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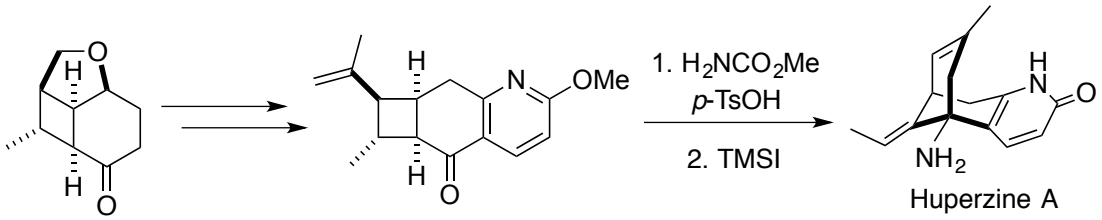


ABSTRACT: An asymmetric total synthesis of the nootropic alkaloid (-)-huperzine A was completed using a cascade sequence initiated by an intramolecular aza-Prins reaction and terminated by a stereoelectronically guided fragmentation of a cyclobutylcarbinyl cation as the key step in assembling the bicyclo[3.3.1]nonene core of the natural product. Intramolecular [2+2]-photocycloaddition of the crotyl ether of (*S*)-4-hydroxycyclohex-2-enone afforded a bicyclo[4.2.0]octanone containing an embedded tetrahydrofuran in which the cyclohexanone moiety was converted to a triisopropylsilyl enol ether and functionalized as an allylic azide. The derived primary amine was acylated with α-phenylselenylacrylic acid and the resulting amide was reacted with trimethylaluminum to give a [2+2]-cycloadduct which underwent retroaldol fission to produce a fused α-phenylselenyl δ-lactam. Periodate oxidation of this lactam led directly to an α-pyridone which was converted to a fused 2-methoxypyridine. Reductive cleavage of the activated "pyridylic" C-O bond in this tetracycle and elaboration of the resultant

hydroxy ketone to a diketone was followed by chemoselective conversion of the methyl ketone in this structure to an endo isopropenyl group. Condensation of the remaining ketone with methyl carbamate in the presence of acid initiated the programmed cascade sequence and furnished a known synthetic precursor to huperzine A. Subsequent demethylation of the carbamate and the methoxypyridine, accompanied by in situ decarboxylation of the intermediate carbamic acid, gave (-)-huperzine A.

INTRODUCTION

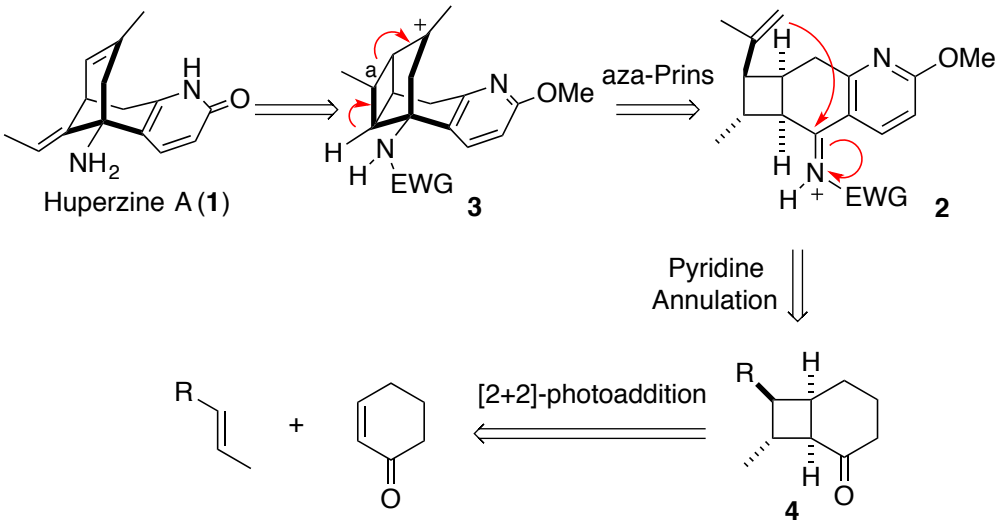
The seminal publications by Woodward and Hoffmann five decades ago that set forth "rules" governing, among other reactions, the addition of one alkene unit to another[1] has spawned a vast body of research on both the theoretical and synthetic implications of the [2+2]-cycloaddition process.[2] A rationale based on "orbital symmetry", or more precisely upon orbital correlation diagrams that consider the relationship of HOMO and LUMO electronic states of reactants, explained that while cycloaddition of two alkenes in their ground electronic states was thermally "forbidden", the corresponding cycloaddition with one of the alkenes in an electronically excited state would be "allowed". In the latter case, a cyclobutane would result, initially in an electronically excited state but relaxation to ground state would follow.[3] Deciding what "forbidden" actually means in energy terms is not always straightforward[4] but a practical consequence of the Woodward-Hoffmann paradigm is that extensive use has been made of photochemistry to excite an alkene in the presence of a second ground state alkene to prepare cyclobutanes.[5] An early application of this principle to the synthesis of a natural product (and one inspired by the insight brought to cycloaddition processes by Woodward himself during his

legendary research group meetings of the 1960's) was our synthesis of the bourbonene sesquiterpenoids, where photocycloaddition of cyclopentenone to a substituted cyclopentene installed the central cyclobutane in these tricyclic structures.[6]

The ease with which cyclobutanes can be synthesized photochemically taken with the fact that the four-membered carbocycle contains *ca*. 26 kcal/mol of strain energy[7] has led to a rich portfolio of synthetic applications resulting from release of that ring strain.[8] Examples include cycloreversion of a cyclobutane to form two new alkene units, a process employed in our synthesis of byssochlamic acid,[9] ring expansion to a cyclopentane,[10] and ring scission to generate new cyclic or acyclic entities possessing diminished strain relative to the starting cyclobutane.[11,12] A cyclobutane cleavage pathway that can be characterized as a "downhill" progression in energy terms is the conceptual basis for our synthesis of the *Lycopodium* alkaloid huperzine A (**1**).[13] Huperzine A, a constituent of the club moss *Huperzia serrata* (Thunb.), has attracted attention as a result of claims that the compound has restorative properties for cognitive impairment and has the ability to improve memory function. Historically, *H. serrata* has been used in China under the name Chien Tseng Ta to treat a variety of illnesses including Alzheimer's dementia.[14] Although huperzine A is easily accessible from its natural source and is often sold as a component of herbal remedies, the compound continues to be a target of opportunity among synthetic organic chemists.

The first synthesis of huperzine A as its racemate was completed by Kozikowski who used a tandem Michael-aldol sequence to fabricate the bicyclo[3.3.1]nonene portion of the molecule.[15] The route was subsequently improved by the Kozikowski group[16] and then adapted to an

asymmetric synthesis of natural (-)-huperzine A.[17] A synthesis of racemic **1** almost identical to that of Kozikowski has been published by Ji.[18] Kozikowski later developed a second route to **1** using a palladium-catalyzed bicycloannulation to construct the bicyclo[3.3.1]nonene core[19] and this strategy has been utilized by both Terashima in a synthesis of (-)-**1**[20] and by Langlois in a formal synthesis of (+)-**1**.[21] Two recent syntheses of huperzine A using novel approaches, one by Fukuyama[22] and the other by Lin,[23] have been reported.



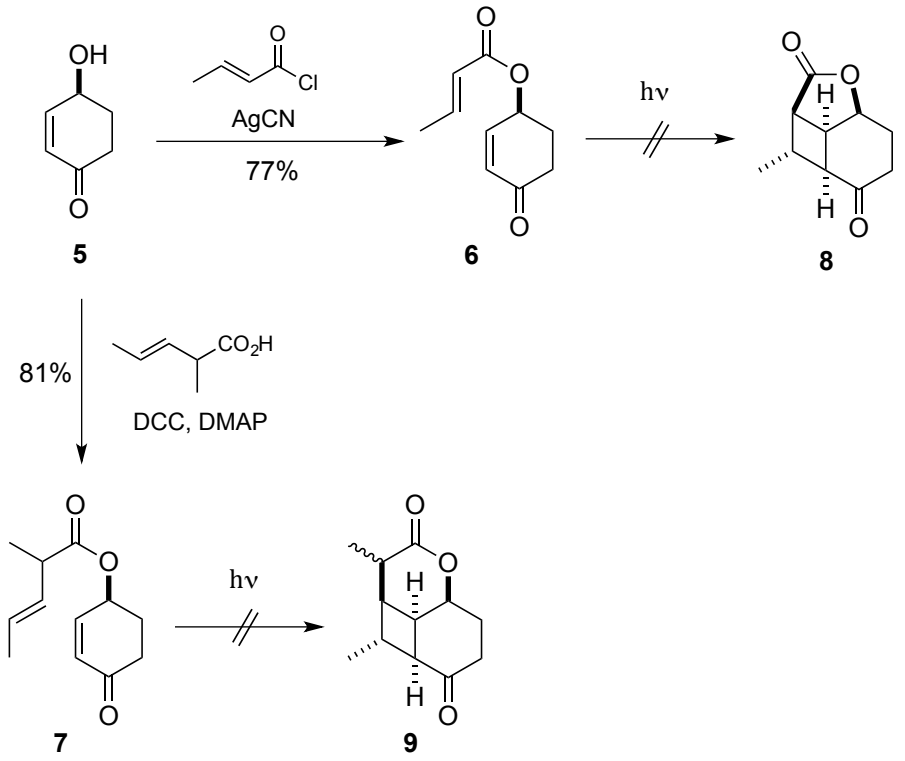
Scheme 1. Proposed Route to Huperzine A Using an Aza-Prins-cyclobutylcarbinyl Cation Fragmentation Cascade

RESULTS AND DISCUSSION

Our approach to **1** was based on the proposition that release of strain in a cyclobutane embedded within a structure such as **2** could be used to generate the less strained bicyclo[3.3.1]nonene

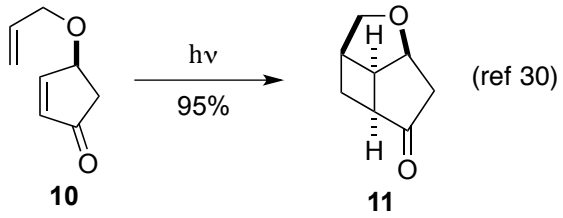
framework of **1** (Scheme 1).[24] The event designed to release that strain would be fragmentation of bond "a" in cyclobutylcarbinyl cation **3**, the cation being formed via an intramolecular aza-Prins reaction[25] of **2**. While alternative fragmentation modes of the cyclobutane in **3** are certainly conceivable, the orbital alignment suggested by the arrows in Scheme 1 implies that a stereoelectronic bias should favor the fragmentation pathway we desire. The retrosynthetic direction from **2** envisioned construction of a bicyclo[4.2.0]octane precursor **4** via [2+2]-photocycloaddition of a cyclohexenone to a suitably functionalized alkene,[26] with the methoxypyridine unit in **2** being fused to this template in a subsequent operation. As it happened, a [2+2]-cycloaddition and fragmentation of the resultant cyclobutane also featured in the methoxypyridine annulation en route to **2**.

Our goal from the outset was an asymmetric synthesis of huperzine A in its natural absolute configuration and it was recognized that a plausible way to achieve this would be to incorporate a stereogenic center in one of the photo partners leading to **4**. Maximum stereocontrol would be assured if the photocycloaddition were intramolecular[27] and a decision was made to link the two photo addends through a functional group in the cyclohexenone partner. An attractive starting point based on this precept was (*S*)-(-)-4-hydroxycyclohex-2-enone (**5**), prepared from (-)-quinic acid by the method of Danishefsky.[28] However, our first approach to the bicyclooctane core of **4** via photocycloaddition of an unsaturated ester derived from **5** proved to be flawed since neither crotonate **6**, prepared from **5** and crotonyl chloride, nor ester **7**, obtained from **5** with (*E*)-2-methyl-3-pentenoic acid, afforded any trace of cycloadducts **8** and **9** upon irradiation (Scheme 2). Instead, complex mixtures were produced in each case.



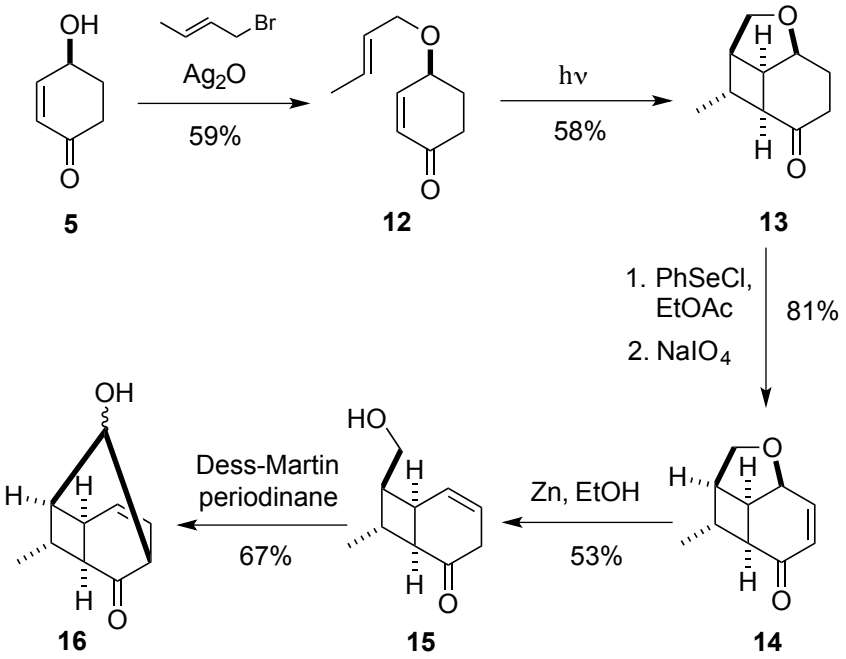
Scheme 2. Attempted Photocycloaddition of Unsaturated Esters of 4-Hydroxycyclohex-2-enone

While these failed sequences were disappointing, we were aware that previous studies by others[29] had shown that unsaturated ethers tethered to a photoreactive cyclic enone readily undergo intramolecular [2+2]-cycloaddition. For example, Garibaldi et al. reported that irradiation of 3-allylyoxycyclopent-2-enone (**10**) gave tricyclic adduct **11** in high yield (Scheme 3).[30]



Scheme 3. Intramolecular Photocycloaddition of 3-Allyloxycylopent-2-enone

Based on this precedent, we used Martin's method[31] to prepare crotyl ether **12** as a prospective photo substrate by treatment of **5** with trans crotyl bromide and silver(I) oxide. After exploratory studies to determine optimal reaction conditions, intramolecular [2+2]-adduct **13** was obtained in a consistent 55-60% yield upon irradiation of **12** through Pyrex glass with a 450W medium pressure mercury lamp (Scheme 4). It was important to use degassed dichloromethane as solvent for this reaction which was carried out at 0 °C and was generally complete within two hours. Since four new stereocenters were generated in **13** from the single stereogenic carbon in **12**, verification of the configuration of **13** was undertaken using nOe experiments. The proton correlations shown in Figure 1 confirmed that cycloaddition of **12** had occurred in a *syn* sense at the cyclohexenone double bond and with preservation of the trans relationship originating in the crotyl appendage.



Scheme 4. Intramolecular Photocycloaddition of (4*S*)-*4*-Crotyloxycyclohex-2-enone and Reductive C-O Cleavage of the Product

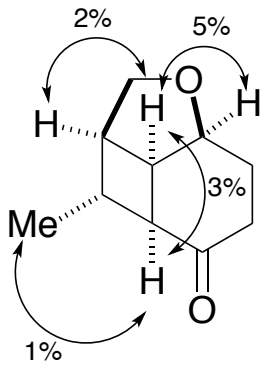


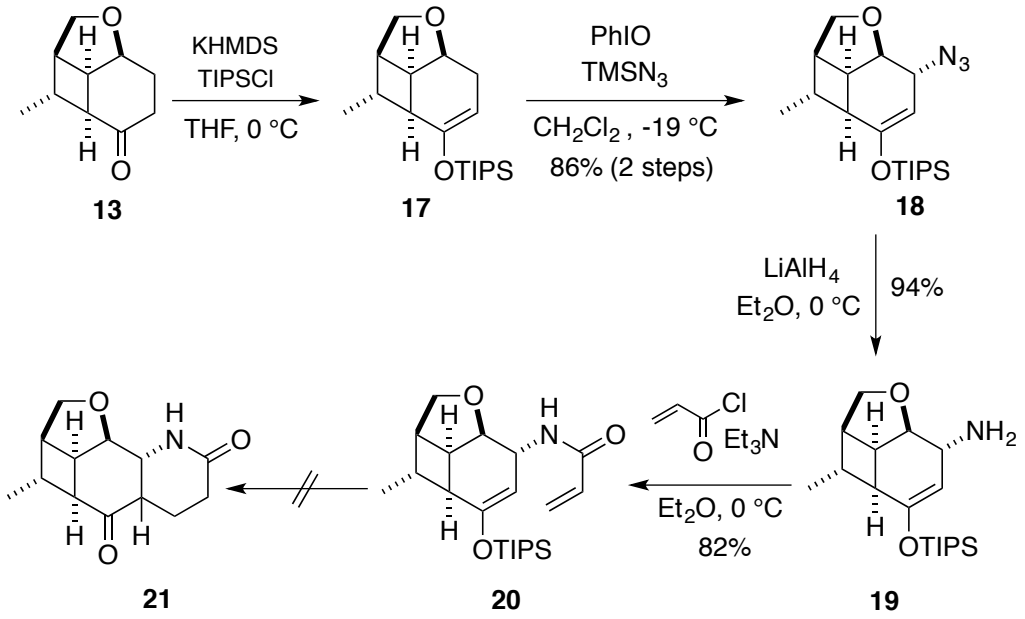
Figure 1. Nuclear Overhauser Enhancement of Irradiated Proton Signals in 13

With **13** in hand, our next goal was fusion of a methoxypyridine unit to this bicyclic substrate. Our initial route envisioned introduction of a 2,3-double bond into **13**, then using the derived cyclohexenone **14** as a dienophile in a [4+2]-cycloaddition with a 1-azadiene.[32] The transformation of **13** to cyclohexenone **14** was straightforward and involved α-selenylation with phenylselenyl chloride followed by in situ oxidation with sodium periodate.[33] Before testing **14** as a dienophile in an aza-Diels-Alder reaction, we took advantage of an opportunity to investigate reductive cleavage of the allylic C-O bond of the tetrahydrofuran since the resulting primary alcohol would be a logical platform for advance toward the endo isopropenyl group of **2**. An extensive search for a suitable method to effect this reductive scission revealed that only Yadav's protocol[34] using zinc in refluxing ethanol was successful in producing **15**, other reductants generally returning saturated ketone **13** as the major product. Oxidation of **15** to an aldehyde which would precede completion of a path to the isopropenyl substituent of **2** surprisingly afforded the intramolecular aldol product **16**, a result that in retrospect could have been foreseen given the endo disposition of the transient aldehyde and its proximity to the β,γ-unsaturated ketone. Attempts to reverse the formation of **16** were unsuccessful and installation of the isopropenyl group of **2** was therefore deferred to a later step.

It was evident that formation **16** upon oxidation of **15** could have been avoided if a pyridine ring were fused to **13** so that enolization of the ketone was blocked. Attention therefore returned to enone **14** as a prospective dienophile partner for an aza-Diels-Alder reaction that would create a δ-lactam for eventual aromatization to a pyridine. In this scenario, the C-O bond for reductive cleavage would become pseudo-benzylic, i.e. "pyridylic", and consequently should be more susceptible towards fission than the corresponding C-O bond in **14**. Unfortunately, **14** failed to

react with any of a variety of 1-azadienes including those bearing methoxy substituents at C-2 and C-4 as well those carrying an activating *N*-dimethylamino substituent,[35] and it became apparent from these experiments that the combination of a weak dienophile with a 1-azadiene was an incompatible pairing for cycloaddition. This approach to annulation of the pyridine moiety of **2** was therefore abandoned in favor of a stepwise plan.

The first step in our new route to **2** envisioned conjugate addition of azide to enone **14** but this reaction encountered the twin difficulties of facile reversibility and clean separation of an unstable product from starting material. As a result, we were unable to force the reaction to completion. A timely solution to this problem appeared in a publication from the Magnus laboratory which reported that treatment of a triisopropylsilyl enol ether with trimethylsilyl azide and iodosobenzene gave an allylic azide in good yield.[36] Application of the Magnus protocol to **13** first required preparation of silyl enol ether **17** which, after brief chromatographic purification, was exposed to iodosobenzene and trimethylsilyl azide at low temperature (Scheme 5). The reaction afforded an excellent yield of azide **18** as a single stereoisomer whose exo configuration was proven by proton-proton coupling constants in its NMR spectrum (Figure 2). Reduction of **18** with lithium aluminum hydride furnished primary amine **19** which was reacted *in situ* with acryloyl chloride to yield amide **20**.



Scheme 5. Synthesis of Acrylamide 20 from Photoadduct 13

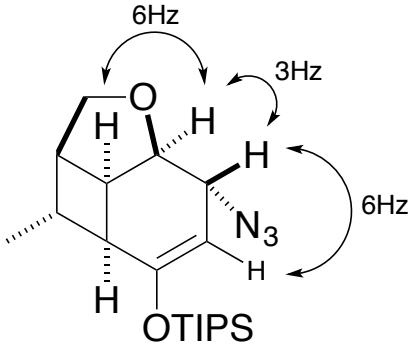
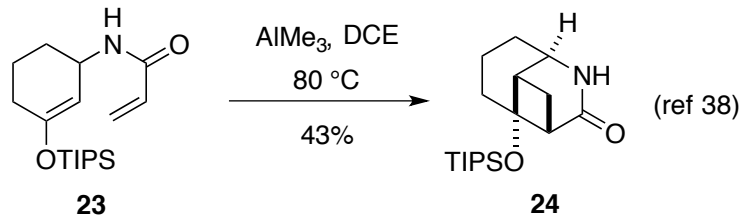


Figure 2. Proton-proton Coupling Constants in Azide 18

It was hoped that silyl enol ether **20 w**ould undergo Lewis acid-catalyzed intramolecular Mukaiyama-Narasaka conjugate addition[37] to generate δ-lactam **21** but hydrolysis of the silyl

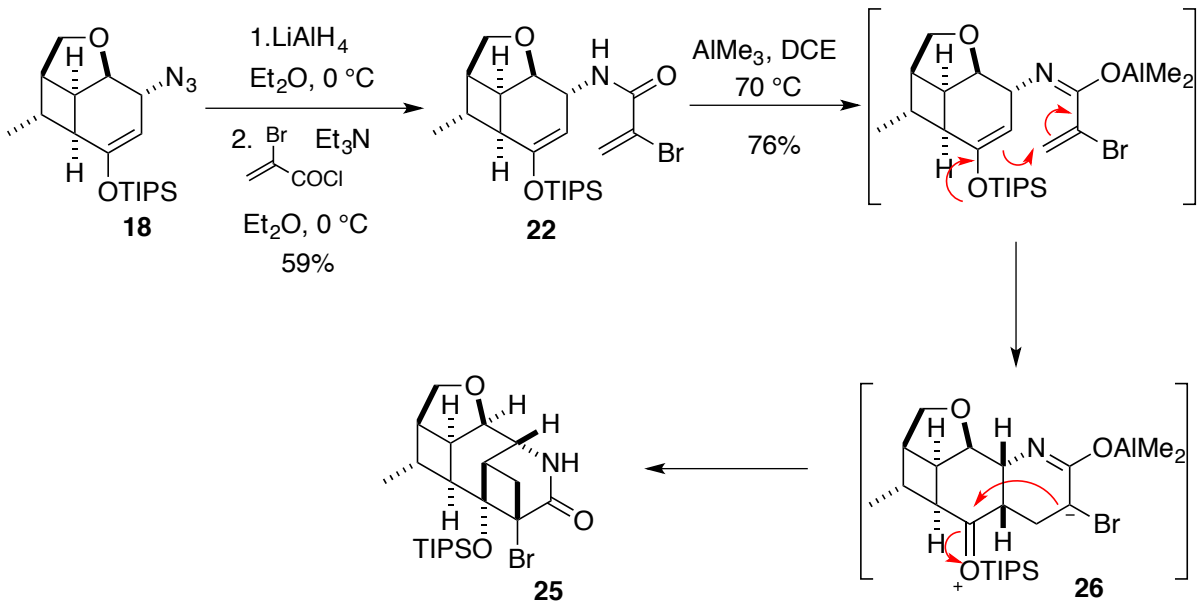
enol ether and subsequent β elimination of the acrylamide moiety intervened to regenerate **14**. On the supposition that an α-bromo amide would provide a more compliant acceptor for ring closure, amine **19** was acylated with α-bromoacryloyl chloride to afford **22** but this bromo amide suffered the same fate as **20** when Narasaka cyclization was attempted. At this point, a second publication from the Magnus lab came to our attention in the form of a report describing intramolecular trimethylaluminum-catalyzed [2+2]-cycloaddition of acrylamide **23** to give **24** (Scheme 6).[38]



23 **24**

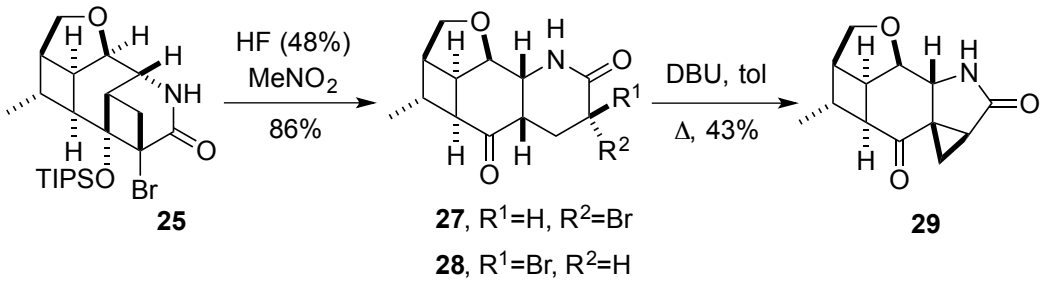
Scheme 6. Magnus' Trimethylaluminum-mediated [2+2]-Cycloaddition of Acrylamide 23

The Magnus reaction conditions applied to **22** led smoothly to crystalline pentacyclic adduct **25** (Scheme 7). It is noteworthy that the configuration of the nine stereogenic carbons in the congested framework of **25** emanate from the single stereocenter in **5** and that **25** is quite stable despite the presence of ring strain associated with two embedded cyclobutanes. Although formally a [2+2]-cycloaddition, the transformation of **22** to **25** falls outside the scope of the Woodward-Hoffmann rules and is most likely a stepwise process involving zwitterionic intermediate **26**.



Scheme 7. Trimethylaluminum-mediated [2+2]-Cycloaddition of Bromoacrylamide 22

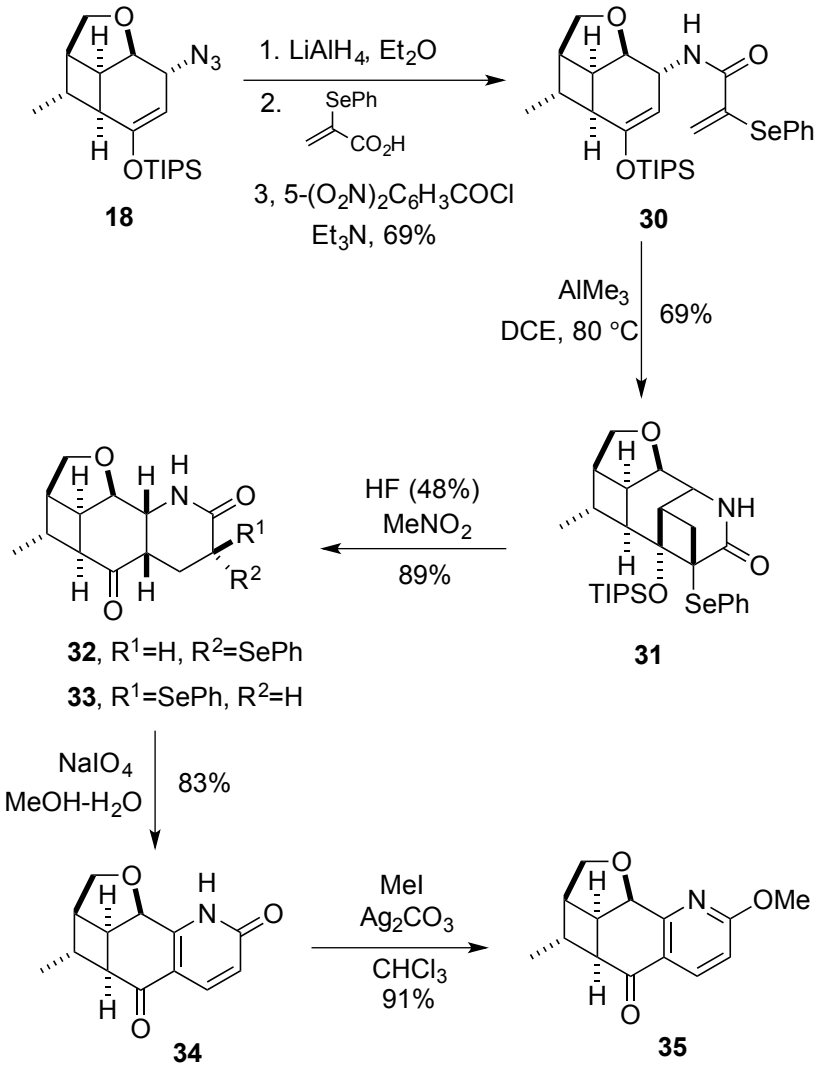
The β-silyloxy carbonyl motif contained within the δ-lactam portion of **25** set the stage for retroaldol fission of the new cyclobutane ring and exposure of **25** to aqueous HF in nitromethane gave α-bromo lactams **27** and **28** in high yield as a 3:1 epimeric mixture (Scheme 8). In principle, base-mediated elimination of HBr from either of these δ-lactams should yield a dihydropyridone from which the methoxypyridine system of **2** could be obtained after aromatization. However, we had not foreseen that basic reaction conditions could also generate a ketone enolate from these keto lactams and that internal alkylation resulting in 1,3-elimination could occur.[39] In fact, exposure of the major bromo lactam **27** to DBU gave fused cyclopropane **29** as the only detectable product and minor isomer **28** suffered the same fate.



Scheme 8. Retroaldol Fission of 25 and Elimination to Cyclopropane 29

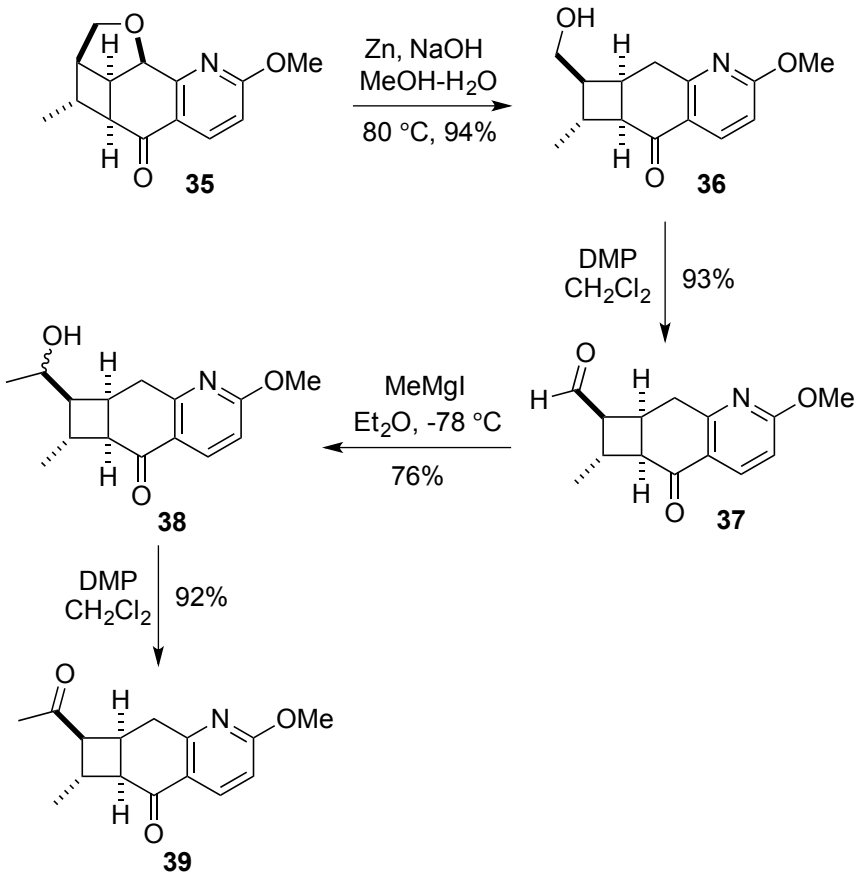
The intramolecular alkylation that produced **29** was avoided by replacing the bromine atom in **22** with a selenium substituent so that formation of an α,β-unsaturated δ-lactam could be accomplished oxidatively rather than by treatment with base. This revision necessitated a return to azide **18**. Coupling of the primary amine from reduction of **18** with α-phenylselenylacrylic acid[40] in the presence of 3,5-dinitrobenzoyl chloride gave amide **30** which upon treatment with trimethylaluminum afforded the expected [2+2]-cycloadduct **31** (Scheme 9). The latter underwent retroaldol fission with aqueous HF in nitromethane to give separable epimeric α-selenyl lactams **32** and **33** in an approximately 1:1 ratio. Exposure of **32** and **33** to sodium periodate revealed that the two α-selenyl lactams behaved differently. Whereas both **32** and **33** formed their respective selenoxides, only that from **33** underwent elimination. The failure of the selenoxide from **32** to give an unsaturated lactam is attributed to an unfavorable steric interaction of the endo phenylselenyloxy substituent in this structure with the ketone carbonyl which prevents correct alignment for a 1,2-syn elimination. Fortunately, a potential loss of material at this late stage was averted when the mixture of α-selenyl lactams was found to equilibrate in favor of **33** (10:1) with excess aqueous HF. A second fortuitous discovery was that reaction of **33** with excess sodium periodate led to fully unsaturated α-pyridone **34**. The dehydrogenation

that occurs after elimination of the selenoxide from **33** to form a transient α,β-unsaturated δ-lactam is probably initiated by oxidation at the activated ring junction but the precise mechanism of this transformation remains unknown. In any event, the foregoing results provided an efficient pathway from **31** to **34** involving exposure of **31** to four equivalents of aqueous HF in nitromethane followed directly by addition of excess sodium periodate to afford **34** in 83% overall yield. Pyridone **34** was converted uneventfully to methoxypyridine **35** with methyl iodide in the presence of silver(I) carbonate.



Scheme 9. Trimethylaluminum-mediated [2+2]-Cycloaddition of α-Phenylselenylacrylamide 30, Retroaldol Cleavage of 31 and Oxidation to Pyridone 34

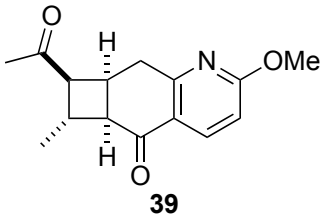
Reductive scission of the activated "pyridylic" C-O bond in **35** was expected to be more facile than cleavage of the analogous C-O bond in **14** but this hypothesis proved to be unfounded. Although hydrogenolysis of **35** using various palladium catalysts including Pearlman's catalyst[41] did produce a primary alcohol under forcing conditions, the reaction was always accompanied by reduction of the keto group. As with **14**, the only satisfactory reagent for effecting reductive cleavage of the C-O bond in **35** proved to be zinc.[34] Activation of zinc using Newman's method[42] and exposure of **35** to an excess of the metal in MeOH containing 0.2M NaOH at reflux gave hydroxy ketone **36** in excellent yield with no detectable reduction of the carbonyl group (Scheme 10). Alcohol **36** was advanced to keto aldehyde **37** upon oxidation with Dess-Martin periodinane[43] and a chemoselective Grignard reaction[44] at the aldehyde of **37** with methylmagnesium bromide produced an inconsequential 1:1 mixture of epimeric hydroxy ketones **38**. Oxidation of the mixture, again with Dess-Martin periodinane,[43] yielded a single diketone **39**.



Scheme 10. Reductive Cleavage of 35 and Oxidation to Diketone 39

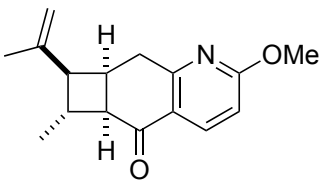
At this point, our blueprint called for differentiating the two ketones of **39** by converting the methyl ketone to the isopropenyl group of **2** whilst leaving the cyclohexanone carbonyl intact for later derivatization as an activated imine. It was reasoned that the cyclohexanone carbonyl of **39** should be relatively unreactive towards methylenating reagents by virtue of its "through conjugation" to the methoxy substituent on the pyridine ring. On the other hand, the endo orientation of the methyl ketone in **39** presents a "hidden" carbonyl to an external reagent that could also render this functional group unreactive. Predictably, attempts to effect selective methylenation of the methyl ketone of **39** using Peterson olefination,[45] Petasis-Tebbe

methylenation[46] or a Wittig reaction[47] met with little success and confirmed that chemoselectivity was difficult to achieve in this structural setting (Scheme 11). Wittig olefination of **39** with methylenetriphenylphosphorane did give a modest yield of **40** along with **41** and the bis methylenated product **42**, and a small bonus accrued from the finding that **41** could be ozonized efficiently to **39** which could then be recycled. Nevertheless, acquisition of **40** from **39** using this late-stage strategy was an impractical means for advancing the synthesis toward **1**.



39

A. (1) $TMSCH_2MgCl$, THF; (2) HF
B. Cp_2TiMe_2, tol
C. Ph_3PCH_3Br, *n*-BuLi, THF



40

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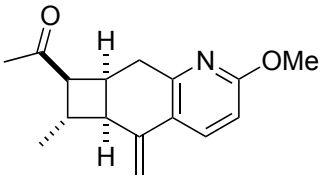

41

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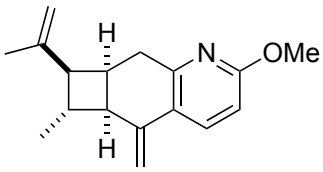
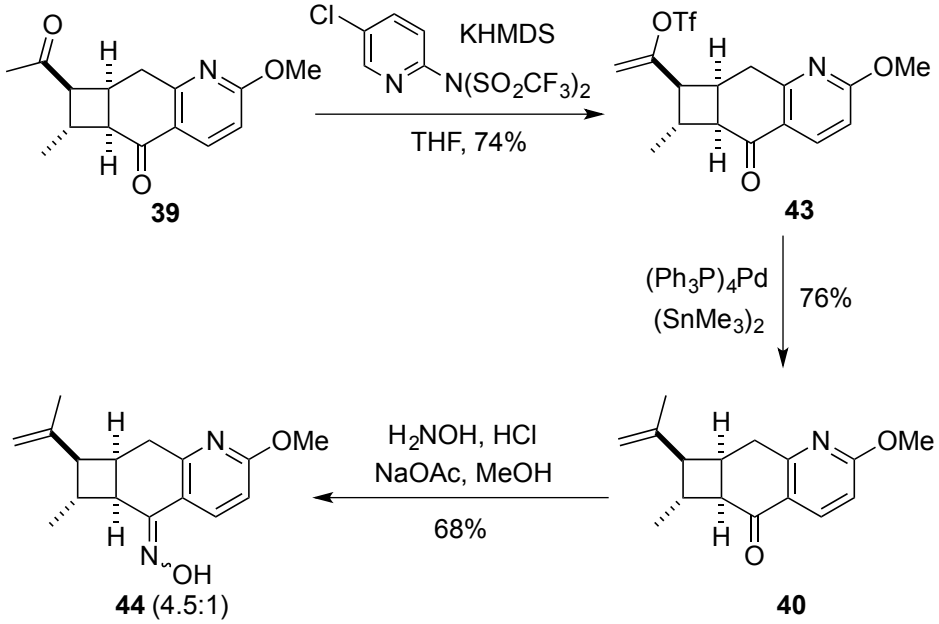


42

A	8%	6%	0%
B	21%	14%	0%
C	32%	13%	4%

Scheme 11. Attempted Methylenation of Diketone 39

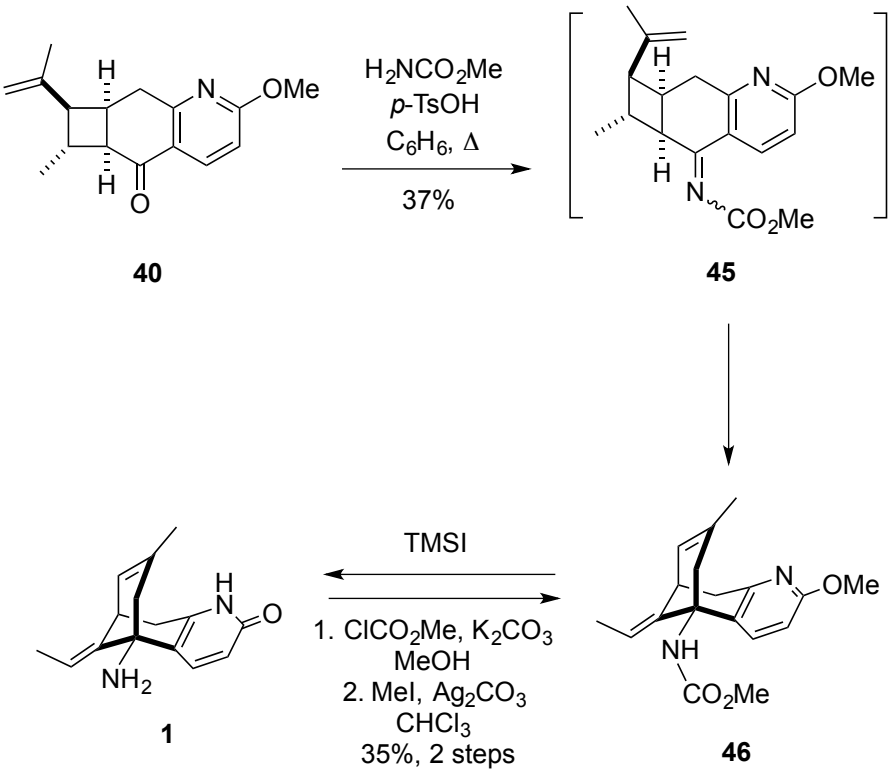
Selective methylenation at the sterically hindered methyl ketone of **39** was solved when it was recognized that this ketone, in contrast to the cyclohexanone carbonyl, was enolizable and that it cleanly formed enol triflate **43** in the presence of base and Comins' reagent[48] (Scheme 12). Subsequent reaction of **43** with hexamethyldistannane and tetrakis(triphenylphosphine)palladium(0) resulted in Stille cross-coupling[49] that replaced the triflate by a methyl group and gave **40** as a crystalline solid in an overall yield of 56% from **39**.



Scheme 12. Conversion of Diketone 39 to Isopropenyl Ketone 40 and its Oxime 44

In contrast to its reluctant engagement with methylenating agents, the cyclohexanone carbonyl of **40** readily condensed with benzylamine and with hydroxylamine hydrochloride, in the latter case forming a mixture of syn and anti oximes **44** (Scheme 13). The possibility that activation of the

mixture of oximes through exposure to a Lewis acid such as $TiCl_4$ could trigger aza-Prins cyclization[25] followed by the cyclobutane fragmentation envisioned in Scheme 1 was investigated briefly but Beckmann rearrangement[50] of **44** to an expanded ε-lactam appeared to be the only outcome from these experiments.



Scheme 13. Conversion of Isopropenyl Ketone 40 to (-)-Huperzine A

A more attractive derivative of **40** for initiating the cascade sequence projected in Scheme 1 appeared to be imino ester **45** since Beckmann rearrangement would be avoided and the reaction cascade, if successful, would lead directly to known compound **46**, the penultimate intermediate in Kozikowski's synthesis of huperzine A.[15] Ketone **40** was therefore condensed with methyl

carbamate in the presence of anhydrous *p*-toluenesulfonic acid in hot benzene, and although carbamate **45** could not isolated its formation was signalled by a color change of the reaction medium to yellow. The color dissipated over several hours and chromatographic purification of the resulting mixture of products afforded **46** whose spectral data matched those published by Kozikowski.[15] Although a mixture of (*E*) and (*Z*) isomers at the exo-ethylidene substituent of **46** could have been anticipated from **45**, Kozikowski showed in the course of his synthetic work that the mixture equilibrates under acidic conditions to yield the thermodynamically favored (*E*) isomer.

Completion of our synthesis of (-)-**1** followed Kozikowski's route[15] and involved treatment of **46** with trimethylsilyl iodide in chloroform (Scheme 13). This reagent caused demethylation of both the methoxypyridine and the methyl carbamate along with concomitant decarboxylation of the intermediate carbamic acid and furnished material identical with natural (-)-huperzine A. Further confirmation that the structure of **46** from **40** had been correctly assigned was obtained by reacting a sample of natural (-)-huperzine A with methyl chloroformate in the presence of potassium carbonate and then treating the resulting urethane with methyl iodide and silver(I) carbonate to yield methoxypyridine **46**.

CONCLUSION

Although shorter pathways to huperzine A than the synthesis described here have appeared,[15-23] our route demonstrates that ring strain inherent in a cyclobutane can be used to advantage in a molecular environment where that strain can be released in a controlled fashion. The exercise of

predicting which of two or more ring cleavage modes will prevail in a particular structural setting is not always easy but, as illustrated in the present work, stereoelectronic factors can guide ring scission toward a preferred reaction pathway. Taken with other ring opening reactions of cyclobutanes such as cycloreversion ("[2-2]"),[9] de Mayo-type retroaldol fission[11] and retro-Mannich fragmentation,[12] it is clear that the four-membered carbocycle offers a valuable resource for the synthesis of natural and non-natural products.

EXPERIMENTAL SECTION

General Techniques

All reactions requiring anhydrous conditions were conducted in flame-dried glass apparatus under an atmosphere of argon. THF, Et_2O, CH_2Cl_2, DMF, benzene and acetonitrile were dried by passage through an activated alumina column under argon. DMSO was distilled from CaH_2 at 15 mm Hg and stored over activated 4Å molecular sieves. Anhydrous MeOH was freshly distilled from CaH_2. Preparative chromatographic separations were performed on silica gel (35-75 μm); reactions were followed by TLC analysis using silica plates with fluorescent indicator (254 nm) and visualized with a UV lamp or phosphomolybdic acid. Reactions were performed at various scales depending upon availability of the starting material and reflect the practical limitation that reactions in a lengthy synthetic sequence must be carried out many times, often by different individuals. Melting points were measured on a capillary melting point apparatus. Optical rotations were measured with a polarimeter at ambient temperature using a 1 mL capacity cell with 1 dm path length. Infrared (IR) spectra were recorded using a thin film supported on KBr

discs or dispersed in a KBr pellet. ^{1}H and ^{13}C NMR spectra were recorded in Fourier transform mode at the field strength specified on a 300, 400 or 700 MHz spectrometer. Spectra were obtained on $CDCl_3$ solutions in 5 mm diameter tubes, and chemical shifts in ppm (part per million) are quoted relative to the residual signals of chloroform (δ_H 7.26 ppm, or δ_C 77.0 ppm). Multiplicities in the ^{1}H NMR spectra are described as: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad; coupling constants (*J*) are reported in Hz. Low (MS) and high (HRMS) resolution mass spectra were measured at 70 ev using a quadrupole analyzer and are reported with ion mass/charge (*m/z*) ratios as values in atomic mass units.

4-Oxocyclohex-2-en-1-yl (*E*)-But-2-enoate (6). To a solution of AgCN (35 mg, 0.27 mmol) and 4-hydroxycyclohex-2-en-1-one (30 mg, 0.27 mmol) in benzene (2 mL) at room temperature was added crotonyl chloride (31 mg, 0.29 mmol). The mixture was stirred for 2 h at room temperature and was heated for 6 h at 80 °C. After cooling to room temperature, the mixture was diluted with Et_2O (20 mL), washed with 10% aqueous $NaHCO_3$, and dried over anhydrous $MgSO_4$. The solvent was removed under vacuum and the residue was chromatographed on silica, using 10% EtOAc in hexane as eluent, to give 37 mg (77%) of **6** as a colorless oil: IR (neat) 2961, 1718, 1687, 1257, 1102 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.9 (dd, *J* = 1.2, 7.1 Hz, 3H), 2.0-2.2 (m, 1H), 2.3-2.5 (m, 2H), 2.6 (m, 1H), 5.6 (m, 1H), 5.8-5.9 (dq, *J* = 1.7, 15.4 Hz, 1H), 6.0-6.1 (m, 1H), 6.8-6.9 (ddd, *J* = 1.6, 2.7, 10.5 Hz, 1H), 6.9-7.1 (dq, *J* = 7.1, 15.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.0, 28.7, 34.9, 67.3, 122.0, 130.7, 146.0, 147.8, 165.5, 197.9.

4-Oxocyclohex-2-en-1-yl (*E*)-2-Methylpent-3-enoate (7). To a solution of 4-hydroxycyclohex-

2-en-1-one (0.10 g, 0.85 mmol) in Et_2O (2 mL) at room temperature was added sequentially DCC (0.19 g, 0.93 mmol) and DMAP (0.01 g, 0.09 mmol). The mixture was stirred for 4 h at room temperature and the precipitated *N*,*N*-dicyclohexylurea was filtered off. The filtrate was washed with water (3 x 1 mL), aqueous 5% AcOH (3 x 1 mL) and water (3 x 1 mL), and was dried over anhydrous $MgSO_4$. The solvent was removed under vacuum and the residue was chromatographed on silica, using 25% EtOAc in hexane as eluent, to give 0.14 g (81%) of **7** as a mixture of two diastereomers: IR (neat) 2934, 1735, 1692, 1246, 1165, 1138 $cm^{-}1$; ^1H NMR (300 MHz, $CDCl_3$) δ 1.25 (d, J = 7.0 Hz, 3H), 1.69 (dd, *J* = 2.1, 7.1 Hz, 3H), 2.09 (m, 1H), 2.35 (m, 2H), 2.47 (m, 1H), 2.60 (m, 1H), 3.48 (m, 1H), 5.40 (m, 1H), 5.59 (m, 2H), 6.05 (m, 1H), 6.83 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.0, 17.5, 28.4, 28.5, 34.8, 37.7, 67.4, 67.5, 126.5, 128.9, 130.7, 130.8, 147.4, 147.5, 174.2, 197.8.

(*S*,*E*)-4-(But-2-en-1-yloxy)cyclohex-2-en-1-one (12). To a solution of 4-hydroxycyclohex-2-en-1-one (0.33 g, 2.94 mmol) in crotyl bromide (2.5 mL) at 0 °C was added silver(I) oxide (1.7 g, 7.36 mmol) in several portions. The mixture was stirred for 6 h at room temperature, after which the excess silver(I) oxide was filtered off and excess crotyl bromide was removed under reduced pressure. The residue was chromatographed on silica, using 15% EtOAc in hexane as eluent, to give 0.81 g (59%) of **5** as a colorless oil: $[\alpha]_D^{23}$ -122 (*c* 1.51, $CHCl_3$); IR (neat) 2946, 2851, 1686, 1251, 1094, 968 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.74 (dd, *J* = 1.2, 6.8 Hz, 3H), 1.91-2.05 (m, 1H), 2.28-2.40 (m, 2H), 2.53-2.65 (m, 1H), 3.98 (m, 2H), 4.20 (m, 1H), 5.53-5.65 (dtq, *J* = 1.2, 6.7, 15.4 Hz, 1H), 5.67-5.85 (dtq, *J* = 1.3, 6.8, 15.3 Hz, 1H), 5.98 (m, 1H), 6.97 (ddd, *J* = 2.2, 3.2, 10.8 Hz, 1H), 5.21 (s, 2H), 5.27 (d, *J* = 13.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ

17.7, 29.1, 35.2, 72.0, 127.0, 129.5, 130.2, 150.7, 198.7; MS (CI) *m/z* 167 (M+H), 149, 141, 123, 113; HRMS (CI) *m/z* 167.1066 (calcd for $C_{10}H_{15}O_2$: 167.1072).

(2a*R*,2a^1*R*,3*R*,3a*S*,6a*S*)-3-Methylhexahydro-2*H*-cyclobuta[*cd*]benzofuran-4(2a*H*)-one (13). A Pyrex photolysis apparatus was charged with a solution of **12** (0.91 g, 5.48 mmol) in CH_2Cl_2 (300 mL) and argon was passed through the solution for 2 h. The solution was cooled to 0 °C and irradiated with a 450W medium-pressure mercury lamp for 2 h, after which the solvent was evaporated under reduced pressure. The residue was chromatographed on silica, using 15% EtOAc in hexane as eluent, to give 0.52 g (58%) of **13**: $[\alpha]_D^{23}$ +238 (*c* 2.3, $CHCl_3$); IR (neat) 2954, 2925, 2861, 1697, 1175, 1057, 1013 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.19 (d, *J* = 7.1 Hz, 3H), 1.91 (ddd, *J* = 2.3, 4.6, 14.2, 14.3 Hz, 1H), 2.08-2.28 (m, 2H), 2.39-2.50 (m, 2H), 2.58 (m, 1H), 2.85-2.95 (ddd, *J* = 8.6, 14.2, 15.8 Hz, 1H), 3.02 (q, *J* = 8.8 Hz, 1H), 3.57 (dd, *J* = 4.5, 9.0 Hz, 1H), 3.85 (d, *J* = 9.1 Hz, 1H), 3.98 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.5, 27.4, 32.7, 37.8, 39.2, 45.4, 47.8, 72.5, 74.0, 211.7; MS (CI) *m/z* 167 (M+H), 157, 149, 141, 137, 123, 113, 95; HRMS (CI) *m/z* 167.0992 (calcd for $C_{10}H_{15}O_2$: 167.0994).

(2a*R*,2a^1*R*,3*R*,3a*S*,6a*S*)-3-Methyl-2a^1,3,3a,6a-tetrahydro-2*H*-cyclobuta[*cd*] benzofuran-4(2a*H*)-one (14). To a solution of **13** (20 mg, 0.12 mmol) in EtOAc (4 mL) was added phenylselenyl chloride (35 mg, 0.18 mmol) and the mixture was stirred for 1 h at room temperature. The mixture was washed with saturated aqueous $NaHCO_3$ (1 mL) and saturated aqueous NaCl (1 mL), and was concentrated under reduced pressure. The residue was dissolved in THF (4 mL) and water (2 mL) and the solution was treated with $NaIO_4$ (77 mg, 0.36 mmol). The mixture was stirred for 3 h at room temperature and was poured into a mixture

of Et_2O (10 mL) and water (5 mL). The organic phase was separated, the aqueous phase was extracted with EtOAc (3 x 10 mL), and the combined organic extract was washed with brine and dried over anhydrous $MgSO_4$. The solvent was removed under vacuum and the residue was chromatographed on silica, using 15% EtOAc in hexane as eluent, to give 16 mg (81%) of **14** as a colorless oil: $[\alpha]_D^{23}$ +175 (*c* 1.0, $CHCl_3$); IR (neat) 2955, 2924, 2862, 1668, 1044 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.27 (d, *J* = 7.0 Hz, 3H), 2.31 (m, 1H), 2.58 (dd, *J* = 8.4, 8.5 Hz, 1H), 2.70 (m, 1H), 3.17 (ddd, *J* = 8.2, 8.2, 8.4 Hz, 1H), 3.59 (dd, *J* = 4.7, 9.8 Hz, 1H), 3.80 (d, *J* = 9.7 Hz, 1H), 4.38 (dd, *J* = 5.1, 8.3 Hz, 1H), 6.15 (d, *J* = 10.0 Hz, 1H) 7.08 (dd, *J* = 5.2, 10.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.0, 37.4, 39.4, 44.2, 46.0, 70.4, 71.1, 131.6, 144.7, 198.0; MS (CI) *m/z* 165 (M+H), 147, 139, 135, 111, 95; HRMS (CI) *m/z* 165.0915 (calcd for $C_{10}H_{13}O_2$: 165.0916).

7-Hydroxymethyl-8-methylbicyclo[4.2.0]oct-4-en-2-one (15). To a solution of Zn-Cu dust (98 mg) in dry EtOH (3 mL) was added a solution of **13** (49 mg, 0.12 mmol) in dry EtOH (1 mL) under argon and the mixture was refluxed for 10 h. The solution was cooled to room temperature and filtered and the filtrate was concentrated under vacuum. The residue was chromatographed on silica, using 30% EtOAc in hexane as eluent, to give 26 mg (52%) of **15** as a colorless oil: IR (neat) 3419, 2920, 2862, 1699, 1257, 1020 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.19 (d, *J* = 6.7 Hz, 3H), 2.20-2.43 (m, 1H), 2.64 (m, 1H), 2.81-2.90 (m, 1H), 3.00-3.14 (m, 1H), 3.29-3.38 (m, 1H), 3.65-3.71 (m, 1H), 5.88 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.3, 36.9, 37.0, 37.4, 47.6, 49.7, 62.8, 124.6, 125.9, 208.2.

9-Hydroxy-8-methyltricyclo[3.3.1.$0^{2,7}$]non-3-en-6-one (16). To a solution of **15** (14 mg, 0.082

mmol) in CH_2Cl_2 (3 mL) was added Dess-Martin periodinane (52 mg, 0.123 mmol) and the mixture was stirred for 1.5 h at room temperature. The solution was diluted with Et_2O (5 mL), aqueous 10% $Na_2S_2O_3$ (2 mL) was added and the mixture was stirred for 20 min. The solution was washed with brine (5 mL) and was extracted with Et_2O (2 x 20 mL). The extract was dried over anhydrous $MgSO_4$, the solvent was removed under vacuum and the residue was chromatographed on silica, using 15% EtOAc in hexane as eluent, to give 9 mg (67%) of **16** as a colorless oil: IR (neat) 3409, 2959, 1719, 1073 cm-1; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.48 (d, *J* = 7.0 Hz, 3H), 2.42 (m, 2H), 2.57 (m, 1H), 3.25 (m, 1H), 3.62 (m, 1H), 4.04 (m, 1H), 6.19 (m, 1H), 6.32 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.5, 33.8, 38.3, 41.9, 51.3, 58.5, 73.8, 131.6, 132.6, 209.9.

(((2a*R*,2a^1*R*,3*R*,3a*S*,6*R*,6a*R*)-6-Azido-3-methyl-2a,2a^1,3,3a,6,6a-hexahydro-2*H*-cyclobuta[*cd*]benzofuran-4-yl)oxy)triisopropylsilane (18). To a solution of **13** (0.20 g, 1.20 mmol) and TIPSCI (0.31 mL, 1.44 mmol) in THF (5 mL) at 0 °C was added slowly KHMDS (2.9 mL, 0.5M solution in toluene, 1.44 mmol) and the solution was stirred for 30 min at room temperature. The solution was diluted with Et_2O (20 mL), washed with water and brine, and dried over $MgSO_4$. The solvent was removed under vacuum and the residue was chromatographed on silica, using 20% EtOAc in hexane as eluent, to give crude silyl enol ether **17**. This material was dissolved in CH_2Cl_2 (10 mL) and iodosobenzene (0.32 g, 1.44 mmol) was added to the solution. The resulting suspension was cooled to -19 °C, trimethylsilyl azide (CAUTION! this compound can generate explosive hydrazoic acid, 0.38 mL, 2.89 mmol) was added and the mixture was stirred at -19 °C for 45 min, at which point the suspension had become a colorless solution. The mixture was allowed to warm to room temperature, the

solvent was removed under vacuum, and the residue was filtered and washed with a 1:1 mixture of Et_2O (30 mL) and hexane (30 mL). The filtrate was concentrated under vacuum and the residue was chromatographed on silica, using 4% EtOAc in hexane as eluent, to give 0.32 g (73%) of **18** as a colorless oil: $[\alpha]_D^{23}$ -110 (*c* 1.2, $CHCl_3$); IR (neat) 2946, 2866, 2099, 1649, 1377, 1228, 1199 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.05 (dd, *J* = 2.2, 7.1 Hz, 18H), 1.12-1.28 (m, 3H), 1,22 (d, *J* = 7.0 Hz, 3H), 1.90 (m, 1H), 2.29 (dd, *J* = 6.6, 8.3 Hz, 1H), 2.49 (ddd, *J* = 5.1, 5.2, 8.3 Hz, 1H), 3.08 (ddd, *J* = 6.7, 8.4, 8.7 Hz, 1H), 3.51 (dd, *J* = 5.0, 9.2 Hz, 1H), 3.75 (d, *J* = 9.5 Hz, 1H), 3,79 (dd, *J* = 3.1, 6.6 Hz, 1H), 4.20 (dd, *J* = 2.2, 6.7 Hz, 1H), 4.83 (d, *J* = 6.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.5 (3C), 17.9 (7C), 21.8, 34.5, 38.6, 40.0, 44,4, 58.7, 72.6, 93.9, 157.8; MS (CI) *m/z* 364 (M+H), 321, 266, 165, 157, 131; HRMS (CI) *m/z* 364.2419 (calcd for $C_{19}H_{34}N_3O_2Si$: 364.2402).

***N*-(-3-Methyl-4-((triisopropylsilyl)oxy)-2a,2a^1,3,3a,6,6a-hexahydro-2*H*-cyclobuta[*cd*]benzofuran-6-yl)acrylamide (20).** To a solution of **18** (0.26 g, 0.74 mmol) in Et_2O (6 mL) at 0 °C was added $LiAlH_4$ (41 mg, 1.09 mmol) and the suspension was stirred for 1 h. The mixture was diluted with Et_2O and the reaction was quenched with 15% aqueous NaOH (0.078 mL). The mixture was stirred with $MgSO_4$ (2.63 g) for 2 h, then was filtered and the collected solid was washed with EtOAc. Removal of the solvent under vacuum left crude amine **19** (0.24 g). To a solution of the crude amine and Et_3N (0.12 mL, 0.87 mmol) in Et_2O (6 mL) at 0 °C was added acryloyl chloride (0.076 mL, 0.94 mmol) and the solution was stirred for 1h. The mixture was diluted with Et_2O (30 mL), washed with aqueous 0.1N HCI and brine, and dried over $MgSO_4$. The solvent was removed under vacuum and the residue was chromatographed on silica, using 5% MeOH in CH_2Cl_2 as eluent, to give 0.24 g (84%) of **20** as

a colorless oil: IR (neat) 3273 (br), 2944, 2865, 1655, 1532, 1223, 1196 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.08 (dd, *J* = 3.4, 7.0 Hz, 18H), 1.10-1.23 (m, 3H), 1.20 (d, *J* = 7.0 Hz, 3H), 1.92 (m, 1H), 2.20 (dd, *J* = 6.9, 9.2 Hz, 1H), 2.43 (m, 1H), 2.96 (m, 1H), 3.48 (dd, *J* = 5.2, 9.1 Hz, 1H), 3.78 (d, *J* = 9.1 Hz, 1H), 3.82 (dd, *J* = 2.2, 6.9 Hz, 1H), 4.79 (d, J = 6.2 Hz, 2H), 4.90 (m, 1H), 5.15 (m, 1H), 5.62 (dd, J = 1, 10 Hz, 1H), 6,01 (dd, *J* = 10, 17 Hz, 1H), 6,25 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.6 (3C), 17.9 (6C), 21.9, 33.9, 38.2, 40.0, 44,4, 47.2, 72.6, 76.3, 97.3, 126.4, 130.8, 155.7, 164.3; HRMS (CI) *m/z* 392.2622 (calcd for $C_{22}H_{38}NO_3Si$: 392.2621).

2-Bromo-*N*-((2a*R*,2a^1*R*,3*R*,3a*S*,6*R*,6a*R*)-3-methyl-4-((triisopropylsilyl)oxy)-2a,2a^1,3,3a,6,6a-hexahydro-2*H*-cyclobuta[*cd*]benzofuran-6-yl)acrylamide (22). To a solution of **18** (0.263 g, 0.742 mmol) in Et_2O (7 mL) at 0 °C was added $LiAlH_4$ (0.041 g, 1.09 mmol) and the suspension was stirred for 1 h. The mixture was diluted with Et_2O and the reaction was quenched with 15% aqueous NaOH (0.078 mL). The mixture was stirred with $MgSO_4$ (2.63 g) for 2 h, then was filtered and the collected solid was washed with EtOAc. Removal of the solvent under vacuum left virtually pure **19** (0.24 g). In a separate flask, a solution of 2-bromoacrylic acid (0.44 g, 2.90 mmol), oxalyl chloride (0.76 mL, 8.69 mmol) and a catalytic amount of DMF in CH_2Cl_2 (5 mL) was stirred at room temperature for 12 h. The solvent was removed in vacuo and the resulting α-bromoacryloyl chloride was added to a solution of **19,** prepared above, and Et_3N (0.30 mL, 2.17 mmol) in Et_2O (8 mL) at 0 °C. The solution was stirred for 1 h at 0 °C and diluted with Et_2O (30 mL). The solution was washed with aqueous 0.1N HCI and brine, dried over $MgSO_4$ and concentrated under vacuum to leave a residue which was chromatographed on silica, using 13% EtOAc in hexane as eluent, to give 0.22 g (59%) of **22** as a colorless oil: IR (neat) 3325 (br), 2943, 2864, 1657, 1495, 1223, 1196

cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08 (dd, *J* = 3.4, 7.0 Hz, 18H), 1.12-1.21 (m, 3H), 1.20 (d, *J* = 7.0 Hz, 3H), 1.92 (m, 1H), 2.23 (dd, *J* = 6.9, 9.2 Hz, 1H), 2.47 (ddd, *J* = 5.3, 5.8, 8.4 Hz, 1H), 2.99 (m, 1H), 3.49 (dd, *J* = 5.2, 9.1 Hz, 1H), 3.78 (d, *J* = 9.1 Hz, 1H), 3.82 (dd, *J* = 2.2, 6.9 Hz, 1H), 4.81 (m, 2H), 6,00 (d, *J* = 1.2 Hz, 1H), 6,22 (br d, *J* = 6.8 Hz, 1H), 7.00 (d, *J* = 1.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.5 (3C), 17.9 (6C), 21.9, 33.9, 38.2, 40.0, 44,4, 48.3, 72.7, 75.9, 97.0, 122.7, 127.5, 156.3, 159.8; MS (CI) *m/z* 470 (M+H), 428, 400, 392, 321, 193, 165, 157; HRMS (CI) *m/z* 470.1728 (calcd for $C_{22}H_{37}BrNO_3Si$: 470.1726).

(1*R*,1a*R*,1a^1*R*,3a*R*,4a*R*,6*R*,6b*S*)-6-Bromo-1-methyl-6a-((triisopropylsilyl)oxy)decahydro-1*H*-4,6-(epiminomethano)dicyclobuta[*cd*,*f*]benzofuran-7-one (25). To a solution of **22** (11 mg, 0.021 mmol) in CH_2Cl_2 (2 mL) was added Me_3Al (0.027 mL, 2M in hexane, 0.027 mmol) and the solution was stirred at 70 °C for 24 h. The solution was diluted with EtOAc (10 mL), washed with aqueous $NaHCO_3$ (0.5 mL) and brine, and dried over $MgSO_4$. The solvent was removed under vacuum and the residue was chromatographed on silica, using 50% EtOAc in hexane as eluent, to give 7.6 mg (76%) of **25** as a pale yellow solid: IR (neat) 3296 (br), 2944, 2925, 2866, 1689, 1459, 1195, 1127 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.13-1 23 (m, 21H), 1.12 (d, *J* = 7.1 Hz, 3H), 1.79 (dd, *J* = 6.6, 9.0 Hz, 1H), 2.19 (m, 1H), 2.20 (ddd, *J* = 5.4, 5.6, 8.7 Hz, 1H), 2.29 (d, *J* = 9.0 Hz, 1H), 2.85 (m, 1H), 3.00 (dd, *J* = 7.1, 9.0 Hz, 1H), 3.10 (ddd, *J* = 1.2, 5.5, 7.0 Hz, 1H), 3.69 (dd, *J* = 5.4, 9.1 Hz, 1H), 3.90 (dd, *J* = 6.8, 6.9 Hz, 1H), 3.92 (d, *J* = 9.2 Hz, 1H), 4.09 (m, 1H), 6.11 (br, s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.5 (3C), 18.5 (Si-^{i}Pr), 18.6 (Si-^{i}Pr), 22.4, 33.9, 36 2, 36.9, 37.9, 38.4, 41.2, 50.9, 69.0, 75.9, 77.9, 81.4, 172.6; MS (CI) *m/z* 470 (M+H), 428, 406, 390, 362, 321, 250, 232; HRMS (CI) *m/z* 469.1638 (calcd for $C_{22}H_{36}BrNO_3Si$: 469.1648).

(2a*R*,2a^1*R*,3*R*,3a*S*,4a*S*,8a*R*,8b*R*)-6-Bromo-3-methyloctahydro-2*H*-cyclobuta-[3,4]benzofuro[7,6-*b*]pyridine-4,7-(2a*H*,2a^1*H*)-dione (27 and 28). To a solution of **25** (195 mg, 0.415 mmol) in $MeNO_2$ (20 mL) was added aqueous HF (48%, 1 mL) and the solution was stirred for 2 h. The mixture was diluted with EtOAc (50 mL), washed with aqueous $NaHCO_3$ (10 mL) and brine, and dried over $MgSO_4$. The solvent was removed under vacuum and the residue was chromatographed on silica, using 90% EtOAc in hexane and 1% MeOH in EtOAc as eluent, to give 83 mg (64 %) of **27** as a colorless oil and 29 mg (22%) of **28** as a colorless oil. **27**: IR (neat) 3193 (br), 3062 (br), 2950, 2916, 2862, 1676, 942 cm-1; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.27 (d, *J* = 7.1 Hz, 3H), 2.20 (m, IH), 2.48-2,60 (m, 2H), 2.71 (dd, *J* = 6.8, 9.4 Hz, 1H), 2.95 (m, 1H), 3.09 (ddd, *J* = 4.0, 4.1, 15.3 Hz, 1H), 3.38 (m, 1H), 3.66 (dd, *J* = 5.2, 9.3 Hz, 1H), 3.87 (dd, *J* = 4.0, 6.7 Hz, 1H), 3.95 (d, *J* = 9.4 Hz, 1H), 4.38 (dd, *J* = 4.1, 5.1 Hz, 1H), 4.48 (dd, *J* = 4.0, 6.9 Hz, 1H), 6.43 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.7, 31.2, 36.9, 38.6, 39.6, 41.1, 44.2, 45.4, 54.2, 73.8, 76.1, 169.3, 210.6; MS (CI) *m/z* 314 (M+H), 276, 264, 236, 166; HRMS (CI) *m/z* 314.0393 (calcd for $C_{13}H_{17}BrNO_3$: 314.0392). **28:** IR (neat) 3210 (br), 3085 (br), 2953, 2923, 2863, 1681, 1270, 1179, 1109 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.21 (d, *J* = 7.1 Hz, 3H), 2.10-2.30 (m, 2H), 2.55 (dd, *J* = 8.8, 8.9 Hz, 1H), 2.68 (m, 1H), 3.18 (m, 3H), 3.62 (dd, *J* = 4.2, 10.6 Hz, 1H), 3.90 (d, *J* = 10.6 Hz, 1H), 3.91 (m, 1H), 4.47 (dd, *J* = 3.3, 3.4 Hz, 1H), 4.53 (dd, *J* = 7.0, 10.7 Hz, 1H), 6.53 (br, s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.0, 32.6, 37.1, 37.7, 40.8, 41.1, 44.6, 46.7, 56.8 72.7, 75.8, 168.9, 208.5; MS (CI) m/z 314 (M+H), 276, 264, 250, 236, 166; HRMS (CI) *m/z* 314.0390 (calcd $C_{13}H_{17}BrNO_3$: 314.0392).

(2a*R*,2a^1*R*,3*R*,3a*S*,4a*S*,5a*S*,7a*R*,7b*R*)-3-Methyloctahydrocyclobuta[3,4]-benzofuro[7,6-

***b*]cyclopropa[*c*]pyrrole-4,6-(2a^1*H*,7b*H*)-dione (29)**. To a solution of the mixture of **27** and **28** (3 mg, 0.011 mmol) in toluene (4 mL) was added DBU (0.0043 mL, 0.029 mmol) and the solution was refluxed for 4 h. The cooled solution was diluted with Et_2O (10 mL), washed with brine, and dried over $MgSO_4$. The solvent was removed under vacuum and the residue was chromatographed on silica, using 80% EtOAc in hexane and 1% MeOH in EtOAc as eluent, to give 1 mg (43%) of **29** as a colorless oil: IR (neat) 2920, 2847, 1699, 1459, 1406, 1064 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.13 (dd, *J* = 5.2, 5.2 Hz, 1H), 1,25 (d, *J* = 7.0 Hz, 3H), 1.91 (dd, *J* = 4.3, 9.3 Hz, 1H), 2.19 (dd, *J* = 5.1, 9.4 Hz, 1H), 2.30 (m, 1H), 2.51 (dd, *J* = 6.9, 9.2 Hz, 1H), 3.59 (ddd, *J* = 5.1, 5.3, 7.1 Hz, 1H), 3.48 (m, 1H), 3.57 (dd, *J* = 5.0, 9.2 Hz, 1H), 3.78 (d, *J* = 5.2 Hz, 1H), 3.90 (d, *J* = 9.3 Hz, 1H), 4.29, (s, 1H), 5.65 (br, s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.2, 21.8, 30.0, 35.5, 36.7, 38.4, 44.9, 45.4, 58.9, 73.3, 77.6, 174.5, 206.1; MS (CI) *m/z* 234 (M+H), 180, 164; HRMS (CI) *m/z* 234.1125 (calcd for $C_{13}H_{16}NO_3$: 234.1130).

***N*-((2a*R*,2a^1*R*,3*R*,3a*S*,6*R*,6a*R*)-3-Methyl-4-((triisopropylsilyl)oxy)-2a,2a^1,3,3a,6,6a-hexahydro-2*H*-cyclobuta[*cd*]benzofuran-6-yl)-2-(phenylselanyl)acrylamide (30).** To a solution of **18** (29 mg, 0.078 mmol) in Et_2O (1 mL) at 0 °C was added $LiAlH_4$ (5 mg, 0.117 mmol) and the suspension was stirred for 1 h. The mixture was diluted with Et_2O and the reaction was quenched with 15% aqueous NaOH (0.017 mL). The mixture was stirred with $MgSO_4$ (0.5 g) for 2 h, then was filtered and the collected solid was washed with EtOAc. The solvent was removed under vacuum to leave crude **19**. In a separate flask, a solution of 3,5-dinitrobenzoyl chloride (37 mg, 0.163 mmol) and Et_3N (0.045 mL, 0.325 mmol) in CH_2Cl_2 (1 mL) was prepared and a solution of α-phenylselenoacrylic acid (37 mg, 0.163 mmol) in CH_2Cl_2 (1 mL) was added. The mixture was stirred for 1 h at room temperature, a solution of crude **19**

prepared above and DMAP (1 mg, 0.008 mmol) in CH_2Cl_2 (0.5 mL) was added, and the mixture was stirred for 1 h. The solvent was removed under vacuum and the residue was chromatographed on silica, using 15% EtOAc in hexane as eluent, to give 30 mg (69%) of **30** as a colorless oil: $[\alpha]_D^{23}$ -0.47 (c 1.51, $CHCl_3$); IR (neat) 3395 (br), 2944, 2864, 1655, 1649, 1491, 1477, 1223, 1196; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.00-1,15 (m, 21H), 1.17 (d, *J* = 7.0 Hz, 3H), 1.85 (m, 1H), 2,02 (dd, *J* = 6.9, 8.1 Hz, 1H), 2 29-2.40 (m, 2H), 3.40 (dd, *J* = 4.2, 9.1 Hz, 1H), 3.58 (dd, *J* = 2.2, 6.8 Hz, 1H), 3.70 (d, *J* = 9.2 Hz, 1H), 4.67 (d, *J* = 7.0 Hz, 1H), 4.73 (ddd, *J* = 3.3, 7.1, 7.2 Hz, 1H), 6.10 (s, 1H), 6.40 (br, d, *J* = 7.1 Hz, 1H), 6,91 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.6 (3C), 18.0 (6C), 22,0, 33.6, 38.2, 39.9, 44.3, 48.0, 72.6, 75.9, 97.3, 127.5, 129.5, 131.1, 131.3, 133.1, 133.2, 156.0, 162.8; MS (CI) *m/z* 547 (M+), 478, 432, 392, 350, 321, 236, 159; HRMS (CI) *m/z* 547.2023 (calcd for $C_{28}H_{41}NO_3SiSe$: 547.2021).

(1*R*,1a*R*,1a^1*R*,3a*R*,4a*R*,6*R*,6b*S*)-1-Methyl-6-(phenylselenyl)-6a-((triisopropylsilyl)oxy)decahydro-1*H*-4,6-(epiminomethano)dicyclobuta[*cd*,*f*]benzofuran-7-one (31). To a solution of **30** (150 mg, 0.275 mmol) in CH_2Cl_2 (10 mL) was added Me_3Al (0.42 mL, 2M in hexane, 0.824 mmol) and the solution was stirred at 80 °C for 38 h. The solution was diluted with CH_2Cl_2 (30 mL), saturated aqueous potassium tartrate (30 mL) was added, and the mixture was stirred vigorously for 15 min. The separated aqueous phase was extracted with CH_2Cl_2 (3 x 20 mL) and the combined organic solution was dried over $MgSO_4$. The solvent was removed under vacuum and the residue was chromatographed on silica, using 90% EtOAc in hexane as eluent, to give 104 mg (69 %) of **31** as a colorless solid: $[\alpha]_D^{23}$ -8.3 (*c* 1.8, $CHCl_3$); IR (neat) 3237 (br), 3067 (br), 2955, 2862, 1677, 1470, 1201, 1147, 1123 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.05 (d, *J* = 7.0 Hz, 3H), 1.13-1.31 (m, 21H), 1.79 (dd, *J* = 7.0, 9.3 Hz, 1H),

2.02-2.20 (m, 3H), 2.84 (m, 1H), 3.02 (m, 1H), 3.69 (dd, *J* = 5.2, 9.2 Hz, 1H), 3.84 (dd, *J* = 5.2, 5.3 Hz, 1H), 3.94 (d, *J* = 9.1 Hz, 1H), 4.02 (dd, *J* = 4.7, 4.8 Hz, 1H), 5.80 (br, s, 1H), 7.18 (m, 3H), 7.60 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.6 (3C), 18.7 (Si-^{i}Pr), 18.8 (Si-^{i}Pr), 22.5, 34.1, 35.2, 36.7, 38,1, 39.6, 41.2, 51.4, 64.9, 76.0, 78.1, 82.5, 127.3, 127.9, 128.4, 135.4, 175.4; MS (CI) *m/z* 547 (M+), 478, 432, 390, 322, 276, 251; HRMS (CI) *m/z* 547.2025 (calcd for $C_{28}H_{41}NO_3SiSe$: 547.2021).

(2a*R*,2a^{1}*R*,3*R*,3a*S*,4a*S*,8a*R*,8b*R*)-3-Methyl-6-(phenylselanyl)octahydro-2*H*-cyclobuta[3,4]benzofuro[7,6-*b*]pyridine-4,7-(2a*H*,2a^{1}*H*)-dione (32 and 33). To a solution of **31** (14 mg, 0.026 mmol) in $MeNO_2$ (1.9 mL) was added aqueous HF (48%, 0.1 mL) and the solution was stirred at room temperature for 2 h. The mixture was diluted with EtOAc (20 mL), washed with aqueous $NaHCO_3$ (5 mL) and brine, and dried over $MgSO_4$. The solvent was removed under vacuum and the residue was chromatographed on silica, using 90% EtOAc in hexanes as eluent, to give 4 mg (40%) of **32** as a colorless oil and 5 mg (50%) of **33** as a colorless oil. **32**: IR (neat) 3184 (br), 3070 (br), 2951, 2934, 2859, 1693, 1660, 1475, 1395 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18 (d, *J* = 7.1 Hz, 3H), 1.80 (ddd, *J* = 5.1, 11.7, 14.2 Hz, 1H), 2.19 (m, 1H), 2.50 (dd, *J* = 8.2, 8.4 Hz, 1H), 2.62 (ddd, *J* = 4.0, 6.9, 7.0 Hz, 1H), 2.83 (ddd, *J* = 3.5, 8.2, 14.1 Hz, 1H), 3.01 (dd, *J* = 4.1, 7.1 Hz, 1H), 3.10 (ddd, *J* = 7.2, 7.3, 8.2 Hz, 1H), 3.58 (dd, *J* = 4.0, 10.8 Hz, 1H), 3.82 (dd, *J* = 3.4, 7.1 Hz, 1H), 3.84 (d, *J* = 10.8 Hz, 1H), 4.01 (dd, *J* = 8.2, 11.0 Hz, 1H), 4,08 (dd, *J* = 3.3, 3.4 Hz, 1H), 7.02 (s, 1H), 7.32 (m, 3H), 7.63 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.0, 28.8, 37.1, 37.7, 37.8, 40.3, 44.6, 46.9, 56.6, 72.8, 76.0, 127.6, 128.4, 129.1, 135.4, 172.1, 209.0; MS (CI) *m/z* 390 (M+H), 310, 264, 236, 217, 159; HRMS (CI) *m/z* 390.0766 (calcd for $C_{19}H_{22}NO_3{}^{78}Se$: 390.0773). **33**: ^{1}H NMR (300 MHz, $CDCl_3$) δ

1.24 (d, *J* = 7.1 Hz, 3H), 2.12-2.30 (m, 2H), 2.57 (m, 1H), 2.68 (dd, *J* = 8.2, 8.2 Hz, 1H), 2.79 (ddd, *J* = 5.1, 5.1, 15.6 Hz, 1H), 2.94 (ddd, J = 5.0, 5.1, 5.1 Hz, 1H), 3.30 (ddd, *J* = 7.1, 7.1, 7.2 Hz, 1H), 3.60 (dd, *J* = 5.2, 9.8 Hz, 1H), 3.84 (dd, *J* = 4.1, 6.9 Hz, 1H), 3.89 (d, *J* = 9.8 Hz, 1H), 3.99 (dd, *J* = 5.1, 7.1 Hz, 1H), 4.30 (dd, *J* = 4.1, 4.2 Hz, 1H), 6.78 (br, s, 1H), 7.29 (m, 3H), 7,70 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.5, 28.2, 37.2, 39.0, 39.6, 40.1, 44.5, 45.6, 55.0, 73.5, 76.4, 128.1, 129.0, 129.9, 134.9, 172.9, 210.9.

(2a*R*,2a^1*R*,3*R*,3a*S*,8b*R*)-3-Methyl-3,3a,8,8b-tetrahydro-2*H*-cyclobuta[3,4]benzofuro[7,6-*b*]pyridine-4,7-(2a*H*,2a^1*H*)-dione (34). To a solution of **31** (21 mg, 0.037 mmol) in $MeNO_2$ (10 mL) was added dropwise aqueous HF (48%, 0.06 mL, 0.15 mmol) and the mixture was stirred for 1.5 h at room temperature. The solvent was removed under reduced pressure and the residue was taken up into MeOH (5 mL) and H_2O (13 mL). To this solution was added a solution of $NaIO_4$ (24 mg, 0.11 mmol) in H_2O (0.2 mL) and the mixture was stirred for 15 h at room temperature. The solvent was removed under reduced pressure and the residue was taken up into $CHCl_3$ (20 mL). The solution was washed with saturated $NaHCO_3$ (2 mL) and brine (5 mL), and the combined aqueous washings were extracted with $CHCl_3$ (4 x 20 mL). The combined organic extract was dried over $MgSO_4$ and the solvent was removed under vacuum to leave a residue which was chromatographed on silica, using 2% MeOH in EtOAc as eluent, to give 7 mg (83%) of **34** as a colorless solid: mp 197-199 °C; $[\alpha]_D^{23}$ -114.8 (*c* 1.51, $CHCl_3$); IR (neat) 2958, 1655, 1638, 1408, 1285, 1248; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30 (d, *J* = 7.0 Hz, 3H), 1.35 (m, 1H), 2.75 (dd, *J* = 8.8, 8.9 Hz, 1H), 2.80 (m, 1H), 3.37 (ddd, *J* = 8.8, 8.8, 8.9 Hz, 1H), 3.57 (dd, *J* = 4.2, 9.0 Hz, 1H), 3.89 (d, *J* = 9.0 Hz, 1H), 4.77 (d, *J* = 8.9 Hz, 1H), 6.60 (d, *J* = 10.7 Hz, 1H), 8.05 (d, *J* = 10.8 Hz, 1H), 12.50 (br, s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.2,

37.5, 39.3, 43.3, 46.0, 72.1, 72.2, 114.2, 120.9, 138.6, 151.2, 165.2, 193.1; MS (CI) *m/z* 232 (M+H), 223, 203, 189, 174, 149, 131, 121; HRMS (CI) *m/z* 232.0970 (calcd for $C_{13}H_{14}NO_3$: 232.0974).

(2a*R*,2a^1*R*,3*R*,3a*S*,8b*R*)-7-Methoxy-3-methyl-2a^1,3,3a,8b-tetrahydro-2*H*-cyclobuta[3,4]benzofuro[7,6-*b*]pyridin-4(2a*H*)-one (35). To a solution of **34** (29 mg, 0.126 mmol) in $CHCl_3$ (2 mL) was added Ag_2CO_3 (173 mg, 0.628 mmol) and MeI (0.47 mL, 7.53 mmol) and the mixture was stirred for 40 h at room temperature. The mixture was filtered through a pad of Celite which was washed with Et_2O (10 mL) and the filtrate was concentrated under reduced pressure. The residue was chromatographed on silica, using 30% EtOAc in hexanes as eluent, to give 28 mg (91%) of **35** as a colorless solid: mp 100-102 °C; $[\alpha]_D^{23}$ -3.8 (*c* 2.0, $CHCl_3$); IR (neat) 2949, 2920, 2857, 1671, 1594, 1484, 1324, 1269 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.35 (d, *J* = 7.0 Hz, 3H), 2.34 (m, 1H), 2.73 (dd, *J* = 8.7, 8.8 Hz, 1H), 2.78 (ddd, *J* = 4.1, 6.8, 7.1 Hz, 1H), 3,32 (dd, *J* = 8.8, 8.8, 8.9 Hz, 1H), 3.68 (dd, *J* = 4.2, 9.2 Hz, 1H), 3.85 (d, *J* = 9.2 Hz, 1H), 4.05 (s, 3H), 4.79 (d, *J* = 7.1 Hz, 1H), 6,80 (d, *J* = 9.1 Hz, 1H), 8.20 (d, *J* = 9.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.5, 37.2, 39.0, 43.9, 46.1, 54.2, 71.9, 77.1, 112.4, 122.8, 137.9, 159.0, 166.6, 196.7; MS (CI) *m/z* 246 (M+H), 216, 192, 175; HRMS (CI) *m/z* 246.1127 (calcd for $C_{14}H_{16}NO_3$: 246.1132).

(5a*S*,6*R*,7*R*,7a*R*)-7-(Hydroxymethyl)-2-methoxy-6-methyl-6,7,7a,8-tetrahydrocyclobuta[*g*]quinolin-5(5a*H*)-one (36). To a solution of **35** (20 mg, 0.082 mmol) in 0.2M NaOH in MeOH (20 mL) was added activated Zn (0.54 g, 8.2 mmol) and the suspension was stirred for 2 h at 90 °C. An additional quantity (0.54 g) of activated Zn was added to the

mixture which was stirred for a further 4 h at 90 °C. The cooled mixture was neutralized with 1N HCI in MeOH (4 mL) and was filtered through a pad of Celite. The filtrate was concentrated under reduced pressure and the residue was chromatographed on silica, using 40% EtOAc in hexanes as eluent, to give 19 mg (94%) of **36** as a colorless solid: mp 107-110 °C; IR (neat) 3394 (br), 2916, 2853, 1668, 1625, 1589, 1328 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.11 (d, *J* = 6.9 Hz, 3H), 2.35 (m, 2H), 2.75 (dd, *J* = 8.2, 8.2 Hz, 1H), 3.10 (m, 3H), 3.67 (dd, *J* = 6.9, 11.1 Hz, 1H), 3.73 (dd, *J* = 8.1, 11.2 Hz, 1H), 4.00 (s, 3H), 6.74 (d, *J* = 9.3 Hz, 1H), 8.07 (d, *J* = 9.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.8, 29.1, 37.9 (2C), 45.4, 46.7, 53.9, 62.0, 109.8, 123.0, 137.6, 162.8, 166.3, 198.0; MS (CI) *m/z* 248 (M+H), 230, 204, 190; HRMS (CI) *m/z* 248.1284 (calcd for $C_{14}H_{18}NO_3$: 248.1287).

(5a*S*,6*R*,7*R*,7a*R*)-2-Methoxy-6-methyl-5-oxo-5,5a,6,7,7a,8-hexahydrocyclobuta[*g*]quinoline-7-carbaldehyde (37). To a solution of **36** (13 mg, 0.053 mmol) in CH_2Cl_2 (3 mL) was added Dess-Martin periodinane (38 mg, 0.11 mmol). The solution was stirred for 1 h at room temperature, then was diluted with Et_2O (5 mL) and 10% aqueous $Na_2S_2O_3$ (2 mL) was added. The mixture was stirred for 20 min and the aqueous phase was separated and extracted with Et_2O (10 mL). To the combined organic extract was added saturated aqueous $NaHCO_3$ (5 mL) and the mixture was stirred for 20 min. The separated organic layer was washed with water (3 mL) and brine (3 mL), and was dried over anhydrous $MgSO_4$. The solvent was removed under vacuum and the residue was chromatographed on silica, using 30% EtOAc in hexanes as eluent, to give 12 mg (93%) of **37** as a colorless oil: IR (neat) 2955, 2925, 1710, 1666, 1590, 1572, 1409, 1321, 1262 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.39 (d, *J* = 6.9 Hz, 3H), 2.80 (dd, *J* = 8.1, 8.1 Hz, 1H), 3.02 (m, 4H), 3.45 (m, 1H), 3.98 (s, 3H), 6.67 (d, *J* = 9.9 Hz, 1H), 8,09 (d, *J* =

9.9 Hz, 1H), 9.80 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.6, 29.7, 31.2, 34.5, 46.0, 54.0 (2C), 110.3, 123.0, 137.5, 161.4, 166.5, 196.8, 201.7; MS (CI) *m/z* 246 (M+H), 217, 202, 160; HRMS (CI) m/z 246.1126 (calcd for $C_{14}H_{16}NO_3$: 246.1130)

(5a*S*,6*R*,7*R*,7a*R*)-7-(1-Hydroxyethyl)-2-methoxy-6-methyl-6,7,7a,8-tetrahydrocyclobuta[*g*]quinolin-5(5a*H*)-one (38). To a solution of **37** (25 mg, 0.10 mmol) in CH_2Cl_2 (4 mL) at -78 °C was added dropwise MeMgI (1.5M in Et_2O, 0.1 mL, 0.15 mmol) and the solution was stirred for 1 h at -78 °C. The reaction was quenched with water, the mixture was allowed to warm to room temperature and Et_2O (20 mL) was added. The separated ethereal layer was washed with saturated aqueous $NaHCO_3$ (5 mL) and brine (3 mL), and was dried over anhydrous $MgSO_4$. The solvent was removed under vacuum and the residue was chromatographed on silica, using 30% EtOAc in hexanes as eluent, to give 9 mg (40%) of **38a** and 8 mg (36%) of **38b** as colorless oils. **38a**: IR (neat) 3408, 2959, 2891, 1650, 1586, 1322, 1269, 1020 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.16 (d, *J* = 6.9 Hz, 3H), 1.10 (d, *J* = 7.0 Hz, 3H), 1,60 (s, 1H), 2.05 (dd, *J* = 9.1, 18.0 Hz, 1H), 2.25 (m, 1H), 2,70 (dd, *J* = 9.2, 9.3 Hz, 1H), 3.10 (m, 2H), 3.25 (dd, *J* = 11.9, 20.2 Hz, 2H), 3.87 (m, 1H), 3.99 (s, 3H), 6.68 (d, *J* = 9.1 Hz, 1H), 8.07 (d, *J* = 9.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.9, 21.8, 29.5 (2C), 37.6, 46.2, 51.1, 53.9, 67.6, 109.7, 123.0, 130.9, 137.5, 163.0, 166.3, 198.0; MS (CI) *m/z* 262 (M+H), 244, 228, 175, 146; HRMS(CI) *m/z* 262.1444 (calcd for $C_{15}H_{20}NO_3$: 262.1443). **38b**: IR (neat) 3457 (br), 2954, 2920 ,1669, 1591, 1484, 1415, 1318, 1269 cm^{-1}; ^{1}H NMR (300 MHz, $CDCI_3$) δ 1.22 (d, *J* = 6.9 Hz, 3H), 1.39 (d, *J* = 7.0 Hz, 3H), 1.59 (s, 3H), 2.03 (m, 1H), 2.65 (m, 2H), 2.95 (m, 2H), 3,13 (dd, *J* = 11.8, 20.1 Hz, 2H), 4.00 (m, 1H), 4,01 (s, 3H), 6.64 (d, *J* = 8.8 Hz, 1H), 8.06 (d, *J* = 8.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCI_3$) δ 21.6, 22.8, 29.6, 30.1, 38.9, 46.4, 51.0, 53.9,

68.6, 109.8, 124.3, 137.5, 164.7, 166.7, 197.7; MS (CI) *m/z* 262 (M+H), 244, 228, 204, 175, 146; HRMS (CI) m/z 262.1439 (calcd for $C_{15}H_{20}NO_3$: 262.1443).

(5a*S*,6*R*,7*R*,7a*R*)-7-Acetyl-2-methoxy-6-methyl-6,7,7a,8-tetrahydrocyclobuta [*g*]quinolin-5(5a*H*)-one (39). To a solution of **38** (24 mg, 0.092 mmol) in CH_2Cl_2 (3 mL) was added Dess-Martin periodinane (67 mg, 0.184 mmol) and the solution was stirred for 2 h at room temperature. The solution was diluted with Et_2O (30 mL)**,** 10% aqueous $Na_2S_2O_3$ (5 mL) was added and the mixture was stirred for 10 min. The aqueous phase was separated and extracted with Et_2O (10 mL). To the combined organic solution was added saturated aqueous $NaHCO_3$ (5 mL) and the mixture was stirred for 10 min. The separated organic layer was washed with water (5 mL) and brine (5 mL), and was filtered through anhydrous $MgSO_4$. The filtrate was concentrated under vacuum and the residue was chromatographed on silica, using 30% EtOAc in hexanes as eluent, to give 22 mg (92%) of **39** as a colorless oil: $[\alpha]_D^{23}$ -6.8 (*c* 1.6 $CHCl_3$); IR (neat) 2944, 2925, 1704, 1674, 1630, 1591, 1567, 1415, 1327, 1264 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.31 (d, *J* = 6.9 Hz, 3H), 2.15 (s, 3H), 2.70 (dd, *J* = 8.5, 8.6 Hz, 1H), 2.90 (dd, *J* = 10.8, 17.3 Hz, 1H), 3.01 (m, 3H), 3.31 (m, 1H), 3.97 (s, 3H), 6.65 (d, *J* = 9.0 Hz, 1H), 8.07 (d, *J* = 8.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.3, 29.1, 30.1, 32.0, 35.0, 45.1, 53.9, 54.8, 110.1, 122.8, 137.4, 161.8, 166.3, 196.7, 207.1; MS (CI) *m/z* 260 (M+H), 216, 204, 175, 146; HRMS (CI) *m/z* 260.1287 (calcd for $C_{15}H_{18}NO_3$: 260.1287).

(5a*S*,6*R*,7*R*,7a*R*)-2-Methoxy-6-methyl-7-(prop-1-en-2-yl)-6,7,7a,8-tetrahydrocyclobuta[*g*]quinolin-5(5a*H*)-one (40). A. From 39. To a suspension of dried methyltriphenylphosphonium bromide (521 mg, 1.46 mmol) in THF (10 mL) under argon at 0

°C was added dropwise *n*-BuLi (0.567 mL, 1.55M in hexane, 0.878 mmol). The solution was stirred for 1 h then was left to stand for 2 h at 0 °C. To a solution of **39** (25 mg, 0.095 mmol) in THF (7 mL) at -78 °C was added dropwise the supernatant solution of Wittig reagent prepared above (1.77 mL, 0.142 mmol) and the solution was stirred for 1 h at -78 °C. The reaction was quenched with water, the mixture was allowed to warm to room temperature and Et_2O (20 mL) was added. The separated ethereal layer was washed with saturated aqueous $NaHCO_3$ (5 mL) and brine (3 mL), and was dried over anhydrous $MgSO_4$. The solvent was removed under vacuum and the residue was chromatographed on silica, using 5% EtOAc in hexanes and then 15% EtOAc in hexanes as eluent, to give 7 mg (27%, 54% based on recovered **39**) of **40** as a colorless oil: IR (neat) 2948, 2869, 1669, 1591, 1570, 1481, 1410, 1321, 1261 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.31 (d, *J* = 6.9 Hz, 3H), 1.71 (s, 3H), 2.74 (m, 3H), 2 88 (dd, *J* = 8.9, 17.2 Hz, 1H), 3.02 (m, 2H), 4.00 (s, 3H), 4.70 (s, 1H), 4.96 (d, *J* = 1.2 Hz, 1H), 6.64 (dd, *J* = 8.1, 9.0 Hz, 1H), 8.10 (d, *J* = 9.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.1, 22.2, 29.3, 32 5, 37.7, 46.1, 50.6, 54.3, 110.2, 111.3, 123.0, 137.9, 143 2, 163.8, 166.6, 197.8; MS (CI) *m/z* 257 (M+), 242, 228, 190, 175, 163, 149, 135; HRMS (CI) *m/z* 257.1420 (calcd for $C_{16}H_{19}NO_2$: 257.1416).

B. From 43. To a solution of **43** (20 mg, 0.051 mmol) in dioxane (2 mL) were added hexamethyldistannane (18 mg, 0.055 mmol), LiCl (7 mg, 0.17 mmol), tetrakis(triphenylphosphine)palladium (3 mg, 0.003 mmol) and a crystal of BHT. The mixture was heated at 90 °C for 4 h, then was cooled to room temperature and treated with pyridine (0.2 mL) followed by a solution of pyridinium fluoride (1.5M in THF, 0.4 mL). The mixture was stirred for 20 h at room temperature and filtered through Celite. The filtrate was washed with HCl (10%) and brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by chromatography on silica as described above to give 11 mg (76%)

of **40**.

2-Methoxy-6-methyl-5-methylene-5,5a,6,7,7a,8-hexahydrocyclobuta [*g*]quinolin-7-yl)ethan-1-one (41). IR (neat) 2957, 2919, 1704, 1594, 1474, 1304, 1262, 1029 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.24 (d, *J* = 6.9 Hz, 3H), 2.10 (s, 3H), 2.68 (m, 2H), 2.80 (m, 2H), 3.05 (m, 1H), 3.91 (s, 1H), 3.97 (m, 1H), 4.94 (dd, *J* = 1.0, 2.0 Hz, 1H), 5.24 (dd, *J* = 1.0, 2.0 Hz, 1H), 6.59 (d, *J* = 9.0 Hz, 1H), 7.63 (d, *J* = 8.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.8, 31.9, 34.0, 37.2, 42.1, 53.9, 55.1, 108.2, 109.2, 125.4, 136.0, 144.7, 154.1, 136.6, 208.3; HRMS (CI) *m/z* 258.1494 (calcd for $C_{16}H_{20}NO_2$: 258.1494).

2-Methoxy-6-methyl-5-methylene-7-(prop-1-en-2-yl)-5,5a,6,7,7a,8-hexahydrocyclobuta[*g*]quinolone (42). IR (neat) 2949, 2919, 1591, 1475, 1404, 1316, 1259 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.21 (d, *J* = 6.9 Hz, 3H), 1.71 (s, 3H), 2.39 (m, 3H), 2.60 (dd, *J* = 9, 9 Hz, 1H), 2.75 (m, 4H), 3.91 (s, 3H), 4.60 (s, 1H), 4.87 (s, 1H), 4.91 (s, 1H), 5.24 (s, 1H), 6.59 (d, *J* = 8 Hz, 1H), 7.68 (d, *J* = 8.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.1, 22.6, 30.8, 33.9, 42.5, 50.3, 53.9, 107.2, 108.7, 110.4, 124.9, 135.8, 144.1, 145.0, 155.5, 163.5; HRMS (CI) *m/z* 255.1618 (calcd for $C_{17}H_{21}NO$: 255.1623).

1-((5a*S*,6*R*,7*R*,7a*R*)-2-Methoxy-6-methyl-5-oxo-5,5a,6,7,7a,8-hexahydrocyclobuta[*g*]quinolin-7-yl)vinyl Trifluoromethanesulfonate (43). To a solution of **39** (3.0 mg, 0.012 mmol) in THF (4 mL) at -78 °C was added dropwise KHMDS (0.058 mL, 0.5M in toluene, 0.029 mmol) and the solution was stirred for 30 min at -78 °C. The solution was warmed to 0 °C, a solution of *N*-(5-chloro-2-pyridyl)triflimide (6 mg, 0.015 mmol) in THF

(0.5 mL) was added, and the mixture was stirred for 12 h at room temperature. The mixture was diluted with Et_2O (20 mL), water (5 mL) was added, and the phases were separated. The aqueous portion was extracted with Et_2O (2 x 10 mL) and the combined organic extract was washed with brine and was filtered through anhydrous $MgSO_4$. The filtrate was concentrated under reduced pressure and the residue was purified by chromatography on silica, using 25% EtOAc in hexanes as eluent, to give 3.1 mg (74%) of **43** as a colorless oil: IR (neat) 2962, 2924, 1669, 1592, 1556, 1418, 1266, 1212, 1142, 913 cm^{-1} ^1H NMR (300 MHz, $CDCl_3$) δ 1.40 (d, *J* = 6.9 Hz, 3H), 2.69 (m, 1H), 2.78 (dd, *J* = 8.8, 10.3 Hz, 1H), 3.10 (m, 4H), 4,00 (s, 3H), 4.99 (dd, *J* = 1.2, 4.8 Hz, 1H), 5.35 (d, *J* = 4.8 Hz, 1H), 6 68 (d, *J* = 9.9 Hz, 1H), 8.10 (d, *J* = 9.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.8, 29.6, 32.2, 38.6, 45.8, 46 8, 54.5, 106.0, 110.7, 123.0, 137.9, 155.2, 162.6, 166.9, 196.6; MS (CI) *m/z* 392 (M+H), 258, 242, 214, 190, 175, 146, ; HRMS (Cl) *m/z* 392.0775 (calcd for $C_{16}H_{17}F_3NO_5S$: 392.0780).

2-Methoxy-6-methyl-7-(prop-1-en-2-yl)-6,7,7a,8-tetrahydrocyclobuta[*g*]quinolin-5(5a*H*)-one Oxime (44). To a suspension of **40** (3.3 mg, 0.013 mmol) in MeOH (2 mL) was added $NH_2OH.HCl$ (2.2 mg, 0.032 mmol) and $NaOAc.3H_2O$ (6.1 mg, 0.045 mmol) and the mixture was stirred for 48 h at 85 °C. After cooling to room temperature, the mixture was concentrated under vacuum and the residue was diluted with $CHCl_3$ (20 mL). The organic solution was washed with brine (5 mL) and was dried over anhydrous $MgSO_4$. The solvent was removed under vacuum and the residue was chromatographed on silica, using 10% ethyl acetate in hexanes as eluent, to give syn and anti isomers of **44** [1.8 mg (51%) of the major isomer and 0.4 mg (12%) of the minor isomer]. Major isomer: IR (neat) 2928, 1596, 1482, 1324, 1256, 1070 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.37 (d, *J* = 6.9 Hz, 3H), 1.74 (s, 3H), 2.63 (m, 3H), 2.70

(m, 1H), 3.25 (m, 2H), 3.94 (s, 3H), 4.70 (s, 1H), 4.90 (s, 1H), 6.57 (d, J = 9.0 Hz, 1H), 6.92 (br, 1H), 7.95 (d, J = 9.2 Hz, 1H); HRMS (CI) *m/z* 272.1527 (calcd for $C_{16}H_{20}N_2O_2$: 272.1525).

Methyl ((5*S*,*E*)-11-Ethylidene-2-methoxy-7-methyl-5,6,9,10-tetrahydro-5,9-methanocycloocta[*b*]pyridin-5-yl)carbamate (46). A. From 40. To a solution of **40** (12.0 mg, 0.045 mmol) in benzene (1.5 mL) was added methyl carbamate (4.0 mg, 0.055 mmol) and anhydrous *p*-toluenesulfonic acid (2.0 mg, 0.012 mmol). The solution was heated at 60 °C for 2.5 h, then was cooled to room temperature, washed with HCl (10%), and dried over anhydrous $MgSO_4$. The solution was filtered through a pad of Celite which was washed with Et_2O (3 mL), and the filtrate was concentrated under reduced pressure. The residue was purified by chromatography on silica, using 30% EtOAc in hexane as eluent, to give 4.4 mg (37%) of **46** as a colorless oil: IR (neat) 3325, 1714, 1597, 1529, 1475, 1422, 1322, 1304, 1257, 1034 cm-1; 1H NMR (300 MHz, $CDCl_3$) δ 1.53 (s, 3H), 1.73 (d, J = 1.5 Hz, 3H), 2.25 (d, J = 6.8 Hz, 1H), 2.60 (d, J = 6.4 Hz, 1H), 2.83 (d, J = 6.8 Hz, 1H), 3.07 (d, J = 6.4 Hz, 1H), 3.64 (s, 1H), 3.90 (s, 3H), 5.00 (s, 1H), 5.38 (q, J = 2.2 Hz, 1H), 5.47 (d, J = 1.8 Hz, 1H), 6.57 (J = 6.6 Hz, 1H), 7.58 (d, J = 6.6 Hz, 1H); ^{13}C NMR δ 12.5, 22.6, 33.9, 39.4, 49.1, 51.9, 53.3, 58.7, 108.5, 111.8, 125.6, 130.1, 131.8, 135.4, 136.8, 153.2, 154.8, 162.5; HRMS (CI) m/z 315.1688 (calcd for $C_{18}H_{23}N_2O_3$: 315.1703).

B. From 1. To a solution of **1** (10 mg, 0.04 mmol) in MeOH (1 mL) at 0 °C was added K_2CO_3 (5.5 mg, 0.06 mmol) and methyl chloroformate (3.3 μL, 4.0 mg, 0.04 mmol). The suspension was stirred for 2 h at room temperature, during which reaction progress was monitored by TLC (10% MeOH in CH_2Cl_2) until consumption of **1** was complete. The mixture was poured into

water and extracted with CH_2Cl_2 (3 x 10 mL), and the combined extract was washed with brine and dried over $MgSO_4$. The solvent was removed under vacuum to provide crude huperzine A methyl carbamate.

To a solution of the crude carbamate obtained above in $CHCl_3$ (1 mL) were added Ag_2CO_3 (11 mg, 0.04 mmol) and MeI (5 μL, 12 mg, 0.08 mmol). The mixture was stirred at reflux until TLC (40% EtOAc in hexane, 5% MeOH in CH_2Cl_2) indicated complete consumption of the starting material. The mixture was cooled to room temperature and was filtered to remove precipitated solids. The filtrate was concentrated under reduced pressure and the residue was purified by chromatography on silica, using 5-10% EtOAc in hexanes as eluent, to give 4.4 mg of **46** (35%), identical with material prepared by method A.

(-)-Huperzine A (1). To a solution of **46** (3.0 mg, 10 μmol) in $CHCl_3$ (0.3 mL) was added slowly TMSI (14 μL, 0.1 mmol) and the mixture was refluxed for 6 h. The solvent was removed under reduced pressure and the residue was taken up into CH_2Cl_2 (3 mL). The solution was poured into a mixture of saturated aqueous $NaHCO_3$ and saturated aqueous $Na_2S_2O_3$ which was extracted with CH_2Cl_2 (3 x 5 mL). The combined extract was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by chromatography on silica, using 10% MeOH in EtOAc as eluent, to give **1** (2.0 mg, 80%) as a colorless solid: ^{1}H NMR ($CDCl_3$) δ 1.28 (br s, 2H), 1,55 (s, 3H), 1.68 (d, J = 6.7 Hz, 3H), 2.11 (d, J = 17.0 Hz, 1H), 2.16 (d, J = 17.0 Hz, 1H), 2.74 (dd, J = 1.5, 16.8 Hz, 1H), 2.90 (dd, J = 5.0, 16.8 Hz, 1H), 3.56-3.65 (m, 1H), 5.41 (d, J = 4.8 Hz, 1H), 5.49 (q, J = 6.7 Hz, 1H), 6.42 (d, J = 9.4 Hz, 1H), 7.91 (d, J = 9.4 Hz, 1H).[17]

ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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