Chiral Acetylenic Sulfoxide in Enantioselective Synthesis of Tetrahydroisoquinoline and Tetrahydro-β-carboline Alkaloids. Total Synthesis of (*R*)-(+)-Carnegine and (*R*)-(+)-Tetrahydroharman

Albert W. M. Lee,* Wing Hong Chan, Yi Tao and Yu Kai Lee
Department of Chemistry, Hong Kong Baptist College, 224 Waterloo Road, Kowloon, Hong Kong

Michael addition of 2-(3,4-dimethoxyphenyl)ethylamine **3** or tryptamine **4** onto chiral acetylenic sulfoxides **2** followed by acid induced cyclization afforded the basic alkaloid skeleton of tetrahydroisoquinoline and tetrahydro-β-carboline in high to moderate diastereoselectivity. Optically pure (*R*)-(+)-carnegine and (*R*)-(+)-tetrahydroharman have been synthesized.

Tetrahydroisoquinoline and tetrahydro-β-carboline are two important classes of alkaloids. The latter is also a key intermediate in the preparation of many indole alkaloids. Various achiral[1] and chiral[2] syntheses of these two alkaloid classes had been reported. In the achiral syntheses, the Pictet–Spengler and the Bischler–Napieralski reactions were the most widely used approaches. For the enantioselective syntheses, the chiral formamidines[2a,b] developed by Meyers are particularly worthy of note. Both the tetrahydroisoquinoline and the tetrahydro-β-carboline can be synthesized in high enantioselectivity through this methodology.

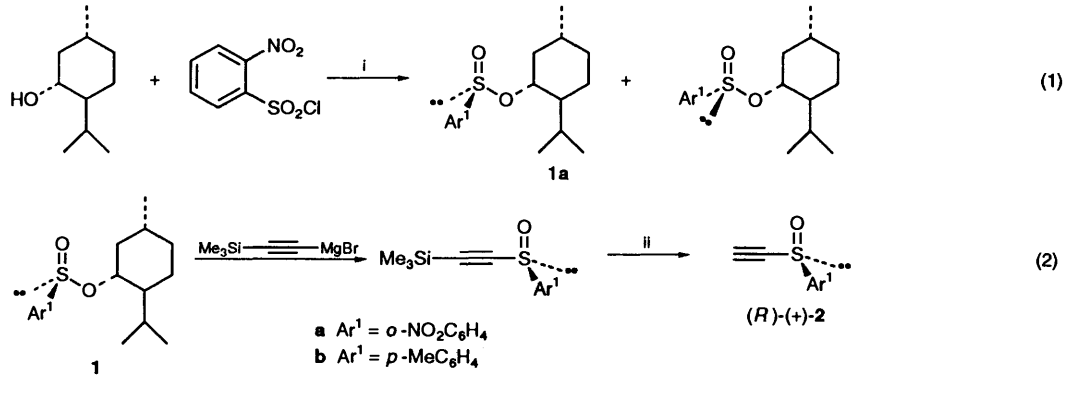
The uses of the stereogenic sulfur centre of a chiral sulfoxide to achieve enantioselective control in asymmetric synthesis have been studied by several research teams.[3] In particular, much attention has been focused on the carbanion chemistry α to the chiral sulfoxides and the Michael addition and cycloaddition reactions of chiral vinyl sulfoxides. Recently, we launched a programme on the study of chiral acetylenic sulfoxides in enantioselective synthesis. The first example was the diastereoselective Diels–Alder reaction.[4] Subsequently a synthesis of the basic tetrahydroisoquinoline nucleus with high diastereoselectivity has also been achieved.[5] The methodology is now extended to the tetrahydro-β-carboline series. The results of enantioselective syntheses of two alkaloid classes, as exemplified by the total syntheses of (*R*)-(+)-carnegine **11** and (*R*)-(+)-tetrahydroharman **14**, are now reported in detail.

Results and Discussion

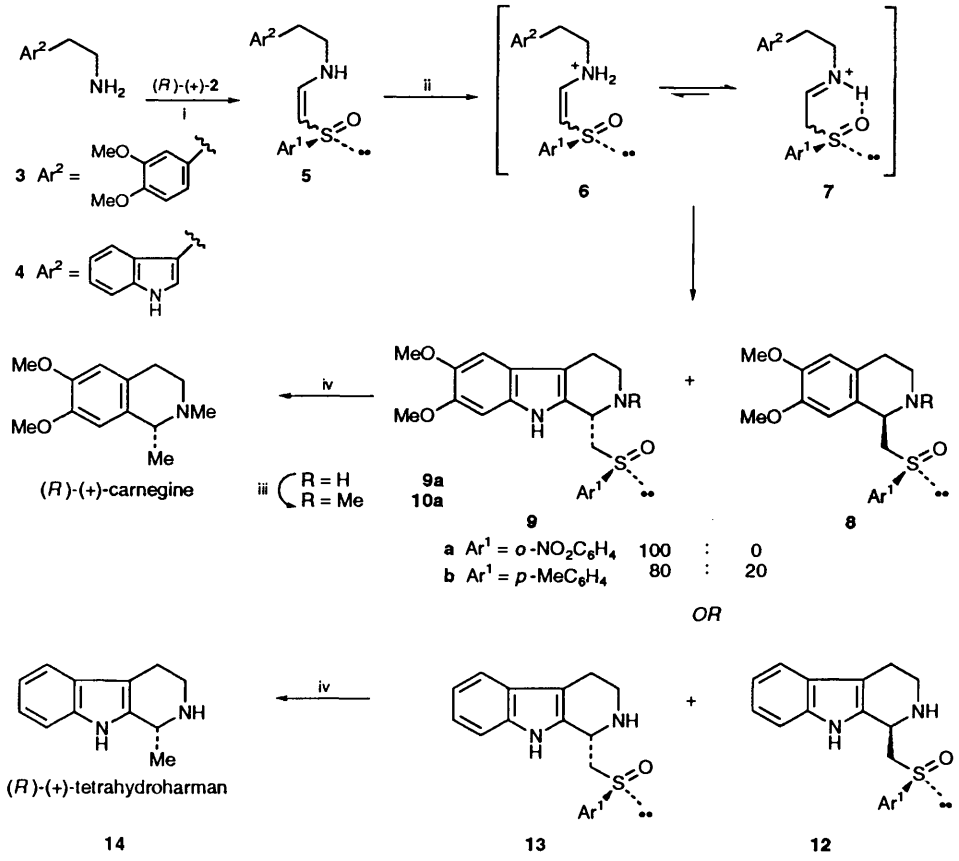
Preparation of Chiral Acetylenic Sulfoxides.—Among several known methods for the preparation of chiral sulfoxides, Anderson synthesis[6] still remains as a reliable synthetic route. We wanted to study the effect of the substituent on the benzene ring of the aryl acetylenic sulfoxide **2**, and therefore we needed a reliable access to the corresponding optically pure starting sulfinates for the Anderson synthesis. The simple sulfinate, (*S*)-(−)-menthyl *p*-toluenesulfinate **1b** is commercially available in optically pure form. To prepare (S_s)-(−)-menthyl *o*-nitrobenzenesulfinate **1a**, we used an efficient procedure developed by Sharpless[7] [Scheme 1, eqn. (1)]. By adopting the Sharpless procedure, a diastereoisomeric mixture of sulfinates was obtained in a ratio of 3:1. The major diastereoisomer **1a** can be obtained in optically pure form after recrystallization twice from ethanol. With both the optically pure *o*-nitrobenzene, and the *p*-toluene sulfinates **1a** and **1b** at our disposal, treatment with trimethylsilylethynylmagnesium bromide in toluene [Scheme 1, eqn. (2)] followed by hydrolysis of the trimethylsilyl group on silica gel during chromatography separation afforded the chiral acetylenic sulfoxides (*R*)-(+)-ethynyl *o*-nitrophenyl sulfoxide **2a** and (*R*)-(+)-ethynyl *p*-tolyl sulfoxide **2b** in good yields. Since inversion takes place at the sulfur centres of the starting chiral sulfinates,[6] the optical purity and the absolute configuration of the prepared sulfoxides can be ensured.

Michael Addition and Cyclization.—In our approach to the alkaloid syntheses, we viewed the acetylenic sulfoxide as a two-carbon synthon for the C-1/C-1′ carbons of the tetrahydroisoquinoline and tetrahydro-β-carboline basic skeleton. Two crucial bonds were to be formed in a one-pot reaction. First, a carbon–nitrogen bond was formed through Michael addition of an amine. Without isolation of the addition intermediate, a carbon–carbon bond was then built by acid induced cyclization of the electron rich aromatic ring to the β-carbon of the chiral sulfoxide. Besides the sulfoxide chirality, a new chiral centre was created at the C-1 position of the alkaloid moieties. Control of diastereoselectivity was to be achieved in this one-pot addition–cyclization sequence.

Sulfoxides **2a** and **2b** were very good Michael acceptors.



Scheme 1 *Reagents and conditions:* i, CH_2Cl_2, $(MeO)_3P$, Et_3N (ref. 7); ii, silica gel



Scheme 2 *Reagents and conditions:* i, solvent, room temp. (see Table 1); ii, TFA or TsOH; iii, CH_2O, $NaCNBH_3$, MeCN; iv, Raney nickel

Table 1 Diastereoselectivity on cyclization of **5**

Entry	Ar^1	Ar^2	Solvent	Acid	T/°C	Diastereoisomeric ratio **9**:**8** or **13**:**12**	Yield (%)[a]
1	o-$NO_2C_6H_4$	3,4-$(MeO)_2C_6H_3$	$CHCl_3$	TFA	0	**9a** only	65
2	o-$NO_2C_6H_4$	3,4-$(MeO)_2C_6H_3$	$CHCl_3$	TFA	R.t.[b]	**9a** only	35
3	o-$NO_2C_6H_4$	3,4-$(MeO)_2C_6H_3$	$CHCl_3$	BF_3–Et_2O	0	**9a** only	20
4	o-$NO_2C_6H_4$	Indol-3-yl	CH_2Cl_2	TFA	−60	3:2	61
5	o-$NO_2C_6H_4$	Indol-3-yl	$CHCl_3$	TFA	−60	7:3	60
6	o-$NO_2C_6H_4$	Indol-3-yl	MeCN	TFA	−40	7:3	60
7	o-$NO_2C_6H_4$	Indol-3-yl	MeOH	TsOH	−30	8:2	93
8	p-MeC_6H_4	3,4-$(MeO)_2C_6H_3$	$CHCl_3$	TFA	0	2:1	45
9	p-MeC_6H_4	Indol-3-yl	$CHCl_3$	TFA	−60	3:2	85
10	p-MeC_6H_4	Indol-3-yl	MeOH	TsOH	−30	7:3	91

[a] Overall yield from **2**. [b] R.t. = room temperature.

Addition of 2-(3,4-dimethoxyphenyl)ethylamine **3** and tryptamine **4** onto these sulfoxides were very facile reactions in many solvents (Scheme 2). The Michael adduct β-aminovinyl sulfoxides **5** were not isolated. Treatment with an acid such as trifluoroacetic acid or toluene-*p*-sulfonic acid effected the crucial cyclization to build up the alkaloid ring systems. The cyclizations were also very facile. They took place almost instantaneously at 0 °C for the dimethoxyphenyl ring, and at −60 °C for the indole ring respectively.

There are several factors that affected the diastereoselectivity and yield of this Michael addition–cyclization sequence. They are the substituent on the benzene ring of the sulfoxide, and the type of acid and solvent used. In both the tetrahydroisoquinoline and tetrahydro-β-carboline series, we found that the *o*-nitrophenylacetylenic sulfoxide **2a** gave better diastereoselectivity than the *p*-tolylacetylenic sulfoxide **2b**. For the tetrahydroisoquinoline series, only one diastereoisomer **9a** could be isolated (entries 1–3, Table 1) when **2a** was used. In the tetrahydro-β-carboline series, under optimized conditions (entry 7, Table 1), the best diastereoselectivity achieved was 8:2 (**13a**:**12a**) with **2a** as the starting chiral sulfoxide.

The substituent effect on the diastereoselectivity could be rationalized as follows. Under the influence of acid, the protonated enamine **6** and iminium ion **7** were in equilibrium with the latter as the predominant species. As shown in structure **7**, a hydrogen bond could exist between the iminium hydrogen and the sulfoxide oxygen forming a six-membered ring intermediate. We speculate that this intramolecular hydrogen bonding which locked the conformation of the molecule might be responsible for the observed diastereoselectivity of the subsequent cyclization. An electron withdrawing *o*-nitro substituent in close proximity to the sulfoxide could further

stabilize the presumed hydrogen bond to yield a higher diastereoselectivity.

A Lewis acid such as boron trifluoride could also facilitate the cyclization. However, a fairly messy reaction was observed and a poor isolated yield of the desired product was obtained (entry 3, Table 1). For the tetrahydro-β-carboline series, polar solvent gave better diastereoselectivity and toluene-*p*-sulfonic acid afforded cleaner reactions of over 90% isolated yields (entries 7 and 10, Table 1).

Total Synthesis of (R)-(+)-*Carnegine and* (R)-(+)-*Tetrahydroharman.*—Compound **9a** was the only diastereoisomer isolated from this one-pot Michael addition–cyclization reaction sequence with **2a** as the starting chiral sulfoxide. Reductive methylation with sodium cyanoborohydride and aqueous formaldehyde in acetonitrile[8] gave rise to **10a**. From ^1H and ^{13}C NMR spectroscopy and TLC, once again there was no sign of the existence of the other diastereoisomer. Raney nickel desulfurization in water-saturated diethyl ether[9] afforded optically pure (*R*)-(+)-carnegine **11**[10] in good yield.

In the tetrahydro-β-carboline series, diastereoisomers **12a** and **13a** could be easily separated by column chromatography on silica gel. The major diastereoisomer **13a** was transformed into optically pure (*R*)-(+)-tetrahydroharman **14**[11] through Raney nickel desulfurization (80% yield). The optically pure tetrahydro-β-carboline alkaloid was therefore synthesized in a three-step reaction sequence with an overall yield of 57% from acetylenic sulfoxide **2a**.

Experimental

Diethyl ether was distilled from sodium benzophenone ketyl immediately before use. Toluene was distilled from calcium hydride and stored over 4 Å molecular sieves. All other reagents and solvents were reagent grade. Melting points are uncorrected. NMR spectra were recorded on a Bruker WM 250 (250 MHz for ^1H) or JEOL JNM-EX 270 (270 MHz for ^1H and 67.8 MHz for ^{13}C) spectrometer in $CDCl_3$ with tetramethylsilane as an internal standard. *J* Values are given in Hz. Optical rotations were measured in path length cells of 1 cm on a JASCO Model Dip 370 digital polarimeter; $[\alpha]_D$ values are given in deg cm^2 g^{-1}. Mass spectral (MS) data were obtained on a A.E.I. MS50 mass spectrometer. Elemental analyses were performed at the Shanghai Institute of Organic Chemistry, The Chinese Academy of Sciences.

(1R,2S,5R)-(−)-*Menthyl* (S_s)-o-*Nitrobenzenesulfinate* **1a**.—To a mixture of *o*-nitrobenzenesulfonyl chloride (52 g, 0.25 mol) and (−)-menthol (20 g, 0.13 mol) in 800 cm^3 of dichloromethane under a nitrogen atmosphere, triethylamine (25.9 cm^3, 0.26 mol) was added. After 15 min, trimethyl phosphite (30 cm^3, 0.25 mol) was introduced into the reaction mixture. After the exothermic reaction had subsided, the mixture was refluxed for 1 h. The cooled mixture was washed with HCl (1 mol dm^{-3}), saturated aq. $NaHCO_3$ and saturated aq. NaCl. The organic layer was dried over anhydrous magnesium sulfate, and evaporated on a rotary evaporator to give the crude brown solid. Purification by column chromtagraphy (silica gel) with ethyl acetate–light petroleum (5:95) as eluent gave both diastereoisomers (30 g, 70% yield). Recrystallization of the products twice from ethanol (95%) gave pure title compound **2a** (14 g, 33% yield) as a light yellow solid, m.p. 102–103 °C (from ethanol): $[\alpha]_D^{26}$ −449.1 (*c* 2.00, acetone); ν_{max}/cm^{-1} 1540 and 1350 (NO_2–) and 1320 and 1140 (–OSO–); δ_H(270 MHz; $CDCl_3$) 0.75 (3 H, d, *J* 6.6, $CHCH_3$), 0.84 (3 H, d, *J* 7.3, $CHCH_3$), 0.97 (3 H, d, *J* 6.6, $CHCH_3$), 1.02–1.69 (7 H, m), 2.03–2.07 (1 H, m, *CH*CHO), 2.34–2.38 (1 H, m, *CH*CHO), 4.11–4.21 (1 H, dt, *J* 4.3 and 10.5, CHO), 7.71 (1 H, dd, *J* 8.1 and 7.6, ArH), 7.74 (1 H, dd, *J* 8.1 and 7.6, ArH), 7.89 (1 H, d, *J* 8.1, ArH) and 7.92 (1 H, d, *J* 8.1, ArH); δ_C(67.8 MHz; $CDCl_3$) 15.47, 20.72, 22.01, 23.20, 25.16, 31.74, 33.87, 41.26, 47.82, 80.92, 124.83, 126.13, 132.27, 134.68, 142.68 and 145.62 (Found: C, 59.1; H, 7.0; N, 4.2; S, 10.2. $C_{16}H_{23}NO_4S$ requires C, 59.05; H, 7.12; N, 4.30; S, 9.85%).

Synthesis of Chiral Acetylenic Sulfoxides **2a** *and* **2b**.—To a suspension of magnesium (0.37 g, 15 mmol) in dried diethyl ether (20 cm^3) under a nitrogen atmosphere, ethyl bromide (1.1 cm^3, 15 mmol) was introduced. The resultant mixture was refluxed for 1 h. After cooling to room temperature, excess ethynyltrimethylsilane (2.5 cm^3, 18 mmol) was added and the solution was refluxed for another hour. The diethyl ether used was then replaced by toluene (20 cm^3). To the toluene solution at 0 °C, substituted benzenesulfinate **1** (6.2 mmol) in 5 cm^3 of toluene was introduced. The mixture was stirred at room temperature for 1 h, then saturated aq. ammonium chloride (60 cm^3) was added. The mixture was extracted with dichloromethane (4 × 20 cm^3). The combined organic layers was dried and evaporated to dryness to give crude product. The crude product was redissolved in acetonitrile (15 cm^3) and excess potassium fluoride (1.8 g, 31 mmol) was added. The solution was stirred at room temperature for 30 min and then the solvent was removed and water (30 cm^3) was added. The product was extracted with dichloromethane (3 × 15 cm^3). The combined organic layers was dried and evaporated on a rotary evaporator. Purification by flash chromatography on silica gel (eluted with ethyl acetate–light petroleum, 10:90) afforded the acetylenic sulfoxide.

2a: M.p. 116–118 °C (decomp.) $[\alpha]_D^{26}$ +363.9 (*c* 0.38, chloroform); ν_{max}/cm^{-1} 3200 (≡C–H), 2050 (–C≡C–), 1520 and 1350 ($-NO_2$) and 1040 (–SO–); δ_H(270 MHz; $CDCl_3$), 3.46 (1 H, s, C≡C–H), 7.79 (1 H, m, ArH), 8.02 (1 H, m, ArH) and 8.40 (2 H, m, ArH); δ_C(67.5 MHz; $CDCl_3$) 80.5, 86.7, 125.65, 125.97, 132.1, 135.8, 141.5 and 144.1 (Found: C, 49.25; H, 2.3; N, 7.0; S, 16.4. $C_8H_5NO_3S$ requires C, 49.23; H, 2.58; N, 7.18; S, 16.42%).

2b: M.p. 38–40 °C; δ_H(270 MHz; $CDCl_3$), 2.45 (3 H, s, $ArCH_3$), 3.70 (1 H, s, C≡CH), 7.37 (2 H, d, *J* 8.1, ArH) and 7.73 (2 H, d, *J* 8.1, ArH); δ_C(67.5 MHz, $CDCl_3$) 21.5, 81.8, 90.0, 125.5, 130.3, 140.0 and 142.9.

Michael Addition–Cyclization of **3** *onto* (R)-(+)-**2a**. *Preparation of* (1S,S_R)-6,7-*Dimethoxy*-1-(o-*nitrophenylsulfinylmethyl*)-1,2,3,4-*tetrahydroisoquinoline* **9a**.—To a stirred solution of sulfoxide **2a** (496 mg, 2.54 mmol) in chloroform (15 cm^3) at room temperature, was added dropwise 2-(3,4-dimethoxyphenyl)ethylamine (460 mg, 2.54 mmol). The solution was stirred at room temperature for 2 h. Without isolating the Michael adduct **5**, the solution was cooled to 0 °C in an ice–water bath prior to the addition of trifluoroacetic acid (16 cm^3, 17.8 mmol). The mixture was stirred at 0 °C for 4 h. Aq. ammonia (14%) was added to the solution. The organic product was extracted with chloroform (3 × 25 cm^3). The combined organic layers were dried over anhydrous sodium sulfate and then evaporated on a rotary evaporator to give the crude cyclized product which was further purified by flash column chromatography over silica gel using methanol–ethyl acetate (1:10) as eluent to afford the title compound **9a** as a light yellow solid (604 mg, 65%), m.p. 186–188; $[\alpha]_D^{26}$ +211.4 (*c* 0.18, chloroform); ν_{max}/cm^{-1} 3500 (–NH), 1530 and 1360 ($-NO_2$) and 1040 (–SO–); δ_H(250 MHz; $CDCl_3$) 1.94 (1 H, br s, NH), 2.70–2.79 (2 H, m, CH_2NH), 2.93 (1 H, dd, *J* 3.2 and 12.8, SOCH), 3.25–3.34 (2 H, m, $ArCH_2$), 3.68 (1 H, dd, *J* 11.6 and 12.8, SOCH), 3.80 (3 H, s, OCH_3), 3.84 (3 H, s, OCH_3), 4.67 (1 H, dd, *J* 3.2 and 11.6, Ar*CH*NH), 6.52 (1 H, s, ArH), 6.59 (1 H, s, ArH), 7.67–7.73 (1 H, m, ArH), 7.95–8.02 (1 H, m, ArH), 8.31 (1 H, dd, *J* 1.1 and 8.1, ArH) and 8.44

(1 H, dd, *J* 1.3 and 7.1, ArH); δ_C(62.5 MHz; $CDCl_3$) 28.9, 39.4, 50.9, 56.1, 56.3, 63.2, 109.9, 112.9, 125.1, 127.0, 128.0, 128.1, 131.2, 135.5, 144.8, 144.9, 148.0 and 148.5 [Found: (M − *o*-$NO_2C_6H_4SOH)^+$, 205.1096. $C_{12}H_{15}NO_2$ requires (*M* − *o*-$NO_2C_6H_4SOH)^+$, 205.1103].

Michael Addition–Cyclization of **3** *onto* (R)-(+)-**2b**. *Preparation of* (1R,S_R)-6,7-*Dimethoxy*-1-p-*tolylsulfinylmethyl*-1,2,3,4-*tetrahydroisoquinoline* **8b** *and* (1S,S_R)-6,7-*Dimethoxy*-1-p-*tolylsulfinylmethyl*-1,2,3,4-*tetrahydroisoquinoline* **9b**.—The addition–cyclization of **3** onto (*R*)-(+)-**2b** was carried out under the conditions identical to the preparation of **9a** as mentioned above. However, purification of the crude products by flash column chromatography on silica gel using methanol–ethyl acetate (1:10) as eluent afforded **8b** and **9b** in a 2:1 ratio in a total yield of 45%. The ^1H and ^{13}C NMR spectra of **8b** and **9b** are identical with those reported in literature.[12]

(1S,S_R)-N-*Methyl*-6,7-*dimethoxy*-1-p-*tolylsulfinylmethyl*-1,2,-3,4-*tetrahydroisoquinoline* **10a**.—To a solution of **9a** (0.386 g, 1 mmol) in acetonitrile (5 cm^3) and aq. formaldehyde (37%, 1.0 cm^3) was added sodium cyanoborohydride (80 mg, 1.3 mmol). After 30 min the pH of the solution was adjusted to neutral by the dropwise addition of glacial acetic acid. After stirring at room temperature for 6 h, the mixture was concentrated by evaporation, treated with NaOH (2 mol dm^{-3}; 4 cm^3), and then extracted with chloroform (3 × 25 cm^3). The combined extracts were dried (anhydrous Na_2SO_4) and then evaporated to dryness. The crude product was purified by flash chromatography on silica gel using ethyl acetate as eluent. The pure product **10a** (360 mg, 90%) was obtained as a yellow solid; m.p. 174–176 °C (decomp.); $[\alpha]_D^{26}$ +256.7 (*c* 0.24, chloroform); ν_{max}/cm^{-1} 1530 and 1355 (–NO_2) and 1040 (–SO–); δ_H(250 MHz; $CDCl_3$) 2.47–2.39 (1 H, m, C*H*NH), 2.66 (3 H, s, NCH_3), 2.82 (1 H, dd, *J* 4.1 and 12.8, SOCH), 2.96–3.17 (2 H, m, $ArCH_2$), 3.43–3.54 (1 H, m, ArC*H*NH), 3.62 (1 H, dd, *J* 11.8 and 12.6, SO_2CH), 3.79 (3 H, s, $ArOCH_3$), 3.83 (3 H, s, $ArOCH_3$), 4.23 (1 H, dd, *J* 4.1 and 11.9, ArC*H*NH), 6.53 (1 H, s, ArH), 6.59 (1 H, s, ArH), 7.64–7.71 (1 H, m, ArH), 7.94–8.00 (1 H, m, ArH), 8.28 (1 H, dd, *J* 1.1 and 8.1, ArH) and 8.42 (1 H, dd, *J* 1.4 and 7.9, ArH) [Found: (M − *o*-$NO_2C_6H_4SOH)^+$, 219.1253. $C_{13}H_{17}NO_2$ requires (*M* − *o*-$NO_2C_6H_4SOH)^+$, 219.1259].

(R)-(+)-*Carnegine* {(R)-(+)-1,2,3,4-*Tetrahydro*-6,7-*dimethoxy*-1,2-*dimethylisoquinoline*} **11**.—To a stirred solution of **10a** (200 mg, 0.5 mmol) in water-saturated diethyl ether (10 cm^3), Raney nickel (W-2, 5.0 g) was introduced. After 1 h the mixture was diluted with diethyl ether (3 × 20 cm^3) and the solution decanted. The combined organic solutions were dried over anhydrous sodium sulfate, filtered and then evaporated. The crude product was purified by flash chromatography on silica, to give pure title compound **11** (128 mg) as a viscous oil, $[\alpha]_D^{26}$ +27.6 (*c* 0.15, ethanol) {lit.,[10] $[\alpha]_D^{18}$ +23.4 (*c* 0.15, ethanol)}; δ_H(250 MHz; $CDCl_3$) 1.40 (3 H, d, *J* 5.0, $ArCHCH_3$), 2.46 (3 H, s, NCH_3), 2.60–3.10 (4 H, m, $ArCH_2CH_2N$), 3.58 (1 H, q, *J* 5.0 C*H*CH_3), 3.82 (6 H, s, 2 × $ArOCH_3$), 6.58 (1 H, s, ArH) and 6.62 (1 H, s, ArH). The spectroscopic data were identical with those reported in literature.[12]

Michael Addition–Cyclization of **4** *onto* (R)-(+)-**2a**. *Preparation of* (1R,S_R)-1-(o-*Nitrophenylsulfinylmethyl*)-1,2,3,4-*tetrahydro*-β-*carboline* **12a** *and* (1S,S_R)-1-(o-*Nitrophenylsulfinylmethyl*)-1,2,3,4-*tetrahydro*-β-*carboline* **13a**.—To a methanol solution (20 cm^3) of tryptamine **4** (260 mg, 1.62 mmol) was added sulfoxide **2a** (300 mg, 1.55 mmol in 6 cm^3 of methanol) and the mixture was stirred at room temperature under a nitrogen atmosphere. As indicated by TLC, the formation of **5** was completed within 2.5 h. The mixture was then cooled to −30 °C and toluene-*p*-sulfonic acid monohydrate (2.95 g, 15.5 mmol) was introduced in one portion. After stirring at −30 °C for 30 min, the mixture was poured into ice-cooled saturated aq. sodium hydrogen carbonate (20 cm^3), basified with sodium hydroxide (3 mol dm^{-3}) and then extracted with dichloromethane (3 × 20 cm^3). The combined organic extracts were dried, filtered and evaporated to dryness under reduced pressure. The crude products were purified by column chromatography on silica gel using hexane–ethyl acetate (35:65) as eluent to give the title compounds **12a** (102 mg, 19%) and **13a** (409 mg, 74%) as yellow crystalline solids. **12a**: M.p. 167–168 °C (decomp.); $[\alpha]_D^{23}$ +251.7 (*c* 0.4, chloroform); ν_{max}/cm^{-1} 3380 (–NH), 1510 and 1340 (NO_2–) and 1025 (–SO–); δ_H(270 MHz; $CDCl_3$) 1.82 (1 H, br s, D_2O exchangeable, NH), 2.78 (2 H, m, CH_2N), 3.12 (1 H, dd, *J* 5.4 and 12.6, SOCH), 3.30 (2 H, m, $ArCH_2$), 3.66 (1 H, dd, *J* 7.2 and 12.6, SOCH), 4.90 (1 H, dd, *J* 5.4 and 7.2, ArCHN), 7.04–7.75 (4 H, m, ArH), 7.74 (1 H, m, ArH), 7.99 (1 H, m, ArH), 8.32–8.42 (2 H, m, ArH) and 8.82 (1 H, br s, D_2O exchangeable NH); δ_C(67.8 MHz; $CDCl_3$) 22.44, 41.55, 49.34, 62.01, 109.97, 111.14, 118.24, 119.42, 122.01, 125.37, 126.49, 127.13, 131.71, 132.90, 135.74, 135.83, 143.34 and 144.70. **13a**: M.p. 146–147 °C (decomp.); $[\alpha]_D^{23}$ +328.7 (*c* 0.5, chloroform); ν_{max}/cm^{-1} 3300 (–NH), 1530 and 1350 (NO_2–) and 1030 (–SO–); δ_H(270 MHz; $CDCl_3$) 1.61 (1 H, br s, D_2O exchangeable), 2.78 (2 H, m, CH_2N), 2.96–3.21 (2 H, m, $ArCH_2$), 3.42 (1 H, dd, *J* 4.7 and 14.0, SOCH), 3.77 (1 H, dd, *J* 6.9 and 14.0, SOCH), 4.43 (1 H, dd, *J* 4.7 and 6.9, ArCHN), 7.04–7.75 (4 H, m, ArH), 7.74 (1 H, m, ArH), 7.99 (1 H, m, ArH), 8.40 (2 H, m, ArH) and 9.22 (1 H, br s, NH, exchangeable with D_2O); δ_C(67.8 MHz; $CDCl_3$) 22.97, 41.98, 48.14, 58.40, 109.27, 111.30, 118.17, 119.34, 121.96, 125.72, 127.12, 127.66, 131.86, 133.35, 135.35, 135.72, 141.40 and 144.83 (Found: M^+, 355.0989. $C_{18}H_{17}N_3O_3S$ requires, M^+, 355.0992).

Michael Addition–Cyclization of **4** *onto* (R)-(+)-**2b**. *Preparation of* (1R,S_R)-1-(p-*Tolylsulfinylmethyl*)-1,2,3,4-*tetrahydro*-β-*carboline* **12b** *and* (1S,S_R)-1-(p-*Tolylsulfinylmethyl*)-1,2,3,4-*tetrahydro*-β-*carboline* **13b**.—The addition–cyclization of **4** onto (*R*)-(+)-**2b** was carried out under conditions identical with those for the preparation of compounds **12a** and **13a** as mentioned above. Purification of the crude products by column chromatography on silica gel using methanol–ethyl acetate (1:10) as eluent afforded title compounds **12b** and **13b** in a 3:7 ratio at a total yield of 91%. **12b**: ν_{max}/cm^{-1} 3280 (–NH) and 1020 (–SO–); δ_H(270 MHz; $CDCl_3$) 1.77 (1 H, br s, D_2O exchangeable, NH), 2.42 (3 H, s, CH_3Ar), 2.76 (2 H, m, CH_2N), 3.02 (1 H, dd, *J* 4.9 and 13.6, CHSO), 3.18–3.27 (2 H, m, $ArCH_2$), 3.40 (1 H, dd, *J* 4.4 and 13.6, CHSO), 4.80 (1 H, dd, *J* 4.3 and 4.9, ArCHN), 7.05–7.18 (2 H, m, ArH), 7.32–7.60 (6 H, m, ArH) and 9.54 (1 H, br s, NH); δ_C(67.8 MHz; $CDCl_3$) 21.44, 22.55, 42.50, 49.80, 63.83, 108.99, 111.38, 118.04, 119.14, 121.74, 123.97, 126.97, 130.19, 133.59, 135.76, 140.24 and 142.05. **13b**: ν_{max}/cm^{-1} 3300 (–NH) and 1020 (–SO–); δ_H(270 MHz; $CDCl_3$) 1.71 (1 H, br s, D_2O exchangeable, NH), 2.42 (3 H, s, CH_3Ar), 2.70 (2 H, m, CH_2N), 3.05 (1 H, dd, *J* 14.3 and 2.4, CHSO), 2.92–3.13 (2 H, m, $ArCH_2$), 3.55 (1 H, dd, *J* 14.3 and 6.6, CHSO), 4.79 (1 H, dd, *J* 2.4 and 6.5, ArCHN), 7.04–7.18 (2 H, m, ArH), 7.35–7.57 (6 H, m, ArH) and 9.85 (1 H, br s, NH); δ_C(67.8 MHz; $CDCl_3$) 21.40, 22.45, 42.86, 47.67, 58.98, 108.57, 111.47, 118.01, 119.08, 121.67, 124.31, 127.10, 130.26, 133.23, 135.69, 137.61 and 141.82 (Found: M^+, 324.1294. $C_{19}H_{20}N_2OS$ requires, M^+, 324.1301).

(R)-(+)-1,2,3,4-*Tetrahydroharman* {(R)-(+)-2,3,4,9-*Tetrahydro*-1-*methyl*-3H-*pyrido*[3,4-b]*indole*} **14**.—To a stirred ice-cooled solution of compound **13a** (0.55 g, 1.55 mmol) in methanol (30 cm^3) was added Raney nickel (5 g). This mixture

was stirred for 4 h at 0 °C under a nitrogen atmosphere, then filtered and evaporated. The crude product was purified by column chromatography on silica gel using methanol–ethyl acetate (2:8) as eluent to give the title compound **14** as a light yellow solid (0.23 g, 80%), m.p. 70–70.5 °C (decomp.); $[\alpha]_D^{21}$ +53 (*c* 2, ethanol) {lit.,[11] $[\alpha]_D^{25}$ −52 (*c* 2.0, ethanol) for (*S*)-(−)-tetrahydroharman}. The spectroscopic data were identical with those reported in the literature.[11]

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References

1 For reviews on the various total syntheses of the tetrahydroisoquinoline and tetrahydro-β-carbolines series, see: (*a*) T. Kametain, in *Total Synthesis of Natural Products*, ed. J. ApSimon, Wiley, New York, 1977, vol. 3, pp. 1–272; (*b*) J. P. Kutney, in *Total Synthesis of Natural Products*, ed. J. ApSimon, Wiley, New York, 1977, vol. 3, pp. 273–288.

2 (*a*) A. I. Meyers, *Aldrichimica Acta*, 1985, **18**, 59; (*b*) T. Highsmith and A. I. Meyers, 'Asymmetric Synthesis of Alkaloids: The α-Alkylation of Nitrogen Heterocycles *via* Formamidine-Mediated Chiral Carbanions,' in *Advances in Heterocyclic Natural Product Synthesis*, JAI Press, Greenwich, 1991; (*c*) P. D. Bailey and S. P. Hollinshead, *J. Chem. Soc., Perkin Trans. 1*, 1988, 739; (*d*) P. D. Bailey, S. P. Hollinshead and Z. Bauter, *J. Chem. Soc., Chem. Commun.*, 1985, 1507.

3 For reviews, see: (*a*) G. H. Posner, in *The Chemistry of Sulfones and Sulfoxides*, eds. S. Patai, Z. Rappoport and C. J. M. Stirling, Wiley, New York, 1988, pp. 828–850; (*b*) G. H. Posner, in *Asymmetric Synthesis*, ed. J. D. Morrison, Academic Press, New York, 1983, vol. 2, part A, pp. 225–242.

4 A. W. M. Lee, W. H. Chan and M. S. Wong, *J. Chem. Soc., Chem. Commun.*, 1988, 1585.

5 A. W. M. Lee, W. H. Chan and Y. K. Lee, *Tetrahedron Lett.*, 1991, **32**, 6861.

6 K. K. Anderson, *Tetrahedron Lett.*, 1962, 93; *J. Org. Chem.*, 1964, **29**, 1953.

7 J. M. Klunder and K. B. Sharpless, *J. Org. Chem.*, 1987, **52**, 2598.

8 R. J. Borch and A. I. Hassid, *J. Org. Chem.*, 1972, **37**, 1673.

9 C. R. Johnson and C. J. Stark, Jr., *J. Org. Chem.*, 1982, **47**, 1193.

10 A. R. Battersby and T. P. Edwards, *J. Chem. Soc.*, 1960, 1214; S. D. Brown, J. E. Hodkins, J. L. Massingill Jr. and M. G. Reinecke, *J. Org. Chem.*, 1972, **37**, 1825; S. G. Pyne, *J. Chem. Soc., Chem. Commun.*, 1986, 1686.

11 K. Yamada, M. Takeda and T. Iwakuma, *J. Chem. Soc., Perkin Trans. 1*, 1983, 265; H. Akimoto, K. Okamura, M. Yui, J. Shioiri, M. Kuramoto and S. Yamada, *Chem. Pharm. Bull.*, 1974, **22**, 2614.

12 This compound has been prepared by Pyne by a different route, see: S. G. Pyne and B. Dikic, *J. Org. Chem.*, 1990, **55**, 1932.

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