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The Quest for a Practical Synthesis of Morphine Alkaloids and Their Derivatives by Chemoenzymatic Methods

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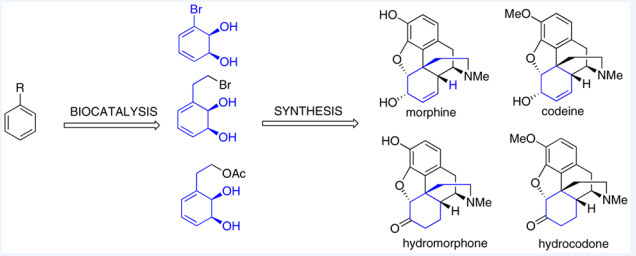
Josephine W. Reed and Tomas Hudlicky*

Department of Chemistry, Brock University, 500 Glenridge Avenue, St. Catharines, Ontario L2S 3A1, Canada

Supporting Information

CONSPECTUS: We became interested in approaches to morphine in the early 1990s following our immersion into the new program on the enzymatic dihydroxylation of aromatics. Larry Kwart, a former classmate of one of us at Rice University, who worked with our group at Virginia Tech in the mid-1980s, introduced to us the use of blocked mutants of *Pseudomonas putida* (*Pp*39D) for the production of arene-*cis*-dihydrodiols. Larry had gained expertise in microbiology from a postdoctoral stay with David Gibson, who discovered this unique enzymatic transformation, and he helped us to establish a strong program in chemoenzymatic synthesis that continues to this day. Without his pioneering effort, none of our accomplishments in chemoenzymatic synthesis, including the various approaches to morphine, would have materialized.



Here we trace the evolution of our approaches to morphine alkaloids and some commercial opiate-derived medicinal agents. The design features and chronology of our approaches are discussed in a way that allows the reader to appreciate a number of errors that were made in conception as well as in execution. Experience acquired from many failed or less-than-effective attempts has finally led to an "almost reasonable" total synthesis, the key concept being based on our very first but unsuccessful attempt more than two decades ago. The irony of this accomplishment has not been lost on us. Each section of this Account presents a summary of distinctly different approaches to morphine alkaloids. Each ends with a short and philosophical lesson that was (or should have been) learned in the process.

We intend for this Account to offer more than the history of a search for the perfect design solution to a synthetic problem. In today's era of rapid and often careless publication of results, it should serve also as a reminder that the success and the integrity of synthetic ventures depends on perseverance, adjustment of strategy, improvements of previous attempts, and serious attention to the quality of experimental data.

Although somewhat satisfied with our latest accomplishment in morphinan synthesis, we plan to improve our design in the hope that a six-step synthesis is no longer in the realm of fantasy. With more than 20 years of effort in this area, our continuing involvement may qualify as obsession.

1. INTRODUCTION

Tom writ, his readers still slept o'er his book. For Tom took opium, and they opiates took.

Sir Thomas Browne, mock epitaph for Thomas Shadwell, English dramatist and poet, who died of opium overdose, 1692.

Morphine: much has been written about the oldest drug known to man.[1,2] Sir William Osler, a Canadian physician, called morphine "God's own medicine", advocating the use of natural substances in medical applications.[3] Before and after Serturner's isolation of the active ingredient of opium in 1806, writers commemorated its effects.[4] It took 125 years from its isolation by Serturner for the structure of morphine to be solved and two more decades before Gates reported the first total synthesis.[5] During the period of structure elucidation of morphine (and other natural products), scores of organic reactions that we now take for granted were discovered. After Gates's synthesis and during the golden era of total synthesis of natural products, many other syntheses of morphine alkaloids followed. The effort continues to the present day. And yet, with almost 30 total syntheses on record, no truly practical preparation of this alkaloid, or the medicinal agents derived from it, has materialized.[6] A synthesis of morphine competitive in cost with its isolation should be no longer than five or six steps and originate from commodity chemicals. The latest figures on the annual *legal consumption* of morphine and codeine, Figure 1, demonstrate that the scale of any industrial *de novo* synthesis must be achieved at metric ton levels. Such an accomplishment is unrealistic given the state of the art of synthesis. Even if the most efficient synthesis to date, reported by Rice, were implemented at large-scale, the cost of morphine would be prohibitive.

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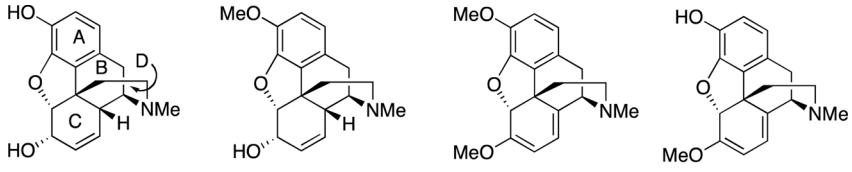

Figure 1. Morphine and congeners: their annual production and (legal) consumption.[7]

2. HISTORICAL OVERVIEW

Morphine (**1**) and some of its congeners isolated from the latex of the opium poppy are shown in Figure 1. The fascinating history of this molecule began with its isolation in 1806 by Serturner,[8] a German pharmacist, who was also the first to perform some limited animal and human dose studies.[8d,9] When Serturner's follow-up paper, published in 1817,[8b] was translated into English in 1818,[8c,d] the translator(s) made the following interesting comment:

> *We are surprised that the former memoir of Mr. Serturner has not more attracted the attention of chemists; not in France, where it appears to have been unknown, but on the rest of the continent... We are not afraid to declare, that the discovery of morphium will open a new field, and that we shall soon acquire precise notions with respect to poisons drawn from vegetables or animals...*

The arduous elucidation of its structure was completed in 1925 (performed on codeine once its relationship to morphine was established) and reviewed in 1998.[10] The biosynthetic pathway of morphine in the opium poppy has been largely elucidated, with the alkaloid arising from L-tyrosine.[11]

The existence of endogenous morphine-like compounds in mammalian cells was first hypothesized as early as 1903,[12] and a biosynthetic pathway similar to that in plants was postulated in 1970.[13] Morphine was first identified in bovine brain and adrenal tissue in 1985.[14] The occurrence and biosynthesis of endogenous morphine in mammals have been recently reviewed.[15] The milestones in the history of morphine and its structure elucidation are listed in Table 1.

Given that production of morphine and opiate-derived pharmaceuticals is fully dependent on natural sources, pursuit of alternate methods is a good idea. So far, strategies involving tissue culture or fermentation cannot compete in titer or in cost with morphine obtained by isolation. Although the cost of producing morphine fluctuates around $600−1200/kg (accurate figures are not available because such information constitutes a closely guarded trade secret), it is still far below the cost of fermentation or synthesis. Of course, efforts toward biological and organic syntheses should continue as insurance against possible interruption in supply because of either climate or political instability.

Advances in molecular biology have allowed for the development (by chemical mutagenesis) of *top1*, a strain of opium poppy that produces thebaine and oripavine at the expense of morphine and codeine.[16] The dry weight yields of alkaloids from *top1* poppies (compared with traditional *Papaver somniferum L.*) are as follows: thebaine 2% (0.1%), oripavine 0.8% (0.03%), codeine 0.01% (0.1%), and morphine 0.05% (2.4%). There are now other mutant strains of poppies that produce a mixture of thebaine and oripavine[17] as well as those that produce only thebaine.[18]

Table 1. Summary of Historical Milestones in Morphine Chemistry

3400 BCE	cultivation of poppies by Sumerians in Mesopotamia (Tigris−Euphrates)
2000	use in the Mediterranean region, Europe, North Africa
1550	use in Egypt; first written record (Ebers Papyrus)
700	use by the Assyrians (Babylon)
700	Homer's *Odyssey* ("nepenthe", the drug of forgetfulness, was an opium preparation)
77 CE	Dioscorides (Greece) described method for obtaining opium from poppies
150	Galen (Rome) recommended "mithridate", an opium concoction to patients
183	Hannibal's suicide with opium
900	Arab texts on "af-yum" (ufian, asium)
1525	Paracelsus invents laudanum
1700	*Mysteries of Opium Reveal'd* — Dr. John Jones
1790−1840	use by Coleridge, Shelley, De Quincey, Crabbe
1806	**isolation of morphine (Serturner)**
1828	beginning of "organic chemistry": synthesis of urea (Wöhler)
1831	empirical formula for morphine established (Liebig)
1833	**isolation of codeine (Robiquet)**
1839−1842	First Opium War (China and Great Britain)
1842	correct empirical formula for codeine established (Gerhardt)
1847	correct empirical formula for morphine established (Laurent)
1874	**synthesis of heroin (Wright)**
1881	isolation of phenanthrene after pyrolysis of morphine (von Gerichten)
1906	attachment of *N*-ethylamino bridge (Knorr)
1925	attachment of C-terminus (Robinson)
1927	**structure proof of morphine (Robinson, Gulland, Schopf)**
1952	**total synthesis of morphine (Gates)**
1954	X-ray structure and absolute stereochemistry of morphine (Mackay, Hodgkin)
1980	**first practical synthesis of morphine (Rice)**
1985	morphine identified in mammalian cells
2004	development of mutant poppies (*top1*) producing thebaine and oripavine
2005	morphine biosynthesis in mammalian cells confirmed
2011	patent issued for production of thebaine and oripavine in poppies
2012	global production: morphine, 440 tons; codeine, 381 tons; thebaine, 145 tons; oripavine, 23 tons
2014	low titer production of morphine alkaloids in yeast reported

Adapted from ref 20b, Page 729. Copyright 2007 Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission.

Recently, Smolke showed that recombinant yeast can convert thebaine into certain opiates, albeit in low titers.[19] A biocatalytic synthesis of morphine or other opiates would be a major breakthrough provided the yields were at practical levels.

The effort toward the total synthesis of morphine and related alkaloids continues unabated. A review published in 2012[6a] lists

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26 total or partial syntheses. Connectivity analysis for morphine leads to recognition of complete "synthetic dissonance".[20] The difficulty in designing a convergent approach in which the connectivity of any two segments is experimentally feasible has been discussed on several occasions.[6b,20b] The dissonant assignments for morphine with both nitrogen and oxygen priorities (Figure 2) demonstrate the impossibility of an electrostatically neutral design.

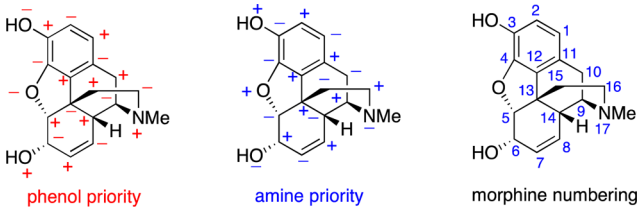

Figure 2. Dissonant connectivity of morphine and morphine numbering system. Parts of the figure reproduced with permission from ref 6b (Copyright 2005 Georg Thieme Verlag) and from ref 20b, page 732 (Copyright 2007 Wiley-VCH Verlag GmbH & Co. KGaA).

3. TOTAL SYNTHESIS EFFORT TO DATE

All styles are good except the boring kind.

Voltaire

The chronology of total syntheses of morphine, codeine, and closely related derivatives is shown in Table 2. Not listed are several partial syntheses from advanced intermediates. A summary of these and advanced model studies and strategies can be found in our 1996 review[6e] and in more recent reviews.[6a,b]

Strategies used in the design of the morphine skeleton range from cycloadditions to radical or metal-promoted cascades, as well as C−H insertion. Most bond disconnections anticipate the construction of rings B, C, and D. To our knowledge there is no report of a synthesis of morphine involving a *de novo* assembly of the aromatic ring A by the cyclotrimerization strategy that has been used to synthesize aromatic steroids and certain alkaloids.[21] Essentially all bonds in rings B, C, and D have been subjected to strategic disconnections in the published syntheses. These strategies were discussed in detail in recent reviews,[6] and some that are similar to our approaches are mentioned here.

4. DEVELOPMENT OF OUR DESIGN FOR MORPHINANS

The hardest thing of all is to find a black cat in a dark room, especially if there is no cat.

Confucius

We first attempted to design a synthesis of morphine in the early 1990s. At that time, our early ventures into chemoenzymatic methodology with the blocked mutant *P. putida* 39/D had yielded syntheses of zeylena and simple sugars.[53] We had also converted diol **5**, derived from toluene by enzymatic dihydroxylation, into a prostaglandin intermediate.[54] We envisioned applying the strategy to a model study toward part of morphine because diol **5** has the same absolute stereochemistry as ring C.

4.1. Cycloaddition Approaches

We initiated a model study based on [4 + 2] cycloaddition (Scheme 1). After protection of the distal alcohol in **5**, we attached sorbyl bromide to the proximal hydroxyl and subjected the dienyl ether to an intramolecular Diels−Alder reaction;

Table 2. Chronological Summary of Total Syntheses of Morphine and Derivatives

year	author	target	steps	ref
1952	Gates	morphine	31	5
1954	Ginsburg	dihydrothebainone	21	22
1967	Grewe	dihydrothebainone	9	23
1980	Rice	dihydrocodeinone	14	24
1982	Evans	thebainone	12	25
1983	White	codeine	8[a]	26
1983	Rapoport	codeine	26	27
1987	Fuchs	codeine	23	28
1992	Tius	thebainone	24	29
1992	Parker	dihydrocodeinone	11	30
1993	Overman	dihydrocodeinone	14	31
1996	Mulzer	dihydrocodeinone	15	32
1996	Parsons	morphine	5[b]	33
1997	White	*ent*-morphine	28	34
1997	Mulzer	dihydrocodeinone	18	35
2001	Ogasawara	dihydrocodeinone	21	36
2002	Taber	morphine	27	37
2002	Trost	codeine	15	38
2006	Fukuyama	morphine	25	39
2007	Hudlicky	*ent*-codeine	15	40
2008	Iorga/Guillou	codeine	17	41
2008	Chida	dihydroisocodeine	24	42
2009	Hudlicky	codeine	18	9
2009	Magnus	codeine	13	43
2009	Stork	codeine	22	44
2010	Fukuyama	morphine	18	45
2011	Hudlicky	*ent*-neopinone	15	46
2011	Metz	codeine	23	47
2013	Hudlicky	hydrocodone	21	48
2014	Hudlicky	*ent*-codeine	15	49
2014	Hudlicky	*ent*-hydromorphone	12	50
2014	Opatz	dihydrocodeine	14	51
2014	Gaunt	morphine	25[c]	52

[a]Advanced starting material was used. [b]Only the last five steps were described. [c]Formal synthesis, 18 steps to known intermediate.

however, the expected adduct **7** was not detected. Instead the tricyclic adduct **8** was obtained and converted into enone **9**[55] in three steps, including a Cope rearrangement. Beginning again, we reduced the less substituted olefin in **5** and then proceeded with the [4 + 2] cycloaddition of **10** to obtain a tricyclic adduct, assigned at that time as **11a** (α-C-9).

Six years later we completed an advanced model study based on *cis*-diol **12** (from β-azidoethylbenzene) or diol **13**, (from β-bromoethylbenzene), with two carbons in place for the incipient ethylamino bridge in **1**. Conversion of **12** into **14** and subsequent cycloaddition yielded tricycle **15**, assigned as shown with the β-stereochemistry of the C-9 methyl group (morphine numbering). At this time, we corrected the structure of **11a** to **11b** (β-C-9).[56]

Attaining tricycles **9** and **15** was exciting. All five stereogenic centers of morphine are correctly set in **15**, and having two different stereochemical outcomes at C-9 (**9** vs **11b** and **15**) allowed us to design a dual strategy in the next model study, Figure 3.

It was easy for us to see the subsequent transformations of diol **13** to either **16** or **18** and thence into tricyclic systems **17** or **19**, each with orthogonally disposed functionalities for closure of the ethylamino bridge in **20**. Manipulating the placement of a leaving group (LG) and a nucleophile (Nu) in the starting material and then choosing one or both methods of cycloaddition should ultimately lead to a complete morphine skeleton such as **21**.

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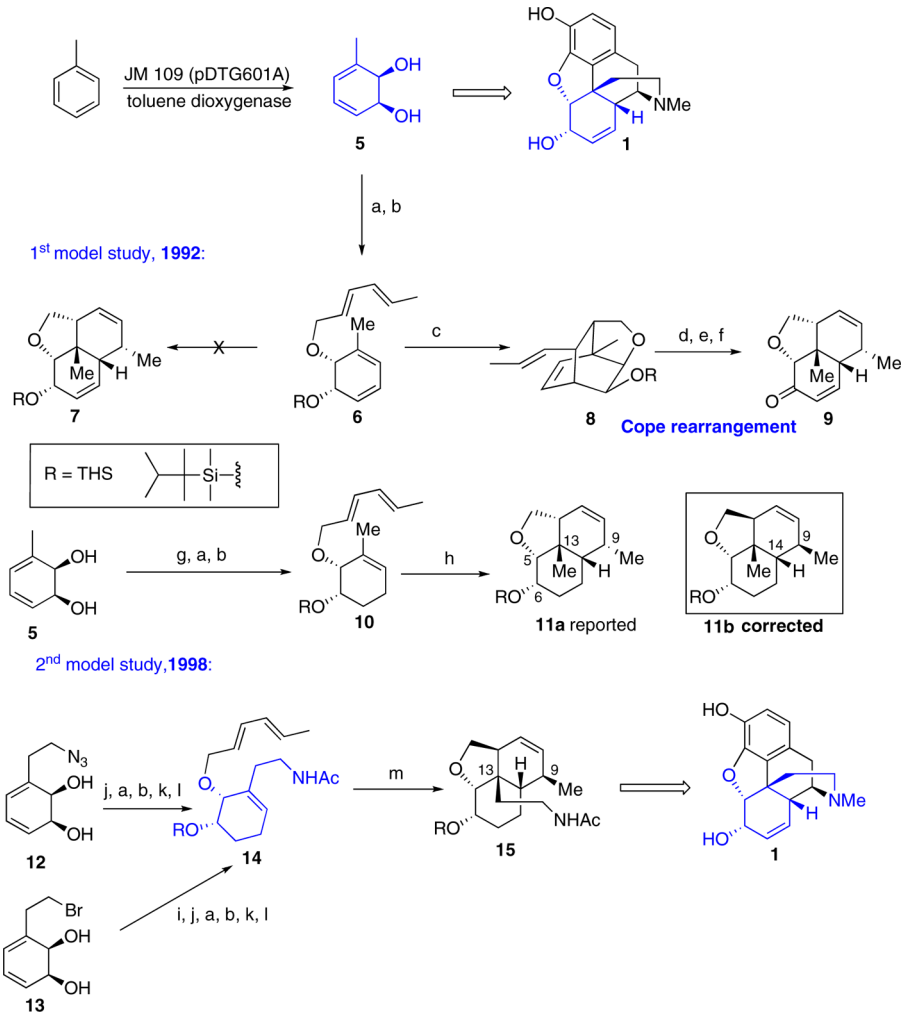
Scheme 1. Early Cycloaddition-Based Model Studies[a]



[a]Reagents and conditions: (a) THSCl, imidazole, DMF, 0 °C, 18 h; (b) NaH, sorbyl bromide, THF, 0 °C, then rt, 30 h; (c) CCl_4, 77 °C, 7 h; (d) Bu_4NF, H_2O, THF, rt, 24 h; (e) PCC, CH_2Cl_2, rt, 21 h; (f) xylenes, 250 °C (sealed tube), 22 h; (g) potassium azodicarboxylate (PAD), HOAc, MeOH, 0 °C to rt; (h) toluene, 210 °C (sealed tube), 24 h; (i) NaN_3, DMF; (j) PAD, HOAc, MeOH, 0 °C to rt, 14 h; (k) PPh_3, 0.4% H_2O, THF, 45 °C, 18 h; (l) Ac_2O, pyridine, rt, 2 h; (m) toluene, 239 °C (sealed tube), 20 h.

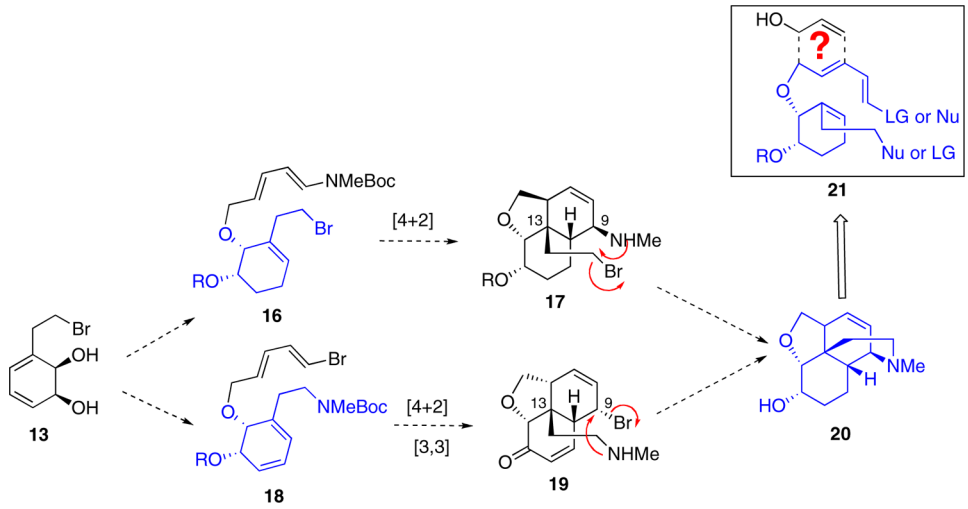


Figure 3. Advanced model proposed for the construction of morphine by dual strategy.

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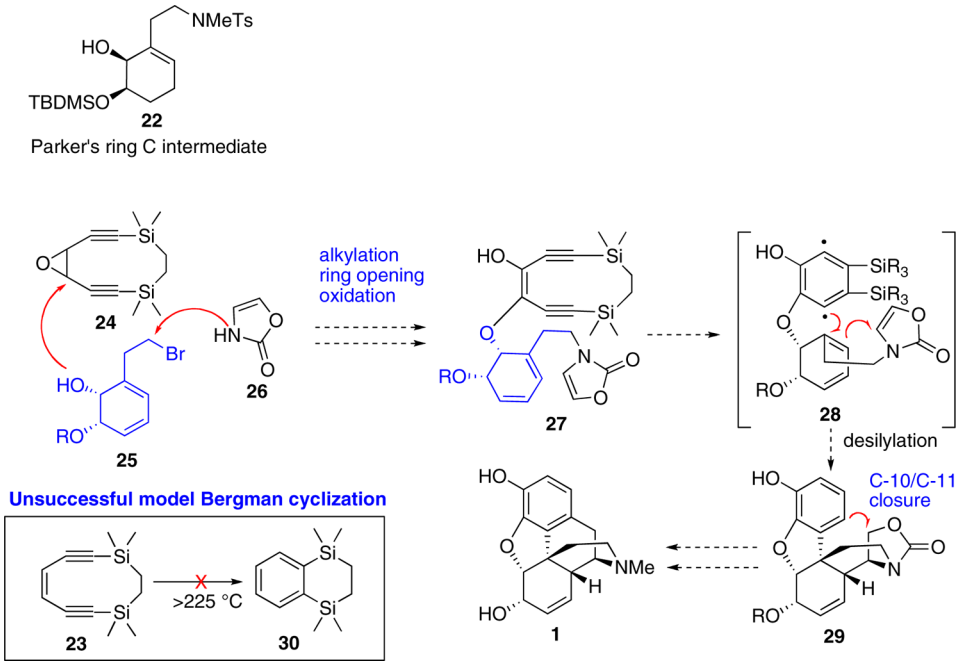

Figure 4. Bergman cyclization cascade design for morphine.

Our progress stopped here for a variety of "philosophical" reasons. We could not arrive at a reasonable way to incorporate the three additional carbons required for **21**. Of course, oxidative dearomatization of phenols (the process providing the eventual solution to the design of precursors such as **21**) had been known since the 1950s[57] and other oxidants besides lead(IV), such as Dess–Martin periodinane,[58] were also known to accomplish such a task. The required components for completing the design were known, even to us; but these were not in the forefront of our chemical imagination at the time, and we did not integrate this existing information with pattern recognition.[59] It took another 20 years before the design of an intermediate such as **21** finally materialized, resulting in a very short synthesis of hydromorphone.[50] We learned an important lesson on information processing, retention of information, and pattern recognition.

***Lesson 1**: In a productive and efficient design, all of the components required for reduction to practice must be recognized and mutually connected by pattern recognition. A single missing item becomes a zero multiplier for the entire process.*

4.2. Radical Cascade Approaches

The definition of insanity is doing the same thing over and over and expecting different results.

Rita Mae Brown in *Sudden Death* (1983) (attributed to Albert Einstein and others)

In 1992, Parker published a creative synthesis of dihydrocodeinone based on a radical cascade[30] that produced a racemate; the second-generation approach was enantioselective.[30b] We were inspired by the idea that a diol such as **22** might be accessible in optically pure form from *β*-bromoethylbenzene and diol **13**. Our initial ambitious design involved a Bergman cyclization cascade as shown in Figure 4. Our plan was to convert the cyclic enediyne **23** to its epoxide, which was to be opened with the C-2 hydroxyl of **25** (previously alkylated with oxazol-2(3*H*)-one **26**). After oxidation, the enolized **27** would undergo the Bergman cyclization to diradical **28**, whose further closure and protodesilylation would provide **29**, easily convertible to morphine.

Had it been successful, the synthesis would have been one of the shortest at that time, provided, of course, that we could prepare enediyne **23** in fewer than the 10 steps that were actually required. Unfortunately, the model substrate **23** was inert to Bergman cyclization even at temperatures above 225 °C, an observation rationalized by the detrimental effect of adjacent silicon atoms on the reaction intermediates.[60]

Undeterred, we adjusted the radical cascade strategy and utilized the aryl ether **31** in a second-generation approach, this time toward codeine, Scheme 2.

Aryl ether **31** was accessible in six steps from diol **13**. The major difficulty was the disappointing 28% yield for the second Mitsunobu inversion of the C-5 hydroxyl (morphine numbering) because of hindrance from the adjacent TBS group. Even more disappointing were the results of the cyclization: complex mixtures were produced, from which we were able to isolate **32** (incorrect C-14 stereochemistry) in ∼15% yield and **33**, with the correct configuration at C-9/C-14, as a minor component. Detailed analysis of the stereochemical outcome[60] led to the conclusion that the stereochemical integrity of C-9/C-14 centers cannot be controlled during a cascade cyclization of conformationally free ether **31**. On the plus side, identification of isoquinoline **34**, isolated as a minor component and originating as depicted in Scheme 2, inspired a new design via the enzymatic dihydroxylation of dibromide **38**.

Diol **39** was transformed into oxazol-2(3*H*)-one **40**, which underwent radical cyclization to the octahydroisoquinoline **41**. The second radical cyclization of aryl ether **42**, obtained by Mitsunobu inversion at C-5, led to **43**, with the *epi*-configuration at C-14. The oxazolidinone moiety was reduced to furnish the *N*-methyl functionality, and alcohol **44** was cyclized to either *ent*-10-hydroxy-morphinan **45** or the C-6/C-14 epimer of *ent*-dihydrocodeine **46**, Scheme 3.

None of our radical cyclization approaches was highly stereoselective, with major products produced in the *epi*-configuration at C-14. Although the syntheses of complete morphinan skeletons

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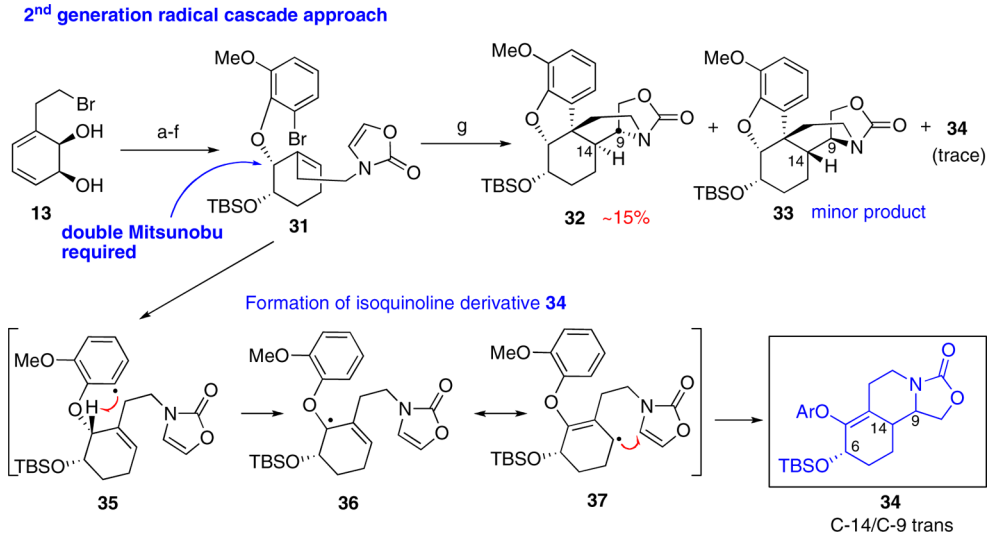
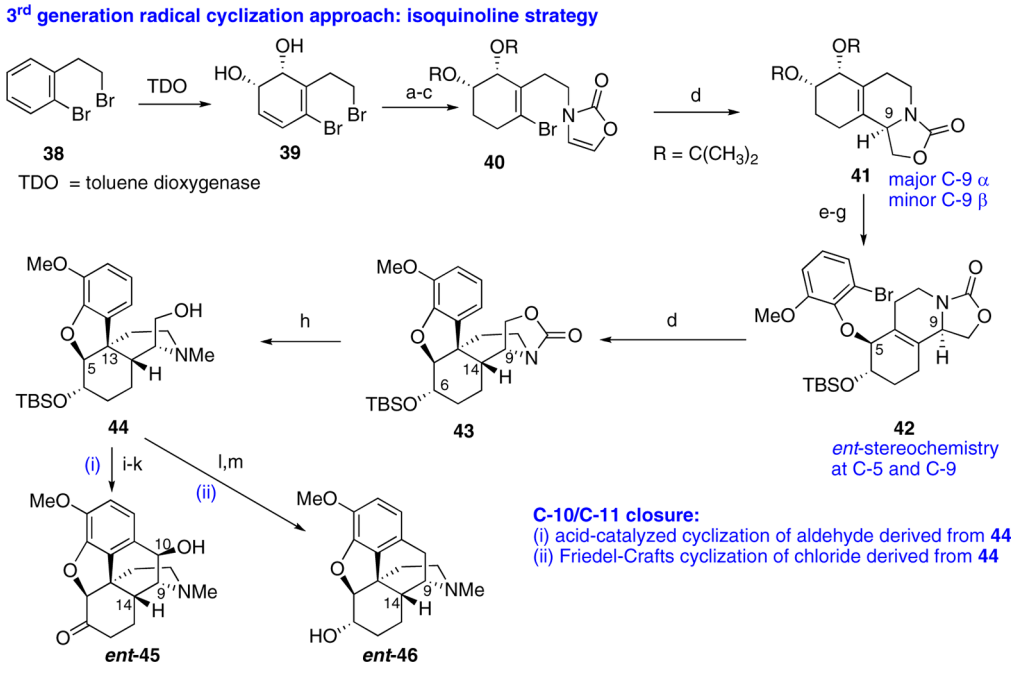
Scheme 2. Second-Generation Radical Cyclization Approach[a]



[a]Reagents and conditions: (a) potassium azodicarboxylate (PAD), HOAc; (b) TBSOTf, CH_2Cl_2, *i*-Pr_2Et; (c) *n*-Bu_3P, DEAD, $PhCO_2H$, THF; (d) oxazol-2(3*H*)-one, NaH, DMSO; (e) NaOH, H_2O; (f) *n*-Bu_3P, DEAD, 2-methoxy-6-bromophenol, THF; (g) $(TMS)_3SiH$, AIBN, PhH, 140 °C (sealed tube).

Scheme 3. Third-Generation Radical Cyclization Approach[a]



[a]Reagents and conditions: (a) potassium azodicarboxylate (PAD), HOAc; (b) 2,2-dimethoxypropane (DMP), acetone, TsOH, rt, 3 h; (c) oxazol-2(3*H*)-one, NaH, DMSO, 0 °C to rt, 12 h; (d) *n*-Bu_3SnH, AIBN, PhH, reflux, 1 h; (e) DOWEX50×8−100, MeOH, rt, 12 h; (f) TBSOTf, *i*-Pr_2NEt, CH_2Cl_2, −78 °C, 4 h; (g) *n*-Bu_3P, DEAD, THF, 2-methoxy-6-bromophenol, 0 °C, 1.5 h; (h) DIBAL-H, CH_2Cl_2, 0 °C, 0.5 h; (i) TBAF, THF, rt, 4 h; (j) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 to 0 °C, 4 h; (k) CF_3SO_3H (neat) rt, 10 min; (l) MsCl, Et_3N, LiCl, THF, 0 °C, 6 h; (m) $AlCl_3$, PhH, reflux.

were relatively short, the lack of stereoselectivity rendered them ineffective. It became clear that a radical cascade cannot proceed with stereoselectivity in conformationally flexible compounds, such as the bromoarene **31**. Nevertheless, these failures provided important information toward future design of Heck reaction cascades and, ultimately, to a successful cycloaddition approach.

***Lesson 2**: Stereoselectivity cannot be expected in those processes leading to morphine skeleton that proceed through conformationally flexible transition states. It would have been wise to read more of the literature before the experiments, not after! Parker's radical cascade seems to be a unique exception.*

4.3. Heck Cyclization Approaches

The disappointing results from our radical cascade approaches led us to recognize that the configuration at C-5 controls subsequent bond-forming events. Thus, the stereochemistry at C-6 can be adjusted by an oxidation−reduction sequence with the C-13 center set cis to C-6, and the C-14/C-9 relationship can be controlled before or during cyclization. The radical cyclization

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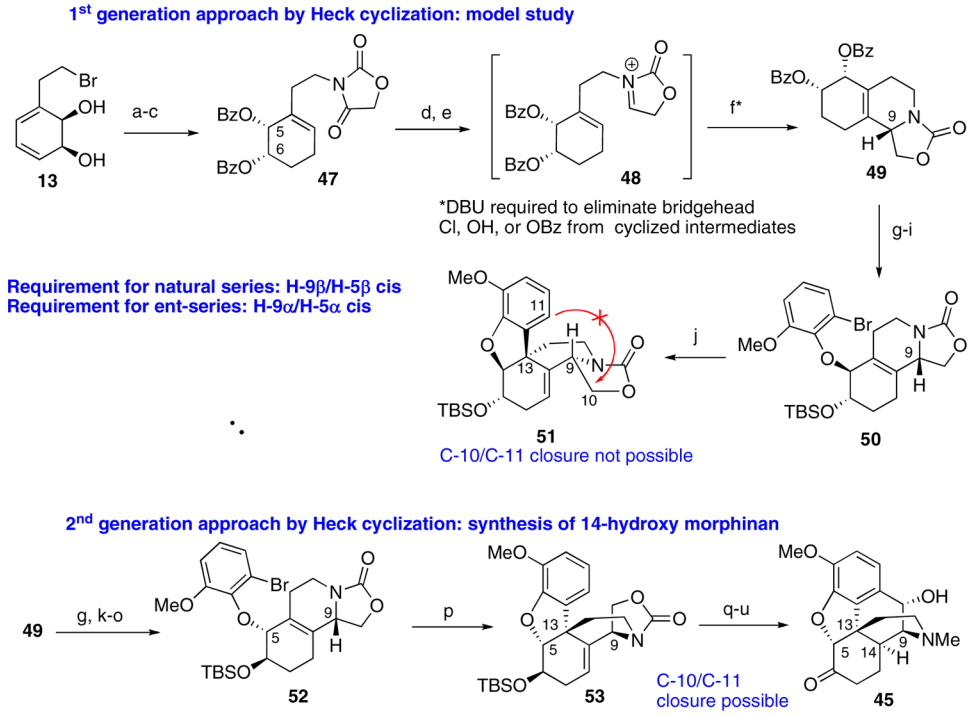
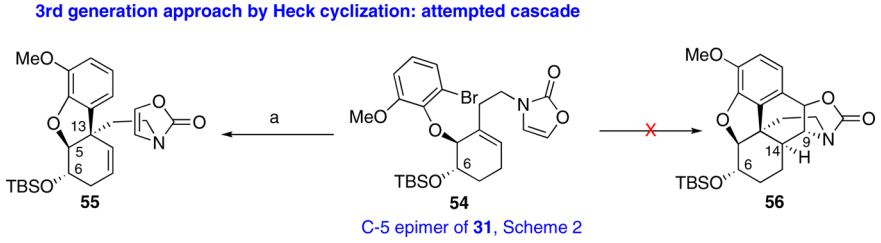
Scheme 4. First[61a] and Second[62] Generations of Heck Cyclization Approaches[a]



[a]Reagents and conditions: (a) potassium azodicarboxylate (PAD), HOAc, MeOH; (b) $PhCO_2H$, DCC, DMAP, CH_2Cl_2, 0 °C to rt, 12 h; (c) oxazolidinedione, 1,1,3,3-tetramethylguanidine,THF, reflux, 48 h; (d) $NaBH_4$, MeOH, 0 °C, 0.5 h; (e) BF_3, CH_2Cl_2, 0 °C to rt, 12 h, or $AlCl_3$, CH_2Cl_2, 0 °C to rt, 12 h; (f) DBU, DMSO, reflux; (g) LiOH, MeOH; (h) TBSOTf, imidazole, DMF; (i) *n*-Bu_3P, DEAD, 2-methoxy-6-bromophenol, THF, reflux, 5 days; (j) $Pd(PPh_3)_4$, proton sponge, PhMe, reflux; (k) TsCl, pyridine, DMAP; (l) $PhCO_2H$, PPh_3, DEAD, THF; (m) MeONa, MeOH, THF; (n) potassium 2-bromo-6-methoxyphenoxide, DME, 18-C-6, reflux; (o) TBSOTf, *i*-Pr_2NEt, CH_2Cl_2; (p) $Pd(PPh_3)_4$, proton sponge, PhMe, reflux, 21 h; (q) DIBAL-H, CH_2Cl_2; (r) H_2, PtO_2, HOAc; (s) TBAF, THF, H_2O; (t) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; (u) CF_3SO_3H, rt, 0.5 h.

Scheme 5. Attempted Heck Cascade[61ca]



[a]Reagents and conditions: (a) $Pd(PPh_3)_4$, PPh_3, Et_3N, PhMe, 120 °C (sealed tube), 19 d.

of **40** produced isoquinoline **41** as the major product (2:1) with the *ent*-configuration of C-9. In contrast, isoquinoline **49**, with C-9 in the natural configuration, was the major product of an acyl-imminium closure of **48**, Scheme 4.[61] The Heck closure of **50** yielded neopinone-type intermediate **51** in 57% yield. A double Mitsunobu of the C-5 center (morphine numbering) in **49** provided the opportunity to synthesize the natural enantiomer of 10-hydroxymorphinan **45** via the Heck cyclization of **52** and C-10/C-11 closure of **53**.[62]

Both syntheses of *ent*-**45** and **45** yielded the *epi*-configuration at C-14, but in different ways, the former from radical cyclization and the latter from hydrogenation of the C-8/C-14 olefin. Attempts at a Heck cascade of **54** failed; only the first cyclization occurred with a low yield of **55** in the *ent* series, Scheme 5. It would be a few years before we pursued the next-generation strategy.

In 2007, we synthesized (+)-codeine by a double Heck cyclization strategy,[40] inspired in part by Trost's report.[38] The short synthesis also led to (−)-codeine via double Mitsunobu inversion at C-5, accomplished by opening the allylic *β*-epoxide generated from the *cis*-diol in **13**, Scheme 6.[9] In our hands, Trost's hydroamination was not successful and had to be modified. We eventually learned that the best and most reliable conditions for C-9 amination were those reported by Parker in 1992.[30]

Our fourth-generation approach validated our hypothesis that the C-5 center controlled all subsequent bond-forming events in any cyclizations to the morphine skeleton. It was clear that Parker's unique stereoselective cascade could not be applied to nonrigid systems and that all future generation approaches must proceed in stepwise manner.

Lesson 3: *After 15 years, we recognized that stepwise bond construction is more effective than a cascade approach and finally achieved an enantiodivergent synthesis.*

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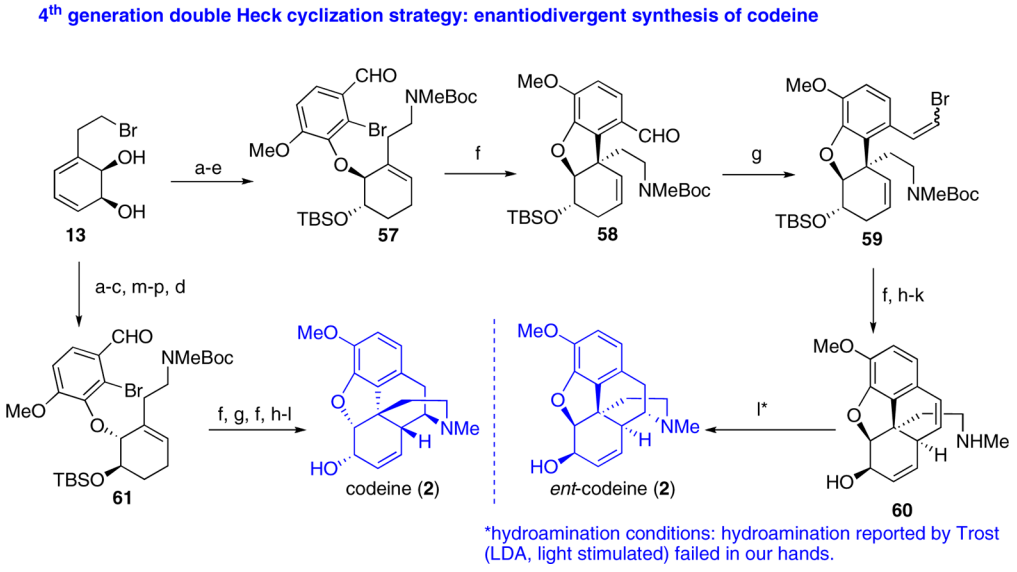
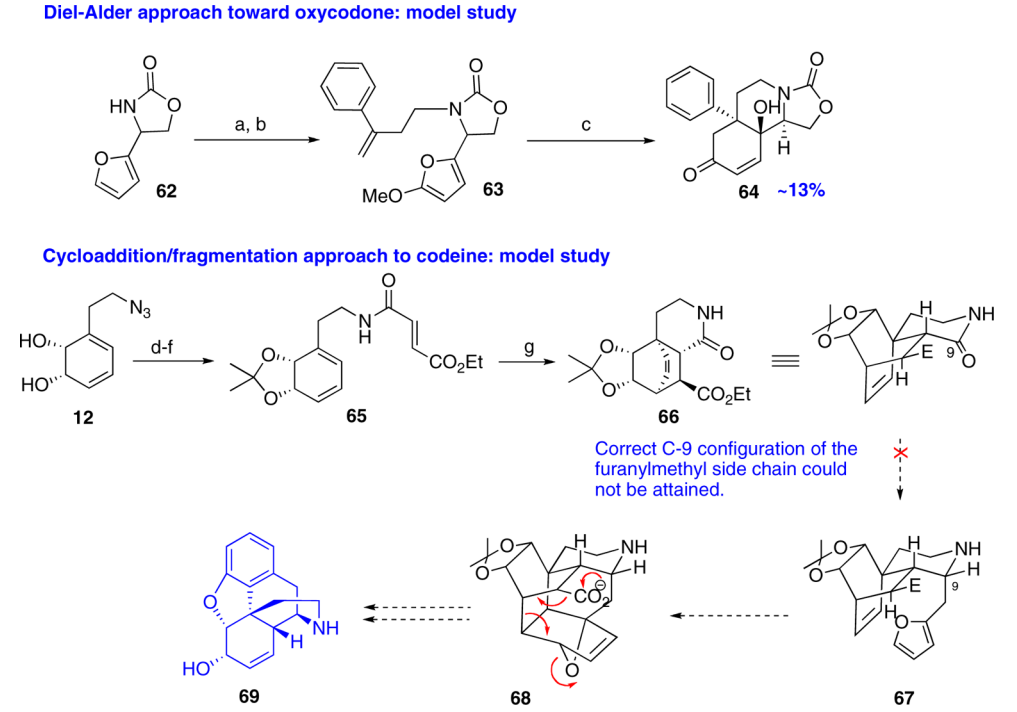
Scheme 6. Enantiodivergent Synthesis of Codeine by Double Heck Cyclization[a]



[a]Reagents and conditions: (a) potassium azodicarboxylate (PAD), HOAc, MeOH, 0 °C; (b) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 0 °C to rt; (c) $MeNH_2$, K_2CO_3, THF, −40 °C to rt; then $(Boc)_2O$, Et_3N, MeOH; (d) TBSCl, imidazole, CH_2Cl_2, −78 °C to rt; (e) *n*-Bu_3P, DIAD, 5-bromovanilin, THF, 0 °C to rt; (f) $Pd(OAc)_2$, Ag_2CO_3, dppf, toluene, 110 °C, 3 h; (g) $BrCH_2PPh_3Br$, *t*-BuOK, THF, −60 °C; (h) TBAF, THF, rt; (i) IBX, DMF, rt; (j) $NaBH_4$, $CeCl_3$, H_2O, MeOH, 0 °C; (k) TFA, CH_2Cl_2, 0 °C to rt; (l) $Hg(OAc)_2$, Et_3N, THF, 48 h; then $LiAlH_4$, rt, 2 h; (m) TsCl, Et_3N, DMAP, 0 °C to rt; (n) DIAD, PPh_3, THF, *p*-NO_2PhCO_2H, 0 °C; (o) NaOMe, MeOH, THF, 0 °C; (p) potassium salt of 5-bromovanilin, DME-DMF, 18-crown-6, 80 °C, 48 h.

Scheme 7. Miscellaneous Approaches to Morphinans[a]



[a]Reagents and conditions: (a) Br_2, MeOH, then camphor sulfonic acid, PhH, reflux; (b) NaH, mesylate of 2-phenyl-4-hydroxybutene, DMSO, rt; (c) toluene, >250 °C (sealed tube); (d) 2,2-dimethoxypropane (DMP), TsOH, CH_2Cl_2, rt, 45 min; (e) PPh_3, THF, H_2O, rt, 22 h; (f) DCC, ethyl fumaric acid, 0 °C to rt, 18 h; (g) PhH, reflux, 21 h.

4.4. Miscellaneous Approaches

We pursued other strategies such as one based on intramolecular furan Diels−Alder reactions[63] and a rather ambitious fragmentation approach that was not successful.[64] A model study for an approach to oxycodone (Scheme 7) yielded a short (three steps from the known furan derivative **62**[65]) but low-yielding synthesis of the tricyclic hydroxyenone **64**.[63] We envisioned two successive Diels−Alder cyclizations in amide **65**, the first providing bridged isoquinolone **66** and the second depending on an *endo*-situated furanylmethyl side chain in **67**, which eluded us. In principle, the

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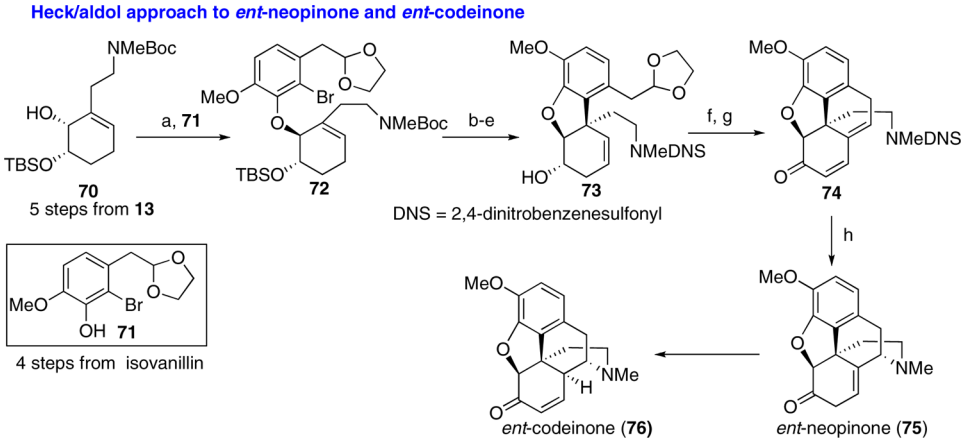
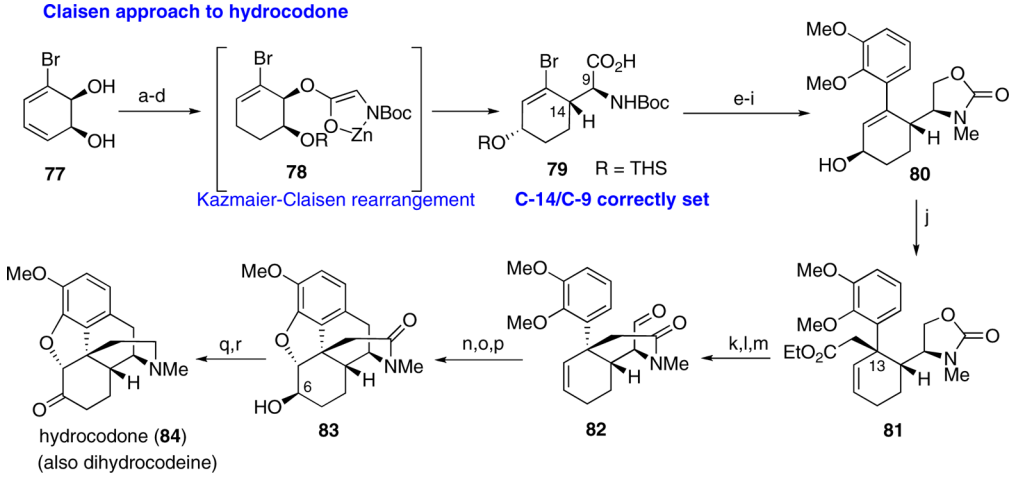
Scheme 8. Synthesis of *ent*-Neopinone[46a]



[a]Reagents and conditions: (a) DIAD, Bu_3P, THF, 0 °C to rt, 12 h; (b) $Pd_2(dba)_3$, *t*-Bu_3P, K_2CO_3, toluene, 110 °C, 16 h; (c) TBAF, THF, −78 °C to rt, 16 h; (d) TFA, CH_2Cl_2, 0 °C, 15 min; (e) DNS-Cl, *i*-Pr_2NEt, CH_2Cl_2, rt, 20 min; (f) IBX, EtOAc, 80 °C, 4 h; (g) 50% aqueous TFA, PhMe, 50 °C, 2 h, then MsCl, *i*-Pr_2NEt, CH_2Cl_2, 0 °C, 30 min; (h) thioglycolic acid, *i*-Pr_2NEt, CH_2Cl_2, 0 °C, 30 min.

Scheme 9. Synthesis of Hydrocodone by Claisen Rearrangement Strategy[48a]



[a]Reagents and conditions: (a) potassium azodicarboxylate (PAD), HOAc, MeOH; (b) thexyldimethylsilyl chloride, imidazole, CH_2Cl_2, −78 °C to rt; (c) *N*-Boc glycine, DCC, DMAP, CH_2Cl_2; (d) LDA, $ZnCl_2$,THF, −78 °C to rt, 18 h; (e) CH_2N_2, Et_2O then DBU, THF, reflux to eqilibrate C-9 isomers; (f) 2,3-dimethoxyphenylboronic acid, $Pd(dppf)_2Cl_2$, Cs_2CO_3, THF, reflux; (g) TBAF, THF; *n*-Bu_3P, DEAD, $PhCO_2H$, THF, 0 °C to rt; $LiAlH_4$, THF, 0 °C to rt; (h) NaH, DMF, 0 °C to rt; (i) NaH, MeI, THF, 0 °C; (j) $MeC(OMe)_3$, *o*-NO_2Phenol, 130 °C, 6 d; (k) 59% aqueous NaOH, MeOH, 80 °C; (l) HBTU, *i*-Pr_2NEt, CH_2Cl_2, rt; (m) Dess−Martin periodinane, CH_2Cl_2; (n) $BF_3{\cdot}OEt_2$, CH_2Cl_2, −10 °C to rt, 3 h; (o) Ph_2SiHCl, $InCl_3$, DCE, reflux, 20 h; (p) *m*-CPBA, CH_2Cl_2, 0 °C to rt, then camphorsulfonic acid, THF, reflux; (q) $LiAlH_4$, dioxane, reflux; (r) Dess−Martin periodinane, CH_2Cl_2, 0 °C to rt, 2.5 h.

fragmentation of **68** could lead to morphinan skeleton **69**, Scheme 7.[63]

The Heck−aldol approach (Scheme 8) was originally designed to study intramolecular aza-Prins and Mannich cyclizations of the olefinic aldehyde derived from **73**. Because these proved unsuccessful, we resorted to an intramolecular aldol cyclization and subsequent 1,6-conjugate addition to dienone **74**, completing the synthesis of *ent*-neopinone,[46] according to a similar approach by Fukuyama.[45]

***Lesson 4**: Sometimes increasing the effort on an arduous project does not produce improvements. It is more effective to change direction and focus on other ideas to provide new inspiration.*

4.5. Recent Solutions

Things are often exactly as they seem. Confusing isn't it.

Richard Butchins

More recently, we were successful with strategies based on Claisen rearrangements[48] and [2 + 3] nitrone cycloadditions.[49] Although we had accomplished a Kazmaier−Claisen rearrangement of the glycinate enolate derived from diol **77** to amino acid **78** as early as 1997, the project did not progress for a variety of reasons. Returning to it after more than 15 years, we successfully implemented this strategy by manipulating the amino acid moiety, adding a second Claisen rearrangement to set the C-13 center followed by C-10/C-11 closure of **79**, Scheme 9.[48] Amide **83** was converted to hydrocodone and dihydrocodeine according to Chida's synthesis.[42]

A nitrone cycloaddition of **87** led to the *epi*-configuration of C-9. This outcome, different from that reported by Metz,[47] was corrected by Hofmann elimination and subsequent hydroamination of **90** to *ent*-codeinone, Scheme 10.[49]

We also discovered that aldehyde **91**, the precursor to nitrone **87**, on exposure to SmI_2 cyclized readily to tetracyclic morphinans **92** (formed via Prins reaction catalyzed by Sm(III)) and **93**

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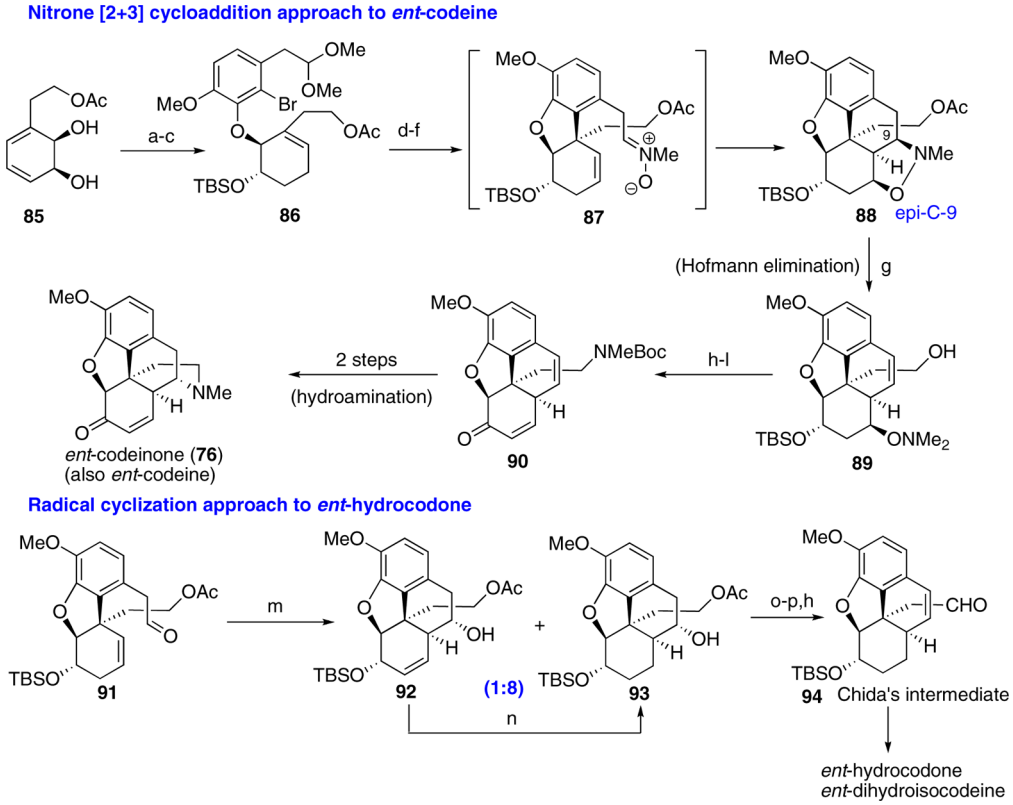
Scheme 10. Cycloaddition and Radical Cyclization Approaches[49a]



[a]Reagents and conditions: (a) potassium azodicarboxylate (PAD), HOAc, MeOH; (b) TBSCl, imidazole, DMF; (c) DIAD, *n*-Bu_3P, methoxy acetal derivative of phenol **71**; (d) $Pd_2(dba)_3$, K_2CO_3, *t*-Bu_3P, toluene, reflux, 16 h; (e) 50% aqueous TFA, PhMe, 50 °C, 30 min; (f) NHMeOH (HCl), *i*-Pr_2NEt, toluene, reflux, 5 h; (g) Meerwein's salt, CH_2Cl_2, rt, 2 h; then $LiAlH_4$, THF, rt, 30 min; (h) Dess–Martin periodinane, CH_2Cl_2; (i) $NH_2Me(HCl)$, Et_3N, Ti(*i*-PrO)$_4$, MeOH; then $NaBH_4$, MeOH; (j) $(Boc)_2O$, EtOH; (k) TBAF, THF; (l) Dess–Martin periodinane, CH_2Cl_2; (m) SmI_2, HMPA, THF, rt, 20 h; (n) H_2, Pd/C, MeOH; (o) MsCl, Et_3N, CH_2Cl_2; (p) NaOH, H_2O, MeOH.

(formed by radical cyclization). Both were converted to Chida's intermediate and to *ent*-hydrocodone, as shown in Scheme 10.[49]

***Lesson 5**: That some projects seemed to have taken an inordinate amount of time may be explained by the nature and attitude of persons engaged in the project. Ernest Wenkert once said "When the proposed chemistry on paper makes sense the success or failure at the bench is strictly the function of the operator." Wiser words have never been spoken.*

4.6. Return to the Original Idea

> *Good judgment comes from experience. Experience comes from bad judgment.*
>
> attributed to Mullah Nasrudin, 13th century

Sometimes ideas based on pattern recognition require substantial incubation before they can be successfully implemented. It seems that the initial intuitive idea based on imagery and superimposition of patterns almost always ends up being the correct one. This is precisely how the initial idea of using *cis*-dienediols for morphine design originated, by seeing the required patterns in a snow-covered tree![66] That we were not successful the first time was a tactical problem, not a strategic one; we simply did not connect the oxidative aromatization of phenols to the design of a suitable compound such as **21**, Figure 3.

Returning to our cycloaddition strategy, we were rewarded with one of the shortest syntheses of a morphinan.[50] Scheme 11 shows the solution to the cycloaddition design we had pursued more than 20 years ago. Coupling of the C-ring unit with phenol **95** and elaboration to styrene **97** provided the precursor to the oxidative dearomatization accomplished with $Pb(OAc)_4$ or IBX.[67] We were further inspired by the recent work of Rodrigo, who also approached morphinan synthesis through dearomatization/cycloaddition strategy.[68] Dienone **98** underwent intramolecular cycloaddition to the tetracyclic phenanthrene core **99**, which, after rearomatization, was rapidly converted to the full morphinan skeleton **102** by Parker's hydroamination. *ent*-Hydromorphone was attained in just five operations from aryl ether **96** (11 steps from diol **13**). The current strategy could be further improved by replacing chemical oxidants with electrochemical oxidation in the dearomatization step. Such improvements will be pursued during the subsequent generations. For the moment, however fleeting, we are content with this accomplishment.

***Lesson 6**: Never give up on the original idea!*

5. OUTLOOK

We have summarized our efforts toward (and obsession with) a practical synthesis of morphine and opiate-derived agents. Our quest for practicality is in no small part aided by experience acquired from our long collaboration on industrial projects. For the last 10 years, we have been working with Noramco, Inc., on process development for commercial analgesics and antagonists such as buprenorphine, oxymorphone, oxycodone, and naltrexone, naloxone, and nalbuphine. The results of our work in this area have been reported in many publications and summarized

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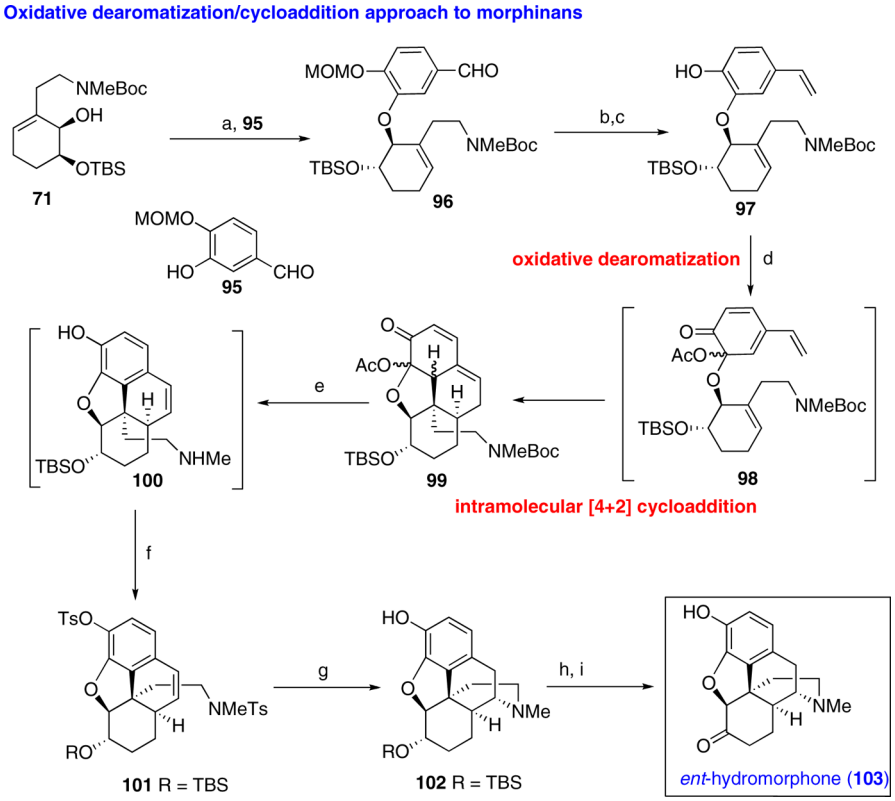
Scheme 11. Short Synthesis of *ent*-Hydromorphone[a]



[a]Reagents and conditions: (a) tetramethylazodicarboxamide, *n*-Bu_3P, THF, −10 °C to rt, 22 h; (b) CH_3PPh_3Br, BuLi, THF, −78 to 0 °C; then reflux 4 h; (c) $ZnBr_2$, 1-dodecanethiol, CH_2Cl_2, 0 °C to rt, 10 min; (d) $Pb(OAc)_4$, DCE, reflux 4 h; (e) TFA, CH_2Cl_2, 0 °C, 15 min; (f) TsCl, Et_3N, CH_2Cl_2, 0 °C to rt, 10 h; (g) Li, *t*-BuOH, $NH_{3(l)}$,THF, −78 °C, 10 min; (h) TBAF, THF, rt, 6 h; (i) *t*-BuOK, PhCOPh, PhMe, DME, 85 °C, 8 h.

recently.[69] Industrial process development demands the credibility of reported yields and precise communication of results.[70] Our participation in real-world projects, coupled with more fundamental endeavors, positions us to be able to further refine another generation of morphinan synthesis. Perhaps in time an almost-ideal five- or six-step synthesis will materialize if the craft of synthesis continues to progress. Organic synthesis is a tenuous and under-appreciated field. We end with a comment made recently by Marc Tius with the hope that future endeavors within our guild deliver the required paradigm shift(s).

> *Consider that if you could resurrect an organic chemist from 100 years ago, he would recognize most of the glassware in the lab, and once he spent a month reading about transition metal reagents and a few other novelties from the past 50 years he could understand pretty much everything we are doing, because the goals of organic synthesis have scarcely changed in a century. Now think about performing the same thought experiment with a biologist. The biologist of 100 years ago would be completely mystified by today's biology. Organic synthesis either finds its mojo again or this branch of chemistry as we know it and practice it will be extinct.*
>
> Marc Tius, October 2014

■ ASSOCIATED CONTENT

Supporting Information

Additional relevant references are included in this section. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: thudlicky@brocku.ca.

Notes

The authors declare no competing financial interest.

Biographies

A North Carolina native, **Josephine Reed** was educated at the University of North Carolina at Greensboro (B.A., English), Appalachian State University (B.A., biology and chemistry), and Virginia Tech (Ph.D., chemistry, with Professor David Kingston). She has worked with Tomas Hudlicky and his group for more than 25 years. She has expanded her efforts in supporting faculty in the natural and health sciences through her position as Research Officer in Brock University's Office of Research Services.

Tomas Hudlicky was born in 1949 in Prague, Czechoslovakia. In 1968, he immigrated to the U.S. He received his B.S. in chemistry in 1973 (Virginia Tech) and went on to pursue graduate studies in the field of indole alkaloid total synthesis, earning his Ph.D. in 1977 (Rice University, Professor Ernest Wenkert). After a postdoctoral fellowship (Univeristy of Geneva, Professor Wolfgang Oppolzer), he began his research career at Illinois Institute of Technology in 1978, returned to Virginia Tech in 1982, then moved to the University of Florida in Gainesville in 1995. In 2003, Hudlicky accepted an offer from Brock University, where he is currently Canada Research Chair in Organic Synthesis and Biocatalysis. Current research interests include the development of enantioselective synthetic methods, bacterial dioxygenase-mediated degradation of aromatics, design and synthesis of

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fluorinated inhalation anesthetic agents, synthesis of morphine and Amaryllidaceae alkaloids, and design of unnatural oligosaccharide conjugates with new molecular properties.

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■ DEDICATION

Dedicated to the memory of Christie Hopkins Boros (1964−2012).

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