Stereoselective Additions of Chiral α-Sulfinyl Ketimine Anions to Ene Esters. Asymmetric Syntheses of Indolo[2,3-*a*]quinolizidine and Yohimban Alkaloids†

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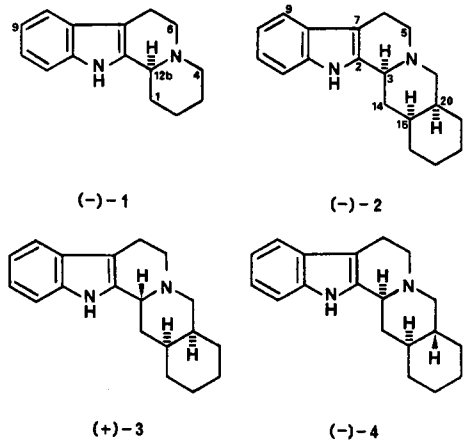
The in-situ 1,4-addition/ring-closure reactions of chiral α-sulfinyl ketimine anions with acyclic and cyclic ene esters offer a simple, convenient route for the construction of chiral cyclic alkaloids having a nitrogen-atom ring juncture. Asymmetric induction in the conjugate-addition reaction of the carbanions derived from α-sulfinyl ketimines possessing chiral sulfur with various cyclic and acyclic ene esters, subsequent ring-closure reaction, and reduction of the resulting β-sulfinyl enamides were utilized in the syntheses of (−)-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine [(−)-1], (−)-alloyohimban [(−)-2], (+)-3-*epi*-alloyohimban [(+)-3], and (−)-yohimban [(−)-4].

Introduction

In the study of the enantioselective synthesis of cyclic alkaloids having a nitrogen-atom ring juncture, the addition reactions of chiral α-sulfinyl ketimines with various ene esters were investigated.[1] Several analogues have been reported: silyl aldimines,[2] tin aldimines,[3] β-aminoalkenephosphonates,[4] α-sulfinyl oxazolines,[5] α-sulfinyl hydrazones,[6] β-aminoalkenenitriles,[7] and β-aminoalkene esters.[7] This report describes the asymmetric induction exhibited in the conjugate addition reaction of the carbanion derived from α-sulfinyl ketimines possessing chiral sulfur with various acyclic and cyclic ene esters, the subsequent cyclization to lactams, and the stereoselectivity in reductions of the resulting β-sulfinyl enamides. This method is demonstrated in the synthesis of (−)-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine [(−)-1],[8] (−)-alloyohimban [(−)-2],[9] (+)-3-*epi*-alloyohimban [(+)-3],[9] and (−)-yohimban [(−)-4].[9]



Results and Discussion

I. Conjugate Addition of Chiral α-Sulfinyl Ketimine Anions to Ene Esters and Stereoselective Reduction of β-Sulfinyl Enamides. We initially prepared (*R*)-sulfinyl ketimine (+)-**5** from the reaction of the magnesiated α-anion of (*R*)-*p*-tolyl methyl sulfoxide (**6**) (generated from the reaction of **6** and (diisopropylamino)-magnesium bromide) with 4-bromobutanenitrile in THF at 0 °C for 1 h. Only an 18% yield (of theoretical) of (+)-**5** was obtained; 54% of the starting sulfoxide was recovered (Scheme I). An acid–base reaction apparently takes place between the anion and 4-bromobutanenitrile, and the latter undergoes intramolecular cyclization to give cyanocyclopropane. With α-lithiomethyl *p*-tolyl sulfoxide only recovered sulfoxide **6** and cyanocyclopropane were obtained

† This paper is dedicated to Professor Hitosi Nozaki on the occasion of his 70th birthday.

‡ Fellow of the Alfred P. Sloan Foundation, 1989–1993.

(1) Some of the pertinent transformations and products described in this paper were reported by us in a short Communication (Hua, D. H.; Bharathi, S. N.; Takusagawa, F.; Tsujimoto, A.; Panangadan, J. A. K.; Hung, M.-H.; Bravo, A. A.; Erpelding, A. M. *J. Org. Chem.* **1989**, *54*, 5659). There were, unfortunately, several serious errors in that Communication, some of which were brought to our attention by Professors A. I. Meyers and J. Aube to whom we are grateful. We have now pointed out and corrected these errors (Additions and Corrections, *J. Org. Chem.*, in press). In referring to the work described in the earlier Communication, the present paper incorporates the corrected information.

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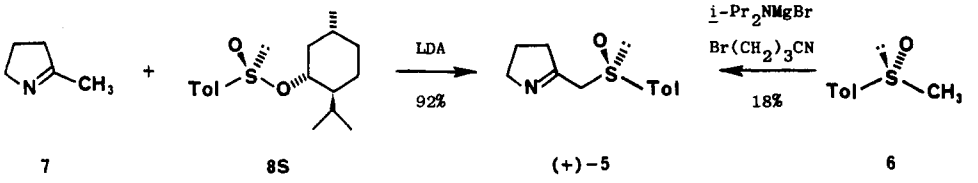
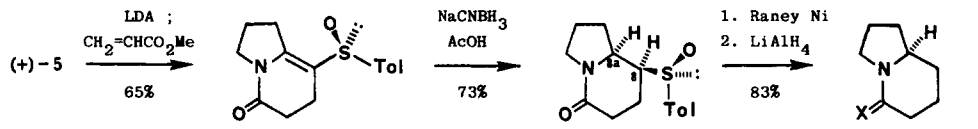
0022-3263/91/1956-6998$02.50/0

Scheme I



7 8S (+)-5 6

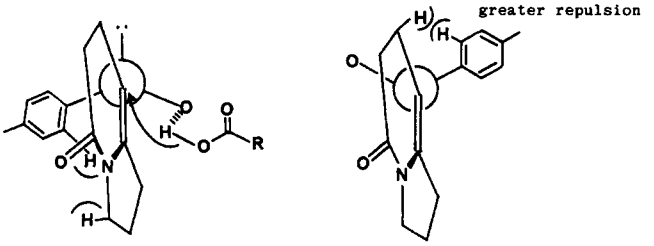
Scheme II



9 10 11 : X = O 12 : X = H2

under the same conditions. A better preparative method was sought. Treating 3 equiv of α-lithiated 3,4-dihydro-5-methyl-2*H*-pyrrole (**7**)[10] with *l*-(−)-(*S*)-menthyl *p*-toluenesulfinate (**8S**)[11] in THF at −50 °C for 1 h provided 92% yield of (+)-**5** with the identical optical rotation of **5** obtained from the first method (Scheme I). The *R* configuration at the sulfur atom shows that nucleophilic substitution at sulfur of **8S** with α-lithiated ketimine **7** proceeds with complete inversion of configuration.

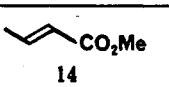
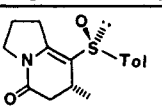
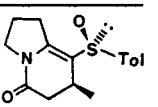
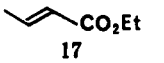
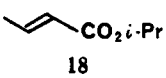
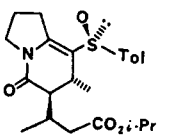
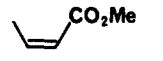
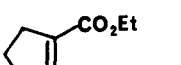
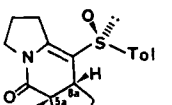
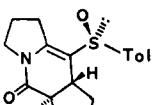
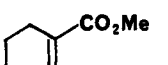
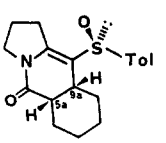
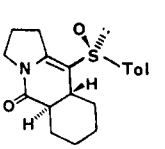
Treatment of sulfinyl ketimine (+)-**5** with 1 equiv of *n*-BuLi (or LDA) in THF followed by 1.2 equiv of methyl acrylate afforded 65% yield of indolizidinone **9**. Apparently, **9** is formed from the 1,4-addition reaction of the sulfinyl ketimine anion of **5** with methyl acrylate: the attack occurs from the α-carbon of the sulfoxide to give the enolate anion which abstracts a proton from α-CH of the sulfoxide moiety; ring closure follows. A higher yield of **9** (76%) was obtained by treating (+)-**5** with 2.1 equiv of LDA followed by 1.2 equiv of ethyl 3-bromopropanoate. Remarkably, the reduction of **9** with $NaCNBH_3$ in acetic acid with a catalytic amount of CF_3CO_2H is completely stereoselective, giving a 79% yield of **10** as a single enantiomer. The stereochemistry at C-8a of **10** was proven by degradation of **10** to (*R*)-(−)-indolizidine [(*R*)-**12**][12] by the two-step sequence: (i) desulfurization with W-2 Raney nickel in refluxing ethanol (98% yield) and (ii) reduction of the resulting amide **11** with lithium aluminum hydride in ether (85% yield).[13] The stereochemistry at C-8 of **10** was assumed on the basis of the coupling constant, $J_{8,8a}$ = 5.2 Hz, obtained from ^1H NMR irradiation experiments. The bulky sulfinyl group should be in the equatorial position, requiring the C_8-H to be in the axial position. The observed *J* value of 5.2 Hz suggests an axial–equatorial coupling which in turn suggests that C_{8a}-H is equatorial, in line with the NMR results reported by Speckamp.[14] Although asymmetric addition to chiral α-sulfinyl-α,β-unsaturated carbonyl compounds is known,[15] chiral β-sulfinyl enamides like **9** have only been reported from this laboratory.[1] In the reduction of **9** to **10**, presumably the acid stereoselectively protonates the double-bonded C-8 (**13a**) as depicted in Figure 1, and the resulting α-amido carbocation is attacked by the hydride from the opposite



13a 13b

Figure 1.

Table I. 1,4-Addition of the Lithiated Anion of (+)-5 with Various Ene Esters

entry	ene ester	products (% yield)	
1	 14	 15 (53)	 16 (27)
2	 17	15 (54)	16 (27)
3	 18	15 (45)	 19 (16)
4	 20	15 (15)	16 (13)
5	 21	 22 (70)	 23 (2)
6	 24	 25 (60)	 26 (6)

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(12) Ringdahl, B.; Pinder, A. R.; Pereira, W. E.; Oppenheimer, N. J., Jr.; Craig, J. C. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1.

(13) It can be assumed that (*R*)-**12** prepared here is 100% optically pure, since the precursor **10** is 100% enantiomerically pure.

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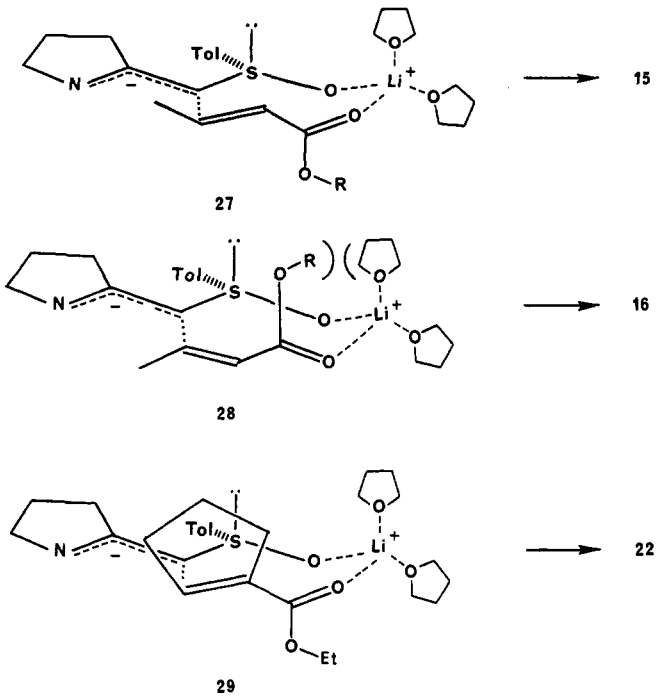
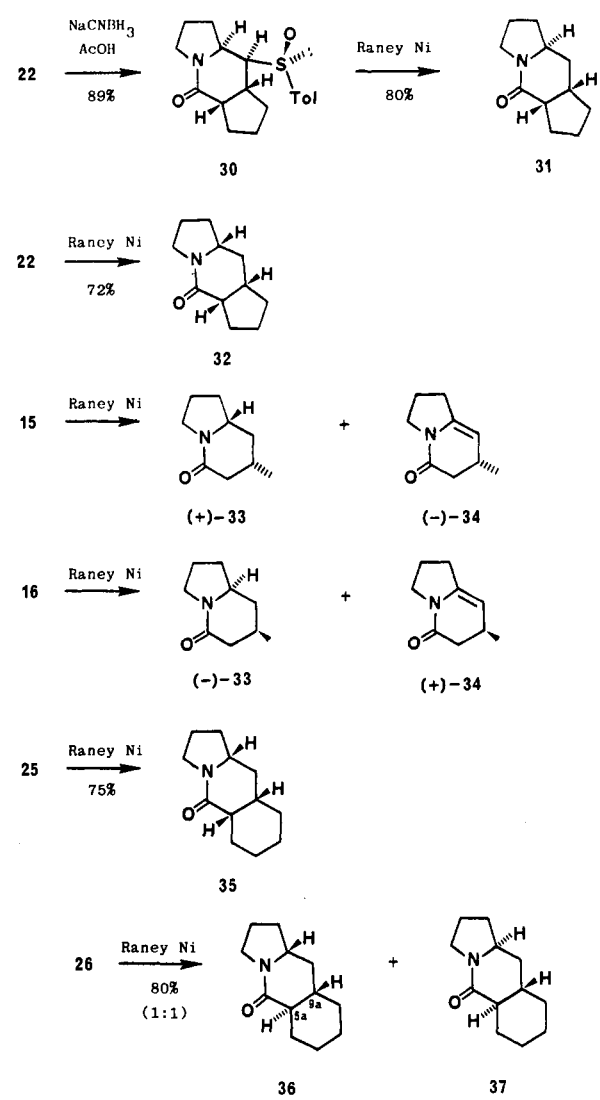


Figure 2.

side of the bulky sulfinyl group.

The anion derived from (+)-5 also underwent 1,4-addition reactions with various ene esters; the results are summarized in Table I. The reaction of the lithiated anion of (+)-5 and (*E*)-methyl or -ethyl 2-butenoate (**14** or **17**) gave 53–54% yield of indolizidinone **15** and 27% yield of its diastereomer **16** (entries 1 and 2), while with (*Z*)-methyl 2-butenoate (**20**), **15** and **16** were isolated in 15% and 13% yield, respectively (entry 4). However, excellent stereoselectivity was obtained with (*E*)-isopropyl 2-butenoate (**18**) (entry 3). Indolizidinone **15** was isolated in 45% yield along with the diadduct **19** (16% yield); 10% of (+)-**5** was recovered and no **16** was detected. With (*E*)-*tert*-butyl 2-butenoate, under the same reaction conditions, only starting materials were recovered. Various reaction conditions have been tried to suppress the formation of **19**, and the best results are listed in entry 3. Treatment of indolizidinone **15** with LDA in THF at −78 °C followed by 2-butenoate **18** afforded an 82% yield of diadduct **19**. ^1H and ^{13}C NMR spectra of **19** indicated a single diastereomer, and the C-6 stereochemistry is assumed in that the ene ester **18** approaches the enolate ion of **15** from the opposite side of C-7 methyl.[16a] The C-1′ stereochemistry is not assignable.[16b,c] The stereochemistry of **16** was investigated by X-ray diffraction.[17] Similar high stereoselectivities were observed when ethyl 1-cyclopentenecarboxylate (**21**) and methyl 1-cyclohexenecarboxylate (**24**) were used. The cis tricyclic adducts **22** and **25**, respectively, were isolated as major products (entries 5 and 6) along with small amounts of the trans tricyclic compounds **23** and **26**, respectively. None of the other possible stereoisomers was detected. A single-crystal X-ray structure determination of **22** firmly established the stereochemistry at S, C-5a, and C-8a.[1] The absolute configuration of **22** was determined

Scheme III



by the heavy-atom (sulfur) anomalous dispersion techniques, and the stereochemistry of **25** is implied by the structure of **22**. The sign of optical rotations of **22** and **25** is the same as that of their reduced products (vide infra; **32** and **35**). The stereochemistry of the minor products **23** and **26** is based on coupling constants, $J_{5a,8a}$ = 14 Hz for **23** and $J_{5a,9a}$ = 13 Hz for **26** (axial–axial coupling), and the reduction products (vide infra; **35–37**) from **25** and **26**. These results and studies of the allyl sulfoxides[18] suggest two transition states **27** and **28** (Figure 2) leading to **15** and **16**, respectively. Since **15** is the major product, **27** would be the favorable transition state. When the size of the alkyl group (R) of the 2-butenoate increases (such as in **18**), steric repulsion between the OR group of the 2-butenoate and the pseudoaxial tetrahydrofuran ligand will further reduce the stability of transition state **28**. Hence, **15** and **19** were formed exclusively. A similar transition state (**29**) can explain the formation of **22**. The tetracoordination of Li^+ and the chelation of the O atom of tetrahydrofuran to Li^+ in lithiated carbanions have been reported.[19,20]

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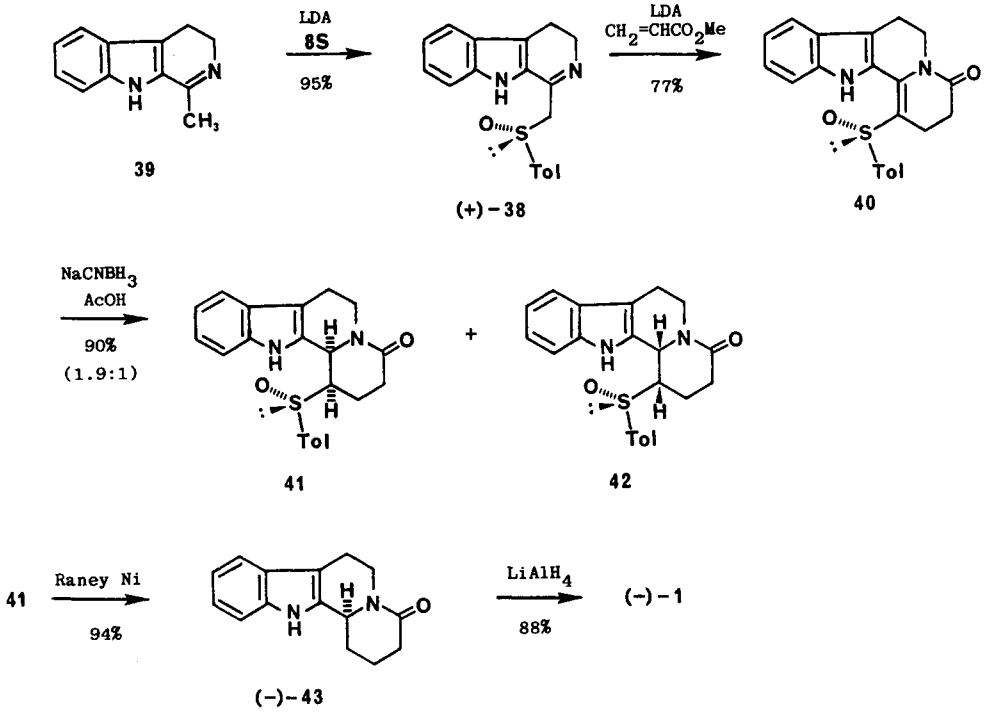
Scheme IV



Reductions of β-sulfinyl enamides (such as **9**) in most cases were stereoselective. Scheme III summarizes the results of the reductions of enamides **15**, **16**, **22**, **25**, and **26**. Treatment of sulfinyl enamide **22** with 3 equiv of $NaCNBH_3$ in acetic acid and a catalytic amount of CF_3CO_2H gave a single isomer **30** (89% yield) which, on desulfurization with Raney nickel in ethanol, provided tricyclic amide **31** (80% yield). Its diastereomer **32** was prepared by direct desulfurization of **22** with Raney nickel (a single isomer; 72% yield). Since the hydrogenation of indolizines[21] proceeded exclusively from the opposite side of the alkyl substituent on the rings, the C-9a of **32** should be the *S* configuration. Consequently, C-9a of **31** should be the *R* configuration. The stereochemistry at C-9 of **30** was implied by the product structure from the reduction of **9**. Because the stereoselectivity of the reduction of β-sulfinyl enamides with Raney nickel is better than with sodium cyanoborohydride (vide infra; section II) and the number of stereocenters of the reduced products is one fewer in the Raney nickel case, the reduction of compounds **15**, **16**, **25**, and **26** was studied with Raney nickel. Reduction of **15** with Raney nickel gave a 68% yield of (+)-**33**, an enantiomer of (-)-**33** which was prepared by reduction of **16** with Raney nickel (65% yield). The desulfurized compounds, 1,2,3,5,6,7-hexahydro-7-methyl-5-indolizinones **34**, were also obtained (~20%) in both cases. Hydrogenation of (-)-**34** with hydrogen and Pd/C in ethyl acetate gave a 91% yield of (+)-**33**. A similar result was obtained with enamide **25** in which tricyclic amide **35** was produced in a 75% yield as a single isomer. On the other hand, reduction of the minor adduct **26** with Raney nickel gave both isomers **36** and **37** (80% yield; 1:1). Diastereomers **36** and **37** are not separable by TLC and chromatography; however, the ^{13}C NMR spectrum clearly indicated two isomers and is different from that of **35**. Hence, the configuration at C-5a and -9a of **26** was established to be trans.

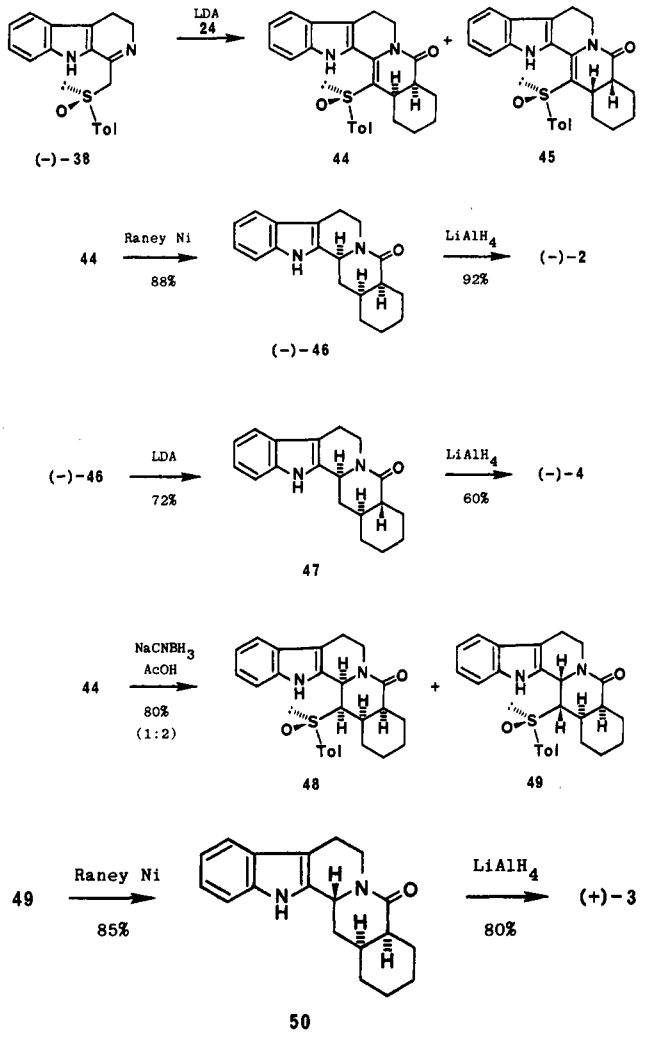
II. Syntheses of (-)-1,2,3,4,6,7,12,12b-Octahydroindolo[2,3-*a*]quinolizine [(-)-1], (-)-Alloyohimban [(-)-2], (+)-3-*epi*-Alloyohimban [(+)-3], and (-)-Yohimban [(-)-4]. To demonstrate the generality of the method, this 1,4-addition reaction was utilized in the asymmetric synthesis of indole alkaloids (-)-**1**, (-)-**2**, (+)-**3**, and (-)-**4**. The same procedure as that used in the preparation of **5** was employed to prepare sulfoxides (+)-**38** and (-)-**38**, respectively, from harmalan (**39**) with sulfinates **8S** and **8R** (Scheme IV). Treatment of **39** with 2 equiv of LDA in THF at 0 °C followed by the addition of 1 equiv of *l*-(-)-(*S*)-menthyl *p*-toluenesulfinate (**8S**) at -50 °C gave a 95% yield of (+)-**38**; with *d*-(+)-(*R*)-menthyl *p*-toluenesulfinate (**8R**), (-)-**38** (90% yield) was obtained. Addition of the anion of (+)-**38** (derived from (+)-**38** and 1.2 equiv of LDA in THF) with methyl acrylate at 25 °C for 4 h provided a 77% yield of **40**. Contrary to the stereoselective reductions described above (Scheme III), the reduction of **40** with $NaCNBH_3$ in AcOH at 25 °C for 3 h provided a 90% yield of a mixture of **41** and **42** in a ratio of 1.9:1. The two isomers were separated by column chromatography. Diastereomer **41** was soluble in the usual chromatographic solvents i.e., CH_2Cl_2, $CHCl_3$, and ether. On the other hand, diastereomer **42** was only slightly soluble in these solvents. The stereochemistry at C-12b of **41** and **42** was determined by transforming them into antipodes (-)-(*S*)-**1** and (+)-(*R*)-**1**, respectively (vide infra), while the syn disposition at C-1 and C-12b is based on coupling constants, $J_{1,12b}$ = 2 Hz for **41** and 1 Hz for **42** (the chemical shifts were assigned from ^1H NMR 2D COSY experiments). Desulfurization of **41** with Raney nickel in EtOH–THF at 65 °C followed by reduction with $LiAlH_4$ in ether gave a 83% yield of (-)-**1**.[8b] Antipode (+)-**1** was similarly synthesized from **42**. Reduction of **40** directly with Raney nickel gave racemic **43** ($[\alpha]_D$ = 0).

The addition reaction of the anion of (-)-**38** with methyl 1-cyclohexenecarboxylate at 25 °C for 1 h, and then 60 °C for 14 h, gave a 42% yield of **44**, 5% yield of **45**, and 35%

(20) We thank one of the reviewers for pointing out the chelation of THF with lithium and the possible role of the s-cis/s-trans ratio of the enolates in the transition state in influencing the selectivity of the products: Chamberlin, A. R.; Reich, S. H. *J. Am. Chem. Soc.* **1985**, *107*, 1440.

(21) (a) Sonnet, P. E.; Netzed, D. A.; Mendoza, R. *J. Heterocycl. Chem.* **1979**, *16*, 1041. (b) Sonnet, P. E.; Oliver, J. E. *J. Heterocycl. Chem.* **1975**, *12*, 289.

Scheme V



recovery of (-)-38 (separated by column chromatography) (Scheme V). The absolute configuration at C-15 and 20 of 44 and 45 was determined by converting them into (-)-2, (+)-3, and (-)-4 (vide infra, known stereochemistry). Unexpectedly, the absolute configurations of these two new chiral centers of the major product 44 were opposite to those, respectively, of 22. Hence, the transition state would be similar to that of 28. Desulfurization of 44 with Raney nickel in EtOH gave an 88% yield of a single isomer, (-)-alloyohimban-21-one (46). On the other hand, desulfurization of 45 with Raney nickel under the same conditions provided the antipode (+)-46. Reduction of (-)-46 with lithium aluminum hydride in THF provides a 92% yield of (-)-2.[9c-f] Epimerization of (-)-46 with 2.5 equiv of LDA in THF followed by protonation with AcOH at -30 °C gave 72% yield of yohimban-21-one (47); 18% of (-)-46 was recovered. Reduction of 47 with $LiAlH_4$ furnished yohimban [(-)-4][9c] (60% yield). The reduction of 44 with $NaCNBH_3$-AcOH gave two C-3 isomers, 48 and 49, in a ratio of 1:2. These results are similar to those provided by 40 (vide supra). These nonstereoselective reductions can be rationalized by the presumption that the energy differences required for the initial protonation at C-12b of 40 and C-3 of 44 in both faces are small due to the large planar indole-ring system. The stereochemistry shown for C-14 of 48 and 49 was derived from the coupling constant $J_{3,14}$ = 7 Hz for 48 and 1 Hz for 49 (equatorial-axial coupling). Desulfurization of 48 and 49 gave alloyohimban-21-one [(-)-46] (89% yield) and 3-*epi*-alloyohimban-21-one (50) (85% yield), respectively. Finally, 50 was converted into (+)-3-*epi*-alloyohimban [(+)-3][9c] by reduction with $LiAlH_4$ (80% yield).

Antipodes (+)-2, (-)-3, and (+)-4 were also synthesized from sulfoxide (+)-38 as described above.

Conclusions

Facile chiral syntheses of functionalized indolizidines and quinolizidines have now been accomplished by 1,4-additions of the anions of chiral α-sulfinyl ketimines to ene esters, followed by ring closure. (*E*)-Isopropyl 2-butenoate provides enantioselectively the corresponding 1,4-adduct. Transition states of the 1,4-addition reaction were proposed. Subsequent reductions of the β-sulfinyl enamides, in most cases, are also stereoselective. By this methodology, (-)-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]-quinolizine [(-)-1] and the yohimbanoids (-)-2, (+)-3, and (-)-4 were synthesized in five and four steps, respectively, from harmalan.

Experimental Section

General Methods. Nuclear magnetic resonance spectra were obtained at 400 MHz for ^1H and 100 MHz for ^{13}C in deuteriochloroform, unless otherwise indicated. Infrared spectra are reported in wavenumbers (cm^{-1}). EI MS were taken under the conditions of 75 eV, 300 μA, and 3 KV, and FAB MS were taken in Xe gas, 2 KV, using glycerol and *m*-nitrobenzyl alcohol as the matrix. Davisil silica gel, grade 643 (200–425 mesh), was used for the flash chromatographic separation. (+)-(*R*)-4,5-Dihydro-2-[[(4-methylphenyl)sulfinyl]methyl]-3*H*-pyrrole (5) was obtained from 3,4-dihydro-5-methyl-2*H*-pyrrole (7) in 92% yield as described.[22] Methyl 1-cyclohexenecarboxylate (25) was purchased from Aldrich. Ethyl 1-cyclopentenecarboxylate (22) was prepared according to the reported procedure.[23]

(+)-(*R*)-4,5-Dihydro-2-[[(4-methylphenyl)sulfinyl]-methyl]-3*H*-pyrrole (5) from (*R*)-Methyl *p*-Tolyl Sulfoxide (6). To a solution of 7 mL (50 mmol) of diisopropylamine in 60 mL of THF under argon at 25 °C was added 21 mL (52 mmol) of ethylmagnesium bromide (2.5 M solution in THF). The solution was heated at reflux for 1 h, cooled to 25 °C, and transferred into a cold (-30 °C) solution of 3.08 g (20 mmol) of (*R*)-methyl *p*-tolyl sulfoxide (6)[24] in 90 mL of THF via cannula under argon. The solution was stirred at 0 °C for 45 min, and 7.2 mL (40 mmol) of hexamethylphosphoramide (HMPA) followed by 3 mL (30 mmol) of 4-bromobutanenitrile were added. The solution was stirred at 0 °C for 30 min, poured into 300 mL of H_2O, and extracted three times with CH_2Cl_2. The combined extracts were washed with water twice then with brine, dried ($MgSO_4$), concentrated, and the residue was column chromatographed on silica gel, using gradient mixtures of hexane and ethyl acetate, and ethyl acetate and methanol as eluant to give 0.8 g (18% yield) of (+)-5 and 1.66 g (54% recovery) of 6. The $[\alpha]_D$ and NMR spectra of sulfinyl ketimine (+)-5 obtained by this method are identical with those of (+)-5 prepared from ketimine 7.[22]

The following example serves as the general procedure for the 1,4-addition reactions of sulfoxide (+)-5 with methyl acrylate, ene esters 14, 17, 18, 20, 21, and 24.

(-)-(*S*)-1,2,3,5,6,7-Hexahydro-8-[(4-methylphenyl)-sulfinyl]-5-indolizinone (9). To a cold (-78 °C) solution of 0.53 g (2.4 mmol) of sulfinyl ketimine (+)-5 in 15 mL of THF under argon was added a cold (-25 °C) solution of 3 mmol of LDA in 5 mL of THF via cannula. After the brown solution was stirred at -78 °C for 1 h, 0.25 g (2.9 mmol) of methyl acrylate was added via syringe. The solution was stirred at -78 °C for 15 min and at 25 °C for 2 h, poured into 50 mL of H_2O, and extracted three times with CH_2Cl_2. The combined organic extracts were washed with water and brine, dried ($MgSO_4$), and concentrated, and the residue was column chromatographed on silica gel, using gradient

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mixtures of hexane and ethyl acetate, and ethyl acetate and methanol as eluant to give 0.429 g (65% yield) of indolizidinone **9**; mp 140–142 °C, $[\alpha]^{20}_D$ −27.83° (*c* 0.945, CH_2Cl_2); ^1H NMR δ 7.42 (d, *J* = 8 Hz, 2 H, ortho H), 7.30 (d, *J* = 8 Hz, 2 H, meta H), 3.82 (ddd, *J* = 5, 12, 7 Hz, 1 H, CHN), 3.68 (m, 1 H), 3.24 (dt, *J* = 18, 7 Hz, 1 H), 3.04 (dt, *J* = 18, 7 Hz, 1 H), 2.6 (m, 2 H), 2.41 (s, 3 H, CH_3), 2.43 (m, 1 H), 2.08 (quintet, *J* = 7 Hz, 1 H), 1.93 (m, 1 H); ^{13}C NMR δ 168.2 (s, CO), 148.1 (s, NC=), 140.7 (s, Ar), 139.2 (s, Ar), 129.8 (d, 2C, Ar), 124.2 (d, 2C, Ar), 111.9 (s, =CS), 46.0 (t); 31.0 (t), 29.3 (t), 21.7 (t), 21.3 (q), 16.4 (t); MS *m/z* EI 275 (M^+); CI 276 (M + 1). Anal. Calcd for $C_{15}H_{17}NO_2S$: C, 65.43; H, 6.22; N, 5.09; S, 11.64. Found: C, 65.17; H, 6.50; N, 4.88; S, 11.53.

When 1.0 equiv of methyl acrylate and 1.1 equiv of *n*-BuLi were used instead of LDA, a 65% yield of **9** was isolated.

(−)-(7*R*,S*S*)-1,2,3,5,6,7-Hexahydro-7-methyl-8-[(4-methylphenyl)sulfinyl]-5-indolizinone (15) and (+)-(7*S*,S*S*)-1,2,3,5,6,7-Hexahydro-7-methyl-8-[(4-methylphenyl)-sulfinyl]-5-indolizinone (16). Reaction conditions were similar to those described above except (*E*)-methyl crotonate (**14**) was used. After **14** was added, the reaction mixture was stirred at 25 °C for 20 h. **15**: mp 142–143 °C; $[\alpha]^{22}_D$ = −106° (*c* 0.51, CH_2Cl_2); ^1H NMR δ 7.49 (d, *J* = 8 Hz, 2 H, *o*-H), 7.29 (d, *J* = 8 Hz, 2 H, *m*-H), 3.89 (m, 1 H), 3.67 (m, 1 H), 3.24 (m, 1 H), 2.99 (m, 2 H), 2.64 (dd, *J* = 16, 6 Hz, 1 H, C6-H), 2.08 (m, 2 H, C2-H), 0.35 (d, *J* = 7 Hz, 3 H, Me); ^{13}C NMR δ 168.6 (s, CO), 147.5 (s, CN), 141.0 (s, Ar), 139.3 (s, Ar), 129.8 (d, Ar), 124.3 (d, Ar), 117.8 (s, CS), 46.1 (t, C3), 40.2 (t, C1), 29.3 (t, C6), 23.2 (d, C7), 21.8 (t, C2), 21.4 (q, Me), 18.9 (q, Me); MS *m/z* EI 289 (M^+). Anal. Calcd for $C_{16}H_{19}NO_2S$: C, 66.41; H, 6.62. Found: C, 66.33; H, 6.79.

16: mp 177–178 °C; $[\alpha]^{22}_D$ = +69° (*c* 0.24, CH_2Cl_2); ^1H NMR δ 7.43 (d, *J* = 8 Hz, 2 H, *o*-H), 7.30 (d, *J* = 8 Hz, 2 H, *m*-H), 3.82 (m, 1 H), 3.7 (m, 1 H), 3.28 (dt, *J* = 17, 6 Hz, 1 H), 2.99 (dt, *J* = 17, 9 Hz, 1 H), 2.49 (m, 1 H), 2.41 (s, 3 H, Me), 2.28 (m, 2 H), 2.1 (m, 2 H), 1.21 (d, *J* = 7 Hz, 3 H, Me); ^{13}C NMR δ 167.9 (s, CO), 147.3 (s, CN), 140.6 (s, 2 C, Ar), 129.8 (d, 2 C, Ar), 124.2 (d, 2 C, Ar), 117.2 (s, CS), 45.8 (t, C3), 40.0 (t, C1), 29.3 (t, C6), 26.5 (d, C7), 21.9 (t, C2), 21.3 (q, 2 C, Me); MS *m/z* CI 290 (M + 1). Anal. Calcd for $C_{16}H_{19}NO_2S$: C, 66.41; H, 6.62. Found: C, 66.52; H, 6.57.

(+)-(6*R*,7*R*,S*S*)-1,2,3,5,6,7-Hexahydro-6-[2-(isopropoxycarbonyl)-1-methylethyl]-7-methyl-8-[(4-methylphenyl)-sulfinyl]-5-indolizinone (19). Reaction conditions were similar to those described above except 0.9 equiv of (*E*)-isopropyl crotonate (**18**) was used. And after **18** was added at −78 °C, the cooling bath was removed, and the reaction was stirred at 25 °C for 2 h. Chromatographic separation of the crude product gave a 45% yield of **15**, 16% yield of diadduct **19** and 10% recovery of (+)-**5**. **19**: $[\alpha]^{22}_D$ = +32.5° (*c* 0.4, CH_2Cl_2); ^1H NMR δ 7.5 (d, *J* = 8 Hz, 2 H, *o*-H), 7.29 (d, *J* = 8 Hz, 2 H, *m*-H), 5.0 (hept, *J* = 6 Hz, 1 H, CHO), 3.82 (m, 1 H, CHN), 3.69 (dt, *J* = 12, 7 Hz, 1 H, CHN), 3.21 (dt, *J* = 16, 8 Hz, 1 H), 3.02 (dt, *J* = 17, 7 Hz, 1 H), 2.88 (q, *J* = 7 Hz, 1 H), 2.5 (dd, *J* = 15, 5 Hz, 1 H), 2.41 (s, 3 H, *p*-Me), 2.39 (m, 1 H), 2.2 (d, *J* = 8 Hz, 1 H), 2.1 (m, 3 H), 1.24, 1.23 (2 d, *J* = 7 Hz, 6 H, 2 Me), 0.98 (d, *J* = 7 Hz, 3 H, C1′ Me), 0.33 (d, *J* = 7 Hz, C7 Me); ^{13}C NMR δ 171.8 (s, CO), 170.0 (s, CO), 146.2 (s, CN), 141.0 (s, Ar), 139.0 (s, Ar), 129.7 (d, Ar), 124.3 (d, Ar), 116.4 (s, CS), 67.5 (d, CO), 53.6 (d, C6), 46.0 (t, C3), 38.8 (t, C1), 31.1 (d, C7), 29.0 (t, C2′), 26.9 (d, C1′), 21.8 (q), 21.8 (q), 21.7 (q), 21.3 (t, C2), 19.6 (q), 17.4 (q); MS *m/z* FAB 418 (M + 1), 402, 259, 245, 215, 199. Anal. Calcd for $C_{23}H_{31}NO_4S$: C, 66.16; H, 7.48. Found: C, 66.07; H, 7.56.

(5a*S*,8a*R*,S*S*)-1*H*-9-[(4-Methylphenyl)sulfinyl]-2,3,5,5a,6,7,8,8a-octahydro-5-oxocyclopent[*f*]indolizine (22) and (5a*R*,8a*R*,S*S*)-1*H*-2,3,5,5a,6,7,8,8a-Octahydro-9-[(4-methylphenyl)sulfinyl]-5-oxocyclopent[*f*]indolizine (23). 22: mp 145–147 °C; $[\alpha]^{20}_D$ −82.6 (*c* 0.54, CH_2Cl_2); ^1H NMR δ 7.45 (d, *J* = 8 Hz, 2 H, ortho H), 7.28 (d, *J* = 8 Hz, 2 H, *m*-H), 3.87 (ddd, *J* = 8, 6, 2 Hz, 1 H, C-12 H), 3.68 (dt, *J* = 14.5, 7 Hz, 1 H, C-12 H), 3.31 (dt, *J* = 16, 8.5 Hz, 1 H, C-10 H), 3.02 (m, 2 H, C-10 H, C-7 H), 2.85 (td, *J* = 9, 3 Hz, 1 H, C-3 H), 2.41 (s, 3 H, CH_3), 2.28 (m, 1 H, C-6 H), 2.08 (m, 2 H, C-11 H), 1.86 (m, 1 H, C-6 H), 1.4 (m, 1 H, C-5 H), 1.3 (m, 1 H, C-5 H), 0.7 (m, 2 H, C-4 H); ^{13}C NMR δ 171.0 (s, CO), 146.4 (s, NC=), 140.8 (s, Ar), 139.8 (s, Ar), 129.7 (d, 2C, Ar), 124.3 (d, 2 C, Ar), 116.0 (s, C=), 46.7 (t, C-12), 45.5 (d, C-3), 34.2 (d, C-7), 32.0 (t, C-4), 29.7 (t, C-10), 27.5 (t, C-6), 23.2 (t, C-5), 21.8 (t, C-11), 21.4 (q, CH_3); the ^1H and ^{13}C NMR chemical shifts assignments are derived from irradiation decoupling experiments and 2D COSY experiments; MS *m/z* EI 315 (M^+), CI 316 (M + 1). Anal. Calcd for $C_{18}H_{21}NO_2S$: C, 68.54; H, 6.71; N, 4.44; S, 10.16. Found: C, 68.77; H, 6.83; N, 4.21; S, 10.09.

23: $[\alpha]^{22}_D$ = +138.7° (*c* 0.3, CH_2Cl_2); ^1H NMR δ 7.45 (d, *J* = 8 Hz, 2 H, *o*-H), 7.27 (d, *J* = 8 Hz, 2 H, *m*-H), 3.81 (ddd, *J* = 12, 6, 5.7 Hz, 1 H, C-12 H), 3.7 (dt, *J* = 12, 7.5 Hz, 1 H, C-12 H), 3.27 (dt, *J* = 17, 5 Hz, 1 H, C-10 H), 2.95 (ddd, *J* = 17, 9, 3 Hz, 1 H, C-10 H), 2.77 (m, 1 H, C-3 H), 2.41 (s, 3 H, CH_3), 2.28 (m, 1 H, C-7 H), 2.1 (m, 2 H, C-11 H), 1.98 (m, 1 H, C-4 H), 1.85 (m, 1 H, C-5 H), 1.3 (m, 2 H, C-6 H), 0.57 (m, 1 H, C-4 H); ^{13}C NMR δ 171.1 (s, CO), 151.0 (s), 140.3 (s), 129.6 (d, Ar), 128.8 (s), 124.6 (d, Ar), 123.8 (s), 50.5 (d), 45.4 (t), 41.9 (d), 29.2 (t), 26.4 (t), 23.8 (t), 22.8 (t), 22.4 (t), 21.3 (q); MS *m/z* EI 315 (M^+), CI 316 (M + 1). Anal. Calcd for $C_{18}H_{21}NO_2S$: C, 68.54; H, 6.71. Found: C, 68.29; H, 6.93.

(5a*S*,9a*R*,S*S*)-1,2,3,5,5a,6,7,8,9,9a-Decahydro-10-[(4-methylphenyl)sulfinyl]-5-oxopyrrolo[1,2-*b*]isoquinoline (25) and (5a*R*,9a*R*,S*S*)-1,2,3,5,5a,6,7,8,9,9a-Decahydro-10-[(4-methylphenyl)sulfinyl]-5-oxopyrrolo[1,2-*b*]isoquinoline (26). 25: mp 140–142 °C; $[\alpha]^{22}_D$ = −152° (*c* 0.565, CH_2Cl_2); ^1H NMR δ 7.49 (d, *J* = 8 Hz, 2 H, *o*-H), 7.29 (d, *J* = 8 Hz, 2 H, *m*-H), 3.89 (dt, *J* = 12, 7 Hz, 1 H), 3.68 (dt, *J* = 12, 7 Hz, 1 H), 3.23 (dt, *J* = 17, 8 Hz, 1 H), 3.02 (dt, *J* = 17, 8 Hz, 1 H), 2.8 (m, 1 H), 2.67 (broad s, 1 H), 2.41 (s, 3 H, *p*-Me), 2.08 (m, 2 H), 1.5–0.8 (series of m, 7 H), 0.3 (broad s, *J* = 14 Hz, 1 H); ^{13}C NMR δ 170.9 (s, CO), 147.5 (s, =C), 140.9 (s, Ar), 139.1 (s, Ar), 129.6 (d, Ar), 124.2 (d, Ar), 117.3 (d, =C), 46.2 (t), 42.5 (d), 30.8 (d), 29.2 (t), 27.7 (t), 25.7 (t), 24.5 (t), 22.0 (t), 21.9 (t), 21.3 (q); MS *m/z* FAB 330 (M + 1), 314, 277, 185 (100), 93, 75, 56. Anal. Calcd for $C_{19}H_{23}NO_2S$: C, 69.27; H, 7.04. Found: C, 68.91; H, 7.38.

26: $[\alpha]^{22}_D$ = +82.4° (*c* 0.25, CH_2Cl_2); ^1H NMR δ 7.43 (d, *J* = 8 Hz, *o*-H), 7.28 (d, *J* = 8 Hz, *m*-H), 3.82 (ddd, *J* = 12, 7, 4 Hz, 1 H), 3.75–3.58 (m, 2 H), 3.24 (m, 1 H), 2.92 (dtd, *J* = 17, 8, 3 Hz, 1 H), 2.71 (broad t, *J* = 8 Hz, 1 H), 2.42 (s, 3 H, *p*-Me), 2.32 (m, 2 H), 2.1–1.95 (m, 3 H), 1.6 (m, 2 H), 1.1 (m, 2 H), 0.42 (qd, *J* = 12, 3 Hz, 1 H); ^{13}C NMR δ 170.5 (s, CO), 149.5 (s, =C), 141.8 (s, Ar), 139.9 (s, Ar), 129.7 (d, Ar), 124.3 (d, Ar), 113.7 (s, =C), 46.3 (d), 46.0 (t), 39.6 (d), 29.9 (t), 28.6 (t), 26.4 (t), 25.3 (t), 25.3 (t), 21.7 (t), 21.3 (q); MS *m/z* FAB 330 (M+1), 315. Anal. Calcd for $C_{19}H_{23}NO_2S$: C, 69.27; H, 7.04. Found: C, 69.07; H, 7.19.

Reaction of the Anion of (+)-5 with Ethyl 3-Bromopropanoate. Formation of Indolizidinone 9. To a cold (−78 °C) solution of 2.81 g (12.7 mmol) of (+)-**5** in 10 mL of THF under argon was added 28 mmol of LDA in 25 mL of THF and 16 mL of hexane. After the brown solution was stirred at −78 °C for 30 min, 1.94 mL (15 mmol) of ethyl 3-bromopropanoate was added. The solution was stirred at −78 °C for 30 min and at 25 °C for 6 h, poured into 100 mL of H_2O, and extracted three times with CH_2Cl_2. The combined organic extracts were washed with water and brine, dried ($MgSO_4$), and concentrated, and the residue was column chromatographed on silica gel to give 2.67 g (76% yield) of (−)-**9**.

The following example serves as the general procedure for the reduction of β-sulfinyl enamides with $NaCNBH_3$.

(+)-(8*S*,8a*S*,S*R*)-8-[(4-Methylphenyl)sulfinyl]-1,2,3,5,6,7,8,8a-octahydro-5-indolizinone (10). To a cold (0 °C) solution of 2.67 g (9.71 mmol) of (−)-**9** in 15 mL of acetic acid and 20 mg of trifluoroacetic acid was added 1.987 g (29 mmol) of $NaCNBH_3$. The solution was stirred at 25 °C for 2 h and 50 °C for 3 h, cooled to 0 °C, neutralized with 3 N NaOH, and extracted three times with CH_2Cl_2 (100 mL each). The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated, and the residue was column chromatographed on silica gel, using gradient mixtures of hexane and ethyl acetate, and ethyl acetate and MeOH as eluant, to give 2.125 g (79% yield) of sulfoxide **10**. No other isomer was detected by the NMR analysis of all other concentrated fractions from column chromatography: mp 138–140 °C; $[\alpha]^{20}_D$ +181.1° (*c* 0.475, CH_2Cl_2); ^1H NMR δ 7.49 (d, *J* = 8 Hz, 2 H, o-H), 7.34 (d, *J* = 8 Hz, 2 H, *m*-H), 3.96 (quintet, *J* = 5 Hz, 1 H, CHN), 3.68 (dt, *J* = 12, 8 Hz, 1 H, CHN), 3.53 (dt, *J* = 12, 9 Hz, 1 H, CHN), 3.01 (q, *J* = 5.5 Hz, 1 H, CHS), 2.69 (ddd, *J* = 15, 11, 6 Hz, 1 H), 2.43 (s, 3 H, CH_3), 2.43–1.8 (m, 7 H); ^{13}C NMR δ 169.0 (s, CO), 141.4 (s, Ar), 139.3 (s, Ar), 129.9

(d, Ar), 124.3 (d, Ar), 60.0 (d, CN), 58.4 (d, CS), 44.5 (t, CN), 29.5 (t), 29.3 (t), 22.5 (t), 21.2 (q), 18.5 (t). MS *m/z* EI 277 (M^+). Anal. Calcd for $C_{15}H_{19}NO_2S$: C, 64.95; H, 6.90. Found: C, 64.87; H, 7.11.

The following example serves as the general procedure for the desulfurization with W-2 Raney nickel.

(−)-(8a*R*)-Octahydro-5-indolizinone (11). To a solution of 0.3 g (1.08 mmol) of (+)-**10** in 10 mL of ethanol under argon was added 1 g of W-2 Raney nickel.[25] The mixture was stirred at reflux for 1 h, diluted with ether (100 mL), filtered through Celite, and concentrated, and the residue was filtered through a short silica gel column, using a 1:1 mixture of hexane and ether as eluant to give 0.147 g (98% yield) of (−)-**11**: $[\alpha]^{20}_D$ −2.4° (*c* 0.75, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 3.62 (dt, *J* = 10, 8 Hz, 1 H, CHN), 3.48 (td, *J* = 9, 2 Hz, 1 H, CHN), 3.4 (m, 1 H, CHN), 2.45 (dd, *J* = 6.6, 16 Hz, 1 H), 2.28 (ddd, *J* = 7, 12, 18 Hz, 1 H), 2.5 (m, 2 H), 1.93 (m, 2 H), 1.72 (m, 2 H), 1.45 (m, 1 H), 1.3 (m, 1 H); ^{13}C NMR δ 169.1 (s, CO), 59.3 (d, CHN), 44.8 (t, CH_2N), 33.5 (t), 31.0 (t), 29.1 (t), 22.1 (t), 21.1 (t); IR (neat) ν 2930, 2860, 1640, 1445 cm^{-1}; MS *m/z* EI 139 (M^+). Anal. Calcd for $C_8H_{13}NO$: C, 69.03; H, 9.41; N, 10.06. Found: C, 68.87; H, 9.69; N, 10.27.

(−)-(8a*R*)-Octahydroindolizine (12). To a solution of 0.126 g (0.91 mmol) of (−)-**11** in 10 mL of ether under argon was added 69 mg (1.82 mmol) of $LiAlH_4$. The mixture was stirred at 25 °C for 2 h, diluted with moist ether and few drops of water, and filtered through Celite. The solvent was removed by distillation to give 97 mg (85% yield) of (−)-**2**: $[\alpha]^{20}_D$ −11.3° (*c* 1.76, EtOH) [lit.[12] $[\alpha]^{20}_D$ −10.2 ± 0.6° (*c* 1.76, EtOH)]; ^{1}H NMR δ 3.1 (m, 1 H, CHN), 3.05 (td, *J* = 9, 2 Hz, 1 H, CHN), 2.06 (q, *J* = 9 Hz, 1 H), 1.95 (td, *J* = 11, 3 Hz, 1 H), 1.88–1.2 (m, 11 H); ^{13}C NMR δ 64.4 (d, CN), 54.3 (t, CN), 53.1 (t, CN), 31.1 (t), 29.7 (t), 25.5 (t), 24.6 (t), 20.7 (t). MS *m/z* EI 125 (M^+).

(5a*S*,8a*R*,9*S*,9a*S*,S*R*)-1*H*-Decahydro-9-[(4-methylphenyl)sulfinyl]-5-oxocyclopent[*f*]indolizine (30). The above $NaCNBH_3$–AcOH procedure was followed to reduce **22** and provided an 89% yield of **30**: $[\alpha]^{22}_D$ = +136° (*c* 0.25, CH_2Cl_2); ^{1}H NMR (chemical shift assignments are derived from irradiation experiments) δ 7.44 (d, *J* = 8 Hz, 2 H, *o*-H), 7.33 (d, *J* = 8 Hz, 2 H, *m*-H), 4.06 (td, *J* = 10, 3 Hz, 1 H, 9aH), 3.7 (m, 1 H, 3-H), 2.4 (td, *J* = 12, 3 Hz, 1 H, 3-H), 2.98 (q, *J* = 10 Hz, 1 H, 5aH), 2.79 (d, *J* = 2 Hz, 1 H, 9-H), 2.68 (q, *J* = 10 Hz, 1 H, 8aH), 2.53 (m, 1 H, 1-H), 2.42 (s, 3 H, *p*-Me), 2.28–2.10 (m, 3 H, C-1, C-2, C-6 Hs), 1.89 (m, 1 H), 1.78–1.3 (series of m, 5 H); ^{13}C NMR δ 172.4 (s, CO), 141.1 (s, Ar), 140.4 (s, Ar), 130.0 (d, 2 C, Ar), 124.1 (d, 2 C, Ar), 66.7 (d, C9a), 54.5 (d, C9), 45.5 (t, C3), 43.9 (d, C5a), 34.1 (d, C8a), 32.9 (t), 32.8 (t), 30.0 (t), 25.5 (t), 22.8 (t), 21.3 (q); MS *m/z* FAB 318 (M + 1), 317. Anal. Calcd for $C_{18}H_{23}NO_2S$: C, 68.10; H, 7.30. Found: C, 67.89; H, 7.54.

(5a*S*,8a*S*,9a*R*)-1*H*-Decahydro-5-oxocyclopent[*f*]indolizine (31). The above W-2 Raney nickel-EtOH procedure was followed but conducted at 25 °C for 1 h under hydrogen (1 atm) to desulfurize **30** and gave an 80% yield of **31**. Yields of the desulfurization product depend on the quality of Raney nickel, and the best yields were obtained when freshly prepared W-2 Raney nickel was used: $[\alpha]^{22}_D$ = +17.6° (*c* 0.085, CH_2Cl_2); ^{1}H NMR δ 3.5 (m, 3 H), 2.74 (q, *J* = 7 Hz, 1 H), 2.44 (m, 1 H), 2.2–1.4 (series of m, 12 H); ^{13}C NMR δ 173.1 (s, CO), 53.9 (d), 45.4 (t), 44.4 (d), 36.5 (t), 33.8 (d), 33.6 (t), 33.0 (t), 31.8 (t), 26.2 (t), 22.5 (t); MS *m/z* EI 179 (M^+). Anal. Calcd for $C_{11}H_{17}NO$: C, 73.70; H, 9.56. Found: C, 73.95; H, 9.81.

(5a*S*,8a*S*,9a*S*)-1*H*-Decahydro-5-oxocyclopent[*f*]indolizine (32). The above W-2 Raney nickel–EtOH procedure was followed to reduce **22** but conducted at 25 °C for 2 h under hydrogen (1 atm) and gave a 72% yield of **32**: $[\alpha]^{22}_D$ = +17.5° (*c* 0.2, CH_2Cl_2); ^{1}H NMR δ 3.52–3.41 (m, 3 H), 2.66 (q, *J* = 9 Hz, 1 H), 2.35 (m, 1 H), 2.15–1.91 (m, 5 H), 1.88–1.67 (m, 3 H), 1.6–1.3 (m, 3 H), 1.03 (q, *J* = 11 Hz, 1 H); ^{13}C NMR 172.3 (s, CO), 58.5 (d), 44.9 (t), 44.8 (d), 37.4 (t), 35.7 (d), 33.5 (t), 33.3 (t), 29.9 (t), 24.5 (t), 22.8 (t); MS *m/z* EI 179 (M^+). Anal. Calcd for $C_{11}H_{17}NO$: C, 73.70; H, 9.56. Found: C, 73.45; H, 9.81.

(+)-(7*S*,8a*R*)-7-Methyloctahydro-5-indolizinone [(+)-33]. The above Raney nickel–EtOH procedure was followed to reduce **15** but conducted at 25 °C for 2 h under hydrogen (1 atm) and gave a 68% yield of (+)-**33** and 20% yield of (−)-**34**. (+)-**33**: $[\alpha]^{22}_D$ = +8.0° (*c* 0.25, CH_2Cl_2); ^{1}H NMR δ 3.57 (m, 1 H, 8aH), 3.43 (m, 2 H, 3-H), 2.50 (d, *J* = 13 Hz, 1 H, 6-H), 2.1–1.7 (m, 7 H), 1.41 (m, 1 H), 1.02 (d, *J* = 7 Hz, 3 H, Me); ^{13}C NMR δ 168.9 (s, CO), 59.0 (d, C8a), 44.5 (t, C3), 39.7 (t, C6), 37.6 (t), 33.3 (t), 28.5 (d, C7), 22.2 (t), 21.6 (q, Me); MS *m/z* EI 153 (M^+), 136, 111, 83, 74, 70, 61 (100). Anal. Calcd for $C_9H_{15}NO$: C, 70.55; H, 9.87. Found: C, 70.27; H, 10.05.

(−)-(7*S*,8a*S*)-7-Methyloctahydro-5-indolizinone [(−)-33]. The above Raney nickel–EtOH procedure was followed to reduce **16** but conducted at 25 °C for 2 h under hydrogen (1 atm) and gave a 65% yield of (−)-**33** and 18% yield of (+)-**34**. (−)-**33**: $[\alpha]^{22}_D$ = −8.0° (*c* 0.25, CH_2Cl_2). Spectral data are identical with those of (+)-**33**.

(−)-(7*R*)-1,2,3,5,6,7-Hexahydro-7-methyl-5-indolizinone [(−)-34]: $[\alpha]^{22}_D$ = −21.4° (*c* 0.30, CH_2Cl_2); ^{1}H NMR δ 4.85 (broad s, 1 H, =CH), 3.9–3.7 (m, 2 H, CH_2N), 2.57–2.47 (m, 4 H), 2.12–2.02 (m, 3 H), 1.02 (d, *J* = 6 Hz, 3 H, Me); MS *m/z* 151 (M^+), 149, 136. Anal. Calcd for $C_9H_{13}NO$: C, 71.49; H, 8.67. Found: C, 71.31; H, 8.88.

(5a*S*,9a*S*,10a*R*)-Dodecahydro-5-oxopyrrolo[1,2-*b*]isoquinoline (35). The above Raney nickel–EtOH procedure was followed to reduce **25** but conducted at 25 °C for 1 h under hydrogen (1 atm) and gave a 75% yield of (+)-**35**: $[\alpha]^{22}_D$ = +34.6° (*c* 0.37, CH_2Cl_2); ^{1}H NMR δ 3.54 (m, 1 H, 10a-H), 3.40 (m, 2 H, 3-H), 2.35 (dt, *J* = 12, 5 Hz, 1 H, 5a-H), 2.30 (m, 2 H), 1.93 (m, 2 H), 1.8–1.7 (m, 3 H), 1.68–1.55 (m, 3 H), 1.48–1.4 (m, 3 H), 1.38–1.25 (m, 2 H); ^{13}C NMR δ 172.6 (s, CO), 58.9 (d, C10a), 44.4 (t, C3), 42.3 (d, C5a), 33.5 (t), 32.8 (d, C9a), 30.9 (t), 30.5 (t), 26.8 (t), 25.8 (t), 22.2 (t), 21.4 (t); MS *m/z* EI 193 (M^+). Anal. Calcd for $C_{12}H_{19}NO$: C, 74.57; H, 9.91. Found: C, 74.39; H, 10.28.

(5a*R*,9a*S*,10a*R*)- and (5a*R*,9a*S*,10a*S*)-Dodecahydro-5-oxopyrrolo[1,2-*b*]isoquinolines (36 and 37). The above Raney nickel–EtOH procedure was followed to reduce **26** but conducted at 25 °C for 2.5 h under hydrogen (1 atm) and gave a mixture of **36** and **37** (80% yield; 1:1, measured from the ^{13}C NMR spectrum): $[\alpha]^{22}_D$ = +9.5° (*c* 0.2, CH_2Cl_2); ^{1}H NMR δ 3.67–3.54 (m, 1 H, CHN), 3.49–3.36 (m, 1 H, CHN), 2.43 (d, *J* = 13 Hz, 0.5 H), 2.19 (d, *J* = 12 Hz, 0.5 H), 2.15–1.1 (m, 16 H); ^{13}C NMR δ 172.6 (s, CO), 170.7 (s, CO), 59.0 (d, C10a), 54.3 (d, C10a), 47.4 (t, C3), 44.9 (t, C3), 44.5 (d, C5a), 44.3 (d, C5a), 39.3 (t), 36.1 (t), 35.8 (d, C9a), 35.3 (d, C9a), 34.7 (t), 33.7 (t), 33.4 (t), 33.4 (t), 27.7 (t), 26.7 (t), 26.6 (t), 25.9 (t), 25.9 (t), 25.7 (t), 23.0 (t), 22.2 (t); MS *m/z* EI 193 (M^+). Anal. Calcd for $C_{12}H_{19}NO$: C, 74.57; H, 9.91. Found: C, 74.38; H, 10.03.

3,4-Dihydro-1-methyl-β-carboline (39).[26] Harmalan (**39**) was prepared from 3-[2-(*N*-acetylamino)ethyl]indole and P_2O_5 in refluxing xylene[26] in 90% yield: ^{1}H NMR δ 8.56 (bs, 1 H, NH), 7.59 (d, *J* = 8 Hz, 1 H, Ar), 7.39 (d, *J* = 8 Hz, 1 H, Ar), 7.28 (t, *J* = 8 Hz, 1 H, Ar), 7.15 (t, *J* = 8 Hz, 1 H, Ar), 3.87 (t, *J* = 8 Hz, 2 H, CH_2N), 2.87 (t, *J* = 8 Hz, 2 H, CH_2), 2.38 (s, 3 H, CH_3); ^{13}C NMR δ 158.3 (s), 137.1 (s), 129.3 (s), 125.5 (s), 124.3 (d), 120.1 (d), 120.0 (d), 116.3 (s), 112.1 (d), 38.0 (t), 21.8 (t), 19.4 (q).

(+)-(*R*)-3,4-Dihydro-1-[[(4-methylphenyl)sulfinyl]methyl]-β-carboline [(+)-38]. To a cold (0 °C) solution of 1.54 g (8.37 mmol) of β-carboline **39** in 20 mL of THF under argon was added a cold (−25 °C) solution of 16.7 mmol of LDA in 5 mL of THF and 10 mL of hexane via cannula. The brown solution was stirred at 0 °C for 15 min and then cooled to −78 °C. To this solution was added a solution of 1.23 g (4.19 mmol) of (−)-(*S*)-*l*-menthyl *p*-toluenesulfinate (**8S**)[11] in 5 mL of THF via cannula. After the orange solution was stirred at −78 °C for 1 h, it was poured into 100 mL of H_2O and 100 mL of CH_2Cl_2, and the aqueous layer was extracted with CH_2Cl_2 three times (100 mL each). The combined CH_2Cl_2 extracts were washed with brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel, using a gradient mixture of hexane and methanol as eluant, to give 1.30 g (95% yield based on **8S**) of (+)-**38** and 0.616 g (40% recovery) of **39**: $[\alpha]^{22}_D$ = +411° (*c* 0.66, CH_2Cl_2); mp 160 °C dec; ^{1}H NMR δ 9.49 (bs, 1 H, NH), 7.56 (d, *J* = 8 Hz, 1 H, Ar), 7.47 (d, *J* = 8 Hz, 1 H, Ar), 7.43 (d, *J* = 8 Hz, 2 H, Tol), 7.3 (t, *J* = 8 Hz, 1 H, Ar), 7.27 (d, *J* = 8 Hz, 2 H, Tol), 7.15 (d, *J* = 8 Hz, 1 H, Ar), 4.19 (d, *J* = 13 Hz, 1 H, CHS), 3.95 (d, *J* = 13

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Hz, 1 H, CHS), 3.84 (dt, J = 15 Hz, 8 Hz, 1 H, CHN), 3.41 (dt, J = 15 Hz, 9 Hz, 1 H, CHN), 2.77 (m, 2 H, CH_2), 2.38 (s, 3 H, CH_3); ^{13}C NMR δ 153.9 (s), 142.1 (s), 137.5 (s), 129.9 (d, 2 C), 128.9 (s), 125.2 (s), 124.7 (d), 124.3 (d, 2 C), 120.2 (d), 120.0 (d), 119.5 (s), 117.7 (s), 112.9 (d), 63.7 (t), 49.1 (t), 21.4 (t), 19.4 (q). Anal. Calcd for $C_{19}H_{18}N_2OS$: C, 70.78; H, 5.63. Found: C, 70.51; H, 5.79.

(-)-(*S*)-3,4-Dihydro-1-[[(4-methylphenyl)sulfinyl]methyl]-β-carboline [(-)-38]. Following the same procedure as those of (+)-38 but using (+)-(*R*)-*d*-menthyl *p*-toluenesulfinate (8R), (-)-38 was obtained in 90% yield; $[\alpha]^{22}_D$ = -410° (*c* 0.66, CH_2Cl_2).

(-)-(*S*)-2,3,4,6,7,12-Hexahydro-1-[(4-methylphenyl)sulfinyl]-4-oxoindolo[2,3-*a*]quinolizine (40). To a cold (-78 °C) solution of 1.61 g (5 mmol) of (+)-38 in 24 mL of THF was added a cold (-25 °C) solution of 6 mmol of LDA in 7 mL of THF and 3 mL of hexane. After the yellow solution was stirred at -78 °C for 1 h, 0.516 g (6 mmol) of methyl acrylate was added via syringe. The solution was stirred at 25 °C for 5 h, diluted with 100 mL of H_2O, and extracted three times with CH_2Cl_2 (100 mL each). The combined organic extracts were washed with water and brine, dried ($MgSO_4$), and concentrated, and the residue was column chromatographed on silica gel, using gradient mixtures of hexane and ethyl acetate, and ethyl acetate and MeOH as eluant, to give 1.46 g (77% yield) of (-)-40 and 0.19 g (12% recovery) of (+)-38: $[\alpha]^{22}_D$ = -550° (*c* 0.115, CH_2Cl_2); mp 105-106 °C; ^1H NMR δ 9.63 (s, 1 H, NH), 7.56 (d, J = 8 Hz, 1 H), 7.52 (d, J = 8 Hz, 1 H), 7.46 (d, J = 8 Hz, 2 H, Tol), 7.3 (td, J = 8 Hz, 1 Hz, 1 H), 7.22 (d, J = 8 Hz, 2 H, Tol), 7.15 (td, J = 8 Hz, 1 Hz, 1 H), 4.43 (dt, J = 13 Hz, 5 Hz, 1 H, CHN), 3.9 (dt, J = 13 Hz, 7 Hz, 1 H, CHN), 2.96 (t, J = 6 Hz, 2 H), 2.71 (dt, J = 16 Hz, 6 Hz, 1 H), 2.47 (m, 2 H), 2.36 (s, 3 H, CH_3), 2.1 (m, 1 H); ^{13}C NMR δ 169.4 (C=O), 141.0, 138.4, 138.1, 135.6, 129.7, 125.3, 125.1, 124.9, 124.1, 120.3, 119.2, 118.6, 117.1, 102.2, 39.9, 31.5, 21.1, 20.6, 15.9; MS m/z FAB 377 (M + 1), 376. Anal. Calcd for $C_{22}H_{20}N_2O_2S$: C, 70.19; H, 5.35. Found: C, 69.93; H, 5.57.

(+)-(1*R*,12b*R*,S*R*)-1-[(4-Methylphenyl)sulfinyl]-1,2,3,4,6,7,12,12b-octahydro-4-oxoindolo[2,3-*a*]quinolizine (41) and (+)-(1*S*,12b*S*,S*R*)-1-[(4-Methylphenyl)sulfinyl]-1,2,3,4,6,7,12,12b-octahydro-4-oxoindolo[2,3-*a*]quinolizine (42). To a solution of 2.5 g (6.65 mmol) of (-)-40 in 54 mL of acetic acid was added 0.835 g (13.3 mmol) of $NaCNBH_3$. The solution was stirred at 25 °C for 2.5 h and carefully neutralized with a solution of 37.8 g of NaOH in 150 mL of H_2O. The solid precipitate was collected by filtration, washed with water, and column chromatographed on silica gel, using a gradient mixture of CH_2Cl_2 and MeOH [MeOH is needed to dissolve (+)-42] as eluant to give 1.47 g (59% yield) of (+)-41 and 0.792 g (32% yield) of (+)-42.

(+)-41: $[\alpha]^{22}_D$ = +444° (*c* 0.28, CH_2Cl_2); mp 200-202 °C; ^1H NMR δ 8.83 (s, 1 H, NH), 7.58 (d, J = 8 Hz, 2 H, Tol), 7.47 (d, J = 8 Hz, 1 H), 7.45 (d, J = 8 Hz, 1 H), 7.36 (d, J = 8 Hz, 2 H, Tol), 7.2 (t, J = 8 Hz, 1 H), 7.09 (t, J = 8 Hz, 1 H), 4.77 (dd, J = 13 Hz, 6 Hz, 1 H, C6H), 4.6 (bs, 1 H, C12bH), 3.25 (ddd, J = 13 Hz, 3 Hz, 2 Hz, 1 H, CHS), 3.15 (m, 1 H, C6H), 2.77 (td, J = 13 Hz, 5 Hz, 1 H, C7H), 2.58 (m, 3 H), 2.42 (s, 3 H, CH_3), 2.35 (m, 1 H), 2.19 (m, 1 H); ^{13}C NMR δ 170.0 (C=O), 142.7, 135.7, 130.6, 129.5, 128.9, 124.4, 124.1, 122.2, 119.4, 118.0, 112.0, 111.4, 62.6, 56.0, 45.0, 32.6, 21.5, 21.2, 20.2; MS m/z FAB 379 (M + 1). Anal. Calcd for $C_{22}H_{20}N_2O_2S$: C, 69.81; H, 5.86. Found: C, 69.56; H, 6.01.

(+)-42: $[\alpha]^{22}_D$ = +149° [*c* 0.15, $CHCl_3$-MeOH (1:1)]; mp 185-188 °C; ^1H NMR δ 9.41 (broad s, 1 H, NH), 7.5 (d, J = 8 Hz, 1 H), 7.4 (d, J = 8 Hz, 2 H, *o*-H), 7.31 (d, J = 8 Hz, 1 H), 7.24 (d, J = 8 Hz, 2 H, *m*-H), 7.19 (t, J = 8 Hz, 1 H), 7.12 (t, J = 8 Hz, 1 H), 5.44 (s, 1 H, C12b-H), 4.96 (dd, J = 12, 5 Hz, 1 H, C6-H), 3.71 (m, 1 H, C6-H), 3.28 (m, 1 H), 3.14 (m, 1 H), 3.03 (td, J = 12, 4 Hz, 1 H), 2.75 (dd, J = 16, 4 Hz, 1 H), 2.61 (m, 1 H), 2.4 (s, 3 H, *p*-Me), 2.7 (m, 1 H), 1.85 (m, 1 H); ^{13}C NMR (DMSO-d_6) 170.7 (s, CO), 140.6 (s), 140.0 (s), 136.9 (s), 130.2 (s), 129.8 (d, 2 C, Tol), 126.2 (s), 124.0 (d, 2 C, Tol), 121.7 (d), 119.0 (d), 118.3 (d), 111.6 (d), 110.5 (s), 69.9 (d, C12b), 62.0 (d, CS), 53.7 (t), 29.8 (t), 21.0 (t), 20.3 (t), 16.0 (q); MS m/z FAB 379 (M + 1), 378. Anal. Calcd for $C_{22}H_{20}N_2O_2S$: C, 69.81; H, 5.86. Found: C, 69.93; H, 6.03.

(-)-(*S*)-1,2,3,4,6,7,12,12b-Octahydro-4-oxoindolo[2,3-*a*]quinolizine [(-)-43].[27] To a solution of 0.5 g (1.32 mmol) of sulfoxide 41 in 25 mL of EtOH and 25 mL of THF under argon was added 0.5 g of W-2 Raney nickel. The mixture was then stirred at 65 °C for 3 h, cooled to 25 °C, diluted with CH_2Cl_2, and filtered through Celite. The filtrate was concentrated and column chromatographed on silica gel, using a mixture of CH_2Cl_2 and MeOH as eluant to give 0.299 g (94% yield) of (-)-43: $[\alpha]^{22}_D$ = -230° (*c* 1.02, $CHCl_3$) (lit.[8b] $[\alpha]^{22}_D$ -23°); mp 244-247 °C (lit.[8b] mp 245-247 °C); ^1H NMR δ 8.4 (bs, 1 H, NH), 7.5 (d, J = 7 Hz, 1 H), 7.33 (d, J = 7 Hz, 1 H), 7.18 (t, J = 7 Hz, 1 H), 7.12 (t, J = 7 Hz, 1 H), 5.17 (m, 1 H), 4.78 (m, 1 H), 2.87 (m, 2 H), 2.77 (m, 1 H), 2.5 (m, 1 H), 2.48 (m, 2 H), 2.0-1.7 (m, 3 H); ^{13}C NMR δ 169.3 (C=O), 136.3 (s), 133.4 (s), 126.8 (s), 122.0 (d), 119.7 (d), 118.3 (d), 111.0 (d), 109.3 (s), 54.5 (d), 40.2 (t), 32.4 (t), 29.0 (t), 21.0 (t), 19.3 (t); MS m/z FAB 241 (M + 1), 240.

(+)-(*R*)-1,2,3,4,6,7,12,12b-Octahydro-4-oxoindolo[2,3-*a*]quinolizine [(+)-43]. Following the same procedure described above, but starting with sulfoxide (+)-42, a 92% yield of (+)-43 was obtained; $[\alpha]^{22}_D$ = +227° (*c* 1.02, $CHCl_3$).

(-)-(*S*)-1,2,3,4,6,7,12,12b-Octahydroindolo[2,3-*a*]quinolizidine (1).[27] To a solution of 0.4 g (1.67 mmol) of lactam (-)-43 in 24 mL of THF under argon was added 0.252 g (6.63 mmol) of lithium aluminum hydride. The mixture was stirred at 25 °C for 5 h, and the excess of $LiAlH_4$ was carefully destroyed with 0.3 mL of H_2O at 0 °C. To the mixture was added 20 mL of 1 N NaOH and 100 mL of CH_2Cl_2, and the white precipitate was removed by filtration through Celite. The filtrate was extracted three times with CH_2Cl_2. The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated, and the residue was column chromatographed on silica gel, using a gradient mixture of ethyl acetate and MeOH as eluant, to give 0.332 g (88% yield) of (-)-1: $[\alpha]^{22}_D$ = -82° (*c* 1, MeOH) (lit.[8d] $[\alpha]^{22}_D$ -84°); mp 146-149 °C; ^1H NMR δ 7.81 (s, 1 H, NH), 7.46 (d, J = 8 Hz, 1 H), 7.29 (d, J = 8 Hz, 1 H), 7.11 (t, J = 8 Hz, 1 H), 7.08 (t, J = 8 Hz, 1 H), 3.31 (d, J = 12 Hz, 1 H), 3.08 (m, 3 H), 2.67 (m, 2 H), 2.4 (m, 2 H), 2.07 (m, 1 H), 1.84 (m, 1 H), 1.75 (m, 2 H), 1.6 (m, 1 H); ^{13}C NMR δ 136.0 (s, C11a), 135.2 (s, C12a), 127.4 (s, C7b), 121.3 (d, C10), 119.4 (d, C9), 118.1 (d, C8), 110.7 (d, C11), 108.1 (s, C7a), 60.0 (d, C12b), 55.3 (t, C4), 53.3 (t, C6), 29.7 (t, C1), 25.4 (t, C3), 24.1 (t, C2), 21.3 (t, C7); MS m/z EI 227, 226 (M^+).

(S*R*,15*R*,20*S*)-3,14-Didehydro-14-[(4-methylphenyl)sulfinyl]alloyohimban (44) and (S*R*,15*S*,20*R*)-3,14-Didehydro-14-[(4-methylphenyl)sulfinyl]alloyohimban (45). To a cold (-50 °C) solution of 1.65 g (5.12 mmol) of (-)-38 in 20 mL of THF was added a cold (-25 °C) solution of 6.15 mmol of LDA in 5 mL of THF and 3.8 mL of hexane. After the yellow solution was stirred at -50 °C for 1 h, 0.86 g (6.15 mmol) of methyl 1-cyclohexenecarboxylate (24) was added via syringe. The solution was stirred at 60 °C for 14 h, cooled to 25 °C, diluted with 200 mL of H_2O, and extracted four times with CH_2Cl_2 (100 mL each). The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated, and the residue was column chromatographed on silica gel, using gradient mixtures of hexane and ethyl acetate, and ethyl acetate and MeOH as eluant, to give 0.925 g (42% yield) of less polar isomer 44, 0.11 g (5% yield) of more polar isomer 45, and 0.578 g (35% recovery) of sulfinyl ketimine (-)-38.

44: (less polar; TLC solvent: 2% THF in CH_2Cl_2); $[\alpha]^{22}_D$ = +342° (*c* 0.52, CH_2Cl_2); ^1H NMR δ 9.71 (s, 1 H, NH), 7.57 (d, J = 8 Hz, 1 H, Ar), 7.44 (d, J = 8 Hz, (s), 7.31 (t, J = 8 Hz, 1 H, Ar), 7.23 (d, J = 8 Hz, 2 H, Tol), 7.17 (t, J = 8 Hz, 1 H, Ar), 5.24 (ddd, J = 11, 3, 2 Hz, 1 H, CHN), 3.24 (td, J = 11, 4 Hz, 1 H, CHN), 2.95 (m, 2 H, CH_2Ar), 2.5 (m, 1 H), 2.37 (s, 3 H, CH_3), 2.33 (d, J = 10 Hz, 1 H), 2.27 (d, J = 3 Hz, 1 H), 1.92 (d, J = 13 Hz, 1 H), 1.7-1.2 (m, 6 H); ^{13}C NMR δ 170.7 (s, C=O), 140.9 (s), 140.9 (s), 140.4 (s), 138.2 (s), 134.1 (s), 129.8 (d), 125.7 (s), 125.1 (d), 124.9 (d), 124.1 (d), 120.6 (s), 120.3 (d), 119.3 (d), 118.7 (s), 112.2 (d), 41.4 (d), 40.2 (t), 32.8 (d), 29.6 (t), 25.7 (t), 25.4 (t), 21.6 (t), 21.2 (q), 21.0 (t); HRMS calcd for $C_{26}H_{26}N_2O_2S$ 430.554, found 430.554; MS m/z FAB 431 (M + 1), 413 (M - 18), 369, 246, 211, 185 (100), 167, 154, 137, 93, 75. Anal. Calcd for $C_{26}H_{26}N_2O_2S$: C, 72.53; H, 6.09. Found: C, 72.37; H, 6.28.

45: (more polar; TLC solvent: 2% THF in CH_2Cl_2); $[\alpha]^{22}_D$ = +229° (*c* 0.91, CH_2Cl_2); ^1H NMR δ 9.37 (s, 1 H, NH), 7.58 (d, J = 8 Hz, 2 H, Tol), 7.57 (d, J = 7 Hz, 1 H), 7.39 (d, J = 7 Hz, 1

(27) Spectral data were identical with those reported.[8b,d,9d,f]

H), 7.3 (t, J = 7 Hz, 1 H), 7.26 (d, J = 8 Hz, 2 H, Tol), 7.14 (t, J = 7 Hz, 1 H), 5.29 (ddd, J = 14, 3, 2 Hz, 1 H, CHN), 3.2 (td, J = 14, 5 Hz, 1 H, CHN), 3.1–2.88 (m, 2 H, CH_2Ar), 2.73 (m, 1 H), 2.67 (bs, 1 H), 2.44 (d, J = 10 Hz, 1 H), 2.39 (s, 3 H, CH_3), 1.7–0.8 (m, 7 H); ^{13}C NMR δ 171.4 (C=O), 141.1, 140.0, 138.0, 133.9, 130.2, 130.0, 126.0, 125.2, 125.1, 124.4, 120.5, 119.5, 119.2, 112.0, 45.5, 41.0, 36.2, 33.1, 29.7, 28.0, 22.5, 21.3, 20.9; MS m/z EI 431 (M + 1), 430 (M^+), 414, 383, 382, 371, 365, 339 (100). Anal. Calcd for $C_{26}H_{26}N_2O_2S$: C, 72.53; H, 6.09. Found: C, 72.40; H, 6.28.

(−)-Alloyohimban-21-one [(−)-46]. To a solution of 0.4 g (0.93 mmol) of **44** in 10 mL of EtOH was added 0.5 g of W-2 Raney nickel. After the mixture was stirred at 25 °C for 5 h, it was diluted with 50 mL of MeOH containing 5% of NH_4OH, filtered through Celite, and concentrated, and the residue was column chromatographed on silica gel, using gradient mixtures of hexane and ether, and ether and MeOH as eluant, to give 0.24 g (88% yield) of (−)-**46**: $[\alpha]^{22}_D$ = −153° (c 0.1, CH_2Cl_2); mp 195–198 °C; ^1H NMR δ 7.78 (s, 1 H, NH), 7.5 (d, J = 8 Hz, 1 H), 7.33 (d, J = 8 Hz, 1 H), 7.19 (t, J = 8 Hz, 1 H), 7.13 (t, J = 8 Hz, 1 H), 5.13 (q, J = 8 Hz, 1 H, C3H), 4.78 (dd, J = 11, 5 Hz, 1 H, CHN), 2.8 (m, 2 H), 2.55 (dt, J = 12, 5 Hz, 1 H), 2.31 (m, 1 H), 2.15 (q, J = 12 Hz, 1 H), 2.08 (m, 1 H), 1.96 (m, 1 H), 1.7–1.26 (m, 8 H); ^{13}C NMR δ 173.0 (C=O), 136.4, 133.8, 126.9, 122.0, 119.7, 118.3, 111.0, 109.0, 54.2, 43.3, 40.2, 30.6, 30.2, 29.8, 26.5, 25.6, 21.1, 21.0; MS m/z FAB 295 (M + 1). Anal. Calcd for $C_{19}H_{22}N_2O$: C, 77.52; H, 7.53. Found: C, 77.41; H, 7.73.

Following the same procedure but using isomer **45**, antipode (+)-**46** was isolated in 85% yield.

*The following procedure serves as the general method for the reduction of latams **46**, **47**, and **50** with $LiAlH_4$.*

(−)-Alloyohimban [(−)-2].[27] To a solution of 0.1 g (0.34 mmol) of (−)-3-alloyohimban-21-one [(−)-**46**] in 12 mL of THF under argon was added 26 mg (0.68 mmol) of lithium alumium hydride. After the mixture was stirred at 25 °C for 2 h, it was diluted with 0.1 mL of H_2O, 100 mL of CH_2Cl_2, and 10 mL of 0.5 N NaOH. The methylene chloride layer was separated, and the aqueous layer was extracted twice with CH_2Cl_2. The combined extract was washed with water and brine, dried ($MgSO_4$), and concentrated, and the residue was column chromatographed on silica gel, using a gradient mixture of hexane and ether as eluant, to give 88 mg (92% yield) of (−)-**2**: mp 156–157 °C (recrystallized from a mixture of ether and acetone) (lit.[9c] mp 156–157 °C); $[\alpha]^{22}_D$ = −166° (c 0.4, pyridine) (lit.[9c] $[\alpha]^{22}_D$ −166°); ^1H NMR δ 7.69 (bs, 1 H, NH), 7.45 (d, J = 8 Hz, 1 H), 7.27 (d, J = 8 Hz, 1 H), 7.11 (t, J = 8 Hz, 1 H), 7.07 (t, J = 8 Hz, 1 H), 3.18 (bd, J = 8 Hz, 1 H, C3H), 2.98 (m, 2 H), 2.75 (dd, J = 11.2, 1 Hz, 1 H), 2.67 (dd, J = 12, 4 Hz, 1 H), 2.55–2.48 (m, 2 H), 2.0–1.25 (series of m, 12 H); ^{13}C NMR[27] δ 136.0 (C13), 135.6 (C2), 127.6 (C8), 121.2 (C11), 119.3 (C10), 118.1 (C9), 110.7 (C12), 108.2 (C7), 60.5 (C21), 53.8 (C3), 53.4 (C5), 36.7 (C14), 34.8 (C15), 34.6 (C20), 30.5 (C19), 26.6 (C17), 26.5 (C18), 21.8 (C16), 20.8 (C6); MS m/z EI 280 (M^+), 279 (100), 278, 277, 235, 221, 199, 184, 168.

Yohimban-21-one (47). To a cold (−78 °C) solution of 0.2 g (0.68 mmol) of alloyohimban-21-one [(−)-**46**] in 4 mL of THF under argon was added a cold (−78 °C) solution of 1.7 mmol of LDA in 5 mL of THF via cannula. After the solution was stirred at −78 °C for 30 min and −20 °C for 30 min, the reaction was quenched with a solution of 0.102 g of AcOH in 1 mL of ether, diluted with 20 mL of H_2O, and extracted three times with CH_2Cl_2 (50 mL each). The combined extracts were washed with brine, dried ($MgSO_4$), concentrated, and the residue was column chromatographed on silica gel, using gradient mixtures of hexane and ether, and ether and MeOH as eluant, to give 0.144 g (72% yield) of **47** and 36 mg (18% recovery) of (−)-**46**: $[\alpha]^{22}_D$ = +215° [c 0.31, CH_2Cl_2–MeOH (1:1)]; mp 233–234 °C; ^1H NMR 7.88 (broad s, 1 H, NH), 7.5 (d, J = 8 Hz, 1 H, C12-H), 7.32 (d, J = 8 Hz, 1 H, C9-H), 7.17 (t, J = 8 Hz, 1 H), 7.13 (t, J = 8 Hz, 1 H), 5.16 (m, 1 H, C3-H), 4.79 (m, 1 H, C5-H), 2.84 (m, 2 H), 2.75 (m, 1 H), 2.48 (broad d, J = 14 Hz, 1 H), 2.34 (dd, J = 10, 5 Hz, 1 H), 1.9–1.77 (m, 4 H), 1.7–1.1 (series of m, 8 H); ^{13}C NMR [$CDCl_3$–CD_3OD (1:1)] δ 171.6 (s, CO), 136.3 (s), 133.6 (s), 126.4 (s), 121.5 (d), 119.1 (d), 117.9 (d), 110.9 (d), 108.1 (s), 54.0 (d, C3), 47.0 (d, C20), 40.3 (t), 36.1 (d, C15), 35.4 (t), 32.8 (t), 27.3 (t), 26.1 (t), 25.3 (t), 20.9 (t); MS m/z EI 294 (M^+). Anal. Calcd for $C_{19}H_{22}N_2O$: C, 77.52; H, 7.53. Found: C, 77.35; H, 7.81.

(−)-Yohimban [(−)-4].[28] Reduction of **47** with $LiAlH_4$ gave a 60% yield of (−)-**4**: $[\alpha]^{22}_D$ = −79° (c 0.34, EtOH) (lit.[9c] $[\alpha]^{22}_D$ −79.2°); mp 204–206 °C (lit.[9c] mp 206.5–207 °C); ^1H NMR δ 7.7 (broad s, 1 H, NH), 7.46 (d, J = 8 Hz, 1 H), 7.28 (d, J = 8 Hz, 1 H), 7.12 (t, J = 8 Hz, 1 H), 7.07 (t, J = 8 Hz, 1 H), 3.28 (dd, J = 10, 1.6 Hz, 1 H, C3-H), 3.08 (dd, J = 11, 6 Hz, 1 H), 3.01 (m, 1 H), 2.89 (dd, J = 11, 4 Hz, 1 H), 2.71 (dd, J = 15, 4 Hz, 1 H), 2.61 (td, J = 11, 5 Hz, 1 H), 2.12 (t, J = 11 Hz, 1 H), 1.98 (dt, J = 12, 3 Hz, 1 H), 1.8–1.0 (series of m, 11 H); ^{13}C NMR δ 136.0 (s, C13), 135.1 (s, C2), 127.6 (s, C8), 121.2 (d, C11), 119.3 (d, C10), 118.1 (d, C9), 110.7 (d, C12), 108.1 (s, C7), 62.1 (t, C21), 60.3 (d, C3), 53.2 (t, C5), 42.0 (d, C20), 42.0 (d, C15), 37.1 (t, C14), 32.9 (t, C16), 30.4 (t, C18), 26.4 (t, C19), 26.0 (t, C6), 21.8 (t, C17); MS m/z EI 280 (M^+).

(−)-(S*R*,14*R*)-14-[(4-Methylphenyl)sulfinyl]alloyohimban-21-one (48) and (−)-(S*R*,14*S*)-14-[(4-Methylphenyl)sulfinyl]-3-*epi*-alloyohimban-21-one (49). To a solution of 0.3 g (0.698 mmol) of enamide **44** in 18 mL of AcOH under argon was added 44 mg (0.7 mmol) of $NaCNBH_3$. The solution was stirred at 25 °C for 2 h, diluted with CH_2Cl_2, neutralized with 100 mL of 3 N NaOH, and extracted three times with CH_2Cl_2 (100 mL each). The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated, and the residue was column chromatographed on silica gel, using gradient mixtures of hexane and CH_2Cl_2, and CH_2Cl_2 and MeOH as eluant, to give 81 mg (26.7% yield) of **48** and 0.161 g (53.3% yield) of **49**.

Sulfoxide 48: $[\alpha]^{22}_D$ = −129° (c 0.15, CH_2Cl_2); ^1H NMR δ 10.25 (s, 1 H, NH), 7.7 (d, J = 8 Hz, 2 H, Tol), 7.52 (d, J = 8 Hz, 1 H), 7.44 (d, J = 8 Hz, 1 H), 7.35 (d, J = 8 Hz, 2 H, Tol), 7.21 (t, J = 8 Hz, 1 H), 7.12 (t, J = 8 Hz, 1 H), 5.35 (d, J = 7 Hz, 1 H, CHN), 5.12 (dd, J = 13, 4 Hz, 1 H, CHN), 3.23 (d, J = 7 Hz, 1 H, CHS), 2.99 (td, J = 12, 3 Hz, 1 H, CHN), 2.83 (m, 1 H), 2.71 (bs, 1 H), 2.48 (m, 1 H), 2.45 (s, 3 H, CH_3), 1.7–0.8 (m, 9 H); ^{13}C NMR δ 172.2 (s, C=O), 143.8 (s), 138.9 (s), 136.5 (s), 132.5 (s), 130.5 (d, 2 C), 126.7 (d, 2 C), 126.3 (s), 122.1 (d), 119.5 (d), 118.3 (d), 111.7 (d), 109.7 (s), 70.8, 70.5, 40.6, 38.9, 35.4, 30.4, 26.1, 25.7, 21.6, 21.2, 20.8. Anal. Calcd for $C_{26}H_{28}N_2O_2S$: C, 72.19; H, 6.52. Found: C, 72.01; H, 6.77.

Sulfoxide 49: $[\alpha]^{22}_D$ = −241° (c 0.85, CH_2Cl_2); ^1H NMR δ 8.52 (s, 1 H, NH), 7.57 (d, J = 8 Hz, 2 H, Tol), 7.47 (d, J = 8 Hz, 1 H), 7.44 (d, J = 8 Hz, 1 H), 7.35 (d, J = 8 Hz, 2 H, Tol), 7.19 (t, J = 8 Hz, 1 H), 7.08 (t, J = 8 Hz, 1 H), 4.67 (dd, J = 12, 6 Hz, 1 H, CHN), 4.48 (bs, 1 H, C3H), 3.49 (dd, J = 11, 3 Hz, 1 H, CHN), 3.16 (m, 1 H), 2.73 (td, J = 13, 5 Hz, 1 H), 2.6–2.5 (m, 3 H), 2.42 (s, 3 H, CH_3), 2.11 (dd, J = 11, 3 Hz, 1 H), 1.9 (bd, J = 13 Hz, 1 H), 1.76 (m, 1 H), 1.62 (m, 4 H), 1.42 (m, 1 H); ^{13}C NMR δ 173.9 (s, C=O), 142.5 (s), 135.6 (s), 135.0 (s), 130.7 (d, 2 C), 129.6 (s), 127.1 (s), 124.6 (d, 2 C), 122.0 (d), 119.3 (d), 118.0 (d), 112.0 (d), 111.1 (s), 61.6, 56.5, 44.9, 44.7, 30.9, 27.1, 26.2, 25.5, 21.5, 20.9, 20.0. Anal. Calcd for $C_{26}H_{28}N_2O_2S$: C, 72.19; H, 6.52. Found: C, 71.93; H, 6.81.

3-*epi*-Alloyohimban-21-one (50). The above Raney nickel–EtOH procedure [**44** → (−)-**46**] was followed to reduce **49** and gave 85% yield of **50**: $[\alpha]^{22}_D$ = +118° (c 0.3, CH_2Cl_2); mp 236–238 °C; ^1H NMR δ 7.78 (s, 1 H, NH), 7.46 (d, J = 8 Hz, 1 H), 7.29 (d, J = 8 Hz, 1 H), 7.14 (t, J = 8 Hz, 1 H), 7.08 (t, J = 8 Hz, 1 H), 5.16 (dd, J = 13, 4 Hz, 1 H, CHN), 4.88 (dd, J = 10, 5 Hz, 1 H, CHN), 2.8 (m, 2 H, CH_2Ar), 2.72 (dd, J = 14, 2 Hz, 1 H), 2.5 (m, 2 H), 2.32 (dt, J = 13, 5 Hz, 1 H), 2.06 (m, 1 H), 1.91 (td, J = 13, 3 Hz, 1 H), 1.74 (m, 1 H), 1.7–1.2 (m, 6 H); ^{13}C NMR δ 171.0 (C=O), 136.2, 134.0, 127.1 122.0, 119.8, 118.3, 110.9, 109.7, 51.4, 42.3, 40.6, 33.2, 32.3, 28.0, 27.0, 25.1, 23.1, 21.2. Anal. Calcd for $C_{19}H_{22}N_2O$: C, 77.52; H, 7.53. Found: C, 77.37; H, 7.80.

(+)-3-*epi*-Alloyohimban (3).[28] The above $LiAlH_4$ procedure was followed to reduce **50** and gave 80% yield of **3**: mp 210–213 °C (lit.[9c] mp 213.5–214 °C); $[\alpha]^{22}_D$ = +188° (c 0.4, pyridine) (lit.[9c] $[\alpha]^{22}_D$ +190.4°); ^1H NMR δ 7.76 (bs, 1 H, NH), 7.45 (d, J = 8 Hz, 1 H, Ar), 7.28 (d, J = 8 Hz, 1 H, Ar), 7.11 (t, J = 8 Hz, 1 H, Ar), 7.09 (t, J = 8 Hz, 1 H, Ar), 3.48 (q, J = 7 Hz, 1 H, C3H), 3.1–2.96 (m, 2 H, CH_2Ar), 2.73–2.58 (m, 4 H, CH_2N), 2.2 (m, 1 H), 2.0–1.23 (m, 11 H); ^{13}C NMR δ 136.0 (C13), 135.4 (C2), 127.6 (C8), 121.2

(28) ^{13}C NMR data of yohimban alkaloids have been summarized: Wenkert, E.; Chang, C.-J.; Chawla, H. P. S.; Cochran, D. W.; Hagaman, E. W.; King, J. C.; Orito, K. *J. Am. Chem. Soc.* **1976**, *98*, 3645. However, some chemical shifts were not the same, our data are reported.

(C11), 119.3 (C10), 118.0 (C9), 110.7 (C12), 108.3 (C7), 62.1 (C21), 60.3 (C3), 53.4 (C5), 37.0 (C20), 34.8 (C15), 32.8 (C14), 29.7 (C16), 26.7 (C18), 26.3 (C19), 21.8 (C6), 20.8 (C17); MS m/z EI 281, 280 (M^+, 100), 279, 265, 251, 237, 223, 209, 197, 184, 169, 156.

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Registry No. (-)-1, 10252-12-7; (-)-2, 483-26-1; (+)-3, 483-25-0; (-)-4, 523-06-8; (+)-5, 123642-79-5; 6, 1519-39-7; 8S, 1517-82-4; 9, 123642-81-9; 10, 123642-82-0; 11, 123749-02-0; 12, 89772-92-9; 14, 623-43-8; 15, 137119-54-1; 16, 137119-55-2; 17, 623-70-1; 18, 6284-46-4; 19, 137008-15-2; 20, 4358-59-2; 21, 10267-94-4; 22, 123642-83-1; 23, 123749-03-1; 24, 18448-47-0; 25, 137008-16-3; 26, 137119-56-3; 30, 137008-17-4; 31, 137008-18-5; 32, 137119-57-4; (+)-33, 137008-19-6; (-)-33, 137119-58-5; (+)-34, 137008-20-9; (-)-34, 137008-21-0; 35, 137008-22-1; 36, 137119-59-6; 37, 137119-60-9; (+)-38, 123642-80-8; (-)38, 137008-23-2; 39, 525-41-7; 46, 123642-84-2; 41, 137119-61-0; 42, 123642-85-3; (+)-43, 137119-62-1; (-)-43, 103321-76-2; 44, 137119-63-2; 45, 137119-64-3; *+)-46, 137119-65-4; (-)-46, 137119-66-5; 47, 137119-67-6; 48, 137119-68-7; 49, 137120-71-9; 50, 137119-69-8; CH_2=$CHCO_2Me$, 96-33-3; $BrCCH_2)_3CN$, 5332-06-9; $BrCCH_2)_2CO_2Et$, 539-74-2.

Supplementary Material Available: Two-dimensional COSY ^1H NMR spectra for 41, 44, and 50 (5 pages). Ordering information is given on any current masthead page.

Singlet Oxygen Oxidation of Substituted Furans to 5-Hydroxy-2(5*H*)-furanone[1]

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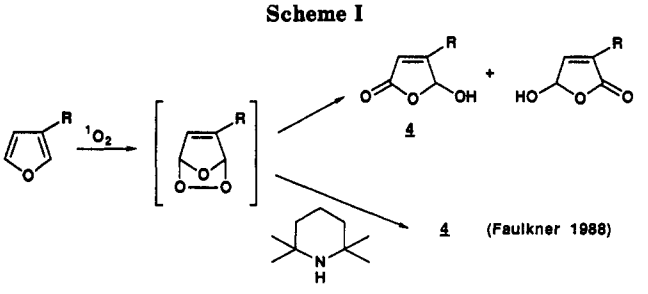
The conditions for the regiospecific singlet oxygen oxidation of various 2,4-disubstituted furans **9** to 4-substituted-2(5*H*)-furanones **3** are developed. The presence of a C-2 substituent (e.g., trimethylsilyl, *tert*-butyldimethylsilyl, or tributylstannyl) in **9** is an absolute requirement for the formation of the 4-substituted-5-hydroxy-2(5*H*)-furanone regioisomer **3**. When the C-2 substituent is triethylsilyl (TES) or TBDMS, however, apart from **3**, the corresponding 5-trialkylsiloxy derivative **11** is also isolated in a significant amount. These silyl acetals are unexpectedly stable but can be hydrolyzed back to **3** on stirring with dilute acid. The formation of silyl acetals, to our knowledge, has never been reported in the singlet oxygen oxidation of (trialkylsilyl)furan. A plausible mechanism for their formation is proposed. The presence of a catalytic amount of water in the oxidation of 2-(trialkylsilyl)-4-substituted-furans not only eliminates the formation of the silyl acetals but also speeds up the rate of the oxidation process. Moreover, the oxidation can then be carried out at 0 °C instead of at -78 °C. Oxidation of 2-(1-hydroxyalkyl)-4-substituted-furans in the absence of a reducing agent gives little or no sign of 2,5-disubstituted-6-hydroxy-3(2*H*)-pyranone **23** but instead **26** selectively. Thus, the (1-hydroxy)alkyl group can be utilized as the trialkylsilyl or trialkylstannyl group in dictating the regioselectivity in the singlet oxygen oxidation of substituted furans.

Introduction

The antiinflammatory properties of manoalide (**1**)[2] and luffarielloide (**2**)[3] in vivo have stimulated interest in developing a general and versatile method for constructing the 5-hydroxy-2(5*H*)-furanone nucleus. As part of our ongoing manoalide program, we desired to develop an efficient synthesis of a series of 4-substituted-5-hydroxy-2(5*H*)-furanones that contained an α-acetoxy group on the 4-alkyl chain (**3**). Herein we report the details of our general synthesis of this group based upon a thorough study of singlet oxygen oxidation of furans.

Scheme I



Results and Discussion

A number of methods have been developed for the synthesis of 5-hydroxy-2(5*H*)-furanones;[4] however, the one

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