# Studies Culminating in the Total Synthesis of (*dl*)-Morphine†,[1]

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The development of a vinyl sulfone based strategy that resulted in the synthesis of (*dl*)-morphine from 2-allylcyclohexane-1,3-dione and isovanillin is detailed.

## Introduction

The heteropentacyclic topology of the morphine alkaloids coupled with their unique pharmacological profile has prompted several total synthetic efforts.[2] Several years ago we initiated a total synthesis of morphine based on the efficient conversion of **1** into **2a,b** under the conditions of metal–halogen exchange (99%, Scheme I).[3] A recent communication from this laboratory described the completion of this effort.[4] This paper reports the chemical details of this total synthesis.

The penultimate target of the synthetic plan was codeinone **3a**, a well-precedented progenitor of morphine (Scheme II).[5] Retro-Michael cleavage of the C9–N bond produced amino dienone **4a**. In practice, we have reported a relay study which demonstrated the spontaneous 1,6-Michael addition that occurred upon biphasic neutralization of the amino dienone salt **4b**.[6] Elaboration of the target dienone **4c** was planned to proceed via functional group manipulation of the tetracyclic sulfone **5**. Thus, in an extrapolation of the **1** → **2a,b** conversion, sulfone **5** was envisaged to be synthesized via the tandem intramolecular conjugate addition/intramolecular alkylation reaction of γ-(aryloxy)vinyl sulfone **6a**, initiated by metal–halogen exchange. This tandem strategy had been demonstrated in both the intra- and intermolecular versions by this group with less sterically demanding substrates.[3,7] A convergent assembly of **6a** from the vinyl epoxy sulfone **7** and the phenol **8** was planned.

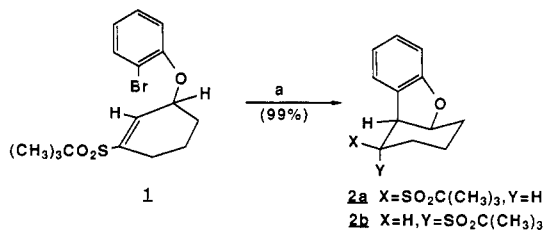
## Results

**Phenol Synthesis.** The tetrasubstituted phenols used throughout this study were synthesized from commercially available isovanillin (Scheme III).[8] Bromination of isovanillin with bromine in sodium acetate buffered acetic acid regiospecifically produced 2-bromoisovanillin (**9a**) in 68% isolated yield.[9] Methoxymethylation of **9a** under standard conditions afforded MOM ether **9b** (94%) which was converted to the styrene **10a** via biphasic Wittig methenelation (86%).[10] Methanolysis of **10a** provided the styrylphenol **10b** (93%) used in our early studies. Hydroboration of **10a** with disiamylborane followed by oxidation afforded the phenethyl alcohol **11a** (95%).[11] Methanolysis of **11a** gave phenol **11b** (91%), which upon treatment with carbon tetrabromide and triphenylphosphine in acetonitrile produced phenethyl bromide **8** (92%).[12] Thus the requisite phenol **8** was available in six steps and 43% overall yield from isovanillin.

**Epoxide Synthesis and Attempted Coupling.** Our initial attempts to assemble the carbon skeleton of **7** by the alkylation of 1,3-cyclohexanedione with *N*-tosylaziridine (TAZ)[13] (**13**) were unsuccessful. A variety of conditions reported to favor C- over O-alkylation returned only O-alkylated product.[14] However, alkylation of the masked 1,3-dione, dihydrodimethoxybenzene **12**, according to the Piers protocol,[15] with TAZ (**13**) followed by alkylation of the resulting sulfonamide anion intermediate with methyl iodide and hydrolysis of the crude product, afforded the 2-substituted 1,3-dione **14a** in good yield (80–85%). This process was conveniently performed on a 100-mmol scale (Scheme IV).

β-Sulfonyl enone **15c** was initially synthesized by the acid-catalyzed reaction of **14a** with thiophenol to produce the sulfide **15b** (74%) followed by MCPBA oxidation (94%). Our desire to expedite the **14a** → **15c** transfor-

**Scheme I**[a]




**1** **2a** X=SO2C(CH3)3,Y=H **2b** X=H,Y=SO2C(CH3)3

[a] (a) *t*-BuLi/THF/−78 °C (**2a**:**2b** 96:4).

† Dedicated to E. J. Corey on the occasion of his 60th birthday.

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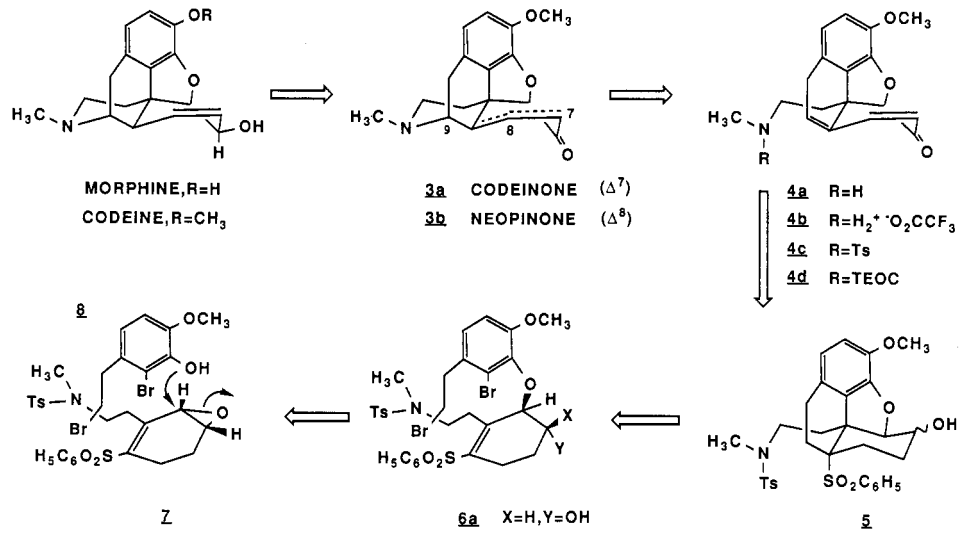
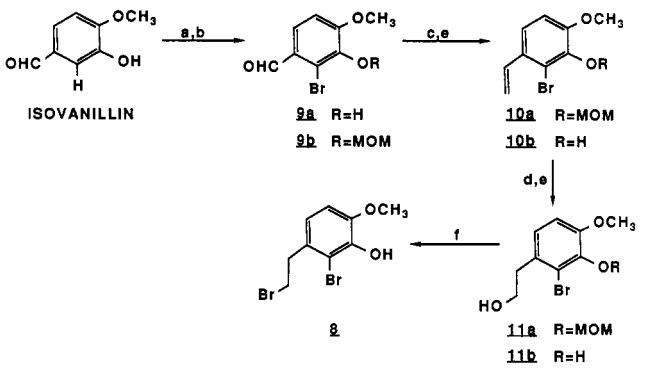
**Scheme II**[a]




[a] TEOC = $(CH_3)_3SiCH_2CH_2OCO$-.

**Scheme III**[a]




[a] (a) $Br_2$/HOAc/NaOAc, 2 h, 25 °C (68%); (b) $H_3COCH_2Cl$/NaH/DMF, 18 h, 25 °C (94%); (c) $(C_6H_5)_3P^+$–$CH_3I^-$/5 N NaOH/$C_6H_6$, 12 h, 25 °C (86%); (d) $(Sia)_2BH$/THF, 1 h, 4 °C, then $H_2O_2$/NaOH, 1 h, 4 °C (95%); (e) TsOH/$CH_3OH$, 4 h, 25 °C (93% **10b**, 91% **11b**); (f) $CBr_4$/$(C_6H_5)_3P$/$CH_3CN$, 1 h, 25 °C (92%).

mation and avoid the use of large quantities of MCPBA was realized by conversion of the dione **14a** into the enol mesylate **15a** with mesyl chloride and triethylamine (100%) followed by the treatment of **15a** with sodium benzenesulfinate in NMP (82%). Reduction of the enone sulfone **15c** with DIBAL-H or sodium borohydride/cerium(III) chloride[16] afforded the allylic alcohol **16a** in good yield (>90%).

A number of attempts to synthesize diene **17** by the dehydration of alcohol **16a** were unsuccessful, resulting in decomposition and/or multicomponent mixtures. These included the treatment of **16a** with $POCl_3$/pyridine,[17a] iodine (toluene),[17b] Burgess' reagent (benzene),[17c] sulfuric acid (dichloromethane), *p*-toluenesulfonic acid (benzene), and pyridinium tosylate (toluene).

Treatment of **16a** with mesyl chloride and triethylamine in dichloromethane afforded mesylate **16b** (100%) which was unstable to chromatographic purification on silica gel. DBU-mediated elimination of mesylate **16b** produced the allylic sulfone **18**, demonstrating the enhanced allylic acidity of γ-oxidovinyl sulfones, a property which plagued our efforts at several junctions (vide infra). Palladium(0)-catalyzed elimination of the mesylate **16b** afforded the diene **17** in gratifying 82% yield.[18] Standard epoxidation of **17** with MCPBA proved rather low yielding; however, MCPBA epoxidation in the presence of solid sodium bicarbonate produced the epoxide **7** in 94% yield.[19]

The synthetic approach (see Scheme II) called for acid- or base-catalyzed opening of epoxide **7** at the activated allylic position by a substituted phenol to produce the *trans*-(aryloxy)hydroxy ethers similar to **6a**. Several attempts to realize this epoxide opening with **7** and *o*-bromophenol or phenols **10b** and **8** were unsuccessful. These included the phenol and $BF_3$ etherate (dichloromethane), the lithium phenoxide (ethanol or NMP), the lithium phenoxide and trimethylaluminum (toluene), and the TBS-protected phenol and TMSOTf, among many others. Our inability to detect the desired phenyl ethers as even minor products in these reactions forced us to abandon this approach to the synthesis of the cyclization substrates **6a**.

**Model Cyclization Studies.** In spite of our lack of success in opening epoxide **7** with phenols, we pursued the total synthesis by studying the intramolecular cyclization of the γ-(aryloxy)vinyl sulfone **19** under the conditions of metal–halogen exchange (Scheme V). This substrate, **19**, was synthesized by the Mitsunobu coupling (triphenylphosphine/diethyl azodicarboxylate, TPP/DEAD)[20] of styrylphenol **10b** and alcohol **16a** (95%). Treatment of **19** (0.025 M in THF/hexane, 1/1) with *n*-butyllithium at −78 °C followed by quench produced only the allylic sulfone **20** (26% isolated),[21] a product expected to arise by competitive γ-deprotonation to produce sulfone-stabilized allylic anion [**20**-Li] followed by kinetic quench α to the phenyl sulfone moiety.

It seemed prudent to probe the mechanism of this deleterious process before proceeding with our synthetic

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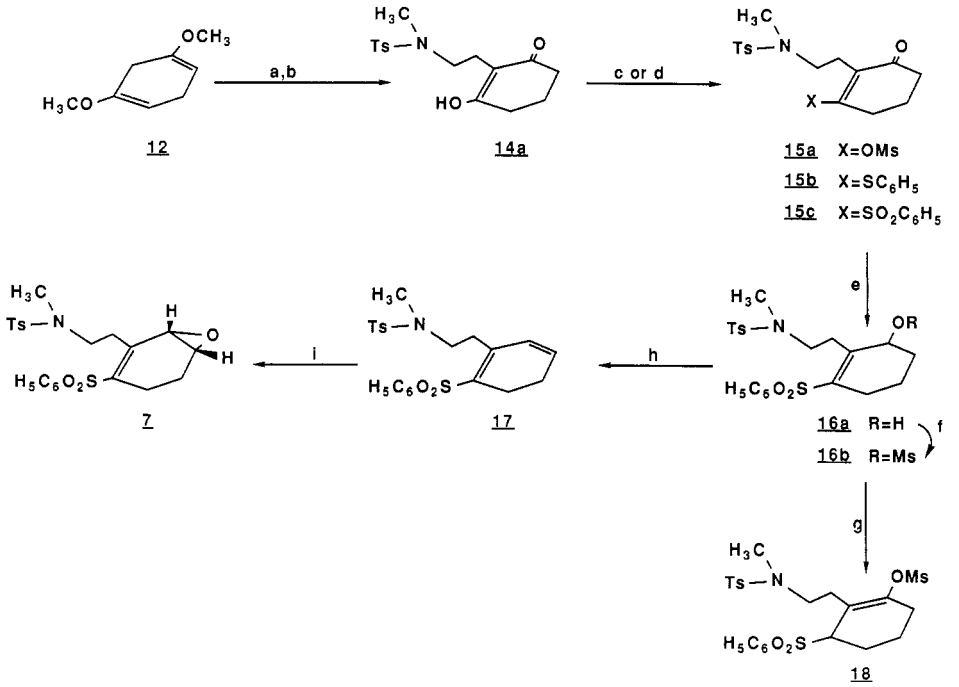
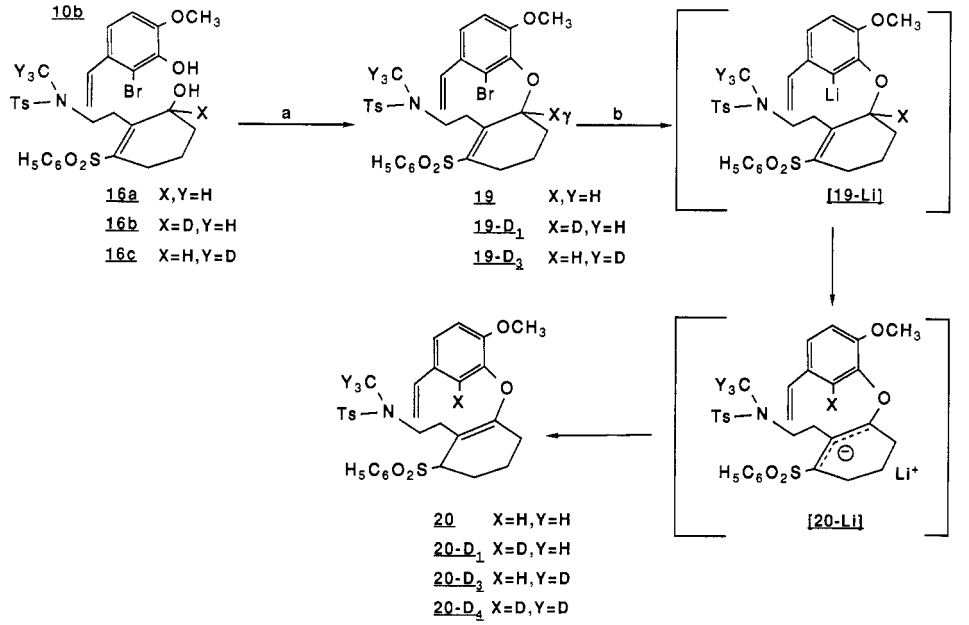
(21) $^1H$ NMR analysis of the crude product verified that **20** was indeed the major product. Silica gel chromatographic purification of **20** as well as the other vinyl ethers encountered in this study was hampered by competing hydrolysis.

**Scheme IV**[a]




[a] (a) *t*-BuLi/THF/HMPA/TAZ **13**, −78 °C, then $CH_3I$, −78 °C → 25 °C; (b) $(CH_3)_2CO$/2 N HCl, 0.5 h, 4 °C (80–85%); (c) $C_6H_5SH$/cat. TsOH/$C_6H_6$, 16 h, 80 °C (74%), then MCPBA/$CH_2Cl_2$, 16 h, 25 °C (94%); (d) MsCl/$Et_3N$/$CH_2Cl_2$, −78 °C → 4 °C (100%), then $C_6H_5SO_2^-Na^+$/NMP, 8 days, 25 °C (82%); (e) DIBAL-H/THF, −78 °C → 4 °C (99%); (f) MsCl/$Et_3N$/$CH_2Cl_2$, −78 °C → 4 °C (100%); (g) DBU/$C_6H_5CH_3$, 16 h, 111 °C; (h) $(C_6H_5)_3P$/Pd[$(C_6H_5)_3P]_4$/THF, 0.75 h, 60 °C (84%); (i) MCPBA/$NaHCO_3$/$CH_2Cl_2$, 3 h, 25 °C (94%).

**Scheme V**[a]

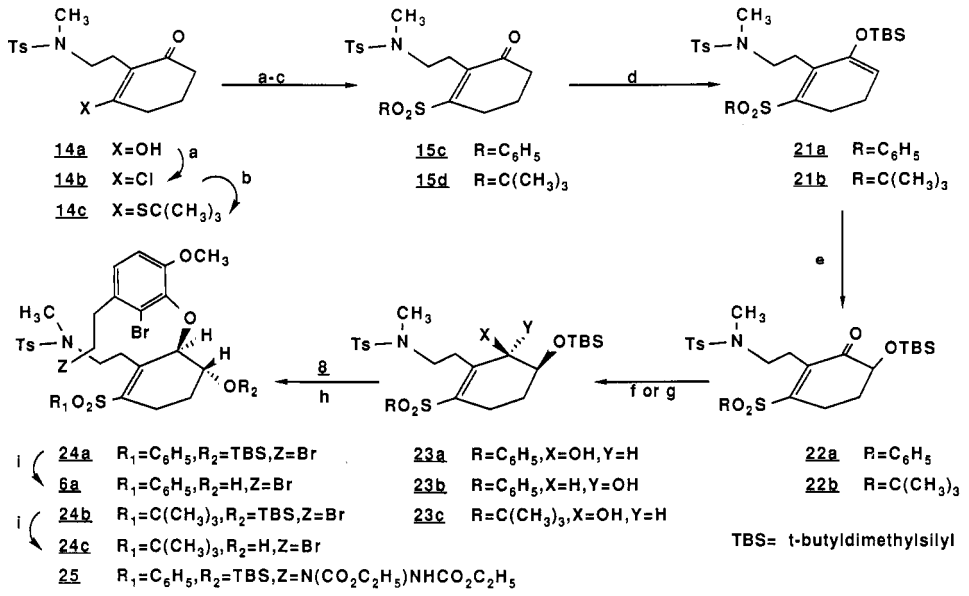



[a] (a) $(C_6H_5)_3P$/DEAD/THF, 15 min, 25 °C (95% **19**, 81% **19**-$D_1$, 73% **19**-$D_3$); (b) *n*-BuLi/THF/hexane, −78 °C (26%).

effort. An experiment employing deuterium-labeled analogues of **19** unequivocably demonstrated the intramolecularity of this γ-deprotonation. The deuterium-labeled γ-(aryloxy)vinyl sulfones **19**-$D_1$ and **19**-$D_3$ were synthesized in the same manner as **19** (Schemes IV and V) with slight variation. The deuteriomethine of **19**-$D_1$ was introduced by sodium borodeuteride/cerium(III) chloride reduction of enone sulfone **15c**. The deuteriomethyl of **19**-$D_3$ was introduced by the quenching of the TAZ alkylation of **12** with trideuteriomethyl iodide. Mitsunobu coupling as before afforded **19**-$D_1$ and **19**-$D_3$.

Individual treatment of **19**-$D_1$ and **19**-$D_3$ (0.05 M in THF/hexane, 1/1) with *n*-butyllithium, as before, provided the following results: metal–halogen exchange of **19**-$D_1$ produced only the monodeuterioallyl sulfone **20**-$D_1$ by $^1H$ NMR analysis of the crude reaction mixture (26% isolated). The position of deuterium on the aryl ring of **20**-$D_1$ demonstrated that the metalating reagent, *n*-butyllithium, was indeed reacting via metal–halogen exchange to produce aryllithium intermediate [**19**-Li] and was not directly participating in the γ-deprotonation. Similarly, **19**-$D_3$ produced **20**-$D_3$ (26% isolated).

**Scheme VI**[a]




[a] (a) $(C_6H_5)_3P/CCl_4/CH_3CN$, 2 h, 25 °C (92%); (b) $(CH_3)_3CSH/NaH/THF$, 0.5 h, 4 °C (95%); (c) $MCPBA/CH_2Cl_2$, 3.5 h, −20 °C → 25 °C (91%); (d) $TBSOTf/Et_3N/CH_2Cl_2$, 4 h, 25 °C (77% **21a**); (e) $MCPBA/CH_2Cl_2$, 0.5–4 h, −78 °C → 25 °C (68% **22a**, 65% **22b**); (f) $CeCl_3/NaBH_4/CH_3OH/CH_2Cl_2$, 0.25 h, −20 °C (99% **23a**, 98% **23c**); (g) $Al(O\text{-}i\text{-}Pr)_3/C_6H_5CH_3/(CH_3)_2CHOH$, 6 h, 120 °C (48% **23b**); (h) $n\text{-}Bu_3P/DEAD/THF$, 0.75 h, 4 °C → 25 °C (87% **24a**, 55% **24b**); (i) 48% $HF/CH_3CN$, 3.5 h, 25 °C (98% **6a**, 100% **24c**).

In an experiment designed to demonstrate intramolecular deprotonation, an equimolar mixture of **19**-$D_1$ and **19**-$D_3$ (0.05 M in THF/hexane, 1/1) was treated with *n*-butyllithium at −78 °C followed by quench. Chromatographic isolation provided a mixture of deuterium-labeled allyl sulfones **20**-M (34%). Mass spectral analysis of **20**-M utilizing the relative ion abundance of the $[(M + H) - HSO_2C_6H_5]^+$ ions verified that the γ-deprotonation process was >95% *intra*molecular.[22] That is, allyl sulfone mixture **20**-M was composed of **20**-$D_1$ and **20**-$D_3$, but *no* **20** or **20**-$D_4$.

**Alternate Synthesis of Cyclization Substrate 6a.** Reasoning that the required cyclization substrates, i.e., those containing the vicinal oxido moiety, might provide a handle through which the unfavorable γ-deprotonation process could be avoided, we approached their synthesis with the new strategy depicted in Scheme VI. Returning to the enone sulfone **15c**, treatment with *tert*-butyldimethylsilyl triflate (TBSOTf) and triethylamine in dichloromethane produced the silyl dienyl ether **21a**, which was routinely oxidized after an aqueous workup with MCPBA to afford the α-silyloxy enone sulfone **22a** (68% from **15c**).[23] Attempts to improve the yield in this two-step conversion by focusing on the time/temperature variables in the oxidation were not successful and were complicated by the inability to separate **21a** and **22a** by TLC. The oxidation did not occur at a convenient rate at −78 °C. The stability of **21a** was demonstrated on several occasions when it survived the aqueous workup and silica gel chromatography employed to isolate **22a**. An attempt to use solid sodium bicarbonate buffered MCPBA oxidation resulted in a lower yield of **22a** (42%). Cerium(III) chloride mediated sodium borohydride reduction of **22a** efficiently produced the *cis*-silyloxy alcohol **23a** (99%). The cis stereochemistry of **23a** was assumed on the basis of steric approach control in the reduction and verified by further chemical transformations.

The coupling of **23a** and the phenol **8** was accomplished by a modified Mitsunobu procedure. An equimolar mixture of the alcohol **23a** and the phenol **8** (in THF) was treated with a slight excess of an equimolar mixture of tri-*n*-butylphosphine (TBP) and DEAD. Using this protocol, **24a** was obtained in 87% yield after simple silica gel plug chromatography. The usual Mitsunobu reagents (TPP/DEAD) did not produce any **24a** under several different mixing protocols. The standard Mitsunobu mixing procedure of adding tri-*n*-butylphosphine to a mixture of DEAD, alcohol **23a**, and phenol **8** in THF produced **24a** (53%) accompanied by **25** (16%) and returned **23a** (21%) and **8** (27%).

Treatment of **24a** with tetrabutylammonium fluoride in THF brought about desilylation accompanied by competitive dehydrobromination of the phenethyl bromide moiety. Alcohol **6a** was cleanly obtained from **24a** by cleavage with 48% HF in acetonitrile (98%).[24]

Our suspicions that the acidity of the γ-methine proton could be moderated by the electronic nature of the sulfone moiety led us to synthesize the comparable *tert*-butyl sulfone cyclization adducts **24b** and **24c**. This was accomplished by application of the previously described chemistry to *tert*-butyl enone sulfone **15d** (Scheme VI).

Initially we attempted to synthesize **15d** by the addition–elimination reaction of lithium *tert*-butyl sulfinate[25] and enol mesylate **15a** (Scheme IV). While TLC experiments suggested the viability of this approach, an alternative route, proceeding via the vinylogous thiol ester **14c**, was also examined. The reaction of mesylate **15a** with sodium *tert*-butyl mercaptide produced **14c** accompanied by moderate amounts of dione **14a**. This difficulty was overcome by conversion of the dione **14a** into the enol chloride **14b** with TPP and carbon tetrachloride in acetonitrile (92%).[26] The addition–elimination reaction of

(22) This data was obtained in the CI mode (70 eV) on a Finnigan 4000 mass spectrometer by Ms. A. Rothwell of the Purdue University Mass Spectrometry Laboratory and analyzed by Dr. Karl Wood, Department of Chemistry, Purdue University, West Lafayette, IN 47907.

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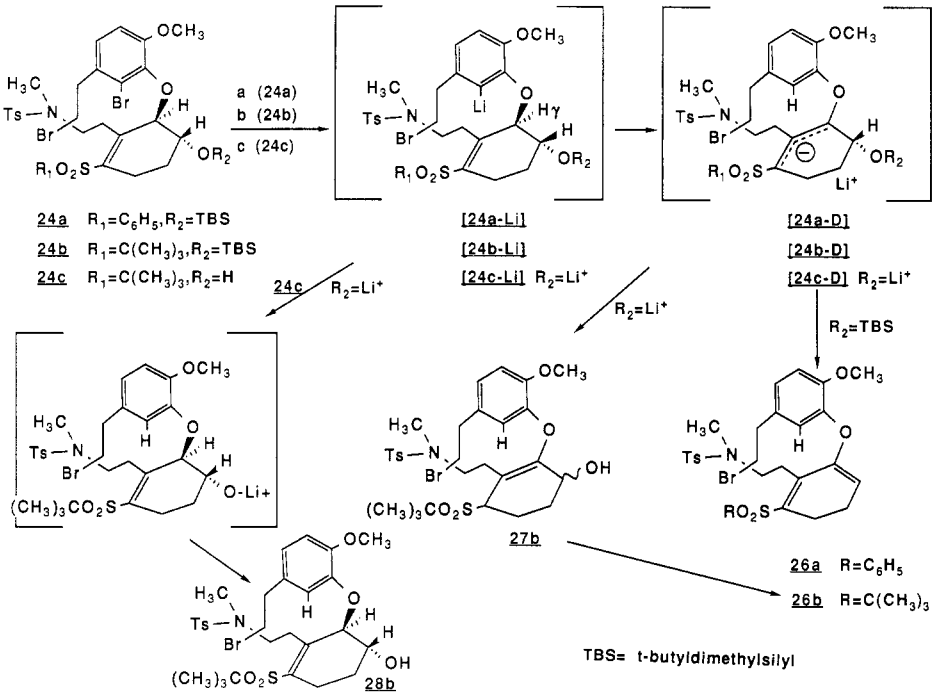
**Scheme VII**[a]




[a] (a) NaH/*t*-BuLi/THF, −78 °C → 25 °C (50% **26a**); (b) LiH/*n*-BuLi/THF, −78 °C → 25 °C (64%); (c) LiH/*n*-BuLi/THF, −78 °C → 25 °C (33% **27b**, 19% **28b**).

**14b** with sodium *tert*-butyl mercaptide afforded the vinylogous thiol ester **14c** cleanly (95%). MCPBA oxidation of **14c** produced the desired enone sulfone **15d** (91%).

**Double Cyclization Reaction of *trans*-Oxidovinyl Sulfones.** Treatment of **24a** (0.045 M in THF) with 2.0 equiv of *tert*-butyllithium at −78 °C followed by brief warming of the reaction mixture and quench produced the dienyl ether **26a** in 50% isolated yield (Scheme VII). Thus, aryllithium intermediate [**24a**-Li] preferentially underwent γ-deprotonation to produce the sulfone-stabilized allylic anion [**24a**-D], which eliminated lithium silanoxide under the reaction conditions to afford **26a**. Unfortunately, the *tert*-butyl sulfone **24b** similarly afforded **26b** in 64% yield.

The alcohols **6a** and **24c** obviously contained acidic protons, which necessitated deprotonation prior to the metal–halogen exchange step of the double cyclization reaction. We had hoped that this requirement would allow the introduction of a variety of metal counterions and thus provide functionality with which to influence the reaction course. In practice, we were unable to implement this strategy. Treament of **6a** with excess sodium *or* potassium hydride at −78 °C did not produce the desired alkoxide intermediates, as ascertained by the alkyllithium stoichiometry necessary to consume **6a**. Furthermore, warming these reaction mixtures prior to metal–halogen exchange led to decomposition of **6a**, presumably as a result of alkoxide formation followed by alkoxide-mediated γ-deprotonation and dehydrobromination of the phenethyl bromide moiety.

For this reason, these double cyclization reactions were performed with an extra equivalent of alkyllithium reagent under the assumption that alcohol deprotonation would precede metal–halogen exchange. In practice, treatment of **24c** (0.05 M in THF) at −78 °C with 2.3 equiv of *n*-butyllithium followed by quench afforded the allyl sulfone **27b** as a single isomer of undetermined stereochemistry (33%) and the debrominated vinyl sulfone **28b** (19%). This latter product presumably arose via the intermolecular quench of aryllithium intermediate [**24c**-Li] with **24c**, although this issue was not investigated.[27] That **28b** had not arisen via premature external quench of the intermediate [**24c**-Li] was evident by the observed presence (TLC) of **28b** in the reaction mixture after the addition of 1.0 equiv of *n*-butyllithium. As a structure proof, the allyl sulfone **27b** was converted to the dienyl sulfone **26b** by mesylation followed by DBU-mediated elimination. Again, similar results were obtained with the phenyl sulfone **6a**. Thus, γ-deprotonation was the preferred reaction path of these *trans*-oxidovinyl sulfones upon metal–halogen exchange.[28]

**Synthesis of *cis*-Oxidovinyl Sulfones.** The reluctance of the *trans*-oxidovinyl sulfones to undergo double cyclization led to the synthesis of the corresponding *cis*-oxidovinyl sulfones **30a–d** (Scheme VIII). Having the trans alcohol **6a** in hand, we first investigated the direct epimerization of the hydroxyl moiety via Mitsunobu esterification. Employing either formic, benzoic, or dichloroacetic acids in combination with DEAD and either TPP or TBP produced no reaction at room temprature and multicomponent mixtures upon heating.

Returning to the Mitsunobu coupling strategy that had successfully produced **24a** required the trans alcohol **23b** (Scheme VI) as starting material to produce the *cis*-silyloxy ether **30b**. The requisite alcohol **23b** was prepared in modest yield (48%) by the MPV reduction[29] of ketone **22a** with freshly prepared aluminum isopropoxide. Unfortunately, alcohol **23b** did not couple with phenol **8** efficiently

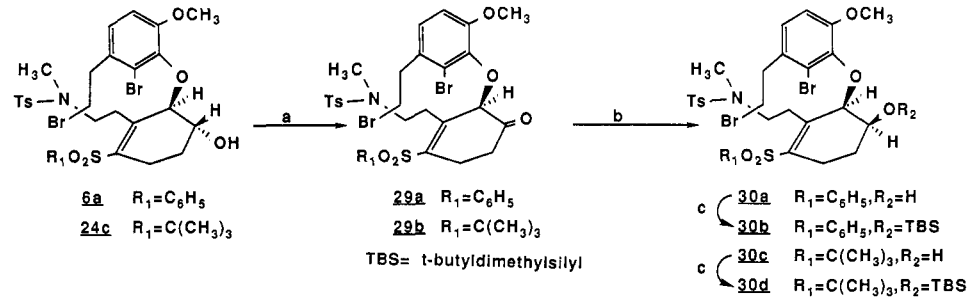
(26) Gruber, L.; Tomoskozi, I.; Radics, L. *Synthesis* **1975**, 708.

(27) Similar interferences have been reported by other investigators: Beak, P.; Chen, C.-W. *Tetrahedron Lett.* **1985**, *26*, 4979. Narasimhan, N. S.; Ammanamanchi, R. *J. Chem. Soc., Chem. Commun.* **1985**, 1368.

(28) Attempts to relate this reluctance to undergo the double cyclization reaction to a preferred ground-state conformation of the substrates **6a**, **24a**, **24b**, and **24c** by high field NMR was unsuccessful.

(29) Wilds, A. L in *Organic Reactions*; Adams, R., Ed.; John Wiley and Sons: New York, 1944; Vol. 2, p 178.

**Scheme VIII**[a]




[a] (a) Jones reagent/$C_6H_6$/$H_2O$, 24 h, 25 °C (88% **29a**, 87% **29b**); (b) DIBAL-H/THF, 0.5 h, −78 °C (92% **30a** from **6a**, 57% **30c** from **24c**); (c) TBSOTf/pyridine/$CH_2Cl_2$, 0.75 h, −20 °C (76% **30b**, 87% **30d**).

under Mitsunobu conditions and produced the coupled product **30b** in only 6% yield under forcing conditions.

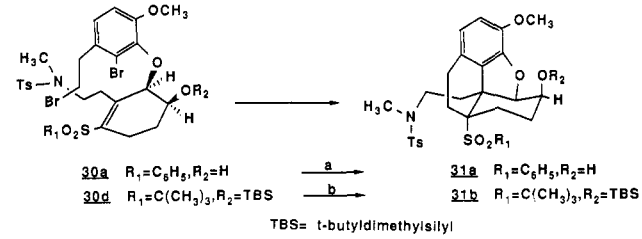
We next investigated the application of an oxidation/reduction sequence to trans alcohol **6a**. A number of oxidants were examined for the **6a** → **29a** conversion. The modified Cr(VI) reagents[30] PCC, PCC (sodium acetate), and PCC (3A sieves) all gave incomplete oxidation even when used in excess, while extended reaction times led to decomposition. Systems employing triethylamine (e.g., pyridine–$SO_3$[31] and Swern[32]) totally consumed the alcohol **6a** but produced an inseparable mixture of ketone **29a** and presumably the corresponding enone (by base-catalyzed isomerization). Thus, this demonstrated sensitivity of ketone **29a** to triethylamine and silica gel chromatography suggested that an oxidant allowing a simplified aqueous workup was required.

Oxidation with $RuO_2$/$NaIO_4$[33] was too severe and Jones reagent (0.4 M Cr(VI), 0.65 M $H_2SO_4$) was slow, leading to decomposition. The biphasic Brown oxidation[34] was successful with an organic phase of ether or benzene but the latter solvent was preferred because it gave a cleaner reaction (88% crude). This method was characterized, however, by extended reaction times (6–24 h) and by variable oxidant stoichiometry necessary for complete consumption of **6a** but was routinely used because no olefin isomerization was observed and ketone **29a** was simply obtained by water and aqueous bicarbonate washes of the separated benzene reaction phase.

DIBAL-H reduction of **29a** proceeded without complication to afford the cis alcohol **30a** in excellent yield (92% from **6a**). Silylation with TBSOTf and pyridine produced the *cis*-silyloxy ether **30b** (76%). The analogous *tert*-butyl vinyl sulfones **30c** and **30d** were synthesized in the same manner.

**Double Cyclization Reaction of *cis*-Oxidovinyl Sulfones.** Treatment of the *cis*-hydroxy ether **30a** (0.04 M in THF) with excess KH at 0 °C followed by 2.15 equiv of *n*-butyllithium at −100 °C and quench gratifyingly afforded a 53% yield of the highly crystalline tetracyclic sulfone **31a** while demonstrating the reluctance of the alcohol moiety to deprotonation by the KH (Scheme IX). Surprisingly, the *cis*-silyloxy ether **30b** with *n*-butyllithium afforded the dienyl ether **26a** (37%, Scheme VII), the product of γ-deprotonation/elimination, and returned 28% of **30b**. In contrast, the analogous *tert*-butyl sufone **30d** under the same conditions produced a 43% yield of

**Scheme IX**[a]




[a] (a) KH/*n*-BuLi/THF, −100 °C → 78 °C (53%); (b) LiH/*n*-BuLi/THF, 0.75 h, −78 °C → 25 °C (43%).

the doubly cyclized adduct **31b** and returned 25% of **30d**.

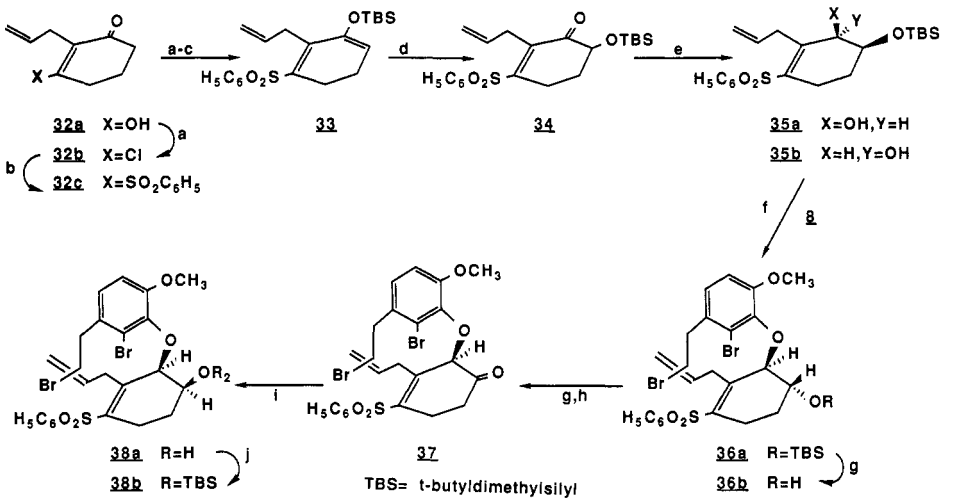
The excitement of the attainment of these long pursued goals was diminished by the results of a parallel study in these labs.[6] In short, the advanced intermediate **4c** (Scheme II) was synthesized from thebaine and resisted all efforts at sulfonamide protecting group removal without disruption of the sensitive diene necessary for the penultimate 1,6-Michael addition.

**Synthesis of Masked Amine Cyclization Substrates.** The exploration of the learning curve of this synthetic strategy required one final iteration. Use of an allyl group as a masked equivalent of the ethylamine moiety was felt to provide the necessary latitude to complete the total synthesis of morphine. To this end, 2-allyl-1,3-cyclohexanedione (**32a**) was prepared by the procedure of Stetter (Scheme X).[35] Treatment of dione **32a** with oxalyl chloride afforded the chloride **32b** (82%), which was conveniently isolated by distillation.[36] The addition–elimination reaction of sodium benzenesulfinate and chloride **32b** to produce sulfone **32c** was dramatically improved by the use of benzene as the reaction solvent and the inclusion of a catalytic amount of tetra-*n*-butylammonium hydrogen sulfate (92%). Formation of the silyl dienyl ether **33**, followed by MCPBA oxidation as before, afforded the α-silyloxy ketone **34** (62% from **32c**). Cerium(III)-mediated sodium borohydride reduction of **34** produced the cis (**35a**, 89%) and trans (**35b**, 8%) alcohols.

Modified Mitsunobu coupling as before yielded the trans ether **36a** (80%), which was desilylated with 48% HF in acetonitrile to afford the alcohol **36b** (93%). At this point it was discovered that homogeneous oxidation of alcohol **36b** with concentrated Jones reagent (2.7 M Cr(VI), 4 M $H_2SO_4$) proceeded cleanly in acetone at 4 °C to provide ketone **37** (90%). Direct DIBAL-H reduction of the ketone **37** provided the cis alcohol **38a** (85% from **36b**). Silylation

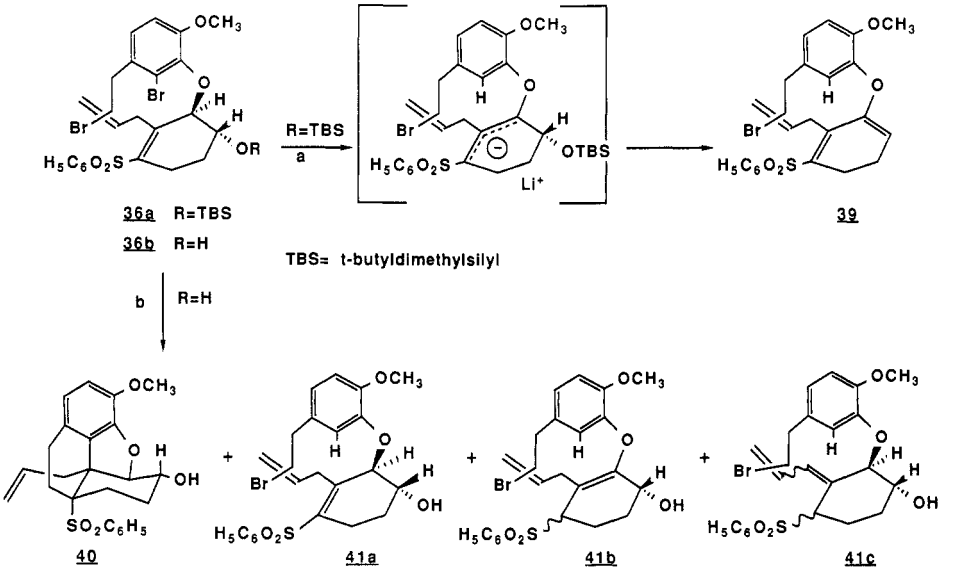
(30) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647. Herscovici, J.; Antonakis, K. *J. Chem. Soc., Chem. Commun.* **1980**, 561.
(31) Parikh, J. R.; Doering, W. v. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505.
(32) Huang, S. L.; Omura, K.; Swern, D. *J. Org. Chem.* **1976**, *41*, 3329.
(33) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936.
(34) Brown, H. C.; Garg, C. P. *J. Am. Chem. Soc.* **1961**, *83*, 2952.
(35) Stetter, H.; Dierichs, W. *Chem. Ber.* **1952**, *85*, 1061.
(36) Clark, R. D.; Heathcock, C. H. *J. Org. Chem.* **1976**, *41*, 636. Tamura, Y.; Kato, S.; Yoshimura, Y.; Nishimura, T.; Kita, Y. *Chem. Pharm. Bull.* **1974**, *22*, 1291.

**Scheme X**[a]




[a] (a) $(COCl)_2/CHCl_3$, 2 h, 25 °C → 61 °C (82%); (b) $C_6H_5SO_2^-Na^+$/cat. $n$-$Bu_4N^+HSO_4^-/C_6H_6$, 40 h, 60 °C (92%); (c) TBSOTf/$Et_3N$/$CH_2Cl_2$, 1 h, −20 °C → 25 °C; (d) MCPBA/$CH_2Cl_2$, 2.5 h, −78 °C → 4 °C (62% from **32c**); (e) $CeCl_3/NaBH_4/CH_3OH/CH_2Cl_2$, 0.5 h, −20 °C (89% **35a**, 8% **35b**); (f) $n$-$Bu_3P$/DEAD/THF, 0.5 h, 4 °C → 25 °C (80%); (g) 48% HF/$CH_3CN$, 34 h, 25 °C (93%); (h) Jones reagent/$(CH_3)_2CO$, 1 h, 4 °C (91%); (i) DIBAL-H/THF, 0.25 h, −78 °C → −10 °C (85%); (j) TBSOTf/pyridine/$CH_2Cl_2$, 1 h, −78 °C → 20 °C (96%).

**Scheme XI**[a]




[a] (a) $n$-BuLi/THF, −78 °C → 25 °C (40%); (b) $n$-BuLi/THF, −78 °C → −20 °C (<8% **40**, 5% **41a**, 22% **41b**, 18% **41c**).

of **38a** as before produced the *cis*-silyloxy ether **38b** (96%).

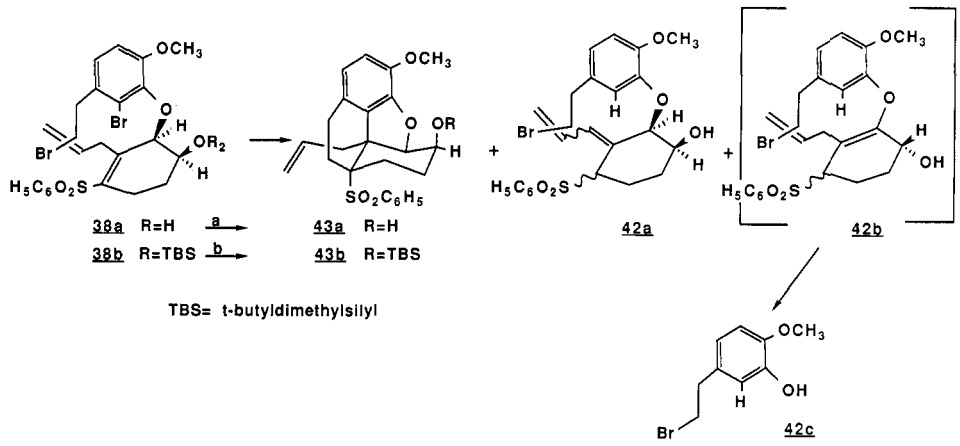
**Double Cyclization Reaction of Allyl Substrates.** The double cyclization reaction of this trans series paralleled that of the tosamidoethyl series. Treatment of **36a** under the conditions of metal–halogen exchange ($n$-butyllithium) followed by brief warming produced quite cleanly the dienyl ether **39** (40% chromatographed) via γ-deprotonation and silanoxide elimination (Scheme XI). The double cyclization reaction of the *trans*-hydroxy ether **36b** produced a complex mixture. Treatment of **36b** with 2.1 equiv of $n$-butyllithium followed by quench and extensive chromatographic purification afforded a fraction enriched in the desired tetracyclic sulfone **40** representing less than 8% of the reaction yield.[37] The balance of the product mixture yielded the diene **41c** (18%) as a single isomer of undetermined stereochemistry, which resulted from γ-deprotonation followed by kinetic quench, the debrominated vinyl sulfone **41a** (5%), and the allyl sulfone **41b** (22%) as a single isomer of undetermined stereochemistry. An authentic sample of **40** was prepared by aqueous sodium borohydride reduction of ketone **44** (70%, Scheme XIII).[38]

The *cis*-hydroxy ether **38a**, under the now standard conditions of deprotonation/metal–halogen exchange, afforded a 46% yield of the tetracyclic sulfone **43a** by direct crystallization of the crude product mixture (Scheme XII). Chromatography of the mother liquor produced an additional 17% of **43a** and 10–20% of the diene **42a** as a single isomer of undetermined stereochemistry. The presence of allyl sulfone **42b** in the crude product mixture was inferred by the isolation of the phenol **42c** in one instance. The structure of **43a** was verified by single-crystal X-ray analysis.[4] The double cyclization reaction of the *cis*-silyloxy ether **38b** also produced the tetracyclic

(37) This fraction consisted of two parts **40** to one part **41c** by integration of the 470-MHz $^1H$ NMR spectrum.

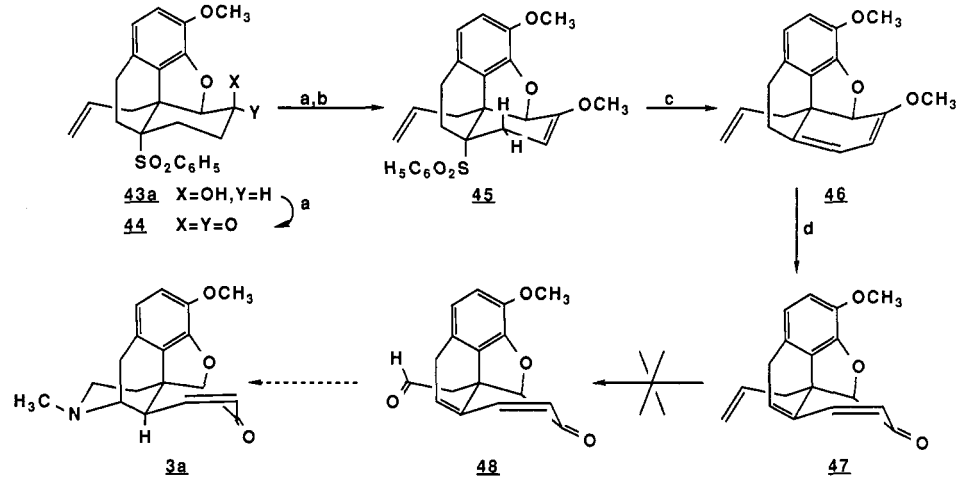
(38) Wunderly, S. W.; Brochmann-Hanssen, E. *J. Org. Chem.* **1977**, *42*, 4277.

**Scheme XII**[a]




[a] (a) *n*-BuLi/THF, −78 °C → 4 °C (63% **43a**, 10–20% **42a**); (b) *n*-BuLi/THF, −78 °C → 4 °C (10% **38b**, 42% **39** (Scheme XI), 17% **43b**).

**Scheme XIII**[a]




[a] (a) $(CF_3CO)_2O$/DMSO/$CH_2Cl_2$, 0.75 h, −78 °C, then $Et_3N$, 0.5 h, −78 °C → −20 °C (95%); (b) $(CH_3O)_3CH/CH_3OH$/PTSA, 12 h, 64 °C (91%); (c) $(CH_3)_3CO^-K^+$/THF, 2.5 h, 25 °C (86%); (d) DDQ/Dowex 50X-8, 36 h, 25 °C (40%).

sulfone **43b**, albeit in low yield (17%). The major product of this reaction was the dienyl ether **39** (42%, Scheme XI).

**"Late" Amine Introduction.** With reasonable quantities of the tetracyclic sulfone **43a** in hand, our thoughts turned to the introduction of the requisite methylamino moiety. The most direct strategy entailed the elaboration of the dienone moiety to produce triene **47** followed by selective oxidative cleavage of the isolated, allyl olefin to yield the aldehyde dienone **48** (Scheme XIII). Sequential reductive amination/1,6-Michael reaction (or vice versa) of **48** with methylamine would preclude the use and removal of an amine protecting group.

To this end, Swern oxidation of alcohol **43a** afforded the highly crystalline ketone **44** (95%). Activation of the vicinal sulfone protons to faciliate E2 phenyl sulfone elimination was accomplished by the conversion of **44** into the methyl enol ether **45** (91%) under standard conditions. Treatment of **45** with potassium *tert*-butoxide (THF) cleanly afforded the methyl dienyl ether **46** (86%).

Attempted oxidation of this homoannular dienyl ether **46** with excess palladium(II) acetate produced a multicomponent mixture.[39] DDQ oxidation of **46** to dienone **47** was examined in some detail because similar oxidations of steroidal 3-ethoxy 3,5-dienes to 4,6-dien-3-ones with DDQ in 95% aqueous acetone are reported to be high yielding.[40] Under these reaction conditions, **46** produced only aromatic products via furan ring opening. An examination of the literature revealed that the oxidation of enol ethers with DDQ can be facilitated by acid catalysis. Indeed, the reaction of **46** with DDQ (THF) with stoichiometric *p*-toluenesulfonic acid or Dowex 50X-8 ($H^+$) produced a new product which aromatized upon extended reaction times.[41] By using excess DDQ (2–5 equiv added in portions), the dienone **47** could be obtained reproducibly in 40% yield.

With the desired dienone **47** in hand, the selective oxidative cleavage of the allyl olefin was investigated. The selective ozonation of isolated olefins in the presence of enones has been reported by metering ozone consumption in the reaction mixture with indicator azo dyes[42] and suggested that Sudan 7B dye possessed the desired reactivity. Attempts to ozonize allyl dienone **47** under these conditions produced a complex mixture of polar products, among which the aldehyde **48** was not observed. The transformation of **47** to **48** was also not successful with catalytic osmium tetraoxide/sodium periodate oxidation, nor did stoichiometric osmium tetraoxide oxidation yield

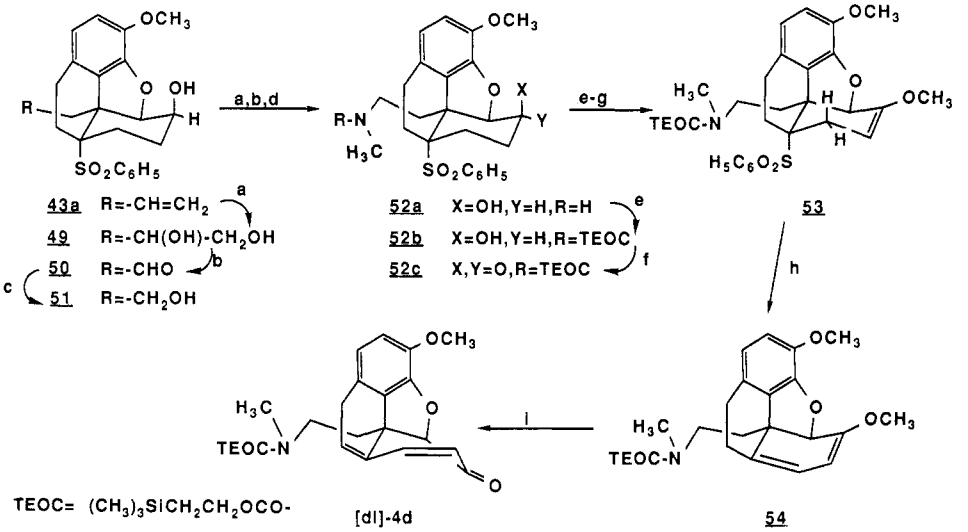
(39) Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011.

(40) Pradhan, S. K.; Ringold, H. J. *J. Org. Chem.* **1964**, *29*, 601.

(41) This conclusion was drawn from the vivid fluorescent quenching of this compound on a silica gel TLC plate under short wave UV irradiation.

(42) Veysoglu, T.; Mitscher, L. A.; Swayze, J. K. *Synthesis* **1980**, 807.

**Scheme XIV**[a]




[a] (a) Cat. $OsO_4$/NMO/aq. $(CH_3)_2CO$, 10 h, 25 °C (90%); (b) $Pb(OAc)_4/CHCl_3$, 0.1 h, 25 °C (91% from **43a**); (c) $NaBH_4/THF/H_2O$, 0.15 h, 25 °C (60%); (d) $H_3CNH_2$–HCl/$CH_3OH/NaBH_3CN$, 15 h, 25 °C (93%); (e) $TMSCH_2CH_2OCOCl/CH_2Cl_2$/aq $NaHCO_3$, 0.7 h, 25 °C (92%); (f) $(CF_3CO)_2O$/DMSO/$CH_2Cl_2$, 1 h, −78 °C, then $Et_3N$, 0.5 h, −78 °C → −20 °C (95%); (g) $(CH_3O)_3CH/CH_3OH$/PTSA, 2 h, 64 °C, then (e) (79%); (h) $(CH_3)_3CO^-K^+$/THF, 3 h, 25 °C (91%); (i) DDQ/PTSA/$CHCl_3/H_2O$, 8 h, 25 °C (40%).

a stable diol. Thus, our inability to effect selective cleavage of the allyl moiety led us to a less speculative strategy for the completion of the total synthesis.

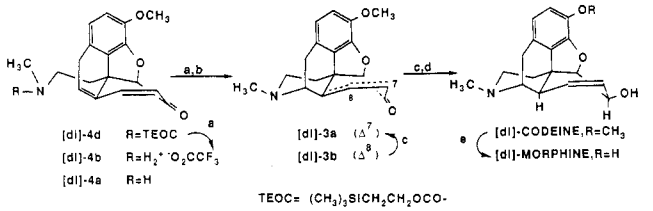
**"Early" Amine Introduction.** This strategy obviously entailed introduction of the methylamine moiety before formation of the dienylic system. This necessitated the use of an amine protecting group and the ((trimethylsilyl)ethyl)oxy carbamate (TEOC) was the natural choice in light of our relay work.[6] It was our intention to convert the tetracyclic sulfone **43a** into the racemic TEOC dienone (*dl*)-**4d**, thus completing a formal total synthesis of racemic morphine.

To this end, we first attempted to synthesize the aldehyde **50** via the ozonation of the sulfone **43a** in methanol (Scheme XIV). NMR analysis of the crude reaction mixture suggested that significant competing oxidation of the aromatic ring had occurred, producing a complex mixture of aldehydes. Metered ozonation of **43a** with Sudan 7B dye[42] gave clean partial conversions (TLC), but attempts to run the ozonation to completion resulted in product mixtures.

Biphasic osmium tetraoxide/sodium periodate cleavage[43] of **43a** afforded a 77% yield of aldehyde **50**. A two-step sequence, however, proceeding through the synthesis of diol **49** (1/1 diastereomer mixture) via catalytic osmium tetraoxide/*N*-methylmorpholine *N*-oxide[44] treatment of **43a** followed by lead tetraacetate cleavage[45] was the method of choice to synthesize **50** (91%).

The reductive amination of **50** with excess methylamine hydrochloride and sodium cyanoborohydride in methanol[46] produced the amine **52a** in 93% yield, after acid/base extractive partitioning to remove nonbasic impurities. Comparison of the NMR spectrum of the crude nonbasic material isolated to that of diol **51**, synthetized by sodium borohydride reduction of aldehyde **50**, demonstrated that competitive reduction of aldehyde **50** during the reductive amination was not occurring. Schotten–Baumann acylation of **52a** with TEOC-Cl afforded the carbamate **52b** (92%). Interpretation of the NMR spectra ($^1H$ and $^{13}C$) of these compounds containing the TEOC carbamate was complicated by rotational isomerism.

**Scheme XV**[a]




[a] (a) $CF_3CO_2H$, 0.1 h, 25 °C (90%); (b) $CHCl_3$/aq. $NaHCO_3$, 0.3 h, 25 °C (65%); (c) $HCl/Et_2O/CH_2Cl_2$, 0.5 h, 25 °C, then 0.2 N NaOH/$CHCl_3$ (95%); (d) $NaBH_4/CH_3OH$, 0.5 h, 25 °C (95%); (e) $BBr_3/CHCl_3$, 0.5 h, 25 °C (50% from [dl]-**3a**,**3b**).

The application of previously developed chemistry allowed the completion of the synthesis.[6] Swern oxidation of alcohol **52b** with trifluoroacetic anhydride/triethylamine afforded the ketone **52c** (95%). Treatment of ketone **52c** with trimethyl orthoformate and *p*-toluenesulfonic acid in methanol as before afforded the methyl enol ether **53** but also caused partial cleavage of the TEOC moiety and necessitated acylation of the crude reaction mixture again under Schotten–Baumann conditions to afford 79% isolated yields of **53**. Potassium *tert*-butoxide mediated elimination of benzenesulfinate from **53** afforded the methyl dienyl ether **54** in excellent yield (91%).

The DDQ oxidation of **54** to dienone (*dl*)-**4d** was problematical. Acid catalysis was again beneficial as was the use of greater than 1 equiv of DDQ to drive the oxidation to completion. In practice, a biphasic system consisting of chloroform/water provided a convenient reaction medium. Filtration of the organic reaction phase over a neutral alumina plug followed by silica gel chromatography afforded 40–45% reproducible yields of (*dl*)-**4d**, identical in all respects with the natural **4d** obtained from thebaine and reported in our relay study.[6]

Simple dissolution of (*dl*)-**4d** in trifluoroacetic acid followed by evaporation afforded the racemic amino

(43) Pappo, R.; Allen, D. S., Jr.; Lemieux, R. U.; Johnson, W. S. *J. Org. Chem.* **1956**, *21*, 478.
(44) VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, 1973.
(45) Criegee, R. *Ber.* **1931**, *64*, 260.
(46) Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2897.

dienone salt (dl)-**4b**, which was directly subjected to biphasic neutralization (chloroform/aqueous sodium bicarbonate) to afford a mixture of racemic codeinone ((dl)-**3a**) and neopinone ((dl)-**3b**), in 65% isolated yield (Scheme XV). This mixture was isomerized to (dl)-**3a** via the intermediacy of (dl)-8-chlorodihydrocodeinone, as described by Rapoport and Barber.[47] Sodium borohydride reduction of (dl)-**3a** afforded racemic codeine, which was O-demethylated with $BBr_3$ to produce racemic morphine.[5] Comparison of racemic morphine to an authentic sample of natural morphine (TLC, LRMS, 200-MHz $^1H$ NMR and $^{13}C$ NMR) verified the completion of the total synthesis.

## Experimental Section

**General.** All reactions were performed in oven- or flame-dried flasks under a positive pressure of argon or nitrogen. Reaction temperatures refer to external bath temperature unless otherwise noted. Tetrahydrofuran and ether were distilled under nitrogen from sodium benzophenone ketyl. Potassium *tert*-butoxide was used as a saturated solution in THF (2.2 M) containing a trace of KH to insure dryness. *n*-Butyllithium titer was determined by duplicate titration of menthol in THF at −78 °C with 2,2′-bipyridyl as an indicator. *tert*-Butyllithium titer was determined by duplicate titration of menthol in benzene at 25 °C with the same indicator. All reactions were monitored by TLC on precoated thin layer (0.25 mm) silica gel 60F-254 plates obtained from EM Reagents.

$^1H$ NMR spectra were recorded on Perkin-Elmer R-32 (90 MHz), Varian XL-200 (200 MHz, NSF CHE-8004246), and Nicolet 470-MHz instruments (NIH RR01077). Spectra were collected in deuteriochloroform unless otherwise noted and are reported in δ (ppm) shifts from tetramethylsilane (0.0) or internal chloroform (7.26) standards, multiplicity, proton count, and coupling constant (hertz). Assignment of multiplicity makes use of the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; cm, complex multiplet; om, overlapping multiplet; um, unresolved multiplet; br, broad; CRI, carbamate rotational isomerism. $^{13}C$ NMR spectra were recorded on a Varian CFT-20 (20 MHz) or a Varian XL-200 (50 MHz) instruments. Fully decoupled and off-resonance or APT[48] spectra are reported. Spectra were collected in deuteriochloroform unless otherwise noted and referenced to the center line of the deuteriochloroform triplet (77.0). Off-resonance spectra are assigned by using the s, d, t, q convention. ATP spectra are assigned an o (odd) for carbons with one or three attached hydrogens and e (even) for carbons with no or two attached hydrogens. Routine mass spectra were run by the Purdue University Mass Spectrometry Laboratory: low resolution on a Finnigan 4000 instrument with a Nova 4 data system (NSF CHE-8010832) at 70 eV; high-resolution on a Kratos MS 50 instrument. Combustion analysis was performed by the Purdue Chemistry Department Microanalysis Laboratory.

Experimental procedures for the following compounds can be found in the supplementary material: **2a/2b, 6a, 7, 10b, 14a, 14a-$D_3$, 14b, 14c, 15a, 15b, 15c, 15c-$D_3$, 15d, 16a, 16a-$D_1$, 16a-$D_3$, 16b, 17, 18, 19, 19-$D_1$, 19-$D_3$, 20, 20-$D_1$, 20-$D_3$, 21a, 21b, 22a, 22b, 23a, 23b, 23c, 24a, 24b, 24c, 25, 26a, 26b, 27b, 28b, 29a, 29b, 30a, 30b, 30c, 30d, 31a, 31b, 39, 41a, 41b, 41c, 43b, 44, 45, 46, 47.**

**(dl)-3a(*R*),9b(*S*)-Dihydro-5-methoxy-9b-[2-[methyl(((2-trimethylsilyl)ethyl)oxy)carbonyl)amino]ethyl]-phenanthro[4,4a,4b,5-*bcd*]furan-3(8*H*)-one [(dl)-4d].** A solution of **54** (87 mg, 0.19 mmol) in chloroform/water (5 mL/2 mL) was treated with a slurry of DDQ (recrystallized, 18 mg, 0.08 mmol) and *p*-toluenesulfonic acid (15 mg, 0.08 mmol) in chloroform (1 mL). After 1 and 2 h, additional DDQ (18 mg)/*p*-toluenesulfonic acid (15 mg) additions were made. After 7 h, additional DDQ (18 mg) was added. One hour later, the organic reaction phase was separated and filtered through a neutral, dry alumina column with chloroform, followed by THF. The eluent was evaporated to an oil and purified by flash chromatography (ethyl acetate/hexane) to afford 33 mg (40%) of (dl)-**4d**. The TLC (ethyl acetate/hexane, 2/1), IR, MS, $^1H$ NMR (470 MHz), and $^{13}C$ NMR of this material matched those of natural **4d**;[6] high-resolution mass spectroscopy (*m/z*) calcd for $C_{24}H_{31}NO_5Si$ 441.1971, found 441.1983.

**2-Bromo-3-(2′-bromoethyl)-6-methoxyphenol (8).** An acetonitrile solution of **11b** (16.0 g, 64.8 mmol) under argon was treated with triphenylphosphine (17.0 g, 64.8 mmol). The resulting solution was cooled to 4 °C and treated, in one portion, with carbon tetrabromide (21.5 g, 64.8 mmol). After 1 h, additional triphenylphosphine (8.5 g, 32.4 mmol) and carbon tetrabromide (10.7 g, 32.4 mmol) were added to the reaction mixture. After 1 h, the reaction mixture was evaporated to an oil and this was partitioned between dichloromethane/ether (5/1) and 5% NaOH solution (400 mL). The precipitated sodium phenolate was collected by filtration, and the basic aqueous phase of the filtrate was collected. The organic phase of the filtrate was extracted with water (2 × 200 mL). These aqueous extracts were combined with the filtrate aqueous phase and the solid sodium phenolate and this mixture was diluted with sufficient water to give solution. The resulting aqueous solution was washed with dichloromethane (2×) and acidified (pH 2) by the addition of a 5% HCl solution. This mixture was extracted with dichloromethane (3×) and the combined extract dried ($MgSO_4$). Filtration followed by evaporation gave 19.6 g (98%) of crude crystalline **8**; recrystallization of this material from hexane returned 16.65 g (83%) of **8**: mp 86–87 °C; TLC (hexane/ether, 3/2) $R_f$ 0.30; $^1H$ NMR (90 MHz) 6.78 (s, 2 H), 5.95 (s, 1 H), 3.85 (s, 3 H), 3.55 (t, 2 H, 7 Hz), 3.22 (t, 2 H, 7 Hz); $^{13}C$ NMR (50 MHz) 146.07 (e), 143.37 (e), 131.14 (e), 121.37 (o), 110.48 (e), 109.46 (o), 56.35 (o), 39.10 (e), 31.48 (e); IR ($CHCl_3$) 2.88 (br), 6.75 (s), 7.80 (br s) μm; mass spectrum, *m/z* [CI] 313, 311, 309 ($M^+ + 1$), 231, 229; [EI] 312, 310, 308 ($M^+$), 217, 215; high-resolution mass spectrum (*m/z*), calcd for $C_9H_{10}Br_2O_2$ 307.9047, found 307.9041.

**2-Bromoisovanillin (9a).** A suspension of recrystallized isovanillin (50.0 g, 329 mmol), powdered anhydrous sodium acetate (54.5 g, 664 mmol), and iron powder (1.5 g) in glacial acetic acid (300 mL) under nitrogen was treated dropwise, over 15 min, with a solution of bromine (18 mL, 351 mmol) in acetic acid (60 mL). The reaction temperature rose during the course of the addition and the reaction mixture became quite thick. One hour after the completion of the addition, the reaction mixture was poured into ice water (2 L) and the nearly colorless precipitate was collected on a filter, washed with cold water (500 mL), and air dried. Drying to constant weight under vacuum afforded 52.3 g (69%) of **9a** as a grey powder, homogeneous by TLC and 90-MHz NMR: TLC (ethyl acetate/dichloromethane, 1/9) $R_f$ 0.53; $^1H$ NMR (90 MHz, DMSO-$d_6$) 7.90 (br s, 1 H), 7.45 (br d, 1 H, 8 Hz), 7.08 (br d, 1 H, 8 Hz), 3.95 (br s, 3 H).

**2-Bromo-3-(methoxymethoxy)-4-methoxybenzaldehyde (9b).** A suspension of hexane-washed NaH (6.6 g, 275 mmol) in DMF (100 mL) under nitrogen at 4 °C was treated, dropwise over 25 min, with a solution of **9a** (52.3 g, 226 mmol) in DMF (400 mL). When hydrogen evolution was complete, the cooling bath was removed and mechanical stirring continued for 30 min. The reaction mixture was recooled to 4 °C and treated dropwise, over 5 min, with chloromethyl methyl ether (19.0 mL, 249 mmol). Fifteen minutes later, the cooling bath was removed and stirring was continued for 20 h. The reaction mixture was poured into ice water (1 L) and extracted with ether (4 × 300 mL). The combined extract was washed with 5% NaOH solution (100 mL, ether back-extract, then 1 × 100 mL), water (4 × 250 mL), and saturated NaCl solution (1 × 300 mL) and dried ($MgSO_4$). Filtration followed by evaporation afforded 58.4 g (94%) of **9b** as a colorless solid; this material could be recrystallized from ether/hexane, mp 52–54 °C, but was routinely used without recrystallization: TLC (ethyl acetate/dichloromethane, 1/9) $R_f$ 0.62; $^1H$ NMR (90 MHz) 10.33 (s, 1 H), 7.74 (d, 1 H, 9 Hz), 6.99 (d, 1 H, 9 Hz), 5.19 (s, 2 H), 3.92 (s, 3 H), 3.64 (s, 3 H); high-resolution mass spectrum (*m/z*), calcd for $C_{10}H_{11}BrO_4$ 273.9841, found 273.9836.

**2-Bromo-3-(methoxymethoxy)-4-methoxystyrene (10a).** A 2-L, three-neck round-bottom flask fitted with a mechanical stirrer was charged with 5 N NaOH solution (1.08 L), aldehyde **9a** (23.2 g, 100 mmol), methyltriphenylphosphonium iodide (84 g, 208 mmol), and benzene (400 mL). The mixture was vigorously stirred at room temperature for 20 h. The organic layer was separated and the aqueous layer was extracted with benzene. The combined

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extract was dried ($K_2CO_3$) and a small amount of radical inhibitor, 4,4′-thiobis(6-*tert*-butyl-*m*-cresol), was added to discourage polymerization. Filtration followed by evaporation produced an oil, which was purified by flash chromatography on coarse silica gel (ethyl acetate/hexane) to afford 19.7 g (86%) of **10a**: TLC (ethyl acetate/hexane, 1/9) $R_f$ 0.16; $^1$H NMR (90 MHz) 7.32 (d, 1 H, 9 Hz), 7.06 (dd, 1 H; 17, 11 Hz), 6.87 (d, 1 H, 9 Hz), 5.58 (d, 1 H, 17 Hz), 5.26 (d, 1 H, 11 Hz)8 5.17 (s, 2 H), 3.85 (s, 3 H), 3.65 (s, 3 H); $^{13}$C NMR (50 MHz) 152.71 (e), 143.21 (e), 135.70 (o), 131.42 (e), 121.99 (o), 119.52 (e), 115.01 (e), 111.49 (o), 98.63 (e), 57.99 (o), 56.08 (o); IR ($CHCl_3$) 3.23 (sh, w), 3.37 (m), 3.51 (m), 6.28 (sh, s), 6.73 (s), 6.94 (sh, s), 7.14 (sh, m), 7.25 (sh, s), 7.80 (s), 7.92 (s), 8.22 (m); 8.65 (s), 9.25 (s), 9.70 (s), 10.25 (s), 11.00 (s), 12.40 (s) μm; mass spectrum, *m/z* [CI] 275, 273 ($M^+$ + 1), 231, 229; [EI] 274, 272 ($M^+$), 193.

**2-[2′-Bromo-3′-(methoxymethoxy)-4′-methoxyphenyl]-ethanol (11a).** A THF solution (50 mL) of 2-methyl-2-butene (9.8 mL, 92.3 mmol) under argon at 4 °C was treated with a $BH_3$–THF solution (1 M, 44.0 mL, 44.0 mmol) and stirred for 1 h at 4 °C. To this was added dropwise, rapidly, a THF solution (20 mL) of **10a** (8.0 g, 29.3 mmol). After 5 min, the cooling bath was removed and after 1 h, the reaction was recooled to 4 °C and carefully treated with 10% NaOH solution (22 mL) followed by dropwise addition of 30% $H_2O_2$ (18.5 mL) at a rate such that the internal reaction temperature remained below 20 °C. The cooling bath was removed and after 1 h at room temperature, the reaction mixture was diluted with water and extraction with ether (3×). The combined extract was washed with 5% HCl solution, water, saturated $NaHCO_3$ solution, and saturated NaCl solution and dried ($K_2CO_3$). Filtration followed by evaporation and pumping (to remove 2-methyl-2-butanol) afforded 8.1 g (95%) of **11a**: TLC (chloroform/ether, 3/2) $R_f$ 0.27; $^1$H NMR (90 MHz) 6.95 (d, 1 H, 8 Hz), 6.75 (d, 1 H, 8 Hz), 5.10 (s, 2 H), 3.75 (s, obscuring t, 3 + 2 H), 3.60 (s, 3 H), 2.90 (t, 2 H, 7 Hz), 2.12 (t, 1 H, 6 Hz, O*H*).

**2-(2′-Bromo-3′-hydroxy-4′-methoxyphenyl)ethanol (11b).** In the same manner as for **10b**, **11a** (21.8 g, 74.9 mmol) and *p*-toluenesulfonic acid monohydrate (190 mg, 1.0 mmol) in methanol (100 mL) afforded after crystallization from chloroform 16.82 g (91%) of **11b**: mp 113–115 °C; TLC (chloroform/ether, 3/2) $R_f$ 0.25; $^1$H NMR (90 MHz) 6.80 (s, 2 H), 6.15 (br s, 1 H), 3.85 (s obscuring t, 3 + 2 H), 2.97 (t, 2 H, 7 Hz), 1.70 (br s, 1 H); $^{13}$C NMR (20 MHz) 145.83 (s), 143.40 (s), 130.66 (s), 121.38 (d), 110.98 (s), 109.55 (d), 62.19 (t), 56.38 (q), 38.78 (t); IR ($CHCl_3$) 6.70 (s), 7.75 (br s) μm; mass spectrum, *m/z* [CI] 249, 247 ($M^+$ + 1), 231, 229; [EI] 248, 246 ($M^+$), 217, 215; high-resolution mass spectrum (*m/z*), calcd for $C_9H_{11}BrO_3$ 245.9892, found 245.9895.

**3-Chloro-2-(2′-propenyl)cyclohex-2-enone (32b).** A solution of **32a** (15.1 g, 100 mmol) in chloroform (100 mL) under nitrogen was treated with oxalyl chloride (18.2 mL, 210 mmol) dropwise at a rate sufficient to maintain brisk gas evolution (1 h). Upon completion of the addition the reaction mixture was refluxed 1 h. After cooling, the volatiles were removed on the rotary evaporator and the residue was vacuum distilled to afford 13.67 g (81%) of **32b** as a colorless liquid: bp 65 °C (1 mmHg) [lit.[36] bp 96 °C (7 mmHg)]; TLC (ether) $R_f$ 0.63; $^1$H NMR (90 MHz) 6.00–5.52 (cm, 1 H), 5.03 (d, 1 H, 18 Hz), 5.00 (d, 1 H, 8 Hz), 3.18 (d, 2 H, 7 Hz), 2.78 (t, 2 H, 6 Hz), 2.47 (t, 2 H, 7 Hz), 2.25–1.90 (m, 2 H); $^{13}$C NMR (50 MHz) 195.21 (e), 153.96 (e), 135.12 (e), 133.49 (o), 115.47 (e), 36.85 (e), 34.76 (e), 30.45 (e), 21.67 (e); IR (neat) 3.32 (w), 5.94 (s), 6.13 (s), 7.00 (m), 7.43 (s), 7.74 (s), 8.15 (s), 8.40 (m), 9.30 (w), 10.0 (w), 10.60 (s), 10.90 (m) μm; mass spectrum, *m/z* (relative intensity) [CI] 173, 171 ($M^+$ + 1, 31, 100); [EI] 172, 170 ($M^+$, 6, 22), 157, 155 (6, 24), 135 (87), 79 (100).

**3-(Phenylsulfonyl)-2-(2′-propenyl)cyclohex-2-enone (32c).** A vigorously stirred mixture of **32b** (25.6 g, 151 mmol), sodium benzenesulfinate (37 g, 226 mmol), and tetra-*n*-butylammonium bisulfate (5.1 g, 15.1 mmol) in benzene (200 mL) under argon was heated at 55–65 °C for 40 h. The cooled reaction mixture was treated with water and the organic phase collected. The aqueous phase was extracted with ether. The combined organic phase and ether extract was washed with water and saturated NaCl solution and dried ($MgSO_4$). Filtration and evaporation followed by flash chromatography (ethyl acetate/hexane) on coarse silica gel (2 L) afforded 38.5 g (92%) of crystalline **32c**; this was recrystallized from ether/hexane: mp 44.5–45.5 °C; TLC (ether/hexane, 1/1) $R_f$ 0.20; $^1$H NMR (470 MHz) 7.90 (d, 2 H, 7.8 Hz), 7.66 (t, 1 H, 7.4 Hz), 7.57 (t, 2 H, 7.8 Hz), 5.77–5.70 (cm, 1 H), 5.01 (d, 1 H, 17.0 Hz), 4.97 (d, 1 H, 9.8 Hz), 3.63 (d, 2 H, 6.2 Hz), 2.62 (t, 2 H, 5.9 Hz), 2.44 (t, 2 H, 6.5 Hz), 2.05–1.93 (cm, 2 H); $^{13}$C NMR (50 MHz) 197.04 (e), 152.07 (e), 140.94 (e). 139.32 (e), 134.21 (o), 133.78 (o), 129.17 (o), 127.47 (o), 116.36 (e), 37.20 (e), 28.88 (e), 27.01 (e), 21.45 (e); IR (film) 3.35 (w), 5.90 (s), 6.10 (w), 6.90 (m), 7.62 (s), 8.65 (s), 9.20 (m), 10.00 (m), 10.80 (br m) μm; mass spectrum, *m/z* (relative intensity) [CI] 277 ($M^+$ + 1, 100); [EI] 276 ($M^+$, 2), 151 (24), 135 (22), 126 (14), 105 (23), 91 (72); high-resolution mass spectrum (*m/z*), calcd for $C_{15}H_{16}O_3S$ 276.0816, found 276.0820. Anal. Calcd: C, 65.20; H, 5.84; S, 11.58. Found: C, 65.27; H, 5.79; S, 11.55.

**3-[(*tert*-Butyldimethylsilyl)oxy]-1-(phenylsulfonyl)-2-(2′-propenyl)-1,3-cyclohexadiene (33).** A solution of **32c** (30.1 g, 109 mmol) and triethylamine (45.5 mL, 327 mmol) in dichloromethane (300 mL) under argon was cooled to −20 °C and treated dropwise, over 0.5 h, with TBSOTf (31.3 mL, 136 mmol). After the addition was complete, the cooling bath was removed, and 1 h later, the reaction mixture was washed with cold 2% HCl solution, water, and saturated $NaHCO_3$ solution and dried ($Na_2SO_4$). Filtration was followed by evaporation of the clear amber solution of **33** to a volume of 0.5 L, which was used directly in the next step; an analytical sample was obtained by flash chromatography (ether/hexane) of a small aliquot: TLC (ether/hexane, 1/1) $R_f$ 0.49; $^1$H NMR (90 MHz, $CH_2Cl_2$ (5.27 ppm) reference) 8.03–7.75 (m, 2 H), 7.68–7.38 (m, 3 H), 6.10–5.58 (cm, 1 H), 5.18 (t, 1 H, 5 Hz), 5.04 (d, 1 H, 18 Hz), 4.99 (d, 1 H, 9 Hz), 3.69 (d, 2 H, 7 Hz), 2.63–2.25 (cm, 2 H), 2.28–1.96 (cm, 2 H), 0.95 (s, 9 H), 0.16 (s, 6 H); $^{13}$C NMR (50 MHz) 148.59 (e), 144.58 (e), 141.97 (e), 135.10 (o), 133.22 (o), 132.91 (o), 128.97 (o), 127.18 (o), 115.71 (e), 107.46 (o), 30.00 (e), 25.72 (o), 24.51 (e), 21.62 (e), 18.13 (e), −4.73 (o); IR (film) 3.35 (s), 6.10 (m), 6.35 (m), 6.80 (b, m), 6.90 (m), 7.50 (br m), 7.65 (s), 7.95 (s), 8.25 (s), 8.70 (br m), 9.20 (m) μm; mass spectrum, *m/z* (relative intensity) [CI] 391 ($M^+$ + 1, 13), 277 (100); [EI] 390 ($M^+$, 0.1), 333 (7), 151 (14); high-resolution mass spectrum (*m/z*), calcd for $C_{21}H_{30}O_3SSi$ 390.1677, found 390.1683.

**6-[(*tert*-Butyldimethylsilyl)oxy]-3-(phenylsulfonyl)-2-(2′-propenyl)cyclohex-2-enone (34).** A dichloromethane solution (0.5 L of **33** (109 mmol theory) under argon was cooled to −78 °C and treated with MCPBA (80%, 25.9 g, 120 mmol) in one portion. After 15 min at −78 °C, the reaction temperature was allowed to rise to −20 °C over 30 min followed by 0 °C for 30 min. At this point, TLC analysis (ether/hexane, 1/1, *p*-anisaldehyde development) indicated incomplete conversion and starch/iodide paper indicated that no MCPBA remained. The reaction mixture was recooled to −78 °C and treated with MCPBA (80%, 5.0 g, 23 mmol) and the warming cycle repeated. The reaction mixture was washed with 20% $NaHSO_3$ solution, 10% $NaHCO_3$ solution, and saturated NaCl solution and dried ($Na_2SO_4$). Filtration followed by evaporation and flash chromatography (ether/hexane) on coarse silica gel (2.5 L) afforded 27.5 g (62%) of **34** as a colorless solid; an analytical sample was prepared by recrystallization from ether/hexane: mp 64–65 °C; TLC (ether/hexane, 1/1) $R_f$ 0.49; $^1$H NMR (470 MHz) 7.90 (d, 2 H, 7.5 Hz), 7.66 (t, 1 H, 7.3 Hz), 7.56 (t, 2 H, 7.9 Hz), 5.74–5.66 (cm, 1 H), 4.98 (d, 1 H, 17.1 Hz), 4.95 (d, 1 H, 10.3 Hz), 4.09 (dd, 1 H, 10.2, 4.3 Hz), 3.65 (dd, 1 H, 13.7, 6.5 Hz), 3.59 (dd, 1 H, 13.7, 6.5 Hz), 2.78 (dt, 1 H, 18.8, 5.1 Hz), 2.70–2.60 (cm, 1 H), 2.16–2.08 (cm, 1 H), 2.05–1.95 (cm, 1 H), 0.84 (s, 9 H), 0.08 (s, 3 H), 0.02 (s, 3 H); $^{13}$C NMR (50 MHz) 196.54 (e), 150.86 (e), 140.19 (e), 139.55 (e), 133.88 (o), 133.82 (o), 129.77 (o), 127.60 (o), 116.68 (e), 72.59 (o), 30.60 (e), 29.34 (e), 25.47 (o), 25.09 (e), 18.02 (e), −4.82 (o), −5.58 (o); IR (film) 3.30 (m), 5.82 (s), 6.05 (w), 6.80 (br w), 6.90 (m), 7.60 (s), 7.95 (m), 8.70 (s), 9.20 (m), 10.10 (s), 10.50 (m) μm; mass spectrum, *m/z* (relative intensity) [CI] 407 ($M^+$ + 1, 100), 391 (17), 349 (25); [EI] 407 ($M^+$ + 1, 2) 349 (100), 207 (38), 125 (89), 115 (36); high-resolution mass spectrum (*m/z*) calcd for $C_{21}H_{30}O_4SSi$ + H (self-protonating in EI) 407.1704, found 407.1716. Anal. Calcd C, 62.04; H, 7.44; S, 7.87; Si, 6.89. Found: C, 62.07, H, 7.87; S, 7.80; Si, 6.47.

***cis*-4-[(*tert*-Butyldimethylsilyl)oxy]-3-hydroxy-1-(phenylsulfonyl)-2-(2′-propenyl)cyclohexene (35a) and *trans*-4-[(*tert*-Butyldimethylsilyl)oxy]-3-hydroxy-1-(phenylsulfonyl)-2-(2′-propenyl)cyclohexene (35b).** In the same manner as **23a** was prepared, crude **34** (3.37 g, 7.87 mmol), cerium(III) chloride (1.94 g, 7.87 mmol), and sodium borohydride

(284 mg, 7.48 mmol) afforded, after an aqueous workup and flash chromatography (ether/hexane), 550 mg of **33**, 2.53 g (89%, corrected for recovered **33**) of **35a**, and 238 mg (8%) of **35b**; TLC (ether/hexane, 1/1) $R_f$ 0.32 (**35a**), 0.23 (**35b**).

**35a**: $^1$H NMR (470 MHz) 7.86 (d, 2 H, 7.7 Hz), 7.59 (t, 1 H, 7.6 Hz), 7.51 (t, 2 H, 7.5 Hz), 5.87–5.78 (cm, 1 H), 5.10 (d, 1 H, 17.1 Hz), 5.06 (d, 1 H, 10.0 Hz), 4.04 (μm, 1 H), 3.90 (dd, 1 H, 13.8, 5.2 Hz), 3.84–3.79 (cm, 1 H), 3.22 (dd, 1 H, 13.7, 7.7 Hz), 2.53 (d, 1 H, 5.6 Hz, O*H*), 2.43 (um, 2 H), 1.86–1.79 (cm, 1 H), 1.66–1.60 (cm, 1 H), 0.84 (s, 9 H), 0.06 (s, 6 H); $^{13}$C NMR (50 MHz) 146.98 (e)8 140.99 (e), 136.33 (e), 135.02 (o), 133.08 (o), 128.98 (o), 127.11 (o), 117.00 (e), 69.11 (o), 68.87 (o), 34.13 (e), 26.07 (e), 25.56 (o), 24.50 (e), 17.82 (e), −4.69 (o), −5.11 (o); IR (film) 2.75 (m), 3.33 (s), 6.12 (m), 6.80 (br m), 6.90 (m), 7.65 (s), 7.95 (s), 8.70 (s), 9.15 (b, s), 9.90 (w), 10.20 (w), 10.90 (m) μm; mass spectrum, *m/z* (relative intensity) [CI] 523 ($M^+$ + TBS, 100), 409 ($M^+$ + 1, 55), 391 (63), 277 (13); [EI] 523 ($M^+$ + TBS, 3), 483 (25), 409 ($M^+$ + 1, 2), 391 (38), 351 (45), 210 (37); high-resolution mass spectrum (*m/z*), calcd for $C_{21}H_{32}O_4SSi$ + H 409.1860, found 409.1873.

**35b**: $^1$H NMR (470 MHz) 7.84 (d, 2 H, 7.7 Hz), 7.57 (t, 1 H, 7.6 Hz), 7.48 (t, 2 H, 7.7 Hz), 5.68–5.59 (cm, 1 H), 5.04 (d, 1 H, 17.1 Hz), 4.99 (d, 1 H, 10.2 Hz), 3.90 (br s, 1 H, obscuring dd, 1 H, 5.3 Hz), 3.80 (um, 1 H), 3.17 (dd, 1 H, 14.2, 7.4 Hz), 2.42 (μm, 2 H), 1.86–1.79 (cm, 1 H), 1.70–1.64 (cm, 1 H), 0.77 (s, 9 h), 0.0 (s, 6 H); $^{13}$C NMR (50 MHz) 145.82 (e), 141.23 (e), 136.98 (e), 134.65 (o), 133.10 (o), 129.01 (o), 127.22 (o), 117.29 (e), 71.96 (o), 69.84 (o), 34.38 (e), 25.58 (o), 23.31 (e), 17.80 (e), −4.85 (o), −4.95 (o); IR (film) 2.80 (m), 3.32 (s), 6.10 (w), 6.80 (br w), 6.90 (m), 7.65 (s), 7.97 (m), 8.70 (s), 9.10 (m), 9.20 (m), 9.55 (m), 10.90 (br m) μm; mass spectrum, *m/z* (relative intensity) [CI] 523 ($M^+$ + TBS, 12), 409 ($M^+$ + 1, 74), 391 (12), 277 (100); [EI] 391 (1), 351 (18), 135 (18), 125 (22); high-resolution mass spectrum (*m/z*), calcd for $C_{21}H_{32}O_4SSi$ + H (self-protonating) 409.1860, found 409.1869.

***trans*-3-[2′-Bromo-3′-(2″-bromoethyl)-6′-methoxyphenoxy]-4-[(*tert*-butyldimethylsilyl)oxy]-1-(phenylsulfonyl)-2-(2‴-propenyl)cyclohexene (36a).** A solution of diethyl azodicarboxylate (95%, 0.31 mL, 1.89 mmol) in THF (5 mL) under argon at 4 °C was treated with tri-*n*-butylphosphine (95%, 0.49 mL, 1.89 mmol) and stirred for 10 min at 4 °C. This solution was added over 2 min to a solution of **35a** (910 mg, 1.57 mmol) and 8 (487 mg, 1.57 mmol) in THF (10 mL) under argon at room temperature. After 45 min, the reaction mixture was evaporated to an oil. This water dissolved in ether and washed with 2% NaOH solution, water, and saturated $NaHCO_3$ solution and dried ($Na_2SO_4$). Filtration followed by evaporation and flash chromatography (ethyl acetate/hexane) afforded 1.15 g (84%) of **36a** contaminated by 8; a repetition of the aqueous workup afforded 1.10 g (80%) of **36a** as a syrup: TLC (ether/hexane, 1/1) $R_f$ 0.33; $^1$H NMR (470 MHz) 7.90 (d, 2 H, 7.8 Hz), 7.59 (t, 1 H, 7.5 Hz), 7.50 (t, 2 H, 7.8 Hz), 6.96 (d, 1 H, 8.5 Hz), 6.82 (d, 1 H, 8.5 Hz), 5.68–5.59 (cm, 1 H), 4.94 (d, 1 H, 9.7 Hz), 4.79 (d, 1 H, 17.1 Hz), 4.65 (br s, 1 H), 4.16 (br d, 1 H, 14.6 Hz), 4.06 (br s, 1 H), 3.81 (s, 3 H), 3.51 (t, 2 H, 7.5 Hz), 3.22 (t, 2 H, 7.5 Hz), 2.80 (dd, 1 H, 14.5, 7.1 Hz), 2.51 (um, 2 H), 2.30–2.22 (cm, 1 H), 1.78 (br d, 1 H, 11.8 Hz), 0.74 (s, 9 H), −0.09 (s, 3 H), −0.12 (s, 3 H); $^{13}$C NMR (50 MHz) 151.56 (e), 144.27 (e), 142.88 (e), 141.31 (e), 139.22 (e), 134.86 (o), 132.98 (o), 131.27 (e), 128.90 (o), 127.38 (o), 125.69 (o), 119.99 (e), 116.47 (e), 110.99 (o), 78.07 (o), 66.04 (o), 55.81 (o), 39.25 (e), 34.91 (e), 31.39 (e), 25.53 (o), 24.93 (e), 22.33 (e), 17.81 (e), −5.20 (o); IR (neat) 3.30 (m), 6.10 (w), 6.25 (m), 6.70 (s), 6.90 (m), 7.05 (m), 7.60 (s), 7.80 (s), 7.90 (s), 8.70 (s), 9.10 (br s), 9.70 (br s) μm; mass spectrum, *m/z* (relative intensity) [CI] 817, 815, 813 ($M^+$ + TBS; 4, 8, 3), 703, 701, 699 ($M^+$ + 1, 10, 25, 10), 391 (100); high-resolution mass spectrum (*m/z*), calcd for $C_{30}H_{40}Br_2O_5SSi$ + H 699.0810, found 699.0813.

***trans*-3-[2′-Bromo-3′-(2″-bromoethyl)-6′-methoxyphenoxy]-4-hydroxy-1-(phenylsulfonyl)-2-(2‴-propenyl)cyclohexene (36b).** A solution of **36a** (7.8 g, 11.2 mmol) in acetonitrile (150 mL) in a polyethylene flask was untreated with 48% HF (15 mL) and stirred at room temperature. Additional 48% HF was added after 3 h (5 mL) and 24 h (5 mL). After 34 h total, the reaction mixture was carefully poured into saturated $NaHCO_3$ solution and extracted with chloroform. The combined extract was dried ($Na_2SO_4$), filtered, and evaporated to yield crude **36b**. Recrystallization from ether afforded 5.43 g (83%) of **36b**. Flash chromatography (ether/hexane) of the mother liquor afforded an additional 650 mg (10%) of **36b**; an analytical sample was prepared by recrystallization from ether/hexane: mp 120–121.5 °C; TLC (ether) $R_f$ 0.37; $^1$H NMR (470 MHz) 7.91 (d, 2 H, 7.5 Hz), 7.62 (t, 1 H, 7.3 Hz), 7.54 (t, 2 H, 7.9 Hz), 6.97 (d, 1 H, 8.6 Hz), 6.83 (d, 1 H, 8.6 Hz), 5.82–5.73 (cm, 1 H), 4.99 (d, 1 H, 10.6 Hz), 4.86 (d, 1 H, 17.0 Hz), 4.81 (d, 1 H, 2.9 Hz), 4.14 (br s, 1 H), 3.82 (s, 3 H), 3.51 (t, 2 H, 7.5 Hz), 3.21 (t, 2 H, 7.5 Hz), 3.02 (dd, 1 H, 14.6, 7.6 Hz), 2.64–2.54 (cm, 1 H), 2.46 (br d, 1 H, 18.1 Hz), 2.29–2.22 (cm, 1 H), 1.88–1.84 (cm, 1 H); $^{13}$C NMR (50 MHz) 151.50 (e), 144.35 (e), 143.65 (e), 141.01 (e), 138.69 (e), 135.03 (o), 133.23 (o), 131.40 (e), 129.09 (o), 127.48 (o), 125.66 (o), 119.75 (e), 116.75 (e), 111.23 (o), 79.17 (o), 66.80 (o), 55.96 (o), 39.31 (e), 34.55 (e), 31.36 (e), 25.04 (e), 22.46 (e); IR (film) 2.78 (m), 3.35 (m), 6.10 (m), 6.25 (m), 6.73 (s), 6.90 (m), 7.10 (m), 7.70 (br s), 8.70 (s), 9.20 (br m) 9.70 (br s) μm; mass spectrum, *m/z* (relative intensity) [CI] 589, 587, 585 ($M^+$ + 1, 2, 4, 2), 395 (8), 277 (100), 259 (24), 231, 229 (14, 14); [EI] 312, 310, 308 (44, 100, 48), 217, 215 (72, 75). Anal. Calcd for $C_{24}H_{26}Br_2O_5S$: C, 49.31; H, 4.49; Br, 27.03; S, 5.47. Found: C, 49.21; H, 4.59; Br, 26.96; S, 5.46.

**2-[2′-Bromo-3′-(2″-bromoethyl)-6′-methoxyphenoxy]-4-(phenylsulfonyl)-3-(2‴-propenyl)cyclohex-3-enone (37).** A solution of **36b** (85 mg, 0.15 mmol) in acetone (3 mL) was cooled to 0 °C and treated dropwise with a solution of Jones reagent (0.07 mL of a 2.67 M solution) over 1 h. After an additional 1 h at 0 °C, the reaction mixture was evaporated and the residue partitioned between benzene and water. The organic phase was collected and the aqueous phase extracted with benzene. The combined extract was washed with water, 10% $NaHCO_3$ solution, and saturated NaCl solution and dried ($Na_2SO_4$). Filtration followed by evaporation and pumping afforded 77 mg (91%) of **37** as a colorless foam: TLC (ether) $R_f$ 0.44; $^1$H NMR (470 MHz) 7.92 (d, 2 H, 7.8 Hz), 7.65 (t, 1 H, 7.5 Hz)8 7.57 (t, 2 H, 7.8 Hz), 6.98 (d, 1 H, 8.3 Hz), 6.80 (d, 1 H, 8.6 Hz), 5.87–5.75 (cm, 1 H), 5.08 (d, 1 H, 8.8 Hz), 5.05 (d, 1 H, 15.7 Hz), 4.82 (s, 1 H), 4.22 (bdd, 1 H, 14.3, 4.0 Hz), 3.77 (s, 3 H), 3.50 (t, 2 H, 7.5 Hz obscuring m, 1 H), 3.21 (t, 2 H, 7.3 Hz obscuring m, 1 H), 2.99 (dt, 1 H, 16.0, 6.8 Hz), 2.79 (dt, 1 H, 16.8, 6.5 Hz), 2.37 (t, 1 H, 16.0, 5.9 Hz); $^{13}$C NMR (50 MHz) 203.29 (e), 151.30 (e), 146.00 (e), 142.88 (e), 140.22 (e), 140.15 (e), 133.62 (o), 133.51 (o), 131.19 (e), 129.28 (o), 127.37 (o), 126.19 (o), 119.66 (e), 117.60 (e), 111.15 (o), 79.85 (o), 55.64 (o), 39.05 (e), 34.52 (e), 34.28 (e), 31.13 (e), 25.74 (e); IR (film) 3.35 (m), 5.78 (s), 6.10 (w), 6.25 (m), 6.75 (s), 6.95 (m), 7.70 (br s), 8.70 (s), 9.20 (m), 9.70 (br s) μm; mass spectrum, *m/z* (relative intensity) [CI] 587, 585, 583 ($M^+$ + 1, 13, 27, 16), 445, 443, 441 (45, 100, 11), 399 (69), 364, 363, 362 (24, 16, 22); [EI] 312, 310, 308 (1, 2, 1), 231, 229 (1, 1), 217, 215 (4, 4); high-resolution mass spectrum (*m/z*), calcd for $C_{24}H_{24}Br_2O_5S$ + H 582.9784, found 582.9772.

***cis*-3-[2′-Bromo-3′-(2″-bromoethyl)-6′-methoxyphenoxy]-4-hydroxy-1-(phenylsulfonyl)-2-(2‴-propenyl)cyclohexene (38a).** A solution of **37** (1.77 mmol theory) in THF (20 mL) under argon was cooled to −78 °C and treated dropwise with a DIBAL-H/hexane solution (1.0 M, 3.17 mL). The reaction was warmed to −10 °C over 15 min and carefully poured into cold 5% HCl solution and extracted with ether (2×) and dichloromethane (1×). The combined extract was washed with water, saturated $NaHCO_3$ solution, and dried ($Na_2SO_4$). Filtration followed by evaporation gave crude **38a**, which was filtered through a silica gel pad (flash grade, chloroform/ether), the filtrate was evaporated, and the residue was recrystallized from chloroform/ether to afford 885 mg (85% from (36b) of **38a** in 2 crops: mp 142.5–143.5 °C; TLC (ether) $R_f$ 0.37; $^1$H NMR (470 MHz) 7.91 (d, 2 H, 7.5 Hz), 7.64 (t, 1 H, 7.3 Hz), 7.55 (t, 2 H, 7.9 Hz), 6.99 (d, 1 H, 8.3 Hz), 6.85 (d, 1 H, 8.5 Hz), 5.74–5.63 (cm, 1 H), 4.96 (d, 1 H, 9.0 Hz), 4.95 (br s, 1 H), 4.69 (d, 1 H, 17.5 Hz)8 4.05 (bdd, 1 H, 14.1, 4.4 Hz), 3.85 (s, 3 H), 3.79–3.72 (cm, 1 H), 3.55–3.42 (cm, 2 H), 3.34 (d, 1 H, 5.9 Hz, O*H*), 3.19 (dt, 2 H, 7.3, 3.0 Hz), 2.69–2.51 (cm, 3 H), 2.17–2.05 (cm, 1 H), 1.92–1.84 (cm, 1 H); $^{13}$C NMR (50 MHz) 151.03 (e), 144.33 (e), 144.02 (e), 140.72 (e), 138.39 (e), 134.59 (o), 133.36 (o), 131.71 (e), 129.10 (o), 127.55 (o), 126.01 (o), 120.18 (e), 117.30 (e), 111.12 (o), 78.85 (o), 67.40 (o), 56.07 (o), 39.09 (e), 35.75 (e), 31.25 (e), 25.85 (e), 25.01 (e); IR (film) 2.75 (m), 3.30 (m), 6.10 (w), 6.25 (m), 6.70 (s), 6.90 (m), 7.65 (br s), 8.70 (s), 9.20 (m), 9.70 (s) μm; mass spectrum, *m/z* (relative intensity) [CI] 589, 587, 583 ($M^+$ + 1, 1, 2, 1), 543, 541 (1, 1), 391 (8), 277 (100), 259 (11); [EI] 312, 310, 308 ($M^+$, 20, 51, 22), 266,

264 (28, 20), 217, 215 (73, 78). Anal. Calcd for $C_{24}H_{26}Br_2O_5S$: C, 49.31; H, 4.49; Br, 27.03; S, 5.47. Found: C, 49.26; H, 4.53; Br, 26.92; S, 5.47.

***cis*-3-[2′-Bromo-3′-(2″-bromoethyl)-6′-methoxyphenoxy]-4-[(*tert*-butyldimethylsilyl)oxy]-1-(phenylsulfonyl)-2-(2‴-propenyl)cyclohexene (38b).** A solution of **38a** (520 mg, 0.86 mmol) and pyridine (0.21 mL, 2.57 mmol) in dichloromethane (10 mL) under argon was cooled to −78 °C and treated with TBSOTf (0.24 mL, 1.03 mmol). After a few minutes the reaction temperature was raised to −20 °C and stirring continued 1 h. The reaction mixture was poured into cold 5% HCl solution and the organic phase collected, washed with water and saturated $NaHCO_3$ solution, and dried ($Na_2SO_4$). Filtration followed by evaporation and flash chromatography (ether/hexane) afforded 595 mg (96%) of **38b**; an analytical sample was obtained by recrystallization from chloroform/ether: mp 115.5–117.5 °C; TLC (ether/hexane, 1/1) *Rf* 0.38; $^1$H NMR (470 MHz) 7.89 (d, 2 H, 7.70 Hz), 7.63 (t, 1 H, 7.2 Hz), 7.55 (t, 2 H, 7.6 Hz), 6.86 (d, 1 H, 8.4 Hz), 6.77 (d, 1 H, 8.4 Hz), 5.92–5.80 (cm, 1 H), 5.35 (br d, 1 H, 1.7 Hz), 5.08 (1 H, 10.2 Hz), 4.97 (d, 1 H, 17.1 Hz), 4.09 (br dd, 1 H, 14.3, 4.1 Hz), 3.81 (s, 3 H), 3.72 (dt, 1 H, 11.5, 3.3 Hz), 3.53–3.40 (cm, 2 H), 3.24–3.10 (cm, 2 H), 2.95 (dd, 1 H, 14.1, 7.8 Hz), 2.60–2.45 (cm, 3 H), 1.75–1.66 (μm, 1 H), 0.64 (s, 9 H), −0.08 (s, 3 H), −0.19 (s, 3 H); $^{13}$C NMR (50 MHz) 150.59 (e), 145.59 (e), 144.86 (e), 140.61 (e), 138.65 (e), 135.11 (o), 133.27 (o), 131.40 (e), 129.09 (o), 127.46 (o), 124.15 (o), 119.30 (e), 116.43 (e), 110.95 (o), 76.65 (o), 71.10 (o), 55.63 (o), 39.55 (e), 35.13 (e), 31.28 (e), 26.96 (e), 25.45 (o), 24.89 (e), 17.87 (e), −5.16 (o), −5.33 (o); IR (film) 3.30 (m), 6.10 (w), 6.25 (s), 6.70 (s), 6.90 (m), 7.10 (m), 7.65 (br s), 7.80 (s), 7.95 (m), 8.70 (s), 9.20 (m), 9.65 (br m) μm; mass spectrum, *m/z* (relative intensity) [CI] 703, 701, 699, 391 (100), 259 (33); [EI] 391, (51), 73 (100). Anal. Calcd for $C_{30}H_{40}Br_2O_5SSi$: C, 51.42; H, 5.76; Br, 22.55; S, 4.57; Si, 4.00. Found: C, 51.15; H, 5.45; Br, 22.48; S, 4.75.

**(*dl*)-1,2,3,3a(*R*),8,9,9a,9b-Octahydro-3(*R*)-hydroxy-5-methoxy-9a(*R*)-(phenylsulfonyl)-9b(*S*)-(2′-propenyl)-phenanthro[4,4a,4b,5-*bcd*]furan (40).** A solution of **44** (10 mg, 0.024 mmol) in THF (2 mL) and water (0.5 mL) was treated with an alkaline sodium borohydride solution (0.26 M $NaBH_4$ in 4% KOH solution, 0.1 mL, 0.026 mmol). After 10 min the reaction mixture was poured into cold 5% HCl solution and extracted with dichloromethane. The combined extract was washed with water and saturated $NaHCO_3$ solution and dried ($Na_2SO_4$). Filtration followed by evaporation and flash chromatography (chloroform/ether) afforded 7.0 mg (70%) of **40** and 2.0 mg (20%) of **43a**: TLC (chloroform/ethyl acetate, 9/1) $R_f$ 0.17 **40**, 0.33 (**43a**).

**40**: recrystallized from chloroform/ether; mp 210–211 °C; $^1$H NMR (470 MHz) 7.94 (d, 2 H, 7.5 Hz), 7.69 (t, 1 H, 7.6 Hz), 7.59 (t, 2 H, 7.8 Hz), 6.75 (d, 1 H, 8.4 Hz), 6.61 (d, 1 H, 8.4 Hz), 5.77–5.67 (cm, 1 H), 4.87 (d, 1 H, 6.6 Hz), 4.87 (d, 1 H, 10.3 Hz), 4.79 (d, 1 H, 17.0 Hz), 3.87 (s, 3 H), 3.44–3.38 (cm, 1 H), 3.03–2.88 ((cm, 4 H), 2.61 (br s, 1 H, O*H*), 2.55–2.47 (cm, 1 H), 2.40–2.29 (m, 1 H), 1.85–1.79 (cm, 1 H), 1.61–1.55 (cm, 1 H), 1.40 (dt, 1 H, 15.6, 2.4 Hz), 1.13 (dt, 1 H, 15.8; 3.0 Hz); $^{13}$C NMR (50 MHz) 143.87 (e), 143.79 (e), 137.23 (e), 143.31 (o), 133.80 (o), 130.55 (e), 129.40 (o), 129.07 (o), 123.68 (e), 119.85 (o), 117.49 (e), 114.33 (o), 96.82 (o), 71.62 (o), 69.87 (e), 56.66 (o), 50.38 (e), 40.87 (e), 26.77 (e), 26.60 (e), 25.79 (e), 22.71 (e); IR ($CHCl_3$) 2.78 (m), 3.30 (m), 3.40 (m), 6.12 (s), 6.22 (w), 6.65 (s), 6.90 (s), 7.80 (br s), 8.75 (s), 9.25 (br s) μm; 4), 285 (100), 243 (7), 143 (10); [EI] 426 ($M^+$, 1, 243 (100), 199 (62); high-resolution mass spectrum (*m/z*), calcd for $C_{24}H_{26}O_5S$ 426.1501, found 426.1518.

**Double Cyclization of 38a. (*dl*)-1,2,3,3a(*R*),8,9,9a,9b-Octahydro-3(*S*)-hydroxy-5-methoxy-9a(*R*)-(phenylsulfonyl)-9b(*S*)-(2′-propenyl)phenanthro[4,4a,4b,5-*bcd*]-furan (43a), *cis*-2-(3′-(2″-Bromoethyl)-6′-methoxyphenoxy)-1-hydroxy-3-(2‴-propen-1‴-ylidene)-4-(phenylsulfonyl)cyclohexane (42a), and 3-(2′-Bromoethyl)-6-methoxyphenol (42c).** A solution of **38a** (1.02 g, 1.74 mmol) in THF (30 mL, treated with 25 mg of LiH) under argon was cooled to −78 °C and treated dropwise, over 5 min, with *n*-butyllithium (1.55 M, 2.30 mL, 2.05 equiv). Ten minutes after the completion of the addition, the reaction mixture was warmed to 4 °C and 30 min later quenched by the addition of saturated $NH_4Cl$ solution. Aqueous workup as before followed by recrystallization of the crude product mixture from chloroform/ether afforded 340 mg (46%) of **43a**; flash chromatography (toluene/ethyl acetate) of the mother liquor afforded 123 mg (17%) of **43a**, 35 mg (9%) of **42c**, and 135 mg (7%) of a mixture of **42a** and its geometrical diene isomer. Pure **42a** was obtained by recrystallization from a similarly executed **38a** double cyclization reaction; TLC (chloroform/ethyl acetate, 4/1) $R_f$ 0.31 (**43a**), 0.39 (**42a**), 0.59 (**42c**).

**43a**: recrystallized from chloroform/ether; mp 140.5–141.5 °C; $^1$H NMR (470 MHz) 7.92 (d, 2 H, 7.8 Hz), 7.68 (t, 1 H, 7.4 Hz), 7.59 (t, 2 H, 7.8 Hz), 6.74 (d, 1 H, 8.2 Hz), 6.61 (d, 1 H, 8.3 Hz), 5.72–5.62 (cm, 1 H), 5.09 (d, 1 H, 5.5 Hz), 4.92 (d, 1 H, 10.4 Hz), 4.89 (d, 1 H, 17.7 Hz), 4.42–4.37 (m, 1 H), 3.86 (s, 3 H), 3.08–2.86 (cm, 4 H), 2.62–2.52 (cm, 1 H), 2.19 (d, 1 + H, 4.8 Hz), 1.85 (dd, 1 H, 11.7, 7.8 Hz), 1.60–1.53 (cm, 1 H), 1.33–1.20 (cm, 2 H); $^{13}$C NMR (50 MHz) 146.01 (e), 141.39 (e), 137.22 (e), 133.66 (o), 129.98 (e), 129.51 (o), 128.96 (o), 123.66 (e), 119.86 (o), 117.93 (o), 114.07 (o), 89.59 (o), 69.94 (e), 65.67 (o), 56.42 (o), 49.47 (e), 42.23 (e), 27.69 (e), 24.52 (e), 23.15 (e), 22.50 (e); IR (film) 2.80 (br m), 3.35 (br m), 6.10 (w), 6.20 (w), 6.65 (s), 6.92 (s), 7.80 (br s), 8.72 (br s), 9.25 (s), 10.90 (br s) μm; mass spectrum, *m/z* (relative intensity) [CI] 427 ($M^+$ + 1, 2), 409 (7), 285 (100), 267 (34), 243 (18), 181 (34), 143 (16); [EI] 426 ($M^+$, 1), 385 (6), 243 (100), 199 (44), 77 (49). Anal. Calcd for $C_{24}H_{26}SO_5$: C, 67.58; H, 6.15; S, 7.50. Found: C, 67.35; H, 6.37; S, 7.48.

**42a**: recrystallized from chloroform/ether; mp 150.5–152 °C; $^1$H NMR (470 MHz) 7.97 (d, 2 H, 7.6 Hz), 7.64 (t, 1 H, 7.5 Hz), 7.55 (t, 2 H, 7.8 Hz), 7.24 (d, 1 H, 1.5 Hz), 6.92 (dd, 1 H, 8.4, 1.8 Hz), 6.85 (d, 1 H, 8.4 Hz), 6.35 (d, 1 H, 11.2 Hz), 6.32–6.23 (cm, 1 H), 5.36 (d, 1 H, 16.1 Hz), 5.21 (d, 1 H, 9.9 Hz), 4.82 (d, 1 H, 3.0 Hz), 4.34 (br d, 1 H, 9.9 Hz), 3.88 (s, 3 H), 3.78 (d, 1 H, 6.4 Hz), 3.60–3.43 (cm, 2 H), 3.12–2.95 (cm, 2 H), 2.52–2.42 (m, 1 H), 2.29 (br d, 1 H, 15.4 Hz), 1.83–1.70 (cm, 2 + H); $^{13}$C NMR (50 MHz) 150.38 (e), 147.60 (e), 141.06 (o), 139.22 (e), 133.39 (o), 132.11 (e), 130.62 (o), 128.98 (o), 128.98 (o), 127.50 (e), 124.90 (o), 124.03 (o), 122.87 (e), 111.76 (o), 79.45 (o), 70.94 (o), 67.99 (o), 55.87 (o), 38.54 (e), 33.26 (e), 24.84 (e), 23.41 (e); IR ($CHCl_3$) 2.88 (br m), 3.33 (sh, m), 3.38 (br m), 6.22 (w), 6.32 (w), 6.62 (s), 6.92 (m), 7.58 (s), 7.65 (s), 7.95 (s), 8.80 (s), 9.35 (m), 9.75 (m), 10.20 (m), 10.80 (m) μm; mass spectrum, *m/z* (relative intensity) [CI] 491, 489 (1, 1), 409 (1), 349, 347 (5, 5), 143 (100), 117 (55); [EI] 348, 346 (34, 32), 245, 243 (30, 30), 232, 230 (32, 32), 137 (79), 117 (100). Anal. Calcd for $C_{24}H_{27}BrO_5S$: C, 56.91; H, 5.34; Br, 15.59; S, 6.32. Found: C, 56.82, H, 5.37, Br, 15.82; S, 6.30.

**42c**: $^1$H NMR (90 MHz) 7.02–6.78 (cm, 3 H), 5.72 (s, 1 H, O*H*), 3.90 (s, 3 H), 3.58 (t, 2 H, 8 Hz), 3.10 (t, 2 H, 8 Hz); IR (film) 2.83 (br m), 3.38 (m), 3.42 (m), 6.30 (m), 6.63 (s), 6.97 (m), 7.91 (s), 8.12 (m), 8.30 (m), 8.70 (m), 8.95 (m), 9.70 (m), 11.0 (s) μm; mass spectrum, *m/z* (relative intensity) [CI] 233, 232, 231, 230 ($M^+$ + 1, $M^+$; 8, 14, 10, 13), 151 (47); [EI] 232, 230 ($M^+$, 38, 36), 151 (34) 137 (100).

**(*dl*)-9b(*S*)-(2′(*R*,*S*),3′-Dihydroxypropyl)-1,2,3,3a-(*R*),8,9,9a,9b-octahydro-3(*S*)-hydroxy-5-methoxy-9a(*R*)-(phenylsulfonyl)phenanthro[4,4a,4b,5-*bcd*]furan (49).** A solution of **43a** (140 mg, 0.33 mmol) in acetone/water (3/2, 10 mL) at room temperature was treated with *N*-methylmorpholine *N*-oxide monohydrate (50 mg, 0.36 mmol) followed by an osmium tetraoxide solution (0.04 M in THF, 0.17 mL, 7 μmol). After 10 h the reaction mixture was treated with an aqueous slurry of $Na_2S_2O_4$ (50 mg) and Florisil (200 mg) and filtered. The filtrate was adjusted to pH 7.0 by the addition of dilute $H_2SO_4$ solution, saturated by the addition of solid NaCl, and extracted with ethyl acetate. The combined extract was dried ($Na_2SO_4$), filtered, and evaporated to yield 137 mg (solvent corrected, 90%) of **49** as a 1:1 mixture of diastereomers: TLC (chloroform/methanol, 9/1) $R_f$ 0.35, 0.29; $^1$H NMR (90 MHz) 8.05–7.80 (d, 2 H), 7.75–7.50 (m, 3 H), 6.82 (d, 1 H, 9 Hz), 6.65 (d, 1 H, 9 Hz), 5.41 (d, 0.5 H, 6 Hz), 5.08 (d, 0.5 H, 6 Hz), 4.40 (br s, 1 H), 3.85 (s, 3 H, obscuring m, 1 H), 3.60–1.20 (cm, 12 H); mass spectrum, *m/z* (relative intensity) [CI] 461 ($M^+$ + 1), 443, (2), 319 (100), 301 (83), 143 (71); [EI] 460 ($M^+$, 20), 442 (<1), 318 (76), 243 (100), 199 (67), 77 (78).

**(*dl*)-9b(*S*)-(2′-Oxoethyl)-1,2,3,3a(*R*),8,9,9a,9b-octahydro-3(*S*)-hydroxy-5-methoxy-9a(*R*)-(phenylsulfonyl)-phenanthro[4,4a,4b,5-*bcd*]furan (50).** A solution of **49** (0.33 mmol theory) in chloroform (10 mL) under argon was treated dropwise, over 5 min, with a solution of lead tetraacetate (153 mg, 0.35 mmol) in chloroform (5 mL). Five minutes after the completion of the addition, the reaction mixture was treated with

saturated $NaHCO_3$ solution. The organic phase was separated and the aqueous phase was extracted with dichloromethane. The combined extract was filtered and dried ($Na_2SO_4$). Filtration followed by evaporation and flash chromatography (ethyl acetate) afforded 129 mg (91% from **43a**) of **50**; an analytical sample was obtained by recrystallization from chloroform/ether: mp 183–184.5 °C; TLC (ethyl acetate) $R_f$ 0.48; $^1$H NMR (470 MHz) 9.61 (t, 1 H, 2.9 Hz), 7.93 (d, 2 H, 7.8 Hz), 7.72 (t, 1 H, 7.4 Hz), 7.62 (t, 2 H, 7.8 Hz), 6.78 (d, 1 H, 8.3 Hz), 6.68 (d, 1 H, 8.3 Hz), 5.20 (d, 1 H, 5.7 Hz), 4.37–4.33 (m, 1 H), 3.86 (s, 3 H), 3.31 (dd, 1 H, 14.3, 2.5 Hz), 3.10 (dd, 1 H, 14.2, 3.3 Hz), 3.02 (dd, 1 H, 17.5, 7.4 Hz), 2.84–2.75 (cm, 1 H), 2.62–2.54 (cm, 1 H), 2.45 (br t, 1 H, 12.9 Hz), 2.00 (br d, 1 H, 1.1 Hz, O*H*), 1.91 (dd, 1 H, 14.3, 7.1 Hz), 1.76–1.67 (cm, 1 H), 1.54–1.48 (cm, 1 H), 1.08 (dt, 1 H, 15.7, 3.9 Hz); $^{13}$C NMR (50 MHz) 200.27 (o), 145.50 (e), 141.94 (e), 136.51 (e), 134.11 (o), 129.60 (o), 129.20 (o), 129.07 (e), 123.14 (e), 120.95 (o), 114.67 (o), 90.08 (o), 69.34 (e), 65.66 (o), 56.47 (o), 50.80 (e), 47.40 (e), 27.51 (e), 24.56 (e), 22.62 (e), 21.42 (e); IR ($CHCl_3$) 2.78 (m), 3.30 (m), 3.37 (m), 3.40 (m), 3.52 (w), 5.82 (s), 6.10 (w), 6.22 (w), 6.62 (s), 6.92 (s), 7.80 (br s), 8.75 (s), 9.10 (m), 9.30 (s) μm; mass spectrum, *m/z* (relative intensity) [CI] 428 ($M^+$ + 3), 385 (42), 287 (17), 243 (100), 225 (23); [EI] 428 ($M^+$, 9); 287, 286 (13, 14), 243 (69), 199 (100); high-resolution mass spectrum (*m/z*), calcd for $C_{23}H_{24}SO_6$ 428.1294, found 428.1297.

**(*dl*)-1,2,3,3a(*R*),8,9,9a,9b-Octahydro-3(*S*)-hydroxy-5-methoxy-9b(*S*)-(2′-hydroxyethyl)-5-methoxy-9a(*R*)-(phenylsulfonyl)phenanthro[4,4a,4b,5-*bcd*]furan (51).** A solution of **50** (70 mg, 0.16 mmol) in THF/methanol (1:1, 4 mL) was treated with sodium borohydride (6 mg, 0.16 mmol). After 10 min the reaction mixture was poured into cold 5% HCl solution and extracted with dichloromethane. The combined extract was washed with water and saturated $NaHCO_3$ solution and dried ($Na_2SO_4$). Filtration followed by evaporation and flash chromatography (ethyl acetate/hexane) afforded 45 mg (60%) of **51** as a colorless solid: TLC (ethyl acetate) *Rf* 0.29; $^1$H NMR (470 MHz) 7.93 (d, 2 H, 7.6 Hz), 7.69 (t, 1 H, 7.5 Hz), 7.60 (t, 2 H, 7.9 Hz), 6.77 (d, 1 H, 8.2 Hz), 6.65 (d, 1 H, 8.2 Hz), 5.17 (d, 1 H, 5.6 Hz), 4.42–4.37 (m, 1 H), 3.87 (s, 3 H), 3.65–3.56 (cm, 2 H), 2.96 (dd, 1 H, 17.2, 8.1 Hz), 2.93–2.86 (cm, 1 H), 2.73–2.68 (cm, 1 H), 2.62–2.54 (cm, 1 H), 2.41–2.36 (cm, 1 H), 2.28–2.21 (cm, 1 H), 2.12 (br s, 1 H, O*H*), 1.89 (dd, 1 H, 13.9, 7.3 Hz), 1.70–1.56 (br s overlapping cm, 2 H), 1.38–1.30 (cm, 1 H), 1.21 (dt, 1 H, 15.9, 4.9 Hz); IR (film) 2.83 (br s), 3.40 (m), 6.12 (w), 6.23 (w), 6.65 (m), 6.94 (s), 7.52 (w), 7.82 (br s), 8.42 (w), 8.60 (w), 8.90 (s), 9.20 (s), 9.40 (s), 10.90 (br s) μm; mass spectrum, *m/z* (relative intensity) [CI] 430 ($M^+$ + 1, 2), 413 (4), 289 (100), 282 (26), 271 (45), 143 (31); [EI] 430 ($M^+$, 22), 299 (8), 271 (86), 243 (90), 199 (53); high-resolution mass spectrum (*m/z*), calcd for $C_{23}H_{26}SO_6$ 430.1450, found 430.1455.

**(*dl*)-1,2,3,3a(*R*),8,9,9a,9b-Octahydro-3(*S*)-hydroxy-5-methoxy-9b(*S*)-[2-(methylamino)ethyl]-9a(*R*)-(phenylsulfonyl)phenanthro[4,4a,4b,5-*bcd*]furan (52a).** A solution of **50** (1.22 g, 2.85 mmol) and methylamine hydrochloride (5.77 g, 8.6 mmol) in methanol (60 mL) was stirred at room temperature under argon. After 1.5 h, sodium cyanoborohydride (180 mg, 2.85 mmol) was added. After 15 h, the reaction mixture was evaporated to a solid and dissolved in a 5% HCl solution with vigorous stirring (*Caution* HCN!). The resulting cloudy solution was extracted with dichloromethane (2×) and the aqueous solution was adjusted to pH 12.0 by the addition of 50% KOH solution. The basic aqueous phase was saturated by the addition of solid NaCl and extracted with dichloromethane. Drying ($Na_2SO_4$) of the combined extract followed by filtration and evaporation afforded 1.18 g (93%) of **52a** as a colorless solid; an analytical sample was obtained by recrystallization from dichloromethane/hexane: mp 194–196 °C; TLC (chloroform/methanol/concentrated $NH_4OH$, 90/10/0.1) $R_f$ 0.17; $^1$H NMR (470 MHz) 7.92 (d, 2 H, 7.4 Hz), 7.68 (t, 1 H, 7.4 Hz), 7.59 (t, 2 H, 7.9 Hz)8 6.75 (d, 1 H, 8.4 Hz), 6.62 (d, 1 H, 8.3 Hz), 5.11 (d, 1 H, 5.4 Hz), 4.41 (dd, 1 H, 4.6, 2.1 Hz), 3.87 (s, 3 H), 3.03–2.86 (cm, 2 H), 2.71 (dt, 1 H, 11.0, 6.5 Hz), 2.62–2.50 (cm, 2 H), 2.43–2.23 (cm, 2 H), 2.32 (s, 3 H), 2.18–2.07 (cm, 1 H), 1.87 (dd, 1 H, 13.4, 7.6 Hz), 1.56–1.48 (cm, 1 H), 1.37–1.20 (cm, 2 H); $^{13}$C NMR (50 MHz) 146.23 (e), 141.26 (e), 137.40 (e), 133.56 (o), 129.69 (e), 129.54 (o), 128.89 (o), 123.69 (e), 120.05 (o), 114.01 (o), 90.35 (o), 70.15 (e), 65.52 (o), 56.31 (o), 48.44 (e), 47.51 (e), 38.01 (e), 36.05 (o), 27.78 (e), 24.37 (e), 23.16 (e), 22.45 (e); IR (film) 2.82 (br shoulder, m), 3.02 (br m), 3.50 (s), 6.12 (w), 6.22 (w), 6.67 (s), 6.92 (s), 7.82 (s), 8.75 (s), 9.37 (s) μm; mass spectrum, *m/z* (relative intensity) [CI] 444 ($M^+$ + 1, 100), 302 (27), 143 (19); [EI] 443 ($M^+$, 2) 302 (12), 243 (13), 44 (100); high-resolution mass spectrum (*m/z*), calcd for $C_{24}H_{29}NO_5S$ 443.1766, found 443.1758.

**(*dl*)-1,2,3,3a(*R*),8,9,9a,9b-Octahydro-3(*S*)-hydroxy-5-methoxy-9b(*S*)-[2-[methyl(((2-(trimethylsilyl)ethyl)oxy)carbonyl)amino]ethyl]-9a(*R*)-(phenylsulfonyl)phenanthro[4,4a,4b,5-*bcd*]furan (52b).** A vigorously stirred biphasic mixture of **52a** (1.15 g, 2.6 mmol) and $K_2CO_3$ (716 mg, 5.2 mmol) in dichloromethane (50 mL) and water (50 mL) was treated with TEOC-Cl (0.50 mL, 2.73 mmol). After 40 min, the organic reaction phase was separated and the aqueous reaction phase was extracted with dichloromethane. The combined extract was dried ($Na_2SO_4$), filtered, and evaporated to afford 1.41 g (92%) of **52b** as a colorless foam; an analytical sample was obtained by recrystallization from chloroform/ether: mp 159–161 °C; TLC (ethyl acetate/hexane, 1/1) $R_f$ 0.14; $^1$H NMR (90 MHz, $CHCl_3$ ref 7.26 ppm) 8.04–7.82 (m, 2 H), 7.72–7.50 (cm, 3 H), 6.77 (d, 1 H, 9 Hz), 6.60 (d, 1 H, 9 Hz), 5.08 (d, 1 H, 6 Hz), 4.38 (br s, 1 H), 4.03 (t, 2 H, 8 Hz), 3.82 (s, 3 H), 3.57–1.05 (cm, 12 H), 0.87 (μm, 2 H), −0.05 (s, 9 H); $^{13}$C NMR (50 MHz) 156.26 (e), 146.03 (e), 141.56 (e), 137.33 (e), 133.82 (o), 129.70 (o), 129.24 (o), 129.10 (o), 123.73 (e), 120.57 (o), 114.15 (o), 90.48 (o), 70.01 (e), 65.82 (o), 63.12 (e), 56.42 (o), 48.08, 47.96 (e, CRI); 45.47, 47.96 (e, CRI), 35.85 (e), 34.43, 34.33 (o, CRI), 28.00 (e), 24.47 (e), 23.15 (e), 22.59 (e), 17.65 (e), −1.54 (o); IR ($CHCl_3$) 2.79 (w), 3.32 (m), 3.38 (m), 5.95 (br s), 6.10 (w), 6.21 (w), 6.65 (m), 6.92 (m), 7.12 (m), 7.72 (s), 7.80 (s), 8.58 (s), 8.72 (s), 9.25 (s), 9.40 (s) μm; mass spectrum, *m/z* (relative intensity) [CI] 588 ($M^+$ + 1, 10), 560 (42), 418 (100), 143 (24); [EI] 587 ($M^+$, 1), 559 (<1), 244 (12), 243 (14), 73 (100); high-resolution mass spectrum (*m/z*), calcd for $C_{30}H_{41}NO_7SSi$ 587.2373, found 587.2377.

**(*dl*)-5-Methoxy-9b(*S*)-[2-[methyl(((2-(trimethylsilyl)ethyl)oxy)carbonyl)amino]ethyl]-1,2,3,3a(*R*),8,9,9a,9b-octahydro-9a(*R*)-(phenylsulfonyl)phenanthro[4,4a,4b,5-*bcd*]furan-3-one (52c).** A solution of DMSO (55 μL, 0.77 mmol) in dichloromethane (9 mL) under argon was cooled to −78 °C and treated dropwise with trifluoroacetic anhydride (72 μL, 0.51 mmol). After 10 min this mixture was treated dropwise with a solution of **52b** (150 mg, 0.26 mmol) in dichloromethane (0.5 mL + 0.5 mL). This was stirred 45 min at −78 °C followed by the addition of triethylamine (0.18 mL, 1.28 mmol). After 5 min the reaction mixture was warmed to −20 °C and after 30 min washed with cold 5% HCl solution and water and dried ($Na_2SO_4$). Filtration followed by evaporation and flash chromatography (chloroform/ether) afforded 142 mg (95%) of **52c**: TLC (ether) $R_f$ 0.30; $^1$H NMR (90 MHz, $CHCl_3$, ref 7.26 ppm) 7.98–7.82 (m, 2 H), 7.75–7.53 (cm, 3 H), 6.76 (d, 1 H, 9 Hz), 6.62 (d, 1 H, 9 Hz), 5.08 (s, 1 H), 4.03 (t, 2 H, 8 Hz), 3.82 (s, 3 H), 3.60–1.10 (cm, 12 H), 2.76 (s, 3 H), 0.87 (um, 2 H), −0.08 (s, 9 H); $^{13}$C NMR (50 MHz) 204.94 (e), 156.22 (e), 145.26 (e), 142.78 (e), 136.92 (e), 134.36 (o), 129.42 (o), 129.18 (o), 127.28 (e), 123.25 (e), 121.27 (o), 115.54 (o), 90.96 (o), 69.01 (e), 63.22 (e), 56.82 (o), 51.42 (e), 45.62 (br e), 35.23 (e), 34.43 (br o), 26.85 (e), 26.63 (e), 22.52 (e), 17.66 (e), −1.54 (o); IR ($CHCl_3$) 3.32 (m), 3.39 (m), 5.80 (s), 5.95 (br s), 6.12 (w), 6.23 (w), 6.35 (w), 6.65 (s), 6.92 (s), 7.72 (s), 7.85 (s), 8.58 (s), 8.74 (s), 9.33 (s), 9.60 (m) μm; mass spectrum, *m/z* (relative intensity) [CI] 558 ($M^+$ + 1 − $C_2H_4$, 9), 196 (100), 143 (12); [EI] 557 ($M^+$ − $C_2H_4$, 1), 241 (8), 160 (8), 73 (100); high-resolution mass spectrum (*m/z*), calcd for $C_{30}H_{39}NO_7SSi - C_2H_4$ fragment 557.1903, found 557.1913.

**(*dl*)-3,5-Dimethoxy-9b(*S*)-[2-[methyl(((2-(trimethylsilyl)ethyl)oxy)carbonyl)amino]ethyl]-9a(*R*)-(phenylsulfonyl)-1,3a(*R*),8,9,9a,9b-hexahydrophenanthro[4,4a,4b,5-*bcd*]furan (53).** A solution of **52c** (0.71 g, 1.2 mmol), trimethyl orthoformate (0.66 mL, 6.1 mmol), and *p*-toluenesulfonic acid (95 mg, 0.50 mmol) in methanol (15 mL) under argon was refluxed for 2 h. The cooled reaction mixture was poured into saturated $NaHCO_3$ solution, diluted with dichloromethane, and treated with TEOC-Cl (0.09 mL, 0.5 mmol) with vigorous stirring. After 10 min, the organic phase was separated and the aqueous phase extracted with dichloromethane. The combined extract was dried ($Na_2SO_4$), filtered, and evaporated to yield an oil, which was recrystallized from chloroform/ether to afford 460 mg (63%) of **53**: mp 109–110.5 °C; evaporation of the mother liquor followed

by subjection of the residue to the above reaction conditions provided an additional 116 mg (16%) of crystalline **53**: TLC (ether) $R_f$ 0.41; $^1$H NMR (470 MHz) 7.88 (d, 2 H, 7.6 Hz), 7.68 (t, 1 H, 7.4 Hz), 7.57 (t, 2 H, 7.7 Hz), 6.78–6.69 (m, 1 H), 6.61 (d, 1 H, 8.1 Hz), 5.29 (br s, 1 H), 4.31 (br d, 1 H, 5.9 Hz), 4.15–4.02 (m, 2 H), 3.83–3.82 (br s, 3 H total, CRI), 3.54 (s, 3 H), 3.31–2.95 (cm, 3 H), 285–2.83 (s, 3 H total, CRI), 2.72–2.56 (m, 3 H), 2.35–2.16 (cm, 1 H), 2.06 (d, 1 H, 18.2 Hz), 1.90–1.83 (um, 1 H), 1.57 (dd, 1 H, 18.2, 6.7 Hz), 1.02–0.87 (cm, 2 H), 0.01 (s, 9 H); $^{13}$C NMR (50 MHz) 156.28 (e), 154.12 (e), 145.07 (e), 143.04 (e), 137.86 (e), 133.76 (o), 129.24 (o), 128.96 (o), 128.75, 128.66 (e, CRI), 123.86 (e), 120.22 (o), 114.56 (o), 91.33 (o), 88.36 (o), 70.65 (e), 63.15 (e), 56.50 (o), 54.63 (o), 48.59 (e), 45.33 (br e), 34.35 (br o), 33.83 (e), 28.40 (e), 25.72 (e), 22.78 (e), 17.69 (e), −1.55 (o); IR ($CHCl_3$) 3.31 (m), 3.38 (m), 5.84 (s), 5.95 (s), 6.10 (w), 6.22 (w), 6.63 (m), 6.92 (m), 7.35 (m), 7.72 (m), 7.80 (m), 8.58 (m), 8.72 (s), 9.20 (m), 11.00 (s), 11.60 (m), 11.90 (m) μm; mass spectrum, $m/z$ (relative intensity) [CI] 600 ($M^+$ + 1, 7), 572 (48), 430 (33), 358 (83), 314 (100); [EI] 599 ($M^+$, 1) 255 (18), 174 (12), 73 (100); high-resolution mass spectrum ($m/z$), calcd for $C_{31}H_{41}NO_7SSi$ 599.2373, found 599.2381.

***(dl)*-3,5-Dimethoxy-9b(*S*)-[2-[methyl(((2-(trimethylsilyl)ethyl)oxy)carbonyl)amino]ethyl]-3a(*R*),8,9,9b-tetrahydrophenanthro[4,4a,4b,5-*bcd*]furan (54).** A solution of **53** (275 mg, 0.46 mmol) in THF (15 mL) under argon was treated with potassium *tert*-butoxide solution (2.2 M in THF, 0.85 mL, 1.87 mmol, 4.1 equiv). After 3 h the reaction mixture was poured into saturation $NaHCO_3$ solution and extracted with dichloromethane, and the combined extract was dried ($Na_2SO_4$). Filtration followed by evaporation and flash chromatography [ether/hexane/triethylamine (2%)] afforded 190 mg (91%) of **54**: TLC (ether) $R_f$ 0.62; $^1$H NMR (470 MHz) 6.61 (br d, 1 H, 7.9 Hz), 6.57 (br d, 1 H, 7.9 Hz), 5.53 (br s, 2 H), 5.02 (d, 1 H, 6.4 Hz), 4.15 (dt, 2 H, 9.0, 2.9 Hz), 3.83 (s, 3 H), 3.60 (br s, 3 H), 3.47–3.38 (um, 1 H), 3.32–3.22 (um, 1 H), 3.18–2.75 (overlapping br m, 3 H), 2.88, 2.86 (br s, 3 H total, CRI), 2.49–2.40 (cm, 1 H), 2.24–2.15 (um, 1 H), 1.87 (dt, 1 H, 12.3, 4.9 Hz), 1.00 (um, 2 H), 0.04 (s, 9 H); $^{13}$C NMR (50 MHz) 156.32 (e), 151.40 (e), 145.02 (e), 142.74 (e), 133.94 (e), 131.84 (e), 127.22 (e), 119.54 (o), 115.87 (o), 112.11 (o), 96.35 (o), 88.22 (o), 63.38 (e), 56.19 (o), 54.83 (o), 50.15 (e), 45.22 (br e), 35.59 (br e), 34.45 (br o), 26.19 (e), 17.74 (e), −1.58 (o); IR (neat) 3.40 (br s), 5.85 (s), 5.94 (s), 6.02 (m), 6.15 (m), 6.20 (s), 6.67 (s), 6.90 (s), 7.15 (s), 8.78 (s), 9.10 (s), 9.62 (br s) μm; mass spectrum, $m/z$ (relative intensity) [CI] 458 ($M^+$ + 1, 65), 430 (100), 314 (4), 174 (12); [EI] 457 ($M^+$, 1), 429 (1), 174 (11), 116 (11), 73 (100); high-resolution mass spectrum ($m/z$), calcd for $C_{25}H_{35}NO_5Si$ 457.2284, found 457.2280.

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**Supplementary Material Available:** Experimental procedures for the compounds listed in the General section of the Experimental Section (48 pages). Ordering information is given on any current masthead page.

# (*E*)-4-Lithio-4-tosylbutenone Dimethyl Ketal: A New and Versatile β-Acylvinyl Anion Equivalent in Organic Synthesis

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The lithiation of (*E*)-4-tosylbutenone dimethyl ketal (**12**) with methyllithium at −20 °C led to the new β-acylvinyl anion equivalent (*E*)-4-lithio-4-tosylbutenone dimethyl ketal (**13**). The treatment of intermediate **13** with different electrophilic reagents (water, deuterium oxide, trimethylchlorosilane, methyl iodide or allyl bromide, aldehydes, acetic anhydride, carboxylic acid chlorides, ethyl chloroformate, phenyl isocyanate, or dimethyl disulfide) afforded, after careful hydrolysis, the corresponding functionalized ketal derivatives **12–21** or **22**. When the alkylation reaction of **13** with different alkyl halides was followed by acid hydrolysis, the expected alkylated tosyl ketones **23** were obtained directly. In the case of the reaction of the anion **13** with aldehydes, the in situ acid hydrolysis yielded 3-tosylfurans **25**. Monoprotected enediones **18** and keto ester **19** were deprotected by treatment with aqueous trifluoroacetic acid leading to cis-configurated enediones **27** or keto ester **28**. Finally, under basic conditions, compound **27** underwent cyclization to the corresponding cyclopentenones **29**. All the above-described transformations take place in a stereoselective manner yielding either the *E* products or the corresponding cyclized products. This result is consistent with a stereoselective formation of the (*Z*)-vinyllithium **13**, which reacts in an $S_E$ process with retention of configuration.

## Introduction

The chemistry of β-acylvinyl anion equivalents of the type **1** has received great attention recently because of their ability to provide the α,β-unsaturated acyl functionality.[1] Intermediates of this type can also be considered as sp$^2$-hybridized homoenolate equivalents.[1] In general, the corresponding organolithium derivatives have been prepared by starting directly from β-functionalzed α,β-unsaturated carbonyl compounds or their derivatives through two ways: (a) a kinetic β-deprotonation to afford intermediates of the type **2b,c**,[3] **3**,[3-5] **4**,[4,5] **5**,[4,5] **6**,[5] **7**,[6,7] or **8**;[8] (b) a bromine–lithium exchange reaction to give the unsub-

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