Enantioselective Pummerer-type rearrangement by reaction of *O*-silylated ketene acetal with enantiopure α-substituted sulfoxides

Yasuyuki Kita,*[a] Norio Shibata,[a] Seiji Fukui,[a] Masahiko Bando[b] and Shigekazu Fujita[a]

[a] *Faculty of Pharmaceutical Sciences, Osaka University, 1-6 Yamada-oka, Suita, Osaka 565, Japan*

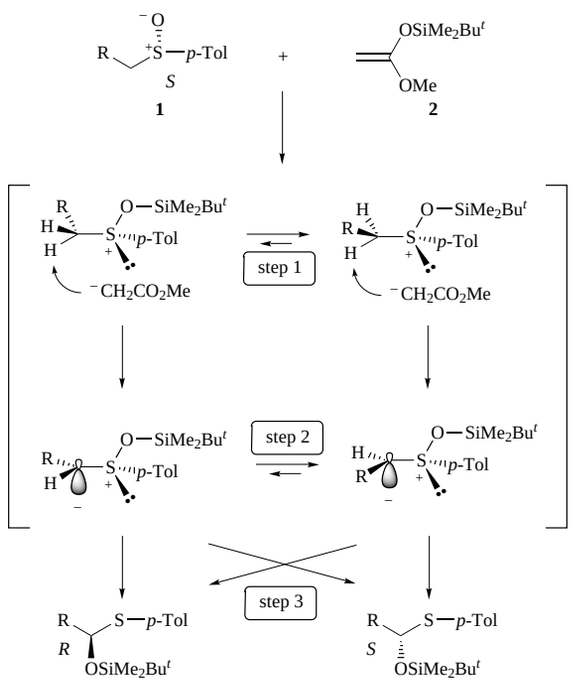
[b] *Second Tokushima Institute of New Drug Research, Otsuka Pharmaceutical Co., Ltd., Kagasuno 463-10, Kawauchi-cho, Tokushima 771-01, Japan*

Chiral non-racemic α-substituted sulfoxides have been allowed to react with *O*-silylated ketene acetals in the presence of a catalytic amount of ZnI_2 in THF to give chiral non-racemic α-siloxy sulfides in >99% ee. This is the highest enantioselectivity reported to date for the Pummerer reaction.

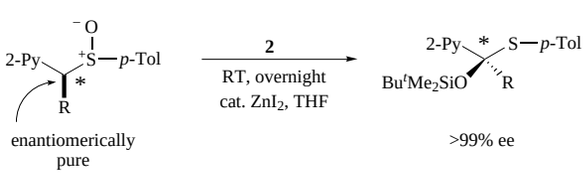
The Pummerer reaction of sulfoxides is a useful method for the synthesis of α-substituted sulfides and has attracted considerable attention from both synthetic and mechanistic points of view.[1] The stereoselective Pummerer reaction of optically active sulfoxides is of significant importance because it would provide access to chiral, non-racemic α-substituted sulfides. Although stereogenecity transfer from the sulfur of chiral, non-racemic sulfoxides to the α-carbon to the sulfur in the sulfoxides has been reported,[2] the degree of asymmetric induction in an acyclic system was quite low [2b–e,3] probably because a sulfurane intermediate is formed by reaction of the generated acetate anion. The enantioselectivity was considerably improved by the addition of 1,3-dicyclohexylcarbodiimide (DCC) as an effective acetate anion scavenger, but the chemical yield significantly decreased.[2e,3,4] Recently, we reported the first highly enantioselective silicon-induced Pummerer-type rearrangement in acyclic chiral non-racemic sulfoxides **1** using *O*-methyl-*O*-*tert*-butyldimethylsilyl ketene acetal **2**, which gave chiral non-racemic α-siloxy sulfides under mild conditions in high yield.[5] The extent of asymmetric transformation, however, never exceeded 90% ee. To develop the optimal asymmetric transformation of **1**, it is quite important to determine in which step(s) racemization occurs (Scheme 1).

Recently, we have shown, by a detailed deuterium-labelling experiment,[6] that the silicon-induced Pummerer rearrangement of **1** proceeded with highly diastereoselective deprotonation of the α-methylene proton in step 1 and *anti* elimination of the siloxy group in step 3. In addition, very recently, we briefly communicated the first highly enantioselective Pummerer rearrangement of chiral, non-racemic α-substituted sulfoxides **3** and **4** leading to enantiomerically enriched α-siloxy sulfides **8** and **9** in high yields (Scheme 2). In this paper, we describe a full account of our studies on the highly asymmetric Pummerer-type rearrangement of chiral, non-racemic α-substituted sulfoxides using *O*-silylated ketene acetal **2**.

Since we learned that the deprotonation step of the α-methylene protons plays a significant role in the stereoselectivity, we selected compounds **3** and **4** which have two stereogenic centres: the α-carbon and sulfur atom. The starting chiral non-racemic compounds **3** and **4** were easily prepared in stereoselective form using a reported method.[7] Thus, to a solution of the sulfoxide **7** in THF was dropwise added a solution of LDA in THF, followed by methyl iodide (in the case of sulfoxide **3**) or ethyl iodide (in the case of sulfoxide **4**). Work-up gave a diastereoisomeric mixture of *syn* and *anti*-**3** or **4**, each diastereoisomer being isolated in a pure state by careful flash column chromatography.



Scheme 1



Scheme 2

Surprisingly, high stereogenicity transfer was observed in the reaction of **3** and **4** with **2**. Thus, treatment of both (C_SS_S)-(−)-*anti*-**3** or **4** and (C_SS_R)-(−)-*syn*-**3** or **4** with **2** in the presence of a catalytic amount of ZnI_2 in THF† gave enantiomerically pure α-siloxy sulfide [(*R*)-**8** or **9**].[8] (Table 1, runs 1, 2, 4 and 5), the stereochemistry of sulfoxide having no effect on the configuration of the product. The introduction of a stereogenic centre α to a sulfoxide dramatically improved the enantioselectivity from 88% ee to >99% ee.

† The reaction in MeCN gave slightly lower selectivities.

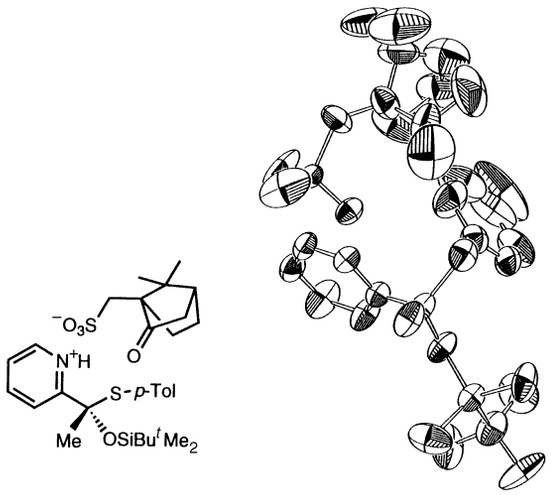
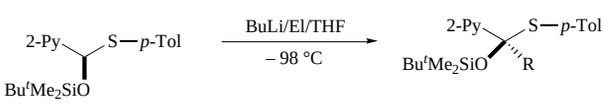


Fig. 1 ORTEP drawing of (*S*)-(+)-**8**·(*S*)-CSA salt with atomic labels. H atoms are omitted for clarity.

Reaction of the other α-substituted sulfoxides **5** and **6** with **2** gave either recovery of starting sulfoxide or the α-siloxy sulfide **10** in low yield (Table 1, runs 8 and 9). Since these results suggested to us that the pyridyl group influenced the way in which the Pummerer reaction proceeded, we have examined this problem in more detail.

The configuration of the quaternary carbon produced was determined from the following chemical procedures. The protonation of the α-lithio carbanion of (*R*)-**11** with MeOH and MeOD to (*R*)-**11** and (*R*)-**11D** suggested that the electrophilic substitution proceeds with retention of configuration.[8] The lithiation of (*R*)-**11** and subsequent alkylation then gave (*R*)-**8**, **9** with retention of configuration (Scheme 3). The stereo-



(*R*)-**11** El = MeOH, MeOD, MeI, EtI

(*R*)-**11**: R = H, yield = 8%, $[\alpha]_D^{18}$ + 1.2 (*c* 0.25, acetone)
(*R*)-**11D**: R = D, yield = 32%, $[\alpha]_D^{18}$ + 0.53 (*c* 0.9, acetone)
(*R*)-**8**: R = Me, yield = 77%, $[\alpha]_D^{19}$ – 5.2 (*c* 2.0, cyclohexane)
(*R*)-**9**: R = Et, yield = 56%, $[\alpha]_D^{19}$ – 1.1 (*c* 1.5, cyclohexane)

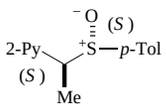
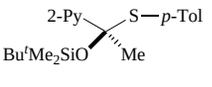
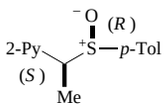
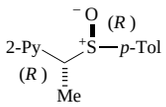
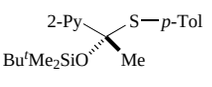
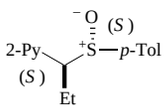
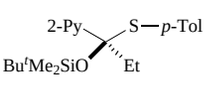
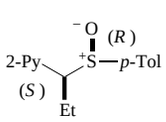
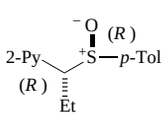
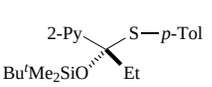
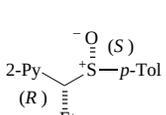
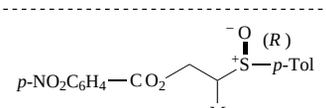
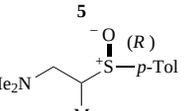
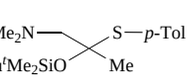
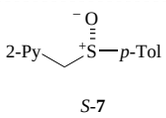
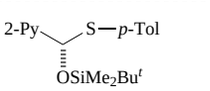
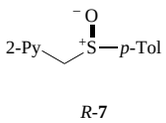
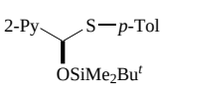
Scheme 3

chemistry of (*S*)-**8** was established by X-ray analysis. Compounds (*R*)-**8** and (*S*)-**8** were obtained as a salt with (1*S*)-(+)-10-camphorsulfonic acid [(*S*)-CSA] from a MeOH–Et_2O solution. Each diastereoisomeric salt was recrystallized, but the only crystals suitable for X-ray analysis were those of the salt of (*S*)-**8**. The known absolute configuration of (*S*)-CSA in the crystal allowed the identification of the *S*-configuration of the asymmetric centre in **8** (Fig. 1).

This high stereocontrol of the reaction is explained as follows. In both isomers, (−)-*anti*-**3**, **4** and (−)-*syn*-**3**, **4**, the deprotonation step is completely controlled, the deprotonated hydrogen having an *anti*-periplanar orientation with respect to the S–O bond. The α-methylene deprotonation step proceeds by way of an E2-type elimination to give the ylide intermediates **A** and **B**‡. The siloxy anion then rearranges on the same face as the

‡ In the case of the α-lithio carbanion of *syn*- and *anti*-phenethyl phenyl sulfoxides, the larger substituents in conformation **C** sterically avoid unfavourable interactions and are rapidly rotated into the more stable conformer **C**′ in which the phenyl rings are orientated *trans* to one another (Scheme 4).[9] In our silicon-induced Pummerer reaction, if the ylide rotation step (step 2) is the racemization step, the compounds produced, **8** and **9**, should have the opposite sign of the $[\alpha]_D$ value from (−)-*anti*-**3**, **4** and (−)-*syn*-**3**, **4**.

Table 1 Asymmetric Pummerer-type rearrangement by *O*-silylated ketene acetal[a]

Run	Sulfoxide[b]	Product	Yield (%)	Ee (%)[c]
1	 (C_SS_S)-(−)-*anti*-**3**	 (*R*)-**8**	70	>99
2	 (C_SS_R)-(−)-*syn*-**3**	(*R*)-**8**	49	>99
3	 (C_RS_R)-(+)-*anti*-**3**	 (*S*)-**8**	69	>99
4	 (C_SS_S)-(−)-*anti*-**4**	 (*R*)-**9**	61	>99
5	 (C_SS_R)-(−)-*syn*-**4**	(*R*)-**9**	72	>99
6	 (C_RS_R)-(+)-*anti*-**4**	 (*S*)-**9**	57	>99
7	 (C_RS_S)-(+)-*syn*-**4**	(*S*)-**9**	75	>99
8	 **5**	No reaction		
9	 **6**	 **10**	23	—
10	 *S*-**7**	 *S*-**11**	64 66[d]	79 83
11	 *R*-**7**	 *R*-**11**	61[d]	82

[a] All reactions were carried out in THF. [b] Starting sulfoxides (**3**, **4**, **7**) were prepared by reporting methods. [c] Ee values were determined by ^{1}H NMR ($CDCl_3$ and C_6D_6) with Eu(hfc)$_3$. [d] Reactions were carried out in MeCN.

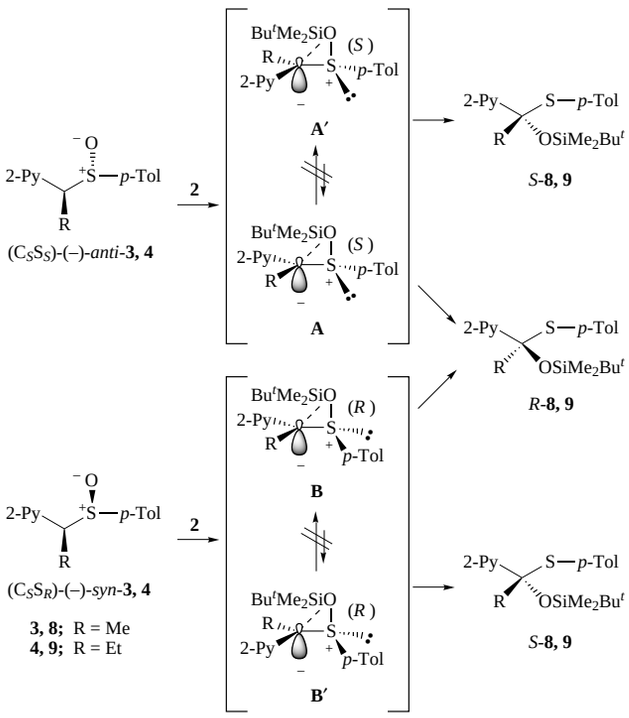
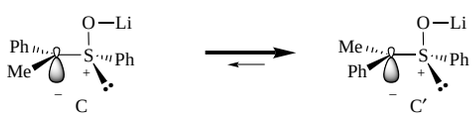


Fig. 2



Scheme 4

S–O group. This result suggests that the ylide rotational step (step 2, *i.e.* between **A** and **A′** **B** and **B′**) is different from the racemization step (Fig. 2), the latter having occurred during the deprotonation (step 1). As expected, the extent of asymmetric induction of the chiral sulfoxides (*S*)- and (*R*)-**7**, which have two α-protons never exceeded 83% (Table 1, runs 10 and 11).

In conclusion, deprotonation (step 1) is the most important step in order to ensure high enantiomeric purity and an optimal asymmetric Pummerer reaction of chiral non-racemic acyclic sulfoxides.

Experimental

All mps are determined on a Yanaco micro melting point apparatus and are uncorrected. IR absorption spectra were recorded on Shimadzu FTIR-8100 spectrophotometers with $CHCl_3$ as a solvent. ^{1}H NMR spectra were measured on Hitachi R-250 HT (250 MHz), JEOL JNM-EX270 (270 MHz), and JEOL JNM-GX500 (500 MHz) spectrometers with $CDCl_3$ as a solvent and TMS as an internal standard, unless otherwise noted. Mass spectra (MS) and high-resolution MS were obtained on ESCO EMD-05A and JEOL JMS-D300 mass spectrometers. Optical rotations were measured in 1 dm cells of 1 cm^3 capacity with a Perkin-Elmer 241 instrument and are recorded in units of 10^{-1} deg cm^2 g^{-1}. E. Merck silica gel 60 (70–230 mesh ASTM) for column chromatography and E. Merck precoated TLC plates with silica gel F_{254} for preparative TLC(PLC) were used. Organic layers were dried with anhydrous Na_2SO_4. The known sulfoxides (+)-*anti*-**3**[7] and (*R*)-**7**[7] were prepared by a reported method, whilst other starting sulfoxides were prepared by the same procedure as that reported.[7]

(1*S*, S_S)-(−)-1-(2-Pyridyl)-1-(4-methylphenylsulfinyl)ethane (−)-*anti*-3

Compound (*S*)-**7** (1.00 g, 4.32 mmol), lithium diisopropylamide (LDA) [prepared from diisopropylamine (0.91 cm^3, 6.48 mmol) and a 1.6 mol dm^{-3} solution of butyllithium (BuLi) in hexane (4.0 cm^3, 6.48 mmol)], methyl iodide (4 cm^3, 64.25 mmol) and THF 20 cm^3 gave a mixture of (−)-*anti*-**3** and (+)-*syn*-**3** (880 mg, 83%). Compound (−)-*anti*-**3** was isolated in a pure state by recrystallization; white crystals, mp 90 °C (diisopropyl ether); $[\alpha]_D^{21}$ −235.0 (*c* 1.0, $CHCl_3$) (Found: C, 68.25; H, 6.15; N, 5.60; S, 12.95. $C_{14}H_{15}NSO$ requires C, 68.55; H, 6.15; N, 5.70; S, 13.05%).

(1*R*, S_R)-(+)-1-(2-Pyridyl)-1-(4-methylphenylsulfinyl)ethane and (1*S*, S_R)-(−)-1-(2-pyridyl)-1-(4-methylphenylsulfinyl)ethane (+)-*anti*-3 and (−)-*syn*-3

Compound (*R*)-**7** (3.00 g, 13.0 mmol), lithium diisopropylamide (LDA) [prepared from diisopropylamine (2.73 cm^3, 19.5 mmol) and a 1.6 mol dm^{-3} solution of BuLi in hexane (12.2 cm^3, 19.5 mmol)], methyl iodide (4 cm^3, 64.25 mmol) and THF (75 cm^3) gave a mixture of (+)-*anti*-**3** and (−)-*syn*-**3** (2.90 g, 91%). Each diastereoisomer was isolated in a pure state by careful flash column chromatography. Compound (+)-*anti*-**3**: white crystals, mp 90 °C (diisopropyl ether); $[\alpha]_D^{21}$ +235.0 (*c* 1.0, $CHCl_3$) {lit.,[5] mp 92–93 °C; $[\alpha]_D^{25}$ +239.7 (*c* 0.7, $CHCl_3$)}. Compound (−)-*syn*-**3**: colourless oil: $[\alpha]_D^{21}$ −23.6 (*c* 0.5, $CHCl_3$); δ_H 1.63 (3H, d, *J* 7.26, 2-Me), 2.37 (3H, s, Me), 3.98 (1H, q, *J* 7.26, 1-H), 7.06 (1H, d, *J* 7.92, PyH), 7.16–7.27 (5H, m, ArH and PyH), 7.58 (1H, dt, *J* 1.65 and 7.59, PyH) and 8.54 (1H, d, *J* 3.96, PyH); *m*/*z* 245 (M^+) (Found: M^+, 245.0876. $C_{15}H_{11}NOS$ requires *M*, 245.0874).

(1*S*, S_S)-(−)-1-(2-Pyridyl)-1-(4-methylphenylsulfinyl)propane and (1*R*, S_S)-(+)-1-(2-pyridyl)-1-(4-methylphenylsulfinyl)propane (−)-*anti*-4 and (+)-*syn*-4

To a solution of (*S*)-**7** (700 mg, 3.03 mmol) in THF (5 cm^3) was dropwise added a solution of LDA [prepared from diisopropylamine (0.64 cm^3, 4.54 mol) and a 1.6 mol dm^{-3} solution of BuLi in hexane (2.8 cm^3, 4.54 mmol)] in THF at −78 °C under nitrogen. The mixture was stirred for 1 h, after which ethyl iodide (5.0 cm^3, 6.25 mmol) was dropwise added to it. After 2 h, the mixture was quenched with water and then extracted with CH_2Cl_2. The extract was dried and concentrated under reduced pressure. The residue was purified by column chromatography with 50–100% AcOEt in hexane to give a mixture of the diastereoisomers (−)-*anti*-**4** and (+)-*syn*-**4** (728.2 mg, 93%). Each diastereoisomer was isolated in a pure state by careful flash column chromatography. Compound (−)-*anti*-**4**: colourless oil; $[\alpha]_D^{19}$ −276 (*c* 0.3, $CHCl_3$); ν_{max}/cm^{-1} 1044; δ_H 0.89 (3H, t, *J* 7.3, 3-Me), 1.97–2.11 (2H, m, 2-H_2), 2.28 (3H, s, Me), 3.77 (1H, dd, *J* 5.5 and 10.1, 1-H), 7.05–7.10 (5H, m, ArH and PyH), 7.18 (1H, d, *J* 7.3, PyH), 7.56 (1H, dt, *J* 1.8 and 7.3, PyH) and 8.30–8.35 (1H, m, PyH); *m*/*z* 259 (M^+) (Found: M^+, 259.1040. $C_{15}H_{17}NOS$ requires *M*, 259.1031). Compound (+)-*syn*-**4**: colourless crystals; mp 70–71 °C (diisopropyl ether); $[\alpha]_D^{21}$ +138 (*c* 0.3, $CHCl_3$); ν_{max}/cm^{-1} 1048; δ_H 0.90 (3H, t, *J* 7.3, 3-Me), 2.22–2.42 (2H, m, 2-H), 2.33 (3H, s, Me), 3.77 (1H, dd, *J* 5.0 and 10.6, 1-H), 6.91 (1H, d, *J* 7.8, PyH), 7.05–7.20 (5H, m, ArH and PyH), 7.53 (1H, dt, *J* 1.7 and 7.6) and 8.51–8.54 (1H, m, PyH); *m*/*z* 259 (M^+) (Found: M^+, 259.1047. $C_{15}H_{17}NOS$ requires *M*, 259.1031).

(1*R*, S_R)-(−)-1-(2-Pyridyl)-1-(4-methylphenylsulfinyl)propane and (1*S*, S_R)-(+)-1-(2-pyridyl)-1-(4-methylphenylsulfinyl)propane (+)-*anti*-4 and (−)-*syn*-4

Compound (*R*)-**7** (1.00 g, 4.32 mmol), LDA [prepared from diisopropylamine (0.91 cm^3, 6.49 mmol) and a 1.6 mol dm^{-3} solution of BuLi in hexane (4.0 cm^3, 6.40 mmol)], ethyl iodide (0.72 cm^3, 9.00 mmol) and THF (20 cm^3) gave a mixture of the diastereoisomers (+)-*anti*-**4** and (−)-*syn*-**4** (1.06 g, 95%). Each diastereoisomer was isolated in a pure state by careful flash column chromatography. Compound (+)-*anti*-**4**: colourless oil, $[\alpha]_D^{21}$ +277 (*c* 0.6, $CHCl_3$); *m*/*z* 259 (M^+) (Found: M^+, 259.1046.

$C_{15}H_{17}NOS$ requires *M*, 259.1031). Compound (−)-*syn*-**4**: colourless crystals, mp 70–71 °C (diisopropyl ether); $[\alpha]_D^{21}$ −138 (*c* 0.5, $CHCl_3$); *m*/*z* 259 (M^+) (Found: C, 69.45; H, 6.65; N, 5.35; S, 12.10%; M^+, 259.1037. $C_{15}H_{17}NOS$ requires C, 69.45; H, 6.60; N, 5.40; S, 12.35%; *M*, 259.1031).

(*R*)-Pyridylmethyl 4-methylphenyl sulfoxide (*R*)-7
White crystals, mp 104 °C (benzene–hexane); $[\alpha]_D^{20}$ −250.5 (*c* 2.0, $CHCl_3$) {lit.,[7] $[\alpha]_D^{25}$ +259.7 (*c* 0.7, $CHCl_3$)}.

(*S*)-Pyridylmethyl 4-methylphenyl sulfoxide (*S*)-7
2-Methylpyridine (188 mg, 2.02 mmol), (*S*)-(+)-1-methyl 4-methylbenzenesulfinate (594 mg, 2.02 mmol), 1.6 mol dm^{-3} BuLi in hexane (1.26 cm^3, 2.02 mmol) and THF 5 cm^3 gave (*S*)-**7** (240 mg, 60%) as white crystals, mp 104 °C (benzene–hexane); $[\alpha]_D^{20}$ +250.8 (*c* 2.0, $CHCl_3$).

General procedure for the Pummerer-type reaction of an *O*-silylated ketene acetal 2 with the sulfoxides 3, 4 and 7
To a solution of the sulfoxide **3**, **4** or **7** (0.1 mmol) and ZnI_2 (0.01–0.02 mmol) in dry MeCN (or THF) at 0 °C–RT, the acetal **2** (0.3–0.5 mmol) was added dropwise. The reaction mixture was stirred for 4–12 h under nitrogen after which it was poured into saturated aqueous sodium hydrogen carbonate and repeatedly extracted with CH_2Cl_2. The extract was washed with brine, dried and evaporated. The residue was purified by PLC to give the corresponding α-siloxy sulfide, **8**, **9** or **11** in yields in the range 49–79%.

(1*R*)-1-*tert*-Butyldimethylsiloxy-1-(2-pyridyl)ethyl 4-methylphenyl sulfide (*R*)-8. (i) (−)-*anti*-**3** (58.7 mg, 0.239 mmol), **2** (135 mg, 0.718 mmol), ZnI_2 (7.7 mg, 0.024 mmol) and THF (2 cm^3) gave (*R*)-**8** (60.1 mg, 70%, >99% ee) as a colourless oil; $[\alpha]_D^{19}$ −23.3 (*c* 1.2, cyclohexane); ν_{max}/cm^{-1} 1586 and 1572; δ_H 0.13 and 0.27 (each 3H, each s, $SiMe_2$), 0.95 (9H, s, $SiBu^t$), 2.11 and 2.26 (each 3H, each s, Me × 2), 6.91 and 7.01 (each 2H, each d, *J* 7.9, ArH), 7.04–7.08, (1H, m, PyH), 7.35 (1H, d, *J* 7.92, PyH), 7.47 (1H, dt, *J* 1.98 and 7.92, PyH) and 8.53–8.55 (1H, m, PyH); *m*/*z* 359 (M^+) (Found: C, 66.70; H, 8.15; N, 3.90; S, 8.70%; M^+, 359.1745. $C_{20}H_{29}NOSSi$ requires C, 66.80; H, 8.15; N, 3.90; S, 8.90%; *M*, 359.1739).

(ii) (−)-*syn*-**3** (34.7 g, 0.141 mmol), **2** (80.0 mg, 0.424 mmol), ZnI_2 (4.5 mg, 0.014 mmol) THF (2 cm^3) gave (*R*)-**8** (24.6 mg, 49%, >99% ee). Colourless oil; $[\alpha]_D^{19}$ −22.6 (*c* 0.9, cyclohexane).

(1*S*)-1-*tert*-Butyldimethylsiloxy-1-(2-pyridyl)ethyl 4-methylphenyl sulfide (*S*)-8. (+)-*anti*-**3** (44.1 mg, 0.180 mmol), **2** (101.3 mg, 0.539 mmol), ZnI_2 (5.7 mg, 0.018 mmol) and THF (2.5 cm^3) gave (*S*)-**8** (44.4 mg, 69%, >99% ee) as a colourless oil; $[\alpha]_D^{19}$ +23.2 (*c* 0.9, cyclohexane); *m*/*z* 359 (M^+) (Found: C, 66.70; H, 8.15; N, 3.85; S, 8.70%; M^+, 359.1736. $C_{20}H_{29}NOSSi$ requires C, 66.80; H, 8.15; N, 3.90; S, 8.90%, *M*, 359.1739).

(1*R*)-1-*tert*-Butyldimethylsiloxy-1-(2-pyridyl)propyl 4-methylphenyl sulfide (*R*)-9. (i) (−)-*anti*-**4** (27.7 mg, 0.107 mmol), **2** (60.2 mg, 0.320 mmol), ZnI_2 (3.8 mg, 0.011 mmol) and THF (2 cm^3) gave (*R*)-**9** (24.5 mg, 61%, >99% ee) as a colourless oil; $[\alpha]_D^{17}$ −54.1 (*c* 0.555, cyclohexane); ν_{max}/cm^{-1} 1586 and 1574; δ_H-(C_6D_6) 0.37 and 0.51 (each 3H, each s, $SiMe_2$), 0.96 (3H, t, *J* 7.3, 3-Me), 1.14 (9H, s, $SiBu^t$), 1.97 (3H, s, Me), 2.40 and 3.06 (each 1H, each dq, *J* 7.3 and 14.5, 2-H_2), 6.53 (1H, ddd, *J* 1.0, 5.0 and 7.6, PyH), 6.77 and 7.30 (each 2H, each d, *J* 7.9, ArH), 7.07 (1H, dt, *J* 1.7 and 7.6, PyH), 7.63 (1H, dt, *J* 1.0 and 7.6, PyH) and 8.36 (1H, ddd, *J* 1.0, 1.7 and 5.0, PyH); *m*/*z* 373 (M^+) (Found: C, 66.95; H, 8.30; N, 3.70; S, 8.15%; M^+, 373.1923. $C_{21}H_{31}NOSSi$ requires C, 67.50; H, 8.40; N, 3.75; S, 8.60%; *M*, 373.1896).

(ii) (−)-*syn*-**4** (39.5 mg, 0.152 mmol), **2** (85.9 mg, 0.457 mmol), ZnI_2 (4.8 mg, 0.015 mmol) and THF (1.5 cm^3) gave (*R*)-**9** (40.7 mg, 72%, >99% ee). Colourless oil; $[\alpha]_D^{18}$ −54.0 (*c* 1.2, cyclohexane).

(1*S*)-*tert*-Butyldimethylsiloxy-1-(2-pyridyl)propyl 4-methylphenyl sulfide (*S*)-9. (i) (+)-*anti*-**4** (65.3 mg, 0.252 mmol), **2** (142 mg, 0.755 mmol), ZnI_2 (8.0 mg, 0.025 mmol) and THF (2.5 cm^3) gave (*S*)-**9** (53.9 mg, 57%, >99% ee) as a colourless oil; $[\alpha]_D^{22}$ +56.2 (*c* 1.2, cyclohexane); *m*/*z* 373 (M^+) (Found: C, 67.50; H, 8.40; N, 3.90; S, 8.45%; M^+, 373.1882. $C_{21}H_{31}NOSSi$ requires C, 67.50; H, 8.40; N, 3.75; S, 8.60%; *M*, 373.1896).

(ii) (+)-*syn*-**4** (30.6 mg, 0.118 mmol), **2** (67 mg, 0.354 mmol), ZnI_2 (3.8 mg, 0.012 mmol) and THF (1.5 cm^3) gave (*S*)-**9** (33.1 mg, 75%, >99% ee) as a colourless oil; $[\alpha]_D^{18}$ +54.1 (*c* 1.6, cyclohexane).

(*S*)-*tert*-Butyldimethylsiloxy(2-pyridyl)methyl 4-methylphenyl sulfide (*S*)-11. (i) (*S*)-**7** (72.9 mg, 0.315 mmol), **2** (178 mg, 0.946 mmol), ZnI_2 (10.2 mg, 0.032 mmol) and MeCN (2 cm^3) gave (*S*)-**11** (71.6 mg, 66%, 83% ee) as a colourless oil; $[\alpha]_D^{22}$ −30.2 (*c* 0.5, acetone); ν_{max}/cm^{-1} 1588 and 1572; δ_H −0.09 and 0.02 (each 3H, each s, $SiMe_2$), 0.85 (9H, s, $SiBu^t$), 2.31 (s, 3H, Me), 6.16 (s, 1H, CH), 7.04 and 7.28 (each 2H, each d, *J* 7.3, ArH), 7.12 (1H, dd, *J* 4.6 and 7.3, PyH), 7.52–7.59 (1H, m, PyH) and 8.53 (1H, d, *J* 4.58, PyH); *m*/*z* 345 (M^+) (Found: M^+, 345.1575. $C_{19}H_{27}NOSSi$ requires *M*, 345.1583).

(ii) (*S*)-**7** (50.0 mg, 0.216 mmol), **2** (122 mg, 0.648 mmol), ZnI_2 (6.9 mg, 0.022 mmol) and THF (3 cm^3) gave (*S*)-**11** (47.7 mg, 64%, 79% ee) as a colourless oil; $[\alpha]_D^{22}$ −28.8 (*c* 0.9, acetone).

(1*R*)-*tert*-Butyldimethylsiloxy(2-pyridyl)methyl 4-methylphenyl sulfide (*R*)-11. (*R*)-**7** (70.0 mg, 0.303 mmol), **2** (170 mg, 0.908 mmol), ZnI_2 (9.6 mg, 0.030 mmol) and MeCN (2 cm^3) gave (*R*)-**11** (63.8 mg, 61%, 82% ee) as a colourless oil; $[\alpha]_D^{22}$ +29.6 (*c* 1.0, acetone); *m*/*z* 345 (M^+) (Found: C, 65.75; H, 7.80; N, 4.00; S,. 9.10%; M^+, 345.1554. $C_{19}H_{27}NOSSi$ requires C, 66.00; H, 7.90; N, 4.05; S, 9.30%; *M*, 345.1583).

Determination of the configuration of (*R*)-8
(i) (*R*)-**11**. To a solution of (*R*)-**11** (59.6 mg, 0.173 mmol) in THF (1.5 cm^3) was dropwise added a 1.6 mol dm^{-3} solution of BuLi in hexane (0.52 cm^3, 0.868 mmol) at −95 °C under nitrogen. Immediately MeOH (1 cm^3) was added to the reaction mixture followed by water to quench the reaction; the mixture was then extracted with CH_2Cl_2. The extract was washed with saturated aqueous NH_4Cl and brine, dried and concentrated under reduced pressure. The residue was purified by column chromatography with 10% AcOEt in hexane to give (*R*)-**11** (5.0 mg, 8%); $[\alpha]_D^{18}$ +1.2 (c 0.25, acetone).

(ii) (*R*)-**11D**. To a solution of (*R*)-**11** (58.0 mg, 0.168 mmol) in THF (1.5 cm^3) was dropwise added a 1.6 mol dm^{-3} solution of BuLi in hexane (0.50 cm^3, 0.840 mmol) at −95 °C under nitrogen. Immediately MeOD (1 cm^3) was added to a reaction mixture followed by deuterium oxide (1 cm^3) to quench the reaction; the mixture was then extracted with CH_2Cl_2. The extract was washed with saturated aqueous NH_4Cl and brine, dried and concentrated under reduced pressure. The residue was purified by column chromatography with 10% AcOEt in hexane to give (*R*)-**11D** (18.7 mg, 32%) as an oil; $[\alpha]_D^{18}$ +0.53 (*c* 0.9, acetone); ν_{max}/cm^{-1} 1580 and 1566; δ_H −0.09 and 0.02 (each 3H, each s, $SiMe_2$), 0.85 (9H, s, $SiBu^t$), 2.31 (3H, s, Me), 7.04 (2H, d, *J* 7.3, ArH), 7.10–7.16 (1H, m, PyH), 7.28 (2H, d, *J* 7.3, ArH), 7.26–7.29 (1H, m, PyH), 7.56 (1H, t, *J* 6.4, PyH) and 8.53 (1H, d, *J* 4.6); *m*/*z* 346 (M^+) (Found: M^+, 346.1638. $C_{19}H_{26}DNOSSi$ requires *M*, 346.1644).

(iii) (*R*)-**8**. To a solution of (*R*)-**11** (51.1 mg, 0.148 mmol) and methyl iodide (0.05 cm^3, 0.740 mmol) in THF (1.5 cm^3) was dropwise added a 1.7 mol dm^{-3} solution of BuLi in hexane (0.26 cm^3, 0.43 mmol) at −95 °C under nitrogen. Immediately MeOH (1 cm^3) and water were added to the reaction mixture which was then extracted with CH_2Cl_2. The extract was washed with saturated aqueous NH_4Cl and brine, dried and concentrated under reduced pressure. The residue was purified by column chromatography with 10% AcOEt in hexane to give (*R*)-**8** (41.1 mg, 77%) as an oil; $[\alpha]_D^{18}$ −5.18 (*c* 2.0, cyclohexane).

(iv) (*R*)-**9**. To a solution of (*R*)-**11** (50.9 mg, 0.147 mmol) and ethyl iodide (0.06 cm^3, 0.735 mmol) in THF (1.5 cm^3) was

dropwise added a 1.7 mol dm^{-3} solution of BuLi in hexane (0.28 cm^3, 0.46 mmol) at −95 °C under nitrogen. Immediately MeOH (1 cm^3) and water were added to the reaction mixture which was then extracted with CH_2Cl_2. The extract was washed with saturated aqueous NH_4Cl and brine, dried and concentrated under reduced pressure. The residue was purified by column chromatography with 10% AcOEt in hexane to give (*R*)-**9** (30.8 mg, 56%) as an oil; $[\alpha]_D^{19}$ −1.06 (*c* 1.5, cyclohexane).

(*S*)-8·(*S*)-CSA salt

To a solution of (*S*)-**8** (69.2 mg, 0.200 mmol) in Et_2O (1 cm^3) was added a solution of (*S*)-camphorsulfonic acid (46.5 mg, 0.200 mmol) in Et_2O (1 cm^3). Storage of this mixture at 0 °C for 1 h gave colourless needles which were isolated and washed with a small quantity of Et_2O to afford the sulfonic acid salt of (*S*)-**8** as colourless needles (91.0 mg, 77%). The salt recrystallized from MeOH–Et_2O as colourless crystals, mp 118–119 °C; δ_H 0.27 and 0.47 (each 3H, each s, $SiMe_2$), 0.88 (3H, s, Me), 0.98 (9H, s, $SiBu^t$), 1.18 (3H, s, Me), 1.35–1.44 (1H, m), 1.81 (1H, ddd, *J* 4.5, 9.9 and 14.5), 1.90 (1H, d, *J* 18.0), 1.97–2.10 (2H, m), 2.24 (3H, s, Me), 2.32 (1H, t, *J* 4.2), 2.37 (3H, s, Me), 2.76–2.87 (1H, m), 3.01 (1H, d, *J* 15), 3.54 (1H, d, *J* 15), 6.91 and 7.03 (each 2H, each d, *J* 8.1, ArH), 7.54 (1H, d, *J* 7.7, PyH), 7.58 (1H, t, *J* 6.8, PyH), 7.97 (1H, dt, *J* 1.7 and 7.7, PyH) and 9.38 (1H, d, *J* 6.8, PyH).

X-Ray analysis of (*S*)-8·(*S*)-CSA salt

The needle crystal used for X-ray study had dimensions of approximately 0.1 × 0.2 × 0.5 mm. Crystal data: $C_{30}H_{45}NO_5S_2Si$, $M_r = 591.8$, monoclinic, space group $P2_1$, $a = 8.904(5)$ Å, $b = 13.098(4)$ Å, $c = 14.103(3)$ Å, $\beta = 92.78(3)°$, $V = 1643(1)$ $Å^3$, $Z = 2$, $D_x = 1.196$ g cm^{-3} and μ(Mo-Kα) = 2.25 cm^{-1}.

Data collection and processing. The intensities were measured on a Rigaku AFC-5S four-circle diffractometer using graphite-monochromated Mo-Kα radiation and $\omega/2\theta$ scans to $2\theta_{max}$ = 50 °C. Three standard reflections were monitored every 150 measurements. Final lattice parameters were obtained from a least-squares refinement using 25 reflections. The data were corrected for Lorentz and polarization factors. Decay and absorption correction were not applied. Of the 3059 independent reflections collected, 1741 with $I > 2.0\sigma(I)$ were used for structure determination and refinement.

Structure solution and refinement. The structure was solved by direct methods using the TEXSAN crystallographic software package.[10] All non-H atoms were found in the Fourier map. All H atoms were included at geometrically calculated positions and not refined. The refinement of atomic parameters was carried out by the full matrix least-squares refinement, using anisotropic temperature factors for all non-H atoms. The final refinement converged with $R = 0.083$ and $R_w = 0.088$ for 361 parameters. The minimum and maximum peaks in the final difference Fourier map were −0.36 and 0.46 e $Å^{-3}$. Tables of atomic co-ordinates, bond lengths, bond angles and thermal parameters are available on request from the Cambridge Crystallographic Data Centre.§ Any such request should be accompanied by a full bibliographic citation for this work together with the reference number CCDC 207/116.

§ For details of the Scheme see Instructions for Authors (1997), *J. Chem. Soc., Perkin Trans. 1*, 1997, Issue 1.

References

1 R. Pummerer, *Chem. Ber.*, 1909, **42**, 2282; 1910, **43**, 1401; L. Horner and P. Kaiser, *Justus Liebigs Ann. Chem.*, 1959, **626**, 19; L. Horner, *Justus Liebigs Ann. Chem.*, 1960, **631**, 198; Reviews, see: T. Durst, *Advances in Organic Chemistry*, 1969, **6**, 285; T. Numata and S. Oae, *Yuki Gosei Kagaku Kyokai Shi*, 1977, **35**, 726, (*Chem. Abstr.*, 1978, **88**, 5639s); J. P. Marino, *Topics in Sulfur Chemistry*, ed. A. Senning, George Thieme Publishers, Stuttgart, 1976, vol. 1, p. 1; T. Numata, *Yuki Gosei Kagaku Kyokai Shi*, 1978, **36**, 845 (*Chem. Abstr.*, 1979, **90**, 136847x); S. Oae and T. Numata, *The Pummerer Type of Reactions*, in *Isotopes in Organic Chemistry*, ed. E. Buncel and C. C. Lee, Elsevier, New York, 1980, vol. 5, ch. 2; S. Oae, T. Numata and T. Yoshimura, *Heterosulphonium Salts*, in *The Chemistry of the Sulphonium Group*, ed. C. J. M. Stirling and S. Patai, John Wiley & Sons, New York, 1981, Part 2, ch. 15; O. D. Lucchi, U. Miotti and G. Modena, *Organic Reactions*, 1990, **40**, 157.

2 (*a*) B. Stridsberg and S. Allenmark, *Acta Chem. Scand., Ser. B*, 1974, **28**, 591; 1976, **30**, 219; (*b*) T. Numata and S. Oae, *Tetrahedron Lett.*, 1977, 1337; (*c*) T. Numata, O. Itoh and S. Oae, *Chem. Lett.*, 1977, 909; (*d*) M. Mikolajczyk, A. Zatorski, S. Grzejszczak, B. Costisella and W. Midura, *J. Org. Chem.*, 1978, **43**, 2518; (*e*) T. Numata, O. Itoh and S. Oae, *Tetrahedron Lett.*, 1979, 1869; (*f*) S. Wolfe, P. M. Kazmaier and H. Auski, *Can. J. Chem.*, 1979, **57**, 2404.

3 T. Numata, O. Itoh, T. Yoshimura and S. Oae, *Bull. Chem. Soc. Jpn.*, 1983, **56**, 257; O. Itoh, T. Numata, T. Yoshimura and S. Oae, *Bull. Chem. Soc. Jpn.*, 1983, **56**, 266.

4 J. E. McCormick and R. S. McElhinney, *Chem. Commun.*, 1969, 171; S. Glue, I. T. Kay and M. R. Kipps, *Chem. Commun.*, 1970, 1158; T. Kaneko, Y. Okamoto and K. Hatada, *J. Chem. Soc., Chem. Commun.*, 1987, 1511.

5 Y. Kita, N. Shibata and N. Yoshida, *Tetrahedron Lett.*, 1993, **34**, 4063; Y. Kita, N. Shibata, N. Yoshida and S. Fujita, *J. Chem. Soc., Perkin Trans. 1*, 1994, 3335.

6 Y. Kita, N. Shibata, N. Yoshida, S. Fukui and C. Fujimori, *Tetrahedron Lett.*, 1994, **35**, 2569; Y. Kita, N. Shibata, N. Yoshida, N. Kawano, C. Fujimori, N. Yoshikawa and S. Fujita, *J. Chem. Soc., Perkin Trans. 1*, 1995, 2829.

7 N. Furukawa, E. Hosono, H. Fujihara and S. Ogawa, *Bull. Chem. Soc. Jpn.*, 1990, **63**, 461.

8 Alkylation of the heteroatom substituted organolithium compound, V. K. Aggarwal, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 175; D. Hoppe, F. Hintze and P. Tebben, *Angew. Chem., Int. Ed. Engl.*, 1990, **29**, 1422.

9 M. Marsch, W. Massa, K. Harms, G. Baum and G. Boche, *Angew. Chem., Int. Ed. Engl.*, 1986, **25**, 1011; G. Boche, *Angew. Chem., Int. Ed. Engl.*, 1989, **28**, 277.

10 TEXSAN, TEXRAY Structure Analysis Package, Molecular Structure Corporation, 3200 Research Forest Drive, The Woodlands, TX 77381, USA, 1985.

Paper 7/02020A
Received 24*th March* 1997
Accepted 27*th March* 1997