Highly Enantioselective Approach to Indolizidines: Preparation of (+)-(1*S*,8a*S*)-1-Hydroxyindolizidine and (−)-Slaframine†

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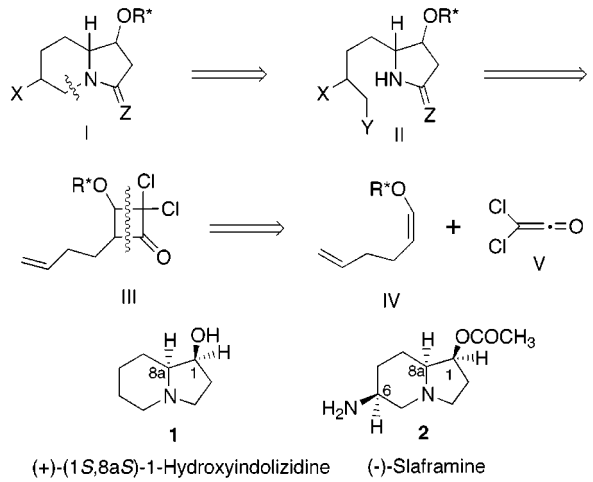
A highly stereoselective approach to (−)-slaframine and its probable biosynthetic precursor (+)-(1*S*,8a*S*)-1-hydroxyindolizidine has been developed based on a diastereofacially selective cycloaddition of dichloroketene with a chiral dienol ether.

Indolizidine alkaloids, due to their structural diversity, number, and dynamic, chemoecologically important role in Nature, have over the last several decades been highly popular targets for synthesis.[1] The common denominator of the overwhelming majority of the enantioselective syntheses disclosed to date, however, has been the use of chiral pool material either to set or to allow eventual relay access to one or more of the stereocenters of the natural substances. The less frequent, but potentially more flexible and arguably more satisfying approach involving the use of either internal or external auxiliaries for this purpose has so far been limited, at least in part, by a paucity of suitable methods.

We have previously described an effective, facially discriminating cycloaddition methodology that diastereoselectively provides a variety of cyclobutanones and shown that it can be translated into an efficient, enantioselective means for accessing cyclopentenone, γ-lactone, pyrrolidine, and amino acid natural products.[2] For extension to the indolizidines, it was envisaged that a central, advanced intermediate **I** might be obtained through cyclization of the corresponding pyrrolidinone or pyrrolidine **II**, which in turn could be generated by Beckmann ring expansion, reduction, and side-chain functionalization from the 2 + 2 cycloadduct of chiral enol ether **IV** with dichloroketene (Chart 1). The intermediates **I**−**IV**, each being open to ready modification, would provide entry to a range of indolizidines[1] (and pyrrolizidines[3]). Furthermore, with occurrence of the anticipated high degree of facial selectivity in the cycloaddition,[2,4] excellent enantiopurity would result in the indolizidine final products. In this paper it is demonstrated that this chemistry can in fact be so extended to provide potentially flexible access to the indolizidine alkaloids through the synthesis of hydroxy indolizidine **1**[5] and slaframine **2**.[6]

Chart 1



Slaframine, an unusual toxin produced by the mold *Rhizoctonia leguminicola*, can infect members of the *Leguminosae* family and lead to excess salivation ("slobber syndrome"), liver damage, and eventual death in ruminants that graze on the contaminated feed.[7] Elegant studies by Harris and co-workers on the biosynthesis of this alkaloid in *R. leguminicola* have identified (+)-(1*S*,-8a*S*)-1-hydroxyindolizidine (**1**) as a highly probable intermediate, engendered from L-lysine via L-pipecolic acid.[8] Potential use to improve ruminant digestion and chemo-

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† This paper is dedicated with admiration to Prof. James A. Marshall on the occasion of his 65th birthday.

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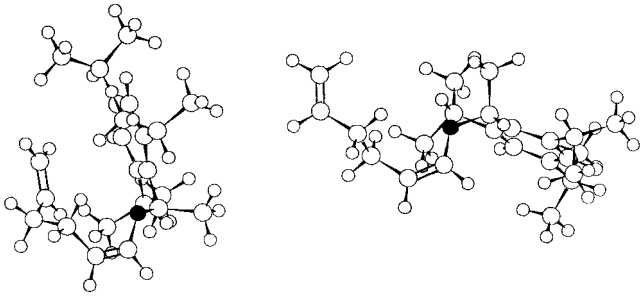
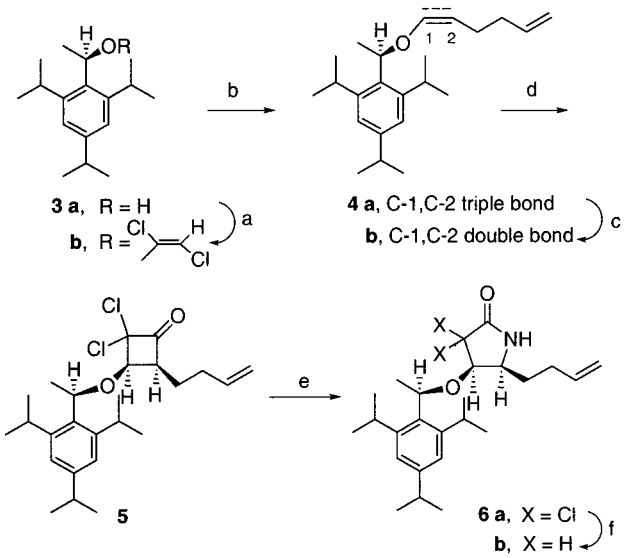


Figure 1. The two lowest-energy conformations of dienol ether **4b** (• = enol oxygen, $\Delta E = 0.3$ kcal/mol).

Scheme 1



Key: [a]KH, THF; $Cl_2C{=}CHCl$ (81%). [b]C_4H_9Li, THF; 3-butenyl triflate. [c]Pd/$BaSO_4$, H_2, C_5H_5N, 1-hexene. [d]Cl_3CCOCl, Zn-Cu, $(C_2H_5)_2O$. [e]$NH_2OSO_2C_6H_2(CH_3)_3$, CH_2Cl_2; Al_2O_3. [f]Zn-Cu, CH_3OH, NH_4Cl (50% overall from **3b**); recrystallization (64%).

therapeutic application for the treatment of cholinergic dysfunction have been suggested for slaframine.[9]

On the basis of antecedent[2e−i] and conformation analysis (Figure 1),[10] the *R* enantiomer of 1-(triisopropylphenyl)ethanol (**3a,** Scheme 1), a generally effective inductor for chiral enol ether−dichloroketene cycloaddition,[4] appeared to be the appropriate one for producing (+)-(1*S*,-8a*S*)-1-hydroxyindolizidine and (−)-slaframine. After conversion of this alcohol into the dichloroenol ether **3b** (81%), treatment with 2.05 equiv of butyllithium and then excess 3-butenyl triflate produced the sensitive enynol ether **4a**,[11] which was used without purification. Closely monitored catalytic hydrogenation of **4a** with palladium on barium sulfate in the presence of 1-hexene in pyridine[11,12] provided dienol ether **4b** together with variable, but usually small amounts of over-reduced material and trans isomer, both of which could be readily removed later in the synthesis (see Experimental Section). In situ generated dichloroketene[13] then entered smoothly into cycloaddition with this dienol ether with high diastereoselectivity (95:5, ^{1}H NMR) and apparent total regioselectivity for the more electron-rich double bond to give α,α-dichlorocyclobutanone **5**. The presence of the chloro substituents and the strain inherent in **5** combined to produce a rapid and highly regioselective ring expansion reaction under Tamura's Beckmann conditions[14] and generate **6a**, which on dechlorination[15] afforded the crystalline lactam **6b** in 50% overall yield from **3b** (87%/step). Recrystallization then gave stereochemically pure (≥98%) lactam, with suitable crystals for X-ray crystallography.[16] Gratifyingly, the *S* configuration at C-4 and C-5, as had been predicted on the basis of molecular modeling and precedent, was indeed found.

1-Hydroxyindolizidine **1** provided a relatively simple target for examining the key pyrrolidine → indolizidine transformation (**II** → **I**). Toward this end, lactam **6b** was

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(10) Molecular modeling was performed on an IBM RS 6000 workstation running Insight II Discover 98.0 (MSI, San Diego). The structure was energy minimized with the force field cvff.frc. and the minimization algorithm VA09A. The molecular dynamics was performed at 500 K in a vacuum (dielectric constant fixed at 1; 200000 steps of 1 fs) and consisted of generation of 400 structures. These depicted conformations are lowest in energy by ≥1.0 kcal/mol. (The next lowest in energy would also be expected to undergo cycloaddition largely on the C_α-si face.)

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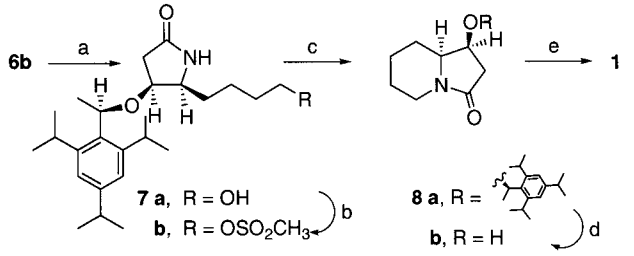
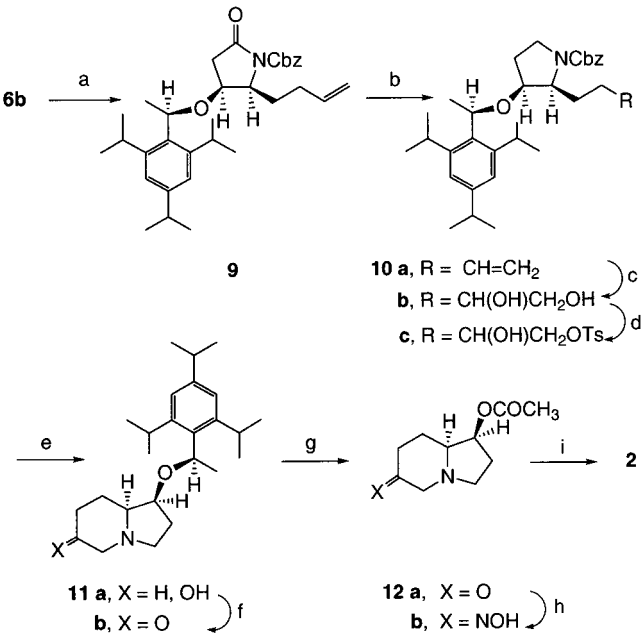
(16) Two independent conformers, with slightly different geometries, coexist in the atomic arrangement. Crystal data for $C_{25}H_{39}N_1O_2$, monoclinic $P2_1$, $a = 6.119(1)$, $b = 16.871(2)$, $c = 24.244(2)$ Å, $\beta = 90.76(1)°$, $V = 2502.6(5)$ Å^3, $Z = 4$, $d_{calcd} = 1.023$ g/cm^3, $F(000) = 848$, 2θ range 3.35−41.9°, 8285 measured reflections. 2381 independent reflections, with $I > 0\sigma(I)$, $R = 0.073$, $R_w = 0.038$, GOF = 2.05. Two H-bonds (N−H···O) link the two independent conformers of the compound. Full lists of fractional atomic coordinates, bond lengths and angles, and thermal parameters have been deposited as Supporting Material with the Cambridge Crystallographic Data Centre.

Scheme 2



Key: [a]Sia_2BH, THF; H_2O_2, NaOH (75%). [b]CH_3SO_2Cl, $(C_2H_5)_3N$, CH_2Cl_2. [c]NaH, THF/DMF (88%, 2 steps). [d]CF_3COOH, CH_2Cl_2 (87%). [e]$LiAlH_4$, THF (76%).

Scheme 3



Key: [a]C_4H_9Li, CbzCl, THF (92%). [b]$LiB(C_2H_5)_3H$, THF; $(C_2H_5)_3SiH$, $BF_3{\cdot}O(C_2H_5)_2$, CH_2Cl_2 (70%). [c]OsO_4, $(CH_3)_3NO$, $(CH_3)_3COH/H_2O$ (67%). [d]$(C_4H_9)_2SnO$, CH_3OH; TsCl, $(C_2H_5)_3N$ (94%). [e]H_2, $Pd(OH)_2$, CH_3OH; $(C_2H_5)_3N$, CH_2Cl_2 (97%). [f]$(COCl)_2$, DMSO, $(C_2H_5)_3N$, CH_2Cl_2 (88%). [g]CF_3COOH, CH_2Cl_2; $(CH_3CO)_2O$, $(C_2H_5)_3N$, DMAP, CH_2Cl_2 (87%, 2 steps). [h]$NH_2OH{\cdot}HCl$, C_5H_5N, C_2H_5OH (71%). [i]H_2 (3 atm), PtO_2, C_2H_5OH/HCl (55%).

converted by hydroboration followed by oxidation into alcohol **7a**, which was then mesylated conventionally to produce **7b** (Scheme 2). While several base−solvent combinations failed to generate indolizidinone **8a** from lactam **7b** due to competitive inductor elimination, pleasingly, it was found that sodium hydride in THF/DMF at room temperature for 2 h yielded the desired product without significant secondary reactions and in high yield. Indolizidinone **8a** was then subjected to acid induced inductor cleavage, which was followed by lithium aluminum hydride reduction to produce smoothly (+)-(1*S*,8a*S*)-1-hydroxyindolizidine (**1**), the identity of which was confirmed through direct spectral comparison with independently prepared material.[5d] With the feasibility of the key pyrrolidine → indolizidine transformation demonstrated, the more challenging slaframine synthesis was addressed (Scheme 3).

In parallel with the approach to hydroxyindolizidine **1**, lactam **6b** was initially subjected to various olefin functionalization−cyclization procedures; however, in the present case cyclization was invariably slow and inductor elimination significant. Therefore, the lactam reduction was advanced to this point in the synthetic sequence. This reduction could best be achieved by using Pedregal and co-workers' super hydride−triethylsilane procedure[17] (70%), after first converting lactam **6b** to its benzyloxycarbonyl (Cbz) derivative **9** (92%). Osmium tetraoxide-mediated dihydroxylation of the double bond and subsequent highly selective monotosylation of the in situ generated dibutylstannoxane derivative[18] produced in 87% overall yield the desired cyclization substrate, tosylate **10c**, as a mixture of hydroxy epimers. Hydrogenation of this material over Pearlman's catalyst triggered cyclization through reductive cleavage of the Cbz group (without any inductor hydrogenolysis!) to give now in nearly quantitative yield the indolizidinediol derivative **11a**. Swern oxidation of this substance then provided the corresponding ketone in 88% yield.

The triisopropylphenylethyl group, having served its last function, was now cleaved by exposure of ketone **11b** to trifluoroacetic acid at ambient temperature, and the resulting hydroxy ketone, without purification, was immediately acetylated to generate in 87% overall yield the known[6b,g,m] keto acetate **12a**. The final steps, oxime formation and reduction, were effected as described by Wasserman and Vu[6g] to provide slaframine **2** as an unstable oil, with spectral characteristics in complete accord with those reported in the literature. Furthermore, *N*-Cbz and *N*-acetyl slaframine, prepared from this synthetic material, provided spectra that were indistinguishable from those of samples derived from natural[6g] and independently synthesized[6i] slaframine, respectively.

In conclusion, a new, effective asymmetric approach to indolizidines based on diastereofacially selective 2 + 2 cycloaddition of dichloroketene with chiral enol ethers has been demonstrated. This approach, one of few not to involve chiral pool material, is expected to allow general access to not only indolizidine, but also pyrrolizidine natural products.

Experimental Section

The reaction mixture was generally poured into water, and the separated aqueous phase was then thoroughly extracted with the specified solvent. After being washed with 10% aqueous HCl and/or $NaHCO_3$ (if required), water, and saturated aqueous NaCl, the combined organic phases were dried over anhyd Na_2SO_4 or $MgSO_4$ and then filtered and concentrated under reduced pressure on a Büchi Rotovapor to yield the crude reaction product. Tetrahydrofuran and ether were distilled from sodium−benzophenone and dichloromethane, dimethylformamide, pyridine, dimethyl sulfoxide, and triethylamine were distilled from calcium hydride.

2-[(*R*)-1-((*E*)-1,2-Dichlorovinyloxy)ethyl]-1,3,5-triisopropylbenzene (3b). An argon-flushed flask was charged with 1.43 g (12.5 mmol) of a 35% suspension of potassium hydride in mineral oil. The mineral oil was removed by washing with pentane and the flask was capped with a rubber septum and connected to a Nujol-filled bubbler by means of a syringe needle. A solution of (*R*)-(+)-1-(2,4,6-triisopropylphenyl)ethanol (**3a**)[4] (1.40 g, 5.64 mmol) in 20 mL of THF was then added dropwise. The mixture was stirred until hydrogen evolution was complete (ca 3 h), cooled to −50 °C, and treated

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dropwise with trichloroethylene (0.560 mL, 0.819 g, 6.24 mmol), after which the reaction mixture was allowed to warm to 20 °C over 1 h, whereupon a few drops of methanol were added. The crude product was isolated with pentane in the usual way and purified by filtration through silica gel (pretreated with 2.5% triethylamine, v/v) with pentane to afford 1.57 g (81%) of pure enol ether **3b**: mp 38−41 °C (pentane); $[\alpha]^{20}_D$ +16.0 (*c* 1.0, chloroform); IR 3086, 1623, 1609, 1078, 1049 cm^{-1}; ^1H NMR (200 MHz) δ 1.23−1.30 (m, 18 H), 1.67 (d, J = 6.9 Hz, 3 H), 2.85 (hept, J = 6.9 Hz, 1 H), 3.32−3.75 (m, 2 H), 5.57 (s, 1 H), 5.96 (q, J = 6.9 Hz, 1 H), 7.03 (s, 2 H); ^{13}C NMR (50.3 MHz) δ 21.0 (CH_3), 23.9 (CH_3), 24.5 (CH_3), 24.8 (CH_3), 29.5 (CH), 34.1 (CH), 76.5 (CH), 98.3 (CH), 122.1 (C), 131.3 (C), 143.0 (C), 148.5 (C); mass spectrum (EI), *m*/*z* 343 and 341 (M^+), 231 (100%). Anal. Calcd for $C_{19}H_{28}Cl_2O$: C, 66.47; H, 8.22. Found: C, 66.63; H, 8.36.

2-[(*R*)-1-((*Z*)-Hexa-1,5-dienyloxy)ethyl]-1,3,5-triisopropylbenzene (4b). To a solution of 8.96 g (26.1 mmol) of dichloro enol ether **3b** in 90 mL of anhydrous THF at −78 °C was added dropwise 23.2 mL (53.4 mmol) of 2.3 M *n*-butyllithium in hexanes. The reaction mixture was allowed to warm to −40 °C and then treated dropwise over 10 min with 7.40 g (36.2 mmol) of 3-butenyl trifluoromethanesulfonate.[19] The solution was stirred at −28 °C for 20 h, whereupon it was poured into cold saturated aqueous ammonium chloride. The product was isolated with pentane in the usual way to give 9.63 g of 2-[(*R*)-1-(hex-5-en-1-ynyloxy)-ethyl]-1,3,5-triisopropylbenzene (**4a**), which was used below immediately: IR 3050, 2266, 1640, 1608, 1265 cm^{-1}; ^1H NMR (200 MHz) δ 1.20−1.30 (m, 18 H), 1.69 (d, J = 6.8 Hz, 3 H), 2.00−2.15 (m, 4 H), 2.86 (hept, J = 6.9 Hz, 1 H), 3.19−3.45 (m, 2 H), 4.85−4.96 (m, 2 H), 5.52−5.78 (m, 2 H), 7.01 (s, 2 H); ^{13}C NMR (50.3 MHz) δ 17.3 (CH_2), 21.6 (CH_3), 23.9 (CH_3), 24.1 (CH_3), 29.3 (CH), 34.0 (CH_2), 34.1 (CH), 37.7 (C), 82.8 (CH), 89.8 (C), 115.0 (CH_2), 121.9 (C), 131.0 (C), 137.5 (CH), 148.4 (C).

A mixture of 9.63 g of acetylene **4a**, 9.00 mL (6.05 g, 72.0 mmol) of 1-hexene, and 0.400 g of 10% palladium on barium sulfate in 160 mL of dry pyridine was stirred under hydrogen (balloon pressure) for 4 h at 0 °C, whereupon the hydrogen was replaced with argon, and the reaction mixture was diluted with pentane and filtered over Celite. The filtrate was thoroughly washed with water, saturated aqueous copper sulfate, water, and saturated aqueous ammonium chloride, dried over sodium sulfate, and concentrated under reduced pressure to provide 9.18 g of diene ether **4b**, which was used below without delay: IR 3050, 1665, 1639, 1608, 1084 cm^{-1}; ^1H NMR (200 MHz) δ 1.17−1.27 (m, 18 H), 1.58 (d, J = 6.9 Hz, 3 H), 2.00−2.33 (m, 4 H), 2.84 (hept, J = 6.8 Hz, 1 H), 3.30−3.62 (m, 2 H), 4.25 (dt, J = 6.9, 6.5 Hz, 1 H), 4.88−5.07 (m, 2 H), 5.30 (q, J = 6.9 Hz, 1 H), 5.70−5.90 (m, 1 H), 5.94 (d, J = 6.2 Hz, 1 H), 6.99 (s, 2 H); ^{13}C NMR (50.3 MHz) δ 22.5 (CH_3), 23.6 (CH_2), 23.9 (CH_3), 24.6 (CH_3), 29.0 (CH), 33.9 (CH_2), 34.0 (CH), 75.2 (CH), 105.3 (CH), 114.3 (CH_2), 121.9 (C), 133.1 (C), 138.8 (CH), 144.2 (CH), 147.7 (C); mass spectrum (CI), *m*/*z* 328 (M^+, 0.3%), 231 (80%), 230 (100%). HRMS *m*/*e* calcd for $C_{23}H_{36}O$ (M^+) + Li: 335.2926. Found: 335.2914.

(3*R*,4*S*)-4-But-3-enyl-2,2-dichloro-3-[(*R*)-1-(2,4,6-triisopropylphenyl)ethoxy]cyclobutanone (5). To a stirred mixture of 9.10 g of enol ether **4b** and 3.0 g (ca. 46 mmol) of Zn−Cu couple in 300 mL of ether under argon was added over 1.5 h a solution of 3.80 mL (6.19 g, 34.0 mmol) of freshly distilled trichloroacetyl chloride in 90 mL of ether. After an additional 1 h, the ether solution was separated from the excess couple and added to a large volume of pentane, and the resulting mixture was partially concentrated under reduced pressure in order to precipitate the zinc chloride. The supernatant was decanted and washed successively with a cold aqueous solution of sodium bicarbonate, water, and brine and then dried over anhydrous sodium sulfate. Evaporation of the solvent under reduced pressure left 11.03 g of cyclobutanone **5** (containing ca. 5% of its diastereomer (δ 4.57 ppm)), as an oil: IR 3050, 1807, 1608, 1068 cm^{-1}; ^1H NMR (200 MHz) δ 1.02−1.38 (m, 18 H), 1.64 (d, J = 6.8 Hz, 3 H), 1.70−2.40 (m, 3 H), 2.86 (hept, J = 6.9 Hz, 2 H), 3.15−3.40 (m, 1 H), 3.40−3.60 (m, 1 H), 3.82 (hept, J = 6.9 Hz, 1 H), 4.29 (d, J = 9.2 Hz, 1 H), 4.95−5.10 (m, 2 H), 5.43 (q, J = 6.7 Hz, 1 H), 5.60−5.85 (m, 1 H), 6.98 (d, J = 1.7 Hz, 1 H), 7.06 (d, J = 2.0 Hz, 1 H); mass spectrum (CI) *m*/*z* 438 (M^+, 0.01%), 231 (100%). HRMS *m*/*e* calcd for $C_{25}H_{36}Cl_2O_2$ (M^+) + Li: 445.2252. Found: 445.2304.

(4*S*,5*S*)-5-But-3-enyl-4-[(*R*)-1-(2,4,6-triisopropylphenyl)-ethoxy]pyrrolidin-2-one (6b). A solution of 11.03 g of cyclobutanone **5** in 240 mL of dichloromethane was treated with 6.50 g (30.2 mmol) of *O*-mesitylenesulfonylhydroxylamine and a small amount of sodium sulfate and stirred at 20 °C for ca. 2 h. After filtration of the mixture over Celite, the solvent was removed under reduced pressure and the resulting material in 10 mL of toluene was placed on a column of basic alumina (600 g, Merck activity 1) and eluted rapidly with methanol. Evaporation of the solvents left a yellow solid, which was triturated with dichloromethane, which was then filtered over Celite and evaporated under reduced pressure to afford 11.65 g of (4*R*,5*S*)-5-but-3-enyl-3,3-dichloro-4-[(*R*)-1-(2,4,6-triisopropylphenyl)ethoxy]pyrrolidin-2-one (**6a**), used directly below: IR 3404, 3224, 3061, 1731, 1641, 1601 cm^{-1}; ^1H NMR (200 MHz) δ 1.15−1.40 (m, 18 H), 1.69 (d, J = 6.8 Hz, 3 H), 2.22−2.38 (m, 1 H), 2.61 (m, 2 H), 2.85 (hept, J = 6.9 Hz, 2 H), 3.33 (hept, J = 6.9 Hz, 1 H), 3.42−3.55 (m, 1 H), 3.75−3.98 (m, 1 H), 4.41 (d, J = 7.5 Hz, 1 H), 4.92−5.10 (m, 2 H), 5.60−5.85 (m, 2 H), 6.96 (d, J = 1.7 Hz, 1 H), 7.05 (d, J = 1.7 Hz, 1 H),7.25−7.45 (br s, 1 H); mass spectrum (CI) *m*/*z* 471 ($M + NH_4^+$, 27%), 265 (100%), 231 (58%).

The above dichloro lactam **6a** in 130 mL of methanol previously saturated with ammonium chloride was stirred with 3.2 g (ca. 49 mmol) of zinc−copper couple at 20 °C under argon for 3 h, whereupon the mixture was filtered to remove the excess couple. The filtrate was concentrated under reduced pressure, and the residue was then processed with dichloromethane in the usual way to give crude lactam **6b**. Purification of this material by dry silica gel chromatography with ethyl acetate in hexane provided 4.94 g (50% overall yield from dichloro enol ether **3b**, 87%/step) of pyrrolidinone as a yellow solid. Recrystallization of this material from methanol−water provided 3.16 g (64% recovery) of stereochemically pure (≥98%) **6b**, containing, however, a small amount of the saturated (butyl) compound (subsequently eliminated in the purification of **7a** and **10b**) (HPLC: Lichrosorb column, 5 mm, 2-propanol: hexane = 5:95, 1 mL/min., t_R 10.2 min (versus 9.6 min for the trans diastereomer and the saturated derivative and 13.8 min for the cis diastereomer). Pyrrolidinone **6b**: mp 126 °C (methanol−water); $[\alpha]^{20}_D$ +73 (*c* 1.5, chloroform); IR (film) 3216, 3053, 1697, 1641, 1608, 1265 cm^{-1}; ^1H NMR (500 MHz) δ 1.10−1.32 (m, 18 H), 1.51 (d, J = 6.6 Hz, 3 H), 1.54−1.64 (m, 1 H), 1.74−1.82 (m, 1 H), 2.03 (hept, J = 7.5 Hz, 1 H), 2.14 (hept, J = 7.2 Hz, 1 H), 2.46 (AB of ABX, δ_a = 2.44, δ_b = 2.48, J_{ab} = 16.5 Hz, J_{ax} = 7.1 Hz, J_{bx} = 7.4 Hz, 2 H), 2.83 (hept, J = 6.9 Hz, 1 H), 3.13 (hept, J = 6.6 Hz, 1 H), 3.54−3.60 (m, 1 H), 3.84 (hept, J = 6.7 Hz, 1 H), 4.11 (q, J = 7.0 Hz, 1 H), 4.90−5.09 (m, 3 H), 5.70−5.80 (m, 1 H), 6.48 (br s, N−H), 6.93 (s, 1 H), 7.02 (s, 1 H); ^{13}C NMR (50.3 MHz) δ 23.0 (CH_3), 23.8 (CH_3), 24.2 (CH_3), 24.9 (CH_3), 25.1 (CH_3), 28.0 (CH), 28.9 (CH_2), 29.0 (CH), 30.3 (CH_2), 33.9 (CH), 36.5 (CH_2), 57.3 (CH), 71.2 (CH), 72.7 (CH), 115.2 (CH_2), 120.5 (CH), 123.2 (CH), 132.2 (C), 137.8 (CH), 145.7 (C), 147.5 (C), 148.7 (C), 175.5 (C); mass spectrum (EI), *m*/*z* 385 (M^+, 4%), 231 (67%), 230 (74%), 43 (100%). Anal. Calcd for $C_{25}H_{39}NO_2$: C, 77.87; H, 10.19; N, 3.63. Found: C, 77.61; H, 10.06; N, 3.74.

(4*S*,5*S*)-5-(4-Hydroxybutyl)-4-[(*R*)-1-(2,4,6-triisopropylphenyl)ethoxy]pyrrolidin-2-one (7a). To a stirred solution of lactam **6b** (0.788 g, 2.04 mmol) in 6.8 mL of THF at 0 °C was added 3.2 mL (8.3 mmol) of a freshly prepared 2.6 M solution of disiamylborane in THF. The resulting solution was stirred at 20 °C for 5 h, cooled to 0 °C, and carefully treated with 4 mL of water, 4 mL of 3 M aqueous sodium hydroxide, and 4 mL of 30% aqueous hydrogen peroxide. The mixture was vigorously stirred for 20 h at 20 °C and then filtered through

(19) Prepared from 3-buten-1-ol and triflic anhydride according to the general procedure described in Salomon, M. F.; Salomon, R. G.; Gleim, R. D. *J. Org. Chem.* **1976**, *41*, 3983−3987.

Celite with ethyl acetate. The crude product was isolated with ethyl acetate in the usual way and purified by dry silica gel column chromatography with methanol in ethyl acetate to give 0.622 g (75%) of alcohol **7a**: mp 145−147 °C; $[\alpha]^{21}_D$ +68.0 (*c* 0.2, chloroform); IR 3432, 3242, 1693, 1608 cm^{-1}; ^1H NMR (300 MHz) δ 1.13−1.27 (m, 19 H), 1.52 (d, J = 6.7 Hz, 3 H), 1.30−1.78 (m, 5 H), 1.87−2.10 (br s, 1 H), 2.46 (AB of ABX, δ_a = 2.48, δ_b = 2.44, J_{ab} = 16.5 Hz, J_{ax} = 7.3 Hz, J_{bx} = 6.9 Hz, 2 H), 2.83 (hept, J = 6.9 Hz, 1H), 3.12 (hept, J = 6.8 Hz, 1H), 3.54−3.63 (m, 3 H), 3.84 (hept, J = 6.6 Hz, 1 H), 4.11 (pseudo q, X of ABX, J_{ax} = 7.3 Hz, J_{bx} = 6.9 Hz, 1 H), 5.03 (q, J = 6.7 Hz, 1 H), 6.65−6.90 (br s, 1 H), 6.93 (s, 1 H), 7.02 (s, 1 H); ^{13}C NMR (75.5 MHz) δ 22.4 (CH_2), 23.3 (CH_3), 24.0 (CH_3), 24.4 (CH_3), 25.0 (CH_3), 25.1 (CH_3), 25.3 (CH_3), 28.2 (CH), 29.2 (CH), 29.3 (CH_2), 32.3 (CH_2), 34.1 (CH), 36.7 (CH_2), 57.9 (CH), 62.4 (CH_2), 71.5 (CH), 73.0 (CH), 120.7 (CH), 123.4 (CH), 132.4 (C), 145.9 (C), 147.8 (C), 148.9 (C), 175.6 (C); mass spectrum (CI), *m*/*z* 404 (MH^+, 100%), 264 (10%), 231 (44%). Anal. Calcd for $C_{25}H_{41}NO_3$: C, 74.40; H, 10.24; N, 3.47. Found: C, 74.32; H, 10.08; N, 3.58.

(1*S*,8a*S*)-1-[(*R*)-1-(2,4,6-Triisopropylphenyl)ethoxy]-hexahydroindolizin-3-one (8a). To a stirred solution of 0.622 g (1.54 mmol) of alcohol **7a** and 0.500 mL (0.363 g, 3.59 mmol) of triethylamine in 6.2 mL of dichloromethane at 0 °C was added dropwise 0.275 mL (0.407 g, 3.55 mmol) of methanesulfonyl chloride. The resulting solution was stirred at 0 °C for 1.5 h, diluted with 30 mL dichloromethane, and then treated with 2 mL of water. The crude product was isolated in the usual way to afford 0.701 g of crude mesylate **7b**, which was used without further purification: IR 3225, 1696, 1607, 1355 cm^{-1}; ^1H NMR (300 MHz) δ 1.14−1.40 (m, 20 H), 1.45−1.56 (m, 4 H), 1.63−1.78 (m, 3 H), 2.44 (AB of ABX, δ_a = 2.46, δ_b = 2.42, J_{ab} = 16.4 Hz, J_{ax} = 7.2 Hz, J_{bx} = 7.2 Hz, 2 H), 2.82 (hept, J = 6.9 Hz, 1 H), 2.97 (s, 3 H), 3.09−3.15 (m, 1 H), 3.51−3.57 (m, 1 H), 3.82 (hept, J = 6.6 Hz, 1 H), 4.11 (pseudo q, X of ABX, J_{ax} = 7.2 Hz, J_{bx} = 7.2 Hz, 1H), 4.19 (t, J = 6.5 Hz, 2 H), 5.03 (q, J = 6.7 Hz, 1 H), 6.92 (s, 1 H), 7.01 (s, 1 H), 7.03 (s, 1 H); ^{13}C NMR (75.5 MHz) δ 22.2 (CH_2), 23.1 (CH_3), 23.9 (CH_3), 24.2 (CH_3), 24.9 (CH_3), 25.1 (CH_3), 28.1 (CH), 29.1 (CH_2), 29.1 (CH), 29.4 (CH_2), 33.9 (CH), 36.4 (CH_2), 37.4 (CH_3), 57.5 (CH), 69.6 (CH_2), 71.4 (CH), 72.7 (CH), 120.6 (CH), 123.2 (CH), 132.1 (C), 145.8 (C), 147.7 (C), 148.7 (C), 175.2 (C); mass spectrum (CI), *m*/*z* 482 (MH^+, 100%), 386 (94%), 264 (28%), 231 (90%).

A solution of 0.701 g (ca. 1.46 mmol) of crude mesylate **7b** in 10 mL of THF was added to a stirred mixture of 0.300 g of sodium hydride (7.50 mmol, 60% in mineral oil) in 12 mL of THF and 4 mL of freshly distilled DMF at 20 °C. The resulting mixture was stirred for 2 h, cooled to 0 °C, and then carefully treated with water. The crude reaction product was isolated with ether in the normal way and purified by dry silica gel column chromatography with ethyl acetate in pentane to afford 0.525 g (88%) of indolizidinone **8a**: mp 144−145 °C; $[\alpha]^{20}_D$ +86.3 (*c* 1.0, chloroform); IR 1682, 1608 cm^{-1}; ^1H NMR (300 MHz) δ 1.15−1.26 (m, 19 H), 1.29−1.40 (m, 2 H), 1.49 (d, J = 6.8 Hz, 3 H), 1.54−1.72 (m, 2 H), 1.85−1.96 (m, 1 H), 2.49−2.59 (m, 3 H), 2.83 (hept, J = 6.9 Hz, 1 H), 3.14 (hept, J = 6.9 Hz, 1 H), 3.39−3.45 (m, 1 H), 3.85 (hept, J = 6.8 Hz, 1 H), 4.01 (m, 1 H), 4.08−4.14 (m, 1 H), 5.06 (q, J = 6.8 Hz, 1 H), 6.92 (s, 1 H), 7.01 (s, 1 H); ^{13}C NMR (75.5 MHz) δ 23.4 (CH_3), 24.0 (CH_2), 24.2 (CH_3), 24.6 (CH_3), 24.8 (CH_2), 25.2 (CH_3), 25.5 (CH_3), 25.5 (CH_3), 25.8 (CH_2), 28.2 (CH), 29.4 (CH), 34.2 (CH), 37.6 (CH_2), 40.6 (CH_2), 61.5 (CH), 69.8 (CH), 70.7 (CH), 121.0 (CH), 123.5 (CH), 132.3 (C), 146.4 (C), 147.9 (C), 149.1 (C), 171.4 (C). Anal. Calcd for $C_{25}H_{39}NO_2$: C, 77.87; H, 10.19; N, 3.63. Found: C, 77.92; H, 10.35; N, 3.63.

(1*S*,8a*S*)-1-Hydroxyhexahydroindolizin-3-one (8b). A 0.618-g (1.60 mmol) sample of lactam **8a** in 10 mL of dichloromethane was stirred with 1.00 mL (1.48 g, 13.0 mmol) of trifluoroacetic acid at 20 °C for 2.5 h, whereupon chloroform was added, and the reaction mixture was concentrated to dryness under reduced pressure. Purification of the resulting solid by dry silica gel column chromatography with methanol in ethyl acetate afforded 0.217 g (87%) of alcohol **8b**: mp 149−157 °C (dec); $[\alpha]^{20}_D$ +26.9 (*c* 1.5, acetone); IR 3268, 1651 cm^{-1}; ^1H NMR (300 MHz) δ 1.21−1.47 (m, 2 H), 1.53−1.70 (m, 3 H), 1.93−1.98 (m, 1 H), 2.32 (dd, J = 17.3, 1.7 Hz, 1 H), 2.37−2.53 (br s, 1 H), 2.55−2.67 (m, 2 H), 6.78 (ddd, J = 10.9, 4.9, 4.9 Hz, 1 H), 4.04−4.10 (m, 1 H), 4.33−4.38 (m, 1 H); ^{13}C NMR (75.5 MHz) δ 23.2 (CH_2), 24.0 (CH_2), 24.6 (CH_2), 40.3 (CH_2), 41.0 (CH_2), 61.7 (CH), 66.3 (CH), 172.2 (C); mass spectrum (CI), *m*/*z* 156 (MH^+, 81%), 134 (1%). HRMS *m*/*e* calcd for $C_8H_{13}NO_2$ (M^+): 155.0946. Found: 155.0959.

(1*S*,8a*S*)-Octahydroindolizin-1-ol (1). A mixture of alcohol **8b** (0.130 g 0.84 mmol) and lithium aluminum hydride (0.255 g, 6.72 mmol) in 18 mL of THF was stirred at 20 °C for 24 h. After being diluted with 13 mL of THF, the mixture was cooled to 0 °C and carefully treated with 0.255 mL of water, 0.255 mL of 10% aqueous sodium hydroxide, and 0.770 mL water. The resulting mixture was stirred for 40 min at 20 °C and then treated with anhydrous sodium sulfate. Filtration of the mixture and concentration of the filtrate under reduced pressure gave the crude product, which was purified by column chromatography on silica gel with 0−15% methanol saturated with ammonia in chloroform to give 0.090 g (76%) of indolizidine **1**, as a clear oil: $[\alpha]^{25}_D$ +22.5 (*c* 1.0, ethanol) (lit. +20.2,[5f] +27[5d]), $[\alpha]^{22}_D$ +17.4 (*c* 0.4, chloroform) (lit.[5h] +16.4, +18.1); IR 3386 cm^{-1}; ^1H NMR (300 MHz) δ 1.21 (m, 1 H), 1.42−1.70 (m, 6 H), 1.80−1.99 (m, 3 H), 2.13 (m, 1 H), 2.26 (m, 1 H), 3.07 (m, 2 H), 4.03 (br s, 1 H); ^{13}C NMR (50.3 MHz) δ 23.9 (CH_2), 25.2 (CH_2), 25.3 (CH_2), 33.3 (CH_2), 52.8 (CH_2), 53.6 (CH_2), 68.8 (CH), 73.0 (CH); mass spectrum (CI), *m*/*z* 142 (MH^+, 61%), 124 (10%), 110 (100%). The ^1H NMR spectrum was in perfect agreement with that of an independently prepared[5d] sample (spectrum kindly provided by Professor C. Harris). HRMS *m*/*e* calcd for $C_8H_{15}NO$ (M^+): 141.1154. Found: 141.1151.

Benzyl (2*S*,3*S*)-2-But-3-enyl-5-oxo-3-[(*R*)-1-(2,4,6-triisopropylphenyl)ethoxy]pyrrolidine-1-carboxylate (9). To a solution of lactam **6b** (1.80 g, 4.67 mmol) in 36 mL of dry THF at −78 °C were added 2.50 mL (5.25 mmol) of a 2.1 M solution of *n*-butyllithium in hexane and, after 30 min, 1.40 mL (1.67 g, 9.81 mmol) of benzyl chloroformate. The reaction mixture was allowed to warm to 0 °C and stirred at this temperature for 1 h. The crude product was isolated with ether in the usual manner and purified by dry silica gel chromatography with 15% ethyl acetate in hexane to give 2.22 g (92%) of pyrrolidinone **9**: mp 73 °C (methanol−water); $[\alpha]^{25}_D$ +90 (*c* 1.5, chloroform); IR 3065, 1788, 1754, 1724, 1607, 1288, 1266 cm^{-1}; ^1H NMR (300 MHz) δ 1.07−1.33 (m, 18 H), 1.54 (d, J = 6.5 Hz, 3 H), 1.58−1.72 (m, 2 H), 1.92−2.20 (m, 3 H), 2.66 (AB of ABX, δ_a = 2.63, δ_b = 2.70, J_{ab} = 15.8 Hz, J_{ax} = 8.7 Hz, J_{bx} = 6.7 Hz, 2 H), 2.83 (hept, J = 7.0 Hz, 1 H), 3.02−3.18 (m, 1 H), 3.74−3.88 (m, 1 H), 4.03−4.15 (m, 2 H), 4.18−4.29 (m, 1 H), 4.86−4.97 (m, 2 H), 5.04 (q, J = 6.7 Hz, 1 H), 5.15−5.30 (m, 2 H), 5.64−5.80 (m, 1 H), 6.93 (br s, 1 H), 7.03 (br s, 1 H), 7.25−7.40 (m, 5 H); ^{13}C NMR (50.3 MHz) δ 22.9 (CH_3), 23.8 (CH_3), 24.0 (CH_3), 24.9 (CH_3), 28.0 (CH), 28.3 (CH_2), 29.0 (CH), 30.2 (CH_2), 33.8 (CH), 38.0 (CH_2), 59.6 (CH), 60.0 (CH), 67.9 (CH_2), 69.5 (CH), 69.7 (CH), 71.5 (CH), 114.6 (CH_2), 120.5 (CH), 123.2 (CH), 128.0 (CH), 128.2(CH), 128.4 (CH), 131.5 (C), 131.8 (C), 135.0 (C), 137.8 (CH), 145.7 (C), 147.6 (C), 148.5 (C), 151.0 (C), 170.4 (C); mass spectrum (CI) *m*/*z* 520 (MH^+, 100%), 519 (M^+, 10%), 231 (6%). Anal. Calcd for $C_{33}H_{45}NO_4$: C, 76.26; H, 8.73; N, 2.70. Found: C, 76.06; H, 8.65; N, 2.63.

Benzyl (2*S*,3*S*)-2-But-3-enyl-3-[(*R*)-1-(2,4,6-triisopropylphenyl)ethoxy]pyrrolidine-1-carboxylate (10a). To a stirred solution of lactam **9** (2.20 g, 4.23 mmol) in 14 mL of THF at −78 °C under argon was added dropwise 7.10 mL (7.10 mmol) of a 1 M solution of lithium triethylborohydride in THF. The resulting solution was stirred for 30 min at −78 °C, quenched with saturated aqueous sodium bicarbonate solution (11 mL), and then allowed to warm to 0 °C. Ten drops of 30% aqueous hydrogen peroxide were added, and the mixture was then stirred for 30 min at 0 °C. The crude product was isolated with dichloromethane in the usual way to yield 2.06 g of the corresponding α-hydroxypyrrolidine, which was used immediately below.

A stirred solution of this material and 0.700 mL (0.509 g, 4.38 mmol) of triethylsilane in 60 mL of dry dichloromethane

at −78 °C was treated with 0.700 mL (0.784 g, 5.52 mmol) of boron trifluoride diethyl etherate and then, after 30 min, the same amounts of these two reagents were again added. After being stirred for an additional 2 h at −78 °C, the reaction mixture was treated with 6.5 mL of saturated aqueous sodium bicarbonate solution, and the crude product was isolated with dichloromethane in the usual way. Purification of this material by dry silica gel chromatography with 10−15% ethyl acetate in hexane afforded 1.50 g (70%) of pyrrolidine **10a**, as an oil: $[\alpha]^{25}_D$ +38 (*c* 1.6, chloroform); IR 3061, 1704, 1641, 1608, 1411 cm^{-1}; ^1H NMR (200 MHz, C_7D_8, 80 °C) δ 0.90−1.20 (m, 18 H), 1.29 (d, J = 6.7 Hz, 3 H), 1.35−1.80 (m, 5 H), 1.85−2.08 (m, 2 H), 2.58 (hept, J = 6.7 Hz, 1 H), 2.90−3.18 (m, 2 H), 3.56 (q, J = 9.0 Hz, 1 H), 3.65−3.88 (m, 1 H), 4.56−4.94 (m, 5 H), 5.40−5.70 (m, 1 H), 6.75−7.08 (m, 7 H); ^{13}C NMR (50.3 MHz, C_7D_8, 80 °C) δ 23.5 (CH_3), 24.4 (CH_3), 25.2 (CH_3), 25.5 (CH_3), 29.5 (CH_2), 31.2 (CH_2), 34.7 (CH), 43.4 (CH_2), 59.0 (CH), 67.0 (CH_2), 72.9 (CH), 77.4 (CH), 114.4 (CH_2), 128.1 (CH), 128.4 (CH), 128.7 (CH), 134.0 (C), 137.7 (C), 138.1 (C), 139.5 (CH), 148.1 (C), 155.2 (C); mass spectrum (CI) *m*/*z* 506 (MH^+, 4%), 505 (M^+, 2%), 231 (19%), 230 (26%). HRMS *m*/*e* calcd for $C_{33}H_{47}NO_3$ (M^+) + Li: 512.3716. Found: 512.3710.

Benzyl (2*S*,3*S*)-2-(3,4-Dihydroxybutyl)-3-[(*R*)-1-(2,4,6-triisopropylphenyl)ethoxy]pyrrolidine-1-carboxylate (10b). To a solution of 1.83 g (3.62 mmol) of carbamate **10a** in 10.8 mL of *tert*-butyl alcohol, and 3.2 mL of water were added 0.400 g (3.60 mmol) of trimethylamine oxide dihydrate and 2.0 mL (0.16 mmol) of a 2.5% solution of osmium tetraoxide in *tert*-butyl alcohol. The reaction mixture was refluxed, with additional trimethylamine oxide dihydrate (0.200 g, 1.80 mmol) being added at 1 h intervals over the first 3 h. After being refluxed for 12 h, the reaction mixture was allowed to cool to 20 °C and was treated with a solution of 2.80 g of sodium hydrogen sulfite in 36 mL of water and then stirred for 15 min. The crude product was isolated with ethyl acetate in the usual manner and purified by dry silica gel chromatography with 10−20% ethyl acetate in hexane (to elute a small amount of saturated side chain material) and then methanol to afford 1.31 g (67%) of diol **10b**: mp 38 °C; $[\alpha]^{25}_D$ +39 (*c* 1.6, chloroform); IR 3430, 1701, 1607, 1415 cm^{-1}; ^1H NMR (200 MHz, C_7D_8, 80 °C, diastereomers) δ 0.98−1.28 (m, 18 H), 1.37 (d, J = 6.8 Hz, 3 H), 1.30−1.92 (m, 4 H), 2.43 (q, J = 7.2 Hz, 1 H), 2.65 (hept, J = 6.8 Hz, 1 H), 2.90−3.94 (m, 12 H), 4.80−5.20 (m, 3 H), 6.80−7.18 (m, 7 H); ^{13}C NMR (50.3 MHz, C_7D_8, 80 °C, diastereomers) δ 23.3 (CH_3), 24.2 (CH_3), 25.0 (CH_3), 25.3 (CH_3), 26.0 (CH_2), 26.2 (CH_2), 29.2 (CH_2), 30.6 (CH_2), 30.8 (CH_2), 34.5 (CH), 43.3 (CH_2), 46.7 (CH_2), 59.0 (CH), 59.2 (CH), 67.2 (CH_2), 67.2 (CH_2), 72.7 (CH), 72.9 (CH), 76.9 (CH), 77.1 (CH), 128.1 (CH), 128.3 (CH), 128.7 (CH), 133.8 (C), 133.9 (C), 137.6 (C), 137.8 (C), 137.8 (C), 148.1 (C), 155.4 (C), 155.5 (C); mass spectrum (CI) *m*/*z* 540 (MH^+, 3%), 539 (M^+, 0.4%), 231 (71%). Anal. Calcd for $C_{33}H_{49}NO_5 \cdot 0.25\ H_2O$: C, 72.76; H, 9.17; N, 2.57. Found: C, 72.96; H, 9.35; N, 2.62.

Benzyl (2*S*,3*S*)-2-(3-Hydroxy-4-(toluene-4-sulfonyloxy)-butyl]-3-[(*R*)-1-(2,4,6-triisopropylphenyl)ethoxy]pyrrolidine-1-carboxylate (10c). A solution of 0.034 g (0.063 mmol) of diol **10b** in 0.34 mL of methanol was treated with 0.017 g (0.068 mmol) of dibutyltin oxide and then refluxed for 45 min. After being allowed to cool to 20 °C, the reaction mixture was treated with 0.068 mL (0.049 g, 0.49 mmol) of triethylamine and 0.088 g (0.46 mmol) of *p*-toluenesulfonyl chloride and stirred for 10 min, whereupon a saturated solution of aqueous sodium bicarbonate was added. The crude product was isolated with dichloromethane and then stirred in 1.25 mL of THF with 0.25 mL of water and 0.25 mL of triethylamine for 2 h, after which time the product was isolated with ether in the usual way and purified by dry silica gel chromatography with 20−30% ethyl acetate in hexane to give 0.041 g (94%) of tosylate **10c**: mp 45−46 °C (pentane−dichloromethane); $[\alpha]^{25}_D$ +27 (*c* 1.5, chloroform); IR 3437, 1697, 1609, 1461, 1360 cm^{-1}; ^1H NMR (200 MHz, C_7D_8, 60 °C, diastereomers) δ 1.02−1.34 (m, 20 H), 1.44 (d, J = 6.8 Hz, 3 H), 1.35−1.85 (m, 6 H), 1.90 (s, 3 H), 2.74 (hept, J = 6.8 Hz, 1 H), 2.84−3.30 (m, 2 H), 3.52−4.08 (m, 4 H), 4.82−5.10 (m, 5 H), 6.75 (d, J = 7.9 Hz, 2 H), 6.90−7.22 (m, 7 H), 7.66 (dd, J = 8.5, 2.6 Hz, 2 H); ^{13}C NMR (50.3 MHz, C_7D_8, 60 °C, diastereomers) δ 23.4 (CH_3), 24.3 (CH_3), 25.4 (CH_3), 26.0 (CH_3), 26.1 (CH_3), 29.3 (CH_2), 30.5 (CH_2), 34.7 (CH_2), 43.3 (CH_2), 58.5 (CH), 58.9 (CH), 67.1 (CH_2), 67.3 (CH_2), 69.9 (CH), 70.0 (CH), 72.5 (CH), 74.4 (CH_2), 76.8 (CH), 128.4 (CH), 128.5 (CH), 128.8 (CH), 130.1 (CH), 133.8 (C), 134.9 (C), 137.7 (C), 137.9 (C), 144.4 (C), 148.2 (C), 155.4 (C), 155.6 (C); mass spectrum (CI) *m*/*z* 694 (MH^+, 0.6%), 522 (2.8%), 231 (72%). Anal. Calcd for $C_{40}H_{55}NO_7S$: C, 69.23; H, 7.99; N, 2.02; S, 4.62. Found: C, 69.52; H, 8.14; N, 2.19; S, 4.29.

(1*S*,8a*S*)-1-[(*R*)-1-(2,4,6-Triisopropylphenyl)ethoxy]octahydroindolizin-6-ol (11a). A mixture of 1.30 g (1.87 mmol) of tosylate **10c** and 0.130 g of palladium hydroxide in 18 mL of methanol was stirred under hydrogen overnight at 20 °C, whereupon the hydrogen was replaced with argon, and the reaction mixture was diluted with methanol and filtered over Celite. The residue obtained on evaporation of the methanol under reduced pressure was dissolved in 32 mL of dichloromethane, treated with 0.560 mL (0.407 g, 4.02 mmol) of triethylamine, and then refluxed for 2.5 h. After being allowed to cool to room temperature, the reaction mixture was processed in the usual way, and the crude product was purified by dry silica gel chromatography with 0−25% methanol in dichloromethane to give 0.700 g (97%) of alcohol **11a**, as a mixture of hydroxy epimers: $[\alpha]^{25}_D$ +64 (*c* 1.2, chloroform); IR 3404, 1608 cm^{-1}; ^1H NMR (500 MHz, major diastereomer) δ 1.20−1.29 (m, 18 H), 1.30−1.39 (m, 1 H), 1.47 (d, J = 6.7 Hz, 3 H), 1.50−1.54 (m, 1 H), 1.63−1.74 (br s, 1 H), 1.83−2.08 (m, 6 H), 2.82 (hept, J = 6.9 Hz, 2 H), 3.01−3.07 (m, 1 H), 3.11 (d, J = 11.0 Hz, 1 H), 3.21 (hept, J = 6.7 Hz, 1 H), 3.76 (m, 1 H), 3.84 (br s, 1 H), 3.93 (hept, J = 6.7 Hz, 1 H), 5.07 (q, J = 6.8 Hz, 1 H), 6.91 (s, 1 H), 7.01 (s, 1 H); ^{13}C NMR (50.3 MHz, major diastereomer) δ 19.7 (CH_2), 23.3 (CH_3), 23.3 (CH_3), 24.2 (CH_3), 25.2 (CH_3), 25.3 (CH_3), 25.6 (CH_3), 27.6 (CH), 29.0 (CH), 30.5 (CH_2), 30.7 (CH_2), 33.9 (CH), 53.3 (CH_2), 59.4 (CH_2), 65.2 (CH), 68.2 (CH), 69.0 (CH), 76.2 (CH), 120.5 (CH), 123.0 (CH), 132.6 (C), 146.1 (C), 147.2 (C), 149.2 (C); mass spectrum (CI) *m*/*z* 388 (MH^+, 69%), 231 (11%), 156 (100%). HRMS *m*/*e* calcd for $C_{25}H_{41}NO_2$ (M^+) + H: 388.3215. Found: 388.3229.

(1*S*,8a*S*)-1-[(*R*)-1-(2,4,6-Triisopropylphenyl)ethoxy]-hexahydroindolizin-6-one (11b). To a stirred solution of 0.380 mL (0.553 g, 4.36 mmol) of oxalyl chloride in 8.5 mL of dichloromethane at −60 °C under argon was added 0.570 mL (0.627 g, 8.03 mmol) of dimethyl sulfoxide. After being stirred for 10 min at −60 °C, a solution of 0.700 g (1.80 mmol) of **11a** in 8.5 mL of dichloromethane was added dropwise. The mixture was allowed to warm to −40 °C, stirred for 1.5 h at this temperature, and then treated with 2.50 mL (1.82 g, 17.9 mmol) of triethylamine. After being stirred for 15 min at −40 °C, the reaction mixture was allowed to warm to room temperature and was then processed with dichloromethane in the usual way to give the crude product. Purification of this material by filtration through silica gel (pretreated with 2.5% triethylamine, v/v) with 20−100% ethyl acetate in hexane afforded 0.610 g (88%) of ketone **11b**: mp 79−80 °C (hexane); $[\alpha]^{25}_D$ +64 (*c* 1.5, chloroform); IR 1724, 1608 cm^{-1}; ^1H NMR (500 MHz) δ 1.10−1.30 (m, 18 H), 1.50 (d, J = 6.8 Hz, 3 H), 1.86−1.95 (m, 1 H), 1.96−2.26 (m, 5 H), 2.52 (d, J = 13.4 Hz, 1 H), 2.69 (d, J = 14.9 Hz, 1 H), 2.83 (hept, J = 6.9 Hz, 2 H), 3.06−3.17 (m, 1 H), 3.22 (hept, J = 6.8 Hz, 1 H), 3.53 (d, J = 14.9 Hz, 1 H), 3.81−3.96 (m, 2 H), 5.10 (q, J = 6.8 Hz, 1 H), 6.93 (br s, 1 H), 7.02 (br s, 1 H); ^{13}C NMR (62.5 MHz) δ 22.8 (CH_2), 23.4 (CH_3), 23.9 (CH_3), 24.1 (CH_3), 25.3 (CH_3), 25.7 (CH_3), 27.6 (CH), 29.0 (CH), 31.0 (CH_2), 33.9 (CH), 38.1 (CH_2), 53.4 (CH_2), 64.0 (CH_2), 65.7 (CH), 68.8 (CH), 75.0 (CH), 120.6 (CH), 123.0 (CH), 132.1 (C), 146.3 (C), 147.4 (C), 149.1 (C), 206.8 (C); mass spectrum (CI) *m*/*z* 386 (MH^+, 76%), 231 (100%). HRMS *m*/*e* calcd for $C_{25}H_{39}NO_2$ (M^+): 385.2981. Found: 385.2986.

(1*S*,8a*S*)-6-Oxooctahydroindolizin-1-yl Acetate (12a). To a stirred solution of 0.610 g (1.58 mmol) of ketone **11b** in 10 mL of dichloromethane at 20 °C was added 0.720 mL (1.06 g, 9.35 mmol) of trifluoroacetic acid. After being stirred for 1 h, the reaction mixture was concentrated at 20 °C under reduced pressure to give the corresponding crude keto alcohol.

A solution of the above keto alcohol, 3.30 mL (2.40 g, 23.68 mmol) of triethylamine, 1.20 mL (1.30 g, 12.72 mmol) of acetic anhydride, and a few crystals of DMAP in 27 mL of dichloromethane was stirred for 4 h at 20 °C. The reaction mixture was then processed with dichloromethane in the usual manner to give the crude product, which was purified by dry silica gel chromatography to afford 0.270 g (87%) of keto acetate **12a**: mp 79−80 °C (hexane); $[\alpha]^{25}_D$ +34 (*c* 1.9, chloroform); IR 1737, 1731, 1246 cm^{-1}; ^1H NMR (250 MHz) δ 1.71−2.55 (m, 8 H), 2.02 (s, 3 H), 2.72 (d, J = 14.3 Hz, 1 H), 3.15 (td, J = 8.9, 2.4 Hz, 1H), 3.52 (d, J = 14.3 Hz, 1 H), 5.22−5.32 (m, 1 H); ^{13}C NMR (62.5 MHz) δ 21.0 (CH_3), 22.9 (CH_2), 31.4 (CH_2), 37.6 (CH_2), 53.1 (CH_2), 63.7 (CH_2), 64.9 (CH), 73.6 (CH), 170.5 (C), 205.3 (C); mass spectrum (EI) *m*/*z* 197 (M^+, 12%), 154 (10%). HRMS *m*/*e* calcd for $C_{10}H_{15}NO_3$ (M^+): 197.1052. Found: 197.1058.

(1*S*,8a*S*)-6-(Hydroxyimino)octahydroindolizin-1-yl Acetate (12b). A solution of 0.034 g (0.17 mmol) of keto acetate **12a** and 0.040 g (0.58 mmol) of hydroxylamine hydrochloride in 0.780 mL of 2:1 ethanol−pyridine was refluxed for 4 h, whereupon the solvents were evaporated under reduced pressure, and the crude reaction product was isolated with dichloromethane in the usual way. Purification of this material by dry silica gel chromatography with 0−80% methanol in ether furnished 0.026 g (71%) of oxime **12b**, as a 3:1 mixture of the syn and anti isomers: IR 3312, 1730, 1676, 1118 cm^{-1}; ^1H NMR (200 MHz), major isomer: δ 1.45−1.94 (m, 4 H), 2.03 (s, 3 H), 2.08−2.42 (m, 3 H), 2.64 (d, J = 12.3 Hz, 1 H), 3.19 (t, J = 8.2 Hz, 1 H), 3.36−3.52 (m, 1 H), 3.65 (d, J = 12.3 Hz, 1 H), 5.19−5.32 (m, 1 H), 8.00−8.30 (br s, 1 H); minor isomer: δ 1.52−2.72 (m, 9 H), 2.04 (s, 3 H), 3.21 (td, J = 9.0, 1.3 Hz, 1 H), 4.61 (d, J = 13.4 Hz, 1 H), 5.20−5.30 (m, 1 H); ^{13}C NMR (62.5 MHz, major isomer) δ 21.0 (CH_3), 21.4 (CH_2), 22.9 (CH_2), 31.0 (CH_2), 52.8 (CH_2), 56.4 (CH_2), 66.5 (CH), 74.1 (CH), 155.0 (C), 170.9 (C); mass spectrum (FAB) *m*/*z* 213 (MH^+).

(1*S*,6*S*,8a*S*)-6-Aminooctahydroindolizin-1-yl Acetate (Slaframine, 2). A mixture of 0.033 g (0.16 mmol) of the oximes **12b**, 0.040 g of platinum oxide, and 0.20 mL of concd HCl in 3 mL of ethanol was placed under 3 atm of hydrogen and vigorously stirred for 6 h, after which it was filtered, and the filtrate was concentrated at 20 °C. The residue was dissolved in chloroform, which was washed with aqueous sodium carbonate and brine, dried over anhyd sodium sulfate, filtered, and then concentrated at 20 °C under reduced pressure. The resulting crude product was purified rapidly on silica gel with chloroform to give 0.017 g (55%) of slaframine **2**, as an unstable oil that darkens in air: IR 3363, 1737 cm^{-1}; ^1H NMR (500 MHz) δ 1.42−1.62 (m, 1 H), 1.62−1.87 (m, 5 H), 1.94−2.10 (m, 1 H), 2.05 (s, 3 H), 2.12 (dd, J = 11.4, 1.9 Hz, 1 H), 2.16−2.32 (m, 1 H), 2.87−3.15 (m, 4 H), 3.17 (br s, 1 H), 5.16−5.25 (m, 1 H); mass spectrum (FAB) *m*/*z* 199 (MH^+), 185, 93. The ^1H NMR spectrum was in excellent agreement with that of an independently synthesized[6l] sample (spectrum kindly provided by Professor D. H. Hua). HRMS *m*/*e* calcd for $C_{10}H_{18}N_2O_2$ (M^+) + H: 199.1446. Found: 199.1445.

(1*S*,6*S*,8a*S*)-6-(Benzyloxycarbonylamino)octahydroindolizin-1-yl Acetate (*N*-Cbz-slaframine). A solution of 0.005 g (0.025 mmol) of slaframine (**2**), 0.020 mL (0.015 g, 0.144 mmol) of triethylamine, 0.011 mL (0.013 g, 0.077 mmol) of benzyl chloroformate, and a small crystal of DMAP in 0.300 mL of dichloromethane at 0 °C was stirred for 2 h. The crude product was isolated with ether in the usual manner and purified by dry silica gel chromatography to provide in quantitative yield *N*-Cbz-slaframine, which displayed a high-field ^1H NMR spectrum in perfect agreement with that of the Cbz derivative prepared from natural slaframine (spectrum kindly provided by Professor H. Wasserman).

(1*S*,6*S*,8a*S*)-6-(Acetylamino)octahydroindolizin-1-yl Acetate (*N*-acetylslaframine). A solution of 0.017 g (0.086 mmol) of slaframine (**2**) in 0.50 mL of pyridine and 0.50 mL of acetic anhydride was stirred at 20 °C for 4 h, whereupon the solvents were removed under reduced pressure. The resulting residue was processed with chloroform in the usual way, and the crude product was purified by dry silica gel chromatography with 100% chloroform to yield 0.014 g (68%) of *N*-acetylslaframine: mp 138 °C (ether−pentane) (lit. 136−138 °C,[6h] 138−140 °C,[6o] 139−141 °C,[6i] 140−141 °C[6k]); $[\alpha]^{20}_D$ −11.8 (*c* 1.3, ethanol) (lit. -10,[6s] −11.2,[6i] −12.9,[6r] −13.5,[6q] −14.6,[6k] −15.7,[6o] −18.8[6h]); IR 3437, 1731, 1658, 1511, 1259 cm^{-1}; ^1H NMR (250 MHz) δ 1.32−2.32 (m, 9 H), 1.98 (s, 3 H), 2.07 (s, 3 H), 2.90−3.10 (m, 2 H), 4.16 (d, J = 7.9 Hz, 1 H), 5.22 (t, J = 5.5 Hz, 1 H), 6.30 (br s, 1 H); ^{13}C NMR (75 MHz) δ 20.6 (CH_2), 21.1 (CH_3), 23.5 (CH_3), 29.7 (CH_2), 30.5 (CH_2), 43.8 (CH), 53.0 (CH_2), 57.5 (CH_2), 67.4 (CH), 74.8 (CH), 169.2 (C), 170.7 (C); mass spectrum (CI) *m*/*z* 241 (MH^+, 100%), 181 (18%), 121 (19%). The ^1H NMR spectrum was in excellent agreement with that of an independently prepared[6i] sample (spectrum kindly provided by Professor W. H. Pearson). HRMS *m*/*e* calcd for $C_{12}H_{20}N_2O_3$ (M^+) + H: 241.1552. Found: 241.1569.

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