JOC Article

Preparation of Perhydroisoquinolines via the Intramolecular Diels−Alder Reaction of *N*-3,5-Hexadienoyl Ethyl Acrylimidates: A Formal Synthesis of (±)-Reserpine

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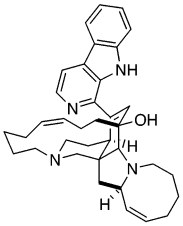
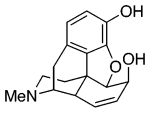
The intramolecular Diels−Alder reaction of *N*-3,5-hexadienoyl ethyl acrylimidates provides an efficient method for the synthesis of cis-fused hexahydroisoquinolones. As a demonstration of the stereochemical control offered by this cycloaddition, two approaches to the construction of the DE rings of reserpine are reported. In the second entry, *N*-((4-(trimethylsilyl)ethoxymethoxy)methyl-6-benzyloxy-3*Z*,5*E*-hexadienoyl)-1-aza-2-ethoxy-1,3-butadiene (**40**) undergoes cycloaddition to produce as the major product (4a*S**,7*R**,8a*S**)-7-benzyloxy-5-((2-trimethylsilyl)ethoxymethoxy)methyl-3,4,4a,7,8,8a-hexahydroisoquinol-3-one (**41**). Cycloadduct **41** is then stereospecifically elaborated to (4a*S**,5*S**,6*R**,7*R**,8a*R**)-6-methoxy-5-methoxycarbonyl-7-(3,4,5-trimethoxy)benzoyldecahydroisoquinoline-2-carboxylic acid methyl ester (**3**), a key intermediate previously transformed to reserpine.

Introduction

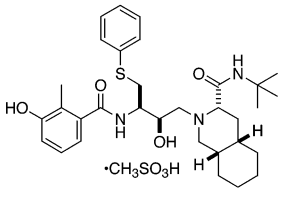
Perhydroisoquinoline ring systems are a common structural feature found in a variety of biologically active natural products and pharmaceuticals.[1] The occurrence of perhydroisoquinolines in medicinally important compounds has spurred a large research effort directed toward their preparation. Representative octahydroisoquinoline-containing natural products includes morphine from the opioid family and manzamine A from the manzamine alkaloid family.[2] A number of pharmaceuticals also contain perhydroisoquinoline ring systems including several HIV-1 protease inhibitors including Viracept.[3]



manzamine A



morphine



Viracept®

Perhaps no group of compounds has contributed more to the development of methodology for perhydroisoquinoline synthesis than the yohimbine alkaloids. Isolated from species of the Indian shrub *Rauwolfia*, the yohimbine alkaloids were traditionally used as a cure-all for ailments including cholera and insanity.[4] Clinical interest in these alkaloids stemmed from potent antihypertensive and sedative effects elicited by extracts from the roots and bark of *Rauwolfia serpentia*. The principle compound of medicinal interest, (−)-reserpine (**1**, Scheme 1), was isolated and structurally characterized in 1955.[5]

In addition to reserpine's interesting biological properties, its complex molecular structure poses a significant synthetic challenge. The E ring of reserpine contains five contiguous asymmetric centers embedded in a cis-fused perhydroisoquinoline ring system. The difficulties associated with the construction of the stereochemically complex perhydroisoquinoline ring system present in reserpine have stimulated the development of a number of synthetic approaches, which have culminated in both total and formal syntheses of reserpine.[6,7] Indeed, the broad range of synthetic methodologies applied to the synthesis of reserpine underscores its utility as a target for the development of novel synthetic transformations.

* Corresponding author.

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(5) Dorfman, L.; Furlenmeier, A.; Huebner, C. F.; Lucas, R.; MacHullamy, H. B.; Mueller, J. M.; Schlittler, E.; Schwyzer, R.; St. Andre, A. F. *Helv. Chim. Acta* **1954**, *37*, 59−75.

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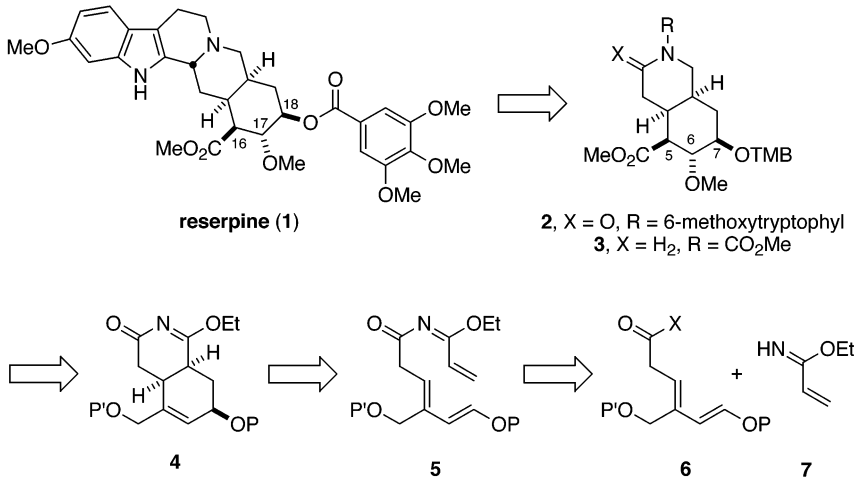
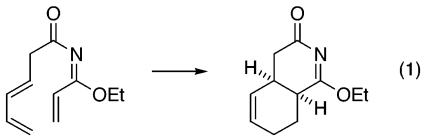
SCHEME 1



In this manner, reserpine has stood as a milestone by which to test the utility of synthetic methodology.

Our laboratory has been involved in the utilization of intramolecular Diels−Alder reactions for the preparation of perhydroisoquinoline ring systems (eq 1). The intramolecular Diels−Alder reaction of *N*-3,5-hexadienoyl ethyl acrylimidates allows for a mild and efficient synthesis of *cis*-fused hexahydroisoquinolones.[8] The hexahydroisoquinolone cycloadducts produced from the reaction are highly functionalized and hold considerable potential for stereoselective elaboration. As a demonstration of this potential, the synthesis of perhydroisoquinoline **3**, an intermediate previously transformed to reserpine, is described below.


(1)

Results and Discussion

At the outset of our studies, two potential targets were identified which differed in the oxidation state of the C3 (isoquinoline numbering) carbon atom and substitution on nitrogen (Scheme 1). As the hexahydroisoquinolone cycloadducts produced from the Diels−Alder reaction of *N*-3,5-hexadienoyl ethyl acrylimidates can be processed to afford either the perhydroisoquinol-3-one by partial reduction or perhydroisoquinoline by complete reduction, both oxidation states can be accessed via a common Diels−Alder adduct.[8b] Preparation of Woodward intermediate **2**, which incorporates the DE rings as an perhydroisoquinol-3-one, would permit regioselective closure of ring C.[7a,b] Alternatively the synthesis of perhydroisoquinoline **3**, a late stage intermediate in Wender's synthesis of reserpine, leads to a regioisomeric mixture upon oxidative cyclization leading to C-ring formation.[7d,e] With these considerations in mind, Woodward intermediate **2** was chosen as our initial goal.

Our retrosynthetic strategy for the assembly of targets **2** and **3**, which compromise the fully elaborated DE rings of reserpine, is outlined in Scheme 1. Perhydroisoquinolines **2** or **3** would arise from reduction and functional group manipulation of hexahydroisoquinolone **4**, which in turn arises from the intramolecular Diels−Alder cycloaddition of *N*-3,5-hexadienoyl ethyl acrylimidate **5**. In this approach, all E ring functionality is confined to the diene fragment **6**, which upon cyclization in the tether endo mode would establish three of the five asymmetric centers. Diels−Alder precursor **5** would result from the coupling of hexadienoic acid **6** with 1-aza-2-ethoxy-1,3-butadiene (**7**).

The efficient preparation of substituted 3,5-hexadienoic acids of type **6** was central to the success of our outlined strategy (Scheme 1). As such, several pathways for their synthesis were devised via the intermediacy of 2,4-hexadienoic acids. While the deconjugation of 2,4-hexadienoic acid derivatives has been documented,[8b,9] few examples containing substitution at both the 4 and 6-positions have been reported; this highlighted the need for exploratory studies of this key isomerization with regard to olefin geometry about the starting 2,4-hexadienoic acid derivatives to deliver the required 3(*Z*),5(*E*) hexadienoic acid derivatives.

First Generation Approach: Preparation of Perhydrosoquinol-3-one 24. Transition-metal-mediated couplings of a vinylorganometallic with a vinyl halide

(7) For total syntheses of reserpine, see: (a) Woodward, R. B.; Bader, F. E.; Bickel, H.; Frey, A. J.; Kierstead, R. W. *J. Am. Chem. Soc.* **1956**, *78*, 2023−2025. (b) Woodward, R. B.; Bader, F. E.; Bickel, H.; Kierstead, R. W. *Tetrahedron* **1958**, *2*, 1−57. (c) Pearlman, B. A. *J. Am. Chem. Soc.* **1979**, *101*, 6404−6408. (d) Wender, P. A.; Schaus, J. M.; White, A. W. *J. Am. Chem. Soc.* **1980**, *102*, 6157−6159. (e) Wender, P. A.; Schaus, J. M.; White, A. W. *Hetereocycles* **1987**, *25*, 263−270. (f) Martin, S. F.; Grzejszczak, S.; Rüeger, H.; Williamson, S. A. *J. Am. Chem. Soc.* **1985**, *107*, 4072. (g) Martin, S. F.; Rüeger, H.; Williamson, S. A.; Grzejszczak, S. *J. Am. Chem. Soc.* **1987**, *109*, 6124−6136. (h) Stork, G. *Pure Appl. Chem.* **1989**, *61*, 439−442. (i) Hanessian, S.; Pan, J. W.; Carnell, A.; Bouchard, H.; Lesage, L. *J. Org. Chem.* **1997**, *62*, 465−473.

(8) (a) Shea, K. J.; Svoboda, J. J. *Tetrahedron Lett.* **1986**, *27*, 4837−4840. (b) Gutierrez, A. J.; Shea, K. J.; Svoboda, J. J. *J. Org. Chem.* **1989**, *54*, 4335−4344. (c) Sparks, S. M.; Shea, K. J. *Tetrahedron Lett.* **2000**, *41*, 6721−6724. (d) Sparks, S. M.; Shea, K. J. *Org. Lett.* **2001**, *3*, 2265−2267.

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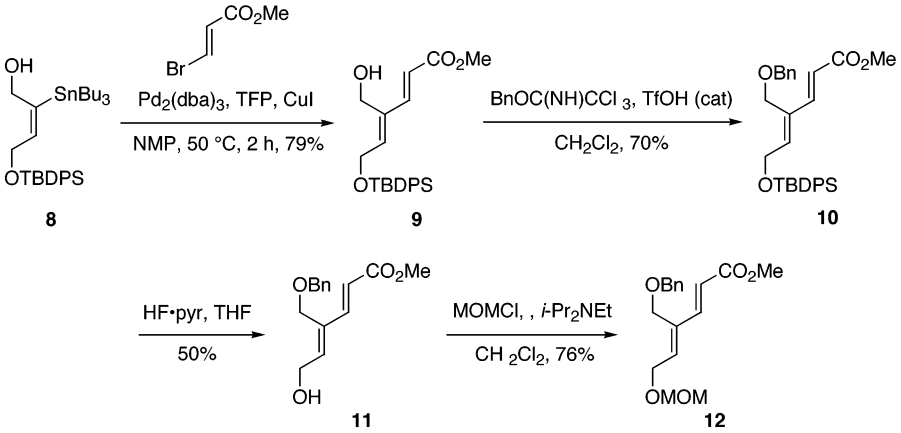
SCHEME 2



were deemed the most expedient route to the required 3,5-hexadienoic acid (via a 2,4-hexadienoic acid derivative). On the basis of the starting geometry of the coupling partners, all possible olefin isomers of the intermediate 2,4-hexadienoic acid derivatives are accessible, thus allowing for a thorough examination of the key deconjugation step with regard to the configuration of the 2,4-hexadienoic ester.

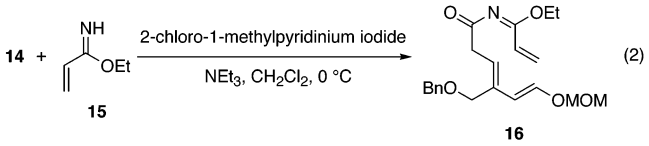
The synthesis of our first generation diene of type **6** was initiated via a Stille coupling protocol.[10] A survey of conditions for the Stille coupling of stannane **8**[11] with methyl 3(*E*)-bromoacrylate[12] revealed the use of $Pd_2(dba)_3$ (2 mol %), 2-trifurylphosphine (TFP, 16 mol %), and stoichiometric copper iodide (1.4 equiv) in *N*-methylpyrrolidinone (NMP) at 65 °C afforded conjugated ester **9** in good yield.[13] Other standard conditions employed to effect Stille couplings either returned starting materials ($Pd(PPh_3)_4$, THF, 70 °C) or provided a mixture of geometric isomers ($PdCl_2(MeCN)_2$, DMF), highlighting the problems associated with the use of α-substituted vinylstannanes in the Stille coupling.[14] Benzylation of the primary hydroxyl utilizing the conditions developed by Bundle[15] afforded protected diene **10** (Scheme 2). Attempted deconjugation of diene **10** resulted in a complex reaction mixture, potentially due to the instability of the resulting silylenol ether to the reaction conditions. To circumvent this complication, the silyl protecting group was converted to the more robust methoxymethyl ether via silyl deprotection (HF•pyr, THF) followed by alkylation (MOMCl, *i*-Pr_2NEt, CH_2Cl_2).

Kinetic deconjugation of 2,4-hexadienoic ester derivative **12** was accomplished with lithium diisopropylamide (LDA, 1.1 equiv)/hexamethylphosphoramide (HMPA)/

FIGURE 1.

THF, −78 °C, which gave, following an acidic quench (10% HCl), a single product in 70% isolated yield. Both ^1H NMR and subsequent chemical studies established that the reaction gave the 3(*Z*),5(*E*)-dienoic ester **13** (Figure 1). Exclusive formation of 5(*E*) stereochemistry from the 4(*Z*) precursor was somewhat surprising and implies that rotamer **12A** is the reacting species at −78 °C. Hydrolysis of ester **13** (KOH/aq MeOH) provided acid **14** in quantitative yield.

The Diels−Alder precursor was prepared by coupling of diene acid **14** with *O*-ethylvinylimidate (**15**, eq 2).[8b]



Several coupling methods were screened including carbodiimide mediated coupling (DCC) and activation of acid **14** as the acyl chloride ($(COCl)_2$, cat. DMF, CH_2Cl_2) but failed due to product hydrolysis during silica gel chromatography and decomposition of the intermediate acyl chloride, respectively. These failures suggested a method was required which minimized exposure to silica gel and provided a reactive intermediate which would not undergo decomposition, as did the acyl chloride. This was achieved with the coupling acid **14** and imidate **15** mediated by 2-chloro-1-methylpyridinium iodide, the Mukaiyama reagent.[16] When acid **14**, imidate **15**, and the Mukaiyama salt were stirred at 0 °C in the presence of 2 equiv of triethylamine, Diels−Alder precursor **16** was isolated in 83% yield following purification via quick filtration of the reaction mixture through a short plug of

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(13) (a) Farina, V.; Kapadia, S.; Krishnan, B.; Wang, C.; Liebeskind, L. S. *J. Org. Chem.* **1994**, *59*, 5905−5911. (b) Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585−9595. (c) Liebeskind, L. S.; Fengl, R. W. *J. Org. Chem.* **1990**, *55*, 5359−5364.

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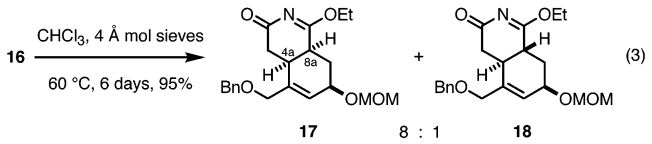
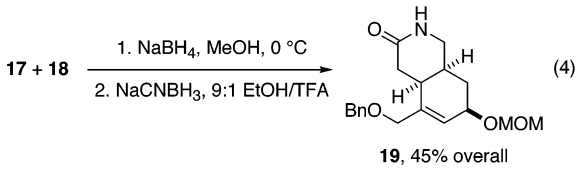
silica gel. Low yields (~5%) of cycloadduct **17** (eq 3) were also detected in the reaction mixture of the coupling reaction, suggesting the possibility that an incipient *N*-acyl iminium ion may be present and undergoing cycloaddition at 0 °C. This possibility suggests that the cycloaddition may be catalyzed by protonic or Lewis acids.



(3)

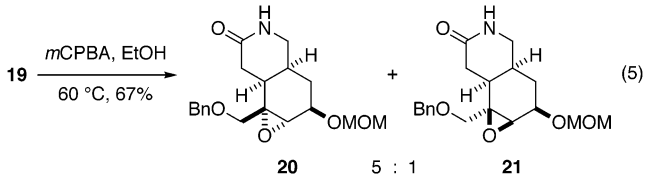
With the Diels–Alder precursor in hand, conditions to effect the key transformation were examined. Several solvents were screened which indicated chloroform as a superior solvent for both chemical yield and diastereomeric ratio. When a dilute solution (0.05 M) of precursor **16** in $CHCl_3$ was heated to 60 °C in chloroform containing 4 Å molecular sieves, two cycloadducts were isolated in 95% combined yield (eq 3). Gas chromatography indicated an 8:1 ratio of cycloadducts. An analytical sample of the major cycloadduct (**17**) could be obtained in low yield by silica gel chromatography; however, in practice the isomeric mixture was taken directly into the reduction sequence. The major cycloadduct **17** was assigned the cis-ring fusion on the basis of ^{1}H NMR ($J_{H4a-H8a}$ = 5.3 Hz) corresponding to an endo tether mode of cycloaddition. This level of diastereoselectivity is consistent with our earlier examination of substitution on the diene partner. In this study a 4-methyl-substituted precursor afforded a 9.5:1 diastereomeric ratio favoring cis-ring fusion, whereas a 6*E*-methoxy substituent provided a decreased 5:1 ratio also favoring the cis-ring junction.[8b]

Attempted elaboration of **17** to intermediate **2** required *N*-acylimidate reduction followed by functional group manipulation of the E-ring. Reduction was accomplished by a two-step sequence initiated by treatment of the diastereomeric imidates **17** and **18** with excess $NaBH_4$ in MeOH to furnish the intermediate ethoxy lactams, which were further reduced by $NaCNBH_3$ in a 9:1 mixture of EtOH/TFA to afford isoquinol-3-one **19** in 45% yield for the two steps following chromatographic separation of the trans-fused diastereomer (eq 4). With the D-ring functionality in hand, efforts were directed toward installation of the C17 methoxy group.



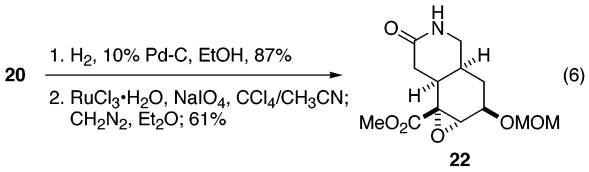
(4)

Attempted hydroboration of the trisubstituted olefin of lactam **19** employing 1 equiv of BH_3·THF provided returned starting material in addition to reduced lactam byproducts.[17] While protection of the amide nitrogen atom of **19** may have allowed for a successful hydroboration to occur, the added protection and deprotection steps detracted from our overall approach. This complication led to the introduction of the C6 oxygen atom via a two step epoxidation/epoxide fragmentation approach. This sequence was initiated by *m*-CPBA epoxidation in EtOH at 60 °C to provide a 5:1 ratio of separable epoxides in 67% yield (eq 5). Formation of α-epoxide **20** as the major isomer was confirmed by X-ray crystallography, which corroborated the stereochemical assignments. A study of solvents for this reaction revealed a diminished diastereomeric ratio (2:1) when the reaction was run in CH_2Cl_2, potentially indicating the ability of the C7 methoxymethyl group to partially direct the epoxidation to the *β*-face of the olefin. Utilization of a solvent capable of hydrogen bonding (EtOH) diminished this interaction to afford a higher ratio favoring α-epoxide **20**.



(5)

In preparation for the epoxide fragmentation reaction, conversion of the C5 benzyloxymethyl to a carbomethoxy group was undertaken (eq 6). Hydrogenolysis (10% Pd–C, EtOH, 12 h, 87%) of the benzyl protecting group followed by ruthenium-catalyzed oxidation ($RuCl_3$·H_2O, $NaIO_4$, CCl_4/CH_3CN)[18] and esterification employing ethereal diazomethane afforded ester **22** (61% yield for two steps).



(6)

Reduction of epoxy ester **22** was attempted with several mild reducing reagents including Al/Hg and Zn/AcOH in MeOH, which both resulted in recovered starting material. However, when ester **22** was treated with 2.1 equiv of sodium in liquid ammonia at −78 °C, low yields (10%) of opened epoxides **24** and **25** were isolated following a methanol quench. Lactam **24** could be exclusively isolated in low yield under identical conditions substituting solid NH_4Cl for MeOH in the quenching step. In both reactions, 50% of the starting material could be recovered. Upon increasing the amount of sodium metal in liquid ammonia at −78 °C to 4.1 equiv followed by quenching with an excess of NH_4Cl, no starting material was detected and a 50% yield of **24** was isolated (Scheme 3). The stereochemistry of the newly formed carbomethoxy was determined by examination of the coupling constants of H5 at 2.68 ppm. Coupling constants of 4.6 Hz (J_{H5-H4a}) and 10.7 Hz (J_{H5-H6}) indicate that the carbomethoxy group is equatorial. This result suggests a kinetic quench of trianion **23** from the α-face. The overall transformation of **22** to **24** entails a regioselective addition of H_2 across an epoxy C–O bond with retention of configuration, which provides the fully stereochemically elaborated DE rings of reserpine.

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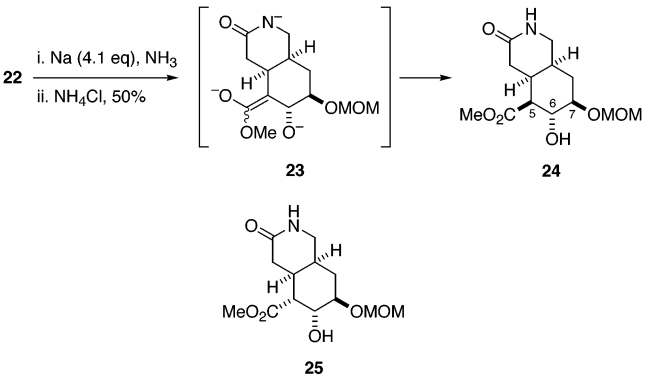
SCHEME 3



The remaining transformations to form the Woodward intermediate **2** from lactam **24** required methylation of the C6 hydroxyl group and alkylation of the amide nitrogen atom with a 6-methoxytryptophyl electrophile. Several attempts at methylating the sterically congested C6 hydroxyl resulted in partial epimerization of the C5 carbomethoxy group. Indeed, several studies have documented the difficult nature of this methylation due to the hindered nature of the hydroxyl group, which is shielded by equatorial substituents on both sides. Additionally, model efforts aimed at the alkylation of valerolactam with various 3-(2-substituted)indole electrophiles furnished 3-vinylindole as the major product via an E2 elimination pathway. The elimination pathway, endemic to substitution reactions of 3-(2-haloethyl)indoles with metalated amides,[19] could be bypassed by employing an indoline electrophile which could be subsequently oxidized to the required indole. This approach was successfully applied in our synthesis of (±)-alloyohimbane;[8c] however, the C5 carbomethoxy group present in lactam **24** precluded its application in this case due to potential epimerization.

Limited quantities of lactam **24** in addition to the problems associated with the final transformations resulted in a strategic change in our synthesis plan. Perhydroisoquinoline **3** was chosen as a second-generation target, which would allow for the refinement of our approach. Several goals including a more efficient synthesis of the 3,5-hexadienoic acid of type **6** and one-step C6 hydroxyl installation with increased diastereoselectivity were set to streamline the synthetic route.

Second Generation Approach: Synthesis of Substituted 2,4-Hexadienoic Esters. A Suzuki coupling protocol was explored for our next entry into the required 2,4-hexadienoic ester (Scheme 4).[20] Protection of alcohol **26**[21] as its methoxymethyl ether afforded vinyl iodide **27**. Suzuki coupling of known boronic ester **28**[22] with iodide **27** proceeded in the presence of $Pd(PPh_3)_4$ (3 mol %) and sodium methoxide in refluxing toluene/methanol to afford 2(*E*),4(*E*)-hexadienoic ester **29** in 75% yield.

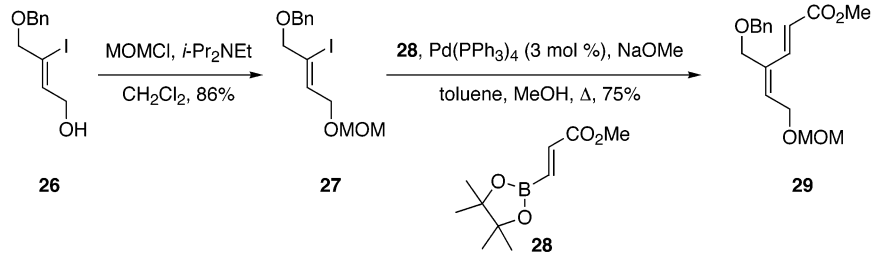
The kinetic deconjugation of dienoic ester **29** was next examined. Slow addition of diene **29** to a solution of LDA (1.2 equiv) and *N*,*N*-dimethylpropyleneurea (DMPU) in THF at −78 °C followed by an acidic quench (10% HCl) led to the formation of two inseparable isomers in a 3.6:1.0 ratio as determined by integration of the ^{1}H NMR spectrum (Scheme 5). The ^{1}H NMR spectrum of the mixture revealed the major isomer to contain the 3(*Z*),5(*E*) geometry (**30**, $J_{H5-H6} = 12.5$ Hz). Due to signal overlap in the ^{1}H NMR spectrum of the minor isomer, the mixture was saponified which revealed the minor isomer to contain the 3(*Z*),5(*Z*) geometry (**33**, $J_{H5-H6} = 7.2$ Hz). Various conditions were screened for the deconjugation of diene **29** with no improvement in the isomeric ratio.

While the isomeric mixture of acids **32** and **33** could be carried through to the key Diels−Alder cycloaddition, a more selective method for preparation of the 3(*Z*),5(*E*)-hexadienoic acid was sought. Toward this end, a modified version of the Stille coupling approach we previously explored (Scheme 2) was undertaken.[10] Palladium-catalyzed hydrostannylation[23] of alkynoate **34**[24] with tributyltin hydride (TBTH) followed by DIBALH reduction afforded vinylstannane **35** (Scheme 6). Subjecting vinylstannane **35** to the Stille conditions that were previously employed (Scheme 2) at a slightly higher temperature (65 °C) and for a longer duration (3 h) delivered conjugated ester **36** in high yield. Protection of the hydroxyl group of diene **36** as a β-trimethylsilylethoxymethoxy ether (SEM) furnished 2,4-hexadienoic ester **37** in 92% yield. The preparation of diene **37** from alkynoate **34** in four steps represents a substantial improvement over our initial route to 2(*E*),4(*Z*)-dienoic esters (Scheme 2).

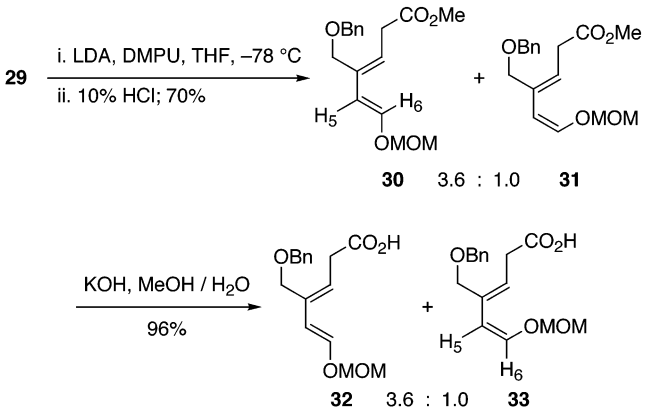
With the preparation of 2(*E*),4(*Z*)-dienoic ester **37** secured, the key deconjugation was investigated. In the event, slow addition of ester **37** to a solution of LDA and DMPU in THF at −78 °C followed by a methanolic quench afforded a single product in 89% yield (Scheme 7). Both ^{1}H NMR ($J_{H5-H6} = 12.6$ Hz) and subsequent chemical studies established that the reaction gave exclusively the 3(*Z*),5(*E*) dienoic acid ester (**38**). Saponification yielded diene acid **39** in 97% yield. With the preparation of dienoic acid **39** in six steps and 53% overall yield from alkynoate **34** accomplished, the crucial intramolecular Diels−Alder cycloaddition was examined.

Synthesis of Perhydroisoquinoline 3: A Formal Synthesis of (±)-Reserpine. The completion of the synthesis of perhydroisoquinoline **3** entailed two objectives, preparation of the Diels−Alder precursor followed

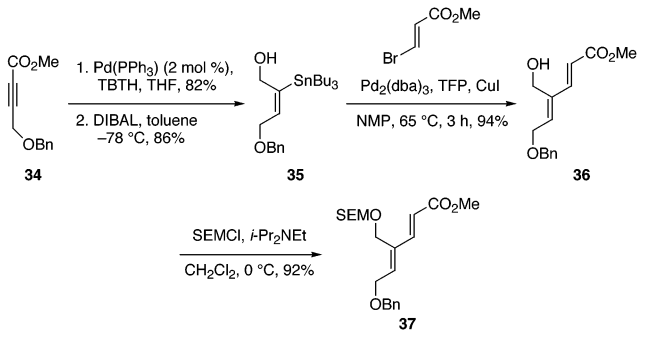
SCHEME 4



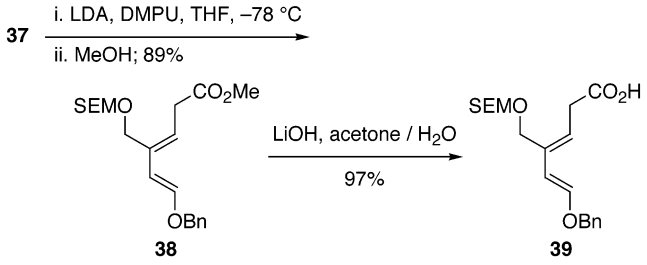
SCHEME 5



SCHEME 6



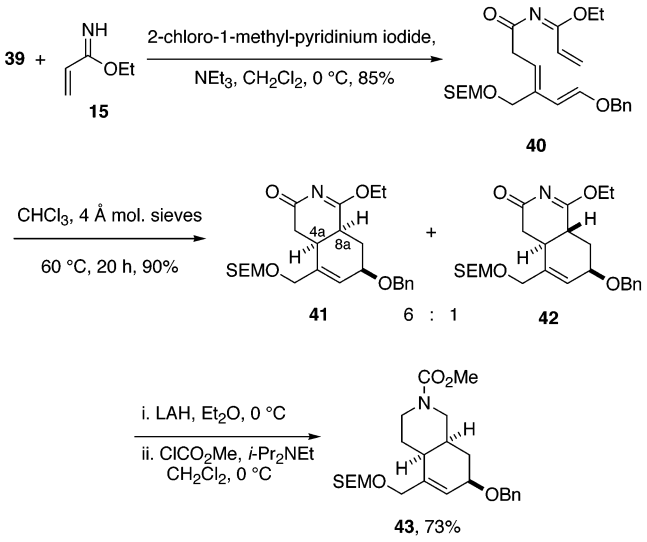
SCHEME 7



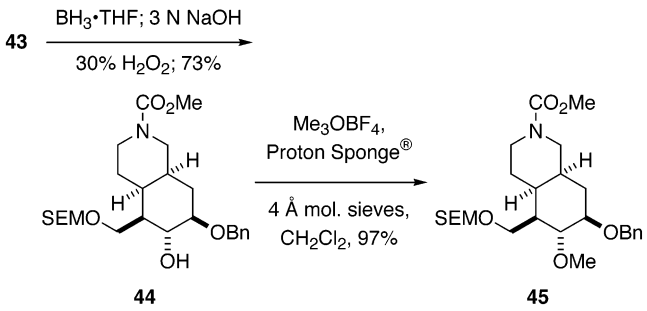
by cycloaddition and elaboration of the E-ring. These goals were accomplished in the following manner.

In analogy with our initial entry, the Diels–Alder substrate was prepared by the coupling of 1-aza-2-ethoxy-1,3-butadiene (**15**)[8b] with 3,5-hexadienoic acid **39** mediated by 2-chloro-1-methylpyridinium iodide (Scheme 8).[16] This method provided *N*-acylvinylimidate **40** in 85% isolated yield after filtration of the reaction mixture through silica gel. Cycloaddition occurred in refluxing chloroform to provide a 6:1 ratio of cycloadducts in 90% yield. The major cycloadduct, **41**, was assigned the cis-ring fusion on the basis of ^{1}H NMR ($J_{H4a-H8a}$ = 5.5 Hz), corresponding to a tether endo cycloaddition. This key

SCHEME 8



SCHEME 9



cycloaddition sets three of the five stereocenters required for the DE perhydroisoquinoline ring system in reserpine. In addition, the resulting unsaturation at C5–C6 allows for the one-step formation of the C5 and C6 stereocenters. First, however, the *N*-acylimidate functionality of the mixture of diastereomeric cycloadducts was reduced with lithium aluminum hydride and acylated with methyl chloroformate to afford methyl carbamate **43** in 73% overall yield for the two steps following chromatographic separation of the trans-fused diastereomer.

Introduction of the C6 hydroxy group was next examined. Treatment of olefin **43** with BH_3•THF complex was followed by oxidation (H_2O_2, NaOH) to afford a single alcohol (**44**) in 73% yield (Scheme 9). The stereochemistry of the newly formed alcohol was secured by ^{1}H HMR. Proton coupling constants of 10 Hz indicated a trans diaxial relationship between the protons at C5 and C7 with the C6 proton ($J_{H5-H6} = J_{H6-H7} = 10.0$ Hz). Methyl ether formation using conditions previously employed for related systems (*n*-BuLi, THF, −78 °C; MeOTf) provided a complex reaction mixture with only a low yield of the desired product (<10%).[8d,25] This problem was overcome by treatment of alcohol **44** with trimethyloxonium tetrafluoroborate (6 equiv), Proton Sponge (7 equiv), and 4 Å molecular sieves in CH_2Cl_2 to furnish methyl ether **45** in 97% yield.[26]

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(21) Rawal, V. H.; Isawa, S. *J. Org. Chem.* **1994**, *59*, 2685–2686.
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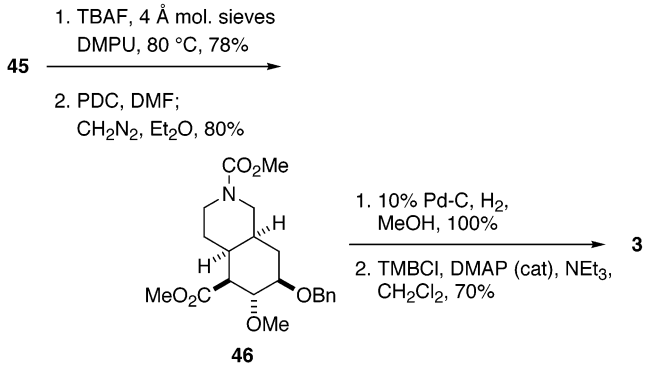
SCHEME 10



Completion of the synthesis of perhydroisoquinoline **2** required conversion of the C5 hydroxymethyl group to a methyl ester and conversion of the C7 benzyloxy group to the 3,4,5-trimethoxybenzoyl (TMB) group. This was accomplished by removal of the SEM protecting group with TBAF in DMPU containing 4 Å molecular sieves[27] followed by PDC oxidation of the resulting primary alcohol and esterification (CH_2N_2, Et_2O, 0 °C) to yield methyl ester **46** (Scheme 10). The final stage of the synthesis required installation of the 3,4,5-trimethoxybenzoyl ester, which was accomplished by hydrogenolysis (10% Pd−C, H_2, MeOH, 100%) of the benzyl protecting group followed by esterification with 3,4,5-trimethoxybenzoyl chloride (TMBCl) to provide the desired target, decahydroisoquinoline **3**. Confirmation of the stereochemistry of synthetic **3** was secured by comparison of the ^{1}H and ^{13}C NMR spectra of synthetic **3** to that recorded for natural **3** prepared from (−)-reserpine.[7d]

In conclusion, we have established that the intramolecular Diels−Alder reaction of *N*-3,5-hexadienoyl ethyl acrylimidates provides an efficient method for the preparation of cis-fused hexahydroisoquinolines. The syntheses of decahydroisoquinolone **24** and decahydroisoquinoline **3**, an intermediate that contains five of the six stereocenters of reserpine and constitutes its formal synthesis, demonstrates the utility of this reaction for the preparation of stereochemically complex perhydroisoquinoline containing natural products.

Experimental Section

General Methods. Tetrahydrofuran, diethyl ether, methylene chloride, and benzene were dried by filtration through alumina according to the procedure described by Grubbs.[28] All other solvents were distilled from drying agents (CaH_2 or Na/benzophenone) immediately prior to use. Glassware was cleaned by soaking in an alcoholic KOH solution overnight and rinsing with water; glassware was oven dried overnight. All reactions were run under a N_2 atmosphere. Volatile solvents were removed under reduced pressure using a Büchi rotary evaporator; this procedure is referred to as removing solvents in vacuo. Thin-layer chromatography was run on precoated plates of silica gel with a 0.25 mm thickness containing 60F-254 indicator (Merck). Liquid chromatography was performed using forced flow (flash chromatography) of the indicated solvent system on 230−400 mesh silica gel (E. Merck reagent silica gel 60).

Proton NMR spectra were recorded on a Bruker Avance DRX (500 MHz). The chemical shifts are reported in the δ scale in ppm with the solvent indicated as the internal reference. Coupling constants (J) are reported in Hz, and the splitting abbreviations used are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Carbon NMR are obtained using the above instrument operating at 125.8 MHz (Avance DRX) using the solvent indicated as the internal reference. Infrared spectra (FTIR) were obtained using an Analect RFX-40 FTIR spectrometer. High-resolution mass spectra (HRMS) (EI, 70 eV or CI, isobutane or ammonia) were obtained on a VG 7070E high-resolution mass spectrometer or Fisons Autospec mass spectrometer.

Methyl 6-(*tert*-butyldiphenylsiloxy)-4-hydroxymethyl-2*E*,4*Z*-hexadienoate (9). A degassed Solution of 4-*tert*-butyldiphenylsiloxy-2(*E*)-(tributylstannyl)-2-buten-1-ol (**8**, 0.5 g, 0.8 mmol) and methyl 3(*E*)-bromoacrylate (0.13 g, 0.8 mmol) in 1-methyl-2-pyrrolidinone (4 mL) was added via cannula to a degassed solution of $Pd_2(dba)_3$ (15 mg, 0.016 mmol, 2 mol %), tri-2-furylphosphine (30 mg, 0.13 mmol, 8 mol %), and CuI (0.22 g, 1.14 mmol) in 1-methyl-2-pyrrolidinone (4 mL). The solution was heated to 50 °C for 2.5 h, cooled, and then poured onto 10% aqueous KF (5 mL) and water (5 mL). The solution was stirred for 20 min and then filtered through Celite. The mixture was extracted with Et_2O (2 × 20 mL), and the organics were separated, dried ($MgSO_4$), and concentrated. The residue was chromatographed (10% to 15% EtOAc/hexane) to afford 0.26 g (79%) of diene **9** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.66 (d, J = 7.5 Hz, 4 H), 7.46−7.38 (m, 6 H), 7.24 (d, J = 15.9 Hz, 1 H), 6.12 (t, J = 6.1 Hz, 1 H), 6.06 (d, J = 15.9 Hz, 1 H), 4.20 (d, J = 6.1 Hz, 2 H), 4.17 (s, 2 H), 3.76 (s, 3 H), 1.59 (br s, 1 H), 1.05 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 167.6, 145.9, 141.0, 136.8, 135.5, 132.9, 129.9, 127.8, 118.0, 60.6, 57.4, 51.6, 26.7, 19.1; IR (NaCl film) 3444, 3062, 2948, 2844, 1713, 1620, 1310, 1108, 1031 cm^{-1}; HRMS (CI) calcd for $C_{24}H_{31}O_4Si$ (MH^+) 411.1991, obsd 411.1974.

Methyl 6-(*tert*-Butyldiphenylsiloxy)-4-(benzyloxy)methyl-2*E*,4*Z*-hexadienoate (10). To a solution of diene **9** (0.41 g, 1.0 mmol) in CH_2Cl_2 (10 mL) was added benzyl 2,2,2-trichloroacetimidate (0.28 g, 1.1 mmol) followed by triflic acid (1 drop). The reaction was stirred for 10 h, concentrated, and redissolved in EtOAc (20 mL). The reaction mixture was then washed with saturated $NaHCO_3$ (20 mL), dried ($MgSO_4$), concentrated, and chromatographed (hexane to 15% EtOAc/hexane) to afford 0.35 g (70%) of diene **10** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.66−7.63 (m, 4 H), 7.47−7.36 (m, 6 H), 7.29−7.25 (m, 4 H), 7.20−7.19 (m, 2 H), 6.24 (t, J = 6.0 Hz, 1 H), 6.04 (d, J = 15.9 Hz, 1 H), 4.39 (d, J = 6.0 Hz, 2 H), 4.33 (s, 2 H), 3.98 (s, 2 H), 3.77 (s, 3 H), 1.06 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 167.6, 146.2, 143.4, 137.6, 135.5, 133.3, 133.1, 129.8, 128.4, 127.8, 127.7, 127.7, 118.0, 72.0, 64.0, 60.8, 51.6, 26.7, 19.1; IR (NaCl film) 3064, 2939, 2855, 1718, 1619, 1311, 1107 cm^{-1}; HRMS (CI) calcd for $C_{31}H_{37}O_4Si$ (MH^+) 501.2461, found 501.2468.

Methyl 4-Benzyloxymethyl-6-hydroxy-2*E*,4*Z*-hexadienoate (11). HF·pyridine (2 mL) was added to a solution of diene **10** (0.65 g, 1.30 mmol) in THF (12 mL) in a polyethylene bottle. The solution was stirred 2 h, and then saturated $NaHCO_3$ was added slowly until bubbling ceased. The layers were separated, and the aqueous layer was extracted with Et_2O (20 mL). The combined organic layers were combined and washed with brine (10 mL), dried ($MgSO_4$), concentrated, and chromatographed (30% EtOAc/hexane) to afford 0.17 g (50%) of diene **11** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.37−7.29 (m, 5 H), 7.28 (d, J = 15.9 Hz, 1 H), 6.23 (t, J = 6.5 Hz, 1 H), 6.04 (d, J = 15.9 Hz, 1 H), 4.51 (s, 2 H), 4.30 (d, J = 6.5 Hz, 2 H), 4.21 (s, 2 H), 3.76 (s, 3 H), 2.80 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 167.5, 146.0, 142.2, 137.4, 134.8, 128.6, 128.0, 127.9, 118.3, 72.6, 64.2, 59.2, 51.6; IR (NaCl film) 3429, 3033, 2949, 2855, 1713, 1619, 1306, 1170, 1071 cm^{-1}; HRMS (CI) calcd for $C_{15}H_{19}O_4$ (MH^+) 263.1283, obsd 263.1276.

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Methyl 6-(Methoxymethoxy)-4-benzyloxymethyl-2*E*,4*Z*-hexadienoate (12). MOMCl (0.08 g, 0.97 mmol) was added to a solution of alcohol **11** (0.17 g, 0.65 mmol) and *i*-Pr_2NEt (0.15 g, 0.97 mmol) in CH_2Cl_2 (6 mL). The solution was stirred for 12 h and then concentrated and redissolved in EtOAc (10 mL). The reaction mixture was washed with saturated $NaHCO_3$ (10 mL), dried ($MgSO_4$), concentrated, and chromatographed (30% EtOAc/hexane) to give 0.15 g (76%) of diene **12** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.37−7.29 (m, 5 H), 7.28 (d, J = 16.0 Hz, 1 H), 6.18 (t, J = 6.4 Hz, 1 H), 6.10 (d, J = 15.9 Hz, 1 H), 4.61 (s, 2 H), 4.49 (s, 2 H), 4.25 (d, J = 6.4 Hz, 2 H), 4.20 (s, 2 H), 3.75 (s, 3 H), 3.35 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 167.5, 145.8, 139.7, 137.7, 135.2, 128.5, 127.9, 118.6, 96.0, 72.3, 64.1, 63.6, 55.4, 51.6; IR (NaCl film) 3033, 2949, 2876, 1708, 1624, 1306, 1170, 1107, 1040 cm^{-1}; HRMS (CI) calcd for $C_{17}H_{23}O_5$ (MH^+) 307.1545, obsd 307.1552.

4-(Benzyloxy)methyl-6-(methoxymethoxy)-3(*E*),5(*E*)-hexadienoic Acid (14). To a solution of lithium diisopropyl amide (84.7 mmol) in THF (190 mL) at −78 °C was added HMPA (12.7 mL, 72.8 mmol), and the solution was stirred for 30 min. Ester **12** (23.3 g, 72.8 mmol) dissolved in THF (80 mL) was added dropwise over 1.5 h, maintaining the temperature below −72 °C. The mixture was stirred for 2 h and poured onto 10% HCl (160 mL). The organic layer was separated and washed with saturated $NaHCO_3$ (150 mL), H_2O (150 mL), and brine (150 mL). The solvent was dried ($MgSO_4$) and concentrated in vacuo. (An analytical sample was purified by chromatography on silica gel eluting with hexanes/EtOAc (4:1) to provide diene **13** as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36−7.29 (m, 5 H), 6.74 (d, J = 12.0 Hz, 1 H), 5.79 (d, J = 12.0 Hz, 1 H), 5.67 (t, J = 6.0 Hz, 1 H), 4.83 (s, 2 H), 4.48 (s, 2 H), 4.16 (s, 2 H), 4.13 (q, J = 7.0 Hz, 2 H), 3.40 (s, 3 H), 3.15 (d, J = 6.0 Hz, 2 H), 1.26 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 171.4, 145.4, 138.0, 134.3, 128.3, 127.9, 127.6, 122.1, 111.4, 95.9, 71.6, 64.6, 60.7, 55.8, 33.6, 14.1; IR (NaCl film) 2956, 2935, 2898, 1733, 1654 cm^{-1}.) The resulting yellow oil was dissolved in MeOH (250 mL) and was added to a stirred solution of KOH (6.5 g, 0.101 mol) in H_2O (250 mL) at 0 °C. The mixture was stirred for 4 h during which time the solution became homogeneous. The solvent was reduced to 250 mL in vacuo and washed with Et_2O (100 mL). The aqueous phase was acidified to pH = 3 with 10% HCl and extracted with ether (5 × 100 mL). The extracts were dried ($MgSO_4$) and concentrated to afford 13.7 g (70%) of acid **14** as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36−7.29 (m, 5 H), 6.69 (d, J = 12.0 Hz, 1 H), 5.76 (d, J = 12.0 Hz, 1 H), 5.63 (t, J = 6.0 Hz, 1 H), 4.82 (s, 2 H), 4.50 (s, 2 H), 4.13 (s, 2 H), 3.39 (s, 2 H), 3.18 (d, J = 6.0 Hz, 2 H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 175.7, 145.6, 137.6, 135.1, 128.5, 128.3, 121.3, 111.4, 96.0, 72.0, 64.7, 55.9, 33.6; IR (NaCl film) 3500−3200, 2954, 2900, 1656, cm^{-1}; HRMS (CI) calcd for $C_{16}H_{20}O_5$ (M^+) 292.1311, obsd 292.1309.

***N*-(4-(Benzyloxy)methyl-6-(methoxymethoxy)-3(*E*),5-(*E*)-hexadienoyl)-2-ethoxy-1-aza-1,3-butadiene (16).** A solution of acid **14** (13.0 g, 44.7 mmol), imidate **15** (4.43 g, 44.7 mmol), and NEt_3 (15.0 mL, 107.6 mmol) in CH_2Cl_2 (150 mL) was added dropwise over 30 min to a suspension of 2-chloro-1-methylpyridinium iodide (13.7 g, 53.7 mmol) in CH_2Cl_2 (250 mL) at 0 °C. The solution was stirred 4 h at 0 °C and then concentrated to one-quarter of the original volume and filtered through a pad of SiO_2 eluting with 30% EtOAc/hexane. The filtrate was concentrated in vacuo to afford 13.9 g (83%) of imidate **16** as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35−7.30 (m, 5 H), 6.73 (d, J = 12.3 Hz, 1 H), 6.15 (dd, J = 16.8, 2.4 Hz, 1 H), 6.06 (dd, J = 17.1, 9.6 Hz, 1 H), 5.79 (d, J = 12.6 Hz, 1 H), 5.69 (t, J = 7.8 Hz, 1 H), 5.66 (dd, J = 9.6, 2.4 Hz, 1 H), 4.83 (s, 2 H), 4.47 (s, 2 H), 4.15 (q, J = 7.2 Hz, 2 H), 3.40 (s, 3 H), 3.28 (d, J = 7.5 Hz, 2 H), 1.33 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 183.1, 156.2, 145.3, 138.0, 134.3, 128.3, 127.9, 127.6, 127.4, 125.5, 122.3, 111.6, 95.9, 71.6, 64.8, 62.7, 55.8, 38.5, 13.8; IR (NaCl film) 2933, 2898, 1702, 1656, 1587 cm^{-1}; HRMS (CI) calcd for $C_{21}H_{28}NO_5$ (MH^+) 374.1960, obsd 374.1939.

(4a*S,7*R**,8a*S**)-5-Benzyloxymethyl-1-ethoxy-7-(methoxymethoxy)-3,4,4a,7,8,8a-hexahydroisoquinol-3-one (17).** A solution of vinylimidate **16** (13.9 g, 37.7 mmol) in $CHCl_3$ (700 mL) containing 4 Å molecular sieves was heated to reflux for 6 days. The solution was cooled, filtered through Celite, and concentrated in vacuo to afford 13.2 g (95%) of an 8:1 mixture of diastereomeric cycloadducts **17** and **18** as a yellow oil. An analytical sample was purified in low yield by chromatography on silica gel eluting with hexanes/EtOAc (2:1). **17**: ^{1}H NMR (500 MHz, $CDCl_3$) 7.36−7.28 (m, 5 H), 5.83 (br s, 1 H), 4.73 (d, J = 6.9 Hz, 1 H), 4.70 (d, J = 6.9 Hz, 1 H), 4.50 (d, J = 11.9 Hz, 1 H), 4.47 (d, J = 11.9 Hz, 1 H), 4.40−4.38 (m, 2 H), 4.33 (m, 1 H), 4.04 (d, J = 12.0 Hz,1 H), 3.89 (d, J = 12.0 Hz, 1 H), 3.39 (s, 3 H), 2.85−2.74 (m, 2 H), 2.68 (ddd, J = 11.5, 6.1, 5.3 Hz, 1 H), 2.35 (dd, J = 14.1, 11.6 Hz, 1 H), 2.30 (ddd, J = 12.4, 8.1, 5.9 Hz, 1 H), 1.74 (ddd, J = 12.6, 9.6, 7.1 Hz, 1 H), 1.37 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 182.3, 181.8, 138.1, 137.7, 128.2, 127.8, 127.8, 127.7, 95.4, 72.6, 71.7, 71.4, 64.2, 55.5, 35.6, 34.3, 31.5, 28.4, 14.0; IR (NaCl film) 2962, 2931, 2888, 1706, 1587 cm^{-1}; HRMS (CI) calcd for $C_{21}H_{28}NO_5$ (MH^+) 374.1960, obsd 374.1968.

(4a*S,7*R**,8a*S**)-5-Benzyloxymethyl-1-ethoxy-7-(methoxymethoxy)-1,2,3,4,4a,7,8,8a-octahydroisoquinol-3-one.** Sodium borohydride (6.60 g, 174.5 mmol) was added in two portions to a solution of imidate cycloadducts **17** and **18** (13.2 g, 35.4 mmol) in MeOH (170 mL) at 0 °C. The reaction was stirred at 0 °C for 1 h and then concentrated to one-half the original volume and diluted with CH_2Cl_2 (200 mL). The organic phase was washed with saturated $NaHCO_3$ (100 mL), H_2O (100 mL), and brine (100 mL) and dried ($MgSO_4$). The solvent was filtered through Florisil and concentrated in vacuo to give 9.3 g (70%) of ethoxy lactam as an oil. An analytical sample was purified with loss of ca. 30% of the material by chromatography on silica gel eluting with EtOAc: ^{1}H NMR (500 MHz, $CDCl_3$) 7.38−7.28 (m, 5 H), 6.18 (br s, 1 H), 5.70 (s, 1 H), 4.75 (d, J = 7.0 Hz, 1 H), 4.74 (d, J = 5.3 Hz, 1 H), 4.70 (d, J = 7.0 Hz, 1 H), 4.49 (d, J = 12.0 Hz, 1 H), 4.46 (d, J = 12.0 Hz, 1 H), 4.29 (br dd, J = 8.5, 7.6 Hz, 1 H), 4.00 (d, J = 12.1 Hz, 1 H), 3.87 (d, J = 12.1 Hz, 1 H), 3.63 (m, 1 H), 3.52 (m, 1 H), 3.39 (s, 2 H), 2.63−2.56 (m, 2 H), 2.30−2.19 (m, 3 H), 1.47 (ddd, J = 16.2, 13.1, 10.2 Hz, 1 H), 1.24 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 171.0, 140.4, 137.9, 128.5, 127.8, 127.7, 127.0, 95.1, 84.5, 72.6, 72.5, 71.8, 64.3, 55.4, 35.2, 30.3, 22.9, 15.3; IR (NaCl film) 3207, 2975, 2931, 1664, 1469 cm^{-1}; HRMS (CI) calcd for $C_{21}H_{29}NO_5$ (M^+) 376.2124, obsd 376.2022; calcd for $C_{19}H_{23}NO_4$ ($M - CH_3CH_2OH^+$) 330.1705, obsd 330.1699.

(4a*S,7*R**,8a*R**)-5-Benzyloxymethyl-7-(methoxymethoxy)-1,2,3,4,4a,7,8,8a-octahydroisoquinol-3-one (19).** Soduim cyanoborohydride (2.76 g, 43.95 mmol) was added in one portion to a solution of ethoxy lactam (5.50 g, 14.65 mmol) in EtOH (65 mL) at ambient temperature. The solution was stirred for 30 min and then cooled to 0 °C. Trifluoroacetic acid (6.5 mL) was added dropwise over 15 min, and the resulting solution was stirred for 5 h. The mixture was then concentrated in vacuo and redissolved in $CHCl_3$ (200 mL). Saturated $NaHCO_3$ (50 mL) was added to the stirring mixture over 15 min, the layers were then separated, and the aqueous phase was extracted with $CHCl_3$ (3 × 50 mL). The combined extracts were dried ($MgSO_4$), concentrated in vacuo, and purified by chromatography on silica gel eluting with CH_2Cl_2/2-propanol (10:1) to afford 3.16 g (65%) of lactam **19** as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36−7.26 (m, 5 H), 6.38 (br s, 1 H), 5.71 (s, 1 H), 4.72 (d, J = 7.0 Hz, 1 H), 4.70 (d, J = 7.0 Hz, 1 H), 4.51 (d, J = 12.0 Hz, 1 H), 4.46 (d, J = 12.0 Hz, 1 H), 4.32 (dd, J = 8.0, 7.5 Hz, 1 H), 4.02 (d, J = 12.0 Hz, 1 H), 3.88 (d, J = 12.0 Hz, 1 H), 3.55 (dd, J = 12.5, 5.0 Hz, 1 H), 3.16 (dt, J = 11.5, 3.5 Hz, 1 H), 2.66 (dd, J = 20.0, 7.0 Hz, 1 H), 2.64 (m, 1 H), 2.25 (dd, J = 20.0, 12.0 Hz, 1 H), 2.06 (dd, J = 13.5, 2.0 Hz, 1 H), 1.96 (dd, J = 12.0, 4.5 Hz, 1 H), 1.81 (ddd, J = 13.0,

9.5, 9.2 Hz, 1 H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 171.4, 140.9, 137.9, 128.8, 128.4, 127.7, 126.2, 95.5, 72.9, 72.5, 71.7, 55.4, 46.4, 33.9, 31.8, 30.2, 29.9; IR (NaCl film) 3224, 2935, 2884, 1664, 1494 cm^{-1}; HRMS (CI) calcd for $C_{19}H_{26}NO_4$ (MH^+) 332.1855, obsd 332.1869.

(4a*S,5*R**,6*S**,7*R**,8a*R**)-5-Benzyloxymethyl-7-(methoxymethoxy)decahydroisoquinol-3-one-5,6-oxirane (20) and (4a*S**,5*S**,6*R**,7*R**,8a*R**)-5-Benzyloxymethyl-7-(methoxymethoxy)decahydroisoquinol-3-one-5,6-oxirane (21).** Lactam **19** (1.02 g, 3.08 mmol) was dissolved in EtOH (15 mL), and 85% *m*-CPBA (2.5 g, 12.3 mmol) was added in one portion. The reaction was heated to reflux for 48 h and cooled. The solvent was concentrated in vacuo. The resulting solid was redissolved in CH_2Cl_2 (75 mL) and washed with sodium bisulfite (40 mL), saturated $NaHCO_3$ (2 × 40 mL), H_2O (40 mL), and brine (40 mL). The organic layer was dried ($MgSO_4$) and concentrated to give 0.71 g (67%) of epoxides **20** and **21** as an oil in a 5:1 ratio as determined by ^{1}H NMR. Purification by chromatography on silica gel eluting with CH_2Cl_2/2-propanol (10:1) afforded 0.55 g of major epoxide **20** as a colorless oil. The oil was triturated with Et_2O and recrystallized with Et_2O/CH_2Cl_2 to furnish X-ray quality crystals. **20**: mp 118−119 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38−7.28 (m, 5 H), 6.35 (br s, 1 H), 4.73 (d, J = 12.0 Hz, 1 H), 4.59 (d, J = 11.9 Hz, 1 H), 4.50 (d, J = 11.9 Hz, 1 H), 4.05 (dd, J = 9.4, 7.8 Hz, 1 H), 3.90 (d, J = 11.5 Hz, 1 H), 3.48 (dd, J = 12.4, 4.4 Hz, 1 H), 3.38 (s, 3 H); 3.19 (d, J = 11.5 Hz, 1 H), 3.09 (ddd, J = 12.4, 4.2, 1.5 Hz, 1 H), 3.02 (s, 1 H), 2.78 (ddd, J = 9.0, 7.0, 4.0 Hz, 1 H), 2.62 (dd, J = 18.0, 6.7 Hz, 1 H), 2.35 (dd, J = 18.0, 12.1 Hz, 1 H), 2.01 (m, 1 H), 1.77 (ddd, J = 13.4, 7.5, 2.4 Hz, 1 H), 1.57 (ddd, J = 14.1, 12.7, 9.5 Hz); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 170.1, 137.5, 128.3, 127.7, 127.6, 95.6, 73.4, 70.8, 70.4, 63.4, 57.0, 55.5, 46.4, 31.2, 30.1, 27.9, 24.0; IR (NaCl film) 3299, 3029, 2944, 1666 cm^{-1}; HRMS (CI) calcd for $C_{19}H_{26}NO_5$ (MH^+) 348.1811, obsd 348.1793. Anal. Calcd for $C_{19}H_{25}NO_5$: C, 65.69; H, 7.25; N, 4.03. Found: C, 65.72; H 7.23; N 4.00. **21**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39−7.30 (m, 5 H), 6.28 (br s, 1 H), 4.75 (s, 2 H), 4.56 (d, J = 11.9 Hz, 1 H), 4.50 (d, J = 12.2 Hz, 1 H), 4.00 (ddd, J = 10.5, 5.6, 1.6 Hz, 1 H), 3.53 (d, J = 10.8 Hz, 1 H), 3.46 (ddd, J = 12.7, 5.6, 1.5 Hz, 1 H) 3.41 (s, 3 H), 3.38 (d, J = 10.8 Hz, 1 H), 3.32 (s, 1 H), 3.03 (dt, J = 12.7, 3.4 Hz, 1 H), 2.64 (dd, J = 15.3, 9.6 Hz, 1 H), 2.55 (m, 1 H), 2.51 (dd, J = 15.6, 5.9 Hz, 1 H), 1.79 (m, 1 H), 1.68 (ddd, J = 13.9, 10.9, 10.2 Hz, 1 H), 1.55 (ddd, J = 13.9, 5.6, 2.5 Hz, 1 H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 172.6, 137.5, 128.4, 127.8, 127.7, 95.4, 73.9, 73.5, 72.8, 63.4, 59.8, 55.4, 45.5, 30.3, 29.7, 29.0, 26.7; IR (NaCl film) 3212, 2938, 2888, 1666,1496 cm^{-1}; LRMS (CI) *m*/*z* (relative intensity) 348 (MH^+, 100), 332 (8), 302 (8), 107 (38).

(4a*S,5*R**,6*S**,7*R**,8a*R**)-5-Hydroxymethyl-7-(methoxymethoxy)decahydroisoquinol-3-one-5,6-oxirane.** Epoxide **20** (1.39 g, 4.00 mmol) was dissolved in EtOH (25 mL), and 10% Pd/C (42.5 mg, 0.40 mmol Pd) was carefully added in one portion. The flask was evacuated, and an atmosphere of H_2 was introduced (1 atm). The reaction was stirred for 12 h and then filtered through Celite. The solvent was concentrated in vacuo to afford 0.89 g (87%) of debenzylated epoxide as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.18 (br s, 1 H), 4.73 (d, J = 5.5 Hz, 1 H), 4.70 (d, J = 5.5 Hz, 1 H), 4.06 (dd, J = 9.1, 8.7 Hz, 1 H) 3.89 (dd, J = 12.0, 2.5 Hz, 1 H) 3.55 (dd, J = 12.0, 4.3 Hz, 1 H) 3.50 (dd, J = 12.0, 4.3 Hz, 1 H), 3.39 (s, 3 H), 3.21 (br s, 1 H), 3.15 (ddd, J = 12.6, 4.2, 2.4 Hz, 1 H), 2.65 (ddd, J = 10.8, 4.7, 4.1 Hz, 1 H) 2.61 (dd, J = 17.5, 6.8 Hz, 1 H), 2.36 (dd, J = 17.5, 10.9 Hz, 1 H), 2.12 (m, 1 H), 2.04 (br d, J = 12.0 Hz, 1 H), 1.81 (m, 1 H), 1.59 (ddd, J = 14.0, 12.5, 9.5 Hz, 1 H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 169.9, 95.6, 70.3, 64.4, 62.2, 57.7, 55.6, 46.4, 31.3, 29.9, 27.9, 24.0; IR (NaCl film) 3309, 2931, 1654 cm^{-1}; HRMS (CI) calcd for $C_{12}H_{20}NO_5$ (MH^+) 258.1342, obsd 258.1355.

(4a*S,5*R**,6*S**,7*R**,8a*R**)-5-Methoxycarbonyl-7-(methoxymethoxy)decahydroisoquinol-3-one-5,6-oxirane (22).** Sodium periodate (0.34 g, 1.61 mmol) was added to a solution of epoxy alcohol (0.10 g, 0.40 mmol) in a mixture of CCl_4 (1 mL), CH_3CN (1 mL), and H_2O (1 mL). $RuCl_3 \cdot H_2O$ (1.8 mg, 0.009 mmol) was added, and the reaction was vigorously stirred for 2 h. The mixture was then diluted with CH_2Cl_2 (20 mL), and H_2O (20 mL) was added. The layers were separated, and the organic layer was filtered through Celite and recombined with the aqueous layer. The solvents were removed in vacuo, and the resulting solid was dissolved in boiling EtOH (20 mL). The solution was filtered, and the solvent was concentrated in vacuo. The residue was dissolved in THF (5 mL) and treated with excess ethereal diazomethane for 1 h. The solvent was concentrated, and the resulting oil was purified by chromatography on silica gel eluting with EtOAc/EtOH (10:1) to afford 66 mg (61%) of ester **22** as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.45 (br s, 1 H), 4.77 (d, J = 6.9 Hz, 1 H), 4.74 (d, J = 6.9 Hz, 1 H), 4.12 (t, J = 8.5 Hz, 1 H), 3.79 (s, 3 H), 3.67 (s, 1 H), 3.52 (dd, J = 12.5, 4.3 Hz, 1 H), 3.43 (s, 3 H), 3.12 (ddd, J = 12.5, 4.3, 1.8 Hz, 1 H), 2.99 (dd, J = 18.2, 6.7 Hz, 1 H), 2.90 (ddd, J = 11.4, 6.9, 4.6 Hz, 1 H), 2.38 (dd, J = 18.2, 11.5 Hz, 1 H), 2.08 (m, 1 H), 1.84 (ddd, J = 14.0, 8.2, 3.2 Hz, 1 H), 1.65 (ddd, J = 13.8, 11.7, 8.9 Hz, 1 H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 170.1, 168.7, 95.7, 69.6, 61.0, 59.1, 55.7, 52.8, 46.2, 31.4, 30.6, 27.2, 24.2; IR (NaCl film) 3201, 2954, 2896, 1735, 1664 cm^{-1}; HRMS (CI) calcd for $C_{13}H_{20}NO_6$ (MH^+) 286.1289, obsd 286.1292.

(4a*S,5*S**,6*R**,7*R**,8a*R**)-5-Methoxycarbonyl-6-hydroxy-7-(methoxymethoxy)-decahydroisoquinol-3-one (24).** Epoxide **22** (0.11 g, 0.39 mmol) dissolved in THF (5 mL) was stirred in a flask equipped with a low-temperature thermometer, N_2 inlet, and Dewar condenser. The reaction was cooled to −78 °C, and dry ice/acetone was placed in the condenser. Gaseous ammonia (ca. 30 mL) was condensed in the flask at −78 °C and stirred for 5 min. Sodium metal (37 mg, 1.61 mmol) was added in one portion, and the reaction was stirred for 1 h until the faint blue color disappeared. Solid ammonium chloride (0.5 g, 9.3 mmol) was added in one portion at −78 °C and stirred for 15 min. The cooling bath and condenser were removed, and the liquid ammonia was evaporated. THF (30 mL) was added to the residue with stirring to break up the resulting solid. The solution was filtered, and the solids were washed with THF (3 × 20 mL). The filtrate and washings were combined, and the solvent was concentrated in vacuo to afford 92 mg of a slightly colored oil. The oil was purified by chromatography on silica gel eluting with CH_2Cl_2/2-propanol (4:1) to afford 56 mg (50%) of lactam **24** as a white foam: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.92 (br s, 1 H), 4.80 (m, 2 H), 4.02 (dd, J = 10.5, 9.5 Hz, 1 H), 3.77 (s, 3 H), 3.59 (dd, J = 12.4, 4.7 Hz, 1 H), 3.49 (ddd, J = 11.4, 9.0, 5.2 Hz, 1 H), 3.46 (s, 3 H), 3.18 (ddd. J = 12.4, 4.1, 1.3 Hz, 1 H), 2.68 (dd, J = 10.7, 4.6 Hz, 1 H), 2.62 (m, 1 H), 2.43 (dd, J = 18.7, 12.2 Hz, 1 H), 2.30 (dd, J = 18.3, 6.8 Hz, 1 H), 2.08 (m, 1 H), 1.92 (dt, J = 13.3, 3.9 Hz, 1 H), 1.84 (m, 1 H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 171.9, 170.1, 97.0, 82.0, 69.5, 55.8, 52.2, 51.1, 46.2, 33.6, 31.9, 30.0, 29.4; IR (NaCl film) 3349, 2931, 1737, 1658 cm^{-1}; HRMS (CI) calcd for $C_{13}H_{22}NO_6$ (MH^+) 288.1447, obsd 288.1452.

4-Benzyloxy-3-iodobut-2(*Z*)-en-1-ol (26). To a stirring solution of 4-benzyloxy-2-butyn-1-ol (1.0 g, 5.67 mmol) in Et_2O (20 mL) at 0 °C was added Red-Al (4.4 mL, 3.2 M in toluene) dropwise. The solution was warmed to room temperature and stirred for 12 h. The solution was then cooled to 0 °C and EtOAc (0.5 g, 0.55 mL, 5.67 mmol) was added dropwise and stirred 10 min. The solution was then cooled to −78 °C and iodine (2.16 g, 8.51 mmol) was added in one portion. The solution was stirred at −78 °C for 40 min and then warmed to room temperature and stirred 2 h. The reaction mixture was poured onto saturated $Na_2S_2O_3$ (30 mL) and extracted with EtOAc (2 × 80 mL). The extracts were washed with brine (50 mL), dried ($MgSO_4$), concentrated, and chromatographed (15% EtOAc/Hexane) to afford 2.04 g (66%) of 4-benzyloxy-3-iodo-2(*Z*)-buten-1-ol (**26**) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.37−7.29 (m, 5 H), 6.27 (t, J = 5.7 Hz, 1 H), 4.53 (s, 2 H), 4.28 (d, J = 5.7 Hz, 2 H), 4.18 (s, 2 H), 1.61 (s, 1 H); ^{13}C NMR

($CDCl_3$) δ 137.5, 135.9, 128.5, 127.9, 127.9, 104.6, 77.5, 71.8, 66.6; IR (NaCl film) 3396, 3032, 2918, 2861, 1639, 1451, 1354, 1089 cm^{-1}; HRMS (CI) calcd for $C_{11}H_{12}IO_2$ ($M - H^+$) 302.9883, obsd 302.9881.

(*Z*)-1-Benzyloxy-2-iodo-4-methoxymethoxy-2-butene (27). To a solution of 4-benzyloxy-3-iodo-2(*Z*)-buten-1-ol (1.99 g, 6.53 mmol) in CH_2Cl_2 (60 mL) was added *i*-Pr_2NEt (2.11 g, 2.8 mL, 16.35 mmol) followed by chloromethyl methyl ether (1.05 g, 1.0 mL, 13.07 mmol). The solution was stirred 12 h, poured onto saturated $NaHCO_3$ (50 mL), and separated. The organics were washed with brine (50 mL), dried ($MgSO_4$), concentrated, and chromatographed (5% EtOAc/hexane) to afford 1.95 g (86%) of iodide **27** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.37−7.28 (m, 5 H), 6.26 (tt, J = 5.4, 1.2 Hz, 1 H), 4.66 (s, 2 H), 4.53 (s, 2 H), 4.22−4.19 (m, 4 H), 3.39 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 137.6, 133.8, 128.4, 127.9, 127.8, 105.0, 96.2, 77.6, 71.8, 71.1, 55.4; IR (NaCl film) 3030, 2929, 2872, 1650, 1451, 1103, 1041 cm^{-1}; HRMS (CI) calcd for $C_{13}H_{17}IO_3$ (M^+) 348.0224, obsd 348.0220.

Methyl 6-(Methoxymethoxy)-4-(benzyloxy)methyl-2*E*,4*E*-hexadienoate (29). To a stirred solution of iodide **27** (0.2 g, 0.57 mmol) and $Pd(PPh_3)_4$ (33 mg, 0.02 mmol) in toluene (2 mL) was added boronic ester **28** (0.18 g, 0.86 mmol) dissolved in toluene (1 mL) followed by 0.5 M NaOMe in MeOH (1.37 mL). The solution was heated to reflux for 13 h, cooled, and poured onto saturated NH_4Cl (10 mL). The mixture was extracted with EtOAc (2 × 10 mL), and the organics were dried ($MgSO_4$), concentrated, and chromatographed (10% to 20% EtOAc/hexane) to afford 0.12 g (69%) of diene **29** as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 7.58 (d, J = 16.0 Hz, 1 H), 7.37−7.27 (m, 5 H), 6.13 (t, J = 6.5 Hz, 1 H), 6.10 (d, J = 16.1 Hz, 1 H), 4.66 (s, 2 H), 4.52 (s, 2 H), 4.37 (d, J = 6.5 Hz, 2 H), 4.18 (s, 2 H), 3.76 (s, 3 H), 3.39 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 167.4, 137.9, 137.8, 135.3, 133.9, 128.4, 127.8, 120.1, 96.1, 72.3, 70.9, 63.0, 55.4, 51.7, the lack of 15 carbon signals indicates two signals are overlapping; IR (NaCl film) 2952, 2884, 1713, 1616, 1280, 1172, 1041 cm^{-1}; HRMS (CI) calcd for $C_{17}H_{22}O_5$ (M^+) 306.1467, obsd 306.1469.

Methyl 4-Benzyloxy-2-butynoate (34). To a stirred solution of 3-benzyloxy-1-propyne (12.9 g, 88 mmol) in THF (300 mL) at −78 °C was added *n*-BuLi (11.0 mL, 97 mmol, 8.8 M) dropwise. After addition was complete, the reaction was stirred 30 min at −78 °C and then warmed to −20 °C for 20 min. The solution was cooled back to −78 °C, and methyl chloroformate (10.8 g, 8.86 mL, 115 mmol) was added in one portion. The reaction was stirred at −78 °C for 30 min and then warmed to room temperature. The reaction mixture was then poured onto saturated NH_4Cl (200 mL) and extracted with EtOAc (2 × 200 mL). The extracts were washed with brine (50 mL), dried ($MgSO_4$), concentrated, and chromatographed (5% EtOAc/hexane) to afford 15.0 g (83%) of methyl 4-benzyloxy-2-butynoate (**34**) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.37−7.29 (m, 5 H), 4.62 (s, 2 H), 4.29 (s, 2 H), 3.80 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 153.5, 136.7, 128.5, 128.1, 83.6, 77.9, 72.0, 56.7, 52.8; the absence of one carbon signal indicates two signals are overlapping; IR (NaCl film) 3032, 2955, 2861, 2236, 1720, 1433, 1261, 1060 cm^{-1}.

Methyl (*E*)-4-Benzyloxy-2-tributylstannyl-2-butenoate. To a solution of alkynoate **34** (2.0 g, 9.8 mmol) and $Pd(PPh_3)_4$ (0.22 g, 0.2 mmol) in THF (28 mL) was added Bu_3SnH (2.85 g, 2.63 mL, 9.8 mmol) dropwise. The reaction was stirred for 30 min, concentrated, diluted with hexane (20 mL), filtered through Celite, concentrated, and chromatographed (10% EtOAc/hexane) to give 3.97 g (82%) of methyl (*E*)-4-benzyloxy-2-tributylstannyl-2-butenoate as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.37−7.27 (m, 5 H), 6.31 (t, J = 4.9 Hz, $J(^{119}Sn-H)$ = 29.7 Hz, 1 H), 4.53 (s, 2 H), 4.45 (d, J = 4.9 Hz, 2 H), 3.66 (s, 3 H), 1.53−1.44 (m, 6 H), 1.30 (septet, J = 7.4 Hz, 6 H), 1.02−0.90 (m, 6 H), 0.88 (t, J = 7.3 Hz, 9 H); ^{13}C NMR ($CDCl_3$) δ 170.8, 152.2, 138.1, 136.5, 128.4, 127.9, 127.7, 72.7, 70.4, 51.4, 28.9, 27.2, 13.6, 10.2; IR (NaCl film) 2955, 2853, 1707, 1608, 1450, 1201, 1086 cm^{-1}; HRMS (CI) calcd for $C_{20}H_{31}O_3Sn$ ($M - Bu^+$) 439.1299, obsd 439.1303.

4-Benzyloxy-2(*E*)-tributylstannyl-but-2-en-1-ol (35). To a solution of methyl (*E*)-4-benzyloxy-2-tributylstannyl-2-butenoate (1.0 g, 2.0 mmol) in toluene (10 mL) at −78 °C was added Dibal-H (2.8 mL of a 1.5 M solution, 4.14 mmol) dropwise. After 90 min at −78 °C, the reaction was warmed to room temperature and quenched with saturated sodium potassium tartrate (20 mL). The aqueous layer was extracted with EtOAc (2 × 20 mL), and the extracts were dried ($MgSO_4$), concentrated, and chromatographed (10% EtOAc/Hexane) to afford 0.8 g (86%) of stannane **35** as a colorless oil: ^{1}H NMR ($CDCl_3$) 7.37−7.27 (m, 5 H), 5.78 (tt, J = 5.8, 2.0 Hz, $J^{119}Sn-H$ = 33.6 Hz, 1 H), 4.52 (s, 2 H), 4.33 (d, J = 2.0 Hz, 2 H), 4.06 (d, 5.7 Hz, 2 H), 1.69 (t, J = 5.0 Hz, 1 H), 1.58−1.43 (m, 6 H), 1.32 (septet, J = 7.3 Hz, 6 H), 0.99−0.87 (m, 6 H), 0.89 (t, J = 7.3 Hz, 9 H); ^{13}C NMR ($CDCl_3$) δ 150.6, 138.0, 135.2, 128.4, 127.9, 127.7, 72.3, 66.9, 63.7, 29.2, 27.4, 13.7, 10.1; IR (NaCl film) 3449, 2913, 2849, 1452, 1357, 1068 cm^{-1}; HRMS (FAB) calcd for $C_{23}H_{40}O_2SnNa$ ($M + Na^+$) 491.1948, obsd 491.1941.

Methyl 6-(Benzyloxy)-4-hydroxymethy-2*E*,4*E*-hexadienoate (36). A degassed solution of 4-benzyloxy-2(*E*)-tributylstannyl-but-2-en-1-ol (**35**) (5.62 g, 12.0 mmol) and methyl (*E*)-3-bromoacrylate (2.18 g, 13.2 mmol) in NMP (25 mL) was cannula transferred to a degassed solution of $Pd_2(dba)_3$ (0.22 g, 0.24 mmol), tri-2-furyl phosphine (0.44 g, 1.92 mmol), and CuI (3.20 g, 16.8 mmol) in NMP (95 mL). The solution was heated to 65 °C for 3.5 h, cooled to room temperature, and poured onto 10% KF (20 mL) and water (60 mL). The mixture was extracted with EtOAc (4 × 100 mL), and the extracts were filtered through Celite, concentrated, and redissolved in EtOAc (50 mL). The organics were washed with water (30 mL) and brine (30 mL), dried ($MgSO_4$), concentrated, and chromatographed (20% EtOAc/hexane) to afford 2.98 g (94%) of diene **36** as a gold oil: ^{1}H NMR ($CDCl_3$) δ 7.38−7.29 (m, 5 H), 7.26 (d, J = 16.0 Hz, 1 H), 6.17 (t, J = 6.2 Hz, 1 H), 6.12 (d, J = 16.0 Hz, 1 H), 4.55 (s, 2 H), 4.31 (s, 2 H), 4.26 (d, J = 6.2 Hz, 2 H), 3.76 (s, 3 H), 1.77 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 167.5, 145.7, 139.0, 138.1, 137.5, 128.5, 128.0, 127.9, 118.3, 73.0, 66.0, 57.4, 51.7; IR (NaCl film) 3442, 3023, 2952, 2856, 1716, 1620, 1315, 1100, 1016 cm^{-1}; HRMS (CI) calcd for $C_{15}H_{19}O_4$ (MH^+) 263.1283, obsd 263.1279.

Methyl 6-(Benzyloxy)-4-((2-trimethylsilyl)ethoxymethoxy)methyl-2*E*,4*E*-hexadienoate (37). To a solution of alcohol **36** (9.5 g, 36.2 mmol) in CH_2Cl_2 (65 mL) at 0 °C was added *i*-Pr_2NEt (23.4 g, 181.0 mmol) followed by SEMCl (9.06 g, 54.33 mmol). The solution was allowed to warm to room temperature and stirred 12 h. The reaction mixture was diluted with CH_2Cl_2 (100 mL), washed with saturated $NaHCO_3$ (50 mL) and brine (50 mL), dried ($MgSO_4$), and concentrated. The residue was chromatographed (10% EtOAc/hexane) to afford 13.0 g (92%) of SEM ether **37** as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 7.36−7.29 (m, 5 H), 7.28 (d, J = 15.8 Hz, 1 H), 6.23 (t, J = 6.3 Hz, 1 H), 6.10 (d, J = 15.9 Hz, 1 H), 4.62 (s, 2 H), 4.53 (s, 2 H), 4.29 (d, J = 6.3 Hz, 2 H), 4.24 (s, 2 H), 3.75 (s, 3 H), 3.60 (t, J = 8.7 Hz, 2 H), 0.94 (t, J = 8.7 Hz, 2 H), 0.01 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 167.5, 145.8, 140.4, 137.7, 134.8, 128.5, 127.8, 127.8, 118.5, 93.8, 72.7, 66.3, 65.5, 61.1, 51.6, 18.1, −1.5; IR (NaCl film) 2952, 1716, 1620, 1171, 1040 cm^{-1}; HRMS (FAB) calcd for $C_{21}H_{32}O_5SiNa$ ($M + Na^+$) 415.1917, obsd 415.1906.

Methyl 6-(Benzyloxy)-4-(2-(trimethylsilyl)ethoxymethoxy)methyl-3*E*,5*E*-hexadienoate (38). To a solution of diisopropylamine (0.62 g, 6.11 mmol) in THF (70 mL) at −78 °C was added *n*-BuLi (2.54 mL, 6.11 mmol, 2.4 M) dropwise. The solution was stirred for 30 min, and then DMPU (0.65 g, 5.09 mmol) was added and the mixture allowed to stir an additional 30 min. Ester **37** (2.0 g, 5.09 mmol) dissolved in THF (30 mL) was then added dropwise at 0.4 mL/min. After addition was complete, the solution was stirred for 30 min, MeOH (5 mL) was added, and the mixture wasstirred 3 min. The reaction mixture was poured onto water (200 mL) and EtOAc (75 mL).

The organics were separated, washed with aq $NaHCO_3$, H_2O, and brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed (10% EtOAc/hexane) to afford 1.78 g (89%) of 3,5-hexadienoic ester **38** as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 7.36−7.29 (m, 5 H), 6.85 (d, J = 12.9 Hz, 1 H), 5.66 (d, J = 12.4 Hz, 1 H), 6.65 (t, J = 7.5 Hz, 1 H), 4.80 (s, 2 H), 4.63 (s, 2 H), 4.20 (s, 2 H), 3.68 (s, 3 H), 3.63 (t, J = 8.4 Hz, 2 H), 3.25 (d, J = 7.5 Hz, 2 H), 0.95 (t, J = 8.5 Hz, 2 H), 0.02 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 172.0, 147.9, 136.8, 134.3, 128.5, 128.0, 127.5, 121.5, 108.6, 93.4, 71.7, 65.3, 61.8, 51.9, 33.3, 18.2, −1.4; IR (NaCl film) 2952, 1740, 1650, 1620, 1159, 1040 cm^{-1}; HRMS (TOFES) calcd for $C_{21}H_{32}O_5SiNa$ (M + Na^+) 415.1917, obsd 415.1917.

6-(Benzyloxy)-4-(2-(trimethylsilyl)ethoxymethoxy)-methyl-3*E*,5*E*-hexadienoic Acid (39). A solution of LiOH·H_2O (0.57 g, 13.6 mmol) in water (11 mL) was added to a solution of ester **38** (1.78 g, 4.53 mmol) in acetone (18 mL). The solution was stirred for 90 min and then acidified to a pH = 2 with 1% HCl. The mixture was extracted with Et_2O (2 × 40 mL), and the extracts were dried ($MgSO_4$) and concentrated. The residue was chromatographed (5% MeOH/CH_2Cl_2) to afford 1.66 g (97%) of acid **29** as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 7.37−7.28 (m, 5 H), 6.88 (d, J = 12.7 Hz, 1 H), 5.67 (d, J = 12.5 Hz, 1 H), 5.64 (t, J = 7.5 Hz, 1 H), 4.81 (s, 2 H), 4.66 (s, 2 H), 4.22 (s, 2 H), 3.66−3.63 (m, 2 H), 3.30 (d, J = 7.6 Hz, 2 H), 0.98−0.95 (m, 2 H), 0.02 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 176.1, 147.8, 136.4, 134.4, 128.3, 127.8, 127.3, 120.7, 108.2, 93.1, 71.7, 65.5, 61.7, 33.7, 18.3, −1.1; IR (NaCl film) 3500−2500 (br), 3033, 2952, 1713, 1650, 1034 cm^{-1}; HRMS (TOFES) calcd for $C_{20}H_{30}O_5SiNa$ (M + Na^+) 401.1760, obsd 401.1766.

***N*-(4-(2-(Trimethylsilyl)ethoxymethoxy)methyl-6-benzyloxy-3*E*,5*E*-hexadienoyl)-1-aza-2-ethoxy-1,3-butadiene (40).** A solution of acid **39** (1.56 g, 4.12 mmol), imidate **15** (0.41 g, 4.12 mmol), and NEt_3 (1.00 g, 1.4 mL, 9.86 mmol) in CH_2Cl_2 (20 mL) was added dropwise over 90 min to a suspension of 2-chloro-1-methylpyridinium iodide (1.26 g, 4.94 mmol) in CH_2Cl_2 (30 mL) at 0 °C. The solution was stirred for 90 min and then concentrated to half of the original volume and filtered through a pad of SiO_2 eluting with 30% EtOAc/hexane. The filtrate was concentrated in vacuo to afford 1.61 g (85%) of imidate **40** as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 7.20−7.17 (m, 2 H), 7.15−7.11 (m, 2 H), 7.09 (d, J = 12.6 Hz, 1 H), 7.08−7.05 (m, 1 H), 6.24 (dd, J = 17.1, 10.8 Hz, 1 H), 5.97 (d, J = 17.1 Hz, 1 H), 5.90 (t, J = 7.4 Hz, 1 H), 5.78 (d, J = 12.8 Hz, 1 H), 5.19 (d, J = 10.8 Hz, 1 H), 4.61 (s, 2 H), 4.96 (s, 2 H), 4.29 (s, 2 H), 3.93 (q, J = 7.1 Hz, 2 H), 3.64 (t, J = 8.1 Hz, 2 H), 3.46 (d, J = 7.4 Hz, 2 H), 0.95 (t, J = 7.1 Hz, 3 H), 0.95 (t, J = 8.1 Hz, 2 H), 0.00 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 182.5 (2), 157.1, 148.7, 137.9, 135.0, 129.0, 128.1, 126.9, 126.6, 123.0, 109.7, 93.6, 71.9, 65.7, 62.9, 62.4, 39.3, 18.7, 14.2, −0.9; IR (NaCl film) 3032, 2951, 2893, 1693, 1659, 1601, 1156, 1072 cm^{-1}; HRMS (CI) calcd for $C_{25}H_{36}NO_5Si$ (M − H^+) 458.2363, obsd 458.2367.

(4a*S,7*R**,8a*S**)-7-Benzyloxy-1-ethoxy-5-(2-(trimethylsilyl)ethoxymethoxy)methyl-3,4,4a,7,8,8a-hexahydroisoquinol-3-one (41).** A solution of **40** (1.61 g, 3.50 mmol) and 4 Å molecular sieves in $CHCl_3$ (250 mL) was heated to 60 °C for 24 h. The reaction mixture was cooled to room temperature and filtered through Celite. The filtrate was concentrated and filtered through a pad of SiO_2 eluting with 3% MeOH/CH_2Cl_2 to afford 1.44 g (90%) of a 6:1 mixture of cycloadducts **41** and **42** as a yellow oil. **41**: ^{1}H NMR ($CDCl_3$) δ 7.37−7.28 (m, 5 H), 5.92 (s, 1 H), 4.65 (s, 2 H), 4.63 (d, J = 10.3 Hz, 1 H), 4.59 (d, J = 10.3 Hz, 1 H), 4.45−4.34 (m, 2 H), 4.20 (t, J = 7.3 Hz, 1 H), 4.07 (d, J = 12.3 Hz, 1 H), 3.99 (d, J = 12.3 Hz, 1 H), 3.65−3.57 (m, 2 H), 2.82−2.76 (m, 2 H), 2.71−2.64 (m, 1 H), 2.37 (dd, J = 17.0, 14.0 Hz, 1 H), 2.35−2.29 (m, 1 H), 1.77 (td, J = 12.8, 9.5 Hz, 1 H), 1.34 (t, J = 7.1 Hz, 3 H), 0.97−0.91 (m, 2 H), 0.01 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 182.1, 181.6, 138.0, 137.7, 128.4, 127.8, 127.6, 127.4, 94.3, 73.0, 70.6, 68.6, 65.4, 64.1, 35.6, 34.3, 31.8, 27.8, 18.1, 14.0, −1.4; IR (NaCl film) 3062, 2951, 2883, 1707, 1586, 1248, 1096 cm^{-1}; HRMS (FAB) calcd for $C_{25}H_{38}NO_5Si$ (MH^+) 460.2519, obsd 460.2530.

(4a*S,7*R**,8a*R**)-7-Benzyloxy-5-(2-(trimethylsilyl)-ethoxymethoxy)methyl-1,2,3,4,4a,7,8,8a-octahydroisoquinoline-2-carboxylic Acid Methyl Ester (43).** To a suspension of lithium aluminum hydride (0.66 g, 17.5 mmol) in Et_2O (20 mL) at 0 °C was added a solution of cycloadducts **41** and **42** (1.61 g, 3.50 mmol) in Et_2O (15 mL) dropwise. The solution was allowed to warm to room temperature and stirred for 10 h. The reaction was quenched by sequential addition of H_2O (0.66 mL), 10% NaOH (0.66 mL), and H_2O (2.0 mL). The solution was filtered and concentrated to afford a colorless oil (1.39 g). The oil was dissolved in CH_2Cl_2 (20 mL), and the solution was cooled to 0 °C. Diisopropylethylamine (2.00 g, 15.7 mmol) was added followed by methyl chloroformate (1.00 g, 10.5 mmol). The reaction was stirred for 90 min, poured onto H_2O (50 mL), and extracted with CH_2Cl_2 (50 mL). The extracts were dried ($MgSO_4$), concentrated, and chromatographed (25% EtOAc/CH_2Cl_2) to afford 1.17 g (73%) of carbamate **43** as a colorless oil: ^{1}H NMR (DMSO, 363 K) δ 7.35−7.24 (m, 5 H), 5.70 (s, 1 H), 4.59 (s, 2 H), 4.53 (s, 2 H), 4.16 (t, J = 7.2 Hz, 1 H), 4.01 (d J = 12.5 Hz, 1 H), 3.95 (dquintets, J = 13.1, 2.2 Hz, 1 H), 3.91 (d, J = 12.5 Hz, 1 H), 3.87 (d, J = 13.5 Hz, 1 H), 3.61−3.57 (m, 2 H), 3.59 (s, 3 H), 3.05 (dd, J = 13.5, 3.6 Hz, 1 H), 2.76 (td, J = 12.9, 3.0 Hz, 1 H), 2.23−2.28 (m, 1 H), 1.85−1.72 (m, 3 H) 1.55 (td, J = 12.9, 9.4 Hz, 1 H), 1.37 (qd, J = 12.6, 4.4 Hz, 1 H), 0.91−0.87 (m, 2 H), 0.01 (s, 9 H); ^{13}C NMR (C_6D_6, 333 K) δ 156.5, 141.1, 140.2, 128.8, 128.1, 127.8, 126.8, 94.9, 75.5, 70.6, 69.7, 65.8, 52.5, 49.8, 44.9, 36.2, 33.9, 29.5, 27.9, 18.8, −0.9; IR (NaCl film) 2953, 2866, 1702, 1241, 1057 cm^{-1}; HRMS (CI) calcd for $C_{25}H_{40}NO_5Si$ (MH^+) 462.2676, obsd 462.2675.

(4a*S,5*S**,6*R**,7*R**,8a*R**)-7-Benzyloxy-6-hydroxy-5-(2-(trimethylsilyl)ethoxymethoxy)methyldecahydroisoquinoline-2-carboxylic Acid Methyl Ester (44).** To a solution of olefin **43** (0.75 g, 1.63 mmol) in THF (27 mL) at 0 °C was added a solution of BH_3·THF (8.12 mL of a 1 M solution, 8.12 mmol) dropwise. The reaction was allowed to warm to room temperature and stir for 12 h. The solution was then cooled to 0 °C, and 10 mL of 3 N NaOH was added followed by 10 mL of 30% H_2O_2. The solution was stirred for 2 h and then diluted with H_2O (30 mL) and CH_2Cl_2 (30 mL). The reaction mixture was then acidified to pH = 3 with 10% HCl and extracted with CH_2Cl_2 (2 × 30 mL). The extracts were dried ($MgSO_4$), concentrated, and chromatographed (30% EtOAc/hexanes) to afford 0.57 g (73%) of alcohol **44** as a colorless oil: ^{1}H NMR (DMSO, 363 K) 7.37−7.29 (m, 4 H), 7.25−7.21 (m, 1H), 4.63 (d, J = 12.2 Hz, 1 H), 4.61 (d, J = 12.2 Hz, 1 H), 4.59 (s, 2 H), 4.26 (d, J = 3.7 Hz, 1 H), 4.06 (br d, J = 13.1 Hz, 1 H), 3.82 (br d, J = 13.3 Hz, 1 H), 3.79 (dd, J = 9.9, 4.3 Hz, 1 H), 3.60−3.55 (m, 1 H), 3.57 (s, 3 H), 3.44 (t, J = 10.0 Hz, 1 H), 3.31−3.24 (m, 2 H), 2.94 (dd, J = 13.3, 3.2 Hz, 1 H), 2.62 (td, J = 12.7, 3.5 Hz, 1 H), 2.01−1.96 (m, 1 H), 1.79−1.67 (m, 3 H), 1.49−1.35 (m, 3 H), 0.91−0.86 (m, 2 H), 0.01 (s, 9 H); ^{13}C NMR (C_6D_6, 333 K) δ 156.5, 139.9, 129.0, 128.1, 96.0, 84.0, 72.0, 71.6, 67.6, 65.8, 52.6, 49.7, 45.8, 45.2, 36.6, 35.6, 29.0, 22.0, 18.8, −0.9, one aromatic signal is coincident with the solvent peak; IR (NaCl film) 3462, 2949, 2875, 1698, 1057 cm^{-1}; HRMS (FAB) calcd for $C_{25}H_{41}NO_6SiNa$ (M + Na^+) 502.2601, obsd 502.2604.

(4a*S,5*S**,6*R**,7*R**,8a*R**)-7-Benzyloxy-6-methoxy-5-(2-(trimethylsilyl)ethoxymethoxy)methyldecahydroisoquinoline-2-carboxylic Acid Methyl Ester (45).** To a solution of alcohol **44** (0.45 g, 0.15 mmol) in CH_2Cl_2 (40 mL) was added Proton Sponge (1.40 g, 6.57 mmol), 4 Å molecular sieves (0.90 g), and Me_3OBF_4 (0.83 g, 5.62 mmol). The solution was stirred vigorously for 3.5 h and then filtered. The solid was washed with EtOAc, and the organics were washed with water (50 mL) and 10% $CuSO_4$ (50 mL). The organics were dried ($MgSO_4$), concentrated, and chromatographed (40% EtOAc/hexane) to afford 0.45 g (98%) of methyl ether **45** as a colorless oil: ^{1}H NMR (DMSO, 363 K) 7.36−7.23 (m, 5 H), 4.64−4.54 (m, 4 H),

4.06 (br d, J = 13.1 Hz, 1 H), 3.82 (d, J = 13.2 Hz, 1 H), 3.67 (dd, J = 9.8 4.0 Hz, 1 H), 3.62−3.57 (m, 2 H), 3.58 (s, 3 H), 3.50 (t, J = 9.7 Hz, 1 H), 3.46−3.40 (m, 1 H), 3.39 (s, 3 H), 3.02 (dd, J = 11.1, 8.8 Hz, 1 H), 2.94 (dd, J = 13.2, 3.4 Hz, 1 H), 2.62 (td, J = 12.6, 3.5 Hz, 1 H), 2.03−1.96 (m, 1 H), 1.84−1.76 (m, 2 H), 1.74−1.66 (m, 1 H), 1.55−1.39 (m, 3 H), 0.91−0.86 (m, 2 H), 0.02 (s, 9 H); ^{13}C NMR (C_6D_6, 333 K) δ 156.5, 140.3, 128.9, 128.1, 127.8, 96.0, 84.3, 81.8, 72.1, 66.9, 65.7, 60.9, 52.5, 49.6, 46.3, 45.2, 36.7, 35.5, 30.2, 21.9, 18.8, −0.9; IR (NaCl film) 2949, 2874, 1698, 1453, 1108 cm^{-1}; HRMS (CI) calcd for $C_{26}H_{44}NO_6Si$ (MH^+) 494.2937, obsd 494.2933.

(4a*S,5*S**,6*R**,7*R**,8a*R**)-7-Benzyloxy-6-methoxy-5-(hydroxy)methyldecahydroisoquinoline-2-carboxylic Acid Methyl Ester.** A solution of TBAF (1.01 mL, 1.01 mmol, 1.0 M in THF) was added to ether **45** (0.10 g, 0.20 mmol) in a pear-shaped flask. The mixture was placed under vacuum to remove the THF, and then DMPU (1.5 mL) was added under a N_2 atmosphere. Powdered 4 Å molecular sieves (0.15 g) were added, and the solution was heated to 80 °C for 4 h. The solution was then cooled to room temperature and diluted with Et_2O (15 mL). The organics were washed with water (5 mL) and brine (5 mL) and dried ($MgSO_4$). The organics were then concentrated and chromatographed (EtOAc) to afford 57 mg (78%) of the primary alcohol as a colorless oil: ^{1}H NMR (DMSO, 363 K) 7.36−7.23 (m, 5 H), 4.62 (d, J = 12.0 Hz, 1 H), 4.55 (d, J = 12.0 Hz, 1 H), 4.06 (br d, J = 13.1 Hz, 1 H), 3.89 (br s, 1 H), 3.83 (d, J = 13.2 Hz, 1 H), 3.72−3.67 (m, 1 H), 3.58 (s, 3 H), 3.44−3.38 (m, 2 H), 3.39 (s, 3 H), 2.99 (dd, J = 11.1, 8.8 Hz, 1 H), 2.96−2.93 (m, 1 H), 2.63 (td, J = 12.9, 3.2 Hz, 1 H), 2.03 (dq, J = 12.7, 4.2 Hz, 1 H), 1.82−1.76 (m, 1 H), 1.70−1.61 (m, 2 H), 1.57−1.51 (m, 1 H), 1.43 (q, J = 12.9 Hz, 1 H), 1.40 (qd, J = 12.9, 4.8 Hz, 1 H); ^{13}C NMR (C_6D_6, 333 K) δ 156.5, 140.1, 128.9, 128.1, 127.9, 84.4, 84.2, 72.0, 64.3, 61.0, 52.5, 49.4, 48.0, 45.0, 37.7, 35.5, 30.1, 22.0; IR (NaCl film) 3478, 2929, 2866, 1681, 1454, 1106 cm^{-1}; HRMS (CI) calcd for $C_{20}H_{28}NO_5$ ($M - H^+$) 362.1967, obsd 362.1974.

(4a*S,5*S**,6*R**,7*R**,8a*R**)-7-Benzyloxy-6-methoxy-5-methoxycarbonyldecahydroisoquinoline-2-carboxylic Acid Methyl Ester (46).** To a solution of the preceding alcohol (46 mg, 0.13 mmol) in DMF (2.0 mL) was added PDC (0.24 g, 0.63 mmol), and the solution was stirred for 20 h. Cold 0.1 N HCl (3 mL) was then added, and the mixture was extracted with Et_2O (3 × 5 mL). The extracts were dried ($MgSO_4$) and concentrated. The residue was dissolved in Et_2O (2 mL) and cooled to 0 °C. Diazomethane in Et_2O was added to the mixture until a yellow color persisted. The mixture was then stirred for 10 min and quenched by addition of acetic acid. The solution was diluted with Et_2O (10 mL), washed with water (5 mL) and brine (5 mL), dried ($MgSO_4$), and concentrated. The residue was chromatographed (EtOAc) to afford 39 mg (80%) of ester **46** as a colorless oil: ^{1}H NMR (DMSO, 363 K) δ 7.36−7.23 (m, 5 H), 4.64 (d, J = 12.1 Hz, 1 H), 4.55 (d, J = 12.1 Hz, 1 H), 4.03 (br d, J = 13.4 Hz, 1 H), 3.83 (d, J = 13.3 Hz, 1 H), 3.64 (s, 3 H), 3.58 (s, 3 H), 3.46−3.39 (m, 2 H), 3.43 (s, 3 H), 2.93 (dd, J = 13.3, 3.2 Hz, 1 H), 2.63 (td, J = 13.0, 3.0 Hz, 1 H), 2.59−2.55 (m, 1 H), 2.10−2.04 (m, 1 H), 1.88−1.78 (m, 2 H), 1.53 (qd, J = 13.1, 4.6 Hz, 1 H), 1.42 (q, J = 12.4 Hz, 1 H), 1.19 (br d, J = 13.4 Hz, 1 H); ^{13}C NMR (C_6D_6, 333 K) δ 172.4, 156.4, 140.1, 128.9, 128.0, 127.9, 83.5, 80.5, 72.1, 61.4, 53.3, 52.6, 51.3, 49.1, 44.7, 38.1, 35.3, 29.8, 23.4; IR (CCl_4) 2951, 2871, 1742, 1705, 1448, 1107 cm^{-1}; HRMS (CI) calcd for $C_{21}H_{29}NO_6$ (M^+) 391.1995, obsd 391.1993.

(4a*S,5*S**,6*R**,7*R**,8a*R**)-7-Hydroxy-6-methoxy-5-methoxycarbonyldecahydroisoquinoline-2-carboxylic Acid Methyl Ester.** To a solution of ester **46** (37 mg, 0.095 mmol) in MeOH (2 mL) was added 10% Pd−C (5 mg). The solution was purged with N_2 and then placed under a H_2 atmosphere. The reaction mixture was stirred for 10 h, filtered through Celite, and concentrated. The residue was chromatographed (5% MeOH/CH_2Cl_2) to afford 28 mg (100%) of the secondary alcohol as a colorless solid: mp 160−162 °C; ^{1}H NMR (DMSO, 363 K) δ 4.46 (d, J = 5.8 Hz, 1 H), 4.03 (br d, J = 13.3 Hz, 1 H), 3.81 (d, J = 13.3 Hz, 1 H), 3.62 (s, 3 H), 3.58 (s, 3 H), 3.42 (s, 3 H), 3.42−3.36 (m, 1 H), 3.25 (dd, J = 11.1, 8.8 Hz, 1 H), 2.92 (dd, J = 13.3, 3.3 Hz, 1 H), 2.62 (td, J = 12.8, 2.8 Hz, 1 H), 2.07−2.01 (m, 1 H), 1.81 (br d, J = 13.3 Hz, 1 H), 1.57−1.42 (m, 3 H), 1.18 (br d, J = 13.4 Hz, 1 H); ^{13}C NMR (C_6D_6, 333 K) δ 172.5, 156.4, 82.0, 75.8, 61.2, 52.8, 52.5, 51.3, 49.0, 44.8, 38.4, 35.5, 32.6, 23.5; IR (CCl_4) 3611, 3468, 2951, 2862, 1741, 1706, 1448, 1242, 1098 cm^{-1}; HRMS (CI) calcd for $C_{14}H_{23}NO_6$ (M^+) 301.1525, obsd 301.1522.

(4a*S,5*S**,6*R**,7*R**,8a*R**)-6-Methoxy-5-methoxycarbonyl-7-(3,4,5-trimethoxy)benzoyldecahydroisoquinoline-2-carboxylic Acid Methyl Ester (3).** To a solution of alcohol (22 mg, 0.073 mmol) in CH_2Cl_2 (1.5 mL) were added NEt_3 (30 mg, 40 μL), DMAP (5 mg), and 3,4,5-trimethoxybenzoyl chloride (37 mg, 0.14 mmol). The solution was stirred 20 h, diluted with EtOAc (10 mL), and washed with water (5 mL), saturated $NaHCO_3$ (5 mL), and brine (5 mL). The organic layer was dried ($MgSO_4$), concentrated, and chromatographed (70% EtOAc/hexanes) to afford 25 mg (70%) of ester **3** as a colorless oil: ^{1}H NMR (C_6D_6, 333 K) δ 7.53 (s, 2 H), 5.24 (ddd, J = 11.8, 9.5, 5.1 Hz, 1 H), 4.30−4.00 (br m, 1 H), 3.85 (dd, J = 11.0, 9.6 Hz, 1 H), 3.85−3.80 (m, 1 H), 3.80 (s, 3 H), 3.60 (s, 3 H), 3.43 (s, 9 H), 3.38 (s, 3 H), 2.62 (dd, J = 11.1, 4.9 Hz, 1 H), 2.36 (dd, J = 13.5, 3.3 Hz, 1 H), 2.16 (td, J = 13.0, 3.0 Hz, 1 H), 1.95 (dt, J = 12.8, 4.1 Hz, 1 H), 1.75 (q, J = 13.0 Hz, 1 H), 1.73−1.68 (m, 1 H), 1.45 (qd, J = 13.1, 4.7 Hz, 1 H), 1.22−1.16 (m, 1 H), 1.06−1.00 (m, 1 H); ^{13}C NMR (C_6D_6, 333 K) δ 172.2, 166.0, 156.3, 154.4, 144.6, 126.4, 108.9, 78.8, 78.4, 61.2, 60.9, 56.5, 53.1, 52.5, 51.4, 48.7, 44.6, 37.8, 34.9, 29.7, 23.4; IR (CCl_4) 3000, 2953, 2839, 1741, 1708, 1415, 1132 cm^{-1}; HRMS (CI) calcd for $C_{24}H_{33}NO_{10}$ (M^+) 495.2104, obsd 495.2092.

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

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