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Total Synthesis of (+)-Sieboldine A: Evolution of A Pinacol-Terminated Cyclization Strategy

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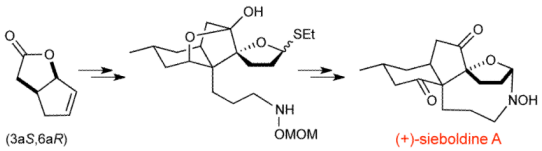
Abstract



This article describes synthetic studies that culminated in the first total synthesis of the *Lycopodium* alkaloid sieboldine A. During this study a number of pinacol-terminated cationic cyclizations were examined to form the *cis*-hydrindanone core of sieboldine A. Of these, a mild Au(I)-promoted 1,6-enyne cyclization that was terminated by a semipinacol rearrangement proved to be most efficient. Fashioning the unprecedented *N*-hydroxyazacyclononane ring embedded within the bicyclo[5.2.1]decane-*N*,*O*-acetal moiety of sieboldine A was a formidable challenge. Ultimately, the enantioselective total synthesis of (+)-sieboldine A was completed by forming this ring in good yield by cyclization of a protected-hydroxylamine thioglycoside precursor.

Introduction

The *Lycopodium* family of alkaloids displays a diverse array of complex molecular structures, which for years have served to stimulate innovation in organic synthesis.[1] Although the biological profile of only a few alkaloids of this family has been studied in detail, several are known to exhibit important biological activities. Notably (−)-huperzine A (**1**), an acetylcholinesterase inhibitor, is currently undergoing clinical evaluation for the treatment of Alzheimer's disease and schizophrenia (Figure 1).[2,3]

In 2003, Kobayashi and co-workers reported the isolation of (+)-sieboldine A (**2**) as a minor alkaloid of the Japanese club moss *Lycopodium sieboldii* together with the known alkaloid (+)-alopecuridine (**3**).[4] Extensive NMR and single-crystal X-ray analysis secured the unprecedented structure of sieboldine A. This structurally unique *Lycopodium* alkaloid was reported to inhibit electric eel acetylcholinesterase with an IC_{50} value of 2.0 μM, which is comparable to that reported for (±)-huperzine A (IC_{50} 1.6 μM), and also exhibited modest cytoxicity towards murine lymphoma L1210 cells (IC_{50} 5.1 μg/mL).[4]

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Supporting Information. Copies of ^1H and ^{13}C NMR spectra of new compounds (PDF); CIF files for compounds **33**, **39**, and **59**. This material is available free of charge via the Internet at http://pubs.acs.org.

Motivated largely by its distinctive structure, (+)-sieboldine A (**2**) was selected as a worthy target for total synthesis. Sieboldine A contains an unprecedented *N*-hydroxyazacyclononane ring embedded in a bicyclo[5.2.1]decane-*N*,*O*-acetal; the fragment shown in red in Figure 1. These functionalities were previously unknown in natural products and in the chemical literature as a whole. Sieboldine A also contains a *cis*-hydrindane, the distinctive structural feature of the fawcettimine class of *Lycopodium* alkaloids.[1] Herein we describe the evolution of a synthetic sequence that culminated in the first total synthesis of (+)-sieboldine A (**2**) in 2010.[5] In 2011, Tu and coworkers reported the total synthesis of (±)-alopecuridine (**3**) and its conversion to (±)-sieboldine A by the biomimetic sequence first postulated by Kobayashi.[4,6]

Results and Discussion

Synthesis Plan

Our synthetic planning was influenced by the anticipated sensitivity of the hydroxylamine *N*,*O*-acetal functionality of sieboldine A (**2**). As a result, we envisaged forming the *N*-hydroxyazacyclononane ring at a late stage in the synthesis by intramolecular condensation of a tethered hydroxylamine side chain with the five-membered lactol **4** (X = OH) or a derivative (Scheme 1).[7] Spirotricyclic tetrahydrofuran **4** was seen arising from α-methylene *cis*-hydrindandione **5** by conjugate addition of a two-carbon fragment followed by oxidation of the resulting enolate or silyl derivative from the less-hindered convex face.

Because of the many previous syntheses of *Lycopodium* alkaloids of the fawcettimine class,[8] a variety of approaches for forming the *cis*-hydrindanone portion of sieboldine A were conceivable. In earlier work from our laboratory, we had used a pinacol-terminated Prins cyclization to assemble this fragment in total syntheses of (−)-magellanine and (+)-magellaninone.[9,10] We were attracted again to this strategy in the present context, envisaging *cis*-hydrindandione **6** as the direct precursor of α-methylene dione **5**. If the alkoxymethyl side chain of the cyclopentane ring of **6** were to be introduced in a pinacol-terminated cyclization, the progenitor of *cis*-hydrindandione **6** would be an intermediate such as **7**. This projected cascade sequence would examine for the first time whether an alkene π-nucleophile containing two inductively deactivating oxygen substituents would be viable in a Prins–pinacol transformation. As indicated in intermediates **7**–**9**, the C15 methyl group could be incorporated at the outset, or potentially introduced after forming the *cis*-hydrindanone ring. Although several steps would be involved in introducing the C15 methyl group at the *cis*-hydrindanone stage, this strategy would allow the pivotal Prins–pinacol reaction (**8** → **7**) to be quickly examined. Our initial investigations pursued this strategy.

Prins–Pinacol Rearrangement to Assemble the *cis*-Hydrindanone Core in the C-15 Demethyl Series

As precursor **8** (R^1 = H) should be readily available from the reaction of vinyl organometallic **10** and cyclopentanone **9** (R^1 = H), synthesis of an appropriate vinyl iodide fragment **13** began with readily available 6-(*tert*-butyldiphenylsiloxy)-2-hexynoate (**11**).[11] Stannylcupration of this ynoate, followed by quenching with MeOH at −78 °C afforded vinylstannane **12** (>20:1 *E*:*Z*) in high yield (Scheme 2).[12] Reduction of the methyl ester of **12**, etherification of the resulting primary alcohol with phenol under Mitsunobu conditions,[13] and stereospecific tin–halogen exchange gave (*E*)-vinyl iodide **13** in 68% overall yield from **11**. This series of reactions could be carried out efficiently to access **13** on scales up to 60 g.

Coupling of vinyl iodide **13** with cyclopentanone **14**[14] initially proved challenging. Using *s*-BuLi in the iodide–lithium exchange of iodide **13**,[15] followed by addition of ketone **14** at

low temperatures (−100→−78 °C) provided a 1:1 ratio of adduct **15** to the *cis*-alkene resulting from protodeiondination of **13** (Scheme 3).[16] In order to suppress competitive enolization, (*E*)-vinyl iodide **13** was converted to the corresponding lithium reagent with 1.65 equiv of *s*-BuLi and added to a slurry of $CeCl_3$ in THF at −78 °C. After formation of the vinylcerium species, ketone **14** was added at −78 °C to give tertiary allylic alcohol **15** in 81% yield. Addition of anhydrous LiCl to the cerium slurry, a procedure initially reported by Knochel,[17] improved the yield of allylic alcohol **15** to 96% (>10:1 diastereoselectivity).[18] Silylation of tertiary allylic alcohol **15** with TMS-imidazole and a catalytic amount of tetrabutylammonium fluoride (TBAF) provided the Prins–pinacol precursor **16** in 76% yield.[19]

The pivotal Prins–pinacol reaction of alkenyl acetal **16** was studied in detail (Scheme 4). Exposure of alkenyl acetal **16** to 0.9 equiv of BCl_3, $BF_3{\cdot}OEt_2$, or TMSOTf in CH_2Cl_2 at −78 °C and quenching the reaction at low temperature gave either a complex mixture of products or largely bicyclic acetal **17** resulting from desilylation of **16**. However in the presence of 0.9 equiv of $SnCl_4$ (in CH_2Cl_2 at −78 °C→0 °C), precursor **16** provided *cis*-hydrindanone **19**, a 5.6:1 mixture of α:β methoxy epimers, in 51% yield together with 25% of a less-polar byproduct. Upon isolation, this byproduct was shown to be the Prins cyclization product **18**; particularly diagnostic were signals for the allylic methine and methylene hydrogens between 4.20 and 4.63 ppm.

Hydrindene **18** would arise from deprotonation of the axial β-hydrogen of tertiary carbocation intermediate **B** prior to the desired semipinacol shift to give Prins–pinacol product **19**. The formation of Prins cyclization byproducts similar to hydrindene **18** had not been observed in appreciable yields in other closely related Prins–pinacol cascades studied in our laboratory.[10] The intervention of this pathway in the present case is attributed to enhanced acidity of the axial methine hydrogen resulting from the presence of the inductively electron-withdrawing phenoxymethyl substituent.

Numerous attempts were made to minimize this undesired Prins cyclization pathway (**16**→**A**→**B**→**18**). Variation of the reaction temperature had little effect. For example, allowing the reaction to warm slightly to −60 °C and maintaining it at this temperature for 14 h resulted in full consumption of dimethyl acetal **16**;[20] however, the ratio of Prins–pinacol product **19** to the elimination product **18** was not improved. Initiating the reaction at higher temperatures resulted in substantial decomposition of the starting alkenyl acetal. The use of polar solvents such as $MeNO_2$ or *i*-$PrNO_2$ led to little or no improvement in the yield of **19** (Entries 5 and 6, Table 1).[21] Conversely, employing $TiCl_4$ instead of $SnCl_4$ resulted in an enhanced 70% yield of Prins–pinacol product **19** (a 4.3:1 mixture of α:β methoxy epimers) with decreased the formation of byproduct **18** (Table 1, Entry 7). We attribute this improvement to the increased strength of the Ti–Cl bond relative to the Sn–Cl bond and the resulting decreased basicity of the conjugate anion.[22]

Elaboration of the *N*-Hydroxyazacyclononane Ring in the Demethyl Series

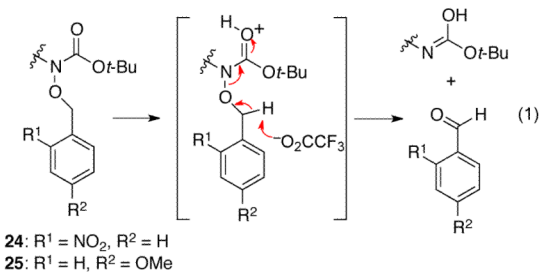
With *cis*-hydrindanone **19** in hand, we chose to utilize this intermediate to investigate strategies for forming the *N*-hydroxyazacyclononane ring. We anticipated that what we learned in this series would be applicable to intermediates that incorporated the C15 methyl group, because an equatorial methyl substituent at C15 should not influence the conformation of intermediates containing a *cis*-hydrindanane ring system. The mixture of *cis*-hydrindanone epimers undoubtedly could be processed further, however, for the sake of convenience the readily separated major epimer α-**19** was typically employed in subsequent transformations. Oxidation of the methoxy group of the α-**19** directly to the ketone using catalytic RuO_4 was low yielding, as oxidative decomposition of the phenyl ether was

observed.[23,24] Unable to convert the methyl ether directly into a ketone, two-step procedures were investigated.[25] Attempted demethylation of **19** with a variety of reagents (e.g. BBr_3, chlorocatacholborane, bromocatacholborane, Me_2BBr, $AlBr_3$/EtSH) were unpromising, with side products resulting from the partial cleavage of the TBDPS group being observed. Trimethylsilyl iodide (5–10 equiv) rapidly converted the silyl ether of α-**19** to the corresponding iodide and subsequently cleaved the methyl ether (Scheme 5).[26] However, yields in this transformation were found to be variable and sensitive to the water content of the reaction mixture. Addition of 5 equiv of H_2O to the reaction mixture and heating to 50 °C reproducibly provided **20** in 68% yield,[27] thereby implicating HI in the reaction. Our singular attempt to cleave methyl ether **19** by reaction with HI (5 equiv, 50% aqueous in MeCN at room temperature) resulted only in decomposition.

As a prelude to incorporating the remaining two carbons of the tetrahydrofuran ring, the alcohol substituent of intermediate **20** was oxidized with Dess–Martin periodianane,[28] and the resulting β-phenoxyketone was exposed to 1.2 equiv of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in THF at 0 °C to give α-methylene ketone **21** in 71% yield over 2 steps (Scheme 5). Initial attempts to append the final two carbons by Mukaiyama–Michael reaction of enedione **21** with the ketene silyl acetals (TMS or TBS) generated from phenylthioacetate were unpromising.[29] Cyclocondensation of ethyl vinyl ether with enedione **21** at 100 °C in a sealed tube provided dihydropyran **22**, albeit in low yield. However, europium(III)-catalyzed cyclocondensation was highly efficient,[30] providing oxatricyclic product **22** in 86% yield. The primary alkyl iodide was unaffected during this series of transformations, which allowed for straightforward incorporation of various *N*- and *O*-protected hydroxylamines to furnish intermediates **23**–**27**. This late-stage diversification was valuable, as determining how the hydroxylamine fragment should be functionalized proved challenging (see below).

As a prelude to investigating formation of the *N*-hydroxyazacyclononane ring,[31] elaboration of tricyclic dihydropyrans **23**–**27** to the corresponding spirocyclic tetrahydrofuran lactols was investigated (Scheme 6). Epoxidation of dihydropyran precursor **23** occurred cleanly from the convex face to give a putative epoxide intermediate **C** that transformed in situ to tricyclic tetrahydrofuran **D** (a mixture of ethoxy epimers by ^1H NMR analysis).[32] In an attempt to remove both Boc groups and concurrently form the *N*-hydroxyazacyclononane ring, this mixture was exposed at room temperature to an excess of TFA in CH_2Cl_2. Instead of forming the nine-membered ring, condensation of the *N*-3-(hydroxyamino)propyl chain with the C13 carbonyl gave rise to tetracyclic nitrone **28** as the major product in 28% yield over the 2 steps.

We next investigated formation of the *N*-hydroxyazacyclononane ring independently from the oxidation-rearrangement step. Oxidation of tricyclic dihydropyrans **24**–**27** with *m*-CPBA in CH_2Cl_2 followed by hydrolysis of the resulting mixture of tricyclic acetal epimers in TFA/H_2O/THF (1:1:3) at room temperature provided spirotricyclic lactols **29**–**32** as ~1:1 mixture of epimers. To our surprise, attempts to remove the Boc group from the hydroxylamine side chains of intermediates **29** or **30** with TFA at room temperature in CH_2Cl_2 resulted in substantial cleavage of the N–O bond, with an aldehyde being identified by ^1H NMR analysis as a substantial byproduct. One potential mechanism for this apparently unknown fragmentation is suggested in eq 1. Other acidic conditions (AcOH, HCl, AcCl/MeOH), as well as thermal conditions, also resulted in substantial N–O bond fragmentation.



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Protecting groups for the hydroxylamine that might be removed under non-acidic conditions were also investigated. Attempts to remove the allyl carbamate from **31** by standard palladium(0) catalysis conditions ($Pd(PPh_3)_4$; Et_3SiH, dimedone, or morpholine) or the nosyl group from **32** with thiophenol and K_2CO_3[33] resulted in complex reaction mixtures (Scheme 6). Immediately after removal of the nosyl group from **32**, the IR absorption of the cyclohexanone carbonyl (1696 cm^{-1}) was significantly weaker than that of the cyclopentanone carbonyl (1744 cm^{-1}); if left standing, the intensity of the cyclohexanone band continued to decrease. These observations suggest that after deprotection, the hydroxylamine side chain eventually cyclizes with the C13 carbonyl to form tetracyclic carbinolamine **E**. Such an outcome has considerable precedent dating from Heathcock's inaugural total synthesis of the *Lycopodium* alkaloid fawcettimine.[34]

To prevent formation of the six-membered nitrone upon unveiling the tethered hydroxylamine, we explored masking the C13 carbonyl by reduction. Reduction of tricyclic dihydropyran ketone **23** with 1.0 equiv of $NaBH_4$ in MeOH at 0 °C took place largely from the convex face. Without purification, this crude alcohol intermediate was directly epoxidized with 1.2 equiv of *m*-CPBA (Scheme 7). Exposure of the resulting mixture of products to TFA in CH_2Cl_2 (1:3) in the presence of $MgSO_4$ at room temperature gave rise to one major product **33**, which was isolated in 25% overall yield from **23**. Single-crystal X-ray analysis established that cyclization had taken place not on nitrogen, but on the hydroxylamine oxygen to give pentacyclic product **33** having a rare 1,2-oxazacyclodecane ring. In the off chance that 1,2-oxazacyclodecane **33** was less stable than the corresponding bicyclo[5.2.1]decane-*N*,*O*-acetal, it was exposed at room temperature to 1.1 equiv of camphorsulfonic acid (CSA) in $CDCl_3$. Monitoring this reaction by ^1H NMR for 24 h provided no evidence for isomerization to form the desired *N*-hydroxyazacyclononane ring. We concluded that the hydroxyl group of the *N*-3-(hydroxyamino)propyl chain would require masking during the cyclization event.

We turned to investigate elaboration of tricyclic dihydropryan **27** in which the hydroxylamine side chain is masked on oxygen with a *p*-methoxybenzyl (PMB) group. Reduction of **27** with $NaBH_4$ in MeOH at 0 °C, followed by oxidation and acidic hydrolysis to provided a ca. 1:3 mixture of the equatorial alcohol product **34** and the tetracyclic dilactol **35** resulting from cyclization of the axial alcohol epimer (Scheme 8). It was later discovered that the use of 2 equiv of DIBALH in CH_2Cl_2 at −78 °C in the reduction step of this sequence strongly favored hydride addition from the equatorial vector to provide ultimately tetracyclic intermediate **35** in 63% overall yield from **27**.[35,36]

We turned to explore forming the *N*-hydroxyazacyclononane ring from intermediate **35** (Scheme 9). Removal of the nosyl group from **35** by reaction with thiophenol and K_2CO_3

gave intermediate **36** in good yield. Attempts to effect the cyclization of the *N*-3-(alkoxyamino)propyl chain by exposing **36** to dichloroacetic acid (10 mol% in CH_2Cl_2) or pyridinium *p*-toluenesulfonic acid (PPTS) in pyridine resulted in complex reaction mixtures. Condensation to form the azacyclononane ring was attempted by heating amino lactol **36** to 80 °C in benzene; however, this treatment resulted largely in N–O bond fragmentation. Efforts to induce dehydrative condensation by subjecting amino lactol **36** to $MgSO_4$, or a combination of $MgSO_4$ and $ZnCl_2$, also were unrewarded. Moreover, attempted activation of lactol **36** with Lewis acids or under Mitsunobu[37] conditions did not promote azacyclononane ring formation. Our inability to detect formation of the azacyclononane ring under Brønsted acidic, Lewis acidic, thermal, or dehydrative reaction conditions suggested that the conditions investigated were likely incompatible with the fragile bicyclo[5.2.1]decane-*N*,*O*-acetal. With this in mind, our focus shifted to investigating milder cyclization conditions by utilizing a more activated derivatives of the five-membered lactol.

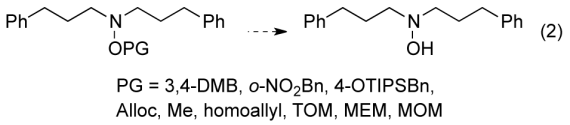
Schmidt-type glycosylation conditions proved more successful.[38] Thus, exposure of amino lactol **36** to 1.8 equiv of Cl_3CCN and 10 mol% DBU in CH_2Cl_2 (0.09 M) led directly to the formation of pentacyclic product **37** in 26% yield (Scheme 10).[39] Formation of the bicyclo[5.2.1]decane-*N*,*O*-acetal was confirmed by 2D NMR experiments that showed a 10 Hz HMBC coupling between a hydrogen at C9 and the anomeric carbon (C1). When the equatorial C13 alcohol **38** lacking the cyclic (C13–O–C5–OH) hemiacetal was subjected to identical cyclization conditions, cyclization was not observed. Efforts to improve the ring-closure were made by evaluating a variety of bases, solvents, and reagent concentrations (DBU, K_2CO_3; CH_2Cl_2, CH_3CN), but no improvement in yield were realized. Although formation of a trichloroacetimidate in the presence of a basic secondary amine has been reported,[40] trichloroacetonitrile is known to readily react with primary and secondary amines in the absence of base to form amidines.[41] Competitive formation of an amidine by reaction of the secondary hydroxylamine and trichloroacetonitrile might well be occurring; however, this presumption was not confirmed by the isolation of amidine products.

With a method established to form the bicyclo[5.2.1]decane-*N*,*O*-acetal, we examined restoring the C13 ketone (Scheme 11). Exposure of cyclic hemiacetal **37** to a catalytic amount of $Pr_4N^+RuO_4^-$ (TPAP)[42] and 4-methylmorpholine *N*-oxide (NMO) in CH_2Cl_2 uneventfully provided crystalline diketone **39**, whose structure was verified by X-ray crystallographic analysis.

Removal of the *p*-methoxybenzyl group from intermediate **39** would yield 15-demethylsieboldine A (**40**). Oxidative (CAN, DDQ) and hydrogenolytic (Pd/C or $Pd(OH)_2$ with H_2 or NH_4CO_2H) conditions were evaluated initially without success. The *N*,*O*-acetal of tetracyclic **39** was found to be stable upon exposure to 1–10 equiv of bromocatecholborane, BBr_3 or TMSI (buffered with 2,6-di-*tert*-butyl-4-methylpyridine, DTBMP) in CH_2Cl_2 even after extended periods at room temperature; although higher temperatures did eventually result in decomposition of the starting material. Subjecting **39** to 48% aqueous HF in acetonitrile at 70 °C provided trace amounts of the free hydroxylamine **40**. Allowing *N*,*O*-acetal **39** to react with 1.0 equiv of $ZrCl_4$ in acetonitrile at 70 °C afforded crude **40** (~30% yield by ^1H NMR analysis);[43] however, this product could not be isolated cleanly from the reaction mixture. The difficulties encountered in removing the PMB group led us to seek alternate protecting groups for the hydroxylamine oxygen that would be cleaved under milder conditions. Unable to introduce the protected hydroxylamine fragment at a late stage,[44] several silyl *O*-protected hydroxylamines were appended to alkyl iodide **22**. TBS-protected **41** was elaborated by the previously described three-step sequence, but the TBS group was cleaved under the aqueous TFA conditions resulting in low and variable yields of lactol **44** (0–20%, Scheme 12).[45] The TIPS-protected substrate **42** was somewhat better, providing **45** in 36% yield for the 3 steps. Removal of the Ns-group from silyl-

protected hydroxylamine **44** or **45**, followed by exposure to CCl_3CN and DBU in CH_2Cl_2, did not result in azacyclononane ring formation. The lack of observed cyclization of the TBS- or TIPS-protected hydroxylamines was attributed to the steric bulk of these silyl groups. The stability of the 2-trimethylsilylethyl (TMSE) group along with its minimal steric bulk suggested that it might provide a solution to the demanding protecting group requirements. TMSE analog **43** was elaborated to **46** in 54% overall yield. Removal of the Ns-group from **46** afforded amino lactol **49**, which cyclized under the trichloroacetimidate conditions to form tetracyclic product **50** in 23% yield as a major product. To examine removal of the TMSE group, hemiacetal **50** was first oxidized with TPAP to furnish diketone **51**. However, a variety of fluoride conditions (TBAF, CsF, KF, TASF, $LiBF_4$, HF·pyridine, aqueous HF, NH_4F) at room temperature were unsuccessful in removing the TMSE group from tetracyclic intermediate **51**, providing recovered starting material. Subjecting **51** to fluoride conditions at 100 °C for a prolonged period of time resulted in substantial decomposition.

At this point we decided to evaluate the suitability of other oxygen protecting groups in a simple model system. In choosing potential *O*-protected hydroxylamines to examine, several factors were considered. First, the facile oxidation of hydroxylamines to nitrones[46] under oxidative conditions eliminated protecting groups removed under conventional oxidative conditions. Second, we eliminated groups requiring reductive or hydrogenolysis conditions, because of concerns with the potential N–O bond reduction of the hydroxylamine.[47] Third, to favor formation of the *N*-hydroxyazonane ring, we wanted to minimize as much as possible steric bulk in the vicinity of the hydroxylamine nitrogen. The nine protecting groups depicted in eq 2 were evaluated. Of these, the methoxymethyl ether (MOM) group captured our attention, as it was smoothly removed to give *N*,*N*-bis(3-phenyl)hydroxylamine when exposed to bromocatecholborane or BBr_3 in CH_2Cl_2 at −78 °C.



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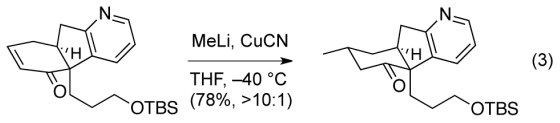
Introduction of the C15 Methyl Group by Conjugate Addition

Prior to incorporating what we had learned about constructing the bicyclo[5.2.1]decane-*N*,*O*-acetal moiety of sieboldine A in a final synthesis sequence, we briefly examined whether the C15 methyl group could be incorporated efficiently after formation of the *cis*-hydrindanone ring. The obvious possibility was to dehydrogenate an intermediate such as *cis*-hydrindanone **19** to the corresponding conjugated enone and introduce the C15 methyl group by conjugate addition of a methyl nucleophile. We expected this latter functionalization would occur preferentially from the convex face—by axial addition to conformer **G**[48,49a]—to give hydrindanone **53** (Figure 2). Although we were aware of no close precedent at the time, this expectation was in accord with the well-established preference of 5-substituted-2-cyclohexen-1-ones to undergo conjugater addition from the face opposite the 5-substituent.[49]

Salient results of our exploration of this approach for incorporating the C15 methyl group are summarized in Scheme 13. After evaluating several methods to introduce the double bond (selenoxide elimination, *o*-iodoxybenzoic acid (IBX) oxidation, DDQ or CAN oxidation, and *N*-*tert*-butylbenzenesulfonimidoyl chloride dehydrogenation),[50] Saegusa

oxidation was found most reliable and scalable.[51] In this way, *cis*-hydrindenones α-**54** and β-**54** were formed in 85% and 61% yields from their respective ketone precursors.[52] Reaction of α-**54** with the homocuprate generated from MeLi and $CuBr{\cdot}SMe_2$ in Et_2O at 0 °C gave a single product in 94% yield, which was eventually shown to be hydrindanone α-**52** in which methyl addition had taken place from the concave face. Subjecting the β-methoxy epimer, β-**54**, to identical conditions gave methyl epimers β-**52** and β-**53** in a 1.4:1 ratio and 74% combined yield.[53,54]

After these studies were completed, two examples of conjugate additions to structurally related enones were reported from the groups of Hiroya (eq 3)[55] and Elliott (eq 4).[56] Consistent with our original expectations, in both cases the methyl nucleophile added preferentially from the convex face. We speculate that the unexpected stereochemical outcome in the conjugate addition to enones **54** is a result of the large 3-(*tert*-butyldiphenylsiloxy)propyl substituent being oriented toward the cyclohexenone ring to avoid interactions with the vicinal phenoxymethyl substituent, which itself is thrust toward the angular substituent to minimize interactions with the adjacent methoxy group. This situation is illustrated in the molecular mechanics model of *cis*-hydrindenone α-**54** (Figure 3).[57] Consistent with this analysis, methylcuprate addition to β-methoxy enone **55**, which lacks the bulky *tert*-butyldimethylsiloxy group, took place preferentially from the convex face to give product **56** and its methyl epimer in a ratio of 1.6:1 (eq 5).



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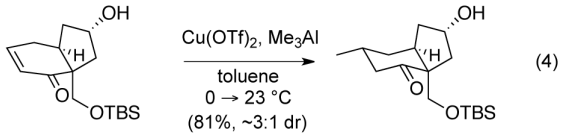

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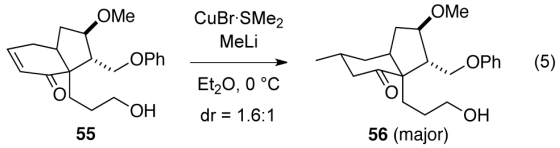

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(5)

Rigorous proof that methyl addition to enones α- and β-**54** had taken place preferentially from the concave face was not obtained until the α-epimer was elaborated further (Scheme 14). Thus, *cis*-hydrindanone α-**52** was transformed to tricyclic dihydropyran **57** by the 5-step sequence shown in Scheme 5. Sequential reaction of intermediate **57** with DIBALH at low temperature, *m*-CPBA and aqueous TFA provided as the major product spirotricyclic

tetrahydrofuran **58**. Our first hint that methyl introduction into the cyclohexane ring had taken place from the concave face was provided by the NMR and IR spectra of tricyclic intermediate **58**, which clearly showed—in contrast to the related intermediate **35** in the demethyl series—that **58** did not exist as a tetracyclic (C13–O–C5–OH) hemiacetal. Rigorous proof that the relative configuration of the C15 methyl substituent was opposite to that of sieboldine A was obtained from single-crystal X-ray analysis of the minor product, tetracyclic acetal **59**. Moreover, the relative configuration of **59** at C4 was opposite to that of major product **58**, consistent with it arising from epoxidation of the alcohol intermediate generated from α-**57** from the concave face.

Early Incorporation of the C15 Methyl Group and Optimization of the Synthesis of the *cis*-Hydrindanone Intermediate

As it appeared unlikely that the C15 methyl group could be introduced efficiently after constructing a *cis*-hydrindenone intermediate, we turned to examine installing the methyl group prior to the Prins–pinacol reaction. Several sequences for preparing a 4-methylcyclopentanone intermediate having a trans 2-carbon side chain at C2 (e.g., intermediate **9** with R^1 = Me, Scheme 1) were explored. The route initiating from known tetrahydrocyclopenta[*b*]furan-2-one **60** proved to be the most practical, and was especially attractive as convenient access to the 3a*S*,6a*R* enantiomer had been described.[58,59] Organocopper-promoted S_N2' anti-opening of allylic lactone (3a*S*,6a*R*)-**60**,[60] followed by iodolactonization of the carboxylic acid product, a sequence developed by Curran *et al.*, provided iodolactone **61** in 93% yield.[61] Slow addition of iodolactone **61** to a refluxing slurry of $LiAlH_4$ in THF gave diol **62**,[62] which was selectively silylated[63] and the secondary alcohol oxidized with Dess–Martin periodinane[28] to give *trans*-substituted cyclopentanone **63** in 73% overall yield from lactone **60**.

Coupling vinyl iodide **13** to cyclopentanone **63** required minor modifications of the previously developed conditions. Efficient addition of the vinylcerium reagent generated from **13** to ketone **63** necessitated slowly warming the reaction mixture to room temperature overnight (Scheme 16). Silylation of tertiary allylic alcohol product **64**, followed by Swern oxidation of the primary TES ether[64,65] afforded aldehyde **65** in 77% yield over 2 steps. Exposure of aldehyde **65** to trimethylorthoformate and a catalytic amount of pyridinium *p*-toluenesulfonate (PPTS) provided the requisite alkenyl acetal Prins–pinacol precursor **66** bearing the C15 methyl group.[66]

Examination of the Prins–pinacol cascade with alkenyl acetal **66** was facilitated by our earlier investigations in the model series lacking the C15 methyl substituent. Using the previously optimized Prins–pinacol conditions, a solution of dimethyl acetal **66** in CH_2Cl_2 was exposed to 0.9 equiv of $TiCl_4$ (CH_2Cl_2, −78→−20 °C) to give hydrindanones **53** in 40% yield as a 2.2:1 mixture of α:β methoxy epimers (Table 2). Varying the stoichiometry of $TiCl_4$ or the silyl protecting group of the precursor resulted in no significant improvements in yield.[67] The unsatisfactory yield obtained in the Prins–pinacol reaction of **66** forced us to explore other methods to initiate the desired cationic cyclization event.

We had previously described several alternate methods for initiating cationic cyclization-pinacol cascade reactions.[10b,68] Of these methods, use of a keteneiminium ion-initiated cyclization-pinacol rearrangement was enticing, as it would directly afford dione product **70** (Scheme 17). The requisite ketoamide **68** was readily synthesized from iodolactone **61** in 69% yield over 3 steps. Cerium-mediated addition of the lithium reagent derived from **13** to cyclopentanone **68** and subsequent silylation provided precursor **69**. Exposure of amide **69** to 1.1–1.3 equiv Tf_2O and 1.5 equiv of 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) in 1,2-dichloroethane at −20 °C resulted in formation of a colorless precipitate and loss of 17 mass

units as determined by low resolution mass spectrometry; thus suggesting the formation of keteneiminium intermediate **H**.[69] However, warming the reaction mixture to room temperature and eventually to reflux did not provide any evidence that the desired transformation to iminium intermediate **I** had occurred.[70]

Lack of success with the Prins or keteneiminium ion-initiated cyclizations to form the *cis*-hydrindane core of sieboldine A directed our attention to the related pinacol-terminated 1,6-enyne cyclization reported by Kirsch, Rhee *et al.* in 2008.[71] The requisite alkyne precursor **71** was synthesized in 90% yield by homologation of aldehyde **65** with 1.6 equiv of the Ohira–Bestmann reagent (Scheme 18).[72] Exposure of 1,6-enyne **71** to 10 mol% of $PPh_3Au^+SbF_6^-$ and 1.1 equiv of *i*-PrOH in CH_2Cl_2 (Table 3, Entry 2) yielded a 1:1 ratio of the desired pinacol-terminated cyclization product **72** and byproduct **73**[73] resulting from a Claisen-terminated heterocyclization pathway (**J**→**L**→**73**). Homogenous gold catalysis is known to be sensitive to ligand effects, and altering the electronic nature of the ligand on the cationic gold complex resulted in a significant change in the product distribution of this reaction (Table 3).[74] A trend similar to that reported by Kirsch and Rhee was observed wherein electron-rich gold(I) complexes improved the selectivity for the pinacol-terminated cyclization.[71a] Using [(*t*-Bu)$_2$P(*o*-biphenyl)]AuSbF$_6$ the pinacol-terminated product **72** and byproduct **73** were formed in a >10:1 ratio (Table 3, Entry 8). Computational studies by Toste, Goddard *et al.* have suggested that the steric size of the 2-(di-*tert*-butylphosphino)biphenyl ligand inhibits back-bonding stabilization between the metal center and the alkyne, effectively increasing the carbocationic nature of the gold alkyne species.[75,76] In the present case, the reduced Au-dπ to C-pπ orbital overlap likely favors cationic olefin cyclization over the heterocyclization pathway.[77] The Au(I) initiated cascade **71**→**72** was readily scalable to a gram-scale reaction providing *cis*-hydrindanone **72** in 84% yield (Table 3, Entry 9).

Completion of the Total Synthesis of (+)-Sieboldine A

With access to gram quantities of enantioenriched *cis*-hydrindanone **72** in hand, we turned to see if the chemistry defined in the C15-demethyl series would allow (+)-sieboldine A to be prepared in a straight forward fashion. Fortunately that proved to be the case with one important modification (Scheme 19). The final elaboration to sieboldine A began by oxidative cleavage of the exomethylene group of **72** by ozonolysis, a transformation that required careful monitoring to prevent the formation of over-oxidation products. After quenching the ozonide with dimethyl sulfide at −78 °C and allowing the reaction to room temperature overnight, a solvent swap from CH_2Cl_2 to acetonitrile followed by addition of 1.2 equiv of DBU at 0 °C to the crude diketone delivered methylene enone **74** in 75% yield from **72**. Cyclocondensation of enone **74** with ethyl vinyl ether afforded dihydropyran **75** in 86% yield.[30] Selective reduction of the C13 carbonyl of tricyclic intermediate **75** with DIBALH in CH_2Cl_2 at −78 °C, followed by epoxidation of the dihydropyran with 1.2 equiv of dimethyldioxirane (DMDO) in CH_2Cl_2 at 0 °C gave rise to a tricyclic dihydropyran intermediate as a 1:1 mixture of ethoxy epimers. Initial attempts to convert this intermediate to the corresponding dilactol (i.e., the C15-methyl analog of intermediate **35**, Scheme 8) with TFA/H_2O/THF (1:1:3) were low yielding and plagued by partial cleavage of the TBDPS group.

Thioglycosides are commonly utilized in carbohydrate chemistry to form bonds at the anomeric carbon and are activated under a variety of mild reaction conditions.[78] With this in mind, the mixture of ethoxy epimers formed from DMDO oxidation of **75** was redissolved in CH_2Cl_2 containing 5 equiv of EtSH, cooled to −78 °C and exposed to 1.1 equiv of $BF_3{\cdot}OEt_2$ to give thioglycoside **76** in 53% yield (Scheme 19).[79] Removal of the TBDPS group of **76** with 3 equiv of TBAF in THF, coupling with *N*-(methoxymethoxy)-2-

nitrobenzenesulfonamide under Mitsunobu conditions,[80] and removal of the nosyl group provided intermediate **77**.

Several conditions were examined for forming the final azacyclononane ring from thioglycoside precursor **77** (Table 4). Exposure of **77** to mercury or silver salts, tris(4-bromophenyl)ammoniumyl hexachloroantimonate (TBPA),[81] or *p*-nitrobenzenesulfenyl triflate ($NO_2PhSOTf$)[82] provided product **78** harboring the desired *N*-alkoxyazacyclononane ring in low yields, 10–28% (Table 4, Entries 1–4). Activation of thioglycoside **77** with 5 equiv of dimethyl(methylthio)sulfonium triflate (DMTST)[83,84] in CH_2Cl_2 (0.009 M) at 0 °C was somewhat better, giving **78** in 37% yield (Table 4, Entry 5). The cyclization was further improved by slow addition of thioglycoside **77** to a solution of 5 equiv DMTST in MeCN (0.009 M) at −20 °C which delivered pentacyclic intermediate **78** in a notable 51% yield (Table 4, Entry 7).

The total synthesis of (+)-sieboldine A was completed in two additional steps (Scheme 20). Oxidation of the cyclic hemiacetal unit of **78** with TPAP provided diketone **79** in 88% yield. The MOM ether of **79** could be removed to give (+)-sieboldine A, albeit in low yield (<40%), by reaction with a large excess (5–20 equiv) of bromocatecholborane, BBr_3, TMSBr, or BCl_3 at room temperature, Fortunately, we discovered that deprotection with 2 equiv of bromodimethylborane[85] (0 °C in CH_2Cl_2) was more efficient, delivering (+)-sieboldine A (**2**) in 67% yield. Synthetic (+)-sieboldine A (**2**) exhibited ^1H and ^{13}C NMR spectra and optical rotation {$[\alpha]^{23}_D$ +141 (*c* 0.4, MeOH); lit.[4] $[\alpha]_D$ +139 (*c* 0.3, MeOH)} indistinguishable from those reported for the natural sample.[4,86]

Conclusion

The first total synthesis of the *Lycopodium* alkaloid (+)-sieboldine A has been accomplished in 20 steps from (3a*S*,6a*R*)-tetrahydrocyclopenta-[*b*]-furan-2-one (**60**). The synthesis features the efficient formation of the unique *N*-hydroxyazacyclononane ring by cyclization of a thioglycoside precursor. Our success in constructing sieboldine A in this way required that the hydroxy group of the tethered hydroxylamine be masked with a protecting group (methoxymethyl) that did not decrease the reactivity of the nitrogen and could be removed in the presence of the delicate the bicyclo[5.2.1]decane-*N*,*O*-acetal moiety. The synthesis also illustrates the use of Au(I)-catalyzed activation of an alkyne to promote a cyclization-pinacol sequence, first introduced by Rhee and Kirsch,[71] which in demanding contexts can be superior to Lewis acid-activation of an acetal.

Experimental Section

Experimental procedures and characterization data for the preparation of vinyl iodide **13**, *N*-(methoxymethoxy)-2-nitrobenzenesulfonamide, and compounds **60**–**65**, **71**–**79**, and **2** have been reported previously.[5]

General Procedure for Adding Vinylcerium Reagents to Cyclopentanone Intermediates. Preparation of (1**S*,2*S**)-1-((*E*)-6-(*tert*-Butyldiphenylsilyloxy)-1-phenoxyhex-2-en-3-yl)-2-(2,2-dimethoxyethyl)cyclopentanol (15)

A cyclohexane solution of *s*-BuLi (13.3 mL, 12.9 mmol, 0.97 M, 1.65 equiv)[87] was added dropwise to THF (26 mL) at −78 °C forming a clear bright yellow solution. A solution of vinyl iodide **13**[5] (6.50 g, 11.7 mmol, 1.50 equiv) and THF (8.5 mL) was added dropwise; the internal temperature was monitored during the addition to insure the temperature did not exceed −50 °C. After the addition, the solution was stirred at −78 °C for 15 min. In a separate flask, a previously prepared slurry of anhydrous $CeCl_3$ (4.41 g, 17.9 mmol, 1.70 equiv)[88], anhydrous LiCl (1.12 g, 26.5 mmol, 3.40 equiv), and THF (39 mL) was cooled to

−78 °C and a cyclohexane solution of *s*-BuLi was added dropwise until a pale yellow color persisted (ca. 1.0 mL). The vinyllithium species was cannulated to the $CeCl_3 \cdot 2LiCl$ slurry producing an orange suspension, which was stirred at −78 °C for 30 min. A solution of cyclopentanone **14**[14] (1.34 g, 7.79 mmol, 1.00 equiv) and THF (8.5 mL) was then added dropwise, resulting in the disappearance of the orange color. The suspension was allowed to slowly warm to rt over 12 h. The solution was then partitioned between Et_2O (100 mL) and 10% aq. AcOH (100 mL). The layers were separated and the aqueous phase was extracted with Et_2O (2 × 100 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ (50 mL) followed by a wash with brine (30 mL). The organic phase was dried over $MgSO_4$, filtered through a plug of cotton, and concentrated under reduced pressure. Purification by flash column chromatography (24:75:1 EtOAc/hexanes/Et_3N) afforded a 14:1 ratio of tertiary alcohol **15** and its (1*S**, 2*R**) diasteromer (4.50 g, 96% yield) as a clear colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (dd, *J* = 8.0, 1.4 Hz, 4H), 7.41 (t, *J* = 7.3 Hz, 2H), 7.36 (t, *J* = 7.5 Hz, 4H), 7.25 (t, *J* = 8.6 Hz, 2H), 6.93 (t, *J* = 7.3 Hz, 1H), 6.87 (d, *J* = 7.8 Hz, 2H), 5.90 (t, *J* = 6.3 Hz, 1H), 4.60 (d, *J* = 6.3 Hz, 2H), 4.38 (dd, *J* = 7.2, 4.2 Hz, 1H), 3.67 (t, *J* = 5.1 Hz, 2H), 3.28 (s, 3H), 3.25 (s, 3H), 2.26–2.20 (m, 1H), 2.17–2.11 (m, 1H), 2.05–1.99 (m, 1H), 1.95–1.91 (m, 2H), 1.87–1.83 (m, 1H), 1.76–1.69 (m, 2H), 1.67–1.57 (m, 4H), 1.52–1.47 (m, 1H), 1.05 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.8, 147.1, 135.6, 133.8, 129.7, 129.5, 127.7, 120.7, 120.5, 114.7, 104.0, 85.1, 65.0, 63.8, 52.8, 52.7, 42.7, 39.9, 33.6, 31.7, 30.1, 26.9, 25.1, 22.1, 19.3; IR (thin film) 3437, 2955, 2930, 1496, 1240, 1112 cm^{-1}; HRMS-ESI (*m*/*z*) $[M + Na]^+$ calcd for $C_{37}H_{50}O_5SiNa$ 625.3325; found, 625.3318.

tert-Butyl((*E*)-4-((1*S**,2*S**)-2-(2,2-dimethoxyethyl)-1-(trimethylsilyloxy)cyclopentyl)-6-phenoxyhex-4-enyloxy)diphenylsilane (16)

A solution of tetra-*n*-butylammonium fluoride in THF (0.17 mL, 0.17 mmol, 1.0 M, 0.01 equiv) was added dropwise to a solution of tertiary alcohol **15** (10.0 g, 17.0 mmol, 1.00 equiv), TMS-imidazole (5.1 mL, 35 mmol, 2.0 equiv), and DMF (44 mL) at rt. After 3 h, the solution was partitioned between water (500 mL) and Et_2O (250 mL), the layers were separated, and the aqueous phase was extracted with Et_2O (3 × 200 mL). The combined organic layers were washed with water (500 mL) then brine (500 mL), dried over $MgSO_4$, filtered through a plug of cotton, and concentrated under reduced pressure. Purification by flash chromatography (1:10:89 Et_3N/EtOAc/hexanes) afforded silyl ether **16** as a colorless oil (9.0 g, 76% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (dd, *J* = 7.9, 1.3 Hz, 4H), 7.42 (tt, *J* = 7.3, 2.0 Hz, 2H), 7.36 (t, *J* = 6.8 Hz, 4H), 7.24 (t, *J* = 7.9 Hz, 2H), 6.91 (t, *J* = 7.4 Hz, 1H), 6.87 (dd, *J* = 8.8, 1.0 Hz, 2H), 5.83 (t, *J* = 6.4 Hz, 1H), 4.59 (dd, *J* = 6.4, 2.9 Hz, 2H), 4.37 (dd, *J* = 7.6, 4.4 Hz, 1H), 3.69–3.64 (m, 2H), 3.29 (s, 3H), 3.21 (s, 3H), 2.26–2.20 (m, 1H), 2.04–2.00 (m, 1H), 1.97–1.91 (m, 1H), 1.88–1.84 (m, 1H), 1.83–1.78 (m, 1H), 1.77–1.71 (m, 2H), 1.69–1.62 (m, 3H), 1.61–1.60 (m, 1H), 1.49–1.43 (m, 1H), 1.42–1.36 (m, 1H), 1.05 (s, 9H), 0.07 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.9, 145.6, 135.6, 133.8, 129.7, 129.4, 127.7, 121.9, 120.5, 114.8, 104.2, 88.1, 64.9, 63.8, 53.2, 51.7, 44.5, 36.4, 33.6, 30.9, 29.6, 26.9, 25.2, 22.1, 19.3, 2.0; IR (thin film) 2975, 2956, 1251 cm^{-1}; HRMS-ESI (*m*/*z*) $[M + Na]^+$ calcd for $C_{40}H_{58}O_5Si_2Na$ 697.3721; found, 697.3737.

tert-Butyl((*E*)-4-((3a*S**,6a*S**)-2-methoxyhexahydro-2*H*-cyclopenta[*b*]furan-6a-yl)-6-phenoxyhex-4-enyloxy)diphenylsilane (17)

A 1 M solution of TMSOTf in CH_2Cl_2 (0.015 mL, 0.081 mmol, 0.98 equiv) was added dropwise to a solution of acetal **16** (0.050 g, 0.083 mmol, 1.00 equiv), 2,6-di-*tert*-butyl-4-methylpyridine (34 mg, 0.17 mmol, 2.0 equiv), and CH_2Cl_2 (1.5 mL) at −78 °C. The solution was allowed to warm to −20 °C. After 20 min, the solution was quenched at −20 °C by adding triethylamine (93 μL, 0.66 mmol) and then partitioned between sat. aq. $NaHCO_3$ (10 mL) and CH_2Cl_2 (5 mL). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with brine (10

mL), dried over $MgSO_4$, filtered through a plug of cotton, and concentrated under reduced pressure. Purification by column chromatography (1:9 EtOAc/hexanes) afforded cyclic acetal **17** (39 mg, 83% yield) as a colorless oil and a mixture of methoxy epimers: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, *J* = 7.0 Hz, 2H), 7.45–7.42 (m, 2H), 7.40–7.36 (m, 4H), 7.29–7.25 (m, 4H), 6.94 (q, *J* = 7.0 Hz, 1H), 6.89 (dd, *J* = 2.0, 8.0 Hz, 2H), 5.92 (t, *J* = 6.0 Hz, 0.5H), 5.84 (t, *J* = 6.5 Hz, 0.5H), 5.07 (dd, *J* = 2.5, 5.5 Hz, 0.5H), 5.04 (d, *J* = 5.5 Hz, 0.5H), 4.60 (d, *J* = 6.0 Hz, 1H), 4.57 (t, *J* = 5.5 Hz, 1H), 3.70–3.68 (m, 2H), 3.37 (s, 1.5H), 3,34 (s, 1.5H), 2.78 (q, *J* = 6.0 Hz, 0.5H), 2.43 (dt, *J* = 0.5, 8.0 Hz, 0.5H), 2.30–2.19 (m, 2H), 2.17–2.09 (m, 1H), 2.08–1.97 (m, 1H), 1.88–1.79 (m, 2H), 1.77–1.71 (m, 1H), 1.70–1.60 (m, 4H), 1.53 (dd, *J* = 0.5, 11.5 Hz, 1H), 1.06 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.94 (C), 158.90 (C), 147.2 (C), 146.1 (C), 135.8 (CH), 133.9 (C), 129.9 (CH), 129.6 (CH), 127.9 (CH), 120.7 (CH), 119.3 (CH), 119.1 (CH), 114.8 (CH), 106.9 (CH), 106.5 (CH), 99.6 (C), 98.4 (C), 65.1 (CH_2), 64.0 (CH_2), 63.9 (CH_2), 55.9 (CH_3), 55.3 (CH_3), 45.4 (CH), 44.9 (CH), 41.1 (CH_2), 40.9 (CH_2), 39.7 (CH_2), 38.8 (CH_2), 34.5 (CH_2), 33.9 (CH_2), 29.9 (C), 27.1 (CH_3), 25.6 (CH_2), 24.8 (CH_2), 24.3 (CH_2), 19.4 (C); IR (thin film) 2951, 2858, 1598, 1495, 1239, 1108 cm^{-1}; HRMS-ESI (*m*/*z*) $[M + Na]^+$ calcd for $C_{36}H_{46}O_4SiNa$ 593.3063; found, 593.3057.

General Procedure for the Prins–Pinacol Reactions of Acetal Precursors

Preparation of 18, α-19, and β−19. A solution of $TiCl_4$ and CH_2Cl_2 (10.4 mL, 10.4 mmol, 1.0 M, 0.900 equiv) was added dropwise to a solution of dimethyl acetal **16** (7.84 g, 11.6 mmol, 1.00 equiv) and CH_2Cl_2 (230 mL) at −78 °C resulting immediately in a bright orange solution. The solution was then placed in a −20 °C (ice–acetone) bath, and maintained for 20 min. The orange solution then was treated with Et_3N (12.9 mL, 92.8 mmol, 8.00 equiv) then MeOH (3.75 mL, 92.8 mmol, 8.00 equiv) resulting in the loss of color. The cold mixture was partitioned between saturated aqueous $NaHCO_3$ (200 mL) and CH_2Cl_2 (100 mL) resulting in the formation of a colorless precipitate. The triphasic mixture was then passed through a pad of Celite®. The liquid phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 200 mL). The combined organic layers were washed with brine (500 mL), dried over $MgSO_4$, filtered through a plug of cotton, and concentrated under reduced pressure. The residue was purified by flash chromatography (1:9 EtOAc/hexanes → 2:3 EtOAc/hexanes) to afford the following three products.

tert-Butyl(3-((3a*S**,7a*S**)-6-methoxy-5-(phenoxymethyl)-3a-(trimethylsilyloxy)-2,3,3a,6,7,7a-hexahydro-1*H*-inden-4-yl)propoxy)diphenylsilane (18)

First eluting was elimination product **18** (0.107 g, 1.4% yield) as a clear colorless oil comprised of an unassigned mixture of methoxy epimers. The major diastereomer was characterized as follows: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (dd, *J* = 7.9, 1.4 Hz, 4H), 7.50–7.43 (m, 6H), 7.31 (t, *J* = 8.0 Hz, 2H), 6.96–6.94 (m, 3H), 4.62 (dd, *J* = 5.3, 3.0 Hz, 1H), 4.41–4.39 (m, 1H), 4.31 (dd, *J* = 8.6, 3.7 Hz, 1H), 4.20 (dd, *J* = 11.0, 8.6 Hz, 1H), 3.71 (dd, *J* = 9.9, 6.2 Hz, 1H), 3.68 (dd, *J* = 9.9, 6.3 Hz, 1H), 3.48 (s, 3H), 2.50–2.44 (m, 1H), 2.21 (dt, *J* = 11.0, 4.0 Hz, 1H), 2.09–2.03 (m, 2H), 1.83 (td, *J* = 11.9, 4.0 Hz, 1H), 1.71–1.52 (m, 6H), 1.44–1.41 (m, 1H), 1.11 (s, 9H), 0.06 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.8, 159.3, 135.7, 134.4, 134.3, 129.5, 129.3, 127.61, 127.60, 119.9, 114.4, 92.5, 71.9, 65.1, 64.7, 54.4, 53.9, 46.9, 42.5, 39.1, 30.5, 28.7, 27.0, 25.9, 20.4, 19.3, 0.1; IR (thin film) 2951, 1495, 1106 cm^{-1}; HRMS-ESI (*m*/*z*) $[M + Na]^+$ calcd for $C_{39}H_{54}O_4Si_2Na$ 665.3458; found, 665.3451.

(2*S**,3*S**,3a*S**,7a*S**)-3a-(3-(*tert*-Butyldiphenylsilyloxy)propyl)-2-methoxy-3-(phenoxymethyl)hexahydro-1*H*-inden-4(2*H*)-one (α-19)

The major hydrindanone diastereomer **α-19** eluted next as a clear colorless oil (3.44 g, 52% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (d, *J* = 7.6 Hz, 4H), 7.42–7.40 (m, 2H), 7.38–7.35 (m, 4H), 7.27–7.23 (m, 2H), 6.91 (t, *J* = 7.3 Hz, 1H), 6.88–6.86 (dd, *J* = 8.7, 1.0 Hz, 2H), 4.16 (t, *J* = 8.7 Hz, 1H), 3.99 (dd, *J* = 9.3, 4.7 Hz, 1H), 3.89 (dd, *J* = 10.3, 6.3 Hz, 1H), 3.69–3.64 (m, 1H), 3.58–3.53 (m, 1H), 3.26 (s, 3H), 2.77 (dd, *J* = 13.3, 5.5 Hz, 1H), 2.53 (quintet, *J* = 7.3 Hz, 1H), 2.41 (dt, *J* = 16.1, 5.6 Hz, 1H), 2.32–2.26 (m, 1H), 1.99–1.93 (m, 1H), 1.85–1.78 (m, 2H), 1.76–1.69 (m, 5H), 1.47–1.40 (m, 1H), 1.39–1.33 (m, 1H), 1.04 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.9, 158.9, 135.7, 135.6, 134.1, 134.0, 129.6, 129.4, 127.6, 120.5, 114.6, 80.6, 64.1, 63.5, 59.0, 57.5, 47.8, 43.4, 39.3, 36.4, 29.1, 28.6, 28.0, 26.9, 22.0, 19.2; IR (thin film) 3071, 2927, 2856, 1697, 1472, 1242 cm^{-1}; HRMS-ESI (*m*/*z*) [M + Na]$^+$ calcd for $C_{36}H_{46}O_4SiNa$ 593.3063; found, 593.3055.

(2>*R**,3*S**,3a*S**,7a*S**)-3a-(3-(*tert*-Butyldiphenylsilyloxy)propyl)-2-methoxy-3-(phenoxymethyl)hexahydro-1*H*-inden-4(2*H*)-one (β-19)

The minor hydrindanone diastereomer **β-19** eluted last as a clear colorless oil (0.861 g, 13% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (dd, *J* = 8.0, 1.3 Hz, 4H), 7.41 (t, *J* = 7.2 Hz, 2H), 7.37–7.33 (m, 4H), 7.23 (d, *J* = 7.7 Hz, 2H), 6.93 (t, *J* = 7.3 Hz, 1H), 6.83 (d, *J* = 7.8 Hz, 2H), 4.02 (dd, *J* = 9.6, 5.0 Hz, 1H), 3.84 (dd, *J* = 9.5, 6.4 Hz, 1H), 3.80 (quint., *J* = 3.6 Hz, 1H), 3.61–3.55 (m, 2H), 3.29 (s, 3H), 3.13 (q, *J* = 4.8 Hz, 1H), 2.43–2.39 (m, 2H), 2.34–2.28 (m, 1H), 2.19 (dt, *J* = 13.9, 7.8 Hz, 1H), 1.99–1.96 (m, 1H), 1.91–1.86 (m, 1H), 1.77–1.63 (m, 4H), 1.54–1.44 (m, 2H), 1.34–1.29 (m, 1H), 1.01 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.7, 158.8, 135.6, 133.9, 129.7, 129.6, 129.5, 127.7, 120.8, 114.5, 83.8, 66.7, 64.0, 59.6, 56.8, 47.5, 44.8, 38.7, 36.1, 28.6, 28.2, 26.9, 26.0, 22.5, 19.2; IR (thin film) 3071, 2859, 1703, 1429, 1242 cm^{-1}; HRMS-ESI (*m*/*z*) [M + Na]$^+$ calcd for $C_{36}H_{46}O_4SiNa$ 593.3063; found, 593.3061.

An additional 0.330 g (5.0 %) of the desired hydrindanone products **α-19** and **β-19** was obtained from the mixed fractions of this column.

(2*S**,3*S**,3a*S**,7a*S**)-2-Hydroxy-3a-(3-iodopropyl)-3-(phenoxymethyl)hexahydro-1*H*-inden-4(2*H*)-one (20)

TMSCl (7.5 mL, 59 mmol, 10 equiv)[89] was added dropwise to a solution of NaI (8.9 g, 59 mmol, 10 equiv)[90] and dry MeCN (49 mL) at rt with vigorous stirred for 20 min, which resulted in formation of a colorless precipitate. The freshly prepared solution of TMSI was decanted from the precipitate via syringe and added dropwise to a solution of methyl ether **α-19** (3.4 g, 5.9 mmol, 1.0 equiv), H_2O (0.53 mL, 30 mmol, 5.0 equiv), and MeCN (17 mL). The solution was then heated to 50 °C for 2 h. The resulting brown solution was cooled to rt, diluted with Et_2O (100 mL) and treated with 1:1:1 H_2O/sat. aq. $NaHCO_3$/sat. aq. $Na_2S_2O_3$ (100 mL) and stirred for 15 min, resulting in disappearance of the brown color. The layers were separated and the aqueous phase was extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with brine (150 mL), dried over $MgSO_4$, filtered through a plug of cotton, and concentrated under reduced pressure. Purification by flash chromatography (2:3 EtOAc/hexanes) provided iodoalcohol **20** (1.7 g, 68% yield) as a pale yellow oil: ^{1}H NMR (500 MHz, C_6D_6) δ 7.14 (t, *J* = 8.0 Hz, 2H), 6.90 (d, *J* = 8.0 Hz, 2H), 6.85 (t, *J* = 7.3 Hz, 1H), 4.27–4.23 (m, 1H), 4.21 (t, *J* = 9.1 Hz, 1H), 4.06 (dd, *J* = 9.4, 4.8 Hz, 1H), 2.79–2.74 (m, 1H), 2.66–2.61 (m, 1H), 2.57–2.53 (m, 1H), 2.14–2.11 (m, 1H), 2.07–2.02 (m, 1H), 1.99–1.95 (m, 1H), 1.77 (td, *J* = 12.5, 3.8 Hz, 1H), 1.69–1.61 (m, 2H), 1.57–1.46 (m, 2H), 1.43–1.37 (m, 1H), 1.34–1.13 (m, 3H), 0.98–0.92 (m, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ 212.1, 158.9, 129.5, 120.9, 114.5, 71.3, 63.8, 58.6, 48.4, 43.1, 39.5, 38.3, 32.9, 29.8, 27.5,

21.9, 6.4; IR (thin film) 3456, 2935, 1694, 1600, 1497, 1243 cm^{-1}; HRMS-ESI (*m*/*z*) [M + Na]$^+$ calcd for $C_{19}H_{26}IO_3$ 429.0927; found, 429.0935.

(3a*S**,7a*S**)-3a-(3-Iodopropyl)-3-methylenetetrahydro-1*H*-indene-2,4(5*H*,6*H*)-dione (21)

Dess–Martin periodinane (1.45 g, 3.42 mmol 1.50 equiv)[28] was added in one portion to a stirring suspension of iodoalcohol **20** (0.975 g, 2.28 mmol) and $NaHCO_3$ (1.92 g, 22.8 mmol, 10.0 equiv) in CH_2Cl_2 (12.7 mL) and stirred vigorously for 20 min. The suspension was treated with 10% aq. $Na_2S_2O_3$ (10.0 mL) and stirred for 15 min. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered through a plug of cotton, and concentrated under reduced pressure to provide the dione (0.917 g, 94%). A solution of 1,8-diazabicyclo[5.4.0]undec-7-ene and THF (4.74 mL, 2.37 mmol, 0.50 M, 1.10 equiv) was added dropwise to a solution of dione (0.917 g, 2.15 mmol, 1.00 equiv) and THF (43 mL) at 0 °C. The cooling bath was removed and the pale brown solution was stirred for 20 min, the solution was then partitioned between sat. aq. NH_4Cl (75 mL) and Et_2O (50 mL), the layers were separated and the aqueous phase was extracted with Et_2O (2 × 50 mL). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, filtered through a plug of cotton, and concentrated under reduced pressure. Purification by flash chromatography (15:85 EtOAc/hexanes) provided endione **21** (0.543 g, 76% yield) as a pale yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.13 (s, 1H), 5.21 (s, 1H), 3.22 (dt, *J* = 9.6, 6.3 Hz, 1H), 3.09 (dt, *J* = 9.6, 7.3 Hz, 1H), 2.64 (dd, *J* = 18.2, 7.6 Hz 1H), 2.59–2.54 (m, 1H), 2.41 (dtd, *J* = 15.7, 4.5, 1.7 Hz, 1H), 2.33 (td, *J* = 11.9, 5.4 Hz, 1H), 2.21 (dd, *J* = 18.2, 2.0 Hz, 1H), 1.98–1.90 (m, 3H), 1.82 (dt, *J* = 15.3, 6.9 Hz, 2H), 1.74–1.59 (m, 2H), 1.42–1.33 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.6, 204.0, 146.8, 120.3, 60.3, 42.6, 38.6, 38.5, 37.2, 29.62, 29.60, 22.8, 6.6; IR (thin film) 2925, 1727, 1636, 1447, 1231 cm^{-1}; HRMS-ESI (*m*/*z*) [M + Na]$^+$ calcd for $C_{13}H_{17}IO_2Na$ 355.0171; found, 355.0168.

(4b*S**,8a*S**)-2-Ethoxy-4b-(3-iodopropyl)-3,4,4b,6,7,8,8a,9-octahydro-2*H*-1-oxafluoren-5-one (22)

In one portion $Eu(fod)_3$ (228 mg, 0.220 mmol, 0.100 equiv) was added to a stirred solution of endione **21** (0.731 g, 2.20 mmol, 1.00 equiv) in ethyl vinyl ether (4.3 mL, 46 mmol, 21 equiv), and the reaction was maintained at rt for 18 h. The solution was concentrated under reduced pressure. Purification by flash chromatography (1:15:84 Et_3N/EtOAc/hexanes) provided dihydropyran **22** as an approximately 1:1 mixture of ethoxy epimers (0.766 g, 86% yield) as a clear oil. The product was stored in a benzene matrix at −20 °C in a base-washed vial. ^{1}H NMR (500 MHz, C_6D_6) δ 4.88 (s, 1H, single diastereomer), 4.85 (s, 1H, single diastereomer), 3.82–3.74 (m, 1H), 3.41–3.34 (m, 1H), 2.91–2.81 (m, 3H), 2.62–2.52 (m, 2H), 2.18–2.12 (m, 3H), 2.04–1.85 (m, 2H), 1.78–1.72 (m, 4H), 1.62–1.59 (m, 1H), 1.53–1.40 (m, 3H), 1.37–1.31 (m, 1H), 1.11 (t, *J* = 7.1 Hz, 3H, single diastereomer), 1.04 (t, *J* = 7.1 Hz, 3H, single diastereomer); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.6, 214.0, 150.7, 150.5, 109.5, 109.3, 98.4, 98.3, 63.9, 62.30, 62.28, 39.3, 38.6, 38.3, 37.2, 36.9, 35.9, 35.6, 29.48, 29.46, 28.9, 28.8, 26.81, 26.78, 19.7, 19.4, 16.0, 15.9, 15.44, 15.38, 7.3, 7.0; IR (thin film) 2931, 1692, 1627, 1227, 1064 cm^{-1}; HRMS-ESI (*m*/*z*) [M + Na]$^+$ calcd for $C_{17}H_{25}O_3INa$ 427.0746; found, 427.0737.

2-(4-Methoxybenzyloxy)isoindoline-1,3-dione

Diisopropyl azodicarboxylate (21.7 mL, 0.110 mol, 1.10 equiv) was slowly added dropwise to a solution of *N*-hydroxyphthalimide (15.0 g, 92.0 mmol, 1.00 equiv), triphenylphosphine (26.5 g, 101 mmol, 1.10 equiv), 4-methoxybenzyl alcohol (11.5 mL, 92.0 mmol, 1.00 equiv), and CH_2Cl_2 (600 mL) at 0 °C. After completion of the addition the cold bath was removed and the solution was stirred at rt for 16 h. The solution was then concentrated under

reduced pressure and recrystallized in hot EtOH (700 mL). The solution was slowly cooled to rt and left standing overnight. Crystals were filtered and washed with cold EtOH (2 × 100 mL). The crystals were recrystallized a second time with EtOH (600 mL) to afford 2-(4-methoxybenzyloxy)isoindoline-1,3-dione (20.2 g, 82% yield) as colorless crystals: mp 141–142 °C, ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81–7.79 (m, 2H), 7.74–7.72 (m, 2H), 7.45 (d, *J* = 8.5 Hz, 2H), 6.88 (d, *J* = 9.0 Hz, 2H), 5.15 (s, 2H), 3.80 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.8 (C), 160.7 (C), 134.6 (CH), 131.9 (CH), 129.1 (C), 126.1 (C), 123.7 (CH), 114.1 (CH), 79.7 (CH_2), 55.5 (CH_3); IR (thin film) 2963, 1727 cm^{-1}; HRMS-ESI (*m*/*z*) [M + Na]$^+$ calcd for $C_{16}H_{13}O_4NNa$ 306.0742; found, 306.0746.

N-(4-Methoxybenzyloxy)-2-nitrobenzenesulfonamide

Hydrazine hydrate (1.17 mL, 20.4 mmol, 51%, 1.10 equiv) was added dropwise to a solution of 2-(4-methoxybenzyloxy)isoindoline-1,3-dione (5.00 g, 18.6 mmol, 1.00 equiv) in THF (60 mL) at rt. After completion of the addition a colorless precipitate appeared and the solution was stirred at rt for 1 h. Then pyridine (3.00 mL, 37.1 mmol, 2.00 equiv) was added by syringe followed by addition of 2-nitrobenzenesulfonyl chloride (4.12 g, 18.6 mmol, 1.00 equiv) in one portion to the suspension. The resulting cloudy orange solution was stirred at rt for 2 h. The solution was then partitioned between Et_2O (100 mL) and sat. aq. NH_4Cl (75 mL). The aqueous phase was extracted with Et_2O (3 × 100 mL) and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered through a plug of cotton and concentrated under reduced pressure. The residue was triturated with *i*-PrOH (100 mL) resulting in the formation of a colorless solid. The solid was filtered and washed with *i*-PrOH (100 mL) and recrystallized by dissolving in hot acetone (100 mL) followed by addition of an equal volume of hexanes (100 mL) and cooling to −4 °C overnight. The solid was filtered and washed with hexanes to give *N*-(4-methoxybenzyloxy)-2-nitrobenzenesulfonamide (2.39 g, 38% yield) as colorless crystals: mp 165–167 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.25 (t, *J* = 4.7 Hz, 1H), 8.08 (s, 1H), 7.88 (t, *J* = 4.3 Hz, 1H), 7.80–7.77 (m, 2H), 7.32 (d, *J* = 8.3 Hz, 2H), 6.90 (d, *J* = 8.3 Hz, 2H), 5.01 (s, 2H), 3.82 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.4 (C), 148.7 (C), 134.9 (CH), 133.9 (CH), 133.1 (CH), 131.5 (CH), 130.7 (C), 127.2 (C), 125.8 (CH), 114.2 (CH), 79.8 (CH_2), 55.6 (CH_3); IR (thin film) 3267, 2902, 1612, 1536, 1514, 1247, 1175 cm^{-1}; HRMS-ESI (*m*/*z*) [M + Na]$^+$ calcd for $C_{14}H_{14}O_6N_2SNa$ 361.0470; found, 361.0460.

Allyl 4-methoxybenzyloxycarbamate

Hydrazine hydrate (0.12 mL, 2.0 mmol, 1.0 equiv) was added dropwise to a solution of 2-(4-methoxybenzyloxy)isoindoline-1,3-dione (0.556 g, 1.96 mmol, 1.00 equiv) in EtOH (57 mL) and stirred at rt for 14 h during which time a colorless precipitate formed. The precipitate was filtered and washed with EtOH (20 mL). The washes were combined and concentrated under reduced pressure. The residue was diluted in a solution of THF (3.9 mL), 1N NaOH (3 mL), and Et_3N (0.41 mL) and cooled to 0 °C. Allylchloroformate (0.23 mL, 2.2 mmol, 1.1 equiv) was added dropwise and stirred for 10 min; the cold bath was removed and stirred for 14 h at rt. The solution was then partitioned between EtOAc (50 mL) and H_2O (50 mL) and the aqueous phase was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$, filtered through a plug of cotton, and concentrated under reduced pressure. Purification by flash chromatography (3:7 EtOAc/hexanes) provided allyl 4-methoxybenzyloxycarbamate (189 mg, 41% yield) as a clear oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (s, 1H), 7.32 (d, *J* = 8.5 Hz, 2H), 6.89 (d, *J* = 8.5 Hz, 2H), 5.95–5.89 (m, 1H), 5.32 (dd, *J* = 1.0, 17.0 Hz, 1H), 5.25 (d, *J* = 10.5 Hz, 1H), 4.81 (s, 2H), 4.64 (d, *J* = 6.0 Hz, 2H), 3.81 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.1 (C), 157.4 (C), 132.2 (CH), 131.1 (CH), 127.6 (C), 118.8 (CH), 114.1 (CH), 78.5 (CH_2), 66.6 (CH_2), 55.5 (CH_3); IR (thin film) 3284, 2938, 2838, 1727, 1612, 1514, 1250 cm^{-1}; HRMS-ESI (*m*/*z*) [M + Na]$^+$ calcd for $C_{12}H_{15}NO_4Na$ 260.0899; found, 260.0895.

2-(2-Nitrobenzyloxy)isoindoline-1,3-dione

2-(2-Nitrobenzyloxy)isoindoline-1,3-dione was synthesized as reported by Sebesta and co-workers.[91] Sodium acetate (1.90 g, 23.2 mmol) was added to a solution of *N*-hydroxyphthalimide (3.78 g, 23.2 mmol) in DMF (230 mL) at rt causing the appearance of a deep red color. 2-Nitrobenzyl bromide (5.01 g, 23.2 mmol) was then added to the solution followed by heated to 80 °C under a cold water condenser. After 14 h the solution became a clear yellow solution and was cooled to rt and partitioned between EtOAc (200 mL) and water (1 L). The aqueous phase was extracted with EtOAc (3 × 200 mL). The combined organic layers were washed with brine (200 mL), dried over $MgSO_4$, filtered through a plug of cotton, and concentrated under reduced pressure to afford 2-(2-nitrobenzyloxy)isoindoline-1,3-dione as a crystalline yellow solid (6.91 g, 99% yield). The product was carried on without further purification. ^{1}H NMR spectra matched those reported by Sebasta.[91]

tert-Butyl 2-nitrobenzyloxycarbamate

Hydrazine hydrate (0.640 mL, 10 mmol, 1.0 equiv) was added dropwise to a solution of 2-(2-nitrobenzyloxy)isoindoline-1,3-dione (3.00 g, 10.0 mmol, 1.00 equiv) in EtOH (100 mL) at rt and stirred for 16 h during which time a colorless precipitate formed. The precipitate was filtered and washed with EtOH. The washes were combined and concentrated under reduced pressure to provide a yellow solid. The yellow residue was combined with $(Boc)_2O$ (2.29 g, 10.5 mmol, 1.05 equiv) and suspended in a mixture of THF (50 mL), H_2O (50 mL) and Et_3N (1.53 mL). The biphasic mixture was stirred vigorously for 5 h at rt. The mixture was partitioned between Et_2O (100 mL) and H_2O (100 mL) and the aqueous phase was extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with brine (75 mL), dried over $MgSO_4$, filtered through a plug of cotton, and concentrated under reduced pressure. The residue was recrystallized with acetone/hexanes to afford *tert*-butyl 2-nitrobenzyloxycarbamate (0.59 g, 22% yield) as pale yellow crystals: mp 98–99 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (d, J = 8.0 Hz, 1H), 7.77 (d, J = 7.5 Hz, 1H), 7.65 (t, J = 8.0 Hz, 1H), 7.49 (t, J = 8.0 Hz, 1H), 7.30 (br s, 1H), 5.29 (s, 2H), 1.48 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.9 (C), 148.2 (C), 133.8 (CH), 132.5 (C), 130.2 (CH), 129.0 (CH), 125.1 (CH), 82.5 (C), 75.2 (CH_2), 28.4 (CH_3); IR (thin film) 3271, 2980, 1719, 1527 cm^{-1}; HRMS-ESI (*m*/*z*) $[M + Na]^+$ calcd for $C_{12}H_{16}N_2O_5Na$ 291.0957; found, 291.0958.

N-(*tert*-Butyldimethylsilyloxy)-2-nitrobenzenesulfonamide

Pyridine (2.19 mL, 27.2 mmol, 2.00 equiv) followed by 2-nitrobenzenesulfonyl chloride (3.01 g, 13.6 mmol, 1.00 equiv) was added in one portion to a solution of *O*-(*tert*-butyldimethylsilyl)hydroxylamine[92] (2.00 g, 13.6 mmol, 1.00 equiv) in THF (45 mL). The solution was stirred at rt for 14 h and then partitioned between sat. aq. NH_4Cl (300 mL) and Et_2O (150 mL). The layers were separated and the aqueous phase was extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with brine (75 mL), dried over $MgSO_4$, filtered through a plug of cotton, and concentrated under reduced pressure. Purification by flash chromatography (1:4 EtOAc/hexanes) provided *N*-(*tert*-butyldimethylsilyloxy)-2-nitrobenzenesulfonamide (2.14 g, 47% yield) as a pale orange solid: mp 73–75 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (dd, J = 1.4, 7.4 Hz, 1H), 7.90 (dd, J = 1.4, 7.8 Hz, 1H), 7.81 (doublet of quintets J = 1.6, 7.6 Hz, 2H), 7.66 (s, 1H), 0.89 (s, 9H), 0.26 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.9 (C), 134.9 (CH), 134.4 (CH), 132.8 (CH), 130.3 (C), 125.7 (CH), 20.1 (CH_3), 18.3 (C), −5.0 (CH_3); IR (thin film) 3266, 2932, 1541, 1396, 1362, 1181 cm^{-1}; HRMS-ESI (*m*/*z*) $[M + H]^+$ calcd for $C_{12}H_{21}N_2O_5SSi$ 333.0941; found, 333.0948.

2-Nitro-*N*-(triisopropylsilyloxy)benzenesulfonamide

Hydroxylamine hydrochloride (695 mg, 10.0 mmol, 1.00 equiv) was added to a solution of ethylenediamine (540 μL, 10.0 mmol, 1.0 equiv) in CH_2Cl_2 (4.3 mL) and stirred at rt for 24 h. To the resulting biphasic mixture was added a solution of TIPSCl (2.14 mL, 10.0 mmol, 1.00 equiv) in CH_2Cl_2 (1 mL) in five portions via syringe. The mixture was stirred for 36 h and filtered. The precipitate was washed with CH_2Cl_2 (2 × 5 mL). The combined washes were evaporated under reduced pressure and the residue was purified by Kugelrohr distillation to afford *O*-triisopropylsilyl)hydroxylamine as a clear oil (1.20 g, 63% yield). Pyridine (1.03 mL, 12.7 mmol, 2.00 equiv) followed by 2-nitrobenzenesulfonyl chloride (1.41 g, 6.34 mmol, 1.00 equiv) was added in one portion to a solution of *O*-triisopropylsilyl)hydroxylamine (1.20 g, 6.34 mmol, 1.00 equiv) in CH_2Cl_2 (16 mL). The solution was stirred at rt for 14 h in which a colorless precipitate appeared. The mixture was partitioned between H_2O (50 mL) and CH_2Cl_2 (50 mL) and the aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered through a plug of cotton, and concentrated under reduced pressure. Purification by flash chromatography (3:7 EtOAc/hexanes) afforded *N*-(diisopropylsilyloxy)-2-nitrobenzenesulfonamide (0.87 g, 37% yield) as a yellow orange solid: mp 94–96 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 (dd, *J* = 1.8, 7.4 Hz, 1H), 7.91 (dd, *J* = 1.6, 7.5 Hz, 1H), 7.83–7.79 (m, 2H), 7.64 (s, 1H), 1.27 (septet, *J* = 7.3 Hz, 3H), 1.09 (d, *J* = 7.4 Hz, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.9 (C), 134.8 (CH), 134.5 (CH), 132.7 (CH), 130.3 (C), 125.6 (CH), 17.9 (CH_3), 12.1 (CH); IR (thin film) 3251, 2949, 1538 cm^{-1}; HRMS-ESI (*m*/*z*) $[M + Na]^+$ calcd for $C_{15}H_{26}O_5N_2SSiNa$ 397.1230; found, 397.1223.

2-(2-(Trimethylsilyl)ethoxy)isoindoline-1,3-dione

2-(2-(Trimethylsilyl)ethoxy)isoindoline-1,3-dione was prepared as described by Kikugawa and co-workers[93] with minor modifications. Diisopropyl azodicarboxylate (5.80 mL, 24.9 mmol, 1.02 equiv) was slowly added dropwise to a solution of *N*-hydroxyphthalimide (4.00 g, 24.5 mmol, 1.00 equiv), 2-trimethylsilyl ethanol (3.51 mL, 24.5 mmol, 1.00 equiv), triphenylphosphine (7.07 g, 26.8 mmol, 1.1 equiv) and anhydrous chloroform (41 mL) at 0° C. After completion of the addition the cold bath was removed and the mixture was allowed to stir at rt for 14 h. The solution was then partitioned between CH_2Cl_2 (200 mL) and H_2O (300 mL) and the aqueous phase was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, filtered through a plug of cotton, and concentrated under reduced pressure. Purification by flash chromatography (1:1 EtOAc/benzene) afforded 2-(2-(trimethylsilyl)ethoxy)isoindoline-1,3-dione (4.58 g, 71% yield) as a gray solid: mp 95–96 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83–7.85 (m, 2H), 7.74–7.76 (m, 2H), 4.26–4.30 (m, 2H), 1.20–1.23 (m, 2H), 0.06 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.0 (C), 134.6 (CH), 129.2 (C), 123.7 (CH), 76.7 (CH_2), 17.2 (CH_2), −1.2 (CH_3); IR (thin film) 2953, 1790, 1733 cm^{-1}; HRMS-ESI (*m*/*z*) $[M + Na]^+$ calcd for $C_{13}H_{17}NO_3SiNa$ 286.0876; found, 286.0885.

2-Nitro-*N*-(2-(trimethylsilyl)ethoxy)benzenesulfonamide

Hydrazine hydrate (2.19 mL, 19.2 mmol, 51%, 1.10 equiv) was added dropwise to a solution of 2-(2-(trimethylsilyl)ethoxy)isoindoline-1,3-dione (4.58 g, 17.4 mmol, 1.00 equiv) in CH_2Cl_2 (60 mL). A colorless precipitate formed and the solution was stirred at rt for 1 h. Pyridine (2.81 mL, 34.8 mmol, 2.00 equiv) followed by 2-nitrobenzenesulfonyl chloride (3.85 g, 17.4 mmol, 1.00 equiv) was added in one portion to the suspension and the mixture became a dark yellow. The suspension was allowed to stir at rt for 14 h. The suspension was then partitioned between sat. aq. NH_4Cl (300 mL) and CH_2Cl_2 (150 mL) and the aqueous phase was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with brine (75 mL), dried over $MgSO_4$, filtered through a plug of cotton, and concentrated under reduced pressure. Purification by flash chromatography (3:7 EtOAc/hexanes) afforded

2-nitro-*N*-(2-(trimethylsilyl)ethoxy)benzenesulfonamide (1.90 g, 49% yield) as a tan amorphous solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24–8.22 (m, 1H), 8.05 (s, 1H), 7.91–7.90 (m, 1H), 7.86–7.75 (m, 2H), 4.15 (m, 2H), 0.97 (m, 2H), 0.04 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.8 (C), 134.7 (CH), 134.0 (CH), 133.0 (CH), 130.8 (CH), 125.8 (C), 76.0 (CH_2), 17.2 (CH_2), −1.2 (CH_3); IR (thin film) 3245, 2955, 1733, 1543, 1362 cm^{-1}; HRMS-ESI (*m*/*z*) [M + Na]$^+$ calcd for $C_{11}H_{18}N_2O_5SSiNa$ 341.0603; found, 341.0604.

General Procedure for the S_N2 Addition of Protected Hydroxylamines

Iodide **22** (771 mg, 1.91 mmol, 1.00 equiv), K_2CO_3 (396 mg, 2.86 mmol, 1.50 equiv) and protected hydroxylamine (0.700 g, 2.00 mmol, 1.05 equiv) were suspended in DMF (3.2 mL) and stirred at rt for 16 h. The mixture was partitioned between Et_2O (50 mL) and H_2O (200 mL). The aqueous phase was extracted with Et_2O (3 × 70 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered through a plug of cotton, and concentrated under reduced pressure. Isolated dihydropyrans were approximately 1:1 mixtures of ethoxy epimers. The tricyclic dihydropyrans products were stored in a benzene matrix at −20 °C in base-washed vials.[94]

(4b*S**,8a*S**)-2-Ethoxy-4b-(3-*bis*(*tert*-butoxycarbonyl)hydroxyaminopropyl)-3,4,4b,6,7,8,8a,9-octahydro-2*H*-1-oxafluoren-5-one (23)

Following the general procedure, iodide **22** (0.038 g, 0.094 mmol) was converted to an approximately 1:1 mixture of ethoxy epimers **23**. Purification by flash chromatography (3:1:96 EtOAc/Et_3N/benzene) provided **23** (0.042 g, 88% yield) as a colorless foam: ^{1}H NMR (500 MHz, C_6D_6) δ 4.83 (dd, *J* = 3.9, 2.4 Hz, 1H), 4.81 (dd, *J* = 3.7, 2.4 Hz, 1H), 3.83–3.73 (m, 1H), 3.70 (br s, 2H), 3.38–3.32 (m, 1H), 2.55–2.50 (m, 1H), 2.48–2.44 (m, 1H), 2.14–1.94 (m, 5H), 1.86–1.50 (m, 8H), 1.43 (s, 9H), 1.42 (s, 9H), 1.33 (s, 9H), 1.32 (s, 9H), 1.31–1.26 (m, 2H), 1.20–1.12 (m, 1H), 1.09 (t, *J* = 7.1 Hz, 3H), 1.04 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 212.1, 211.5, 154.9, 154.8, 152.8, 152.7, 150.1, 149.8, 109.9, 109.6, 98.21, 98.20, 83.6, 83.5, 81.3, 81.2, 63.4, 62.0, 50.72, 50.68, 39.2, 39.0, 38.4, 38.1, 36.83, 36.79, 32.3, 32.0, 29.0, 28.7, 27.8, 27.2, 26.9, 26.8, 22.41, 22.38, 19.8, 19.4, 16.3, 15.9, 15.2, 15.1; IR (thin film) 2935, 1785, 1692, 1370, 1150 cm^{-1}; HRMS-ESI (*m*/*z*) [M + Na]$^+$ calcd for $C_{27}H_{43}NO_8Na$ 532.2886; found, 532.2880.

(4bS*,8aS*)-2-Ethoxy-4b-(3-(tert-butyoxycarbonyl-2-nitrobenzyloxy)aminopropyl)-3,4,4b,6,7,8,8a,9-octahydro-2H-1-oxafluoren-5-one (24)

Following the general procedure, iodide **22** (0.047 g, 0.12 mmol) and *tert*-butyl 2-nitrobenzyloxycarbamate were converted to an approximately 5:1 mixture of ethoxy epimers **24**. Purification by flash chromatography (3:1:96 EtOAc/Et_3N/benzene) provided **24** (0.063 g, 99% yield) as a colorless oil. Data for major diastereomer: ^{1}H NMR (500 MHz, C_6D_6) δ 7.53–7.51 (m, 2H), 6.93–6.89 (m, 1H), 6.65 (t, *J* = 7.5 Hz, 1H), 5.26 (s, 2H), 4.85–4.83 (m, 1H), 3.80–3.74 (m, 1H), 3.53–3.47 (m, 2H), 3.39–3.33 (m, 1H), 2.58 (ddt, *J* = 15.8, 8.9, 2.8 Hz, 1H), 2.21–1.97 (m, 5H), 1.88–1.81 (m, 1H), 1.76–1.70 (m, 1H), 1.66–1.51 (m, 5H), 1.42 (s, 9H), 1.35–1.22 (m, 4H), 1.04 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 211.6, 156.4, 150.2, 148.4, 132.5, 131.7, 130.5, 128.2, 124.1, 109.7, 98.2, 80.7, 72.7, 63.5, 62.1, 50.2, 39.1, 38.1, 36.8, 32.1, 29.0, 27.9, 26.9, 22.2, 19.4, 16.0, 15.1; IR (thin film) 2933, 1698, 1530, 1368, 1162 cm^{-1}; HRMS-ESI (*m*/*z*) [M + Na]$^+$ calcd for $C_{29}H_{40}N_2O_8Na$ 567.2682; found, 567.2670.

(4b*S**,8a*S**)-2-Ethoxy-4b-(3-(4-methoxybenzyloxy-*tert*-butyoxycarbonyl) aminopropyl)-3,4,4b,6,7,8,8a,9-octahydro-2*H*-1-oxafluoren-5-one (25)

Following the general procedure, iodide **22** (0.100 g, 0.247 mmol) and *O*-(*tert*-butoxycarbonyl)-*N*-(4-methoxybenzyl) hydroxylamine[95] were converted to an

approximately 1:1 mixture of ethoxy epimers **25**. Purification by flash chromatography (3:1:96 EtOAc/Et_3N/benzene) provided **25** as a colorless film (0.088 g, 67% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (d, *J* = 8.6 Hz, 2H, single diastereomer), 7.31 (d, *J* = 8.7 Hz, 2H, single diastereomer), 6.87 (d, *J* = 8.6 Hz, 2H), 5.00 (br s, 1H), 4.75 (s, 2H), 3.84–3.81 (m, 1H), 3.80 (s, 3H), 3.58–3.56 (m, 1H), 3.36–3.34 (m, 2H), 2.66–2.56 (m, 1H), 2.41 (septet, *J* = 4.7 Hz, 1H), 2.34–2.28 (m, 1H), 2.25–2.16 (m, 1H), 2.08 (t, *J* = 15 Hz, 1H), 1.97–1.54 (m, 9H), 1.49 (s, 9H), 1.46–1.44 (m, 3H), 1.19 (t, *J* = 7.2 Hz, 3H, single diastereomer), 1.17 (t, *J* = 7.1 Hz, 3H, single diastereomer); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.6, 214.3, 159.9, 159.8, 156.59, 156.56, 150.4, 150.1, 131.1, 131.0, 128.0, 127.9, 113.8, 109.7, 109.4, 98.5, 98.4, 81.2, 81.1, 76.5, 63.9, 63.8, 62.5, 62.4, 55.3, 50.2, 39.20, 39.17, 38.7, 38.3, 36.9, 32.2, 31.7, 29.3, 29.1, 28.4, 26.9, 26.8, 22.1, 22.0, 19.8, 19.4, 16.3, 16.0, 15.4, 15.3; IR (thin film) 2933, 2854, 1694, 1248 cm^{-1}; HRMS-ESI (*m*/*z*) $[M + Na]^+$ calcd for $C_{30}H_{43}NO_7Na$ 552.2937; found, 552.2936.

(4bS*,8aS*)-2-Ethoxy-4b-(3-(allyloxycarbonyl-4-methoxybenzyloxy)aminopropyl)-3,4,4b, 6,7,8,8a,9-octahydro-2H-1-oxafluoren-5-one (26)

Following the general procedure, iodide **22** (0.105 g, 0.260 mmol) and allyl 4-methoxybenzyloxycarbamate were converted to an approximately 1:1 mixture of ethoxy epimers **26**. Purification by flash chromatography (3:1:96 EtOAc/Et_3N/benzene) provided **26** (0.104 g, 78% yield) as a colorless foam: ^{1}H NMR (500 MHz, C_6D_6) δ 7.33 (d, *J* = 7.7 Hz, 2H), 6.76 (d, *J* = 8.7 Hz, 2H, single diastereomer), 6.75 (d, *J* = 8.6 Hz, 2H, single diastereomer), 5.83–5.76 (m, 1H), 5.19 (d, *J* = 17.2 Hz, 1H), 5.00 (d, *J* = 10.5 Hz, 1H), 4.86 (d, *J* = 11.1 Hz, 2H), 4.82 (d, *J* = 11.7 Hz, 1H), 4.59 (br s, 2H), 3.77 (sextet, *J* = 8.0 Hz, 1H), 3.52 (t, *J* = 6.5 Hz, 1H, single diastereomer), 3.47 (t, *J* = 6.8 Hz, 1H, single diastereomer), 3.37–3.33 (m, 1H), 3.27 (s, 3H, single diastereomer), 3.26 (s, 3H, single diastereomer), 2.52–2.47 (m, 1H), 2.18–2.01 (m, 4H), 1.96–1.93 (m, 1H), 1.83–1.69 (m, 3H), 1.63–1.49 (m, 5H), 1.27–1.24 (m, 2H), 1.19–1.16 (m, 1H), 1.07 (t, *J* = 7.2 Hz, 3H, single diastereomer), 1.03 (t, *J* = 7.1 Hz, 3H, single diastereomer); ^{13}C NMR (125 MHz, C_6D_6) δ 212.1, 211.6, 160.03, 160.01, 157.1, 157.0, 150.1, 149.8, 132.85, 132.83, 131.0, 128.24, 128.19, 117.22, 117.19, 113.76, 113.75, 109.9, 109.7, 98.22, 98.20, 76.60, 76.56, 66.1, 66.0, 63.50, 63.48, 62.1, 54.4, 50.6, 50.5, 39.1, 39.0, 38.4, 38.1, 36.83, 36.78, 32.4, 32.1, 29.0, 28.7, 26.9, 26.8, 22.2, 22.1, 19.7, 19.4, 16.2, 16.0, 15.1; IR (thin film) 2933, 1694 cm^{-1}; HRMS-ESI (*m*/*z*) $[M + Na]^+$ calcd for $C_{29}H_{39}NO_7Na$ 536.2625; found, 536.2634.

(4b*S**,8a*S**)-2-Ethoxy-4b-(3-(4-methoxybenzyloxy-2-nitrobenzenesulfonyl) aminopropyl)-3,4,4b,6,7,8,8a,9-octahydro-2*H*-1-oxafluoren-5-one (27)

Following the general procedure, iodide **22** (0.281 g, 0.695 mmol) and *N*-(4-methoxybenzyloxy)-2-nitrobenzenesulfonamide were converted to an approximately 1:1 mixture of ethoxy epimers **27**. Purification by flash chromatography (10:1:89 EtOAc/Et_3N/benzene) to provide **27** (0.376 g, 88% yield) as a colorless foam: ^{1}H NMR (500 MHz, C_6D_6) δ 7.89 (d, *J* = 7.7 Hz, 1H, single diastereomer), 7.86 (d, *J* = 7.7 Hz, 1H, single diastereomer), 7.39–7.37 (m, 2H), 6.78 (t, *J* = 8.9 Hz, 2H), 6.68–6.59 (m, 3H), 5.25–5.18 (m, 2H), 4.83 (br s, 1H), 3.80–3.76 (m, 1H), 3.39–3.34 (m, 1H), 3.30 (s, 3H, single diastereomer), 3.29 (s, 3H, single diastereomer), 3.15 (br s, 2H), 2.55–2.50 (m, 1H), 2.18–2.11 (m, 1H), 2.05–1.86 (m, 4H), 1.77–1.67 (m, 2H), 1.58–1.22 (m, 8H), 1.05 (t, *J* = 7.1 Hz, 3H), 0.91–0.89 (m, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ 212.0, 211.6, 160.30, 160.27, 150.3, 150.1, 149.9, 149.8, 134.1, 134.0, 132.40, 132.36, 131.8, 131.7, 130.01, 129.99, 127.4, 127.3, 125.9, 125.8, 123.0, 113.94, 113.91, 109.7, 109.6, 98.4, 98.2, 79.84, 79.80, 63.7, 63.5, 62.02, 62.00, 54.44, 54.43, 54.1, 54.0, 39.3, 39.1, 38.5, 38.2, 36.8, 36.7, 32.6, 32.4, 29.3, 28.8, 26.9, 26.8, 22.2, 22.0, 19.8, 19.5, 16.3, 15.8, 15.2; IR (thin film) 2933, 2856, 1686, 1547 cm^{-1}; HRMS-ESI (*m*/*z*) $[M + Na]^+$ calcd for $C_{31}H_{38}N_2O_9SNa$ 637.2195; found, 637.2193.

(4b*S**,8a*S**)-2-Ethoxy-4b-(3-tertbutylddimethylsilyoxy-2-nitrobenzenesulfonyl)aminopropyl)-3,4,4b,6,7,8,8a,9-octahydro-2*H*-1-oxafluoren-5-one (41)

Following the general procedure, iodide **22** (723 mg, 1.79 mmol) and *N*-(*tert*-butyldimethylsilyloxy)-2-nitrobenzenesulfonamide (625 mg, 1.88 mmol) were converted to tricycle **41** as an approximately 1:1 mixture of ethoxy epimers. Purification by flash chromatography (5:1:94 EtOAc/Et_3N/benzene) provided tricyclic dihydropyran **41** (698 mg, 69% yield) as a clear oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (d, *J* = 7.8 Hz, 1H), 7.68 (t, *J* = 7.8 Hz, 1H), 7.59 (t, *J* = 7.6 Hz, 1H), 7.45 (d, *J* = 7.9 Hz, 1H), 4.93 (m, 1H), 3.76–3.72 (m, 1H), 3.51–3.46 (m, 1H), 3.12–3.01 (m, 2H), 2.51–2.47 (m, 1H), 2.35–2.19 (m, 2H), 2.10–1.98 (m, 1H), 1.81 (quintet, *J* = 3.8 Hz, 1H), 1.79–1.71 (m, 1H), 1.66–1.64 (m, 1H), 1.60–1.58 (m, 4H), 1.56–1.47 (m, 2H), 1.37–1.33 (m, 3H), 1.23 (sextet, *J* = 7.5 Hz, 1H), 1.12 (q, *J* = 3.4 Hz, 3H), 1.05 (d, *J* = 7.4 Hz, 4H), 0.95 (s, 1H), 0.85 (s, 6H), 0.17 (s, 2H), 0.15 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) complex spectra due to mixture of epimers peaks observed are listed δ 214.6, 150.9, 150.6, 134.9, 134.7, 133.3, 130.9, 128.6, 123.6, 123.5, 109.6, 109.4, 98.7, 98.5, 64.1, 64.0, 62.7, 62.6, 56.2, 56.1, 39.5, 39.4, 38.9, 37.2, 37.0, 32.4, 31.9, 29.7, 29.4, 27.1, 27.0, 26.2, 22.4, 22.2, 20.0, 19.6, 18.4, 17.9, 16.4, 16.1, 15.5, 12.9, 12.8, −4.18, −4.23; IR (thin film) 2931, 2859, 1691, 1549, 1375, 1179 cm^{-1}; HRMS-ESI (*m*/*z*) [M + Na]$^+$ calcd for $C_{29}H_{44}N_2O_8SSiNa$ 631.2485; found, 631.2480.

(4b*S**,8a*S**)-2-Ethoxy-4b-(3-triisopropylsilyoxy-2-nitrobenzenesulfonyl)aminopropyl)-3,4,4b,6,7,8,8a,9-octahydro-2*H*-1-oxafluoren-5-one (42)

Following the general procedure, iodide **22** (0.900 g, 2.23 mmol) and 2-nitro-*N*-(triisopropylsilyloxy)benzenesulfonamide (876 mg, 2.34 mmol) were coverted to tricycle **42** as an approximately 1:1 mixture of ethoxy epimers. Purification by flash chromatography (5:1:94 EtOAc/Et_3N/benzene) provided tricyclic dihydropyran **42** (1.32 g, 91% yield) as a clear oil: ^{1}H NMR (500 MHz, C_6D_6) δ 8.04 (t, *J* = 7.8 Hz, 1H), 6.82 (t, *J* = 7.6 Hz, 1H), 6.74–6.70 (m, 2H), 4.85–4.82 (m, 1H), 3.76–3.74 (m, 1H), 3.39–3.26 (m, 3H), 2.55–2.45 (m, 1H), 2.17–2.01 (m, 5H), 1.72–1.66 (m, 1H), 1.57–1.52 (m, 3H), 1.37–1.29 (m, 4H), 1.37–1.29 (m, 4H), 1.15 (d, *J* = 4.3 Hz, 9H) 1.07 (d, *J* = 9.3 Hz, 9H), 1.02–0.91 (m, 5H); ^{13}C NMR (125 MHz, C_6D_6) complex spectra due to mixture of epimers peaks observed are listed δ 213.0, 212.5, 170.6, 151.1, 150.9, 150.1, 134.7, 132.9, 130.6, 128.9, 127.4, 123.6, 110.1, 109.8, 98.9, 98.7, 64.3, 62.8, 60.5, 56.9, 39.9, 38.8, 37.6, 33.1, 32.7, 29.9, 29.4, 27.5, 22.3, 20.4, 19.9, 18.4, 16.4, 15.8, 13.2; IR (thin film) 2944, 1693, 1549, 1464, 1179 cm^{-1}; HRMS-ESI (*m*/*z*) [M + Na]$^+$ calcd for $C_{32}H_{50}O_8N_2SSiNa$ 673.2955; found, 673.2941.

(4b*S**,8a*S**)-2-Ethoxy-4b-(3-(2-(trimethylsilyl)ethyloxy-2-nitrobenzenesulfonyl) aminopropyl)-3,4,4b,6,7,8,8a,9-octahydro-2*H*-1-oxafluoren-5-one (43)

Following the general procedure described above, iodide **22** (0.900 g, 2.23 mmol) and 2-nitro-*N*-(2-(trimethylsilyl)ethoxy)benzenesulfonamide were converted to tricyclic dihydropyran **43** as an approximately 1:1 mixture of ethoxy epimers. Purification by flash chromatography (5:1:94 EtOAc/Et_3N/benzene) afforded tricyclic dihydropyran **43** (1.29 g, 97% yield) as a brown oil: ^{1}H NMR (500 MHz, C_6D_6) δ 7.88 (dd, *J* = 14.8, 7.4 Hz, 1H), 6.73 (q, *J* = 6.8 Hz, 1H), 6.65–6.58 (m, 2H), 4.82 (m, 1H), 4.47–4.33 (m, 2H), 3.78 (m, 1H), 3.36 (m, 1H), 3.17 (br s, 1H), 2.60–2.48 (m, 1H), 2.13 (m, 1H), 2.07–1.88 (m, 4H), 1.72–1.67 (m, 2H), 1.59–1.37 (m, 4H), 1.32–1.13 (m, 4H), 1.13–1.03 (m, 6H), 0.91 (t, *J* = 7.2 Hz, 1H), −0.02 (s, 9H); ^{13}C NMR (125 MHz, C_6D_6) δ 211.9 (C), 150.7 (C), 134.6 (CH), 133.0 (CH), 130.5 (CH), 126.9 (C), 123.8 (CH), 110.3 (CH_2), 98.9 (CH), 76.7 (CH_2), 64.2 (CH_2), 62.7 (C), 60.4 (C), 54.5 (C), 39.9 (CH_2), 39.0 (CH_2), 37.6 (CH_2), 33.3 (CH_2), 29.7 (CH_2), 27.6 (CH_2), 23.0 (CH_2), 20.9 (CH_2), 20.2 (CH_2), 17.8 (CH_2), 16.5 (CH_2), 15.9 (CH_2), 14.5 (CH_3), −1.2 (CH_3); IR (thin film) 2948, 1692, 1549, 1375, 1179 cm^{-1}; HRMS-ESI (*m*/*z*) [M + Na]$^+$ calcd for $C_{28}H_{42}O_8N_2SSiNa$ 617.2329; found, 617.2339.

Tetracyclic nitrone 28

Solid *m*-CPBA (0.013 g, 0.059 mmol, 1.5 equiv) was added in one portion to a solution of dihydropyran **23** (0.020 g, 0.039 mmol, 1.0 equiv) in CH_2Cl_2 (1.2 mL) at −78 °C. After addition, the mixture was placed in a −20 °C ice–acetone bath and maintained for 30 min. The solution was poured into a 1:1:1 solution of H_2O/sat. aq. $Na_2S_2O_3$/sat. aq. $NaHCO_3$ (1 mL) and stirred vigorously at rt for 30 min. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered through a plug of cotton, and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (0.3 mL), and CF_3CO_2H (0.3 mL) was added. The solution was maintained at rt for 8 h. The solution was then transferred carefully into a stirred biphasic mixture of CH_2Cl_2 (10 mL) and sat. aq. $NaHCO_3$ (10 mL) resulting in a vigorous evolution of gas. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered through a plug of cotton, and concentrated under reduced pressure. Purification by preparatory thin-layer chromatography (1:9 MeOH/$CHCl_3$) afforded nitrone **28** (0.003 g, 28% yield) as a pale yellow oil: ^{1}H NMR (500 MHz, CD_3OD) δ 5.08–5.07 (m, 1H), 3.89–3.87 (m, 2H), 3.70 (m, 1H), 2.75 (dd, *J* = 19.6, 10.0 Hz, 1H, single diastereomer), 2.63 (dd, *J* = 19.7, 8.7 Hz, 1H, single diastereomer), 2.43–2.38 (m, 1H, single diastereomer), 2.34–2.18 (m, 4H), 2.15–1.82 (m, 8H), 1.78 −1.50 (m, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 214.4, 212.5, 156.6, 155.9, 106.7, 106.0, 93.3, 92.8, 57.7, 57.2, 44.4, 42.4, 39.0, 37.3, 31.5, 31.0, 30.4, 29.1, 28.6, 27.2, 26.8, 26.5, 26.0, 23.8, 23.7, 21.09, 21.06, 19.4, 18.3; IR (thin film) 3448, 2933, 1748, 1580, 1185 cm^{-1}; HRMS-ESI (*m*/*z*) [M + Na]$^+$ calcd for $C_{15}H_{21}NO_4Na$ 302.1368; found, 302.1373.

General Procedure for Epoxidation–Acidic Rearrangement

Preparation of *tert*-Butyl 3-((1′*R**,3a’*S**,7a’*S**)-5-hydroxy-2′,7′-dioxodecahydro-3*H*-spiro[furan-2,1′-indene]-7a’-yl)propyl(2-nitrobenzyloxy)carbamate (29). Solid *m*-CPBA (0.053 g, 0.23 mmol, 1.9 equiv) was added in one portion to a solution of dihydropyran (0.063 g, 0.12 mmol, 1.0 equiv) in CH_2Cl_2 (0.6 mL) at −78 °C. After addition, the mixture was placed in a −20 °C ice–acetone bath, and maintained for 30 min. The solution was then poured into a 1:1:1 solution of H_2O/sat. aq. $Na_2S_2O_3$/sat. aq. $NaHCO_3$ (1 mL) and stirred vigorously at rt for 30 min. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered through a plug of cotton, and concentrated under reduced pressure. The residue was dissolved in THF (0.6 mL) and H_2O (0.2 mL). The biphasic mixture was cooled to 0 °C, and CF_3CO_2H (0.2 mL) was added dropwise resulting in a single-phase solution. The solution was allowed to warm to rt over 2 h, and maintained at rt for an additional 8 h. The solution was then transferred carefully into a stirred biphasic mixture of Et_2O (10 mL) and sat. aq. $NaHCO_3$ (10 mL) resulting in a vigorous evolution of gas. The layers were separated and the aqueous layer was extracted with Et_2O (2 × 10 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered through a plug of cotton, and concentrated under reduced pressure. Purification by flash chromatography (2:3 EtOAc/hexanes) afforded lactol **29** (0.036 g, 58% yield) as a pale yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.0 Hz, 1H), 7.70 (d, *J* = 7.6 Hz, 1H), 7.65 (t, *J* = 7.5 Hz, 1H), 7.50 (t, *J* = 7.7 Hz, 1H), 5.35 (br s, 1H), 5.20 (s, 2H), 3.46–3.41 (m, 1H), 3.39–3.33 (m, 1H), 2.56–2.43 (m, 3H), 2.40–2.32 (m, 1H), 2.23–2.19 (m, 1H), 2.13–1.80 (m, 7H), 1.64–1.62 (m, 2H), 1.52–1.44 (m, 1H), 1.48 (s, 9H), 1.39–1.37 (m, 1H), 0.92–0.85 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 217.4, 213.8, 211.6, 156.3, 148.4, 133.4, 131.2, 130.9, 129.2, 124.7, 100.7, 99.9, 92.4, 91.7, 81.9, 72.9, 58.8, 58.2, 49.7, 42.2, 42.1, 40.4, 39.9, 37.4, 37.3, 34.4, 34.0, 30.4, 30.2, 29.9, 29.4, 28.3, 25.1, 24.2, 22.9, 22.8, 22.6, 22.5; IR (thin film) 2939, 1748, 1698, 1368, 1162 cm^{-1}; HRMS-ESI (*m*/*z*) [M + Na]$^+$ calcd for $C_{27}H_{36}N_2O_9Na$ 555.2319; found, 555.2327.

tert-Butyl 3-((1′*R**,3a′*S**,7a′*S**)-5-hydroxy-2′,7′-dioxodecahydro-3*H*-spiro[furan-2,1′-indene]-7a′-yl)propyl(4-methoxybenzyloxy)carbamate (30)

Following the general procedure, dihydropyran **25** (0.044 g, 0.083 mmol) was converted to an approximately 1:1 mixture of lactol epimers. Purification by flash chromatography (2:3 EtOAc/hexanes) afforded lactol **30** (0.016 g, 37% yield) as a pale yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8.5 Hz, 2H), 6.89 (d, *J* = 8.5 Hz, 2H), 5.35 (br s, 1H), 4.75 (s, 2H), 3.82 (s, 3H), 3.39–3.28 (m, 2H), 2.55–2.41 (m, 4H), 2.39–2.30 (m, 1H), 2.24–2.16 (m, 1H), 2.13–1.80 (m, 7H), 1.53–1.50 (m, 2H), 1.51 (s, 9H), 1.39–1.34 (m, 1H), 0.84 (qd, *J* = 12.5, 4.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 217.3, 213.8, 213.7, 211.6, 159.9, 156.5, 131.2, 131.1, 127.8, 113.90, 113.86, 100.7, 99.9, 92.4, 91.7, 81.4, 76.5, 76.4, 58.8, 58.2, 55.3, 49.8, 42.2, 42.1, 40.4, 39.9, 37.4, 37.3, 34.4, 34.0, 30.4, 30.2, 30.0, 29.5, 28.4, 25.0, 24.2, 22.95, 22.93, 22.6, 22.5; IR (thin film) 3379, 2925, 1748, 1698, 1250 cm^{-1}; HRMS-ESI (*m*/*z*) [M + Na]$^+$ calcd for $C_{28}H_{39}NO_8Na$ 540.2573; found, 540.2572.

Allyl 3-((1′*R**,3a′*S**,7a′*S**)-5-hydroxy-2′,7′-dioxodecahydro 3*H*-spiro[furan-2,1′-indene]-7a′-yl)propyl(4-methoxybenzyloxy)carbamate (31)

Following the general procedure, dihydropyran **26** (0.040 g, 0.078 mmol) was converted to an approximately 1:1 mixture of lactol epimers. Purification by flash chromatography (2:3 EtOAc/hexanes) afforded lactol **31** (0.020 g, 50% yield) as a pale yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8.3 Hz, 2H), 6.88 (d, *J* = 8.4 Hz, 2H), 5.95 (ddt, *J* = 17.0, 10.6, 5.6 Hz, 1H), 5.36–5.33 (m, 2H), 5.26 (d, *J* = 10.4 Hz, 1H), 4.78 (s, 2H), 4.65 (d, *J* = 5.6 Hz, 2H), 3.82 (s, 3H), 3.37–3.33 (m, 2H), 2.48–2.40 (m, 3H), 2.37–2.30 (m, 2H), 2.20–2.15 (m, 1H), 2.09–1.81 (m, 7H), 1.54–1.50 (m, 2H), 1.41–1.35 (m, 1H), 0.85–0.83 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 217.3, 213.77, 213.68, 211.6, 160.0, 157.1, 132.3, 131.1, 127.6, 118.3, 113.9, 100.5, 99.9, 92.4, 91.7, 66.7, 58.7, 58.2, 55.3, 50.0, 42.2, 42.1, 40.4, 39.9, 37.4, 37.3, 34.4, 34.0, 30.4, 30.1, 29.9, 29.5, 25.1, 24.2, 22.9, 22.6, 22.5; IR (thin film) 3464, 2954, 1748, 1698, 1250 cm^{-1}; HRMS-ESI (*m*/*z*) [M + Na]$^+$ calcd for $C_{27}H_{35}NO_8Na$ 524.2260; found, 524.2258.

N-(3-((1′*R**,3a′*S**,7a′*S**)-5-Hydroxy-2′,7′-dioxodecahydro-3*H*-spiro[furan-2,1′-indene]-7a′-yl)propyl)-*N*-(4-methoxybenzyloxy)-2-nitrobenzenesulfonamide (32)

Following the general procedure, dihydropyran **27** (0.017 g, 0.027 mmol) was converted to an approximately 1:1 mixture of lactol epimers. Purification by flash chromatography (2:3 EtOAc/hexanes) afforded lactol **27** (0.006 g, 38% yield) as a pale yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (d, *J* = 8.0 Hz, 1H), 7.75 (t, *J* = 7.7 Hz, 1H), 7.66 (t, *J* = 7.7 Hz, 1H), 7.55 (d, *J* = 7.9 Hz, 1H), 7.34 (d, *J* = 8.4 Hz, 2H), 6.90 (d, *J* = 8.0 Hz, 2H), 5.36–5.33 (m, 1H), 5.03–5.01 (m, 2H), 3.82 (s, 3H), 3.08–2.87 (m, 2H), 2.52–2.30 (m, 5H), 2.24–1.79 (m, 8H), 1.56–1.51 (m, 1H), 1.42–1.36 (m, 1H), 1.32–1.23 (m, 1H), 0.80 (q, *J* = 13.0 Hz, 1H, single diastereomer), 0.79 (q, *J* = 13.3 Hz, 1H, single diastereomer); ^{13}C NMR (125 MHz, $CDCl_3$) δ 216.9, 213.4, 213.2, 211.3, 160.1, 149.7, 134.8, 132.6, 131.6, 131.0, 127.01, 126.99, 125.7, 123.6, 113.9, 100.7, 99.8, 92.2, 91.5, 79.58, 79.55, 58.5, 58.0, 55.2, 53.4, 42.2, 42.1, 40.3, 39.7, 37.4, 37.3, 34.2, 33.8, 30.3, 30.0, 29.7, 29.3, 25.1, 24.1, 22.6, 22.55, 22.46; IR (thin film) 3464, 2981, 1748, 1696, 1547, 1376 cm^{-1}; HRMS-ESI (*m*/*z*) [M + Na]$^+$ calcd for $C_{29}H_{34}N_2O_{10}SNa$ 625.1832; found, 625.1838.

1,2-Oxazacyclodecane 33

Solid $NaBH_4$ (0.005 g, 0.1 mmol) was added in one portion to a solution of dihydropyran **23** (0.065 g, 0.13 mmol) in MeOH (0.6 mL) at 0 °C. After the addition, the cooling bath was removed and the reaction was stirred at rt for 3 h. The mixture was partitioned between CH_2Cl_2 (10 mL) and sat. aq. $NaHCO_3$ (10 mL). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed

with brine (20 mL), dried over $MgSO_4$, filtered through a plug of cotton, and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (0.8 mL) and cooled to −78 °C. A solution of *m*-CPBA (0.035 g, 0.15 mmol) and CH_2Cl_2 (0.4 mL) was added dropwise. The mixture was placed in a −20 °C ice–acetone bath, and maintained for 30 min. The solution was then poured into a 1:1:1 solution of H_2O/sat. aq. $Na_2S_2O_3$/sat. aq. $NaHCO_3$ (1 mL) and stirred vigorously at rt for 30 min. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered through a plug of cotton, and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (0.6 mL), and $MgSO_4$ (0.030 g) was added. CF_3CO_2H (0.2 mL) was added to the biphasic mixture. The suspension was maintained at rt for 1 h. The solution was then decanted carefully into a stirred biphasic mixture of CH_2Cl_2 (5 mL) and sat. aq. $NaHCO_3$ (5 mL) resulting in a vigorous evolution of gas. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered through a plug of cotton, and concentrated under reduced pressure. The residue was purified by preparatory thin-layer chromatography (0.25 mm SiO_2 plate, 1:4 acetone/CH_2Cl_2) to afford 1,2-oxaazacyclodecane **33** (0.009 g, 25% yield over three steps) as a pale yellow oil that solidified upon standing at rt. Crystallization by slow evaporation from $CHCl_3$ afforded an X-ray quality crystal: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.54 (s, 1H, N*H*), 5.47 (d, *J* = 5.9 Hz, 1H), 3.75 (s, 1H), 3.18 (d, *J* = 12.9 Hz, 1H), 2.69 (d, *J* = 11.0 Hz, 1H), 2.61 (t, *J* = 12.0 Hz, 1H), 2.55–2.48 (m, 2H), 2.30 (t, *J* = 11.6 Hz, 1H), 2.25–2.18 (m, 2H), 2.15–2.07 (m, 1H), 1.97 (t, *J* = 11.1 Hz, 1H), 1.93–1.87 (m, 1H), 1.80–1.72 (m, 3H), 1.57–1.51 (m, 1H), 1.48–1.38 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 105.5 (CH), 105.1 (C), 96.0 (C), 78.3 (CH), 53.2 (CH_2), 46.7 (C), 35.4 (CH_2), 32.2 (CH), 31.3 (CH_2), 25.2 (CH_2), 23.33 (CH_2), 23.31 (CH_2), 21.0 (CH_2), 18.5 (CH_2), 14.7 (CH_2); IR (thin film) 3284, 2929, 1457, 1322 cm^{-1}; HRMS-ESI (*m*/*z*) $[M + Na]^+$ calcd for $C_{15}H_{23}NO_4Na$ 304.1525; found, 304.1524.

General Procedure for $NaBH_4$ Reduction–Oxidation–Acidic Rearrangement Sequence. Preparation of *N*-(3-((1′*R**,3a′*S**,7a′*R**)-5,7′-Dihydroxy-2′-oxodecahydro-3*H*-spiro[furan-2,1′-indene]-7a′-yl)propyl)-*N*-(4-methoxybenzyloxy)-2-nitrobenzenesulfonamide (34) and *N*-2-Nitrobenzenesulfonyl-*O*-(4-methoxybenzyl) hemiacetal 35

Solid $NaBH_4$ (0.020 g, 0.52 mmol) was added in one portion to a solution of dihydropyran (0.320 g, 0.52 mmol) in MeOH (5.2 mL) at 0 °C. After the addition, the cooling bath was removed and the solution was warmed to rt. After 1.5 h, the mixture was partitioned between CH_2Cl_2 (50 mL) and sat. aq. $NaHCO_3$ (50 mL). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, filtered through a plug of cotton, and concentrated under reduced pressure. Solid *m*-CPBA (0.99 mmol, 1.9 equiv) was added in one portion to a solution of dihydropyran residue in CH_2Cl_2 (4.0 mL) at −78 °C. After addition, the mixture was placed in a −20 °C ice–acetone bath, and maintained for 30 min. The solution was then poured into a 1:1:1 solution of H_2O/sat. aq. $Na_2S_2O_3$/sat. aq. $NaHCO_3$ (3 mL) and stirred vigorously at rt for 30 min. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 15 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered through a plug of cotton, and concentrated under reduced pressure. The residue was dissolved in THF (6.0 mL) and H_2O (2.0 mL). The biphasic mixture was cooled to 0 °C, and CF_3CO_2H (2.0 mL) was added dropwise resulting in a single-phase solution. The solution was allowed to warm to rt over 2 h, and maintained at rt for an additional 8 h. The solution was then transferred carefully into a stirred biphasic mixture of Et_2O (50 mL) and sat. aq. $NaHCO_3$ (50 mL) resulting in a vigorous evolution of gas. The layers were separated and the aqueous layer was extracted with Et_2O (2 × 30 mL). The combined organic layers were washed with brine (50 mL), dried

over $MgSO_4$, filtered through a plug of cotton, and concentrated under reduced pressure to give an approximate 1:3 mixture of alcohol **34** and hemiacetal **35**, which were separated by flash chromatography (3:2 EtOAc/hexanes). First eluting was alcohol **34** (0.051 g, 16% yield over three steps) as a colorless foam. This sample was not pure, as NMR spectra showed the presence of additional minor component that was inseparable by preparatory TLC, flash chromatography, or HPLC chromatography; this impurity could be the oxepane resulting from closure of C1 onto the C13 hydroxyl: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02–8.00 (m, 1H), 7.76–7.74 (m, 1H), 7.68–7.65 (m, 1H), 7.56 (t, *J* = 7.3 Hz, 1H), 7.39–7.35 (m, 2H), 6.91–6.89 (m, 2H), 5.34–5.32 (m, 1H, single constitutional isomer), 5.25 (br s, 1H, single constitutional isomer), 5.08–4.94 (m, 2H), 3.81 (s, 3H), 3.23 (br s, 1H, single constitutional isomer), 3.21 (br s, 1H, single constitutional isomer), 3.03 (br s, 2H, single constitutional isomer), 2.90 (br s, 2H, single constitutional isomer), 2.69 (br s, 1H), 2.58–2.00 (m, 6H), 1.93–1.81 (m, 2H), 1.66–1.63 (m, 1H), 1.53–1.42 (m, 6H), 1.06–1.05 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 218.3, 214.8, 160.3, 160.2, 149.8, 134.9, 134.8, 132.7, 132.4, 131.9, 131.7, 131.1, 131.0, 127.1, 127.0, 126.2, 126.1, 123.8, 123.6, 114.04, 113.96, 99.7, 98.0, 96.3, 96.2, 94.8, 80.0, 79.9, 70.0, 69.7, 55.4, 55.3, 54.6, 53.5, 48.7, 48.2, 36.5, 36.0, 35.5, 35.3, 34.6, 34.2, 32.2, 32.1, 24.6, 24.2, 23.7, 23.5, 23.4, 23.30, 23.26, 22.3, 18.9, 18.8; IR (thin film) 3481, 2927, 1746, 1374, 1177 cm^{-1}; HRMS-ESI (*m*/*z*) $[M + Na]^+$ calcd for $C_{29}H_{36}N_2O_{10}SNa$ 627.1989; found, 627.1981. Next, hemiacetal **35** (0.157 g, 50% yield over three steps) was obtained as a colorless foam. Compound **35** was not a single set of lactol epimers. One possible explanation involves ring-opening the hemi-acetal at C5: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (d, *J* = 7.8 Hz, 1H), 7.74 (t, *J* = 7.3 Hz, 1H), 7.66–7.64 (m, 1H), 7.55–7.53 (m, 1H), 7.33 (d, *J* = 8.5 Hz, 2H), 6.90 (d, *J* = 8.4 Hz, 2H), 5.38–5.37 (m, 1H), 4.99 (br s, 2H), 3.82 (s, 3H), 3.77 (s, 1H), 3.00 (br s, 2H), 2.41–2.34 (m, 1H), 2.27–2.16 (m, 1H), 2.01–1.99 (m, 2H), 1.89–1.64 (m, 6H), 1.53–1.51 (m, 2H), 1.38–1.18 (m, 4H), 0.88–0.86 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.3, 149.7, 134.8, 132.8, 131.6, 131.0, 126.9, 126.0, 123.6, 114.1, 105.3, 98.7, 95.4, 80.1, 78.9, 55.4, 54.3, 45.9, 36.3, 34.0, 32.1, 29.8, 25.2, 23.1, 23.0, 21.7, 20.6, 14.4; IR (thin film) 3421, 2937, 1374, 1175 cm^{-1}; HRMS-ESI (*m*/*z*) $[M + Na]^+$ calcd for $C_{29}H_{36}N_2O_{10}SNa$ 627.1989; found, 627.1985.

General Procedure for Reduction with DIBALH–Oxidation–Acidic Rearrangement

A solution of diisobutylaluminum hydride (2.74 mL, 2.74 mmol, 1M in CH_2Cl_2, 2.00 equiv) was added to a solution of tricyclic dihydropyran (0.862 mg, 1.37 mmol, 1.00 equiv) in THF (4.6 mL) at −78 °C. The solution was maintained at −78 °C for 1 h and then warmed to 0 °C and quenched with a solution of sat. aq. Rochelle's salt (10 mL) and stirred for 1 h at rt. The mixture was then partitioned between CH_2Cl_2 (40 mL) and H_2O (50 mL). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered through a plug of cotton, and concentrated under reduced pressure. The residue (0.863 g, 1.37 mmol) was dissolved in CH_2Cl_2 (6.9 mL) and cooled to −78 °C. Solid *m*-CPBA (0.405 g, 1.64 mmol, 1.20 equiv) was added in one portion and the mixture was placed in a −20 °C ice–acetone bath, and maintained for 30 min. The solution was then poured into a 1:1:1 solution of H_2O/sat. aq. $Na_2S_2O_3$/sat. aq. $NaHCO_3$ (15 mL) and stirred vigorously at rt for 30 min. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered through a plug of cotton, and concentrated under reduced pressure. The residue was dissolved in THF (4.0 mL), and H_2O (2.0 mL) was added. Trifluoroacetic acid (2.0 mL) was then added resulting in a single-phase solution. The solution was stirred at rt for 12 h and then partitioned between Et_2O (40 mL) and sat. aq. $NaHCO_3$ (50 mL) resulting in the vigorous evolution of gas. The layers were separated and the aqueous phase was extracted with Et_2O (3 × 30 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered through a plug of cotton, and concentrated under reduced pressure.

N-2-Nitrobenzenesulfonyl-*O*-(*tert*-butyldimethylsilyl) tetracyclic hemiacetal 44

Following the general procedure, dihydropyran **41** (251 mg, 0.411 mmol) was converted to tetracyclic hemiacetal **44**. Purification by flash chromatography (3:2 EtOAc/hexanes) provided tetracyclic hemiacetal **44** (53 mg, 21% yield) as a clear colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (d, *J* = 7.3 Hz, 1H), 7.79 (t, *J* = 7.0 Hz, 1H), 7.71 (t, *J* = 7.6 Hz, 1H), 7.55 (d, *J* = 7.8 Hz, 1H), 5.37 (d, *J* = 4.6 Hz, 1H), 3.79 (s, 1H), 3.18–3.08 (m, 2H), 2.41–2.35 (m, 1H), 2.20 (t, *J* = 11.5 Hz, 2H), 2.06–1.97 (m, 2H), 1.83–1.59 (m, 5H), 1.59–1.45 (m, 4H), 1.40–1.26 (m, 4H), 1.16 (dt, *J* = 4.6, 14.2 Hz, 1H), 0.95 (s, 9H), 0.27 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.6 (C), 134.6 (CH), 133.5 (CH), 131.0 (CH), 126.5 (C), 123.5 (CH), 105.5 (C), 98.8 (CH), 95.6 (C), 79.2 (CH), 56.4 (CH_2), 46.1 (C), 36.5 (CH_2), 34.1 (CH_2), 32.4 (CH_2), 29.9 (CH_2), 27.1 (CH_3), 26.2 (CH_2), 25.4 (CH_2), 23.4 (CH_2), 23.3 (C), 21.8 (CH_2), 20.6 (CH_2), 18.4 (CH_2), 14.7 (CH_2), −4.2 (CH_3); IR (thin film) 3353, 2930, 2252, 1747, 1548 cm^{-1}; HRMS-ESI (*m*/*z*) [M + Na]$^+$ calcd for $C_{27}H_{42}N_2O_9SSiNa$ 621.2278; found, 621.2291.

N-2-Nitrobenzenesulfonyl-*O*-(triisopropylsilyl) Tetracyclic Hemiacetal 45

Following the general procedure, dihydropyran **42** (1.3 g, 2.0 mmol) was converted to tetracyclic hemiacetal **45**. Purification by flash chromatography (3:2 EtOAc/hexanes) provided tetracyclic hemiacetal **45** (0.46 g, 36% yield) as a clear oil: ^{1}H NMR (500 MHz, C_6D_6) δ 8.05 (d, *J* = 7.7 Hz, 1H), 6.73–6.71 (m, 1H), 6.61 (br s, 2H), 5.30 (br s, 1H), 3.61 (br s, 1H), 3.33–3.26 (m, 2H), 2.42–2.40 (m, 1H), 2.34 (t, *J* = 11.0 Hz, 1H), 2.22–2.18 (m, 1H), 1.93–1.88 (m, 3H), 1.77–1.72 (m, 3H), 1.69–1.63 (m, 2H), 1.36–1.28 (m, 7H), 1.16 (d, *J* = 7.0 Hz, 18H), 1.05–0.95 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.9 (C), 134.7 (CH), 132.9 (CH), 130.7 (CH), 128.9 (C), 123.5 (CH), 106.0 (C), 99.3 (CH), 95.8 (C), 79.3 (CH), 56.9 (CH_2), 46.3 (C), 36.9 (CH_2), 34.8 (CH_2), 32.8 (CH_2), 30.6 (CH_2), 25.9 (CH), 23.7 (CH_2), 21.2 (CH), 20.9 (CH), 18.5 (CH_3), 15.3 (C), 13.2 (CH_2); IR (thin film) 3361, 2943, 1741, 1549, 1374, 1178 cm^{-1}; HRMS-ESI (*m*/*z*) [M + Na]$^+$ calcd for $C_{30}H_{48}O_9N_2SSiNa$ 663.2748; found, 663.2751.

N-2-Nitrobenzenesulfonyl-*O*-2-(trimethylsilyl)ethyl Tetracyclic Hemiacetal 46

Following the general procedure, tricyclic dihydropyran **43** (401 mg, 0.673 mmol) was converted to tetracyclic hemiacetal **46**. Purification by flash chromatography (3:2 EtOAc/hexanes) provided hemiacetal **46** (211 mg, 54%) as a colorless foam: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (d, *J* = 7.6 Hz, 1H), 7.79 (t, *J* = 6.8 Hz, 1H), 7.70 (t, *J* = 7.5 Hz, 1H), 7.57 (d, *J* = 7.4 Hz, 1H), 5.58–5.34 (m, 1H), 4.97 (br s, 1H), 4.10 (m, 2H), 3.78 (m, 1H), 3.05 (br s, 2H), 2.48–2.39 (m, 1H), 2.21 (t, *J* = 12.1 Hz, 2H), 2.11–1.94 (m, 2H), 1.93–1.33 (m, 13H), 0.96 (t, *J* = 8.7 Hz, 2H), 0.02 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.9 (C), 135.0 (CH), 132.9 (CH), 131.1 (CH), 126.3 (C), 123.8 (CH), 105.5 (C), 98.8 (CH), 95.6 (C), 79.3 (CH), 76.5 (CH_2), 64.0 (CH_2), 54.2 (CH_2), 46.0 (C), 36.4 (CH_2), 34.3 (CH_2), 32.3 (CH), 29.9 (CH_2), 25.4 (CH_2), 23.5 (CH_2), 23.4 (CH_2), 21.9 (CH_2), 20.6 (CH_2), 17.4 (CH_2), 14.6 (CH_2), −1.2 (CH_3); IR (thin film) 3369, 2949, 2251, 1734, 1549, 1375, 1178 cm^{-1}; HRMS-ESI (*m*/*z*) [M + Na]$^+$ calcd for $C_{26}H_{40}O_9N_2SSiNa$ 607.2122; found, 607.2125.

General Procedure forRemoval of the Nosyl Group.[33] Preparation of *O*-4-Methoxybenzyl hydroxylamine 36

A solution of PhSH[96] and DMF[97] (3.28 mL, 0.656 mmol, 0.200 M in PhSH, 1.10 equiv) was added to a vial containing *N*-Ns hydroxyamine **35** (0.360 g, 0.596 mmol, 1.00 equiv) (0.360 g, 0.596 mmol, 1.00 equiv) and solid K_2CO_3 (0.164 g, 1.19 mmol, 2.00 equiv). The heterogeneous mixture was stirred vigorously under an Ar atmosphere at rt for 2.5 h. The mixture was then partitioned between CH_2Cl_2 (20 mL) and H_2O (30 mL). The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 30 mL). The combined

organic layers were washed with brine (80 mL), dried over $MgSO_4$, filtered through a plug of cotton, and concentrated under reduced pressure. Purification by flash chromatography (pH 7 buffered SiO_2[98], 2:3 acetone/hexanes) provided amino lactol **36** (0.211 g, 84% yield) as a colorless foam: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 5.53–5.52 (m, 1H), 5.42–5.41 (m, 1H), 4.64 (s, 2H), 4.62 (s, 2H), 3.82–3.79 (m, 4H), 2.85 (t, *J* = 7.0 Hz, 2H), 2.50–2.44 (m, 1H), 2.24–2.10 (m, 2H), 2.08–1.93 (m, 3H), 1.84–1.72 (m, 4H), 1.67–1.18 (m, 6H), 0.97–0.84 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.7, 130.5, 130.2, 114.1, 105.4, 98.8, 95.7, 79.2, 76.0, 55.6, 53.3, 46.3, 36.7, 34.3, 32.5, 25.6, 23.9, 23.4, 22.3, 20.6, 14.7; IR (thin film) 3253, 2937, 1462, 1249 cm^{-1}; HRMS-ESI (*m*/*z*) $[M + H]^+$ calcd for $C_{23}H_{34}NO_6$ 420.2386; found, 420.2393.

O-Triisopropylsilyl hydroxylamine 48

Following the general procedure for Ns-removal, *N*-Ns hydroxylamine **45** (350 mg, 0.547 mmol), was converted to amino lactol **48**. Purification by flash chromatography (pH 7 buffered SiO_2[98], 1:1 EtOAc/hexanes) provided amino lactol **48** (0.211 g, 84% yield) as a colorless foam: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.39 (d, *J* = 3.2 Hz, 1H), 3.80 (s, 1H), 2.94–2.83 (m, 2H), 2.85 (t, *J* = 6.8 Hz, 2H), 2.46 (d, *J* = 10.8 Hz, 1H), 2.21–2.10 (m, 2H), 2.00–1.95 (m, 2H), 1.85–1.79 (m, 2H), 1.73 (dt, *J* = 3.5, 11.8 Hz, 2H), 1.64–1.57 (m, 2H), 1.50–1.45 (m, 2H), 1.45–1.41 (m, 2H), 1.37–1.35 (m, 3H), 1.16–1.09 (m, 3H), 1.06 (m, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 105.4, 98.6, 95.6, 79.1, 55.5, 46.1, 36.5, 34.2, 32.4, 25.5, 23.8, 23.3, 21.7, 20.5, 18.4, 14.7, 12.0; IR (thin film) 3355, 2944, 1464, 1200 cm^{-1}; HRMS-ESI (*m*/*z*) $[M + H]^+$ calcd for $C_{24}H_{46}NO_5Si$ 456.3145; found, 456.3140.

O-2-(Trimethylsilyl)ethyl hydroxylamine 49

Following the general procedure, *N*-Ns hydroxylamine **46** (301 mg, 0.524 mmol) was converted to amino lactol **49**. Purification by flash chromatography (pH 7 buffered SiO_2[98], 2:3 acetone/hexanes) afforded amino lactol **49** (188 mg, 89% yield) as a colorless foam: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.58–5.42 (m, 1H), 3.83 (s, 1H), 3.72 (t, *J* = 8.4 Hz, 2H), 2.85 (q, *J* = 6.8 Hz, 2H), 2.50–2.43 (m, 2H), 2.31–2.14 (m, 2H), 2.11–1.98 (m, 2H), 1.88–1.72 (m, 5H), 1.66–1.20 (m, 9H), 0.89 (t, *J* = 8.1 Hz, 2H), 0.01 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 105.4 (C), 98.7 (CH), 95.7 (C), 95.5 (CH_2), 79.2 (CH), 71.4 (CH_2), 53.3 (CH_2), 46.2 (C), 36.5 (CH_2), 35.9 (CH_2), 34.3 (CH_2), 32.5 (CH), 25.5 (CH_2), 23.9 (CH_2), 23.4 (CH_2), 22.2 (CH_2), 20.6 (CH_2), 17.5 (CH_2), 14.7 (CH_2), −1.1 (CH_3); IR (thin film) 3379, 2947, 1745, 1249 cm^{-1}; HRMS-ESI (*m*/*z*) $[M + H]^+$ calcd for $C_{20}H_{37}O_5NSiH$ 400.2519; found, 400.2515.

O-4-Methoxybenzyl octahydroazonine 37

A solution of DBU and CH_2Cl_2 (0.10 mL, 0.060 mmol, 0.60 M in DBU) was added dropwise to a solution of amino lactol **36** (0.211 g, 0.504 mmol) and CH_2Cl_2 (5.9 mL). Trichloroacetonitrile (0.09 mL, 0.9 mmol) was added to the solution and maintained at rt for 18 h. The solution was concentrated under reduced pressure, and the residue was purified by flash chromatography (1:30:69 aq. NH_4OH/acetone/hexanes) to give octahydroazonine **37** (0.061 g, 26% yield) as a colorless film: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.6 Hz, 2H), 6.84 (d, *J* = 8.6 Hz, 2H), 5.25 (br s, 1H), 4.58 (d, *J* = 11.5 Hz, 1H), 4.54 (d, *J* = 11.5 Hz, 1H), 3.80 (s, 3H), 3.66 (s, 1H), 3.35 (dd, *J* = 9.5, 15.6 Hz, 1H), 2.65–2.54 (m, 2H), 2,24 (t, *J* = 11.6 Hz, 2H), 2.18–2.12 (m, 1H), 2.03–1.97 (m, 1H), 1.87–1.72 (m, 4H), 1.65 (dd, *J* = 3.6, 11.9 Hz, 2H), 1.54–1.25 (m, 5H), 1.15–1.07 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.3 (C), 130.4 (CH), 130.3 (C), 113.6 (CH), 105.3 (C), 94.9 (CH), 93.2 (C), 79.0 (CH), 73.7 (CH_2), 55.3 (CH_3), 50.6 (CH_2), 46.0 (C), 35.7 (CH_2), 31.6 (CH), 28.7 (CH_2), 25.5 (CH_2), 25.4 (CH_2), 23.2 (CH_2), 21.6 (CH_2), 18.0 (CH_2), 14.7 (CH_2); IR (thin film) cm^{-1}; HRMS-ESI (*m*/*z*) $[M + H]^+$ calcd for $C_{23}H_{32}NO_5$ 402.2281; found, 402.2276.

O-2-(Trimethylsilyl)ethyl octahydroazonine 50

A 0.471 M solution of DBU (100.0 μL, 0.0471 mmol, 0.10 equiv) in CH_2Cl_2 was added to a solution of amino lactol **49** (188 mg, 0.471 mmol, 1.00 equiv) in CH_2Cl_2 (4.70 mL). Trichloroacetonitrile (50.0 μL, 0.707 mmol, 1.50 equiv) was then added dropwise and after the addition the solution was capped and stirred for 14 h at rt. The solution was concentrated and purified by flash chromatography (1:20:79 aq. NH_4OH/acetone/chloroform) to afford octahydroazonine **50** (0.042 g, 23% yield) as a clear colorless film: ^{1}H NMR (500 MHz, C_6D_6) δ 5.50 (br s, 1H), 3.80 (dt, *J* = 2.6, 8.0 Hz, 2H), 3.55 (s, 1H), 3.46 (dd, *J* = 9.9, 14.9 Hz, 1H), 2.62 (m, 1H), 2.59 (m, 2H), 2.24–2.08 (m, 2H), 1.99–1.86 (m, 2H), 1.79–1.72 (m, 3H), 1.59 (m, 1H), 1.40–1.10 (m, 5H), 1.11–0.98 (m, 2H), 0.93 (t, *J* = 7.8 Hz, 2H), 0.74 (t, *J* = 12.9 Hz, 1H), 0.00 (s, 9H); ^{13}C NMR (125 MHz, C_6D_6) δ 106.4 (C), 95.1 (CH), 93.9 (C), 79.3 (CH), 69.0 (CH_2), 51.3 (CH_2), 46.5 (C), 36.7 (CH_2), 32.4 (CH), 29.5 (CH_2), 26.2 (CH_2), 23.9 (CH_2), 22.2 (CH_2), 19.0 (CH_2), 18.0 (CH_2), 17.8 (CH_2), 15.6 (CH_2), −0.9 (CH_3); HRMS-ESI (*m*/*z*) $[M + Na]^+$ calcd for $C_{20}H_{35}O_4NSiNa$ 404.2233; found, 404.2228.

General Procedure for TPAP Oxidation.[42] Preparation of Diketooctahydroazonine 39

Solid *N*-methylmorpholine-*N*-oxide (0.028 g, 0.24 mmol, 1.5 equiv), octahydroazonine **37** (0.064 g, 0.16 mmol), 1.0 equiv), and oven-dried powdered 4Å mol. sieves (0.027 g) were suspended in CH_2Cl_2 (0.9 mL) and stirred at rt for 10 min. A solution of $(n\text{-}Pr)_4NRuO_4$ (TPAP) and CH_2Cl_2 (1.6 mL, 0.016 mmol, 0.010 M in TPAP, 0.10 equiv) was added resulting in a dark green liquid phase. The mixture was maintained at rt for 1 h, then filtered through a plug of Celite®, and concentrated under reduced pressure. Purification by flash chromatography (1:20:79 aq. NH_4OH/acetone/hexanes) provided diketooctahydroazonine **39** (0.055 g, 86% yield) as a colorless crystalline solid. Slow evaporation from MeOH provided single crystals suitable for x-ray analysis:^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8.2 Hz, 2H), 6.91 (d, *J* = 8.5 Hz, 2H), 5.04 (d, *J* = 7.0 Hz, 1H), 4.62 (d, *J* = 11.9 Hz, 1H), 4.59 (d, *J* = 12.2 Hz, 1H), 3.86 (s, 3H), 3.33–3.28 (m, 2H), 2.79–2.69 (m, 2H), 2.64–2.44 (m, 4H), 2.30–2.22 (m, 1H), 2.18–2.15 (m, 1H), 2.14–1.85 (m, 6H), 1.78–1.71 (m, 2H), 1.66–1.64 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.9 (C), 210.4 (C), 159.4 (C), 130.5 (CH), 129.8 (C), 113.6 (CH), 95.7 (CH), 91.2 (C), 74.1 (CH_2), 61.7 (C), 55.3 (CH_3), 51.0 (CH_2), 38.6 (CH_2), 38.1 (CH), 35.5 (CH_2), 30.7 (CH_2), 28.0 (CH_2), 25.3 (CH_2), 23.4 (CH_2), 21.9 (CH_2), 19.0 (CH_2); IR (thin film) 2925, 2854, 1756, 1698, 1515, 1248 cm^{-1}; HRMS-ESI (*m*/*z*) $[M + Na]^+$ calcd for $C_{23}H_{29}NO_5Na$ 422.1943; found, 422.1941; mp (dec) 145–148 °C.

O-2-(Trimethylsilyl)ethyl diketooctahydroazonine 51

Following the general TPAP oxidation procedure, octahydroazonine **50** (42 mg, 0.11 mmol) was converted to diketooctahydroazonine **51**. Purification by filtration through a plug of SiO_2 (100% EtOAc) provided diketooctahydroazonine **51** (38 mg, 91% yield) as a clear colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.07 (d, *J* = 7.4 Hz, 1H), 3.66 (t, *J* = 8.7 Hz, 2H), 3.37–3.34 (m, 2H), 2.77–2.65 (m, 2H), 2.57–2.40 (m, 4H), 2.31–2.17 (m, 1H), 2.12–1.81 (m, 7H), 1.80–1.57 (m, 3H), 0.95–0.83 (m, 2H), 0.00 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 215.2 (C), 210.5 (C), 95.8 (CH), 91.4 (C), 69.3 (CH_2), 61.9 (C), 51.2 (CH_2), 38.9 (CH_2), 38.3 (CH), 35.7 (CH_2), 30.8 (CH_2), 28.4 (CH_2), 25.5 (CH_2), 23.6 (CH_2), 22.1 (CH_2), 19.1 (CH_2), 17.5 (CH_2), −1.13 (CH_3); IR (thin film) 2945, 1760, 1705, 1424, 1242, 834 cm^{-1}; HRMS-ESI (*m*/*z*) $[M + Na]^+$ calcd for $C_{20}H_{33}O_4NSiNa$ 402.2077; found, 402.2081.

General Procedure for Saegusa Oxidation. (2*S**,3*S**,3a*S**,7a*S**)-3a-(3-(*tert*-Butyldiphenylsilyloxy)propyl)-2-methoxy-3-(phenoxymethyl)-3,3a,7,7a-tetrahydro-1*H*-inden-4(2*H*)-one (α-54)

Freshly titrated *n*-BuLi (3.33 mL, 8.24 mmol, 1.45 equiv) was added dropwise to a solution of diisopropylamine (1.20 mL, 8.52 mmol, 1.50 equiv) in THF (26 mL) at 0 °C. After addition, the pale yellow solution was stirred for 15 min. The solution of lithium diisopropylamine was cooled to −78 °C and chlorotrimethylsilane[89] (3.60 mL, 28.4 mmol, 5.00 equiv) was added and stirred for 5 min followed by dropwise addition of a solution of ketone **19** (3.24 g, 5.68 mmol, 1.00 equiv) in THF (12 mL) at −78 °C. The solution was maintained at −78 °C for 20 min and then anhydrous Et_3N (12 mL) was added and allowed to stir for 30 min. The reaction was warmed to 0 °C and quenched with 2M pH 7 buffer. The layers were separated and the aqueous phase was extracted with ether (3 × 100 mL). The combined organic phases were washed with brine (100 mL), dried over $MgSO_4$, filtered through a plug of cotton, and concentrated under reduced pressure. The resulting oil was left on a high-vacuum line (1 mmHg) overnight and the enol silane was of sufficient purity to carry-on without further purification. $Pd(OAc)_2$ (1.33 g, 5.94 mmol) was added in one portion to a solution of enol silane (3.47 g, 5.40 mmol) in anhydrous DMSO (22 mL). A balloon of oxygen with cannula needle was inserted to slowly bubble O_2 through the suspension and the mixture was slowly warmed to 55 °C and maintained for 12 h. After consumption of the starting material the flask was cooled to rt and the suspension was partitioned between 1N HCl (250 mL) and ether (100 mL). The aqueous phase was extracted with ether (3 × 100 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ (100 mL) followed by brine (100 mL). The organic phase was dried over $MgSO_4$, filtered through a plug of cotton and concentrated under reduced pressure. Purification by column chromatography (1:4 EtOAc/hexanes) provided hydrindene **α-54** (2.75 g, 85% yield) as a clear colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (d, *J* = 7.3 Hz, 4H), 7.41 (td, *J* = 7.4, 1.3 Hz, 2H), 7.35 (td, *J* = 7.3, 1.5 Hz, 4H), 7.25 (t, *J* = 8.0 Hz, 2H), 6.91 (t, *J* = 7.3 Hz, 1H), 6.89 (d, *J* = 7.8 Hz, 2H), 6.80 (dt, *J* = 8.5, 4.7 Hz, 1H), 6.03 (d, *J* = 10.2 Hz, 1H), 4.21 (t, *J* = 9.0 Hz, 1H), 4.11 (dd, *J* = 9.3, 4.4 Hz, 1H), 3.88–3.85 (m, 1H), 3.66–3.61 (m, 1H), 3.57–3.53 (m, 1H), 3.26 (s, 3H), 2.67–2.64 (m, 1H), 2.63–2.59 (m, 1H), 2.55–2.50 (m, 1H), 2.24 (d, *J* = 19.6 Hz, 1H), 2.03 (ddd, *J* = 13.5, 8.1, 3.4 Hz, 1H), 1.82 (td, *J* = 12.6, 4.5 Hz, 1H), 1.71–1.63 (m, 2H), 1.50–1.40 (m, 2H), 1.03 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.9, 159.0, 147.5, 135.7, 135.6, 134.1, 134.0, 129.6, 129.4, 129.2, 127.6, 120.5, 114.7, 80.2, 64.1, 63.4, 57.6, 55.0, 49.1, 39.6, 37.8, 29.6, 28.6, 28.2, 26.9, 19.2; IR (thin film) 2960, 2858, 1661, 1600, 1497, 1243 cm^{-1}; HRMS-ESI (*m*/*z*) $[M + H]^+$ calcd for $C_{36}H_{45}O_4Si$ 569.3087; found, 569.3099.

(2*R**,3*S**,3a*S**,7a*S**)-3a-(3-(*tert*-Butyldiphenylsilyloxy)propyl)-2-methoxy-3-(phenoxymethyl)-3,3a,7,7a-tetrahydro-1*H*-inden-4(2*H*)-one (β-54)

Following the general procedure, hydrindanone **β-19** (1.29 g, 2.26 mmol) was converted into hydrindenone **β-54**. Purification by column chromatography (1:4 EtOAc/hexanes) provided hydrindenone **β-54** (786 mg, 61% yield) as a clear colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51(d, *J* = 6.8 Hz, 4H), 7.30 (t, *J* = 7.2 Hz, 2H), 7.24 (t, *J* = 7.1 Hz, 4H), 7.14 (t, *J* = 8.4 Hz, 2H), 6.84 (t, *J* = 7.4 Hz, 1H), 6.76 (d, *J* = 7.9 Hz, 2H), 6.63–6.60 (m, 1H), 5.91 (d, *J* = 10.1 Hz, 1H), 4.01 (dd, *J* = 4.1, 9.5 Hz, 1H), 3.80–3.76 (m, 2H), 3.49–3.44 (m, 2H), 3.17 (s, 3H), 3.00 (m, 1H), 2.49–2.44 (m, 2H), 2.30 (dd, *J* = 4.3, 17.9 Hz, 1H), 2.24 (pentet, 1H), 1.61 (dt, *J* = 4.0, 13.5 Hz, 1H), 1.55–1.37 (m, 3H), 1.36–1.28 (m, 1H), 0.89 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.8 (C), 159.1 (C), 145.7 (CH), 135.8 (CH), 134.1 (C), 129.8 (CH), 129.7 (CH), 128.6 (CH), 127.81 (CH), 121.1 (CH), 114.8 (CH), 83.9 (CH), 67.2 (CH_2), 64.3 (CH_2), 56.9 (C), 56.4 (CH_3), 47.8 (CH), 41.5 (CH), 37.8 (CH_2), 28.5 (CH_2), 28.4 (CH_2), 27.3 (CH_2), 27.0 (CH_3), 19.4 (C); IR (thin film) 1669, 1600, 1497, 1242 cm^{-1}; HRMS-ESI (*m*/*z*) $[M + Na]^+$ calcd for $C_{36}H_{44}O_4SiNa$ 591.2906; found, 591.2905.

General Procedure for Methyl Cuprate Addition. Preparation of (2*S**,3*S**,3a*S**,7a*S**)-3a-(3-(*tert*-Butyldiphenylsilyloxy)propyl)-2-methoxy-6-methyl-3-(phenoxymethyl)hexahydro-1*H*-inden-4(2*H*)-one (α-52)

A solution of MeLi (21.7 mL, 29.8 mmol, 1.37 M in Et_2O, 6.20 equiv) was added dropwise to a suspension of CuBr•Me_2S[99] (3.01 g, 14.6 mmol, 3.05 equiv) in Et_2O (96 mL) at −78 °C, producing a bright yellow precipitate. The mixture was warmed to 0 °C, resulting in a clear colorless solution. A solution of hydrindenone **54** (2.73 g, 4.80 mmol, 1.00 equiv) in Et_2O (7 mL) was then added dropwise. The solution was maintained for 10 min and then treated with a 9:1 solution of sat. aq. NH_4Cl/NH_4OH (50 mL). The mixture was partitioned between water (100 mL) and Et_2O (100 mL). The layers were separated and the aqueous phase was extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with brine (75 mL), dried over $MgSO_4$, filtered through a plug of cotton, and concentrated under reduced pressure. Purification by flash chromatography (1:9 EtOAc/hexanes) provided β-methyl ketone **α-52** (2.63 g, 94% yield) as a clear oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68–7.65 (m, 4H), 7.43–7.35 (m, 6H), 7.25 (td, *J* = 7.0, 1.6 Hz, 2H), 6.91 (t, *J* = 7.3 Hz, 1H), 6.86 (dd, *J* = 8.7, 1.0 Hz, 2H), 4.18 (t, *J* = 9.2 Hz, 1H), 4.00 (td, *J* = 7.0, 3.7 Hz, 1H), 3.88 (dd, *J* = 9.2, 4.4 Hz, 1H), 3.71–3.70 (m, 1H), 3.59–3.54 (m, 1H), 3.22 (s, 3H), 2.71–2.67 (m, 1H), 2.44–2.41 (m, 1H), 2.32 (ddd, *J* = 14.6, 3.0, 2.2 Hz, 1H), 2.10 (dd, *J* = 16.0, 12.8 Hz, 1H), 2.00 (ddd, *J* = 14.2, 8.0, 3.7 Hz, 1H), 1.88 (ddd, *J* = 14.2, 7.0, 2.3 Hz, 1H), 1.82–1.72 (m, 3H), 1.61 (td, *J* = 12.7, 4.6 Hz, 1H), 1.58 (s, 9H), 1.42–1.33 (m, 2H), 1.10 (q, *J* = 12.7 Hz, 1H), 0.96 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.6 (C), 158.8 (C), 135.6 (CH), 134.1 (C), 129.5 (CH), 129.3 (CH), 127.6 (CH), 120.4 (CH), 114.6 (CH), 80.2 (CH), 64.2 (CH_2), 63.2 (CH_2), 58.7 (C), 57.6 (CH_3), 48.8 (CH), 46.3 (CH), 42.8 (CH), 39.1 (CH_2), 38.6 (CH_2), 31.0 (CH_2), 28.6 (CH_2), 26.9 (CH_3), 25.8 (CH_2), 22.1 (CH_3), 19.2 (C); IR (thin film) 2958, 1694, 1600, 1497, 1243 cm^{-1}; HRMS-ESI (*m*/*z*) [M + Na]$^+$ calcd for $C_{37}H_{48}O_4SiNa$ 607.3220; found, 607.3200.

(2*R**,3*S**,3a*S**,7a*S**)-3a-(3-(*tert*-Butyldiphenylsilyloxy)propyl)-2-methoxy-6-methyl-3-(phenoxymethyl)hexahydro-1*H*-inden-4(2*H*)-one (β-52 and β-53)

Following the general procedure for methyl cuprate addition, hydrindenone **β-54** was converted to hydrindanones **β-52** and **β-53**. Purification by flash chromatography (1:9 EtOAc/hexanes) provided β-methyl ketones **β-52** and **β-53**. Eluting first was **β-53** (247 mg, 30% yield) as a clear oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (d, *J* = 6.8 Hz, 4H), 7.41 (t, *J* = 7.3 Hz, 2H), 7.35 (t, *J* = 7.3 Hz, 4H), 7.25 (t, *J* = 7.6 Hz, 2H), 6.94 (t, *J* = 7.3 Hz, 1H), 6.83 (d, *J* = 8.0 Hz, 2H), 4.02 (dd, *J* = 4.5, 9.5 Hz, 1H), 3.82 (dd, *J* = 6.0, 8.9 Hz, 2H), 3.56 (t, *J* = 6.1 Hz, 2H), 3.26 (s, 3H), 2.43 (m, 1H), 2.38–2.35 (m, 1H), 2.25–2.19 (m, 2H), 2.05 (t, *J* = 7.8 Hz, 1H), 1.85 (dt, *J* = 8.8, 13.5 Hz, 1H), 1.76 (d, *J* = 12.3 Hz, 1H), 1.66–1.58 (m, 2H), 1.56 (m, 1H), 1.47–1.40 (m, 3H), 1.01 (s, 9H), 0.99 (d, overlapping signal, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.6 (C), 159.1 (C), 135.8 (CH), 134.0 (C), 129.89 (CH), 129.87 (CH), 127.9 (CH), 121.0 (CH), 114.7 (CH), 83.8 (CH), 67.3 (CH_2), 64.1 (CH_2), 58.7 (C), 56.6 (CH_3), 47.3 (CH_2), 46.0 (CH), 44.8 (CH), 36. 8 (CH_2), 33.6 (CH_2), 29.4 (CH_2), 28.8 (CH_2), 28.7 (CH), 27.q (CH_3), 22.4 (CH_3), 19.4 (C); IR (thin film) 3070, 2954, 1703, 1600 cm^{-1}; HRMS-ESI (*m*/*z*) [M + Na]$^+$ calcd for $C_{37}H_{48}O_4SiNa$ 607.3220; found, 607.3226. Eluting second was **β-52** (316 mg, 38% yield) as a clear oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (d, *J* = 7.1 Hz, 4H), 7.41 (m, 2H), 7.37 (t, *J* = 6.0 Hz, 4H), 7.25 (t, *J* = 8.1 Hz, 2H), 6.92 (t, *J* = 7.3 Hz, 1H), 6.83 (d, *J* = 8.1 Hz, 2H), 3.97 (dd, *J* = 6.3, 9.5 Hz, 1H), 3.92 (dd, *J* = 6.7, 9.5 Hz, 1H), 3.75–3.68 (m, 2H), 3.60–3.55 (m, 1H), 3.36 (s, 3H), 2.33 (m, 1H), 2.26 (d, *J* = 9.8 Hz, 2H), 2.22–2.16 (m, 1H), 1.91 (m, 1H), 1.74 (m, 2H), 1.65–1.60 (m, 2H), 1.56 (m, 1H), 2.38 (pentet, *J* = 7.8 Hz, 2H), 1.13–1.08 (m, 1H), 1.05 (s, 9H), 1.00 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.8 (C), 158.9 (C), 135.9 (CH), 134.3 (C), 129.8 (CH), 129.6 (CH), 127.9 (CH), 121.0 (CH), 114.8 (CH), 85.0 (CH), 66.2 (CH_2), 64.5 (CH_2), 59.1 (C), 58.0 (CH_3), 52.2 (CH), 46.2 (CH), 43.4 (CH), 38.5 (CH_2), 36.8 (CH_2), 32.5 (CH_2),

28.5 (CH_2), 27.2 (CH_3), 25.4 (CH_2), 22.3 (CH_3), 19.5 (C); IR (thin film) 3070, 2936, 2859, 1701, 1600 cm^{-1}; HRMS-ESI (*m*/*z*) $[M + Na]^+$ calcd for $C_{37}H_{48}O_4SiNa$ 607.3220; found, 607.3216. Additionally, a small amount of mixed fractions was recovered (54 mg, 6% yield).

(2*R**,3*S**,3a*S**,7a*S**)-3a(3-Hydroxypropyl)-2-methoxy-3-(phenoxymethyl)-3,3a,7,7a-tetrahydro-1*H*-inden-4(2*H*)-one (55)

A solution of TBAF in THF (1.1 mL, 1M) was added dropwise to a stirring solution of β-**54** (0.20 g, 0.35 mmol) in THF (3.5 mL). The solution was maintained at rt for 2 h before quenching with sat. aq. $NaHCO_3$. The mixture was extracted with Et_2O (3 × 20 mL) and the combined organic layers were washed with brine (25 mL), dried over $MgSO_4$, filtered through a plug of cotton and concentrated under reduced pressure. The residue was purified by flash column chromatography (3:2 EtOAc/hexanes) to afford **55** (42 mg, 36%) as a clear oil. ^1H NMR (500 MHz, $CDCl_3$) δ 7.29 (t, *J* = 7.9 Hz, 2H), 6.95 (t, *J* = 7.3 Hz, 1H), 6.90 (d, *J* = 8.1 Hz, 2H), 6.76–6.74 (m, 1H), 6.03 (d, *J* = 10.1 Hz, 1H), 4.14 (dd, *J* = 4.2, 9.5 Hz, 1H), 3.95 (dd, *J* = 6.5, 9.4 Hz, 1H), 3.89–3.87 (m, 1H), 3.52 (t, *J* = 6.2 Hz, 2H), 3.27 (s, 3H), 3.07 (br s, 1H), 2.60–2.57 (m, 1H), 2.43 (dd, *J* = 4.3, 17.0 Hz, 1H), 2.36–2.31 (m, 1H), 1.78–1.71 (m, 2H), 1.64–1.54 (m, 2H), 1.51–1.44 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.9 (C), 159.0 (C), 146.2 (CH), 129.8 (CH), 128.6 (CH), 121.2 (CH), 114.9 (CH), 83.9 (CH), 67.2 (CH_2), 63.1 (CH), 56.9 (CH_3), 56.1 (C), 48.3 (CH), 41.3 (CH), 37.7 (CH_2), 28.5 (C), 28.1 (CH_2), 27.5 (CH_2); IR (thin film) 3426, 2931, 1769, 1666, 1594, 1496, 1242 cm^{-1}; HRMS-ESI (*m*/*z*) $[M + Na]^+$ calcd for $C_{20}H_{26}O_4Na$ 353.1729; found, 353.1721.

(2*R**,3*S**,3a*S**,6*R**,7a*S**)-3a-(3-Hydroxypropyl)-2-methoxy-6-methyl-3-(phenoxymethyl)hexahydro-1*H*-indene-4(2*H*)-one (56)

Following the general procedure for methyl cuprate addition, hydrindenone **55** (10.0 mg, 0.03 mmol) was converted into a 1.6:1 mixture of methyl epimers as determined by ^1H NMR (9.8 mg, 94%) with β-methyl ketone **56** as the major diastereomer. For chemical comparison and to assign the major and minor diastereomeric products, the crude residue above was converted as follows into β-**52** and β-**53**. The crude product was dissolved in pyridine (0.3 mL). DMAP (single crystal) was added followed by addition of TBDPSCl (15 μL, 0.05 mmol). The reaction mixture was stirred at rt for 18 h and then concentrated under reduced pressure. Purification by flash chromatography (1:9 EtOAc/hexanes) provided (2*R**,3*S**,3a*S**,7a*S**)-3a-(3-(*tert*butyldiphenylsilyloxy)propyl)-2-methoxy-6-methyl-3-(phenoxymethyl)hexahydro-1*H*-inden-4(2*H*)-one 15 mg (86% over 2 steps) in a 1.6:1 ratio (β-**53**:β-**52**) as determined by ^1H NMR.

(2*S**,3*S**,3a*S**,7a*S**)-2-Hydroxy-3a-(3-iodopropyl)-6-methyl-3-(phenoxymethyl)hexahydro-1*H*-inden-4(2*H*)-one

TMSCl[89] (11.2 mL, 87.9 mmol, 10.0 equiv) was added dropwise to a solution of NaI[90] (13.2 g, 87.9 mmol, 10.0 equiv) and dry MeCN (73 mL) at rt and vigorously stirred for 20 min, which resulted in formation of a colorless precipitate. The freshly prepared solution of TMSI was decanted from the precipitate via syringe and added dropwise to a solution of methyl ether α-**52** (5.14 g, 8.79 mmol, 1.0 equiv), H_2O (0.791 mL, 44.0 mmol, 5.00 equiv), and MeCN (17 mL). The solution was then heated to 50 °C for 2 h. The resulting brown solution was cooled to rt, diluted with Et_2O (200 mL) and treated with 1:1:1 H_2O/sat. aq. $NaHCO_3$/sat. aq. $Na_2S_2O_3$ (200 mL) and stirred for 15 min, resulting in disappearance of the brown color. The layers were separated and the aqueous phase was extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with brine (150 mL), dried over $MgSO_4$, filtered through a plug of cotton, and concentrated under reduced pressure. Purification by flash chromatography (1:4 EtOAc/hexanes) provided (2*S**,3*S**,3a*S**,7a*S**)-2-Hydroxy-3a-

(3-iodopropyl)-6-methyl-3-(phenoxymethyl)hexahydro-1*H*-inden-4(2*H*)-one (2.35 g, 61%) as a pale yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.6 Hz, 2H), 6.97 (t, *J* = 7.4 Hz, 1H), 6.89 (d, *J* = 7.8 Hz, 2H), 4.71 (m, 1H), 4.23 (t, *J* = 9.3 Hz, 1H), 3.90 (dd, *J* = 4.4, 9.1 Hz, 1H), 3.22 (m, 1H), 3.09 (q, *J* = 9.3 Hz, 1H), 2.65 (m, 1H), 2.45 (m, 1H), 2.32 (d, *J* = 16.2 Hz, 1H), 2.02 (m, 2H), 1.92–1.96 (m, 3H), 1.58–1.78 (m, 5H), 1.16 (q, *J* = 12.9 Hz, 1H), 0.98 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.3, 158.5, 129.8, 121.4, 114.7, 71.5, 63.7, 58.9, 48.7, 46.2, 43.0, 40.7, 38.6, 31.5, 30.3, 30.2, 22.3, 6.9; IR (thin film) 3465, 2950, 1692, 1598, 1496, 1242 cm^{-1}; HRMS-ESI (*m*/*z*) $[M + Na]^+$ calcd for $C_{20}H_{27}IO_3Na$ 465.0903; found, 465.0899.

(3a*S**,7a*S**)-3a-(3-Iodopropyl)-6-methyl-3-methylenetetrahydro-1*H*-indene-2,4(5*H*,6*H*)-dione

Dess–Martin periodinane[28] (2.37 g, 5.59 mmol, 1.5 equiv) was added in one portion to a stirring solution of (2*S**,3*S**,3a*S**,7a*S**)-2-hydroxy-3a-(3-iodopropyl)-6-methyl-3-(phenoxymethyl)hexahydro-1*H*-inden-4(2*H*)-one (2.35 g, 5.31 mmol, 1.00 equiv), solid $NaHCO_3$ (4.46 g, 53.1 mmol, 10.0 equiv), and CH_2Cl_2 (30 mL). The mixture was stirred vigorously for 15 min, then treated with 10% aq. $Na_2S_2O_3$ (15 mL) and stirred for an additional 15 min. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine (40 mL), dried over $MgSO_4$, filtered through a plug of cotton, and concentrated under reduced pressure to afforded the dione (3.04 g, 90% yield) as a pale yellow oil. Due to the propensity to eliminate PhOH, the dione was carried on without purification. 1,8-diazabicyclo[5.4.0]undec-7-ene[100] (1.14 mL, 7.63 mmol, 1.1 equiv) was added dropwise to a solution of dione (3.04 g, 6.93 mmol, 1.00 equiv) and THF (150 mL) at 0 °C. The cooling bath was removed and the pale brown solution was stirred for 30 min. The solution was then partitioned between sat. aq. NH_4Cl (100 mL) and EtOAc (150 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with aq. NaOH (2 M, 100 mL) then brine (100 mL), dried over $MgSO_4$, filtered through a plug of cotton, and concentrated under reduced pressure to afford (3a*S**,7a*S**)-3a-(3-iodopropyl)-6-methyl-3-methylenetetrahydro-1*H*-indene-2,4(5*H*,6*H*)-dione (2.39 g, 6.90 mmol) as a colorless oil. Due to the sensitivity of (3a*S**,7a*S**)-3a-(3-iodopropyl)-6-methyl-3-methylenetetrahydro-1*H*-indene-2,4(5*H*,6*H*)-dione, it was carried on without further purification.

3-Propyl *N*-(methoxymethoxy)-2-nitrobenzenesulfonamide dihydropyran 57

$Eu(fod)_3$ (0.72 g, 0.690 mmol, 0.10 equiv) was added in one portion to a solution of endione (2.39 g, 6.90 mmol, 1.00 equiv) in ethyl vinyl ether (11.0 mL, 145 mmol, 21.0 equiv) and the mixture was stirred at rt for 18 h. The homogenous solution was concentrated under reduced pressure. Purification by flash chromatography (10:89:1 EtOAc/hexanes/Et_3N) provided the 3-iodopropyl dihydropyran as an approximately 1:1 mixture of ethoxy epimers (2.55 g, 89 % yield over three steps) as a pale yellow oil: ^{1}H NMR (500 MHz, C_6D_6) δ 4.81 (t, *J* = 3.6 Hz, 1H, single diastereomer), 3.74–3.83 (m, 1H), 3.28–3.40 (m, 1H), 2.67–2.84 (m, 2H), 2.54–2.61 (m, 1H), 2.23 (t, *J* = 3.7 Hz, 2H, single diastereomer), 2.02–2.11 (m, 1H), 1.85 (dq, *J* = 5.2, 13.0 Hz, 3H), 1.67–1.76 (m, 3H), 1.54–1.64 (m, 2H), 1.40–1.49 (m, 1H), 1.32–1.37 (m, 1H), 1.25 (dt, *J* = 4.0, 12.2 Hz, 1H), 1.07 (t, *J* = 5.0 Hz, 3H, single diastereomer), 0.89 (s, *J* = 12.2 Hz, 1H), 0.60 (d, *J* = 6.5 Hz, 3H, single diastereomer); ^{13}C NMR (125 MHz, C_6D_6) δ 211.3 (C), 150.3 (C), 110.4 (CH_2), 99.1 (CH), 64.3 (CH_2), 61.8 (C), 48.4 (CH_2), 40.6 (CH_2), 40.1 (CH), 38.9 (CH_2), 37.1 (CH_2), 30.3 (CH_2), 29.4 (C), 27.6 (CH), 22.4 (CH_3), 16.4 (CH_2), 15.9 (CH_2), 7.8 (CH_2); IR (thin film) 2924, 1684, 1380, 1285 cm^{-1}; HRMS-ESI (*m*/*z*) $[M + Na]^+$ calcd for $C_{18}H_{27}IO_3Na$ 441.0903; found, 441.0903. Following the general procedure for the S_N2 reaction with protected hydroxylamines, *N*-(methoxymethoxy)-2-nitrobenzenesulfonamide (0.614 g, 2.34 mmol) and 3-iodopropyl dihydropyran (0.611 g, 2.13 mmol) were converted to **57**. Purification by flash

chromatography (10:1:89 EtOAc/Et_3N/benzene) afforded **57** (1.13 g, 95% yield) as colorless foam. Product **57** was isolated as a 1:1 mixture of ethoxy epimers: ^{1}H NMR (500 MHz, C_6D_6) δ 7.78 (d, *J* = 7.5 Hz, 0.5H), 7.75 (d, *J* = 8.5 Hz, 0.5H), 6.63 (q, *J* = 6.4 Hz, 1H), 6.56 (d, *J* = 13.2 Hz, 1H), 6.53 (m, 1H), 5.07 (d, *J* = 5.1 Hz, 0.5H), 5.04 (d, *J* = 5.0 Hz, 0.5H), 4.97 (d, *J* = 5.0 Hz, 0.5H), 4.94 (d, *J* = 4.9 Hz, 0.5H), 4.81 (m, 1H), 3.78 (m, 1H), 3.36 (m, 1H), 3.10 (br s, 1H), 3.15 (s, 3H), 3.14 (m, 1H), 2.65 (m, 1H), 2.27–2.23 (m, 2H), 1.87 (m, 1H), 1.95–1.57 (m, 8H), 1.48–1.32 (m, 3H), 1.08–1.03 (m, 3H), 0.99–0.88 (m, 1H), 0.66 (d, *J* = 6.5 Hz, 1.5H), 0.63 (d, *J* = 6.5 Hz, 1.5H); ^{13}C NMR (125 MHz, C_6D_6) δ 211.8 (C), 150.4 (C), 135.0 (CH), 132.5 (CH), 130.8 (CH), 128.9 (C), 126.7 (C), 123.9 (CH), 110.3 (CH_2), 103.2 (CH_2), 98.8 (CH), 64.2 (CH_2), 61.8 (C), 57.7 (CH_3), 54.8 (C), 48.5 (CH_2), 40.5 (CH_2), 40.0 (C), 38.5 (CH), 33.2 (CH_2), 29.5 (CH_2), 27.6 (CH), 23.4 (CH_2), 22.4 (CH_3), 16.4 (CH_2), 15.8 (CH_3); IR (thin film) 2927, 2360, 1685, 1548 cm^{-1}; HRMS-ESI (*m*/*z*) [M + Na]$^+$ calcd for $C_{26}H_{36}N_2O_9SNa$ 575.2039; found, 575.2031.

N-(3-((1′*R**,3a′*S**,7a′*R**)-5,7′-Dihydroxy-5′-methyl-2′-oxodecahydro-3*H*-spiro[furan-2,1′-indene]-7a′-yl)propyl)-*N*-(methoxymethoxy)-2-nitrobenzenesulfonamide (58) and Tetracyclic acetal 59

Following the general procedure for the DIBALH reduction–oxidation–acidic rearrangement sequence, dihydropyran **57** (1.13 g, 2.04 mmol) was converted into tetracyclic acetal **58** and tricycle **59**. Purification by column chromatography (1:1 EtOAc/hexanes): Eluting first was tetracyclic acetal **59** (127 mg, 11% yield) as a colorless crystalline solid. Slow evaporation from MeOH afforded single crystals for X-ray analysis: mp 144–145 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (dd, *J* = 1.1, 8.0 Hz, 1H), 7.81 (dt, *J* = 1.2, 7.7 Hz, 1H), 7.73 (dt, *J* = 1.1, 7.8 Hz, 1H), 7.59 (dd, *J* = 0.9, 7.9 Hz, 1H), 5.53 (d, *J* = 4.8 Hz, 1H), 4.97 (dd, *J* = 7.9, 12.4 Hz, 2H), 3.81 (t, *J* = 4.2 Hz, 1H), 3.44 (s, 3H), 3.10 (br m, 2H), 2.55 (dd, *J* = 9.0, 19.3 Hz, 1H), 2.32 (dd, *J* = 3.1, 19.4 Hz, 1H), 2.17–2.00 (m, 2H), 1.95–1.81 (m, 4H), 1.77–1.71 (m, 1H), 1.69–1.63 (m, 2H), 1.50 (td, *J* = 4.1, 14.7 Hz, 1H), 1.43 (br m, 3H), 1.34–1.27 (m, 1H), 1.06 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.3 (C), 156.2 (C), 135.4 (CH), 132.7 (CH), 131.3 (CH), 126.4 (C), 124.0 (CH), 102.9 (CH_2), 98.7 (CH_2), 88.2 (C), 71.7 (CH), 57.8 (CH_3), 54.2 (CH_2), 43.2 (CH), 42.9 (CH), 37.2 (CH_2), 36.8 (CH_2), 35.7 (CH_2), 33.2 (CH_2), 29.5 (CH_2), 27.1 (CH), 24.5 (CH_3), 22.6 (CH_2), 21.3 (C); IR (thin film) 2953, 2917, 2254, 1751, 1547, 1374, 1178 cm^{-1}; HRMS-ESI (*m*/*z*) [M + Na]$^+$ calcd for $C_{24}H_{32}O_9N_2SNa$ 547.1726; found, 547.1722. Eluting second was tricycle **58** (0.773 g, 68% yield) as a colorless foam: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (d, *J* = 7.9 Hz, 1H), 7.82 (t, *J* = 7.7 Hz, 1H), 7.75 (t, *J* = 7.7 Hz, 1H), 7.60 (d, *J* = 7.9 Hz, 1H), 5.57 (dd, *J* = 2.4, 4.6 Hz, 1H), 5.03–4.95 (m, 2H), 4.11 (dq, *J* = 1.7, 7.1 Hz, 1H), 3.88–3.85 (m, 1H), 3.46 (s, 3H), 3.21–3.09 (m, 2H), 2.59–2.52 (m, 1H), 2.41 (dd, *J* = 19.3, 8.0 Hz, 1H), 2.30–2.23 (m, 1H), 2.12–1.91 (m, 4H), 1.90–1.84 (m, 2H), 1.80–1.73 (m, 2H), 1.68–1.61 (m, 1H), 1.55–1.51 (m, 1H), 1.43–1.38 (m, 1H), 1.33 (dt, *J* = 3.3, 9.5 Hz, 1H), 1.26 (dt, *J* = 1.6, 7.1 Hz, 1H), 1.05 (dt, *J* = 4.6, 13.6 Hz, 1H), 0.95 (dd, *J* = 2.4, 6.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 219.4 (C), 150.1 (C), 135.4 (CH), 132.7 (CH), 131.4 (CH), 126.2 (C), 124.1 (CH), 102.9 (CH_2), 100.9 (CH), 92.2 (C), 72.4 (CH), 57.9 (CH_3), 53.9 (CH_2), 49.2 (CH_2), 41.2 (CH_2), 40.7 (CH_2), 39.4 (CH_2), 36.4 (CH), 34.6 (CH_2), 30.5 (CH), 28.9 (CH_2), 28.3 (CH_2), 22.2 (CH_3), 21.5 (C); IR (thin film) 3354, 2953, 1743, 1548, 1374, 1179 cm^{-1}; HRMS-ESI (*m*/*z*) [M + Na]$^+$ calcd for $C_{24}H_{34}N_2O_{10}SNa$ 565.1832; found, 565.1837.

tert-Butyl(2-((1*S**,2*S**,4*R**)-2-(*tert*-butyldimethylsilyloxy)-4-methylcyclopentyl)ethoxy)dimethylsilane

TBSCl (10.6 g, 77.2 mmol, 3.10 equiv) was added in one portion to a solution of diol **62** (3.26 g, 22.7 mmol, 1.00 equiv), imidazole (4.94 g, 72.5 mmol, 3.20 equiv) and DMF (150 mL) at rt and stirred for 15 h. The solution was then partitioned between H_2O (500 mL) and EtOAc (100 mL). The layers were separated and the aqueous phase was extracted with

EtOAc (3 × 150 mL). The combined organic layers were washed with H_2O (150 mL) then brine (100 mL), dried over $MgSO_4$, filtered through a plug of cotton, and concentrated under reduced pressure. Purification by flash chromatography (100% hexanes) afforded *tert*-butyl(2-((1*S*,*2*S*,*4*R**)-2-(*tert*butyldimethylsilyloxy)-4-methylcyclopentyl)ethoxy)dimethylsilane (7.44 g, 88% yield) as a clear colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.09 (s, 1H), 3.66–2.57 (m, 2H), 2.32–2.22 (m, 1H), 1.98–1.91 (m, 1H), 1.79 (dd, *J* = 8.0, 12.0 Hz, 1H), 1.70 (sextet, *J* = 7.0 Hz, 1H), 1.64 (dq, *J* = 3.0, 9.5 Hz, 1H), 1.51–1.44 (m, 1H), 1.29–1.26 (m, 2H), 0.97 (d, *J* = 7.0 Hz, 3H), 0.90 (s, 9H), 0.88 (s, 9H), 0.05 (s, 6H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 76.5 (CH), 62.8 (CH_2), 44.7 (CH_2), 41.4 (CH), 37.5 (CH_2), 33.4 (CH_2), 30.2 (CH), 26.2 (CH_3), 20.0 (CH_3), 22.6 (CH_3), 18.7 (C), 18.4 (C), −4.1 (CH_3), −4.6 (CH_3), −4.9 (CH_3); IR (thin film) 2951, 1462, 1253, 1099, 1051 cm^{-1}; HRMS-ESI (*m*/*z*) $[M + H]^+$ calcd for $C_{20}H_{45}O_2Si_2$ 373.2958; found, 373.2950.

2-((1*S**,2*S**,4*R**)-2-(*tert*-Butyldimethylsilyloxy)-4-methylcyclopentyl)ethanol

A solution of HF•pyridine (8.4 mL, CAUTION! HF is extremely dangerous and caustic; the reaction was carried out in a Nalgene bottle.) was added dropwise to a solution of *tert*-butyl(2-((1*S*,*2*S*,*4*R**)-2-(*tert*-butyldimethylsilyloxy)-4-methylcyclopentyl)ethoxy)dimethylsilane (4.78 g, 11.2 mmol, 1.0 equiv), THF (110 mL) and pyridine (11 mL) at 0 °C. After stirring for 10 min the solution was warmed to rt and stirred for 1.5 h. The reaction was quenched with sat. aq. $NaHCO_3$ (100 mL) and the solution was extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with sat. aq. $CuSO_4$ (50 mL), followed by H_2O (2 × 100 mL), and brine (100 mL). The organic phase was dried over $MgSO_4$, filtered through a plug of cotton, and concentrated under reduced pressure. Purification by flash chromatography (1:9 EtOAc/hexanes) provided 2-((1*S*,*2*S*,*4*R**)-2-(*tert*-butyldimethylsilyloxy)-4-methylcyclopentyl)ethanol (2.12 g, 73% yield) as a pale yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.15–1.13 (m, 1H), 3.70–3.60 (m, 2H), 2.26 (sextet, *J* = 7.0 Hz, 1H), 2.02–1.95 (m, 1H), 1.83 (dd, *J* = 2.0, 8.0 Hz, 1H), 1.81–1.74 (m, 1H), 1.69–1.63 (m, 1H), 1.56 (sextet, *J* = 6.5 Hz, 1H), 1.52 (br s, 1H), 1.34–1.25 (m, 1H), 0.97 (d, *J* = 7.0 Hz, 3H), 0.88 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 76.4 (CH), 62.6 (CH_2), 44.3 (CH_2), 41.8 (CH), 37.7 (CH_2), 33.5 (CH_2), 30.1 (CH), 26.1 (CH_3), 22.6 (CH_3), 18.4 (C), −4.1 (CH_3), −4.7 (CH_3); IR (thin film) 3342, 2952, 2858, 1253, 1051 cm^{-1}; HRMS-ESI (*m*/*z*) $[M + H]^+$ calcd for $C_{14}H_{31}O_2Si$ 259.2093; found, 259.2090.

tert-Butyl((1*S**,2*S**,4*R**)-2-(2,2-dimethoxyethyl)-4-methylcyclopentyloxy)dimethylsilane

A solution of DMSO (0.89 mL, 12.5 mmol, 2.7 equiv) in CH_2Cl_2 (3 mL) was slowly added dropwise (keeping the internal temperature below −60 °C) to a solution of oxalyl chloride (0.50 mL, 6.0 mmol, 1.3 equiv) in CH_2Cl_2 (23 mL) at −78 °C. The resulting solution was stirred for 15 min at −78 °C and then a solution of 2-((1*S*,*2*S*,*4*R**)-2-(*tert*-butyldimethylsilyloxy)-4-methylcyclopentyl)ethanol (1.2 g, 4.6 mmol, 1.0 equiv) was added dropwise and the solution was stirred for 40 min. Et_3N (3.3 mL, 23.0 mmol, 5.0 equiv) was added at −78 °C and stirred for 10 min before warming to 0 °C. The solution was stirred at 0 °C for 1 h and then partitioned between sat. aq. $NaHCO_3$ (75 mL) and CH_2Cl_2 (100 mL). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with brine (75 mL), dried over $MgSO_4$, filtered through a plug of cotton, and concentrated under reduced pressure to afford the corresponding aldehyde (1.93 g, 92% yield). Pyridinium *p*-toluenesulfonate (11 mg, 0.044 mmol, 0.005 equiv) was added to a solution of the aldehyde (2.27 g, 8.85 mmol, 1.00 equiv), trimethylorthoformate (14.5 mL, 133 mmol, 15.0 equiv) and CH_2Cl_2 (30 mL) and stirred at rt for 7 h. The solution was filtered through a plug of Florisil® and eluted with Et_2O. The eluent was concentrated under reduced pressure to afford *tert*-butyl((1*S*,*2*S*,*4*R**)-2-(2,2-

dimethoxyethyl)-4-methylcyclopentyloxy)dimethylsilane (2.53 g, 94% yield) as a clear colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.40 (t, *J* = 6.0 Hz, 1H), 4.11 (t, *J* = 4.0 Hz, 1H), 3.32 (s, 3H), 3.31 (s, 3H), 2.35–2.22 (m, 1H), 1.96–1.91 (m, 1H), 1.82–1.77 (m, 2H), 1.58 (q, *J* = 5.5 Hz, 1H), 1.55–1.51 (m, 1H), 1.33–1.30 (m, 1H), 1.24–1.21 (m, 1H), 0.98 (d, *J* = 7.0 Hz, 3H), 0.88 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 104.2 (CH), 76.4 (CH), 53.0 (CH_3), 52.5 (CH_3), 44.7 (CH_2), 40.7 (CH), 37.6 (CH_2), 32.9 (CH_2), 30.2 (CH), 26.1 (CH_3), 22.5 (CH_3), 18.3 (C), −4.1 (CH_3), −4.6 (CH_3); IR (thin film) 2953, 1472, 1463, 1253, 1127, 1054 cm^{-1}; HRMS-ESI (*m*/*z*) [M + Na]$^+$ calcd for $C_{16}H_{34}O_3SiNa$ 325.2174; found, 325.2166.

(1*S**,2*S**,4*R**)-2-(2,2-Dimethoxyethyl)-4-methylcyclopentanol

A 1 M solution of TBAF in THF (15 mL, 15 mmol) was added to neat *tert*-butyl((1*S**,2*S**,4*R**)-2-(2,2-dimethoxyethyl)-4-methylcyclopentyloxy)dimethylsilane (0.890 g, 2.94 mmol) and heated to 50 °C for 2 h. After cooling to room temperature the solution was partitioned between Et_2O (30 mL) and brine (30 mL). The layers were separated and the aqueous phase was extracted with Et_2O (3 × 30 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered through a plug of cotton, and concentrated under reduced pressure. Purification by flash chromatography (3:7 EtOAc/hexanes) afforded (1*S**,2*S**,4*R**)-2-(2,2-dimethoxyethyl)-4-methylcyclopentanol (0.462 g, 84% yield) as a clear colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.42 (dd, *J* = 3.0, 7.0 Hz, 1H), 4.14 (t, *J* = 4.5 Hz, 1H), 3.39 (s, 3H), 3.32 (s, 3H), 2.45 (br s, 1H), 2.31 (m, 1H), 2.02 (m, 1H), 1.91 (dd, *J* = 8.0, 14.0 Hz, 1H), 1.81 (dt, *J* = 7.0, 10.0 Hz, 1H), 1.71–1.68 (m, 1H), 1.62 (q, *J* = 9.5 Hz, 1H), 1.38–1.32 (m, 2H), 0.97 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 105.1 (CH), 74.9 (CH), 54.9 (CH_3), 52.2 (CH_3), 43.7 (CH_2), 40.9 (CH), 38.5 (CH_2), 33.2 (CH_3), 30.3 (CH), 22.4 (CH_3); IR (thin film) 3436, 2950, 2867, 1656, 1454 cm^{-1}; HRMS-ESI (*m*/*z*) [M + Na]$^+$ calcd for $C_{10}H_{20}O_3Na$ 211.1310; found, 211.1306.

(2*S**,4*R**)-2-(2,2-Dimethoxyethyl)-4-methylcyclopentanone

A solution of DMSO (470 μL, 6.6 mmol) in CH_2Cl_2 (1.5 mL) was slowly added dropwise (maintaining an internal temperature below −50 °C during the addition) to a solution of oxalyl chloride (270 μL, 3.2 mmol) in CH_2Cl_2 (12 mL) at −78 °C. After completion of the addition the solution was stirred for 15 min at −78 °C and then a solution of (1*S**,2*S**,4*R**)-2-(2,2-dimethoxyethyl)-4-methylcyclopentanol (0.462 g, 2.46 mmol) in CH_2Cl_2 (10 mL) was added slowly and stirred for 45 min at −78 °C. EtN(*i*-Pr)$_2$ (2.14 mL, 12.3 mmol) was added and stirred at −78 °C for 15 min and then allowed to warm to 0 °C over 1 h. The cold solution was quenched with pH 7 buffer (20 mL) and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$, filtered through a plug of cotton, and concentrated under reduced pressure. Purification by flash chromatography (3:7 EtOAc/hexanes) provided (2*S**,4*R**)-2-(2,2-dimethoxyethyl)-4-methylcyclopentanone (0.398 g, 87% yield) as a clear colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.47 (t, *J* = 5.5 Hz, 1H), 3.29 (s, 3H), 3.28 (s, 3H), 2.34–2.29 (m, 3H), 1.98 (td, *J* = 5.0, 14.0 Hz, 1H), 1.90 (dd, *J* = 0.5, 14.0 Hz, 1H), 1.88–1.77 (m, 2H), 1.51 (m, 1H), 1.05 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 221.2 (C), 103.1 (CH), 53.4 (CH_3), 52.7 (CH_3), 46.4 (CH_2), 42.9 (CH), 37.3 (CH_2), 33.4 (CH_2), 28.3 (CH), 20.9 (CH_3); IR (thin film) 2955, 1738, 1455 cm^{-1}; HRMS-ESI (*m*/*z*) [M + Na]$^+$ calcd for $C_{10}H_{18}O_3Na$ 209.1154; found, 209.1159.

(1*S**,2*S**,4*R**)-1-((*E*)-6-(*tert*-Butyldiphenylsilyloxy)-1-phenoxyhex-2-en-3-yl)-2-(2,2-dimethoxyethyl)-4-methylcyclopentanol

Following the general vinylcerium addition procedure, vinyl iodide **13**[5] (1.79 g, 3.21 mmol, 1.50 equiv) was added to (2*S**,4*R**)-2-(2,2-dimethoxyethyl)-4-methylcyclopentanone (398

mg, 2.14 mmol, 1.00 equiv) to provide (1*S**,2*S**,4*R**)-1-((*E*)-6-(*tert*butyldiphenylsilyloxy)-1-phenoxyhex-2-en-3-yl)-2-(2,2-dimethoxyethyl)-4-methylcyclopentanol. Purification by column chromatography (24:1:75 EtOAc/Et_3N/hexanes) provided (1*S**,2*S**,4*R**)-1-((*E*)-6-(*tert*-butyldiphenylsilyloxy)-1-phenoxyhex-2-en-3-yl)-2-(2,2-dimethoxyethyl)-4-methylcyclopentanol (887 mg, 67% yield) as a clear colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, *J* = 6.8 Hz, 4H), 7.45 (t, *J* = 7.4 Hz, 2H), 7.40 (t, *J* = 7.4 Hz, 4H), 7.28 (t, *J* = 7.4 Hz, 2H), 6.95 (t, *J* = 7.3 Hz, 1H), 6.91 (d, *J* = 7.7 Hz, 2H), 5.94 (dt, *J* = 2.5, 6.2 Hz, 1H), 4.63 (d, *J* = 6.3 Hz, 2H), 4.40–4.38 (m, 1H), 3.72 (t, *J* = 5.6 Hz, 2H), 3.31 (s, 3H), 3.28 (s, 3H), 2.43–2.38 (m, 1H), 2.33–2.15 (m, 3H), 1.85–1.75 (m, 4H), 1.73–1.68 (m, 2H), 1.59–1.50 (m, 3H), 1.10 (s, 9H), 1.04 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.0 (C), 147.1 (C), 135.8 (CH), 134.0 (C), 129.9 (CH), 129.7 (CH), 127.9 (CH), 120.9 (CH), 114.9 (CH), 104.2 (CH), 86.1 (C), 77.5 (CH), 65.2 (CH_2), 64.1 (CH_2), 53.0 (CH_3), 52.9 (CH_3), 49.1 (CH_2), 41.5 (CH), 38.9 (CH_2), 33.9 (CH_2), 32.4 (CH_2), 30.4 (CH), 27.1 (CH_3), 25.3 (CH_2), 22.1 (CH_3), 19.5 (C); IR (thin film) 3462, 3070, 2950, 1599, 1239, 1111 cm^{-1}; HRMS-ESI (*m*/*z*) $[M + Na]^+$ calcd for $C_{38}H_{52}O_5SiNa$ 639.3481; found, 639.3486.

tert-Butyl((*E*)-4-((1*S**,2*S**,4*R**)-2-(2,2-dimethoxyethyl)-4-methyl-1-(trimethylsilyloxy)cyclopentyl)-6-phenoxyhex-4-enyloxy)diphenylsilane (66a)

A solution of tetra-*n*-butylammonium fluoride in THF (13 μL, 0.013 mmol, 1.0 M, 0.01 equiv) was added dropwise to a solution of (1*S**,2*S**,4*R**)-1-((*E*)-6-(*tert*-butyldiphenylsilyloxy)-1-phenoxyhex-2-en-3-yl)-2-(2,2-dimethoxyethyl)-4-methylcyclopentanol (874 mg, 1.42 mmol, 1.0 equiv), TMS-imidazole (420 μL, 2.8 mmol, 2.0 equiv), and DMF (3.6 mL) and stirred at rt for 3 h. The solution was partitioned between water (50 mL) and Et_2O (25 mL). The layers were separated and the aqueous phase was extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with water (50 mL) then brine (50 mL), dried over $MgSO_4$, filtered through a plug of cotton, and concentrated under reduced pressure. Purification by flash chromatography (1:5:94 Et_3N/EtOAc/hexanes) afforded alkene acetal **66a** (759 mg, 77% yield) as a clear colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, *J* = 7.8 Hz, 4H), 7.44–7.41 (m, 2H), 7.38 (t, *J* = 6.9 Hz, 4H), 7.26 (t, *J* = 8.2 Hz, 2H), 6.92 (t, *J* = 7.2 Hz, 1H), 6.88 (d, *J* = 7.9 Hz, 2H), 5.83 (t, *J* = 6.4 Hz, 1H), 4.63–4.56 (m, 3H), 4.37 (dd, *J* = 4.2, 6.8 Hz, 1H), 3.68 (t, *J* = 5.7 Hz, 3H), 2.32–2.26 (m, 3H), 1.98–1.90 (m, 2H), 1.82 (dt, *J* = 3.2, 9.9 Hz, 1H), 1.76–1.64 (m, 4H), 1.59–1.51 (m, 2H), 1.48–1.35 (m, 2H), 1.22 (t, *J* = 7.0 Hz, 2H), 1.09 (s, 9H), 1.01 (d, *J* = 6.9 Hz, 3H), 0.09 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.1 (C), 145.6 (C), 135.8 (CH), 134.1 (C), 129.9 (CH), 129.8 (CH), 127.9 (CH), 122.6 (CH), 120.9 (CH), 115.1 (CH), 104.4 (CH), 89.3 (C), 77.2 (CH), 65.2 (CH_2), 64.1 (CH_2), 53.5 (CH_3), 51.8 (CH_3), 45.7 (CH_2), 43.3 (CH), 38.2 (CH_2), 33.1 (CH_2), 30.1 (CH), 27.2 (CH_3), 25.6 (CH_2), 23.7 (CH_3), 19.5 (C), 2.6 (CH_3); IR (thin film) 3071, 2954, 2860, 1599, 1250, 1112, 1078 cm^{-1}; HRMS-ESI (*m*/*z*) $[M + Na]^+$ calcd for $C_{41}H_{60}O_5Si_2Na$ 711.3877; found, 711.3867.

tert-Butyl((*E*)-4-((1*S**,2*S**,4*R**)-2-(2,2-dimethoxyethyl)-4-methyl-1-(triethylsilyloxy)cyclopentyl)-6-phenoxyhex-4-enyloxy)diphenylsilane (66)

Pyridinium *p*-toluenesulfonate (1.0 mg) was added to a stirring solution of aldehyde **65**[5] (356 mg, 0.510 mmol, 1.00 equiv), trimethylorthoformate (840 μL, 7.6 mmol), and CH_2Cl_2 (1.7 mL) and stirred at rt for 5 h. The solution was eluted through a plug of silica gel and flushed with CH_2Cl_2. The solution was concentrated under reduced pressure to provide dimethyl acetal **66** (272 mg, 73% yield) as a clear colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, *J* = 7.2 Hz, 4H), 7.42 (t, *J* = 7.3 Hz, 2H), 7.37 (t, *J* = 7.3 Hz, 4H), 7.25 (d, *J* = 8.0 Hz, 2H), 6.92 (t, *J* = 7.0 Hz, 1H), 6.87 (d, *J* = 8.2 Hz, 2H), 5.85 (t, *J* = 6.4 Hz, 1H), 4.59 (t, *J* = 6.0 Hz, 2H), 4.34 (dd, *J* = 4.2, 7.7 Hz, 1H), 3.67 (t, *J* = 5.7 Hz, 2H), 3.28 (s, 3H), 3.21 (s, 3H), 2.30–2.26 (m, 2H), 1.89 (dd, *J* = 7.6, 13.8 Hz, 1H), 1.85–1.80 (m, 1H), 1.77–1.71 (m,

1H), 1.70–1.62 (m, 2H), 1.49–1.35 (m, 2H), 1.06 (s, 9H), 1.00 (d, *J* = 7.0 Hz, 3H), 0.92 (t, *J* = 7.9 Hz, 12H), 0.58 (q, *J* = 7.8 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.1 (C), 145.5 (CH), 135.8 (C), 134.1 (CH), 129.9 (CH), 129.6 (CH), 127.9 (CH), 122.3 (CH), 120.7 (CH), 115.0 (CH), 104.3 (CH), 89.0 (C), 65.0 (CH_2), 64.2 (CH_2), 53.4 (CH_3), 51.8 (CH_3), 46.3 (CH_2), 43.6 (CH), 38.4 (CH_2), 33.8 (CH_2), 31.3 (CH_2), 30.1 (CH), 27.2 (CH_3), 25.6 (CH_2), 22.8 (CH_3), 19.5 (c), 7.6 (CH_3), 7.1 (CH_2); IR (thin film) 2953, 2873, 1598, 1110 cm^{-1}; HRMS-ESI (*m*/*z*) $[M + Na]^+$ calcd for $C_{44}H_{66}O_5Si_2Na$ 753.4346; found, 753.4332.

(2*S**,3*S**,3a*S**,7a*S**)-3a-(3-(*tert*-Butyldiphenylsilyloxy)propyl)-2-methoxy-6-methyl-3-(phenoxymethyl)hexahydro-1*H*-inden-4(2*H*)-one (53α)

A 1 M solution of $TiCl_4$ in CH_2Cl_2 (34 μL, 0.061 mmol, 0.5 equiv) was added to a solution of dimethyl acetal **66** (0.050 g, 0.068 mmol, 1.0 equiv) in CH_2Cl_2 (1.4 mL) at −78 °C. The red solution was allowed to warm to −20 °C and stirred for 20 min. The solution was quenched at −20 °C by addition of triethylamine (77 μL, 0.55 mmol, 8.0 equiv) followed by MeOH (23 μL, 0.55 mmol, 8.0 equiv) resulting in the disappearance of color. The cold solution was partitioned between sat. aq. $NaHCO_3$ (10 mL) and CH_2Cl_2 (5 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 7 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered through a plug of cotton, and concentrated under reduced pressure. Purification by column chromatography (1:4 EtOAc/hexanes) afforded hydrindanones **53α** and **53β** (17 mg, 42% yield combined, 2.2:1 dr α:β) as a clear colorless oils. **53α:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (d, *J* = 7.1 Hz, 4H), 7.43–7.34 (m, 6H), 7.25 (t, *J* = 8.0 Hz, 2H), 6.92 (t, *J* = 7.3 Hz, 1H), 6.87 (d, *J* = 8.3 Hz, 2H), 4.16 (dd, *J* = 7.0, 9.4 Hz, 1H), 4.03 (dd, *J* = 5.5, 9.4 Hz, 1H), 3.80 (q, *J* = 5.5 Hz, 1H), 3.65 (m, 1H), 3.55 (m, 1H), 3.28 (s, 3H), 2.87 (q, *J* = 5.9 Hz, 1H), 2.62 (dq, *J* = 2.7, 5.7 Hz, 1H), 2.40 (q, *J* = 9.6 Hz, 1H), 2.00 (q, *J* = 8.6 Hz, 2H), 1.94 (ddd, *J* = 5.1, 9.3, 13.6 Hz, 1H), 1.85 (dt, *J* = 4.0, 13.1 Hz, 1H), 1.71–1.60 (m, 3H), 1.56–1.47 (m, 2H), 1.31 (m, 1H), 1.04 (s, 9H), 1.01 (d, *J* = 5.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 215.6 (C), 159.2 (C), 135.8 (CH), 134.2 (C), 129.8 (CH), 129.6 (CH), 127.9 (CH), 120.7 (CH), 114.8 (CH), 80.9 (CH), 64.1 (CH_2), 63.8 (CH_2), 58.1 (C), 57.7 (CH_3), 48.2 (CH_2), 46.9 (CH), 42.9 (CH), 36.0 (CH_2), 35.3 (CH_2), 30.6 (CH_2), 28.9 (CH_2), 28.4 (CH), 27.1 (CH_3), 22.3 (CH_3), 19.5 (C); IR (thin film) 3070, 2952, 2857, 1699, 1600, 1244, 1111 cm^{-1}; HRMS-ESI (*m*/*z*) $[M + Na]^+$ calcd for $C_{37}H_{48}O_4SiNa$ 607.3220; found, 607.3224.

tert-Butyl((*E*)-4-((3a*S**,5*R**,6a*S**)-2-methoxy-5-methylhexahydro-2*H*-cyclopenta[*b*]furan-6a-yl)-6-phenoxyhex-4-enyloxy)diphenylsilane

A 1 M solution of TMSOTf in CH_2Cl_2 (50μL, 0.05 mmol, 0.98 equiv) was added to a solution of acetal **66** (35mg, 0.051 mmol, 1.0 equiv), 2,6-di-*tert*-butyl-4-methylpyridine (21 mg, 0.10 mmol, 2.0 equiv), and CH_2Cl_2 (1.1 mL) at −78 °C. The solution was allowed to warm to −20 °C and stirred for 20 min. The solution was quenched at −20 °C by adding triethylamine (42 μL, 0.41 mmol) and then the cold solution was partitioned between sat. aq. $NaHCO_3$ (10 mL) and CH_2Cl_2 (5 mL). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered through a plug of cotton, and concentrated under reduced pressure. Purification by column chromatography (1:9 EtOAc/hexanes) afforded *tert*-butyl((*E*)-4-((3a*S**,5*R**,6a*S**)-2-methoxy-5-methylhexahydro-2*H*-cyclopenta[*b*]furan-6a-yl)-6-phenoxyhex-4-enyloxy)diphenylsilane (25 mg, 83% yield) as a clear colorless oil. Isolated as an approximately 1:1 mixture of methoxy epimers: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, *J* = 6.7 Hz, 8H), 7.43 (m, 4H), 7.37 (t, *J* = 7.3 Hz, 8H), 7.24 (m, 4H), 6.95–6.90 (m, 2H), 6.89 (d, *J* = 8.6 Hz, 4H), 5.89 (t, *J* = 6.3 Hz, 1H, single diastereomer), 5.83 (t, *J* = 6.3 Hz, 1H, single diastereomer), 5.06 (dd, *J* = 2.1, 5.3 Hz, 1H), 5.00 (d, *J* = 4.5 Hz, 1H), 4.58 (m, 4H), 3.70 (q, *J* = 4.3 Hz, 4H), 3.37 (s, 3H, single diastereomer), 3.31 (s, 3H, single diastereomer), 2.84 (q, *J* = 8.5 Hz, 1H), 2.51 (t, *J* = 7.4 Hz,

1H), 2.31–2.04 (m, 6H), 2.02–1.91 (m, 2H), 1.82–1.61 (m, 6H), 1.46–1.32 (m, 4H), 1.28–1.23 (m, 4H), 1.08 (s, 9H, single diastereomer), 1.07 (s, 9H, single diastereomer), 1.00 (d, J = 6.4 Hz, 3H, single diastereomer), 0.99 (d, J = 6.4 Hz, 3H, single diastereomer); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.1 (C), 147.5 (C), 146.1 (C), 135.8 (CH), 134.1 (C), 129.9 (CH), 129.6 (CH), 127.9 (CH), 120.9 (CH), 119.6 (CH), 119.3 (CH), 115.0 (CH), 106.9 (CH), 106.5 (CH), 99.7 (C), 98.2 (C), 65.3 (CH_3), 64.2 (CH_3), 55.8 (CH_2), 55.5 (CH_2), 49.9 (CH), 47.2 (CH), 45.6 (CH_2), 44.9 (CH_2), 43.3 (CH), 42.9 (CH), 41.7 (CH), 40.5 (CH), 33.8 (CH), 32.2 (CH_2), 27.1 (CH_2), 25.8 (CH_3), 19.6 (CH_2), 19.0 (CH_2); IR (thin film) 3070, 2952, 2858, 1599, 1496, 1240, 1111 cm^{-1}; HRMS-ESI (m/z) [M + Na]$^+$ calcd for $C_{37}H_{48}O_4SiNa$ 607.3220; found, 607.3220.

(3a*S**,5*R**,6a*S**)-5-Methylhexahydro-2*H*-cyclopenta[*b*]furan-2-one (67)

Bu_3SnH (3.24 mL, 12.03 mmol, 1.60 equiv) was added dropwise to a solution of iodolactone **61**[5] (2.00 g, 7.52 mmol, 1.00 equiv), AIBN (123 mg, 0.75 mmol, 0.100 equiv), and benzene (25 mL) and the solution was heated to reflux for 1 h. After cooling to rt NaF (947 mg, 22.56 mmol, 3.00 equiv) was added and stirred for 1 h. The heterogeneous suspension was loaded directly onto a silica gel column. Purification by flash chromatography (100% hexanes → 1:3 EtOAc/hexanes) afforded lactone **67** (1.02 g, 97% yield) as a clear colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.01 (t, J = 6.4 Hz, 1H), 2.98 (q, J = 8.9 Hz, 1H), 2.83 (dd, J = 10.8, 18.5 Hz, 1H), 2.27 (dd, J = 3.2, 18.5 Hz, 1H), 2.20–2.11 (m, 2H), 1.73–1.65 (m, 1H), 1.49–1.42 (m, 1H), 1.34–1.25 (m, 1H), 1.03 (d, J = 6.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.2 (C), 86.9 (CH), 42.5 (CH_2), 42.3 (CH_2), 37.9 (CH), 36.7 (CH_2), 31.6 (CH), 18.9 (CH_3); IR (thin film) 2955, 1775, 1172 cm^{-1}; HRMS-ESI (m/z) [M + Na]$^+$ calcd for $C_8H_{12}O_2Na$ 163.0735; found, 163.0733.

2-((1*S**,2*S**,4*R**)-2-Hydroxy-4-methylcyclopentyl)-1-(pyrrolidin-1-yl)ethanone

Lactone **67** (1.05 g, 7.49 mmol, 1.00 equiv) and pyrrolidine (6.26 mL, 75.0 mmol, 10.1 equiv) were diluted in toluene and heated to 110 °C for 16 h. After cooling to rt the solution was concentrated under reduced pressure. Purification by flash chromatography (100% EtOAc) eluted first recovered starting material **67** (259 mg, 14% recovery), followed by 2-((1*S**,2*S**,4*R**)-2-hydroxy-4-methylcyclopentyl)-1-(pyrrolidin-1-yl)ethanone (1.36 g, 86% yield) as a clear colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.24 (s, 1H), 3.78 (s, 1H), 3.44 (m, 4H), 2.49–2.39 (m, 2H), 2.35–2.27 (m, 2H), 1.93 (pentet, J = 6.7 Hz, 2H), 1.87–1.81 (m, 3H), 1.61 (dt, J = 8.5, 12.8 Hz, 1H), 1.39 (m, 2H), 0.94 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.6 (C), 74.4 (CH), 47.1 (CH_2), 45.7 (CH_2), 43.2 (CH_2), 40.7 (CH), 38.7 (CH_2), 35.3 (CH_2), 30.6 (CH), 26.1 (CH_2), 24.5 (CH_2), 21.7 (CH_3); IR (thin film) 3418, 2950, 2868, 1619, 1452 cm^{-1}; HRMS-ESI (m/z) [M + Na]$^+$ calcd for $C_{12}H_{21}NO_2Na$ 234.1470; found, 234.1466.

(2*S**,4*R**)-4-Methyl-2-(2-oxo-2-(pyrrolidin-1-yl)ethyl)cyclopentanone (68)

Dess–Martin periodinane[28] (1.51 g, 3.56 mmol, 1.50 equiv) was added to a solution solution of 2-((1*S**,2*S**,4*R**)-2-hydroxy-4-methylcyclopentyl)-1-(pyrrolidin-1-yl)ethanone (496 mg, 2.37 mmol, 1.0 equiv) in CH_2Cl_2 (12 mL). The suspension was stirred vigorously at room temperature for 30 min then treated with 10% aq. $Na_2S_2O_3$ (5 mL) and stirred for 15 min. The biphasic solution was partitioned between sat. aq. $NaHCO_3$ (10 mL) and CH_2Cl_2 (10 mL). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (20 mL) dried over $MgSO_4$, filtered through a plug of cotton, and concentrated under reduced pressure. Purification by flash chromatography (4:1 EtOAc/hexanes) provided cyclopentanone **68** (413 mg, 83% yield) as a clear colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.44 (t, J = 6.9 Hz, 2H), 3.38 (m, 2H), 2.69 (t, J = 8.8 Hz, 1H), 2.64 (dd, J = 3.4, 15.4 Hz, 1H), 2.53 (dd, J = 8.1, 17.9 Hz,

1H), 2.49–2.41 (m, 2H), 2.01–1.92 (m, 5H), 1.84 (pentet, J = 6.6 Hz, 2H), 1.09 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 221.6 (C), 169.5 (C), 46.8 (CH_2), 46.4 (CH_2), 45.9 (CH_2), 42.9 (CH_3), 36.8 (CH_2), 35.4 (CH_2), 28.1 (CH), 26.4 (CH_2), 24.6 (CH_2), 21.3 (CH_3); IR (thin film) 3485, 2955, 2873, 1734, 1634, 1450 cm^{-1}; HRMS-ESI (m/z) $[M + Na]^+$ calcd for $C_{12}H_{19}NO_2Na$ 232.1313; found, 232.1306.

2-((1*S**,2*S**,4*R**)-2-((*E*)-6-(*tert*-Butyldiphenylsilyloxy)-1-phenoxyhex-2-en-3-yl)-4-methyl-2-(triethylsilyloxy)cyclopentyl)-1-(pyrrolidin-1-yl)ethanone (69)

Following the general procedure for vinylcerium addition, vinyl iodide **13**[5] (1.65 g, 2.96 mmol, 1.50 equiv) was added to cyclopentanone **68** (0.412 g, 1.97 mmol, 1.00 equiv) to provide the tertiary allylic alcohol. Purification by flash chromatography (3:2 EtOAc/hexanes) provided the tertiary alcohol contaminated with residual cyclopentanone **68**. The mixture was carried forward to the next step. TESOTf (740 μL, 3.3 mmol, 3.0 equiv) was added dropwise to a solution of the tertiary allylic alcohol (0.70 g, 1.1 mmol, 1.0 equiv) and 2,6-lutidine (765 μL, 6.56 mmol, 6.00 equiv) in CH_2Cl_2 (6.1 mL) at 0 °C. The solution was stirred for 1 h and then partitioned between sat. aq. $NaHCO_3$ (20 mL) and CH_2Cl_2 (15 mL). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered through a plug of cotton, and concentrated under reduced pressure. Purification by flash chromatography (3:7 EtOAc/hexanes) afforded silyl ether **69** (0.36 g, 43% yield over 2 steps) as a clear colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, J = 7.5 Hz, 4H), 7.41 (t, J = 7.2 Hz, 2H), 7.37 (t, J = 7.6 Hz, 4H), 7.24, (t, J = 8.2 Hz, 2H), 6.91 (t, J = 7.3 Hz, 1H), 6.85 (d, J = 7.9 Hz, 2H), 5.77 (t, J = 6.5 Hz, 1H), 4.60 (dq, J = 6.7, 14.1 Hz, 2H), 3.67 (t, J = 5.3 Hz, 2H), 3.40 (q, J = 6.0 Hz, 2H), 3.28 (m, 1H), 3.21 (m, 1H), 2.35–2.25 (m, 4H), 2.07 (dd, J = 9.3, 15.8 Hz, 1H), 1.98 (dt, J = 4.2, 12.3 Hz, 1H), 1.92–1.86 (m, 3H), 1.81 (q, J = 6.8 Hz, 2H), 1.71–1.56 (m, 5H), 1.06 (s, 9H), 1.01 (d, J = 6.8 Hz, 3H), 0.94 (t, J = 7.8 Hz, 9H), 0.60 (q, J = 7.6 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.1 (C), 158.9 (C), 145.7 (C), 135.9 (CH), 134.0 (C), 129.9 (CH), 129.6 (CH), 127.9 (CH), 122.0 (CH), 120.7 (CH), 115.1 (CH), 88.9 (C), 65.1 (CH_2), 64.1 (CH_2), 46.7 (CH_2), 46.1 (CH_2), 45.7 (CH_2), 44.2 (CH), 38.6 (CH_2), 34.0 (CH_2), 33.8 (CH_2), 30.2 (CH_3), 27.2 (CH), 26.4 (CH_2), 25.9 (CH_2), 24.7 (CH_2), 22.6 (CH_3), 19.5 (C), 7.6 (CH_3), 7.0 (CH_2); IR (thin film) 3067, 2952, 2872, 1643, 1599 cm^{-1}; HRMS-ESI (m/z) $[M + Na]^+$ calcd for $C_{46}H_{67}O_4Si_2NNa$ 776.4506; found, 776.4487.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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52. Conducting the Saegusa oxidation with a catalytic amount of $Pd(OAc)_2$, or in the absence of an oxygen atmosphere, provided lower yields.

53. A variety of other Cu-, Ni-, and Pd-promoted conjugate addition procedures were also examined, with all giving largely or exclusively the undesired product **53**.

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86. A sample of natural sieboldine A is apparently no longer available.

87. Commercially obtained *s*-BuLi was filtered through a PTFE filter prior to titration and use.

88. The slurry was prepared by vigorously stirring anhydrous $CeCl_3$, anhydrous LiCl, and THF for 2 h at rt under a N_2 atmosphere immediately prior to use.

89. TMSCl was freshly distilled prior to use over CaH_2.

90. Sodium iodide was dried overnight in a vacuum oven at 100 °C, 40 mmHg, and weighed quickly on the benchtop prior to use.

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96. PhSH was distilled prior to use.

97. Prior to use in this reaction, the PhSH solution in DMF was sparged with Ar for 30 min.

98. Buffered SiO_2 was prepared by mixing pH 7 buffer (7% by wt) with dry SiO_2 and tumbling overnight.

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100. DBU was dried by distillation from CaH_2 prior to use.

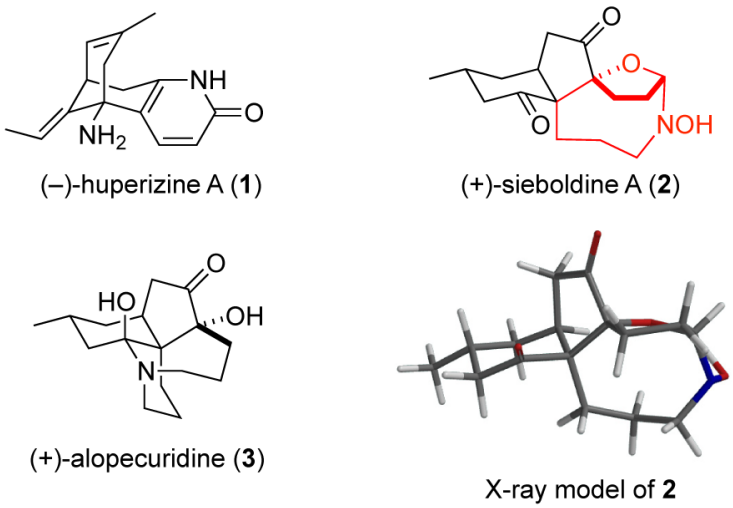


Figure 1.
Structure of (−)-Huperizine A, (+)-Sieboldine A and (+)-Alopecuridine and X-ray Model[4] of (+)-sieboldine A.

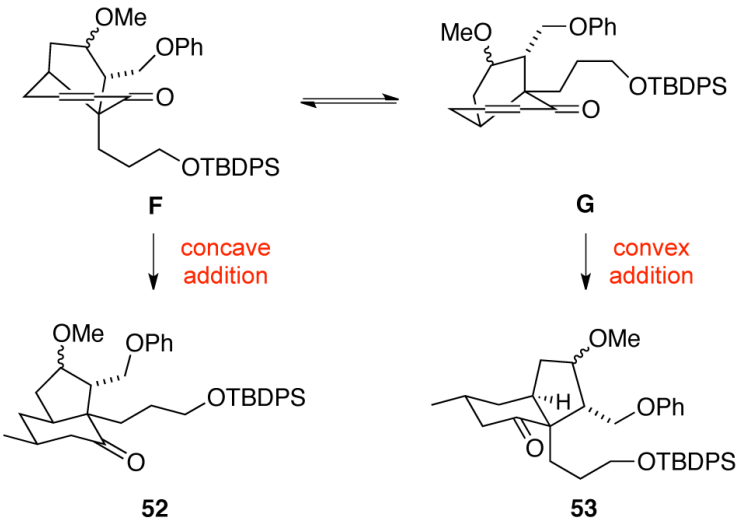


Figure 2.
Products Arising by Axial Addition of Methyl to the Two Conformers of a cis-Hydrindenone Intermediate.

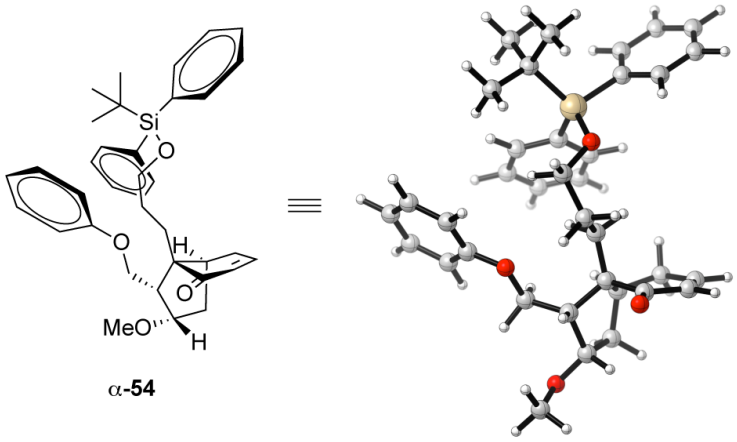
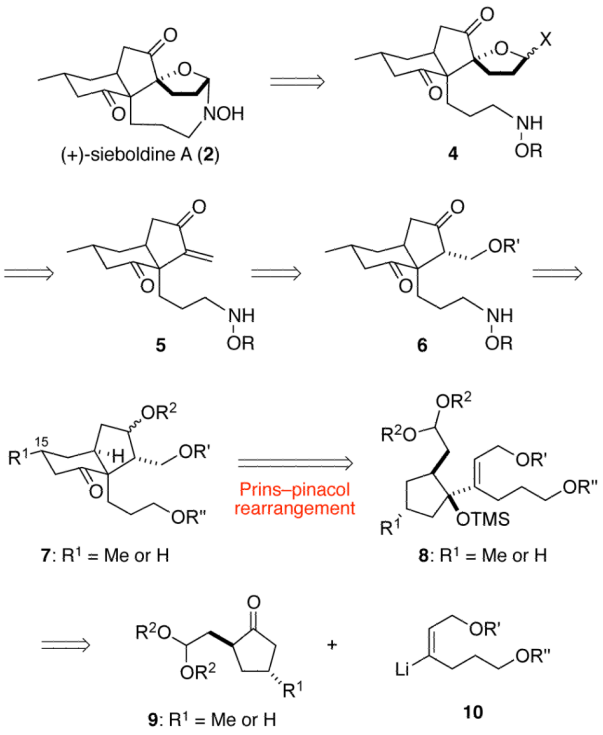
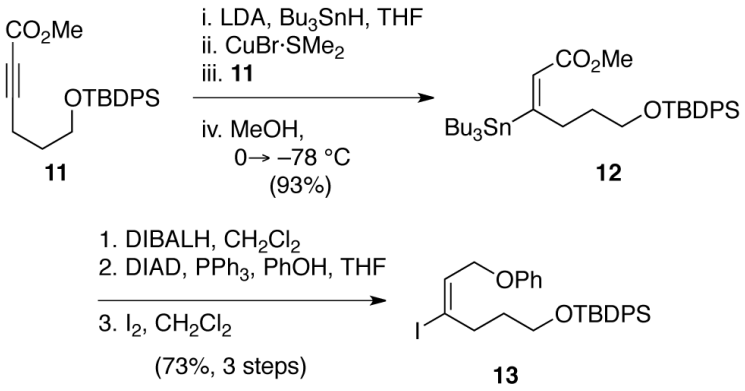


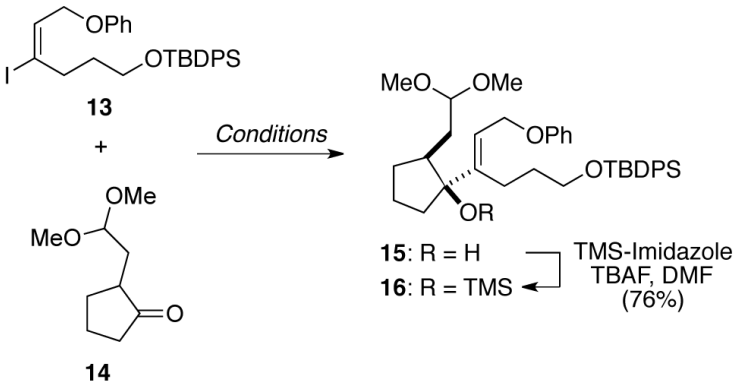
Figure 3.
A Low-Energy Conformer of *cis*-Hydrindenone **α-54** Showing Shielding of the Proximal Face of the Enone by the 3-(*tert*-Butyldiphenylsiloxy)propyl Side Chain.[57]



Scheme 1.
Initial Retrosynthetic Analysis of Sieboldine A.

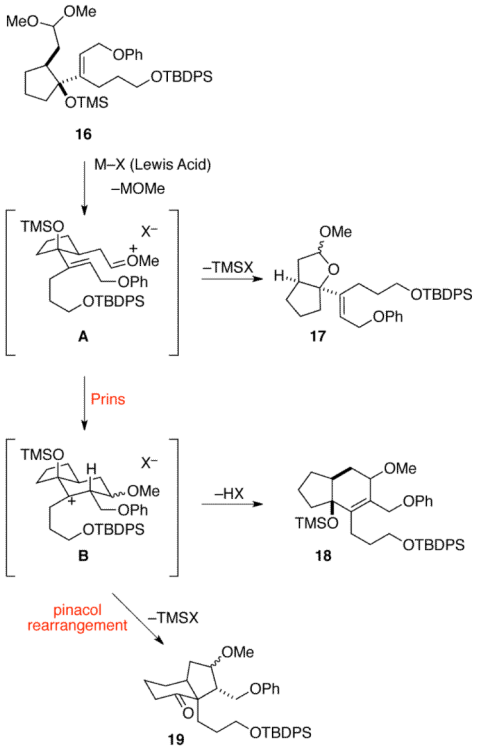


Scheme 2.
Synthesis of Vinyl Iodide **13**.

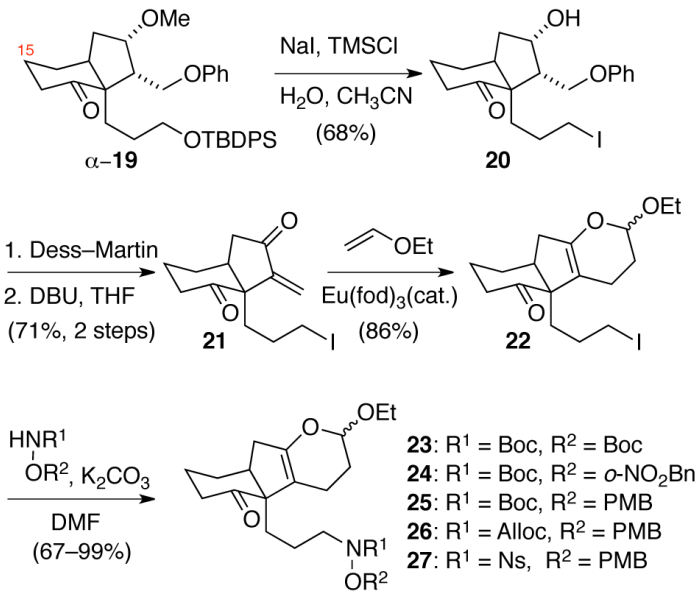


Entry	Conditions	Yield
1	*s*-BuLi, THF, –78 °C	~50%
2	*s*-BuLi, $CeCl_3$, THF, –78 °C	81%
3	*s*-BuLi, $CeCl_3$·2LiCl, THF, –78 °C	96%

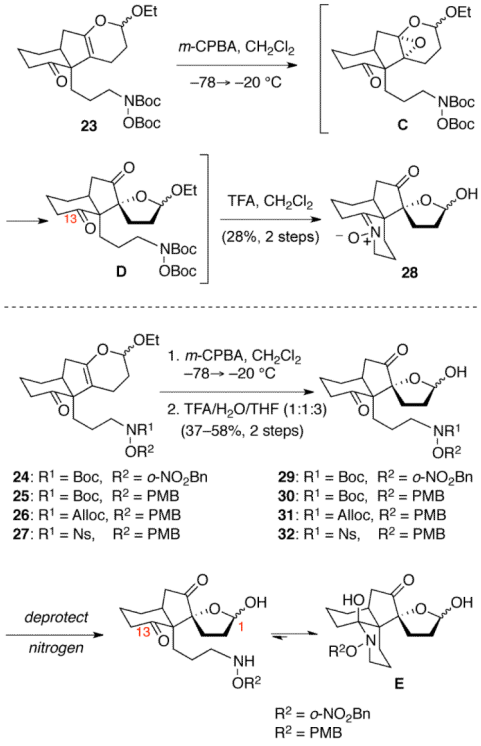
Scheme 3.
Nucleophilic Addition to Cyclopentanone **14**.



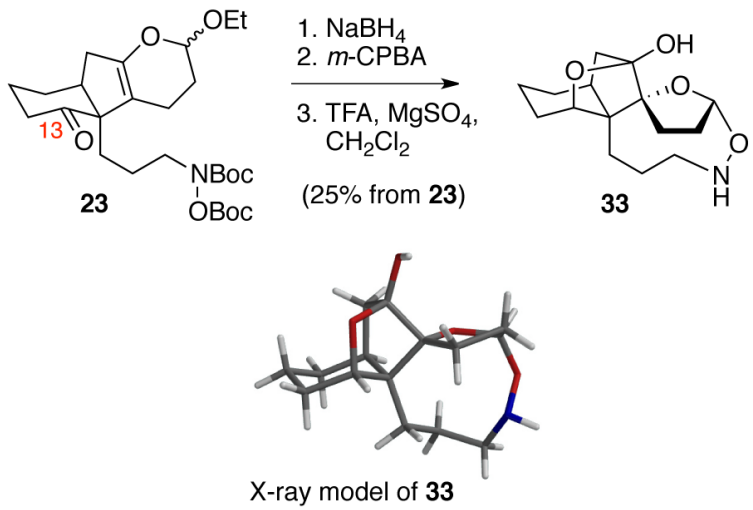
Scheme 4.
Prins–Pinacol Rearrangement to Form the *cis*-Hydrindanone Core.



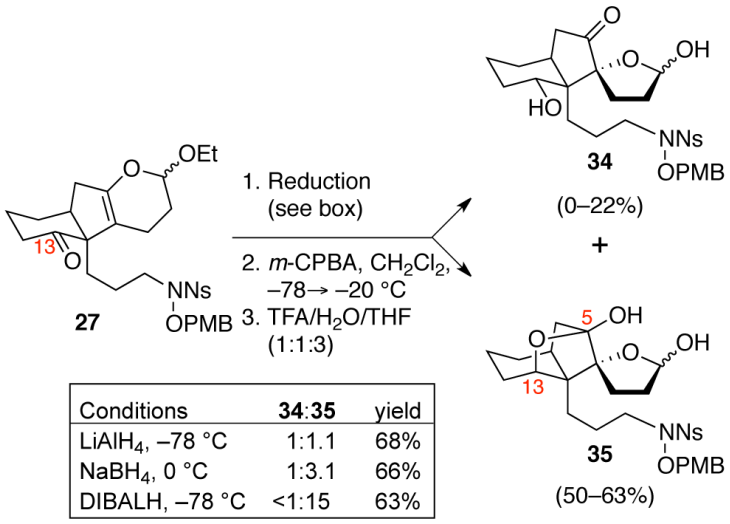
Scheme 5.
Elaboration of *cis*-Hydrindanone **19** in the Demethyl Series.



Scheme 6.
Initial Attempts to Form the Tetrahydrofuran and *N*-Hydroxycyclononane Rings.

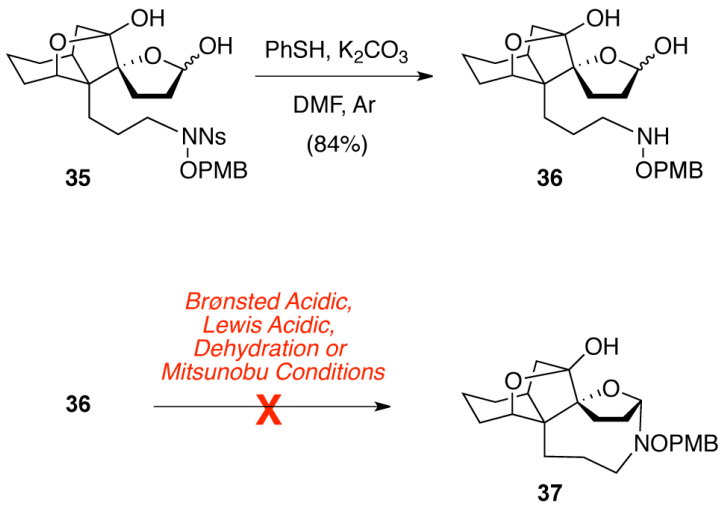


Scheme 7.
Formation of 1,2-Oxazacyclodecane **33**.

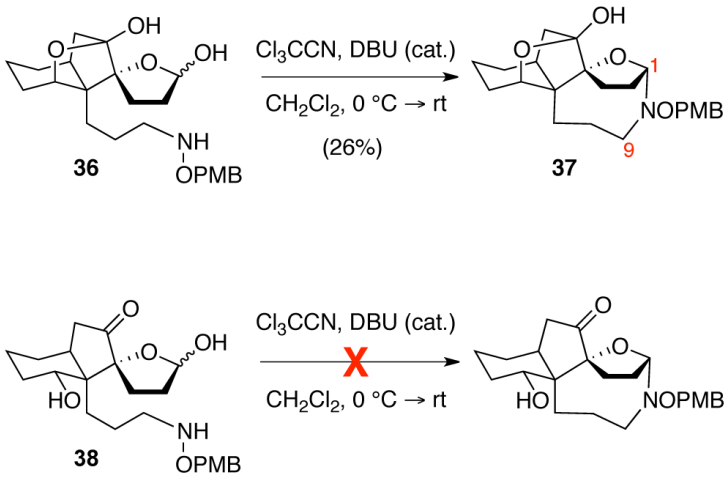


Conditions	**34**:**35**	yield
$LiAlH_4$, –78 °C	1:1.1	68%
$NaBH_4$, 0 °C	1:3.1	66%
DIBALH, –78 °C	<1:15	63%

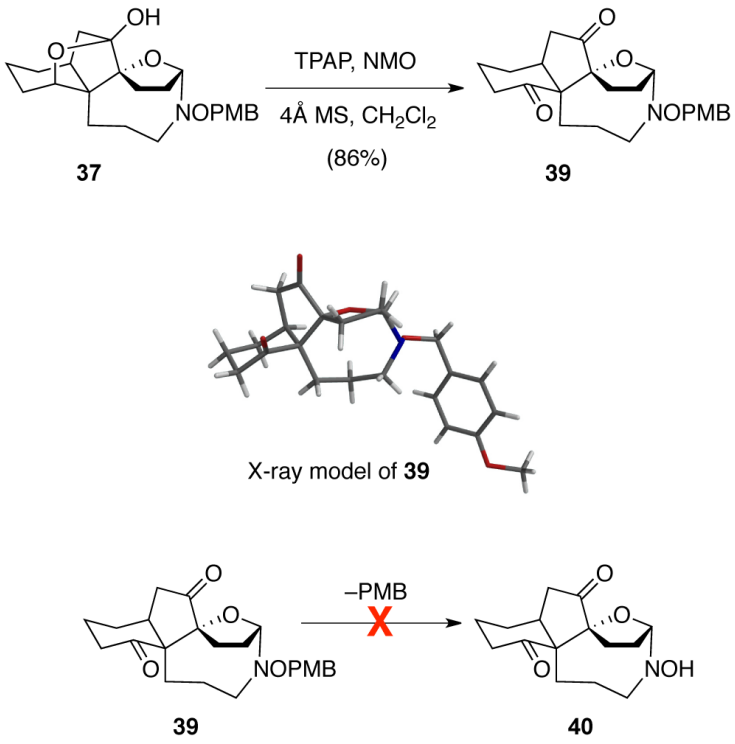
Scheme 8.
Protection of the C13 Carbonyl and Oxidation.



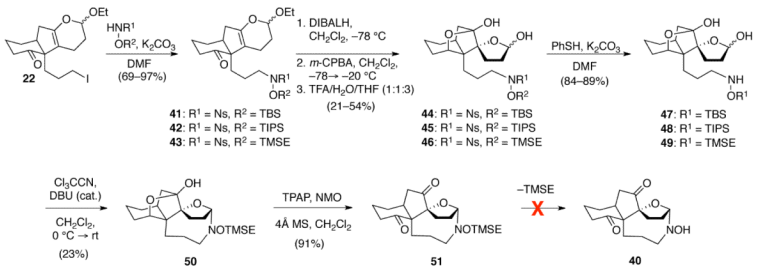
Scheme 9.
Unsuccessful Attempts to Form the *N*-Hydroxyazacyclononane Ring.



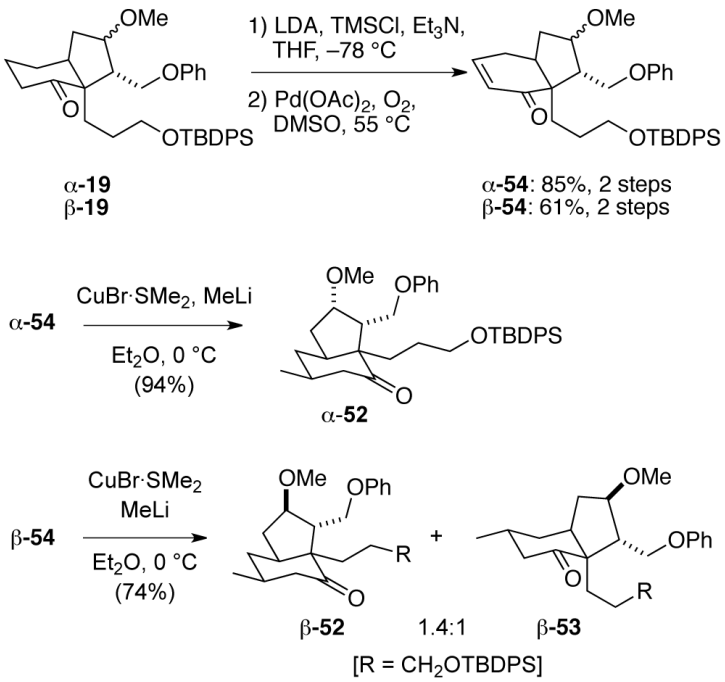
Scheme 10.
Formation of the *N*-Alkoxyazacyclononane Ring.



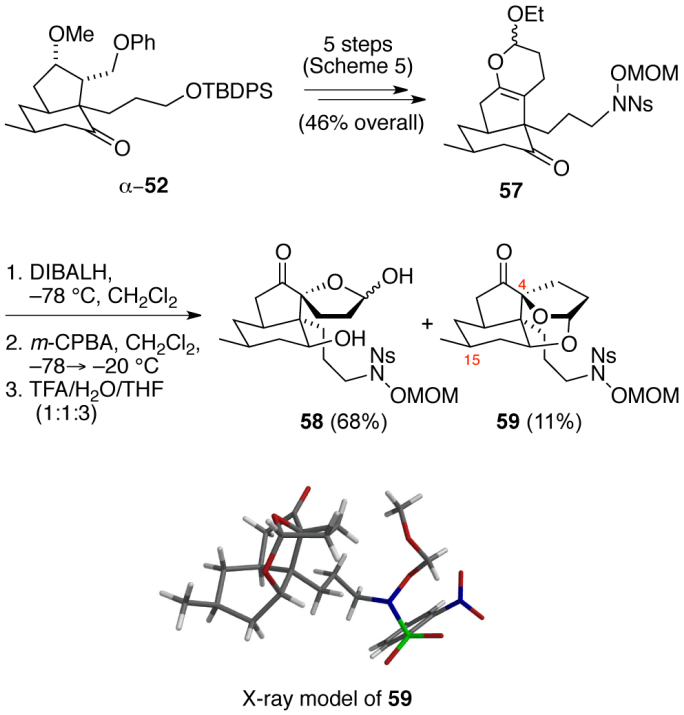
Scheme 11.
Oxidation of **37** to the Dione and Attempted Removal of the PMB Group.



Scheme 12.
Evaluation of Alternative *O*-Protecting Groups.



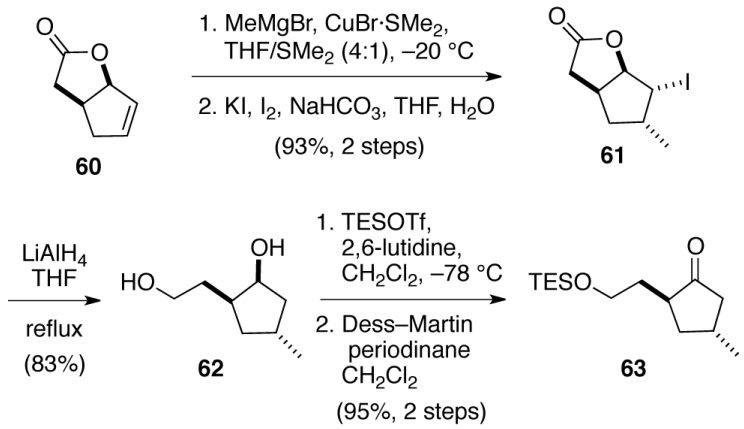
Scheme 13.
Introduction of the C15 Methyl into an Enone Precursor



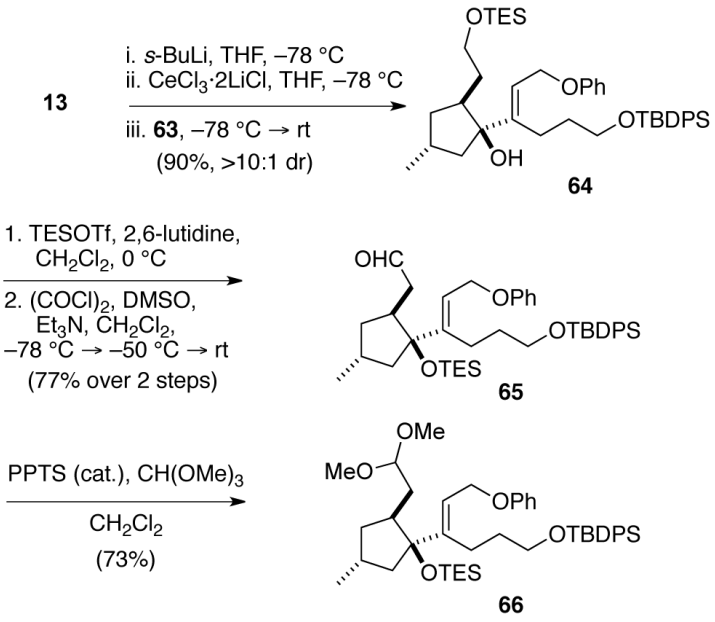
X-ray model of **59**

Scheme 14.

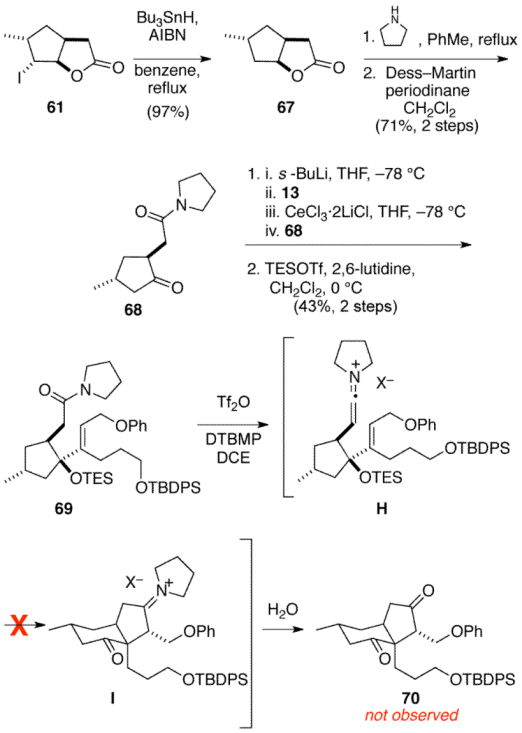
X-Ray Confirmation of the Unnatural Relative Configuration of the C15 Methyl Substituent.



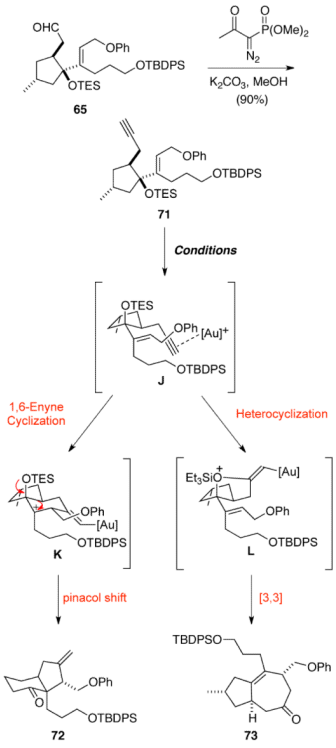
Scheme 15.
Synthesis of 2,4-*trans*-Disubstituted Cyclopentanone **63**.



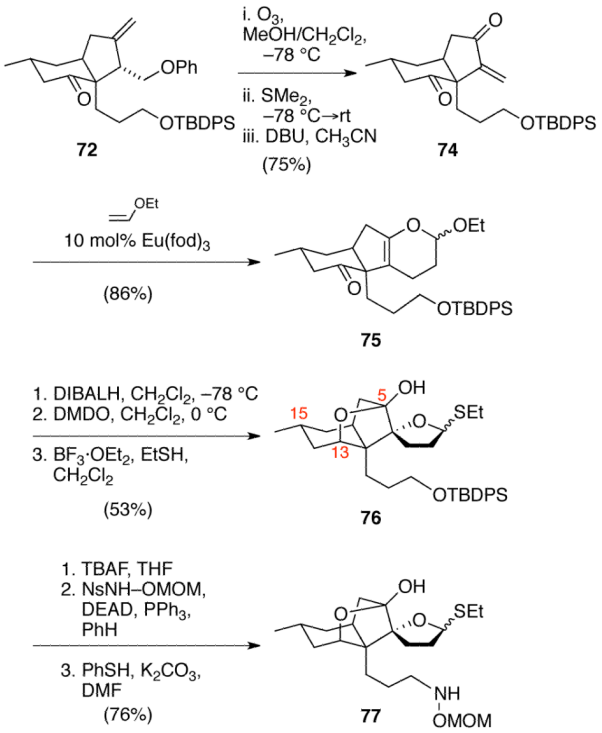
Scheme 16.
Formation of Prins–Pinacol Precursor **66**.



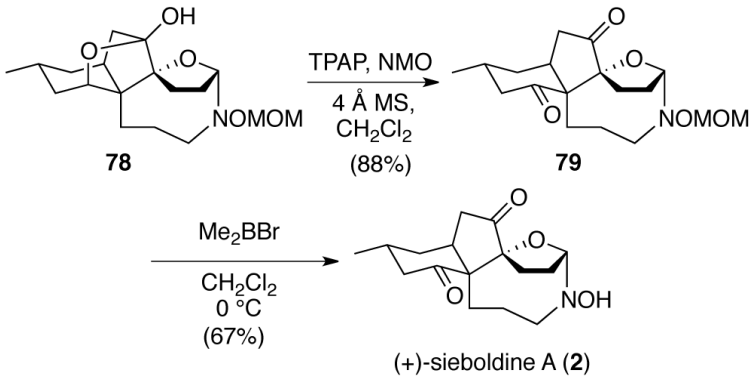
Scheme 17.
Attempted Pinacol-terminated Keteneiminium Ion Cyclization.



Scheme 18.
Au(I)-Catalyzed Pinacol-terminated 1,6-Enyne Cyclization.



Scheme 19.
Elaboration of *cis*-Hydrindanone **72** to Thioglycoside Intermediate **77**.



Scheme 20.
Completion of the Total Synthesis of Sieboldine A.

Table 1

Lewis Acid Activation of Dimethyl Acetal **16**.

Entry	Conditions[a]	18:19[b]	Yield[c]
1	BCl_3, CH_2Cl_2, −78 °C	nd	complex mixture
2	$BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 °C	nd	**17** major
3	TMSOTf, CH_2Cl_2, −78 °C	nd	83% **17**
4	$SnCl_4$, CH_2Cl_2, −78→−20 °C	1.0:2.0	51% **19**
5	$SnCl_4$, $MeNO_2$, 0 °C	nd	complex mixture
6	$SnCl_4$, i-$PrNO_2$, −78→−20 °C	1.0:2.8	54% **19**
7	$TiCl_4$, CH_2Cl_2, −78→ −20 °C	<1:8	70% **19**

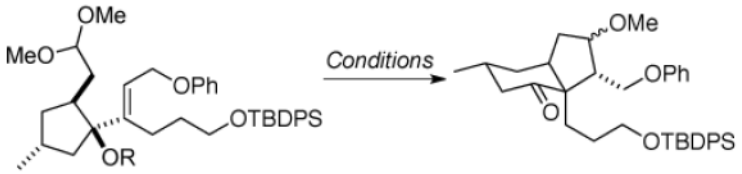
[a] 0.9 equiv of Lewis acid were used;

[b] Ratios determined by integration of ^{1}H NMR spectra of unpurified reaction mixtures;

[c] isolated yields; nd = not determined.

Table 2

Prins–Pinacol Rearrangement with the C15 Methyl Group Incorporated.



66a: R = TMS
66: R = TES

53α/53β

R	Conditions	Yield
TMS	0.9 equiv $TiCl_4$	29%
TMS	0.5 equiv $TiCl_4$	13%
TES	0.5 equiv $TiCl_4$	42%
TES	0.9 equiv $TiCl_4$	40%

Table 3

Au(I) Catalysts and Selectivity for Pinacol-terminated 1,6-Enyne Cyclization.

Entry	Conditions[a]	Yield (72:73)
1	10 mol% $[Au(PPh_3)]_3OBF_4$	NR
2	10 mol% PPh_3AuCl[b]	94% (1:1)
3	10 mol% Me_3PAuCl[b]	90% (1.5:1)
4	10 mol% Et_3PAuCl[b]	91% (2:1)
5	10 mol% μ-$(Ph_2P)_2CH_2Au_2Cl_2$[c]	85% (2:1)
6	10 mol% *t*-Bu_3PAuCl [b]	88% (2.5:1)
7	10 mol% (NHC)AuCl[b]	89% (3:1)
8	10 mol% [(*t*-Bu) $_2$P(*o*-biphenyl)]AuCl[b]	95% (10:1)
9	10 mol% [(*t*-Bu) $_2$P(*o*-biphenyl)]AuCl[b,d]	84% (13:1)

[a] All reactions were carried out on a 0.03 mmol scale at 0.05 M in CH_2Cl_2 with 1.1 equiv *i*-PrOH at rt;

[b] 5 mol% $AgSbF_6$;

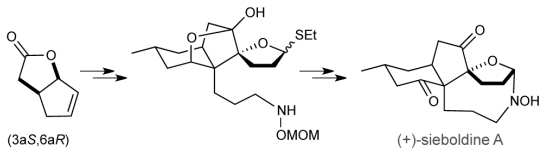
[c] 9 mol% $AgSbF_6$;

[d] conducted on 3.2 mmol scale;

NR = no reaction

Table 4

Activation Conditions for Formation of the *N*-Alkoxyazacyclononane Ring.



Entry	Conditions	Yield
1	$NO_2PhSOTf$, DTBMP, 4Å MS, CH_2Cl_2, −78 °C	10%
2	$HgCl_2$, $CaCO_3$, 4Å MS, CH_2Cl_2, rt	16%
3	TBPA, 4Å MS, CH_3CN	18%
4	$AgPF_6$, DTBMP, 4Å MS, CH_2Cl_2, 0 °C	28%
5	DMTST, DTBMP, 4Å MS, CH_2Cl_2, 0 °C	37%
6	DMTST, DTBMP, 4Å MS, CH_2Cl_2, 0 °C, inverse addition	42%
7	DMTST, DTBMP, 4Å MS, CH_3CN, −20 °C, inverse addition	51%

DTBMP = 2,6-di-*tert*-butyl-4-methylpyridine; TBPA = tris(4-bromophenyl)ammoniumyl hexachloroantimonate; DMTST = dimethyl(metylthio)sulfonium triflate