jm00223a012.

39. a) Forrest, William H., Jr.; Bellville, J. Weldon. Respiratory effects of alphaprodine in man. Obstetrics & Gynecology (New York, NY, United States) (1968). 31, 61-8. DOI: 10.1097/00006250-196801000-00010. CAN68:28426.

39.b) Abdel-Monem, M. M., Harris, P. A., & Portoghese, P. S. (1972). Pharmacokinetics, metabolism, and urinary excretion of [3H]-alphaprodine in dogs. Journal of Medicinal Chemistry, 15(7), 706-708. doi:10.1021/jm00277a003.
c) Dykstra, Linda A.; Leander, J. David. Electric shock titration: effects of meperidine, anileridine and alphaprodine. Pharmacology, Biochemistry and Behavior. (1978). 8,387-9. DOI:10.1016/0091-3057(78)90074-6. CAN89:173547.
d) Leander, J. David. Comparison of morphine, meperidine, anileridine, and alphaprodine on schedule-controlled responding and analgesia. Pharmacology, Biochemistry and Behavior.(1980) 12, 797-801. CAN93:107060.

40. Fries, D. S., & Portoghese, P. S. (1976). Stereochemical studies on medicinal agents. 20. Absolute configuration and analgetic potency of .alpha.-promedol enantiomers. The role of the C-4 chiral center in conferring stereoselectivity in axial- and equatorial-phenylprodine congeners. Journal of Medicinal Chemistry, 19(9), 1155-1158. doi:10.1021/jm00231a014.

41. McElvain, S. M. (1924). Piperidine Derivatives. A Cyclic And An Open-Chain Compound Related In Structure To Cocaine. Journal of the American Chemical Society, 46(7), 1721-1727. doi:10.1021/ja01672a025.

42. Schaefer, J. P., & Bloomfield, J. J. (2004). The Dieckmann Condensation (Including the Thorpe-Ziegler Condensation) Organic Reactions: John Wiley & Sons, Inc. http://dx.doi.org/10.1002/0471264180.or015.01.

43. Wang, Z. (2010). Dieckmann Condensation Comprehensive Organic Name Reactions and Reagents: John Wiley & Sons, Inc. DOI: 10.1002/9780470638859.conrr189.

44. Jelena Popović-Djordjević, Stepan Stepanović, Ljiljana Došen-Mićović, Evica Ivanović & Milovan D. Ivanović (2016) High-yielding method for preparation of carbocyclic or N-containing heterocyclic β-keto esters using in situ activated sodium hydride in dimethyl sulphoxide, Green Chemistry Letters and Reviews, 9:1, 61-68, DOI: 10.1080/17518253.2016.1145744.

45. a)For the recent review see: Vardanyan, Ruben S.; Hruby, Victor J. Fentanyl-related compounds and derivatives: current status and future prospects for pharmaceutical applications. Future Medicinal Chemistry 2014, 6, 385-412. DOI:10.4155/fmc.13.215
b)For Fentanyl Transdermal Patches see:
https://medlineplus.gov/druginfo/meds/a601202.html
c) For fentanyl oral transmucosal delivery systems see:Satheesh Madhav, N. V., Semwal, R., Semwal, D. K., & Semwal, R. B. (2012). Recent trends in oral transmucosal drug delivery systems: an emphasis on the soft palatal route. Expert Opinion on Drug Delivery, 9(6), 629-647. doi:10.1517/17425247.2012.679260

46. For the references prior to 1997., see: Ivanović, Milovan D. Sinteze Analoga Fentanila. PhD Thesis, University of Belgrade, Faculty of Chemistry, Belgrade, SR Yugoslavia (1998).

47. Paul A. J. Janssen, 1-Aralkyl- 4 - (N -Aryl - Carbonyl Amino) Piperidines And Related Compounds US Patent 3,164,600 (1965).

48. P. A. J. Janssen and C. A. M. van der Eycken in: Drugs Affecting the CNS (A. Burger, ed.), Vol. 2, p. 25, Dekker, New York (1968).

49. Casy, A. F., Hassan, M. M. A., Simmonds, A. B., & Staniforth, D. (1969). Structure-activity relations in analgesics based on 4-anilinopiperidine. Journal of Pharmacy and Pharmacology, 21(7), 434-440. doi:10.1111/j.2042-7158.1969.tb08284.x.

50. Casy, A. F., & Huckstep, M. R. (1988). Structure-Activity Studies of Fentanyl. Journal of Pharmacy and Pharmacology, 40(9), 605-608. doi:10.1111/j.2042-7158.1988.tb05318.x.

51. Lobbezoo, M. W., Soudijn, W., & Van Wijngaarden, I. (1981). Opiate receptor interaction of compounds derived from or structurally related to fentanyl. Journal of Medicinal Chemistry, 24(7), 777-782. doi:10.1021/jm00139a003

52. a) Bagley, J. R., Wynn, R. L., Rudo, F. G., Doorley, B. M., Spencer, H. K., & Spaulding, T. (1989). New 4-(heteroanilido)piperidines, structurally related to the pure opioidagonist fentanyl, with agonist and/or antagonist properties. Journal of Medicinal Chemistry, 32(3), 663-671. doi:10.1021/jm00123a028.
b) Llama, E. F., Del Campo, C., & Capo, M. (1991). New heteroaryl derivatives of fentanyl. Journal of Pharmacy and Pharmacology, 43(1), 68-69. doi:10.1111/j.2042-7158.1991.tb05456.x

53. a) Guram, A. S. (2016). 2016 Paul N. Rylander Award Address: Enabling Palladium/Phosphine-Catalyzed Cross-Coupling Reactions for Practical Applications. Organic Process Research & Development, 20(10), 1754-1764. doi:10.1021/acs.oprd.6b00233.
b) Lundgren, Rylan J.; Stradiotto, Mark. Recent advances in the Buchwald-Hartwig amination reaction enabled by the application of sterically demanding phosphine ancillary ligands. Aldrichimica Acta. (2012) 45, 3, 59-65. ISSN:0002-5100.

54. Riley, T. N., Hale, D. B., & Wilson, M. C. (1973). 4-anilidopiperidine analgesics I: Synthesis and analgesic activity of certain ring-methylated 1-substituted 4-propananilidopiperidines. Journal of Pharmaceutical Sciences, 62(6), 983-986. doi:10.1002/jps.2600620627

55. Zee, S.-H., & Wang, W.-K. (1980). A New Process for the Synthesis of Fentanyl. Journal of the Chinese Chemical Society, 27(4), 147-149. doi:10.1002/jccs.198000026

56. Mićović, I. V., Roglić, G. M., Ivanović, M. D., Došen-Mićović, L., Kiricojević, V. D., & Popović, J. B. (1996). The synthesis of lactam analogues of fentanyl. Journal of the Chemical Society, Perkin Transactions 1(16), 2041-2050. doi:10.1039/P19960002041.

57. Van Bever, W. F. M., Niemegeers, C. J. E., & Janssen, P. A. J. (1974). Synthetic analgesics. Synthesis and pharmacology of the diastereoisomers of N-[3-methyl-1-(2-phenylethyl)-4-piperidyl]- N-phenylpropanamide and N-[3-methyl-1-(1-methyl-2-phenylethyl)-4-piperidyl]-N-phenylpropanamide. Journal of Medicinal Chemistry, 17(10), 1047-1051. doi:10.1021/jm00256a003.

58. Burke, T. R., Jacobson, A. E., Rice, K. C., Silverton, J. V., Simonds, W. F., Streaty, R. A., & Klee, W. A. (1986). Probes for narcotic receptor mediated phenomena. 12. cis-(+)-3-Methylfentanyl isothiocyanate, a potent site-directed acylating agent for delta opioid receptors. Synthesis, absolute configuration, and receptor enantioselectivity. Journal of Medicinal Chemistry, 29(6), 1087-1093. doi:10.1021/jm00156a030.

59. Kim, C. H., Rothman, R. B., Jacobson, A. E., Mattson, M. V., Bykov, V., Streaty, R. A., Rice, K. C. (1989). Probes for narcotic receptor mediated phenomena. 15. (3S,4S)-(+)-trans-3-Methylfentanyl isothiocyanate, a potent site-directed acylating agent for the .delta.-opioid receptors in vitro. Journal of Medicinal Chemistry, 32(6), 1392-1398. doi:10.1021/jm00126a040.

60. Ivanović Milovan D., Mićović I.V., Vučković Sonja M., Prostran Milica Š., Todorović Zoran M., Kricojević V.D., Đorđević J.B., Došen-Mićović Ljiljana I. The synthesis and preliminary pharmacological evaluation of racemic cis and trans 3-alkylfentanyl analogues. Journal of the Serbian Chemical Society. (2004). 69, 511-526.doi.org/10.2298/JSC0407511I

61. Mićović, I. V., Ivanović, M. D., Piatak, D. M., & Bojić, V. D. (1991). A Simple Method for Preparation of Secondary Aromatic Amines. Synthesis, 1991(11), 1043-1045. doi:10.1055/s-1991-26642.

62. Mićović, I. V., Ivanović, M. D., Roglić, G. M., Kiricojević, V. D., & Popović, J. B. (1996). Preparation of secondary amines by reductive amination with metallic magnesium. Journal of the Chemical Society, Perkin Transactions 1(3), 265-269. doi:10.1039/P19960000265.

63. a) Vučković, S.; Prostran, M.; Ivanović, M.; Došen-Mićović, Lj.; Todorović, Z.; Nešić, Z.; Stojanović, R.; Divac, N.; Miković, Z., Fentanyl Analogs: Structure-Activity-Relationship Study. Current Medicinal Chemistry (2009). 16, 2468-2474. DOI:10.2174/092986709788682074.
b)Mićović, I. V., Ivanović, M. D., Vuckovic, S. M., Prostran, M. Š., Došen-Mićović, L., & Kiricojević, V. D. (2000). The Synthesis and preliminary pharmacological evaluation of 4-Methyl fentanyl. Bioorganic & Medicinal Chemistry Letters, 10(17), 2011-2014. doi:http://dx.doi.org/10.1016/S0960-894X(00)00394-2

64. Mićović, I. V.; Ivanović, M. D.; Vučković, S.; Jovanović-Mićić, D.; Beleslin, D.; Došen-Mićović, Lj.; Kiricojević, V. D. 3-Carbomethoxy fentanyl: synthesis, pharmacology and conformational analysis. Heterocyclic Communications. (1998). 4, 171-179. ISSN:0793-0283.

65. Jevtić, I. I., Došen-Mićović, L. I., Ivanović, E. R., Todorović, N. M., & Ivanović, M. D. (2017). Synthesis of Orthogonally Protected (±)-3-Amino-4-anilidopiperidines and (±)-3-N-Carbomethoxyfentanyl. Synthesis, 49(14), 3126-3136. doi:10.1055/s-0036-1588985.

66. Jevtić, I. I.; Došen-Mićović, L.; Ivanović, E. R.; Ivanović, M. D., Hofmann Rearrangement of Carboxamides Mediated by N-Bromoacetamide. Synthesis 2016, 48, 1550-1560. DOI: 10.1055/s-0035-1561405

67. Scheunemann, M., Hennig, L., Funke, U., & Steinbach, J. (2011). High regiocontrol in the nucleophilic ring opening of 1-aralkyl-3,4-epoxypiperidines with amines—a short-step synthesis of 4-fluorobenzyltrozamicol and novel anilidopiperidines. Tetrahedron, 67(19), 3448-3456. doi:https://doi.org/10.1016/j.tet.2011.03.045.

68. Lalinde Nhora L., Moliterni John; Spencer H.Kenneth. N-aryl-N-(1-substituted-3-alkoxy-4-piperidinyl) amides and pharmaceutical compositions and methods employing such compounds. US Patent 4,994,471 (1991).

69. Brackeen Marcus F.; Feldman Paul L. Analgesic N-phenyl-N-(3-or 1-3-Me-4-piperidinyl) amides. US Patent 5,130,321 (1992).

70. Janssen Paul Adriaan Jan; Van Daele Georges Henri Paul. N-(4-Piperidinyl)-N-Phenylamides And Carbamates. US Patent 3,998,834 (1976).

71. a) Feasel, M. G., Wohlfarth, A., Nilles, J. M., Pang, S., Kristovich, R. L., & Huestis, M. A. (2016). Metabolism of Carfentanil, an Ultra-Potent Opioid, in Human Liver Microsomes and Human Hepatocytes by High-Resolution Mass Spectrometry. The AAPS Journal, 18(6), 1489-1499. doi:10.1208/s12248-016-9963-5.
b) Hawkinson, J. E., Acosta-Burruel, M., & Espitia, S. A. (2000). Opioid activity profiles indicate similarities between the nociceptin/orphanin FQ and opioid receptors. European Journal of Pharmacology, 389(2), 107-114. doi:http://dx.doi.org/10.1016/S0014-2999(99)00904-8.
c) Van den Abeele G; Camu F. Clinical evaluation of the analgesic potency of lofentanil in postoperative pain. Acta anaesthesiologica Belgica. Volume 34, 41-7. 1983. ISSN:0001-5164. PubMed ID:6133403. Journal Code:0421022. Belgium.

72. Reynolds, L.; Rauck, R.; Webster, L.; DuPen, S.; Heinze, E.; Portenoy, R.; Katz, N.; Charapata, S.; Wallace, M.; Fisher, D. M., Relative analgesic potency of fentanyl and sufentanil during intermediate-term infusions in patients after long-term opioid treatment for chronic pain. PAIN 2004, 110, 182-188. 10.1016/j.pain.2004.03.024.

73. Janssens Frans. N-phenyl-N-(4-piperidinyl) amides. US Patent 4167574 (1979).

74. a) Huang, Bao-Shan; Deutsehe, Kirsten Hansen; Lalinde, Nhora Lucia; Terrell, Ross Clark; Kudzma, Linas Vladas. N-Aryl-N-(4-Piperidinyl)amides and pharmaceutical compositions and meods employing such compounds. EP 0160 422 (1985).
b) Bao-Shan Huang; Ross C. Terrell; Kirsten H. Deutsche; Linas V. Kudzma; Nhora L. Lalinde. N-Aryl-N-(4-Piperidinyl)amides and pharmaceutical compositions and meods employing such compounds. US Patent 4,584,303 (1986).

75. a) Janssen, D. L.; Swan, G. E.; Raath, J. P.; McJames, S. W.; Allen, J. L.; de Vos, V.; Williams, K. E.; Anderson, J. M.; Stanley, T. H., Immobilization and Physiologic Effects of the Narcotic A-3080 in Impala (Aepyceros melampus). Journal of Zoo and Wildlife Medicine 1993, 24, 11-18. ISSN: 10427260, 19372825.
b)
https://www.fda.gov/downloads/AnimalVeterinary/DevelopmentApprovalProcesMinorUseMinorSpecies/UCM530322.pdf

76. Feldman, P. L., & Brackeen, M. F. (1990). A novel route to the 4-anilido-4-(methoxycarbonyl)piperidine class of analgetics. The Journal of Organic Chemistry, 55(13), 4207-4209. doi:10.1021/jo00300a047

77. a) Feldman, Paul L.; James, Michael K.; Brackeen, Marcus F.; Johnson, Michael Ross; Leighton, Harry Jefferson. N-Phenyl-N-(4-piperidinyl)amides useful as analgesics. EP 0 383 579 A1 (1990).
b) Feldman, P. L.; James, M. K.; Brackeen, M. F.; Bilotta, J. M.; Schuster, S. V.; Lahey, A. P.; Lutz, M. W.; Johnson, M. R.; Leighton, H. J., Design, synthesis, and pharmacological evaluation of ultrashort- to long-acting opioid analgesics. Journal of Medicinal Chemistry 1991, 34, 2202-2208. DOI: 10.1021/jm00111a041.
c) http://www.ultiva.com/-/media/ultiva/ultiva%20dosing%20guide%20(4).pdf
d) https://db.cbg-meb.nl/Pars/h103428.pdf

78. Kudzma, L. V.; Severnak, S. A.; Benvenga, M. J.; Ezell, E. F.; Ossipov, M. H.; Knight, V. V.; Rudo, F. G.; Spencer, H. K.; Spaulding, T. C., 4-Phenyl- and 4-heteroaryl-4-anilidopiperidines. A novel class of analgesic and anesthetic agents. Journal of Medicinal Chemistry 1989, 32, 2534-2542. DOI: 10.1021/jm00132a007.

79. Malaquin, S., Jida, M., Gesquiere, J.-C., Deprez-Poulain, R., Deprez, B., & Laconde, G. (2010). Ugi reaction for the synthesis of 4-aminopiperidine-4-carboxylic acid derivatives. Application to the synthesis of carfentanil and remifentanil. Tetrahedron Letters, 51(22), 2983-2985. doi:http://dx.doi.org/10.1016/j.tetlet.2010.03.120.
80. For reviews on Ugi and related reaction see:
a) Váradi, A., Palmer, T., Notis Dardashti, R., & Majumdar, S. (2016). Isocyanide-Based Multicomponent Reactions for the Synthesis of Heterocycles. Molecules, 21(1), 19. 10.3390/molecules21010019.
b) Alvim, H. G. O., da Silva Junior, E. N., & Neto, B. A. D. (2014). What do we know about multicomponent reactions? Mechanisms and trends for the Biginelli, Hantzsch, Mannich, Passerini and Ugi MCRs. RSC Advances, 4(97), 54282-54299. doi:10.1039/C4RA10651B.
c) Denmark, S. E., & Fan, Y. (2005). Catalytic, Enantioselective α-Additions of Isocyanides: Lewis Base Catalyzed Passerini-Type Reactions. The Journal of Organic Chemistry, 70(24), 9667-9676. doi:10.1021/jo050549m.

81. a) Pirrung, M. C., & Wang, J. (2009). Multicomponent Reactions of Cyclobutanones. The Journal of Organic Chemistry, 74(8), 2958-2963. doi:10.1021/jo802170k.
b) Maison, W., Schlemminger, I., Westerhoff, O., & Martens, J. (2000). Multicomponent synthesis of novel amino acid–nucleobase chimeras: a versatile approach to PNA-monomers. Bioorganic & Medicinal Chemistry, 8(6), 1343-1360. doi:http://dx.doi.org/10.1016/S0968-0896(00)00066-3
c) Keating, T. A., & Armstrong, R. W. (1995). Molecular Diversity via a Convertible Isocyanide in the Ugi Four-Component Condensation. Journal of the American Chemical Society, 117(29), 7842-7843. doi:10.1021/ja00134a044

82. Barton, D. H. R.; Blazejewski, J.-C.; Charpiot, B.; Finet, J.-P.; Motherwell, W. B.; Papoula, M. T. B.; Stanforth, S. P., Pentavalent organobismuth reagents. Part 3. Phenylation of enols and of enolate and other anions. Journal of the Chemical Society, Perkin Transactions 1 1985, 2667-2675. DOI: 10.1039/P19850002667

83. For the recent reviews see:
a) Monnier, F., & Taillefer, M. (2009). Catalytic C-C, C-N, and C-O Ullmann-Type Coupling Reactions. Angewandte Chemie International Edition, 48(38), 6954-6971. doi:10.1002/anie.200804497.
b) Evano, G., Blanchard, N., & Toumi, M. (2008). Copper-Mediated Coupling Reactions and Their Applications in Natural Products and Designed Biomolecules Synthesis. Chemical Reviews, 108(8), 3054-3131. doi:10.1021/cr8002505.

84. a) Beringer, F. M., Geering, E. J., Kuntz, I., & Mausner, M. (1956). Diaryliodonium Salts. IV. Ion Pairs and Copper Catalysis in the Reactions of Diphenyliodonium Ions with Halide Ions and Hydroxylic Solvents. The Journal of Physical Chemistry, 60(2), 141-150. doi:10.1021/j150536a002
b) Beringer, F. M., Daniel, W. J., Galton, S. A., & Rubin, G. (1966). Phenylation of Monoketones with Diphenyliodonium Chloride1. The Journal of Organic Chemistry, 31(12), 4315-4318. doi:10.1021/jo01350a551.

85. Tinnis, F., Stridfeldt, E., Lundberg, H., Adolfsson, H., & Olofsson, B. (2015). Metal-Free N-Arylation of Secondary Amides at Room Temperature. Organic Letters, 17(11), 2688-2691. doi:10.1021/acs.orglett.5b01079.

86. Helsley, G. C., Lunsford, C. D., Welstead, W. J., Boswell, R. F., Funderburk, W. H., & Johnson, D. N. (1969). Synthesis and analgetic activity of some 1-substituted 3-pyrrolidinylanilides and dihydrobenzoxazinones. Journal of Medicinal Chemistry, 12(4), 583-586. doi:10.1021/jm00304a005

87. Deruiter, J., Andurkar, S., Riley, T. N., Walters, D. E., & Noggle, F. T. (1992). Investigation of the synthesis and analgesic activity of 1-substituted 4-(propananilido)perhydroazepines. Journal of Heterocyclic Chemistry, 29(4), 779-786. doi:10.1002/jhet.5570290417

88. Lobbezoo, M. W., Soudijn, W., & Van Wijngaarden, I. (1981). Opiate receptor interaction of compounds derived from or structurally related to fentanyl. Journal of Medicinal Chemistry, 24(7), 777-782. doi:10.1021/jm00139a003

89. Cometta-Morini, C., Maguire, P. A., & Loew, G. H. (1992). Molecular determinants of mu receptor recognition for the fentanyl class of compounds. Molecular Pharmacology, 41(1), 185. ISSN:0026-895X

90. a) Bagley, J. R., & Riley, T. N. (1977). Synthesis and conformational analysis of isomeric 3-propananilidotropanes. Journal of Heterocyclic Chemistry, 14(4), 599-602. doi:10.1002/jhet.5570140412
b) Riley, T. N., & Bagley, J. R. (1979). 4-Anilidopiperidine analgesics. 2. A study of the conformational aspects of the analgesic activity of the 4-anilidopiperidines utilizing isomeric N-substituted 3-(propananilido)nortropane analogs. Journal of Medicinal Chemistry, 22(10), 1167-1171. doi:10.1021/jm00196a004

91. Fernandez, M. J.; Huertas, R. M.; Galvez, E.; Orjales, A.; Berisa, A.; Labeaga, L.; Gago, F.; Fonseca, I.; Sanz-Aparicio, J.; Cano, F. H.; Albert, A.; Fayos, J., Synthesis, and structural, conformational and pharmacological studies of new fentanyl derivatives of the norgranatane system. Journal of the Chemical Society, Perkin Transactions 2 1992, 687-695. DOI: 10.1039/P29920000687

92. a) Law, S.-J.; Lewis, D. H.; Borne, R. F., Synthesis and stereochemical analysis of isomeric N-substituted 5- and 6-propanilido-2-azabicyclo[2.2.2]octanes. Journal of Heterocyclic Chemistry 1978, 15, 273-280. doi:10.1002/jhet.5570150218.
b) Borne, R. F., Law, S.-J., Kapeghian, J. C., & Masten, L. W. (1980). Evaluation of 2-Azabicyclo[2.2.2]loctane Analogs of 4-Anilidopiperidine Analgesics. Journal of Pharmaceutical Sciences, 69(9), 1104-1106. doi:http://dx.doi.org/10.1002/jps.2600690934

93. Jagerovic, N.; Cano, C.; Elguero, J.; Goya, P.; Callado, L. F.; Javier Meana, J.; Girón, R. o.; Abalo, R.; Ruiz, D.; Goicoechea, C.; Isabel Martín, M., Long-Acting Fentanyl Analogues: Synthesis and Pharmacology of N-(1-Phenylpyrazolyl)-N-(1-phenylalkyl-4-piperidyl)propanamides. Bioorganic & Medicinal Chemistry 2002, 10, 817-827. DOI: 10.1016/S0968-0896(01)00345-5

94. Petrov, R. R.; Vardanyan, R. S.; Lee, Y. S.; Ma, S.-W.; Davis, P.; Begay, L. J.; Lai, J. Y.; Porreca, F.; Hruby, V. J., Synthesis and evaluation of 3-aminopropionyl substituted fentanyl analogues for opioid activity. Bioorganic & Medicinal Chemistry Letters 2006, 16, 4946-4950. DOI: 10.1016/j.bmcl.2006.06.040

95. Lee, Y. S.; Petrov, R.; Park, C. K.; Ma, S.-w.; Davis, P.; Lai, J.; Porreca, F.; Vardanyan, R.; Hruby, V. J., Development of Novel Enkephalin Analogues that Have Enhanced Opioid Activities at Both μ and δ Opioid Receptors. Journal of Medicinal Chemistry 2007, 50, 5528-5532. 10.1021/jm061465o.

96. Lee, Y. S.; Kulkarani, V.; Cowell, S. M.; Ma, S.-w.; Davis, P.; Hanlon, K. E.; Vanderah, T. W.; Lai, J.; Porreca, F.; Vardanyan, R.; Hruby, V. J., Development of Potent μ and δ Opioid Agonists with High Lipophilicity. Journal of Medicinal Chemistry 2011, 54, 382-386. DOI: 10.1021/jm100982d.

97. Vardanyan, R.; Vijay, G.; Nichol, G. S.; Liu, L.; Kumarasinghe, I.; Davis, P.; Vanderah, T.; Porreca, F.; Lai, J.; Hruby, V. J., Synthesis and investigations of double-pharmacophore ligands for treatment of chronic and neuropathic pain. Bioorganic & Medicinal Chemistry 2009, 17, 5044-5053. 10.1016/j.bmc.2009.05.065

98. Dardonville, C.; Jagerovic, N.; Callado, L. F.; Meana, J. J., Fentanyl derivatives bearing aliphatic alkaneguanidinium moieties: a new series of hybrid molecules with significant binding affinity for μ-opioid receptors and I2-imidazoline binding sites. Bioorganic & Medicinal Chemistry Letters 2004, 14, 491-493. DOI: 10.1016/j.bmcl.2003.10.048

99. Wright, W. B.; Brabander, H. J.; Hardy, R. A., N-(tert-Aminoalkyl)-Propionanilides: A New Series Of Potent Analgesics. Journal of the American Chemical Society 1959, 81, 1518-1519. DOI: 10.1021/ja01515a067.

100. Casy, A. F., Hassan, M. M. A., Simmonds, A. B., & Staniforth, D. (1969). Structure-activity relations in analgesics based on 4-anilinopiperidine. Journal of Pharmacy and Pharmacology, 21(7), 434-440. doi:10.1111/j.2042-7158.1969.tb08284.x

101. Ivanović Milovan D., Mićović I.V., Vučković Sonja M., Prostran Milica Š., Todorović Zoran M., Ivanović Evica R., Kiricojević Vesna D., Đorđević J.B., Došen-Mićović Ljiljana I. The synthesis and pharmacological evaluation of (±)-2, 3- seco-fentanyl analogues. Journal of the Serbian Chemical Society 2004, 69, 11, 955-968. DOI: 10.2298/JSC0411955I.

102. For the early hystory of methadone ("amidon") see: Defalque, R. J., & Wright, A. J. (2007). The Early History of Methadone. Myths and Facts. Bulletin of Anesthesia History, 25(3), 13-16. doi:10.1016/S1522-8649(07)50035-1.

103. a) Easton, N. R., Gardner, J. H., & Stevens, J. R. (1947). A New Synthesis and Confirmation of the Structure of Amidone1. Journal of the American Chemical Society, 69(12), 2941-2942. doi:10.1021/ja01204a006
b) Howe, E. E., & Sletzinger, M. (1949). Resolution of dl-Methadone and dl-Isomethadone. Journal of the American Chemical Society, 71(8), 2935-2936. doi:10.1021/ja01176a514.
c) Larsen, A. A., Tullar, B. F., Elpern, B., & Buck, J. S. (1948). The Resolution of Methadone and Related Compounds. Journal of the American Chemical Society, 70(12), 4194-4197. doi:10.1021/ja01192a065.
d) Brode, W. R., & Hill, M. W. (1948). The Optical Resolution Of Amidone 1. The Journal of Organic Chemistry, 13(2), 191-193. doi:10.1021/jo01160a004.
e) Howe Eugene E; Max Tishler. Salts Of d-Amidone With An Optically Active Acid And Process For Resolving dl-Amidone. US Patent 2644010 (1953).
f) Zaugg Harold E. Resolution Of Dl-Methadone. US Patent 2,983,757 (1961).
g) Taylor John J. Process for the preparation of 2,2-diphenyl-4-(dimethylamino)-pentane nitrile. US Patent 4,242,274 (1980).
h) Ali Asaraf; Ismail Rusli; Tan Soo Choon. (R)-6-(Dimethylamino)-4,4-Diphenylheptan-3-One. WO 2013077720 A1 (2013).

104. Bishara, R. H. (1974). Methadone Hydrochloride. Analytical Profiles of Drug Substances, 3, 365-439. doi:http://dx.doi.org/10.1016/S0099-5428(08)60074-X

105. Mattick, RP; Breen, C; Kimber, J; Davoli, M; (2009) Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. Cochrane Database of Systematic Reviews (3). ISSN 1469-493X DOI: 10.1002/14651858.CD002209.pub2

106. Satzinger Gerhard. Substituted Cyclohexenes, Derivatives Thereof And Processes For Obtaining Same. US Patent US 3,557,127A (1971).

107. Falkenberg Wolfgang; Schneider Ulrich; Thyes Marco; Wenz Conny. Method for producing atropic acid ethyl ester. US Patent 6,509,493 (2003).

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