Review

Morphinan Alkaloids and Their Transformations: A Historical Perspective of a Century of Opioid Research in Hungary †

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Posted Date: 14 February 2025

doi: 10.20944/preprints202502.1085.v1

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Review

Morphinan Alkaloids and Their Transformations: A Historical Perspective of a Century of Opioid Research in Hungary †

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† Dedicated to the memory of Professor Leendert Maat (1933–2017), a highly esteemed and beloved mentor, collaborator, colleague and friend, and an inexhaustible source of knowledge about morphinans and other alkaloids.

Abstract: The word opium derives from ancient Greek word ὄπιον (ópion) for the juice of any plant, but today means the air-dried seed capsule latex of *Papaver somniferum*. Alkaloid chemistry began with the isolation of morphine from crude opium by Friedrich Wilhelm Adam Sertürner in 1804. More than a century later, the Hungarian pharmacist János Kabay opened new perspectives for the direct isolation of morphine from dry poppy heads and straw without the labor-intensive harvesting of opium. In 2015, Kabay's life and achievements obtained official recognition as constituting a «Hungarikum», thereby entering the national repository of matters of unique cultural value. To this day, the study of *Papaver* alkaloids is a focus of medicinal chemistry, which the (perhaps unstated) aspiration to obtain an opioid with lesser abuse potential and side effects, while retaining good analgesic properties. We begin this review with a brief account of opiate biosynthesis, followed by a detailed presentation of semisynthetic opioids, emphasizing efforts of the Alkaloida Chemical Company, founded in 1927 by János Kabay, and the morphine alkaloid group of the University of Debrecen.

Keywords: Alkaloida Chemical company; azidomorphine; biosynthesis; codeine isomers; desomorphine; epimerization; 6,14-ethenomorphinans; Mitsunobu-reaction; morphinan alkaloids; morphine; nomenclature; nucleophilic substitution; stereochemistry; University of Debrecen

Contents

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„Az ember ezt, ha egykor ellesi,
Vegykonyhájában szintén megteszi. –
Te nagy konyhádba helyzéd embered,
S elnézed néki, hogy kontárkodik,
Kotyvaszt, s magát Istennek képzeli.”

Madách Imre: Az ember tragédiája

“Man will certainly learn this by watching
And will simulate it in his kitchen. -
You put into your great kitchen your man
And of his bungling you take no notice,
He brews and fancies himself to be God.”

Imre Madách: Tragedy of the man (translation: Tomschey, O.)

1. Introduction

The word opium has its origin in the ancient Greek ὄπιον (ópion), which the referred to the juice of any plant, belying the profound importance of specifically the juice of *Papaver somniferum* in ancient and contemporary medicine. The German apothecary and pioneer of alkaloid chemistry Friedrich Wilhelm Adam Sertürner (1783–1841) began working on opium extraction in 1804, first describing a crude preparation that he designated *principium somniferum* and later morphium, after Morphius, the Greek god of dreams. His isolation of pure morphine (**1**, Figure 1.) from raw opium was the first of any alkaloid [1]. Throughout history, opium, morphine, and its semisynthetic derivatives have been a double-edged sword, being indispensable in medicine, while also bringing crises of dependency and overdose. The touting of oxycodone (14-hydroxydihydrocodeinone) as an analgesic with supposedly superior safety profile was surely a factor in the exacerbation of the opioid crisis in some countries [2], now made worse by the availability of synthetic compounds such of astonishing potency as fentanyl and the even stronger nitazines.

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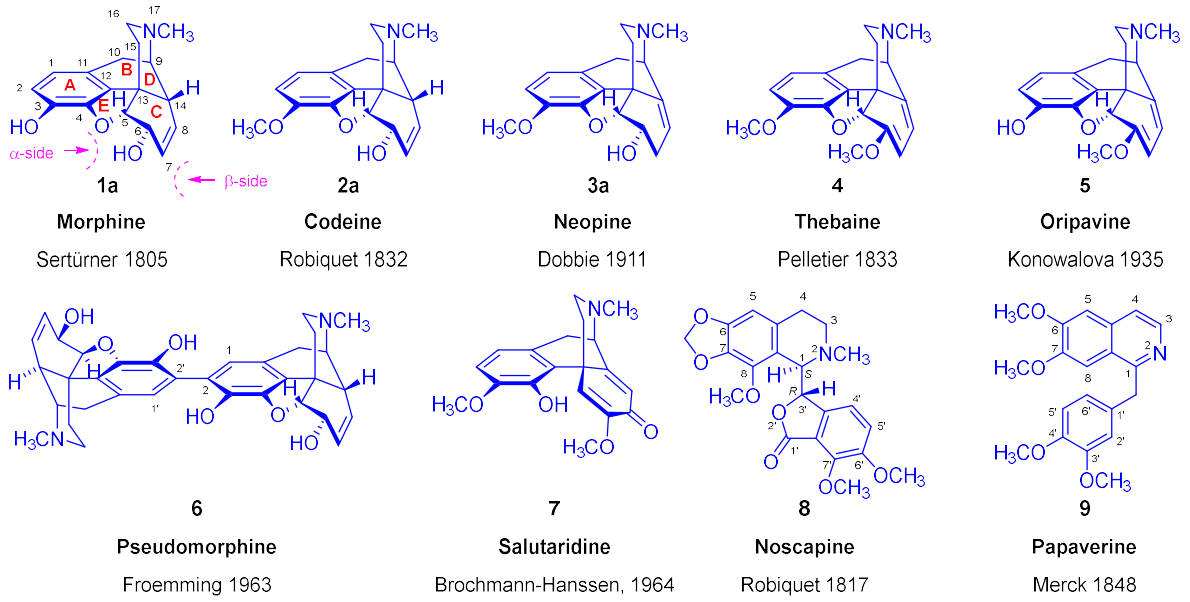

Figure 1. Chemical structures of selected poppy alkaloids.

Alkaloida Chemical Company (Alkaloida Vegyészeti Gyár) was founded by the Kabay brothers János, Péter and József in Bűdszentmihály (former Tiszabűd and Szentmihály; since 1952 Tiszavasvári) in Hungary [3,4], with signing of the foundation agreement on September 10, 1926 [5]. The principal founder, pharmacist János Kabay (1896-1936) is notable for his 1925 patent [6] on the innovative «green method» for extracting directly opiate alkaloids from parts of the poppy plant, thus circumventing the inefficient and labour-intensive process of opium harvesting by resin collection collection of the resin [6]. Further improvements in 1931 enabled the commercially viable extraction of the key alkaloids, morphine (**1a**) and an alkaloid mixture of mainly codeine (**2a**) and narcotine/noscapine (**8**) from the previously worthless straw and dried capsules of the poppy plant («dry method») [6]. The foundation of the Hungarian morphine alkaloid-industry, Kabay's process was adopted the world over [7,8].

Kossuth Lajos University (Kossuth Lajos Tudományegyetem, KLTE; today University of Debrecen, Hungary) established its Institute of Organic Chemistry in 1947. The early 1950s saw a strong initiative by Ministries of the Hungarian Heavy Industries and Education to form regionally important connections between new industrial centres and nearby universities. The long-standing collaboration between the Institute of Organic Chemistry of KLTE and Alkaloida arose as a direct result of these efforts. Rezső Bognár (1913-1990) [9], a former student of the Emil Fischer (1852–1919) associate Géza Zemplén (1883–1956), received in 1950 the appointment as head of the Institute of Organic Chemistry. Early in his tenure, Bognár placed special emphasis on joint efforts with Alkaloida specialists to optimize the Kabay-technology, aiming to obtain higher yields of the valuable opiate alkaloids codeine, thebaine, narceine, neopine, and narcotoline [10–14]. During 1979–1995, Sándor Makleit (1930–2012) became head of the Department of Organic Chemistry and its morphine alkaloid research group, in which capacity he coordinated interactions between KLTE and Alkaloida. Upon Makleit's retirement, Sándor Berényi (1947–2019) redirected research towards an emphasis on aporphine-chemistry *via* the rearrangement of morphinans. The contributions of László Szilágyi (NMR), Gyula Batta (NMR), and Zoltán Dinya (IR, MS) were essential in the field of structural analysis of the new synthetic morphinan derivatives. Sándor Hosztafi (1952–), formerly of the Alkaloida Chemical Company, has contributed enormously to the field of semi-synthetic morphinans, aporphine derivatives and other poppy alkaloids, and remains active at the Department of Pharmaceutical Chemistry of Semmelweis University, Budapest.

In this account, we cannot omit mentioning the long-standing cooperation between the Debrecen morphine alkaloid research group and Semmelweis University (Department of Pharmacology, Budapest) for the pharmacological analysis of newly synthesized opioid receptor (OR) ligands. These

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investigations were first directed by József Knoll (1925–2018) and Zsuzsanna Fürst (1939–). The biochemical characterization of new semi synthetic alkaloids was performed under guidance of Anna Borsodi, Sándor Benyhe and Géza Tóth at the Biological Research Center of the Hungarian Academy of Sciences (MTA Szegedi Biológiai Központ, Biokémiai Intézet, Szeged), and at Gedeon Richter Pharmaceuticals (Richter Gedeon Vegyészeti Gyár, Budapest).

Given this historical and personal background, we now present a comprehensive account of opiate alkaloid chemistry, placing our focus on the extensive contributions in recent decades of the Hungarian research group in morphine alkaloids in Debrecen and at the Alkaloida Chemical Company in the field of morphinan syntheses, as part of a concerted search for novel structures and synthetic approaches. We begin with a brief presentation of opiate nomenclature, stereochemistry, and the biosynthesis of morphinan alkaloids.

2. Chemistry

2.1. Poppy Alkaloids

The diverse alkaloids of *Papaver somniferum* are categorized based on their chemical structures [15–19]. The well-known of these are benzylisoquinoline- (I), morphinan- (II), aporphine- (III), benzo[c]phenantridine- (IV), papaverrubine- (V), narceine-typ- (VI), protoberberine- (VII), protopine- (VIII), phthalideisoquinoline (IX), with ground scaffolds presented in Figure 2.

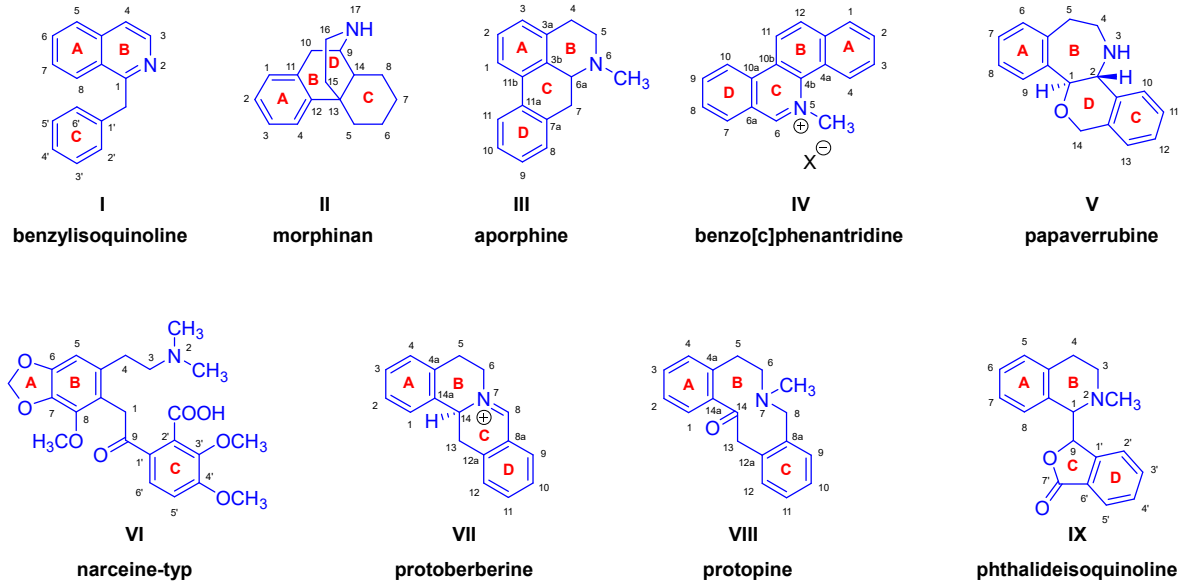

Figure 2. Ground scaffolds of poppy alkaloids.

2.2. The Stereochemistry of Morphinans

There are two theoretical sterical arrangements in the case of decalin and morphinans (Figure 3), depending on the ring-junction of the A/B-ring and B/C-ring, respectively [17]. For *cis*-decalins, the H-1 and H-6 hydrogens and for cis-morphinans, the H-14 and the C^{13} – C^{15} bond are on the same face. In *trans*-decalins the H-1 and H-6 hydrogens and in B/C-*trans*-morphinans, the H-14 and the C^{13}-C^{15} bond are on the opposite face. In naturally- occurring morphinan alkaloids, the junction of the B- and C-rings is a B/C-*cis* fusion analogous to *cis*-decalin as shown in structure **IIa** of Figure 3, where **IIb** presents the structure of a B/C-*trans*-morphinan. It is not possible to convert a morphinan (B/C-*cis*-morphinan) into an isomorphinan (B/C-*trans*-morphinan) by rotation of molecular parts without breaking chemical bonds. The absolute configurations of the C-14 chiral carbon differ for the isomers: 14*R* (morphinan) and 14*S* (isomorphinan).

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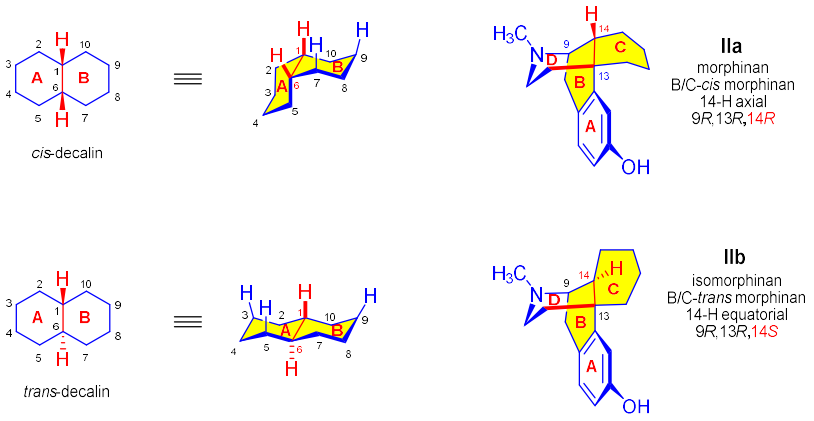

Figure 3. Structures of B/C-*cis* and B/C-*trans* morphinans.

Morphine (**1a**, Figure 4) and a significant number of its derivatives have a T-shaped three-dimensional molecular geometry. The isomers of morphine (**1a**, Figure 4, Table 1) and codeine (**2a**) have five chiral carbons: positions 5, 6, 9, 13, and 14. In **1a** and **2a**, the carbon-carbon double bond is situated in position C7-C8 ($\Delta^{7,8}$), the ring-C has a flattened boat conformation, and the allylic hydroxyl group in position C-6 is pseudo-equatorial. The C6 in **1a** and **2a** has absolute configuration *S*. In the C-6 epimer molecules isomorphine (**1b**, α-isomorphine, Figure 4) and isocodeine (**2b**), the 6-hydroxyl group is located above the plane of the ring-C in a pseudo-axial position. The C-6 in **1b** and **2b** has absolute configuration *R*.

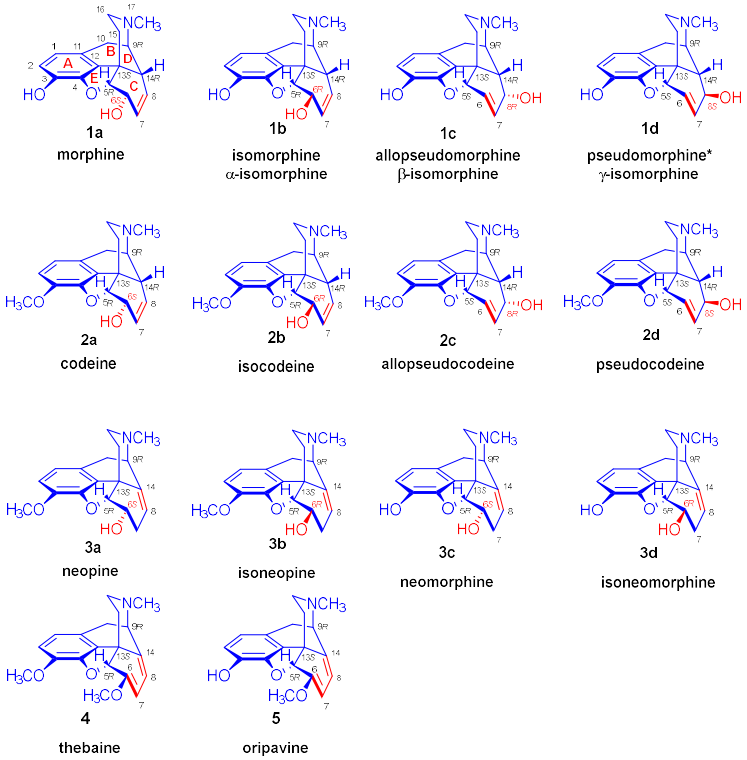

Figure 4. Chemical structures of selected morphinan alkaloids and their synthetic derivatives. * Makleit-Bognár nomenclature.

Further $\Delta^{6,7}$ isomers for morphine (**1a**) and codeine (**2a**) are known as allopseudomorphine (**1c**, also known as β-isomorphine), γ-isomorphine (**1d**), allopseudocodeine (**2c**) and pseudocodeine (**2d**). In these compounds, the alcoholic hydroxyl group connects to the position-8 of the ring-C. Of the ring-C carbons, C-5, C-6, C-7, C-8 and C-13 are in the same plane, while C-14 is located above them.

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The ring-C of the compounds has an envelope conformation. In allopseudomorphine (**1c**) and allopseudocodeine (**2c**) the 8-OH is pseudo-axial and the configuration of C-8 is *R*. The two isomers with $\Delta^{6,7}$ double bond and pseudo-equatorial 8-hydroxyl group, γ-isomorphine (**1d**) and pseudocodeine (**2d**), have 8*S* absolute configuration. Figure 4 and Table 1 provide an overview of the structure and the absolute configuration of the parent compounds.

The neopine (**3a**), isoneopine (**3b**), neomorphine (**3c**) and neoisomorphine (**3d**) derivatives also have a $\Delta^{8,14}$ unsaturated bond in ring-C. These compounds have only four asymmetric carbon atoms (5, 6, 9 and 13), since the $\Delta^{8,14}$ double bond C-14 is no longer asymmetric. The C-ring is rigid and of half chair conformation. In the cases of neopine (**3a**) and neomorphine (**3c**), the 6-hydroxy group is in pseudo-axial position and the carbon-6 has absolute configuration *S*. In compounds of the 6-beta series, like isoneopine (**3b**) and isoneomorphine (**3d**), the 6-OH is pseudo-equatorial and the carbon-6 has configuration *R*. The poppy alkaloids with a conjugated 6,8-dien system in ring-C: thebaine (**4**) and oripavine (**5**), have only three asymmetric carbons, with the absolute configurations 5*R*, 9*R*, and 13*S*.

Table 1. Absolute configuration of the selected morphinan alkaloids and their semisynthetic derivatives depicted in Figure 4.

Comp.	Name	Position of the C=C double bond	Position					
			5	6	8	9	13	14
1a	morphine	$\Delta^{7,8}$	5*R*	6*S*	-	9*R*	13*S*	14*R*
1b	isomorphine*	$\Delta^{7,8}$	5*R*	6*R*	-	9*R*	13*S*	14*R*
1c	allopseudomorphine**	$\Delta^{6,7}$	5*S*	-	8*R*	9*R*	13*S*	14*R*
1d	γ-isomorphine	$\Delta^{6,7}$	5*S*	-	8*S*	9*R*	13*S*	14*R*
2a	codeine	$\Delta^{7,8}$	5*R*	6*S*	-	9*R*	13*S*	14*R*
2b	isocodeine	$\Delta^{7,8}$	5*R*	6*R*	-	9*R*	13*S*	14*R*
2c	allopseudocodeine	$\Delta^{6,7}$	5*S*	-	8*R*	9*R*	13*S*	14*R*
2d	pseudocodeine	$\Delta^{6,7}$	5*S*	-	8*S*	9*R*	13*S*	14*R*
3a	neopine	$\Delta^{8,14}$	5*R*	6*S*	-	9*R*	13*S*	-
3b	isoneopine	$\Delta^{8,14}$	5*R*	6*R*	-	9*R*	13*S*	-
3c	neomorphine	$\Delta^{8,14}$	5*R*	6*S*	-	9*R*	13*S*	-
3d	isoneomorphine	$\Delta^{8,14}$	5*R*	6*R*	-	9*R*	13*S*	-
4	thebaine	$\Delta^{6,7}$ and $\Delta^{8,14}$	5*R*	-	-	9*R*	13*S*	-
5	oripavine	$\Delta^{6,7}$ and $\Delta^{8,14}$	5*R*	-	-	9*R*	13*S*	-

* isomorphine: known also as α-isomorphine; ** allopseudomorphine: known also as β-isomorphine.

2.3. Biosynthesis of Morphinan Alkaloids

A suite of five *O*-methyltransferases and two *N*-methyltransferase enzymes contribute to benzyisoquioline alkaloid (BIA) biosynthesis [20] in five genera of flowering plants, including *Papaveraceae* (poppy), and *Ranunculaceae* (buttercup). The phytochemical synthesis of morphine alkaloids begins with *L*-tyrosine (**10**) *via* a branching pathway that yields on one side tyramine (**11**) through the action of *L*-tyrosine decarboxylase, which is a dimeric pyridoxal-phosphate dependent enzyme [21]. A phenolase enzyme then transforms the tyramine product (**11**) to dopamine (**13**). In the right-hand branch, *L*-tyrosine (**10**) gives rise to the keto acid 4-hydroxyphenylpyruvate (**12**) *via* *L*-tyrosine deaminase [22], and then the corresponding acetaldehyde (**14**) *via* a specific decarboxylase. Condensation of the two products (dopamine (**13**) and 4-hydroxyphenylacetaldehyde (**14**)) to form (*S*)-norclaurine (**15**) proceeds *via* an asymmetric Pictet–Spengler condensation, which is catalysed by the enzyme norclaurine synthase [23]. Mechanistic studies of the norcoclaurine synthase enzyme

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derived from *Thalictum flavium* (yellow meadow-rue) indicated a two-step cyclization of the putative iminium ion intermediate, which constitutes the first committed step in the formation of poppy BIAs.

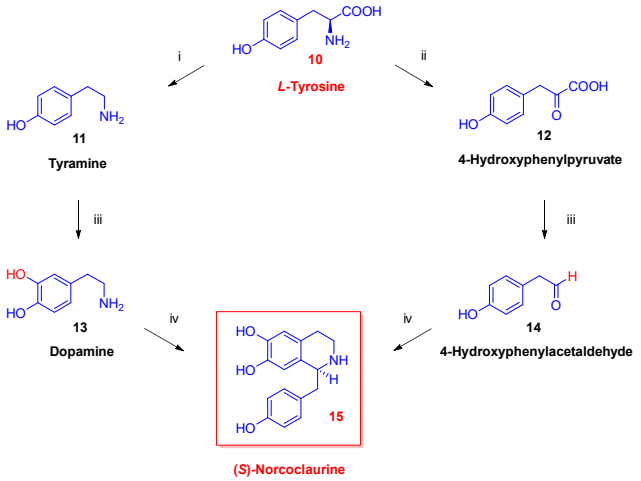

Figure 5. Biosynthesis of (*S*)-norcoclaurine. *Reactions catalysed by enzymes*: (i): *L*-tyrosine decarboxylase (TyrDC); (ii): *L*-tyrosine transaminase (TyrAT); (iii): phenolase; (iv): 4-hydroxy-phenylpyruvate decarboxylase (4HPPDC).

Once formed, (*S*)-norclaurine (**15**, Figure 5.) undergoes a series of enzymatic methylations, first by norcoclaurin-6-*O*-methyltransferase in the presence of the co-substrate *S*-adenosylmethionine (SAM), which represents a key rate-limiting step in benzyisoquioline synthesis [24], followed by tetrahydrobenzylizochinoline-*N*-methyltransferase. The product (*S*)-*N*-methyl-coclaurine (**17**) undergoes ring-hydroxylation by a phenolase enzyme or a higher affinity P450-dependent monooxygenase (CYP80B1) in poppy [25], and then a further SAM-dependent *O*-methyltransferase reaction to give (*S*)-reticulin ((*S*)-**19**). Interestingly, reticulin in the traditional food *Annona muricata* (soursop) may be responsible for dopamine neuron degeneration resulting in a form of parkinsonism that is endemic in the island of Guadeloupe [26].

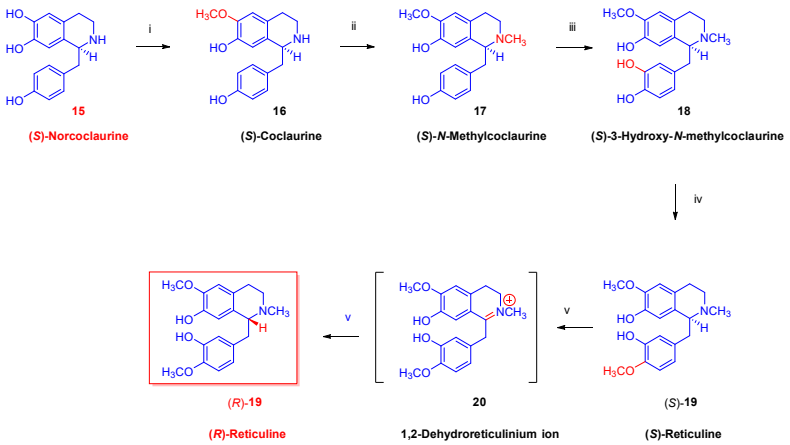

Figure 6. Biosynthesis of (*R*)-reticuline. *Reagents and conditions*: (i): norcoclaurine-6-*O*-methyltransferase; (ii): tetrahydrobenzylisoquinoline-*N*-methyltransferase; (iii): phenolase; (iv): (*S*)-3'-hydroxy-*N*-methylcoclaurine-4'-*O*-methyltransferase; (v): 1,2-dehydroreticuline synthase, NADPH-dependent reductase.

A specific NADPH-dependent reductase isomerizes (*S*)-reticuline ((*S*)-**19**) to (*R*)-reticuline ((*R*)-**19**). After ring closure of (*R*)-reticuline ((*R*)-**19**, Figure 6.) *via* an NADPH/O_2-dependent enzyme yielding salutidarine (**7**), an NADPH/$NADP^{\oplus}$-dependent oxidoreductase yields (7*S*)-salutaridinol (**21**), which is then ring-acetylated by an acetyl coenzyme A-dependent enzyme; spontaneous de-acetylation gives thebaine (**4**, paramorphine), which gains its common name from the anciet Greco-

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Egyptian city of Thebes. In rat brain preparations, thebaine (**4**) has only weak binding affinity for ORs [27], and unlike the synthetic enantiomer (+)-thebaine [28], has little analgesic potency. Having been long-regarded as a useless side-product of poppy-extraction, thebaine (**4**) now has an annual global market value of USD 1 billion, serving as starting material in the industrial production of opiate agonists (e.g., oxycodone, oxymorphone), antagonists (Nal-compounds: naloxone, naltrexone, nalbuphine), and Diels-Alder type Bentley-compounds (buprenorphine, etorphine, diprenorphine). The ORs in brain present important targets for molecular imaging by positron emission tomography (PET), as presented in an extensive review [29]. In particular, thebaine (**4**) is a precursor for the radiosynthesis of various PET tracers, for OR imaging (see section 2.12.). It has been known since the 1970s that thebaine (**4**) predominates in *Papaver bracteatum* (the Armenian poppy), which contains only a small amount of other alkaloids [30,31]. Alternately, Zenk and researchers at Tasmanian Alkaloids obtained the morphine (**1a**) free *Papaver somniferum* plant designated as top1 (top: **t**hebaine - **o**ripavine – **p**oppy) through genetic modification [32]. The genetic cultivar contains predominantly thebaine (**4**, 1.65 %) and oripavine (**5**, 0.43 %) but no morphine (**1a**, 0 %) or codeine (**2a**, 0 %).

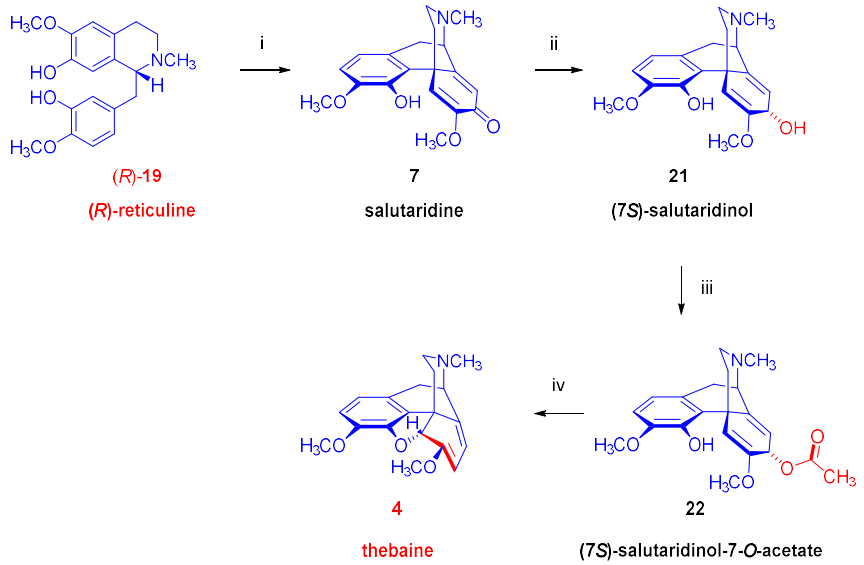

Figure 7. Biosynthesis of thebaine from (*R*)-reticuline. *Reagents and conditions*: (i): salutaridine-synthase, (NADPH, O_2); (ii): NADPH-dependent salutaridine-oxydoreductase, (NADPH, $NADP^{\oplus}$); (iii): salutaridinol-7-*O*-acetyltransferase (AcCoA, CoA); (iv): spontaneous (pH 8–9, - AcOH).

Thebaine (**4**, Figure 7) yields morphine (**1a**) by two parallel pathways in the opium poppy. In one pathway, an enol ether hydrolase enzyme forms neopinone (**23**), which equilibrates to codeinone (**24**), an alkaloid with about one-third the analgesic potency of codeine (**2a**). An NADPH-dependent reductase converts codeinone (**24**) to codeine (**2a**), which is demethylated to yield the still more potently analgesic morphine (**1a**). In the other pathway, 3-*O*-demethylation of thebaine (**4**) yields oripavine (**5**), which is also a potent analgesic, albeit with high toxicity. Oripavine (**5**) is important industrially as the precursor for synthetic opiates (i.e., etorphine and buprenorphine); in the poppy plant, oripavine (**5**) undergoes enolether hydrolysis to yield morphinone (**25**), which has similar analgesic potency to that of codeine (**2a**). Conversion of morphinone (**25**) to morphine (**1a**) entails an NADPH-dependent codeinone reductase, various isoforms of which also catalyze the reduction of certain other intermediates of morphine (**1a**) biosynthesis [33]. Interestingly, morphine biosynthesis in the poppy plant entails compartmentation in several cell types [34,35]; the initial steps occur in sieve elements of the phloem, whereas the conversion of salutaridine (**7**) to thebaine (**4**) predominantly takes place in adjacent laticifers, where the main morphine accumulation occurs.

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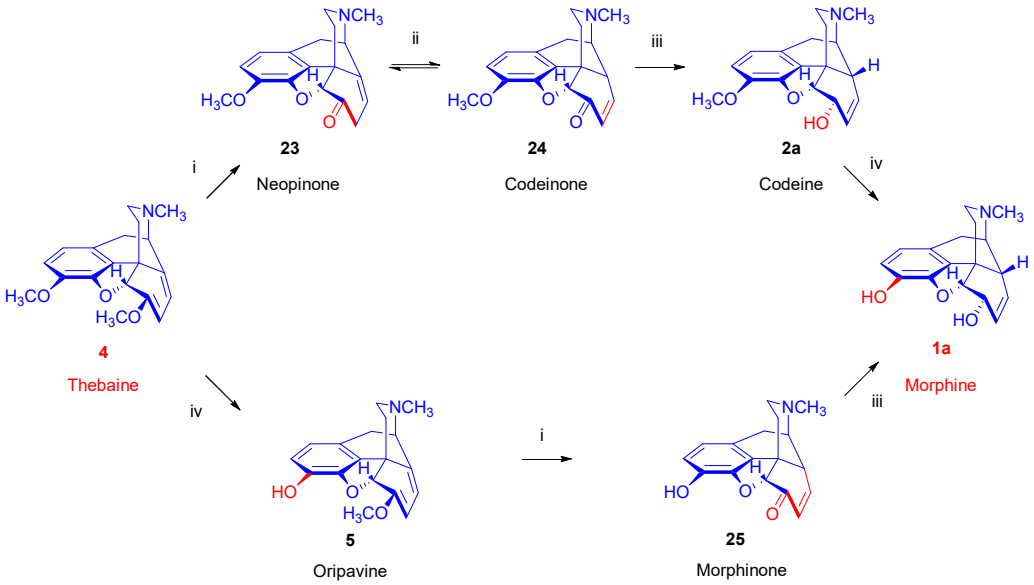

Figure 8. Biosynthesis of morphine from thebaine. *Reagents and conditions*: (i): enolether hydrolysis; (ii): chemical equilibrium; (iii): codeinone reductase; (iv): 3-*O*-demethylation.

Raw opium is the dried latex from seedpods of the opium poppy, which naturally contains a mixture of thebaine alkaloids and intermediates, the composite of which contribute to its somnorific/analgesic effects and toxicity. The principle alkaloid in opium samples from south East Asia was morphine (11-23%), with lesser amounts of codeine (2-4%) and thebaine (1-3%) [36]. Poppy straw from various *Papaver somniferum* cultivars used in oil seed production in the Czech Republic had relatively invariant alkaloid concentrations across three consecutive harvests [37]. Cluster analysis distinguished cultivars with high morphine concentration (1.6%) and relatively low levels of other alkaloids, versus cultivars with the oppositive relationships. Comestible poppy seeds also contain various alkaloids, extending over a >100-fold concentration range, depending on the source [38]. Baking substantially reduces the alkaloid content of poppy seeds, such that it would be practically impossible to obtain intoxication from Bejgli, a traditional Hungarian Christmas cake, although there are case reports of opioid-dependent individuals consuming poppy seeds by the kilogram [39]. On the other hand, there are reports of lethal codeine (**2a**) /morphine (**1a**) overdose among poppy seed tea drinkers [40], and in drinkers of tea made with «home grown» dried seed pods [41]. Thebaine (**4**) is a pro-convulsant at high doses and poppy seeds with a particularly high content of thebaine (**4**, Figure 8.) caused serious neuromuscular toxicity poisoning in tea drinkers in Australia [42]. Thus, the toxicity of poppy products depends upon factors such as the particular cultivar, growing conditions, and mode of preparation.

The opioid receptors (ORs) [43] regulate numerous (patho)physiological processes being involved in pain modulation, euphoria, reward behaviours, and substance abuse, with involvement in the pathophysiology of various psychiatric disorders, epilepsy, and neurodegenerative conditions such Alzheimer's disease (AD) [44]. Endogenous opioid peptide ligands and exogenous opioids activate several types of G-protein coupled (GPCR) receptors (μ-OR, δ-OR κ-OR, NOP). The concept of «biased agonism» underlies the search for OR ligands elicting therapeutic effects, but with lesser risk of toxicity and dependence [45,46]. In general OR agonists inhibit the enzyme adenyl cyclase (AC), thus decreasing the intracellular cAMP level, and thereby inhibiting the voltage-gated $Ca^{2\oplus}$ ion channels while activating $K^{\oplus}$ efflux. The result hyperpolarisation inhibits the presynaptic release of neurotransmitters (e.g., dopamine (DA), norepinephrine (NE), acetylcholine (ACh), γ-aminobutyric acid (GABA)), which produce a variety of effects including sedation, central analgesia, and euphoria.

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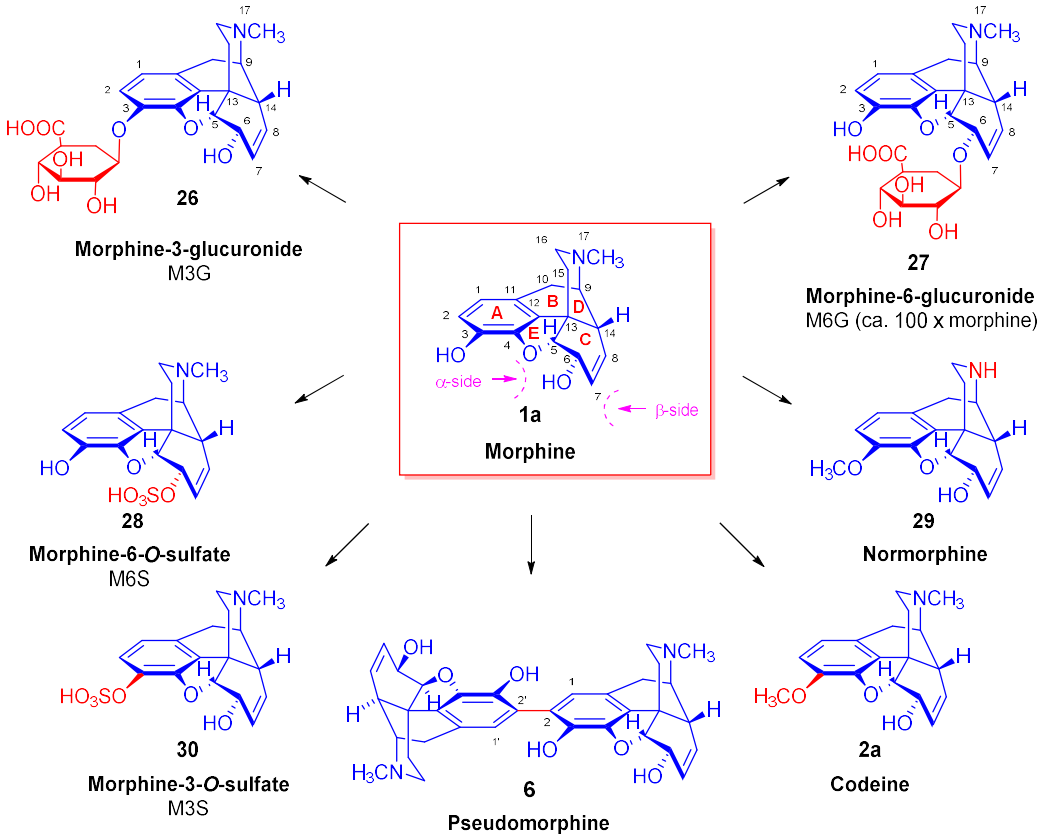

Figure 9. Structures of selected morphine metabolites.

Morphine (**1a**) yields a number of metabolites in humans by various metabolic pathways [47]. The most important morphine metabolites are M3G (**26**, Figure 9), and M6G (**27**), which form by glucuronidation catalysed by hepatic uridine 5′-diphosphoglucuronyltransferase (UGT). The sulfation of **1a** by hepatic sulfotransferase (SULT1A3) results in morphine-3-sulfate (**30**, M3S), and morphine-6-sulfate (**28**, M6S). The N^{17}-demethylation of **1a** by cytochrome P450 (CYP450) gives normorphine (**29**), and the oxidative dimerization lead to pseudomorphine (**6**, 2,2′-bimorphine). The SAM-dependent 3-*O*-methylation of morphine (**1a**) to codeine (**2a**) can occur in liver, lung or kidney.

The chemical structures of some phase I and phase II metabolites of morphine are depicted in Figure 9.

2.4. The Makleit-Bognár Nomenclature

In 1968, Makleit and Bodnár [48] proposed the introduction of a new nomenclature for morphine derivatives. According to this nomenclature, naming of all ring-C substituted semisynthetic compounds derives from the isomers of codeine (**2a-d**, Figure 4, Figure 10). The Makleit-Bognár nomenclature requires only prior knowledge of names and stereochemistry of the basic four codeine isomers: codeine (**2a**), isocodeine (**2b**), allopseudocodeine (**2c**) and pseudocodeine (**2d**).

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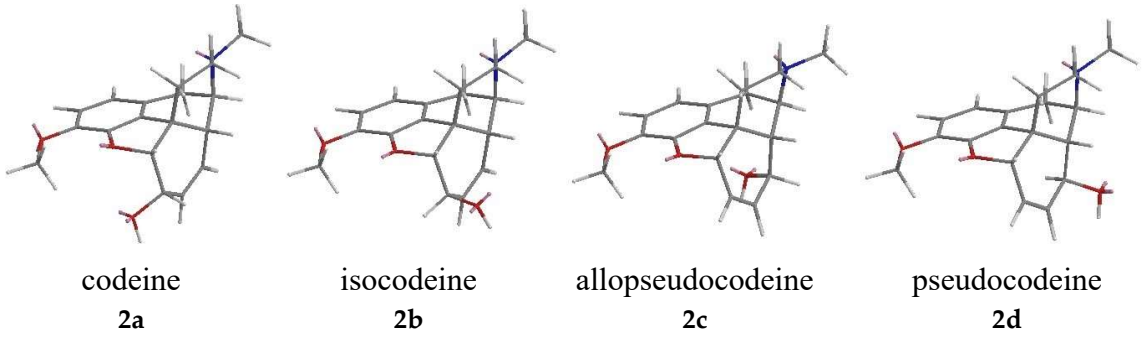

Figure 10. 3D structures of codeine isomers.

Makleit and Bognár suggested abandoning the previously used names for morphine isomers, α- (**1b**), β- (**1c**) and γ-isomorphine (**1d**), in favour of isomorphine (**1b**), allopseudomorphine (**1c**), and pseudomorphine (**1d**), all in analogy to the codeine isomer nomenclature. They also proposed adoption of the rational name "2,2'-bimorphine" to replace the old name of the poppy alkaloid bis-derivative pseudomorphine (**6**, Figure 1). This simplified nomenclature is generalizable for all in ring-C substituted derivatives, and faithfully reflects their structure and stereochemistry. Ergo, chemists can ascertain quickly and precisely the name and exact structure of any new derivatives, knowing the names and structures of the four codeine isomers (**2a**-**d**, Figure 4, Figure 10). We note that the position of a substituent below and above the plane ring-C differs for C-6 and C-8; if a C-6 substituent is pseudo-axial, it lies above of the plane of the ring-C, while a C-8 a pseudo-axial substituent is below the ring-C.

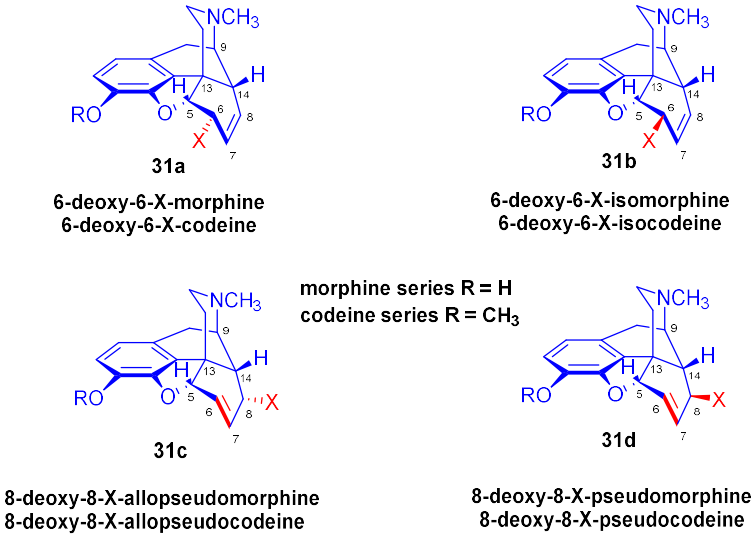

Figure 11. Examples for the application of the Makleit-Bognár nomenclature.

The term "deoxy-X" is a proposed term for all in ring-C modified derivatives, rendering redundant the descriptions (6α, 6β, 8α, 8β), as the name already specifies the exact structure of the compound. For interpretation of this nomenclature, we present numerous examples in Figure 11. Like the Maat-nomenclature system [49] in the field of the Diels-Alder adducts of morphinan-6,8 dienes [50], chemists have not universally adopted the rational Makleit-Bognár nomenclature [48], despite its considerable advantages.

2.5. Early Syntheses of Morphine Derivatives with Pharmaceutical Importance

Opiates are plant products formed by a series of enzymatic reactions as outlined above, whereas chemistry has built upon the rather sparse selection of poppy alkaloid scaffolds to generate countless

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derivatives. After elaborating the Kabay-Bognár technology for the isolation of morphine (**1a**) and its accompanying alkaloids from dry poppy straw and heads [10], the transformation of morphine (**1a**) to other active pharmaceutical ingredients came into focus at Alkaloida and the University of Debrecen.

Morphine (**1a**) was converted to codeine (**2a**) by methylation of the phenolic 3-hydroxyl group by aryl trimethylammonium hydroxides (Rodionov's method [51,52]). Methods were elaborated for the synthesis of benzylmorphine (**32**, 7,8-didehydro-4,5α-epoxy-6α-hydroxy-17-methyl-3-phenylmethoxy-morphinan), ethylmorphine (**33**, 7,8-didehydro-4,5α-epoxy-6α-hydroxy-17-methyl-3-ethoxy-morphinan) and pholcodine (**34**, 7,8-didehydro-4,5-epoxy-6α-hydroxy-17-methyl-3-(2-(4-morpholinyl)ethoxy)-morphinan) [53] on an industrial scale starting from morphine (**1a**, Figure 12). The latter compound (**34**) became clinically significant because of its lesser toxicity and proclivity to induce respiratory depression in comparison to morphine (**1a**), and due to its more favourable sedative effect as compared to codeine (**2a**) or other morphine derivatives. Application of pholcodine (**34**) as an antitussive agent in the treatment of dry non-productive cough for young patients and adults has been widespread, and **34** was for a long time the second-most important active pharmaceutical ingredient (API) manufactured from morphine (**1a**) [8]. Neuromuscular blocking agents (NMBAs) are among the leading causes life-threatening drug-induced perioperative anaphylaxis. Novel studies performed by Mertes *et al.* [54] confirmed a remarkable relationship between application of pholcodine (**34**) and other quaternary ammonium derivatives and the risk for NMBA-related perioperative anaphylaxis mediated by immunoglobulin E (IgE). This association lead to the withdrawal of pholcodine-containing antitussive-syrups and cold medicines from the EU and UK markets [55].

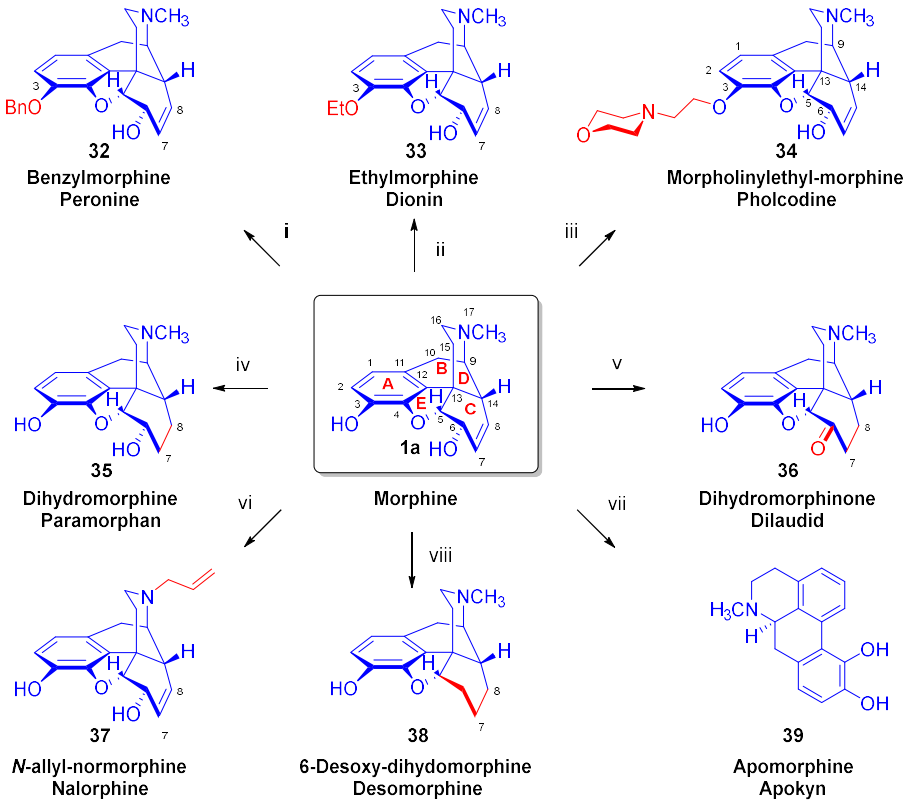

Figure 12. Industrial scale syntheses of some morphine derivatives. *Reagents and conditions*: (i): benzyl bromide, NaOEt, EtOH, heating; (ii): ethyl bromide, NaOEt, EtOH, 100 °C, 2 h; (iii): morpholinylethylchloride hydrochloride, NaOEt, ethanol, reflux, 1 h, 72 %; (iv): H_2, Pd-C, 1 N HCl or diluted AcOH; (v): catalytic rearrangement; (vi): (1) BrCN, $CHCl_3$, reflux; (2) A: KOH, H_2O, EtOH, 50 °C, B: diluted HCl, heating; (3) allyl bromide, $NaHCO_3$, EtOH, reflux, 10 h; (vii): cc. HCl, sealed tube; (viii) see details in section 2.6.

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Dihydromorphine (**35**, paramorphan) was synthesized by heterogeneous catalytic hydrogenation of the $\Delta^{7,8}$ double bond of morphine (**1a**) in dilute acetic acid. Dihydromorphinone (**36**, dilaudid) was prepared either by catalytic rearrangement of **1** or by Oppenauer oxidation of dihydromorphine (**35**). Szabó and Bognár from the KLTE developed a procedure for the preparation and purification [56] of the OR antagonist N^{17}-allyl-normorphine (**37**, nalorphine). The synthesis starts from morphine (**1a**, route [57]: **1** → diacetylmorphine → diacetyl-N^{17}-cyano-normorphine → normorphine → **37**) using (among other approaches) the von Braun method [58] for the *N*-demethylation step. Apomorphine (**39**), a dopamine receptor agonist that, can relieve motor symptoms of Parkinson's disease, was synthesized from morphine (**1a**) with concentrated hydrochloric acid. Berényi *et al.* [59,60] later investigated in detail the mechanism of the morphine (**1a**) → apomorphine (**39**) rearrangement. For details of the desomorphine (**38**) synthesis [61], see section 2.7 and Figure 16.

2.6. Reduction of Thebaine

Thebaine (**4**) comprises a 6,8-diene and an enol ether function in ring-C, which together correspond to a 1-methoxy-1,3-cyclohexadiene sub-structural unit [16,17]. The B and C-rings together form a *trans*-3,4,8,9-tetraline system, while the C and D-rings constitute a *trans*-1,2,3,4,5,10-hexahydro-isoquinoline subunit. An easily attacked part of the molecule is the C^5-O bond of the dihydrofuran-ring-E, which is a part of the C^4-O-C^5-C^6=C^7 allylether system. The characteristics of these sub-structures enable a large variety of reactions for thebaine (**4**) in manner sensitive to reaction conditions. This is particularly apparent its reduction with various reagents or during catalytic hydrogenation under different reaction conditions, which results in a diverse array of products (Figure 13).

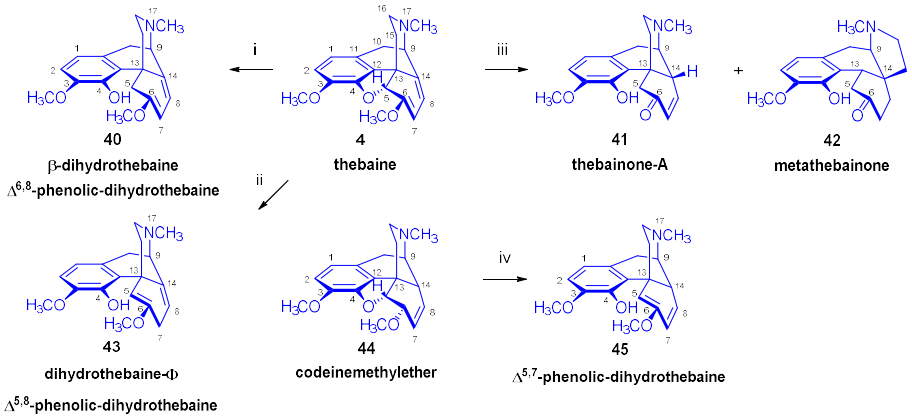

Figure 13. Reduction of thebaine with chemical reducing agents. *Reagents and conditions*: (i): $LiAlH_4$, benzene, diethyl ether or THF, reflux, 8 h, 22-27 %; (ii): Na, NH_3 (liq.), 90 %; (iii): 5 equiv. $SnCl_2$, cc HCl, sealed tube, 100 °C, 20 min, 53 % (**42**); (iv): NaOEt, EtOH.

Indeed, the targeted reduction of thebaine is a very challenging process [62,63]. Neither application of chemical reducing agents nor the heterogeneous catalytic hydrogenation result in a sole product. In the first case, reduction in basic- or acidic- media, yields products containing a phenolic hydroxyl group due to the opening of the E-ring. Treatment of thebaine (**4**) with sodium in hot ethanol results in dihydrothebaine-Φ (**43**, $\Delta^{5,8}$-phenolic dihydrothebaine) as main product [64]. Bentley *et al.* [65,66] found that the application of sodium – liquid ammonia gave dihydrothebaine-Φ (**43**) in 90 % yield and a small amount of β-dihydrothebaine [67], along with approximately 10 % $\Delta^{6,8}$-phenolic-dihydrothebaine (**40**). Razdan *et al.* [67] reported that treatment of thebaine (**4**) with an excess of potassium in liquid ammonia gave a 1:1 mixture of **40** and **43** in 95 % yield, from which **40** could be isolated in 34 % overall crystalline yield. Treatment of **43** with K/liquid ammonia in the presence of $Fe(NO_3)_3$ produced a 1:1 mixture of **40** and **43** in 79 % yield. When performing the

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reduction with $LiAlH_4$, in benzene – diethyl ether (or THF) [68,69], β-dihydrothebanie (**40**) was obtained in low (22–27 %) yield. The third isomer $\Delta^{5,7}$-phenolic dihydrothebaine (**45**) can be prepared from codeinemethylether (**44**) by treatment with sodium ethylate [62]. Reduction of thebaine (**4**) with stannous chloride ($SnCl_2$) gave thebainone-A (**41**), or metathebainone (**42**) *via* rearrangement of the carbon scaffold. The yield of the reduction of thebaine (**4**) to **40** with the intact conjugated 6,8-diene system was greatly improved by the finding of Linders *et al.* [70], whereby reduction with zinc under alkaline conditions resulted in almost quantitative conversion to dihydrothebaine (**40**).

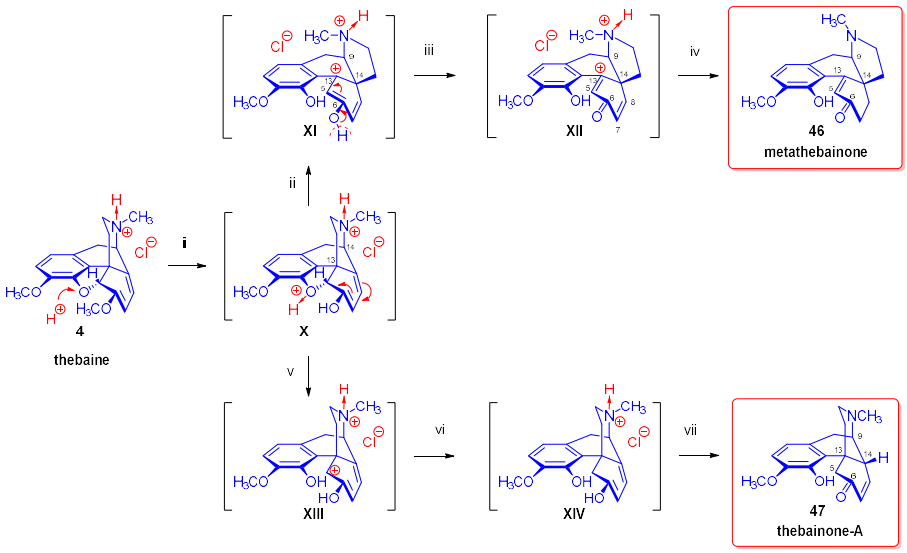

Figure 14. Mechanism of the formation of metathebainone and thebainone-A. *Reagent and elementary step of the reaction*: (i): **A**: + HOH, **B**: - CH_3OH, **C**: + $H^{\oplus}$; (ii): rearrangement; (iii): -$H^{\oplus}$; (iv): H_2/catalyst; (v): heterolysis of the C^5-O bond; (vi): + $2e^{\ominus}$, + $H^{\oplus}$; (vii): ketonisation with 1,4-mechanism.

For the formation of metathebainone (**46**) and thebainone-A (**47**), Robinson [71] suggested the following reaction mechanism (Figure 14): (i) the enolether group of the hydrochloric salt of thebaine undergoes hydrolysis and an unstable addition product (**X**) is formed *via* proton attack on the oxygen of the E-ring; (ii) rearrangement: heterolysis of the C^5-O bond, electron system shift, anionotrop rearrangement of the ethanamine side-chain from C^{13} to C^{14} (**XI**); (iii) intermediate (**XI**) stabilizes *via* proton losing/transmission to (**XII**); (iv) formation of metathebainone (**46**) *via* saturation of the easily accessible $\Delta^{7,8}$-double bond. Experimental conditions leading to the formation of thebainone-A (**47**) were: (v) the unstable intermediate (**X**) transforms to (**XIII**) *via* heterolysis of the C^5-O bond; (vi) formation of (**XIV**) through uptake of $H^{\oplus}$ and $2e^{\ominus}$; (vii) ketonizaion of (**XIV**) through a 1,4-mechanism to thebainone-A (**47**).

As noted above, thebaine (**4**) is a non-analgesic neuromuscular toxin, long regarded as a nuisance side-product of poppy extraction. However, its conversion to pharmacologically useful semisynthetic opiates has since become the objective of concerted efforts. Catalytic hydrogenation of thebaine (**4**) results in a complex mixture of products depending on the reaction conditions (e.g., pH of the solution, type of catalyst) [72]. The main driving force of these investigations in mid-20th century Hungary was to study the possibilities for transformation of thebaine (**4**) *via* dihydrothebaine (**48**) to dihydrocodeinone (**49**, hydrocodone), an API (active pharmaceutical ingredient) used for the treatment of moderate to serve pain and as a cough suppressant. Szabó and Bognár [73,74] performed detailed research into the catalytic reduction of thebaine (**4**) as a function of reaction conditions (e.g., type of catalyst, pressure, concentration, temperature, pH, rate of hydrogen uptake). They isolated from the product mixtures a large number of morphinan derivatives e.g., dihydrothebaine (**48**), dihydrocodeinone (**49**), dihydrothebainone (**52**), β-dihydrothebainone, etc., (see also Figure 15) [73,74]. For characterization of the obtained products, Szabó and Bognár undertook a careful analysis of their infrared spectra and photometry combined with paper chromatography. This enabled them

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to detect more than twenty morphinans in the product mixture. They also performed their syntheses through independent reaction routes, and reported in detail the mechanisms of product formation [73,74].

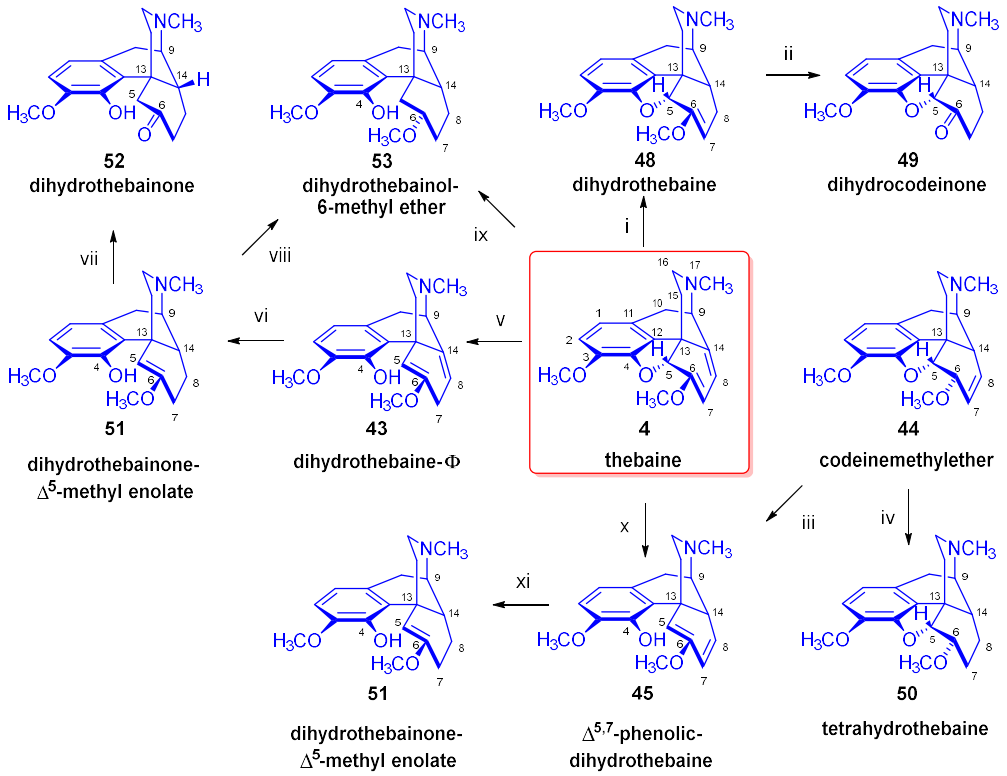

Figure 15. Products of the reduction of thebaine [73,74]. *Reagents and conditions*: (i): from **4** hydrochloride salt, H_2, atmospheric pressure, 0.08 M hydrochloric acid (2.8 fold), 10 % Pd-C (0.1 fold), 62 %; (ii): 5 equiv. 5 M hydrochloric acid, RT, 24 h, quant.; (iii): NaOEt, EtOH; (iv): H_2, 10 % Pd-C (4 m/m %), 1 M hydrochloric acid, quant.; (v); Na, NH_3 (liq.), 90 % [64,70,71]; (vi): H_2, PtO_2, $NaHCO_3$, EtOH, 45 % or H_2, Pd-$SrCO_3$, EtOH, 50 %; (vii): **A**: AcOH, or 1M HCl, RT **B**: H_2, 10 % Pd-C; (viii): 10 % Pd-C, EtOH, or directly from **4** base by catalytic reduction in neutral solution (5 % Pd-$BaSO_4$, EtOH), alternatively by catalytic reduction (H_2, PtO_2) of β-dihydrothebaine (**40**) [69]; (ix): H_2, 5 % Pd-$BaSO_4$, EtOH [60] or H_2, Pt black, $NaHCO_3$, EtOH; (x): H_2, 1,6-hydrogen addition [C^5-O; C^{14}] on the allylether group combined with the 6,8-diene system [75]; alternatively from codeine (**2a**), codeine → codeine-*N*-oxide → codeine-*N*-oxide-6-*O*-methylether → codeine-6-methylether → phenolic $\Delta^{5,7}$-dihydrothebaine (**45**) [64,74]; (xi): H_2, 10 % Pd-C, $NaHCO_3$, EtOH, RT, 7 h [74]; by application of H_2, 10 % Pd-C, 1 M hydrochloric acid, thebainone-A and dihydrothebainone (**52**) formed [74].

The occurence of parallel and consecutive side-reactions during the heterogenous catalytic hydrogenation of thebaine (**4**) is explicable by the following processes (Figure 15):

(A) 1,2-Addition of hydrogen to the $\Delta^{7,8}$-bond bond of thebaine (**4**). This results in dihydrothebaine (**48**), which is transformable to dihydrocodeinone (**49**) through hydrolysis.

(B) 1,4-Addition of hydrogen to the conjugated system of thebaine (**4**) in ring-C leads to codeine methyl ether (**44**), which is reducible to tetrahydrothebaine (**50**).

(C) 1,4-Addition of hydrogen to the oxygen atom of the E-ring and to C-7. This constitutes a hydrogenolysis of the allyl ether group, which results in the opening of the ether bridge. In the first step $\Delta^{5,8}$-phenolic-dihydrothebaine (**43**, dihydrothebaine-Φ) is formed, which can be transformed to dihydrothebainone-Δ^5-methylenolate (**51**). The enol ether hydrolysis of this compound results in dihydrothebainone (**52**). Subsequent hydrogenation leads to dihydrothebainol-6-methyl ether (**53**).

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(D) 1,6-Addition of hydrogen to the oxygen atom of the E-ring and to C-14. This process results in $\Delta^{5,7}$-phenolic-dihydrothebaine (**45**). Following/further hydrogenation of the latter compound forms dihydrothebainone-Δ^{5}-methyl enolate (**51**) and dihydrothebainol-6-methyl ether (**53**).

2.7. Synthesis of Desomorphine

Very recently, the chemistry, synthesis, and pharmacology of desomorphine (**38**) was reviewed in considerable detail [76–78]. One can deduce the structure of 6-desoxymorphine derivatives from C-6 hydroxy compounds by formal elimination of the hydroxy group or from 6-ketomorphinans by reduction. Due to their increased lipophilicity (and consequently greater brain penetration), these derivatives have higher analgesic potency compared to OR ligands with hydroxy and keto groups in position-6. This suggests that a substitution in position-6 is not essential for a high OR affinity. Indeed, Rapoport and Bonner reported in 1951 [79] that Δ^{7}-desoxymorphine (**57**, 6-desoxymorphine, desomorphine-E, for binding affinity see [80]: K_i (μOR) = 2.9 nM, K_i (δOR) = 11.8 nM, K_i (κOR) = 44.5 nM, δ/μ = 4, κ/μ = 16), prepared from Δ^{7}-desoxycodeine (for binding affinity see [80]: K_i (μOR) = 305 nM, K_i (δOR) = 4520 nM, K_i (κOR) = 3090 nM, δ/μ = 15, κ/μ = 10) by 3-*O*-demethylation with pyridine hydrochloride at 220 °C (6 min, N_2 atmosphere), had ~ 8.5-fold higher analgesic potency than morphine (**1a**), consistent with the much higher μ-OR affinity. Comparing the analgesic properties of various morphine derivatives (mouse hot-plate test) Eddy *et al.* [81,82] found the following order of relative potencies (in brackets): desomorphine (11.7) > dihydromorphinone (7.0) > dihydromorphine (1.2) > morphine (1.0) > dihydrodesoxycodeine (0.72) > dihydrocodeinone (0.66) > dihydrocodeine (0.17).

6-Desoxydihydromorphine (**38**, 4,5α-epoxy-17-methylmorphinan-3-ol, also known as dihydrodesoxymorphine-D, and desomorphine) differs structurally from morphine (**1a**) with respect to the absence of the alcoholic hydroxyl group in position C-6α and the saturation of the $\Delta^{7,8}$-double bond in ring-C. Desomorphine (**38**) and morphine (**1a**) both have a T-shaped 3D structure, although in in **38** the ring-C has a chair conformation, while in **1a** has a boat conformation. Desomorphine (**38**) is about 8-10 times more potent than morphine (**1a**) in the mouse hot-plate test [83] (ED_{50} (**38**) = 0.14 μmol/kg, ED_{50} (**1a**) = 3.3 μmol/kg).

Furthermore, desomorphine (**38**) has a rapid onset and shorter duration of analgesic action, and is accompanied with higher toxicity (rat LD_{50} (**38**) = 27 mg/kg, LD_{50} (**1a**) = 226–318 mg/kg [84]). Desomorphine (**38**) is suggested to be a high affinity μ-OR agonist, as evident by its potent analgesic effects [85], but its subtype selectivity is unknown. The synthesis of **38** was already described in the 1930s by Small and colleagues in the course of their search for new analgesics with a lesser addictive pharmacological profile compared to morphine (**1a**) [86,87]. In the 1950s, desomorphine (**38**) served as an API under the trade names Desomorphine® and Permonid® (Hoffmann-La Roche) in the USA and in Switzerland. The early syntheses of **38** were performed from morphine (**1a**), codeine (**2a**), dihydromorphine (**35**), or desoxymorphine-C (a $\Delta^{6,7}$-didehydro compound: 17-methyl-4,5α-epoxy-3-hydroxy-6,7-didehydro-morphinan). The 6β-chloro derivatives α-chlorocodide (**59b**, Figure 16), α-chloromorphide, or α-chlorodihydromorphide were prepared with thionyl chloride ($SOCl_2$) from the corresponding starting morphinan (**1a**, **2a**, **35**) (note: α- and β- descripts are not sterical but positional: α: 6-substituted and β: 8-substituted). Thereafter the respective halogenocodides (e.g., α-chlorocodide (**59b**) or β-chlorocodide (**65a**), Figure 17) or halogenomorphides were subjected to catalytic hydrogenation [87] for reduction of the double bond in ring-C and dehalogenation. These reactions were performed in methanol or in diluted hydrochloric acid in the presence of $Pd/BaSO_4$. Depending upon the character of the substrate and the applied reaction and solvent conditions, these reactions gave desomorphine (**38**) in a yield of ~ 30-83 %.

In 1956, Bognár and Makleit [61] developed four-step procedures for the preparation of dihydro-6-desoxymorphine (**38**) from morphine (**1a**, Figure 16, route A: **1a** → **35** → **54** → **58** → **38**; route B: **1a** → **55** → **54** → **58** → **38**). They first synthesized 3-*O*-acetyl-dihydromorphine (**54**) from morphine (**1a**) *via* dihydromorphine (**35**) or *via* 3-*O*-acetylmorphine (**55**). They performed the partial acetylation by the method of Welsh [88] with acetic anhydride in the presence of aqueous $NaHCO_3$ solution. The

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$\Delta^{7,8}$-double bond of 3-*O*-acetylmorphine (**55**) was saturated (H_2, Pd-C) in aqueous acidic media (HCl, pH 6-6.5). 3-*O*-Acetyl-dihydromorphine (**54**) was converted with *p*-toluene-sulfonyl chloride in pyridine to 3-*O*-acetyl-dihydromorphine tosylate (**58**), which was then treated with $LiAlH_4$ according to the method of Schmid and Karrer [89] in THF. This hydrogenolysed (hydrogen substituted) the tosyloxy group in position-6, in concert with 3-*O*-deacetylation, giving the desired 6-desoxydihydromorphine (**38**) in an overall yield of 7.7%.

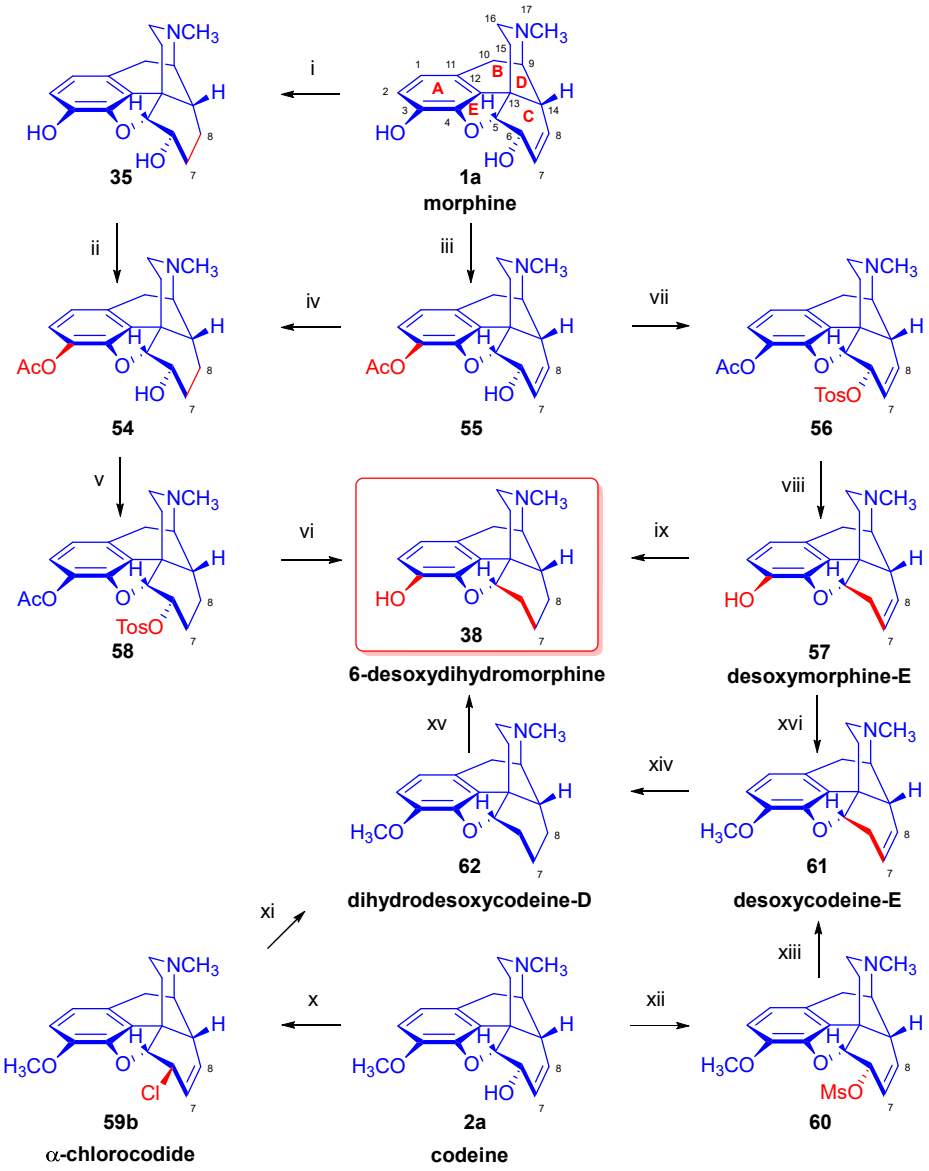

Figure 16. Synthesis of 6-desoxydihydromorphine. *Reagents and conditions*: (i): H_2, Pd-C, 1 N HCl or diluted AcOH; (ii): acetic anhydride, aqueous $NaHCO_3$ solution, 63%; (iii): H_2, 10% Pd-C, aqueous HCl (pH 6-6.5), 96%; (iv): acetic anhydride, aqueous $NaHCO_3$ solution, 92%; (v): TosCl, pyridine, **A**. 0 °C, 2 h, **B**. RT, 16 h, 51%; (vi): $LiAlH_4$, THF, **A**. reflux, 3 h, **B**. RT, 16 h, 25%; (vii): TosCl, pyridine, ; **A**: 0 °C, 2 h, **B**: RT, overnight; (viii): $LiAlH_4$, THF, reflux, 3 h, nitrogen stream; (ix): H_2, PtO_2, MeOH, 1 h; (x): $SOCl_2$;, reflux, 1.5 h; (xi): H_2, Pd-$BaSO_4$, MeOH or 1 N HCl, 30–80 %; (xii): MsCl, Et_3N, CH_2Cl_2, 0 °C, 1 h; (xiii); $LiAlH_4$, THF, RT, 1 h; (xiv): H_2, PtO_2, MeOH, 4 Bar, 1 h; (xv): BBr_3, CH_2Cl_2, RT, 30 min; (xvi): CH_2N_2, Et_2O, 48 h, 0–4 °C.

In 1975, Makleit *et al.* [90] published a novel route for the preparation of desomorphine (**38**) starting from morphine (route: **1a** → 3-*O*-acetylmorphine (**55**) → 3-*O*-acetylmorphine tosylate (**56**) → desoxymorphine-E (**57**) → **38**). The authors concluded that with lithium aluminium hydride reduction of 3-*O*-acetylmorphine tosylate (**56**), the presence of the allylic system in ring-C facilitates the elimination reaction [90], thus giving higher yield compared to the analogous reaction of 3-*O*-

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acetyldihydromorphine tosylate (**58**) [61]. Desoxymorphine-E (**57**, $\Delta^{7,8}$-didehydro) was converted with diazomethane to desoxycodeine-E (**61**, $\Delta^{7,8}$-didehydro) or by catalytic reduction (H_2, PtO_2, MeOH, 1 h) quantitatively to desoxydihydromorphine-D (**38**).

In 2012, the research group of Chen [91] described a novel protocol for the synthesis of desomorphine (**38**) from codeine (**2a**, route: **2a** → **60** → **61** → **62** → **38**). Codeine mesylate (**60**) was treated with 2 equiv. of $LiAlH_4$ in THF (0 °C, 30 min and RT for 1 h) to yield desoxycodeine-E (**61**) in 93 % yield. The latter compound (**61**) was hydrogenated (H_2, PtO_2, MeOH, 4 Bar, 1 h) to dihydodesoxycodeine-D (**62**) in quantitative yield. 3-*O*-Demethylation of **62** was achieved by application of boron tribromide in dichloromethane to yield **38** in 43 % yield. The overall yield of the synthesis of **38** was 38 % starting from codeine (**2a**). The authors also performed the synthesis of a deuterium labelled version of desomorphine staring from dihydrodesoxycodeine-D in a three-step procedure.

Tragically, desomorphine (**38**) is the main active component [92] of the illicit designer drug krokodil (street name, from Russian word for crocodile: крокодил, also known as Russian magic, krok/crok, flesh-eating heroin, poor man's heroin), which has spread as a cheap substitute of heroin in the former Soviet countries in the past two decades [84,91,93,94]. The illicit synthesis of desomorphine (**38**), utilizes codeine phosphate or codeine sulphate tablets sold at pharmacies as a cough suppressant. Operators reportedly use gasoline/petrol to extract the free base of **2a** liberated from the tablets by addition a strong alkali (KOH, NaOH). According to one street method (route: codeine (**2a**) → iodocodide (**59c**) → dihydrodesoxycodeine-D (**62**) → **38**), the extracted codeine (**2a**) is treated with iodine (iodine tincture), hydrochloric acid, and red phosphorus (from match heads) for dehalogenation. Heating of the mixture gives a very complex product mixture containing **38** as the main component, along with perhaps 50 different morphinan derivatives [95], with carryover of residual phosphorus, heavy metals, and highly toxic by-products. Naloxone serves as an antidote for acute krokodil toxicity, but is naturally ineffective against somatic injury arising from subcutaneous or intravenous injection of such a terrible concoction. Indeed, the street name krokodil refers to the necrotic skin changes associated with its use. Habitual krokodil users also suffer from horrendous wounds including deep tissue destruction, limb amputation auto-imputation of fingers, and osteonecrosis of facial bones and teeth.

2.8. Nucleophilic Substitution Reactions in the Morphine-Series

The nucleophilic substitution reaction of arylsulfonyl- or alkysulfonyl- esters (tosyl, mesyl, nosyl, brosyl, mesityl) leaving groups is a fundamental transformation [96,97] for the exchange of primary and secondary hydroxyl groups to other substituents in biology organic chemistry, and radiochemistry for the production of PET tracers [98]. In 1956, Stork and Clarke [99] studied the reactions of codeine tosylate (**63a**) with $Cl^{\ominus}$, $Br^{\ominus}$, $I^{\ominus}$, and piperidine nucleophiles. The reaction of **63a** with chloride anion (LiCl, acetone, reflux, 4 h) gave the kinetic product α-chlorocodide (**59b**, 6β-chloro-$\Delta^{7,8}$-deoxycodeine, 6-chloro-6-desoxyisocodeine) in quantitative yield according to S_N2 mechanism (substitution with inversion). α-Chlorocodide (**59b**) is unstable and isomerizes readily to its thermodynamic isomer β-chlorocodide (**65a**, 8β-chloro-$\Delta^{6,7}$-deoxycodeine, 8-chloro-8-desoxypseudocodeine, S_Ni'). Heating codeine tosylate (**63a**) in benzene for 36 h with piperidine 6-piperidocodide (**64**) was obtained in 87 % yield. In the reaction of codeine tosylate (**63a**) with bromide (LiBr, acetone, reflux, 2.5 h) or iodide (NaI, acetone, reflux, 2.5 h) anions, there was formation of the corresponding β-halocodide derivatives (pseudocodeine series, S_N2' ($S_N2 + S_Ni'$)) (**65b**, bromide, 98 % and **65c**, iodide, 43 %).

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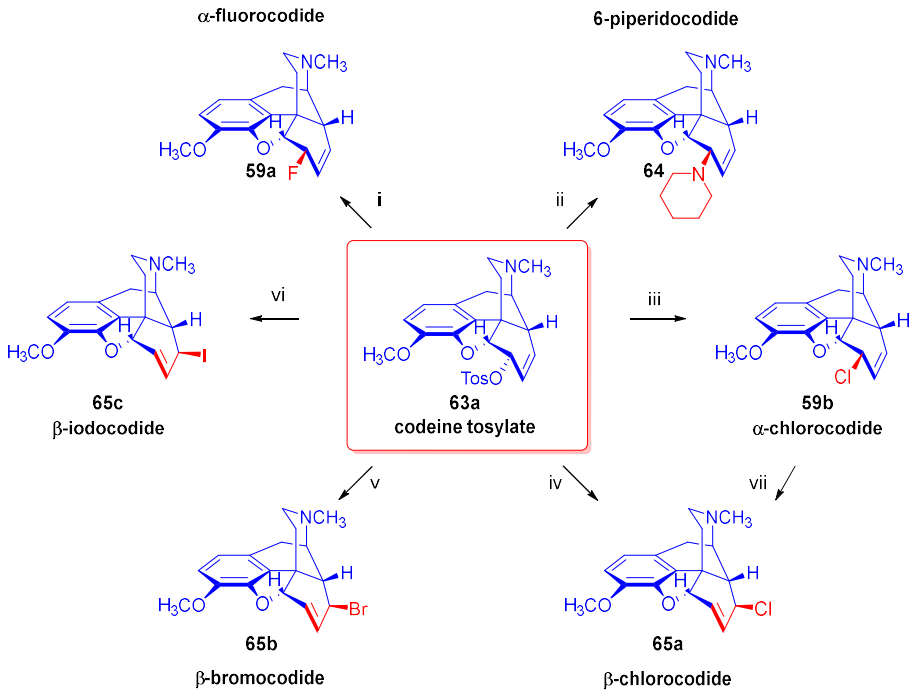

Figure 17. Reactions of codeine tosylate with nucleophiles. *Reagents and conditions*: (i): Bu_4NF, acetonitrile, reflux, 4 h, 48 %; (ii): piperidine, benzene, reflux, 36 h. 87 %; (iii): A. LiCl, acetone, reflux, 4 h, quant. or B. LiCl, DMF, 40 °C, 5 h, 76 %; (iv): LiCl, DMF, 120 °C, 5 h, 33 %; (v): LiBr, acetone, reflux, 2.5 h, 98 %; (vi): NaI, acetone, reflux, 2.5 h, 43 %; (vii): DMF, 120 °C, 10 h, 41 %.

Bognár *et al.* [100] synthesized 6-deoxy-6-fluoroisocodeine (**59a**) from codeine tosylate (**63a**) with tetrabutylammonium fluoride in acetonitrile in 48 % yield, and determined its configuration of the C-6 carbon by NMR spectroscopy. They found that the 6β-fluoro compound (**59a**) would not isomerize to the corresponding 8β-fluoro-derivative (β-fluorocodide, pseudocodeine series). In 1976, Makleit *et al.* [101] studied the substitution reaction of codeine tosylate (**63a**) with $Cl^{\ominus}$ nucleophile (LiCl) in *N*,*N*-dimethylformamide. They found that reaction temperature had a significant influence on the course of the reaction; at lower temperatures (40 °C, 5 h) there was formation of the kinetic product α-chlorocodide (**59b**, S_N2, 76 %) while at higher temperatures (e. g., 120 °C, 10 h) the thermodynamic isomer β-chlorocodide (**65a**, $S_N2 + S_Ni'$, 33 %) was the predominant product. They also detected high temperature conversion of the 6β-chloro (**59b**) to the 8β-chloro (**65a**) isomer (120 °C, 10 h, 41 %).

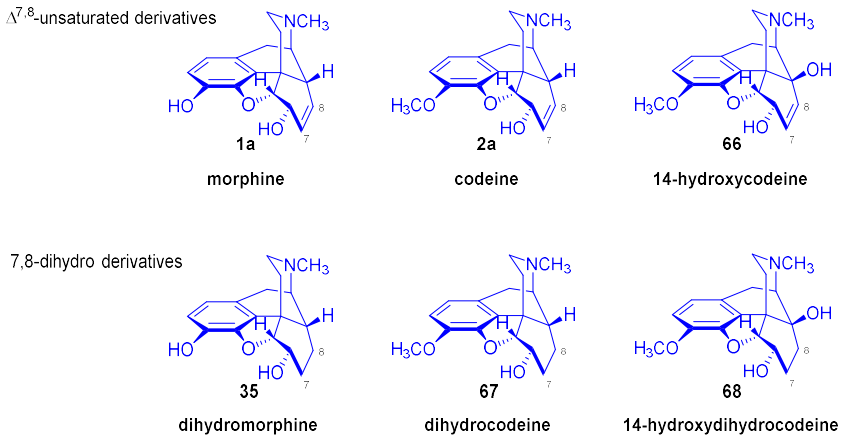

Figure 18. Structures of derivatives belonging to the "*morphine-series*" defined by Makleit and Bognár.

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Makleit [102,103] thoroughly investigated the synthesis of tosyl and mesyl derivatives in the so-called morphine series ($\Delta^{7,8}$-unsaturated derivatives: morphine (**1a**), codeine (**2a**), 14-hydroxycodeine (**66**) and their 7,8-dihydro derivatives: dihydromorphine (**35**), dihydrocodeine (**67**), 14-hydroxydihydrocodeine (**68**), Figure 18). His objective was to study their nucleophilic substitution reactions, and to clarify the reaction mechanism, through production of numerous semisynthetic morphinan derivatives [102,103]. The Makleit group further showed that the C-ring of the $\Delta^{7,8}$-unsaturated derivatives (**1a**, **2a**, **66**, Figure 18) has a flattened boat conformation with the C-6 hydroxyl group having an allylic alcohol character in a pseudo equatorial position. Conversely, the C-ring in the 7,8-dihydro series (**35**, **67**, **68**, Figure 18) has the chair conformation, with the C6-OH in an axial position. In both cases, the hydroxyl group connects to an asymmetric carbon in position-6. They prepared sulfonate esters of codeine (**2a**) and dihydrocodeine (**67**) by application of previously well-established methods resulting in codeine tosylate (**63a**, 58 %, Figure 19), codeine mesylate (**63b**, 16 %), dihydrocodeine tosylate (**71a**, 75 %), and dihydrocodeine mesylate (**71b**, 23 %) respectively [103,104].

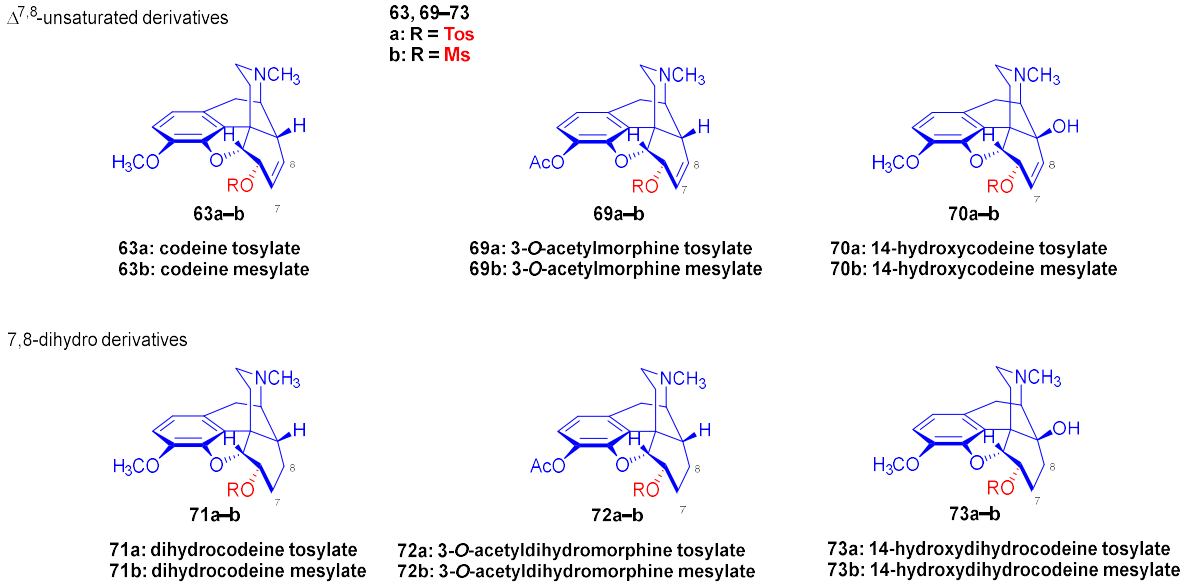

Figure 19. Sulfonate esters of selected morphine derivatives.

2.8.1. Reactions of 7,8-dihydro Compounds

The reactions of the 7,8-dihydro-6α-sulfonate esters (**71–73**) with the nucleophile anions $H^{\ominus}$, $N_3^{\ominus}$, $CH_3COS^{\ominus}$, and $CH_3COO^{\ominus}$ in polar aprotic solvents occur according to the S_N2 mechanism *via* Walden-inversion, yielding products of the *iso*-series. Dihydrocodeine tosylate (**71a**) reacted with $N_3^{\ominus}$ nucleophile resulted in 6-desoxy-6-azido-dihydroisocodeine (**74a**, Figure 20) [48,104,105], while 14-hydroxydihydrocodeine tosylate (**73a**) under identical conditions (10 equiv., NaN_3, DMF, 100 °C, 24 h) with the same reagent gave 6-desoxy-6-azido-14-hydroxydihydroisocodeine (**74b**, 31 %) [106]. Reduction of the 6-azido compounds (**74a–b**) with $LiAlH_4$ [104] or by catalytic hydrogenation [106] led to the corresponding 6-amino (6-beta-amino or 6-amino-dihydroisocodeine) derivatives (**75a–b**).

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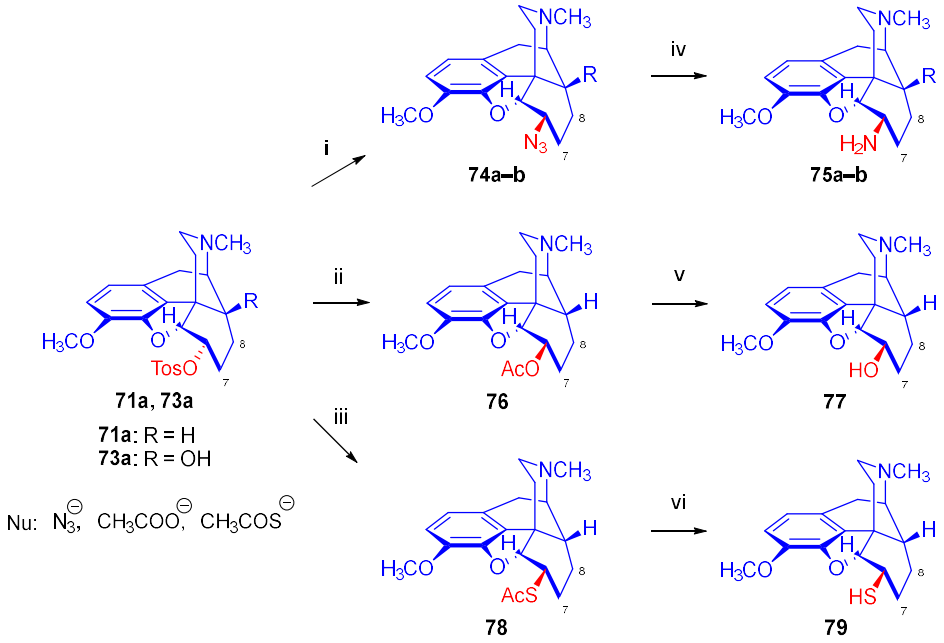

Figure 20. Reaction of the sulfonate esters of 7,8-dihydro derivatives with nucleophiles. *Reagents and conditions*: (i): NaN_3, DMF, H_2O, 100 °C, 24 h, R = H, 83 %, R = OH, 67 %; (ii): from **71b**, AcOH, Ac_2O, NaOAc, reflux, 31 h; (iii): $KSCOCH_3$, DMF, 100 °C, 24 h; under N_2 atmosphere; (iv): $LiAlH_4$, Et_2O, reflux, 3 h, 60 % or H_2, 10 % Pd-C, MeOH; (v): alkaline hydrolysis, (ii+iv) 21 %; (vi): NaOMe, MeOH, room temperature, 24 h, 91 %.

Makleit and Bognár [107] accomplished the epimerization of the C-6 chiral centres of codeine (**2a**) and dihydrocodeine (**67**). The acetolysis of codeine tosylate (**63a**) with 10 % acetic acid (reflux, 4 h) gave isocodeine (**2b**) in 16 % yield [107]. In the 1990s, the Makleit group developed protocols resulting in higher yields for the derivatives of the iso-series *via* application of the Mitsunobu reaction (see section 2.11.). 6-*O*-Acetyl-dihydroisocodeine (**76**) was prepared starting from dihydrocodeine mesylate (**71b**) with acetic acid, acetic anhydride, and sodium acetate (reflux, 31 h). Subsequently, 6-*O*-deacetylation of **76** was achieved by alkaline hydrolysis to yield dihydroisocodeine (**77**), with overall 21 % yield from dihydrocodeine mesylate (**71b**)). When dihydrocodeine tosylate (**71a**) was treated with $CH_3COS^{\ominus}$ nucleophile ($KSCOCH_3$, DMF) 6-acetylthio-dihydroisocodeine (**78**) was obtained [108,109]. This latter compound was deacetylated with sodium methylate to 6-desoxy-6-thiol-dihydroisocodeine (**79**). Upon reacting 3-*O*-acetyl-dihydromorphine tosylate (**72a**) with hydride anion ($LiAlH_4$), there was elimination of the tosyloxy group to yield 6-desoxydihydromorphine (**38**) [61].

2.8.2. Reactions of $\Delta^{7,8}$-Unsaturated Derivatives

Sulfonate esters (6α-*O*-tosyl and 6α-*O*-mesyl) of $\Delta^{7,8}$-unsaturated derivatives react with different nucleophiles either according to an S_N2 mechanism to give 6β-substituted derivatives, or *via* an S_N2 reaction accompanied by allylic rearrangement (an $S_N2 + S_Ni'$ mechanism) to result in 8-substituted-8-desoxypseudo compounds (supposed mechanism see later in section 2.9.1., Figure 39). Both the character of the nucleophile and the stereochemical properties of the substrates are of crucial importance in determining the reaction mechanism. For example, codeine tosylate (**63a**) with LiCl gave α-chlorocodide (**59b**) [99], whereas the reaction of isocodeine tosylate (**81**) under identical conditions with the same reagent resulted in β-chlorocodide (**65a**) [106].

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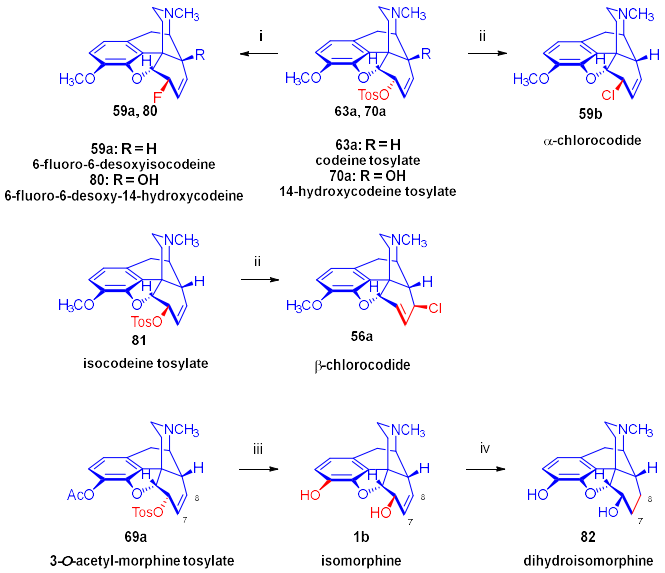

Figure 21. Reaction of selected 6-*O*-tosylates of $\Delta^{7,8}$-unsaturated morphinans. *Reagents and conditions*: (i): 1.6 equiv. Bu_4NF, CH_3CN, reflux, 4 h, 48 % [100]; (ii): LiCl, acetone, reflux, 4 h. (iii): 10 % AcOH (aq.), reflux, 4 h; (iv): H_2, $BaSO_4$/Pd-C, EtOH, 90 %).

Codeine tosylate (**63a**) with tetrabutylammonium fluoride in acetonitrile [100] led to the formation of 6-fluoro-6-desoxyisocodeine (**59a**, Figure 21). The isolated 6α-fluoro-type compound (**59a**, α-fluorocodide) cannot isomerize to the 8β-fluoro-type (β-fluorocodide) derivative. Compound **59a** was also prepared from pseudocodeine tosylate (see structure **97** later in section 2.8.3., Figure 25) with tetrabutylammonium fluoride (5.4 equiv., CH_3CN, reflux, reflux, 29 h) in poor yield (10 %) [110]. 6-Fluoro-6-desoxy-14-hydroxyisocodeine (**80**) was prepared from 14-hydroxycodeine tosylate (**70a**) under identical conditions [106]. When codeine tosylate (**63a**) was treated with 10 % acetic acid (reflux, 4 h), the main direction of the reaction was towards formation of isocodeine (**2b**, 16 % isolated yield) [107] without allylic rearrangement. This method was also applicable for the synthesis of isomorphine (**1b**, 16 %) from 3-*O*-acetylmorphine tosylate (**69a**) with subsequent preparation of. dihydroisomorphine (**82**) through catalytic reduction of isomorphine (**1b**) [111].

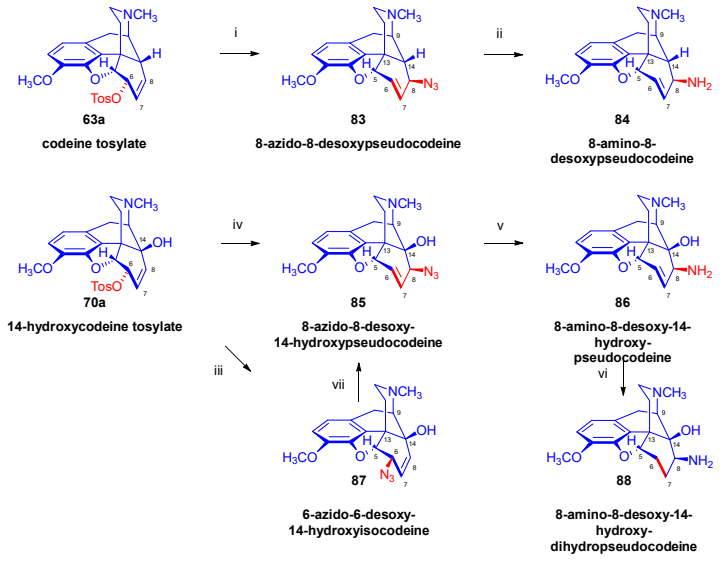

Figure 22. Synthesis of 8-substituted-8-desoxypseudocodeine derivatives. *Reagents and conditions*: (i): 10 equiv. NaN_3, DMF, H_2O, 100 °C, 4 h, 65 %; (ii): $LiAlH_4$, Et_2O, reflux, 3 h, 46 %; (iii): 1.25 equiv. NaN_3, DMF, H_2O, 100

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°C, 4 h, 38 %; (iv): 1.25 equiv. NaN_3, DMF, H_2O, 100 °C, 8 h, 46 %; (v): $LiAlH_4$, Et_2O, reflux, 3 h, 25 %; (vi): H_2, Pd-C, MeOH, 75 %; (vii): DMF, 100 °C, 6 h, 83 %.

Codeine tosylate (**63a**) with azide anion (NaN_3) in *N*,*N*-dimethylformamide gave 8-azido-8-desoxypseudocodeine (**83**, 8-azidocodide, Figure 22), which was converted to 8-amino-8-desoxypseudocodeine (**84**, 8-aminocodide) with lithium aluminum hydride [48,104]. Azidolysis of 14-hydroxycodeine tosylate (**70a**) with 1.25 equiv. of sodium azide gave 6-azido-6-desoxy-14-hydroxyisocodeine (**87**, 38 %) when the reaction mixture was heated at 100 °C for 4 h [106]. While the application of the same 0.25 % NaN_3 excess and longer reaction time (100 °C, 8h) led to 8-azido-8-desoxy-14-hydoxypseudocodeine (**85**, 46 %). 6-Azido-6-desoxy-14-hydoxyisocodeine (**87**) was isomerized by heating in DMF (100 °C, 6 h) 83 %) to **85** in 83 % yield [106]. The reduction of 8-azido-8-desoxy-14-hydoxypseudocodeine (**85**) with $LiAlH_4$ gave 8-amino-8-desoxy-14-hydoxypseudocodeine (**86**), although the catalytic hydrogenation led to 8-amino-8-desoxy-14-hydoxydihydropseudocodeine (**88**) [106].

The treatment of codeine tosylate (**63a**) with $CH_3COS^{\ominus}$ nucleophile ($KSCOCH_3$, DMF) [109] led to 8-acetylthio-8-desoxypseudocodeine (**89**, Figure 23), which was deacetylated with sodium methylate to give 8-thiol-8-desoxypseudocodeine (**90**). Oxidation of the latter compound gave an 8,8′-didesoxy-8,8′-pseudocodeinyl disulphide type compound. Surprisingly, the reaction of codeine tosylate (**63a**) with thiocyanate anion ($^{\ominus}S{=}C{=}N$, KSCN, in acetone) gave (in a kinetically second order reaction) the product 8-isothiocyanato-8-desoxypseudocodeine (**92**, -NCS) instead of the expected 8-thiocyanato-8-desoxyspeudocodeine (**91**, -SCN) [109].

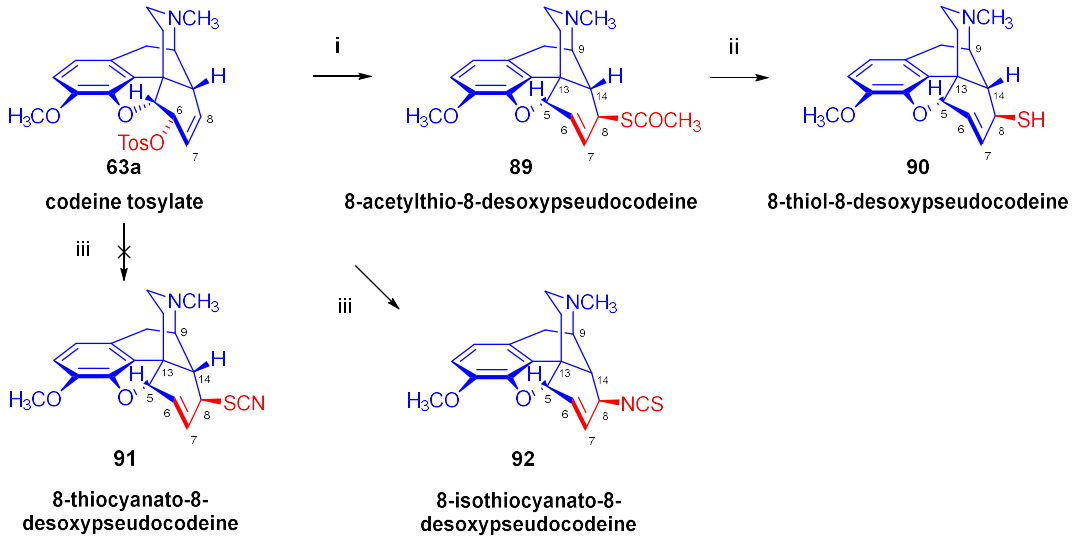

Figure 23. Reaction of codeine tosylate (**63a**) with $CH_3COS^{\ominus}$ and $^{\ominus}SCN$ nucleophiles. *Reagents and conditions*: (i): 2 equiv. $KSCOCH_3$, DMF, 100 °C, 5 h, N_2 atmosphere, 57 %; (ii): NaOMe, MeOH, room temperature, N_2 atmosphere, dark, 24 h, 38 %; (iii): 2 equiv. KSCN, acetone, reflux, 2.5 h, 48 %.

Analogous reaction of 3-*O*-acetylmorphine tosylate (**69a**, Figure 24) with $CH_3COS^{\ominus}$ led to 3-*O*-acetyl-8-acetylthio-8-desoxypseudomorphine (**93**), which was deacetylated with sodium methylate to 8-thiol-8-desoxypseudomorphine (**94**) [109]. he treatment of **69a** with potassium thiocyanate resulted in 3-*O*-acetyl-8-isothiocyanato-8-desoxypseudomorphine (**95**) [112]. Reaction of **69a** with $N_3^{\ominus}$ anion gave 8-azido-8-desoxypseudomorphine (**96**, Makleit-Bognár nomenclature, 8-azido-8-desoxy-γ-isomorphine).

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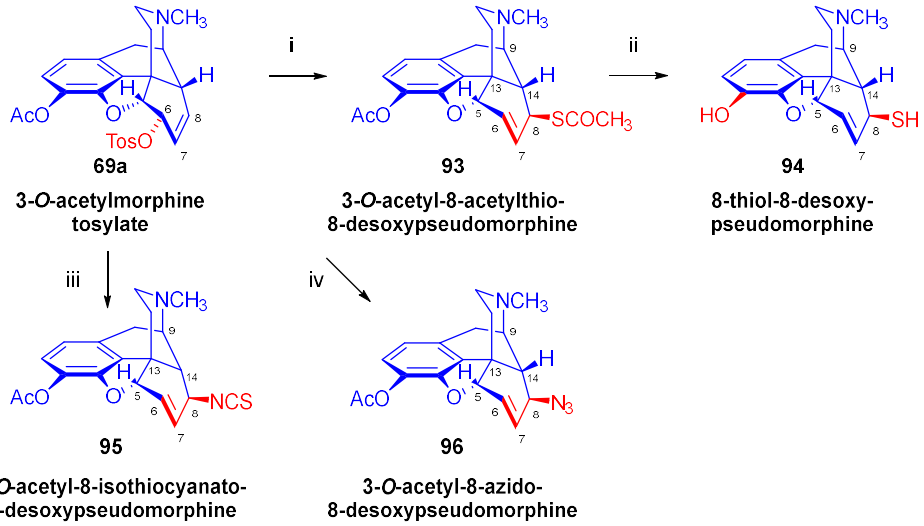

Figure 24. Reaction of 3-*O*-acetylmorphine tosylate with nucleophiles (following the Makleit-Bognár nomenclature [48]; γ-isomorphine derivatives). *Reagents and conditions*: (i): 2 equiv. $KSCOCH_3$, DMF, 100 °C, 5 h, N_2 atmosphere, 43 %; (ii): NaOMe, MeOH, room temperature, N_2 atmosphere, dark, 24 h, 42 %; (iii): 2 equiv. KSCN, reflux, 2.5 h, 90 %; (iv): NaN_3, DMF, H_2O, 100 °C, 4 h (**96** → **128**).

2.8.3. Reactions of pseudocodeine tosylate.

In the early 1970s, Makleit *et al.* [104] extended their studies on the nucleophilic substitution reaction of sulfonate esters to the $\Delta^{6,7}$-double bond containing pseudocodeine tosylate (**97**, Figure 25). Pseudocodeine (**2d**) was prepared from α-chlorocodide (**59b**) by hydrolysis according to the method of Small and Lutz [113]. The tosyl ester (**97**) was prepared from **2d** in 76 % yield. They investigated the substitution reactions by application of a large variety of nucleophilic reagents. Using the reagents type-X ($F^{\ominus}$, $Cl^{\ominus}$ or piperidine) *isocodeine* derivatives (**99**) were formed either by an S_N1' or S_N2' mechanism in a yield of range 10–65 %. Using type-Y nucleophiles ($Br^{\ominus}$, $I^{\ominus}$, $NCS^{\ominus}$, $N_3^{\ominus}$, $CH_3COS^{\ominus}$) *pseudocodeine* derivatives (**98**) were isolated in poor yields (10-52 %). In these latter cases the mechanism of the reaction was either S_N1 accompanied by retention or a combination of S_N2' and S_Ni'.

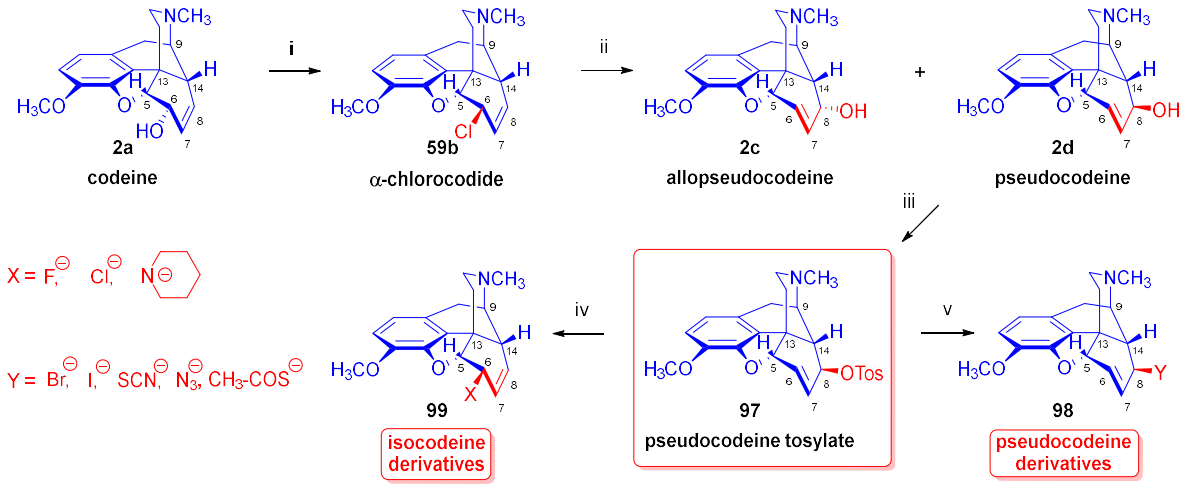

Figure 25. Reactions of pseudocodeine tosylate with various nucleophiles. *Reagents and conditions*: (i): PCl_5, chloroform, room temperature, 2 h, 90-95 %; (ii): water, acetic acid, reflux, 3 h, **2c**: 15 %, **2d**: 38 %; (iii): TosCl, pyridine, 0–5°C, 2 h, and then room temperature, 24 h, 76 %; (iv): **X** = **A**. Bu_4NF, acetonitrile reflux, 19 h, 10%; **B**. LiCl, acetone, reflux, 25 h, 16 %; **C**. piperidine, benzene, reflux, 127 h, 65%; (v): **Y** = **A**: LiBr, acetone, reflux, 19 h,

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52 %; **B**. NaI, acetone, reflux, 19 h, 26%; **C**. KSCN, acetone, reflux, 16.6 h, 15 %; **D**. NaN_3, DMF, 100 °C, 8 h, 30 %; **E**. $KSCOCH_3$, DMF, 100 °C, 8 h, 10%.

The corresponding products were isolated in poorer yields despite more vigorous reaction conditions, and longer reaction times in comparison to the analogous reactions of codeine tosylate (**63a**). The authors undertook comparative solvolysis of pseudocodeine tosylate (**97**) and codeine tosylate (**63a**) in an acetic acid - potassium acetate system, finding that the solvolysis of 8β-*O*-tosylate (**97**) solvolysis occurred slower than that of the 6α-*O*-Tos (**63a**) following in both cases a first-order reaction. They investigated more thoroughly the reaction of pseudocodeine tosylate (**97**) with piperidine, definitively showing formation of 6β-(1-piperidinyl) derivative (**64**, 6-piperidocodide) by an S_N1' reaction mechanism.

2.8.4. Neopine Derivatives

The neopine derivatives (e.g., isoneopine (**3b**), Figure 26.) are critical starting materials for the synthesis of B/C-*trans*-morphinans, which can be very difficult to produce [114,115]. In the 1970s, Berényi, Makleit, and Bognár worked out numerous syntheses for the preparation of neopine (**3a**) [116] and isoneopine (**3b**) [117]. Furthermore, Berényi, Makleit, and Dobány developed an improved method for the isolation of natural neopine (**3a**) from poppy straw [118], without interfering with the original Kabay-process. In 1977, Makleit *et al.* [116] reported an efficient method for the preparation of neopine (**3a**) from thebaine (**4**) *via* 14-chlorocodeine (structure see later: **124a** in Figure 37). The reduction of the latter compound (**124a**) was achieved with sodium bis(2-methoxyethoxy)aluminium hydride. The overall yield for neopine (**3a**) from thebaine (**4**) was 72 %. In 1980, Berényi and Makleit [117] published a novel method for the preparation of isoneopine (**3b**), wherein azidolysis of neopine mesylate (**100**) resulted in 6-deoxy-6-azido-isoneopine (**101**) in 75 % yield. The latter compound was reduced with Zn/NaI/DMF to 6-deoxy-6-amino-isoneopine (**102**, 65 %). Treatment of the amino compound (**102**) with $NaNO_2$ in acetic acid gave 6-*O*-acetylisoneopine (**103**, 90 %) and finally the alkaline hydrolysis of the 6-*O*-acetyl group resulted quantitively in isoneopine (**3b**). The overall yield from neopine (**3a**) was 44 %.

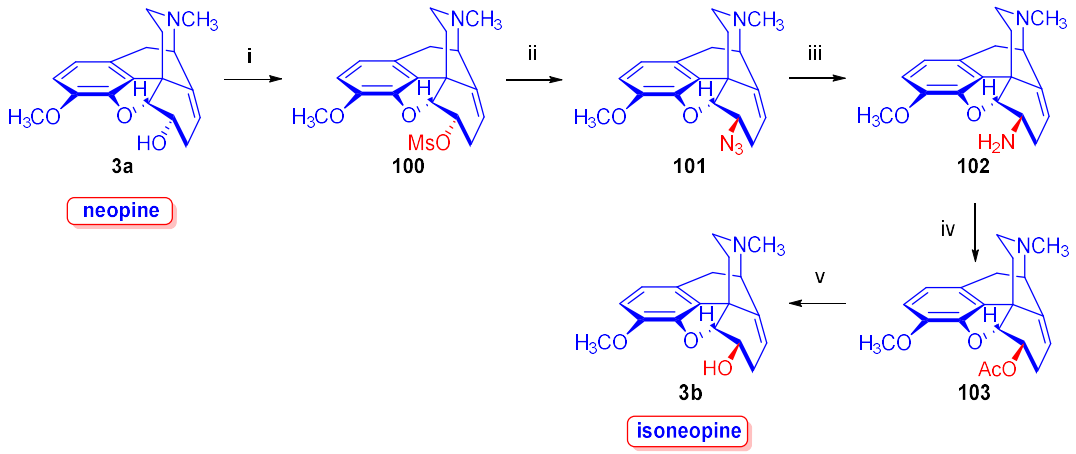

Figure 26. Synthesis of isoneopine. *Reagents and conditions*: (i): MsCl, pyridine, room temperature, 24 h; (ii): NaN_3, DMF, H_2O, 75 %; (iii): Zn, NaI, DMF, reflux, 6 h, 65 %; (iv): $NaNO_2$, AcOH, 20 °C, 24 h, 90 %; (v): KOH, EtOH, reflux, 10 min, quant.

Taking advantage of the availability of neopine (**3a**) in large quantities, Berényi *et al.* [119] prepared 6-*O*-mesylneopine (**100**, Figure 27.) for the investigation of its substitution reactions with nucleophile partners ($F^{\ominus}$, $Cl^{\ominus}$, $Br^{\ominus}$, $I^{\ominus}$, $N_3^{\ominus}$). When 6-*O*-mesylneopine (**100**) was reacted with tetrabutylammonium fluoride in acetonitrile (reflux, 2 h), 6-demethoxythebaine (**105**, 77 %) was

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obtained. In the reaction of neopine mesylate (**100**) with iodide anions (10 equiv. NaI, DMF, 120 °C, 30 h), 6-demethoxythebaine (**105**, 21 %) was isolated, with 36 % recovery of the starting material (**100**).

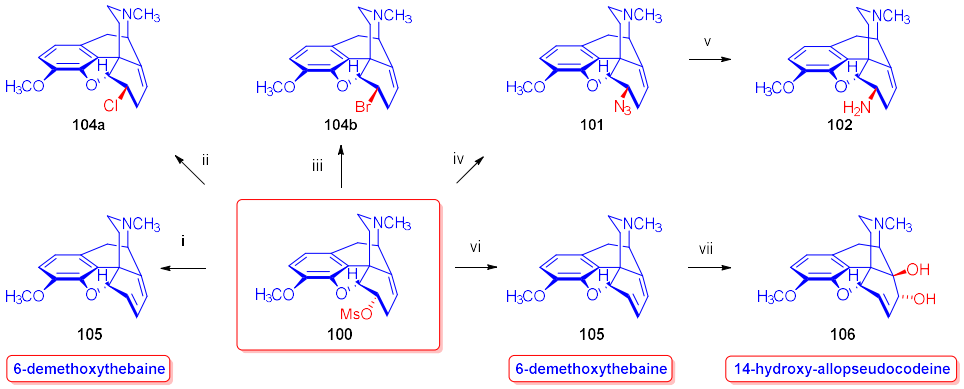

Figure 27. Reactions of 6-*O*-mesylneopine with nucleophiles. *Reagents and conditions*: (i): 5 equiv. Bu_4NF, CH_3CN, reflux, 2.5 h, 77 %; (ii): 10 equiv. LiCl, DMF, 120 °C, 6 h, 38 %; (iii): 10 equiv. LiBr, DMF, 120 °C, 11 h, 32 %; (iv): 10 equiv. NaN_3, DMF, 100 °C, 24 h, 55 %; (v): $LiAlH_4$, Et_2O, reflux, 1 h, 32 %; (vi): 10 equiv. NaI, DMF, 120 °C, 30 h, 21 % (**105**), and 36 % recovered neopine mesylate (**100**); (vii): 85 % formic acid, 30 % H_2O_2, 40 °C, 2 h, 71 %.

Applying chloride anions (10 equiv. LiCl, DMF, 120 °C, 6 h), 6-deoxy-6-chloro-isoneopine (**104a**) and 6-demethoxythebaine (**105**) were formed in a ratio of 6:4 [119]. Using bromide anions as nucleophile (10 equiv. LiBr, DMF, 120 °C, 11h), 6-deoxy-6-bromo-isoneopine (**104b**, 32 %) and 6-demethoxythebaine (**105**, 31 %) were isolated, with 10 % recovery of starting material (**100**). The 6-β position of the halogen substituent in compounds **104a** and **104b** (Cl, Br) was substantiated by NMR spectroscopy, in which value of the geminal coupling of the H-5 and H-6 protons ($^3J_{5,6}$ = 9.5–10 Hz) was characteristic for both compounds. The azidolysis of neopine mesylate (**100**), with 10 equivalents of NaN_3 in DMF (120 °C, 24 h) resulted in 6-deoxy-6-azido-isoneopine (**101**, 55 %). The latter compound (**101**) was converted to 6-deoxy-6-amino-isoneopine (**102**) by heterogenous catalytic reduction (H_2, 50 % acetic acid, platinum oxide). The authors concluded that the first step of these reactions is an S_N2 nucleophile substitution resulting in the corresponding 6-desoxy-6-haloisoneopines (**104a–b**) followed by a second elimination step resulting in 6-demethoxythebaine (**105**). 6-Desoxy-6-bromo-isoneopine (**104b**) was converted to 6-demethoxythebaine (**105**, reflux, 4 h, 72 %) with tetrabutylammonium fluoride, while 6-deoxy-6-chloro-isoneopine (**104a**) gave according to 50% conversion a 1:1 mixture of 6-demethoxythebaine (**105**) and the starting material (**104a**). Based on these observations, Hutchins *et al.*, and Beyerman, Maat, and Crabbendam reported improved preparations of 6-demethoxythebaine (**105**) in high yiels either from neopine (**3a**) or from codeine (**2a**) via isocodeine (**2b**) or β-bromocodide (**65b**) [120]. The reaction of thebaine (**4**) with peracids, peracetic acid (CH_3CO-OOH) or performic acid (HCO-OOH) [121] resulted in 14-hydroxycodeinone (structure see later **132** in Figure 40) by 1,4-addition of hydroxyl groups to the 6,8-conjugated system followed by methanol-elimination from the 6-hemiacetal intermediate.

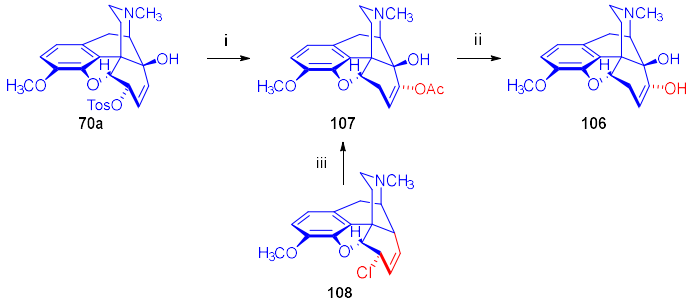

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Figure 28. Synthesis of 14-hydroxy-allopseudocodeine. *Reagents and conditions*: (i): AcOH-H_2O 7:1 (v/v), reflux, 4 h, 39 % [122]; (ii): KOH, MeOH-H_2O 3:1 (v/v), reflux, 1 h; (iii): **A**. 10 % AcOH, reflux, 4 h, 45 % [123], **B**. KOH, MeOH-H_2O 4:1 (v/v), 40–50 °C, 1 h.

The analogous treatment of 6-demethoxythebaine (**105**, Figure 27) with formic acid and hydrogen peroxide [119] gave 14-hydroxy-allopseudocodeine (**106**, 71 %). This latter compound was also prepared previously by Currie *et al.* [122] from 6-*O*-tosyl-14-hydroxycodeine (**70a**, Figure 28) in an S_N2' reaction (70 % AcOH) through 8-*O*-acetyl-14-hydroxy-allopseudocodeine (**107**) and subsequent alkaline hydrolysis. Seki *et al.* [123] prepared **106** from 14-hydroxy-α-chlorocodide (**108**) *via* acetolysis with 10 % AcOH and subsequent hydrolysis.

2.8.5. Alkyl Mesylate and Allyl Halide Structural Units in the Same Molecule

Studying the relative reactivity of alkyl mesylates (C^8-C^7- C^6-OMs) and allyl halides (C^{14}=C^8-C^7-X) Simon *et al.* [124] investigated the nucleophilic substitution reactions of 6-*O*-mesyl-7α-haloneopine derivatives (**112a–b**, Figure 30) containing both structural units in the same molecule. The starting materials 7α-chloroneopine (**111a**) and 7α-bromoneopine (**111b**) were prepared in three steps from thebaine (**4**) by the method of Abe *et al.* [125] (Figure 29). In brief, thebaine (**4**) was reacted with *N*-bromosuccinimide to give 14-bromocodeinone (**109**) [126]. This latter compound was stereoselectively reduced with $NaBH_4$ to 14-bromocodeine (**110**). The treatment of **110** with concentrated hydrochloric acid or 48% hydrobromic acid resulted in the corresponding 7α-haloneopines (**111a–b**).

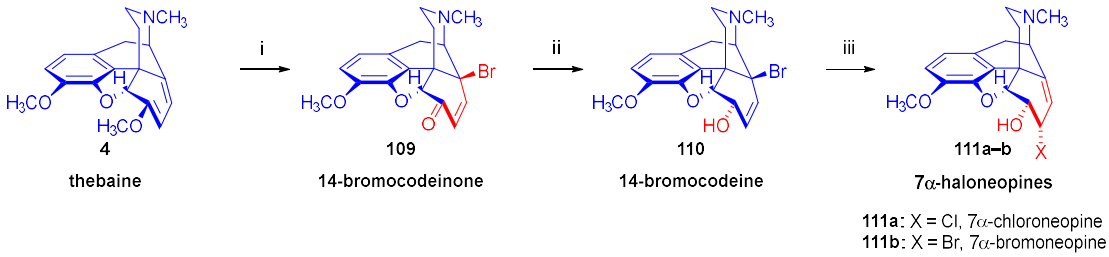

Figure 29. Synthesis of 7α-haloneopines from thebaine. *Reagents and conditions*: (i): *N*-bromosuccinimide, acetone-water 2:1 (v/v), 71 %; (ii): $NaBH_4$, benzene, MeOH, 5-10 °C, 1h, 94 %; (iii): cc. HCl, 5-10 °C, overnight, 90 %, or 48 % HBr, 0-5 °C, overnight.

Nucleophilic substitution reactions of 6-*O*-mesyl-7α-chloro-neopine (**112a**) and 6-*O*-mesyl-7α-bromoneopine (**112b**) were studied with the following nucleophiles: $Cl^{\ominus}$, $Br^{\ominus}$, $I^{\ominus}$, $N_3^{\ominus}$ [124] (Figure 30). When 6-*O*-mesyl-7α-chloroneopine (**112a**, Figure 30) was reacted with azido anions (5 equiv. NaN_3), there was formation of a complex product mixture. The column chromatography isolated the main product 7-chloro-6-demethoxythebaine (**113a**, 31 %) and the side products 6-*O*-mesyl-7β-azidoneopine (**114**, 10 %) and 6-*O*-mesyl-6-demethoxythebaine (**115**, 5 %).

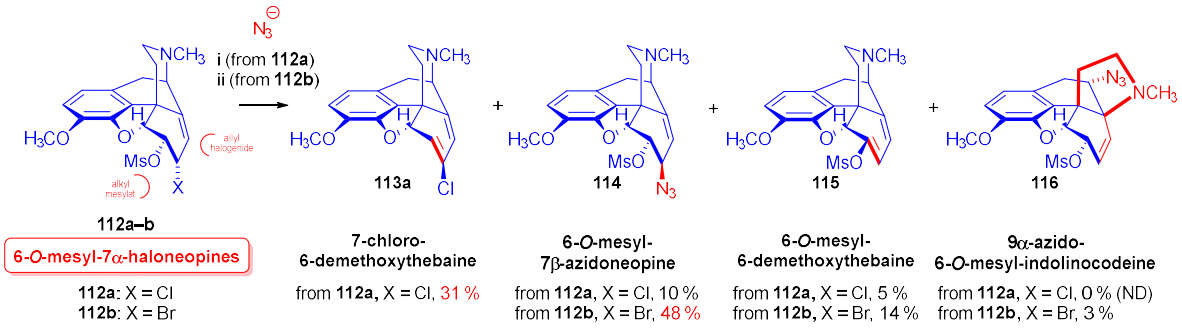

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Figure 30. Azidolysis of 6-*O*-mesyl-7*α*-haloneopines. *Reagents and conditions*: (i): 5 equiv. NaN_3, DMF, H_2O, 100 °C, 8 h; (ii) 5 equiv. NaN_3, DMF, H_2O, 100 °C, 20 min.

Reacting 6-*O*-mesyl-7*α*-bromoneopine (**112b**, Figure 30) with 5 equiv. of sodium azide in *N*,*N*-dimethylformamide (addition of water was necessary to dissolve NaN_3), the main product was 6-*O*-mesyl-7β-azidoneopine (**114**, 48 %). The isolated side products were 6-*O*-mesyl-6-demethoxythebaine (**115**, 14%) and 9*α*-azido-6-*O*-mesyl-indolinocodeine (**116**, 3 %).

Studying the reactions of 6-*O*-mesyl-7*α*-chloroneopine (**112a**, Figure 31) with 5 equivalents of reagent (LiCl, LiBr, KI) [124], the main product with chloride anions (5 equiv. LiCl, DMF, 100 °C, 24 h) was 7-chloro-6-demethoxythebaine (**113a**, 39 %), with isolation of 6-chloro-6-demethoxythebaine (**118a**, 18 %) and 6-*O*-mesyl-7β-chloroneopine (**117a**, 3 %) side products. Using LiBr as the source of nucleophile under otherwise identical conditions, the main reaction was methanesulfonic acid elimination, which resulted in 7-chloro-6-demethoxythebaine (**113a**, 31 %) and 6-bromo-6-demethoxythebaine (**118b**, 18 %), as well as 6-*O*-mesyl-7β-bromoneopine (**117b**, 13 %). In the presence of iodine anions (5 equiv. KI, DMF, 100 °C, 48 h), the main product was 6-demethoxythebaine (**105**, 34 %).

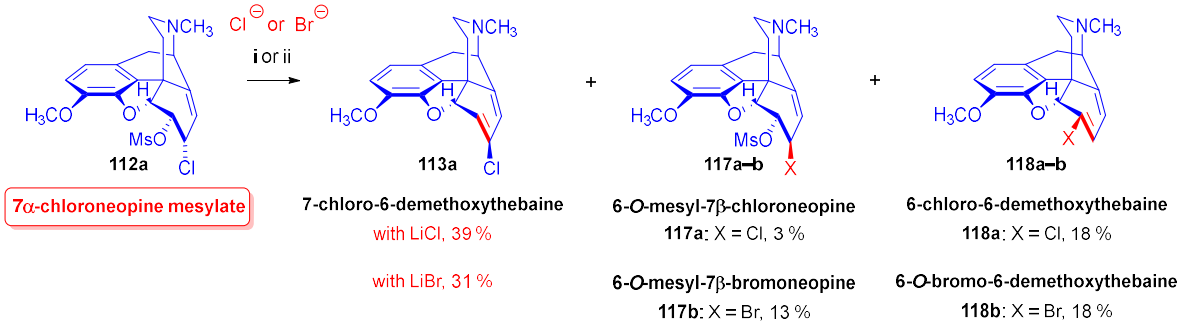

Figure 31. Reaction of 6-*O*-mesyl-7*α*-chloroneopine with $Cl^{\ominus}$ and $Br^{\ominus}$ nucleophiles. *Reagents and conditions*: (i): 5 equiv. LiCl, DMF, 100 °C, 24 h; (ii): 5 equiv. LiBr, DMF, 100 °C, 24 h.

Shorter reaction times (20–40 min) were applied in studying the reactions of 7*α*-bromoneopine mesylate (**112b**, Figure 32) with $Cl^{\ominus}$, $Br^{\ominus}$, and $I^{\ominus}$ nucleophiles. With LiCl, the main product was 6-*O*-mesyl-7β-chloroneopine (**117a**, 19 %), with additional isolation of 6-*O*-mesyl-6-demethoxythebaine (**115**, 7 %). When **112b** was reacted with LiBr, the products were 6-*O*-mesyl-7β-bromoneopine (**117b**, 24%), 7-bromo-6-demethoxythebaine (**113b**, 3 %), and 6-*O*-mesyl-6-demethoxythebaine (**115**, 6 %). Applying potassium iodide, 6-demethoxythebaine (**105**, 72 %) was the single isolated product. The study [124] also presented an elegant and efficient method for the preparation of 7-halo-6-demethoxythebaines (**113a–b**).

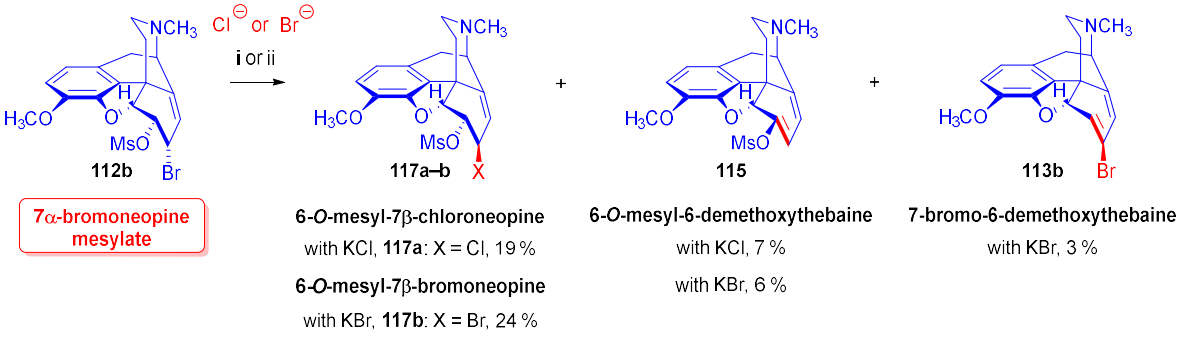

Figure 32. Reaction of 6-*O*-mesyl-7*α*-bromoneopine with nucleophiles. *Reagents and conditions*: (i): 5 equiv. LiCl, DMF, 100 °C, 30 min; (ii): 5 equiv. LiBr, DMF, 100 °C, 20 min.

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When boiling 6-*O*-mesyl-7α-chloroneopine (**112a**, Figure 33.) or 6-*O*-mesyl-7α-bromoneopine (**112b**) in the presence of potassium *tert*-butylate in methanol, the main reaction was methanesulfonic acid elimination ($E_{1,2}$ (-CH_3SO_2OH)). 7-Chloro-6-demethoxythebaine (**113a**) was prepared as the sole product in 95 % yield from **112a**, and 7-bromo-6-demethoxythebaine (**113b**) was the main product in 50 % from **112b**.

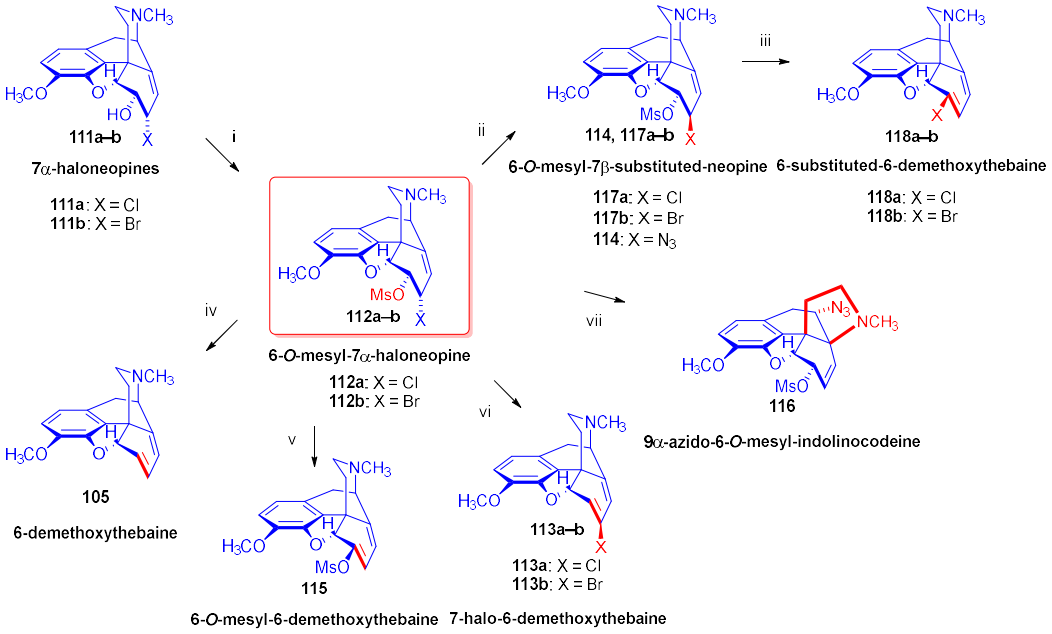

Figure 33. Nucleophilic substitution reactions of 7α-haloneopine mesylates. *Reagents and conditions*: (i): MsCl, Et_3N, CH_2Cl_2, 15 min, from **111a**, X = Cl, 61 %, from **111b**, X = Br, 51 %; (ii): $Nu^{\ominus}$ = $Cl^{\ominus}$, $Br^{\ominus}$, $N_3^{\ominus}$, S_N2; (iii): S_Ni + -H; (iv): $Nu^{\ominus}$ = $I^{\ominus}$, S_N2 + $E_{1,2}$; (v): $Nu^{\ominus}$ = $N_3^{\ominus}$, $E_{1,2}$ (-HCl) or Nu = $Cl^{\ominus}$, $Br^{\ominus}$, $N_3^{\ominus}$, $E_{1,2}$ (- HBr); (vi): Nu = $Cl^{\ominus}$, $Br^{\ominus}$, $I^{\ominus}$, $N_3^{\ominus}$, $E_{1,2}$ (- CH_3SO_2OH); (vii): $Nu^{\ominus}$ = $N_3^{\ominus}$.

2.8.6. Substrates Containing Double Allylic System

2.8.6.1. Substrates with Allyl Halide and Allyl Tosylate Sub-Units

Berényi *et al.* [127] was the first to study the nucleophilic substitution reactions of 6-*O*-tosyl-14-halocodeine substrates (**119a–b**), which possess a double allylic system: allyl halide (C^7=C^8-X^{14}) and allyl tosylate (C^8=C^7-C^6-OTos) in the same molecule. They investigated reactions of 14-chlorocodeine tosylate (**119a**, Figure 34) [127] and 14-bromocodeine tosylate (**119b**) [126] with $Cl^{\ominus}$, $Br^{\ominus}$, $N_3^{\ominus}$ nucleophiles. Surprisingly, 6-chloro-6-demethoxythebaine (**118a**, 68 %) as well as 6-bromo-6-demethoxythebaine (**180b**, 74 %) was isolated when the more stable 14-chlorocodeine tosylate (**119a**) was reacted with $Cl^{\ominus}$, $Br^{\ominus}$ anions (LiX, X = Cl. Br, DMF, 100 °C, 24 h).

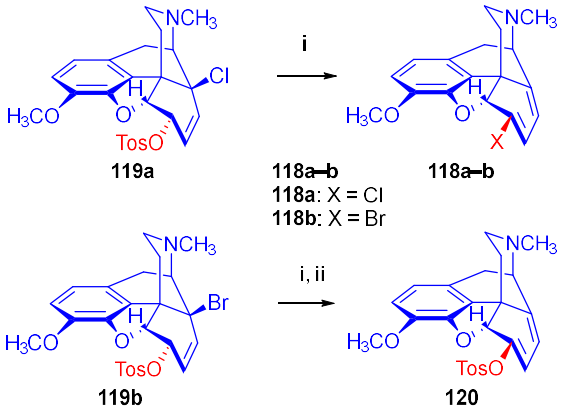

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Figure 34. Reaction of 6-*O*-tosyl-14-halocodeines with nucleophiles. *Reagents and conditions*: (i): 6 equiv. LiCl, or 5 equiv. LiBr, DMF, 100 °C, 24 h; (ii): without any nucleophilic partner, DMF, 100 °C, 2 h.

Interestingly, 6-*O*-tosyl-14-bromocodeine (**119b**) gave 6-*O*-tosyl-6-demethoxythebaine (**120**) under similar conditions. Heating 6-*O*-tosyl-14-bromocodeine (**119b**) in DMF (100 °C, 2 h) without any nucleophilic reagent gave the latter compound (**120**, 26 %). A further surprising result was that 6-*O*-tosyl-6-demethoxythebaine (**120**) did not react with $Cl^{\ominus}$ or $Br^{\ominus}$ anions.

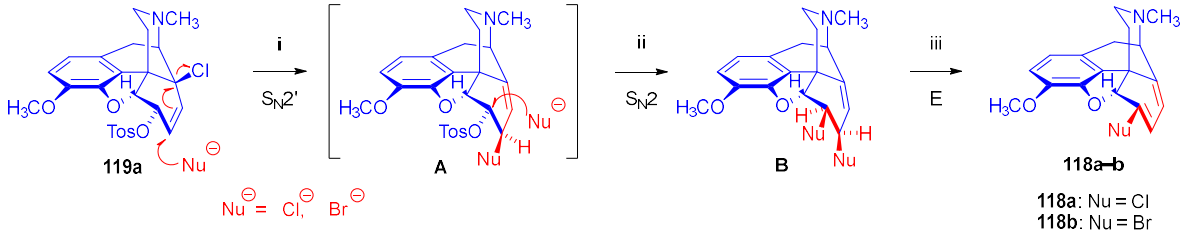

Figure 35. Supposed elementary steps of the formation of 6-halo-6-demethoxythebaines.

The authors [127] explained the complicated formation of 6-halo-6-demethoxythebaine derivatives (**118a–b**) by the following elementary steps (Figure 35). (i): S_N2' reaction: nucleophilic attack at position-7, resulting in 6-*O*-tosyl-7-substituted-neopine (**A**); (ii): S_N2 reaction: further nucleophile attack on the 6-tosyloxy group, resulting in 6-deoxy-6β,7β-disubstituted neopine (**B**). (iii): 1,4-elimination reaction.

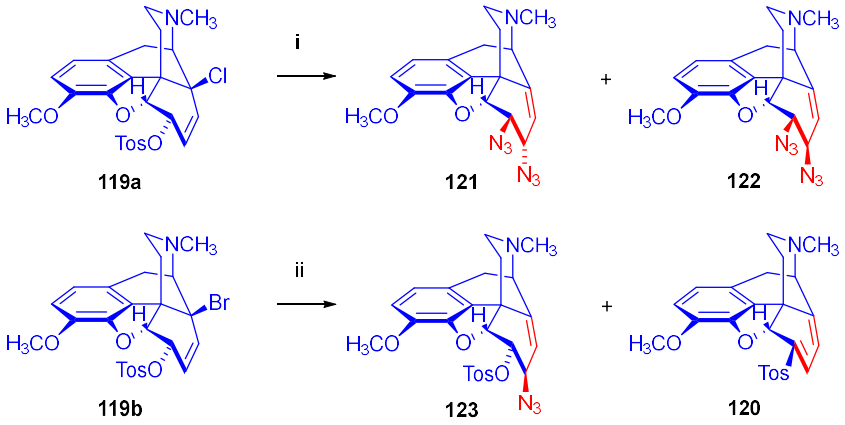

Figure 36. Azidolysis of 14-chlorocodeine tosylate and 14-bromocodeine tosylate. *Reagents and conditions*: (i): NaN_3, DMF, H_2O, 100 °C, 24 h; (ii): NaN_3, DMF, 100 °C, 2 h.

The azidolysis [127] of 14-chlorocodeine tosylate (**119a**, Figure 36) with 2.5 equiv. NaN_3 resulted in 6-deoxy-6β,7*α*-diazido-neopine (**121**, 27 %) as main product and 6-deoxy-6β,7β-diazido-neopine (**122**, 7 %) as a minor by-product. Carrying out the azidolysis of **119a** with 2.5 equiv. trimethylsilyl azide in DMF at 100 °C, yielded 6-*O*-tosyl-6-demethoxythebaine (**120**) and 6-deoxy-6β,7β-diazido-neopine (**122**) in a ratio of approximately 1:1, with a significant amount of starting material (**119a**) remaining in the product mixture after 24 h reaction time. When 6-*O*-tosyl-14-bromocodeine (**119b**) was reacted with azido anions (2.5 equiv. NaN_3), the major product was 6-*O*-tosyl-7β-azidoneopine (**123**, 25 %), with lesser amount of 6-*O*-tosyl-6-demethoxythebaine (**120**, 16 %) in 16 % yield [127]. The reactivity sequence of the leaving groups was as follows: allyl bromide > allyl tosylate > allyl chloride.

2.8.6.2. Substrates Containing Double Allyl Halide Sub-Structural Units

In 1988, Berényi *et al.* [128] reported the substitution reactions of 6β,14-dichlorodesoxycodeine (**125a**) and 6β-chloro-14-bromodesoxycodeine (**125b**, Figure 37), containing double allyl halide

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(C^7=C^8-C^{14}-X and C^8=C^7-C^6-Cl) sub-structural units with the nucleophiles $Cl^{\ominus}$, $Br^{\ominus}$, and $N_3^{\ominus}$ applied as LiCl and LiBr and NaN_3 respectively. They also studied reactions in hot DMF in absence of a nucleophilic partner. The authors claimed that only leaving groups ($Cl^{\ominus}$, $Br^{\ominus}$) linked to the tertiary C^{14} carbon (C^7=C^8-C^{14}-X) took part in nucleophilic substitution reactions among the investigated 6β-chloro-14-halodesoxycodeines (**125a–b**).

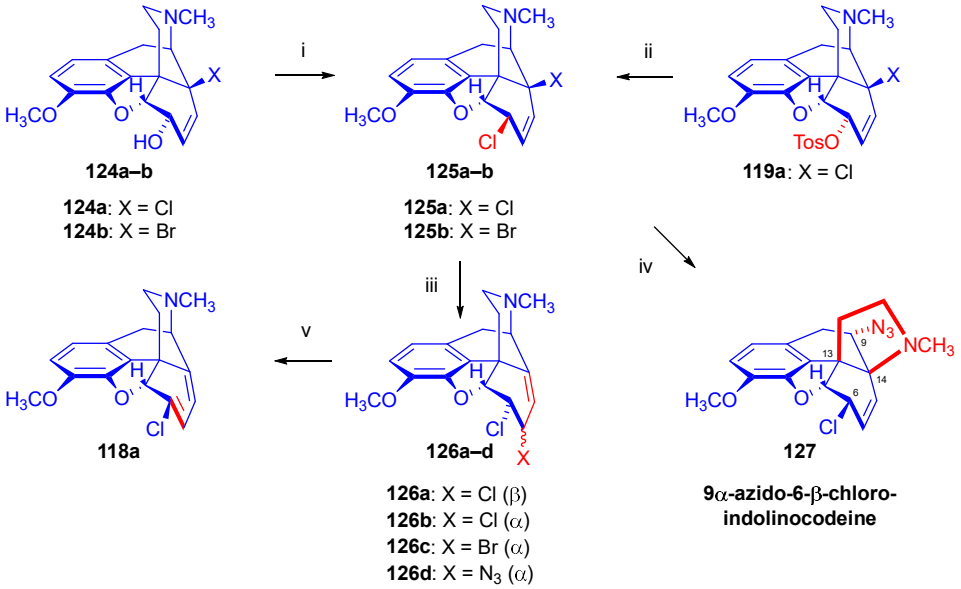

Figure 37. Nucleophilic substitution reactions of derivatives containing double allyl halide system. *Reagents and conditions*: (i): 2 equiv. PCl_5, $CHCl_3$, 0 °C, 2 h, **125a** (66 %), **125b** (53 %); (ii): 6 equiv. LiCl, DMF, 100 °C, 8 h; (iii): **A**: 10 equiv. LiCl, DMF, 100 °C, 30 min, **126a** (42 %) and **126b** (4 %); **B**: 5 equiv. LiBr, DMF, reflux, 4 h, **126c** (16 %); **C**: 5 equiv. NaN_3, DMF, H_2O, 100 ° C, 1 h, **126d** (44 %) and **127** (8 %); (iv): 5 equiv. NaN_3, DMF, H_2O, 100 °C, 1 h, **126d** (48 %) and **127** (7 %); (v): from **126c**, standing at RT for a few days.

The starting materials **125a** and **125b** for these investigations were prepared from 14-chlorocodeine (**124a**) [126] and 14-bromocodeine (**124b**, thebaine (**4**) → 14-bromocodeinone (**109**) → **1b**), respectively [129]. The reaction of **124a** with 2 equiv. phosphorus pentachloride in chloroform gave **125a** in 66 % yield, and the analogous reaction of 14-bromocodeine (**124b**) gave **125b** in 53 % yield. They also prepared **125a** from 14-chlorocodeine tosylate (**119a**) with LiCl.

6β-Chloro-14-bromodeoxycodeine (**125b**, C^7=C^8-C^{14}-Br and C^8=C^7-C^6-Cl) reacted readily with $Cl^{\ominus}$ anion (10 equiv. LiCl) in DMF, giving 6β-chloro-7β-bromodesoxyneopine (**126a**) as main product in 42 % yield, with further isolation of 6α-chloro-7β-bromodesoxyneopine (**126b**) in 4 % yield by column chromatographic separation of the mother liquor. Application of $Br^{\ominus}$ nucleophile (5 equiv. LiBr, DMF) for **125b**, gave 6-β-chloro-7β-bromodesoxyneopine (**126c**) in 16 % yield. Using $N_3^{\ominus}$ anions (5 equiv. NaN_3, DMF, 100 °C, 1 h) gave 6β-chloro-7α-azidodesoxyneopine (**126d**, 44 %) and 6β-chloro-9α-azidodesoxyindolinocodeine (**127**, 8 %). After heating of **125b** in DMF at 100 °C for 30 min in the absence of $Nu^{\ominus}$ unreacted starting material (**125b**), 6β-chloro-7β-bromodesoxyneopine (**126c**), and 6-chloro-6-demethoxythebaine (**118a**) were separated from the product mixture by column chromatography. Extending the reaction time (1 h) gave 6-chloro-6-demethoxythebaine (**118a**) in 62 % yield.

The reaction of 6β,14-dichlorodesoxycodeine (**125a**, C^7=C^8-C^{14}-Cl and C^8=C^7-C^6-Cl) with $Br^{\ominus}$ anions (5 equiv. LiBr, DMF, 100 °C, 8 h) led to 6-chloro-6-demethoxythebaine (**118a**) in 72 % yield. Azidolysis of **125a** under identical conditions as described above for **125b** resulted similarly in 6β-chloro-7β-bromodesoxyneopine (**126c**, 48 %) and 6-chloro-6-demethoxythebaine (**118a**, 7 %). After heating of **125a** in DMF at 110 °C without $Nu^{\ominus}$ reagent for 30 min, 6-chloro-6-demethoxythebaine (**118a**, 60 %), 6β-chloro-7β-chlorodesoxyneopine (**126a**, 4 %) and 6β-chloro-7α-chlorodesoxyneopine (**126b**, 1 %) were isolated. Upon continued the heating for 24 h, 6-chloro-6-demethoxythebaine (**118a**)

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was obtained in 72 % yield. The differences in reactivity of the allyl chloride (C^7=C^8-C^{14}-Cl and C^8=C^7-C^6-Cl) and allyl bromide (C^7=C^8-C^{14}-Br) subunits of the molecules manifested in the differing times required for whole conversion *via* an elimination reaction ($E_{1,2}$ type) in the absence of a $Nu^{\ominus}$ reagents. Thus, conversion of 6β-chloro-14-bromodesoxycodeine (**125b**) to 6-chloro-6-demethoxythebaine (**118a**) took one hour, whereas conversion of 6β,14-dichlorodesoxycodeine (**125a**) required 24 h.

2.9. Azidomorphinans

Organic azides [130–132] are suitable building blocks for the synthesis of a broad range of nitrogen-containing scaffolds. Due to the high electrophilicity of the azido group (mesomeric structures: -N=N-N: ↔ -N=$N^{\oplus}$=$N^{\ominus}$ ↔ -$N^{\ominus}$-$N^{\oplus}$≡N ↔ -$N^{\ominus}$-N=$N^{\oplus}$), organic azides are prone to react with various nucleophiles [133,134], and furthermore serve as starting materials for a large variety of transformations (e.g., reactions with electrophiles, cycloaddition, 1,3-cycloaddition with alkynes = click reaction, reduction to amines, etc.). Incorporation of the azido pharmacophore into a bioactive scaffold can be advantageous in providing new molecules with desirable pharmacological profiles, including increased potency, and other biochemical and pharmacological characteristics [135].

Cocker *et al.* [136] and later Willner *et al.* [137] thoroughly investigated the displacement by $N_3^{\ominus}$ and other nucleophile of *N*-acetylated 7-aminocephalosporanic acid (7-ACA) derivatives. The prepared 3-azidomethyl-3-cephem analogues were effective in inhibiting the growth of gram-negative bacteria [136,137].

Azidomazenil (8-azido-5,6-dihydro-5-methyl-6-oxo-4*H*-imidazo-1,4-benzodiazepine-3-carboxylic acid ethyl ester, Ro-15,4513, Hoffmann-La-Roche), the azido analogue of the 1,4-benzodiazepine derivative flumazenil (Ro-15,1788, Hoffmann-La-Roche), a partial inverse $GABA_A$ receptor ($GABA_AR$) agonist, blocks the electrophysiological and behavioural effects of low to moderate ethanol doses [138]. Indeed, $GABA_ARs$ may mediate the rewarding effects of ethanol, which require binding at the benzodiazepine-binding site (cBZR) of the α5-subunit of the $GABA_AR$ [139]. In 1992, the ^{11}C-labelled version of Ro-15,4513 was developed by Halldin *et al.* [140] for PET imaging of benzodiazepine receptors in living human brain [139].

The azido analogue of levorphan and its tritiated version N^{17}-(4-azidophenyl-$CH_2C(^3H)_2$)-norlevorphan were synthesized by Winter *et al.* [141] in 1972. N^{17}-Desmethyl-levorphan was reacted with β-(4-azidophenyl)ethyl bromide in methanol (K_2CO_3, 42 °C, 90 h) to yield the target compound, which was 4-fold more effective (ED_{50} = 0.78 mg/kg) than levorphan as an analgesic in the mouse hot-plate test, perhaps due to its greater lipophilicity and brain penetration.

2.9.1. Azidomorphine Analogues

6-Azido substituted morphine derivatives have a conspicuous analgesic effect [142,143], having a 50–300 fold increase in analgesic potency relative to morphine (**1a**) for the case of a 6-azido substitution of dihydroisomorphine (**82**, Figure 21) [144]. Spanning several decades, the research group of Makleit paid particular attention to investigating the nucleophilic substitution reaction of the sulfonate esters of the morphine series (see Figure 18 and Figure 19). They studied extensively the azidolysis of 6-*O*-tosyl and 6-*O*-mesyl esters of different morphinans and the subsequent transformations to the corresponding amino derivatives. In 1968, Bognár and Makleit investigated the syntheses of aminocodide and aminomorphide derivatives (Figure 38) [48], at a time when only a few in ring-C amino substituted morphinan derivatives were known. Furthermore, the absolute stereochemistry of these compounds, 6-aminocodide, 8-aminocodide (**84**) and 8-aminodihydrocodide (**75a**) where uncertain at that times. As starting points in the $\Delta^{7,8}$ unsaturated series, they used the sulfonate esters of codeine (**2a**) and 3-*O*-acetylmorphine (**55**). These materials readily reacted with azide anion ($N_3^{\ominus}$), giving the 8β-azides azidocodide (**83**) as well 8-azidomorphide (**128**) i.e., products belonging to the to the pseudocodeine or γ-isomorphine series (pseudomorphine derivatives, according to the Makleit-Bognár nomenclature).

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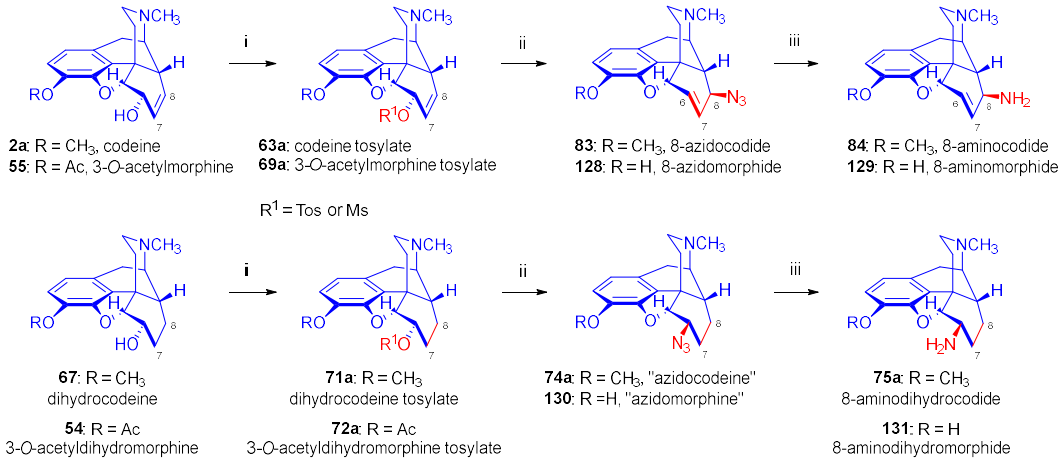

Figure 38. Synthesis of aminocodide and aminomorphide derivatives [45]. *Reagents and conditions*: (i): TosCl or MsCl, pyridine, A. 0 °C, 2 h, B. room temperature 24 h; (ii): 1.25 equiv. NaN_3, DMF, H_2O, 100 °C, 4 h (**83**,**128**) 24 h (**74a**,**130**); (iii): 3–8 equiv. $LiAlH_4$, Et_2O, reflux, 3 h.

The nucleophile substitution of codeine tosylate (**63a**) with azide anion ($N_3^{\ominus}$) can occur according to an S_N2' reaction mechanism (Figure 39), whereby the azide anion attacks the $\Delta^{7,8}$-double bond at C-8 position to give the 8β-azide (**XV**, Nu = N_3, **83**) directly. Another possible mechanism is an S_N2 reaction followed by allylic rearrangement ([3,3]-suprafacial sigmatropic rearrangement, S_Ni' mechanism), where the nucleophile ($N_3^{\ominus}$) attacks the C-6 position. The hypothesized 6β-azide (**XVI**, Nu = $N_3^{\ominus}$, allylic azide) intermediate undergoes an allylic rearrangement, which shifts the new substituent from C-6 into the C-8 position to give 8-azidocodide (**XV**, Nu = $N_3^{\ominus}$, **83**).

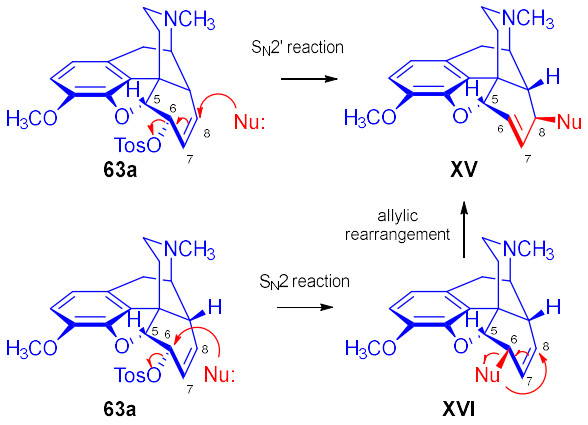

Figure 39. Supposed mechanism of the synthesis of 8-azidocodide. Nu = $N_3^{\ominus}$.

The analogous reaction of 6-*O*-sulfonate esters belonging to the 7,8-dihydro series (e.g., **71a, 72a**) [104] with the $N_3^{\ominus}$ nucleophile gave the corresponding 6β-azides: 6-desoxy-6-azidodihydroisocodeine (**74a**, "azidocodeine") [105] and 6-desoxy-6-azidodihydroisomorpine (**130**, "azidomorphine") [105], with inversion of the configuration in a stereospecific nucleophile substitution reaction (S_N2). The azides (**83**,**128** and **74a**,**130**) were reduced with $LiAlH_4$ in THF to their corresponding 8β-amino (**84**,**129**) or 6β-amino (**75a**,**131**) derivatives.

In a rat hotplate test of analgesia, azidomorphine (**130**, 6-AM, 6-desoxy-6-azidodihydroisomorphine; 3-hydroxy-4,5-α-epoxy-6β-azido-7,8-dihydro-17-methyl- morphinan) [105] was 270-300 times more potent than morphine (ED_{50} (**130**) = 0.016 mg/kg, versus ED_{50} (**1a**) = 4.7 mg/kg), whereas azidocodeine (**74a**, 6-desoxy-6-azidodihydroisocodeine, ED_{50} (**74a**) = 0.36 mg/kg;) was only ten times more potent than morphine (**1a**) [145]. Nonetheless, mice showed lesser propensity for developing physical dependence for azidomorphine (**130**) compared to morphine (**1a**).

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Interestingly, there was a consistent dissociation between the analgesic activity and physical dependence liability in monkeys, rats, and mice [145]. Intensive investigations by Bulaev *et al.* of the pharmacological characteristics *in vivo* of azidomorphine (**130**) in different animal models (rats, rabbits and cats) consistently showed 20–100 times greater analgesic activity compared to morphine (**1a**) [146,147]. Knoll *et al.* [148] demonstrated that azidomorphine (**130**) is metabolized in rats by *N*-demethylation to norazidomorphine and by conjugation with glucuronic acid. In human studies, azidomorphine (**130**) was 40–300 times more potent than morphine (**1a**) [149], relieving severe pain in 0.5–1 mg doses (sc. or. iv.), but with less constipation, vomiting, and euphoria than with equianalgesic doses of morphine (**1a**). When giving a composition containing azidomorphine (**130**, 0.5 mg), the non-narcotic analgesic rimazolium mesylate (1,6-dimethyl-3-carbethoxy-4-oxo-6,7,8,9-tetrahydro-homopyrimidazol, probon, MZ-144; 150 mg) potentiated the analgesic effects, while antagonizing the respiratory depressant effects of **130** [144]. In a human subject, azidomorphine (**130**) was metabolized by conjugation (6-AM-3G) and by reduction to 6-desoxy-6-aminoisomorphine [150].

In 1974, Sasvári *et al.* [151] reported the X-ray structural analysis of azidomorphine (**130**). When exploring the crystal structure of 14-hydroxyazidomorphine (**138**) Kálmán *et al.* [152], found that the substitution of the H-14 of azidomorphine (**130**) with a hydroxy group did not alter the C- and D-ring chair conformation, but did alter the orientation of the 6β-azido group. Tamás *et al.* studied mass spectroscopic fragmentation pathway of azidomorphine (**130**) and its derivatives [153]. Under electron impact (70 eV, source temperature 100–150 °C) azidomorphine analogues gave a remarkably different fragmentation pattern compared to that of the parent morphine alkaloids; the main decomposition route involved the loss of a nitrogen (N_2) molecule in the 6-desoxy-6-azidoisomorphine series (**74a**, **130**, **138**, **144**). Among 8-azido-substituted compounds containing a $\Delta^{6,7}$-double bond in ring C. (e.g., azidomorphide (**128**, 8-desoxy-8-azido-γ-isomorphine) or azidocodide (**83**)), there was loss of the loss of the N_3 radical ($\cdot N{=}N^{\oplus}{=}N^{\ominus}$) due to the allylic effect. Dinya *et al.* [154,155] performed infrared spectroscopic investigations and quantum chemical analysis of azidomorphinans.

Aiming to improve upon the toxicity of azidomorphine (**130**, LD_{50} (**130**) = 8.1 mg/kg; LD_{50} (**1a**) = 320 mg/kg, i.v. in the rat) [145], Makleit *et al.* developed 14-hydroxyazidomorphine" (**138**, 6-desoxy-6-azido-14-hydroxydihydroisomorphine, 3,14β-dihydroxy-4,5α-epoxy-6β-azido-7,8-dihydro-17-methylmorphinan, Figure 40) in 1972 [106,156,157]. The synthesis of **138** from thebaine (**4**) followed seven consecutive steps. In brief, 14-hydroxycodeinone (**132**) was obtained from **4** with hydrogen peroxide and formic acid [123], and the $\Delta^{7,8}$ double bond of **132** was then saturated under heterogenous catalytic conditions (H_2, 10% Pd-C, AcOH) to give oxycodone (**133**). Oxymorphone (**134**) was prepared from **133** by 3-*O*-demethylation with 48% hydrobromic acid. The C-6 keto group of **134** was reduced by sodium borohydride in a stereospecific reaction to 14-hydroxy-dihydromorphine (**135**). The phenolic 3-hydroxyl group of **135** was protected by partial acetylation using the method of Welsh [88] with acetic anhydride ($NaHCO_3$, H_2O). The 6α-hydroxyl group of compound **136** was transformed to sulfonate esters (**137a–b**) with the corresponding reagent (MsCl or TosCl, pyridine, 24 h, RT). Finally, the tosylester (**137a**) was subjected to azidolysis (sodium azide, DMF, H_2O, 100 °C, 24 h) to give the desired azido derivative (**138**) [106,156]. 6-Desoxy-6-azido-14-hydroxydihydroisomorphine (**138**) had similar analgesic potency in the mouse hot plate test as azidomorphine (**130**): ED_{50} (**130**) = 0.024 mg/kg, ED_{50} (**138**) = 0.029 mg/kg) [149], although with lower toxicity. The introduction of the hydroxy group in position-14 of azidomorphine (**130**) conspicuously reduced the toxicity; azidomorphine (**130**) was 6.5 times more toxic in rats and 11.6 times more toxic in mice than 14-hydroxyazidomorphine (**138**) [149]. Human studies indicated 40-fold greater analgesic activity for azidomorphine (**130**) and 14-hydroxyazidomorphine (**138**) compared to morphine (**1a**) [158].

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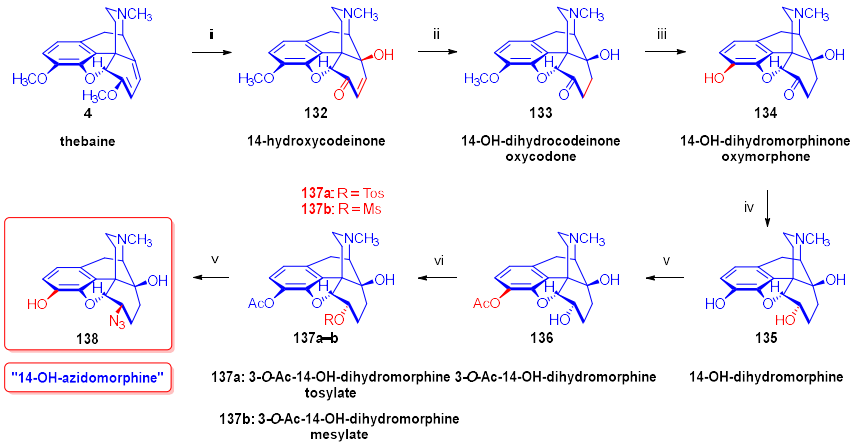

Figure 40. Synthesis of 14-hydroxyazidomorphine. *Reagents and conditions*: (i): formic acid, H_2O_2, 40 °C, 2 h; (ii): H_2, 10% Pd-C, acetic acid; (iii): 48% hydrobromic acid, 120°C, 20 min; (iv): $NaBH_4$, EtOH, 20 °C, 20 h; (v): Ac_2O, $NaHCO_3$, H_2O, 20 °C; (vi): MsCl or TosCl, pyridine, 20 °C, 24 h; (vii): NaN_3, DMF, 100 °C, 24 h, 73 %.

Antitussive activity of **138** was determined and compared with the reference-antitussive codeine (**2a**) using the Gosswald citric acid aerosol-induced cough test in Wistar rats [157]. 14-Hydroxyazidomorphine (**138**) had 1000-fold higher anti-tussive activity compared to codeine (**2a**, AtD_{50} (**2a,** s.c.) = 19.0 mg/kg, AtD_{50} (**138,** s.c.) = 0.021 mg/kg, ratio **2a**/**138** = 904) [157].

In a subsequent study, the same research group [159] performed structure optimization-investigations aiming to identify azidomorphine analogues with a more advantageous pharmacological profile. For synthesis of 3-desoxyazidomorphine (**141**, Figure 41), they first produced the starting material 3-desoxydihydromorphine (**139**) by removal of the 3-hydroxyl group of morphine *via* hydrogenation of morphine-3-(1-phenyltetrazolyl)- or morphine-3-(pyrimidyl)-ether [160]. Under these conditions, the $\Delta^{7,8}$-double bond was also saturated. In the next steps, the tosylester (**140**) was prepared and subjected to azidolysis (sodium azide, DMF, H_2O, 100 °C, 24 h) and transformed to 3-desoxyazidomorphine (**141**) in 20 % yield.

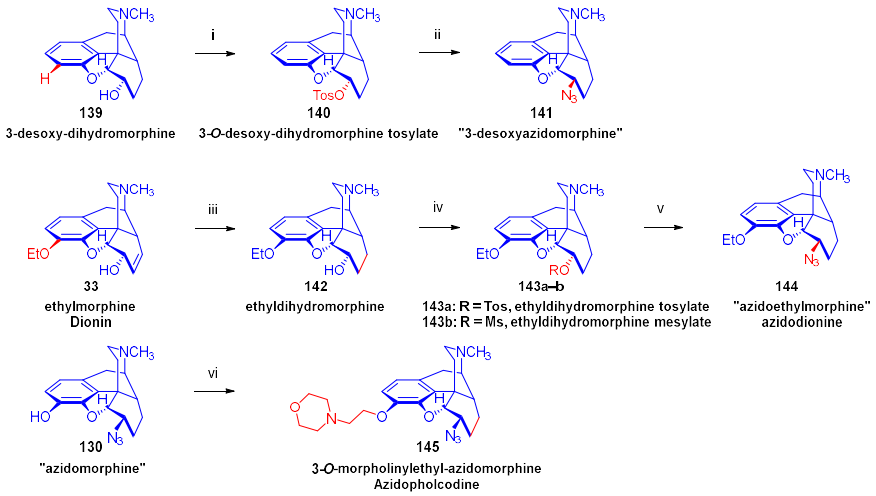

Figure 41. Synthesis of azidomorphine analogues. *Reagents and conditions*: (i): 1 equiv. TosCl, pyridine, room temperature, 24 h, 50 %; (ii): 13 equiv. NaN_3, DMF, H_2O, 100 °C, 24 h, 50 %; (iii): H_2, Raney-Ni, MeOH or EtOH, RT, atmospheric pressure [161]; (iv): **A**. 1.2 equiv. TosCl, pyridine, 0 °C, 2 h, than RT for 24 h, 78 %, or **B**. 1.1 equiv. MsCl, pyridine, 0 °C, 2 h, than room temperature for 24 h, 64 %; (v): 10 equiv. NaN_3, DMF, H_2O, 100 °C, 24 h, 65 %; (vi): 1.4 equiv. morpholinylethylchloride HCl, 2.3 equiv. Na, EtOH, reflux, 1 h, 40 %.

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Analogously, "azidoethylmorphine" (**144**, "3-*O*-ethylazidomorphine", azidodionine, 6-azido-6-desoxy-ethyldihydroisomorphine) [159] was prepared from ethylmorphine (**33**) in three steps (Figure 41). Compound **33** was reduced to 3-*O*-ethyl-dihydromorphine (**142**) [161], which was converted to the esters ethyldihydromorphine tosylate (**143a**) or mesylate (**143b**) [161]. Subsequent azidolysis of the esters (**143a–b**) gave azidoethylmorphine (**144**). Antitussive activity by the Gosswald method in rats was 60-fold higher for azidodionine (**144**) than for codeine (**2a**) (AtD_{50} (**2a,** oral) = 100.0 mg/kg, AtD_{50} (**144,** oral) = 1.67 mg/kg, ratio **2a**/**144** = 59.88) [159,162,163].

3-*O*-Morpholinylethylazidomorphine (**145**, azidopholcodine, Figure 41) [159,162] has also been prepared from morphine (**1a**) in five steps (morphine (**1a**) → ethylmorphine (**33**) → ethyldihydromorphine → 3-*O*-morpholinylethyldihydromorphine → 3-*O*-morpholinylethyldihydromorphine mesylate → **145**), and directly from azidomorphine (**130**) by alkylation with morpholinylethylchloride thanks to the stability of the azido group of **130** against the strong base NaOEt. Azidopholcodine (**145**) had four-fold greater antitussive activity in rats AtD_{50} (**145,** s.c.) = 4.5 mg/kg) as compared to codeine (**2a**) (AtD_{50} (**2a,** s.c.) = 19.0 mg/kg, ratio **2a**/**145** = 4.22) [163].

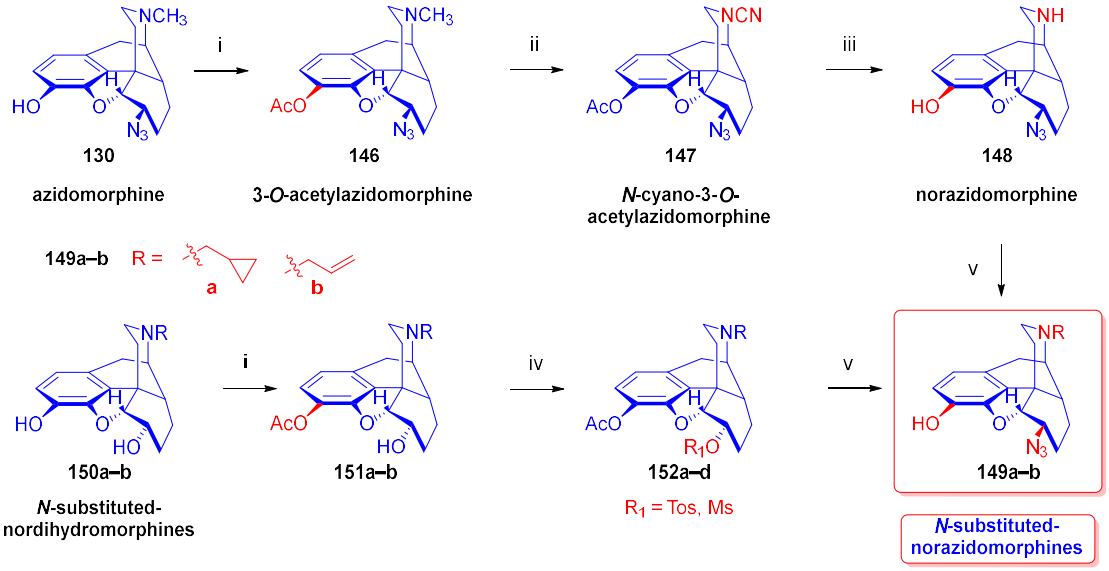

Figure 42. Synthesis of N^{17}-substituted azidomorphine analogues. *Reagents and conditions*: (i): based on Welsh's [88] method: Ac_2O, $NaHCO_3$, H_2O; (ii): 2 equiv. BrCN, 60 °C, 2.5–6 h, 90 %; (iii): 5–10 % aqueous HCl reflux, 5–10 h; (iv): 1.2 equiv. TosCl or MsCl, 20°C, 24 h; (v): 10 equiv. NaN_3, DMF, 100 °C, 24 h.

To study the antagonistic properties in the azidomorphine series, Makleit *et al.* synthesized the N^{17}-substituted analogues (**149a–b**, cyclopropylmethyl, allyl, Figure 42) of azidomorphine (**130**), azidocodeine (**74a**), 14-hydroxyazidomorphine (**138**) and 14-hydroxyazidocodeine [164]. N^{17}-Cyclopropylmethyl-norazidomorphine (**149a**, CAM) and N^{17}-allyl-norazidomorphine (**149b**, AAM) were synthesized *via* two different routes. In the first approach, acetylation of the phenolic hydroxy group in position-3 of azidomorphine (**130**) resulted in 3-*O*-acetylazidomorphine (**146**). The von Braun reaction with cyanogen bromide in the presence of the 6-azido group gave high yields (e.g., **146** → **147** in 90 % yield). Alkaline hydrolysis of the cyanamide (**147**) and subsequent acid hydrolysis gave azidonormorphine (**148**) in 47 % yield. N^{17}-alkylation of **148** with allyl bromide or cyclopropylmethyl bromide resulted in the corresponding N^{17}-substituted-norazidomorphines (**149a–b**). On the other hand, the partial acetylation of N^{17}-cyclopropylmethyl-nordihydromorphine (**150a**) or N^{17}-allyl-nordihydromorphine (**150b**) resulted in the corresponding 3-*O*-acetyl-nordihydromorphines (**151a–b**). The latter compounds were converted into their sulfonate esters (tosyl, mesyl, **152a–d**) for subsequent azidolysis, resulting in the desired analogues (**149a–b**).

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In 1977, Knoll *et al.* [165] reported on their pharmacological investigations of numerous N^{17}-substituted-azidomorphine analogues. They compared the OR opioid receptor antagonistic properties of N^{17}-cyclopropylmethyl-norazidomorphine (**149a**, CAM, Figure 42), N^{17}-allyl-norazidomorphine (**149b**, NAM) and their 14-hydroxy analogues: N^{17}-cyclopropylmethyl-14-hydroxynorazidomorphine (COAM) and N^{17}-allyl-14-hydroxynorazidomorphine (NOAM) relative to reference antagonist (naltrexone, see structure later **199**, Figure 52) in different tissues. Surprisingly, N^{17}-substituted-azidomorphine analogues were potent antagonists in the isolated cat nictitating membrane (CNM) assay, but were extremely potent pure agonists in the guinea-pig ileum (GPI), and mouse vas deferens (MVD) tests. CAM (**149a**) [164] stimulated the A-type receptors, which are involved in behavioural effects of OR ligands (GPI and MVD tests; cholinergic neurotransmission). On the other hand, CAM (**149a**) had greater antagonist potency than naloxone in the CNM test (B-type receptor: responsible for the analgesic, antitussive, and respiratory depressant effects of OR ligands; catechol adrenergic neurotransmission) [165]. Subsequently, Fürst *et al.* tested the antagonistic potencies of **149a–b** in the oxymorphone righting test [166]. The N^{17}-substituted azidomorphines (**149a–b**) were more potent antagonists than nalorphine or pentazocine, but were equipotent with naloxone. N^{17}-Cyclopropylmethyl-norazidomorphine (**149a**, CAM) was suggested to be a κOR subtype agonist based on its agonistic activity in rabbit *vas deferens* (RVD) assay, and given the low potency of naloxone to reverse its agonistic effect in GPI and in MVS tests [166,167]. CAM (**149a**) has a different pharmacological profile from bremazocine or ethylketazocine (EK), which are agonists in the CNM assay.

Inspired by the novel pharmacological profile of the N^{17}-substituted-norazidomorphines (**149a–b**) [165], the Alkaloida research group prepared N^{17}-substituted-norazidoethylmorphine derivatives (**155a–c**, R = CPM, allyl, *n*-propyl, Figure 43) [168] through two independent routes from azidoethylmorphine (**144**) as well from ethyldihydromorphine (**142**).

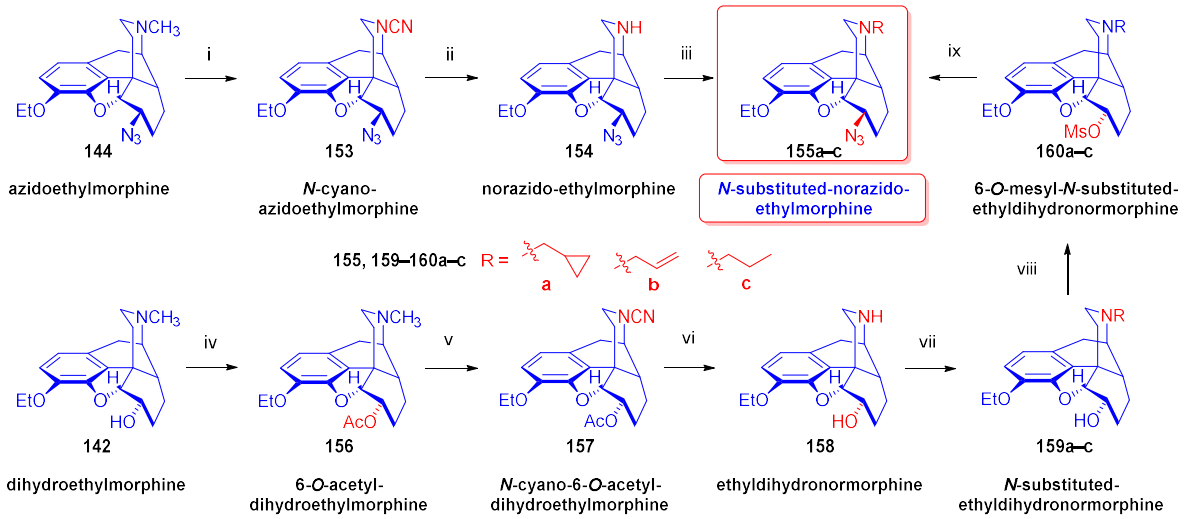

Figure 43. Synthesis of *N*-substituted-norazidoethylmorphine analogues. *Reagents and conditions*: (i): 2.1 equiv. BrCN, $CHCl_3$, reflux, 4 h, 75 %; (ii): 6 % HCl, reflux, 6 h, 95 %; (iii): **A**. cyclopropylmethyl bromide, $NaHCO_3$, EtOH, reflux, 15 h, 46 %; **B**. allyl bromide, $NaHCO_3$, EtOH, reflux, 8 h, 54 %; (iv): Ac_2O, 100 °C, 1 h, 94 %; (v): BrCN, $CHCl_3$, reflux, 4 h, 95 %; (vi): 10 % HCl, reflux, 8 h, 94 %; (vii): **A**. cyclopropylmethyl bromide, $NaHCO_3$, EtOH, reflux, 15 h, 75 %; **B**. allyl bromide, $NaHCO_3$, EtOH, 80 °C, 20 h, 73 %; **C**. *n*-propyl bromide, $NaHCO_3$, 80 °C, 20 h, 58 %; (viii): 1.2 equiv. MsCl, pyridine, room temperature, 24 h, 83 % (R = CPM); (ix): 10 equiv. NaN_3, DMF, H_2O, 100 °C, 24 h, 62 %, R = CPM.

In brief, in the first reaction sequence [168], azidoethylmorphine (**144**, Figure 43) was *N*-demethylated using the von Braun method (BrCN) *via* *N*-cyano-azidoethylmorphine (**153**). The cyanamide (**153**) was hydrolysed with 6 % hydrochloric acid; *N*-demethylation of azidoethylmorphine (**144**) was also achieved easily and in good yields with methyl- or phenyl

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chloroformate. The formed N^{17}-phenyl- or N^{17}-methyl-oxycarbonyl-N^{17}-desmethyl-azidoethylmorphine was converted to norazido-ethylmorphine (**154**) with 25% KOH in ethanol. Subsequent alkylation of N^{17}-desmethyl-azidoethylmorphine (**154**) with cyclopropylmethyl bromide or allyl bromide resulted in N^{17}-cyclopropylmethyl-norazidoethylmorphine (**155a**, ECAM, Figure 43) and N^{17}-allyl-norazidoethylmorphine (**155b**) in yields of 46 and 54 %, respectively.

In a second approach [168], the synthesis of N^{17}-substituted-norazido-ethylmorphines (**155a–c**, Figure 43) was performed in six consecutive transformations starting from ethyldihydromorphine (**142**). The alcoholic hydroxyl group in position-6 of **142** was protected with an acetyl group by treatment with acetic anhydride, resulting in 6-*O*-acetyl-ethyldihydromorphine (**156**, 94 %). The von Braun *N*-demethylation of **156** with cyanogen bromide and subsequent hydrolysis of the cyanamide (**157**) gave ethyldihydronormorphine (**158**). Other routes to N^{17}-desmethyl-dihydromorphine (**158**) entailed treatment of **156** with diethyl azodicarboxylate (DEAD) or with methyl- or phenyl-chloroformate. The *N*-demethylation without protection of the 6-OH function starting directly from ethyldihydromorphine (**142**) was also feasible. Compound **158** was alkylated with the appropriate reagent (cyclopropylmethyl bromide, allyl bromide, *n*-propyl bromide) to N^{17}-substituted-ethyldihydronormorphines (**159a–c**). The compounds **159a–c** were converted into their mesylesters (**160a–c**) and the subsequent azidolysis of these compounds gave target N^{17}-substituted-norazidoethylmorphines (**155a–c**).

The agonist-antagonist characteristics of the synthesized analogues were determined by the hot-plate method in rats. A ten-fold higher morphine (**1a**) dose was necessary to achieve the same analgesic effect in conjunction with 5 mg/kg s.c. ECAM (**155a**) compared to the controls without antagonist co-treatment [168]. With oral application of **155a** (25–30 mg/kg), a 2–3-fold higher morphine (**1a**) doses was required for an equianalgesic effect. Similarly to ECAM (**155a**), the application of N^{17}-allyl-norazidoethylmorphine (**155b**) at 50 mg/kg (s.c.) raised by tenfold the necessary morphine (**1a**) dose. Interestingly, ECAM (**155a**) showed an anorexic effect in food-deprived rats.

2.9.2. 14-Hydroxy-8-azido-8-desoxyallopseudocodeine Derivatives

In 1988, Gulyás *et al.* [169] synthesized a series of 6- and 7-halo substituted 14-hydroxy-8-azido-8-desoxyallopseudocodeine derivatives (Figure 44). The starting materials for these investigations, 6-demethoxythebaine (**105**), 6-chloro- and 6-bromo-6-demethoxythebaine (**118a–b**), 7-chloro- and 7-bromo-6-demethoxythebaine (**113a–b**) were prepared according to earlier protocols of the Makleit group [119,124,170] (see also sections 2.8.4.–2.8.6.). 6-Demethoxythebaine (**105**) was obtained from neopine mesylate (**100**) with tetrabutylammonium fluoride [119], 6-chloro- and 6-bromo-6-demethoxythebaine (**118a–b**), from 14-chloro-codeine tosylate (**119a**) with LiCl or LiBr [170], and finally 7-chloro- and 7-bromo-6-demethoxythebaine (**113a–b**) from 7α-halo-neopine mesylates (**112a–b**) by boiling with potassium *tert*-butylate in methanol [124]. 6-Demethoxythebaine derivatives (**105**, **113a–b**, **118a–b**) were converted to the corresponding 8β,14β-epoxides (**161a–e**, 8β,14β-epoxycodides) with formic acid-hydrogen peroxide (low yields: 22–42 %), or alternatively with disuccinylperoxide or *m*-chloroperbenzoic acid in 10 % formic acid. The epoxides (**161a–e**) were subjected to azidolysis (5 equiv. NaN_3, dioxane, H_2O, 100 °C, 10 h) to give 6- and 7-substituted 14-hydroxy-8-azido-8-desoxyallopseudocodeine derivatives (**162a–e**) [169] in 28–63 % yields.

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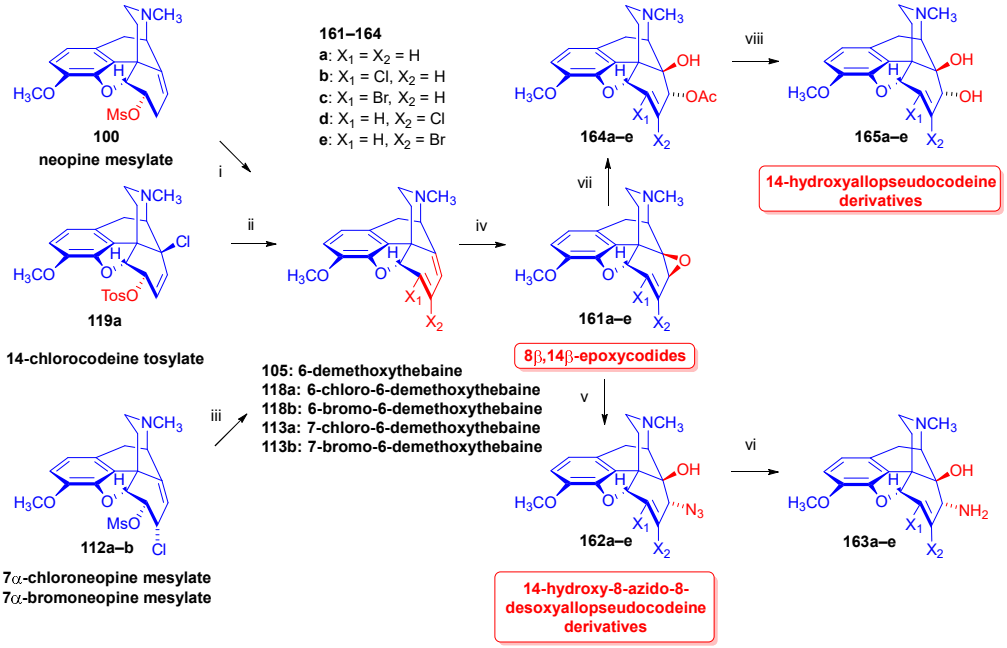

Figure 44. Synthesis of 14-hydroxy-8-azido-8-desoxyallopseudocodeine derivatives. *Reagents and conditions*: (i): 5 equiv. Bu_4NF, CH_3CN, reflux, 2.5 h, 77 %; (ii): 6 equiv. LiCl or 5 equiv. LiBr, DMF, 100 °C, 24 h; (iii): 2.35 equiv. KO*t*-Bu, MeOH, EtOH, reflux, 10 min. from **112a** 95 %, **112b**, 50 %; (iv): A. from **105**, 85 % formic acid, 30 % H_2O_2, 40 °C, 25 min, 25 %; B. from **105**, 10 % formic acid, 90 % *m*-chloroperbenzoic acid, EtOH, 0 °C, 105 min, 53 %; C. from **105**, 2 equiv. disuccinyl peroxide, 10 % formic acid, room temperature, 15 min., 32 %; (v): 5 equiv. NaN_3, dioxane, H_2O, 100 °C, 10 h, 38–77 %; (vi): 85 % hydrazine hydrate, EtOH, reflux, 10 min, 28–63 %; (vii): 10 % AcOH, 70 °C, 1.5 h, 36–83 %; (viii): 10 % KOH solution (aq), EtOH, reflux, 10 min, 36–90 %.

The latter compounds were transformed to the corresponding 8α-amines (**163a–e**) with a yield of 28–63 %. The acetolysis of the epoxides (**161a–e**) was performed with 10 % acetic acid at 70 °C (1.5 h), which gave 8α-acetoxy-14-hydroxy derivatives (**164a–e**, 36–83 %). The hydrolysis of the acetates with 10 % KOH in ethanol resulted in 6- and 7-substituted 14-hydroxyallopseudocodeine derivatives (**165a–e**) [169] in 36–90 % yield.

In a subsequent study, Gulyás and Makleit [171] investigated the reactions of 8β,14β-epoxycodide (**161a**, Figure 45) containing a vinyl-oxirane sub-structural unit. The starting material (**161a**) [169] was prepared from 6-demethoxytebaine (**105**). The reduction of **161a** with lithium aluminium hydride in diethyl ether gave 14-hydroxydesoxycodeine-C (**166**) in 50 % yield. When performing the azidolysis of 8β,14β-epoxycodide (**161a**) with azidotrimethylsilane in the presence of zinc (II) iodide the sole isolated product was 14-trimethylsilyloxy-8-azido-8-desoxyallopseudocodeine (**167**, 60%). Removing the TMS protecting group with sodium fluoride in methanol yielded the same 14-hydroxy-8-azido-8-desoxyallopseudocodeine (**165a**, 67 %), which was prepared earlier from **161a** with sodium azide (dioxane-H_2O, 100 °C, 10 h) [171]. When treating **161a** with $Cl^{\ominus}$ anions in aqueous-acidic acetonitrile (LiCl, 10 % HCl – CH_3CN) [171], there was formation of 6-chloro-14-hydroxyisocodeine (**168**, 14-hydroxy-α-chlorocodide, 20 %), 14-hydroxy-isocodeine (**169**), and 14-hydroxy-allopseudocodeine (**106**).

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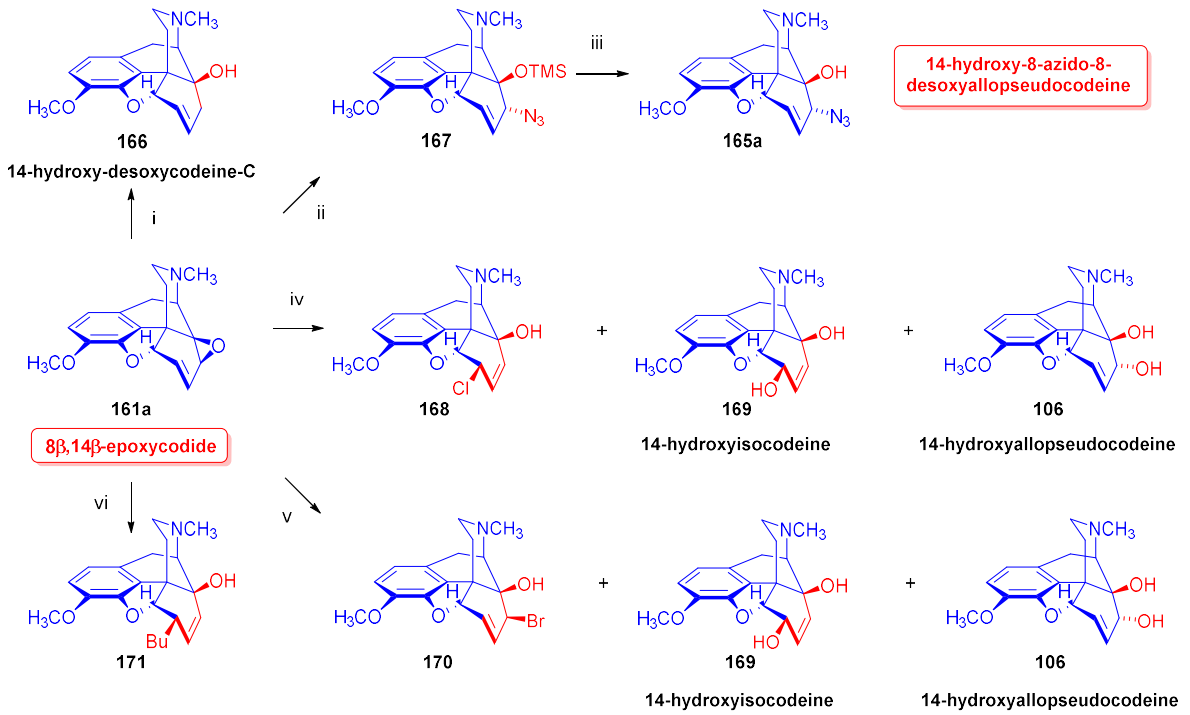

Figure 45. Investigations of the reactions of 8β,14β-epoxycodide. *Reagents and conditions*: (i): 1 equiv. $LiAlH_4$, Et_2O, reflux, 30 min, 50 %; (ii): 3 equiv. trimethylsilyl azide, ZnI_2, CH_2Cl_2, reflux, 90 min, 60 %; (iii): 3 equiv. NaF, MeOH, reflux, 2 h, 67 %; (iv): LiCl, 10 % HCl, acetonitrile, reflux, 2.5 h, **168** (20 %), Σ (**169** + **106**) (12 %), recovered **161a** (22 %); (v): LiBr, 10 % HBr, acetonitrile, 100 °C, 2 h, **170** (31 %), Σ (**169** + **106**) (26 %), recovered **161a** (15 %); (vi): copper (I) iodide, BuLi, diethyl ether, hexane, N_2 atmosphere, - 78 °C, 21 %.

Due to the difficulties encountered during the separation of the solvolysis products, the 6β,14β-dihydroxy (**169**, iso)/8α,14β-dihydroxy (**106**, allopseudo) product ratio was determined by proton NMR spectrum analysis of the mixture, which gave a ratio of 5:6. The analogous reaction of 8β,14β-epoxycodide (**161a**) with $Br^{\ominus}$ ions in aqueous-hydrobromic acid – acetonitrile mixture (LiBr, 10 % HBr – CH_3CN) resulted in 8-bromo-8-desoxy-14-hydroxy-pseudocodeine (**170**, 14-hydroxy-β-bromocodide, 31 %) as the main product, and a mixture of by-products **169**/**106** (ratio: 3:4) [171]. The formation of the main products with different structures, i.e., 6β-chloro (**168**) and 8β-bromo (**170**), is explicable by steric-, electronic- and stability- factors, and is in agreement with the earlier results of Bognár *et al.* [172] concerning the nucleophilic substitutions of 14-hydroxydihydrocodeine tosylate (**73a**). The reaction of **73a** with $F^{\ominus}$ or $Cl^{\ominus}$ nucleophiles gave the corresponding 6-substituted-6-desoxy-14-hydroxydihydroisocodeine derivatives, whereas using $Br^{\ominus}$ anions resulted in 8-bromo-8-desoxy-14-hydroxypseudocodeine (**170**) [172]. The treatment of 8β,14β-epoxycodide (**161a**) with the organocuprate reagent lithium dibutylcuprate ($LiCu(C_4H_9)_2$, prepared *in situ* from copper (I) iodide and butyllithium in diethyl ether -hexane at – 78 °C), resulted in the 6β-butyl derivative (**171**) in 21 % yield [171].

2.9.3. Azido Derivatives of 6,14-ethenomorphinans

Berényi *et al.* investigated the azidolysis of tosylesters (**174a–g**) derived from different in ring C bridged morphinans (Bentley compounds, or 6,14-ethenomorphinans [173–176], **173a–g**, Figure 46) [177,178]. The morphinandienes **4**, **105**, and **118a** were transformed with methyl vinyl ketone or acrolein in a diastereoselective Diels-Alder reaction to the corresponding in ring-C bridged 7-acetyl- (**172a**,**c**,**d**) or 7-formyl- (**172b**) adducts. Next, the keto group (**172a–d**) was reduced with $NaBH_4$ in methanol to a mixture of diastereomeric secondary alcohols (**173a**, **b**, **d–g**) [177] or to the appropriate primary alcohol (**173c**) [178], which were tosylated (TosCl, pyridine, room temperature, 1–6 days) to yield **174a–g**. After separation by column chromatography of the diasteromerically pure tosylates

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(**174a–b**, **174d–g**), they were subjected to azidolysis (NaN_3, 100 °C, 1.5 h). A novel class of morphinans containing a 4-azatetracyclo-[4.4.0.0^{2,4}.0^{3,8}]decane ring system (**176a–g**) was prepared by heating the azides (**175a–g**) in *N*,*N*-dimethylformamide at 100 °C for 24 h.

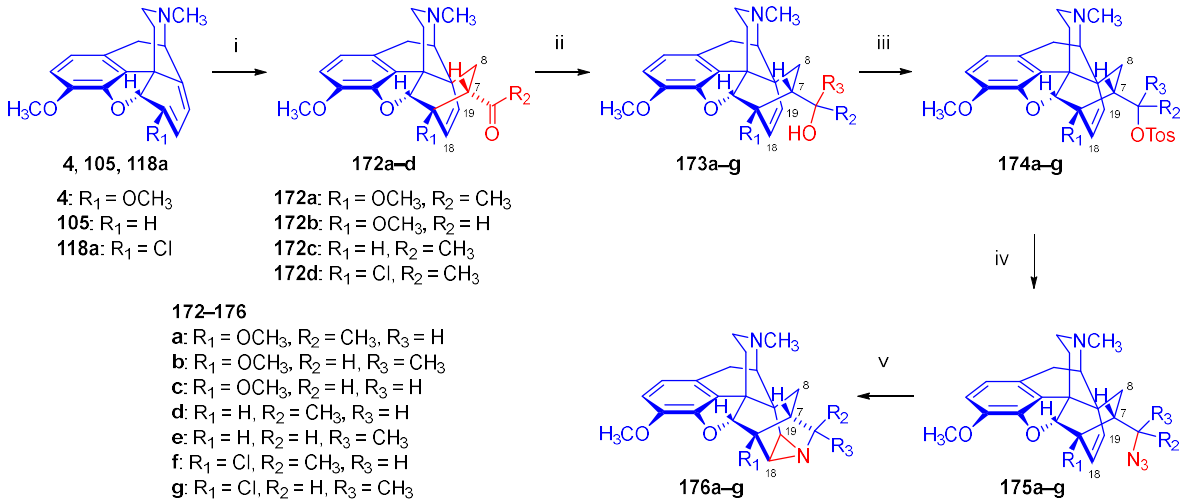

Figure 46. Synthesis of morphinans with an azatetracyclodecane ring system. *Reagents and conditions*: (i): methyl vinyl ketone or acrolein, toluene, reflux, 24 h; (ii): 4.5 equiv. $NaBH_4$, MeOH, 0 °C, 30 min; (iii): 1.5 equiv. TosCl, pyridine room temperature, 1 day for **173d**,**e** and 6 days for **173f**,**g**; (iv): 5 equiv. NaN_3, *N*,*N*-dimethylformamide, H_2O, 100 °C, 1.5 h; (iv and v): 5 equiv. NaN_3, *N*,*N*-dimethylformamide, H_2O, 100 °C, 24 h.

When using longer reaction times for the azidolysis of the tosylates (**174a–g**), substitution and subsequent cyclization by intramolecular addition of the azide to the $\Delta^{18,19}$-double bond resulted directly in the aziridine derivatives **176a–g**. The authors found a significant difference in the course of the reactions for 20*S*- and 20*R*- tosylesters. After azidolysis of the 20*S*-tosylates (**174**), 7-ethylidene derivatives were isolated as major products resulting from an elimination reaction. However, the azidolysis of the 20*R*-tosylates (**174**) under identical conditions lead to the formation the 20*S*-azides (**175**), by inversion of the configuration. Despite detection of the products by TLC, their isolation and characterization was possible in only a few cases (e.g. 20*S*-**175g**, and **175c**) due to their generally low stability. When tosyl ester (**174c**) of the primary alcohol (**173c**) was subjected to azidolysis (5 equiv., NaN_3, DMF, H_2O, 100 °C, 1.5 h), the 7-azidomethyl derivative (**175c**) and the aziridine (**176c**) were formed. After separation by column chromatography, the product ratio **175c**/**176c** was 9:1. The azide **175c** was converted to the aziridine (**176c**, 59 %) by heating in *N*,*N*-dimethylformamide at 100 ° for 24 h. The structure of **175c** was also proven by chemical reaction; its reduction (hydrazine hydrate, Raney-nickel, EtOH, reflux, 30 min) resulted in the primary amine 7α-aminomethyl derivative in 69 % yield. In 1992, Batta *et al.* [179] reported the detailed NMR analysis of the 20*R*- and 20*S* diastereomeric alcohols (**173a–b**, **173d–g**), their tosylates (**174a–b**, **174d–g**), and also the 4-azatetracyclo[4.4.0^{2,4}.0^{3,8}] derivatives (**176a–f**). The authors [177–179] further discussed the differing behaviours of the 20*S* and 20*R* diastereoisomers, explaining the greater predisposition of the 20*S*-tosylates for elimination by the more advantageous, nearly antiperiplanar position of the 20-OTos group to the 7β-H.

The primary and secondary azides (**175a–g**, Figure 46) developed by Berényi *et al.* [177–179] proved to be unstable due to the intramolecular addition of the azido group into the $\Delta^{18,19}$-double bond. They degraded into azatetracyclodecane derivatives (**176a–g**, Figure 46) with nitrogen loss *via* heating or spontaneously at room temperature, and were thus unsuitable as ligands for pharmacological investigations. Therefore, the Makleit research group extended their investigations to the 20-tertiary azides of 18,19-dihydro-6,14-ethenomorphinans. In 1993, Sepsi *et al.* [180] described the synthesis of a series of tertiary azides with morphinan scaffold.

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The first strategy, which was synthesis of the target azides *via* nucleophilic substitution of aryl or alkylsulfonate esters, failed due to conversion of the tertiary alcohols (e.g., 20-methylthevinol, **173a**, Figure 47) into the corresponding 20-*O*-tosylate or mesylate (e.g., **177**). However, the use of hydrazoic acid and BF_3-etherate [181] turned out to be practicable. 20-Methylthevinol (**173a**, Figure 47) thereby converted into the tertiary azide (**178**) in 62 % yield, and its reduction to the corresponding tertiary amine (**179**) was successfully performed (83 %) with hydrazine hydrate/Raney-Ni in ethanol (reflux, 30 min). As expected, the thermal treatment of **178** (DMF, 100 °C, 48 h) gave the aziridine (**180**) as a result of the addition of the azido group into the 6,14-etheno bridge.

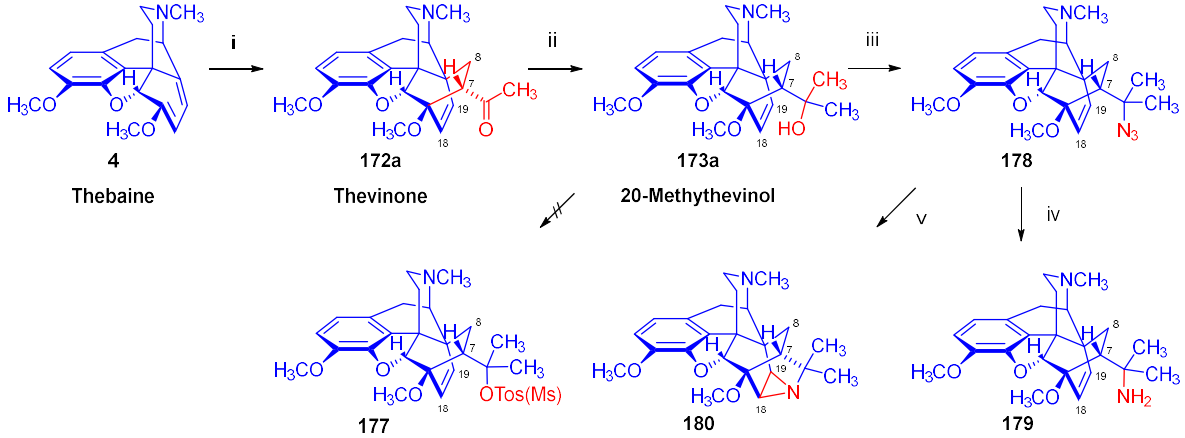

Figure 47. Synthesis of azides in the 6,14-ethenomorphinan series. *Reagents and conditions*: (i): methyl vinyl ketone, reflux, 1 h; (ii): MeMgI, toluene, THF, reflux, 1 h; (iii): 2 equiv. hydrazoic acid, 2 equiv. BF_3-etherate, room temperature, 4 h, 62 %; (iv): 98 % hydrazine hydrate, Raney-Ni, EtOH, reflux, 30 min, 83 %; (v): Δ (-N_2), DMF, 100 °C, 40 h, 64 %.

To avoid the aforementioned ring closure reactions, representatives of the 6,14-ethano series, tertiary alcohols (**182a–e**, Figure 48) prepared from dihydrothevinone (**181**) in Grignard reactions (RMgX, R = Me, Et, *n*Pr, Ph, *t*Bu), were chosen as starting materials for the synthesis of the target tertiary azides (**183a–e**). The replacement of the 20-OH tertiary hydroxyl group of **182b–d** (20*R*-**182b**, 20*R*-**182c**, 20*S*-**182d**, and 20*S*-**182e**) for an azido group with hydrazoic acid and boron trifluoride etherate resulted in a diastereomeric mixture of 20*R* and 20*S* of azides (**183b–d**, 35–44 %) as major products, but also gave elimination products (**184b–d**, 5–13 %). The diastereomeric azides ratios were determined from the ^{1}H-NMR spectra based on the integrals of characteristic signals (20-CH_3, 6-OCH_3, 5β-H): **183b** (4:1), **183c** (3:1), and **183d** (1:1).

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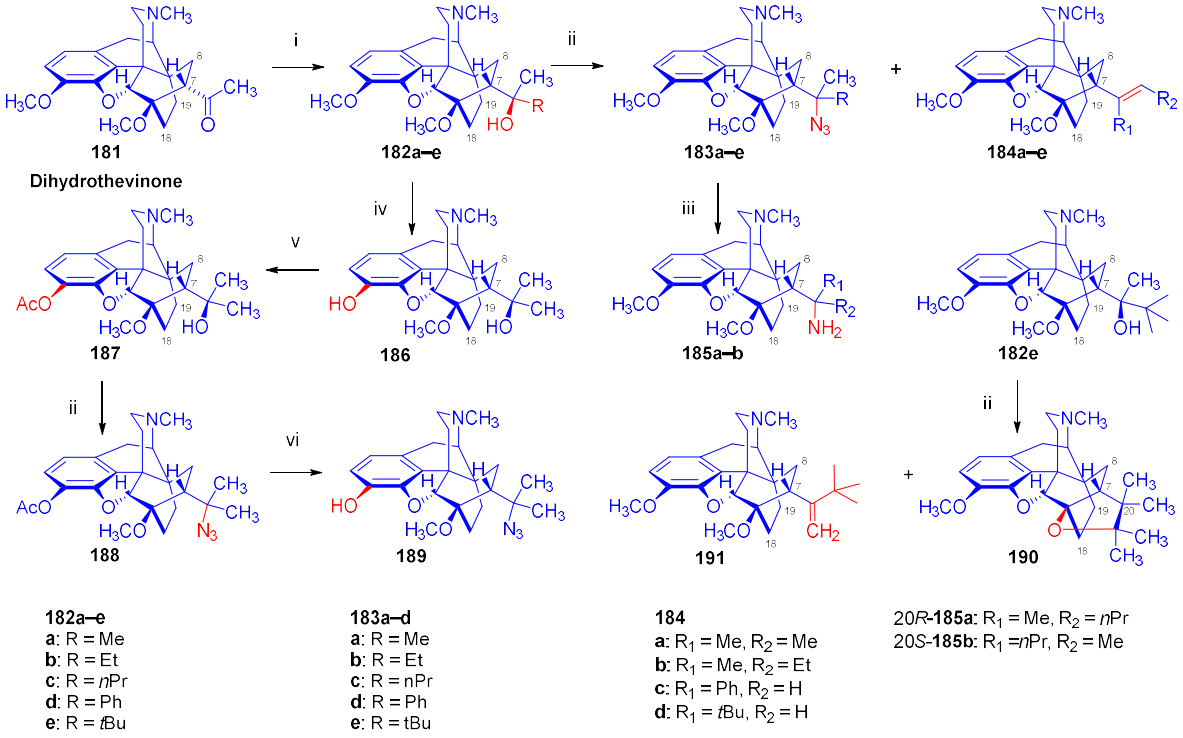

Figure 48. Synthesis azides of 18,19-dihydro derivatives in the 6,14-ethenomorphinan series. *Reagents and conditions*: (i): Grignard reagents (RMgX: MeMgI, EtMgBr, *n*PrMgBr, PhMgBr, *t*BuMgCl), Et_2O or THF-toluene mixtures, reflux, 1–2 h; (ii): 2 equiv. HN_3, 2 equiv. BF_3-etherate, toluene, room temperature, 4 h, **183b–d**: 35–44 % and **184b–d**: 5–13 %; (iii): from **183c**, 8 equiv. hydrazine hydrate, Raney-Ni, ethanol, reflux, 30 min, 20*S*-**185a**: 58 %, 20*R*-**185b**: 18 %; (iv): KOH, diethylene glycol, 210 °C, 90 min; (v): based on Welsh's [88] method: Ac_2O, $NaHCO_3$, H_2O; (vi): 3 equiv. hydroxylamine hydrochloride, 50 °C, 30 min, 79 %.

Efforts to split up the diastereomeric azides (**183b–d**) were unsuccessful, but there was separation of the diastereomeric mixture of amines (**185a–b**), prepared from 20*R*-propyldihyrothevinol (**183c**) by reduction with hydrazine hydrate and Raney-Ni in boiling ethanol. The conversion of 20-*tert*-butyldihydrothevinol (**182e**) to the corresponding tertiary azide (**183e**) failed. Instead of **183e**, the furanocodide derivative (**190**) was isolated as the major product and the anhydro/olefin compound (**191**) as minor by-product. Furanocodides are known acid-catalyzed rearrangement products of thevinols [182,183]. For preparation of the tertiary-azide with orvinol structure (**189**), 20-methydihydrothevinol (**182a**) was 3-*O*-demethylated to 20-methyldihydroorvinol (**186**). The phenolic hydroxyl group of **186** was protected by application of the Welsh method [88]. 3-*O*-Acetyl-dihydroorvinol (**187**) was reacted with hydrazoic acid and $BF_3 \cdot Et_2O$ to give the azide **188** (60 %), which was deprotected with hydroxylamine hydrochloride to yield **189** (79 %). The *tert*-azido-orvinol derivative (**189**) [180] as lead compound was tested for OR agonist properties in the GPI *in vitro* and the mouse hot plate tests (HP) *in vivo*, proving to be an μOR agonist. In the mouse HP tests, **189** and **186** showed 10–18 times higher potency relative to morphine (ED_{50} [mg/kg] = 0.59 (**189**), 0.32 (**186**), 6.0 (**1a**). However, in comparison with the native 20-methyldihydroorvinol (**186**), the azido compound **189** did not show higher relative activity [180].

2.9.4. 6-Azido-6-demethoxythebaine

In 1997, Csutorás *et al.* [184] reported the synthesis of 6-azido-6-demethoxythebaine (**193**, Figure 49) in six consecutive transformations starting from thebaine (**4**). 6-Azido-6-desoxy-14-hydroxyisocodeine (**87**) was prepared from **4** as described earlier by Makleit *et al.* (**4** → **132** → **66** → **70a–b** → **87**, Figure 49) [106]. The sulfonate esters (**70a–b**) were converted to 6-azido-6-desoxy-14-hydroxyisocodeine (**87**) by treatment with NaN_3 in DMF/H_2O at 100 °C for 4 h. A more prolonged reaction time under the same conditions gave 8-azido-8-desoxy-14-hydroxypseudocodeine (**85**)

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through rearrangement. Otherwise, the reaction of **87** with two equivalent PBr_3 resulted in 7β-bromo-6β-azidodesoxyneopine (**192**) in 77 % yield. In that product (**192**), the trans-diaxial orientation of the 7β-bromo substituent relative to the 6α-hydrogen favours hydrogen bromide elimination, which is readily obtained by treatment with potassium *tert*-butoxide in ethanol (room temperature, 30 min, 75 %). The structure of 6-azido-6-demethoxythebaine (**193**) was confirmed by IR and NMR spectra and by chemical reaction. It was stable at – 20 °C, but decomposed within a few days at room temperature due to its vinylazide structural element. In a search for derivatives showing higher stability, the reaction of the azidodiene (**193**) with carbon disulphide in the presence of triphenylphosphine (reflux, 2 h) gave 6-isothiocyanato-6-demethoxythebaine (**194**) in 51 % yield. The hetero Diels-Alder reaction of 6-azido-6,8-morphinandiene (**193**) with 4-phenyl-4*H*-1,2,4-triazoline-3,5-dione (PTAD) at 0 °C readily gave a stable cycloadduct (**195**) in excellent yield.

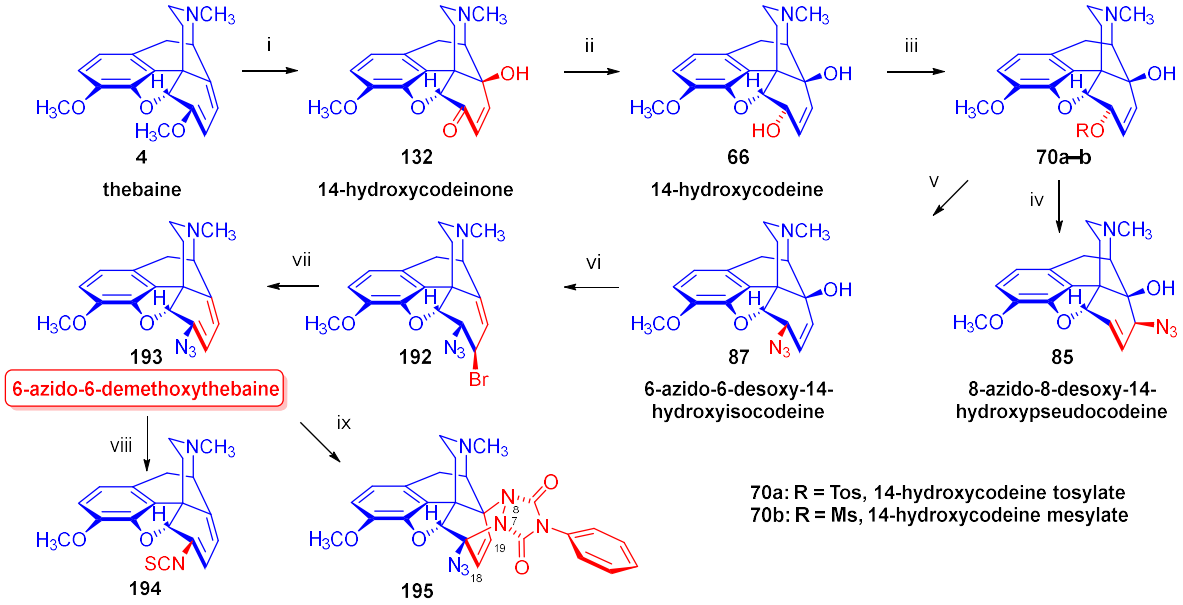

Figure 49. Synthesis of 6-azido-6-demethoxythebaine. *Reagents and conditions*: (i): formic aid, H_2O_2, 40 °C, 2 h; (ii): $NaBH_4$, H_2O, dioxane; (iii): A. TosCl, pyridine, 0 °C, [124], or MsCl, pyridine, 66 % [106]; (iv): 1.25 equiv. NaN_3, DMF, H_2O, 100 °C, 4 h, 38 % [106]; (v): 1.25 equiv. NaN_3, DMF, H_2O, 100 °C, 8 h, 46 % [106]; (vi): 2 equiv. phosphorus tribromide, $CHCl_3$, 50 °C, 2 h, 77 %; (vii): 3.5 equiv. potassium *tert*-butoxide, EtOH, room temperature, 0.5 h, 75 %; (viii): carbon disulfide, triphenylphosphine, reflux, 2 h, 51 %; (ix): 1.2 equiv. 4-phenyl-4*H*-1,2,4-triazoline-3,5-dione (PTAD), acetone, room temperature, 20 min, 71 %.

2.10. Fluorinated Morphinans

Halogenated derivatives of morphine alkaloids have been the subject of continuous interest in organic chemistry [16,18]. Brominated morphinans (e.g. 1-bromo and 1,7-dibromo derivatives of dihydrothebainone and β-dihydrothebainone, 1-bromo-nordihydrothebainone) were valuable intermediates for the first morphine total synthesis accomplished by Gates and Tschudi [185], and were later successfully used for the preparation of B/C-trans-fused 1-bromodihydrocodeinone [186] and for the synthesis of codeine from dihydrothebainone [187,188]. Iodinated and brominated morphinans are precursors for the synthesis of tritiated radioligands [189,190], which are valuable research tools for OR pharmacological investigations. The effects of fluorine incorporation in biologically active derivatives has been thoroughly investigated [191], and are the subject of a very recent comprehensive survey of fluorine-containing morphinans by Sandulenko *et al.* [192].

2.10.1. Ring-C Fluorinated Morphinans

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The morphine alkaloid research group at the University of Debrecen has paid particular attention to the synthesis of in ring-C halogenated morphinan derivatives [18,193]. 6-Fluoro-6-deoxyisocodeine (**59a**, Figure 50) was obtained *via* the S_N2 reaction of codeine tosylate (**63a**) with tetrabutylammonium-fluoride (TBAF) [100] in 48 % yield, and separately from pseudocodeine tosylate (**97**) [110] in an S_N1' reaction with the same nucleophile in acetonitrile, albeit in poor yield (10 %). In 1972, Bognár *et al.* [172] described the synthesis of 6-fluoro-6-deoxy-14-hydroxyisocodeine (**80**) from 14-hydroxycodeine tosylate (**70a**) with TBAF. In an extension of earlier studies of the group [104,106], Somogyi *et al.* [194] investigated the S_N2 type reactions of dihydrocodeine mesylate (**71b**) with halide anions ($F^{\ominus}$, $Cl^{\ominus}$, $Br^{\ominus}$, $I^{\ominus}$).

6-Fluoro-6-deoxydihydroisocodeine (**196a**, 6-fluorodihydrocodide, α-fluorodihydrocodide) was prepared from dihydrocodeine mesylate (**71b**) [194] with tetrabutylammonium fluoride in acetonitrile in low yield. 6-Chloro-6-deoxydihydroisocodeine (**196b**, 6-chlorodihydrocodide, α-chlorodihydrocodide) was also prepared by heating of **71b** for 1 h with ten equiv. of lithium chloride in 75 % yield. When **71b** was treated with LiBr in DMF at 100 °C for 43 h, 6-bromo-6-deoxydihydroisocodeine (**196c**, 6-bromodihydrocodide, α-bromodihydrocodide) was isolated in 26 % yield. Performing this latter reaction at higher temperatures (reflux for 4 h) desoxycodeine-C (**197**, Δ^7-desoxycodeine) was formed in 63 % yield. When treating of **71b** with 10 equiv. of sodium iodide the corresponding 6-iodo derivative could not be isolated, instead **197** was obtained in 29 % yield.

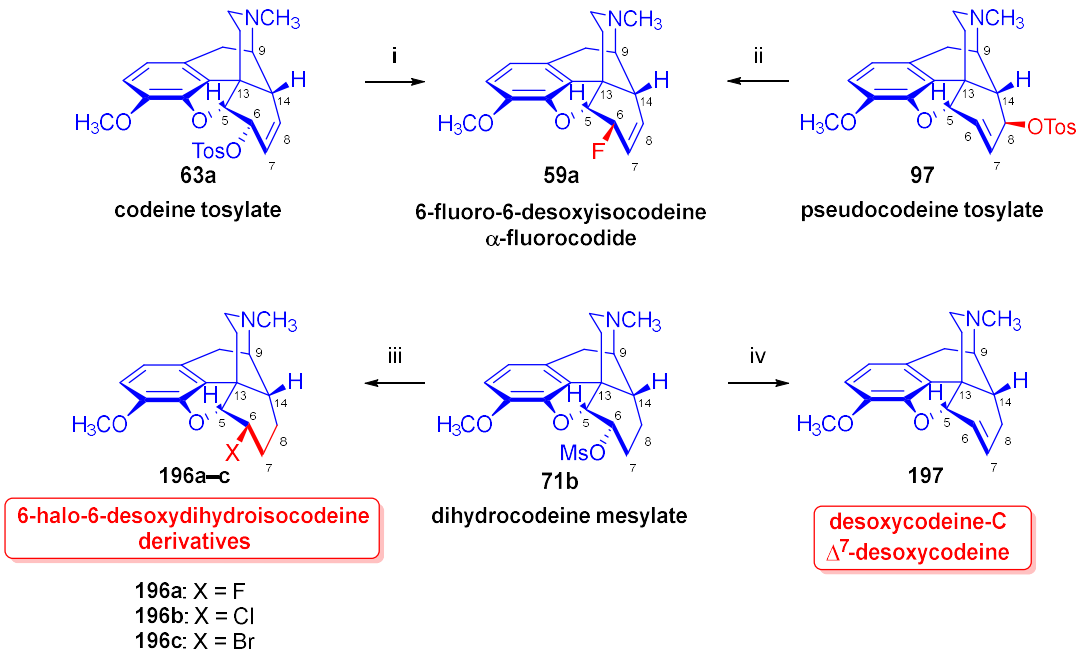

Figure 50. Synthesis of 6-halogene substituted morphinans. *Reagents and conditions*: (i): 1.6 equiv. Bu_4NF, acetonitrile, reflux, 4 h, 48 % [100]; 5.4 equiv. Bu_4NF, CH_3CN, reflux, 29 h, 10 % [110]; (iii) [194]: **A** (Nu = $F^{\ominus}$): 13 equiv. Bu_4NF, acetonitrile, reflux, 12 h, **196a**, 8 %; **B** (Nu = $Cl^{\ominus}$): 10 equiv. LiCl, DMF, reflux, 1 h, **196b**, 75 %; **C** (Nu = $Br^{\ominus}$): 4 equiv. LiBr, 100 °C, 43 h, **196c**, 26 %; (iv) [194]: **A** (Nu = $Br^{\ominus}$): 8 equiv. LiBr, DMF, reflux, 4 h, **197**, 63 %; **B** (Nu = $I^{\ominus}$): 10 equiv. NaI, DMF, reflux, 7 h, **197**, 29 %.

In 1980, Boswell and Henderson [195] reported the fluorination of morphinan-6-ones (e.g., dihydrocodeinone (**49**), and 14-hydroxydihydrocodeinone) with diethylaminosulfur trifluoride (DAST). 6,6-Difluoro compounds were isolated as main products, and 6-monofluoro-$\Delta^{6,7}$ unsaturated derivatives as by-products. In 1984, Ganti [196] synthesized numerous 14-fluoro-analogues of oxymorphone (**198a**, Figure 51), naltrexone (**198b**), and nalbuphine (**198c**) from 6-*O*-protected 14-hydroxy-dihydromorphinones with DAST.

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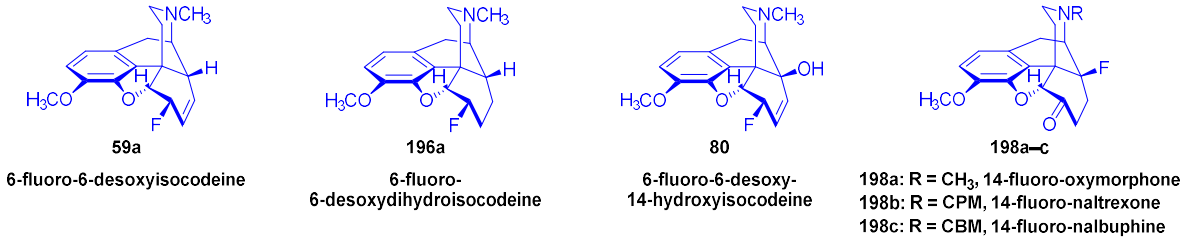

Figure 51. In ring-C fluorinated morphinan derivatives.

In 1984, the research group of Kenner C. Rice [197–202] developed 6β-fluoro-oxymorphol (**204a**, foxy), and 6β-fluoro-naltrexol (**204c**, cyclofoxy) analogues (Figure 52). They performed the synthesis of 6-fluoro-6-desoxy-14-hydroxydihydroisomorphine derivatives (**204a–d**) in two steps from the corresponding 3-*O*-acetyl-6-trifluromethansulfonyloxy-14-hydroxydihydromorphines (**203a–d**).

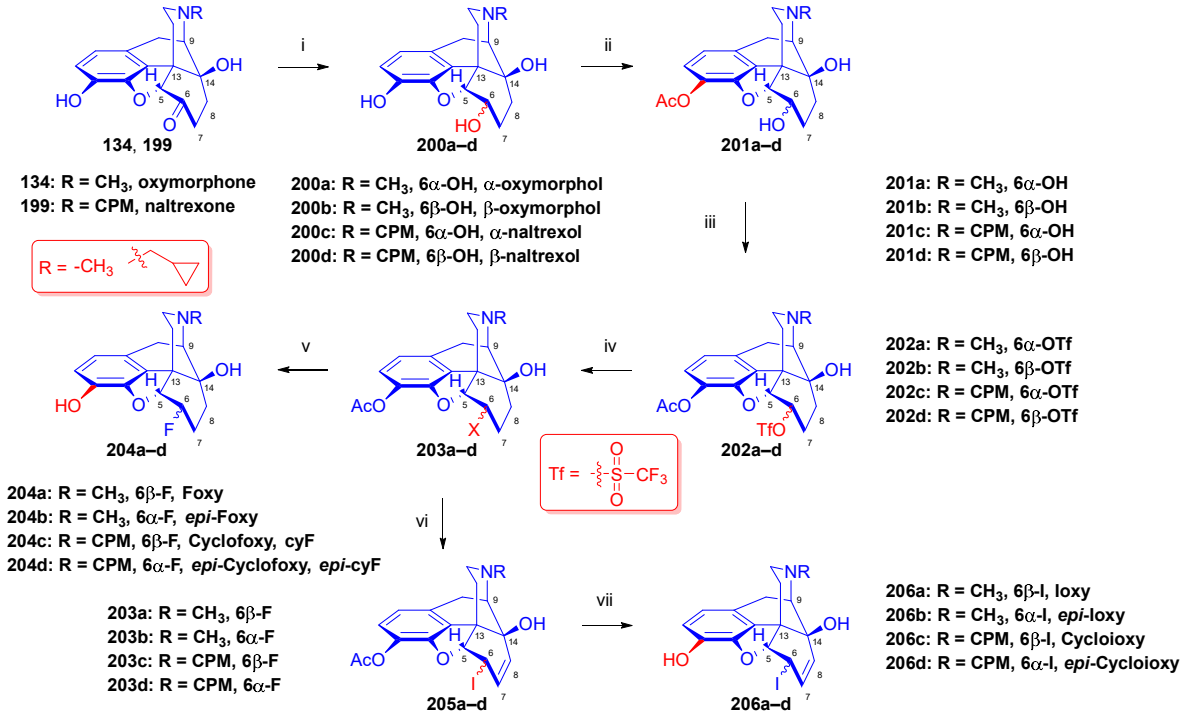

Figure 52. Synthesis of foxy, cyclofoxy and their iodinated derivatives. *Reagents and conditions*: (i): 0.5 equiv. $NaBH_4$, THF, 0 °C, 1 h, 37 %; (ii): Ac_2O, $NaHCO_3$, H_2O, quant.; (iii): 2 equiv. Tf_2O, $CHCl_3$, pyridine, 20 °C, 20 min, 72 %; (iv): 7.2 equiv. KF, 18-crown-6 ether, acetonitrile, reflux, 2 min, 62 %.

For instance, the Rice group prepared cyclofoxy (**204c**, cyF) by introducing the fluorine substituent was in the 6β-position *via* an S_N2 reaction by displacement of the 6α-*O*Tf leaving group of **205c** with fluoride ions (potassium fluoride) in the presence of 18-crown-6 in acetonitrile. They then removed the acetyl-protecting group by treatment the fluorinated intermediate (**203c**) with NH_4OH in methanol. Labelled foxy and cyclofoxy derivatives see in section 2.12.

Woudenberg and Maat prepared chlorine-containing etorphine analogues from the 7-chloro-morphinan-6,8-dienes (7-chloro-6-demethoxythebaine and 7-chloro-5β-methyl-6-demethoxythebaine) in multistep-syntheses [203], and subsequently evaluated their pharmacological characteristics, showing generally high affinity for μOR and variable selectivity for κOR subtypes [204]. The Makleit group investigated Diels-Alder (DA) cycloaddition of the highly reactive dienophile 4-phenyl-4*H*-1,2,4-triazoline-3,5-dione (PTAD) to 7-halomorphinandienes (Cl, Br) [205]. In 1990, studying the DA reaction of thebaine with 2-fluoroacrolein, Jeong *et al.* observed the formation of a diastereomeric mixture of 7-fluoro-7-formyl-DA adducts (**207a–b**, 7α/7β, Figure 53)

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and a hetero-DA adduct [206]. The same research group reported the reactions of thebaine with trifluoromethyl substituted acetylenic dienophiles (trifluoropropyne, hexafluoro-2-butyne) and with perfluoroaldehydes [207]. Hetero Diels-Alder (HDA) reaction of thebaine and 5-methyl-thebaine with trifluoroacetaldehyde resulted in 14-(trifluoro-2-hydroxy-ethyl)-5-methylcodeinone derivatives [208].

In 1992, Berényi and colleagues elaborated a new methodology for the synthesis of 6-fluoro-6-demethoxythebaine derivatives (**208a–c**, N^{17}-substituent: CH_3, H, *n*-propyl) from 14-hydroxy-6-fluoro-6-deoxyisocodeine [209]. They used a microwave-promoted synthesis for acid-catalyzed rearrangement of morphinans and fluoromorphinans (**208a–c**) [210] to yield the corresponding aporphine derivatives. Subsequently, they reported the cycloaddition reaction of 6-fluoro-6-demethoxythebaine with methyl-vinyl ketone and the synthesis and biological evaluation of 6-fluoro-6-demethoxy-20-methylorvinol (**209**) [211,212]. In 2013, Magnus performed the synthesis of 7β-fluorodihydrocodeine (**210**, Figure 53) [213]. The six-step transformation from codeine (**2a**) involved the fluorination of a 6,7-epoxyde intermediate with a hydrogen-fluoride-pyridine complex.

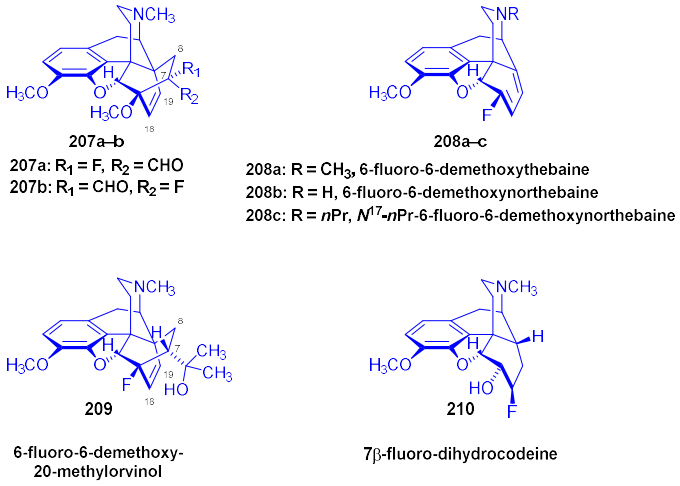

Figure 53. Structures of fluorinated morphinans.

2-Haloaporphines are dopamine agonists that can be synthesized from halomorphinans by acid-catalyzed rearrangement. 2-Fluoro-*N*-*n*-propylnorapomorphine (2F-NPA) [209,214] is the most important member of this class, with extremely high affinity (K_i = 12 pM) and D_2 subtype selectivity (D_2/D_1 > 50,000) [215]. In 1994, Hosztafi and Makleit [216] reported the synthesis of numerous C-1 halogenated (1-chloro and 1-bromo) derivatives of codeine, morphine and their 7,8 dihydro analogues, and subsequently the rearrangement of 1-halogenated-codeines to the corresponding in ring-D substituted 8-halogen-apomorphines [217]. The synthesis of [8,9-^{3}H]apomorphine was accomplished by bromination of apomorphine hydrochloride in trifluoroacetic acid (TFA) with molecular bromine [218] to 8,9-dibromo-apomorphine and following tritium dehalogenation ($^3H_2$, 10% Pd/C, ethanol). Filer [219] presented the radiosynthesis of 8,9-di-[^{18}F]fluoroapomorphine by fluorodestannylation of 8,9-di-(trimethylstannyl)-apomorphine. 8,9-Dibromoapomorphine and/or 8,9-diiodoapomorphine were applied as intermediates for the preparation of the labelling tin precursor.

2.10.2. 1-Fluoro-Substituted Morphinans

In 1974, Lousberg and Weiss [220] reported the first synthesis of 1-fluorocodeine (**216a**) in 1974. Subsequently, Makleit and Dubina [221] published an improved method for its preparation through pyrolysis of diazonium fluoroborate (**215a**) (Balz-Schiemann reaction). 1-Fluorodihydrocodeine (**216b**) was prepared from 1-fluorocodeine (**216a**) by heterogenous catalytic reduction [221].

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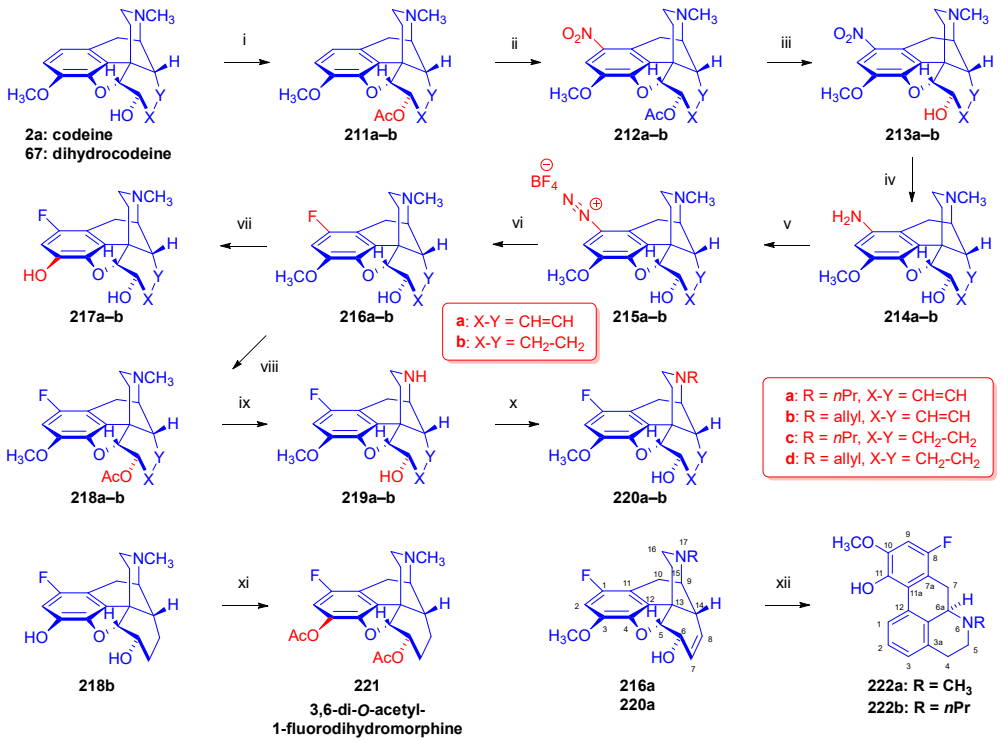

Figure 54. Synthesis of 1-fluoro-substituted codeine derivatives. *Reagents and conditions*: (i): Ac_2O, reflux; (ii): 65 % nitric acid, glacial acetic acid, **A**. 5 °C, 1 h, **B**. room temperature, 1 h; (iii): 10 % NaOH, EtOH, reflux, 1 h; (iv): $SnCl_2$, HCl, room temperature, 2 h; (v): 48 % aqueous HBF_4, EtOH, 2 M $NaNO_2$, -15 °C 10 min; (vi): MgO, 170 °C, 1 h, in vacuo; (vii): BBr_3, $CHCl_3$, room temperature, 1 h; (viii): Ac_2O, reflux, 4 h; (ix): **A**. ACE-Cl, $NaHCO_3$, 1,2-dichloroethane, reflux, 8 h; **B**. MeOH, 50 °C, 1 h; (x): n-propyl bromide or allyl bromide, $NaHCO_3$, DMF, 95 °C, 18 h; (xi): Ac_2O, 100 °C, 1 h; (xii): methane sulfonic acid, 95 °C, 45 min.

In 2016, Hosztafi and Marton [222] synthesized 1-fluoro-substituted codeine derivatives (**220a–b**, N^{17}-allyl, N^{17}-*n*-propyl, Figure 54) and their 7,8-dihydro derivatives (**220c–d**). They first prepared 1-fluoromorphine (**217a**) and 1-fluorodihydromorphine (**217b**) from their respective codeine precursors *via* 3-*O*-demethylation with boron tribromide in chloroform. 1-Fluorocodeine (**216a**) and N^{17}-*n*-propyl-1-fluorocodeine (**220a**) were subjected to acid-catalyzed rearrangement using methansulfonic acid (100 C°, 45 min) to give respectively 8-fluoroapocodeine (**222a**) and N^6-propyl-8-fluoroapocodeine (**222b**), respectively with low yields (20–24 %). 3,6-di-*O*-Acetyl-1-fluorodihydromorphine (**221**) was synthesized by acetylation of 1-fluorodihydromorphine (**218b**) with acetic anhydride (100 °C, 1 h, 55 %). In 2018, Hosztafi *et al.* reported the synthesis of 1-iodo-substituted codeine and dihydrocodeine derivatives [223].

2.10.3. Fluorinated 6,14-ethenomorphinans

In the past decade, the Moiseev research group expended considerable efforts towards the synthesis of fluorinated 6,14-ethenomorphinan derivatives [192]. In 2016, they reported the synthesis of the key starting material for their investigations of the 7α-trifluoroacetyl analogue of thevinone (**172a**): 21,21,21-trifluorothevinone (**224**, Figure 55), starting with thebaine (**4**) [224]. Due to the low stability of the dienophile trifluoromethyl vinyl ketone, the direct conversion of **4** to **224** in a Diels-Alder reaction failed. This led them to adopt a three-step procedure in which thebaine was first converted in a [4+2] cycloaddition reaction with acrolein to the 7α-formyl cycloadduct (**172b**, thevinal, Figure 55). This was reacted with the nucleophilic trifluoromethylating Ruppert-Prakash reagent ($TMSCF_3$) to yield the diastereomeric mixture of the secondary alcohols 20*R*- and 20*S*-**223**, with generation of trifluoromethyl anion ($CF_3^{\ominus}$) in situ from $TMSCF_3$ in the presence of tetrabutylammonium fluoride (TBAF). The mixture of the epimeric alcohols (**223**) was transformed to the desired 21,21,21-trifluorothevinone (**224**) by Swern oxidation. Subsequently Zelentsova *et al.*

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[225] prepared 21,21-difluorothevinone (**225**) and 21-fluorothevinone (**226**) *via* defluorination of 21,21,21-trifluorothevinone (**224**) with magnesium and trimethylsilyl chloride and following acidic hydrolysis of the TMS intermediate. Grignard reaction of **224** with phenylmagnesium bromide gave a mixture of fluorinated 20*R*- and 20*S*-phenylthevinols (**227**) [224,226,227].

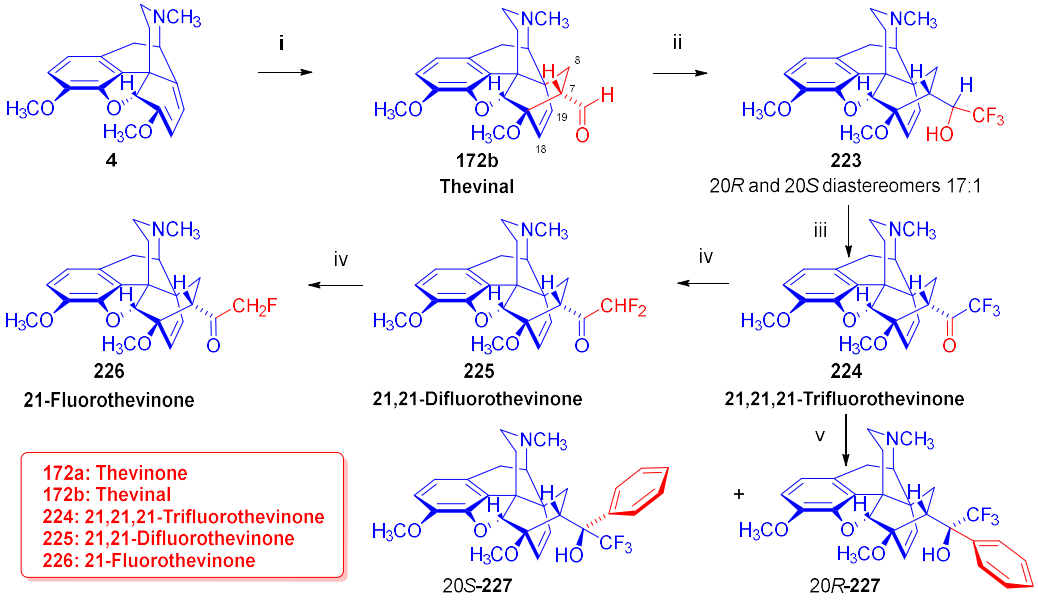

Figure 55. Synthesis of fluorinated 6,14-ethenomorphinan derivatives. *Reagents and conditions*: (i): acrolein, benzene, reflux; (ii): **A**. Me_3SiCF_3, TBAF, THF, **B**. HCl, H_2O; (iii): **A**. oxalyl chloride, DMSO, CH_2Cl_2, - 70 °C, 90 min, **B**. Et_3N, 20 °C, 10 min; (iv): **A**. Mg, Me_3SiCl, -5 °C, 4 h, B. 15 % HCl, 1 h; (v): PhMgPr, THF, 20 °C, 24 h.

In 2023, Sandulenko *et al.* [228] synthesized numerous 20-methyltrifluoro-6-*O*-desmethylorvinols (**229**, **232**, **235**, Figure 56) starting from thevinone (**172a**) and N^{17}-allyl-dihydronorthevinone (**233**). Notable, structure-activity relationships are so far reported for only a few 6-*O*-desmethylorvinols [229]. The addition of Me_3SiCF_3 to thevinone (**172a**) resulted in 20*R*-**228**. Boiling the latter compound with 48 % hydrobromic acid for 30 min led to 20-trifluoromethyl-6-*O*-desmethyl-orvinol (**229**, 60 %) *via* an unusual simultaneous 3-*O*- and 6-*O*-demethylation. For preparation of 20-trifluoromethyl-6-*O*-desmethyl-cyprenorphine (**232**), 20*R*-**228** was *N*-demethylated with ethyl azodicarboxylate to 20-trifluoromethyl-northevinol (**230**). Next, the secondary amine was acylated with cyclopropanecarbonyl chloride, whereupon the resulting N^{17}-acyl compound reduced with lithium aluminium hydride to the N^{17}-cyclopropylmethyl derivative (**231**). *O*-Demethylation of **231** with boron tribromide in dichloromethane at – 78 °C gave **229** in 76 % yield. Analogously, N^{17}-allyl-dihydronothevione (**233**) [230] with Me_3SiCF_3 gave the 20*R*-**234**, which was *O*-demethylated to N^{17}-allyl-20-trifluormethyl-6-*O*-desmethyl-dihydronororvinol (**235**, 53 %). In general, thevinols with tertiary hydroxyl groups in position-20 are acid-sensitive compounds, thus prone to undergo by acid-catalyzed dehydration an enol ether hydrolysis and rearrangement to 14-alkenylcodeinones, anhydro-20-alkylthevinols, or to 5,14-bridged thebainones. The authors attributed the suitability of BBr_3 for *O*-demethylation of fluorinated thevinols to the presence of the EWG CF_3 group in the molecule [226]. The 20-CF_3 group can prevent the formation of a carbocation from the C-20 tertiary alcohols, and accordingly avoid the intramolecular rearrangements mentioned above. The target compounds (**229**, **232**, and **235**) administered s.c. were evaluated for analgesic activity in rodent tail-flick tests in comparison to morphine (**1a**). Their results showed that the introduction of fluorine substituent in position-20 of the orvinol scaffold did not abolish the analgesic properties; 20-trifluoromethyl-6-*O*-desmethyl-orvinol (**229**) showed analgesic activity comparable to that of morphine (**1a**). 20-Trifluoromethyl-6-*O*-desmethyl-cyprenorophine (**232**) with N^{17}-cyclopropylmethyl substituent proved to be a partial agonist with weak analgesic activity and N^{17}-allyl-20-trifluoromethyl-6-*O*-desmethyl-dihydronororvinol (**235**) displayed no analgesic activity.

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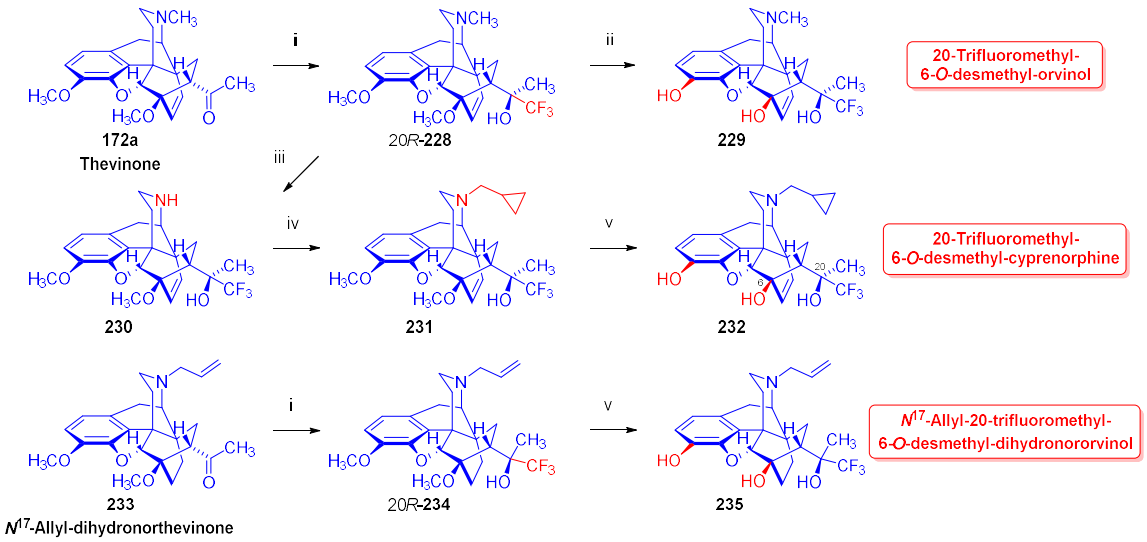

Figure 56. Synthesis of 21,21,21-trifluoro-6-*O*-desmethyl-orvinols. *Reagents and conditions*: (i): 2 equiv. $MeSiCF_3$, (ii): 48 % HBr, reflux, 30 min, 60 %; (iii): **A**. 1.5 equiv. DEAD, benzene, reflux, 24 h, **B**. 1.6 equiv. pyridinium hydrochloride, MeOH, 30 min, 31 %; (iv): **A**. 2.5 equiv. cyclopropanecarbonyl chloride, K_2CO_3, CH_2Cl_2, 20 °C, 6 h, **B**. 4.9 equiv. $LiAlH_4$, THF, reflux, 1 h, 65 %; (v): BBr_3, CH_2Cl_2, -78 °C, 76 %;.

In a subsequent study, the same research group placed their attention on the stereochemistry of the C-20 chiral centre of fluorine containing thevinols [231]. They thoroughly investigated the reactions of 21,21,21-trifluorothevinone (**224**, 7*α*-trifluoroacetyl, Figure 57) with various alkylmagnesium halides- (MeMgI, EtMgBr, *n*PrMgBr, iPrMgBr, *t*BuMgCl) and alkyllithium reagents (*t*BuLi, *i*PrLi) and also the addition of $TMSCF_3$ to thevinone (**172a**) and its analogues (7*α*-acetyl). These studies proved to be fundamental importance in elucidating the structure-activity relationships thevinols and orvinols with different C-20 configuration. The reaction of 7-acyl-type 6,14-ethenomorphinans with Grignard reagents results in complex product mixtures [50,232,233] due to various processes: Grignard addition, reduction of the carbonyl function, and base catalyzed-rearrangement. Sandulenko *et al.* [231] found that the reaction of thevinone (**172a**) and its 7*α*-acyl analogues (7*α*-propionyl, 7*α*-butanoyl) with trimethyl-(trifluoromethyl)-silane in the presence of CsF in THF at room temperature gave a mixture of the tertiary alcohols 20*R*-**236** and 20*S*-**236**, with predominance of the 20*R* isomer. The reaction of 21,21,21-trifluorothevinone (**224**) with two equivalents of methylmagnesium iodide in diethyl ether at room temperature resulted in a 100:67 mixture of the 20*R*-**236** and 20*S*-**236** epimeric tertiary alcohols. In the reaction of **224** with MeMgI, they also studied effects of addition of metal salts (MgX_2, X = Cl, I; $ZnCl_2$, MeOMgI, *t*BuOK) on the product ratio, based on the earlier approach of Zelentsova *et al.* using one-dimensional ^{19}F NMR spectra [227]. When **224** (Figure 57) was reacted with 1.2 equivalent of methyllithium in THF, there formed a mixture of isomeric tertiary alcohols 20*R*-**236** and 20*S*-**236** (R = Me) with predominance of the 20*S* epimer (e.g., at -78 °C, ratio 20*R*/20*S* = 25:100). Reacting 21,21,21-trifluorothevinone (**224**) with RMgX reagents other than MeMgI (R = Et, *n*Bu, *i*Pr, *t*Bu) gave predominant formation of the secondary alcohols **237**.

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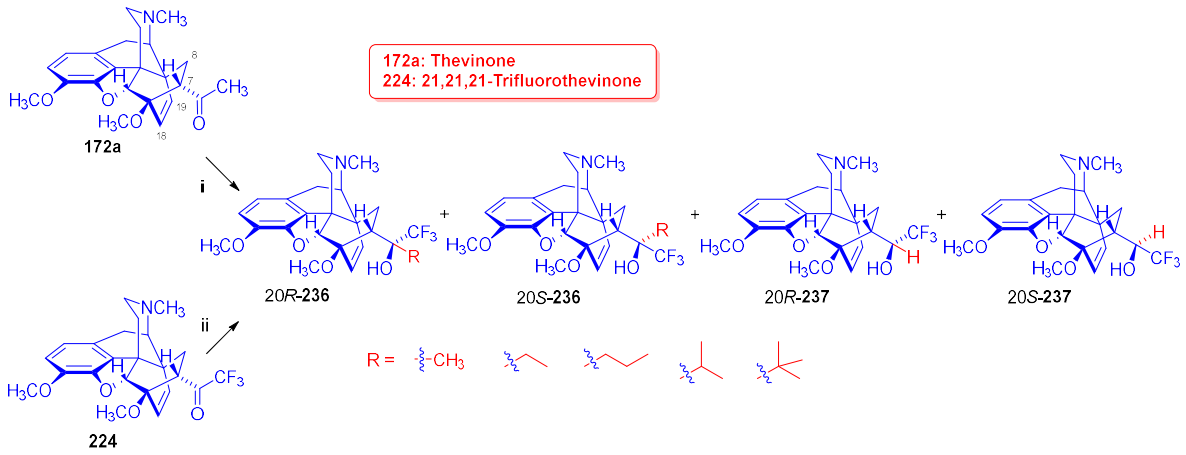

Figure 57. Reaction of thevinones with organometallic reagents. *Reagents and conditions*: (i): Me_3SiCF_3, HCl, H_2O; (ii): **A**. Grignard reagents (MeMgI, EtMgBr, *n*BuMgBr, *i*PrMgBr, *t*BuMgCl), Et_2O or THF, 20 °C, 15 min–18 h; **B**. RLi (MeLi, *i*PrLi, *t*BuLi), Et_2O or THF, -78 °C–20 °C, 15 min–60 h.

In 2023, Zelentsova *et al.* [225] reported the synthesis of 21,21-difluorothevinone (**225**) and 21-fluorothevinone (**226**) by defluorination of 21,21,21-trifluorothevinone (**224**, Figure 55 and Figure 57). Prominent members of the 6,14-ethenomorphinan series buprenorphine, diprenorphine and dihydroetorphine contain a saturated 6,14-ethano bridged C-ring [50,176,234]. Therefore, the next logical step was to try to synthesize the 18,19-dihydro analogues of **224**, **225** and **226**. The direct conversion of **224** to 18,19-dihydro-21,21,21-trifluorothevinone (**238**) by catalytic hydrogenation of the $\Delta^{19,19}$ double bond failed. Even harsh reaction conditions at 60 Bar hydrogen pressure (AcOH, 10 % Pd-C, 55–60 °C, 45 h) gave only 15 % conversion rate, with isolation of the rearranged product **239** in 11 % yield instead of the desired compound (**238**), which is the 7α-trifluoacetyl analogue of dihydrothevinone (**181**). As an alternative route for the synthesis of N^{17}-substituted-20-difluoromethyl-tevinols (**242a–c**), dihydrothevinone (**181**) was refluxed with the pronucleophile (difluoromethyl)trimethylsilane (Me_3SiCHF_2) in HMPA/THF in the presence of CsF to give 20*R*-**240** in 35 % yield. The secondary amine 20*R*-**241** was prepared from 20*R*-**240** by *N*-demethylation with diethyl azodicarboxylate (DEAD) in acetonitrile. Subsequently the target tertiary amines (**242a–c**) were prepared by functionalization with the corresponding alky- or acyl halides with yields in a range of 48–52 %. 20*R*-**242c** was also prepared directly from N^{17}-allyl-dihydronorthevinone (**233**, Figure 58) with Me_3SiCHF_2 in 23 % yield.

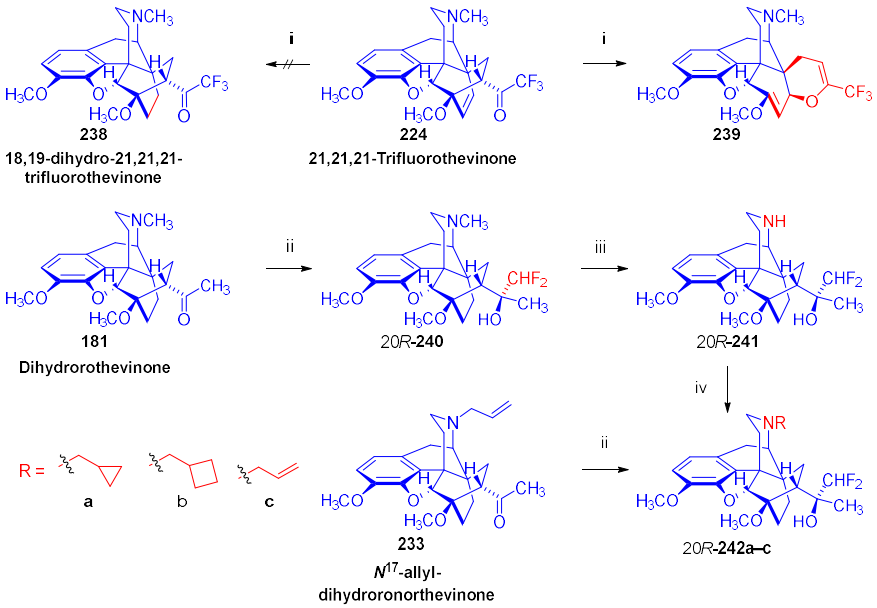

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Figure 58. Synthesis of 21,21-difluorothevinol derivatives. *Reagents and conditions*: (i): H_2, 10 % Pd-C, 60 Bar, 55–60 °C, 45 h, 11 %; (ii): **A**. Me_3SiCHF_2, CsF, HMPA, DMPU, THF, reflux. 10 h, **B**. 15 % HCl (aq.), room temperature, 1 h, 20*R*-**240**, (35 %) and 20*R*-**242c** from **233** (23 %); (iii) **A**. 2 equiv. DEAD, acetonitrile, reflux, 5 h, **B**. 3 equiv. pyridinium hydrochloride, 77 %; (iv): **A**. allyl bromide, $NaHCO_3$, DMF, 90–95 °C, 20 h, 48 %; **B**. (1) cyclopropanecarbonyl chloride, K_2CO_3, CH_2Cl_2, 20 °C, 2 h, (2) $LiAlH_4$, THF, reflux, 1 h, 52 %, **C**. (1) cyclobutanecarbonyl chloride, K_2CO_3, CH_2Cl_2, 20 °C, 2 h, (2) $LiAlH_4$, THF reflux, 2 h, 50 %.

Aiming mind to synthesize the conjugates of 6,14-ethenomorphinans with bioactive molecules, the same research group prepared 7α- and 7β-carboxylic acid esters of thevinone, so called thevinoic acid fluoroalkyl esters, from thebaine (**4**) with β-fluoroalkyl acrylates [235].

Very recently, Finke *et al.* [236] reported a procedure for the preparation of 6-trifluoromethyl substituted morphinans from morphinan-6-ones. 6-Ketomorphinans (e.g., 14-hydroxycodeinone (**132**), 4-*O*-methylsinomenine, 1-iodo-4-*O*-methylsinomenine) were converted to the corresponding 6-trifluoromethyl compounds with (trifluoromethyl)trimethylsilane (Me_3SiCF_3, Ruppert-Prakash reagent) in the presence of Bu_4NF or *t*BuOK.

2.11. Application of the Mitsunobu Reaction in the Morphine Series

The Mitsunobu reaction [237,238] continues to find wide use for the functionalization of alcoholic hydroxyl groups [239], and in the field of alkaloid synthesis [240]. During this reaction, a primary or secondary alcohol (R-OH, e.g., **2a**, Figure 59) substrate, reacts with a pronucleophile (H-Nu (**243**), a compound containing a dissociable proton) in the presence of an azodicarboxylic acid ester (e.g. DEAD, DIAD, ADDP or DTBAD, **244**) and triaryl or trialkylphosphine (**245**, e.g. TPP or TBP, Figure 59). Following a complex reaction sequence, the alcohol (R-OH, **2a**) alkylates the conjugated base ($Nu^{\ominus}$) of the pronucleophile (H-Nu, **243**), forming R-Nu (**246**) as main product, and side products hydrazinecarboxylic acid alkyl ester and the corresponding phosphine oxide (e.g. $Ph_3P{=}O$, **248**).

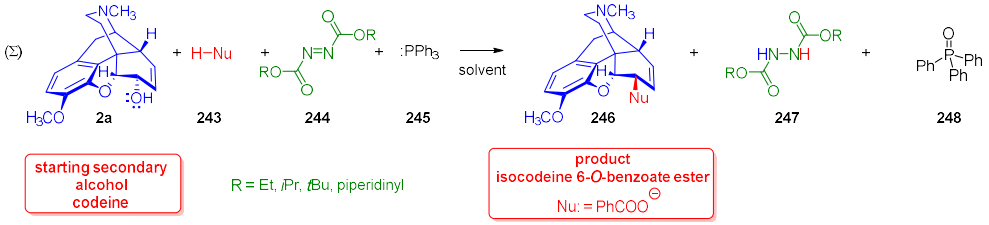

Figure 59. Overall reaction equation of the Mitsunobu reaction of codeine with H-Nu.

The Mitsunobu reaction is an indispensable alternative to classical S_N2 type reactions. Taking place under mild (0-25 °C) and neutral conditions, the reaction operates in dipolar aprotic solvents (e.g. THF, benzene, DMF, acetonitrile). The reaction time (τ) is commonly between 0.5 and 12 hours, with rare instances of more prolonged τ-s. The Mitsunobu reaction is chemoselective: only the alcoholic hydroxyl groups react under such mild conditions. Typically, primary alcohols react more quickly than secondary alcohols, which enables selective acylation of substrates when primary and secondary hydroxyl groups are present in the same molecule. The Mitsunobu reaction is usually stereoselective and yields products with opposite configuration (Walden inversion). Side reactions (elimination or allylic rearrangement) rarely occur. As pronucleophiles, molecules with dissociable protons (pK_a <11) can be used and examples of weak-acidity nucleophiles with higher pK_a value (<15) are also known. The mechanism of the Mitsunobu reaction is depicted in Figure 60.

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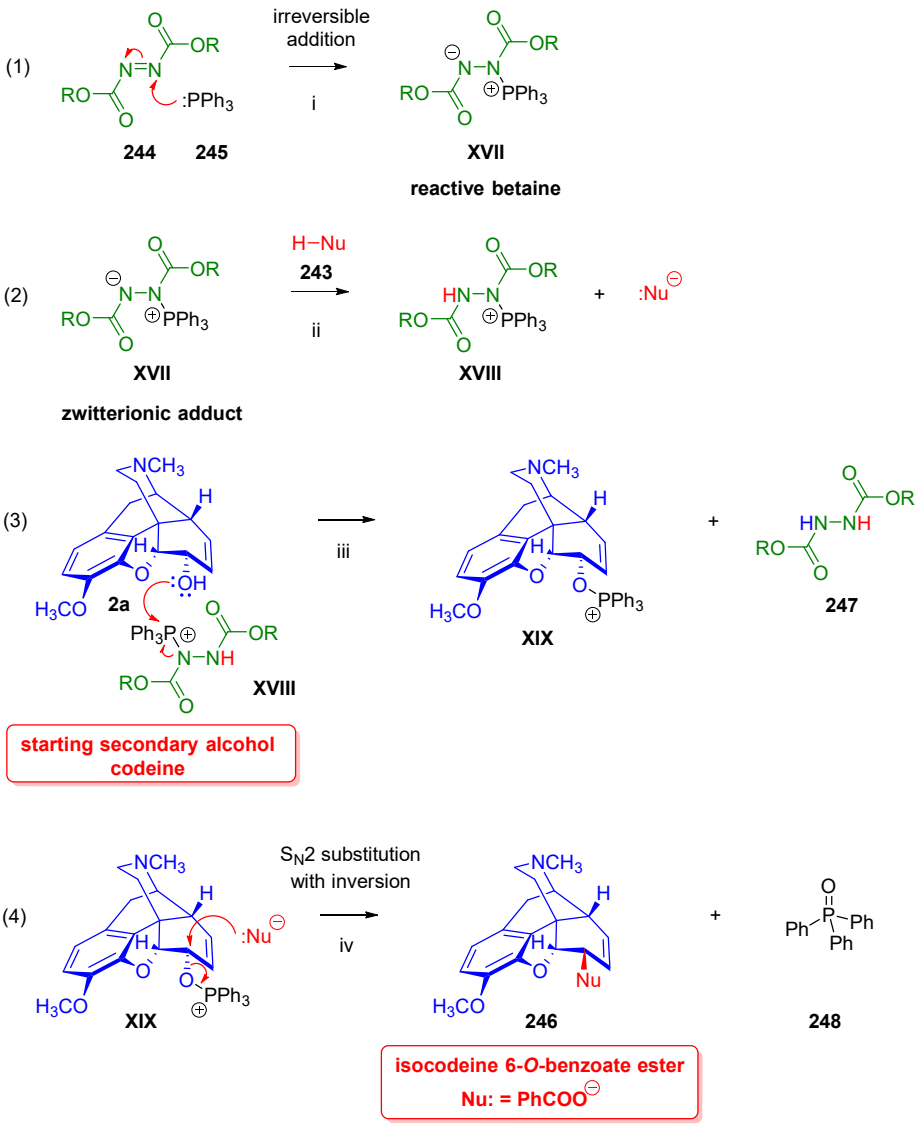

Figure 60. Elementary steps of the Mitsunobu reaction as exemplified by the interaction of codeine R-OH, **2a**) with benzoic acid (H-Nu, **243**).

(1) In the first elementary step of the process, a reactive betaine (**XVII**) is formed from the azodicarboxylic acid ester (**244**) and trialkyl or triarylphosphine (**245**) in an irreversible reaction.
(2) In the second step, the reactive zwitterionic adduct (**XVII**) reacts with the acidic pronucleophile (H-Nu, **243**) to produce the nucleophile ($Nu^{\ominus}$).
(3) The alcoholic hydroxyl group (**2a**) attacks the protonated betaine (**XVIII**) to form an alkoxyphosphonium intermediate (**XIX**). During this process, 1,2-hydrazinecarboxylic acid dialkyl ester (**247**) arises.
(4) The conjugated base form ($Nu^{\ominus}$) of the pronucleophile (H-Nu, **243**) reacts with the alkylphosphonium intermediate (**XIX**), from which emerges the product (R-Nu, **246**) as well as triaryl or trialkylphosphine oxide (**248**). Applying a chiral secondary alcohol as starting substrate a change of the configuration of the chiral centre is to be expected (Walden inversion).

2.11.1. The First Application

Robson and Kosterlitz [241] postulated that denaturation of the OR binding sites in guinea-pig brain homogenates could be achieved by alkylation of the protein with phenoxybenzamine (PBZ). Indeed, incubation of brain preparations with PBZ reduced the specific binding of [^{3}H]dihydromorphine (μ-ORs) and [^{3}H]*D*-Ala^2-*D*-Leu^5]enkephalin (δ-ORs). Conversely, the presence

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of OR ligands (peptides or opiates) protected against the inactivation due to alkylating agents. Smith and Simon [242] found that treatment with the thiol (SH) alkylating reagent *N*-ethylmaleimide (NEM) inhibited the stereospecific binding of tritiated OR ligands (e.g., [^{3}H]*D*-Ala^{2}-*D*-Leu^{5}]enkephalin). Bowen *et al.* [243] postulated that disulphide bonds in the ORs are essential for ligand binding, proposing a three-state allosteric model (μ-agonist, μ-antagonist and δ-agonist-preferring states) under regulation by a "SH" – "S-S" (thiol – disulphide) exchange mechanism.

Based in that hypothesis, Fujii *et al.* [244] investigated in 1988 the possibility of introducing an SH group into the C-6 position of the morphine (**1a**) skeleton. In a first attempt, morphine (**1a**) was reacted with thioacetic acid in the presence of 1,1-dineopentyloxytriethylamine (toluene, 80 °C) to yield the 3-*O*-acetyl-6β-thioester (**250**, Figure 61, 59%) and the 6β-thioester (**249**, 30%). In a second method, morphine (**1a**) was reacted with thioacetic acid under Mitsunobu conditions (diisopropyl azodicarboxylate (DIAD), triphenylphosphine (TPP)). This approach gave predominant formation of 6-*S*-acetyl-6-desoxy-isomorphine (**249**, 73%) and its 3-*O*-acetyl derivative (**250**, 22%). The absolute stereochemistry of the C-6 stereo centre was proven by NMR spectroscopic methods. In the ^{1}H-NMR spectra of compounds **249** and **250**, the coupling constant $^{3}J_{5\beta,6\alpha}$ was 0.5 Hz, which implies a 6β-orientation of the thioacetyl group [245]. Fujii *et al.* [244] went on the hydrolyze *S*-acetyl-6-desoxy-isomorphine (**249**) by treatment with 0.2 M potassium hydroxide in ethanol to give 6β-thiomorphine (**251**, 66%). Interestingly, the analogous reaction of dihydromorphine (**35**) with thioacetic acid (DIAD, TPP) resulted in 3-*O*-acetylmorphine (**254**) as main product (93%) and the corresponding 3-*O*-acetyl-6β-thioacetyl derivative (**253**) as minor product (7%). When dihydrocodeine (**67**) was subjected to the Mitsunobu reaction with thioacetic acid under identical conditions, there was formation of the 6β-thioester (**255**) in almost quantitative yield. 3-*O*-Demethylation with boron tribromide in $CHCl_3$ gave **256** in 86% yield. The latter compound was hydrolyzed with 0.2 M KOH solution in ethanol to afford 6βthio-7,8-dihydro-morphine (**257**). The reaction of 6β-thiomorphine (**251**) and 6β-7,8-dihydro-thiomorphine (**257**) with 2-nitrobenzenesulfenyl chloride (acetonitrile, 0 °C) gave the corresponding disulphides (**252**,**258**).

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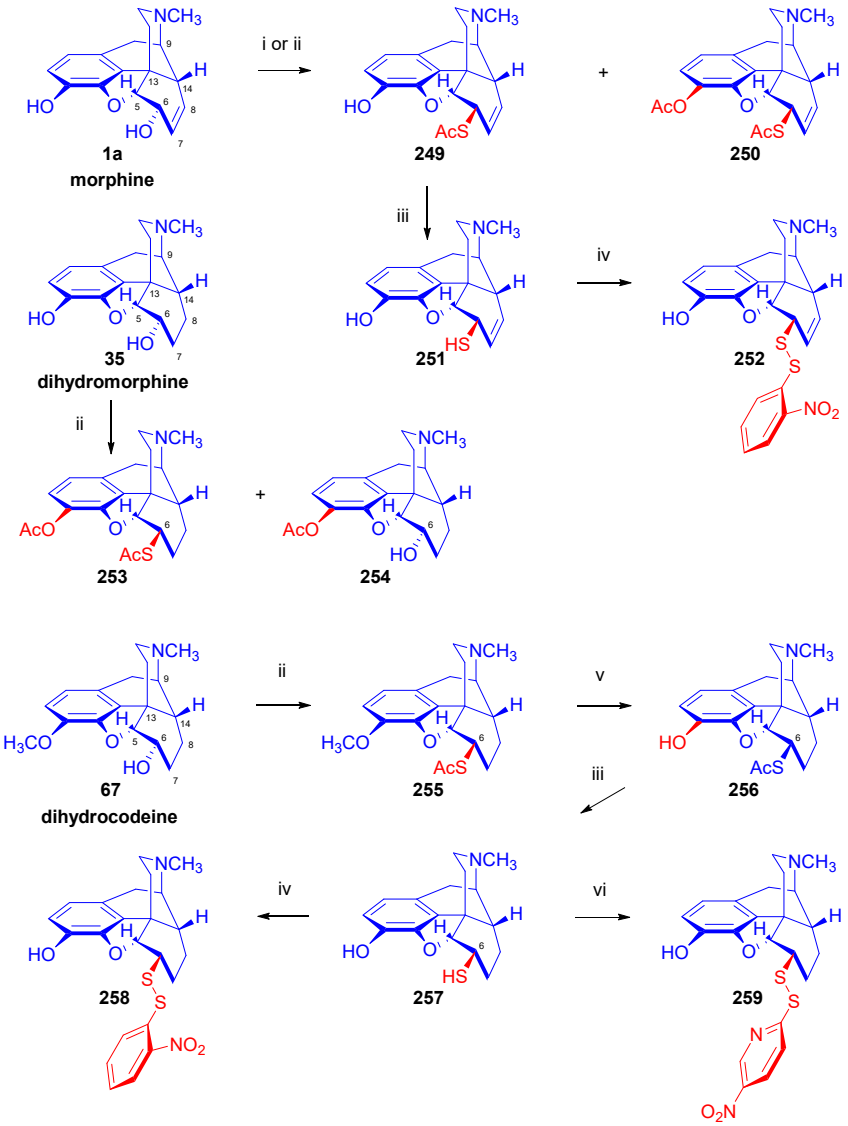

Figure 61. Reaction of morphine, dihydromorphine and dihydrocodeine with thioacetic acid under Mitsunobu conditions. *Reagents and conditions*: (i): thioacetic acid, *N*,*N*-dimethylformamide dineopentyl acetal, toluene, 80 °C; (ii): thioacetic acid, DIAD, TPP, THF, 0 °C; (iii): 0.2 M KOH, ethanol, N_2; (iv): 2-nitrobenzenesulfenyl chloride, acetonitrile or $CHCl_3$, 0 °C; (v): BBr_3, $CHCl_3$, 86% (vi): 5-nitro-2-pyridinesulfenyl chloride, CH_2Cl_2, 0°C, 84 %.

The analgesic activities of 6-*S*-acetyl-6-desoxy-isomorphine (**249**, Figure 61) and the disulphide (**252**) derivative were tested in guinea pig ileum (GPI) [244]. Compound **249** proved to be twice as potent as morphine (**1a**), whereas the disulphide (**252**) was quasi-equipotent with morphine (**1a**).

In 1990, Kanematsu *et al.* [246] synthesized *S*-activated 6-sulfhydryl-dihydoisomorphine (**253**) starting from dihydromorphine (**35**) using Mitsunobu conditions by a modification of the Fujii *et al.* [247] approach (5 eq. AcSH, 5 eq. DIAD and 5 eq. TPP). 6β-7,8-Dihydro-thiomorphine (**257**) was reacted with 5-nitro-2-pyridinesulfenyl chloride (CH_2Cl_2, 0 °C) giving the corresponding disulphide (**259**, 84%). Analgesic activity of the synthesized 6β-(5′-nitro-2′-pyridyldithio)deoxydihydromorphine (**259**) was tested in guinea-pig ileum (GPI) and mouse vas deferens (MVD) preparations giving IC_{50} values of 9.3 and 76 nM, respectively. In mice (MVD), compound **259** had approximately three times higher potency than morphine. They also investigated the thiol-disulphide exchange reaction of the 5′-nitro-2′-pyridyldithio derivative (**259**) with *L*-cysteine methyl ester in DMF.

2.11.2. Preparation of Isomorphine and Isocodeine Derivatives

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At the beginning of the 1990s, there were only a few known morphine derivatives with 6-beta configuration (iso-series, 6β-OH). Their preparation in low yield procedures was only possible by application of complicated multistep syntheses, with the further disadvantage of numerous side-products. In 1969, Makleit and Bognár [107] prepared isocodeine (**2b**) in low yield (16 %) by acetolysis of codeine tosylate (**63a**) with 10 % acetic acid. Subsequently, there was a report of synthesis of isomorphine (**1b**) from 3-*O*-acetylmorphine tosylate (**69a**), and preparation of dihydroisomorphine (**82**) from isomorphine (**1b**) by catalytic reduction [111]. Fleischhacker [248] found higher yields when performing the solvolysis with 70 % acetic acid. In 1971, Kirby and Massey [249] reported the synthesis of isocodeine (**2b**) from codeine (**2a**) in a three-step procedure: codeine (**2a**) → codeine tosylate (**63a**) → isocodeine acetate → isocodeine (**2b**). Codeine tosylate (**63a**) was converted into isocodeine acetate with hexadecyltrimethylammonium acetate, and the alkaline hydrolysis of the resulting 6β-acetate led to isocodeine (**2b**, 68 % overall yield from **2a**). Simon [250] was the first from the Makleit group to investigate extensively the application of the Mitsunobu reaction in the field of morphine alkaloids.

In 1991, Simon *et al.* [251] thereby synthesized numerous isocodeine (**262a–c**, Figure 62) and isomorphine (**262g–j**) derivatives *via* Mitsunobu reaction for the preparation of 6-benzoate esters (**261a–j**) and their subsequent hydrolysis.

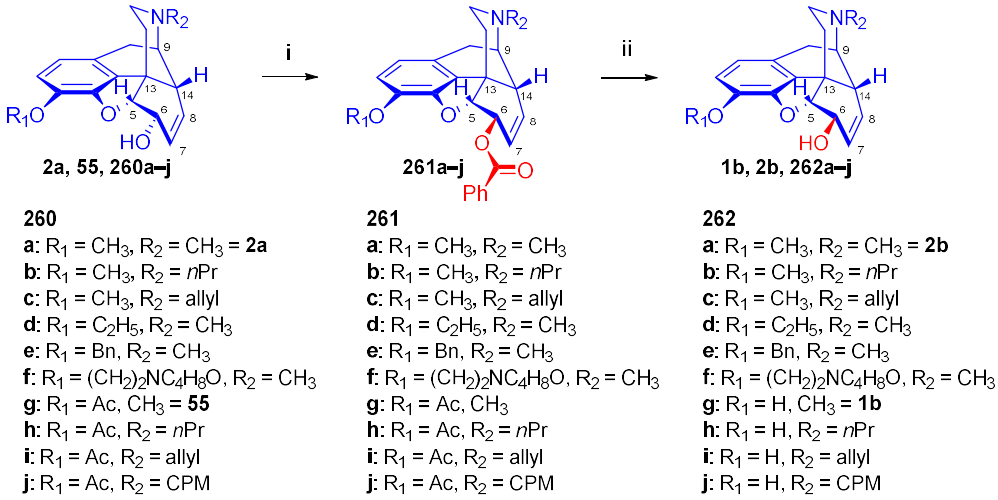

Figure 62. Synthesis of isocodeine and isomorphine derivatives *via* Mitsunobu reaction. *Reagents and conditions*: (i): 2 equiv. benzoic acid, 2 equiv. DEAD, 2 equiv. TPP, benzene, room temperature, 1 h, 29-75%; (ii): 10% KOH (aq.), ethanol, reflux, 10 min, 29-100%.

This elegant two-step method [251] made available for the first time novel isocodeine-isomorphine- derivatives and previously known compounds of the iso series with acceptable yields. In the first step, codeine (**2a**), N^{17}-substituted codeine derivatives (**260b**, **260c**, *n*Pr, allyl), 3-*O*-ethylmorphine (**260d**), 3-*O*-benzylmorphine (**260e**), 3-*O*-morpholinylethyl-morphine (**260f**), 3-*O*-acetylmorphine (**55**) or N^{17}-substituted-3-*O*-acetylmorphine derivatives (**260h–j**, *n*Pr, allyl, cyclopropylmethyl) were reacted with benzoic acid as the acidic pronucleophile (H-Nu, **243**). The Mitsunobu reactions were undertaken in the presence of diethyl azodicarboxylate (DEAD) and triphenylphosphine (TPP, **245**), resulting in the corresponding 6-*O*-benzoyl-isocodeine (**261a–j**) derivatives. The latter compounds were treated with a 10% aqueous potassium hydroxide solution to give the isomorphine and isocodeine derivatives (**262a–j**) with free 6β-hydroxyl group.

In 1994, Friedmann *et al.* [252] investigated the influence of C-6 configuration on the OR affinity of a large number of N^{17}-substituted-morphine derivatives (C-6α-hydroxy, N^{17}-substituent: CH_3 (**1a**), *n*-propyl (**260h**), allyl (**260i**), cyclopropylmethyl (**260j**) N^{17}-substituted-isomorphine (C-6β-hydroxy, **1b**, **262h–j**) and their 7,8-dihydro analogues [251]. They used *in vivo* rat tail-flick, mouse hot plate and *in vitro* isolated GPI assays for the pharmacological characterization [252]. The OR agonist activity of

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the N^{17}-methyl derivatives (morphine (**1a**), isomorphine (**1b**), dihydromorphine (**35**) and dihydroisomorphine (**82**)) were determined by mouse hot plate, rat hot plate and rat tail flick tests, in comparison with morphine (**1a**). The antinociceptive actions of the C-6α and C-6β derivatives did not differ significantly, having relative potencies 0.6–1.9 fold that of morphine (**1a**). In the isolated electrically stimulated GPI preparation, isomorphine (**1b**) was twice as potent as morphine (**1a**), but dihydroisomorphine (**82**) showed only 1.18-fold potency of dihydromorphine (**35**) relative to normorphine. The relative potencies to normorphine were in the range of 1.1–4.4. The epimerization of C-6α to C-6β derivatives had only slight effects on OR activities *in vitro*, but influence the antagonistic effect of the N^{17}-cyclopropylmethyl and N^{17}-allyl compounds. N^{17}-Allyl-dihydronorisomorphine (AD_{50} = 4.0 mg/kg, (s.c) (3.2–7.3), showed a 10-fold increase in antagonist potency compared to the parent N^{17}-allyl-normorphine (**260i**, 0.48 (0.4–0.57)) in the rat tail-flick test vs. morphine.

2.11.3. Reactions of Codeine Isomers and Neopine

In the previously presented experiments, the starting secondary alcohols carried the hydroxyl group at position 6α- of the C-ring of the morphinan skeleton. In 1993, Simon [250] investigated the Mitsunobu reaction of codeine isomers (isocodeine (**2b**), allopseudocodeine (**2c**) and pseudocodeine (**2d**)) with various pronucleophiles (H-Nu compounds) by application of diethyl azodicarboxylate (DEAD) and triphenylphosphine (TPP). These reactions were performed under exactly the same conditions as described above for 6α-hydroxyl derivatives [251].

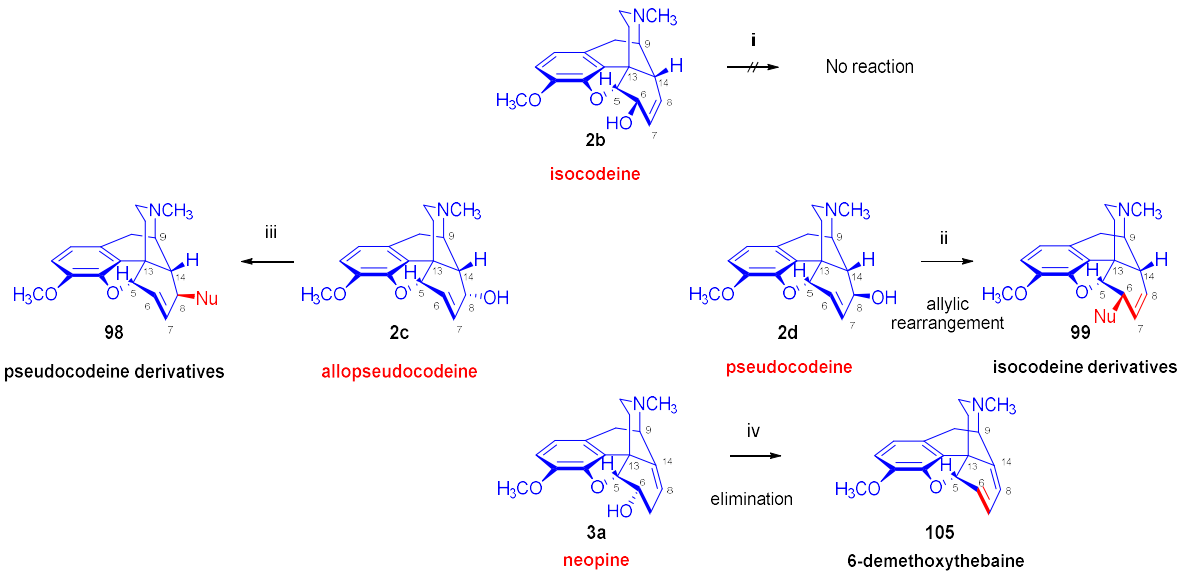

Figure 63. Reaction of isocodeine, allopseudocodeine, pseudocodeine and neopine with various reagents under Mitsunobu conditions. *Reagents and conditions*: (i): H-Nu = benzoic acid or phthalimide, DEAD, TPP; (ii): H-Nu = 4-NO_2-benzoic acid or phthalimide, DEAD, TPP; (iii): **A**: when H-Nu = benzoic acid or 4-NO_2-benzoic acid, DEAD, TPP, no reaction was observed, **B**: when H-Nu = phthalimide, DEAD, TPP, formation of 8β-phthalimido-derivative was observed; (iv): **A**: H-Nu = benzoic acid or phthalimide, DEAD, TPP; **B**: DEAD, TPP.

Upon subjecting isocodeine (**2b**, 6β-OH, Figure 63) to Mitsunobu reaction with benzoic acid or phthalimide, there was no conversion. A previous investigation of the nucleophile substitution reactions of isocodeine tosylate (**81**) by Makleit [102] found formation of pseudocodeine derivatives due to allylic rearrangement. In the Mitsunobu reaction of pseudocodeine (**2d**, 8β-OH) with 4-nitrobenzoic acid or phthalimide, 6β-substituted derivatives (isocodeine series) were formed due to [3,3-sigmatropic] rearrangement. Presumably, the attack of the corresponding nucleophile from the α-side is sterically hindered in an S_N2 type reaction. Makleit, Somogyi and Bognár [110] had similar experiences during investigations of the nucleophile substitution reactions of pseudocodeine tosylate

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(**97**). They found formation of 6-deoxy-6-substituted-isocodeines (**99**) or 8-deoxy-8-substituted-pseudocodeine derivatives (**98**), depending on the nature of the nucleophilic anion [110].

There was no observable reaction when allopseudocodeine (**2c**, 8α-OH) was treated with benzoic acid or 4-nitrobenzoic acid under Mitsunobu conditions [250]. Interestingly, when phthalimide was applied as pronucleophile, there was formation of the 8β- phthalimido derivative (**98**, Nu = NPht, pseudocodeine series), a result corresponding to the Mitsunobu reaction mechanism (8α-hydroxyl (**2c**) → 8-phthalimido-pseudocodeine (**98**)). The authors proved the structure of the synthesized phthalimido compound (**98**) by NMR spectroscopy and by chemical reaction. The reaction of the 8β-phtalimido-compound (**98**, Nu = NPht) with hydrazine hydrate gave the same known 8β-amine (8-amino-pseudocodeine (**84**)) as prepared earlier by Bognár and Makleit [104] *via* another route (codeine (**2a**) → codeine tosylate (**63a**) (or mesylate, **63b**) → 8-azidocodide (**83**) → 8-aminocodide (**84**)).

When choosing neopine (**3a**) as starting material, the replacement of the C-6α secondary alcohol using benzoic acid or phthalimide as Mitsunobu pronucleophile failed [246], although in both cases there was 6-demethoxythebaine (**105**) present in the product mixture. Likewise, when the reaction was performed in the absence of the pronucleophile (H-Nu), only the presence of the elimination product, 6-demethoxythebaine (**105**), could be detected. In the neopine (**3a**) molecule, the 6α-hydroxyl group occupies a position pseudo axial to the 7β-proton, which represents a favourable steric condition for elimination. The elimination reactions of 6-*O*-mesyl-neopine (**100**) derivatives are well known from the literature [119,124,253].

2.11.4. Synthesis of 6β-Aminomorphinans

Conversion of codeine 6-sulfonesters (**63a**, **63b**) to 6β-halo substituted derivatives by nucleophilic substitution (S_N2) was achievable only for $F^{\ominus}$ and $Cl^{\ominus}$ anions [99–101]. The reaction of the sulfonesters with $Br^{\ominus}$ or $I^{\ominus}$ nucleophiles occured *via* a complex mechanism ($S_N2 + S_Ni'$), resulting in 8β-substituted products due to a [3,3] sigmatriopic rearrangement.

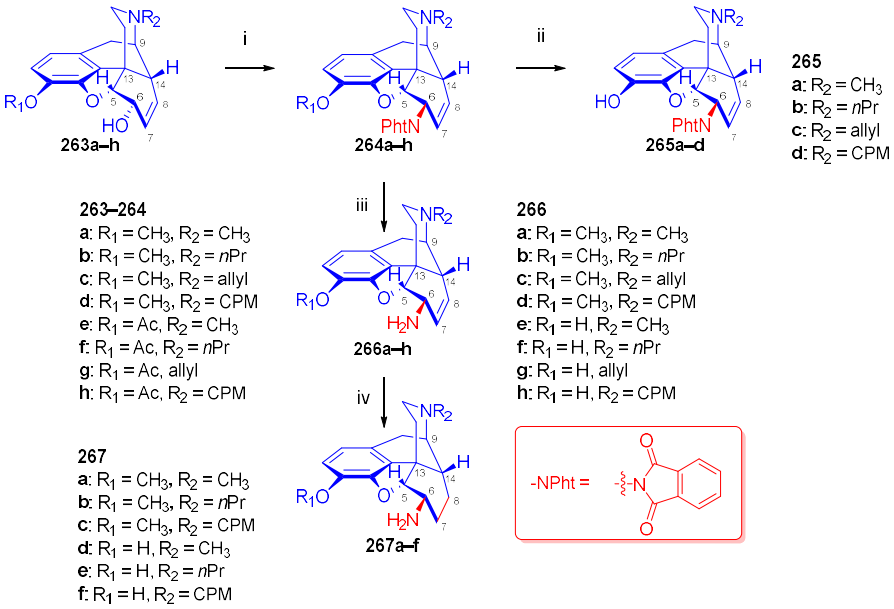

Figure 64. Synthesis of N^{17}-substituted-6β-aminocodeine and 6β-aminomorphine derivatives. *Reagents and conditions*: (i): 2 equiv. phthalimide, 2 equiv. DEAD, 2 equiv. TPP, benzene, 39-92 %; (ii): hydroxylamine hydrochloride, H_2O, EtOH, 50 °C, 10 min; 35-79 %; (iii): 98 % hydrazine hydrate, EtOH, 50-98 %; (iv): H_2, 10 % Pd-C, EtOH, 1 Bar.

We note that for the same reasons, application of $N_3^{\ominus}$ nucleophile and the subsequent reduction of the formed azide gave 8β-amino derivatives. Morphinan-6-ones were employed earlier for production of 6-amino-4,5-epoxymorphinans *via* reductive amination, which resulted in 6α/6β-amino

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epimer mixtures [254–256]. The Makleit research group developed a stereoselective method for the preparation of 6β-aminomorphinans [257]. In 1992, they extended their investigations [257] to a synthesis numerous N^{17}-substituted-6β-aminocodeine (**266a–d**) and N^{17}-substituted-6β-aminomorphine (**266e–h**, Figure 64) derivatives. The carefully-selected starting morphinan derivatives (**263a–h**) all contained a $\Delta^{7,8}$-double bond in ring-C. By treatment of codeine (**2a**), N^{17}-substituted-codeine (**263b–d**), 3-*O*-acetylmorphine (**55**) and 3-*O*-acetyl-N^{17}-substituted-morphine (**263f–h**) derivatives with phthalimide under Mitsunobu conditions (DEAD, TPP, benzene), the corresponding 6β-phthalimido-codeines (**264a–d**) (68-92 %) and 6β-phthalimido-3-*O*-acetylmorphines (**264e–h**) (39-56 %) were formed with inversion of the configuration. Side reactions, e.g., allylic shifts, were not expected. 6β-Phthalimido-morphines (**265a–d**) were prepared by 3-*O*-deacetylation of the compounds **264e–h** with hydroxylamine hydrochloride in aqueous ethanol (50 °C, 10 min). The 6β-phthalimido compounds (**264a–h**) were subjected to hydrazinolysis (see also Gabriel synthesis) to give the primary amine 6β-amino derivatives (**266a–h**) in 50-98 % yield. For preparation of 6β-amino-7,8-dihydro derivatives (**267a–f**), the selected $\Delta^{7,8}$ compounds (**266a**,**b**,**d**,**e**,**f**,**h**) were saturated under heterogenous catalytic conditions (H_2, 10% Pd-C, EtOH). 6β-Amino-dihydrocodeines (**267a–c**) and 6β-amino-dihydromorphines (**267d–f**) were obtained in 37-75 % yield.

The Makleit group [258] accomplished the Mitsunobu reaction of N^{17}-demethyl-N^{17}-substituted-14-hydroxycodeines (**268a–d**, CH_3, *n*Pr, allyl, cyclopropylmethyl) as well as N^{17}-demethyl-N^{17}-substituted-3-*O*-acetyl-14-hydroxymorphines (**268e–h**, Figure 65) with phthalimide.

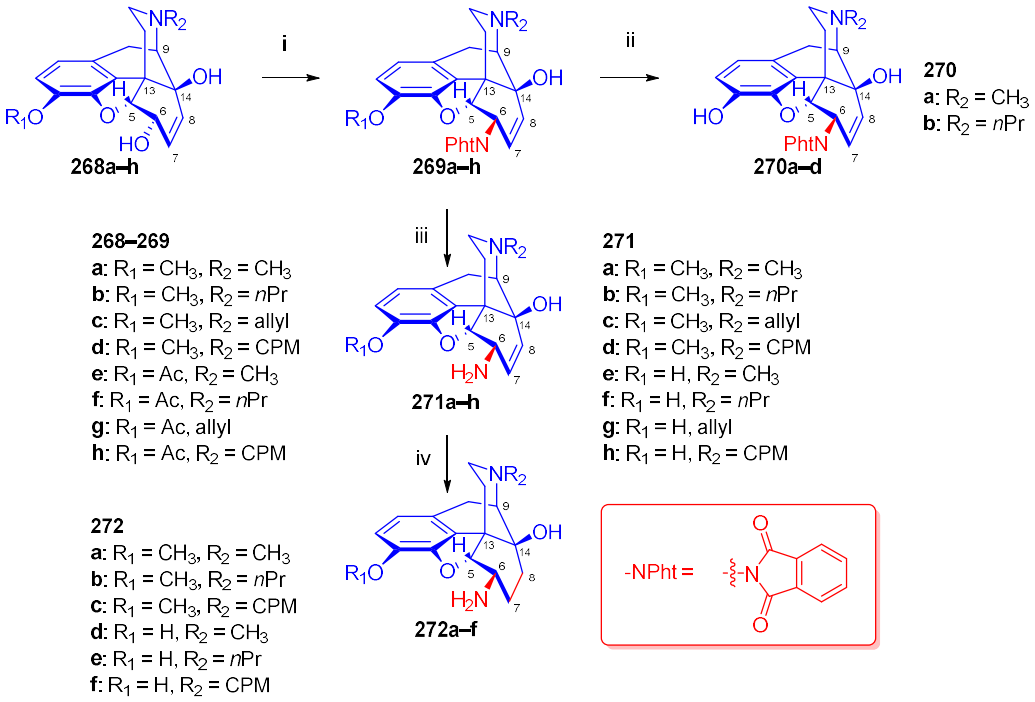

Figure 65. Synthesis of N^{17}-substituted-6β-amino-14-hydroxycodeine and 6β-amino-14-hydroxymorphine derivatives. *Reagents and conditions*: (i): 2 equiv. phthalimide, 2 equiv. DEAD, 2 equiv. TPP, anhydrous benzene, RT, 1 h, 30-65 %; (ii): hydroxylamine hydrochloride, H_2O, EtOH, 50 °C, 10 min; 20-74 %; (iii): 98 % hydrazine hydrate, EtOH, 10-90 %; (iv): H_2, 10 % Pd-C, EtOH, 1 Bar.

The 6β-phthalimido derivatives (**269a–h**) were prepared with yields in a range of 20-65 %, without any observed allyl-migration. The treatment of these compounds with hydrazine hydrate in ethanol yielded 6β-amino-14-hydroxycodeine (**271a–d**) and 14-hydroxymorphine (**271e–h**) derivatives. Most of these 6β-amino derivatives were previously unavailable *via* the sulphonate ester → azide → amine route [48] or by reductive amination of morphinan-6-ones [254,255].

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Continuing their systematic investigations, the Makleit group extended the epimerization studies for compounds saturated in ring-C (7,8-dihydro compounds): dihydromorphines, dihydrocodeines and their 14-hydroxy analogues [259]. Applying benzoic acid as pronucleophile in the Mitsunobu reaction of dihydrocodeine (**67**), there was incomplete conversion. Interestingly, by application of *p*-nitrobenzoic acid instead, the corresponding dihydroisocodeine *p*-nitro benzoate was isolated in a yield of 90 %. Accordingly, 14-hydroxydihydrocodeine (**68**) and N^{17}-substituted-14-hydroxydihydrocodeine derivatives (**273b–c**, Figure 66) were reacted under Mitsunobu conditions (TPP, DEAD) with 4-nitrobenzoic acid in anhydrous benzene to yield the corresponding *p*-nitrobenzoic esters (**274a–h**). Ester cleavage of these compounds was performed by alkaline hydrolysis, giving the desired 6β epimers (**275a–h**) with yields in the range of 37–90 %. In this manner, the authors achieved a new stereoselective synthesis of the human metabolites of naloxone (β-naloxol (**275g**)) and naltrexone (**199**, β-naltrexol (**275h**)).

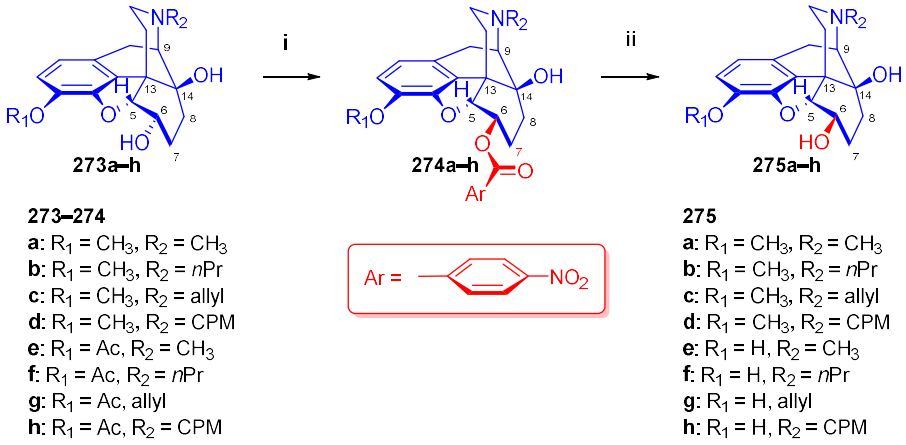

Figure 66. Synthesis of 14-hydroxydihydroisocodeine and 14-hydroxyisomorphine derivatives. *Reagents and conditions*: (i): 2 equiv. 4-nitrobenzoic acid, 2 equiv. TPP, 2 equiv. DEAD, anhydrous benzene, RT, 1 h, 33–79 %; (ii): 10 % KOH aqueous solution, EtOH, reflux, 10 min, 37–90 %.

In a second series of experiments [259], dihydrocodeine- (**67**), 3-*O*-acetyldihydromorphine- (**54**), 14-hydroxydihydrocodeine- (**68**, **276b–d**, X = OH) and 3-*O*-acetyl-14-hydroxydihydromorphine-derivatives (**276e–h**, X = OH, Figure 67) were treated with phthalimide in benzene in the presence of triphenylphosphine and diethyl azodicarboxylate (DEAD) to yield the corresponding 6β-phthalimido compounds (**277a–h**). For hydrolysis of the phenol esters (**277e–h**), they used hydroxylamine hydrochloride in aqueous ethanol giving the corresponding 6β-phthalimido-14-hydroxydihydomorphine derivatives (**278a–d**) with free phenolic hydroxyl group in 58–70 % yield. Treatment of the 6β-phthalimido derivatives (**277a–h**) with hydrazine hydrate led stereoselectively to the 6β-amino compounds (**279a–h**) with 51–90 % yield. At the time, these investigations were considered as novel stereoselective syntheses of 6β-oxymorphamine (**279e**, $R_2 = CH_3$), 6β-naloxamine (**279g**, R_2 = allyl) and 6β-naltrexamine (**279h**), R_2 = cyclopropylmethyl). Szilágyi *et al.* presented detailed NMR analysis of the prepared new compounds [260], and Fürst *et al.* subsequently undertook their pharmacological characterizations [252,261].

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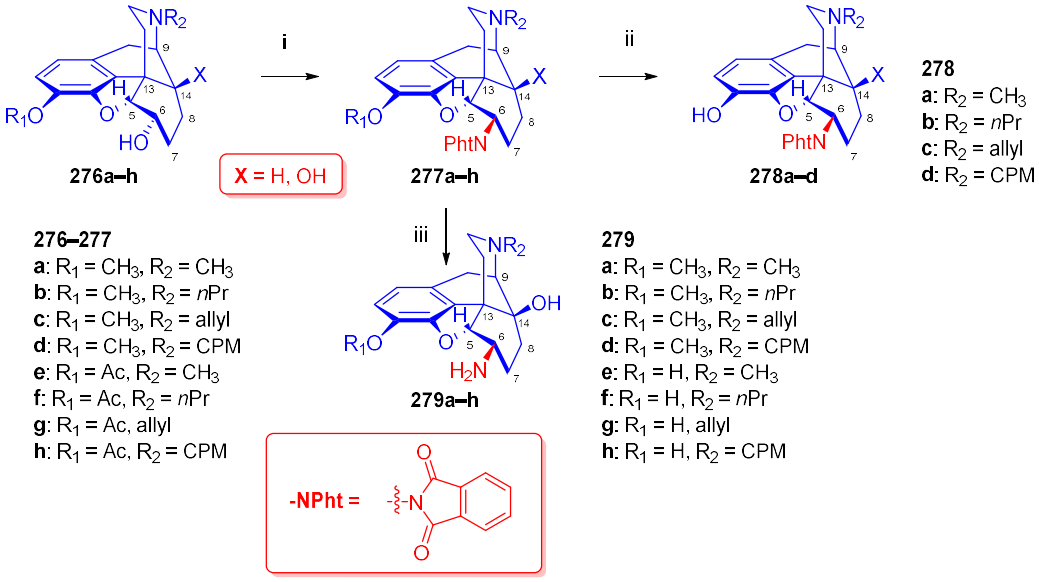

Figure 67. Synthesis of N^{17}-substituted-6β-amino-14-hydroxydihydrocodeine and 6β-amino-14-hydroxydihydromorphine derivatives. *Reagents and conditions*: (i): 2 equiv. phthalimide, 2 equiv. DEAD, 2 equiv. TPP, anhydrous benzene, RT, 1 h, 33-90 %; (ii): hydroxylamine hydrochloride, H_2O, EtOH, 50 °C, 10 min; 25-70 %; (iii): 98 % hydrazine hydrate, EtOH, 35-98 %.

2.11.5. Synthesis of 6β-succinimido Derivatives

Upon reacting codeine (**2a**) with the succinimide pronucleophile (HSu) [257] under identical Mitsunobu conditions as above (DEAD, TPP, benzene), 6β-succinimido-codeine (**280a**, Figure 68) was obtained in 80 % yield. In the case of 3-*O*-acetylmorphine (**55**), only the isolation of the deacetylated 6β-succinimido-morphine (**281b**) was feasible. Saturation of the $\Delta^{7,8}$ double bond under heterogenous catalytic conditios (H_2, 10 % Pd-C, RT, atmospheric pressure) was only achievable for 6β-succinimido derivatives (**280a**, 73 %, **280b**, 55 %). In the case of the appropriate 6β-phthalimido compounds (**264a–h**), the reduction of the $\Delta^{7,8}$ double bond was not realizable under atmospheric pressure.

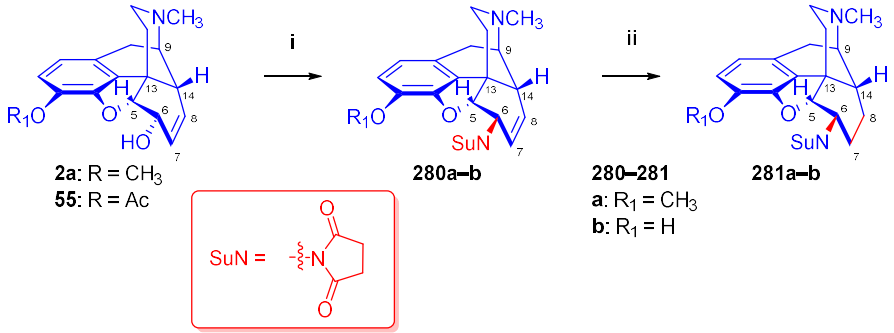

Figure 68. Synthesis of 6β-succinimido codeine and morphine derivatives. Reagents and conditions: (i): 2 equiv. succinimide, 2 equiv. DEAD, 2 equiv. TPP, benzene; (ii): H_2, 10 % Pd-C, EtOH, atmospheric pressure.

2.11.6. Reaction of 14-halogenocodeines

14-Halogenocodeines (**282a–b**, Figure 69) contain both an allyl alcohol (C^8=C^7-C^6-OH) and an allyl halide (C^7=C^8-C^{14}-X) sub-structural unit within the same molecule. Thebaine (**4**) reacted with *N*-halosuccinimides (NCS, NBS) in acetic acid or acetone-water (2:1 (v/v)) gave 14-halocodeinones [126].

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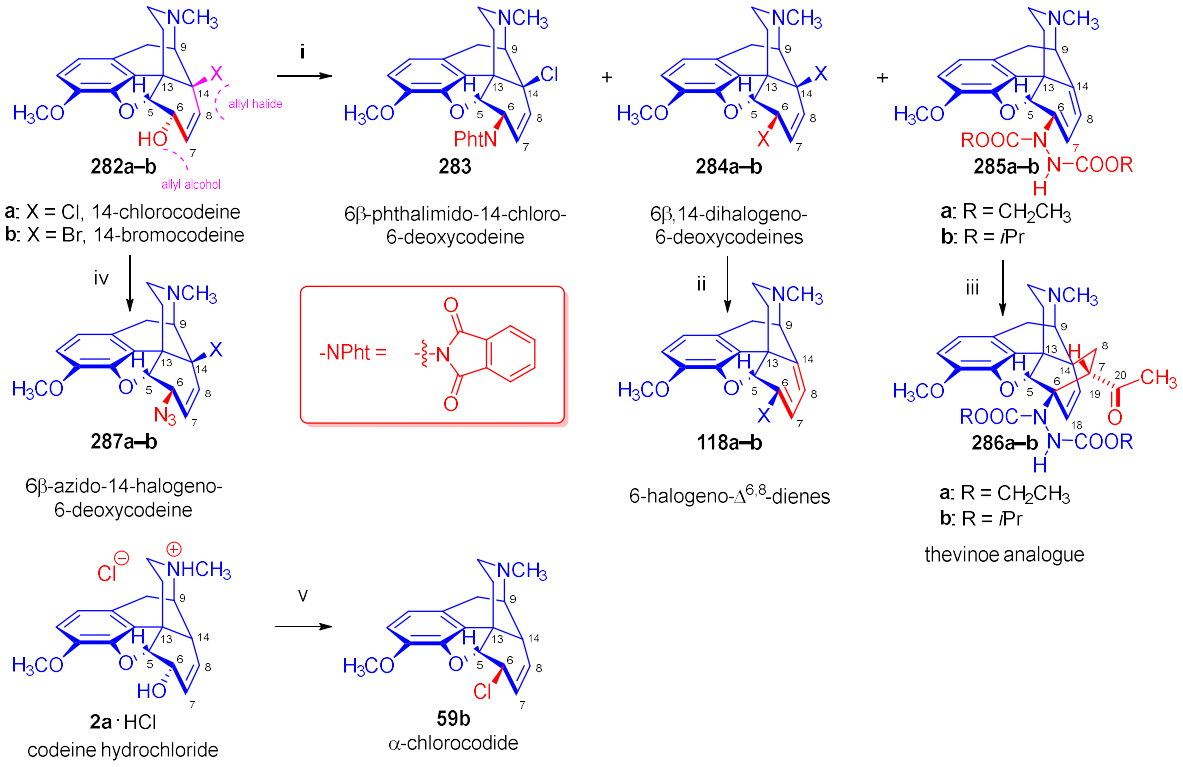

Figure 69. Mitsunobu reaction of 14-halogenocodeines with phthalimide and diphenylphosphoryl azide. *Reagents and conditions*: (i): phthalimide, DEAD, TPP, benzene, RT, 1 h; (ii): *N*,*N*-dimethylformamide, 100 °C, 1 h, [126]; (iii): methyl vinyl ketone, reflux, 1 h; (iv): DPPA, DEAD or DIAD, TPP; (v): DEAD, TPP, benzene, RT, 1 h, 70 %.

The reduction of codeinone derivatives (e.g., codeinone (**24**), 14-hydroxycodeinone (**132**), 1-bromocodeinone, and 14-bromocodeinone (**109**)) with sodium borohydride led stereoselectively to the corresponding codeines (e.g., **282a–b**, 6α-hydroxy compounds). 14-Chlorocodeine (**282a**) [116] and 14-bromocodeine (**282b**) [126] are useful starting materials for the synthesis of neopine derivatives. The reduction of neopinone (**23**) with $NaBH_4$ results in a mixture of neopine (**3a**) and isoneopine (**3b**). Okuda *et al.* [262] found that the $NaBH_4$ reduction of 14-bromocodeinone (**109**) in methanol-water gave three products: the main product neopine (**3a**, 46 %), isoneopine (**3b**, 6 %) and indolinocodeine (28 %) were isolated.

In 1993, Simon *et al.* [263] investigated the Mitsunobu reaction of 14-halogenocodeines (**282a–b**, Figure 69) with phthalimide as pronucleophile in the presence of triphenylphosphine (TPP) and dialkyl azodicarboxylates (DEAD or DIAD) or diphenyl azidophosphate (DPPA). The reaction of 14-chlorocodeine (**282a**) with phthalimide (TPP, DEAD, benzene) resulted in three products. The main product, a $\Delta^{6,8}$-conjugated diene (**285a**) containing a hydrazine dicarboxylic diethyl ester substituent in position-6, was obtained in 36 % yield. Further products, 6β-phthalimido-14-chloro-6-deoxycodeine (**283**, 12 %) formed by inversion and 6β,14-dichloro-6-deoxycodeine (**284a**, 13 %), were isolated by column chromatography in a ratio of about 1:1. Interestingly, when 14-bromocodeine (**282b**) was reacted with phthalimide under identical conditions (TPP, DEAD, benzene, RT, 1 h), there was no observed formation of a 6β-phthalimido derivative, presumably due to the steric hindrance by the bulky 14-bromo substituent. In this case, the main product were the thebaine analogue (**285a**, 34 %) followed by 6β,14-dibromo-6-deoxycodeine (**284b**, X = Br, 25 %). To prove the structure of the $\Delta^{6,8}$-diene (**285a**) with hydrazine dicarboxylic diethyl ester substituent in position-6, it was boiled with methyl vinyl ketone to yield the corresponding DA adduct thevinone analogue (**286a**). In a second approach, 14-halogenocodeines (**282a–b**) were reacted under the above-mentioned conditions (TPP, DEAD) in the absence of a pronucleophile (H-Nu). Formation of 6β,14-dichloro-6-deoxycodeine (**284a**, 32 %) and 6β,14-dibromo-6-deoxycodeine (**284b**, 25 %) as well the $\Delta^{6,8}$-diene (**285a**, 32 %, from

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282a and 25 % from **282b** respectively) were observed. The authors [263] proved the structure of 6β,14-dihalo-6-deoxycodeines (**284a–b**) by spectroscopy and chemical reactions. When these derivatives (**284a–b**) were allowed to react in *N*,*N*-dimethylformamide in the absence of a nucleophile [128], the same 6-halogeno-6-demethoxythebaine (**118a–b**) derivatives were obtained, as had been prepared earlier in the nucleophilic substitution reaction of 14-chlorocodeine tosylate (**119a**) with $Cl^{\ominus}$ and $Br^{\ominus}$ ions, respectively (see section 2.8.6.) [127]. The formation of the 6β,14-dihalo-6-deoxycodeines (**284a–b**) and the $\Delta^{6,8}$-dienes (**118a–b**) in this reaction was explained by the *in-situ* liberation of hydrogen halides (HCl, HBr), which could then act as pronucleophiles in the Mitsunobu reaction. To substantiate the presence of the *in situ* generated H-Nu compound, the hydrochloride addition salt of codeine (**2a**) was allowed to react under Mitsunobu conditions (TPP, DEAD), which gave α-chlorocodide (**59b**, Figure 69) in 70 % yield. In a further approach, 14-halogenocodeines (**282a–b**) were reacted with diphenylphosphorylazide (DPPA) under Mitsunobu conditions, giving the 6β-azido-14-halogeno-6-deoxycodeine derivatives (**287a**, X = Cl, 37 %, **287b**, X = Br, 25 %).

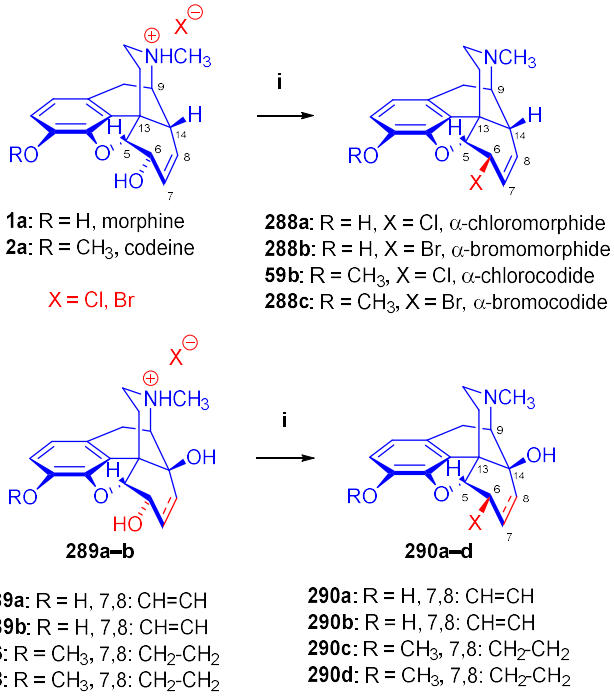

Figure 70. Reaction of the hydrogen halide salts of morphinans under Mitsunobu conditions. *Reagents and conditions*: (i): DEAD or DIAD, TPP, toluene or benzene, room temperature, 1–4 h.

The reaction of morphine (**1a**) or codeine (**2a**) with thionyl chloride resulted in α-chloromorphide (**288a**) and α-chlorocodide (**59b**), respectively [99]. Notably, the reactions of codeine (**2a**) with thionyl bromide [99] or codeine tosylate (**63a**) with lithium bromide [99] both resulted in β-bromocodide (**65b**, Figure 17), the product of thermodynamic control. When hydrogen halide salts (hydrochloride or hydrobromide) of codeine (**2a**) or morphine (**1a**) was allowed to react under Mitsunobu conditions (DEAD, TPP, toluene) in the absence of other nucleophile [264], 6β-halogen substituted derivatives were isolated (e.g., from codeine hydrochloride → α-chlorocodide (**59b**), from codeine hydrobromide → α-bromocodide (**288c**), Figure 70). The importance of the above-mentioned results of Simon *et al.* [264] have to be emphasized, as this was the first isolation of α-bromocodide (**288c**), the product of kinetic control. Analogue reactions starting from the hydrogen halide (HCl, HBr) salts of 14-hydroxy derivatives (14-hydroxycodeine (**66**), 14-hydroxymorphine (**289a**), 14-hydroxydihydrocodeine (**68**) and 14-hydroxydihydromorphine (**289b**)) led to the corresponding 6β-halogen (Cl, Br) substituted compounds (**290a–d**). The reactions of $\Delta^{7,8}$ unsaturated derivatives (**1a**,

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2a, **66**, **289a**) were complete within 1 h, but the conversion proceeded much slower (3–4 h) in the 7,8-dihydro series (**68**, **289b**).

2.11.7. Novel Applications

In this section, we present a few novel examples highlighting potential applications of the Mitsunobu reactions in the field of semisynthetic morphinans, as informed by results of the Makleit group in the 1990s. In 2014, Fujimura *et al.* [265] reported the pharmacological characteristics of the OR ligand TRK-130 (**278d**, naltalimide, *N*-[(5*R*,6*R*,14*S*)-17-cyclopropylmethyl-4,5-epoxy-3,14-dihydroxymorphinan-6-yl]phthalimide). The compound TRK-130 (**278d**), which proved to be a selective partial μOR agonist (K_i for μOR = 0.268, δOR = 121, and κOR = 8.97 nM, respectively, δ/μ = 451, κ/μ = 33.5) [265] in radioligand-binding assays with human ORs. Naltalimide (**278d**) is used as a prophylactic-agent against urinary-incontinence, i.e., overactive bladder (OAB) [265]. The synthesis of naltalimide (**278d**) was achieved by the Simon *et al.* method [259] from 3-*O*-acetyl-N^{17}-cyclopropylmethyl-14-hydroxydihydromorphine (3-*O*-acetyl-α-naltrexol, **276h**, route: **276h** → **277h** → **278d**, X = OH, see also Figure 68) in a Mitsunobu reaction with phthalimide. Izumimoto *et al.* [266] developed an alternative synthesis route for naltalimide (**278d**) and its N^{17}-allyl analogue (**278c**) from β-naltrexamine (**279h**) [259] and β-naloxamine (**279g**) [259], respectively. The corresponding 6β-amine (**279g–h**) was reacted with phthalic anhydride in DMF in the presence of triethylamine at 140 °C [266] to yield the 6β-phthalimido derivatives (**278c–d**) with yields of 34–58 %.

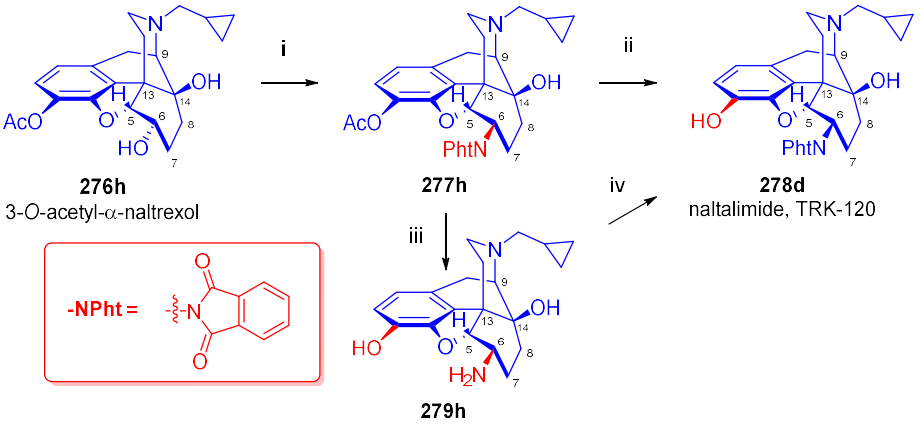

Figure 71. Synthesis of naltalimide. *Reagents and conditions*: (i): 2 equiv. phthalimide, 2 equiv. DEAD, 2 equiv. TPP, anhydrous benzene, RT, 1 h; (ii): hydroxylamine hydrochloride, H_2O, EtOH, 50 °C, 10 min; (iii): 98 % hydrazine hydrate, EtOH; (iv): phthalic anhydride, Et_3N, DMF; 140 °C, 4h.

For potentially treating substance-dependence, the research group of Kenner C. Rice developed heroin vaccine haptens [267,268] (Heroin Hapten (MorHap, **291**, Figure 72)). One of the chosen hapten scaffolds was 6β-amino-6-desoxymorphine (**266e**). For its preparation, they applied the method described earlier by the Makleit group [257]. In brief, they selectively acetylated morphine to 3-*O*-acetylmorphine (**55**) by the Welsh method [88]. They treated that product with phthalimide under Mitsunobu conditions (TPP, DIAD, toluene, RT, 2 h) to yield 6β-phtalimido-3-*O*-acetylmorphine (**264e**, 88 %). The stereochemistry of the phthalimido derivative (**264e**) was substantiated by X-ray crystallographic analysis. The cleavage of the phthalimido protecting group with hydrazine hydrate in ethanol (55 °C, 90min) led to 6β-amino-6-desoxymorphine (**266e**) in 81 % yield. Subsequently, the free 6β-amine was acylated with the activated ester 2,5-dioxopyrrolidin-1-yl 3-(tritylthio)propanoate to the desired hapten (**291**, MorHap). Finaly, the hapten (**291**, MorHap) was conjugated to the carrier protein (tetanus toxoid (TT) or cross-reactive material 197 (CRM_{197})). Antibodies formed due to the immunisation effect of the TT-MorHap conjugate led to nearly complete protection against heroin dependence in mouse experiments.

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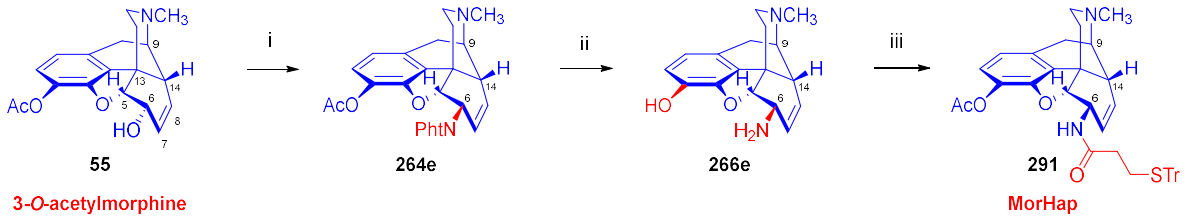

Figure 72. Synthesis of heroin vaccine hapten (MorHap) from 6β-amino-desoxymorphine. *Reagents and conditions*: (i): acetic anhydride, $NaHCO_3$, room temperature, 2 h, 91 %; (ii): phthalimide, DIAD, TPP, toluene, room temperature, 2 h, 88 %; (iii): hydrazine hydrate, 95 % EtOH, 55 °C, 90 min, 81 %; (iv): 1.5 equiv. 2,5-dioxopyrrolidin-1-yl 3-(tritylthio)propanoate, CH_2Cl_2, 2 equiv. Et_3N, room temperature 48 h, 55 %.

Scammels *et al.* [269] prepared fluorescently labelled morphinan-sulfo-Cy5 conjugates for visualization of ORs in living cells. For these bioimaging investigations, they developed a fluorescent partial OR agonist ligand. For the synthesis of C-6 amide pre-congeners first 3-*O*-(4-methoxybenzyl)-6-amino-6-desoxymorphine (**296**, Figure 73), was synthesized from morphine (**1a**) in five steps. The phenolic hydroxyl group of **1a** was protected as PMB (*p*-methoxy-benzyl) ether. Next, 3-*O*-PMB-morphine (**292**) was reacted with benzoic acid under Mitsunobu conditions (DIAD, TPP, toluene) to form the benzoate ester (**293**). The latter compound (**293**) was converted into the 3-*O*-PMB-isomorphine (**294**) by saponification with 1M potassium hydroxide in aqueous ethanol solution. The 6-beta-hydroxyl function of **294** was transformed to a 6*α*-amino group *via* a second Mitsunobu reaction and subsequent phthalimide cleavage. 3-*O*-PMB-isomorphine (**294**) was reacted with phthalimide (DIAD, TPP, toluene) to give 6*α*-phthalimido-3-*O*-PMB-morphine (**295**). The treatment of this latter compound with hydrazine hydrate in ethanol resulted in 3-*O*-PMB-6-amino-6-desoxymorphine (**296**).

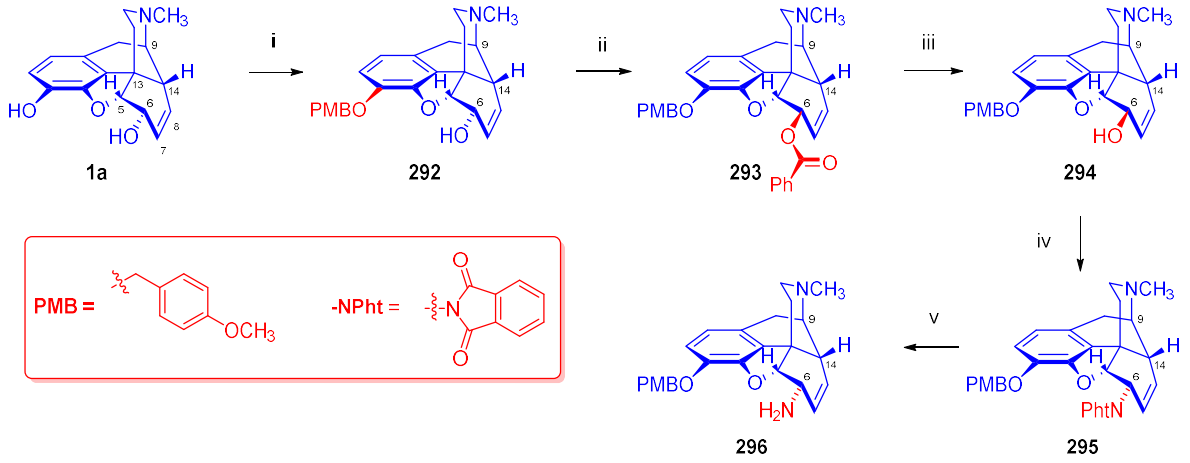

Figure 73. Precursors for the synthesis of fluorescently labelled morphinan-sulfo-Cy5 conjugates. *Reagents and conditions*: (i): PMB-Cl, 3M KOH, DMF, MeOH, room temperature, 4 h, 46 %; (ii): 1.5 equiv. benzoic acid, 1.5 equiv. DIAD, 1.5 equiv. TPP, toluene, 0 °C to room temperature, 4 h; (iii): 1M potassium hydroxide, EtOH, H_2O, reflux, 20 min, 78 % (ii+iii); (iv): 1.5 equiv. phthalimide, 1.5 equiv. DIAD, 1.5 equiv. TPP, toluene, 0 °C to room temperature, 4 h; (v): hydrazine hydrate, EtOH, reflux, 1 h, 34 % (iv+v).

In 1998, the research group of Nagase [270] developed nalfurafine (**300**, TRK-820, 17-cyclopropylmethyl-3,14-dihydroxy-4,5-epoxy-6β-[*N*-methyl-*trans*-3-(3-furyl)-acrylamido]morphinan, Remith®, Figure 74) a 4,5-epoxymorphinan-type OR ligand. TRK-820 (**300**) was selective full, very high affinity agonist for κ-ORs, and a partial agonist for μ-ORs and δ-ORs (K_i (κ-OR) = 75 pM, K_i (μ-OR) = 5.2 nM, K_i (δ-OR) = 161 nM, μ/κ = 69.3, δ/κ = 2146) [271]. TRK-820 (**300**) is an approved pharmaceutical for treatment of haemodialysis-related uremic pruritus and patients with chronic liver diseases. Nalfurafine (**300**) was prepared from naltrexone (**297**) *via* *N*-methyl-β-

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naltrexamide (**299**). The secondary amine (**299**) was acylated with 3-(3-furyl)acryloylchloride to yield **300**. Recently, Suzuki *et al.* [272] synthesized nalfurafine (**300**) and its 10*α*-hydroxy analogues from 3-*O*-acetyl-*α*-naltrexol (**276h**) *via* a modified synthesis route by application of the Mitsunobu reaction.

In the last decade, 6β-acylaminomorphinans [273] and 6β-pyridinyl amidomorphinans were synthesized [274] starting from precursors arising from earlier work by the Makleit group [257].

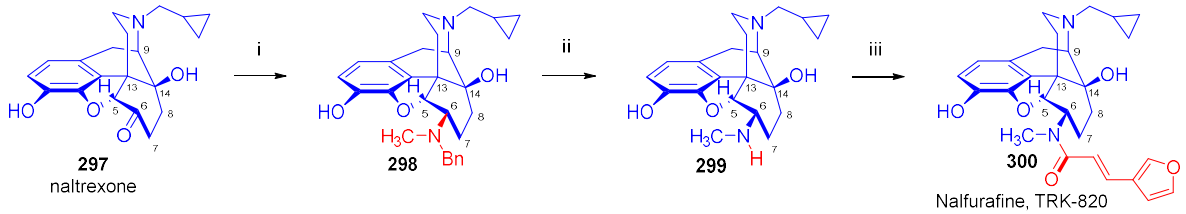

Figure 74. Synthesis of nalfurafine (TRK-820) a selective κ-opioid receptor agonist. *Reagents and conditions*: (i): **A**. *N*-benzylmethylamine, benzoic acid, benzene, 110 °C, 8 h, **B**. $NaBH_3CN$, room temperature, 2 h; (ii): H_2, 10 % Pd-C, EtOH, atmospheric pressure, room temperature, 24 h; (iii): (*E*)-3-(3-furyl)acrylic acid, Et_3N, DMF, CH_2Cl_2, room temperature, 16 h.

2.12. Poppy Alkaloids as Starting Materials for Molecular Imaging

Molecular imaging by positron emission tomography (PET) or single-photon emission computed tomography (SPECT) enables the detection of one or more subtypes of ORs in healthy brain and in pathologies involving opioid neurotransmission [29,275–277]. OR PET radiochemistry development has benefited from the foundational work on opioid chemistry described above, which presented important lead compounds for radiolabeling. As with the lead compounds, some classes of OR PET ligands have incomplete sub-type selectivity, and differ with respect to their agonist/antagonist binding profile. Furthermore, the extreme potency of some opioid agonists calls for particular attention to the molar activity of OR agonist tracers.

OR PET imaging began with development of the μ-OR selective agonist 4-anilidopiperidine derivative carfentanil ([^{11}C]caf) [278] and the μ/κ OR selective antagonist morphinan foxy ([^{18}F]**204a**, [^{18}F]foxy) and cyclofoxy derivatives ([^{18}F]**203a**, acetyl-[^{18}F]cyclofoxy; [^{18}F]**204c**, [^{18}F]cyclofoxy ([^{18}F]FcyF); [^{11}C]**204c**, [^{11}C]cyclofoxy ([^{11}C]cyF)) [197–202] (Figure 75). The synthesis of the [^{18}F]foxy and [^{18}F]cyclofoxy derivatives can start from the poppy alkaloid thebaine (**4**) [279], by conversion to 14-hydroxycodeinone and further synthetic manipulation of the C-ring to introduce the 6β-fluoro group by nucleophilic substitution [198] (see Figure 52).

Following upon the synthesis of the δ-OR selective antagonist *N*1′-([^{11}C]methyl)naltrindole ([^{11}C]MeNTI, (K_i (μ) = 14 nM, K_i (δ) = 0.02 nM, K_i (κ) = 65 nM,) [280] and subsequently *N*1′-(2-[^{18}F]fluoroethyl)naltrindole ([^{18}F]FE-NTI, BU97001, affinities) were prepared [281].

Researchers have developed a range of carbon-11 and fluorine-18 labelled cyclofoxy derivatives (Figure 75), namely [^{11}C]cyclofoxy ([^{11}C]cyF [201]), [^{18}F]foxy [197], [^{18}F]acetylcyclofoxy [199,200] and [^{18}F]cyclofoxy ([^{18}F]FcyF) [197,202]. Among these, the μOR/κOR antagonist [^{18}F]FcyF has served in a study of OR-availability in methadone-treated former opioid addicts [202], revealing lower OR availability of the striatum as compared to healthy volunteers, in measure of the occupancy by methadone.

Notably, Pasternak *et al.* reported on the synthesis of radioiodinated iodobenzoyl derivatives of **279e**, **279g**, and **279h** 6β-oxymorphamine ([^{125}I-BOxyA), 6β-naloxamine ([^{125}IBNalA), and 6β-naltrexamine ([^{125}IBNtxA) in 2011 [282], with potential application for SPECT imaging.

6,14-Ethenomorphinans (orvinols / Bentley compounds) [50,234,283] are in ring-C bridged semisynthetic derivatives of the poppy alkaloid thebaine [279] and/or oripavine [284–286]. Their radiolabelled derivatives are the most frequently used tracers for OR molecular imaging, e.g., the nonselective OR antagonist ^{11}C-diprenorphine ([^{11}C]DPN, **301a**, (K_i (μ) = 0.07 nM, K_i (δ) = 0.23 nM, K_i (κ) = 0.02 nM, Figure 75) [287,288], the partial muOR agonist and kappa antagonist ^{11}C-buprenorphine ([^{11}C]BPN, **301b**) [288,289] (K_i (μ) = 1.5 nM, K_i (δ) = 6.1 nM, K_i (κ) = 2.5 nM, K_i (NOP) = 77.4).

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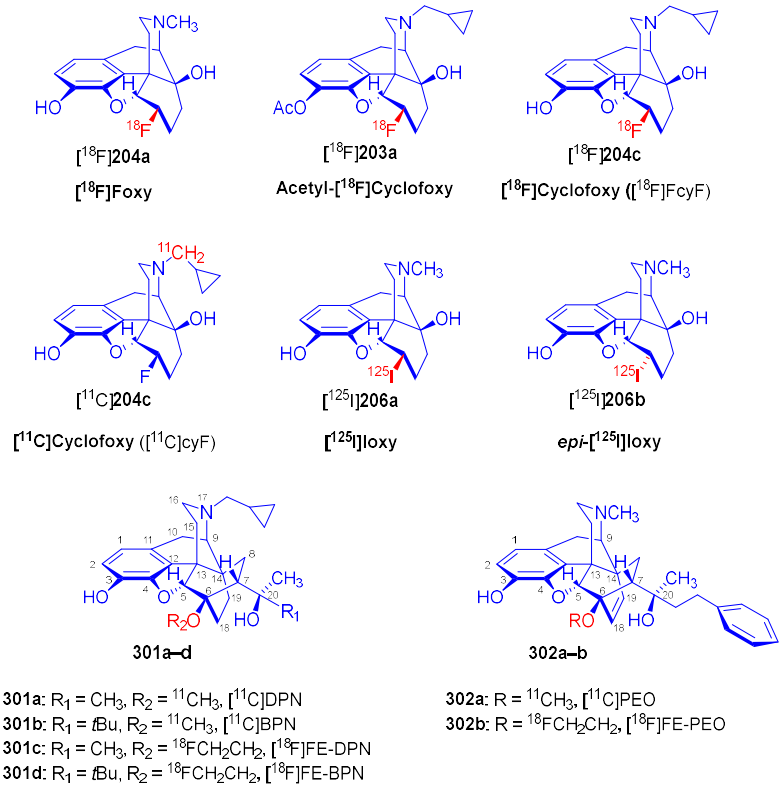

Figure 75. Structures of selected labelled morphinan derivatives.

Following upon development of the agonist ligand ^{11}C-phenethyl-orvinol (**302a**, [^{11}C]PEO) (K_i (μ) = 0.18 nM, K_i (δ) = 5.1 nM, K_i (κ) = 0.12 nM) [290], Schoultz *et al.* reported its ^{18}F-fluorine labelled version, ^{18}F-phenethyl-orvinol (**302b**, [^{18}F]FE-PEO, (K_i (μ) = 0.10 nM, K_i (δ) = 0.49 nM, K_i (κ) = 0.08 nM) [291–293]. In 2000, Wester *et al.* reported the radiosynthesis of the antagonist ligand 6-*O*-(2-[^{18}F]fluoroethyl)-6-*O*-desmethyl-diprenorphine ([^{18}F]FE-DPN, **301c**, K_i (μ) = 0.24 nM, K_i (δ) = 8.00 nM, K_i (κ) = 0.20 nM, Figure 76) [294] thorough an indirect [^{18}F]fluoroethylation procedure. Subsequently, Schoultz *et al.* [295] elaborated a more efficient method for the synthesis of [^{18}F]FE-DPN (**301c**) and [^{18}F]FEOTos and they extended their method also for the radiosynthesis of 6-*O*-(2-[^{18}F]-fluoroethyl)-6-*O*-desmethyl-buprenorphine (**301d**, [^{18}F]FE-BPN, K_i (μ) = 0.24 nM, K_i (δ) = 2.10 nM, K_i (κ) = 0.12 nM) [295]. More recently, Marton *et al.* [296] developed a novel precursor molecule, 6-*O*-(2-tosyloxyethyl)-6-*O*-desmethyl-3-*O*-trityl-diprenorphine (TE-TDDPN, «Henriksen precursor»), for the one-pot, two step nucleophilic radiosynthesis of [^{18}F]FE-DPN ([^{18}F]**301c**). In 2023, the research group of Mikecz [297] optimized the radiosynthesis of [^{18}F]FE-DPN ([^{18}F]**301c**) from the new precursor. Despite its incomplete OR subtype selectivity *in vitro*, 6-*O*-(2-fluoroethyl)-6-*O*-desmethyl-diprenorphine (FE-DPN, **301c**) preferentially binds to the μ-ORs in living brain [298].

2.13. Other Semi-Synthetic Derivatives

In the main part of the review, we presented some selected research topics from the huge body of work from more than five decades of scientific activity of the alkaloid research groups of the University Debrecen and the Alkaloida Chemical Company. In this final section, we seek to highlight some additional important studies. The investigation of Horváth and Makleit [299] is noteworthy due to its importance in the field of the morphine total synthesis. The authors developed an efficient method for the conversion of 6-*O*-demethyl-salutaridine to salutaridine. In the early 1990s, the Makleit research group turned with great interest towards the Bentley-compounds [176,234]. The main driving force was the finding of Lewis *et al.* [300] that buprenorphine, a 6,14-ethenomorphinan type partial μOR agonist and κOR antagonist, serves as an alternate to methadone for the treatment of heroin/diamorphine dependence. Makleit *et al.* developed numerous novel synthesis routes for the

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efficient preparation of buprenorphine, diprenorphine and their N^{17}-substituted analogues. [230,301,302]. Very recently, we provided an overview of their research in the field of C-ring bridged morphinans together with the Diels-Alder adducts of morphinan-6,8-dienes and their transformations dating back almost a century [50]. We cannot omit mention of the investigations of Berényi, who established aporphine-chemistry as a new direction for the Debrecen alkaloid research group. They expended enormous efforts over the years for the synthesis of morphinan-6,8-dienes [50] and their rearrangements to potent dopaminergic aporphine derivatives [279,303]. We emphasize the efforts extending over many years by Hosztafi in methodological research for the *N*-demethylation of morphine alkaloids [304–306]. We also note the thorough investigations carried out by Seller *et al.* [307] for the refinement of the poppy alkaloid extraction technology with the help of modern technical equipment and separation methods.

Summary and Conclusions

In considering the cause-and-effect relationships in the current opioid crisis [308–311], it is important to appreciate the enormous efforts in medicinal chemistry driven by the dream of generations of scientists to find the ideal analgesic with reduced risk of dependence and overdose.

Here, the concept of biased pharmacology at the several OR subtypes presents a model for obtaining therapeutic responses, with lesser risk for dependence and side effects [45,46]. Comprehending the broad scope of this concerted search calls consideration of the historical background of these investigations, and its implications for the new generation of researchers and scholars.

In the present survey, we provide an overview of the organic chemical investigations of morphine alkaloids arising from an historical collaboration between Hungarian research groups in industry (Alkaloida Chemical Company) and academia (University of Debrecen), dating back to the 1950s. We emphasize the historical continuity of this endeavour, building continuously upon the pioneering work by Kabay, now recognized as having been one of the most important morphine alkaloid producers in the world [8]. The privatization of the Alkaloida Chemical Company following the political changes in Hungary in the 1990s brought to an abrupt end the five decades-long close and fruitful collaboration between the Department of Organic Chemistry at the University of Debrecen and the Alkaloida Chemical Company in Tiszavasvári. Our review intends to enshrine and memorialize that exemplary history of industrial/academic collaboration.

Supplementary Materials: The following supporting information can be downloaded at website of this paper posted on Preprints.org, Abbreviations; Figure 1. Morphine alkaloid research group of the Kossuth Lajos University (KLTE) in Debrecen and Alkaloida Chemical Company, Tiszavasvári, Hungary; Scientific titles awarded by the University of Debrecen in the field of poppy alkaloids.

Author Contributions: The manuscript was written with contributions of all the authors. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest: The authors have no conflicts of interest to declare.

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