Total Synthesis of (−)-Reserpine Using the Chiron Approach

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A highly stereocontrolled synthesis of ring D/E precursor to reserpine has been developed starting from (−)-quinic acid as a chiral template. The total synthesis of (−)-reserpine is described through the cyclization of an immonium lactam intermediate.

The total synthesis of the alkaloid reserpine (**1**), has been considered as one of the historic yardsticks by which ingenuity in design and effectiveness in strategy are measured in the annals of natural product synthesis.[1] In this regard, the first synthesis of reserpine by Woodward and co-workers[2] in 1956 stands as a milestone because of its tactical elegance and timely achievement. Although there are numerous reports describing different approaches and ring constructs leading to advanced intermediates,[3] very few have culminated with the total synthesis of the natural product itself. Of these only the Stork synthesis,[4] starting from a chemically resolved, enantiomerically pure precursor, has produced the natural product with the correct absolute configuration as a single isomer. According to a preliminary account,[5] another approach describes the conversion of D-glucose into the Woodward aldehyde intermediate representing ring E in a multistep sequence. The original Woodward synthesis led to natural levorotatory reserpine by virtue of a chemical resolution step of one of the intermediates. Three other syntheses[6−8] have produced the racemic natural product, in addition to isomeric structures.

The choice of (−)-reserpine as a target molecule for a research project in total synthesis more than 40 years after Woodward's tour de force, and the ensuing notable contributions in recent years, deserves some comment. In spite of its imposing structure and constitution, dominated by the presence of a fused pentacyclic motif, the principal challenges from the point of view of synthetic strategy are the functional and stereochemical features found in ring E, and the all important β-H configuration at C-3 (Figure 1). These issues were also recognized in many of the previous syntheses and addressed in different ways, and to varying degrees of success.

New insights into stereocontrolled ring construction, into the assembly of components, overall practicality, novelty of approach, and the obvious merits of laboratory training, were strong incentives for our renewed interest in such an undertaking. This was further heightened by the desire to validate a chosen strategy and to test the feasibility of a free-radical reaction that was admirably suited for a carbocyclization that would generate crucial stereochemistry. As in any approach to synthesis, the choice of starting material may vary widely, since it must accommodate the requirements of one or more key reactions which, in turn, are imposed by the chosen strategy. For example, the Woodward synthesis[2] started with vinyl acrylic acid and quinone and capitalized on a Diels−Alder reaction to construct rings D and E. Interestingly, the final product in this synthesis was isoreserpine, the C-3 epimer of reserpine. Through a series of clever manipulations of functional groups in ring E, thus forcing a conformational change, it was possible to equilibrate the unnatural isomer into (−)-reserpine. The propensity of an acid-catalyzed epimerization of reserpine to isoreserpine has been extensively studied.[9] The isolation of discrete intermediates has convincingly validated a mechanism where the more thermodynamically stable isomer is favored due to a release of steric strain between the bulky axial indole moiety and ring D. This feature has been a primordial stereochemical issue, and a synthetic Achilles heel in subsequent strategies.

Pearlman[6] used an intramolecular photoinduced [2 + 2] cyclization approach starting from 1,4-dihydrobenzoic acid which eventually led to the Woodward ring E precursor. Wender and co-workers[7] devised methods to prepare an intact D/E subunit utilizing methyl 1,2-dihydropyridine-1-carboxylate as starting material, and they proceeded to apply a Diels−Alder/Cope rearrangement sequence to give a *cis*-hydroisoquinoline precursor. Martin and co-workers[8] applied a general strategy adopting an intramolecular Diels-Alder strategy to produce a hydroisoquinoline ring system that comprised the trisubstituted ring D/E subunit. The Wender and Martin syntheses led to racemic reserpine in addition and other

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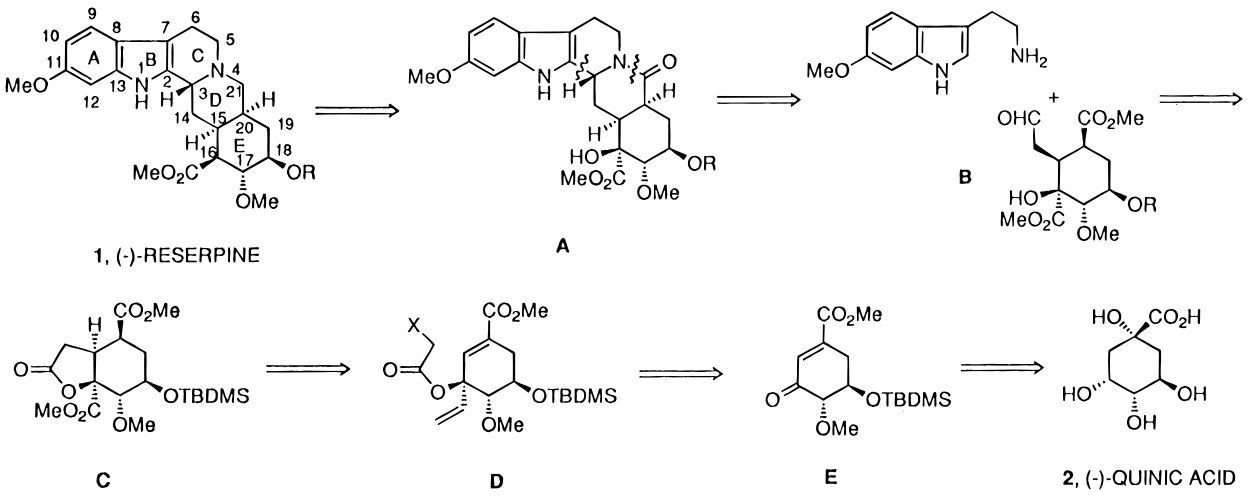

Figure 1.

regioisomers. The Stork synthesis[4] started with enantiomerically pure 3-cyclohexenecarboxylic acid and proceeded with a systematic stereocontrolled introduction of functional groups to produce a pentasubstituted carbocycle representing ring E. Through a clever exploitation of stereoelectronic effects and choice of solvent polarity, Stork and co-workers were able to control the direction of ring closure of the indole moiety through an immonium ion, thus leading to reserpine rather than isoreserpine.

Several elegant strategies have also been reported over the years for the total synthesis of deserpidine[10] (desmethoxy reserpine) as well as related yohimboid alkaloids.[11]

Design, Strategy, and Synthesis. Our strategy for the total synthesis of (−)-reserpine capitalizes on the Chiron Approach[12] and the utilization of the readily available (−)-quinic acid as a chiral template[13] for the construction of ring E. A disconnective analysis is shown in Figure 1. Thus, quinic acid was converted through a series of highly stereocontrolled and efficient chemical reactions into the bicyclic lactone C. Regioselective reduction to the lactol and condensation with 6-methoxytryptamine led to a lactam precursor A which was transformed into reserpine after appropriate functional adjustments. Although quinic acid harbors the intact diol corresponding to C-17/C-18 of reserpine, it lacked the necessary functionality at C-15 and C-16 for the elaboration of the D/E subunit. The plan was to functionalize C-16 with a carbon nucleophile capable of being transformed into the required methoxycarbonyl group and to devise a stereocontrolled two-carbon extension at C-15 utilizing an appropriately substituted ester appendage, relying on an intramolecular free-radical C−C bond formation with transfer of chirality. Below we describe the implementation of this basic strategy and the realization of a stereocontrolled total synthesis of natural reserpine.

Treatment of quinic acid with TsOH in a mixture of benzene and DMF led to a known[14] bicyclic lactone, which was selectively benzylated on the equatorial hydroxyl group via the intermediacy of a stannylene acetal to give **3** (Scheme 1).[15] Methylation in the presence of potassium hydride in THF gave the dimethoxy derivative **4**, which was subjected to catalytic hydrogenolysis using W. Pearlman's catalyst[16] to give **5**. Oxidation with a catalytic amount of ruthenium dioxide and excess sodium periodate produced the ketone **6** which was treated with methanol and $KHCO_3$. Under this mild condition, methanolysis of the lactone was followed by β-elimination to

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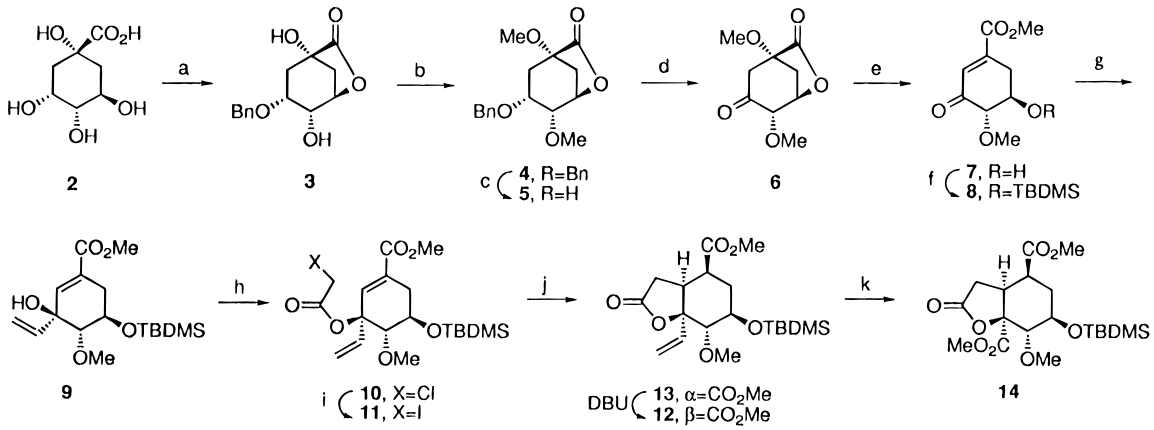
Scheme 1



(a) TsOH/DMF/C_6H_6, then Bu_2SnO/BnBr, 81%; (b) KH/MeI/THF, 90%; (c) $Pd(OH)_2$/C-H_2/MeOH, 98%; (d) $NaIO_4$ $RuO_2.xH_2O$, EtOAc/acetone/H_2O, 90%; (e) $KHCO_3$/MeOH, 85%-90%; (f) TBDMSOTf/2,6-lutidine, 90%; (g) THF/ CH_2=CHMgBr, 90%; (h) DCC/$ClCH_2CO_2H$/DMAP/CH_2Cl_2; (i) CH_3CN/NaI, 80% for two steps; (j) Ph_3SnH/AIBN/C_6H_6, 73%; (k) 1. O_3 then DMS; 2. $NaClO_2$/*t*-BuOH/2-methyl-2-butene/NaH_2PO_4/H_2O; 3.Et_2O/CH_2N_2, 91%-92%;

give the conjugated ester **7** in excellent yield, while minimizing the formation of aromatic byproducts.

The next series of reactions were crucial for the regio- and stereocontrolled introduction of functional groups at C-15 and C-16. The plan was to introduce a vinyl group as a carboxyl precursor at C-16 and to utilize an α-haloacetate ester as a branch for an intramolecular free-radical-mediated conjugate addition[17] across the α,*β*-unsaturated ester group. In order to ensure the *cis*-orientation at the D/E ring function, it was imperative that the introduction of an acetic acid moiety at C-15 take place from the *β*-face of the cyclohexane ring. Once the desired C-15 functionalization was achieved, the tertiary hydroxyl group at C-16 would have to be reduced and the vinyl group oxidatively cleaved under carefully controlled conditions. Base-catalyzed epimerization of the axial methoxycarbonyl group would complete the stereocontrolled introduction of the full complement of functional groups required for ring E.

In the event, treatment of the TBDMS ether derivative **8** with vinylmagnesium bromide in THF led to the C-vinyl carbinol **9** as the major product. It was anticipated that the reagent would approach the ketone from the same side as the methoxy substituent in a chelation-controlled mode.[18] Experimental proof for this hypothesis was secured later in the synthetic sequence, since assignment of stereochemistry at the tertiary carbinol center would be difficult at the level of structure **9**. The next critical reaction was based on earlier studies reported from our laboratory[17] involving the intramolecular free-radical cyclization of α-haloacetates of *δ*-hydroxy α,*β*-unsaturated esters to give the corresponding *γ*-lactones. Until recently, α-acyloxy carbon radicals were considered to be unreactive in conjugate-type additions.[19] The prevailing opinion was that in the presence of tributyltin hydride, such stabilized radicals underwent reduction rather than C−C bond formation. Our studies[17] have shown that efficient and highly stereocontrolled intramolecular cyclizations of α,*β*- and *β*,*γ*-unsaturated α-haloacetates and propionates occur under conditions of slow addition of triphenyltin hydride, to give appropriately substituted 1,4-and 1,5-lactones. The case at hand in the present synthesis was thus particularly appealing as another example of a practical application for our previous results. The required α-haloacetate was prepared by esterification of **9** with chloroacetic acid to give **10**, followed by an exchange with sodium iodide led to the corresponding α-iodoacetate ester **11**. We were now poised to test the efficacy of the α-ester radical intramolecular conjugate cyclization in a polyfunctional substrate such as **11**. Treatment with triphenyltin hydride in the presence of AIBN in refluxing benzene led to the expected lactone **12** and its α-methoxycarbonyl epimer **13**. Treatment of the latter with DBU gave a mixture of **12** (60%) and **13**. The structure and stereochemistry of **12** were definitively ascertained from a single crystal X-ray analysis. The anticipated chelation-controlled attack of the Grignard reagent to give the tertiary carbinol **9** and the subsequent intramolecular free-radical addition reaction to introduce a potential acetic acid unit at C-15 were thus confirmed. It is of interest to point out that the critical reaction to construct ring D in the Stork synthesis[4] capitalized on his well-known α-bromoacetal free-radical carbocyclization.[20] Oxidative cleavage of **12** with ozone, followed by transformation to the corresponding acid and esterification, led to the lactone **14**. Thus, the carbon skeleton and required functionality for rings D/E of reserpine were expediently constructed from quinic acid in 10 steps and 24% overall yield.

With the chiron representing rings D and E in hand, the next crucial issue to be addressed was the assembly of the pentacyclic ring skeleton and the fate of the stereochemistry at C-3. The Woodward synthesis of reserpine[2] utilized a carbocyclic precursor to ring E which contained a C-20 aldehyde and a methoxycarbonyl methyl appendage at C-15. The Stork ring E intermediate[4] comprised an acetaldehyde chain at C-15 and a tosyloxymethyl group at C-20. In both instances, the penta-

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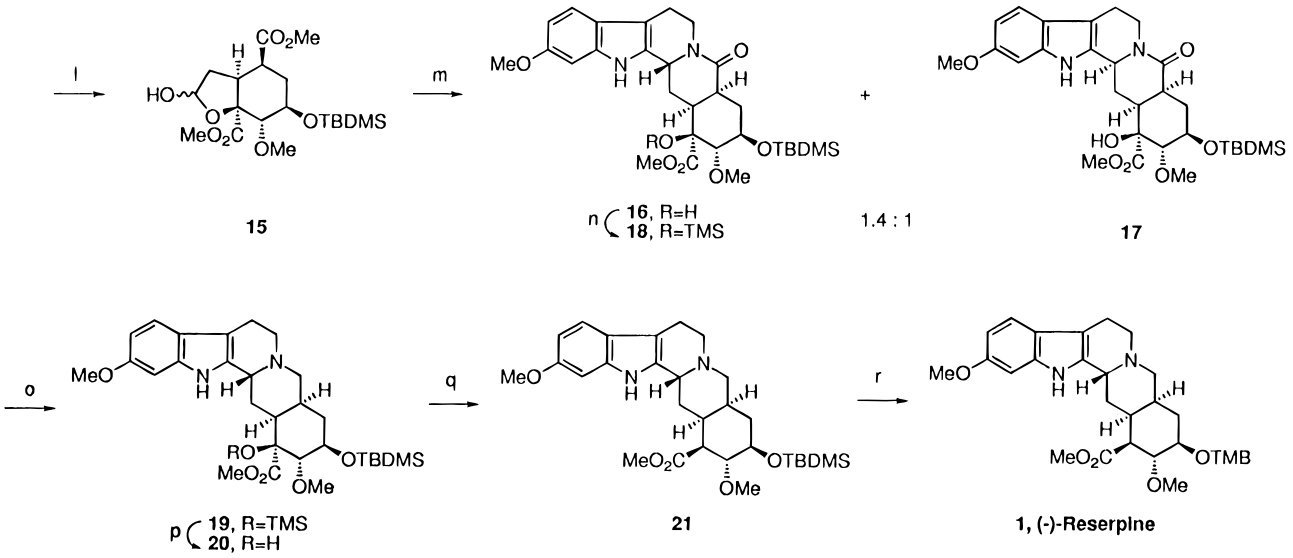
Scheme 2



(l) Sia_2BH/THF, 98%; (m) 6-methoxytryptamine/$PhCH_3$ /$(CH_3)_3CCO_2H$, 90-92%; (n) 2,6-lutidine/TMSOTf/CH_2Cl_2; (o) B_2H_6/THF then HMPA, $HO(CH_2)_2OH$, 84%, for two steps; (p) CH_3CN/HF; (q) 1. CH_2Cl_2/ 2,6-lutidine/TBDMSOTf; 2.SmI_2/HMPA/$HO(CH_2)_2OH$/THF, 30-32%, for three steps; (r) 1. HF/CH_3CN; 2. 3,4,5-trimethoxybenzoyl chloride/Et_3N, 80%.

cyclic skeleton was assembled by condensation with 6-methoxytryptamine utilizing different protocols.

Since compound **14** represented a highly functionalized chiron, a chemoselective method of reduction was needed to differentiate between the three carbonyl groups. Thus, treatment with disamylborane in THF[21] effected smooth and selective transformation of the lactone carbonyl to the corresponding hemiacetal **15** (Scheme 2). This intermediate represents a new functional variant of the Stork aldehyde, and a hemiacetal precursor which was previously transformed to reserpinol[22] via an α-bromoacetal free-radical carbocyclization reaction.

Treatment of **15** with 6-methoxytryptamine in refluxing toluene containing pivalic acid led to a mixture of C-3β and C-3α isomers **16** and **17** in a ratio of 1.4:1 and in an excellent yield of isolated products. Interestingly, the ratio was somewhat diminished when acetic acid was used and many variations of acids showed no improvement (see below). The stereochemical identity of each isomer was ascertained from NMR studies and eventually by conversion of **14** into the natural product. To this end, there remained to effect two functional adjustments of the pentacyclic intermediate **16**, namely deoxygenations of the lactam carbonyl and the tertiary carbinol group. Several attempts to reduce the lactam carbonyl in **16** with diborane were unsuccessful. However, after protection of the tertiary carbinol as the TMS ether, smooth reduction took place to give **19**. Ironically, the deoxygenation of the α-carbomethoxy tertiary alcohol at C-16 as the TMS ether proved difficult with SmI_2, in spite of previous extensive experience in this area within our group[23] and elsewhere.[24] Deoxygenation was possible with SmI_2 of the C-16 unprotected ester **20** to give **21** with concomitant formation of a mixture of unseparable products that contained the C-17 deoxy derivative as epimeric esters. Removal of the silyl ether at C-18 and esterification with 3,4,5-trimethoxybenzoyl chloride gave (−)-reserpine, identical to a sample of the natural product in all respects.

Stereochemical Issues. Previous C-ring closure strategies leading to reserpine and/or isoreserpine have relied on two fundamental reactions that are conceptually related but operationally different. In the original Woodward approach,[2] an intermediate seco C-15 lactam structure was cyclized utilizing the Bischler−Napieralski reaction to create a pentacyclic C-3/N-4 immonium ion which was reduced with sodium borohydride (Figure 2A). Hydride ion attack occurred from a preferred pseudoaxial trajectory to give isoreserpine as the sole product.

The Stork strategy[4] relies on the generation of a seco C-3/N-4 immonium salt which subsequently undergoes acid-catalyzed attack by the indole ring. The conceptual basis of this process was inspired from stereoelectronic considerations, whereby intramolecular attack on an immonium ion salt in a half-chair conformation was expected to favor an axial pro-reserpine approach (Figure 2C).

The Martin[8]−Wender[7] strategies generated a fully saturated *N*-indolylisoquinoline intermediate which was subjected to a mercuric acetate oxidation−cyclization protocol. This reaction sequence was extensively studied originally by Wenkert,[3a] and subsequently by others,[3d] in this area (Figure 2B). The result was a mixture of isomeric C-3/N-4 and N-4/C-20 seco-immonium ions which underwent acid-catalyzed cyclization to give C-3 adducts as well as "inside" isomers resulting from attack at C-20. Martin[8] has explained the direct formation of reserpine (35%), in part, from a favored pseudoaxial approach on a half-chair/chair conformation of the C-3/N-4 immonium ion (Figure 2B). However, the initially formed reserpine (and isoreserpine) were also partially oxidized to the Woodward-type pentacyclic immonium ion intermediate (Figure 2A) under the conditions of the oxidative-cyclization, and it was necessary to include in the procedure an acidic reductive step using zinc and perchloric acid. According to Martin[8] this type of reduc-

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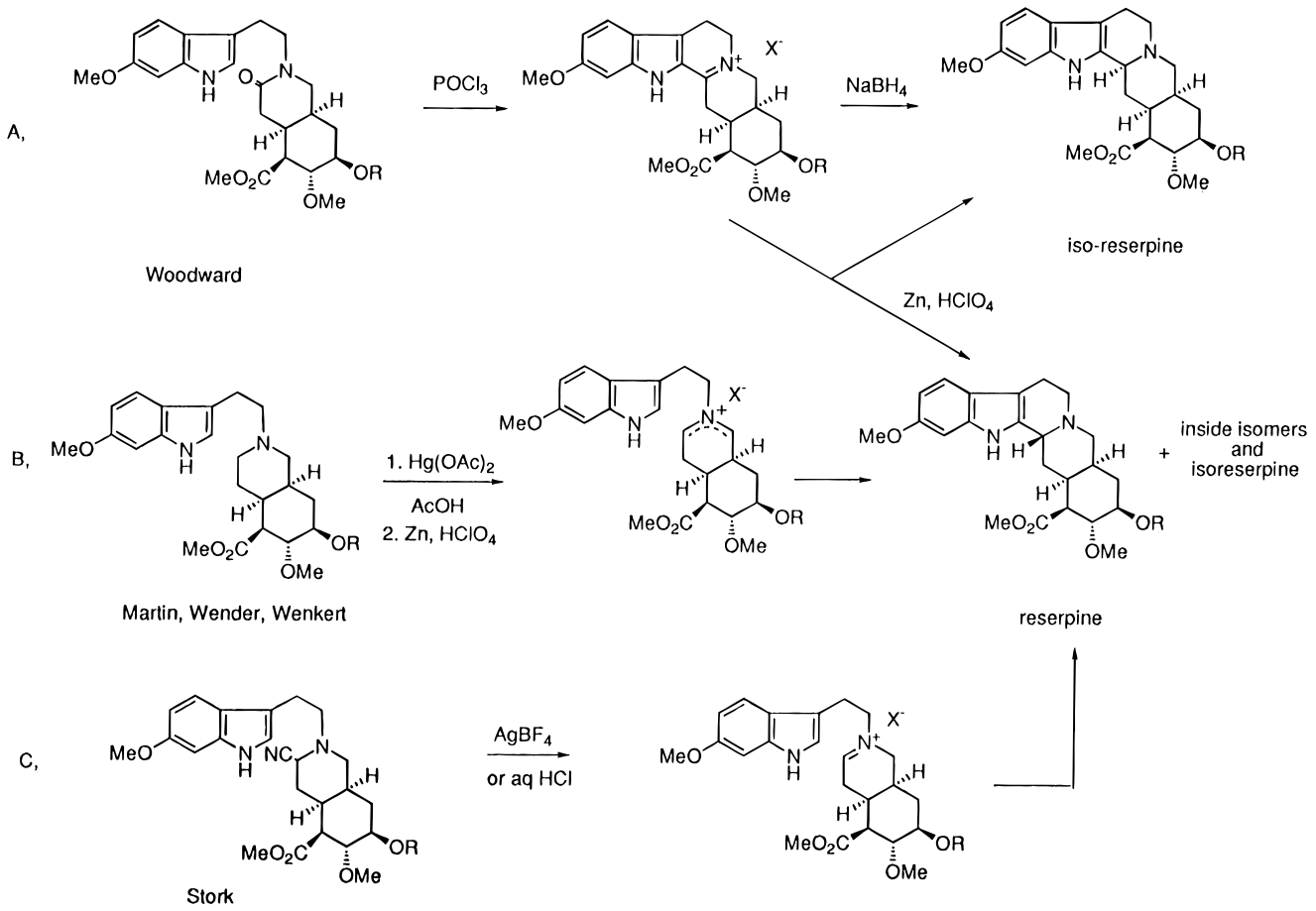

Figure 2.

tion produces an equimolar amount of reserpine and isoreserpine from the Woodward immonium ion (Figure 2A,B).

The Stork strategy[4] exploited the potential for stereoelectronic effects to its fullest through the intermediacy of a C-3 cyanoamine (Figure 2C). Heating such an intermediate in acetonitrile led to the formation of isoreserpine via a pseudoequatorial approach of the indole ring on an α-orientated, tightly bound, immonium cyanide ion-pair. However, generation of a separated ion-pair in the presence of an acid catalyst led, in fact, to the formation of the precursor to reserpine by way of an "unimpeded axial half-chair approach of the indole"[4] (Figure 2C).

It is therefore clear that ensuring the prevalence of a C-3/N-4 immonium ion with a loosely bound anionic counterpart of the type shown in Figure 2C as discussed by Stork,[4] should favor the pseudoaxial trajectory leading to the desired C-3 configuration. This logical premise can unfortunately be overshadowed by a number of kinetic and thermodynamic factors that may be difficult to fully control. A delicate balance exists between the nature of the counter anion, its relative nucleophilicity, the polarity of the solvent, and a series of equilibria between transient intermediates.

Our initial strategy to use quinic acid as a chiral template, and its manipulation to chiron **14** through a series of highly stereocontrolled transformations, was in fact within the realm of predictability. The subsequent steps, which involved the condensation with the indole moiety, while ensuring the correct regiochemistry of attack at C-3 exclusively, carried an element of stereochemical uncertainty.

As previously discussed, the Pictet−Spengler type condensation of the lactol **15** with 6-methoxytryptamine in the presence of pivalic acid in refluxing toluene produced a mixture of the expected **16** and the C-3 isomeric **17** in 92% yield and a ratio of 1.4:1, respectively (by weight). This reflects on a preference for the formation of the pre-reserpine structure **16a** which accounts for 58% of the desired isomer in the mixture (Figure 3). Isomers **16** and **17** did not equilibrate under the reaction conditions employed for the cyclization as evidenced by control experiments. When the condensation of **15** with 6-methoxytryptamine was effected in refluxing benzene in the presence of 1 equiv of pivalic acid, the major product was the imine **22** (Figure 3).

Treatment of the imine **22** with excess pivalic acid in refluxing toluene led to **16** and **17** in a ratio of ~1.4:1 as in the original reaction. A plausible mechanism for the cyclizations leading to **16** and **17** involves attack of the indole moiety on a half-chairlike imine or immonium ion intermediate via pseudoaxial (path a) or pseudoequatorial (path b) approaches to transient intermediates **16a** and **17a**, respectively, followed by spontaneous elimination of methanol and lactam formation (Figure 3).

It is of interest that, regardless of their size, other acids (dry HCl, AcOH, $Me_3SiCH_2CO_2H$, pentafluorobenzoic acid, 1-adamantanecarboxylic acid, camphoric acid) gave a ratio of 1:1 of **16** and **17** in variable yields with or without recovery of the imine **22**. Thus, factors dealing with immonium ion-pairing, ion-shielding, pK_a of the acid, and stereoelectronics play an ever-puzzling role in the continuing saga of the C-3 stereochemical issue of reserpine.

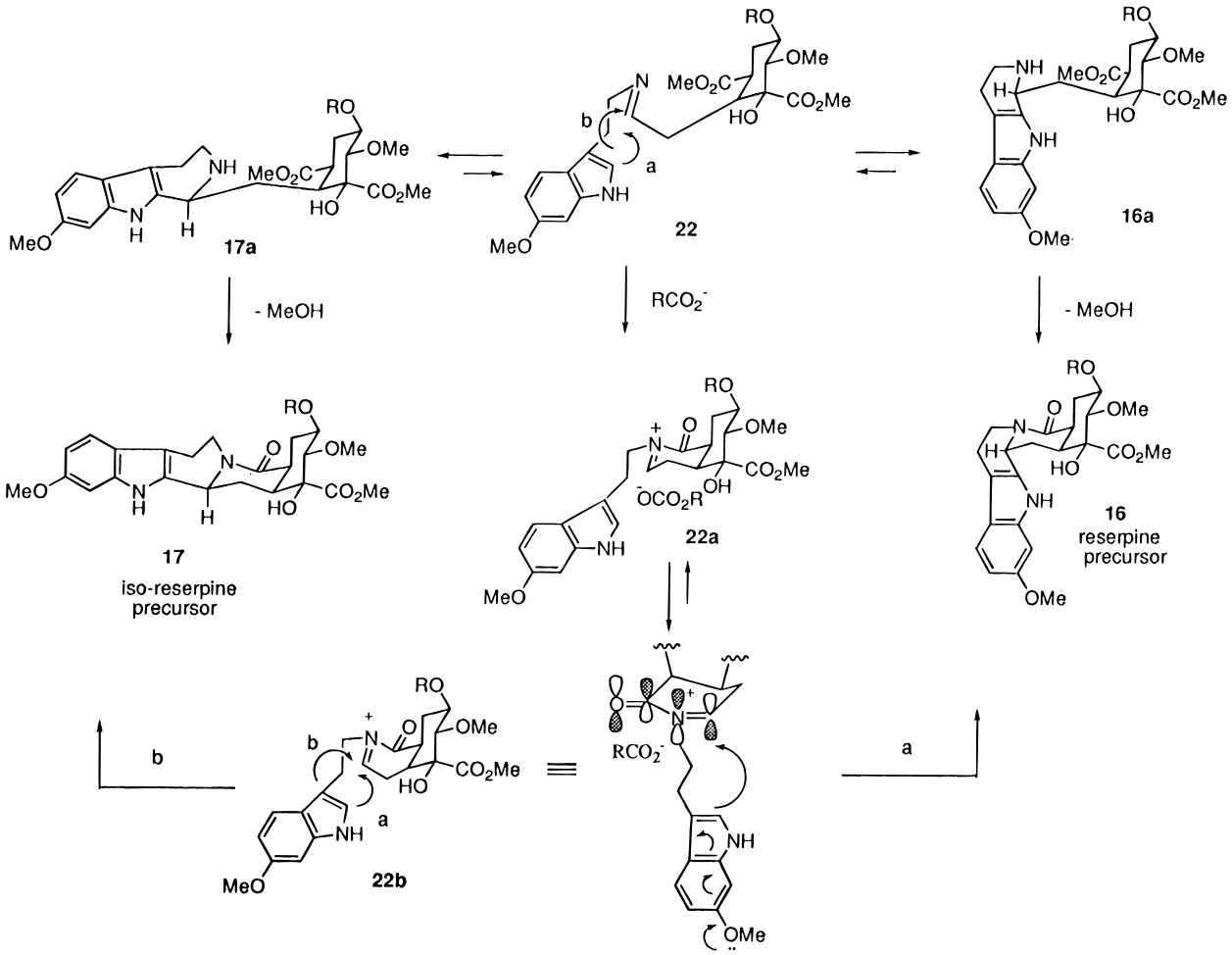

Figure 3.

An alternative mechanistic rationale for the preference of the desired isomer **16** over **17** may depend on the intermediacy of a putative immonium ion lactam structure **22a** (Figure 3). Thus, the initially formed iminium ion may undergo competing attack by the excess anion (Cl^-, carboxylate, sulfonate) to give a transient α-substituted amine which spontaneously loses methanol to give the lactam and then intermediate **22a**. The resulting extended conjugated immonium lactam system (**22a** ↔ **22b**) could benefit from a pseudoaxial approach en route to the desired **16**. Unfortunately, many attempts to intercept intermediates shown in Figure 3 were not possible, and the exact nature of the putative species in going from the imine **22** to **16** and **17** remains unsubstantiated.

In conclusion, we have described a total synthesis of (−)-reserpine from quinic acid in 20 steps and in an overall yield of 2.6%. The ring D/E precursor **14** was obtained from quinic acid in 10 steps and 24% overall yield. The assembly of the pentacyclic skeleton of reserpine involves the preliminary formation of an imine **22**, which can cyclize via pathways involving the intermediacy of indolopiperidines, or an immonium lactam salt (Figure 3), leading in each case to the C-3 configuration found in reserpine as a favored isomer.

In 1956 Woodward used pivalic acid to effect an acid-catalyzed isomerization of isoreserpine C-16/C-18 lactone to the corresponding reserpine derivative.[2] It is of interest to note that the same acid, utilized in our synthesis for a different reason, figures so prominently in the stereochemical outcome of the Pictet−Spengler cyclization. We recall once again, that unlike the case of reserpine and isoreserpine, the pentacyclic lactam structures **16** and **17** are not interconvertible in the presence of pivalic acid. The stereochemical control at C-3 in the total synthesis of reserpine, masterfully orchestrated by Woodward[2] and cleverly manipulated by Stork[4] continues to present fascinating challenges in stereocontrolled total synthesis, as evidenced by our efforts which we have outlined in this paper.

Experimental Section

General Procedures. Melting points are uncorrected. ^1H NMR spectra were recorded at 300-MHz in $CDCl_3$ (unless otherwise indicated), with $CHCl_3$ as reference. ^{13}C NMR spectra were recorded at 75-MHz in $CDCl_3$ (unless otherwise indicated), with $CHCl_3$ as reference. Wherever necessary, ^1H NMR assignments were supported by appropriate homonuclear correlation experiments (COSY). IR spectra of samples were recorded as films. Mass spectra were recorded using electron ionization (EI) at 70 eV or by the fast atom bombardment (FAB) techniques. Optical rotations were measured at 25 °C at the sodium line. Flash chromatography was performed on 230−400 mesh silica gel. Thin-layer chromatography (TLC) was performed on glass plates coated with 0.02 mm layer of silica gel 60 F-254. All solvents were dried, distilled freshly before use or stored dry by common procedures.

(1*S*,3*R*,4*R*,5*R*)-3-(Benzyloxy)-1,4-dihydroxy-6-oxabicyclo[3.2.1]octan-7-one (3). A mixture of (−)-quinic acid (20 g, 104 mmol), *p*-toluenesulfonic acid monohydrate (1.98 g, 10.4 mmol) in 50 mL of DMF, and 180 mL of benzene was heated

under reflux with azeotropic removal of water (Dean−Stark apparatus). After 12 h, the solution was cooled to rt, dibutyltin oxide (30 g, 0.12 mmol) was added, and reflux was continued with removal of water for 4 h. After concentrating to half volume, benzyl bromide (20 mL, 0.168 mmol) was added to the solution and reflux was continued for 6 h. The solvent (benzene, DMF) was removed *in vacuo*, the residue was chromatographed on silica gel [hexanes:EtOAc (1:1 to 1:2)] to give 22.5 g (81%) of the benzyl lactone derivative **3** as a white solid: mp 153 −154 °C; $[\alpha]_D$ −48° (*c* 0.33, $CHCl_3$); IR ($CHCl_3$) ν 3580, 1795, 1610 cm^{-1}; ^1H NMR ($CDCl_3$, 300 Hz) δ 7.35 (m, 5H), 4.85 (t, J = 5.4 Hz, 1H), 4.62 (d, J = 11.4 Hz, 1H), 4.54 (d, J = 11.4 Hz, 1H), 4.19 (t, J = 4.2 Hz, 1H), 3.67 (ddd, J = 4.2, 6.8, 11.2 Hz, 1H), 2.81 (s, 1H), 2.69 (s, 1H), 2.65 (d, J = 11.4 Hz, 1H) 2.30 (ddd, J = 2.8, 6.0, 14.7 Hz, 1H), 2.18 (ddd, 1H, J = 2.8, 6.8, 12.0 Hz), 2.02 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 177.5, 136.8, 128.6, 128.2, 127.7, 75.9, 72.9, 71.9, 71.4, 63.8, 37.3, 36.3; MS (EI) *m*/*e* 264, 246, 228, 218, 208, 188, 173, 162, 147, 127, 105, 91; HRMS calcd for $C_{14}H_{16}O_5$ (M^+) 264.0983; found 264.0997.

(1*R*,3*R*,4*S*,5*R*)-3-(Benzyloxy)-1,4-dimethoxy-6-oxabicyclo[3.2.1]octan-7-one (4). A solution of **3** (10 g, 37.8 mmol) in a mixture of THF and methyl iodide (150 mL, 2:1) was added dropwise to a slurry of 14 g of KH (35 wt % in mineral oil, 122 mmol) in 50 mL of THF at rt under argon. The reaction mixture was stirred for 1 h and then refluxed for 1 h. After careful addition of solid NH_4Cl (3 g) and ether (200 mL) at rt, the solution was added to 100 mL of aqueous NH_4Cl at 0 °C, and the solution was extracted with ether. The organic phase was washed with brine and dried (Na_2SO_4), and the solvent was evaporated *in vacuo*. Flash chromatography (EtOAc:hexanes 5:95 to 40:60) of the oily residue afforded 10 g (90%) of the dimethoxy compound **4** as a colorless oil: $[\alpha]_D$ −25° (*c* 0.33, $CHCl_3$); IR ($CHCl_3$) ν 1798, 1610 cm^{-1}; ^1H NMR ($CDCl_3$, 300 Hz) δ 7.32 (m, 5H), 4.79 (dt, J =1.5, 5.1 Hz, 1H), 4.61 (d, J = 6.0 Hz, 1H), 4.54 (d, J = 6.0 Hz, 1H), 3.78 (t, J = 4.2 Hz, 1H), 3.70 (ddd, J = 4.2, 6.0, 11.0 Hz, 1H), 3.52 (s, 3H), 3.36 (s, 3H), 2.39 (m, 2H), 2.23 (ddd, J = 2.0, 6.0, 8.7 Hz), 2.03 (t, J = 11.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 174.5, 137.4, 128.3, 127.7, 127.4, 76.5, 74.0, 73.9, 73.4, 71.3, 59.5, 52.1, 34.3, 32.5; MS (EI) *m*/*z* 292, 214, 206, 177, 164, 157, 125, 110, 91; HRMS calcd for $C_{16}H_{20}O_5$ (M^+) 292.1330; found 292.1310.

(1*S*,3*R*,4*R*,5*R*)-3-Hydroxy-1,4-dimethoxy-6-oxabicyclo[3.2.1]octan-7-one (5). A solution of 10 g (34.2 mmol) of **4** and 1 g of 20% palladium hydroxide on carbon[16] in 100 mL of methanol was hydrogenated at rt and atmospheric pressure. Hydrogen absorption ceased after the uptake of 1 equiv of hydrogen. The solution was filtered through Celite and evaporated *in vacuo*. The resulting oil was chromatographed on silica gel (hexanes:EtOAc, 1:2) to afford 6.79 g (98%) of **5** as a colorless oil: $[\alpha]_D$ +18.1° (*c* 1.05, $CHCl_3$); IR (neat) ν 3470, 2950, 2850, 1790 cm^{-1}; ^1H NMR ($CDCl_3$, 300 Hz) δ 4.88 (dd, J = 4.8, 6.0 Hz, 1H), 3.88 (m, 1H), 3.68 (t, J = 4.7 Hz, 1H), 3.49 (s, 3H), 3.35 (s, 3H), 2.56 (d, J = 4.5, 2H), 2.24 (m, 2H), 1.79 (t, J = 11.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 174.4, 77.0, 74.9, 73.5, 65.6, 58.7, 51.8, 37.3, 32.0; MS (CI) *m*/*e* 203, 186, 154, 127, 98, 84; HRMS calcd for $C_9H_{15}O_5$ (M^+ + 1) 203.0919; found 203.0962. Anal. Calcd for $C_9H_{14}O_5$: C, 53.46; H, 6.98. Found: C, 53.86; H, 6.90.

(1*R*,4*S*,5*R*)-1,4-Dimethoxy-6-oxabicyclo[3.2.1]octane-3,7-dione (6). To a mixture of 4.4 g (21.7 mmol) of alcohol **5** and 9.7 g (45.3 mmol) of sodium periodate in 84 mL of EtOAc:acetone:H_2O (40:4:40) was added 50 mg of ruthenium(IV) oxide hydrate $RuO_2 \cdot xH_2O$ at rt. After 16 h, the solution was filtered through Celite and extracted with EtOAc. The organic layer was washed with 10% $Na_2S_2O_3$ and brine and then dried (Na_2SO_4) and evaporated *in vacuo*. The resulting solid was crystallized from ether to afford 3.95 g (90%) of **6** as white crystalline solid: mp 85−86 °C; $[\alpha]_D$ −34.2° (*c* 1.08, $CHCl_3$); IR (CCl_4, film) ν 2980−2840, 1790, 1745 cm^{-1}; ^1H NMR ($CDCl_3$, 300 Hz) δ 4.85 (dd, J = 3.9, 6.3 Hz, 1H), 3.58 (m, 1H), 3.48 (s, 3H), 3.47 (s, 3H), 2.98 (dd, J = 0.67, 17.0 Hz, 1H), 2.81 (m, 2H), 2.50 (d, J = 12.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 201.6, 173.4, 78.3, 76.5, 72.3, 58.7, 52.3, 47.3, 31.4; MS (CI) *m*/*e* 201, 170, 155, 98, 84, 72; HRMS calcd for $C_9H_{12}O_5$ (M^+) 200.0684; found 200.0669. Anal. Calcd for $C_9H_{12}O_5$: C, 53.99; H, 6.04. Found: C, 53.68; H, 5.74.

(4*S*,5*R*)-5-Hydroxy-4-methoxy-3-oxocyclohex-1-enecarboxylic acid Methyl Ester (7). To a solution of 1.6 g of **6** (8.0 mmol) in 32 mL of dry MeOH was added portionwise 80 mg of anhydrous $KHCO_3$ (0.8 mmol) under argon, at rt. After stirring for 12 h, the reaction was quenched by addition of solid NH_4Cl (45 mg). The solution was concentrated *in vacuo*, and the residue was directly chromatographed on silica gel (EtOAc:hexanes, 10:90, 20:80, and then 40:60) to afford 1.45 g (90%) of **7** as a light yellow oil: $[\alpha]_D$ −142.0° (*c* 1.12, $CHCl_3$); IR (neat) ν 3950, 2960−2850, 1730, 1700, 1660 cm^{-1}; ^1H NMR ($CDCl_3$, 300 Hz) δ 6.77 (d, J = 2.7 Hz, 1H), 4.05 (ddd, J = 5.3, 9.3, 10.1 Hz, 1H), 3.85 (s, 3H), 3.70 (s, 3H), 3.69 (d, J = 10.2 Hz, 1H), 3.12 (dd, J = 5.5, 18.8 Hz, 1H), 2.74 (s, 1H), 2.60 (ddd, J = 3.1, 9.6, 18.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 198.0, 165.7, 144.7, 131.9, 86.9, 69.3, 59.9, 52.6, 32.2; MS (EI) *m*/*z* 200, 182, 170, 151, 140, 127, 121, 111, 93, 81, 74, 69; HRMS calcd for $C_9H_{12}O_5$ (M^+) 200.0685; found 200.0695.

(4*S*,5*R*)-5-((*tert*-Butyldimethylsilyl)oxy)-4-methoxy-3-oxocyclohex-1-enecarboxylic Acid Methyl Ester (8). To a solution of 1.45 g of alcohol **7** (7.25 mmol) in 18 mL of CH_2Cl_2, under argon at 0 °C, were successively added 1.8 mL of dry 2,6-lutidine (15.4 mmol) and 2.5 mL of *t*-$BuMe_2SiOTf$ (11.0 mmol). The reaction mixture was stirred at 0 °C for 15 min and then diluted with 15 mL of distilled water. The aqueous phase was reextracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Flash chromatography (EtOAc:hexanes, 5:95) of the oily residue afforded 2.04 g (90%) of the silyloxy derivative **8** as a light yellow oil: $[\alpha]_D$ −78.7° (*c* 1.21, $CHCl_3$); IR (neat) ν 2940−2840, 1740, 1690, 1620 cm^{-1}; ^1H NMR ($CDCl_3$, 300 Hz) δ 6.72 (dd, J = 1.2, 2.2 Hz, 1H), 4.13 (ddd, J = 4.7, 7.0, 8.3 Hz, 1H), 3.83 (s, 3H), 3.54 (d, J = 8.9 Hz, 1H), 3.52 (s, 3H), 2.94 (ddd, J = 1.3, 4.8, 18.6 Hz, 1H), 2.58 (ddd, J = 2.3, 7.0, 18.8 Hz, 1H), 0.83 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 197.9, 166.1, 144.3, 131.5, 85.8, 70.4, 59.6, 52.5, 33.0, 25.4, 17.8, −4.9, −5.2; MS (EI) *m*/*e* 257, 225, 197, 169, 131, 89; HRMS for $C_{11}H_{17}O_5Si$ (M^+ − t-Bu) 257.0845; found 257.0798.

(3*S*,4*S*,5*R*)-5-((*tert*-Butyldimethylsilyl)oxy)-3-hydroxy-4-methoxy-3-vinylcyclohex-1-enecarboxylic Acid Methyl Ester (9). To a solution of 2 g (6.37 mmol) of **8** in 100 mL of THF was added dropwise 10 mL of vinylmagnesium bromide (1 M in THF) under argon at −78 °C. The reaction mixture was stirred at −78 °C for 2 h, quenched at this temperature with 20 mL of saturated aqueous solution of NH_4Cl, and allowed to warm to rt. The aqueous phase was extracted with Et_2O, and the combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Flash chromatography (EtOAc:hexanes, 5:95, 10:90, and then 20:80) of the oily residue afforded 1.96 g (90%) of **9** as a colorless oil: $[\alpha]_D$ −47.1° (*c* 0.80, $CHCl_3$); IR (neat) ν 3480, 3100, 2940−2840, 1720, 1650 cm^{-1}; ^1H NMR ($CDCl_3$, 300 Hz) δ 6.69 (s, 1H), 6.02 (dd, J = 10.8, 17.4 Hz, 1H), 5.42 (dd, J = 1.5, 17.4 Hz, 1H), 5.28 (dd, J = 1.5, 10.8 Hz, 1H), 4.23 (ddd, J = 4.5, 4.5, 6.1 Hz, 1H), 3.76 (s, 3H), 3.67 (br, s, 1H), 3.48 (s, 3H), 3.28 (d, J = 6.2 Hz, 1H), 2.62 (ddd, J = 2.1, 4.6, 18.2 Hz, 1H), 2.42 (ddd, J = 1.5, 4.3, 18.2 Hz, 1H), 0.90 (s, 9H), 0.14 (s, 3H), 0.12 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 167.0, 139.3, 138.5, 126.8, 115.4, 84.0, 72.7, 68.1, 60.2, 51.7, 30.3, 25.5, 17.8, −5.0, −5.2; MS (CI) *m*/*e* 325, 285, 253, 221, 193, 147, 131, 116, 89, 75; HRMS calcd for $C_{17}H_{30}O_5Si$ (M^+): 342.1862; found 342.1822.

(3*S*,4*S*,5*R*)-5-((*tert*-Butyldimethylsilyl)oxy)-3-(chloroacetoxy)-4-methoxy-3-vinylcyclohex-1-enecarboxylic Acid Methyl Ester (10). Chloroacetic acid (146 mg, 1.55 mmol, 1.5 equiv), *N*′,*N*-dicyclohexylcarbodiimide (319 mg, 1.55 mmol, 1.5 equiv), and 4-(*N*,*N*-dimethylamino)pyridine (8 mg) were added to a solution of the alcohol **9** (353 mg, 1.03 mmol) in dry dichloromethane (3.5 mL) at rt. The reaction mixture was stirred for 16 h, and then a further quantity of chloroacetic acid (1.5 equiv) and *N*,*N*-dicyclohexylcarbodiimide (1.5 equiv) were added and stirring was continued for another 24 h. After evaporation of the solvent under reduced pressure the crude residue was chromatographed on silica gel (EtOAc:hexanes, 10:90) to give the chloro ester **10** (372 mg, 86%) as a colorless oil: $[\alpha]_D$ −31.1° (*c* 1.75, CCl_4); IR (neat) ν 3100, 2980−2880,

1775, 1720, 1650 cm^{-1}; ^1H NMR ($CDCl_3$, 300 Hz) δ 6.79 (d, J = 2.1 Hz, 1H), 6.01 (dd, J = 10.9, 17.6 Hz, 1H), 5.34 (br, d, J = 10.9 Hz, 1H), 5.14 (br, d, J = 17.6 Hz, 1H), 4.05 (s, 2H), 3.75 (m, 2H), 3.74 (s, 3H), 3.53 (s, 3H), 2.78 (dd, J = 5.5, 17.8 Hz, 1H), 2.34 (ddd, J = 2.9, 8.5, 17.8 Hz, 1H), 0.88 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 169.5, 166.0, 135.6, 135.2, 130.0, 117.8, 87.5, 84.6, 69.0, 61.3, 52.0, 41.2, 34.1, 25.6, 17.9, −4.7, −5.0; MS (EI) *m/e* 418, 387, 361, 329, 267, 253, 235, 221, 188, 174, 147, 116, 102, 89, 73; HRMS calcd for $C_{19}H_{31}ClO_6Si$ (M^+) ^{35}Cl 418.1578; found 418.1592; ^{37}Cl calcd 420.1549; found 420.1554.

(3*S*,4*S*,5*R*)-5-((*tert*-Butyldimethylsilyl)oxy)-3-(iodoacetoxy)-4-methoxy-3-vinylcyclohex-1-enecarboxylic Acid Methyl Ester (11). To a solution of 372 mg of the chloro ester **10** (0.89 mmol) in 5 mL dry acetonitrile were added activated powdered molecular sieves 3 Å and 536 mg of NaI (3.6 mmol, 4 equiv). The reaction mixture was stirred at rt for 18 h. After concentration *in vacuo* and filtration of the residue, the crude product was purified by chromatography on silica gel (EtOAc: hexanes, 10:90) to afford 441 mg (97%) of the iodo ester **11** as a colorless oil: $[\alpha]_D$ −24.4° (*c* 2.25, CCl_4); IR (neat) ν 2980−2880, 1740, 1625 cm^{-1}; ^1H NMR ($CDCl_3$, 300 Hz) δ 6.72 (d, J = 2.8 Hz, 1H), 6.02 (dd, J = 10.8, 17.6 Hz, 1H), 5.32 (d, J = 10.8 Hz, 1H), 5.13 (d, J = 17.1 Hz, 1H), 3.75 (s, 5H), 3.72−3.68 (m, 2H), 3.58 (s, 3H), 2.77 (dd, J = 5.2, 17.6 Hz, 1H), 2.31 (dddd, J = 1.3, 2.9, 7.8, 17.7 Hz, 1H), 0.89 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 167.0, 166.0, 135.5, 135.3, 129.7, 117.5, 86.9, 84.5, 69.1, 61.5, 51.9, 34.0, 26.3, 25.6, 17.8, −4.5, −4.7; MS (EI) *m/e* 510, 479, 469, 453, 327, 295, 267, 253, 235, 169, 128, 89, 73; HRMS calcd for $C_{19}H_{31}IO_6Si$ (M^+) 510.0936; found 510.0949.

(4*S*,4a*R*,6*R*,7*R*,7a*S*)-6-((*tert*-Butyldimethylsilyl)oxy)-7-methoxy-2-oxo-7a-vinyl-octahydrobenzofuran-4-carboxylic Acid Methyl Ester (12) and (4*S*,4a*R*,6*R*,7*R*,7a*S*)-6-((*tert*-Butyldimethylsilyl)oxy)-7-methoxy-2-oxo-7a-vinyloctahydrobenzofuran-4-carboxylic Acid Methyl Ester (13). A solution of the iodo ester **11** (324 mg, 0.635 mmol) in dry benzene (33 mL) was stirred at reflux under an atmosphere of argon with a catalytic amount of azobis(isobutyronitrile) (4 mg). A solution of triphenyltin hydride (401 mg, 1.143 mmol) in dry benzene (24 mL) was added over 5.5 h using a syringe pump. Upon completion of the addition, the reaction was allowed to cool to rt, and the benzene was evaporated under reduced pressure. The crude residue was purified by chromatography (hexanes:ether:dichloromethane, 60:8:32) to give the lactone **12** (124 mg, 51%, Rf = 0.14, hexanes−ether−CH_2Cl_2, 60:8:32) as a white crystalline solid, and the isomeric **13** (53 mg, 22%, Rf = 0.23) as an oil after two chromatographic separations. For lactone **12**: mp 98 °C (recrystallized from hexanes) $[\alpha]_D$ −20° (*c* 1.1, CCl_4); IR (neat) ν 3080, 1790, 1740 cm^{-1}; ^1H NMR ($CDCl_3$, 300 Hz) δ 6.04 (dd, J = 11.1, 17.3 Hz, 1H), 5.53 (br, d, J = 17.3 Hz, 1H), 5.37 (br, d, J = 11.1 Hz, 1H), 3.70 (s, 3H), 3.55 (ddd, J = 4.6, 9.3, 11.2 Hz, 1H), 3.48 (s, 3H), 3.08 (d, J = 9.3 Hz, 1H), 2.89 (ddd, J = 4.8, 10.1, 12.1 Hz, 1H), 2.77 (ddd, J = 4.4, 4.4, 13.6 Hz, 1H), 2.61 (d, J = 12.1 Hz, 1H), 2.60 (d, J = 9.7 Hz, 1H), 2.12 (ddd, J = 4.1, 4.1, 13.8 Hz, 1H), 1.80 (m, 1H), 0.90 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 174.0, 172.1, 133.2, 116.9, 89.5, 87.6, 70.5, 60.7, 52.1, 43.9, 38.3, 30.9, 30.7, 25.6, 17.9, −4.7, −5.1; MS (EI) *m/e* 369, 353, 337, 327, 295, 267, 253, 235, 207, 185, 140, 98, 89, 73; HRMS calcd for $C_{15}H_{23}O_6Si$ (M^+ − t-Bu) 327.1263; found 327.1251. For **13**: $[\alpha]_D$ −2.7° (*c* 1.4, CCl_4); IR (neat, $CHCl_3$) ν 3020, 2975−2296, 1780, 1730 cm^{-1}; ^1H NMR ($CDCl_3$, 300 Hz) δ 6.02 (dd, J = 10.9, 7.3 Hz, 1H), 5.42 (d, J = 17.3 Hz, 1H), 5.29 (d, J = 10.9 Hz, 1H), 4.05 (m, 1H), 3.70 (s, 3H), 3.40 (s, 3H), 3.20 (d, J = 4.6 Hz, 1H), 2.81−2.62 (m, 3H), 2.32−2.21 (m, 1H), 2.00 (ddd, J = 3.0, 11.0, 13.5 Hz, 1H), 1.82 (ddd, J = 4.0, 4.2, 13.5 Hz, 1H), 0.90 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 175.0, 174.0, 135.0, 115.3, 86.0, 81.6, 66.5, 59.6, 51.8, 50.1, 39.3, 38.2, 34.8, 29.8, 25.4, −5.0, −5.3; MS (EI) *m/z* 353, 341, 309, 295, 267, 235, 207, 193, 161, 133, 116, 89, 71; HRMS calcd for $C_{18}H_{29}O_5Si$ (M^+ − OCH_3) 353.1813; found 353.1784.

A solution of lactone **13** (100 mg, 0.26 mmol) in 1 mL of DBU was stirred for 16 h at rt. The mixture was directly chromatographed on silica gel (hexanes:ether:dichloromethane, 60:8:32) to afford 60 mg (60%) of compound **12** and 26 mg of **13**.

(4*S*,4a*R*,6*R*,7*R*,7a*S*)-6-((*tert*-Butyldimethylsilyl)oxy)-7-methoxy-2-oxo-hexahydrobenzofuran-4,7a-dicarboxylic Acid Dimethyl Ester (14). A stream of ozone (Wellsbach generator) was passed through a solution of the olefin **12** (800 mg, 2.08 mmol) in dichloromethane (10 mL) at −78 °C. After the appearance of a blue coloration the ozone flow was stopped and replaced by a flow of argon for 30 min. Dimethyl sulfide (2 mL) was added at −78 °C, and the solution was stirred for 1 h at this temperature, and then the reaction mixture was allowed to warm to rt whereupon it was stirred for 1 h. After removal the solvent *in vacuo*, the residue was dissolved in a mixture of *tert*-butyl alcohol (40 mL) and 2-methyl-2-butene (10 mL) and stirred at rt. A solution of sodium chlorite (1.7 g, 18.9 mmol, 9.2 equiv) and sodium dihydrogen phosphate (1.7 g, 18.9 mmol, 9.2 equiv) in water (17 mL) was added dropwise over a period of 10 min. The reaction was stirred at rt for 2 h, and the volatile components were removed by evaporation under reduced pressure. Water (15 mL) was added and the aqueous solution extracted with hexanes. The aqueous layer was acidified to pH 3 with 10% hydrochloric acid at 0 °C and extracted with ether. The combined ethereal extracts were dried (Na_2SO_4), and the solvent was evaporated to give the crude acid as a gum. To the solution of the crude acid in dry ether (40 mL) was added dropwise a freshly prepared solution of diazomethane in ether at 0 °C until the yellow color persisted. After stirring the reaction mixture for 5 min at 0 °C, excess diazomethane was destroyed by the addition of acetic acid and the resulting solution stirred over a mixture of anhydrous sodium sulfate and sodium carbonate. The reaction mixture was filtered and then concentrated under reduced pressure. The crude product was purified by chromatography on silica gel (EtOAc:hexanes; 30:70) to afford 789 mg of diester lactone **14** (91%) as a white crystalline solid: mp 131−133° C; $[\alpha]_D$ −40.3° (*c* 4.0, $CHCl_3$); IR ($CHCl_3$) ν 1800, 1740 cm^{-1}; ^1H NMR ($CDCl_3$, 300 Hz) δ 4.00 (ddd, J = 13.8, 9.2, 4.6 Hz, 1H), 3.85 (s, 3H), 3.70 (s, 3H), 3.55 (s, 3H), 3.24 (dt, J = 13.8, 4.2 Hz, 1H), 3.10 (d, J = 9.2 Hz, 1H), 3.15−3.00 (m, 1H), 2.70−2.45 (m, 2H), 2.17 (dt, J = 13.8, 4.4 Hz, 1H), 1.70 (dt, J = 11.4, 13.6 Hz, 1H), 0.9 (s, 9H), 0.1 (2 × s, 6H); ^{13}C NMR ($CDCl_3$) δ 172.8, 172.1, 169.0, 89.5 (q), 87.9, 70.1, 61.5, 52.7, 52.2, 40.8, 38.2, 30.1 ($2CH_2$), 25.6, 17.9, −4.7, −5.0; MS (EI) *m/z* 385, 359, 327, 313, 299, 285, 281, 267, 253, 239, 225, 207, 193, 179, 165; HRMS calcd for $C_{18}H_{29}O_7Si$ (M^+ − OCH_3) 385.1682; found 385.1700.

(2*RS*,4*S*,4a*S*,6*R*,7*R*,7a*S*)-6-((*tert*-Butyldimethylsilyl)oxy)-2-hydroxy-7-methoxyhexahydrobenzofuran-4,7a-dicarboxylic Acid Dimethyl Ester (15). To a solution of **14** (300 mg, 0.72 mmol) in 20 mL of dry THF was added 5 mL of disiamylborane (0.5 mmol/mL in THF) at 0 °C under argon. The solution was allowed to warm to rt and stirred for 4 h. Upon completion of the reaction, the solution was quenched with 10 mL of saturated NaCl and extracted with EtOAc. The organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. The residue was chromatographed on silica gel (EtOAc: hexanes, 50:50) to give 295 mg of lactol **15** (98%) as a syrup which was used as such in the next step: IR ($CHCl_3$) ν 3700, 3610 (OH), 1740 (C=O, ester) cm^{-1}.

Lactam 16 and 17. A mixture of the lactol **15** (80 mg, 0.19 mmol), 6-methoxytryptamine (54 mg, 0.28 mmol), and pivalic acid (58 mg, 0.57 mmol) in 10 mL of toluene, under argon, was refluxed with azeotropic removal of water, and the solution was concentrated to half its original volume. After 50 min, the solution was cooled to rt, and the toluene was evaporated *in vacuo*. The residue was purified by chromatography (EtOAc:hexanes, 60:40) to give 56 mg of the 3-β lactam **16** and 40 mg of 3-α lactam **17**, both as white crystalline solids (total yield, 90%). For **16**: mp 223 °C dec; $[\alpha]_D$ +36.83° (*c* 0.6, CH_2Cl_2); IR (CH_2Cl_2) ν 3480, (1740, 1640 cm^{-1}; ^1H NMR ($CDCl_3$, 300 Hz) δ 7.78 (s, 1H), 7.32 (d, J = 8.6 Hz, 1H), 6.84 (d, J = 2.0 Hz, 1H), 6.78 (dd, J = 8.6, 2.3 Hz, 1H), 5.05 (m, 1H), 4.95 (dd, J = 11.8, 7.8, 1H), 4.12−4.00 (m, 2H), 3.81 (s, 3H), 3.75 (s, 3H), 3.55 (s, 3H), 3.26 (d, J = 8.4 Hz, 1H), 3.10−2.85 (m, 3H), 2.60 (m, 2H), 2.40 (m, 1H), 2.20 (m, 2H), 2.15−1.90 (m,

1H), 0.9 (s, 9H), 0.1 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 173.7, 170.8, 156.2, 136.5, 131.6, 121.5, 118.5, 110.3, 109.1, 95.1, 79.4, 70.9, 62.1, 55.5 (2xOCH_3), 53.6 , 52.9, 42.8, 39.1, 36.2, 31.4, 25.6, 21.2, 20.6, 17.5, −4.9, −5.0; MS (FAB) *m/z* 557, 501, 427, 305, 279, 174, 133; HRMS calcd. for $C_{29}H_{42}N_2O_7Si$, 558.2788; found 558.2761. For **17**: mp 232 °C dec; $[\alpha]_D$ −71.4° (*c* 0.6, CCl_4); IR (CH_2Cl_2) ν 3480, 1740, 1640 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 Hz) δ 7.80 (s, 1H), 7.36 (d, J = 8.6 Hz, 1H), 6.85 (d, J = 2.0 Hz, 1H), 6.78 (dd, J = 8.6, 2.3 Hz, 1H), 5.18−5.00 (m, 1H), 4.65 (dd, J = 11.5, 4.9 Hz, 1H), 4.18−3.90 (m, 2H), 3.86 (s, 3H), 3.85 (s, 3H), 3.54 (s, 3H), 3.20−3.10 (m, 1H), 3.09 (d, J = 9.2 Hz, 1H), 2.90−2.65 (m, 4H), 2.40−2.20 (m, 2H), 1.95−1.50 (m, 2H), 0.9 (s, 9H), 0.1 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 174.3, 170.2, 156.7, 137.0, 131.4, 121.1, 118.9, 109.3, 109.2, 95.0, 87.6, 79.7, 71.3, 62.8, 55.7, 53.8, 53.2, 40.2, 39.9, 39.4, 34.3, 25.7, 25.3, 20.9, 17.6, -4.7; MS (FAB) *m/z* 557, 501, 305, 279; HRMS calcd for $C_{29}H_{41}N_2O_7Si$ ($M^+ - 1$) 557.2710; found 557.2683.

Lactam 18. To a solution of **16** (77 mg, 0.138 mmol) in 10 mL of dry dichloromethane were successively added 2,6-lutidine (80 μL, 0.68 mmol) and trimethylsilyl trifluoromethanesulfonate (50 μL, 0.24 mmol). The reaction mixture was stirred for 4 h at rt under argon and then quenched with addition of 10 mL of brine. The aqueous layer was extracted with CH_2Cl_2, the combined organic layers were dried (Na_2SO_4) and evaporated *in vacuo*, and the residue was purified by chromatography on silica gel to give 87 mg (100%) of the silyl derivative **18** as a white solid: mp 130−132 °C dec; $[\alpha]_D$ −40.3° (*c* 0.53, $CHCl_3$); IR ($CHCl_3$) ν 3480, 1760, 1640 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 Hz) δ 7.50 (s, 1H), 7.38 (d, J = 8.6 Hz, 1H), 6.78−6.82 (m, 2H), 4.89−5.00 (m, 2H), 4.05−4.23 (m, 1H), 3.85 (s, 3H), 3.69 (s, 3H), 3.59 (s, 3H), 3.19 (d, J = 8.4 Hz, 1H), 2.81−3.10 (m, 3H), 2.20−2.69 (m, 4H), 1.98−2.08 (m, 1H), 1.80 (m, 1H), 0.96 (s, 9H), 0.26 (s, 9H), 0.12 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 172.4, 171.2, 156.6, 136.4, 131.1, 121.8, 118.7, 111.3, 109.3, 95.0, 88.7, 82.9, 71.5, 62.6, 55.7, 53.6, 52.2, 43.1, 39.4, 38.3, 33.4, 25.8, 22.2, 20.7, 17.9, 2.7, −4.6, −4.7; MS (FAB) *m/z* 629, 279, 174, 133; HRMS calcd for $C_{32}H_{51}N_2O_7Si_2$ (M^+ + H) 631.3266; found 631.3235.

Amine 19. To a solution of the silyl derivative **18** (87 mg, 0.138 mmol) in 5 mL of dry THF was added BH_3·THF (0.40 mL, 0.40 mmol, 1 M in THF) at rt under argon. The solution was stirred for 6 h at this temperature and then quenched by addition of 10 mL of brine. The solution was extracted with EtOAc, and the organic layer was washed with brine and dried (Na_2SO_4). After evaporation of the solvent, the residue was dissolved in 5 mL of dry THF, and HMPA (0.3 mL) and ethylene glycol (0.2 mL) were successively added to destroy the borane complex. The reaction mixture was stirred overnight and then extracted with EtOAc, and the organic layer was washed with brine and dried (Na_2SO_4). After evaporation of the solvent, the residue was purified by chromatography on silica gel to afford 72 mg (84%) of the amine **19** as a white solid: mp 95−97 °C dec; $[\alpha]_D$ ∼0° (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) ν 3460, 1750, 1640 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 Hz) δ 7.45 (s, 1H), 7.35 (d, J = 8.7 Hz, 1H), 6.83 (d, J = 2.1 Hz, 1H), 6.79 (dd, J = 2.1, 8.6 Hz, 1H), 4.50 (s, 1H), 4.19−4.28 (m, 1H), 3.85 (s, 3H), 3.65 (s, 3H), 3.58 (s, 3H), 3.18−3.23 (m, 3H), 2.83−3.02, 2.42−2.58, 2.12−2.25, 1.92−2.05 (m, 1H), 1.60−1.75 (m, 2H), 0.91 (9H, s), 0.25 (9H, s), 0.097 (s, 3H), 0.084 (s, 3H); ^{13}C NMR ($CDCl_3$, 300 Hz) δ 172.9, 156.1, 136.1, 130.9, 122.1, 118.4, 108.8, 107.9, 95.1, 88.6, 84.2, 72.3, 62.5, 60.3, 55.7, 54.0, 51.6, 51.0, 49.5, 33.2, 30.1, 25.8, 21.8, 17.9, 16.7, 2.6, −4.6, −4.7; MS (FAB) *m/z* 617, 585, 527, 495, 299, 253, 241, 200, 174; HRMS calcd for $C_{32}H_{53}N_2O_6Si_2$ (M^+ + 1) 617.3492; found 617.3442.

Compound 21. To a solution of **19** (47 mg, 0.076 mmol) in 2 mL of CH_3CN was added 0.5 mL of HF (48% in water) at 0 °C. The solution was allowed to warm to rt and stirred for 30 min. The reaction was then quenched with saturated $NaHCO_3$. The solution was extracted with EtOAc, and the combined extracts were dried over Na_2SO_4. After removal of the solvent, the residue was dissolved in 5 mL of dry dichloromethane followed by addition of 2,6-lutidine (50 μL) and TBSOTf (20 μL) at 0 °C under argon. After stirring for 10 min, the reaction mixture was quenched with 5 mL of saturated $NaHCO_3$, the aqueous layer was extracted with dichloromethane, and the combined organic layers were dried (Na_2SO_4). After concentration *in vacuo*, the residue was passed through a short silica gel column which was eluted with EtOAc:MeOH, 1:1. After evaporation of the solvent, the residue was dissolved in 1 mL of dry THF under argon; HMPA (0.2 mL), ethylene glycol (0.1 mL), and SmI_2 (1 mL, 0.1M) were successively added to this solution. The resultant violet mixture was stirred for 8 h and then poured into saturated $Na_2S_2O_3$ (5 mL). The aqueous phase was extracted with EtOAc, and the combined extracts were dried (Na_2SO_4). The residue was purified by chromatography on silica gel to give 12 mg (30%) of **21** as a white solid: mp 165−167 °C dec; $[\alpha]_D$ −152° (*c* 0.98, $CHCl_3$); IR ($CHCl_3$) ν 3460, 1745, 1640, 1620 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 Hz) δ 7.48 (s, 1H), 7.34 (d, J = 8.4 Hz, 1H), 6.86 (d, J = 2.1 Hz, 1H), 6.77 (dd, J = 2.1, 8.6 Hz, 1H), 4.50 (br, s, 1H), 3.84 (s, 3H), 3.80 (s, 3H), 3.55 (s, 3H), 3.48−3.55 (m, 2H), 3.19−3.26 (m, 2H), 2.90−3.06 (m, 2H), 2.43−2.55 (m, 3H), 2.18−2.32 (m, 2H), 1.91−2.01 (m, 1H), 1.59−1.83 (m, 3H), 0.92 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H); ^{13}C NMR ($CDCl_3$) 173.2, 155.9, 136.1, 130.6, 122.0, 118.3, 108.7, 107.8, 94.9, 80.7, 76.1, 61.2, 60.2, 55.6, 53.5, 51.8, 51.5, 51.1, 49.2, 34.3, 33.8, 32.3, 25.7, 24.2, 17.8, 16.6, −4.7, −4.9; MS (FAB) *m/z* 529, 174, 133; HRMS calcd for $C_{29}H_{45}N_2O_5Si$ (M^+ + 1) 529.3118; found 529.3098.

(−)-Reserpine (1). To a solution of **21** (15 mg, 0.028 mmol) in 1 mL of CH_3CN was added 0.3 mL of HF (48% in water) at rt. After completion of the reaction (3 h), the solution was neutralized with saturated $NaHCO_3$ and extracted with EtOAc. The organic layer was combined, dried (Na_2SO_4), and concentrated *in vacuo*. After removal of the solvent, the residue was dissolved in 3 mL of dry dichloromethane, and triethylamine (12 μL, 0.086 mmol), 3,4,5-trimethoxybenzoyl chloride (10 mg, 0.047 mmol), and DMAP (1 mg, cat.) were added to this solution under argon at rt. The reaction mixture was stirred overnight and then evaporated *in vacuo*. The crude product was purified by chromatography on silica gel to give 14 mg (80%) of reserpine **1**, identical (^{1}H, ^{13}C NMR, TLC) with an authentic sample: mp 260 °C dec; $[\alpha]_D$ −124° (*c* 0.95, $CHCl_3$); reported,[2] mp 265 °C dec; $[\alpha]_D$ −126° (*c* 1.0, $CHCl_3$); mixed mp, 263−265° dec.

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Supporting Information Available: Copies of ^{1}H NMR and ^{13}C NMR spectra (36 pages). The author has deposited atomic coordinates for **12** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK. 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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