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Article

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Chemoenzymatic total synthesis of hydromorphone by an oxidative dearomatization/intramolecular [4+2] cycloaddition sequence: a 2nd generation approach

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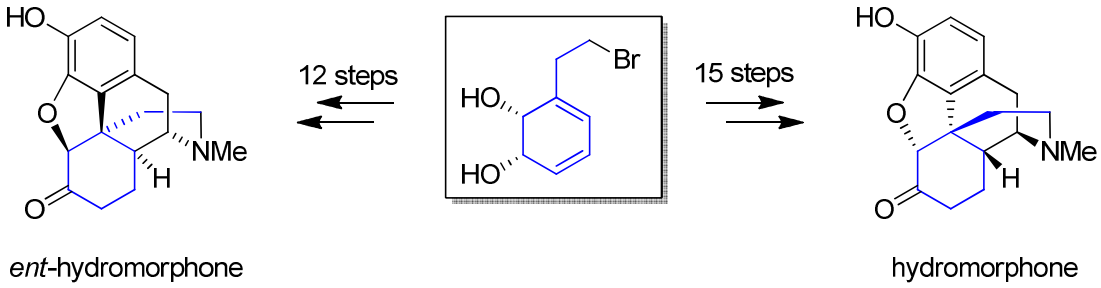
Key words-morphine alkaloids; intramolecular Diels-Alder cycloaddition; oxidative dearomatization; stereochemistry of cycloaddition; hydromorphone synthesis; hypervalent iodine reagents; anodic oxidation

Graphical abstract



ent-hydromorphone hydromorphone

Abstract

A 2nd generation approach to the synthesis of hydromorphone by oxidative dearomatization/Diels-Alder cycloaddition was investigated. Detailed analysis of the stereochemical outcome of the [4+2] cycloaddition was performed first on a truncated model system as well as on the material leading to *ent*-hydromorphone. The

stereochemical assignments were made by NMR and X-ray methods. The 2nd generation synthesis of hydromorphone was completed in both enantiomeric series. Improvements in the dearomatization conditions were attained by using hypervalent iodine reagents instead of $Pb(OAc)_4$. Electrochemical methods of oxidative dearomatization were also investigated. New conditions enabling the rearomatization of ring A from the methoxyketal were developed and a formal synthesis of the natural enantiomer of hydromorphone was completed. Experimental and spectral data are provided for all new compounds.

Introduction

The long-term goals of our research in the synthesis of morphine alkaloids and their medicinally important derivatives are focused on the practicality and efficiency of the synthetic sequence leading to a particular target.[1] The academic effort of many years that we have invested into designing a potentially practical route to these important targets has recently been summarized.[2] In addition, we have also been engaged in process development for the industrially viable synthesis of various opiate-derived agents, as reported in a recent review.[3] We have published improvements for the synthesis of naltrexone (**1**), naloxone (**2**), buprenorphine (**3**), and nalbuphone (**4**), among others.[3] In the industrially relevant projects we focused on the approaches to nororipavine (**5**) and noroxymorphone (**6**) as potentially useful intermediates for the large-scale synthesis of the medicinal agents[3] (Figure 1) (See the Supporting Information Section for the relevant references to process development of the above-named opiate-derived agents).

The challenge of designing a *de novo* synthesis of any morphinan in a manner that would be competitive in cost with compounds derived from naturally occurring alkaloids is

formidable. The most efficient preparation of a morphine alkaloid to date was reported by Rice in 1980;[4] however, no synthesis applicable to commercial production is yet available.

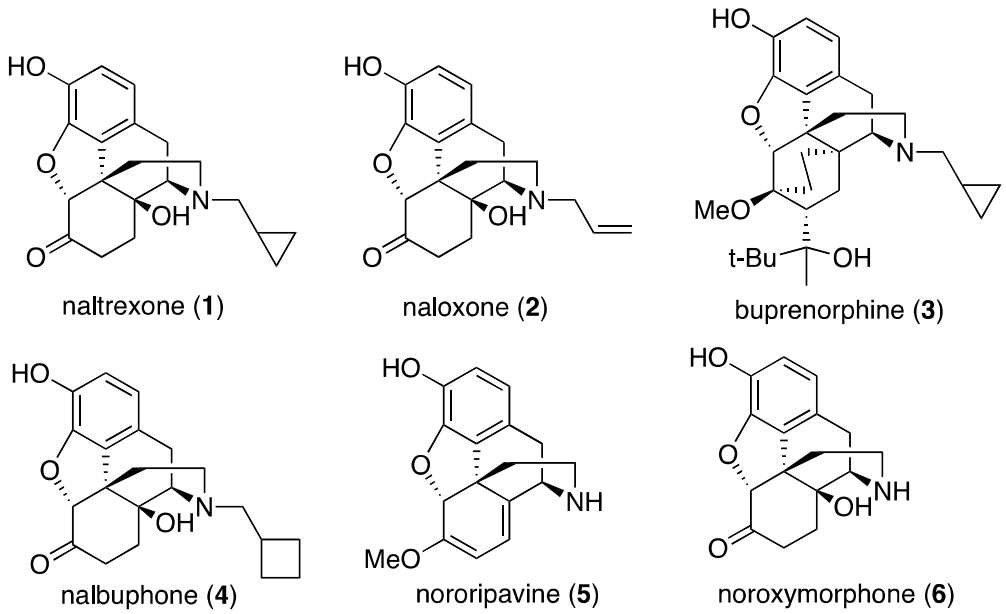
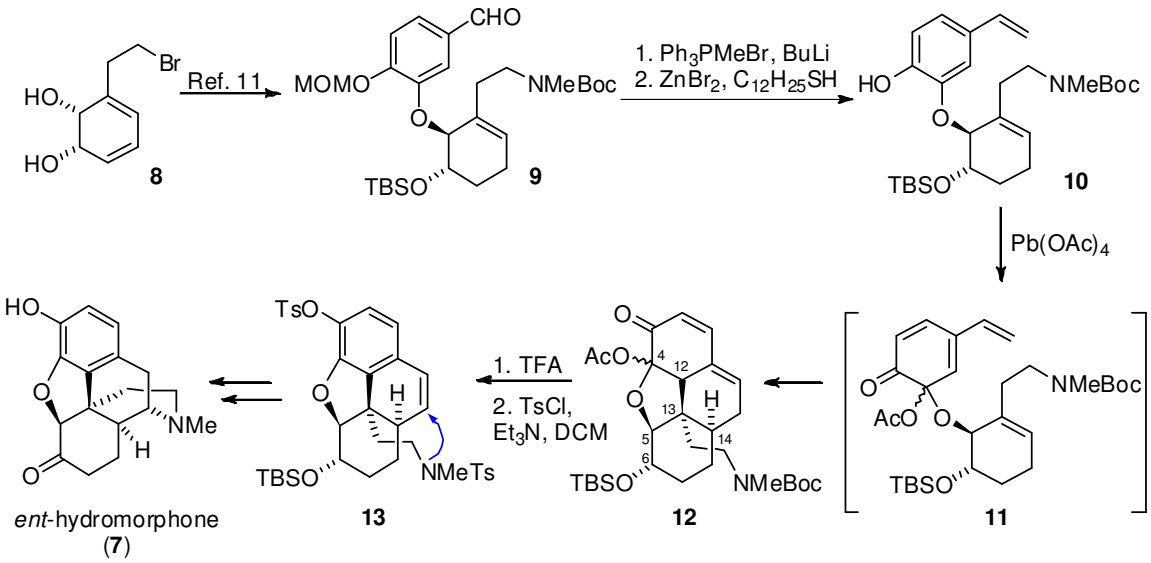


Figure 1. Opiate-derived agents produced by semi-synthesis from natural morphinans.

In 2014 we reported a chemoenzymatic synthesis of *ent*-hydromorphone (**7**)[5] by the intramolecular [4+2] cycloaddition[6] of tetraenone **11**, obtained by oxidative dearomatization of phenol **10** (Scheme 1).



Scheme 1. Synthesis of *ent*-hydromorphone *via* oxidative dearomatization/[4+2] cycloaddition strategy.

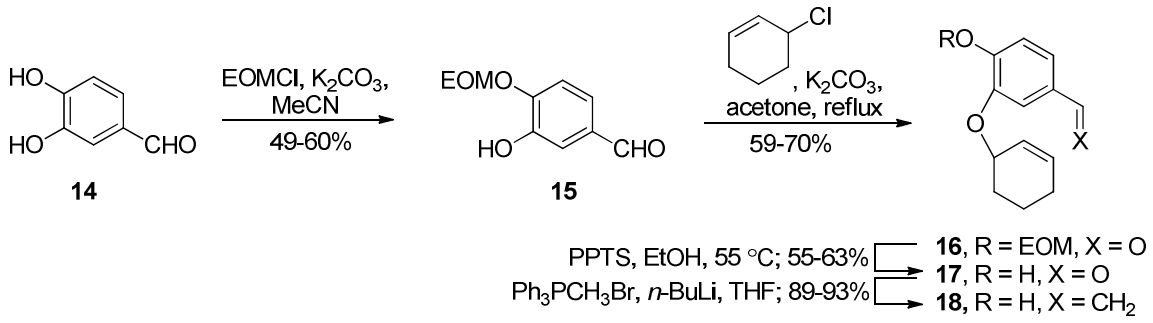
The synthesis began with the enzymatic dihydroxylation of β-bromoethyl benzene by toluene dioxygenase over-expressed in *E.coli* JM109(pDTG601A).[7] Diene diol **8** is produced in the whole cell fermentation on a scale of 10-15 L in multi-gram quantities (10-15 g/L).[8] Diol **8** is converted in five operations to the aryl ether **9** and in two more steps to the key precursor phenol **10**. The cycloadduct **12** rearomatized when treated with trifluoroacetic acid and then immediately reacted with tosyl chloride to provide the protected phenol **13**. The final closure of the ethylamino bridge was accomplished from the *N*-,*O*-ditosylate by employing Parker's method.[9] This relatively short synthesis of hydromorphone in twelve steps from β-bromoethyl benzene constituted, by academic standards, a pleasing accomplishment, yet is still far from having the potential of becoming practical.To achieve practicality several issues need to be addressed. First, the oxidation should be rendered more environmentally benign by using different conditions, such as the use of hypervalent iodine reagents[10] or electrochemical oxidations, instead of

toxic lead tetraacetate. Second, the yields of the cycloaddition reaction needed to be improved. Third, a detailed analysis of the stereochemical outcome of the cycloaddition needed to be performed so that possible double stereoselection could be achieved by using chiral alcohols as the trapping nucleophiles in the oxidative dearomatization. In this paper we report the results of the 2nd generation approach to hydromorphone, improvement in the conditions, and details of the stereochemical course of the key cycloaddition reaction.

Results and discussion

Studies on a model system.

We began the 2nd generation approach by studying other oxidants and the stereochemical course of the cycloaddition reaction on a model substrate **18** (Scheme 2).



Scheme 2. Synthesis of the model compound 18.

The synthesis of **18** started by selective protection of the *para*-hydroxyl group of 3,4-dihydroxybenzaldehyde **14** with the ethoxymethyl (EOM) group, providing phenol **15** in 60%. Alkylation of **15** with 1-chloro-2-cyclohexene (prepared by $LiAlH_4$ reduction of cyclohex-2-enone and chlorination[11] of the allylic alcohol with acetyl chloride) under basic conditions provided the required ether **16** in 59-70% yield. Deprotection of the EOM group using PPTS in ethanol provided phenol **17** in up to 63% yield, with cleavage

of the allylic C–O bond being the main side reaction. Subsequent Wittig olefination yielded the required model substrate **18** on a multigram scale in 89-93% yield.

Electrochemical oxidation of the model substrate.

The electrochemical oxidation and subsequent [4+2] cycloaddition of 2-alkoxyphenols has previously been reported;[12] it was therefore assumed that anodic oxidation of **18** and subsequent Diels-Alder reaction of **19** would yield the desired tetracycle **20** (Scheme 3, a). Cyclic voltammograms of **18** in the presence of increasing concentrations of methanol (in distilled acetonitrile) were recorded (Figure 2). In dry acetonitrile, a broad (and somewhat flattened) wave is observed at *ca*. 0.9 V, and no reverse current is observed, suggesting that the initially formed oxidation product is not long lived under the reaction conditions. As increasing amounts of methanol are added, two sharper oxidation peaks appear, the first of which shifts to more negative potentials as the concentration of methanol is increased. The shifts observed in the presence of methanol suggest that the initially formed oxidation product reacts directly with methanol, presumably *via* nucleophilic attack.

A preparative scale galvanostatic (50 mA) oxidation was performed according to the conditions reported by Quideau. Under these conditions (undivided cell open to the air, methanol, $LiClO_4$ as the supporting electrolyte) only extensive decomposition resulted. We hypothesized that the reaction mixture was absorbing atmospheric moisture due to the open vessel, which would assist in hydrolytic cleavage of **18**; thus the reaction was repeated in a sealed cell under argon and in anhydrous methanol. To our surprise the major product of the reaction was the trimethoxy phenol **21**, with a small quantity of dimethoxy phenol **22** (Scheme 3, b). When the electrolysis was performed using constant

potentials of either 1.2 V or 0.9 V (*vs* Ag/Ag^+ (0.1 M)) the same products were observed. Quideau also performed electrolyses with a 9:1 mixture of acetonitrile and methanol as the solvent; however this did not change the course of the reaction when we attempted this modification.

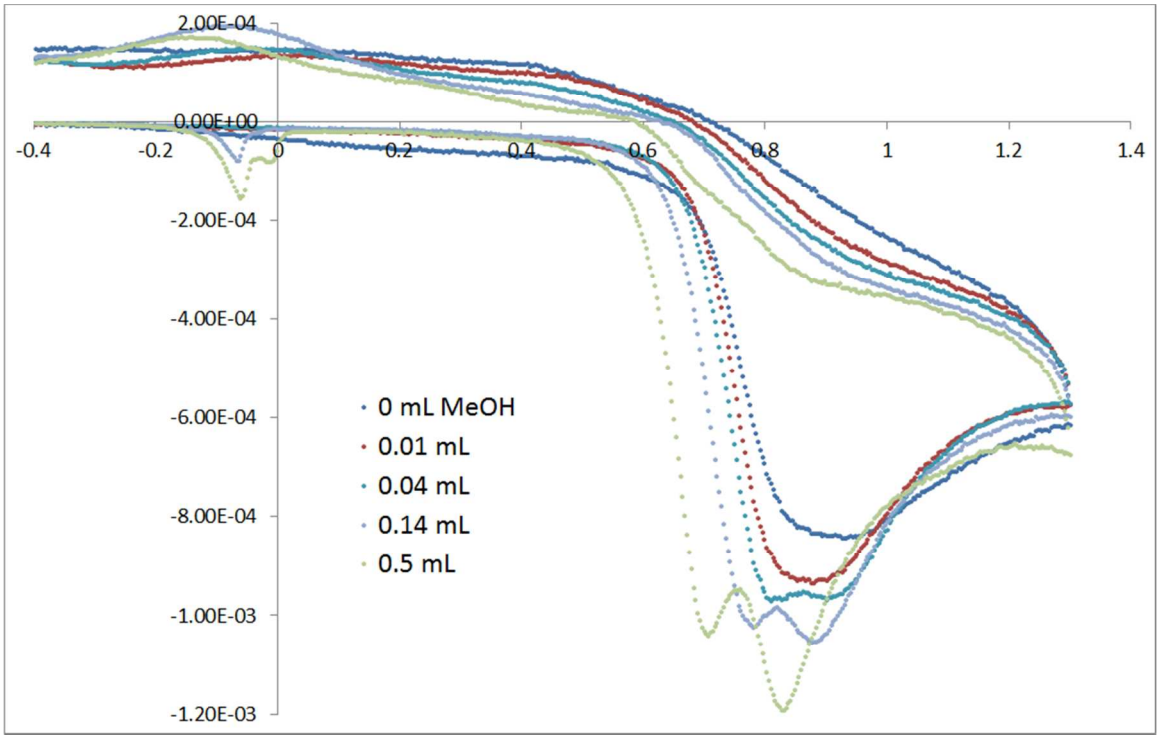
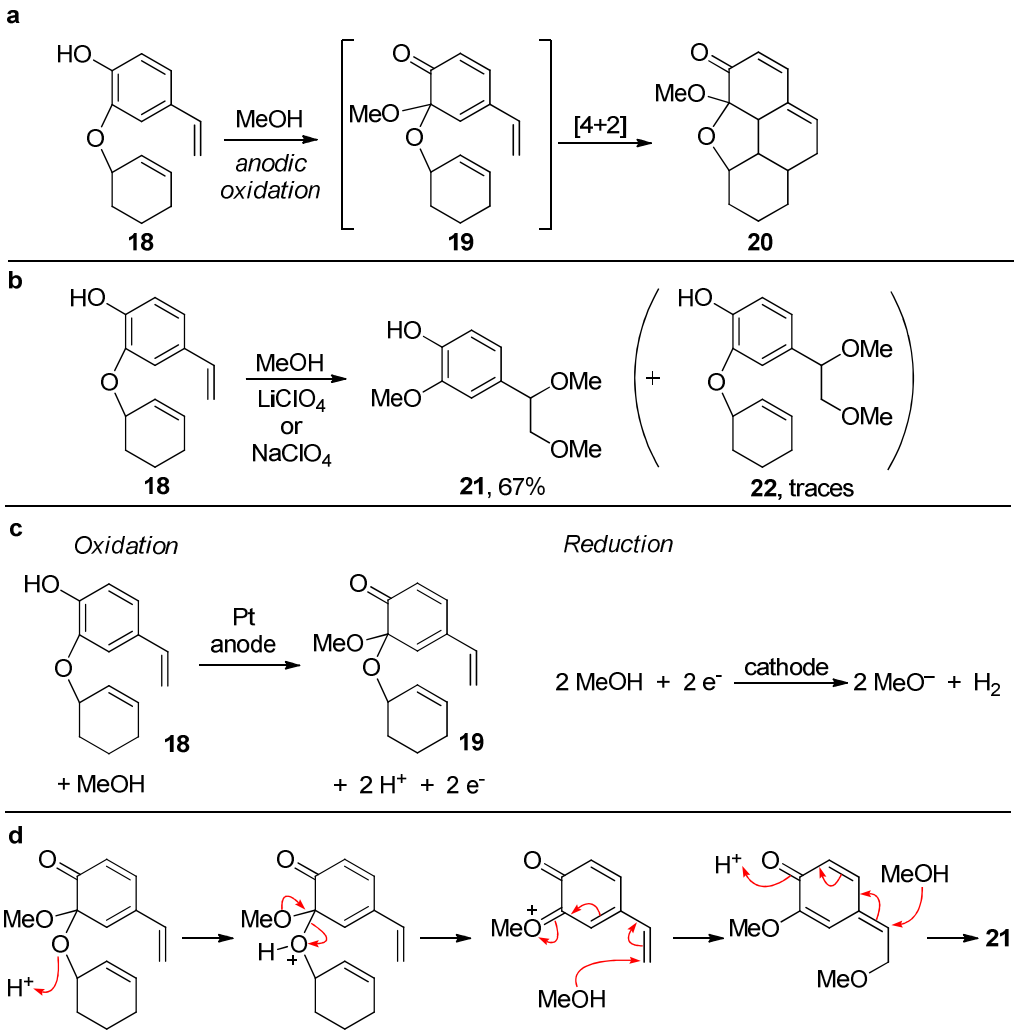


Figure 2. Cyclic voltammograms of 18 in 10 mL anhydrous MeCN with added nucleophile (methanol); scan rate = 500 mV/s, reference electrode = Ag/Ag^+ (0.1 M) in MeCN; supporting electrolyte = $^nBu_4NClO_4$.

This result was rationalized by considering the red-ox half equations (Scheme 3, c). While the intended process is neutral overall, methoxide is generated at the cathode and protons are produced at the anode. It can be expected that the acetal product **19** is the kinetic product, with the methanol adding to the most highly cationic position. However, the strongly acidic conditions local to the cathode resulted in the protonation of the acetal, leading to hydrolysis and subsequent double addition of methanol to the *exo*-vinyl

group, affording the energetically favorable aromatic product (Scheme 3, d). In an attempt to neutralize the acid generated at the cathode, pyridine (with either 2 or 50 equivalents) was added to the electrolysis cell; however, only the methanol addition products were observed.



Scheme 3. Attempts at electrochemical oxidation of the model compound 18. (a) Proposed transformation. (b) Outcome of the electrochemical oxidation. (c) Redox half reactions. (d) Suggested mechanistic explanation of the side product formation.

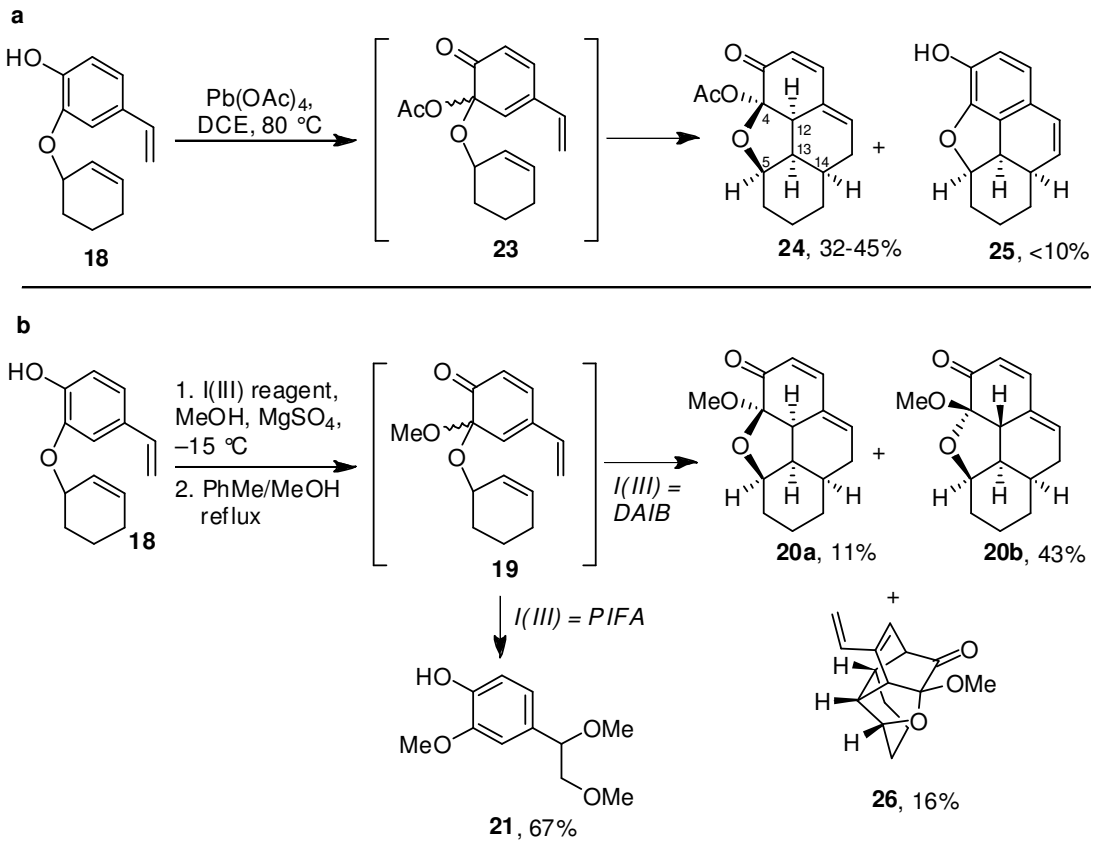
Chemical oxidation of the model substrate using $Pb(OAc)_4$ and alternative oxidants.

When phenol **18** was oxidized using $Pb(OAc)_4$ in refluxing dichloroethane a single isomer **24** could be isolated, albeit in low yields (32-45% over several attempts), along

with up to 10% of the aromatized product **25** (Scheme 4, a). Reaction of **18** with thallium(III) nitrate in methanol did not lead to dearomatization and the use of cerium ammonium nitrate (CAN) led to decomposition. Treatment of **18** with phenyliodinetrifluoroacetate (PIFA) led to the formation of methanol adduct **21** in 67%. We propose that the reaction is catalyzed by trifluoroacetic acid, formed as a by-product during the oxidation step. Treatment of the model substrate **18** with diacetoxyiodobenzene (DAIB) in various solvents (which also served the function of the required nucleophile) led to different outcomes. The use of *iso*-propanol led to a partial conversion, but we observed the formation of a complex mixture containing at least nine products. Hexafluoroisopropanol led to a complete degradation of the starting material. The use of methanol at room temperature resulted in the desired oxidative dearomatization providing dienone **19**.

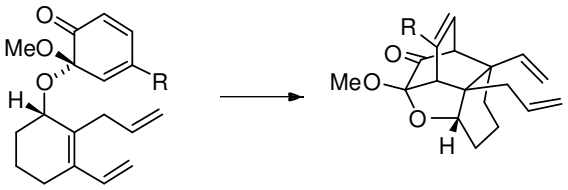
The [4+2] cycloaddition occurred on heating the crude dienone **19** in toluene (120 °C, pressure vial, overnight). [Intermediate **19** was never isolated. However, *in situ* NMR experiment (reaction carried out in the NMR tube) showed the presence (and disappearance) of intermediate **19**, with the progress of the reaction.]

The reaction provided three products; two were identified as diastereomers of the desired cycloadduct (minor **20a** and major **20b**, the stereochemistry of which will be discussed later in this paper) and the third compound, tetracyclic ketone **26**, was identified as the product of an endocyclic [4+2] cycloaddition (Scheme 4, b).



Scheme 4. Oxidation of the model substrate 18 with(a) $Pb(OAc)_4$;and(b) hypervalent iodine [I(III)] reagents.

In 2012 the Rodrigo group performed similar cycloadditions on structurally similar compounds.[13] Despite the fact that Rodrigo's and our system differ with respect to several crucial features (e.g. position of the diene and the dienophile within the structure), the formation of the product derived from the endocyclic cycloaddition pathway was observed in both cases (Figure 3).



27, R = H or
28, R = COOMe

29, R = H or
30, R = COOMe

Figure 3. [4+2] Cycloadditions reported by Rodrigo.

The overall yield of the isolated compounds was 50% (ratio **20a**:**20b**:**26** = 1:3:1, Table 1, Entry 1). In addition, we have observed the formation of additional products arising from the hydrolysis of the ether bond in **18**, perhaps caused by the presence of adventitious water. We did not observe any formation of the side product **21** that was produced during the electrochemical (Scheme 3, b) or PIFA (Scheme 4, b) oxidations. This can be explained by the weaker acidity of acetic acid (formed as a by-product of the oxidation with DAIB) compared to trifluoroacetic acid (formed as a by-product of the oxidation with PIFA), with the stronger acid catalyzing the addition of methanol to the vinyl group (Scheme 3, d).

The results of the optimization studies are summarized in Table 1.When the reaction was carried out at −15°C, followed by the addition of toluene and heating the mixture at reflux, the cycloadducts were isolated in 70% overall yield (Table 1, Entry 2). Lowering the temperature further to −30 and −78 °C did not lead to any improvement (Table 1, Entries 3 and 4, respectively). The effect of the temperature on the cycloaddition was investigated as well. Performing the reaction at 0 °C, followed by heating the mixture at

80 °C led to an improvement compared to heating the mixture at 120 °C (50% at reflux *vs* 61% at 120 °C in a pressure vial, Table 1, Entry 5 *vs* Entry 1). Finally, when the oxidation was carried out at −15 °C in methanol, followed by heating at 80 °C in the toluene/methanol mixture, the products were isolated in overall 68% yield (Table 1, Entry 6). The reaction temperature did affect the yields somewhat but not the distribution of the reaction products, which was in all cases found to be close to 1:3:1 (**20a**:**20b**:**26**).

Table 1. Optimization of reaction conditions for the chemical oxidation of 18.

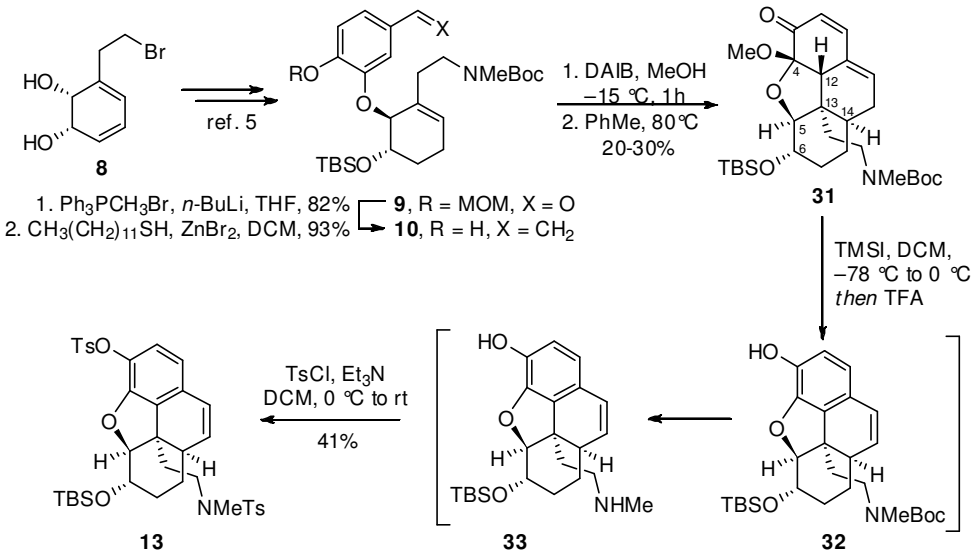
Entry	Oxidant	Solvent	Temperature[a]	Time (h)[a]	Yields (%)[c]	Overall (%)
1	DAIB	MeOH / Tol	0 °C/reflux	1/18	10/30/10	50
2	**DAIB**	**MeOH / Tol**	**−15 °C/reflux**	**1/18**	**11/43/16**	**70**
3	DAIB	MeOH / Tol	−30 °C/reflux	1/18	12/41/13	66
4	DAIB	MeOH / Tol	−78 °C/reflux	1/18	10/41/16	67
5	DAIB	MeOH / Tol	0 °C/80 °C	1/18	7/38/16	61
6	**DAIB**	**MeOH / Tol**	**−15 °C/80 °C**	**1/18**	**7/45/16**	**68**

[a]Oxidation / Cycloaddition
[b]**20a/20b/26**. Yield of **20a** is for an isolated compound. **20b** and **26** were obtained as an inseparable mixture and the ratio was determined by ^{1}H NMR spectroscopic analysis.

A formal synthesis of* ent-*hydromorphone with DAIB as the oxidant in the key step.

The key intermediate **10** has been synthesized previously.[5] The synthesis began with enzymatic dihydroxylation of 2-bromoethylbenzene to the *cis*-diol **8**, which was transformed by the published procedures into aldehyde **9** [$[\alpha]_D^{20}$ =-37.8 (c = 1.5, $CHCl_3$; lit.[5] $[\alpha]_D^{20}$ =-27.6 (c = 1.48, $CHCl_3$) and further to phenol **10** (Scheme 5). In analogy to the model compound **18**, phenol **10** was subjected to the oxidative dearomatization with DAIB (instead of $Pb(OAc)_4$) at −15°C. The reaction mixture was transferred to toluene and heated to either 80 °C or 120 °C (closed pessure vessel) overnight. However, this approach did not result in the desired cyclization and degradation of the material was

observed. It was found that the work-up of the reaction mixture after the oxidation step and performing the cycloaddition in dry, degassed toluene was required to successfully facilitate the cyclization, yielding 20-30% of the desired product **31** (Scheme 5). Contrary to the results observed in the model study, we did not detect any product from the endocyclic cycloaddition nor any minor diastereomers (Scheme 5). Attempts to re-aromatize **31** with TFA failed because of the fast Boc cleavage and subsequent 1,6-conjugated addition of secondary amine to enone. Therefore, conditions, allowing the aromatization prior the Boc cleavage were developed. Treatment of **31** with TMSI at −78°C resulted in re-aromatization of the product, however, according to a ^{1}H NMR analysis of the crude reaction mixture, Boc group remained intact. When compound **31** is first treated with TMSI at −78°C and the reaction mixture is then warmed to 0 °C and treated with TFA, product **33** can be detected by ^{1}H NMR. Treatment of the crude product **33** with TsCl in presence of Et_3N leads to the formation of compound **13**, a known intermediate in the *ent*-hydromorphone synthesis (Scheme 5).

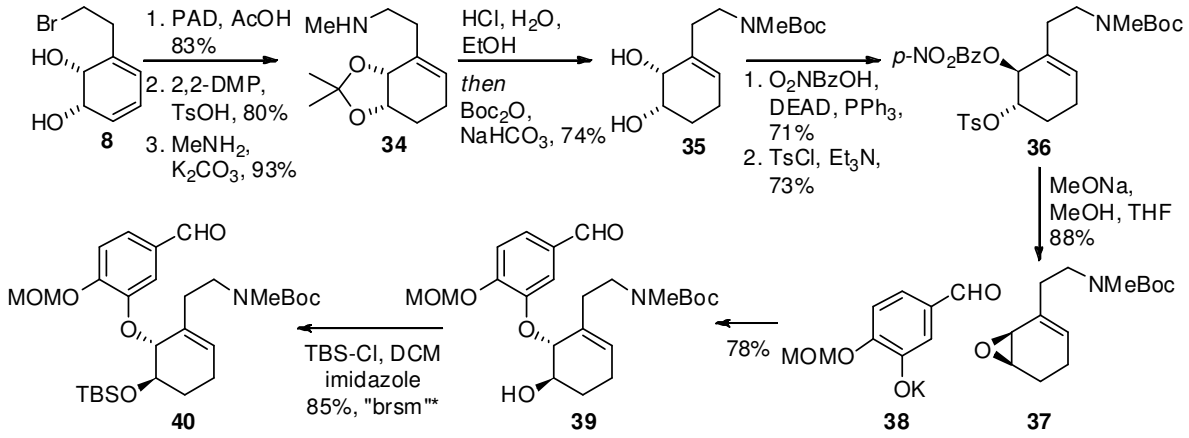


Scheme 5. A formal synthesis of *ent*-hydromorphone (7) with DAIB as an oxidant in the key oxidative dearomatization/[4+2]cycloaddition step, instead of toxic lead tetraacetate.

A formal synthesis of the natural enantiomer.

The unnatural enantiomer of hydromorphone (**7**, (−)-hydromorphone) is a useful synthetic target as any route to it validates a significant percentage of the chemistry required to synthesize the natural, bioactive enantiomer. We have previously reported a strategy for the enantiodivergent synthesis of (+)- and (−)-codeine from 2-phenethylbromide;[14] this strategy can also applied to (+)-hydromorphone. The epoxide **37**, obtained in 7 stepsfrom diol **8**. The diene moiety in **8** was selectively reduced with potassium azodicarboxylate (PAD), the diol functionality was protected as an acetonide, and the halide was displaced by methylamine to yield **34**, as described in literature.[5] Further protection of the amine, hydrolysis of the acetonide, Mitsunobu reaction of **35** at the allylic hydroxyl site and tosylation of the distal hydroxyl provided tosylate **36.** Hydrolysis of the nitrobenzoate led to an *in situ* formation of epoxide **37**, which was opened with potassium phenolate **38** to yield alcohol **39**. Protection of the alcohol using

TBS-Cl and imidazole provided TBS ether **40**, i.e. *ent*-**9**, constituting a formal synthesis of (+)-hydromorphone (Scheme 6).



Scheme 6. Formal synthesis of (+)-hydromorphone (7). [* "brsm" = based on recovered starting material].

Stereochemical outcome of the oxidation/[4+2] cycloaddition sequence in the model system, with $Pb(OAc)_4$ or DAIB as oxidants.

In our 1st generation approach[5] the relative stereochemistry at C-4, C-12, and C-13 was not assigned in adduct **12** (Scheme 1), although the stereochemistry at C-13 was ultimately proved by the completion of the total synthesis. We therefore turned our attention to the assignment of the relative stereochemistry of the cycloadducts. Stereochemical analysis of the cycloadducts was carried out, where possible, by single crystal X-ray diffraction or, in the cases where a suitable single crystal could not be grown, by NMR methods.

The stereochemistry of the major product obtained during the $Pb(OAc)_4$ oxidation/cycladdition sequence of the model substrate **18**, namely **24**, was analyzed by selective 1D NOESY NMR. The observed NOE correlations allowed us to assign the

stereochemistry to be all *syn* around the central furan ring (Figure 4, a; see SI Section for a detailed analysis). A crystal structure was subsequently obtained and confirmed this assignment.

In the case of the oxidation with DAIB, column chromatography of the reaction mixture following the cycloaddition step only allowed for the isolation of the minor diastereomer **20a**; the major diastereomer **20b** and the endocyclic adduct **26** were obtained as an inseparable mixture. The relative configuration of the minor diastereomer **20a** was assigned by ^{1}H and 2D NOESY NMR. Although NOE correlation between H-12 and H-13 could not be directly resolved because of a signal overlap, several other NOE correlations revealed a *syn* configuration among hydrogens H-5, H-12 H-13, H-14 and methoxy group (Figure 4, b).The coupling constant between H-12 an H-13 was found to be 9.8 Hz, similar to the constant found in acetate **24**. Moreover, reduction of the enone and further esterification led to NMR signal separation that allowed observation of NOE correlation between H-12 an H-13. (see SI Section for detailed discussion of assignment).

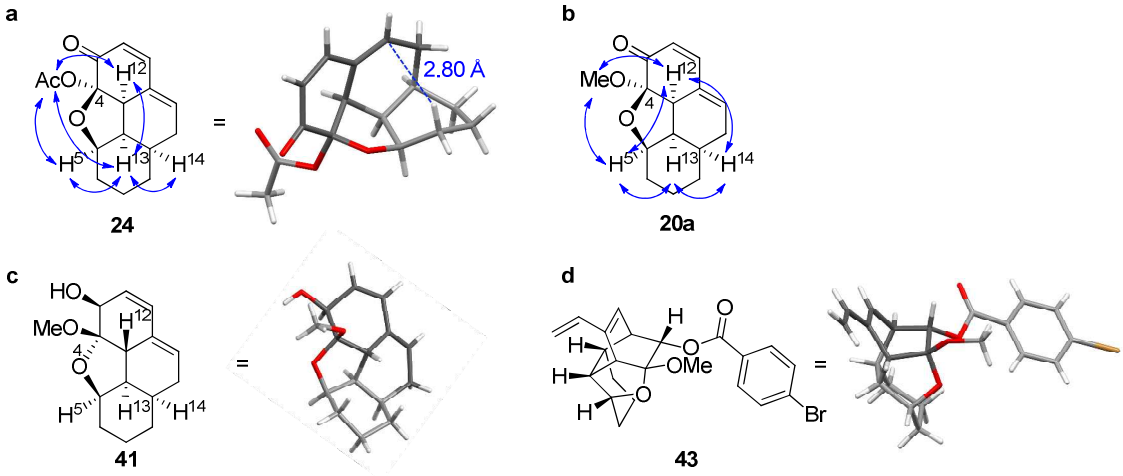
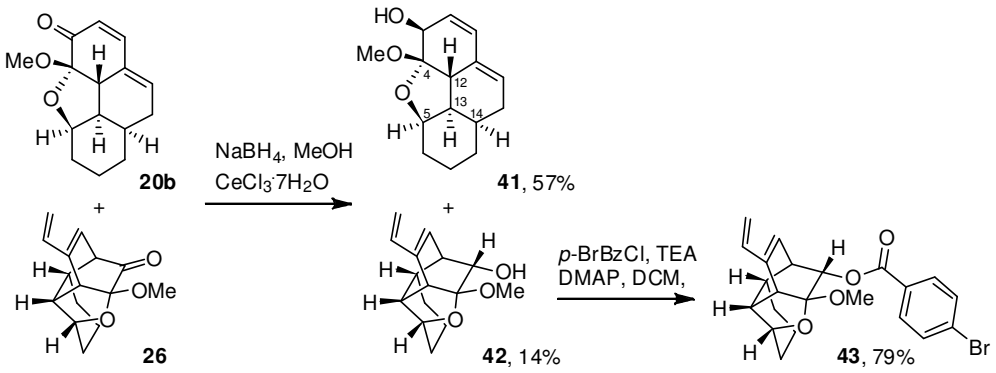


Figure 4. Stereochemistry and structure of cycloadducts: (a) Isolated product of $Pb(OAc)_4$ oxidation/cycloaddition with observed NOE correlations and crystal structure. (b) Minor diastereomer of DAIB oxidation/cycloaddition sequence with observed NOE correlations. (c) Reduced major diastereomer of DAIB

oxidation/cycloaddition sequence and crystal structure. (d) Esterified endocyclic side product from DAIB oxidation/cycloaddition sequence with crystal structure.

In order to separate the major isomer **20b** and endocyclic adduct **26,** the mixture was subjected to Luche reduction conditions to reduce carbonyl functionalities in **20b** and **26**. The reaction provided allylic alcohols **41** and **42**, respectively, which were then separable by column chromatography (Scheme 7).



Scheme 7. Luche reduction of the inseparable mixture of the main isomer 20b and endocyclic product 26 and functionalization of endocyclic alcohol 42.

Single crystal X-ray analysis of **41** revealed a *syn* relationship between hydrogens H-5, H-13 and H-14, with H-12 *anti*. The orientation of the methoxy group was shown to be *syn* to hydrogen H-12 (Figure 4, c).

In order to grow single crystals suitable for X-ray diffraction, alcohol **42** needed to be functionalized with a *p*-bromobenzoyl group to yield ester **43** (Scheme 7). The X-ray structure (Figure 4, d) confirms the assignment of structure **26**, which is consistent with the observation made for similar compounds prepared by Rodrigo (Figure 3).[13]

(For a detailed discussion on stereochemistry analysis see the SI Section).

Stereochemical outcome of the oxidation/[4+2] cycloaddition sequence of intermediate 10.

After the determination of the stereochemistry for the model system, we turned our attention to cycloadducts **12** and **31**. The stereochemistry of both compounds was determined by NMR methods. The assignment was more straightforward in the case of methoxyketal compound **31**, where we could observe a NOE correlation between proton H-6 and H-12, implying that both hydrogens are on the same side of the tetracyclic core and thus *anti* to hydrogens H-5, H-14 and the ethylamino bridge (Figure 5). Such relative stereochemistry would then correspond to the relative stereochemistry of the major product **20b** formed during the model study (Figure 4; a, b, c).

In contrast to the methoxyketal **31** or model compound **24**, the stereochemistry of acetate **12** could not be ascertained by NOESY. However, consideration of the ^{1}H NMR data lead us to propose all-*syn* stereochemistry around the tetrahydrofuran ring in **12**. Comparison of the spectra of acetate **12** and methoxyketal **31** showed substantial disparity (see SI), indicating that the structures were not analogous. In particular, chemical shifts for H-10 and H-6 in **12** and **31** were 0.47 and 0.80 ppm apart. We hypothesized that an all-*syn* geometry would result in the H-6 proton in **12** to be in comparatively close proximity to the π-system of the dienone, resulting in an anisotropic shielding effect of this atom. The same phenomenon was observed on H-6$^{\alpha}$ in the related model compound **24** where the H-6−C10 distance was determined to be 2.80 Å. We thus concluded that the correct stereochemical assignment for the cycloadduct **12** is as depicted in (Figure 5).

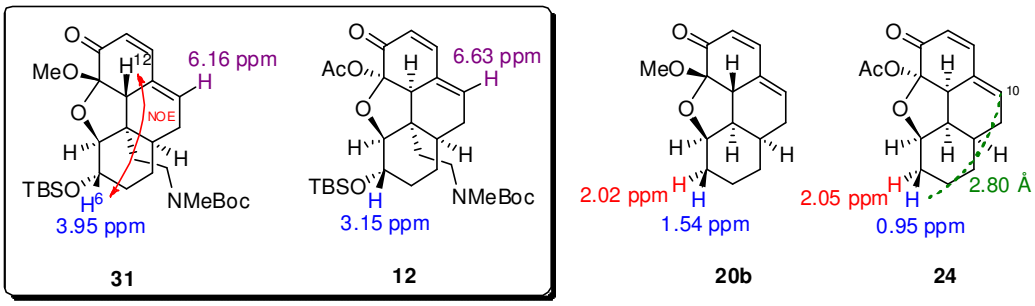


Figure 5. Proposed stereochemical assignments of 31 and acetate 12 and comparison of NMR data (12 and 31 in DMSO-d^6 at 100 °C, 24 and 20b in $CDCl_3$ at room temperature; the C-10–H-6 distance was determined from the crystal structure).

Conclusion

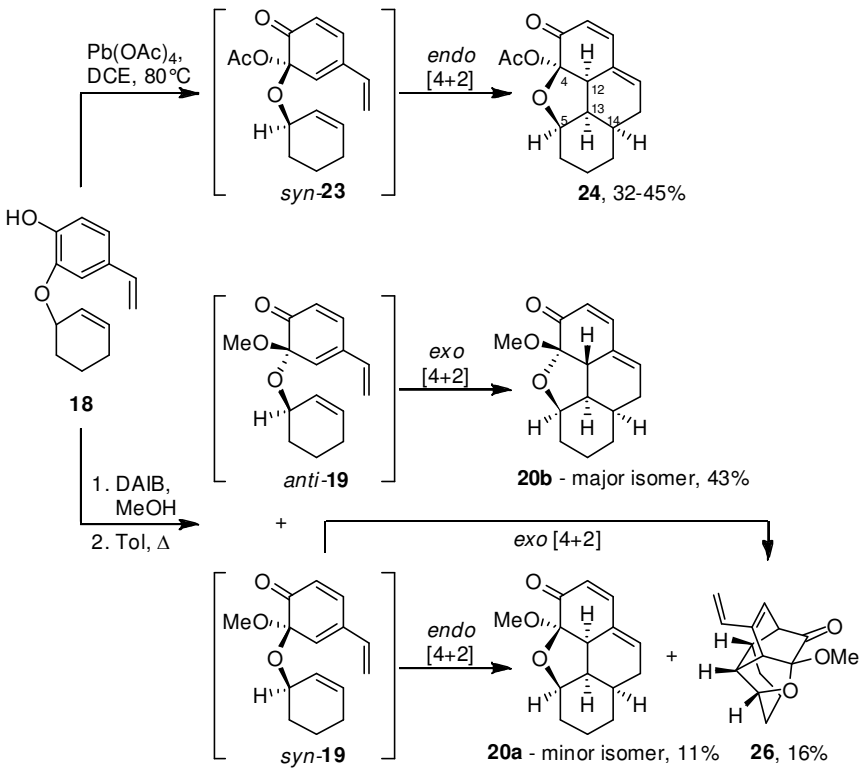
We have developed a 2nd generation formal total synthesis of *ent*-hydromorphone **7**, replacing toxic $Pb(OAc)_4$ by hypevalent iodine compound in the key oxidative dearomatization/[4+2] cycloaddition step. Conditions for this step were investigated on a simplified model system and later applied to the synthesis of methoxyketal **13** a known intermediate in the synthesis of **7**. By establishing conditions for rearomatization of methoxyketal **31**, the formal synthesis of the *ent*-**7** was finalized. In addition, we have reported also a formal total synthesis of the (+)- enantiomer of hydromorphone **7**.

The stereochemical analysis of the cycloadducts from the oxidation/cycloaddition sequence on the model compound **18** was carried out and indicates that using $Pb(OAc)_4$ or DAIB has a crucial impact on the course of the cycloaddition. In the case of $Pb(OAc)_4$, the cycloaddition proceeds from an intermediate *syn*-**23** (*syn* refers to the relationship between the C-4 acetoxy group and hydrogen H-5) that underwent cyclization in an *endo* fashion. In contrast, the outcome of the DAIB oxidation/cyclization sequence is different. The main isolated cycloadduct is formed from an intermediate *anti*-**19** (*anti* refers to the relationship between the C-4 methoxy group and hydrogen H-5) in an *exo* fashion. The minor diastereomer **20a** and endocyclic side product **26** are both formed from *syn*-**19**, in *endo* and *exo* fashion, respectively (Scheme 8).

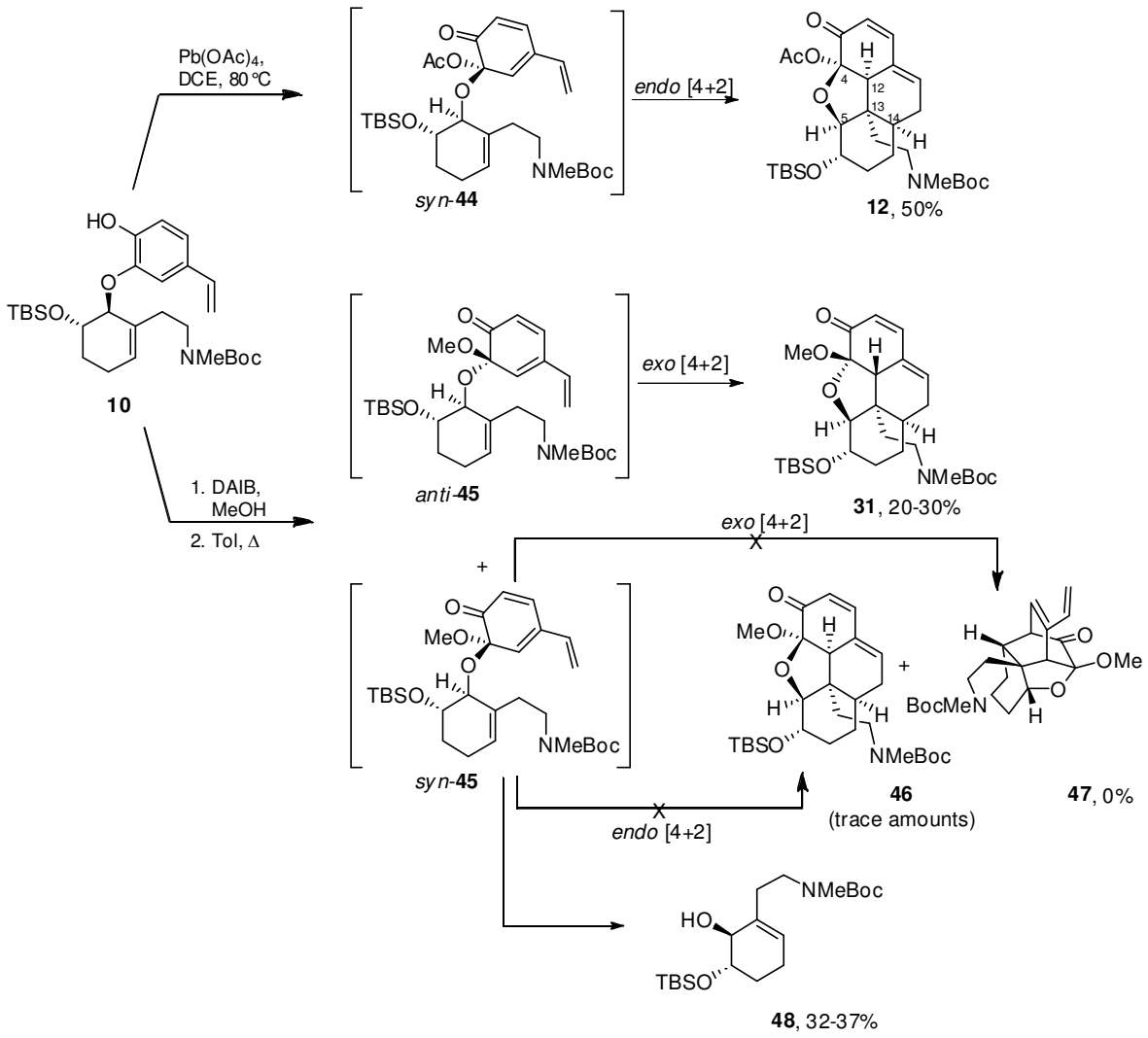
The same trend was observed during the oxidation/cyclization sequence of **10**. Using $Pb(OAc)_4$, the main product obtained was compound **12**, with the all *syn* stereochemistry around the furan ring (Figure 5) formed from an intermediate *syn*-**44** in *endo* fashion. When DAIB was used as an oxidant, the only cycloadduct isolated was compound **31**,

originating from intermediate *anti*-**45**. We did not detect any minor diastereomer **46** nor endocyclic side product **47** (or only trace amounts of **46**, when cyclization was carried out at 120 °C).The reaction mixture after the cyclization was subjected to a careful analysis. Attempts to detect the unreacted diastereomer *anti*-**45**, were unsuccessful. Instead, several aliphatic products resulting from the decomposition of the starting material were detected. Among these the major product was compound **48**, resulting from the elimination of the cyclohexenyl ether (likely from *anti*-**45**) and isolated in 32-37% (Scheme 9).[14] No explanation for this switch in selectivity when $Pb(OAc)_4$ or DAIB is used in the dearomatization is immediately apparent, though we tentatively hypothesize that the residual Pb^{2+} salts formed as by-products of the oxidation may in some way promote the *endo* process over the *exo*. Finally, several attempts were made at potential double diastereoselection in the trapping of intermediates in the oxidative dearomatization with chiral alcohols. These attempts did not lead to positive outcomes. We attempted to perform the DAIB oxidations in the presence of secondary alcohols as isopropanol, hexafluoroisopropanol, and 2-butanol. In each case the use of any larger alcohol led to very complex mixtures and this approach was, for the time being, abandoned.

In conclusion, the quest for practical synthesis of morphinans must continue. We have gained a good understanding of the stereochemical course of the [4+2] cycloaddition approach to hydromorphone and produced 2nd generation, relatively short, formal total syntheses of hydromorphone in both enantiomeric series. However, a true practicality is still a distant task. We will continue to devote further effort to designing shorter approaches to morphinans, as delineated in our recent review.[2]



Scheme 8. Stereochemical course of oxidation of the model compound.



Scheme 9. Oxidation of intermediate 10 using DAIB, leading to the formation of desired product 31 and product of degradation 48.

Experimental Section

Materials and methods.

All solvents were used as obtained unless otherwise stated. All reagents were obtained from commercial sources. NMR analysis was carried out on 300, 400 and 600 spectrometers running Topspin 2.1 and 3.5 software. Probes were equipped with gradients and VT (variable temperature) accessory.

Chemical shifts are given in δ-scale, coupling constants J are given in Hz. Melting points were determined using a capillary melting point apparatus. Mass spectra (HRMS) measurements were recorded using LTQ Orbitrap XL or double focusing sector (DFS) mass spectroscopy and the mass ion was determined by electrospray ionization, fast atom bombardment or electron ionization. Infrared spectra were recorded on a FT-IR spectrophotometer as $CHCl_3$ solutions and are reported in wave numbers (cm^{-1}). Flash grade 60 silica gel was used for column chromatography. TLC was performed on silica gel 60 F_{254}-coated aluminum sheets.

4-(Ethoxymethoxy)-3-hydroxybenzaldehyde (15) The selective protection of the *para*-hydroxyl group in 3,4-dihydroxybenzaldehyde was performed according to a published procedure for protections with the MOM group.[15] 3,4-Dihydroxybenzaldehyde **14** (30g, 0.22 mol) and oven-dried K_2CO_3 (90g, 0.65 mol) were dissolved in freshly distilled acetonitrile (350 mL). The reaction mixture was stirred for 30 min and kept under positive argon pressure. Then, EOMCl (20.15 mL, 0.22 mol) was added at once (an exotherm was observed) and the mixture was stirred overnight. After 15 h, water was added followed by 10% NaOH (350 mL). The mixture was washed with ethyl acetate (350 mL). The aqueous layer was acidified to pH 8-9 and the mixture was extracted three times with ethyl acetate (500 mL). The residual starting material was washed away by saturated solution of sodium carbonate. The organic layer was washed with brine and dried over $MgSO_4$. Evaporation of the solvent provided 21.4-25.9 g (49-60%) of the desired mono-protected phenol as a brown oil.

15: R_f = 0.2 [hexane/EtOAc (2:1)]; IR(neat) ν 3367, 2977, 2896, 1678, 1606, 1585, 1504, 1460, 1442, 1416, 1394, 1345, 1269, 1243, 1201, 1153, 1104, 1081, 964, 881, 787, 755, 655, 621, 583, 541, 499, 459 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.82 (s, 1H), 7.44 (d, J = 1.9 Hz, 1H), 7.39-7.36 (dd, J = 8.3, 1.9 Hz, 1H), 7.22 (d, J = 8.3Hz, 1H), 3.74 (q, J = 7.1 Hz, 2H), 1.22 (t, J = 7.1 Hz, 3H) ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.4, 149.9, 131.5, 124.3, 115.0, 114.5, 94.1, 65.3, 15.1; HRMS (TOF MS ES+) calcd for $[C_{10}H_{12}O_4 + H^+]$: 197.0814. Found 197.0813; Anal.Calcd for $C_{10}H_{12}O_4$: C, 61.22; H, 6.16. Found C, 60.77; H, 6.26.

3-(Cyclohex-2-en-1-yloxy)-4-(ethoxymethoxy)benzaldehyde (16) $LiAlH_4$ (4.9 g) was suspended in dry Et_2O (125 mL) and cooled to 0 °C. After stirring for 15 min a solution of cyclohex-2-enone (25 mL) in Et_2O (50 mL) was added dropwise. Once the addition was complete the reaction mixture was allowed to warm to room temperature and stirred for 3 h. The reaction was then cooled to 0 °C and quenched according to the Fieser procedure: H_2O (4.9 mL), 15% NaOH (4.9 mL) and water (14.7 mL) were added dropwise, after which the reaction mixture was stirred at room temperature for 1 h, and the salts removed by filtration. The solids were washed with Et_2O and the combined ethereal solution was washed with brine, dried (Na_2SO_4), and the solvent removed *in vacuo* to yield the pure allylic alcohol (24.1 g, 95%), which was used as such in the next step.

To a solution of cyclohex-2-enol (5 mL, 50 mmol) in dichloromethane (6 mL) at 0 °C was added acetyl chloride (4 mL, 56 mmol) dropwise. The reaction mixture was stirred for 3 h at 0 °C, after which it was diluted with hexanes (20 mL) and washed with water (2 × 20 mL). The organic layer was dried ($MgSO_4$) and the solvents removed *in vacuo* to yield the corresponding allylic chloride (5.4 g, 93%), which was used without further purification.

To a suspension of K_2CO_3 (0.76 g, 5.5 mmol) in acetone (5 mL) was added phenol **15** (1 g, 5.1 mmol) followed by the addition of the cyclohexenyl chloride (0.64 g, 5.5 mmol). The resulting suspension was refluxed for 18 h. The reaction mixture was allowed to cool to room temperature, filtered, and the solids were washed with acetone (25 mL). The filtrate was evaporated, the crude product was adsorbed on silica gel, and purified by column chromatography (hexane/EtOAc 19:1 to 9:1) to yield the desired product as a yellowish oil (0.99 g, 70%).

16: R_f = 0.1 [hexane/EtOAc (9:1)]; IR(neat) ν 2975, 1686, 1503, 1433, 1392, 1334, 1315, 1255, 1223, 1158, 1125, 1104, 1082, 974, 847, 814, 760, 726, 667, 619, 586 cm^{-1};^{1}H NMR (300 MHz, $CDCl_3$) δ 9.84 (s, 1H), 7.48-7.47 (d, J = 1.9 Hz, 1H), 7.43-7.40 (dd, J = 8.3, 1.9 Hz, 1H), 7.27-7.25 (d, J = 8.3 Hz, 1H), 5.99-5.96 (m, 1H), 5.88-5.85 (m, 1H), 5.33 (s, 2H), 4.85 (br, 1H), 4.78-4.72 (q, J = 7.1 Hz, 2H), 2.16-1.98 (m,2H), 1.97-1.81 (m, 3H), 1.69-1.59 (m, 1H), 1.21 (t, J = 7.1 Hz, 3H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.1, 153.7, 148.7, 132.6, 131.1, 126.3, 126.1, 116.0, 114.3, 93.8, 72.8, 64.8, 28.3, 25.2, 19.2,

15.2; HRMS (TOF MS ES+) calcd for $[C_{16}H_{20}O_4+H]^+$: 277.1434 Found 277.1441; Anal. Calcd for $C_{16}H_{20}O_4$: C, 69.54; H, 7.30.Found C, 69.73; H, 7.36.

3-(Cyclohex-2-en-1-yloxy)-4-hydroxybenzaldehyde (17) The protected phenol **16** (4g, 14.5 mmol) was dissolved in ethanol (150 mL) and PPTS (1.3g, 5.2 mmol) was added. The reaction mixture was heated to 60°C and stirred for 24 h, after which the solvent was evaporated, the remaining mixture was adsorbed on silica gel and subjected to column chromatography (hexanes/EtOAc 9:1 to 4:1), yielding **17** as a white solid (715 mg, 63%).
17: R_f = 0.1 (hexane/EtOAc 9:1); mp 82-83 °C (Hexanes/Ethyl Acetate); IR(neat) ν 3265, 2931, 2863, 1666, 1591, 1508, 1439, 1391, 1255, 1151, 1116, 1034, 925, 903, 860, 805, 728, 655, 629, 583, 529, 463, 454 cm^{-1};^{1}H NMR (300 MHz, $CDCl_3$) δ 9.81 (s, 1H), 7.45 (d, J = 1.8 Hz, 1H), 7.40 (dd, J = 8.0, 1.8 Hz, 1H), 7.04 (d, J = 8.0 Hz, 1H), 6.39 (s, 1H), 6.08 – 5.97 (m, 1H), 5.84 (dd, J = 10.2, 2.9 Hz, 1H), 4.94 (m, J = 3.7, 1.8 Hz, 1H), 2.09 (m, 2H), 2.03 – 1.94 (m, 2H), 1.94 – 1.88 (m, 1H), 1.88 – 1.81 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.0, 152.7, 145.4, 133.4, 127.4, 125.3, 114.7, 111.3, 72.8, 28.3, 25.1, 19.0, HRMS (TOF MS ES+) calcd for $[C_{13}H_{14}O_3+H]^+$: 219.1021 Found 219.1019; Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found C, 71.48; H, 6.47.

2-(Cyclohex-2-en-1-yloxy)-4-vinylphenol (18) A Schlenk tube was charged with methyltriphenylphosphonium bromide (5.8 g, 16.2 mmol) and placed under argon atmosphere. THF (30 mL) was added and the mixture was cooled to −78 °C. *n*-BuLi (5.98 mL, 2.6M) was added slowly and the mixture was allowed to warm to room temperature. The reaction mixture turned orange. After 30 min the mixture was cooled to −78 °C and a solution of the aldehyde **17** (1.01g, 4.6 mmol) in THF (30 mL) was added. The resulting mixture was allowed to slowly warm up to room temperature and then was stirred overnight. Adsorption on silica gel and suction filtration column chromatography[16] with hexane/ethyl acetate mixture (19:1 to 9:1) provided **18** as a yellowish oil (3.3 g, 93%).
18: R_f = 0.2 [hexane/EtOAc (9:1)]; IR(film) ν 3514, 2931, 1628, 1603, 1506, 1432, 1398, 1370, 1265, 1233, 1195, 1151, 1115, 1058, 1022, 9878, 964, 935, 899, 855, 819, 799, 731, 696, 601, 553, 443 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.99-7.00 (d, J = 1.9 Hz,

1H), 6.92-6.91 (d, *J* = 1.9 Hz, 1H), 6.90 (s, 1H), 6.67-6.58 (dd, *J* = 17.6, 10.9 Hz, 1H), 6.03-5.97 (m, 1H), 5.90-5.84 (m, 1H), 5.76 (s, 1H), 5.60-5.54 (dd, *J* = 17.6, 0.8 Hz, 1H), 5.13-5.10 (dd, *J* = 17.6, 0.8 Hz, 1H), 4.85 (br, 1H), 2.22-2.04 (m, 2H), 2.02-1.89 (m, 2H), 1.87-1.77 (m, 1H), 1.74-1.61 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.9, 144.8, 136.8, 132.9, 130.3, 126.0, 120.3, 114.7, 111.5, 111.2, 72.8, 28.6, 25.2, 19.1;HRMS (TOF MS ES+) calcd for $C_{14}H_{16}O_2 + Na^+$: 239.1059 Found 239.1060; Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 77.71; H, 7.62.

4-(1,2-Dimethoxyethyl)-2-methoxyphenol (21) To a cylindrical electrochemical cell equipped with a platinum wire working electrode and copper wire counter-electrode was added phenol **16** (53 mg, 0.24 mmol) and $NaClO_4$ (750 mg, 6.1mmol). The cell was purged with argon and dry, freshly distilled, methanol (50 mL) was added. The solution was stirred for 10 min while being de-gassed with a flow of argon. The solution was then subjected to electrolysis at 50 mA for 15 min (95% conversion). The solvent was removed under reduced pressure, water (10 mL) was added, and the mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4), the solvent removed *in vacuo,* and the residue was purified by column chromatography (gradient column, 9:1 to 1:1 hexanes/EtOAc), and the product was isolated as a colourless oil (35 mg, 67%).

21: R_f = 0.2 [hexane/EtOAc (2:1)]; IR(neat) *v* 3514, 2931, 1628, 1603, 1506, 1432, 1398, 1370, 1265, 1233, 1195, 1151, 1115, 1058, 1022, 9878, 964, 935, 899, 855, 819, 799, 731, 696, 601, 553, 443 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.91 (d, *J* = 8.0 Hz, 1H), 6.87 (d, *J* = 1.7 Hz, 1H), 6.82 (dd, *J* = 8.0, 1.8 Hz, 1H), 5.66 (s, 1H), 4.33 (dd, *J* = 8.2, 3.5 Hz, 1H), 3.92 (s, 3H), 3.59 (dd, *J* = 10.4, 8.2 Hz, 1H), 3.42 (dd, *J* = 10.4, 3.5 Hz, 1H), 3.41 (s, 3H), 3.30 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.9, 145.6, 130.9, 120.4, 114.4, 109.1, 82.9, 77.5, 59.4, 56.9, 56.1. HRMS (TOF MS EI+) calcd for $[C_{11}H_{16}O_4]^+$: 212.1049 Found 212.1043.

General procedure for the oxidation. Phenol **18** (50 mg, 0.23 mmol) and diacetoxyiodobenzene (89.0 mg, 0.28 mmol) were weighed in two separate 20 mL Wheaton vials, sealed with rubber septa, and the atmosphere was exchanged for argon,

following the Schlenk technique. Freshly distilled methanol (5 mL) was added to both vials and the solution of phenol was cooled to −15 °C degrees. The solution of DAIB was then transferred into the solution of the phenol *via* syringe pump over 1 h. After the transfer was finished, the solution was poured into 50 mL round bottom flask or a pressure vial and toluene (10 mL) was added. The resulting mixture was degassed by purging argon through the solution, while the flask was submerged in an ultrasonic bath. After 15 min, the mixture was heated to 80 °C (in a 50 mL round bottom flask) or 120 °C (in a pressure vial) and stirred for 18 h. After the reaction was complete, the mixture was adsorbed onto silica gel and the product was purified by column chromatography (hexane/EtOAc 9:1).

3a-Methoxy-3a^1,4a,4a^1,5,6,7,7a,8-octahydrophenanthro[4,5-*bcd*]furan-3(3a*H*)-one (20a) Isolated as a yellowish oil (6.2 mg, 11%). R_f = 0.2 [hexane/EtOAc (9:1)]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.01 (d, J = 10.2 Hz, 1H), 6.28 (dd, J = 6.8, 3.8 Hz, 1H), 5.91 (d, J = 9.8 Hz, 1H), 4.52 – 4.23 (m, 1H), 3.56 (s, 3H), 3.20 – 2.77 (m, 2H), 2.50 – 2.29 (m, 1H), 2.19 (m, 1H), 1.94 (m, 1H), 1.55 (s, 3H), 1.32 – 1.04 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.3, 145.1, 136.0, 134.5, 124.6, 100.6, 79.5, 51.7, 47.8, 38.3, 31.4, 30.9, 28.2, 27.9, 18.7; HRMS (TOF MS I+) calcd for $[C_{15}H_{18}O_3]^+$: 246.1256 Found 246.1246; Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37. Found: C, 73.41; H, 7.51.

3-Oxo-3,3a,3a1,4a,4a1,5,6,7,7a,8-decahydrophenanthro[4,5-bcd]furan-3a-yl acetate (24) Phenol **18** (216 mg, 1 mmol) was dissolved in 1,2-dichloroethane (10 mL) and the solution was heated to reflux, at which point a solution of lead tetraacetate (531 mg, 1.2 equiv) in 1,2-dichloroethane (10 mL) was added dropwise. The reaction mixture was stirred at reflux for 2 h, after which it was allowed to cool to room temperature, filtered through a pad of Celite, and the solvent was removed *in vacuo*. The dark yellow residue was purified by column chromatography (hexane/EtOAc 19:1 to 4:1) to yield the product (114 mg, 42%) as a yellowish oil.

24: R_f = 0.1 [hexane/EtOAc (9:1)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (d, J = 9.9 Hz, 1H), 6.43 (dt, J = 6.8, 3.6 Hz, 1H), 6.00 (d, J = 9.9 Hz, 1H), 4.62 (td, J = 9.9, 6.8 Hz,

1H), 3.41 (d, *J* = 9.5 Hz, 1H), 3.15 – 3.03 (m, 1H), 2.55 – 2.42 (m, 1H) 2.33 (d, *J* = 1.9 Hz, 1H), 2.12 – 1.93 (m, 1H), 1.83 – 1.55 (m, 2H), 1.45 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ138.3, 132.4, 125.6, 122.7, 108.6, 77.7, 73.1, 50.0, 46.0, 36.7, 32.8, 31.1, 30.5, 29.8, 22.2; HRMS (FAB, NBA matrix) calcd for $[C_{16}H_{18}O_4+Na]^+$: 297.1097 Found 297.1111.

4a,4a1,5,6,7,7a-Hexahydrophenanthro[4,5-*bcd*]furan-3-ol (25) Isolated as a yellowish oil (21.4 mg, 10%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.66 (dd, *J* = 7.9, 1.1 Hz, 1H), 6.56 (d, *J* = 7.9 Hz, 1H), 6.41 (d, *J* = 9.6, 1H), 5.83 (dd, *J* = 9.6, 6.3 Hz, 1H), 5.14 (dt, *J* = 10.0, 8.1 Hz, 1H), 4.82 (s, 1H), 3.60 (t, *J* = 8.1 Hz, 1H), 2.69 – 2.49 (m, 1H), 2.14 – 2.04 (m, 1H), 1.71 – 1.51 (m, 2H), 1.37 – 1.27 (m, 1H), 1.15 – 1.00 (m, 1H), 0.97 – 0.86 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 143.3, 140.6, 130.7, 124.0, 117.6, 115.7, 100.1, 86.9, 77.4, 38.6, 34.3, 29.2, 28.0, 20.3. HRMS (TOF MS EI+) calcd for $[C_{14}H_{14}O_2]^+$: 214.0988 Found 214.0989.

***tert*-Butyl (2-((3*S*,3a*S*,3a1*R*,4a*S*,4a1*R*,9a*R*)-3-((*tert*-butyldimethylsilyl)oxy)-4a-methoxy-5-oxo-1,2,3,3a,3a1,4a,4a1,5,9,9a-decahydrophenanthro[4,5-*bcd*]furan-3a1-yl)ethyl)(methyl)carbamate (31)** Phenol **10** (100 mg, 0.2 mmol) and diacetoxyiodobenzene, (DAIB), (83.1 mg, 0.26 mmol) were weighed into two 20 mL Schlenk flasks, each sealed with a rubber septum, and the atmosphere was exchanged for argon, following the Schlenk technique. Freshly distilled methanol (4.2 mL) was added into both vials and the solution of phenol was cooled to −15 °C degrees. The solution of DAIB was then transferred into the solution of phenol *via* a syringe pump over 1 h. After the transfer was finished, a saturated solution of $NaHCO_3$ was added slowly to the mixture. The mixture was then extracted with dichloromethane (3 ×15 mL), the combined organic layers were dried over $MgSO_4$, and solvents were evaporated under reduced pressure. Crude material was re-dissolved in dry toluene (10 mL).The resulting mixture was degassed by purging argon through the solution, while the flask was submerged in an ultrasonic bath. After 15 min, the mixture was heated to reflux and stirred for 18 h. After the reaction was complete, the mixture was adsorbed on silica gel and the product was

purified by column chromatography (hexane/EtOAc 9:1), yielding the title compound as a yellow oil (21.4 – 32.0 mg 20-30%).

31: R_f= 0.2 [hexane/EtOAc (7:3)]; IR(film) *v* 2959, 2927, 2858, 1681, 1622, 1482, 1462, 1393, 1266 cm^{-1}; $[\alpha]_D^{20}$ = +25.0 (c = 0.45, $CHCl_3$); ^{1}NMR (300 MHz, $CDCl_3$) δ 7.07 (d, *J* = 9.8 Hz, 1H), 6.03 (s, 1H), 5.95 (d, *J* = 9.8 Hz, 1H), 3.92 (dt, *J* = 19.6, 6.2 Hz, 2H), 3.48 (b, 1H), 3.37 (s, 3H), 3.09 (s, 1H), 2.71 (s, 3H), 2.24 (b, 1H), 2.06 (d, *J* = 17.0 Hz, 2H), 1.78 (m, 3), 1.42 (s, 9H), 1.29 – 1.06 (m, 4H), 0.90 (s, 9H), 0.12 (s, 3H), 0.08 (s, 3H).^{13}C NMR (75 MHz, DMSO, 100°C) δ 189.4, 154.1, 142.8, 132.3, 131.7, 124.6, 99.3, 87.4, 72.4, 51.0, 49.7, 49.3, 43.9, 33.1, 32.5, 31.7, 31.5, 28.2, 27. 6, 26.9, 25.2, 17.1, -4.9, -5.1; HRMS (TOF MS FAB+) calcd for $[C_{29}H_{47}NO_6Si+Na]^+$: 556.3065 Found 556.3075.

(4a*S*,4a1*R*,5*S*)-5-((*tert*-Butyldimethylsilyl)oxy)-4a1-(2-(*N*,4-dimethylphenylsulfonamido)ethyl)-4a,4a1,5,6,7,7a-hexahydrophenanthro[4,5-*bcd*]furan-3-yl 4-methylbenzenesulfonate (13) Enone **31** (36 mg, 0.06 mmol) was dissolved in dry dichloromethane (0.65 mL) and the mixture was cooled to -78 °C. TMSI (18.2 μL, 0.13 mmol) was added at once and the mixture was stirred for 30 min. Solution of TFA in dichloromethane (1:4, 4 mL) was added and mixture was stirred at 0°C for 10 min. The reaction mixture was quenched by saturated solution of $NaHCO_3$ and the layers were separated. The organic layer was dried with Na_2SO_4, and the solvent was removed under reduced pressure. The resulting crude mixture was re-dissolved in dichloromethane (0.65 mL), and triethylamine (19.6 μL, 0.14 mmol) and tosyl chloride (27 mg, 0.14 mmol) were added. The mixture was stirred overnight at room temperature. Saturated solution of NH_4Cl was then added and the layers were separated. The organic layer was dried over Na_2SO_4 after which the mixture was adsorbed on silica gel and subjected to column chromatography, yielding the title compound as a yellowish oil (17.4 mg, 41%). Spectral data were in agreement with those in the literature.[5]

***tert*-Butyl (2-((5R,6R)-6-(5-formyl-2-(methoxymethoxy)phenoxy)-5-hydroxycyclohex-1-en-1-yl)ethyl)(methyl)carbamate (39)** Epoxide **37** was prepared according to the procedure described in reference 14. To a solution of **37** in DME (0.5 mL) was added potassium phenoxide **38** followed by the addition of 18-crown-6-ether (3

crystals). The reaction mixture was heated at reflux for 16 h, before it was cooled to room temperature and quenched by the addition of water (2 mL). The layers were separated and the aqueous layer was extracted three times with ethyl acetate. The organic layers were combined, washed three times with a saturated aqueous solution of Na_2CO_3 and brine. The organic layer was dried over anhydrous sodium sulfate, filtered, and the solvent was removed under reduced pressure. The crude residue was purified by flash column chromatography on silica gel (hexane/acetone 4:1) and the title compound was isolated as clear gum (54 mg, 78%).

39: R_f= 0.2 [hexanes:Acetone (4:1)]; IR(film) ν 3430 (br, OH), 2973, 2927, 2850, 1686 (s, C=O) 1582, 1503, 1432, 1392, 1256, 1152, 1124, 1078 cm^{-1}; $[\alpha]_D^{20}$ = -27.6 (c = 1.0, $CHCl_3$); ^{1}NMR (600 MHz, $CDCl_3$, rotameric) δ 9.85, (1H, s, CHO), 7.07 (d, *J* = 9.8 Hz, 1H), 6.03 (s, 1H), 5.95 (d, *J* = 9.8 Hz, 1H), 3.92 (dt, *J* = 19.6, 6.2 Hz, 2H), 3.48 (b, 1H), 3.37 (s, 3H), 3.09 (s, 1H), 2.71 (s, 3H), 2.24 (b, 1H), 2.06 (d, *J* = 17.0 Hz, 2H), 1.78 (m, 3), 1.42 (s, 9H), 1.29 – 1.06 (m, 4H), 0.90 (s, 9H), 0.12 (s, 3H), 0.08 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 190.9, 157.0, 153.6, 148.9, 131.3, 130.4, 130.2, 126.0, 117.6, 115.9, 95.0, 94.8, 80.0, 76.7, 66.2, 56.6, 53.9, 46.5, 34.1, 32.8, 31.7, 29.4, 28.6, 25.4, 24.6, 22.7, 21.0, 14.2 ; HRMS (TOF MS FAB, NBA matrix) calcd for $[C_{23}H_{33}O_7N+Na]^+$: 458.2125 Found: 458.2150.

***tert*-Butyl (2-((5*R*,6*R*)-5-((tert-butyldimethylsilyl)oxy)-6-(5-formyl-2-(methoxymethoxy)phenoxy)cyclohex-1-en-1-yl)ethyl)(methyl)carbamate (40)** To a solution of the alcohol (110 mg, 0.25 mmol) in dichloromethane (2 mL) at -78 °C was added imidazole (34 mg, 0.5 mmol) and TBSCl (41 mg 0.28 mmol). The reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction mixture was quenched with the addition of saturated NH_4Cl and extracted with dichloromethane (3 ×5 mL). The combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4), and the solvent removed in vacuo. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc 9:1) to yield the title compound as a colorless oil (25.2 mg, 20%, 85% based on recoverd starting material).

40: R_f = 0.4 [hexane/EtOAc (70:30)]; $[\alpha]_D^{20}$ = +40.6 (c = 1.5, $CHCl_3$); [For enantiomer **9**: $[\alpha]_D^{20}$ =-37.8 (c = 1.5, $CHCl_3$; lit.[5] $[\alpha]_D^{20}$ =-27.6 (c = 1.48, $CHCl_3$); ^{1}H NMR (600

MHz, $CDCl_3$, rotameric) δ 9.84 (s, 1H), 7.71 (br d, 1H), 7.42 (d, J = 8.0 Hz, 1H), 7.24 (d, J = 8.1 Hz, 1H), 5.67 (s, 1H), 5.27 (s, 2H), 4.73 (s, 1H), 4.06 (br s, 1H), 3.47 (s, 3H), 3.25–3.10 (m, 2H), 2.70 (s, 3H), 2.33–2.09 (m, 4H), 1.90–1.83 (m, 1H), 1.76–1.70 (m, 1H), 1.38 (s, 9H), 0.78 (s, 9H), -0.02 (s, 3H), -0.10 (s, 3H); 13C NMR ($CDCl_3$, 150 MHz, rotameric) δ 191.0, 190.8, 155.7, 152.7, 149.7, 132.7, 132.4, 131.1, 128.6, 128.2, 125.8, 125.2, 115.4, 114.0, 94.8, 80.5,, 80.2, 79.4, 79.2, 70.5, 70.3, 56.5, 48.5, 34.6, 34.4, 32.4, 31.6, 28.55, 28.3, 25.8, 25.8, 25.7, 22.8, 18.0, -4.8, -4.82. Spectral data were in agreement with those in the literature[5].

The Luche reduction of 20b and 26. A mixture of **20a** and **26** (92.5 mg, 0.38 mmol) was dissolved in methanol (1.4 mL) and $CeCl_3.7H_2O$ (212.37 mg, 0.57 mmol) was added. The reaction mixture was purged with argon for 5 min and then the mixture was cooled to 0 °C. $NaBH_4$ (15.5 mg, 0.41 mmol) was added and resulting mixture was stirred at 0 °C for 1 h. After the reaction was complete, ethyl acetate was added and the precipitate was filtered off through a pad of Celite. The mixture was adsorbed on silica gel and the products were purified by column chromatography (hexane/EtOAc 9:1 to 2:1), yielding 57% of **41** and 14% of **42** as white solids.

(3R,3aR,3a^{1}R,4aS,4a1S,7aS)-3a-Methoxy-3,3a,3a1,4a,4a^1,5,6,7,7a,8-decahydrophenanthro[4,5-*bcd*]furan-3-ol (41) Isolated as a white solid (53.7 mg, 57%). R_f = 0.2 [hexane/EtOAc (2:1)]; mp 122-124 °C (hexane/EtOAc); IR(neat) ν 3438, 3027, 2922, 2858, 2821, 1462, 1447, 1420, 1359, 1322, 1301, 1256, 1241, 1208, 1185, 1158, 1133, 1097, 1034, 1016, 982, 971, 944, 928, 900, 879, 849, 817, 778, 764, 739, 699, 603, 582, 562, 527, 497, 478, 459, 416 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.31 – 6.07 (m, 1H), 5.70 (dt, J = 9.8, 1.7 Hz, 1H), 5.55 (dd, J = 6.7, 2.8 Hz, 1H), 4.33 – 4.02 (m, 2H), 3.41 (s, 3H), 2.85 (d, J = 10.0 Hz, 1H), 2.72 – 2.49 (m, 2H), 2.07 (m, 3H), 1.91 (m, 1H), 1.83 – 1.76 (m, 1H), 1.76 – 1.63 (m, 1H), 1.48 (m, 1H), 1.30 – 1.04 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.3, 132.4, 125.5, 122.7, 108.6, 77.7, 73.1, 50.0, 46.0, 36.7, 32.8, 31.1, 30.5, 29.8, 22.2; HRMS (TOF MS EI+) calcd for $[C_{15}H_{20}O_3]^+$: 248.1412 Found 248.1406.

(2a^1,5a,8a)-2-Methoxy-3-vinyl-2a,2a1,5,5a,6,7,8,8a-octahydro-2*H*-2,5-methanonaphtho[1,8-*bc*]furan-9-one (42) Isolated as a white solid (13.2 mg, 14%) R_f= 0.3 [hexane/EtOAc (2:1)]; mp 105-108 °C (hexane/EtOAc); IR(neat) *v* 3432, 2929, 2875, 2836, 1633, 1587, 1455, 1440, 1392, 1367, 1345, 1274, 1258, 1221, 1190, 1131, 1109, 1073, 1052, 1027, 1016, 987, 959, 934, 891, 867, 849, 832, 815, 771, 713, 700, 652, 612, 517, 447, 428 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.46 – 6.27 (m, 2H), 5.24 (d, *J* = 17.7 Hz, 1H), 5.03 (d, *J* = 10.9 Hz, 1H), 4.44 (q, *J* = 3.4 Hz, 1H), 3.56 – 3.43 (m, 2H), 3.37 (s, 3H), 3.26 (d, *J* = 8.3 Hz, 1H), 2.33 (d, *J* = 1.9 Hz, 1H), 2.12 – 1.93 (m, 1H), 1.83 – 1.55 (m, 2H), 1.45 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.3, 132.4, 125.6, 122.7, 108.6, 77.7, 73.1, 50.0, 46.0, 36.7, 32.8, 31.1, 30.5, 29.8, 22.2; HRMS (TOF MS EI+) calcd for $[C_{15}H_{20}O_3]^+$: 248.1412 Found 248.1401.

2-Methoxy-3-vinyl-2a,2a1,5,5a,6,7,8,8a-octahydro-*2H*-2,5-methanonaphtho[1,8-*bc*]furan-9-yl 4-bromobenzoate (43) Alcohol **42** (40 mg, 0.16 mmol), *p*-bromobenzoyl chloride (70.2 mg, 0.32 mmol) and DMAP (19.6 mg, 0.16 mmol) were dissolved in a freshly distilled dichloromethane (2 mL). Dry triethylamine (44 μL, 0.32 mmol) was added *via* syringe and the mixture was stirred for 2 h. The reaction mixture was then passed through a pad of Celite and the solvent was removed in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc 9:1) to yield the title compound as a white solid (54.5 mg, 79%).

43: R_f= 0.4 [hexane/EtOAc (4:1)]; mp 126-129 °C (hexane/EtOAc); ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.98 (d, *J* = 8.7 Hz, 2H), 7.58 (d, *J* = 8.7 Hz, 2H), 6.58 – 6.47 (m, 1H), 6.40 (dd, *J* = 17.4, 10.8 Hz, 1H), 5.29 (d, *J* = 17.4 Hz, 1H), 5.08 (d, *J* = 10.8 Hz, 1H), 4.83 (t, *J* = 1.5 Hz, 1H), 4.50 (d, *J* = 2.6 Hz, 1H), 3.55 (dd, *J* = 4.4, 2.0 Hz, 1H), 3.36 (s, 3H), 2.54 (d, *J* = 7.2 Hz, 1H), 2.18 – 2.02 (m, 3H), 1.91 – 1.77 (m, 1H), 1.76 – 1.58 (m, 2H), 1.39 (s, 1H), 1.25 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.4, 135.5, 135.0, 134.8, 131.7, 131.4, 129.4, 128.1, 112.4, 104.8, 78.9, 75.0, 50.2, 43.3, 42.4, 36.8, 33.80, 3.7, 28.4, 27.6, 15.7; HRMS (TOF MS EI+) calcd for $[C_{22}H_{23}BrO_4]$: 430.0780 Found 430.0774.

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Supporting Information: [A detailed stereochemical analysis by means of 1D or/and 2D NMR techniques for compounds **12**, **20a**, **24**, **31**. ^{1}H-NMR and ^{13}C-NMR spectra for compounds **15**, **16**, **17**, **18**, **20a**, **21**, **24**, **25**, **31**, **39**, **40**, **41**, **42**, **43**. H-H COSY spectra for compounds **20a**, **31**, **41** and HSQC spectra for compounds **41** and **31**. Crystallographic information **24**, **41**, and **43**]

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