Asymmetric Total Synthesis of (−)-Lupinine and (+)-Epilupinine via α-Sulfinyl Ketimine. Stereocontrolled Reduction of β-Sulfinyl Enamines

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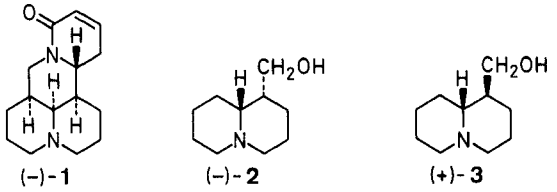
(−)-Lupinine and (+)-epilupinine [(1*R*,9a*R*)- and (1*S*,9a*R*)-octahydro-1-hydroxymethyl-2*H*-quinolizine] were synthesized from (+)-2,3,4,5-tetrahydro-6-[(*R*)-(4-methylphenyl)sulfinylmethyl]pyridine (**4**) in five steps. The intermediate, 3,4,6,7,8,9-hexahydro-1-[(*R*)-(4-methylphenyl)sulfinyl]-2*H*-quinolizine (**7**), was stereoselectively reduced with cerium(III) chloride heptahydrate and sodium borohydride to give predominantly C-9a-*R* isomers, (9a*R*)-octahydro-1-[(*R*)-(4-methylphenyl)sulfinyl]-2*H*-quinolizines.

The facile annulation of α-sulfinyl-ketimine anions with 1,3-diiodopropane[3] has prompted us to investigate the construction of quinolizidine alkaloids and the stereocontrolled reduction of the resulting cyclic chiral β-sulfinyl enamines. Over sixty lupin alkaloids have been isolated from various plants of *Leguminosae*, *Berberidaceae*, and *Chenopodiaceae*.[4−7] The great majority of lupin alkaloids contain the quinolizidine ring. During the studies of the total synthesis of the antitumor agent (−)-sophocarpine [(−)-**1**][8−15] we investigated the two simplest lupin alkaloids, (−)-lupinine [(−)-**2**][16−19] and (+)-epilupinine [(+)-**3**].[20−22] We now report the asymmetric total syntheses of these two lupin alkaloids via annulation of the α-sulfinyl ketimine and subsequent stereocontrolled reduction of the β-sulfinyl enamine.

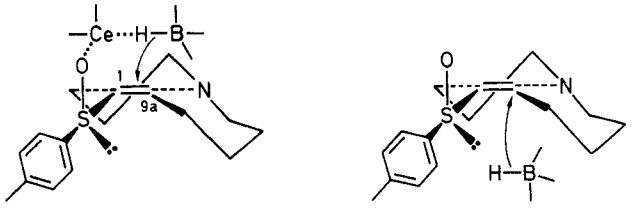


The construction of the quinolizidine ring system followed the same scheme we previously described[3] starting from sulfinyl ketimine **4**. Metallation of 2,3,4,5-tetrahydro-6-methylpyridine (**5**)[23] with lithium diisopropylamide (LDA) in tetrahydrofuran followed by treatment with (−)-(1*R*,2*S*,5*R*)-menthyl (*S*)-(4-methylbenzene)sulfinate (**6S**)[24] gave a 92% yield of (+)-**4** (Scheme **1**). Treatment of (+)-**4** with 1.5 equivalents of LDA in tetrahydrofuran followed by 1.1 equivalents of 1,3-diiodopropane provided β-enamino sulfoxide **7** in 62% yield. Various hydridic reducing agents have been studied for the reduction of the cyclic alkenyl group of enamine **7** and the results are presented in the Table.

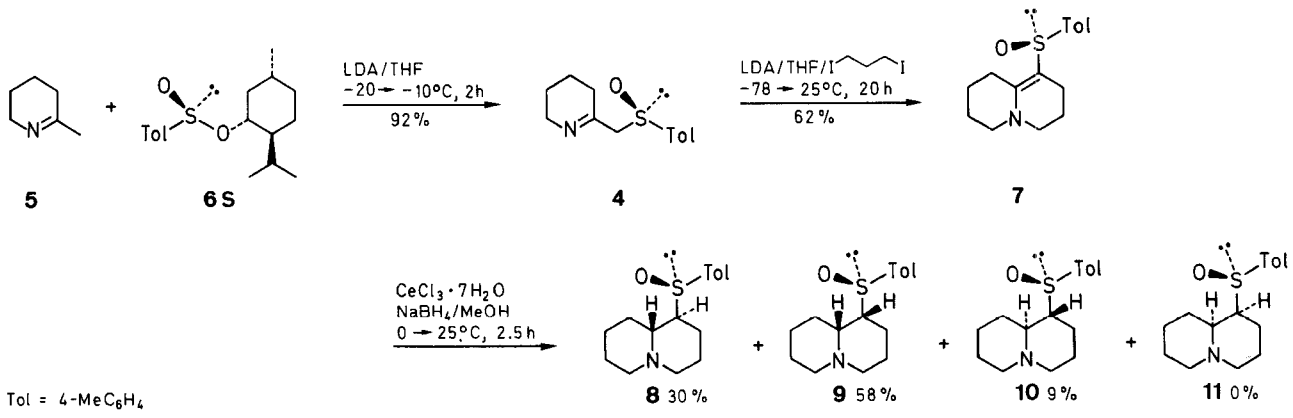
Table. Hydride Reduction of β-Sulfinyl Enamine **7** in MeOH

Entry	Reducing Agent	Conditions		Products Yield (%)			
		Temp. (°C)	Time	**8**	**9**	**10**	**11**
1	$NaBH_4$	0	10 min	–	36	–	59
		25	3 h				
2	$Zn(BH_3CN)_2$	25	6 h	27	31	7	30
3	$CeCl_3/NaBH_4$	25	2 h	30	58	9	–

Interestingly, the C-9a configurations of the major products resulted from reduction with sodium borohydride in methanol and that from reduction with cerium(III) chloride heptahydrate and sodium borohydride in methanol, are opposite. Based on molecular models, a possible explanation is depicted in the Figure, viz, cerium borohydride, formed in situ,[25−26] complexes with the sulfinyl oxygen on the β-face and consequently delivers the hydride from the β-face (**12**; entry 3 of the Table, the selectivity is 10:1); sodium borohydride alone prefers to attack the double bond from the less hindered α-face (**13**, entry 1, although the selectivity is only 1.6:1).[27,28]

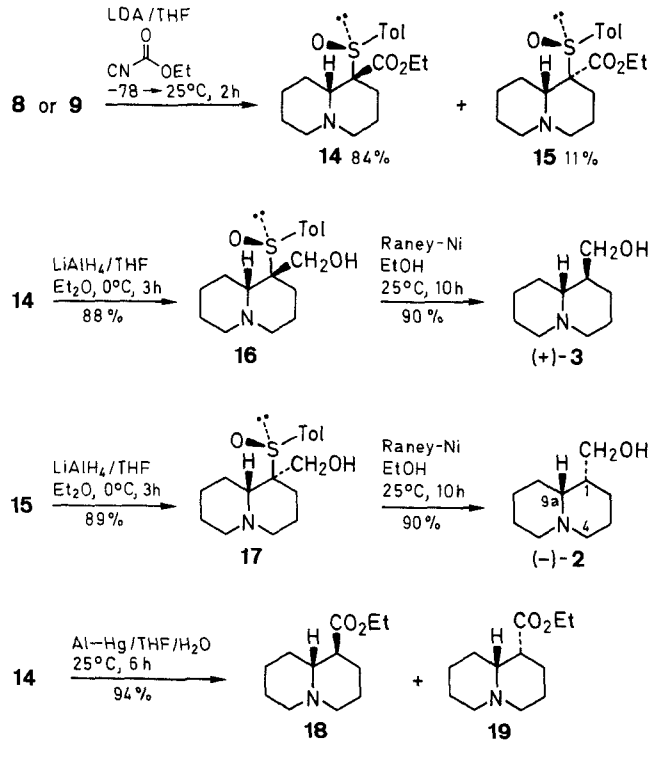


Figure



Scheme **1**

The resulting anions were protonated by methanol from the less hindered face (same side as C-9a H). Reduction of **7** with zinc(II) cyanoborohydride[29] (entry 2) gave all four diastereomers **8**, **9**, **10**, and **11** (ratio of 4:4:1:4). The stereochemistry at C-9a of **8**, **9**, **10**, and **11** (separated by column chromatography) was determined by converting these compounds separately into (−)-lupinine [(−)-**2**] and (+)-epilupinine [(+)-**3**] (*vide infra*). The C-1 stereochemistry was assigned from the coupling constants of H_1-H_{9a} by irradiating the C-2 hydrogens in ^{1}H-NMR experiments of the sulfones derived from the oxidation of **8** and **10** with oxone (potassium peroxymonosulfate).[30] The sulfones derived from **8** and **10** show $J_{1,9a} \approx 11$ Hz [at $\delta = 3.0$ and 3.1 (td, J = 11, 3 Hz), respectively], representing axial-axial coupling. The *cis* isomers, **9** and **11**, were treated separately with LDA in tetrahydrofuran followed by water to give predominantly the *trans* isomers, **8** and **10**, respectively, which are the thermodynamically preferred products. Other reducing agents such as hexakis[hydrido(triphenylphosphine)copper(I)] in benzene,[31] H_2/Pd-C in ethanol, and lithium triethylborohydride in tetrahydrofuran failed to provide a desired product. The conversion of **8** and **9** into (−)-**2** and (+)-**3** is outlined in Scheme **2**. Treatment of either **8** or **9**, separately or combined, with LDA in tetrahydrofuran at −60 °C followed by ethyl cyanoformate gave a 95% yield of **14** and **15** (separated) in a ratio of 8:1. Presumably, ethoxycarbonylation occurred from the less hindered β-face (same side of C-9a H). The stereochemistry was determined by reducing **14** with lithium aluminum hydride in diethyl ether at 0 °C (88% yield) followed by desulfurization of the resulting β-hydroxy sulfoxide **16** with Raney nickel in ethanol to give (+)-**3** (90% yield). Retention of configuration was observed[32] in the desulfurization step.



Scheme 2

Similarly, ester **15** was converted into β-hydroxy sulfoxide **17** and then to (−)-**2** (80% overall yield). Direct hydroxymethylation of the α-sulfinyl carbanion of **8** or **9** with formaldehyde (paraformaldehyde or gaseous formaldehyde was used) in tetrahydrofuran and HMPA failed. A mixture of sulfoxides **8** and **9** was recovered in both cases. In a different approach, **14** was desulfurized with aluminum amalgam in tetrahydrofuran/water to give a 3.6:1 ratio of esters **18** and **19**[16] (94% yield; separated), while **15** under these conditions provided a 1:2 ratio of **18** and **19** (85% yield).

Reduction of **18** and **19**, independently, with lithium aluminum hydride in tetrahydrofuran furnished ~72% yields of (+)-**3** and (−)-**2**, respectively. Antipodes (+)-**2** and (−)-**3** were also synthesized from **10** and **11** as described above. It should be noted that by starting with (+)-(1*S*,2*R*,5*S*)-menthyl (*R*)-(4-methylbenzene)sulfinate (the enantiomer of **6S**), the resulting sulfinyl ketimine (−)-**4** will provide (−)-lupinine [(−)-**2**] as the major product [via the reduction with sodium borohydride (Entry 1 of the Table)]. (+)-Epilupinine [(+)-**3**] has shown significant *in vitro* inhibitory activity against P-388 (LD_{50} = 28 μg/mL) and L1210 (LD_{50} = 20 μg/mL). The studies of the cytotoxic activity with cancer cells and the mechanism of action of lupin alkaloids will be discussed separately.

In summary, quinolizine **7** was stereoselectively reduced with cerium(II) chloride heptahydrate and sodium borohydride to give predominantly C-9a-*R* isomers, **8** and **9** (88% yield; 1:1.9), which were carbonylated into esters **14** and **15** (95% yield; 8:1). Reduction of ester **14** with lithium aluminum hydride (88% yield; to **16**) followed by desulfurization (90% yield) afforded (+)-**3**. Similar treatment of ester **15** gave (−)-**2** (80% yield from **15**). The asymmetric total syntheses of (−)-lupinine **(2)** and (+)-epilupinine **(3)** have been realized, demonstrating the utility of α-sulfinyl-ketimine anions in the construction of chiral bicyclic alkaloids having a nitrogen-atom ring juncture. In addition, the stereocontrolled reduction of β-sulfinyl enamines with cerium(III) chloride/sodium borohydride has clearly illustrated the viability of this method in the asymmetric synthesis of alkaloids. Syntheses of sophocarpine and pyrrolizidines will be reported in due course.

All reagents were of commercial quality from freshly opened containers or distilled. *i*-Pr_2NH, 1-menthol, sodium (4-methylbenzene)sulfinate, 1,3-diiodopropane, $CeCl_3 \cdot 7H_2O$, $NaBH_4$, $LiAlH_4$, ethyl cyanoformate, and analytical TLC plates were purchased from Aldrich Chemical Co. Silica gel (200–425 mesh, Davisil) used in flash chromatography was purchased from Fisher. LDA was prepared from *i*-Pr_2NH and BuLi (1.6 M in hexane) in THF at −20 °C for 30 min under Ar. Melting points were taken using a Thomas Hoover Unimelt apparatus and are uncorrected. Microanalyses were carried out by the MicAnal Organic Microanalysis, Tucson, AZ and observed rotations at the Na-D line were obtained at 25 °C using a Perkin-Elmer 241 polarimeter. IR spectra were recorded using a Perkin-Elmer 1330 spectrophotometer. Mass spectra were measured on a Finnigan 4000 automated gas chromatographed/EI-CI mass spectrometer and a JEOL JMS-DX303HF mass spectrometer. ^{1}H- and ^{13}C-NMR spectra were obtained at 400 and 100 MHz, respectively, using a Brucker WM-400 spectrometer, with TMS as internal standard.

(+)-2,3,4,5-Tetrahydro-6-[(*R*)-(4-methylphenyl)sulfinylmethyl]pyridine (4):

To a cold (−25 °C) solution of LDA (60 mL, 0.0872 mol) in THF (22 mL) under Ar is added 2,3,4,5-tetrahydro-6-methylpyridine (**5**;[23] 6.5 g, 0.067 mol) in THF (30 mL) and the resulting mixture stirred at −20 °C for 15 min. To this solution is added a solution of (−)-(*S*)-menthyl (4-methylbenzene)sulfinate (**6S**;[33] 10.5 g, 0.0357 mol) in THF (30 mL) via cannula. After the yellow solution is stirred at −20 °C for 1.5 h and −10 °C for 0.5 h, it is poured into H_2O (80 mL) and extracted with CH_2Cl_2 (3 × 200 mL). The combined CH_2Cl_2 extracts are washed with brine (50 mL), dried ($MgSO_4$), concentrated, and flash column chromatographed on silica gel (250 g), using mixtures of hexane, Et_2O, and MeOH (gradient) as eluant to give 7.72 g (92% yield) of **4** as an oil: $[\alpha]_D^{22}$ +129° (*c* = 1, $CHCl_3$).

$C_{13}H_{17}NOS$	calc.	C 66.35	H 7.28
(235.4)	found	66.19	7.42

IR (neat): ν = 3020, 2920, 2845, 1635 (s, C=N), 1580, 1480, 1430, 1340, 1080, 1030 (s), 805 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 7.54 (d, 2H, *J* = 8 Hz, *o*-H), 7.32 (d, 2H, *J* = 8 Hz, *m*-H), 3.66 (d, 1H, *J* = 11 Hz, CHS), 3.6 (m, 2H, CH_2N), 3.48 (d, 1H, *J* = 11 Hz, CHS), 2.42 (s, 3H, *p*-Me), 2.26 (m, 1H, C3-H), 2.09 (m, 1H, C3-H), 1.70–1.50 (m, 4H).

^{13}C-NMR ($CDCl_3$): δ = 163.13 (s, C=N), 141.57 (s, Ar), 140.58 (s, Ar), 129.78 (d, 2C, Ar), 124.21 (d, 2C, Ar), 67.49 (t), 53.37 (t), 49.64 (t), 31.3 (t, 2C), 21.3 (t), 19.13 (q).

MS (EI): *m/z* 235 (M^+), CI 236 (M + 1).

3,4,6,7,8,9-Hexahydro-1-[(*R*)-(4-methylphenyl)sulfinyl]-2*H*-quinolizine (7):

To a cold (−78 °C) solution of ketimine **4** (3.1 g, 0.0132 mol) in THF (100 mL) under Ar is added a cold (−25 °C) solution of LDA (14 mL, 0.0198 mol) in THF (100 mL) via cannula. After the brown solution is stirred at −78 °C for 1 h, 1,3-diiodopropane (1.82 mL, 0.0158 mol) is added. The solution is stirred at −78 °C for 2 h and −40 °C for 1 h, and THF (200 mL) is added. After being stirred at 25 °C for 16 h, the solution is poured into H_2O (300 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts are washed with H_2O and brine (50 mL each), dried ($MgSO_4$), concentrated, and flash column chromatographed on silica gel (150 g) using mixtures of hexane, Et_2O, and MeOH (gradient) as eluant to give 2.25 g (62% yield) of **7** as an oil; $[\alpha]_D^{22}$ −77.5° (*c* = 0.9, $CHCl_3$).

$C_{16}H_{21}NOS$	calc.	C 69.78	H 7.69
(275.5)	found	69.52	7.87

IR (neat): ν = 3005, 2960, 2840, 1560 (s), 1475, 1435, 1415, 1340, 1300, 1165, 1085, 1020 (s), 804 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 7.40 (d, 2H, *J* = 8 Hz, *o*-H), 7.24 (d, 2H, *J* = 8 Hz, *m*-H), 3.10–2.90 (m, 4H), 2.83 (dt, 1H, *J* = 11 Hz, 7H), 2.37 (s, 3H, *p*-Me), 2.34 (m, 1H), 2.00–1.60 (m, 8H).

^{13}C-NMR ($CDCl_3$): δ = 150.93 (s, C=), 141.33 (s, Ar), 139.18 (s, Ar), 129.26 (d, 2C, Ar), 124.87 (d, 2C, Ar), 104.1 (s, C=), 51.2 (t, CN), 50.68 (t, CN), 26.04 (t), 23.96 (t), 21.59 (t), 21.32 (t), 21.16 (t), 17.63 (q).

MS (EI): *m/z* 274 (M-1), 273, 257, 246, 224, 213, 182, 168, 153. CI 276 (M + 1).

(1*S*,9a*R*)-Octahydro-1-[(*R*)-(4-methylphenyl)sulfinyl]-2*H*-quinolizine (8), (1*R*,9a*R*)-Octahydro-1-[(*R*)-(4-methylphenyl)sulfinyl]-2*H*-quinolizine (9), (1*R*,9a*S*)-Octahydro-1-[(*R*)-(4-methylphenyl)-sulfinyl]-2*H*-quinolizine (10) and (1*S*,9a*S*)-Octahydro-1-[(*R*)-(4-methylphenyl)sulfinyl]-2*H*-quinolizine (11):

A solution of sulfoxide **7** (0.205 g, 0.745 mmol) and $CeCl_3 \cdot 7H_2O$ (0.56 g, 1.49 mmol) in MeOH (9 mL) is stirred under Ar at 25 °C for 10 min. To it is added $NaBH_4$ (0.187 g, 4.92 mmol) at 0 °C and the mixture is stirred at 25 °C for 2.5 h, diluted with H_2O (20 mL) and extracted with Et_2O (3 × 100 mL). The combined extracts are washed with brine (50 mL), dried ($MgSO_4$), concentrated, and flash column chromatographed on silica gel (70 g), using mixtures of hexanes, Et_2O, and MeOH (gradient) as eluant to give 62 mg (30% yield) of **8**, 120 mg (58% yield) of **9**, and 19 mg (9% yield) of **10**.

8: $[\alpha]_D^{22}$ +157° (*c* = 1.75, $CHCl_3$).

$C_{16}H_{23}NOS$	calc.	C 69.27	H 8.36
(277.5)	found	69.09	8.38

IR (neat): ν = 2940, 2830, 1580, 1030 cm^{-1} (s, SO).

^{1}H-NMR ($CDCl_3$): δ = 7.38 (d, 2H, *J* = 8 Hz, *o*-H), 7.30 (d, 2H, *J* = 8 Hz, *m*-H), 2.86 (d, 1H, *J* = 11 Hz), 2.70 (d, 1H, *J* = 11 Hz), 2.62 (d, 1H, *J* = 9 Hz), 2.40 (s, 3H, *p*-Me), 2.25 (m, 2H), 2.16 (m, 1H), 2.06 (td, 1H, *J* = 12, 3 Hz), 1.86 (br s, 1H), 1.70–1.58 (m, 3H), 1.50 (m, 1H), 1.40 (m, 2H), 1.22 (m, 2H).

^{13}C-NMR ($CDCl_3$): δ = 140.39 (s, Ar), 138.16 (s, Ar), 129.47 (d, 2C, Ar), 123.92 (d, 2C, Ar), 66.63 (d), 61.28 (d), 56.59 (t), 55.33 (t), 30.62 (t), 25.42 (t), 24.01 (t), 23.75 (t), 21.1 (t), 17.8 (q).

MS (EI): *m/z* 278 (M + 1), 277 (M^+), 260, 221, 137.

9: $[\alpha]_D^{22}$ +91° (*c* = 0.95, $CHCl_3$).

$C_{16}H_{23}NOS$	calc.	C 69.27	H 8.36
(277.5)	found	69.91	8.47

^{1}H-NMR ($CDCl_3$): δ = 7.59 (d, 2H, *J* = 8 Hz, *o*-H), 7.30 (d, 2H, *J* = 8 Hz, *m*-H), 2.97 (d, 2H, *J* = 11 Hz), 2.8 (br s, 1H), 2.66 (d, 1H, *J* = 10 Hz), 2.41 (s, 3H, *p*-Me), 2.3 (m, 1H), 2.15 (m, 2H), 1.85 (d, 1H, *J* = 13 Hz), 1.80–1.50 (m, 4H), 1.40–1.20 (m, 4H).

^{13}C-NMR ($CDCl_3$): δ = 142.12 (s, Ar), 139.37 (s, Ar), 129.84 (d, 2C, Ar), 125.8 (d, 2C, Ar), 68.59 (d), 62.83 (d), 56.81 (t), 54.0 (t), 29.54 (t), 25.03 (t, 2C), 23.69 (t), 22.69 (t), 21.36 (q).

MS (EI): *m/z* 277 (M^+).

10: $[\alpha]_D^{22}$ −25.3° (*c* = 1, $CHCl_3$).

$C_{16}H_{23}NOS$	calc.	C 69.27	H 8.36
(277.5)	found	69.31	8.65

^{1}H-NMR ($CDCl_3$): δ = 7.44 (d, 2H, *J* = 8 Hz, *o*-H), 7.32 (d, 2H, *J* = 8 Hz, *m*-H), 2.90 (td, 1H, *J* = 10, 3 Hz, CHS), 2.82 (d, 1H, *J* = 11 Hz), 2.69 (d, 1H, *J* = 11 Hz), 2.43 (s, 3H, *p*-Me), 2.38 (m, 1H), 2.11 (dd, 1H, *J* = 9, 3 Hz), 2.03 (td, 1H, *J* = 11, 3 Hz), 1.82 (m, 2H), 1.70–1.60 (m, 4H), 1.55 (m, 1H), 1.30 (m, 2H), 0.82 (m, 1H).

^{13}C-NMR ($CDCl_3$): δ = 141.63 (s, Ar), 136.63 (s, Ar), 129.53 (d, 2C, Ar), 125.59 (d, 2C, Ar), 65.85 (d), 62.64 (d), 56.43 (t), 55.48 (t), 30.89 (t), 25.20 (t), 24.39 (t), 23.99 (t), 21.42 (t), 21.08 (q).

MS (EI): *m/z* 277 (M^+).

Reduction with $NaBH_4$: To a solution of **7** (0.5 g, 1.8 mmol) in MeOH (6 mL) under argon at 0 °C is added $NaBH_4$ (0.5 g, 13.5 mmol) in small portions. The mixture is stirred at 25 °C for 3 h, diluted with H_2O (15 mL), and extracted with CH_2Cl_2 (3 × 50 mL). The combined extracts are washed with brine (30 mL), dried ($MgSO_4$), concentrated, and flash column chromatographed on silica gel (70 g) using mixtures of hexanes, acetone, and MeOH (gradient) as eluant to give 0.179 g (36% yield) of **9** and 0.294 g (59% yield) of **11**.

11: $[\alpha]_D^{22}$ +81.5° (*c* = 1.9, $CHCl_3$).

$C_{16}H_{23}NOS$	calc.	C 69.27	H 8.36
(277.5)	found	68.89	8.51

^{1}H-NMR ($CDCl_3$): δ = 7.53 (d, 2H, *J* = 8 Hz, *o*-H), 7.29 (d, 2H, *J* = 8 Hz, *m*-H), 2.95 (m, 2H), 2.74 (d, 1H, *J* = 4 Hz), 2.42 (m, 1H), 2.40 (s, 3H, *p*-Me), 2.30–2.10 (m, 4H), 1.94 (qt, 1H, *J* = 13, 3 Hz), 1.83 (d, 1H, *J* = 13 Hz), 1.7 (m, 1H), 1.5 (m, 3H), 1.38 (d, 1H, *J* = 13 Hz), 1.26 (m, 1H).

^{13}C-NMR ($CDCl_3$): δ = 142.42 (s, Ar), 140.9 (s, Ar), 129.73 (d, 2C, Ar), 124.72 (d, 2C, Ar), 66.17 (d), 62.63 (d), 56.69 (t), 53.8 (t), 29.18 (t), 24.85 (t), 23.71 (t), 22.91 (t), 21.88 (t), 21.27 (q).

MS (EI): *m/z* 277 (M^+).

The following example serves as the general procedure for the reactions of sulfoxides **8**, **9**, **10**, and **11** with ethyl cyanoformate.

Ethyl (1*R*,9a*R*)-Octahydro-1-[(*S*)-(4-methylphenyl)sulfinyl]-2*H*-quinolizine-1-carboxylate (14) and Ethyl (1*S*,9a*R*)-Octahydro-1-[(*S*)-(4-methylphenyl)sulfinyl]-2*H*-quinolizine-1-carboxylate (15):

To a cold (−78 °C) solution of sulfoxide **9** (0.287 g, 1.04 mmol) in THF (3 mL) under Ar is added a cold (−25 °C) solution of LDA (1.2 mL, 1.55 mmol) in THF (4 mL) via cannula. After the resulting orange solution is stirred at −78 °C for 1 h and −60 °C for 1 h, a

solution of ethyl cyanoformate (0.13 mL, 1.25 mmol) in THF (1 mL) is added. The yellow solution is stirred at −78 °C for 1 h and 25 °C for 1 h, diluted with H_2O (20 mL), and extracted with CH_2Cl_2 (3 × 70 mL). The combined extracts are washd with brine (50 mL), dried ($MgSO_4$), concentrated, and flash column chromatographed on silica gel (100 g), using mixtures of hexanes, EtOAc, and MeOH (gradient) as eluant to give 0.306 g (84% yield) of **14** and 38 mg (11% yield) of **15**.

14: $[\alpha]_D^{22}$ + 145° (*c* = 1.35, $CHCl_3$).

$C_{19}H_{27}NO_3S$ (349.5) calc. C 65.30 H 7.79 found 65.11 7.93

IR (neat): *v* = 2910, 2840, 1690 (s, C=O), 1580, 1430, 1230, 1190, 1040 cm^{-1} (s, S=O).

^{1}H-NMR ($CDCl_3$): δ = 7.45 (d, 2H, *J* = 8 Hz, *o*-H), 7.28 (d, 2H, *J* = 8 Hz, *m*-H), 4.03 (m, 1H, CHN), 3.84 (m, 2H, OCH_2), 3.10 (m, 1H, CHN), 2.93 (m, 2H), 2.40 (s, 3H, *p*-Me), 2.36 (dd, 1H, *J* = 11, 2 Hz), 2.00 (m, 3H), 1.90–1.60 (m, 5H), 1.21 (m, 2H), 1.04 (2t, 3H, *J* = 7 Hz, Me).

^{13}C-NMR ($CDCl_3$): δ = 166.99 (s, C=O), 142.22 (s, Ar), 136.4 (s, Ar), 129.19 (d, 2C, Ar), 125.78 (d, 2C, Ar), 71.86 (d), 61.08 (t), 59.16 (t), 55.65 (t), 44.52 (s, CS), 25.23 (t), 22.95 (t), 22.4 (t), 21.39 (t), 19.05 (t), 18.32 (q), 13.66 (q, Me).

MS (EI): *m/z* 349 (M^+), 283, 258, 246, 238, 209, 180, 136.

15: $[\alpha]_D^{22}$ + 59° (*c* = 0.65, $CHCl_3$).

$C_{19}H_{27}NO_3S$ (349.5) calc. C 65.30 H 7.79 found 65.17 7.98

^{1}H-NMR ($CDCl_3$): δ = 7.43 (d, 2H, *J* = 8 Hz, *o*-H), 7.25 (d, 2H, *J* = 8 Hz, *m*-H), 4.18 (m, 1H, CH_2O), 4.08 (m, 1H, CH_2O), 2.93 (d, 1H, *J* = 10 Hz), 2.79 (br s, 1H), 2.48 (d, 1H, *J* = 11 Hz), 2.41 (m, 1H), 2.39 (s, 3H, *p*-Me), 2.08 (m, 3H), 1.86 (m, 2H), 1.70 (m, 2H), 1.60 (m, 2H), 1.47 (m, 1H), 1.28 (m, 1H), 1.19 (t, 3H, *J* = 7 Hz, Me).

^{13}C-NMR ($CDCl_3$): δ = 168.93 (s, C=O), 141.89 (s, Ar), 135.83 (s, Ar), 129.21 (d, 2C, Ar), 126.44 (d, 2C, Ar), 72.68 (d), 64.01 (t), 61.22 (t), 57.95 (t), 55.59 (s, CS), 29.67 (t), 25.0 (t), 24.85 (t), 21.76 (t), 21.36 (t), 21.1 (q), 13.96 (t).

MS (EI): *m/z* 349 (M^+).

The following example serves as the general procedure for the reactions of esters **14** and **15** with $LiAlH_4$.

(1*R*,9a*R*)-Octahydro-1-hydroxymethyl-1-[(*S*)-(4-methylphenyl)sulfinyl]-2*H*-quinolizine (16); Typical Procedure:

To a cold (0 °C) solution of ester **14** (0.130 g, 0.37 mmol) in THF (10 mL) and Et_2O (10 mL) under Ar, is added $LiAlH_4$ (28 mg, 0.74 mmol). The mixture is stirred at 0 °C for3 h, diluted with H_2O (50 mL) and extracted with EtOAc (3 × 70 mL). The combined extracts are washed with brine (50 mL), dried ($MgSO_4$), concentrated to give 0.100 g (88% yield) of pure alcohol **16** as an oil: $[\alpha]_D^{22}$ + 113.7° (*c* = 0.75, $CHCl_3$).

$C_{17}H_{25}NO_2S$ (307.5) calc. C 66.41 H 8.20 found 66.18 8.37

IR (neat): *v* = 3500 (s), 1030 cm^{-1} (s).

^{1}H-NMR ($CDCl_3$): δ = 7.61 (d, 2H, *J* = 8 Hz, *o*-H), 7.31 (d, 2H, *J* = 8 Hz, *m*-H), 4.09 (d, 1H, *J* = 12 Hz, CH_2O), 3.75 (d, 1H, *J* = 12 Hz, CH_2O), 3.04 (m, 2H), 2.90 (br s, 1H, OH), 2.50 (m, 1H), 2.42 (s, 3H, *p*-Me), 2.23 (m, 3H), 1.95 (br d, 1H, *J* = 12 Hz), 1.80–1.10 (series of m, 8H).

^{13}C-NMR ($CDCl_3$): δ = 142.20 (s, Ar), 135.82 (s, Ar), 129.55 (d, 2C, Ar), 126.71 (d, 2C, Ar), 65.91 (t, CO), 61.73 (d), 56.56 (t), 53.37 (t), 52.00 (s), 27.82 (t), 25.19 (t), 22.42 (t), 21.75 (t, 2C), 21.41 (q).

MS (EI): *m/z* 307 (M^+), 289.

(1S,9aR)-Octahydro-1-hydroxymethyl-1-[(S)-(4-methylphenyl)-sulfinyl]-2H-quinolizine **(17)**:

$[\alpha]_D^{22}$ + 89.4° (*c* = 0.35, $CHCl_3$).

$C_{17}H_{25}NO_2S$ (307.5) calc. C 66.41 H 8.20 found 66.31 8.48

^{1}H-NMR ($CDCl_3$): δ = 7.40 (d, 2H, *J* = 8 Hz, *o*-H), 7.28 (d, 2H, *J* = 8 Hz, *m*-H), 4.14 (d, 1H, *J* = 11 Hz, CH_2O), 3.16 (d, 1H, *J* = 11 Hz, CH_2O), 2.90 (d, 1H, *J* = 11 Hz), 2.78 (d, 1H, *J* = 11 Hz), 2.62 (dd, 1H, *J* = 11, 2 Hz), 2.44 (m, 1H), 2.41 (s, 3H, *p*-Me), 2.14 (m, 1H), 2.07 (m, 3H), 1.90–1.20 (series of m, 7H).

^{13}C-NMR ($CDCl_3$): δ = 142.09 (s, Ar), 134.79 (s, Ar), 129.41 (d, 2C, Ar), 126.05 (d, 2C, Ar), 65.63 (t, CO), 64.09 (d), 61.34 (t), 57.02 (t), 55.89 (s, CS), 25.43 (t, 2C), 25.28 (t), 24.12 (t), 21.95 (t), 21.41 (q).

MS (EI): *m/z* 307 (M^+).

The following example serves as the general procedure for the reactions of sulfoxides **16** and **17** with W-2 Raney-nickel.

(+)-Epilupinine [(+)-3];[34] Typical Procedure:

To a solution of **16** (70 mg, 0.23 mmol) in EtOH (10 mL) under Ar is added freshly prepared W-2 Raney-Ni (0.1 g).[35] After the mixture is stirred at 25 °C for 10 h, it is diluted with EtOH (50 mL) containing 1% of NH_4OH, filtered through Celite (5 g), concentrated, and passed through a short silica gel (10 g) column using Et_2O/MeOH (9:1) as eluant to give 35 mg (90% yield) of (+)-**3**: mp 78–79 °C (Et_2O/hexane (Lit.[22] 78–79); $[\alpha]_D^{22}$ + 32° (*c* = 0.86, EtOH) [Lit.[22] + 31.2° (*c* = 0.86, EtOH)].

^{1}H-NMR ($CDCl_3$): δ = 3.66 (dd, 1H, *J* = 11, 4 Hz, CH_2O), 3.58 (dd, 1H, *J* = 11, 6 Hz, CH_2O), 2.82 (br, t, 2H, *J* = 12 Hz), 2.10–1.20 (series of m, 14H).

^{13}C-NMR ($CDCl_3$): δ = 64.75 (d, CN), 64.27 (t), 56.89 (t), 56.60 (t), 43.95 (d), 29.77 (t), 28.18 (t), 25.58 (t), 25.01 (t), 24.55 (t).

MS (EI): *m/z* 168 (M − 1), 161, 152, 145, 138, 125, 111, 97, 91, 83.

(−)-Lupinine [(−)-**2**]:[34] (mp 70–71 °C (Et_2O/hexane) (Lit.[18] 70–71 °C); $[\alpha]_D^{22}$ −21° (*c* = 9.5, EtOH) (Lit.[18] −21°, EtOH).

^{1}H-NMR ($CDCl_3$): δ = 4.17 (dd, 1H, *J* = 11, 6 Hz, CH_2O), 3.70 (d, 1H, *J* = 11 Hz, CH_2O), 2.83 (m, 2H), 2.15 (m, 2H), 2.02 (td, 1H, *J* = 11, 3 Hz), 1.90–1.70 (m, 5H), 1.65–1.50 (m, 6H).

^{13}C-NMR ($CDCl_3$): δ = 66.03 (d), 65.1 (t), 57.14 (t), 57.05 (t), 38.11 (d), 31.47 (t), 29.67 (t), 25.59 (t), 24.61 (t), 22.93 (t).

MS (EI): *m/z* 169 (M^+), 168, 166, 152, 138, 124, 111, 97, 83.

Ethyl (1*S*,9a*S*)-Octahydro-1-[(*S*)-(4-methylphenyl)sulfinyl]-2*H*-quinolizine-1-carboxylate (20) and Ethyl (1*R*,9a*S*)-Octahydro-1-[(*S*)-(4-methylphenyl)sulfinyl]-2*H*-quinolizine-1-carboxylate (21):

These two compounds form in a ratio of 1:1.2 are derived from sulfoxides **10** and **11** by following the same procedure described above.

20: $[\alpha]_D^{22}$ + 39.4° (*c* = 1.3, $CHCl_3$).

$C_{19}H_{27}NO_3S$ (349.5) calc. C 65.30 H 7.79 found 65.47 7.99

^{1}H-NMR ($CDCl_3$): δ = 7.45 (d, 2H, *J* = 8 Hz, *o*-H), 7.27 (d, 2H, *J* = 8 Hz, *m*-H), 3.88 (q, 2H, *J* = 7 Hz, OCH_2), 3.42 (m, 1H), 3.07 (td, 1H, *J* = 10, 3 Hz), 2.87 (dd, 1H, *J* = 14, 2 Hz), 2.85 (m, 1H), 2.48 (m, 1H), 2.40 (s, 3H, *p*-Me), 2.11 (m, 1H), 1.95–1.60 (m, 7H), 1.25 (m, 2H), 1.14 (t, 3H, *J* = 7 Hz, Me).

^{13}C-NMR ($CDCl_3$): δ = 167.56 (s, C=O), 141.80 (s, Ar), 137.80 (s, Ar), 129.22 (d, 2C, Ar), 125.68 (d, 2C, Ar), 72.61, 60.97, 57.58, 55.32, 47.00, 25.30, 22.66, 21.40, 19.62, 13.98, 13.95, 13.80.

MS (EI) *m/z*: 349 (M^+).

21: $[\alpha]_D^{22}$ + 14.4° (*c* = 0.25, $CHCl_3$).

$C_{19}H_{27}NO_3S$ (349.5) calc. C 65.30 H 7.79 found 65.01 7.84

^{1}H-NMR ($CDCl_3$): δ = 7.44 (d, 2H, *J* = 8 Hz, *o*-H), 7.25 (d, 2H, *J* = 8 Hz, *m*-H), 3.79 (m, 2H, OCH_2), 3.66 (m, 1H), 3.07 (m, 1H), 2.96–2.80 (m, 2H), 2.48 (m, 1H), 2.39 (s, 3H, *p*-Me), 2.36 (m, 1H), 2.05–1.60 (series of m, 7H), 1.22 (m, 2H), 0.99 (t, 3H, *J* = 7 Hz, Me).

^{13}C-NMR ($CDCl_3$): δ = 168.97 (s, C=O), 142.15 (s, Ar), 136.77 (s, Ar), 129.18 (d, 2C, Ar), 126.06 (d, 2C, Ar), 74.5, 61.78, 61.17, 55.64, 48.81, 28.62, 26.41, 25.45, 24.98, 22.71, 14.18, 13.44.

MS (EI): *m/z* = 349 (M^+).

The following example serves as the general procedure for the

reactions of sulfoxides **14, 15** and the two diastereomers **20** and **21** described above with Al–Hg.

Ethyl (1*S*,9a*R*)-Octahydro-2*H*-quinolizine-1-carboxylate (18) and Ethyl (1*R*,9a*R*)-Octahydro-2*H*-quinolizine-1-carboxylate (19); Typical Procedure:

To a solution of **14** (0.4 g, 1.15 mmol) in THF (20 mL) and H_2O (2 mL) is added freshly prepared Al–Hg (0.4 g).[36] The reaction is monitored by TLC. After the mixture is stirred at 25 °C for 6 h, it is diluted with CH_2Cl_2 (200 mL), filtered through Celite (10 g), washed with brine (50 mL), dried ($MgSO_4$), concentrated and flash column chromatographed on silica gel (100 g), using mixtures of hexanes and Et_2O (gradient) as eluant to give 0.179 g (74% yield) of **18** and 50 mg (21% yield) of **19**.

18: bp 70–75 °C/0.01 Torr (Lit.[16] 75 °C/0.01 Torr; $[\alpha]_D^{22}$ + 9.6° (*c* = 0.65, $CHCl_3$).

$C_{12}H_{21}NO_2$ (211.3) calc. C 68.21 H 10.02 found 67.95 10.31

IR (neat): ν = 2920, 2845, 2790, 2740, 1720 (s, C=O), 1430, 1360, 1310, 1250, 1160, 1140, 1030, 730 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 4.13 (q, 2H, *J* = 7 Hz, OCH_2), 2.81 (t, 2H, *J* = 12 Hz), 2.26 (m, 1H), 2.12–1.88 (m, 4H), 1.72–1.48 (m, 8H), 1.26 (t, 3H, *J* = 7 Hz, Me), 1.25 (m, 1H).

^{13}C-NMR ($CDCl_3$): δ = 174.84 (s, C=O), 63.56 (d), 60.19 (t), 56.62 (t), 56.01 (t), 49.41 (d), 30.82 (t), 28.64 (t), 25.67 (t), 24.51 (t), 14.25 (q).

MS (EI): *m/z* = 211 (M^+), 196, 182, 138.

19: $[\alpha]_D^{22}$ – 5.0° (*c* = 0.4, $CHCl_3$).

$C_{12}H_{21}NO_2$ (211.3) calc. C 68.21 H 10.02 found 68.45 10.40

^{1}H-NMR ($CDCl_3$): δ = 4.16 (m, 2H, OCH_2), 2.92 (m, 2H), 2.59 (br s, 1H), 2.20–2.00 (m, 4H), 1.90 (m, 1H), 1.77 (br d, 1H, *J* = 11 Hz), 1.65–1.48 (m, 6H), 1.30 (m, 1H), 1.25 (t, 3H, *J* = 7 Hz, Me).

^{13}C-NMR ($CDCl_3$): δ = 173.29 (s, C=O), 62.79 (d), 59.88 (t), 57.00 (t), 55.00 (t), 44.41 (d), 29.87 (t), 26.05 (t), 24.89 (t), 24.20 (t), 22.18 (t), 14.30 (q).

MS (EI): *m/z* = 211 (M^+).

The following example serves as the general procedure for the reactions of **18**, **19**, and their antipodes with $LiAlH_4$.

(+)-Epilupinine [(+)-3]; Typical Procedure:

To a cold (0 °C) solution of epilupinic ester **18** (0.13 g, 0.616 mmol) in Et_2O (20 mL), is added $LiAlH_4$ (47 mg, 1.2 mmol). The mixture is stirred at 25 °C for 8 h, diluted with wet Et_2O (100 mL), filtered through Celite (10 g), washed throughly with CH_2Cl_2 (100 mL), and concentrated to give (+)-**3**; yield: 75 mg (72%).

We gratefully acknowledge financial support from the National Cancer Institute (Grant CA51794). We are indebted to Sadahiko Iguchi, Ono Pharmaceutical Co., Osaka, Japan for obtaining mass spectra.

Received: 26 April 1991; revised: 3 July 1991

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