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Synthesis of (±)-7-Hydroxylycopodine

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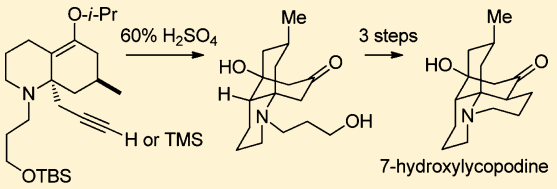
Supporting Information

ABSTRACT: A seven-step synthesis of (±)-7-hydroxylycopodine that proceeds in 5% overall yield has been achieved. The key step is a Prins reaction in 60% sulfuric acid that gave the key tricyclic intermediate with complete control of the ring fusion stereochemistry. A one-pot procedure orthogonally protected the primary alcohol as an acetate and the tertiary alcohol as a methylthiomethyl ether. The resulting product was converted to 7-hydroxydehydrolycopodine by heating with KO-*t*-Bu and benzophenone in benzene followed by acidic workup. During unsuccessful attempts to make optically pure starting material, we observed the selective Pt-catalyzed hydrogenation of the 5-phenyl group of a 4,5-diphenyloxazolidine under acidic conditions and the Pt-catalyzed isomerization of the oxazolidine to an amide under neutral conditions. In attempts to hydroxylate the starting material so that we could adapt this synthesis to the preparation of (±)-7,8-dihydroxylycopodine (sauroine) we observed the novel oxidation of a bicyclic vinylogous amide to a keto pyridine with $Mn(OAc)_3$ and to an amino phenol with KHMDS and oxygen.



INTRODUCTION

The lycopodium alkaloids are a large, extensively studied alkaloid family that have been of interest to synthetic chemists for more than 50 years.[1] Huperzine A (**1**), which is probably the medicinally most significant member of this family, is an acetylcholinesterase inhibitor that may have other important roles including treatment of Alzheimer's disease as discussed in recent reviews (see Figure 1).[2] We were therefore intrigued by

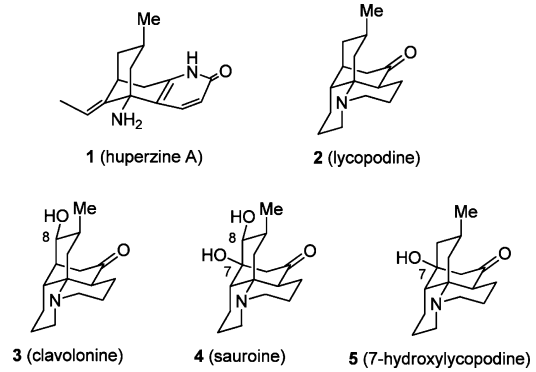


Figure 1. Structures of huperzine A (**1**), lycopodine (**2**), clavolonine (**3**), sauroine (**4**), and 7-hydroxylycopodine (**5**).

the 2009 report[3a] that sauroine (**4**, 7,8-dihydroxylycopodine), which was first reported in 2004,[3b] improves memory retention in the step-down test in male Wistar rats and significantly improves hippocampal plasticity. The isolation of 7-hydroxylycopodine (**5**) was also reported in 2004 without any indication of biological activity.[4]

Racemic lycopodine (**2**) was first synthesized by Stork[5a] and Ayer[5b] in 1968, with additional syntheses by Kim,[5c] Heathcock,[5d] Schumann,[5e] Wenkert,[6a] Kraus,[5f] Grieco,[5g] Padwa,[5h] and Mori[5i] over the next 30 years.[5l] The first synthesis of lycopodine in optically pure form was recently reported by Carter in 2008.[5j,k] 8-Hydroxylycopodine (**3**, clavolonine) was synthesized in racemic form in 1984 by Wenkert[6a] and more recently in optically pure form by Evans,[6b] Breit,[6c] and Fujikoka.[6d]

The bridgehead hydroxy group of sauroine (**4**) and 7-hydroxylycopodine (**5**) is not compatible with most of the approaches that have been used for the synthesis of lycopodine (**2**) and clavolonine (**3**). Fortunately, the presence of a 3-hydroxycyclohexanone suggests that this ring might be formed by an aldol or Prins reaction. We decided to start by synthesizing 7-hydroxylycopodine (**5**) and then to adapt the route to the synthesis of sauroine (**4**) that contains the additional 8-hydroxy group so that these molecules will be available for study of their biological properties.

We envisioned that the fourth and final ring of **5** could be constructed from dihydroxy ketone **6** by oxidation of the primary alcohol to an aldehyde, intramolecular aldol reaction, and dehydration and then hydrogenation as developed by Heathcock[5d] in his lycopodine synthesis and later used by Kraus[5f] and Carter (see Scheme 1).[5j,k] We hoped that we could prepare **6** from diketone **7** with a suitable protecting group on the primary alcohol by an intramolecular aldol reaction. We planned to introduce the side chain ketone of diketone **7** by a Wacker oxidation of the allyl group of ketone **8**, which will be

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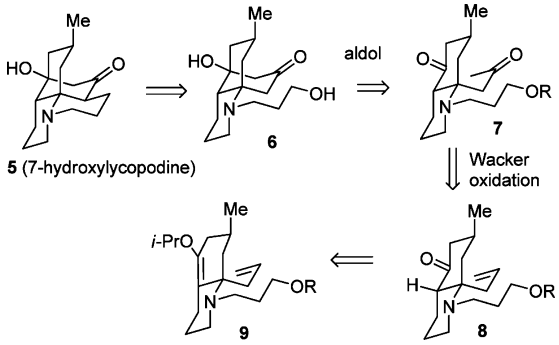
Scheme 1. Retrosynthesis of 7-Hydroxylycopodine



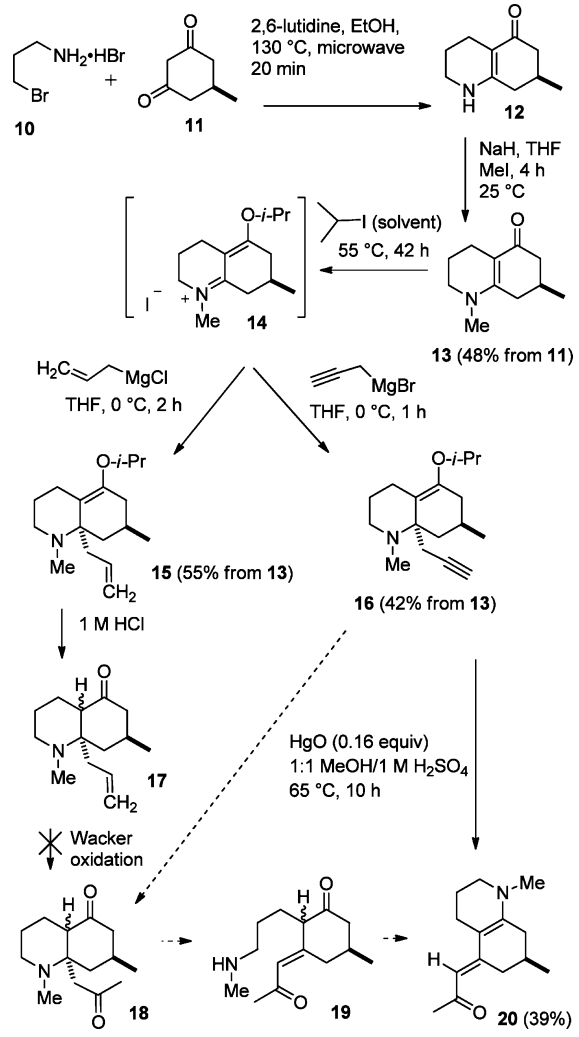
prepared by hydrolysis of enol ether **9**. This approach is intriguing because Wiesner and co-workers developed an efficient route to **15**, the analogue of **9** with an *N*-methyl rather than a protected *N*-hydroxypropyl group, in a very early unsuccessful approach to lycopodine synthesis.[7b] This route to 7-hydroxylycopodine is very short and attractive. Our one major concern was the stereochemistry of protonation of the enol ether of **9** which could give both the desired ketone **8** with a trans ring fusion and the undesired stereoisomer with a cis ring fusion that would lead to 12-*epi*-7-hydroxylycopodine. This was of particular concern because related syntheses by Wiesner led to 12-*epi*-lycopodine, rather than the desired target lycopodine.[7c,d] The brevity of this route is appealing and the stereochemical question is addressed early in the synthesis so we chose to explore this route.[8]

RESULTS AND DISCUSSION

Synthesis of Tricyclic Model 26. We started with a model study designed to prepare the tricyclic skeleton of **6** with an *N*-methyl, rather than an *N*-hydroxypropyl, group because the nitrogen substituent should have no effect on the stereochemistry of the enol ether protonation, Wacker oxidation, or aldol cyclization. Weisner[7b] prepared **12**[9] in unspecified yield by heating 5-methylcyclohexane-1,3-dione (**11**) with 3-amino-1-propanol in benzene at reflux and then heating the resulting vinylogous amide with 1 equiv of pyridine hydroiodide neat at 140 °C for 2 h (see Scheme 2). We prepared **12** by microwave heating diketone **11** with 3-bromopropylammonium bromide (**10**) and 2,6-lutidine in ethanol at 130 °C for 20 min in a modification of a literature procedure for related compounds that heated for 1 h in butanol at reflux (see Scheme 2).[10a] Methylation of vinylogous amide **12** with NaH and iodomethane in THF gave **13**[7b] in 48% overall yield from **11**. Using Wiesner's protocol, we converted **13** to **15** by heating **13** in excess 2-iodopropane for 42 h at 55 °C and concentration to give the unstable salt **14**, which was immediately taken up in THF and treated with allylmagnesium chloride in THF for 2 h at 0 °C to give enol ether **15** as a single stereoisomer in 55% yield from **13**.

Stirring enol ether **15** in 1 M hydrochloric acid for 5 h at 25 °C afforded a ~3:1 mixture of stereoisomeric ketones **17** in 77% yield. The major stereoisomer was easily isolated in pure form, but the stereochemistry of the ring fusion could not be easily assigned by analysis of the NMR spectral data. We therefore used mixture **17** for our initial explorations of the Wacker oxidation. Unfortunately, all attempts to carry out the Wacker oxidation of **17** to give diketone **18** were unsuccessful. We were somewhat concerned that the amino group might be

Scheme 2. Unsuccessful Approaches to Diketone 18



interfering, although Wacker oxidations of amino alkenes to amino methyl ketones have been reported under acidic conditions in which the amine is protonated.[11]

We then attempted to prepare diketone **18** by hydrolysis of enol ether alkyne **16**. Addition of propargylmagnesium bromide to a solution of salt **14** in THF provided enol ether alkyne **16** as a single stereoisomer in 42% yield from vinylogous amide **13**. To our surprise, hydration of the triple bond of **16** with HgO in 1:1 MeOH/1 M aqueous sulfuric acid at 65 °C provided dienone **20** in 39% yield rather than the desired diketone **18**. Presumably, hydrolysis of the alkyne affords the desired dione **18** with a protonated amino group. Elimination of the β-amino group leads to monocyclic amino dione **19**, which condenses with the cyclohexanone to form the fully conjugated δ-amino dienone **20**. In retrospect, the failure of the Wacker oxidation of **17** might be due to the decomposition of the desired diketone **18** under the acidic reaction conditions to give compounds that are further oxidized by Pd(II).

Although enol ether alkyne **16** was initially prepared as a possible precursor to diketone **18**, it fortuitously allowed us to develop a one-step route to the desired model tricyclic hydroxy ketone **26** that does not proceed through diketone **18** (see Scheme 3). In 1965, Wiesner and co-workers reported that treatment of enol ether alkene **15** in 75% sulfuric acid for 12 h at 25 °C afforded tricyclic alkene **24** in 70% yield as a single

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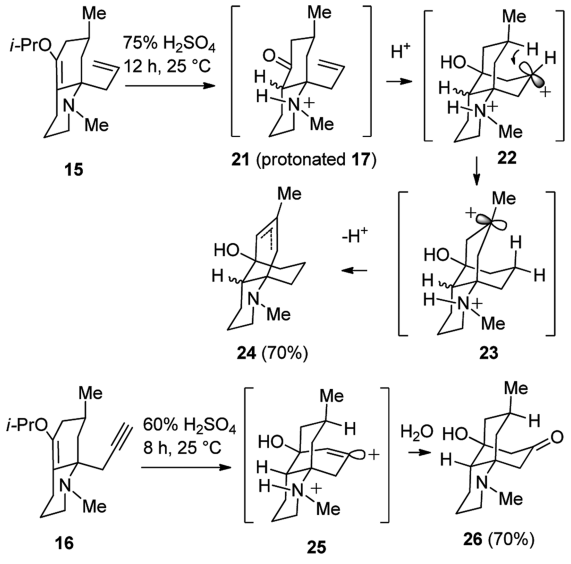
Scheme 3. Synthesis of Model Tricyclic Hydroxy Ketone 26



isomer with unknown stereochemistry at the ring fusion and unknown double bond position.[7b] Acidic hydrolysis of the enol ether afforded ketone **21** (protonated form of ketone **17**), which underwent a Prins cyclization to give secondary cation **22**. A facile transannular 1,5-hydride shift then took place to form the more stable tertiary cation **23**. Loss of a proton then formed the observed product **24**. The desired ring fusion stereochemistry with a β-hydrogen, which would result from the trans-fused stereoisomer of bicyclic ketone **21** was suggested on the basis of kinetic and thermodynamic conformational analysis. However later work from this group leading to two syntheses of 12-*epi*-lycopodine[7c,d] using related chemistry and our observation that hydrolysis of **15** with hydrochloric acid afforded **17** as a ~3:1 mixture of stereoisomers indicate that this stereochemical assignment is far from secure. Unfortunately, the functionality is now in the wrong ring of **24**, which makes it useless for lycopodine synthesis regardless of the stereochemistry at C_{12}.

Enol ether alkyne **16** was treated with aqueous sulfuric acid with the expectation that enol ether hydrolysis and Prins cyclization would occur analogously to give alkenyl cation **25**. A 1,5-hydride shift should not occur because the hydrogen is too far from the vacant sp^2 orbital on the alkenyl cation. Instead, the alkenyl cation should react with water to give an enol that will tautomerize to the desired tricyclic hydroxy ketone **26**. We were pleased to find that reaction of **16** in 60% sulfuric acid for 8 h at 25 °C afforded **26** in 70% yield as a single stereoisomer. The yield was slightly lower in 75% sulfuric acid. In 50% sulfuric acid, the enol ether hydrolyzed to give the ketone, which did not add to the alkyne. The stereochemistry of **26** was assigned from a series of 1D NOESY experiments as shown in Figure 2. The stereochemistry at C_{12} can be unambiguously assigned from the NOEs between H_{12} and H_{14} and between H_6 and H_{11}.

The stereoisomer derived from the cis-fused bicyclic ketone was not observed. The origin of this stereoselectivity is not obvious. The trans-fused bicyclic ketone is calculated by molecular mechanics to be 1.4 kcal/mol more stable than the cis isomer, but bicyclic ketone **17** was formed as a ~3:1 mixture of stereoisomers by hydrolysis of enol ether alkene **15**.

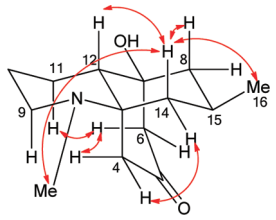
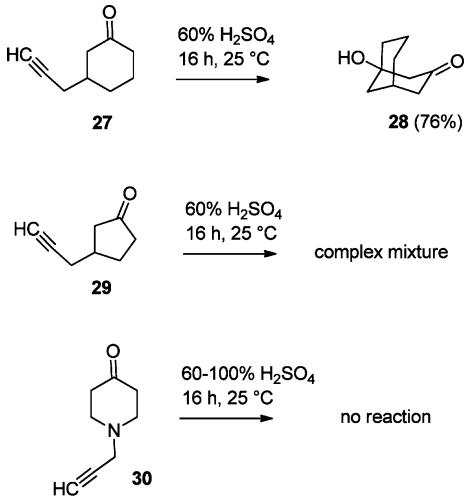


Figure 2. NOEs in tricyclic model **26**.

Prins reactions with alkynes are uncommon, but known.[12] The isolation of β-hydroxy ketones from Prins reactions of keto alkynes is rarely observed because these initial products will usually undergo dehydration to give conjugated ketones. In this case, ring strain prevents dehydration to form a conjugated ketone, which would have a bridgehead double bond.

We briefly explored the scope of this alkyne ketone Prins reaction as a route to bicyclic hydroxy ketones. Stirring 3-propargylcyclohexanone (**27**)[13] in 60% sulfuric acid for 16 h at 25 °C provided 1-hydroxybicyclo[3.3.1]nonan-3-one (**28**)[14] in 76% yield, indicating that the protonated nitrogen of **16** is not necessary for the reaction (see Scheme 4). Similar treatment of

Scheme 4. Prins Reactions of Propargyl Ketones



3-propargylcyclopentanone (**29**)[13] gave a complex mixture, and *N*-propargylpiperidine-4-one (**30**)[15] was recovered unchanged from 60%, 80%, or concentrated sulfuric acid. These initial results suggest that this Prins reaction will be best suited for the synthesis of 1-hydroxybicyclo[3.3.1]nonan-3-ones.

We wanted to explore the trapping of the vinyl cation intermediate with nucleophiles other than water. We therefore explored the reaction of **27** with $EtAlCl_2$ in CH_2Cl_2 (see Scheme 5).[16] Initial reactions in which oxygen was not carefully excluded gave chloroalkenyl ether **31** in about 50% yield. However, when we carefully excluded oxygen, we obtained a complex mixture of products. We hypothesized that $EtAlCl_2$ reacted with oxygen to give EtO_2AlCl_2, which reacted with second molecule of $EtAlCl_2$ to give two molecules of $EtOAlCl_2$, which was responsible for the formation of **31**.[17,18] We therefore treated $EtAlCl_2$ with 1 equiv of EtOH in CH_2Cl_2 for 1 h to give $EtOAlCl_2$ and ethane. Addition of **27** and stirring for 20 h afforded **31** in 71% yield. Presumably $EtOAlCl_2$ reacts with **27** to give **32**, which reacts further to give alkoxonium ion

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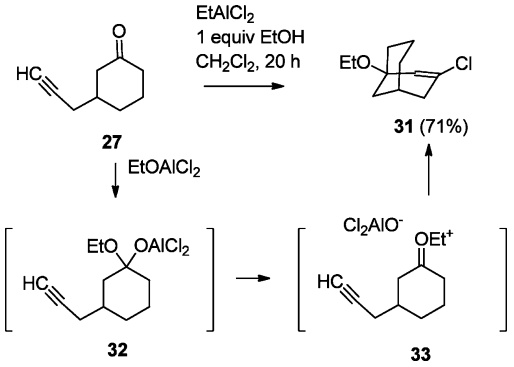
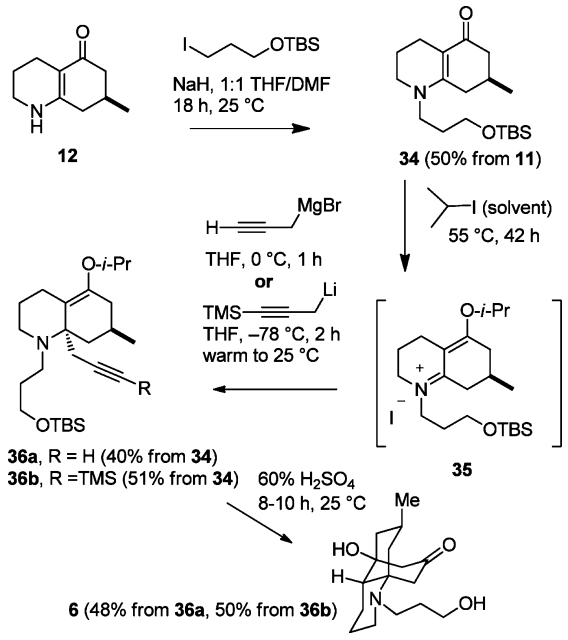
Scheme 5. Cyclization of 3-Propargylcyclohexanone (27) with $EtOAlCl_2$ To Give Vinyl Chloride 31



33, which cyclizes to give **31** after trapping of the vinyl cation with chloride.

Synthesis of 7-Hydroxylycopodine (5). For the synthesis of 7-hydroxylycopodine precursor **6** we needed to replace the methyl group of **13** with a protected hydroxypropyl group. We chose to use the TBS group because it should be stable to the conditions needed to add the propargyl group but then be hydrolyzed without an additional step during the sulfuric acid catalyzed cyclization. Crude vinylogous amide **12** was treated with NaH and then $I(CH_2)_3OTBS$[19] in 1:1 THF/DMF for 18 h at 25 °C to afford **34** in 50% overall yield from 5-methylcyclohexane-1,3-dione (**11**) (see Scheme 6). Heating a

Scheme 6. Preparation of Tricyclic Intermediate 6



solution of **34** in 2-iodopropane for 42 h at 55 °C afforded the intermediate cation **35**, which was treated with propargylmagnesium bromide in THF to yield **36a** in 40% yield from **34**. Stirring a solution of **36a** in 60% aqueous sulfuric acid for 8 h at 25 °C afforded the requisite tricyclic ketone **6** with the required hydroxypropyl side chain in 50% yield. As in the hydrolysis and Prins cyclization of **16**, the hydrolysis and cyclization of **36a** affords **6** as a single stereoisomer whose stereochemistry was established by a series of 1D NOESY experiments that are summarized in Figure 3. The stereochemistry at C_{12} can be unambiguously assigned from the NOEs between H_{12} and H_{14}, between H_6 and H_{11}, and between H_4 and both H_9 and H_{11}.

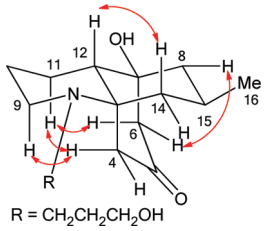


Figure 3. NOEs of 7-hydroxylycopodine intermediate **6**.

Propargylmagnesium bromide is best used immediately, and its preparation requires the use of toxic $HgCl_2$ in addition to magnesium. We therefore explored the use of other propargyl nucleophiles. Trimethylsilylpropargyllithium, which is easily prepared by deprotonation of 1-trimethylsilylpropyne with *n*-BuLi, added to cation **35** to give **36b** in 51% yield. The preparation of **36b** is operationally simpler, proceeds in higher yield, and does not produce mercury-containing waste. The hydrolysis and cyclization of **36b** in 60% sulfuric acid was slightly slower (10 h) than that of **36a** but afforded **6** in comparable yield (50%). During the conversion of **36b** to **6**, the enol ether is hydrolyzed, the TMS alkyne and TBS ether are deprotected and the keto alkyne cyclizes to form the tricyclic hydroxy ketone.

Heathcock was unable to synthesize lycopodine by an intramolecular alkylation of the analogue of **6** lacking the tertiary hydroxy group[20] and therefore used a modified Oppenauer oxidation–aldol reaction with benzophenone and KO-*t*-Bu to form dehydrolycopodine.[5d,21] Unfortunately, with **6** we obtained a complex mixture containing at most 5% of the desired enone **42** using a variety of bases (KO-*t*-Bu, NaO-*t*-Bu, or NaH) and hydride acceptors (benzophenone or fluorenone). We suspect that a retro-aldol reaction of the β-hydroxy ketone took place under the very basic reaction conditions. We therefore explored other oxidation conditions that might oxidize the primary alcohol to the aldehyde in the presence of an amine and tertiary alcohol. Decomposition occurs with PCC, PDC, or excess TPAP. No reaction occurred under Swern or Parikh–Doering conditions. Dess–Martin oxidation formed the β-amino aldehyde which appeared to be oxidized further to give the β-aminoenal $R_2NCH{=}CHCHO$ based on NMR peaks at δ 9.16 (d, 1, J = 7.6 Hz), 7.39 (br d, 1, J = 12.4 Hz), and 5.33 (dd, 1, J = 12.4, 7.6 Hz).[22] Oxidation with IBX in DMSO gave mainly recovered **6** containing a trace of β-aminoenal. Eventually we found that the primary alcohol of **6** could be selectively oxidized to unstable amino aldehyde **37** under Narasaka–Mukaiyama conditions with *t*-BuOMgCl and azodicarbonylpiperidine in THF (see Scheme 7).[23] Unfortunately, all attempts to carry out an intramolecular aldol reaction with **37** to give **42** using either acid (TsOH or AcOH), base (KO-*t*-Bu, K_2CO_3, or pyrrolidine), or salt (piperidinium acetate, dibenzylammonium trifluoroacetate, or piperidinium trifluoroacetate) catalysis resulted in loss of acrolein to form the unstable tricyclic secondary amine **38**.

We therefore decided to protect the tertiary alcohol of **6** and to then reinvestigate the modified Oppenauer oxidation–aldol reaction sequence. The strongly basic and high-temperature conditions of the Oppenauer oxidation preclude the use of an ester or silyl ether protecting group. We initially protected the

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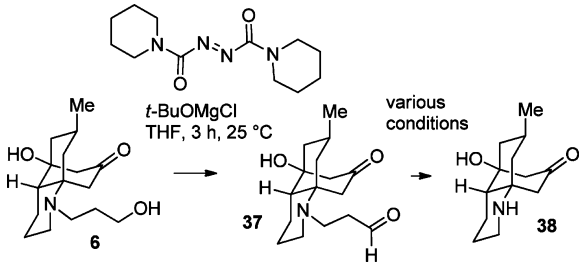
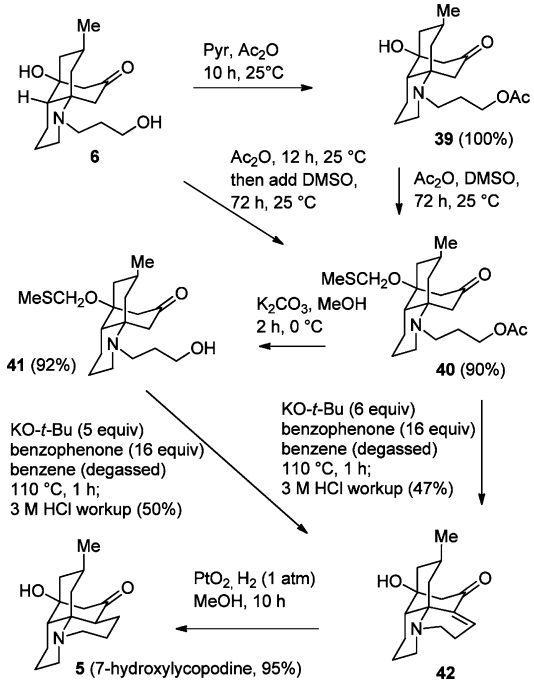
Scheme 7. Preparation and Decomposition of Amino Aldehyde 37



primary alcohol with pyridine and acetic anhydride to give **39** in quantitative yield (see Scheme 8). Attempted benzylation or

Scheme 8. Completion of the Synthesis of 7-Hydroxylycopodine (5)



allylation of the tertiary alcohol of **39** under a variety of conditions led to complex mixtures, recovered starting material or hydrolysis of the acetate. We were also unable to form the tertiary ethoxyethyl or THP ether from the acid-catalyzed reaction of **39** with ethyl vinyl ether or dihydropyran. Eventually, we found that treatment of **39** with acetic anhydride in DMSO generated $MeS{=}CH_2^+$ by a Pummerer rearrangement which reacted with the tertiary alcohol to give methylthiomethyl ether **40** in 90% yield.[24] Hydrolysis of the acetate of **40** with K_2CO_3 in MeOH afforded primary alcohol **41** in 92% yield. This sequence was improved by carrying out the first two steps in a single pot. A solution of **6** in Ac_2O was stirred for 12 h at 25 °C to form the primary acetate. DMSO was added, and stirring was continued for 72 h to form **40** in 90% yield.

We were pleased to find that treatment of **41** with KO-*t*-Bu (5 equiv) and benzophenone (16 equiv) in carefully degassed benzene in a sealed tube at 110 °C for 1 h followed by workup with 3 M hydrochloric acid to cleave the methylthiomethyl protecting group gave 7-hydroxydehydrolycopodine (**42**) in 50% yield. This reaction was carried out with an excess of strong base suggesting that prior deprotection of the primary acetate of **41** was unnecessary. As expected, similar treatment of **40** using an extra equivalent of KO-*t*-Bu afforded **42** in 47% yield. In this step, the primary acetate is cleaved, the resulting alcohol is oxidized to the aldehyde, the aldol reaction closes the final ring, dehydration leads to the enone, and the protecting group is cleaved during workup. Hydrogenation of enone **42** over PtO_2 with 1 atm of H_2 for 10 h afforded 7-hydroxylycopodine (**5**) in 95% yield. The spectral data for the hydrochloride salt of **5** in CD_3OD are identical to those reported for the natural product,[4] thereby confirming the stereochemical assignment of **6** made on the basis of NOE experiments.

Biological Activity. The crude alkaloid extract of *Huperzia Saururus*, which contained no huperzine A (**2**), inhibited human acetylcholinesterase (AChE) with an IC_{50} of 0.58 μg/mL.[3] However, the major alkaloid sauroine (**1**), which constitutes 57−67% of the alkaloid mixture depending on the harvest season, did not inhibit AChE below 10 μg/mL indicating that there are other potent AChE inhibitors in the crude mixture.[3a] Although sauroine is a weak AChE inhibitor it did demonstrate a significant increase of hippocampal plasticity and memory retention in rats.[3c,d] We found that 7-hydroxylycopodine (**5**) is a weak inhibitor of eel AChE and human erythrocyte cholinesterases with an IC_{50} of 1.67 and 2.08 mM (439 and 547 μg/mL), respectively (see Figure 4). At

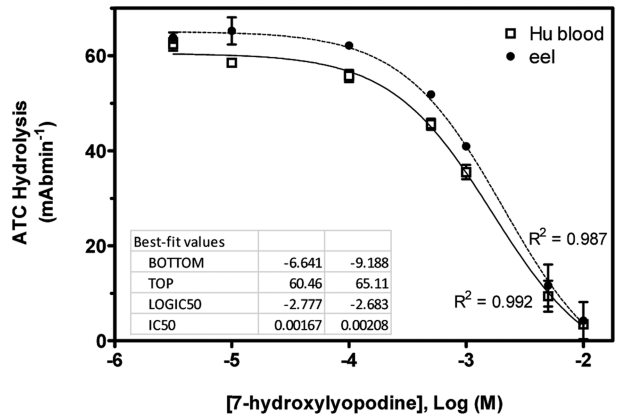


Figure 4. Effect of 7-hydroxylycopodine (**5**) on eel AChE and human whole blood ChE activities. Samples were preincubated with 7-hydroxylycopodine before assay. Values plotted are mean ± SEM. The calculated IC_{50} values are shown in the inset table.

this concentration, 7-hydroxylycopodine does not inhibit human butyrylcholinesterase (data not shown), indicating that the observed IC_{50} of 2.08 mM is due to human erythrocyte AChE inhibition. In contrast, huperzine A inhibits human erythrocyte acetylcholinesterase with an IC_{50} of 0.09 μM.[2a]

Approaches to the Synthesis of Optically Pure 12. We have developed a short, practical, six-step synthesis of (±)-7-hydroxylcyopodine (**5**) from racemic **12**, which is prepared from prochiral 5-methylcyclohexane-1,3-dione (**11**). We briefly explored approaches for the formation of optically pure **12** from **11**. Rychnovsky found that $Cu(OTf)_2$-catalyzed reaction of racemic **43** with amino alcohol **44** afforded **45** in 95% yield as a 20:1 mixture of diastereomers which he used for a synthesis of (−)-lycoperine (see Scheme 9).[25] Unfortunately, as suggested by Rychnovsky's work, we were unable to remove

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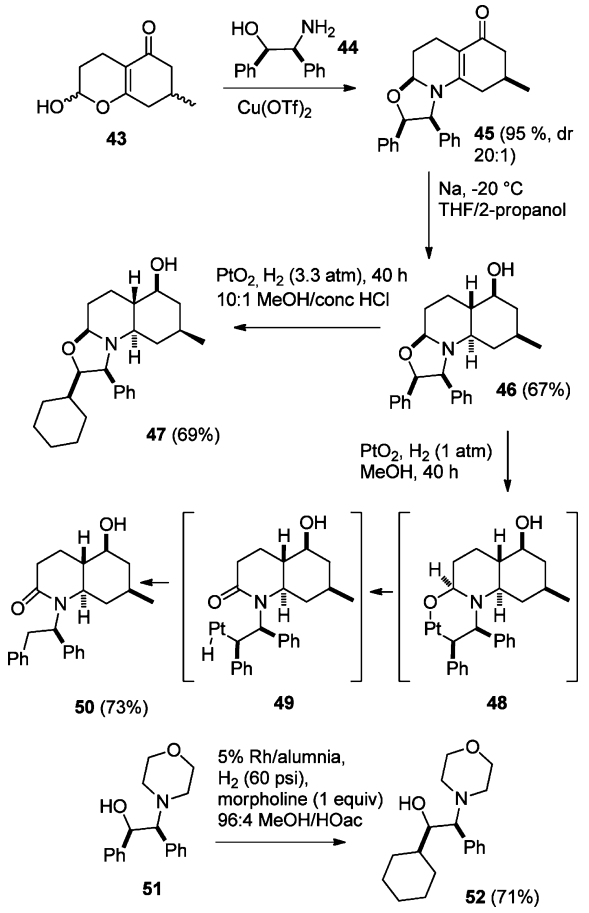
Scheme 9. Hydrogenation and Isomerization of 46



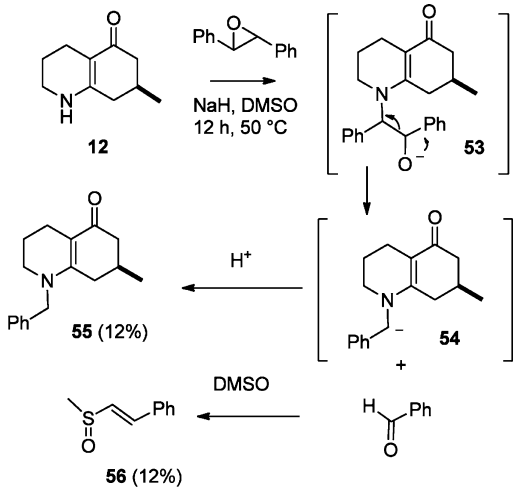
the chiral auxiliary from **45** by hydrogenation (1−3 atm H_2) over Pd/C, $Pd(OH)_2/C$, or PtO_2. We obtained either recovered starting material or complex mixtures, whose spectra suggested that the tetrasubstituted double bond had been partially reduced. We observed an apparent quartet at δ 0.43 (J = 12 Hz) similar to that observed in **46** at δ 0.47, whereas the most upfield ring proton of **45** is at δ 1.55.

Rychnovsky reduced **45** to **46** in 67% yield with sodium in THF/2-propanol and found that reductive removal of the auxiliary from **46** required forcing conditions (500 psi H_2, 20% $Pd(OH)_2$ on carbon) to give a lycoperine precursor.[25] Although the preparation of **12** from **46**, which lacks both the carbonyl group and tetrasubstituted double bond of **45**, would not be straightforward, we briefly examined hydrogenolysis of **46** under milder conditions.

We observed two interesting reactions on attempted hydrogenolysis of **46** over PtO_2 under more moderate H_2 pressures. Stirring a solution of **46** under H_2 (50 psi, 3.3 atm) with PtO_2 in 10:1 MeOH/concd HCl for 40 h selectively hydrogenated one of the two phenyl rings to give **47** in 69% yield. This selectivity is precedented in the hydrogenation of **51** to give **52** over Rh/Al_2O_3 reported by Nugent.[26] Under neutral conditions and 1 atm H_2 with PtO_2 we observed the formation of amide **50** in 73% yield after 40 h. Presumably, platinum inserts in the benzylic carbon−oxygen bond to give **48**, which undergoes a β-hydride elimination to form amide **49**. Reductive elimination would then form **50**. The acidic solution is important for the selective hydrogenation of one benzene ring to give **47**, because hydrogenation of **46** under H_2 (3 atm) and PtO_2 in MeOH for only 10 h afforded only 5−10% of cyclohexane **47**, about 50% of amide **50**, and 40−45% unreacted **46**. The facile isomerization of aminal **46** to amide **50** at 1−3 atm of H_2 may be the reason that forcing conditions (500 psi H_2) were needed for the reductive removal of the protecting group in Rychnovsky's lycoperine synthesis.[25] High H_2 pressure should accelerate hydrogenolytic cleavage of intermediate **48** and thereby prevent the formation of amide **50**.

We then turned to the resolution of racemic **12**. The anion of **12** was acylated with α-acetoxy and α-methoxyphenylacetyl chloride to give diastereomeric vinylogous imides, which were inseparable by TLC. We then decided to react the anion of **12** with *trans*-stilbene oxide in the hope that the two diastereomers of **53** with the stereocenters in closer proximity might be separable. To our surprise, treatment of **12** with NaH and *trans*-stilbene oxide in DMSO at 50 °C for 12 h gave only the *N*-benzyl product **55** (12%) and unsaturated sulfoxide **56** (12%) (see Scheme 10). The structure of **55** was confirmed by its

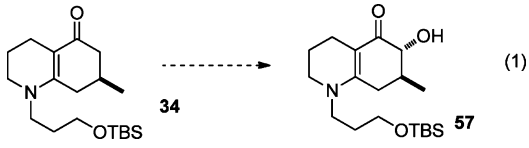
Scheme 10. Fragmentation of Alkoxide 53



preparation from **12**, sodium hydride and benzyl bromide. Presumably, the anion of **12** undergoes the desired S_N2 reaction with *trans*-stilbene oxide to give alkoxide **53**, which fragments to give benzaldehyde and carbanion **54**, which is protonated to give **55**. Condensation of benzaldehyde with DMSO is known to give **56**.[27]

Unfortunately, we were unable to develop an efficient synthesis of optically pure **12**, but our attempts led to the observation of the three unusual reactions, namely, the selective hydrogenolysis of one of two benzene rings of aminal **46** to give **47**, the Pt-catalyzed isomerization of **46** to amide **50**, which may explain why high-pressure conditions are needed for the removal of this chiral auxiliary, and the unusual fragmentation of alkoxide **53** to give benzaldehyde and **55**.

Approaches To Introduce the Additional Hydroxy Group of Sauroine. We then investigated the hydroxylation[28] of **34** to give **57** (see eq 1), which could be elaborated to



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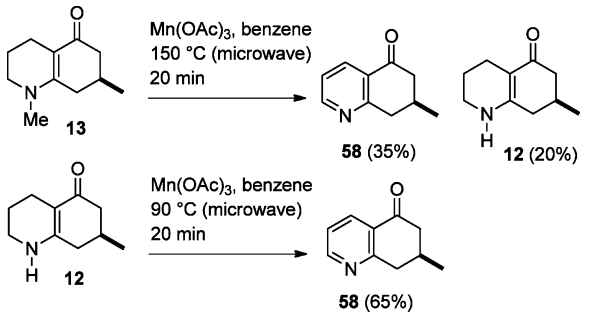
sauroine (**4**) by a route similar to that used for the synthesis of 7-hydroxylycopodine (**5**). Our initial studies were carried out with model **13** with an *N*-methyl group (see Scheme 11). We

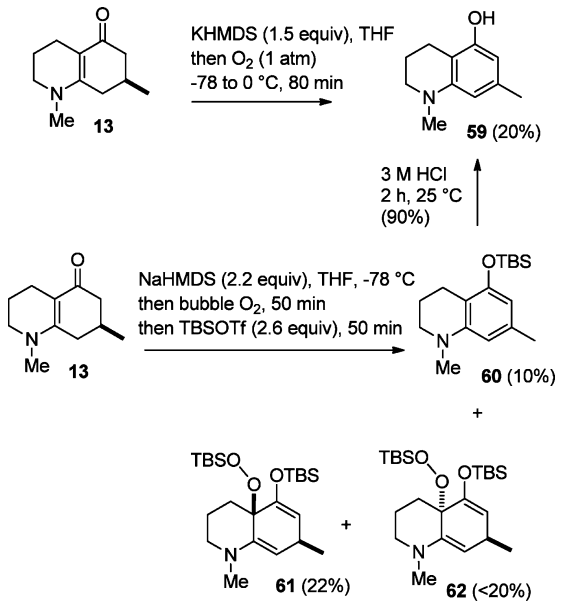
Scheme 11. Oxidation of 12 to Pyridine 58



initially examined the reaction of **13** with $Mn(OAc)_3$ in benzene at elevated temperatures because Watt and Demir had shown that these conditions introduce an α'-acetoxy group onto α,β-unsaturated ketones or β-alkoxy- α,β-unsaturated ketones.[29] Unfortunately, the vinylogous amide **13** reacted differently. Microwave heating a solution of **13** with $Mn(OAc)_3$ in benzene at 150 °C for 20 min afforded a mixture of recovered **13** (35%), demethylated vinylogous amide **12** (20%), and pyridine **58**[30] (35%). We suspected that the slow step was the demethylation to give **12** and confirmed this by the oxidation of **12** with $Mn(OAc)_3$ in benzene which proceeded efficiently to give **58** in 65% yield with microwave heating for 20 min at only 90 °C. This facile oxidation with $Mn(OAc)_3$ to generate the pyridine is synthetically useful but does not provide a procedure for the desired α'-hydroxylation.

We then attempted to form the α'-enolate and trap it with either oxygen, MoO_5·pyr·HMPA, or a sulfonyloxaziridine to introduce the α'-hydroxy group.[31] Treatment of **13** with 1.5 equiv of KHMDS in THF at −78 °C and then stirring under an oxygen atmosphere led to phenol **59** in 20% yield rather than the desired hydroxy compound (see Scheme 12). Similar results were obtained with NaHMDS. Only starting material

Scheme 12



was recovered when we added MoO_5·pyr·HMPA to the enolate. Adding (8,8-dichlorocamphorylsulfonyl)oxaziridine gave recovered starting material at −78 °C and a complex mixture on warming to 0 °C. Silylation of the α'-enolate of **13** to give a silyl ether that could then be hydroxylated was not practical since the required silyl ether would be a very hydrolytically unstable 1-amino-3-silyloxy-1,3-diene. The formation of phenol **59** from **13** could involve trapping of the enolate with oxygen and a fragmentation process or more likely an electron transfer reaction of the enolate to give an α-keto radical which could then be oxidized further to give the phenol. A related oxidation of a cyclohexenone to a phenol with KO-*t*-Bu and oxygen that does not proceed through a hydroperoxide has been reported.[32]

We then tried to prevent formation of phenol **59** by trapping the intermediates with TBSOTf. Vinylogous amide **13** was treated with NaHMDS (2.2 equiv) in THF at −78 °C, oxygen was bubbled through the solution for 50 min, and excess TBSOTf was added. The NMR spectrum of the crude product indicated the presence of a 1:2:2 mixture of **60**, **61**, and **62** in about 50% yield. Flash chromatography provided phenyl silyl ether **60** (10%), which was hydrolyzed with 3 M HCl to give **59** (90% yield) and **61** (22% yield). The other diastereomer **62** decomposed on chromatography. Presumably, deprotonation occurs at the γ-position to give the thermodynamic enolate, which is hydroxylated at the α-position to give the α-hydroperoxy-β,γ-unsaturated ketone, which is enolized by excess base at the α'-position. Trapping with TBSOTf will give bis-silyl ethers **61** and **62**.

MMX calculations with conformational searching were carried out on the bis TMS ethers corresponding to bis TBS ethers **62** and **61** using PCMODEL 9.3. The Boltzmann-averaged coupling constants between the doubly allylic methine hydrogen and the alkene hydrogens were calculated to be 3.1 and 3.1 Hz in the bis-TMS ether corresponding to **62**, in which the methyl and peroxy groups are trans, and 4.3 and 4.3 Hz in the bis-TMS ether corresponding to **61**, in which the methyl and peroxy groups are cis. The stereochemistry of **62** and **61** is tentatively assigned on the basis of the observed coupling constants of 2 and 2 Hz in **62** and 4.4 and 4.4 Hz in **61**.

We examined the deprotection of **61** as a means of confirming the structure assignment. Treatment of **61** with pyridine (2.5 equiv) and pyrdine·$(HF)_x$ (3 equiv) in $CDCl_3$ for 30 min afforded a compound in 40% yield whose structure was eventually established as **65** by careful analysis of 1D and 2D NMR spectra (see Scheme 13). MMX calculations with conformational searching were carried out on the analogue of **65** with TMS rather than TBS ethers using PCMODEL 9.3. The *s*-trans amide conformer is calculated to be 5.4 kcal/mol more stable than the *s*-cis amide conformer. The observed and (calculated) coupling constants between H_{3a} and H_4 [13.2 (12.1) Hz], H_{3b} and H_4 [4.4 (4.1) Hz] and H_4 and H_5 [10.0, (8.6)] correspond closely. A plausible pathway for the conversion of **61** to **65** involves the hydrolysis of the peroxy silyl ether and protonation of the enamine to give cation **63**, which cyclizes to give dioxetane **64**, which fragments[33] to give hexahydro-2,7-azacinedione **65**. A related oxidative cleavage of the ring fusion double bond of 1-acetyl-1,2,3,4,5,6,7,8-octahydro-6-methylquinoline with RuO_4 afforded 1-acetyl-(octahydro)-5-methyl-2,7-azacinedione.[34]

Although we have not achieved the desired α'-hydroxylation of **34** to give sauroine precursor **57**, we have found novel procedures that oxidize vinylogous amide **12** to keto pyridine

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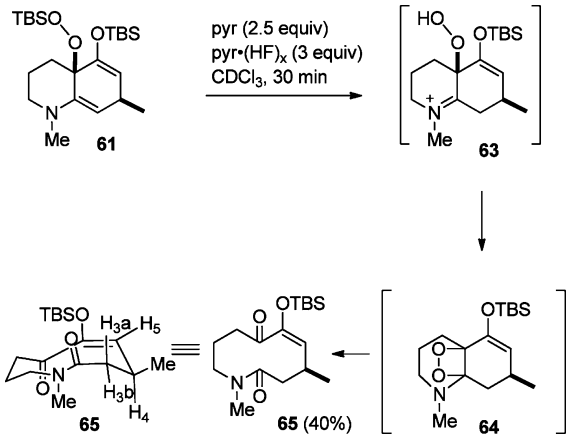
Scheme 13



58 and *N*-methyl vinylogous amide **13** to phenol **59** and that oxygenate **13** at the α- rather than α'-position to give **61** and **62**. Other approaches for the synthesis of **57** are currently being explored.

In conclusion, we have completed a seven-step synthesis of (±)-7-hydroxylycopodine (**5**) from **12** that proceeds in 5% overall yield, making it readily available for biological evaluation. The key step in the synthesis is the Prins reaction of **36a** or **36b** in 60% sulfuric acid to give the key tricyclic intermediate **6** with complete control of the ring fusion stereochemistry. We also developed a one-pot procedure to orthogonally protect the primary alcohol of **6** as an acetate and the tertiary alcohol as a methylthiomethyl ether giving **40**, which was converted to 7-hydroxydehydrolycopodine **42** by heating with KO-*t*-Bu and benzophenone in benzene followed by acidic workup. 7-Hydroxylycopodine inhibits eel and human acetylcholinesterase with an IC_{50} of 1.67 and 2.21 mM, respectively.

We were unable to develop an efficient synthesis of optically pure **12**, but our attempts led to the observation of the three unusual reactions, namely, the selective hydrogenolysis of one of two benzene rings of aminal **46** to give **47**, the Pt-catalyzed isomerization of aminal **46** to amide **50**, and the unusual fragmentation of alkoxide **53** to give benzaldehyde and **55**. Although we have not achieved the desired α'-hydroxylation of **34** to give sauroine precursor **57**, we have found novel procedures that oxidize vinylogous amide **12** to keto pyridine **58** and *N*-methyl vinylogous amide **13** to phenol **59** and that oxygenate **13** at the α- rather than α'-position to give **61** and **62**.

EXPERIMENTAL SECTION

General Experimental Methods. Reactions were conducted in flame- or oven-dried glassware under a nitrogen atmosphere and were stirred magnetically. The phrase "concentrated" refers to removal of solvents by means of a rotary-evaporator attached to a diaphragm pump (15−60 Torr) followed by removal of residual solvents at <1 Torr with an vacuum pump. Flash chromatography was performed on silica gel 60 (230−400 mesh). Analytical thin-layer chromatography (TLC) was performed using silica gel 60 F-254 precoated glass plates (0.25 mm). TLC plates were analyzed by short wave UV illumination or by spraying with permanganate solution (5 g $KMnO_4$ in 495 mL water). THF and ether were dried and purified by distillation from sodium/benzophenone. Et_3N, pyridine, acetonitrile, and benzene were distilled from CaH_2. ^1H and ^{13}C NMR spectra were obtained on a 400 MHz spectrometer in $CDCl_3$ with tetramethylsilane as internal standard unless specifically indicated. Chemical shifts are reported in δ (ppm downfield from tetramethylsilane). Coupling constants are reported in hertz with multiplicities denoted as s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), m (multiplet), and br (broad). IR spectra were acquired on an FT-IR spectrometer and are reported in wavenumbers (cm^{-1}). High-resolution mass spectra were obtained using electrospray ionization (ESI).

2,3,4,6,7,8-Hexahydro-7-methyl-5(1*H*)-quinolinone (12).[7b,9] A solution of 5-methylcyclohexane-1,3-dione (**11**) (1.20 g, 9.5 mmol), 3-bromopropylammonium bromide (**10**) (2.17 g, 9.9 mmol, 1.04 equiv), and 2,6-lutidine (3.2 mL, 2.94 g, 27.5 mmol, 3.0 equiv) in 6 mL of EtOH was heated at 130 °C for 20 min in a microwave reactor. The reaction mixture was quenched by addition of 50 mL of 1 M NaOH and extracted with CH_2Cl_2 (50 mL × 3). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated to about 5 mL. Acetonitrile (30 mL × 2) was added, and the resulting solution was concentrated again to give 1.50 g of crude **12** as a brown powder, which was directly used in the next step without further purification. A small portion was purified by flash chromatography on silica gel (100:1:1 EtOAc/MeOH/NEt_3) to give **12** as a white solid: mp 173−174 °C; ^1H NMR 4.56 (br s, 1, NH), 3.32−3.20 (m, 2), 2.41 (dd, 1, J = 16.8, 3.0), 2.34 (apparent t, 2, J = 6.4), 2.22−2.07 (m, 3), 2.02 (dd, 1, J = 16.8, 11.0), 1.86−1.73 (m, 2), 1.04 (d, 3, J = 6.1); ^{13}C NMR 194.2, 158.6, 104.2, 44.8, 41.5, 37.5, 29.0, 21.2, 21.1, 18.9; IR 3239, 3081, 1573, 1526 (strong).

2,3,4,6,7,8-Hexahydro-1,7-dimethyl-5(1*H*)-quinolinone (13).[7b] To a suspension of NaH (60% in mineral oil, 454 mg, 11.3 mmol) in 2 mL of THF was added dropwise a solution of 750 mg of crude **12** in 10 mL of THF at 0 °C. The mixture was stirred at 0 °C for 10 min, and 0.71 mL (1.62 g, 11.4 mmol) of MeI was added dropwise. The reaction was warmed to room temperature and stirred for 4 h. The reaction was quenched by addition of water (30 mL) at 0 °C. The mixture was extracted with EtOAc (20 mL × 3). The combined organic layers were washed with brine (60 mL), dried over Na_2SO_4, and concentrated. Flash chromatography of the residue on silica gel (100:1:1 EtOAc/MeOH/NEt_3) gave 409 mg (48% from **11**) of **13** as a white solid: mp 46−47 °C; ^1H NMR 3.24−3.17 (m, 2), 2.99 (s, 3), 2.55 (dd, 1, J = 15.9, 4.3), 2.46−2.23 (m, 3), 2.16−1.94 (m, 3), 1.80−1.71 (m, 2), 1.06 (d, 3, J = 6.1); ^{13}C NMR 193.4, 159.6, 105.6, 51.3, 43.9, 38.5, 35.1, 28.8, 21.5, 21.1, 19.5; IR 1611 (weak), 1551 (strong).

***trans*-1,2,3,4,6,7,8,8a-Octahydro-1,7-dimethyl-5-(1-methylethoxy)-8a-(2-propynyl)quinoline (16).** To a resealable tube were added 409 mg (2.3 mmol) of **13** and 3 mL (5.1 g, 30 mmol, 13 equiv) of 2-iodopropane. The reaction mixture was sealed and heated at 55 °C for 42 h, diluted with 9 mL of benzene, and concentrated to remove excess 2-iodopropane to give crude cation **14**.

To a solution of the residue (cation **14**) in 9 mL of THF was added 4.1 mL (1.8 equiv) of propargylmagnesium bromide solution (see below for preparation) at 0 °C. The mixture was kept at 0 °C for 1 h. The reaction was quenched by addition of water (1 mL) at −78 °C and filtered through a pad of Celite. The filtrate was diluted with saturated ammonium chloride solution (20 mL) and extracted with EtOAc (30 mL × 3). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, and concentrated. Flash chromatography of the residue on silica gel (3:2 hexanes/EtOAc) gave 251 mg (42% from **13**) of **16** as a pale yellow oil: ^1H NMR 4.08 (heptet, 1, J = 6.1), 3.01−2.93 (m, 1), 2.74 (dd, 1, J = 17.2, 2.4), 2.69−2.57 (m, 2), 2.43 (dd, 1, J = 17.2, 2.4), 2.38 (s, 3), 2.39−2.35 (m, 1), 2.12−2.03 (m, 2), 2.03 (dd, 1, J = 2.4), 1.87−1.77 (m, 1), 1.68−1.46 (m, 3), 1.28−1.22 (m, 1), 1.20 (d, 3, J = 6.1), 1.14 (d, 3, J = 6.1), 1.01 (d, 3, J = 6.7); ^{13}C NMR 145.3, 121.7, 82.7, 71.5, 68.7, 59.3, 50.8, 43.9, 38.7, 35.0, 25.8, 25.7, 22.9, 22.3, 22.1, 20.8, 19.5; IR 3308, 2112 (weak), 1674 (weak), 1115, 1070; HRMS (ESI) calcd for $C_{17}H_{28}NO$ (MH^+) 262.2165, found 262.2168.

Propargylmagnesium Bromide. To a flame-dried flask was added 1.0 g of Mg, 24 mg of $HgCl_2$, and 4 mL of ether. Propargyl bromide (0.1 mL, 80% in toluene) was added, and the reaction was initiated by heating with a heat gun. The mixture was cooled to 0 °C, and a solution of 1.4 mL of propargyl bromide (80% in toluene) in 8 mL of ether was slowly added over 1 h. The reaction was stirred at 0

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°C for 0.5 h and allowed to settle at 0 °C for 0.5 h to give a ~1 M solution.

1-(2,3,4,6,7,8-Hexahydro-1-methyl-5(1*H*)-quinolinylidene)-2-propanone (20). To a resealable tube was added a solution of 88 mg (0.34 mmol) of **16** in 1 mL of MeOH and a solution of 12 mg (0.055 mmol, 0.16 equiv) of HgO in 1 mL of 1 M H_2SO_4. The reaction was sealed and heated at 65 °C for 10 h. The reaction was cooled to room temperature and diluted with saturated $NaHCO_3$ solution (20 mL). The mixture was extracted with EtOAc (20 mL × 3). The combined organic layers were dried over Na_2SO_4 and concentrated. Flash chromatography of the residue on silica gel (100:1:0.5 EtOAc/MeOH/NEt_3) gave 29 mg (39% from **16**) of **20** as a yellow oil: ^{1}H NMR 5.64 (s, 1), 3.78 (dd, 1, *J* = 17.2, 2.4), 3.28−3.12 (m, 2), 2.93 (s, 3), 2.44 (dd, 1, *J* = 12.0, 2.9), 2.28 (ddd, 1, *J* = 14.0, 4.8, 4.8), 2.20−2.10 (m, 1), 2.13 (s, 3), 2.05 (dd, 1, *J* = 17.2, 11.6), 1.98−1.70 (m, 4), 1.05 (d, 3, *J* = 6.7); ^{13}C NMR 196.4, 157.9, 153.8, 107.5, 103.3, 50.8, 38.6, 35.6, 35.1, 32.0, 28.5, 22.7, 21.7, 21.6; IR 1637 (weak), 1484 (strong), 1400 (strong); HRMS (ESI) calcd for $C_{14}H_{22}NO$ (MH^+) 220.1696, found 220.1694.

(±)- (4a*S*,5*R*,7*S*,8a*S*)-Octahydro-5-hydroxy-1,7-dimethyl-1*H*-5,8a-propanoquinolin-10-one (26). A solution of 163 mg (0.62 mmol) of **16** in 5 mL of 3:2 concd H_2SO_4/H_2O was stirred at room temperature for 8 h. The reaction mixture was quenched by addition of water (5 mL) at 0 °C and neutralized with 6 M NaOH until the pH reached 11. The mixture was saturated with NaCl and extracted with CH_2Cl_2 (30 mL × 5). The combined organic layers were dried over Na_2SO_4 and concentrated. Flash chromatography of the residue on silica gel (100:1:1 EtOAc/MeOH/NEt_3) gave 104 mg (70% from **16**) of **26** as a white solid: mp 124−125 °C; ^{1}H NMR 2.69 (br d, 1, *J* = 12.8, H_{9eq}), 2.66 (br d, 1, *J* = 17.1, H_{4ax}), 2.57 (dd, 1, *J* = 17.1, 1.4, H_{6ax}), 2.46 (ddd, 1, *J* = 12.8, 12.8, 3.1, H_{9ax}), 2.40 (d, 1, *J* = 17.1, H_{6eq}), 2.24 (s, 3, Me_1), 2.18 (d, 1, *J* = 17.1, H_{4eq}), 2.10 (br d, 1, *J* = 12.8, H_{11eq}), 2.09 (br d, 1, *J* = 12.8, H_{14eq}), 1.85 (br dd, 1, *J* = 12.8, 4.4, H_{8eq}), 1.82 (br ddd, 1, *J* = 12.8, 3.2, 3.2, H_{10eq}), 1.70 (ddddd, 1, *J* = 12.8, 12.8, 12.8, 4.0, 4.0, H_{10ax}), 1.61 (br d, 1, *J* = 12.8, H_{12}, showed "W" couplings to H_{4eq} and H_{6eq} in COSY), 1.54−1.42 (m, 1, H_{15}), 1.41 (br, 1, $w_{1/2}$ = 5 Hz, OH), 1.34−1.22 (m, 2, H_{8ax}, H_{11ax}), 1.08 (ddd, 1, *J* = 12.8, 12.8, 1.6, H_{14ax}), 0.92 (d, 3, *J* = 6.7, Me_{16}); ^{13}C NMR 210.0, 72.2, 58.7, 50.6, 50.5, 50.3, 50.2, 46.7, 37.22, 37.19, 25.8, 25.2, 22.4, 20.0; IR 3433 (broad), 1703 (strong), 1032; HRMS (ESI) calcd for $C_{14}H_{24}NO_2$ (MH^+) 238.1807, found 238.1803.

Lycopodine numbering is used so the methyl group is carbon 1 and there are no carbons 2 and 3. A 1D NOESY experiment with irradiation of H_{6ax} at δ 2.57 showed a strong NOE to H_{6eq} at δ 2.40 and weak NOEs to H_{4ax} at δ 2.66 and H_{11ax} at δ 1.28. A 1D NOESY experiment with irradiation of H_{4eq} at δ 2.18 showed a strong NOE to H_{4ax} at δ 2.66 and a weak NOE to H_{14eq} at δ 2.09. A 1D NOESY experiment with irradiation of H_{14ax} at δ 1.08 showed a strong NOE to H_{14eq} at δ 2.09 and weak NOEs to H_{12eq} at δ 1.61, Me_{16} at δ 0.92, Me_1 at δ 2.24, and H_{8ax} at δ 1.28.

1-Hydroxybicyclo[3.3.1]nonan-3-one (28). A solution of propargyl ketone **27**[13] (98 mg, 0.72 mmol) in 2 mL of 3:2 concd H_2SO_4/H_2O was stirred at room temperature for 16 h. The reaction mixture was quenched by addition of water (10 mL) at 0 °C and neutralized with 6 M NaOH until the pH reached 11. The mixture was saturated with NaCl and extracted with EtOAc (20 mL × 3). The combined organic layers were dried over Na_2SO_4 and concentrated. Flash chromatography of the residue on silica gel (1:3 hexanes/EtOAc) gave 72 mg (76% from **27**) of **28** as a white solid: mp 236−238 °C (lit.[14a] mp 233−240 °C; lit.[14b] mp 228−231 °C; lit.[14c] mp 220−223 °C); ^{1}H NMR 2.60 (ddd, 1, *J* = 16.0, 2.0, 2.0), 2.50 (br s, 1, OH), 2.47 (d, 1, *J* = 16.0), 2.42 (dd, 1, *J* = 16.4, 6.0), 2.32 (dd, 1, *J* = 16.4, 1.8), 1.98 (dddd, 1, *J* = 12.0, 2.8, 2.6, 1.8), 1.87−1.76 (m, 3), 1.75−1.46 (m, 4), 1.34 (ddddd, 1, *J* = 13.6, 13.6, 13.6, 4.4, 4.4); ^{13}C NMR 211.0, 71.1, 55.2, 45.6, 41.3, 40.6, 30.64, 30.58, 20.1; IR 3421 (broad), 1693, 1229, 1083, 991, 932, 732. The ^{1}H NMR, ^{13}C NMR, and IR spectral data are identical to those previously reported.[14a]

3-Chloro-1-ethoxybicyclo[3.3.1]non-2-ene (31). To 1 mL of CH_2Cl_2 were added $EtAlCl_2$ (0.2 mL, 0.9 M in heptane, 0.18 mmol, 1.2 equiv) and EtOH (10.5 μL, 0.18 mmol, 1.2 equiv) successively. The mixture was stirred at room temperature for 1 h. A solution of **27** (20 mg, 0.15 mmol) in 1 mL of CH_2Cl_2 was added dropwise. The resulting mixture was stirred at room temperature for 20 h. The reaction was quenched by addition of 1 M HCl solution (5 mL) and extracted with CH_2Cl_2 (5 mL × 3). The combined organic layers were dried over Na_2SO_4 and concentrated. Flash chromatography of the residue on silica gel (25:1 hexanes/EtOAc) gave 21 mg (71% from **27**) of **31** as a colorless oil: ^{1}H NMR 5.72 (s, 1), 3.55 (dq, 1, *J* = 9, 7), 3.45 (dq, 1, *J* = 9, 7), 2.60 (br dd, 1, *J* = 18.4, 6.8), 2.40−2.32 (m, 1), 2.02 (d, 1, *J* = 18.4), 1.96 (br d, 1, *J* = 12.0), 1.69−1.40 (m, 7), 1.19 (t, 3, *J* = 7.2); ^{13}C NMR 133.7, 130.4, 76.2, 57.5, 39.0, 35.5, 35.1, 32.7, 30.4, 20.6, 16.2; IR 1648, 1103, 1087, 1052, 945, 820, 745, 661; HRMS (ESI) calcd for $C_{11}H_{18}ClO$ (MH^+) 201.1041, found 201.1039.

1-(3-(Dimethylethyl)dimethylsiloxypropyl)-2,3,4,6,7,8-hexahydro-7-methyl-5(1*H*)-quinolinone (34). To a suspension of NaH (60% in mineral oil, 650 mg, 16 mmol) in 12 mL of 1:1 THF/DMF at 0 °C was added dropwise a solution of crude **12** (1.50 g, from 9.5 mmol of **11**) in 12 mL of 1:1 THF/DMF. The mixture was stirred at 0 °C for 10 min, and 1-((dimethylethyl)dimethylsiloxy)-3-iodopropane[19] (4.50 g, 15 mmol) was added dropwise. The reaction mixture was warmed to room temperature and stirred for 18 h. The reaction was quenched by addition of water (20 mL) at 0 °C. The mixture was extracted with EtOAc (50 mL × 3). The combined organic layers were washed with brine (150 mL × 5), dried over Na_2SO_4, and concentrated. Flash chromatography of the residue on silica gel (100:1:1 EtOAc/MeOH/NEt_3) gave 1.60 g (50% from **11**) of **34** as a pale yellow oil: ^{1}H NMR 3.62 (t, 2, *J* = 5.1), 3.40 (dt, 1, *J* = 14.6, 7.0), 3.30 (dt, 1, *J* = 14.6, 7.0), 3.27−3.12 (m, 2), 2.59 (br d, 1, *J* = 12.8), 2.42−2.24 (m, 3), 2.12−1.96 (m, 3), 1.86−1.72 (m, 4), 1.03 (d, 3, *J* = 6.1), 0.89 (s, 9), 0.05 (s, 6); ^{13}C NMR 193.6, 159.3, 105.5, 59.6, 49.0, 47.6, 44.1, 34.5, 31.5, 28.9, 25.8 (3 C), 21.4, 21.2, 20.0, 18.1, −5.4 (2 C); IR 1613, 1551 (strong); HRMS (ESI) calcd for $C_{19}H_{36}NO_2Si$ (MH^+) 338.2515, found 338.2519.

***trans*-1,2,3,4,6,7,8,8a-Octahydro-1-(3-(dimethylethyl)-dimethylsiloxypropyl)-7-methyl-5-(1-methylethoxy)-8a-(2-propynyl)quinoline (36a).** To a resealable tube were added 1.60 g (4.7 mmol) of **34** and 9 mL (15.3 g, 90 mmol, 19 equiv) of 2-iodopropane. The reaction mixture was sealed and heated at 55 °C for 42 h, diluted with 27 mL of benzene, and concentrated to remove excess 2-iodopropane to give cation **35**.

To a solution of the residue (cation **35**) in 24 mL of THF, 8.5 mL (1.8 equiv) of propargylmagnesium bromide solution (for the preparation of propargylmagnesium bromide see the preparation of **16**) was added at 0 °C. The mixture was kept at 0 °C for 1 h. The reaction was quenched by addition of water (1 mL) at −78 °C and filtered through a pad of Celite. The filtrate was diluted with saturated ammonium chloride solution (30 mL) and extracted with EtOAc (40 mL × 3). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, and concentrated. Flash chromatography of the residue on silica gel (8:1 hexanes/EtOAc) gave 798 mg (40% from **34**) of **36a** as a pale yellow oil: ^{1}H NMR 4.08 (heptet, 1, *J* = 6.1), 3.68−3.56 (m, 2), 3.11 (ddd, 1, *J* = 12.8, 7.9, 7.9), 3.02−2.93 (m, 1), 2.81 (br d, 1, *J* = 12.2), 2.68 (dd, 1, *J* = 17.1, 2.4), 2.47 (dd, 1, *J* = 17.1, 2.4), 2.42 (ddd, 1, *J* = 12.2, 12.2, 2.4), 2.34 (br d, 1, *J* = 12.5), 2.16−2.00 (m, 3), 1.97 (dd, 1, *J* = 2.4, 2.4), 1.82−1.72 (m, 1), 1.67−1.50 (m, 4), 1.48−1.37 (m, 1), 1.21 (dd, 1, *J* = 12.5, 12.5), 1.18 (d, 3, *J* = 6.1), 1.16 (d, 3, *J* = 6.1), 1.00 (d, 3, *J* = 6.1), 0.90 (s, 9), 0.05 (s, 6); ^{13}C NMR 145.1, 121.3, 83.1, 70.9, 68.6, 61.2, 59.8, 47.0, 46.4, 44.0, 34.7, 32.7, 26.0, 25.9 (3 C), 25.6, 22.8, 22.4, 22.3, 21.2, 20.4, 18.3, −5.26, −5.29; IR 3311, 2113 (weak), 1673 (weak), 1253, 1097 (strong); HRMS (ESI) calcd for $C_{25}H_{46}NO_2Si$ (MH^+) 420.3298, found 420.3298.

***trans*-1,2,3,4,6,7,8,8a-Octahydro-1-(3-(dimethylethyl)-dimethylsiloxypropyl)-7-methyl-5-(1-methylethoxy)-8a-(3-trimethylsilyl-2-propynyl)quinoline (36b).** To a resealable tube was added 1.60 g (4.7 mmol) of **34** and 9 mL (15.3 g, 90 mmol, 19 equiv) of 2-iodopropane. The reaction mixture was sealed and heated at 55 °C for 42 h, diluted with 27 mL of benzene, and concentrated to remove excess 2-iodopropane to give cation **35**.

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The residue (cation **35**) was taken up in 18 mL of THF and the resulting solution was added slowly to a solution of (trimethylsilyl)-propargyllithium (see below) at −78 °C. The mixture was kept at −78 °C for 2 h and slowly warmed to room temperature over 4 h. The reaction was quenched by addition of saturated ammonium chloride solution (20 mL) and water (10 mL). The mixture was extracted with EtOAc (50 mL × 3). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, and concentrated. Flash chromatography of the residue on silica gel (12:1 hexanes/EtOAc) gave 1.19 g (51% from **34**) of **36b** as a pale yellow oil: ^{1}H NMR 4.07 (heptet, 1, J = 6.1), 3.68−3.56 (m, 2), 3.10 (ddd, 1, J = 13.4, 7.9, 7.9), 2.92−3.00 (m, 1), 2.83−2.76 (m, 1), 2.75 (d, 1, J = 17.4), 2.46 (d, 1, J = 17.4), 2.40 (ddd, 1, J = 12.4, 12.4, 2.4), 2.36 (br d, 1, J = 12.2), 2.16−2.02 (m, 3), 1.82−1.71 (m, 1), 1.68−1.50 (m, 4), 1.46−1.35 (m, 1), 1.17 (d, 3, J = 6.1), 1.16 (dd, 1, J = 12.2, 12.2), 1.16 (d, 3, J = 6.1), 0.99 (d, 3, J = 6.1), 0.90 (s, 9), 0.12 (s, 9), 0.04 (s, 6); ^{13}C NMR 144.9, 121.6, 106.3, 87.3, 68.6, 61.2, 59.9, 47.0, 46.3, 43.8, 34.6, 32.7, 26.1, 26.0 (3 C), 25.6, 22.9, 22.4, 22.3, 21.7, 21.2, 18.3, −0.1 (3 C), −5.23, −5.25; IR 2954, 2856, 2171, 1676 (weak), 1250, 1099; HRMS (ESI) calcd for $C_{28}H_{54}NO_2Si_2$ (MH^+) 492.3693, found 492.3692.

(Trimethylsilyl)propargyllithium. To 1-trimethylsilylpropyne (1.10 mL, 7.1 mmol, 1.5 equiv) in 7 mL of THF was slowly added *n*-BuLi (1.6 M, 4.70 mL, 1.6 equiv) at −78 °C. The reaction was kept at −78 °C for 5 min, warmed to −30 °C over 15 min, and kept at 0 °C for 1 h.

(±)-(4a*S*,5*R*,7*S*,8a*S*)-Octahydro-5-hydroxy-1-(3-hydroxypropyl)-7-methyl-1*H*-5,8a-propanoquinolin-10-one (6). A solution of 798 mg (1.9 mmol) of **36a** in 27 mL of 3:2 concd H_2SO_4/H_2O was stirred at room temperature for 8 h. The reaction mixture was quenched by addition of water (30 mL) at 0 °C and neutralized with 6 M NaOH until the pH reached 11. The mixture was saturated with NaCl and extracted with CH_2Cl_2 (90 mL × 5). The combined organic layers were dried over Na_2SO_4 and concentrated. Flash chromatography of the residue on silica gel (100:1:1 EtOAc/MeOH/NEt_3) gave 256 mg (48% from **36a**) of **6** as a white solid.

A solution of 1.17 g (2.4 mmol) of **36b** in 40 mL of 3:2 concd H_2SO_4/H_2O was stirred at room temperature for 10 h. The reaction mixture was quenched by addition of water (40 mL) at 0 °C and neutralized with 6 M NaOH until the pH reached 11. The mixture was saturated with NaCl and extracted with CH_2Cl_2 (120 mL × 5). The combined organic layers were dried over Na_2SO_4 and concentrated. Flash chromatography of the residue on silica gel (100:1:1 EtOAc/MeOH/NEt_3) gave 334 mg (50% from **36b**) of **6** as a white solid: mp 157−158 °C; ^{1}H NMR 5.92 (br, 1, $w_{1/2}$ = 16 Hz, OH), 3.86−3.75 (m, 2, 2 H_3), 3.16−3.04 (m, 2, H_1, H_{9eq}), 2.66 (d, 1, J = 17.1, H_{4ax}), 2.56 (d, 1, J = 16.8, H_{6ax}), 2.49 (br, 1, $w_{1/2}$ = 11 Hz, OH), 2.39 (d, 1, J = 16.8, H_{6eq}), 2.29−2.14 (m, 4, H_1, H_{11eq}, H_{9ax}, H_{14eq}), 2.10 (d, 1, J = 17.1, H_{4eq}), 2.02−1.82 (m, 3, H_2, H_{8eq}, H_{10eq}), 1.62−1.40 (m, 4, H_2, H_{10ax}, H_{12}, H_{15}), 1.35−1.22 (m, 2, H_{8ax}, H_{11ax}), 1.17 (dd, 1, J = 12.8, 12.8, H_{14ax}), 0.95 (d, 3, J = 6.1, Me_{16}); ^{13}C NMR 209.6, 71.9, 64.3, 59.3, 51.0, 50.4, 49.9, 49.4, 46.5, 46.4, 38.2, 27.6, 25.8, 25.0, 22.4, 19.9; IR 3372 (broad), 1702 (strong), 1055, 1032; HRMS (ESI) calcd for $C_{16}H_{28}NO_3$ (MH^+) 282.2069, found 282.2067.

Lycopodine numbering is used so the hydroxypropyl group contains carbon 1−3. A 1D NOESY experiment with irradiation of H_{4ax} at δ 2.66 showed a strong NOE to H_{4eq} at δ 2.10 and weak NOEs to H_{9ax} at δ 2.24 and H_{11ax} at δ 1.28. A 1D NOESY experiment with irradiation of H_{6ax} at δ 2.56 showed a strong NOE to H_{6eq} at δ 2.39 and a weak NOE to H_{11ax} at δ 1.28. A 1D NOESY experiment with irradiation of H_{6eq} at δ 2.39 showed a strong NOE to H_{6ax} at δ 2.56 and a weak NOE to H_{8eq} at δ 1.87. A 1D NOESY experiment with irradiation of H_{14ax} at δ 1.17 showed a strong NOE to H_{14eq} at δ 2.19 and weak NOEs to H_{12eq} at δ 1.58 and Me_{16} at δ 0.94.

(±)-(4a*S*,5*R*,7*S*,8a*S*)-1-(3-Acetoxypropyl)-octahydro-5-(methylthio)methoxy-7-methyl-1*H*-5,8a-propanoquinolin-10-one (40). To a solution of 100 mg (0.36 mmol) of **6** in 3 mL (2.93 g, 37 mmol, 103 equiv) of pyridine was added 1.2 mL (1.30 g, 12.7 mmol, 35 equiv) of acetic anhydride. The mixture was stirred at room temperature for 10 h. The reaction was quenched by addition of 20 mL of saturated $NaHCO_3$ solution. The mixture was extracted with CH_2Cl_2 (20 mL × 3). The combined organic layers were dried over Na_2SO_4 and concentrated to about 5 mL. Toluene (6 mL) was added and the resulting solution was concentrated again to give 115 mg of crude (±)-(4a*S*,5*R*,7*S*,8a*S*)-1-(3-acetoxypropyl)-octahydro-5-hydroxy-7-methyl-1*H*-5,8a-propanoquinolin-10-one (**39**) as a yellow sticky oil, which was directly used in the next step without further purification.

To a solution of 115 mg of the crude primary acetate **39** in 3 mL (3.30 g, 42.2 mmol) of DMSO was added 3 mL (3.24 g, 31.8 mmol) of acetic anhydride. The mixture was stirred at room temperature for 72 h. The reaction was quenched by addition of saturated $NaHCO_3$ solution (30 mL) and extracted with extracted with CH_2Cl_2 (30 mL × 5). The combined organic layers were dried over Na_2SO_4 and concentrated. Most of the remaining DMSO was removed by blowing air on the compound for 6 h. Flash chromatography of the residue on silica gel (1:1 hexanes/EtOAc) gave 136 mg (90% from **6**) of **40** as a pale yellow oil.

Alternatively, a solution of 334 mg (1.2 mmol) of **6** in 8 mL (8.64 g, 84.7 mmol, 70 equiv) of acetic anhydride was stirred overnight under nitrogen. Eight milliliters (8.80 g, 113 mmol, 94 equiv) of DMSO was added, and the reaction mixture was stirred for 72 h. The reaction was quenched by addition of saturated $NaHCO_3$ solution (80 mL) and extracted with CH_2Cl_2 (100 mL × 5). The combined organic layers were dried over Na_2SO_4 and concentrated. Most of the remaining DMSO was removed by blowing air on the compound for 6 h. Flash chromatography of the residue on silica gel (1:1 hexanes/EtOAc) gave 409 mg (90% from **6**) of **40** as a pale yellow oil: ^{1}H NMR 4.52 (s, 2), 4.19−4.06 (m, 2), 2.88 (ddd, 1, J = 13.4, 7.9, 7.9), 2.82 (br d, 1, J = 12.3), 2.75 (d, 1, J = 17.0), 2.57 (d, 1, J = 16.9), 2.54 (d, 1, J = 16.9), 2.26 (ddd, 1, J = 12.3, 12.3, 2.8), 2.19 (s, 3), 2.08 (d, 1, J = 17.0), 2.04 (s, 3), 2.05−1.86 (m, 4), 1.81−1.64 (m, 4), 1.56 (ddddd, 1, J = 12.8, 12.8, 12.8, 4.3, 4.3), 1.49−1.33 (m, 2), 1.24 (dddd, 1, J = 13.1, 13.1, 13.1, 3.7), 0.96 (dd, 1, J = 12.2, 12.2), 0.92 (d, 3, J = 5.5); ^{13}C NMR 210.0, 171.1, 77.7, 66.0, 62.4, 58.9, 48.3, 47.8, 47.1, 46.6, 45.0, 44.6, 38.8, 27.8, 25.4, 25.2, 22.7, 21.0, 20.3, 14.6; IR 1735 (strong), 1705 (strong), 1553, 1241 (strong), 1043 (strong); HRMS (ESI) calcd for $C_{20}H_{34}NO_4S$ (MH^+) 384.2209, found 384.2209.

(±)-(4a*S*,5*R*,7*S*,8a*S*)-Octahydro-1-(3-hydroxypropyl)-5-(methylthio)methoxy-7-methyl-1*H*-5,8a-propanoquinolin-10-one (41). To a solution of 136 mg (0.36 mmol) of **40** in 6 mL of MeOH at 0 °C was added 400 mg (2.9 mmol, 8.0 equiv) of K_2CO_3. The reaction was kept at 0 °C for 2 h and filtered. The filtrate was concentrated and diluted with 10 mL of saturated $NaHCO_3$ solution. The mixture was extracted with CH_2Cl_2 (10 mL × 4). The combined organic layers were dried over Na_2SO_4 and concentrated. Flash chromatography of the residue on silica gel (100:1:1 EtOAc/MeOH/NEt_3) gave 111 mg (92%) of the primary alcohol **41** as a pale yellow sticky oil: ^{1}H NMR 5.47 (br, 1, $w_{1/2}$ = 12 Hz, OH), 4.47 (s, 2), 3.81−3.70 (m, 2), 3.11−2.96 (m, 2), 2.66 (d, 1, J = 17.1), 2.53 (s, 2), 2.23−2.10 (m, 3), 2.14 (s, 3), 2.06 (d, 1, J = 17.1), 2.02 (dd, 1, J = 12.0, 2.8), 1.97−1.89 (m, 2), 1.79 (ddd, 1, J = 10.4, 2.7, 2.7), 1.70 (dd, 1, J = 12.5, 3.2), 1.52 (ddddd, 1, J = 13.2, 13.2, 13.2, 4.0, 4.0), 1.44−1.31 (m, 3), 1.22 (dddd, 1, J = 12.8, 12.8, 12.8, 3.6), 1.12 (dd, 1, J = 11.6), 0.92, (d, 3, J = 5.5); ^{13}C NMR 209.0, 77.5, 66.0, 64.3, 59.0, 49.2, 48.2, 48.1, 46.5, 46.1, 44.5, 38.4, 27.9, 25.5, 24.9, 22.5, 20.0, 14.5; IR 3395 (broad), 1703 (strong), 1041 (strong); HRMS (ESI) calcd for $C_{18}H_{32}NO_3S$ (MH^+) 342.2103, found 342.2104.

(±)-(8a*S*,9*R*,11*S*,12a*R*)- 3,4,6,7,8,8a,9,10,11,12-Decahydro-9-hydroxy-11-methyl-1,9-ethanobenzo[*i*]quinolizin-14-one (42). To a resealable tube was added 100 mg (0.26 mmol) of **40**, 180 mg (1.60 mmol, 6.0 equiv) of KO-*t*-Bu, 780 mg (4.3 mmol, 16 equiv) of benzophenone, and 3 mL of dry benzene. The mixture was subjected to three cycles of freeze−pump−thaw degas protocol and was sealed and heated at 110 °C for 1 h. After cooling to room temperature, the reaction was quenched by addition of 10 mL of 3 M HCl solution. The mixture was extracted with ether (10 mL × 2). The aqueous layer was neutralized with Na_2CO_3 powder until pH 11 was reached. The solution was extracted with CH_2Cl_2 (15 mL × 5). The combined organic layers were dried over Na_2SO_4 and concentrated. Flash chromatography of the residue on silica gel (100:1:1 EtOAc/MeOH/NEt_3) gave 32 mg (47% from **40**) of **42** as a white solid.

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Alternatively, to a resealable tube was added 111 mg (0.32 mmol) of **41**, 182 mg (1.63 mmol, 5.0 equiv) of KO-*t*-Bu, 948 mg (5.2 mmol, 16 equiv) of benzophenone, and 3 mL of dry benzene. The mixture was subjected to three cycles of freeze−pump−thaw degas protocol and was sealed and heated at 110 °C for 50 min. After cooling to room temperature, the reaction was quenched by addition of 12 mL of 3 M HCl solution. The mixture was extracted with ether (12 mL × 2). The aqueous layer was neutralized with Na_2CO_3 powder until pH 11 was reached. The solution was extracted with CH_2Cl_2 (20 mL × 5). The combined organic layers were dried over Na_2SO_4 and concentrated. Flash chromatography of the residue on silica gel (100:1:1 EtOAc/MeOH/NEt_3) gave 42 mg (50% from **41**) of **42** as a white solid: mp >172 °C dec; ^{1}H NMR 7.06 (dd, 1, *J* = 3.7, 3.7), 3.55 (ddd, 1, *J* = 14.7, 11.0, 6.1), 2.75 (dd, 1, *J* = 14.7, 7.3), 2.70−2.50 (m, 5), 2.14 (dd, 1, *J* = 12.8, 2.6), 2.10−1.99 (m, 2), 1.89 (br d, 1, *J* = 12.2), 1.79 (ddd, 1, *J* = 13.2, 2.8, 2.8), 1.65 (ddddd, 1, *J* = 12.8, 12.8, 12.8, 4.0, 4.0), 1.64 (dd, 1, *J* = 12.8, 3.5), 1.49−1.36 (m, 1), 1.35 (ddd, 1, *J* = 12.2, 12.2, 1.6), 1.22 (dd, 1, *J* = 12.0, 12.0), 1.02 (dddd, 1, *J* = 12.8, 12.8, 12.8, 3.7), 0.93 (d, 3, *J* = 6.1); ^{13}C NMR 197.5, 136.9, 136.3, 70.9, 58.4, 50.8, 50.2, 49.01, 49.00, 48.1, 43.9, 25.6, 25.1, 22.2, 21.04, 20.97; IR 3389 (broad), 1680 (strong), 1612 (strong), 1244, 1030; HRMS (ESI) calcd for $C_{16}H_{24}NO_2$ (MH^+) 262.1807, found 262.1805.

(±)-(1*S*,8a*S*,9*R*,11*S*,12a*R*)-Dodecahydro-9-hydroxy-11-methyl-1,9-ethanobenzo[*i*]quinolizin-14-one (7-Hydroxylycopodine, 5). To a solution of 42 mg (0.16 mmol) of **42** in 3 mL of MeOH was added 5 mg of PtO_2. The mixture was stirred under 1 atm of H_2 (balloon) at room temperature for 10 h. The mixture was filtered through a pad of Celite, and the filtrate was concentrated. Flash chromatography of the residue on silica gel (40:1:1 EtOAc/MeOH/NEt_3) gave 40 mg (95%) of **5** as a white solid: mp 201−202 °C; ^{1}H NMR ($CDCl_3$) 3.37 (ddd, 1, *J* = 14.3, 14.3, 3.7, H_{1ax}), 3.12 (ddd, 1, *J* = 12.2, 12.2, 2.8, H_{9ax}), 2.83 (br dd, 1, *J* = 11.6, 2.4, H_4), 2.65 (br d, 1, *J* = 12.2, H_{9eq}), 2.62 (br d, 1, *J* = 12.8, H_{14eq}), 2.61 (br d, 1, *J* = 15.6, H_{6ax}), (The peaks at δ 2.62 ppm and δ 2.61 ppm overlap and are assigned from analysis of the COSY spectra.), 2.56 (dd, 1, *J* = 14.3, 4.9, H_{1eq}), 2.38 (dd, 1, *J* = 15.6, 1.5, H_{6eq}), 2.11−2.01 (m, 2, H_{11eq}, H_{3eq}), 1.89 (ddd, 1, *J* = 12.0, 3.2, 3.2, H_{10eq}), 1.85 (dd, 1, *J* = 12.0, 3.8, H_{8eq}), 1.84 (ddddd, 1, *J* = 13.6, 13.6, 13.6, 4.8, 4.8, H_{2ax}), 1.69 (ddddd, 1, *J* = 12.8, 12.8, 12.8, 3.8, 3.8, H_{10ax}), 1.67 (br dd, 1, *J* = 12.8, 3.1, H_{12}), 1.54 (dddd, 1, *J* = 13.1, 13.1, 13.1, 4.8, H_{3ax}), 1.44 (dddd, 1, *J* = 12.8, 12.8, 12.8, 3.8, H_{11ax}), 1.38 (br d, 1, *J* = 13.6, H_{2eq}), 1.41−1.33 (m, 1, H_{15}), 1.28 (ddd, 1, *J* = 12.0, 12.0, 2.2, H_{8ax}), 0.91 (dd, 1, *J* = 12.8, 12.8, H_{14ax}), 0.89 (d, 3, *J* = 6.1, Me_{16}); (CD_3OD) 3.35 (ddd, 1, *J* = 14.0, 14.0, 3.5, H_{1ax}), 3.23 (ddd, 1, *J* = 12.4, 12.4, 2.3, H_{9ax}), 3.03 (br dd, 1, *J* = 11.6, 2.8, H_4), 2.69 (br d, 1, *J* = 15.6, H_{6ax}), 2.63 (br d, 1, *J* = 12.4, H_{14eq}), 2.58 (br d, 1, *J* = 12.4, H_{9eq}), 2.52 (dd, 1, *J* = 14.0, 4.8, H_{1eq}), 2.25 (dd, 1, *J* = 15.6, 1.2, H_{6eq}), 2.06−1.98 (m, 2, H_{3eq}, H_{11eq}), 1.95−1.85 (m, 2, H_{2ax}, H_{10eq}), 1.79 (br d, 1, *J* = 12.4, H_{8eq}), 1.73−1.46 (m, 4, H_{10ax}, H_{12}, H_{11ax}, H_{3ax}), 1.42 (br d, 1, *J* = 13.6, H_{2eq}), 1.37−1.26 (m, 1, H_{15}), 1.28 (ddd, 1, *J* = 12.4, 12.4, 1.7, H_{8ax}), 0.91 (d, 3, *J* = 5.6, Me_{16}), 0.90 (dd, 1, *J* = 12.6, 12.6, H_{14ax}); (DCl salt in CD_3OD) 3.82 (ddd, 1, *J* = 13.2, 13.2, 2.0), 3.73 (ddd, 1, *J* = 13.6, 13.6, 4.4), 3.30 (m, 1, obscured by the residual solvent peak, assigned from analysis of the COSY spectra), 3.18 (br d, 1, *J* = 13.2), 3.03 (dd, 1, *J* = 13.6, 4.8), 2.75 (br d, 1, *J* = 16.0), 2.71 (dd, 1, *J* = 12.4, 3.0), 2.40 (dd, 1, *J* = 16.0, 1.2), 2.20−2.10 (m, 3), 2.06−1.80 (m, 5), 1.81 (dddd, 1, *J* = 12.8, 12.8, 12.8, 3.2), 1.70−1.58 (m, 1), 1.47−1.33 (m, 2), 1.33 (dd, 1, *J* = 12.4, 12.4), 0.98 (d, 3, *J* = 5.6); ^{13}C NMR ($CDCl_3$) 210.3, 72.5, 59.5, 51.4, 50.9, 50.4, 47.3, 47.1, 42.5, 41.8, 25.4, 25.2, 22.6, 19.6, 19.5, 18.5; (CD_3OD) 212.6, 73.1, 61.2, 52.6, 51.7, 51.1, 48.4, 48.0, 43.3, 43.1, 26.6, 26.3, 23.0, 20.6, 20.4, 19.7; (DCl salt in CD_3OD) 206.6, 72.5, 66.2, 51.9, 51.0, 50.8, 44.1, 40.7, 26.6, 24.2, 22.6, 19.1, 18.9, 18.7 (carbons 1 and 9 are obscured by the residual solvent peak); IR 3458 (broad), 1702 (strong), 1312; HRMS (ESI) calcd for $C_{16}H_{26}NO_2$ (MH^+) 264.1964, found 264.1960.

The data for **5** in CD_3OD are referenced to the residual solvent peaks at δ 3.31 and δ 49.15. The ^{1}H NMR data for **5**·DCl in CD_3OD (also referenced to δ 3.31 for residual CD_2HOD) are identical to those reported for **5**·DCl except that all absorptions are 0.03 ppm downfield. The ^{13}C NMR data for **5**·DCl are referenced to δ 49.3 so that the data match those reported in the literature.[4] The ^{1}H and ^{13}C NMR spectra of natural and synthetic **5**·DCl are shown in Tables S1 and S2 in the Supporting Information.

(1*S*,2*R*,3a*S*,5a*S*,6*S*,8*S*,9a*R*)-2-Cyclohexyldecahydro-8-methyl-1-phenyl-5*H*-oxazolo[3,2-*a*]quinolin-6-ol (47). To a solution of **46**[25] (30 mg, 0.082 mmol) in 2 mL of 1:10 conc HCl/MeOH was added 5 mg of PtO_2. The mixture was shaken in a Parr apparatus at an initial pressure of 50 psi for 40 h. The mixture was filtered through a pad of Celite and the filtrate was concentrated. Flash chromatography of the residue on silica gel (2:1 hexanes/EtOAc) gave 21 mg (69%) of **47** as a colorless sticky oil: $[\alpha]^{22}_D$ = −5.1 (*c* 0.25, CH_2Cl_2); ^{1}H NMR 7.60−7.53 (br, 1), 7.34−7.25 (br, 1), 7.22−7.15 (br, 2), 7.12−7.05 (br, 1), 3.85 (d, 1, *J* = 7.9, H-1), 3.80 (dd, 1, *J* = 10.0, 2.5, H-3a), 3.63 (dd, 1, *J* = 9.2, 7.9, H-2), 3.25 (ddd, 1, *J* = 10.4, 10.4, 4.0, H-6), 2.33−2.22 (m, 2), 2.14 (dddd, 1, *J* = 11.6, 3.0, 2.9, 2.5), 1.92−1.80 (m, 2), 1.72−1.55 (m, 2), 1.52−1.24 (m, 6), 1.19−0.90 (m, 6), 0.82 (ddd, 1, *J* = 12.0, 12.0, 12.0), 0.72 (d, 3, *J* = 6.8), 0.70−0.62 (m, 2), 0.33 (ddd, 1, *J* = 12.0, 12.0, 12.0); ^{13}C NMR 142.9, 130.2 (br), 128.6 (br), 127.6 (br), 126.9 (br), 126.6, 93.4, 86.3, 72.8, 65.5, 62.5, 49.5, 43.8, 39.8, 37.7, 29.5, 29.4, 28.9, 28.8, 26.4, 25.5, 25.4, 25.2, 21.8; IR 1453, 1096, 1029, 1009, 735, 702; HRMS (ESI) calcd for $C_{24}H_{36}NO_2$ (MH^+) 370.2746, found 370.2743.

A COSY experiment showed a cross peak between H_1 at δ 3.85 and H_2 at δ 3.63. A COSY experiment showed cross peaks between H_{3a} at δ 3.80 and the hydrogens at δ 2.14, at δ 1.64. A COSY experiment showed cross peaks between H_2 at δ 3.63 and H_1 at δ 3.85, the hydrogen at δ 1.00. A COSY experiment showed cross peaks between H_6 at δ 3.25 and the hydrogens at δ 1.82, at δ 1.11, and at δ 0.82.

(4a*S*,5*S*,7*S*,8a*R*)-5-Hydroxy-7-methyloctahydro-1-[(1*R*)-1,2-diphenylethyl]-2(1*H*)-quinolinone (50). To a solution of **46**[25] (30 mg, 0.082 mmol) in 2 mL of MeOH was added 5 mg of PtO_2. The mixture was stirred under 1 atm of H_2 (balloon) at room temperature for 40 h. The mixture was filtered through a pad of Celite and the filtrate was concentrated. Flash chromatography of the residue on silica gel (1:1 hexanes/EtOAc) gave 22 mg (73%) of **50** as a sticky colorless oil: $[\alpha]^{22}_D$ = −55 (*c* 0.11, CH_2Cl_2); ^{1}H NMR 7.43−7.19 (m, 10), 4.75 (br, 1, PhCH), 3.87 (dd, 1, *J* = 13.4, 10.8, $PhCH_2$), 3.30 (dd, 1, *J* = 13.4, 5.6, $PhCH_2$), 3.02 (ddd, 1, *J* = 10.4, 10.4, 4.4, H-5), 2.46 (ddd, 1, *J* = 18.0, 4.8, 1.4, H-3), 2.29 (ddd, 1, 18.0, 12.8, 6.0, H-3), 2.11 (br dd, 1, *J* = 10.8, 10.8), 1.99 (dddd, 1, *J* = 12.8, 6.0, 2.4, 2.4), 1.93 (br d, 1, 13.6), 1.88 (ddd, 1, *J* = 12.8, 4.0), 1.79−1.67 (m, 1), 1.33−1.16 (m, 1), 1.19 (dddd, 1, *J* = 12.4, 10.0, 10.0, 2.4), 0.92 (ddd, 1, *J* = 11.6, 11.6, 11.6), 0.87 (d, 3, *J* = 6.4), 0.83 (ddd, 1, *J* = 11.6, 11.6, 11.6), 0.72 (dddd, 1, *J* = 12.8, 12.8, 12.8, 5.2);^{13}C NMR 171.1, 141.0 (br), 139.1, 129.4 (2 C), 128.3 (2 C), 128.1(2 C), 126.8 (2 C), 126.5, 126.4, 71.6, 63.4 (br), 62.7 (br), 48.2, 43.5, 40.0, 37.7, 33.9, 28.7, 21.8, 21.4; IR 1623, 1455, 1275, 1261, 750, 701; HRMS (ESI) calcd for $C_{24}H_{30}NO_2$ (MH^+) 364.2277, found 364.2275.

A COSY experiment showed cross peaks between the hydrogen at δ 4.75(PhCH) and the hydrogens at δ 3.87 ($PhCH_2$), at δ 3.30 ($PhCH_2$). A COSY experiment showed cross peaks between H_5 at δ 3.02 and the hydrogens at δ 1.88, at δ 1.19, and at δ 0.92. A COSY experiment showed a cross peak between H_3 at δ 2.46 and H_3 at δ 2.29

1-Benzyl-2,3,4,6,7,8-hexahydro-7-methyl-5(1*H*)-quinolinone (55) and [(1*E*)-2-(Methylsulfinyl)ethenyl]benzene (56). To a suspension of NaH (60% in mineral oil, 20 mg, 0.50 mmol, 2.3 equiv) in 1 mL of DMSO at room temperature under N_2 was added dropwise a solution of **12** (36 mg, 0.22 mmol) in 2 mL of DMSO. The mixture was stirred at room temperature for 20 min, and a solution of stilbene oxide (72 mg, 0.37 mmol, 1.7 equiv) in 1 mL of DMSO was added dropwise. The resulting mixture was heated to 50 °C and stirred for 12 h. The reaction was quenched by addition of water (5 mL) at room temperature. The mixture was extracted with EtOAc (10 mL × 3). The combined organic layers were washed with brine (20 mL × 4), dried over Na_2SO_4, and concentrated. Flash chromatography of the residue on silica gel (100:1:1 EtOAc/MeOH/NEt_3) gave 4.3 mg (12% from **12**) of **56** as a colorless oil followed by 6.7 mg (12% from **12**) of **55** as a colorless sticky oil.

Data for **55**: ^{1}H NMR 7.38 (dd, 2, *J* = 7.3, 7.3), 7.31 (dd, 1, *J* = 7.3, 7.3), 7.16 (d, 2, *J* = 7.3), 4.58 (d, 1, *J* = 17.1), 4.43 (d, 1, *J* = 17.1),

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3.26−3.21 (m, 2), 2.56−2.30 (m, 4), 2.20−1.98 (m, 3), 1.92−1.74 (m, 2), 1.01 (d, 3, J = 6.1); ^{13}C NMR 194.0, 159.0, 137.1, 128.9 (2 C), 127.4, 125.9 (2 C), 106.0, 54.0, 49.5, 44.0, 34.8, 29.0, 21.4, 21.1, 19.8; IR 1674, 1607, 1550, 1275, 1263, 749, 699; HRMS (ESI) calcd for $C_{17}H_{22}NO$ (MH^+) 256.1696, found 256.1702.

Data for **56**: ^{1}H NMR 7.50−7.22 (m, 5), 7.25 (d, 1, J = 15.6), 6.90 (d, 1, J = 15.6), 2.71 (s, 3). These data are identical to those previously reported.[27]

1-Benzyl-2,3,4,6,7,8-hexahydro-7-methyl-5(1*H*)-quinolinone (55). To a suspension of NaH (60% in mineral oil, 65 mg, 1.6 mmol, 2.0 equiv) in 1 mL of 1:1 THF/DMF, a solution of **12** (131 mg, 0.80 mmol) in 1 mL of 1:1 THF/DMF was added dropwise at 0 °C. The mixture was stirred at 0 °C for 20 min, and 0.15 mL (210 mg, 1.2 mmol, 1.5 equiv) of BnBr was added dropwise. The reaction was warmed to room temperature and stirred for 18 h. The reaction was quenched by addition of water (5 mL) at 0 °C. The mixture was extracted with EtOAc (5 mL × 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, and concentrated. Flash chromatography of the residue on silica gel (100:1:1 EtOAc/MeOH/NEt_3) gave 142 mg (70% from **12**) of **55** as a colorless sticky oil with ^{1}H NMR, ^{13}C NMR, and IR spectral data identical to those of **55** prepared from **12** and stilbene oxide.

7,8-Dihydro-7-methyl-5(6*H*)-quinolinone (58). To a solution of **13** (15 mg, 0.084 mmol) in 1 mL of benzene was added $Mn(OAc)_3$ (86 mg, 0.37 mmol, 4.4 equiv). The resulting mixture was heated at 150 °C for 20 min in a microwave reactor. The reaction mixture was quenched by addition of saturated $NaHSO_3$ solution (10 mL) and extracted with EtOAc (10 mL × 3). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. Flash chromatography of the residue on silica gel (100:1:1 EtOAc/MeOH/NEt_3) gave 4.7 mg (35%) of **58** as a colorless oil, followed by 5.3 mg (35% recovered) of **13** as a pale yellow oil, and then 2.6 mg (20%) of **12** as a white solid.

To a solution of **12** (10 mg, 0.061 mmol) in 1 mL of benzene, $Mn(OAc)_3$ (60 mg, 0.26 mmol, 4.3 equiv) was added. The resulting mixture was heated at 90 °C for 20 min in a microwave reactor. The reaction mixture was quenched by addition of saturated $NaHSO_3$ solution (10 mL) and extracted with EtOAc (10 mL × 3). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. Flash chromatography of the residue on silica gel (100:1:1 EtOAc/MeOH/NEt_3) gave 6.5 mg (67%) of **58** as a colorless oil, followed by 1.5 mg (15%) of recovered **12** as a white solid.

Data for **58**: ^{1}H NMR 8.69 (dd, 1, J = 4.8, 1.9), 8.27 (dd, 1, J = 8.0, 1.9), 7.29 (dd, 1, J = 8.0, 4.8), 3.23 (dd, 1, J = 17.0, 3.6), 2.86 (dd, 1, J = 17.0, 10.4), 2.78 (dd, 1, J = 12.4, 1.9), 2.48−2.36 (m, 1), 2.37 (dd, 1, J = 12.4, 12.4), 1.20 (d, 3, J = 6.4); ^{13}C NMR 198.0, 163.0, 153.6, 134.8, 127.6, 122.2, 46.6, 40.8, 29.2, 21.2; IR 1689, 1584, 1457, 1293, 912, 731. The ^{1}H NMR spectral data are identical to those previously reported.[30]

1,2,3,4-Tetrahydro-1,7-dimethyl-5-quinolinol (59). To a solution of **13** (8.0 mg, 0.048 mmol) in 1.5 mL of THF was added a solution of KHMDS (0.5 M in toluene, 0.15 mL, 1.5 equiv) at −78 °C under N_2. The mixture was stirred at the same temperature for 20 min, and O_2 was introduced to the reaction container from a balloon via a syringe. The reaction was slowly warmed to 0 °C over 50 min and stirred at 0 °C for 30 min. The reaction was quenched by addition of saturated Na_2SO_3 solution (5 mL). The mixture was extracted with EtOAc (5 mL × 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, and concentrated. Flash chromatography of the residue on silica gel (5:1 hexanes/EtOAc) gave 1.6 mg (20%) of **59** as a white solid: mp 95−96 °C; ^{1}H NMR 6.08 (s, 1), 6.01 (s, 1), 4.53 (br s, 1, OH), 3.16 (t, 2, J = 5.6), 2.87 (s, 3), 2.63 (t, 2, J = 6.8), 2.22 (s, 3), 1.98 (tt, 2, J = 6.8, 5.6); ^{13}C NMR 153.2, 147.9, 136.9, 105.8, 105.0, 104.6, 50.9, 39.8, 21.9, 21.6, 20.6; IR 1618, 1580, 1517, 1273, 1124, 915, 807, 748; HRMS (ESI) calcd for $C_{11}H_{16}NO$ (MH^+) 178.1232, found 178.1232. Similar results were obtained using NaHDMS.

5-(Dimethylethyl)dimethylsiloxy-1,2,3,4-tetrahydro-1,7-dimethylquinoline (60), (±)-(4a*R*,7*S*)-5-(Dimethylethyl)-dimethylsiloxy-4a-((dimethylethyl)dimethylsilyl)dioxy-1,2,3,4,4a,7-hexahydro-1,7-dimethylquinoline (61), and (±)-(4a*S*,7*S*)-5-(Dimethylethyl)dimethylsiloxy-4a-((dimethylethyl)dimethylsilyl)dioxy-1,2,3,4,4a,7-hexahydro-1,7-dimethylquinoline (62). To a solution of **13** (180 mg, 1.0 mmol) in 8 mL of THF at −78 °C was added a solution of NaHMDS (1.0 M in THF, 2.2 mL, 2.2 equiv), and the mixture was stirred at the same temperature for 50 min. Oxygen (dried over $CaSO_4$) was bubbled into the solution for 50 min at the same temperature. To the solution was added TBSOTf (0.60 mL, 2.6 mmol, 2.6 equiv), and the resulting mixture was stirred at the same temperature for 50 min. The reaction was quenched by addition of saturated $NaHCO_3$ solution (30 mL) and extracted with Et_2O (30 mL × 3). The combined organic layers were dried over $MgSO_4$ and concentrated. Flash chromatography of the residue on MeOH−deactivated silica gel (50:1 hexanes/EtOAc) gave 30 mg (10%) of **60** as a colorless liquid, 10 mg of a mixture of **60**, **61** and **62** (1:4:10) as a pale yellow liquid, and 98 mg (22%) of **61** as a pale yellow liquid.

Data for **60**: ^{1}H NMR 6.10 (s, 1), 6.01 (s, 1), 3.13 (t, 2, J = 5.6), 2.86 (s, 3), 2.63 (t, 2, J = 6.8), 2.22 (s, 3), 1.93 (tt, 2, J = 6.8, 5.6), 0.99 (s, 9), 0.21 (s, 6); ^{13}C NMR 153.2, 147.9, 136.1, 110.7, 108.1, 105.4, 51.1, 39.7, 25.8 (3 C), 22.2, 21.8, 21.7, 18.3, −4.1 (2 C); IR 1606, 1576, 1269, 1191, 1135, 836, 778.

The structure of **60** was confirmed by hydrolysis of **60** (20 mg, 0.068 mmol) in 2 mL of 3 M HCl at room temperature for 2 h. The reaction was quenched by addition of saturated $NaHCO_3$ solution (20 mL) and extracted with EtOAc (20 mL × 3). The combined organic layers were dried over Na_2SO_4 and concentrated. Flash chromatography of the residue on silica gel (5:1 hexanes/EtOAc) gave 11 mg (90%) of **59** as a white solid with mp, ^{1}H NMR, ^{13}C NMR, and IR spectral data identical to those of **59** prepared from **13**, KHMDS and oxygen.

Data for **61**: ^{1}H NMR 5.01 (br d, 1, J = 4.4), 4.72 (br d, 1, J = 4.4), 2.92 (br dd, 1, J = 10.8, 5.2), 2.86−2.77 (m, 1), 2.43 (ddd, 1, J = 12.4, 10.8, 3.2), 2.43 (s, 3), 2.32−2.24 (m, 1), 2.12−1.96 (m, 1), 1.52−1.42 (m, 2), 1.09 (d, 3, J = 7.2), 0.94 (s, 9), 0.87 (s, 9), 0.19 (s, 3), 0.18 (s, 3), 0.10 (s, 6); ^{13}C NMR 146.8, 142.5, 112.1, 108.5, 78.4, 53.9, 40.5, 30.9, 30.8, 26.2 (3 C), 25.8 (3 C), 22.4, 20.4, 18.20, 18.18, −4.4, −5.1, −5.5, −5.8; IR 1686, 1647, 1178, 913, 835, 745; HRMS (ESI) calcd for $C_{23}H_{46}NO_3Si_2$ (MH^+) 440.3016, found 440.3021.

A COSY experiment showed large cross peaks between the hydrogen at δ 2.86−2.77 and the hydrogens at δ 5.01, δ 4.72, and δ 1.09. A COSY experiment showed a small cross peak for W coupling between the hydrogens at δ 5.01 and at δ 4.72.

The data for **62** were obtained by comparing the NMR spectra of **60**, **61**, and the mixture of all three: ^{1}H NMR 4.97 (dd, 1, J = 2, 2), 4.65 (dd, 1, J = 2, 2), 2.97−2.88 (m, 2), 2.50−2.42 (m, 1), 2.45 (s, 3), 2.32−2.24 (m, 1), 2.12−1.96 (m, 1), 1.52−1.40 (m, 2), 1.02 (d, 3, J = 7.2), 0.94 (s, 9), 0.84 (s, 9), 0.20 (s, 3), 0.18 (s, 3), 0.10 (s, 6); ^{13}C NMR 147.0, 142.3, 113.4, 109.5, 78.1, 53.8, 40.5, 31.0, 30.8, 26.1(3 C), 25.8 (3 C), 23.5, 20.4, 18.22, 18.20, −4.4, −4.9, −5.4, −5.8.

A COSY experiment showed large cross peaks between the hydrogen at δ 2.97−2.88 and the hydrogens at δ 4.97, δ 4.65, and δ 1.02. A COSY experiment showed a small cross peak for W coupling between the hydrogens at δ 4.97 and at δ 4.65.

6-(Dimethylethyl)dimethylsiloxy-1,3,4,8,9,10-hexahydro-1,4-dimethyl-2,7-azecinedione (65). To a solution of **61** (22 mg, 0.050 mmol) in 1 mL of $CDCl_3$, pyridine (10 μL, 0.012 mmol, 2.5 equiv) and pyr·$(HF)_x$ (4 μL, 0.15 mmol, 3 equiv) were added successively. The reaction was stirred at rt for 30 min. The solvent was evaporated, and flash chromatography on silica gel (3:1 hexanes/EtOAc) gave 6.5 mg (40%) of **65** as a colorless oil: ^{1}H NMR 4.66 (d, 1, J = 10.0), 4.41 (ddd, 1, J = 13.6, 10.4, 3.6), 3.05−2.94 (m, 1), 2.82 (ddd, 1, J = 15.2, 12.0, 2.0), 2.80 (s, 3), 2.69 (dd, 1, J = 13.2, 4.4), 2.43 (ddd, 1, J = 13.6, 4.0, 4.0), 2.23−2.11 (m, 1), 2.08 (ddd, 1, J = 15.2, 8.0, 1.9), 1.94 (dd, 1, J = 13.2, 13.2), 1.94−1.84 (m, 1), 1.09 (d, 3, J = 6.8), 0.90 (s, 9), 0.21 (s, 3), 0.14 (s, 3); ^{13}C NMR 203.2, 172.3, 150.5, 115.1, 47.0, 45.0, 37.8, 36.0, 26.2, 25.5 (3 C), 23.6, 21.0, 18.0, −4.7, −4.8; IR 1696, 1636, 1258, 1225, 1084, 1067, 913, 837, 745; HRMS (ESI) calcd for $C_{17}H_{32}NO_3Si$ (MH^+) 326.2151, found 326.2150. The fully assigned spectral data as determined by analysis of COSY, HSQC,

and HMBC 2D NMR spectra are shown in Table S3 in the Supporting Information.

Assay for Acetylcholinesterase Activity. Inhibition of acetylcholinesterase activity was determined with a modified micro-Ellman assay.[35a,b] 7-Hydroxylycopodine was initially dissolved in 0.12 M HCl to a concentration of 0.076 M and then diluted in saline (0.15 M sodium chloride) as needed. Electric eel (*Electrophorus electricus*) acetylcholinesterase (AChE) (15 U/mL) was preincubated with 7-hydroxylycopodine for 15 min, and then 0.075 U of preincubated enzyme was added to the reaction mixture containing 7-hydroxylycopodine at the preincubation concentration, 1 mM acetylthiocholine (ATC), 0.1 mM 4,4′-dithiopyridine, and 50 mM pH 8.0 sodium phosphate buffer. The reaction was monitored for 5 min at 325 nm in a SpectraMax Plus 96 well plate reader at 24 °C. Human whole blood was diluted initially 1:10 in saline and then 1:2 with 7-hydroxylycopodine solution of the appropriate concentration. To distinguish ATC hydrolysis by human blood AChE and butyrylcholinesterase (BChE), blood samples were first treated with 3.33 mM tetramonoisopropyl pyrophosphortetramide (Iso-OMPA) prior to 7-hydroxylycopodine. BChE activities were determined with 1.0 mM butyrylthiocholine (BTC) as the substrate. IC_{50} values were calculated from nonlinear regression analysis of the plotted data using GraphPad Prism Ver. 4.0.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Tables of spectral data and copies of ^{1}H and ^{13}C NMR spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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