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Chemoenzymatic enantiodivergent total syntheses of (+)- and (−)-codeine☆

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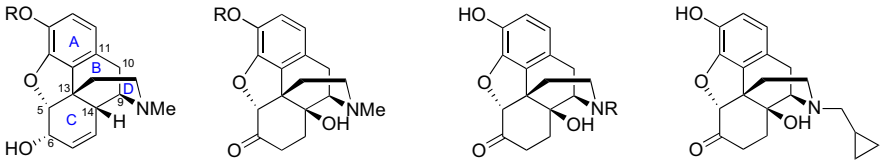
ABSTRACT

Whole-cell fermentation of β-bromoethylbenzene with the recombinant strain *Escherichia coli* JM109 (pDTG601) that over-expresses toluene dioxygenase provided the corresponding *cis*-dihydrodiol **19**, which served as a starting material for both enantiomers of codeine. The key intermediate for the synthesis of (+)-codeine was diol **25b**, whose Mitsunobu coupling with bromoisovanillin was followed by an intramolecular Heck cyclization to aldehyde **35b**. Elaboration of this material to vinyl bromide **27b** allowed for the second Heck cyclization **36b**. Adjustment of the C-6 stereogenic center and hydroamination completed the synthesis of *ent*-codeine in 14 steps from β-bromoethylbenzene. Diol **33b** was converted via Mitsunobu reaction to epoxide **29**, whose allylic opening with bromoisovanillin provided ether **54**, the enantiomer of **35b**. The synthesis of (−)-codeine was completed via two Heck cyclizations and a hydroamination protocol, in an analogous manner as that of *ent*-codeine. In addition, both enantiomers of epoxide **29**, convenient precursors for the coupling with bromoisovanillin, were prepared from diol **33b** by Mitsunobu reactions and cyclizations of the *trans*-diol moiety. Spectral and experimental data are provided for all compounds.

1. Introduction

Morphine (**1**), codeine (**2**), and other naturally occurring morphinans serve as starting materials for the semisynthesis of all 4,5-epoxymorphinans used in the practice of medicine such as the analgesic oxycodone (**3**) and the antagonists naloxone (**5**) and naltrexone (**6**), shown in Figure 1.[2] The legal consumption of morphine and morphine-derived agents approaches 400 metric tons annually while only estimates are available for the illicit use of opiates such as heroin, hydrocodone, and oxycodone.[3] Morphine, codeine, thebaine, and other morphinans originate from natural sources, namely the latex of opium poppies, grown primarily in Afghanistan, Turkey, India, and Tasmania. A number of records can be ascribed to morphine. It is probably the world's oldest known drug, with records of consumption of opium dating to 1500 BC.[4] It was the first natural product isolated in a pure state, by Sertürner in 1806.[5] His efforts showed that morphine had the same effect on animals (dogs) as opium and in a follow-up paper in 1817 he published the procedure for its isolation from opium. Sertürner also reported the preparation of morphine salts (sulfate, hydrochloride, and nitrate) and investigated their chemical properties. The first human subjects studies are also credited to him; he and three boys almost overdosed



1 morphine, R = H
2 codeine, R = Me
3 oxycodone, R = Me
4 noroxymorphone, R = H
5 naloxone, R = allyl
6 naltrexone

Figure 1. Morphine, codeine, and their C-14 hydroxylated derivatives.

during the experiments with pure morphine. It may hold the record as the compound that evaded complete structure elucidation for the longest time—from 1806 to 1925 when Robinson and Gulland proposed the correct structure, lacking only the relative and

☆ See Ref. 1.

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absolute stereochemistry.[6] The stereochemical assignment was essentially complete by 1952 and confirmed also by the first total synthesis by Gates.[7] The absolute stereochemistry was established by degradation studies[8] as well as by X-ray analysis[9] in 1955. Finally, it is probably one of the most frequently synthesized alkaloids on record: as of this writing there have been more than 25 total syntheses of morphine (or codeine) reported in the literature[10]; the most recent syntheses are those of Fukuyama (Mannich-type closure),[11] Guillou (Heck reaction/hydroamination),[12] and Stork (Diels–Alder of benzofuran).[13]

cyclization approach, for example, the one reported by Parker that provided codeine with full stereocontrol at C-14 and C-9.[16]

Our 1998 adaptation of Parker's design to our own radical cyclization approach to morphine resulted in the production of morphine skeleton, but epimeric at C-14.[17] In subsequent generations, we modified the radical cyclization strategy to one that would employ the Heck reaction with the expectation that the process was more likely to be stereoselective. Overman,[18] Cheng,[19] Hsin,[20] and Trost[21] have already used the Heck reaction successfully for assembling the morphine skeleton; these approaches are summarized in Figure 2.

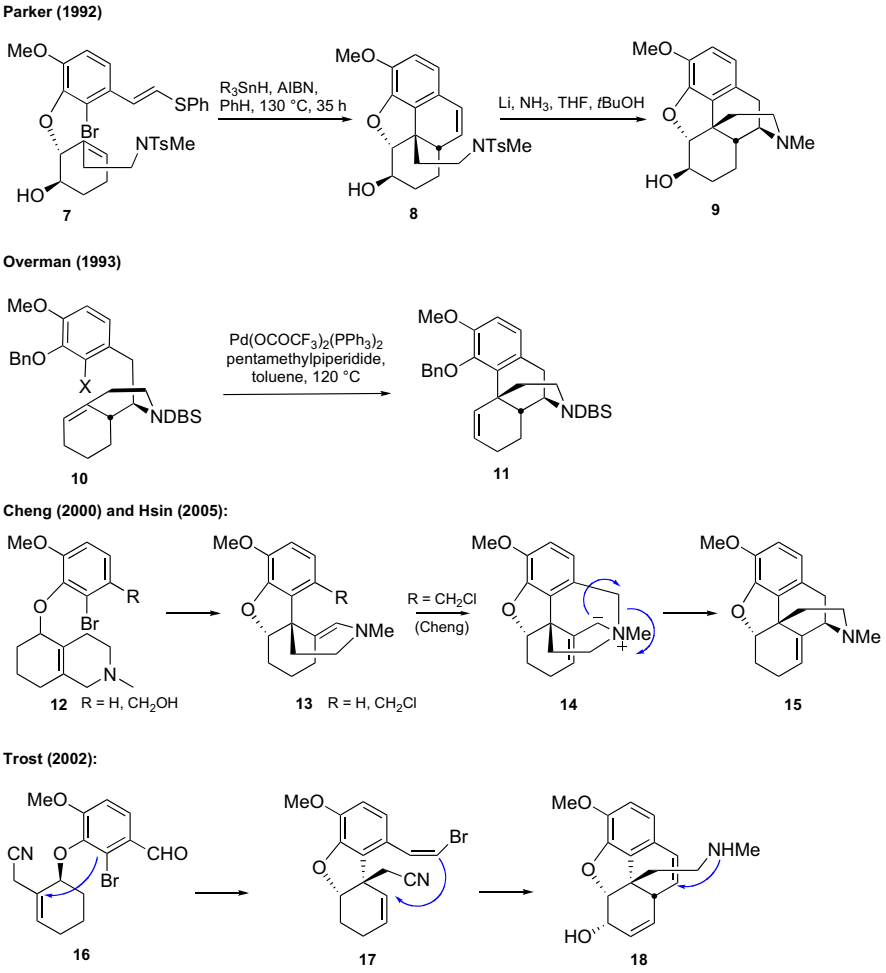


Figure 2. Radical (Parker) and Heck cyclization strategies employed in design of morphinan syntheses.

Despite its popularity as a target for synthesis, only one practical preparation with commercial potential exists to date. The most efficient synthesis of morphine, performed in either enantiomeric form, was reported by Rice in 1980,[14] and this accomplishment offers hope for a solution to potential supply problem on a scale needed by the medical community.

The very real possibility of a natural or a political disaster in those regions producing morphine and codeine jeopardizes the supply of this important agent and its derivatives. A practical synthetic or biosynthetic solution would obviate a potential problem.

Morphine is an example of a very complex molecule for its size owing to its completely dissonant connectivity.[15] Solutions to an effective design are consequently plagued with arduous introduction of functionalities as well as problems in the control of the five contiguous stereogenic centers. One possible solution to the efficient assembly of morphine or codeine is a cascade

We have examined several chemoenzymatic strategies commencing with the enantiopure diol **19** and involving Heck cyclizations.[22] In the *ent*-series, pentacycle **21** was obtained by Heck cyclization from aryl bromide **20**, and in the natural series 10-hydroxy-14α-dihydrocodeinone was prepared from **24** by C-10/C-11 closure.[23] The combination of elements of the double Heck cyclization reported by Trost with a chemoenzymatic approach resulted in the synthesis of *ent*-codeine in 13 operations from β-bromoethylbenzene, as shown in Figure 3.

Our enantiodivergent approach to codeine is based on the generation of diene diol **19** via enzymatic dihydroxylation of β-bromoethylbenzene, whose side chain becomes the ethyl amino bridge of morphine. The retrosynthetic reasoning shown in Figure 4 relies on the recognition that the configuration of the C-5 stereogenic center is the controlling element for all of the subsequent carbon–carbon bond-forming events. The C-6 stereochemistry is often adjusted by an oxidation–reduction sequence, which is well

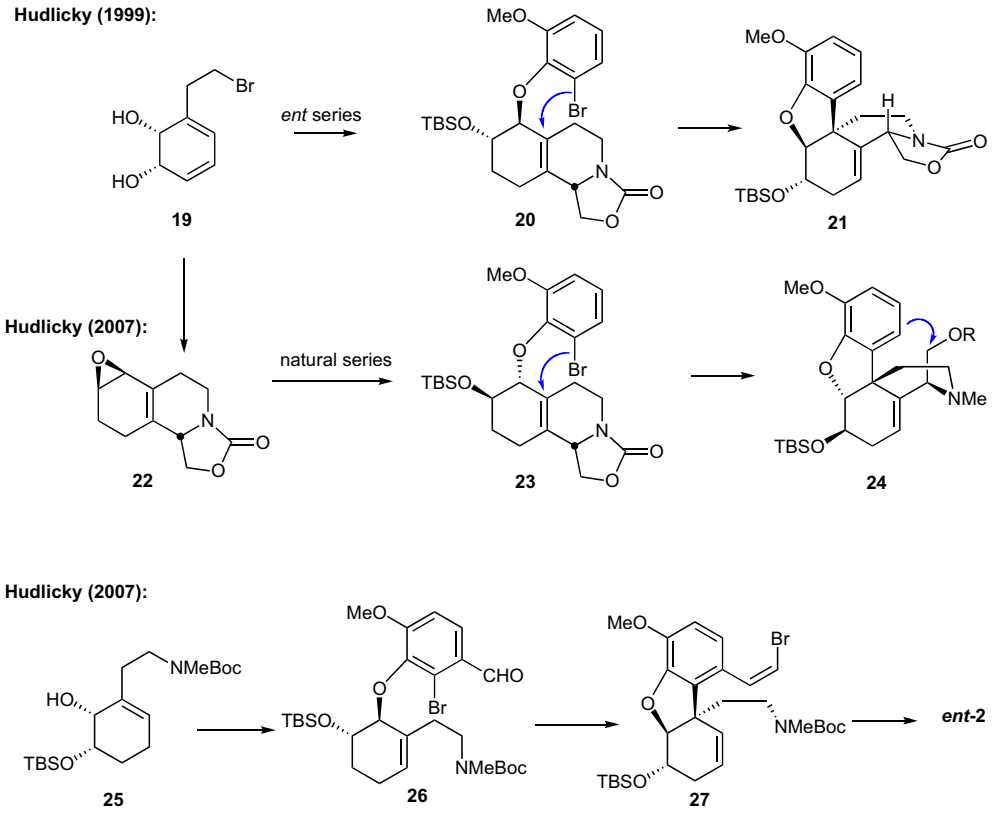


Figure 3. Chemoenzymatic approaches to morphine alkaloids via Heck cyclizations.

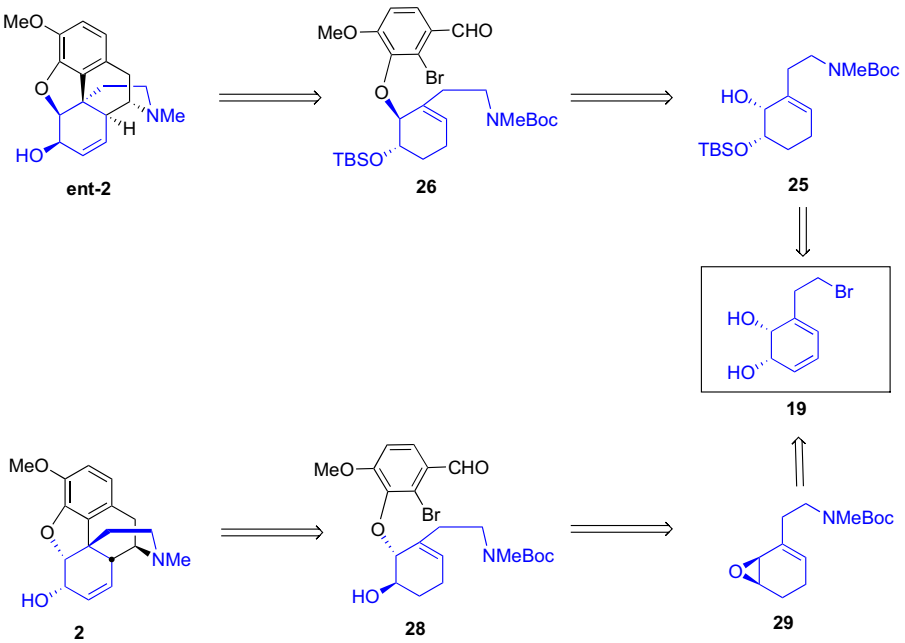
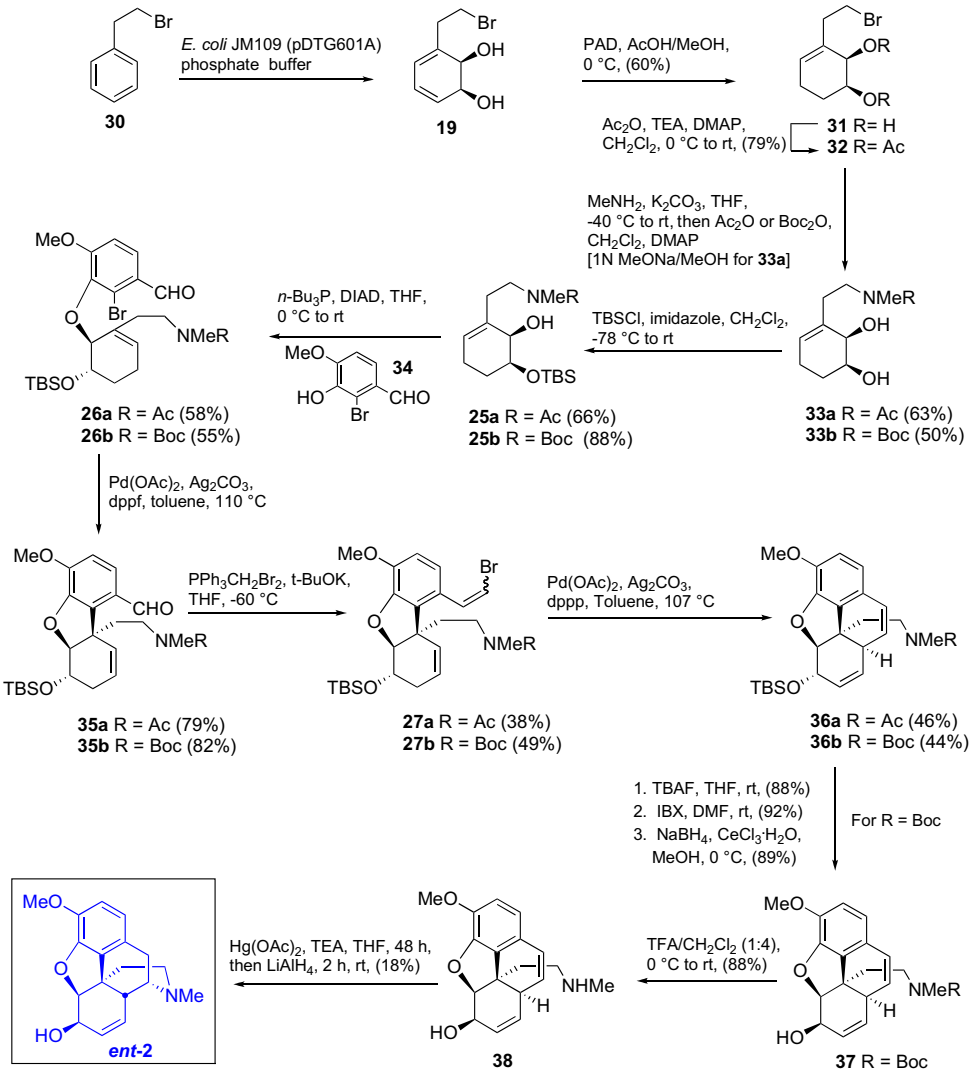


Figure 4. Disconnection analysis for enantiodivergent synthesis of codeine.

developed and guaranteed to deliver the C-6 configuration *syn* to the C-5 bridge. The C-13 center will be formed *syn* to the C-5 ether linkage, and the fate of C-14 and C-9 configuration is then determined by the structural constraints of intermediates containing fixed configurations at C-13 and C-5 (for example, compounds of type **27a**, **b**, Scheme 1). Finally, the C-9 center is created by hydroamination or a similar reaction; its configuration is, by definition, predefined by the existing framework.

This analysis then requires efficient approach to the connection of the aryl ether fragment to the enantiopure ring C, which can be accomplished by means of either a single or a double Mitsunobu reaction. The single Mitsunobu attachment of an aryl fragment to **25** has been shown to work well and has been reduced to practice in the synthesis of *ent*-codeine (**2**). The double Mitsunobu inversion of C-5 has been plagued, however, with difficulties arising from the severe steric influence of the C-6 TBSO group. In several of our past



Scheme 1.

approaches, especially in the synthesis of a C-10-hydroxymorphinan by a radical cascade approach,[17,24] this step was the lowest yielding transformation in the sequence, so an alternative solution had to be found. The generation of the allylic epoxide **29** would solve the problem of attachment of the ring A moiety provided the regiochemistry of the epoxide opening could be controlled.

2. Results and discussion

The synthesis of *ent*-codeine began with the saturation of the *cis* olefin in diene diol **19** with potassium azadicarboxylate to produce diol **31**, which was converted to diacetate **32**, Scheme 1. Exposure of this material to methylamine resulted in the displacement of the bromide and generation of the *N*-methylamine moiety with concomitant deacylation of the protected diol. In our initial approach to (+)-codeine, we chose to protect the *N*-methyl moiety as an acetamide, a choice that was later shown to have been less than fortunate. It was found that the best yield of **33a** was obtained by exhaustive acylation of the initially obtained *N*-methylamine followed by base-catalyzed hydrolysis (NaOMe, MeOH, and THF) of the diacetate to **33a**, whose distal hydroxyl group was then protected as its TBS ether (**25a**). The connection of the ring A fragment to C-5 was accomplished by Mitsunobu reaction of bromoisovanillin (**34**) in the presence of *n*-Bu_3P. (No reaction occurred with PPh_3.) With the aryl bromide **26a** in hand, the first of the two Heck reactions was carried out and mediated by Pd(0), generated in situ, and in the presence of a free ligand (diphenylphosphinoferrocene or dppf) with silver carbonate as base. The cyclization produced the tricyclic ether **35a** in 79% yield.

Conversion of the aldehyde to vinyl bromides **27a** was accomplished in modest yield by treatment with bromomethyltriphenylphosphonium bromide and *t*-BuOK at −55 °C, as we were unable to repeat the procedure published by Trost, who prepared the vinyl bromide in two steps by first Corey–Fuchs homologation (91%) of the aldehyde followed by chemoselective radical debromination (88%) to the required *Z*-vinyl bromide. Because the application of the same conditions for the first step to compound **35a** led to the recovery of only trace amounts of product, we used the Wittig protocol instead. The second Heck cyclization produced, in moderate yield, the complete phenanthrene core of the target compound under conditions similar to the first Heck sequence except that the ligand was changed to diphenylphosphinopropane (dppp). The rather modest yield can be explained by the fact that we obtained a mixture of *Z*- and *E*-isomers (approximately 2:1, *Z*:*E*, vide NMR analysis) after the Wittig reaction and only the *Z*-isomer can further react to produce the desired compound. Trost obtained a 65% yield of the cyclized product when only the *Z*-isomer was

used, thus the yields of the Heck cyclizations to the phenanthrene core compare favorably.

With the attainment of **36a** our attention was turned to the removal of the acetamide group so that we could apply Trost's photochemical hydroamination protocol to styrene **38** once the standard adjustment of stereochemistry at C-6 was accomplished. To our dismay we were never able to generate the secondary amine from **36a** under any conditions (hydrazine, KOH, t-BuOK/KOH, etc.). Under forceful conditions and elevated temperatures, isomerization of the olefins or elimination of the C-6 ether took place, and we were forced to abandon this particular approach. We repeated the synthesis with a less robust protecting group in place. (Similar problems with amide hydrolysis plagued also our first synthesis of pancratistatin and greatly complicated the completion of the synthesis.[25])

Returning to diacetate **32**, we discovered that its amination with methylamine, followed by protection with Boc anhydride, led cleanly to **33b** without the over-acylation observed with acetic anhydride. Protection of **33b** as its TBS ether **25b** was followed by Mitsunobu reaction with bromoisovanillin **34**[26] to provide aldehyde **26b**, Scheme 1. The Heck cyclization to **35b** was followed by the Wittig reaction and a second Heck cyclization of **27b** to **36b**. Both proceeded in reasonable yields and without the attendant C-14 epimerization observed in the acetate series during the second Heck cyclization.

At this stage the stereochemistry at C-6 was adjusted by desilylation, IBX oxidation, and reduction to attain the allylic alcohol **37**, which was deprotected with trifluoroacetic acid to yield the secondary amine **38**, whose enantiomer had been reported by Trost. Although the attainment of **38** formalized the synthesis, we decided to repeat Trost's hydroamination protocol consisting of irradiating the solution of lithium amide derived by treatment of **38** with LDA. In our hands, we never observed a closure to codeine under these conditions after many attempts, even with complete details provided to us by Professor Tang. It is clear that the reproducibility of this closure is questionable and does not constitute a general method. To solve this problem we resorted to oxymercuration procedure followed by a reductive workup with lithium aluminum hydride. This sequence yielded *ent*-codeine (**2**) in a total of 14 steps (13 operations) from β-bromoethylbenzene.

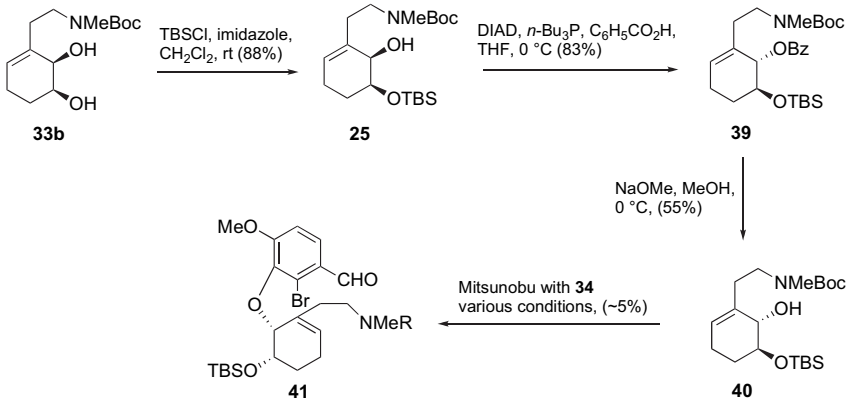
To approach the synthesis of the natural enantiomer of codeine we first considered a double Mitsunobu inversion at C-5 (morphine numbering) despite the rather poor results obtained in our 1998 radical cyclization approach. Thus diol **33b** was silylated to **25** at the distal hydroxyl with TBSCl and a Mitsunobu inversion with benzoic acid provided benzoate **39**, which was hydrolyzed to the free alcohol **40**, Scheme 2. Standard Mitsunobu conditions with bromoisovanillin (**34**) yielded at best ~5% yield of the aryl ether **41**. Various modifications of the Mitsunobu protocol failed to increase the yield of the product substantially. This approach was therefore abandoned in favor of pursuing the preparation of epoxide **29**.

To accomplish this transformation, we reacted diol **33b** with *p*-nitrobenzoic acid under Mitsunobu conditions reported by Banwell[27] in order to invert either hydroxyl. To our surprise the Mitsunobu reaction provided exclusively **42**, Scheme 3, via inversion at the proximal hydroxyl, perhaps delivered to this site by anchimeric assistance of the carbamate via an intramolecular hydrogen-bonded intermediate. To confirm this result **33b** was converted to tosylate **43**. Mitsunobu reaction of this material yielded the benzoate ester **44**, which was also obtained by tosylation of alcohol **42**. Treatment of *p*-nitrobenzoate **44** with sodium methoxide furnished directly the desired allylic epoxide (−)-**29** suitable for coupling with bromoisovanillin (**34**).

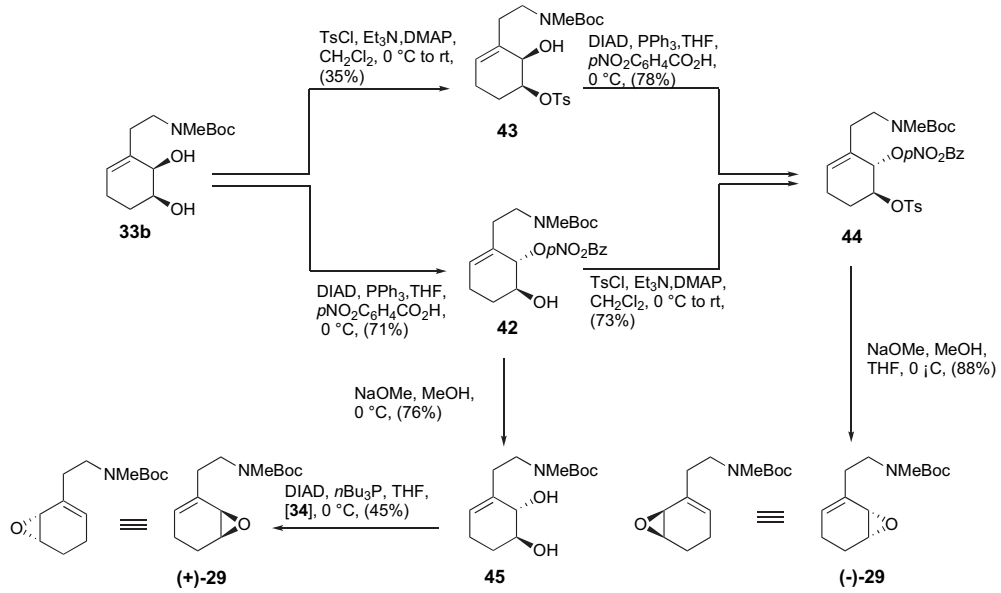
At this point we wished to establish whether the failure of the double Mitsunobu was strictly the function of the steric hindrance of the TBS group in **40**. Hydrolysis of *p*-nitrobenzoate **42** provided the *trans*-diol **45**. Another attempt was made at the coupling of bromoisovanillin at the allylic site. No aryl ether was detected in the reaction mixture, but epoxide (+)-**29** was isolated in 45% yield. Although there is some precedent for the formation of epoxides from 1,2-*trans*-diols,[28] we were delighted by this result as it provided an enantiomer of the epoxide that could be used in the preparation of *ent*-codeine. With both enantiomers of **29** available, the coupling of the ring A fragment was now possible in both enantiomeric series by an allylic opening (certainly a more convenient method) instead of Mitsunobu coupling.

With the required epoxide **29** in hand, we turned to the investigation of conditions for coupling of **29** with bromoisovanillin. After extensive model studies, we determined that the optimal conditions for S_N2 opening of the vinyl oxirane required the use of rigorously dry potassium phenoxide in the presence of 18-crown-6 and a chelating solvent such as DME. Under these conditions the aryl ether **46** was obtained in 78% yield, Scheme 4. These conditions, however, initially failed with the potassium phenoxide **47** derived from bromoisovanillin, perhaps because of the electron-withdrawing effect of the aldehyde moiety. Thus the potassium phenoxide derived from the acetal of bromoisovanillin, namely **48**, was used in the reaction with **29**. To our surprise, the desired ether **49** was obtained in low yield, with the free aldehyde **28** as the major product; however, it is not clear how the acetal hydrolysis occurred under the reaction conditions. Further optimization of the conditions (DME/DMF, 1:1, 18-crown-6, 80 °C) led to the desired aryl ether **28** in 75% yield along with a low yield of an interesting byproduct, the tricyclic dioxane derivative **50**, presumably formed by an intramolecular addition to the isovanillin ring, as shown in Scheme 4. This material was formed exclusively at higher reaction temperatures.

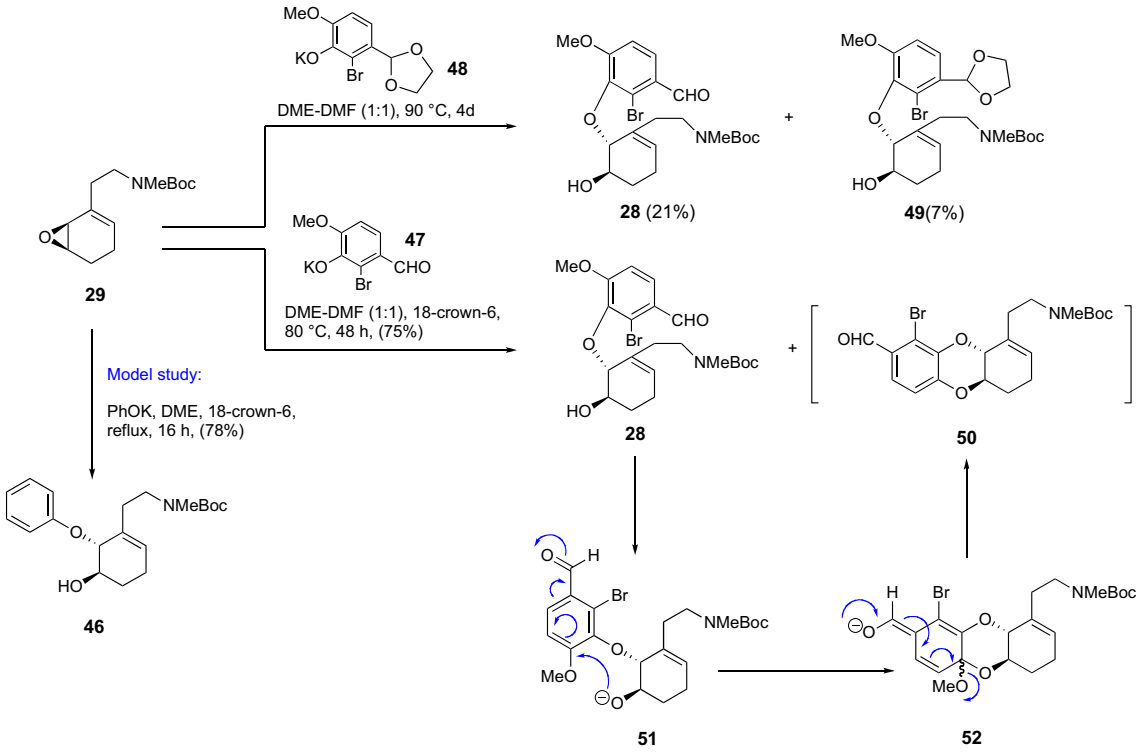
With the required aryl ether **28** in hand we turned to the completion of the synthesis of natural (−)-codeine by following



Scheme 2.



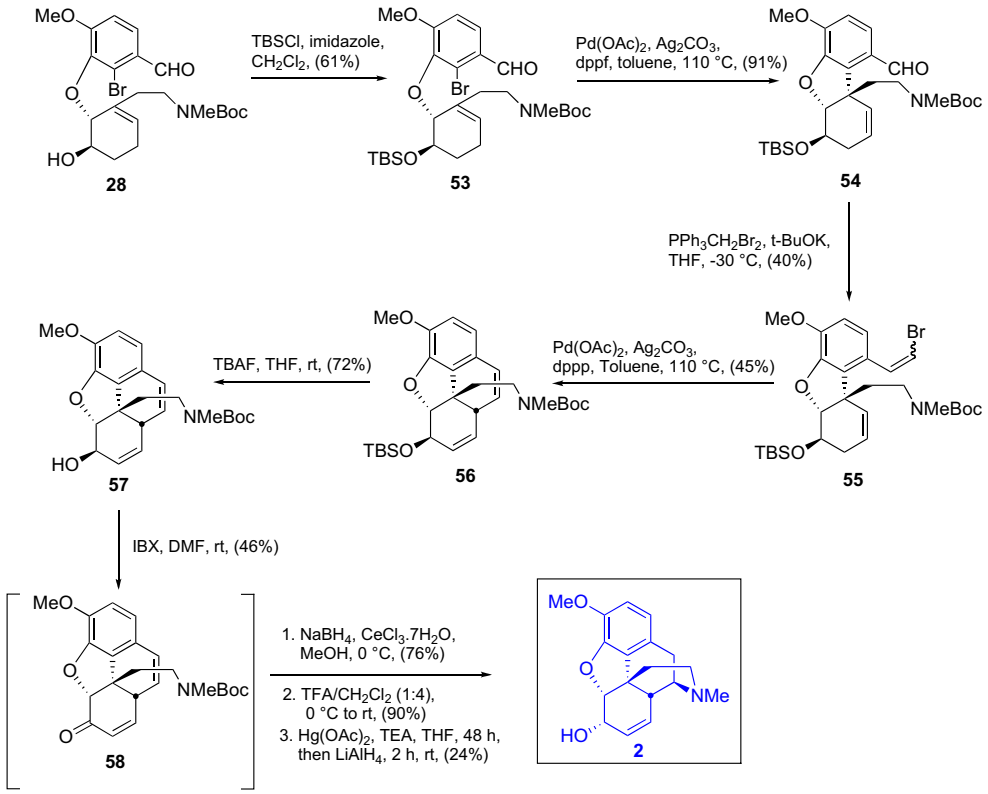
Scheme 3.



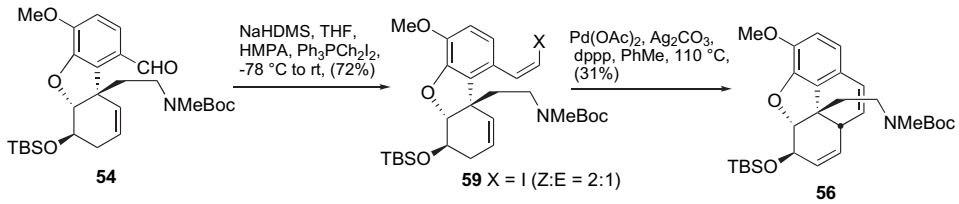
Scheme 4.

closely the sequence used to attain *ent*-**2**. The alcohol in **28** was protected as its TBS ether **53** (identical in all respects to **26b**, Scheme 1, except for the optical rotation), then the first Heck cyclization was performed to provide the tricycle **54** in 91% yield, nearly identical to the yield obtained in the (+)-series as well as in Trost's synthesis, Scheme 5. The aldehyde was converted to a mixture of vinyl bromides **55** in a ratio of approximately 2:1 (identical to the ratio obtained in the *ent*-series), and the second Heck cyclization yielded the complete phenanthrene skeleton **56** with the C-14 stereogenic center correctly established.

Deprotection of the silyl ether furnished allylic alcohol **57**, which was subjected to IBX oxidation in order to adjust the configuration at C-6. In contrast to the similar maneuver executed during the synthesis of *ent*-**2** where this oxidation proceeded nearly quantitatively, enone **58** was obtained as an inseparable mixture (1:1) with another compound, probably resulting from the use of excess oxidizing agent. The mixture was therefore taken through the remaining steps: reduction of the enone with sodium borohydride, hydrolysis of the Boc carbamate with trifluoroacetic acid, and an oxymercuration protocol to establish C-9 stereogenic center. In each of these steps the additional byproduct carried over from the IBX oxidation proved inseparable from the main component of the reaction. The final mixture was purified by careful flash column chromatography. (−)-Codeine was isolated in low yield and matched with a sample of



Scheme 5.



Scheme 6.

the natural product. The identity of the byproduct has not been established at this time and will have to await the repetition of the synthesis along with optimization of the last several steps.

In an attempt to improve the yield and the isomeric ratios in the generation of the vinyl bromide precursor to the second Heck cyclization, we searched for conditions to produce only the desired *Z*-isomer. We were able to produce the desired isomer in a better ratio (but at the expense of somewhat lower yields in the subsequent Heck cyclization) by following a protocol published by Stork.[29] His procedure employs $(Ph_3P^+CH_2I)I^-$ and leads to predominantly *Z*-1-iodo-1-alkenes. When we subjected aldehyde **54** to the conditions shown in Scheme 6, we obtained the iodo alkene **59** in 72% yields as a mixture of *Z*/*E* isomers (2:1). (Stork reported ratios of *Z*/*E* of 13:1 for the iodo olefin derived from benzaldehyde.) We have repeated the reaction with benzaldehyde and obtained the same result; however, application of the procedure to the more complex aldehyde **54** led to only a slight improvement.

3. Conclusions

In summary, we have completed enantiodivergent syntheses of (+)- and (−)-codeine from a single enantiomer of the *cis*-diol **19**, which was obtained by the toluene dioxygenase hydroxylation of β-bromoethylbenzene. A new procedure was developed for the coupling of ring A moiety to the enantiopure ring C fragment that involved a regioselective allylic opening of vinyl oxirane **29** (generated in both enantiomeric series) with the phenoxide of ring A. The accessibility of either (+)- or (−)-**29** from the same precursor simplifies the coupling procedure especially in the natural series where Mitsunobu conditions proved completely ineffective because of severe steric hindrance and represents a major improvement in the chemoenzymatic strategy toward morphine alkaloids. Further refinements and optimization need to be made in the control of isomeric ratios of the vinyl halides required for the second Heck coupling step as well as in the hydroamination protocol. The latter issue appears to have been solved in the recent synthesis of codeine by Guillou[12] who used Parker's conditions (a dissolved metal reduction of *N*-methyltosylamide) to accomplish the construction of C-9 stereogenic center in 51% yield. These are the major issues that require investigation for the next generation approach to codeine and derivatives.

4. Experimental section

4.1. General

*4.1.1. (1S,2R)-3-(2-Bromoethyl)-3-cyclohexene-1,2-diol, 1,2-diacetate (**32**).* To a solution of diol **31**[30] obtained by diimide reduction of diol

19 (1.45 g, 6.55 mmol) in DCM (20 mL) at 0 °C were added triethylamine (5.50 mL, 39.30 mmol), acetic anhydride (1.85 mL, 19.65 mmol), and DMAP (0.16 g, 1.31 mmol). The reaction mixture was warmed to ambient temperature, stirred for 16 h, and then quenched by the addition of a saturated aqueous solution of $NaHCO_3$ (20 mL). The layers were separated, and the aqueous layer was extracted with DCM. The organic layers were combined and washed three times with cold 1 N aqueous HCl, three times with saturated aqueous solution of $NaHCO_3$, and brine. The organic layer was dried over anhydrous magnesium sulfate. Filtration and evaporation of the solvent gave a crude oil, which was purified by flash column chromatography (hexanes/ethyl acetate, 15:1–3:1) to give diacetate **32** as a clear and colorless oil (1.58 g, 79%). R_f 0.50 (hexanes/ethyl acetate, 3:1); $[\alpha]_D^{22}$ −120.5 (*c* 0.9, CH_2Cl_2); IR (film) ν_{max}: 2947, 1738, 1434 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 5.80 (t, *J*=3.3 Hz, 1H), 5.47 (d, *J*=3.3 Hz, 1H), 4.99 (dt, *J*=11.7, 3.6 Hz, 1H), 3.39 (td, *J*=7.2, 2.4 Hz, 2H), 2.47–2.56 (m, 2H), 2.20–2.24 (m, 2H), 2.08 (s, 3H), 1.99 (s, 3H), 1.83–1.90 (m, 1H), 1.71–1.77 (m, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.7, 170.2, 131.2, 130.4, 70.0, 67.3, 37.4, 30.6, 24.0, 22.2, 20.9, 20.9 ppm; HRMS (EI) (M^+) calcd for $C_{12}H_{17}NO_4Br$: 304.0310, found 304.0317; Anal. Calcd for $C_{12}H_{17}NO_4Br$: C 47.23% H 5.62%, found C 47.42% H 5.67%.

*4.1.2. N-[2-[(5S,6R)-5,6-Dihydroxy-1-cyclohexen-1-yl]ethyl]-N-methyl-carbamic acid-1,1-dimethylethyl ester (**33b**).* Bromide **32** (6.34 g, 20.8 mmol) was dissolved in THF (20 mL) and transferred to a 50 mL thick-walled reaction vessel containing K_2CO_3 (1.61 g, 11.6 mmol) and a magnetic stirring bar. The reaction vessel was cooled to −40 °C, and the solution was saturated with methylamine by bubbling gaseous methylamine from a lecture bottle through the solution for 15 min. The reaction vessel was sealed, and the mixture stirred at rt for 48 h. The vessel was cooled to −40 °C before it was carefully opened. Potassium salts were removed by filtration and rinsed with DCM (20 mL). The solvent was removed and the residue was dissolved in DCM (50 mL). Boc anhydride (8.53 g, 37.4 mmol) was added to the solution and the reaction mixture was cooled to 0 °C. Triethylamine (5.20 mL, 37.4 mmol) and DMAP (0.24 g, 2.0 mmol) were added to the reaction mixture, which was warmed to rt over 24 h. A saturated aqueous solution of NH_4Cl was added and the layers were separated. The aqueous layer was extracted with DCM and the organic extracts were combined. The organic layer was washed three times with a saturated aqueous solution of Na_2CO_3, brine, and then dried over anhydrous sodium sulfate. The solution was filtered and the solvent was removed under reduced pressure. Purification of the crude residue by flash column chromatography (hexanes/ethyl acetate, 6:1–1:2) afforded the title compound **33b** as colorless oil (2.79 g, 50%). R_f 0.20 (hexanes/ethyl acetate, 1:1); IR (film) ν_{max}: 3383, 2974, 2930, 1693, 1672, 1396, 1158, 988 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 5.43 (br s, 1H), 4.87 (br s, 1H), 3.96 (br s, 2H), 3.56 (br s, 1H), 2.99 (d, *J*=8.8 Hz, 1H), 2.91 (br s, 1H), 2.86 (s, 3H), 2.42–2.30 (m, 1H), 2.18 (d, *J*=13.4 Hz, 1H), 2.03 (br s, 2H), 1.74–1.63 (m, 1H), 1.60–1.45 (m, 1H), 1.43 (s, 9H) ppm; ^{13}C NMR (150 MHz, $CHCl_3$) δ: 157.0, 133.9, 128.8, 79.9, 70.0, 69.8, 48.3, 34.8, 34.0, 28.3, 25.4, 24.8 ppm; MS (EI) *m*/*z* (%): 144 (12), 110 (110), 57 (71), 44 (100); HRMS (EI) (M^+−57) calcd for $C_{14}H_{25}NO_4$: 271.1784, found 271.1787.

*4.1.3. N-[2-[(5S,6R)-5-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-6-hydroxy-1-cyclohexen-1-yl]ethyl]-N-methyl-carbamic acid-1,1-dimethylethyl ester (**25b**).* To a solution of diol **33b** (656 mg, 2.0 mmol) in DCM (8 mL) at −78 °C was added imidazole (272 mg, 4.0 mmol) followed by the addition of TBDMS-chloride (330 mg, 2.2 mmol). The reaction mixture was warmed to rt over 14 h and then quenched by the addition of a saturated aqueous solution of NH_4Cl. The layers were separated, and the aqueous layer was extracted twice with DCM. The organic layers were combined and washed with cold 2% aqueous HCl, saturated aqueous solution of $NaHCO_3$, then dried over anhydrous magnesium sulfate. Evaporation of the solvent gave a crude oil, which was purified by flash column chromatography (hexanes/ethyl acetate, 1:1–0:1) to give the mono-silyl derivative **25b** as a clear and colorless oil (678 mg, 88%). R_f 0.47 (DCM/ethyl acetate, 96:4); $[\alpha]_D^{24}$ −22.6 (*c* 0.5, $CHCl_3$); IR (film) ν_{max}: 3556, 3475, 2953, 2857, 1692, 1472, 1392, 1253, 1085 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) (mixture of rotamers) δ: 5.54 (s, 1H), 5.52 (s, 1H), 3.98 (s, 1H), 3.90 (s, 1H), 3.79 (s, 1H), 3.77 (s, 1H), 3.26–3.20 (m, 2H), 2.85 (s, 3H), 2.82 (s, 3H), 2.39–2.32 (m, 2H), 2.30–2.23 (m, 2H), 2.13 (br s, 2H), 1.98 (br s, 2H) 1.80–1.72 (m, 2H), 1.54 (s, 2H), 1.44 (s, 18H), 0.9 (s, 18H), 0.11 (s, 6H), 0.10 (s, 6H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ: 155.7, 134.8, 126.6, 79.0 (br), 71.0, 68.8, 48.4, 47.2, 34.1, 33.3, 32.8, 28.4, 25.8, 25.4, 25.3, 24.3, 24.1, 18.1, −4.4, −4.8 ppm; MS (EI) *m*/*z* (%): 228 (21), 197 (21), 136 (12), 74 (22), 73 (15), 57 (63), 44 (100); HRMS (EI) (M^+−57) calcd for $C_{12}H_{30}NO_4Si$: 328.1944, found 328.1946; Anal. Calcd for $C_{20}H_{39}NO_4Si$: C 62.10% H 10.22%, found C 62.29% H 10.19%.

*4.1.4. N-[2-[(5S,6S)-6-(2-Bromo-3-formyl-6-methoxyphenoxy)-5-[[(1,1-dimethylethyl) dimethylsilyl]oxy]-1-cyclohexen-1-yl]ethyl]-N-methyl-carbamic acid-1,1-dimethylethylester (**26b**).* To a solution of DIAD (1.02 mL, 5.21 mmol) in THF (10 mL) at −10 °C, was added tributylphosphine (1.69 mL, 5.21 mmol) dropwise. The solution was stirred at −10 °C for 10 min, then it was transferred dropwise to a solution of bromoisovanillin **34** (0.93 g, 4.01 mmol) and monoprotected diol **25b** (1.39 g, 3.61 mmol) in THF (2 mL) at −78 °C. Once the addition was completed, the reaction vessel was warmed to rt and stirred at ambient temperature for 48 h. The solvent was removed under reduced pressure and the crude mixture was subjected to column chromatography (DCM/ethyl acetate, 100:0–98:2). Compound **26b** was isolated as colorless oil (1.19 g, 55%). R_f 0.81 (DCM/EtOAc, 96:4); $[\alpha]_D^{22}$ +59.1 (*c* 0.35, $CHCl_3$); IR (film) ν_{max}: 3007, 2952, 2929, 2857, 1688, 1578, 1481, 1275, 1252, 1173, 1085, 1028, 1005, 836 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) (two rotamers) δ: 10.30 (s, 1H), 7.75 (d, *J*=8.6 Hz, 1H), 7.00 (d, *J*=8.6 Hz, 1H), 5.79–5.90 (m, 1H), 4.57 (br s, 1H), 3.94–4.04 (m, 4H), 3.40–3.65 (m, 1H), 3.22 (br s, 1H), 2.85 (s, 3H), 2.37–2.57 (m, 2H), 2.17–2.28 (m, 2H), 2.02–2.10 (m, 1H), 1.65–1.74 (m, 1H), 1.46 (s, 9H), 0.76 (s, 9H), −0.12 (s, 3H), −0.17 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ: 191.3, 157.9, 155.8, 144.6, 130.9, 130.3, 127.7, 125.9, 123.5, 110.9, 80.3, 79.1, 67.7, 56.1, 48.9, 48.3, 41.5, 35.0, 33.4, 32.7, 28.5, 25.6, 25.4, 20.8, 18.0, −4.9, −5.1 ppm; MS (EI) *m*/*z* (%): 312 (28), 269 (10), 268 (45), 237 (24), 136 (31), 109 (14), 75 (27), 73 (33), 57 (47), 44 (100); HRMS (EI) (M^+−73) calcd for $C_{24}H_{35}NO_5BrSi$: 524.1468, found 524.1464; Anal. Calcd for $C_{28}H_{44}NO_6BrSi$: C 56.18% H 7.41%, found C 56.09% H 7.65%.

*4.1.5. N-[2-[(5aS,6S,9aR)-6-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-1-formyl-6,7-dihydro-4-methoxy-9a(5aH)-dibenzofuranyl]ethyl]-N-methyl-carbamic acid-1,1-dimethylethyl ester (**35b**).* To aryl bromide **26b** (205 mg, 0.34 mmol) dissolved in degassed (N_2) toluene (5 mL) were added sequentially silver carbonate (283 mg, 1.03 mmol), diphenylphosphino ferrocene (57 mg, 0.10 mmol), and $Pd(OAc)_2$ (12 mg, 0.05 mmol). The reaction mixture was heated to 110 °C (preheated oil bath) in a Teflon-sealed Schlenk tube (10 mL) for 1 h, before it was cooled to rt. The remaining black reaction mixture was filtered through Celite and washed with several portions of $CHCl_3$. The filtrate was concentrated and adsorbed onto a mixture of silica gel and charcoal. Purification by flash column chromatography (DCM/ethyl acetate, 4:1) gave 146 mg (82%) of the title compound **35b** as colorless oil. R_f 0.80 (DCM/ethyl acetate, 96:4); $[\alpha]_D^{24}$ +12.5 (*c* 0.6, $CHCl_3$); IR (film) ν_{max}: 3008, 2953, 2930, 2856, 2734, 1692, 1610, 1571, 1436, 1366, 1285, 1250, 1170, 1155, 1046, 837 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) (two rotamers) δ: 9.90 (s, 1H), 9.89 (s, 1H), 7.38 (d, *J*=8.2 Hz, 2H), 6.86–6.93 (m, 2H), 6.40–6.49 (m, 1H), 6.32–6.40 (m, 1H), 5.65–5.72 (m, 2H), 4.54–4.80 (m, 2H), 3.95 (s, 6H), 3.91 (br s,

2H), 3.32 (br s, 1H), 3.16–3.25 (m, 1H), 2.93–3.03 (m, 2H), 2.78 (s, 6H), 2.01–2.29 (m, 8H), 1.43 (s, 18H), 0.91 (s, 18H), 0.14 (s, 6H), 0.04 (s, 6H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) (two rotamers) δ: 190.6, 155.5, 150.2, 147.5, 133.6, 130.4, 129.8, 129.2, 126.5, 124.1, 110.4, 90.9, 89.9, 79.5, 68.8, 68.4, 56.0, 55.9, 51.8, 45.3, 44.6, 36.4, 35.5, 34.7, 34.6, 34.1, 31.6, 30.5, 29.1, 28.4, 25.8, 25.7, 25.3, 22.7, 20.7, 18.1, 14.1, 11.4, −4.7, −5.2 ppm; MS (EI) *m*/*z* (%): 162 (12), 144 (17), 136 (12), 118 (13), 117 (18), 92 (32), 91 (38), 88 (11), 75 (46), 73 (38), 57 (87), 44 (100); HRMS (EI) (M^+−57) calcd for $C_{24}H_{34}NO_6Si$: 460.2155, found 460.2150; Anal. Calcd for $C_{28}H_{43}NO_6Si$: C 64.96% H 8.37%, found C 64.87% H 8.46%.

*4.1.6. N-[2-[(5aS,6S,9aR)-1-(2-Bromoethenyl)-6-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-6,7-dihydro-4-methoxy-9a(5aH)-dibenzofuranyl]ethyl]-N-methyl-carbamic acid-1,1-dimethylethyl ester (**27b**).* Potassium *tert*-butoxide (2.91 g, 26.0 mmol) was added to a solution of ylide (prepared by refluxing a solution of triphenylphosphine (15 g, 57.0 mmol)) and methylene bromide (22.3 g, 115 mmol) in toluene (100 mL) for 24 h. The mixture was cooled to 0 °C, the precipitate was collected by filtration, washed with toluene, and dried under reduced pressure (12.2 g, 28.0 mmol) in THF (100 mL) at −30 °C. The solution was stirred at −30 °C for 5 min and then aldehyde **35b** (4.05 g, 7.8 mmol) was added. The mixture was stirred at −30 °C until TLC analysis indicated full conversion (20 min). The reaction mixture was quenched with brine (40 mL) and the aqueous layer was extracted twice with ethyl acetate (50 mL). The organic layers were combined, dried over anhydrous magnesium sulfate, and filtered. The concentrated residue was purified by flash column chromatography (hexanes/ethyl acetate, 9:1–4:1) to give the title compound as colorless oil (2.05 g, 49%). R_f 0.56 (hexanes/ethyl acetate, 4:1); $[\alpha]_D^{21}$ +46.6 (*c* 1.2, $CHCl_3$); IR (film) ν_{max}: 2952, 2929, 2855, 1691, 1620, 1502, 1366, 1282, 1156, 1122, 837 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) (two isomers, ratio 2:1) δ: 7.10 (d, *J*=8.4 Hz, 1H), 6.70–6.86 (m, 3H), 6.56 (d, *J*=13.9 Hz, 1H), 6.52 (d, *J*=7.9 Hz, 1H), 5.86–5.99 (m, 2H), 5.66–5.81 (m, 2H), 4.46–4.60 (m, 2H), 3.94–4.03 (m, 2H), 3.89 (s, 3H), 3.87 (s, 3H), 3.18–3.48 (br s, 2H), 2.89–3.04 (m, 2H), 2.80 (s, 3H), 2.76 (s, 3H), 2.31 (t, *J*=4.5 Hz, 1H), 2.25 (t, *J*=2.8 Hz, 1H), 2.03–2.18 (m, 2H), 1.80–2.03 (m, 4H), 1.43–1.48 (m, 20H), 0.92 (s, 18H), 0.15 (s, 3H), 0.14 (s, 3H), 0.05 (s, 3H), 0.05 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) (two isomers, ratio 2:1) δ: 155.5, 147.1, 145.3, 145.0, 130.2, 129.0, 128.6, 124.7, 122.5, 119.5, 111.7, 110.9, 108.6, 106.7, 89.8, 89.1, 79.5, 68.9, 68.3, 65.9, 55.9, 55.8, 55.7, 51.0, 50.9, 45.2, 37.1, 34.2, 30.4, 30.3, 29.7, 28.5, 28.5, 25.8, 25.7, 25.7, 18.1, 15.3, −3.5, −4.7, −5.2 ppm; MS (EI) *m*/*z* (%): 536 (4), 436 (7), 144 (8), 118 (6), 88 (14), 86 (29), 84 (44), 75 (21), 73 (38), 59 (33), 57 (61), 47 (10), 44 (100), 41 (18), MS (ES-pos) *m*/*z* (%): 618 (100), 616 (92), 553 (20), 477 (14), 476 (52); HRMS (EI) (M^+−57) calcd for $C_{25}H_{35}NO_5BrSi$: 536.1467, found 536.1461; Anal. Calcd for $C_{29}H_{44}NO_5BrSi$: C 58.57% H 7.46%, found C 59.48% H 7.87%.

*4.1.7. N-[2-[(3S,3aS,9aS,9bR)-3-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-3,9a-dihydro-5-methoxyphenanthro[4,5-bcd]furan-9b(3αH)-yl]ethyl]-N-methyl-carbamic acid-1,1-dimethylethyl ester (**36b**).* Vinyl bromide **27b** (788 mg, 1.33 mmol) was dissolved in degassed (N_2) toluene (20 mL) and transferred to a 50 mL Teflon-sealed Schlenk tube containing a magnetic stirring bar. Silver carbonate (1.10 g, 4.0 mmol), diphenylphosphinopropane (164 mg, 0.4 mmol), and $Pd(OAc)_2$ (45 mg, 0.2 mmol) were added sequentially. The tube was flushed with nitrogen, sealed, and placed in a preheated oil bath at 110 °C for 3 h. The black reaction mixture was filtered through Celite and washed with several portions of $CHCl_3$. The filtrate was adsorbed onto a mixture of silica gel and charcoal and loaded onto a silica gel column. Elution with DCM/ethyl acetate, 4:1 gave compound **36b** as a yellow oil (300 mg, 44%). R_f 0.55 (hexanes/ethyl acetate, 4:1); IR (film) ν_{max}: 2954, 2929, 2856, 1697, 1507, 1438, 1391, 1365, 1279, 1162, 1094, 865 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) (two rotamers) δ: 6.69 (d, *J*=8.0 Hz, 1H), 6.63 (d, *J*=8.0 Hz, 1H), 6.40–6.48 (m, 1H), 5.85 (dd, *J*=9.2, 5.8 Hz, 1H), 5.59–5.73 (m, 1H), 5.55 (d, *J*=9.8 Hz, 1H), 4.64–4.74 (m, 1H), 4.04–4.15 (m, 1H), 3.90 (s, 3H), 3.16–3.28 (m, 1H), 3.05–3.14 (m, 2H), 2.68–2.80 (m, 3H), 1.92–2.01 (m, 1H), 1.80–1.91 (m, 1H), 1.38–1.46 (m, 10H), 0.92 (s, 9H), 0.16 (s, 3H), 0.07 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) (two rotamers) δ: 155.5, 144.7, 141.7, 129.6, 128.2, 128.0, 127.7, 124.1, 117.8, 113.0, 102.1, 95.0, 85.7, 79.3, 68.8, 56.5, 45.1, 38.8, 36.4, 34.7, 34.2, 28.4, 25.8, 25.3, 18.1, −4.7, −4.9 ppm; MS (EI) *m*/*z* (%): 440 (2), 370 (10), 356 (11), 355 (12), 299 (10), 281 (8), 238 (18), 225 (17), 224 (83), 223 (14), 158 (9) 117 (8), 102 (54), 75 (41), 73 (63), 59 (38), 58 (59), 57 (99), 44 (100), 41 (22); HRMS (EI) (M^+−73) calcd for $C_{25}H_{34}NO_4Si$: 440.2257, found 440.2250.

*4.1.8. N-[2-[(3R,3aS,9aS,9bR)-3,9a-Dihydro-3-hydroxy-5-methoxyphenanthro[4,5-bcd]furan-9b(3αH)-yl]ethyl]-N-methyl-carbamic acid-1,1-dimethylethyl ester (**37**).* To compound **36b** (278 mg, 0.54 mmol) dissolved in THF (3 mL) was added TBAF (0.6 mL, 1 M in THF) and the reaction mixture was stirred at ambient temperature for 1 h. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (DCM/MeOH, 95:5) to give the free alcohol *N*-[2-[(3*S*,3a*S*,9a*S*,9b*R*)-3,9a-dihydro-3-hydroxy-5-methoxyphenanthro[4,5-*bcd*]furan-9b(3α*H*)-yl]ethyl]-*N*-methyl-carbamic acid-1,1-dimethylethyl ester as a colorless oil (190 mg, 88%). R_f 0.50 (DCM/MeOH, 95:5); $[\alpha]_D^{21}$ −80.5 (*c* 1.2, $CHCl_3$); IR (film) ν_{max}: 3417, 2974, 2933, 1675, 1633, 1507, 1438, 1366, 1280, 1162, 1051, 878 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) (two rotamers) δ: 6.68 (d, *J*=9.1 Hz, 1H), 6.64 (d, *J*=6.0 Hz, 1H), 6.40–6.50 (m, 1H), 5.83 (br s, 1H), 5.75 (d, *J*=9.91 Hz, 1H), 5.61 (br s, 1H), 4.70–4.82 (m, 1H), 4.14 (br s, 1H), 3.89 (s, 3H), 3.21–3.42 (m, 1H), 3.05–3.20 (m, 2H), 2.72–2.80 (m, 3H), 2.38–2.65 (m, 1H), 1.90–2.08 (m, 1H), 1.75–1.90 (m, 1H), 1.35–1.50 (m, 9H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) (two rotamers) δ: 155.5, 145.4, 144.1, 128.3, 128.0, 127.6, 127.2, 123.9, 123.3, 118.1, 117.9, 112.5, 95.2, 79.4, 68.7, 68.6, 56.2, 44.9, 44.4, 43.2, 43.0, 39.3, 38.6, 36.1, 37.0, 34.2, 28.4 ppm; MS (EI) *m*/*z* (%): 399 (1), 256 (10), 242 (21), 241 (47), 238 (21), 225 (25), 224 (89), 223 (23), 213 (11), 209 (17), 181 (12), 152 (10), 102 (30), 88 (11), 85 (14), 83 (20), 59 (27), 58 (35), 57 (100), 44 (27); HRMS (EI) calcd for $C_{23}H_{29}NO_5$: 399.2046, found 399.2043.

The free alcohol (157 mg, 0.39 mmol) obtained by desilylation of **36b** was dissolved in DMF (2 mL) and IBX (110 mg, 0.42 mmol) was added at rt. After complete consumption of starting material (TLC) the reaction mixture was quenched with water (20 mL). The phases were separated and the aqueous phase was extracted with DCM (3×20 mL). The organic layers were combined, washed with a saturated aqueous solution of $NaHCO_3$, then dried over anhydrous sodium sulfate. Filtration and removal of the solvent under reduced pressure gave the crude product, which was purified by flash column chromatography (DCM/ethyl acetate, 4:1) to afford the corresponding enone *N*-[2-[(3*aS*,9*aS*,9*bR*)-3,9a-dihydro-5-methoxy-3-oxophenanthro[4,5-*bcd*]furan-9b(3α*H*)-yl]ethyl]-*N*-methyl-carbamic acid-1,1-dimethylethyl as a colorless oil (142 mg, 92%). R_f 0.68 (DCM/ethyl acetate, 90:10); $[\alpha]_D^{21}$ +61.4 (*c* 1.4, $CHCl_3$); IR (film) ν_{max}: 2928, 1683, 1508, 1438, 1393, 1366, 1281, 1153, 1050, 808 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) (two rotamers) δ: 6.70 (br s, 1H), 6.58–6.66 (m, 1H), 6.58 (dd, *J*=11.8, 1.3 Hz, 1H), 6.08–6.18 (m, 1H), 5.87 (t, *J*=7.5 Hz, 1H), 4.90 (s, 1H), 3.91 (s, 3H), 3.68–3.74 (br s, 1H), 3.28–3.77 (m, 2H), 3.05–3.23 (m, 1H), 2.78 (s, 3H), 1.86–2.04 (m, 2H), 1.37–1.48 (m, 9H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) (two rotamers) δ: 194.0, 155.4, 146.1, 145.7, 145.0, 144.7, 129.0, 128.6, 127.8, 126.3, 124.6, 124.2, 122.1, 119.2, 119.0, 113.9, 87.3, 79.6, 56.6, 45.0, 44.8, 44.4, 38.5, 37.6, 35.2, 34.2, 29.7, 28.4 ppm; MS (EI) *m*/*z* (%): 397 (1), 254 (23), 241 (14), 240 (77), 239 (38), 238 (12), 225 (17), 211 (14), 149 (12), 102 (21), 97 (13), 85 (27), 83 (35), 71 (20), 70 (10), 69 (18), 59 (24), 58 (23), 57 (100), 56 (13), 55 (23), 44 (31), 43 (38), 41 (31); HRMS (EI) calcd for $C_{23}H_{27}NO_5$: 397.1889, found 397.1895.

To the enone (123 mg, 0.31 mmol) dissolved in methanol (3 mL), was added $CeCl_3 \cdot 7H_2O$ (182 mg, 0.62 mmol). The reaction mixture was stirred at ambient temperature for 5 min and then cooled to 0 °C. $NaBH_4$ (13 mg, 0.34 mmol) was added portion-wise and the mixture was stirred at 0 °C for 20 min. The solvent was removed under reduced pressure and the residue was suspended in DCM (15 mL). The organic layer was washed with a saturated aqueous solution of NH_4Cl (15 mL), dried over anhydrous sodium sulfate, filtered, and the volatiles were removed under reduced pressure. The residue was purified by flash column chromatography (DCM/MeOH, 95:5) to give 110 mg (89%) of alcohol **37**. R_f 0.48 (DCM/MeOH, 95:5); $[\alpha]_D^{22}$ +98 (*c* 0.5, $CHCl_3$); IR (film) ν_{max}: 3449, 2973, 2932, 1690, 1637, 1507, 1457, 1393, 1366, 1269, 1160, 1089, 1051, 798 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 6.63 (d, *J*=8.0 Hz, 1H), 6.58 (d, *J*=8.0 Hz, 1H), 6.51 (d, *J*=9.3 Hz, 1H), 6.00 (dd, *J*=9.3, 6.2 Hz, 1H), 5.81 (d, *J*=10.0 Hz, 1H), 5.28 (dd, *J*=10.0, 2.3 Hz, 1H), 5.15 (br s, 1H), 4.17–4.28 (m, 1H), 3.85 (s, 3H), 3.22–3.45 (m, 1H), 2.80–2.99 (m, 2H), 2.76 (s, 3H), 2.05–2.22 (m, 1H), 1.76–1.99 (m, 1H), 1.42 (s, 9H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) (two rotamers) δ: 178.4, 155.5, 145.4, 144.1, 128.3, 128.0, 127.2, 123.9, 118.1, 117.9, 112.5, 95.2, 79.4, 68.7, 56.2, 44.9, 44.4, 43.2, 43.0, 39.3, 36.9, 34.2, 28.4 ppm; MS (EI) *m*/*z* (%): 399 (14), 343 (12), 246 (43), 242 (34), 241 (87), 240 (11), 252 (13), 224 (12), 223 (11), 213 (16), 209 (16), 181 (16), 88 (23), 86 (56), 84 (56), 59 (25), 58 (33), 57 (100), 55 (12); HRMS (EI) calcd for $C_{23}H_{29}NO_5$: 399.2046, found 399.2044.

*4.1.9. (3R,3aS,9aS,9bR)-3,3a,9a,9b-Tetrahydro-5-methoxy-9b-[2-(methylamino)ethyl]-phenanthro[4,5-bcd]furan-3-ol (**38**).* To compound **37** (105 mg, 0.26 mmol) dissolved in DCM (3 mL) was added trifluoroacetic acid (0.5 mL) dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 2 h and then the solvent was removed under reduced pressure. The residue was suspended in $CHCl_3$ and washed with a saturated aqueous solution of Na_2CO_3 and brine. The aqueous layers were combined and extracted with $CHCl_3$. The organic layers were combined, dried over anhydrous magnesium sulfate, filtered, and then the solvent was evaporated. The crude product was purified by flash column chromatography (DCM/MeOH, 4:1) to give 69 mg (88%) of amine (+)-**38**. $[\alpha]_D^{22}$ +112.5 (*c* 0.4, $CHCl_3$); (lit.[21d] −118.1 (*c* 0.7, $CHCl_3$)); IR (film) ν_{max}: 3583, 3311, 3032, 2931, 2851, 1635, 1573, 1506, 1457, 1381, 1270, 1194, 1161, 1050 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 6.64 (d, *J*=7.9 Hz, 1H), 6.58 (d, *J*=7.9 Hz, 1H), 6.50 (d, *J*=9.0 Hz, 1H), 6.00 (dd, *J*=9.3, 6.4 Hz, 1H), 5.77–5.85 (m, 1H), 5.29 (dt, *J*=10.1, 2.5 Hz, 1H), 5.16 (d, *J*=6.1 Hz, 1H), 4.19–4.26 (m, 1H), 3.85 (s, 3H), 2.78–2.86 (m, 1H), 2.71 (td, *J*=5.2, 2.9 Hz, 1H), 2.31–2.49 (m, 2H), 2.36 (s, 3H), 2.06–2.19 (m, 2H), 1.78–1.92 (m, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 146.2, 143.8, 132.0, 129.2, 127.6, 125.1, 123.7, 117.8, 112.0, 90.5, 66.0, 56.0, 57.9, 45.4, 37.7, 36.4, 35.9, 25.8 ppm; MS (EI) *m*/*z* (%): 299 (9), 242 (53), 240 (16), 225 (24), 197 (13), 152 (10), 59 (100), 44 (54); HRMS (EI) calcd for $C_{18}H_{21}NO_3$: 299.1521, found 299.1517.

4.1.10. (+)-Codeine (ent-2). Amine (+)-**38** (50 mg, 0.17 mmol) dissolved in THF (5 mL) was added to a mixture of $Hg(OAc)_2$ (80 mg, 0.25 mmol) and triethylamine (60 μL, 0.40 mmol) in THF (2 mL). The mixture was stirred for 48 h and then a solution of $LiAlH_4$ in THF (0.46 mL (1 M THF), 0.46 mmol) was added dropwise. The reaction mixture was stirred for 2 h and then quenched with saturated aqueous solution of Na_2CO_3 (2 mL). The aqueous phase was extracted with $CHCl_3$ (3×3 mL). The organic layers were combined and dried over anhydrous sodium sulfate. The mixture was filtered and the solvent was evaporated under reduced pressure. The concentrated product was purified by flash column chromatography (DCM/MeOH/NH_4OH, 80:20:1) affording (+)-codeine ***ent*-2** (10 mg, 0.03 mmol, 17.6%). R_f 0.75 (DCM/MeOH, 4:1); $[\alpha]_D^{22}$ +130 (*c* 0.3, EtOH) (lit.[31] +137.5 (*c* 0.16, EtOH)); IR (film) ν_{max}: 3402, 2930, 2839, 1634, 1603, 1504, 1452, 1277, 1254, 1121, 1054, 942 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ: 6.69 (d, *J*=8.2 Hz, 1H), 6.60 (d, *J*=8.2 Hz, 1H), 5.74 (m, 1H), 5.31 (m, 1H), 4.93 (d, *J*=6.5 Hz, 1H), 4.20–4.23 (m, 1H), 3.87 (s, 3H), 3.72 (m, 1H), 3.41–3.46 (m, 1H), 3.08 (d, *J*=18.5 Hz, 1H), 2.74–2.81 (m, 1H), 2.65–2.72 (m, 1H), 2.51 (s, 3H), 2.44–2.50 (m, 1H), 2.34–2.42 (m, 1H), 2.11–2.21 (m, 1H), 1.92 (d, *J*=12.4 Hz, 1H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ: 146.3, 142.3, 133.7, 130.8, 127.9, 119.7, 112.9, 91.2, 66.3, 59.0, 56.3, 46.5, 42.9, 42.8, 40.4, 35.4, 29.9, 20.6 ppm; MS (EI) *m*/*z* (%): 300 (21), 299 (100), 298 (14), 229 (19), 188 (13), 162 (23), 124 (22), 115 (12), 59 (14), 42 (13); HRMS (EI) calcd for $C_{18}H_{21}NO_3$: 299.1521, found 299.1520.

*4.1.11. N-[2-[(5S,6R)-5-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-6-benzoyloxy-1-cyclohexen-1-yl]ethyl]-N-methyl-carbamic acid-1,1-dimethylethyl ester (**39**).* To a stirred solution of alcohol **25b** (360 mg, 0.94 mmol) and benzoic acid (171 mg, 1.40 mmol) in THF (12 mL) at 0 °C, was added a solution of the Mitsunobu reagent [previously prepared by addition of DIAD (568 mg, 2.81 mmol) to a stirred solution of freshly distilled tributylphosphine (736 mg, 2.81 mmol) in THF (10 mL) at 0 °C], and the mixture was warmed to rt. After 16 h, silica gel was added to the reaction mixture and the solvent was removed under reduced pressure. The crude residue was subjected to flash column chromatography (hexanes/ethyl acetate, 15:1–1:1) to give compound **39** as a clear and colorless oil (380 mg, 83%). R_f 0.55 (hexanes/ethyl acetate, 1:1); $[\alpha]_D^{23}$ −5.6 (*c* 0.8, $CHCl_3$); IR (film) ν_{max}: 3030, 2956, 2859, 1718, 1692, 1472, 1392, 1253, 1085 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ: 8.08 (d, *J*=7.8 Hz, 2H), 7.59 (t, *J*=7.8 Hz, 1H), 7.47 (t, *J*=7.8 Hz, 2H), 5.79–5.68 (m, 1H), 5.52 (br s, 1H), 4.03 (br s, 1H), 3.18–3.35 (m, 2H), 2.69–2.81 (m, 3H), 2.20–2.29 (m, 2H), 2.09–2.20 (m, 2H), 1.81–1.91 (m, 1H), 1.71–1.80 (m, 1H), 1.45 (s, 9H), 0.89 (s, 9H), 0.07 (s, 3H), 0.02 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ: 166.2, 155.7, 133.0, 131.5, 130.3, 129.7, 129.1, 128.7, 128.4, 79.3, 74.6, 74.3, 69.9, 48.2, 47.7, 34.8, 34.4, 32.4, 31.6, 31.5, 28.5, 27.9, 25.7, 22.7, 22.5, 17.9, 14.2, −4.76, −4.82 ppm; HRMS (EI) (M^+−57) calcd for $C_{27}H_{43}NO_5Si$: 489.2911, found 428.2916.

*4.1.12. N-[2-[(5S,6S)-5-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-6-hydroxy-1-cyclohexen-1-yl]ethyl]-N-methyl-carbamic acid-1,1-dimethylethyl ester (**40**).* To a solution of compound **39** (370 mg, 0.76 mmol) in MeOH (5 mL) was added 1 M NaOH (2.3 mL, 2.3 mmol) and the resulting reaction mixture was stirred at rt for 18 h. Brine was added and MeOH was removed on the rotary evaporator. The aqueous layer was extracted five times with ethyl acetate and the organic layers were combined and dried over anhydrous sodium sulfate. The solution was filtered and the solvent was removed under reduced pressure to yield a colorless oil, which was purified by flash column chromatography (hexanes/ethyl acetate 8:1–5:1) to yield compound **40** as a colorless oil (160 mg, 55%). R_f 0.62 (hexanes/ethyl acetate, 2:1); $[\alpha]_D^{23}$ −12.6 (*c* 0.8, $CHCl_3$); IR (film) ν_{max}: 3584, 2976, 2931, 1698, 1482, 1393, 1365, 1162 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ: 5.42 (br s, 1H), 3.87–4.11 (m, 1H), 3.69–3.87 (m, 2H), 2.88 (s, 3H), 2.25–2.45 (m, 1H), 2.08–2.22 (m, 2H), 1.85–2.01 (m, 1H), 1.65–1.79 (m, 1H), 1.58–1.62 (m, 2H), 1.44 (s, 9H), 0.89 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ: 155.5, 129.3, 122.0, 80.1, 75.9, 75.6, 49.9, 48.4, 34.3, 33.5, 32.6, 28.2, 25.4, 25.2, 25.2, 24.3, 24.0, 17.9, −4.6, −4.8 ppm; MS (EI) *m*/*z* (%): 367 (1), 272 (16), 228 (55), 197 (35), 185 (19), 153 (13), 144 (24), 136 (22), 127 (12), 88 (20), 75 (60), 73 (36), 57 (87), 45 (11), 44 (100); HRMS (EI) (M^+−18) calcd for $C_{20}H_{37}NO_3Si$: 367.2543, found 367.2542.

*4.1.13. N-[2-[(5S,6S)-5-Hydroxy-6-(4-nitro-benzoyloxy)-1-cyclohexen-1-yl]ethyl]-N-methyl-carbamic acid-1,1-dimethylethyl ester (**42**).* A magnetically stirred suspension of *cis*-diol **33b** (200 mg, 0.74 mmol) in toluene (5 mL) at 0 °C was treated with *p*-nitrobenzoic acid (369 mg, 2.21 mmol) and triphenylphosphine (291 mg, 1.11 mmol). DIAD (209 mg, 1.04 mmol) was added dropwise and the

reaction mixture was warmed to rt and stirred for 18 h. The reaction was quenched by the addition of a saturated aqueous solution of $NaHCO_3$. The layers were separated and the aqueous layer was extracted with ethyl acetate. The organic layers were combined and washed with brine, dried over anhydrous sodium sulfate, and filtered. The solvent was evaporated and the residue was purified by flash column chromatography (hexanes/ethyl acetate, 12:1–1:1) to give the title compound **42** as a colorless oil (220 mg, 71%). R_f 0.38 (hexanes/ethyl acetate, 1:1); $[\alpha]_D^{22}$ −41.6 (*c* 0.6, $CHCl_3$); IR (film) ν_{max}: 3424, 2977, 2931, 1722, 1692, 1529, 1396, 1270, 1161, 1102 cm^{-1}; ^1H NMR (600 MHz, acetone-d_6) (two rotamers) δ: 8.39 (d, *J*=8.4 Hz, 4H), 8.32 (d, *J*=8.4 Hz, 4H), 5.64–5.81 (m, 4H), 4.38 (br s, 1H), 4.24 (br s, 1H), 4.02 (br s, 2H), 3.60 (br s, 1H), 3.41 (br s, 1H), 3.23 (br s, 1H), 3.08 (br s, 1H), 2.88 (br s, 1H), 2.82 (s, 3H), 2.76 (s, 3H), 2.12–2.39 (m, 8H), 1.88–1.99 (m, 2H), 1.71–1.82 (m, 2H), 1.46 (s, 18H) ppm; ^{13}C NMR (150 MHz, acetone-d_6) (two rotamers) δ: 164.6, 156.3, 150.7, 130.90, 130. 86, 129.1, 123.6, 78.4, 76.5, 75.3, 69.2, 68.8, 68.3, 47.7, 46.6, 33.6, 33.4, 31.6, 31.4, 27.6, 27.5, 22.7, 22.5, 21.9 ppm; MS (EI) *m*/*z* (%): 420 (1), 167 (14), 144 (35), 120 (14), 118 (11), 110 (29), 109 (13), 103 (43), 88 (10), 76 (51), 65 (15), 59 (17), 57 (83), 45 (13), 44 (100); HRMS (EI) calcd for $C_{21}H_{28}N_2O_7$: 420.1897, found 420.1901; Anal. Calcd for $C_{21}H_{27}N_2O_7$: C 59.99% H 6.71%, found C 60.02% H 7.24%.

*4.1.14. N-[2-[(5S,6R)-[6-Hydroxy-5-(4-methylbenzenesulfonyl)-1-cyclohexen-1-yl]ethyl]-N-methyl-carbamic acid-1,1-dimethylethyl ester (**43**).* To a solution of diol **33b** (2.0 g, 7.4 mmol) and tosylchloride (2.5 g, 13.3 mmol) in DCM (20 mL) were added triethylamine (1.9 g, 18.5 mmol) and DMAP (catalytic amount) at 0 °C. The reaction mixture was warmed to rt and was stirred until complete consumption of starting materials (TLC, 18 h). The solution was diluted with DCM (20 mL) and washed three times with a saturated aqueous solution of Na_2CO_3, three times with a saturated aqueous solution of NH_4Cl, and brine. The organic layer was dried over anhydrous sodium sulfate, filtered, and the solvent was removed under reduced pressure. Purification of the crude residue by flash column chromatography afforded the tile compound **43** as colorless oil (1.1 g, 35%) and 0.9 g (45%) of recovered starting material. R_f 0.48 (hexanes/ethyl acetate, 1:1); $[\alpha]_D^{22}$ +107.1 (*c* 0.10, $CHCl_3$); IR (film) ν_{max}: 3400, 2918, 2849, 1689, 1672, 1599, 1483, 1453, 1395, 1364, 1180, 1123, 1098 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) (two rotamers) δ: 7.78–7.92 (m, 2H), 7.31–7.39 (m, 2H), 5.38–5.59 (m, 1H), 4.56–4.69 (m, 1H), 4.00–4.23 (m, 2H), 3.58–3.70 (m, 1H), 3.18–3.39 (m, 1H), 3.00–3.13 (m, 1H), 2.82 (s, 3H), 2.45 (s, 3H), 2.26–2.37 (m, 1H), 2.08–2.19 (m, 2H), 1.95–2.07 (m, 2H), 1.41 (br s, 9H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ: (two rotamers): 156.4, 144.5, 134.3, 134.0, 129.8, 127.8, 127.4, 81.4, 79.6, 68.1, 47.6, 34.0, 33.8, 28.3, 24.3, 23.9, 22.5, 21.7 ppm; HRMS (EI) (M^+−73) calcd for $C_{17}H_{22}NO_5S$: 352.1219, found 352.1228; Anal. Calcd for $C_{21}H_{31}NO_6S$: C 59.27% H 7.34%, found C 59.34% H 7.18%.

*4.1.15. N-[2-[(5S,6S)-[5-(4-Methylbenzenesulfonyl)-6-(4-nitro-benzoyloxy)-1-cyclohexen-1-yl]ethyl]-N-methyl-carbamic acid-1,1-dimethylethyl ester (**44**). 4.1.15.1. By tosylation of alcohol **42**.* To a solution of nitrobenzoate **42** (2.3 g, 5.5 mmol) in DCM (30 mL) were added tosylchloride (5.2 g, 27.4 mmol), triethylamine (7.6 mL, 54.8 mmol), and DMAP (60 mg) at 0 °C. The reaction mixture was warmed to rt and stirred for 22 h, before it was quenched by the addition of water (20 mL). The layers were separated and the aqueous layer was extracted three times with DCM (20 mL). The organic extracts were combined, washed three times with a saturated aqueous solution of Na_2CO_3, three times with a saturated aqueous solution of NH_4Cl, and brine. The organic layers were dried over anhydrous sodium sulfate, filtered, and the solvent was evaporated under reduced pressure. Purification of the crude residue by flash column chromatography (hexanes/ethyl acetate, 9:1–1:1) gave the title compound **44** as colorless solid (2.5 g, 78%). Mp 135–136 °C (hexanes/ethyl acetate); R_f 0.48 (hexanes/ethyl acetate, 2:1); $[\alpha]_D^{23}$ +81.6 (*c* 0.9, $CHCl_3$); IR (film) ν_{max}: 3112, 3054, 2976, 2931, 1730, 1691, 1599, 1529, 1454, 1350, 1266, 1190, 1101, 914 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) (two rotamers) δ: 8.28 (d, *J*=7.9 Hz, 2H), 8.10 (d, *J*=8.8 Hz, 2H), 7.71 (d, *J*=7.9 Hz, 2H), 7.11–7.18 (m, 2H), 5.80–5.88 (m, 1H), 5.73–5.76 (m, 1H), 4.88–4.93 (m, 1H), 3.28–3.45 (m, 1H), 3.08–3.16 (m, 1H), 2.70–2.78 (m, 3H), 2.30 (s, 3H), 2.22–2.28 (m, 2H), 2.09–2.19 (m, 2H), 1.95–2.09 (m, 2H), 1.43 (s, 9H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) (two rotamers) δ: 164.0, 155.6, 150.6, 144.7, 134.0, 131.0, 130.9, 129.2, 129.7, 128.6, 127.6, 123.4, 79.9, 79.6, 79.2, 72.8, 72.4, 47.6, 47.0, 34.2, 31.3, 30.7, 28.5, 26.7, 23.2, 23.0, 21.6 ppm; HRMS (EI) (M^+-73) calcd for $C_{24}H_{25}N_2O_8S$: 501.1326, found 501.1330; Anal. Calcd for $C_{28}H_{34}N_2O_9S$: C 58.52% H 5.96%, found C 58.78% H 6.02%.

*4.1.15.2. By Mitsunobu reaction of alcohol **43**.* To a solution of TBS-protected diol **43** (450 mg, 1.06 mmol) in toluene (10 mL) at 0 °C were added *p*-nitrobenzoic acid (531 mg, 3.18 mmol) and triphenylphosphine (417 mg, 1.59 mmol), followed by the dropwise addition of DIAD (299 mg, 1.48 mmol). The reaction mixture was warmed to rt and stirred for 18 h. The reaction was quenched by the addition of a saturated aqueous solution of $NaHCO_3$. The layers were separated and the aqueous layer was extracted with ethyl acetate. The organic layers were combined and washed with brine, dried over anhydrous sodium sulfate, and filtered. The solvent was evaporated and the residue was purified by flash column chromatography (hexanes/ethyl acetate, 15:1–1:1) to give the title compound **44** as a colorless solid (474 mg, 78%). Data (mp, R_f value, ^1H NMR and ^{13}C spectra, $[\alpha]_D$) were found identical to those of compound **44** obtained by tosylation of alcohol **42**.

*4.1.16. N-[2-[(5S,6R)-[5,6-Dihydroxy-1-cyclohexen-1-yl]ethyl]-N-methyl-carbamic acid-1,1-dimethylethyl ester (**45**).* To a solution of compound **42** (200 mg, 0.48 mmol) in MeOH (3 mL) was added 1 M NaOH (1.43 mL, 1.43 mmol) and the resulting reaction mixture was stirred at rt for 18 h. Brine was added and MeOH was removed on the rotary evaporator. The aqueous layer was extracted five times with ethyl acetate and the organic layers were combined and dried over anhydrous sodium sulfate. The solution was filtered and the solvent was removed under reduced pressure to yield a colorless oil, which was purified by flash column chromatography (hexanes/ethyl acetate, 4:1–1:3) to yield compound **45** as a colorless oil (98 mg, 76%). R_f 0.10 (hexanes/ethyl acetate, 1:1); $[\alpha]_D^{23}$ +17.6 (*c* 1.0, $CHCl_3$); IR (film) ν_{max}: 3430, 2975, 2929, 1695, 1673, 1484, 1397, 1366, 1158, 1048 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 5.34 (br s, 1H), 3.96–4.06 (m, 1H), 3.62–3.78 (m, 2H), 3.58 (br s, 2H), 2.98–3.18 (m, 1H), 2.82 (s, 3H), 2.31–2.43 (m, 1H), 2.20–2.31 (m, 1H), 1.95–2.20 (m, 2H), 1.82–1.95 (m, 1H), 1.55–1.71 (m, 1H), 1.45 (s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 156.7, 134.6, 126.7, 79.8, 74.7, 73.2, 47.8, 34.1, 32.6, 28.5, 28.3, 27.2, 23.7 ppm; HRMS (EI) calcd for $C_{14}H_{25}NO_4$: 271.1784, found 271.1782.

*4.1.17. tert-Butyl-2-(7-oxa-bicyclo[4.1.0]hept-2-en-2-yl)ethylmethyl-carbamate (+)-(**29**). 4.1.17.1. From trans-diol **45**.* A solution of *trans*-diol **45** (80 mg, 0.30 mmol) in THF (1 mL) at 0 °C was treated with bromoisovanillin **34** (205 mg, 0.89 mmol) and triphenylphosphine (116 mg, 0.44 mmol). DIAD (89 mg, 0.44 mmol) was added dropwise and the reaction mixture was warmed to rt and stirred for 18 h. The reaction was quenched by the addition of a saturated aqueous solution of $NaHCO_3$. The layers were separated and the aqueous layer was extracted with ethyl acetate. The organic layers were combined and washed with brine, dried over anhydrous sodium sulfate, and filtered. The solvent was evaporated and the residue was purified by flash column chromatography (hexanes/ethyl acetate, 5:1–1:1) to give the title compound (+)-**29** as a colorless oil (30 mg, 45%). R_f 0.40 (hexanes/ethyl acetate, 2:1); $[\alpha]_D^{22}$ +20.6 (*c* 0.25, $CHCl_3$); IR (film) ν_{max}: 2976, 2931, 1692, 1482, 1393, 1365. 1134 cm^{-1}; ^1H NMR

(600 MHz, $CDCl_3$) δ: 5.63 (d, J=6.6 Hz, 1H), 3.54 (br s, 1H), 3.38–3.53 (m, 1H), 3.12–3.30 (m, 2H), 2.89 (br s, 3H), 2.32–2.48 (m, 2H), 2.16–2.28 (m, 1H), 1.88–2.04 (m, 2H), 1.52–1.60 (m, 1H), 1.48 (s, 9H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ: 155.7, 132.1, 127.3, 79.7, 55.4, 50.2; 48.4, 47.8, 34.8, 34.5, 34.2, 28.5, 20.8, 20.2 ppm; MS (EI) m/z (%): 253 (1), 144 (34), 110 (24), 88 (10), 57 (94), 44 (100); HRMS (EI) calcd for $C_{14}H_{23}NO_3$: 253.1678, found 253.1680; Anal. Calcd for $C_{14}H_{23}NO_3$: C 66.37% H 9.15%, found C 66.37% H 9.09%.

*4.1.18. tert-Butyl-2-(7-oxa-bicyclo[4.1.0]hept-2-en-2-yl)ethylmethylcarbamate (−)-(**29**). 4.1.18.1. From compound **44**.* Compound **44** (1.70 g, 2.96 mmol) was dissolved in THF (30 mL) and 0.5 M sodium methoxide solution in MeOH (7.1 mL) was added dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 1 h, before it was quenched by the addition of a saturated aqueous solution of NH_4Cl (50 mL). The organic solvent was removed under reduced pressure and the aqueous layer was extracted five times with ethyl acetate. The organic extracts were combined and dried over anhydrous sodium sulfate. The solution was filtered and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (hexanes/ethyl acetate, 9:1–3:1) to give the title compound (−)-**29** as colorless oil (0.66 g, 88%). $[\alpha]_D^{22}$ −21.0 (c 0.25, $CHCl_3$).

*4.1.19. N-[2-[(5R,6R)-[5-Hydroxy-6-phenoxy-1-cyclohexen-1-yl]-ethyl]-N-methyl-carbamic acid-1,1-dimethylethyl ester (**46**).* To a solution of epoxide (−)-**29** (50 mg, 0.20 mmol) in DME (0.5 mL) was added potassium phenoxide (52 mg, 0.40 mmol) followed by the addition of 18-crown-6-ether (catalytic amount). The reaction mixture was heated at reflux for 16 h, before it was cooled to rt 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 (hexanes/ethyl acetate, 5:1–1:1) and the title compound **46** was isolated as colorless oil (54 mg, 78%). R_f 0.35 (hexanes/ethyl acetate, 2:1); $[\alpha]_D^{23}$ −33.2 (c 0.59, $CHCl_3$); IR (film) ν_{max}: 3429, 2975, 2928, 1694, 1670, 1596, 1492, 1454, 1396, 1366, 1228, 1164, 1078 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.31 (t, J=7.4 Hz, 2H), 7.07 (d, J=7.4 Hz, 2H), 6.98 (t, J=7.4 Hz, 1H), 5.70–5.73 (m, 1H), 4.69–4.72 (m, 1H), 4.15–4.19 (m, 1H), 3.85–3.93 (m, 1H), 3.63 (d, J=6.4 Hz, 1H), 2.86 (s, 3H), 2.73–2.80 (m, 1H), 2.13–2.32 (m, 3H), 2.04–2.11 (m, 1H), 1.77–1.85 (m, 2H), 1.46 (s, 9H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ: 158.6, 157.0, 130.6, 129.7, 121.1, 115.6, 79.9, 73.6, 66.0, 46.3, 34.0, 32.7, 28.5, 24.4, 20.7 ppm; HRMS (EI) calcd for $C_{20}H_{29}NO_4$: 347.2097, found 347.2084; Anal. Calcd for $C_{20}H_{29}NO_4$: C 69.14% H 8.41%, found C 68.85% H 8.49%.

*4.1.20. N-[2-[(5R,6R)-6-(2-Bromo-3-formyl-6-methoxyphenoxy)-5-hydroxy-1-cyclohexen-1-yl]ethyl]-N-methyl-carbamic acid-1,1-dimethylethylester (**28**).* To a solution of epoxide (−)-**29** (90 mg, 0.375 mmol) in DME (0.5 mL) and DMF (0.5 mL) was added potassium phenoxide derivative **47** (260 mg, 1.126 mmol), followed by the addition of 18-crown-6-ether (catalytic amount). The reaction mixture was heated at 80 °C for 48 h, before it was cooled to rt and diluted with diethyl ether (20 mL). The organic layer was extracted three times with a saturated aqueous solution of Na_2CO_3 (10 mL), ten times with water (0.5 mL) and brine. The organic layer was dried over anhydrous sodium sulfate, filtered, and the solvent was removed under reduced pressure. Purification by flash column chromatography (hexanes/ethyl acetate, 4:1–1:1) gave the title compound **28** (130 mg, 75%) and tricyclic compound **50** (8 mg, 5%). Compound **28**: colorless oil; R_f 0.35 (hexanes/ethyl acetate, 3:2); $[\alpha]_D^{23}$ −93.0 (c 0.2, $CHCl_3$); IR (film) ν_{max}: 3428, 3088, 2975, 2931, 2869, 2741, 1678, 1579, 1482, 1440, 1367, 1276, 1253, 1164, 1029, 938 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 10.27 (s, 1H), 7.73 (d, J=8.6 Hz, 1H), 6.97 (d, J=8.6 Hz, 1H), 5.71–5.75 (m, 1H), 4.78–4.82 (m, 1H), 3.98–4.06 (m, 2H), 3.95 (s, 3H), 3.53 (br s, 1H), 2.89 (s, 3H), 2.80–2.87 (m, 1H), 2.65–2.79 (m, 1H), 2.22–2.37 (m, 2H), 2.03–2.21 (m, 2H), 1.80–1.89 (m, 1H), 1.42 (s, 9H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ: 191.3, 158.1, 157.1, 144.7, 130.9, 130.4, 127.6, 126.1, 123.4, 111.0, 80.0, 76.9, 66.4, 56.1, 46.3, 34.0, 32.8, 28.5, 28.5, 24.3, 20.7 ppm; HRMS (EI) (M^+−73) calcd for $C_{18}H_{21}NO_5$: 410.0603, found 410.0601; Anal. Calcd for $C_{22}H_{30}BrNO_6$: C 54.55% H 6.24%, found C 54.68% H 6.41%.

*4.1.21. tert-Butyl-2-((4aR,10aR)-6-bromo-7-formyl-1,2,4a,10a-tetrahydrodibenzo [b,e][1,4] dioxin-4-yl)ethylmethylcarbamate (**50**).* Colorless oil; R_f 0.42 (hexanes/ethyl acetate, 3:1); $[\alpha]_D^{22}$ +168.3 (c 0.5, $CHCl_3$); IR (film) ν_{max}: 2975, 2931, 2873, 1686, 1591, 1561, 1477, 1392, 1280, 1160, 1052, 969 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d_6) (two rotamers) δ: 10.14 (s, 1H), 7.46 (d, J=8.7 Hz, 1H), 7.12 (d, J=8.7 Hz, 1H), 5.58–5.66 (m, 1H), 4.60–4.79 (m, 1H), 4.10–4.25 (m, 1H), 3.47–3.78 (m, 1H), 2.74–2.88 (m, 3H), 2.52–2.64 (m, 1H), 2.13–2.47 (m, 4H), 1.63–1.87 (m, 2H), 1.28–1.44 (s, 9H) ppm; ^{13}C NMR (600 MHz based on HSQC, DMSO-d_6) (two rotamers) δ: 190.7, 127.9, 123.9, 117.2, 76.5, 75.5, 40.3, 34.1, 30.1, 28.3, 25.7, 23.9 ppm; HRMS (EI) calcd for $C_{21}H_{26}BrNO_5$: 451.0994, found 451.0995; Anal. Calcd for $C_{21}H_{26}BrNO_5$: C 55.76% H 5.79%, found C 56.51% H 5.96%.

*4.1.22. N-[2-[(5R,6R)-6-(2-Bromo-3-formyl-6-methoxyphenoxy)-5-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-1-cyclohexen-1-yl]ethyl]-N-methyl-carbamic acid-1,1-dimethylethylester (**53**).* To a solution of alcohol **28** (15 mg, 0.03 mmol) in diethyl ether (0.5 mL) were added imidazole (8.2 mg, 0.12 mmol) and TBDMSCl (9.1 mg, 0.06 mmol) at −60 °C. The reaction mixture was warmed to rt and stirred at ambient temperature for 18 h. The reaction mixture was diluted with DCM (5 mL) and extracted three times with a saturated aqueous solution of NH_4Cl. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and filtered. Evaporation of the solvent and purification of the crude residue by flash column chromatography gave the title compound **53** as colorless oil (11 mg, 61%). Data for **53** is identical to data of **26b** except for $[\alpha]_D^{21}$ −55.8 (c 0.325, $CHCl_3$); **26b** $[\alpha]_D^{22}$ +59.1 (c 0.35, $CHCl_3$).

*4.1.23. N-[2-[(5aR,6R,9aS)-6-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-1-formyl-6,7-dihydro-4-methoxy-9a(5aH)-dibenzofuranyl]ethyl]-N-methyl-carbamic acid-1,1-dimethylethyl ester (**54**).* Following the same procedure as for the preparation of compound **35b**, using compound **53** (380 mg, 0.64 mmol), $Pd(OAc)_2$ (22 mg, 0.10 mmol), dppf (105 mg, 0.19 mmol), and Ag_2CO_3 (533 mg, 1.91 mmol) as starting materials, gave 301 mg (91%) of compound (−)-**54**. Data for (−)-**54** (^{1}H NMR spectra, R_f value) are identical to those of compound **35b**, except for optical rotation. **54**: $[\alpha]_D^{22}$ −8.5 (c 0.60, $CHCl_3$); **35b**: $[\alpha]_D^{24}$ +12.5 (c 0.60, $CHCl_3$).

*4.1.24. N-[2-[(5aR,6R,9aS)-1-(2-Bromoethenyl)-6-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-6,7-dihydro-4-methoxy-9a(5aH)-dibenzofuranyl]ethyl]-N-methyl-carbamic acid-1,1-dimethylethyl ester (**55**).* Following the same procedure as for the preparation of compound **27b**, using compound (−)-**54** (0.75 g, 1.45 mmol), ylide (prepared by refluxing a solution of triphenylphosphine (15 g, 57.0 mmol) and methylene bromide (22.3 g, 115 mmol) in toluene (100 mL) for 24 h. The mixture was cooled to 0 °C and the precipitate was collected by filtration. The product was washed with toluene and dried under reduced pressure (1.26 g, 2.90 mmol), and potassium *tert*-butoxide (0.31 g, 2.76 mmol), gave 344 mg (40%) of compound **55**. Data for **55** (^{1}H NMR spectra, R_f value) are identical to those of compound **27b**, except for optical rotation. **55**: $[\alpha]_D^{21}$ −37.1 (c 1.30, $CHCl_3$); **27b** $[\alpha]_D^{21}$ +46.6 (c 1.20, $CHCl_3$).

*4.1.25. N-[2-[(3R,3aR,9aR,9bS)-3-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-3,9a-dihydro-5-methoxyphenanthro[4,5-bcd]furan-9b(3αH)-yl]ethyl]-N-methyl-carbamic acid-1,1-dimethylethyl ester (**56**).* Following the same procedure as for the preparation of compound **36b**, using compound (−)-**55** (325 mg, 0.55 mmol), $Pd(OAc)_2$ (31 mg, 0.14 mmol), dppp (111 mg, 0.27 mmol), and Ag_2CO_3 (451 mg, 1.64 mmol) as starting materials, gave 127 mg (45%) of compound **56**. Data for **56** (^{1}H NMR spectra, R_f value) are identical to those of compound **36b**, except of optical rotation: $[\alpha]_D^{22}$ +22.1 (*c* 0.3, $CHCl_3$).

*4.1.26. N-[2-[(3S,3aR,9aR,9bS)-3,9a-Dihydro-3-hydroxy-5-methoxyphenanthro[4,5-bcd]furan-9b(3αH)-yl]ethyl]-N-methyl-carbamic acid-1,1-dimethylethyl ester (**57**).* Following the same procedure as for the preparation of compound **37**, using compound **56** (125 mg, 0.24 mmol) and TBAF (0.27 mL, 1 M in THF) as starting materials, gave 72 mg (72%) of alcohol **57**. Data for **57** (^{1}H NMR spectra, R_f value) are identical to those of compound **37**, except for optical rotation. **57**: $[\alpha]_D^{21}$ +68.5 (*c* 0.65, $CHCl_3$); **37** $[\alpha]_D^{21}$ −80.5 (*c* 1.20, $CHCl_3$).

*4.1.27. (3S,3aR,9aR,9bS)-3,3a,9a,9b-Tetrahydro-5-methoxy-9b-[2-(methylamino)ethyl]-phenanthro[4,5-bcd]furan-3-ol (**58**).* To alcohol **57** (70 mg, 0.18 mmol) dissolved in DMF (2 mL) was added IBX (49 mg, 0.18 mmol) at rt. The reaction mixture was stirred at rt for 2 h (TLC indicated unreacted starting material) and additional IBX (15 mg, 0.05 mmol) was added. After complete consumption of starting material (TLC) the reaction mixture was quenched with water (20 mL). The phases were separated and the aqueous phase was extracted with DCM (3×20 mL). The organic layers were combined, washed with a saturated aqueous solution of $NaHCO_3$, then dried over anhydrous sodium sulfate. Filtration and removal of the solvent under reduced pressure gave the crude product, which was purified by flash column chromatography (DCM/ethyl acetate, 9:1–4:1) to afford 60 mg of a mixture of two compounds. Exhaustive purification by flash column chromatography gave 7 mg in 90% purity of compound **58** and 50 mg of a 1:1 mixture of compounds (**58** and a yet unidentified byproduct). Data for **58** (^{1}H NMR spectra, R_f value) are nearly identical to its enantiomer obtained during the preparation of **37**, except for optical rotation. **58**: $[\alpha]_D^{22}$ −59.2 (*c* 0.35, $CHCl_3$); corresponding enantiomer of the enone produced in the conversion of **36b** to **37**: $[\alpha]_D^{21}$ +61.4 (*c* 1.4, $CHCl_3$).

*4.1.28. (−)-Codeine (**2**).* To a mixture of compounds (1:1, **58** and unidentified byproduct) (50 mg) dissolved in methanol (1 mL), was added $CeCl_3 \cdot 7H_2O$ (70 mg, 0.19 mmol). The reaction mixture was stirred at ambient temperature for 5 min and then cooled to 0 °C. $NaBH_4$ (5 mg, 0.14 mmol) was added in one portion and the mixture was stirred at 0 °C for 20 min. The solvent was removed under reduced pressure and the residue was suspended in DCM (10 mL). The organic layer was washed with a saturated aqueous solution of NH_4Cl (10 mL), dried over anhydrous sodium sulfate, filtered and the volatiles were removed under reduced pressure. The residue was purified by flash column chromatography (DCM/MeOH, gradient and DCM/ethyl acetate, gradient) to give 38 mg of a mixture of compounds (1.25:1).

To this mixture of compounds (38 mg) dissolved in DCM (1 mL) was added trifluoroacetic acid (0.25 mL) dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 2 h and then the solvent was removed under reduced pressure. The residue was suspended in $CHCl_3$ and washed with a saturated aqueous solution of Na_2CO_3 and brine. The aqueous layers were combined and extracted with $CHCl_3$. The organic layers were combined, dried over anhydrous magnesium sulfate, filtered, and then the solvent was evaporated. The crude product was purified by flash column chromatography (DCM/MeOH, 4:1) to give 28 mg of a mixture of compounds (1.25:1).

This mixture of compounds (28 mg) dissolved in THF (1 mL) was added to a mixture of $Hg(OAc)_2$ (45 mg, 0.14 mmol) and triethylamine (33 μL, 0.23 mmol) in THF (1 mL). The mixture was stirred for 48 h and then a solution of LAH in THF (10 mg, 0.25 mmol in 1 mL of THF) was added dropwise. The reaction mixture was stirred for 2 h and then quenched with saturated aqueous solution of Na_2CO_3 (2 mL). The aqueous phase was extracted with $CHCl_3$ (3×3 mL). The organic layers were combined and dried over anhydrous sodium sulfate. The mixture was filtered and the solvent was evaporated under reduced pressure. The concentrated product (26 mg) was purified by flash column chromatography (DCM/MeOH/NH_4OH, 100:0:0–90:10:1) affording (−)-codeine (4.2 mg, 0.014 mmol, 8% over four steps). Data for (−)-codeine (**2**) (^{1}H NMR spectra, R_f value) are identical to those of (+)-codeine (**2**); $[\alpha]_D^{20}$ −124.6 (*c* 0.15, EtOH), (lit.[7b] $[\alpha]_D^{27}$ −137 (*c* 1.15, EtOH)).

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Supplementary data

General methods, experimental data for compounds **33a**, **25a**, **26a**, **35a**, **27a**, **36a**, **59**, **56** (from **59**), and copies of proton and carbon spectra for all reported compounds are provided. Supplementary data associated with this article can be found in online version, at doi:10.1016/j.tet.2009.09.052.

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