# Synthesis of Optically Pure $\Delta^4$-Tetrahydroquinolinic Acids and Hexahydroindolo[2,3-*a*]quinolizines from L-Aspartic Acid. Racemization on the Route to Vindoline

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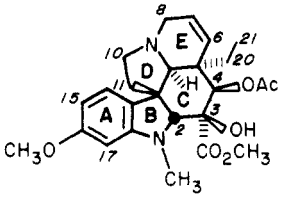
Optically pure $\Delta^4$-tetrahydroquinolinic acids and hexahydroindolo[2,3-*a*]quinolizines have been prepared from L-aspartic acid and used in a route to vindoline. The carboxyl functions of L-aspartic acid were regioselectively differentiated to form the $\alpha$-*tert*-butyl $\beta$-methyl ester (**10**). Mono-N-alkylation of **10** followed by N-protection, intramolecular alkylation, iodination, and dehydroiodination gave $\Delta^3$-tetrahydroquinolinate **17**. Deconjugative alkylation and nitrogen deprotection afforded optically pure 3-ethyl-$\Delta^4$-tetrahydroquinolinate **3** in 14% yield from L-aspartic acid. This $\Delta^4$-tetrahydropyridine on coupling with 6-methoxytryptophyl bromide followed by $\alpha$-amino acid decarbonylation and iminium ion cyclization afforded hexahydroindoloquinolizines **4a** and **4b**. These optically pure compounds were converted to the aspidospermidine derivative **6** following literature protocols. The overall yield of **6** from L-aspartic acid was 5%. In the transformation of **4a** and **4b** to **6** via **5a** or **5b**, loss of optical integrity occurred due to a reversible Mannich reaction. This reversible Mannich reaction as it applies to indoloquinolizines **4a**, **4b**, **28a**, **28b**, **42**, and **43** was studied in order to assess the role of the C-15 functionality and the conditions necessary for reaction to occur. It was demonstrated that hexahydroindoloquinolizines with an aldehyde or ketone at C-15 undergo reversible Mannich reactions under a variety of conditions, whereas the corresponding ester was inert.

Interest in the Aspidosperma alkaloids is manifest by the continued activity directed to the synthesis of various members of this family. Since the first synthesis of an Aspidosperma alkaloid in 1963,[1] many routes have been used to prepare these unique pentacycles. One general approach has been to synthesize the C, D, and E rings and then attach the A and B rings via a Fischer indole cyclization. Mimics of the biosynthetic pathway have yielded successful routes to some of these alkaloids, and other syntheses have used the highly reactive oxindoles or indoles as the templates upon which the rest of the skeleton is assembled. Syntheses of members of this family of alkaloids have been extensive.[2]

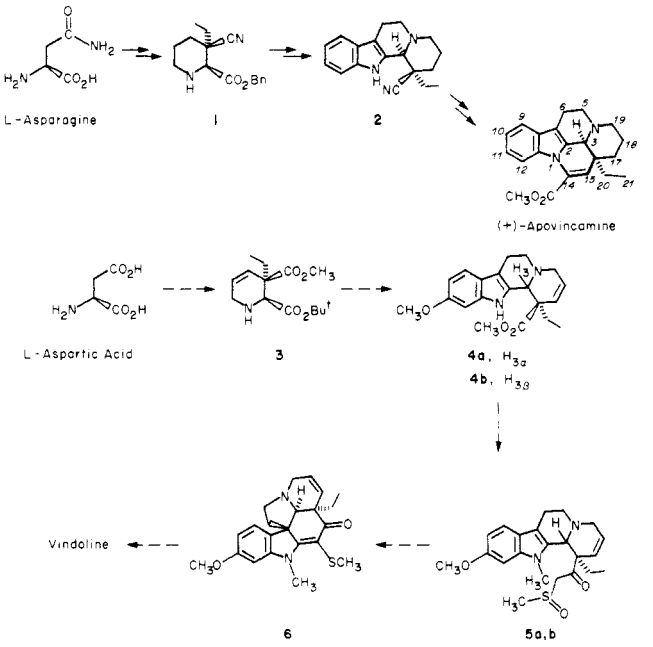
One of the most important members of the Aspidosperma family, vindoline,[3] is part of the potent oncolytic



VINDOLINE

dimeric indole alkaloid vinblastine.[4] Recent work has demonstrated that vinblastine-type dimeric alkaloids can be synthesized by coupling vindoline with catharanthine

**Scheme I. Synthesis of (+)-Apovincamine from L-Asparagine and Projected Synthesis of (+)-Vindoline from L-Aspartic Acid**



using a modified Polonovski reaction.[5] These results provide considerable flexibility in designing routes to these clinically useful drugs and highlight the interest in the total synthesis of the component monomers.

Vindoline has been synthesized several times.[6] Although adequate control of the relative stereochemistry

(1) Stork, G.; Dolfini, J. E. *J. Am. Chem. Soc.* **1963**, *85*, 2872.

(2) A general review of the synthesis of Aspidosperma alkaloids is presented: (a) Kutney, J. P. *The Total Synthesis of Natural Products*; ApSimon, J., Ed.; Wiley-Interscience: New York, 1977; Vol. 3, p 372. (b) Cordell, G. A. *Alkaloids* **1979**, *17*, 199. An excellent leading reference for syntheses of Aspidosperma alkaloids is presented: (c) Magnus, P.; Gallagher, T.; Brown, P.; Pappalardo, P. *Acc. Chem. Res.* **1984**, *17*, 35. Some recent studies on Aspidosperma alkaloids are given: (d) Gramain, J. C.; Husson, H.-P.; Troin, Y. *J. Org. Chem.* **1985**, *50*, 5517. (e) Magnus, P.; Pappalardo, P. A. *J. Am. Chem. Soc.* **1986**, *108*, 212. (f) Magnus, P.; Cairns, P. M. *J. Am. Chem. Soc.* **1986**, *108*, 217. (g) Kuehne, M. E.; Seaton, P. J. *J. Org. Chem.* **1985**, *50*, 4790. (h) Kuehne, M. E.; Podhorez, D. E. *J. Org. Chem.* **1985**, *50*, 924. (i) Wenkert, E.; Porter, B.; Simmons, D. P.; Ardisson, J.; Kunesch, N.; Poisson, J. *J. Org. Chem.* **1984**, *49*, 3733. (j) Overman, L. E.; Sworin, M.; Burk, R. M. *J. Org. Chem.* **1983**, *48*, 2685. (k) Yoshida, K.; Nomura, S.; Ban, Y. *Tetrahedron* **1985**, *41*, 5495. (l) Raucher, S.; Klein, P. *J. Org. Chem.* **1986**, *51*, 123.

(3) Gorman, M.; Neuss, N.; Biemann, K. *J. Am. Chem. Soc.* **1962**, *84*, 1058.

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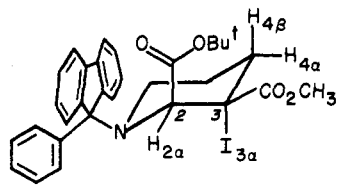
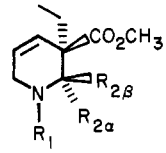
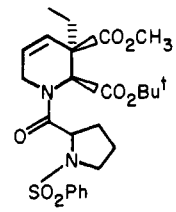


**Figure 1.** Conformational structure of pipecolate **16** leading to facile elimination of $H_{4\beta}I_{3\alpha}$ and formation of $\Delta^3$-tetrahydroquinolinate **17**.

about the C ring has been achieved, no chirospecific synthesis has been reported. Recently, we presented a synthesis of optically pure (+)-apovincamine using L-asparagine as the chiral educt.[7] The asymmetry at C-2 of L-asparagine was used to set the stereochemistry at C-3 of pipecolate **1**. Coupling of the pipecolate with tryptophyl bromide and subsequent decarbonylation of the tertiary $\alpha$-amino acid followed by iminium ion cyclization yielded the octahydroindolo[2,3-*a*]quinolizine **2**.[8] Using similar methodology $\Delta^4$-tetrahydroquinolinate **3** should be available from L-aspartic acid. After coupling **3** with 6-methoxytryptophyl bromide and closing to hexahydroindoloquinolizine **4**, we planned to use the recently disclosed acid-promoted Pummerer rearrangement of $\beta$-keto sulfoxide **5** to obtain aspidospermidine derivative **6**.[6f,9] The pentacycle **6** should then be convertible to (+)-vindoline following literature procedures.[6a,f] The synthesis for (+)-apovincamine and the projection to (+)-vindoline are depicted in Scheme I.

A critical aspect of the proposed synthesis is introduction of unsaturation to form $\Delta^4$-tetrahydroquinolinate **3**. It





**3**, $R_1 = R_{2\alpha} = H$; $R_{2\beta} = CO_2Bu^t$
**22**, $R_1 = Bn$; $R_{2\alpha} = H$; $R_{2\beta} = CO_2Bu^t$
**23**, $R_1 = Bn$; $R_{2\alpha} = CO_2Bu^t$; $R_{2\beta} = H$

**24**

has been demonstrated that *N*-(9-phenylfluorenyl)-3-cyanopipecolates[7] exist with the 2-carboxyl function axial in order to avoid nonbonded interactions with the large nitrogen protecting group. As a consequence of this stereochemical feature, attack of electrophiles at C-3 occurs predominately from the less hindered $\alpha$ face. Applying these concepts to the present case (Figure 1), if introduction of iodine, a good nucleophugal group, at C-3 proceeds to give $I_\alpha$, then a facile E2 reaction would be predicted to give the desired $\alpha,\beta$-unsaturated ester because the dihedral angle between $H_{4\beta}$ and $I_{3\alpha}$ is 180°. For the E2 reaction to occur with the C-3 epimer, however, is questionable since the dihedral angle between $I_{3\beta}$ and $H_{2\alpha}$ and $H_{4\alpha,\beta}$ is 45°. Since the *N*-(9-phenylfluorenyl)pipecolates are rigid molecules we could not expect chair-chair equilibration to convert any $I_{3\beta}$ to $I_{3\alpha}$. Therefore, introduction of iodine, or any other nucleophugal group, at C-3 must be stereospecific in order to properly orient the E2 reaction.

The other major question in our proposed scheme is the stereochemical requirement in the conversion of **5** to **6**. Tetracycle **5a** is readily converted to pentacycle **6**, but the rearrangement of **5b** to **6** has not been reported.[6f] A proposed mechanism for this acid-promoted rearrangement (see below, Scheme V, path a) involves C-2 attack of the indole at the highly electrophilic C-14 of the thionium ion. Wagner–Meerwein rearrangement of C-3 to C-7 (eburnamenine numbering, e.g., apovincamine) then yields a carbonium ion at C-2 which rapidly loses a proton at C-3 (aspidospermidine numbering, e.g., vindoline) to yield **6**.[6f] Since Wagner–Meerwein shifts result in retention of stereochemistry at the migrating carbon,[10] then the configuration at C-3 of tetracycle **5** will determine the stereochemistry at C-19 of the aspidospermidine compound, provided no equilibration takes place after pentacycle **6** is formed. With $H_{3\beta}$, however, the rearrangement would yield an epimer of **6** at C-19 if the pentacycle with $H_{19\beta}$ is stable or does not equilibrate to give $H_{19\alpha}$ via a reversible Mannich reaction. Also, it appears that attack of the indole at C-14 is less likely to occur with $H_{3\beta}$ since the conformation of the hexahydroquinolizine portion of **5b** leaves C-14 at a considerable distance from C-2. Since iminium ion cyclization to form indoloquinolizidines gives a mixture of epimers at C-3, the question of the stereochemistry needed to gain access to indoline **6** could be addressed.[7] If it were shown that H-3 must be $\alpha$ in order to rearrange **5a** to **6**, this could be accommodated by converting **4b** to a mixture of **4a** and **4b** via acid-promoted equilibration and thus keep our synthetic scheme operable.[7,11]

## Results and Discussion

**Tetrahydroquinolinates from L-Aspartic Acid.** One of the major problems in synthesizing pipecolate **1** from L-asparagine was the need to use a benzyl ester protecting group in combination with the C-3 cyano function. Upon subsequent introduction of the ethyl group a substantial amount of the product was alkylated both at C-3 and the benzylic position of the benzyl ester. Separation proved to be cumbersome when the reaction was conducted on a large scale. In order to avoid this problem and the accompanying deprotection of a benzyl ester in the presence of an alkene, $\alpha$-*tert*-butyl $\beta$-methyl L-asparate was chosen as the chiral precursor for our synthesis. Different esters were used for protecting the C-1 and C-4 carboxyls to assure selective hydrolysis later in the synthesis. L-Aspartic acid was regioselectively esterified at the C-4 carboxyl using thionyl chloride in methanol.[12] A small amount of the C-1 methyl ester (<2%) was formed; however, it could be removed by recrystallization at a later stage. The *N*-benzyloxycarbonyl derivative[12] **8** was then converted to *tert*-butyl ester **9** in 64% yield from L-aspartic acid.[13] Reductive cleavage at the nitrogen gave the crystalline acetate salt **10** in 85% yield after recrystallization.

A three-carbon fragment was needed to span the nitrogen and C-3 of **10** to obtain $\Delta^4$-tetrahydroquinolinate **3**. Several bis-electrophiles, or potential bis-electrophiles, were tested to optimize the initial N-alkylation. Amine alkylation of **10** with 3-chlorobromopropane, 3-chloropropylmesylate,[15] 3-chloropropyltresylate,[7] and 3-bromo-

(7) Christie, B. D.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 1239.
(8) Johansen, J. E.; Christie, B. D.; Rapoport, H. *J. Org. Chem.* **1981**, *46*, 4914.
(9) Andriamialisoa, R. Z.; Langlois, N.; Langlois, Y. *J. Chem. Soc., Chem. Commun.* **1982**, 1118.
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(15) Crossland, R. K.; Servis, K. L. *J. Org. Chem.* **1970**, *35*, 3195.

propanol all proceeded in moderate yields (50–60%) with the major byproducts being N,N-dialkylated material and polar products. 3-Chlorobromopropane was the three-carbon unit of choice because of its ready availability and the ease of isolation of *N*-chloropropyl derivative **11**. 3-Chlorobromopropane and **10** with $NaHCO_3$ in $CH_3CN$ at 80 °C for 8 h yielded **11** reproducibly in approximately 60% on a moderate scale (0.03 mol). Following the protocol used previously for ring closure to **1**, the secondary amine **11** was converted to its *N*-9-phenylfluorenyl ($\phi$F) derivative **12**. Exchange of chloride for iodide using excess NaI in $CH_3CN$ produced **13** in 80% recrystallized yield from **11**.[7]

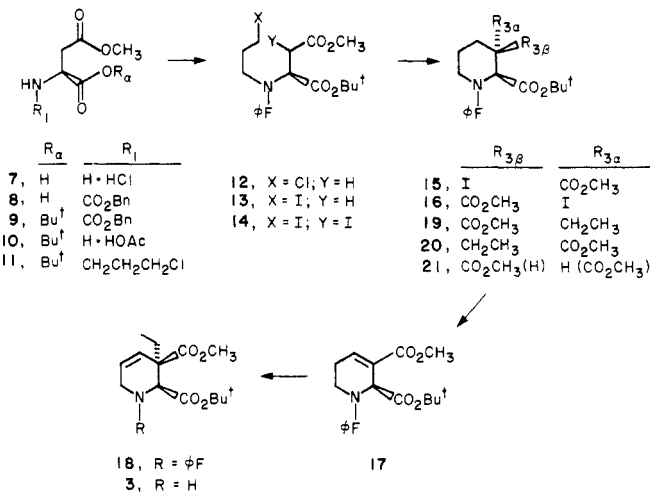
The next transformation to be carried out was intramolecular carbon alkylation followed by C-3 functionalization. In order to accomplish these goals without loss of optical integrity it was necessary to regiospecifically deprotonate at C-3 for both the acyclic, **13**, and cyclic compound, **21**. Previously, we have demonstrated that proton abstraction at C-2 is totally suppressed at low temperature using LDA as the base with the nitrogen of an L-asparagine derivative protected with 9-(9-phenylfluorene).[7] For the acyclic cases, H-3 removal is favored over H-2 because it is less hindered, being further away from the bulky nitrogen protecting group, and C-3 is less substituted than C-2. Kinetic deprotonation at C-3 in the cyclic compounds is solely a manifestation of the *N*-phenylfluorenyl substituent hindering approach of the base at C-2. Given regiospecific deprotonation at C-3, then use of 200 mol % of LDA should allow intramolecular alkylation and C-3 functionalization to occur in one step.

Treating **13** with 230 mol % of LDA at −78 °C for 30 min and at −48 °C for 4 h and then inversely quenching with iodine at −78 °C gave three products,[16] the noncyclized diiodo **14** and the cyclized monoiodo diastereomers **15** and **16**, in a ratio of 3/12/85. The diiodo byproduct is a result of C-3 anion formation followed by quenching with iodine. If the entire reaction was conducted at −78 °C, approximately 15–30% of diiodo **14** resulted. Thus, raising the temperature increased the intramolecular alkylation rate without causing any deprotonation at C-2 (see below). The ratio of **16**/**15** changed to 5/1 when the inverse quench was done at −78 °C followed by warming to room temperature. The selectivity for **16** results from electrophilic attack of iodine from the least hindered side of the pipecolate as discussed previously. The enolate was also quenched with *N*-iodosuccinimide and dimethyl sulfide[17] but no enhanced selectivity resulted.

Dehydroiodination of the mixture of **15** and **16** to give **17** was effected with excess DBU in benzene at 65 °C.[18] With these conditions, however, only **16** was converted to **17** and unchanged isomer **15** was recovered. This result was not surprising since, as previously discussed, the stereoselectronics of the $E_2$ reaction were more favorable for **16** than **15**.

Since the next transformation was deprotonation of **17** followed by kinetic alkylation with ethyl iodide to give **18**, we considered the possibility of obtaining **18** in one step by treating the mixture of **15** and **16** with 200 mol % of LDA followed by quenching with ethyl iodide. Treating **15** and **16** with 250 mol % of LDA at −78 °C for 1 h and then quenching with excess ethyl iodide yielded **19** and **20** in a greater than 95/5 ratio in 87% yield. Although this reaction did not give the desired product **18**, applying the same conditions to **14** and **15** and inversely quenching with

**Scheme II. Chirospecific Conversion of L-Aspartic Acid into $\Delta^4$-Tetrahydroquinolinate 3**




iodine in THF at −78 °C generated a 13/5/82 ratio of **14**/**15**/**16**.[19] In this way we were able to convert the undesired epimer **15** to **16**. Thus, the general protocol for converting aspartate **13** to $\Delta^3$-tetrahydroquinolinate **17** was to treat the crude product mixture of **14**, **15**, and **16** with DBU and then separate **14** and **15** from **17**. Byproducts **14** and **15** were then recycled to give again the mixture of **14**, **15**, and **16** which was subjected to the dehydroiodination conditions. Following this procedure **13** was converted to **17** in 69% yield.

Deconjugative alkylation[20] of **17** was effected by the action of 130 mol % of LDA in THF/HMPT at −78 °C followed by quenching with excess ethyl iodide. Nitrogen deprotection was readily accomplished with $TFA/H_2O/CH_3CN$ to give $\Delta^4$-tetrahydroquinolinate **3** in 74% yield from **17**. The selectivity in the deconjugative alkylation reaction was at least 98/2 as shown by $^1H$ NMR on a later intermediate. This high degree of selectivity can be explained by electrophilic attack of ethyl iodide at the face opposite the axial C-2 *tert*-butoxycarbonyl group. The endo double bond could have an enhancing effect on the selectivity since it allows the *tert*-butoxycarbonyl function to reside above the conjugated enolate region without encountering a 1,3 diaxial interaction with $H_{4\beta}$ and thus more effectively block the $\beta$ face. The sequence from L-aspartic acid to **3** is depicted in Scheme II.

At this juncture we needed to assess both the diastereomeric and optical purity of **3** which provides an ideal substrate for these determinations. Reacting **3** with benzyl bromide/$Et_3N$ in $CH_3CN$ gave **22** in 90% yield, and warming **22** in THF with 500 mol % of LDA to room temperature and then quenching with water gave a 2/1 isomeric mixture of **22** and **23**. By doping pure **22** with this mixture of **22** and **23**, we demonstrated that **22** was greater than 98% diastereomerically pure. The diagnostic peaks in the $^1H$ NMR were the methyl triplets at 0.87 and 0.77 ppm for **23** and **22**, respectively. Derivatizing **3** with both D,L- and L-*N*-(benzenesulfonyl)proline gave **24** in high yield. After demonstrating that the diastereomers formed by using the D,L-proline derivative could be separated by

(16) Rathke, M. W.; Lindert, A. *Tetrahedron Lett.* **1971**, 3395.
(17) Trost, B. M.; Salzmann, T. N. *J. Am. Chem. Soc.* **1973**, *95*, 6840.
(18) Oediger, H.; Moller, F.; Eiter, K. *Synthesis* **1972**, 591.

(19) At least 200 mol % of LDA was needed to drive the reaction to completion. One equivalent of LDA probably reacts with the $\alpha$ iodo ester in an $S_N2$ fashion to give the enolate and *N*-iododiisopropylamine. The second equivalent may be used in reaction with the *N*-iododiisopropylamine to form LiI and *N,N,N',N'*-tetraisopropylhydrazine. Similar observations have been reported. Dubois, J.-E.; Lion, C.; Dugast, J.-Y. *Tetrahedron Lett.* **1983**, *24*, 4207.
(20) Herrmann, J. L.; Kieczykowski, G. R.; Schlessinger, R. H. *Tetrahedron Lett.* **1973**, 2433.

analytical HPLC, we showed that **3** derivatized with L-*N*-(benzenesulfonyl)proline was greater than 99% diastereomerically pure. Thus, the sequence to **3** proceeded with >98% enantiomeric purity.

**Synthesis of Hexahydroindoloquinolizine and Aspidospermidine Derivatives.** The next stage of the sequence involved elaboration of **3** to the indoloquinolizines **28a** and **28b**. These steps were accomplished in high yield by first treating **3** with 6-methoxytryptophyl bromide[21] and $NaHCO_3$ in $CH_3CN$ to give **25** in 87% yield followed by selective hydrolysis of the *tert*-butyl ester by heating in 90% formic acid. The *N*-formyl derivative **27** was formed as a byproduct in 15–20% yield, but this was easily converted to **26** by treating the crude hydrolysate with 200 mol % of sodium methoxide. Following this procedure the pure $\alpha$-amino acid **26** was obtained in 93% yield.

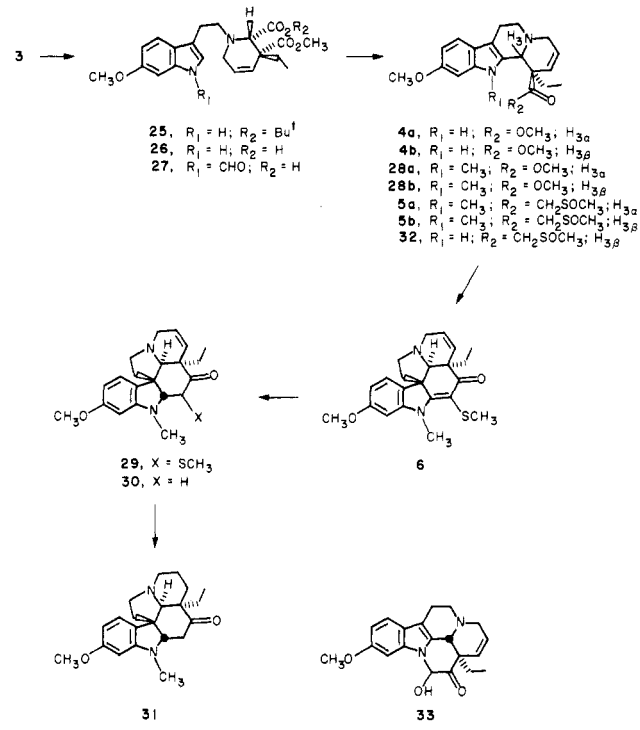
Heating **26** at 105 °C in phenylphosphoryl dichloride for 10 min and then quenching with saturated $NaHCO_3$ gave an 80% yield of **4a** and **4b** in a 1/4 ratio.[8] This ratio reflects a kinetic preference for **4b** since treating pure **4a** or **4b** with TFA at 60 °C for 2 h gives **4a** and **4b** in a ratio of 3.6/1.[22] Methylation at the indole nitrogen to give **28b** was achieved in 86% yield on treating **4b** with 150 mol % of KH in DMF at −10 °C followed by quenching with methyl iodide. Treating **4a** under the same conditions gave only a small amount of **28a** and mostly polar material believed to result from quaternization of the tertiary amine.[23]

Both the IR and $^1H$ NMR spectra of **4a** and **4b** show characteristic absorptions indicative of trans quinolizidine configurations. Given these configurations, molecular models of **4a** show the lone pair of electrons on nitrogen oriented away from the convex face of **4a**, whereas the lone pair of **4b** point into the more hindered concave face. Therefore, quarternization would be expected to be faster with **4a** than **4b**. This rapid alkylation of **4a**'s quinolizidine nitrogen was avoided by using excess KH in DMF at 0 °C and then cooling to −48 °C before quenching with methyl iodide. This procedure gives **28a** in 94% yield after chromatography.

Following a similar procedure to that described,[6f] **28b** was converted to the very polar $\beta$-keto sulfoxide **5b**. Heating a solution of **5b** with *p*-toluenesulfonic acid in THF at reflux for 20 min produced **6** from **28b** in 67% yield. Since it has been shown that **5a** can be rearranged to **6** under identical conditions, our initial concern that the stereochemistry at C-3 might adversely influence the result of the acid-promoted skeletal rearrangement was unwarranted.[6f]

Surprisingly, the optical rotation of **6** obtained from either **5a** or **5b** was nearly zero. Not knowing whether the low rotation was due to **6** having an inherently low rotation or being racemic, we converted **6** into the known vindoline degradation product **31**.[3,6d] Following literature precedent, **6** was transformed to **30** by $NaCNBH_3$ reduction of the vinylogous amide followed by Ra–Ni hydrogenolysis of the methylthio group.[6f] Reduction of the double bond with 5% Pt/C in EtOH/EtOAc under 1 atm of $H_2$ gave **31** in 70% yield. The melting point, 115 °C (lit.[3,6d] mp 130–132 °C), and optical rotation, $[\alpha]_D$ <1° (lit.[6d] $[\alpha]_D$ +12°), of **31** were obviously different than the reported values. Thus **31** was racemic and it seemed highly probable that **6** was also. The synthetic sequences described are collected in Scheme III.

**Scheme III. Elaboration of $\Delta^4$-Tetrahydroquinolinate 3 into Hexahydroindoloquinolizines and Pentacyclic Vindoline Analogues**




In order to establish that racemization had occurred most probably in the transformation of **5** to **6**, and not in the sequence from **3** to **5** or **6** to **31**, the optical purities of **4b**, **5b**, and **6** needed to be determined. The enantiomeric purities were assessed by doping the compounds in question with the chiral shift reagent tris[3-((heptafluoropropyl)hydroxymethylene)-*d*-camphorato]ytterbium(III) ($Yb(hfc)_3$) and analyzing the $^1H$ NMR spectra for doubling of peaks. As standards for these optical purity determinations the racemates of **4b**, **5b**, and **6** were synthesized in an analogous manner to the optically pure series beginning with *d,l-tert*-butyl *cis*-3-(methoxycarbonyl)pipecolate.[8] Analysis of the racemic series doped with $Yb(hfc)_3$ showed doubling of the aromatic methoxy and/or *N*-methyl resonances for all of the compounds. Analysis of the optically pure series using the same conditions showed **4b** and **5b** to be optically pure, within the limits of detection (90–95%), but **6** was racemic. These results unambiguously demonstrated that the optical integrity of the system was lost in the conversion of **5** to **6**.

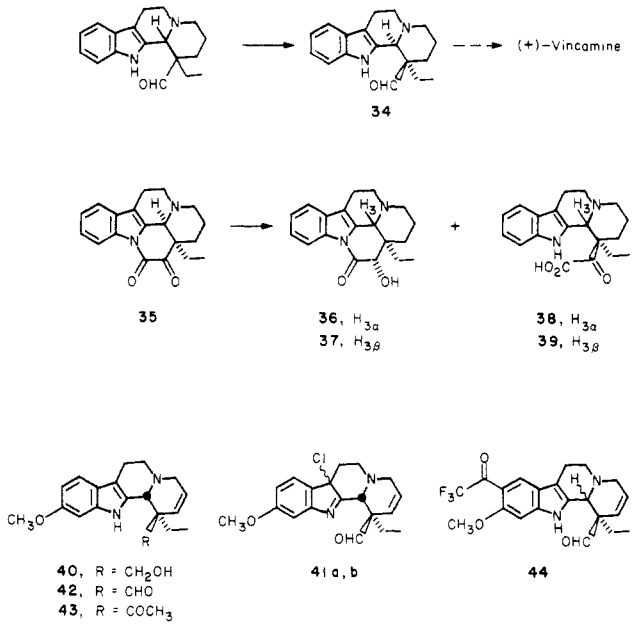
The most plausible explanation for this racemization being an acid-catalyzed reversible Mannich reaction, we examined nonacidic means to promote the skeletal rearrangement. Treating **5a** or **5b** with trifluoroacetic anhydride and 2,6-di-*tert*-butyl-4-methylpyridine in toluene at −23 °C gave racemic **6**. Other solvents were also tried, but all of the reactions produced optically inactive pentacycle. These results demonstrate that the racemization process operating in converting **5** to **6** is extremely mild and rapid. Treating **32** with pTSA in THF at room temperature did not give an indoline derivative, rather it gave pentacycle **33**. The structure of **33** was confirmed by $^{13}C$ NMR using the DEPT pulse sequence[24] and C, H, and N analysis. The

(21) Feldman, P. L.; Rapoport, H. *Synthesis*, in press.

(22) The diastereoselectivity in the iminium ion closure could be explained by axial attack of the indole onto the most stable conformer of the intermediate with the methoxycarbonyl axial and ethyl equatorial. This rationalization, however, does not seem to be general given data from other cyclizations performed in these laboratories.[7] The two isomers were assigned unambiguously by comparison of the spectral data of **5b** with the known racemate.[6f]

(23) The varied rates of quaternization of indoloquinolizidine nitrogens with methyl iodide have been used in conjunction with spectral data to assign the stereochemistry of several related alkaloids: Shamma, M.; Richey, J. M. *J. Am. Chem. Soc.* **1963**, *85*, 2507.

**Scheme IV. Hexahydroindoloquinolizine Substrates for Racemization Studies**




mechanism for this reaction probably involves nucleophilic attack of the indole nitrogen at the thionium carbon followed by exchange of methanethiol with water via an iminium ion intermediate. Even using anhydrous methanesulfonic acid gave **33** upon isolation.

**The Reversible Mannich Reaction with Various Hexahydroindoloquinolizine Systems.** The reversible Mannich reaction in indoloquinolizidine systems has been observed previously; however, a study of the necessary functionality at C-15 and the conditions required to cause this fragmentation have not been reported.[25-27] In a synthesis of (+)-vincamine, (+)-**34** was obtained by equilibrating a mixture of octahydroindoloquinolizine diastereomers via an acid-catalyzed reversible Mannich reaction and then separating it from its antipode via a resolution.[25] Another report stated that treating **35** with NaOMe in MeOH at room temperature for 3 weeks gave **36**, **37**, **38**, and **39** in which the latter three had racemized as a result of a mild reversible Mannich reaction.[26] These two examples (Scheme IV) demonstrate that compounds treated under various conditions and containing different functionality at C-15 are susceptible to reverse Mannich reactions.

In order to survey the functionalities and conditions necessary to effect reversible Mannich reactions in this system, we synthesized a number of optically active hexahydroindoloquinolizines and subjected them to different reaction conditions. These compounds were **4a**, **4b**, **28a**, **28b**, **42**, and **43**. Aldehyde **42** was synthesized by reducing **4b** to **40** with $LiAlH_4$ in THF followed by oxidation to obtain **41** as a mixture of diastereomers. The chloroindolinines **41** were then converted to aldehyde **42** by treatment with excess NaI in HOAc.[27] Ketone **43** was made by reacting ester **4b** with excess MeLi in THF. It should be noted that the aldehyde used for this study was partially racemized. The product obtained using this sequence had a lower rotation than expected for these systems, $[\alpha]_D$ +29°, and upon reducing the aldehyde with $LiAlH_4$ to alcohol **40**, $[\alpha]_D$ +32°, its rotation was considerably lower than that of the alcohol, $[\alpha]$ +205°, obtained by reduction of **4b**. Although significant racemization occurred in the conversion of **4b** to the aldehyde **42**, it was sufficiently enriched in one enantiomer to be suitable for our study.

**Table I. Stability Studies of Various Hexahydroindoloquinolizines**

| | conditions | | | |
|---|---|---|---|---|
| compd | solvent | temp (°C) | time (h) | optical stability |
| **42** | $CH_3OH$/THF | 20 | 5 | racemized |
| **42** | THF | 20 | 3 | stable |
| **42** | THF | 66 | 1 | racemized |
| **42** | DMF | 20 | 1 | stable |
| **42** | DMF | 75 | 1 | racemized |
| **42** | HOAc | 20 | 5 | racemized |
| **43** | $CH_3OH$/THF | 20 | 5 | ~10% racemized |
| **43** | $CH_3OH$/THF | 66 | 5 | racemized |
| **43** | HOAc | 65 | 1 | racemized |
| **43** | TFA | 65 | 1 | stable |
| **4b** | TFA | 65 | 1 | stable |
| **4b** | 1 M NaOMe/MeOH/THF | 65 | 1 | stable |
| **4a** | HOAc | 65 | 1 | stable |
| **28b** | 1 M NaOMe/MeOH/THF | 65 | 1 | stable |
| **28a** | TFA | 65 | 1 | stable |

After these six compounds were synthesized, they were subjected to various conditions: strong acid (TFA), weak acid (HOAc), weak base (NaOMe), and aprotic and protic solvents. As can be seen from the results collected in Table I, the aldehyde **42** is susceptible to reversible Mannich reaction under almost any conditions. This compound racemized at room temperature in HOAc or MeOH and merely upon heating in various aprotic solvents. Starting material was not recovered when **42** was heated in TFA, since electrophilic acylation at C-10 gave **44**.[28]

Ketone **43** also underwent facile reversible Mannich reaction, but it was not as labile as aldehyde **42**. As seen from Table I the ketone undergoes reversible Mannich reaction when stirred with HOAc or MeOH at 65 °C but is surprisingly stable in hot TFA.

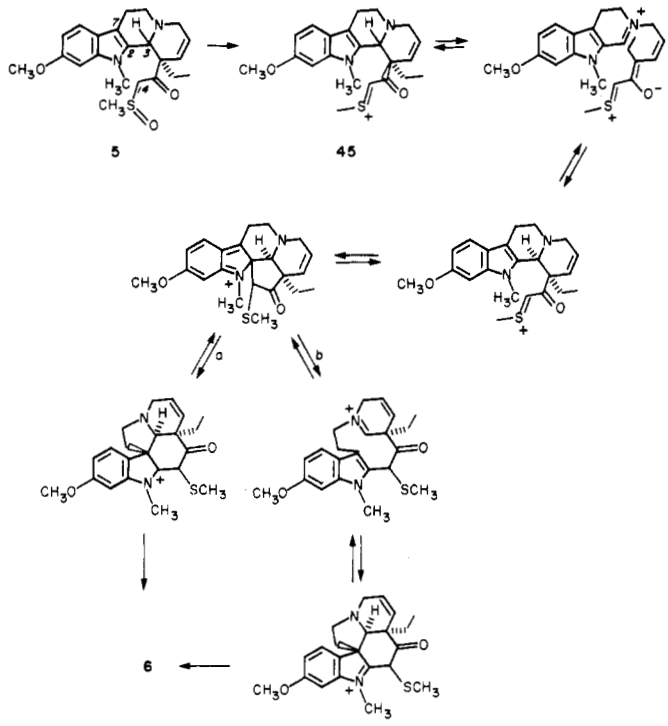
Esters **4a**, **4b**, **28a**, and **28b** do not suffer reversible Mannich reaction under any of the conditions tried. The only reaction these esters undergo is acid-catalyzed epimerization at C-3 in refluxing TFA.[7,11]

From these results we conclude that electrophilic carbonyl carbons at C-15 are very susceptible to reversible Mannich reaction under a variety of conditions. In planning syntheses of optically active materials, both aldehydes and ketones should either be avoided or converted to a more stable functionality. Less reactive groups such as nitriles[29] and esters do not undergo this reversible Mannich reaction and thus serve as safer intermediates in synthesizing optically pure alkaloids.

In view of these results it is not surprising that the Pummerer-promoted skeletal rearrangement of **5** yielded racemic **6**. Formation of the Pummerer intermediate **45** increases the electrophilicity of the C-15 carbonyl carbon and thus a facile reversible Mannich reaction would be predicted. The exact timing of the reversible Mannich

(24) Doddrell, D. M.; Pegg, D. T.; Bendall, M. R. *J. Magn. Reson.* **1982**, *48*, 323.
(25) Oppolzer, W.; Hauth, H.; Pfaffli, P.; Wenger, R. *Helv. Chim. Acta* **1977**, *60*, 1801.
(26) Sapi, J.; Szabo, L.; Baitz-Gac , E.; Kalaus, G.; Szantay, C.; Karsai-Bihatsi, E. *Liebigs Ann. Chem.* **1985**, 1974.
(27) Langlois, Y.; Pouilhes, A.; Genin, D.; Andriamialisoa, R. Z.; Langlois, N. *Tetrahedron* **1983**, *39*, 3755.
(28) The $^1H$ NMR spectrum of **44** showed two singlets in the aromatic region at 6.8 and 8.0 ppm for C-12 and C-9, respectively. The IR spectrum had a new signal at 1675 $cm^{-1}$ which is indicative of the trifluoroacetyl carbonyl stretch.
(29) We have shown that compound **2** remains optically pure after refluxing in TFA for 24 h; **2** has not been subjected to other conditions.

**Scheme V. Proposed Mechanism for Racemization of Tetracyclic β-Keto Sulfoxide 5 during Rearrangement to Pentacycle 6**



reaction in the conversion from **5** to **6** is not known. We think that the mechanism for the formation of **6** from **5** can follow one of two pathways outlined in Scheme V. Since it seems unlikely that C-2 attacks the thionium carbon when H-3 is β as discussed previously, then rapid reversible Mannich reaction inverting the stereochemistry at C-3 is the likely course. The intermediates can then be converted to **6** by using the mechanism proposed earlier, or alternatively via path b. Either pathway seems equally probable.

In summary, we have presented a synthesis of the highly functionalized optically pure 3-ethyl-$\Delta^4$-tetrahydroquinolinate **3** and used it in a route to obtain vindoline. The route proceeded well to give an intermediate which has been taken on to (±)-vindoline,[6f] since in the key rearrangement (**5** → **6**) the optical integrity was lost due to a reversible Mannich reaction. Results are presented which demonstrate that the reversible Mannich reaction is very facile in hexahydroindoloquinolizine systems with highly electrophilic carbons at C-15, yet with less reactive groups at C-15 the retro-Mannich reaction is totally suppressed.

## Experimental Section

**General.** Tetrahydrofuran (THF) was distilled from sodium/benzophenone and diisopropylamine, acetonitrile, dimethylformamide, hexamethylphosphoramide, and dimethyl sulfoxide were distilled from $CaH_2$. Melting points are uncorrected. $^1H$ and $^{13}C$ NMR spectra were determined in $CDCl_3$ and are expressed in ppm downfield from internal tetramethylsilane; IR spectra were taken in $CHCl_3$ unless otherwise stated. Elemental analyses were performed by the Analytical Laboratory, College of Chemistry, University of California, Berkeley, CA. Column chromatography was performed with 70–230 (gravity) or 230–400 (flash) mesh silica gel (EM Reagents). Normal phase high pressure liquid chromatography (HPLC) was carried out with an IBM Microsorb 5 μm column (4.6 mm i.d. × 250 mm). Analytical thin-layer chromatography (TLC) was done with aluminum-backed silica plates (E. Merck). For compounds that do not absorb UV light, the TLC plates were developed by dipping the plates into a $KMnO_4$ solution (3 g of $KMnO_4$, 20 g of $K_2CO_3$, 5 mL of 5% NaOH, 300 mL of $H_2O$) followed by drying with hot air. Organic layers were dried over $Na_2SO_4$, filtered, and concentrated by using a Berkeley rotary evaporator.

***α-tert*-Butyl β-Methyl L-Aspartate–Acetic Acid (10).** To *α-tert*-butyl β-methyl *N*-Cbz-aspartate (**9**,[12,13] 31.1 g, 92.3 mmol) and glacial acetic acid (5.8 mL) was added 10% Pd–C (1.87 g) in methanol (175 mL). The mixture was shaken under 50 psi of hydrogen for 16 h, filtered through Celite, and then concentrated to give a yellow oil which was dissolved in ether, and petroleum ether was added until the solution became opaque. After cooling at −10 °C for several hours, the white crystals that precipitated were collected, washed with cold petroleum ether, and dried under high vacuum: yield, 20.7 g (85%) of **10**: mp 56–57 °C; $[\alpha]^{20}_D$ −0.37° (*c* 10, $CHCl_3$); IR 3300–2350, 3000, 1730 $cm^{-1}$; $^1H$ NMR δ 3.72 (m, 1 H), 3.70 (s, 3 H), 2.74 (m, 2 H), 2.08 (s, 3 H), 1.46 (s, 9 H); $^{13}C$ NMR δ 175.7, 172.3, 171.6, 82.0, 51.8, 51.1, 37.7, 28.0, 21.3. Anal. Calcd for $C_{11}H_{21}NO_6$: C, 50.2; H, 8.0; N, 5.3. Found: C, 50.1; H, 8.0; N, 5.4.

***α-tert*-Butyl β-Methyl L-*N*-(3-Chloropropyl)aspartate (11).** To **10** (8.0 g, 30.4 mmol) were added 3-chlorobromopropane (16.7 g, 10.5 mL, 106 mmol), sodium bicarbonate (7.7 g, 0.912 mol), and acetonitrile (35 mL). The mixture was vigorously stirred at 80 °C for 8 h under nitrogen and then cooled and filtered. Concentrating the filtrate left a residue which was flash chromatographed on silica gel (6/4, hexanes/EtOAc) to yield **11** as an oil: 5.16 g, 61% yield; $[\alpha]^{20}_D$ −8.8° (*c* 1.1, $CHCl_3$); IR (neat) 1730, 1260, 1190, 1140 $cm^{-1}$; $^1H$ NMR δ 3.69 (s, 3 H), 3.61 (t, 2 H, *J* = 6.4 Hz), 3.51 (dd, 1 H, *J* = 5.95), 2.91–2.53 (m, 4 H), 1.9 (m, 2 H), 1.47 (s, 9 H). Anal. Calcd for $C_{12}H_{22}ClNO_4$: C, 51.5; H, 7.9; N, 5.0. Found: C, 51,3; H, 8.0; N, 5.0.

***α-tert*-Butyl β-Methyl L-*N*-(9-Phenylfluorenyl)-*N*-(3-chloropropyl)aspartate (12).** To **11** (12.4 g, 44.3 mmol) were added 9-phenylfluorenyl bromide[7] (16.0 g, 49.8 mmol), potassium phosphate (12.4 g, 58.4 mmol; dried at 400 °C), lead nitrate (12.4 g, 37.4 mmol), and acetonitrile (100 mL). The mixture was stirred at room temperature for 28 h and then filtered, and the solids were washed thoroughly with acetonitrile. The filtrate was concentrated to give crude **12** which was best directly converted to **13** without any purification. Pure **12** could be obtained by recrystallization from absolute ethanol: mp 126–127 °C; $[\alpha]^{20}_D$ +106° (*c* 10, $CHCl_3$); IR 3000, 2890, 1735, 1165 $cm^{-1}$; $^1H$ NMR δ 7.7–7.2 (m, 12 H), 3.76 (dd, 1 H, *J* = 10.9, 3.0 Hz), 3.50 (m, 2 H), 3.46 (s, 3 H), 3.2–2.85 (m, 3 H), 2.62 (dd, 1 H, *J* = 15.5, 10.4), 2.1–1.85 (m, 2 H), 1.78 (dd, 1 H, *J* = 15.7, 3.18), 1.42 (s, 9 H). Anal. Calcd for $C_{31}H_{34}ClNO_4$: C, 71.6; H, 6.6; N, 2.7. Found: C, 71.5; H, 6.6; N, 2.7.

***α-tert*-Butyl β-Methyl L-*N*-(9-Phenylfluorenyl)-*N*-(3-iodopropyl)aspartate (13).** Crude **12** was dissolved in acetonitrile (150 mL), finely powdered sodium iodide (26.5 g, 0.177 mmol) was added, the mixture was stirred at 65 °C for 28 h and then filtered, and the filtrate was evaporated. The residue was dissolved in ethyl acetate, washed with saturated $Na_2S_2O_3$ and water, dried, and evaporated. Crystallization from absolute ethanol gave 21.6 g, 80% yield, of **13** from **11**: mp 135 °C; $[\alpha]^{20}_D$ +109° (*c* 10, $CHCl_3$); IR 3000, 2870, 1730, 1250 $cm^{-1}$; $^1H$ NMR δ 7.7–7.2 (m, 13 H), 3.81–3.74 (dd, 1 H, *J* = 10.9, 3), 3.45 (s, 3 H), 3.18–2.78 (m, 4 H), 2.68–2.55 (dd, 1 H, *J* = 15.6, 3), 2.15–1.88 (m, 2 H), 1.82–1.73 (dd, 1 H, *J* = 15.6, 3), 1.43 (s, 9 H). Anal. Calcd for $C_{31}H_{34}INO_4$: C, 60.9; H, 5.6; N, 2.3. Found: C, 61.2; H, 5.7; N, 2.3.

***α-tert*-Butyl β-Methyl (2*S*,3*S*/3*R*)-*N*-(9-Phenylfluorenyl)-3-iodohexahydroquinolinate (15, 16) and *α-tert*-Butyl β-Methyl (2*S*)-*N*-(9-Phenylfluorenyl)-$\Delta^3$-tetrahydroquinolinate (17).** To a solution of diisopropylamine (2.4 mL, 17.0 mmol) in THF (40 mL) at 0 °C was slowly added *n*-BuLi (10.6 mL of 1.54 M *n*-BuLi in hexanes, 16.4 mmol). After it was stirred at 0 °C for 30 min, the solution was cooled to −78 °C, and a solution of **13** (4 g, 6.54 mmol) in THF (10 mL) was slowly added. The solution was stirred at −78 °C for 1 h, −48 °C for 3 h, and −78 °C for an additional hour. To a solution of iodine (2.5 g, 9.82 mmol) in THF (30 mL) at −78 °C was added the solution of the ester enolate, and after the addition the mixture was stirred an additional 3 h at −78 °C and then allowed to warm to room temperature. The reaction was quenched by addition of 1 M $H_3PO_4$ and then extracted with ether, the organic layer was washed with 1 M $H_3PO_4$, saturated $Na_2S_2O_3$, and saturated $NaHCO_3$, and

drying and evaporating gave a yellow foam which was a mixture of **14**, **15**, and **16**, best purified after the next step.

The mixture was dissolved in benzene (8 mL) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 2.9 mL, 19.62 mmol), heated at 65 °C for 3 h, and then diluted with ether and 1 M $H_3PO_4$. The aqueous phase was extracted with ether which was dried and evaporated to a residue. Flash chromatography on silica gel ($CH_2Cl_2$) gave a 93/7 mixture of **15**/**14** (501 mg) in the first fraction and **17** (2.02 g) in the second. Equilibration of **15** to give **15** and **16** (see below) followed by dehydroiodination under the same conditions described above yielded more **17** (165 mg); total yield 2.19 g, 69%.

**14**: mp 75–79 °C; $^1H$ NMR $\delta$ 7.8–7.15 (m, 13 H), 4.70 (d, 1 H, $J$ = 11.4 Hz), 4.01 (d, 1 H, $J$ = 11.4), 3.96 (s, 3 H), 3.51–3.43 (m, 1 H), 3.31–3.20 (m, 1 H), 2.98 (t, 3 H, $J$ = 6.2), 2.15–1.95 (m, 2 H), 1.1 (s, 9 H); $^{13}C$ NMR 170.2, 168.1, 146.5–119.5 (aromatic region), 82.2, 79.9, 64.8, 52.9, 49.5, 34.7, 27.6, 20.8, 4.0.

**15**: mp 133–135 °C; IR 2980, 1735 $cm^{-1}$; $^1H$ NMR $\delta$ 7.80–7.15 (m, 13 H), 4.18 (s, 1 H), 4.00 (s, 3 H), 3.82–3.70 (m, 1 H), 3.17–3.08 (m, 1 H), 3.05–2.92 (m, 1 H), 2.82–2.73 (m, 1 H), 2.10–1.91 (m, 2 H), 1.03 (s, 9 H).

**16**: mp 140–141 °C; $[\alpha]^{20}_D$ −263° ($c$ 10, $CHCl_3$); IR 3030, 1740 $cm^{-1}$; $^1H$ NMR $\delta$ 7.80–7.20 (m, 13 H), 3.90 (s, 1 H), 3.63 (s, 3 H), 3.33–3.15 (m, 2 H), 2.4–2.1 (m, 3 H), 1.81–1.7 (m, 1 H), 0.96 (s, 9 H). Anal. Calcd for $C_{31}H_{32}INO_4$: C, 61.1; H, 5.3; N, 2.3. Found: C, 61.3; H, 5.2; N, 2.2.

**17**: mp 152.5–153 °C; $[\alpha]^{20}_D$ −538° ($c$ 3.3, $CHCl_3$); IR 3000, 1725, 1670 $cm^{-1}$; $^1H$ NMR $\delta$ 7.72–7.24 (m, 13 H), 6.97 (bt, 1 H, $J$ = 3.73 Hz), 4.50 (s, 1 H), 3.67 (s, 3 H), 3.48–3.34 (m, 1 H), 3.08–2.98 (m, 1 H), 1.93–1.84 (m, 2 H), 1.19 (s, 9 H). Anal. Calcd for $C_{31}H_{31}NO_4$: C, 77.3; H, 6.5; N, 2.9. Found: C, 77.3; H, 6.5; N, 3.1.

**Equilibration of 15.** To a solution of LDA (0.27 mL, 1.93 mmol of diisopropyl amine, 1.2 mL, 1.85 mmol of 1.54 M $n$-BuLi in hexanes, 7 mL of THF) at −78 °C was added a 93/7 mixture of **15**/**14** (501 mg) in THF (3 mL). This solution was stirred for 1 h at −78 °C and then added to a solution of iodine (312 mg, 1.23 mmol) in THF (10 mL) at −78 °C. After stirring for 2 h at −78 °C and then quenching with 1 M $H_3PO_4$, isolation in the manner described above gave a mixture of 460 mg of **14**, **15**, and **16**. The crude product was dehydroiodinated with DBU in benzene and the product purified by column chromatography to give 165 mg of **17**.

***α-tert*-Butyl *β*-Methyl (2*S*,3*R*)-*N*-(9-Phenylfluorenyl)-3-ethyl-Δ⁴-hexahydroquinolinate (18).** To a solution of LDA (2.4 mL, 17.1 mmol of diisopropylamine, 9.7 mL, 14.9 mmol of 1.54 M $n$-BuLi in hexanes, 20 mL of THF) at −78 °C was added hexamethylphosphoramide (3.0 mL, 17.1 mmol). This solution was stirred for 30 min, then a solution of **17** (5.5 g, 11.42 mmol) in THF (9 mL) was added slowly and was stirred for 1 h at −78 °C, and then iodoethane (3.6 mL, 45.7 mmol) was added. This solution was stirred at −78 °C for 6 h, and then methanol (2 mL) was added followed by ether and 1 M $H_3PO_4$. After separation of the ether and further ether extraction, the combined organic phase was washed several times with 1 M $H_3PO_4$ and then once with saturated $NaHCO_3$. Drying and evaporating left a residue which was flash chromatographed on silica gel ($CH_2Cl_2$) to yield **18**, suitable for use in the next step. Recrystallization from ethanol gave pure **18**: mp 153–154 °C; $[\alpha]^{20}_D$ −442° ($c$ 10.1, $CHCl_3$); IR 3000, 1730, 1610, 1460 $cm^{-1}$; $^1H$ NMR $\delta$ 7.80–7.20 (m, 13 H), 6.16 (bd, 1 H, $J$ = 10.3 Hz), 5.83 (ddd, 1 H, $J$ = 10.3, 4.64, 1.74), 3.84 (bd, 1 H, $J$ = 16.6), 3.64 (ddd, 1 H, $J$ = 16.3, 4.67, 1.44), 3.64 (s, 1 H), 3.53 (s, 3 H), 2.38–2.01 (m, 2 H), 0.91 (s, 12 H). Anal. Calcd for $C_{33}H_{35}NO_4$: C, 77.8; H, 6.9; N, 2.8. Found: C, 77.8; H, 6.9; N, 2.8.

***α-tert*-Butyl *β*-Methyl (2*S*,3*R*)-3-Ethyl-Δ⁴-hexahydroquinolinate (3).** The crude **18** was added to acetonitrile (50 mL) and water (4 mL) and the solution cooled to 0 °C. Trifluoroacetic acid (40 mL) was slowly added to the mixture over 10 min, the yellow solution was stirred at 0 °C for 1 h and at room temperature for 1 h, and then it was slowly added to saturated $NaHCO_3$ (350 mL) and extracted with ethyl acetate. The ethyl acetate was extracted with 1 M $H_3PO_4$ (8×) and the combined aqueous phase then was adjusted to pH 9 with saturated aqueous ammonia, extracted with $CH_2Cl_2$, which was dried, and evaporated to give **3** as an oil, 2.28 g, 74% yield from **17**: $[\alpha]^{20}_D$ −66.0°, ($c$ 0.7, $CHCl_3$); IR 2980, 1730, 1165 $cm^{-1}$; $^1H$ NMR $\delta$ 5.83–5.73 (m, 2 H), 3.61 (s, 3 H), 3.46 (s, 1 H), 3.37–3.20 (m, 2 H), 2.05–1.70 (m, 2 H), 1.39 (s, 9 H), 0.87 (t, 3 H, $J$ = 7.51 Hz). Anal. Calcd for $C_{14}H_{23}NO_4$: C, 62.4; H, 8.6; N, 5.2. Found: C, 62.5; H, 8.8; N, 5.2.

***α-tert*-Butyl *β*-Methyl (2*S*,3*S*)-*N*-Benzyl-3-ethyl-Δ⁴-tetrahydroquinolinate (22).** To a solution of **3** (94.5 mg, 0.353 mmol) in acetonitrile (0.5 mL) were added benzyl bromide (0.08 mL, 0.7 mmol) and triethylamine (97 μL, 0.7 mmol), and the solution was stirred for 18 h and then diluted with water and $CH_2Cl_2$. The mixture was extracted twice more with $CH_2Cl_2$, which was dried and evaporated, and the residue was chromatographed on silica gel (3/1 $CH_2Cl_2$/isooctane) to yield **22** as an yellow oil: 114 mg, 90% yield; $[\alpha]^{20}_D$ −94.4° ($c$ 0.48, $CHCl_3$); IR 3000, 1735, 1170 $cm^{-1}$; $^1H$ NMR $\delta$ 7.42–7.22 (m, 5 H), 6.19 (bd, 1 H, $J$ = 10.3 Hz), 5.67 (ddd, 1 H, $J$ = 10.3, 4.29, 2.00), 3.97, 3.78 (d, 2 H, $J$ = 13.4), 3.65 (s, 3 H), 3.57 (s, 1 H), 3.20 (ddd, 1 H, $J$ = 17.0, 4.34, 2.10), 2.98 (bd, 1 H, $J$ = 17.1), 2.10–1.72 (m, 2 H), 1.47 (s, 9 H), 0.77 (t, 3 H, $J$ = 7.60). Anal. Calcd for $C_{21}H_{29}NO_4$: C, 70.2; H, 8.1; N, 3.9. Found: C, 70.0; H, 8.2; N, 3.8.

**Diastereomeric Purity of 3.** To a solution of LDA (0.22 mL, 1.54 mmol of diisopropylamine, 0.89 mL, 1.37 mmol of 1.54 M $n$-BuLi in hexanes, 4 mL of THF) at −78 °C was added **22** (100 mg, 0.279 mmol) in THF (0.5 mL). The deep red solution was stirred for 2 h at −78 °C, warmed to room temperature, quenched with water, and extracted with $CH_2Cl_2$. The organic phase was washed with 1 M $H_3PO_4$ and saturated $NaHCO_3$, dried, and evaporated, and the residue was chromatographed on silica gel (3/1 $CH_2Cl_2$/isooctane). Examination of the $^1H$ NMR spectrum, specifically the methyl triplets ($\delta$ 0.87, 0.77), revealed the diastereomeric ratio of **22**/**23** to be 2/1. Pure **22** was mixed with the appropriate amounts of this 2/1 mixture of **22**/**23** to give samples of **22** with 99%, 98%, and 97% diastereomeric purity. The smallest amount of **23** detected in the $^1H$ NMR spectrum was 2%, thus **22** is >98% diastereomerically pure.

**Optical Purity of 3.** To L-*N*-(benzenesulfonyl)proline acid chloride[30] (116 mg, 0.423 mmol) in acetonitrile (1.0 mL) at 0 °C was added **3** (103 mg, 0.384 mmol) in acetonitrile (0.5 mL), followed immediately by addition of *N*-methylmorpholine (0.085 mL, 0.77 mmol). The solution was stirred at 0 °C for 45 min and then diluted with saturated $NaHCO_3$ and $CH_2Cl_2$. After extracting with $CH_2Cl_2$ the combined organic phase was washed with 1 M $H_3PO_4$, dried, and evaporated to give **24**: 183.5 mg, 94% yield; mp 168–169 °C; $[\alpha]^{20}_D$ −27.9° ($c$ 4.12, $CHCl_3$); IR 3000, 1740, 1675, 1065 $cm^{-1}$; $^1H$ NMR $\delta$ 7.95–7.87 (m, 2 H), 7.62–7.43 (m, 3 H), 6.51 (bd, 1 H, $J$ = 10.5 Hz), 5.70 (d, 1 H, $J$ = 1.13), 5.64 (ddd, 1 H, $J$ = 10.4, 3.00, 3.00), 4.93 (m, 1 H), 4.33 (ddd, 1 H, $J$ = 17.1, 2.86, 2.85), 3.88 (ddd, 1 H, $J$ = 17.2, 2.51, 2.51), 3.75 (s, 3 H), 3.49 (m, 2 H), 2.21–1.58 (m, 5 H), 1.35 (s, 9 H), 0.81 (t, 3 H, $J$ = 7.58). Anal. Calcd for $C_{25}H_{34}N_2O_7S$: C, 59.3; H, 6.8; N, 5.5. Found: C, 59.0; H, 6.9; N, 5.6.

The same reaction was carried out using D,L-*N*-(benzenesulfonyl)proline acid chloride.[30] Normal-phase HPLC analysis (17/3 isooctane/ether) using the appropriate doping experiments demonstrated that **3** was >99% enantiomerically pure.

***α-tert*-Butyl *β*-Methyl (2*S*,3*R*)-*N*-(2-(3-(6-Methoxyindolyl))ethyl)-3-ethyl-Δ⁴-tetrahydroquinolinate (25).** A mixture of **3** (2.28 g, 8.47 mmol), 6-methoxytryptophyl bromide[21] (2.34 g, 9.32 mmol), and sodium bicarbonate (2.13 g, 25.4 mmol) in acetonitrile (8.5 mL) was heated at 60 °C for 15 h. The solution was diluted with water and extracted with ethyl acetate (4×). Drying and evaporating left a residue which was flash chromatographed (6/3/1 hexanes/$CH_2Cl_2$/EtOAc) on silica gel to yield a small amount of recovered 6-methoxytryptophyl bromide and **25** as an oil: 3.27 g, 87% yield; $[\alpha]^{20}_D$ −32.6° ($c$ 5.31, $CHCl_3$); IR 3490, 3410, 2800, 1730, 1640 $cm^{-1}$; $^1H$ NMR $\delta$ 7.85 (bs, 1 H), 7.50 (d, 1 H, $J$ = 8.59), 6.88 (dd, 1 H, $J$ = 14.2, 2.05), 6.79 (dd, 1 H, $J$ = 8.61, 2.22), 6.17 (dd, 1 H, $J$ = 10.3, 0.87), 5.71 (ddd, 1 H, $J$ = 10.3, 4.25, 1.90), 3.85 (s, 3 H), 3.72 (s, 1 H), 3.68 (s, 3 H), 3.33 (ddd, 1 H, $J$ = 17.1, 4.28, 2.09), 3.2–2.9 (m, 5 H), 2.02–1.64 (m, 2 H), 0.81 (t, 3 H, $J$ = 7.59). Anal. Calcd for $C_{25}H_{34}N_2O_5$: C, 67.9; H, 7.7; N, 6.3. Found: C, 67.7; H, 7.7; N, 6.4.

***β*-Methyl α-Hydrogen (2*S*,3*R*)-*N*-(2-(3-(6-Methoxyindolyl))ethyl)-3-ethyl-Δ⁴-tetrahydroquinolinate (26).** A

(30) Maurer, P. J.; Takahata, H.; Rapoport, H. *J. Am. Chem. Soc.* **1984**, *106*, 1095.

solution of **25** (583 mg, 1.32 mmol) in formic acid (10 mL, 90–92%) was heated at 60–65 °C for 2.5 h, then adjusted to pH 6 with 1 M phosphate buffer, and extracted with ethyl acetate (4×). Solid $Na_2CO_3$ was added to the organic phase, a small water phase was removed, and the organic phase was dried and evaporated. The residue was dissolved in THF (10 mL) and cooled to 0 °C, and then sodium methoxide in methanol (2.6 mL, 1 M) was added. The solution was stirred at 0 °C for 15 min, quenched with pH 6 phosphate buffer, and extracted with ethyl acetate. Drying and evaporating yielded material that gave one spot on TLC (EtOAc) and was not purified for the subsequent step. Further purification of **26** could be accomplished by silica gel chromatography (EtOAc): 472 mg, 93% yield; mp 78–80 °C; $[\alpha]^{20}_D$ −77.6° (*c* 0.67, $CHCl_3$); IR 3490, 3450–2600, 1780, 1735 $cm^{-1}$; $^1H$ NMR δ 7.97 (bs 1 H), 7.46 (d, 2 H, *J* = 8.62 Hz), 6.94 (d, 1 H, *J* = 2.16), 6.85 (d, 1 H, *J* = 2.06), 6.78 (dd, 1 H, *J* = 8.61, 2.23), 6.12 (bd, *J* = 10.3), 5.71 (ddd, 1 H, *J* = 10.4, 3.74, 2.38), 3.84 (s, 3 H), 3.66 (s, 3 H), 3.37 (ddd, 1 H, *J* = 17.3, 3.73, 2.26), 3.25–2.87 (m, 5 H), 2.0–1.75 (m, 2 H), 0.82 (t, 3 H, *J* = 7.55). Anal. Calcd for $C_{21}H_{26}N_2O_5$: C, 65.3; H, 6.8; N, 7.3. Found: C, 65.6; H, 6.7; N, 7.1.

**(1*R*,12b*S*)- and (1*R*,12b*R*)-1-(Methoxycarbonyl)-1-ethyl-16-methoxy-1,2,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizines (4a and 4b).** To **26** (472 mg, 1.22 mmol) was added phenylphosphoryl dichloride (2.3 mL). This solution was heated at 105 °C for 10 min, cooled, adjusted to pH 7 by slowly adding saturated $NaHCO_3$, stirred at room temperature for 30 min, and then extracted with ethyl acetate. The combined organic phase was dried and evaporated, and the residue was flash chromatographed on silica gel (3/2 EtOAc/hexanes) to give **4b** (282 mg, 64%) followed by **4a** (72.5 mg, 16%).

**4a**: mp 184 °C; $[\alpha]^{20}_D$ −300° (*c*, 2.85, $CHCl_3$); IR 3700, 3510, 3170, 2860, 2835, 2775, 1730, 1225 $cm^{-1}$; $^1H$ NMR δ 7.78 (bs, 1 H), 7.33 (d, 1 H, *J* = 8.55 Hz), 6.85 (d, 1 H, *J* = 2.17), 6.75 (dd, 1 H, *J* = 8.55, 2.24), 5.96 (ddd, 1 H, *J* = 10.6, 4.55, 1.94), 5.76 (bd, 1 H, *J* = 10.0), 3.84 (s, 3 H), 3.80 (bs, 1 H), 3.48 (s, 3 H), 3.46 (ddd, 1 H, *J* = 16.7, 4,53, 1.64), 3.08 (bd, 1 H, *J* = 16.8), 2.92–2.84 (m, 1 H), 2.72 (m, 2 H), 2.28–1.98 (m, 2 H), 1.07 (t, 3 H, *J* = 7.50). Anal. Calcd for $C_{20}H_{24}N_2O_3$: C, 70.6; H, 7.1; N, 8.2. Found: C, 70.5; H, 7.3; N, 8.1.

**4b**: mp 94–95 °C; $[\alpha]^{20}_D$ +155° (*c*, 2.85, $CHCl_3$); IR 3700, 3430, 3150, 2860, 2840, 2780, 1725, 1225 $cm^{-1}$; $^1H$ NMR δ 8.94 (s, 1 H), 7.35 (d, 1 H, *J* = 8.54 Hz), 6.85 (d, 1 H, *J* = 2.13), 6.75 (dd, 1 H, *J* = 8.57, 2.25), 5.95 (ddd, 1 H, *J* = 10.2, 4.65, 1.40), 5.86 (bd, 1 H, *J* = 10.2), 4.03 (bs, 1 H), 3.86 (s, 3 H), 3.84 (s, 3 H), 3.36 (ddd, 1 H, *J* = 16.8, 4.70, 1.00), 3.13–2.87 (m, 3 H), 2.73–2.63 (m, 2 H), 1.70 (ddd, 2 H, *J* = 15.2, 7.55, 1.89), 0.79 (t, 3 H, *J* = 7.57). Anal. Calcd for $C_{20}H_{24}N_2O_3$: C, 70.6; H, 7.1; N, 8.2. Found: C, 70.3; H, 7.3; N, 8.2.

**(1*R*,12b*S*)-1-(Methoxycarbonyl)-1-ethyl-16-methoxy-12-methyl-1,2,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizine (28a).** To KH (84 mg of 35% KH in oil, 0.736 mmol, washed with pentane) in DMF (1 mL) at 0 °C was added **4a** (100 mg, 0.29 mmol). The mixture was stirred at 0 °C for 10 min and cooled to −48 °C, methyl iodide (20 μL, 0.323 mmol) was added, and the mixture was stirred at −48 °C for 20 min. After the reaction was quenched with pH 6 phosphate buffer, the mixture was extracted with $CH_2Cl_2$ which was dried and evaporated. The residue was purified by flash chromatography on silica gel (3/1 EtOAc/hexanes) to give **28a**: 97 mg, 94% yield; mp 122 °C; $[\alpha]^{20}_D$ −270° (*c* 1.0, $CHCl_3$); IR 3110, 2985, 2930, 2865, 1730 $cm^{-1}$; $^1H$ NMR δ 7.34 (d, 1 H, *J* = 8.36 Hz), 6.77–6.72 (m, 2 H), 5.98 (bs, 2 H), 4.05 (s, 1 H), 3.88 (s, 3 H), 3.63 (s, 3 H), 3.63–3.36 (m, 3 H), 3.18 (s, 3 H), 2.79–2.62 (m, 3 H), 2.27–2.12 (m, 1 H), 1.83–1.70 (m, 1 H), 0.96 (t, 3 H, *J* = 7.35). Anal. Calcd for $C_{21}H_{26}N_2O_3$: C, 71.2; H, 7.4; N, 7.9. Found: C, 71.0; H, 7.4; N, 7.9.

**(1*R*,12b*R*)-1-(Methoxycarbonyl)-1-ethyl-16-methoxy-12-methyl-1,2,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizine (28b).** To KH (252 mg of 35% KH in oil, 2.20 mmol, washed with pentane) in DMF (3 mL) at −10 °C was added **4b** (300 mg, 0.881 mmol) in three portions over a period of 3 min. After 20 min methyl iodide (96 μL, 1.54 mmol) was added and the mixture stirred for 15 min before quenching with pH 6 phosphate buffer. Extracting with $CH_2Cl_2$, drying, and evaporating the combined organic phase and chromatographing the residue on silica gel (3/1 EtOAc/hexanes) gave **28b**: 270 mg, 86% yield; mp 150 °C; $[\alpha]^{20}_D$ +169° (*c* 2.0, $CHCl_3$); IR 2980. 2870, 2840, 2790, 1740 $cm^{-1}$; $^1H$ NMR δ 7.36 (d, 1 H, *J* = 8.47 Hz), 6.77 (dd, 1 H, *J* = 8.50, 2.22), 6.71 (d, 1 H, *J* = 2.10), 6.0 (ddd, 1 H, *J* = 10.0, 4.06, 2.45), 5.68 (bd, 1 H, *J* = 10.1), 4.34 (s, 1 H), 3.87 (s, 3 H), 3.78 (s, 3 H), 3.42 (m, 1 H), 3.35 (s, 3 H), 3.13–2.86 (m, 2 H), 2.78–2.62 (m, 2 H), 1.88–1.43 (m, 2 H), 0.84 (t, 3 H, *J* = 7.50). Anal. Calcd for $C_{21}H_{26}N_2O_3$: C, 71.2; H, 7.4; N, 7.9. Found: C, 70.8; H, 7.3; N, 7.9.

**2,3,6,7-Tetradehydro-16-methoxy-1-methyl-4-oxo-3-(methylthio)aspidospermidine (6)** was prepared from **28a,b** via **5a** or **5b** following the literature procedure in 67% for two steps.[6f] Purification was accomplished by flash chromatography on silica gel (94/4/2 EtOAc/MeOH/$NH_3$ (aqueous)).

**16-Methoxy-1-methyl-4-oxoaspidospermidine (31).** To **30** (20 mg, 59.1 μmol, prepared from **6** via the literature procedure[6f]) in ethanol (2 mL) and ethyl acetate (3 mL) was added 5% Pt/C (10 mg), and this mixture was stirred under 1 atm of $H_2$ for 10 h. After filtering through Celite, concentrating the filtrate, and chromatographing the residue on silica gel (1/1 hexanes/$Et_2O$), crystallization from ether/petroleum ether gave **31**: 14 mg, 70% yield; mp 115 °C (lit.[3,6d] mp of optically active material, 130–132 °C). This compound gives spectral data identical with that reported.[6d]

**17,18-Didehydro-14,15-dihydro-14-hydroxy-11-methoxy-15-oxoeburnamenine (33).** To a solution of THF (6 mL) and $Me_2SO$ (1.5 mL) at −23 °C was added *n*-BuLi (0.96 mL of a 1.54 M *n*-BuLi in hexanes, 1.47 mmol). After it was stirred at 0 °C for 10 min, the solution was cooled to −23 °C and a solution of **4b** (100 mg, 0.294 mmol) in THF (1 mL) was added. After being stirred at 0 °C for 1.5 h, the reaction mixture was diluted with pH 6 phosphate buffer, extracted with $CH_2Cl_2$, dried, and evaporated to give **32** which was homogeneous by TLC (94/4/2 EtOAc/MeOH/$NH_3$ (aqueous)); 107 mg, 98% yield. To crude **32** (50 mg, 0.135 mmol) in THF (2.5 mL) was added methanesulfonic acid (17.5 μL, 0.27 mmol). The yellow solution turned brown and a precipitate formed immediately and redissolved after stirring for a few more minutes. After 15 min the reaction was quenched by adding triethylamine, and the solution was diluted with water and extracted with ethyl acetate. The combined organic phase was dried and evaporated, and the residue was chromatographed on silica gel (3/1 EtOAc/hexanes) to afford **33**: 29 mg, 63% yield; mp 156–158 °C; $[\alpha]^{20}_D$ +134° (*c* 1.6, $CHCl_3$); IR 3510, 2950, 2920, 2850, 2810, 2750, 1730, 1620 $cm^{-1}$; $^1H$ NMR δ 7.39 (d, 1 H, *J* = 8.56 Hz), 7.01 (d, 1 H, *J* = 2.23), 6.85 (dd, 1 H, *J* = 8.57, 2.29), 6.35 (bd, 1 H, *J* = 10.2), 5.86 (m, 1 H), 5.82 (d, 1 H, *J* = 4.34), 3.95 (d, 1 H, *J* = 4.31), 3.89 (s, 3 H), 3.52 (m, 2 H), 3.22–2.60 (m, 5 H), 1.94 (m, 1 H), 1.14 (m, 1 H), 0.76 (t, 3 H, *J* = 7.68); $^{13}C$ NMR (DEPT combined 45°, 90°, and 180° pulse sequence experiments) 127.9 (CH), 126.6 (CH), 119.5 (CH), 110.6 (CH), 95.4 (CH), 79.0 (CH), 58.9 (CH), 56.1 ($CH_3$), 54.5 ($CH_2$), 51.6 ($CH_2$), 26.8 ($CH_2$), 21.6 ($CH_2$), 9.2 ($CH_3$). Anal. Calcd for $C_{20}H_{22}N_2O_3$: C, 71.0; H, 6.6; N, 8.3. Found: C, 70.9; H, 6.6; N, 8.3.

**(1*R*,12b*R*)-1-Ethyl-1-(hydroxymethyl)-16-methoxy-1,2,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizine (40).** To a solution of $LiAlH_4$ (17.5 mg, 0.44 mmol) in THF (8 mL) at 0 °C was added **4b** in THF (2 mL) dropwise. The reaction was stirred at room temperature for 1.5 h and then quenched with water and extracted with ethyl acetate. The combined organic phase was dried and evaporated, and the residue was chromatographed on silica gel (EtOAc) to give **40**: 87 mg, 95% yield; mp 175–176 °C; $[\alpha]^{20}_D$ +205° (*c* 1.0, $CHCl_3$); IR 3350, 2960, 2860, 2820, 2770, 1640 $cm^{-1}$; $^1H$ NMR δ 9.91 (s, 1 H), 7.35 (d, 1 H, *J* = 8.53 Hz), 6.83 (d, 1 H, *J* = 2.20), 6.74 (dd, 1 H, *J* = 8.55, 2.26), 5.96 (ddd, 1 H, *J* = 10.2, 4.99, 1.61), 5.41 (bd, 1 H, *J* = 10.3), 3.93–3.85 (m, 1 H), 3.84 (s, 3 H), 3.72–3.63 (m, 2 H), 3.38 (ddd, 1 H, *J* = 16.7, 4.98, 1.45), 3.18–2.88 (m, 4 H), 2.72–2.58 (m, 2 H), 1.70–1.47 (m, 1 H), 1.45–1.32 (m, 1 H), 0.82 (t, 3 H, *J* = 7.64).

**(1*R*,12b*R*)-1-Ethyl-1-formyl-16-methoxy-1,2,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizine (42) via 41.** To oxalyl chloride (78 μL, 0.90 mmol) in $CH_2Cl_2$ (8 mL) at −78 °C was added dimethyl sulfoxide (27 μL, 0.38 mmol) dropwise. This solution was stirred at −78 °C for 20 min and then **40** (70 mg, 0.225 mmol) in $CH_2Cl_2$ (2 mL) was added dropwise. The reaction was stirred at −78 °C for 30 min and then triethylamine (1 mL) was added. After being stirred five more minutes at −78 °C, the solution was warmed to 0 °C, diluted with pH 6 phosphate buffer, and ex-

tracted with $CH_2Cl_2$. Drying and evaporating the $CH_2Cl_2$ left a residue which was filtered through silica gel (1/1 hexanes/EtOAc). Evaporation left 68 mg, 88% yield of a mixture of **41a** and **41b** that was used immediately. To an acetic acid (2 mL) solution of **41a,b** (68 mg, 0.197 mmol) was added NaI (147 mg, 0.985 mmol). This solution was stirred for 2 h at room temperature and then neutralized with saturated $NaHCO_3$. The mixture was extracted with $CH_2Cl_2$ and the combined organic phase was washed with saturated $Na_2S_2O_3$, dried, and evaporated. The residue was chromatographed on silica gel (1/1 hexanes/EtOAc) to give 29 mg, 47% yield of a yellow oil which partially decomposed upon standing at room temperature for a few days.

**41** (major epimer): IR 2960, 2880, 2855, 1725 $cm^{-1}$; $^1H$ NMR $\delta$ 9.68 (s, 1 H), 7.37 (d, 1 H, $J$ = 8.23 Hz), 7.24 (d, 1 H, $J$ = 2.26), 6.81 (dd, 1 H, $J$ = 8.23, 2.31), 5.88 (bd, 1 H, $J$ = 10.1), 5.69 (bd, 1 H, $J$ = 10.1), 4.72 (s, 1 H), 3.84 (s, 3 H), 3.56-3.41 (m, 1 H), 3.09-2.85 (m, 3 H), 2.63-1.93 (m, 3 H), 0.81 (t, 3 H, $J$ = 7.54).

**42**: $[\alpha]^{20}_D$ +29.4° ($c$ 1.0, $CHCl_3$); IR 3460, 2950, 2850, 2830, 2760, 1725, 1635 $cm^{-1}$; $^1H$ NMR $\delta$ 9.78 (s, 1 H), 8.33 (bs, 1 H), 7.34 (d, 1 H, $J$ = 8.56 Hz), 6.83 (d, 1 H, $J$ = 2.13), 6.75 (dd, 1 H, $J$ = 8.55, 2.24), 6.15 (ddd, 1 H, $J$ = 10.1, 4.83, 1.56), 5.84 (bd, 1 H, $J$ = 10.0), 3.95 (s, 1 H), 3.84 (s, 3 H), 3.41 (ddd, 1 H, $J$ = 17.1, 4.91, 1.52), 3.20-2.85 (m, 3 H), 2.75-2.60 (m, 2 H), 1.74-1.50 (m, 2 H), 0.90 (t, 3 H, $J$ = 7.45); mass spectrum, calcd for $C_{19}H_{22}N_2O_2$, $m/e$ 310.1681, found $m/e$ 310.1679.

**(1*R*,12b*R*)-1-Acetyl-1-ethyl-16-methoxy-1,2,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizine (43).** To a solution of **4b** (200 mg, 0.588 mmol) in THF (10 mL) at 0 °C was slowly added methyllithium (1.9 mL of 1.5 M MeLi in $Et_2O$, 2.82 mmol). The reaction was stirred at 0 °C for 15 min, quenched with pH 6 phosphate buffer, and extracted with EtOAc which was dried and evaporated, and the residue was chromatographed on silica gel (7/3 hexanes/EtOAc) to yield **43**: 150 mg, 79% yield; mp 95 °C; $[\alpha]^{20}_D$ +143° ($c$ 1.1, $CHCl_3$); IR 3460, 2960, 2860, 2830, 2770, 1705, 1635 $cm^{-1}$; $^1H$ NMR $\delta$ 8.31 (bs, 1 H), 7.33 (d, 1 H, $J$ = 8.54 Hz), 6.83 (d, 1 H, $J$ = 2.15), 6.74 (dd, 1 H, $J$ = 8.53, 2.24), 6.08 (ddd, 1 H, $J$ = 10.2, 5.05, 1.61), 5.81 (bd, 1 H, $J$ = 10.2), 3.92 (s, 1 H), 3.84 (s, 3 H), 3.42 (ddd, 1 H, $J$ = 16.5, 5.06, 1.32), 3.18-2.87 (m, 3 H), 2.72-2.59 (m, 2 H), 2.36 (s, 3 H), 1.90-1.50 (m, 2 H), 0.75 (t, 3 H, $J$ = 7.56); mass spectrum, calcd for $C_{20}H_{24}N_2O_2$ $m/e$ 324.1838, found $m/e$ 324.1843.

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# Single-Operation Synthesis of Vinylsilanes from Alkenes and Hydrosilanes with the Aid of $Ru_3(CO)_{12}$

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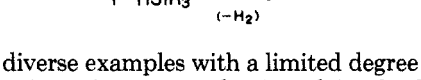
Alkenes ($RCH{=}CH_2$, where R = $C_6H_5$, $p$-$CH_3C_6H_4$, $p$-$CH_3OC_6H_4$, $p$-$ClC_6H_4$, 2-naphthyl, $(CH_3)_3C$, $Me_3SiO(CH_3)_2C$, $n$-$C_4H_9O$, and $Et_3Si$) with $HSiEt_3$ with $Ru_3(CO)_{12}$ as a catalyst gave corresponding vinylsilanes (**1**, **6-13**) without formation of simple addition products. Hydrosilanes such as $HSiMe_3$, $HSiEt_2Me$, $HSiPhMe_2$, and $HSi(OEt)_3$ also yielded vinylsilanes. Alkenes having a hydrogen atom at the allylic position (1-hexene, allylbenzene, 3-phenoxyprop-1-ene, vinylcyclohexane, $\beta$-methylstyrene, $\alpha$-methylstyrene, 2-hexene) formed mixtures of vinylsilanes and allylsilanes. The ratio of vinylsilane **16** to allylsilane **17** decreased with an increase in temperature and with time. Substituted styrenes with a hydrosilane in the presence of 1-hexene gave vinylsilanes **1** and **6-8** in good yields based on the styrenes along with $n$-hexane.

Vinylsilanes have recently been shown to be versatile intermediates in organic synthesis.[2] Various methods are available for the preparation of vinylsilanes. Most of them utilize alkynes (hydrosilylation of alkynes or hydrogenation of silylacetylene), carbonyl compounds (diazoation/lithiation/thermolysis in the presence of chlorosilanes), or vinyl halides (metalation followed by silylation) as starting materials. The reaction (eq 1) is of a type not easy to achieve, since alkenes with hydrosilanes usually produce corresponding alkylsilanes by hydrosilylation.[3]



(1)

Several diverse examples with a limited degree of success of the reaction of eq 1 can be found in the literature. Nesmeyanov and co-workers reported that the reaction of ethylene with $HSiEt_3$ in the presence of a catalytic amount of $Fe(CO)_5$ gave the corresponding vinylsilane and the similar reaction of propene or 1-decene gave a mixture of an alkylsilane and an alkenylsilane.[4] Some rhodium and osmium complexes have been described to be effective as the catalyst for the reaction of styrene with hydrosilanes, leading to vinylsilanes $RhCl(PPh_3)_3$[5], $Rh(dmg)_2PPh_3$[6], $Rh(acac)_3$,[7] and $H_2OsCl_6{\cdot}2H_2O$.[8] Related reactions have also been known for Pt, Ni, Ir-C, Ru-C, Ru-$Al_2O_3$, and Re-C catalysts.[8] Maitlis and co-workers reported that the reaction of 1-hexene with $HSiEt_3$ in the presence of $(RhC_5Me_5)_2Cl_4$ gave a mixture of an alkylsilane and an alkenylsilane.[9] Photocatalyzed reaction of alkenes with trialkylsilanes in the presence of metal carbonyls [$Fe(CO)_5$, $Fe_3(CO)_{12}$, $Ru_3(CO)_{12}$, $Os_3(CO)_{12}$] to give a mixture of the corresponding alkyl- and alkenylsilanes has been reported

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