# Utilization of the Intramolecular Cycloaddition−Cationic π-Cyclization of an Isomünchnone Derivative for the Synthesis of (±)-Lycopodine†

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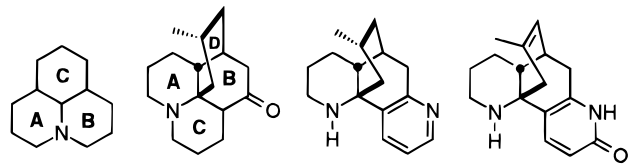
A new annulation sequence leading to the tetracyclic skeleton of the *Lycopodium* family of alkaloids is effected by using the tandem cycloaddition−cationic π-cyclization reaction of an isomünchnone dipole as the key strategic element. Synthesis of the required α-diazo imide precursor involved treating 5-methylcyclohex-2-en-1-one with the organocopper reagent derived from 3-methoxybenzyl chloride in the presence of chlorotrimethylsilane. Ozonolysis of the resulting silyl enol ether followed by a Wittig reaction and conversion to the desired α-diazo imide was carried out using standard malonylacylation and diazotization procedures. Treatment of the α-diazo imide with rhodium(II) perfluorobutyrate afforded a transient 1,3-dipole which subsequently cycloadded across the tethered π-bond. The resulting cycloadduct was treated with $BF_3$·2AcOH to give a rearranged tetracyclic compound derived from a Pictet−Spengler-type cyclization of an *N*-acyliminium ion. The rearranged product was subsequently converted into a key intermediate previously used for the synthesis of (±)-lycopodine.

## Introduction

Hexahydrojulolidine (**1**) contains the basic ring skeleton of many *Lycopodium* alkaloids,[1] and numerous synthetic routes toward this class of compounds have been described in the literature.[2] The *Lycopodium* alkaloids continue to be of interest as synthetic targets due to the wide range of biological properties they exhibit.[3−5] For example, lycopodine (**2**) was first recognized as a medicinal agent as early as the 19th century and was utilized in Chinese folk medicine for the treatment of skin disorders.[6] Recently, huperzine B (**4**) (*Huperzia serrata*), the structural analog of lycodine (**3**), has been shown to be a potent reversible inhibitor ($IC_{50}$ = $10^{-7}$ M) of acetylcholine esterase and thus shows promise in the treatment of Alzheimer's disease.[7]




**1** hexahydrojulolidine **2** lycopodine **3** lycodine **4** huperzine B

Earlier reports from our laboratories[8] have described a general method for the synthesis of complex nitrogen polyheterocycles (*i.e.,* **7**) from readily available α-diazo imides (*i.e.,* **5**). As shown in Scheme 1, isomünchnone cycloadducts such as **6** were employed as masked *N*-acyliminium[9] ions for cationic π-cyclizations[10] as an approach to B-ring homologues of erythrinane alkaloids.[11] As an extension of our earlier work dealing with tandem cyclization−cycloadditions,[12] we planned to use this method as the key sequence in the synthesis of (±)-lycopodine (**2**).

To date, there have been seven independent syntheses of (±)-lycopodine,[13−19] the first by Stork[13] and Ayer[14] in 1968. The strategy utilized in these approaches has generally been divided into three distinct classes. The

† This paper is dedicated to William G. Dauben on the occasion of his 78th birthday.

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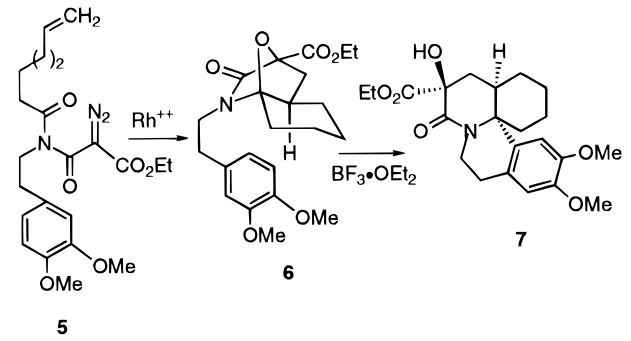
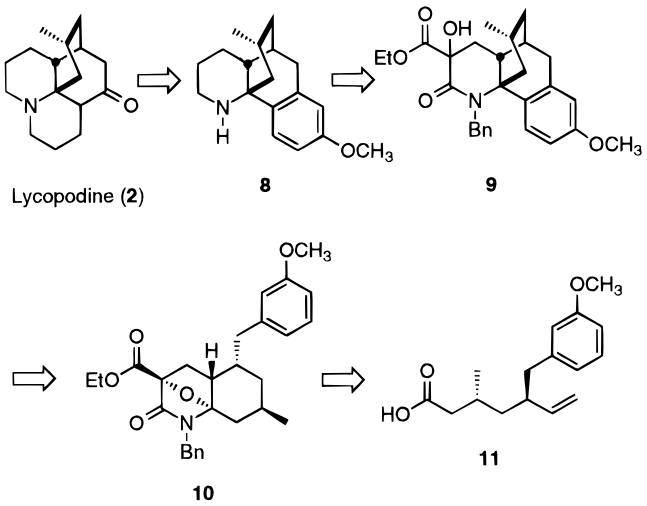
**Scheme 1**



**Scheme 2**

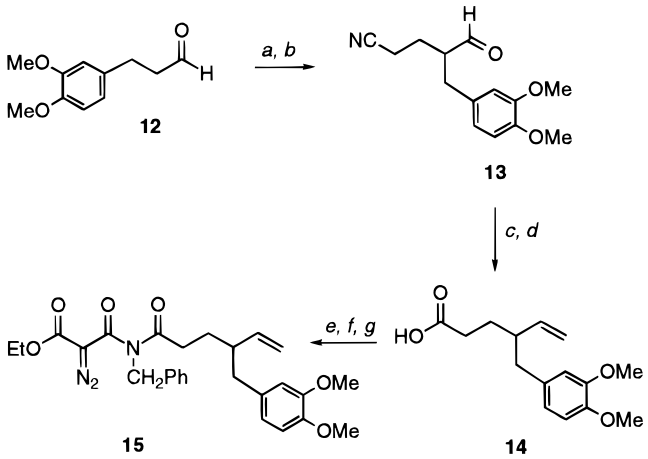


original Stork synthesis closely resembled the proposed biosynthesis and involved an intramolecular cationic π-cyclization onto a tetrasubstituted octahydroquinoline iminium ion derivative to create the ABD-ring skeleton.[20] Another approach relies on the further functionalization of an *all-cis* hexahydrojulolidine ABC-ring skeleton,[15−18] whereas the third approach makes use of a bridgehead olefin from a preassembled BD-ring system.[19] The intramolecular isomünchnone cycloadduct **10** was envisaged as the precursor of the key Stork intermediate **8** (*via* **9**) (Scheme 2). The heart of our plan was the formation of the latter intermediate by a Pictet−Spengler cyclization of the *N*-acyliminium ion derived from **10** (*vide infra*). Central to this strategy was the expectation that the bicyclic iminium ion originating from **10** would exist in a chairlike conformation. Cyclization of the aromatic ring onto the iminium ion center should take place most readily from the axial position.[13,14] The readily available heptenoic acid **11** would serve as the precursor for the α-diazo imide, the direct progenitor of the isomünchnone dipole. In this paper, we detail the extension of our tandem cycloaddition−cationic π-cyclization protocol to the formal synthesis of (±)-lycopodine (**2**).

## Results and Discussion

Our initial set of goals was (i) to develop a synthesis of the prerequisite α-diazo imide system necessary for

**Scheme 3**[a]



[a] Reagents: (a) pyrrolidine, $K_2CO_3$; (b) $CH_2$=CHCN, $CH_3CN$, 10% HCl; (c) $Ph_3P$=$CH_2$; (d) KOH; (e) $Im_2CO$, $PhCH_2NH_2$; (f) $ClCOCH_2CO_2Et$; (g) $MsN_3$, $NEt_3$.

the tandem sequence of reactions, (ii) to demonstrate that intramolecular dipolar cycloaddition would provide rings A and D of the lycopodine skeleton, and (iii) to utilize the dipolar cycloadduct as a masked *N*-acyliminium ion for cationic π-cyclization with the neighboring aromatic ring. Toward this end, diazo imide **15** was synthesized as a model system (Scheme 3) because it could be prepared easily from the readily available 3-(3,4-dimethoxyphenyl)propionaldehyde (**12**). Conjugate addition of the pyrrolidine enamine derived from **12** to acrylonitrile followed by aqueous hydrolysis afforded nitrile **13** in 81% yield. The resultant alkene derived from Wittig methylenation was hydrolyzed under basic conditions to give hexenoic acid **14** in 65% yield for the two-step sequence. Treatment of **14** with 1,1-carbonyldiimidazole followed by quenching with benzylamine afforded the corresponding *N*-benzylamide in 90% yield. Using a modified literature procedure,[21] the benzylamide we subjected to N-malonylacylation to afford the corresponding malonamic acid ethyl ester in 88% yield. The imido ester was treated with mesyl azide in the presence of triethylamine[22] to provide α-diazo imide **15** in 95% yield as a pale yellow oil.

Addition of rhodium(II) perfluorobutyrate ($Rh_2pfb_4$) to a solution of **15** in $CH_2Cl_2$ at 25 °C effected loss of nitrogen and cyclization to the isomünchnone dipole, which underwent an intramolecular cycloaddition with the alkene function to give cycloadduct **16** in 80% isolated yield (Scheme 4). The assignment of the stereochemistry of **16** was based on the comparison of NMR signals of **16** with related substrates.[12,23] The formation of the *endo*-cycloadduct with respect to the carbonyl ylide dipole is in full accord with molecular mechanics calculations which show a large ground state energy difference between the two diastereomers. In the previous article,[12] we identified $BF_3$·$OEt_2$ as the Lewis acid that routinely gave the highest yield of rearranged product from the isomünchnone cycloadduct. This also proved to be the case with cycloadduct **16**. Thus, treatment of **16** with $BF_3$·$OEt_2$ afforded the tetracyclic lactam **17** in 80% yield as a single diastereomer. Once again, the assignment

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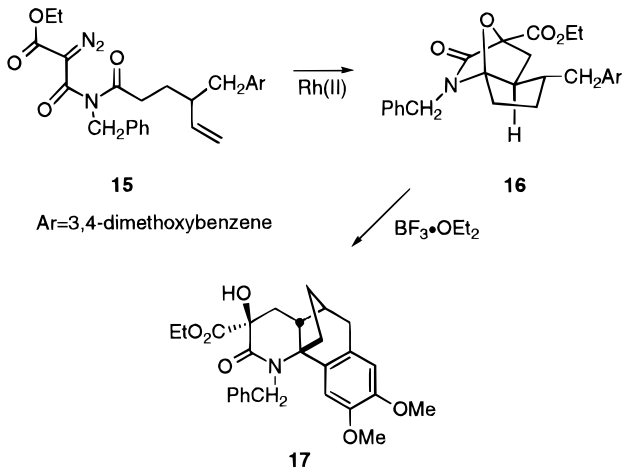
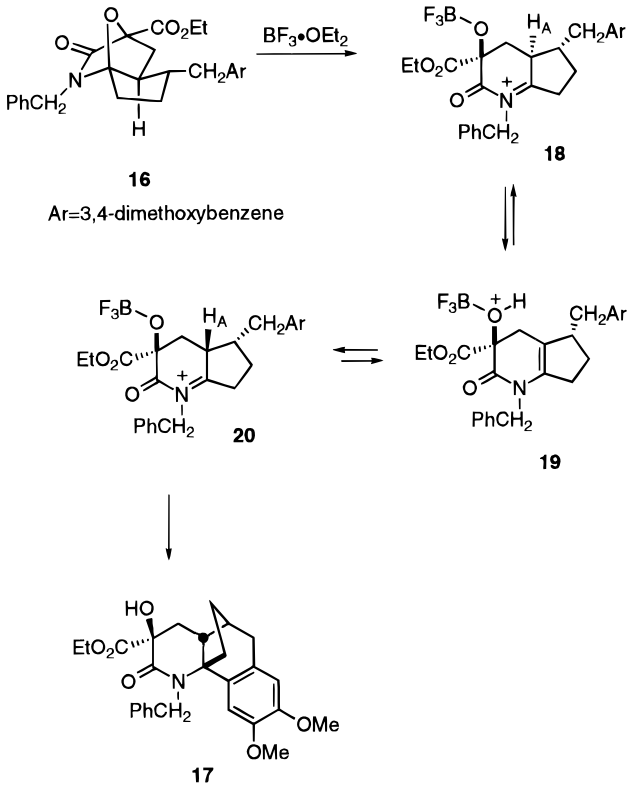
**Scheme 4**



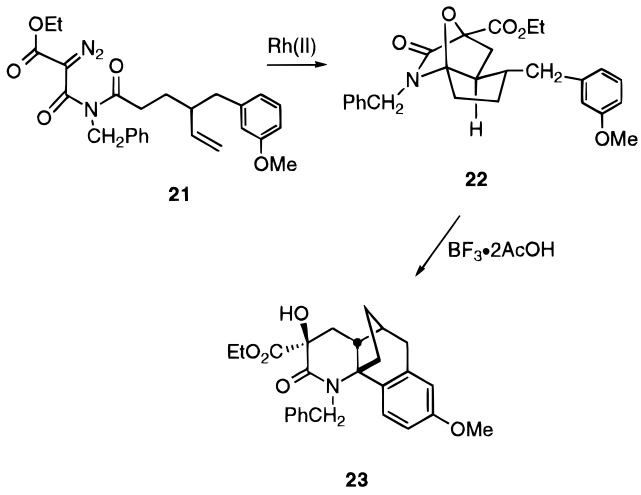

**Scheme 5**



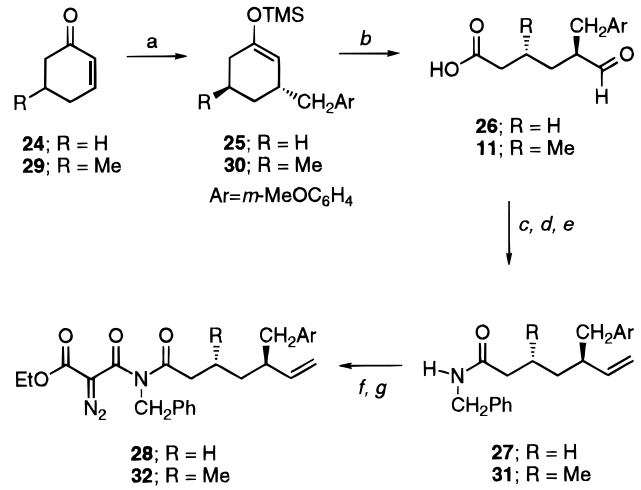

of stereochemistry was based (NMR) on related substrates previously synthesized in these laboratories.[12,23] To account for the *syn* relationship of the ring junction proton of **17** with the newly formed hydroxyl group, we suggest that the two diastereomeric *N*-acyliminium ions **18** and **20** equilibrate under the reaction conditions. The intermediate *N*-acyliminium ion **18** derived from the initial Lewis acid-assisted ring opening of **16** undergoes rapid proton loss to produce the transient tetrasubstituted enamide **19** (Scheme 5). Intramolecular axial reprotonation of **19** from the $\beta$-face generates the diastereomeric iminium ion **20.** This species then undergoes intramolecular cationic $\pi$-cyclization with the dimethoxy-substituted aromatic ring, through a transition state in which the bridgehead hydrogen atom and the tethered aromatic group on the cyclopentane ring possess a preferred *anti* arrangement in the cyclopentane ring.

Having established the feasibility of intramolecular $\pi$-cyclization from an isomünchnone cycloadduct containing a diactivated aryl group, we investigated the possibility of performing a similar tandem cycloaddition−cyclization with the closely related diazo imide **21**. In the case of **21**, it is not clear whether the monosubstituted aromatic ring, a synthon for the lycopodine B ring,[13] is capable of undergoing the desired 6-*exo*-*trig* cyclization. Therefore, α-diazo imide **21** was synthesized starting from 2-cyclopenten-1-one using a procedure similar to that outlined in Scheme 6 (*vide infra*) and was subjected to rhodium(II)-catalyzed decomposition. The highest yield of intramolecular cycloaddition was achieved using 1 mol % of $Rh_2(pfb)_4$ in $CH_2Cl_2$ at 25 °C. Exposure of **21** to these conditions for 24 h provided the expected isomünchnone cycloadduct **22** in 89% yield (Scheme 6). Substrate **22** was then subjected to $BF_3$·2AcOH in $CH_2Cl_2$ at 25 °C, effecting cyclization to the desired azacycle **23** in 93% yield. In this case, $BF_3$·2AcOH was found to be the most effective Lewis acid for the cyclization.

**Scheme 6**



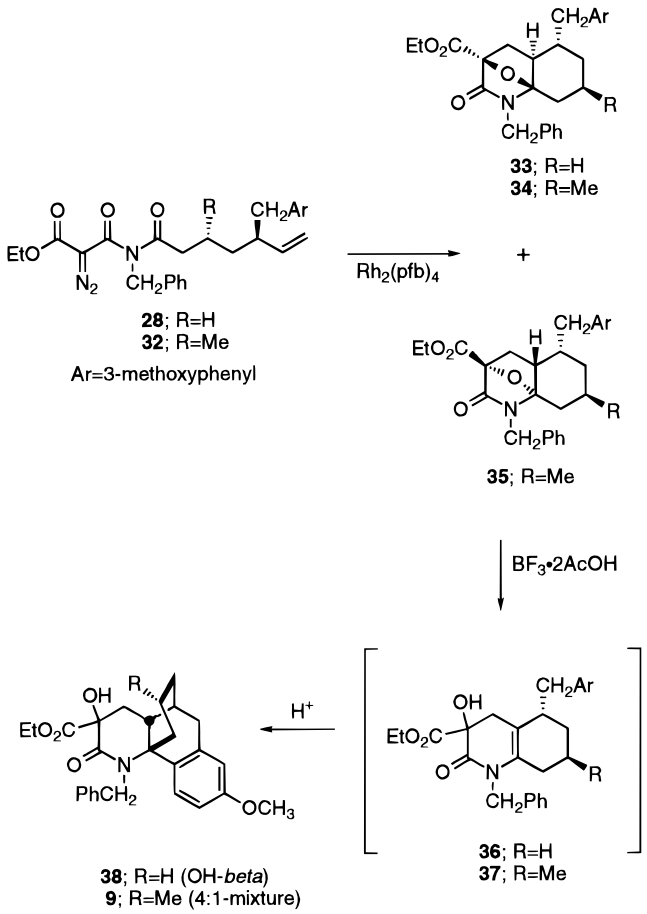

**Scheme 7**[a]




[a] Reagents: (a) *m*-$MeOC_6H_4CH_2MgC$, CuI, HMPA, TMSCl; (b) $O_3$; (c) $Ph_3P{=}CH_2$; (d) $Im_2CO$; (e) $BnNH_2$; (f) $ClCOCH_2CO_2Et$; (g) $MsN_3$, $NEt_3$.

In light of the successful $\pi$-cyclization of isomünchnone adduct **22** to yield the octahydroethanobenzo[*h*]quinoline derivative **23**, we next tried to perform the tandem cycloaddition−cyclization process to produce the corresponding propanobenzo[*h*]quinoline derivative. Therefore, substrate **28**, a one-carbon homologue of diazo imide **21**, was synthesized by the seven-step process outlined in Scheme 7. Treatment of cyclohexenone **24** with the organocopper[24] reagent derived from 3-methoxybenzyl chloride in the presence of chlorotrimethylsilane[25] fol-

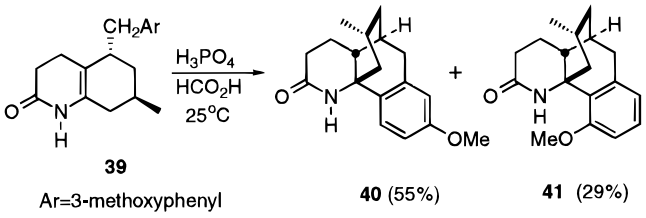
**Scheme 8**




lowed by ozonolysis of the silyl enol ether **25** afforded carboxylic acid **26** in 73% yield. Wittig olefination followed by reaction with 1,1-carbonyldiimidazole and quenching of the reaction with benzylamine produced the substituted amide **27** in 80% yield. Conversion to the desired α-diazo imide system **28** was straightforward using established malonylacylation[21] and diazotization[22] procedures. Preparation of the closely related methyl analogue **32**, necessary for the lycopodine synthesis, was accomplished in an analogous manner. In the case of cyclohexenone **29**, the conjugate addition is highly stereoselective with respect to the C-5 methyl group,[26] thereby establishing an *anti* relationship between the methyl and *p*-methoxybenzyl substituents.

The reaction of α-diazo imide **28** with a catalytic quantity of rhodium(II) perfluorobutyrate in $CH_2Cl_2$ at 25 °C provided cycloadduct **33** (95%) as a single diastereomer in which cycloaddition of the isomünchnone dipole occurred *anti* to the 3-methoxybenzyl substituent. (See Scheme 8). Assignment of the stereochemistry was based (NMR) on related substrates previously synthesized in these laboratories.[12,23] Formation of the *endo*-cycloadduct with respect to the carbonyl ylide dipole is in full accord with molecular mechanics calculations which show a large energy difference between the two diastereomers. When **33** was exposed to $BF_3$·2AcOH in $CH_2Cl_2$ at 0 °C, the cyclized product **38** was isolated in 90% yield as a single diastereomer. The relative stereochemistry of **38** was established by a single-crystal X-ray analysis.[27]

Similarly, the critical rearrangement of diazo imide **32** to the oxabicyclic amide was effected by exposure to $Rh_2(pfb)_4$ which resulted in the isolation of the expected cycloadduct as a 3:2 mixture of *endo*-diastereomers (**34** and **35**) in 97% yield. Exposure of the diastereomeric mixture to $BF_3$·2AcOH generated the tetracyclic amide **9** as a 4:1 mixture of diastereomers (71%) about the tertiary hydroxyl center. The stereoselection of this cyclization may be understood in terms of an argument put forth by Stork to account for the stereochemical outcome of a related cyclization.[13] The bridgehead hydrogen atom and the tethered aromatic ring possess an *anti* arrangement in the cyclohexylidene ring of the bicyclic iminium ion when cyclization occurs. Cyclization of the diastereomeric *N*-acyliminium salt, in which the bridgehead hydrogen atom and the tethered aromatic ring are in a *syn* arrangement, to give the *epi*-derivative of **9** is not observed because the cyclohexylidene ring must adopt an unfavorable boat conformation. Consequently, the initially formed iminium ion derived from **35** can easily cyclize, but the isomeric iminium ions obtained from **33** or **34** must first undergo proton loss to give the corresponding enamides **36** and **37**. This is followed by reprotonation and a subsequent π-cyclization to give **9**. It is also interesting to note that cyclization of both **34** and **35** occurs regiospecifically to give the product derived from *para* attack with respect to the methoxy group. In contrast, cyclization of **39** in the Stork synthesis gives the corresponding mixture of regioisomers (*i.e.*, **40** and **41**). Apparently, the steric effect of the *N*-benzyl group directs cyclization away from the methoxy group.




Lactam **9** contains the proper ring skeleton needed for lycopodine except that it is overfunctionalized. Before attempting to convert **9** into the Stork relay intermediate **8**, we decided to first examine the deoxygenation of a related model system (*i.e.*, **38**). A modification[28] of the original Barton−McCombie deoxygenation reaction[29] was found to be the method of choice. Treatment of **38** with NaH and phenyl chlorothionoformate gave the stable, easily handled phenyl thiocarbonate derivative. Heating this ester in toluene at 75 °C with slow addition of a solution of 2,2′-azobis(isobutyronitrile) (AIBN) and tributyltin hydride afforded the deoxygenated lactam **42**, which was isolated as a 3:2 mixture of diastereomers in 80% yield (Scheme 9). Substrate **42** was hydrolyzed to the corresponding carboxylic acid which was readily decarboxylated upon heating in *p*-xylene at 160 °C to give *N*-benzyl lactam **43** in 87% yield. To our surprise, subjection of **43** to catalytic ($PtO_2$) hydrogenation gave

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(27) The authors have deposited atomic coordinates for structures **38** and **46** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, CB2 1EZ, U.K.

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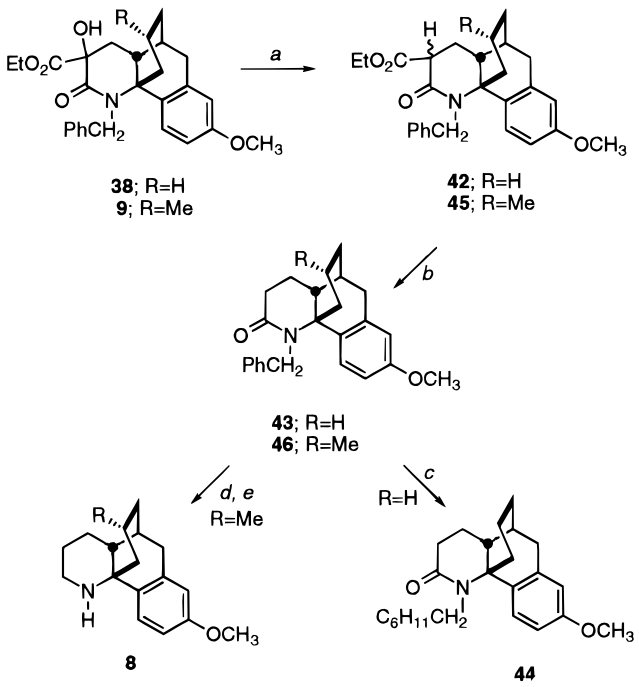
**Scheme 9**[a]




[a] Reaction conditions: (a) $C_6H_5OCSCl$, NaH, *n*-$Bu_3SnH$, AlBN, 45 °C; (b) KOH, $H_2O$, 160 °C; (c) $H_2$, $PtO_2$; (d) $LiAlH_4$, ether/THF; (e) $H_2$, Pd/C.

only the cyclohexyl derivative **44** in almost quantitative yield. We were able, however, to effect debenzylation of the related structure **46** (R = Me) by a different procedure. Lactam **46** was synthesized from the Barton−McCombie reaction of **9** which gave **45** (96%) as a 3:2 mixture of diastereomers. The mixture was hydrolyzed to the corresponding carboxylic acids which, upon thermal decarboxylation, gave *N*-benzyl lactam **46** (85% overall yield) as a single diastereomer whose structure was unequivocally established by a single-crystal X-ray analysis.[27] Reduction of **46** with $LiAlH_4$ (81%) followed by debenzylation *via* catalytic hydrogenation (Pd/C) afforded the key Stork intermediate **8**.[13] The preparation of **8** constitutes a formal total synthesis of (±)-lycopodine (**2**).[13]

In summary, a new strategy for the synthesis of (±)-lycopodine has been developed which is based on a sequential dipolar cycloaddition−*N*-acyliminium ion cyclization. This approach is particularly attractive as the starting α-diazo imide can be prepared efficiently on a large scale, and the cycloaddition and cyclization reactions are highly stereospecific. We are currently investigating the application of the methodology outlined here to other alkaloidal targets.

## Experimental Section

Melting points are uncorrected. Mass spectra were determined at an ionizing voltage of 70 eV. Unless otherwise noted, all reactions were performed in flame-dried glassware under an atmosphere of dry nitrogen. Solutions were evaporated under reduced pressure with a rotary evaporator, and the residue was chromatographed on a silica gel column using an ethyl acetate−hexane mixture as the eluent unless specified otherwise.

**General Procedure for the Synthesis of Diazo Imides.** A solution containing 5.0 mmol of the appropriate amide and 10.0 mmol of ethyl malonyl chloride in 15 mL of anhydrous benzene was heated at reflux for 1 h. After being cooled to rt, the reaction mixture was diluted with ether and washed with 10% aqueous NaOH and brine. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography to give the malonamic acid ethyl ester. A variation of the procedure described by Taber and co-workers[22] was used to prepare the diazo imide system. To a solution containing 2 mmol of the appropriate imide and 2.2 mmol of mesyl azide in 5 mL of acetonitrile or $CH_2Cl_2$ was added 4.0 mmol of $NEt_3$ under $N_2$ at rt. After the mixture was stirred for 3 h, the solvent was removed under reduced pressure and the residue was subjected to flash silica gel chromatography.

**4-(3,4-Dimethoxybenzyl)hex-5-enoic Acid (14).** To a solution containing 9.92 g (47.19 mmol) of 3-(3,4-dimethoxyphenyl)propionic acid in 100 mL of a 1:1 mixture of $Et_2O$/THF was added 26 mL (51.9 mmol) of $BH_3{\cdot}SMe_2$ dropwise at 0 °C. After the addition was complete, the reaction was heated at 75 °C for 1.5 h. The reaction was cooled to rt and filtered through a Celite plug using $CH_2Cl_2$, and the filtrate was concentrated under reduced pressure to provide 9.26 g (100%) of 3-(3,4-dimethoxyphenyl)propanol (lit.[30]) as a clear oil which was used in the next step without further purification.

A suspension of 14.24 g (66.06 mmol) of pyridinium chlorochromate and 14.0 g of Celite in 300 mL of $CH_2Cl_2$ was vigorously stirred for 30 min. The mixture was cooled to 0 °C, and 9.26 g (47.19 mmol) of the above alcohol in 100 mL of $CH_2Cl_2$ was added dropwise over 20 min. The reaction was stirred for 2 h at 0 °C, warmed to 25 °C, filtered through a Florisil plug, and washed with EtOAc. The filtrate was concentrated under reduced pressure to provide 7.3 g (80%) of 3-(3,4-dimethoxyphenyl)propionaldehyde (**12**) (lit.[31]) as a thick yellow oil: IR (neat) 2932, 2833, 1722, 1514, 1260 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) δ 2.76 (t, 2H, *J* = 7.2 Hz), 2.90 (t, 2H, *J* = 7.2 Hz), 3.85 (s, 3H), 3.86 (s, 3H), 6.72 (m, 2H), 6.79 (d, 1H, *J* = 8.4 Hz), 9.81 (s, 1H); $^{13}C$ NMR ($CDCl_3$, 75 MHz) δ 26.2, 44.0, 54.5, 110.0, 110.3, 118.7, 131.5, 146.0, 147.4, 200.3.

To a solution containing 5.30 g (27.28 mmol) of the above aldehyde in 200 mL of benzene were added 6.83 mL (81.85 mmol) of pyrrolidine and 11.31 g (81.85 mmol) of $K_2CO_3$. The reaction was stirred at rt for 3 h, filtered through a Celite plug, and concentrated under reduced pressure. The resulting oil was taken up in 100 mL of acetonitrile, and to this solution were added 10.80 mL (163.7 mmol) of acrylonitrile and 0.50 g of 4 Å molecular sieves. After the mixture was heated at 105 °C for 24 h and cooled to rt, 200 mL of ether was added. The organic layer was washed with $H_2O$, followed by 10% aqueous HCl and brine, dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure. The crude residue was subjected to flash silica gel chromatography to give 5.48 g (81%) of 5-(3,4-dimethoxyphenyl)-4-formylpentanenitrile (**13**) as a clear oil: IR (neat) 2936, 2244, 1721, 1514 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) δ 1.73 (m, 1H), 2.01 (m, 1H), 2.38 (t, 2H, *J* = 6.6 Hz), 2.71 (dd, 1H, *J* = 13.6, 7.8 Hz), 2.83 (m, 1H), 3.03 (dd, 1H, *J* = 13.6, 7.8 Hz), 3.86 (s, 6H), 6.68−6.71 (m, 2H), 6.81 (d, 1H, *J* = 8.1 Hz), 9.73 (s, 1H); $^{13}C$ NMR ($CDCl_3$, 75 MHz) δ 14.8, 23.4, 34.4, 51.3, 55.6, 111.2, 111.6, 118.8, 120.7, 129.4, 147.7, 148.9, 202.4.

To a flask charged with 4.12 g (11.56 mmol) of methyltriphenylphosphonium bromide in 100 mL of THF at 0 °C was added 5.52 mL (12.16 mmol) of 2.2 M *n*-BuLi, and the solution was stirred at rt for 30 min. To this solution was added 1.44 g (5.76 mmol) of the above aldehyde in 20 mL of THF. The reaction mixture was stirred for 2 h and warmed to rt, the reaction was quenched with brine, and 80 mL of $H_2O$ was added to the mixture. The aqueous solution was extracted with ether, and the organic extracts were dried over $Na_2SO_4$. Removal of the solvent under reduced pressure followed by flash silica gel chromatography afforded 1.20 g (65%) of 4-(3,4-dimethoxybenzyl)hex-5-enenitrile as a yellow oil: IR (neat) 2240, 1590, 1254, 763 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) δ 1.52 (m, 1H), 1.81 (m, 1H), 2.18−2.47 (m, 3H), 2.54−2.70 (m, 2H), 3.86 (s, 3H), 3.87 (s, 3H), 5.04 (d, 1H, *J* = 16.5 Hz), 5.08 (d, 1H, *J* = 9.6 Hz), 5.53 (dt, 1H, *J* = 16.5 and 9.6 Hz), 6.65 (s, 1H), 6.67 (d, 1H, *J* = 7.8 Hz), 6.78 (d, 1H, *J* = 7.8 Hz); $^{13}C$ NMR ($CDCl_3$, 75 MHz) δ 14.6, 28.7, 40.6, 44.4, 55.4, 110.7, 112.0, 116.5, 119.2, 120.7, 131.3, 139.4, 147.0, 148.3.

(30) Frydman, B.; Deulofev, V. *Tetrahedron* **1962**, *18*, 1063.
(31) Denniff, P.; Whiting, D. A. *J. Chem. Soc., Chem. Commun.* **1976**, 712.

To a solution of 1.10 g (4.49 mmol) of the above nitrile in 50 mL of a 3:2 EtOH/$H_2O$ mixture was added 2.52 g (44.9 mmol) of KOH. The mixture was heated at 95 °C for 12 h, cooled to 0 °C, and acidified with 10% aqueous HCl. The aqueous mixture was extracted with ether, dried over $Na_2SO_4$, and concentrated under reduced pressure. The crude residue was subjected to flash silica gel chromatography to give 4-(3,4-dimethoxybenzyl)hex-5-enoic acid (**14**) as a clear oil: IR (neat) 3295, 1707, 1513, 1259, 1029 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 1.54 (m, 1H), 1.80 (m, 1H), 2.24−2.40 (m, 3H), 2.60 (d, 2H, $J$ = 6.9 Hz), 3.85 (s, 6H), 4.93 (d, 1H, $J$ = 17.1 Hz), 5.01 (d, 1H, $J$ = 10.2 Hz), 5.56 (dt, 1H, $J$ = 17.1 and 10.2 Hz), 6.66 (s, 1H), 6.67 (d, 1H, $J$ = 8.4 Hz), 6.77 (d, 1H, $J$ = 8.4 Hz), 11.17 (brs, 1H); $^{13}C$ NMR ($CDCl_3$, 75 MHz) $\delta$ 28.5, 31.8, 41.2, 45.1, 55.7, 111.0, 112.4, 115.8, 121.1, 132.4, 141.0, 147.2, 148.5, 179.9. Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.15; H, 7.63. Found: C, 68.09; H, 7.72.

***N*-Benzyl-2-diazo-N-[4-(3,4-dimethoxybenzyl)hex-5-enoyl]malonamic Acid Ethyl Ester (15).** To a solution of 0.57 g (2.18 mmol) of carboxylic acid **14** in 15 mL of $CH_2Cl_2$ was added 0.42 g (2.61 mmol) of 1,1-carbonyldiimidazole at rt. The solution was stirred for 2 h, was cooled to 0 °C, and was treated with 0.31 mL (2.83 mmol) of benzylamine, and the reaction mixture was stirred overnight at rt. Concentration under reduced pressure followed by flash silica gel chromatography gave 0.61 g (90%) of 4-(3,4-dimethoxybenzyl)-hex-5-enoic acid benzylamide as a clear oil: IR (neat) 1642, 1548, 1028, 914 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 1.56 (m, 1H), 1.86 (m, 1H), 2.09 (m, 1H), 2.20−2.32 (m, 2H), 2.59 (d, 2H, $J$ = 6.9 Hz), 3.83 (s, 6H), 4.38 (m, 2H), 4.86 (d, 1H, $J$ = 17.1 Hz), 4.96 (d, 1H, $J$ = 10.2 Hz), 5.55 (m, 1H), 5.66 (brs, 1H), 6.64 (s, 1H), 6.65 (d, 1H, $J$ = 8.7 Hz), 6.75 (d, 1H, $J$ = 8.7 Hz), 7.23−7.34 (m, 5H); $^{13}C$ NMR ($CDCl_3$, 75 MHz) $\delta$ 29.4, 33.4, 40.9, 42.9, 45.0, 55.3, 110.7, 112.2, 115.1, 120.8, 126.8, 127.1, 128.0, 132.3, 138.1, 141.1, 146.7, 148.1, 172.6; Anal. Calcd for $C_{22}H_{27}NO_3$: C, 74.75; H, 7.70; N, 3.96. Found: C, 74.68; H, 7.72; N, 3.89.

N-Malonylacylation of 0.5 g of the above amide was carried out in the standard manner to give 0.55 g of *N*-benzyl-*N*-[4-3,4-dimethoxybenzyl)hex-5-enoyl]malonamic acid ethyl ester (88%) as a clear oil: IR (neat) 2932, 1738, 1699, 1515, 1028 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 1.27 (t, 3H, $J$ = 7.2 Hz), 1.47 (m, 1H), 1.77 (m, 1H), 2.18 (m, 1H), 2.43 (m, 1H), 2.53 (d, 2H, $J$ = 7.2 Hz), 2.56 (m, 1H), 3.84 (s, 6H), 3.89 (s, 2H), 4.19 (q, 2H, $J$ = 7.2 Hz), 4.77 (d, 1H, $J$ = 17.1 Hz), 4.88 (d, 1H, $J$ = 10.2 Hz), 4.98 (s, 2H), 5.43 (dt, 1H, $J$ = 17.1 and 10.2 Hz), 6.60 (d, 1H, $J$ = 8.7 Hz), 6.61 (s, 1H), 6.74 (d, 1H, $J$ = 8.7 Hz), 7.17 (d, 2H, $J$ = 6.9 Hz), 7.22−7.35 (m, 3H); $^{13}C$ NMR ($CDCl_3$, 75 MHz) $\delta$ 14.0, 28.2, 34.5, 41.2, 44.9, 46.4, 46.8, 55.7, 61.1, 110.8, 112.3, 115.7, 121.0, 126.0, 127.3, 128.7, 132.3, 136.4, 141.1, 147.1, 148.5, 167.2, 168.7, 175.9; Anal. Calcd for $C_{27}H_{33}NO_6$: C, 69.34; H, 7.12; N, 3.00. Found: C, 69.25; H, 7.05; N, 2.98.

A 0.48 g sample of the above compound was subjected to the standard diazo transfer conditions to give 0.45 g of *N*-benzyl-2-diazo-*N*-[4-(3,4-dimethoxybenzyl)hex-5-enoyl]malonamic acid ethyl ester (**15**) (95%) as a yellow oil: IR (neat) 2136, 1717, 1648, 1323, 1028 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 1.27 (t, 3H, $J$ = 6.9 Hz), 1.50 (m, 1H), 1.80 (m, 1H), 2.21 (m, 1H), 2.40−2.53 (m, 2H), 2.54 (d, 2H, $J$ = 6.9 Hz), 3.84 (s, 6H), 4.22 (q, 2H, $J$ = 6.9 Hz), 4.82 (d, 1H, $J$ = 16.8 Hz), 4.86 (s, 2H), 4.91 (d, 1H, $J$ = 10.5 Hz), 5.47 (m, 1H), 6.63 (m, 2H), 6.74 (d, 1H, $J$ = 8.4 Hz), 7.28 (m, 5H); $^{13}C$ NMR ($CDCl_3$, 75 MHz) $\delta$ 14.1, 28.7, 33.9, 41.3, 42.6, 45.0, 49.0, 55.7, 61.6, 110.8, 112.4, 115.6, 121.0, 127.0, 127.3, 128.5, 132.4, 136.9, 141.2, 147.0, 148.4, 160.4, 166.1, 175.5.

**9-Benzyl-4-(3,4-dimethoxybenzyl)-8-oxo-10-oxa-9-aza-tricyclo-[5.2.1.$0^{1,5}$]decane-7-carboxylic Acid Ethyl Ester (16).** A solution of 1.15 g (2.33 mmol) of diazo imide **15** in 20 mL of $CH_2Cl_2$ at rt was treated with 5 mg of rhodium(II) perfluorobutyrate. The reaction mixture was stirred for 6 h at rt and was concentrated under reduced pressure. The resulting residue was subjected to flash silica gel chromatography to give 0.91 g (80%) of 9-benzyl-4-(3,4-dimethoxybenzyl)-8-oxo-10-oxa-9-azatricyclo[5.2.1.$0^{1,5}$]decane-7-carboxylic acid ethyl ester (**16**) as a clear oil: IR (neat) 1749, 1721, 1259, 1029, 731 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 1.30 (t, 3H, $J$ = 7.2 Hz), 1.43 (m, 1H), 1.55−1.61 (m, 2H), 1.88−2.04 (m, 5H), 2.35 (dd, 1H, $J$ = 13.3 and 6.9 Hz), 2.46 (dd, 1H, $J$ = 13.3 and 6.9 Hz), 3.79 (s, 3H), 3.80 (s, 3H), 4.31 (q, 2H, $J$ = 7.2 Hz), 4.36 (d, 1H, $J$ = 15.6 Hz), 4.46 (d, 1H, $J$ = 15.6 Hz), 6.48 (s, 1H), 6.49 (d, 1H, $J$ = 8.4 Hz), 6.69 (d, 1H, $J$ = 8.4 Hz), 7.24 (m, 5H); $^{13}C$ NMR ($CDCl_3$, 75 MHz) $\delta$ 14.0, 24.4, 31.9, 34.5, 39.9, 43.4, 45.9, 53.6, 55.6, 62.0, 88.4, 106.6, 111.0, 111.6, 120.5, 127.5, 127.7, 128.6, 132.2, 136.3, 147.3, 148.6, 165.7, 170.5; HRMS calcd for $C_{27}H_{31}NO_6$ 465.2151, found 465.2122.

**1-Benzyl-8,9-dimethoxy-3-hydroxy-2-oxo-1,2,3,4,4a,5,6,10b-octahydro-5,10b-ethanobenzo[*h*]quinoline-2-carboxylic Acid Ethyl Ester (17).** To a solution containing 0.21 g (0.45 mmol) of cycloadduct **16** in 12 mL of $CH_2Cl_2$ at rt was added 0.11 mL (0.90 mmol) of $BF_3{\cdot}OEt_2$. After being warmed to rt, the reaction mixture was stirred for 5 h, the reaction was quenched with MeOH, and the reaction mixture diluted with $CH_2Cl_2$. After the solution was extracted with $H_2O$, the organic extracts were dried over $Na_2SO_4$ and concentrated under reduced pressure and the resulting crude residue was subjected to flash silica gel chromatography to give 0.17 g (80%) of 1-benzyl-8,9-dimethoxy-3-hydroxy-2-oxo-1,2,3,4,4a,5,6,10b-octahydro-5,10b-ethanobenzo[*h*]quinoline-2-carboxylic acid ethyl ester (**17**) as a white solid: mp 151−152 °C; IR (neat) 3438, 1748, 1647, 1509, 1258 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 0.94 (t, 3H, $J$ = 7.5 Hz), 1.50 (m, 1H), 2.03−2.18 (m, 5H), 2.48 (m, 1H), 2.55−2.65 (m, 2H), 2.90 (dd, 1H, $J$ = 16.9 and 3.6 Hz), 3.79 (s, 3H), 3.83 (s, 3H), 3.94 (s, 1H), 3.96 (m, 2H), 4.45 (d, 1H, $J$ = 15.3 Hz), 5.55 (d, 1H, $J$ = 15.3 Hz), 6.58 (s, 1H), 6.63 (s, 1H), 7.21−7.33 (m, 5H); $^{13}C$ NMR ($CDCl_3$, 75 MHz) $\delta$ 13.4, 28.8, 31.1, 34.5, 35.1, 39.3, 42.8, 49.9, 55.7, 55.8, 61.7, 68.4, 75.3, 107.9, 111.7, 124.6, 126.2, 126.7, 128.4, 133.7, 137.8, 147.4, 147.8, 170.5, 172.0; Anal. Calcd for $C_{27}H_{31}NO_6$: C, 69.66; H, 6.71; N, 3.01. Found: C, 69.58; H, 6.71; N, 2.95.

**4-(3-Methoxybenzyl)hex-5-enoic Acid Benzylamide.** To a solution of 2.96 g (121.8 mmol) of magnesium mesh in 15 mL of THF at −20 °C was added 3.89 mL (26.79 mmol) of 3-methoxybenzyl chloride. After the Grignard reagent was stirred for 30 min at −20 °C, the solution was warmed to rt and was added to a mixture containing 4.64 g (24.36 mmol) of CuI and 5.09 mL (29.2 mmol) of HMPA in 25 mL of THF at −78 °C. The organocopper species was stirred for 1 h at −78 °C. To this solution was added 15.46 mL (121.8 mmol) of chlorotrimethylsilane followed by 1.0 g (12.18 mmol) of 2-cyclopenten-1-one. The reaction mixture was stirred for 30 min at −78 °C, and the reaction was quenched with 16.97 mL (122.8 mmol) of $Et_3N$ and 2 mL of $H_2O$. The mixture was filtered through a Celite plug with EtOAc, and the extracts were washed with cold $H_2O$, dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure to provide the crude silyl enol ether which was used in the next step without purification.

A solution of the above compound in 100 mL of a 3:1 mixture of MeOH/$CH_2Cl_2$ at −78 °C was saturated with ozone for 30 min. After the reaction mixture was purged wtih oxygen, 4.47 mL (60.9 mmol) of dimethyl sulfide was added and the solution was allowed to warm to rt. After being stirred for 5 h, the reaction mixture was concentrated under reduced pressure and subjected to flash silica gel chromatography to give 1.53 g (53%) of 5-(3-methoxyphenyl)-4-formylpentanoic acid as a yellow oil: IR (neat) 3100 (broad), 2939, 1709, 1595, 1253 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 1.89 (m, 1H), 1.96 (m, 1H), 2.35 (m, 2H), 2.70 (m, 2H), 2.95 (m, 1H), 3.75 (s, 3H), 6.71 (m, 3H), 7.18 (t, 1H, $J$ = 7.8 Hz), 9.64 (s, 1H); $^{13}C$ NMR ($CDCl_3$, 75 MHz) $\delta$ 23.0, 30.1, 31.0, 35.0, 55.0, 111.7, 114.6, 121.1, 129.5, 139.4, 159.6, 178.3, 203.6; Anal. Calcd for $C_{26}H_{29}O_5$: C, 66.07; H, 6.83. Found: C, 65.92; H, 6.79.

To a flask charged with 2.56 g (7.17 mmol) of methyltriphenylphosphonium bromide in 100 mL of THF at 0 °C was added 3.0 mL (7.50 mmol) of 2.5 M *n*-BuLi, and the solution was stirred at 0 °C for 35 min. To this solution was added 0.77 g (3.26 mmol) of the above aldehyde in 50 mL of THF. The reaction mixture was stirred for 3 h at 0 °C, the reaction was quenched with brine, the reaction mixture was recooled to 0 °C, and 50 mL of a 5% aqueous HCl solution was added. After being stirred for 15 min, the reaction mixture was extracted with ether and the organic extracts were dried over

$Na_2SO_4$, filtered, and concentrated under reduced pressure. The crude hexenoic acid obtained was used in the next step without further purification.

To a solution of the above compound in 30 mL of $CH_2Cl_2$ was added 0.79 g (4.89 mmol) of 1,1′-carbonyldiimidazole at rt. The solution was stirred for 2 h and cooled to 0 °C, 0.89 mL (8.15 mmol) of benzylamine was added, and the reaction mixture was stirred for 12 h at rt. The solution was concentrated under reduced pressure and subjected to flash silica gel chromatography to give 0.54 g (51%) of 4-(3-methoxybenzyl)-hex-5-enoic acid benzylamide as a clear oil: IR (neat) 3288 (broad), 1637, 1253 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 1.56 (m, 1H), 1.84 (m, 1H), 2.01−2.12 (m, 1H), 2.18−2.30 (m, 2H), 2.60 (dd, 2H, $J$ = 7.0 and 3.9 Hz), 3.75 (s, 3H), 4.36 (d, 2H, $J$ = 5.7 Hz), 4.85 (d, 1H, $J$ = 17.1 Hz), 4.94 (dd, 1H, $J$ = 10.2 and 1.5 Hz), 5.54 (m, 1H), 5.88 (brs, 1H), 6.68 (m, 3H), 7.15 (t, 1H, $J$ = 7.8 Hz), 7.20−7.32 (m, 5H); $^{13}C$ NMR ($CDCl_3$, 75 MHz) $\delta$ 29.7, 34.2, 41.8, 43.3, 45.1, 54.9, 111.0, 114.9, 115.5, 121.5, 127.2, 127.6, 128.5, 128.9, 138.3, 141.3, 141.5, 159.3, 172.6; Anal. Calcd for $C_{21}H_{25}NO_2$: C, 77.97; H, 7.80; N, 4.33. Found: C, 77.84; H, 7.75; N, 4.18.

***N*-Benzyl-2-diazo-*N*-[4-(3-methoxybenzyl)hex-5-enoyl]-malonamic Acid Ethyl Ester (21).** N-Malonylacylation of 0.52 g of 4-(3-methoxybenzyl)hex-5-enoic acid benzylamide was carried out in the normal manner to give 0.55 g of *N*-benzyl-*N*-[4-(3-methoxybenzyl)hex-5-enoyl]malonamic acid ethyl ester (90%) as a clear oil: IR (neat) 3068, 1737, 1694, 1154 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 1.27 (t, 3H, $J$ = 7.2 Hz), 1.48 (m, 1H), 1.76 (m, 1H), 2.21 (m, 1H), 2.42 (dd, 1H, $J$ = 8.8 and 6.3 Hz), 2.50 (dd, 1H, $J$ = 8.8 and 5.4 Hz), 2.55 (d, 2H, $J$ = 6.9 Hz), 3.77 (s, 3H), 3.89 (s, 2H), 4.20 (q, 2H, $J$ = 7.2 Hz), 4.77 (d, 1H, $J$ = 17.1 Hz), 4.88 (dd, 1H, $J$ = 10.2 and 1.8 Hz), 4.97 (s, 2H), 5.43 (m, 1H), 6.63−6.72 (m, 3H), 7.12−7.19 (m, 3H), 7.25−7.35 (m, 3H); $^{13}C$ NMR ($CDCl_3$, 75 MHz) $\delta$ 13.8, 28.0, 34.2, 41.4, 44.4, 46.1, 46.5, 54.7, 60.8, 110.8, 114.6, 115.4, 121.2, 125.8, 127.1, 128.5, 128.7, 136.3, 140.7, 141.1, 159.1, 167.0, 168.4, 175.6; Anal. Calcd for $C_{26}H_{31}NO_5$: C, 71.36; H, 7.15; N, 3.20. Found: C, 71.28; H, 7.03; N, 3.27.

A 0.58 g sample of the above compound was subjected to the standard diazo transfer conditions to give 0.6 g of *N*-benzyl-2-diazo-*N*-[4-(3-methoxybenzyl)hex-5-enoyl]malonamic acid ethyl ester (**21**) (99%) as a yellow oil: IR (neat) 3060, 2128, 1709, 1645 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 1.26 (t, 3H, $J$ = 7.2 Hz), 1.50 (m, 1H), 1.79 (m, 1H), 2.24 (m, 1H), 2.42 (dd, 1H, $J$ = 9.0 and 6.6 Hz), 2.49 (dd, 1H, $J$ = 9.3 and 5.4 Hz), 2.57 (dd, 2H, $J$ = 6.9 and 2.7 Hz), 3.77 (s, 3H), 4.22 (q, 2H, $J$ = 7.2 Hz), 4.82 (d, 1H, $J$ = 17.1 Hz), 4.86 (s, 2H), 4.91 (dd, 1H, $J$ = 10.3 and 1.8 Hz), 5.47 (m, 1H), 6.65−6.72 (m, 3H), 7.15 (t, 1H, $J$ = 7.8 Hz), 7.21−7.32 (m, 5H); $^{13}C$ NMR ($CDCl_3$, 75 MHz) $\delta$ 14.0, 28.7, 33.8, 41.6, 42.4, 44.6, 48.9, 54.8, 61.6, 110.9, 114.7, 115.5, 121.4, 126.9, 127.2, 128.4, 128.8, 136.8, 141.0, 141.3, 159.2, 160.3, 166.0, 175.4.

**9-Benzyl-4-(3-methoxybenzyl)-8-oxo-10-oxa-9-aza-tricyclo[5.2.1.$0^{1,5}$]decane-7-carboxylic Acid Ethyl Ester (22).** A 0.57 g (1.22 mmol) sample of diazo imide **21** in 10 mL of $CH_2Cl_2$ at rt was treated with 5 mg of rhodium(II) perfluorobutyrate for 24 h. The reaction mixture was concentrated under reduced pressure, and the residue was subjected to flash silica gel chromatography to give 0.47 g (89%) of 9-benzyl-4-(3-methoxybenzyl)-8-oxo-10-oxa-9-azatricyclo[5.2.1.$0^{1,5}$]decane-7-carboxylic acid ethyl ester (**22**) as a clear oil: IR (neat) 2932, 1716, 1744, 1588, 1225 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 1.34 (t, 3H, $J$ = 7.2 Hz), 1.48 (m, 1H), 1.60 (t, 1H, $J$ = 4.0 Hz), 1.64 (d, 1H, $J$ = 4.2 Hz), 1.92−2.10 (m, 5H), 2.43 (dd, 1H, $J$ = 16.6 and 6.9 Hz), 2.52 (dd, 1H, $J$ = 13.2 and 6.9 Hz), 3.77 (s, 3H), 4.35 (q, 2H, $J$ = 7.2 Hz), 4.38 (d, 1H, $J$ = 15.6 Hz), 4.51 (d, 1H, $J$ = 15.6 Hz), 6.55 (d, 1H, $J$ = 1.9 Hz), 6.60 (d, 1H, $J$ = 7.5 Hz), 6.72 (dd, 1H, $J$ = 8.1 and 1.9 Hz), 7.15 (t, 1H, $J$ = 8.1 Hz), 7.26−7.35 (m, 5H);$^{13}C$ NMR ($CDCl_3$, 75 MHz) $\delta$ 14.0, 24.4, 31.9, 34.4, 40.3, 43.3, 45.6, 53.5, 54.9, 61.9, 88.4, 106.5, 111.2, 114.2, 120.8, 127.4, 127.6, 128.6, 129.1, 136.2, 141.2, 159.4, 165.6, 170.5; HRMS calcd for $C_{26}H_{29}NO_5$ 435.2045, found 435.2053.

**1-Benzyl-3-hydroxy-8-methoxy-2-oxo-1,2,3,4,4a,5,6,10b-octahydro-5,10b-ethanobenzo[*h*]quinoline-2-carboxyl-ic Acid Ethyl Ester (23).** To a flask containing 0.10 g (0.23 mmol) of cycloadduct **22** in 5 mL of $CH_2Cl_2$ was added 0.32 mL (2.30 mmol) of $BF_3$·2AcOH, and the solution was stirred at rt for 24 h. The reaction was quenched with 5 mL of EtOH, and the reaction mixture was extracted with water. The organic extracts were concentrated under reduced pressure, and the crude residue was subjected to flash silica gel chromatography to give 0.093 g of 1-benzyl-3-hydroxy-8-methoxy-2-oxo-1,2,3,4,4a,5,6,10b-ethanobenzo[*h*]quinoline-2-carboxylic acid ethyl ester (**23**) (93%) as a white solid: mp 172−173 °C; IR (neat) 3438, 2932, 1744, 1637, 1246 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 0.97 (t, 3H, $J$ = 7.2 Hz), 1.49 (m, 1H), 2.03−2.17 (m, 5H), 2.49 (m, 1H), 2.60−2.69 (m, 2H), 2.96 (dd, 1H, $J$ = 17.4 and 3.9 Hz), 3.79 (s, 3H), 3.98 (s, 1H), 4.00 (q, 2H, $J$ = 7.2 Hz), 4.39 (d, 1H, $J$ = 15.6 Hz), 5.61 (d, 1H, $J$ = 15.6 Hz), 6.65 (d, 1H, $J$ = 2.7 Hz), 6.74 (dd, 1H, $J$ = 8.7 and 2.7 Hz), 7.10 (d, 1H, $J$ = 8.7 Hz), 7.23−7.35 (m, 5H); $^{13}C$ NMR ($CDCl_3$, 75 MHz) $\delta$ 13.6, 28.9, 31.2, 35.1, 39.1, 42.8, 50.2, 55.1, 61.8, 68.4, 75.5, 112.2, 113.9, 125.6, 126.2, 126.7, 128.5, 134.2, 134.3, 138.1, 158.4, 170.5, 172.2; Anal. Calcd for $C_{26}H_{29}NO_5$: C, 71.69; H, 6.72; N, 3.22. Found: C, 71.64; H, 6.70; N, 3.18.

**5-(3-Methoxybenzyl)hept-6-enoic Acid Benzylamide (27).** To a mixture containing 2.53 g (104 mol) of magnesium metal in 12 mL of THF at −20 °C was added 3.32 mL (10.4 mmol) of 3-methoxybenzyl chloride. After being stirred for 30 min at −20 °C, the solution was allowed to warm to rt over 1.5 h. The resulting benzyl Grignard reagent was transferred *via* cannula into a flask containing 3.96 g (20.8 mmol) of CuI and 4.34 mL (24.9 mmol) of HMPA in 25 mL of THF at −78 °C. The organocopper reagent was stirred for 1 h at −78 °C, and then 7.92 mL (62.4 mmol) of chlorotrimethyl silane was added followed by 1.01 mL (10.4 mmol) of 2- cyclohexen-1-one. The mixture was stirred for 30 min at −78 °C, and the reaction was quenched by the addition of 8.69 mL (62.4 mmol) of $Et_3N$ and 2 mL of $H_2O$. The mixture was filtered through Celite using EtOAc, and the organic extracts were washed with $H_2O$, dried over $Na_2SO_4$, and concentrated under reduced pressure.

The above silyl enol ether was dissolved in 100 mL of a 3:1 mixture of MeOH/$CH_2Cl_2$ at −78 °C and was saturated with an ozone stream for 30 min. After the mixture was purged with oxygen, 4 mL (50.0 mmol) of dimethyl sulfide was added and the solution was slowly allowed to warm to rt. After being stirred at rt for 5 h, the reaction mixture was concentrated under reduced pressure and subjected to flash silica gel chromatography to give 2.4 g (92%) of 5-(3-methoxybenzyl)-6-oxohexanoic acid (**26**) as a yellow oil: IR (neat) 3174, 2939, 1712, 1599, 1488 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 1.49−1.73 (m, 4H), 2.34 (t, 2H, $J$ = 6.6 Hz), 2.61−2.66 (m, 1H), 2.71 (dd, 1H, $J$ = 13.5 and 6.9 Hz), 2.97 (dd, 1H, $J$ = 13.5 and 6.9 Hz), 3.78 (s, 3H), 6.73 (m, 3H), 7.19 (t, 1H, $J$ = 7.8 Hz), 9.66 (s, 1H), 10.65 (bs, 1H); $^{13}C$ NMR ($CDCl_3$, 75 MHz) $\delta$ 21.9, 27.7, 33.7, 34.9, 52.9, 55.0, 111.6, 114.7, 121.2, 129.5, 139.9, 159.6, 179.1, 204.0.

To a flask containing 2.57 g (7.19 mmol) of methyltriphenylphosphonium bromide in 60 mL of THF at 0 °C was added 3.42 mL (7.52 mmol) of a 2.2 M *n*-BuLi solution, and the mixture was stirred at 0 °C for 35 min. To the red-colored Wittig anion was added 0.82 g (3.27 mmol) of aldehyde **26** in 10 mL of THF. The mixture was stirred for 3 h at rt, the reaction was quenched with brine, the mixture was cooled to 0 °C, and 50 mL of 5% aqueous HCl was added. After being stirred for 15 min, the mixture was extracted with ether and the ether layer was dried over $Na_2SO_4$. Concentration under reduced pressure afforded the expected heptenoic acid as a yellow oil which was used in the next step without further purification.

To a solution of the above compound in 30 mL of $CH_2Cl_2$ was added 0.79 g (4.90 mmol) of 1,1′-carbonyldiimidazole at rt. The mixture was stirred for 2 h and cooled to 0 °C, and 0.71 mL (4.90 mmol) of benzylamine was added. The solution was stirred overnight and then concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography to give 0.88 g (80%) of 5-(3-methoxybenzyl)hept-6-enoic acid benzylamide (**27**) as a clear oil: IR (neat) 3288, 3068, 2918, 1644, 697 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 1.29 (m, 1H), 1.45 (m, 1H), 1.59 (m, 1H), 1.72 (m, 1H), 2.16 (m, 2H), 2.29 (m, 1H), 2.59 (d, 2H, $J$ = 6.9 Hz), 3.78 (s, 3H), 4.41 (d, 2H, $J$ = 5.4 Hz), 4.90 (d, 1H, $J$ = 18.0 Hz), 4.95 (d, 1H, $J$

= 11.4 Hz), 5.59 (m, 2H), 6.68 (s, 1H), 6.70 (s, 1H), 6.73 (s, 1H), 7.16 (t, 1H, $J$ = 7.8 Hz), 7.25−7.35 (m, 5H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 23.3, 33.4, 36.5, 41.6, 43.4, 45.2, 55.0, 110.9, 114.9, 115.0, 121.6, 127.3, 127.6, 128.5, 128.9, 138.3, 141.7, 141.9, 159.3, 172.6; Anal. Calcd for $C_{22}H_{27}NO_2$: C, 78.29; H, 8.07; N, 4.15. Found: C, 78.03; H, 7.89; N, 4.18.

***N*-Benzyl-2-diazo-*N*-[5-(3-methoxybenzyl)hept-6-enoyl]-malonamic Acid Ethyl Ester (28).** N-Malonylacylation of 0.8 g of the above amide was carried out in the normal manner to give 0.85 g of *N*-benzyl-*N*-[5-(3-methoxybenzyl)hept-6-enoyl]-malonamic acid ethyl ester as a clear oil (98%): IR (neat) 2932, 1738, 1700, 1602, 1154, 698 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 1.17 (m, 1H), 1.26 (t, 3H, $J$ = 6.9 Hz), 1.31 (m, 1H), 1.47 (m, 1H), 1.62 (m, 1H), 2.18 (m, 1H), 2.43 (m, 2H), 2.53 (d, 2H, $J$ = 7.2 Hz), 3.76 (s, 3H), 3.88 (s, 2H), 4.18 (q, 2H, $J$ = 6.9 Hz), 4.80 (d, 1H, $J$ = 17.1 Hz), 4.89 (d, 1H, $J$ = 10.2 Hz), 4.97 (s, 2H), 5.50 (m, 1H), 6.65 (m, 3H), 7.12−7.18 (m, 3H), 7.23−7.34 (m, 3H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 14.0, 21.9, 33.0, 36.5, 41.6, 45.1, 46.4, 46.8, 55.0, 61.2, 110.8, 115.0, 121.5, 125.9, 127.3, 128.8, 128.9, 136.4, 141.5, 141.7, 159.3, 167.2, 168.7, 175.9; Anal. Calcd for $C_{27}H_{33}NO_5$: C, 71.80; H, 7.37; N, 3.10. Found: C, 71.65; H, 7.29; N, 3.02.

A 0.8 g sample of the above compound was subjected to the standard diazo transfer conditions to give 0.85 g of *N*-benzyl-2-diazo-N-[5-(3-methoxybenzyl)hept-6-enoyl]malonamic acid ethyl ester (**28**) as a yellow oil (96%): IR (neat) 2932, 2134, 1715, 1650, 1601, 1491, 779 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 1.20 (m, 1H), 1.28 (t, 3H, $J$ = 7.2 Hz), 1.35 (m, 1H), 1.50 (m, 1H), 1.65 (m, 1H), 2.22 (m, 1H), 2.44 (m, 2H), 2.55 (m, 2H), 3.78 (s, 3H), 4.24 (q, 2H, $J$ = 7.2 Hz), 4.83 (d, 1H, $J$ = 17.1 Hz), 4.88 (s, 2H), 4.89 (d, 1H, $J$ = 10.2 Hz), 5.53 (ddt, 1H, $J$ = 17.1, 10.2, 8.7 Hz), 6.65−6.73 (m, 3H), 7.16 (t, 1H, $J$ = 7.8 Hz), 7.24−7.31 (m, 5H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 14.1, 22.3, 33.2, 36.0, 41.6, 45.2, 49.0, 55.0, 61.7, 72.8, 110.9, 114.9, 115.0, 121.6, 127.0, 127.4, 128.5, 128.8, 136.9, 141.6, 141.8, 159.3, 160.4, 166.2, 175.5.

**10-Benzyl-5-(3-methoxybenzyl)-9-oxo-11-oxa-10-aza-tricyclo[6.2.1.0$^{1,6}$]undecane-8-carboxylic Acid Ethyl Ester (33).** A 1.60 g (3.35 mmol) sample of diazo imide **28** in 30 mL of $CH_2Cl_2$ was treated with 5 mg of rhodium(II) perfluorobutyrate, and the mixture was stirred at rt for 24 h. The solution was concentrated under reduced pressure, and the residue was subjected to flash silica gel chromatography to give 1.44 g (95%) of 10-benzyl-5-(3-methoxybenzyl)-9-oxo-11-oxa-10-azatricyclo[6.2.1.0$^{1,6}$]undecane-8-carboxylic acid ethyl ester (**33**) as a clear oil: IR (neat) 1749, 1721, 1599, 1105, 697 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 0.85 (m, 1H), 1.39 (t, 3H, $J$ = 6.9 Hz), 1.45−1.66 (m, 5H), 1.74 (dd, 1H, $J$ = 13.5 and 5.1 Hz), 1.83 (dd, 1H, $J$ = 12.9 and 7.3 Hz), 2.13 (m, 2H), 2.26 (dd, 1H, $J$ = 12.9 and 7.3 Hz), 2.60 (dd, 1H, $J$ = 13.5 and 3.6 Hz), 3.78 (s, 3H), 4.40 (s, 2H), 4.42 (m, 2H), 6.56 (s, 1H), 6.61 (d, 1H, $J$ = 7.5 Hz), 6.72 (dd, 1H, $J$ = 8.1 and 2.1 Hz), 7.15 (t, 1H, $J$ = 8.1 Hz), 7.26−7.31 (m, 5H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 14.1, 20.5, 27.7, 29.6, 36.2, 40.9, 43.1, 44.7, 47.7, 55.0, 62.1, 86.1, 97.3, 111.1, 115.0, 121.5, 127.5, 127.7, 128.6, 129.1, 136.6, 140.8, 159.4, 165.9, 170.9; HRMS calcd for $C_{27}H_{31}NO_5$ 449.2202, found 449.2195.

**1-Benzyl-3-hydroxy-8-methoxy-2-oxo-1,2,3,4,4a,5,6,10b-octahydro-5,10b-propanobenzo[*h*]quinoline-2-carboxylic Acid Ethyl Ester (38).** To a flask containing 1.20 g (2.67 mmol) of cycloadduct **33** in 100 mL of $CH_2Cl_2$ was added 3.72 mL (26.7 mmol) of $BF_3$·2AcOH, and the mixture was stirred at rt for 24 h. The reaction was quenched with 5 mL of EtOH, and the mixture was washed with 100 mL of $H_2O$. The organic layer was dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure. The crude residue was subjected to flash silica gel chromatography to give 1.05 g (88%) of 1-benzyl-3-hydroxy-8-methoxy-2-oxo-1,2,3,4,4a,5,6,10b-octahydro-5,10b-propanobenzo[*h*]quinoline-2-carboxylic acid ethyl ester (**38**) as a crystalline solid: mp 154−155 °C; IR (neat) 3445, 1748, 1642, 1499, 1240, 728 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 0.98 (t, 3H, $J$ = 7.2 Hz), 1.23 (m, 1H), 1.43−1.47 (m, 1H), 1.54−1.64 (m, 2H), 1.68−1.72 (m, 1H), 1.85 (dd, 1H, $J$ = 13.8 and 3.3 Hz), 1.98−2.02 (m, 1H), 2.15−2.24 (m, 2H), 2.44 (dt, 1H, $J$ = 13.2 and 3.0 Hz), 2.60 (d, 1H, $J$ = 18.3 Hz), 3.04 (dd, 1H, $J$ = 18.3 and 7.2 Hz), 3.79 (s, 3H), 3.99 (q, 2H, $J$ = 7.2 Hz), 4.02 (s, 1H), 4.69 (d, 1H, $J$ = 15.9 Hz), 5.66 (d, 1H, $J$ = 15.9 Hz), 6.64 (d, 1H, $J$ = 2.7 Hz), 6.75 (dd, 1H, $J$ = 8.7 and 2.7 Hz), 7.17 (d, 1H, $J$ = 8.7 Hz), 7.21−7.35 (m, 5H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 13.6, 18.7, 31.7, 32.6, 33.7, 34.2, 37.9, 39.4, 47.9, 55.1, 61.9, 63.4, 75.1, 112.3, 112.4, 126.0, 126.4, 126.5, 128.5, 131.3, 137.8, 138.7, 158.2, 170.0, 172.1; Anal. Calcd for $C_{27}H_{31}NO_5$: C, 72.13; H, 6.96; N, 3.11. Found: C, 72.15; H, 6.96; N, 3.14.

**5-(3-Methoxybenzyl)-3-methylhept-6-enoic Acid Benzylamide (31).** To a mixture containing 2.21 g (98.80 mol) of magnesium metal in 12 mL of THF at −20 °C was added 3.13 mL (9.97 mmol) of 3-methoxybenzyl chloride. After being stirred for 30 min at −20 °C, the solution was allowed to warm to rt over a 1.5 h interval. The resulting Grignard reagent was transferred *via* cannula into a flask containing 4.15 g (21.79 mmol) of CuI and 3.91 mL (21.79 mmol) of HMPA in 25 mL of THF at −78 °C. The organocopper reagent was stirred for 1 h at −78 °C, and then 8.07 mL (63.56 mmol) of chlorotrimethylsilane (at −30 °C) was added, followed by 1.0 g (9.08 mmol) of 5-methylcyclohex-2-en-1-one[24] (at −30 °C). The mixture was stirred for 30 min at −78 °C, and the reaction was quenched with 8.86 mL (63.6 mmol) of $Et_3N$ and 2 mL of $H_2O$. The mixture was filtered through Celite using EtOAc, and the extracts were washed with cold $H_2O$, dried over $Na_2SO_4$, and concentrated under reduced pressure.

The above silyl enol ether was dissolved in 100 mL of a 3:1 mixture of MeOH/$CH_2Cl_2$ at −78 °C and was saturated with an ozone stream for 30 min. After the solution was purged with oxygen, 4 mL (50.0 mmol) of dimethyl sulfide was added, and the solution was slowly allowed to warm to rt. After being stirred at rt for 5 h, the mixture was concentrated under reduced pressure and subjected to flash silica gel chromatography to give 1.51 g (63%) of 5-(3-methoxybenzyl)-3-methyl-6-oxohexanoic acid (**11**) as a light yellow oil: IR (neat) 3274, 1707, 1599, 1488, 1262 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 0.99 (d, 3H, $J$ = 6.6 Hz), 1.43 (m, 1H), 1.63 (quin, 1H, $J$ = 6.9 Hz), 2.07 (m, 1H), 2.17 (m, 1H), 2.32 (dd, 1H, $J$ = 15.0 and 5.7 Hz), 2.69 (m, 1H), 2.73 (dd, 1H, $J$ = 19.6 and 6.6 Hz), 2.91 (m, 1H), 3.78 (s, 3H), 6.73 (m, 3H), 7.19 (t, 1H, $J$ = 7.8 Hz), 9.65 (d, 1H, $J$ = 2.1 Hz), 10.65 (brs, 1H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 19.7, 27.8, 35.1, 35.2, 40.9, 50.9, 55.0, 111.6, 114.7, 121.1, 129.4, 139.8, 159.5, 178.1, 204.2; Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.15; H, 7.63. Found: C, 68.06; H, 7.46.

To a 8.37 g (23.43 mmol) sample of methyltriphenylphosphonium bromide in 150 mL of THF at 0 °C was added 9.40 mL (23.4 mmol) of 2.5 M *n*-BuLi, and the mixture was stirred at 0 °C for 35 min. To the red-colored Wittig anion was added 2.95 g (11.16 mmol) of aldehyde **11** in 25 mL of THF. The reaction mixture was stirred for 3 h at rt, the reaction was quenched with brine, the reaction mixture was cooled to 0 °C, and then 100 mL of 5% aqueous HCl was added. After being stirred at rt for 15 min, the reaction mixture was extracted with ether and the organic layer was dried over $Na_2SO_4$ and concentrated under reduced pressure. The resulting heptenoic acid that was isolated was used in the next step without further purification.

To a solution of the above heptenoic acid in 50 mL of $CH_2Cl_2$ at rt was added 2.71 g (16.74 mmol) of 1,1′-carbonyldiimidazole. The solution was stirred for 2 h, cooled to 0 °C, and 3.06 mL (27.90 mmol) of benzylamine was added. After being stirred at rt overnight, the solution was concentrated under reduced pressure and subjected to flash silica gel chromatography to give 2.82 g (72%) of 5-(3-methoxybenzyl)-3-methylhept-6-enoic acid benzylamide as a yellow oil: IR (neat) 3288, 1643, 1453, 1259, 697 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 0.94 (d, 3H, $J$ = 6.6 Hz), 1.18−1.40 (m, 2H), 1.82 (dd, 1H, $J$ = 13.5 and 8.7 Hz), 2.07 (m, 1H), 2.25 (dd, 1H, $J$ = 13.5 and 5.1 Hz), 2.38 (m, 1H), 2.51 (m, 1H), 2.62 (m, 1H), 3.76 (s, 3H), 4.39 (d, 2H, $J$ = 5.7 Hz), 4.87 (d, 1H, $J$ = 17.4 Hz), 4.93 (d, 1H, $J$ = 10.5 Hz), 5.59 (m, 1H), 5.77 (m, 1H), 6.69 (m, 3H), 7.15 (t, 1H, $J$ = 7.8 Hz), 7.23−7.33 (m, 5H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 20.4, 28.5, 41.4, 41.7, 43.0, 43.5, 43.6, 55.0, 110.9, 114.7, 115.1, 121.7, 127.4, 127.7, 128.6, 128.9, 138.4, 141.9, 142.2, 159.3, 172.1; Anal. Calcd for $C_{23}H_{29}NO_2$: C, 78.58; H, 8.32; N, 3.99; Found: C, 78.37; H, 8.42; N, 3.84.

***N*-Benzyl-2-diazo-N-[5-(3-methoxybenzyl)-3-methylhept-6-enoyl]malonamic Acid Ethyl Ester (32).** N-Malonylacylation of a 0.8 g sample of the above amide was carried out

in the normal manner to give 0.9 g of *N*-benzyl-N-[5-(3-methoxybenzyl)-3-methylhept-6-enoyl]malonamic acid ethyl ester as a clear oil (96%): IR (neat) 1739, 1698, 1602, 1487, 1033 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 0.85 (d, 3H, $J$ = 6.3 Hz), 1.19 (m, 1H), 1.28 (t, 3H, $J$ = 7.2 Hz), 2.07−2.21 (m, 3H), 2.43−2.61 (m, 4H), 3.78 (s, 3H), 3.90 (d, 2H, $J$ = 3.9 Hz), 4.20 (q, 2H, $J$ = 7.2 Hz), 4.69 (d, 1H, $J$ = 17.1 Hz), 4.86 (d, 1H, $J$ = 10.2 Hz), 4.98 (d, 2H, $J$ = 4.8 Hz), 5.51 (dt, 1H, $J$ = 17.1 and 10.2 Hz), 6.64−6.67 (m, 2H), 6.72 (d, 1H, $J$ = 8.1 Hz), 7.14−7.19 (m, 2H), 7.27 (m, 2H), 7.34 (t, 2H, $J$ = 6.9 Hz); $^{13}C$ NMR ($CDCl_3$, 75 MHz) $\delta$ 14.0, 20.4, 27.2, 41.1, 41.7, 42.9, 43.0, 46.4, 46.8, 55.0, 61.2, 110.8, 114.7, 115.1, 121.5, 125.9, 127.3, 128.7, 128.9, 136.5, 141.7, 141.9, 159.3, 167.2, 168.7, 175.4; Anal. Calcd for $C_{28}H_{35}NO_5$: C, 72.22; H, 7.58; N, 3.01. Found: C, 72.11; H, 7.46; N, 3.04.

A 0.8 g sample of the above compound was subjected to the standard diazo transfer conditions to give 0.82 g of *N*-benzyl-2-diazo-N-[5-(3-methoxybenzyl)-3-methylhept-6-enoyl]malonamic acid ethyl ester (**32**) as a yellow oil (98%): IR (neat) 2128, 1720, 1648, 1323, 696 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 0.81 (d, 3H, $J$ = 6.6 Hz), 1.38 (m, 1H), 1.25 (t, 3H, $J$ = 7.2 Hz), 2.04 (m, 1H), 2.15 (dd, 1H, $J$ = 15.6 and 8.4 Hz), 2.22 (m, 1H), 2.37−2.46 (m, 2H), 2.50−2.60 (m, 2H), 3.74 (s, 3H), 4.21 (q, 2H, $J$ = 7.2 Hz), 4.71 (d, 1H, $J$ = 17.1 Hz), 4.83 (m, 3H), 5.48 (dt, 1H, $J$ = 17.1 and 10.2 Hz), 6.61−6.69 (m, 3H), 7.12 (t, 1H, $J$ = 7.8 Hz), 7.19−7.30 (m, 5H); $^{13}C$ NMR ($CDCl_3$, 75 MHz) $\delta$ 14.1, 20.3, 27.7, 41.2, 41.5, 42.3, 42.6, 42.9, 49.0, 54.9, 61.7, 110.8, 114.6, 115.0, 121.6, 127.1, 127.2, 127.3, 128.5, 128.8, 137.0, 141.9, 159.2, 160.3, 166.3, 174.7.

**10-Benzyl-5-(3-methoxybenzyl)-3-methyl-9-oxo-11-oxa-10-azatricyclo[6.2.1.0$^{1,6}$]undecane-8-carboxylic Acid Ethyl Ester (34).** A sample containing 0.90 g (1.86 mmol) of diazo imide **32** in 30 mL of $CH_2Cl_2$ was treated with 5 mg of rhodium(II) perfluorobutyrate at rt for 24 h. The mixture was concentrated under reduced pressure, and the residue was subjected to flash silica gel chromatography to give 0.82 g (95%) of 10-benzyl-5-(3-methoxybenzyl)-3-methyl-9-oxo-11-oxa-10-azatricyclo[6.2.1.0$^{1,6}$]undecane-8-carboxylic acid ethyl ester (**34** and **35**) as a 3:2 mixture of diastereomers. The minor diastereomer was a crystalline solid: mp 142−143 °C; IR (neat) 1750, 1722, 1599, 1454, 732 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 0.73 (m, 1H), 0.82 (d, 3H, $J$ = 6.6 Hz), 1.35 (t, 3H, $J$ = 7.2 Hz), 1.37−1.53 (m, 3H), 1.85 (m, 1H), 1.97−2.07 (m, 2H), 2.18 (d, 1H, $J$ = 13.5 Hz), 2.30 (dd, 1H, $J$ = 13.2 and 3.3 Hz), 2.50 (dd, 1H, $J$ = 13.5 and 10.5 Hz), 2.67 (dd, 1H, $J$ = 13.8 and 5.4 Hz), 3.73 (s, 3H), 4.38 (q, 2H, $J$ = 7.2 Hz), 4.30 (d, 1H, $J$ = 15.6 Hz), 4.48 (d, 1H, $J$ = 15.6 Hz), 6.60 (m, 2H), 6.68 (dd, 1H, $J$ = 8.1 and 2.4 Hz), 7.13 (t, 1H, $J$ = 7.8 Hz), 7.25 (m, 5H); $^{13}C$ NMR ($CDCl_3$, 75 MHz) $\delta$ 14.2, 21.8, 22.0, 30.8, 35.1, 35.3, 35.4, 36.1, 43.2, 44.4, 55.0, 62.1, 85.3, 98.0, 111.0, 114.3, 121.0, 127.6, 127.7, 128.7, 129.2, 136.5, 142.6, 159.5, 165.8, 171.1; Anal. Calcd for $C_{28}H_{33}NO_5$: C, 72.54; H, 7.19; N, 3.02. Found: C, 72.29; H, 7.18; N, 2.96.

**1-Benzyl-3-hydroxy-8-methoxy-12-methyl-2-oxo-1,2,3,4,4a,5,6,10b-octahydro-5,10b-propanobenzo[*h*]quinoline-2-carboxylic Acid Ethyl Ester (9).** To a flask containing 0.77 g (1.66 mmol) of the above mixture of diastereomeric cycloadducts (**34**/**35**) in 100 mL of $CH_2Cl_2$ was added 2.31 mL (16.6 mmol) of $BF_3$·2AcOH, and the solution was stirred at rt for 36 h. The reaction was quenched with 5 mL of EtOH, and the reaction mixture was washed with water. The organic extracts were concentrated under reduced pressure, and the crude residue was subjected to flash silica gel chromatography to give 0.51 g (71%) of 1-benzyl-3-hydroxy-8-methoxy-12-methyl-2-oxo-1,2,3,4,4a,5,6,10b-octahydro-5,10b-propanobenzo[*h*]quinoline-2-carboxylic acid ethyl ester (**9**) as a crystalline solid: mp 73−74 °C; IR (neat) 1744, 1641, 1259, 1119, 729 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 0.67 (d, 3H, $J$ = 6.0 Hz), 0.95 (t, 3H, $J$ = 7.2 Hz), 1.23−1.37 (m, 3H), 1.70 (m, 1H), 1.84 (dd, 1H, $J$ = 13.8 and 2.7 Hz), 1.98 (m, 1H), 2.13−2.21 (m, 2H), 2.37 (m, 1H), 2.58 (d, 1H, $J$ = 18.3 Hz), 3.01 (dd, 1H, $J$ = 18.3 and 7.2 Hz), 3.75 (s, 3H), 3.96 (q, 2H, $J$ = 7.2 Hz), 4.03 (s, 1H), 4.70 (d, 1H, $J$ = 15.9 Hz), 5.59 (d, 1H, $J$ = 15.9 Hz), 6.60 (s, 1H), 6.72 (d, 1H, $J$ = 8.4 Hz), 7.14 (d, 1H, $J$ = 8.7 Hz), 7.19−7.29 (m, 5H); $^{13}C$ NMR ($CDCl_3$, 75 MHz) $\delta$ 13.4, 21.5, 24.9, 31.9, 32.9, 33.8, 39.0, 42.4, 46.3, 47.8, 55.0, 61.7, 63.5, 75.0, 112.2, 112.3, 125.9, 126.2, 126.4, 128.3, 131.9, 137.4, 138.6, 158.0, 169.9, 171.9; HRMS calcd for $C_{28}H_{33}NO_5$ 470.2518, found 470.2519.

**1-Benzyl-8-methoxy-2-oxo-1,2,3,4,4a,5,6,10b-octahydro-5,10b-propanobenzo[*h*]quinoline-2-carboxylic Acid Ethyl Ester (42).** To a solution containing 0.50 g (1.15 mmol) of benzo[*h*]quinoline **38** in 20 mL of THF was added 0.055 g (2.30 mmol) of NaH (60% dispersion in mineral oil), and the mixture was stirred at rt for 30 min. To this mixture was added 0.48 mL (3.45 mmol) of phenyl chlorothionocarbonate *via* syringe, and the reaction mixture was stirred overnight at rt. The reaction was quenched with an aqueous $NH_4Cl$ solution, and the reaction mixture was extracted with ether. The ether extracts were washed with brine, dried over $Na_2SO_4$, and filtered. The solution was concentrated under reduced pressure, and the residue was subjected to flash silica gel chromatography to give 0.58 g (88%) of 1-benzyl-8-methoxy-2-oxo-2-((phenoxy(thiocarbonyl))oxy)-1,2,3,4,4a,5,6,10b-octahydro-5,10b-propanobenzo[*h*]quinoline-2-carboxylic acid ethyl ester as a white solid: mp 75−76 °C; IR (neat) 1746, 1661, 1495, 729 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 1.12 (t, 3H, $J$ = 7.2 Hz), 1.18 (m, 1H), 1.40−1.44 (m, 1H), 1.52−1.61 (m, 2H), 1.66−1.71 (m, 1H), 1.96−2.00 (m, 1H), 2.16 (m, 1H), 2.43 (dt, 1H, $J$ = 12.6 and 3.3 Hz), 2.54−2.70 (m, 2H), 3.02−3.15 (m, 2H), 3.75 (s, 3H), 4.00 (m, 2H), 4.70 (d, 1H, $J$ = 15.9 Hz), 5.69 (d, 1H, $J$ = 15.9 Hz), 6.62 (d, 1H, $J$ = 2.4 Hz), 6.72 (dd, 1H, $J$ = 8.7 and 2.4 Hz), 7.10−7.30 (m, 10H), 7.38 (t, 1H, $J$ = 7.8 Hz); $^{13}C$ NMR ($CDCl_3$, 75 MHz) $\delta$ 13.6, 18.6, 30.9, 31.6, 32.3, 33.5, 38.1, 39.4, 48.9, 55.0, 60.2, 62.4, 63.1, 85.5, 112.3, 112.4, 121.8, 126.2, 126.3, 126.4, 126.5, 128.4, 129.4, 130.5, 137.9, 138.7, 153.1, 158.2, 163.7, 165.8, 191.2.

To a solution containing 0.43 g (0.74 mmol) of the above thionocarbonate in 10 mL of toluene was added 0.12 g (0.74 mmol) of AIBN, followed by 1.0 mL (3.71 mmol) of tributyltin hydride. The solution was heated at 75 °C for 5 h, cooled to rt, and concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography to give 0.26 g (80%) of 1-benzyl-8-methoxy-2-oxo-1,2,3,4,4a,5,6,10b-octahydro-5,10b-propanobenzo[*h*]quinoline-2-carboxylic acid ethyl ester (**42**) as a 3:2 inseparable mixture of diastereomers: mp 51−55 °C; IR (neat) 1736, 1642, 1496, 730 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 1.26 (t, 3H, $J$ = 7.2 Hz), 1.39−1.69 (m, 5H), 1.75−2.03 (m, 2H), 2.07−2.16 (m, 2H), 2.29 (m, 1H), 2.53 (d, 1H, $J$ = 18.3 Hz), 3.00−3.17 (m, 2H), 3.76 (s, 3H), 4.19 (m, 2H), 4.59 (d, 0.7H, $J$ = 16.2 Hz), 4.61 (d, 0.3H, $J$ = 16.2 Hz), 5.71 (d, 0.7H, $J$ = 16.2 Hz), 5.74 (d, 0.3H, $J$ = 16.2 Hz), 6.61 (s, 1H), 6.72 (d, 1H, $J$ = 8.7 Hz), 7.08 (d, 1H, $J$ = 8.7 Hz), 7.14−7.31 (m, 5H); HRMS calcd for $C_{27}H_{31}NO_4$ 433.2253, found 433.2254.

**1-Benzyl-8-methoxy-2-oxo-1,2,3,4,4a,5,6,10b-octahydro-5,10b-propanobenzo[*h*]quinoline (43).** A solution containing 0.40 g (0.92 mmol) of the ester **42** in 8 mL of a 2 M aqueous KOH solution was heated at 95 °C for 24 h. The reaction mixture was cooled to rt and acidified with concentrated HCl. The solution was poured into 10 mL of $H_2O$ and extracted with EtOAc. The EtOAc extracts were dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure. The crude residue was taken up in xylene and heated at 160 °C for 3 h. After being cooled to rt, the reaction mixture was concentrated under reduced pressure and subjected to flash silica gel chromatography to give 0.30 g (87%) of 1-benzyl-8-methoxy-2-oxo-1,2,3,4,4a,5,6,10b-octahydro-5,10b-propanobenzo[*h*]quinoline (**43**) as a crystalline solid: mp 155−156 °C; IR (neat) 1642, 1605, 1495, 728 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 1.15 (dt, 1H, $J$ = 13.5 and 4.2 Hz), 1.40−1.81 (m, 6H), 1.96−2.09 (m, 2H), 2.16−2.30 (m, 2H), 2.52 (t, 1H, $J$ = 8.1 Hz), 2.58 (t, 1H, $J$ = 8.1 Hz), 3.11 (dd, 1H, $J$ = 18.1 and 7.2 Hz), 3.77 (s, 3H), 4.59 (d, 1H, $J$ = 15.9 Hz), 5.76 (d, 1H, $J$ = 15.9 Hz), 6.63 (s, 1H), 6.73 (dd, 1H, $J$ = 8.7 and 2.4 Hz), 7.12 (d, 1H, $J$ = 8.7 Hz), 7.19−7.34 (m, 5H); $^{13}C$ NMR ($CDCl_3$, 75 MHz) $\delta$ 18.8, 22.8, 31.1, 31.6, 33.2, 33.8, 38.1, 42.8, 47.0, 55.0, 62.3, 112.3, 112.4, 125.9, 126.2, 126.3, 128.3, 132.6, 138.1, 140.0, 157.9, 172.1; Anal. Calcd for $C_{24}H_{27}NO_2$: C, 79.73; H, 7.54; N, 3.87. Found: C, 79.76; H, 7.56; N, 3.91.

**1-Cyclohexyl-8-methoxy-2-oxo-1,2,3,4,4a,5,6,10b-octahydro-5,10b-propanobenzo[*h*]quinoline (44).** To a solution containing 0.26 g (0.71 mmol) of amide **43** in 5 mL of a 4:1 mixture of MeOH/AcOH was added 40 mg (0.17 mmol) of $PtO_2$.

The mixture was hydrogenated at 40 psi for 24 h. At the end of this time, the mixture was filtered through Celite and washed with EtOAc. The filtrate was concentrated under reduced pressure and subjected to flash silica gel chromatography to give 0.20 g (99%) of 1-cyclohexyl-8-methoxy-2-oxo-1,2,3,4,4a,5,6,10b-octahydro-5,10b-propanobenzo[*h*]quinoline (**44**) as a crystalline solid: mp 136−137 °C; IR (neat) 2925, 2847, 1641, 1498, 729 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 1.02 (m, 2H), 1.20 (m, 4H), 1.47−1.86 (m, 12H), 1.96−2.08 (m, 3H), 2.17 (m, 1H), 2.35 (dt, 1H, $J$ = 16.8 and 7.8 Hz), 2.53 (d, 1H, $J$ = 18.3 Hz), 3.11 (dd, 1H, $J$ = 18.3 and 7.5 Hz), 3.20 (dd, 1H, $J$ = 13.5 and 7.5 Hz), 3.75 (s, 3H), 4.13 (dd, 1H, $J$ = 13.5 and 7.5 Hz), 6.58 (d, 1H, $J$ = 2.4 Hz), 6.66 (dd, 1H, $J$ = 8.7 and 2.4 Hz), 6.97 (d, 1H, $J$ = 8.7 Hz);$^{13}C$ NMR ($CDCl_3$, 75 MHz) $\delta$ 19.2, 22.8, 26.1, 26.3, 30.8, 31.4, 31.5, 33.5, 33.9, 38.6, 38.8, 42.1, 49.5, 54.9, 61.5, 112.1, 112.2, 125.9, 133.3, 138.0, 157.7, 172.4; Anal. Calcd for $C_{24}H_{33}NO_2$: C, 78.42; H, 9.07; N, 3.81. Found: C, 78.50; H, 9.05; N, 3.89.

**1-Benzyl-8-methoxy-12-methyl-2-oxo-1,2,3,4,4a,5,6,10b-octahydro-5,10b-propanobenzo[*h*]quinoline-2-carboxylic Acid Ethyl Ester (45).** To a solution containing 0.51 g (1.09 mmol) of alcohol **9** in 20 mL of THF was added 0.11 g (2.73 mmol) of NaH (60% dispersion in mineral oil), and the mixture was stirred at rt for 30 min. To this mixture was added 0.45 mL (3.28 mmol) of phenyl chlorothionocarbonate *via* syringe, and the reaction mixture was stirred overnight at rt. The reaction was quenched with an aqueous $NH_4Cl$ solution and the mixture was extracted with ether. The ether extracts were washed with brine, dried over $Na_2SO_4$, and filtered. The solution was concentrated under reduced pressure, and the residue was subjected to flash silica gel chromatography to give 0.52 g (80%) of 1-benzyl-8-methoxy-12-methyl-2-oxo-2-((phenoxy(thiocarbonyl))oxy)-1,2,3,4,4a,5,6,10b-octahydro-5,10b-propanobenzo[*h*]quinoline-2-carboxylic acid ethyl ester as a white solid: mp 70−71 °C; IR (neat) 2911, 1741, 1661, 1495, 728 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 0.70 (d, 3H, $J$ = 5.7 Hz), 1.15 (t, 3H, $J$ = 7.2 Hz), 1.31 (m, 3H), 1.74 (m, 1H), 2.01 (m, 1H), 2.22 (m, 1H), 2.41 (m, 1H), 2.58−2.72 (m, 2H), 3.08−3.17 (m, 2H), 3.78 (s, 3H), 4.03 (q, 2H, $J$ = 7.2 Hz), 4.75 (d, 1H, $J$ = 15.6 Hz), 5.67 (d, 1H, $J$ = 15.6 Hz), 6.63 (s, 1H), 6.73 (d, 1H, $J$ = 8.7 Hz), 7.12−7.22 (m, 3H), 7.28−7.44 (m, 8H).

To a solution containing 0.51 g (0.85 mmol) of the above thionocarbonate in 10 mL of toluene was added 0.14 g (0.85 mmol) of AIBN, followed by 1.14 mL (4.25 mmol) of tributyltin hydride. The solution was heated at 45 °C for 5 h, cooled to rt, and concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography to give 0.37 g (96%) of 1-benzyl-8-methoxy-12-methyl-2-oxo-1,2,3,4,4a,5,6,10b-octahydro-5,10b-propanobenzo[*h*]quinoline-2-carboxylic acid ethyl ester (**45**) as a 3:2 inseparable mixture of diastereomers: mp 48−49 °C; IR (neat) 1731, 1643, 1495, 1265, 730 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 0.71 (d, 3H, $J$ = 5.4 Hz), 1.28 (t, 3H, $J$ = 7.2 Hz), 1.34 (m, 2H), 1.67 (m, 2H), 1.85 (m, 1H), 2.00 (m, 2H), 2.21 (m, 2H), 2.56 (d, 0.67H, $J$ = 18.3 Hz), 2.59 (d, 0.33H, $J$ = 18.3 Hz), 3.03 (d, 0.33H, $J$ = 7.2 Hz), 3.09 (d, 0.67H, $J$ = 7.2 Hz), 3.15 (m, 1H), 3.78 (s, 3H), 4.22 (m, 2H), 4.64 (d, 0.67H, $J$ = 15.9 Hz), 4.66 (d, 0.33H, $J$ = 15.9 Hz), 5.68 (d, 0.67H, $J$ = 15.9 Hz), 5.71 (d, 0.33H, $J$ = 15.9 Hz), 6.61 (s, 1H), 6.73 (d, 1H, $J$ = 8.4 Hz), 7.09 (d, 1H, $J$ = 8.4 Hz), 7.19−7.33 (m, 5H); HRMS calcd for $C_{28}H_{33}NO_4$ 447.2409, found 447.2349.

**1-Benzyl-8-methoxy-12-methyl-2-oxo-1,2,3,4,4a,5,6,10b-octahydro-5,10b-propanobenzo[*h*]quinoline (46).** A solution containing 0.38 g (0.85 mmol) of ester **45** in 8 mL of a 2 M aqueous KOH solution was heated at 95 °C for 24 h. The reaction mixture was cooled to rt and acidified with concentrated HCl. The solution was poured into 10 mL of $H_2O$ and extracted with EtOAc. The EtOAc extracts were dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure. The crude residue was taken up in xylene and heated at 160 °C for 3 h. After being cooled to rt, the reaction mixture was concentrated under reduced pressure and subjected to flash silica gel chromatography to give 0.27 g (85%) of 1-benzyl-8-methoxy-12-methyl-2-oxo-1,2,3,4,4a,5,6,10b-octahydro-5,10b-propanobenzo[*h*]quinoline (**46**) as a crystalline solid: mp 131−132 °C; IR (neat) 1641, 1606, 1496, 1266, 729 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 0.70 (d, 3H, $J$ = 6.3 Hz), 1.24 (m, 2H), 1.34 (m, 1H), 1.56−1.81 (m, 4H), 2.02 (m, 1H), 2.18−2.28 (m, 2H), 2.52 (dd, 1H, $J$ = 17.2 and 8.1 Hz), 2.56 (d, 1H, $J$ = 18.6 Hz), 3.11 (dd, 1H, $J$ = 18.6 and 7.5 Hz), 3.78 (s, 3H), 4.62 (d, 1H, $J$ = 15.9 Hz), 5.71 (d, 1H, $J$ = 15.9 Hz), 6.61 (s, 1H), 6.71 (dd, 1H, $J$ = 8.7 and 2.7 Hz), 7.11 (d, 1H, $J$ = 8.7 Hz), 7.19−7.34 (m, 5H); $^{13}C$ NMR ($CDCl_3$, 75 MHz) $\delta$ 21.7, 22.5, 25.1, 31.1, 31.9, 33.6, 42.5, 42.6, 46.8, 47.0, 55.0, 62.5, 112.2, 112.5, 125.9, 126.3, 126.4, 128.3, 133.4, 137.8, 139.9, 158.0, 172.1; Anal. Calcd for $C_{25}H_{29}NO_2$: C, 79.95; H, 7.79; N, 3.72. Found: C, 80.06; H, 7.70; N, 3.63.

**8-Methoxy-12-methyl-1,2,3,4,4a,5,6,10b-octahydro-1*H*-5,10b-propanobenzo[*h*]quinoline (8).** To a flask containing 0.21 g (0.55 mmol) of benzo[*h*]quinoline **46** in 8 mL of a 1:1 mixture of $Et_2O$/THF was added 5.51 mL (5.51 mmol) of a 1 M solution of $LiAlH_4$ in THF at 0 °C. The solution was slowly warmed to rt, was stirred for 1 h at 25 °C, and was then heated at 75 °C for an additional 48 h. After being cooled to rt, the mixture was cooled to 0 °C and the reaction was quenched with 10 mL of a 5% aqueous NaOH solution. The aluminum salts were filtered and washed with ether. The filtrate was poured into 20 mL of $H_2O$, and the mixture was extracted with ether. The ether extracts were dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure. The crude residue was subjected to flash silica gel chromatography to give 0.127 g (81%) of 1-benzyl-8-methoxy-12-methyl-1,2,3,4,4a,5,6,10b-octahydro-5,10b-propanobenzo[*h*]quinoline as a tan oil: IR (neat) 1604, 1491, 1237, 906, 730 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 0.79 (d, 3H, $J$ = 5.1 Hz), 0.93 (m, 1H), 1.19 (m, 1H), 1.36 (m, 2H), 1.40−1.61 (m, 3H), 1.74−1.84 (m, 2H), 1.90 (dt, 1H, $J$ = 12.6 and 3.3 Hz), 2.04 (m, 1H), 2.48−2.54 (m, 2H), 2.66 (m, 1H), 3.13 (dd, 1H, $J$ = 16.9 and 6.9 Hz), 3.82 (s, 3H), 4.22 (d, 2H, $J$ = 7.8 Hz), 6.66 (s, 1H), 6.83 (dd, 1H, $J$ = 8.7 and 2.4 Hz), 7.27 (m, 1H), 7.39 (t, 2H, $J$ = 7.2 Hz), 7.55 (d, 2H, $J$ = 7.2 Hz), 7.76 (d, 1H, $J$ = 8.7 Hz); $^{13}C$ NMR ($CDCl_3$, 75 MHz) $\delta$ 21.6, 22.5, 26.6, 27.1, 32.6, 34.6, 39.4, 44.1, 45.7, 48.2, 51.1, 54.9, 59.9, 111.9, 112.0, 126.2, 127.4, 127.8, 128.0, 134.7, 139.6, 142.9, 157.3; HRMS calcd for $C_{25}H_{31}NO$ 361.2405, found 361.2393.

To a solution containing 0.13 g (0.35 mmol) of the above amine in 5 mL of a 4:1 mixture of $CH_2Cl_2$/MeOH was added 50 mg of 10% Pd/C. The mixture was hydrogenated at 30 psi for 20 h. At the end of this time, the mixture was filtered through Celite and washed with EtOAc. The filtrate was concentrated under reduced pressure and subjected to flash silica gel chromatography to give 89 mg (90%) of 8-methoxy-12-methyl-1,2,3,4,4a,5,6,10b-octahydro-1*H*-5,10b-propanobenzo[*h*]quinoline (**8**) as a yellow oil: IR (neat) 2705, 1602, 1502, 1253, 784 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 0.79 (m, 3H), 0.85 (m, 2H), 1.24−1.41 (m, 3H), 1.54−1.79 (m, 3H), 1.87 (m, 1H), 2.05 (m, 1H), 2.09 (m, 2H), 2.53 (d, 1H, $J$ = 18.0 Hz), 2.81 (t, 1H, $J$ = 12.9 Hz), 3.07 (dd, 1H, $J$ = 18.0 and 6.6 Hz), 3.19 (d, 1H, $J$ = 12.3 Hz), 3.78 (s, 3H), 6.64 (s, 1H), 6.85 (dd, 1H, $J$ = 8.7 and 2.1 Hz), 7.77 (d, 1H, $J$ = 8.7 Hz); $^{13}C$ NMR ($CDCl_3$, 75 MHz) $\delta$ 21.5, 23.6, 24.6, 25.8, 31.9, 33.3, 40.3, 41.8, 42.8, 47.9, 54.9, 60.1, 112.7, 113.0, 126.4, 126.9, 139.0, 158.2; HRMS calcd for $C_{18}H_{25}NO$ 271.1936, found 271.1930.

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**Supporting Information Available:** $^1H$ NMR and $^{13}C$ NMR spectra for all compounds with high-resolution mass spectra together with ORTEP drawings for structures **38** and **46** (9 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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