$PhCOCH_2HgCl$ in the presence of 2.5 mmol of the enol ether for 22 h in 5 mL of PhH (90%)–Me_2SO (10%) gave after workup 12% of 2-(benzoylmethyl)cyclohexanone, 13% of $PhCOCH_2CH_2COPh$, and 14% of $PhCOCH_3$.

2,3,4,4a,10,10a-Hexahydro-(1α,4α,4aα,10aα)-1*H*-1,4-methanophenanthren-9-one (11a). A mixture of 0.5 mmol of $PhCOCH_2HgCl$ and 2.5 mmol of norbornene in 5 mL of PhH (90%)–Me_2SO (10%) was irradiated at 350 nm for 16 h. Workup yielded **11a** (42%), $PhCOCH_3$ (5%), and 1,4-diphenyl-1,4-butanedione (3%). Pure **11a** was obtained by column chromatography with ethyl acetate (5%)–hexane (95%) as eluent: ^1H NMR ($CDCl_3$) δ 7.78 (dd, 1 H, *J* = 7.5, 1.2 Hz), 7.50 (dt, 1 H, *J* = 7.5, 1.5 Hz), 7.32 (d, 1 H, *J* = 7.5 Hz), 7.26 (t, 1 H, *J* = 7.5 Hz), 3.05 (d, 1 H, *J* = 8.4 Hz), 2.72 (dd, 1 H, *J* = 15.6, 9.0 Hz), 2.50 (dd, 1 H, *J* = 15.6, 4.2 Hz), 2.40–2.30 (m, 1 H), 2.24 (br s, 1 H), 2.10 (br s, 1 H), 1.74–1.48 (m, 3 H), 1.44–1.34 (m, 1 H), 1.26 (d, 1 H, *J* = 10.8 Hz), 1.01 (d, 1 H, *J* = 10.8 Hz); ^{13}C NMR ($CDCl_3$) δ 199.97, 145.43, 133.75, 133.27, 129.12, 125.79, 125.06, 46.89, 45.58, 44.79, 42.04, 39.44, 32.60, 30.00, 29.50; MS *m/z* calcd for M^+ 212.12012, found 212.12049.

Reaction of *o*-$BrC_6H_4COCH_2HgCl$ with Norbornene: Formation of 11a,b. Photolysis (350 nm) of 0.50 mmol of *o*-$BrC_6H_4COCH_2HgCl$ with 5 mmol of norbornene in 5 mL of Me_2SO for 17 h yielded 8% of **11a** and 28% of **11b**. The *o*-bromotetralone derivative **11b** had a GCMS, *m/z* (rel intensity) 292 (M^+, 36), 290 (M^+, 37), 225 (60), 224 (88), 223 (73), 222 (78), 143 (26), 128 (21), 115 (100).

Reaction of *o*-$IC_6H_4COCH_2HgCl$ with Norbornene: Formation of 11a,c. Photolysis of 0.50 mmol of the mercurial and 5.0 mmol of norbornene in 5 mL of Me_2SO at 350 nm for 22 h yielded after workup 15% of **11a** and a small amount of **11c**: GCMS *m/z* (rel intensity) 338 (M^+, 100), 271 (67), 270 (96), 144 (20), 128 (19), 127 (7), 115 (73).

Registry No. 1 (R = Me), 4202-12-4; **2**, 14439-02-2; **5a**, 124316-33-2; **11a**, 124375-87-7; **11b**, 124286-47-1; **11c**, 124286-48-2; $PhCOCH_2HgCl$, 28531-58-0; Me_2CHNO_2, 79-46-9; $MeCH_2NO_2$, 79-24-3; H_3CNO_2, 75-52-5; $PhCH_2NO_2$, 622-42-4; $PhCH(Me)NO_2$, 7214-61-1; $EtCH(CO_2Et)_2$, 133-13-1; $MeCH(CO_2Et)_2$, 609-08-5; $H_2C(CO_2Et)_2$, 105-53-3; $PhCH(CO_2Et)_2$, 83-13-6; Me_3COCH_3, 75-97-8; $PhCOCHMe_2$, 611-70-1; $PhCOCH_2Me$, 93-55-0; $PhCOCH_2Ph$, 451-40-1; $PhCOCHPh_2$, 1733-63-7; $Ph_2CHC{\equiv}N$, 86-29-3; $PhCOCH_2CMe_2NO_2$, 124286-37-9; $PhCOCH{=}Me_2$, 5650-07-7; $PhCOCH_2CHMeNO_2$, 7404-78-6; $PhCOCH{=}C(Me)NO_2$, 124286-38-0; $PhCO(CH_2)_2NO_2$, 62847-52-3; $O_2NCH_2H_8Cl$, 124286-39-1; $PhCOCH_2CH(Ph)NO_2$, 124286-40-4; $PhCH{=}C(Ph)NO_2$, 1215-07-2; $PhCH(NO_2)CH(NO_2)Ph$, 67765-80-4; (*S*,*S*)-$PhC(Me)(NO_2)C(Me)(NO_2)Ph$, 124286-41-5; (*R*,*S*)-$PhC(Me)(NO_2)C(Me)(NO_2)Ph$, 22486-14-2; $PhCOCH_2C(Et)(CO_2Et)_2$, 124286-42-6; $PhCOCH_2C(Me)(CO_2Et)_2$, 124286-43-7; $PhCOCH_2CH(CO_2Et)_2$, 94011-49-1; $PhCOCH_2CH(Ph)(CO_2Et)_2$, 124286-44-8; $PhC(CO_2Et)_2C(CO_2Et)_2Ph$, 117720-83-9; $PhCO(CH_2)_2COCMe_3$, 56079-45-9; $PhCOCH_2CMe_2COPh$, 124286-45-9; $PhCOCH_2CH(Me)COPh$, 15982-59-9; $PhCOCH(Ph)CH_2COPh$, 4441-01-4; $PhCOCH(Ph)CH(Ph)COPh$, 10516-92-4; $PhCOC(Ph)_2C(Ph)_2COPh$, 113680-01-6; $Ph_2C(CN)C(CN)Ph_2$, 3122-21-2; $(MeO)_3P$, 121-45-9; $PhCOCH_2P(O)(OMe)_2$, 1015-28-7; $(PhCOCH_2)_2Hg$, 37160-45-5; $PhCOCH_2P(O)(OEt)_2$, 3453-00-7; $(EtO)_3P$, 122-52-1; $Ph\text{-}CO(CH_2)_2COPh$, 495-71-6; *o*-$BrC_6H_4COCH_2HgCl$, 124286-49-3; *o*-$IC_6H_4COCH_2HgCl$, 124286-50-6; dimethyl 1-cyclohexenyl phosphate, 3719-53-7; (2-oxocyclohexyl)mercury chloride, 14839-64-6; *N*-methyl-2-(benzolmethyl)pyrrole, 124286-46-0; *N*-methylpyrrole, 96-54-8; *N*-morpholino-1-cyclohexene, 670-80-4; 2-(benzoylmethyl)cyclohexanone, 33553-23-0; cyclohexanone trimethylsilyl enol ether, 6651-36-1; norbornene, 498-66-8.

Supplementary Material Available: NMR spectra of $PhCOCH_2P(O)(OMe)_2$ (^1H), $PhC(OMe)(Me)P(O)(OMe)_2$ (^1H, ^{13}C), $PhC(=CH_2)OP(O)(OMe)_2$ (^1H), $PhC(=CH_2)OCH_2SCH_3$ (^1H, ^{13}C), N-methyl-2-(benzoylmethyl)pyrrole (^1H, ^{13}C), and **11a** (^1H, ^{13}C) (17 pages). Ordering information is given on any current masthead page.

Stereochemistry of the Intermolecular and Intramolecular Conjugate Additions of Amines and Anions to Chiral (*E*)- and (*Z*)-Vinyl Sulfoxides. Total Syntheses of (*R*)-(+)-Carnegine and (+)- and (−)-Sedamine[1]

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Received June 15, 1989

The intramolecular addition of incipient amine anions to chiral (*E*)- and (*Z*)-vinyl sulfoxides occurs in the same diastereofacial sense, giving chiral isoquinoline and piperidine derivatives that differ in relative stereochemistry at C-2. In contrast, the conjugate addition reactions of (*E*)- and (*Z*)-β-styryl *p*-tolyl sulfoxide with benzylamine and $LiCH(CO_2Et)_2$ are diastereoconvergent processes. The same major diastereomeric product is obtained in each case. We have attempted to rationalize the stereochemical outcome of the addition of nucleophiles to chiral vinyl sulfoxides according to the type of nucleophilic reagent employed (either chelating/hydrogen bonding or nonchelating) and from a consideration of possible transition states.

The addition of nucleophiles to chiral vinyl sulfoxides has proven to be a useful method for the asymmetric synthesis of chiral molecules and natural products.[2,3] A detailed understanding of the steric and electronic factors that control the stereochemical course of these reactions, however, remains unclear. Recent theoretical calculations

(1) Chiral Sulfur Compounds. Part 9. Part 8: Pyne, S. G.; Dikic, B. *J. Chem. Soc., Chem. Commun.* **1989**, 826–827.

(2) For intramolecular examples see: (a) Hansen, J. J.; Kjaer, A. *Acta. Chem. Scand., Ser. B* **1974**, *28*, 418–424. (b) Pyne, S. G.; Chapman, S. L. *J. Chem. Soc., Chem. Commun.* **1986**, 1688–1689. (c) Pyne, S. G. *Tetrahedron Lett.* **1987**, *28*, 4737–4740. (d) Solladie, G.; Moine, G. *J. Am. Chem. Soc.* **1984**, *106*, 6097–6098. (e) Iwata, C.; Fujita, M.; Hattori, K.; Uchida, S.; Imanishi, T. *Tetrahedron Lett.* **1985**, *26*, 2221–2224. (f) Hirama, M.; Hioki, H.; Ito, S.; Kabuto, C. *Tetrahedron Lett.* **1988**, *29*, 3121–3124. (g) Iwata, C.; Fujita, M.; Moritani, Y.; Hattori, K.; Imanishi, T. *Tetrahedron Lett.* **1987**, *28*, 3135–3138, and references therein.

(3) For intermolecular examples see: (a) Abbot, D. J.; Colonna, S.; Stirling, C. J. M. *J. Chem. Soc., Chem. Commun.* **1971**, 471. (b) Abbot, D. J.; Colonna, S.; Stirling, C. J. M. *J. Chem. Soc., Perkin Trans. 1* **1976**, 492–498. (c) Tsuchihashi, G.; Mitamura, S.; Inove, S.; Ogura, K. *Tetrahedron Lett.* **1973**, 323–326. (d) Tsuchihashi, G.; Mitamura, S.; Ogura, K. *Tetrahedron Lett.* **1976**, 855–858. (e) Posner, G. H. *Acc. Chem. Res.* **1987**, *20*, 72–78. (f) Holton, R. A.; Kennedy, R. M.; Kim, H.; Krafft, M. E. *J. Am. Chem. Soc.* **1987**, *109*, 1597–1600. (g) Pyne, S. G.; Griffith, R.; Edwards, M. *Tetrahedron Lett.* **1988**, *29*, 2089–2092. (h) Davis, R.; Kern, J. R.; Kurz, L. J.; Pfister, J. R. *J. Am. Chem. Soc.* **1988**, *110*, 7873–7874. (i) Takaki, K.; Maeda, T.; Ishikawa, M. *J. Org. Chem.* **1989**, *54*, 58–62.

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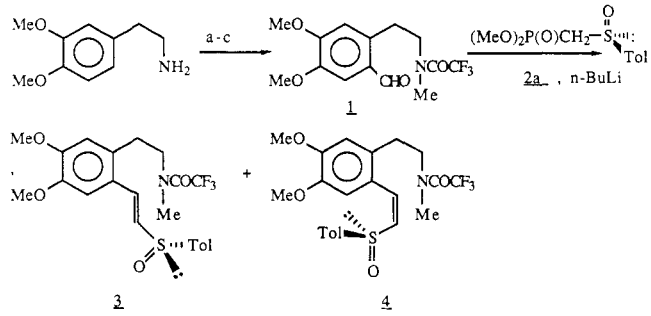
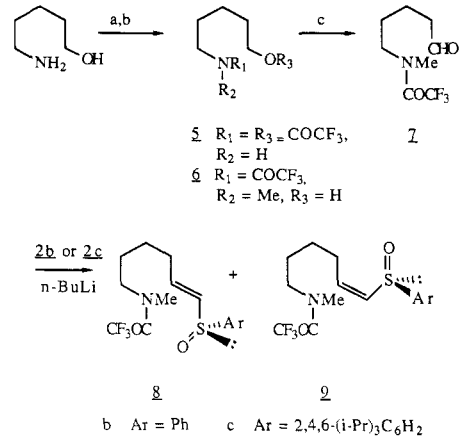
Scheme I



[a] $(CF_3CO)_2$, pyridine, 76%. [b] MeI, KOH, acetone, 100%. [c] Hexamethylenetetramine, CF_3COOH, 41%.

Scheme II

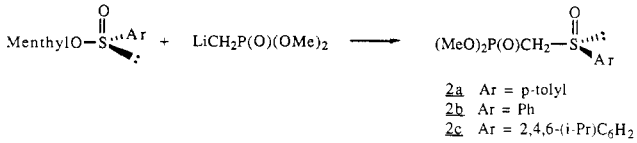


[a] $(CF_3CO)_2$, pyridine, 93%. [b] MeI, KOH, acetone, 63%. [c] PDC (87%) or PCC (92%).

on the conjugate addition of hydride to (*Z*)-1-propenyl methyl sulfoxide suggest a reactive conformation in which the S=O bond is syn coplanar to the carbon–carbon double bond.[4] Other workers have suggested different reactive conformations based on steric[2b,3a,b,g–i] and stereoelectronic considerations.[3c,d] We report here our studies on the intramolecular and intermolecular addition of nucleophiles to chiral (*E*)- and (*Z*)-vinyl sulfoxides.

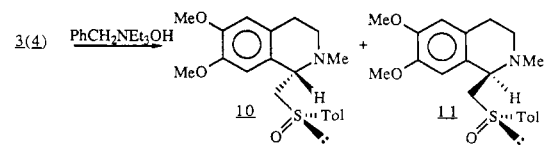
Intramolecular Conjugate Addition of Amines to Chiral (*E*)- and (*Z*)-Vinyl Sulfoxides

Synthesis of Substrates. The pairs of isomeric (*E*)- and (*Z*)-vinyl sulfoxides **3** and **4** and **8** and **9** were prepared from the Horner–Wittig reaction of the aldehydes **1** and **7**, respectively, with the lithium salt of (dimethoxyphosphoryl)methyl aryl sulfoxide (**2**).



The aldehydes **1** and **7** were prepared according to Schemes I and II, respectively. The (*E*)- and (*Z*)-vinyl sulfoxides were readily separated by column chromatography. Chiral (+)-(*R*)-(dimethoxyphosphoryl)methyl phenyl sulfoxide (**2b**, $[\alpha]^{25}_D$ +143°, *c* 5.0, acetone) and racemic (dimethoxyphosphoryl)methyl 2,4,6-triisopropylphenyl sulfoxide (**2c**) were prepared for the first time by a method analogous to that described for the preparation of (+)-(*R*)-**2a** from their corresponding aryl menthyl sulfinates[5] and (dimethoxyphosphoryl)methyllithium.[6]

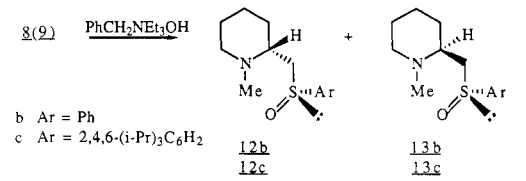
Table I. Cyclization of Vinyl Sulfoxides 3 and 4



vinyl sulfoxide	base[a]	solvt	temp,[b] °C	diastereoselection[c] 10:11
3	BTEA⁺OH⁻	CH_2Cl_2	−40	42:58
3	BTEA⁺OH⁻	MeOH	−40	38:62
3	LiOH	MeOH, H_2O	0	37:63
4	BTEA⁺OH⁻	CH_2Cl_2	−40	83:17
4	BTEA⁺OH⁻	MeOH	−40	84:16

[a] $BTEA^+$ is benzyltriethylammonium ion. [b] Reaction time 1 h at 0 °C or 40 h at −40 °C. [c] Determined by ^1H NMR.

Table II. Cyclization of Vinyl Sulfoxides 8 and 9 with Benzyltriethylammonium Hydroxide



vinyl sulfoxide	solvt	temp,[a] °C	diastereoselection[b] 12:13
8b	CH_2Cl_2	−40	91:9
8b	$PhCH_3$	0	83:17
8b	MeOH	−40	70:30
9b	CH_2Cl_2	−40	16:84
9b	$PhCH_3$	0	21:79
9b	MeOH	−40	30:70
8c	CH_2Cl_2	−40	93:7
8c	$PhCH_3$	0	89:11
8c	MeOH	−40	72:28

[a] Reaction time 1 h at 0 °C or 40 h at −40 °C. [b] Determined by ^1H NMR.

The Horner–Wittig reaction of the lithium salt of **2b** and aldehyde **7** in tetrahydrofuran (THF) gave a mixture of **8b** and **9b** (**8b**:**9b**, 68:32, 72%) which could be separated by column chromatography. The addition of hexamethylphosphoric triamide (HMPA/THF, 1:9) as cosolvent resulted in a marginal improvement in the stereoselectivity (**8b**:**9b**, 75:25, 69%), while the use of the sodium salt of **2b** (from $NaN(TMS)_2$) with toluene as cosolvent had an adverse effect on the product stereoselectivity (**8b**:**9b**, 59:41, 52%). The reaction of the lithium anion of **2c** with **7** in THF, however, showed a higher stereoselectivity in favor of the *E* isomer **8c** (**8c**:**9c**, 83:17, 89%).

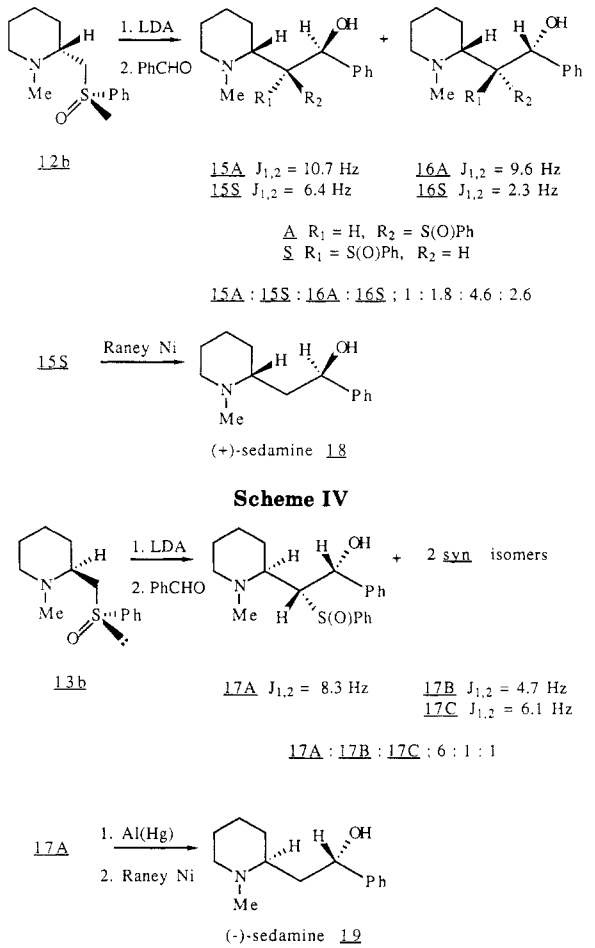
Intramolecular Cyclizations. Treatment of either **3** or **4** with benzyltriethylammonium hydroxide at −40 °C for 40 h in protic or aprotic solvent gave a mixture of the diastereomeric isoquinoline derivatives **10** and **11** as summarized in Table I. Diastereomerically pure isoquinoline **10** could be obtained in high yield (82%) from **4** after

(4) (a) Kahn, S. D.; Hehre, W. J. *J. Am. Chem. Soc.* **1986**, *108*, 7399–7400. (b) Khan, S. D.; Dobbs, K. D.; Hehre, W. J. *J. Am. Chem. Soc.* **1988**, *110*, 4602–4606.

(5) Klunder, J. M.; Sharpless, K. B. *J. Org. Chem.* **1987**, *52*, 2598–2602.

(6) Mikolajczyk, M.; Midura, W.; Grzejszczak, S.; Zatorski, A.; Chefczynska, A. *J. Org. Chem.* **1978**, *43*, 473–478.

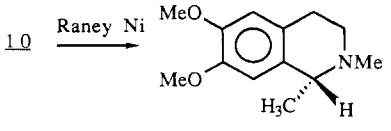
Scheme III



Scheme IV

chromatography. This compound could be recovered diastereomerically pure after exposure to the basic cyclization conditions, indicating that **10** and **11** arise from a kinetically controlled reaction. The isomeric vinyl sulfoxides **3** and **4** underwent cyclization in the opposite diastereochemical sense. A similar trend was found for the base-promoted cyclization of **8** and **9** which resulted in a mixture of the diastereomeric piperidine derivatives **12** and **13** (Table II). In contrast to **3** and **4**, the diastereoselectivity in the cyclization reactions of **8** and **9** showed a significant dependence on solvent polarity. A very marginal enhancement in diastereoselection was achieved from cyclization of the 2,4,6-triisopropylphenyl analogue **8c**.

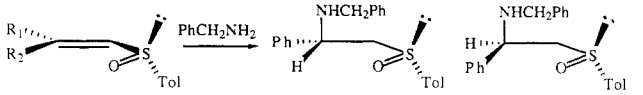
Proof of Stereochemistry. Reductive desulfurization of **10** with Raney nickel gave (*R*)-(+)-carnegine (**14**) in 51% yield ($[\alpha]^{18}_D$ +23.4° (*c* 1.5, ethanol); lit.[7] for (*S*)-(−)-carnegine $[\alpha]^{22}_D$ −24.9° (*c* 4.45, ethanol)) which had spectral properties (NMR, MS) identical with those of (*S*)-(−)-carnegine.[8]



14

While the relative stereochemistry of **12b** and **13b** was evident from ^{1}H NMR and NOE difference spectroscopy,[9]

Table III. Reaction of Vinyl Sulfoxides 20T and 20C with Benzylamine (3 mol equiv) at 80 °C



20T R_1 = Ph, R_2 = H
20C R_1 = H, R_2 = Ph

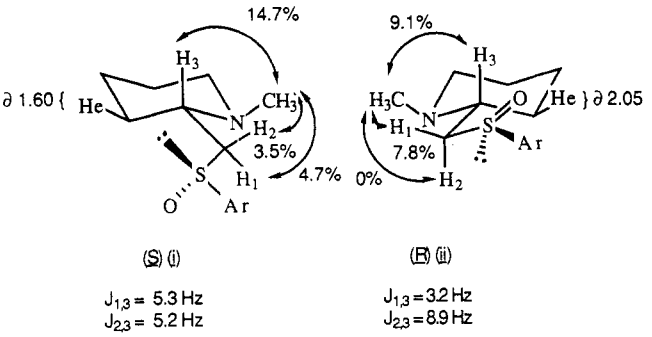
21 22

vinyl sulfoxide	time, days	solvt	diastereoselection[a] 21:22	yield, %
20T	20	EtOH	87:13	53[b]
20T	7	PhH	75:25	6[b]
20C	7	EtOH	86:14	64[b]
20C	20	EtOH	85:15	72[c]
20C	6	PhH	84:16	50[b]

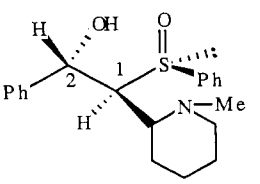
[a] Determined by ^{1}H NMR (400 MHz). [b] Percent conversion by ^{1}H NMR (400 MHz). [c] Isolated yield from chromatography.

their absolute stereochemistry was established by conversion of **12b** and **13b** to (+)-sedamine and (−)-sedamine, respectively (Schemes III and IV). Deprotonating **12b** or **13b** with lithium diisopropylamide (LDA) at −78 °C and then quenching the resulting carbanion with benzaldehyde gave a mixture of diastereomeric aldol products (Schemes III and IV). The relative stereochemistry at C-1 and C-2 of these products (syn or anti)[10] was evident from ^{1}H NMR coupling constants[11] and their absolute stereochemistry from the conversion to optically active sedamine. Direct reductive desulfurization of **15S** gave (+)-sedamine (**18**, $[\alpha]^{22}_D$ +65° (*c* 0.1, ethanol), lit.[12] $[\alpha]^{18}_D$ +91.5° (*c* 3.29, ethanol)) accompanied by 10–15% of allosedamine. These compounds were identical (NMR, TLC) with authentic

(9) The magnitude of the NOE enhancements (from selective irradiation of the N*Me*) and proton–proton coupling constants suggests the predominant conformations (*S*)-(i) and (*R*)-(ii) for **13b** and **12b**, respectively. The 2*R* stereochemistry for **12b** ((*R*)-(ii)) can be inferred from the unusually low field chemical shift for He. Only in conformation (*R*)-(ii) does this proton lie in the deshielding zone of the sulfoxide group.



(10) We use the stereochemical descriptors syn and anti according to: Masamune, S.; Ali, Sk. A.; Snitman, D. L.; Garvey, D. S. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 557–558. Figure i illustrates the anti stereochemistry for **15A** and the numbering at C-1 and C-2.



(i)

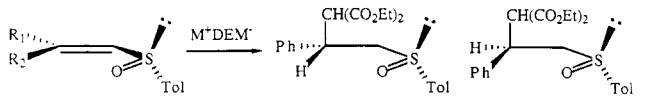
(11) See, for example: (a) Kingsbury, C. A.; Averbach, A. *J. Org. Chem.* **1971**, *36*, 1737–1742. (b) Brunet, E.; Garcia Ruano, J. L.; Martinez, M. C.; Rodriguez, J. H. *Tetrahedron* **1984**, *40*, 2023–2034.

(12) Beyerman, H. C.; Eenshuistra, J.; Eveleens, W.; Zweistra, A. *Recl. Trav. Chim., Pays-Bas* **1959**, *78*, 43–58.

(7) Batterby, A. R.; Edwards, T. P. *J. Chem. Soc.* **1960**, 1214–1222.

(8) A copy of the ^{1}H NMR of (*S*)-(−)-carnegine was kindly supplied by Prof. M. G. Reinecke.

Table IV. Reaction of Vinyl Sulfoxides 20T and 20C with the Anion of Diethyl Malonate (MDEM)



20T R_1 = Ph, R_2 = H 23 24
20C R_1 = H, R_2 = Ph

vinyl sulfoxide	counter-ion (M^+)	solvt	T^a °C/ time, h	diastereo-selection[c] 23:24	yield, % (% conversion)[c]
20T	Na^+	EtOH	rf[b]/13	19:81[d]	87[d]
20T	Na^+	EtOH	85/48	17:83	(100)
20T	Li^+	THF	rf[b]/115	78:22[d]	60[d]
20T	Na^+	DMF	85/144	34:66	(19)
20C	Na^+	EtOH	85/48	95:5	67 (100)
20C	Li^+	THF	rf[b]/114	96:4	65 (100)
20C	Na^+	DMF	85/144	89:11	(45)

[a] External bath temperature. [b] rf means heated at reflux. [c] Determined by ^1H NMR (400 MHz). [d] From Tsuchihashi.[3c,d]

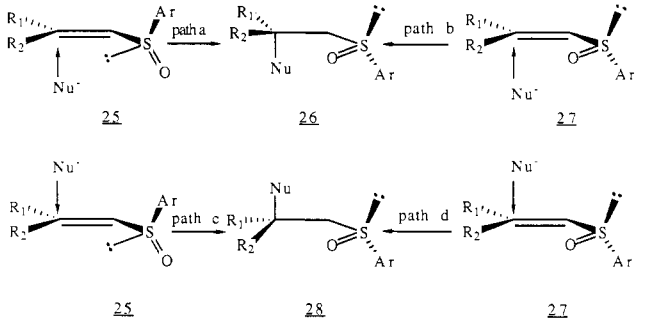
samples.[13] Evidently some racemization occurred during the reductive desulfurization process. This problem was overcome in the case of **17A** by first reduction to the sulfide with aluminum amalgam[14] and then Raney nickel reduction to give (−)-sedamine (**19**, $[\alpha]^{22}_D$ −87.8° (*c* 0.1, ethanol), lit.[12] $[\alpha]^{20}_D$ −92.5° (*c* 4.06, ethanol)) in high optical purity. The relative stereochemistry proposed for the triisopropylphenyl derivatives **12c** and **13c**, while not conclusive, was based on a comparison of their ^1H NMR spectra with those of **12b** and **13b**.

Intermolecular Additions of Nucleophiles to (*E*)- and (*Z*)-β-Styryl *p*-Tolyl Sulfoxide

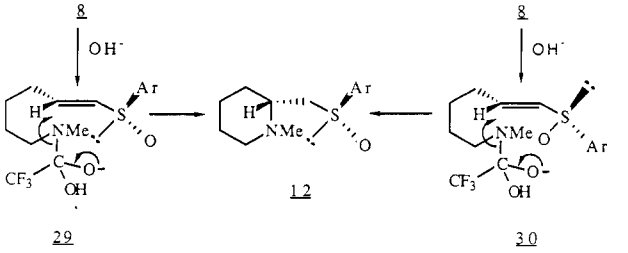
Intermolecular Addition of Benzylamine. In contrast to the above-mentioned intramolecular examples the intermolecular addition of benzylamine to isomeric (*E*)- and (*Z*)-vinyl sulfoxides is a diastereoconvergent process under kinetically controlled conditions (Table III).[3g] For example, the addition of benzylamine to either (*R*)-(*E*)- or (*R*)-(*Z*)-β-styryl *p*-tolyl sulfoxide in ethanol solution gives essentially an identical mixture (87:13) of diastereomeric adducts **21** and **22**. The reaction of the *E* isomer **20T** with benzylamine was less selective when benzene was employed as solvent. In contrast, the diastereoselection for the analogous reactions of the *Z* isomer **20C** was independent of solvent polarity. The absolute stereochemistry of **21** was established by reductive desulfurization of **21** over Raney nickel to give (+)-(*R*)-*N*-benzyl-*N*-(1-benzylethyl)amine[3g] (see Experimental Section). The contrast in stereochemical outcome between the intramolecular and intermolecular additions of amine to (*E*)- and (*Z*)-vinyl sulfoxides prompted an examination of the addition of the anion of diethyl malonate to **20T** and **20C**.

Addition of Diethyl Malonate to (*R*)-(*E*)- and (*R*)-(*Z*)-β-Styryl *p*-Tolyl Sulfoxides (20T and 20C). Tsuchihashi[3c,d] has reported the addition of the anion of diethyl malonate (DEM) to (*R*)-(*E*)-β-styryl *p*-tolyl sulfoxide (**20T**) and found the diastereoselection was dependent upon both solvent and metal counterion. We have

Scheme V



Scheme VI



examined the stereochemical outcome of the addition of the anion of DEM to both (*E*)-**20T** and (*Z*)-**20C** under various reaction conditions (Table IV). Our results for the addition of the sodium salt of DEM (NaDEM) to (*E*)-**20T** in ethanol are in accord with those reported by Tsuchihashi.[3c,d] These workers also reported a reverse in product diastereoselection for the addition of the lithium salt of DEM (LiDEM) in tetrahydrofuran (THF).[3d] In contrast to (*E*)-**20T**, the addition of NaDEM in ethanol or LiDEM in THF to (*Z*)-**20C** was highly diastereoselective (**23:24** ≥95:≤5) and **23** was the major diastereomeric product in each case. Poorer diastereoselection was observed from the addition of NaDEM in dimethylformamide to either (*E*)-**20T** or (*Z*)-**20C**.

Clearly isomeric (*E*)- and (*Z*)-β-styryl *p*-tolyl sulfoxides (**20T** and **20C**) exhibit different reactivities and diastereoselectivities in their reactions with the anion of DEM and benzylamine. The conjugate addition reactions of (*E*)-**20T** and (*Z*)-**20C** with benzylamine with LiDEM in THF are diastereoconvergent processes.

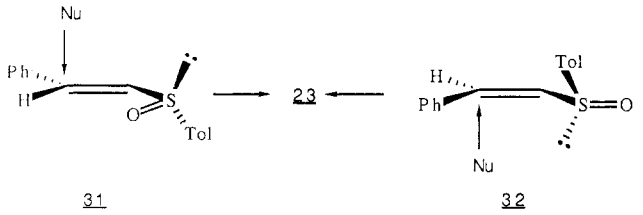
Discussion on Stereochemical Outcome

We and others have suggested the reactive conformations **27**[3g,i,4] (S=O bond and the C=C bond are syn coplanar) and **25**[2b,3a,b] (S lone electron pair and C=C bond coplanar) to account for the stereochemical outcome of nucleophilic addition to vinyl sulfoxides (Scheme V). On the basis of purely steric considerations, nucleophilic attack on **25** and **27** has been suggested to occur from the alkene face anti to the bulky *p*-tolyl group (Scheme V, paths a and d). Theoretical calculations on methyl vinyl sulfoxide suggest that s-cis conformation **27** may be more stable than **25** and that nucleophilic attack on **27** and **25** would occur anti to the lone electron pair on sulfur, i.e., from the same face as the sterically demanding *p*-tolyl substituent (Scheme V, paths b and c). Indeed the stereochemical outcome of our intramolecular additions can be rationalized by invoking nucleophilic attack on either a conformation analogous to **25** (**29**, Scheme VI) from the least hindered diastereotopic face or the s-cis conformation **30**, anti to the lone electron pair on sulfur (Scheme VI). We suggest that these above reactions occur via cyclization of an incipient amino anion because of the large difference

(13) We are indebted to Prof. H. C. Beyerman and Prof. L. Maat (Delft University of Technology) for providing authentic samples of (±)-sedamine and (±)-allosedamine and Prof. J. J. Tufariello (State University of New York, Buffalo) for providing NMR spectra. Reductive desulfurization of **15A** gave an inseparable mixture of allosedamine (^1H NMR (in part) 5.13 (dd, *J* = 3.5, 10.7 Hz, 1 H), 2.97 (m, 1 H), 2.42 (s, 3 H)) and sedamine (ca. 20% of mixture).

(14) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1964**, *86*, 1639–1640.

Scheme VII



in reaction rates between our intramolecular reactions (~40 °C, 2 days) and intermolecular reactions ($t_{1/2}$ = 6 days, 85 °C). Such tetrahedral intermediates as proposed in Scheme VI are known to have a significant lifetime, especially when the stabilizing CF_3 group is involved.[15]

Tsuchihashi[3c,d] has suggested a reactive conformation different from **25** and **27** to account for the effect of counterion and solvent on the diastereofacial selection in the reaction of (*E*)-**20T** with MDEM. Clearly this rationale cannot be extended to the reaction of (*Z*)-**20C** with LiDEM in THF. The individual reactions of (*E*)-**20T** and (*Z*)-**20C** with LiDEM must either proceed via different reactive conformations or involve the same reactive conformation but with nucleophilic attack from opposite diastereotopic faces of the alkene. The same is true for the individual reactions of (*E*)-**20T** and (*Z*)-**20C** with benzylamine. For the reaction of (*E*)-**20T** and (*Z*)-**20C** with NaDEM in ethanol, the stereochemical outcome can be adequately explained by using either reaction path a or path b in Scheme V.[16] Little coordination of the sulfoxide moiety of **20T** and **20C** would be expected by sodium ion in ethanol solvent. Accordingly, with Hehre's classification of nucleophiles,[4] NaDEM in ethanol may be considered a type B nucleophile (nonchelating reagent), and path b (Scheme V) would be anticipated since nucleophilic addition occurs anti to the more electron rich of the alkene.[16]

Hehre has suggested that for reactions of vinyl sulfoxides with chelating reagents (e.g., organometallic reagents, type C reagents) reaction may occur through a chelated cyclic chair transition state in which the metal cation is coordinated to the electron pair on sulfur.[4b] One may extend these ideas to account for the preferred formation of **23** from the reaction of (*E*)-**20T** and (*Z*)-**20C** with LiDEM (type C reagent) in THF and **21** from these same substrates with benzylamine, via an analogous transition state that involves hydrogen bonding of the amine to the electron pair on sulfur.[17]

We have previously suggested the *s-cis*-**31** and *s-trans*-**32** reactive conformations for the reactions of (*E*)-**20T** and (*Z*)-**20C** with benzylamine.[3g] Indeed the stereochemical outcome of the above reactions with both LiDEM and benzylamine can be accounted for by nucleophilic attack on these conformations from the least sterically demanding diastereotopic face of the alkene (Scheme VII). The exact role of the metal cation and the extent of hydrogen bonding between benzylamine and the sulfoxide moiety[18] in these reactions is not certain and awaits further experimental investigations.

Experimental Section

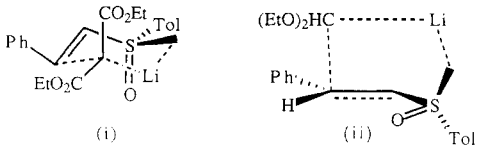
General Procedures. Nuclear magnetic resonance (NMR) spectra were recorded on a JEOL FX 90Q Fourier transform NMR spectrometer and on a JEOL JNM/GX400 Fourier transform NMR spectrometer. Each signal is described in terms of its chemical shift in ppm from TMS (internal standard). Multiplicity and coupling constants are then given. Abbreviations used to denote NMR spectral signals are s, singlet; d, doublet; t, triplet; q, quartet; hept, heptet; br, broad; v, variable in position. All spectra were run in $CDCl_3$. Infrared spectra were recorded on a Perkin-Elmer Model 783 infrared spectrophotometer as thin films unless otherwise noted. Major absorptions are listed in wavenumbers (cm^{-1}). Mass spectra were recorded on a Vacuum Generator V.G. 12-12 mass spectrometer in the chemical ionization mode with isobutane. High-resolution mass spectra were recorded on a JEOL JMS-DX300 mass spectrometer at the Victorian College of Pharmacy. Elemental analyses were performed at the Australian National University Analytical Services Unit. Melting points were determined in open capillaries and are uncorrected. The following abbreviations are used: THF, tetrahydrofuran; nBuLi, *n*-butyllithium; EtOAc, ethyl acetate; hex, hexane. The term "dried" refers to the organic extract being dried over anhydrous $MgSO_4$ unless otherwise stated. The term "evaporation" implies the removal of organic solvents on a Büchi rotoevaporator (water aspirator pressure), followed by the removal of the last traces of solvent with a high-vacuum pump (ca. 0.1 mmHg). Tetrahydrofuran and ether were dried over sodium metal and distilled from a purple solution of sodium/benzophenone and stored under nitrogen. Other solvents were dried by using standard techniques. Column chromatography was performed on silica gel (0.063–0.2 mm, Merck). Thin-layer chromatography (TLC) was carried out on plastic-backed silica gel plates F_{254} (Merck), and preparative thick-layer chromatography on glass plates (20 × 20 cm × 2 mm) coated with silica gel F_{254} (Merck). Reactions involving nBuLi, LDA, or sodium bis(trimethylsilyl)-amide were performed in glassware that had been oven-dried and cooled in a desiccator prior to use and under an atmosphere of dry nitrogen. Optical rotations were performed on a Carl Zeiss polarimeter (Model 53202); concentrations reported are in g/100 mL.

5-(Trifluoroacetamido)pentyl Trifluoroacetate (5). To a solution of 5-amino-1-pentanol (9.00 g, 87.24 mmol) in dry CH_2Cl_2 (80 mL) and pyridine (17.3 mL, 220 mmol) at 0 °C, under nitrogen was added, slowly dropwise, trifluoroacetic anhydride (17.0 mL, 192 mmol). The mixture was stirred for 10 min at 0 °C and then a further 45 min at room temperature. The reaction mixture was then cooled to 0 °C and extracted with cold 5% HCl (3 × 25 mL), water (3 × 25 mL), and 5% $NaHCO_3$ (3 × 25 mL). The organic extract was dried and evaporated to give a pale yellow oil (19.39 g, 93%): IR 3200–3480, 2940, 1785, 1710, 1560, 1350, 1199; ^1H NMR 6.82 (br and v, 1 H, N*H*), 4.37 (t, 2 H), 3.38 (t, 2 H), 1.20–2.00 (m, 6 H); ^{13}C NMR 22.58, 27.56, 28.15, 39.57, 67.73, 114.74 (q, J_{CF} = 287 Hz), 115.88 (q, J_{CF} = 287 Hz), 157.38 (q, J_{CF} = 37 Hz), 157.48 (q, J_{CF} = 37 Hz); MS (EI) 295 (M^+), 226 (M – CF_3^+), 182 (M – $OCOCF_3^+$), 168, 152.

(15) Capon, B.; Dosunmu, D. I.; Matossanchez, M. *Advances in Physical Organic Chemistry*; Academic Press: New York, 1985; Vol. 21, pp 37.

(16) Hehre[4] has incorrectly depicted the diastereoisomer **23** as the major product arising from the addition of NaDEM in ethanol to **20T** (*E*).

(17) (a) One could consider the idealized cyclic chair transition state (i) or the chelated transition state (ii); however, the former would appear unlikely on geometric grounds when one realizes the impossible orbital overlap between the electron pair on sulfur and the lithium cation. Furthermore, chelation of the lithium cation to the sulfoxide oxygen rather than the electron pair would be expected for recent reports. See: Boche, G. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 277–297. (b) Sulfoxide complexes of platinum(II) and palladium(II) are known, however, in which the metal is coordinated to sulfur rather than oxygen. See: Kitching, W.; Moore, C. J.; Doddrell, D. *Inorg. Chem.* **1970**, *9*, 541–549.



(18) By analogy with the reactions of vinyl sulfones with amines, the reactions of **20T** and **20C** with benzylamine most likely involve a hydrogen-bonded transition state incorporating the vinyl sulfoxide and two molecules of amine in aprotic solvent or vinyl sulfoxide, amine, and solvent for reactions in ethanol. Indeed, the faster rate of reaction that is observed in our reactions with ethanol as solvent when compared to benzene is clearly consistant with a rate expression that involves the concentration of the solvent for reactions in ethanol. For a kinetic study on the reactions of vinyl sulfones with amines, see: McDowell, S. T.; Stirling, C. J. M. *J. Chem. Soc. B* **1967**, 343–348.

***N*-Methyl-*N*-(5-hydroxy-1-pentyl)trifluoroacetamide (6).**[19] To a solution of the trifluoroacetate **5** (9.60 g, 32.52 mmol) in dry acetone (100 mL) was added methyl iodide (8.13 mL, 130 mmol), and the mixture was stirred at room temperature for 30 min. Anhydrous powdered KOH (7.29 g, 130 mmol) was added and the mixture was heated to reflux (5 min) and then cooled. The solution was decanted from the KOH and the residue was washed once with dry acetone (20 mL). The acetone solutions were combined and evaporated, yielding a yellow oil, which was then dissolved in 80 mL of cold CH_2Cl_2 and extracted with cold water (3 × 25 mL). The organic layer was dried and evaporated to yield a yellow oil (crude yield 7.55 g): ^{1}H NMR showed the presence of the acetone aldol product 4-hydroxy-4 methyl-2-pentanone (^{1}H NMR) 3.42 (s, 1 H, O*H*), 2.64 (s, 2 H), 2.18 (s, 3 H), 1.26 (s, 6 H)) in significant amounts. This impurity was removed by careful distillation (50–60 °C) under vacuum, leaving the desired alcohol (4.37 g, 63%): IR 3100–3700, 2940, 1690, 1370, 1250, 1195, 1150; ^{1}H NMR 3.62 (t, 2 H), 3.50–3.30 (m, 2 H), 3.00–3.12 (m, 3 H, NCH_3 amide resonances), 2.46 (br s and v, 1 H, O*H*), 1.20–2.00 (m, 6 H); MS 213 (M + H$^+$).

***N*-Methyl-*N*-(5-oxo-1-pentyl)trifluoroacetamide (7). Method A: Oxidation Using PDC.**[20] To a rapidly stirred suspension of dried and finely powdered PDC (8.37 g, 21.1 mmol) in dry CH_2Cl_2 (30 mL) was added a solution of the alcohol **6** (3.00 g, 14.1 mmol) in CH_2Cl_2 (10 mL) at room temperature. The suspension darkened immediately and was stirred for 2 h. After this time further PDC (2.77 g, 7.00 mmol) was added and the mixture was stirred overnight. The black suspension was diluted with ether (100 mL), and the solution was decanted from the insoluble oxides. The chromium salts were washed further (2 × 50 mL) with ether and the ether extracts were combined and then filtered through a pad of silica gel and Celite. The filtrate was dried and then evaporated giving the aldehyde **7** as an oil (2.59 g, 87%).

Method B: Oxidation Using PCC.[21] To a rapidly stirred suspension of dried and finely powdered PCC (2.28 g, 10.56 mmol) in dry CH_2Cl_2 (9 mL) was added a solution of the alcohol **6** (1.5 g, 7.04 mmol) in CH_2Cl_2 (6 mL) at room temperature. After 2 h the mixture was diluted with ether (50 mL) and then worked up as described above for the PDC oxidation of **6**. The aldehyde **7** (1.37 g, 92%) was obtained as a colorless oil: IR 2940, 2725, 1725, 1690, 1460, 1420, 1245, 1190; ^{1}H NMR 9.77 (s, 1 H), 3.45–3.14 (m, 2 H), 3.00–3.12 (m, 3 H), 2.52–2.50 (m, 2 H), 1.31–1.73 (m, 4 H); MS 212 (M + H$^+$, 90%), 140 (100%).

(+)-(*R*)-(Dimethylphosphonyl)methyl Phenyl Sulfoxide (2b). To a solution of dimethyl methanephosphonate (2.48 g, 0.02 mol) in dry THF (30 mL), at −78 °C under nitrogen, was added a solution of nBuLi in hexane (0.022 mol). The mixture was stirred at −78 °C for 30 min. A solution of (−)-menthyl (−)-(*S*)-benzenesulfinate (2.80 g, 0.01 mol; $[\alpha]^{25}_D$ −196° (*c* 1.0, acetone), lit.[22] $[\alpha]_D$ −200° (*c* 0.2, acetone)) in dry THF (20 mL) was then added. After 30 min the mixture was warmed slowly to −20 °C and then quenched by the addition of aqueous NH_4Cl solution. The organic solvents were evaporated, and the aqueous layer was extracted with petroleum ether (1 × 25 mL) to remove menthol and then with $CHCl_3$ (3 × 25 mL). The combined $CHCl_3$ extracts were dried and evaporated. After careful removal of dimethyl methanephosphonate under reduced pressure, the product was obtained as a colorless oil (1.86 g, 75%, R_f 0.39 (5% MeOH/$CHCl_3$)): $[\alpha]^{25}_D$ +143° (*c* 5.0, acetone); ^{1}H NMR 7.75 (m, 2 H), 7.55 (m, 3 H), 3.82 and 3.75 (d, each 3 H, J_{POCH_3} = 11.29 Hz), 3.42 (t, H_A) and 3.29 (t, H_B; diastereomeric mylene protons $J_{AB} \sim J_{AP} = J_{BP} \sim$ 14.80 Hz); ^{13}C NMR 144.80, 131.67, 129.43, 124.16 54.35 (d, J_{PCH_3} = 139.6 Hz), 53.21 (d J_{POCH_3} = 6.32 Hz); 53.05 (d, J_{POCH_3} = 6.32 Hz); MS 249 (M + H)$^+$), 217, 177.

(Dimethylphosphonyl)methyl 2,4,6-Triisopropylphenyl Sulfoxide (2c). The title compound was prepared in a fashion analogous to **2b** except that the reaction was stirred for 2 h at −78 °C after the addition of the menthyl 2,4,6-triisopropylphenylsulfinate[5] (0.50 g, 1.22 mmol) and then overnight at room temperature. Compound **2c** was obtained after workup and column chromatography (silica, 5% MeOH/$CHCl_3$) as a white solid (123 mg (26%)): mp 140–142 °C; R_f 0.344 (5% MeOH/$CHCl_3$); ^{1}H NMR 7.10 (s, 2 H); 3.84 and 3.46 (t, 2 H, diastereomeric methylene protons H_A and H_B, $J_{AP} = J_{BP} = J_{AB}$ = 14.8 Hz), 3.78 and 3.76 (d, 6 H, diastereomeric methoxy protons J_{POCH_3} = 11.29 Hz), 2.88 (sept, 1 H), 1.20–1.40 (m, 19 H); ^{13}C NMR 153.04, 149.91, 122.98, 53.06 (d, J_{POCH_3} = 6.6 Hz), 51.21 (d, J_{PCH_2} = 139.7 Hz), 34.39, 28.24, 24.39, 23.71; MS 375 (M + H)$^+$, 359, 251, 233, 171, 125. Anal. Calcd for $C_{18}H_{31}SO_4P$: C, 57.72; H, 8.36. Found: C, 57.78; H, 8.60.

(*E*)- and (*Z*)-(*SR*)-*N*-Methyl-*N*-[6-(phenylsulfinyl)hex-5-en-1-yl]trifluoroacetamide (8b and 9b). To a solution of **2b** (3.72 g, 0.015 mol) in dry THF (25 mL) was added a solution of nBuLi in hexane (0.016 mol) at −78 °C under nitrogen. After 1 h a pale yellow solution of the lithium derivative was obtained. A solution of the aldehyde **7** (3.17 g, 0.015 mol) in dry THF (20 mL) was then added dropwise at −78 °C, and stirring was continued at that temperature for 30 min. The mixture was then warmed slowly to room temperature and stirred for 2 h. The reaction was quenched by the addition of saturated NH_4Cl solution (50 mL). The organic solvents were evaporated, and the aqueous layer was extracted with $CHCl_3$ (3 × 25 mL). The combined $CHCl_3$ extracts were washed with water (25 mL), dired, and evaporated to give the crude product. ^{1}H NMR of the crude product revealed an *E*:*Z* ratio of 68:32. Column chromatography (silica, 1:1 EtAc/hex) allowed separation of the *E* and *Z* isomers to yield pure **8b** (oil, 3.31 g, R_f = 0.61, EtOAc) and **9b** (oil, 1.58 g, R_f = 0.53, EtOAc): IR 2940, 2860, 1690, 1445, 1245, 1190, 1145, 1090, 1040, 750, 690; ^{1}H NMR 7.60–7.20 (m, 5 H), 3.70–3.50 (m, 2 H), 3.36–2.85 (m, 3 H, NCH_3 amide resonances), 2.25–2.10 (m, 2 H), 1.60–1.15 (m, 4 H); olefinic resonances (**8b**) 6.15 (d, 1 H, J = 15.16 Hz), 6.51 (d of t, 1 H, J = 6.4, 15.16 Hz), (**9b**) 6.22 (m, 1 H), 6.14 (m, 1 H); ^{13}C NMR (**8b**) 156.84 (q, J_{CF} = 37 Hz), 144.31, 139.24, 135.86, 130.73, 129.17, 124.25, 115.46 (q, J_{CF} = 287 Hz), 48.88, 31.23, 27.47, 25.66, 24.98; MS 334 ((M + H)$^+$), 210, 196, 182, 140; HRMS calcd for $C_{15}H_{19}NOSF_3$ 334.1088, found 334.1080.

***N*-Methyl-*N*-[6-((2,4,5-triisopropylphenyl)sulfinyl)hex-5-en-1-yl]trifluoroacetamide (8c and 9c).** To a solution of **2c** (338 mg, 0.9 mmol) in dry THF (5 mL) at −78 °C was added a solution of nBuLi (1.15 mmol) in hexane under nitrogen. The mixture was allowed to stire for 2 h. A solution of the aldehyde (0.3 g, 0.14 mmol) in THF (3 mL) was added dropwise at −78 °C and the solution was stirred for 2 h at −78 °C then warmed slowly to room temperature and allowed to stir for a further 2 h. Workup was as described for the preparation of **8c** and **9b**. Flash chromatography (silica, 1:1 EtOAc/hex) gave pure **8c** as an oil (369 mg, 89%): R_f (*E*) isomer) 0.60 (1:1 EtOAc/hex), minor (*Z*) isomer 0.52 (1:1 EtOAc/hex); IR 2960, 2940, 2870, 1695, 1598, 1460, 1245, 1190, 1140, 1100, 1050; ^{1}H NMR 0.08–1.90 (m, 22 H), 2.25–2.35 (m, 2 H), 2.28 (s, 1 H), 2.95–3.15 (m, 3 H, NCH_3 amide resonance), 3.30–3.55 (m, 2 H), 7.06 (s, 2 H); olefinic resonances (**9c**) 6.72 (d, J = 10.1 Hz, 1 H), 6.15 (dt, J = 7.5, 10.1 Hz), (**8c**) 6.43 (m, 2 H), selective decoupling at 2.3 ppm simplified this multiplet as two doublets (J = 15.1 Hz); ^{13}C NMR (**8c**) 156.81 (q, J = 37 Hz), 152.61, 150.37, 136.85, 134.41, 134.23, 122.99, 115.35 (q, J = 286 Hz), 48.95, 34.26, 31.53, 28.11, 25.96, 25.33, 24.69, 23.82, 23.57; MS 460 ((M + H)$^+$), 423, 235, 208, 196, 140; HRMS calcd for $C_{24}H_{36}NO_2SF_3$ 460.2497, found 460.2455.

(+)-(2*R*,*SR*)- and (2*S*,*SR*)-*N*-Methyl-2-[(phenylsulfinyl)methyl]piperidine (12b and 13b). Benzyltrimethylammonium hydroxide solution (2 M in MeOH, 1.6 mL) was added to a flask under nitrogen, and the methanol was evaporated under reduced pressure. CH_2Cl_2 (1 mL) was added and then evaporated to remove any traces of methanol. Then 5 mL of dry CH_2Cl_2 was added, and the solution cooled to −40 °C. A solution of the phenyl vinyl sulfoxide **8b** (250 mg, 0.75 mmol) in CH_2Cl_2 (5 mL) was added, and the mixture was stirred for 40 h at −40 °C or until TLC showed no starting vinyl sulfoxide. The mixture was then extracted with EtOAc and water; the EtOAc layer was dried and evaporated. The diastereoselectivity of the cyclization was determined by ^{1}H NMR. Diastereomerically pure **12b** and **13b** respectively were obtained by column chromatography (silica, 2.5% MeOH/$CHCl_3$, R_f = 0.57 and 0.51 (10% MeOH/$CHCl_3$), respectively) as oils (combined yield, 123 mg,

(19) This procedure was a modification of the one reported: Johnstone, R. A. W.; Payling, D. W.; Thomas, C. *J. Chem. Soc. C* **1969**, 2223–2224.
(20) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399–402.
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69%). **12b**: $[\alpha]^{20}_D$ +230 (*c* 1.4, $CHCl_3$); ^1H NMR (a and e refer to axial and equatorial protons, respectively) 7.66 (2 H), 7.52 (3 H), 3.15 (dd, *J* = 3.2, 13.1 Hz, 1 H, H-1′), 2.83 (m, 1 H, H-6e), 2.70 (dd, *J* = 8.9, 13.1 Hz, 1 H, H-2′), 2.56 (m, 1 H, H-2a), 2.26 (s, 3 H), 2.23 (m, 1 H, H-6a), 2.05 (m, 1 H, H-3e), 1.74 (m, 1 H, H-4e), 1.63 (m, 3 H, H-3a, 5a, 5e), 1.38 (m, H-4a); ^{13}C NMR 144.89, 130.83, 129.18, 123.95, 61.34, 58.41, 55.72, 42.79, 30.78, 25.55, 23.12; MS 238 ((M + H)$^+$), 167, 149, 127, 111; HRMS calcd for $C_{13}H_{19}NO_3$ 238.1266, found 238.1265. **13b**: ^1H NMR 7.66 (2 H), 7.52 (3 H), 3.00 (dd, *J* = 5.3, 13.9 Hz, 1 H, H-1′), 2.89 (dd, *J* = 5.2, 13.9 Hz, 1 H, H-2′), 2.83 (m, 1 H, H-6e), 2.62 (m, 1 H, H-2a), 2.38 (s, 3 H), 2.26 (1 H, m, H-6a), 1.60 (m, 2 H, H-3e, 4e), 1.58 (m, 2 H, H-5e, 5a), 1.51 (m, 1 H, H-3a), 1.36 (m, 1 H, H-4a); ^{13}C NMR 144.89, 130.83, 129.18, 123.95, 62.12, 58.16, 55.53, 42.80, 31.91, 24.63, 23.17; MS 238 ((M + 1)$^+$), 167, 149, 127, 111.

***N*-Methyl-2-[((2,4,6-triisopropylphenyl)sulfinyl)methyl]piperidine (12c).** This compound was prepared in a fashion analogous to **12b** from 2,4,6-triisopropylphenyl vinyl sulfoxide **8c**. Compound **13c** was obtained as an oil in 57% yield after column chromatography (R_f 0.37 (5% MeOH/$CHCl_3$)); ^1H NMR 7.08 (br s, 2 H), 2.89 (dd, *J* = 6.9, 13.7 Hz), 2.87 (dd, *J* = 6.9, 13.7 Hz), 2.81 (m, 1 H), 2.68 (m, 1 H), 2.31 (s, 3 H), 2.27 (m, 1 H), 2.13 (m, 1 H), 1.73 (m, 1 H), 1.64 (m, 3 H), 1.42 (m, 1 H), 1.31 (d, *J* = 8 Hz, 3 H), 1.23 (d, *J* = 8 Hz, 6 H); ^{13}C NMR 152.52, 149.78, 133.32, 123.23, 59.64, 56.18, 42.46, 34.26, 29.92, 28.11, 24.79, 24.55, 24.21, 23.67, 22.84; MS 364 ((M + H)$^+$, 15%); HRMS calcd for $C_{22}H_{37}NOS$ 364.2674, found 364.2628.

Aldol Reaction of 12b and 13b: *N*-Methyl-2-[2′-hydroxy-2′-phenyl-1′-(phenylsulfinyl)ethyl]piperidine (16 and 17). To a solution of **12b** (70 mg, 0.295 mmol) in THF (3 mL) was added via syringe a solution of LDA (0.4 M, 0.398 mmol) in THF. After 45 min benzaldehyde (0.472 mmol, 0.048 mL) was added. After 40 min at −78 °C the mixture was quenched with saturated NH_4Cl solution (1 mL). Saturated Na_2CO_3 solution (10 mL) and CH_2Cl_2 (20 mL) were added, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2×), and the combined extract was dried (K_2CO_3) and evaporated. Column chromatography (silica gel, 2.5–5% MeOH/$CHCl_3$) gave **16A** (37 mg, R_f 0.62, 5% MeOH/$CHCl_3$), **16S** (containing 8% of **15A**, 31 mg, R_f 0.49), and **15S** (33 mg, R_f 0.27). **16A**: ^1H NMR 7.87 (dd, 2 H), 7.52–7.27 (m, 8 H), 5.56 (br s, O*H*, 1 H), 5.27 (d, *J* = 9.6 Hz, 1 H), 3.93 (dd, *J* = 2.8, 9.6 Hz), 2.77 (dd, *J* = 1.8, 11.4 Hz), 2.08 (dq, *J* = 4.1, 13.1 Hz), 1.90 (dd, *J* = 3.4, 13.1 Hz, 1 H), 1.77 (m, 2 H), 1.67 (dt, *J* = 3.1, 11.4 Hz, 1 H), 1.64 (s, 3 H), 1.53 (m, 2 H), 0.98 (m, 1 H); MS 344 ((M + H)$^+$, 31%), 218 ((M − PhSO)$^+$, 75%), 201 (100%), 200 (92%). **16S**: ^1H NMR 7.78–6.97 (m, 10 H), 5.51 (d, *J* = 2.3 Hz, 1 H), 4.70 (s, 1 H, O*H*), 2.95 (t, *J* = 2.4 Hz, 1 H), 2.91 (br d, 1 H), 2.58 (br d, 1 H), 2.37 (dt, *J* = 2.6, 11.1 Hz), 2.18 (qd, *J* = 3.4, 13.1 Hz, 1 H), 2.01 (td, *J* = 3.8, 11.6 Hz, 1 H), 1.92 (s, 3 H), 1.86 (m, 1 H), 1.62 (m, 2 H), 1.26 (m, 1 H); MS 344 ((M + H)$^+$, 17%), 218 ((M − PhSO)$^+$, 95%), 217 (92%), 200 (67%), 127 (100%). **15S**: ^1H NMR 7.78–7.2 (m, 10 H), 5.20 (d, *J* = 6.4 Hz, 1 H), 3.55 (t, *J* = 6.7 Hz, 1 H), 2.98 (dt, 1 H), 2.33 (m, 1 H), 2.17 (s, 3 H), 1.54 (m, 1 H), 1.46 (m, 2 H), 1.29 (m, 1 H), 1.15 (m, 1 H), 0.84 (m, 1 H); MS 344 ((M + H)$^+$, 8%), 218 ((M − PhSO)$^+$, 27%), 217 (29%), 200 (100%). **15A**: ^1H NMR (in part) 5.48 (d, *J* = 10.7 Hz). **17A**: ^1H NMR (in part) 5.31 (d, *J* = 8.3 Hz, 1 H), 3.1–2.9 (m, 2 H), 2.63 (s, 3 H); MS 344 ((M + H)$^+$).

***N*-Methyl-*N*-(2-(2′-formyl-4′,5′-dimethoxyphenyl)ethyl)trifluoroacetamide (1).** A mixture of *N*-methyl-*N*-(2-(3′,4′-dimethoxyphenyl)ethyl)trifluoroacetamide (3 g, 10.3 mmol, prepared from 3,4-dimethoxyphenethylamine according to Scheme I; ^1H NMR 6.57 (m, 3 H), 3.83 (s, 6 H), 3.61 (t, 2 H), 3.02, 2.96, 2.95 (singlets, 3 H, N(CH_3)$COCF_3$), 2.82 (t, 2 H); MS 292 (((M + H)$^+$), 100%)), hexamethylenetetramine (2.89 g, 20.6 mmol), and trifluoroacetic acid (15 mL) was heated to reflux under nitrogen for 12 h.[23] The solution was then cooled and then evaporated to dryness. A solution of sodium acetate (6.7 g) in ice water (10 mL) was added, and the mixture was stirred at room temperature for 10 min. The solution was extracted with CH_2Cl_2 (3×), and the combined extracts were washed with 10% $NaHCO_3$, dried, and evaporated. Column chromatography (silica gel, 30% EtOAc/hex) gave aldehyde **1** (1.36 g, 40%, EtOAc/hex, R_f 0.2) as a white solid, which must be stored under nitrogen in the freezer; ^1H NMR 10.07 (s, 1 H), 7.31 (s, 1 H), 6.77 (s, 1 H), 3.96 (s, 3 H), 3.95 (s, 3 H), 3.59 (m, 2 H), 3.32 (m, 2 H), 3.16, 3.11, 3.09 (singlets, 3 H, N(CH_3)$COCF_3$); MS 320 ((M + H)$^+$, 100%).

(*R*)-(*E*)-*N*-Methyl-*N*-[2-(2-(2′-(*p*-tolylsulfinyl)-1′-ethenyl)-4,5-dimethoxyphenyl)ethyl]trifluoroacetamide (3) and (*R*)-(*Z*)-4. Compounds **3** and **4** were prepared in a fashion analogous to **8b** and **9b** from aldehyde **1** and (+)-(*R*)-dimethoxyphosphoryl)methyl *p*-tolyl sulfoxide (**2a**).[6] The pure products were obtained as colorless oils after column chromatography (silica gel, 50% EtOAc/hex, combined yield 62%).

3: ^1H NMR 7.62 (d, *J* = 15 Hz, 1 H), 7.61 (d, *J* = 8 Hz, 1 H), 7.34 (d, *J* = 8 Hz, 1 H), 6.94 (s, 1 H), 6.71 (d, *J* = 15 Hz, 1 H), 6.68 (s, 1 H), 3.87 (s, 3 H), 3.84 (s, 3 H), 3.61 (m, 2 H), 3.10, 3.05, 3.04 (singlets, 3 H, N(CH_3)$COCF_3$), 3.1–3.0 (m, 2 H), 2.42 (s, 3 H); IR 1680, 1605, 1510, 1370, 1180, 1145, 1090; MS 456 ((M + H)$^+$, 42%), 292 (50%), 149 (100%).

4: ^1H NMR 7.54 (d, *J* = 8 Hz, 1 H), 7.35 (d, *J* = 10 Hz, 1 H), 7.32 (d, *J* = 8 Hz, 1 H), 7.18 (s, 1 H), 6.73 (s, 1 H), 6.54 (d, *J* = 10 Hz, 1 H), 3.91 (s, 6 H), 3.50 (m, 2 H), 3.02, 3.00 (singlets, N(CH_3)$COCF_3$), 2.88 (m, 2 H), 2.41 (s, 3 H); MS 456 ((M + H)$^+$, 100%).

(+)-(*IR*,*SR*)-*N*-Methyl-3,4-dihydro-6,7-dimethoxy-1-[(*p*-tolylsulfinyl)methyl]isoquinoline (10) and (*IS*,*SR*)-11. The vinyl sulfoxide **4** (40 mg) was cyclized in CH_2Cl_2 as described above for the preparation of **12b** and **13b**. Preparative TLC (5% MeOH/EtOAc) gave **10** (25.8 mg, 82%) and **11** (4.4 mg, 14%).

10: solid, mp 70–72 °C, $[\alpha]^{23}_D$ +206 (*c* 1.1, $CHCl_3$); ^1H NMR 7.53 (d, *J* = 8.1 Hz, 2 H), 7.27 (d, *J* = 8.1 Hz, 2 H), 6.55 (s, 2 H), 4.17 (dd, *J* = 3.8, 10.4 Hz), 3.83 (s, 3 H), 3.80 (s, 3 H), 3.08 (dd, *J* = 10.4, 13.4 Hz, 1 H), 3.00 (dd, *J* = 3.8, 13.4 Hz, 1 H), 2.62 (s, 3 H), 2.39 (s, 3 H); ^{13}C NMR 147.87, 147.73, 141.87, 141.00, 129.77, 126.75, 126.26, 123.77, 111.62, 110.37, 65.94, 57.30, 55.98, 55.83, 45.24, 41.83, 22.55, 21.23; MS 219 (65%, M − TolSOH), 206 (100%, M − TolSOCH$_2$). Anal. Calcd for $C_{20}H_{25}NO_3S$: C, 66.85; H, 6.96; N, 3.90. Found: C, 66.8; H, 7.3; N, 4.2.

11: oil; ^1H NMR 7.63 (d, *J* = 8.1 Hz, 2 H), 7.33 (d, *J* = 8.1 Hz, 2 H), 6.58 (s, 1 H), 6.53 (s, 1 H), 3.85 (s, 3 H), 3.81 (s, 3 H), 3.69 (t, *J* = 6.7 Hz, 1 H), 3.46 (dd, *J* = 6.9, 13.1 Hz, 1 H), 3.15 (m, 1 H), 2.99 (dd, *J* = 6.6, 13.1 Hz, 1 H), 2.87 (m, 2 H), 2.47 (m, 1 H), 2.43 (s, 3 H), 2.35 (s, 3 H); ^{13}C NMR 147.98, 147.49, 141.48, 141.04, 129.77, 126.90, 125.67, 124.60, 111.72, 110.40, 63.45, 57.64, 55.93, 55.79, 45.88, 41.44, 23.87, 21.33.

Synthesis of (+)-(*R*)-Carnegine (14). A stirred solution of **10** (25 mg) in water-saturated ether (3 mL) was treated with Raney nickel (W-2, 2.9 g). After 1 h the mixture was diluted with ether and the solution decanted (3×). The combined solutions were dried, filtered, and then evaporated. The crude product was purified by acid extraction purification and then filtration through a short column of alumina, giving 7.7 mg of pure **14** as a viscous oil: $[\alpha]^{18}_D$ +23.4° (*c* 1.5, EtOH); (lit.[7] (*S*)-(−)-carnegine $[\alpha]^{22}_D$ −24.9° (*c* 4.45, EtOH); ^1H NMR as previously reported by us;[8,24] MS 222 ((M + H)$^+$, 98%), 206 (M − CH_3, 100%).

Synthesis of (−)-Sedamine. A solution of **17A** (20 mg) in THF/H_2O (2 mL, 9:1) was treated first with aluminum amalgam (250 mg) at 0 °C (10 min) and then at room temperature (1 h) as previously described.[14] The crude sulfide (^1H NMR 4.87 (d, *J* = 8.8 Hz, 1 H), 3.43 (dd, *J* = 6.9, 8.8 Hz, 1 H), 2.53 (s, 3 H)) was treated with Raney nickel as described above except ethanol was employed as solvent. The crude product was purified by an acid extraction purification and then precipitation from pentane solution at −78 °C. This compound was identical by TLC and ^1H NMR to an authentic sample:[13] mp 59–61 °C (lit.[12] mp 61–62 °C); $[\alpha]^{22}_D$ −87.8° (*c* 0.1, ethanol); (lit.[12] $[\alpha]_D$ −92.5° (*c* 4.06, ethanol); ^1H NMR 7.41–7.21 (m, 5 H), 4.9 (dd, *J* = 2.8, 10.7 Hz, 1 H), 3.10 (m, 1 H), 2.89 (m, 1 H), 2.59 (m, 1 H), 2.51 (s, 3 H), 2.13 (m, 1 H), 2.81–1.26 (m, 6 H); MS 220 (17%, M + H$^+$), 98 (100%, M$^+$ − PhCH(OH)CH_2).

(*IS*,*SR*)-*N*-Benzyl-[1-phenyl-2-(*p*-tolylsulfinyl)ethyl]amine (21) and (*IR*,*SR*)-22. A solution of **20** (100 mg) and benzylamine (3 mol equiv) in ethanol (0.4 mL) was heated in a

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sealed tube at 85 °C. The reaction mixture was evaporated and analyzed by ^{1}H NMR (400 MHz). On a preparative run **20C** (100 mg) was treated as above at 100 °C for 20 days. Preparative TLC (10% MeOH/$CHCl_3$) gave a pure mixture of **21** and **22** (100 mg, 72%) as a colorless oil.

21: ^{1}H NMR 7.8–7.2 (m, 14 H), 4.22 (dd, J = 2.9, 10.5 Hz, 1 H), 3.69 (d, J = 13.1 Hz, 1 H), 3.59 (d, J = 13.1 Hz, 1 H), 3.06 (dd, J = 10.5, 13.5 Hz, 1 H), 2.91 (dd, J = 2.9, 13.1 Hz, 1 H), 2.39 (s, 3 H); ^{13}C NMR (in part) 65.15, 57.05, 51.31, 21.27; MS 350 ((M + H)$^+$, 25%), 210 (50%), 91 (100%); HRMS calcd for $C_{22}H_{24}NOS$ 350.1579, found 350.1646.

22: ^{1}H NMR (in part) 3.83 (d, J = 13.1 Hz, 1 H), 3.79 (d, J = 13.1 Hz, 1 H), 3.18 (m, 1 H), 2.91 (dd, J = 4.6, 13.3 Hz, 1 H), 2.86 (dd, J = 7.9, 13.3 Hz, 1 H); ^{13}C NMR (in part) 65.54, 58.81, 51.16, 21.27.

Conversion of 21 to (+)-(*R*)-*N*-Benzyl-(1-phenylethyl)-amine. A mixture of **21** and **22** (5:1, 363 mg) in ethanol (5 mL) was treated with Raney nickel as described above. Purification by acid extraction and then column chromatography (silica gel, EtOAc/hex 1:1) gave pure (+)-(*R*)-*N*-benzyl-*N*-(1-phenylethyl)-amine as a colorless oil (68 mg): $[\alpha]^{25}_D$ +23.7 (*c* 1.35, EtOH), lit.[27] +56.2 (*c* 1.07, EtOH); ^{1}H NMR (in part) 3.8 (q, J = 6.6 Hz, 1 H), 3.65 (d, J = 13.1 Hz, 1 H), 3.58 (d, J = 13.1 Hz, 1 H), 1.36 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (in part) 57.4, 51.6, 24.4; MS 212 ((M + H)$^+$, 45%), 154 (100%).

Diethyl (*IS*,*SR*)-[1′Phenyl-2′-(*p*-tolylsulfinyl)ethyl]-malonate (23) and (*IR*,*SR*)-24. To a solution of diethyl malonate (190 mg, 1.2 mmol) in THF (0.5 mL) at −78 °C under nitrogen was added nBuLi (0.49 mL, 0.78 mmol, 1.6 M in hexane). The mixture was warmed to room temperature, and **20C** (100 mg, 0.4 mmol) in THF (0.5 mL) was added. The solution was refluxed for 6.5 days and then cooled to room temperature. CH_2Cl_2 (50 mL) was then added, and the solution was washed with saturated NH_4Cl solution (2 × 25 mL), dried, and evaporated. The ratio of **23** and **24** was determined by ^{1}H NMR (400 MHz) on the crude reaction mixture. Column chromatography (EtOAc/hexane, 1:1) gave pure **23** (105 mg, 65%). The ^{1}H NMR spectral data for **23** and **24** were very similar to those reported by Tsuchihashi.[3c,d]

23: ^{1}H NMR 7.5–7.2 (m, 5 H), 4.17 (q, J = 7.2 Hz, 2 H), 3.92 (dq, J = 2, 7.2 Hz, 2 H), 3.82 (d, J = 9.2 Hz, 1 H), 3.56 (m, 1 H), 3.45 (dd, J = 8.7, 12.9 Hz, 1 H), 3.34 (dd, J = 5.5, 12.9 Hz, 1 H), 2.41 (s, 3 H), 1.23 (t, J = 7.2 Hz, 3 H), 0.99 (t, J = 7.2 Hz, 3 H); ^{13}C NMR 167.5, 167.3, 141.9, 138.9, 130.0, 128.6, 128.3, 127.8, 124.7, 61.7, 61.4, 57.3, 40.5, 21.4, 14.0, 13.7; MS 403 (20%, M + H$^+$).

24: ^{1}H NMR 7.5–7.2 (m, 9 H), 4.19 (m, 2 H), 4.07 (m, 1 H), 3.97 (q, J = 7.2 Hz, 2 H), 3.74 (d, J = 9.5 Hz, 1 H), 3.25 (dd, J = 3.8, 12.8 Hz, 1 H), 3.04 (dd, J = 11.6, 12.8 Hz, 1 H), 2.39 (s, 3 H), 1.23 (t, J = 7.2 Hz, 3 H), 1.04 (t, J = 7.2 Hz, 3 H); ^{13}C NMR 167.5, 167.0, 141.5, 138.4, 136.0, 129.9, 128.8, 128.6, 127.9, 124.0, 63.0, 61.7, 61.5, 57.6, 40.5, 21.3, 14.0, 13.8; MS 403 (30%, M + H$^+$).

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Registry No. 1, 109985-71-9; 1 (deformyl deriv), 110527-65-6; **2a**, 63268-43-9; **2b**, 123934-65-6; **2c**, 123934-66-7; **3**, 109985-72-0; **4**, 109985-73-1; **5**, 123934-62-3; **5** (R_1 = R_2 = R_3 = H), 2508-29-4; **6**, 123934-63-4; **7**, 123934-64-5; **8b**, 123934-67-8; **8c**, 123934-70-3; **9b**, 123934-68-9; **9c**, 123934-71-4; **10**, 109985-76-4; **11**, 109985-75-3; **12b**, 123934-72-5; **13b**, 123934-73-6; **13c**, 123934-69-0; **14**, 51745-28-9; **15a**, 124019-83-6; **15s**, 124019-84-7; **16a**, 124093-68-1; **16s**, 123934-74-7; **17a**, 124019-85-8; *syn*-**17** (isomer 1), 124019-86-9; *syn*-**17** (isomer 2), 124019-87-0; **18**, 67008-23-5; **19**, 497-88-1; **20I**, 41103-85-9; **20C**, 63268-44-0; **21**, 118653-58-0; **22**, 118620-49-8; **23**, 41103-88-2; **24**, 41379-03-7; $(MeO)_2P(O)CH_3$, 756-79-6; $PhCH_2NH_2$, 100-46-9; (*R*)-$PhCH(CH_3)NHCH_2Ph$, 38235-77-7; $CH_2(CO_2Et)_2$, 105-53-3; (−)-menthyl (*S*)-benzenesulfinate, 34513-32-1; (−)-menthyl (*S*)-2,4,6-triisopropylbenzenesulfinate, 124019-82-5.

Notes

Preparation of 3-Acetyl-2-hydroxyindoles via Rhodium Carbenoid Aromatic C–H Insertion[1]

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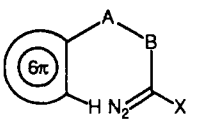
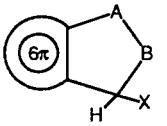
A number of recent reports have described the annulation of both five- and six-membered ring carbocycles[2] and five-membered ring heterocycles[3] into aromatic and heteroaromatic rings via rhodium carboxylate catalyzed decomposition of diazo compounds such as **1**.

We have described, in a 1987 communication, the preparation of 2-hydroxy-3-acetylfurans, example **d**



1

a: A = CH_2; B = C=O; X = H; 6π = phenyl
b: A = CH_2; B = CH_2C=O; X = H; 6π = phenyl
c: A = CH_2; B = SO_2; X = H, CO_2Et, $COCH_3$; 6π = phenyl, 2-thienyl
d: A = O; B = C=O; X = $COCH_3$; 6π = phenyl, naphthyl



2

above.[3b] These compounds exist in the furan form rather than as the tautomeric 3-acetylbenzofuran-2-ones. In this note, we report the extension of the insertion reaction to the preparation of 3-acetyl-2-hydroxyindoles **4** by reaction of the appropriate α-diazo anilides **3** with 5 mol % of Rh_2OAc_4 in refluxing benzene. The further extension of the cyclization reaction to the preparation of 2-hydroxyindoles bearing a CO_2Et group at C_3 of the indole or indoles bearing a strongly electron withdrawing group such as NO_2 was not successful. N-Unsubstituted indoles (R = H in

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