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Toward a Practical Synthesis of Morphine. The First Several Generations of a Radical Cyclization Approach[1]

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Received 4 September 1997; revised 3 November 1997

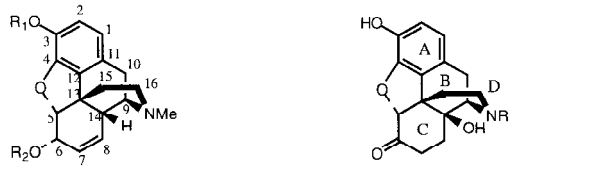
Abstract: A radical cyclization approach to the complete skeleton of morphine was investigated in several iterations. The first attempt at a radical cascade via a Bergman-type intermediate derived from ene-diyne **10** failed during a model study in which 10-membered silicon-tethered ene-diyne **17** proved inert to Bergman cyclization conditions. A second model study involving ene-diyne **27**, functionalized with an allyl group, underwent Claisen rearrangement to **32** in preference to a Bergman-type cyclization. Several simple model studies were performed with bromophenols appended to protected diols **40** and **50**, respectively, to determine the feasibility of C12–C13 bond formation in the former case and the cascade closure C12–C13/C14–C9 in the latter via radical species generated from the aryl halides. The second-generation approach employed the diene diol **7a** derived biocatalytically from β-bromoethylbenzene via oxidation with *E. coli* JM109(pDTG601), its conversion to cyclization precursor **55**, and the radical cyclization to **56a**,**b**. The conditions and the outcome of this process are discussed in detail along with the rationalization of stereochemistry of the cyclization, which furnished C14-*epi* configuration in **56a** in low yield.

The third-generation synthesis relied on stepwise radical cyclization of vinyl bromide **67** derived from *o*-bromo-β-ethylbenzene (also by biocatalytic means) and equipped with an oxazolidone as the radical acceptor group. Isoquinoline derivatives **68a** and **68b** were obtained as a mixture of isomers, the major of which, **68a**, was converted via a second tin-mediated cyclization to the pentacyclic compound **78**, also possessing C14-*epi* configuration. The stepwise radical cyclization proceeded in higher yields, produced cleaner reaction mixtures, and was also performed with the more flexible alcohol **87**, whose tin-mediated closure produced a 1:1 mixture of C14 epimers, tetracyclic compounds **81** and **89**. Finally, tetracycle **80** or pentacycle **79** was converted to oxo aldehyde **83** and cyclized to the complete morphinan skeleton, **84**, in the *ent*-C14-*epi* series. Additionally, preliminary studies were performed on direct closures of chloride **82** to **85**, via a C10/C11 alkylation of a sp^3-hybridized center. The three generations of synthetic effort are discussed in detail and physical and spectral data are provided for all new compounds. The relative merits of tandem *vs.* stepwise radical cyclization are evaluated and projections for future work are indicated.

Key words: enzymatic dioxygenation, radical cyclization, isoquinoline alkaloids, approach to (+)-morphine, *ent*-morphinans

Introduction

The consumption of morphine[1] (**1**) in the United States is approaching one hundred metric tons annually.[2] The world's oldest drug on record,[3a] today used routinely as both an analgesic and an anesthetic,[3b] is available by commercial processing of raw opium from *Papaver somniferum* grown in those latitudes that favor the biogenesis of morphinans.[4] As of this writing, all morphine for medicinal as well as illicit use originates in natural sources. Despite years of research focused on plant tissue culture production and microbial transformations of morphine alkaloids[5] as well as the enzymology of morphine biogenesis,[6] the probability of large scale production by biological means remains uncertain, at least for the foreseeable future. Equally elusive has been the effort by the synthetic community to furnish morphine in a manner that would rival isolation in terms of economics. Morphine serves as a convenient starting material for other medicinally important substances (Figure 1) such as codeine (**2**), as well as for the (illicit) production of heroin (**3**). Various antagonists, such as naloxone (**4**) and naltrexone (**5**), are chemically synthesized via noroxymorphone (**6**) and its derivatives, themselves produced from morphine by semisynthesis.



1 $R_1 = R_2 = H$, morphine[7a]
2 $R_1 = Me$, $R_2 = H$, codeine[7b]
3 $R_1 = R_2 = Ac$, heroin[7c]
4 R = allyl, naloxone
5 R = cyclopropylmethyl, naltrexone
6 R = H, noroxymorphone

Figure 1. Common Morphine-Derived Alkaloids in Use Today

Since Gates' first synthesis[8a] of morphine in 1956 there have been fewer than twenty total or formal total syntheses of morphine[8] reported in the literature, all recently reviewed.[9] The most efficient to date, that of Rice,[8i] provided the title alkaloid in 29% overall yield, still not sufficiently competitive with isolation. There have also been many ingenious approaches to the architecturally difficult skeleton of morphine.[10] It is clear from the combined synthetic experience of those organic chemists who have together committed 40+ years of serious effort toward a concise and practical synthesis that morphine stands out as a target of difficulty. In this manuscript, we report the first few iterations of an approach based on a cascade of bond-forming reactions which furnished the skeleton of **1** in 13 steps: an accomplishment far removed from the goal of achieving the entire synthetic sequence in under 8 steps; nevertheless, it is a valuable first step.

Results and Discussion

We selected several topologically independent strategies to approach the morphine synthesis in a practical manner. Biomimetic in principle continues to be our approach via the intramolecular Diels–Alder reaction, the initial results[11] of and recent progress[12] of which, have been disclosed. The approach discussed herein evolved from considerations of a radical cascade as the most efficient means of the rapid assembly of the carbon skeleton (Fig-

ure 2). The question of stereoselectivity in such a cascade was unclear, especially with respect to the C14 stereocenter, which has proved notoriously difficult to control in many of the reported syntheses. Nevertheless, we initially placed the overall brevity of the assembly above stereoselectivity issues in ultimate importance.

The Bergman Cascade Approach. The idea of simultaneously creating ring A and a phenyl radical for a cyclization cascade[13] is shown in Figure 2. The original concept assumed that diene **7a**[14a] would be derived via fermentation of β-bromoethylbenzene with *P. putida*[15] and its recombinant organisms available through the efforts of Gibson.[16] This particular diene diol and others derived from β-substituted ethyl benzenes, have recently been used in several synthetic ventures.[12,17,18]

After alkylation of oxazolidone **8** with **7b** protected at the distal hydroxyl, the free alcohol was envisioned as a nucleophilic partner for the coupling with diyne epoxide **9** in an overall equivalent of the Williamson ether synthesis of the intermediate aryl ether **11**. Note that the electronics of this design are opposite to those of traditional Williamson syntheses, i.e., the alkyl, not the aryl unit bears the nucleophilic oxygen. The oxidation of the *trans*-diol derived from **9** would provide the hydrogen bonded species **10** whose tendency toward Bergman cyclization should be the function of interatomic distance *c–d* between the acetylenic termini. The aryl diradical **11** would undergo cyclization and yield **12** after protodesilylation of the silicon tethers introduced to control *c–d* distance in **9** and **10**. The precedent for cyclization of 10-membered ene-diynes that possess the structural features of **9**, found in compounds **13–16**, was indeed favorable as shown in Figure 3. Molecular dynamics (Cache) performed on a truncated version of **10**, namely **17**, predicted a cyclization temperature of 60–75 °C with *c–d* distance of 3.38 Å. From the literature data it is expected that the ene-diynes having a *c–d* distance less than 3.20 Å suffer spontaneous closure while those with a *c–d* distance greater than 3.20–3.31Å are stable at ambient temperature.[21]

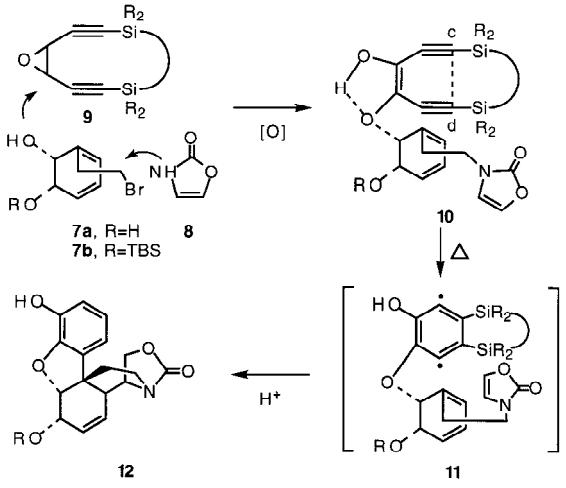


Figure 2. Bergman Cyclization Approach to Morphine

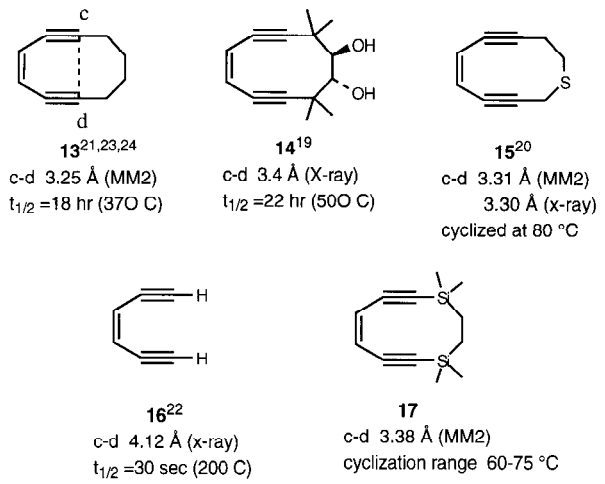
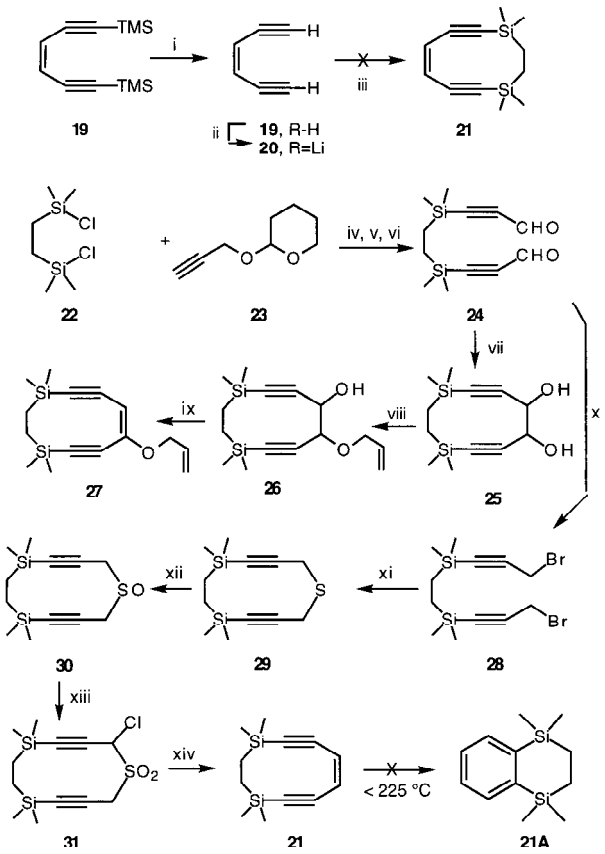


Figure 3. Cyclization Parameters of some Bergman Precursors

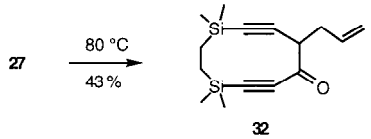


Reagents: i LiOH, THF, H_2O, ii BuLi, THF, iii bis(chlorodimethylsilyl)ethane, iv EtBr, Mg, v H_3O^+, vi CrO_3, vii SmI_2, viii Bu_2SnO, allyl bromide, ix Tf_2O, pyridine, CH_2Cl_2 then DBU, r.t., x CBr_4, PPh_3, CH_2Cl_2, xi Na_2S, xii MCPBA, xiii a) SO_2Cl_2, CH_2Cl_2, –78 °C b) MCPBA, CH_2Cl_2, 0 °C, xiv MeLi.

Scheme 1

With this information we undertook the synthesis of a model system with structural features of **10** as shown in Scheme 1. The ene-diyne **21** was synthesized in yields not exceeding ~20% by two rather laborious routes. In the first of these, Vollhardt's method of coupling *cis*-dichloroethylene with trimethylsilyl acetylene[25] was adapted to produce **18** which was subjected to desilylation in aque-

ous LiOH and the free bisacetylene **19** metalated with BuLi. The dianion **20** was quenched to produce the ten-membered ene-diyne **21** in low yields, with recovery of the material complicated by its volatility. The second route, Scheme 1, relied on the SmI_2-mediated McMurry-type coupling[26] of the known dialdehyde[27] **24** derived by oxidation of the corresponding diol. This material was available in reasonable yield by a known procedure from protected propargylic alcohol **23**. Diol **25** was initially subjected to several procedures for elimination, including a Corey–Winter[28] reaction which had shown some success for Semmelhack.[24] No ene-diyne was detected in any of these reactions. We chose an alternate route from diol **24**, which was converted, via dibromide **28**, to a cyclic sulfoxide, and ultimately taken to the Ramberg–Backlund precursor **31**.[29] Treatment of the chlorosulfone with MeLi at –78 °C in diethyl ether afforded a low yield of **21** (<20%). Disappointingly, it has been shown to be stable to thermolysis up to 225 °C and no cycloaromatization to the expected and independently synthesized product **21a** was detected. Despite the predicted geometry and *c–d* distance, which bode favorably for a low reaction temperature, the material proved inert and this was attributed, at least for the moment, to the electronic effect of tethering silicon atoms. Several cases reported in the literature describe long-range effect of silicon tethers on the cyclization rates and attendant temperatures occasionally requiring > 600 °C.[27] The final evidence for the probable lack of utility of this cascade approach became available by thermolysis of enol ether **27**, whose cyclization parameters portrayed, quite accurately, those foreseen in compound **10**. The enol ether was prepared from diol **25** by monoallylation[30] and subsequent elimination of the allyl mesylate. At the predicted cyclization temperature of 65 °C this material was found completely inert. After 60 hours at 80 °C the starting material was consumed. No evidence of Bergman-type products was found but ketone **32** was isolated in 43% yield, indicating that the energetics for the Claisen rearrangement in **27** are more favorable than Bergman cyclization. The project was abandoned at this point until such time that a solution to the detrimental influence of silicon tethers is found.



The Tandem Radical Cyclization. Because of the failure of the Bergman cyclization approach, in which the aryl radical would have been generated in situ, we chose a more direct route where the required radical species originated in the reduction of an aryl halide. One of the apparent advantages of this approach, depicted in Figure 4, was the possibility of incorporation of several enzymatic transformations into the synthetic pathway. Diol **7a** remains accessible from β-bromoethylbenzene through the first oxidation step in the natural degradation pathway of arenes in the wild strains of *Pseudomonas putida*.[31]

The second step in the pathway utilized by the wild strain consists of further oxidation of the arene-*cis*-diol by cate-

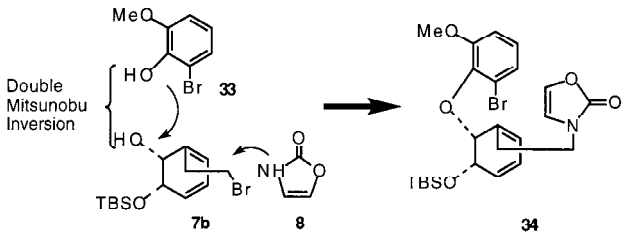
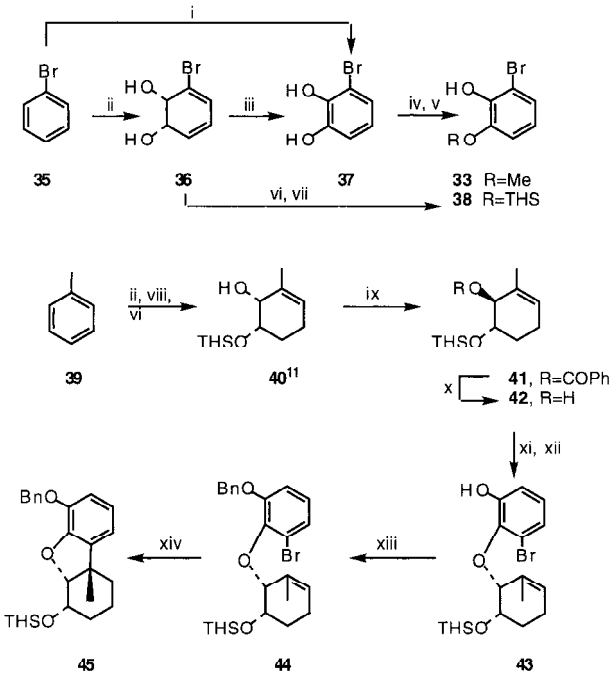


Figure 4. Tandem Radical Cyclization Approach

chol dehydrogenase to a catechol which then suffers an *ortho* cleavage and is ultimately channeled through further enzymatic steps to acetate as a carbon source for the organism. Gibson developed not only blocked mutants[15] of *Pseudomonas* but also recombinant strains[16] of *E. coli* in which further enzyme expression beyond either the first step [*P. putida* 39/D; *E. coli* JM109(pDTG601)] or the second step [*E. coli* (pDTG602)][16] is arrested. Thus the required catechol **33** can be obtained from bromobenzene by the use of the latter mutant organism and one further chemical step, namely selective alkylation of the "distal" phenol group.

Model Study: C12–C13 bond. To validate the chemistry contained in this approach, we chose the simplest system, capable of only a single radical closure, as shown in Scheme 2. The required catechol **33** was prepared from bromobenzene or 2-methoxyphenol as previously reported by Hoshino[32] and used as a nucleophile in the second Mitsunobu inversion[33] of the alcohol **42** derived from toluene diol via alcohol **40**.[11] For the initial model study the thexyl derivative **38** was chosen because we had not yet manufactured the catechol enzymatically and this material was prepared by a protection/oxidation sequence from **36**.

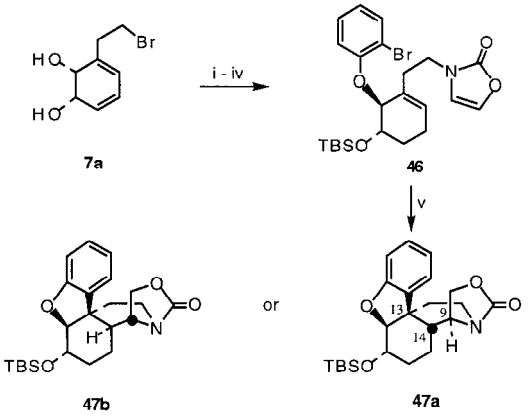


Reagents: i *P. putida* TG02C, ii JM109 (pDTG601), iii Jones oxidation, iv MeI, acetone, v TMSI, vi THSCl, imidazole, DMF, vii oxalyl chloride, DMSO, Et_3N, -78 °C to 0 °C, viii potassium azodicarboxylate, HOAc, ix benzoic acid, Bu_3P, DEAD, THF, x NaOMe, MeOH, xi **38**, Bu_3P, DEAD, THF, xii H_3O^+, xiii benzyl bromide, K_2CO_3, acetone, xiv Bu_3SnH, AIBN, toluene, reflux.

Scheme 2

The first Mitsunobu inversion provided the benzoate **41**, from which transesterification with NaOMe in MeOH liberated the alcohol **42**. The second Mitsunobu reaction of alcohol **42** and thexyloxy bromophenol **38** gave ultimately derivative **44**, after the labile thexyl group in the condensation product had been replaced by a benzyl moiety in **43**. The protected ether **44** was exposed to AIBN/Bu_3SnH in refluxing toluene to afford a 50 % yield of tricycle **45** containing three of the five stereogenic centers of morphine in the correct absolute configuration. With this promising result we turned to the assembly of the entire morphine skeleton.

Model Study: C14–C9 bond. To provide initial information about the relative stereochemistry at C14–C9, traditionally the pitfall of most syntheses of morphine, we designed a simple model cyclization shown in Scheme 3. The less substituted alkene in diene diol **7b** was reduced with diimide and the C6-hydroxyl protected as a TBS-ether (See structures **49** and **50**, Scheme 4). Mitsunobu reaction with *o*-bromophenol, followed by displacement of the primary alkyl bromide with the sodium salt of oxazolidone **8**, furnished the protected *trans*-diol **46** which was exposed to Bu_3SnH/AIBN in refluxing toluene to furnish pentacyclic product **47** in approximately 10% yield. ^1H NMR analysis established the relationship of the C14–H and C9–H as *trans*; however, it was not possible to discern the configuration relative to C5 or C6 and the product was assigned as either **47a** or **47b**.

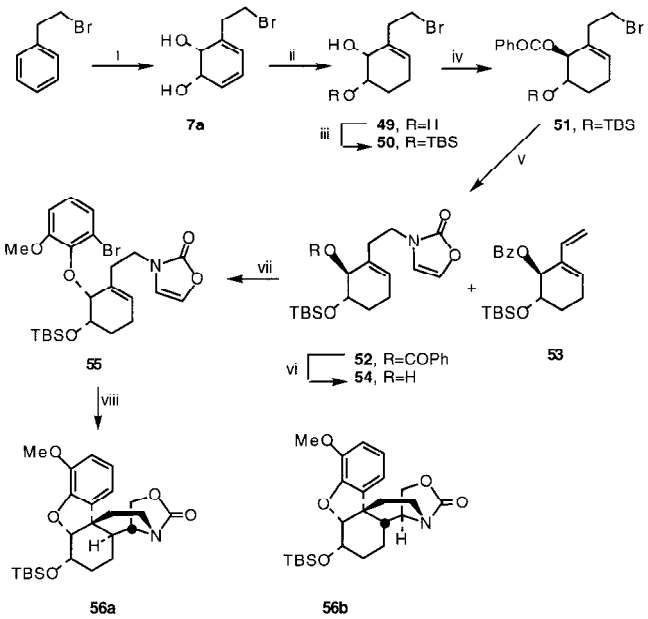


Reagents: i potassium azodicarboxylate, AcOH, ii TBSOTf, iii *o*-bromophenol, Bu_3P, DEAD, THF, iv NaH, 2-oxazolidone, v Bu_3SnH, AIBN.

Scheme 3

The results of the two aforementioned model studies validated the premise of the tandem radical cyclization considered for the assembly of the morphine skeleton. Conceptually similar to the strategy employed by Parker[8p] (except for the connectivity of C11–C10–C9 atoms) the proposed sequence would create the two crucial bonds (C12/C13 and C14/C9) in a cascade manner and it was assumed that the C14/C9 stereochemistry would be subject to some degree of control (*vis-à-vis* Parker's experience). The two novel issues in our approach were the anticipated C10/C11 closure of an otherwise intact skeleton and the incorporation of chirality into ring C by the enzymatic oxidation. [Note: The compounds synthesized in the course of the model studies as well as those prepared during the study of the Bergman cyclization (**21**, **25–32**, **41–47**) were characterized only to permit the ultimate judgment as to the future merits of that particular approach. All of the compounds have either led to a dead end investigation or validated the completion of a preliminary model study and therefore were not characterized as fully as the intermediates in the subsequent application (see Experimental Section for partial characterization of these intermediates)].

Tandem Radical Cyclization: First Generation. Based on the results of the simple model studies we turned to the objective of assembling the entire morphine skeleton. *β*-Bromoethylbenzene was subjected to enzymatic dihydroxylation to yield the homochiral diol **7a**[14a] which was reduced to give **49**,[14a] protected as a TBS-ether at the distal hydroxyl group (**50**) and further transformed via a Mitsunobu inversion to benzoate **51**, in 85 % yield (Scheme 4). The alkylation of this material with oxazolidone **8** did not proceed without problems. As reported in a preliminary communication, elimination to diene **53** took place quite readily; in principle this diene could be "recycled" via a hydroboration/oxidation/displacement sequence to furnish better yields of **52** (See Scheme 6 for recycling of a similar compound, **71**[14b]). Hydrolysis of the benzoate and Mitsunobu inversion of the alcohol with bromophenol **33** gave the penultimate precursor for the radical cyclization, ether **55**, which was exposed to $(TMS)_3SiH$/AIBN to afford a complex mixture of more than six products. Laborious chromatographic separation provided no more than a modest 15% yield of the pentacyclic material **56a**, whose analysis by NMR techniques established the *epi*-C14 configuration as shown. Although not identified unambiguously, the isomer **56b** was also isolated as a minor



Reagents: i JM109(pDTG601), ii potassium azodicarboxylate, AcOH, iii TBDMSOTF, CH_2Cl_2, iPr_2NEt, iv benzoic acid, nBu_3P, DEAD, THF, v 2-oxazolidone, NaH, DMSO, vi aq NaOH, vii **33**, nBu_3P, DEAD, THF, viii $(TMS)_3SiH$, AIBN, benzene, 140 °C, sealed tube

Scheme 4

product. Among the various byproducts isolated from the reaction mixture we also identified the enol ether **58** which probably originated in the hydrogen abstraction route shown in Figure 5. The stereochemistry of the two protons in **58**, corresponding to C14 and C9 of morphine, was established as *trans*, but the relative stereochemistry with respect to C6 remained undetermined.

A few comments regarding the course of this cascade sequence are in order. First, the reaction produced complex mixtures which proved very difficult to separate and monitor by traditional methods (TLC, HPLC). Second, the course of the crucial C14–C9 bond formation would become extremely difficult to evaluate without the accurate knowledge of the stereochemical identity of all products which originated in the double closure. Third, the conformations of the radical species at C14 prior to the closure will depend on the bulk of the substituent at the C6 oxygen as well as the exact placement of the oxazolidone ring at the time of bond formation. (See Figure 6 for the likely possible conformation of the intermediate radical species **59**). Finally, the radical closure of a species derived from the unreduced diene **60** would produce the allylic radical **61** (Figure 7) whose fate in further bond formation would be affected by the additional 10–12 kcal/mol of allylic stabilization. The comparison of the four possible conformations in both **56** and **62** indicates that the transition state "b", leading in both cases to the correct C14–C9 stereochemistry, is the least concave of the four conformers.

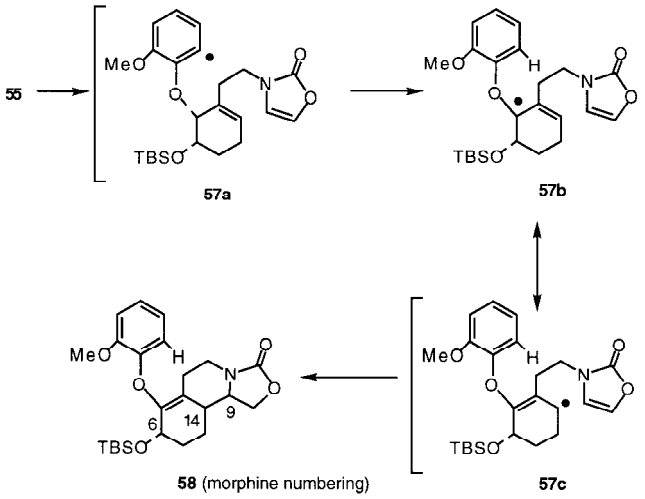


Figure 5. Formation of Enol Ether **58** by Intramolecular H-Abstraction

The possibility for stereocontrol through the manipulation of the peripheral protecting groups could be pursued in future studies. The conformations of **56** and **62** illustrate the difficulty in predicting the precise outcome of C14–C9 stereochemistry. Consequently, we turned to the examination of a stepwise radical cyclization approach in which the C9 stereochemistry would be set in the first step and the steric fate of C14 would become dependent on the facial selectivity of a hydrogen abstraction process, rather than the relatively slower bond-forming process. As it turned out following this particular study, the two strategies can be related analytically with regard to the conformations (See Figures 6 and 7).

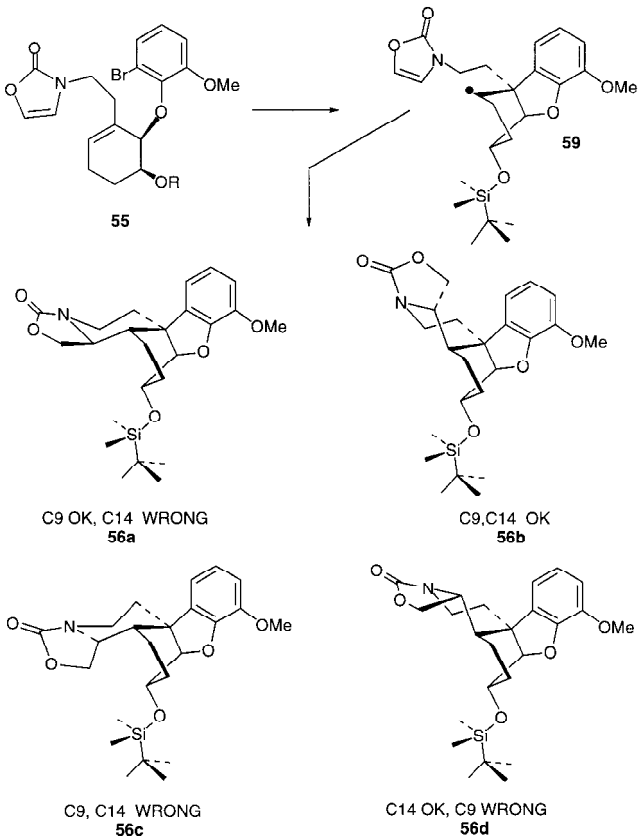


Figure 6. Conformations of the Four Possible Isomers at C14/C5

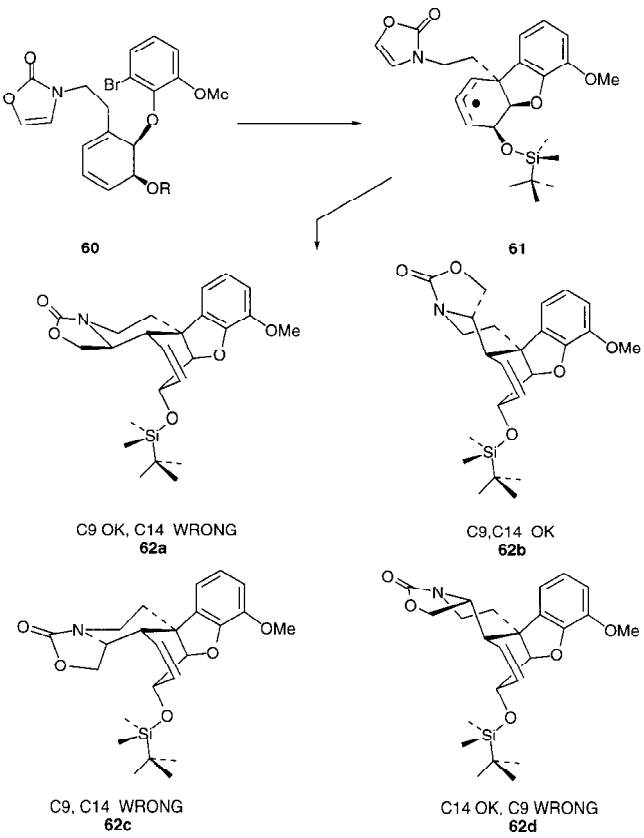
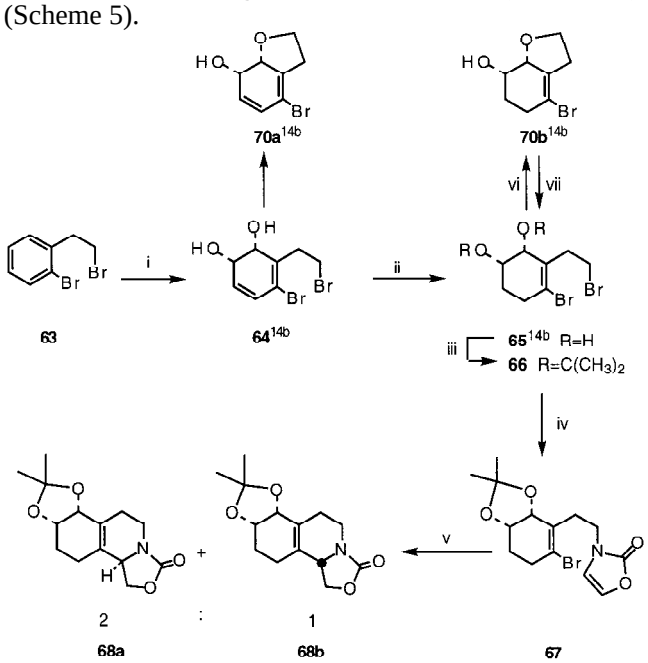


Figure 7. Conformation of Isomers in Which Ring C Retains Unsaturation

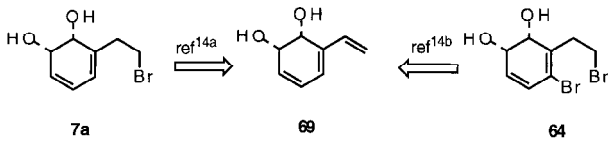
Stepwise Radical Cyclization: Second Generation. The biooxidation of *o*-bromo-*β*-bromoethylbenzene was examined with the expectation that the larger *β*-bromoethyl group would direct the enzymatic placement of the *cis*-diol. Fortuitously, this turned out to be the case and diol **64**[14b] was isolated from the broth of fermentation of **63** with recombinant organism *E. coli* JM109(DTG601A), (Scheme 5).



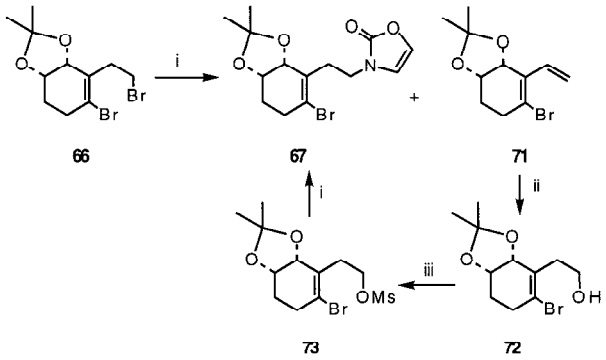
Reagents: i JM109(pDTG601A), ii potassium azodicarboxylate, AcOH, iii 2,2-dimethoxypropane, *p*TSA, iv 2-oxazolone, NaH, DMSO, v *n*Bu_3SnH, AIBN, benzene, reflux, vi Cs_2CO_3, acetone, vii Et_4NBr, $BF_3.Et_2O$, CH_2Cl_2.

Scheme 5

The structure and absolute stereochemistry of **64**[14b] was determined, along with the absolute stereochemistry of **7a**,[14a] by correlation with the styrene-derived *cis*-diol **69**,[34] whose absolute configuration has been firmly established.[35] The yields of **64** were low and the mass balance of **64** and starting material **63** proved extremely low. We attributed this yield problem to the differences in the intracellular transport rates for the two compounds. While the yield of **7a** is among the highest for any arene *cis*-diol (>10 g/L), diol **64** became available in 200 mg/L with over 50% of the fate of **63** unaccounted for. Nevertheless, we proceeded with the synthesis under the assumption that the biooxidation would be optimized in the future, were this approach found synthetically viable. Note also that the presence of benzofuran derivatives **70a** and **70b** contributed to the low yield of either **64** or **65**. In the latter case **65** was regenerated from **70b** as shown in Scheme 6 and as previously described.[14b]



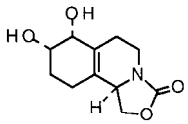
Reduction of the diene in **64** with potassium azodicarboxylate followed by the introduction of oxazolone provided **67** along with a substantial amount of styrene **71** resulting from the base-induced elimination. This material was "recycled" as shown in Scheme 6 by a hydroboration/oxidation/mesylation sequence, to provide useful quantities of the cyclization precursor.



Reagents: i 2-oxazolone, NaH, DMSO, ii 9-BBN, THF, followed by H_2O_2/NaOH, iii MsCl, *i*Pr_2NEt, CH_2Cl_2.

Scheme 6

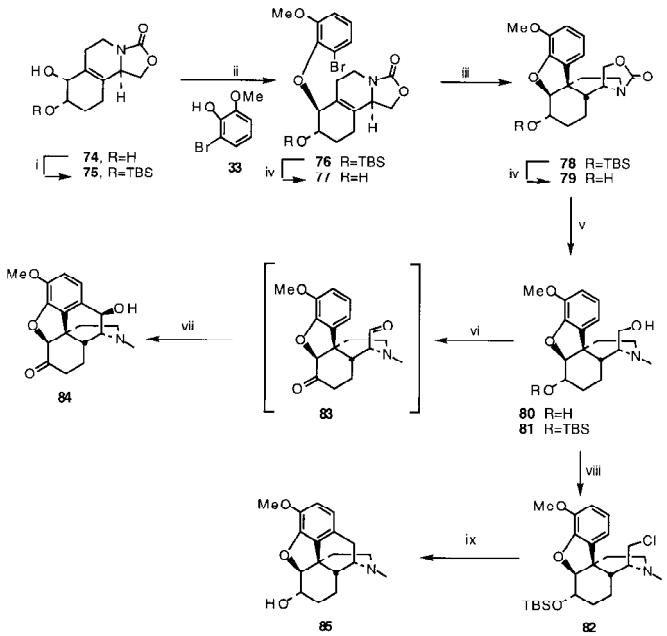
Exposure of **67** to Bu_3SnH/AIBN provided octahydroisoquinolines **68a** and **68b** in a 2:1 ratio in favor of the isomer possessing the *epi*-C9 configuration. The lack of selectivity in the closure may be attributed to the marginal steric effect of the distant acetonide moiety. The combined yield of the cyclization was high and the two compounds were easily isolated from a clean reaction mixture. The stereochemistry of **68a** was determined by a single crystal X-ray crystallography of the free diol **74**.[1]



Because of the greater availability of **68a** we chose to pursue the synthesis of the *ent*-morphine skeleton, since only a single Mitsunobu inversion is required for the introduction of the catechol moiety. An assumption was made that the synthesis of *ent*-morphine would be an appropriate model study for the approach to the natural enantiomer from **68b** at such time as the control in setting the C9 center would either be absolute in either direction, or at least lead to a 1:1 mixture of isomers. In the latter event the synthesis would be enantiodivergent from the same intermediate, mimicking the strategy of Rice.[8i]

A Mitsunobu inversion with phenol **33** generated the precursor for the second cyclization, ether **76**,[1] whose exposure to Bu_3SnH/AIBN gave a clean yield of pentacycle **78**, Scheme 7.[1] The stereochemistry at C14 was determined to be in the *epi* configuration (the coupling constant between C14 and C9 was found to be 11 Hz, see Experimental Section), presumably because the final act of hydrogen atom abstraction occurred from the convex face of the conformer **86a**. A reasonable explanation of this stereochemical outcome is to invoke the rigidity of the 6-5 system and the reluctance to favor the conformation **86b** in which the concave face would be more accessible. That

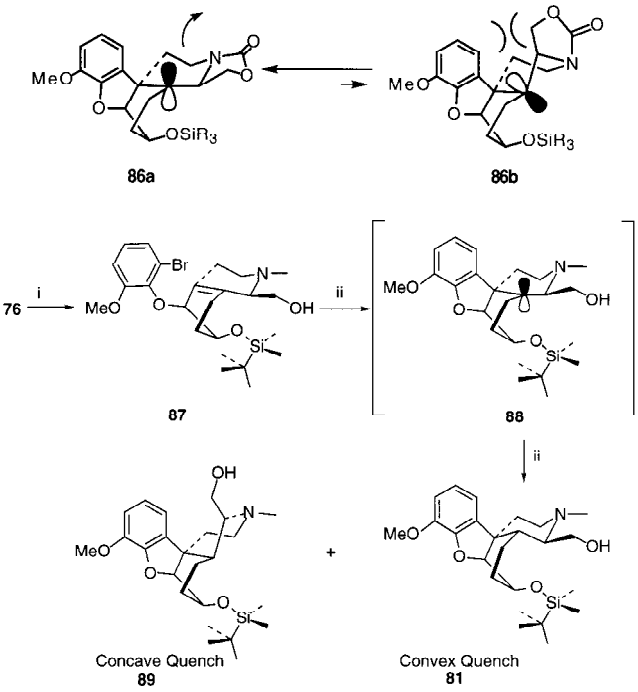
the reason for exclusive *epi*-C14 quench was not the presence of the bulky silyl group was ascertained by performing the cyclization on the free alcohol **77** and obtaining **79** with the same result: *epi*-C14 configuration, Scheme 7. The above arguments became even more credible when the cyclization was performed on the more flexible system such as alcohol **87**, Scheme 8. The reduction of the oxazolidone moiety, usually performed on **78** after the cyclization to generate **81** and prepare the C10 center for the final connection to C11, was done with **76** instead, generating **87** which was subjected to the radical cyclization. With this substrate, a 1:1 mixture of C14 epimers, **81** and **89**, was isolated confirming the fact that the silyl group located on the concave face of the intermediate radical **88** had no influence on the final quenching event. Rather it is the increase in the flexibility of the system that allows **88** to adopt the less concave conformation leading to **89** in addition to that leading to **81**, Scheme 8. In future studies, the control of stereochemistry will be enhanced by designing a cyclization precursor that will favor maximization of the conformation apparently operating in the formation of **89**.



Reagents: i TBSTf, iPr$_2$NEt, CH_2Cl_2, –78°C, ii **33**, nBu_3P, DEAD, THF, iii nBu_3SnH, AIBN, benzene, reflux, iv TBAF, THF, v DIBAL-H, CH_2Cl_2, vi oxalyl chloride, DMSO, Et_3N, CH_2Cl_2, vii trifluoromethanesulfonic acid, viii MsCl, Et_3N, THF, ix $AlCl_3$, benzene, reflux.

Scheme 7

To complete the synthesis of the *ent*-morphinan skeleton, the pentacyclic compound **78** was deprotected, the oxazolidone moiety was reduced to yield diol **80** which was subjected to a double Swern oxidation to yield the rather unstable oxo aldehyde **83**. Exposure of this material to trifluoromethanesulfonic acid led to the formation of alcohol **84**, containing the complete morphinan skeleton. The synthesis terminated here, even though a reduction of this compound would furnish *ent-epi*-dihydrocodeine based on the known stereochemistry of the reductions at C6. Additionally, conversion of **81** via its mesylate to chloride **82** provided the opportunity to perform the first-ever closure of a C10–C11 bond on an intermediate in which the benzofuran bridge is in place and where C10 is sp^3 hybridized. A preliminary evidence [HRMS (CI/methane): 302.1812, ($C_{18}H_{23}NO_3$+H) requires 302.1756; (FAB): 324.1574, ($C_{18}H_{23}NO_3$+Na) requires, 324.1575] indicated that upon exposure to $AlCl_3$ in benzene pentacycle **85** was produced. The minute scale of the reaction precluded full characterization of products. Future work will need to address this procedure on a scale where manipulation of aluminum chloride catalyst proceeds without substantial hydrolysis.



Reagents: i DIBAL-H, CH_2Cl_2, ii nBu$_3$SnH, AIBN, benzene, reflux.

Scheme 8

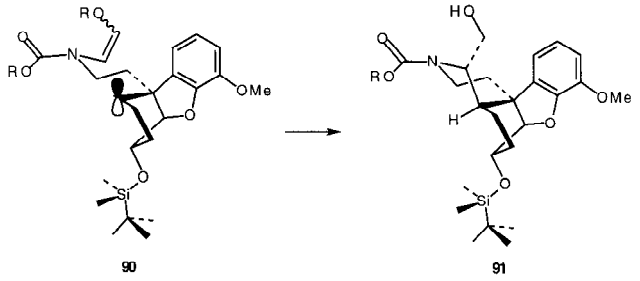
Stereochemistry of Radical Cyclization. From the results obtained in the parallel experiments with **76**, **77**, and **87** several rationalizations can be extended also to the explanations of results in the cascade cyclization. Figure 6 showed the four possible outcomes of a radical cyclization that led to the formation of **56a** and small amounts of **56b**. The transition state operating in the closure of the radical **59** may resemble the conformations of the product with a substantial sp^2 character still connected at C14. In such a case, the course of this cyclization would parallel the events described for the transformations of **76** to **81** and **87** to **81** and **89**. If this argument is correct, then performing the tandem cyclization on a more flexible system, such as **91**, may lead to the enhancement of the tendency to assume conformations that will maximize production of **56b**. The "open" form, **91**, can be synthesized easily by a conversion of halide or azide of the side chain to a carbamate and its condensation with α-bromoacetaldehyde (or its dimethylketal), obtained by the method of Kraus by ozonolysis of 1,4-dibromobut-2-ene.[36] The closure of the radical such as **90** may lead to maximization of the correct C14/C9 absolute stereochemistry through the less convex shape.

Another way in which the more "planar" (or less convex) conformation required for **56b** might be allowed would be by performing the cyclization on **60** in which the original double bonds of the arene *cis*-diol **7a** have been retained, Figure 7. Formation of radical **61** and its further behavior should parallel the arguments offered above: in order to maximize the conformation leading to the correct isomer **62b**, the systems must attain a more "planar" configuration. This can either be achieved by the introduction of the additional sp^2 centers into the C ring or by not restricting the flexibility of conformers with the rigid oxazolidone ring. It is relatively easy to see in Figures 6 and 7 that of the four conformations, the three that lead to the incorrect epimers are all relatively convex while the one leading to the correct configuration at C14 and C9 is relatively flat.

At this point, the best assumption for the next generation improvement would be the following:

1. Perform the stepwise cyclization on the flexible hydroxy methyl compound and study the influence of hydrogen donor groups attached to the hydroxyl.
2. Perform the tandem cyclization of the "open form" of oxazolidone which maintains the radical recipient functionality (i.e., enol ether **90**).
3. Devise other methods of cyclization for octahydroisoquinoline **68** (electrochemical or acid-catalyzed), and study the stereochemical outcome.

The attainment of the correct configuration at C14 relative to C9 constitutes one of the pivotal problems in morphine synthesis as the majority of total syntheses attests to. The multigeneration approach to the synthesis of this alkaloid will hopefully resolve this problem adequately in the not too distant future.



90 **91**

Conclusions

The first few steps that were necessary to evaluate the radical cyclization approach to the morphine skeleton have been completed. The traditional problem of controlling the C14 stereochemistry materialized in our approach as well and in the future ameliorations serious attention will be given to the events that control the conformations of either the cyclization precursors (cascade approach) or the cyclized radical species just before the hydrogen atom abstraction (stepwise approach). To achieve the promise of a practical synthesis of this alkaloid, as insinuated in the title of this paper, careful attention must also be given to the overall number of operations and to the practical execution of each step. To this end, the enzymatic generation of the key building blocks will almost certainly be retained. On the other hand, more effective means will be explored for the step-to-step manipulation of these synthons in terms of both procedures and yield. Electrochemical means of oxidation, reduction, and C–C bond formation will specifically be looked at in this regard as a promising replacement technology for the more traditional methods. We look forward to reporting further results of our quest for morphine synthesis in the future.

1,1,8,8-Tetramethyl-1,8-disilacyclodeca-2,6-diyne-4,5-diol (25):
The corresponding dialdehyde derived from diol **24** (2.4 g, 9.6 mmol) was added neat to a solution of SmI_2 [320 mL, 31.6 mmol (0.1 M solution in THF)], under vigorous stirring at r.t. The initial deep blue color of the SmI_2 solution changed to dark orange within 30 seconds following the addition of the dialdehyde. After stirring for 15 min, a precipitate developed. The lanthanide species was then dissolved in 4 mL of 0.1 N aq HCl solution. Evaporation of the combined organic layers afforded **25** (2.12 g, 87% crude) as a brown foam; mp 113–114 °C (benzene/hexanes); R_f = 0.3 (2:1 hexanes/EtOAc).

IR (CCl_4): ν = 3375 (br), 3005, 2961, 1407 cm^{-1}.
^1H NMR (400 MHz, $CDCl_3$,): δ = 4.40 (d, J = 4.0 Hz, 2H), 2.25 (d, J = 4.0 Hz, 2H), 0.74 (s, 4H), 0.17 (s, 12H).
^{13}C NMR (100 MHz, $CDCl_3$,): δ = 104.5, 93.6, 68.9, 7.9, –2.5, –3.0.
MS: m/z = 252 (M^+, 10), 235 (100), 145 (45).

1,1,8,8-Tetramethyl-1,8-disilacyclodeca-2,6-diyne-5-(2-propenyloxy)-4-ol (26):
A 250 mL flask containing diol **25** (1.78 g, 7.06 mmol) was charged with benzene and Bu_2SnO (2.10 g, 8.48 mmol). The mixture was refluxed overnight with azeotropic removal of H_2O until the Bu_2SnO was completely dissolved, indicating the end of the reaction. After evaporation of the solvent, 4 g of product were obtained which, without further purification was dissolved in excess allyl bromide. After 2 days at reflux, the starting material was consumed and silica gel was added to the mixture. The solvents were removed under reduced pressure and the residue was purified by column chromatography (hexanes/EtOAc 4:1) to furnish the monoallyl ether **26** (740 mg, 36%) as a yellow oil; R_f = 0.5 (hexanes/EtOAc 10:1).

IR (neat): ν = 3400, 2945, 2900, 2160,1250 cm^{-1}.
^1H NMR (400 MHz, $CDCl_3$,): δ = 5.91 (m, 1H), 5.33 (d, J = 16 Hz, 1H), 5.23 (d, J = 12 Hz, 1H), 4.53 (dd, J = 7, 4 Hz, 1H), 4.29 (dd, J = 12.5, 6 Hz, 1H), 4.21 (d, J = 7 Hz, 1H), 4.03 (dd, J = 12.5, 6 Hz, 1H), 2.45 (d, J = 4 Hz, 1H), 0.74 (s, 2H), 0.72 (s, 2H), 0.16 (s, 6H), 0.15 (s, 6H).
^{13}C NMR (67.5 MHz, $CDCl_3$,): δ = 133.7, 118.2, 103.5, 102.1, 94.3, 92.8, 75.1, 70.6, 67.2, 7.7, –2.3, –3.1.
MS: m/z = 292 (M^+, 2%), 251 (18), 145 (100).

1,1,8,8-Tetramethyl-1,8-disilacyclodeca-2,6-diyne-5-(2-propenyloxy)-4-ene (27):
To the allyl ether **26** (190 mg, 0.651 mmol) in CH_2Cl_2 at 0 °C was added pyridine (0.13 mL, 1.628 mmol) followed by dropwise addition of triflic anhydride (0.16 mL, 0.976 mmol). After stirring at 0 °C for 15 min, the mixture was poured into 1% HCl (10 mL), and extracted with CH_2Cl_2. The combined organic phases were dried (Na_2SO_4), filtered and evaporated. The mixture was quickly passed through a plug of silica (hexanes/EtOAc 25:1) to give the corresponding triflate (89.6 mg, 32%) as a colorless oil, which was used immediately in the next reaction.

The triflate was dissolved in benzene (6 mL). DBU (0.035 mL, 0.212 mmol) was added dropwise at r.t. After stirring for 15 min, the solution turned aquamarine in color, silica gel (100 mg) was added, and the solvent was evaporated. The mixture was applied directly to a flash silica column (hexanes/EtOAc 98:2) to yield **27** (28 mg, 48 %) as a colorless oil; R_f = 0.3 (hexanes/EtOAc 98:2).

IR (neat): ν = 2817, 2120 cm^{-1}.
^1H NMR (400 MHz, $CDCl_3$): δ = 5.91 (m, 1H), 5.31 (s, 1H), 5.33 (d, J = 16 Hz, 1H), 5.26 (d, J = 16, 1H), 4.39 (d, J = 5.6 Hz, 2H), 0.39 (s, 4H), 0.04 (s, 12H).

^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 148.1, 132.2, 118.5, 101.2, 98.8, 95.2, 84.1, 70.2 (di), 9.7, 7.9, –0.3, –2.3.
MS (EI): *m/z* = 274 (35%), 245 (41), 73 (100).

Bis[1,2-dimethylsilyl-2-(propynylbromo)]ethane (28):
To a stirred solution of diol **24** (11.0 g, 43.3 mmol) and CBr_4 (27 g, 86.6 mmol) in CH_2Cl_2 (200 mL) at 0 °C was added dropwise a solution of PPh_3 (34 g, 130 mmol) in CH_2Cl_2 (100 mL). The mixture was stirred overnight and the resulting orange solution was filtered and the solvent evaporated. Filtration of the residue and trituration with Et_2O yielded 18 g of crude compound. The oil was purified by flash chromatography (hexanes/CH_2Cl_2 4:1) to afford **28** (11.1 g, 68%) as a colorless oil; R_f = 0.4 (hexanes/CH_2Cl_2 4:1).

Found: C, 38.00; H, 5.36. ($C_{12}H_{20}Br_2Si_2$) requires: C, 37.90; H, 5.31%.
IR (neat): ν = 2960, 2170, 1245, 1200 cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.92 (s, 4H), 0.58 (s, 4H), 0.16 (s, 12H).
^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 100.5, 91.4, 14.6, 8.1, –2.6.
MS: *m/z* = 380 (M^+, 2%), 223 (60), 175 (60), 147 (80).

5-Thia-1,1,8,8-tetramethyl-1,8-disilacyclodeca-2,6-diyne (29):
The dibromide **28** (1.0 g, 2.64 mmol) was dissolved in CH_2Cl_2 (26 mL) and H_2O (35 mL). After complete dissolution tetrabutylammonium bromide (0.27 g, 0.789 mmol) and $Na_2S.9H_2O$ (0.76 g, 3.16 mmol) were added under vigorous stirring. After 2 h, the layers were separated and the organic extract washed with H_2O, dried and removed under reduced pressure to afford a pale yellow solid. Purification by flash column chromatography (hexanes/CH_2Cl_2 4:1) afforded **29** (120 mg, 18%) as a white solid; mp 118–121 °C; R_f = 0.4 (hexanes/CH_2Cl_2 2:1).

Found: C, 55.44; H, 8.07. ($C_{12}H_{20}SSi_2.0.5.H_2O$) requires: C, 55.11; H, 8.09 %.
IR (CCl_4): ν = 2910, 2360, 2343, 1186 cm^{-1}.
^{1}H NMR (270 MHz, $CDCl_3$): δ = 3.39 (s, 4H), 0.57 (s, 4H), 0.12 (s, 12H).
^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 101.1, 87.4, 19.9, 8.6, –2.3.
MS: *m/z* = 252 (M^+, 1%), 224 (100), 209 (90), 147 (35).

5-Thia-1,1,8,8-tetramethyl-1,8-disilacyclodeca-2,6-diyne 5-Oxide (30):
To a precooled (–30 °C) solution of the sulfide **29** (1.4 g, 5.56 mmol) in CH_2Cl_2 (85 mL) was added MCPBA (1.6 g, 5.67 mmol). After 30 min, dimethyl sulfide (4 mL) was added and the mixture was stirred for an additional 15 min. The reaction was concentrated under reduced pressure, and the residue dissolved in Et_2O. The organic solution was washed with sat. $NaHCO_3$ (2 × 60 mL) and brine (1 × 30 mL), dried ($MgSO_4$), filtered, and evaporated to afford 1.3 g of a light yellow semi-solid residue. Purification by flash column chromatography (Et_2O) afforded **30** (940 mg, 63%) as a white solid; mp 177–178 °C; R_f = 0.5 (Et_2O).

Found: C, 53.67; H, 7.58. ($C_{12}H_{20}OSSi_2$) requires: C, 53.66; H, 7.52 %.
IR (CCl_4): ν = 2960, 2910, 2170, 2343, 1186 cm^{-1}.
^{1}H NMR (270 MHz, $CDCl_3$): δ = 3.39 (s, 4H), 0.57 (s, 4H), 0.12 (s, 12H).
^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 101.1, 87.4, 19.9, 8.6, –2.3.
MS: *m/z* = 252 (M^+, 1%), 224 (100), 209 (90), 147 (35).

5-Thia-1,1,8,8-tetramethyl-4-chloro-1,8-disilacyclodeca-2,6-diyne 5,5-Dioxide (31):
To a –78 °C solution of sulfoxide **30** (248 mg, 0.925 mmol) in CH_2Cl_2 (20 mL) was added pyridine (0.26 mL, 3.24 mmol) followed by SO_2Cl_2 (1.9 mL of a 1 M solution in CH_2Cl_2, 1.94 mmol). After 1.5 h, the solution was quenched with H_2O (4 mL) and warmed to r.t. The mixture was extracted with sat. $NaHCO_3$ solution (5 mL), H_2O (5 mL), sat. $CuSO_4$ solution (2 × 5 mL) and brine (10 mL). The organic solution was dried ($MgSO_4$), filtered, and evaporated to afford a residue that was dissolved in CH_2Cl_2, cooled to 0 °C and treated with MCPBA (495 mg, 2.87 mmol). The mixture was stirred overnight and then two drops of Me_2S were added. After stirring for 15 min, the mixture was washed with $NaHCO_3$ solution (10 mL), and H_2O (10 mL), dried ($MgSO_4$), filtered, and evaporated to afford 425 mg of a foamy residue. Purification by flash column chromatography (CH_2Cl_2/hexanes 10:1) afforded **31** (263 mg, 90%) as a pale yellow solid; R_f = 0.5 (CH_2Cl_2/hexanes 10:1).

Found: C, 43.55; H, 5.80. ($C_{12}H_{20}ClO_2SSi_2.0.5.H_2O$) requires: C, 43.94; H, 6.14 %.
IR ($CHCl_3$): ν = 2980, 2910, 2190, 1800 cm^{-1}.
^{1}H NMR (270 MHz, $CDCl_3$): δ = 5.74 (dd, *J* = 12, 2.6, 1H), 4.32 (m, 1H), 4.15 (m, 1H), 0.66 (s, 4H), 0.18 (s, 12H).
^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 99.8, 94.4, 59.7, 42.9, 8.2, –2.8.
MS: *m/z* = 319 (2), 157 (28), 139 (100).

1,1,8,8-Tetramethyl-1,8-disilacyclodeca-2,6-4-ene (21):
To a –78 °C solution of MeLi (0.47 mL of a 1.6 M solution in Et_2O, 0.75 mmol) in Et_2O (8 mL), was added sulfone **31** (200 mg, 0.63 mmol) dissolved in Et_2O (15 mL). Immediately after the addition was complete, sat. aq ammonium chloride was added and the mixture was diluted with pentane and H_2O. The organic layer was separated, dried ($MgSO_4$), filtered, and evaporated to afford 140 mg of an orange oil. Purification by flash column chromatography (pentane/Et_2O 98:2) afforded **21** (263 mg, 90%) as a colorless semi-solid; R_f = 0.3 (pentane/Et_2O 98:2).

IR (neat): ν = 2900, 2110 cm^{-1}.
UV (CH_3CN): λ_{max} = 274, 290.
^{1}H NMR (270 MHz, $CDCl_3$): δ = 6.0 (s, 2H), 0.66 (s, 4H), 0.16 (s, 12H).
^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 121.8, 103.0, 100.2, 8.7.

1,1,8,8-Tetramethyl-1,8-disilacyclodeca-2,6-diyne-5-propenyl-4-one (32):
Enediyne **27** (3 mg, 0.01 mmol) was dissolved in benzene-d_6 (0.8 mL) and transferred to a thick-walled NMR tube. Cyclohexa-1,3-diene (0.08 mL, 0.8 mmol) was added to the mixture, and the sample was degassed for 30 min with a stream of Ar. After heating the sample at 55 °C for 8 h, the starting material remained unchanged. The reaction temperature was increased to 80 °C, and after 60 h the starting material was consumed. Evaporation of the solvents yielded **32** (1.3 mg, 43 %) as a yellow oil; R_f = 0.5 (hexanes/EtOAc 10:1).
IR (neat): ν = 2810, 2100, 1725 cm^{-1}.
^{1}H NMR (270 MHz, $CDCl_3$): δ = 5.84 (m, 1 H), 5.12 (m, 2H), 3.27 (m, 1H), 2.50 (m, 2H), 0.23 (s, 4H), 0.17 (s, 12 H).
^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 185.4, 133.6, 117.9, 106.7, 104.0, 100.1, 91.7, 48.1, 35.4, 7.9, –2.6, –3.3.

(1*R*,6*R*)-6-Thexyloxy-2-methylcyclohex-2-enyl-(2-phenylacetate) (41):
A THF solution (5 mL) of a phosphine reagent [prepared from DEAD (142 mg, 0.905 mmol) and tributylphosphine (225 mg, 0.905 mmol)] was added dropwise to a precooled solution (0 °C) of alcohol **40** (120.0 mg, 0.444 mmol) and benzoic acid (110.5 mg, 0.905 mmol) in THF (5 mL) and stirred at r.t. for 20 h. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (EtOAc/hexane 1:9) to yield **41** (113 mg, 68 %) as a viscous, colorless oil; R_f = 0.25 (EtOAc/hexane 1:9); $[\alpha]_D^{25}$ +103.2 (*c* = 1.18, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.08 (d, *J* = 1.2 Hz, 1H), 8.05, (d, *J* = 1.4 Hz, 1H), 7.99 (tt, *J* = 7.8, 1.7 Hz, 2H), 7.66 (br t, *J* = 1.22 Hz, 1H), 7.55 (tt, *J* = 7.8, 1.2 Hz, 1H), 5.40 (d, *J* = 4.9 Hz, 1H), 4.00 (hept, *J* = 5.2, 3.1, 2.2 Hz, 1H), 2.20 (m, 1H), 2.05 (m, 1H), 1.81 (m, 1H), 1.74 (m, 1H), 1.68 (br d, 1H), 1.56 (sep, *J* = 6.5 Hz, 1H), 0.82 (d, 6H), 0.78 (d, 6H), 0.10 (s, 3H), 0.08 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.3, 132.8, 130.5, 130.3, 129.7, 128.3, 126.8, 75.7, 69.7, 34.2, 27.9, 22.4, 20.2, 18.5, –2.7, –2.9.

(1*R*,6*R*)-6-Thexyloxy-2-methylcyclohex-2-en-1-ol (42):
A solution of ester **41** (214 mg, 0.571 mmol) in MeOH/NaOMe (12 mL, trace) was stirred at r.t. for 46.5 h. The mixture was concentrated under reduced pressure to give a residue which was dissolved in benzene and purified by column chromatography (EtOAc/hexane

3:7) to afford alcohol **42** (143.9 mg, 93%) as a colorless, viscous oil; R_f = 0.60 (EtOAc/hexane 3:7).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.41 (br s, 1H), 3.87 (br s, 1H), 3.74 (ddd, *J* = 10.2, 6.7, 3.5 Hz, 1H), 2.06 (m, 2H), 1.99 (d, *J* = 4.1 Hz, 1H), 1.76 (m, 4H), 1.63 (m, 2H), 0.88 (br d, *J* = 6.9 Hz, 6H), 0.84 (s, 6H), 0.14 (s, 3H), 0.12 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ = 133.6, 123.8, 75.1, 74.0, 34.2, 29.7, 28.5, 23.6, 20.4, 19.4, 18.6, –2.3, –2.8.

3-Bromo-2-{[(1*R*,6*S*)-6-thexyloxy]-2-methylcyclohex-2-enyl}oxyphenol (43):
To a precooled solution (0 °C) of alcohol **42** (75 mg, 0.277 mmol) and Bu_3P (112 mg, 0.554 mmol) in THF (2 mL) was added dropwise DEAD (96.6 mg, 0.554 mmol). After stirring for 2 min a solution of phenol **38** (110 mg, 0.333 mmol) in THF (2 mL) was added dropwise. The cooling bath was removed and the mixture was stirred for 12.5 h. The mixture was concentrated under reduced pressure to afford 42.6 mg of crude silyl protected **43**. This was dissolved in THF (5 mL), and treated with TBAF (57 mg). After 9 h of stirring at r.t., H_2O (15 mL) was added, and the THF distilled off under reduced pressure. The product was extracted with CH_2Cl_2 (5 × 15 mL), dried ($MgSO_4$), and after filtration, the solvent was removed under reduced pressure to give crude phenol **43** (~30 mg). The crude material was taken on directly to the next step.

Benzyl (3-Bromo-2-{[(1*R*,6*S*)-6-thexyloxy-2-methylcyclohex-2-enyl]oxy}phenyl Ether (44):
The solution of phenol **43** (34.5 mg, 0.0781 mmol) and benzyl bromide (20.0 mg, 0.117 mmol) in acetone (2.5 mL) was treated with K_2CO_3 (55 mg, 0.390 mmol) and vigorously stirred. After 5 h, the solid was filtered off and the filtrate was concentrated under reduced pressure. The residue (41 mg) was purified by column chromatography (EtOAc/hexanes 1:9) to afford **44** (21.4 mg, 51%) as a viscous, colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37 (m, 5H), 7.14 (dd, *J* = 7.6, 1.8 Hz, 1H), 6.87 (m, 1H), 5.53 (br s, 1H), 5.07 (s, 2H), 4.87 (t, *J* = 5.4 Hz, 1H), 4.22 (br s, 1H), 2.09 (m, 1H), 1.82 (m, 1H), 1.79 (s, 3H), 1.62 (p, *J* = 6.9 Hz, 1H), 1.55 (s, 1H), 1.41 (m, 1H), 0.88 (s, 3H), 0.86 (s, 3H), 0.82 (s, 6H), 0.11 (s, 3H), 0.09 (s, 3H).

(5a*R*,6*S*,9a*S*)-9a-Methyl-6-thexyloxy-5a,6,7,8,9,9a-hexahydrodibenzo[*b*,*d*]furan-4-yl Benzyl Ether (45):
The solution of the bromide **44** (21.0 mg, 0.039 mmol) and Bu_3SnH (23.0 mg, 0.078 mmol) in refluxing toluene (3.0 mL) was treated with AIBN. After 24 h of reflux, the reaction was concentrated under reduced pressure, and the residue was purified by column chromatography (benzene) to yield tricyclic ether **45** (9.8 mg, 55%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44 (m, 2H), 7.35 (m, 2H), 7.29 (m, 1H), 6.75 (m, 2H), 6.70 (dd, *J* = 6.3, 2.3 Hz, 1H), 5.18 (s, 2H), 4.38 (t, *J* = 4.9 Hz, 1H), 3.80 (m, 1H), 2.13 (m, 1H), 1.88 (m, 1H), 1.79 (m, 2H), 1.63 (m, 2H), 1.58 (s, 3H), 1.35 (m, 1H), 0.90 (s, 3H), 0.88 (s, 3H), 0.83 (d, *J* = 6.0 Hz, 6H), 0.08 (s, 3H), 0.05 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.0, 144.0, 140.0, 137.3, 128.5, 127.8, 127.4, 121.1, 114.7, 113.8, 88.8, 71.1, 66.5, 42.5, 34.1, 28.5, 24.8, 22.7, 20.2, 19.6, 18.6, –2.7, –2.9.

(3*S*,4*S*)-3-(1-Bromo-2-phenyloxy)-4-(*tert*-butyldimethylsilyloxy)-2-[2-(3-oxazolone)ethyl]cyclohexene (46):
To a solution of alcohol **50** (204.3 mg, 0.609 mmol) and 2-bromophenol (112.8 mg, 0.609 mmol) in THF (10 mL) was added the Mitsunobu reagent [prepared from Bu_3P (296 mg, 1.462 mmol) and DEAD (255 mg, 1.462 mmol) in THF (10 mL) precooled to 0 °C]. The cooling bath was removed and the mixture was stirred for 5 h, at which time TLC indicated disappearance of starting material. The solvent was removed under reduced pressure and the crude product was dissolved in Et_2O (50 mL). After washing with H_2O (20 mL) and brine (20 mL), the combined organic phase was dried ($MgSO_4$), filtered, and concentrated. The crude product was purified by column chromatography (EtOAc/hexane 95:5) to yield the intermediate (3*S*,4*S*)-2-(2-bromoethyl)-3-(1-bromo-2-phenyloxy)-4-(*tert*-butyldimethylsilyloxy)cyclohexene (132 mg, 44%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.26 (m, 1H), 7.24 (dt, *J* = 7.2, 0.9, 1H), 6.83 (dt, *J* = 7.5, 1.4 Hz, 1H), 5.80 (br s, 1H), 4.63 (br d, *J* = 4.7 Hz, 1H), 4.04 (m, 1H), 3.41 (dd, *J* = 7.9, 6.9 Hz, 2H), 2.80 (m, 1H), 2.56 (m, 1H), 2.20 (m, 2H), 1.90 (m, 1H), 1.72 (m, 1H), 0.82 (s, 9H), 0.01 (s, 3H), –0.11 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.3, 133.5, 132.2, 129.5, 128.3, 122.1, 115.0, 112.7, 79.4, 70.0, 37.5, 31.9, 27.8, 25.7, 22.4, 18.9, –5.0.

To a solution of oxazolone **8** (21 mg, 0.247 mmol) in DMSO (5 mL) was added NaH (10 mg, 0.25 mmol). The mixture was stirred for 15 min to complete the formation of the sodium salt and the intermediate bromide (121 mg, 0.247 mmol) in DMSO (2 mL) was added dropwise via syringe. After stirring at r.t. for 20 h, the reaction was diluted with Et_2O (50 mL) and quenched with H_2O (30 mL). The organic phase was separated, washed with brine (2 × 20 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (EtOAc/hexane 3:7) to afford **46** (68 mg, 56%) as a viscous oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.64 (dd, *J* = 7.8, 1.5 HZ, 1H), 7.36 (dt, *J* = 7.3, 1.7 Hz, 1H), 7.27 (dd, *J* = 8.2 Hz, 1H), 6.94 (br t, *J* = 7.8 Hz, 1H), 6.80 (d, *J* = 2.0 Hz, 1H), 6.64 (d, *J* = 2.0 Hz, 1H), 5.79 (dt, *J* = 3.8 Hz, 1H), 4.80 (br d, *J* = 4.1 Hz, 1H), 4.13 (m, 1H), 3.74 (m, 2H), 2.70 (br m, 1H), 2.42 (br m, 1H), 2.28 (m, 1H), 2.16 (m, 1H), 2.00 (m, 1H), 1.80 (m, 1H), 0.91 (s, 9 H), 0.12 (s, 3H), 0.10 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.0, 133.5, 130.3, 130.3, 128.5, 122.2, 116.3, 115.0, 112.5, 79.5, 69.8, 42.7, 33.9, 27.6, 25.7, 22.4, –4.9, –4.9.

10-*tert*-Butyldimethylsilyloxy-8,16,18-dioxazapentacyclo-[11.7.0.0^{1,9}.0^{2,7}.0^{14,18}]icosa-2(7),3,5-trien-17-one (47):
To a degassed (Ar sparge) solution of **46** (67 mg, 0.135 mmol) in toluene (10 mL) was added Bu_3SnH (78.9 mg, 73 µL, 0.271 mmol) and AIBN (cat.). The reaction vessel was submerged into a preheated oil bath (110 °C) and allowed to reflux for 16 h. Two additional spatula tips of AIBN were added and the reaction was stirred at reflux an additional 5 h. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography (benzene/Et_2O 9:1). Two compounds with similar R_f were isolated as a mixture, which was further purified by preparative TLC (EtOAc/hexane 1:1) to afford pentacycle **47** (5.5 mg, 10%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26 (m, 1H), 6.97 (br t, *J* = 7.3 Hz, 1H), 6.86 (m, 2H), 4.48 (t, *J* = 8.1 Hz, 1H), 4.18 (br s, 1H), 4.10 (dd, *J* = 8.7, 5.5 Hz, 1H), 3.83 (ddd, *J* = 13, 6, 1 Hz, 1H), 3.40 (ddd, *J* = 10.1, 8, 5.6, 1H), 2.80 (dt, *J* = 12.8, 3.7 Hz, 1H), 2.65 (dm, *J* = 13 Hz, 1H), 2.20 (dt, *J* = 10.1, 5.9 Hz, 1H), 1.50–1.80 (bm, app 6H), 0.81 (s, 9H), –0.05 (s, 3H), –0.12 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.8, 129.5, 123.3, 121.5, 115.3, 66.8, 65.1, 60.1, 41.2, 40.2, 30.6, 29.0, 28.3, 26.8, 25.7, 24.6, 19.7, 17.3, 13.6, –2.4, –2.6.
MS (CI): *m/z* = 416 ($M+H^+$, 28%), 358 (100), 313 (25), 190 (30), 151 (30),
HRMS: 416.2276, ($C_{23}H_{33}NO_4Si$+H) requires, 416.2257.

(3*R*,4*S*)-2-(2-Bromoethyl)-4-(*tert*-butyldimethylsilyloxy)-3-hydroxycyclohexene (50):
To a stirred solution of the diol **49** (1.634 g, 7.39 mmol) in anhyd CH_2Cl_2 (50 mL) under Ar, was added diisopropylethylamine (2.70 mL, 15.52 mmol) and the mixture cooled to –78 °C, resulting in a white suspension. After 10 min, *tert*-butyldimethylsilyl triflate (1.87 mL, 8.13 mmol) was added dropwise, and stirring/cooling continued. After 5 h, further TBSTf (0.85 mL, 3.70 mmol) was added dropwise, and the stirred mixture allowed to slowly warm to r.t. overnight. After 20 h, H_2O (80 mL) and saturated aqueous NH_4Cl (30 mL) were added, and the resulting mixture extracted with further CH_2Cl_2 (4 × 80 mL). The combined organic fractions were dried ($MgSO_4$), filtered and reduced in vacuo to yield a brown oil. Further purification by

flash chromatography (silica ratio 50:1, hexane/EtOAc, gradient elution, 50:1 to 20:1), yielded silyl ether **50** (1.166 g, 47% from **7a**) as a colorless oil; R_f = 0.30 (hexane/EtOAc 19:1); $[\alpha]_D^{25}$ = –42.0 (*c* = 1.0, $CHCl_3$).

IR: (thin film): ν = 3552, 2932, 1256, 1087 cm^{-1}.
^1H NMR (400 MHz, $CDCl_3$): δ = 5.65 (m, 1H), 3.90 (t, *J* = 3.5 Hz, 1H), 3.81 (dt, *J* = 10.6, 2x 3.7 Hz, 1H), 3.53 (m, 2H), 2.76 (m, 1H), 2.63 (m, 2H), 2.18 (m, 1H), 2.03 (m, 1H), 1.78 (m, 1H), 1.57 (m, 1H), 0.92 (s, 9H), 0.11 (s, 6H).
^{13}C NMR (100 MHz, $CDCl_3$): δ = 134.7 (C), 127.7 (CH), 70.7 (CH), 68.6 (CH), 38.4 (CH_2), 31.8 (CH_2), 25.7 (3 × CH_3), 25.4 (CH_2), 23.9 (CH_2), 18.0 (C), –4.5 (CH_3), –4.9 (CH_3).
MS (EI, 70 eV): *m/z* = 335 ($M+H^+$, 10%).
HRMS: 335.1042, ($C_{14}H_{28}O_2{}^{79}BrSi$) requires, 335.1042.
Also isolated, in varying amount, was the *bis* silylated compound; R_f = 0.59 (hexane/EtOAc 19:1); $[\alpha]_D^{25}$ –42.2 (*c* = 1.0, $CHCl_3$).
IR (thin film): ν = 2995, 1470, 1255, 1090 cm^{-1}.
^1H NMR (400 MHz, $CDCl_3$): δ = 5.65 (br t, *J* = 3.3 Hz, 1H), 3.96 (br s, 1H), 3.72 (dt, *J* = 10.5, 2x 2.8 Hz, 1H), 3.42 (m, 2H), 2.57 (t, *J* = 7.9 Hz, 2H), 2.16 (m, 1H), 2.01 (m, 1H), 1.90 (m, 1H), 1.51 (m, 1H), 0.90 (s, 9H), 0.89 (s, 9H), 0.12 (s, 3H), 0.10 (s, 3H), 0.08 (s, 3H), 0.07 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.4 (C), 125.9 (CH), 72.2 (CH), 71.2 (CH), 37.6 (CH_2), 32.0 (CH_2), 26.1 (6x CH_3), 25.4 (CH_2), 24.7 (CH_2), 18.4 (2x C), -3.6 (CH_3), –4.3 (CH_3), –4.4 (CH_3), –4.6 (CH_3).

(3*S*,4*S*)-3-Benzoyloxy-4-*tert*-butyldimethylsilyoxy-2-(2-bromoethyl)cyclohexene (51):
To stirred solution of alcohol **50** (4.609 g, 13.74 mmol) and benzoic acid (1.846 g, 15.12 mmol) in anhyd THF (12 mL) at 0 °C, was added a solution of the Mitsunobu reagent [previously prepared by addition of DEAD (4.786 g, 27.48 mmol) to a stirred solution of tributylphosphine (5.559 g, 27.48 mmol) in anhyd THF (10 mL) at 0 °C], and the mixture allowed to warm to r.t. with stirring. After 16 h, solvent was removed in vacuo to yield a brown oil, which was prepurified by passage through a silica plug with benzene. Further purification by flash chromatography (silica 300 g, benzene) yielded benzoate **51** (5.117 g, 84%) as a highly viscous, colorless oil, which solidified on prolonged standing; mp 65–66 °C (benzene); R_f = 0.20 (hexane/EtOAc 19:1); $[\alpha]_D^{25}$ +102.0 (*c* = 1.0, $CHCl_3$).

IR: (KBr disc): ν = 2930, 1710, 1260, 1110, 840 cm^{-1}.
^1H NMR (400 MHz, $CDCl_3$): δ = 8.05 (dm, *J* = 8.5 Hz, 2H), 7.57 (ddt, *J* = 7.9, 6.9, 1.4 Hz, 1H), 7.45 (tm, *J* = 7.6 Hz, 2H), 5.84 (br t, *J* = 3.6 Hz, 1H), 5.40 (d, *J* = 4.4 Hz, 1H), 4.02 (ddd, *J* = 7.0, 4.7, 2.9 Hz, 1H), 3.45 (m, 2H), 2.60 (m, 1H), 2.50 (m, 1H), 2.30 (m, 1H), 2.11 (m, 1H), 1.82 (m, 1H), 1.74 (m, 1H), 0.84 (s, 9H), 0.50 (s, 3H), 0.30 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.1 (C), 133.0 (CH), 130.8 (C), 130.3 (CH), 130.1 (C), 129.7 (2 × CH), 128.4 (2 × CH), 73.4 (CH), 69.2 (CH), 37.5 (CH_2), 31.1 (CH_2), 27.2 (CH_2), 25.6 (3 × CH_3), 22.1 (CH_2), 17.8 (C), –4.86 (CH_3), –4.88 (CH_3).
MS (EI, 70 eV)**:** *m/z* 439 (M^+, 10%), 359 (MH^+, 100).
HRMS: 439.1291, ($C_{21}H_{32}O_3{}^{79}BrSi$) requires, 439.1304.

(3*S*,4*S*)-3-Benzoyloxy-4-*tert*-butyldimethylsilyl-2-[2-(oxazol-2-on-1-yl)ethyl]cyclohexene (52):
To a stirred suspension of NaH (0.3353 g, 1.40 mmol) in anhyd DMSO (20 mL) was added, in one portion, the oxazolone **8** (1.1885 g, 13.97 mmol) and the resulting mixture stirred at r.t. for 20 min. After this time, the mixture was cooled slightly (~10 °C) and a solution of bromide **51** (5.1168 g, 11.64 mmol) in DMSO (40 mL) was added dropwise. The mixture was allowed to warm to r.t. with stirring. After 18 h, the reaction was cooled to 0 °C and quenched with brine (200 mL) and H_2O (200 mL). The resulting mixture was extracted with EtOAc (1 × 200 mL, 3 × 100 mL), the combined organic fractions were washed with brine (1 × 50 mL), dried (Na_2SO_4) and the solvent was removed in vacuo to yield a pale yellow oil. Further purification by flash chromatography (silica 200 g, EtOAc/hexane 1:1) yielded pure ester **52** (3.683 g, 71%) as a highly viscous, colorless oil; R_f = 0.14 (hexane/EtOAc 4:1); $[\alpha]_D^{25}$ + 83.7 (*c* = 1.0, $CHCl_3$).

IR (thin film): ν = 2930, 1750, 1720, 1260 cm^{-1}.
^1H NMR (400 MHz, $CDCl_3$): δ = 8.07 (m, 2H), 7.59 (ddt, *J* = 8.0, 6.8, 2 × 1.3 Hz, 1H), 7.46 (m, 2H), 6.70 (d, *J* = 2.1 Hz, 1H), 6.53 (d, *J* = 2.1 Hz, 1H), 5.76 (br t, *J* = 4.0 Hz, 1H), 5.47 (d, *J* = 4.6 Hz, 1H), 4.05 (ddd, *J* = 7.4, 4.9, 2.7 Hz, 1H), 3.74 (ddd, *J* = 13.9, 7.3, 5.0 Hz, 1H), 3.60 (ddd, *J* = 14.2, 8.4, 7.0 Hz, 1H), 2.38 (m, 1H), 2.25 (m, 2H), 2.12 (m, 1H), 1.85 (m, 1H), 1.75 (m, 1H), 0.84 (s, 9H), 0.07 (s, 3H), 0.04 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.2 (C), 155.5 (C), 133.1 (CH), 131.0 (CH), 129.8 (C), 129.6 (2 × CH), 129.4 (C), 128.4 (2 × CH), 116.3 (CH), 73.3 (CH), 69.4 (CH), 42.2 (CH_2), 33.1 (CH_2), 27.3 (CH_2), 25.6 (3 × CH_3), 22.1 (CH_2), 17.9 (C), –4.9 (2 × CH_3).
MS (EI, 70 eV): *m/z* = 444 ($M+H^+$, 20%), 428 ($M\text{-}CH_3{}^+$, 42).
HRMS: 444.2204, ($C_{24}H_{34}NO_5Si$) requires, 444.2206.

Also isolated was the elimination product, **(3*R*)-Benzoyloxy-(4*S*)-*tert*-butyldimethylsilyloxy-2-vinylcyclohexene (53):** (0.459 g, 11%) as a colorless oil; R_f = 0.49 (hexane/EtOAc 19:1); $[\alpha]_D^{25}$ + 246.4 (*c* = 1.0, $CHCl_3$).
IR (thin film): ν = 2930, 2860, 1720, 1260, 1090 cm^{-1}.
^1H NMR (400 MHz, $CDCl_3$): δ = 8.05 (m, 2H), 7.55 (m, 1H), 7.43 (m, 2H), 6.31 (dd, *J* = 17.6, 11.1 Hz, 1H), 6.11 (dd, *J* = 5.0, 3.0 Hz, 1H), 5.62 (d, *J* = 3.2 Hz, 1H), 5.11 (d, *J* = 17.7 Hz, 1H), 4.90 (d, *J* = 11.0 Hz, 1H), 4.10 (t, *J* = 4.9 Hz, 1H), 2.44 (m, 1H), 2.17 (dm, *J* = 18.9 Hz, 1H), 1.85 (dddd, *J* = 13.5, 10.7, 5.5, 2.0 Hz, 1H), 1.75 (m, 1H), 0.89 (s, 9H), 0.15 (s, 3H), 0.11 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.5 (C), 137.5 (CH), 134.1 (CH), 132.9 (CH), 131.7 (C), 130.3 (C), 129.7 (2 × CH), 128.3 (2 × CH), 111.2 (CH_2), 68.7 (CH), 67.5 (CH), 25.7 (3 × CH_3), 21.8 (CH_2), 21.3 (CH_2), 18.1 (C), –4.8 (CH_3), –5.0 (CH_3).
MS (CI/methane): *m/z* = 359 ($M+H^+$, 1%), 237 ($M\text{-}PhCO_2{}^+$, 52).
HRMS: 359.2030, ($C_{21}H_{31}O_3Si$) requires, 359.2042.

(3*R*,4*S*)-3-[2-(1-Bromo-3-methoxy)phenyloxy]-4-(*tert*-butyldimethylsilyloxy)-2-[2-(3-oxazolone)ethyl]cyclohexene (55):
To a stirred solution of benzoate **52** (3.683 g, 8.30 mmol) in MeOH (50 mL) at r.t., was added 1 M aq NaOH (20 mL), resulting in mild emulsification. After 6 h, the MeOH was removed in vacuo, brine (100 mL) was added, and the resulting mixture extracted with EtOAc (3 × 150 mL). The combined organic fractions were dried ($MgSO_4$), filtered and reduced in vacuo to yield the intermediate alcohol **54** as a highly viscous, colorless oil, which was used directly without further purification.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.77 (d, *J* = 2.1 Hz, 1H), 6.54 (d, *J* = 2.1 Hz, 1H), 5.39 (br t, *J* = 3.0 Hz, 1H), 3.94 (m, 1H), 3.87 (ddd, *J* = 6.4, 7.6, 16.0 Hz, 1H), 3.74 (ddd, *J* = 3.2, 5.9, 9.1 Hz, 1H), 3.64 (dt, *J* = 6.4 x 2, 13.9 Hz, 1H), 2.75 (d, *J* = 5.6 Hz, 1H), 2.52 (m, 1H), 2.37 (m, 1H), 2.10 (m, 1H), 1.98 (m, 1H), 1.77 (m, 1H), 1.60 (m, 1H), 0.9 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.1 (C), 132.7 (C), 127.8 (2 × C), 116.0 (CH), 73.62 (CH), 73.58 (CH), 43.13 (CH_2), 34.2 (CH_2), 27.5 (CH_2), 25.8 (3 × CH_3), 23.1 (CH_2), 18.0 (C), –4.5 (CH_3), –4.7 (CH_3).
To a stirred solution of the alcohol **54** (2.54 g, 7.48 mmol) and phenol **33** (1.52 g, 7.48 mmol) in anhyd THF (10 mL) under Ar at 0 °C, was added dropwise a solution of the Mitsunobu reagent [previously prepared by addition of DEAD (2.356 mL, 14.96 mmol) to a stirred solution of Bu_3P (3.727 mL, 14.96 mmol) in anhyd THF (30 mL) at 0 °C], and the mixture was allowed to warm to r.t. with stirring. After 6 h, the solvent was removed in vacuo to yield a brown oil, which was prepurified by passage through a silica plug (hexane/EtOAc 3:2). Further purification by flash chromatography (silica ratio 200:1, hexane/EtOAc 3:2) yielded aryl ether **55**, (1.095 g, 28%) as a highly viscous, colorless oil; R_f = 0.22 (hexane/EtOAc 2:1); $[\alpha]_D^{25}$ –179.5 (*c* = 1.0, $CHCl_3$).

IR (KBr disc): ν = 3150, 2960, 1750, 1470, 1260, 1120, 840 cm^{-1}.
^1H NMR (400 MHz, $CDCl_3$): δ = 7.07 (dd, *J* = 7.2, 2.4 Hz, 1H), 6.79 (m, 2H), 6.70 (d, *J* = 1.8 Hz, 1H), 6.61 (d, *J* = 1.8 Hz, 1H), 5.58 (m, 1H), 5.13 (d, *J* = 2.9 Hz, 1H), 3.88 (s, 3H), 3.87 (m, 1H), 3.74 (m, 2H), 2.69 (m, *J* = ~7Hz, 1H), 2.55 (m, 1H), 2.44 (m, 1H), 2.21 (m, 1H), 2.04 (m, 1H), 1.58 (m, 1H), 0.60 (s, 9H), –0.10 (s, 3H), –0.28 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.9 (C), 151.8 (C), 146.6 (C), 131.6 (C), 131.2 (2 × CH), 125.6 (CH), 122.8 (CH), 117.5 (C), 116.8 (CH), 111.3 (CH), 78.2 (CH), 73.0 (CH), 55.6 (CH_3), 43.1 (CH_2), 35.2 (CH_2), 25.7 (CH_2), 25.6 (3 × CH_3), 24.9 (CH_2), 17.9 (C), –5.0 (CH_3), –5.4 (CH_3).
MS (EI, 70 eV): *m/z* = 524 (M^+, 1%), 468 (M-*tert*-Bu^+, 40).
HRMS: 524.1467, ($C_{24}H_{35}NO_5{}^{79}BrSi$) requires, 524.1468.

10-*tert*-Butyldimethylsilyloxy-6-methoxy-(1*S*,10*S*,13*S*,14*R*)-8,16,18-dioxazapentacyclo[11.7.0.0^{1,9}.0^{2,7}.0^{14,18}]icosa-2(7),3,5-trien-17-one (56a):
A large, heavy walled, resealable glass tube was fitted with a septum, subjected to vacuum flame drying, Ar flooding three times, and allowed to cool under Ar. Bromide **55** (215 mg, 0.410 mmol) was taken up in anhyd benzene (3 × 14 mL) and added to the tube. The resulting solution (~0.01 M) was rigorously degassed under a stream of Ar for 30 min. After that time, tris(trimethylsilyl)silane (190 µL, 0.615 mmol) was added, followed by a catalytic quantity of AIBN, while taking precautions to exclude oxygen. The tube was sealed, and the solution heated to 140 °C in an oil bath. Further AIBN was added over regular intervals (~5 h), and after 20 h, additional TTMSS (63 µL, 0.205 mmol). After 24 h total, heat was removed, the tube allowed to cool, and opened. Solvent was removed in vacuo, and the residue subjected to purification by a combination of flash chromatography (silica ratio 100:1, hexane/EtOAc 3:2) and preparative HPLC (Supelco C_{18} reverse phase column, MeOH/H_2O 90:10, 15 mL/min). Further purification of the enriched fractions yielded pentacycle **56a** (15.4 mg, 8%) as a white solid; R_f = 0.50 (hexane/EtOAc 1:1); $[\alpha]_D^{25}$ –11.5 (*c* = 0.2, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.82 (t, *J* = 7.8 Hz, 1H), 6.74 (dd, *J* = 8.1, 1.1 Hz, 1H), 6.60 (dd, *J* = 7.4, 1.1 Hz, 1H), 4.57 (d, *J* = 4.0 Hz, 1H), 4.53 (t, *J* = 8.3 Hz, 1H), 4.21 (td, *J* = 6.2, 6.2, 4.1 Hz, 1H), 3.99 (dd, *J* = 8.6, 5.7 Hz, 1H), 3.87 (s, 3H), 3.83 (ddd, *J* = 13.7, 5.0, 2.9 Hz, 1H), 3.74 (ddd, *J* = 11.0, 7.8, 5.8 Hz, 1H), 2.99 (ddd, *J* = 13.7, 12.1, 3.3 Hz, 1H), 2.01 (ddd, *J* = 10.9, 5.4, 2.7 Hz, 1H), 1.81 (m, 1H), 1.70 (ddd, *J* = 14.3, 12.3, 5.1 Hz, 1H), 1.65 (dt, *J* = 8.1, 6.0, 6.0 Hz, 1H), 1.23 (ddt, *J* = 14.3, 2 × 5.7, 2.7 Hz, 1H), 0.76 (s, 9H), 0.06 (s, 6H).
^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.5 (C), 144.1 (C), 135.1 (C), 121.3 (CH), 113.6 (CH), 112.3 (CH), 110.4 (C), 87.1 (CH), 68.3 (CH_2), 68.2 (CH), 55.9 (CH_3), 55.5 (CH), 47.8 (CH_2), 40.3 (CH), 37.6 (CH_2), 36.4 (CH_2), 25.7 (3 × CH_3), 24.2 (CH_2), 18.4 (C), –4.8 (CH_3), –5.0 (CH_3).

Also isolated were various amounts of tetracyclic enol ether **58**:
^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.92 (m, 2H), 6.82 (m, 2H), 4.46 (t, *J* = 8.5 Hz, 1H), 4.25 (br s, 1H), 4.08 (dd, *J* = 8.9, 5.5 Hz, 1H), 3.89 (s, 3H), 3.80 (ddd, *J* = 13.0, 6.1, 1.4 Hz, 1H), 3.40 (ddd, *J* = 10.1, 7.9, 5.5 Hz, 1H), 2.75 (dt, *J* = 12.8, 3.7 Hz, 1H), 2.64 (br d, *J* = 14.2 Hz, 1H), 2.15 (m, 1H), 1.82 (m, 2H), 1.67 (m, 3H), 0.96 (s, 9H), –0.05 (s, 3H), –0.18 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.7, 148.7, 147.7, 147.1, 123.1, 121.9, 120.5, 114.4, 112.0, 66.8, 65.4, 60.1, 55.8, 41.4, 40.1, 30.7, 25.7, 24.6, 19.7, 17.9, –5.2, –5.3.

6-Bromo-7-(2-bromoethyl)-2,2-dimethyl-(3a*S*,7a*R*)-4,5-dihydrobenzo[*d*][1,3]dioxole (66):
The PAD reduced diol **65** (776 mg, 2.59 mmol) was dissolved in acetone (10 mL). 2,2-Dimethoxypropane (6 mL) and a catalytic amount of *p*-TsOH were added. After stirring the mixture at r.t. for 3 h the contents were concentrated to afford 843 mg of a brown oil. Purification by flash chromatography (10% deactivated silica gel, hexane/EtOAc 9:1), yielded **66** (790 mg, 90%) as a pale yellow oil; R_f = 0.21 (hexane/EtOAc, 20:1); $[\alpha]_D^{25}$ +93.7 (*c* = 1.2, $CHCl_3$).

Found: C, 39.18; H, 4.42. ($C_{11}H_{16}O_2Br_2$) requires: C, 38.85; H, 4.74%.
IR (neat): ν = 3100, 2900, 1100 cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.52 (d, *J* = 4.4 Hz, 1H), 4.38 (1m, 1H), 3.54 (m, 1H), 2.83 (m, 3H), 2.42 (ddd, *J* = 17.5, 4.3, 3.4 Hz, 1H), 2.03 (m, 1H), 1.87 (m, 1H), 1.37 (s, 3H), 1.35 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ = 132.0 (C), 126.2 (C), 109.1 (C), 75.7 (CH), 72.4 (CH), 37.2 (CH_2), 31.7 (CH_2), 27.8 (CH_3), 26.5 (CH_2), 26.2 (CH_2).
MS: *m/z* = 342 (M^{+2}, 4%), 340 (M^+, 10), 259 (31), 183 (62), 55 (100).
HRMS: 337.9515, ($C_{11}H_{16}O_2{}^{79}Br_2$) requires, 337.9517.

3-[2-(6-Bromo-2,2-dimethyl-(3a*S*,7a*R*)-4,5-dihydrobenzo[*d*][1,3]dioxol-7-yl)]ethyl-2,3-dihydro[1,3]oxazol-2-one (67):
A flame dried, Ar filled flask was charged with oxazol-2-one **8** (1.085 g, 12.75 mmol) and NaH (460 mg, 11.5 mmol, 60% susp., Aldrich) and cooled to 0 °C. Anhyd DMSO (5 mL) was added via syringe and the cooling bath was removed. After stirring for 15 min at r.t. (to complete the salt formation), the mixture was placed in a ice bath and allowed to partially solidify. The solution of the acetonide (2.168 g, 6.375 mmol) in DMSO (3 mL) was added dropwise. An additional 2 mL of DMSO was used to rinse the flask containing the acetonide and was subsequently added to the mixture. The temperature was allowed to rise gradually to r.t. overnight. The mixture was diluted with Et_2O (10 mL) and quenched with H_2O/brine mixture (1:1, 10 mL). After further extraction with Et_2O (3 × 30 mL) and drying ($MgSO_4$), the combined organic extracts were filtered through a plug of Celite and evaporated to dryness to give 2.4 g of a crude oil. Purification by flash chromatography (hexane/EtOAc 7:3), yielded *N*-alkylated compound **67** (843 mg, 38%) and somewhat impure **71** (981.2 mg, 59%). The latter was used without purification in the hydroboration/oxidation sequence described below.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.82 (dd, *J* = 17.7, 11.3 Hz, 1H), 5.60 (d, *J* = 16.6 Hz, 1H), 5.29 (d, *J* = 11.3 Hz, 1H), 4.81 (d, *J* = 5.3 Hz, 1H), 4.39 (m, 1H), 2.54 (dt, *J* = 18, 5.3, Hz 1H), 2.02 (m, 1H), 1.86 (m, 1H), 1.41 (s, 3H), 1.39 (s, 3H).
In a similar procedure, starting with **73** the desired product **67** was obtained in 60 % yield.
67: R_f = 0.43 (hexane/EtOAc, 1:1); $[\alpha]_D^{27}$ +42.4 (*c* = 0.83, $CHCl_3$).
Found: C, 48.78; H, 5.27. ($C_{14}H_{18}O_4NBr$) requires: C, 48.84; H, 5.28%.
IR (neat): ν = 3490, 3200, 1520, 1350 cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.77 (d, *J* = 2.1 Hz, 1H), 6.57 (d, *J* = 2.1 Hz, 1H), 4.54 (d, *J* = 5.5 Hz, 1H), 4.36 (ddd, *J* = 5.3, 5.3, 3.0 Hz, 1H), 3.87 (m, 1H), 3.63 (m, 1H), 2.69 (m, 3H), 2.38 (ddd, *J* = 17.2, 4.6, 4.6 Hz, 3H), 1.97 (m, 1H), 1.86 (m, 1H).
^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.6 (C), 130.4 (C), 127.4 (CH), 136.6 (CH), 115.8 (CH), 109.0 (C), 75.2 (CH), 72.5 (CH), 41.4 (CH_2), 33.4 (CH_2), 31.9 (CH_2), 27.7 (CH_3), 26.4 (CH_2), 26.3 (CH_3).
MS (EI): *m/z* = 344 ($M+H^+$, 56%), 286 (100), 264 (48), 206 (62).
HRMS: 344.0520, ($C_{14}H_{19}O_4{}^{79}BrN$) requires, 344.0498.

Procedure for regeneration of **67**:
2-(6-Bromo-2,2-dimethyl-(3a*S*,7a*R*)-4,5-dihydrobenzo[*d*][1,3]dioxol-7-yl)ethanol (72):
The crude (3a*R*,7a*S*)-5-bromo-2-2-dimethyl-4-vinyl-3a,6,7,7a-tetrahydro-1,3-benzodioxole **71** (2.9 g, ~11.19 mmol) was dissolved in anhyd THF (20 mL) and a solution of 9-BBN (54 mL, 27 mmol, 0.5 M sol. in THF, Aldrich) was added via syringe. After stirring at r.t. for 20 h, the mixture was cooled to 0 °C, and H_2O (2 mL), an aqueous solution of NaOH (6 mL, 3M), EtOH (10 mL) and H_2O_2 (10 mL, 30%) were added. The oxidation was complete after 30 min, and the mixture was concentrated under reduced pressure. The residue was diluted with H_2O/brine mixture (1:1, 60 mL) and extracted with EtOAc (5 x 50 mL). The combined organic phases were dried ($MgSO_4$), filtered through a plug of Celite, and evaporated to dryness. Flash column chromatography (silica gel, 87 g, EtOAc/hexanes 1:1) afforded **72** (1.392 g, 45%); R_f = 0.50 (hexane/EtOAc 7:3); $[\alpha]_D^{26}$ +87.4 (*c* = 1.00, $CHCl_3$).
Found: C, 47.50; H, 6.30. ($C_{11}H_{17}O_3Br$) requires: C, 47.67; H, 6.18%.
IR (neat): ν = 3400, 2950, 2930 cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.52 (d, *J* = 5.6 Hz, 1H), 4.38 (m, 1H), 3.77 (m, 2H), 2.56 (m, 2H), 2.41 (m, 3H), 2.0 (m, 1H), 1.90 (m, 1H), 1.38 (s, 3H), 1.28 (s, 3 H).
^{13}C NMR (100 MHz, $CDCl_3$): δ = 132.0 (C), 126.2 (C), 109.0 (C), 76.1 (CH), 72.6 (CH), 60.9 (CH_2), 38.1 (CH_2), 32.0 (CH_2), 27.6 (CH_3), 26.8 (CH_2), 26.2 (CH_3).
MS (EI): *m/z* = 277 (M^+, 80%), 261 (38), 200 (82), 139 (100).
HRMS: 277.0404, ($C_{11}H_{18}{}^{79}BrO_3$) requires, 277.0439.

5-Bromo-4-(2-methanesulfonyloxyethyl)-2,2-dimethyl-(3a*S*,7a*R*)-6,7-dihydrobenzo[*d*][1,3]dioxole (73):
A solution of (3a*R*,7a*S*)-4-(2-hydroxyethyl)-3a,6,7,7a-tetrahydro-1,3-benzodioxole (1.297 g, 4.68 mmol) and diisopropylethylamine (1.63 mL, 9.36 mmol) in anhyd CH_2Cl_2 (20 mL) was cooled to 0 °C, and mesyl chloride (0.707 mL, 5.614 mmol) was added via syringe. The mixture was allowed to warm up to r.t. over a period of 30 min and was quenched with brine (30 mL). Extraction with CH_2Cl_2 (3×50 mL), drying ($MgSO_4$), filtration and evaporation of the solvent afforded 1.78 g of crude product. Further purification by flash chromatography (silica gel, 80 g, EtOAc/hexanes 1:1) gave the desired mesylate **73** (1.595 g, 95%), which was immediately used in the next step.

2,2-Dimethyl-(3a*R*,9a*R*,11aS)-4,5,10,11-tetrahydro[1,3]dioxolo[4,5-*f*]oxazolo[4,3-*a*]isoquinolin-7-one (68a): and **2,2-Dimethyl-(3a*R*,9a*S*,11a*S*)-4,5,10,11-tetrahydro[1,3]dioxolo[4,5-*f*]oxazolo[4,3-*a*]isoquinolin-7-one (68b):**
A flame dried round bottom flask was set under static Ar and charged with the solution of **67** (2.75 g, 8.0 mmol) in freshly distilled benzene (500 mL). After degassing, (stream of Ar, 30 min.) Bu_3SnH (2.15 mL, 16.0 mmol) was added via glass pipette followed by AIBN (132 mg, 0.80 mmol). The mixture was heated to reflux for 1 h. The solvent was evaporated and the crude product was disproportionated between MeCN and hexane. The MeCN phase was evaporated to dryness, and the residue was purified by flash chromatography (silica gel, 6:4 hexane/EtOAc) to give **68a** (1.193 g, 56%) as the major isomer and **68b** (0.633 g,31 %) as the minor isomer.

(68a) (Major Isomer):
R_f = 0.16 (hexane/EtOAc 7:3); $[\alpha]_D^{25}$ –100.8 (*c* = 0.66, $CHCl_3$).
Found: C, 62.98; H, 7.25; N, 5.08. ($C_{14}H_{19}NO_4$) requires: C, 63.34; H, 7.22; N, 5.28%.
IR (neat): ν = 2980, 1760 cm^{-1}.
^1H NMR (400 MHz, $CDCl_3$): δ = 4.49 (t, *J* = 8.8 Hz, 1H), 4.24 (m, 3H), 3.97 (m, 2H), 3.01 (ddd, *J* = 13.6, 11.6, 4.8 Hz, 1H), 2.32 (d, *J* = 12.4 Hz, 1H), 2.21 (m, 1H), 2.01 (m, 1H), 1.83 (m, 3H), 1.37 (s, 6H).
^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.4 (C), 130.2 (C), 128.4 (C), 108.5 (C), 73.6 (CH), 72.7 (CH), 66.7 (CH_2), 54.9 (CH), 38.3 (CH_2), 28.0 (CH_3), 26.2 (CH_3), 25.4 (CH_2), 24.1 (CH_2), 21.0 (CH_2).
MS (EI): *m/z* = 265 (M^+, 8%), 190 (100), 151 (39), 105 (48).
HRMS**:** 266.1392, ($C_{14}H_{20}NO_4$) requires, 266.1393

(68b) (Minor Isomer):
mp 102–105 °C; R_f = 0.09 (hexane/EtOAc, 7:3); $[\alpha]_D^{26}$ +201.2 (*c* = 0.89, $CHCl_3$).
Found: C, 63.31; H, 7.19; N, 5.27. ($C_{14}H_{19}NO_4$) requires C, 63.34; H, 7.22; N, 5.28%.
IR (neat): ν = 2980, 1720 cm^{-1}.
^1H NMR (400 MHz, $CDCl_3$): δ = 4.47 (t, *J* = 8.5 Hz, 1H), 4.35 (m, 1H), 4.26 (m, 1H), 3.98 (q, *J* = 6.6 Hz, 1H), 3.91 (t, *J* = 7.9 Hz, 1H), 3.01 (ddd, *J* = 13.3, 11.9, 4.7 Hz, 1H), 2.55 (m, 1H), 2.12 (m, 2H), 1.87 (d, *J* = 16.0 Hz, 1H), 1.71 (m, 1H), 1.36 (s, 3H), 1.31 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ = 129 (C), 128.3 (C), 108.9 (C), 75.7 (CH), 72.4 (CH), 66.8 (CH_2), 55.0 (CH), 37.8 (CH_2), 27.9 (CH_3), 26.5 (CH_3), 25.5 (CH_2), 24.3 (CH_2), 19.7 (CH_2).
MS (EI): *m/s* = 265 (M^+, 2%), 250 (28), 190 (51), 105 (100).
HRMS: 266.1394, ($C_{14}H_{20}NO_4$) requires, 266.1393.

5-Bromo-4-(2-methanesulfonyloxyethyl)-2,2-dimethyl-(3a*S*,7a*R*)-6,7-dihydrobenzo[*d*][1,3]dioxole (73):
^1H NMR (400 MHz, $CDCl_3$): δ = 4.48 (br d, *J* = 5.3 Hz, 1H), 4.41 (m, 1H), 4.35 (m, 2H), 3.02 (s, 3H), 2.75 (m, 3H), 2.41 (dt, *J* = 17.0, 5.0 Hz, 1H), 2.02 (m 1H), 1.88 (m, 1H), 1.36 (s, 3H), 1.34 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ = 129.7, 126.8, 109.1, 75.8, 72.4, 67.3, 37.5, 33.6, 31.7, 27.8, 26.4, 26.2.

7,8-Dihydroxy-(7*R*,8*S*,10b*R*)-5,6,7,8,9,10-hexahydrooxazolo[4,3-*a*]isoquinolin-3-one (74):
A suspension of the acetonide **68a** (1.16 g, 4.37 mmol) and Dowex 50X8-100 strongly acidic resin (625 mg) in aq MeOH (50 mL, 90%) was stirred at r.t. overnight. The mixture was filtered through a plug of silica gel and evaporated to dryness. Purification by flash chromatography (silica gel, EtOAc/EtOH 8:2) afforded pure diol **74** (923.2 mg, 94%); mp 150–153 °C; R_f = 0.43 (EtOAc/MeOH 4:1); $[\alpha]_D^{30}$ –22.8 (*c* = 0.67, MeOH).

Found: C, 58.41; H, 6.75; N, 6.16. ($C_{11}H_{16}NO_4$) requires: C, 58.66; H, 6.71; N, 6.22%.
IR (KBr): ν = 2870, 1740 cm^{-1}.
^1H NMR (400 MHz, $CDCl_3$): δ = 4.47 (t, *J* = 8.7 Hz, 1H), 4.25 (t, *J* = 6.7 Hz, 1H), 3.97 (m, 2H), 3.89 (s, 1H), 3.75 (s, 1H), 3.06 (ddd, *J* = 13, 11, 4.7 Hz, 1H), 2.61 (d, *J* = 4.7 Hz, 1H), 2.40 (m, 1H), 2.25 (m, 1H), 1.97 (s, 2H), 1.80 (m, 2H), 1.70 (s, 1H).
^{13}C NMR (100 MHz, $CDCl_3$): δ = 130.4 (C), 130.1 (C), 124.9 (C), 69.0 (CH), 68.3 (CH), 66.6 (CH_2), 55.3(CH), 38.1 (CH_2), 25.3 (CH_2), 24.9 (CH_2), 24.3 (CH_2).
MS (CI): *m/z* = 226 (M^+, 100%), 207 (18), 190 (29).
HRMS: 266.1064, ($C_{11}H_{16}NO_4$) requires, 226.1072.

7-Hydroxy-8-*tert*-butyldimethylsilyloxy-(7*R*,8*S*,10b*S*)-5,6,7,8,9,10-hexahydrooxazolo[4,3-*a*]isoquinolin-3-one (75):
The solution of the diol **74** (882.7 mg, 3.912 mmol) and diisopropylethylamine (1.363 mL, 7.824 mmol) in CH_2Cl_2 (200 mL) was stirred and cooled to –78 °C. A solution of *tert*-butyldimethylsilyltrifluoromethanesulfonate (1.078 mL, 4.694 mmol) in CH_2Cl_2 (50 mL) was added dropwise during a period of 30 min and the stirring at –78 °C was continued for 4 h. The reaction was quenched at –78 °C with H_2O (60 mL) and allowed to warm up to r.t. The CH_2Cl_2 layer was separated, and the aqueous phase was extracted with CH_2Cl_2 (2×50 mL). The combined organic extracts were dried ($MgSO_4$), filtered through Celite and evaporated to dryness. The crude product was dissolved in a mixture of EtOAc/hexane (7:3, 50 mL) and passed through a plug of silica gel. The filtrate was evaporated to dryness and purified by flash chromatography (silica gel, EtOAc/hexane 7:3) to yield the desired product **75** (1.135 g, 85.5%) and bis-protected 7,8-di(*tert*-butyldimethylsilyloxy)-(7*R*,8*S*,10b*S*)-5,6,7,8,9,10-hexahydro[1,3]oxazolo[4,3-*a*]isoquinolin-3-one (173 mg, 10%). The latter was cleaved using tetrabutylammonium fluoride to regenerate the starting diol **74**.

(75):
mp 200–201 °C; R_f = 0.40 (EtOAc/hexane 7:3); $[\alpha]_D^{24}$ –180.9 (*c* = 1.1, $CHCl_3$).
Found: C, 59.97; H, 8.63; N, 3.91. ($C_{17}H_{29}NO_4Si$) requires: C, 60.14; H, 8.61; N, 4.13%.
IR (KBr): ν = 3510, 2920, 2895, 2840, 1745, 1405, 1370, 1305, 1245, 1173, 1100, 1050, 973, 920, 820 cm^{-1}.
^1H NMR (400 MHz, $CDCl_3$): δ = 4.44 (t, *J* = 8.4 Hz, 1H), 4.21 (br t, *J* = 6.9 Hz, 1H), 3.97 (d , *J* = 6.7 Hz, 1H), 3.94 (dd, *J* = 6.7 , 4.4 Hz, 1H), 3.73 (m, 2H), 3.06 (ddd, *J* = 13.6, 11.6, 4.88 Hz, 1H), 2.73 (br s, 1H), 2.37 (br dd, *J* = 17.1, 2.1 Hz, 1H), 2.24 (m, 1H), 1.87 (m, 3H), 1.60 (m, 1H), 0.9 (s, 9H), 0.1 (s, 6 H).
^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.3 (C), 131.1 (C), 130.0 (C), 70.3 (CH), 68.5 (CH), 55.4 (CH), 38.0 (CH_2), 25.7 (CH_3), 24.9 (CH_2), 24.4 (CH_2), 18.0 (C), –4.5 (CH_3), –4.9 (CH_3).
MS (CI): *m/z* = 340 ($M+H^+$, 100%), 322 (10), 282 (12), 208 (1), 191 (6), 190 (47).
HRMS: 340.1958, ($C_{17}H_{30}NO_4Si$) requires, 340.1944.

7-(2-Bromo-6-methoxyphenyloxy)-8-*tert*-butyldimethylsilyloxy-(7*S*,8*S*,10b*R*)-5,6,7,8,9,10-hexahydrooxazolo[4,3-*a*]isoquinolin-3-one (76):
A solution of **75** (551 mg, 1.623 mmol) and 6-bromo-2-methoxyphenol (346 mg, 1.704 mmol) in THF (10 mL) was cooled to 0 °C with stirring. To this solution, a reagent, prepared from Bu_3P (657 mg, 3.246 mmol) and DEAD (565 mg, 3.246 mmol) in THF (10 mL), was added dropwise and the mixture was stirred at 0 °C for 90 min. The reaction was quenched with MeOH (3 mL), and the solvent was evaporated at reduced pressure. The crude product (1.003 g) was further purified by flash chromatography (silica gel, 86 g, EtOAc: hexane 1:1) to yield pure **76** (803 mg, 94%) as a viscous, colorless oil; R_f = 0.23 (CH_2Cl_2/acetone 97:3); T_r = 8.80 min., (Prodigy 5 μ, 80% MeCN/20% H_2O, 5 mM Et_3N.HOAc, 1.0 mL/min., UV λ_{max} 236 nm); $[\alpha]_D^{27}$ –11.5 (*c* = 1.1, $CHCl_3$).

Found: C, 54.59; H, 6.41; N, 2.26. ($C_{24}H_{34}BrNO_5Si$) requires: C, 54.96; H, 6.53; N, 2.67%.
IR (KBr): ν = 3440, 2930, 2850, 1760, 1570, 1470, 1450, 1440, 1260, 1120, 1080, 1030, 840, 750 cm^{-1}.
^1H NMR (500 MHz, $CDCl_3$): δ = 7.12 (dd, *J* = 1.5, 7.9 Hz, 1H), 6.92 (t, *J* = 2x 8.1 Hz, 1H), 6.85 (dd, *J* = 8.2, 1.5 Hz, 1H), 4.53 (d, *J* = 8.9, 8.1 Hz, 1H), 4.39 (br s 1H), 4.31 (br t, *J* = 8.9 Hz, 1H), 4.07 (m, 2H), 3.93 (dd, *J* = 13.1, 6.1 Hz, 1H), 3.84 (s, 3H), 3.01 (ddd, *J* = 13.1, 11.9, 4.4 Hz, 1H), 2.53 (m, 1H), 2.33 (m, 1H), 2.16 (m, 1H), 1.99 (br d, *J* = 16.9 Hz, 1H), 1.7 (m, 2H), 0.78 (s, 9H), –0.08 (s, 3H), –0.12 (s, 3H).
^{13}C NMR (125 MHz, $CDCl_3$): δ = 157.1 (C). 153.4(C), 144.2 (C), 132.4 (C), 125.9 (C), 125.1 (CH), 124.9 (CH), 118.1 (CH), 111.5 (CH), 81.6 (CH), 67.5 (CH_2), 66.9 (CH), 55.7 (CH_3), 54.5 (CH), 38.1 (CH_2), 27.9 (CH_2), 25.6 (CH_3), 25.1 (CH_2), 20.5 (CH_2), 18.0 (C), –5.1 (CH_3), –5.2 (CH_3).
MS (FAB): *m/z* = 524 (M^+, 7%), 322 (65), 190 (100).
HRMS: 524.1450, ($C_{24}H_{35}NO_5{}^{79}BrSi$) requires, 524.1468.

7-(2-Bromo-6-methoxyphenyloxy)-8-hydroxy-(7*S*,8*S*,10b*R*)-5,6,7,8,9,10-hexahydrooxazolo[4,3-*a*]isoquinolin-3-one (77):
To a solution of silyl ether **76** (39 mg, 0.076 mmol) in THF (2 mL) was added TBAF/silica (30 mg) and TBAF/H_2O (30 mg). The mixture was stirred at r.t. for 3.5 h. The crude mixture was concentrated under reduced pressure and purified by column chromatography (silica gel, EtOAc) to afford alcohol **77** (31.2 mg, quant.) as an oil; R_f = 0.30 (CH_2Cl_2/Et_2O 8:2); T_r = 6.86 min., (Prodigy 5 μ, 35% MeCN/65% H_2O, 5 mM Et_3N.HOAc, 1.0 mL/min., UV λ_{max} 254 nm).
^1H NMR (400 MHz, $CDCl_3$): δ = 7.13 (dd, *J* = 8.1, 1.7 Hz, 1H), 6.91 (t, *J* = 8.2 Hz, 1H), 6.85 (dd, *J* = 8.2, 1.5, 1H), 4.66 (br s, 1H), 4.50 (t, *J* = 8.7 Hz, 1H), 4.30 (br t, *J* = 6.9 Hz, 1H), 4.18 (m, 1H), 4.04 (t, *J* = 8.1 Hz, 1H), 3.95 (dd, *J* = 13.1, 6.6 Hz, 1H), 3.84 (s, 3H), 3.02 (ddd, *J* = 13.3 11.9, 4.4 Hz, 1H), 2.60 (m, 1H), 2.20 (m, 1H), 2.00 (m, 3H), 1.80 (m, 1H).
^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.0, 153.0, 144.8, 131.1, 127.7, 125.2, 124.8, 117.5, 111.7, 83.4, 69.4, 55.7, 54.8, 37.9, 27.3, 26.2, 22.1.

10-*tert*-Butyldimethylsilyloxy-6-methoxy-(1*R*,9*S*,10*S*,13*S*,14*R*)-8,16,18-dioxazapentacyclo[11.7.0.0^{1,9}.0^{2,7}.0^{14,18}]icosa-2(7),3,5-trien-17-one (78):
A solution of **76** (747 mg, 1.425 mmol) in benzene (500 mL) was degassed at r.t. with a stream of Ar (30 min.). Bu_3SnH (1.659 g, 5.7 mmol, glass pipette), followed by AIBN (90 mg, 0.548 mmol) was added and the reaction flask was submerged into a preheated (100 °C) oil bath. HPLC (Prodigy 5μ ODS2, 80% MeCN/20% H_2O, 5 mM Et_3N.AcOH buffer, UV λ_{max} 210 nm, 1.0 mL/min.) indicated complete reaction after 50 min. The solvent was removed in vacuo and the remaining oil was distributed between MeCN (100 mL) and hexane (200 mL). The MeCN phase was extracted with hexane (2 × 100 mL), and the combined hexanes back-washed with MeCN (100 mL). The combined MeCN extracts were evaporated in vacuo to yield 833 mg of crude product. Column chromatography (silica gel, 86 g, CH_2Cl_2/acetone 97:3) gave the pure pentacycle **78** (297.1 mg, 47%); R_f = 0.53 (EtOAc/hexanes 1:1); T_r = 14.4 min., (Prodigy 5μ ODS2, 80% MeCN/20%H_2O, 5 mM triethylammonium acetate, UV λ_{max} 210 nm, 1.0 mL/min.); $[\alpha]_D^{28}$ + 23.3 (*c* = 0.89, $CHCl_3$).
Found: C, 64.26; H, 7.99; N, 3.20. ($C_{24}H_{36}NO_5Si$) requires: C, 64.69; H, 7.92; N, 3.14%.
IR ($CHCl_3$): ν = 3010, 2930, 1750, 1620, 1450, 1270, 1120, 910, 840 cm^{-1}.
^1H NMR (500 MHz, $CDCl_3$): δ = 6.87 (dd, *J* = 8.1, 7.3 Hz, 1H), 6.79 (dd, *J* = 8.1, 1.1 Hz, 1H), 6.63 (dd, *J* = 7.5, 1.1 Hz, 1H), 4.49 (d, *J* = 5.6 Hz, 1H), 4.46 (t, *J* = 8.1 Hz, 1H), 4.08 (ddd, *J* = 11.1, 7.9, 5.5 Hz, 1H), 4.02 (dd, *J* = 8.4, 5.7 Hz, 1H), 3.86 (s, 3H), 3.79 (ddd, *J* = 13.9, 5.3, 2.0 Hz, 1H), 3.68 (ddd, *J* = 8.9, 5.5, 5.5 Hz, 1H), 3.09 (ddd, *J* = 13.3, 13.3, 2.9 Hz, 1H), 2.13 (ddd, *J* = 11.0, 5.3, 2.1 Hz, 1H), 1.78 (m, 1H), 1.67 (m, 1H), 1.55 (m, 2H), 1.47 (m, 1H), 1.35 (m, 1H), 0.9 (s, 9H), 0.14 (s, 3H), 0.02 (s, 3H).
^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.8, 145.8, 145.7, 135.6, 122.1, 113.5, 112.3, 89.4, 71.8, 67.6, 56.0, 54.0, 48.6, 38.5, 37.7, 35.4, 26.4, 25.8, 20.2, 18.0.
MS (FAB) *m/z* = 446 ($M+H^+$, 100%), 388 (25), 312 (3), 270 (2), 209 (3).
HRMS: 446.2340, ($C_{24}H_{36}NO_5Si$) requires, 446.2363.

10-Hydroxy-6-methoxy-(1*R*,9*S*,10*S*,13*S*,14*R*)-8,16,18-dioxazapentacyclo[11.7.0.0^{1,9}.0^{2,7}.0^{14,18}]icosa-2(7),3,5-trien-17-one (79):
The solution of TBS-pentacycle **78** (116 mg, 0.260 mmol) and tetrabutylammonium fluoride trihydrate (100 mg) in THF (5 mL) was stirred at r.t. for 4 h. The mixture was filtered through Celite, washed with MeOH and evaporated to dryness. The crude product was purified by flash chromatography (silica gel, 86 g, CH_2Cl_2/acetone 7:3) to yield the desired alcohol **79** (86 mg, quant.).
Cyclization from **77**: To a degassed (Ar sparge) solution of **77** (44.4 mg, 0.108 mmol) in benzene (25 mL) was added Bu_3SnH (63 mg, 58 µl, 0.216 mmol) followed by AIBN (cat.). The reaction vessel was submerged into a preheated oil bath and refluxed was maintained until HPLC indicated the disappearance of starting material, approx. 80 min. The solvent was evaporated under reduced pressure and the oily residue was disproportionated between hexane (60 mL) and MeCN (30 mL). The MeCN layer was extracted with hexane two additional times (2 × 30 mL), and the MeCN was evaporated under reduced pressure. The crude residue was purified by column chromatography (EtOAc/EtOH/NH_4OH 90:5:5) to afford alcohol **79** (10.3 mg, 29%), spectral characteristics of which were identical to those obtained by the TBAF mediated deprotection; mp 118–120 °C; R_f = 0.45 (benzene/dioxane/aq NH_4OH/H_2O 50:40:5:5); T_r = 6.88 min, (Prodigy 5μ ODS2, 30% MeCN/70% H_2O, 5 mM triethylammonium acetate, UV λ_{max} 236 nm, 1.0 mL/min.); $[\alpha]_D^{25}$ +31.3 (*c* = 0.38, $CHCl_3$).
Found: C, 50.49; H, 4.94; N, 3.07. ($C_{18}H_{21}NO_5$+$CHCl_3$) 450.744 (Solvate with $CHCl_3$, four analyses) requires: C, 50.63; H, 4.90; N, 3.10%.
IR ($CHCl_3$): 2936, 1749, 1614, 1492, 1455, 1283, 1215, 908 cm^{-1}.
^1H NMR (500 MHz, $CDCl_3$): δ = 6.92 (t, *J* = 7.8 Hz, 1H), 6.80 (dd, *J* = 8.7, 1.0 Hz, 1H), 6.65 (dd, *J* = 7.8, 1.0 Hz, 1H), 4.53 (d, *J* = 7.3 Hz, 1H), 4.52 (t, *J* = 8,8 Hz, 1H), 4.05 (dd, *J* = 8.8, 5.9 Hz, 1H), 3.89 (ddd, *J* = 11.2, 8.1, 5.9 Hz, 1H), 3.88 (s, 3H), 3.80 (ddd, *J* = 13.9, 5.1, 1.7 Hz, 1H), 3.63 (ddd, *J* = 11.7, 7.3, 5.9 Hz, 1H), 3.07 (ddd, *J* = 13.4, 13.4, 3.8 Hz, 1H), 2.19 (ddd, *J* = 11.2, 4.6, 2.2 Hz, 1H), 1.81 (ddd, *J* = 14.2, 2.4, 2.4 Hz, 1H), 1.75 (m, 1H), 1.65 (ddd, *J* = 13.7, 3.4, 3.4 Hz, 1H), 1.53 (ddd, *J* = 13.2, 11.7, 2.9 Hz, 1H), 1.46 (ddd, *J* = 14.7, 6.4, 3.4 Hz, 1H), 1.37 (ddd, *J* = 13.3, 13.2, 4.9 Hz, 1H).
^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.7 (C), 145.9 (C), 145.1(C), 135.5 (C), 122.4 (CH), 113.2 (CH), 112.0 (CH), 89.6 (CH), 71.7 (CH), 67.6 (CH_2), 55.9 (CH_3), 53.4 (CH), 49.0 (CH_2), 38.6 (CH), 37.6 (C), 34.6 (CH_2), 25.1 (CH_2), 21.1 (CH_2).
MS (FAB): *m/z* = 332 (M^+, 100%), 242 (9), 155 (36), 118 (57).
HRMS: 332.1500, ($C_{18}H_{21}NO_5$+H) requires, 332.1498.

5-Hydroxymethyl-13-methoxy-4-methyl-(1*R*,5*R*,6*S*,9*S*,10*S*)-11,4-oxazatetracyclo[8.7.0^{1,6}.0^{12,17}]heptadeca-12(17)13,15-trien-9-ol (80):
A flame dried round-bottom flask was set under static Ar, and was charged with the solution of the pentacyclic alcohol **79** (86 mg, 0.259 mmol) in CH_2Cl_2 (20 mL). The stirred solution was cooled to 0 °C and solution of DIBAL-H in THF (2.6 mL, 1M, Aldrich) was added, dropwise. After 30 min., HPLC (Primesphere 5μ, C18HC, 30% MeCN/70% H_2O, 5 mM ammonium carbonate, 1.0 mL/min., UV λ_{max} 284 nm) indicated complete conversion and the reaction was quenched at 0 °C with H_2O (1.8 mL), followed by MeOH (1.8 mL) and sat. aq $NaHCO_3$ (3.6 mL). The mixture was allowed to warm to r.t. and the solid was filtered off and washed with CH_2Cl_2 (4 × 40 mL). The combined filtrates were dried (Na_2SO_4) and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (silica gel, 85 g, EtOAc/EtOH/aq NH_4OH 75:20:5) to yield the pure product **80** (72 mg, 87 %) as a viscous, colorless oil; R_f = 0.4 (EtOAc/ EtOH/aq NH_4OH 75:20:5); T_r = 2.99 min. (Primesphere 5μ, C18HC, 30% MeCN/70% H_2O, 5mM ammonium carbonate, 1.0 mL/min., UV λ_{max} 284 nm); $[\alpha]_D$ ^{26} +34.7 (*c* = 1.51, $CHCl_3$).
IR ($CHCl_3$): ν = 2960, 1380, 1130, 1220, 770 cm^{-1}.
1H NMR (500 MHz, $CDCl_3$): δ = 6.87 (t, *J* = 7.8 Hz, 1H), 6.75 (d, *J* = 8.3 Hz, 1H), 6.73 (d, *J* = 7.8 Hz, 1H), 4.49 (d, *J* = 7.3 Hz, 1H), 3.89

(dd, *J* = 11.7, 2.9 Hz, 1H), 3.85 (s, 3H), 3.64 (dd, *J* = 11.7, 1.0 Hz, 1H), 3.58 (ddd, *J* = 11.7, 6.8, 5.8 Hz, 1H), 2.78 (ddd, *J* = 12.2, 3.4, 3.4 Hz, 1H), 2.57 (bdd, *J* = 10.7, 3.4, ~1.5 Hz, 1H), 2.54 (ddd, *J* = 12.2, 12.2, 2.0 Hz, 1H), 2.35 (s, 3H), 2.21 (br d, *J* = 10.7 Hz, 1H), 1.73 (m, 3H), 1.65 (m, 1H), 1.46 (m, 3H).

^{1}H NMR (500 MHz, benzene-d_6): δ = 6.76 (t, *J* = 7.8 Hz, 1H), 6.59 (d, *J* = 3.2 Hz), 6.57 (d, *J* = 4.7 Hz, 1H), 4.47 (d, *J* = 7.1 Hz, 1H), 3.63 (dd, *J* = 11.7, 3.1 Hz, 1H), 3.47 (s, 3H), 3.46 (m, 1H), 3.43 (br d, *J* = 10.9 Hz, 1H), 2.58 (br d, *J* = 10.7 Hz, 1H), 2.26 (dt, *J* = 12.1, 3.6 Hz, 1H), 2.03 (td, *J* = 12.7, 2.2 Hz, 1H), 1.90 (s, 3H), 1.77 (br d, *J* = 10.9 Hz, 1H), 1.60 (dt, *J* = 13.8, 1.9 Hz, 1H), 1.35 (br m, 5H).
^{13}C NMR (125 MHz, $CDCl_3$): δ = 145.7, 145.2, 137.3, 122.1, 113.5, 111.5, 90.0, 72.9, 63.4, 58.4, 55.9, 52.0, 49.2, 42.8, 35.6, 33.3, 25.8, 22.6.

MS (FAB): *m/z* = 320 (M+H$^+$, 100%), 288 (38), 219 (3), 213 (3), 169 (5), 154 (10), 137 (15), 109 (21), 94 (44).
HRMS (FAB): 320.1877, ($C_{18}H_{26}NO_4$+H) requires, 320.1862.

5-Hydroxymethyl-9-*tert*-butyldimethylsilyoxy-13-methoxy-4-methyl-(1*R*,5*R*,6*S*,9*S*,10*S*)-11,4-oxazatetracyclo[8.7.0.0^{1,6}.0^{12,17}]hep-tadeca-12(17),13,15-triene (81):
A solution of the pentacyclic substrate **78** (25.0 mg, 0.056 mmol) in freshly distilled CH_2Cl_2 (6 mL) was set under static Ar atmosphere, and cooled with stirring to 0 °C. A solution of DIBAL-H (281 µL, 1M in CH_2Cl_2, Aldrich) was added via syringe. Stirring at 0 °C was continued for 1 h, and the mixture was allowed to warm up to r.t. After additional 2 h, the reaction was quenched with H_2O (0.8 mL), followed by MeOH (0.8 mL) and sat. aq $NaHCO_3$ (1.6 mL) and stirring continued for 30 min. The solid was filtered off, washed with CH_2Cl_2 (6 × 6 mL) and H_2O (6 × 6 mL). The organic phase was separated, dried ($MgSO_4$), and the solvent was evaporated under reduced pressure to yield the crude product (27 mg). HPLC analysis (Primesphere 5m C18HC, 70% MeCN/30% H_2O, 5 mM triethylammonium acetate, UV λ_{max} 210 nm, 1.0 mL/min.) indicated 79% purity. Column chromatography (silica gel, 15 g, EtOAc/EtOH/NH_4OH 70:25:5) gave pure **81** (19.3 mg, 79%); R_f = 0.53 (EtOAc/EtOH/NH_4OH 70:25:5); T_r = 7.94 min. (Primesphere 5μ C18HC, 70% MeCN/30% H_2O, 5 mM triethylammonium acetate, UV λ_{max} 210 nm, 1.0 mL/min.).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.87 (dd, *J* = 8.1, 7.5 Hz, 1H), 6.77 (dd, *J* = 8.2, 1.1 Hz, 1H), 6.74 (dd, *J* = 7.3, 1.1 Hz, 1H), 4.45 (d, *J* = 6.6 Hz, 1H), 3.90 (dd, *J* = 11.9, 3.2 Hz, 1H), 3.86 (s, 3H), 3.64 (dd, *J* = 11.6, 1.0 Hz, 1H), 3.57 (m, 1H), 2.77 (ddd, *J* = 12.1, 3.8, 3.8 Hz, 1H), 2.63 (ddd, *J* = 12.7, 12.7, 2.4 Hz, 1H), 2.57 (br d, *J* = 11.2 Hz, 1H), 2.38 (s, 3H), 2.33 (br d, *J* = 10.7 Hz, 1H), 1.76 (ddd, *J* = 14.2, 2.9, 2.9 Hz, 1H), 1.50 (m, 4H), 0.90 (s, 9H), 0.13 (s, 3H), 0.02 (s, 3H).
^{13}C NMR (125 MHz, $CDCl_3$): δ = 145.7, 145.6, 137.6, 121.6, 113.5, 111.9, 90.7, 73.3, 63.5, 58.4, 55.9, 51.9, 49.1, 42.7, 35.8, 33.2, 27.6, 25.8, 22.6, 22.2, 18.1.

5-Chloromethyl-9-*tert*-butyldimethylsilyoxy-13-methoxy-4-methyl-(1*R*,5*R*,6*S*,9*S*,10*S*)-11,4-oxazatetracyclo[8.7.0.0^{1,6}.0^{12,17}] heptadeca-12(17),13,15-triene (82):
A flame dried round-bottom flask was set under static Ar atmosphere, and was charged with LiCl (30 mg, 0.708 mmol). A solution of substrate **81** (12.0 mg, 0.028 mmol) in CH_2Cl_2 (3 mL) was introduced via syringe, followed by Et_3N (5.6 mg, 0.055 mmol, in 100 µL of CH_2Cl_2, stock solution). The mixture was cooled with stirring to 0 °C and a solution of MsCl (2.57 µL, 0.033 mmol) in CH_2Cl_2 (100 µL, stock solution) was added. The reaction was monitored via HPLC (Prodigy 5 μ, 80% MeCN/20% H_2O, 5 mM triethylammonium acetate, UV λ_{max} 236 nm, 1.0 mL/min.). The starting material (T_r = 5.16 min) disappeared within 1 h, and the mixture contained 72% of the (presumed) mesylate (T_r = 6.03 min.), and 9% of the desired chloride (T_r = 12.5 min.). After a total of 6 h, HPLC indicated less than 3% of the mesylate and solvent was removed under reduced pressure. Flash chromatography (silica gel, 8.6 g, EtOAc, saturated with NH_4OH) yielded pure **82** (10.9 mg, 87%) as a viscous oil; R_f = 0.55 (EtOAc/EtOH/NH_4OH 70:25:5); T_r = 12.51 min. (Prodigy 5μ, 80 % MeCN/ 20 % H_2O, 5 mM triethylammonium acetate, UV λ_{max} 236 nm, 1.0 mL/min.).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.87 (t, *J* = 7.81 Hz, 1H), 6.77 (d, *J* = 7.6 Hz, 1H), 6.74 (d, *J* = 7.3 Hz, 1H), 4.46 (d, *J* = 6.6 Hz, 1H), 3.86 (s, 3H), 3.20 (ABq, *J* = 12.7 Hz, 2H), 3.60 (m, 1H), 3.05 (dd, *J* = 14.2, 7.1 Hz, 1H), 2.83 (ddd, *J* = 12.0, 3.9, 3.9 Hz, 1H), 2.53 (m, 3H), 2.41 (s, 3H), 2.30 (dddd, *J* = 11.2, 11.2, 3.7, 3.7 Hz, 1H), 1.95 (br d, *J* = 10.3 Hz, 1H), 1.6 (m, 3H), 0.90 (s, 3H), 0.14 (s, 3H), 0.01 (s, 3H).

13-Methoxy-4-methyl-9-oxo-(1*R*,5*R*,6*S*,10*S*)-11,4-oxazatetracyclo[8.7.0^{1,6}.0^{12,17}]heptadeca-12,(17),13,15-triene-5-carbaldehyde (83):
A flame dried round-bottom flask was set under static Ar atmosphere, charged with CH_2Cl_2 (4 mL) and oxalyl chloride (86 µL, 2 M solution in CH_2Cl_2, Aldrich, 0.172 mmol,). The mixture was cooled to –78 °C and a CH_2Cl_2 solution of DMSO (344 µl, 1M, 0.344 mmol) was introduced via syringe. After stirring for 10 min. a solution of the tetracyclic diol **80** (5.5 mg, 0.0172 mmol) in CH_2Cl_2 (1.0 mL) was added and the temperature was allowed to warm up to 0 °C during 4 h. A CH_2Cl_2 solution of Et_3N (412 µL, 0.412 mmol, 1M) was added, the cooling bath was removed and stirring was continued for an additional 30 min. The reaction was quenched with sat. $NaHCO_3$ (2.0 mL, 1:10 solution), stirred for 5 min and the organic solvent was separated. The aqueous layer was further extracted with CH_2Cl_2 (2 × 4 mL), the combined organic phases were dried (Na_2SO_4) and the solvent was removed under reduced pressure. Column chromatography (silica gel, 5.4 g, EtOAc/ethanol/aq NH_4OH 90:5:5) gave the pure product (3.6 mg, 66%) as a viscous oil, which was used immediately in the next step; R_f = 0.6 (EtOAc/EtOH/aq NH_4OH 90:5:5); T_r = 12.8 min. (Primesphere 5 μ, C18HC, 30 % MeCN / 70 % H_2O, 5 mM ammonium carbonate, UV λ_{max} 283 nm, 1.0 mL/min.).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.45 (s, 1H), 6.93 (t, *J* = 7.8 Hz, 1H), 6.79 (d, *J* = 7.3 Hz, 1H), 6.70 (t, *J* = 7.8 Hz, 1H), 4.60 (s, 1H), 3.88 (s, 3H), 3.87 (m, 1H), 2.90 (br d, *J* = 12.2 Hz, 1H), 2.50 (m, 5H), 2.27 (s, 3H), 2.20 (m, 2H), 1.88 (ddd, *J* = 13.9, 2.4, 2.4 Hz, 1H), 1.77 (dddd, *J* = 14.9, 14.9, 7.6, 3.4 Hz, 1H).

10-Hydroxy-14-*epi*-*ent*-dihydrocodeinone (84):
The crude oxo aldehyde **83** (12.0 mg, 0.038 mmol) was dissolved in trifluoromethanesulfonic acid (neat, 400 μL) at r.t. A deep red colored solution resulted. The reaction progress was monitored by HPLC (Prodigy 5μ, ODS2, MeCN/H_2O 30:70, 5 mM ammonium acetate buffer, 1.0 mL/min., UV λ_{max} 210 nm), which, after 10 min indicated complete disappearance of the starting material ($T_{r,\,SM}$ = 11.10 mins, T_r, product 3.97 min).

The mixture was diluted with $CHCl_3$ (8 mL), cooled to –5 °C, and carefully quenched with 5 g of ice. The aqueous layer was basified (1.0 M KOH), and extracted with $CHCl_3$ (6 × 6 mL). The combined organic extracts were dried (Na_2SO_4), and the solvent was removed under reduced pressure to yield 9.3 mg of the crude base, as an viscous oil. Column chromatography (silica gel, 7.0 g, $CHCl_3$/MeOH/NH_4OH 90:9:1) gave 6.9 mg (58 %) of the pure morphinan; R_f = 0.30 ($CHCl_3$/MeOH/NH_4OH 90:9:1); λ_{max} (MeCN): 286, 248, 236 and 214 nm.

^{1}H NMR (500 MHz, benzene-d_6): δ = 6.84 (dd, *J* = 8.3, 0.7 Hz, 1H), 6.67 (d, *J* = 8.3 Hz, 1H), 4.80 (s, 1H), 4.18 (s, 1H), 3.65 (s, 3H), 2.77 (br d, *J* = 2.1 Hz, 1H), 2.28 (m, 1H), 2.20 (s, 3H), 2.10 (m, 1H), 2.08 (dd, *J* = 10.2, 6.2 Hz, 1H), 1.99 (dt, *J* = 12.2, 3.6 Hz, 1H), 1.86 (ddd, *J* = 16.0, 10.6, 2.1 Hz, 1H), 1.76 (dt, *J* = 12.6, 5.7 Hz, 1H), 1.31 (m, 1H).
^{1}H NMR (500 MHz, MeOH-d_4): δ = 6.95 (dd, *J* = 8.3, 0.7 Hz, 1H), 6.84 (d, *J* = 8.3 Hz, 1H), 4.98 (s, 1H), 4.97 (s, 1H), 3.88 (s, 3H), 2.99 (br d, *J* = 2.1 Hz, 1H), 2.77 (ddd, *J* = 13.1, 10.4, 6.2 Hz, 1H), 2.72 (dt, *J* = 12.3, 3.5 Hz, 1H), 2.57 (dd, *J* = 11.8, 4.9 Hz, 1H), 2.53 (s, 3H), 2.47 (dt, *J* = 12.8, 5.3 Hz, 1H), 2.38 (m, 1H), 2.29 (dt, *J* = 12.2, 3.5 Hz, 1H), 1.89 (br dt, *J* = 13.0, 3.2 Hz, 1H), 1.75 (br d, *J* = 13.3 Hz, 1H), 1.60 (br d, *J* = 10.3 Hz, 1H).
MS (FAB-Glycerine): *m/z* = 316.1561 (52%), 298.1383 (100), 225.1987 (62), 207.0850 (10), 115.0453 (6), 98.0988 (5).
MS (FAB-NBA): *m/z* = 316.1546 (62%), 225.1802 (17), 107.0620 (21).

MS (EI, 70 eV): *m/z* = 315.1511 (62%), 258.1210 (17), 224.1931 (18), 143.1195 (38), 98.0914 (56), 70.0646 (100).
HRMS (FAB-Glycerine): 316.1561 (1.2 mmu), ($C_{18}H_{22}NO_4$+H) requires, 316.1549. For $(M+H)^+ - H_2O$: 298.1383 (6.0 mmu), ($C_{18}H_{22}NO_4$+H) – H_2O requires 298.1443.
FAB-Nitrobenzyl alcohol: 316.1546 (0.3 mmu), ($C_{18}H_{22}NO_4$+H) requires 316.1549.
EI (70 eV): 315.1511 (-4 mmu), ($C_{18}H_{21}NO_4$) requires, 315.1471.

The authors are grateful to Mallinckrodt Specialty Chemicals, TDC Research, Inc., NSF (CHE-9315684, CHE-9521489, and CHE-9615112) and the University of Florida for financial support of this work. Special thanks are extended to Khalil A. Abboud (University of Florida) for determination of the absolute stereochemistry of diol ***74*** *and Matthew R. Ellis (Summer Undergraduate Research Participant) for his assistance in preparation of some starting materials.*

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b) The primary medical use of morphine is for the relief of very strong pain, such as that derived from severe wounds, some tumors or major surgery procedures. Because morphine acts on respiratory function in higher doses while maintaining no influence on cardiac activity it is an ideal anesthetic for heart surgery. Derivatives of morphine such as codeine are used as cough suppressants, while antagonists such as naloxone or naltrexone are used in the treatment of accidental overdose. Further chemical manipulation of morphine and other natural opium alkaloids provides a wide family of agonists and antagonists that have become essential in modern medical procedures.
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