Synthesis of (4*S*,5*R*)-(−)-4-Methyl-5-phenyloxazolidine-2-selone: A Chiral Auxiliary Reagent Capable of Detecting the Enantiomers of (*R*,*S*)-Lipoic Acid by ^{77}Se Nuclear Magnetic Resonance Spectroscopy

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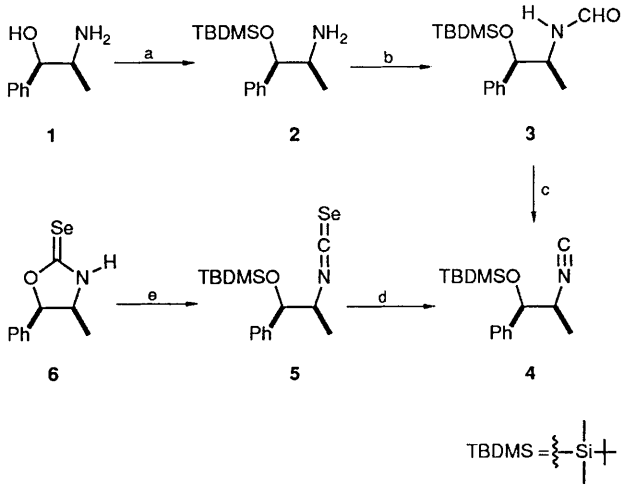
(4*S*,5*R*)-(−)-4-Methyl-5-phenyloxazolidine-2-selone was constructed in 5 steps on the 10-gram scale. ^{77}Se NMR spectroscopic studies revealed that this selone served as a remarkably sensitive chiral auxiliary agent which readily distinguished the selone-coupled (*R*,*S*)-lipoic acid ($\Delta\delta$ 0.119 ppm), even though its chiral centre was separated by 8 bonds from the observed nucleus.

We have recently reported that the ^{77}Se nucleus of the selenocarbonyl group exhibits sufficient electronic sensitivity to permit the detection and quantitation of remotely disposed chiral centres by ^{77}Se NMR spectroscopy.[1] In this ongoing study we have taken advantage of the ^{77}Se chemical shift sensitivity of the selone (selenocarbonyl) by placing it in a rigid chiral environment, thereby enabling this functional group to report on distant chiral centres. In this report we disclose a synthesis of a selone chiral auxiliary reagent derived from norephedrine and demonstrate its remarkable chemical shift sensitivity by observing a $\Delta\delta$-value of 0.119 ppm for the diastereoisomers which result from the coupling of the reagent to (*R*,*S*)-lipoic acid.

Results and Discussion

Two reports describing the synthesis of oxazolidineselones have appeared.[2] While both procedures describe a one-pot synthesis, each requires the use of mercury salts and carbon diselenide. Our approach, while multi-step, has several advantages: (i) the synthesis is readily performed to give greater than 10 grams of the selone, (ii) any commercially available chiral amino alcohol can be used, (iii) common and relatively inexpensive reagents are employed, most of which do not need any special handling or waste disposal, and (iv) the use of carbon diselenide as a selenocarbonyl-transfer agent is obviated.

It is well known that amines will react with isoselenocyanates to give the corresponding selenoureas[3] while the addition of alcohols has been reported to occur under forcing conditions.[4] We chose to devise an intramolecular annulation in order to take advantage of isoselenocyanate chemistry for the construction of the selone **6** (Scheme 1). The synthesis was initiated with the treatment of norephedrine **1** with *tert*-butyldimethylsilyl chloride (TBDMSCl) in the presence of triethylamine, and afforded what appeared to be a mixture of the protected amine or alcohol, in variable ratios, in 70% yield. Eventually it was found that simple heating of this mixture to reflux in benzene gave the corresponding silyl ether **2** exclusively as determined by ^{1}H NMR spectroscopy. Use of the less expensive reagent trimethylsilyl chloride, under identical conditions, gave poor yields (less than 30%). In addition, the conditions used in the subsequent step caused cleavage of the trimethylsilyl ether, therefore the use of this protecting group was abandoned. The amine was then converted into the formamide **3** by reaction with formic acid with azeotropic removal of water. Dehydration of the formamide **3** to the isocyanide **4** was effected with phosphorus trichloride oxide in the presence of triethylamine at



Scheme 1 *Reagents and yields:* (a) TBDMSCl, triethylamine, methylene dichloride (57.8 g, 70%); (b) formic acid (95%); (c) $POCl_3$ (1 mol equiv.), triethylamine (3 mol equiv.), methylene dichloride (70%), 16% formamide recovered; (d) Se^0 (2 mol equiv.), $CHCl_3$; (e) TBAF (1 mol equiv.), THF (64% combined yield for d and e)

0 °C for 5 min.[5] Typically, on a 15-gram scale the reaction gave a 70% yield of the isocyanide **4** along with 16% recovery of the formamide reactant. Longer reaction times or changes in the amount of triethylamine or phosphorus trichloride oxide resulted in decreased yields of the products. However, if the reaction was run on the 0.1- 1.0-gram scale, the yield of the isocyanide improved to 85%. The isocyanide **4** was then taken up in chloroform, elemental selenium (2 mol equiv.) was added, and the suspension was refluxed for 5 h. Filtration followed by concentration afforded the crude isoselenocyanate **5**. Purification of the isoselenocyanate can be performed by using silica gel column chromatography. However, on the 15-gram scale it was easier to delay purification until after the last step. Cleavage of the silyl ether with tetrabutylammonium fluoride (TBAF) in tetrahydrofuran (THF) was followed by ring closure to give the selone **6**. Purification of crude selone **6** by flash silica gel column chromatography gave a combined 64% yield for the last two steps.

It has been reported that selones such as **6**, are stable indefinitely at −25 °C in the absence of light.[2] At 50 °C decomposition of compound **6** (neat) occurred readily when the selone was in the presence of light and oxygen. However, if the same experiment was performed in the absence of light the selone exhibited no decomposition over a period of 24 h.

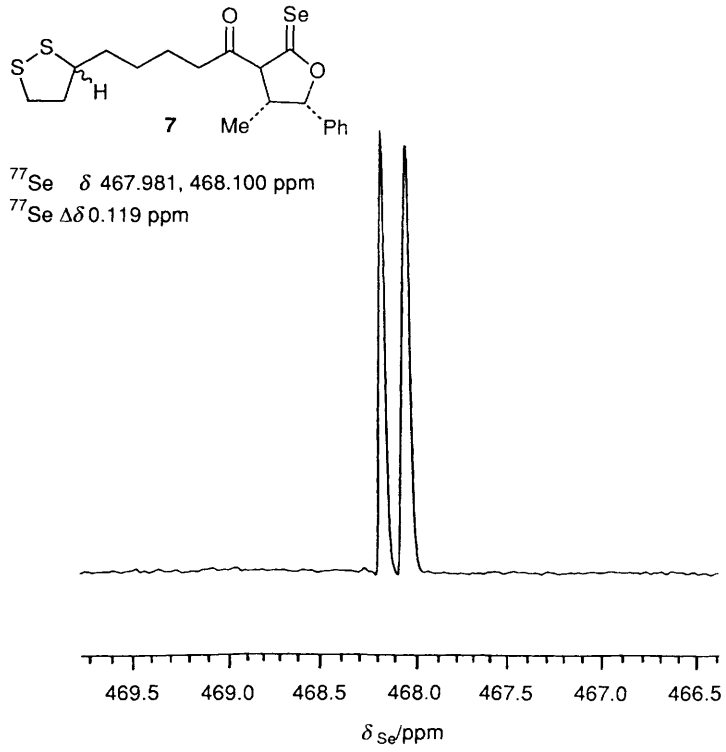


Fig. 1 The selenium-77 spectrum of compound **7** was obtained at 7.05 T. Measurements were made using a 5-mm NMR tube with $CDCl_3$ as an internal lock solvent. A 0.3 mol dm^{-3} solution was used and 10 789 scans were acquired using a pulse angle of 30° and a recycle time of 3.0 s. Digitization (Hz/pt) of 0.35 Hz was obtained using a 64K data table and a sweep width of 200 ppm.

We have found that methylene dichloride solutions of selone **6**, in the presence of oxygen at −25 °C, did not show any evidence of decomposition (TLC and ^{1}H NMR analysis) over a period of 7 months.

Selenium reagents have enjoyed widespread use in synthetic organic chemistry for selective transformations, such as selenoxide eliminations,[6] selenium dioxide oxidations,[7] and radical initiated carbocyclizations that employ seleno-esters.[8] However, only recently has the selenium atom been exploited as a novel spectroscopic reporter group in the study of various inorganic, organic and biochemical systems.[9] The sensitivity of the ^{77}Se nucleus (6.93 × 10^{-3} with respect to ^{1}H and 2.98 compared with ^{13}C), its natural abundance (7.5%) and spin ($I\frac{1}{2}$) make it an excellent candidate for an NMR reporter nucleus. Selenium has the special feature of possessing a large chemical-shift range (~3400 ppm), and the selenium nucleus is extremely sensitive to its electronic environment.[10] For example, comparison of ^{77}Se and ^{31}P chemical shifts reveals that the sensitivity of selenium shielding to changes in electronic structure is several times greater than that of phosphorus.[11]

In designing a selenium-containing chiral auxiliary, we wanted to take advantage of several features reported for compounds containing the selenocarbonyl group (C=Se): (i) The range of ^{77}Se chemical shifts for selenocarbonyl groups (~2600) is larger than that for any other type of selenium moiety and spans more than 80% of the current limits of the chemical-shift range,[12] (ii) the T_1s (spin-lattice relaxation times) of ^{77}Se selenocarbonyls are relatively short (1–8 s), while those for dialkyl selenides, especially the diaryl and dibenzyl selenides, are relatively long (27.0 s),[13] and (iii) selenocarbonyl groups display enhanced sensitivity toward small changes in the electronic environment of the selenium atom and its directly bonded carbon atom as compared with selenides and di-selenides.[14] These attributes of the selenium atom make it an excellent reporter group for a wide variety of systems.

In an effort to establish the boundary of sensitivity of selones such as **6** to discern remotely disposed chiral centres by ^{77}Se NMR spectroscopy, we evaluated the racemate of lipoic acid by coupling the acid to selone **6**. To the best of our knowledge, other NMR chiral auxiliary agents have failed to distinguish the enantiomers of (*R*,*S*)-lipoic acid wherein the chiral centre is distant from the observed nucleus. Furthermore, with the exception of Williams' use of Mosher's ester[15] to measure the enantiomeric excess of an intermediate (9 bonds distant from the observing fluorine-19 nucleus) in his synthesis of the natural product (−)-brevianamide B,[16] the use of NMR chiral auxiliary agents usually are limited to discerning chiral centres 4–5 bonds removed from the observing nucleus.[1] In the resulting mixture of diastereoisomers created from the coupling of selone **6** to lipoic acid,[17] the chiral centre of the lipoyl group is 9 atoms (8 bonds) separated from the selenium atom. Quite remarkably, the ^{77}Se NMR spectrum of the latter mixture features two clearly resolved resonances which are separated by 0.119 ppm 1). These results demonstrate that selones such as **6** represent a new generation of chiral auxiliary reagents which have at least doubled the limits of detection of the agents currently employed.

Experimental

General.—The ^{1}H, ^{13}C and ^{77}Se NMR spectra were recorded for $CDCl_3$ solutions on an IBM NR-80, Bruker AM-300 or AM-500 spectrometer. ^{1}H chemical shifts are expressed in ppm deshielded with respect to tetramethylsilane at δ 0.0 ppm; *J*-values are given in Hz; ^{13}C chemical shifts are referenced with respect to internal $CDCl_3$ (δ_C 77.0 ppm); ^{77}Se chemical shifts are expressed in ppm deshielded with respect to a 60% (v/v) solution of Me_2Se in $CDCl_3$.[18] Positive chemical shifts denote resonances deshielded with respect to the reference. Typically, the selenium-77 NMR spectra were obtained in the Fourier transform mode on a Bruker AM-300 superconducting spectrometer at 7.05 T. Measurements were made at, or near,

ambient probe temperature in 5 mm NMR tubes with $CDCl_3$ as an internal lock solvent. All spectra were acquired in the proton-decoupled mode; generally, 0.15–0.30 mol dm^{-3} solutions were used and 128–1024 scans were acquired using a pulse angle of 30° and a recycle time of 2.2 s. A resolution of 0.1 ppm was obtained using a 32K data table and a sweep width of 100 ppm. Use of a higher-field NMR instrument (500 MHz) resulted in increased peak broadening. IR spectra were recorded on a Perkin-Elmer 1600 FTIR spectrometer for CCl_4 solutions unless otherwise noted. Accurate mass spectra were measured on a VG 70SQ GC/MS spectrometer. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, TN. Analytical TLC was carried out on glass plates (silica gel 60 Å, 250 μm thickness) obtained from Analtech. TLC visualization was accomplished with a UV lamp, I_2 staining, and an ethanolic solution of phosphomolybdic acid (PMC). Liquid chromatography separations were carried out on silica gel by using the Still protocol.[19] The columns were hand-packed with silica gel 60 (230–400 mesh, Merck). Pressures used were usually 5–8 psi. Fractions were monitored by TLC.

Elemental selenium (200 mesh), norephedrine, *tert*-butyldimethylsilyl chloride, 95% formic acid, phosphorus trichloride-oxide, and tetrabutylammonium fluoride (1.0 mol dm^{-3} in THF) were obtained from Aldrich Chemical Company and were used without purification. Triethylamine was distilled over calcium hydride and stored over KOH prior to use. Methylene dichloride was distilled over calcium hydride. THF was distilled over potassium benzophenone ketyl prior to use.

Moisture-sensitive reactions were performed in flame-dried glassware under a positive pressure of nitrogen or argon.

(1S,2R)-2-(tert-*Butyldimethylsiloxy*)-1-*methyl*-2-*phenylethylamine* **2**.—In a single-necked, round-bottom flask fitted with a septum and a stirrer bar were placed (1*R*,2*S*)-norephedrine **1** (50 g, 0.33 mol) and DMSCl (50 g, 0.33 mol) in freshly distilled methylene dichloride (500 cm^3). Triethylamine (33.33 g, 0.33 mol) was added *via* a syringe at room temperature to the stirred mixture under nitrogen. The mixture was then stirred overnight, filtered, then poured onto diethyl ether (20 cm^3) and filtered again. The crude reaction product was concentrated at reduced pressure and purified by flash column chromatography (3% MeOH–CH_2Cl_2, v/v). Evaporation of the solvent gave the silyl ether **2** as a pale yellow oil (57.8 g, 70%); ν_{max}/cm^{-1} 3387, 2930, 1666, 1462, 1363, 1254, 1090 and 1065; δ_H −0.22 (3 H, s), −0.006 (3 H, s), 0.85 (9 H, s), 0.97 (3 H, d, *J* 6.5), 1.39 (2 H, br s), 2.85–3.05 (1 H, m), 4.37 (1 H, d, *J* 5.2) and 7.21–7.26 (5 H, m); δ_C −5.2, −4.8, 18.0, 18.7, 25.7, 53.4, 80.0, 126.9, 127.2, 127.7 and 141.8; *m/z* 250.1621 ($M^+ - CH_3$). Calc. for $C_{14}H_{24}NOSi$: *m/z* 250.1627 (2.4 ppm error).

(1S,2R)-N-[2-(tert-*Butyldimethylsiloxy*)-1-*methyl*-2-*phenylethyl*]*formamide* **3**.—In a 1 dm^3 single-necked, round-bottom flask fitted with a Dean–Stark trap and a stirrer bar were placed **2** (55.8 g, 0.21 mol), (89%) formic acid (50 cm^3) and benzene (700 cm^3). The solution was refluxed for 20 h under nitrogen, extracted with diethyl ether (2 × 200 cm^3), then washed with saturated aq. $NaHCO_3$ and dried over magnesium sulphate. The crude reaction product was concentrated under reduced pressure. Purification was performed by flash column chromatography (70% diethyl ether–hexane, v/v). Evaporation of the solvent gave the *formamide* **3** as a pale yellow oil (58.8 g, 95%), ν_{max}/cm^{-1} 3445, 2956, 1696, 1490, 1365, 1257, 1200, 1090, 1070 and 1028; δ_H[which indicated the presence of *E* and *Z* formamides (1:0.35)] *E*-isomer: −0.22 (3 H, s), −0.004 (3 H, s), 0.88 (9 H, s), 0.93 (3 H, d, *J* 6.8), 4.05–4.20 (1 H, m), 4.83 (1 H, d, *J* 3.3), 6.26 (1 H, apparent d, *J* 12, NH), 7.18–7.32 (m) and 8.05 (1 H, s); *Z*-isomer: −0.24 (3 H, s), −0.016 (3 H, s), 0.85 (9 H, s), 1.03 (3 H, d, *J* 6.8), 3.42–3.60 (1 H, m), 4.50 (1 H, d, *J* 4.5), 5.85 (1 H, apparent t, *J* 10), 7.18–7.32 (m) and 7.85 (d, *J* 12, 1-H); δ_C −5.2, −4.8, 13.2, 16.6, 18.0, 18.1, 25.7, 25.8, 50.1, 54.1, 75.9, 77.8, 126.1, 126.9, 127.2, 127.8, 127.9, 128.1, 139.9, 141.4, 160.3 and 163.8; *m/z* 278.1569 ($M^+ - CH_3$). $C_{15}H_{24}NO_2Si$ requires *m/z* 278.1576 (2.5 ppm error) (Found: C, 65.5; H, 9.3. $C_{16}H_{27}NO_2Si$ requires C, 65.09; H, 9.09%).

(1S,2R)-2-(tert-*Butyldimethylsiloxy*)-1-*methyl*-2-*phenylethyl Isocyanide* **4**.—In a 250 cm^3 single-necked, round-bottom flask fitted with a septum and a stirrer bar was placed a solution of compound **3** (15.3 g, 52 mmol) in freshly distilled methylene dichloride (100 cm^3). At 0 °C, while being stirred under nitrogen, the solution was treated with $POCl_3$ (4.86 cm^3, 52 mmol) and triethylamine (22 cm^3, 158 mmol, 3.04 mol equiv.) *via* syringe. The mixture was stirred for 5 min, then poured into silica gel, and the mixture was filtered. The silica gel was rinsed with diethyl ether several times. The filtrate was concentrated under reduced pressure and purified by flash column chromatography [10% diethyl ether–hexane, v/v] to give compound **4**, then with 75% diethyl ether–hexane (v/v) to give recovered substrate **3**. Evaporation of the solvent gave the *isocyanide* **4** as a pale yellow oil (9.7 g, 68%) and recovered substrate **3** (2.5 g, 16%); compound **4** showed ν_{max}/cm^{-1} 2958, 2932, 2895, 2136, 1699, 1485, 1473, 1380, 1260, 1201, 1143, 1105, 1076 and 1027; δ_H −0.13 (3 H, s), 0.13 (3 H, s), 0.93 (9 H, s), 1.29 (3 H, d, *J* 7), 3.65–3.80 (1 H, m), 4.75 (1 H, d, *J* 4.6) and 7.35–7.40 (5 H, m); δ_C −5.2, −4.8, 16.1, 18.1, 25.6, 56.6 (t, J_{C-N} 6.2), 76.4, 126.5, 128.1, 139.9 and 156.4 (t, J_{C-N} 5); *m/z* 218.1008 ($M^+ - CMe_3$). $C_{12}H_{16}NOSi$ requires *m/z* 218.1001 (3.2 ppm error) (Found: C, 69.3; H, 9.0. $C_{16}H_{25}NOSi$ requires C, 69.76; H, 9.15%).

(1S,2R)-2-(tert-*Butyldimethylsiloxy*)-1-*methyl*-2-*phenylethyl Isoselenocyanate* **5**.—In a single-necked, 250 cm^3, round-bottom flask fitted with a refluxing condenser and a stirrer bar were placed compound **4** (37.0 g, 0.135 mol) and elemental selenium powder (100 mesh, >99.5%) (21.2 g, 268 mmol, 1.99 mol equiv.) in chloroform (stock; 50 cm^3). The mixture was heated to reflux and stirred under a blanket of nitrogen for 5 h. The reaction mixture was then filtered to remove unchanged selenium powder, and the filtrate was concentrated under reduced pressure to give the crude *compound* **5** which was obtained as a red oil (48.4 g, 0.136 mol). This material was used immediately in the next step; $\lambda_{max}(CHCl_3)/cm^{-1}$ 256 (ε 1417 dm^3 mol^{-1} cm^{-1}); ν_{max}/cm^{-1} 2930, 2859, 2118, 1472, 1288, 1140, 1098 and 1027; −0.15 (3 H, s), 0.11 (3 H, s). 0.91 (9 H, s), 1.29 (3 H, d, *J* 6.6), 3.85–3.95 (1 H, m), 4.75 (1 H, d, *J* 4.7) and 7.23–7.42 (5 H, m); δ_C −4.6, −4.2, 16.5, 18.5, 26.2, 61.0, 77.2, 124.2 (N=C=Se, J_{Se-C} 292), 127.0, 128.7, 128.8 and 140.3; δ_{Se} −346.9; *m/z* 340.0640 ($M^+ - CH_3$). $C_{15}H_{22}NOSeSi$ requires *m/z* 340.0636 (1.2 ppm error) (Found: C, 54.1; H, 7.15. $C_{16}H_{25}NOSeSi$ requires C, 54.22; H, 7.11%).

(4S,5R)-4-*Methyl*-5-*phenyloxazolidine*-2-*selone* **6**.—In a single-necked, 250 cm^3, round-bottom flask fitted with a septum and a stirrer bar was placed a solution of compound **5** (22 g, 62 mmol) in freshly distilled THF (150 cm^3) and the resulting solution was chilled to 0 °C. Under nitrogen, TBAF [1.0 mol dm^{-3} solution in THF (62 cm^3)] was added *via* syringe. The mixture was stirred for 30 min, followed by silica gel filtration. The filtrate was concentrated at reduced pressure and the residue was purified by flash column chromatography (distilled, deoxygenated diethyl ether). Evaporation of the solvent gave compound **6** as a pale yellow solid (9.45 g, 64% overall yield for two steps), $\lambda_{max}(CHCl_3)/nm$ 278 (ε 19 000); $\nu_{max}(CDCl_3)/cm^{-1}$ 3400, 3100, 2900, 1630, 1450, 1330, 1260 and 1130; δ_H 0.86 (3 H, d, *J* 6.7), 4.35–4.45 (1 H, m), 5.95 (1 H, d, *J* 9.1) and 7.22–7.38 (5 H, m); δ_C 16.3, 56.8, 88.1, 126.2,

128.6, 129.0, 133.0 and 188.2 (J_{Se-C} 242); δ_{Se} 125.8; *m/z* 241.0007 (M^+). Calc. from $C_{10}H_{11}NOSe$: M, 241.0006 (0.4 ppm error).

(4S,5R)-3-[5-(1,2-*Dithiolan*-3-*yl*)-1-*oxopentyl*]-4-*methyl*-5-*phenyloxazolidine*-2-*selone* **7**.*—In a 25 cm^3, round-bottom flask fitted with a septum and containing a magnetic stirrer bar was placed (*R,S*)-lipoic acid (0.3 g, 1.59 mmol). To this was added freshly distilled methylene dichloride (10 cm^3) followed by the addition of dicyclohexylcarbodiimide (0.325 g, 1.58 mmol) at room temperature. The mixture was stirred for 1 h at this temperature. The selone **6** was then added as a solution in methylene dichloride (5 cm^3). The reaction mixture was stirred overnight, then was filtered through a pad of silica gel and concentrated to give the crude product. Purification by silica gel (230–400 mesh) flash chromatography (40% methylene dichloride–hexanes v/v) afforded compound **7** (0.2 g, 59%), $\nu_{max}(CCl_4)/cm^{-1}$ 2934, 1706, 1354, 1272, 1187 and 980; δ_H 0.86 (3 H, d, *J* 6.7), 1.43–1.53 (2 H, m), 1.60–1.73 (4 H, m), 1.79–1.90 (1 H, m), 2.35–2.45 (1 H, m), 3.02–3.13 (2 H, m), 3.29–3.35 (1 H, m), 3.42–3.55 (2 H, m), 4.95 (1 H, dq, *J* 13.6 and 6.8), 5.69 (1 H, d, *J* 7.4) and 7.24–7.37 (5 H, m); δ_C 14.1, 24.1, 28.3, 34.4, 37.6, 37.7, 38.8, 56.1, 59.4, 84.9, 125.8, 128.5, 128.7, 131.7, 173.5 and 188.3 (J_{Se-C} 242); δ_{Se} 467.98 and 468.1; *m/z* 429.0336 (M^+). $C_{18}H_{23}NO_2S_2Se$ requires *m/z*, 429.0335 (0.2 ppm error) (Found: C, 50.7; H, 5.6. Calc. for $C_{18}H_{23}NO_2S_2Se$ requires C, 50.46; H, 5.41%).

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* A U.S. Patent application has been filed to cover the use of compound **6** for the detection of enantiomeric excesses and absolute configurational assignment at chiral centres.

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