

With compliments of the Author

Recent Progress in the Synthesis of Morphine Alkaloids

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Abstract: Recent accomplishments in the field of total synthesis of morphine alkaloids are reviewed. Approaches to the skeleton of morphine are included as are various efforts towards related medicinally important agents. The literature coverage begins after the publication of our last update in 2000 and continues mid-way through 2004.

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Key words: morphine, total synthesis, alkaloids, approaches to morphine skeleton, morphine analogs and mimics

1 Introduction

Morphine (**1**) and codeine (**2**), the principal constituents of opium, continue to attract the attention of synthetic chemists. The use of opium has been documented as far back as 3000 B.C., to the Sumerians, who lived in the Mesopotamian region now a part of southern Iraq.¹ Most people are familiar with compounds such as morphine and heroin (**3**), as well as some of the morphine antagonists such as naltrexone (**4**) and naloxone (**5**), see Figure 1. The legal medicinal use of morphine in the U.S. exceeds 80,000 kg/year, and the world-wide illicit market for narcotics is estimated at more than \$760 billion – a sum exceeding the combined GNP of all but a few economies on the planet.^{1,2} All morphine used today originates in natural opium, which is supplied primarily from India, Afghanistan, and Turkey where the poppies contain up to

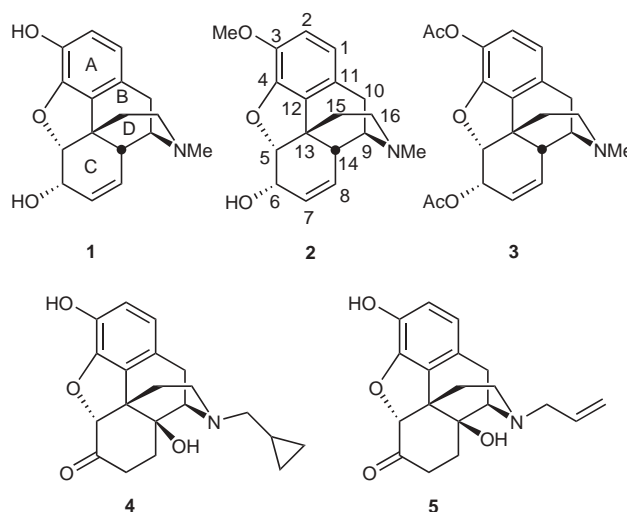


Figure 1 Morphine, congeners, and synthetic derivatives

20% of morphine in their latex. The antagonists **4** and **5** are manufactured from morphine by semisynthesis in several steps. To date there is no reported synthesis of the alkaloid (excepting perhaps that of Rice, see Table 1) that would show promise for a large-scale manufacturing.

The possibility of a fully synthetic supply of morphine is nevertheless important as the availability of natural morphine depends on the political stability of a very few regions of the world. Political unrest or ecological disasters could jeopardize the availability of morphine for medical use, which is important as an analgesic and as an anesthetic.^{2,3}

Several reviews have been published on the total synthesis of morphine alkaloids;⁴ our own most recent update appeared in 2000.^{4d} Since then at least three total syntheses and several approaches have appeared attesting to the undiminished interest of synthetic chemists in this fascinating molecule. A concise feature article discussing history, use, and synthesis of morphine by White was published in 2002.^{4c}

Morphine seems to be a simple alkaloid compared to, for example, diterpene alkaloids such as atisine, but a close examination of its structure (with an eye for an efficient design) reveals problems in connectivity. This is especially true for derivatives oxygenated at C-14.

Following Evans's terminology of consonance and dissonance⁵ and taking into account that morphine itself functions as an amino acid, the two disconnection analy-

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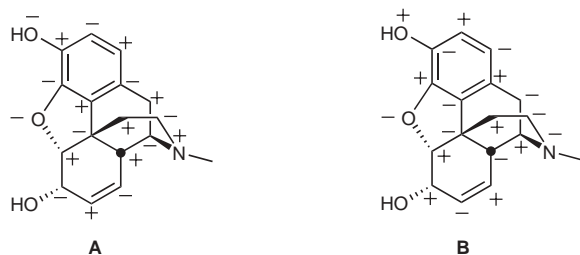


Figure 2 Dissonant relationships in morphine connectivity (A = phenol priority, B = amine priority)

ses in terms of polarization begin with either the phenolic oxygen (A) or the tertiary amine (B), as shown in Figure 2. It is immediately obvious that there can be no possible assignment in which the alternating charges match or in which one of the priority atoms does not re-

ceive an incorrect charge. This ‘dissonance’ no doubt expresses itself in almost all published syntheses where one or another part of the molecule suffers during the execution of the synthesis. The more arduous design elements in the structures of morphine (**1**) and noroxymorphine (**6**) are shown in Figure 3.

2 Total Syntheses

Our 1996 review covered all total syntheses of morphine including approaches and references to dissertations.^{4a} An updated list of all total and formal syntheses as of this writing is shown in Table 1. Since the publication of our 2000 update^{4d} three total syntheses have been reported; these are discussed in detail in this review along with other approaches to the morphine ring system.

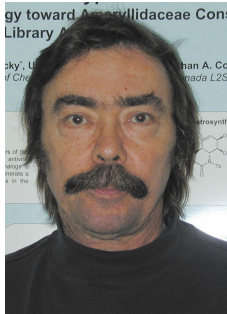
Biographical Sketches



Josef Zezula was born in 1976 in Czechoslovakia, now the Czech Republic. In 1994 he was accepted at the Institute of Chemical Technology, Prague, where he worked in research group of Professor I. Stibor in the area of calixarene-based macromolecules. After he

received his MSc degree in 1999, he moved to the United States to pursue graduate studies at the University of Florida, Gainesville, under the direction of Tomas Hudlicky. In 2003 he completed PhD studies, which were focused on the use of products of microbial oxida-

tion of arenes in approaches towards the morphine skeleton. Currently he is a visiting fellow at the National Institutes of Health in Bethesda, Maryland, working in the research group of Dr. K. C. Rice.



Tomas Hudlicky was born in 1949 in Prague, Czechoslovakia, where he received his elementary and middle school education. He was denied access to higher forms of education beyond grade 9 and worked for a number of years in odd jobs around the city as well as a process chemist apprentice in pharmaceutical industry. In 1968 he emigrated to the U.S. with his family and continued his educational experience by attending Blacksburg High School, dropping out in the spring of 1969. Accepted as a probational student at Virginia tech in the fall of that year he graduated with a BSc in chemistry in 1973 and pursued graduate studies at Rice University under the direction of Professor Ernest Wenkert in indole alkaloid total synthesis. Fol-

lowing his PhD in 1977, he spent a year as a postdoctoral fellow with Professor Wolfgang Oppolzer at the university of Geneva working on the synthesis of isocomene. In 1978 he joined the faculty at Illinois Institute of Technology to start his independent career in the field of general methods of synthesis for triquinane sesquiterpenes and other natural products containing five-membered rings. The development of [4+1] and [3+2] annulation methodologies dates to this period of time. In 1982 he moved back to his alma mater, Virginia Tech where he rose to the rank of Professor in 1988. One year later at the 20-year reunion of his High School class of '69 he was awarded his High School Diploma. The next phase of his research involved the use of

prokaryotic enzymes in generating useful chiral metabolites for asymmetric synthesis. In 1995 he moved to the University of Florida and in 2003 he accepted a position at Brock University as Canada Research Chair Professor of Chemistry and Biocatalysis.

His current research interests include the development of enantioselective synthetic methods, biocatalysis, total synthesis of morphine and amaryllidaceae alkaloids, isolation and use of metabolites derived by enzymatic dihydroxylation of aromatics, design of inositol-containing oligomers, and organic electrochemistry. His hobbies include skiing, martial arts, music, and hockey and he enjoys all of these with his 14-year old son Jason.

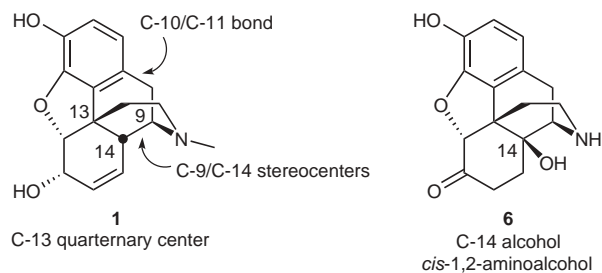


Figure 3 Key design considerations for morphine and noroxymorphine

Table 1 Total and Formal Syntheses of Morphine and its Derivatives

Principle author	Date	Product (no. of steps)	Yield (%)
Gates	1952	(-)-Morphine (23)	0.01 ⁶
Ginsberg	1954	<i>rac</i> -Dihydrothebainone (21)	8.86 ^{a,7}
Grewe	1967	<i>rac</i> -Dihydrothebainone (9)	0.81 ⁸
Rice	1980	(-)-Dihydrocodeinone (10)	29.00 ⁹
Evans	1982	<i>rac</i> - <i>O</i> -Me-thebainone-A (12)	16.67 ¹⁰
Rapoport	1983	<i>rac</i> -Codeine (26)	1.15 ¹¹
Fuchs	1988	<i>rac</i> -Codeine (22)	1.53 ¹²
Tius	1992	<i>rac</i> -Thebainone-A (28)	0.97 ¹³
Parker	1992	<i>rac</i> -Dihydrocodeinone (12)	9.42 ¹⁴
Overman	1993	(-)-Dihydrocodeinone (14)	4.43 ¹⁵
Mulzer	1996	(-)-Dihydrocodeinone (15)	11.50 ¹⁶
Parsons	1996	Morphine	0.88 ^{b,17}
White	1997	(+)-Morphine (28)	3.00 ¹⁸
Hudlicky	1998	10-Hydroxy- <i>ent</i> - <i>epi</i> -dihydrocodeinone (14)	2.70 ¹⁹
Cheng	2000	<i>rac</i> -Desoxycodeine-D (15)	13.26 ²⁰
Ogasawara	2000	<i>rac</i> -3,4-Dimethoxy-6-morphinanone (29)	0.25 ²¹
Ogasawara	2001	(-)-Dihydrocodeinone ethylene ketal (24)	0.37 ²²
Taber	2002	(-)-Morphine (27)	0.51 ²³
Trost	2002	(-)-Codeine (15)	6.78 ²⁴

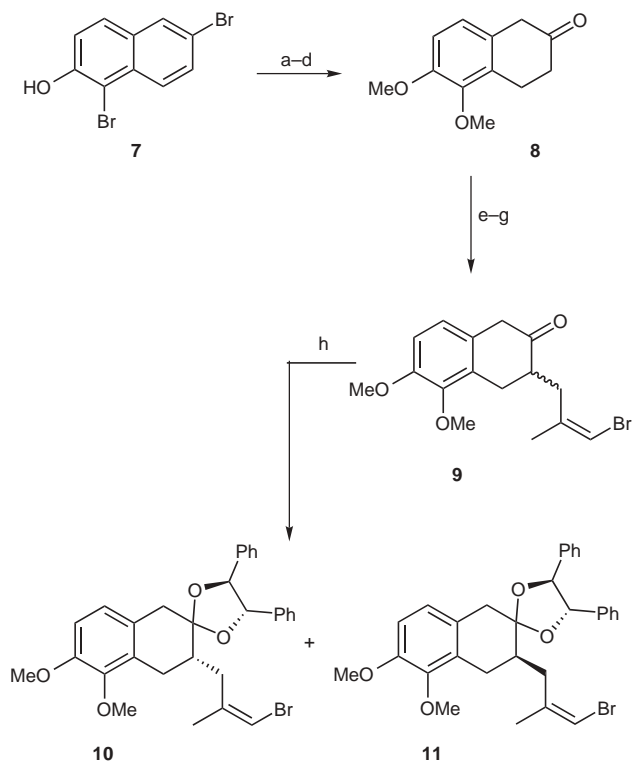
^a First 16 steps.

^b Last 5 steps.

Note: Key transformations in the Schemes are depicted in blue.

2.1 Taber

In 2002 Taber²³ published a total synthesis of (-)-morphine starting from tetralone **9**, which provided the AB-ring system and the carbon atoms needed for the construction of the C-ring. Compound **9** had been prepared from



Scheme 1 Reagents and conditions: (a) MeI, K₂CO₃, DMF (97%); (b) MeONa, collidine, CuI, MeOH, Δ (89%); (c) Na, EtOH, Δ; (d) HCl, H₂O, Δ (76%, 2 steps); (e) (MeO)₂CO, MeONa, Δ (76%); (f) LDA (2 equiv), THF, 0 °C; (g) LiCl, DMSO, H₂O, Δ (80%, 2 steps); (h) *p*-TsOH, (*S,S*)-(-)-hydrobenzoin, HC(OEt)₃, CH₂Cl₂ (86%).

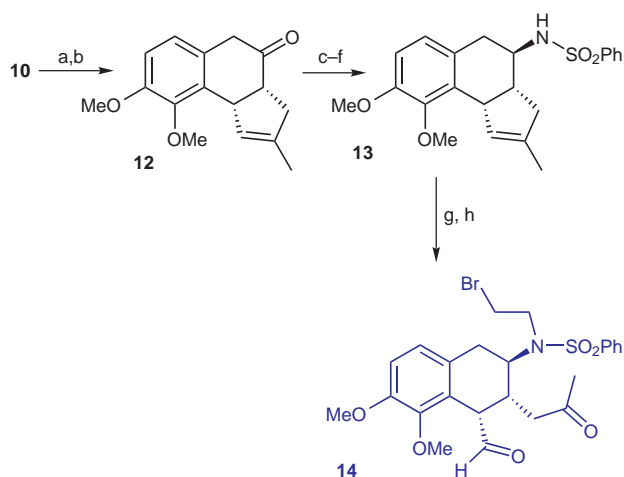
1,6-dibromo-2-naphthol (**7**) in 7 steps utilizing modified literature procedures.²⁵

Several issues deserve mention from strategic as well as tactical viewpoints. First, the incorporation of asymmetry was accomplished by resolution of racemic **9** via diastereomeric ketals derived from (*S,S*)-(-)-hydrobenzoin to give **10** and **11**, which were separated by column chromatography (Scheme 1).

The undesired diastereomer **11** was easily recycled to racemic **9** by reflux in aqueous acetic acid. Second, the cyclization of ketal **10** via alkylidene carbene C–H insertion²⁶ followed by hydrolysis gave the enantiomerically pure ketone **12**, which, unlike tetralone **9**, cannot racemize because of the large energy difference between *cis*- and *trans*-fused hydrindanones (Scheme 2).

Taber introduced the nitrogen atom along with the remaining two carbons necessary for the construction of the D-ring to provide the key intermediate, keto aldehyde **14** as shown in Scheme 2. Third, both C- and D-rings were closed in a single operation, as shown in Scheme 3.

The introduction of the nitrogen atom required the stereoselective reduction of ketone **12** with L-Selectride to the α-alcohol, which was converted, with inversion of configuration, to the corresponding azide by Mitsunobu coupling.²⁷ Reduction and protection gave sulfonamide **13**. The key intermediate in Taber's synthesis, the keto alde-



Scheme 2 Reagents and conditions: (a) KHMDS, Et₂O (77%); (b) HOAc, H₂O, Δ (80%); (c) L-Selectride, THF, 0 °C (97%); (d) (PhO)₂P(O)N₃, DEAD, Ph₃P, THF; (e) LiAlH₄, EtOH, Et₂O; (f) PhSO₂Cl, Et₃N, CH₂Cl₂ (43%, 3 steps); (g) BrCH₂CH₂Br, NaOH, TBAB, PhMe, Δ (83%); (h) O₃, CH₂Cl₂, -70 °C, PPh₃ (85%).

hyde **14**, was prepared by alkylation of **13** and subsequent ozonolysis of the methylcyclopentene ring (Scheme 2).

Tetracyclic morphinan **15** was prepared by a selective double cyclization of **14**, the first step of which involved the intramolecular alkylation of the aldehyde enolate to close the D-ring. In the second step, a Robinson annulation provided enone **15** in excellent yield (Scheme 3). Reduction of **15** with NaBH₄ gave a single alcohol, which upon brief exposure to BBr₃ provided the ether bridge to yield pentacycle **16**. Deprotection of phenylsulfonamide **16** by dissolving metal reduction failed, but Red-Al in refluxing toluene was found effective, and the resulting amine was immediately protected as its carbamate.

The oxidation state of ring C was adjusted by stereoselective epoxidation directed by the steric hindrance from the

aromatic ring. Regioselective opening of the epoxide provided selenide **17**, whose oxidation followed by elimination gave alcohol **18**, with the incorrect configuration of the hydroxyl at the C-6 (Scheme 3).

Codeine was prepared by the known oxidation–reduction sequence, and morphine was obtained by further treatment with BBr₃ by the procedure reported by Rice²⁸ in a total of 27 steps from naphthol **7** and in 0.5% overall yield.

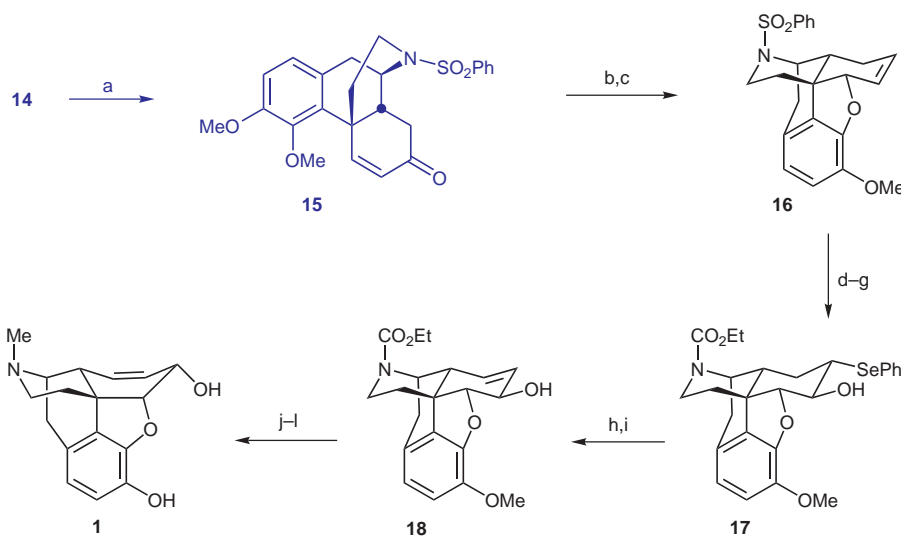
2.2 Trost

Trost's enantioselective total synthesis of (–)-codeine and (–)-morphine²⁴ appeared in 2002 soon after Taber's report. Chirality was introduced via asymmetric allylic alkylation of phenol **21**¹² with ester **20**²⁹ (readily available in two steps from glutaraldehyde), catalyzed by palladium in the presence of chiral bis-phosphine ligand **19** to give the aryl ether **22** in good yield and ee (72 and 88%, respectively, Scheme 4).

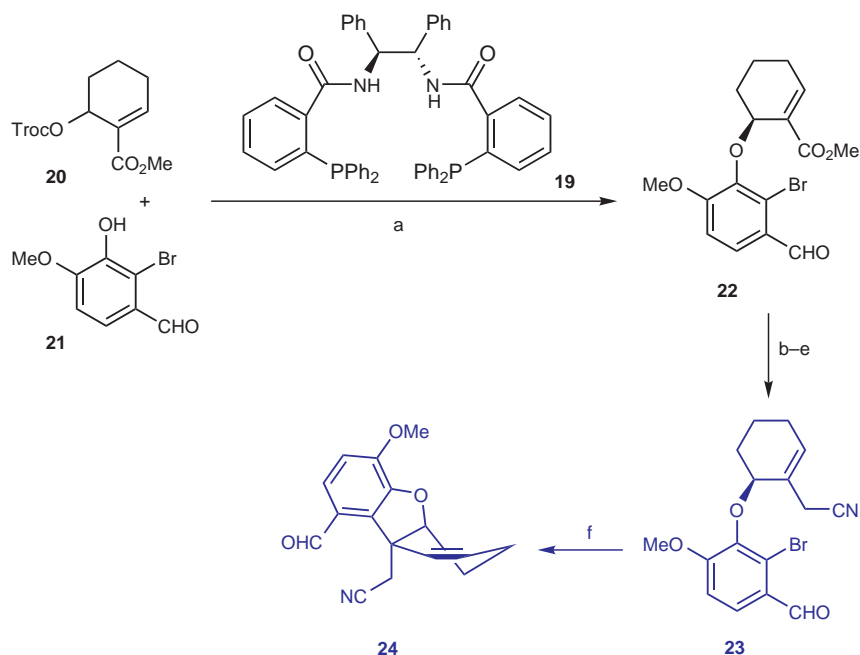
The key features of Trost's synthesis are the Heck cyclization of nitrile **23**, which contain the A- and C-rings, to the tricyclic ether **24** and the Heck vinylation of **25** to furnish the tetracycle **26** (Scheme 5). The D-ring was closed by an intramolecular hydroamination to produce codeine.

Nitrile **23** was prepared in four steps as described in Trost's earlier report on the synthesis of alkaloid (–)-galanthamine.³⁰ The optical purity of **23** was improved to 96% ee by recrystallization. The key step, establishing the C-13 quaternary center, was accomplished by Heck coupling of **23** to give tricyclic ether **24** in excellent yield (Scheme 4).

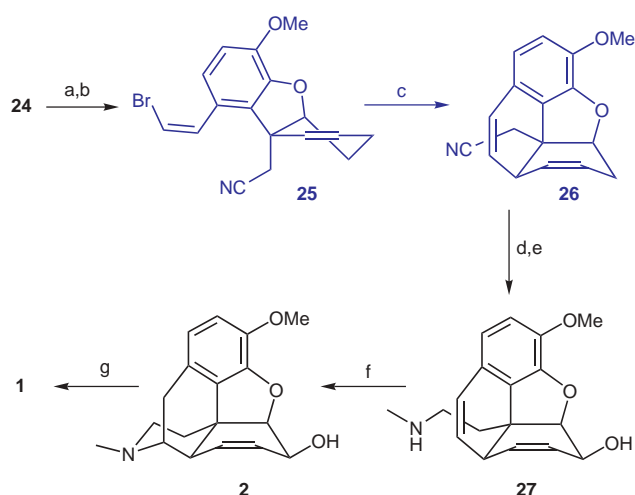
Cyclization precursor **25** was prepared in two steps by Corey–Fuchs olefination³¹ followed by chemoselective reduction to the (Z)-vinylbromide.³² Intramolecular Heck vinylation gave olefin **26**, completing the construction of the phenanthrene core of morphine (Scheme 5).



Scheme 3 Reagents and conditions: (a) K₂CO₃, TBAB, toluene, Δ (92%); (b) NaBH₄, EtOH (92%); (c) BBr₃, CH₂Cl₂, -40 °C (70%); (d) Red-Al, toluene, Δ; (e) ClCO₂Et, Et₃N, CH₂Cl₂ (78%); (f) {[C₈H₁₇]₃NCH₃}⁺₃{PO₄[W(O)(O₂)₂]₄}³⁻, H₂O₂, DCE, Δ (75%); (g) PhSeSePh, NaBH₄, EtOH, Δ (75%); (h) NaIO₄, THF, H₂O; (i) Na₂CO₃, toluene, H₂O (58%); (j) MnO₂, CH₂Cl₂; (k) LiAlH₄, THF, Δ (75%); (l) BBr₃ (86%).



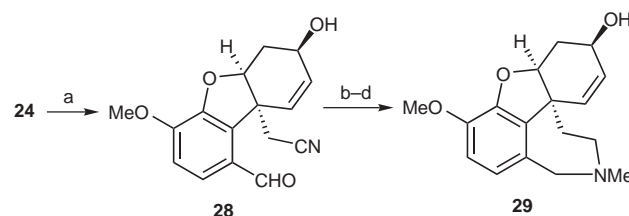
Scheme 4 Reagents and conditions: (a) **19**, $[\eta^3\text{-C}_3\text{H}_3\text{PdCl}]_2$, Et₃N, CH₂Cl₂, r.t. (72%); (b) TsOH, CH(OMe)₃, MeOH; (c) DIBALH, toluene, -78 °C (85%); (d) PPh₃, acetonecyanohydrin, DIAD, Et₂O; (e) TsOH, THF, H₂O (76%); (f) Pd(OAc)₂, dppp, Ag₂CO₃, toluene, 107 °C (91%). Troc = 2,2,2-trichloroethoxycarbonyl, DIAD = diisopropyl azodicarboxylate, dppp = bis(diphenylphosphonyl)propane.



Scheme 5 Reagents and conditions: (a) CBr₄, Ph₃P, CH₂Cl₂ (91%); (b) Pd(PPh₃)₄, *n*-Bu₃H, toluene (88%); (c) Pd(OAc)₂, dppp, Ag₂CO₃, toluene (65%); (d) SeO₂, 1,4-dioxane, 75 °C, then DMP, r.t. (58%); (e) DIBALH, CH₂Cl₂, Et₂O, then NH₄Br, MeNH₂, then NaBH₄ (89%); (f) LDA, THF with tungsten bulb (57%); (g) BBr₃.

Allylic oxidation with SeO₂ and treatment with Dess–Martin periodinane gave the corresponding enone, which was reduced, along with the nitrile, in a one-pot procedure by DIBALH to give an imine–aluminum complex. Addition of ammonium bromide in dry methanol quenched the excess hydride and furnished the free imine, which was reacted with methylamine. Finally, the addition of sodium borohydride resulted in the formation of the desired secondary amine **27** in good overall yield from olefin **26** (Scheme 5).

Intramolecular hydroamination of **27**, promoted by irradiation of the basic solution by an ordinary tungsten lamp, yielded (–)-codeine in good yield. Morphine was obtained by O-demethylation, following the procedure of Rice.²⁸ (–)-Codeine was obtained in 15 steps from guaiacol derivative **21** in an overall yield of 7%. It should be mentioned that compound **24** also served as an intermediate for total synthesis of (–)-galanthamine (**29**) as shown in Scheme 6.



Scheme 6 Reagents and conditions: (a) SeO₂, Na₂HPO₄, 1,4-dioxane (64%); (b) MeNH₂, MeOH; (c) DIBALH (4 equiv), then aq NaH₂PO₄; (d) NaCNBH₃ (b–d in one pot, 62%).

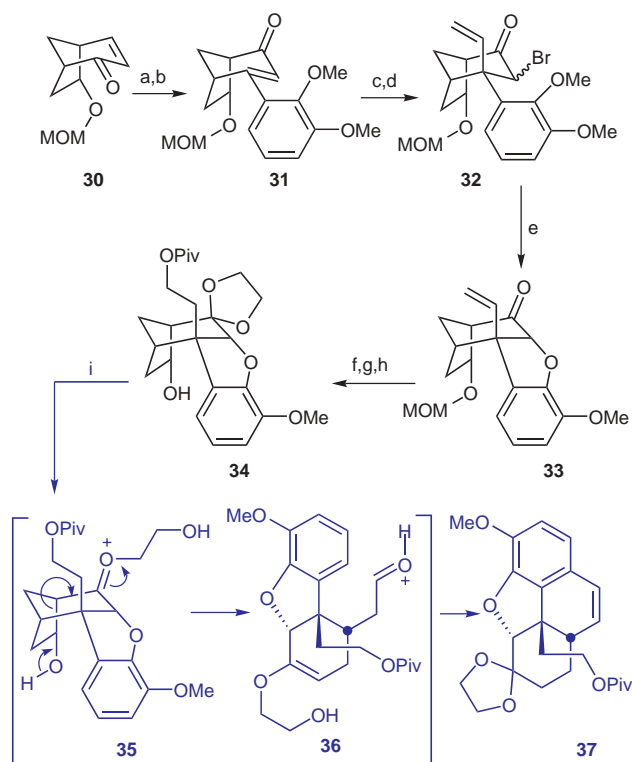
2.3 Ogasawara

In 2001 Ogasawara published²² a concise route to the ethylene ketal of (–)-dihydrocodeinone starting from enantiopure bicyclic enone **30**,³⁴ a compound that exhibits convex-face selectivity because of its sterically biased framework. Enone **30** has served the author well in several other syntheses, most notably in his preparation of vernolepin.³⁵ In this approach to the morphine skeleton, rings A and C were constructed in two steps via the attack of lithiated veratrol (ring A) onto the carbonyl to give the tertiary alcohol, which was oxidized with concomitant transposition to enone **31**. The vinyl moiety was introduced accord-

ing to Mulzer's conditions^{16a} via a diastereoselective 1,4-addition of vinyl cuprate followed by bromination with NBS to give bromoketone **32** (Scheme 7).

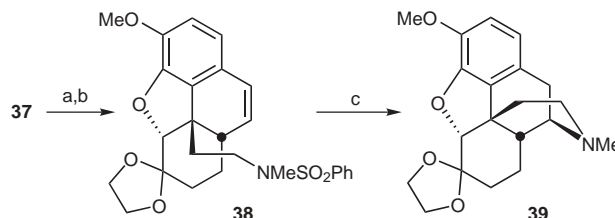
The ether bridge was constructed by heating **32** in dimethylformamide to provide dihydrobenzofuran **33**. After protection of the ketone as a ketal, the hydroboration-oxidation sequence was carried out to give the primary alcohol, protected as pivalate **34** (Scheme 7).

Closure of ring B was accomplished by heating **34** in benzene and ethylene glycol in the presence of a catalytic amount of TsOH. Ogasawara proposed that the ketal is first converted into its oxonium ion **35**, which then undergoes a retro-aldol cleavage of the bicyclic system to afford the corresponding protonated aldehyde **36**. The final cyclization, accelerated by the *para*-methoxy group, occurs at this stage to form the B-ring. The presence of ethylene glycol in the reaction mixture seemed to accelerate this cyclization. Tetracycle **37** was obtained in good yield as a single isomer (Scheme 7).



Scheme 7 Reagents and conditions: (a) 3-Li-veratrol, THF, -78°C ; (b) PCC, CH_2Cl_2 (81% for 2 steps); (c) CH_2CHMgCl , $\text{CuBr}\cdot\text{SMe}_2$, TMSCl , HMPA , THF (75%); (d) NBS, CH_2Cl_2 , r.t. (99%); (e) DMF, Δ (82%); (f) $(\text{CH}_2\text{OTMS})_2$, TfOTMS (cat.), CH_2Cl_2 (71%); (g) $\text{BH}_3\cdot\text{SMe}_2$, then H_2O_2 , NaOH (72%); (h) Piv-Cl , pyridine (87%); (i) $(\text{CH}_2\text{OH})_2$, TsOH (cat.), toluene, Δ (50%).

Synthesis of the complete pentacyclic skeleton was accomplished by the introduction of the tosylamide moiety in two steps followed by reductive detosylation with concomitant cyclization¹⁴ to give the ethylene ketal of (–)-dihydrocodeine **39** (Scheme 8). The key intermediate **39** was prepared in 12 steps from the bicyclic ketone **30** in 6% overall yield.

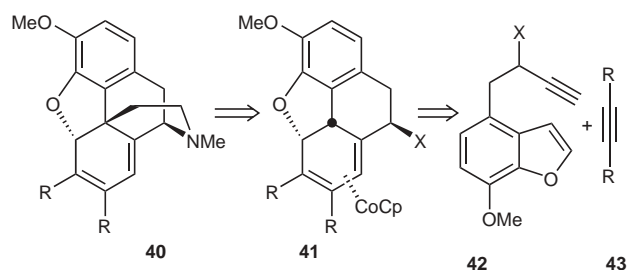


Scheme 8 Reagents and conditions: (a) LiAlH_4 , THF, r.t. (100%); (b) PhSO_2NHMe , 1,1'-(azodicarbonyl)dipiperidine, Bu_3P , THF (78%); (c) Li , NH_3 , *t*-BuOH, THF (70%).

3 Approaches to the Morphine Skeleton

3.1 Vollhardt

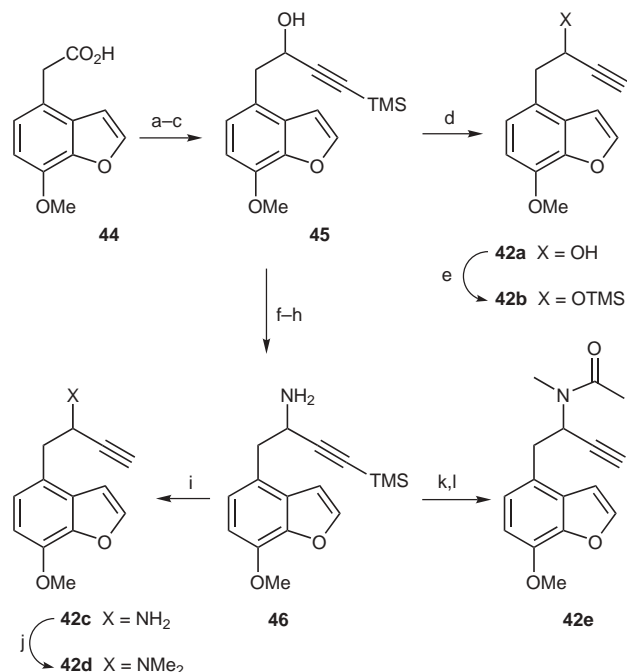
In his approach published in 2000, Vollhardt envisioned simultaneous closure of the B- and the C-rings in the morphine skeleton by a CpCo -mediated [2+2+2] cycloaddition of functionalized 4-(3-butynyl)-benzofurans³⁷ such as **42** with arynes **43** (Scheme 9).



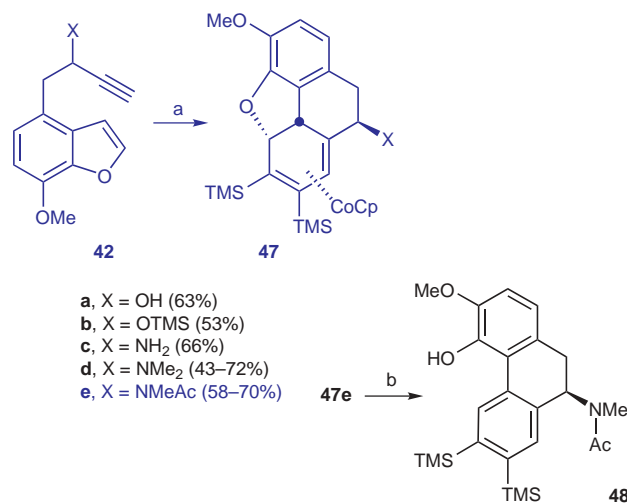
Scheme 9

The precursor for the required 4-(3-butynyl)-benzofurans was prepared from the readily available³⁸ acid **44** by its conversion into the (*S*)-ethylthioester. Reduction with $\text{Et}_3\text{SiH-Pd/C}$ ³⁹ gave the corresponding aldehyde, which was transformed into alcohol **45** by the reaction with lithium trimethylsilylacetylene. The requisite benzofurans **42a–e** were obtained from **45** by standard procedures (Scheme 10).

Reactions of **42a–e** with bis(trimethylsilyl)acetylene (BTMSA) in the presence of $\text{CpCo}(\text{C}_2\text{H}_4)_2$ successfully yielded the corresponding crystalline cobalt complexes **47a–e** in good yields (Scheme 11). The [2+2+2] cyclizations proceeded in a remarkably diastereospecific fashion providing only one of four possible diastereomers and securing the correct configurations at C-5, C-13, and C-9. Oxidative removal of the metal in complex **47e** furnished dihydrophenanthrene **48**. Future adjustments in the strategy toward morphine therefore should rely on derivatives of **42** substituted at the 3-position. Such functionalization would serve a double purpose: to provide the required carbons for the ethylamino bridge (ring D) and, more importantly, to prevent the aromatization of ring C following the removal of the cobalt complex. One can assume that the stereochemical fate of C-13 center in such functionalized benzofurans will parallel that observed in the formation of **47**.



Scheme 10 Reagents and conditions: (a) EtSH, DMAP, DCC, CH₂Cl₂, 0–23 °C (99%); (b) TES, 10% Pd/C, CH₂Cl₂ (88%); (c) TMSCLi, THF, –78 °C to 23 °C (79%); (d) aq 10% KOH, THF (100%); (e) (TMS)₂NH, TMSCl, toluene, Δ (90%); (f) MsCl, pyridine, –15 °C to 23 °C (99%); (g) NaN₃, DMF, 23 °C (94%); (h) SnCl₂·2H₂O, MeOH, 23 °C (100%); (i) BnMe₃NF, THF, 23 °C (92%); (j) aq 37% HCHO, NaBH₃CN, MeCN, 23 °C, then HOAc, 23 °C (37%); (k) Ac₂O, pyridine, CH₂Cl₂ (90%); (l) KOH, MeI, DMSO, 23 °C (97%).



Scheme 11 Reagents and conditions: (a) BTMSA, CpCo(C₂H₄)₂, Et₂O, 0 °C or 23 °C; (b) Fe(NO₃)₃·9H₂O, H₂O–MeCN–THF, –78 °C to 23 °C (92%).

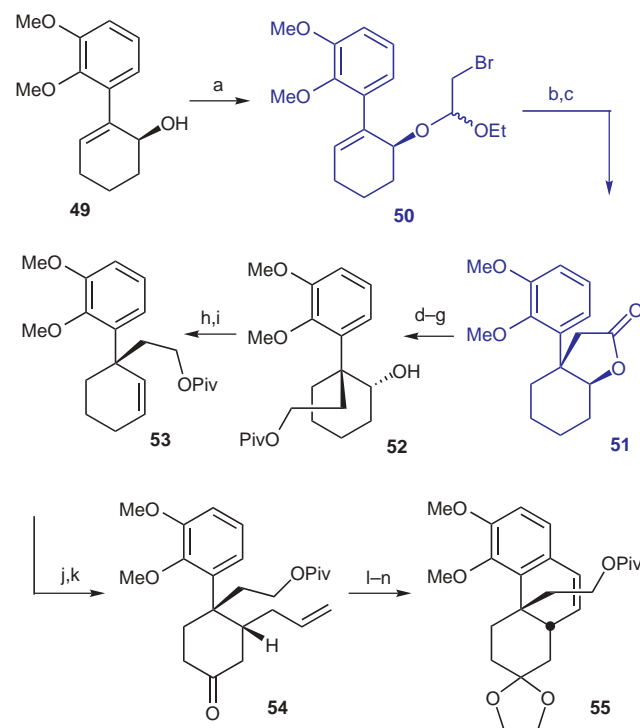
3.2 Ogasawara

In 2000 Ogasawara reported an interesting synthesis of 3,4-dimethoxy-7-morphinanone²¹ starting from *rac*-2-(2,3-dimethoxyphenyl)cyclohexen-1-ol (**49**),^{7a,40} which was resolved by an established protocol.⁴⁰ Stirring *rac*-**49** with vinyl acetate (1.0 equiv) in *t*-butyl methyl ether for

three days in the presence of the lipase PS (*Pseudomonas cepacia*, Amano) provided the enantiopure acetate of (+)-(*R*)-**49** (47%) along with the enantioenriched alcohol (–)-(*S*)-**49** (97% ee, 48%). The diastereoselective synthesis described below was carried out with the racemate of **49**.

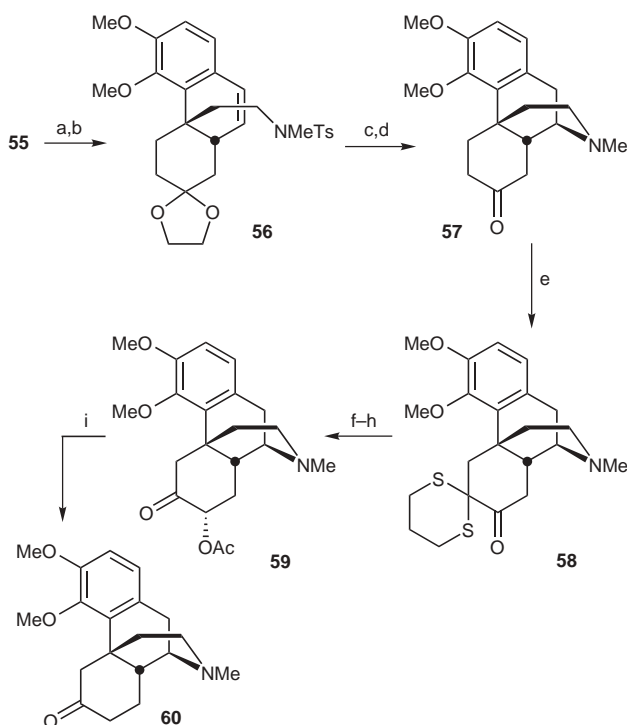
The C-13 quaternary center was constructed by a radical cyclization of the Stork bromoacetal, which was introduced by alkylation of **49** with ethyl vinyl ether in the presence of *N*-bromosuccinimide to provide the key precursor **50**. With the C-13 center set, the cyclic hemiacetal was oxidized to lactone **51**.

Reductive cleavage and selective protection of the primary alcohol as its pivalate allowed the conversion of the secondary alcohol to its xanthate, the pyrolysis of which in the original β-configuration in **51** did not yield the desired olefin. The stereochemistry of the secondary alcohol was inverted by an oxidation–reduction sequence to give the α-isomer **52** (Scheme 12). The xanthate derived from **52** eliminated upon pyrolysis to give olefin **53**. Allylic oxidation of **53** provided the corresponding enone, which was treated with allyl trimethylsilane under Sakurai's conditions to give **54**.³³ The phenanthrene core of morphine was completed by oxidative cleavage of the olefin in **54**, followed by cyclization under acidic conditions in the presence of ethylene glycol to furnish the tricyclic ketal **55** (Scheme 12).



Scheme 12 Reagents and conditions: (a) ethyl vinyl ether, NBS, Et₂O (96%); (b) Bu₃SnH, AIBN, benzene (48%); (c) MCPBA, BF₃·OEt₂ (89%); (d) LiAlH₄, THF (98%); (e) Piv-Cl, pyridine; (f) PDC, CH₂Cl₂, (96%); (g) NaBH₄, *i*-PrOH (82%); (h) MeI, CS₂, NaH; (i) *o*-C₆H₄Cl₂, Δ (73%); (j) CrO₃·3,5-(Me)₂pyrazole (81%); (k) CH₂CH=CH₂TMS, TiCl₄, CH₂Cl₂ (71%); (l) (CH₂OH)₂, TsOH (cat.), benzene, Δ (97%); (m) OsO₄ (cat.), NaIO₄ (83%); (n) (CH₂OH)₂, TsOH (cat.), benzene, Δ (85%).

The ethyl amino bridge was introduced in three steps: the reductive deprotection of the pivalate, conversion of the alcohol to sulfonamide **56** by the Mitsunobu reaction, and the radical closure of the D-ring according to Parker's conditions¹⁴ (reductive desulfonation followed by an intramolecular cyclization, Scheme 13). Hydrolysis of the ketal to ketone **57** completed the synthesis of the tetracyclic morphinan. Structural correlation with a known material was carried out by the conversion of **57** to its α -diketone monothioether **58**, which was reduced and protected as the acetate **59** (Scheme 13). The dithiane moiety was cleaved under oxidative conditions and the α -acetate was reductively removed by treatment with samarium(II) iodide to give the racemic morphinan **60**, corresponding to the known O-methylated derivative of Gates's ketone.^{6,10} The unoptimized synthesis of **60** from alcohol **49** required 23 steps and proceeded with an overall yield of 0.8%.



Scheme 13 Reagents and conditions: (a) LiAlH_4 , THF; (b) MeNHTs , Bu_3P , 1,1'-(azodicarbonyl)dipiperidine (84%); (c) Na , naphthalene, THF (89%); (d) TsOH , aq acetone (97%); (e) pyrrolidine, benzene, then $\text{TsS}(\text{CH}_2)_3\text{STs}$, Et_3N (73%); (f) NaBH_4 , MeOH (97%); (g) Ac_2O , Et_3N (96%); (h) $\text{PhI}(\text{OTFA})_2$, aq MeCN (61%); (i) SmI_2 , THF (37%).

Ogasawara has also reported a total synthesis of morphinan alkaloid (–)-*O*-methylpallidine,³⁶ which possesses the *B/C-trans*-hydrophenanthrene framework. The strategy employed the versatile bicyclic enone **30**. In this approach to morphinan skeleton, the nitrogen atom was introduced early in the synthesis by the condensation of the lithium salt of acetonitrile with the carbonyl in **30**. The product was transformed in three steps to enone **61** via re-

duction, conversion to a carbamate, and oxidation with concomitant 1,3-transposition, as was done in his approach to dihydrocodeinone. The quaternary center in **62** was constructed by the regioselective 1,4-addition of an aryl cuprate to the enone in **61** (Scheme 14).

When ketone **62** was heated in benzene in the presence of *p*-toluenesulfonic acid and ethylene glycol cleavage of the bicyclic ring system occurred to give intermediate aldehyde **63**, which underwent cyclization, presumably via the quinone methide **64**. Surprisingly, an intramolecular nucleophilic attack of the carbamate nitrogen provided tetracycle **65**, instead of the expected formation of C-9/C-10 double bond (Scheme 14).

Carbamate **65** was therefore reduced and subjected to subsequent sulfonation with phenylsulfonyl chloride, resulting in the eliminative ring cleavage to give olefin **66** (Scheme 15) possibly through the intermediacy of a quinone methide. This result suggests that the formation of **65** may have been avoided by allowing the initial reaction to proceed under equilibrium conditions where the expected olefin might have formed from **64**. Ring D was closed using the well-established reductive protocol of Parker,¹⁴ followed by deprotection of the ketal moiety to give ketone **67**.

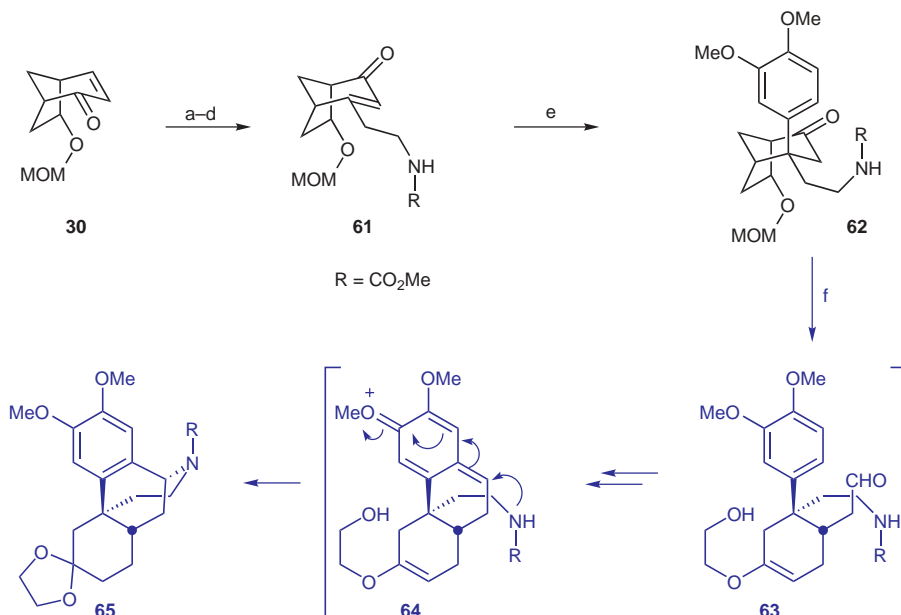
In order to complete the synthesis, the oxidation state of the C-ring had to be adjusted. This was accomplished by reaction of ketone **67** with trimethylenedithiosylate in the presence of base to give dithiane **68**. The synthesis was completed by oxidative cleavage of the thioketal followed by installation of the α -methoxyenone. (–)-*O*-Methylpallidine (**69**) was thus prepared in 12 steps from the chiral building block **30** in an overall yield of 5% after correction for the recovered starting material isolated after the final step (Scheme 15).

3.3 Cheng

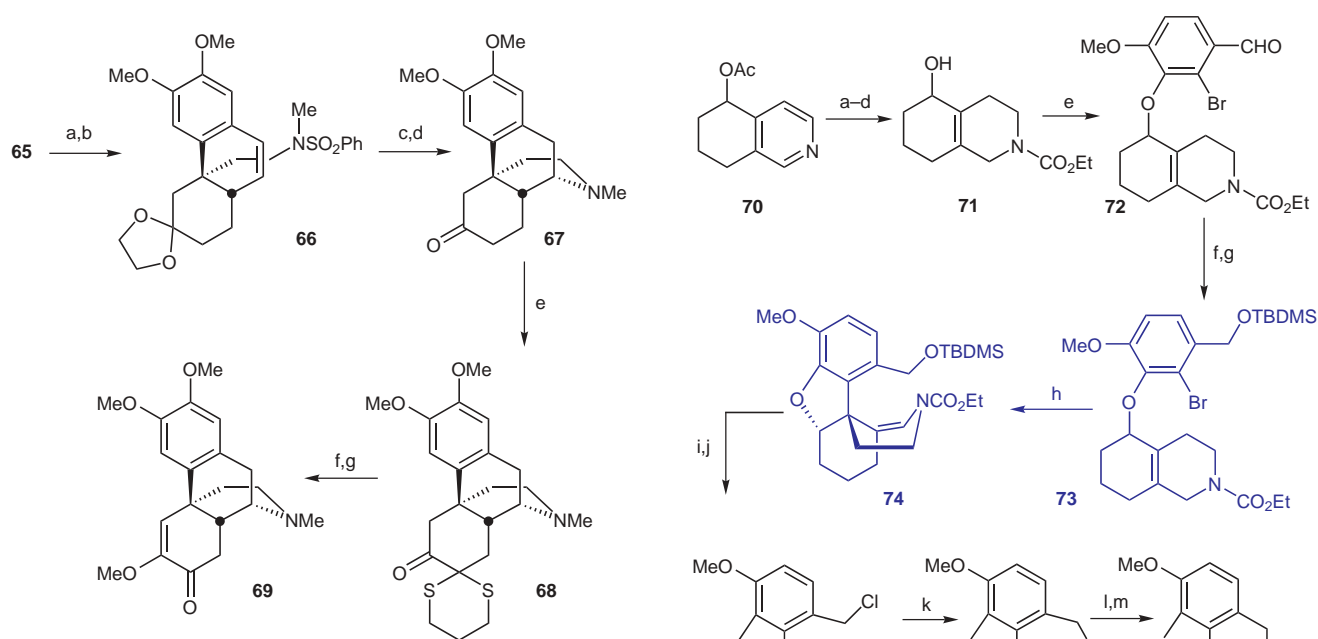
In 2000 Cheng published a total synthesis of *rac*-desoxycodeine-D featuring an intramolecular Heck coupling as the key step.²⁰ Readily available substituted tetrahydroisoquinoline derivative **70** was alkylated with methyl iodide and reduced with sodium borohydride to give the desired octahydroisoquinoline skeleton.

The tertiary amine was converted to its carbamate and the acetate hydrolyzed to alcohol **71**. The aryl ether was introduced under Mitsunobu's conditions to provide **72**, the precursor for the Heck cyclization (Scheme 16). Aldehyde **72** was reduced and the tertiary C-13 center was established by Heck coupling in moderate yield (46%); the yield was significantly increased by the protection of the benzylic alcohol as the *t*-butyl dimethylsilyl ether **73** prior to the Heck coupling. Tetracyclic enamine **74** was transformed to benzyl chloride **75** in two steps.

The attempted closure of ring B by palladium-catalyzed cyclization of the benzyl chloride onto the olefin resulted in *N*-benzylation, and **76** was isolated. This setback was rectified by methylation of the amine to give the



Scheme 14 Reagents and conditions: (a) MeCN, BuLi, THF, -78°C , (92%); (b) LiAlH_4 , THF; (c) ClCO_2Me , Et_3N , CH_2Cl_2 (75%, 2 steps); (d) PCC, CH_2Cl_2 (89%); (e) $3,4\text{-(MeO)}_2\text{C}_6\text{H}_3\text{MgBr}$, $\text{CuBr}\cdot\text{SMe}_2$, TMSCl, HMPA, THF, then TBAF (75%); (f) $(\text{CH}_2\text{OH})_2$, TsOH (cat.), toluene, Δ (77%).



Scheme 15 Reagents and conditions: (a) LiAlH_4 , THF, Δ (95%); (b) PhSO_2Cl , Et_3N , CH_2Cl_2 , 0°C to r.t. (82%); (c) Li, NH_3 , *t*-BuOH, THF, -78°C (76%); (d) TsOH (cat.), aq acetone, Δ (90%); (e) pyrrolidine, $\text{CH}_2(\text{CH}_2\text{STs})_2$ (76%); (f) MCPBA, -30°C then dilute HCl, Δ (69%); (g) TsOH, MeOH, Δ (44%, based on recovery of starting material).

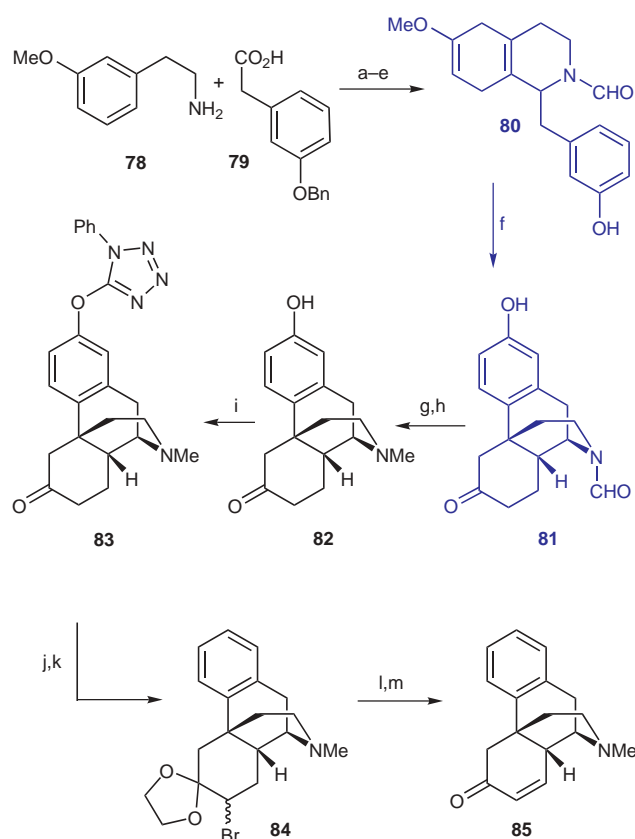
corresponding quarternary salt, which upon exposure to phenyllithium underwent Stevens' rearrangement to afford *rac*-desoxycodine-D (**77**) in good yield (Scheme 16).

Scheme 16 Reagents and conditions: (a) MeI, CH_2Cl_2 , r.t.; (b) NaBH_4 , MeOH (85%); (c) ClCO_2Et , KHCO_3 , DCE, Δ ; (d) NaOH, MeOH (86%); (e) 2-bromoisovanillin, DEAD, *n*-Bu₃P, THF (85%); (f) NaBH_4 , MeOH (88%); (g) TBDMSCl, imidazole, THF; (h) $\text{Pd}(\text{OAc})_2$, PPh_3 , Et_3N , MeCN (62%, 2 steps); (i) TBAF, THF (95%); (j) NCS, PPh_3 , THF (96%); (k) $\text{Pd}(\text{PPh}_3)_4$, Et_3N , MeCN, (59%); (l) MeI, CH_2Cl_2 ; (m) PhLi, Et_2O (83%, 2 steps).

3.4 Passarella

Passarella's 2002 synthesis⁴¹ of 7,8-didehydro-6-morphinanone utilized the Grewe cyclization,⁸ a well-established synthetic sequence, as the key step. Condensation of neat 3-methoxyphenethylamine (**78**) with 3-benzyloxyphenylacetic acid (**79**) gave the corresponding amide, which was cyclized under Bischler–Napieralski conditions.

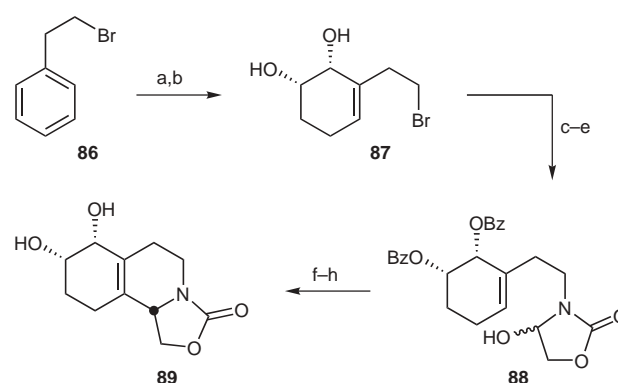
Reduction of the adduct to the corresponding tetrahydroisoquinoline and Birch reduction provided, after the formylation of the nitrogen atom, the key cyclization precursor **80**. Grewe cyclization of **80** gave ketone **81**⁴² in good yield, and tetracycle **82** was attained following the hydrolysis of the formyl group and reductive amination (Scheme 17). Phenol **82** was converted to tetrazole derivative **83**, which was hydrogenated over Pd/C in formic acid to give the corresponding deoxygenated aromatic compound.^{42,43} Bromoketalization⁴⁴ provided **84** and further adjustments led to *rac*-7,8-didehydro-6-morphinanone (**85**) in a total of 13 steps and overall yield of 3.1%.



Scheme 17 Reagents and conditions: (a) 200 °C, 5 h (80%); (b) PCl_5 , CH_2Cl_2 , r.t. (67%); (c) NaBH_4 , MeOH (97%); (d) Li, NH_3 , THF-*t*-BuOH, -78 °C (95%); (e) HCO_2Et , DMF (95%); (f) 80% H_2SO_4 , Et_2O , 25 °C (82%); (g) HCl, MeOH (96%); (h) HCHO, Pd/C (40%); (i) 5-chloro-1-phenyl-1*H*-tetrazole, K_2CO_3 , DMF (65%); (j) H_2 , HCO_2H , Pd/C (74%); (k) $(\text{CH}_2\text{OH})_2$, Br_2 , 70 °C (50%); (l) *t*-BuOK, DMSO, 85 °C; (m) 3 N HCl, MeOH (87%).

3.5 Hudlicky

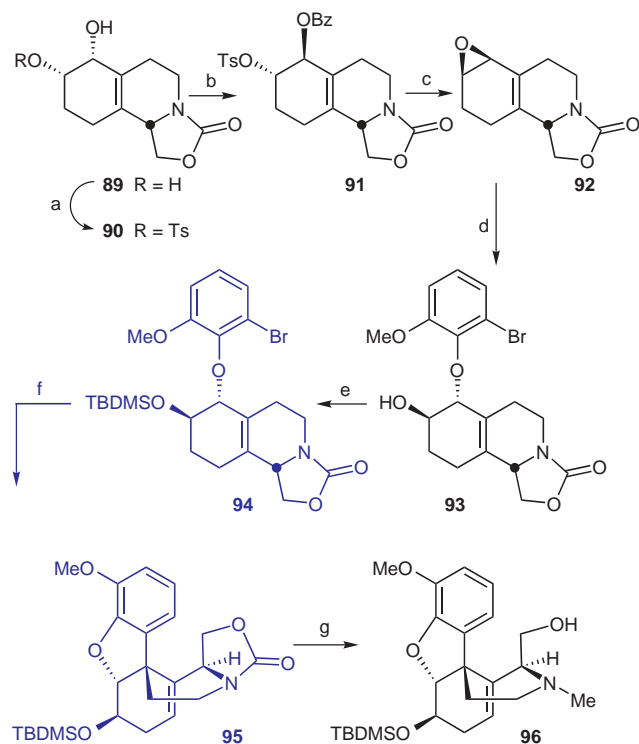
In 1999 we published an enantioselective synthesis of octahydroisoquinoline intermediate **89** (Scheme 18).⁴⁵ The homochiral diol **87** was obtained in two steps from phenethyl bromide **86** by whole-cell fermentation with *E. coli* JM 109 (pDTG 601)⁴⁶ to give corresponding cyclohexadiene diol, which was regioselectively reduced by diimide. Diol **87** was protected as the dibenzoate then treated with oxazolidine-1,4-dione. Partial reduction of the oxazolidine-1,4-dione moiety with sodium borohydride in methanol gave the cyclization precursor **88**. Hemiaminal **88**, upon exposure to aluminium chloride in methylene chloride, furnished a mixture of *cis*- and *trans*-decahydroisoquinoline chlorides, which were subjected to elimination to give the tetrasubstituted olefin. Hydrolysis of the benzoates yielded diol **89**, which was used as a starting material in our new study of introducing the aryl ether at C-5 with the correct stereochemistry.



Scheme 18 Reagents and conditions: (a) *E. coli* JM 109 pDTG601; (b) potassium azodicarboxylate, HOAc, MeOH (80%); (c) BzOH, DCC, CH_2Cl_2 (83%); (d) oxazolidine-1,4-dione, $(\text{Me}_2\text{N})_2\text{CNH}$, THF (77%); (e) NaBH_4 , MeOH (80%); (f) AlCl_3 , CH_2Cl_2 (57%, *cis:trans* = 3.7:1); (g) DBU, DMSO, 100 °C (25%); (h) MeONa, MeOH, THF (85%).

To accomplish the attachment of the aryl fragment, diol **89** was monotosylated at C-6 (morphine numbering) to **90**. The recovered starting material was recycled to improve the overall yield of this step. Next, the benzoate was introduced via the Mitsunobu reaction²⁷ to give the *trans*-tosylate-benzoate **91**, which was converted to epoxide **92** by treatment with methanolic sodium methoxide in tetrahydrofuran (Scheme 19). Opening of epoxide **92** with the potassium salt of bromoguaiacol gave corresponding aryl ether **93**, with the correct stereochemistry at C-5. Protection of the alcohol as *t*-butyl dimethylsilyl ether gave cyclization precursor **94** (Scheme 19).

The crucial C-13 quaternary center was established by an intramolecular Heck coupling of **94**, which led to the pentacyclic morphinan **95**, which has the correct stereochemistry at C-5, C-13 and C-9 and the neopine-type unsaturation required in the C-ring of morphine. Reductive cleavage of carbamate **95** provided the amino alcohol **96**,⁴⁷ which is set up for the C-10–C-11 closure of the B-ring to complete the carbocyclic skeleton of morphine.



Scheme 19 Reagents and conditions: (a) TsCl (1.05 equiv), pyridine, DMAP (45% based on recovered starting material); (b) BzOH, PPh₃, DEAD, THF (79%); (c) MeONa, MeOH, THF (68%); (d) potassium 2-bromo-6-methoxyphenoxide, DME, Δ (80%); (e) TBDMSOTf, Et(*i*-Pr)₂N, CH₂Cl₂ (74%); (f) Pd(PPh₃)₄, Proton-Sponge, toluene, Δ (74%); (g) DIBALH, CH₂Cl₂ (69%).

3.6 Hudlicky

We envisioned a disconnection of morphine to a highly functionalized glycine derivative such as **99** through the application of the chelated Kazmaier–Claisen rearrangement⁴⁸ (Figure 4). The key feature of this particular strategy was the anticipated control of both C-9 and C-14 during the Claisen rearrangement, which was expected to proceed through either a boat or a chair transition state from a chelated *Z*-enolate derived from glycinate **99**. Suzuki coupling of glycine derivative **98** with an aryl boronic acid would lead to the advanced intermediate **97** in which the C-10–C-11 closure through acylation would provide the phenanthrene core of morphine.

Among the options for the establishment of the C-13 center were a second Claisen rearrangement, or an intramolecular functionalization from either the nitrogen atom or the proximal oxygen of the aromatic ring. An added feature of this strategy was the recognition that both key fragments, homochiral diol **100** (for ring C) and bromocatechol **101** (for ring A) could be derived biocatalytically from bromobenzene by the use of two recombinant organisms, each expressing the appropriate enzymes.

Gibson⁴⁹ developed the clones *E. coli* JM109 (pDTG601) and *E. coli* JM109 (pDTG602). The former expresses toluene dioxygenase (TDO) and its use in the whole-cell fermentation of bromobenzene leads to **100**. The latter strain overexpresses TDO as well as dihydrodiol dehydrogenase (DHDH) and provides substituted catechols in reasonable yields.⁵⁰ We were able to generate **104** via **101** by employing this strategy. The synthesis of advanced intermediate **97** (Scheme 20) was published in 1997⁵¹ and provided some surprising observations.

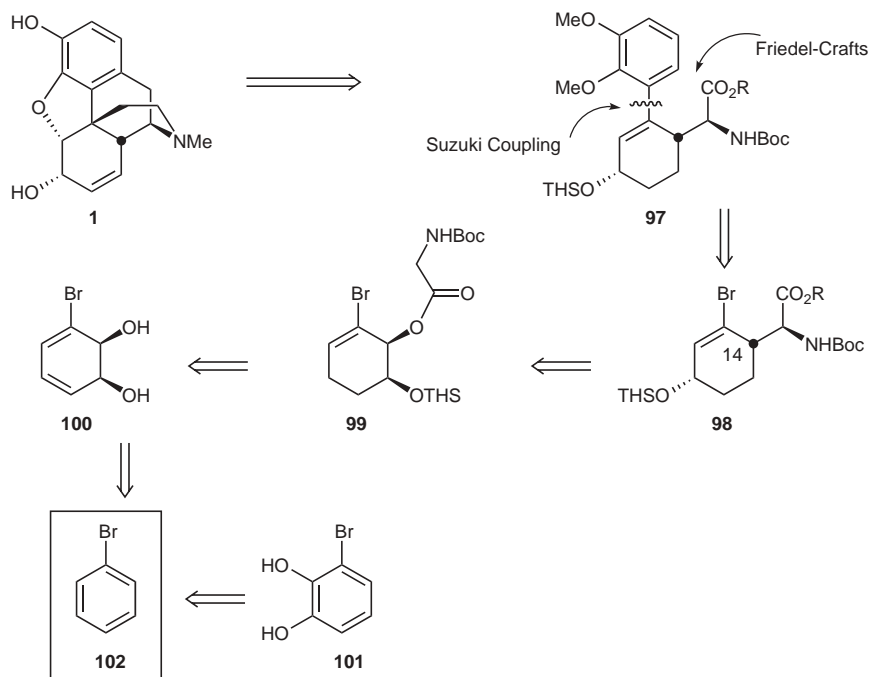
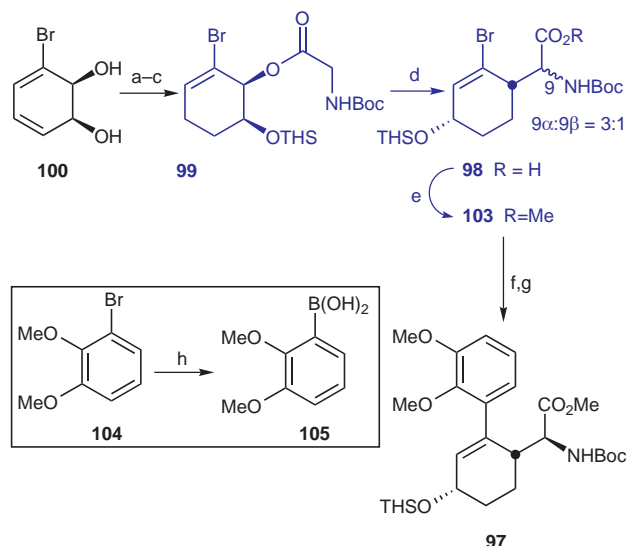


Figure 4 Kazmaier–Claisen strategy for morphine synthesis



Scheme 20 Reagents and conditions: (a) potassium azodicarboxylate, HOAc, MeOH, 0 °C (85–95%); (b) THSCl, imidazole, DMF, –5 °C (80–90%); (c) Boc-Gly, DCC, DMAP, CH₂Cl₂ (75–90%); (d) LDA, THF, ZnCl₂, –78 °C to r.t. (80%); (e) CH₂N₂, Et₂O, r.t. (>95%); (f) DBU, THF, Δ (65%); (g) **105**, Pd(PPh₃)₄ (0.03 mol%), Na₂CO₃, benzene–EtOH, Δ (45–70%); (h) *t*-BuLi, B(OEt)₃, NH₄Cl (sat.).

First, the chelated Claisen rearrangement appeared to proceed through both transition states, chair and boat, which were very similar in energy, and as a result mixtures of α - and β -epimers of **98** were obtained, in line with literature precedent for densely substituted substrates.⁴⁸ Fortunately, esters **103** were equilibrated under basic conditions to the (apparently) more stable isomer **103b**.^{51,52} A plausible explanation for this isomerization is that there is a hydrogen bond between the halogen and the carbamate proton. The C-9 ester (morphine numbering) is axial in **103a** and equatorial in **103b** (Figure 5).

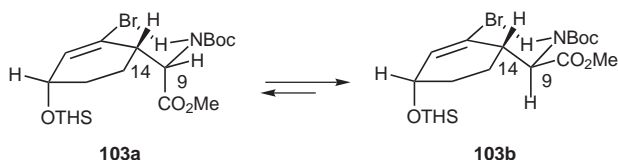
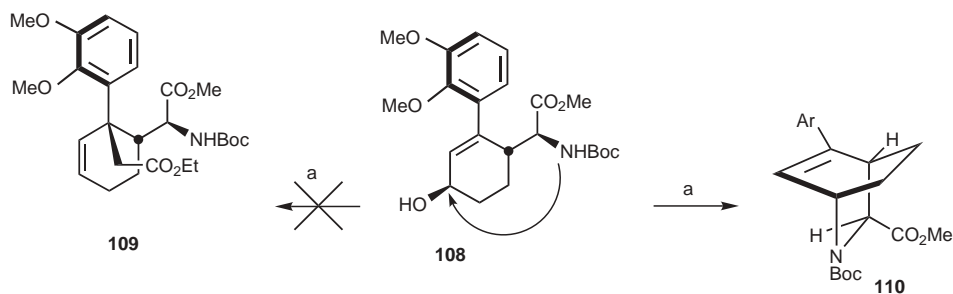
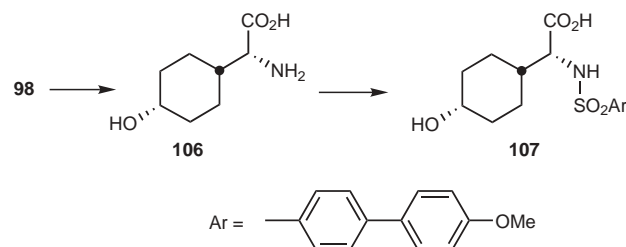


Figure 5 Equilibration of C-9 isomers



Scheme 22 Reagents and conditions: (a) (EtO)₃CCH₃, C₂H₅CO₂H, 160 °C.

This argument is supported by the fact that only the bromo and chloro derivatives were susceptible to such an equilibration, whereas alkyl- or aryl-substituted amino esters such as **108** were found to be inert under basic conditions. During the pursuit of this project we also discovered, serendipitously, that 4-hydroxycyclohexyl glycines with α -stereochemistry of the amino group, such as **106**, were useful in the preparation of various MMP inhibitors (Scheme 21).^{52,53}

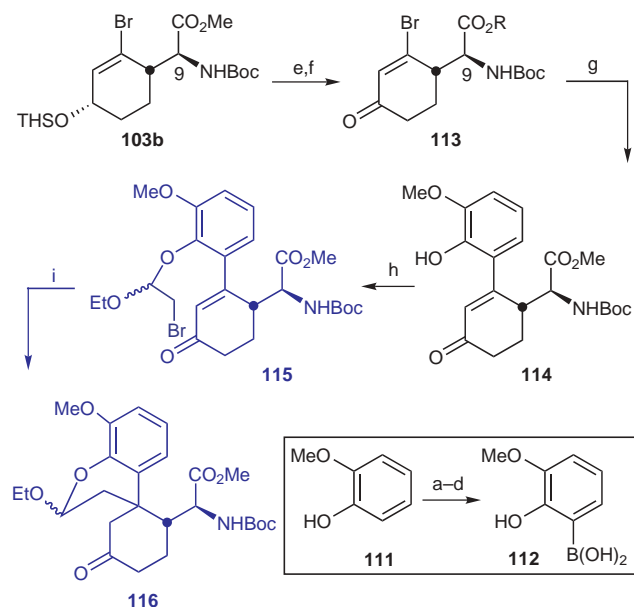


Scheme 21 Design of MMP inhibitors.

Further functionalization of **97** was investigated in several ways. Allylic alcohol **108**, obtained from **97** by a Mitsunobu sequence, did not yield ester **109** as expected according to the well-documented process of this type described by Mulzer.^{16d} Rather the product of solvolysis and subsequent intramolecular amination, the bicyclo[2.2.2]azaoctane **110** was isolated (Scheme 22).⁵²

We reasoned that the second Claisen rearrangement failed because the β -face of the allylic alcohol may have been hindered by the methoxy group in the atropisomer-like structure **108**. For this reason the free phenol **114** was prepared from **111** by modifications of the route described in Scheme 23.

Enone **114** was prepared by Suzuki coupling of boronic acid **112** and β -bromo enone **113** is available from THS-protected alcohol **103b**. This compound was also coupled with boronate **112** and both compounds were tested in subsequent tethered radical cyclizations. Model studies performed with β -(2-hydroxyphenyl)cyclohexenone indicated that both α -bromoacetates and bromoacetals lead to smooth cyclizations and generated the quaternary center in good yields. Applications of this strategy to **114** and the corresponding THS-ether were not as successful. Only



Scheme 23 Reagents and conditions: (a) Br_2 , $t\text{-BuNH}_2$, toluene, -78°C to r.t. (60%); (b) MOMCl , $i\text{-Pr}_2\text{NEt}$, CH_2Cl_2 (80%); (c) $n\text{-BuLi}$, $\text{B}(i\text{-PrO})_3$, THF, -78°C to r.t. (75–95%); (d) 6 M HCl , THF (1:1) (90%); (e) TBAF, THF (87%); (f) PCC, CH_2Cl_2 (95%); (g) **112**, $\text{Pd}(\text{PPh}_3)_4$, Na_2CO_3 (2 M), benzene–EtOH, Δ (45–75%); (h) $\text{BrCH}_2\text{CH}(\text{OEt})\text{Br}$, DMAP, Et_3N , CH_2Cl_2 , 0°C (79%); (i) $n\text{-Bu}_3\text{SnH}$, AIBN, benzene, Δ (20%).

the enone-acetal **115** cyclized, albeit in a low yield of ca. 20%, to provide after tedious purification tricyclic ketone **116** with the C-13 center set (Scheme 23).^{52,54} Equally disappointing were attempts to construct the C-10/C-11 connection by Friedel–Crafts chemistry according to established procedures of this type published by Ginsberg.⁷

The fact that the well-documented Claisen rearrangement failed with **108** coupled with a similar failure of cuprate additions to **114** strongly supports the existence of atropoisomers such as **108**. Successful application of the above two protocols has been reported by Mulzer on compounds possessing the closed phenanthrene core.^{16a,c} Mulzer also noted the possibility of atropoisomers in the biphenyl-like structures of type **108**.^{16a} The protected glycine side chain clearly exhibits a hindering influence on the subsequent functionalizations, which tested well on simpler model compounds. Attempts to establish relative stereochemistry of the C-13 center in **116** and construct the complete phenanthrene core continue.

4 Unnatural Analogues and Mimics

4.1 Rice

The 5-phenylmorphans, discovered by May and Murphy⁵⁵ in 1955, are an interesting class of μ -opioid receptor selective agonists or antagonists, depending on substitution pattern. In recent years Rice's group prepared a series of bridged phenylmorphans with variations in the angle be-

tween the aromatic and the piperidine ring, and also in the substitution pattern of the aromatic ring. Possible oxide-bridged racemic phenylmorphans isomers can be visualized by connecting oxygen sequentially to each of the positions labeled a–f on the structure shown in Figure 6.⁵⁶

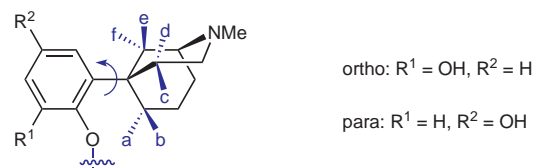
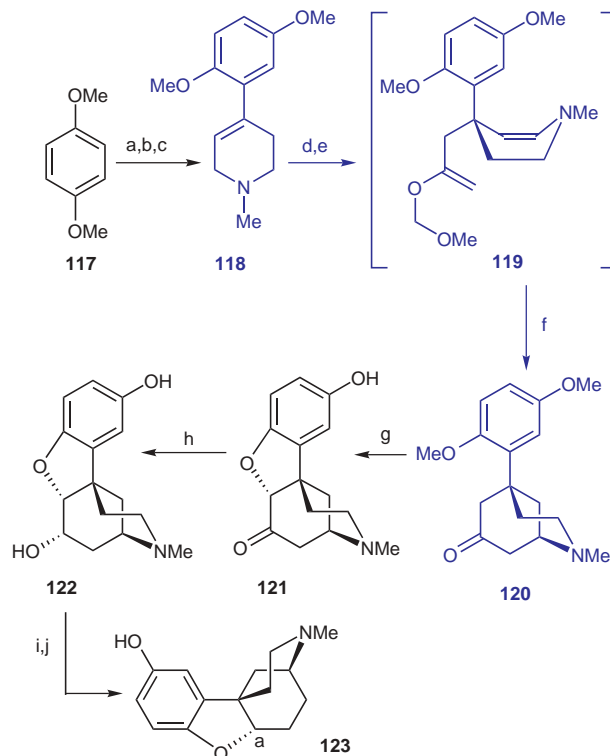


Figure 6



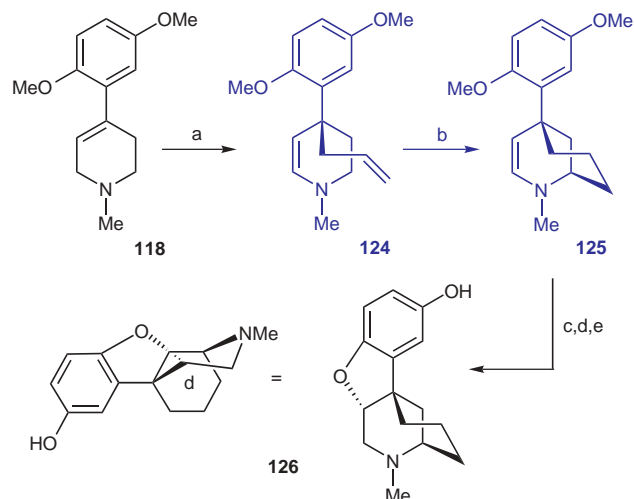
Scheme 24 Reagents and conditions: (a) $n\text{-BuLi}$, Et_2O ; (b) 1-methylpiperidin-4-one; (c) TsOH , toluene or aq H_2SO_4 (54%); (d) $n\text{-BuLi}$, Et_2O ; (e) 3-chloro-2-methoxypropene; (f) HCl , aq MeOH , Δ (34%); (g) Br_2 , CHCl_3 , BF_3 , then NaOH (32%); (h) K-Selectride, THF (76%); (i) MsCl , Et_3N , CHCl_3 (76%); (j) LiEt_3BH , THF, Δ (47%).

In 2002 Rice published his synthesis of ether-bridged *para*-a-phenylmorphane,⁵⁶ utilizing a modified Evans procedure⁵⁷ to obtain compound **118** by reaction of the lithiated 1,4-dimethoxybenzene **117** with 1-methylpiperidin-4-one, followed by elimination under acidic conditions (Scheme 24). The phenylmorphane skeleton was prepared from **118** in three steps. Lithiation of the allylic amine gave the corresponding delocalized benzylic anion, which was alkylated with 3-chloro-2-(*O*-methylmethoxy)propene (Okahara's reagent⁵⁸) to give **119**. Evans used a similar strategy in his synthesis of morphine¹⁰ (see Table 1).

Heating of crude **119** in acidic medium led to an intramolecular Mannich reaction to provide the tricyclic amino ketone **120**. Bromination of the ketone and generation of the free phenol with BBr_3 followed by treatment with sodium hydroxide yielded the *para*-a bridged phenylmorphinan **121**. Further transformations provided the target morphinan **123** as shown in Scheme 24. Similar sequence was employed to prepare *ortho*-a phenylmorphinan analogue of **122** starting from 1,2-dimethoxybenzene.

Intermediate **118** was also utilized by Rice to prepare *para*-d-isomer of the bridged 5-phenylmorphinan **126**.⁵⁹ Compound **118** was lithiated and the resulting benzylic anion trapped by allyl bromide to provide enamine **124**. Exposure of **124** to formic acid in phosphoric acid yielded bicyclic compound **125** (Scheme 25).

Bromination of enamine **125**, followed by reduction of the double bond with sodium cyanoborohydride gave the corresponding bromide. Free phenols were generated by treatment with excess BBr_3 and the ether bridge was closed upon alkaline work up to provide phenylmorphinan **126** (Scheme 25).

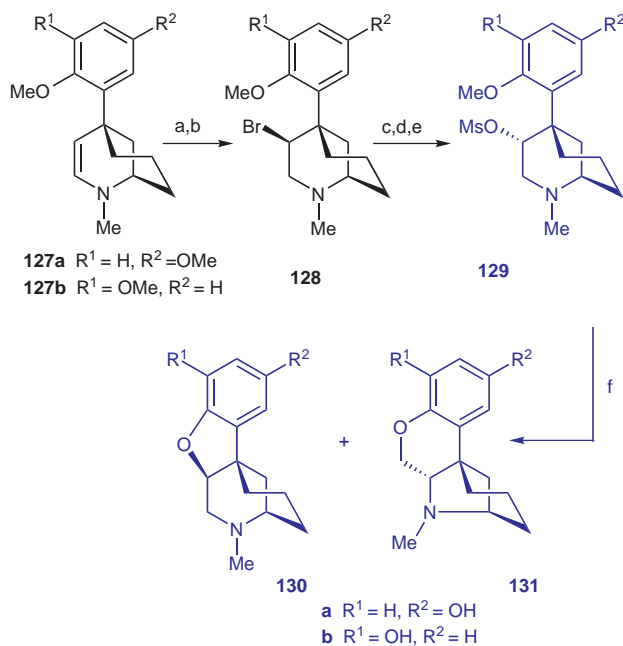


Scheme 25 Reagents and conditions: (a) *n*-BuLi, THF, allyl bromide (80%); (b) HCO_2H , H_3PO_4 , r.t. (52%, oxalate); (c) *N*-bromoacetamide, THF (47%); (d) NaBH_3CN , MeOH, HCl (55%, oxalate); (e) BBr_3 (10 equiv), CHCl_3 , r.t. to reflux, then aq KOH (60%, hydrochloride).

Similar procedure was also employed to provide *para*- and *ortho*-c-phenylmorphans.⁶⁰ Bromides **128a,b** were converted to the corresponding benzoates with the inversion of stereochemistry and alkaline hydrolysis followed by mesylation gave the cyclization precursors **129a,b** (Scheme 26).

Dealkylation of the aromatic oxygen atoms by reaction with the excess of BBr_3 , followed by alkaline work up furnished mixtures of two products, **130** and **131**, their ratios strongly depending on the substitution pattern of the aromatic ring.

Derivative **129a**, which has *para*-methoxy groups, required reflux in chloroform in order to generate the free

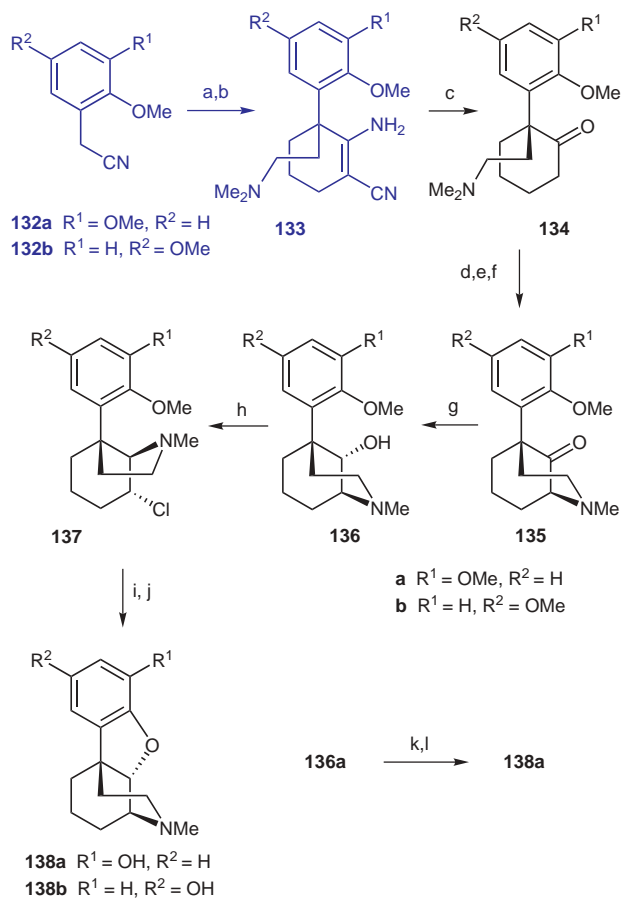


Scheme 26 Reagents and conditions: (a) *N*-bromoacetamide, THF (47%); (b) NaBH_3CN , MeOH, HCl (55%, oxalate); (c) PhCO_2K , DMF (86%); (d) LiOH, MeOH, H_2O (70%); (e) MsCl, Et_3N , CHCl_3 (96%); (f) BBr_3 (10 equiv), CHCl_3 , r.t. to reflux, then aq KOH (**130a**, 11%; **131a**, 41%; **130b**, 70%; **131b**, 6%).

phenols, and the formation of the corresponding *para*-benzoquinone was observed. After quenching with methanol, the quinone was reduced with sodium borohydride and subsequent alkaline work up gave the desired product **130a** in a low yield. Compound **131a** was isolated as a major product, resulting from the formation of an aziridinium intermediate and its opening with phenoxide.

The *ortho*- and *para*-f-phenylmorphans were reported recently by Rice.⁶¹ Synthesis of the key intermediates **135a,b** was published in 1999.⁶² Benzonitriles **132a,b** were alkylated consecutively with *N,N*-dimethylaminoethyl chloride and 5-bromovaleronitrile in the presence of sodium amide and the resulting dinitriles underwent a Thorpe–Ziegler cyclization to give cyano enamines **133**. Acid hydrolysis of **133** provided ketones **134**, which were brominated at the α -positions. Heating the bromoketones gave the corresponding cyclic quaternary salts, which upon pyrolysis in 1-nonanol furnished tertiary amines **135a** and **135b** (Scheme 27).

Reduction of ketones **135** provided regioselectively β -alcohols **136**, which upon treatment with mesyl chloride gave, surprisingly, the rearranged chlorides **137**. Treatment of **137** with BBr_3 followed by alkaline work up led to the bridged products **138**. An alternative strategy for the synthesis of **138a** took advantage of the Mitsunobu coupling, as shown in Scheme 27. To date eight out of the possible twelve oxide-bridged racemic phenylmorphans (Figure 6) have been prepared and work is underway to complete the series.

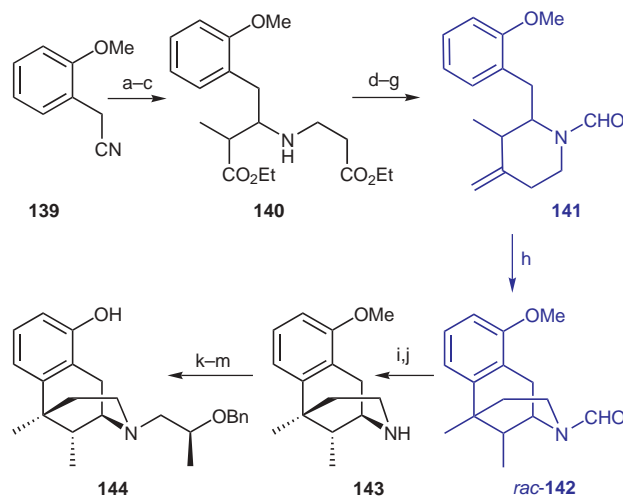


Scheme 27 Reagents and conditions: (a) NaNH₂, ClCH₂CH₂NMe₂ (41–71%, oxalates); (b) NaNH₂ (3 equiv), Br(CH₂)₄CN (58–65%); (c) H₂O, HCl, H₃PO₄ (75–82%, hydrobromides); (d) Br₂, CHCl₃ (80–82%); (e) NH₄OH; then xylenes, Δ; (f) Δ, 1-nonanol (44–51% over 3 steps); (g) H₂/PtO₂ or NaBH₄, MeOH (87–97%, hydrochlorides); (h) MsCl, Et₃N, CHCl₃, r.t. (41–76%); (i) BBr₃, CHCl₃, Δ; (j) concd NH₄OH, CHCl₃ (51–80%); (k) BBr₃, CHCl₃, –78 °C to 0 °C (78%); (l) PPh₃, DEAD, Et₃N, THF (43%).

4.2 Grauert

Grauert's 2002 synthesis of several benzomorphanes⁶³ (a family of unnatural compounds related to morphine and utilized in medicine, e.g., pentazocine and phenazocine)⁶⁴ relied on the synthetic strategy shown in Scheme 28. 2-Methoxybenzyl nitrile **139** was treated with ethyl 2-bromopropionate in the presence of zinc and the intermediate imine was reduced with sodium cyanoborohydride. Addition of ethyl acrylate yielded diester **140**. Piperidine ring was closed via Dieckman condensation, followed by alkaline hydrolysis to give the corresponding 4-piperidone derivative. Wittig reaction and subsequent N-formylation gave cyclization precursor **141**. The cyclization in trifluoromethanesulfonic acid furnished the racemic benzomorphan **142**.

Deprotection of the amine and resolution with (+)-tartaric acid provided the (–)-enantiomer **143**. The methyl ether moiety was converted to the free phenol by hydrobromic acid, and various substituents were introduced on the nitrogen via an acylation–reduction sequence to give de-



Scheme 28 Reagents and conditions: (a) ethyl 2-bromopropionate, Zn, CH₂Cl₂; (b) NaBH₃CN, EtOH (61%); (c) CH₂=CHCO₂Et, EtOH (quant.); (d) *t*-BuOK, toluene; (e) NaOH, EtOH (65%); (f) PPh₃, MeBr, *t*-BuOK, THF (73%); (g) HCO₂*n*-Bu, toluene (quant.); (h) MsOH (96%); (i) HCl; (j) (*R*)-(+)-tartaric acid (24%, 2 steps); (k) HBr, (77%), (l) (*S*)-2-benzyloxypropionyl chloride, Et₃N, CH₂Cl₂; (m) LiAlH₄, THF (55%, 2 steps).

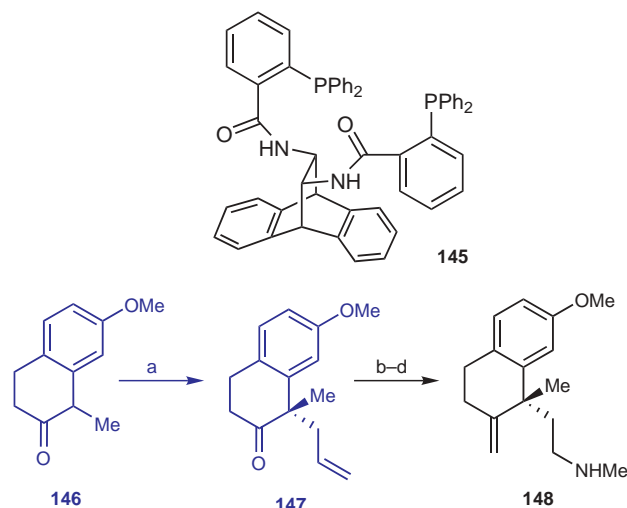
sired tertiary amines, e.g. **144**. Compounds such as **144** were tested as blockers of sodium channels, with possible use in the treatment of thromboembolic stroke.⁶³

4.3 Trost

In 2003 Trost published an enantioselective approach to the synthesis of benzomorphan via migratory hydroamination.⁶⁵ Tetralone **146** was prepared from commercially available 7-methoxy-2-tetralone in high yield according to a procedure reported by Kuehne.⁶⁶ The chirality was introduced by palladium-catalyzed asymmetric allylic alkylation of prochiral ketone **146** with allyl bromide in the presence of *R,R*-ligand **145** and cesium carbonate. Olefin **147**, obtained in good yield and ee as shown in Scheme 29, was converted to the exocyclic alkene.

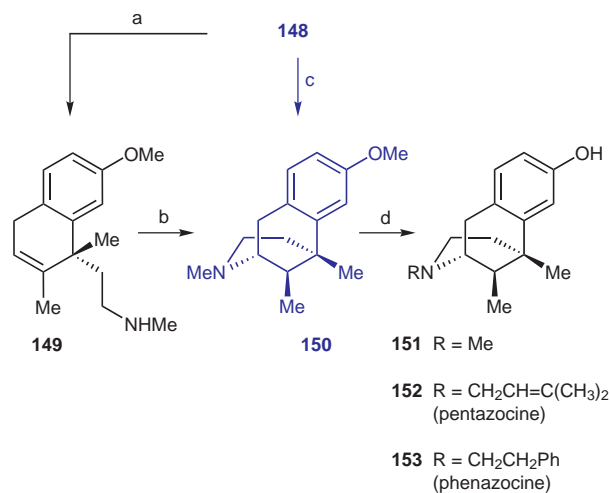
The *N*-methylated amine **148** was obtained in good yield by a stepwise oxidative cleavage of the terminal olefin followed by reductive amination. Initial attempts to induce migratory amination of **148** by treatment with LDA were not successful. To avoid such drawbacks **148** was isomerized to the endocyclic olefin **149** whose exposure to LDA resulted in cycloisomerization to furnish the desired benzomorphan **150** as a single diastereomer.

The necessity of isomerization of **148** under acidic conditions prior to cycloisomerization was resolved by addition of TMEDA to reaction mixture, allowing the direct conversion of **148** to **150** in one step, at the expense of slightly longer reaction times. Demethylation of **150** gave (–)-metazocine (**151**) in good yield (Scheme 30). This enantioselective approach to benzomorphan is short and efficient, and (–)-metazocine was obtained in 8 steps from a commercially available starting material in 46% overall yield.



Scheme 29 Reagents and conditions: (a) allyl acetate, (η^3 -C₃H₅PdCl)₂ (0.5%), **145** (1.0%), DME, Cs₂CO₃ (90%, 91% ee); (b) CH₂=PPh₃, THF (98%); (c) OsO₄ (2%), NMO; (d) NaIO₄, (75%); (d) MeNH₂, MgSO₄, NaBH₄ (88%).

Trost also successfully prepared (–)-pentazocine (**152**) by an analogous route, having changed the N-substituent, to prove the scope and selectivity of the migratory hydroamination (Scheme 30). Moreover, this strategy presents the possibility of access to both enantiomers of substituted benzomorphan, taking advantage of both palladium-catalyzed asymmetric alkylation of simple ketones and the highly diastereoselective migratory hydroamination.



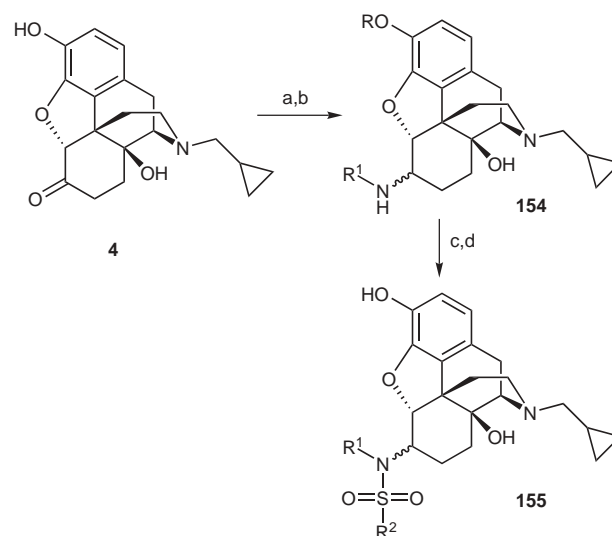
Scheme 30 Reagents and conditions: (a) TsOH (1.5 equiv), toluene, Δ (98%); (b) BuLi (0.2 equiv), *i*-Pr₂NH, THF, r.t., 30 min (quant.); (c) BuLi (0.2 equiv), *i*-Pr₂NH (0.2 equiv), TMEDA (0.4 equiv), THF, r.t., 8 h (98%); (d) BBr₃, CH₂Cl₂ (95%).

4.4 Ohno

In 2002 Ohno and coworkers published a combinatorial type synthesis of novel morphinan opioid ligands based on naltrexone **4**.⁶⁷ The library synthesis was performed on solid-phase and sequential diversification was achieved

via reductive amination followed by sulfonation. Sodium cyanoborohydride in DMF–MeOH–HOAc or DMF–HOAc proved to be the reagents of choice after optimization of the reduction step. Ratio of C-6 β - to α -epimers **154** was determined to be 2.9:1 (in case of methylamine) and up to 7.6:1 (aniline).

Sulfonation of methylamine derivative with tosyl or mesyl chloride was achieved in the presence of diisopropylethyl amine in dichloromethane. Treatment of the resulting resin with 10% TFA in methylene chloride provided the salt of the corresponding sulfonate **155** in quantitative yield (Scheme 31). On the basis of those preliminary results 13 alkyl amines R¹NH₂ and 25 arylsulfonyl chlorides ArSO₂Cl were selected as building blocks and in this fashion the synthesis of the library of 339 morphinans was accomplished.

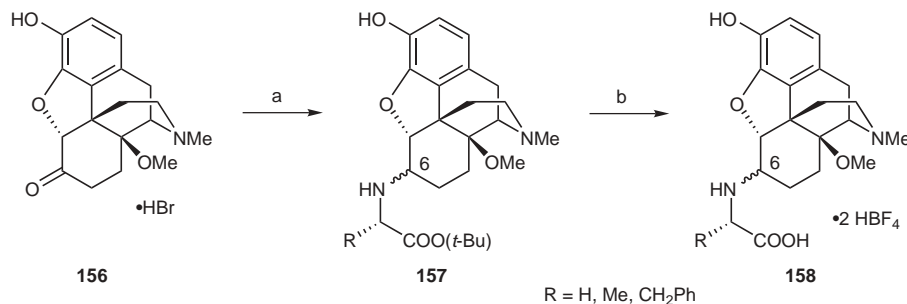


Scheme 31 Reagents and conditions: (a) Wang resin, DEAD, PPh₃, THF; (b) R¹NH₂ (free or HCl salt), NaBH₃CN, DMF–MeOH–HOAc or DMF–HOAc (75–94%); (c) R²SO₂Cl, (*i*-Pr)₂EtN, CH₂Cl₂; (d) 10% TFA, CH₂Cl₂.

4.5 Schmidhammer

A similar modification of morphinans by a reductive amination to furnish zwitterionic derivatives was reported in 2003 by Schmidhammer.⁶⁸ Reductive amination of 14-*O*-methyloxymorphone hydrobromide **156** with glycine *t*-butyl ester hydrochloride, alanine *t*-butyl ester hydrochloride and phenylalanine *t*-butyl ester hydrochloride in the presence of sodium borohydride in ethanol provided mixtures of corresponding C-6 α - and β -epimeric amines of type **157**. The separation of epimers was achieved by MPLC and the treatment of the products with tetrafluoroboric acid in methylene chloride afforded the corresponding bis(tetrafluoroborates) **158** (Scheme 32).

Compounds of type **158** serve as examples of opioids with zwitterionic moieties, which should lead to greatly reduced access to CNS without substantially reducing



Scheme 32 Reagents and conditions: (a) $(t\text{-Bu})\text{O}_2\text{CCH}(\text{R})\text{NH}_2\cdot\text{HCl}$, NaBH_3CN , EtOH (11–28%); (b) HBF_4 , CH_2Cl_2 (78–95%).

opioid activity. Preliminary binding assays in rat brain homogenates showed high affinities towards μ -opioid receptors (K_i 0.77–2.58 nM, morphine: 6.55 nM, **156**: 0.10 nM).⁶⁸

5 Conclusions and Outlook

Morphine and its derivatives occupy a prominent place in modern medicine. Morphine continues to challenge the creativity of synthetic chemists; but, despite many imaginative approaches, a synthesis that would produce this alkaloid at a cost below \$1000 per kg is not on the horizon. The search for a practical synthesis should continue, especially in view of the uncertain political climate in the Middle East and Asia, the regions of primary supply of the natural product.

Even though it appears that an industrial scale synthesis (e.g., fewer than 8 steps, costing less than \$1000 per kg, and starting with commodity chemicals) is beyond the reach of current practice, it is still a worthwhile goal that can be attained in the near future. Perhaps the successful preparation will result from the combined use of knowledge accumulated in the three primary areas connected with morphine alkaloids: biosynthesis, plant culture, and chemical synthesis.

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