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Preparation of Enantiopure 6-(3-Indolyl)-2-piperidones and Conjugate Additions to a 3,4-Didehydro Derivative

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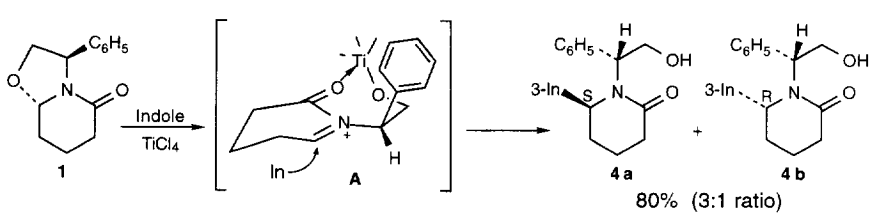
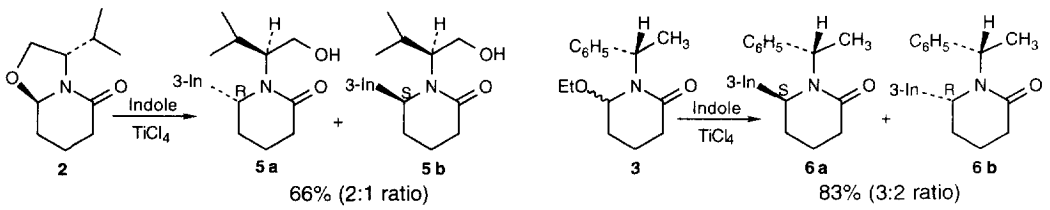
Abstract: Amidoalkylation of chiral non-racemic lactams **1-3** with indole in the presence of $TiCl_4$ provides enantiopure 6-(3-indolyl)-2-piperidones **4a,b-6a,b**. The stereochemical course of the conjugate addition of a variety of functionalized carbon nucleophiles to 5,6-dihydro-2-pyridone **11**, derived from **4a**, is studied. Copyright © 1996 Elsevier Science Ltd

The 3-(2-piperidyl)indole moiety is present in a large number of indole alkaloids, belonging to different structural types.[1] Although several procedures have been used for the elaboration of this unit in the context of the synthesis of indole alkaloids, the preparation of enantiopure 3-(2-piperidyl)indoles has been little explored.[2] We have recently reported the preparation of the chiral non-racemic oxazolopiperidones **1** and **2**[3,4] and have shown the potential of **1** in the synthesis of diversely substituted enantiopure piperidines.[3,5] We present here i) the use of both these bicyclic lactams[6] and alcoxypiperidone **3** to assemble enantiopure 6-(3-indolyl)-2-piperidones and ii) the introduction of functionalized substituents at the 4-position of the piperidone ring via conjugate addition of carbon nucleophiles to a 5,6-dihydro-2-pyridone derivative.

Treatment of oxazolopiperidone **1** with indole in CH_2Cl_2 solution at 25°C for 30 min in the presence of $TiCl_4$ afforded a 3:1 mixture of 6-(3-indolyl)-2-piperidones **4a** and **4b** in 80% yield (Scheme 1).[7,8] Minor amounts of the indole dimer (2,3-dihydro-2,3'-biindole, **7**) were also formed. The preferential attack of indole on the most accessible face of the acyl iminium ion **A**, generated by Lewis acid-promoted opening of the oxazolidine ring,[9] accounts for the observed stereoselectivity. The absolute configuration of the new stereogenic center of the minor isomer **4b** was determined as *R* by X-ray crystallography. When the reaction was carried out at lower temperatures (-20°C), the ratio **4a/4b** was higher (83:17), but the chemical yield



Scheme 1



Scheme 2

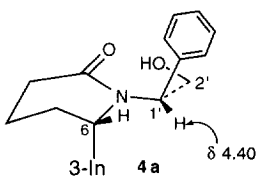
decreased to 31%, whereas longer reaction times (24h, 25°C) resulted in the formation of the 6*R* isomer **4b** as the major product (65% yield, 37:63 ratio). This result suggested that **4a** is the kinetic product and **4b** the thermodynamic one. Accordingly, each isomer, **4a** and **4b**, was separately converted to an identical epimeric mixture, in which **4b** predominated (ratio 15:80), after an additional treatment with $TiCl_4$ for 24 h. This epimerization can be explained by considering the cleavage of the piperidone N-C_6 bond, promoted by the Lewis acid, with subsequent recyclization of the resulting 3-alkylideneindolenine. In this manner, both isomeric indolylpiperidones, **4a** (6*S*) and **4b** (6*R*), are easily accessible in satisfactory yield.

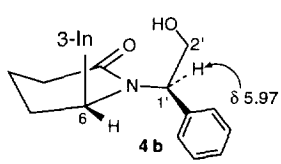
Under similar conditions (indole, $TiCl_4$, CH_2Cl_2, 25°C, 30 min), oxazolopiperidone **2** and alcoxypiperidone **3** led to the respective indolylpiperidones **5a**, **b** (2:1 ratio) and **6a**, **b** (3:2 ratio) in the yields indicated in Scheme 2. In the former case, after longer reaction times (4h), the ratio **5a/5b** increased to 3:1 in favor of **5a**. In this series, the ratio of isomers **5a/5b** after equilibration with $TiCl_4$ was 7:3. The lower stereoselectivity of these reactions as compared with the amidoalkylation of **1** reflects that the two diastereotopic faces of the acyl iminium ions derived from **2** and **3** are more similarly accessible than in **A**, in the former case as a consequence of the larger size of the isopropyl substituent[10] and in the latter because a cyclic chelate cannot be formed.

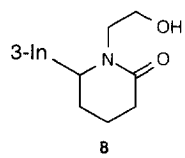
Table 1. Significant ^{13}C-NMR Data of 6-(3-Indolyl)-2-piperidones [a]

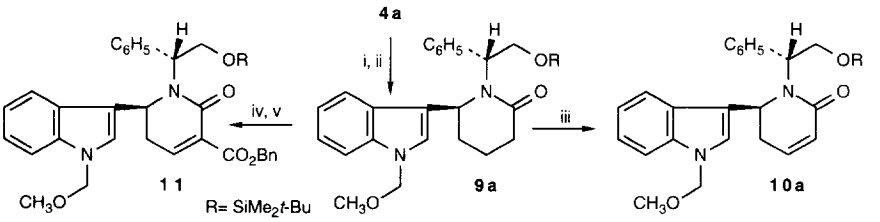
	C-2	C-3	C-4	C-5	C-6	C-1'	C-2'	Other
4a	173.0	32.7	16.4	29.5	57.0	68.0	64.5	
4b	173.1	31.5	16.1	29.3	50.5	59.7	62.5	
5a	172.8	32.4	16.9	29.7	59.8	71.8	63.4	19.5, 20.0[c]
5b[b]	173.7	31.2	16.1	29.3	50.8	63.5	61.9	20.1[c]
6a	171.1	32.7	16.7	30.1	57.5	54.6		18.5[d]
6b	171.2	31.2	16.3	29.4	49.5	51.8		17.1[d]
8[e]	173.4	31.8	17.2	29.7	56.4	49.8	61.9	

[a] Measured in $CDCl_3$ solution at 50.3 MHz. [b] Measured in $CDCl_3$-CD_3OD solution. [c] $CHMe_2$. [d] Me.
[e] Prepared in 92% yield by amidoalkylation of 5-oxo-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine with indole.





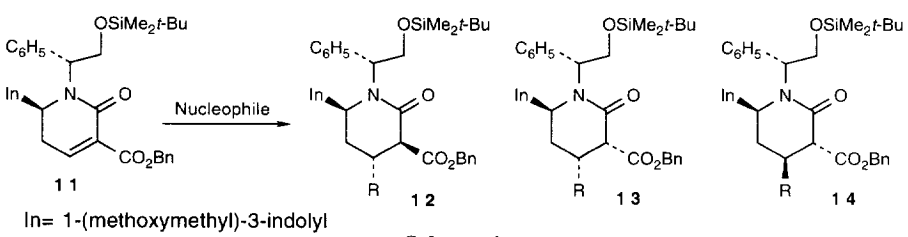




Scheme 3. Reagents and Conditions: i) *t*-BuMe2SiCl, imidazole, DMF, 35°C; ii) KH, ClCH2OCH3, THF, 0°C; iii) LDA, PhSeCl, HMPA, THF, -78°C, then *m*-CPBA; iv) LDA, ClCO2Bn, THF, -78°C; v) NaH, PhSeCl, DMF-benzene, reflux, then *m*-CPBA.

The absolute configuration at C-6 in indolylpiperidones **5a,b** and **6a,b** was assigned by correlating their NMR data with those of **4a,b**, in particular the shielding of C-6 and C-1' (see Table 1) and the deshielding of H-1' in epimers **b** as compared with epimers **a**. These differences can be rationalized by considering half-chair conformations for the piperidone ring, in which the indolyl substituent adopts a pseudoaxial disposition[11] to avoid the steric interactions with the *N*-substituent, whereas the phenyl (or isopropyl) group lies as far as possible from indole. The *syn*-1,3 relationship between the indolyl and the hydroxymethyl (in **4** and **5**) or methyl (in **6**) groups in epimers **b** accounts for the shielding of C-6 and C-1', whereas in this conformation the lactam carbonyl group significantly deshields the methine proton at C-1'.

The introduction of substituents at the piperidine 4-position required the previous functionalization of this position, taking advantage of the lactam carbonyl group. With this aim, after protection of the hydroxy group and the indole ring of indolylpiperidone **4a**, the protected lactam **9a** was converted to the 5,6-dihydro-2-pyridone **10a** by phenylselenation followed by *m*-CPBA oxidative elimination of the resulting selenide (Scheme 3). Similarly, the epimer **4b** was converted to the corresponding α,β–unsaturated lactam **10b**. However, not surprisingly when taking into account the low reactivity of α,β-unsaturated lactams without an additional electron-withdrawing group at the α-position,[12] lactam **10a** did not react with the anion derived



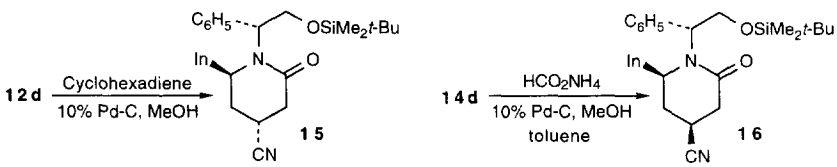
Scheme 4

Table 2. Conjugate Additions to Unsaturated Lactam 11

Entry	Nucleophile	Conditions	Products	R	Yield[a] (ratio)
a	(MeS)3CH, *n*-BuLi	THF, -78°C, 7h	**12a+13a**	C(SMe)3	50% (1:5)[b]
b	(MeS)2CHCO2Me, NaH	THF, -78°C, 2h	**12b+13b**	C(SMe)2CO2Me	62% (5:1.5)
c	PhSOCH2CO2Me, NaH	THF, -78°C, 2h	**12c +13c**	CH(SOPh)CO2Me	50%[c]
d	Et2AlCN	C6H6-toluene, 25°C,12h	**12d+14d**	CN	68% (2:5)

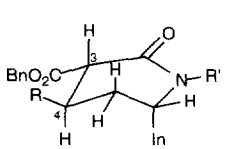
[a] After purification by column chromatography. [b] The major isomer epimerizes to **12a** on treatment with aqueous Ba(OH)2. [c] Complex mixture of isomers due to the presence of two stereogenic centers in R. Isomers **12c** were predominant.

from tris(methylthio)methane. Probably, the bulky pseudoaxial indolyl substituent contributes to the lack of reactivity of **10a**.[13] In contrast, unsaturated ester lactam **11**, which was prepared by benzyloxycarbonylation of **9a**, followed by selenation and subsequent elimination of phenylsulfenic acid by way of the corresponding selenoxide, proved to be reactive towards a variety of nucleophiles. The results are summarized in Scheme 4 and Table 2. Both tris(methylthio)methyllithium (entry **a**) and the enolates derived from methyl bis(methylthio)acetate (entry **b**) and methyl (phenylsulfinyl)acetate (entry **c**) gave C-3 epimeric mixtures (**12 + 13**), in which the new substituent at the piperidine 4-position is *trans* with respect to the indolyl substituent. Epimers **12**, in which the benzyloxycarbonyl substituent is equatorial, were predominant (entries **b** and **c**) or became predominant after equilibration (entry **a**). In contrast, hydrocyanation[14] of unsaturated lactam **11** with diethylaluminium cyanide led to diastereomeric mixtures (**12d + 14d**) in which the major isomer has a *cis*-relationship between the cyano and indolyl substituents. In all cases the yields ranged from acceptable to good.

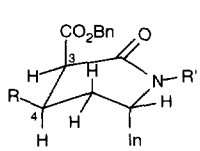


The configurational stability of C-6 in 6-(3-indolyl)-2-piperidones[2b] under the hydrocyanation conditions was confirmed because lactam **9a** was recovered unchanged (the epimer **9b** was not detected) after treatment with Et_2AlCN at room temperature for 28 h. In the cyano series, debenzylation of the benzyloxycarbonyl group followed by decarboxylation afforded the corresponding *trans*- and *cis*-4,6-disubstituted piperidones **15** and **16**.

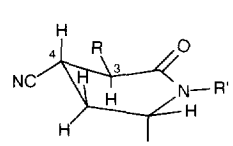
The stereochemical assignment of indolylpiperidones **12-16** was effected from their NMR data, with the aid of ^1H-^1H decoupling and NOE difference experiments, by assuming the preferred conformations depicted below, in which the indolyl substituent adopts a pseudoaxial disposition,[11] whereas the substituent at the piperidine 4-position is equatorial. It is worth mentioning the half-boat conformation of the 4,6-*cis* epimers **14d** and **16**, which relieves the steric 1,3-*syn* interactions that would exist in the normal half-chair conformation. Diagnostic ^1H-NMR data were the J values of H-6, thus indicating the pseudoequatorial disposition of this proton, and H-3/H-4 (see figure). The ^{13}C-NMR chemical shifts (Table 3) are in agreement with the above assignments. The shielding of C-5 in **13a** as compared with **12a** confirms the axial disposition of the benzyloxycarbonyl group and, therefore, the 3,4-*cis* relationship in isomers **13**. On the other hand, supporting the pseudoequatorial disposition of the benzyloxycarbonyl group in 4-cyanopiperidones **12d** and **14d**, no epimerization was observed when they were separately treated with LDA in THF.



12 $J_{3,4}$ ~ 11 Hz
R'= (*R*)-CHPhCH$_2$OSiMe$_2$*t*-Bu



13 $J_{3,4}$ ~ 5.5 Hz



14d R= CO_2Bn $J_{3,4}$ ~ 10.5 Hz
16 R= H

Table 3. Significant ^{13}C-NMR Data of 4-Substituted 6-(3-Indolyl)-2-piperidones[a]

	C-2	C-3	C-4	C-5	C-6	CO_2CH_2	CH_2OCH_3		NCH	CH_2OSi	4-Substituent
12a	170.6	52.1	42.1	31.5	53.9	166.6	67.4	77.2	55.5	64.3	64.1	14.3, 73.9
12b	170.5	53.3	37.6	31.4	52.3	166.4	67.4	77.2	55.4	64.2	64.1	13.1,13.4,52.6,66.7,169.4
12d	168.2	51.5	24.5	32.0	52.2	165.3	68.0	77.2	55.8	63.7	63.5	110.4
13a	170.3	51.9	43.0	28.4	55.1	167.5	67.6	77.3	55.9	67.2	66.3	13.6, 71.2
14d	168.3	54.0	26.9	33.1	52.9	163.2	68.6	77.9	56.5	63.7	65.0	114.4
15[b]	167.5	34.4	23.4	32.1	51.6			77.4	55.9	62.9	63.8	120.4
16	167.0	35.6	22.8	33.8	53.2			77.4	55.9	62.2	63.9	119.8

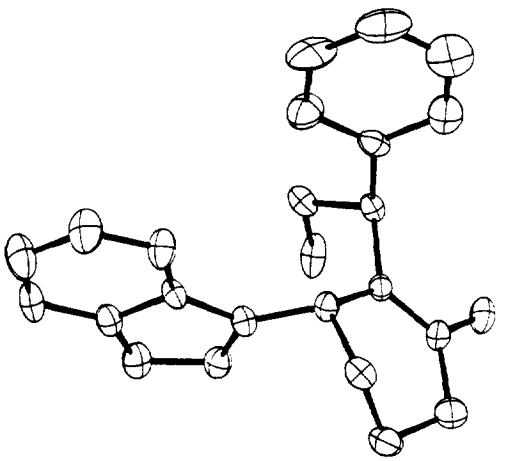
[a] Measured in $CDCl_3$ at 75.4 MHz. [b] In $CDCl_3$-CD_3OD solution.

EXPERIMENTAL SECTION

General. Melting points were determined in a capillary tube on a Büchi apparatus and are uncorrected. ^{1}H- and ^{13}C-NMR spectra were recorded on a Varian Gemini-200 instrument (200 and 50.3 MHz, respectively) or on a Varian Gemini-300 instrument (300 and 75.4 MHz, respectively). Chemical shifts are expressed in parts per million (δ) relative to internal Me_4Si. IR spectra were recorded on a Nicolet 205 FT-IR spectrophotometer. Mass spectra were determined on a Hewlett-Packard 5988A mass spectrometer or on a Autospec-VG (HRMS). Optical rotations were measured on a Perkin-Elmer 241 polarimeter using a 1 dm cell with a total volume of 1 ml. Flash chromatography was carried out on SiO_2 (silica gel 60, SDS, 0.040-0.060 mm). Drying of organic extracts during the work-up of reactions was performed over anhydrous Na_2SO_4. Microanalyses were performed on a Carlo Erba 1106 analyzer by the Centro de Investigación y Desarrollo (CSIC), Barcelona.

(6*S*)- and (6*R*)-1-[(1*R*)-2-Hydroxy-1-phenylethyl]-6-(3-indolyl)-2-piperidone (4a and **4b).** $TiCl_4$ (0.15 ml, 1.4 mmol) was added to a solution of oxazolopiperidone **1**[3,4] (300 mg, 1.38 mmol) and indole (485 mg, 4.14 mmol) in anhydrous CH_2Cl_2 (3 ml). After stirring at 25°C for 30 min, the mixture was poured into 10% aqueous Na_2CO_3 and extracted with CH_2Cl_2. The combined organic extracts were dried and concentrated to give a residue which, after column chromatography (98:2 AcOEt-EtOH), afforded dimer **7** (340 mg) and indolylpiperidones **4a** (270 mg, 59%) and **4b** (100 mg, 21%). **4a**: $[\alpha]^{22}_D$ +67.5 (*c* 0.3, EtOH); IR ($CHCl_3$) 3267, 1615 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) 1.60-2.20 (m, 4H, H-4 and H-5), 2.65 (m, 2H, H-3), 3.98 (dd, *J*=12.4, 3.0 Hz, 1H, OCH_2), 4.15 (dd, *J*=12.4, 6.8 Hz, 1H, OCH_2), 4.40 (dd, *J*=6.8, 3.0 Hz, 1H, NCH), 4.84 (t, *J*=4.4 Hz, 1H, H-6), 7.10-7.50 (m, 10H, ArH), 8.42 (br s, 1H, NH); ^{13}C-NMR, Table 1; mp 110-112°C (C_6H_6-hexane). Anal. Calcd for $C_{21}H_{22}N_2O_2$: C, 75.46; H, 6.58; N, 8.37. Found: C, 75.45; H, 6.66; N, 8.27. **4b**: $[\alpha]^{22}_D$ -78.4 (*c* 0.3, EtOH); IR (film) 3285, 1609 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) 1.60-1.95 (m, 5H, H-4, H-5, and OH), 2.65 (m, 2H, H-3), 3.92 (m, 2H, OCH_2), 4.76 (br s, 1H, H-6), 5.97 (dd, *J*=7.8, 6.6 Hz, 1H, NCH), 7.05-7.45 (m, 10H, ArH), 8.25 (br s, 1H, NH); ^{13}C-NMR, Table 1; mp 105-108°C (C_6H_6-hexane). Anal. Calcd for $C_{21}H_{22}N_2O_2$: C, 75.46; H, 6.58; N, 8.37. Found: C, 75.75; H, 6.59; N, 7.98.

X-Ray Crystal Structure of 4b. Crystal data: $C_{21}H_{22}N_2O_2 \cdot 1/2\ C_6H_6$. Fw = 373.48, orthorhombic, *a* = 10.328(2), *b* = 15.560(3), *c* = 24.944(5)Å. V = 4009(2)Å^3, $C222_1$, Dx = 1.237 g cm^{-3}. Z = 8. F(000) = 1592.0, λ(Mo Kα) = 0.71069 Å, μ(Mo Kα) = 0.85 cm^{-1}. A prismatic crystal (0.1x0.1x0.2 mm) was selected and mounted on an Enraf-Nonius CAD4 diffractometer. Unit cell parameters were determined from automatic centring of 25 reflections ($12 \leq \theta \leq 21°$) and refined by least-squares method. Intensities were collected with graphite monochromatized Mo Kα radiation, using ω/2θ scan technique.



2574 Reflections were measured in the range $2 \leq \theta \leq 30^{o}$, 1403 of which were assumed as observed applying the condition $I \geq 2.5\ \sigma(I)$. Three reflections were measured every two hours as orientation and intensity control, significant intensity decay was not observed. Lorentz-polarization, but no absorption corrections were made. The structure was solved by direct methods, using the MULTAN system of computer program[15] and refined by full-matrix least-squares method, with the SHELX76 computer program.[16] The minimized function was $\Sigma\ w\ ||Fo| - |Fc||^2$, where $w=(\sigma^2(Fo) + 0.0037\ |Fo|^2)^{-1}$. f, f' and f'' were taken from International Tables of X-Ray Crystallography.[17] 24 H atoms were located from a difference synthesis and refined with an overall isotropic temperature factor. The final R factor was 0.052 (wR = 0.057) for all observed reflections. Number of refined parameters was 328. Maximum shift/e.s.d = 0.07. Maximum and minimum peaks in final difference synthesis was 0.2 and -0.2 $e\text{Å}^{-3}$, respectively. Complete data have been deposited at the Cambridge Crystallographic Data Centre.

(6*R*)- and (6*S*)-1-[(1*S*)-2-Hydroxy-1-isopropylethyl]-6-(3-indolyl)-2-piperidone (5a and **5b).** Operating as above, from oxazolopiperidone **2**[3,18] (500 mg, 2.73 mmol) were obtained dimer **7** (620 mg), indolylpiperidone **5a** (364 mg, 45%), and the C-6 epimer **5b** (175 mg, 21%) after column chromatography (AcOEt). **5a**: $[\alpha]^{22}_{D}$ +22.4 (*c* 0.5, EtOH); IR (film) 3393, 3210, 1591 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) 0.95 and 1.09 (2d, *J*=6.3 Hz, 6H, $2CH_3$), 1.50-1.90 (m, 2H, H-4), 2.10 (m, 2H, H-5), 2.30-2.70 (m, 3H, H-3 and C*H*Me_2), 3.65 (m, 3H, OCH_2 and NCH), 4.85 (t, *J*=4.5 Hz, 1H, H-6), 6.12 (br s, 1H, OH), 7.05 (d, *J*=2.3 Hz, 1H, H-2'), 7.17 (m, 2H, H-5' and H-6'), 7.31 (d, *J*=7.5 Hz, 1H, H-7'), 7.52 (d, *J*=7.5 Hz, 1H, H-4'), 9.15 (br s, 1H, NH); ^{13}C-NMR, Table 1; mp 170-173°C (C_6H_6). Anal. Calcd for $C_{18}H_{24}N_2O_2$: C, 71.97; H, 8.05; N, 9.32. Found: C, 72.03; H, 8.14; N, 8.99. **5b**: $[\alpha]^{22}_{D}$ -15.4 (*c* 0.15, EtOH); IR (film) 3300-3000, 1595 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) 0.94 and 0.95 (2d, *J*=6.3 Hz, 6H, $2CH_3$), 1.69-1.88 (m, 3H, H-4, and OH), 2.08 (m, 2H, H-5), 2.22 (m, 1H, C*H*Me_2), 2.55 (ddd, *J*=17.8, 10.3, 7.9 Hz, 1H, H-3), 2.64 (ddd, *J*=17.8, 7.1, 2.7 Hz, 1H, H-3), 3.49 (dd, *J*=11.8, 8.2 Hz, 1H, OCH_2), 3.75 (dd, *J*=11.8, 2.7 Hz, 1H, OCH_2), 4.20 (m, 1H, NCH), 5.08 (t, *J*=3.8 Hz, 1H, H-6), 7.14-7.30 (m, 2H, H-5', H-6'), 7.32 (d, *J*=2.4 Hz, 1H, H-2'), 7.42 (d, *J*=8.2 Hz, 1H, H-7'), 7.57 (d, *J*=7.9 Hz, 1H, H-4'), 8.33 (br s, 1H, NH); ^{13}C-NMR, Table 1; mp 193-195°C (C_6H_6-hexane). Anal. Calcd for $C_{18}H_{24}N_2O_2$: C, 71.97; H, 8.05; N, 9.32. Found: C, 71.99; H, 8.08; N, 9.22.

(6*S*)- and (6*R*)-6-(3-Indolyl)-1-[(1*S*)-1-phenylethyl]-2-piperidone (6a and **6b).** Operating as above (reaction time 4 h), from 6-ethoxylactam **3**[19] (100 mg, 0.4 mmol) were obtained dimer **7** (60 mg), indolylpiperidone **6a** (60 mg, 47%), and the C-6 epimer **6b** (40 mg, 31%) after column chromatography (AcOEt). **6a**: $[\alpha]^{22}_{D}$ +51.5 (*c* 1.0, EtOH); IR (film) 3420, 3266, 1625 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) 1.60 (m, 2H, H-4), 1.72 (d, *J*=7.0 Hz, 3H, CH_3), 2.05 (m, 2H, H-5), 2.56 (m, 2H, H-3), 5.07 (m, 2H, H-6 and NCH), 6.80 (d, *J*=2.6 Hz, 1H, H-2'), 7.00-7.40 (m, 8H, ArH), 7.50 (d, *J*=7.7 Hz, 1H, H-4'), 8.15 (br s, 1H, NH); ^{13}C-NMR, Table 1; mp 147-149°C (C_6H_6-hexane). Anal. Calcd for $C_{21}H_{22}N_2O$: C, 79.21; H, 6.95; N, 8.79. Found: C, 79.16; H, 6.99; N, 8.70. **6b**: $[\alpha]^{22}_{D}$ -60.2 (*c* 1.0, EtOH); IR (film) 3210, 1609 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) 1.26 (d, *J*=7.3 Hz, 3H, CH_3), 1.50-2.00 (m, 4H, H-4 and H-5), 2.62 (m, 2H, H-3), 4.73 (br

s, 1H, H-6), 6.20 (q, *J*=7.3 Hz, 1H, NCH), 7.00 (d, *J*=2.6 Hz, 1H, H-2'), 7.05-7.50 (m, 9H, ArH), 8.52 (br s, 1H, NH); ^{13}C-NMR, Table 1; mp 169-172°C (C_6H_6). Anal. Calcd for $C_{21}H_{22}N_2O$: C, 79.21; H, 6.95; N, 8.79. Found: C, 79.13; H, 7.07; N, 8.66.

Epimerization of 6-(3-Indolyl)-2-piperidones 4a and 5b. A solution of indolylpiperidone **4a** (100 mg, 0.30 mmol) and $TiCl_4$ (0.33 ml, 3.0 mmol) in anhydrous CH_2Cl_2 (10 ml) was stirred at 25°C until no change in the ratio of isomers **4a/4b** was observed by TLC (24 h). The mixture was poured into saturated aqueous Na_2CO_3, and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were dried and concentrated, and the oily residue (98 mg) was chromatographed to give **4a** (15 mg) and **4b** (80 mg). Operating as described for **4a** but starting from **4b** (100 mg), a mixture of **4a** and **4b** was obtained in a 18:82 ratio.

Operating as above, from **5b** (100 mg, 0.33 mmol) was obtained a mixture of **5a** (70 mg) and **5b** (30 mg) after column chromatography. Starting from **5a** (50 mg), and following the above procedure, a mixture of **5a** and **5b** was obtained in a 67:33 ratio.

(6*S*)-1-[(1*R*)-2- [(*tert*-Butyldimethylsilyl)oxy] -1- phenylethyl]-6-[1-(methoxymethyl)-3-indolyl]-2-piperidone (9a). A mixture of indolylpiperidone **4a** (3.6 g, 10.7 mmol), *t*-butyldimethylsilyl chloride (1.9 g, 12.6 mmol), and imidazole (1.8 g, 27 mmol) in DMF (7.5 ml) was stirred at 35°C for 10 h. The resulting mixture was washed with saturated aqueous $NaHCO_3$, and the aqueous layer was extracted with Et_2O. The combined organic extracts were dried and concentrated to give a residue (4.5 g, 10.0 mmol) which was dissolved in anhydrous THF (20 ml). The solution was slowly added to a suspension of an excess of KH (3.2 g) in anhydrous THF (80 ml) at 0°C. The mixture was stirred for 30 min, TMEDA (1.65 ml, 11 mmol) was added, the stirring was continued for 30 min, and then chloromethyl methyl ether (0.85 ml, 11 mmol) was added. After the mixture was stirred for 1.5 h at 0°C, the excess of hydride was destroyed with H_2O, and the temperature was allowed to raise to 25°C. The mixture was washed with brine and extracted with Et_2O.The combined organic extracts were dried and concentrated, and the residue was chromatographed (AcOEt) to give pure **9a** (4.3 g, 81%): IR (film) 1639 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) -0.06 (s, 6H, $SiMe_2$), 0.81 (s, 9H, CMe_3), 1.60-1.80 (m, 2H, H-4), 1.95-2.15 (m, 2H, H-5), 2.50 (ddd, *J*=18.0, 10.0, 7.2 Hz, 1H, H-3), 2.60 (ddd, *J*=18.0, 7.0, 2.7 Hz, 1H, H-3), 3.17 (s, 3H, OCH_3), 4.31 (d, *J*=6.7 Hz, 2H, CH_2OSi), 4.80 (t, *J*=6.7 Hz, 1H, NCH), 5.01 (t, *J*=4.3 Hz, 1H, H-6), 5.28 and 5.34 (2d, *J*=11.0 Hz, 2H, NCH_2), 6.89 (s, 1H, H-2'), 7.12-7.50 (m, 9H, ArH); ^{13}C-NMR ($CDCl_3$, 50.3 MHz) -5.6 ($SiMe_2$), 16.8 (C-4), 18.1 (SiC), 25.8 (C(CH_3)$_3$), 29.7 (C-5), 32.7 (C-3), 53.8 (C-6), 55.8 (OCH_3), 64.0 (NCH), 64.9 (CH_2OSi), 77.2 (NCH_2), 110.2 (C-7'), 116.5 (C-3'), 118.7 (C-4'), 120.0 (C-5'), 122.4 (C-6'), 126.5 (C-3'a), 126.9 (C-2), 127.2 (C-*p*), 127.9 (C-*o*), 128.5 (C-*m*), 136.9 (C-7'a), 139.3 (C-*ipso*), 171.0 (C=O). Anal. Calcd for $C_{29}H_{40}N_2O_3Si$: C, 70.69; H, 8.17; N, 5.68. Found: C, 70.77; H, 8.25; N, 5.68.

(6*R*)-1-[(1*R*)-2-[(*tert*-Butyldimethylsilyl)oxy]-1-phenylethyl] -6- [1-(methoxymethyl)-3-indolyl] -2-piperidone (9b). Operating as above, **4b** (1 g, 3.0 mmol) was converted to piperidone **9b** (1.2 g, 76%): IR (film) 1640 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) -0.07 (s, 3H, $SiCH_3$), -0.04 (s, 3H, $SiCH_3$), 0.8 (s, 9H, CMe_3), 1.55-2.00 (m, 4H, H-4 and H-5), 2.55 (m, 2H, H-3), 3.1 (s, 3H, OCH_3), 3.80 (dd, *J* = 10.2, 7.0 Hz, 1H, CH_2OSi), 4.19 (dd, *J* = 10.2, 7.3 Hz, 1H, CH_2OSi), 4.94 (m, 1H, H-6), 5.33 and 5.36 (2d, *J* = 11.0 Hz, 2H, NCH_2), 5.35 (masked, 1H, NCH), 6.94 (s, 1H, H-2'), 7.10-7.15 (m, 9H, ArH); ^{13}C-NMR ($CDCl_3$, 50.3 MHz) -5.4 ($SiCH_3$), -5.6 ($SiCH_3$), 17.0 (C-4), 18.0 (SiC), 25.7 (C(CH_3)3), 30.0 (C-5), 32.3 (C-3), 53.5 (C-6), 55.7 (OCH_3), 62.4 (NCH and CH_2OSi), 77.3 (NCH_2), 110.2 (C-7'), 117.1 (C-3'), 118.8 (C-4'), 120.1 (C-5'), 122.5 (C-6'), 126.5 (C-3a'), 127.0 (C-2'), 127.9 (C-*p*), 128.4 (C-*o*), 128.9 (C-*m*), 136.7 (C-7a'), 138.2 (C-*ipso*), 170.7 (C=O). Anal. Calcd for $C_{29}H_{40}N_2O_3Si$: C, 70.69; H, 8.17; N, 5.68. Found: C, 70.66; H, 8.18; N, 5.67.

(6*S*) - 1- [(1*R*)-2-[(*tert*-Butyldimethylsilyl)oxy]-1-phenylethyl]-6-[1-(methoxymethyl)-3-indolyl]-5,6-dihydro-2-pyridone (10a). A solution of indolylpiperidine **9a** (2.0 g, 4 mmol) in anhydrous THF (10 ml) was slowly added to a solution of LDA (5.42 ml of a 1.5 M solution in cyclohexane, 8.13 mmol) in anhydrous THF (10 ml) at -78°C, and the mixture was stirred for 35 min. Then, a solution of phenylselenyl chloride (780 mg, 4.07 mmol) and HMPA (0.92 ml, 5.3 mmol) in THF (10 ml) was added. The stirring was continued, and a solution of additional phenylselenyl chloride (780 mg, 4.07 mmol) in THF (10 ml) was added dropwise for a period of 2 h. The resulting mixture was poured into aqueous $NaHCO_3$, and the aqueous layer was extracted with Et_2O. The combined organic extracts were dried and concentrated, and the residue was chromatographed (1:1 AcOEt-hexane) to give the intermediate selenide (960 mg, 40%) and starting material **9a** (700 mg). A mixture of the above selenide (960 mg, 1.48 mmol) and *m*-CPBA (78%, 920 mg, 4.2 mmol) in CH_2Cl_2 (12 ml) was stirred at 0°C for 1 h and at 25°C for 30 min. The resulting suspension was washed successively with saturated aqueous $NaHCO_3$ and brine. The combined aqueous phases were extracted with CH_2Cl_2, and the resulting organic solution was dried and concentrated. The residue was chromatographed (Et_2O) to give pure **10a** (405 mg, 54%): IR (film) 1661, 1608 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) 0.12 (s, 3H, $SiCH_3$), 0.13 (s, 3H, $SiCH_3$), 0.96 (s, 9H, CMe_3), 2.67 (ddd, *J*=17.4, 6.1, 1.7 Hz, 1H, H-5), 2.90-3.10 (masked, 1H, H-5), 3.07 (s, 3H, OCH_3), 4.22 and 4.36 (2dd, *J*=10.7, 6.6 Hz, 2H, CH_2OSi), 5.19 and 5.29 (2d, *J*=11.0 Hz, 2H, NCH_2), 5.33 (masked, 1H, H-6), 5.55 (t, *J*=6.6 Hz, 1H, NCH), 6.16 (dd, *J*=7.3, 2.5 Hz, 1H, H-3), 6.34 (m, 1H, H-4), 6.67 (s, 1H, H-2'), 7.04-7.50 (m, 9H, ArH); ^{13}C-NMR ($CDCl_3$, 50.3 MHz) -5.6 ($SiMe_2$), 18.0 (SiC), 25.0 ($C(CH_3)_3$), 31.1 (C-5), 49.3 (C-6), 55.5 (OCH_3), 59.4 (NCH), 63.3 (CH_2OSi), 77.0 (NCH_2), 110.0 (C-7'), 115.2 (C-3'), 118.1 (C-4'), 119.7 (C-5'), 121.9 (C-6'), 125.9 (C-2'), 126.1 (C-3'a), 127.0 (C-3), 127.5 (C-*p*), 128.4 (C-*o*), 128.7 (C-*m*), 136.3 (C-7'a), 136.8 (C-4), 137.7 (C-*ipso*), 164.3 (C=O). Anal. Calcd for $C_{29}H_{38}N_2O_3Si \cdot 1/2\ H_2O$: C, 69.70; H, 7.85; N, 5.60. Found: C, 69.36; H, 7.81; N, 5.22.

(6*R*) - 1-[(1*R*)-2-[(*tert*-Butyldimethylsilyl)oxy]-1-phenylethyl]-6-[1-(methoxymethyl)-3-indolyl]-5,6-dihydro-2-pyridone (10b). Operating as above, **9b** (1 g, 2.0 mmol) was converted to an intermediate selenide (350 mg, 27%) and then to the unsaturated lactam **10b** (140 mg, 53%): IR (film) 1663, 1609 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) -0.13 (s, 3H, $SiCH_3$), -0.10 (s, 3H, $SiCH_3$), 0.73 (s, 9H, CMe_3), 2.45 (ddd, *J*= 17.6, 6.1, 1.8 Hz, 1H, H-5), 2.70 (dm, *J*= 17.6 Hz, 1H, H-5), 3.18 (s, 3H, OCH_3), 3.83 (dd, *J*= 10.4, 7.4 Hz, 1H, CH_2OSi), 3.97 (dd, *J*= 10.4, 6.2 Hz, 1H, CH_2OSi), 5.00 (dm, *J*= 6.0 Hz, 1H, H-6), 5.32 and 5.39 (2d, *J*= 11.0 Hz, 2H, NCH_2), 5.70 (dd, *J*= 7.4, 6.2 Hz, 1H, NCH), 6.09 (dd, *J*= 9.8, 2.4 Hz, 1H, H-3), 6.25 (m, 1H, H-4), 7.02 (s, 1H, H-2'), 7.10-7.50 (m, 9H, ArH); ^{13}C-NMR ($CDCl_3$, 50.3 MHz) -6.0 ($SiCH_3$), -5.9 ($SiCH_3$), 17.6 (SiC), 25.3 ($C(CH_3)_3$), 31.1 (C-5), 48.8 (C-6), 55.4 (OCH_3), 58.9 (NCH), 61.4 (CH_2OSi), 77.2 (NCH_2), 110.0 (C-7'), 116.0 (C-3'), 118.0 (C-4'), 119.8 (C-5'), 122.0 (C-6'), 125.2 (C-2'), 126.0 (C-3a'), 126.4 (C-3), 127.5 (C-*p*), 127.8 (C-*o*), 128.2 (C-*m*), 136.2 (C-7a'), 136.7 (C-4), 138.4 (C-*ipso*), 163.7 (C=O). Anal Calcd for $C_{29}H_{38}N_2O_3Si \cdot 1/2\ H_2O$: C, 69.70; H, 7.85; N, 5.60. Found: C, 69.93; H, 7.98; N, 5.33.

(6*S*)-3-(Benzyloxycarbonyl)-1-[(1*R*)-2-[(*tert*-butyldimethylsilyl)oxy]-1-phenylethyl]-6-[1-(methoxymethyl)-3-indolyl]-5,6-dihydro-2-pyridone (11). A solution of LDA (18.1 ml of a 1.5 M solution in cyclohexane, 27.1 mmol) was slowly added to a solution of indolylpiperidone **9a** (4.3 g, 8.73 mmol) in anhydrous THF (190 ml) at -78°C, and the mixture was stirred for 1 h. Then, benzyl chloroformate (1.25 ml, 8.86 mmol) was added, and the stirring was continued for 2 h. The mixture was poured into saturated aqueous $NaHCO_3$, and the aqueous phase was extracted with Et_2O. The combined organic extracts were dried and concentrated, and the resulting oil was chromatographed (7:3 Et_2O-hexane) to give **(6*S*)-3-(benzyloxycarbonyl)-1-[(1*R*)-2-[(*tert*-butyldimethylsilyl)oxy]-1-phenylethyl]-6-[1-(methoxymethyl)-3-indolyl]-2-piperidone** (4.8 g, 90%) as a mixture of epimers, which were not separated: IR (film) 1739, 1658 cm^{-1}; ^{13}C-NMR ($CDCl_3$, 50.3 MHz) -5.7 ($SiMe_2$), 18.0 (SiC), 20.9 and 21.3 (C-4), 25.7 ($C(CH_3)_3$), 27.3 and 28.1 (C-5), 49.0 and 50.3 (C-6), 53.3 and 55.0 (C-3), 55.5 and 55.7 (OCH_3), 64.1 and 65.6 (NCH), 64.4 and 65.7 (OCH_2), 66.9 (CH_2OSi), 77.1

(NCH_2), 110.3 (C-7'), 115.1 and 115.7 (C-3'), 118.1 and 118.7 (C-4'), 120.2 (C-5'), 122.3 and 122.6 (C-6'), 126.3 (C-3'a), 126.5 and 126.7 (C-2'), 127.3 and 127.8 (C-*p*), 135.5 (C-7'a), 135.6, 136.4, 137.0 and 138.7 (C-*ipso*), 166.6 and 167.1 (CO_2), 171.2 (C=O). Anal. Calcd for $C_{37}H_{46}N_2O_5Si$: C, 70.89; H, 7.39; N, 4.47. Found: C, 70.86; H, 7.46; N, 4.27. A solution of the above ester (1 g, 1.6 mmol) in anhydrous C_6H_6 (10 ml) was slowly added to a suspension of NaH (71 mg of 55% oil dispersion, 1.6 mmol) in C_6H_6 (30 ml) and DMF (12 ml) at 90°C, and the mixture was stirred for 1 h 30 min. The temperature was lowered to 25°C, and a solution of phenylselenyl chloride (306 mg, 1.59 mmol) in C_6H_6 (5 ml) was added. After being stirred for 1 h, the reaction mixture was poured into brine. The aqueous layer was extracted with Et_2O, and the combined organic extracts were washed with water, dried, and concentrated. The resulting oil (1.3 g) was chromatographed (1:1 Et_2O-hexane) to give an epimeric mixture of selenides (710 mg, 58%), which was dissolved in CH_2Cl_2 (15 ml) and treated with *m*-CPBA (78%, 539 mg, 2.4 mmol) at 0°C for 1 h and at 25°C for 30 min. Workup as in the above preparation of **10a**, followed by column chromatography (9:1 Et_2O-hexane) gave the unsaturated lactam **11** (500 mg, 88%; 46% overall yield from **9a**): $[\alpha]^{22}_D$ -45.1 (*c* 1.0, EtOH); IR (film) 1733, 1662, 1630 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) 0.07 (s, 3H, $SiCH_3$), 0.09 (s, 3H, $SiCH_3$), 0.91 (s, 9H, CMe_3), 2.78 (ddd, *J*=17.6, 6.7, 2.5 Hz, 1H, H-5), 2.93 (s, 3H, OCH_3), 3.09 (ddd, *J*=17.6, 6.3, 2.5 Hz, 1H, H-5), 4.15 and 4.31 (2dd, *J*=10.8, 6.3 Hz, 2H, CH_2OSi), 5.06 and 5.19 (2d, *J*=11.0 Hz, 2H, CH_2O), 5.20 and 5.30 (2d, *J*=12.4 Hz, 2H, CH_2O), 5.31 (dm, *J*=5.3 Hz, 1H, H-6), 5.60 (t, *J*=6.3 Hz, 1H, NCH), 6.66 (s, 1H, H-2'), 7.20-7.50 (m, 15H, H-4 and ArH); ^{13}C-NMR ($CDCl_3$, 50.3 MHz) -5.6 ($SiMe_2$), 18.0 (SiC), 25.8 ($C(CH_3)_3$), 31.2 (C-5), 49.3 (C-6), 55.5 (OCH_3), 59.3 (NCH), 63.4 (CO_2CH_2), 66.6 (CH_2OSi), 77.6 (NCH_2), 110.3 (C-7'), 114.4 (C-3'), 118.0 (C-4'), 120.0 (C-5'), 122.2 (C-6'), 126.1 (C-3'a), 127.2 (C-2'), 127.4 and 127.5 (C-*p*), 127.9, 128.2, 128.3, 128.6 (C-*o* and C-*m*), 130.2 (C-3), 135.8 (C-7'a), 136.4 and 137.5 (C-*ipso*), 143.6 (C-4), 161.1 and 164.0 (C=O). Anal. Calcd for $C_{37}H_{44}N_2O_5Si \cdot 1/2\ H_2O$: C, 70.11; H, 7.14; N, 4.14. Found: C, 70.08; H, 6.93; N, 3.82.

Conjugate Addition of Tris(methylthio)methyl-lithium to Dihydropyridone 11. A solution of *n*-BuLi (0.3 ml of a 1.6M solution in hexane, 0.5 mmol) was slowly added to a solution of tris(methylthio)methane (0.06 ml, 0.5 mmol) in anhydrous THF (2 ml) at -78°C, and the mixture was stirred at this temperature for 1 h. Then, dihydropyridone **11** (100 mg, 0.16 mmol) was added to the resulting suspension, and the stirring was continued at -78°C for 7 h. The temperature was raised to 25°C, the mixture was poured into saturated aqueous $NaHCO_3$, and the aqueous layer was extracted with Et_2O. The combined organic extracts were dried and concentrated, and the resulting residue was chromatographed (3:2 Et_2O-hexane) to give **(3*S*,4*R*,6*S*)-3-(benzyloxycarbonyl)-1-[(1*R*)-2-[(*tert*-butyldimethylsilyl)oxy]-1-phenylethyl]-6-[1-(methoxymethyl)-3-indolyl]-4-[tris(methylhio)methyl]-2-piperidone (12a)** (10 mg, 8%) and the 3*R* epimer **13a** (52 mg, 42%). **12a**: IR (film) 1750, 1648 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) -0.02 (s, 3H, $SiCH_3$), 0.02 (s, 3H, $SiCH_3$), 0.82 (s, 9H, CMe_3), 1.79 (s, 9H, $(SMe)_3$), 2.02-2.09 (m, 1H, H-5), 2.53 (dt, *J*=13.2, 3.0 Hz, 1H, H-5), 2.90 (ddd, *J*=12.7, 10.5, 3.0 Hz, 1H, H-4), 3.04 (s, 3H, OCH_3), 4.02 (d, *J*=10.5 Hz, 1H, H-3), 4.18 and 4.34 (2dd, *J*=10.5, 6.6 Hz, 2H, CH_2OSi), 4.79 (t, *J*=6.6 Hz, 1H, NCH), 5.05 (dd, *J*=3.5, 3.0 Hz, 1H, H-6), 5.10-5.36 (m, 4H, $2CH_2O$), 7.20-7.40 (m, 15H, ArH); ^{13}C-NMR, Table 3. Anal. Calcd for $C_{41}H_{54}N_2O_5S_3Si$: C, 63.19; H, 6.98; N, 3.59. Found: C, 63.21; H, 7.01; N, 3.59. **13a**: IR (film) 1732, 1651 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) -0.07 (s, 3H, $SiCH_3$), -0.06 (s, 3H, $SiCH_3$), 0.82 (s, 9H, CMe_3), 1.75 (s, 9H, $(SMe)_3$), 2.57 (dm, *J*=12.5 Hz, 1H, H-5), 2.75 (ddd, *J*=12.5, 5.3, 1.5 Hz, 1H, H-4), 3.08 (td, *J*=12.5, 5.2 Hz, 1H, H-5), 3.23 (s, 3H, OCH_3), 4.08 (dd, *J*=5.3, 1.2 Hz, 1H, H-3), 4.28 and 4.52 (2dd, *J*=9.5, 7.1 Hz, 2H, CH_2OSi), 4.38 (t, *J*=7.1 Hz, 1H, NCH), 5.01 (dd, *J*=5.2, 1.0 Hz, 1H, H-6), 5.24 (s, 2H, CH_2O), 5.36 and 5.47 (2d, *J*=11.0 Hz, 2H, CH_2O), 7.20-7.50 (m, 15H, ArH); ^{13}C-NMR, Table 3.

Conjugate Addition of the Sodium Salt of Methyl Bis(methylthio)acetate to Dihydropyridone 11. A mixture of NaH (55%, 7 mg of oil dispersion, 0.16 mmol) and methyl bis(methylthio)acetate[20] (26.6 mg,

0.16 mmol) in anhydrous THF (2 ml) was stirred at 25°C for 2 h and then was transferred via cannula to a solution of indolylpiperidone **11** (100 mg, 0.16 mmol) in anhydrous THF (2 ml) at -78°C. The resulting solution was stirred for 2 h and poured into saturated aqueous $NaHCO_3$, and the aqueous layer was extracted with Et_2O. Drying and evaporation of the combined organic extracts left an oil (120 mg), which was chromatographed (1:1 Et_2O-hexane) to give **(3*S*,4*R*,6*S*)-3-(benzyloxycarbonyl)-1-[(1*R*)-2-[(*tert*-butyldimethylsilyl)oxy] - 1-phenylethyl]- 4 -[(methoxycarbonyl)bis(methylthio)methyl]- 6 -[1-(methoxymethyl)-3-indolyl]-2-piperidone (12b)** (63 mg, 50%) and 15 mg of a mixture of isomers enriched in **13b**. **12b**: $[\alpha]^{22}_D$ -4.5 (*c* 1.5, EtOH); IR (film) 1733, 1648 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) 0.02 (s, 3H, $SiCH_3$), 0.03 (s, 3H, $SiCH_3$), 0.86 (s, 9H, CMe_3), 1.60 (s, 3H, SCH_3), 1.80 (s, 3H, SCH_3), 2.09 (td, *J*=13.2, 4.5 Hz, 1H, H-5), 2.43 (dt, *J*=13.2, 2.8 Hz, 1H, H-5), 3.07 (s, 3H, OCH_3), 3.14 (ddd, *J*=13.2, 10.6, 2.8 Hz, 1H, H-4), 3.42 (s, 3H, CO_2CH_3), 4.00 (d, *J*=10.6 Hz, 1H, H-3), 4.21 and 4.39 (2dd, *J*=10.6, 6.5 Hz, 2H, CH_2OSi), 4.88 (t, *J*=6.5 Hz, 1H, NCH), 5.10 (dd, *J*=4.5, 2.8 Hz, 1H, H-6), 5.12 and 5.29 (2d, *J*=11.0 Hz, 2H, CH_2O), 5.15 and 5.24 (2d, *J*=11.1 Hz, 2H, CH_2O), 7.10-7.50 (m, 15H, ArH); ^{13}C-NMR, Table 3. Calcd for $C_{42}H_{54}N_2O_7S_2Si$: C, 63.71; H, 6.88; N, 3.54; S, 8.10. Found: C, 63.31; H, 6.80; N, 3.34; S, 7.88. The most significant data in the ^{1}H-NMR espectrum ($CDCl_3$, 300 MHz) of **13b** was $J_{3,4}$= 5.6 Hz.

Conjugate Addition of the Sodium Salt of Methyl 2-(Phenylsulfinyl)acetate to Dihydropyridone 11. A mixture of NaH (55%, 10 mg of oil dispersion, 0.22 mmol) and methyl 2-(phenylsulfinyl)acetate (32 mg, 0.16 mmol) in anhydrous THF (2 ml) at 0°C was stirred for 2 h. Then, a solution of dihydropyridone **11** (100 mg, 0.16 mmol) in anhydrous THF (2 ml) was slowly added to the resulting suspension at -78°C. The mixture was stirred at this temperature for 2 h and poured into saturated aqueous $NaHCO_3$. The aqueous layer was extracted with Et_2O, and the combined organic extracts were dried and concentrated. The resulting oil (132 mg) was chromatographed (9:1 Et_2O-hexane) to give a mixture of isomers of **12c** and **13c** (67 mg, 50%), which could not be separated by column chromatography. After successive purifications, a fraction enriched in the major isomers, **(3*S*,4*R*,6*S*)-3-(benzyloxycarbonyl)-1-[(1*R*)-2-[(*tert*-butyldimethylsilyl)oxy]-1-phenylethyl]- 4 -[(methoxycarbonyl)(phenylsulfinyl)methyl]-6 -[1-(methoxymethyl)-3-indolyl]-2 -piperidone (12c)**, could be isolated: ^{1}H-NMR ($CDCl_3$, 300 MHz) -0.07 (s, 3H, $SiCH_3$), -0.03 (s, 3H, $SiCH_3$), 0.82 (s, 9H, CMe_3), 2.12 (td, *J*=13.1, 4.6 Hz, 1H, H-5), 2.64 (dm, *J*=13.1 Hz, 1H, H-5), 2.98 (s, 3H, OCH_3), 3.15 (m, 1H, H-4), 3.55 (s, 3H, CO_2CH_3), 3.66 (d, *J*=11.5 Hz, 1H, H-3), 3.74 (d, *J*=11.7 Hz, 1H, SCH), 4.27 (m, 2H, CH_2OSi), 4.88 and 5.07 (2d, *J*=11.0 Hz, 2H, CH_2O), 4.90 (masked, 1H, NCH), 4.93 and 5.28 (2d, *J*=12.3 Hz, 2H, CH_2O), 5.15 (m, 1H, H-6), 6.80 (s, 1H, H-2'), 7.10-7.50 (m, 19H, ArH).

Conjugate Addition of Et2AlCN to Dihydropyridone 11. A mixture of dihydropyridone **11** (100 mg, 0.16 mmol) and Et_2AlCN (0.02 ml, 0.16 mmol) in anhydrous C_6H_6 (2 ml) and toluene (0.5 ml) was stirred at 0°C for 2 h 30 min. Additional Et_2AlCN (0.02 ml, 0.16 mmol) was added, and the stirring was continued at 25°C for 12 h. The mixture was washed with aqueous NH_4Cl, and the aqueous layer was extracted with Et_2O. The combined organic extracts were dried and concentrated, and the resulting oil (97 mg) was chromatographed (1:1 Et_2O-hexane) to give **(3*S*,4*R*,6*S*)-3-(benzyloxycarbonyl)-1-[(1*R*)-2-[(*tert*-butyldimethylsilyl)oxy]-1-phenylethyl]-4-cyano-6-[1-(methoxymethyl)-3-indolyl]-2-piperidone (12d)** (21 mg, 20%) and the **3*R*,4*S*,6*S*** isomer **14d** (50 mg, 48%). **12d**: $[\alpha]^{22}_D$ +9.5 (*c* 0.2, EtOH); IR (film) 2243, 1741, 1655 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) 0.06 (s, 6H, $SiMe_2$), 0.87 (s, 9H, CMe_3), 2.33 (td, *J*=13.0, 4.0 Hz, 1H, H-5), 2.45 (dt, *J*=13.0, 3.5 Hz, 1H, H-5), 3.08 (s, 3H, OCH_3), 3.44 (ddd, *J*=13.0, 11.5, 3.5 Hz, 1H, H-4), 3.81 (d, *J*=11.5 Hz, 1H, H-3), 4.16 and 4.35 (2dd, *J*=10.7, 7.0 Hz, 2H, CH_2OSi), 5.03 (t, *J*=7.0 Hz, 1H, NCH), 5.14 (s, 2H, CH_2O), 5.20 (dd, *J*=4.0, 3.5 Hz, 1H, H-6), 5.24 and 5.35 (2d, *J*=12.3 Hz, 2H, CH_2O), 6.90 (s, 1H, H-2'), 7.15-7.50 (m, 14H, ArH); ^{13}C-NMR, Table 3. Anal. Calcd for $C_{38}H_{45}N_3O_5Si$: C, 70.01; H, 6.95; N, 6.14. Found: C, 69.64; H, 7.04; N, 5.98. **14d**: $[\alpha]^{22}_D$ +30.6 (*c* 0.35, EtOH); IR (film) 2245, 1743, 1656 cm^{-1}; ^{1}H-NMR

($CDCl_3$, 300 MHz) -0.15 (s, 3H, $SiCH_3$), -0.11 (s, 3H, $SiCH_3$), 0.76 (s, 9H, CMe_3), 2.63 (m, 2H, H-5), 3.17 (s, 3H, OCH_3), 3.55 (ddd, *J*=10.6, 8.4, 6.4 Hz, 1H, H-4), 4.00 (d, *J*=10.6 Hz, 1H, H-3), 4.18 and 4.24 (2dd, *J*=10.5, 6.6 Hz, 2H, CH_2OSi), 4.90 (t, *J*=6.6 Hz, 1H, NCH), 5.00 (t, *J*=7.1 Hz, 1H, H-6), 5.28 and 5.34 (2d, *J*=12.2 Hz, 2H, CH_2O), 5.34 (s, 2H, CH_2O), 6.90 (s, 1H, H-2'), 7.17-7.50 (m, 14H, ArH); ^{13}C-NMR, Table 3. Anal. Calcd for $C_{38}H_{45}N_3O_5Si.H_2O$: C, 68.07; H, 7.01; N, 6.10. Found: C, 68.39; H, 6.86; N, 5.76.

(4*R*,6*S*)-1 -[(1*R*)-2 -[(*tert*-Butyldimethylsilyl)oxy]-1 -phenylethyl]-4 -cyano-6 -[1 -(methoxymethyl)-3 -indolyl]-2-piperidone (15). A mixture of indolylpyperidone **12d**, (30 mg, 0.046 mmol), 1,4-cyclohexadiene (0.14 ml, 1.46 mmol), and 10% Pd-C (20 mg) in MeOH (3 ml) was refluxed for 4 h. The catalyst was removed by filtration, and the filtrate was concentrated under vacuum. The residue was dissolved in AcOEt (10 ml), and the solution was washed with brine, dried and evaporated to give an oil which was chromatographed (1:1 AcOEt-hexane) affording indolylpiperidone **15** (5 mg, 21%): IR (film) 2350, 1647 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz) -0.04 (s, 3H, $SiCH_3$), 0.06 (s, 3H, $SiCH_3$), 0.85 (s, 9H, CMe_3), 2.29 (td, *J*=12.5, 4.5 Hz, 1H, H-5), 2.46 (ddd, *J*=12.5, 4.5, 2.5 Hz, 1H, H-5), 2.74 (dd, *J*=20.0, 13.5 Hz, 1H, H-3), 2.94 (ddd, *J*=20.0, 6.5, 1.5 Hz, 1H, H-3), 2.97 (m, 1H, H-4), 3.14 (s, 3H, OCH_3), 4.12 and 4.36 (2dd, *J*=10.5, 7.0 Hz, 2H, CH_2OSi), 5.05 (t, *J*=7.0 Hz, 1H, NCH), 5.20 (m, 1H, H-6), 5.28 (s, 2H, NCH_2), 6.90 (s, 1H, H-2'), 7.15-7.50 (m, 9H, ArH); ^{13}C-NMR, Table 3 .

(4*S*,6*S*)-1 -[(1*R*)-2 -[(*tert*-Butyldimethylsilyl)oxy]-1 -phenylethyl]-4 -cyano-6 -[1 -(methoxymethyl)-3 -indolyl]-2-piperidone (16). A mixture of indolylpiperidone **14d** (120 mg, 0.18 mmol), ammonium formate (91 mg, 1.44 mmol), and 10% Pd-C in MeOH (3 ml) was stirred at 25°C for 18 h, filtered, and concentrated. The residue was taken up in toluene (14 ml), and the solution was refluxed for 2 h. The mixture was poured into brine, the aqueous layer was extracted with AcOEt, and the combined organic extracts were dried and concentrated to give pure indolylpiperidone **16** (90 mg, 94%): $[\alpha]^{22}_D$+3.2 (*c* 1.5, EtOH); IR (film) 2355, 1647 cm^{-1};^{1}H-NMR ($CDCl_3$, 500 MHz) -0.18 (s, 3H, $SiCH_3$), -0.15 (s, 3H, $SiCH_3$), 0.74 (s, 9H, CMe_3), 2.47 (m, 1H, H-5), 2.53 (dt, *J*=14.0, 8.5 Hz, 1H, H-5), 2.90 (dd, *J*=17.0, 10.0 Hz, 1H, H-3), 2.92 (ddd, *J*=17.0, 6.0, 2.0 Hz, 1H, H-3), 3.04 (m, 1H, H-4), 3.17 (s, 3H, OCH_3), 4.13 and 4.28 (2dd, *J*=10.5, 7.0 Hz, 2H, CH_2OSi), 4.92 (t, *J*=7.0 Hz, 1H, NCH), 4.97 (dd, *J*=8.5, 5.5 Hz, 1H, H-6), 5.25 and 5.32 (2d, *J*=11.5 Hz, 2H, NCH_2), 6.90 (s, 1H, H-2'), 7.11-7.47 (m, 9H, ArH); ^{13}C-NMR, Table 3.

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