

# Synthesis of Morphine Alkaloids and Derivatives

Uwe Rinner and Tomas Hudlicky

**Abstract** This review summarizes recent developments in the total synthesis of morphine alkaloids and some of the semisynthetic derivatives. The literature is covered for the period of 5 years after the publication of the last review in 2005. The syntheses that appeared in this period are covered in detail and are placed in the context of all syntheses of opiate alkaloids since the original one published by Gates in 1952. The introduction covers the historical aspects of total synthesis of these alkaloids. The synthesis of some of the medicinally useful derivatives is reviewed in the last section along with some of the methodology required for their preparation.

**Keywords** Alkaloids · Analgesia · Codeine · Demethylation · Morphine · Total synthesis

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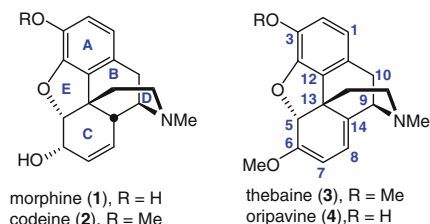
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## Abbreviations

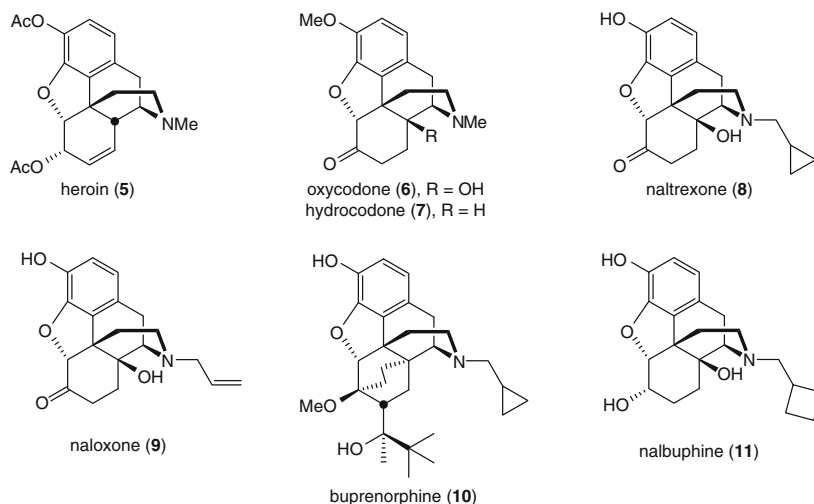
|          |                                               |
|----------|-----------------------------------------------|
| 2,4-DNPH | 2,4-Dinitrophenylhydrazine                    |
| BHT      | Butylated hydroxytoluene                      |
| CSA      | Camphorsulfonic acid                          |
| DDQ      | Dichloro dicyano benzoquinone                 |
| DEAD     | Diethyl azodicarboxylate                      |
| DIAD     | Diisopropyl azodicarboxylate                  |
| DMAP     | 4-Dimethylaminopyridine                       |
| DNsCl    | 2,4-Dinitrobenzene-sulfonyl chloride          |
| dpa      | Dibenzylidenacetone                           |
| dppf     | 1,1'- <i>Bis</i> (diphenylphosphino)ferrocene |
| dppp     | 1,3- <i>Bis</i> (diphenylphosphino)propane    |
| EDCI     | 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide |
| IBX      | 2-Iodoxybenzoic acid                          |
| KHMDS    | Potassium <i>bis</i> (trimethylsilyl)amide    |
| LiHMDS   | Lithium <i>bis</i> (trimethylsilyl)amide      |
| MCPBA    | 3-Chloroperbenzoic acid                       |
| NaHMDS   | Sodium <i>bis</i> (trimethylsilyl)amide       |
| NBS      | <i>N</i> -Bromosuccinimide                    |
| PAD      | Potassium azodicarboxylate                    |
| PPTS     | Pyridinium <i>p</i> -toluenesulfonate         |
| TBAF     | <i>tetra-n</i> -Butylammonium fluoride        |
| TCDI     | Imidazole 1,1'-thiocarbonyldiimidazole        |
| TFA      | Trifluoroacetic acid                          |

## 1 Introduction

Morphine (**1**) and its congeners, codeine (**2**), thebaine (**3**), and oripavine (**4**), Fig. 1, as well as other minor constituents of the opium poppy latex, continue to garner interest of the chemical community for a number of reasons. The focus on the total synthesis of these alkaloids in the academic sector has not waned and now spans almost 60 years since the seminal disclosure of the first synthesis by Gates in 1952 [1, 2].



**Fig. 1** Morphine and congeners



**Fig. 2** Opiate-derived agonists and antagonists for legal and illicit (i.e., heroin) use

The medical community requires a constant supply of morphine and other analgesic agents for pain control. The unnatural derivatives of morphine, whether agonists or antagonists, are all derived by semisynthesis from the naturally occurring alkaloids harvested primarily in Asia and Tasmania for legal consumption. The extent of illicit use of morphine and other derivatives, such as heroin (5), Fig. 2, can only be estimated but likely exceeds \$800 billion annually. Some opiate-derived products, such as the analgesics oxycodone (6) and hydrocodone (7), enjoy a widespread legal as well as illicit use. The antagonists and mixed agonists, all derived by semisynthesis, include naltrexone (8) for treatment of alcohol addiction [3], naloxone (9) for treatment of opiate overdose [4], buprenorphine (10), and nalbuphine (11), Fig. 2.

Naltrexone is an opioid receptor antagonist used primarily in the management of alcohol and/or opioid dependence. It is marketed in generic form as its hydrochloride salt, naltrexone hydrochloride, and sold under the trade names Revia™ and Depade™. Naltrexone and its active metabolite 6-β-naltrexol are competitive antagonists at μ- and κ-opioid receptors, and to a lesser extent at δ-opioid receptors [5]. Naloxone is a drug used to counter the effects of opioid

overdose, for example, heroin or morphine overdose. Naloxone is specifically used to counteract life-threatening depression of the central nervous system and respiratory system. It is also used in combination drugs such as Suboxone™ (buprenorphine and naloxone, 4:1). Nalbuphine is a synthetic opioid used commercially as an analgesic under a variety of trade names, including Nubain™. It is a mixed agonist/antagonist, noteworthy in part for the fact that at low dosages it is much more effective in women than in men, and may even increase pain in men [6], leading to its discontinuation in the UK in 2003. Nalbuphine is indicated for the relief of moderate to severe pain. It can also be used as a supplement to balanced anesthesia, for preoperative and postoperative analgesia, and for obstetrical analgesia during labor and delivery.

It is difficult to estimate accurately the worldwide requirements for these compounds. In the US, the DEA manufacturing quota in 2007 for oxymorphone for conversion to other medically important derivatives was 12 tons, compared to 1.8 tons for sale. Total consumption may be as high as 16.8 tons.<sup>1</sup> Estimates for combined naltrexone and naloxone production worldwide might therefore be around 10 tons for 2007. The worldwide demand for the compounds, shown in Figs. 1 and 2, whether legal or illicit, is tremendous and depends entirely on the supply of natural opiates. The estimates for the production of opiates worldwide are shown below in Tables 1 and 2.<sup>2</sup>

To date there is no practical source of morphine, either by chemical synthesis or through fermentation, that would compete with the cost of isolation. Of course, part of the reason that natural morphine is so inexpensive is the low-wage investment in harvesting it, mostly in Afghanistan, Turkey, and India. Were the workers there paid “western” wages, the price could never be as low as it is today (~\$400–700/kg). It is very likely that in the event of a natural or a political emergency in those regions that produce morphine and other opiates the price of the medicinal derivatives would climb sharply, and, at that time, the synthetic approaches would receive enhanced credibility. The use of morphine and derivatives in medicine is permanently entrenched in our society and the pricing of “synthetic” morphine, however formidable, would not lead to a decrease in legal use.

**Table 1** Worldwide production of raw materials. Designated as alkaloids contained in poppy straw (tons) (see footnote 1)

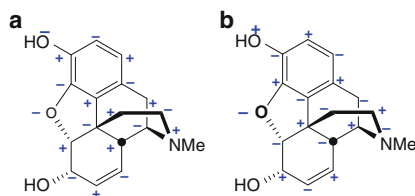
| Opiate        | 2003  | 2004  | 2005  | 2006  | 2007  |
|---------------|-------|-------|-------|-------|-------|
| Morphine (1)  | 349.9 | 300.8 | 333.4 | 333.8 | 287.5 |
| Codeine (2)   | 13.1  | 12.9  | 10.9  | 14.7  | 23.7  |
| Thebaine (3)  | 65.4  | 77.0  | 94.4  | 92.2  | 125.5 |
| Oripavine (4) | 19.1  | 21.8  | 24.7  | 22.0  | 23.6  |

<sup>1</sup>[http://www.incb.org/pdf/technical-reports/narcotic-drugs/2008/tables\\_of\\_reported\\_statistics.pdf](http://www.incb.org/pdf/technical-reports/narcotic-drugs/2008/tables_of_reported_statistics.pdf).

<sup>2</sup>The authors thank Dr. Phil Cox, Noramco, Inc. for providing the information in Tables 1 and 2.

**Table 2** Worldwide production of opiates in tons (numbers in *brackets* represent production in the US) (see footnote 1)

| Opiate                             | 2003         | 2004         | 2005         | 2006          | 2007          |
|------------------------------------|--------------|--------------|--------------|---------------|---------------|
| Morphine ( <b>1</b> ) <sup>a</sup> | 376.7 (99.0) | 354.7 (88.0) | 397.6 (96.0) | 415.8 (102.0) | 440.0 (112.2) |
| Codeine ( <b>2</b> ) <sup>a</sup>  | 288.7 (67.9) | 298.9 (63.7) | 309.8 (70.4) | 317.5 (73.4)  | 349.3 (77.0)  |
| Oxycodone ( <b>6</b> )             | 51.5 (41.1)  | 52.5 (40.3)  | 56.5 (40.3)  | 66.9 (49.7)   | 75.2 (55.7)   |
| Hydrocodone ( <b>7</b> )           | 29.8 (29.7)  | 32.1 (31.9)  | 35.6 (35.5)  | 39.7 (39.6)   | 38.2 (37.9)   |

<sup>a</sup>Includes morphine/codeine for conversion to other products**Fig. 3** Dissonant relationship in morphine connectivity (**a** = phenol priority, **b** = amine priority)<sup>3,4</sup>

Morphine has a fascinating history that can be gleaned by reading a number of sources [7, 8], that discuss its pharmacology [9, 10] and societal and historical impact on humans. The isolation of morphine precedes by some 25 years the “official” beginning of organic chemistry, the synthesis of urea by Wöhler. Its isolation from opium by Sertürner in 1805 [11–13] led to more than a century of effort before the final structure elucidation was completed [14]. Sertürner was also the first person to document “animal and human trials” with the newly isolated natural product [15]. Morphine, with its impact on chemists as well as on society in general, is likely one of the very few chemical entities that everyone recognizes.

Morphine’s synthesis remains a serious challenge to this day. Until recently, the formal synthesis published by Kenner Rice [16] was its most efficient preparation. In 2009, Magnus reported a route to codeine with a reported overall yield of approximately 17% [17]. All academic syntheses reported in the literature, creative as these may be, suffer from lack of practicality, with the sole exception of Rice’s disclosure, which has potential for scale-up.

Morphine, although not particularly complex, suffers from a complete “dissonant connectivity” (shown in Fig. 3) (Evans, 1972, Consonant and dissonant relationships. An organizational model, unpublished manuscript) [20], as we have previously

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<sup>4</sup>Hudlicky T, Reed, JW: the Way of Synthesis. Evolution of Design and Methods. Page 732. Publication year 2007. Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission.

pointed out on several occasions [18, 19]. Starting from either the phenolic oxygen (a) or the tertiary amine (b), it is not possible to draw a polarization assignment in which all electronegative atoms avoid an incorrect positive charge or in which alternating charges match. Because of this fact almost any strategy applied to the construction of morphine skeleton will, sooner or later, require major tactical maneuvers leading to an increase in the step-count and hence a decrease in practicality.

These issues have been addressed in detail in many previous reviews [18, 21–26]. Since our update on morphine synthesis was published 5 years ago in *Synlett* [18], several new approaches have appeared in the literature. This review summarizes the recent accomplishments and also provides for an update in methods used to approach some of the semisynthetic opiates.

The summary of accomplishments in the total synthesis of morphine alkaloids is depicted in Table 3. Most authors target codeine as the ultimate synthetic target; its attainment represents a formal total synthesis of morphine as Rice demonstrated its conversion to morphine by *O*-demethylation with  $\text{BBr}_3$  [55]. Such a strategy has

**Table 3** Summary of syntheses of morphine and derivatives

| Principal author   | Year | Target                                 | Steps          | Overall yield (as reported) |
|--------------------|------|----------------------------------------|----------------|-----------------------------|
| Gates [1, 2]       | 1952 | Morphine                               | 31             | 0.06                        |
| Ginsburg [27, 28]  | 1954 | <i>rac</i> -Dihydrothebainone          | 21             | 8.9                         |
| Grewe [29, 30]     | 1967 | <i>rac</i> -Dihydrothebainone          | 9              | 0.81                        |
| Rice [16]          | 1980 | Dihydrocodeinone                       | 14             | 29.7                        |
| Evans [31]         | 1982 | <i>rac</i> - <i>O</i> -Me-thebainone A | 12             | 16.7                        |
| White [32]         | 1983 | Codeine                                | 8 <sup>a</sup> | 1.8                         |
| Rapoport [33]      | 1983 | <i>rac</i> -Codeine                    | 26             | 1.2                         |
| Fuchs [34, 35]     | 1987 | <i>rac</i> -Codeine                    | 23             | 1.3                         |
| Tius [36]          | 1992 | <i>rac</i> -Thebainone-A               | 24             | 1.1                         |
| Parker [37, 38]    | 1992 | <i>rac</i> -Dihydrocodeinone           | 11             | 11.1                        |
| Overman [39]       | 1993 | Dihydrocodeinone                       | 14             | 1.9                         |
| Mulzer [40]        | 1996 | Dihydrocodeinone                       | 15             | 9.1                         |
| Parsons [41]       | 1996 | Morphine                               | 5 <sup>b</sup> | 1.8                         |
| White [42]         | 1997 | <i>ent</i> -Morphine                   | 28             | 3.0                         |
| Mulzer [43]        | 1997 | Dihydrocodeinone                       | 18             | 5.7                         |
| Ogasawara [44, 45] | 2001 | Dihydrocodeinone ethylene ketal        | 21             | 1.5                         |
| Taber [46]         | 2002 | Morphine                               | 27             | 0.51                        |
| Trost [47, 48]     | 2002 | Codeine                                | 15             | 6.8                         |
| Fukuyama [49]      | 2006 | <i>rac</i> -Morphine                   | 25             | 6.7                         |
| Hudlicky [50]      | 2007 | <i>ent</i> -Codeine                    | 15             | 0.23                        |
| Iorga/Guillou [51] | 2008 | <i>rac</i> -Codeine                    | 17             | 0.64                        |
| Chida [52]         | 2008 | <i>rac</i> -Dihydroisocodeine          | 24             | 3.8                         |
| Hudlicky [15]      | 2009 | Codeine                                | 18             | 0.19                        |
| Magnus [17]        | 2009 | <i>rac</i> -Codeine                    | 13             | 20.1                        |
| Stork [53]         | 2009 | <i>rac</i> -Codeine                    | 22             | 2.0                         |
| Fukuyama [54]      | 2010 | Morphine                               | 18             | 4.8                         |

<sup>a</sup>*N*-Norreticuline was used as advanced starting material

<sup>b</sup>Only the last five steps of the synthesis have been published in the cited journal

a historical basis as, in the early days of structure elucidation, chemists found it easier to perform degradation on codeine because it was air stable. Morphine is more difficult to handle for several reasons. First, it has the properties of an amino acid, and, second, it is easily oxidized by air (hence the dark color of raw opium). Once it was established that morphine and codeine differ only by the absence or presence of the *O*-methyl group, all subsequent work was carried out with codeine.

Modern approaches no doubt subscribe to a similar strategy for the same reasons and thus most published syntheses stop at the stage of codeine. The syntheses are listed chronologically, with the yields “as reported.” It is impossible to validate the claimed yields, especially overall yields, in cases where the reactions are performed on very small scales. Claims of reaction product yields above 94% are clearly erroneous in nature and should be viewed with suspicion. Similarly, the credibility of overall yields above 2 or 3% is questionable, as explained in a recent treatise on accuracy in reporting isolated product yields [56]. An exception to this statement are the yields reported in the synthesis of Rice [16], which was performed on a multigram scale.

## 2 Early Syntheses of Morphine

The following section highlights two milestone achievements in morphine synthesis. In 1952, Gates published the first total synthesis of the title alkaloid [1, 2] and was thus able to prove the structure of morphine proposed by Robinson in 1925 to be correct [57]. In addition, both enantiomers of morphine can be accessed following the published route as Gates performed a resolution of an advanced intermediate (see Scheme 2, compound 20). Although Gates did not benefit from modern synthetic methods and structure elucidation techniques such as NMR spectroscopy, he was able to determine the identity of synthetic intermediates by derivatization and degradation studies of natural morphine. Written almost 60 years ago, the original report demonstrates the amazing knowledge of reactions, purification, and structure determination abilities of early synthetic chemists. Gates’s full paper, as well as the earlier papers dealing with model studies, should be recommended reading assignment for all students of organic synthesis.

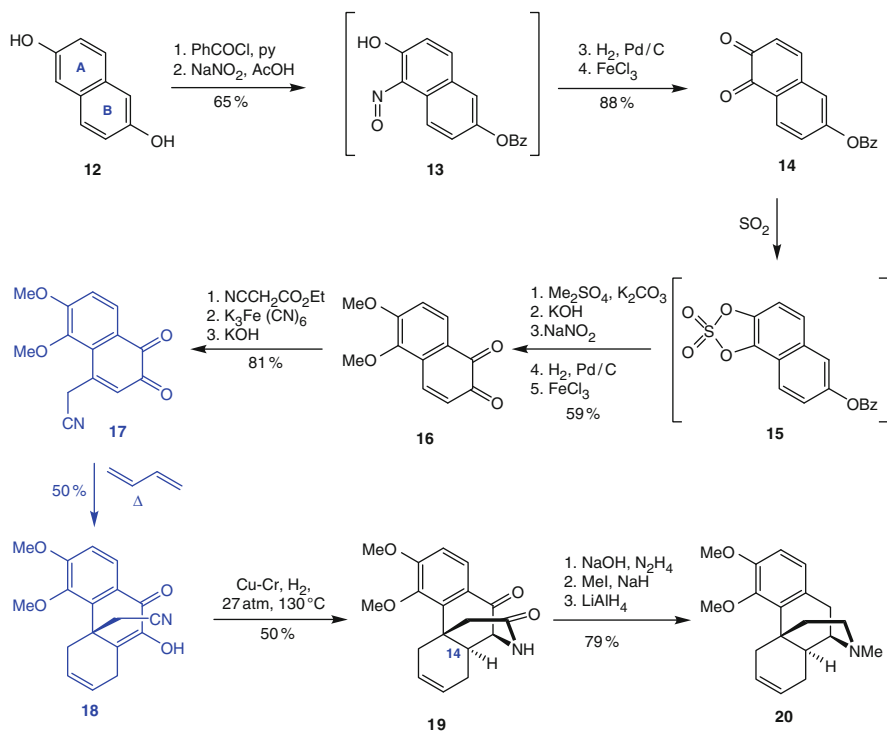
The very short and highly efficient biomimetic synthesis of morphine [16, 32] by Rice stands out in terms of overall yield and brevity; no subsequent contribution to this area exceeds this milestone achievement. The route follows the biosynthetic pathway and delivers dihydrocodeinone in almost 30% overall yield.

Although the syntheses of morphine by Gates and Rice have been reviewed on several occasions [14, 19, 24], they are included in this review as they constitute important highlights in the history of morphine research against which all other approaches should be judged. (For clarity and better understanding, the key transformations in featured syntheses are depicted in blue color within the schemes).

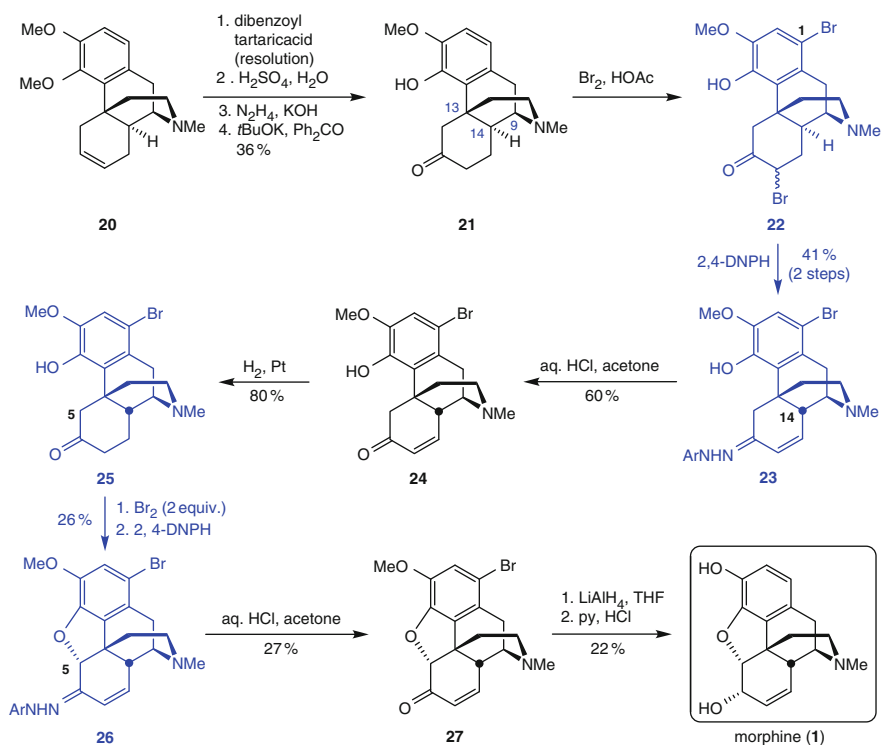
## 2.1 Gates (1952)

Gates utilized 2,6-dihydroxynaphthalene (**12**) as starting material and synthon for the A,B-ring system of morphine [58]. As outlined in Scheme 1, monoprotection to the corresponding benzoyl naphthol was followed by nitrosation (**13**) and formation of ortho quinone **14**. When treated with sulfur dioxide, cyclic sulfate **15** was formed which upon exposure to dimethyl sulfate provided the methylated catechol. An identical second nitrosation protocol delivered the B-ring of the alkaloid (**16**) for conjugate addition of ethyl cyanoacetate and subsequent reoxidation ( $K_3Fe(CN)_6$ ). Decarboxylation under basic conditions gave nitrile **17**, which served as precursor for the key cycloaddition reaction. Diketone **18** (shown as enol) was obtained when nitrile **17** was heated with butadiene and the material was subjected to a copper chromite reduction, which provided amide **19**. A sequence involving Wolff–Kishner reduction, methylation, and  $LiAlH_4$  reduction then afforded morphinan **20**.

With morphinan **20** in hand, the stage was set for the deracemization and functionalization of the D ring of the alkaloid. Resolution of racemic amine **20** with dibenzoyl tartrate (Scheme 2) afforded the isomer with correct configuration at C9 and C13 but epimeric at C14. The identity of the synthetic material was unambiguously confirmed



**Scheme 1** Gates's synthesis of morphine – part 1

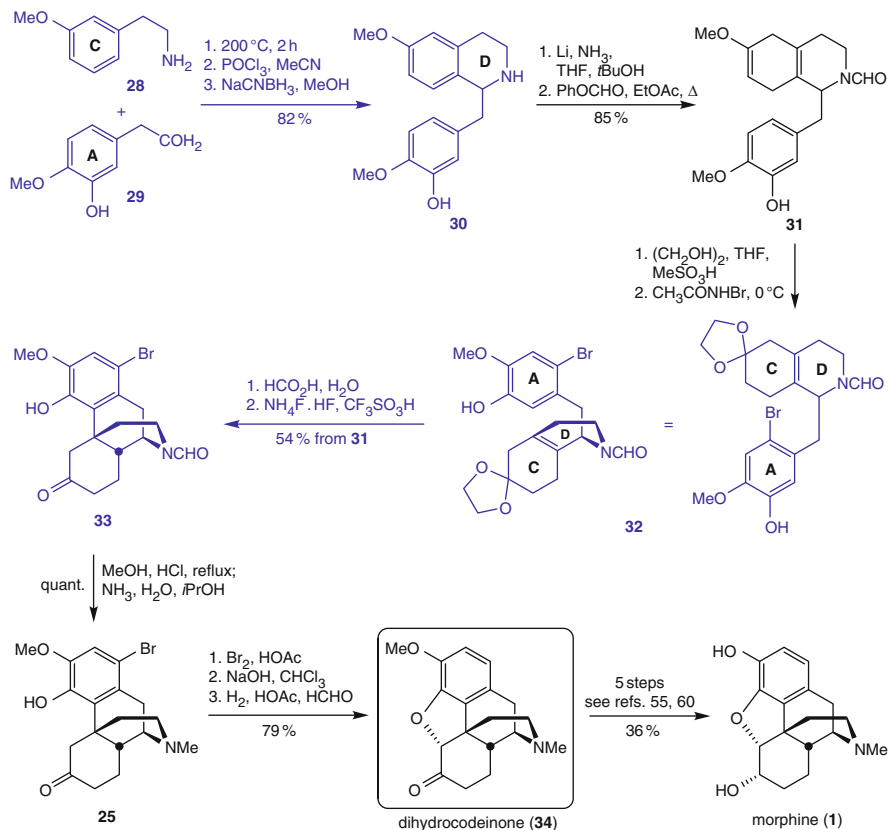


**Scheme 2** Gates's synthesis of morphine – part 2

by direct comparison with degradation products obtained from natural codeine, thus confirming the structure of the morphinan skeleton as postulated by Robinson [57]. Furthermore, the remaining steps in the forward synthesis were facilitated by access to larger amounts of material from natural sources. Regioselective hydration and selective monodemethylation with hydrazine and  $\text{KOH}$  in ethylene glycol were followed by a modified Oppenauer oxidation and ketone **21** was obtained.  $\alpha$ -Bromination (along with bromination of the aromatic ring) afforded **22**, which, upon reaction with 2,4-dinitrophenylhydrazine (2,4-DNPH), gave **23** with concomitant epimerization at C14 to the thermodynamically more favored natural configuration. Hydrolysis of the hydrazone and hydration gave **25**, which was brominated and treated with 2,4-DNPH, resulting in the closure of the dihydrofuran ring (**26**). Hydrolysis of the hydrazone delivered the  $\alpha,\beta$ -unsaturated ketone **27**, which was converted into codeine via hydrogenation and reduction of the ketone and the aryl bromide. The use of the unsaturated hydrazone for both epimerization and  $\alpha$ -bromination of the C5 position was indeed ingenious and attests to the level of thought that Gates had given to this protocol. Demethylation with hydrochloric acid in pyridine as described by Rapoport [59] concluded the first total synthesis and the final structure proof of morphine (**1**).

## 2.2 Rice (1980)

Rice achieved the shortest and the most efficient formal synthesis of morphine via a biomimetic approach with a Grewe cyclization as the key step (Scheme 3). Condensation of amine **28** and acid **29** is followed by a Bischler–Napieralski reaction and sodium cyanoborohydride reduction to establish the C,D-ring of the alkaloid (**30**). Birch reduction and subsequent N-formylation with phenyl formate gave the methyl enol ether **31**. Ketalization and bromination of the aromatic ring, to protect the para position, afforded **32** as the precursor for the key electrophilic cyclization reaction as described previously by Grewe [29]. This reaction was achieved via treatment of **32** with formic acid to release the  $\beta,\gamma$ -unsaturated ketone and subsequent exposure to  $\text{NH}_4\text{F} \cdot \text{HF}$  in TfOH. Morphinan **33** was deformed and converted into **25** by reductive amination before the dihydrofuran ring was established via bromination of the  $\alpha$ -position of the ketone and deprotonation of the phenol. The aryl bromide was removed by hydrogenation in the presence

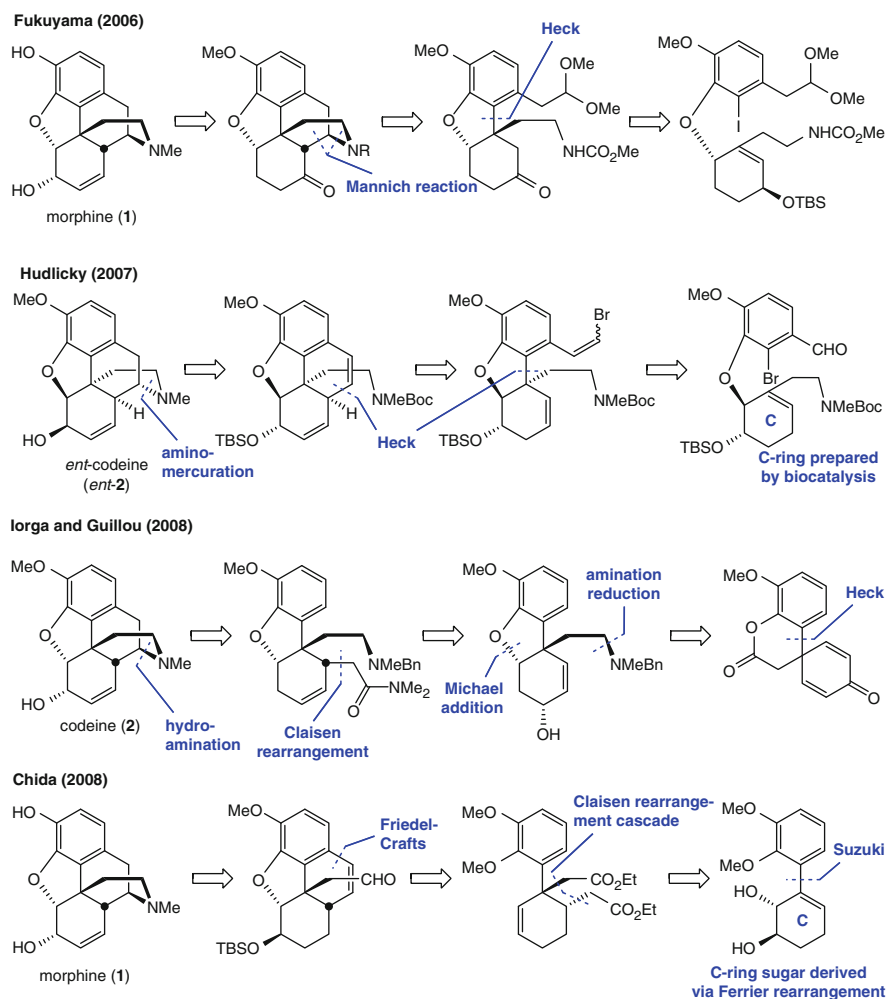


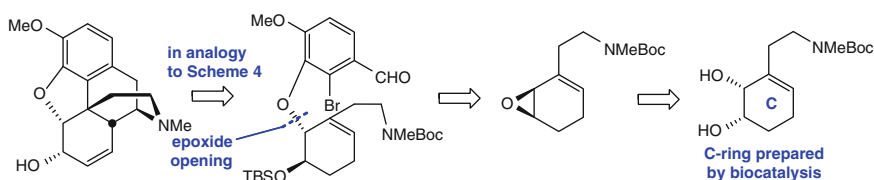
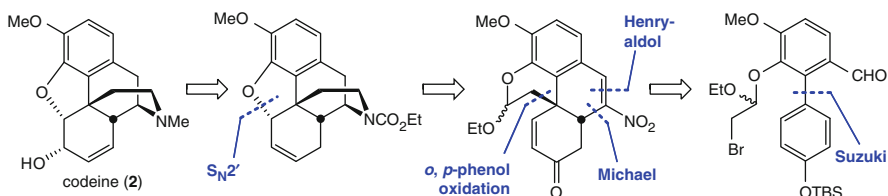
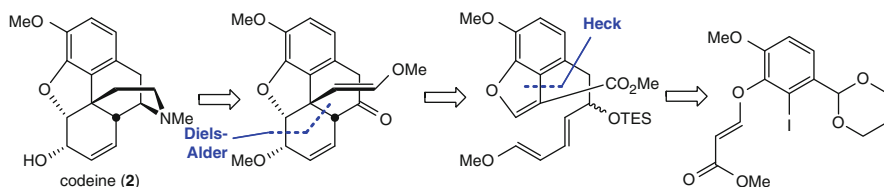
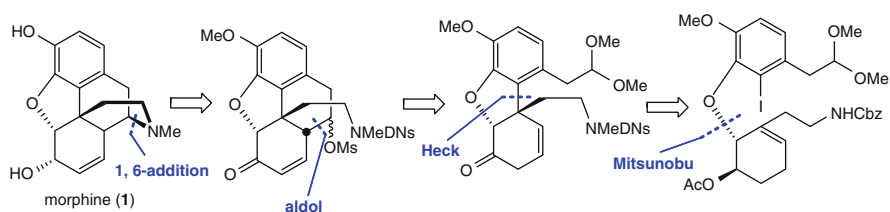
**Scheme 3** Rice's biomimetic synthesis of morphine

of formaldehyde and dihydrocodeinone (**34**) was isolated. The conversion of this material to morphine has been described before [55, 60] and the preparation of dihydrocodeinone (**34**) constituted the formal synthesis of codeine and/or morphine.

### 3 Recent Syntheses of Morphine and/or Codeine

This section summarizes all syntheses of morphine and codeine published since the last major review in this area was published in 2005 [18]. A general overview of the key strategic elements in all syntheses discussed within this section is provided in Schemes 4 and 5.

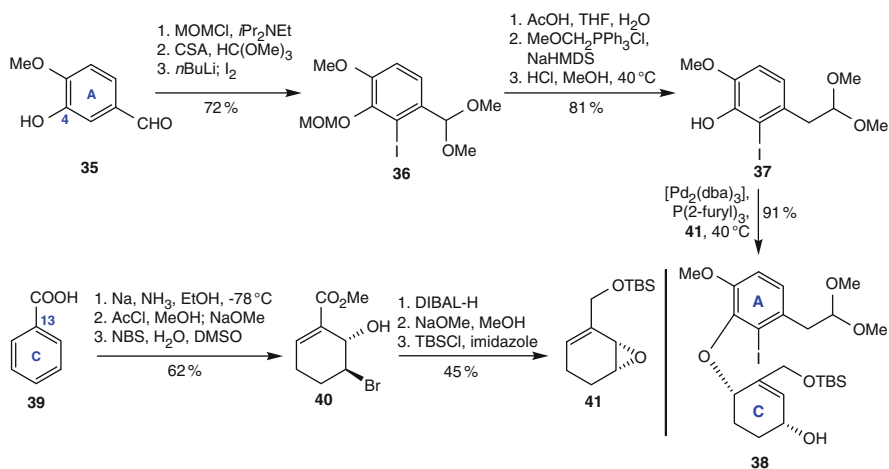


**Hudlicky (2009)****Magnus (2009)****Stork (2009)****Fukuyama (2010)****Scheme 5** Overview of strategies in the recent syntheses of morphinans – part 2**3.1 Fukuyama (2006)**

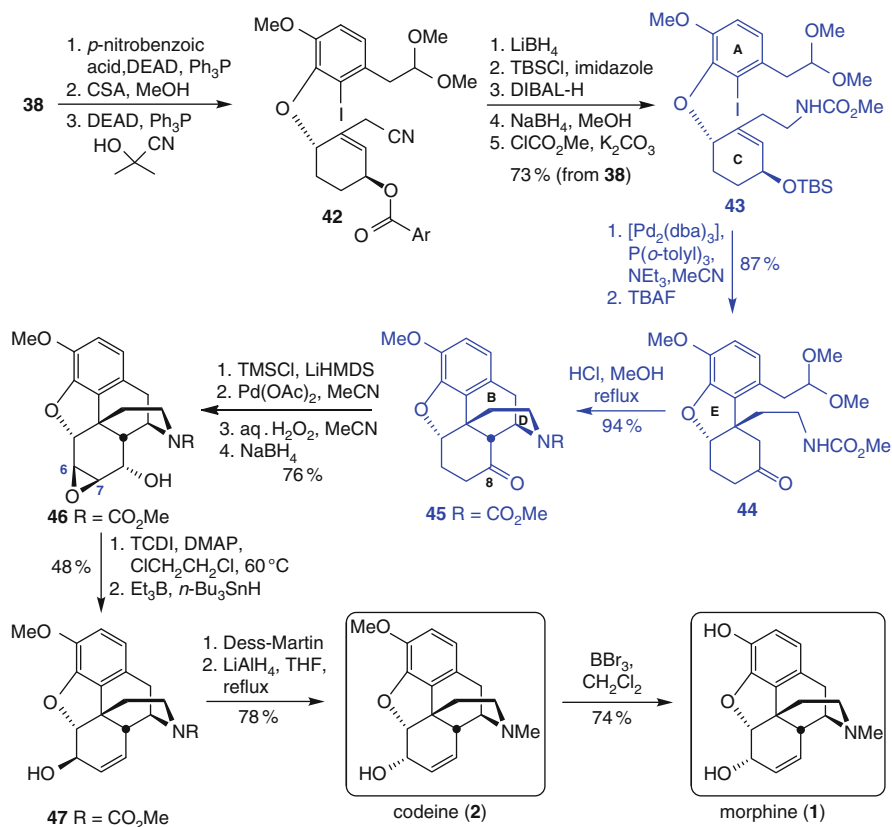
In 2006, Fukuyama presented an approach to codeine and morphine based on a Tsuji–Trost coupling and intramolecular Heck reaction as key steps [49, 61]. The synthesis was carried out in the racemic manifold; however, by devising an alternative stereoselective route to epoxide **41**, access to either the natural or the enantiomeric form of morphine could be achieved.

As outlined in Scheme 6, isovanillin (**35**) was converted to aryl iodide **36** via MOM-protection, protection of the aldehyde, and subsequent iodination. Hydrolysis of the acetal and Wittig olefination delivered phenol **37** after exposure of the intermediate aldehyde to methanolic hydrochloric acid. Epoxide **41**, the coupling partner of phenol **37** in the key Tsuji–Trost-reaction, was synthesized from benzoic acid following a procedure developed by Fukuyama for the synthesis of strychnine [62]. Birch reduction of benzoic acid with subsequent isomerization of one double bond into conjugation was followed by esterification and bromohydrin formation (**40**). The ester was reduced and the bromohydrin was treated with base to provide the epoxide. Silylation concluded the preparation of epoxide **41**, the coupling partner for iodide **37**, and both fragments were reacted in the presence of palladium to attain iodide **38**.

The configuration of the secondary alcohol in **38** (Scheme 7) was inverted by means of a Mitsunobu reaction with *p*-nitrobenzoic acid, and the silyl ether was cleaved under acidic conditions. The primary alcohol was converted into nitrile **42** under Mitsunobu conditions utilizing the cyanohydrin derived from acetone. Reductive cleavage of the *p*-nitrobenzyl ester was followed by TBS protection of the resulting secondary alcohol and the installation of a methyl carbamate (**43**) before the key Heck cyclization was achieved in excellent yield. The silyl enol ether obtained after this crucial transformation was cleaved and ketone **44** was obtained as single isomer. Next, the B and D rings were closed, presumably via an intramolecular Mannich-type reaction, by heating carbamate **44** to reflux in methanolic hydrogen chloride. With morphinan **45** in hand, Fukuyama turned his attention to the functionalization of the C-ring of the alkaloid. Epoxidation of the  $\alpha,\beta$ -unsaturated ketone obtained after a Segusa-oxidation protocol furnished alcohol **46** after sodium borohydride reduction. The hydroxy moiety was converted into a thiocarbonate and subjected to radical reaction conditions resulting in epoxide



**Scheme 6** Fukuyama's synthesis of morphine – part 1

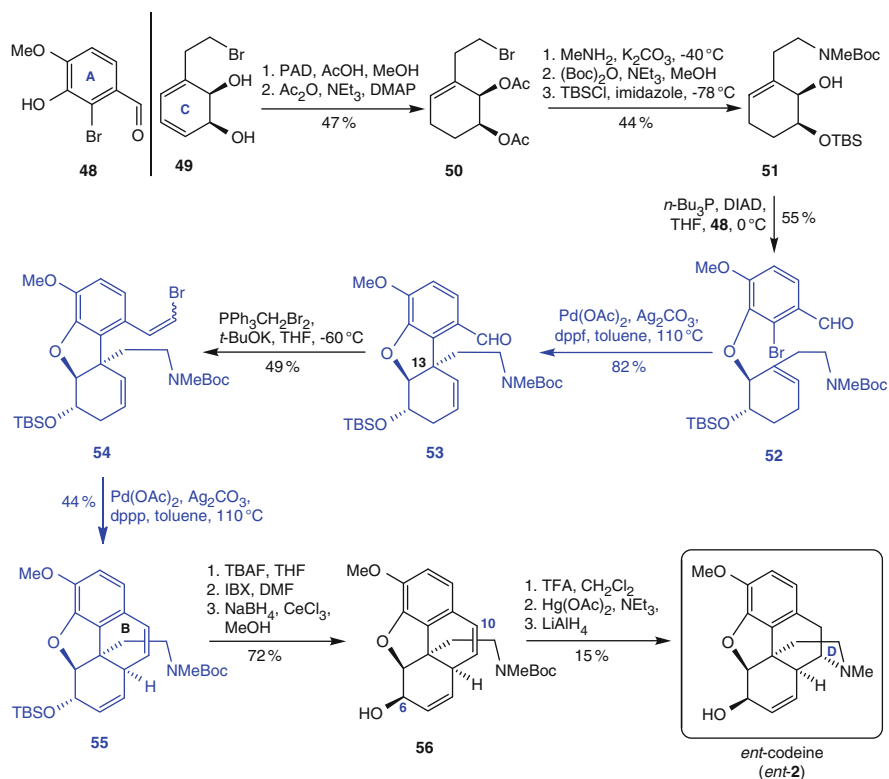


**Scheme 7** Fukuyama's synthesis of morphine – part 2

opening and formation of allylic alcohol **47**. The synthesis of codeine (**2**) was accomplished after inversion of the alcohol via the known oxidation/reduction sequence [46, 60]. Morphine (**1**) was obtained after cleavage of the methyl ether following a procedure published by Rice in 1977 [55].

### 3.2 Hudlicky (2007)

In 2007, Hudlicky and co-workers reported the preparation of *ent*-codeine (*ent*-**2**) with the enzymatically derived cyclohexadiene diol **49** as the starting material (Scheme 8) [50]. Key steps in this synthesis involve the introduction of the aryl moiety via a Mitsunobu reaction, a Heck reaction to establish the carbon bond between the aromatic ring and C13 followed by a second Heck reaction to close



**Scheme 8** Hudlicky's synthesis of *ent*-codeine

the B-ring with concomitant shift of the double bond into the position present in the natural product and final closure of the D-ring.

Whole cell oxidation of  $\beta$ -bromoethylbenzene with recombinant *Escherichia coli* JM109 (pDTG601A) [63] afforded cyclohexadiene-*cis*-diol **49**, which was selectively reduced with potassium azodicarboxylate (PAD) before the hydroxy functionalities were protected as acetate **50**. The *bis*-acetate was reacted with methylamine and the corresponding secondary amine was obtained with concomitant cleavage of the acetate functionalities. N-Boc-protection and silylation of the distal hydroxy functionality resulted in allylic alcohol **51**, which served as coupling partner in a Mitsunobu reaction with phenol **48**. Intramolecular Heck cyclization of aryl bromide **52** afforded aldehyde **53** in excellent yield as a single isomer. A Wittig reaction was then used to introduce a vinyl bromide moiety and served to prepare the substrate for the second Heck cyclization reaction to close the B-ring and simultaneously shift the double bond in the position present in the natural product. The configuration of the C6 hydroxy group in **55** was corrected via the known oxidation/reduction sequence [46, 60] after the cleavage of the silyl ether and **56** was isolated. The closure of the

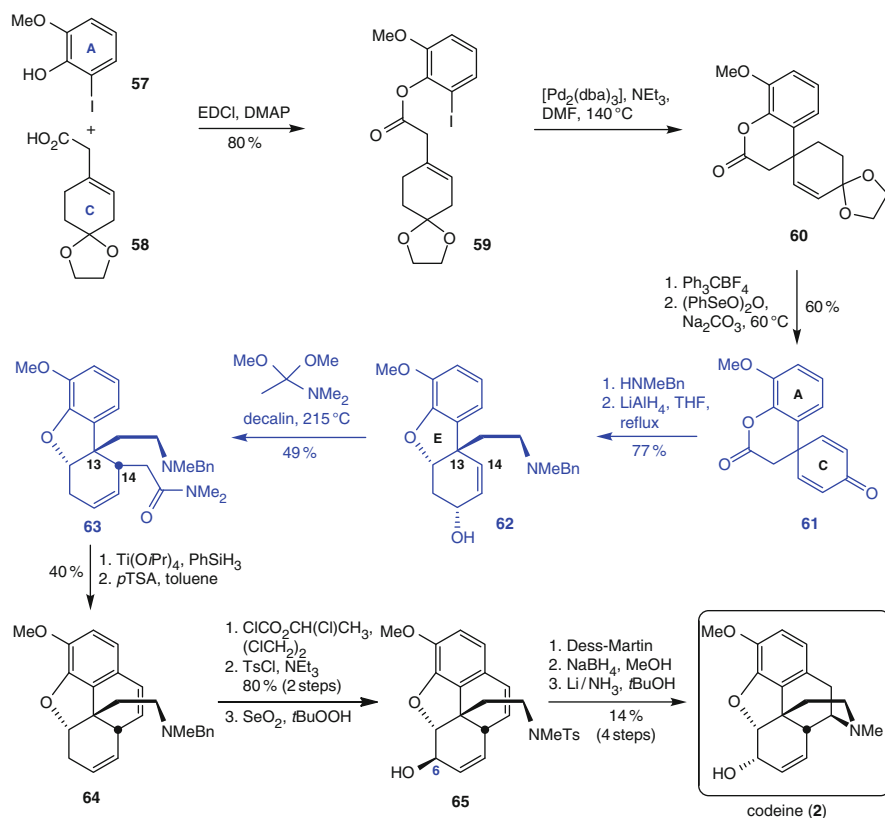
D-ring concluded the synthesis of *ent*-codeine. All attempts to repeat the hydroamination protocol published by Trost for the same synthetic intermediate [47, 48] failed and a different strategy for this operation had to be devised. The D-ring was established by removal of the Boc-protecting group followed by aminomercuriation of the benzylic double bond and intramolecular trapping of the resulting organomercurial species by the ethylamino sidechain. The final steps required the reduction ( $\text{LiAlH}_4$ ) of the organomercury compounds formed during the aminomercuriation protocol.

Two years after the publication of *ent*-codeine, Hudlicky also presented a route towards codeine (natural series) employing the same enzymatically derived starting material (49) [15]. The synthesis of the natural isomer is outlined in Sect. 3.5.

### 3.3 Iorga and Guillou (2008)

Iorga and Guillou presented a route to racemic codeine with a lactone opening/Michael addition sequence and an Eschenmoser–Claisen rearrangement as key steps (Scheme 9) [51]. Acid 58, accessible by Birch reduction of *p*-methoxyphenylacetic acid and subsequent ketalization with ethylene glycol, was esterified with 2-iodo-6-methoxyphenol (57). Subsequent Heck cyclization of ester 59 delivered spirocyclic lactone 60. Hydrolysis of the ketal and oxidation of the corresponding  $\alpha,\beta$ -unsaturated ketone delivered lactone 61, which was allowed to react with *N*-methylbenzylamine, resulting in lactone opening and amide formation. Upon reduction with  $\text{LiAlH}_4$  in refluxing THF, the amine 62 was obtained. During the course of this reaction the deprotonated phenol acted as the nucleophile in a Michael-type addition with concomitant formation of the E-ring. Thus, the exocyclic two-carbon chain in 58 served a dual purpose: it was used as a convenient tether for the intramolecular Heck cyclization of 59 and later provided the ethylamino bridge to complete ring D of morphine.

The allylic alcohol was subjected to an Eschenmoser–Claisen rearrangement with dimethylacetamide dimethylacetal to introduce the C14 substituent in a stereoselective manner. Reduction of the amide to the corresponding aldehyde with phenyl silane in the presence of  $\text{Ti}(\text{O}i\text{Pr})_4$  was followed by an acid-promoted closure of the C-ring of codeine. In order to prevent N-oxidation, the amine was converted to the corresponding tosylamide, via debenzylation and treatment with tosyl chloride, before the allylic alcohol was introduced by the reaction of the alkene with selenium dioxide (65). The stereochemistry of the C6 hydroxy functionality was corrected by applying the well-known oxidation/reduction protocol [46, 60] before the benzylic double bond was reductively removed under Birch conditions. Codeine (2) was obtained in 17 steps with an overall yield of approximately 0.6%.



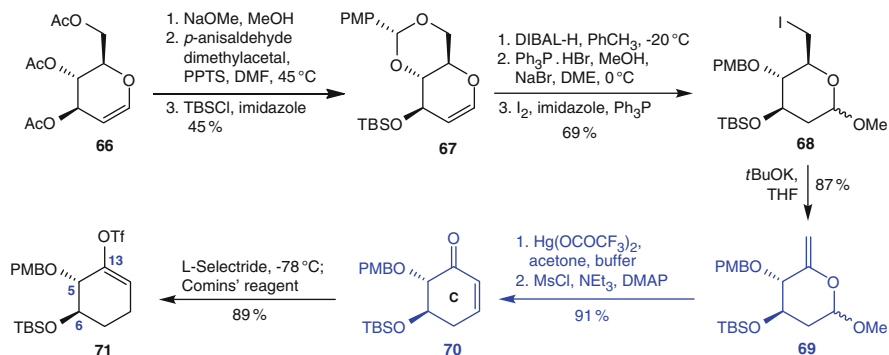
**Scheme 9** Iorga and Guillou's synthesis of codeine

### 3.4 Chida (2008)

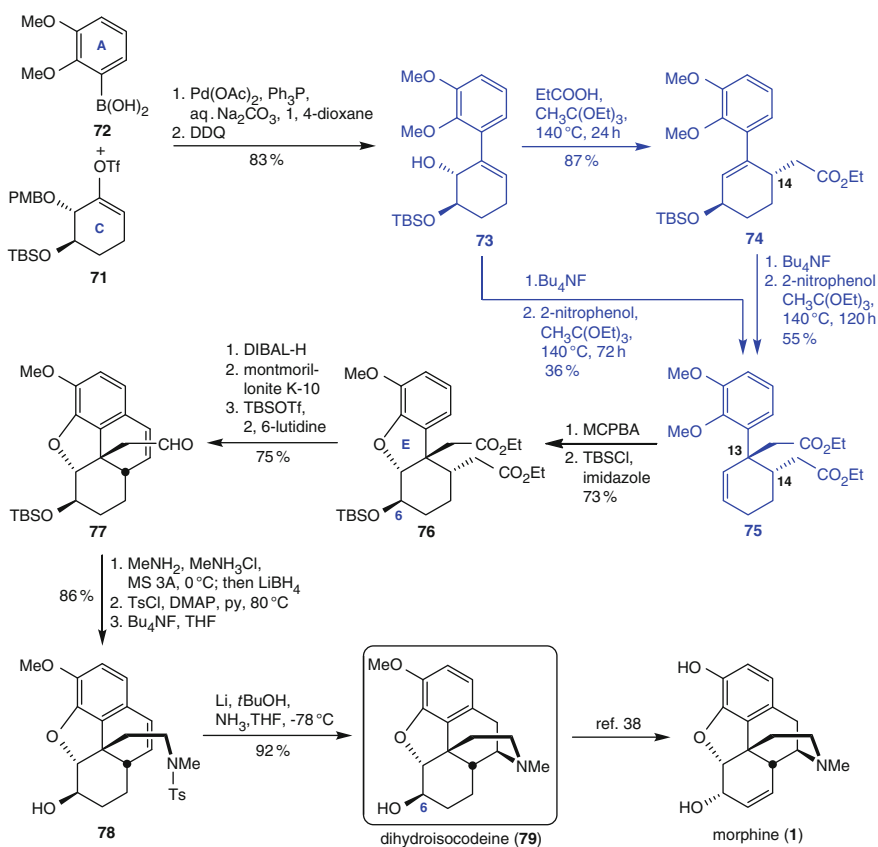
With the preparation of racemic dihydroisocodeine (**79**), Chida reported a formal synthesis of morphine [52]. The synthesis is based on a cascade of sequential Claisen rearrangements of an allylic vicinal diol derivative as key steps. The Claisen rearrangement protocol, as an efficient strategy for the installation of the C13 quaternary carbon, was successfully employed in the preparation of the Amaryllidaceae alkaloid galanthamine, published 1 year before the synthesis of dihydroisocodeinone [64].

With commercially available tri-*O*-acetyl-D-glucal (**66**) as the requisite chiral starting material, dihydroisocodeine was obtained in 24 synthetic operations. The route to the alkaloid is outlined in Schemes 10 and 11.

The C-ring of morphine was prepared from tri-*O*-acetyl-D-glucal (**66**) as shown in Scheme 10. Saponification of the acetate moieties in **66** under basic conditions was followed by treatment with *p*-anisaldehyde dimethylacetal before the C6 hydroxy functionality (morphine numbering) was protected as its silyl ether (**67**).



Scheme 10 Chida's synthesis of dihydroisocodeine – part 1



Scheme 11 Chida's synthesis of dihydroisocodeine – part 2

Reductive cleavage of the *para*-methoxyphenyl (PMP-) group released the primary alcohol and the compound was converted into the corresponding methyl glycoside upon reaction with methanol in the presence of  $\text{Ph}_3\text{P.HBr}$  [65]. Subsequently, the primary alcohol was replaced by iodine to yield **68** to pave the way for the introduction of the exomethylene functionality required for the key Ferrier's carbocyclization reaction. Carbocycle **70** was obtained after exposure of 5-enopyranoside **69** to  $\text{Hg}(\text{OCOCF}_3)_2$  in acetone/acetate buffer and the subsequent  $\beta$ -elimination. The synthesis of the C-ring of the alkaloid was completed by 1,4-reduction and formation of the vinyl triflate **71** with the Comins' reagent.

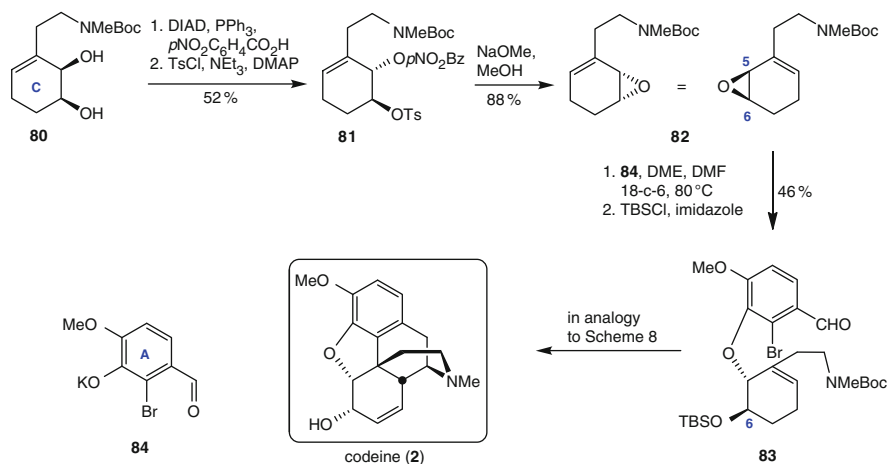
Suzuki coupling of vinyl triflate **71** with boronic acid **72** (Scheme 11) was followed by the cleavage of the PMB ether by means of a dichloro dicyano benzoquinone (DDQ) oxidation to afford allylic alcohol **73** in good yield. When treated with triethyl orthoacetate, the first Claisen rearrangement of **73** took place and ester **74** was obtained in nearly 90% yield as a single stereoisomer. The silyl ether was then cleaved and the corresponding alcohol was used in a second Claisen rearrangement, which delivered the *bis*-ester **75** in 55% yield. *Bis*-ester **75** could also be obtained in a cascade Claisen sequence as shown in Scheme 11. To this end the silyl group in **73** was cleaved to afford the corresponding diol which was then treated with triethyl orthoacetate and heated to 140 °C for 72 h in the presence of 2-nitrophenol, allowing the product of the double Claisen rearrangement, namely compound **75**, to be isolated in 36% yield.

The E-ring of morphine was installed via epoxidation of the C5–C6 double bond and simultaneous dealkylating/epoxide opening sequence using MCPBA as oxidant. Silylation of the secondary alcohol at C6 (**76**) was followed by elaboration of the B-ring of the alkaloid. This was accomplished by DIBAL-H reduction of both ester functionalities in **76** to the corresponding aldehydes and subsequent Friedel-Crafts type cyclization reaction. Elimination of the resulting hydroxyl group afforded alkene **77**. Reductive amination and tosylation of the nitrogen gave **78** after cleavage of the C6 silyl ether. The D-ring was finally established upon treatment of **78** under Birch conditions and dihydroisocodeine **79** was obtained. As this material was previously successfully converted into morphine [38] this achievement formalized the synthesis.

### 3.5 Hudlicky (2009)

Two years after the synthesis of *ent*-codeine [50], Hudlicky published a route to the natural enantiomer of the alkaloid [15]. With biocatalytically-derived cyclohexadiene-*cis*-diol **49** (Scheme 8), the same starting material in the synthesis of the enantiomer of the natural product was utilized. The strategic difference between the two syntheses is based on the preparation of epoxide **82** obtained via a Mitsunobu inversion/elimination protocol of the diol **80** (Scheme 12).

The cyclohexadiene-*cis*-diol **49**, derived enzymatically from  $\beta$ -bromoethylbenzene, was converted into Boc-protected amine **80** as described previously and



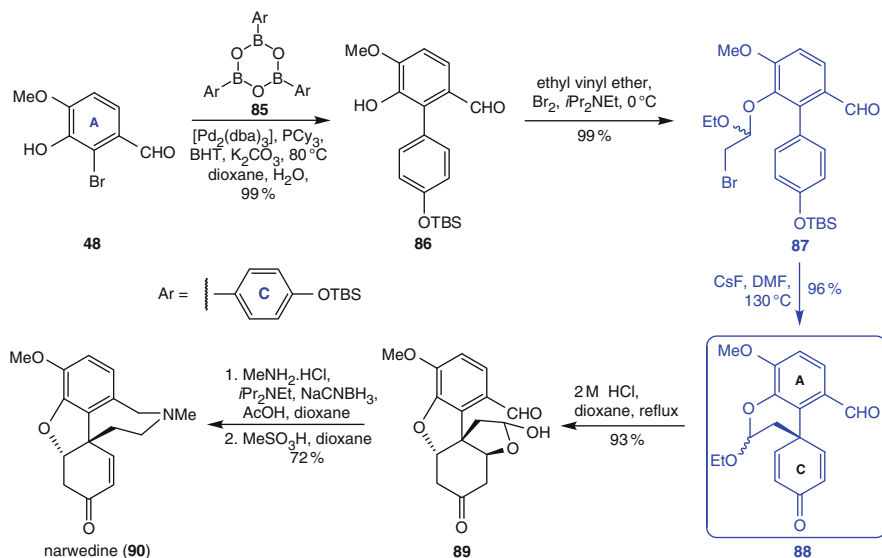
**Scheme 12** Hudlicky's synthesis of codeine

outlined in Scheme 8. Inversion of the allylic alcohol by means of a Mitsunobu reaction was followed by tosylation of the remaining hydroxyl functionality (**81**). Basic hydrolysis of the *p*-nitrobenzoate afforded epoxide **82**, which served as the electrophile in the reaction with the potassium salt of bromoisovanillin (**84**). Silylation of the C6 hydroxy group (morphine numbering) afforded aryl bromide **83** and the remaining steps in the route to codeine were carried out in analogy to the preparation of the enantiomer published in 2007. With this slight modification of the synthetic strategy, the natural product and the enantiomeric series of the target compound become available utilizing the same biocatalytically-derived starting material.

### 3.6 Magnus (2009)

In 2009, Magnus published an approach towards codeine that also constitutes a formal synthesis of the Amaryllidaceae alkaloid galanthamine by the preparation of narwedine (**90**) via a common precursor [17]. Key step in the reaction sequence is an *o-p*-phenolic oxidation resulting in the aforementioned common precursor of galanthamine and codeine.

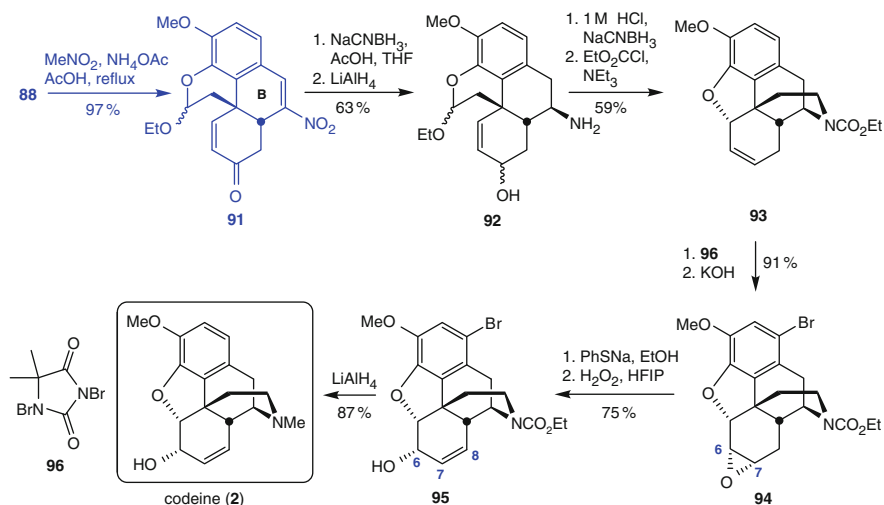
Commercially available bromoisovanillin (**48**) was reacted with the triarylboroxine **85** in a Suzuki cross-coupling to afford biphenyl **86** as outlined in Scheme 13. Reaction of this phenol with ethyl vinyl ether in the presence of bromine afforded ether **87** which was converted into spirocycle **88** by treatment with cesium fluoride in DMF at 130 °C. Spirocycle **88** served as common intermediate in the syntheses of both natural products mentioned above.



**Scheme 13** Magnus's synthesis of codeine – part 1

Acid-catalyzed hydrolysis of **88** afforded **89**, which upon reductive amination conditions followed by treatment with methanesulfonic acid gave narwidine (**90**). Racemic narwidine is known to yield enantiomerically pure galanthamine – the corresponding allylic alcohol – by spontaneous resolution and subsequent L-selectride reduction [66]. Thus, the preparation of narwidine concludes the formal synthesis of the Amaryllidaceae alkaloid galanthamine.

The synthesis of codeine from the common intermediate **88** is shown in Scheme 14. Reaction of enone **88** with nitromethane gave **91** via a Henry-aldol/Michael addition cascade with *cis*-relationship between the newly formed B-ring and the C-ring. The benzylic double bond in **91** was reductively removed with sodium cyanoborohydride before the compound was treated with  $\text{LiAlH}_4$  to afford allylic alcohol **92**. Reductive amination established the morphinan skeleton and the secondary amine was protected as carbamate (**93**). With the morphinan skeleton in hand, the remaining operations were devoted to the functionalization of the C-ring of the alkaloid. The double bond was shifted to the position present in the natural product with concomitant installation of the hydroxy functionality, with the correct stereochemical relationship, via epoxide **94**. Treatment of alkene **93** with 5,5-dimethyl-1,3-dibromohydantoin (**96**) resulted in the formation of the corresponding bromohydrin, which, upon exposure to base, delivered the epoxide. As the bromohydrin formation step also resulted in the bromination of the aromatic A-ring of codeine, an additional reduction step had to be added to the reaction sequence. Treatment of epoxide **94** with thiophenolate and subsequent oxidation with hydrogen peroxide in hexafluoroisopropanol (HFIP) completed the functionalization of the C-ring (**95**) and codeine (**2**) was obtained after a final  $\text{LiAlH}_4$  reduction to remove the aryl bromide.

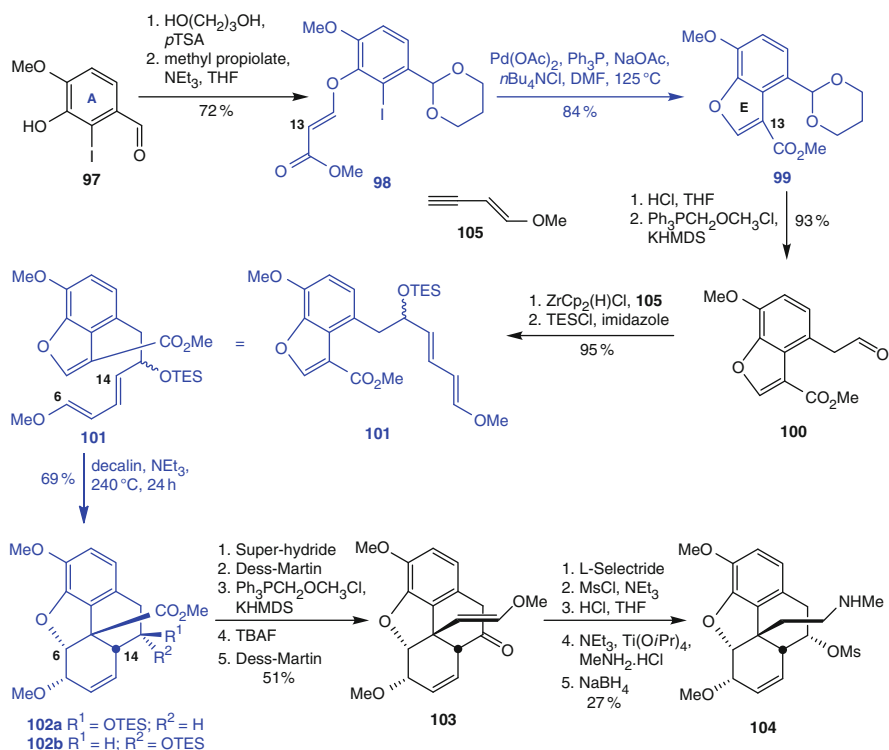


**Scheme 14** Magnus's synthesis of codeine – part 2

### 3.7 Stork (2009)

Stork's strategy towards racemic morphine comprises a Diels–Alder cycloaddition reaction of a benzofuran to establish the B- and C-ring of morphine as the key step [53]. The reaction sequence started with the ketalization of iodoisovanillin **97** (Scheme 15). Subsequently, the phenol was reacted with methyl propiolate to afford **98** as precursor for the installation of the benzofuran moiety via a palladium-catalyzed Heck cyclization (**99**). Next, the key intermediate was prepared for the Diels–Alder reaction. Hydrolysis of the acetal under acidic conditions and Wittig homologation afforded aldehyde **100**, which was converted to diene **101** via hydrozirconation of acetylene **105** employing the Schwartz reagent and subsequent reaction with aldehyde **100** followed by silylation of the secondary alcohol.

When heated to 240 °C in decalin, Diels–Alder precursor **101** underwent the desired cycloaddition reaction and afforded **102a** as the major product. It is noteworthy that four contiguous stereocenters in the correct relative configuration required for the preparation of the natural product were established in this operation and only a minor amount of **102b**, diastereomeric at C9, was formed during the course of the reaction. As the closure of the D-ring was envisaged to proceed via mesylate **104**, the diastereomeric mixture of **102a** and **102b** was not separated, as the C9 alcohol had to be oxidized to the corresponding carbonyl at a later stage. Before this oxidation was carried out, the ester was converted into an aldehyde as precursor for a Wittig reaction to form the corresponding enol ether. Desilylation and subsequent Dess–Martin oxidation of the C9-hydroxy moiety resulted in ketone **103**, which was reduced and mesylated to afford selectively the required stereoisomer for the formation of the D-ring. The methylamino functionality was introduced via a reductive amination protocol after hydrolysis of the enol ether (**103**).



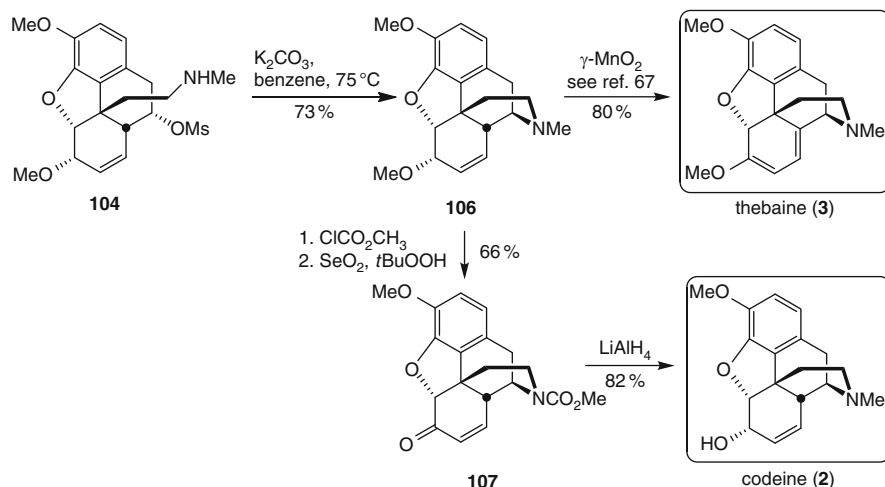
**Scheme 15** Stork's synthesis of thebaine and codeine – part 1

The closure of the D-ring succeeded under basic conditions via an  $\text{S}_{\text{N}}2$  displacement of the mesylate by the secondary amine (Scheme 16). Morphinan **106** was then successfully converted into thebaine (**3**) via manganese dioxide mediated oxidation following a procedure by Rapoport [67].

Direct cleavage of the allylic methyl ether in **106** with boron tribromide afforded codeine in only minor amounts. Better yields were obtained when **106** was converted to the corresponding carbamate before a selenium dioxide mediated oxidation delivered ketone **107**. Stereoselective reduction of the ketone and concomitant generation of the *N*-methyl group concluded the synthesis of codeine [60, 68]. This synthesis reported by Stork and co-workers provided a closure to several years of research, some of which has been reported in Ph.D. dissertations [69].

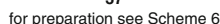
### 3.8 Fukuyama (2010)

In 2006, Fukuyama reported his first synthesis of morphine [49], followed 4 years later by an improved route [54]. As shown in Scheme 17, cyclohexenone (**108**) was



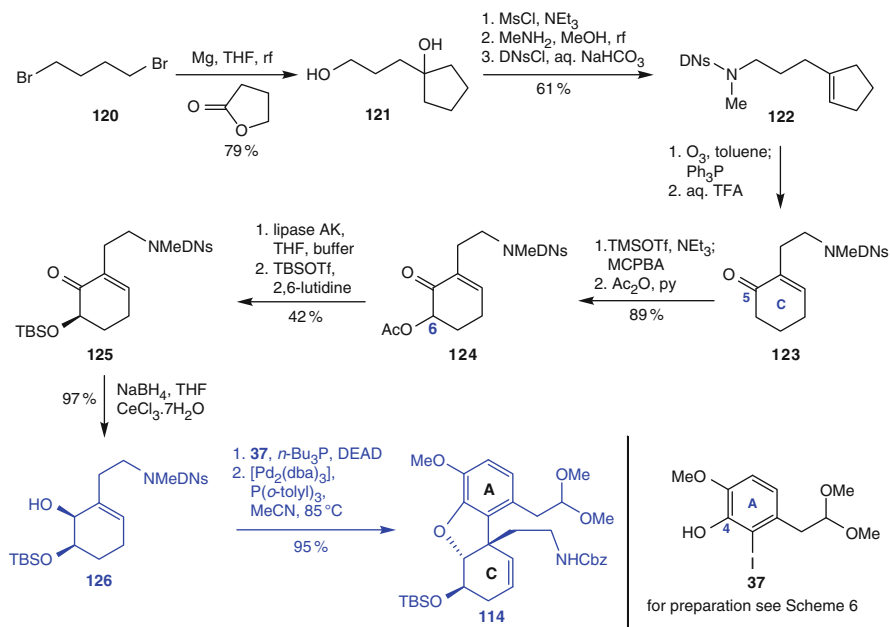
**Scheme 16** Stork's synthesis of thebaine and codeine – part 2

subjected to  $\alpha$ -acetoxylation and subsequent iodination to afford iodoketone **109**. Enzymatic resolution of the racemic material with lipase AK yielded alcohol **110**, which was silylated before the  $\alpha,\beta$ -unsaturated ketone was converted to allylic alcohol **111** via Luche reduction. Palladium-catalyzed Suzuki-Miyaura coupling of iodide **111** with boron reagent **119** afforded alcohol **112**, which was used in a Mitsunobu reaction with phenol **37** (for the preparation of this compound see Sect. 3.1 of this review) to give the precursor for the intramolecular Heck reaction with the requisite stereochemistry at C5 (**113**). The cyclization proceeded in high yield and afforded **114**. Reduction of the carbamate was followed by protection of the secondary amine with 2,4-dinitrobenzene-sulfonyl chloride (DNsCl) before the silyl group was cleaved and the resulting alcohol oxidized to the corresponding ketone **115**. Exposure of this  $\beta,\gamma$ -unsaturated ketone to TFA resulted in hydrolysis of the acetal and subsequent closure of the B-ring via an intramolecular aldol reaction. Mesylation of the secondary hydroxy moiety furnished **116** and prepared the compound for the elimination reaction and subsequent construction of the D-ring of the alkaloid. Treatment of mesylate **116** with base resulted only in the elimination of the  $\beta$ -epimer while the  $\alpha$ -epimer remained unchanged and harsher reaction conditions led to decomposition of the starting material. Therefore, the 2,4-dinitrobenzene-sulfonyl group in **116** was cleaved with mercaptoacetic acid and Hünig's base resulting in elimination of both epimeric mesylates with subsequent closure of the D-ring and a mixture of neopinone (**117**) and codeinone (**118**) was obtained. Presumably, this closure proceeds via 1,6-addition of the amine to the dienone **128** (Scheme 19) formed by the elimination of the mesylates. Such strategy was used previously by Fuchs in his morphine synthesis [34, 35]. The synthesis of morphine was completed by acid mediated conversion of the mixture of neopinone and codeinone to pure codeinone [35] and subsequent sodium borohydride

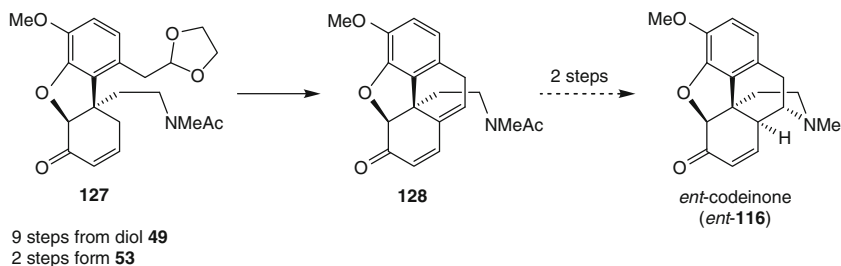


reduction to yield codeine. Morphine was obtained by reaction with boron tribromide following the procedure first reported by Rice [55].

Fukuyama also presented an alternative route to the advanced intermediate **114** as shown in Scheme 18 with an early introduction of the protected amino functionality. Reaction of  $\gamma$ -butyrolactone with the Grignard reagent derived from 1,4-dibromobutane (**120**) afforded diol **121**. Mesylation of the primary hydroxyl functionality with concomitant elimination of the tertiary one was followed by reaction with methylamine and protection of the resulting secondary amine to give alkene **122**. Ozonolysis of the double bond in **122** and subsequent intramolecular aldol condensation of the resulting ketoaldehyde afforded cyclohexenone **123**. Rubottom oxidation and acetylation gave **124**, which served as substrate in the lipase-



**Scheme 18** Fukuyama's synthesis of codeine and morphine – alternative route to intermediate **114**



**Scheme 19** Hudlicky's approach to *ent*-codeinone

catalyzed resolution in close analogy to the approach discussed above. Silylation (**125**) and Luche reduction delivered allylic alcohol **126**, which was used in a Mitsunobu reaction with previously described phenol **37**. The preparation of intermediate **114** was achieved by intramolecular Heck cyclization forming the E-ring of morphine.

At the time of Fukuyama's publication a virtually identical approach was nearing completion in the Hudlicky group. Enone **127** (Scheme 19), analogous to **115**, was synthesized in the *ent*-series in nine steps from diol **49**, previously used in the synthesis of *ent*-codeine, Scheme 8. Cyclization of **127** to dienone **128** leaves only two steps to complete *ent*-codeinone (*ent*-**116**) [70, 71].

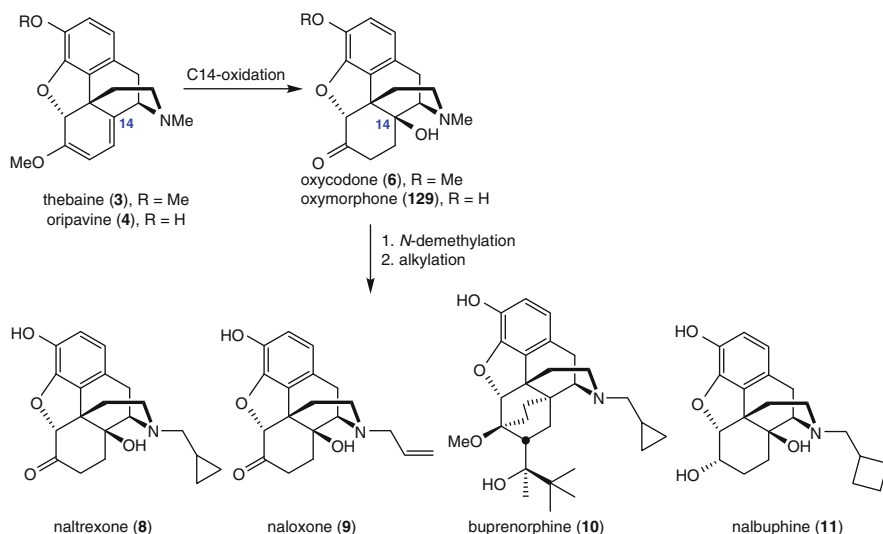
## 4 Medicinally Important Derivatives of Morphine

The preparation of medicinally important derivatives of morphine has recently been summarized in a review article [72]. Therefore, this section only provides a general outline.

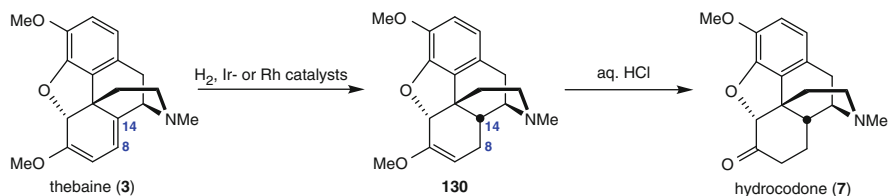
The commercial production of medicinally useful opiate-derived products is faced with two major challenges. The first of these is the introduction of the C14 hydroxy group and the second is the formal exchange of the *N*-methyl group for another alkyl group such as allyl (naloxone, **9**), methylcyclopropyl (naltrexone, **8**, buprenorphine, **10**) or methylcyclobutyl groups (nalbuphine, **11**) as outlined in Scheme 20 [72–77].

The oxidation of C14 is best accomplished by oxidation of either thebaine (**3**) or oripavine (**4**) and the large-scale production of the corresponding ketones has been adequately solved. Such methods include, for example, the addition of singlet oxygen to thebaine (**3**) and subsequent reduction of the resulting endoperoxide [78, 79] or treatment of (**3**) with formic acid and hydrogen peroxide [80]. The preparation of hydrocodone, hydromorphone, and related derivatives can be accomplished via hydrogenation utilizing transition metal catalysts [81–83]. In 2007, Hudlicky reported studies on regioselective hydrogenation of thebaine (**3**) with rhodium and iridium catalysts to form 8,14-dihydrothebaine (**130**), which can be converted to hydrocodone (**7**) via acidic hydrolysis of the enoether as shown in Scheme 21 [84].

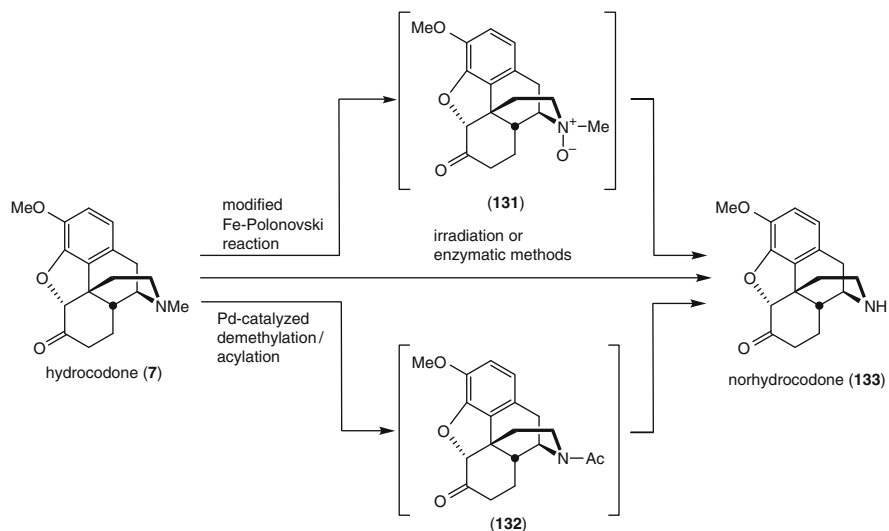
The second issue, the exchange of the *N*-alkyl group, is much more challenging. The current methods include the use of reagents such as cyanogen bromide (von Braun demethylation) [85, 86] or methyl chloroformate [87–91]. Neither is



**Scheme 20** Preparation of medicinally important morphine derivatives



**Scheme 21** Hudlicky's transition metal catalyzed conversion of thebaine to hydrocodone



**Scheme 22** *N*-Demethylation strategies of hydrocodone

particularly environmentally sound or efficient and the actual exchange of a methyl group for any other alkyl group requires multiple steps. Demethylation under irradiation was reported by Scammells [92]. Despite promising results on simple substrates, the method fails to deliver demethylated derivatives of the more complex alkaloids or derivatives in good yield. Once the *N*-demethylation is accomplished the secondary amine in *O*-protected noroxymorphone is alkylated with the particular alkyl halide.

Among the more modern methods of *N*-demethylation of hydrocodone are palladium-catalyzed *N*-demethylation/acylation as reported by Hudlicky [93, 94], or iron-mediated reduction of *N*-oxides published by Scammells [95]. Scammells developed different modifications of this variation of the Polonovski protocol and the reaction can be carried out via a two step procedure (oxidation and in situ demethylation of the activated alkaloid) [96] or under very mild conditions in acetate buffer [97]. Quite recently, a protocol was reported utilizing ferrocene as demethylation catalyst [98].

Alternative methods for the demethylation include biocatalytic protocols mediated by fungal cytochromes [99, 100]. Scheme 22 summarizes the methods discussed above.

## 5 Conclusion and Outlook

Eight total syntheses of morphine or congeners have been reported in the last 5 years, attesting to no shortage of new ideas or strategies. The interest in this fascinating molecule will no doubt continue, yet a truly practical synthesis of the title alkaloid still remains a distant dream. In order even to approach the current price per kilogram, a synthesis would have to be five to six steps long starting with commodity chemicals. A potential for a practical synthesis may exist in the realm of fermentation provided the biosynthetic pathway could be coded into a single plasmid and used to over-express the required enzymes in a robust bacterial carrier. A proof of principle has been attained through the work of Kutchan with the cloning and expression of codeinone reductase in *E. coli* [101].

Another possibility for practical synthesis could come from the combination of fermentation for attaining specific steps with semisynthesis to complete the preparation. Currently, we are fully dependent on natural sources of morphine and all medicinally useful derivatives are made by semisynthesis. Perhaps more important goals for the future generations of chemists would be to focus on the *de novo* total synthesis of the derivatives themselves rather than morphine or codeine. Perhaps we will see some effort devoted to this most worthwhile task in the near future.

## Addition

After the manuscript has been accepted for publication, a synthesis of codeine was published featuring a Claisen-rearrangement and a 1,3-dipolar nitronc cycloaddition as key steps: Erhard T, Ehrlich G, Metz, P (2011) A Total Synthesis of (+/–)-codeine by 1,3-Dipolar Cycloaddition. *Angew Chem Int Ed* doi: 10.1002/anie.201007448.

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