Application of Homochiral Lithium Amide Base Chemistry to a Thiane Oxide System

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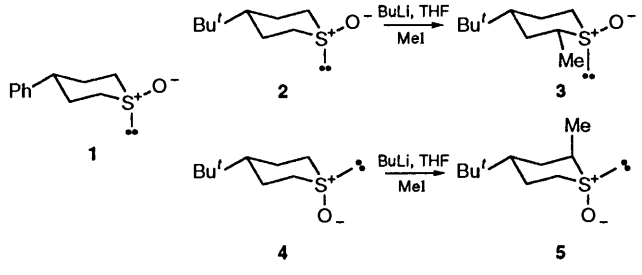
Treatment of the thiane oxide **6** with a homochiral lithium amide (HCLA) base **7**, followed by electrophilic quench of the so-formed sulfoxide carbanion with Me_3SiCl, MeI or Bu^tCO_2Et, gives the optically active products (+)-**8**, (+)-**11** and (+)-**12**, respectively, in 55–60% enantiomeric excess (ee). The reaction of **6** with the HCLA base **9** can be carried out in the presence of Me_3SiCl (*in situ* quench conditions), in which case a silylation–*in situ* kinetic resolution process occurs, furnishing (−)-**8** in low chemical yield, in up to 69% ee. Further transformations of thiane oxides (+)-**8** and (+)-**11** involving reduction or removal of the ring sulfur atom were conducted, in order to establish the absolute configuration of the products. Highly stereoselective reduction of the keto sulfoxide (+)-**12** was also carried out, leading ultimately to an epoxide product **20** *via* opening of the thiane ring.

A number of recent reports have described useful asymmetric transformations mediated by homochiral lithium amide (HCLA) bases.[1] Our interest in this area has focused primarily on the conversion of prochiral cyclic ketones into optically active products, particularly enol silanes.[2] However, part of our continuing interest in the chemistry of HCLA bases lies in exploring their application to the asymmetric transformation of other types of functional group, and we recently demonstrated that the HCLA base chemistry can be applied to a simple cyclic sulfoxide system.[3] Here we describe in detail how this approach can generate chiral non-racemic products from a substituted thiane oxide by direct discrimination between enantiotopic hydrogens or by kinetic resolution.

Our decision to examine a cyclic sulfoxide as a substrate for asymmetric transformation using an HCLA base was made bearing in mind the well-established stereoselectivity of both sulfoxide deprotonations and subsequent electrophilic quenches.[4] In particular, the base treatment of certain six-membered ring sulfoxides (thiane oxides) such as **1** is known to result in preferential removal of the equatorially orientated hydrogens of the diastereotopic pairs, as indicated by deuterium labelling studies.[5] Other work has shown that, when the anions derived from such sulfoxides are treated with MeI, methylation occurs *trans* to the S=O bond with good to excellent stereoselectivity, *e.g.* **2** gives only **3**, and **4** gives mainly **5** (Scheme 1).[6]

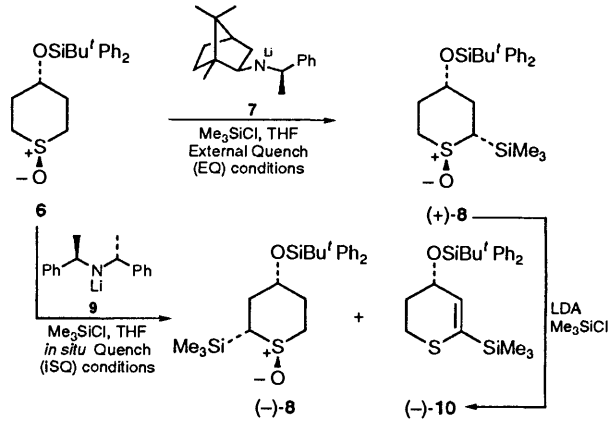


1 2 3 4 5

Scheme 1

Thus, the thiane oxide system appeared an excellent candidate for asymmetric transformation by kinetically controlled selection between the most labile pair of enantiotopic hydrogens, using an HCLA base, followed by stereoselective sulfoxide anion substitution.

We initiated our investigation in this area by treating the readily available *trans* sulfoxide **6** with the camphor-derived base **7** and then adding Me_3SiCl. Under these external quench (EQ) conditions the α-silyl sulfoxide (+)-**8** is formed in 91% yield and with an enantiomeric excess (ee) of *ca.* 60% as estimated from ^1H NMR experiments in the presence of the chiral shift reagent Eu(hfc)$_3$ (Scheme 2).†



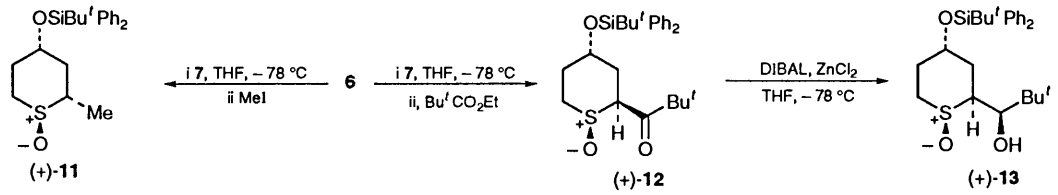
Scheme 2

The relative configuration shown, with the silyl group being introduced *trans* to the S=O bond, followed the stereochemical outcome observed in the methylation of **2**, and was fully confirmed by a single crystal X-ray determination.‡ The absolute configuration of the product was unknown at this stage, but was later assigned by correlation with known thianes, *vide infra*.

Analogous reactions with HCLA base **9** give interesting results. Using an *external* Me_3SiCl quench as above (Me_3SiCl added *after* mixing base and sulfoxide) racemic **8** is obtained. However, reactions done using an *in situ* quench (ISQ—Me_3SiCl added to HCLA base *before* addition of sulfoxide) give mixtures of (−)-**8** (10–20%, 65–69% ee) and (−)-**10**

† Eu(hfc)$_3$ = tris[3-heptafluoropropylhydroxymethylene)-(+)-camphorato]europium(III) derivative.

‡ Full details of this structure determination can be found in the following paper.



Scheme 3

(30–50%) along with quantities of starting sulfoxide and some polysilylated products. The vinyl sulfide **10** arises *via* a Me_3SiCl-mediated Pummerer-type reaction of **8** which, although having literature precedent, has not been observed previously at such low temperatures.[7] Significantly, a vinyl sulfide product is not obtained using HCLA base **7**, even with internal quench conditions.

The improved level of induction obtained using base **9** under internal rather than external quench conditions was intriguing. In attempts to control this reaction by altering the amount of base used, we noticed that, as the level of overall conversion into **10** increased, the ee of (−)-**8** (recovered in reduced quantity) also increased. One explanation that occurred to us was that *racemic* **8** is formed under *either* EQ or ISQ type reaction conditions, but that in the case of the internal quench an *in situ* kinetic resolution occurs in the subsequent conversion into **10**. That this is indeed the case was shown by reaction of a sample of (+)-**8** with 2 equiv. of LDA in the presence of Me_3SiCl, which gave (−)-**10**. This result shows that (−)-**8** and (−)-**10** are of the *opposite* enantiomeric series and, therefore, a kinetic resolution explains the result. In addition we independently established the viability of a kinetic resolution by treating *racemic* **8** with **9** and Me_3SiCl to give optically active (−)-**8** and (−)-**10**, although with a lower apparent level of selectivity than the previous *in situ* tandem silylation–kinetic resolution.

This novel type of kinetic resolution may be useful in other sulfoxide systems; however, with cyclic sulfoxides the process is difficult to control and inefficient, due to the availability of acidic hydrogens at two sites α to the sulfoxide, which results in considerable polysilylation. We therefore elected to examine reactions involving alternative electrophiles, under EQ conditions.

Having shown that the non-racemic α-silyl sulfoxide **8** could be obtained in EQ reactions using HCLA base **7** and Me_3SiCl, we examined the use of other electrophiles in similar reactions. Thus reaction of **6** with HCLA base **7**, and then addition of an excess of MeI, gives (+)-**11** directly, in 85% yield. The assignment of relative configuration of this product was made from its ^1H NMR spectrum and, in particular, by comparison with the spectrum of **8** (the all-equatorial arrangement of groups around the ring in the latter compound having been demonstrated by X-ray analysis).

Similar direct asymmetric modification of **6** by treatment with base **7**, and then addition of Bu^{t}CO$_2$Et was also carried out to give a single keto sulfoxide (+)-**12** in good yield (Scheme 3).*

The relative configuration shown is based on a detailed ^1H NMR analysis (including COSY) and a single-crystal X-ray determination carried out on hydroxy sulfoxide **13**, derived from **12** by reduction with DIBAL/$ZnCl_2$.†

It is uncertain if the stereochemical outcome of the acylation to give **12** is due to kinetic or thermodynamic control, but **12** was shown to be the most stable epimeric keto sulfoxide since no epimerisation occurred on treatment with base. Also, we were able to prepare the epimer of **12** (at C-2) by reaction of the carbanion of **6** with Bu^{t}COCl. A single keto sulfoxide was produced in low yield (38%), which was completely isomerised to **12** on treatment with base (NaOMe). Attempts to determine if the selective formation of **12** from the acylation of **6** is due to *in situ* formation of an intermediate keto sulfoxide anion, by quenching with D_2O, gave inconclusive results.

Although the origin of the stereoselectivity remains uncertain, this stereochemical result appears quite general for the analogous reactions with a number of other esters, and contrasts with the methylation and silylation described above in that the new substituent is introduced *cis* to the S=O bond. The change in the stereochemical outcome in the acylations is also accompanied by a change in the preferred conformation of the thiane oxide ring. Whereas the silylated and methylated products **8** and **11** have an all-equatorial disposition of groups around the ring, compounds **12** and **13** adopt a conformation having the substituent at the α-carbon equatorial, and both the OSiBu^{t}Ph$_2$ and sulfoxide oxygen groups *axially* disposed.

The ee of the products **12** and **13** was determined as *ca.* 55%, by examination of their ^1H NMR spectra in the presence of Eu(hfc)$_3$ and (*R*)-TFAE,‡ respectively. Although the ee of the methylated product **11** could not be determined directly using these methods, the level of asymmetric induction in this case is also 55–60%, as indicated by comparison of the optical rotation of derived products with literature rotation data, *vide infra*. Recrystallisation of the optically active hydroxy sulfoxide **13**, obtained *via* **12** using HCLA base **7**, from Et_2O–light petroleum gave crystals having a very low rotation. After repeated crystallisations (× 3), and filtering of the precipitated racemate, the hydroxy sulfoxide **13** recovered from the mother liquor was of high optical purity (> 95%) as indicated by ^1H NMR spectrum in the presence of (*R*)-TFAE. The HCLA base strategy can, therefore, be used to access thiane oxide products of high optical purity, provided that a method is available for enantiomeric enrichment, although at present the modest levels of induction in the key asymmetric step make this rather inefficient.

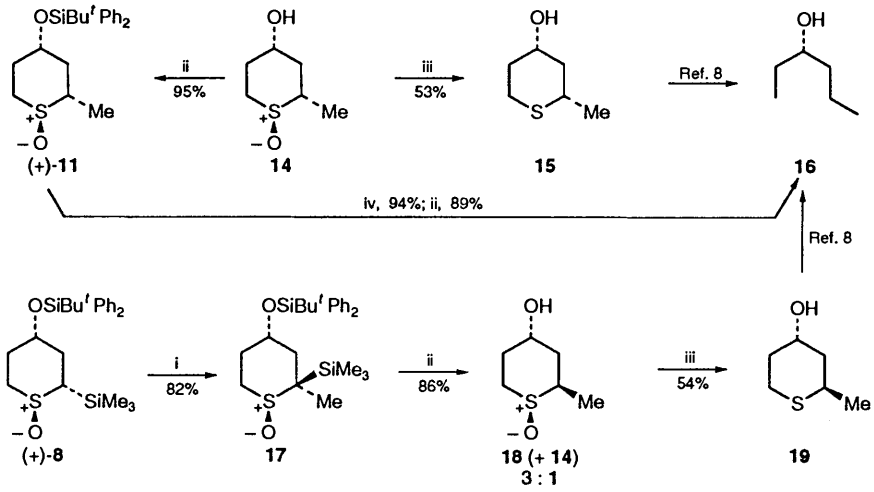
Following the assignment of relative configuration and the determination of ee values, we required a method to establish the absolute configurations of the non-racemic products shown above. This was done by converting (+)-**8** and (+)-**11** into materials of known absolute configuration *via* the sequences of transformations shown in Scheme 4.

The first sequence of reactions straightforwardly correlates the methylated product (+)-**11** with the thiane **15**, which had been prepared previously in optically pure form by using horse liver alcohol dehydrogenase.[8] A second sequence was devised in order to correlate the silyl sulfoxide (+)-**8** with either **15** or **19**, which involved regio- and stereo-selective methylation of (+)-**8** to give **17**, followed by removal of the silicon groups and sulfoxide reduction. We were initially surprised that this sequence proceeded to give mainly the hydroxy sulf-

* Our original assignment of relative stereochemistry for compound **12** is incorrect (P. J. Cox, A. Persad and N. S. Simpkins, *Synlett*, 1992, 197). Full details of revised assignments for this and related keto sulfoxide compounds can be found in the following paper.

† Full details of this structure determination can be found in the following paper.

‡ (*R*)-TFAE = (*R*)-(−)-2,2,2-trifluoro-1-(9-anthryl)ethanol.



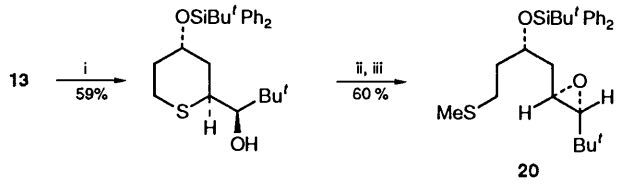
Scheme 4 *Reagents and conditions:* i, LDA, THF, MeI; ii, TBAF, THF, room temp.; iii, $LiAlH_4$, THF; iv RaNi, EtOH, reflux

oxide **18**, and subsequently the thiane **19**, epimeric with the corresponding compounds **14** and **15** obtained earlier. This is presumably due to stereoselective *protonation* of an intermediate α-sulfinyl carbanion, formed by desilylation of **17**, *trans* to the S=O bond, following the same stereochemical trend as observed previously for methylation and silylation.[9]

Comparison of the optical rotation data of **15** and **19** with the literature values allows assignment of the absolute configurations shown, as well as confirming the level of asymmetric induction in the initial asymmetric reactions of **6**. As shown in Scheme 4, we also carried out a correlation of (+)-**11** with (*S*)-hexan-3-ol, by desulfinylation with Raney nickel, followed by deprotection.

The above results show that a range of substituted thiane oxides are available by a HCLA base-mediated symmetry-breaking strategy, starting with a symmetrical sulfoxide. The desulfinylation of the optically active sulfoxides provides a novel route to non-racemic alcohols such as **16**. However, in such simple cases, the destruction of two asymmetric centres (one at carbon and one at sulfur) which accompanies the desulfinylation is unattractive. We therefore sought an alternative protocol, which would allow the retention of multiple asymmetric centres in thiane ring-opened products.

We realised this plan by developing a stereospecific method for the conversion of hydroxy sulfoxides such as **13** into functionalised epoxides.[10] This method was applied to the non-racemic sulfoxides **13** (>95% ee), obtained by optical enrichment, as described above, to give the epoxide **20** as shown in Scheme 5.



Scheme 5 *Reagents and conditions:* i, BH_3·THF, THF; ii, Me_3O^+ BF_4^-, CH_2Cl_2; iii, $NaOH_{(aq.)}$

Thus, reduction of **13**, using borane–tetrahydrofuran complex (which we found to be somewhat superior to $LiAlH_4$ in this case), followed by alkylation on sulfur and treatment with base gives the desired product **20**. The *trans* stereochemistry shown for this epoxide follows from that of the starting hydroxy sulfoxide, assuming that thiane ring opening occurs by stereospecific internal substitution.[11] Examination of the ^1H NMR spectrum of **20** reveals a relatively small coupling (J = 2.4 Hz) between the two hydrogens attached to the epoxide ring, in accord with our assignment.[12]

This stereoselective approach to functionalised epoxides is quite general, and has been applied to a number of other racemic examples, derived from keto sulfoxides related to **12**.[10]

In conclusion, we have shown for the first time that a prochiral cyclic sulfoxide can be converted directly into scalemic products by the action of an HCLA base. This type of approach allows entry to a range of cyclic and acylic products by using the cyclic sulfoxide as a disposable template. Further study of these reactions, including the use of different sulfoxide ring sizes and aspects of the kinetic resolution of sulfoxides is underway.

Experimental

Melting points for solid products were determined using a Reichert Microscope apparatus, and are uncorrected. IR spectra were recorded on a Philips PU96706, Pye Unicam SP3-100 or Perkin-Elmer 1720 FTIR instrument. NMR spectra were recorded on a Bruker WP80, Bruker AM 250, Jeol FX270 or Bruker AM400 machine, with Me_4Si as internal standard. J Values are recorded in Hz and multiplicities indicated for ^{13}C NMR were obtained using a DEPT sequence. Mass spectra were recorded on AEI 902 or VG micromass 70E spectrometers. Microanalyses were performed at the microanalytical laboratory at Nottingham University using a Perkin-Elmer 240B elemental analyser. Optical rotations were measured using a Jasco DIP 370 polarimeter. $[\alpha]_D$ Values are given in units of 10^{-1} deg cm^2 g^{-1}. Analytical TLC was performed on Merck precoated silica gel F_{254} plates. Preparative chromatography was carried out on columns of Merck Keiselgel 60 (230–400 mesh). Solvents were purified by standard techniques.

Preparation of the Sulfoxide **6**.—(i) *Preparation of* 4-(*tert-butyldiphenylsilyloxy*)*thiane*. To a solution of thian-4-ol (7.5 g, 64 mmol) in DMF (60 cm^3) was added imidazole (9.59 g, 0.14 mol), followed by *tert*-butyl(chloro)diphenylsilane (19.29 g, 70 mmol). The mixture was stirred overnight and then poured into saturated aqueous NH_4Cl (50 cm^3). The product was extracted into light petroleum (2 × 150 cm^3) and the combined extracts were washed with water (3 × 100 cm^3), brine (100 cm^3), water (3 × 100 cm^3) and finally brine (100 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure. Flash column chromatography (5% Et_2O in light petroleum) of the residue gave the title thiane as a yellow oil (22.17 g, 98%) (Found: C, 70.7; H, 8.0. $C_{21}H_{28}OSSi$ requires C, 70.73; H,

7.91%); ν_{max}(film)/cm^{-1} 2932, 2857, 1589, 1428, 1110 and 1087; δ_H(250 MHz, $CDCl_3$) 1.07 (9 H, s) 1.84 (4 H, m, 3-CH_2, 5-CH_2), 2.35 and 2.93 (4 H, 2 × m, 2-CH_2, 6-CH_2), 3.81 (1 H, m, 4-CH) and 7.20–7.70 (10 H, m, 2 × Ph); δ_C(62.5 MHz, $CDCl_3$) 19.5 (C), 25.5 (CH_2), 27.3 (CH_3), 36.0 (CH_2), 69.2 (CH), 127.8 (CH), 129.9 (CH), 134.6 (C) and 136.0 (CH); *m/z* 299 (M^+ − Bu^t, 79%), 199 (100) and 57 (19).

(ii) *Preparation of* 4-(tert-*butyldiphenylsilyloxy*)*thiane* 1-*oxide*. Oxone® (0.88 g, 1.43 mmol) was added to a solution of 4-(*tert*-butyldiphenylsilyloxy)thiane (0.51 g, 1.43 mmol) in MeOH (40 cm^3) at −70 °C. The mixture was warmed to room temperature with stirring, the solids were filtered off and the filtrate was evaporated under reduced pressure. Flash column chromatography (Et_2O) of the residue yielded firstly the *trans*-sulfoxide **6** as a white solid (0.263 g, 63%), m.p. 118–119 °C (Found: C, 67.9; H, 7.7. $C_{21}H_{28}O_2SSi$ requires C, 67.70; H, 7.57%); ν_{max}(KBr)/cm^{-1} 2960, 1588, 1428, 1385, 1111 and 1047; δ_H(250 MHz, $CDCl_3$) 1.08 (9 H, s, Bu^t), 1.65 (2 H, m, 3-CH_{eq}, 5-CH_{eq}), 2.34 (2 H, br dd, *J* 14 and 14, 3-CH_{ax}, 5-CH_{ax}), 2.72 (2 H, br d, *J* 13, 2-CH_{eq}, 6-CH_{eq}), 3.05 (2 H, ddd, *J* 13, 13 and 3, 2-CH_{ax}, 6-CH_{ax}), 4.07 (1 H, m, 4-CH) and 7.34–7.65 (10 H, m, 2 × Ph); δ_C(62.5 MHz, $CDCl_3$) 19.2 (C), 23.0 (CH_2), 26.8 (CH_3), 41.0 (CH_2), 65.3 (CH), 127.8 (CH), 129.9 (CH), 133.5 (C) and 135.5 (CH); *m/z* 372 (M^+, 0.04%), 315 (36) and 117 (100); followed by the corresponding *cis*-sulfoxide as a colourless oil (0.095 g, 23%), ν_{max}(film)/cm^{-1} 2848, 1589, 1462, 1361, 1101 and 978; δ_H(250 MHz, $CDCl_3$) 1.01 (9 H, s, Bu^t), 1.59 (2 H, m), 2.03 (2 H, m), 2.69 (2 H, br dd, *J* 10), 3.07 (2 H, ddd, *J* 13, 13 and 3, 2-CH_{ax}, 6-CH_{ax}), 3.75 (1 H, m, 4-CH) and 7.19–7.59 (10 H, m, 2 × Ph).

Asymmetric Synthesis of the Silyl-substituted Thiane Oxide (+)-**8** *using the HCLA Base* **7**.—A solution of the HCLA base **7** was prepared by treatment of the corresponding secondary amine (0.19 g, 0.74 mmol) in THF (2 cm^3) under nitrogen at −78 °C with a solution of BuLi (1.6 mol dm^{-3} solution in hexanes; 0.46 cm^3, 0.74 mmol), followed by warming to room temperature for 1 h. The resulting yellow solution was recooled to −78 °C and added dropwise to a solution of the sulfoxide **6** (0.19 g, 0.51 mmol) in THF (5 cm^3) at −78 °C. The mixture was stirred at −78 °C for 1 h and then Me_3SiCl (0.5 cm^3, 4 mmol) was added to it. After the mixture had been stirred for a further 15 min, saturated aqueous $NaHCO_3$ (10 cm^3) was added to it and the organic product extracted into Et_2O (2 × 20 cm^3). The combined extracts were dried ($MgSO_4$), and evaporated under reduced pressure and the resulting residue was subjected to column chromatography (Et_2O) to give **8** as a colourless oil (206 mg, 91%), $[\alpha]_D^{21}$ +28 (*c* 2.05 in CH_2Cl_2) (Found: C, 64.9; H, 8.5. $C_{24}H_{36}O_2SSi_2$ requires C, 64.81; H, 8.16%); ν_{max}(film)/cm^{-1} 3080, 2980, 2960, 1600, 1440, 1400, 1260, 1125, 1095, 1065 and 850; δ_H(400 MHz, $CDCl_3$) 0.10 (9 H, s, $SiMe_3$), 0.98 (9 H, s, Bu^t), 1.46 (1 H, ddd, *J* 14, 14 and 10, 3-CH_{ax}), 1.72–1.89 (3 H, m, 2-CH_{ax}, 3-CH_{eq}, 5-CH_{ax}), 2.01–2.06 (1 H, m, 5-CH_{eq}), 2.44 (1 H, ddd, *J* 13, 13 and 3, 6-CH_{ax}), 3.21 (1 H, ddd, *J* 12, 4 and 3, 6-CH_{eq}), 3.61 (1 H, m, 4-CH) and 7.19–7.62 (10 H, m, Ph); *m/z* 387 (M^+ − Bu^t, 13%), 371 (M^+ − $SiMe_3$, 65) 199 (100) and 73 (80). ^{1}H NMR experiments in the presence of the shift reagent Eu(hfc)$_3$ showed this sample to have an ee of 60% (splitting of Bu^t signal, shifted to *ca.* 1.55 ppm).

Reaction of the Sulfoxide **6** *with the HCLA Base* **9**.—A solution of the HCLA base **7** was prepared by treatment of the corresponding secondary amine (0.124 g, 0.55 mmol) in THF (5 cm^3) under nitrogen at −78 °C with a solution of BuLi (1.6 mol dm^{-3} solution in hexanes; 0.34 cm^3, 0.55 mmol), followed by warming to room temperature for 1 h. The resulting yellow solution was recooled to −78 °C and Me_3SiCl (0.5 cm^3, 4 mmol) was added dropwise to it. This was followed after 5 min by the dropwise addition of a solution of the sulfoxide **6** (0.19 g, 0.51 mmol) in THF (2 cm^3); the mixture was then stirred at −78 °C for a further 30 min before work-up as described above. Column chromatography (EtOAc–light petroleum) of the residue gave, firstly, the vinyl silane (−)-**10** as a colourless oil (75 mg, 33%), $[\alpha]_D^{28}$ −68.2 (*c* 0.7 in CH_2Cl_2) (Found: C, 67.8; H, 8.4. $C_{24}H_{34}OSSi_2$ requires C, 67.55; H, 8.03%); ν_{max}(film)/cm^{-1} 2980, 2890, 1600, 1580, 1485, 1440, 1380, 1345, 1265 1120 and 1050; δ_H (250 MHz, $CDCl_3$) 0.10 (9 H, s), 1.08 (9 H, s), 1.81 (1 H, m, 5-CH), 2.15 (1 H, m, 5-CH), 2.73 (1 H, m, 6-CH_{eq}), 3.10 (1 H, ddd, *J* 13, 12 and 3, 6-CH_{ax}), 4.17 (1 H, ddd, *J* 4.5, 4.5 and 4.5, 4-CH), 5.73 (1 H, d, *J* 4.5, 3-CH) and 7.37–7.75 (10 H, m); *m/z* 369 (M^+ − Bu^t, 57%), 353 (12), 199 (100) and 73 (75), followed by (−)-**8** (23 mg, 10%), $[\alpha]_D^{25}$ −28.4 (*c* 4.6 in CH_2Cl_2), with spectral characteristics as described above.

Conversion of (+)-**8** *into* (−)-**10** *using LDA*.—A solution of LDA was prepared by addition of BuLi (1.6 mol dm^{-3} solution in hexanes; 0.25 cm^3, 0.4 mmol) to a solution of diisopropylamine (0.058 cm^3, 0.4 mmol) in THF (2 cm^3) at −78 °C, under nitrogen, followed by warming to 0 °C for 30 min. A solution of the silyl sulfoxide (+)-**8** {90 mg, 0.2 mmol, $[\alpha]_D^{28}$ +30 (*c* 1.3 in CH_2Cl_2)} in THF (2 cm^3) was then added to the mixture which was then stirred for 20 min before the addition of Me_3SiCl (0.5 cm^3, 4 mmol). After 1 h at 0 °C saturated aqueous $NaHCO_3$ (5 cm^3) was added to the mixture which was then extracted with Et_2O (2 × 30 cm^3). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure and flash column chromatography (light petroleum) of the residue yielded (−)-**10** (93 mg, 90%), $[\alpha]_D^{22}$ −133 (*c* 0.5 in CH_2Cl_2) with spectral characteristics as described above.

Preparation of the Methylated Sulfoxide (+)-**11** *using the HCLA Base* **7**.—A solution of the HCLA base **7**, prepared from the corresponding secondary amine (0.19 g, 0.74 mmol) as described above and cooled to −78 °C, was added slowly dropwise to the sulfoxide **6** (190 mg, 0.51 mmol) in THF (5 cm^3) at −78 °C. The reaction mixture was stirred for 1 h at −78 °C and then MeI (0.1 cm^3, 1.5 mmol) was added to it. After having been stirred for a further 15 min the mixture was treated with saturated aqueous $NaHCO_3$ (10 cm^3) and extracted with Et_2O (2 × 20 cm^3). The combined extracts were then dried ($MgSO_4$) and evaporated under reduced pressure. Column chromatography (10% light petroleum in Et_2O) of the residue yielded (+)-**11** (160 mg, 81%) as a colourless oil, $[\alpha]_D^{21}$ +13.3 (*c* 0.6 in CH_2Cl_2) (Found: C, 68.3; H, 8.2. $C_{22}H_{30}O_2SSi$ requires C, 68.35; H, 7.82%); ν_{max}(film)/cm^{-1} 2959, 2930, 1590, 1473, 1428, 1110, 1080 and 1039; δ_H(250 MHz, $CDCl_3$) 0.93 (9 H, s, Bu^t), 1.24 (3 H, d, *J* 7, Me), 1.44–1.73 (2 H, m, 3-CH_{ax}, 5-CH_{ax}), 1.85–2.06 (2 H, m, 3-CH_{eq}, 5-CH_{eq}), 2.29–2.43 (2 H, m, 2-CH_{ax}, 6-CH_{ax}), 3.06 (1 H, ddd, *J* 13, 6 and 3, 6-CH_{eq}), 3.65 (1 H, dddd, *J* 10, 10, 4 and 4, 4-CH) and 7.14–7.56 (10 H, m, 2 × Ph); δ_C(67.8 MHz, $CDCl_3$) 16.4 (CH_3), 19.1 (C), 26.9 (CH_3), 30.9 (CH_2), 38.8 (CH_2), 47.4 (CH_2), 55.9 (CH), 69.4 (CH), 127.8 (CH), 130.0 (CH), 133.6 (C) and 135.7 (CH); *m/z* 329 (M^+ − Bu^t, 76%), 313 (81), 199 (56) and 131 (100).

Preparation of the Keto Sulfoxide (+)-**12** *using the HCLA Base* **7**.—To a stirred solution of the HCLA base **7** (0.81 mmol) in THF (4.0 cm^3) (prepared as described above) at −78 °C under an atmosphere of nitrogen, was added a solution of the sulfoxide **6** (200 mg, 0.54 mmol) in THF (4.0 cm^3). After the mixture had been stirred for 1.5 h Bu^tCO_2Et (0.17 cm^3, 1.08 mmol) was added to it in one portion and the whole maintained at −78 °C for a further 20 min. Saturated aqueous NH_4Cl (10 cm^3) was then added to the mixture which was then extracted with CH_2Cl_2 (3 × 10 cm^3). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure

and the residue purified by flash column chromatography (50% EtOAc–light petroleum) to give the product as a white foam (178 mg, 72%), $[\alpha]_D^{25}$ +14.6 (*c* 1.1 in CH_2Cl_2) (Found: C, 68.35; H, 8.2. $C_{26}H_{36}O_3SSi$ requires C, 68.42; H, 7.89%); ν_{max}(film)/cm^{-1} 3071, 2929, 2887, 1704, 1486, 1426, 1109, 1070, 1048 and 1008; δ_H(270 MHz, $CDCl_3$) 1.11 (9 H, s), 1.21 (9 H, s), 1.45 (1 H, dd, *J* 14 and 3.3, 3-CH_{eq}), 1.61 (1 H, dd, *J* 13 and 3.4, 5-CH_{eq}), 2.36 (1 H, dd, *J* 13 and 13, 5-CH_{ax}), 2.54 (1 H, ddd, *J* 14, 14 and 1.7, 3-CH_{ax}), 2.91 (1 H, ddd, *J* 14, 3 and 3, 6-CH_{eq}), 3.11 (1 H, ddd, *J* 14, 14 and 3, 6-CH_{ax}), 4.26 (1 H, br s, 4-CH_{eq}), 4.42 (1 H, dd, *J* 12 and 2.4, 2-CH), 7.35–7.48 (6 H, m) and 7.62–7.68 (4 H, m); δ_C(6.25 MHz, $CDCl_3$) 19.2 (C), 21.6 (CH_2), 26.0 (CH_2), 26.3 (CH_3), 27.0 (CH_3), 42.3 (CH_2), 45.0 (C), 55.0 (CH), 65.4 (CH), 127.9 (CH), 130.1 (CH), 133.2 (C), 135.6 (CH) and 208.6 (C=O); *m/z* (EI) 399 (M^+ − Bu^t, 100%), 381 (9), 199 (73) and 183 (16). Analysis of the ^{1}H NMR spectrum in the presence of Eu(hfc)$_3$ indicated an ee of 55% for this material (splitting of Bu^t signal, shifted to *ca.* 2.3 ppm).

Reduction of (+)-**12** *using* DIBAL/$ZnCl_2$.—Dry $ZnCl_2$ (224 mg, 1.65 mmol) was added to a stirred solution of the non-racemic keto sulfoxide **12** (628 mg, 1.38 mmol) in THF (10 cm^3) under N_2 and the mixture stirred at room temperature for 30 min. The mixture was then cooled to −78°C and DIBAL (1 mol dm^{-3} solution in hexanes; 1.38 cm^3) was added dropwise to it. After the mixture had been stirred at −78 °C for a further 20 min it was treated with MeOH (10 cm^3) and evaporated under reduced pressure. The involatile residue was taken up in water (10 cm^3) and extracted with CH_2Cl_2 (3 × 10 cm^3). The combined organic extracts were washed with aqueous 2 mol dm^{-3} NaOH (10 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure. Flash column chromatography of the residue (EtOAc) gave **13** as a white foam (382 mg, 60%), $[\alpha]_D^{25}$ +7.7 (*c* 0.95 in CH_2Cl_2) (Found: C, 68.3; H, 8.3. $C_{26}H_{38}O_3SSi$ requires C, 68.12; H, 8.30%); ν_{max}(film)/cm^{-1} 3380, 3072, 2957, 2859, 1472, 1428, 1112, 1070 and 1009; δ_H(270 MHz, $CDCl_3$) 0.83 (9 H, s), 1.01 (9 H, s), 1.46 (1 H, br d, *J* 14, 5-CH_{eq}), 1.74 (1 H, br d, *J* 14.5, 3-CH_{eq}), 2.14 (1 H, br t, *J* 14, 5-CH_{ax}), 2.29 (1 H, t, *J* 14.5, 3-CH_{ax}), 2.72 (1 H, br d, *J* 14, 6-CH_{eq}), 3.00 (1 H, dt, *J* 14 and 3, 6-CH_{ax}), 3.12 (1 H, br d, *J* 11, 2-CH_{ax}), 3.35 (1 H, br s, OH), 3.81 (1 H, s, C*H*OH), 4.17 (1 H, br s, 4-CH), 7.24–7.36 (6 H, m) and 7.52–7.56 (4 H, m); δ_C(67.8 MHz, $CDCl_3$) 19.2 (C), 21.7 (CH_2), 24.5 (CH_2), 26.4 (CH_3), 26.7 (CH_3), 36.0 (C), 41.3 (CH_2), 50.0 (CH), 65.6 (CH), 81.4 (CH), 127.83 (CH), 130.04 (CH), 133.5 (C) and 135.7 (CH); *m/z* (FAB) 459 (M^+ + H, 55%), 441 (M^+ − H_2O, 10), 401 (M^+ − Bu^t, 9), 135 (86) and 57 (100).

Examination of the ^{1}H NMR in the presence of (*R*)-TFAE (4 equiv.) indicated the ee of this sample to be 55% (splitting of Bu^t signal at *ca.* 0.9 ppm). The sample of **13** obtained above was thrice recrystallised from Et_2O–light petroleum (1:1) to give samples of almost racemic hydroxy sulfoxide (racemic **13** has m.p. 127–129 °C). Evaporation of the final mother liquor gave a sample of **13** (125 mg, 20% overall from **12**), $[\alpha]_D^{25}$ +16.4 (*c* 1.0 in CH_2Cl_2), which appeared to be enantiomerically pure, as judged by NMR examination in the presence of (*R*)-TFAE.

Correlation of (+)-**11** *with the Thiane* **15**.—(i) *Deprotection of* (+)-**11**. To a solution of the sulfoxide (+)-**11** {216 mg, 0.56 mmol, $[\alpha]_D^{30}$ +14.8 (*c* 2.84 in CH_2Cl_2)} in THF (3 cm^3) at 0 °C was added a solution of Bu_4NF in THF (1 mol dm^{-3} solution in THF; 0.67 cm^3). The mixture was allowed to warm to room temperature and, after 24 h, it was evaporated under reduced pressure. The residue was subjected to column chromatography (acetone) to give **14** as a colourless liquid (78.4 mg, 95%), $[\alpha]_D^{31}$ +68.6 (*c* 1.32 in CH_2Cl_2); ν_{max}(film)/cm^{-1} 3360, 2920, 2884, 1455, 1428, 1291, 1095, 1062 and 1007; δ_H(250 MHz, $CDCl_3$) 1.45 (3 H, d, *J* 7, CH_3), 1.52–1.85 (2 H, m, 3-CH_{ax}, 5-CH_{ax}), 2.14–2.35 (2 H, m, 3-CH_{eq}, 5-CH_{eq}), 2.65–2.82 (2 H, m, 6-CH_{eq}, 2-CH_{ax}), 3.34 (1 H, m, 6-CH_{ax}) and 3.87 (1 H, m, 4-CH).

(ii) *Reduction of* **14** *with* $LiAlH_4$. The hydroxy sulfoxide **14** (66 mg, 0.45 mmol) in THF (2 cm^3) under N_2 was heated at reflux with $LiAlH_4$ (17 mg, 0.45 mmol) for 1 h after which a second portion of $LiAlH_4$ (17 mg) was added to it. The mixture was then heated at reflux overnight after which a third portion of $LiAlH_4$ (17 mg) was added to it. The mixture was then heated at reflux for an additional 24 h after which it was cooled, poured carefully into aqueous 2 mol dm^{-3} HCl (150 cm^3) and, extracted with CH_2Cl_2 (3 × 70 cm^3). The combined extracts were dried (Na_2SO_4), and evaporated under reduced pressure. Flash column chromatography (50% EtOAc–light petroleum) of the residue gave the thiane **15** (31 mg, 53%) as a colourless oil, $[\alpha]_D^{30}$ +2.7 (*c* 2.18 in $CHCl_3$) {lit.,[8] $[\alpha]_D^{22}$ +4.0 (*c* 1.0 in $CHCl_3$)}; δ_H(250 MHz, $CDCl_3$) 1.24 (3 H, d, *J* 6.8), 1.30–1.55 (2 H, m), 2.20–2.30 (3 H, m, 1 H D_2O exch.), 2.62–2.94 (3 H, m, 2-CH, 6-CH_2) and 3.56 (1 H, m, 4-CH).

Correlation of (+)-**11** *with* (S)-*Hexan*-3-*ol*.—(i) *Raney nickel desulfurisation of* (+)-**11**. The sulfoxide (+)-**11** {200 mg, 0.52 mmol, $[\alpha]_D^{30}$ +14.8 (*c* 2.84 in CH_2Cl_2)} was heated at reflux in EtOH (5 cm^3) with Raney nickel (*ca.* 0.6 g) for 2 d. The reaction mixture after being allowed to cool was filtered through Kieselguhr and evaporated under reduced pressure. Flash column chromatography (light petroleum) of the residue yielded the required desulfinylated intermediate (the silicon protected hexan-3-ol) (165 mg, 94%) as a colourless liquid, $[\alpha]_D^{28}$ −3.3 (*c* 1.1 in CH_2Cl_2); ν_{max}(film)/cm^{-1} 2960, 2932, 1429, 1112, 1071 and 1018; δ_H(250 MHz, $CDCl_3$) 0.75 (3 H, t, *J* 7, CH_3), 0.78 (3 H, t, *J* 7, CH_3), 1.05 (9 H, s, Bu^t), 1.17–1.53 (6 H, m, 3 × CH_2), 3.67 (1 H, m, CHOSi) and 7.32–7.74 (10 H, m, 2 × Ph); δ_C(68 MHz, $CDCl_3$) 9.18 (CH_3), 14.2 (CH_3), 18.1 (CH_2), 19.4 (C), 27.1 (CH_3), 28.9 (CH_2), 38.0 (CH_2), 74.1 (CH), 127.4 (CH), 129.3 (CH), 134.9 (C) and 135.9 (CH); *m/z* 283 (M^+ − Bu^t, 69.8%) and 199 (100).

(ii) *Deprotection to give non-racemic hexan*-3-*ol*. The *tert*-butyldiphenylsilyl ether obtained in (i) (30 mg, 0.088 mmol) was dissolved in THF (1 cm^3) and a solution of BuNF in THF (1 mol dm^{-3} solution in THF; 1.0 cm^3) was added to it. The resulting mixture was stirred at room temperature for 12 h after which the THF was evaporated under reduced pressure and the residue subjected to flash column chromatography (30–50% Et_2O–light petroleum) to give non-racemic hexan-3-ol (8 mg, 89%) as a colourless liquid, $[\alpha]_D^{26}$ +5.0 (*c* 0.8 in $CHCl_3$) {lit.[8] $[\alpha]_D^{20}$ +7.8 (*c* 0.3 in $CHCl_3$)}; identical spectroscopically with an authentic sample.

Correlation of (+)-**8** *with the Thiane* **19**.—(i) *Methylation of* (+)-**8**. A solution of BuLi (1.6 mol dm^{-3} solution in hexanes; 0.66 cm^3, 1.05 mmol) was added to a solution of the silyl sulfoxide (+)-**8** {0.425 g, 0.96 mmol, $[\alpha]_D^{28}$ +28.8 (*c* 1.9 in CH_2Cl_2)} in THF (10 cm^3) under a nitrogen atmosphere and the mixture was stirred for 30 min. MeI (0.2 cm^3, 3.2 mmol) was then added to it and the whole allowed to warm to room temperature over 15 min. After this saturated aqueous $NaHCO_3$ (10 cm^3) was added to the mixture which was then extracted with Et_2O (2 × 40 cm^3). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure. Flash column chromatography of the residue (70% Et_2O–light petroleum) yielded **17** (0.36 g, 82%) as a colourless solid, m.p. 122–123 °C, $[\alpha]_D^{17}$ +11 (*c* 3 in CH_2Cl_2) (Found: C, 65.5; H, 8.6. $C_{25}H_{38}O_2SSi_2$ requires C, 65.45; H, 8.35%); ν_{max}(KBr)/cm^{-1} 2953, 2935, 2858, 1589, 1427, 1385, 1112, 1074 and 1043;

δ_H(250 MHz, $CDCl_3$) 0.04 (9 H, s, $SiMe_3$), 1.00 (3 H, s, CH_3), 1.06 (9 H, s), 1.58 (2 H, m), 1.75 (1 H, m), 2.05 (1 H, br d, *J* 14), 2.73 (1 H, ddd, *J* 14 and 4, 6-CH_{ax}), 2.90 (1 H, ddd, *J* 14, 4 and 4, 6-CH_{eq}), 3.90 (1 H, m, 4-CH) and 7.40–7.76 (10 H, m, 2 × Ph); *m/z* 443 (M^+ − Me, 47%), 442 (100), 402 (61) and 200 (30).

(ii) *Desilylation to give* **18**. To a solution of the sulfoxide from (i) (0.36 g, 0.79 mmol) in THF (10 cm^3) at 0 °C was added BuNF (1 mol dm^{-3} solution in THF; 1.55 cm^3) and the mixture stirred at room temperature overnight. It was then evaporated under reduced pressure and the residue subjected to flash chromatography to give **18** (74.1 mg, 64%) as a colourless liquid $[\alpha]_D^{21}$ +76 (*c* 1.8 in CH_2Cl_2); ν_{max}(film)/cm^{-1} 3294, 2957, 2877, 1462, 1424, 1341, 1259, 1177, 1067, 1055 and 1021; δ_H(250 MHz, $CDCl_3$) 1.25 (3 H, d, *J* 7, CH_3), 1.58–1.68 (2 H, m, 3-CH_{eq}, 5-CH_{eq}), 2.15 (1 H, ddd, *J* 14, 14 and 2.5, 3-CH_{ax}), 2.35 (1 H, ddm, *J* 14 and 14, 5-CH_{ax}), 2.75–2.99 (3 H, m, 6-CH_2, 2-CH_{eq}), 3.16 (1 H, br s, OH) and 4.12 (1 H, br s, 4-CH); δ_C(67.8 MHz, $CDCl_3$) 16.7 (CH_3), 21.0 (CH_2), 30.6 (CH_2), 39.9 (CH_2), 44.0 (CH) and 62.9 (CH); accompanied by **14** (24.9 mg, 22%).

(iii) *Reduction of* **18** *with* $LiAlH_4$. A solution of the hydroxy sulfoxide **18** (74 mg, 0.5 mmol) in THF (10 cm^3) was heated at reflux with $LiAlH_4$ (10 mg, 0.26 mmol) for 10 h. The mixture was cooled and water (1 cm^3) was added to it followed by saturated aqueous NH_4Cl (10 cm^3). The mixture was extracted into EtOAc (2 × 50 cm^3) and the combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure. Flash column chromatography of the residue yielded **19** (35.6 mg, 54%) as a colourless oil, $[\alpha]_D^{21}$ +8.3 (*c* 1.6 in $CHCl_3$) {lit.,[8] $[\alpha]_D^{20}$ +14.8 (*c* 1.1 in $CHCl_3$)}; ν_{max}(film)/cm^{-1} 3386, 2921, 1450, 1426, 1217 and 1045; δ_H(250 MHz, $CDCl_3$) 1.20 (3 H, d, *J* 6, CH_3), 1.52–2.05 (5 H, m, 2-CH, 3-CH_2, 5-CH_{ax} and OH), 2.42 (1 H, ddd, *J* 14, 4 and 4, 6-CH_{eq}), 3.07 (1 H, ddd, *J* 14, 12 and 3.5, 6-CH_{ax}), 3.25 (1 H, m, 2-CH_{eq}) and 4.17 (1 H, m, 4-CH); δ_C(68 MHz, $CDCl_3$) 21.5 (CH_3), 23.0 (CH_2), 31.0 (CH), 33.6 (CH_2), 42.7 (CH_2) and 65.7 (CH).

Conversion of (+)-**13** *into the Epoxide* **20**.—(i) *Reduction of the sulfoxide* **13** *using* BH_3·THF. To a stirred solution of (+)-**13** {70 mg, 0.15 mmol, $[\alpha]_D^{25}$ +16.4 (*c* 1.0 in CH_2Cl_2)} in THF (5.0 cm^3) under argon was added BH_3·THF (1 mol dm^{-3} solution in THF; 0.62 cm^3). The mixture was stirred at room temperature for 24 h and then saturated aqueous NH_4Cl (5 cm^3) was added to it followed by water (10 cm^3). The mixture was extracted with CH_2Cl_2 (3 × 10 cm^3) and the combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure. Column chromatography of the residue (5% EtOAc in light petroleum) gave the desired thiane intermediate as a colourless oil (40 mg, 59%), $[\alpha]_D^{25}$ −21.6 (*c* 3.5 in CH_2Cl_2); ν_{max}(film)/cm^{-1} 3447, 3070, 2930, 2857, 1487, 1427, 1110, 1070 and 1009; δ_H(270 MHz, $CDCl_3$) 0.83 (9 H, s), 1.03 (9 H, s), 1.51–1.85 (4 H, m, 1 H D_2O exch.), 2.00 (1 H, dm, *J* 13, 5-CH_{eq}), 2.35 (1 H, dt *J* 13 and 3.6, 2-CH), 3.22 (1 H br s, C*H*OH), 3.42 (1 H, dt, *J* 13 and 2.7, 6-CH_{ax}), 3.76 (1 H, dt, *J* 13 and 2.3, 6-CH_{eq}), 4.25 (1 H, br s, 4-CH), 7.32–7.43 (6 H, m) and 7.62 (4 H, m); δ_C(67.8 MHz, $CDCl_3$) 19.3 (C), 23.8 (CH_2), 26.8 (CH_3), 27.1 (CH_3), 33.2 (CH_2), 35.2 (CH_2), 36.0 (C), 38.0 (CH), 67.1 (CH), 81.8 (CH), 127.7 (CH), 129.7 (CH), 134.0 (C) and 135.8 (CH); *m/z* (FAB) 443 (M^+ + H, 1.1%), 385 (M^+ − Bu^t, 30), 365 (6.8), 199 (50) and 135 (100).

(ii) *The Epoxide* **20**. To a stirred solution of the thianol obtained in (i) (35 mg, 0.08 mmol) in CH_2Cl_2 (10 cm^3) under N_2 was added $Me_3O^+BF_4^-$ (18 mg, 0.12 mmol). After 1.5 h, aqueous 5% NaOH (0.5 cm^3) was added to the solution which was then stirred for a further 18 h. It was then diluted with water (5 cm^3) and extracted with CH_2Cl_2 (3 × 10 cm^3). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure. Column chromatography of the residue gave the epoxide **20** as a colourless oil (22 mg, 60%), $[\alpha]_D^{25}$ +9.0 (*c* 2.0 in CH_2Cl_2) (Found: C, 70.9; H, 9.2. $C_{27}H_{40}O_2SSi$ requires C, 71.05; H, 8.83%); ν_{max}(film)/cm^{-1} 3070, 2957, 2930, 2857, 1487, 1427, 1111 and 1072; δ_H(250 MHz, $CDCl_3$) 0.83 (9 H, s), 1.07 (9 H, s), 1.64 (2 H, t, *J* 6, CHOSiBu^t$Ph_2C$$H_2$CHO), 1.73–1.82 (2 H, m, SCH_2CH_2), 1.95 (3 H, s), 2.24 (1 H, d, *J* 2.4, Bu^{t}C*H*O), 2.45 (2 H, m, SCH_2), 2.81 (1 H, dt, *J* 5.8 and 2.4, Bu^{t}CHOC*H*), 4.00 (1 H, quint, *J* 5.8), 7.35–7.48 (6 H, m) and 7.67–7.73 (4 H, m); δ_C(63 MHz, $CDCl_3$) 15.0 (CH_3), 19.1 (C), 25.5 (CH_3), 26.7 (CH_3), 29.5 (CH_2), 30.4 (C), 36.4 (CH_2), 39.3 (CH_2), 51.8 (CH), 66.4 (CH), 70.5 (CH), 127.3 (CH), 129.4 (CH), 133.7 (CH) and 135.6 (CH); *m/z* (FAB) 457 (M^+ + H, 15%), 329 (61), 309 (21), 199 (66), 135 (97) and 61 (100).

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